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Biogenetically Inspired Synthesis of Lingzhiol

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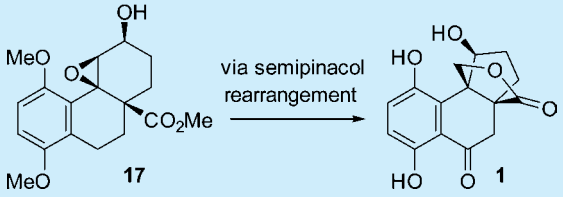
Supporting Information

ABSTRACT: A concise stereo- and enantioselective synthesis of lingzhiol has been achieved featuring a biogenetically inspired Brønsted acid catalyzed semipinacol rearrangement of a glycidyl alcohol intermediate.



In 2013, Cheng et al. reported isolation of a structurally unprecedented meroterpenoid from the mushroom *Ganoderma lucidum* widely used in traditional Chinese medicine under the name *ling-zhi*.[1] Somewhat unusually, the natural product, named lingzhiol (Figure 1), proved to be a racemate.

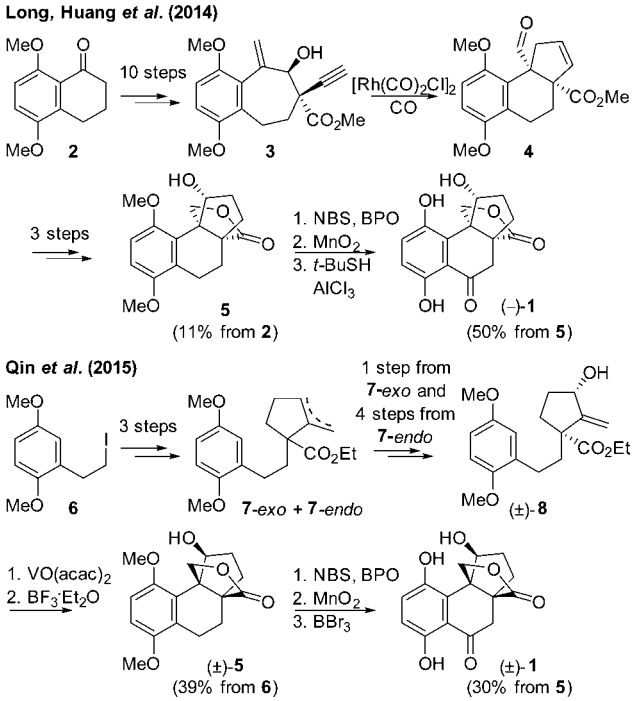
Figure 1. (±)-Lingzhiol and its natural source.

It was found to possess potent and selective inhibitory activity toward p-Smad3, a transcription protein implicated in renal fibrosis. Its enantiomers were separated by semipreparative HPLC and shown to have comparable activities. Extraction of lingzhiol from its natural source,[1b] while adequate for preliminary pharmacological studies, is expected to be impractical in the long run due to its very low content (ca. 1 ppm in dry *ling-zhi*) and, besides, cannot provide access to its unnatural analogs. These two considerations clearly point to the need for a concise and flexible synthetic route to this molecule. Recent publication of two total syntheses of lingzhiol[2] summarized in Scheme 1 prompts us to disclose our own results in this direction.

Our interest in devising a synthetic strategy for lingzhiol led us to look for clues in its biosynthesis. In contrast to the biogenetic proposal offered by Cheng's isolation team,[1a] we hypothesized that it probably proceeds via the semipinacol rearrangement of the putative glycidol intermediate **11** followed by the aldehyde reduction and lactonization (Scheme 2). Several synthetic counterparts of the rearrangement step, all of which require Lewis acid catalysis, have been described in the literature.[3]

Known ketoester **13**[4] was converted into tricyclic enone (±)-**15** via the classical Robinson annulation[5] (Scheme 3). Its

Scheme 1. Previous Syntheses of Lingzhiol[a]



[a]NBS = *N*-Bromomethylsuccinimide; BPO = benzoyl peroxide.

reduction into (±)-**16** under the Luche conditions[6] proceeded with good diastereoselectivity when conducted at a low temperature. The greatest surprise awaited us in the epoxidation step (Scheme 4). Indeed, within minutes after adding *m*-CPBA to a solution of (±)-**16** in deuterated chloroform we observed not only the expected *syn*-glycidol (±)-**17** but also a sizable aldehyde peak in the ^{1}H NMR spectrum (**18**). This indicated that the proposed rearrangement occurred spontaneously via the Brønsted acid catalysis by either

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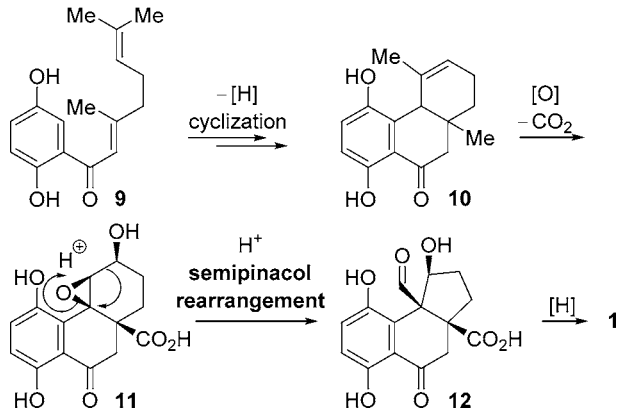
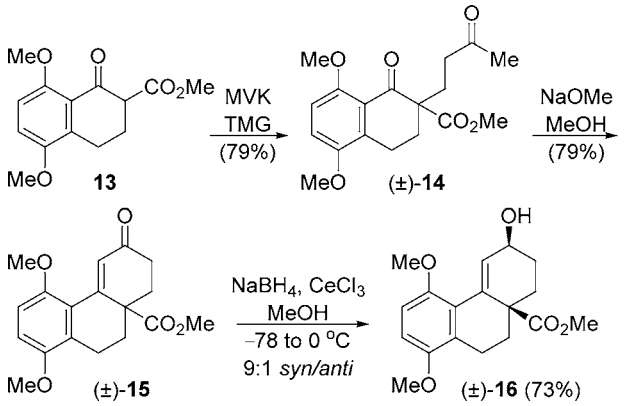
Scheme 2. Proposed Biosynthesis of Lingzhiol

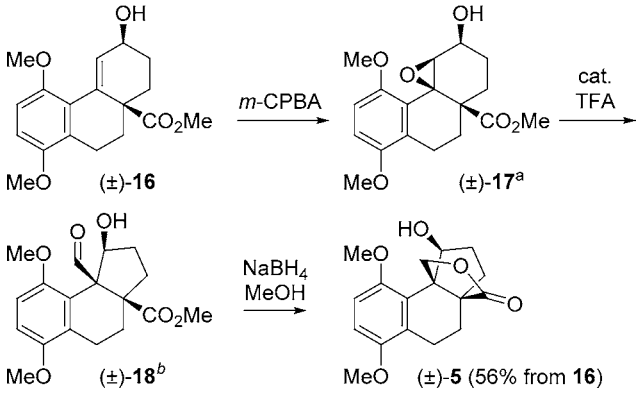


Scheme 3. Preparation of the Rearrangement Precursor 16[a]



[a]MVK = Methyl vinyl ketone; TMG = *N,N,N′,N′*-tetramethylguanidine.

Scheme 4. Semipinacol Rearrangement and Completion of the Formal Synthesis of Lingzhiol 1[a]

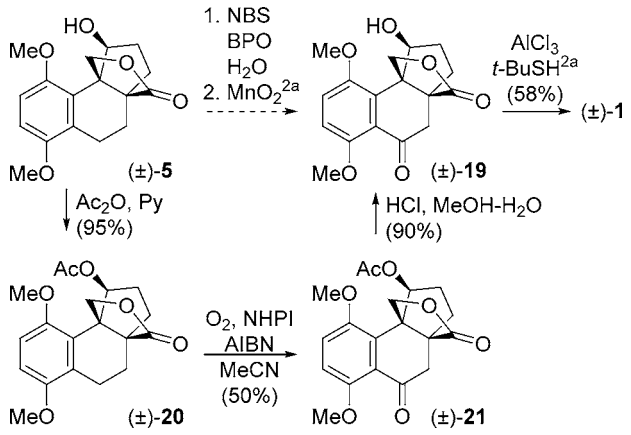


[a]Observed by ^{1}H NMR, not isolated. [b]*m*-CPBA = *m*-chloroperbenzoic acid; TFA = trifluoroacetic acid.

m-chlorobenzoic acid or adventitious DCl in the solvent. The unprecedented ease with which it took place can be rationalized by the perfect orbital overlap of the intermediate carbocation with the benzene ring. Addition of 20 mol % of trifluoroacetic acid completed the rearrangement. Borohydride reduction of the crude aldol (±)-**18**[7] led directly to the diastereomerically pure lactone (±)-**5**, an advanced intermediate in both previous syntheses of lingzhiol.[2] Overall, its preparation (6 steps, 26% overall yield from the commercially available 5,8-dimethoxytetralone **2**) compared favorably with the two previous routes (Scheme 1).[8]

Although the formal synthesis of (±)-lingzhiol **1** was thus achieved, we decided to complete the preparation of the natural product in order to continue its biological testing. Unfortunately, the one-pot benzylic oxidation sequence described by Long, Huang et al.[2a] and later used by Qin et al.[2b] did not give any of the expected product (±)-**19** in our hands (Scheme 5).

Scheme 5. Completion of the Synthesis[a]

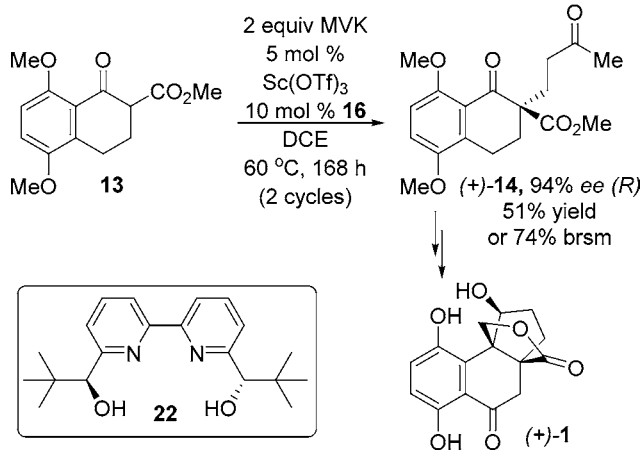


[a]NHPI = *N*-hydroxyphthalimide.

An alternative three-step sequence proceeding via aerobic oxidation[9] proved to be more reliable. Demethylation of the phenol hydroxyls following the original protocol[2a] delivered the racemic natural product.

The synthetic scheme described above is readily rendered enantioselective by employing an asymmetric catalytic version of the Michael addition step (**13** → **14**) (Scheme 6).

Scheme 6. Enantioselective Synthesis of (+)-Lingzhiol[a]



[a]MVK = Methyl vinyl ketone; DCE = 1,2-dichloroethane.

Kobayashi's protocol[10] employing the scandium triflate complex of Bolm's ligand[11] **22** produced diketone **14** in 94% *ee*. Its transformation into enantioenriched (+)-lingzhiol proceeded through the steps already established in the racemic synthesis, with similar yields.

In conclusion, we have developed a concise new approach to lingzhiol based on an original biogenetic proposal. The

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remarkable ease of the semipinacol rearrangement of glycidol **17** bodes well for the application of our strategy to the synthesis of analogs of lingzhiol and related structures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03212.

Experimental procedures and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(7) Direct borohydride reduction was advantageous, because prolonged exposure of aldol **18** to acid or attempted chromatography led to its epimerization to the *anti*-diastereomer (see Supporting Information).

(8) Iodide **6** is not commercially available.

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