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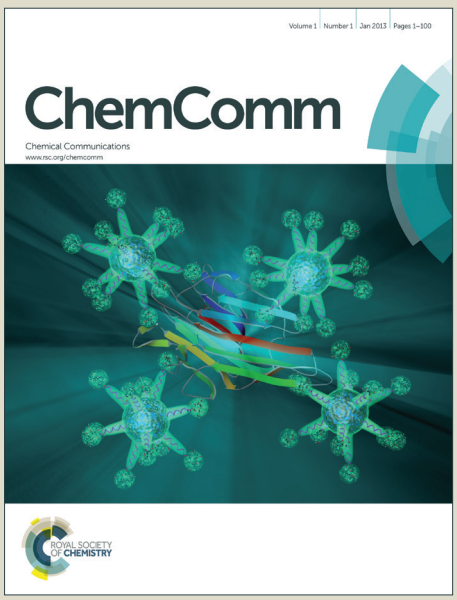

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A Concise Synthesis of (±)-Lingzhiol via Epoxy-arene Cyclization

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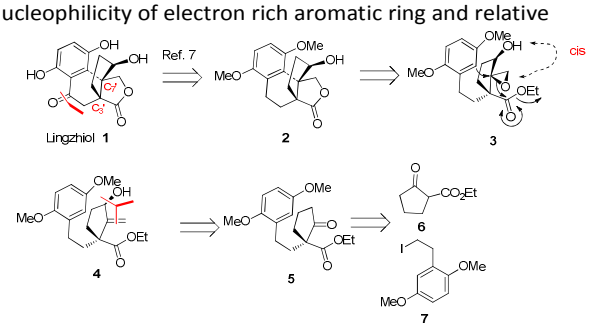
A concise synthesis of (±)-Lingzhiol has been achieved. The key reaction involves one-step construction of 5/5/6/6 tetra-ring backbone of Lingzhiol via epoxy-arene cyclization.

Ganoderma lucidum, also known as Lingzhi in Chinese, has been used as a magic herb for nourishment and complement of deficiency issues by nobility in China for centuries. It also gains reputation in the West. Polysaccharides and triterpenoids[1] have been considered as major ingredients responsible for its various medical effects such as antiaging[2], immunoregulation[3], anticancer[4, 5]. Despite huge amounts of investigations on this species, careful experimental design could still result in the isolation of natural product with totally different structure and bioactivity. In 2013, Lingzhiol, a meroterpenoid from *G. lucidum* reported by us, was proven to have potent inhibitory effect on phosphorylation of Smad3 which is implicated in chronic kidney disease such as diabetic nephropathy (DN)[6]. In this regard, Lingzhiol could be a promising leading compound of DN. To conduct in vivo experiment, sufficient amount of Lingzhiol is required. Moreover, the intriguing cage-like architecture of 1 also arose our great interest. Therefore, we initiated its total synthesis. Herein, we report a rapid construction of 5/5/6/6 backbone via epoxy-arene cyclization, which ensured a concise total synthesis of (±)-Lingzhiol (**1**).

Structurally, Lingzhiol has an unprecedented rotary door-shaped 5/5/6/6 ring system with two consecutive quaternary carbons. Construction of these two carbons is the key step to achieve total synthesis. A 17-step asymmetric synthesis of (-)-Lingzhiol was reported for the first time by Prof. Yang[7] via a Rh-catalysed [3+2] cycloaddition, which efficiently constructed two quaternary carbon centres at one-step. Considering the nucleophilicity of electron rich aromatic ring and relative position of hydroxyl group in lactone, we envisioned that the carbon at 7' could be formed by epoxy-arene cyclization[8-10] as illustrated in Scheme 1. Consequently, the retrosynthetic analysis is depicted. Lingzhiol **1** was supposed to be an oxidation product of lactone **2** [7] which could be synthesized by above mentioned strategy from epoxide **3**. Allylic epoxide **3** could be obtained from allylic alcohol **4** which is accessible by Wittig reaction of **5** and subsequent oxidation at allylic position. Keto ester **5** could be easily obtained by alkylation of commercially available ethyl 2-oxocyclopentanecarboxylate **6** with iodide **7**[11]. The relative *trans* configuration between secondary OH group and aromatic ring could be guaranteed when the aromatic ring attack occurred from buttom side of epoxy unit, which is supposed to be *cis* to secondary OH as a result of Sharpless allylic alcohol epoxidation[12].



Scheme 1. Retrosynthetic analysis of **1**.

Our synthesis commenced with alkylation of ethyl 2-oxocyclopentanecarboxylate with aryl ethyl iodide **7**, which was synthesized by $LiAlH_4$ reduction of 2,5-dimethoxy phenyl acetic acid to primary alcohol and subsequent iodine substitution. Keto ester **5** with a quaternary carbon was isolated in 78% yield (Scheme 2). Unfortunately, direct introduction of exo double bond to give **9** via Wittig reaction or Takai olefination[13, 14] resulted in complete recovery of starting material from 0℃ to r.t. and decomposition at elevated temperature. This result is hard to understand because remote n→π* interaction between carbonyl and

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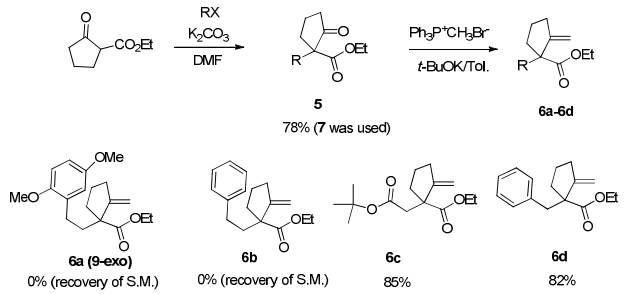
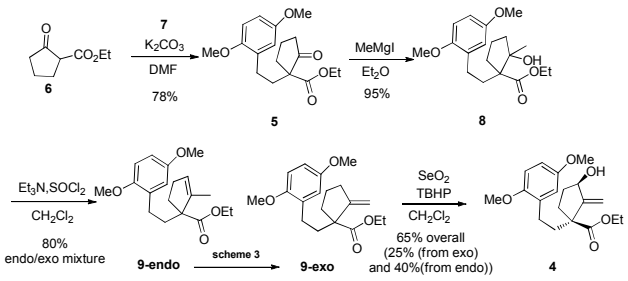
aromatic ring is generally weak[15]. To investigate the reaction, we prepared similar ketone with tertiary carbon. Upon subjection to Wittig reaction condition, **6b** was not formed neither. Considering the fact that **6c** was obtained effectively, it is clear that aromatic ring played a critical role in decreasing the electrophilicity of carbonyl group. However, **6d**, only one methylene unit short, was isolated in high yield; In this case, phenyl ring is difficult to approach carbonyl group because the rigidity of sp3 hybridization of benzyl carbon. In contrast, with longer, more flexible side chain, aromatic ring in **5** might sterically block the carbonyl group, therefore, leaded to inactivation of ketone.



Scheme 2. Investigation of Wittig reaction.

Hence, an alternative strategy was adopted: formation of tertiary alcohol **8** by MeMgI addition to **5a** and subsequent dehydration could be a choice (Scheme 3). Not surprisingly, inseparable mixture of **9**-exo and **9**-endo were isolated in 90% yield and the best endo/exo ratio, determined by ^{1}H NMR, was low as 2.2:1 even using excess thionyl chloride and triethylamine (Table 1)[16]. Despite considerable endeavor, like utilizing bulky dehydration reagent propylphosphonic anhydride (T3P)[17], not much improvement was achieved due to steric hindrance. However, considering the reaction mechanism of selenium dioxide[18] and its oxophilicity, ester chelation with selenium might provide a rate different in allylic oxidation between exo/endo isomers, thus making isolation of these isomers possible. To our delight, when the isomers of **9** were subjected to selenium dioxide oxidation, in the presence of reoxidant TBHP, the endo isomer was isolated intactly, followed by desired allylic alcohol **4** during flash chromatography. Its relative configuration of OH was confirmed from X-ray crystal information of lactone **2**. This might result from the assistance of ester group.



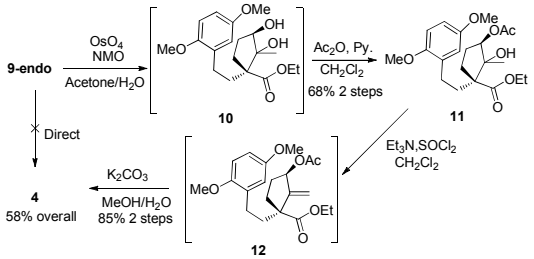
Scheme 3. Synthesis of allylic alcohol **4**

Table 1. Optimization of endo/exo ratio with different organic bases.

entry	base	solvent	condition	Ratio[a](endo/exo)
1	Py.	THF	reflux	4.5:1
2	Py.	THF	-78℃	5:1
3	Py.	CH_2Cl_2	r.t	7:1
4	Py.	CH_2Cl_2	-78℃	10:1
5	DMAP	THF	-78℃	6.8:1
6	DMAP	CH_2Cl_2	r.t	3.6:1
8	DMAP	CH_2Cl_2	-78℃	5.6:1
9	DIPEA	THF	-78℃	11.8:1
10	DBU	THF	-78℃	16.9:1
11	Et_3N	THF	-78℃	4.5:1
12	Et_3N	THF	reflux	5.1:1
13	Et_3N	CH_2Cl_2	r.t	3.5:1
14	Et_3N	CH_2Cl_2	-78℃	2.2:1

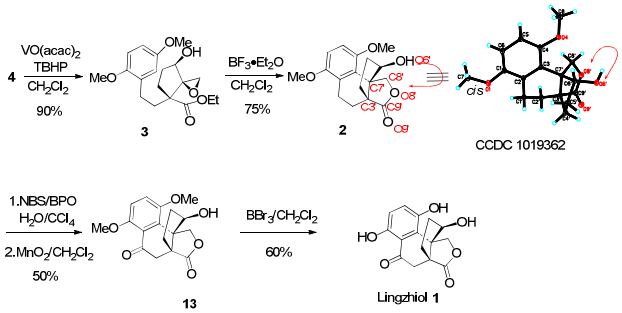
a ^{1}H NMR ratio

Owing to the higher yield of the thermodynamically stable endo isomer, further utilization of it was studied. After extensive trials, we succeeded in transforming it into allylic alcohol **4** in two consecutive operations (Scheme 4). Dihydroxylation of **9**-endo with OsO_4 and subsequent selective acetylation of secondary alcohol with acetic anhydride gave tertiary alcohol **11** in 68% yield. Dehydration with thionyl chloride in the presence of triethylamine and deacetylation proceeded nicely to afford allylic alcohol **4** in high yield. Thus, complete utilization of **9**-endo isomer was realized. Alternatively, direct conversion of **9**-endo into **4**, such as Prof. Baran's method[19] using $Pd(OAc)_2$, was unsuccessful.



Scheme 4. Transformation of endo to exo allylic alcohol **4**.

Routine Sharpless epoxy reaction ($VO(acac)_2$, TBHP) of allylic alcohol **4** set the stage for cyclization as key step (Scheme 5). The relative configuration of epoxide **3** was inferred from epoxidation mechanism and confirmed by crystal of lactone **2**. As expected, epoxy-arene cyclization proceeded smoothly when treated with $BF_3.OEt_2$, and luckily, lactone **2** was isolated in 75% yield, which suggested a simultaneous *in situ* lactone formation. The *cis* configuration between OH and ester in **2** was explicitly shown in X-ray crystal diffraction. The benzyl position of **13** was oxidized into ketone following Prof. Yang's protocol[7]. Demethylation by BBr_3 afforded (±)-Lingzhiol. The ^1H and ^{13}C spectra of synthesized Lingzhiol are indiscriminate as reported.



Scheme 5. Rapid construction of 5/5/6/6 tetra-ring skeleton. TBHP: tert-butyl hydroperoxide; BPO: benzoyl peroxide.

In summary, a concise total synthesis of (±)-Lingzhiol has been achieved in 8 linear steps, 7.8% overall yield. It features a one-step construction of 5/5/6/6 ring system via epoxy-arene cyclization and *in situ* formation of lactone.

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