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Biomimetic Total Syntheses of (+)-Dihydrolyfoline and (−)-5-*epi*-Dihydrolyfoline

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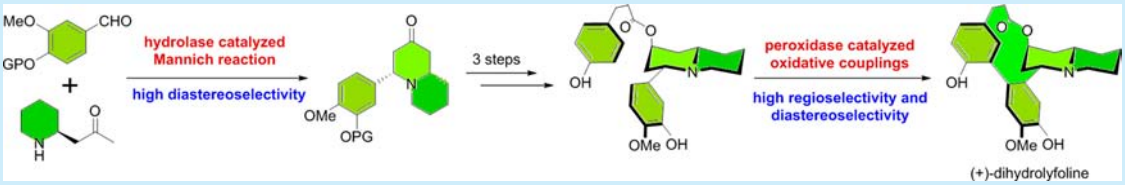
Supporting Information



ABSTRACT: The first asymmetric total syntheses of (+)-dihydrolyfoline and (−)-5-*epi*-dihydrolyfoline have been achieved in five and six steps with 4.6% and 14% overall yields, respectively, in which the chiral biaryl axes were constructed in a highly regioselective and stereoselective manner via a biogenetic enzymatic oxidative couplings of phenols, and the requisite quinolizidinone cores were prepared by an enzymatic Mannich reaction.

The Lythraceae alkaloid family (Figure 1), first isolated from *Decodon verticillatus* (L.) Ell in 1962,[1] exhibits a diverse

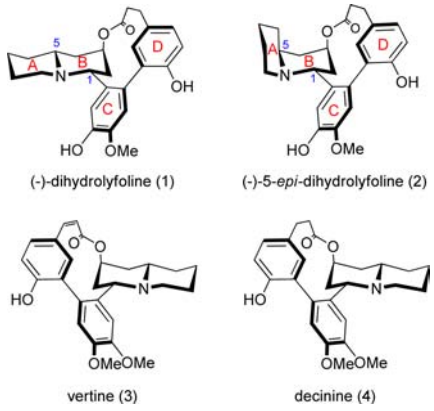
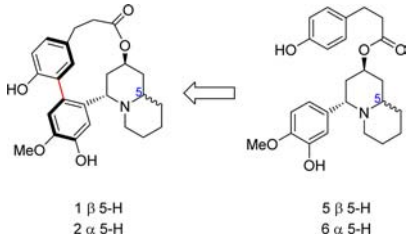


Figure 1. Representative natural Lythraceae alkaloids.

array of biological activities,[2] including anti-inflammatory, antispasmodic, diuretic, hypoglycemic, and antihypertensive properties and effects. Structurally, most alkaloids of this family feature a quinolizidine skeleton and a 12-membered macrocyclic ester ring, which contains a chiral biaryl axis. In 2009, two new members of this family, dihydrolyfoline (**1**) and 5-*epi*-dihydrolyfoline (**2**), were isolated from the plant *Lagerstroemia indica*.[3]

The biological properties and the novel chemical structure of the Lythraceae alkaloids make these natural products highly attractive targets for chemical synthesis. Biosynthetically, the chiral biaryl axes of these alkaloids are proposed to be formed by oxidative phenolic couplings (Scheme 1). According to this hypothesis, in 1970, Schwarting and co-workers attempted to

Scheme 1. Biosynthetic Analysis of Quinolizidine Alkaloids



couple diphenol **5** using $FeCl_3$, $K_3[Fe(CN)_6]$, electrolytic oxidation, and catalytic oxygenation, but all these methods failed to yield dihydrolyfoline **1**.[4] A few years later, Quick and co-workers tried to use vanadium(V) (e.g., VOF_3, $VOCl_3$) as oxidants to couple **5** and its derivatives, but this effort was also unsuccessful.[5] In 2010, Kündig and co-workers described the first total synthesis of vertine **3**, which employed a RCM reaction as the key reaction to construct the macrocyclic ring and the chiral axis.[6,7] In 2012, Yang and co-workers finished the total synthesis of decinine **4**, but an attempted regioselective deprotectation of the methoxyl group of **4** was unsuccessful in obtaining dihydrolyfoline **1**.[8]

Although several syntheses of this kind of natural products were reported, it is still a formidable challenge to regioselectively

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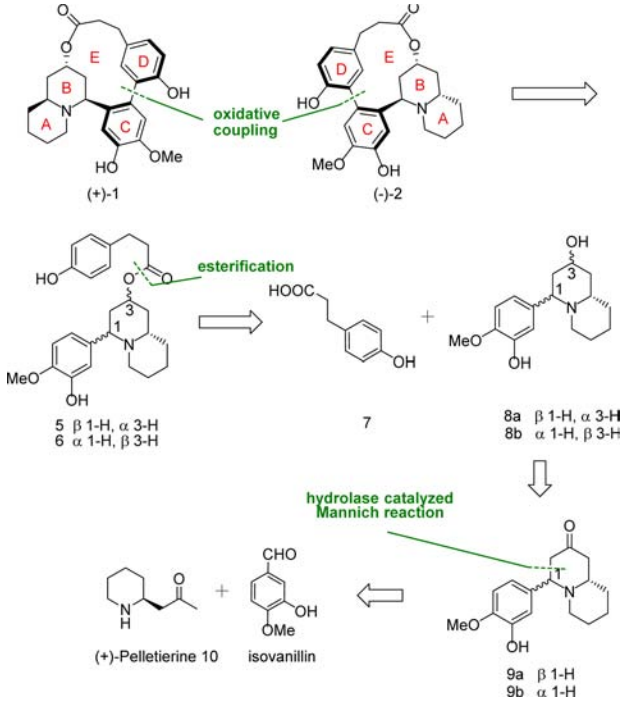
and enantioselectively synthesize the Lythraceae alkaloid family of natural products via the intramolecular oxidative biaryl coupling reaction of phenols.[9] The main obstacles lie in the following: (1) the desirable products would be further oxidized under the general oxidation conditions; (2) the strain coming from the macro ring and chiral biaryl makes the intramolecular couplings disfavored comparing to the intermolecular ones; (3) the regioselectivity of coupling reactions is not finely controlled; (4) it is also difficult to control the stereochemistry of the strained chiral biaryl axis.

In recent decades, biosynthesis has attracted intensive interest in natural product synthesis. Enzymes have several advantages, such as high efficiency, environmental friendliness, etc. However, the enzyme also has very high specificity, which means only the specific substrates could undergo enzyme catalysis reactions.[10] This limits the applications of enzyme catalysis reactions in organic synthesis, especially in the total synthesis of natural products. Several literature reports had indicated that peroxidases can catalyze the oxidative coupling of diphenol in the presence of H_2O_2;[11] however, this reaction has been scarcely applied in total synthesis of macrocyclic skeleton of natural products.

In this paper, we document an enzymatic oxidative coupling process to construct the strained macrocyclic rings and the chiral biaryl axes of (+)-dihydrolyfoline and (−)-5-*epi*-dihydrolyfoline efficiently. We also developed an enzymatic catalyzed Mannich reaction to construct the requisite quinolizidine core of these natural products. Moreover, we applied this biomimetic strategy to achieve the total syntheses of (+)-dihydrolyfoline and (−)-5-*epi*-dihydrolyfoline from readily available materials.

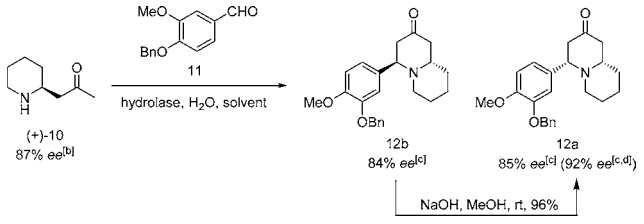
Our retrosynthetic analysis is outlined in Scheme 2. We envisioned that (+)-**1** and (−)-**2** would be biogenetically derived from diphenols **5** and **6**, through oxidative coupling reactions, respectively. Diphenols **5** and **6** could arise by esterification of 3-(4-hydroxyphenyl)propanoic acid **7** with secondary alcohols **8a** and **8b**, respectively. The important intermediates, quinolizidineone **9a** and **9b**, would be generated via a hydrolase catalyzed Mannich transformation from (+)-pelletierine **10** and isovanillin, by which the stereochemistry of C1 could be installed. (+)-Pelletierine **10** was easily prepared on the basis of Bella's work.[12]

Scheme 2. Biosynthetic Analysis of Quinolizidine Alkaloids and Retrosynthetic Analysis



Our synthesis commenced with the Mannich reaction between (+)-pelletierine **10** and aldehyde **11** catalyzed by hydrolase. Even though many studies on construction of qunlindine structure have been reported by Quick et al., how to control the stereochemistry of C1 and C5 of the structure represents a significant synthetic challenge.[13] There is no desirable product generated in the blank test demonstrating that the Mannich process was indeed catalyzed by hydrolase. After screening of different hydrolases, temperatures, and solvents, almost all hydrolases we used, including α-amylase, β-amylase, γ-amylase, lipase, and papain, could catalyze this Mannich reaction (Table 1). In this process, DMSO, 1,4-dioxane, and acetonitrile are all suitable solvents, and the optimum temperature is about 40 °C. Pleasingly, only the kinetic product **12b** was obtained. Importantly, **12b** can isomerize to **12a** in 96% yield under the condition of NaOH/MeOH at room temperature for 72 h.[6] Determination of the configuration of **12a** and **12b** was accomplished according to Kündig's work.[6]

Table 1. Optimization of the Mannich Process Catalyzed by Hydrolase



entry	hydrolase	solvent	temp (°C)	yield of **12b**[a] (%)
1		dioxane	25	N.R.
2	α-amylase	dioxane	25	20
3	β-amylase	dioxane	25	23
4	γ-amylase	dioxane	25	18
5	papain	dioxane	25	20
6	lipase	dioxane	25	25
7	lipase	CH_3CN	25	21
8	lipase	DMSO	25	17
9	lipase	dioxane	35	28
10	lipase	dioxane	40	35

[a]Yields based upon isolation of the corresponding isovanillin. [b]Reported in ref 12. [c]Determined by chiral HPLC analysis (Chiracel AD). [d]After recrystallization.

Then, stereoselective reduction of the quinolizidinone **12a** by L-Selectride followed by treatment with methanol and water in turn afforded the intermediate **13** (Scheme 3).[14] The esterification of 4-(benzyloxy)phenylpropanoic acid and secondary alcohol **13** was accomplished in a facile process using EDCI and DMAP providing the desired ester **15** in 82% yield. Deprotection of the two benzyl groups was performed by exposure of ester **15** to 10% $Pd(OH)_2/C$ and H_2 atmosphere in ethyl acetate at room temperature, affording diphenol **5** in 84% yield. Similarly, diphenol **6** could be obtained from quinolizidinone **12b** by the three-step sequence including reduction, esterification, and deprotection in 63% overall yield.

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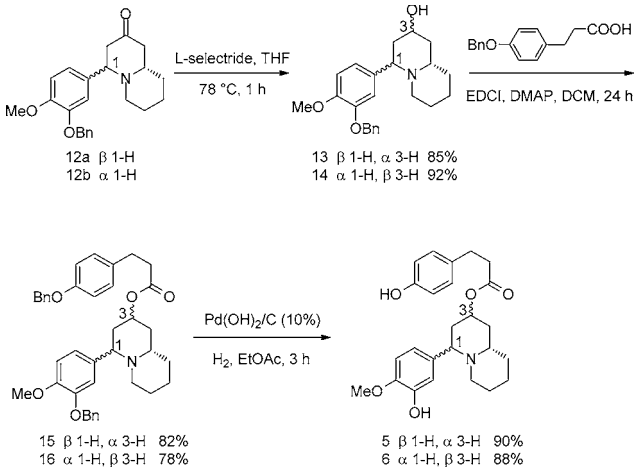
Scheme 3. Syntheses of Diphenol 5 and 6



With diphenols **5** and **6** in hand, we pursued the oxidative coupling process. Horseradish peroxidase (HRP), which is the most common and commercially available peroxidase, was selected as the catalyst.[15] In order to maintain the activity of HRP, oxidative coupling would be carried out in a buffer solution. However, the solubility of diphenols **5** and **6** is very poor in aqueous media. To solve this problem, water-soluble organic solvents (e.g., dioxane, acetonitrile, ethanol) were used to increase the solubility of diphenols **5** and **6**. In consideration of the possibility of inactivation and deactivation of HRP by organic solvents, heterogeneous solvent systems also have been investigated. The results are exhibited in Figure 2.

There is no coupling product in the blank test, illustrating that the oxidative coupling process was indeed catalyzed by HRP. As shown in Figure 2A, the homogeneous solvent system gave a better result than the heterogeneous system, and dioxane was shown to be the optimal additive organic solvent. It was also demonstrated that the optimum pH value for this HRP catalysis process is about 5.0 (Figure 2B). The phosphate buffer (pH varies from 3.0 to 8.0) always gave the coupling product in low yields (Figure 2C), while the acetic buffer could proceed in satisfactory yields. It suggests that acetate ion might act as a ligand of the central iron atom of HRP and promote the enzymatic reaction. Interestingly, diphenol **5** could deliver (+)-**1** only in 15−20% yield, but the yield of (−)-**2** from diphenol **6** could be up to 50−65% (Figure 2D). Notably, a single coupling product (MW = 423) was separated in the oxidative couplings of diphenols **5** and **6**, respectively. That means both the regioselectivity and diastereoselectivity of oxidative couplings of phenols are very high. All ^{1}H and ^{13}C NMR as well as UV spectral data for our synthetic (+)-dihydrolyfoline and (−)-5-*epi*-dihydrolyfoline matched those provided in the isolation report.[3]

In summary, the total syntheses of (+)-dihydrolyfoline and (−)-5-*epi*-dihydrolyfoline have been accomplished in five and six steps with 4.6% and 14% overall yields, respectively. The syntheses feature a hydrolase-catalyzed Mannich process to diastereoselectively construct quinolizidine structure and biogenetic enzymatic oxidative couplings of phenols to form the strained macrocyclic ring and the chiral biaryl axis with high regioselectivity and diastereoselectivity. This work constitutes the first example of using oxidative couplings of phenols to synthesize Lythraceae alkaloids, which proved to be very difficult as previous research.[4,5] Due to the specificity of the enzyme catalysis, our results confirm the biogenesis hypothesis of

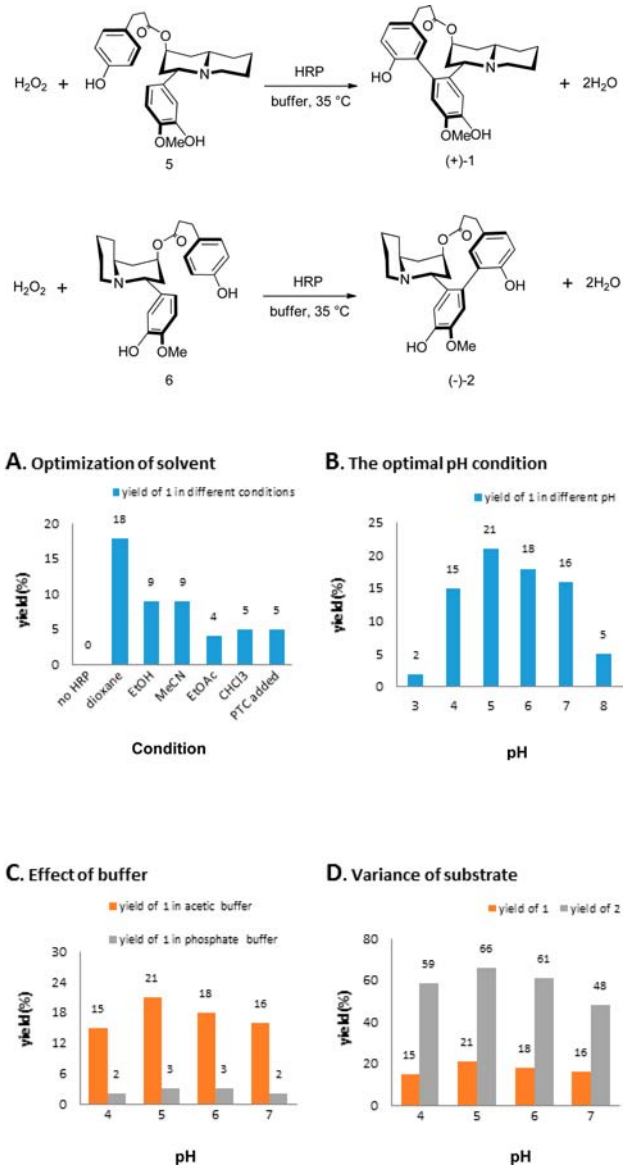


Figure 2. Oxidative coupling reaction catalyzed by HRP. Conditions unless otherwise noted: diphenol **5** as the substrate, 0.18 equiv of 3% H_2O_2 added per hour, 35 °C, 10 h; (A) pH 6 acetate buffer; when phase transfer catalyst (diisooctyl phosphate) was added, $CHCl_3$ as solvent; (B) acetic buffer and dioxane as solvent; (C) acetic buffer or phosphate buffer, dioxane as solvent; (D) acetic buffer, dioxane as solvent. For substrate **5**: 0.18 equiv of 3% H_2O_2 added per hour, 35 °C, 10 h. For substrate **6**: 0.18 equiv of 3% H_2O_2 added per quarter hour, 35 °C, 3 h.

Schwarting and suggest the natural products dihydrolyfoline and 5-*epi*-dihydrolyfoline might be formed by this mode in the plant *Lagerstroemia indica*.[4] Further studies on a more efficient biosynthesis of other Lythraceae family are underway, and our results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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