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Highly Convergent Total Synthesis of (+)-Lithospermic Acid via a Late-Stage Intermolecular C−H Olefination

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Supporting Information

ABSTRACT: The total synthesis of (+)-lithospermic acid is reported, which exploits two successive C−H activation reactions as key steps. Rh-catalyzed carbene C−H insertion reaction utilizing Davies's catalyst was used to forge dihydrobenzofuran core, and a late-stage intermolecular C−H olefination coupled the olefin unit with the dihydrobenzofuran core to construct the molecule in a highly convergent manner.

Since its first isolation and characterization in 1975,[1] lithospermic acid has been implicated as an active component in *Danshen*, one of the most popular traditional herbs used in the treatment of cardiovascular disorders, cerebrovascular diseases, various types of hepatitis, chronic renal failure, and dysmenorrhea (Figure 1).[2] Recent studies have shown that (+)-lithospermic acid (**1**) has potent and nontoxic anti-HIV activity.[3] Not surprisingly, the total synthesis of lithospermic acid and its derivatives has attracted significant interest.[4] Preparation of racemic heptamethyl lithospermate was first reported by the Jacobson group in 1979,[5] while the first total synthesis of (+)-lithospermic acid was accomplished by the Ellman and Bergman group,[6] which elegantly showcased their C−H activation/hydroarylation reaction en route to the chiral dihydrobenzofuran core. Herein, we report a synthesis of (+)-lithospermic acid greatly facilitated by two key C−H functionalization reactions, including an intermolecular C−H olefination of arenes, through which the dihydrobenzofuran core and the olefin unit are coupled at a late stage of the synthesis to achieve the highest convergency.

Since demethylation of heptamethyl lithospermate through a two-step deprotection sequence to give lithospermic acid had already been demonstrated,[6a] we focused our efforts on the assembly of hexamethyl lithospermate **2** (Figure 2). Inspired by a number of total syntheses using C−H olefination of indoles and pyrroles,[7] we envisioned that **2** could be prepared by an intermolecular C−H olefination of acid **4** with acrylate **3**, which would put to the test our recently developed carboxyl-directed C−H olefination reaction (Figure 2),[8] especially in the presence of other potentially more reactive electron-rich arenes and two potentially racemizable chiral stereocenters (C20 and C21). This disconnection would also enable a highly convergent approach toward the synthesis of **2**. Olefin **3** can be readily made in three steps from commercially available rosmarinic acid. We decided to construct the chiral dihydrobenzofuran **4** from diazo intermediate **6** through another C−H functionalization, an intramolecular asymmetric C−H carbene insertion using Davies's Rh(II) catalyst[9] and a chiral auxiliary developed by Fukuyama.[10]

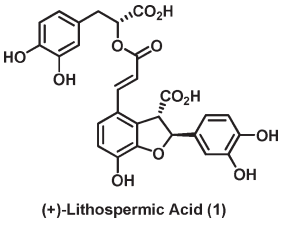

Figure 1. (+)-Lithospermic acid (**1**).

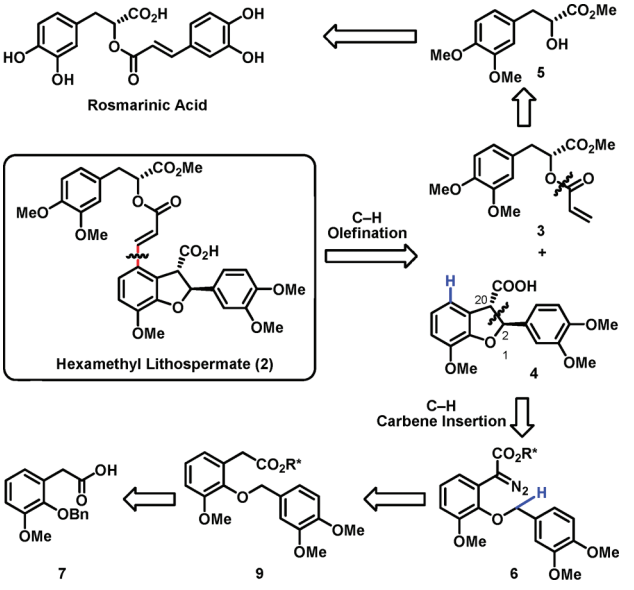

Figure 2. Retrosynthesis of (+)-lithospermic acid.

Following the above-mentioned synthetic plan, we began our experimental efforts to prepare the diazo intermediate **6**. We initially attempted to use a 3,4-dimethoxybenzyl protecting group for the phenol of phenylacetic acid **7**; unfortunately, the 3,4-methoxybenzyl protecting group proved to be incompatible with the synthetic sequence leading to this phenylacetic acid skeleton (the 3,4-methoxylbenzyl moiety was cleaved under oxidative conditions). Thus, we instead prepared **7** from readily available *o*-eugenol in three steps (see Supporting Information).

Reacting **7** with pyrrolidinyl (*S*)-lactamide under Mitsunobu conditions appended the lactamide-type chiral auxiliary **8** in 83%

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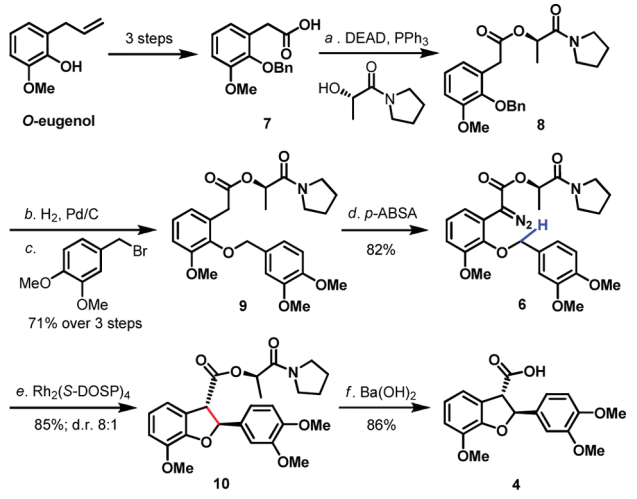
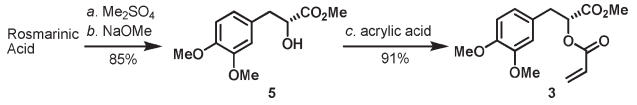
Scheme 1. Synthesis of Dihydrobenzofuran Carboxylic Acid 4[a]



[a] Reagents and conditions: (a) pyrrolidinyl (*S*)-lactamide (1.2 equiv), PPh_3 (1.2 equiv), DEAD (1.2 equiv), toluene, 0 to 23 °C, 2 h; (b) H_2 (balloon), Pd/C (5 mol %), MeOH, 23 °C, 12 h; (c) 3,4-dimethoxybenzyl bromide (1.45 equiv), K_2CO_3 (2 equiv), THF (2 equiv), 80 °C, overnight, 71% over three steps; (d) *p*-ABSA (2 equiv), DBU (2 equiv), MeCN, 0 to 23 °C, 24 h, 82%; (e) Rh_2(*S*-DOSP)$_4$ (0.5 mol %), CH_2Cl_2, 23 °C, 2 h, 85%, dr 8:1; (f) $Ba(OH)_2 \cdot 8H_2O$ (1.1 equiv), THF/MeOH (1:1), 0 to 23 °C, 4 h, 86%.

Scheme 2. Synthesis of Acrylate 3[a]



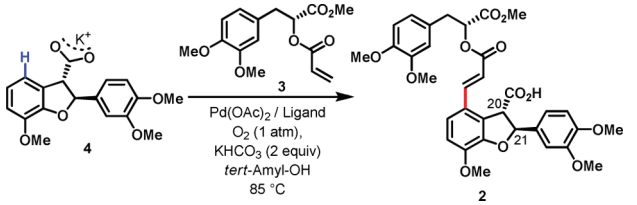
[a] Reagents and conditions: (a) Me_2SO_4 (10 equiv), K_2CO_3 (10 equiv), acetone, reflux, 10 h, 97%; (b) NaOMe (1 equiv), MeOH, 23 °C, 2 h, 88%; (c) acrylic acid (1.5 equiv), EDC-HCl (2 equiv), DMAP (2 equiv), CH_2Cl_2, 0 to 23 °C, 91%.

yield (Scheme 1).[11] Removal of the benzyl group gave the corresponding phenol in quantitative yield, which was then protected with 3,4-dimethoxybenzyl bromide in the presence of K_2CO_3 to provide the cyclization precursor **9** in 86% yield. Treatment of **9** with diazo transfer reagent in the presence of DBU at room temperature afforded diazo compound **6** in 82% yield,[9d] which was isolated and immediately treated with 0.5 mol % of Davies's catalyst, Rh_2(*S*-DOSP)$_4$. Gratifyingly, the C−H insertion reaction proceeded smoothly at room temperature and provided the *trans*-dihydrobenzofuran core **10** in good yield and diastereoselectivity (85%, 8:1 dr). Both CH_2Cl_2 and hexanes were found to be effective solvents for the cyclization reaction. Basic hydrolysis conditions afforded the carboxylic acid **4** in 86% yield.

Next, we prepared the acrylate coupling partner **3** (Scheme 2). Alcohol **5** was synthesized by pentamethylation of rosmarinic acid and subsequent hydrolysis.[6a] By treating alcohol **5** with acrylic acid in the presence of EDC and DMAP at room temperature, acrylate **3** was obtained in 91% yield. Compound **3** is stable when stored at 0 °C.

With carboxylic acid **4** and acrylate **3** in hand, we were ready to test the key C−H olefination step. While this strategy promised

Table 1. Synthesis of Hexamethyl Lithospermate 2



entry	$Pd(OAc)_2$ (mol %)	time (h)	ligand	yield (%)
1	5	12	5 mol % BQ	31
2	5	24	5 mol % BQ	50
3	5	2	10 mol % Ac-Ile-OH	93
4	2	10	4 mol % Ac-Ile-OH	91

to assemble the lithospermic acid backbone at a late stage in a highly convergent manner, several potential complications could jeopardize such an approach. First, the presence of multiple electron-rich and hence reactive arenes could cause nonselective C−H olefination reactions. Second, the two chiral centers adjacent to the esters (C20 and C21) could be prone to racemization under the reaction conditions. Third, intermolecular C−H olefination of two relatively large fragments involves considerable entropy costs compared to previous intramolecular C−H olefinations used in synthesis.[7] Finally, the carboxyl directing group is pointing away from the target C−H bonds with an approximate dihedral angle of 50° (estimated using ChemBio 3D). Nonetheless, despite these disadvantages, we hoped that combination of the directing power of the carbonyl group of carboxyl potassium salt and ligand acceleration[8] could deliver this late-stage C−H olefination process.

Consistent with our hypothesis, olefination of **4** with **3**, when carried out in the presence of 5 mol % of $Pd(OAc)_2$, 5 mol % of Ac-Ile-OH, and 2 equiv of $KHCO_3$ in a solution of *tert*-amyl alcohol at 85 °C for 2 h under 1 atm O_2, afforded the desired product **2** in 93% isolated yield (Table 1, entry 3). Catalyst loading can be lowered to 2 mol % with prolonged reaction time (entry 4). In the absence of Ac-Ile-OH ligand, olefination of **4** under the optimized conditions also proceeded, albeit giving significantly lower yields (entries 1, 2). This late-stage coupling of two structurally complex substrates represents the most sophisticated application of arene C−H olefination to date and demonstrates the broad applicability of this transformation to natural product synthesis. Mechanistically, these results further showcase the directing power of weak coordination of Pd(II) with the carbonyl group of the carboxyl potassium salt formed in situ.

To confirm the structure of **2**, we converted **2** into two previously characterized derivatives, dimethyl ester **11** and diacid **12** (Scheme 3). Treatment of monomethyl ester **2** with diazomethane gave dimethyl ester **11** in 96% yield. Treatment of **2** or **11** under Nicolaou's hydrolysis conditions afforded diacid **12** in 91% yield.[12] ^1H and ^{13}C NMR spectra of **11** and **12** were in good agreement with those reported by Ellman and Bergman (see Supporting Information).[6a]

These results encouraged us to perform the two-step demethylation procedure that would complete the synthesis of the natural product. Conversion of monoacid **2** to diacid **12** under

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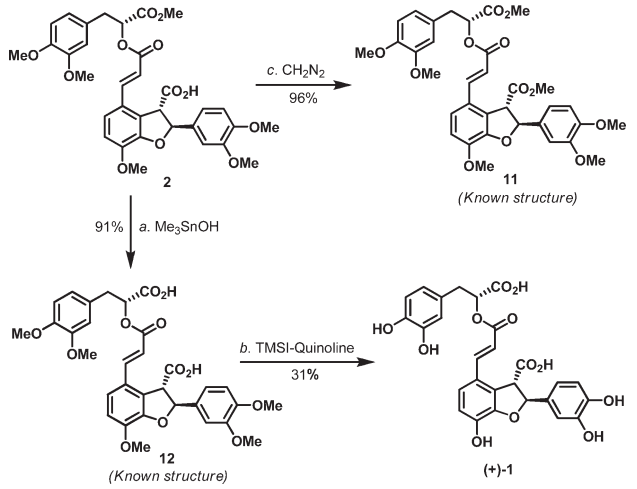
Scheme 3. Completion of the Synthesis of (+)-Lithospermic Acid[a]



[a] Reagents and conditions: (a) Me_3SnOH (3 equiv), 1,2-dichloroethane, 80 °C, 24 h, 91%; (b) 1-trimethylsilylquinolinium iodide (40 equiv), neat, 130 °C, 3 h, 31%; (c) CH_2N_2, Et_2O, 0 °C, 10 min, 96%.

Nicolaou's conditions[12] and subsequent treatment of diacid **12** with TMSI−quinoline[6a] gave the natural product (+)-lithospermic acid (**1**) in 31% yield (Scheme 3).

In summary, total synthesis of (+)-lithospermic acid was accomplished in 12 steps and 11% overall yield from *o*-eugenol. The highly convergent strategy employed was made possible by two C−H functionalization reactions, including a late-stage Pd-catalyzed intermolecular C−H olefination reaction accelerated by the amino acid ligand Ac-Ile-OH, the most sophisticated application to date of arene C−H olefination to the synthesis of complex natural products.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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