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Enantioselective Total Synthesis of (+)-Lithospermic Acid

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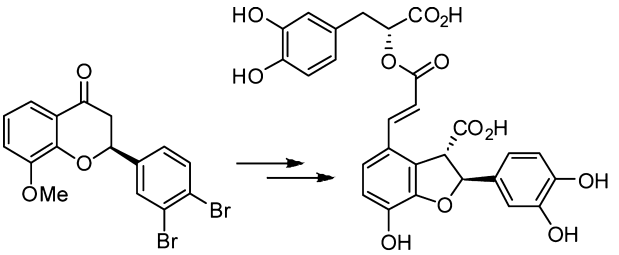
ABSTRACT



(+)-lithospermic acid (1)

An enantioselective synthesis of (+)-lithospermic acid, a potent anti-HIV agent, has been accomplished in a convergent manner in nine steps. The synthesis features an enantioselective intramolecular oxa-Michael addition catalyzed by a quinidine derivative, a hypervalent iodine-mediated rearrangement of chromanone to dihydrobenzofuran, an enantioselective α-oxyamination, and an intermolecular C−H olefination.

Lithospermic acid (**1**) was first isolated from the root of *Lithospermum ruderale* in 1963 by Johnson and co-workers (Figure 1).[1] It was fully characterized as a trimer of caffeic acid A in 1975 by Carmack et al. and Wagner et al. independently.[2,3] Lithospermic acid is an active ingredient of the Chinese herb *Danshen* and shows important biological properties. It exhibited inhibitory activity on proliferation and migration of rat vascular smooth muscle cells.[4] More recently, lithospermic acid showed anti-HIV activity by inhibiting HIV-1 integrase with an IC_{50} value of 1.4 μM.[5] Rosmarinic acid (**2**), the dimer of caffeic acid (**3**), has shown an IC_{50} value of 5 μM against HIV-1 integrase.[5] In view of its important biological properties, there has been much interest in lithospermic acid. The first racemic synthesis of heptamethyl lithospermate was reported by Jacobson and Raths in 1979.[6] The first enantioselective synthesis of (+)-lithospermic acid was achieved by Bergman, Ellman and co-workers using an asymmetric intramolecular alkylation via rhodium-catalyzed C−H activation.[7] In 2011, Yu and co-workers reported the synthesis of (+)-lithospermic acid using an intermolecular C−H olefination reaction as the key step.[8] Since then, two formal syntheses were reported by Coster et al.[9] and Hwu et al.[10] As part of our interest to explore anti-HIV properties of lithospermic acid, we plan to devise an effective route that is amenable to the preparation of structural variants. Herein, we report our synthesis of (+)-lithospermic acid.

Our retrosynthetic analysis of (+)-lithospermic acid (**1**) is outlined in Figure 2. Strategic disconnection of C_1-C_7 results in dihydrobenzofuran **4** and acrylate derivative **5**. We planned to utilize an intermolecular C−H olefination similar to Yu and co-workers[8] to couple compounds **4** and **5**. The functionalized dihydrobenzofuran **4** would be

(1) Johnson, G.; Sunderwirth, S. G.; Gibian, H.; Coulter, A. W.; Gassner, F. X. *Phytochemistry* **1963**, *2*, 145–150.

(2) (a) Kelley, C. J.; Harruff, R. C.; Carmack, M. *J. Org. Chem.* **1976**, *41*, 449–455. (b) Kelley, C. J.; Mahajan, J. R.; Brooks, L. C.; Neubert, L. A.; Breneman, W. R.; Carmack, M. *J. Org. Chem.* **1975**, *40*, 1804–1815.

(3) Wagner, H.; Whittmann, D.; Schafer, W. *Tetrahedron Lett.* **1975**, *8*, 547–550.

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(5) (a) Abd-Elazem, I. S.; Chen, H. S.; Bates, R. B.; Huang, R. C. C. *Antiviral Res.* **2002**, *55*, 91–106. (b) Tewtrakul, S.; Miyashiro, H.; Nakmur, N.; Hattori, M.; Kawahata, T.; Otake, T.; Yoshnaga, T.; Fujiwara, T. *Phytother. Res.* **2003**, *17*, 232–239.

(6) Jacobson, R. M.; Raths, R. A. *J. Org. Chem.* **1979**, *44*, 4013–4014.

(7) (a) O'Malley, S. J.; Tan, K. J.; Watzke, A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13496–13497. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655.

(8) Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 5767–5769.

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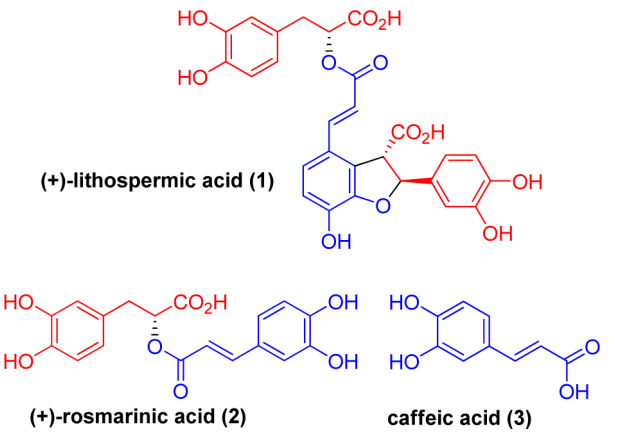

Figure 1. Structures of caffeic acid and derivatives (**1**–**3**).

constructed in an optically active form by a hypervalent iodine-promoted rearrangement of optically active chromanone derivative **6**. Such a chromanone can be prepared in enantioselective manner by using either organometallic chiral catalysts[11] or organocatalysts.[12] We planned to prepare chromanone derivative **6** in optically active form by an intramolecular oxa-Michael reaction catalyzed by a chiral quinidine derivative followed by decarboxylation. The requisite alkylidene β-keto ester **7** would be prepared via Knoevenagel condensation of β-keto ester **8** with an appropriately substituted benzaldehyde. The optically active α-hydroxy ester core in **5** would be obtained by a proline-catalyzed asymmetric α-oxyamination[13] of dihydrocinnamaldehyde **9** as the key step.

As shown in Scheme 1, synthesis of alkylidene β-keto ester **7** was accomplished by Knoevenagel condensation of β-keto ester **8** and 3,4-dibromobenzaldehyde in the presence of a catalytic amount of piperidinium acetate (5 mol %) in benzene at reflux for 6 h.[14] This provided **7** in 27% yield on gram scale. Keto ester **7** was subjected to the oxa-Michael reaction, catalyzed by chiral quinidine-derived catalyst **10** at 23 °C for 48 h.[12] The resulting product was treated with 2 equiv of *p*-TsOH and heated at 80 °C for 2 h to provide chromanone **6** in 97% yield.[15] The enantiomeric purity of **6** was shown to be 91% *ee*, and after single recrystallization it could be improved up to 99% *ee*.

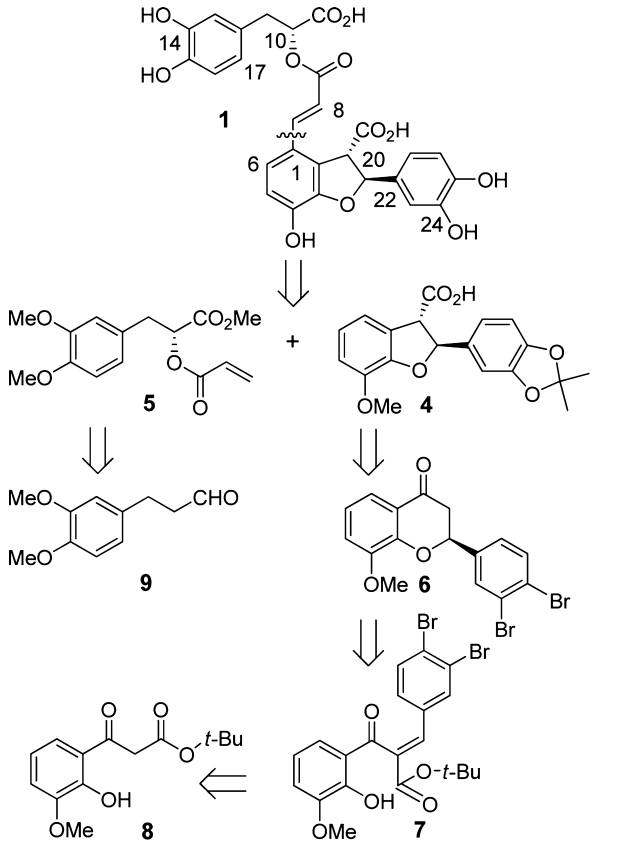

Figure 2. Retrosynthesis of (+)-lithospermic acid.

Following the synthesis of chromanone **6**, we then explored the key rearrangement of **6** to dihydrobenzofuran **11** using a reported protocol[16] employing phenyliodine diacetate (PIDA) as the oxidant in the presence of H_2SO_4 in trimethylorthoformate. These conditions did not provide any appreciable amount of desired rearranged product. However, we found that a combination of phenyliodine *bis*(trifluoroacetate) (PIFA) and anhydrous formic acid in trimethylorthoformate in the presence of concentrated H_2SO_4 resulted in the desired ring contraction product dihydrobenzofuran **11** as a single product in 61% yield. Optical purity was fully retained in the product (99% *ee*). Of particular note, the electron-withdrawing bromines are important for this rearrangement. Our attempted rearrangement of the corresponding dimethoxy derivative provided a complex mixture of products. To convert the dibromo derivative to the corresponding phenols, we planned to carry out a Miyaura borylation with pinacolborane.[17] We first examined the coupling reaction with $Pd(MeCN)Cl_2$/SPhos catalytic systems. These conditions resulted in only one C-Bpin bond

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(13) (a) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038–6039. (b) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247–4250. (c) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809. (d) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293–8296. (e) Kano, T.; Mii, H.; Maruoka, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 6638–6641.

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(15) Wang., H.-F.; Xiao, H.; Wang, X.-W.; Zhao, G. *Tetrahedron* **2011**, *67*, 5389–5394.

(16) (a) Prakash, O.; Tanwar, M. P. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1168–1171. (b) Juhasz, L.; Szilagyi, L.; Antus, S.; Visy, J.; Zsila, F.; Simonyi, M. *Tetrahedron* **2002**, *58*, 4261–4265.

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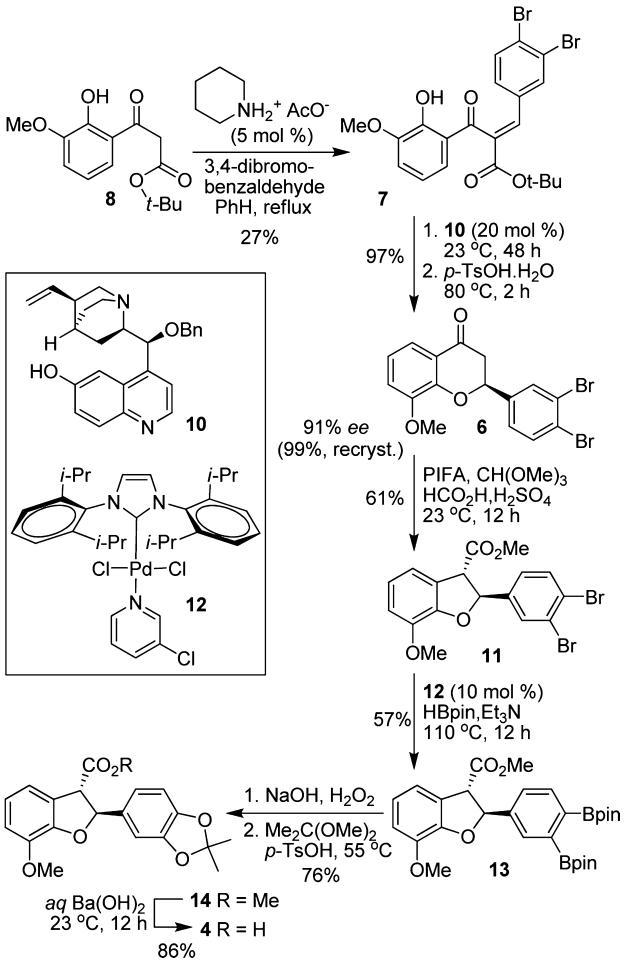
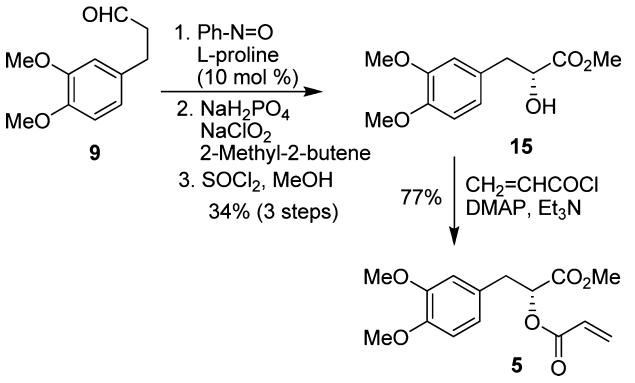
Scheme 1. Synthesis of Dihydrobenzofuran **4**



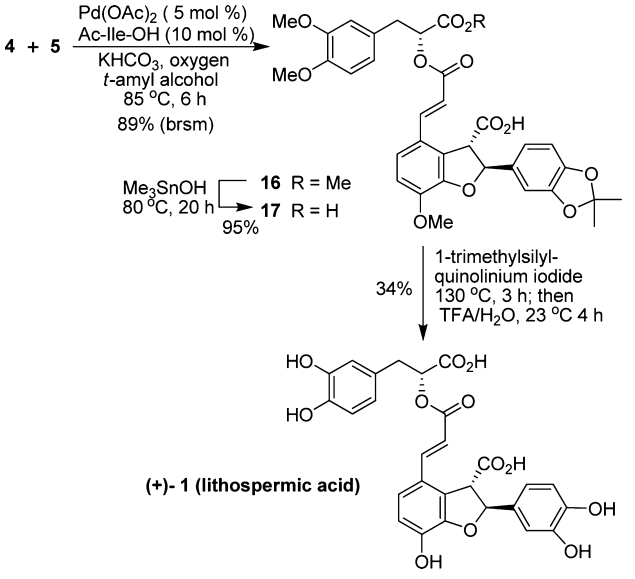
formation along with other undesired products. Subsequent optimization attempts with other phosphine ligands proved ineffective. However, the use of a palladium *N*-heterocyclic carbene (NHC) catalytic system, PEPPSI (**12**),[18] provided the desired coupling product bis-borane **13** in 57% yield. Treatment of **13** with aqueous NaOH and H_2O_2, followed by protection of the resulting diol with dimethoxypropane in the presence of a catalytic amount of *p*-TsOH, afforded isopropylidene derivative **14** in 76% yield for the two steps. Subsequent saponification of methyl ester **14** with aqueous barium hydroxide at 23 °C furnished carboxylic acid **4** for the intermolecular C−H olefination reaction.

Previous syntheses of α-hydroxyesters for lithospermic acid involved the hydrolysis of rosmarinic acid, limiting substrate scope. We planned to use the proline catalyzed α-oxyamination of an aldehyde to introduce the hydroxyl group, which would expand the diversity of the substrate scope. Optically active synthesis of acrylate derivative **5** is shown in Scheme 2 using aldehyde **9** as starting material. This was subjected to an α-oxyamination protocol developed by MacMillan and co-workers.[13c] The resulting α-oxyamino aldehyde was exposed to the Pinnick oxidation conditions to give rise to α-substituted acid. Treatment of the resulting acid with $SOCl_2$ in methanol furnished methyl ester **15**. Methyl ester **15** was obtained in 98% *ee* and 34% yield in a three-step sequence without any purification of intermediates. Reaction of ester **15** with acryloyl chloride and Et_3N in the presence of a catalytic amount of DMAP provided **5**, the other partner for the intermolecular C−H olefination reaction.

Scheme 2. Synthesis of Acrylate **5**



Scheme 3. Synthesis of Lithospermic Acid



The coupling of dihydrobenzofuran **4** and acrylate **5** involved an intermolecular C−H olefination reaction similar to that utilized by Wang and Yu in their synthesis.[8] As shown in Scheme 3, using the reported Ac-Ile-OH/$Pd(OAc)_2$ combination, coupling product **16** was obtained as the only product in 89% yield (brsm). Hydrolysis of **16** with the trimethyltin hydroxide reagent as described by

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Nicolaou and co-workers[19] afforded diacid **17** in 95% yield. Treatment of diacid **17** with TMSI-quinoline[7a] and subsequent exposure to aqueous trifluoroacetic acid (TFA) provided synthetic (+)-**1** in 34% yield. The spectroscopic data of our synthetic (+)-lithospermic acid {$[\alpha]_D^{23} = +75$ (*c* 0.2, MeOH)} are in complete agreement with those of the natural product.[1,2]

In summary, we have accomplished an enantioselective synthesis of (+)-lithospermic acid. The synthesis features a number of interesting transformations. The chromanone derivative **6** was prepared by an organocatalytic reaction using a quinidine derivative with high enantioselectivity and isolated yield. Hypervalent iodine-promoted rearrangement of chromanone **6** proceeded to provide dihydrobenzofuran **11** with retention of configuration. The synthesis also features a functional group transformation of dibromobenzene to a *bis* pinacol borane derivative by a Pd-catalyzed reaction with a PEPPSI ligand. Furthermore, we have utilized an efficient asymmetric α-oxyamination of an aldehyde to prepare α-hydroxy ester required for **1**, offering variations of substrate scope for analogs. The current synthesis is amenable to a variety of structural analogs of lithospermic acid for optimization of HIV-integrase activity. Further research is in progress in our laboratory.

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Supporting Information Available. Experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.