ORGANIC LETTERS

2012
Vol. 14, No. 19
5046–5049

Enantioselective Total Synthesis of (+)-Lithospermic Acid

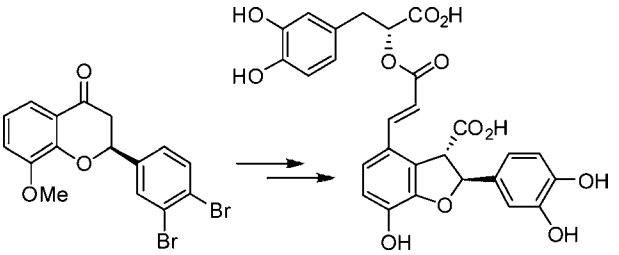
Arun K. Ghosh,* Xu Cheng, and Bing Zhou

Department of Chemistry and Department of Medicinal Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907, United States

akghosh@purdue.edu

Received August 15, 2012

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.

(4) Chen, L.; Wang, W.-Y.; Wang, Y.-P. *Acta Pharm. Sinica* **2009**, *30*, 1245–1252.

(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.

(9) Fischer, J.; Savage, G. P.; Coster, M. J. *Org. Lett.* **2011**, *13*, 3376–3379.

(10) Varadaraju, R. G.; Hwu, J. R. *Org. Biomol. Chem.* **2012**, *10*, 5456–5465.

10.1021/ol302273r
Published on Web 09/14/2012

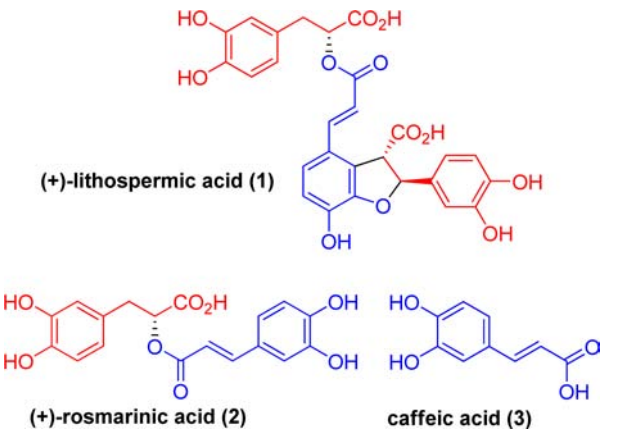


Figure 1. Structures of caffeic acid and derivatives (**1**–**3**).

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*.

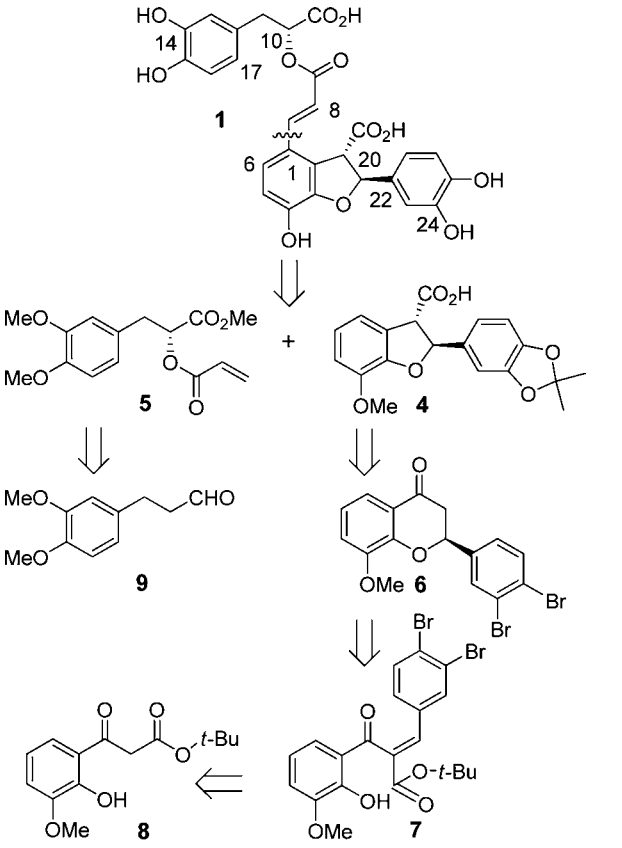


Figure 2. Retrosynthesis of (+)-lithospermic acid.

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

(11) (a) Korenaga, T.; Hayashi, K.; Akaki, Y.; Maenishi, R.; Sakai, T. *Org. Lett.* **2011**, *13*, 2022–2025. (b) Han, F.; Chen, G.; Zhang, X.; Liao, J. *Eur. J. Org. Chem.* **2011**, 2928–2931.

(12) (a) Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3830–3831. (b) Wang, H.-F.; Cui, H.-F.; Chai, Z.; Li., P.; Zheng, C.-W.; Yang, Y.-Q.; Zhao, G. *Chem.—Eur. J.* **2009**, *15*, 13299–13303.

(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.

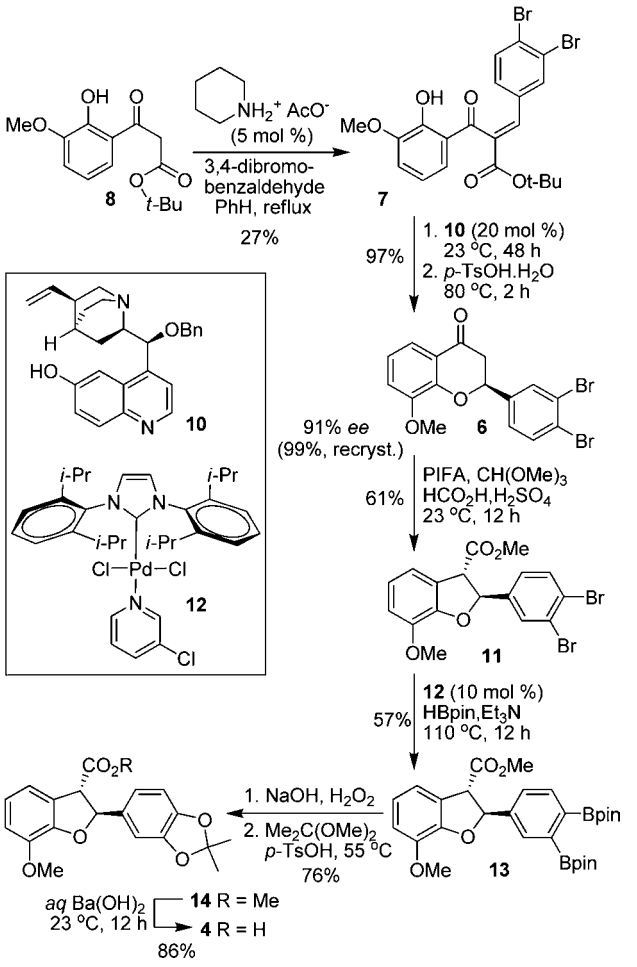
(14) Wang, H.; Luo, J.; Han, X.; Lu, Y. *Adv. Synth. Catal.* **2011**, *353*, 2971–2975.

(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.

(17) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510. (b) Billingsley, K. L.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 5589–5591.

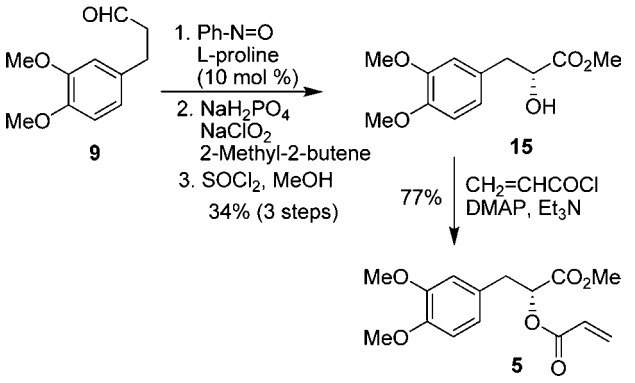
Scheme 1. Synthesis of Dihydrobenzofuran **4**



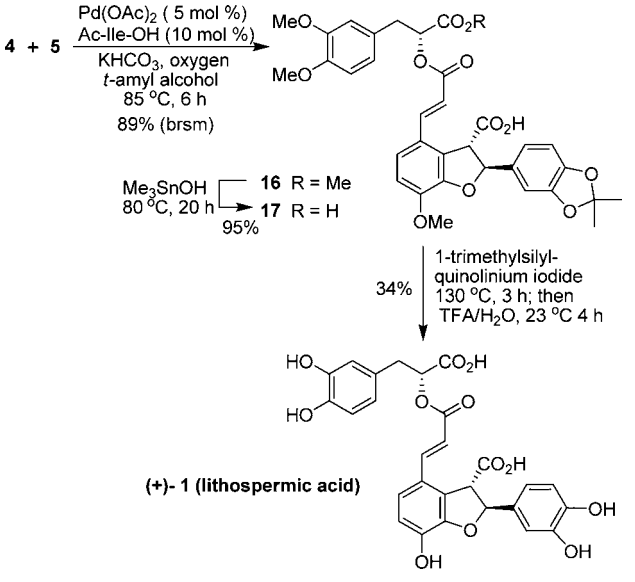
formation along with other undesired products. Subsequent optimization attempts with other phosphine ligands proved ineffective. However, the use of a palladium *N*-heterocyclic carbene (NHC) catalytic system, PEPPSI (**12**),[18] provided the desired coupling product bis-borane **13** in 57% yield. 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

(18) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; O'Brien, C. J.; Valente, C. *Chem.—Eur. J.* **2007**, *13*, 150–157.

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.

Acknowledgment. Financial support of this work was provided by the National Institutes of Health (GM53386).

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

The authors declare no competing financial interest.

(19) Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1378–1382.