Published in final edited form as:

Org Lett. 2012 October 5; 14(19): 5046–5049. doi:10.1021/ol302273r.

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, IN 47907

Arun K. Ghosh: akghosh@purdue.edu

Abstract

An enantioselective synthesis of (+)-lithospermic acid, a potent anti-HIV agent, has been accomplished in a convergent manner in 9 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 -oxamination, and an intermolecular C-H olefination.

Lithospermic acid (**1**) was first isolated from the root of *Lithospermum ruderales* in 1963 by Johnson and coworkers.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 showed 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 IC₅₀ value of 1.4 μ M.⁵ Rosmarinic acid (**2**), the dimer of caffeic acid (**3**), has shown an IC₅₀ value of 5 μ M 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 Rath 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 C₁-C₇ results in dihydrobenzofuran **4** and acrylate derivative **5**. We

Correspondence to: Arun K. Ghosh, akghosh@purdue.edu.

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

planned to utilize a intermolecular C-H olefination similar to Yu and co-workers⁸ to attach dihydrobenzofuran **4** and acrylate derivative **5**. The functionalized dihydrobenzofuran **4** would be constructed in optically active form by a hypervalent iodine-promoted rearrangement of optically active chromanone derivative **6**. Such chromanone can be prepared in enantioselective manner either by using organometallic chiral catalysts¹¹ or using organocatalysts.¹² We planned to prepare chromanone derivative **6** in optically active form by an intramolecular oxa-Michael reaction catalyzed by chiral quinidine derivative followed by decarboxylation. The requisite alkylidene β -keto ester **7** would be prepared via Knoevenagel condensation of β -keto ester **8** and appropriately substituted benzaldehyde. Optically active α -hydroxy ester core in **5** would be obtained by a proline-catalyzed asymmetric α -oxyamination¹³ of dihydrocinnamaldehyde **9** as the key step.

As shown in Scheme 1, synthesis of alkylidene β -keto ester **7** commenced 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 has 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 equivalents of *p*-TsOH and heated at 80 °C for 2 h to provide chromanone **6** in 97% yield.¹⁵ Enantiomeric purity of **6** was shown to be 91% *ee* and after single recrystallization it could be improved up to 99% *ee*. Following the synthesis of chromanone **6**, we then explored the key rearrangement of **6** to dihydrobenzofuran **11** using reported protocol¹⁶ employing phenyliodine diacetate (PIDA) as the oxidant in the presence of H₂SO₄ 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 H₂SO₄ 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 Suzuki reaction with pinacolborane. We first examined the coupling reaction with Pd(MeCN)Cl₂/SPhos catalytic systems.¹⁷ These conditions resulted in only one C-Bpin bond formation along with other products. Subsequent optimization attempts with other phosphine ligands proved ineffective. However, the use of 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 H₂O₂, 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 in **14** with aqueous barium hydroxide at 23 °C furnished carboxylic acid **4** for the intermolecular C-H olefination reaction.

Previous syntheses of α -hydroxyester for lithospermic acid involved the hydrolysis of rosmarinic acid and therefore substrate scope is limited. We planned to use the proline catalyzed α -oxyamination of aldehyde to introduce the hydroxyl group, which would expand the diversity of substrate scope. Optically active synthesis of acrylate derivative **5** is shown in Scheme 2 using aldehyde **9** as starting material. This was subjected to α -oxyamination protocol developed by MacMillan and coworkers.^{13c} The resulting α -oxyamino aldehyde was exposed to the Pinnick oxidation conditions to give rise to α -substituted acid. Treatment of resulting acid with SOCl₂ 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 Et₃N in the

presence of a catalytic amount of DMAP provided **5**, the other partner for the intermolecular C-H olefination reaction.

The coupling of dihydrobenzofuran **4** and acrylate **5** involved a similar intermolecular C-H olefination reaction utilized by Wang and Yu in their synthesis.⁸ As shown in Scheme 3, using 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 trimethyltin hydroxide reagent as described by Nicolaou and co-workers¹⁹ 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 {[α]_D²³ = +75 (*c* 0.2, MeOH)} is 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 *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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

References

1. Johnson G, Sunderwirth SG, Gibian H, Coulter AW, Gassner FX. *Phytochemistry*. 1963; 2:145–150.
2. (a) Kelley CJ, Harruff RC, Carmack M. *J Org Chem*. 1976; 41:449–455. (b) Kelley CJ, Mahajan JR, Brooks LC, Neubert LA, Breneman WR, 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 WY, Wang YP. *Acta Pharm Sinica*. 2009; 30:1245–1252.
5. (a) Abd-Elazem IS, Chen HS, Bates RB, Huang RCC. *Antiviral Res*. 2002; 55:91–106. [PubMed: 12076754] (b) Tewtrakul S, Miyashiro H, Nakmur N, Hattori M, Kawahata T, Otake T, Yoshnaga T, Fujiwara T. *Phytother Res*. 2003; 17:232–239. [PubMed: 12672152]
6. Jacobson RM, Raths RA. *J Org Chem*. 1979; 44:4013–4014.
7. (a) O'Malley SJ, Tan KJ, Watzke A, Bergman RG, Ellman JA. *J Am Chem Soc*. 2005; 127:13496–13497. [PubMed: 16190703] (b) Colby DA, Bergman RG, Ellman JA. *Chem Rev*. 2010; 110:624–655. [PubMed: 19438203]
8. Wang DH, Yu JQ. *J Am Chem Soc*. 2011; 133:5767–5769. [PubMed: 21443224]
9. Fischer J, Savage GP, Coster MJ. *Org Lett*. 2011; 13:3376–3379. [PubMed: 21648396]
10. Varadaraju RG, Hwu JR. *Org Biomol Chem*. 2012; 10:5456–5465. [PubMed: 22669348]
11. (a) Korenaga T, Hayashi K, Akaki Y, Maenishi R, Sakai T. *Org Lett*. 2011; 13:2022–2025. [PubMed: 21413690] (b) Han F, Chen G, Zhang X, Liao J. *Eur J Org Chem*. 2011:2928–2931.

12. (a) Biddle MM, Lin M, Scheidt KA. *J Am Chem Soc.* 2007; 129:3830–3831. [PubMed: 17348659]
(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. [PubMed: 19899096]
13. (a) Momiyama N, Yamamoto H. *J Am Chem Soc.* 2003; 125:6038–6039. [PubMed: 12785817] (b) Zhong G. *Angew Chem Int Ed.* 2003; 42:4247–4250. (c) Brown SP, Brochu MP, Sinz CJ, MacMillan DWC. *J Am Chem Soc.* 2003; 125:10808–10809. [PubMed: 12952459] (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 MP. *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. Billingsley KL, Buchwald SL. *J Org Chem.* 2008; 73:5589–5591. [PubMed: 18576604]
18. Organ MG, Abdel-Hadi M, Avola S, Hadei N, Nasielski J, O'Brien CJ, Valente C. *Chem Eur J.* 2007; 13:150–157. [PubMed: 17143919]
19. Nicolaou KC, Estrada AA, Zak M, Lee SH, Safina BS. *Angew Chem Int Ed.* 2005; 44:1378–1382.

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

Figure 2.
Retrosynthesis of (+)-lithospermic acid

Scheme 1.
The synthesis of dihydrobenzofuran **4**

Scheme 2.
The synthesis of acrylate **5**

Scheme 3.
Synthesis of lithospermic acid