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Asymmetric Synthesis of (*R*)-Antofine and (*R*)-Cryptopleurine via Proline-Catalyzed Sequential α-Aminoxylation and Horner−Wadsworth−Emmons Olefination of Aldehyde

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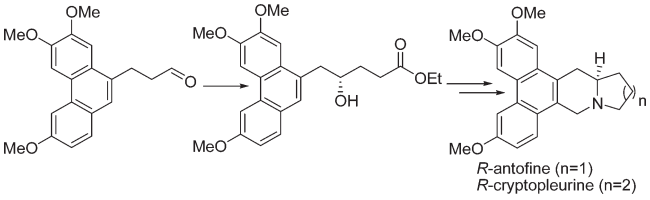
Received August 6, 2010



Naturally occurring phenanthroindolizidine alkaloids (*R*)-antofine and phenanthroquinolizidine alkaloids (*R*)-cryptopleurine have been synthesized in high optical purity via proline-catalyzed sequential α-aminoxylation and Horner−Wadsworth−Emmons olefination of aldehyde. Both enantiopure forms of proline are commercially available, and thus, in principle, both isomers of antofine and cryptopleurine can be accessed with the new method.

The phenanthroindolizidine and phenanthroquinolizidine alkaloids are structurally related groups of pentacyclic natural products primarily found in the *Asclepiadaceae* and *Moracea* plant families. To date, more than 60 structurally related phenanthroindolizidine and phenanthroquinolizidine alkaloids together with their seco derivatives and *N*-oxides have been isolated from various natural sources.[1] Among them, (*R*)-tylophorine (**1**), (*R*)-antofine (**2**), and (*R*)-cryptopleurine (**3**) are well-known representative members (Figure 1). These alkaloids possess diverse biological properties, including antitumor, antiviral, antiamoebic, antibacterial, antiinflammatory, and antifungal activities.[1] Among these interesting biological activities, the most intriguing property is the profound cytotoxic activity against various cancer cell lines.[2] In the early 1960s, tylocrebrine (**4**), a positional isomer of tylophorine (**1**), was advanced to clinical trials but failed due to central nervous system (CNS) toxicity, manifested by ataxia and disorientation.[3] This disappointing clinical result discouraged further consideration of these alkaloids for drug development. However, medicinal interest in these alkaloids was revived in the 1990s. In the National Cancer Institute's 60 tumor cell line assay, a number of these compounds showed potent and uniform activity against 54 human tumor cell lines with mean $GI_{50} < 10^{-8}$ M.[4] Moreover, their mode of action appears to be different from that of other known anticancer compounds.[5]

Because of their remarkable bioactivities coupled with extremely limited supply and interesting structures, these alkaloids have attracted much attention from the synthetic community. In the past decade, a number of impressive efforts toward the synthesis of these alkaloids have appeared in the literature.[1,2d,i,6] Because the chiral centers of these alkaloids are located α to the nitrogen atom, α-amino acids and their derivatives such as proline, glutamic acid, aminoadipate, pyroglutamate, and D-serine methyl ester hydrochloride have been widely used as the sources of the chiral center in the asymmetric synthesis of these alkaloids.[2i,6c,i,7] Apart from that, a few other strategies have been used in asymmetric synthesis of these alkaloids, including a chiral auxiliary approach,[8] a chiral allylic alcohol,[6b] enantioselective catalysis for intramolecular alkene carboamination,[6c] and enantioselective

(1) Reviews: (a) Li, Z.; Jin, Z.; Huang, R. *Synthesis* **2001**, 2365–2378. (b) Gellert, E. *J. Nat. Prod.* **1982**, *45*, 50–73. (c) Bick, I. R. C.; Sinchai, W. *The Alkaloids* **1981**, *19*, 193–220. (d) Govindachari, T. R.; Viswanathan, N. *Heterocycles* **1978**, *11*, 587–613. (d) Chemler, S. R. *Curr. Bioact. Compd.* **2009**, *5*, 2–19.

(2) (a) Strk, D.; Lykkeberg, A. K.; Christensen, J. B.; Budnik, A.; Abe, F.; Jaroszewski, J. W. *J. Nat. Prod.* **2002**, *65*, 1299–1302. (b) Luo, Y.; Liu, Y.; Luo, D.; Gao, X.; Li, B.; Zhang, G. *PlantaMed.* **2003**, *69*, 842–845. (c) Banwell, M. G.; Bezos, A.; Burns, C.; Kruszeknicki, I.; Parish, C. R.; Su, S.; Sydnes, M. O. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 181–185. (d) Chuang, T. H.; Lee, S. J.; Yang, C. W.; Wu, P. L. *Org. Biomol. Chem.* **2006**, *4*, 860–867. (e) Fu, Y.; Lee, S. K.; Min, H. Y.; Lee, T.; Lee, J.; Cheng, M.; Kim, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 97–100. (f) Yang, C. W.; Chuang, T. H.; Wu, P. L.; Huang, W. H.; Lee, S. J. *Biochem. Biophys. Res. Commun.* **2007**, *354*, 942–948. (g) Gao, W.; Busson, S.; Grill, S. P.; Gullen, E. A.; Hu, Y. C.; Huang, X.; Zhong, S.; Kaczmarek, C.; Gutierrez, J.; Francis, S.; Baker, D. C.; Yu, S.; Cheng, Y. C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4338–4342. (h) Gao, W. L.; Chen, A. P. C.; Leung, C. H.; Gullen, E. A.; Fürstner, A.; Shi, Q.; Wei, L.; Lee, K. H.; Cheng, Y. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 704–709. (i) Yang, X.; Shi, Q.; Bastow, K. F.; Lee, K. H. *Org. Lett.* **2010**, *12* (7), 1416–1419.

(3) Suffness, M.; Douros, J. In *Anticancer Agents Based on Natural Product Models*; Cassady, J. M., Douros, J. D., Eds.; Academic Press: London, 1980; Med. Chem. Vol. 16, pp 465−487.

(4) The 60 cell line NCI test data, along with in vivo data, can be accessed from the NSC numbers: http://dtp.nci.nih.gov/dtpstandard/dwindex/index.jsp.

(5) Gao, W.; Lam, W.; Zhong, S.; Kaczmarek, C.; Baker, D. C.; Cheng, Y. C. *Cancer Res.* **2004**, *64*, 678–688.

(6) For the most recent examples, see: (a) Kim, S.; Lee, J.; Lee, T.; Park, H. G.; Kim, D. *Org. Lett.* **2003**, *5*, 2703–2706. (b) Kim, S.; Lee, T.; Lee, E.; Lee, J.; Fan, G. J.; Lee, S. K.; Kim, D. *J. Org. Chem.* **2004**, *69*, 3144–3149. (c) Furstner, A.; Kennedy, J. W. *Chem. Eur. J.* **2006**, *12*, 7398–7410. (d) Kim, S.; Lee, Y. M.; Lee, J.; Lee, T.; Fu, Y.; Song, Y.; Cho, J.; Kim, D. *J. Org. Chem.* **2007**, *72*, 4886–4891. (e) Zeng, W.; Chemler, S. R. *J. Org. Chem.* **2008**, *73*, 6045–6047. (f) McIver, A.; Young, D. D.; Deiters, A. *Chem. Commun.* **2008**, *39*, 4750–4752. (g) Yamashita, S.; Kurono, N.; Senboku, H.; Tokuda, M.; Orito, K. *Eur. J. Org. Chem.* **2009**, 1173–1180. (h) Rossiter, L. M.; Slater, M. L.; Giessert, R. E.; Sakwa, S. A.; Herr, R. J. *J. Org. Chem.* **2009**, *74*, 9554–9557. (i) Stoye, A.; Opatz, T. *Org. Lett.* **2010**, *12*, 2140–2141. (j) Yang, X. M.; Shi, Q.; Bastow, K. F.; Lee, K. H *Org. Lett.* **2010**, *12*, 1416–−1419. (k) Ambrosini, L. M.; Cernak, T. A.; Lambert, T. H. *Tetrahedron* **2010**, *66*, 4882–4887.

(7) (a) Faber, L.; Wiegrebe, W. *Helv. Chim. Acta* **1976**, *59*, 2201–2212. (b) Buckley, T. F.; Rapoport, H. J. *J. Org. Chem.* **1983**, *48*, 4222–4232. (c) Nordlander, J. E.; Njoroge, F. G. *J. Org. Chem.* **1987**, *52*, 1627–1630.

Published on Web 09/16/2010 DOI: 10.1021/jo101510x

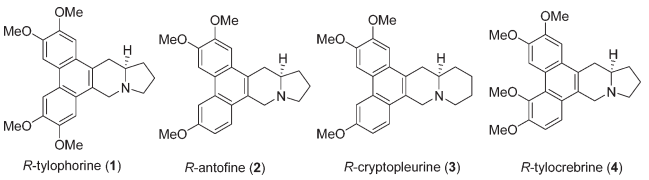
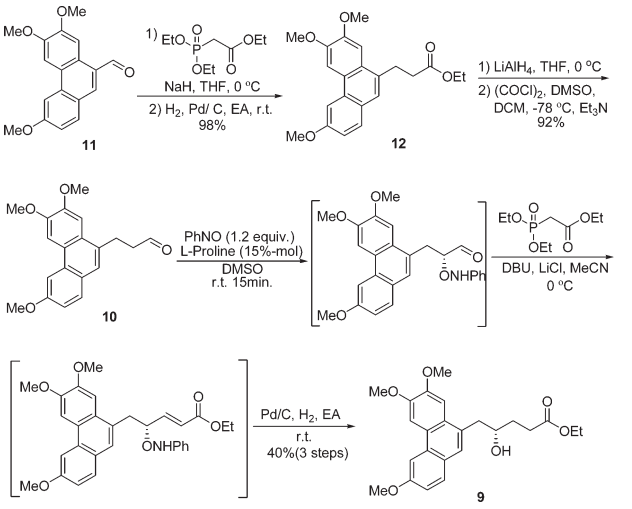


FIGURE 1. Representative structures of phenanthroindolizidine and phenanthroquinolizidine alkaloids.

phase-transfer alkylation.[6a] Although these elegant and creative synthetic approaches provided a sustainable source for bioactivity studies, a more efficient and practical synthetic methodology to these alkaloids would still be desirable. As part of our ongoing research into the synthesis and biological evaluation of phenanthroindolizidine and phenanthroquinolizidine alkaloids,[9] we have explored a novel asymmetric approach to these alkaloids. Herein, we wish to report the asymmetric synthesis of naturally occurring (*R*)-antofine (**2**) and (*R*)-cryptopleurine (**3**) using this new synthetic route.

In recent years, organocatalysis has become a rapidly growing research field in organic synthesis and has the advantage of being highly selective and reducing synthetic manipulations.[10] In this field, proline, an abundant, inexpensive amino acid available in both enantiomeric forms, has emerged as arguably the most practical and versatile organocatalyst.[11] Also, proline had already been employed in a variety of asymmetric reactions, including aldol,[12] Diels–Alder,[13] Michael addition,[14] and α-functionalization.[15] Among them, proline-catalyzed direct α-aminoxylation of

SCHEME 1. Proline-Catalyzed Sequential α-Aminoxylation and Horner–Wadsworth–Emmons Olefination of Phenanthryl Propanal 10



aldehyde with nitrosobenzene Horner–Wadsworth–Emmons olefination[16,17] created the chiral center at the position α to the oxygen atom and generated a functionalized side chain simultaneously. We envisaged that this could be transformed into the E ring of phenanthroindolizidine and phenanthroquinolizidine alkaloids after several straightforward steps. The pentacyclic skeleton of the target natural products could be constructed by employing Pictet–Spengler annulation of the 2-arylmethylpyrrolidine **5** and 2-arylmethylpiperidine **6**.[6a–d,h,8c] The cyclization precursors **5** could be obtained through several steps from azide **7**, which was derived from **9** directly. The cyclization precursors **6** could be prepared from the amino alcohol **8**.[6b] The amino alcohol **8** could be synthesized from **9** after elaborating the side chain via a Wittig–Levine reaction[18] and introducing the nitrogen atom by nucleophilic substitution. The key intermediate **9** was envisioned to arise from phenanthryl propanal **10** via sequential α-aminoxylation and Horner–Wadsworth–Emmons olefination followed by subsequent Pd/C reduction. The phenanthryl propanal **10** could be prepared from the readily available phenanthryl aldehyde **11**.[9d,19]

With these considerations in mind, our synthesis commenced with phenanthryl aldehyde **11**, which was derived from the commercially available homoveratric acid and *p*-anisaldehyde via the conventional five steps according to a previously reported procedure.[9d,19] As shown in Scheme 1, olefination of aldehyde **11** with triethyl phosphonoacetate and subsequent catalytic hydrogenation afforded ester **12** in an overall yield of 98%. Ester **12** was reduced with $LiAlH_4$ and after oxidation under Swern oxidation conditions gave the desired phenanthryl propanal **10** with 92% overall yield. Then, aldehyde **10** was subjected to α-aminoxylation with nitrosobenzene (1.2 equiv) and L-proline (15% mol) at room temperature followed by in situ Horner–Wadsworth–Emmons olefination with triethyl phosphonoacetate to furnish an aminooxy olefinic ester, which was directly subjected to hydrogenation conditions without time-consuming purification.

(8) (a) Comins, D. L.; Chen, X.; Morgan, L. A. *J. Org. Chem.* **1997**, *62*, 7435–7438. (b) Ihara, M.; Takino, Y.; Tomotake, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2287–2292. (c) Suzuki, H.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1995**, *60*, 6114–6122. (d) David, D.; Stéphane, L.; Axel, C.; Eric, D.; Pierre, G. *Eur. J. Org. Chem.* **2010**, 1943–1950.

(9) (a) An, T. Y.; Huang, R. Q.; Yang, Z.; Zhang, D. K.; Li, G. R.; Yao, Y. C.; Gao, J. *Phytochemistry* **2001**, *58*, 1267–1269. (b) Jin, Z.; Li, S. P.; Wang, Q. M.; Huang, R. Q. *Chin. Chem. Lett.* **2004**, *15* (10), 1164–1166. (c) Wang, K. L.; Lü, M. Y.; Wang, Q. M.; Huang, R. Q. *Tetrahedron* **2008**, *64*, 7504–7510. (d) Wang, K. L.; Lü, M. Y.; Yu, A.; Zhu, X. Q.; Wang, Q. M. *J. Org. Chem.* **2009**, *74*, 935–938. (e) Cui, M. B.; Wang, Q. M. *Eur. J. Org. Chem.* **2009**, 5445–5451. (f) Wang, Z. W.; Li, Z.; Wang, K. L.; Wang, Q. M. *Eur. J. Org. Chem.* **2010**, 292–299. (g) Wang, Z. W.; Wang, Q. M. *Tetrahedron Lett.* **2010**, *51*, 1377–1379. (h) Wang, K. L.; Su, B.; Wang, Z. W.; Wu, M.; Li, Z.; Hu, Y. N.; Fan, Z. J.; Mi, N.; Wang, Q. M. *J. Agric. Food Chem.* **2010**, *58* (5), 2703–2709.

(10) (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726–3748. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175. (c) Houk, K. N.; List, B. *Acc. Chem. Res.* **2004**, *37*, 487.

(11) For a review of proline-catalyzed asymmetric reactions, see: List, B. *Tetrahedron* **2002**, *58*, 5573–5590.

(12) (a) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Cordova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343–1345. (b) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396. (c) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799.

(13) (a) Sabitha, G.; Fatima, N.; Reddy, E. V.; Yadav, J. S. *Adv. Synth. Catal.* **2005**, *347*, 1353–1355. (b) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III *Synlett* **2003**, 1910–1914.

(14) Hechavarria Fonseca, M. T.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958–3960.

(15) For α-functionalization reviews see: (a) Franzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304. (b) Guillena, G.; Ramon, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492. (c) Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995–2997.

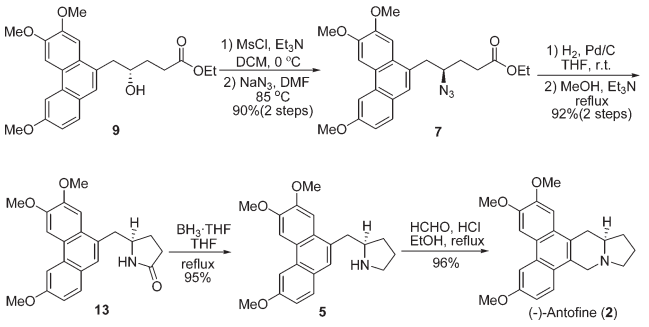
(16) (a) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247–4250. (b) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809. (c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293–8296.

(17) (a) Zhong, G.; Yu, Y. *Org. Lett.* **2004**, *6*, 1637–1639. (b) Kondekar, N. B.; Kumar, P. *Org. Lett.* **2009**, *11*, 2611–2614.

(18) Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150–6151.

(19) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661–3666.

SCHEME 2. Synthesis of (*R*)-Antofine (2)

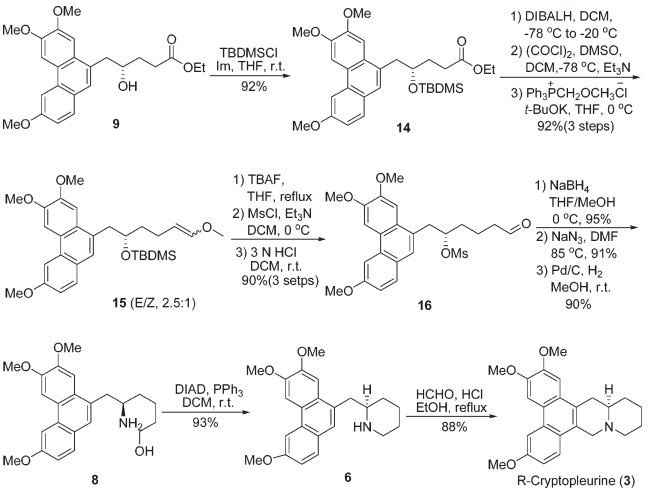


Simultaneous reduction of both the C=C bond and the anilinoxy group with 10% Pd/C, H_2 (1 atm) providied the desired γ-hydroxy ester (*S*)-**9** in reasonable overall yield (40%, from **10**) with excellent enantioselectivity (> 99% ee, determined by chiral HPLC analysis). Using D-proline as catalyst, the (*R*)-**9** was obtained similarly (36% yield, > 99% ee).

With the key intermediate **9** in hand, the asymmetric synthesis of antofine and cryptopleurine could be achieved. Naturally occurring (*R*)-antofine was first synthesized from (*S*)-**9** through six straightforward steps, as described below (Scheme 2). Activation of the hydroxy group with methanesulfonyl chloride and substitution with sodium azide produced azide **7** in 90% yield over two steps, in which the nitrogen atom was introduced and the chirality was inverse. The E ring was formed by reduction of the azide group of **7** following intramolecular cyclization to afford lactam **13** in 92% overall yield. At the beginning, reduction of lactam **13** was carried out with lithium aluminum hydride. To our disappointment, 2-arylmethylpyrrolidine **5** was obtained in poor yields (< 10%). After failing in several efforts, we changed the reduction reagent. Using a borane−tetrahydrofuran complex solution, lactam **13** was transformed smoothly to amine **5** in high yield (95%). Finally, the Pictet−Spengler cyclomethylenation of 2-(arylmethyl)pyrrolidine **5** using the reported reaction conditions[6a−d] afforded (*R*)-antofine (**2**) in 96% yield with excellent enantioselectivity (> 98% ee, determined by chiral HPLC analysis). The analytical information obtained from our synthesized (*R*)-antofine (**2**) agreed with the data reported in the literature.[2i,6a−d,9f]

Having accomplished the synthesis of (*R*)-antofine (**2**), we then turned our attention to the synthesis of naturally occurring (*R*)-cryptopleurine (**3**). Elaboration of the side chain has been carried out as shown in Scheme 3. The hydroxy group of alcohol **9** was protected with TBDMSCl/imidazole to give silyl ether **14** in 92% yield. DIBALH reduction of **14** and subsequent Swern oxidation and further Wittig olefination with methoxymethyl phosphorus ylide afforded enol ether **15** as a mixture of *E* and *Z* isomers in 92% overall yield. Deprotection, mesylation, and hydrolysis in one pot furnished aldehyde **16** in 90% overall yield. Due to the poor solubility of **16** in methanol, the reduction of this aldehyde with $NaBH_4$ was carried out in mixed solvent, which provided an alcohol (95% yield) that was converted into the known amino alcohol **8**[6b] after substitution with sodium azide and reduction with Pd/C (91 and 90% yields, respectively). It is worth noting that the amino alcohol **8** we obtained is a white solid and the optical rotation is higher than the values reported in the literature.[6b] According to the reported procedure,[6b] the amino alcohol **8** was cyclized

SCHEME 3. Synthesis of (*R*)-Cryptopleurine (3)



employing a Mitsunobu reaction to give 2-(arylmethyl)piperidine **6** in 93% yield. Finally, the Pictet−Spengler cyclomethylenation of 2-(arylmethyl)piperidine **6** using the reported reaction conditions,[6b−d,9e] afforded (*R*)-cryptopleurine (**3**) in 88% yield with excellent enantioselectivity (> 99% ee, determined by chiral HPLC analysis). The analytical information obtained from our synthesized (*R*)-cryptopleurine (**3**) agreed with the data reported in the literature.[2i,6b−d,9g]

In conclusion, asymmetric total syntheses of the representative naturally occurring phenanthroindolizidine alkaloids (*R*)-antofine and phenanthroquinolizidine alkaloids (*R*)-cryptopleurine via proline-catalyzed sequential α-aminoxylation and Horner−Wadsworth−Emmons olefination of phenanthryl propanal were accomplished in high optical purity. The advantages of this approach are as follows: (a) both enantiopure forms of the commercially available and inexpensive proline can be used as asymmetric catalysts, and thus, both isomers of antofine and cryptopleurine can be accessed; (b) easily available compounds can be used as synthetic materials, (c) mild reaction conditions and simple, environmentally friendly procedures can be employed.

Experimental Section

Ethyl 3-(2,3,6-Trimethoxyphenanthren-10-yl)propanoate (12). To a suspention of NaH (2.4 g, 60% in oil, 60 mmol) in THF (100 mL) was carefully added triethyl phosphonoacetate (13.5 g, 60 mmol) dissolved in THF (60 mL) at 0 °C, and the mixture was stirred at this temperature for 1 h. Then phenanthryl aldehyde **11** (14.8 g, 50 mmol) dissolved in THF (600 mL) was added dropwise. The resulting reaction mixture was stirred at 0 °C over 2 h and was then quenched by adding aqueous NH_4Cl. The biphasic mixture was warmed to room temperature, and then the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a green solid which was redissolved in EtOAc (600 mL) and was charged with Pd/C (1.0 g). The reaction mixture was stirred for 24 h under a balloon filled with hydrogen gas at room temperature. The mixture was filtered, and the filtrate was evaporated. The residue was purified by chromatography on silica gel (petroleum ether (60−90 °C)/EtOAc, 3:1) to give compound **12** (18.0 g, 48.9 mmol, 98%) as a white solid.

3-(2,3,6-Trimethoxyphenanthren-10-yl)propanal (10). Compound **12** (18.0 g, 48.9 mmol) was dissolved in THF (500 mL),

to which $LiAlH_4$ (2.3 g, 60 mmol) was added carefully at 0 °C. The resulting reaction mixture was stirred at 0 °C over 2 h and was then quenched by adding water, and this mixture was then filtered and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a white solid. The crude product was used in the next step without further purification.

To a stirred solution of oxalyl chloride (12.7 g, 100 mmol) in CH_2Cl_2 (300 mL) at −78 °C was added dropwise a solution of dimethyl sulfoxide (17.4 g, 200 mmol) in CH_2Cl_2 (60 mL) under an atmosphere of N_2. After being stirred at −78 °C for 30 min, a solution of the above crude product in CH_2Cl_2 (300 mL) was added dropwise. The resulting reaction mixture was stirred at −78 °C for 3 h, and then the triethylamine (30.0 g, 300 mmol) was added dropwise. Then the mixture was warmed to room temperature and stirred for an additional 30 min. The reaction was quenched with a solution of saturated aqueous potassium hydrogenphosphate. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a yellow solid which was purified by chromatography on silica gel (petroleum ether (60−90 °C)/EtOAc, 2:1) to give compound **10** (14.6 g, 45.1 mmol, 92%) as a white solid.

(*S*)-Ethyl 4-Hydroxy-5-(2,3,6-trimethoxyphenanthren-10-yl)-pentanoate (9). To a solution of phenanthryl propanal **10** (6.28 g, 20.0 mmol) and nitrosobenzene (2.56 g, 24.0 mmol) in anhydrous DMSO (250 mL) was added L-proline (0.35 g, 3.0 mmol) at 20 °C. The mixture was rigorously stirred for 15 min (the reaction mixture changed from green to yellow during this time) and then cooled to 0 °C. Thereafter, a premixed and cooled (0 °C) solution of triethyl phosphonoacetate (13.45 g, 60.0 mmol), DBU (9.12 g, 60.0 mmol), and LiCl (2.52 g, 60.0 mmol) in CH_3CN (100 mL) was added quickly (1−2 min) at 0 °C. The resulting mixture was warmed to room temperature over 2 h and quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum. This reaction mixture was poured into water (500 mL) and extracted with CH_2Cl_2 (5 × 100 mL). The combined organic layers were washed several times with water and brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo to give a crude product, which was directly subjected to the next step without purification. To the above crude product in ethyl acetate was added Pd/C (0.8 g, 10%) under hydrogenation conditions, and the reaction mixture was stirred for 48 h. On completion of the reaction, the mixture was filtered through a pad of Celite and concentrated in vacuo to give the crude product **9**, which was purified by chromatography on silica gel (petroleum ether (60−90 °C)/EtOAc, 3:2) to give (*S*)-**9** (3.30 g, 40% yield) as a white solid. Chiral HPLC analysis (Chiral AD-H, *n*-heptane/isopropyl alcohol 70:30, 1.0 mL min^{-1}, 12.38 min (*S* isomer), 17.16 min (*R* isomer)) showed that the product **9** had an enantiomeric excess of >99%.

(*R*)-Ethyl 4-Azido-5-(2,3,6-trimethoxyphenanthren-10-yl)-pentanoate (7). To a cooled solution (0 °C) of **9** (1.65 g, 4.0 mmol) and triethylamine (0.81 g, 8.0 mmol) in CH_2Cl_2 (60 mL) was added MsCl (0.92 g, 8.0 mmol) under an atmosphere of N_2. The mixture was stirred at 0 °C for 2 h and then quenched with water. The aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (petroleum ether (60−90 °C)/EtOAc, 2:1) to give a colorless solid which was redissolved in dimethylformamide (8 mL); to this solution was added NaN_3 (0.52 g, 8.0 mmol) at room temperature, and the mixture was warmed to 85 °C and stirred for 8 h. The mixture was cooled to room temperature, and water was added. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (petroleum ether (60−90 °C)/EtOAc, 3:1) to give compound **7** (1.57 g, 3.6 mmol, 90%) as a white solid.

(*R*)-5-((2,3,6-Trimethoxyphenanthren-10-yl)methyl)pyrrolidin-2-one (13). A solution of **7** (1.31 g, 3.0 mmol) in THF (60 mL) was charged with Pd/C (0.2 g). The reaction mixture was stirred for 36 h under a balloon filled with hydrogen gas at room temperature. The mixture was filtered, and the filtrate was evaporated. The residue was redissolved in methanol (60 mL), and to this solution was added triethylamine (0.61 g, 6.0 mmol). The resulting reaction mixture was refluxed for 8 h. After it was cooled to room temperature, the reaction mixture was concentrated in vacuo to give a gray solid which was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 30:1) to provide compound **13** (1.00 g, 2.7 mmol, 92%) as a white solid.

(*R*)-2-((2,3,6-trimethoxyphenanthren-10-yl)methyl)pyrrolidine (5). $BH_3 \cdot THF$ (1 M in THF, 10.0 mL, 10.0 mmol) was slowly added to a solution of **13** (0.73 g, 2.0 mmol) in THF (50 mL). After it was refluxed for 12 h, the reaction mixture was cooled to room temperature and quenched with aqueous HCl (3 mol/L, 20 mL). The resulting mixture was refluxed for an additional 3 h and then cooled to room temperature and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 10:1, 1% NH_4OH) to give compound **5** (0.66 g, 1.9 mmol, 95%) as a white solid.

Acknowledgment. We thank the National Key Project for Basic Research (No. 2010CB126100) and the National Natural Science Foundation of China (Nos. 20872072, 30890143) for financial support.

Supporting Information Available: Text and figures giving experimental details with complete characterization data for all compounds, ^1H and ^{13}C NMR spectra for all compounds, and HPLC data of compound **9**, (*R*)-antofine, and (*R*)-cryptopleurine. This material is available free of charge via the Internet at http://pubs.acs.org.