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Asymmetric Total Syntheses of (−)-Antofine and (−)-Cryptopleurine Using (*R*)-(*E*)-4-(Tributylstannyl)but-3-en-2-ol

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The asymmetric total syntheses of the representative phenanthroindolizidine and phenanthroquinolizidine alkaloids, (−)-antofine and (−)-cryptopleurine, are described. An efficient synthetic pathway to the key intermediate **12**, in enantiomerically pure form, was achieved by using a chiral building block (*R*)-**9** and the Overman rearrangement with a total transfer of chirality. The problem of constructing the pyrrolidine and piperidine rings was successfully addressed, primarily by using a ring-closing metathesis reaction and a cross-metathesis reaction, respectively.

Introduction

The phenanthroindolizidine and phenanthroquinolizidine alkaloids are structurally related groups of pentacyclic natural products. Since the first isolation of tylophorine (**1**, Figure 1) in 1935,[1] more than 60 alkaloids and their seco-analogues have been reported. These alkaloids are well-known for their characteristic biological properties, especially for their profound cytotoxic activity.[2] Due to their exceptional bioactivity and unusual architecture, many unique and interesting synthetic methodologies have been reported.[3]

Recently, we described the first total synthesis of (−)-antofine (**2**, Figure 1),[4] whose IC_{50} values against drug-sensitive and multidrug-resistant cancer cell lines are in the low nanomolar range.[5] The key step of our synthesis was the creation of a stereogenic center by using the enantioselective catalytic phase transfer alkylation together with a ring-closing metathesis for pyrrolidine ring construction. As part of our ongoing research into the preparation and biological evaluation of phenanthroindolizidine natural products and their analogues, we have since developed a new synthetic approach to these alkaloids. Herein, we describe a new enantioselective synthetic route to (−)-antofine (**2**) and a representative phenanthroquinolizidine, (−)-cryptopleurine (**3**).

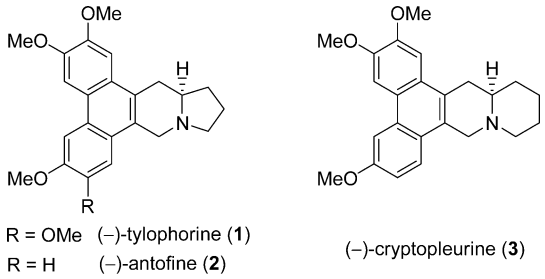

FIGURE 1. Chemical structures of compound **1**−**3**.

Results and Discussion

The retrosynthetic analysis of **2** and **3** is shown in Scheme 1. The pentacyclic skeleton of the target natural products could be constructed by employing the reported Pictet−Spengler annulation of 2-arylmethylpyrrolidine **4** and 2-arylmethylpiperidine **5**, which were previously synthesized via a different synthetic route. The cyclization precursors **4** and **5** should be accessible from the allylamine **6** by sequential metathesis and hydrogenation. The key intermediate **6** was in turn envisioned to arise from the chiral allylic alcohol **7**, via the Overman rearrangement of the corresponding allyl imidate. Further analysis indicated that the requisite allylic alcohol **7** could be synthesized from the readily available phenanthryl bromide **8**[4] and the chiral building block (*R*)-**9**,[6] for which we recently reported an efficient enzymatic preparation method.

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(3) For a good review with citations, see: (a) Li, Z.; Jin, Z.; Huang, R. *Synthesis* **2001**, 2365−2378. (b) Bick, I. R. C.; Sinchai, W. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. 19, pp 193−220. (c) Gellert, E. *J. Nat. Prod.* **1982**, *45*, 50−73.
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(5) (a) Stærk, D.; Lykkeberg, A. K.; Christensen, J.; Budnik, B. A.; Abe, F.; Jaroszewski, J. W. *J. Nat. Prod.* **2002**, *65*, 1299−1302. (b) Lee, S. K.; Nam, K.-A.; Heo, Y.-H. *Plant Med.* **2003**, *69*, 21−25.

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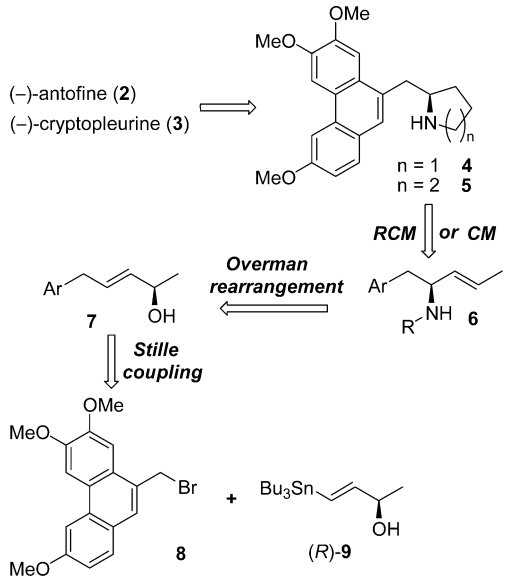
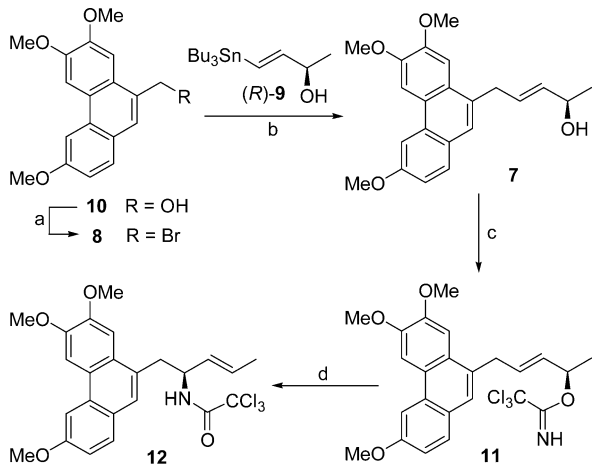
SCHEME 1. Retrosynthetic Analysis of (−)-Antofine and (−)-Cryptopleurine



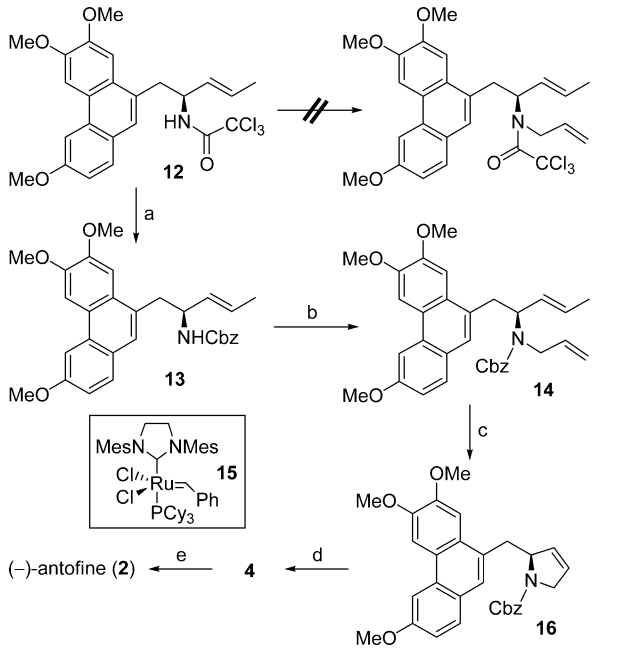
SCHEME 2[a]



[a] Reagents and conditions: (a) CBr_4, PPh_3, CH_3CN, 0 °C, 1 h, 98%; (b) (*R*)-**9**, $Pd(CH_3CN)_2Cl_2$ (5 mol %), DMF, rt, 2 h, 95%; (c) CCl_3CN, DBU, CH_2Cl_2, 0 °C, 2 h, 99%; (d) toluene, reflux, 12 h, 93%.

The starting material for our synthesis was the known phenanthryl alcohol **10**, which was obtained from the commercially available homoveratric acid and *p*-anisaldehyde via the conventional four-step sequence according to the previously reported procedure.[7] Treatment of **10** with CBr_4 and PPh_3 provided bromide **8** (Scheme 2), which appeared to be sensitive to silica gel chromatography. It was very important to minimize the residency time of this compound on the chromatography column to obtain a high isolation yield (>98%).[4] With multigram quantities of **8** in hand, we then investigated the Stille coupling of phenanthryl bromide **8** with (*R*)-(*E*)-4-(tributylstannyl)but-3-en-2-ol ((*R*)-**9**, >99% ee) in the presence of palladium as a catalyst.[8] Different palladium sources and solvents were examined for this coupling reaction.

SCHEME 3[a]



[a] Reagents and conditions: (a) (i) 5 N NaOH, $EtOH/CH_2Cl_2$, 50 °C, 1 day; (ii) Cbz-Cl, THF, rt, 1 h, 87%. (b) Allyl bromide, NaH, THF/HMPA, rt, 3 h, 100%. (c) **15** (5 mol %), CH_2Cl_2, rt, 2 h, 98%. (d) H_2, 10% Pd/C, MeOH, rt, 2 h, 63%. (e) HCHO, HCl, EtOH, reflux, 3 days, 80%, in the dark.

Of these, the $Pd(CH_3CN)_2Cl_2$/DMF system was found to be superior to other combinations. With this system, reaction occurred at room temperature to give the desired (*E*)-allylic alcohol **7** in 95% yield. Alcohol **7** was then treated with trichloroacetonitrile and DBU to afford trichloroacetimidate **11** in 99% yield. Since **11** is not stable for storage, it was used directly after silica gel chromatography. Thermal Overman rearrangement[9] of **11** in boiling toluene provided the (*E*)-allylic trichloroacetamide **12** as the only identifiable product in 99% ee and 93% yield. Chirality was conserved during the reaction, and as a result, the stereochemistry originating from the chiral building block (*R*)-**9** was transferred to the allylic amine **12**.

Initially, we explored the direct N-allylation of trichloroacetamide **12** (Scheme 3). Our attempts at accomplishing the N-allylation of **12**, using various methods,[10] such as the allyl halide/base and π-allylpalladium complex, were not successful and provided only the recovered starting material, presumably, at least in part, due to the electron-deficient nature of the trichloroacetamide nitrogen. Thus, we decided to change the trichloroacetyl group of **12** to the benzyloxycarbonyl group. Hydrolysis of the trichloroacetamide **12** was performed in the presence of excess 5 N NaOH in $EtOH/CH_2Cl_2$. In the same reaction flask, the resulting free amine was con-

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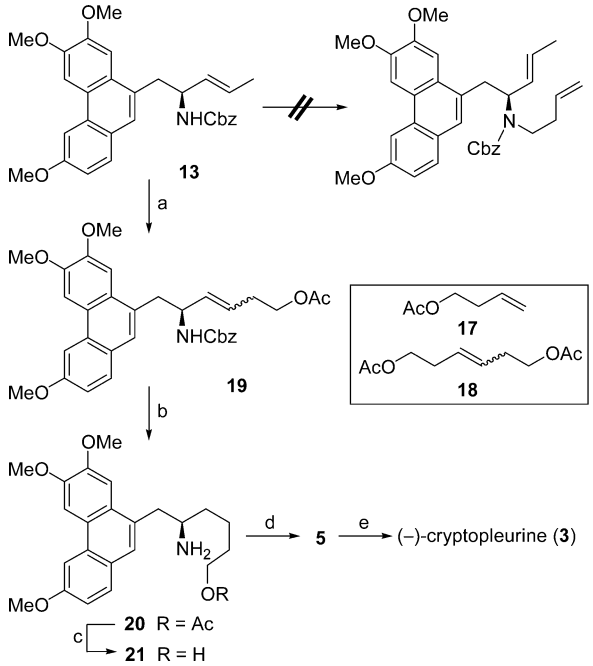
(7) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661−3666.
(8) For the Pd-catalyzed couplings of vinylstannane and benzyl bromide, see: Crisp, G. T.; Glink, P. T. *Tetrahedron* **1994**, *50*, 3213−3234.
(9) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901−2910.
(10) Several conditions: (1) allyl bromide, NaH, DMF; (2) allyl bromide, KHMDS, THF; (3) allyl bromide, K_2CO_3, TBAI, acetone, reflux; (4) allyl alcohol, DEAD, PPh_3, THF; (5) allyl acetate, $Pd(PPh_3)_4$, K_2CO_3, THF, 60 °C; (6) allyl methyl carbonate, $[Allyl-PdCl]_2$, PPh_3, THF, 60 °C.

verted directly to the Cbz derivative **13** in 87% yield. The subsequent N-allylation of the Cbz-protected amine **13** with allyl bromide and NaH in THF/HMPA successfully provided the desired bis-allylamine **14** in nearly quantitative yield.

The remaining main steps to (−)-antofine required the construction of the pyrrolidine ring with a bis-allylamine moiety and the Pictet−Spengler annulation of the 2-arylmethylpyrrolidine (Scheme 3). These steps were accomplished by employing reaction conditions analogous to those of our previous synthesis.[4] The ring-closing metathesis[11] of **14** was successfully performed with a commercially available second-generation Grubbs' catalyst **15** in CH_2Cl_2 at room temperature, to produce the desired 2,5-dihydropyrrole derivative **16** in 98% yield. Subsequent catalytic hydrogenation effected simultaneous reduction of the alkene and deprotection of the benzyloxycarbonyl protecting group to give the previously known pyrrolidine **4**[4,12] in 63% yield. Finally, the Pictet−Spengler cyclomethylenation of 2-arylmethylpyrrolidine **4**, using the previously reported reaction conditions[4,11−13] (formaldehyde, HCl, EtOH, reflux), generated the central piperidine ring to afford (−)-antofine (**2**) in 80% yield. The spectroscopic data (^1H and ^{13}C NMR) obtained for the synthetic material were in agreement with those reported for the naturally occurring compound. The optical rotation measured for the synthetic **2** {$[\alpha]^{19}_D$ −125.2 (*c* 1.27, $CHCl_3$)} is within the range of values reported for the natural antofine.[14]

With the key intermediate **13** in hand, we next turned our attention to the preparation of (−)-cryptopleurine (**3**). At first, we explored the direct N-homoallylation of **13** with 4-bromo-1-butene under several different conditions (Scheme 4). However, these attempts were all unsuccessful.[15] In view of the failure of the direct N-homoallylation approach, we next turned our attention to cross-metathesis[16] for piperidine ring construction. To our delight, the cross-metathesis coupling of the internal olefin **13** with the terminal olefin, homoallyl acetate **17** (4 equiv), catalyzed by the second-generation Grubbs' catalyst **15** (5 mol %) in refluxing CH_2Cl_2 for 1 day, successfully gave the desired heterodimers **19** as an inseparable *E*/*Z* mixture (38%, 4:1 *E*/*Z*) along with the recovered starting material (54%).[17] Moreover, when the known homoallyl acetate homodimer **18**[18] was employed as a coupling

SCHEME 4[a]



[a] Reagents and conditions: (a) **17** or **18**, **15** (5 mol %), CH_2Cl_2, reflux, 1 day, 38% with **17** or 82% with **18**; (b) H_2, 10% Pd/C, MeOH, rt, 4 h, 95%; (c) 5 N NaOH, MeOH, rt, 1 day, 90%; (d) DIAD, PPh_3, CH_2Cl_2, rt, 15 h, 68%; (e) HCHO, HCl, EtOH, reflux, 2 days, 67%, in the dark.

partner in the same reaction conditions, the cross-metathesis proceeded more efficiently, to give mainly **19** in 82% yield with an *E*/*Z* ratio of 8:1 (96% yield based on the recovered starting material) along with a small amount of recovered starting material (14%).[19] We believe that this successful homologation of the internal olefin will broaden the utility of this cross-metathesis in natural product synthesis.

Hydrogenation of an *E*/*Z* mixture of **19** resulted in the reduction of the double bond and simultaneous deprotection of the Cbz group to give **20** (95% yield), which was saponified in a methanolic aqueous NaOH solution to afford amino alcohol **21** (90% yield). The obtained amino alcohol **21** was then subjected to Mitsunobu reaction conditions[20] employing PPh_3 and DIAD in CH_2Cl_2 at room temperature. This effected the necessary ring closure and provided the previously known piperidine **5**[12] in 68% yield. The final step toward (−)-cryptopleurine (**3**), through the Pictet−Spengler annulation of 2-arylmethylpiperidine **5**, was carried out as described above. Treatment of **5** with formaldehyde in boiling acidic ethanol afforded (−)-cryptopleurine (**3**) (67% yield), whose $[\alpha]_D$ value {$[\alpha]^{21}_D$ −108.7 (*c* 1.03, $CHCl_3$)} and ^1H and ^{13}C NMR spectra were in agreement with those reported in the literature.[21]

In conclusion, asymmetric total syntheses of the representative naturally occurring phenanthroindolizidine

(11) For a good review about the application of the ring-closing metathesis reaction to the synthesis of piperidine and pyrrolidine, see: Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693−3712.

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(14) Optical rotation values of natural antofine range from −32 to −165°. See: (a) Cavé, A.; Leboeuf, M.; Moskowitz, H.; Ranaivo, A.; Bick, I. R. C.; Sinchai, W.; Nieto, M.; Sevenet, T.; Cabalion, P. *Aust. J. Chem.* **1989**, *42*, 2243−2263. (b) Baumgartner, B.; Erdelmeier, C. A. J.; Wright, A. D.; Rali, T.; Sticher, O. *Phytochemistry* **1990**, *29*, 3327−3330. (c) Li, X.; Peng, J.; Onda, M. *Heterocycles* **1989**, *29*, 1797−1808. (d) Herbert, R. B.; Moody, C. J. *Phytochemistry* **1972**, *11*, 1184−1184. (e) Capo, M.; Saa, J. M. *J. Nat. Prod.* **1989**, *52*, 389−390. (f) Wiegrebe, W.; Faber, L.; Brockmann, H., Jr.; Budzikiewicz, H.; Krueger, U. *Liebigs Ann. Chem.* **1969**, *721*, 154−162. See also refs 3−5 and 12.

(15) (a) Takahata, H.; Banba, Y.; Ouchi, H.; Nemoto, H.; Kato, A.; Adachi, I. *J. Org. Chem.* **2003**, *68*, 3603−3607. (b) Gille, S.; Ferry, A.; Billard, T.; Langlois, B. R. *J. Org. Chem.* **2003**, *68*, 8932−8935.

(16) For a recent review about olefin cross-metathesis, see: Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923.

(17) Employment of the first-generation Grubbs' catalyst in the same reaction conditions did not provide the desired heterodimers **19**.

(18) Maishal, T. K.; Sinha-Mahapatra, D. K.; Paranjape, K.; Sarkar, A. *Tetrahedron Lett.* **2002**, *43*, 2263−2267.

(19) For a precedent about selective cross-metathesis of internal olefins with homodimer, see: Morgan, J. P.; Morrill, C.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 67−70.

(20) (a) Mitsunobu, O. *Synthesis* **1981**, 1−28. (b) Balasubramanian, T.; Hassner, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2201−2205.

and phenanthroquinolizidine alkaloids, (−)-antofine and (−)-cryptopleurine, were accomplished. We developed an efficient synthetic pathway to the important intermediate **12** in enantiomerically pure form by using a chiral building block (*R*)-**9** and the Overman rearrangement with a total transfer of chirality. Construction of the pyrrolidine and piperidine rings was successfully accomplished in our approach, primarily due to the use of a metathesis reaction. We believe that the protocol outlined above is efficient enough to apply to the synthesis of other members of this important class of natural products, as well as to other modified analogues.

Experimental Section

(*R*)-5-(3,6,7-Trimethoxyphenanthren-9-yl)pent-3-en-2-ol (7). To a solution of (*R*)-(*E*)-4-(tributylstannyl)but-3-en-2-ol ((*R*)-**9**) (799 mg, 2.21 mmol) and phenanthryl bromide **8**[4] (667 mg, 1.85 mmol) in DMF (9 mL) was added $Pd(CH_3CN)_2Cl_2$ (28 mg, 0.11 mmol, 5 mol %). The reaction mixture was stirred at room temperature for 2 h and then quenched with 10% KF solution. After being stirred for an additional 10 min, it was then diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was purified by flash silica gel column chromatography (hexane/EtOAc, 1:1) to give (*E*)-allylic alcohol **7** (617 mg, 95%) as a white solid: mp 139 °C; $[\alpha]^{20}_D$ +4.34 (*c* 0.91, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, J = 6.3 Hz, 3H), 1.60 (s, 1H), 3.75 (d, J = 6.3 Hz, 2H), 4.00 (s, 3H), 4.02 (s, 3H), 4.10 (s, 3H), 4.31 (ddq, J = 0.9, 6.6, 6.3 Hz, 1H), 5.67 (tdd, J = 1.5, 6.6, 15.3 Hz, 1H), 5.94 (dtd, J = 0.9, 6.3, 15.3 Hz, 1H), 7.17 (dd, J = 2.4, 8.7 Hz, 1H), 7.35 (s, 1H), 7.42 (s, 1H), 7.72 (d, J = 8.7 Hz, 1H), 7.82 (d, J = 2.4 Hz, 1H), 7.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 36.3, 55.3, 55.6, 55.8, 68.5, 103.6, 103.7, 104.9, 115.2, 124.5, 124.6, 125.9, 126.5, 128.5, 129.5, 130.2, 130.8, 136.0, 148.4, 149.0, 157.7; IR ($CHCl_3$) υ_{max} 3497, 2967, 2834, 1611, 1474, 1236 (cm^{-1}); MS (EI) (*m*/*z*) 352 (M^+, 100), 281 (23), 268 (27), 105 (21), 83 (18), 71 (26), 57 (34); HRMS (EI) calcd for $C_{22}H_{24}O_4$ (M^+) 352.1674, found 352.1672.

2,2,2-Trichloro-acetimidic Acid (*R*)-1-Methyl-4-(3,6,7-trimethoxyphenanthren-9-yl)but-2-enyl Ester (11). To a solution of (*E*)-allylic alcohol **7** (616 mg, 1.75 mmol) in CH_2Cl_2 (5 mL) was added CCl_3CN (0.35 mL, 3.49 mmol) and DBU (30 μL, 0.19 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The volatiles were evaporated, and the residue was purified by flash silica gel column chromatography (hexane/EtOAc, 2:1, 1% triethylamine) to give trichloroacetimidate **11** (861 mg, 99%) as a colorless oil: $[\alpha]^{21}_D$ +22.0 (*c* 0.66, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (d, J = 6.3 Hz, 3H), 3.82 (d, J = 6.0 Hz, 2H), 4.017 (s, 3H), 4.023 (s, 3H), 4.12 (s, 3H), 5.52 (ddq, J = 0.9, 6.6, 6.3 Hz, 1H), 5.71 (tdd, J = 1.5, 6.6, 15.6 Hz, 1H), 6.15 (dtd, J = 0.9, 6.3, 15.6 Hz, 1H), 7.19 (dd, J = 2.7, 8.7 Hz, 1H), 7.35 (s, 1H), 7.45 (s, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 2.1 Hz, 1H), 7.92 (s, 1H), 8.28 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 36.4, 55.4, 55.7, 55.9, 75.7, 91.8, 103.66, 103.71, 105.0, 115.3, 124.6, 124.7, 126.0, 126.5, 129.6, 130.3, 130.5, 130.6, 131.5, 148.5, 149.0, 157.8, 161.7; IR ($CHCl_3$) υ_{max} 3337, 2936, 2832, 1659, 1611, 1474 (cm^{-1}); MS (EI) (*m*/*z*) 495 (M^+, 2), 334 (33), 319 (12), 288 (11), 281 (100), 237 (8), 202 (8), 165 (9), 152 (11), 83 (9), 57 (17); HRMS (EI) calcd for $C_{24}H_{24}NO_4Cl_3$ (M^+) 495.0770, found 495.0771.

(*S*)-2,2,2-Trichloro-*N*-[1-(3,6,7-trimethoxyphenanthren-9-ylmethyl)but-2-enyl]acetamide (12). A solution of trichloroacetimidate **11** (884 mg, 1.78 mmol) in toluene (18 mL) was heated to reflux for 12 h. The solvent was removed, and the residue was purified by flash silica gel column chromatography (hexane/EtOAc, 3:1) to give (*E*)-allylic trichloroacetamide **12** (820 mg, 93%) as a white solid: mp 145−146 °C; $[\alpha]^{21}_D$ −22.1 (*c* 0.95, $CHCl_3$); the enantioselectivity was determined by chiral HPLC analysis (CHIRALCEL OD-H, hexane/2-propanol (95:5, v/v); flow rate, 1.0 mL/min; λ 254 nm; retention time, *S* (major) 29.46 min, *R* (minor) 38.33 min, 99% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (d, J = 5.1 Hz, 3H), 3.08 (dd, J = 8.4, 13.8 Hz, 1H), 3.54 (dd, J = 5.4, 13.8 Hz, 1H), 3.99 (s, 3H), 4.09 (s, 3H), 4.13 (s, 3H), 4.81 (m, 1H), 5.47−5.64 (m, 2H), 6.79 (br d, J = 7.5 Hz, 1H), 7.17 (dd, J = 2.4, 8.7 Hz, 1H), 7.36 (s, 1H), 7.64 (s, 1H), 7.69 (d, J = 8.7 Hz, 1H), 7.81 (d, J = 2.4 Hz, 1H), 7.88 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 38.8, 53.2, 55.4, 55.9, 56.2, 92.7, 103.7, 103.8, 104.9, 115.4, 124.7, 125.6, 126.5, 126.6, 127.6, 128.6, 128.8, 129.6, 130.6, 148.7, 149.5, 158.0, 161.0; IR ($CHCl_3$) υ_{max} 3335, 3002, 2938, 1703, 1611, 1474 (cm^{-1}); MS (EI) (*m*/*z*) 495 (M^+, 3), 281 (100), 265 (3), 237 (5), 165 (3), 152 (3), 71 (1), 55 (1); HRMS (EI) calcd for $C_{24}H_{24}NO_4Cl_3$ (M^+) 495.0770, found 495.0772.

(*S*)-[1-(3,6,7-Trimethoxyphenanthren-9-ylmethyl)but-2-enyl]carbamic Acid Benzyl Ester (13). To a solution of (*E*)-allylic trichloroacetamide **12** (531 mg, 1.07 mmol) in CH_2Cl_2 (2 mL) and EtOH (4 mL) was added 5 N NaOH (1 mL). The reaction mixture was stirred at 50 °C for 1 day. The volatiles were evaporated to give allylamine intermediate. To a solution of allylamine intermediate in THF (5 mL) was added benzyl chloroformate (0.60 mL, 4.20 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1 h. It was then diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 3:1) afforded the Cbz derivative **13** (454 mg, 87%) as a white solid: mp 164 °C; $[\alpha]^{18}_D$ −1.71 (*c* 1.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (d, J = 4.5 Hz, 3H), 3.03 (m, 1H), 3.50 (m, 1H), 4.02 (s, 3H), 4.12 (s, 6H), 4.63 (m, 1H), 4.89 (br s, 1H), 5.09 (br s, 2H), 5.41−5.55 (m, 2H), 7.18 (dd, J = 2.7, 8.7 Hz, 1H), 7.33 (br s, 5H), 7.37 (s, 1H), 7.71 (d, J = 8.7 Hz, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.92 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 40.3, 52.9, 55.5, 55.9, 56.2, 66.6, 103.8, 105.3, 115.3, 124.6, 125.8, 126.4, 126.9, 127.0, 128.0, 128.4, 128.7, 129.7, 130.3, 130.5, 136.5, 148.6, 149.4, 149.5, 155.7, 157.9; IR ($CHCl_3$) υ_{max} 3356, 2936, 1713, 1611, 1474 (cm^{-1}); MS (EI) (*m*/*z*) 485 (M^+, 3), 315 (5), 281 (70), 265 (3), 237 (4), 223 (3), 204 (10), 160 (23), 91 (100), 57 (3); HRMS (EI) calcd for $C_{30}H_{31}NO_5$ (M^+) 485.2202, found 485.2204.

(*S*)-Allyl-[1-(3,6,7-trimethoxyphenanthren-9-ylmethyl)-but-2-enyl]carbamic Acid Benzyl Ester (14). To a solution of **13** (94 mg, 0.19 mmol) in THF (4 mL) and HMPA (0.4 mL) were added NaH (23 mg, 0.58 mmol, 60% dispersion in mineral oil) and allyl bromide (80 μL, 0.97 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h, and then diluted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. The solvent was removed, and the residue was purified by flash silica gel column chromatography (hexane/EtOAc, 3:1) to give bis-allylamine **14** (100 mg, 100%) as a colorless oil: $[\alpha]^{19}_D$ −43.1 (*c* 1.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (br d, J = 4.2 Hz, 3H), 3.25−4.04 (m, 4H), 4.01 (s, 3H), 4.11 (s, 6H), 4.82 (dd, J = 7.2, 14.4 Hz, 1H), 5.01−5.14 (m, 4H), 5.52 (m, 1H), 5.69−5.76 (m, 2H), 7.17 (dd, J = 2.4, 8.7 Hz, 1H), 7.11−7.31 (m, 6H), 7.61 (br s, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.83 (d, J = 1.5 Hz, 1H), 7.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 37.4, 48.0, 55.5, 55.9, 59.3, 66.8, 103.8, 103.9, 105.0, 115.2, 116.2, 124.6, 125.9, 126.0, 126.8, 127.7, 127.8, 128.3, 128.8, 129.2, 129.4, 129.7, 130.4, 135.3, 148.5, 149.4, 155.7, 157.9; IR ($CHCl_3$) υ_{max} 2938, 2834, 2361, 1694, 1611, 1455 (cm^{-1}); MS (EI) (*m*/*z*) 525 (M^+, 3), 315 (3), 281 (8), 265 (3), 244 (12), 223 (3), 200 (11), 91 (100), 65 (5), 57 (4); HRMS (EI) calcd for $C_{33}H_{35}NO_5$ (M^+) 525.2515, found 525.2514.

(*S*)-2-(3,6,7-Trimethoxyphenanthren-9-ylmethyl)-2,5-dihydro-pyrrole-1-carboxylic Acid Benzyl Ester (16). To a solution of bis-allylamine **14** (153 mg, 0.29 mmol) in CH_2Cl_2 (3 mL) was added second-generation Grubbs' catalyst **15** (12

(21) Optical rotation values of natural cryptopleurine range from −96.7 to −106°. See: (a) Gellert, E.; Riggs, N. V. *Aust. J. Chem.* **1954**, *7*, 113−114. (b) Suzuki, H.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1995**, *60*, 6114−6122. (c) Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1995**, *36*, 935−936. See also refs 3, 7, and 12.

mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 2 h. The volatiles were removed, and the residue was purified by flash silica gel column chromatography (hexane/EtOAc, 3:1 to 1:2, gradient) to give 2,5-dihydropyrrole **16** (138 mg, 98%) as a white solid: mp 184−186 °C; $[\alpha]^{19}_D$ +14.0 (*c* 1.41, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) (two rotamers in a 5:2 ratio) major rotamer δ 2.79 (dd, J = 10.8, 12.9 Hz, 1H), 4.01−4.27 (m, 3H), 4.02 (s, 3H), 4.13 (s, 3H), 4.21 (s, 3H), 5.02 (m, 1H), 5.21 (d, J = 12.3 Hz, 1H), 5.28 (d, J = 12.3 Hz, 1H), 5.73 (m, 2H), 7.18 (dd, J = 2.7, 8.7 Hz, 1H), 7.34−7.44 (m, 6H), 7.73 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.93 (s, 1H), 8.15 (s, 1H), minor rotamer δ 2.93 (dd, J = 9.9, 13.5 Hz, 1H), 3.74 (s, 1H), 3.93−4.35 (m, 3H), 4.02 (s, 3H), 4.10 (s, 3H), 5.08 (m, 1H), 5.24 (d, J = 12.3 Hz, 1H), 5.35 (d, J = 12.3 Hz, 1H), 5.52 (m, 1H), 5.77 (m, 1H), 7.19 (dd, J = 2.1, 8.7 Hz, 1H), 7.31−7.46 (m, 7H), 7.70 (d, J = 8.7 Hz, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (two rotamers ratio 5:2) major rotamer δ 39.1, 53.6, 55.5, 56.0, 56.6, 64.8, 66.6, 103.5, 103.8, 106.2, 115.3, 124.7, 125.0, 125.9, 127.1, 127.88, 127.94, 128.5, 128.6, 129.5, 129.6, 130.3, 130.4, 137.0, 148.7, 149.7, 154.7, 157.9, minor rotamer δ 39.8, 54.1, 55.6, 64.0, 67.2, 105.2, 115.5, 124.6, 126.3, 128.2, 129.7, 130.6, 149.4; IR ($CHCl_3$) υ_{max} 2936, 1699, 1611, 1472 (cm^{-1}); MS (EI) (*m*/*z*) 483 (M^+, 1), 316 (8), 282 (16), 237 (3), 223 (1), 202 (4), 158 (11), 152 (2), 91 (100), 65 (8), 51 (2); HRMS (EI) calcd for $C_{30}H_{29}NO_5$ (M^+) 483.2045, found 483.2044.

(*R*)-2-(3,6,7-Trimethoxyphenanthren-9-ylmethyl)pyrrolidine (4). To a solution of **16** (73 mg, 0.15 mmol) in MeOH (6 mL) was added 10% Pd/C (73 mg, 100 wt %). The reaction mixture was hydrogenated (1 atm) with vigorous stirring at room temperature for 2 h. It was then diluted with CH_2Cl_2, filtered through Celite, and concentrated. The residue was purified by flash silica gel column chromatography (CH_2Cl_2/MeOH, 7:1, 1% NH_4OH) to give 2-arylmethylpyrrolidine **4** (33 mg, 63%) as a white solid: mp 144−148 °C; $[\alpha]^{18}_D$ −5.61 (*c* 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (m, 1H), 1.74 (m, 1H), 1.88 (m, 2H), 2.85−2.94 (m, 2H), 3.11 (m, 1H), 3.22 (dt, J = 6.9, 14.1 Hz, 2H), 3.56 (dt, J = 14.1, 6.6 Hz, 1H), 3.99 (s, 3H), 4.05 (s, 3H), 4.09 (s, 3H), 7.17 (dd, J = 2.4, 8.7 Hz, 1H), 7.41 (s, 1H), 7.48 (s, 1H), 7.74 (d, J = 8.7 Hz, 1H), 7.80 (d, J = 2.4 Hz, 1H), 7.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 30.9, 37.4, 45.2, 55.4, 55.9, 56.4, 59.2, 103.7, 103.8, 104.5, 115.4, 124.6, 125.2, 125.7, 126.2, 128.9, 129.8, 130.5, 148.7, 149.5, 158.0; IR (KBr) υ_{max} 2934, 2831, 1611, 1516 (cm^{-1}); MS (FAB) (*m*/*z*) 352 ($[M + H]^+$, 51), 282 (23), 154 (13), 136 (11), 70 (100); HRMS (FAB) calcd for $C_{22}H_{26}NO_3$ ($[M + H]^+$) 352.1913, found 352.1905.

(−)-Antofine (2). To a solution of 2-arylmethylpyrrolidine **4** (33 mg, 0.09 mmol) in EtOH (2 mL) was added 37% formaldehyde (500 μL) and concentrated HCl (50 μL). The reaction mixture was refluxed for 3 days in the dark. The reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 and treated with 10% HCl. The aqueous layer was extracted with CH_2Cl_2 twice, and the combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 10:1) afforded the desired product (−)-antofine (**2**) (27 mg, 80%) as a white solid: mp 212−214 °C (lit.[14] mp 206−211 °C); $[\alpha]^{19}_D$ −125.2 (*c* 1.27, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.74 (m, 1H), 1.89 (m, 1H), 2.02 (m, 1H), 2.21 (m, 1H), 2.42 (m, 2H), 2.86 (m, 1H), 3.28 (dd, J = 2.4, 15.6 Hz, 1H), 3.44 (dt, J = 1.8, 8.5 Hz, 1H), 3.64 (d, J = 14.7 Hz, 1H), 3.99 (s, 3H), 4.04 (s, 3H), 4.08 (s, 3H), 4.66 (d, J = 14.7 Hz, 1H), 7.18 (dd, J = 2.5, 9.0 Hz, 1H), 7.27 (s, 1H), 7.78 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 2.5 Hz, 1H), 7.87 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 31.2, 33.6, 53.8, 55.0, 55.4, 55.8, 55.9, 60.1, 103.8, 103.9, 104.6, 114.8, 123.5, 124.1, 124.2, 125.5, 126.6, 127.0, 130.1, 148.3, 149.3, 157.4; IR (KBr) υ_{max} 1622, 1512 (cm^{-1}); MS (EI) (*m*/*z*) 363 (M^+, 24), 294 (100), 279 (11); HRMS (CI) calcd for $C_{23}H_{26}NO_3$ ($[M + H]^+$) 364.1912, found 364.1913.

(*S*)-5-Benzyloxycarbonylamino-6-(3,6,7-trimethoxyphenanthren-9-yl)hex-3-enyl Acetate (19). To a solution of **13** (206 mg, 0.424 mmol) and homoallyl acetate homodimer **18** (171 mg, 0.854 mmol) in CH_2Cl_2 (10 mL) was added second-generation Grubbs' catalyst **15** (19 mg, 0.022 mmol). The reaction mixture was heated to reflux for 1 day and then cooled to room temperature. It was concentrated to dryness. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 3:1 to 1:1, gradient) to give **19** (193 mg, 82%) as a colorless oil and **13** (29 mg, 14%): ^{1}H NMR (300 MHz, $CDCl_3$) (*E*/*Z* mixture, ratio 8:1) (*E*)-isomer δ 1.93 (s, 3H), 2.25 (m, 2H), 3.01 (m, 1H), 3.54 (m, 1H), 3.89−3.96 (m, 2H), 4.02 (s, 3H), 4.12 (s, 6H), 4.65 (m, 1H), 4.90 (br s, 1H), 5.09 (s, 2H), 5.37−5.47 (m, 1H), 5.56 (dd, J = 6.0, 15.6 Hz, 1H), 7.18 (dd, J = 2.4, 9.0 Hz, 1H), 7.33 (br s, 6H), 7.36 (s, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.84 (d, J = 2.4 Hz), 7.92 (s, 1H), (*Z*)-isomer δ 1.84 (s, 3H), 2.25 (m, 2H), 3.56−3.66 (m, 2H), 3.89−3.96 (m, 2H), 4.02 (s, 3H), 4.12 (s, 6H), 4.84−4.92 (m, 2H), 5.11 (s, 2H), 5.34−5.48 (m, 2H), 7.17 (dd, J = 2.7, 9.0 Hz, 1H), 7.33 (br s, 7H), 7.69 (d, J = 8.7 Hz, 1H), 7.83 (br d, J = 1.8 Hz), 7.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (*E*)-isomer δ 20.7, 31.4, 40.2, 52.6, 55.4, 55.9, 56.1, 63.4, 66.6, 103.7, 105.1, 115.3, 124.6, 125.6, 126.3, 126.7, 127.2, 128.0, 128.4, 129.6, 130.5, 131.8, 136.4, 148.6, 149.5, 155.6, 157.9, 170.8; IR ($CHCl_3$) υ_{max} 3360, 2938, 1715, 1611, 1473, 1145 (cm^{-1}); MS (EI) (*m*/*z*) 557 (M^+, 8), 463 (3), 449 (5), 281 (100), 237 (7), 91 (31); HRMS (CI) calcd for $C_{33}H_{36}NO_7$ ($[M + H]^+$) 558.2492, found 558.2491.

(*R*)-5-Amino-6-(3,6,7-trimethoxyphenanthren-9-yl)hexyl Acetate (20). Following the same procedure as for **4**, from *E*/*Z* mixture **19** (290 mg, 0.520 mmol) in MeOH (5 mL) and 10% Pd/C (145 mg, 50 wt %), after a reaction time of 4 h, free amine **20** (210 mg, 95%) was obtained as a colorless oil: $[\alpha]^{20}_D$ −12.6 (*c* 1.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (m, 1H), 1.64 (m, 5H), 1.99 (s, 3H), 2.68 (dd, J = 8.1, 13.2 Hz, 1H), 3.05 (m, 1H), 3.27−3.39 (m, 2H), 3.99−4.12 (m, 2H), 4.01 (s, 3H), 4.03 (s, 3H), 4.10 (s, 3H), 7.18 (dd, J = 2.4, 8.7, 1H), 7.37 (s, 1H), 7.48 (s, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.83 (d, J = 2.4 Hz, 1H), 7.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 22.5, 28.4, 37.1, 41.7, 50.6, 55.1, 55.4, 55.5, 64.0, 103.3, 103.5, 104.4, 115.1, 124.5, 125.5, 126.1, 129.3, 129.7, 130.1, 148.3, 148.8, 157.6, 170.7; IR ($CHCl_3$) υ_{max} 3462, 2936, 1734, 1609, 1474, 1113 (cm^{-1}); MS (EI) (*m*/*z*) 425 (M^+, 3), 282 (100), 267 (6), 144 (26), 84 (28); HRMS (EI) calcd for $C_{25}H_{31}NO_5$ (M^+) 425.2202, found 425.2205.

(*R*)-5-Amino-6-(3,6,7-trimethoxyphenanthren-9-yl)hexan-1-ol (21). To a solution of **20** (177 mg, 0.416 mmol) in MeOH (4 mL) was added 5 N NaOH (1 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 day. After the reaction mixture was cooled to room temperature, water was added. The resulting mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 9:1 to 4:1, gradient) gave amino alcohol **21** (143 mg, 90%) as a milky oil: $[\alpha]^{20}_D$ −46.1 (*c* 0.89, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 1.45 (m, 6H), 2.68 (dd, J = 8.1, 13.2 Hz, 1H), 3.12−3.20 (m, 2H), 3.46 (m, 2H), 3.86 (s, 3H), 3.89 (s, 3H), 3.94 (s, 3H), 7.05 (dd, J = 2.4, 8.7, 1H), 7.16 (s, 1H), 7.30 (s, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.66 (br d, J = 1.5 Hz, 1H), 7.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD) δ 22.0, 32.0, 36.1, 40.8, 50.4, 55.1, 55.5, 55.6, 61.3, 103.4, 103.7, 104.4, 115.3, 124.7, 125.5, 125.7, 126.0, 129.1, 129.4, 130.2, 148.4, 148.9, 157.7; IR ($CHCl_3$) υ_{max} 3351, 2934, 1609, 1474, 1113 (cm^{-1}); MS (EI) (*m*/*z*) 383 (M^+, 3), 282 (100), 102 (43), 85 (40); HRMS (EI) calcd for $C_{23}H_{29}NO_4$ (M^+) 383.2096, found 383.2095.

(*R*)-2-(3,6,7-Trimethoxyphenanthren-9-ylmethyl)piperidine (5). To a solution of amino alcohol **21** (61 mg, 0.159 mmol) in CH_2Cl_2 (16 mL) were added DIAD (80 μL, 0.406 mmol) and PPh_3 (106 mg, 0.404 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 15 h. The solvent was removed, and the residue was purified by flash silica gel

column chromatography (CH_2Cl_2/MeOH, 10:1) to give 2-arylmethylquinolizidine **5** (39 mg, 68%) as a white solid: mp 147−148 °C; $[\alpha]^{20}_D$ −18.8 (*c* 0.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (m, 2H), 1.73−1.83 (m, 5H), 1.97 (m, 1H), 2.87 (dt, *J* = 2.4, 12.6 Hz, 1H), 3.26−3.33 (m, 2H), 3.54 (br d, *J* = 12.3 Hz, 1H), 3.99 (s, 3H), 4.08 (s, 3H), 4.19 (s, 3H), 7.14 (dd, *J* = 2.4, 9.0 Hz, 1H), 7.41 (s, 1H), 7.61 (s, 1H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.78 (d, *J* = 2.4 Hz, 1H), 7.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 22.7, 28.7, 37.8, 45.1, 55.5, 55.9, 56.7, 57.1, 103.8, 103.9, 105.0, 115.4, 124.8, 125.5, 126.2, 126.8, 126.9, 129.8, 130.7, 148.8, 149.9, 158.1; IR (KBr) υ_{max} 3400, 2938, 1611, 1474, 1113 (cm^{-1}); MS (EI) (*m*/*z*) 365 (M^+, 1), 282 (27), 84 (100); HRMS (CI) calcd for $C_{23}H_{28}NO_3$ ($[M + H]^+$) 366.2069, found 366.2066.

(−)-Cryptopleurine (3). Following the same procedure as for **2**, from 2-arylmethylquinolizidine **5** (26 mg, 71 μmol) in EtOH (2 mL), 37% formaldehyde (500 μL), and concentrated HCl (40 μL), after a reaction time of 2 days, (−)-cryptopleurine (**3**) (18 mg, 67%) was obtained as a white solid: mp 191−192 °C (lit.[21] 195−197 °C); $[\alpha]^{21}_D$ −108.7 (*c* 1.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (m, 1H), 1.54 (m, 1H), 1.77−1.81 (m, 2H), 1.88 (d, *J* = 12.2 Hz, 1H), 2.03 (d, *J* = 11.5 Hz, 1H), 2.30 (dt, *J* = 3.9, 11.2 Hz, 1H), 2.39 (t, *J* = 10.1 Hz, 1H), 2.88 (dd, *J* = 10.7, 15.9 Hz, 1H), 3.08 (dd, *J* = 3.1, 16.4 Hz, 1H), 3.27 (d, *J* = 11.1 Hz, 1H), 3.63 (d, *J* = 15.4 Hz, 1H), 4.01 (s, 3H), 4.06 (s, 3H), 4.10 (s, 3H), 4.44 (d, *J* = 15.4 Hz, 1H), 7.19 (dd, *J* = 2.4, 9.0 Hz, 1H), 7.25 (s, 1H), 7.79 (d, *J* = 9.0 Hz, 1H), 7.89 (d, *J* = 2.4 Hz, 1H), 7.90 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.6, 26.2, 34.0, 34.9, 55.7, 56.1, 56.2, 56.5, 57.8, 104.1, 104.1, 105.0, 115.0, 123.6, 123.9, 124.3, 124.7, 125.8, 126.7, 130.3, 148.5, 149.6, 157.6; IR ($CHCl_3$) υ_{max} 2930, 1611, 1470, 1125 (cm^{-1}); MS (EI) (*m*/*z*) 377 (M^+, 32), 294 (100), 279 (15), 251 (17), 208 (15), 189 (14), 165 (17), 83 (10), 69 (9), 55 (27); HRMS (EI) calcd for $C_{24}H_{27}NO_3$ (M^+) 377.1991, found 377.1992.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **2**−**5**, **7**, **12**−**14**, and **19** and HPLC data of compound **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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