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Collective Asymmetric Synthesis of (−)-Antofine, (−)-Cryptopleurine, (−)-Tylophorine, and (−)-Tylocrebrine with *tert*-Butanesulfinamide as a Chiral Auxiliary

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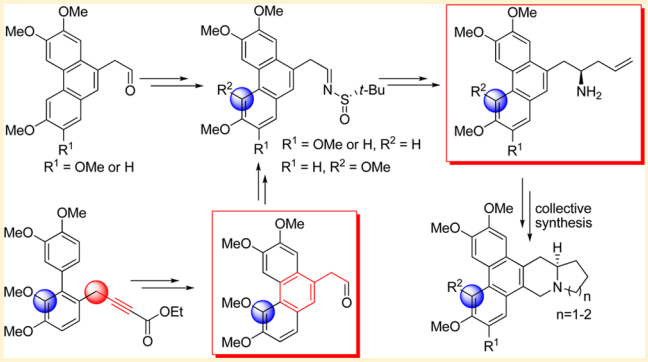
Supporting Information

ABSTRACT: A collective asymmetric synthesis of phenanthroindolizidine and phenanthroquinolizidine alkaloids (−)-antofine, (−)-cryptopleurine, (−)-tylophorine, and (−)-tylocrebrine was achieved by means of a reaction sequence involving efficient generation of chiral homoallylic amine intermediates by asymmetric allylation of the corresponding *tert*-butanesulfinyl imine. From these intermediates, the pyrrolidine and piperidine rings were constructed by means of an intramolecular S_N2 substitution reaction and a ring-closing metathesis reaction, respectively. The unusual C5-methoxy-substituted phenanthrene moiety of (−)-tylocrebrine was generated by means of an $InCl_3$-catalyzed cycloisomerization reaction of an *o*-propargylbiaryl compound.



INTRODUCTION

Approximately 100 phenanthroindolizidine and phenanthroquinolizidine alkaloid natural products together with their derivatives, including (−)-antofine (**1**), (−)-cryptopleurine (**2**), (−)-tylophorine (**3**), and (−)-tylocrebrine (**4**), have been isolated.[1,2] During the past two decades, these structurally related alkaloids have attracted great interest because they exhibit diverse biological activities, including antibacterial,[3] antiasthmatic,[4] anticancer,[2] and anti-inflammatory[5] activities. In addition, we recently reported that some of these compounds also possess antiviral activity against tobacco mosaic virus.[6] (−)-Tylocrebrine was also advanced to clinical trials in the 1960s but eventually failed owing to its toxicity to the central nervous system.[7]

To facilitate investigation of the biological activities of these alkaloids, researchers have developed a number of methods for their synthesis. Among these methods, organocatalysis,[8] enantioselective transition-metal-catalyzed carboamination of alkenes,[9] enantioselective alkylation[10] by means of a phase-transfer reagent, and the use of chiral building blocks[11] or a chiral auxiliary[12] are the most efficient methods reported for the synthesis of optically active phenanthroindolizidine and phenanthroquinolizidine alkaloids. The D and E rings have been constructed in one step by a [2 + 2 + 2] cycloisomerization reaction,[13] an intramolecular Diels−Alder cycloaddition reaction,[14] and a Schmidt/Bischler−Napieralski/imine reduction sequence.[15] As part of our continuing studies of the synthesis and bioactivity of these compounds, we developed a practical approach to the collective asymmetric synthesis of four phenanthroindolizidine and phenanthroquinolizidine alkaloids from common chiral homoallylic amine intermediates, which were synthesized by means of a chiral auxiliary, *tert*-butanesulfinamide.

First reported by Ellman in 1997,[16] enantiomerically pure *tert*-butylsulfinamide is regarded as an ideal auxiliary for the synthesis of chiral amines because of its low cost and ease of removal from reaction products. More importantly, addition of nucleophiles to *tert*-butanesulfinyl imines proceeds with excellent diastereoselectivity to permit the synthesis of amine-containing compounds.[17] In particular, chiral homoallyl amines, which are versatile precursors for the synthesis of complex molecules, can be achieved by metal-mediated allylation[18] of *tert*-butanesulfinyl imines and subsequent removal of the chiral auxiliary. Herein, we report that a homoallyl amine building block could be transformed to the D and E rings of phenanthroindolizidine and phenanthroquinolizidine alkaloids; specifically, this powerful strategy enabled us to synthesize **1**−**4**.

RESULTS AND DISCUSSION

Our retrosynthetic analysis of compounds **1**−**3** is shown in Scheme 1. We envisioned that the target molecules could be constructed by means of a late-stage Pictet−Spengler annulation[8a,9,10,11d] of a 2-(arylmethyl)pyrrolidine or 2-(arylmethyl)piperidine (**5**), which could in turn be obtained from homoallyl amine derivatives **6** and **7**. We expected that these amines could be easily obtained from chiral homoallyl

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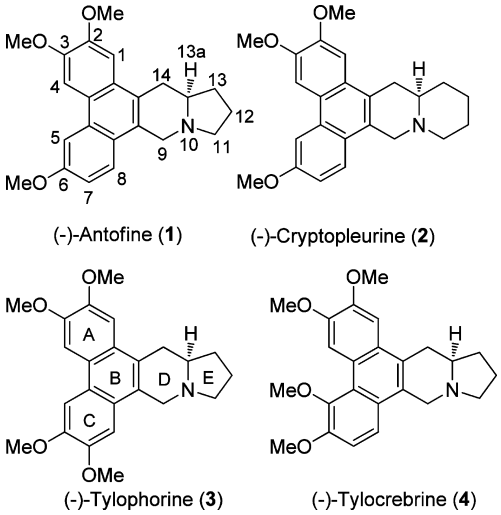
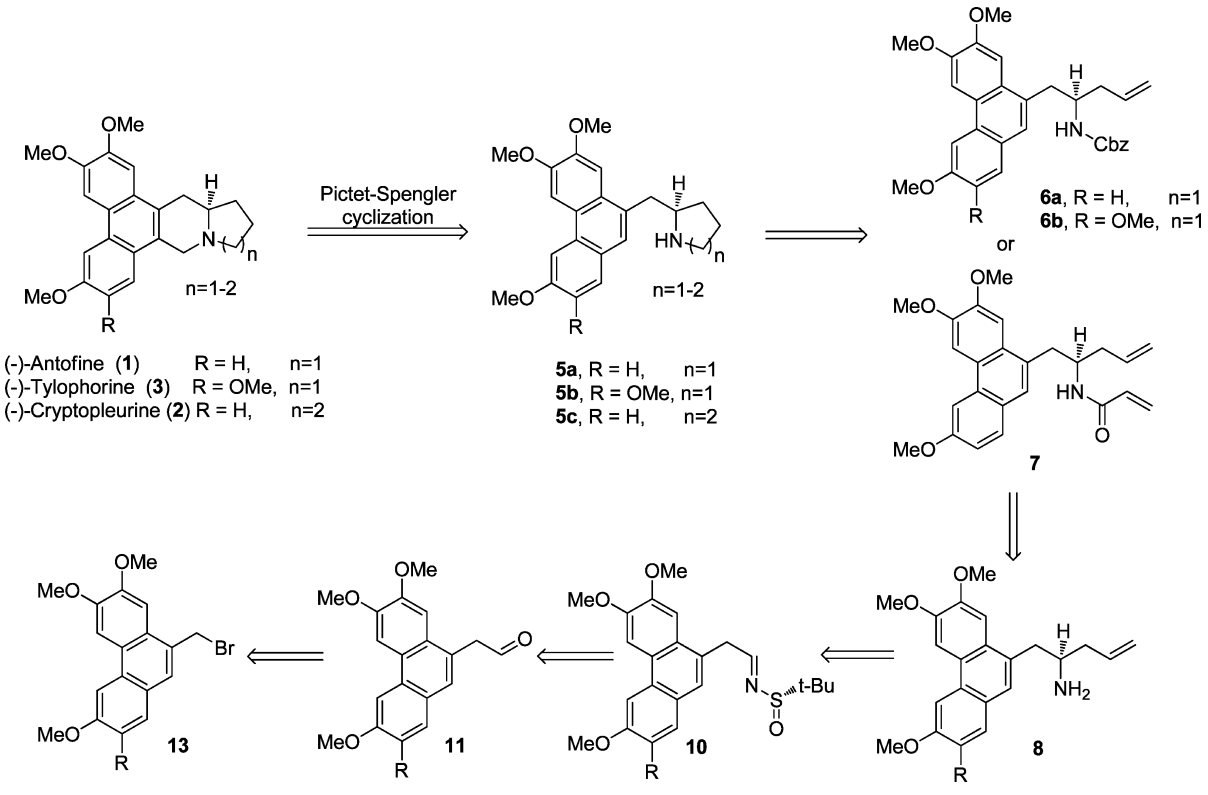


amines **8** which are obtained by allylation of *tert*-butanesulfinyl imines **10**. Imines **10** could be readily accessed by direct condensation of phenanthrylacetaldehydes **11** with *tert*-butylsulfinamide under mild conditions. Aldehydes **11** could be prepared from phenanthrylmethyl bromides **13**, which are readily available by means of a procedure developed in our group.

We began our synthesis from phenanthrylmethyl bromides **13**, which were obtained as described previously.[6] First, compounds **13** were converted to phenanthrylacetonitriles **12** (Scheme 2) by means of a nucleophilic substitution reaction with NaCN, and subsequent reduction of the cyano group[19] with DIBALH gave aldehydes **11**, which were directly condensed with *tert*-butanesulfinamide in the presence of copper(II) sulfate[20] to give enantiomerically pure *tert*-butanesulfinyl imines **10**. Sulfinimines such as **10** have a tendency to isomerize to their enamine tautomers[21] **14**, but fortunately, we detected no such tautomerization of either **10a** or **10b**. Zinc-mediated allylation of **10** by means of Lin's modification[18a] afforded the anticipated *anti*-adducts **9** with excellent diastereoselectivity (de > 99% deduced from the ^{1}H spectrum) and in up to 91% yield. HCl-mediated removal of the *tert*-butanesulfinyl group[22] cleanly provided free amines **8**.

Amines **8** contained all the desired atoms for intermediates **5**, and the stereocenter had been introduced with control of absolute chemistry. To efficiently convert **8** to **5**, we had to functionalize the double bond. Therefore, chiral amines **8** were converted to benzyl carbamates **6** (Scheme 3), which were subjected to hydroboration−oxidation to afford primary alcohols **15**; subsequent mesylation afforded mesylates **16** in high yield. Initially, we envisioned that the pyrrolidine ring of **5** could be formed by removal of the Cbz protecting group from **16** by Pd/C-catalyzed hydrogenolysis, followed by intramolecular nucleophilic attack of the amine on the OMs group. Unfortunately, the hydrogenolysis reaction did not proceed in nonalcoholic solvents (e.g., CH_2Cl_2, EtOAc, or THF), and when methanol or ethanol was used as the solvent, the reaction of **16a** led to the formation of *N*-methylpyrrolidine **17a** or *N*-ethylpyrrolidine **17b**, respectively,[23] as well as the recovery of starting material (^{1}H NMR, ^{13}C NMR, and HRMS spectra are available in the Supporting Information). However, cyclization of **16a** with NaH in THF at 0 °C afforded **18a**,[24] and subsequent removal of the Cbz protecting group with (TMS)I in CH_2Cl_2 in the same pot gave **5a**. Compound **5b** was obtained more efficiently from key intermediate **6b** in one pot without purification over four steps. Finally, Pictet−Spengler annulation of the 2-(arylmethyl)pyrrolidines under standard conditions[8a,9,10,11d] (formaldehyde, HCl, EtOH, reflux) gen-

Scheme 1. Retrosynthetic Analysis of (−)-Antofine (1), (−)-Cryptopleurine (2), and (−)-Tylophorine (3)



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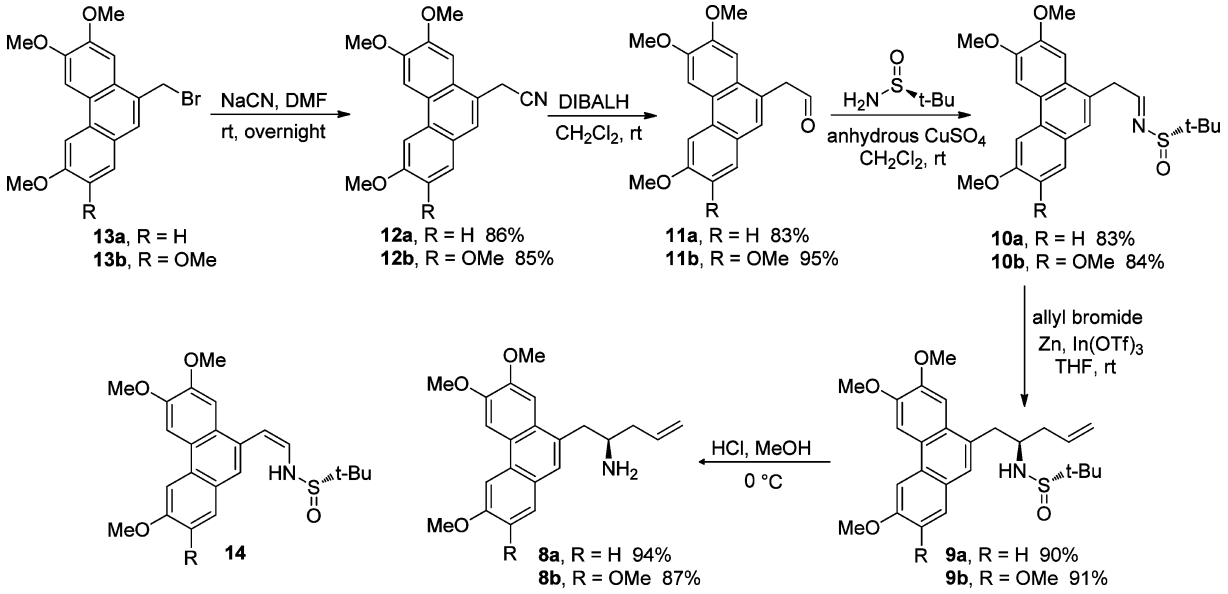
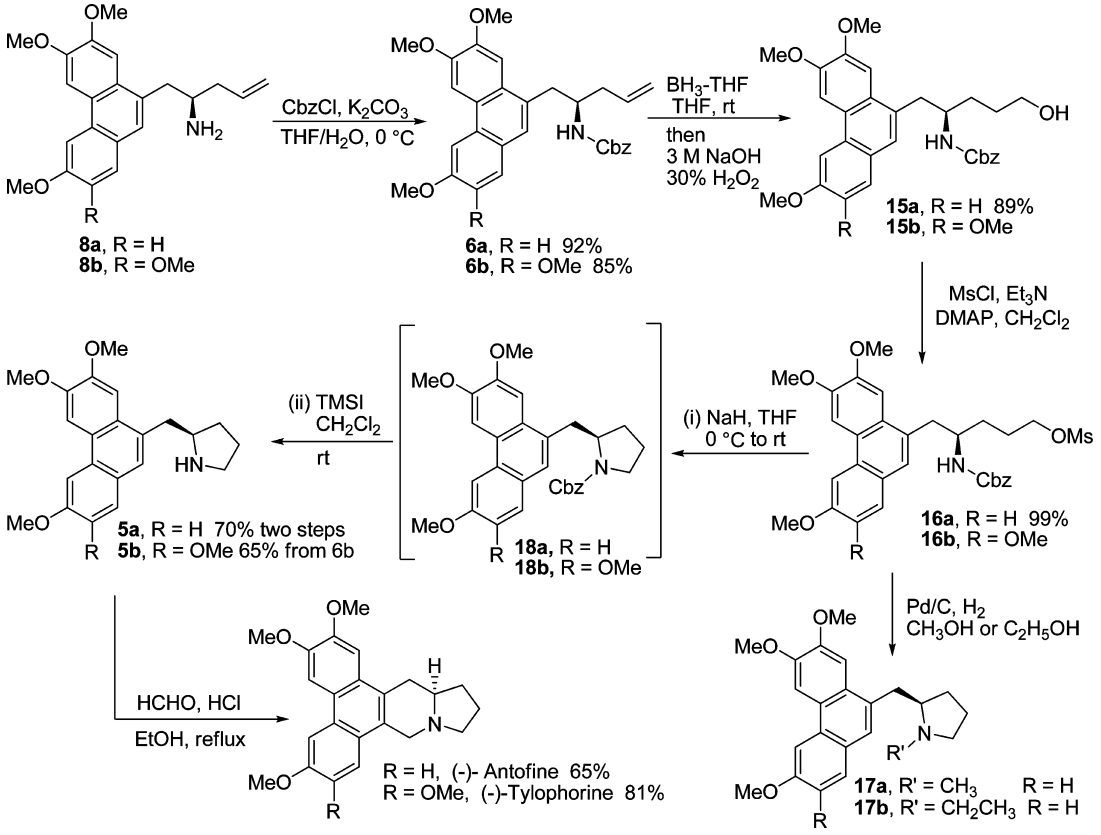
Scheme 2. Synthesis of Chiral Homoallyl Amines 8



Scheme 3. Syntheses of (−)-Antofine (1) and (−)-Tylophorine (3)



erated (−)-antofine (**1**) and (−)-tylophorine (**3**). The ^{1}H and ^{13}C NMR spectra of synthetic **1** and **3** agreed well with the reported spectra, and the optical rotation values of **1** {$[\alpha]_D^{20}$ = −109.0 (c = 1, $CHCl_3$)} and **3** {$[\alpha]_D^{20}$ = −87.0 (c = 1, $CHCl_3$)} also agreed with previously reported values for synthetic (−)-antofine[8a,11d] and (−)-tylophorine.[9a,11b]

We next focused our attention on the preparation of (−)-cryptopleurine (**2**) from intermediate **8a** by means of a ring-closing metathesis (RCM) reaction, which is one of the most powerful methods for the synthesis of medium-sized rings.[25] Acylation of amine **8a** with acryloyl chloride afforded RCM precursor **7**, which contains all the atoms for the E ring of the target natural product (Scheme 4). The RCM reaction of **7** was performed with a commercially available second-generation Grubbs catalyst (**20**) in CH_2Cl_2 at room temperature to form 6-(arylmethyl)-5,6-dihydropyridin-2(1*H*)-one **19** in 93% yield. Subsequent catalytic hydrogenation of the double bond in methanol followed by reduction of the resulting six-membered

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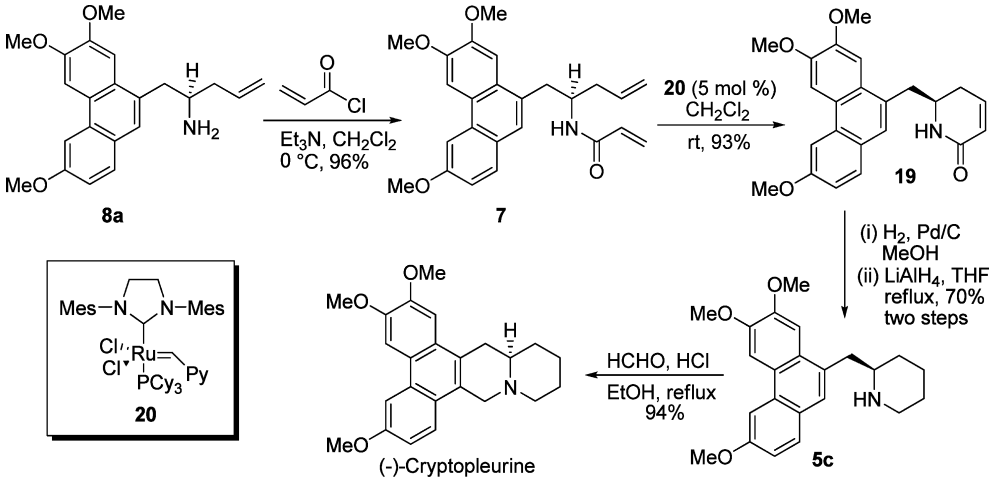
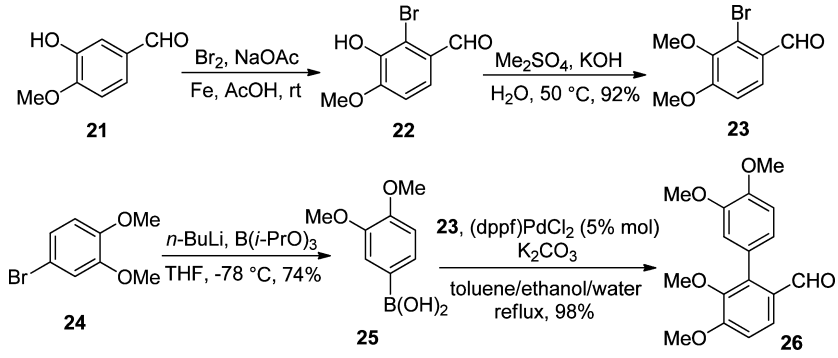
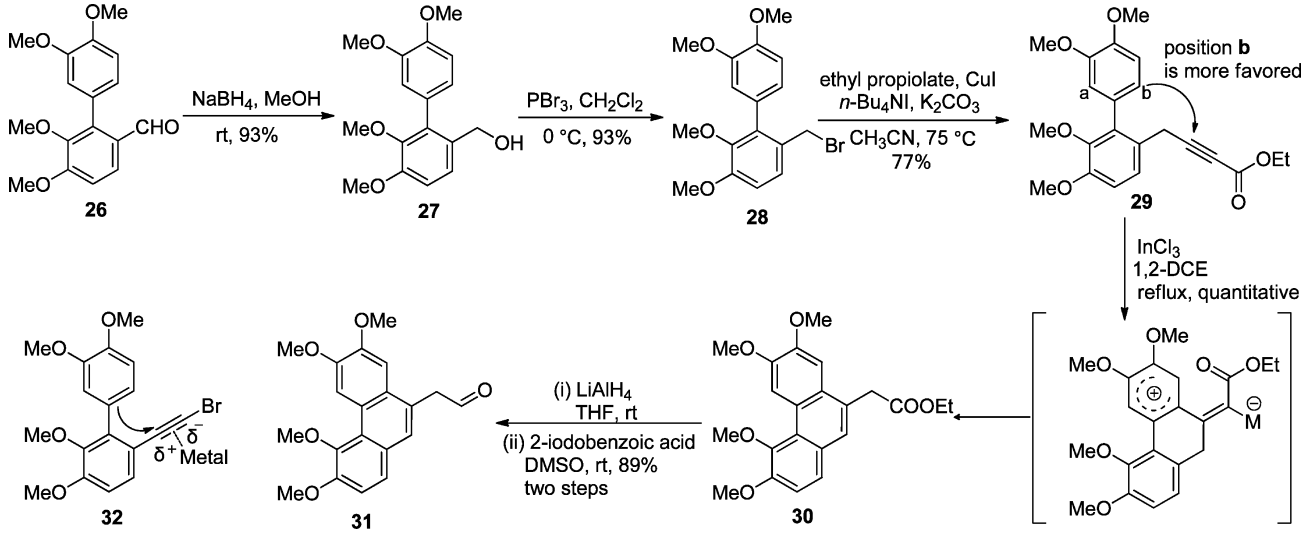
Scheme 4. Synthesis of (−)-Cryptopleurine (2)



Scheme 5. Synthesis of Biarylbenzaldehyde 26



Scheme 6. Synthesis of Phenanthrylacetaldehyde 31



lactam using $LiAlH_4$ in refluxing THF yielded 2-(arylmethyl)-piperidine **5c** in 70% yield. Finally, reaction of **5c** under Pictet–Spengler annulation conditions yielded **2** in 94% yield; the spectroscopic data (^1H and ^{13}C NMR) and the optical rotation $\{[\alpha]_D^{21} = -92.4$ (c = 1, $CHCl_3$)$\}$ of the compound were in agreement with those previously reported for synthetic (−)-cryptopleurine.[8a,11d]

Having accomplished the synthesis of **1**–**3**, we turned our attention to the synthesis of (−)-tylocrebrine (**4**),[26] which has an unusual methoxy group at C5 of the phenanthrene ring.

For the construction of methoxy-substituted phenanthrene rings in phenanthrylmethyl bromides **13a** and **13b** (Scheme 1), the predominant method is dehydrogenative coupling of biaryl substrates, and the robust $FeCl_3$-mediated oxidative coupling method developed in our laboratory[27] is particularly useful, owing to its tolerance for preinstalled aryl substituents.

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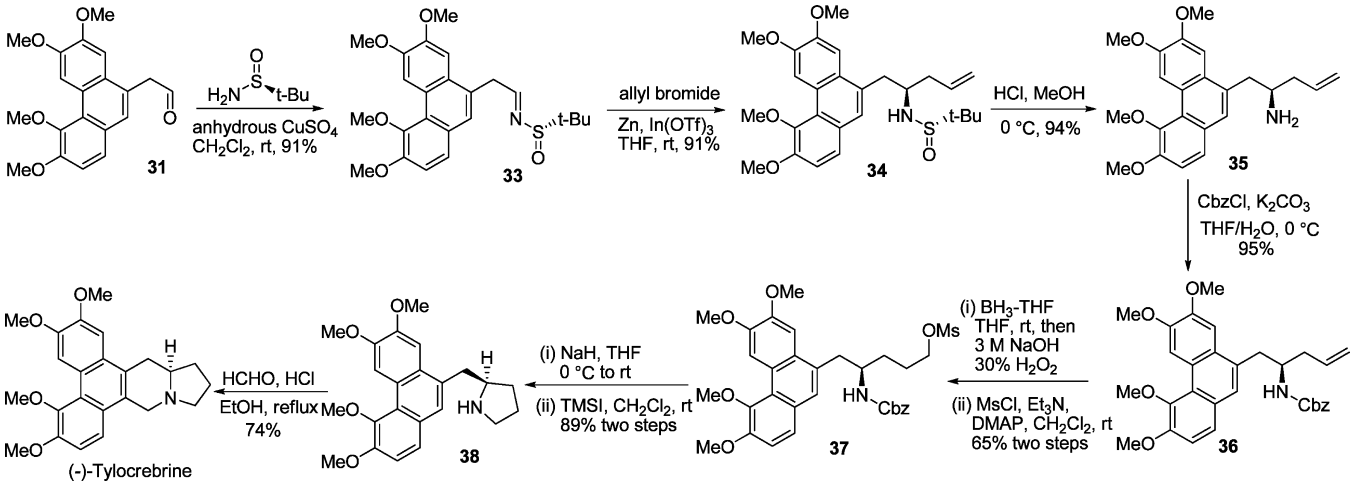
Scheme 7. Synthesis of (−)-Tylocrebrine (4)



However, the inaccessibility of certain phenanthrene substitution patterns, such as the pattern in **4**, is a major drawback. To solve this problem, we employed Fürstner's transition-metal-catalyzed cycloisomerization reaction[28] of *o*-alkynylbiaryls. Sequential bromination and O-methylation of isovanillin (**21**) provided tetrasubstituted bromobenzaldehyde derivative **23**. As expected, a (dppf)$PdCl_2$-catalyzed Suzuki−Miyaura coupling reaction of **23** with boronic acid **25**, which was prepared from the corresponding aryl bromide **24** by reaction with *n*-BuLi and B(*i*-PrO_3), gave biarylbenzaldehyde **26** in 98% yield (Scheme 5).

With aldehyde **26** in hand, we constructed the 5-methoxy-substituted phenanthrene moiety (Scheme 6). We initially considered substrate **32**, but we expected that, under transition-metal-catalyzed cycloisomerization conditions, a 5-*exo-dig* cyclization would be preferred over a 6-*endo-dig* cyclization, owing to the electron-withdrawing bromide atom. This potential regioselectivity problem inspired us to explore an alternative route by considering the stereoelectronic properties and the enthalpy of the transition state of the cyclization reaction. According to Baldwin's rule,[29] the difference in favorability between 5-*exo-dig* and 6-*endo-dig* ring-closure reactions is small, and therefore, the substrate's stereoelectronic properties play a crucial role in the nucleophilic attack of the alkyne by the aromatic ring. We postulated that if a methylene group was inserted between the biaryl and alkynyl groups, we could take advantage of the fact that a 6-*exo-dig* reaction is more favored than a 7-*endo-dig* reaction. We also postulated that an electron-withdrawing ester substituent on the alkyne would stabilize the anion formed by the cyclization reaction. The combination of these two effects might solve this regioselectivity problem. The feasibility of this approach was confirmed by Kim et al.,[30] who recently used a similar method to control the regioselectivity of cycloisomerization reactions of *o*-propargylbiaryls.

With these considerations in mind, we reduced biaryl aldehyde **26** to biaryl alcohol **27** with $NaBH_4$ in methanol, and subsequent bromination with PBr_3 in CH_2Cl_2 cleanly gave **28** (Scheme 6). A simple copper-promoted coupling reaction[30,31] of biaryl bromide **28** with ethyl propiolate smoothly gave *o*-propargylbiaryl **29**. Refluxing **29** in 1,2-DCE readily provided 6-*exo-dig* product **30** with nearly quantitative yield, and none of the 7-*endo-dig* product was detected. Moreover, only one regioisomer was found, which demonstrates that the phenyl ring preferred to attack the alkyne at the less hindered position. After the oxidation state of the side chain was changed by reduction and oxidation reactions, **30** was readily converted to acetaldehyde **31** in one pot.

We next allowed aldehyde **31** to react with the *tert*-butylsulfinamide auxiliary to complete our synthesis of **4** (Scheme 7). Use of the previously described condensation conditions afforded compound **33**, and subsequent asymmetric allylation of the C═N bond followed by smooth removal of the auxiliary group afforded homoallyl amine **35**, which was protected with a Cbz group (**36**). Changing the oxidation state of the double bond under hydroboration−oxidation conditions gave the primary alcohol, which was mesylated without purification to give compound **37** in high yield. Intermediate 4-(arylmethyl)pyrrolidine **38** was obtained through intramolecular S_N2 substitution and the corresponding deprotection process. Finally, **4** was synthesized via a Pictet−Spengler annulation reaction in 74% yield; the specific rotation {$[\alpha]_D^{22}$ = −90.4 (*c* = 1, $CHCl_3$)} and ^1H and ^{13}C NMR spectra were in agreement with those reported in the literature.[11c]

CONCLUSION

In summary, we accomplished a collective asymmetric synthesis of four phenanthroindolizidine and phenanthroquinolizidine natural products: (−)-antofine, (−)-cryptopleurine, (−)-tylophorine, and (−)-tylocrebrine. The key steps were as follows: (1) facile asymmetric allylation of a C═N bond to generate a chiral homoallyl amine intermediate, (2) construction of the pyrrolidine and piperidine rings via a common building block, and (3) most notably, a quantitative $InCl_3$-catalyzed cycloisomerization of an *o*-propargylbiaryl compound to afford the C5-methoxy-substituted phenanthrene ring system of (−)-tylocrebrine. This strategy offers a practical approach to the synthesis of phenanthrene derivatives with other substitution patterns.

EXPERIMENTAL SECTION

General Information. All chemicals were of analytical grade, and anhydrous solvents were prepared by standard methods before use. ^1H NMR and ^{13}C NMR spectra were obtained by using a 400 MHz NMR spectrometer with $CDCl_3$ or DMSO-d_6 as the solvent. Melting points were uncorrected. High-resolution mass spectrometry (HRMS) analysis was performed with an FTICR-MS spectrometer. Optical rotations were measured with an auto digital polarimeter.

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Compound 12a. To a stirred solution of 10-(bromomethyl)-2,3,6-trimethoxyphenanthrene (**13a**) (6.7 g, 18.55 mmol) in anhydrous DMF (300 mL) was added NaCN (1.36 g, 27.82 mmol) in one portion, and the mixture was stirred overnight. Water (600 mL) was added, and the solution was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give **12a** as a white solid (4.9 g, 86%): mp 192−193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.85 (s, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.71 (s, 1H), 7.23 (d, J = 8.8 Hz, 1H), 7.16 (s, 1H), 4.13 (s, 3H), 4.10 (s, 2H), 4.08 (s, 3H), 4.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 149.7, 149.1, 131.0, 130.1, 125.4, 125.2, 124.8, 124.7, 120.7, 117.7, 115.8, 104.0, 103.9, 103.3, 56.0, 55.9, 55.5, 22.3; HRMS (ESI) m/z calcd for $C_{19}H_{18}NO_3$ $[M + H]^+$ 308.1281, found 308.1284.

Compound 12b. Intermediate **12b** was synthesized from 9-(bromomethyl)-2,3,6,7-tetramethoxyphenanthrene (10.4 g, 26.57 mmol) by using a procedure similar to that described for **12a** as a white solid (7.6 g, 85%): mp 239−241 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.77 (s, 1H), 7.69 (s, 1H), 7.23 (s, 1H), 7.13 (s, 1H), 4.14 (s, 3H), 4.13 (s, 3H), 4.12 (s, 2H), 4.07 (s, 3H), 4.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 149.3, 149.1, 149.05, 125.7, 125.0, 124.7, 124.4, 123.7, 121.3, 117.8, 108.2, 103.6, 103.3, 102.6, 56.1, 56.0, 56.0, 22.4; HRMS (ESI) m/z calcd for $C_{20}H_{20}NO_4$ $[M + H]^+$ 338.1387, found 338.1386.

Compound 11a. To a solution of compound **12a** (3.0 g, 9.76 mmol) in CH_2Cl_2 (200 mL) was added DIBALH (1.0 M in hexane, 14.65 mL, 14.65 mmol) at room temperature via a syringe. After the resulting solution was stirred for 2.5 h, 3 M HCl (50 mL) was added, and the solution was stirred vigorously for 1 h. The mixture was extracted with CH_2Cl_2, and the organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude aldehyde was purified by column chromatography (CH_2Cl_2:EtOAc = 40:1) to afford the aldehyde **11a** as a white solid (2.5 g, 83%): mp 185−186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.93 (s, 1H), 7.85 (s, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.57 (s, 1H), 7.22 (d, J = 8.8 Hz,1H), 7.20 (s, 1H), 4.12 (s, 3H), 4.05 (s, 2H), 4.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 158.4, 149.6, 148.9, 131.0, 129.9, 127.4, 126.6, 125.7, 124.8, 123.2, 115.7, 104.5, 103.9, 103.8, 56.0, 55.9, 55.5, 49.3; HRMS (ESI) m/z calcd for $C_{19}H_{19}O_4$ $[M + H]^+$ 311.1278, found 311.1278.

Compound 11b. Compound **11b** was synthesized from **12b** (1.0 g, 2.96 mmol) by using a procedure similar to that described for **11a** as a white solid (0.95 g, 95%): mp 206−208 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (t, J = 2.4 Hz, 1H), 7.86 (s, 1H), 7.80 (s, 1H), 7.56 (s, 1H), 7.22 (s, 1H), 7.21 (s, 1H), 4.15 (s, 3H), 4.14 (s, 3H), 4.07 (d, J = 2.4 Hz, 1H), 4.05 (s, 3H), 4.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 148.3, 148.0, 147.84, 147.78, 125.6, 125.0, 124.3, 123.9, 123.2, 122.8, 106.8, 103.3, 102.2, 101.6, 55.0, 54.9, 54.8, 54.8, 48.2; HRMS (ESI) m/z calcd for $C_{20}H_{21}O_5$ $[M + H]^+$ 341.1384, found 341.1385.

Compound 10a. To a solution of (*R*)-2-methyl-2-propanesulfinamide (0.39 g, 3.22 mmol) in CH_2Cl_2 (8 mL) was added anhydrous $CuSO_4$ (1.03 g, 6.44 mmol) followed by the aldehyde **11a** (1.2 g, 3.87 mmol). The mixture was stirred at room temperature for 48 h. Then the reaction mixture was filtered through a short pad of Celite, and the filter cake was washed with CH_2Cl_2. After concentration, the crude product was purified by column chromatography (CH_2Cl_2:EtOAc = 10:1) to afford **10a** as a yellow foam (1.33 g, 83%): mp 58−60 °C; $[\alpha]_D^{25}$ = 135.0 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, J_1 = 5.2 Hz, J_2 = 5.6 Hz, 1H), 7.94 (s, 1H), 7.85 (d, J = 2.4 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.55 (s, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.21 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 4.30 (dd, J_1 = 6.0 Hz, J_2 = 15.2 Hz, 1H), 4.19 (dd, J_1 = 4.8 Hz, J_2 = 15.6 Hz, 1H), 4.13 (s, 3H), 4.04 (s, 3H), 4.03 (s, 3H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 158.3, 149.4, 148.9, 130.8, 129.9, 126.4, 126.3, 126.0, 125.8, 124.9, 115.6, 104.9, 104.0, 103.9, 56.8, 56.0, 55.9, 55.5, 40.9, 22.3; HRMS (ESI) m/z calcd for $C_{23}H_{28}NO_4S$ $[M + H]^+$ 414.1734, found 414.1735.

Compound 10b. Compound **10b** was synthesized from **11b** (1.0 g, 2.94 mmol) by using a procedure similar to that described for **10a** as a yellow foam (0.90 g, 84%): mp 98−100 °C; $[\alpha]_D^{25}$ = 130.8 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (t, J = 5.2 Hz, 1H), 7.85 (s, 1H), 7.78 (s, 1H), 7.51 (s, 1H), 7.41 (s, 1H), 7.19 (s, 1H), 4.31 (dd, J_1 = 6.0 Hz, J_2 = 15.2 Hz, 1H), 4.19 (dd, J_1 = 5.2 Hz, J_2 = 15.6 Hz, 1H), 4.13 (s, 6H), 4.04 (s, 3H), 4.03 (s, 3H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 149.3, 149.1, 149.0, 148.8, 126.7, 126.2, 125.7, 125.3, 125.1, 124.2, 108.1, 104.9, 103.5, 102.8, 56.9, 56.1, 56.0, 55.9, 40.9, 22.4; HRMS (ESI) m/z calcd for $C_{24}H_{30}NO_5S$ $[M + H]^+$ 444.1839, found 444.1840.

Compound 9a. To a solution of activated zinc powder (0.42 g, 6.38 mmol), $In(OTf)_3$ (1.80 g, 3.51 mmol), and compound **10a** (1.32 g, 3.192 mmol) in freshly distilled THF (15 mL) under the protection of argon was added allyl bromide (0.56 mL, 6.384 mmol), and the solution was stirred overnight at room temperature. Brine (20 mL) was added to quench the reaction, and the solution was extracted with CH_2Cl_2. The organic phase was washed with brine and dried over Na_2SO_4. After concentration, the residue was purified by column chromatography (CH_2Cl_2:MeOH = 20:1) to afford **9a** as a white foam (1.30 g, 90%): mp 70−72 °C; $[\alpha]_D^{25}$ = 46.1 (c = 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.85 (d, J = 2.4 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.46 (s, 1H), 7.43 (s, 1H), 7.19 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 5.88−5.77 (m, 1H), 5.25−5.20 (m, 2H), 4.12 (s, 6H), 4.02 (s, 3H), 3.79−3.75 (m, 1H), 3.57 (d, J = 4.0 Hz, 1H), 3.47 (dd, J_1 = 6.0 Hz, J_2 = 14.0 Hz, 1H), 3.05 (dd, J_1 = 8.0 Hz, J_2 = 14.0 Hz, 1H), 2.54−2.48 (m, 1H), 2.39−2.31 (m, 1H), 1.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 149.5, 148.7, 134.4, 130.5, 129.6, 129.1, 126.8, 126.4, 125.7, 124.8, 119.4, 115.5, 104.7, 103.9, 103.8, 56.1, 56.0, 55.8, 55.58, 53.68, 39.9, 39.7, 22.5; HRMS (ESI) m/z calcd for $C_{26}H_{34}NO_4S$ $[M + H]^+$ 456.2203, found 456.2205.

Compound 9b. Compound **9b** was synthesized from **10b** (0.75 g, 1.69 mmol) by using a procedure similar to that described for **9a** as a white foam (0.80 g, 91%): mp 81−82 °C; $[\alpha]_D^{25}$ = 42.6 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.78 (s, 1H), 7.45 (s, 1H), 7.43(s, 1H), 7.17 (s, 1H), 5.88−5.78 (m, 1H), 5.25−5.20 (m, 2H), 4.13 (s, 3H), 4.12 (s, 3H), 4.11 (s, 3H), 4.03 (s, 3H), 3.78−3.75 (m, 1H), 3.60 (d, J = 3.6 Hz, 1H), 3.49 (dd, J_1 = 5.6 Hz, J_2 = 14.0 Hz, 1H), 3.06 (dd, J_1 = 8.0 Hz, J_2 = 14.0 Hz, 1H), 2.55−2.49 (m, 1H), 2.39−2.32 (m, 1H), 1.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 148.9, 148.8, 134.5, 129.8, 126.3, 126.0, 125.3, 124.9, 123.9, 119.3, 107.8, 104.7, 103.4, 102.7, 56.1, 56.0, 55.9, 55.8, 53.8, 39.8, 39.7, 22.6; HRMS (ESI) m/z calcd for $C_{27}H_{36}NO_5S$ $[M + H]^+$ 486.2309, found 486.2306.

Compound 8a. The sulfonamide **9a** (0.48 g, 1.05 mmol) was dissolved in MeOH (20 mL), and this solution was cooled to 0 °C. Concentrated hydrochloric acid (0.19 mL, 2.2 equiv) was added, and the reaction mixture was stirred at 0 °C for 10 h. Then the solvent was evaporated, water was added, and acid−base workup afforded the free amine, which was extracted with CH_2Cl_2. The organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography (CH_2Cl_2:EtOAc = 20:1) to give homoallyl amine **8a** as a yellow oil (0.35 g, 94%): $[\alpha]_D^{25}$ = −11.7 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.50 (s, 1H), 7.37 (s, 1H), 7.19 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 5.98−5.87 (m, 1H), 5.24−5.17 (m, 2H), 4.12 (s, 3H), 4.05 (s, 3H), 4.02 (s, 3H), 3.39−3.30 (m, 2H), 2.89 (dd, J_1 = 8.0 Hz, J_2 = 13.2 Hz, 1H), 2.41−2.35 (m, 1H), 2.31−2.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 149.3, 148.7, 135.0, 130.5, 129.7, 126.5, 126.0, 125.8, 124.9, 118.4, 115.4, 104.8, 103.9, 103.9, 55.98, 55.96, 55.6, 50.7, 41.7, 40.9; HRMS (ESI) m/z calcd for $C_{22}H_{26}NO_3$ $[M + H]^+$ 352.1907, found 352.1910.

Compound 8b. Compound **8b** was synthesized from **9b** (0.76 g, 1.57 mmol) by using a procedure similar to that described for **8a** as a white soild (0.52 g, 87%): mp 157−159 °C; $[\alpha]_D^{25}$ = 6.8 (c = 1.0, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.75 (s, 1H), 7.44 (s, 1H), 7.34(s, 1H), 7.17 (s, 1H), 5.95−5.89 (m, 1H), 5.23−5.16 (m, 2H), 4.12 (s, 3H), 4.11 (s, 3H), 4.03 (s, 6H), 3.35 (dd, J_1 = 3.2 Hz, J_2 = 13.6 Hz, 1H), 3.30−3.23 (m, 1H), 2.80 (dd, J_1 = 8.8 Hz, J_2 = 13.2 Hz, 1H), 2.39−2.33 (m, 1H), 2.28−2.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 148.8, 148.7, 148.4, 135.5, 131.0, 126.1, 125.3, 125.0, 123.7, 117.9, 107.8, 104.8, 103.3, 102.7, 56.0, 55.9, 55.8,

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50.6, 42.4, 41.6; HRMS (ESI) m/z calcd for $C_{23}H_{28}NO_4$ $[M + H]^+$ 382.2013, found 382.2018.

Compound 6a. To a vigorously stirred solution of homoallyl amine **8a** (0.34 g, 0.968 mmol) in THF (7 mL) and H_2O (3 mL) was added K_2CO_3 powder (0.20 g, 1.45 mmol) under an ice bath. After 10 min, CbzCl (250 mg, 1.45 mmol) was added via a syringe. The mixture was stirred at 0 °C for 2 h, diluted with water (20 mL), and extracted with CH_2Cl_2, and the organic layer was dried over Na_2SO_4. After concentration, the residue was purified by column chromatography (CH_2Cl_2:EtOAc = 1:1) to afford **6a** as a white solid (0.43 g, 92%): mp 177−178 °C; $[\alpha]_D^{25}$ = −14.2 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.88 (d, J = 2.0 Hz, 1H), 7.86 (s, 1H), 7.72 (d, J = 9.2 Hz, 1H), 7.41 (s, 1H), 7.39−7.29 (m, 5H), 7.19 (d, J = 8.8 Hz, 1H), 5.86−5.76 (m, 1H), 5.17−5.04 (m, 4H), 4.86−4.83 (m, 1H), 4.71 (s, 1H), 4.16 (s, 3H), 4.13 (s, 3H), 4.02 (s, 3H), 3.65−3.60 (m, 1H), 2.98−2.90 (m, 1H), 2.38−2.32 (m, 1H), 2.23−2.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 155.9, 149.7, 148.7, 136.5, 134.1, 130.6, 129.6, 129.3, 128.51, 128.48, 128.1, 127.6, 126.9, 126.8, 126.2, 125.7, 124.7, 118.5, 115.4, 105.5, 103.8, 103.7, 66.6, 56.4, 56.0, 55.5, 50.3, 39.4, 37.5; HRMS (ESI) m/z calcd for $C_{30}H_{32}NO_5$ $[M + H]^+$ 486.2275, found 486.2271.

Compound 6b. Compound **6b** was synthesized from **8b** (0.34 g, 0.891 mmol) by using a procedure similar to that described for **6a** as a white solid (0.38 g, 85%): mp 175−176 °C; $[\alpha]_D^{25}$ = −17.2 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.83 (s, 1H), 7.78 (s, 1H), 7.39 (s, 1H), 7.37−7.29 (m, 5H), 7.16 (s, 1H), 5.87−5.77 (m, 1H), 5.16−5.07 (m, 4H), 4.84 (d, J = 7.2 Hz, 1H), 4.18−4.11 (m, 10H), 4.03 (s, 3H), 3.63 (dd, J_1 = 5.2 Hz, J_2 = 14.0 Hz, 1H), 2.95 (dd, J_1 = 9.6 Hz, J_2 = 13.6 Hz, 1H), 2.38−2.32 (m, 1H), 2.23−2.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 149.0, 148.9, 148.8, 136.5, 134.1, 130.0, 128.5, 128.1, 126.0, 125.7, 125.6, 124.9, 124.0, 118.6, 107.9, 105.5, 103.2, 102.8, 66.6, 56.4, 56.1, 56.0, 55.8, 50.4, 39.4, 37.6; HRMS (ESI) m/z calcd for $C_{31}H_{34}NO_6$ $[M + H]^+$ 516.2381, found 516.2384.

Compound 15a. To a solution of Cbz-protected homoallyl amine **6a** (0.24 g, 0.49 mmol) in THF (5 mL) was slowly injected BH_3−THF (1 mL, 1 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. Then 3 M NaOH (3.0 mL) and 30% aqueous H_2O_2 (3 mL) were added successively. One hour later, saturated NaCl solution was added, and the mixture was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and then concentrated. The residue was purified by column chromatography (CH_2Cl_2:MeOH = 40:1) to give **15a** as a white solid (0.22 g, 89%): mp 156−158 °C; $[\alpha]_D^{25}$ = −10.6 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.80 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.40 (s, 1H), 7.38−7.28 (m, 5H), 7.18 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 5.10 (s, 2H), 4.14 (m, 4H), 4.12 (s, 3H), 4.02 (s, 3H), 3.60−3.53 (m, 3H), 2.96−2.89 (m, 1H), 1.72−1.66 (m, 2H), 1.54−1.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 156.2, 149.6, 148.7, 136.5, 130.6, 129.7, 129.2, 128.5, 128.1, 128.0, 126.8, 126.2, 125.8, 124.7, 115.4, 105.4, 103.8, 103.7, 66.6, 62.4, 56.3, 56.0, 55.6, 51.1, 40.6, 30.2, 28.9; HRMS (ESI) m/z calcd for $C_{30}H_{34}NO_6$ $[M + H]^+$ 504.2381, found 504.2376.

Compound 16a. To a mixture of **15a** (0.14 g, 0.28 mmol), Et_3N (42.2 mg, 0.42 mmol), and 4-DMAP (5.0 mg, 0.042 mmol) in CH_2Cl_2 (10 mL) was added methanesulfonyl chloride (47.8 mg, 0.42 mmol) at 0 °C. After 1 h, the solution was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (petroleum ether:EtOAc = 2:1) to give **16a** as a white solid (0.16 g, 99%): mp 131−132 °C; $[\alpha]_D^{25}$ = −6.7 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.76 (s, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.40 (s, 1H), 7.39−7.29 (m, 5H), 7.19 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 5.11 (t, J = 13.2 Hz, 2H), 4.75 (d, J = 9.2 Hz, 1H), 4.20−4.05 (m, 9H), 4.02 (s, 3H), 3.58 (dd, J_1 = 4.0 Hz, J_2 = 13.6 Hz, 1H), 2.90 (dd, J_1 = 9.2 Hz, J_2 = 13.2 Hz, 1H), 2.78 (s, 3H), 1.94−1.82 (m, 1H), 1.79−1.71 (m, 1H), 1.68−1.61 (m, 1H), 1.52−1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 156.1, 149.7, 148.8, 136.4, 130.6, 129.7, 128.8, 128.5, 128.1, 128.0, 126.6, 126.3, 125.7, 124.7, 115.5, 105.2, 103.8, 103.8, 69.4, 66.7, 56.3, 56.0, 55.5, 50.7, 40.7, 37.0, 29.7, 25.8; HRMS (ESI) m/z calcd for $C_{31}H_{39}N_2O_8S$ $[M + NH_4]^+$ 599.2422, found 599.2430.

Compound 5a. To a stirred solution of **16a** (0.26 g, 1.45 mmol) in THF (15 mL) was added NaH (0.05 g 2.08 mmol) at 0 °C. The solution was stirred at room temperature for 2 h, quenched with water, and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated. The residue was redissolved in CH_2Cl_2 (10 mL). To this solution was added (TMS)I (0.12 mL, 0.82 mmol), and the resulting solution was stirred at room temperature for 1.5 h. After methanol was added to quench the reaction, the solution was concentrated. The residue was purified by column chromatography to give **5a** as a yellow solid (0.11 g, 70% over two steps): mp 143−145 °C {lit.[8a] mp 144−146 °C}; $[\alpha]_D^{20}$ = −16.4 (c = 0.5, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 9.2 Hz, 1H), 7.69 (s, 1H), 7.60 (s, 1H), 7.48 (s, 1H), 7.20 (s, 1H), 7.15 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 4.21−4.14 (m, 1H), 4.07 (s, 3H), 4.01 (s, 3H), 3.87 (s, 3H), 3.84−3.79 (m, 1H), 3.62−3.54 (m, 1H), 3.40−3.30 (m, 2H), 2.20−2.13 (m, 1H), 2.02−1.91 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.0, 149.5, 148.9, 130.5, 129.7, 128.1, 125.6, 125.2, 124.6, 116.0, 105.0, 104.8, 104.1, 59.1, 56.0, 55.9, 55.6, 44.8, 34.9, 29.8, 22.8; HRMS (ESI) m/z calcd for $C_{22}H_{26}NO_3$ $[M + H]^+$ 352.1907, found 352.1914.

Compound 5b. Compound **5b** was synthesized from **6b** (0.42 g, 0.82 mmol) by using a procedure similar to the steps described previously for **5a** as a white solid (0.14 g, 65%): mp 150−152 °C; $[\alpha]_D^{20}$ = −9.6 (c = 1, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) 7.53 (s, 1H), 7.49 (s, 1H), 7.38 (s, 1H), 7.21 (s, 2H), 4.06 (s, 3H), 4.04 (s, 4H), 4.01 (s, 3H), 3.97 (s, 3H), 3.77 (dd, J_1 = 4.8 Hz, J_2 = 14.8 Hz, 1H), 3.58−3.51 (m, 1H), 3.39−3.32 (m, 1H), 3.21 (dd, J_1 = 9.2 Hz, J_2 = 14.0 Hz, 1H), 2.15−2.10 (m, 1H), 1.97−1.87 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.0, 148.9, 148.7, 148.6, 128.7, 125.6, 124.8, 124.7, 124.4, 123.7, 108.1, 104.7, 104.5, 103.7, 59.0, 55.9, 55.9, 55.4, 54.9, 44.1, 34.8, 29.6, 22.7. HRMS (ESI) m/z calcd for $C_{23}H_{28}NO_4$ $[M + H]^+$ 382.2013, found 382.2020.

(−)-Antofine (1). To a solution of **5a** (0.10 g, 0.28 mmol) in ethanol (10 mL) was added 37% formaldehyde (2 mL), followed by concd HCl (0.4 mL). The resulting solution was refluxed for 6 h in the dark, and this solution was concentrated to dryness in vacuo. The crude was redissolved in CH_2Cl_2, and water was added. The aqueous solution was extracted with CH_2Cl_2, and the organic phase was successively washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (CH_2Cl_2:MeOH = 20:1) and afforded **1** (65 mg, 65%) as a white solid: mp 203−204 °C {lit.[8a] mp 208−209 °C}; $[\alpha]_D^{20}$ = −109.0 (c = 1, $CHCl_3$) {lit.[8a] $[\alpha]_D^{20}$ = −117.0 (c = 1.75, $CHCl_3$), lit.[10] $[\alpha]_D^{22}$ = −108.2 (c = 0.71, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.30 (s, 1H), 7.21 (dd, J_1 = 2.4 Hz, J_2 = 9.2 Hz, 1H), 4.75 (d, J = 14.8 Hz, 1H), 4.11 (s. 3H), 4.07 (s. 3H), 4.02 (s. 3H), 3.81 (d, J = 14.8 Hz, 1H), 3.58−3.49 (m, 1H), 3.38 (dd, J_1 = 2.8 Hz, J_2 = 16.0 Hz, 1H), 3.08−2.97 (m, 1H), 2.79−2.50 (m, 2H), 2.35−2.26 (m, 1H), 2.14−2.06 (m, 1H), 2.01−1.94 (m, 1H), 1.88−1.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 149.4, 148.4, 130.2, 126.8, 125.7, 125.2, 124.1, 123.8, 123.5, 114.9, 104.6, 103.9, 103.7, 60.3, 56.0, 55.8, 55.5, 54.8, 53.3, 33.0, 31.0, 21.4; HRMS (ESI) m/z calcd for $C_{23}H_{26}NO_3$ $[M + H]^+$ 364.1907, found 364.1911.

(−)-Tylophorine (3). The same procedure as that for (−)-antofine was followed. A solution of 2-(arylmethyl)pyrrolidine **5b** (0.20 g, 0.52 mmol) in EtOH (10 mL), 37% formaldehyde (3 mL), and concd HCl (0.5 mL) was refluxed for 9 h in the dark. After workup, **3** was obtained as a white solid (0.17 g, 81%): mp 268−270 °C {lit.[9a] mp 272−274 °C}; $[\alpha]_D^{20}$ = −87.0 (c = 1, $CHCl_3$); {lit.[11c] $[\alpha]_D^{22}$ = −99 (c = 1, $CHCl_3$), lit.[28c] $[\alpha]_D^{20}$ = −77.6 (c = 0.65, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 2H), 7.32 (s, 1H), 7.17 (s, 1H), 4.64 (d, J = 14.4 Hz, 1H), 4.12 (s, 6H), 4.06 (s, 6H), 3.68 (d, J = 14.8 Hz, 1H), 3.51−3.47 (m, 1H), 3.41−3.37 (m, 1H), 2.96−2.89 (m, 1H), 2.54−2.44 (m, 2H), 2.30−2.22 (m, 1H), 2.09−2.02 (m, 1H), 1.96−1.91 (m, 1H), 1.82−1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 148.5, 148.4, 126.2, 125.8, 124.3, 123.6, 123.4, 103.9, 103.4, 103.3, 103.0, 60.2, 56.0, 55.9, 55.8, 55.1, 54.0, 33.7, 31.2, 21.6; HRMS (ESI) m/z calcd for $C_{24}H_{28}NO_4$ $[M + H]^+$ 394.2013, found 394.2017.

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Compound 7. To a solution of **8a** (0.45 g, 1.28 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (0.36 mL, 2.56 mmol) at 0 °C, followed by acryloyl chloride (0.17 g, 1.92 mmol) via a syringe. The solution was stirred at 0 °C for 1 h, and water was added. The aqueous solution was extracted with CH_2Cl_2, and the organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (CH_2Cl_2:MeOH = 40:1) to give **7** (500 mg, 96%) as a white solid: mp 170−171 °C; $[\alpha]_D^{25}$ = −34.0 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.93 (s, 1H), 7.86 (d, J = 2.0 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.42 (s, 1H), 7.19 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.27 (dd, J_1 = 1.2 Hz, J_2 = 16.8 Hz, 1H), 6.09 (dd, J_1 = 10.4 Hz, J_2 = 17.2 Hz, 1H), 5.87−5.78 m (m, 1H), 5.65 (dd, J_1 = 1.2 Hz, J_2 = 10.4 Hz, 1H), 5.60 (d, J = 7.6 Hz, 1H), 5.15 (s, 1H), 5.14−5.10 (m, 1H), 4.53−4.46 (m, 1H), 4.21 (s, 3H), 4.13 (s, 3H), 4.02 (s, 3H), 3.70 (dd, J_1 = 4.0 Hz, J_2 = 13.6 Hz, 1H), 2.93 (dd, J_1 = 9.6 Hz, J_2 = 13.6 Hz, 1H), 2.39−2.33 (m, 1H), 2.25−2.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 158.0, 149.8, 148.8, 134.2, 131.1, 130.7, 129.6, 129.2, 126.9, 126.28, 126.25, 125.7, 124.6, 118.5, 115.4, 105.8, 103.8, 103.6, 56.6, 56.0, 55.6, 48.7, 38.8, 37.1; HRMS (ESI) m/z calcd for $C_{25}H_{28}NO_4$ $[M + H]^+$ 406.2013, found 406.2010.

Compound 19. To a solution of **7** (0.46 g, 1.13 mmol) in CH_2Cl_2 (25 mL) was added Grubbs's second-generation catalyst **20** (48 mg, 0.057 mmol). The solution was stirred at room temperature for 10 h under argon. The solvent was evaporated, and the crude mixture was purified by column chromatography (CH_2Cl_2:MeOH = 40:1) to give target compound **19** as a white solid (0.40 g, 93%): mp 207−208 °C; $[\alpha]_D^{25}$ = 8.6 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.85 (d, J = 2 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.48 (s, 1H), 7.27 (s, 1H), 7.22 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.68−6.63 (m, 1H), 5.95 (d, J = 10.0 Hz, 1H), 5.46 (s, 1H), 4.13 (s, 3H), 4.12−4.08 (m, 1H), 4.05 (s, 3H), 4.03 (s, 3H), 3.40 (dd, J_1 = 5.6 Hz, J_2 = 14.0 Hz, 1H), 3.18 (dd, J_1 = 8.8 Hz, J_2 = 14.0 Hz, 1H), 2.55−2.48 (m, 1H), 2.44−2.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 158.3, 149.5, 149.0, 140.4, 130.7, 129.9, 127.1, 126.3, 126.0, 125.6, 125.2, 124.8, 115.7, 104.2, 104.2, 103.9, 56.03, 56.0, 55.6, 50.6, 39.5, 30.5; HRMS (ESI) m/z calcd for $C_{23}H_{24}NO_4$ $[M + H]^+$ 378.1700, found 378.1699.

Compound 5c. A solution of **19** (0.22 g, 0.583 mmol) in MeOH (20 mL) was stirred with activated Pd/C (25 mg, 10%) under H_2 (1 atm) at room temperature for 10 h, at which time TLC indicated complete consumption of starting material. The solution was filtered, and the filtrate was concentrated in vacuo. The residue was redissolved in THF (20 mL), and $LiAlH_4$ powder (50 mg, 1.32 mmol) was added slowly to this solution at 0 °C. Then the solution was refluxed for 1.5 h. After cooling, ice−water was added slowly, and the mixture was extracted with CH_2Cl_2. The organic phase was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (CH_2Cl_2:MeOH = 20:1) to give **5c** as a white solid (0.15 g, 70%): mp 147−149 °C {lit.[11d] mp 147−148 °C}; $[\alpha]_D^{20}$ = −19.2 (c = 1, $CHCl_3$) {lit.[8a] $[\alpha]_D^{20}$ = −20.6 (c = 1, $CHCl_3$), lit.[11d] $[\alpha]_D^{20}$ = −18.8 (c = 1, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.84 (d, J = 2.0 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.50 (s, 1H), 7.45 (s, 1H), 7.19 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 4.12 (s. 3H), 4.08 (s. 3H), 4.01 (s. 3H), 3.25 (dd, J_1 = 5.6 Hz, J_2 = 13.6 Hz, 1H), 3.16−3.06 (m, 2H), 3.03−2.95 (m, 1H), 2.55 (dd, J_1 = 3.2 Hz, J_2 = 11.6 Hz, 1H), 1.86−1.76 (m, 2H), 1.66−1.54 (m, 2H), 1.46−1.38 (m, 1H), 1.37−1.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 149.3, 148.7, 130.4, 129.7, 129.2, 126.6, 126.0, 125.8, 124.9, 115.4, 105.0, 103.9, 103.8, 56.4, 56.1, 56.0, 55.5, 46.7, 40.9, 32.6, 29.7, 25.5, 24.5; HRMS (ESI) m/z calcd for $C_{23}H_{28}NO_3$ $[M + H]^+$ 366.2064, found 366.2058.

(−)-Cryptopleurine (2). The same procedure as that for (−)-antofine was followed. To a solution of **5c** (100 mg, 0.27 mmol) in ethanol (6 mL) were successively added 37% formaldehyde (2 mL) and concd HCl (0.4 mL). The solution was refluxed for 11 h in the dark. After workup, **2** was obtained as a white solid (97 mg, 94%): mp 191−192 °C {lit.[11d] mp 195−197 °C}; $[\alpha]_D^{21}$ = −92.4 (c = 1, $CHCl_3$) {lit.[11d] $[\alpha]_D^{21}$ = −108.7 (c = 1, $CHCl_3$), lit.[8a] $[\alpha]_D^{20}$ = −87.2 (c = 1, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.90 (d, J = 2.8 Hz, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.26 (s, 1H), 7.20 (dd, J_1 = 2.4 Hz, J_2 = 9.2 Hz, 1H), 4.47 (d, J = 15.2 Hz, 1H), 4.11 (s. 3H), 4.07 (s. 3H), 4.01 (s. 3H), 3.67 (d, J = 15.2 Hz, 1H), 3.30 (d, J = 11.2 Hz, 1H), 3.12 (dd, J_1 = 3.6 Hz, J_2 = 16.4 Hz, 1H), 2.96−2.87 (m, 1H), 2.48−2.40 (m, 1H), 2.36−2.29 (m, 1H), 2.09−2.02 (m, 1H), 1.92−1.88 (m, 1H), 1.84−1.80 (m, 2H), 1.60−1.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 148.3, 147.3, 129.1, 125.4, 124.3, 123.3, 123.1, 122.6, 122.4, 113.8, 103.7, 102.8, 56.5, 55.1, 55.0, 54.9, 54.5, 33.5, 32.5, 24.8, 23.2; HRMS (ESI) m/z calcd for $C_{24}H_{28}NO_3$ $[M + H]^+$ 378.2064, found 378.2064.

Compound 23. 2-Bromo-3-hydroxy-4-methoxybenzylaldehyde (**22**) (7.0 g, 30.30 mmol) was dissolved in a solution of KOH (3.1 g, 55.45 mmol) in water (35 mL). To the vigorously stirred bright yellow solution was added dimethyl sulfate (6.1 g, 48.48 mmol) dropwise within a period of 10 min at 50 °C. After being stirred for another 10 min, the pale yellow solution containing the solid product was cooled and filtered. The precipitate was washed twice with 1 M NaOH and water and then dissolved in CH_2Cl_2. The resulting solution was washed with brine and dried over Na_2SO_4. After removal of solvent under reduced pressure, white solid **23** was obtained (6.8 g, 92%): mp 82−83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 7.75 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 3.97 (s, 3H), 3.89. (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 158.8, 146.5, 127.5, 126.6, 123.3, 111.1, 60.8, 56.4.

Compound 25. 4-Bromoveratrole (**24**) (5.0 g, 23.00 mol) was added to dry THF (250 mL) under argon, and the reaction mixture was cooled to −78 °C for 30 min. To this solution was added n-BuLi (2.4 M, 19.2 mL, 46.10 mmol) dropwise via a constant-pressure drop funnel. After addition of the n-BuLi, the solution was stirred for another hour. B(i-PrO)$_3$ (8.0 mL, 34.50 mmol) was added dropwise at −78 °C, and the reaction mixture was allowed to warm room temperature over 3−4 h. The solution was quenched with 3 M HCl to pH 2−3, and the mixture was extracted with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (petroleum ether:EtOAc = 1:1) to give **25** as a white solid (3.1 g, 74%): mp 224−225 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 3.95 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.6, 147.9, 127.7, 117.2, 110.9, 55.33, 55.26.

Compound 26. To a solution of 3,4-dimethoxyphenylboronic acid (**25**) (2.41 g, 13.24 mmol) and 2-bromo-3,4-dimethoxybenzylaldehyde (**23**) (3.25 g, 13.24 mmol) in toluene/ethanol/water (4:2:1, 140 mL) was added K_2CO_3 (3.66 g, 26.48 mmol). The solution was stirred and degassed with argon three times, and catalyst (dppf)$PdCl_2$ (0.48 g, 5% mol.) was added. The dark solution was warmed to reflux for 6 h with the total consumption of starting material. Then the solution was cooled to room temperature, water (100 mL) was added, and the solution was extracted with EtOAc. The combined organic phase was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (petroleum ether:EtOAc = 4:1) to afford **26** as a white solid (3.90 g, 98%): mp 125−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.92 (s, 1H), 6.88 (d, J = 8.0 Hz, 1H), 3.99 (s, 3H), 3.95 (s, 3H), 3.88 (s, 3H), 3.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 157.5, 148.8, 148.4, 146.2, 140.0, 128.4, 125.3, 124.5, 123.3, 113.7, 111.1, 110.5, 60.7, 56.0, 55.9, 55.8; HRMS (ESI) m/z calcd for $C_{17}H_{19}O_5$ $[M + H]^+$ 303.1227, found 303.1228.

Compound 27. To a stirred solution of aldehyde **26** (4.0 g, 13.24 mmol) from the previous step in methanol (300 mL) was added $NaBH_4$ (1.0 g, 26.46 mmol) at 0 °C, and the solution was stirred at room temperature. After TLC analysis showed the complete consumption of starting material (1 h), 3 M HCl (20 mL) was added to quench the reaction. This solution was preconcentrated and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated to afford **27** as a colorless oil (3.7 g, 93%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.4 Hz, 1H), 6.95 (s, 1H), 6.93 (s, 1H), 6.87 (m, 2H), 4.41 (s, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 3.86 (s, 3H), 3.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

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152.4, 148.4, 148.2, 135.7, 132.2, 128.3, 124.0, 121.8, 113.1, 111.3, 110.7, 63.1, 60.7, 55.8, 55.8; HRMS (ESI) m/z calcd for $C_{17}H_{20}NaO_5$ $[M + Na]^+$ 327.1203, found 327.1201.

Compound 28. To a stirred solution of 2-(3,4-dimethoxyphenyl)-3,4-dimethoxybenzyl alcohol (**27**) (3.6 g, 11.83 mmol) in dry CH_2Cl_2 (300 mL) at 0 °C was added dropwise a solution of PBr_3 (3.84 g, 14.20 mmol) in CH_2Cl_2 (15 mL). The solution was stirred at room temperature for 3 h, and ice−water was added. This mixture was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered, and concentrated to give **28** as a colorless oil (4.05 g, 93%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.4 Hz, 1H), 6.97−6.92 (m, 4H), 4.31 (d, J = 3.2 Hz, 2H), 3.95 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 148.3, 148.2, 146.7, 136.7, 129.1, 127.8, 126.4, 121.8, 113.0, 111.59, 110.60, 60.7, 55.8, 55.8, 55.8, 33.1; HRMS (ESI) m/z calcd for $[C_{17}H_{19}BrO_4 - Br]^+$ 287.1278, found 287.1283.

Compound 29. To a solution of compound **28** (200 mg, 0.54 mmol) in dry acetonitrile (3 mL) were successively added CuI (104 mg, 0.54 mmol), K_2CO_3 (75.3 mg, 0.54 mmol), $(n\text{-Bu})_4NI$ (201 mg, 0.54 mmol), and ethyl propiolate (165 μL, 1.63 mmol), and the mixture was stirred at 75 °C for 5 h. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (petroleum ether:EtOAc = 5:1) to give **29** as a yellow oil (160 mg, 77%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 3.6 Hz, 1H), 6.92 (d, J = 4.0 Hz, 1H), 6.83−6.79 (m, 2H), 4.21 (q, J = 7.2 Hz, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.54 (s, 3H), 3.40 (d, J = 7.2 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 152.1, 148.5, 148.2, 146.9, 136.1, 128.4, 125.6, 124.3, 121.7, 112.9, 111.5, 110.8, 87.4, 74.4, 61.8, 60.7, 55.9, 55.8, 55.8, 22.8, 14.0; HRMS (ESI) m/z calcd for $C_{22}H_{25}O_6$ $[M + H]^+$ 385.1646, found 385.1646.

Compound 30. To a solution of coupling product **29** (250 mg, 0.65 mmol) from the previous step in 1,2-DCE (10 mL) was added $InCl_3$ (14.4 mg, 0.065 mmol). Under the protection of argon, the mixture was warmed to reflux for 1 h, and TLC showed complete consumption of the starting material. The solution was cooled to room temperature and filtered through a pad of Celite, and then the filtrate was concentrated. The crude product was purified by column chromatography (petroleum ether:EtOAc = 5:1) to give **30** as a yellow oil (130 mg, quantative): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 7.61 (d, J = 11.6 Hz, 1H), 7.52 (s, 1H), 7.42 (s, 1H), 7.29 (d, J = 12.0 Hz, 1H), 4.16 (q, J = 9.2 Hz, 2H), 4.08 (s, 3H), 4.05 (s, 3H), 4.04 (s, 3H), 4.01 (s, 2H), 3.95 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 151.1, 148.7, 148.1, 145.7, 127.4, 127.3, 126.6, 124.9, 124.6, 124.1, 112.4, 109.1, 104.5, 61.0, 60.0, 56.5, 55.7, 55.7, 40.4, 14.2; HRMS (ESI) m/z calcd for $C_{22}H_{25}O_6$ $[M + H]^+$ 385.1646, found 385.1645.

Compound 31. To a stirred solution of the corresponding acetic ester **30** (2.39 g, 6.21 mmol) in THF (100 mL) was added $LiAlH_4$ (472 mg, 12.42 mmol), and the mixture was stirred at room temperature for 30 min. The reaction was quenched with diluted HCl and extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to yield the expected ethyl alcohol as an oil which was used in the next step without any purification. To a solution of the crude alcohol in DMSO (20 mL) was added IBX (5.22 g, 18.63 mmol), and the crimson solution was stirred at room temperature for 2 h. The solution was diluted with H_2O (100 mL), and the white precipitate was filtered out and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered, and purified by column chromatography (petroleum ether:EtOAc = 5:1) to give the corresponding aldehyde **31** as a yellow solid (1.5 g, 71% for two steps): mp 106−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, J = 2.8 Hz, 1H), 7.35 (s, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.55 (s, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.20 (s, 1H), 4.09 (s, 3H), 4.05 (s, 5H), 4.03 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 151.1, 148.7, 148.1, 145.6, 127.7, 127.2, 127.0, 124.6, 124.5, 123.9, 123.8, 112.4, 109.0, 104.0, 59.8, 56.3, 55.5, 49.1; HRMS (ESI) m/z calcd for $C_{20}H_{21}O_5$ $[M + H]^+$ 341.1384, found 341.1388.

Compound 33. Following the procedure of compound **10**, compound **33** was synthesized from **31** (1.0 g, 2.94 mmol) as a yellow oil (0.99 g, 91%): $[\alpha]_D^{25}$ = 131.2 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.23 (t, J = 5.6 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.50 (s, 1H), 7.41 (s, 1H), 7.29 (d, J = 8.8 Hz, 1H), 4.28 (dd, J_1 = 5.6 Hz, J_2 = 15.2 Hz, 1H), 4.16 (dd, J_1 = 4.8 Hz, J_2 = 15.6 Hz, 1H), 4.08 (s, 3H), 4.04 (s, 6H), 3.95 (s, 3H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 151.1, 148.6, 148.1, 145.7, 127.2, 127.1, 126.7, 126.6, 124.7, 123.9, 112.5, 109.1, 104.4, 59.9, 56.7, 56.4, 55.61, 55.59, 40.8, 22.2; HRMS (ESI) m/z calcd for $C_{24}H_{30}NO_5S$ $[M + H]^+$ 444.1839, found 444.1846.

Compound 34. Following the procedure of compound **9**, compound **34** was synthesized from **33** (0.90 g, 2.03 mmol) as a white solid (0.89 g, 91%): mp 154−155 °C; $[\alpha]_D^{25}$ = 38.8 (c = 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.44 (s, 2H), 7.28 (d, J = 8.8 Hz, 1H), 5.88−5.77 (m, 1H), 5.26−5.18 (m, 2H), 4.12 (s, 3H), 4.09 (s, 3H), 4.04 (s, 3H), 3.95 (s, 3H), 3.83−3.75 (m, 1H), 3.56 (d, J = 3.6 Hz, 1H), 3.47 (dd, J_1 = 6.0 Hz, J_2 = 14.0 Hz, 1H), 3.04 (dd, J_1 = 8.0 Hz, J_2 = 14.0 Hz, 1H), 2.55−2.48 (m, 1H), 2.39−2.31 (m, 1H), 1.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 148.7, 148.0, 145.7, 134.4, 129.7, 127.3, 127.2, 127.2, 124.6, 124.5, 123.7, 119.3, 112.5, 109.1, 104.2, 60.0, 56.5, 55.9, 55.73, 55.66, 53.5, 39.8, 39.7, 22.5; HRMS (ESI) m/z calcd for $C_{27}H_{36}NO_5S$ $[M + H]^+$ 486.2309, found 486.2310.

Compound 35. Following the procedure of compound **8**, compound **35** was synthesized from **34** (0.85 g, 1.75 mmol) as a colorless oil (0.63 g, 94%): $[\alpha]_D^{25}$ = −7.3 (c = 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.45 (s, 1H), 7.37 (s, 1H), 7.29 (d, J = 8.8 Hz, 1H), 5.98−5.88 (m, 1H), 5.26−5.15 (m, 2H), 4.09 (s, 3H), 4.05 (s, 3H), 4.03 (s, 3H), 3.95 (s, 3H), 3.40−3.30 (m, 2H), 2.84 (dd, J_1 = 8.4 Hz, J_2 = 13.2 Hz, 1H), 2.42−2.33 (m, 1H), 2.31−2.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 148.5, 148.0, 145.8, 135.3, 130.7, 127.4, 127.3, 126.4, 124.8, 124.6, 123.7, 118.1, 112.6, 109.2, 104.4, 60.0, 56.5, 55.72, 55.68, 50.4, 42.3, 41.5; HRMS (ESI) m/z calcd for $C_{23}H_{28}NO_4$ $[M + H]^+$ 382.2013, found 382.2020.

Compound 36. Following the procedure of compound **6**, compound **36** was synthesized from **35** (0.57 g, 1.49 mmol) as a colorless oil (0.73 g, 95%): $[\alpha]_D^{25}$ = −16.3 (c = 2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 7.87 (s, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.41−7.32 (m, 6H), 7.29 (s, 1H), 5.88−5.76 (m, 1H), 5.18−5.06 (m, 4H), 4.85 (d, J = 8.0 Hz, 1H), 4.71 (d, J = 6.0 Hz, 1H), 4.17 (s, 3H), 4.09 (s, 3H), 4.04 (s, 3H), 3.95 (s, 3H), 3.63 (dd, J_1 = 4.8 Hz, J_2 = 13.6 Hz, 1H), 2.91 (dd, J_1 = 9.6 Hz, J_2 = 13.6 Hz, 1H), 2.38−2.30 (m, 1H), 2.20−2.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 150.8, 148.9, 148.1, 145.8, 136.5, 134.1, 129.9, 128.53, 128.48, 128.1, 127.6, 127.5, 127.4, 126.9, 126.7, 124.5, 123.9, 118.6, 112.4, 108.9, 105.1, 66.6, 60.0, 56.6, 56.3, 55.7, 50.2, 39.4, 37.6; HRMS (ESI) m/z calcd for $C_{31}H_{34}NO_6$ $[M + H]^+$ 516.2381, found 516.2381.

Compound 37. Following the procedure of compounds **15** and **16**, compound **37** was synthesized from **36** (0.72 g, 1.40 mmol) as a white solid (0.55 g, 65% over two steps): mp 56−58 °C; $[\alpha]_D^{25}$ = −8.0 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 7.74 (s, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.39−7.32 (m, 6H), 7.28 (d, J = 9.2 Hz, 1H), 5.11 (t, J = 12.8 Hz, 2H), 4.76 (d, J = 8.4 Hz, 1H), 4.17−4.07 (m, 9H), 4.04 (s, 3H), 3.95 (s, 3H), 3.57 (dd, J_1 = 3.2 Hz, J_2 = 13.6 Hz, 1H), 2.88 (dd, J_1 = 9.6 Hz, J_2 = 13.2 Hz, 1H), 2.80 (s, 3H), 1.92−1.84 (m, 1H), 1.79−1.72 (m, 1H), 1.69−1.62 (m, 1H), 1.51−1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 150.9, 148.9, 148.1, 145.7, 136.4, 129.4, 128.5, 128.1, 128.0, 127.4, 127.2, 126.8, 124.6, 124.5, 123.8, 112.5, 109.0, 104.7, 69.4, 66.7, 60.0, 56.5, 56.2, 55.7, 50.5, 40.8, 37.0, 29.7, 25.8; HRMS (ESI) m/z calcd for $C_{32}H_{41}N_2O_9S$ $[M + NH_4]^+$ 629.2527, found 629.2524.

Compound 38. Following the procedure of compound **5**, compound **38** was synthesized from **37** (0.45 g, 0.74 mmol) as a yellow solid (0.25 g, 89% over two steps): mp 230 °C; $[\alpha]_D^{20}$ = −16.8 (c = 0.5, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.54 (s, 1H), 7.35 (s, 1H), 7.22 (d, J = 8.4 Hz, 1H), 4.26−4.19 (m, 1H), 4.14 (s, 3H), 4.05 (s, 3H), 4.03−4.00 (m, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 3.64−3.56 (m, 1H), 3.50 (dd, J_1 =

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10.0 Hz, J_2 = 13.6 Hz, 1H), 3.40−3.33 (m, 1H), 2.21−2.12 (m, 1H), 2.06−1.92 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.0, 148.7, 148.1, 145.2, 128.6, 126.7, 126.5, 125.9, 124.7, 124.0, 123.1, 113.4, 108.9, 104.7, 59.5, 59.0, 56.5, 55.7, 55.3, 44.8, 35.0, 29.8, 22.8; HRMS (ESI) m/z calcd for $C_{23}H_{28}NO_4$ $[M + H]^+$ 382.2013, found 382.2020.

(−)-Tylocrebrine (4). Following the procedure of (−)-antofine (**1**) and (−)-tylophorine (**3**), (−)-tylocrebrine was prepared from intermediate **38** (0.15 g, 0.39 mmol) as a yellow solid (0.12 g, 74%): mp 207−209 °C {lit.[26] mp 218−220 °C}; $[\alpha]_D^{22}$ = −90.4 (c = 1, $CHCl_3$) {lit.[11c] $[\alpha]_D^{22}$ = −105 (c = 1, $CHCl_3$), lit.[26] $[\alpha]_D^{24}$ = −45 ± 2 (c = 0.74, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.30 (s, 1H), 7.27 (d, J = 8.8 Hz, 1H), 4.70 (d, J = 14.8 Hz, 1H), 4.07 (s, 3H), 4.06 (s, 3H), 4.03 (s, 3H), 3.92 (s, 3H), 3.72 (d, J = 14.8 Hz, 1H), 3.49 (t, J = 7.6 Hz, 1H), 3.32 (s, J = 15.6 Hz, 1H), 2.96 (dd, J_1 = 10.8 Hz, J_2 = 15.2 Hz, 1H), 2.65−2.46 (m, 2H), 2.31−2.20 (m, 1H), 2.11−2.01 (m, 1H), 1.99−1.89 (m, 1H), 1.87−1.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 148.6, 147.8, 146.2, 127.7, 126.2, 125.5, 123.5, 123.3, 118.7, 112.0, 109.0, 103.4, 60.2, 60.0, 56.4, 55.7, 54.9, 53.7, 33.3, 31.0, 21.5; HRMS (ESI) m/z calcd for $C_{24}H_{28}NO_4$ $[M + H]^+$ 394.2013, found 394.2021.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of compounds **1**−**12**, **15**−**17**, **19**, **22**, **23**, **25**−**31**, and **33**−**38**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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