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An Enantioselective Strategy for the Synthesis of (*S*)-Tylophorine via One-Pot Intramolecular Schmidt/Bischler−Napieralski/Imine-Reduction Cascade Sequence

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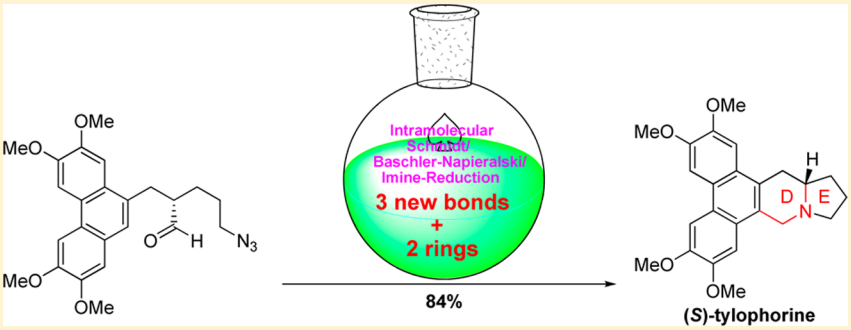
Supporting Information



ABSTRACT: A novel enantioselective strategy for the total synthesis of (*S*)-tylophorine was developed in an overall yield of 48% with more than 99% ee from readily avaliable azido acid and phenanthryl alcohol. This route features an Evans stereoselective alkylation and an unprecedented one-pot intramolecular Schmidt/Bischler−Napieralski/imine-reduction cascade sequence, in which three new bonds and two rings formed in 84% yield. The intramolecular Schmidt rearrangement of the azido aldehyde was proved to be racemization-free.

Phenanthroindolizidine and phenanthroquinolizidine alkaloids represent a group of pentacyclic natural products, which were mainly isolated from the *Tylophora*, *Pergularia*, and *Cynanchum* species.[1] To date, more than 60 members of this class are known and have inspired increasing interest over the past decade for their newfound potent anticancer[2] and anti-inflammatory activities.[3] For example, tylophorine arrests carcinoma cells in the G1 phase by downregulation of cyclin A2 expression,[4] while (*R*)-antofine exerts its cytotoxic effects via cell cycle arrest in the G2/M phase.[5] A surprising and interesting find is that the unnaturally occurring (*S*)-tylophorine is much more potent for the inhibition of cancer cell growth.[6] Consequently, a number of synthetic strategies were developed,[7] which include using chiral building blocks,[7b−d] chiral auxiliary approach,[7a] enantioselective phase-transfer alkylation, and enantioselective catalysis for intramolecular alkene carboamination.[7e] Intramolecular Diels−Alder strategy was also employed, in which the DE ring was constructed in one step. As a continuation of studies on the synthesis and bioactivity evaluation,[8] herein we report an unprecedented one-pot intramolecular Schmidt/Bischler−Napieralski/imine-reduction cascade sequence to construct the DE ring of phenanthroindolizidine alkaloid.

Since the first intramolecular Schmidt reaction was reported in 1991,[9] it has become an important and effective strategy to construct ring systems featuring a nitrogen atom at the ring fusion position.[10] In most applications of this valuable chemistry, ketones[11] and carbocations[12] (generally generated from tertiary alcohols and olefins) are usually used as electrophilic components, and seminal work has been done in this area by Aubé[9,11,13] and Pearson.[12,14] In contrast, little work has been done on the corresponding chemistry of aldehyde, and it was always less efficient, mainly due to elimination and the competition resulting from hydride or alkyl migration.[15] Besides the concerns mentioned above, stereochemistry in the intramolecular Schmidt rearrangement of aldehyde was also an important noteworthy consideration. As shown in Scheme 1, azido aldehyde (**I**), when activated by Lewis acid or Bronsted acid, could lead to the formation of azidohydrin (**III**) intermediate, which would furnish formamide (path a, alkyl migration) and/or lactam (path b, hydride migration). Although there was no precedent to the best of our knowledge, we believe the resulting formamide or lactam, if activated by suitable reagent, can produce electrophilic imine cation **IV** or imine **V** respectively, which would be a valuable employable synthetic intermediate in cascade reaction.

On the basis of the rational analysis, we designed a one-pot intramolecular Schmidt/Bischler−Napieralski/imine-reduction cascade sequence to construct the DE ring of phenanthroindo-

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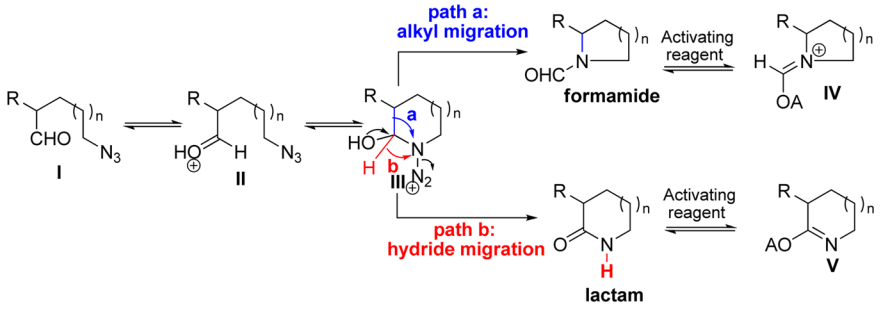
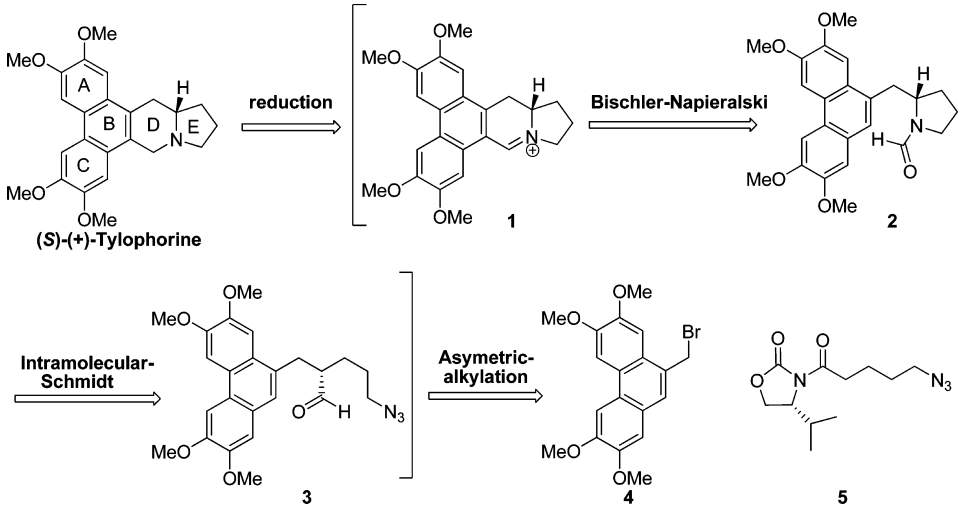
Scheme 1. Intramolecular Schmidt Rearrangement of Azido Aldehyde



Scheme 2. Retrosynthesis of (*S*)-Tylophorine

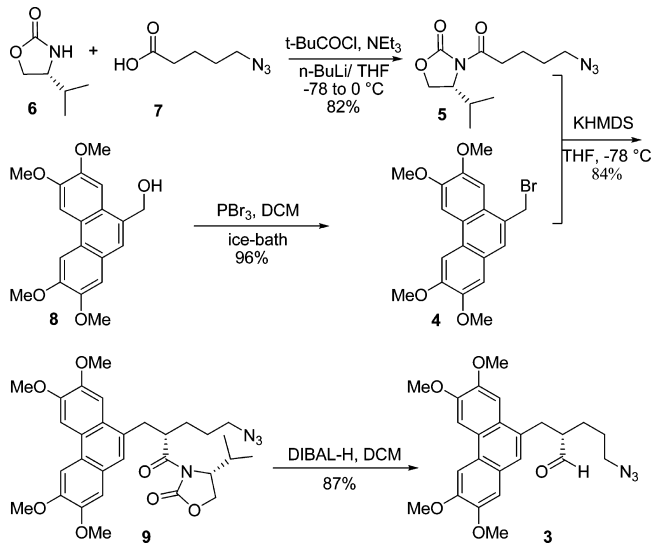


lizidine alkaloids. Using (*S*)-tylophorine as an example, retrosynthetic analysis is shown in Scheme 2. The target molecule could be accessible via reduction from imine cation **1**, which was envisioned to be produced from formamide **2** through Bischler−Napieralski reaction, while formamide **2** could be derived from azido aldehyde **3** via Schmidt reaction. The stereogenic center of azido aldehyde **3** was planed to introduce with the assistance of Evans stereoselective alkylation from readily available phenanthryl bromide **4** and azido *N*-acylated oxazolidinone **5**.

Synthesis of the azido aldehyde **3** started with the coupling of the known auxiliary **6**[16] and azido acid **7**,[17] which gave *N*-acylated oxazolidinone **5** under standard conditions[18] (Scheme 3). Phenanthryl bromide **4**[19] was prepared using the reported method and used immediately without further purification due to its instability. Stereoselective alkylation of compound **5** went smoothly when KHMDS was used as base to give compound **9** as a single diastereomer (determined by NMR) after purification by column chromatography, while other bases such as LDA, LiHMDS, and NaHMDS proved to be less effective. After reductive removal of the auxiliary with DIBAL-H, azido aldehyde **3** was obtained.

With the key intermediate **3** in hand, we first investigated the regioselectivity and stereochemistry of the intramolecular Schmidt rearrangement (Scheme 4). After extensive conditions screening, $TiCl_4$ and CF_3COOH were found to be effective for promotion of the reaction, which furnished the desired formamide **2** (formed via alkyl migration), and it is worth noting that formamide **2** was stable enough for column chromatographic purification. Fortunately, formation of lactam

Scheme 3. Synthesis of Key Intermediate Azido Aldehyde 3



(formed via H migration) was not detected, and no racemization was found in this step.[20] In order to execute the desired cascade sequence in one pot, $(CF_3CO)_2O$ was chosen as the activating reagent for the Bischler−Napieralski reaction. As expected, formamide **2** vanished 20 min after addition of $(CF_3CO)_2O$, and then sodium borohydride was added to the reaction mixture, which furnished (*S*)-tylophorine in 84% isolated yield based on azido aldehyde **3** with an enantiomeric excess of more than 99% (HPLC, Chiral AD, see Supporting

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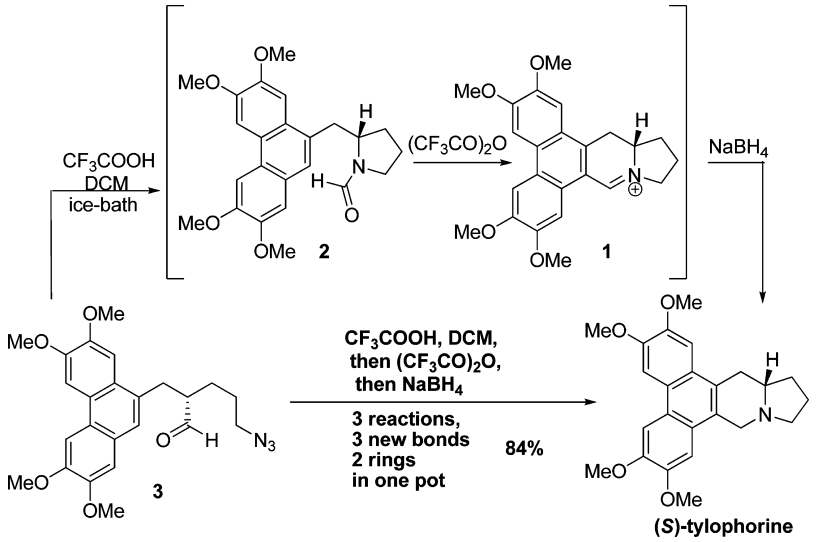
Scheme 4. Completion of the Synthesis of (*S*)-Tylophorine



Information). The spectrum of our synthesized sample matched well with reported data, and the optical rotation ($[\alpha]_D^{25}$ +82.8 (*c* 0.5, $CHCl_3$)) is slightly higher than the reported value (lit.[7d] $[\alpha]_D^{22}$ +78.9 (*c* 0.5, $CHCl_3$)).

In summary, we have developed a concise and novel enantioselective strategy for the total synthesis of (*S*)-tylophorine. Key features include (1) a stereoselective alkylation to introduce the stereogenic center, which also enables the synthesis of the antipode by converting the Evans auxiliary; (2) an unprecedented one-pot Schmidt/Bischler–Napieralski/Imine-reduction cascade sequence, in which three new bonds and two rings formed in 84% yield; and (3) an intramolecular Schmidt rearrangement that was proved to be racemization-free, which may find further application in the synthetic chemistry.

EXPERIMENTAL SECTION

General Information. The melting points were determined with an X-4 binocular microscope melting-point apparatus and are uncorrected. ^{1}H NMR spectra were obtained by using Bruker AV 400 spectrometer. Chemical shifts (δ) are given in parts per million (ppm) and were measured downfield from internal tetramethylsilane. ^{13}C NMR spectra were recorded by using a Bruker AV 400 instrument (100 MHz) and $CDCl_3$ as solvent. Chemical shifts (δ) are reported in parts per million. High-resolution mass spectra were obtained with an FT-ICR MS spectrometer (Ionspec, 7.0 T). Optical rotations were measured with a Autopol IV auto digital polarimeter (Rudolph Research Analytical). The enantiomeric excesses were determined by HPLC with a Chiralcel AD-H column using an Agilent 1100 instrument. All anhydrous solvents were dried and purified by standard techniques just before use. All reagents were purchased from commercial suppliers without further purification. Reactions were monitored by thin layer chromatography on plates (GF254) using UV light as visualizing agent. If not noted otherwise, flash column chromatography used silica gel (200–300 mesh).

5-Azidopentanoic Acid (7).[16] To a solution of bromo acid methyl ester (1.94 g, 10 mmol) in acetone/water (15 mL/5 mL) was added sodium azide (1.3 g, 20 mmol), and then the reaction mixture was heated under reflux overnight. After removal of the solvent in vacuo, residue was partitioned between DCM and water. After separation, aqueous phase was extracted with DCM (50 mL × 3), and the combined organic extracts were washed with water, brine, dried over Na_2SO_4 and evaporated to dryness to give azido ester as colorless oils, which without further purification was dissolved in MeOH/water (25 mL/20 mL). KOH (1.12 g, 20 mmol) was added at 0 °C, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was evaporated in vacuo, and residue was partitioned between DCM and water. After extraction with DCM (50 mL × 2), the aqueous phase was acidified to pH 1 with 1N aqueous HCl and then extracted with EtOAc (50 mL × 3). The combined organic phase was dried over Na_2SO_4 and concentrated to dryness to give azido acid **7** (1.22 g, 85%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (t, *J* = 6.4 Hz, 1H), 2.41 (t, *J* = 7.2 Hz, 1H), 1.80–1.62 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 51.0, 33.2, 28.2, 21.8.

(*R*)-4-Isopropyloxazolidin-2-one (6).[17] To a solution of D-valinol (2.0 g, 20 mmol) in diethylcarbonate (4.76 g, 40 mmol) in a 50 mL round flask equipped with a short-path distillation apparatus was added potassium carbonate (0.28 g, 2 mmol). The reaction mixture was heated to 130 °C for 3 h. Brine (50 mL) was added to the residue and then extracted with DCM (50 mL × 2). After concentration in vacuo, a light yellow oil was obtained, to which ether (20 mL) was added. Compound **6** (2.03 g, 79%) precipitated as a white crystalline solid: mp 75–76 °C, lit.[17] 67–70 °C; $[\alpha]_D^{25}$ −14.2 (*c* 4.1, $CHCl_3$), lit.[17] $[\alpha]_D^{22}$ −13.1 (*c* 4.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 1H), 4.44 (t, *J* = 8.8 Hz, 1H), 4.10 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.61 (dd, *J* = 13.6, 6.8 Hz, 1H), 1.73 (dq, *J* = 13.6, 6.8 Hz, 1H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H).

(*R*)-3-(5-Azidopentanoyl)-4-isopropyloxazolidin-2-one (5). To a solution of compound **6** (5.2 g, 40 mmol) in THF (100 mL) was added *n*-BuLi (20 mL, 48 mmol, 2.4 M in THF) dropwise at −78 °C under an atmosphere of Ar. The mixture was stirred at this temperature for 30 min. In another flask, azide acid **7** (6.9 g, 48 mmol) and triethylamine (9.4 mL, 68 mmol) were taken in THF (150 mL) at 0 °C, to which pivaloyl chloride (6.3 g, 52 mmol) was added slowly. After 30 min of stirring at this temperature, the lithio-oxazolidinone was added to this freshly formed mixed anhydride. The mixture was quenched with saturated aqueous ammonium chloride and extracted with EtOAc (50 mL × 3). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (100 mL), saturated aqueous NH_4Cl (100 mL), and brine (100 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give compound **5** (8.2 g, 82%) as a coloress oil: $[\alpha]_D^{25}$ −68.2 (*c* 3.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50–4.38 (m, 1H), 4.28 (dd, *J* = 9.0, 2.8 Hz, 1H), 4.22 (dd, *J* = 9.0, 2.8 Hz, 1H), 3.32 (t, *J* = 6.5 Hz, 2H), 3.10–2.85 (m, 2H), 2.43–2.33 (m, 1H), 1.82–1.63 (m, 4H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 154.1, 77.4, 77.1, 76.8, 63.4, 58.4, 51.1, 34.9, 28.4, 28.3, 21.5, 18.0, 14.7; HRMS (ESI) calcd for $C_{11}H_{18}N_4NaO_3$ $(M + Na)^+$ 277.1271, found 277.1269.

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9-(Bromomethyl)-2,3,6,7-tetramethoxyphenanthrene (4). To a solution of compound **8** (4.9 g, 15 mmol) in DCM (300 mL) was added PBr_3 (6.1 g, 22.5 mmol in DCM (40 mL)) dropwise through a constant pressure funnel at 0 °C. The reaction mixture was stirred at this temperature for 2 h and then quenched with ice−water (200 mL). After separation, the organic layer was washed with ice−water (200 mL × 5) and brine (200 mL), dried over Na_2SO_4, and concentrated in vacuo to give bromide **4** (5.6 g, 14.4 mmol, 96%) as a white solid: mp 207−209 °C, lit.[19] 195−197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.68 (s, 1H), 7.60 (s, 1H), 7.47 (s, 1H), 7.12 (s, 1H), 4.93 (s, 2H), 4.10 (s, 3H), 4.09 (s, 3H), 4.08 (s, 3H), 3.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 149.3, 149.0, 148.7, 128.7, 126.4, 125.6, 125.2, 124.0, 108.4, 104.9, 103.3, 102.7, 56.1, 56.1, 56.0, 55.9, 33.8.

(*R*)-3-((*S*)-5-Azido-2-((2,3,6,7-tetramethoxyphenanthren-9-yl)methyl)pentanoyl)-4-isopropyloxazolidin-2-one (9). To a solution of compound **5** (0.8 g, 3.1 mmol) in THF (50 mL) was added KHMDS (3.4 mL, 3.4 mmol, 1 M in THF) via a syringe dropwise at −78 °C under an atmosphere of Ar. One hour later, bromide **4** (1.2 g, 2.9 mmol in THF (80 mL)) was added slowly via a syringe. The reaction mixture was stirred at this temperature overnight and then quenched with aqueous saturated ammonium chloride. After separation, the aqueous layer was extracted with EtOAc (100 mL × 3). The combined organic phase was washed with brine (100 mL × 2), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give compound **9** (1.4 g, 2.4 mmol, 84%) as a white solid: mp 69−71 °C; $[\alpha]_D^{25}$ −26.5 (*c* 1.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.75 (s, 1H), 7.56 (s, 1H), 7.43 (s, 1H), 7.14 (s, 1H), 4.63−4.53 (m, 1H), 4.49−4.42 (m, 1H), 4.20 (t, *J* = 8.8 Hz, 1H), 4.11 (s, 3H), 4.11 (s, 6H), 4.10−4.06 (m, 1H), 4.01 (s, 3H), 3.58 (dd, *J* = 13.2, 8.0 Hz, 1H), 3.20 (t, *J* = 6.8 Hz, 2H), 3.12 (dd, *J* = 13.2, 8.0 Hz, 1H), 2.12−2.01 (m, 1H), 1.94−1.83 (m, 1H), 1.64−1.43 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 153.6, 149.1, 149.0, 148.89, 148.8, 130.1, 126.1, 126.0, 125.4, 124.9, 124.0, 108.0, 105.1, 103.4, 102.8, 62.9, 58.4, 56.2, 56.1, 56.0, 56.0, 51.2, 42. 6, 36.8, 29.0, 28.3, 26.8, 17.9, 13.8; HRMS (ESI) calcd for $C_{30}H_{36}N_4NaO_7$ $(M + Na)^+$ 587.2476, found 587.2479.

(*S*)-5-Azido-2-((2,3,6,7-tetramethoxyphenanthren-9-yl)-methyl)pentanal (3). To a solution of compound **9** (0.60 g, 1.06 mmol) in DCM (80 mL) was added DIBAL-H (3.2 mL, 3.2 mmol, 1 M in hexane) at −78 °C under an atmosphere of Ar. The reaction mixture was stirred at this temperature overnight and then quenched with aqueous saturated ammonium chloride. After separation, the aqueous layer was extracted with DCM (50 mL × 2). The combined organic phase was washed with brine (100 mL × 2), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give azido aldehyde **3** (0.40 g, 87%) as a white solid: mp 86−88 °C; $[\alpha]_D^{25}$ −22.2 (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (d, *J* = 2.4 Hz, 1H), 7.86 (s, 1H), 7.78 (s, 1H), 7.42 (s, 1H), 7.32 (s, 1H), 7.18 (s, 1H), 4.14 (s, 3H), 4.13 (s, 3H), 4.06 (s, 3H), 4.04 (s, 3H), 3.51 (dd, *J* = 14.6, 7.0 Hz, 1H), 3.32−3.20 (m, 2H), 3.09 (dd, *J* = 14.6, 7.0 Hz, 1H), 2.90−2.82 (m, 1H), 1.94−1.84 (m, 1H), 1.77−1.67 (m, 2H), 1.65−1.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 149.2, 149.0, 148.8, 129.9, 126.1, 125.2, 125.2, 124.9, 123.9, 108.1, 104.4, 103.7, 102.8, 56.1, 56.1, 55.9, 55.9, 51.3, 51.2, 33.2, 26.5, 26.4; HRMS (ESI) calcd for $C_{24}H_{26}N_3O_5$ $(M - H)^-$ 436.1878, found 436.1874.

(*S*)-Tylophorine. To a solution of azido aldehyde **3** (150 mg, 0.34 mmol) in DCM (30 mL) was added CF_3COOH (1.5 mL) in a dropwise manner at room temperature. Thirty minutes later, azido aldehyde **3** vanished (monitored by TLC), and then $(CF_3CO)_2O$ (1.5 mL) was added to the reaction mixture dropwise. Twenty minutes later, aqueous KOH was added until the pH of the reaction mixture was about 5, and then sodium borohydride (42 mg, 1.1 mmol) was added in one portion. Thirty minutes later, the reaction was quenched with water (20 mL). After separation, the aqueous layer was extracted with DCM (20 mL × 2), and the combined organic phase was washed with brine (20 mL × 2), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on basic Al_2O_3 to give (*S*)-tylophorine (112 mg, 0.28 mmol) as a white solid: mp 281−283 °C, lit.[7b] mp 280−283 °C, lit.[8b] mp 282−284 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 2H), 7.31 (s, 1H), 7.16 (s, 1H), 4.63 (d, *J* = 14.7 Hz, 1H), 4.12 (s, 6H), 4.06 (s, 6H), 3.68 (d, *J* = 14.6 Hz, 1H), 3.48 (t, *J* = 8.1 Hz, 1H), 3.37 (d, *J* = 16.1 Hz, 1H), 2.97−2.86 (m, 1H), 2.48 (d, *J* = 8.8 Hz, 2H), 2.25 (d, *J* = 5.6 Hz, 1H), 2.04 (d, *J* = 7.5 Hz, 1H), 1.94 (s, 1H), 1.79 (d, *J* = 9.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 148.5, 148.4, 126.3, 126.1, 125.9, 124.4, 123.6, 123.4, 104.0, 103.4, 103.3, 103.1, 60.2, 56.1, 55.9, 55.8, 55.2, 54.0, 33.8, 31.3, 21.6; $[\alpha]_D^{25}$ +82.8 (*c* 0.5, $CHCl_3$), lit.[7b] $[\alpha]_D^{22}$ +78.9 (*c* 0.5, $CHCl_3$); ee >99%, determined by HPLC; HRMS (ESI) calcd for $C_{24}H_{29}NO_4$ $(M + H)^+$ 394.2018, found 394.2022.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for compounds **3**−**7**, **9**, and (*S*)-tylophorine, and HPLC for (*S*)-tylophorine and racemic tylophorine. 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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