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# An enantioselective strategy for the total synthesis of (*S*)-tylophorine *via* catalytic asymmetric allylation and a one-pot DMAP-promoted isocyanate formation/ Lewis acid catalyzed cyclization sequence†

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A new asymmetric total synthesis of a phenanthroindolizidine alkaloid (*S*)-tylophorine is reported, which features a catalytic asymmetric allylation of aldehydes and an unexpected one-pot DMAP promoted isocyanate formation and Lewis acid catalyzed intramolecular cyclization reaction. In addition, White's direct C–H oxidation catalyst system converting monosubstituted olefins to linear allylic acetates was also employed for late-stage transformation.

## Introduction

Phenanthroindolizidine alkaloids are a series of natural products that exist primarily in Asclepiadaceae and Moracea plant families.[1] In 1935, the first phenanthroindolizidine alkaloid (*R*)-tylophorine (Fig. 1) was reported.[2] Subsequently, over 60 members of this family and their biological activities were reported. Because of their interesting structures and profound activities, such as anti-tumor and anti-inflammatory activities,[3] great attention has been paid to their medical research over the past decade.[4] For example, although both tylophorine and antofine exhibit good inhibitory effects against cancer cells, they express their cytotoxic effects in totally different ways.[5,6] Another interesting phenomenon is that the antipode of naturally occurring (*R*)-tylophorine was much effective in arresting the growth of cancer cells.[7] Therefore, great attention has been paid to the development of synthetic strategies.[7,8] Because there is a nitrogen atom positioned at the α position of the chiral centers of these alkaloids, readily available chiral building blocks such as α-amino acids and their derivatives were usually employed as starting materials.[8c–e] Some other impressive enantioselective strategies include: (1) the chiral auxillary approach;[8f,q] (2) enantioselective catalytic phase-transfer alkylation;[8a] (3) organocatalyzed enantioselective functionalization;[8g] (4) transition-metal catalyzed asymmetric carboamination of alkenes;[8i] and (5) the stereospecific Overman rearrangement.[8b]

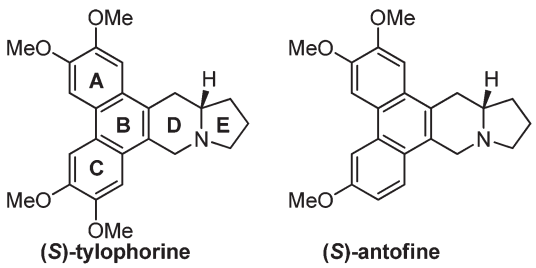


**Fig. 1** Structure of representative phenanthroindolizidine alkaloids.

As a continuation of our studies on the total synthesis and biological evaluation of phenanthroindolizidine alkaloids,[8d,j,n,q,9] herein, we describe the development of a novel enantioselective strategy for the synthesis of (*S*)-tylophorine, which features a catalytic Keck asymmetric allylation to install the stereogenic center, an unexpected one-pot DMAP-promoted isocyanate formation followed by Lewis acid catalyzed cyclization to construct the D ring, and White's direct C–H oxidation of terminal alkenes to execute a late-stage functional group transformation.

## Results and discussion

Enantioselective addition of allylic nucleophiles to aldehydes is an important tool for the synthesis of chiral secondary homoallylic alcohols. The most efficient and widely used way to achieve this transformation is to use allylic organometallic

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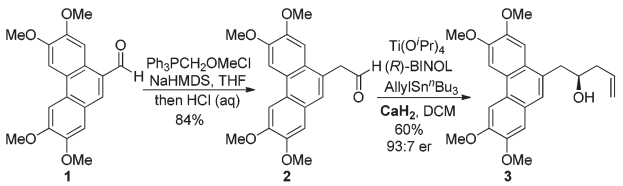
reagents in the presence of chiral Lewis acid catalysts, among which the $Ti^{(IV)}$-BINOL complex first reported by the Mikami and Keck group independently has been studied extensively.[10] We envisaged that this powerful synthetic methodology could be utilized in the total synthesis of phenanthroindolizidine alkaloids to introduce the stereocenters.

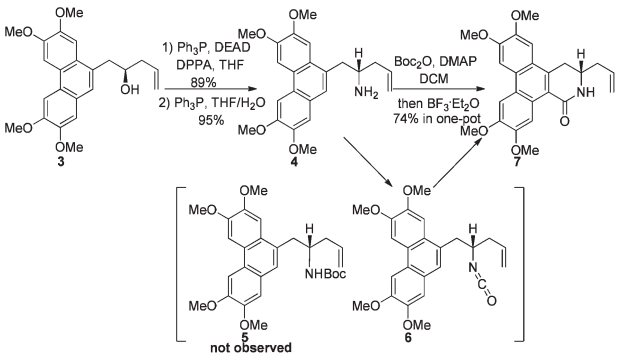
Using a similar modified synthetic procedure developed by us,[8g] the known phenanthryl aldehyde **1** could be readily prepared. The precursor **2** for the catalytic enantioselective allylation could be obtained from readily available aldehyde **1** *via* the Wittig reaction followed by acidic hydrolysis in 84% yield. It is worth noting that NaHMDS was proved to be the optimal base for the Wittig reaction; other bases such as *n*-BuLi, LDA, *t*-BuOK, and KHMDS gave inferior results or no products. With the phenanthryl acetaldehyde **2** in hand, we began to investigate the catalytic asymmetric allylation. Although reactions of aliphatic, aromatic and unsaturated aldehydes with allyltributylstannane in the presence of a catalytic amount of chiral Ti-BINOL complex were reported to give high yield and good enantioselectivity,[11] to the best of our knowledge, enantioselective allylation of phenylacetaldehydes has not been reported. One potential side-reaction is the homo-Aldol reaction, which will largely decrease the efficiency and enantioselectivity of the catalytic allylation. When the phenanthryl acetaldehyde **2** was subjected to Keck's standard procedures,[10b] the reaction underwent very slowly and gave the desired homoallylic alcohol **3** with a low yield (<50%) and poor enantioselectivity (<4 : 1 er). After extensive screening of reaction conditions, it was found that when a 4 Å molecular sieve used as an additive in the Keck's procedure was replaced with $CaH_2$, both the yield and enantioselectivity were drastically increased (60% yield and 93 : 7 er). It was assumed that $CaH_2$ could promote the formation of the active catalyst BINOL/Ti(IV) complex and reduce the occurrence of the potential homo-Aldol reaction which may be attributed to the low solubility of $CaH_2$ in the reaction intermediate. Because there was no precedent using $CaH_2$ as an additive, the role of it in the catalytic asymmetric allylation deserves further investigation (Scheme 1).

The homoallylic alcohol **3** was then converted to the homoallylic amine **4** smoothly through a Mitsunobu reaction, followed by a Staudinger reduction. With the amine **4** in hand, we initially wanted to protect the free amine with di-*tert*-butyl carbonate ($Boc_2O$) in DCM using 4-dimethylaminopyridine (DMAP) as a catalyst. Unexpectedly, no desired Boc-protected product **5** was obtained. The resulting product was then characterized as isocyanate **6**, which can be isolated by flash chromatography in a moderate yield and verified by $^1H$ and $^{13}C$ NMR and HRMS. Although isocyanates are very important intermediates in the synthesis of biological compounds, such as pharmaceuticals and agrochemicals, the most widely utilized methods for their synthesis are phosgenation of amines and thermolysis of carbamates, where environmental and safety problems and/or harsh reaction conditions are usually needed.[12] Although there were sporadic reports on the DMAP catalyzed isocyanate formation,[13] they were usually ignored and rarely employed as a general synthetic tool. Therefore, we then optimized the isocyanate-forming reaction and investigated several other common bases. It was found that DMAP was indispensable for this transformation, and when it was replaced with triethylamine or pyridine, the Boc-protected product **5** was produced in high yield, giving no isocyanate **6**. When 20% DMAP was used as the catalyst, isocyanate **6** could be isolated by flash chromatographic purification in a nearly quantitative yield. With the isocyanate **6** in hand, we envisioned that the D ring of tylophorine could be constructed if the isocyanate was activated. After screening of various Lewis acids and Brønsted acids, we were glad to find out that the desired cyclized product **7** could be obtained in good yield when $BF_3{\cdot}Et_2O$ was used as the catalyst. To simplify the experimental operations, the isocyanate-forming reaction and the following Lewis acid catalyzed cyclization were executed in one pot, giving **7** in 74% yield, during which thin-layer chromatography was used to monitor the completion of the isocyanate-forming step (Scheme 2).

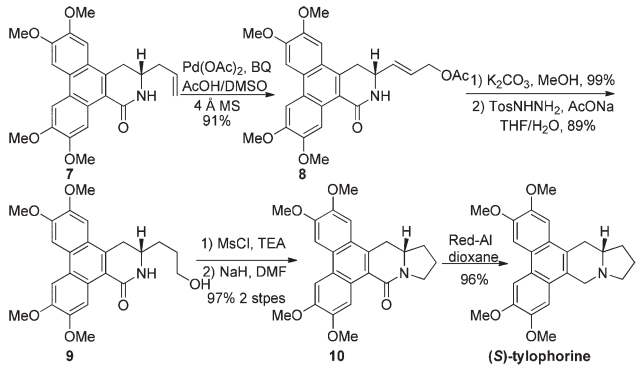
With the lactam **7** in hand, the remaining work to complete the synthesis was to convert the terminal alkene to a proper leaving group and then to construct the E ring of tylophorine. Due to the presence of the secondary amide group in compound **7**, hydroboration of the terminal double bond was proved to be very problematic. Recently, White's group reported addition of dimethylsulfoxide (DMSO) to the $Pd(OAc)_2$/benzoquinone (BQ)/AcOH catalyst system of monosubstituted olefins, giving linear allylic acetates with good region- and stereoselectivities.[14] Gratifyingly, olefin **7** was converted to allylic acetate **8** smoothly in 91% yield using White's synthetic procedure,[14] and no other regioisomer or stereoisomer was isolated. After removal of the acetyl group, the




**Scheme 1** Synthesis of homoallylic alcohol **3**.




**Scheme 2** Synthesis of intermediate **7**.




Scheme 3 Completion of synthesis of (*S*)-tylophorine.

double bond in compound **8** was reduced with a diimide, generated *in situ* by treatment of $TsNHNH_2$ with NaOAc/THF/$H_2O$ heated at reflux,[15] giving alcohol **9** in a nearly quantitative yield. It is noteworthy that hydrogenation catalyzed by transition-metals such as Pd/C, Pt/C or $PtO_2$ was inefficient for this transformation. After methanesulfonation and intramolecular substitution, alcohol **9** was transformed into lactam **10** efficiently. Reduction of lactam **10** with Red-Al afforded (*S*)-tylophorine in 96% yield with 85% enantiomeric excess measured by chiral HPLC (Chiral AD-H, see ESI†).[16] The NMR spectra of the synthetic sample matched well with reported data, and the optical rotation of (*S*)-tylophorine ($[\alpha]_D^{25}$ +64.2 (*c* 0.6, $CHCl_3$)) is in agreement with that reported previously ($[\alpha]_D^{21}$ +73.0 (*c* 0.7, $CHCl_3$)) (Scheme 3).[17]

## Conclusion

In summary, we have developed an enantioselective strategy for the total synthesis of (*S*)-tylophorine. The key features include (1) catalytic asymmetric allylation to introduce the stereogenic center, which also enables the synthesis of the antipode by converting the chiral ligand BINOL; (2) an unexpected mild and efficient one-pot DMAP promoted isocyanate-forming reaction/intramolecular cyclization, to potential applications in synthetic chemistry of which attention should be paid; (3) White's robust direct C–H oxidation used for late-stage transformation.

## Experimental

### General methods

The melting points were determined with X-4 binocular microscope melting-point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. $^1$H NMR spectra were obtained using a Bruker AV 400 spectrometer. Chemical shifts ($\delta$) were given in parts per million (ppm) and were measured downfield from the internal reference tetramethylsilane. $^{13}$C NMR spectra were recorded using a Bruker AV 400 (100 MHz) and $CDCl_3$ or $CD_3OD$ as the solvent. Chemical shifts ($\delta$) are reported in parts per million. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, b = broad, td = triple doublet, dt = double triplet, dq = double quartet, m = multiplet. High-resolution mass spectra were obtained with an FT-ICR MS spectrometer (Ionspec, 7.0 T). Optical rotations were measured with an Autopol IV auto digital polarimeter (Rudolph Research Analytical). The enantiomeric excesses were determined by HPLC with a Chiralcel AD-H column using the Agilent 1100 instrument.

All anhydrous solvents were dried and purified by standard techniques just before use. All reagents were purchased from commercial suppliers and used without further purification. Reactions were monitored by thin layer chromatography on plates (GF254) supplied by Yantai Chemicals (China) using UV light as a visualizing agent. If not specially mentioned, flash column chromatography uses silica gel (200–300 mesh) supplied by Tsingtao Haiyang Chemicals (China).

**2-(2,3,6,7-Tetramethoxyphenanthren-9-yl)acetaldehyde (2).** To a solution of $Ph_3CH_2OMeCl$ (10.2 g, 30 mmol) in THF (100 mL) was added NaHMDS (15 mL, 2 M, 30 mmol) dropwise at −30 °C under an atmosphere of nitrogen. 30 min later, aldehyde **1** (3.26 g, 10 mmol) in THF (60 mL) was added *via* a syringe. The reaction mixture was warmed to room temperature naturally. 2 h later, aqueous HCl (100 mL, 6 M) was added slowly. After the completion of hydrolysis, the reaction mixture was extracted with EA (50 mL × 3). The combined organic layer was concentrated, and then the crude product was purified by column chromatography to give compound **2** (2.8 g, 84%) as a white solid: mp 198–199 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.77 (s, 1H), 7.85 (s, 1H), 7.79 (s, 1H), 7.55 (s, 1H), 7.21 (s, 1H), 7.20 (s, 1H), 4.13 (s, 6H), 4.07 (d, $J$ = 2.4 Hz, 2H), 4.04 (s, 3H), 4.02 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.1, 149.4, 149.1, 149.0, 148.9, 126.7, 126.1, 125.4, 125.1, 124.3, 123.9, 107.9, 104.5, 103.4, 102.7, 56.0, 56.0, 55.9, 55.8, 49.2; HRMS (ESI) calcd for $C_{20}H_{21}O_5$ $(M + H)^+$ 341.1384, found 341.1389.

**(*R*)-1-(2,3,6,7-Tetramethoxyphenanthren-9-yl)pent-4-en-2-ol (3).** To a solution of (*R*)-BINOL (57.2 mg, 0.2 mmol) in DCM (5 mL) were added $CaH_2$ (42.0 mg, 1.0 mmol) and Ti(O-iPr)$_4$ sequentially at room temperature. The reaction mixture was stirred at this temperature for 3 h, and then aldehyde **2** (33.9 mg, 1.0 mmol) was added. After stirring at this temperature for 10 min, the reaction mixture was cooled to −78 °C and then tributylallylstannane (0.34 mL, 1.11 mmol) was added. The resulting mixture was stirred at this temperature for 30 min, and then was placed in a refrigerator at −20 °C for 6 days. The reaction mixture was quenched with saturated aqueous KF (5 mL). After stirring for 1 h, water (20 mL) was added, and then extracted with DCM (20 mL × 3). The combined organic layer was washed with brine and concentrated *in vacuo*. The crude product was purified by column chromatography to give alcohol **3** (0.23 g, 60%, 93 : 7 er: Phenomenex Lux Cellulose-1 column) as a yellow solid: mp 182–183 °C; $[\alpha]_D^{25}$ +4.9 (*c* 1.10, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.83 (s, 1H), 7.77 (s, 1H), 7.48 (s, 1H), 7.38 (s, 1H), 7.18 (s, 1H), 6.02–5.88 (m, 1H), 5.23 (dd, $J$ = 15.6, 8.0 Hz, 2H), 4.15–4.05 (m, 1H), 4.13 (s, 3H), 4.11 (s, 3H), 4.04 (s, 3H), 4.03 (s, 3H), 3.35 (dd, $J$ = 14.0,

4.4 Hz, 1H), 3.09 (dd, $J$ = 14.0, 8.0 Hz, 1H), 2.48–2.35 (m, 2H), 1.84 (d, $J$ = 2.8 Hz, 1H, $D_2O$ exchangeable); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 149.1, 148.9, 148.9, 148.6, 134.7, 130.1, 126.2, 125.6, 125.4, 125.1, 123.9, 118.4, 108.0, 104.9, 103.4, 102.8, 70.5, 56.1, 56.0, 55.9, 41.6, 40.9; HRMS (ESI) calcd for $C_{23}H_{27}O_5$ $(M + H)^+$ 383.1853, found 383.1861.

**(*S*)-1-(2,3,6,7-Tetramethoxyphenanthren-9-yl)pent-4-en-2-amine (4).** To a solution of alcohol **3** (0.38 g, 1.0 mmol) and $PPh_3$ (0.52 g, 2.0 mmol) in THF (30 mL) were added DEAD (0.35 g, 2.0 mmol) and then DPPA (0.55 g, 2.0 mmol). The reaction mixture was stirred at room temperature overnight. After concentration, the crude material was dissolved in DCM (50 mL), which was washed with water and brine, and then concentrated *in vacuo*. The resulting crude product was purified by column chromatography to give the azido (0.36 g, 89%) as a white solid: mp 160–161 °C; $[\alpha]_D^{25}$ −11.5 ($c$ 0.80, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.86 (s, 1H), 7.78 (s, 1H), 7.49 (s, 1H), 7.32 (s, 1H), 7.20 (s, 1H), 5.99–5.87 (m, 1H), 5.23 (dd, $J$ = 15.6, 8.0 Hz, 2H), 4.14 (s, 3H), 4.12 (s, 3H), 4.05 (s, 3H), 4.04 (s, 3H), 3.86–3.77 (m, 1H), 3.31 (dd, $J$ = 14.4, 6.0 Hz, 1H), 3.23 (dd, $J$ = 14.4, 7.6 Hz, 1H), 2.45 (t, $J$ = 6.7 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 149.2, 149.0, 149.0, 148.8, 133.8, 129.3, 126.2, 126.0, 125.2, 125.1, 124.0, 118.8, 108.1, 104.4, 103.6, 102.9, 62.3, 56.1, 56.1, 55.9, 55.9, 38.8, 38.1; HRMS (ESI) calcd for $C_{23}H_{26}N_3O_4$ $(M + H)^+$ 408.1918, found 408.1924. To a solution of the azido (0.20 g, 0.5 mmol) obtained above in THF (25 mL) and water (3 mL) was added $PPh_3$ (0.26 g, 1.0 mmol). The reaction mixture was stirred at 60 °C overnight. The solvent was evaporated *in vacuo*, and then EA (40 mL) was added. The mixture was extracted with aqueous HCl (1 M, 30 mL × 2). The combined aqueous phase was basified with aqueous NaOH till pH > 12, and then extracted with DCM (30 mL × 2). Then, the combined organic layer was washed with brine, dried over sodium sulfate, concentrated *in vacuo*, giving amine **4** (0.18 g, 95%) as a white solid: mp 182–183 °C; $[\alpha]_D^{25}$ −11.5 ($c$ 0.80, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.84 (s, 1H), 7.78 (s, 1H), 7.47 (s, 1H), 7.37 (s, 1H), 7.18 (s, 1H), 6.02–5.86 (m, 1H), 5.27–5.14 (m, 2H), 4.13 (s, 3H), 4.12 (s, 3H), 4.04 (s, 3H), 4.03 (s, 3H), 3.37 (dd, $J$ = 13.6, 4.0 Hz, 1H), 3.35–3.27 (m, 1H), 2.83 (dd, $J$ = 13.6, 8.4 Hz, 1H), 2.45–2.32 (m, 1H), 2.31–2.21 (m, 1H), 1.42 (brs, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 149.0, 148.9, 148.9, 148.5, 135.7, 131.2, 126.2, 125.4, 125.1, 123.8, 117.9, 108.0, 105.0, 103.4, 102.8, 100.0, 56.1, 56.1, 55.9, 50.8, 42.7, 41.8; HRMS (ESI) calcd for $C_{23}H_{28}NO_4$ $(M + H)^+$ 382.2013, found 382.2019.

**(*S*)-9-(2-Isocyanatopent-4-en-1-yl)-2,3,6,7-tetramethoxyphenanthrene (6).** To a solution of amine **4** (38.1 mg, 0.1 mmol) and DMAP (2.4 mg, 0.02 mmol) in DCM (10 mL) was added $Boc_2O$ (26.2 mg, 0.12 mmol). The reaction mixture was stirred for 30 min at room temperature, diluted with DCM (20 mL), and then quenched with diluted aqueous HCl. After separation, the organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product, which was purified by short flash column chromatography (PE–EA 2 : 1, $R_f$ = 0.5) to give isocyanate **6** (29 mg, 71%) as a white solid: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.86 (s, 1H), 7.78 (s, 1H), 7.48 (s, 1H), 7.28 (s, 1H), 7.20 (s, 1H), 5.99–5.86 (m, 1H), 5.27 (d, $J$ = 6.2 Hz, 1H), 5.24 (s, 1H), 4.14 (s, 3H), 4.12 (s, 3H), 4.05 (s, 3H), 4.05 (s, 3H), 4.01–3.91 (m, 1H), 3.37 (dd, $J$ = 14.2, 5.2 Hz, 1H), 3.19 (dd, $J$ = 14.2, 8.2 Hz, 1H), 2.55–2.40 (m, 2H); HRMS (ESI) calcd for $C_{24}H_{26}NO_5$ $(M + H)^+$ 408.1805, found 408.1800.

**(*S*)-3-Allyl-6,7,10,11-tetramethoxy-3,4-dihydrodibenzo[*f*,*h*]isoquinolin-1(2*H*)-one (7).** To a solution of amine **4** (38.1 mg, 0.1 mmol) and DMAP (2.4 mg, 0.02 mmol) in DCM (10 mL) was added $Boc_2O$ (26.2 mg, 0.12 mmol). The reaction mixture was stirred for 30 min at room temperature, and then $BF_3{\cdot}Et_2O$ (0.5 mL, 30%) was added. 1 h later, the reaction was diluted with DCM (20 mL) and then quenched with aqueous HCl (1 M, 10 mL). After separation, the organic layer was washed with water (20 mL), aqueous $Na_2CO_3$ (20 mL), and brine (20 mL), dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by column chromatography on basic aluminum oxide to give compound **7** (30.0 mg, 74%) as a white solid: mp 224–226 °C; $[\alpha]_D^{25}$ +174.0 ($c$ 1.23, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.01 (s, 1H), 7.83 (s, 1H), 7.78 (s, 1H), 7.34 (s, 1H), 6.00 (brs, 1H), 5.92–5.80 (m, 1H), 5.30 (d, $J$ = 8.2 Hz, 1H), 5.28 (d, $J$ = 9.6 Hz, 1H), 4.15 (s, 3H), 4.12 (s, 3H), 4.08 (s, 3H), 4.07 (s, 3H), 3.87–3.77 (m, 1H), 3.42 (dd, $J$ = 15.8, 3.9 Hz, 1H), 3.08 (dd, $J$ = 15.8, 11.6 Hz, 1H), 2.67–2.57 (m, 1H), 2.43 (dt, $J$ = 14.2, 8.4 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 167.7, 150.6, 149.1, 148.9, 148.8, 134.4, 133.4, 127.0, 124.5, 124.2, 123.1, 120.6, 119.4, 108.0, 104.9, 103.1, 102.4, 56.0, 56.0, 55.9, 55.9, 48.9, 39.6, 32.3; HRMS (ESI) calcd for $C_{24}H_{26}NO_5$ $(M + H)^+$ 408.1805, found 408.1814.

**(*R*,*E*)-3-(6,7,10,11-Tetramethoxy-1-oxo-1,2,3,4-tetrahydrodibenzo[*f*,*h*]isoquinolin-3-yl)allyl acetate (8).** To a suspension of $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), benzoquinone (BQ, 217 mg, 2 mmol) and 4 Å MS (217 mg) in DMSO (6 mL) and AcOH (6 mL) was added compound **7** (0.41 g, 1.0 mmol). The reaction mixture was stirred at 40 °C for 24 h, and then diluted with DCM (30 mL). The suspension was filtered through celite and washed with DCM. The filtrate was washed with water (30 mL) and brine (30 mL), and concentrated *in vacuo*. The crude product was purified by column chromatography to give compound **8** (0.42 g, 91%) as a white solid: mp 182–183 °C; $[\alpha]_D^{25}$ +145.8 ($c$ 0.54, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.03 (s, 1H), 7.82 (s, 1H), 7.78 (s, 1H), 7.32 (s, 1H), 5.96 (d, $J$ = 3.6 Hz, 2H), 5.92 (s, 1H), 4.61 (d, $J$ = 3.2 Hz, 2H), 4.41–4.32 (m, 1H), 4.15 (s, 3H), 4.12 (s, 3H), 4.08 (s, 3H), 4.06 (s, 3H), 3.48 (dd, $J$ = 16.0, 4.4 Hz, 1H), 3.22 (dd, $J$ = 16.0, 10.4 Hz, 1H), 2.10 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.7, 167.3, 150.7, 149.2, 149.0, 148.9, 133.8, 132.9, 127.9, 127.1, 124.5, 124.1, 123.1, 120.3, 108.1, 104.9, 103.19, 102.4, 63.8, 56.0, 56.0, 55.9, 55.9, 52.0, 32.7, 21.0; HRMS (ESI) calcd for $C_{26}H_{28}NO_7$ $(M + H)^+$ 466.1860, found 466.1869.

**(*S*)-3-(3-Hydroxypropyl)-6,7,10,11-tetramethoxy-3,4-dihydrodibenzo[*f*,*h*]isoquinolin-1(2*H*)-one (9).** To a solution of compound **8** (0.23 g, 0.5 mmol) in methanol (30 mL) was added $K_2CO_3$ (0.27 g, 3.0 mmol), and then the reaction mixture was stirred at room temperature overnight. After evaporation of the solvent, the residue was dissolved in DCM (40 mL), which was

washed with water (30 mL) and brine (30 mL), and concentrated *in vacuo*. The crude product was purified by column chromatography to give the alcohol quantitatively as a white solid: mp 269–271 °C; $^1$H NMR (400 MHz, DMSO) $\delta$ 8.99 (s, 1H), 8.13 (brs, 1H, $D_2O$ exchangeable), 8.03 (s, 1H), 8.00 (s, 1H), 7.48 (s, 1H), 5.90–5.69 (m, 2H), 4.75 (brs, 1H, $D_2O$ exchangeable), 4.24 (s, 1H), 4.07 (s, 3H), 4.03 (s, 3H), 3.96 (s, 3H), 3.91 (d, $J$ = 3.2 Hz, 2H), 3.87 (s, 3H), 3.48 (dd, $J$ = 16.4, 5.0 Hz, 1H), 3.25 (dd, $J$ = 16.4, 7.6 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 166.5, 156.0, 149.3, 148.9, 148.8, 134.2, 132.6, 129.5, 126.6, 124.6, 124.0, 123.5, 120.9, 108.5, 106.0, 104.4, 104.0, 61.2, 56.4, 56.2, 56.0, 55.6, 50.9, 32.2; HRMS (ESI) calcd for $C_{24}H_{26}NO_6$ $(M + H)^+$ 424.1755, found 424.1760. To the solution of alcohol obtained above in 1 : 1 THF–$H_2O$ (30 mL) was added *p*-toluenesulfonylhydrazide (1.4 g). The reaction mixture was heated to reflux, and over the course of 4 h a solution of sodium acetate (2.0 g) in $H_2O$ (10 mL) was added. Heating was continued for an additional 3 hours. The mixture was then concentrated to *ca.* 10 mL, saturated aqueous $NH_4Cl$ (20 mL) and water (10 mL) were added, and the product was extracted with $CH_2Cl_2$ (30 mL × 2). The combined extracts were evaporated, and the crude product was purified by column chromatography to give compound **9** (0.19 g, 89%) as a white solid: mp 244–245 °C; $[\alpha]_D^{25}$ +150.7 (*c* 1.16, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.99 (s, 1H), 7.83 (s, 1H), 7.79 (s, 1H), 7.33 (s, 1H), 6.47 (brs, 1H), 4.15 (s, 3H), 4.12 (s, 3H), 4.08 (s, 3H), 4.06 (s, 3H), 3.83–3.74 (m, 3H), 3.51–3.38 (m, 2H), 3.09 (dd, $J$ = 15.8, 11.0 Hz, 1H), 1.93–1.76 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.1, 150.6, 149.1, 148.9, 148.8, 134.7, 127.0, 124.5, 124.1, 123.2, 120.5, 108.0, 104.9, 103.1, 102.5, 62.2, 56.1, 56.0, 55.9, 55.8, 49.9, 32.6, 31.4, 28.5; HRMS (MALDI) calcd for $C_{24}H_{28}NO_6$ $(M + H)^+$ 426.1911, found 426.1905.

**(*S*)-2,3,6,7-Tetramethoxy-12,13,13a,14-tetrahydrodibenzo[*f*,*h*]-pyrrolo[1,2-*b*]isoquinolin-9(11*H*)-one (10).** To a solution of compound **9** (85 mg, 0.2 mmol) in $CH_2Cl_2$ (20 mL) were added $Et_3N$ (24.2 mg, 0.24 mmol) and MsCl (27.4 mg, 0.24 mmol). After stirring for 1 h, the reaction was quenched with aqueous saturated ammonium chloride and concentrated *in vacuo*. The aqueous layer was extracted with $CH_2Cl_2$ (10 mL × 3). The combined extracts were washed with water (10 mL × 2) and brine (10 mL × 2), dried over $Na_2SO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give the sulfonate quantitatively, which was then dissolved in THF (20 mL), and then NaH (7.2 mg, 0.3 mmol) was added. The reaction mixture was heated at reflux for 3 hours. After cooling to room temperature, the reaction was quenched with aqueous ammonium chloride, and then concentrated *in vacuo*. The aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried over $Na_2SO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give compound **10** (78.9 mg, 97%) as a white solid: mp 280–282 °C; $[\alpha]_D^{25}$ +165.4 (*c* 1.04, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.03 (s, 1H), 7.83 (s, 1H), 7.78 (s, 1H), 7.35 (s, 1H), 4.15 (s, 3H), 4.12 (s, 3H), 4.09 (s, 3H), 4.07 (s, 3H), 3.99–3.76 (m, 3H), 3.61 (dd, $J$ = 15.6, 4.0 Hz, 1H), 2.95 (dd, $J$ = 15.4, 13.4 Hz, 1H), 2.50–2.39 (m, 1H), 2.51–2.41 (m, 1H), 2.25–2.14 (m, 1H), 2.06–1.88 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 164.7, 150.3, 148.9, 148.8, 148.7, 133.3, 126.7, 124.4, 124.3, 123.2, 122.5, 108.0, 104.8, 103.1, 102.3, 56.0, 55.9, 55.9, 55.2, 45.4, 33.9, 32.6, 23.6; HRMS (MALDI) calcd for $C_{24}H_{26}NO_5$ $(M + H)^+$ 408.1805, found 408.1805.

**(*S*)-Tylophorine.** To a solution of the lactam **10** (81.4 mg, 0.2 mmol) in dry dioxane (20 mL) was added sodium bis-(2-methoxyethoxy)aluminium hydride (3.0 mmol, 3.5 M in toluene) and the mixture was refluxed for 2 h in the dark. After evaporation of the solvents, the residue was diluted with water (20 mL) and then basified with aqueous NaOH. The mixture was extracted with $CH_2Cl_2$ (20 mL × 4), and the combined extracts were washed with water, dried over $MgSO_4$, and filtered. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel to give (*S*)-Tylophorine (75.5 mg, 96%) as a white solid: mp 281–283 °C; $[\alpha]_D^{25}$ +64.2 (*c* 0.57, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.83 (s, 1H), 7.83 (s, 1H), 7.32 (s, 1H), 7.16 (s, 1H), 4.64 (d, $J$ = 14.8 Hz, 1H), 4.12 (s, 6H), 4.06 (s, 3H), 4.06 (s, 3H), 3.68 (d, $J$ = 14.8 Hz, 1H), 3.49 (td, $J$ = 8.6, 1.8 Hz, 1H), 3.38 (dd, $J$ = 15.8, 2.4 Hz, 1H), 2.92 (dd, $J$ = 15.4, 10.5 Hz, 1H), 2.56–2.43 (m, 2H), 2.31–2.21 (m, 1H), 2.12–2.00 (m, 1H), 1.99–1.88 (m, 1H), 1.85–1.73 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 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; HRMS (ESI) calcd for $C_{24}H_{28}NO_4$ $(M + H)^+$ 394.2013, found 394.2015.

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