Organic & Biomolecular Chemistry

Accepted Manuscript

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An Enantioselective Strategy for the Total Synthesis of (*S*)-Tylophorine via Catalytic Asymmetric Allylation and One-Pot DMAP-Promoted Isocyanate Formation/Lewis Acid Catalyzed Cyclization Sequence

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

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A new asymmetric total synthesis of phenanthroindolizidine alkaloid (*S*)-tylophorine was reported, which features a catalytic asymmetric allylation of aldehyde 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 olefin to linear allylic acetate 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 interest has been paid on 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 on 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) chiral auxillary approach;[8f, 8q] 2) enantioselective catalytic phase-transfer alkylation;[8a] 3) organocatalyzed enantioselective functionalization;[8g] 4) transition-metal catalyzed asymmetric carboamination of alkene;[8i] and 5) stereosepecfic Overman rearrangement[8b].

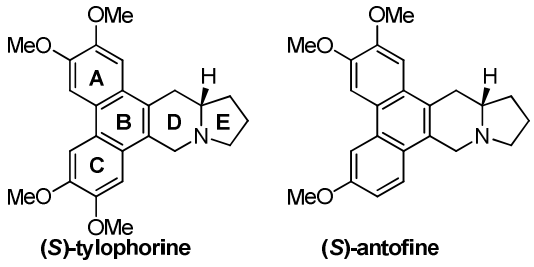
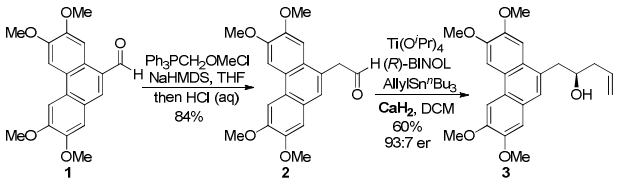


Fig. 1 Structure of representative phenanthroindolizidine alkaloids.

As a continuation of our studies on the total synthesis and biological evaluation on phenanthroindolizidine alkaloids,[8d, 8j,8n, 8q, 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 D ring, and White`s direct C-H oxidation of terminal alkene to execute a late-stage functional group transformation.

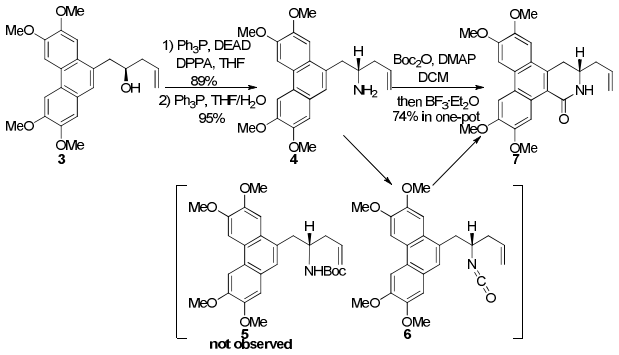
Results and discussion

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 reagents in the presence of chiral Lewis acid catalysts, among which $Ti^{(IV)}$-BINOL complex first reported by 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.



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

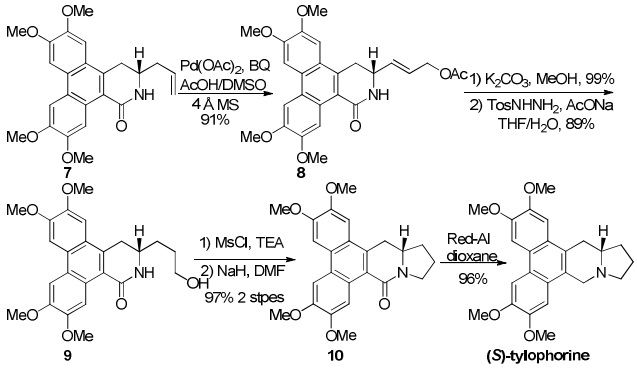
Using a similar modified synthetic procedure developed by us,[8g] the known phenanthryl aldehyde **1** could be readily prepared. The precursor **2** for the catalytic enantioselective allylation could be obtained from readily available aldehyde **1** via Wittig reaction followed by acidic hydrolysis in 84% yield. It is worth to note 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 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 low yield (< 50%) and poor enantioselectivity (< 4:1 er). After extensive screening of reaction conditions, it was found that when 4Å molecular



Scheme 2 Synthesis of intermediate **7**.

sieve used as additive in the Keck`s procedure was replaced with CaH_2, both the yield and enantioselecitvity were drastically increased (60% yield and 93:7 er). It was assumed that CaH_2 could promote the formation of active catalyst BINOL/Ti(IV) complex and reduce the occurrence of the potential homo-Aldol reaction as may attribute to the low solubility of CaH_2 in the reaction intermediate. Because there was no precedent using CaH_2 as additive, the role of it in the catalytic asymmetric allylation deserves further investigation.

The homoallylic alcohol **3** was then converted to 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 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 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 of 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 isocyanates formation examples,[13] they were usually ignored and rarely employed as a general synthetic tool. Therefore, we then optimized the isocynate-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, Boc-protected product **5** was produced in high yield, giving no isocynate **6**. When 20% DMAP was used as catalyst, isocyanate **6** could be isolated by flash chromatographic purification in nearly quantitative yield. With the isocyanate **6** in hand, we envisioned that D ring of tylophorine could be constructed if the isocyanate was activated. After screening of various Lewis acids andbrønsted acids, it was glad to find that the desired cyclized product **7** could be obtained in good yield when $BF_3.Et_2O$ was used as 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 3 Completion of synthesis of (*S*)-tylophorine.

With the lactam **7** in hand, the remaining work to complete the synthesis was to convert the terminal alkene to proper leaving group and then to construct E ring of tylophorine. Due to the presence of secondary amide group in compound **7**, hydroboration of the terminal double bond was proved to be very problematic. Recently, White group reported that 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 were

isolated. After removing of acetyl group, double bond in compound **8** was reduced with diimide, generated in situ by treatment of $TsNHNH_2$ with NaOAc/THF/H_2O heated at reflux,[15] giving alcohol **9** in nearly quantitatively yield. Noteworthy, hydrogenation catalyzed by transition-metal such as Pd/C, Pt/C or PtO_2 was inefficient for this transformation. After methansulfonation and intramolecular substitution, alcohol **9** was transformed to 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 Supporting Information).[16] The NMR spectra of the synthetic sample matched well with reported data, and the optical rotation of (*S*)-tylophorine ($[\alpha]^{25}{}_D$ + 64.2 (c 0.6, $CHCl_3$)) is in agreement with that reported previously ($[\alpha]^{21}{}_D$ + 73.0 (c 0.7, $CHCl_3$)).[17]

Conclusion

In summary, we have developed an enantioselective strategy for the total synthesis of (*S*)-tylophorine. Key features include 1) catalytic asymmetric allylation to introduce the stereogeniccenter, 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, potential applications in the synthetic chemistry of which should be paid attention; 3) White`s robust direct C-H oxidation used for late-stage transformation.

Experimental

General methods

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

All anhydrous solvents were dried and purified by standard techniques just before use.All reagents were purchased from commercial suppliers without furtherpurification. Reactions were monitored by Thin Layer Chromatography on plates (GF254) supplied by YantaiChemicals (China) using UV light as visualizing agent. If not specially mentioned, flash columnchromatography 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). 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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) was added CaH_2 (42.0 mg, 1.0 mmol) and $Ti(O\text{-}iPr)_4$ 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 put in 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). 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; $[\alpha]^{25}{}_D$ +4.9 (*c* 1.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) was 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; $[\alpha]^{25}{}_D$ –11.5 (*c* 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 wate (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). 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; $[\alpha]^{25}_D$ –11.5 (*c* 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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, organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to give crude product, which was purified by a short flash column chromatography (PE/EA 2:1, Rf = 0.5) to give isocyanate **6** (29 mg, 71%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 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; $[\alpha]^{25}_D$ + 174.0 (*c* 1.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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. Crude product was purified by column chromatography to give compound **8** (0.42 g, 91%) as a white solid: mp 182–183 °C; $[\alpha]^{25}_D$ +145.8 (*c* 0.54, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 solvent, the residue was dissolved in DCM (40 mL), which was washed with water (30 mL) and brine (30 mL), and concentrated in vacuo. 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) δ 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) δ 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 (30 mL × 2). The combined extracts were evaporated, and crude product was purified by column chromatography to give compound **9** (0.19 g, 89%) as a white solid: mp 244–245 °C; $[\alpha]^{25}_D$ + 150.7 (*c* 1.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) was added Et_3N (24.2 mg, 0.24 mmol) and MsCl (27.4 mg, 0.24 mmol) was added. 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 extracted 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; $[\alpha]^{25}_D$ + 165.4 (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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; $[\alpha]^{25}_D$ + 64.2 (*c* 0.57, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) 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; HRMS (ESI) calcd for $C_{24}H_{28}NO_4$ $(M + H)^+$ 394.2013, found 394.2015.

Acknowledgements

We are grateful to the National Key Project for Basic Research (2010CB126100), the National Natural Science Foundation of China (21132003, 21121002, 21372131), the Tianjin Natural Science Foundation (11JCZDJC20500), and Specialized Research Fund for the Doctoral Program of Higher Education (20130031110017) for generous financial support for our programs.

Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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