Tetrahedron 69 (2013) 2996–3001

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Concise synthesis of tylophorine

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ARTICLE INFO

Article history:
Received 29 November 2012
Received in revised form 25 January 2013
Accepted 31 January 2013
Available online 8 February 2013

Keywords:
Phenanthroindolizidine alkaloid
Tylophorine
Stevens rearrangement
Double Suzuki coupling
Symmetry for synthesis design

ABSTRACT

The phenanthroindolizidine alkaloid tylophorine has been synthesized in the (*R*)- and racemic forms. One of the routes involves three steps from a known compound employing a Stevens rearrangement as the pivotal reaction. The phenanthrene moiety was constructed by either a base-catalyzed cyclization of 2-alkynylbiphenyls or a double Suzuki coupling of a 2,2′-dibromobiphenyl with *vic*-bis(pinacolatoboryl) alkene in other routes.

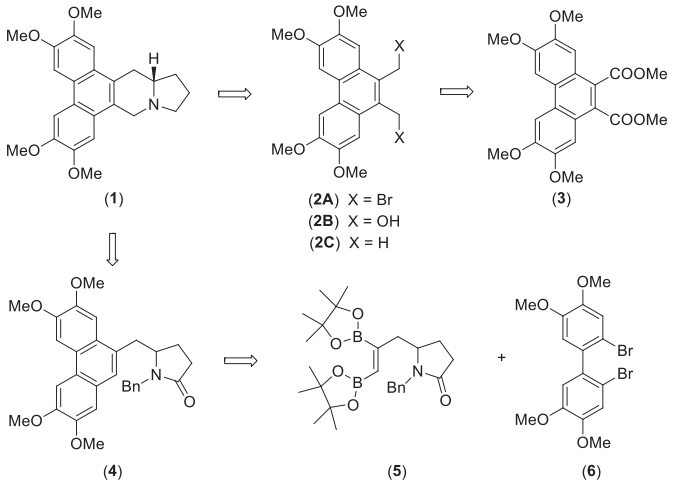
1. Introduction

The pentacyclic alkaloid tylophorine (**1**) is present in *Tylophora indica*, whose leaves having been used in India since ancient times for the treatment of asthma, bronchitis, rheumatism, and dysentery.[1] First isolated in 1935,[2] **1** was shown to contain an indolizidine subunit fused to a phenanthrene system, which heralded discovery of homologous phenanthroquinolizidine alkaloids. At present more than 60 members of the two families have been isolated and characterized from plants of the *Asclepiadaceae* and *Moraceae* families.[1b,3] Because these substances possess outstanding biological and pharmacological activities, including antitumor, anti-inflammatory, antiviral, antibiotic, and cytotoxic effects, they make themselves attractive synthetic targets.

Since 1960, more than a dozen synthetic approaches for racemic tylophorine and related compounds have been on records.[4] For assembly of enantiomeric tylophorine, after establishment of its absolute configuration by a synthesis from glutamic acid,[5a] routes that make use of chirons (proline,[5b,f,h,i] pyroglutamate[5e]) and chiral auxiliaries or based on stereoselective reactions (Grignard additions[5d] and double Michael reactions[5c]) and asymmetric catalysis (copper[5g] or palladium[5k]-catalyzed intramolecular alkene carboamination) have been examined.

2. Discussion

Our interest in the synthesis of tylophorine was derived from the relevance of molecular symmetry in synthetic design.[6] Previous works from our laboratories encompass elaboration of sesquiterpenes, such as longifolene, occidol, tavacpallescensin, cuparene/herbertene, β-cuparenone, platyphyllide, isocyano-neopupukeanane, and of several alkaloids including cryptolepine/cryptotackiene, anatoxin-a, nicotyrine, ellipticine, tangutorine, eburnamonine, and tacamonine. Tylophorine was identified as one of our targets due to its incorporation of a symmetrical phenanthrene moiety to permit synthetic design based on either symmetrical biphenyls or phenanthrene intermediates. Depicted in Schemes 1 and 2 are some of our initial retrosynthetic ideas, which had undergone modification during the subsequent investigation.



Scheme 1. Retrosynthetic analysis (**1**).

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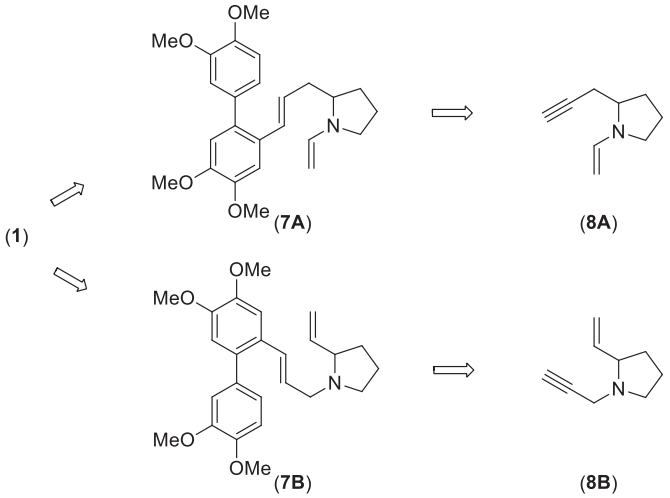
0040-4020/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tet.2013.02.014



Scheme 2. Retrosynthetic analysis (**2**).

A succinct route to racemic tylophorine employs a symmetrical 9,10-bis(bromomethyl)phenanthrene **2A**, which can be prepared by two methods. The one starting from veratrole is via 2,2′-dibromo-4,4′,5,5′-tetramethoxybiphenyl (**6**)[7] on successive treatment with *n*-butyllithium, $(THF)_3CrCl_3$, and dimethyl acetylenedicarboxylate[8] to deliver **3**[4l] was concluded on reduction with $LiAlH_4$ (to **2B**) and bromination with PBr_3. A more convenient protocol involves preparation of **2C** from veratrole in two steps in 49% yield by the method of Weisgraber and Weiss,[9] followed by benzylic bromination with NBS (yield 64%).

As our initial attempts at using **2A** to alkylate the *N*-Boc derivative of 2-lithiopyrrolidine were not successful, we turned to a strategy involving formation of spirocyclic ammonium salts for a Stevens rearrangement. Regioselective generation of the desired ammonium ylide dictates the pyrrolidine nucleophile to contain an auxiliary group at C-2 and reaction with 2-trimethylsilylpyrrolidine was assayed using a fluoride base. The reaction did not proceed cleanly therefore the *N*-Boc derivative of 2-tri-*n*-butylstannylpyrrolidine **9**[10] was used instead. The free amine was released from **9** on treatment with *B*-bromocatecholborane and sodium hydroxide, and its quaternization to give **10** was carried out immediately by mixing with **2C**. Stevens rearrangement on treatment **10** with *n*-butyllithium finally provide tylophorine in 37% yield (Fig. 1).

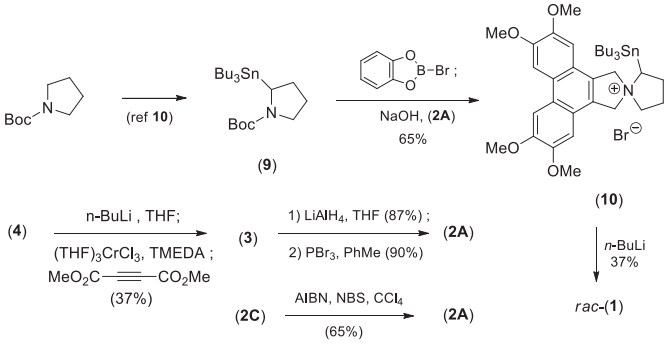


Fig. 1. Synthesis of tylophorine via Stevens rearrangement.

A second route we developed pertains to annulation by a twofold Suzuki coupling[11] of 2,2′-dibromo-4,5,4′,5′-tetramethoxybiphenyl (**6**) with pyrrolidone **5** derived from **11B** and possessing a (*Z*)-2,3-bis(pinacolatoboryl)-2-propenyl group at C-5 (Fig. 2). The resulting phenanthrene **4** was then deoxygenated on reaction with $LiAlH_4$ to **12A** and further *N*-debenzylated (H_2, Pd/C) to provide the

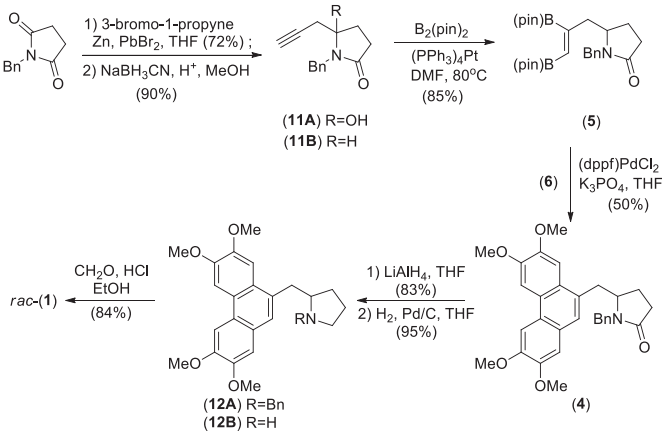


Fig. 2. Synthesis of tylophorine starting from a twofold Suzuki coupling.

tylophorine precursor **12B** that requires only a Pictet–Spengler reaction with acidic formaldehyde to complete another synthesis. Access to **11B** from *N*-benzylsuccinimide was based on a Barbier propargylation[12] and reduction with $NaBH_3CN$ under acidic conditions.[13]

We also investigated some variants to the synthesis. Initially we planned to pursue construction of two rings by a tandem Sonogashira–Heck coupling based on a 2,2′-dihalobiphenyl. This effort did not lead to the desired intermediate therefore a less ambitious approach was adopted (Fig. 3). It started from a Sonogashira coupling of 5-propargyl-1-benzyl-2-pyrrolidone **11B** with 2-iodo-4,5,3′,4′-tetramethoxybiphenyl (**13**)[5f] that is obtainable (54% yield) from Suzuki coupling of 4,5-diiodo-1,2-dimethoxybenzene[14] with 3,4-dimethoxyphenylboronic acid. The product **14** (96%) underwent cyclization through isomerization to an allene by DBU[15] resulted in the phenanthrene **4** (93% yield).

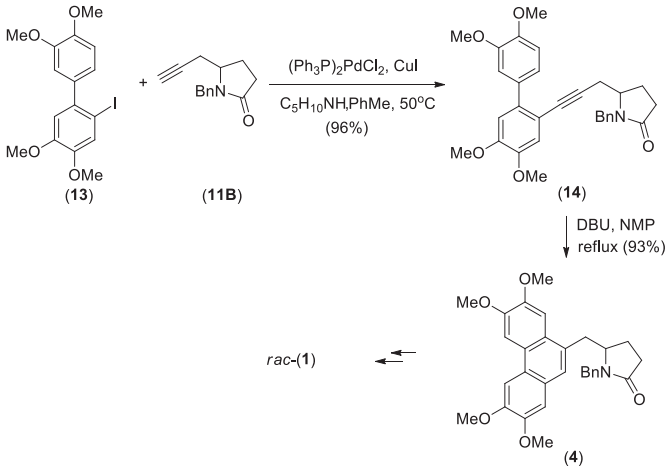


Fig. 3. Synthesis of racemic tylophorine involving a Sonogashira coupling.

The coupling-cyclization sequence was repeated with the iodobiphenyl **13** and (*R*)-1-propargyl-2-oxopyrrolidinyl-5-methyl *t*-butyldimethylsilyl ether (**16**) that was available from (*R*)-pyroglutamic acid.[16] Note the different position of the propargyl group in the pyrrolidine ring. As a chiral product **17** containing all the skeletal carbon atoms was generated, the stage was set for ring closure and removal of the excess oxygen functionalities. In the event, a reaction sequence consisting of desilylation, Dess–Martin oxidation, cyclization, and a two-stage reduction (Et_3SiH, $BF_3{\cdot}Et_2O$; $LiAlH_4$) accomplished the task. (*R*)-(−)-Tylophorine was isolated.

In summary, we have developed four routes for the efficient synthesis of tylophorine. This work further supports our belief that symmetry consideration is meritorious in synthesis design. Of interest is the method based on the Stevens rearrangement, which we completed in 2010, has also been independently conceived and pursued on a somewhat different precursor[4q] (Fig. 4).

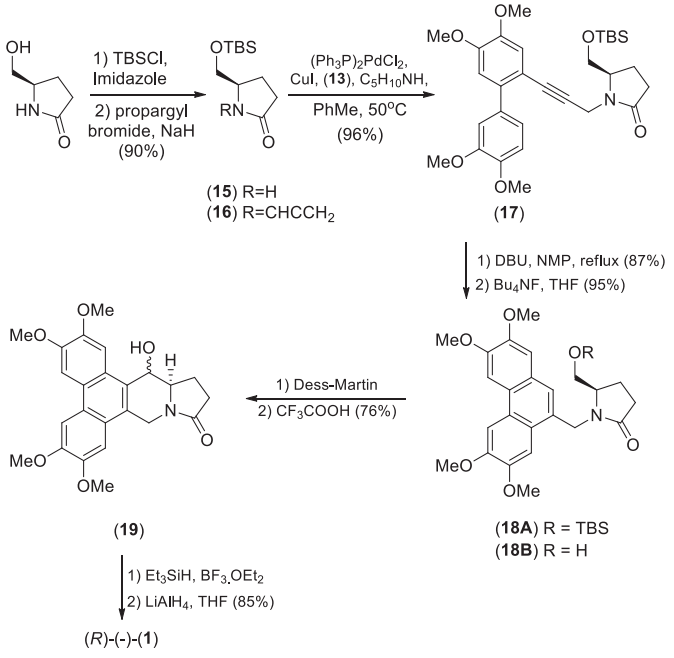


Fig. 4. Synthesis of (*R*)-tylophorine involving a Sonogashira coupling.

3. Experimental section

3.1. General methods

NMR spectra were recorded with $CDCl_3$ as solvent, at 300 and 75/100 MHz, respectively for ^1H and ^{13}C absorptions. Chemical shift are in parts per million relative to 0 for TMS. Mass spectra including HRMS were obtained with electron impact ionization at 70 eV or electrospray ionization, where indicated. IR spectra were recorded as neat films or KBr pellets (for solids). Melting points, determined with a Laboratory Devices apparatus, are uncorrected.

*3.1.1. 9,10-Bis(bromomethyl)-2,3,6,7-tetramethoxyphenanthrene (**2A**) from **3**.* To a solution of **3** (249 mg, 0.6 mmol) in THF (15 mL) at 0 °C was added $LiAlH_4$ (137 mg, 3.6 mmol) in portions. After stirred at room temperature for 3 h, the mixture was quenched with water, filtered through Celite and evaporated to dryness to give a white solid (**2B**) without further purification.

Thus the solid was dissolved in toluene (30 mL) and treated with PBr_3 (60 μL, 0.63 mmol). After stirred at room temperature for 1.5 h, the mixture was quenched with water and extracted with dichloromethane. The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude residue that was purified by flash column chromatography on SiO_2 (petroleum ether/CH_2Cl_2, 1:2) to afford **2A** (246 mg, 85%) as a yellow solid: mp 246–248 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (s, 2H), 7.48 (s, 2H), 5.09 (s, 4H), 4.11 (s, 6H), 4.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 149.1, 128.6, 125.5, 124.0, 104.8, 103.1, 56.0, 55.9, 27.8; IR (KBr) 3001, 2931, 1620, 1480, 1466, 1457, 1439, 1252, 1197, 1043, 836, 787 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{20}O_4Br$ 481.9728, found 481.9725.

*3.1.2. 9,10-Bis(bromomethyl)-2,3,6,7-tetramethoxyphenanthrene (**2A**) from **2C**.* A mixture of **2C** (817 mg, 2.506 mmol), AIBN (42 mg, 0.256 mmol), NBS (989 mg, 5.556 mmol) in CCl_4 (13 mL) was refluxed for 8 h. On cooling to room temperature water was added to the reaction mixture and the product was extracted into CH_2Cl_2, which was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed and flash chromatography on SiO_2 (petroleum ether/CH_2Cl_2, 1:2) afforded **2A** (780 mg, 65%) as yellow solid.

*3.1.3. 5,6,9,10-Tetramethoxy-2′-(tri-n-butylstannyl)-1,3-dihydrospiro [dibenzo[e,g]isoindole-2,1′-pyrrolidinium bromide (**10**).* To a solution of **9** (230 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) was dropwise added *B*-bromocatecholborane (0.2 M in CH_2Cl_2, 3 mL, 0.6 mmol), and after 10 min, 2 N NaOH (5 mL). It was followed by the addition of **2A** (240 mg, 0.5 mmol) in CH_2Cl_2 (12 mL). The resulting mixture was stirred at room temperature for 4 h, separated into layers and the aqueous phase extracted with CH_2Cl_2. The combined organic extract was dried over $MgSO_4$, evaporated and purified by flash chromatography on basic Al_2O_3 (CH_2Cl_2/MeOH, 80:1 to 15:1) to afford **10** (220 mg, 0.32 mmol, 65%) as light yellow solid: mp 80–82 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 2H), 7.02 (s, 1H), 6.94 (s, 1H), 5.75 (d, *J*=14.9 Hz, 1H), 5.28 (d, *J*=14.0 Hz, 1H), 5.17 (d, *J*=14.6, 1H), 4.84 (d, *J*=14.4 Hz, 1H), 4.31–4.37 (m, 2H), 4.14 (s, 6H), 4.03 (s, 6H), 3.71–3.77 (m, 1H), 2.37–2.58 (m, 4H), 0.83–1.04 (m, 18H), 0.66 (t, *J*=7.0 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 149.6, 149.5, 149.3, 125.9, 124.9, 123.80, 120.30, 120.21, 104.98, 104.80, 103.46, 103.40, 69.35, 68.87, 68.82, 68.16, 56.77, 56.58, 56.09, 56.0, 28.4, 27.3, 26.9, 22.6, 13.2, 9.4; IR (KBr) 2954, 2924, 2852, 1610, 1520, 1496, 1481, 1431, 1248, 1199, 1158, 1038, 851, 768, 748 cm^{-1}; HRMS (ESI) calcd for $C_{36}H_{54}{}^{*}Sn\ NO_4{}^{+}$ 676.3095, found 676.3122.

*3.1.4. Synthesis (±)-tylohporine (**1**) by Stevens rearrangement.* To a solution of **10** (76.4 mg, 0.10 mmol) in THF (4 mL) at −78 °C was add *n*-BuLi (2.5 M in hexane, 0.08 mL, 0.2 mmol) then warmed up to −35 °C and stirred for 18 h. Upon quenching with saturated $NaHCO_3$ the product was extracted into CH_2Cl_2. The combined organic extract was washed brine, dried over anhydrous Na_2SO_4, concentrated, and purified by flash chromatography on SiO_2 (CH_2Cl_2/MeOH, 20:1) to afford (±)-tylophorine **1** (15 mg, 37%) as a light yellow solid: mp 284–286 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 2H), 7.25 (s, 1H), 7.08 (s, 1H), 4.61 (d, *J*=14.4 Hz, 1H), 4.11 (s, 6H), 4.04 (s, 6H), 3.67 (d, *J*=15.0 Hz, 1H), 3.43–3.51 (m, 1H), 3.32 (d, *J*=15.8 Hz, 1H), 2.88–2.97 (m, 1H), 2.44–2.62 (m, 2H), 2.23–2.69 (m, 1H), 2.03–2.06 (m, 1H), 1.95–1.99 (m, 1H), 1.79–1.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 148. 5, 148.4, 126.0, 125.6, 124.1, 123.6, 123.3, 103.8, 103.2, 103.1, 102.9, 60.2, 56.0, 55.9, 55.8, 54.9, 53.4, 33.2, 31.0, 21.5; MS (ESI): *m*/*z* 394 ($M+H^+$); IR (KBr) 2951, 2922, 2854, 2830, 1618, 1514, 1468, 1426, 1247, 1212, 1149, 1018, 843, 773 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{27}NO_4$ 393.1940, found 393.1938.

*3.1.5. 1-Benzyl-5-hydroxy-5-(2-propynyl)pyrrolidin-2-one (**11A**).* To a mixture of *N*-benzylsuccinimide (946 mg, 5.0 mmol), Zn granule (651 mg, 10.0 mmol) and $PbBr_2$ (185 mg, 0.5 mmol) in anhydrous THF (3.0 mL) under N_2 was added propargyl bromide (0.6 mL, 7.7 mmol) dropwise over 15 min. The reaction mixture was stirred at room temperature for 30 min, another portion of and propargyl bromide (0.26 mL, 3.3 mmol) in anhydrous THF (7.0 mL) was added. On further stirring for 24 h and quenching with saturated aq NH_4Cl (30.0 mL) the product was extracted into EtOAc, washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by flash column chromatography on SiO_2 (petroleum ether/acetone, 3:1) to afford **11A** (823 mg, 72%) as a white solid: mp 85–86 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24–7.35 (m, 5H), 4.51 (s, 2H), 3.52 (s, 1H), 2.62 (dd, *J*=2.4, 17.0 Hz, 1H), 2.38–2.57 (m, 4H), 2.06–2.16 (m, 1H), 2.00

(s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 137. 8, 128.4, 128.0, 127.6, 91.2, 78.4, 71. 3, 42.4, 32.7, 30.2, 29.3; IR (KBr) 3269, 3208, 1956, 1667, 1498, 1452, 1413, 1359, 1179, 1144, 1084, 958, 715, 691 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{15}NO_2$ 229.1103, found 229.1104; Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.74; H, 6.59; N, 6.11. Found: C, 73.25; H, 6.67; N, 6.06.

*3.1.6. 1-Benzyl-5-(2-propynyl)-2-pyrrolidinone (**11B**).* To a solution of **11A** (1.147 g, 5.0 mmol) in anhydrous MeOH (25 mL) was added bromophenol blue (3 drops, 1 mg/mL) and $NaBH_3CN$ (320 mg, 5.1 mmol). The solution was adjusted to pH ~3 with 6 N HCl and stirred at room temperature for 1.5 h. After neutralized with 6 N NaOH, the mixture was evaporated. The residue was shaken in a mixture of water and EtOAc, separated and the organic solution was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. Flash column chromatography on SiO_2 (petroleum ether/acetone, 4:1) afforded **11A** (182 mg) and **11B** (803 mg, 90% brsm), the latter as a white solid: mp 95–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.36 (m, 5H), 5.06 (d, J=15.3 Hz, 1H), 3.99 (d, J=15.0 Hz, 1H), 3.59 (td, J=4.7, 12.9 Hz, 1H), 2.56–2.68 (m, 1H), 2.37–2.48 (m, 3H), 2.11–2.23 (m, 1H), 1.91–2.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 136.3, 128.7, 127.9, 127.5, 79.2, 71.1, 55.2, 44.1, 30.0, 23.4, 23.0; IR (KBr) 3288, 2935, 1684, 1579, 1496, 1419, 1305, 1251, 1166, 1084, 704 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{15}NO$ 213.1154, found 213.1151; Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.80; H, 7.23; N, 6.45.

*3.1.7. (Z)-1-Benzyl-5-[2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl-2-pyrrolidinone (**5**).* To a solution of **11B** (215 mg, 1.01 mmol) in degassed DMF (10 mL) were added $[B(pin)]_2$ (280 mg, 1.10 mmol) and $(Ph_3P)_4Pt$ (101 mg, 0.08 mmol) sequentially. After stirring at 80 °C for 24 h the mixture was cooled to room temperature, diluted with EtOAc (30 mL), washed with brine, and dried over anhydrous $MgSO_4$. Evaporation and purification by flash column chromatography on SiO_2 (petroleum ether/acetone, 3:1) afford **5** (390 mg, 85%) as a white solid: mp 178–179 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.32 (m, 5H), 5.91 (s, 1H), 5.04 (d, J=15.2 Hz, 1H), 3.96 (d, J=15.2 Hz, 1H), 3.51–3.60 (m, 1H), 2.79 (dd, J=1.5, 12.9 Hz, 1H), 2.28–2.52 (m, 2H), 2.06 (d, J=12.0 Hz, 1H), 1.91–2.00 (m, 1H), 1.68–1.79 (m, 1H), 1.26 (s, 12H), 1.18 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 150.1, 150.0, 136.5, 134.5, 134.4, 134.2, 134.1, 128.3, 127.8, 127.1, 83.6, 83.3, 55.7, 43.7, 42.9, 29.5, 24.6, 24.5, 23.2; IR (KBr) 2980, 2934, 1677, 1615, 1496, 1423, 1348, 1228, 1139, 973, 850, 705 cm^{-1}; HRMS (EI) calcd for $C_{26}H_{29}NO_5{}^{10}B_2$ 465.3087, found 465.3091; Anal. Calcd for $C_{26}H_{29}NO_5B_2$: C, 66.84; H, 8.41; N, 3.00. Found: C, 66.79; H, 8.29; N, 2.83.

*3.1.8. Synthesis of 1-benzyl-5-[(2,3,6,7-tetramethoxyphenan-thren-9-yl)methyl]-2-pyrrolidinone (**4**) by double Suzuki coupling.* A solution of **6** [Ref. 3] (44 mg, 0.10 mmol) and **5** (56 mg, 0.12 mmol) in THF (2 mL) was successively treated with (dppf)$PdCl_2$ (7.4 mg, 0.01 mmol) and 3 N K_3PO_4 (0.2 mL, 0.6 mmol) under N_2, and stirred at 60 °C for 3 days. Dilution with saturated NH_4Cl was followed by extraction with CH_2Cl_2. The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by flash column chromatography on SiO_2 (petroleum ether/acetone, 3:1) to afford **4** (24 mg, 50%) as a white solid: mp 258–260 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.74 (s, 1H), 7.36 (s, 1H), 7.26–7.33 (m, 3H), 7.20 (d, J=7.3 Hz, 2H), 7.15 (s, 1H), 6.92 (s, 1H), 5.22 (d, J=15.6 Hz, 1H), 4.10 (s, 3H), 4.09 (s, 3H), 4.03 (s, 3H), 3.89–3.99 (m, 2H), 3.67 (dd, J=3.8, 13.2 Hz, 1H), 3.55 (s, 3H), 2.73–2.81 (m, 1H), 2.52–2.62 (m, 1H), 2.35–2.46 (m, 1H), 1.79–1.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 148.9, 148.7, 148.7, 148.3, 136.3, 128.6, 128.4, 127.3, 127.2, 125.8, 125.6, 124.8, 124.7, 123.6, 107.7, 103.7, 103.1, 102.4, 55.9, 55.8, 55.8, 55.7, 55.3, 43.9, 37.4, 29.7, 24.1; IR (KBr) 2925, 2837, 1686, 1610, 1512, 1475, 1426, 1257, 1150, 1035, 847, 700 cm^{-1}; HRMS (EI) calcd for $C_{30}H_{31}NO_5$ 485.2202, found 485.2204.

*3.1.9. 1-Benzyl-2-[(2,3,6,7-tetramethoxyphenanthren-9-yl)-methyl] pyrrolidine (**12A**).* To a suspension of **4** (89 mg, 0.18 mmol) in anhydrous THF (15 mL) at 0 °C was added $LiAlH_4$ (35 mg, 0.92 mmol) in portions. After refluxed for 3 h, the mixture was cooled, quenched with aq Na_2SO_4 and filtered through Celite. The filtrate was concentrated, and purified by flash column chromatography on SiO_2 (CH_2Cl_2/MeOH, 40:1) to afford **12A** (71 mg, 83%) as a white solid: mp 105–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.74 (s, 1H), 7.45 (s, 1H), 7.40 (s, 1H), 7.26–7.38 (m, 5H), 7.16 (s, 1H), 4.27 (d, J=12.6 Hz, 1H), 4.10 (s, 3H), 4.08 (s, 3H), 4.01 (s, 3H), 3.99 (s, 3H), 3.57 (d, J=12.6 Hz, 1H), 3.33 (d, J=12.3 Hz, 1H), 2.97–3.03 (m, 2H), 2.90 (d, J=12.9 Hz, 1H), 2.18–2.23 (m, 1H), 1.63–1.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 148.7, 148.4, 139.4, 131.7, 129.0, 128.3, 127.0, 126.3, 125.6, 124.9, 124.8, 123.6, 107.9, 104.8, 103.3, 102.7, 64.3, 59.2, 56.0, 56.0, 55.8, 55.8, 54. 5, 38.8, 31.0, 22.0; IR (KBr) 3001, 2934, 2832, 1619, 1508, 1475, 1429, 1253, 1201, 1151, 1039, 772, 699 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{34}NO_4{}^+$ 472.2482, found 472.2494.

*3.1.10. 2-[(2,3,6,7-Tetramethoxyphenanthren-9-yl)methyl]-pyrrolidine (**12B**).* A suspension of **12A** (48 mg, 0.101 mmol) and 10% Pd/C (53.7 mg, 0.05 mmol) in anhydrous THF (5 mL) was stirred under H_2 (1 atm) for 2 days. The mixture was filtered through Celite and the residue was washed with MeOH (containing 3% $NH_3 \cdot H_2O$). The liquid was evaporated and the product was purified by flash column chromatography on SiO_2 (CH_2Cl_2/MeOH/Et_3N, 20:1:1) to afford **12B** (36.8 mg, 96%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.63 (s, 1H), 7.40 (s, 1H), 7.35 (s, 1H), 7.12 (s, 1H), 5.15 (br s, 1H), 4.04 (s, 3H), 4.03 (s, 6H), 3.97 (s, 3H), 3.64–3.66 (m, 1H), 3.41 (dd, J=7.0, 13.8 Hz, 1H), 3.13–3.25 (m, 2H), 2.94–3.02 (m, 1H), 1.82–1.93 (m, 2H), 1.59–1.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 148.8, 148.7, 148.6, 130.3, 126.1, 125.1, 124.8, 124.7, 123.7, 107.9, 104.5, 103.2, 102.5, 59.1, 56.2, 56.0, 55.9, 55.8, 45.8, 38.3, 31.1, 24.2; IR (KBr) cm^{-1} 3416, 2958, 2835, 1620, 1510, 1475, 1429, 1254, 1150, 1040, 843, 772, 733 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{27}NO_4$ 381.1940, found 381.1941.

*3.1.11. Synthesis of (±)-tylophorine (**1**) by Pictet–Spengler reaction.* To a solution of amine **12B** (36.5 mg, 0.10 mmol) in EtOH (2.5 mL) was added a formalin solution (0.55 mL, 7.34 mmol) and concentrated HCl (55 μL, 0.66 mmol) successively. The reaction mixture was refluxed for 2 days in the dark, evaporated to dryness, and treated with 20% KOH (5 mL). The aqueous phase was extracted with CH_2Cl_2, washed with brine and dried over anhydrous Na_2SO_4. Filtration, concentration, and purification by flash column chromatography on SiO_2 (CH_2Cl_2/MeOH, 20:1) afforded (±)-tylophorine **1** (31.5 mg, 84%) as a light yellow solid: mp 284–286 °C.

*3.1.12. 1-Benzyl-5-[3-(4,4′,5,5′-tetramethoxybiphenyl-2-yl)-2-propynyl]-2-pyrrolidinone (**14**).* To a solution of **13** (200 mg, 0.50 mmol) and **11B** (132 mg, 1.30 mmol) in anhydrous PhMe (4 mL) under N_2 were added piperidine (1.0 mL, 10.1 mmol), $(Ph_3P)_2PdCl_2$ (36 mg, 0.05 mmol), CuI (20 mg, 0.10 mmol) sequentially. The resulting mixture was stirred at 50 °C for 18 h, diluted with water, and extracted with CH_2Cl_2. The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by flash column chromatography on SiO_2 (petroleum ether/acetone, 5:1–3:1) to afford **14** (232 mg, 96%) as a white foam: mp 69–71 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.33 (m, 3H), 7.20 (d, J=7.6 Hz, 2H), 7.04–7.07 (m, 2H), 6.95 (s, 1H), 6.92 (d, J=8.5 Hz, 1H), 6.82 (s, 1H), 4.99 (d, J=15.2 Hz, 1H), 3.92 (d, J=15.2 Hz, 1H), 3.92 (s, 6H), 3.91 (s, 3H), 3.88 (s, 3H), 3.54 (td, J=4.6, 12.9 Hz, 1H), 2.51 (d, J=5.0 Hz, 2H), 2.28–2.47 (m, 2H),

1.98–2.08 (m, 1H), 1.73–1.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 149.0, 148.2, 148.1, 147.6, 137.2, 136.4, 133.3, 128.6, 127.8, 127.4, 121.5, 115.3, 113.1, 112.6, 112.3, 110.8, 85.6, 82.7, 56.0, 55.9, 55.5, 44.0, 29.9, 24.1, 23.5; IR (KBr) 3062, 2933, 2835, 1685, 1602, 1504, 1440, 1252, 1211, 1173, 1025, 858, 763 cm^{-1}; HRMS (EI) calcd for $C_{30}H_{31}NO_5$ 485.2202, found 485.2206.

*3.1.13. 1-Benzyl-5-((2,3,6,7-tetramethoxyphenanthren-9-yl)-methyl)-2-pyrrolidinone (**4**) from isomerization.* A solution of **14** (242 mg, 0.50 mmol) and DBU (120 μL, 0.78 mmol) in anhydrous NMP (5 mL) was refluxed for 3 h. The mixture was cooled, concentrated in vacuo, and purified by flash column chromatography on SiO_2 (petroleum ether/acetone, 3:1–2:1) to afford **4** (222 mg, 92%) as a white solid: mp 258–260 °C.

*3.1.14. (R)-5-(t-Butyldimethylsiloxymethyl)-2-pyrrolidinone (**15**).* To a solution of (*R*)-5-hydroxymethyl-2-pyrrolidinone (2.5 g, 21.5 mmol) in anhydrous CH_2Cl_2 (25 mL) were added TBSCl (3.9 g, 26.0 mmol) and imidazole (2.2 g, 32.5 mmol) successively. The resulting mixture was stirred at room temperature for 4 h, quenched with H_2O (10 mL) and separated into layers. The organic phase was washed with water, brine, dried over Na_2SO_4, and evaporated to afford **15** (4.98 g, 100%) as a colorless oil, which proved to be homogeneous. $[\alpha]_D^{20}$ −46.8 (*c* 0.72, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (br s, 1H), 3.70–3.78 (m, 1H), 3.60 (dd, *J*=4.1, 10.0 Hz, 1H), 3.43 (dd, *J*=7.3, 10.0 Hz, 1H), 2.30–2.36 (m, 2H), 2.09–2.21 (m, 1H), 1.67–1.79 (m, 1H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 66.4, 55.7, 29.9, 25.7, 22.7, 18.0, −5.6; MS (ESI): *m*/*z* 230 ($M+H^+$); IR (KBr) 3220, 3103, 2931, 2858, 1702, 1464, 1256, 1119, 1032, 838, 777, 665 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{24}NO_2Si^+$ 230.1570, found 230.1568; Anal. Calcd for $C_{11}H_{23}NO_2$: C, 57.59; H, 10.11; N, 6.11. Found: C, 57.47; H, 10.36; N, 5.72.

*3.1.15. (R)-5-(t-Butyldimethylsiloxymethyl)-1-(2-propynyl)-2-pyrrolidinone (**16**).* To a solution of **15** (2.42 g, 10.6 mmol) in anhydrous THF (12.5 mL) was added NaH (0.51 g, 60% suspension in mineral oil, 12.7 mmol) in portions at room temperature. After stirring for 0.5 h under N_2, propargyl bromide (1.7 mL, 21.7 mmol) was added via syringe. The resulting mixture was kept at room temperature for 24 h, quenched with saturated NH_4Cl (10 mL), extracted with CH_2Cl_2, washed with brine, and dried over anhydrous Na_2SO_4. After removal of solvent the crude product was purified by flash column chromatography on SiO_2 (petroleum ether/EtOAc, 8:1) to afford **16** (2.56 g, 90%) as a light yellow oil: $[\alpha]_D^{20}$ −21.3 (*c* 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (d, *J*=17.9 Hz, 1H), 3.87–3.91 (m, 1H), 3.79 (dd, *J*=3.5, 10.8 Hz, 1H), 3.73 (d, *J*=17.6 Hz, 1H), 3.63 (dd, *J*=3.8, 10.8 Hz, 1H), 2.42–2.53 (m, 1H), 2.27–2.39 (m, 1H), 2.20 (s, 1H), 2.05–2.16 (m, 1H), 1.82–1.92 (m, 1H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 78.1, 71.9, 63.6, 58.3, 30.4, 30.3, 25.7, 21.1, 18.1, −5.6; IR (KBr) 3312, 3233, 2930, 2857, 2111, 1692, 1471, 1417, 1359, 1253, 1115, 838, 778, 662 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{25}NO_2Si$ 267.1655, found 267.1652; Anal. Calcd for $C_{14}H_{25}NO_2Si$: C, 62.87; H, 9.42; N, 5.24. Found: C, 62.86; H, 9.41; N, 5.24.

*3.1.16. (R)-5-(t-Butyldimethylsiloxymethyl)-1-[3-(3′,4,4′,5-tetramethoxybiphenyl-2-yl)prop-2-ynyl]-2-pyrrolidinone (**17**).* Under N_2, to a solution of **13** (400 mg, 1.00 mmol) and **16** (350 mg, 1.30 mmol) in anhydrous PhMe (8 mL) were added piperidine (2.0 mL, 20.2 mmol), $(Ph_3P)_2PdCl_2$ (70 mg, 0.10 mmol) and CuI (21 mg, 0.11 mmol) sequentially. The resulting mixture was stirred at 50 °C for 24 h, diluted with water, and extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Flash column chromatography on SiO_2 (petroleum ether/acetone, 5:1) afforded **17** (516 mg, 0.96 mmol, 96%) as a yellow oil: $[\alpha]_D^{20}$ −34.2 (*c* 0.64, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, *J*=1.5 Hz, 1H), 7.04 (dd, *J*=1.8, 8.2 Hz, 1H), 6.99 (s, 1H), 6.91 (d, *J*=8.2 Hz, 1H), 6.83 (s, 1H), 4.80 (d, *J*=17.5, 1H), 3.94 (s, 3H), 3.92 (s, 6H), 3.91 (s, 3H), 3.71 (d, *J*=17.9 Hz, 1H), 3.61 (dd, *J*=2.6, 10.3 Hz, 1H), 3.41–3.50 (m, 2H), 2.38–2.47 (m, 1H), 2.24–2.34 (m, 1H), 1.89–1.99 (m, 1H), 1.75–1.86 (m, 1H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 148.9, 147.9, 147.8, 147.3, 137.2, 133.0, 121.0, 114.6, 112.4, 112.4, 111.9, 110.2, 84.1, 83.3, 62.6, 57.5, 55.6, 55.6, 55.5, 30.6, 30.1, 25.3, 20.6, 17.6, −6.0; IR (KBr) 2997, 2932, 2856, 2216, 1693, 1602, 1504, 1463, 1254, 1028, 858, 780 cm^{-1}; HRMS (EI) calcd for $C_{30}H_{41}NO_6Si$ 539.2703, found 539.2706.

*3.1.17. (R)-5-(t-Butyldimethylsiloxymethyl)-1-[(2,3,6,7-tetramethoxyphenanthren-9-yl)methyl]-2-pyrrolidinone (**18A**).* A solution of **17** (219 mg, 0.40 mmol) and DBU (100 μL, 0.65 mmol) in anhydrous NMP (4 mL) was refluxed for 1.5 h, cooled and concentrated in vacuo. Flash column chromatography on SiO_2 (petroleum ether/acetone, 3:1) afforded **18A** (191 mg, 87%) as a white foam: mp 78–80 °C; $[\alpha]_D^{20}$ −99.4 (*c* 0.60, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.77 (s, 1H), 7.67 (s, 1H), 7.46 (s, 1H), 7.18 (s, 1H), 5.60 (d, *J*=14.6 Hz, 1H), 4.26 (d, *J*=14.7 Hz, 1H), 4.12 (s, 3H), 4.11 (s, 3H), 4.03 (s, 6H), 3.82 (dd, *J*=3.2, 10.5 Hz, 1H), 3.53 (dd, *J*=2.7, 10.5 Hz, 1H), 3.35–3.37 (m, 1H), 2.53–2.65 (m, 1H), 2.32 (dt, *J*=7.0, 16.7 Hz, 1H), 1.82–1.90 (m, 2H), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 149.3, 149.0, 148.8, 148.7, 127.9, 126.1, 125.4, 124.8, 124.8, 124.6, 108.0, 105.3, 102.9, 102.6, 62.8, 57.6, 56.2, 56.0, 55.9, 55.8, 43.6, 30.6, 25.7, 21.5, 18.1, −6.0; IR (KBr) 2995, 2855, 2362, 1681, 1614, 1514, 1473, 1437, 1257, 1148, 1033, 837, 776 cm^{-1}; HRMS (EI) calcd for $C_{30}H_{41}NO_6Si$, 539.2703, found 539.2705.

*3.1.18. (R)-5-Hydroxymethyl-1-[(2,3,6,7-tetramethoxyphenanthren-9-yl)methyl]-2-pyrrolidinone (**18B**).* To a solution of **18A** (184 mg, 0.34 mmol) in anhydrous THF (3.5 mL) at 0 °C was added TBAF (0.50 mL, 1.0 *M* in THF, 0.50 mmol), stirred for 2 h and then quenched with saturated NH_4Cl (2 mL). The mixture was partitioned between $CHCl_3$ and water, and the aq phase was extracted with $CHCl_3$. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, evaporated, and purified by flash column chromatography on SiO_2 (CH_2Cl_2/MeOH, 40:1) to afford **18B** (128 mg, 95%) as a white solid: mp 251–253 °C; $[\alpha]_D^{20}$ −97.3 (*c* 0.56, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.76 (s, 1H), 7.62 (s, 1H), 7.51 (s, 1H), 7.18 (s, 1H), 5.43 (d, *J*=14.1 Hz, 1H), 4.34 (d, *J*=14.1 Hz, 1H), 4.11 (s, 6H), 4.03 (s, 6H), 3.81 (d, *J*=10.0 Hz, 1H), 3.43–3.49 (m, 2H), 2.59–2.67 (m, 1H), 2.36–2.41 (m, 1H), 2.12 (br s, 1H), 1.94–1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 149.6, 149.2, 149.1, 148.9, 127.9, 126.4, 125.6, 125.0, 124.7, 124.6, 108.2, 105.1, 103.2, 102.6, 62.6, 58.4, 56.4, 56.1, 56.0, 55.9, 44.4, 30.6, 21.1; IR (KBr) 3531, 2932, 2837, 1655, 1614, 1513, 1477, 1414, 1258, 1149, 1031, 837, 776 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{27}NO_6$, 425.1838, found 425.1839.

*3.1.19. Pentacyclic hydroxylactam **19**.* To a solution of **18B** (108 mg, 0.25 mmol) in anhydrous CH_2Cl_2 (7 mL) at 0 °C was added Dess–Martin periodinane (208 mg, 0.49 mmol). The resulting slurry was stirred at room temperature for 2 h, treated with 2-propanol (1 mL), diluted with saturated aq $NaHCO_3$, and extracted with CH_2Cl_2. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford a white residue. This crude aldehyde was dissolved in anhydrous CH_2Cl_2 (7.5 mL) at 0 °C, and treated with TFA (0.25 mL, 3.25 mmol) for 2 h, then diluted with CH_2Cl_2, and washed with saturated $NaHCO_3$. The aqueous phase was further extracted with CH_2Cl_2 and the combined organic phase was wash with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure. Flash column chromatography on SiO_2 (CH_2Cl_2/acetone, 3:1–1:1) gave **19** (82 mg, 76%) as a white solid: mp 285–287 °C; $[\alpha]_D^{20}$ −144.6 (*c* 0.52, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.57 (s, 1H), 7.55 (s, 1H), 6.43 (s, 1H),

5.01 (s, 1H), 4.82 (d, J=17.2 Hz, 1H), 4.16 (d, J=17.3 Hz, 1H), 4.08 (s, 3H), 4.06 (s, 3H), 4.04 (s, 3H), 3.79 (d, J=8.2 Hz, 1H), 3.62 (br s, 1H), 3.52 (s, 3H), 2.41–2.74 (m, 3H), 2.14–2.26 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 148.8, 148.7, 148.3, 126.8, 124.7, 123.9, 123.2, 122.4, 104.4, 102.7, 102.6, 102.2, 65.4, 58.3, 55.9, 55.7, 55.5, 40.7, 30.7, 18.9; MS (EI): IR (KBr) 3470, 3060, 2960, 2832, 1666, 1620, 1514, 1470, 1425, 1250, 1148, 1018, 834, 726 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{25}NO_6$ 423.1682, found 423.1676.

*3.1.20. Synthesis of (R)-(−)-tylophorine (1) from **19**.* A solution of **19** (85 mg, 0.20 mmol) in anhydrous CH_2Cl_2 (6 mL) was stirred with $BF_3{\cdot}Et_2O$ (0.13 mL, 1.02 mmol) and Et_3SiH (0.17 mL, 1.05 mmol) at −78 °C for 2 h. The mixture was brought to room temperature and kept for another 19 h, neutralized with saturated $NaHCO_3$ (3 mL), extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. To the white residue was suspended in anhydrous THF (18 mL) at 0 °C and $LiAlH_4$ (38.1 mg, 1.00 mmol) was cautiously added. After refluxing for 1 h it was cooled, quenched with $Na_2SO_4{\cdot}10H_2O$ and filtered through Celite. The filtrate was concentrated and purified by flash column chromatography on SiO_2 (CH_2Cl_2/MeOH, 20:1) to afford (*R*)-(−)-tylophorine (**1**) (67.1 mg, 85%) as a light yellow solid: mp 283–285 °C; $[\alpha]_D^{20}$ −80.0 (*c* 0.14, $CHCl_3$). Lit[4] $[\alpha]_D^{30}$ −76.0 (*c* 0.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 2H), 7.29 (s, 1H), 7.13 (s, 1H), 4.63 (d, J=14.9 Hz, 1H), 4.11 (s, 6H), 4.05 (s, 6H), 3.68 (d, J=14.6 Hz, 1H), 3.48 (t, J=7.6 Hz, 1H), 3.35 (d, J=14.9 Hz, 1H), 2.93 (dd, J=10.8, 14.9 Hz, 1H), 2.45–2.54 (m, 2H), 2.20–2.30 (m, 1H), 2.02–2.09 (m, 1H), 1.93–1.99 (m, 1H), 1.72–1.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 148.5, 148.4, 126.0, 125.6, 124.1, 123.6, 123.3, 103.8, 103.2, 103.1, 102.9, 60.2, 56.0, 55.9, 55.8, 54.9, 53.4, 33.2, 31.0, 21.5; IR (KBr) 2950, 2919, 2869, 2830, 1618, 1514, 1469, 1427, 1247, 1212, 1149, 1018, 843, 774 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{27}NO_4$ 393.1946, found 393.1940.

Acknowledgements

Contents of this paper are abstracted from the Ph.D. Thesis [B200818003508028] submitted by Q.-X.L. to the Shanghai Institute of Organic Chemistry on October 10, 2010. The authors are most grateful to Professor Henry N.C. Wong for allowing the work done under his auspices at the Shanghai-Hong Kong Joint Laboratory at SIOC. We also thank the Croucher Foundation for financial support.

References and notes

1. (a) Gopalakrishnan, C.; Shankaranarayan, D.; Kameswaran, L.; Natarajan, S. *Indian J. Med. Res.* **1979**, *69*, 513–520; (b) Gellert, E. *J. Nat. Prod.* **1982**, *45*, 50–73.
2. Rathnagiriswaran, A. N.; Venkatachalam, K. *Indian J. Med. Res.* **1935**, *22*, 433–441.
3. (a) Li, Z.; Jin, Z.; Huang, R. *Synthesis* **2001**, 2365–2379; (b) Bhakuni, D. S. *J. Indian Chem. Soc.* **2002**, *79*, 203–210.
4. (a) Govindachari, T. R.; Lakshmikantham, M. V.; Rajadurai, S. *Chem. Ind.* **1960**, 664; (b) Govindachari, T. R.; Lakshmikantham, M. V.; Rajadurai, S. *Tetrahedron* **1961**, *14*, 284–287; (c) Chauncy, B.; Gellert, E. *Aust. J. Chem.* **1970**, *23*, 2503–2516; (d) Herbert, R. B.; Moody, C. J. *J. Chem. Soc. D* **1970**, 121; (e) Liepa, A. J.; Summons, R. E. *J. Chem. Soc., Chem. Commun.* **1977**, 826–827; (f) Weinreb, S. M.; Khatri, N. A.; Shringarpure, J. *J. Am. Chem. Soc.* **1979**, *101*, 5073–5074; (g) Mangla, V. K.; Bhakuni, D. S. *Tetrahedron* **1980**, *36*, 2489–2490; (h) Khatri, N. A.; Shringarpure, J.; Schmitttthenner, H. F.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6387–6393; (i) Cragg, J. E.; Herbert, R. B.; Jackson, F. B.; Moody, C. J.; Nicolson, I. T. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2477–2485; (j) Iida, H.; Tanaka, M.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1983**, 271–272; (k) Comins, D. L.; Morgan, L. A. *Tetrahedron Lett.* **1991**, *32*, 5919–5922; (l) Pearson, W. H.; Walavalkar, R. *Tetrahedron* **1994**, *50*, 12293–12304; (m) Mclver, A.; Young, D. D.; Deiteres, A. *Chem. Commun.* **2008**, 4750–4752; (n) Yamashita, S.; Kurono, N.; Senboku, H.; Tokuda, M.; Orito, K. *Eur. J. Org. Chem.* **2009**, 1173–1180; (o) Niphakis, M. J.; Georg, G. I. *Org. Lett.* **2011**, *13*, 196–199; (p) Xu, X.; Liu, Y.; Park, C.-M. *Angew. Chem., Int. Ed.* **2012**, *51*, 1–6; (q) Lahm, G.; Stoye, A.; Opatz, T. *J. Org. Chem.* **2012**, *77*, 6620–6623.
5. (a) Buckley, T. F., III; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 4222–4232; (b) Nordlander, J. E.; Njoroge, F. G. *J. Org. Chem.* **1987**, *52*, 1627–1630; (c) Ihara, M.; Takino, Y.; Fukumoto, K.; Kametani, T. *Heterocycles* **1989**, *28*, 63–65; (d) Comins, D. L.; Chen, X. H.; Morgan, L. A. *J. Org. Chem.* **1997**, *62*, 7435–7438; (e) Jin, Z.; Li, S. P.; Wang, Q. M.; Huang, R. Q. *Chin. Chem. Lett.* **2004**, *15*, 1164–1166; (f) Fürstner, A.; Kennedy, J. W. J. *Chem.—Eur. J.* **2006**, *12*, 7398–7410; (g) Zeng, W.; Chemler, S. R. *J. Org. Chem.* **2008**, *73*, 6045–6047; (h) Wang, Z. W.; Li, Z.; Wang, K. L.; Wang, Q. M. *Eur. J. Org. Chem.* **2010**, 292–299; (i) Stoye, A.; Opatz, T. *Org. Lett.* **2010**, *12*, 2140–2141; (j) Yang, X. M.; Shi, Q.; Bastow, K. F.; Lee, K. H. *Org. Lett.* **2010**, *12*, 1416–1419; (k) Mai, D. N.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 12157–12159; (l) Hsu, S.-F.; Ko, C.-W.; Wu, Y.-T. *Adv. Synth. Catal.* **2011**, *353*, 1756–1762.
6. Ho, T.-L. *Symmetry. A Basis for Synthesis Design*; Wiley-Interscience: New York, NY, 1995.
7. McKillop, A.; Turrell, A. G.; Young, D. W.; Taylor, E. C. *J. Am. Chem. Soc.* **1980**, *102*, 6504–6512.
8. Kanno, K.-I.; Liu, Y. H.; Lesato, A.; Nakajima, K.; Takahashi, T. *Org. Lett.* **2005**, *7*, 5453–5456.
9. Weisgraber, K. H.; Weiss, U. *Can. J. Chem.* **1971**, *49*, 2366–2369.
10. Beak, P.; Kerrick, S. T.; Wu, S. D.; Chu, J. X. *J. Am. Chem. Soc.* **1994**, *116*, 3231–3239.
11. Shimizu, M.; Nagao, I.; Tomioka, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 8096–8099.
12. Kim, S. H.; Han, E. H. *Tetrahedron Lett.* **2000**, *41*, 6479–6482.
13. Drage, J. S.; Earl, R. A.; Vollhardt, P. C. *J. Heterocycl. Chem.* **1982**, *19*, 701–702.
14. Lacour, J.; Monchaud, D.; Bernardinelli, G.; Favarger, F. *Org. Lett.* **2001**, *3*, 1407–1410.
15. Wang, Y.; Burton, D. J. *Org. Lett.* **2006**, *8*, 5295–5298.
16. Kurtz, K. C. M.; Hsung, R. P.; Zhang, Y. S. *Org. Lett.* **2006**, *8*, 231–234.