Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 893–900
Tetrahedron

Isolation, structure elucidation, and total synthesis of two new *Chimonanthus* alkaloids, chimonamidine and chimonanthidine

Hiromitsu Takayama,* Yohei Matsuda, Kyohei Masubuchi, Atsushi Ishida, Mariko Kitajima and Norio Aimi

Graduate School of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

Received 5 November 2003; revised 15 November 2003; accepted 17 November 2003

Abstract—Two new tryptamine-related alkaloids, chimonamidine and chimonanthidine, were isolated from the seeds of *Chimonanthus praecox* Link. and their structures including absolute configuration were elucidated by spectroscopic analysis and biomimetic total synthesis from tryptamine.

1. Introduction

Recently, the potent antinociceptive activity of dimeric or polymeric pyrrolidinoindoline alkaloids that interact with opioid receptors has been reported by Elisabetsky–Verotta's group.[1] In our continuous chemical and pharmacological studies of indole alkaloids possessing analgesic activity,[2] we have been interested in compounds of this type, which have been isolated from plants belonging to genera *Calycanthaceae*, *Idiospermaceae*, and *Rubiaceae*.[3] Overman and co-workers have recently made several important contributions to the synthesis of this family of alkaloids.[4] We started with the investigation of the alkaloidal constituents in *Chimonanthus praecox* Link., which was used as folk medicine for the treatment of rheumatic arthritis in China. (+)-Calycanthine and (±)-chimonanthine were isolated from the roots of this plant by a Chinese group.[5] In the present study, we were able to isolate two new alkaloids, chimonamidine (**1**) and chimonanthidine (**2**), together with (+)-calycanthine, (−)-chimonanthine (**10**), (−)-folicanthine (**11**), and (−)-calycanthidine (**12**) from the MeOH extract of *C. praecox* seeds. In this paper, we report the structure elucidation of these new alkaloids by means of spectroscopic analysis and biomimetic total syntheses.

2. Results and discussion

2.1. Chimonamidine (1)

The new compound **1**, obtained as an amorphous powder, exhibited $[\alpha]_D^{19}=-12.6$ (*c* 0.06, EtOH). High-resolution FABMS analysis gave *m/z* 221.1290 $(M+H)^+$ (Δ±0 mmu) and established the molecular formula as $C_{12}H_{16}N_2O_2$. The splitting mode of the protons in the aromatic region (δ 6.74, d *J*=7.6 Hz; δ 7.24, dd *J*=7.6, 7.6 Hz; δ 6.66, dd *J*=7.6, 7.6 Hz; and δ 6.85, d *J*=7.6 Hz) in the ^{1}H NMR spectrum indicated the presence of an *o*-disubstituted benzene ring. Further, the chemical shift of the carbon (δ 148.3) on this benzene ring as well as the HMBC cross-peak between that carbon and the protons of the *N*-Me group (δ 2.85, 3H, s) suggested that **1** contained an *N*-Me aniline residue in the molecule. In addition, ^{1}H NMR, ^{13}C NMR and COSY spectra (Fig. 1) indicated the presence of one carbonyl carbon (δ 175.1), an isolated ethane fragment, one oxygenated quaternary carbon (δ 79.6), and an *N*-Me group, all of which constituted a γ-lactam ring having a hydroxyl function. These two units could be connected by HMBC cross-peaks between the aromatic proton at δ 6.85 (H4) and the oxygenated quaternary carbon (δ 79.6, C3) and between the protons (δ 2.41 and 2.73, $H_2$8) in the ethane bridge and the aromatic quaternary carbon (δ 124.6, C3a), leading to the construction of the structure of the new alkaloid, now named chimonamidine, to be formula **1**.

To establish the above structure inferred by spectroscopic analysis, we initially performed the total synthesis of (±)-**1**. The synthetic strategy was based on the following biogenetic speculation. As shown in Figure 1, a new alkaloid is expected to be formed from tryptamine (**3**) through conversion into an oxindole derivative, introduction of a

Keywords: Alkaloid; Chimonunthus; Isolation; Total synthesis.
* Corresponding author. Tel./fax: +81-432902902;
e-mail address: htakayam@p.chiba-u.ac.jp

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.11.034

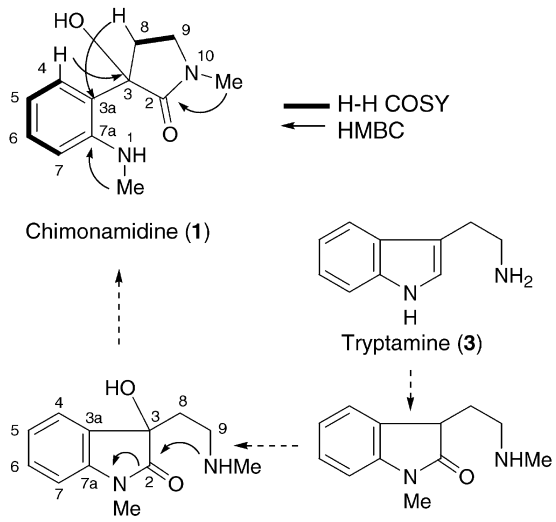
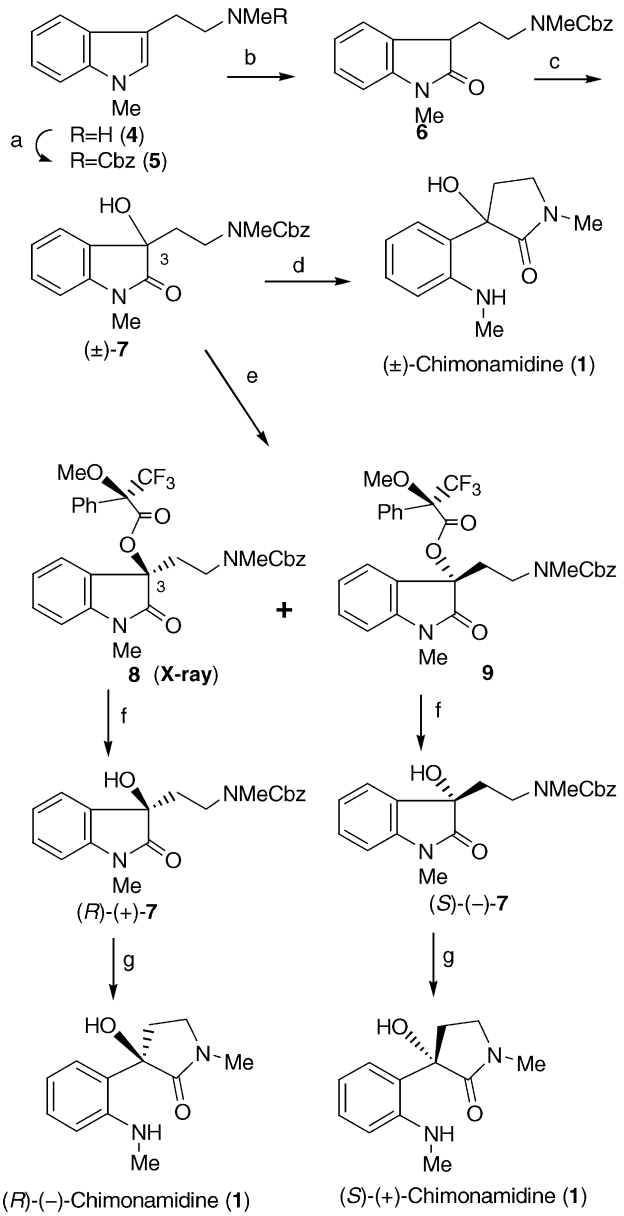


Figure 1. Selected 2D NMR correlations and hypothetical biogenetic route for chimonamidine (**1**).

hydroxyl function to the benzylic position, and transannulation of the lactam ring. Our biomimetic synthesis (Scheme 1) started with the preparation of *N*a,*N*b-dimethyl-*N*b-carbobenzyloxytryptamine (**5**) from a known tryptamine derivative (**4**).[6] The indole ring in **5** was then converted into oxindole (**6**) in 71% yield by oxidation with dimethyl sulfoxide and hydrochloric acid.[7] Next, a hydroxyl group was introduced to the benzylic position (C3) under oxygen atmosphere to give the racemic α-hydroxyketone (**7**) in a quantitative yield. Removal of the protecting group on the nitrogen with trimethylsilyl iodide gave a secondary amine that was gradually and spontaneously converted into the target molecule over two days in 66% isolated yield. The synthetic **1** (mp 213–215 °C) was found to be completely identical with the natural product by comparison of their chromatographic behavior and spectroscopic data including ^{1}H and ^{13}C NMR and MS spectra. Therefore, the structure of chimonamidine was determined to be formula **1**. Next, we synthesized chiral chimonamidine to determine the absolute configuration of the natural product, which exhibited $[\alpha]_D=-12.6$. Initial attempts at the asymmetric hydroxylation of **6** using Davis reagents[8] gave chiral hydroxyketone (**7**) up to 33% enantiomeric excess. Then, we employed an alternative strategy that involved the separation of the diastereomers of chiral ester derivatives. After several attempts, a pair of diastereomeric esters prepared from (+)-MTPA chloride and racemic alcohol (**7**) was found to be separable by SiO_2 column chromatography, and the more polar isomer (**8**) gave a crystal suitable for X-ray crystallographic analysis, revealing that the absolute stereochemistry at C3 in **8** had an *R* configuration. The ester function in **8** and **9** was respectively hydrolyzed with aqueous alkaline solution to afford chiral alcohols, (+)-**7** and (−)-**7**. Their optical purity was confirmed to be 100% ee by chiral HPLC analysis and the CD spectra exhibited antipodal curves, as shown in Figure 2.[9] Finally, the protecting group on the nitrogen in (+)-**7** and (−)-**7** was, respectively, removed with TMSI to give chiral chimonamidines. (*R*)-(−)-Chimonamidine (**1**) obtained from (*R*)-(+)-**7** showed $[\alpha]_D=-178$, whereas the enantiomeric (*S*)-(+)-chimonamidine (**1**) from (*S*)-(−)-**7** exhibited $[\alpha]_D=+171$. As a result, we confirmed that natural chimonamidine



Scheme 1. *Reagents and conditions*: (a) Cbz–Cl, Na_2CO_3, H_2O, CH_2Cl_2, 0 °C, quant. (b) conc. HCl, DMSO, phenol, AcOH, 0 °C, 71%. (c) 1 M NaOH, THF, O_2, rt, quant. (d) TMSI, CH_3CN, 0 °C to rt, 66%. (e) (*S*)-MTPA-Cl, DMAP, CH_2Cl_2, rt; **8**, 43%; **9**, 45%. (f) 0.5 M NaOH, MeOH, rt, quant. (g) TMSI, CH_3CN, 0 °C to rt; 55% from (+)-**7**; 50% from (−)-**7**.

($[\alpha]_D=-12.6$) comprises a mixture slightly enriched with the (*R*)-(−)-enantiomer.[10]

2.2. Chimonanthidine (2)

The new compound **2**, obtained as an amorphous powder, exhibited $[\alpha]_D^{20}=-285$ (*c* 0.05, EtOH). High-resolution FABMS analysis gave *m*/*z* 361.2392 $(M+H)^+$(Δ ±0 mmu) and established the molecular formula as $C_{23}H_{28}N_4$. The UV, ^{1}H and ^{13}C NMR spectra strongly resembled those of known dimeric pyrrolidinoindoline-type alkaloids, chimonanthine (**10**),[3b,11] folicanthine (**11**),[6,12] and calycanthidine (**12**),[13] which were simultaneously isolated from this plant. The ^{1}H NMR spectrum showed the presence of three methyl groups attached to nitrogen atoms. Their chemical shifts, δ 2.36, 2.84, and 2.98, suggested that one methyl group

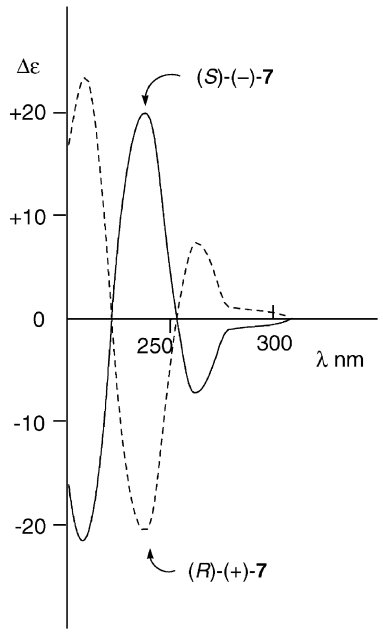


Figure 2. CD spectra of (−)- and (+)-3-hydroxyoxindoles (**7**).

existed on the aliphatic nitrogen atom and the other two were on the nitrogen of aniline function. Therefore, the structure of the new alkaloid, now named chimonanthidine, was deduced to be formula **2** i.e. *N*b-monodemethylfolicanthine (Fig. 3).

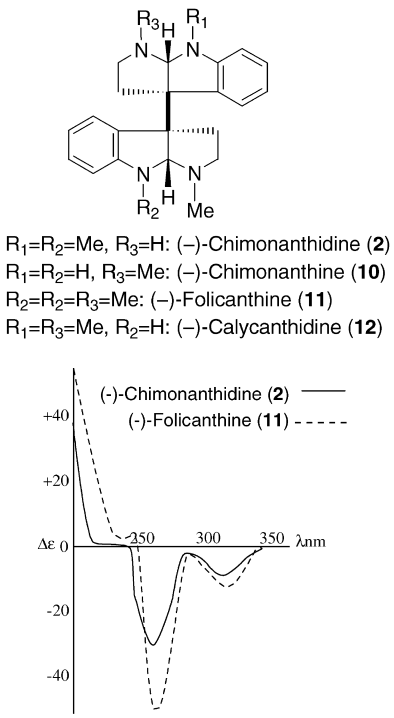


Figure 3. Structures and CD spectra of chimonanthidine (**2**) and folicanthine (**11**).

To establish the above structure inferred by spectroscopic analysis, we attempted the total synthesis of (±)-**2**. Recently, we have developed a new synthetic procedure that uses hypervalent iodine(III) reagents for the dimerization of indole derivatives,[14] and applied it to the concise total synthesis of chimonanthines.[15] We utilized this method for the synthesis of **2** as follows. *N*a-Methyl-*N*b-2-trimethylsilylethoxycarbonyl (Teoc) tryptamine (**14**), prepared from known compound **13**,[16] was treated with 0.5 equiv. phenyliodine (III) bis(trifluoroacetate) (PIFA) in CF_3CH_2OH at −40 °C to give two dimerization products (**15**) and (**16**) in 16 and 21% yields, respectively. To elucidate their relative stereochemistry, those two compounds were transformed into known compounds. On reduction with Red-Al in toluene, the less polar product (**16**) gave *rac*-folicanthine (*rac*-**12**),[6] whereas the more polar one **15** produced *meso*-folicanthine (**17**), demonstrating the relative stereochemistry of the two dimerization products. For the completion of the total synthesis of the new alkaloid, *rac*-(**16**) was employed again for further transformation. Elimination of one of two protecting groups on the nitrogen atoms was carried out by treatment of **16** with 1.0 equiv. tetrabutyl ammonium fluoride in THF at room temperature for 6 h to give the desired monodeprotected amine (**18**) in 33.4% yield together with 51.3% of the recovered starting material. Finally, the remaining carbamate group in **18** was converted into the *N*-methyl function by reduction with Red-Al to furnish target molecule **2** in 73.4% yield. Synthetic **2** was completely identical in all respects (chromatographic behavior; mass; IR; UV; ^1H and ^{13}C NMR) with natural chimonanthidine except for the optical property. The CD spectrum of natural **2** exhibited Cotton curves very similar to those of (−)-folicanthine (**11**), the absolute configuration of which was determined by chemical correlation with (−)-chimonanthine (**10**).[17] The absolute stereochemistry of (−)-chimonanthine has been recently corrected by Overman et al.[18] Therefore, the structure including the absolute configuration of (−)-chimonanthidine was determined to be formula **2** (Scheme 2).

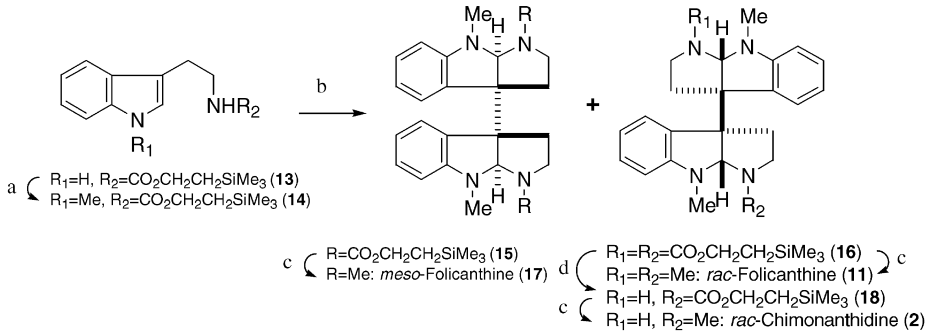
3. Experimental

3.1. General

UV: Recorded in MeOH on a JASCO V-560 instrument. IR: recorded on a JASCO FT/IR-230 spectrophotometer. ^1H and ^{13}C NMR spectra: recorded on JEOL JNM A-400, JNM A-500, JNM ECP-400, or JNM ECP-600 spectrometers, *J* values are given in Hz. EI-MS: direct probe insertion at 70 eV recorded on a JEOL JMS GC-mate spectrometer. FAB-MS: recorded on a JEOL JMS-HX110 mass spectrometer. Optical rotation: measured using a JASCO P-1020 polarimeter. CD: recorded on a JASCO J-720WI spectrometer. TLC: precoated Kieselgel 60 F_{254} plates (Merck, 0.25 mm thick). Column Chromatography: Kieselgel 60 [Merck, 70-230 (for open chromatography) and 230–400 mesh (for flash chromatography)], amino silica gel [Fuji Silysia Chemical, NH-DM1020], medium pressure liquid column chromatography: silica gel prepacked column Kusano CPS-HS-221-05.

3.2. Plant material

The seeds of *Chimonanthus praecox* Link. were collected in June at the medicinal plant garden in the Faculty of Pharmaceutical Sciences, Chiba University, and identified



Scheme 2. *Reagents and conditions*: (a) MeI, NaH, DMF, −20 °C, 94%. (b) 0.5 equiv. PIFA, CF_3CH_2OH, −40 °C; **15**, 16%; **16**, 21%; **14**, 5%. (c) Red-Al, toluene, reflux; *meso*-**17**, 96%. *rac*-**11**, 95%; *rac*-**2**, 73.4%. (d) 1.0 equiv. TBAF, THF, rt, 6 h; **18**, 33.4%; **16**, 51.3%.

by Dr Fumio Ikegami, Graduate School of Pharmaceutical Sciences, Chiba University, Japan. A voucher specimen was deposited at the Herbarium of the Graduate School of Pharmaceutical Sciences, Chiba University.

3.3. Extraction and isolation of alkaloids

The dried powdered seeds (2.5 kg) of *C. praecox* were macerated with MeOH (2.0 L) four times and filtered. The combined filtrates were concentrated under reduced pressure to give a crude extract (97.3 g), which was then dissolved in 10% aqueous acetic acid (2.0 L). The solution was washed with ethyl acetate (600 mL), alkalinized with Na_2CO_3 (pH 10), and then exhaustively extracted with $CHCl_3$. The organic layer was washed with water, dried over $MgSO_4$, and evaporated to give a crude alkaloidal fraction (15.37 g). From this fraction, crude crystalline calycanthine (11.38 g) was directly obtained, a portion (998 mg) of which was recrystallized from ethyl acetate to give pure (+)-calycanthine (632 mg). The mother liquid (3.8 g) of the first crystallization was roughly separated by silica gel flash column chromatography using a $CHCl_3$–MeOH/$CHCl_3$ gradient to give twelve fractions. The 10% MeOH/$CHCl_3$ eluate was recrystallized from ethyl acetate to give 352 mg of (−)-folicanthine (**11**). The 20% MeOH/$CHCl_3$ eluate was purified by SiO_2 medium pressure liquid chromatography (20% MeOH/ethyl acetate) to give 2.6 mg of chimonamidine (**1**) and 22 mg of (−)-calycanthidine (**12**). The 30% MeOH/$CHCl_3$ eluate of the first column chromatography was purified by reverse phase medium pressure liquid chromatography (30% H_2O/MeOH) to give 22 mg of (−)-chimonanthine (**10**) and 13 mg of chimonanthidine (**2**).

3.3.1. Chimonamidine (1). Amorphous powder; $[\alpha]_D^{19}=-12.6$ (*c* 0.06, EtOH); UV (MeOH) λ_{max} 202, 246, 300 nm; IR (neat) ν_{max} 3378, 1695 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.24 (1H, dd, *J*=7.6, 7.6 Hz, H-6), 6.85 (1H, d, *J*=7.6 Hz, H-4), 6.74 (1H, d, *J*=7.6 Hz, H-7), 6.66 (1H, dd, *J*=7.6, 7.6 Hz, H-5), 3.88 (1H, br-s, N_1–H), 3.31 (1H, ddd, *J*=9.8, 9.8, 1.2 Hz, H-9), 3.24 (1H, ddd, *J*=9.8, 9.8, 6.4 Hz, H-9), 2.97 (3H, s, N_{10}–CH_3), 2.85 (3H, s, N_1–CH_3), 2.73 (1H, ddd, *J*=12.8, 6.4, 1.2 Hz, H-8), 2.41 (1H, ddd, *J*=12.8, 9.8, 9.8 Hz, H-8); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.1 (C-2), 148.3 (C-7a), 129.4 (C-6), 125.4 (C-4), 124.6 (C-3a), 116.7 (C-5), 111.7 (C-7), 79.6 (C-3), 45.7 (C-9), 33.0 (C-8), 30.2 and 30.1 (*N*-Me×2); FABMS (NBA) *m/z*: 221 $[M+H]^+$; HRFABMS (NBA) *m/z*: 221.1290 (calcd for $C_{12}H_{17}N_2O_2$, 221.1290).

3.3.2. Chimonanthidine (2). Amorphous powder; $[\alpha]_D^{20}=-285$ (*c* 0.05, EtOH); UV (MeOH) λ_{max} 208, 245, 300 nm; IR (neat) ν_{max} 2938, 1603, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 2.03–2.07 (2H, m, H-3, 3′), 2.24–2.31 (1H, m, H-3′), 2.36 (3H, s, N_1–CH_3), 2.44–2.51 (3H, m, H-2, 3, 2′), 2.61–2.64 (1H, m, H-2), 2.84 (3H, s, $N_{8'}$–CH_3), 2.94–2.97 (1H, m, H-2′), 2.98 (3H, s, N_8–CH_3), 4.18 (1H, br-s, H-8a), 4.58 (1H, br-s, H-8′a), 6.24 (1H, d, *J*=8.1 Hz, H-7′), 6.34 (1H, d, *J*=7.8 Hz, H-7), 6.52 (1H, dd, *J*=7.4, 7.4 Hz, H-5′), 6.56 (1H, dd, *J*=7.6, 7.6 Hz, H-5), 7.00–7.06 (4H, m, H-4, 6, 4′, 6′); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 31.1 ($N_{8'}$–CH_3), 35.0 (C-3), 35.3 (N_8–CH_3), 38.2 (C-3′), 38.3 (N_1–CH_3), 45.6 (C-2′), 53.0 (C-2), 62.4 (C-3a, 3′a), 87.2 (C-8′a), 92.5 (C-8a), 104.7 (C-7′), 106.2 (C-7), 116.2 (C-5′), 116.9 (C-5), 124.3 (C-4′), 124.4 (C-4), 128.4 (C-6, 6′), 131.8 (C-3′b), 132.6 (C-3b), 152.5 (C-7′a), 152.8 (C-7a); FABMS (NBA) *m/z*: 361 $[M+H]^+$; HRFABMS (NBA) *m/z*: 361.2392 (calcd for $C_{23}H_{29}N_4$, 361.2392).

3.3.3. Calycanthidine (12). The ^1H and ^{13}C NMR data of the known alkaloid **12** have not been published so far. Thus, we present them here; ^1H NMR ($CDCl_3$, 500 MHz, VT 50 °C) δ 7.07 (1H, d, *J*=7.3 Hz, H-4), 6.52 (1H, dd, *J*=7.3, 7.3 Hz, H-5), 6.98 (1H, dd, *J*=7.3, 7.6 Hz, H-6), 6.27 (1H, d, *J*=7.6 Hz, H-7), 7.02 (1H, d, *J*=7.3 Hz, H-4′), 6.59 (1H, dd, *J*=7.3, 7.3 Hz, H-5′), 6.92 (1H, dd, *J*=7.3, 7.6 Hz, H-6′), 6.48 (1H, d, *J*=7.6 Hz, H-7′), 4.38 (1H, br-s, 8a-H), 4.42 (1H, br-s, 8a′-H), 2.98 (3H, s, N_8–CH_3), 2.38 (3H, s, N_1–CH_3), 2.33 (3H, s, $N_{1'}$–CH_3), 2.40–2.65 (6H, m, 2-H_2, 2′-H_2, 3-H_1, 3′-H_1), 1.95–2.05 (2H, m, 3-H_1, 3′-H_1); ^{13}C NMR ($CDCl_3$, 125 MHz, VT 50 °C) δ 52.6 (C-2), 35.7 (C-3), 62.8 (C-3a), 132.7 (C-3b), 123.6 (C-4), 116.7 (C-5), 128.1 (C-6), 105.9 (C-7), 152.8 (C-7a), 91.8 (C-8a), 37.9 (N_1–CH_3), 35.4 (N_8–CH_3), 52.6 (C-2′), 35.7 (C-3′), 63.2 (C-3a′), 133.3 (C-3b′), 124.4 (C-4′), 118.2 (C-5′), 127.9 (C-6′), 109.0 (C-7′), 150.8 (C-7a′), 85.0 (C-8a′), 37.0 (N_1–CH_3).

3.4. Synthesis of chimonamidine

3.4.1. *N*a,*N*b-Dimethyl-*N*b-carbobenzyloxytryptamine (5). Under argon atmosphere, a solution of benzyl

chloroformate (2.0 mL, 13.86 mmol) in dry dichloromethane (25 mL) and a solution of Na_2CO_3 (1.336 g) in water (40 mL) were simultaneously added dropwise to a stirred solution of **4** (2.36 g, 12.55 mmol) in dichloromethane (40 mL) at 0 °C. After being stirred at the same temperature for 1 h, the reaction mixture was transferred into a separatory funnel. The organic layer was drawn off and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by pre-packed silica gel column chromatography (10% acetone/chloroform) to give 3.48 g (86%) of **5** as a colorless oil; IR ν_{max} ($CHCl_3$) cm^{-1}: 1692; UV λ_{max} (MeOH) nm: 209, 225.5, 289.5; ^1H NMR (DMSO-d_6, 400 MHz, VT 100 °C) δ 2.87 (3H, s), 2.93 (2H, m), 3.51 (2H, m), 3.70 (3H, s), 5.05 (2H, s), 6.98 (1H, ddd, J=7.9, 7.0, 1.0 Hz), 7.03 (1H, s), 7.12 (1H, ddd, J=7.9, 7.0, 1.0 Hz), 7.30–7.37 (6H, m), 7.49 (1H, d, J=7.9 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz, VT 100 °C) δ 22.8, 31.6, 33.7, 49.0, 65.7, 108.9, 110.5, 117.8, 120.6, 126.6, 126.8, 126.9, 127.1, 127.2, 127.8, 136.5, 136.7, 155.0; FABMS (NBA+KI) *m/z*: 361 $[M+K]^+$; HRFABMS (NBA+KI) *m/z*: 361.1309 (calcd for $C_{20}H_{22}N_2O_2K$ $[M+K]^+$, 361.1318).

3.4.2. Preparation of oxindole (6). To a stirred mixture of conc. HCl (3.20 mL), DMSO (0.81 mL, 11 mmol), and phenol (0.16 mL, 1.9 mmol) in acetic acid (40 mL) was added dropwise a solution of **5** (3.05 g, 9.49 mmol) in acetic acid (10 mL) at 0 °C. Stirring was continued for 10 min at the same temperature. The reaction mixture was poured into chilled water and then alkalinized with saturated aqueous Na_2CO_3 solution. The whole mixture was extracted three times with chloroform. The combined extract was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel flash column chromatography (40% ethyl acetate in *n*-hexane) to give 2.27 g (71%) of **6** as a colorless oil; IR ν_{max} ($CHCl_3$) cm^{-1}: 1695, 1613; UV λ_{max} (MeOH) nm: 208, 254; ^1H NMR (DMSO-d_6, 400 MHz, VT 100 °C) δ 2.06 (2H, m), 2.81 (3H, s), 3.10 (3H, s), 3.29 (1H, m), 3.43 (2H, m), 5.00 (1H, d, J=12.8 Hz), 5.02 (1H, d, J=12.8 Hz), 6.93 (1H, d, J=7.5 Hz), 6.99 (1H, dd, J=7.5, 7.5 Hz), 7.23–7.36 (7H, m); ^{13}C NMR (DMSO-d_6, 100 MHz, VT 100 °C) δ 25.3, 27.6, 33.4, 42.2, 45.2, 65.7, 107.6, 121.3, 123.0, 125.9, 126.9, 127.1, 127.2, 127.4, 127.7, 128.0, 136.6, 143.7, 154.9, 176.0; FABMS (NBA) *m/z*: 339 $[M+H]^+$; HRFABMS (NBA) *m/z*: 339.1704 (calcd for $C_{20}H_{23}N_2O_3$ $[M+H]^+$, 339.1709).

3.4.3. Preparation of (±)-3-hydroxyoxindole (7). Under oxygen atmosphere, a solution of **6** (992 mg, 3.0 mL) in THF (2 mL) and 1 M aqueous NaOH (3.0 mL) was stirred for 4 h at room temperature. The reaction mixture was diluted with water and then extracted three times with chloroform. The combined extract was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (60% ethyl acetate in *n*-hexane) to give 1.21 g (y. quant) of (±)-**7** as colorless prisms; mp 128–129 °C (AcOEt); IR ν_{max} (KBr) cm^{-1}: 3290; UV λ_{max} (MeOH) nm: 209, 258.5; ^1H NMR (DMSO-d_6, 400 MHz, VT 100 °C) δ 2.04 (2H, m), 2.73 (3H, s), 3.08 (3H, s), 3.20 (2H, m), 4.96 (1H, d, J=12.8 Hz), 4.99 (1H, d, J=12.8 Hz), 5.69 (1H, s), 6.93 (1H, dd, J=8.1, 0.9 Hz), 7.02 (1H, ddd, J=7.5, 7.5, 0.9 Hz), 7.26–7.36 (7H, m); ^{13}C NMR (DMSO-d_6, 100 MHz, VT 100 °C) δ 25.2, 33.2, 35.0, 43.0, 65.6, 73.5, 107.8, 118.6, 121.6, 122.9, 126.7, 127.0, 127.7, 128.5, 136.6, 142.7, 154.7, 176.4; FABMS (NBA) *m/z*: 355 $[M+H]^+$. Anal. calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.48; H, 6.29; N, 7.83.

3.4.4. (±)-Chimonamidine (1). To a stirred solution of (±)-**7** (37.4 mg, 0.11 mmol) in dry CH_3CN (3 mL) was added trimethysilyl iodide (60 μL, 0.42 mmol) at 0 °C and the mixture was stirred at the same temperature for 6 h and then at room temperature for 13 h. The reaction mixture was poured into 10% aqueous HCl solution and then extracted with ether. The acidic aqueous layer was alkalinized with 10% aqueous KOH solution and then extracted three times with chloroform. The combined extract was washed with water, dried over solid K_2CO_3, and concentrated to give a residue that was allowed to stand for two days in a desiccator. The thus obtained crude product was recrystallized from ethyl acetate to give 15.4 mg (66%) of (±)-chimonamidine as colorless needles; mp 213–215 °C (AcOEt). Anal. calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.21; H, 7.32; N, 12.55. The synthetic compound was found to be completely identical with the natural product by comparison of their chromatographic behavior and spectroscopic data (^1H and ^{13}C NMR, UV, IR and MS spectra).

3.4.5. Preparation and separation of MTPA-esters (8 and 9). A mixture of (±)-**7** (51.9 mg, 0.147 mmol), (*S*)-MTPA-chloride (41 μL, 0.22 mmol), and DMAP (36.4 mg, 0.29 mmol) in dry dichloromethane (1 mL) was stirred for 1.5 h at room temperature under argon atmosphere. Water was added to the reaction mixture, which was then extracted three times with chloroform. The combined extract was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by pre-packed silica gel column chromatography (acetone/chloroform/*n*-hexane=1:9:10) to give 37.9 mg (y. 45%) of less polar **9** and 35.7 mg (y. 43%) of more polar **8**. **8**; colorless prisms, mp 130–131 °C (MeOH); $[\alpha]_D^{24}$=+9.2 (*c* 0.152, $CHCl_3$); IR ν_{max} (KBr) cm^{-1}: 1729, 1697; UV λ_{max} (MeOH) nm: 214.5, 259; ^1H NMR (DMSO-d_6, 600 MHz, VT 100 °C) δ 2.20 (2H, m), 2.69 (3H, s), 3.19 (3H, s), 3.25 (2H, m), 3.48 (3H, s), 4.98 (1H, d, J=12.6 Hz), 4.99 (1H, d, J=12.6 Hz), 7.07–7.12 (2H, m), 7.26–7.49 (12H, m); ^{13}C NMR (DMSO-d_6, 150 MHz, VT 100 °C) δ 26.9, 34.3, 43.1, 55.8, 66.8, 81.3, 84.8, 109.7, 123.3, 123.5, 124.6, 126.0, 127.85, 127.92, 128.2, 128.8, 129.0, 130.4, 131.1, 131.9, 137.5, 144.4, 155.7, 164.3, 172.8; FABMS (NBA) *m/z*: 571 $[M+H]^+$; HRFABMS (NBA) *m/z*: 571.2103 (calcd for $C_{30}H_{30}N_2O_6F_3$ $[M+H]^+$, 571.2056); CD (*c* 0.195 mmol/L, MeOH, 23 °C) λ nm ($\Delta\varepsilon$): 206 (+12.6), 218 (0), 231 (−15.1), 249 (0), 258 (+2.9), 274 (0). **9**; colorless oil, $[\alpha]_D^{24}$=−5.2 (*c* 0.39, $CHCl_3$); IR ν_{max} (KBr) cm^{-1}: 1728, 1696; UV λ_{max} (MeOH) nm: 214.5, 259; ^1H NMR (DMSO-d_6, 600 MHz, VT 100 °C) δ 2.20 (2H, m), 2.71 (3H, s), 3.20 (3H, s), 3.28 (2H, m), 3.47 (3H, s), 4.97 (1H, d, J=12.6 Hz), 4.98 (1H, d, J=12.6 Hz), 7.07–7.13 (3H, m), 7.25–7.34 (5H, m), 7.41–7.52 (6H, m); ^{13}C NMR (DMSO-d_6, 150 MHz, VT 100 °C) δ 26.9, 34.4, 43.1, 55.7, 66.8, 81.3, 84.9, 109.7, 123.2,

123.3, 124.6, 125.9, 127.7, 127.9, 128.2, 128.8, 129.0, 130.5, 131.1, 132.0, 137.5, 144.5, 155.7, 164.2, 172.9; FABMS (NBA) *m/z*: 571 $[M+H]^+$; HRFABMS (NBA) *m/z*: 571.2048 (calcd for $C_{30}H_{30}N_2O_6F_3$ $[M+H]^+$; 571.2056); CD (*c* 0.195 mmol/L, MeOH, 23 °C) λ nm (Δε): 206 (−21.7), 218 (0), 231 (+24.0), 250 (0), 259 (-5.7), 274 (0).

3.4.6. X-ray crystallographic analysis of 8. All measurements were conducted on a Quantum CCD area detector coupled with a CCD diffractometer with graphite monochromated Mo Kα radiation (λ=0.71069 Å). Crystal data: orthorhombic, $C_{30}H_{29}N_2O_6F_3$ (M_w: 570.56), space group $P2_12_12$ with *a*=9.318(2) Å, *b*=10.628(2) Å, *c*=27.933(5) Å, *V*=2766.1(9) Å^3, *Z*=4, and D_{calc}=1.370 g/cm^3. The structure was solved by direct methods (SIR97) and expanded using Fourier techniques (DIRDIF94). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 6504 reflections ($I>0.00\sigma(I)$, $2\theta<57.35°$) and 371 variable parameters and converged with unweighted and weighted agreement factors of R=0.091 and R_w=0.111.

3.4.7. Alkaline hydrolysis of 8. Under argon atmosphere, a mixture of **8** (15.8 mg, 0.028 mmol) in 0.5 M aqueous NaOH solution (0.5 mL) and MeOH (0.5 mL) was stirred at room temperature for 20 h and then heated under reflux for 1.5 h. The reaction mixture was diluted with water and extracted three times with chloroform. The combined extract was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel short column chromatography (AcOEt) to give 10.6 mg (y. quant) of (+)-**7** as a colorless amorphous powder; $[\alpha]_D^{25}$=+21.3 (*c* 0.67, $CHCl_3$); CD (*c* 0.458 mmol/L, MeOH, 23 °C) λ nm (Δε): 208 (+23.6), 222 (0), 238 (−20.7), 253 (0), 263 (+7.4), 308 (0). This compound was found to be identical with racemate described above by comparison of their chromatographic behavior and spectroscopic data (^{1}H and ^{13}C NMR, IR, UV, and MS spectra).

3.4.8. Alkaline hydrolysis of 9. Under argon atmosphere, a mixture of **9** (6.9 mg, 0.012 mmol) in 0.5 M aqueous NaOH solution (0.5 mL) and MeOH (0.5 mL) was stirred at room temperature for 90 h. The reaction mixture was diluted with water and extracted three times with chloroform. The combined extract was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel short column chromatography (AcOEt) to give 4.7 mg (y. quant) of (−)-**7** as a colorless amorphous powder; $[\alpha]_D^{25}$=−21.3 (*c* 0.58, $CHCl_3$); CD (*c* 0.432 mmol/L, MeOH, 23 °C) λ nm (Δε): 208 (−21.8), 222 (0), 238 (+19.6), 253 (0), 263 (−7.1), 308 (0). This compound was found to be identical with racemate described above by comparison of their chromatographic behavior and spectroscopic data (^{1}H and ^{13}C NMR, IR, UV, and MS spectra).

3.4.9. Preparation of (*R*)-(−)-Chimonamidine. (+)-**7** (185 mg, 0.52 mmol) was treated according to the procedure described above for the synthesis of (±)-**1**. The residue obtained by work-up was allowed to stand for three days in a desiccator and then purified by pre-packed silica gel column chromatography (50% ethyl acetate in *n*-hexane) to give 64 mg (y. 55%) of (−)-chimonamidine **1** as a colorless amorphous powder. $[\alpha]_D^{23}$=−177.8 (*c* 0.17, EtOH); CD (*c* 0.582 mmol/L, MeOH, 23 °C) λ nm (Δε): 201 (−27), 215 (0), 224 (−2.9), 234 (0), 246 (+3.6), 257 (0), 297 (−3.7), 321 (0); HRFABMS (NBA) *m/z*: 221.1308 (calcd for $C_{12}H_{17}N_2O_2$, 221.1290). The synthetic compound was found to be identical with the natural product by comparison of their chromatographic behavior and spectroscopic data (^{1}H and ^{13}C NMR, IR, UV, and MS spectra).

3.4.10. Preparation of (*S*)-(+)-Chimonamidine. (−)-**7** (10 mg, 0.029 mmol) was treated according to the procedure described above. The residue obtained by work-up was allowed to stand for ten days in a desiccator and then purified by pre-packed silica gel column chromatography (50% ethyl acetate in *n*-hexane) to give 3.2 mg (y. 50%) of (+)-chimonamidine **1** as a colorless amorphous powder. $[\alpha]_D^{23}$=+170.7 (*c* 0.18, EtOH); CD (*c* 0.582 mmol/L, MeOH, 23 °C) λ nm (Δε): 202 (+24.4), 215 (0), 226 (+3.1), 237 (0), 251 (−3.2), 257 (0), 298 (+3.5), 321 (0); HRFABMS (NBA) *m/z*: 221.1296 (calcd for $C_{12}H_{17}N_2O_2$, 221.1290). The synthetic compound was found to be identical with the natural product by comparison of their chromatographic behavior and spectroscopic data (^{1}H and ^{13}C NMR, IR, UV, and MS spectra).

3.5. Synthesis of chimonanthidine

3.5.1. *N*a-Methyl-*N*b-2-trimethylsilylethoxycarbonyltryptamine (14). To a stirred solution of **13** (2.2 g, 7.24 mmol) in dry DMF (31 mL) was added sodium hydride (377 mg, 60% dispersion in mineral oil) by portions at −20 °C and the mixture was stirred at the same temperature for 10 min. Iodomethane (0.6 mL, 9.63 mmol) was added to the reaction mixture and stirring was continued for 60 min at 0 °C. The reaction mixture was poured into chilled water and then extracted three times with chloroform. The combined extract was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (66% ethyl acetate in *n*-hexane) to give 2.16 g (94%) of **14** as a colorless oil; IR ν_{max} (neat) cm^{-1}: 3341, 2951, 1698, 1250, 740; UV λ_{max} (MeOH) nm: 205.5, 225.5, 289.5; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.03 (9H, s), 0.96 (2H, dd, *J*=8.5, 8.5 Hz), 2.95 (2H, dd, *J*=6.8, 6.8 Hz), 3.49 (2H, d-like, *J*=6.8 Hz), 3.75 (3H, s), 4.15 (2H, dd, *J*=8.5, 8.5 Hz), 4.69 (1H, br-s), 6.88 (1H, s), 7.11 (1H, ddd, *J*=7.8, 7.8, 1.1 Hz), 7.23 (1H, ddd, *J*=7.8, 7.8, 1.1 Hz), 7.30 (1H, d, *J*=7.8 Hz), 7.59 (1H, d, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −1.5, 17.7, 25.7, 32.5, 41.3, 62.8, 109.2, 111.4, 118.9, 121.7, 126.8, 127.7, 130.7, 156.7; EIMS *m/z* (%): 318 (M^+, 32), 157 (100), 144 (69), 73 (26); HRFABMS (NBA) *m/z*: 318.1755 (calcd for $C_{17}H_{26}N_2O_2Si$, 318.1764).

3.5.2. Dimerization of 14. To a stirred solution of **14** (988 mg, 3.11 mmol) in trifluoroethanol (12.5 mL) was added PIFA (95% purity, 669 mg, 1.55 mmol) at −40 °C and the reaction mixture was stirred at the same temperature for 8 h under argon atmosphere. Aqueous sat. $NaHCO_3$ solution was added to the reaction mixture, which was then extracted three times with chloroform. The combined

extract was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (5% acetone in *n*-hexane) and then by pre-packed silica gel column chromatography (7% acetone in *n*-hexane) to give 159 mg (16%) of **15**, 209 mg (21%) of **16**, and 48 mg (5%) of **14**. **15**; colorless oil, IR ν_{max} (neat) cm^{-1}: 2952, 1700, 1698, 746; UV λ_{max} (MeOH) nm: 208.0, 253.0, 309.5; ^1H NMR ($CDCl_3$, 400 MHz, VT 50 °C) δ 0.05 (18H, s), 1.02 (4H, br-s), 2.16–2.20 (4H, m), 2.71 (6H, br), 2.87–2.98 (2H, m), 3.81–3.91 (2H, br), 4.21 (4H, br), 5.17–5.28 (2H, br), 6.31 (2H, d, J=8.1 Hz), 6.52 (4H, m), 7.08 (2H, dd, J=7.6, 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, VT 50 °C) δ −1.5 ($CO_2CH_2CH_2Si(CH_3)_3$), 17.9 ($CO_2CH_2CH_2Si(CH_3)_3$), 33.1 (N_8-CH_3), 34.7 (br, C-3), 45.1 (C-2), 61.7 (br, $CO_2CH_2CH_2Si(CH_3)_3$), 63.5 (C-3a), 83.4 (br, C-8a), 106.4, 117.1, 123.7, 129.1, 129.6, 152.5 (C-3b, 4, 5, 6, 7, 7a), 155.3 (br, $CO_2CH_2CH_2Si(CH_3)_3$); EIMS *m/z* (%): 634 (M^+, 25), 318 (9.5), 144 (65), 73 (100); HRFABMS (NBA) *m/z*: 634.3380 (calcd for $C_{34}H_{50}N_4O_4Si_2$, 634.3371). **16**; colorless oil, IR ν_{max} ($CHCl_3$) cm^{-1}: 2955, 1687, 766; UV λ_{max} (MeOH) nm: 208.5, 253.5, 310.0; ^1H NMR ($CDCl_3$, 400 MHz, VT 50 °C) δ 0.06 (18H, s), 0.96 (4H, dd, J=7.8, 7.8 Hz), 2.01 (2H, dd, J=5.6, 5.6 Hz), 2.32 (2H, m), 2.82 (2H, br-s), 2.94 (6H, br-s), 3.78–3.88 (2H, br), 4.14 (4H, m), 5.14-5.28 (2H, br), 6.31 (2H, d, J=7.6 Hz), 6.59 (2H, dd-like, J=7.1, 7.1 Hz), 7.06 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz, VT 50 °C) δ −1.5 ($CO_2CH_2CH_2Si(CH_3)_3$), 17.8 ($CO_2CH_2CH_2Si(CH_3)_3$), 32.1 (br, C-3), 33.6 (N_8-CH_3), 45.0 (C-2), 61.0, 62.0 (br, $CO_2CH_2CH_2Si(CH_3)_3$), 63.3 (C-3a), 83.8 (br, C-8a), 105.7, 116.8, 124.0, 129.0, 129.1, 151.9 (C-3b, 4, 5, 6, 7, 7a), 155.0 (br, $CO_2CH_2CH_2Si(CH_3)_3$); EIMS *m/z* (%): 634 (M^+, 11), 318 (7), 144 (57), 73 (100); HRFABMS (NBA) *m/z*: 634.3315 (calcd for $C_{34}H_{50}N_4O_4Si_2$, 634.3371).

3.5.3. Red-Al reduction of 15. To a solution of **15** (17 mg, 0.027 mmol) in dry toluene (3 mL) was added a solution of Red-Al (65% solution of sodium bis(2-methoxyethoxy)-aluminum hydride in toluene, 0.08 mL) at room temperature under argon atmosphere. The reaction mixture was refluxed at 130 °C for 1.5 h. After cooling, 5% aqueous NaOH solution was added and the mixture was filtered using Celite. The filtrate was extracted three times with chloroform and the combined extract was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by amino silica gel column chromatography (50% ethyl acetate in *n*-hexane) to give 9.7 mg (96%) of *meso*-folicanthine **17** as pale yellow crystals: mp 176–178 °C (*n*-hexane/AcOEt); IR ν_{max} ($CHCl_3$) cm^{-1}: 2933, 1602, 1491, 669; UV λ_{max} (MeOH) nm: 207.5, 253.5, 308.0; ^1H NMR (Pyridine-d_5, 600 MHz, VT 90 °C) δ 2.01 (2H, dd, J=4.4, 4.4 Hz), 2.43 (10H, m), 2.53 (2H, m), 2.76 (2H, dd, J=8.5, 8.5 Hz), 4.37 (2H, br-s), 6.45 (2H, d, J=7.7, 7.7 Hz), 6.60 (2H, br-s), 7.12 (2H, dd, J=7.7, 7.7 Hz), 7.16 (2H, s); ^{13}C NMR (Pyridine-d_5, 150 MHz, VT 90 °C) δ 36.0 (N_8-CH_3)*, 36.3 (C-3), 36.6 (N_1-CH_3)*, 52.5 (C-2), 63.6 (C-3a), 91.9 (C-8a), 107.3, 117.4, 124.2, 128.4, 133.8, 155.0 (C-3b, 4, 5, 6, 7, 7a) (*interchangeable); EIMS *m/z*: (%): 374 (M^+, 42), 188 (38), 187 (100), 186 (88), 144 (87); HRFABMS (NBA) *m/z*: 375.2560 (calcd for $C_{24}H_{31}N_4$, 375.2549).

3.5.4. Red-Al reduction of 16. To a solution of **16** (16 mg, 0.026 mmol) in dry toluene (3 mL) was added a solution of Red-Al (65% solution of sodium bis(2-methoxyethoxy)-aluminum hydride in toluene, 0.08 mL) at room temperature under argon atmosphere. The reaction mixture was refluxed at 130 °C for 2 h. After cooling, 5% aqueous NaOH solution was added and the mixture was filtered using Celite. The filtrate was extracted three times with chloroform and the combined extract was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by amino silica gel column chromatography (50% ethyl acetate in *n*-hexane) to give 9.2 mg (95%) of *rac*-folicanthine **11** as pale yellow crystals: mp 172–174 °C (*n*-hexane/AcOEt). The ^1H and ^{13}C NMR and MS spectra were identical with those reported in the literature.[6]

3.5.5. Partial deprotection of carbamates in 16. To a solution of **16** (42 mg, 0.066 mmol) in dry THF (2.5 mL) was added 1.0 M solution of tetrabutylammonium fluoride in THF (66 μL, 0.066 mmol) at 0 °C and the mixture was stirred at room temperature for 6 h. The reaction mixture was poured into chilled water and then extracted three times with chloroform. The combined extract was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (3% methanol in chloroform) to give 11 mg (33.4%) of **18** as a colorless oil and 21.5 mg (51.3%) of starting material **16**. **18**. IR ν_{max} (neat) cm^{-1}: 2951, 1697, 1492, 744; UV λ_{max} (MeOH) nm: 212.0, 254.0, 310.5; ^1H NMR (Pyridine-d_5, 400 MHz, VT 90 °C) δ 0.08 (9H, s), 1.06 (2H, dd, J=8.2, 8.2 Hz), 2.12 (1H, dd, J=11.7, 5.2 Hz), 2.18 (1H, dd, J=12.3, 5.7 Hz), 2.42 (1H, ddd, J=11.2, 11.2, 7.5 Hz), 2.58 (1H, ddd, J=10.8, 10.8, 5.5 Hz), 2.67 (1H, ddd, J=11.9, 11.9, 8.1 Hz), 2.86 (3H, s), 2.96–3.03 (2H, m), 3.12 (3H, s), 4.33 (2H, dd, J=8.2, 8.2 Hz), 4.81 (1H, s), 5.67 (1H, br-s), 6.40 (1H, d, J=7.5 Hz), 6.49 (1H, d, J=7.5 Hz), 6.68 (1H, dd, J=7.5, 7.5 Hz), 6.77 (1H, dd, J=7.4, 7.4 Hz), 7.14 (1H, dd, J=7.5, 7.5 Hz), 7.18–7.21 (1H, m), 7.32 (1H, d, J=7.5 Hz), 7.36 (1H, d, J=7.4 Hz); ^{13}C NMR (Pyridine-d_5, 100 MHz, VT 90 °C) δ −1.5, 18.2, 30.9, 32.5, 35.0, 38.3, 45.4, 46.0, 62.8, 63.4, 79.3, 85.0, 87.8, 105.5, 106.2, 116.6, 117.4, 124.5, 124.6, 129.0, 129.3, 131.1, 131.8, 152.8, 153.3, 155.4; EIMS *m/z* (%): 490 (M^+, 26), 316 (100), 272 (46), 244 (49), 173 (55), 144 (91); HRFABMS (NBA) *m/z*: 491.2807 (calcd for $C_{28}H_{39}N_4O_2Si$, 491.2842).

3.5.6. Red-Al reduction of 18. To a solution of **18** (36 mg, 0.073 mmol) in dry toluene (5 mL) was added a solution of Red-Al (65% solution of sodium bis(2-methoxyethoxy)-aluminum hydride in toluene, 0.13 mL) at room temperature under argon atmosphere. The reaction mixture was refluxed at 130 °C for 2 h. After cooling, 5% aqueous NaOH solution was added and the mixture was filtered using Celite. The filtrate was extracted three times with chloroform and the combined extract was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by amino silica gel column chromatography (75% ethyl acetate in *n*-hexane) to give 19.3 mg (73.4%) of *rac*-chimonanthidine **2** as a colorless amorphous powder. The synthetic compound was found to be completely identical with the natural product by comparison of their chromatographic behavior and spectroscopic data (^1H and ^{13}C NMR, UV, IR and MS spectra).

Acknowledgements

The authors thank to Professor Dr. Kentaro Yamaguchi, Analysis Center of Chiba University, for X-ray crystallographic analysis.

References and notes

1. (a) Amador, T. A.; Verotta, L.; Nunes, D. S.; Elisabetsky, E. *Planta Med.* **2000**, *66*, 770–772. (b) Verotta, L.; Orsini, F.; Sbacchi, M.; Scheildler, M. A.; Amador, T. A.; Elisabetsky, E. *Bioorg. Med. Chem.* **2002**, *10*, 2133–2142.
2. (a) Takayama, H.; Ishikawa, H.; Kurihara, M.; Kitajima, M.; Aimi, N.; Ponglux, D.; Koyama, F.; Matsumoto, K.; Moriyama, T.; Yamamoto, L. T.; Watanabe, K.; Murayama, T.; Horie, S. *J. Med. Chem.* **2002**, *45*, 1949–1956. (b) Takayama, H.; Aimi, N.; Sakai, S. *Yakugaku Zasshi* **2000**, *120*, 959–967, and references cited therein.
3. For a recent review, see: (a) Anthoni, U.; Christophersen, C.; Nielsen, P. H. *Alkaloids: chemical and biological perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, 1999; Vol. 13, pp 163–236. (b) Verotta, L.; Pilati, T.; Tato, M.; Elisabetsky, E.; Amador, T. A.; Nunes, D. S. *J. Nat. Prod.* **1998**, *61*, 392–396. (c) Jannic, V.; Gueritte, F.; Laprevote, O.; Serani, L.; Martin, M.-T.; Sevenet, T.; Potier, P. *J. Nat. Prod.* **1999**, *62*, 838–843. (d) Dachriyanus; Sargent, M. V.; Wahyuni, F. S. *Aust. J. Chem.* **2000**, *53*, 159–160.
4. For a review, see: (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2964. (b) Dounay, A. B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 6261–6271. (c) Kodanko, J. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 2528–2531. (d) Overman, L. E.; Peterson, E. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 2525–2528, and references cited therein.
5. Zhao, H.; Ji, Q.; Wang, M.; Zhao, S.; Wang, Y. *J. Chin. Pharm. Univ.* **1993**, *24*, 76–77.
6. Fang, C.-L.; Horne, S.; Taylor, N.; Rodrigo, R. *J. Am. Chem. Soc.* **1994**, *116*, 9480–9486.
7. Labroo, R. B.; Cohen, L. A. *J. Org. Chem.* **1990**, *55*, 4901–4904.
8. (a) Davis, F. A.; Sheppard, A. C.; Chen, B.-C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679–6690. (b) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919–934.
9. (a) Takayama, H.; Shimizu, T.; Sada, H.; Harada, Y.; Kitajima, M.; Aimi, N. *Tetrahedron* **1999**, *55*, 6841–6846. (b) Monde, K.; Taniguchi, T.; Miura, N.; Nishimura, S.; Harada, N.; Dukor, R. K.; Nafie, L. A. *Tetrahedron Lett.* **2003**, *44*, 6017–6020.
10. Some examples of enantiomerically not pure natural alkaloids have been found in our laboratory. (a) Takayama, H.; Kurihara, M.; Kitajima, M.; Said, I. M.; Aimi, N. *J. Org. Chem.* **1999**, *64*, 1772–1773. (b) Takayama, H.; Kurihara, M.; Kitajima, M.; Said, I. M.; Aimi, N. *Tetrahedron* **2000**, *56*, 3145–3151. (c) Takayama, H.; Ichikawa, T.; Kuwajima, T.; Kitajima, M.; Seki, H.; Aimi, N.; Nonato, M. G. *J. Am. Chem. Soc.* **2000**, *122*, 8635–8639.
11. (a) Hodson, H. F.; Robinson, B.; Smith, G. F. *Proc. Chem. Soc.* **1961**, 465–466. (b) Grant, I. J.; Hamor, T. A.; Robertson, J. M.; Sim, G. A. *J. Chem. Soc. (C)* **1965**, 5678–5683. (c) Tokuyama, T.; Daly, J. W. *Tetrahedron* **1983**, *39*, 41–47. (d) Lajis, N. H.; Mahmud, Z.; Toia, R. F. *Planta Med.* **1993**, *59*, 383–384. (e) Duke, R. K.; Allan, R. D.; Johnston, G. A. R.; Mewett, K. N.; Mitrovic, A. D.; Duke, C. C.; Hambley, T. W. *J. Nat. Prod.* **1995**, *58*, 1200–1208.
12. Hodson, H. F.; Smith, G. F.; Wrobel, J. T. *Chem. Ind.* **1958**, 1551.
13. Saxton, J. E.; Bardsley, W. G.; Smith, G. F. *Proc. Chem. Soc.* **1962**, 148.
14. Ishikawa, H.; Takayama, H.; Aimi, N. *Tetrahedron Lett.* **2002**, *43*, 5637–5639.
15. The syntheses of dimeric pyrrolidinoindoline alkaloids using direct coupling of tryptamine derivatives under various conditions have been reported. (a) Hendrickson, J. B.; Goeschke, R.; Rees, R. *Tetrahedron* **1964**, *20*, 565–579. (b) Hall, E. S.; McCapra, F.; Scott, A. I. *Tetrahedron* **1967**, *23*, 4131–4141. (c) Hino, T.; Kodato, S.; Takahashi, K.; Yamaguchi, H.; Nakagawa, M. *Tetrahedron Lett.* **1978**, 4913–4916. (d) Nakagawa, M.; Sugumi, H.; Kodato, S.; Hino, T. *Tetrahedron Lett.* **1981**, 5323–5326.
16. Kita, Y.; Haruta, J.; Yasuda, H.; Fukunaga, K.; Shirouchi, Y.; Tamura, Y. *J. Org. Chem.* **1982**, *47*, 2697–2700.
17. Natural (−)-chimonanthine was converted to the N_1,N_1'-dimethyl derivative by a two-step operation ((i) $NaN(SiMe_3)_2$, Boc_2O, THF, y. 53% (ii) Red-Al, toluene, y. 43%), which was found to be identical with the natural (−)-folicanthine in all respects including the optical rotations.
18. Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702–7703.