Total Synthesis of (−)-Cephalotaxine

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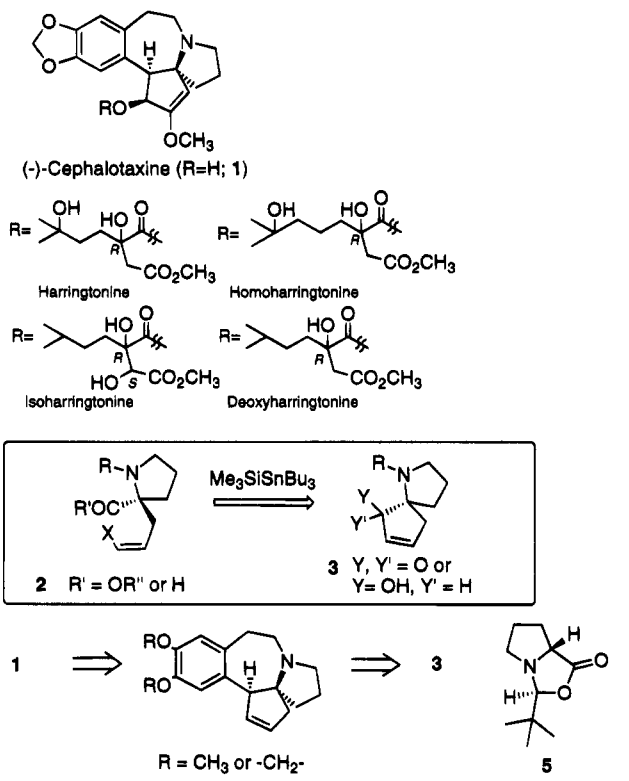
Total synthesis of (−)-cephalotaxine was achieved from D-(+)-proline by a short sequence of steps. The key intermediate, 1-azaspiro[4.4]nonane, was prepared from vinyl iodide, using stannyl anion generated from $Me_3SiSnBu_3$ and CsF, in good yield.

Cephalotaxine (**1**) is the major alkaloid of *Cephalotaxus harringtonia* var. drupacae. The possible antileukemic activity of harringtonine, homoharringtonine, isoharringtonine, and deoxyharringtonine, which are its ester derivatives, has stimulated numerous studies directed toward synthetic cephalotaxine (**1**). Thereby, several elegant total syntheses of racemic cephalotaxine have been achieved.[1] We herein report the total synthesis of (−)-cephalotaxine by a short sequence of steps. The planning of the synthesis of (−)-cephalotaxine (**1**) was based on the following points. The unique skeleton, a 1-azaspiro[4.4]nonane, fused benzazepine system, would be prepared by the reaction of **2** with stannyl anion generated from $Me_3SiSnBu_3$ and F^- as developed by us.[2] For the synthesis of optically active cephalotaxine, the optically pure starting material **2** would be obtained from D-(+)-proline via **5** by Seebach's procedure.[3] The methylenedioxy group on the aromatic ring does not favor the cyclization of the seven-membered ring[4] (Scheme 1).

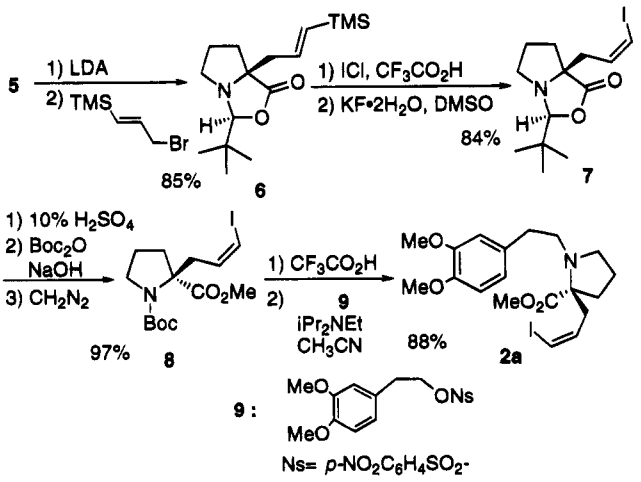
As expected, we were able to obtain compound **2a** in optically active form. Namely, alkylation of **5**,[3] prepared from D-(+)-proline, afforded compound **6** in good yield, which was converted into the vinyl iodide **7** by the usual method.[5] Hydrolysis of **7** with 10% sulfuric acid,[6] followed by treatment with Boc_2O and then CH_2N_2, gave compound **8**. Deprotection of the Boc group with CF_3-COOH, followed by alkylation with **9**[1b,4] in the presence of *i*-Pr_2NEt, proceeded smoothly to give **2a** (Scheme 2).

For the preparation of the 1-azaspiro[4.4]nonane skeleton, our cyclization using the stannyl anion generated from $Me_3SiSnBu_3$ and F^- was employed. To a DMF

Scheme 1



Scheme 2



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(6) Treatment of **7** with 15% HBr in a similar manner did not afford the desired product (starting material 42%), and only a trace of **8** was obtained.

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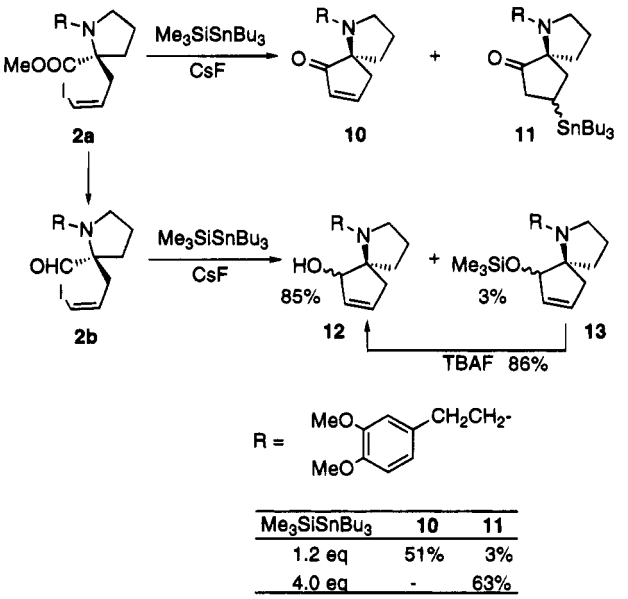
Scheme 3



$Me_3SiSnBu_3$	10	11
1.2 eq	51%	3%
4.0 eq	-	63%

solution of compound **2a** and CsF was added $Me_3SiSnBu_3$ (1.2 equiv) at 0 °C, and the solution was stirred at room temperature for 24 h (Scheme 3). After the usual workup, the desired cyclized product **10** was obtained in 51% yield along with the stannylated product **11** (3% yield). The use of 4 equiv of $Me_3SiSnBu_3$ and CsF gave **11** in 63% yield. Subsequently, the cyclization reaction of the aldehyde moiety and the vinyl iodide with $Me_3SiSnBu_3$ and CsF was examined. Compond **2b**, prepared from **2a** by reduction with $LiAlH_4$ followed by treatment with SO_3–pyridine and DMSO, was treated in a similar manner to give cyclized products **12** and **13** in 85% and 3% yields, respectively. Compound **13** was easily converted into **12** in good yield by treatment with Bu_4NF. For the synthesis of **1**, the latter route was chosen.

Reaction of compound **12** with PPA[4] afforded compound **14**, whose dimethoxy groups were transformed into a methylenedioxy group by the usual method.[7] Treatment of **15** with OsO_4, in the presence of trimethylamine *N*-oxide in AcOH, afforded the diol **16**,[1e] which was oxidized with DMSO and trifluoroacetic anhydride to produce diketone **17** (Scheme 4). A dioxane solution of **17** and dimethoxypropane in the presence of TsOH[1a,e] was refluxed for 8 h to give cephalotaxinone (**18**) in 76% yield. The spectral data of the product were identical with those reported for cephalotaxinone,[1a,e] but the material was found to be racemic [$[\alpha]^{19}_D$ −8.2° (*c* 0.4, EtOH), lit. $[\alpha]^{20}_D$ −135° (*c* 0.95, EtOH)[8]]. The racemization of **18** would occur upon either acid or base treatment, and in this case, would have resulted from acid-induced carbon–carbon bond cleavage, as shown in Scheme 5.

Various attempts to convert the keto carbonyl group of **17** into a methyl enol ether were fruitless.[9] Attempts were made to convert diketone **17** into acetal **19** and then to eliminate MeOH. However, when compound **17** was treated with methyl orthoformate in the presence of TsOH at room temperature (Scheme 6), cephalotaxinone (**18**) was obtained in 47% yield.[12] The spectral data and the $[\alpha]_D$ values of the synthetic cehalotaxinone were in complete agreement with those of natural cephalotaxinone.[8] Finally, treatment of **18** with $NaBH_4$ in MeOH provided (−)-cephalotaxine, $[\alpha]^{20}_D$ −161° (*c* 0.75, $CHCl_3$) [lit. $[\alpha]^{20}_D$ −188° (*c* 0.5, $CHCl_3$)[8]].

This is the first example of a synthesis of (−)-cephalotaxine.

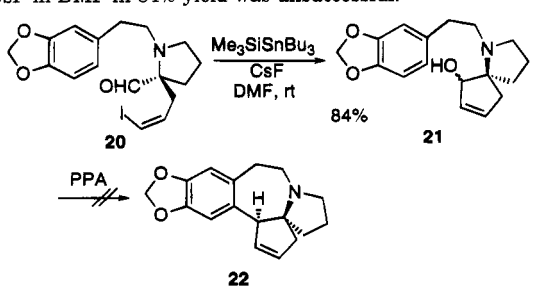
Experimental Section

Solvents were distilled under an argon atmosphere from sodium benzophenone (THF), CaH_2 (DMF, Et_3N), or P_2O_5 (CH_2Cl_2). All other reagents and solvents were purified when necessary by standard procedures. $Me_3SiSnBu_3$[13] was prepared by the literature method. NMR spectra were recorded at 270 and 500 MHz. Melting points are uncorrected.

(*E*)-(2*S*,5*S*)-5-(3-(Trimethylsilyl)-2-propenyl)-2-*tert*-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (6). To a solution of LDA prepared from BuLi (1.69 N hexane solution, 26.0 mL, 43.94 mmol) and diisopropylamine (6.8 mL, 48.52 mmol) in THF (170 mL) was added (2*S*,5*R*)-2-*tert*-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**5**)[3] (7.45 g, 40.63 mmol) in THF (50 mL) at −78 °C, and the solution was stirred at −78 °C for 1 h. To the solution was added a solution of (*E*)-3-bromo-1-(trimethylsilyl)-1-propene[14] (9.42 g, 48.77 mmol) in THF (50 mL) at −78 °C. After the solution was stirred at −78 °C for 13 h, saturated $NaHCO_3$ solution was added and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel [hexane–ethyl acetate (50:1–10:1)] to give a colorless oil of **6** (10.15 g, 85%). **6**: $[\alpha]^{24}_D$ −17.0° (*c* 1.03, $CHCl_3$); IR (neat) 1781, 1617, 1247 cm^{-1}; ^1H NMR (270 MHz) ($CDCl_3$) δ 0.03 (s, 9 H), 0.91 (s, 9 H), 1.49–1.91 (m, 3H), 2.01–2.11 (m, 1 H), 2.46 (dd, *J* = 6.4, 1.2 Hz, 2 H), 2.81 (ddd, *J* = 12.2, 6.7, 2.9 Hz, 1 H), 2.91 (ddd, *J* = 12.2, 10.1, 5.5 Hz, 1 H), 4.22 (s, 1 H), 5.77 (dt, *J* = 18.6, 1.2 Hz, 1 H), 6.04 (dt, *J* = 18.6, 6.4 Hz, 1 H); MS *m/z* 295 (M^+), 280, 252, 238, 210, 182, 154; HRMS *m/z* calcd for $C_{16}H_{29}NO_2Si$ 295.1968, found 295.1970. Anal. Calcd for $C_{16}H_{29}NO_2Si$: C, 65.03; H, 9.89; N, 4.74. Found; C, 64.91; H, 10.03; N, 4.79.

(*Z*)-(2*S*,5*S*)-5-(3-Iodo-2-propenyl)-2-*tert*-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (7). To a solution of **6** (10.15 g, 34.33 mmol) in CH_2Cl_2 (340 mL) and CF_3COOH (13.2 mL,

(7) Cyclization of compound **21** with PPA from **20** using $Me_3SiSnBu_3$ and CsF in DMF in 84% yield was unsuccessful.



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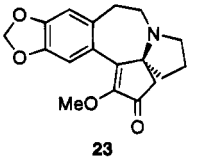
(9) Treatment of **17** with $TMSCHN_2$ in the presence of *i*-Pr_2NEt[10] afforded compound **23** in 30% yield. Treatment of **17** with Me_3SiOMe or Et_3SiOTf[1d,11] in the presence of trifuric acid in CH_2Cl_2 gave **18** in 7% yield (89% conversion yield) or 16% yield (81% conversion yield), respectively [$[\alpha]_D$ −129° (*c* 0.9, EtOH)]. Compound **18** was converted into (−)-cephalotaxine (**1**).



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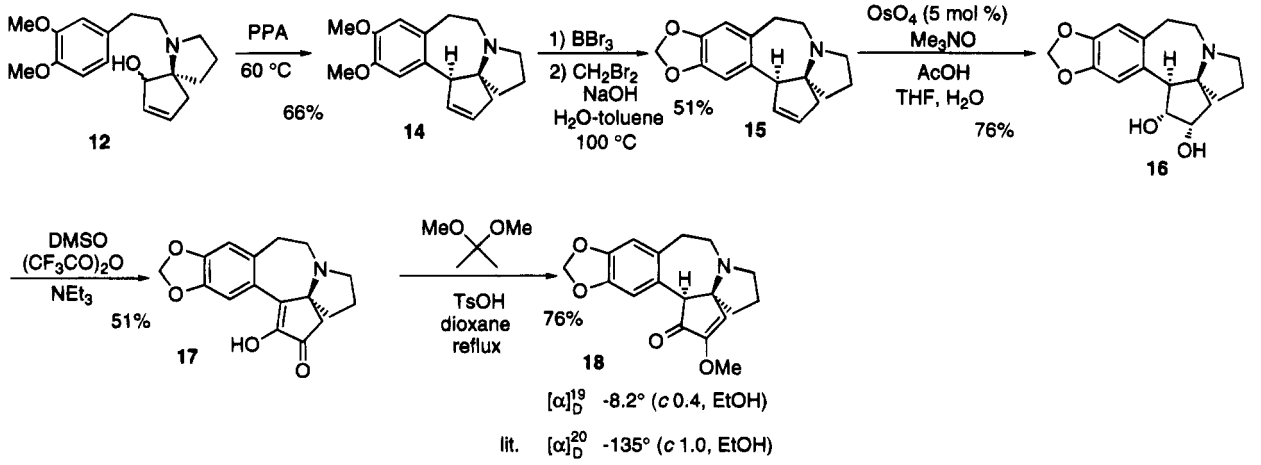
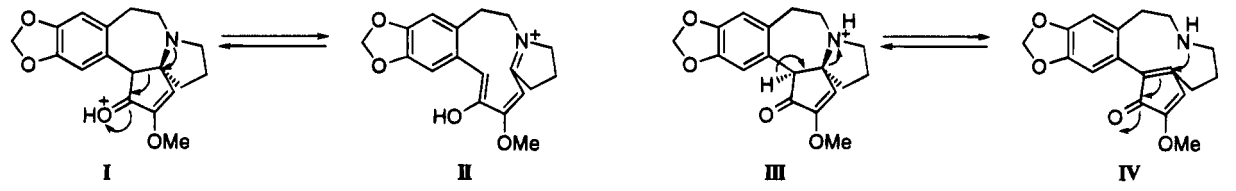
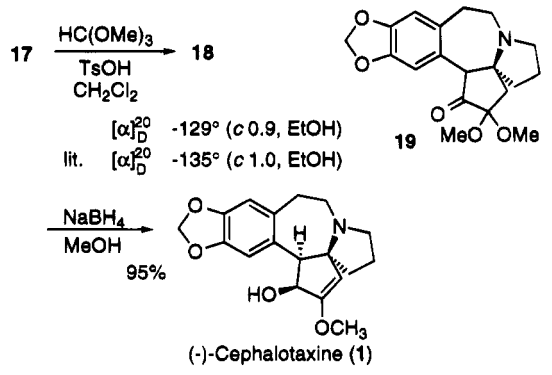
Scheme 4



Scheme 5



Scheme 6



171.34 mmol) was added a solution of ICl (11.15 g, 68.67 mmol) in CH_2Cl_2 (40 mL) at 0 °C,[5] and the solution was stirred at the same temperature for 1 h. To the reaction mixture were added 120 mL of 20% K_2CO_3 solution and then 50 mL of 10% $Na_2S_2O_3$ solution. The aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. To the residue in DMSO (170 mL) was added $KF{\cdot}2H_2O$ (6.46 g, 68.63 mmol) at 0 °C, and the solution was stirred at room temperature for 19 h. Water was added, the aqueous layer was extracted with ethyl acetate, and the organic layer was washed with brine dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel [hexane−ethyl acetate (40:1−20:1)] to give a colorless oil of **7** (10.07 g, 84%). **7**: $[\alpha]^{23}_D$ −28.8° (*c* 1.02, $CHCl_3$); IR (neat) 1779, 1610, 1275 cm^{-1}; ^1H NMR (270 MHz) ($CDCl_3$) δ 0.93 (s, 9 H), 1.58−1.91 (m, 3H), 2.04−2.18 (m, 1 H), 2.45 (ddd, *J* = 14.5, 5.8, 1.5 Hz, 1 H), 2.66 (ddd, *J* = 14.5, 7.0, 0.9 Hz, 1 H), 2.81−3.10 (m, 2 H), 4.27 (s, 1 H), 6.36 (ddd, *J* = 7.5, 7.0, 5.8 Hz, 1 H), 6.43 (ddd, *J* = 7.5, 1.5, 0.9 Hz, 1 H); MS *m/z* 350 (M^+ + 1), 334, 306, 292, 264, 236, 182, 154, 137; HRMS *m/z* calcd for $C_{13}H_{21}INO_2$ 350.0617, found 350.0620. Anal. Calcd for $C_{13}H_{20}INO_2$: C, 44.71; H, 5.77; I, 36.34; N, 4.01. Found; C, 44.78; H, 5.83; I, 36.61; N, 3.94.

(2*S*)-Methyl 1-(*tert*-Butoxycarbonyl)-2-((*Z*)-3-iodo-2-propenyl)pyrrolidine-2-carboxylate (8). A mixture of **7** (1.97 g, 5.64 mmol) and 56 mL of 10% aqueous H_2SO_4 was stirred at room temperature for 24 h. The solution was made basic with NaOH (6.77 g, 169.3 mmol) at 0 °C. To the aqueous solution was added dioxane (56 mL), and di-*tert*-butyl dicarbonate (6.50 mL, 28.29 mmol) was added to the solution at 0 °C. The solution was stirred at room temperature for 24 h. The aqueous layer was acidified with 1 N HCl and then extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in MeOH (30 mL), and a solution of CH_2N_2 in Et_2O was added dropwise at 0 °C. The solvent was removed in vacuo, and the residue was purified by chromatography on silica gel [hexane−ethyl acetate (10:1−3:1)] to give a colorless oil of **8** (2.17 g, 97%). **8**: $[\alpha]^{22}_D$ −55.1° (*c* 1.01, $CHCl_3$); IR (neat) 1743, 1699, 1392, 1257 cm^{-1}; ^1H NMR (270 MHz) ($CDCl_3$) δ 1.42 and 1.45 (s, 9 H), 1.78−2.15 (m, 4 H), 2.84−3.05 (m, 2 H), 3.33−3.79 (m, 2 H), 3.73 (s, 3 H), 6.22 and 6.24 (ddd, *J* = 7.7, 1.6, 1.1 Hz, 1 H), 6.35 and 6.39 (ddd, *J* = 7.7, 1.6, 1.1 Hz, 1 H); MS *m/z* 395 (M^+), 339, 336, 294, 280, 236, 228, 128, 57; HRMS *m/z* calcd for $C_{14}H_{22}INO_4$ 395.0594, found 395.0593. Anal. Calcd for $C_{14}H_{22}INO_4$: C, 42.55; H, 5.61; I, 32.11; N, 3.54. Found; C, 42.71; H, 5.65; I, 31.90; N, 3.42.

(2*S*)-Methyl 2-((*Z*)-3-Iodo-2-propenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]pyrrolidine-2-carboxylate (2a). To the solution of **8** (1.84 g, 4.65 mmol) in CH_2Cl_2 (46 mL) was added CF_3COOH (6.20 mL 80.48 mmol) at 0 °C. After the solution was stirred at room temperature for 2 h, saturated $NaHCO_3$ solution was added and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. To the residue in CH_3CN (23 mL) were added 2-(3,4-dimethoxyphenyl)ethyl alcohol *p*-nitrobenzenesulfonate ester (**9**)[1b,4] (3.40 g, 9.25 mmol) and *i*-Pr_2NEt (4.0 mL, 22.96 mmol) at 0 °C, and the solution was refluxed for 12 h. Solvent was removed in vacuo, and ethyl acetate was added. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel [hexane−ethyl acetate (10:1−3:1)] to give a colorless oil of **2a** (1.89 g, 88%). **2a**: $[\alpha]^{22}_D$ −44.0° (*c* 1.00, $CHCl_3$); IR (neat) 1724, 1608, 1590, 1516, 1262 cm^{-1}; ^1H NMR (270 MHz) ($CDCl_3$) δ 1.70−1.98 (m, 3 H), 2.02−2.10 (m, 1 H), 2.41 (ddd, *J* = 15.4, 6.2, 1.5 Hz, 1 H), 2.48−2.88 (m, 5 H), 2.60 (ddd, *J* = 15.4, 7.0, 1.5 Hz, 1 H), 3.18−3.28 (m, 1 H), 3.67 (s, 3 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 6.03 (ddd, *J* = 7.3, 7.0, 6.2 Hz, 1 H), 6.21 (ddd, *J* = 7.3, 1.5, 1.5 Hz, 1 H), 6.70 (d, *J* = 1.5 Hz, 1 H), 6.72 (dd, *J* = 8.5, 1.5 Hz, 1 H), 6.79 (d, *J* = 8.5 Hz, 1 H); MS *m/z* 459 (M^+), 400, 308, 292, 254; HRMS *m/z* calcd for $C_{19}H_{26}INO_4$ 459.0907, found 459.0936. Anal. Calcd for

$C_{19}H_{26}INO_4$: C, 49.68; H, 5.71; I, 27.63; N, 3.05. Found; C, 49.69; H, 5.78; I, 27.76; N, 3.02.

(5*S*)-1-[2-(3,4-Dimethoxyphenyl)ethyl]-6-oxo-1-azaspiro[4.4]non-7-ene (10). To a solution of CsF (66 mg, 0.44 mmol) and **2a** (121 mg, 0.26 mmol) in DMF (1.8 mL) was added $Me_3SiSnBu_3$ (110 μL, 0.32 mmol) at 0 °C, and the solution was stirred at room temperature for 24 h. Then 10% NH_4OH was added, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel [hexane–ethyl acetate (5:1–1:2)] to give a yellow oil of **10** (41 mg, 51%) and **11** (5 mg, 3%). **10**: $[\alpha]^{30}_D$ −56.3° (*c* 0.71, $CHCl_3$); IR (neat), 1700, 1588, 1516, 1464 cm^{-1}; ^1H NMR (270 MHz) ($CDCl_3$) δ 1.76–1.96 (m, 2 H), 2.01–2.13 (m, 2 H), 2.49–2.77 (m, 4 H), 2.56 (ddd, J = 19.1, 3.1, 2.2 Hz, 1 H), 2.73 (ddd, J = 19.1, 2.7, 2.1 Hz, 1 H), 3.01 (ddd, J = 8.8, 8.7, 4.3 Hz, 1 H), 3.17 (ddd, J = 8.7, 8.6, 6.2 Hz, 1 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 6.08 (ddd, J = 6.1, 2.2, 2.1 Hz, 1 H), 6.68 (d, J = 1.9 Hz, 1 H), 6.69 (dd, J = 8.7, 1.9 Hz, 1 H), 6.76 (d, J = 8.7 Hz, 1 H), 7.60 (ddd, J = 6.1, 3.1, 2.7 Hz, 1 H); MS *m/z* 301 (M^+), 164, 150; HRMS *m/z* calcd for $C_{18}H_{23}NO_3$ 301.1678, found 301.1680. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.74; H, 7.69; N, 4.65. Found; C, 71.66; H, 7.77; N, 4.64. **(5*S*)-1-[2-(3,4-Dimethoxyphenyl)ethyl]-6-oxo-8-(tributylstannyl)-1-azaspiro[4.4]nonane (11)**: $[\alpha]^{28}_D$ −78.5° (*c* 1.22, $CHCl_3$); IR (neat) 1728, 1590, 1514 cm^{-1}; ^1H NMR (270 MHz) ($CDCl_3$) δ 0.82–0.91 (m, 15 H), 1.22–1.50 (m, 12 H), 1.61–2.10 (m, 6 H), 2.22–2.44 (m, 3 H), 2.61–2.80 (m, 4 H), 2.98–3.10 (m, 2 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 6.70–6.80 (m, 3 H); MS *m/z* 592 (M^+), 536, 442, 302, 274; HRMS *m/z* calcd for $C_{30}H_{51}NO_3{}^{120}Sn$ 593.2891, found 593.2875. Anal. Calcd for $C_{30}H_{51}NO_3Sn$: C, 60.82; H, 8.68; N, 2.36. Found; C, 60.74; H, 8.79; N, 2.44.

(2*S*)-2-((*Z*)-3-Iodo-2-propenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]pyrrolidine-2-carbaldehyde (2b). To a solution of $LiAlH_4$ (700 mg, 18.45 mmol) in THF (30 mL) was added **2a** (5.50 g, 11.96 mmol) in THF (30 mL) at −50 °C. After the solution was stirred at −50 °C for 6 h, $Na_2SO_4{\cdot}10H_2O$ was added and the solution was stirred for 1 h. Undissolved material was filtered off, and the filtrate was concentrated. To the residue in DMSO (40 mL) were added Et_3N (8.3 mL, 59.55 mmol) and $SO_3{\cdot}Py$ in DMSO (20 mL) at room temperature. After the solution was stirred at room temperature for 3 h, saturated $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel [hexane–ethyl acetate (5:1–2:1)] to give a colorless oil of **2b** (4.15 g, 81%). **2b**: $[\alpha]^{23}_D$ −36.0° (*c* 1.04, $CHCl_3$); IR (neat) 1722, 1590, 1516, 1464 cm^{-1}; ^1H NMR (270 MHz) ($CDCl_3$) δ 1.71–2.02 (m, 4 H), 2.33 (ddd, J = 14.7, 7.7, 1.1 Hz, 1 H), 2.47 (ddd, J = 14.7, 6.2, 1.5 Hz, 1 H), 2.63–2.85 (m, 4 H), 2.88–2.98 (m, 1 H), 3.12–3.22 (m, 1 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 6.11 (ddd, J = 7.7, 6.2, 6.2 Hz, 1 H), 6.29 (ddd, J = 7.7, 1.5, 1.1 Hz, 1 H), 6.68 (d, J = 1.8 Hz, 1 H), 6.70 (dd, J = 8.1, 1.8 Hz, 1 H), 6.79 (d, J = 8.1 Hz, 1 H), 9.23 (s, 1 H); MS *m/z* 400 (M^+ − CHO, bp), 278, 165, 151; HRMS (M^+ − CHO) *m/z* calcd for $C_{17}H_{23}INO_2$ 400.0774, found 400.0778. Anal. Calcd for $C_{18}H_{24}INO_3$: C, 50.36; H, 5.63; I, 29.56; N, 3.26. Found; C, 50.62; H, 5.66; I, 29.60; N, 3.30.

(5*S*)-1-[2-(3,4-Dimethoxyphenyl)ethyl]-6-hydroxy-1-azaspiro[4.4]non-7-ene (12). To a solution of CsF (980 mg, 6.45 mmol) and **2b** (1.39 g, 3.23 mmol) in DMF (22 mL) was added $Me_3SiSnBu_3$ (2.25 mL, 6.44 mmol) at 0 °C, and the solution was stirred at room temperature for 8 h. Then 10% NH_4OH was added, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel [chloroform–methanol (50:1–10:1)] to give a colorless oil of **12** (830 mg, 85%) and **13** (38 mg, 3%). **12** (major isomer): $[\alpha]^{22}_D$ 86.3° (*c* 1.02, $CHCl_3$); IR (neat) 3390, 1605, 1500, 1483, 1440 cm^{-1}; ^1H NMR (270 MHz) ($CDCl_3$) δ 1.61–2.08 (m, 4 H), 2.15 (ddd, J = 17.2, 4.0, 2.2 Hz, 1 H), 2.28 (ddd, J = 12.1, 9.2, 7.7 Hz, 1 H), 2.41–2.56 (m, 1 H), 2.44 (ddd, J = 17.2, 3.7, 2.2 Hz, 1 H), 2.61–2.79 (m, 4 H), 3.15 (ddd, J = 9.2, 8.8, 5.9 Hz, 1 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 4.65 (brs, 1 H), 5.73 (ddd, J = 6.2, 4.0, 2.2 Hz, 1 H), 5.86 (ddd, J = 6.2, 3.7, 2.2 Hz, 1 H), 6.72 (d, J = 1.8 Hz, 1 H), 6.73 (dd, J = 8.4, 1.8 Hz, 1 H), 6.79 (d, J = 8.4 Hz, 1 H); MS *m/z* 303 (M^+), 246, 164, 152 (bp); HRMS (M^+) *m/z* calcd for $C_{18}H_{25}NO_3$ 303.1834, found 303.1824. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found; C, 71.21; H, 8.39; N, 4.63. **12** (minor isomer): $[\alpha]^{23}_D$ 19.0° (*c* 1.02, $CHCl_3$); IR (neat) 3375, 1588, 1512, 1461 cm^{-1}; ^1H NMR (270 MHz) ($CDCl_3$) δ 1.65–1.94 (m, 3 H), 1.98–2.20 (m, 2 H), 2.45–2.85 (m, 7 H), 3.27–3.29 (m, 1 H), 3.84 (s, 3 H), 3.86 (s, 3 H), 4.18 (brs, 1 H), 5.78 (brs, 2 H), 6.67–6.83 (m, 3 H); MS *m/z* 303 (M^+), 246, 164, 152 (bp); HRMS (M^+) *m/z* calcd for $C_{18}H_{25}NO_3$ 303.1834, found 303.1826. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found; C, 71.12; H, 8.49; N, 4.57. **(5*S*)-1-[2-(3,4-Dimethoxyphenyl)-ethyl]-6-[(trimethylsilyl)oxy]-1-azaspiro[4.4]non-7-ene (13)**: $[\alpha]^{20}_D$ 111.7° (*c* 1.04, $CHCl_3$); IR (neat) 1582, 1512, 1460 cm^{-1}; ^1H NMR (270 MHz) ($CDCl_3$) δ 0.13 (s, 9 H), 1.48–1.59 (m, 1 H), 1.72–1.85 (m, 3 H), 2.17 (ddd, J = 17.1, 4.1, 2.4 Hz, 1 H), 2.25–2.34 (m, 1 H), 2.38 (ddd, J = 17.1, 3.7, 2.0 Hz, 1 H), 2.48–2.98 (m, 5 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 4.60 (brs, 1 H), 5.58 (ddd, J = 6.1, 4.1, 2.0 Hz, 1 H), 5.82 (ddd, J = 6.1, 3.7, 2.4 Hz, 1 H), 6.72 (d, J = 1.9 Hz, 1 H), 6.74 (dd, J = 9.2, 1.9 Hz, 1 H), 6.72 (d, J = 9.2 Hz, 1 H); MS *m/z* 375 (M^+), 360, 286, 246, 224 (bp); HRMS (M^+) *m/z* calcd for $C_{21}H_{33}NO_3Si$ 375.2229, found 375.2220. Anal. Calcd for $C_{21}H_{33}NO_3Si$: C, 67.16; H, 8.86; N, 3.73. Found; C, 67.10; H, 8.96; N, 3.68.

(3a*S*,13b*S*)-3,5,6,8,9,13b-Hexahydro-11,12-dimethoxy-4*H*-cyclopenta[*a*]pyrrolo[2,1-*b*][3]benzazepine (14). A mixture of **12** (299 mg, 0.98 mmol) and polyphosphoric acid (7.25 g) was stirred at 60 °C for 43 h. Saturated $NaHCO_3$ was added, and the solution was made basic (pH = 10) by 20% NaOH solution. The solution was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on alumina [hexane–ethyl acetate (10:1–3:1)] to give colorless crystals of **14** (184 mg, 66%). **14**: mp 74–75 °C; $[\alpha]^{21}_D$ −152.1° (*c* 1.03, $CHCl_3$); IR (KBr) 1604, 1516, 1463, 1450 cm^{-1}; ^1H NMR (500 MHz) ($CDCl_3$) δ 1.67–1.81 (m, 2 H), 1.93–2.04 (m, 3 H), 2.35 (dd, J = 14.0, 6.8 Hz, 1 H), 2.40 (ddd, J = 9.8, 9.5, 6.2 Hz, 1 H), 2.57 (dd, J = 11.6, 7.4 Hz, 1 H), 2.76 (ddd, J = 17.7, 4.4, 2.5 Hz, 1 H), 2.94 (ddd, J = 12.3, 11.6, 6.8 Hz, 1 H), 3.08 (ddd, J = 9.5, 9.0, 4.5 Hz, 1 H), 3.19 (ddd, J = 14.0, 12.3, 7.4 Hz, 1 H), 3.84 (s, 3 H), 3.86 (s, 3 H), 3.88–3.91 (m, 1 H), 5.34 (ddd, J = 5.9, 4.4, 2.2 Hz, 1 H), 5.79 (ddd, J = 5.9, 3.2, 2.5 Hz, 1 H), 6.62 (s, 1 H), 6.68 (s, 1 H); MS *m/z* 285 (M^+, bp), 270, 257, 244, 230; HRMS (M^+) *m/z* calcd for $C_{18}H_{23}NO_2$ 285.1729, found 285.1724. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found; C, 75.87; H, 8.17; N, 4.89.

(3a*S*,14b*S*)-3,5,6,8,9,14b-Hexahydro-4*H*-cyclopenta[*a*]-[1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepine (15). To the solution of **14** (284 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added a 1 M BBr_3 solution in CH_2Cl_2 (4.0 mL, 4.0 mmol) at −78 °C, and the solution was allowed to warm to room temperature for 1.5 h. MeOH (7 mL) was added at 0 °C, and then the low boiling material was evaporated. The residue was dissolved in 1 N HCl (10 mL), and the aqueous layer was washed with chloroform. The aqueous solution was heated for 20 min at 95 °C and then neutralized with saturated $NaHCO_3$ at 0 °C. The aqueous layer was extracted with CH_2Cl_2, and the organic layer was dried over Na_2SO_4 and concentrated. To the residue in toluene (2.0 mL) and H_2O (5.7 mL) were added 20% NaOH solution (2.0 mL, 10.0 mmol) and adogen 464 (26 mg, 0.057 mmol). CH_2Br_2 (0.7 mL, 9.97 mmol) was added to the solution at 0 °C, and the solution was stirred at 100 °C for 3 h. The aqueous layer was extracted with CH_2Cl_2, and the organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on alumina [hexane–ethyl acetate (10:1–3:1)] to give a colorless oil of **15** (137 mg, 51%). **15**: $[\alpha]^{22}_D$ −230.8° (*c* 1.22, $CHCl_3$); IR (neat) 1503, 1486 cm^{-1}; ^1H NMR (270 MHz) ($CDCl_3$) δ 1.66–1.81 (m, 2 H), 1.92–2.05 (m, 3 H), 2.32 (dd, J = 14.0, 6.8 Hz, 1 H), 2.39 (ddd, J = 9.9, 9.5, 6.2 Hz, 1 H), 2.54 (dd, J = 11.7, 7.4 Hz, 1 H), 2.74 (ddd, J = 17.8, 4.4, 2.5 Hz, 1 H), 2.91 (ddd, J = 12.6, 11.7, 6.8 Hz, 1 H), 3.07 (ddd, J = 9.5, 9.0, 4.4 Hz, 1 H), 3.18 (ddd, J = 14.0, 12.6, 7.4 Hz, 1 H), 3.87 (brs, 1 H), 5.52 (ddd, J = 5.9, 4.4, 2.1 Hz, 1 H), 5.79 (ddd, J = 5.9, 5.2,

2.5 Hz, 1 H), 5.88 (d, J = 1.5 Hz, 1 H), 5.89 (d, J = 1.5 Hz, 1 H), 6.59 (s, 1 H), 6.65 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.9, 30.7, 34.7, 43.3, 49.0, 53.5, 62.4, 68.0, 100.7, 109.8, 110.8, 128.7, 131.9, 132.3, 132.3, 145.9, 146.2. MS m/z 269 (M^+, bp), 241, 228, 214; HRMS (M^+) m/z calcd for $C_{17}H_{19}NO_2$ 269.1416, found 269.1421. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11, N, 5.20. Found; C, 75.69; H, 7.28; N, 5.03.

(1*R*,2*S*,3a*S*,14b*R*)-1,2,3,5,6,8,9,14b-Octahydro-4*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]-benzazepine-1,2-diol (16). To a solution of **15** (12 mg, 0.045 mmol) in THF (0.17 mL) and H_2O (20 μL) were added AcOH (26 μL, 0.454 mmol) and Me_3NO (11 mg, 0.097 mmol) at 0 °C. The resulting heterogenious mixture was stirred, and 2% (w/w) OsO_4 in t-BuOH (60 μL, 4.7 mmol) was added at 0 °C. After the solution was stirred at room temperature for 5 h, K_2CO_3 (65 mg) and 15% $NaHSO_3$ were added at 0 °C. The aqueous layer was extracted with CH_2Cl_2, and the organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel [chloroform−methanol (10:1)] to give **16** (11 mg, 76%). **16**: $[\alpha]^{21}_D$ −14.8° (c 0.72, $CHCl_3$); IR (neat) 3387, 1505, 1486 cm^{-1}; ^{1}H NMR (270 MHz) ($CDCl_3$) δ 1.50−2.10 (m, 6 H), 2.27−2.50 (m, 2 H), 2.50−2.65 (m, 2 H), 2.82−3.11 (m, 4 H), 3.10 (d, J = 9.4 Hz, 1 H), 4.29 (brs, 1 H), 4.35−4.45 (m, 1 H), 5.91 (s, 2 H), 6.65 (s, 1 H), 6.68 (s, 1 H); MS m/z 303 (M^+), 286, 258, 229 (bp); HRMS (M^+) m/z calcd for $C_{17}H_{21}NO_4$ 303.1470, found 303.1455.

(3a*S*)-5,6,8,9-Tetrahydro-1-hydroxy-4*H*-cyclopenta[*a*]-[1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-2(3*H*)-one (17). To a solution of DMSO (20 μL, 0.28 mmol) in CH_2Cl_2 (0.4 mL) was added $(CF_3CO)_2O$ (20 μL, 0.14 mmol) at −60 °C. After the solution was stirred at −60 °C for 10 min, **16** (8.3 mg, 0.027 mmol) in CH_2Cl_2 (0.6 mL) was added. The solution was stirred at −60 °C for 1 h, and Et_3N (45 μL, 0.323 mmol) was added. The solution was allowed to warm to 0 °C and stirred for 3 h. Saturated $NaHCO_3$ was added, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel [chloroform−methanol (10:1)] to give **17** (4.2 mg, 51%). **17**: $[\alpha]^{21}_D$ 371.9° (c 0.42, $CHCl_3$); IR (neat) 3406, 1708, 1502, 1484 cm^{-1}; ^{1}H NMR (270 MHz) ($CDCl_3$) δ 1.66−1.97 (m, 4 H), 2.57 (d, J = 18.1 Hz, 1 H), 2.69 (d, J = 18.1 Hz, 1 H), 2.88−3.12 (m, 4 H), 3.23−3.45 (m, 2 H), 5.16 (brs, 1 H), 5.95 (s, 1 H), 5.96 (s, 1 H), 6.67 (s, 1 H), 6.92 (s, 1 H); MS m/z 299 (M^+), 282, 271, 256, 228; HRMS (M^+) m/z calcd for $C_{17}H_{17}NO_4$ 299.1158, found 299.1169.

(−)-Cephalotaxinone (18). To the solution of **17** (9.7 mg, 0.032 mmol) in CH_2Cl_2 (0.65 mL) were added $(MeO)_3CH$ (35 μL, 0.32 mmol) and $TsOH{\cdot}H_2O$ (12 mg, 0.063 mmol) at 0 °C and the solution was stirred at room temperature for 7 h, saturated $NaHCO_3$ was added, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel [chloroform−methanol (50:1−10:1)] to give colorless crystals of **18** (4.8 mg, 47%). **18**: mp 186−187 °C; $[\alpha]^{30}_D$ 109.3° (c 0.85, $CHCl_3$); IR (KBr) 1724, 1626, 1502, 1486 cm^{-1}; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 1.83−1.90 (m, 2 H), 1.96 (ddd, J = 12.2, 7.0, 5.1 Hz, 1 H), 2.10 (ddd, J = 12.2, 10.8, 8.8 Hz, 1 H), 2.43−2.46 (m, 2 H), 2.53 (ddd, J = 11.2, 4.3, 4.2 Hz, 1 H), 2.69 (ddd, J = 9.8, 8.8, 8.2 Hz, 1 H), 2.91 (ddd, J = 10.8, 10.3, 9.8 Hz, 1 H), 3.09 (ddd, J = 8.8, 7.9, 4.2 Hz, 1 H), 3.53 (s, 1 H), 3.79 (s, 3 H), 5.90 (d, J = 1.2 Hz, 1 H), 5.92 (d, J = 1.2 Hz, 1 H), 6.40 (s, 1 H), 6.64 (s, 1 H), 6.70 (s, 1 H); MS m/z 313 (M^+), 298, 285, 282, 270, 254; HRMS (M^+) m/z calcd for $C_{18}H_{19}NO_4$ 313.1314, found 313.1334.

(−)-Cephalotaxine (1). To the solution of **18** (9.1 mg, 0.029 mmol) in MeOH (0.9 mL) was added $NaBH_4$ (44 mg, 1.14 mmol) at −78 °C. After the solution was stirred at room temperature for 1 h, solvent was removed in vacuo. Water was added and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on alumina [hexane−ethyl acetate (10:1−3:1)] to give colorless crystals of **1** (8.7 mg, 95%). **1**: mp 119−121 °C; $[\alpha]^{30}_D$ −161.3° (c 0.75, $CHCl_3$); IR (KBr) 3538, 1652, 1502, 1486 cm^{-1}; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 1.62−1.94 (m, 4 H), 1.95−2.08 (m, 1 H), 2.36 (dd, J = 14.3, 6.6 Hz, 1 H), 2.55−2.64 (m, 2 H), 2.93 (ddd, J = 12.1, 11.0, 7.1 Hz, 1 H), 3.08 (ddd, J = 9.3, 7.7, 4.9 Hz, 1 H), 3.35 (ddd, J = 14.3, 12.1, 7.7 Hz, 1 H), 3.68 (d, J = 9.3 Hz, 1 H), 3.73 (s, 3 H), 4.76 (d, J = 9.3 Hz, 1 H), 4.93 (s, 1 H), 5.90 (s, 2 H), 6.65 (s, 1 H), 6.68 (s, 1 H); MS m/z 315 (M^+), 300, 298, 284, 272; HRMS (M^+) m/z calcd for $C_{18}H_{21}NO_4$ 315.1471, found 315.1472.

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