The First Total Synthesis of (±)-Huperzine B

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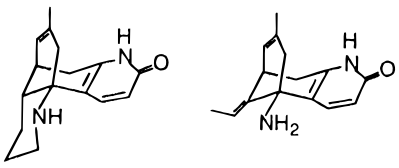
Huperzine B, a new *Lycopodium* alkaloid, exhibits a memory facilitating effect in mice and may be useful as an acetylcholinesterase inhibitor for the treatment of Alzheimer's disease. An efficient synthetic approach to huperzine B has been established successfully. The tetracyclic intermediate **10** is constructed by means of a tandem Michael addition and intramolecular Mannich cyclization using **8** and **9** as two components. Racemic huperzine B is obtained *via* a reaction sequence of 12 steps in 6.6% overall yield.

Introduction

Huperzine B (**1**), a new alkaloid isolated from *Huperzia serrata* (Thunb.) Trev. = *Lycopodium serratum* Thunb.,[1] exhibits a memory facilitating effect in mice.[2] Pharmacologically, it functions as a potent reversible inhibitor of acetylcholinesterase (AChE), with a PI_{50} (negative logarithm of the molar concentration causing 50% inhibition) of 6.1 on AChE from rat erythrocyte membrane,[3] and may be developed into a drug candidate for the treatment of Alzheimer's disease (AD).[4] Of substantial interest was the finding that in experiments performed on unanesthetized rabbits,[5] **1** exhibited a higher therapeutic index due to its longer duration of action in comparison with huperzine A (**2**), another AChE inhibitor which has been approved in China recently as a drug for the treatment of AD.[6] Chemically, huperzine B was found to be a member of the *Lycopodium* alkaloids.[7] Due to the scarcity of **1** in plants, we have engaged in a synthetic approach to this molecule for its further pharmacological investigation. Here we describe the first synthesis of racemic huperzine B.



1 **2**

Results and Discussion

The approach (Scheme 1) began with cyclization of keto ester **3**[8] *via* intramolecular Dieckmann condensation in ethanolic alkali, and the enol salt thus obtained was added to acrylonitrile in refluxing aqueous dioxane, giving the cyanide **4** in a reasonable yield in one pot. After protection of the diketone **4** as enol ether, a reduction of one ketone function with sodium borohydride in the presence of cerium chloride followed by the treatment with HCl afforded the α,β-unsaturated ketone **5**. Ketalization of **5** followed by an exhaustive lithium aluminum hydride reduction of the resulting cyano ester **6** yielded the amino alcohol **7**. Schumann[9] reported the total synthesis of obscurine *via* a tandem Michael addition and intramolecular Mannich reaction between 1,2,3,4-tetrahydro-6-methyl-2-oxopyridine (**9**)[9] and 7-methyl-2,3,4,6,7,8-hexahydroquinoline. Accordingly, the same strategy was employed for the construction of the tetracyclic skeleton of **1**, using **9** and **8** as two components. Thus, the ketal group of **7** was removed by perchloric acid, whereon the cyclic imine **8** was formed spontaneously.

The crude imine **8** was heated under reflux with **9** in dioxane in the presence of perchloric acid, giving **10** in 51% isolated yield. The ketal amine **7** could be used directly as the precursor of the imine **8** under acidic conditions, and the imine formed *in situ* reacted with **9** in one pot. Consequently, the yield of **10** was raised to 89%. Compound **12** was obtained after the protection of the amino group with benzyl chloroformate followed by mesylation of the hydroxyl group. The stereochemistry of **12** was assigned based on comprehensive ^1H and ^{13}C NMR spectral analysis, involving DEPT, COSY, HMQC, HMBC, and NOE experiments (Figure 1).

In the HMBC spectrum, the C-16 methylene protons (δ 4.06), which are assigned by their diagnostic proton chemical shift, show long range C−H couplings with C-8 (δ 37.2), C-15 (δ 34.2), and C-14 (δ 38.4). In the HMQC spectrum, there is a cross peak from C-8 (δ 37.2) to the directly coupled proton H-8a, which is observed at δ 1.35 as a doubled triplet. The smaller coupling (J = 4 Hz) is with H-7 while the triplet splitting is caused by coupling with H-8e (geminal coupling constant approximately 13 Hz) and with H-15a (axial−axial interaction, J approximately 13 Hz). In the $^1H-^1H$ COSY spectrum, H-8a shows a cross peak with H-7 at δ 1.67. In the DEPT spectrum, three methine carbons (C-12, δ 32.8; C-15, δ 33.2; C-7, δ 43.8) are observed which in turn show cross peaks with protons at δ 1.96 (H-12), δ 2.02 (H-15), and δ 1.67 (H-7), respectively. A 5.8% NOE enhancement of H-12 was observed on irradiation of H-8a. All these

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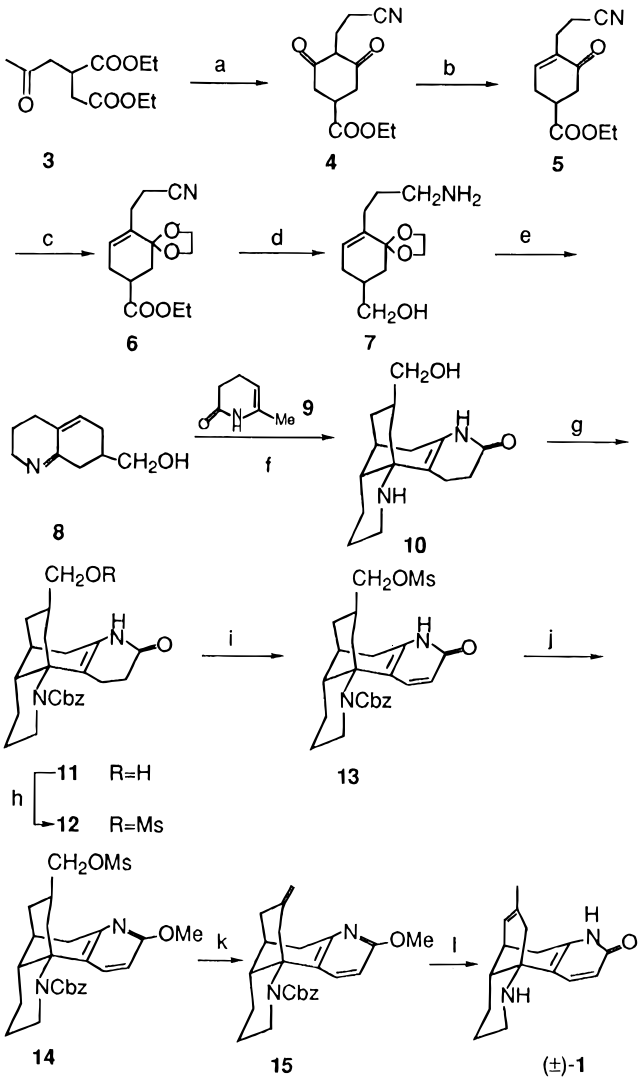
Scheme 1[a]



[a] Reagents and conditions: (a) (i) EtOH, EtONa, reflux, 2 h; (ii) acrylonitrile, H_2O, dioxane, reflux, 2.5 h; (b) (i) CH_2N_2, ether; (ii) $NaBH_4$, $CeCl_3$, MeOH, 0 °C to rt, 3 h, (iii) H^+; (c) $(CH_2OH)_2$, TsOH, benzene, reflux 8 h; (d) $LiAlH_4$, ether, 0 °C, 3 h; (e) 17% $HClO_4$, THF, rt, 4 h; (f) 6-methyl-3,4-dihydropyridin-2-one (**9**), 70% $HClO_4$, dioxane, reflux, 20 h; (g) $ClCOOCH_2Ph$, Na_2CO_3, EtOAc, H_2O, 0 °C, 10 h; (h) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min; (i) SO_2Cl_2, 5 °C, 20 min, then 120 °C, 30 min; (j) Ag_2CO_3, MeI, $CHCl_3$; (k) (i) *o*-$NO_2C_6H_4SeCN$, $NaBH_4$, EtOH; (ii) H_2O_2, THF−H_2O; (l) (i) Me_3SiI, $CHCl_3$, reflux, 10 h, then MeOH, reflux, 10 h; (ii) $CF_3SO_3SiMe_3$, dioxane, reflux, 10 h.

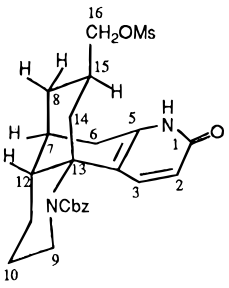


Figure 1.

results revealed that compound **12** has the correct ring connection stereochemistry.

Having the key intermediate **12** in hand, we see the next step is to convert the dihydropyridone moiety into the pyridone. Several attempts at dehydrogenation, using various reagents such as Pd/C,[10] DDQ,[11] $PdCl_2$,[12] $Me_3SiCl-Pd(OAc)_2$,[13] and $(PhSeO)_2O$[14] were unsuccessful. The desired transformation was finally achieved by chlorination of the double bond in **12** with sulfuryl chloride followed by elimination of hydrogen chloride on heating, and **13** was thus obtained in 68% yield.[15] O-Methylation of **13** with Ag_2CO_3-MeI gave **14**. Attempts to convert the methanesulfonate **14** into olefin **15** by means of DBU, *t*-BuOK, or HOAc−NaOAc failed. To our delight, treatment of **14** with *o*-nitrophenyl selenocyanate and sodium borohydride followed by oxidative elimination with hydrogen peroxide afforded olefin **15**.[16] Deprotection of **15** with trimethylsilyl iodide and the shift of exocyclic double bond into endocyclic catalyzed by trimethylsilyl trifluoromethanesulfonate[17] afforded the target molecular (±)-**1** in 6.6% overall yield from **3**.

Conclusion

In summary, the synthetic approach to huperzine B is straightforward and especially efficient in regard to the construction of the tetracyclic ring skeleton *via* a tandem Michael addition and intramolecular Mannich cyclization. The relative configuration of **12** was elucidated by ^1H and ^{13}C NMR spectra. This approach can also serve in the preparation of analogues of **1** for the study of structure−activity relationships.

Experimental Section

General Procedures. All air- or moisture-sensitive reactions were performed in flame-dried glassware under a N_2 atmosphere. Solvents were distilled from appropriate drying agents under a nitrogen atmosphere when necessary. Melting points were not corrected. NMR spectra were recorded at 400 MHz in $CDCl_3$ solution unless noted. Chemical shifts are reported in δ relative to residual $CHCl_3$ (7.27 ppm) for ^1H NMR, and relative to $CDCl_3$ (77.0 ppm) or CD_3OD (49.5 ppm) for ^{13}C NMR. IR spectra were obtained on films or potassium bromide pellets. Mass spectra were determined at an ionizing voltage of 70 eV by electron impact. Anhydrous sodium sulfate was used as drying agent.

Ethyl 4-(2-Cyanoethyl)-3,5-dioxocyclohexane-1-carboxylate (4). Keto ester **3** (11.5 g, 50 mmol) was added dropwise to a solution of sodium ethoxide (sodium [1.20 g, 52 mmol] dissolved in 50 mL of absolute alcohol). After the addition was complete, the resulting mixture was heated at reflux for 2 h, cooled, and concentrated to dryness under reduced pressure. The solid was dissolved in water (30 mL), and dioxane (25 mL) and acrylonitrile (30 mL) were added. The mixture was heated at reflux for 2.5 h and then cooled, neutralized with 6 N HCl, and extracted with CH_2Cl_2. The organic layers were combined, washed with brine and water, and dried. After removal of the solvent, the residue was chromatographed on silica gel (ethyl acetate:petroleum ether = 1:1) to afford 7.62 g of **4** as a white solid (64%): mp 76.5−78 °C. IR (KBr) 2960, 2246, 1728, 1583 cm^{-1}; ^1H NMR δ 4.15 (q, 2H, J = 7.2 Hz), 3.10 (t, 1H, J = 7.0 Hz), 2.72 (d, 4H, J = 7.2 Hz), 2.62 (t, 2H, J = 7.1 Hz), 2.48 (t, 2H, J = 7.0 Hz), 1.25 (t, 3H, J = 7.1 Hz); MS *m*/*z* 237 (M^+),

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208, 180, 164, 132, 117 (100), 91. Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.76; H, 6.33; N, 5.91. Found: C, 60.81; H, 6.41; N, 5.86.

Ethyl 3-Oxo-4-(2-Cyanoethyl)cyclohex-4-ene-1-carboxylate (5). To a stirred suspension of diketo ester **4** (2.45 g, 10.3 mmol) in ether (100 mL) was added CH_2N_2 in ether portionwise until the solid was dissolved. Ether was distilled off, and the residue was dissolved in methanol (100 mL). $CeCl_3 \cdot 7H_2O$ (3.90 g, 10.46 mmol) was added, and the mixture was cooled to 0 °C with an ice-bath. To this solution was added $NaBH_4$ (0.85 g, 22.9 mmol) carefully in small portions, followed by stirring at 0 °C for 30 min, and the mixture was allowed to stand at rt for 2.5 h. Water (30 mL) was added, and the stirring was continued for an additional 2 h. After removal of methanol, 6 N HCl (10 mL) was added, and the mixture was stirred for 20 min and then extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with brine and water, and dried. The solvent was removed, and the residue was chromatographed on silica gel (EtOAc:petroleum ether = 1:8) to give 1.65 g of **5** as an oil (73%): IR (KBr) 2982, 2247, 1732, 1676 cm^{-1}; ^1H NMR δ 6.90 (t, 1H, J = 4.0 Hz), 4.15 (q, 2H, J = 7.0 Hz), 3.05 (m, 1H), 2.65 (m, 4H), 2.50 (m, 4H), 1.25 (t, 3H, J = 7.0 Hz); MS m/z 221 (M^+), 179, 160, 148 (100), 121, 107.

Ethyl 4-(2-Cyanoethyl)-3-(ethylenedioxy)cyclohex-4-ene-1-carboxylate (6). A solution of ketone **5** (2.0 g, 3.05 mmol), ethylene glycol (2 mL, 35.5 mmol), and TsOH (20 mg) in benzene (100 mL) was heated at reflux under a Dean−Stark trap for 8 h to remove water. The reaction mixture was cooled and diluted with EtOAc (100 mL), washed with 5% sodium carbonate (30 mL), and dried. The solvent was removed, and the residue was chromatographed on silica gel (EtOAc:petroleum ether = 1:8) to give 2.2 g of **6** as a colorless oil (92%): IR (KBr) 2980, 2245, 1728, 1678, 1440 cm^{-1}; ^1H NMR δ 5.80 (m, 1H), 4.20 (q, 2H, J = 7.0 Hz), 3.95−4.05 (m, 4H), 3.05 (m,1H), 2.70 (m, 2H), 2.52 (m, 2H), 2.30 (m, 4H), 1.00 (t, 3H, J = 7.0 Hz); MS m/z 265 (M^+) , 220, 205 (100), 208 , 148 , 121. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.16; H, 7.26; N, 5.25.

1-(3-Aminopropyl)-4-(hydroxymethyl)-6-(ethylenedioxy)cyclohex-1-ene (7). To a stirred suspension of $LiAlH_4$ (2.28 g, 60 mmol) in ether (100 mL) was added cyano ester **6** (1.60 g, 6.0 mmol) in 20 mL of ether slowly at 0 °C. After the addition was complete, the reaction mixture was stirred for an additional 2 h at 0 °C and quenched by successive addition of water (2.28 mL), 15% solution of NaOH (2.28 g), and water (6.9 mL). The precipitate was filtered off, and the solid was extracted with ether several times. The organic layers were combined and dried, and the ether was evaporated. Chromatography of the residue on silica gel ($CHCl_3$:MeOH = 6:1) gave 0.87 g of **7** as a light yellow solid (64%): mp 86−87.5 °C. IR (KBr) 3350, 2940, 1570 cm^{-1}; ^1H NMR δ 5.45 (s, 1H), 3.60−3.80 (m, 4H), 3.15 (s, 2H, J = 3.1 Hz), 2.45 (t, 2H, J = 6.3 Hz), 1.86 (d, 1H, J = 11.3 Hz), 1.68 (m, 2H), 1.58 (d, 2H, J = 12 Hz), 1.46 (d, 1H, J = 11.2 Hz), 1.35 (m, 2H), 1.04 (t, 1H, J = 12Hz); MS m/z 227 (M^+) , 208, 203, 154 , 112 (100), 84. Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.44; H, 9.25; N, 6.17. Found: C, 63.28; H, 9.31; N, 6.14.

16-Hydroxy-*N*-demethyl-2,3-dihydrolycodin-1-one (10). Method A: To a stirred solution of ketal **7** (1.78 g, 7.84 mmol) in THF (20 mL) was added a 17% aqueous solution (5 mL) of perchloric acid, and the resulting mixture was stirred at rt for 4 h. THF was evaporated under reduced pressure, and the residue was neutralized with ammonia solution at 0 °C and then extracted with CH_2Cl_2. The organic layers were combined, washed with water, and dried. After removal of the solvent, the residue was added to a mixture of **9** (1.74 g, 15.6 mmol) and 70% perchloric acid (1.7 g, 15 mmol) in dioxane (20 mL), heated at reflux for 20 h, and cooled. The reaction mixture was concentrated and treated with saturated Na_2CO_3 solution (10 mL), extracted with CH_2Cl_2, washed with water, and dried. Removal of the solvent *in vacuo* followed by chromatography of the residue on silica gel ($CHCl_3$:MeOH = 10:1) gave 1.04 g of **10** as a white solid (48%): mp 138.5−140 °C. IR (KBr) 3500, 3100,2697, 1633 cm^{-1}; ^1H NMR (CD_3OD) δ 3.28 (dd, 1H, J = 5.3 Hz, 11.2 Hz), 3.22 (dd, 1H, J = 5.3 Hz, 11.2 Hz),3.06 (d, 1H, J = 11.8 Hz), 3.04 (m, 1H), 2.78 (dt, 1H, J = 4.1 Hz, 12.1 Hz), 2.30−2.40 (m, 3H), 2.28 (dd, 1H, J = 7.4 Hz, 12.0 Hz), 2.18 (m, 1H), 2.08 (m,1H), 1.96 (m, 1H), 1.80 (dd, 1H, J = 3.6 Hz, 12.3 Hz), 1.72 (s, 1H), 1.65 (m, 2H), 1.60 (d, 1H, J = 15.4 Hz), 1.40−1.50 (m, 1H), 1.16−1.23 (m, 2H); ^{13}C NMR (CD_3OD) δ 173.0, 137.0, 105.2, 68.0, 63.2, 43.8, 43.2, 39.2, 38.0, 36.0, 24.3, 32.1, 31.0, 25.4, 24.2, 21.3; MS m/z 276 (M^+), 255, 217, 203 (100), 189, 175, 134, 91. Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.56; H, 8.69; N, 10.14. Found: C, 69.46; H, 8.73; N, 10.02.

Method B: A mixture of ketal amine **7** (0.65 g, 2.8 mmol), 3,4-dihydro-6-methylpyridone **9** (0.6 g, 5.6mmol), and 70% aqueous perchloric acid (0.6 g) in dioxane (5 mL) was heated under reflux for 22 h and cooled. Workup as mentioned above gave 0.70 g (89%) of **10**.

16-Hydroxy-*N*-(benzyloxycarbonyl)-2,3-dihydrolycodin-1-one (11). To a stirred mixture of amine **10** (0.20 g, 0.72 mmol), saturated aqueous Na_2CO_3 (5 mL), and EtOAc (10 mL) was slowly added $ClCOOCH_2Ph$ (1 mL) at 0 °C. After the addition was complete, the reaction mixture was allowed to warm to rt and stirred overnight. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The organic layers were combined, washed with brine and water, and dried. The solvent was removed *in vacuo*, and the residue was chromatographed on silica gel (EtOAc) to give 0.21 g of **11** as a white solid (71%): mp 102−103.5 °C. IR (KBr) 3500, 2980,1720, 1666 cm^{-1}; ^1H NMR δ 7.80 (s, 1H), 7.45 (m, 5H), 5.05 (m, 2H), 4.22 (d, 1H, J = 17 Hz), 4.10 (dd, 1H, J = 7.4Hz, 11 Hz), 3.84 (dd, 1H, J = 5.5 Hz, 10.6 Hz), 3.50 (dd, 1H, J = 5.5 Hz, 10.6 Hz), 2.85 (d, 1H, J = 11.2 Hz), 2.56 (m, 2H), 2.50 (m, 2H), 2.40 (dt, 1H, J = 8.2 Hz, 12 Hz), 2.05−2.10 (m, 2H), 2.00 (m, 1H), 1.90 (t, 1H, J = 7.5 Hz), 1.70 (t, 2H, J = 10.4), 1.64 (m, 1H), 1.60 (1H, d, J = 12.6 Hz), 1.62 (m, 2H), 1.50 (m, 2H), 1.30 (m, 2H); MS m/z 410 (M^+), 391, 319, 203 (100), 177, 152, 91. Anal. Calcd for $C_{24}H_{30}N_2O_4$: C, 70.24; H, 7.32; N, 3.41. Found: C, 70.16; H, 7.38; N, 3.32.

16-(Mesyloxy)-*N*-(benzyloxycarbonyl)-2,3-dihydrolycodin-1-one (12). To a solution of alcohol **11** (0.25 g, 0.61 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (0.5 mL) slowly at 0 °C, and the reaction mixture was stirred at this temperature for 20 min. A solution of mesyl chloride (0.28 mL, 1.74 mmol) in CH_2Cl_2 (1 mL) was added, and the stirring was continued for an additional 20 min. The reaction mixture was diluted with ether (10 mL), washed with brine and water, and dried. After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel (EtOAc:petroleum ether = 1:1) to give 0.26 g of **12** as white solid (87%): mp 103−104 °C. IR (KBr) 2980,1700, 1668 cm^{-1}; ^1H NMR δ 7.80 (s, 1H) 7.33 (m, 5H), 5.04 (s, 2H), 4.22 (d, 1H, J = 13.5 Hz), 4.04 (m, 2H), 2.97 (s, 3H), 2.94 (dd, 1H, J = 3.4 Hz, 12.5 Hz), 2.52 (m, 1H), 2.46 (t, 2H, J = 8.3 Hz), 2.26 (m, 1H), 2.06 (m, 1H), 2.02 (m, 2H), 1.96 (m, 1H), 1.76 (d, 1H, J = 13.3 Hz), 1.70 (m, 2H), 1.67 (m, 1H), 1.60 (m, 1H), 1.60 (d, 1H J = 12.3 Hz), 1.56 (dd, 1H, J = 5.6 Hz, 11.6 Hz), 1.52 (m, 1H), 1.35 (dt, 1H, J = 4.0 Hz, 13.0 Hz); ^{13}C NMR δ 172.0, 156.4, 137.2, 132.5, 128−129 (5C), 110.5, 76.3, 67.5, 63.0, 45.5, 44.3, 38.8, 37.6, 37.2, 33.2, 32.6, 31.0, 29.6, 27.8, 25.5, 21.0; MS m/z 488 (M^+, 100), 409, 337, 257, 201, 149, 91. Anal. Calcd for $C_{25}H_{32}N_2O_6S$: C, 61.47; H, 6.56; N, 5.74. Found: C, 61.32; H, 6.60; N, 5.71.

16-(Mesyloxy)-*N*-(benzyloxycarbonyl)lycodin-1-one (13). To a stirred solution of **12** (0.14 g, 0.3 mmol) in CH_2Cl_2 (6 mL) was slowly added SO_2Cl_2 (0.031 mL 0.31 mmol) at 5 °C , and the stirring was continued for 10 min. After the solvent was distilled off, the residue was heated at 120 °C under N_2 for 20 min and then cooled to 0 °C. The oil thus obtained was treated with 5% aqueous ammonia solution, and the mixture was extracted with CH_2Cl_2. The organic phase was washed with brine and water, and dried. After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel (EtOAc: petroleum ether = 3:1) to give 0.12 g of **13** as white solid (81%): mp 119−120 °C. IR (KBr) ν 3432, 2920, 1700, 1660, 1606 cm^{-1}; ^1H NMR δ 7.46 (m, 5H), 7.18 (d, 1H, J = 9.5 Hz), 6.52 (d, 1H, J = 9.5 Hz), 5.10 (d, 1H, J = 12.3 Hz), 5.04 (d, 1H, J = 12.4 Hz), 4.24 (d, 1H, J = 13.5 Hz), 4.10 (dd, 1H, J = 4.6 Hz, 10.6 Hz), 4.04 (dd, 1H, J = 4.6 Hz, 10.6 Hz), 3.02 (d, 1H, J = 13.9 Hz), 2.96 (s, 3H), 2.46 (m, 3H), 2.10 (d, 1H, J = 12.6 Hz), 2.08 (m, 1H), 1.60−1.30 (m, 3H), 1.58 (m, 3H), 1.40

(m, 2H); MS *m*/*z* 486 (M^+), 461, 425, 369, 335, 291, 200, 235, 91 (100). Anal. Calcd for $C_{25}H_{30}N_2O_6S$: C, 61.73; H, 6.17; N, 5.76. Found: C, 61.58; H, 6.21; N, 5.72.

1-Methoxy-16-(mesyloxy)-*N*-(benzyloxycarbonyl)lycodine (14). To a stirred solution of pyridone **13** (60 mg, 0.12 mmol) and CH_3I (0.15 mL, 2.4 mmol) in $CHCl_3$ (4 mL) was added Ag_2CO_3 (60 mg, 0.28 mmol), and the resulting mixture was stirred in dark for 36 h. The reaction mixture was diluted with EtOAc and filtered. The filtrate was washed with brine and water and dried. After the solvent was removed *in vacuo*, the residue was chromatographed on silica gel (EtOAc:petroleum ether = 1:8) to give 62 mg of **14** as a white solid (99%): mp 68−70 °C. IR (KBr) 2960, 1700, 1598, 1580 cm^{-1}; ^1H NMR δ 7.60 (d, 1H, J = 9.6 Hz), 7.38 (m, 5H), 7.00 (d, 1H, *J* = 9.6 Hz), 5.16 (d, 1H, *J* = 12.2 Hz), 5.12 (d, 1H, *J* = 12.2 Hz), 4.20 (d, 1H, *J* = 13.8 Hz), 4.00 (s, 3H), 3.96 (m, 2H), 3.12 (d, 1H, *J* = 14.8 Hz), 2.96 (s, 3H), 2.86 (d, 1H, *J* = 2.1 Hz), 2.50 (dt, 1H, *J* = 2.8 Hz, 14.4 Hz), 2.20 (dd, 2H, *J* = 4.1 Hz, 12.2 Hz), 2.00 (d, 1H, *J* = 7.8 Hz), 1.52−1.70 (m, 4H), 1.20 (dt, 1H, *J* = 4.6 Hz , 12.7 Hz); MS *m*/*z* 500 (M^+), 399, 339, 267, 213, 91 (100). Anal. Calcd for $C_{26}H_{32}N_2O_6S$: C, 62.40; H, 6.40; N, 5.60. Found: C, 62.25; H, 6.43; N, 5.57.

1-Methoxy-*N*-(benzyloxycarbonyl)-15,16-didehydrolycodine (15). To a stirred suspension of *o*-$NO_2C_6H_4SeCN$ (15 mg, 0.08 mmol) in EtOH (1 mL) was added $NaBH_4$ (3 mg, 0.08 mmol) at rt, and the mixture was stirred for 20 min. Mesylate **14** (40 mg, 0.08 mmol in 1 mL of EtOH) was then added, and the stirring was continued for 24 h. After addition of THF (1 mL), the reaction mixture was cooled to 0 °C, 30% H_2O_2 (0.5 mL) was added, and the mixture was stirred for 36 h at rt. Water was added, and the ethanol was evaporated *in vacuo*. The remaining aqueous phase was extracted with ether. The organic layers were combined, washed with water, and dried. Removal of the solvent and chromatography of the residue on silica gel (EtOAc:petroleum ether = 1:10) gave 22 mg of **15** as syrup (68%): IR (KBr) 2960, 1700, 1640, 1598 cm^{-1}; ^1H NMR δ 7.40 (m, 5H), 7.32 (d, 2H, *J* = 8.5 Hz), 6.60 (d, 1H, *J* = 8.5 Hz), 5.17 (d, 1H, *J* = 11.6 Hz), 5.04 (d, 1H, *J* = 11.6 Hz), 4.70 (d, 1H, *J* = 7.4 Hz), 4.35 (d, 1H, *J* = 1.7 Hz), 4.26 (dt, 1H, *J* = 1.7 Hz, 10.3 Hz), 3.96 (s, 3H), 3.42 (d, 1H, *J* = 12.4 Hz), 3.08 (d, 1H, *J* = 13.5 Hz), 3.00 (dd, 1H, *J* = 3.1 Hz, 12.7 Hz), 2.44 (m, 2H), 2.20−2.30 (m, 2H), 1.72 (d, 1H, *J* = 11.2 Hz), 1.60 (m, 2H), 1.40 (m, 1H), 1.30 (m, 2H); MS *m*/*z* 404 (M^+), 383, 349, 267, 237, 213, 149 (100), 91.

(±)-Huperzine B (1). To a solution of **15** (16 mg, 0.039 mmol) in $CHCl_3$ (2 mL) was added Me_3SiI (20 μL, 0.14 mmol), and the mixture was refluxed for 24 h. After removal of $CHCl_3$ *in vacuo*, the residue was dissolved in methanol (2 mL) and heated under reflux for 12 h. The solvent was evaporated, and the residue was dissolved in dioxane (2 mL). To this solution was added $CF_3SO_3SiMe_3$ (2 μL, 0.104 mmol), and the resulting mixture was heated at 90 °C for 20 h. The solvent was removed under reduced pressure, and the residue was partitioned between 10% aqueous $NaHCO_3$ and $CHCl_3$. The organic layer was separated, and washed with brine, and dried. Flash chromatography of the residue on silica gel after removal of the solvent ($CHCl_3$:MeOH = 9:1) gave 8.2 mg of (±)-**1** as a colorless solid (approximately 80%): mp 266−68 °C. IR (KBr) 3100, 2960, 1700, 1664, 1601,1560 cm^{-1}; ^1H NMR δ 7.74 (d, 1H, *J* = 9.3 Hz), 6.48 (d, 1H, *J* = 9.3 Hz), 5.46 (d, 1H, *J* = 5.1 Hz), 2.84 (dd, 1H, *J* = 5.3 Hz, 18.3 Hz), 2.72 (d, 1H, *J* = 12.0 Hz), 2.46 (d, 1H, *J* = 17.9 Hz), 2.36 (m, 1H), 2.26 (d, 1H, *J* = 12.5 Hz), 2.06 (d, 1H, *J* = 16.7 Hz), 1.86 (d, 1H, *J* = 16.8 Hz), 1.75−1.96 (br s, 1H), 1.67 (d, 1H, *J* = 12.4 Hz), 1.68 (m, 1H), 1.56- 1.59 (m. 3H), 1.52 (s, 3H), 1.25 (m, 1H); ^{13}C NMR δ 164.8, 143.2, 140.6, 132.3, 125.9, 118.0 (2C), 53.1, 47.8, 41.6, 40.3, 34.3, 29.5, 27.9, 25.1, 22.9. MS *m*/*z* 256 (M^+, 100), 241, 227, 213, 201, 173, 115; HRMS calcd for $C_{16}H_{20}N_2O$ 256.1575, found 256.1574.

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