A Robust and Scalable Synthesis of the Potent Neuroprotective Agent (−)-Huperzine A

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Chemical Science

Supporting Information

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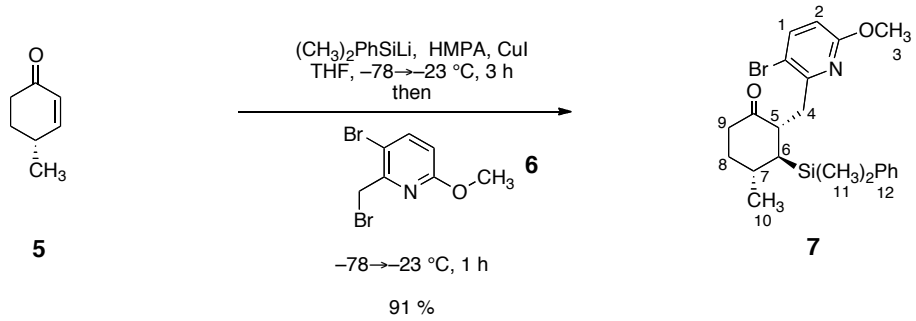
General Experimental Procedures. All reactions were performed in single-neck, flame-dried, round-bottomed flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air and moisture-sensitive liquids were transferred via syringe or stainless steel cannula, or were handled in a nitrogen-filled drybox (working oxygen level <1 ppm). Organic solutions were concentrated by rotary evaporation at 30–33 °C. Flash-column chromatography was performed as described by Still et al,[1] employing silica gel (60 Å, 40–63 μm particle size) purchased from Sorbent Technologies (Atlanta, GA). Analytical thin-layered chromatography (TLC) was performed using glass-plates pre-coated with silica gel (1.0 mm, 60 Å pore size) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) or/and submersion in aqueous potassium permagnate solution ($KMnO_4$), followed by brief heating on a hot plate (120 °C, 10–15 s).

Materials. Commercial solvents and reagents were used as received with the following exceptions. Benzene, dichloromethane, ether, and toluene were purified according to the method of Pangborn et al.[2] Tetrahydrofuran was distilled from sodium/benzophenone under an atmosphere of nitrogen immediately before use. Methanol was distilled from magnesium methoxide under an atmosphere of nitrogen immediately before use. Hexamethylphosphoramide was distilled from calcium hydride and stored under nitrogen. 4-Å Molecular sieves were activated by heating overnight in vacuo (200 °C, 200 mTorr), stored in a gravity oven (120 °C), and were flame-dried in vacuo (100 mTorr) immediately before use. Solutions of phenyldimethylsilyllithium in tetrahydrofuran were prepared according to the procedure of Fleming and co-workers.[3] (*R*)-4-Methyl-cyclohexe-2-ene-1-one (**5**) was prepared from (+)-pulegone according to the procedure of Lee and co-workers.[4] 3-Bromo-2-(bromomethyl)-6-methoxypyri``dine (**6**) was prepared according to the procedure of Kelly and co-workers.[5] Bis(tri-*tert*-butylphosphine)palladium (0) was prepared according to the procedure of Dai and Fu.[6] Methyl *N*-(triethylammoniumsulfonyl)carbamate (Burgess reagent, **12**) was prepared according to the procedure of Burgess and co-workers.[7] Hydrido(hydroxydimethylphosphino)[hydrogen bis(hydroxydimethylphosphino)]platinum (II) (**13**) was prepared according to the procedure of Ghaffar and Parkins.[8] Ethyltriphenylphosphonium bromide was recrystallized from water, and the resulting crystals were dried for 24 h at 50 °C in vacuo.

Instrumentation. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 or 500 MHz at 24 °C, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad, app = apparent), integration, coupling constant in Hertz, and assignment. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100 or 125 MHz at 24 °C, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$, δ 77.0). Distortionless enhancement by polarization transfer spectra [DEPT (135)] were recorded at 100 or 125 MHz at 24 °C, unless otherwise noted. ^{13}C NMR and DEPT (135) data are combined and represented as follows: chemical shift, carbon type [obtained from DEPT (135) experiments]. Attenuated total reflectance Fourier transform infrared spectra (ATR-FTIR) were obtained using a Thermo Electron Corporation Nicolet 6700 FTIR spectrometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of

absorption (s = strong, m = medium, w = weak, br = broad). High-resolution mass spectrometry (HRMS) data were obtained using a Waters UPLC/HRMS instrument equipped with a dual API/ESI high-resolution mass spectrometry detector and photodiode array detector. Unless otherwise noted, samples were eluted over a reverse-phase C_{18} column (1.7 μm particle size, 2.1 × 50 mm) with a linear gradient of 5% acetonitrile–water containing 0.1% formic acid→95% acetonitrile–water containing 0.1% formic acid over 4 min, followed by 100% acetonitrile containing 0.1% formic acid for 1 min, at a flow rate of 600 μL/min. Optical rotations were measured on a Perkin Elmer polarimeter equipped with a sodium (589 nm, D) lamp. Optical rotation data are represented as follows: specific rotation ($[\alpha]_D^{20}$), concentration (g/mL), and solvent.

Synthetic Procedures.[9]



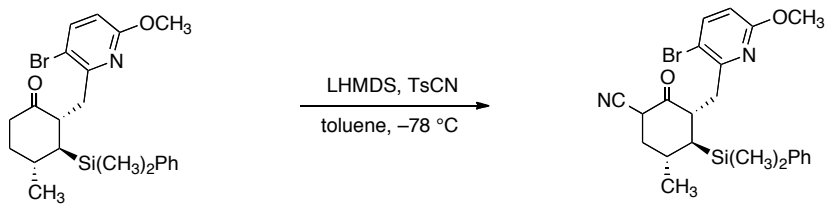
*Step 1: Addition–Alkylation of (R)-4-Methyl-cyclohexe-2-ene-1-one (**5**) (Addition-Alkylation Product **7**):*

Hexamethylphosphoramide (11.4 mL, 65.4 mmol, 3.60 equiv) was added dropwise via syringe to a stirred suspension of cuprous iodide (3.46 g, 18.2 mmol, 1.00 equiv) in tetrahydrofuran (36 mL) at 24 °C. The resulting mixture was cooled to −78 °C. A solution of dimethylphenylsilyllithium in tetrahydrofuran (0.46 M, 79.0 mL, 36.3 mmol, 2.00 equiv) was added dropwise via syringe pump over 30 min to the cold brown suspension. Upon completion of the addition, the mixture was warmed to 0 °C. The resulting solution was stirred for 1 h at 0 °C. The mixture was then cooled to −78 °C. (*R*)-4-Methyl-cyclohexe-2-ene-1-one (**5**, 2.00 g, 18.2 mmol, 1.00 equiv) was added dropwise via syringe over 5 min. Upon completion of the addition, the reaction mixture was warmed to −23 °C. The warmed solution was stirred for 3 h at −23 °C. The reaction mixture was then cooled to −78 °C. A solution of 3-bromo-2-(bromomethyl)-6-methoxypyridine (**6**) in tetrahydrofuran (0.50 M, 40.0 mL, 20.0 mmol, 1.10 equiv) was added dropwise via cannula over 30 min to the cold reaction mixture. Upon completion of the addition, the reaction mixture was warmed to −23 °C. The warmed solution was stirred for 1 h at −23 °C. The product mixture was then warmed over 30 min to 24 °C. The warmed product mixture was eluted through a pad of celite (length/diameter = 3/9 cm). The celite pad was washed sequentially with saturated aqueous sodium bicarbonate solution (100 mL), ethyl acetate (250 mL), saturated aqueous sodium bicarbonate solution (100 mL), and ethyl acetate (250 mL). The biphasic filtrate was collected and transferred to a separatory funnel. The layers that formed were separated. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate solution (2 × 200 mL), distilled water (200 mL), and saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ethyl acetate–hexanes) to afford the addition–alkylation product **7** as a pale-yellow, viscous oil (7.37 g, 91%).

R_f = 0.27 (5% ethyl acetate–hexanes, $KMnO_4$). $[\alpha]_D^{20}$ = −40.8 (*c* 0.10, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.55 (d, 1H, *J* = 8.5 Hz, H_1), 7.45 (dd, 2H, *J* = 8.0, 2.0 Hz, H_{12}), 7.33–7.29 (m, 3H, H_{12}), 6.42 (d, 1H, *J* = 8.5 Hz, H_2), 3.79 (s, 3H, H_3), 3.22–3.12 (m, 2H, H_4/H_5), 2.84 (dd, 1H, *J* = 14.5, 4.5 Hz, H_4), 2.58–2.52 (m, 1H, H_9), 2.23–2.17 (m, 1H, H_9), 2.05–1.94 (m, 2H, H_7/H_8), 1.82–1.75 (m, 1H, H_8), 1.15 (t, 1H, *J* = 6.5 Hz, H_6), 1.00 (d, 3H, 6.5 Hz, H_{10}), 0.32 (app s, 6H, H_{11}). ^{13}C NMR (125 MHz, $CDCl_3$), δ 214.8 (C), 162.2 (C), 154.7 (C), 142.4 (CH), 138.1 (C), 134.0 (CH), 129.3 (CH), 128.0 (CH), 112.2 (C), 110.1 (CH), 53.6 (CH_3), 47.1 (CH), 40.3 (CH_2), 37.3 (CH_2), 34.3 (CH), 31.1 (CH_2), 29.3 (CH), 23.9 (CH_3), –3.0 (CH_3), –3.6 (CH_3). IR (ATR-FTIR), cm^{-1}: 2951 (br), 1709 (s), 1575 (s), 1459 (s), 1417

(s), 1295 (m), 1250 (m), 1111 (m), 1037 (m), 1014 (m), 820 (s), 734 (m), 701 (m). HRMS-CI(m/z): $[M + H]^+$ calcd for $C_{22}H_{29}BrNO_2Si$, 446.1146/448.1125; found, 446.1147/448.1124.

*Steps 2a–c: Synthesis of the Olefination Product **10**:*

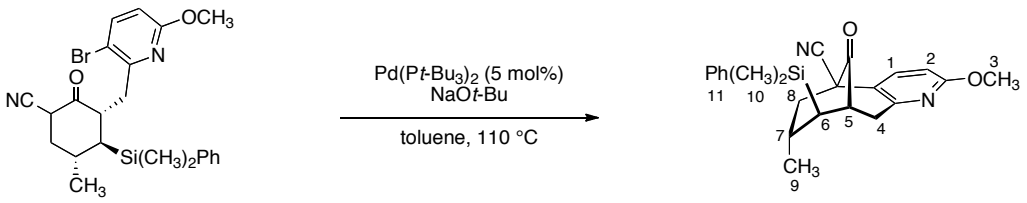


7 **8**

*Step 2a: Cyanation of the Addition-Alkylation Product **7** (α-Cyanoketone **8**):*

A solution of lithium hexamethyldisilazide in toluene (1.00 M, 49.7 mL, 49.7 mmol, 3.00 equiv) was added dropwise over 15 min via syringe pump to a stirred solution of the addition–alkylation product **7** (7.37 g, 16.6 mmol, 1.00 equiv) in toluene (170 mL) at −78 °C. Upon completion of the addition, the reaction mixture was warmed to 0 °C. The warmed solution was stirred for 15 min at 0 °C. The mixture was then cooled to −78 °C. A solution of *p*-toluenesulfonyl cyanide in toluene (1.00 M, 18.2 mL, 18.2 mmol, 1.10 equiv) was added quickly (<1 min) via syringe to the cold reaction mixture. The reaction mixture was stirred for 1 min at −78 °C. The cold product mixture was rapidly diluted with 100 mM aqueous sodium phosphate buffer solution (pH 7, 30 mL). The product mixture was allowed to warm over 30 min to 24 °C, with stirring. The warmed product mixture was diluted with ethyl acetate (200 mL). The diluted product mixture was transferred to a separatory funnel that had been charged with 100 mM aqueous sodium phosphate buffer solution (pH 7, 150 mL). The layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 150 mL). The organic layers were combined, and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford the unpurified α-cyanoketone **8** as a pale-yellow, viscous oil. ^{1}H NMR analysis (400 MHz, $CDCl_3$) indicated >95% conversion to the cyanoketone **8** (mixture of (*R*)-α-cyanoketone, (*S*)-α-cyanoketone, and β-hydroxy-α,β-unsaturated nitrile isomers). The product so obtained was used directly in the following step.

The α-cyanoketone **8** was found to be unstable towards purification by flash-column chromatography. Therefore, further characterization was not attempted.



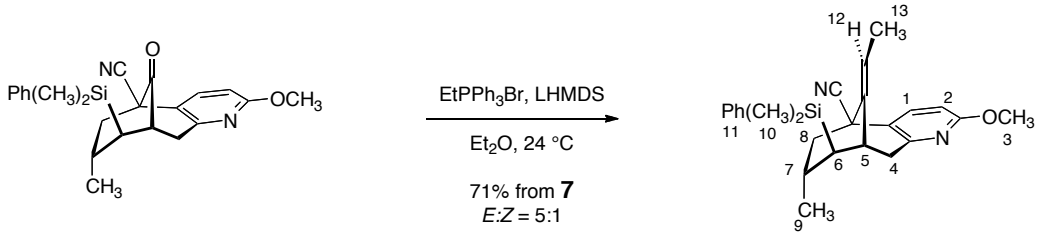
8 **9**

*Step 2b: Cyclization of the α-Cyanoketone **8** (Tricycle **9**):*

A 500-mL round-bottomed flask fused to a Teflon-coated valve was charged with the unpurified α-cyanoketone **8** (16.6 mmol, 1.00 equiv, assuming quantitative yield in the preceding step). The residue was dried by azeotropic distillation with benzene (5.0 mL). The vessel was sealed and the sealed vessel was transferred to a nitrogen-filled drybox. Sodium *tert*-butoxide (1.75 g, 18.2 mmol, 1.10 equiv), bis(tri-*tert*-butylphosphine)palladium (0) (423 mg, 828 μmol, 0.05 equiv) and toluene (170 mL) were added sequentially to the flask. The vessel was sealed, and the sealed vessel was removed from the drybox. The reaction vessel was placed in an oil bath that had been preheated to 110 °C. The reaction mixture was stirred and heated for 12 h at 110 °C. The reaction vessel was removed from the oil bath and the product mixture was allowed to cool over 30 min to 24 °C. The cooled product mixture was diluted with dichloromethane (300 mL). The diluted mixture was transferred to a separatory funnel that had been charged with saturated aqueous sodium bicarbonate solution (400 mL). The layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 500 mL). The organic layers were combined, and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford the unpurified cyclized product **9** as a pale-yellow, viscous oil. ^{1}H NMR analysis (400 MHz, $CDCl_3$) indicated >95% conversion to the cyclized product **9**. The product so obtained was used directly in the following step.

An analytically pure sample of the cyclized product **9** was obtained by flash-column chromatography (eluting with 5% ethyl acetate–hexanes):

R_f = 0.23 (5% ethyl acetate–hexanes, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.64 (d, 1H, J = 9.0 Hz, H_1), 7.51 (dd, 2H, J = 7.0, 1.5 Hz, H_{11}), 7.39−7.29 (m, 3H, H_{11}), 6.74 (d, 1H, J = 8.5 Hz, H_2), 3.91 (s, 3H, H_3), 3.14 (dd, 1H, J = 18.0, 4.5 Hz, H_4), 2.95–2.92 (m, 1H, H_5), 2.82–2.77 (m, 2H, H_4/H_8), 2.15 (dd, 1H, J = 13.5, 10.0 Hz, H_8), 1.85–1.78 (m, 1H, H_7), 1.32 (dd, 1H, J = 10.0, 6.5 Hz, H_6), 0.75 (d, 3H, J = 6.5 Hz, H_9), 0.40 (s, 3H, H_{10}), 0.37 (s, 3H, H_{10}). ^{13}C NMR (125 MHz, $CDCl_3$), δ 206.0 (C), 164.1 (C), 149.5 (C), 138.5 (CH), 136.9 (C), 134.1 (CH), 129.8 (CH), 128.3 (CH), 125.1 (C), 119.2 (C), 111.0 (CH), 53.9 (CH_3), 52.4 (CH_2), 49.9 (C), 44.9 (CH), 42.4 (CH_2), 38.1 (CH), 28.2 (CH), 21.8 (CH_3), −3.4 (CH_3), −3.8 (CH_3). IR (ATR-FTIR), cm^{-1}: 2955 (br), 2268 (w), 1736 (s), 1713 (w), 1599 (m), 1576 (w), 1476 (s), 1424 (m), 1321 (m), 1264 (m), 1130 (m), 1112 (m), 1028 (m), 824 (s), 737 (w), 704 (m). HRMS-CI(m/z): $[M + H]^+$ calcd for $C_{23}H_{27}N_2O_2Si$, 391.1837; found, 391.1839.



9 **10** (5:1 mixture of diastereomers)

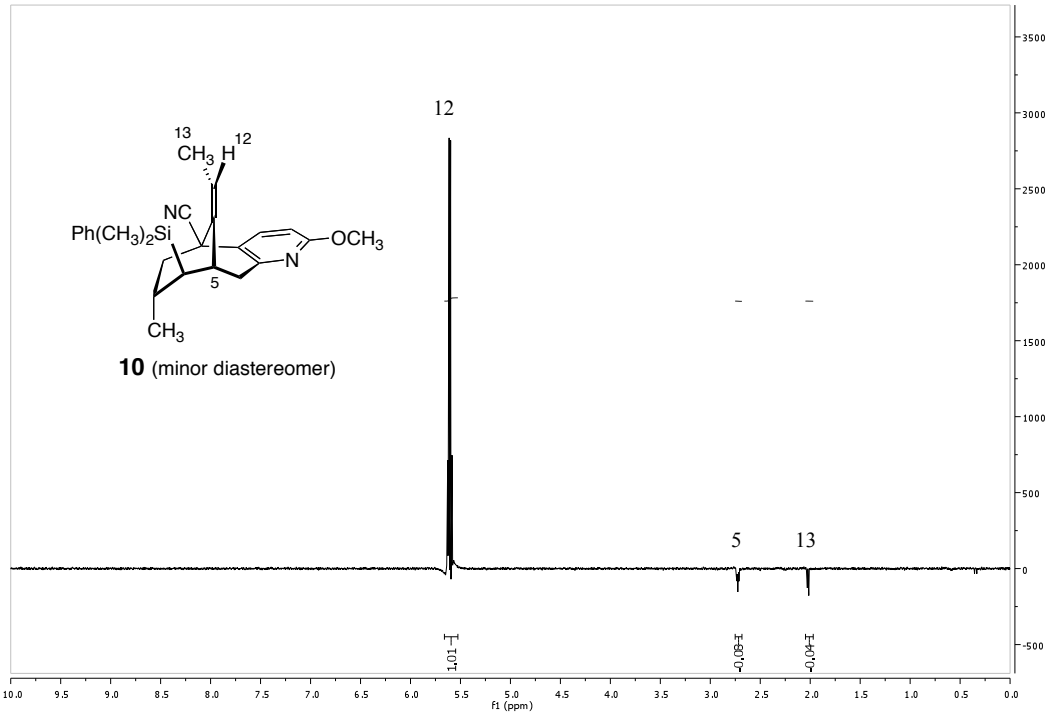
*Step 2c: Olefination of the Cyclized Product **9** (Alkene **10**):*

In a nitrogen-filled drybox, a 500-mL round-bottomed flask was charged sequentially with ethyltriphenylphosphonium bromide (7.38 g, 19.9 mmol, 1.20 equiv) and lithium hexamethyldisilazide (3.33 g, 19.9 mmol, 1.20 equiv). The flask was sealed with a rubber septum, and the sealed flask was removed from the drybox. Ether (200 mL) was added to the flask via syringe. The resulting orange suspension was stirred for 1 h at 24 °C. During this time, the solids dissolved to form a clear orange solution. In a separate flask, a solution of the unpurified cyclized product **9** (16.6 mmol, 1.00 equiv, assuming quantitative yield in the preceeding step) in ether (1.5 L) was prepared. The orange ylide solution was transferred via cannula over 10 min to the flask containing the cyclized product **9** at 24 °C. The reaction mixture was stirred for 12 h at 24 °C. The product mixture was poured into a separatory funnel that had been charged with distilled water (500 mL) and ethyl acetate (500 mL). The layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 500 mL). The organic layers were combined and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ethyl acetate–hexanes) to yield the olefination product **10** as a pale-yellow, viscous oil (4.74 g, 71% from **7**, 5:1 mixture of *E*:*Z* diastereomers).

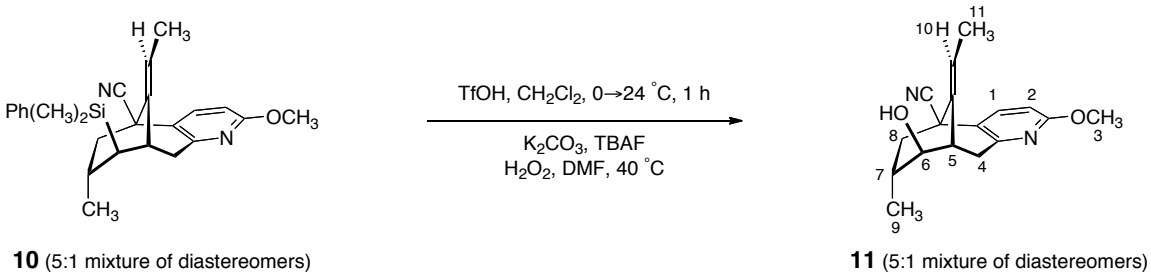
R_f = 0.20 (5% ethyl acetate–hexanes, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$, 5:1 mixture of diastereomers): *E*-olefin (major diastereomer), δ 7.69 (d, 1H, J = 8.4 Hz, H_1), 7.54–7.48 (m, 2H, H_{11}), 7.39–7.34 (m, 3H, H_{11}), 6.64 (d, 1H, J = 8.8 Hz, H_2), 5.95 (q, 1H, J = 6.8 Hz, H_{12}), 3.90 (s, 3H, H_3), 3.37–3.34 (m, 1H, H_5), 2.86 (dd, 1H, J = 17.6, 4.8 Hz, H_4), 2.60–2.55 (m, 1H, H_4), 2.50 (dd, 1H, J = 12.4, 6.0 Hz, H_8), 1.79–1.68 (m, 2H, H_7/H_8), 1.72 (d, 3H, J = 6.8 Hz, H_{13}), 0.77 (dd, 1H, J = 8.8, 5.6 Hz, H_6), 0.63 (d, 3H, J = 6.8 Hz, H_9), 0.37 (s, 3H, H_{10}), 0.36 (s, 3H, H_{10}); *Z*-olefin (minor diastereomer), δ 7.78 (d, 1H, J = 8.8 Hz, H_1), 7.54–7.48 (m, 2H, H_{11}), 7.39–7.34 (m, 3H, H_{11}), 6.67 (d, 1H, J = 8.8 Hz, H_2), 5.60 (q, 1H, J = 7.6 Hz, H_{12}), 3.91 (s, 3H, H_3), 2.94 (dd, 1H, J = 17.6, 4.8 Hz, H_4), 2.75–2.70 (m, 1H, H_5), 2.62–2.46 (m, 2H, H_4/H_8), 2.02 (d, 3H, J = 8 Hz, H_{13}), 1.79–1.68 (m, 2H, H_7/H_8), 0.67−0.60 (m, 1H, H_6), 0.62 (d, 3H, J = 6 Hz, H_9), 0.36 (s, 3H, H_{10}), 0.33 (s, 3H, H_{10}). ^{13}C NMR (100 MHz, $CDCl_3$, 5:1 mixture of diastereomers): *E*-olefin (major diastereomer), δ 163.3 (C), 151.9 (C), 138.3 (C), 137.9 (CH), 134.2 (C), 134.0 (CH), 129.4 (CH), 128.1 (CH), 127.4 (C), 122.7 (C), 118.2 (CH), 109.5 (CH), 53.7 (CH_3), 50.4 (CH_2), 44.4 (C), 42.2 (CH_2), 34.7 (CH), 30.7 (C), 27.7 (CH), 22.3 (CH_3), 12.7 (CH_3), −2.9 (CH_3), −3.3 (CH_3); *Z*-olefin (minor diastereomer), δ 163.3 (C), 152.3 (C), 138.4 (C), 138.0 (CH), 134.0 (CH), 132.7 (C), 129.3 (CH), 128.0 (CH), 127.2 (C), 124.6 (C), 120.6 (CH), 109.6 (CH), 53.8 (CH_3), 51.1 (CH_2), 43.3 (CH_2), 41.9 (CH), 39.7 (C), 34.7 (CH), 27.9 (CH), 22.0 (CH_3), 12.8 (CH_3), −3.0 (CH_3), −3.5 (CH_3). IR (ATR-FTIR), cm^{-1}: 2952 (br), 1598 (m), 1578 (w), 1476 (s), 1426 (m), 1320 (m), 1264 (m), 1112 (w),

1031 (w), 824 (m), 733 (w), 702 (w). HRMS-CI(m/z): $[M + H]^+$ calcd for $C_{25}H_{31}N_2OSi$, 403.2201; found, 403.2198.

The minor diastereomer was shown to be of the *Z*-configuration by NOE analysis (500 MHz, $CDCl_3$):



*Steps 3a–d: Conversion of the Olefination Product **10** to (−)-Huperzine A (**1**):*



10 (5:1 mixture of diastereomers) **11** (5:1 mixture of diastereomers)

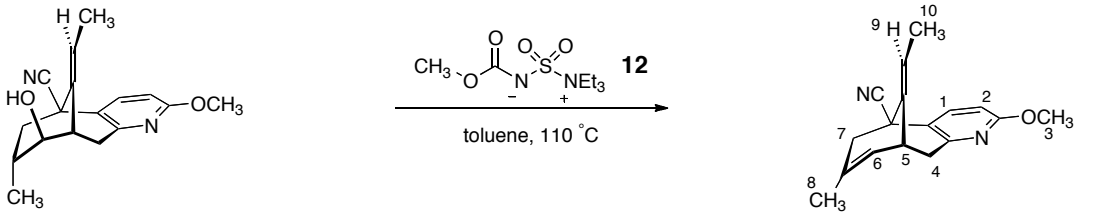
*Step 3a: Tamao-Fleming Oxidation of the Olefination Product **10** (Alcohol **11**):*

Trifluoromethanesulfonic acid (2.29 mL, 26.0 mmol, 2.20 equiv) was added dropwise via syringe over 5 min to a stirred solution of the olefination product **10** (4.74 g, 11.8 mmol, 1.00 equiv) in dichloromethane (59 mL) at 0 °C. The reaction mixture was allowed to warm over 10 min to 24 °C. The reaction mixture was stirred for 1 h at 24 °C. The solvent was evaporated under reduced pressure. The residue obtained was dissolved in *N,N*-dimethylformamide (94 mL). Potassium carbonate (4.89 g, 35.4 mmol, 3.00 equiv) and distilled water (47 mL) were then added in sequence. The resulting milky solution was stirred for 15 min at 24 °C. A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.0 M, 177 mL, 177 mmol, 15.0 equiv) was added, and the resulting mixture was stirred for 1 h at 24 °C. A solution of hydrogen peroxide in water (35%, 30.4 mL, 354 mmol, 30.0 equiv) was then added rapidly and the resulting mixture was warmed to 40 °C. The reaction mixture was stirred and heated for 12 h at 40 °C. The product mixture was cooled over 10 min to 24 °C. The cooled product mixture was transferred to a separatory funnel that had been charged with distilled water (300 mL) and 50% ethyl acetate–hexanes (v/v, 500 mL). The layers that formed were separated. The organic layer was washed sequentially with water (5 × 300 mL) and saturated aqueous sodium chloride solution (2 × 300 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford the unpurified alcohol **11** as a pale-yellow solid (3.35 g). ^{1}H NMR analysis (400 MHz, $CDCl_3$) indicated >95% conversion to the alcohol **11**. The product so obtained was used directly in the following step.

An analytically pure sample of the alcohol **11** was obtained by flash-column chromatography (eluting with 50% ethyl acetate–hexanes):

R_f = 0.30 (50% ethyl acetate–hexanes, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$, 5:1 mixture of diastereomers): *E*-olefin (major diastereomer), δ 7.69 (d, 1H, J = 8.5 Hz, H_1), 6.64 (d, 1H, J = 8.5 Hz, H_2), 6.12 (q, 1H, J = 6.5 Hz, H_{10}), 3.89 (s, 3H, H_3), 3.54 (dd, 1H, J = 6.0, 3.5 Hz, H_6), 3.29–3.27 (m, 1H, H_5), 3.10 (dd, 1H, J = 18.5, 6.5 Hz, H_4), 2.99 (d, 1H, J = 17.5 Hz, H_4), 2.59 (dd, 1H, J = 13.5, 7.0 Hz, H_8), 1.79 (d, 3H, J = 7.0 Hz, H_{11}), 1.87–1.76 (m, 2H, H_7/H_8), 0.71 (d, 3H, J = 7.5 Hz, H_9); *Z*-olefin (minor diastereomer), δ 7.78 (d, 1H, J = 8.5 Hz, H_1), 6.67 (d, 1H, J = 8.5 Hz, H_2), 5.65 (q, 1H, J = 7.5 Hz, H_{10}), 3.90 (s, 3H, H_3), 3.43 (dd, 1H, J = 5.5, 3.5 Hz, H_6), 3.17 (dd, 1H, J = 18.0, 7.0 Hz, H_4), 2.94 (d, 1H, J =

18.0 Hz, H_4), 2.70 (dd, 1H, J = 13.5, 7.5 Hz, H_8), 2.62– 2.60 (m, 1H, H_5), 2.07 (d, 3H, J = 7.0 Hz, H_{11}),1.87–1.76 (m, 2H, H_7/H_8), 0.68 (d, 3H, J = 7.5 Hz, H_9). ^{13}C NMR (125 MHz, $CDCl_3$, 5:1 mixture of diastereomers): *E*-olefin (major diastereomer), δ 163.5 (C), 152.3 (C), 137.7 (CH), 131.5 (C), 126.4 (C), 122.0 (C), 120.4 (CH), 109.7 (CH), 78.4 (CH), 53.8 (CH_3), 44.7 (CH_2), 44.5 (C), 39.1 (CH), 37.9 (CH_2), 34.2 (CH), 17.9 (CH_3), 12.8 (CH_3); *Z*-olefin (minor diastereomer), δ 163.5 (C),152.6 (C),137.5 (CH), 129.8 (C), 126.0 (C), 122.8 (CH), 122.0 (C), 109.7 (CH), 77.9 (CH), 53.8 (CH_3), 49.3 (CH), 45.5 (CH_2), 44.5 (C), 37.9 (CH_2), 34.2(CH), 17.9 (CH_3), 12.8 (CH_3). IR (ATR-FTIR), cm^{-1}: 3431 (br), 2925 (br), 1598 (m), 1577 (w), 1476 (s), 1422 (m), 1323 (m), 1267 (m), 1033 (m), 828 (w), 658 (w). HRMS-CI(m/z): $[M + H]^+$ calcd for $C_{17}H_{21}N_2O_2$, 285.1598; found, 285.1597.



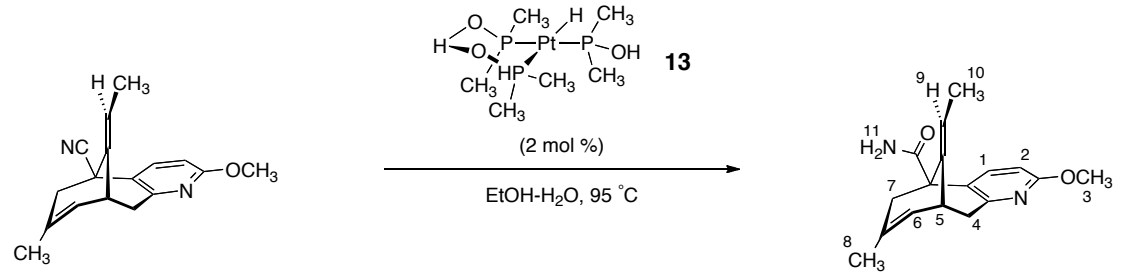
11 (5:1 mixture of diastereomers) **16** (5:1 mixture of diastereomers)

*Step 3b: Dehydration of the Tamao-Fleming Oxidation Product **11** (Alkene **16**):*

A 100-mL round-bottomed flask fused to a Teflon-coated valve was charged sequentially with the unpurified Tamao-Fleming oxidation product **11** (11.8 mmol, 1.00 equiv, assuming quantitative yield in the preceeding step) and methyl *N*-(triethylammoniumsulfonyl)carbamate **12** (3.09 g, 13.0 mmol, 1.10 equiv). Benzene (10 mL) was added and the resulting solution was stirred for 15 min at 24 °C. The solution was concentrated to dryness and the residue obtained was redissolved in toluene (59 mL). The reaction vessel was sealed and the sealed vessel was placed in an oil bath that had been preheated to 110 °C. The reaction mixture was stirred and heated for 12 h at 110 °C. The product mixture was cooled over 30 min to 24 °C. The cooled product mixture was diluted with ethyl acetate (200 mL) and the diluted solution was transferred to a separatory funnel that had been charged with saturated aqueous sodium bicarbonate solution (200 mL). The layers that formed were separated. The aqueous layer was extracted with ethyl acetate (200 mL). The organic layers were combined and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford the alkene **16** as an off-white solid (3.19 g). ^{1}H NMR analysis (400 MHz, $CDCl_3$) indicated >95% conversion to the alkene **16**. The product so obtained was used directly in the following step.

An analytically pure sample of the alkene **16** was obtained by flash-column chromatography (eluting with 10% ethyl acetate–hexanes):

R_f = 0.32 (10% ethyl acetate–hexanes, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$, 5:1 mixture of diastereomers): *E*-olefin (major diastereomer), δ 7.70 (d, 1H, J = 8.8 Hz, H_1), 6.63 (d, 1H, J = 8.8 Hz, H_2), 5.95 (q, 1H, J = 6.8 Hz, H_9), 5.48 (m, 1H, H_6), 3.89 (s, 3H, H_3), 3.62 (m, 1H, H_5), 2.98 (dd, 1H, J = 17.2, 5.2 Hz, H_4), 2.88–2.80 (m, 2H, H_4/H_7), 2.38 (d, 1H, J = 16.8 Hz, H_7), 1.76 (d, 3H, J = 6.8 Hz, H_{10}), 1.55 (s, 3H, H_8); *Z*-olefin (minor diastereomer), δ 7.78 (d, 1H, J = 8.4 Hz, H_1), 6.66 (d, 1H, J = 8.4 Hz, H_2), 5.65 (q, 1H, J = 7.2 Hz, H_9), 5.46 (d, 1H, J = 4.8 Hz, H_6), 3.89 (s, 3H, H_3), 3.10–2.77 (m, 4H, 2 × H_4/H_5/H_7), 2.38 (d, 1H, J = 16.8 Hz, H_7), 2.06 (d, 3H, J = 7.6 Hz, H_{10}), 1.54 (s, 3H, H_8). ^{13}C NMR (100 MHz, $CDCl_3$, 5:1 mixture of diastereomer): *E*-olefin (major diastereomer), δ 163.5 (C), 152.9 (C), 137.7 (CH), 132.3 (C), 130.7 (C), 125.2(CH), 124.8 (C), 121.7 (C), 116.7 (CH), 109.2 (CH), 53.7 (CH_3), 47.5 (CH_2), 44.6 (C), 39.8 (CH_2), 31.6 (CH), 22.6 (CH_3), 12.7 (CH_3); *Z*-olefin (minor diastereomer), δ 163.5 (C), 153.2 (C), 137.7 (CH), 130.9 (C), 130.2 (C), 126.3 (CH), 124.6 (C), 121.7 (C), 119.0 (CH), 109.3 (CH), 53.7 (CH_3), 48.3 (CH_2), 42.1 (CH), 40.7 (CH_2), 40.1 (C), 22.5 (CH_3), 12.3 (CH_3). IR (ATR-FTIR), cm^{-1}: 2934 (br), 1598 (m), 1576 (w), 1476 (s), 1421 (m), 1323 (m), 1268 (m), 1028 (w), 826 (w). HRMS-CI(m/z): $[M + H]^+$ calcd for $C_{17}H_{19}N_2O$, 267.1492; found, 267.1492.



16 (5:1 mixture of diastereomers)

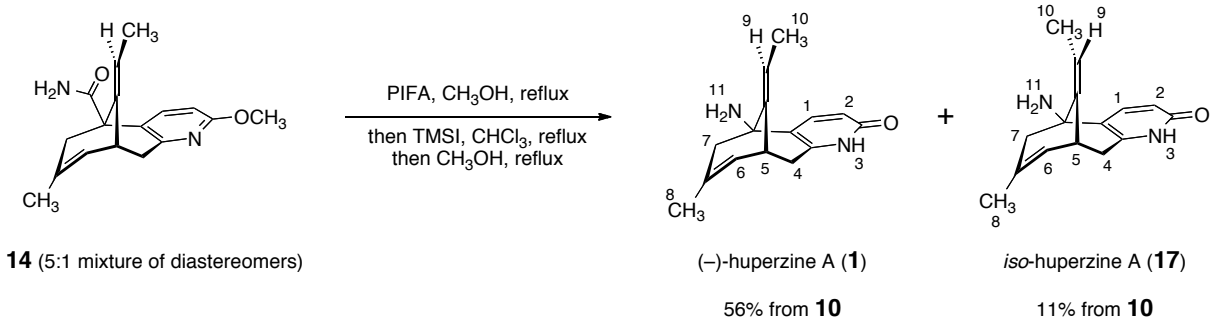
14 (5:1 mixture of diastereomers)

*Step 3c: Hydrolysis of the Nitrile **16** (Amide **14**):*

Hydrido(hydroxydimethylphosphino)[hydrogen bis(hydroxydimethylphosphino)]platinum (II) (**13**, 101 mg, 240 μmol, 0.02 equiv) was added to a solution of the unpurified nitrile **16** (11.8 mmol, 1.00 equiv, assuming quantitative yield in the preceeding step) in ethanol (6.6 mL) and water (3.3 mL) at 24 °C. The resulting mixture was placed in an oil bath that had been preheated to 95 °C. The reaction mixture was stirred and heated for 24 h at 95 °C. The product mixture was cooled over 10 min to 24 °C. The cooled mixture was concentrated to dryness. The residue obtained was dissolved in dichloromethane (15 mL) and chloroform (15 mL), and the resulting solution was filtered through a pad of sodium sulfate. The filtrate was concentrated to afford the amide **14** as an off-white solid (3.60 g). ^{1}H NMR analysis (400 MHz, $CDCl_3$) indicated >95% conversion to the amide **14**. The product so obtained was used directly in the following step.

An analytically pure sample of the amide **14** was obtained by flash-column chromatography (eluting with 50% ethyl acetate–hexanes):

R_f = 0.20 (50% ethyl acetate–hexanes, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$, 5:1 mixture of diastereomers): *E*-olefin (major diastereomer), δ 7.33 (d, 1H, J = 8.5 Hz, H_1), 6.57 (d, 1H, J = 8.5 Hz, H_2), 5.62 (br s, 1H, H_{11}), 5.40 (q, 1H, J = 7.0 Hz, H_9), 5.38–5.35 (m, 1H, H_6), 5.17 (br s, 1H, H_{11}), 3.90 (s, 3H, H_3), 3.60 (m, 1H, H_5), 3.09–3.01 (m, 2H, H_4/H_7), 2.88 (d, 1H, J = 16.5 Hz, H_4), 2.11 (d, 1H, J = 17.5 Hz, H_7), 1.70 (d, 3H, J = 7.0 Hz, H_{10}), 1.53 (s, 3H, H_8); *Z*-olefin (minor diastereomer), δ 7.37 (d, 1H, J = 8.4 Hz, H_1), 6.58 (d, 1H, J = 8.4 Hz, H_2), 5.58 (br s, 1H, H_{11}), 5.54 (q, 1H, J = 16.5 Hz, H_9), 5.38–5.35 (m, 1H, H_6), 5.30 (br s, 1H, H_{11}), 3.90 (s, 3H, H_3), 3.15–3.01 (m, 3H, H_4/H_5/H_7), 2.83 (d, 1H, J = 16.5 Hz, H_4), 2.18 (d, 1H, J = 17.0 Hz, H_7), 1.73 (d, 3H, J = 7.5 Hz, H_{10}), 1.53 (s, 3H, H_8); ^{13}C NMR (125 MHz, $CDCl_3$, 5:1 mixture of diastereomer): *E*-olefin (major diastereomer), δ 176.9 (C), 162.9 (C), 153.8 (C), 138.9 (CH), 138.1 (C), 133.7 (C), 128.5 (C), 124.1 (CH), 115.3 (CH), 108.9 (CH), 54.4 (C), 53.7 (CH_3), 45.3 (CH_2), 39.8 (CH_2), 33.0 (CH), 23.0 (CH_3), 13.0 (CH_3); *Z*-olefin (minor diastereomer), δ 178.4 (C), 162.9 (C), 153.1 (C), 138.5 (CH), 137.1 (C), 133.6 (C), 128.3 (C), 125.9 (CH), 117.5 (CH), 109.2 (CH), 53.7 (CH_3), 51.2 (C), 45.1 (CH_2), 44.2(CH), 39.7 (CH_2), 23.0 (CH_3), 13.0 (CH_3). IR (ATR-FTIR), cm^{-1}: HRMS-CI(m/z): 3346 (br), 2926 (br), 1710 (w), 1664 (s), 1597 (m), 1576 (w), 1475 (s), 1422 (m), 1322 (m), 1267 (w), 1028 (m), 824 (w). $[M + H]^+$ calcd for $C_{17}H_{21}N_2O_2$, 285.1598; found, 285.1601.



*Step 3d: Converstion of the Amide **14** to (−)-Huperzine A (**1**):*

[Bis(trifluoroacetoxy)iodo]benzene (5.58 g, 13.0 mmol, 1.10 equiv) was added to a stirred solution of the unpurified amide **14** (11.8 mmol, 1.00 equiv, assuming quantitative yield in the preceeding step) in methanol (240 mL). The resulting mixture was heated to reflux (bath temperature = 65 °C). The reaction mixture was stirred and heated for 2 h at 65 °C. The product mixture was cooled over 30 min to 24 °C. The cooled mixture was concentrated to dryness. The residue obtained was dissolved in chloroform (120 mL). Iodotrimethylsilane (8.40 mL, 59.0 mmol, 5.00 equiv) was added, and the reaction mixture was heated to reflux (bath temperature = 61 °C). The reaction mixture was stirred and heated for 3 h at 61 °C. The mixture was then cooled over 30 min to 24 °C. Methanol (120 mL) was added and the resulting mixture was heated to reflux (bath temperature = 65 °C). The reaction mixture was stirred and heated for 12 h at 65 °C. The product mixture was then cooled over 30 min to 24 °C. The cooled product mixture was concentrated to dryness. The residue obtained was dissolved in 50% dichloromethane–chloroform (v/v, 200 mL). The resulting solution was transferred to a separatory funnel that had been charged with 1.0 N aqueous sulfuric acid solution (200 mL). The layers that formed were separated. The aqueous layer was then extracted with 50% dichloromethane–chloroform (v/v, 2 × 200 mL). The organic layers were combined and discarded. The aqueous layer was basified with saturated aqueous ammonium hydroxide solution (100 mL, final pH = 12–13). The basified aqueous layer was extracted with 50% dichloromethane–chloroform (v/v, 4 × 200 mL). The organic layers were combined and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% methanol−ethyl acetate) to yield (−)-huperzine A (**1**, 1.61 g, 56%, off-white solid) and the olefin isomer (*iso*-huperzine A, **17**, 310 mg, 11%, off-white solid).

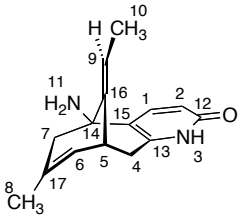
Synthetic (−)-huperzine A (**1**) was identical in all respects [^{1}H NMR, ^{13}C NMR, LC/MS retention time, IR, TLC solvent systems (10% methanol–ethyl acetate, 5% methanol–dichloromethane, 5% methanol–dichloromethane + 1% ammonium hydroxide) and optical rotation] to an authentic sample.

(−)-huperzine A (**1**): R_f = 0.15 (10% methanol–ethyl acetate, $KMnO_4$). t_R = 0.91. $[\alpha]_D^{20}$ = −144 (*c* 0.23, $CHCl_3$), lit. $[\alpha]_D^{25}$ = −150 (*c* 0.12, $CHCl_3$).[10] ^{1}H NMR (500 MHz, $CDCl_3$), δ 13.25 (br s, 1H, H_3), 7.88 (d, 1H, *J* = 9.5 Hz, H_1), 6.37 (d, 1H, *J* = 9.0 Hz, H_2), 5.46 (q, 1H, *J* = 6.5 Hz, H_9), 5.38 (d, 1H, *J* = 4.5 Hz, H_6), 3.59–3.55 (m, 1H, H_5), 2.86 (dd, 1H, *J* = 17.0, 5.0, H_4), 2.73 (dd, 1H, *J* = 16.5, 1.0 Hz, H_4), 2.12 (app s, 2H, H_7), 1.88 (br s, 2H, H_{11}), 1.64 (d, 3H, *J* = 6.5 Hz, H_{10}), 1.51 (s, 3H, H_8).^{13}C NMR (125 MHz, $CDCl_3$), δ 165.5 (C), 143.3 (C), 142.4 (C), 140.3 (CH), 134.1 (C), 124.4 (CH), 122.8 (C), 117.1

(CH), 111.4 (CH), 54.5 (C), 49.2 (CH_2), 35.4 (CH_2), 33.0 (CH), 22.7 (CH_3), 12.5 (CH_3). IR (ATR-FTIR), cm^{-1}: 3355 (br), 1644 (s), 1608 (s), 1552 (m), 1452 (m), 1121 (m), 837 (m). HRMS-CI(m/z): $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$, 243.1492; found, 243.1493.

iso-huperzine A (**17**): R_f = 0.15 (5% methanol–dichloromethane + 1% ammonium hydroxide, $KMnO_4$). $[\alpha]_D^{20} = -121$ (*c* 0.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ 13.10 (br s, 1H, H_3), 7.86 (d, 1H, *J* = 9.6 Hz, H_1), 6.42 (d, 1H, *J* = 9.6 Hz, H_2), 5.41 (q, 1H, *J* = 7.2 Hz, H_9), 5.37 (br s, 1H, H_6), 3.00–2.88 (m, 2 H, H_4/H_5), 2.70 (d, 1H, *J* = 16.0 Hz, H_4), 2.40 (d, 1H, *J* = 16.8, H_7), 2.05 (d, 1H, H_7), 1.93 (d, 3H, *J* = 7.2 Hz, H_{10}), 1.90 (br s, 2H, H_{11}), 1.53 (s, 3H, H_8). ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.5 (C), 143.4 (C), 140.2 (C), 140.0 (CH), 133.7 (C), 125.4 (CH), 123.0 (C), 117.3 (CH), 115.7 (CH), 56.6 (C), 49.8 (CH_2), 44.0 (CH), 36.4 (CH_2), 22.6 (CH_3), 14.0 (CH_3). IR (ATR-FTIR), cm^{-1}: 3380 (br), 2909 (br), 1653 (s), 1611 (m), 1551 (m), 1459 (m), 833 (m), 755 (m), 651 (m). HRMS-CI(m/z): $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$, 243.1492; found, 243.1494.

Comparison of NMR Data of Synthetic and Natural (−)-Huperzine A (**1**)

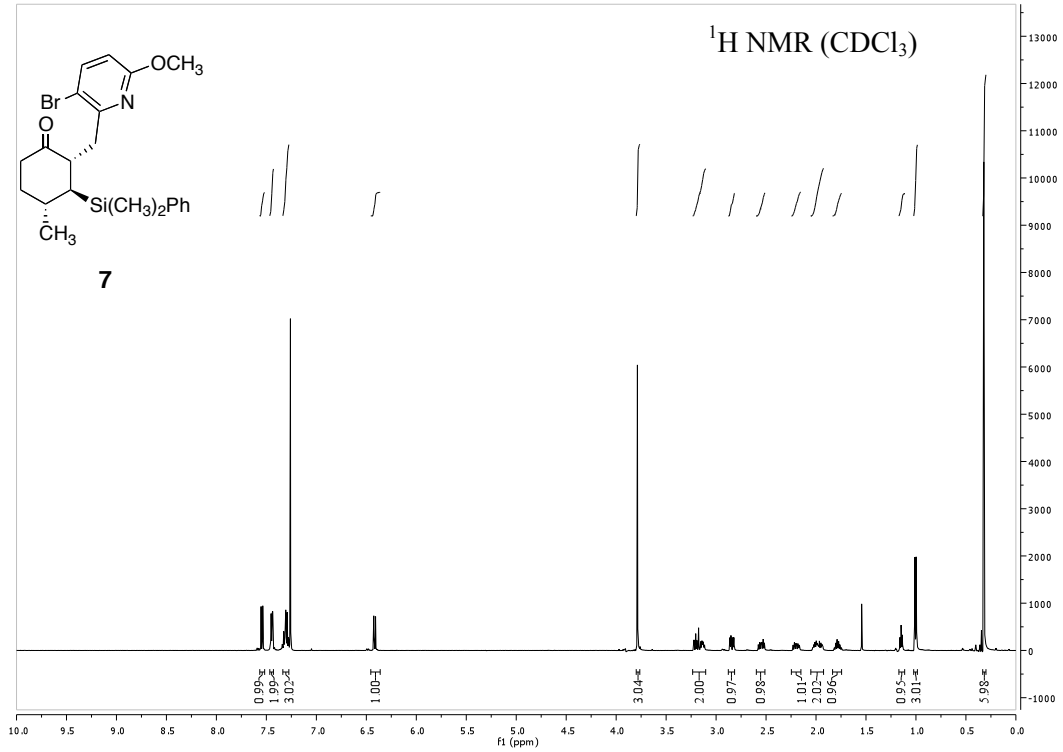


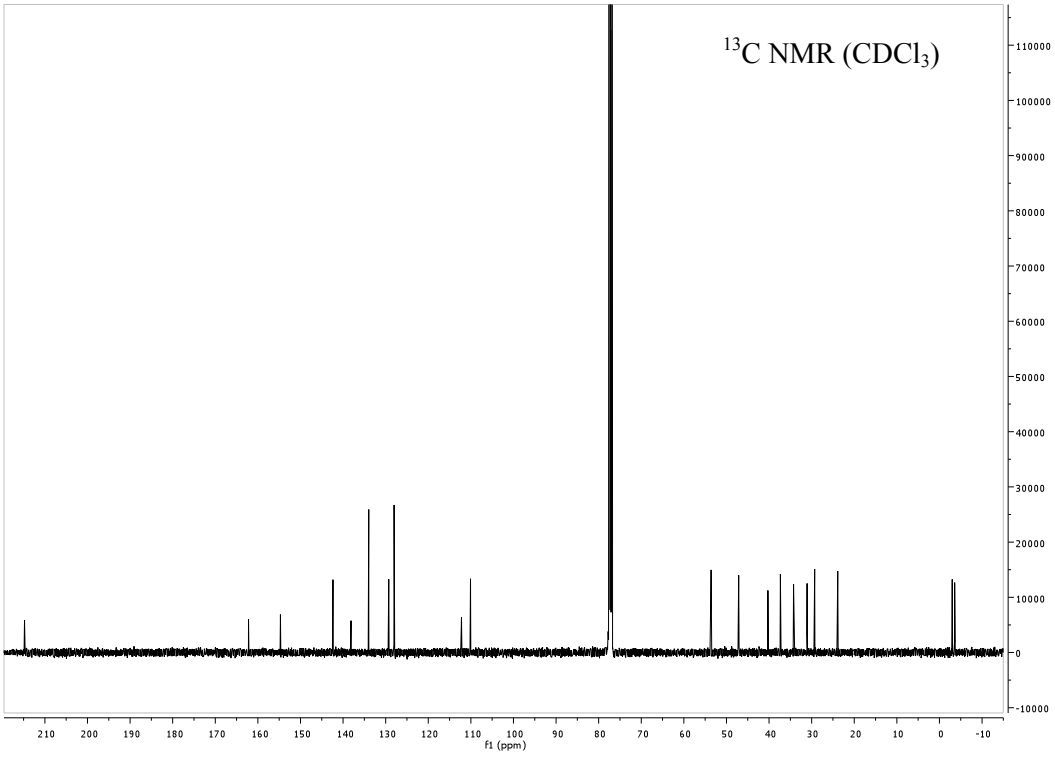
(–)-huperzine A (**1**)

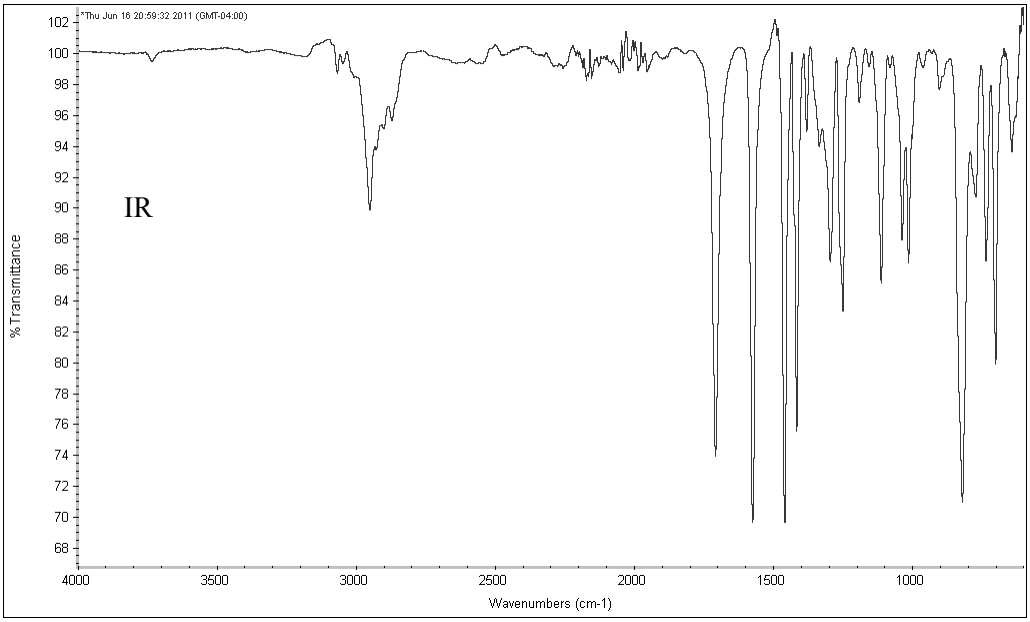
Position	^{1}H NMR Synthetic **1** ($CDCl_3$)	^{1}H NMR Natural **1** ($CDCl_3$)	^{13}C NMR Synthetic **1** ($CDCl_3$)	^{13}C NMR Natural **1** ($CDCl_3$)
1	7.88 (d, *J* = 9.5 Hz)	7.84 (d, *J* = 9.0 Hz)	140.3	140.3
2	6.37 (d, J = 9.0 Hz)	6.38 (d, *J* = 9.0 Hz)	117.1	117.0
3	13.25 (br s)	13.20 (br s)		
4	2.86 (dd, J = 17.0, 5.0 Hz)	2.76	35.4	35.2
4	2.73 (dd, J = 16.5, 1.0 Hz)	2.76	35.4	35.2
5	3.59–3.55 (m)	3.56 (m)	33.0	33.0
6	5.38 (d, *J* = 4.5 Hz)	5.38 (d, *J* = 5.0 Hz)	124.4	124.4
7	2.12 (br s)	2.12 (s)	49.2	49.3
8	1.51 (s)	1.46 (s)	22.7	22.6
9	5.46 (q, *J* = 6.5 Hz)	5.46 (q, *J* = 6.0 Hz)	111.4	111.2
10	1.64 (d, *J* = 6.5 Hz)	1.62 (d, *J* = 7.0 Hz)	12.5	12.3
11	1.88 (br s)	not reported		
12			165.5	165.5
13			142.4	142.6
14			54.5	54.4
15			122.8	123.0
16			143.3	143.3
17			134.4	134.1

Data for natural (−)-huperzine A (**1**) were obtained from the following reference: Liu, J.-S.; Zhu, Y.-L.; Yu, C.-M.; Zhou, Y.-Z.; Han, Y.-T.; Wu, F.-W.; Qi, B.-F. *Can J. Chem.* **1986**, *64*, 837.

Catalog of Nuclear Magnetic Resonance and Infrared Spectra.



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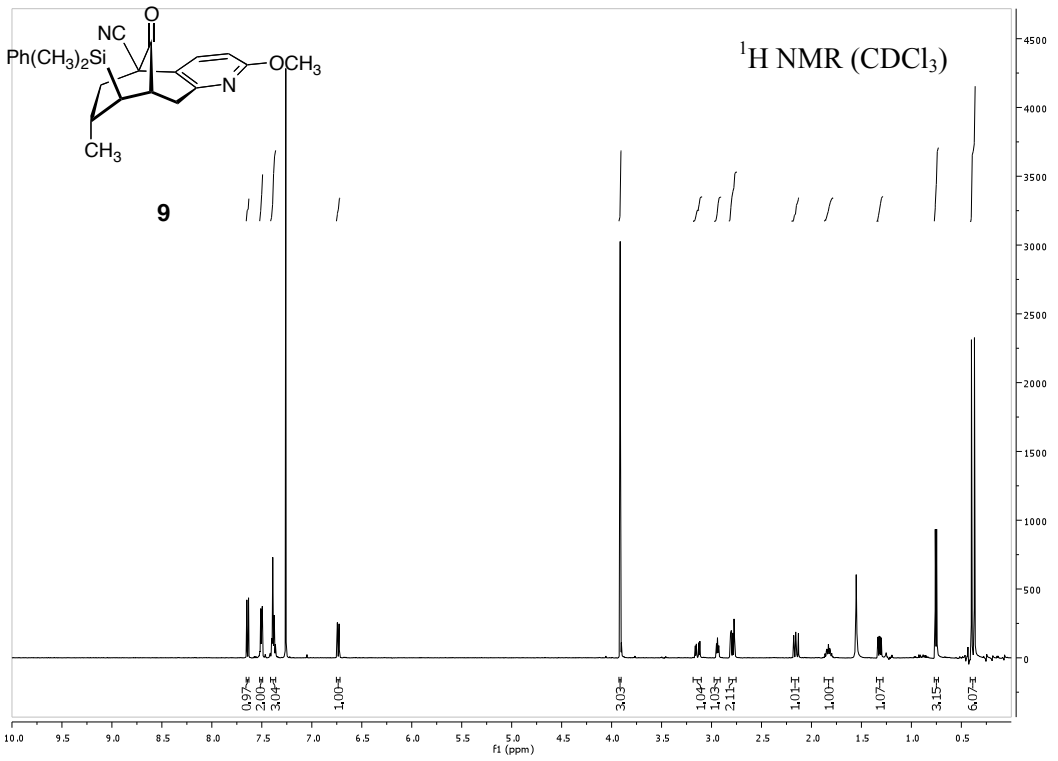
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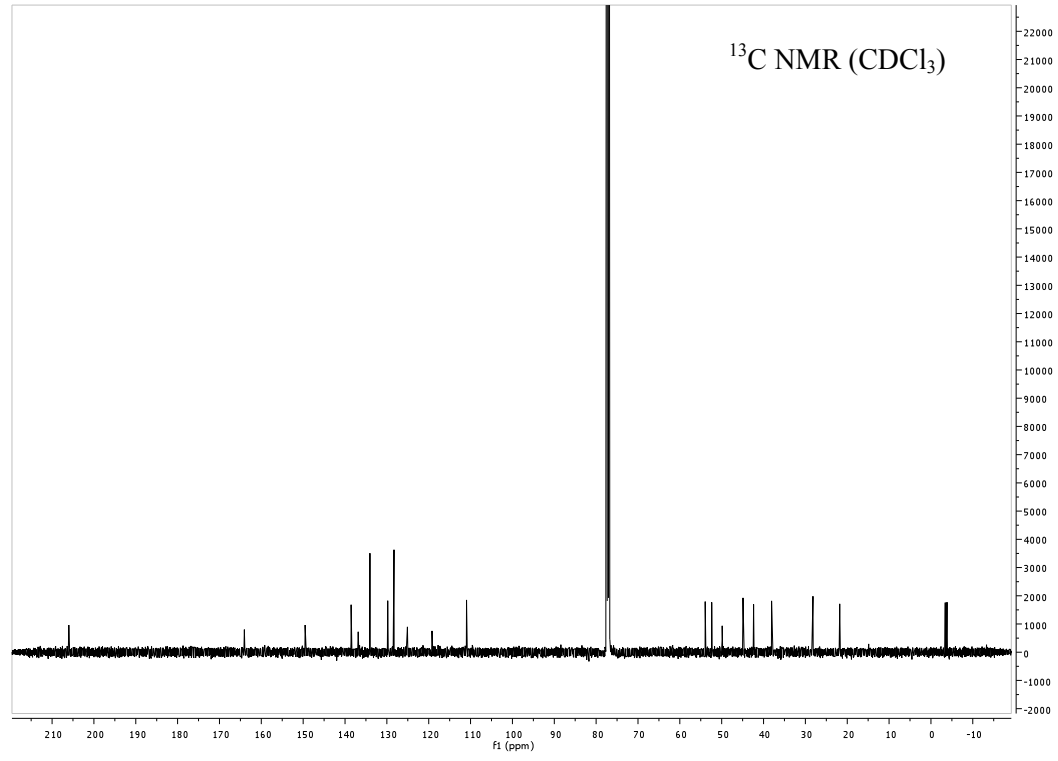
f1 (ppm)


13C NMR (CDCl3)
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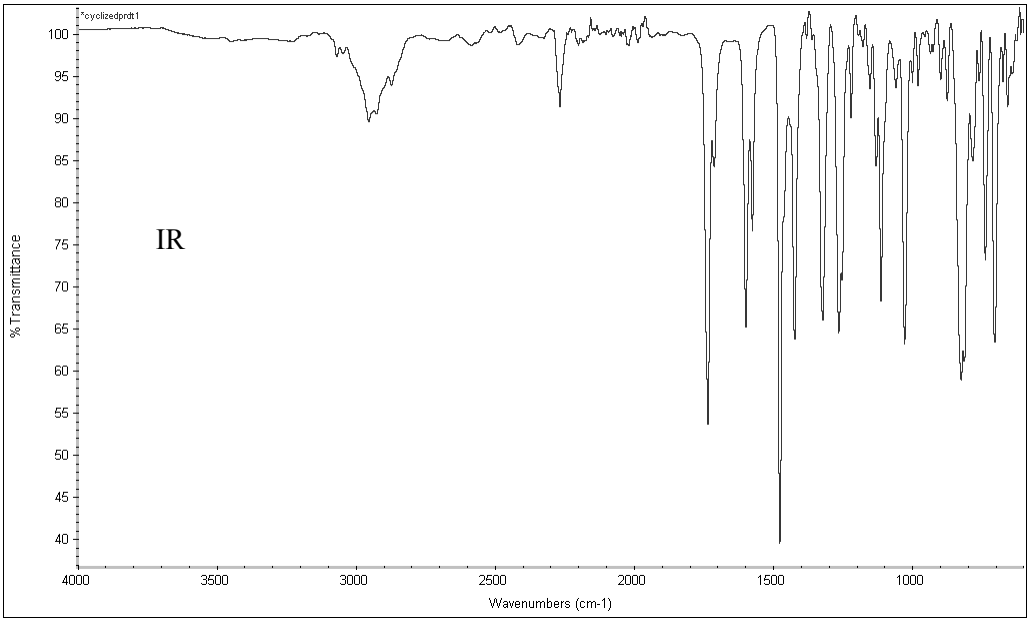
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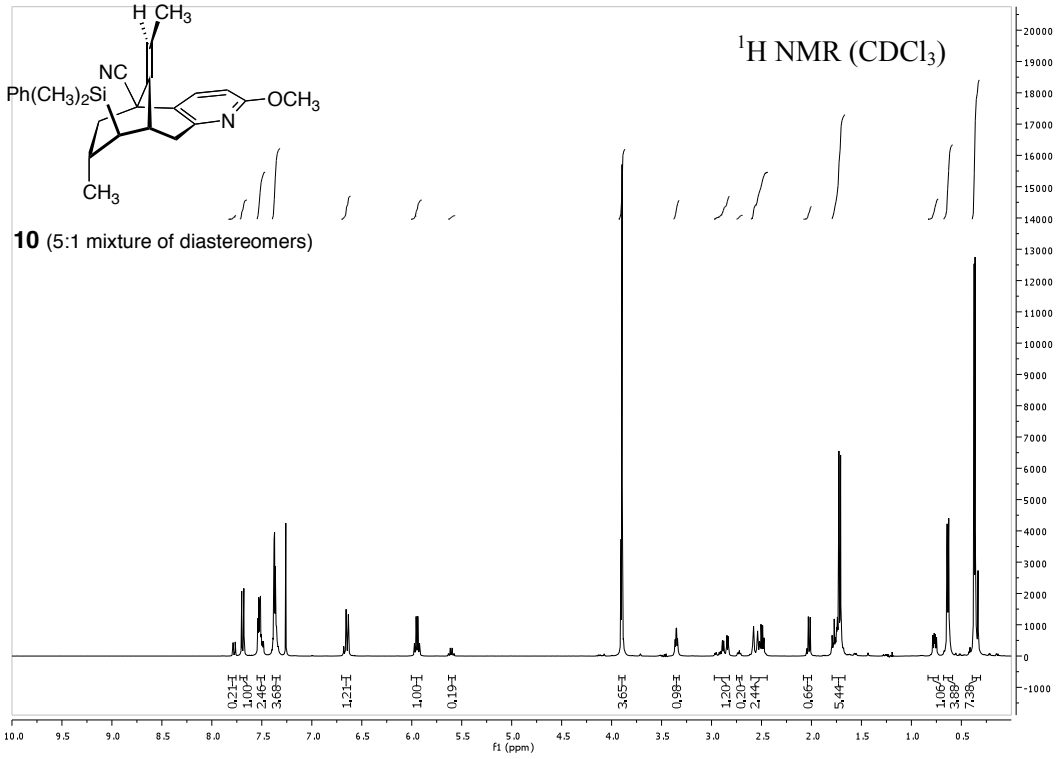
Wavenumbers (cm-1)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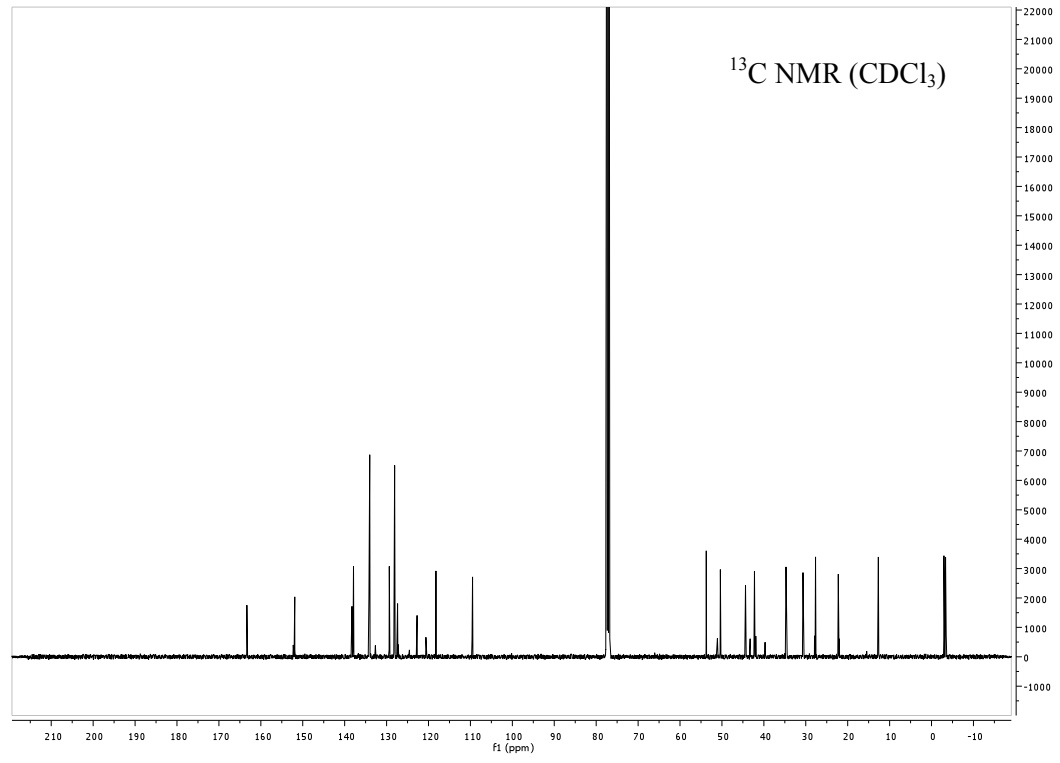
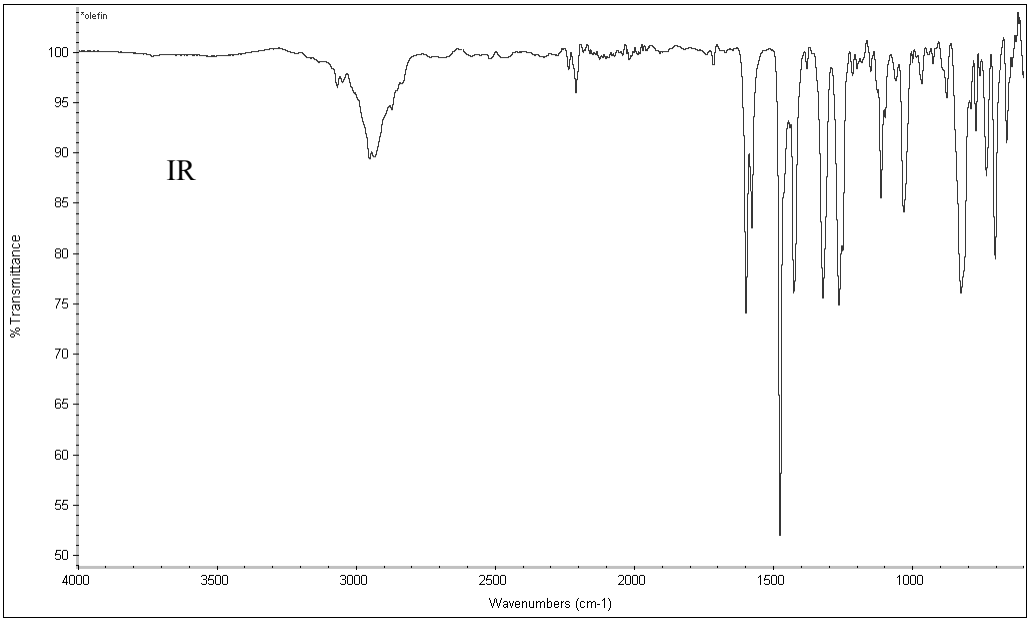
1H NMR (CDCl3)
f1 (ppm)


13C NMR (CDCl3)
f1 (ppm)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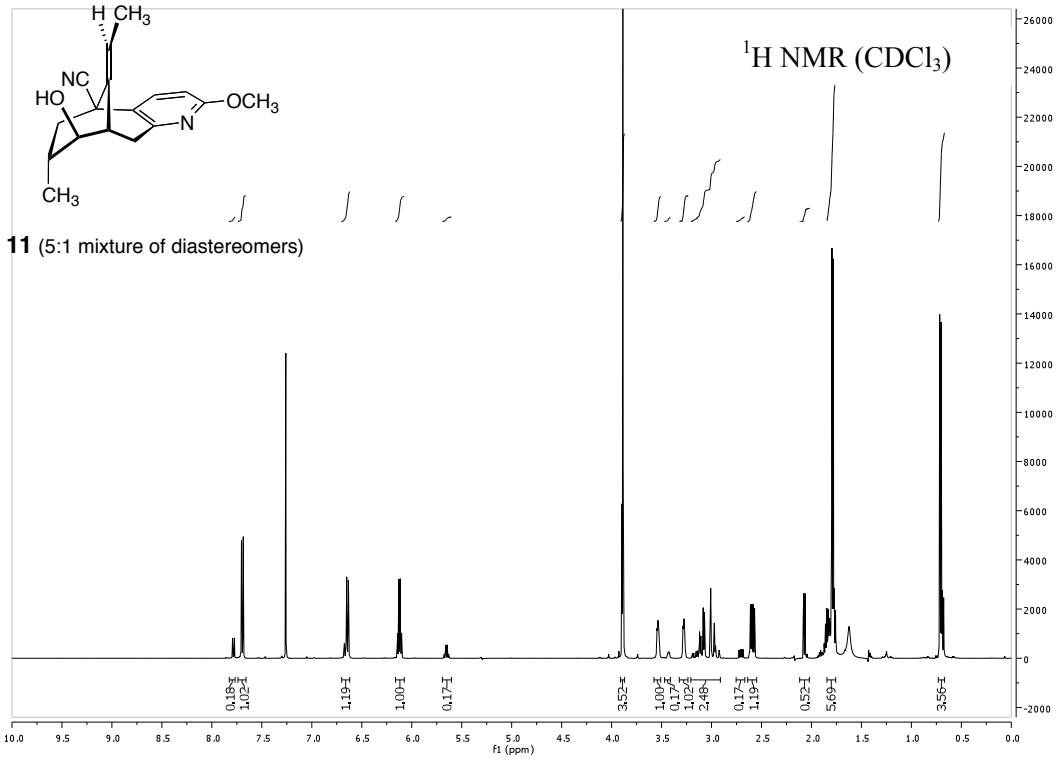
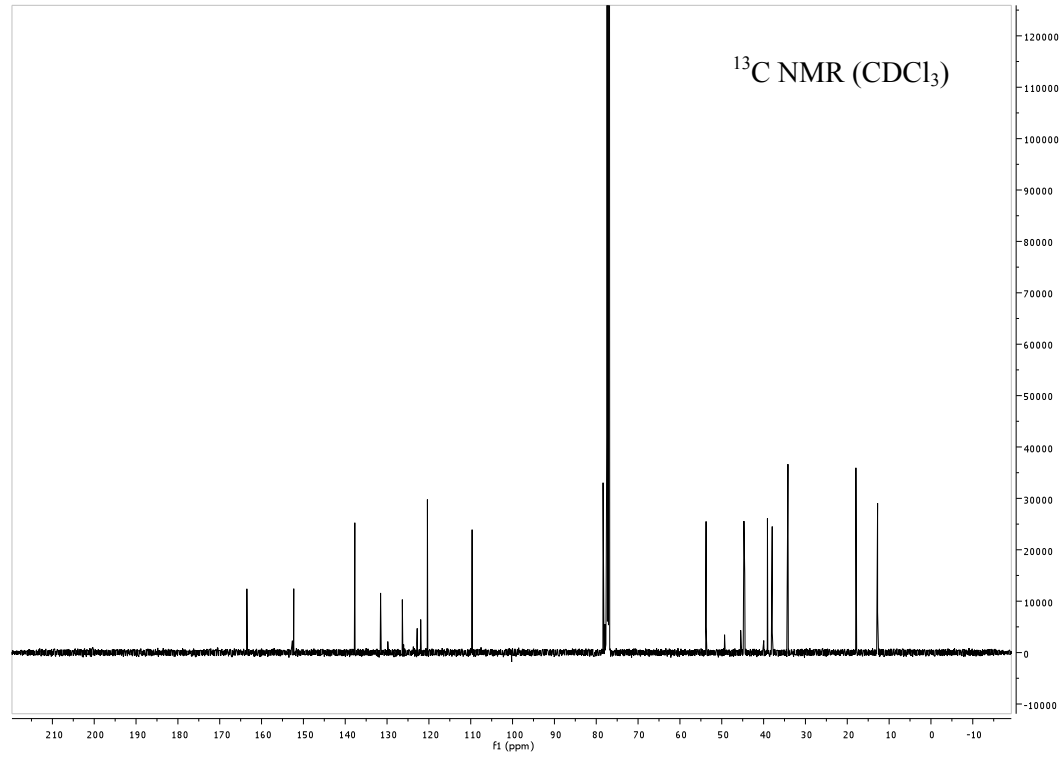
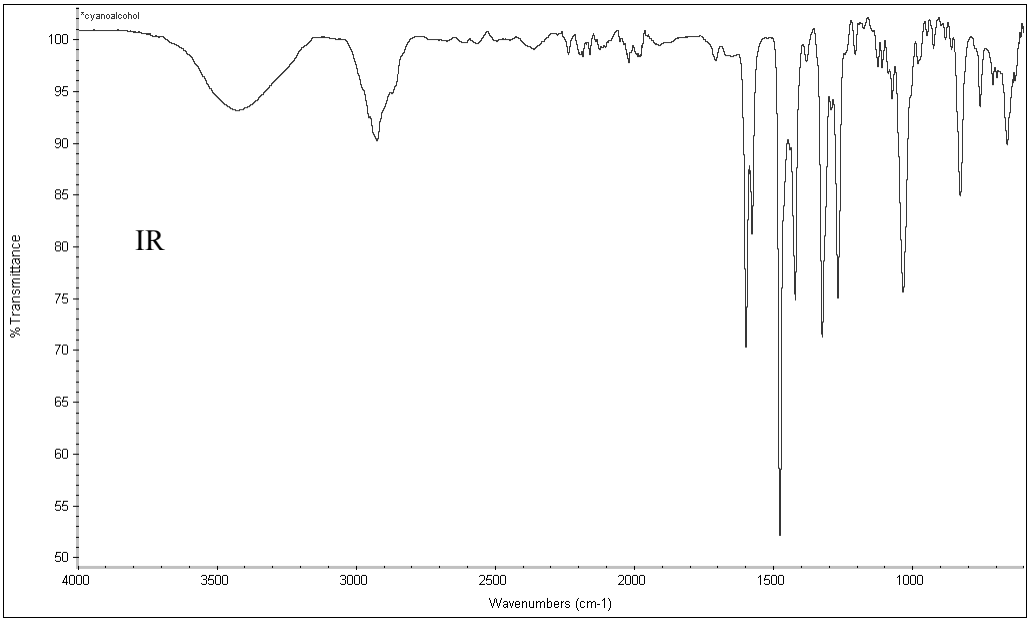
1000
Wavenumbers (cm-1)



11 (5:1 mixture of diastereomers)

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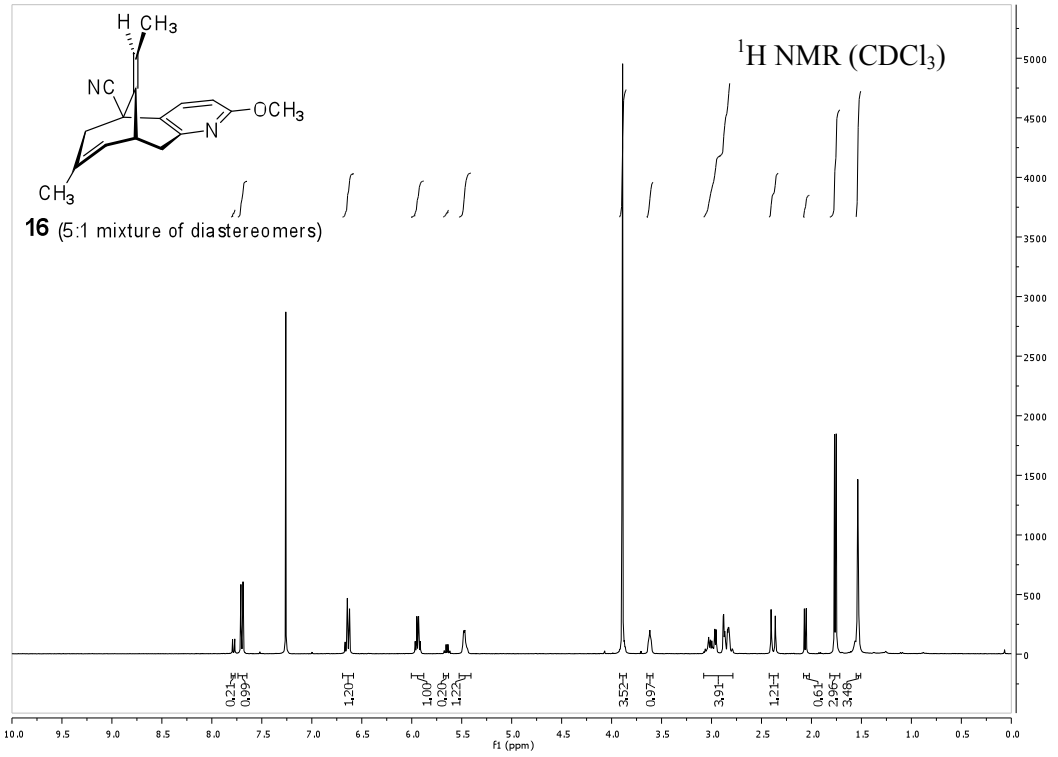
Wavenumbers (cm-1)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OCH3
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CH3
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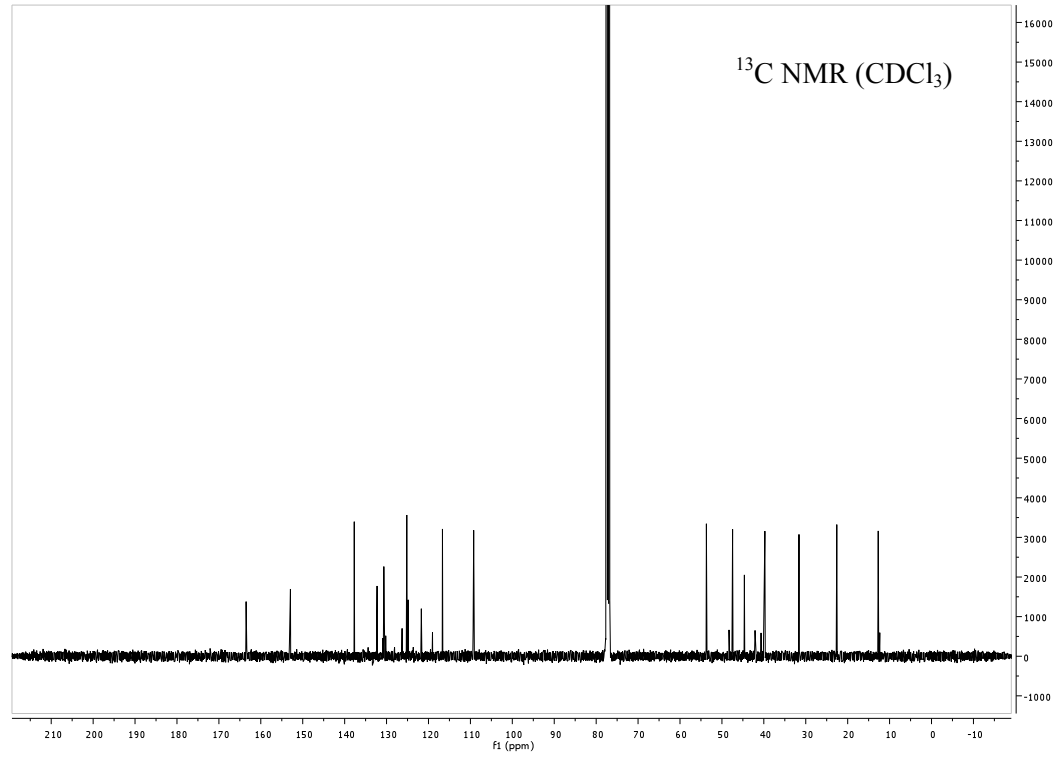
f1 (ppm)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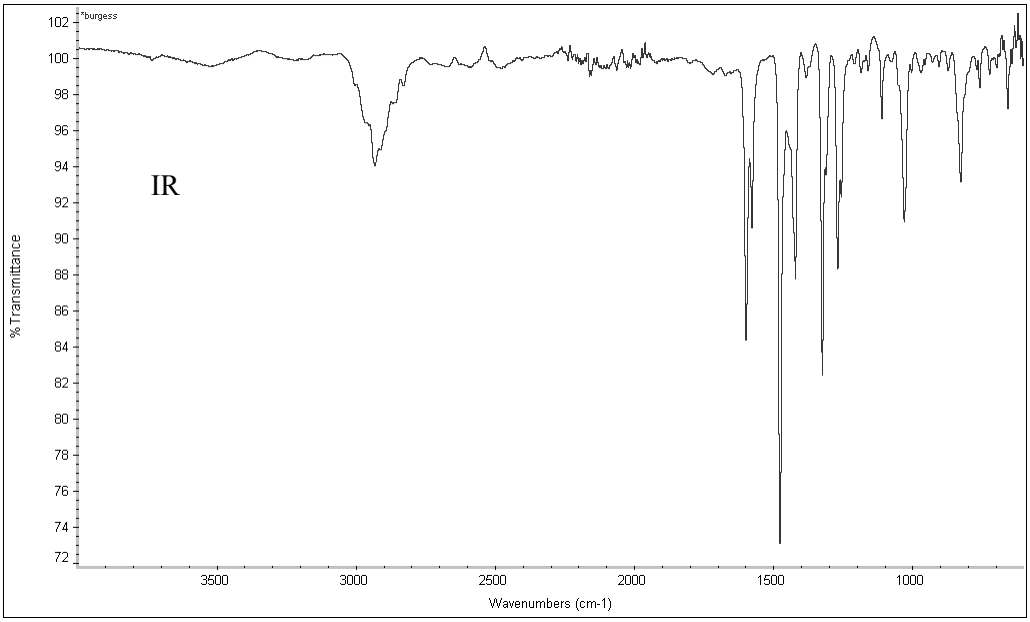
f1 (ppm)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IR
%Transmittance
Wavenumbers (cm-1)
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100
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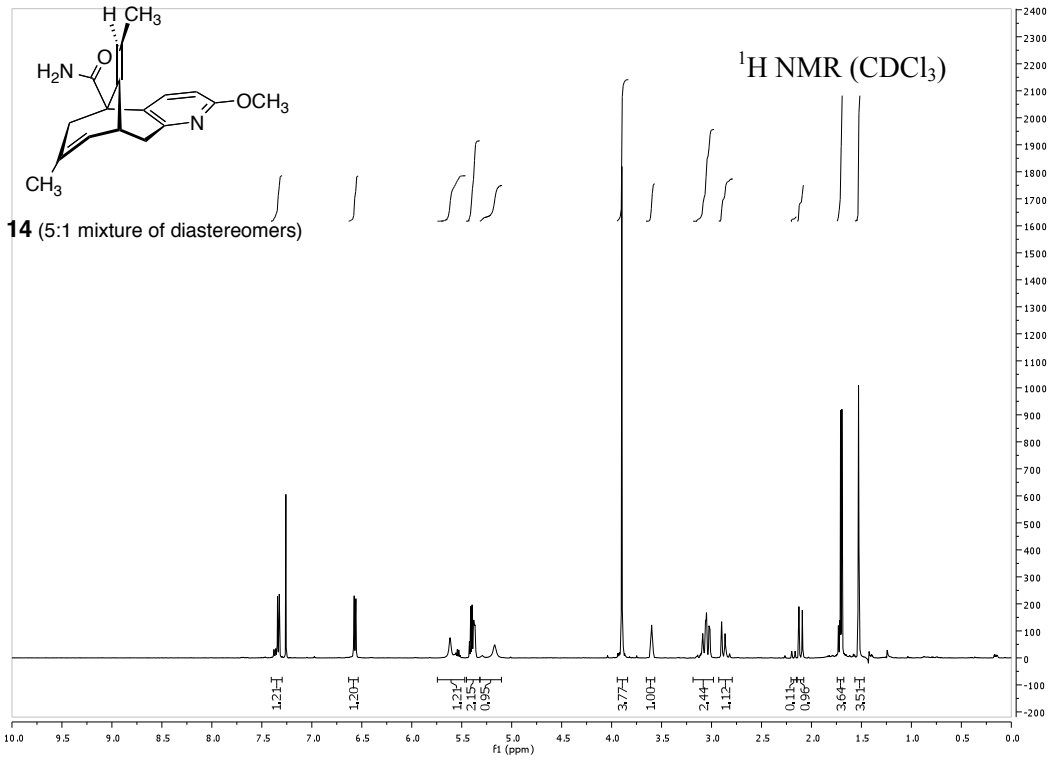
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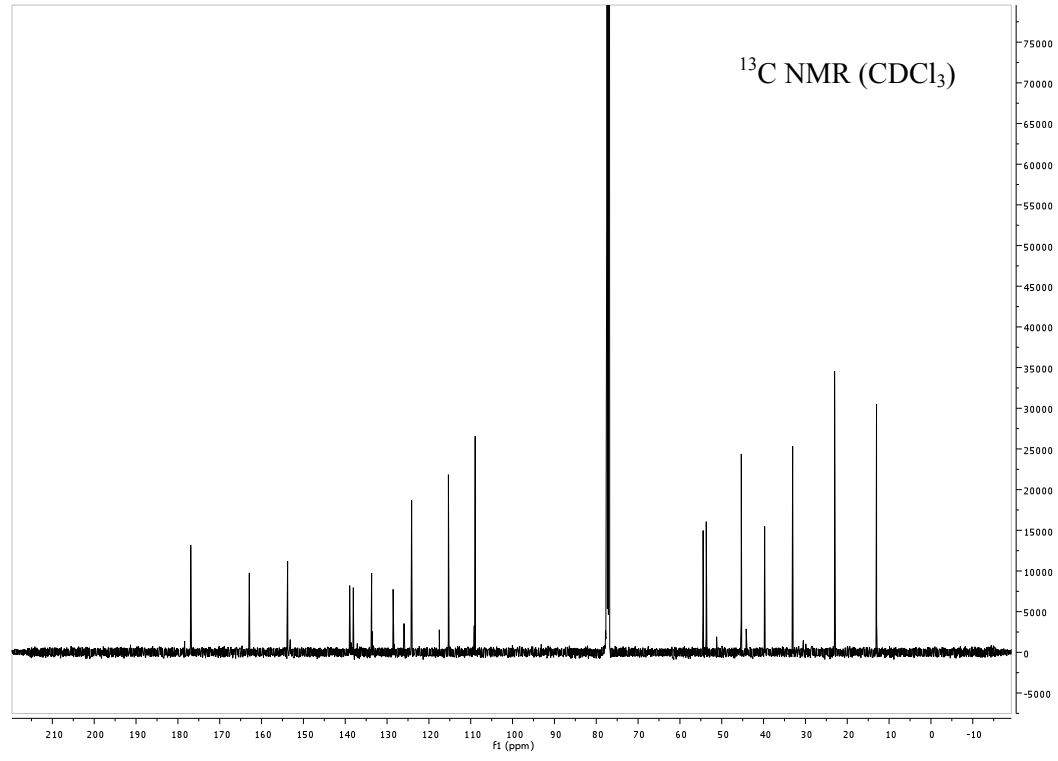
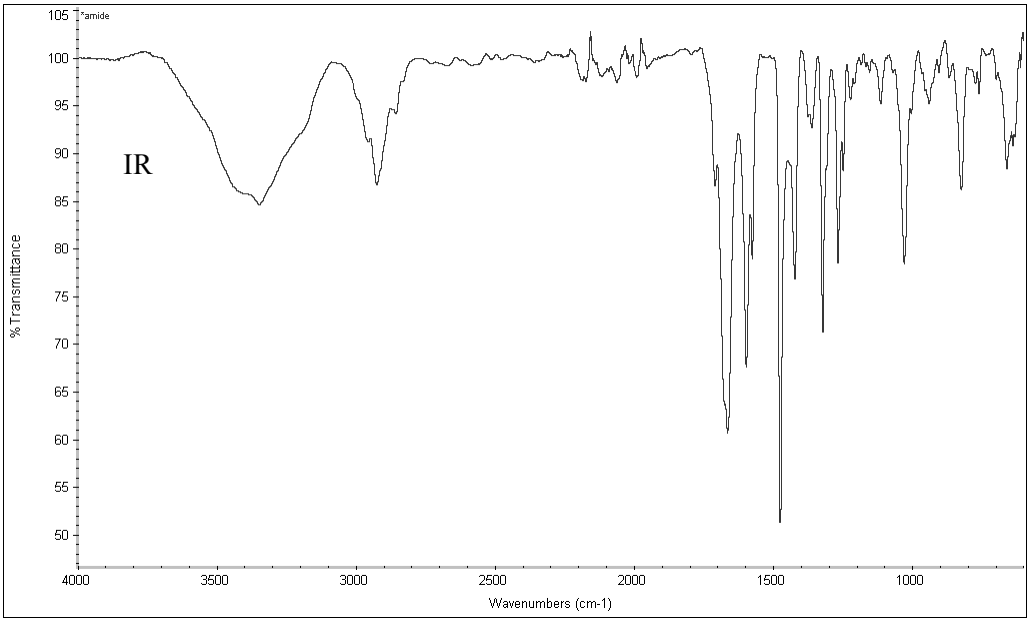
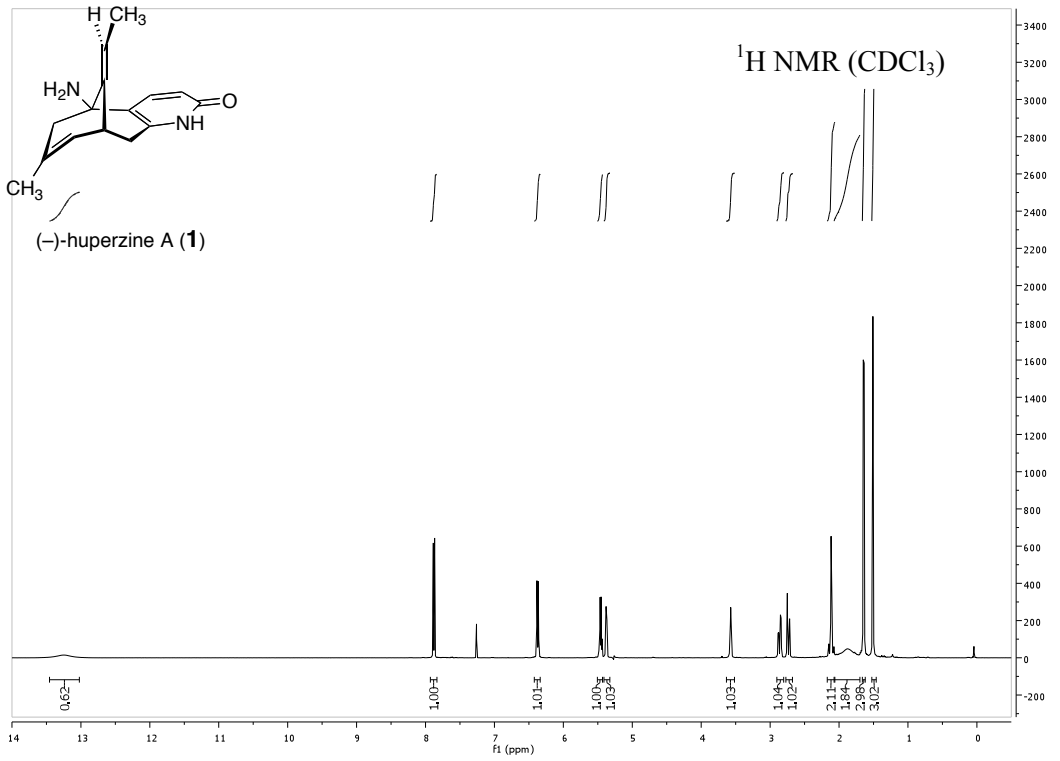
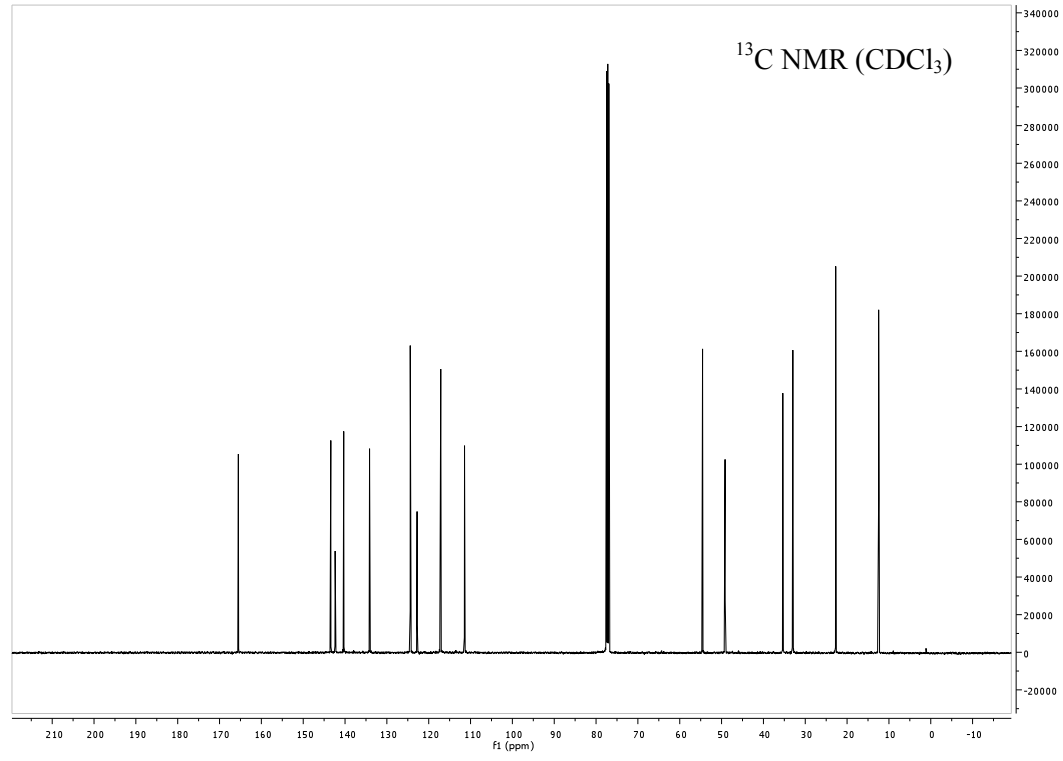
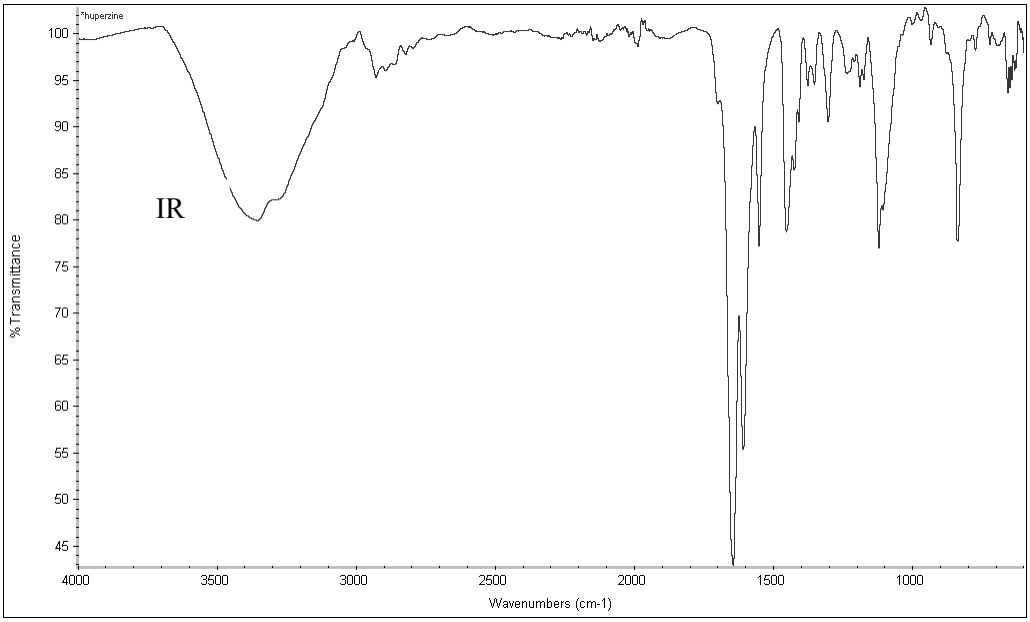
O
H2N
OCH3
N
CH3
14 (5:1 mixture of diastereomers)
1H NMR (CDCl3)
f1 (ppm)

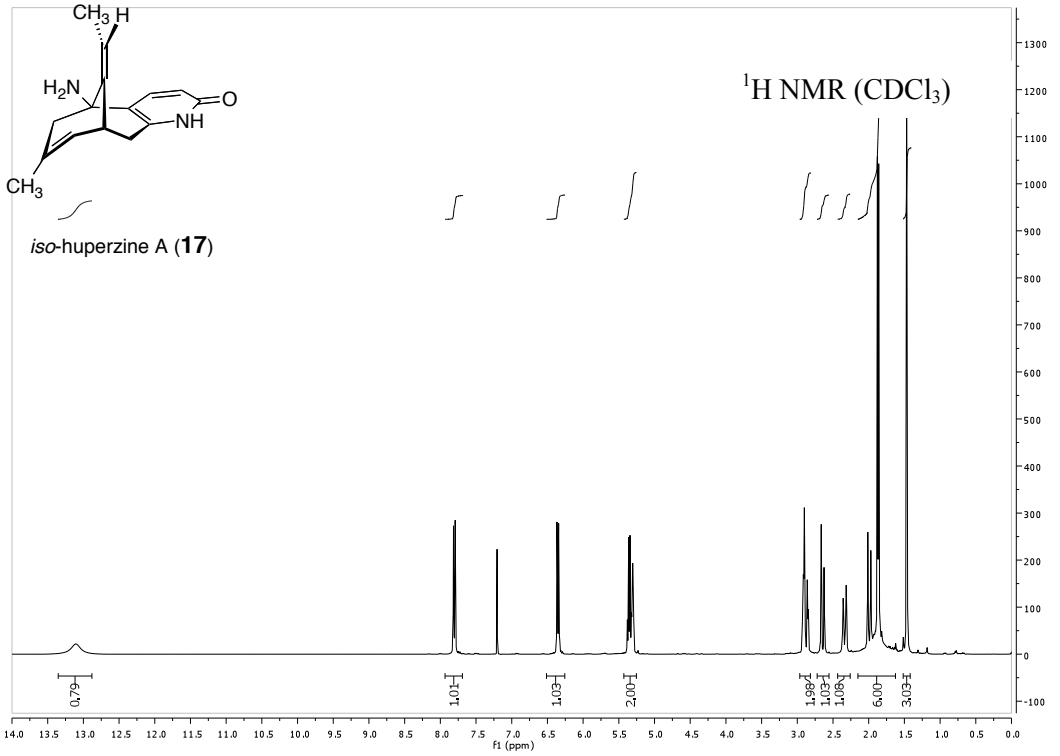

13C NMR (CDCl3)
f1 (ppm)

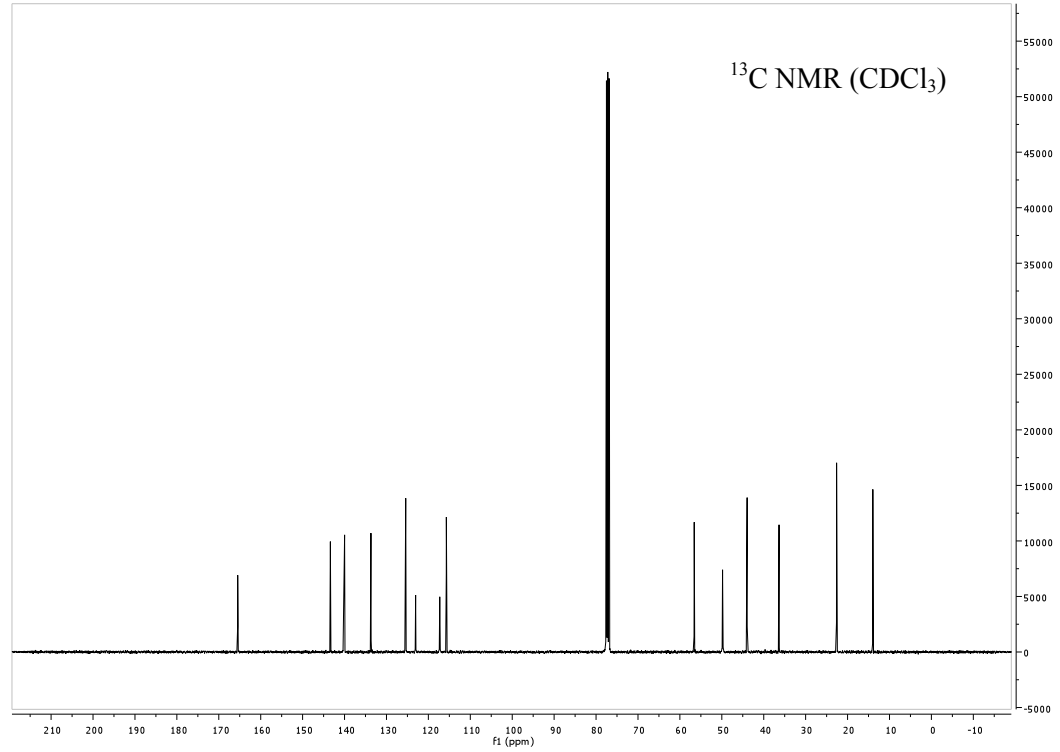


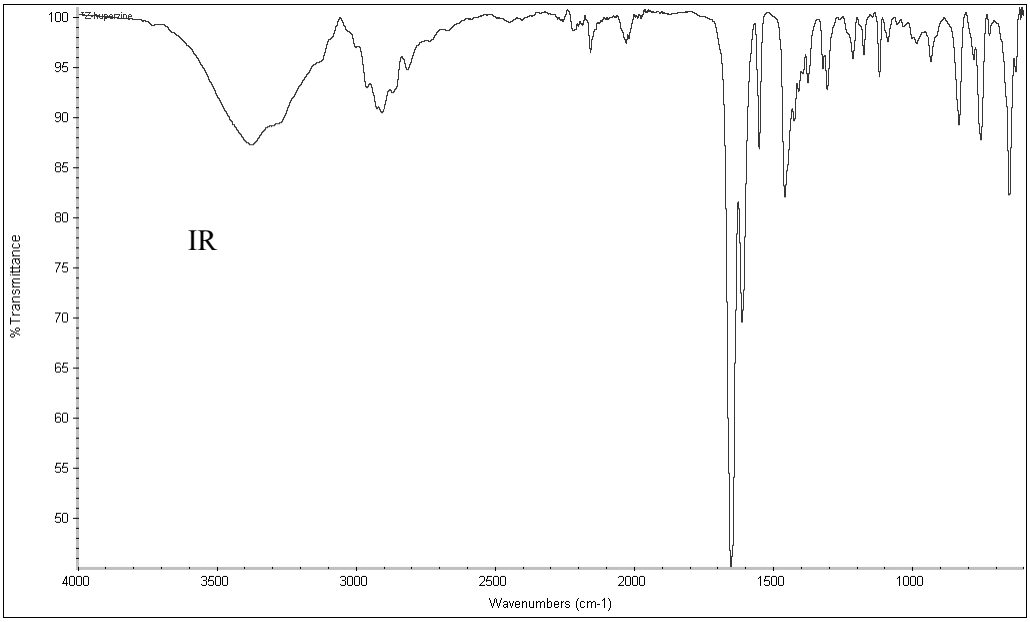

H CH3
H2N
O
NH
CH3
(–)-huperzine A (1)
1H NMR (CDCl3)
0.62
1.00
1.01
1.00
1.03
1.03
1.04
1.02
2.11
1.84
2.96
3.02
f1 (ppm)


13C NMR (CDCl3)
f1 (ppm)


*huperzine
IR
%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


CH3 H
H2N
O
NH
CH3
iso-huperzine A (17)
1H NMR (CDCl3)
0.79
1.01
1.03
2.00
1.98
1.03
1.08
6.00
3.03
f1 (ppm)


13C NMR (CDCl3)
f1 (ppm)


(-)-huperzine
IR
%Transmittance
100
95
90
85
80
75
70
65
60
55
50
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

Bibliography.

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9. For clarity, synthetic intermediates not described in the manuscript are numbered in the Supporting Information beginning with **16**.
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