Electronic Supplementary Material (ESI) for Chemical Communications

Total Syntheses of Mitragynine, Paynantheine and Speciogynine via an Enantioselective Thiourea-Catalysed Pictet-Spengler Reaction

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Supporting Information

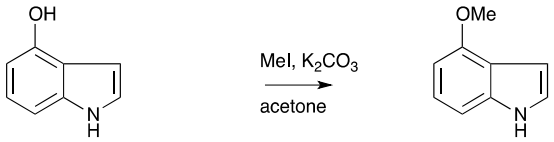
Contents

General remarks:

All ^{1}H-NMR and ^{13}C-NMR (APT) spectra were recorded with a Bruker Avance 400 spectrometer (^{1}H 400 MHz, ^{13}C 100 MHz) in $CDCl_3$ at room temperature. IR spectra were obtained using a Bruker IFS 28 FT-spectrophotometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Analytical thin layer chromatography was performed using Merck TLC plastic roll 500 x 20 cm silica gel F_{254}. Flash chromatography was carried out on Biosolve 60 Å (0.032 – 0.063 mm) silica gel. Ee's were determined on Chiracel® OD-H (Chiral Technologies Europe, 0.46 cm x 25 cm) columns. Melting points were measured with a Leitz-Wetzlar melting point microscope and are uncorrected. Mass spectra and accurate mass measurements were performed using a JEOL JMS-SX/SX 102 A Tandem Mass Spectrometer.

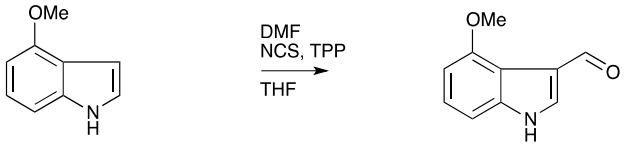
All reactions were carried out in oven-dried glassware with magnetic stirring under nitrogen atmosphere. Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone. Toluene was stored under 4 Å molecular sieves. Commercial reagents and solvents were purchased from Biosolve, Sigma-Aldrich, Fluka or Acros and used as received. 4-Hydroxyindole was purchased from AK Scientific Inc. Powdered 4 Å molecular sieves (Fluka) were dried at 200°C and 0.1 mbar. Aldehyde **8** was prepared according to reference 1. Bromide **6** was prepared following the method of ref. 2. Thioureum **16** was prepared according to Soós et al (ref. 3).

4-Methoxyindole



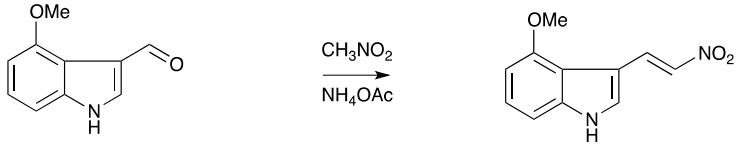
K_2CO_3 (90.0 g, 0.65 mol) and MeI (28.1 g, 0.20 mol) were added to a solution of 4-methoxy-1H-indole (26.6 g, 200 mol) in acetone (400 mL). After stirring the suspension under reflux for 18 h additional MeI (21.0 g, 0.15 mol) was added and refluxing was continued for 24 h. The mixture was filtered over celite, sufficient silica gel was added to the filtrate to absorb the compounds and the solvent was evaporated. Filtration over a glass filter packed with silica, eluting with EtOAc:PE, 1:2 (1.2 L) gave the product as a yellow solidifying oil, containing small amounts of the N-methylated product. Yield 89% (27.1 g, 0.184 mol). Mp 64 – 67 °C; ^{1}H-NMR δ 8.16 (s, 1H); 7.37 (t, 1H, *J* = 8.0 Hz); 7.11 (m, 2H); 6.93 (t, 1H, *J* = 2.6 Hz); 6.77 (d, 1H, *J* = 7.8 Hz); 4.14 (s, 3H); ^{13}C-NMR δ 153.2, 137.1, 122.6, 122.6, 118.4, 104.4, 99.5, 99.4, 55.2. IR 3408, 1615 cm^{-1}. HRMS (FAB): m/z calcd for $(M+H)^+$ $C_9H_{10}ON$: 148.0718; found: 148.0770.

4-Methoxy-indole-3-carboxaldehyde



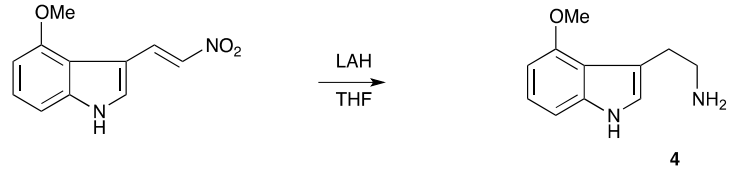
Triphenylphosphine (40.1 g, 153 mmol) was dissolved in dry THF (640 ml) *N*-chlorosuccinimide and (20.41 g, 153 mmol) was added in portions. The suspension was stirred vigorously for 30 min at room temperature. Next DMF (23.5 mL, 306 mmol) was added to the reaction and the mixture was stirred under reflux for 1 h. 4-Methoxyindole (7.5 g, 51 mmol) was added and the mixture was stirred under reflux for 1 h. The reaction mixture was cooled down to room temperature and the THF was evaporated. 640 mL Water (700 ml) was added to the mixture and it was stirred under reflux for 1 h. The mixture was cooled down and basified with 10% NaOH. The aqueous phase was extracted with EtOAc (4 x 200 mL) and the organic layers were combined and evaporated in the presence of silica. Chromatography over a short column with EtOAc:PE, 1:1 and 1:2 gave the product as an orange solid (7.24 g, 41.3 mmol, 81%). Mp 151 - 154 °C; ^{1}H-NMR δ 10.53 (s, 1H); 8.79 (s, 1H); 7.95 (d, 1H, *J* = 3.1 Hz); 7.24 (t, 1H, *J* = 8.1 Hz); 7.10 (d, 1H, *J* = 8.2 Hz); 6.75 (d, 1H, J = 7.9 Hz); 4.03 (s, 3H). ^{13}C-NMR δ 187.6, 153.7, 137.6, 128.4, 123.1, 118.3, 115.6, 105.3, 101.6, 54.8. IR 3246, 1648 cm^{-1}. HRMS (FAB): m/z calcd for $(M+H)^+$ $C_{10}H_{10}O_2N$: 176.0667; found: 176.0712.

4-Methoxy-3-(2-nitrovinyl)-indole



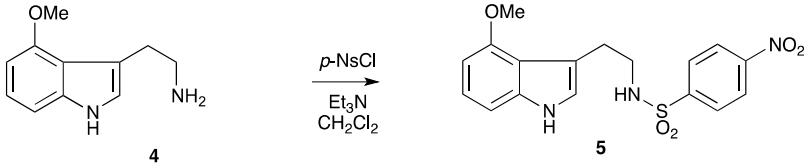
NH_4OAc (3.52 g, 45.6 mmol) and aldehyde (4.0 g, 22.8 mmol) were dissolved in nitromethane (135 mL) and the suspension was heated under reflux for 1 h. The mixture was cooled to room temperature and the solvent evaporated. The remaining solid was dissolved in a small amount of methanol and precipitated slowly with water. The solid was filtered over celite and dried under vacuum. The product (4.80 g, 22.0 mmol, 96%) was obtained as a red solid. Mp: 185 - 188 °C. ^{1}H-NMR δ 8.67 (bs, 1H); 8.52 (d, 1H, *J* = 13.4 Hz); 7.98 (d, 1H, *J* = 13.4 Hz); 7.61 (d, 1H, *J* = 2.7 Hz); 7.25 (d, 1H, *J* = 8.0 Hz); 7.07 (d, 1H, *J* = 8.2 Hz); 6.71 (d, 1H, *J* = 7.9 Hz); 4.04 (s, 3H). ^{13}C-NMR δ 152.9, 138.4, 134.5, 131.9, 130.5, 123.5, 114.4, 107.9, 105.1, 101.3, 54.3. IR: 3285, 2940, 1687, 1612 cm^{-1}. HRMS (FAB): m/z calcd for $(M+H)^+$ $C_{11}H_{11}O_3N_2$: 219.0725, found: 219.0773.

4-Methoxytryptamine[4]



$LiAlH_4$ (8.0 g, 210 mmol) was added to 80 mL of dry THF and cooled to 0 °C. 4-Methoxy-3-(2-nitrovinyl)indole (3.94 g, 18.1 mmol) was dissolved in 200 mL dry THF and added to the mixture with a dropping funnel. After 3 h of reflux the flask was placed in an ice bath and first water (1.3 g / g $LiAlH_4$); then 15% aqueous NaOH (1.3 g / g $LiAlH_4$) and finally again water (3.25 g / g $LiAlH_4$) were carefully added with a dropping funnel. The mixture was stirred vigorously for 15 min and filtered. The solids were washed with Et_2O (5x) and the combined organic layers dried (Na_2SO_4) and evaporated. The product **4** was obtained as a solid (3.42 g, 18.0 mmol, 99%). Mp 105 - 110 °C. ^{1}H-NMR δ 8.06 (bs, 1H); 7.11 (t, 1H, *J* = 7.9 Hz); 6.99 (d, 1H, *J* = 7.7 Hz); 6.91 (d, 1H, *J* = 2.2 Hz); 6.51 (d, 1H, *J* = 7.7 Hz); 3.94 (s, 3H); 3.03 (m, 4H). ^{13}C-NMR δ 154.4, 138.1, 122.1, 121.2, 116.9, 112.9, 104.5, 98.7, 54.7, 42.8, 30.6 ppm. IR: 3400, 2932, 1585 cm^{-1}.

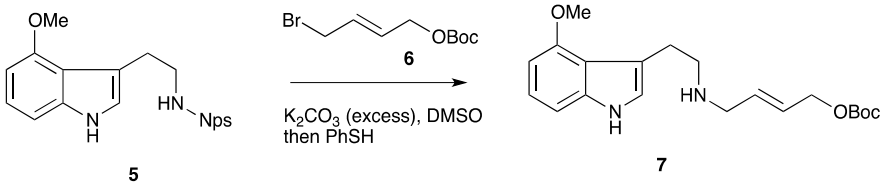
N_b-(4-nitrobenzenesulfonyl)-4-methoxytryptamine (5)



4-Nitrobenzenesulfonyl chloride (4.43 g, 20.0 mmol) was added in 3 portions to a solution of 4-methoxytryptamine **4** (3.42 g, 18.0 mmol) and triethylamine (3.06 ml, 22 mmol) in anhydrous DCM (65 ml).

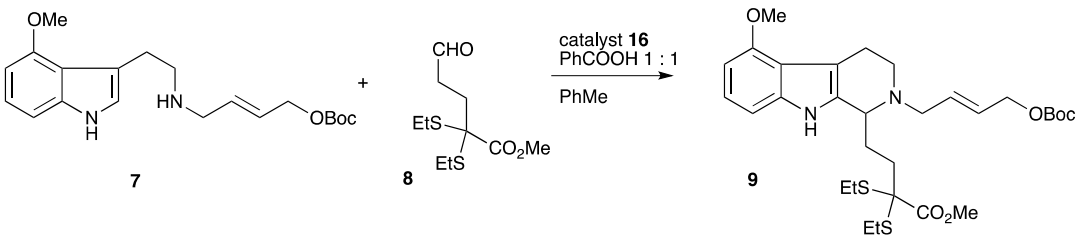
The reaction temperature was kept between 20 and 30 °C by cooling in a water bath. After stirring during 2 h and extractive workup (DCM / aq. $NaHCO_3$) the mixture was purified by chromatography (EtOAc:PE, 1:2 and 2:1) to give **5** as an orange, slowly crystallising glass (5.93 g, 15.8 mmol, 87.4%). Mp: 136 - 140 °C. ^{1}H-NMR δ 7.89 (m, 2H); 7.54 (m, 2H); 7.08 (t, 1H, *J* = 8.0 Hz); 6.88 (d, 1H, *J* = 8.2 Hz); 6.76 (d, 1H, *J* = 2.3 Hz); 6.46 (d, 1H, *J* = 7.8 Hz); 3.92 (s, 3H); 3.40 (m, 2H); 3.00 (m, 2H). ^{13}C-NMR δ 153.2, 148.2, 145.3, 137.6, 126.7, 122.6, 121.3, 121.5, 116.1, 110.6, 104.5, 98.2, 54.4, 44.1, 26.1. IR: 3406, 1528 cm^{-1}. HRMS (FAB): m/z calcd for $(M+H)^+$ $C_{17}H_{18}O_5N_3S$: 376.0922; found: 376.0971.

(E)-*tert*-butyl 4-(2-(4-methoxy-1H-indol-3-yl)ethylamino)but-2-enyl carbonate (7)



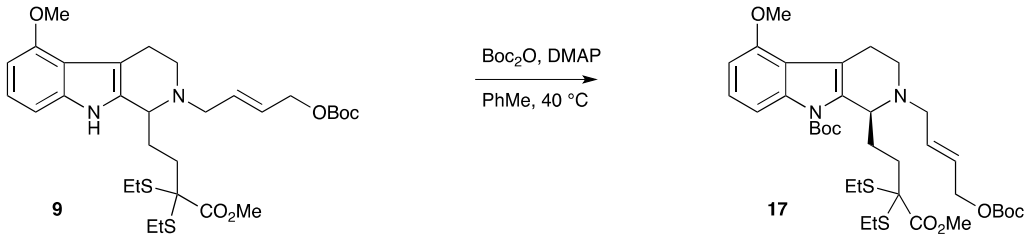
Finely powdered K_2CO_3 (4.10 g, 29.7 mmol) and bromoalkene **6** (2.73 g, 10.9 mmol) were added to a solution of N_b-(4-nitrobenzenesulfonyl)-4-methoxytryptamine **5** (3.71 g, 9.9 mmol) in DMSO (33 mL). After stirring for 4 h at room temperature thiophenol (3.0 mL, 29.7 mmol) was added and stirring was continued during 2 h. The reaction was quenched with water and the aqueous phase was extracted with EtOAc. Some aqueous NH_4Cl was added to facilitate the separation. The organic layers were combined and washed with water. After drying and removal of the solvent the mixture was purified by column chromatography (EtOAc:PE, 1:1; EtOAc; EtOAc:MeOH, 90:10; EtOAc:MeOH:NEt_3, 85:10:5). Product 7 was obtained as a slightly coloured syrup (3.35 g, 9.3 mmol, 94%). ^{1}H-NMR δ 8.64 (bs, 1H); 7.09 (t, 1H, *J* = 8.0 Hz); 6.95 (d, 1H, *J* = 8.1 Hz); 6.87 (s, 1H); 6.49 (d, 1H, *J* = 7.7 Hz); 5.73 (m, 1H); 5.87 (m, 1H); 4.51 (d, 2H, J = 6.2 Hz); 3.92 (s, 3H); 3.30 (d, 2H, *J* = 5.9 Hz); 3.10 (t, 2H, *J* = 6.7 Hz); 2.97 (t, 2H, *J* = 6.7 Hz); 1.50 (s, 9H). ^{13}C-NMR δ 154.6, 153.2, 138.1, 133.5, 125.3, 122.5, 121.1, 117.1, 113.6, 104.5, 99.1, 81.9, 66.9, 54.9, 50.5, 50.1, 27.6, 26.9. IR: 3400, 2932, 1740 cm^{-1}. HRMS (FAB): m/z calcd for $(M+H)^+$ $C_{20}H_{29}O_4N_2$: 361.2083; found: 361.2078.

Organocatalyzed Pictet-Spengler reaction



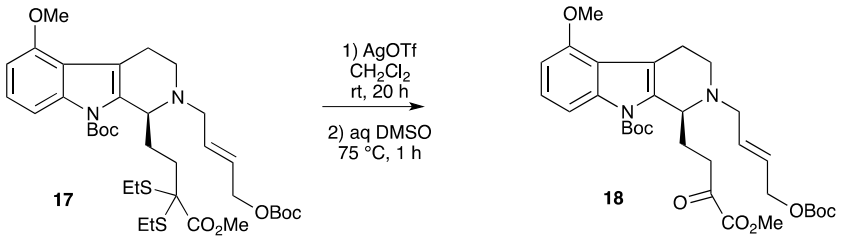
Catalyst **16** (0.330 g, 0.55 mmol, 20 mol%) and benzoic acid (0.067 g, 0.55 mmol, 20 mol%) were added to a solution of tryptamine **7** (1.0 g, 2.77 mmol) in toluene (50 mL) under argon. Next aldehyde **8**[1] (0.83 g, 3.30 mmol) was added and the solution was stirred for 24 h at room temperature. The solvent was evaporated and the resulting oil purified by column chromatography using EtOAc:DCM:PE, 1:4:4. Product **9** was obtained as a colorless glass (1.47 g, 2.5 mmol, 90%). *ee*: 89% (Chiralcel® OD-H, eluent: *n*-heptane:*iso*-propanol = 90:10, flow: 0.6 mL/min); 17.8 min (major) 23.7 (minor). Optical rotation: $[\alpha]_D^{20}$ = -19.6° (c = 1.03, $CHCl_3$). ^{1}H-NMR δ 7.79 (bs, 1H); 7.04 (t, 1H, *J* = 7.9 Hz); 6.94 (d, 1H, *J* = 8.0 Hz); 6.49 (d, 1H, *J* = 7.6 Hz); 5.91 (m, 1H); 5.76 (m, 1H); 4.58 (d, 2H, *J* = 6.1 Hz); 3.91 (s, 3H); 3.78 (s, 3H); 3.67 (t, 1H, *J* = 5.5 Hz); 3.34 (dd, 1H, J = 6.0 Hz, *J* = 14.1 Hz); 3.17 (m, 2H); 3.00 (m, 1H); 2.82 (m, 2H); 2.58 (m, 4H); 2.09 (m, 2H); 1.97 (m, 2H); 1.52 (s, 9H); 1.21 (dt, 6H, *J* = 7.5 Hz, *J* = 13.8 Hz). ^{13}C-NMR δ = 171.3, 154.3, 153.3, 137.1, 133.6, 132.3, 126.4, 122.0, 117.2, 108.5, 104.2, 99.6, 82.1, 67.0, 65.0, 56.4, 55.2, 54.6, 53.0, 46.0, 32.0, 29.1, 27.8, 24.0, 23.4, 20.6, 13.6, 13.3. IR: 3393, 2931, 1723 cm^{-1}. HRMS (FAB): m/z calcd for $(M+H)^+$ $C_{30}H_{45}N_2O_6S_2$: 593.2720; found: 593.2722.

Boc-protection of 9



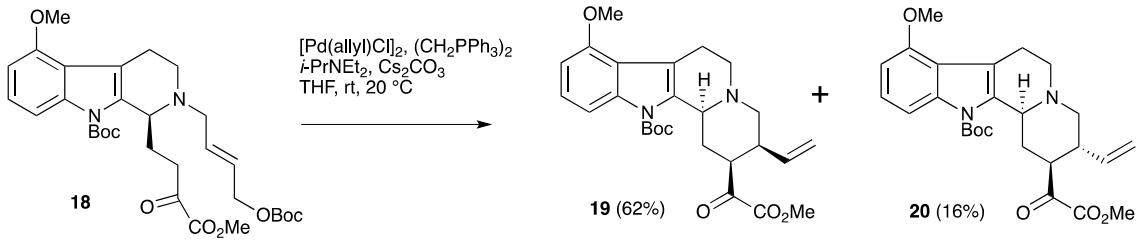
Di-*tert*-butyl dicarbonate (0.37 g, 1.70 mmol) and DMAP (0.035 g, 0.28 mmol) were added to a solution of tetrahydro-*β*-carboline (0.673 g, 1.13 mmol) in toluene (20 mL). The mixture was heated to 40°C and stirred for 1 h. Conversion was checked on TLC. The solvent was evaporated and product 17 was isolated via column chromatography using EtOAc:DCM:PE = 1:4:4 as a colorless glass (0.779 g, 1.12 mmol, 99%). *ee*: 89% (Chiralcel® OD-H, eluent: *n*-heptane:*iso*-propanol = 95:5, flow: 0.5 mL/min); 9.90 (minor); 19.52 (major). Optical rotation: $[\alpha]_D^{20}$ = -21.7° (c = 1.03, $CHCl_3$). ^{1}H-NMR δ 7.72 (d, 1H, *J* = 8.4 Hz); 7.15 (t, 1H, *J* = 8.2 Hz); 6.65 (d, 1H, *J* = 8.0 Hz); 5.90 (m, 1H); 5.73 (m, 1H); 4.58 (d, 2H, *J* = 6.3 Hz); 4.15 (dd, 1H, *J* = 2.3 Hz, *J* = 10.6 Hz); 3.89 (s, 3H); 3.76 (s, 3H); 3.32 (dd, 1H, *J* = 6.5 Hz, *J* = 13.7 Hz); 3.22 (dd, 1H, *J* = 6.5 Hz, J = 13.9 Hz); 3.14 (m, 1H); 2.94 (m, 2H); 2.80 (dd, 1H, *J* = 4.7 Hz, *J* = 16.4 Hz); 2.69 (m, 4H); 2.42 (m, 1H); 2.08 (m, 1H); 1.94 (m, 1H); 1.80 (m, 1H); 1.68 (s, 9H); 1.51 (s, 9H); 1.24 (t, 6H, *J* = 7.5 Hz). ^{13}C-NMR δ = 171.2, 153.9, 153.3, 150.2, 137.6, 134.5, 134.4, 125.8, 124.1, 118.8, 114.0, 108.8, 103.3, 83.5, 81.9, 67.0, 65.3, 57.3, 55.2, 54.8, 52.7, 41.4, 33.2, 30.0, 28.1, 27.7, 23.8, 23.7, 19.1, 13.4, 13.3. IR: 2974, 2933, 1726 cm^{-1}. HRMS (FAB): m/z calcd for $(M+H)^+$ $C_{35}H_{53}N_2O_8S_2$: 693.3244; found: 693.3248.

Deprotection of thioacetal 17



To a solution of thioacetal **17** (0.562 g, 0.811 mmol) in anhydrous DCM (9 mL) was added silver trifluoromethanesulfonate (0.334 g, 1.3 mmol) in two portions, one at the beginning of the reaction and the second after 60 min of stirring. After 20 h of stirring at room temperature the precipitated AgSEt was removed by filtration over celite and the solvent was evaporated. The pyrrolidinium salt (as a mixture of diastereomers) was obtained as a foam in quantitative yield. The salt was hydrolyzed in the next step. ^{1}H-NMR (major diastereomer) δ 7.57 (d, 1H, *J* = 8.5 Hz); 7.25 (t, 1H, *J* = 8.3 Hz); 6.68 (d, 1H, *J* = 8.0 Hz); 6.20 (m, 1H); 5.94 (dt, 1H, *J* = 5.3 Hz, *J* = 15.5 Hz); 5.35 (t, 1H, *J* = 9.0 Hz); 4.58 (d, 2H, *J* = 5.2 Hz); 4.26 (dd, 1H, *J* = 6.2 Hz, *J* = 12.4 Hz); 4.05 (d, 2H, *J* = 7.3 Hz); 4.00 (s, 3H); 3.89 (s, 3H); 3.82 (m, 1H); 3.72 (dd, 1H, *J* = 5.1 Hz; J = 18.8 Hz); 3.12 (m, 5H); 2.84 (m, 1H); 2.4 (m, 1H); 1.68 (s, 9H); 1.48 (s, 9H); 1.30 (t, 3H, *J* = 7.4 Hz). IR: 1733 cm^{-1}. This pyrrrolidinium salt (0.633 g, 0.81 mmol) was dissolved in DMSO (10 mL) and 2.4 mL H_2O was added. A stream of nitrogen gas was directed through the solution and it was stirred for 45 min at 75°C (bath temperature). The reaction mixture was diluted with water (100 mL) and aqueous $NaHCO_3$ solution (5 ml) and the aqueous phase was extracted 3 times with EtOAc. The organic layers were washed with water, dried over Na_2SO_4 and the solvents were evaporated. Flash chromatography (EtOAc:PE, 1:5/ 1:4.5/ 1:4) gave α-ketoester **18** (0.347 g, 0.59 mmol, 73% from **17**). Optical rotation: $[\alpha]_D^{20}$ = -41.9° (c = 0.95, $CHCl_3$). ^{1}H-NMR δ = 7.73 (d, 1H, *J* = 8.4 Hz); 7.18 (t, 1H, *J* = 8.2 Hz); 6.66 (d, 1H, *J* = 8.0 Hz); 5.80 (m, 1H); 5.68 (m, 1H); 4.53 (m, 2H); 4.04 (m, 1H); 3.92 (s, 3H); 3.89 (s, 3H); 3.20 (dd, 1H, *J* = 7.9 Hz, *J* = 13.4 Hz); 3.07 (m, 2H); 2.81 (m, 3H); 2.58 (m, 2H); 2.29 (m, 2H); 1.69 (s, 9H); 1.51 (s, 9H). ^{13}C-NMR δ 188.9, 161.6, 153.8, 153.0, 149.9 137.0, 132.6, 131.5, 127.0, 124.4, 118.4, 113.9, 108.7, 103.2, 83.6, 66.5, 58.1, 55.1, 54.2, 52.3, 38.8, 36.3, 32.5, 28.0, 27.5, 18.8. IR: 2977, 1726, 1576 cm^{-1}. HRMS (FAB): m/z calcd for $(M+H)^+$ $C_{31}H_{43}N_2O_9$: 587.2969; found: 587.2972.

Tsuji-Trost cyclization of 18

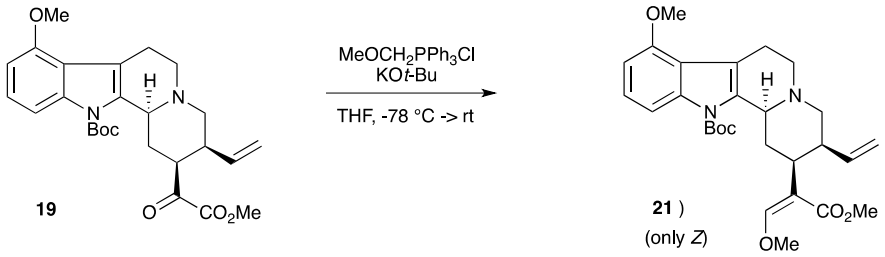


Bis(diphenyphosphino)ethane (0.017 g, 0.042 mmol) was added to a solution of allylpalladium(II) chloride dimer (0.007 g, 0.02 mmol) in anhydrous THF (2 mL) under argon. The solution was stirred for 15 min before it was added to a solution of α-keto-ester **18** (0.233 g, 0.396 mmol) in THF (5 mL) followed by Cs_2CO_3 (0.258 g, 0.793 mmol) and DiPEA (0.135 mL, 0.793 mmol). The reaction mixture was stirred for 20 h at room temperature before it was quenched with dilute aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and the solvents were removed. Purification by column chromatography using EtOAc:PE, 3:1/2:1 gave two C15-C20 isomers in a ratio of *cis*:*trans* = 4 : 1 in a combined yield of 78%.

cis-isomer **19**: 0.114 g (0.245 mmol, 62%). Optical rotation (*ee*: 89%): $[\alpha]_D^{20}$ = -145.8° (c = 1.07, $CHCl_3$). ^{1}H-NMR δ 7.63 (d, 1H, *J* = 8.4 Hz); 7.15 (t, 1H, *J* = 8.2 Hz); 6.63 (d, 1H, *J* = 8.0 Hz); 6.10 (td, 1H, *J* = 9.9 Hz, *J* = 17.2 Hz); 4.99 (m, 2H); 3.87 (s, 3H); 3.86 (s, 3H); 3.56 (dt, 1H, *J* = 3.7 Hz, *J* = 12.4 Hz); 3.03 (m, 5H); 2.88 (m, 2H); 2.67 (m, 1H); 2.25 (d, 1H, *J* = 13.3 Hz); 1.77 (ddd, 1H, *J* = 12.7 Hz, *J* = 12.8 Hz, *J* = 12.7 Hz); 1.63 (s, 9H). ^{13}C-NMR δ 194.7, 161.4, 154.0, 150.5, 138.2, 137.6, 134.3, 124.5, 118.7, 117.2, 116.6, 108.5, 103.5, 83.7, 60.9, 59.8, 55.3, 52.7, 50.9, 49.5, 40.8, 28.2, 27.0, 25.1. IR: 2978, 2942, 2800, 1724, 1606 cm^{-1}. HRMS (FAB): m/z calcd for $(M+H)^+$ $C_{26}H_{33}N_2O_6$: 469.2239; found: 469.2340.

trans-isomer **20**: 0.029 g (0.063 mmol, 16%). Optical rotation (*ee*: 89%): $[\alpha]_D^{20}$ = -38.9° (c = 0.86, $CHCl_3$); ^{1}H-NMR δ 7.69 (d, 1H, *J* = 8.3 Hz); 7.15 (t, 1H, *J* = 8.2 Hz); 6.63 (d, 1H, *J* = 7.9 Hz); 5.60 (m, 1H); 5.06 (m, 2H); 4.30 (d, 1H, *J* = 10.6 Hz); 3.87 (s, 3H); 3.84 (s, 3H); 3.49 (m, 1H); 3.12 (m, 3H); 2.87 (m, 5H); 2.27 (ddd, 1H, *J* = 2.5 Hz, *J* = 3.5 Hz, *J* = 12.8 Hz); 1.68 (s, 9H). ^{13}C-NMR δ 194.7, 161.5, 153.9, 150.1, 137.8, 137.5, 133.7, 124.3, 118.5, 116.9, 115.8, 108.6, 103.4, 83.8, 83.5, 60.2, 59.5, 57.0, 55.2, 52.7, 49.3, 46.3, 37.6, 28.6, 28.0, 24.5. IR: 2977, 2940, 2837, 1726, 1606 cm^{-1}. HRMS (FAB): m/z calcd for $(M+H)^+$ $C_{26}H_{32}N_2O_6$: 469.2294, found: 469.2340.

Wittig reaction with *cis*-isomer 19

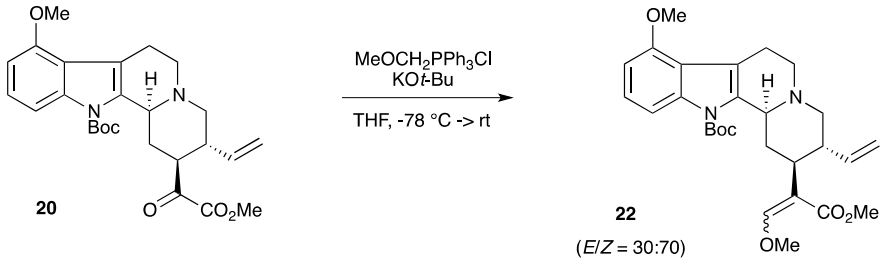


(Methoxymethyl)triphenylphosphonium chloride (0.89 g, 2.59 mmol) was converted to the corresponding ylid with potassium *tert*-butoxide (0.280 g, 2.5 mmol) by stirring during 5 min in THF (10 ml) at rt. The resulting red solution was cooled to -78 °C, causing a colour change to yellow, and was added quickly to a solution of α-ketoester **19** (0.405 g, 0.864 mmol) in THF (10 ml) at – 78°C. The cooling bath was removed, and the yellow solution was stirred for 2 h at rT. Saturated NH*4*Cl solution (10 ml); water (2 ml) and ethyl acetate (10 ml) were added and the resulting 2-layer system was stirred for 24 h. Extractive work-up and chromatography (EtOAc:PE, 1:3, 1:2) gave Z-alkene **21** as a slightly coloured solid (0.419 g, 0.84 mmol, 98%). ^{1}H-NMR δ 7.73 (d, 1H, *J* = 8.4 Hz); 7.18 (t, 1H, *J* = 8.2 Hz); 6.66 (d, 1H, *J* = 8.0 Hz); 6.08 (s, 1H); 6.05 (m, 1H); 5.07 (dd, 1H, *J* = 2.1 Hz, *J* = 10.4 Hz); 4.95 (dd, 1H, *J* = 1.8 Hz, *J* = 17.3 Hz); 3.89 (s, 3H); 3.78 (s, 3H); 3.75 (s, 3H); 3.02 (m, 4H); 2.88 (m, 2H); 2.65 (m, 2H); 2.00 (d, 1H, *J* = 12.0 Hz); 1.64 (s, 9H); 1.50 (m, 1H). ^{13}C-NMR δ 166.8, 156.9, 153.9, 150.4, 138.4, 138.2, 134.4, 124.5, 118.6, 117.0, 116.6, 110.4, 108.2, 103.5, 83.7, 61.9, 61.6, 60.8, 55.3, 51.2, 50.8, 42.6, 39.2, 31.8, 28.1, 25.2. IR: 2944, 2838, 2798, 2751, 1727, 1692, 1645 cm^{-1}. HRMS (FAB): m/z calcd for $(M+H)^+$ $C_{23}H_{29}O_4N_2$: 497.2652; found: 497.2649.

Crystallization to 98% ee:

Product **21** was dissolved in a minimal amount of ethyl acetate and diluted with petroleum ether. After standing for 24 h at room temperature the crystals were removed by filtration. Crystals: 4% *ee*, (0.0485 g) Mp: 151 - 155 °C. Filtrate: 98% *ee*, (glass, 0.371 g, 0.748 mmol, 86% yield from **19**). Optical rotation: $[\alpha]_D^{20}$ = -180° (c = 0.97, $CHCl_3$). HPLC (Chiralcel® OD-H, eluent: *n*-heptane:*iso*-propanol = 90:10, flow: 0.6 mL/min) 12.73 (minor); 15.22 min (major).

Wittig reaction with *trans*-isomer 20



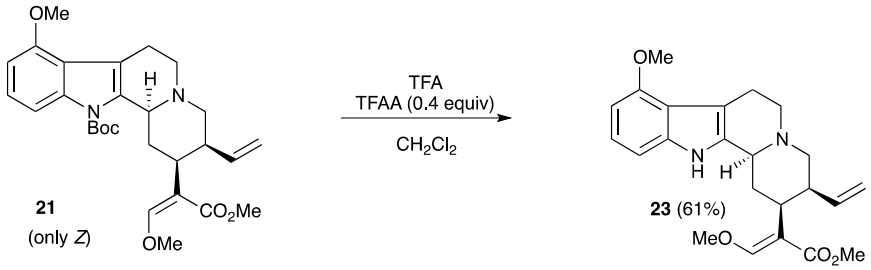
The reaction was performed as described for the synthesis of **21** using ketone **20** (0.109 g, 0.233 mmol) and three equivalents of the phosphonium ylid. Purification through column chromatography gave both the *Z*-and *E*-isomer of **22** in a ratio of 2.5 : 1 (combined yield 0.090 g, 0.181 mmol, 78%)

Z-isomer: (0.064 g, 0.13 mmol, 57%). Optical rotation: (*ee*: 89%) $[\alpha]_D^{20}$ = +2.8° (c = 0.5, $CHCl_3$). ^{1}H-NMR δ = 7.70 (d, 1H, *J* = 8.2 Hz); 7.13 (t, 1H, *J* = 8.2 Hz); 6.62 (d, 1H, *J* = 7.9 Hz); 6.37 (s, 1H); 5.54 (m, 1H); 5.02 (m, 2H); 4.14 (d, 1H, *J* = 10.20 Hz); 3.86 (s, 3H); 3.75 (s, 3H); 3.71 (s, 3H); 3.14 (m, 3H); 2.97 (m, 1H); 2.77 (m, 2H); 2.64 (dq, 1H, *J* = 3.8 Hz, *J* = 11.4 Hz); 2.44 (td, 1H, *J* = 3.6 Hz, *J* = 12.0 Hz); 2.11 (ddd, 1H, *J* = 2.6 Hz, *J* = 3.4 Hz, *J* = 12.9 Hz); 1.73 (m, 1H); 1.65 (s, 9H) ppm. ^{13}C-NMR δ = 166.8, 157.1, 154.0, 150.2, 139.2, 138.0, 134.6, 124.4, 118.7, 116.1, 115.4, 110.7, 108.6, 103.5, 83.6, 61.9, 60.8, 60.3, 58.6, 55.3, 51.1, 47.0, 42.4, 42.2, 34.5, 28.1, 24.6, 14.1. IR: 2937, 1724, 1692, 1639 cm^{-1}. HRMS (FAB): m/z calcd for $(M+H)^+$ $C_{28}H_{37}O_6N_2$: 497.2652; found: 497.2652.

E-isomer: (0.024 g, 0.047 mmol, 21%). ^{1}H-NMR δ 7.78 (d, 1H, *J* = 8.4 Hz); 7.28 (s, 1H); 7.13 (t, 1H, *J* = 8.2 Hz); 6.62 (d, 1H, *J* = 8.0 Hz); 5.53 (m, 1H); 4.96 (m, 2H); 4.20 (d, 1H, *J* = 10.9 Hz); 3.87 (s, 3H); 3.78 (s, 3H); 3.65 (s, 3H); 3.25 (m, 1H); 3.05 (m, 4H); 2.80 (m, 3H); 2.12 (q, 1H, *J* = 12.4 Hz); 1.84 (d, 1H, *J* = 12.8 Hz); 1.64 (s, 9H). ^{13}C-NMR δ 159.4, 154.0, 150.2, 139.9, 138.1, 134.7, 124.4, 118.7, 115.3, 115.1, 112.2, 108.6, 103.5, 83.6, 61.3, 60.9, 58.1, 55.4, 51.0, 46.3, 38.5, 30.8, 28.0, 24.6 ppm. IR: 1726, 1703, 1637 cm^{-1}. HRMS (FAB): m/z calcd for $(M+H)^+$ $C_{28}H_{37}O_6N_2$: 497.2652; found: 497.2652.

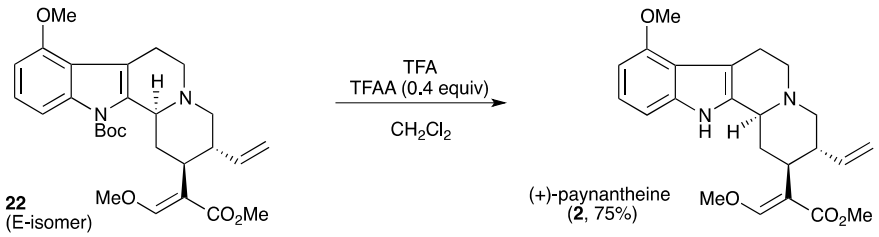
Crystallization of 22 (E-isomer): 22 (E) was dissolved in a minimal amount of ethyl acetate and diluted with petroleum ether. After standing for 24 h at room temperature the crystals were removed by filtration. Crystals: 73% *ee*, 0.0109 g, Mp: 184 - 187°C; filtrate: 98% *ee*, 0.0051 g. The filtrate resulting from the first crystallization was evaporated and the crystallization procedure was repeated, yielding crystals with 99% *ee* (0.005 g). Mp: 183-187°C. Optical rotation: $[\alpha]_D^{20}$ = +53.7° (c = 1.08, $CHCl_3$). HPLC (Chiralcel® OD-H, eluent: *n*-heptane:*iso*-propanol = 95:5, flow: 0.6 mL/min) 16.4 (minor); 18.7 (major).

Synthesis of (-)-dehydro-mitragynine 23



Trifluoroacetic anhydride (4 µl, 0.03 mmol) was added to good quality TFA (3 mL) under anhydrous conditions. The acid-solution was added to a solution of Z-enolether **21** (0.0336 g, 0.068 mmol) in 10 mL DCM under argon. The reaction was stirred for 17 h at room temperature before it was diluted with Et_2O and neutralized with aqueous $NaHCO_3$. The aqueous phase was extracted with Et_2O, the organic layers combined and dried over Na_2SO_4. Purification by column chromatography using EtOAc:PE, 1:2/1:1 gave **23** (0.0164 g, 0.041 mmol, 61%) as a yellow solid. Mp: 84 – 87 °C. Optical rotation: $[\alpha]_D^{20}$ = -104° (c = 0.93, $CHCl_3$). ^{1}H-NMR δ 7.70 (bs, 1H); 7.35 (s, 1H); 7.00 (t, 1H, *J* = 7.9 Hz); 6.90 (d, 1H, *J* = 8.0 Hz); 6.46 (d, 1H, *J* = 7.7 Hz); 6.32 (dt, 1H, *J* = 9.9 Hz, *J* = 17.1 Hz); 4.91 (m, 2H); 3.88 (s, 3H); 3.69 (s, 3H); 3.68 (s, 3H); 3.23 (bd, 1H, *J* = 11.2 Hz); 3.07 (m, 2H); 2.94 (m, 3H); 2.72 (dd, 1H, *J* = 2.9 Hz, *J* = 11.2 Hz); 2.55 (m, 2H); 2.42 (bd, 1H, *J* = 7.6 Hz); 1.86 (bd, 1H, *J* = 12.8 Hz). ^{13}C-NMR δ = 169.0, 160.2, 154.4, 139.4, 137.1, 133.3, 121.8, 117.4, 114.2, 111.0, 107.8, 104.1, 99.6, 61.4, 61.2, 60.9, 60.3, 55.2, 53.5, 51.1, 44.5, 39.0, 30.2, 23.7. IR: 3364, 2936, 2838, 2791, 2752, 1698, 1643, 1597 cm^{-1}. HRMS (FAB): m/z calcd for $(M+H)^+$ $C_{23}H_{29}O_4N_2$: 397.2127; found: 397.2122.

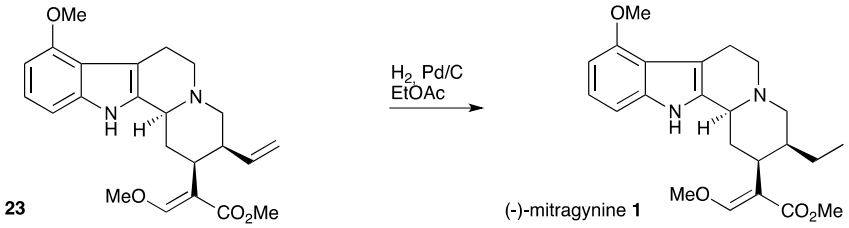
Deprotection of 22 to paynantheine (2)



Trifluoroacetic anhydride (2 µl, 0.015 mmol) was added to good quality TFA (1.5 mL) under anhydrous conditions. This acid-solution was added to a solution of E-enolether **22** (99% ee, 0.023 g, 0.048 mmol) in 5 mL DCM under argon. The reaction was stirred for 17 h at room temperature before it was diluted with Et_2O and neutralized with aqueous $NaHCO_3$. The aqueous phase was extracted with Et_2O, the organic layers combined and dried over Na_2SO_4. Purification by column chromatography using EtOAc:PE, 1:2 and 1:1 gave gave (+)-paynantheine **2** as an off-white glass (0.0181 g, 0.046 mmol, 96%). Optical rotation: $[\alpha]_D^{20}$ = +20.2° (c = 0.91,

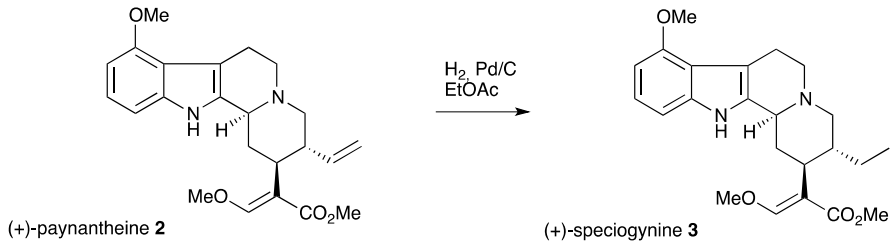
$CHCl_3$). Lit.: $|\alpha|_D^{25}$ = +29.4° (c = 1.2, $CHCl_3$)[5]. ^{1}H-NMR δ 7.73 (bs, 1H); 7.33 (s, 1H); 7.00 (t, 1H, *J* = 7.9 Hz); 6.87 (d, 1H, *J* = 8.1 Hz); 6.46 (d, 1H, *J* = 7.8 Hz); 5.58 (m, 1H); 4.98 (m, 2H); 3.87 (s, 3H); 3.77 (s, 3H); 3.69 (s, 3H); 3.26 (bd, 1H, *J* = 11.6 Hz); 3.17 (m, 1H); 3.02 (m, 4H); 2.75 (dt, 1H, *J* = 3.5 Hz, *J* = 11.7 Hz); 2.58 (dt, 1H, *J* = 4.2 Hz, *J* = 11.2 Hz); 2.27 (t, 1H, *J* = 11.4 Hz); 2.14 (ddd, 1H, *J* = 12.0 Hz, *J* = 12.2 Hz, *J* = 12 Hz); 1.95 (bd, 1H, *J* = 12.5 Hz). ^{13}C-NMR δ 159.8, 154.4, 139.4, 137.4, 133.0, 121.8, 117.5, 115.4, 11,5, 107.8, 104.3, 99.7, 61.5, 61.3, 60.0, 55.3, 53.2, 51.2, 42.8, 33.4, 23.7. IR: ν 3370, 2940, 2847, 2799, 2751, 1703, 1637, 1596, 1569 cm^{-1}. HRMS (FAB): m/z calcd for $(M+H)^+$ $C_{23}H_{29}O_4N_2$: 397.2127; found: 397.2122.

Hydrogenation of 23 to mitragynine (1)



(-)-Dehydro-mitragynine **23** (22.4 mg, 0.0562 mmol) was stirred with 10% Pd/C (5.0 mg) in EtOAc (2 mL) under H_2 (1 atm.) for 18 h. Filtration over celite and evaporation furnished (-)-mitragynine **1** (22.2 mg, 0.0556 mmol, 99%) as an off-white solid, mp 97-105 °C lit. 103-105 °C.[6] Optical rotation after chromatography (EtOAc:PE, 1:1): $|\alpha|_D^{20}$= -128° (c = 1.1, $CHCl_3$) and $|\alpha|_D^{20}$= -122° (c = 1.1, CH_2Cl_2). Lit.: $|\alpha|_D^{20}$ = -126 (c = 1.2, $CHCl_3$).[7] *ee*: 98% (Chiralcel® OD-H, eluent: *n*-heptane:*iso*-propanol = 90:10, flow: 0.6 mL/min); 27.5 (minor); 30.5 (major). ^{1}H-NMR δ 7.73 (bs, 1H); 7.46 (s, 1H); 7.02 (t, 1H, *J* = 7.9 Hz); 6.92 (d, 1H, *J* = 8.0 Hz); 6.48 (d, 1H, *J* = 7.7 Hz); 3.90 (s, 3H); 3.75 (s, 3H); 3.73 (s, 3H); 3.13 (m, 2H); 3.05 (m, 3H); 2.94 (m, 1H); 2.53 (m, 3H); 1.79 (m, 2H); 1.66 (m, 2H); 0.89 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR δ 169.2, 160.5, 154.5, 137.2, 133.7, 121.8, 117.6, 111.5, 107.8, 104.2, 99.7, 61.5, 61.2, 57.7, 55.3, 53.8, 51.3, 40.7, 39.9, 29.9, 23.9, 19.1, 12.8. IR: 3367, 2933, 2849, 2796, 2747, 1703, 1643, 1624 cm^{-1}. HRMS (FAB): m/z calcd for $(M+H)^+$ $C_{23}H_{30}O_4N_2$: 399.2284; found: 399.2291.

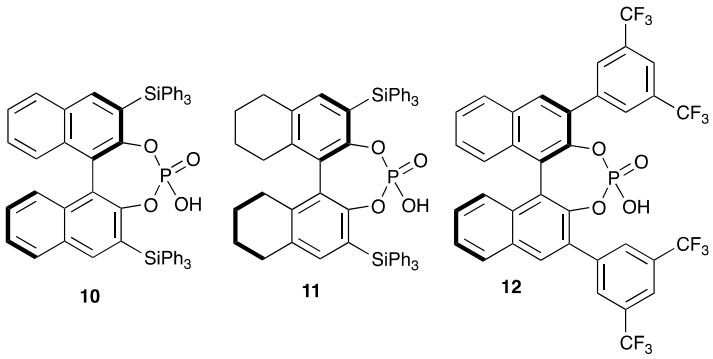
Hydrogenation of (+)-paynantheine (2) to (+)-speciogynine (3)



(+)-paynantheine **2** (+)-speciogynine **3**

(+)-Paynantheine **2** (34.2 mg, 0.0861 mmol) was stirred with 10% Pd/C (6.0 mg) in EtOAc (4 mL) under H_2 (1 atm.) for 18 h. Filtration over celite and evaporation furnished (+)-speciogynine **3** (33.9 mg, 0.0850 mmol, 99%) as a glass. Optical rotation: $[\alpha]_D^{20}$ = +22.8° (c = 0.89, $CHCl_3$); Lit.: $[\alpha]_D^{25}$ = +26.8°(c = 0.85, $CHCl_3$)[5]. ^{1}H-NMR (strong line broadening for all ring protons)[8] δ 7.81 (bs, 1H); 7.36 (bs, 1H); 6.99 (t, 1H, *J* = 7.9 Hz); 6.86 (d, 1H, *J* = 8.1 Hz); 6.45 (d, 1H, *J* = 7.7 Hz); 3.87 (s, 3H); 3.58-3.81 (bs, 6H); 3.28-2.93 (m, 5H); 2.78-2.5 (m, 2H); 2.35-2.20 (m, 1H); 2.15-1.82 (m, 3H); 1.50-1.36 (m, 1H); 1.12-0.97 (m, 1H); 0.87 (t, 3H, *J* = 7.4 Hz). ^{13}C-NMR (incomplete due to broadening of signals)[8] δ 159.9, 154.4, 137.4, 133.1, 121.8, 117.5, 107.7, 104.3, 99.7, 61.7, 60.9, 60.3, 55.3, 53.5, 51.5, 39.9, 38.7, 33.7, 30.6, 29.7, 24.4, 23.7, 11.3. IR: 2936, 2851, 2802, 2750, 1698, 1635, 1597, 1569 cm^{-1}. HRMS (FAB): m/z calcd for $(M+H)^+$ $C_{23}H_{31}O_4N_2$: 399.2284; found: 399.2289.

Binolphosphoric acid catalysis



All yields > 85%

entry	catalyst	drying agent	temperature	*ee* [%]
1	10	MS 4 Å	0 °C	-3
2	11	MS 4 Å	0 °C	7
3	12	MS 4 Å	0 °C	7

Table 1: Variation of the catalyst

entry	catalyst	drying agent	temperature	*ee* [%]
1	10	MS 4 Å	-10 °C	-2
2	11	MS 4 Å	-10 °C	-6
3	12	MS 4 Å	-10 °C	0
4	10	MS 4 Å	-78 °C	11

Table 2: Variation of the temperature

entry	catalyst	drying agent	temperature	*ee* [%]
1	11	MgSO4	-10 °C	-
2	11	Na_2SO4	-10 °C	-9
3	11	-	0°C	-10

Table 3: Variation of drying agents

NMR-tables

^{1}H-NMR data of 1, 2 and 3 taken in $CDCl_3$. Literature values are obtained from ref. 9 and 10

	Mitragynine **1**[10] Natural	Mitragynine **1** Synthetic	Paynantheine **2**[10] Natural	Paynantheine **2** Synthetic	Speciogynine **3**[9] Natural	Speciogynine **3** Synthetic (Strong line-broadening[8])
3	3.14 *brd* (11)	3.17 *brd* (12.5)	3.27 *brd* (11)	3.26 *brd* (11.6)	3.57 *m*	3.6
5	2.89 *m* 2.51 *m*	2.93 *m* 2.5 *m*	3.06 *m* 2.55 *m*	3.02 m 2.62 *ddd* (11.2/11.2/4.3)	3.07 *m* 2.57 *m*	3.0 2.6
6	3.10 *m* 2.51 *m*	3.12 *m* 2.5 *m*	3.17 *m* 2.99 *m*	3.20 *m* 3.02 *m*	2.99 *m* 3.21	3.2 3.2
10	6.43 *brd* (8)	6.48 *d* (7.7)	6.44 *brd* (8)	6.46 *d* (7.7)	6.45 *brd* (8)	6.45 *d* (7.7)
11	6.97 *dd* (8/8)	7.02 *dd* (7.9/7.9)	6.98 *dd* (8/8)	7.00 *dd* (7.9/7.9)	6.99 *dd* (7.9/7.9)	6.99 *dd* (7.9/7.9)
12	6.88 *brd* (8)	6.92 *d* (8.0)	6.86 *brd* (8)	6.87 *d* (8.1)	6.87 *brd* (7.9)	6.86 *d* (8.1)
14	2.49 *m*	2.47 *brdd* (10.7/2.4)	2.10 *m*	2.14 *ddd* (12.0/12.0/12.2)	2.43 *m* (2H)	2.3

	1.78 *m*	1.82 *m*	1.94 *m*	1.95 *m*		
15	3.02 *ddd* (14/4/4)	3.05 *m*	2.74 *ddd* (12/12/3)	2.75 *ddd* (11.7/11.7/3.5)	2.26 *m*	2.3 *m*
17	7.41 *s*	7.46 *s*	7.31 *s*	7.33 *s*	7.36 *brs*	7.36 *brs*
18	0.85 *t* (7.5;3H)	0.89 *t* (7.3;3H)	4.98 *dd* (17.5/2) 4.93 *dd* (10.5/2)	5.03 *dd* (17.2/1.3) (4.98 *dd* (10.3/2.0)	0.86 *t* (7.5;3H)	0.87 *t* (7.4;3H)
19	1.77 *m* 1.18 *m*	1.77 *m* 1.22 *m*	5.56 *m*	5.58 *m*	1.48 *m* 1.17 *m*	1.5 1.2
20	1.60 *m*	1.66 *m*	3.03 *m*	3.02 *m*	2.61 *m*	2.6 *br*
21	2.99 *dd* (12/2.5) 2.43 *dd* (12/3)	3.02 *m* 2.46 *dd* (11.5/2.4)	3.01 *m* 2.27 *m*	3.02 *m* 2.32 *dd* (12.1/11.7)	3.15 *m* 2.05	3.2 *br* 2.0 *br*
9-OCH_3	3.86 *s* (3H)	3.90 (3H)	3.85 *s* (3H)	3.87 *s* (3H)	3.72 *brs* (3H)	3.87 *s* (3H)
17- OCH_3	3.71 *s* (3H)	3.75 (3H)	3.76 *s* (3H)	3.77 *s* (3H)	3.72 *brs* (3H)	3.74 *brs* (3H)
$COOCH_3$	3.69 *s* (3H)	3.73 (3H)	3.67 *s* (3H)	3.69 *s* (3H)	3.67 *s* (3H)	3.74 *brs* (3H)
NH	7.65 *brs*	7.73 *brs*	7.66 *brs*	7.73 *brs*	7.72 *brs*	7.81[8] *brs*

^{13}C-NMR data of 1, 2 and 3 taken in $CDCl_3$. Literature values are obtained from ref. 9 and 10

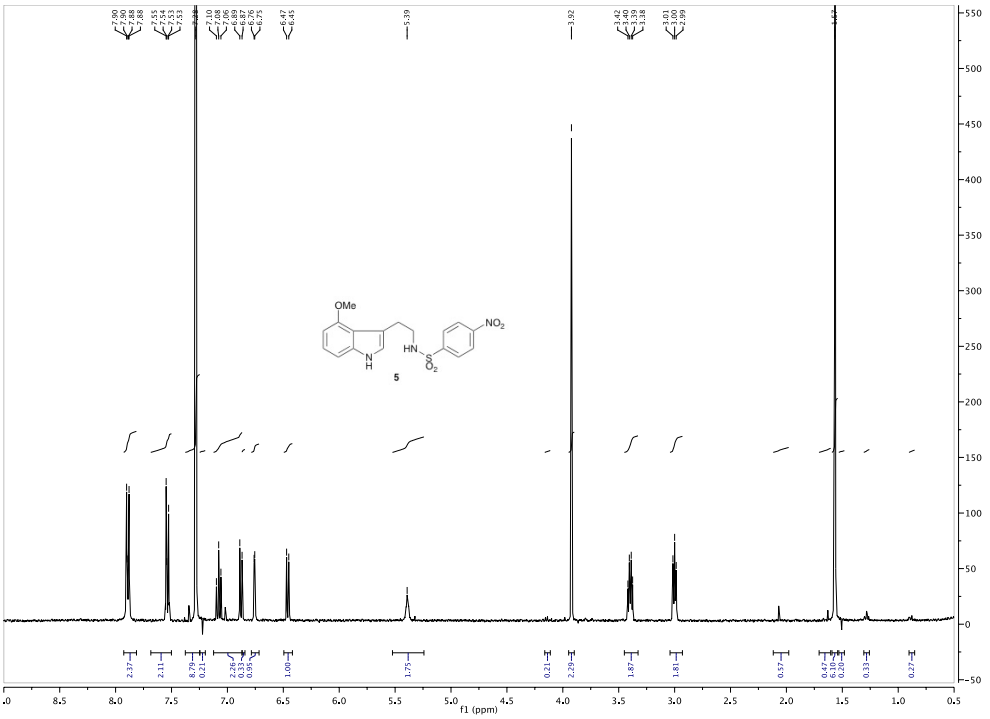
	Mitragynine **1**[9] Natural	Mitragynine **1** Synthetic	Paynantheine **2**[10] Natural	Paynantheine **2** Synthetic	Speciogynine **3**[9] Natural	Speciogynine **3**[8] Synthetic
2	133.7	133.7	133.7	133.0	133.2	133.1
3	61.2	61.2	60.0	60.0	60.4	60.3
5	53.8	53.8	53.2	53.2	53.6	53.5
6	23.9	23.9	23.7	23.7	23.8	23.7
7	107.9	107.8	107.9	107.8	107.8	107.7
8	117.7	117.6	117.5	117.5	117.6	117.6
9	154.5	154.5	154.5	154.4	154.5	154.5
10	99.8	99.7	99.8	99.7	99.7	99.7
11	121.8	121.8	121.9	121.8	121.8	121.8
12	104.1	104.2	104.2	104.3	104.2	104.3
13	137.2	137.2	137.3	137.4	137.3	137.4
14	30.0	29.9	33.4	33.4	33.8	33.7
15	39.9	39.9	38.5	not observed	38.8	38.7
16	111.5	111.5	111.5	111.5	111.7	111.7
17	160.5	160.5	159.8	159.8	159.9	159.9

18	12.9	12.8	115.5	115.4	11.3	11.3
19	19.1	19.1	139.1	139.4	24.4	24.4
20	40.7	40.7	42.9	42.8	40.0	39.9
21	57.8	57.7	61.3	61.3	61.0	60.8
22	169.6	169.2	172.2	not observed	169.5	not observed
9-OCH_3	55.32	55.3	55.3	55.3	55.3	55.3
17- OCH_3	61.5	61.2	61.6	61.5	61.7	61.7
$COOCH_3$	51.3	51.3	51.3	51.2	51.5	51.5

References.

1. a. G. Massiot, T. Mulamba, J. Levy, *Bull. Soc. Chim. Fr.*, 1982, 241-248. b. J. Gonzalez, F. Sanchez and T. Torres, *Synthesis*, 1983, 911-913.
2. M. J. Wanner, E. Claveau, J. H. van Maarseveen and H. Hiemstra, *Chem. Eur. J.*, 2011, **17**, 13680-13683.
3. B. Vakulya, S. Varga, A. Csámpai and T. Soós, *Org. Lett.*, 2005, **7**, 1967-1969.
4. S. Butini, S. Gemma, G. Campiani, S. Franceschini, F. Trotta, M. Borriello, N. Ceres, S. Ros, S. S. Coccone, M. Bernetti, A. M. De, M. Brindisi, V. Nacci, I. Fiorini, E. Novellino, A. Cagnotto, T. Mennini, K. Sandager-Nielsen, J. T. Andreasen, J. Scheel-Kruger, J. D. Mikkelsen and C. Fattorusso, *J. Med. Chem.*, 2009, **52**, 151-169.
5. S. Horie, F. Koyama, H. Takayama, H. Ishikawa, N. Aimi, D. Ponglux, K. Matsumoto and T. Murayama, *Planta Med.*, 2005, **71**, 231-236.
6. G. T. Beng, M. R. Hamdan, M. J. Siddiqui, M. N. Mordi and S. M. Mansor, *Malays. J. Anal. Sc.* 2011, **15**, 54-60.
7. A. H. Beckett, E. J. Shellard and A. N. Tackie, *Planta Med.*, 1965, **13**, 241-246.

8. For an explanation of this linebroadening in the demethoxy (corynantheine) series see: D. Staerk, P.-O. Norrby, and J. W. Jaroszewski, *J. Org. Chem*., 2001, **66**, 2217-2221.
9. M. Kitajima, K. Misawa, N. Kogure, I. M. Said, S. Horie, Y. Hatori, T. Murayama and H. Takayama, *J. Nat. Med.* 2006, **60**, 28-35.
10. A. H. Philipp, D. K. Wissenbach, A. A. Weber, J. Zapp and H. H. Maurer, *J. Chromatography B*, 2011, **879**, 1049-1055.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HN
S
O2
N
H
5
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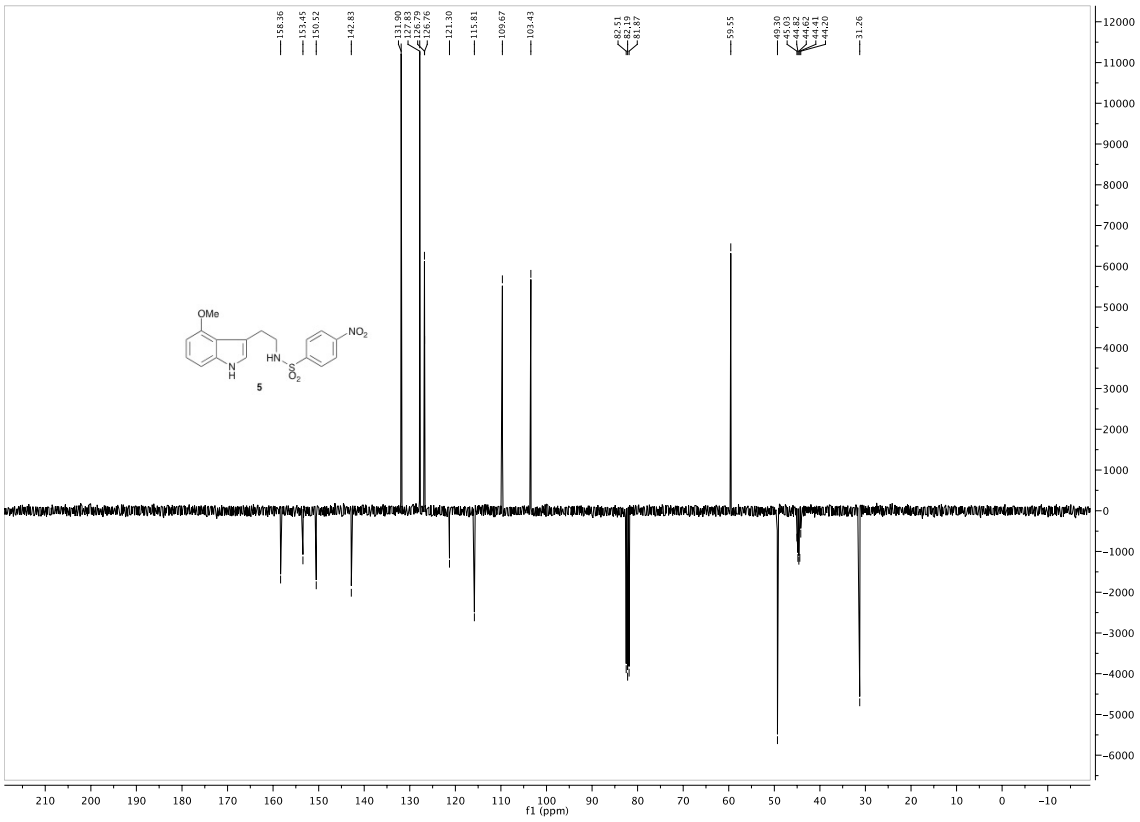
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127.83
126.79
126.76
121.30
115.81
109.67
103.43
82.51
82.19
81.87
59.55
49.30
45.93
44.82
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44.41
44.20
31.26
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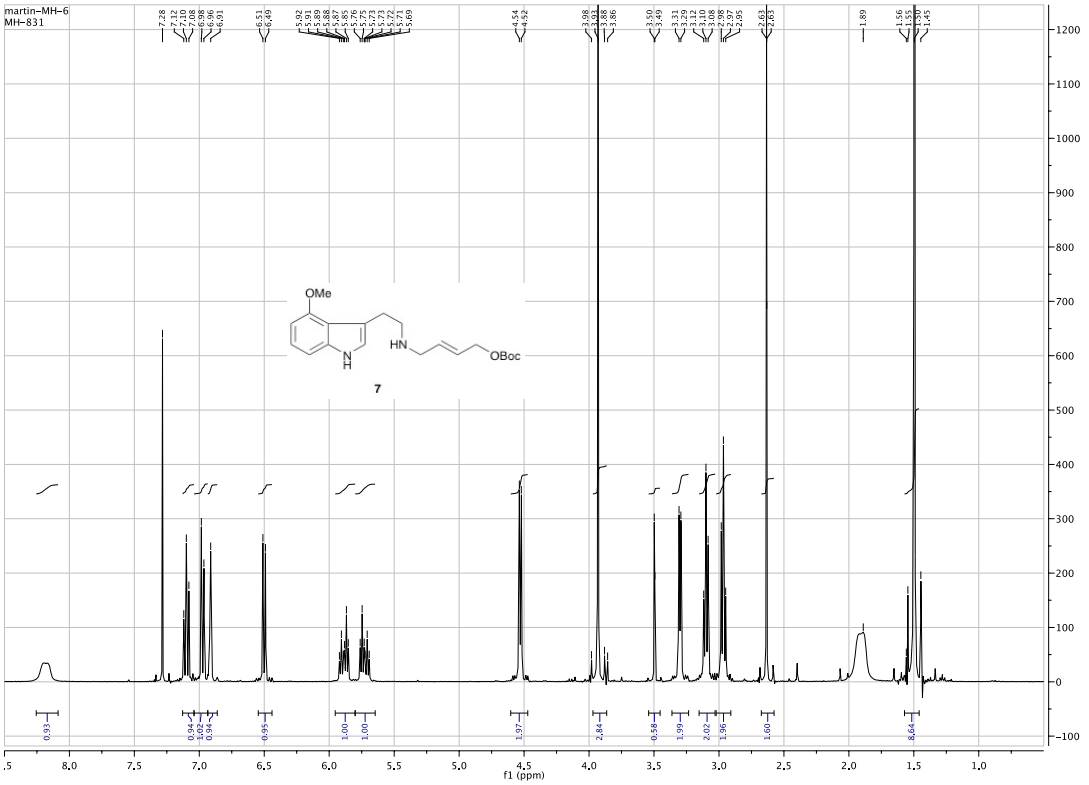
NO2
HN
S
O2
N
H
5
f1 (ppm)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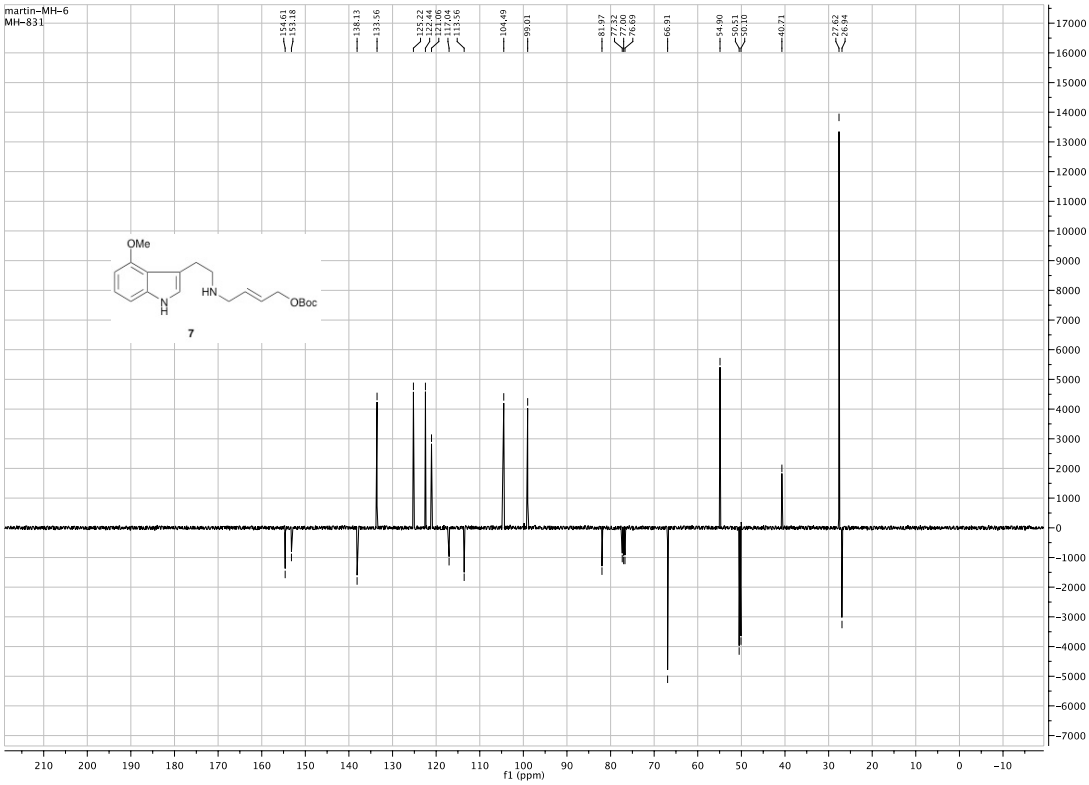
MH-831
OMe
HN
OBoc
7
f1 (ppm)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MH-831
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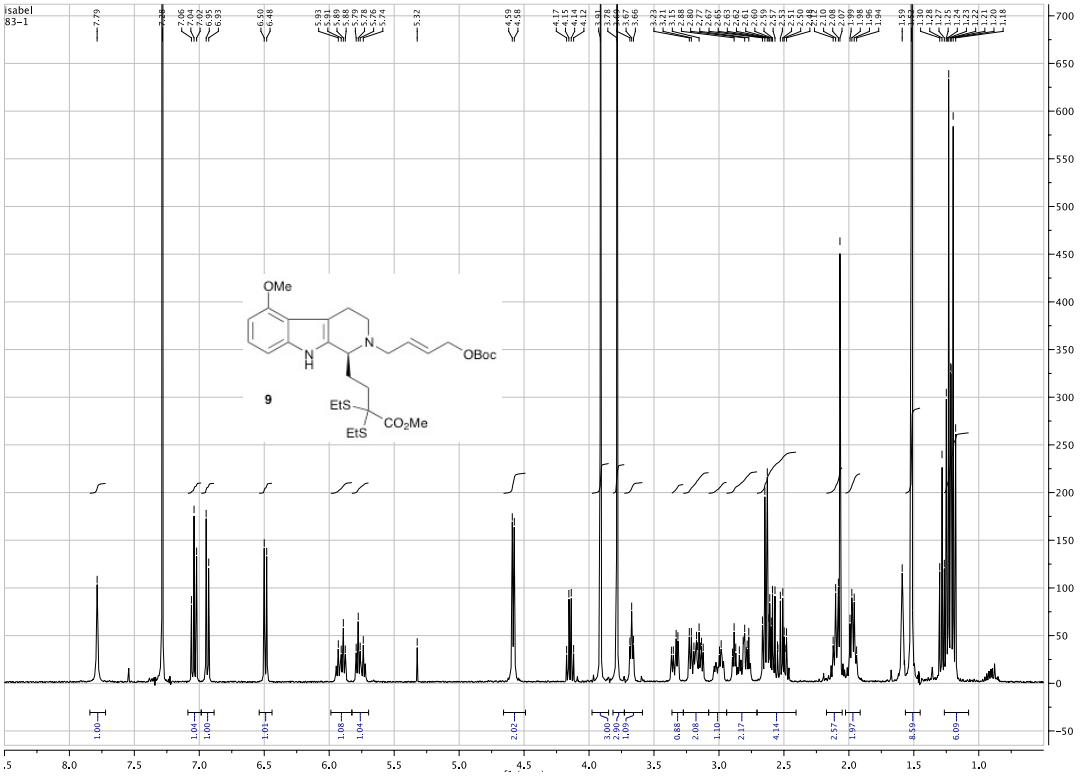
HN
OBoc
7
f1 (ppm)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OBoc
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H
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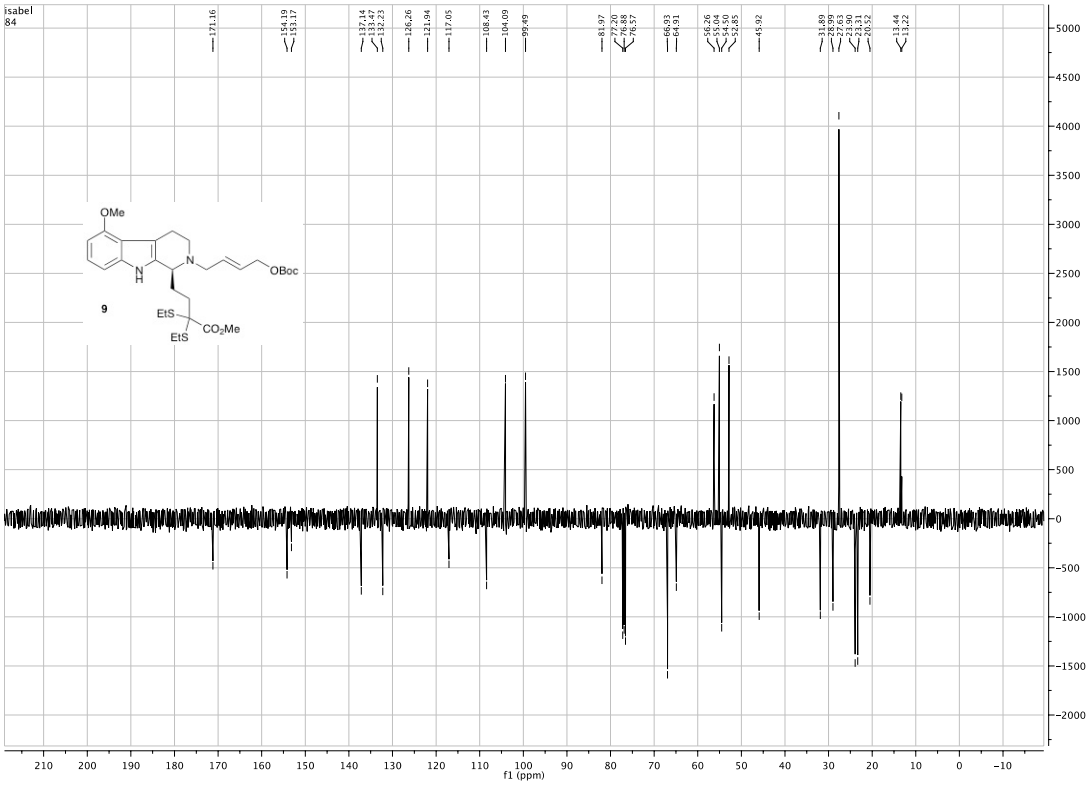
EtS
EtS
CO2Me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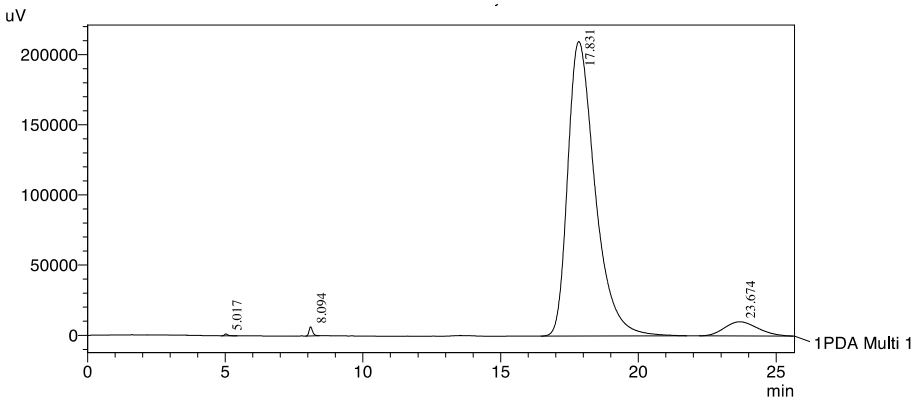
EtS
EtS
CO2Me
f1 (ppm)

9 89% ee



1 PDA Multi 1 / 254nm 4nm

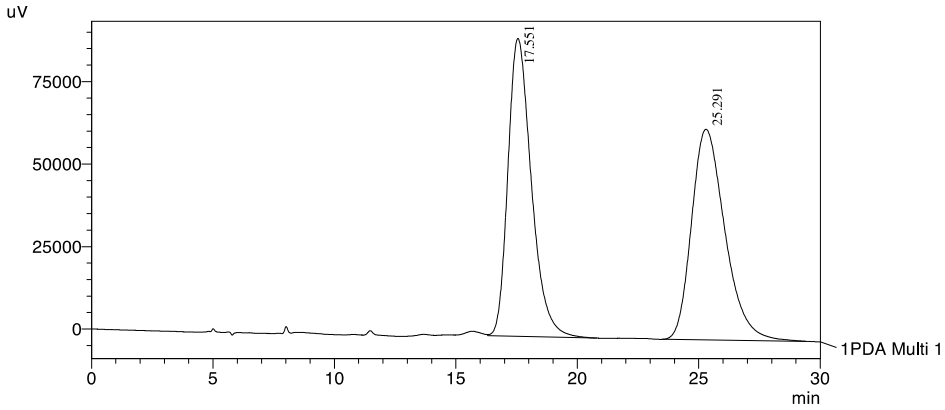
Results

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.017	13262	1368	0.086	0.600
2	8.094	57850	6433	0.375	2.824
3	17.831	14487048	209874	93.981	92.124
4	23.674	856647	10143	5.557	4.452
Total		15414806	227818	100.000	100.000

9 89% ee



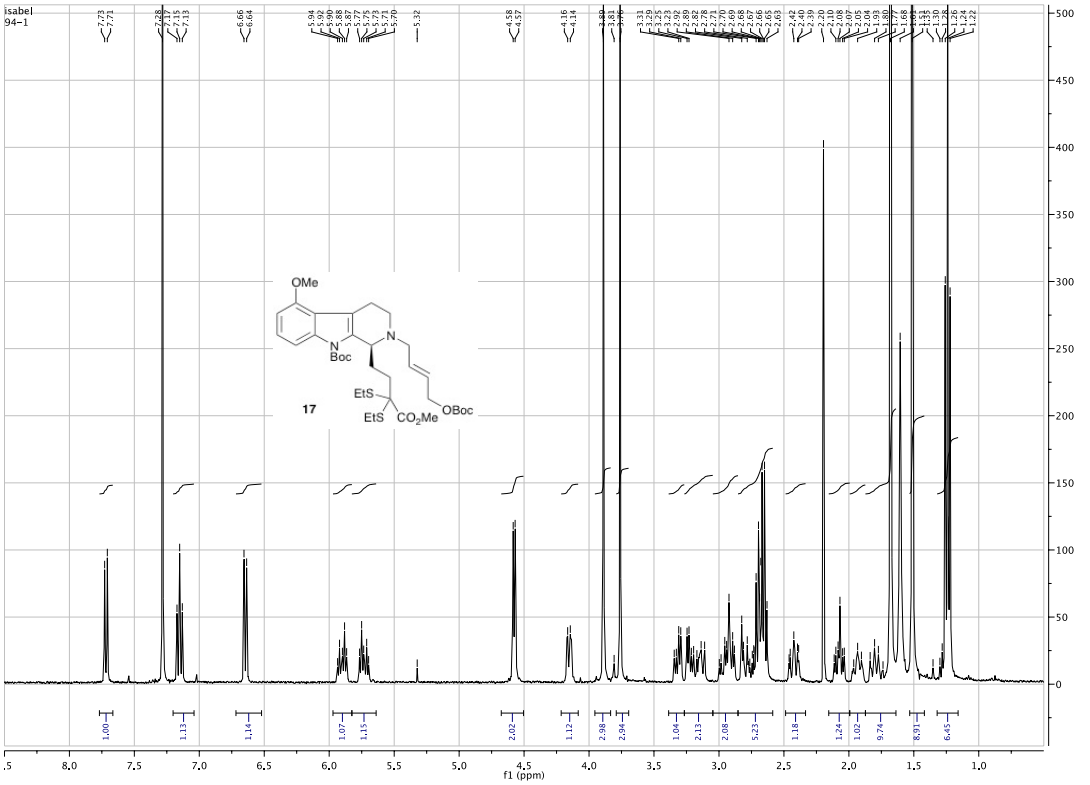
1 PDA Multi 1 / 254nm 4nm

Results

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.551	6075337	90324	49.890	58.580
2	25.291	6102207	63865	50.110	41.420
Total		12177544	154190	100.000	100.000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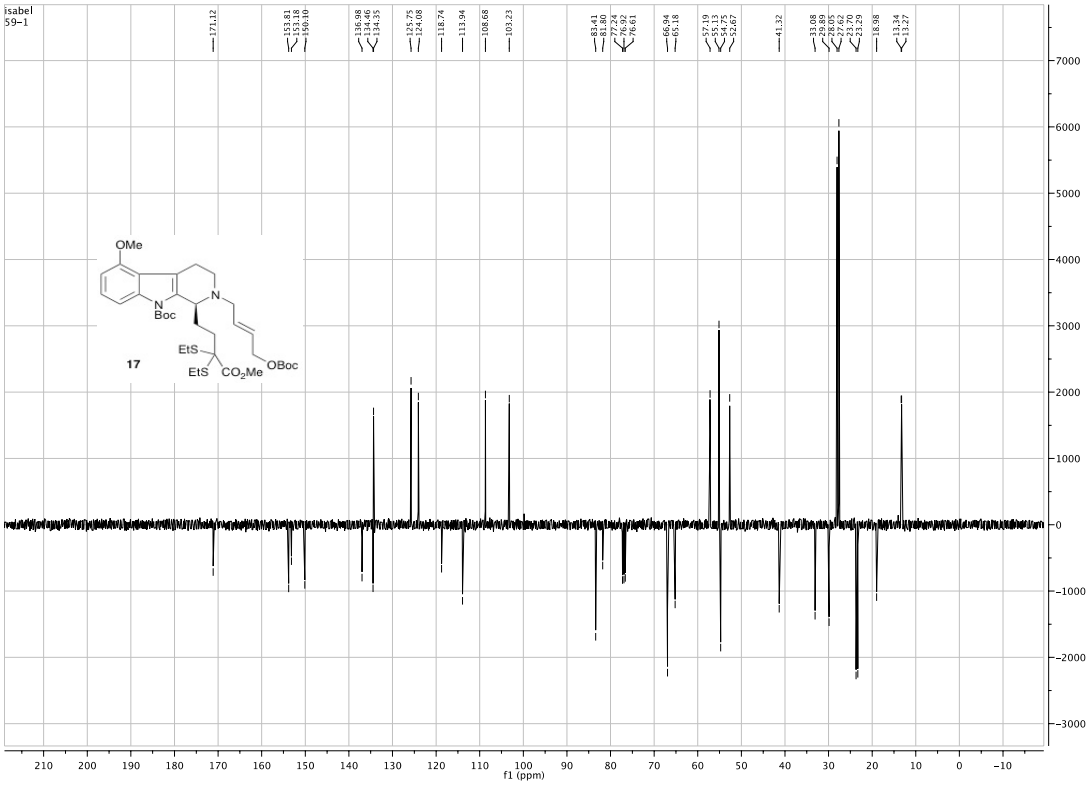
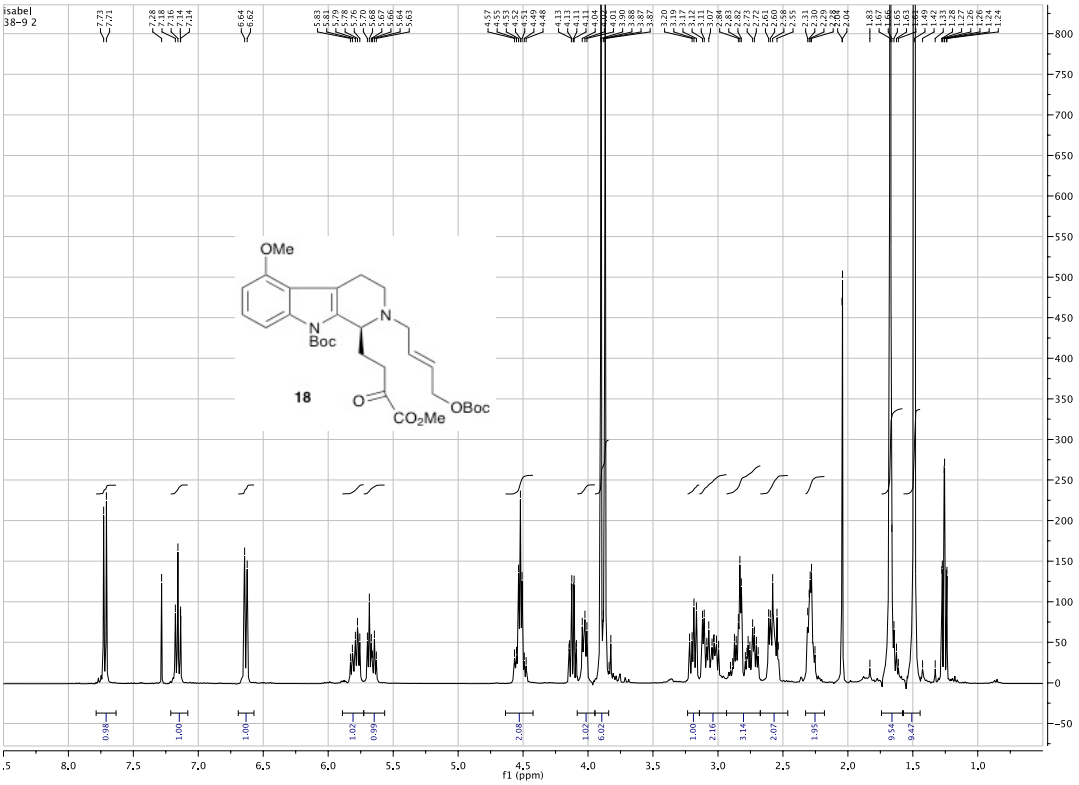
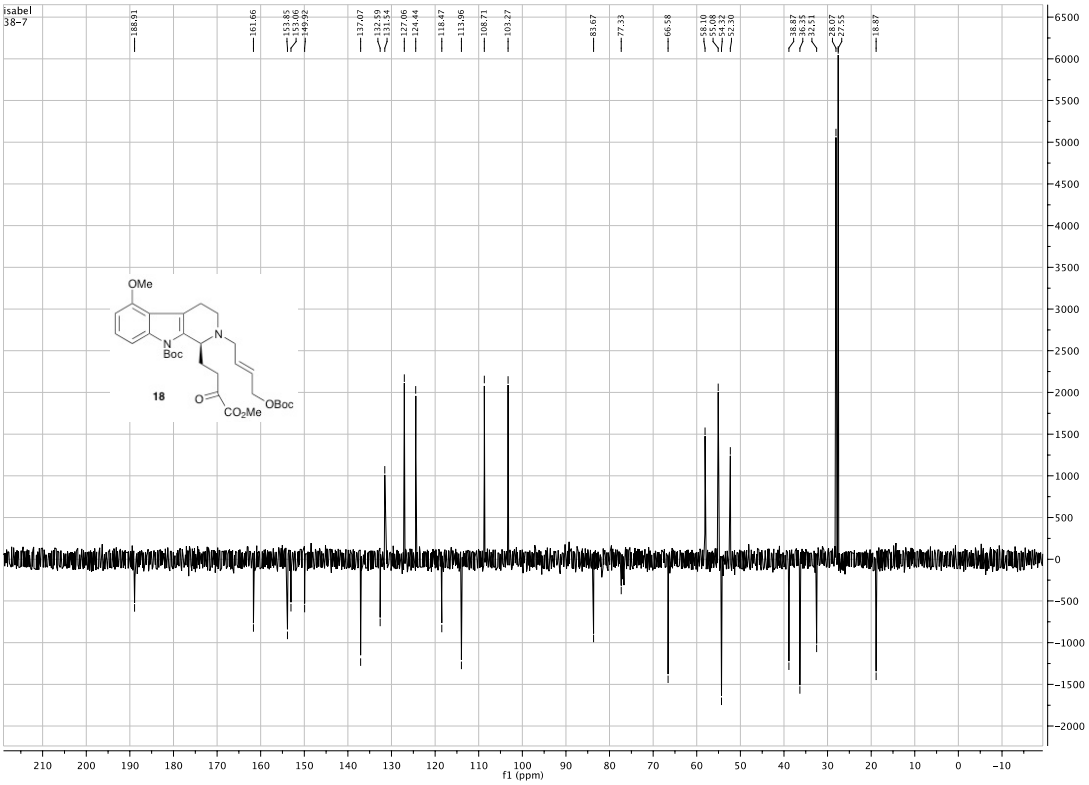
Boc
N
EtS
EtS
CO2Me
OBoc
17
f1 (ppm)


OMe
N
Boc
N
EtS
EtS
CO2Me
OBoc
17
f1 (ppm)


OMe
N
Boc
N
18
O
CO2Me
OBoc
f1 (ppm)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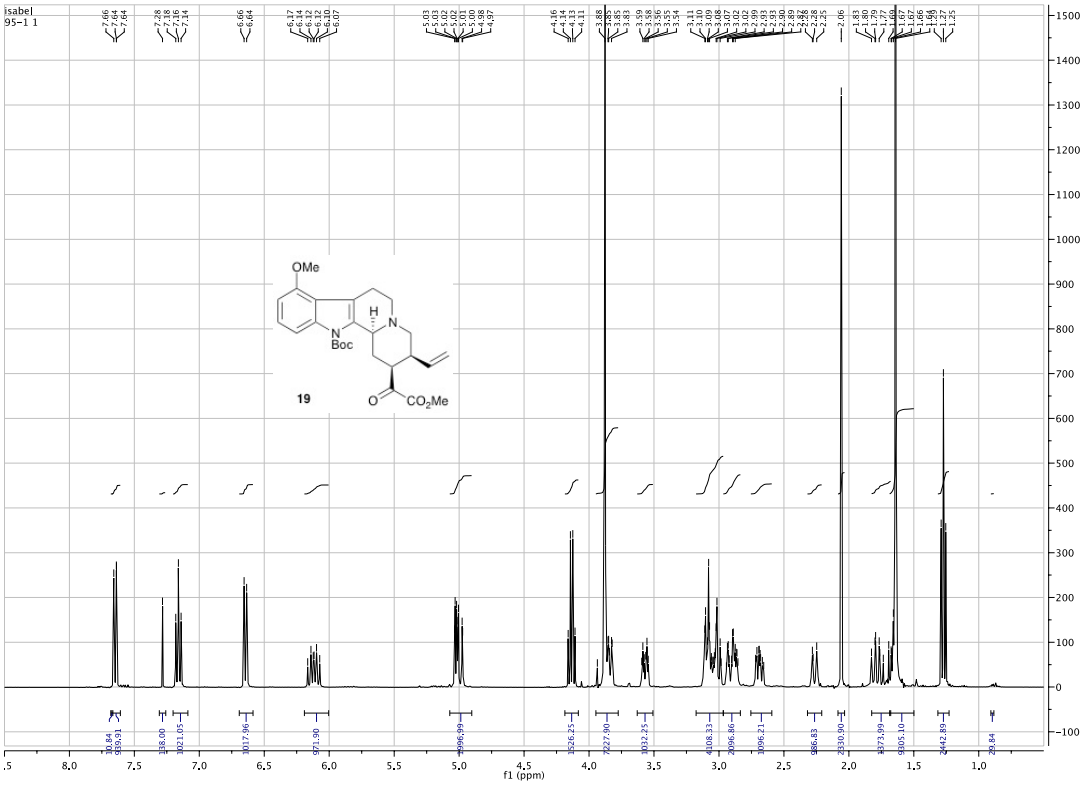
Boc
N
18
O
CO2Me
OBoc
f1 (ppm)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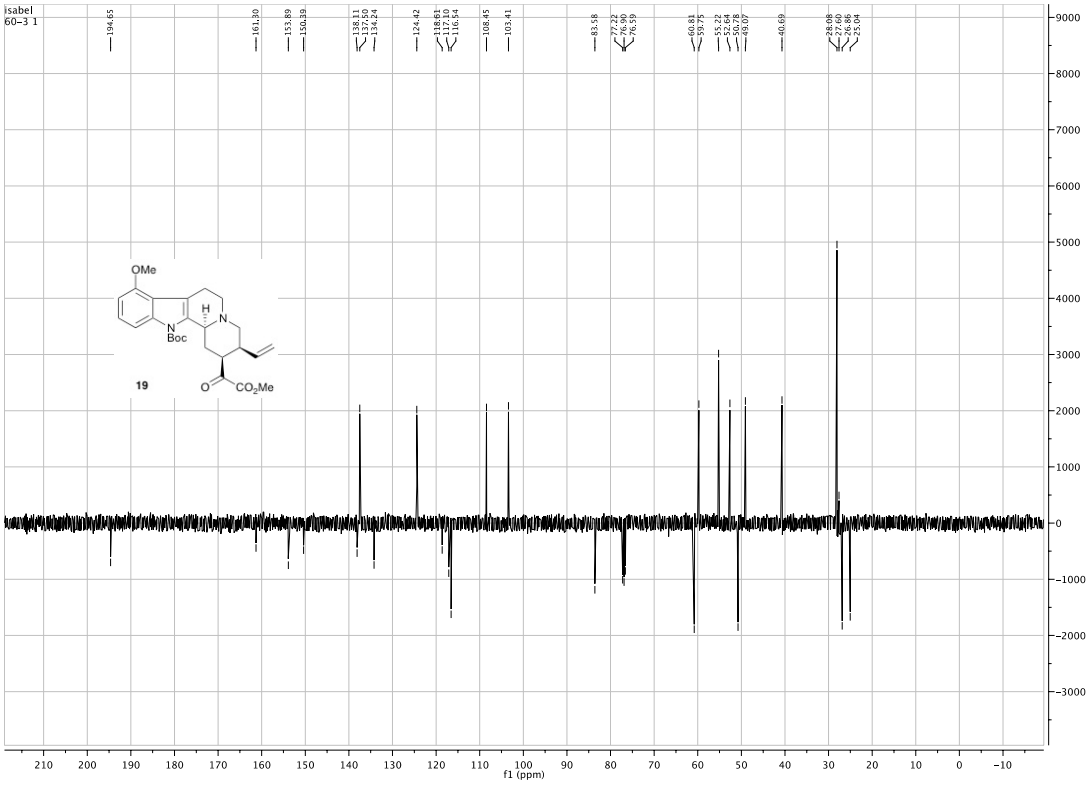
Boc
O
CO2Me
19
f1 (ppm)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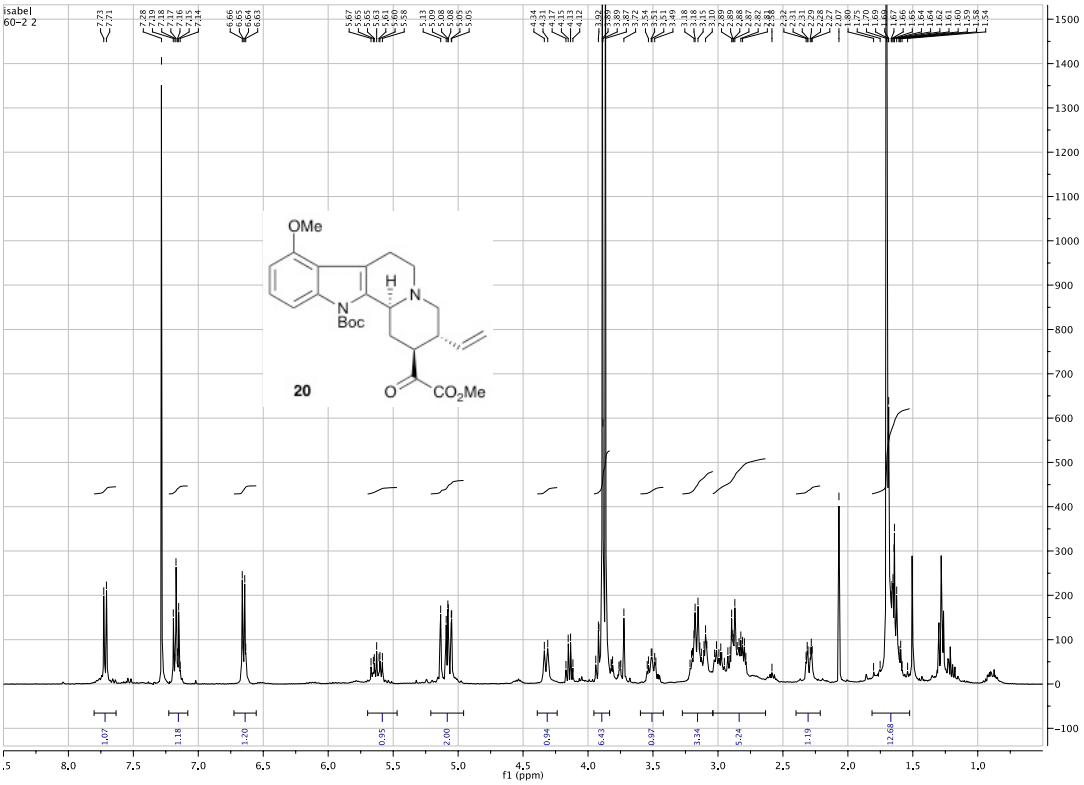
Boc
O
CO2Me
19
f1 (ppm)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Boc
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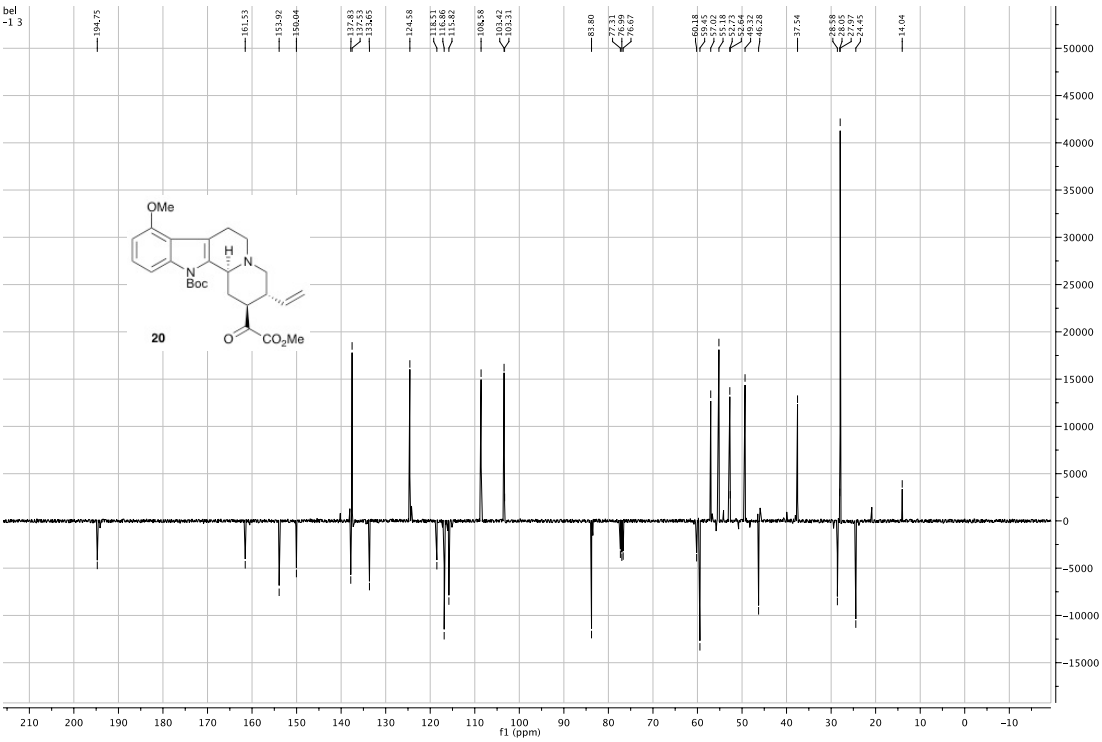
O
CO2Me
f1 (ppm)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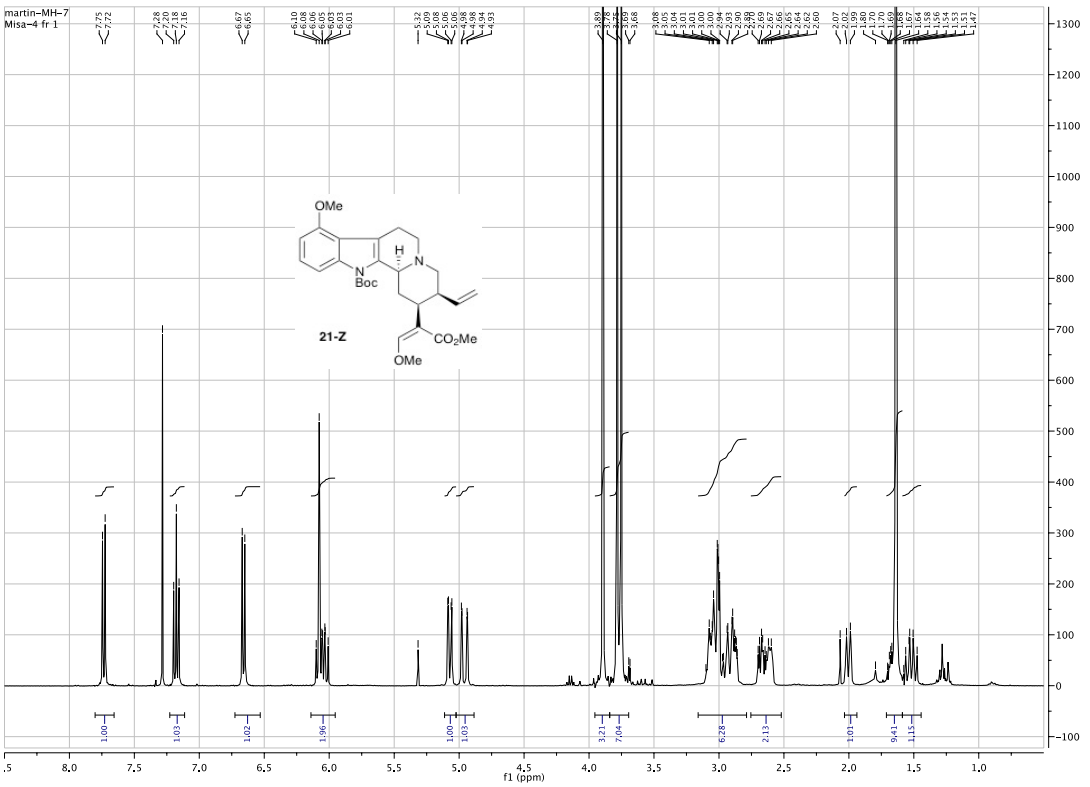
O
CO2Me
f1 (ppm)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Misa-4 fr 1
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Boc
H
N
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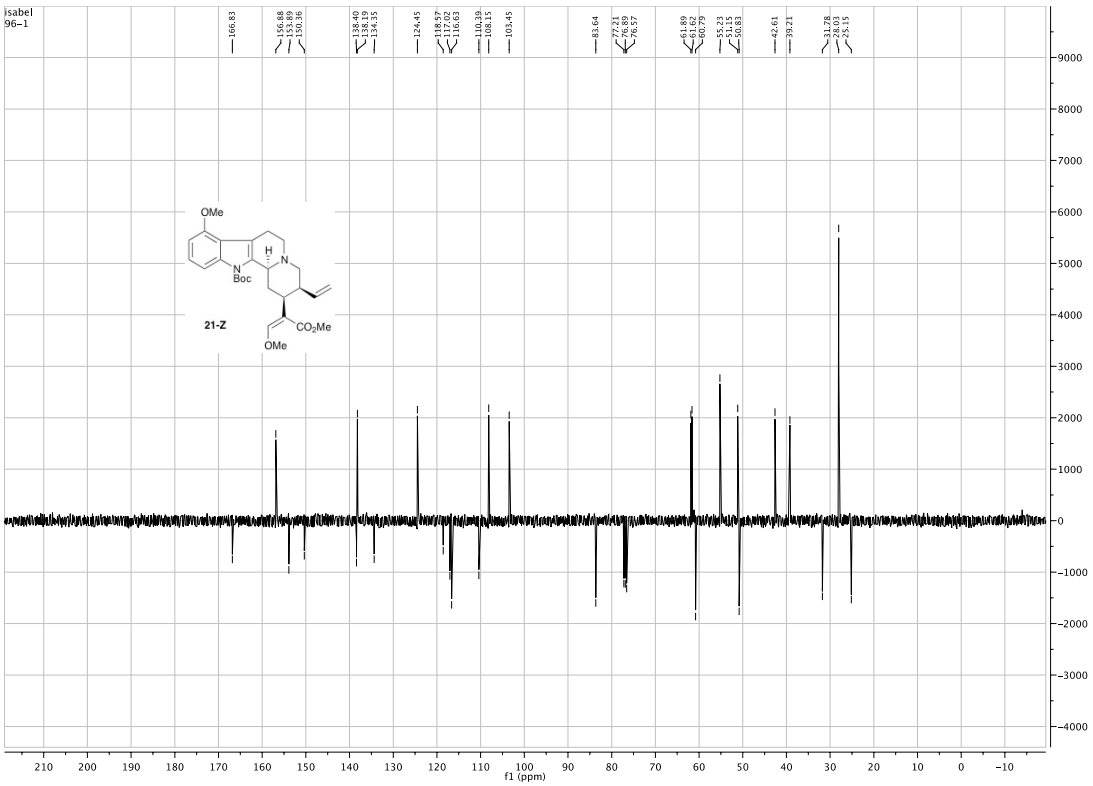
CO2Me
OMe
f1 (ppm)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OMe
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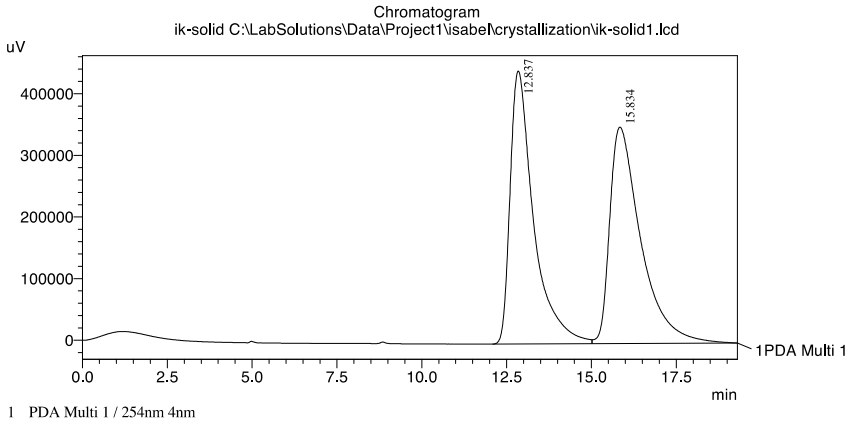
Boc
H
N
21-Z
CO2Me
OMe
f1 (ppm)

Crystallization of 21-Z

Crystals



1 PDA Multi 1 / 254nm 4nm

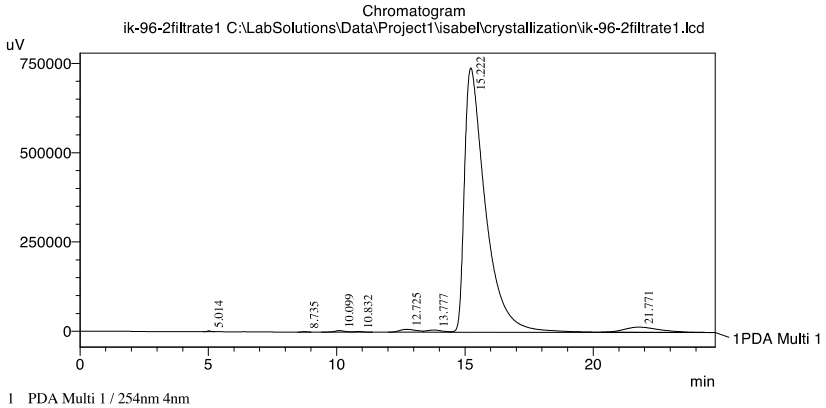
Results

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.837	21345498	443162	48.841	55.786
2	15.834	22358946	351229	51.159	44.214
Total		43704445	794390	100.000	100.000

Filtrate



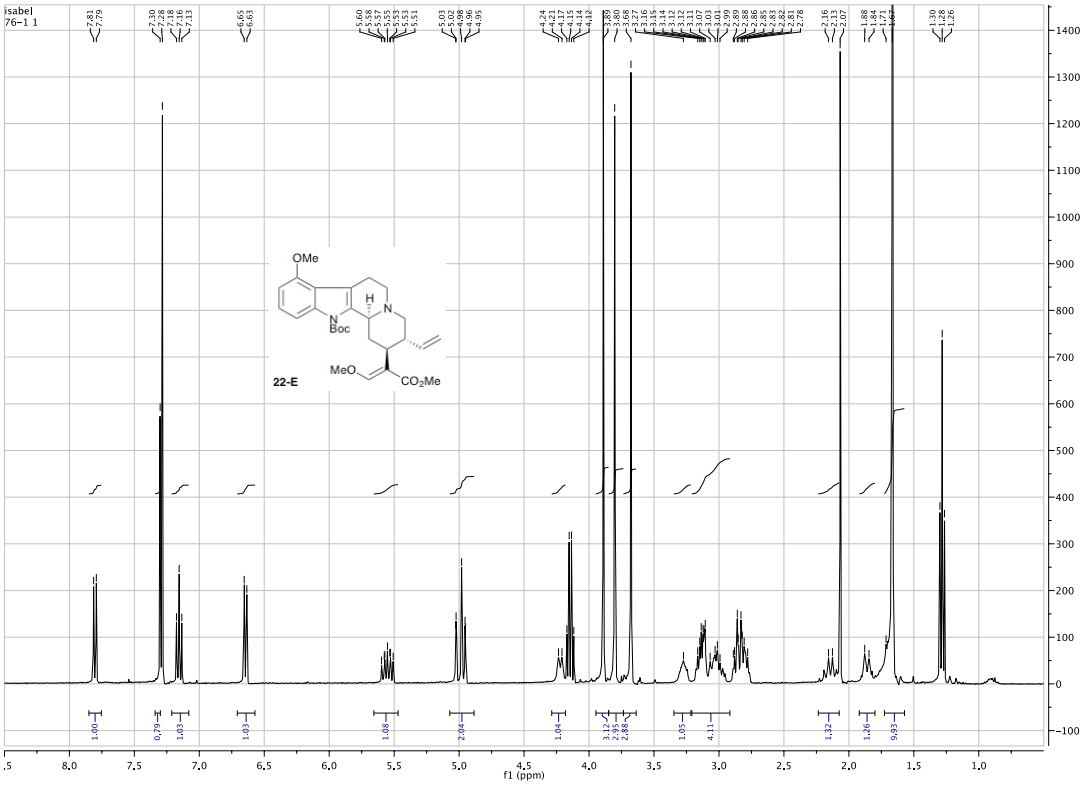
1 PDA Multi 1 / 254nm 4nm

Results

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.014	24703	2647	0.055	0.340
2	8.735	13398	1124	0.030	0.145
3	10.099	109698	4117	0.246	0.529
4	10.832	40001	1651	0.090	0.212
5	12.725	362111	7996	0.812	1.028
6	13.777	258775	6164	0.580	0.792
7	15.222	42439966	739912	95.148	95.124
8	21.771	1355662	14232	3.039	1.830
Total		44604315	777843	100.000	100.000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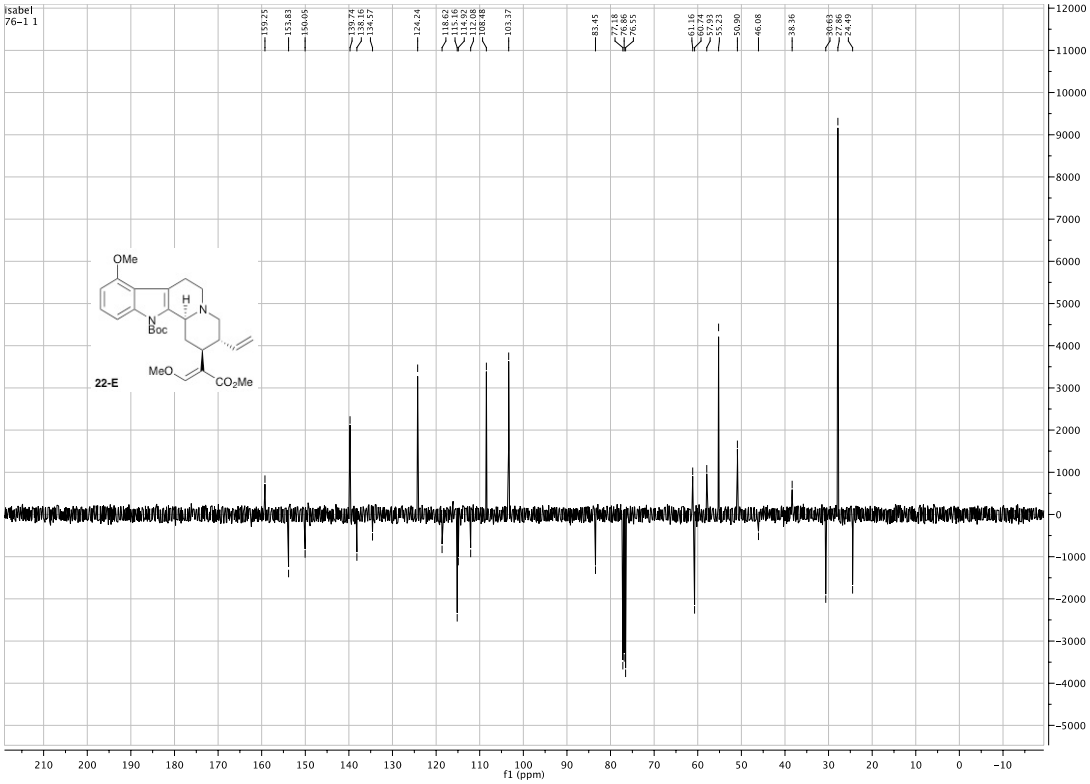
Boc
MeO
CO2Me
22-E
f1 (ppm)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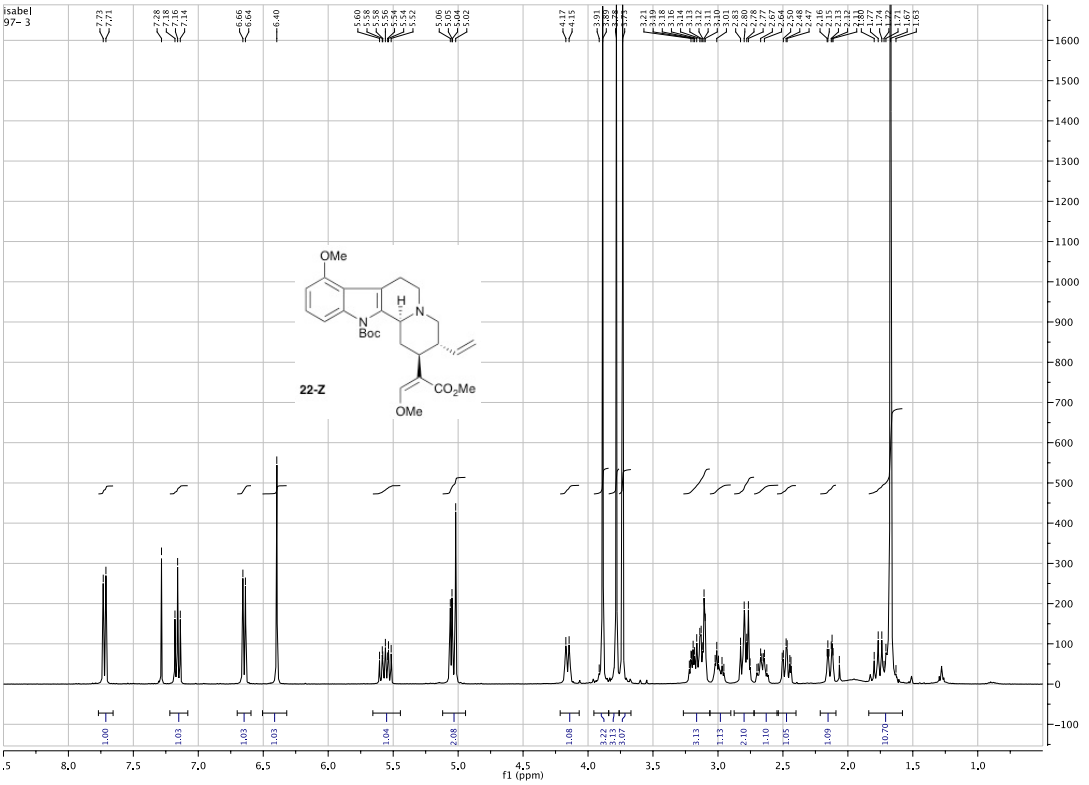
Boc
MeO
CO2Me
22-E
f1 (ppm)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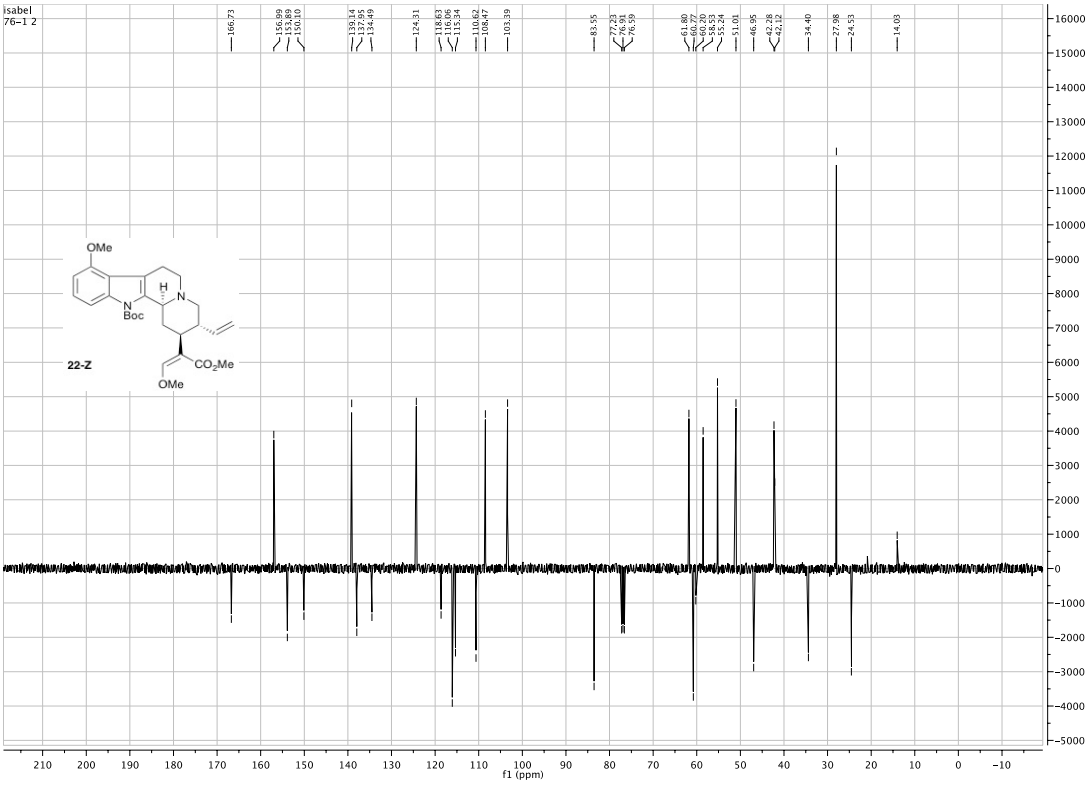
N
N
Boc
22-Z
CO2Me
OMe
f1 (ppm)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Boc
22-Z
CO2Me
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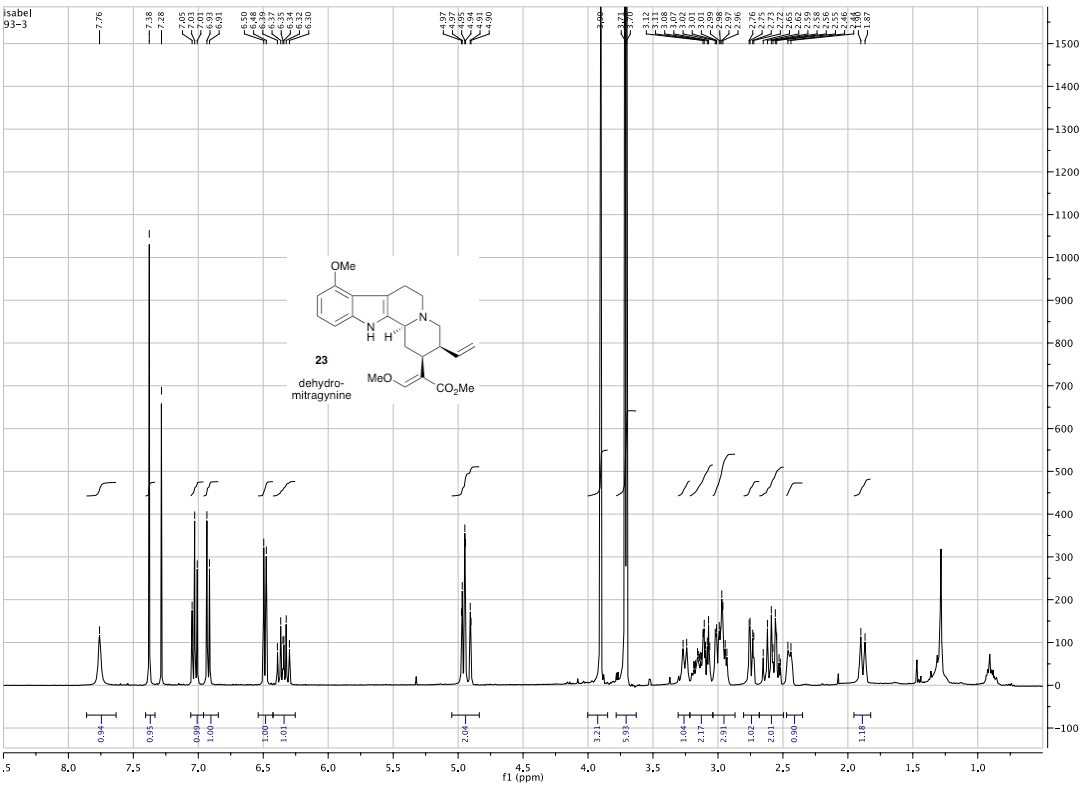
f1 (ppm)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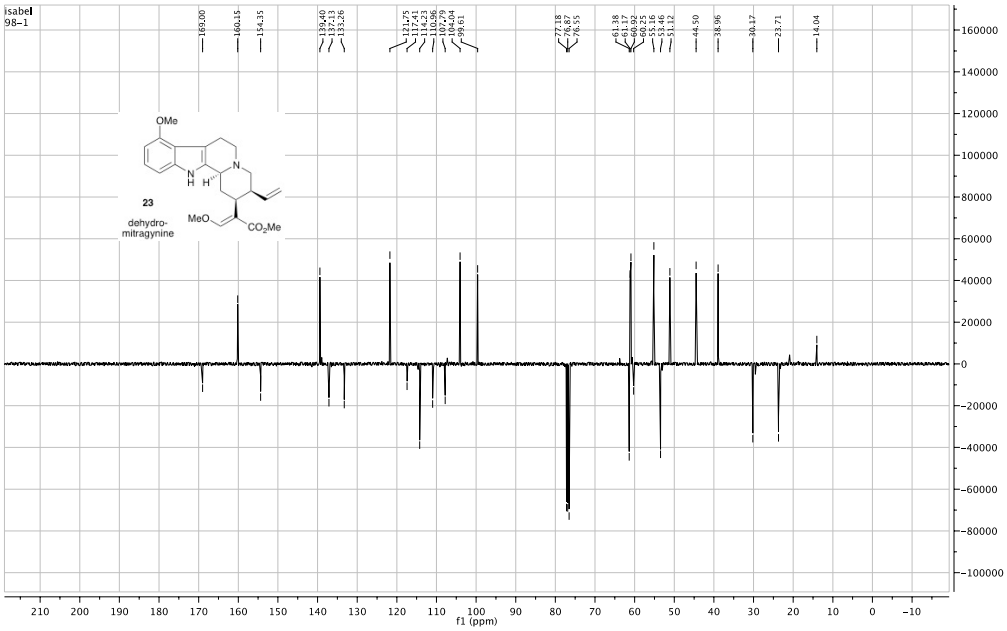
CO2Me
f1 (ppm)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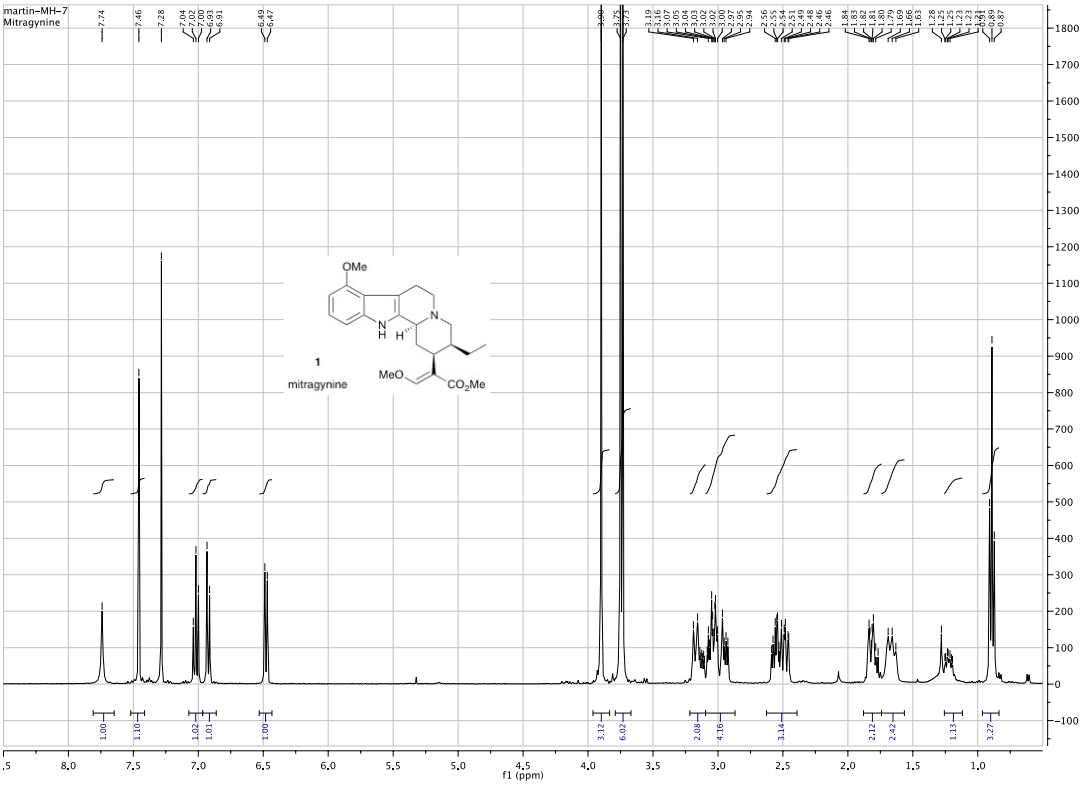
CO2Me
f1 (ppm)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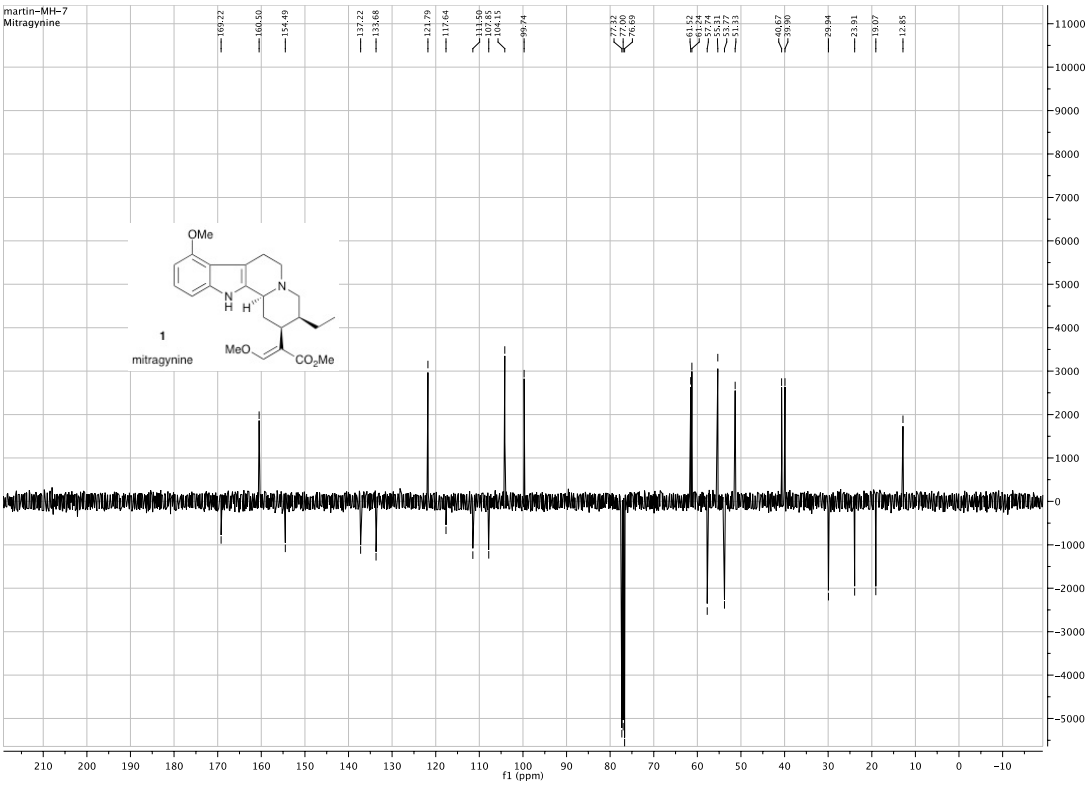
mitragynine
MeO
CO2Me
f1 (ppm)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Mitragynine
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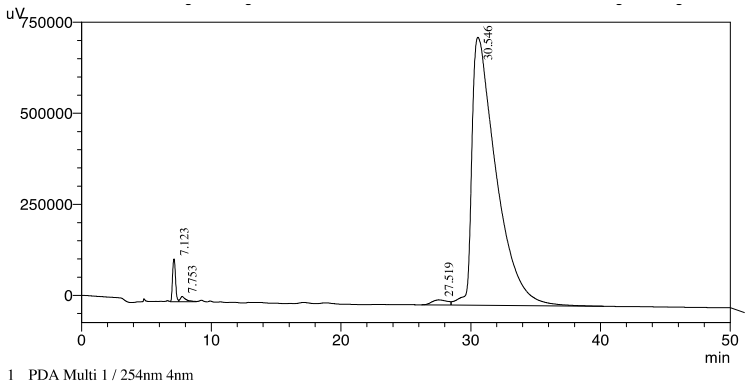
mitragynine
MeO
CO2Me
f1 (ppm)

mitragynine **1** 98% ee



1 PDA Multi 1 / 254nm 4nm

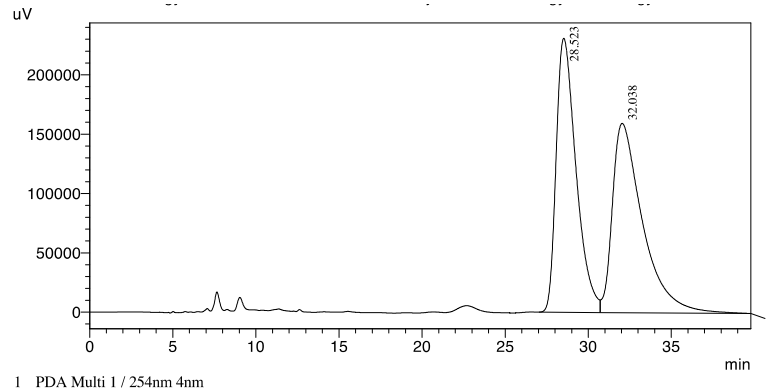
Results

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.123	1858161	117225	1.866	13.307
2	7.753	440884	14195	0.443	1.611
3	27.519	1144151	13761	1.149	1.562
4	30.546	96123327	735728	96.542	83.519
Total		99566524	880909	100.000	100.000

mitragynine **1** racemic



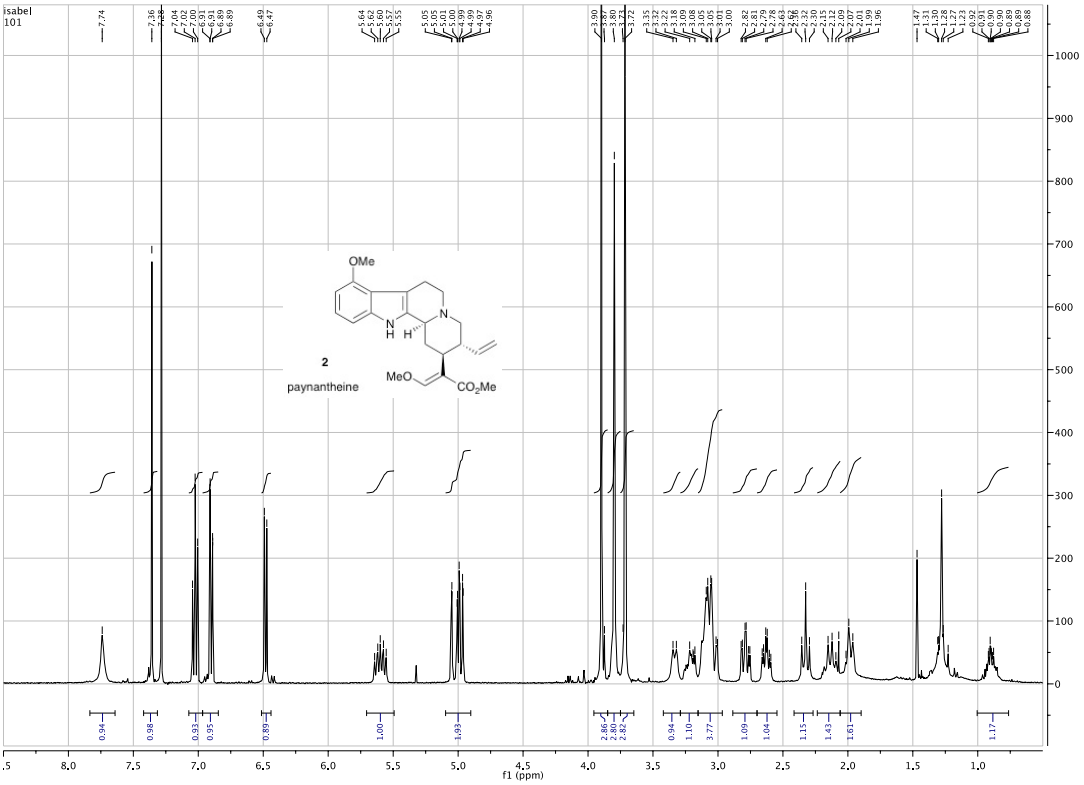
1 PDA Multi 1 / 254nm 4nm

Results

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	28.523	19245046	230922	48.821	59.146
2	32.038	20174198	159506	51.179	40.854
Total		39419244	390427	100.000	100.000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MeO
CO2Me
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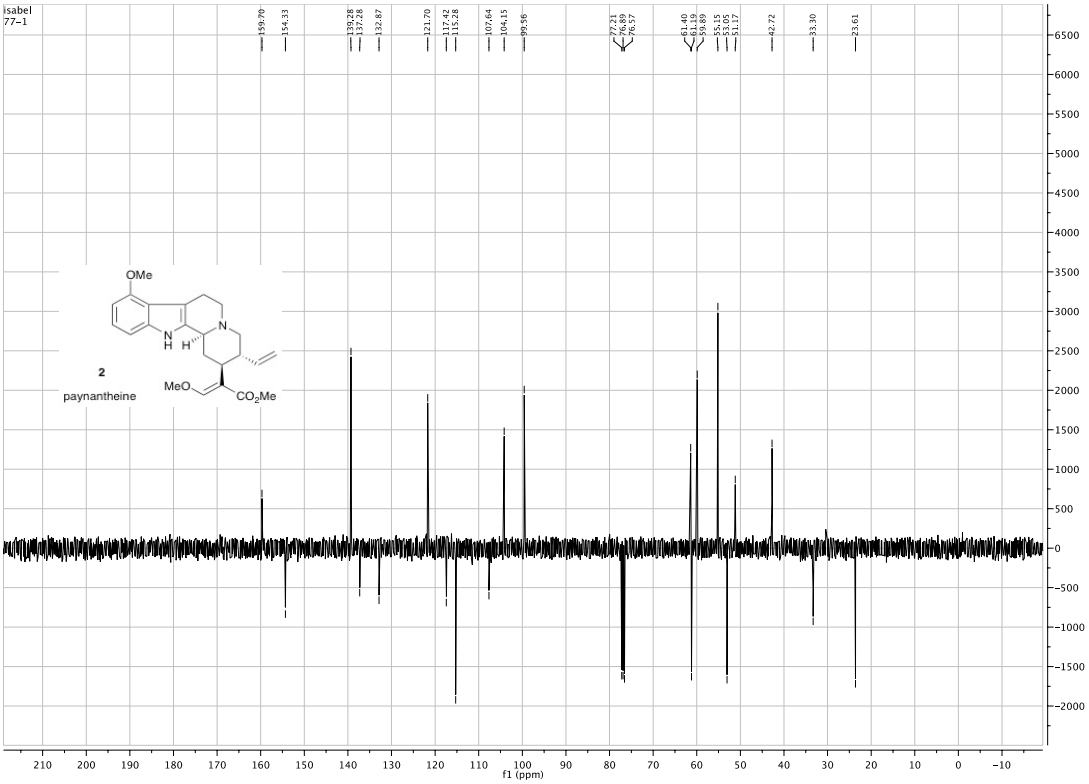
paynantheine
f1 (ppm)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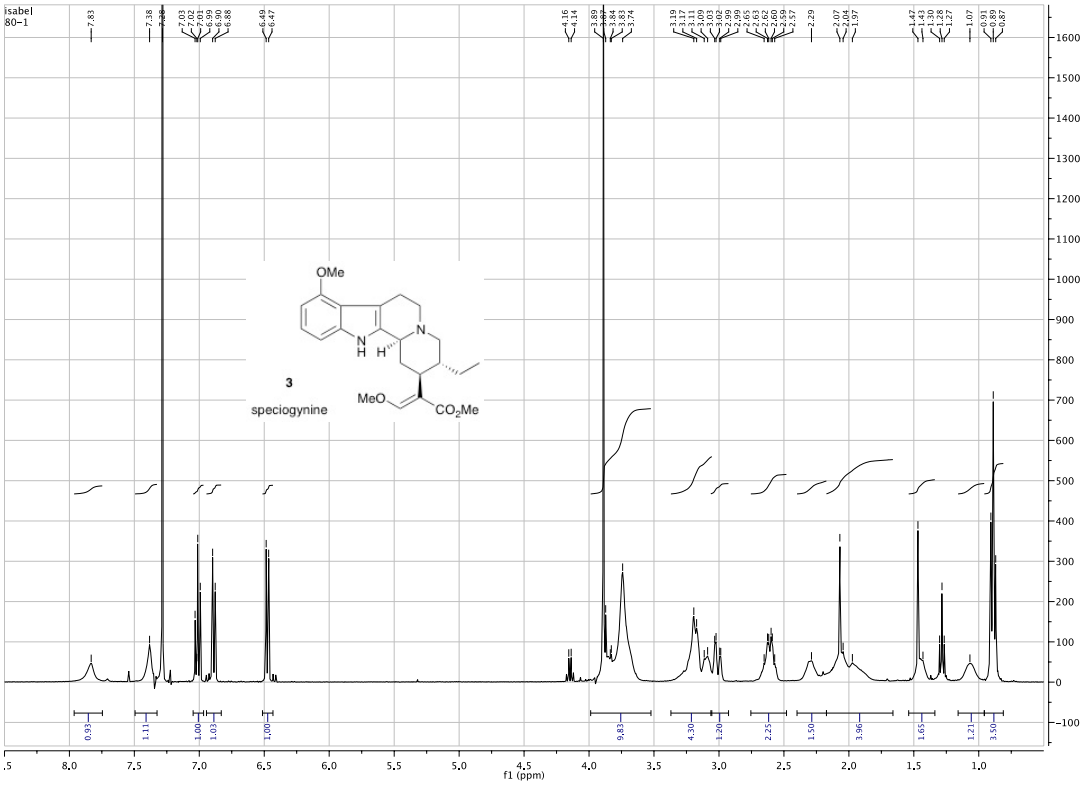
MeO
CO2Me
2
paynantheine
f1 (ppm)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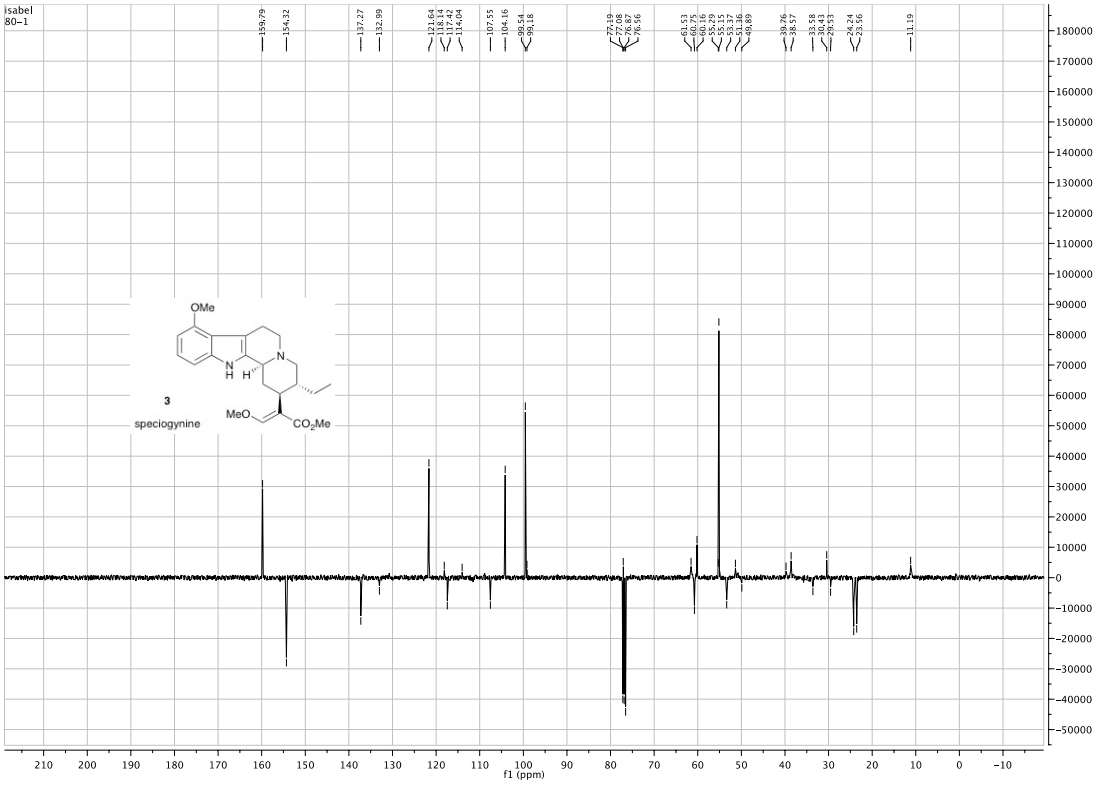
f1 (ppm)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3
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f1 (ppm)