Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

SUPPORTING INFORMATION

A unified synthesis of topologically diverse Aspidosperma alkaloids through divergent iminium-trapping

Marco V. Mijangos*[a] and Luis D. Miranda*[a]

[a] Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán, México City 04510, México.

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GENERAL INFORMATION

All reagents and solvents were obtained from Aldrich and Fluka. Solvents were used anhydrous, freshly distilled before use under an appropriate desiccant and nitrogen, unless specified otherwise. Dicloromethane, acetonitrile, N,N-diisopropylamine, methanol and dimethyl sulfoxide were dried by refluxing them with excess calcium hydride under nitrogen. THF, toluene and benzene were dried by refluxing them with excess sodium metal under nitrogen (using benzophenone as indicator).

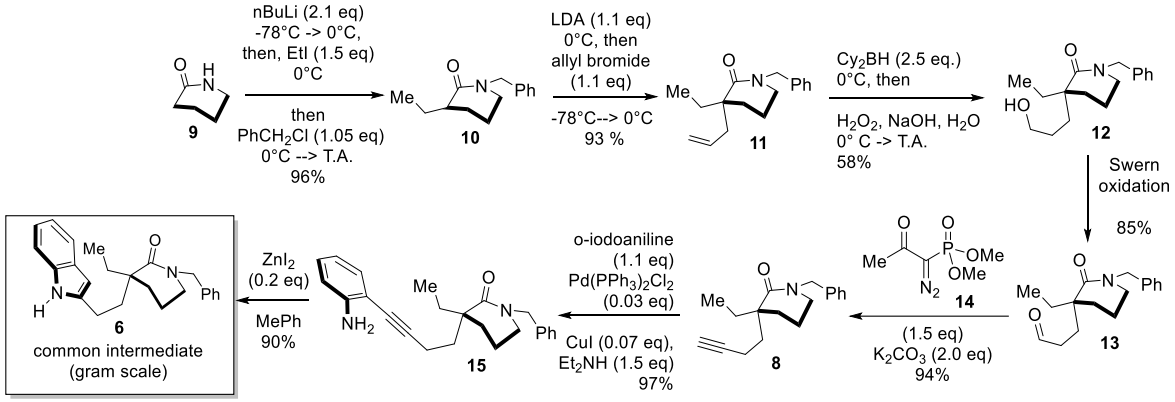
All laboratory material was oven dried at 130°C for 12 hours and chilled under nitrogen prior use. All reactions were carried out under a positive pressure of nitrogen unless otherwise specified. All reactions were magnetically stirred. All oxygen and/or water sensitive solutions where transferred via syringe. Reaction progress was monitored by analytical thin layer chromatography using GF silica plates. Visualization was achieved by shortwave UV light (254 nm) and by phosphomolybdic acid or vanillin TLC-staining.

Melting points were determined on a Fisher apparatus and are uncorrected. Flash column chromatography was conducted under silica gel (230-400 mesh) and mixtures of hexane, ethyl acetate, methanol or methylene chloride as eluents. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Fourier 300 MHz, Jeol, Eclipse 300 MHz or Bruker Avance III 400 MHz spectrometers using $CDCl_3$ or DSMO-d_6 as solvents. Chemical shifts are reported as parts per million downfield from an internal tetramethylsilane standard (δ = 0.0 for ^{1}H) or from solvent references. NMR coupling constants are reported in hertz (Hz). High-resolution mass spectra were recorded with an AccuTOFLC equipped with an ionSense DART controller ionization source. IR spectra were obtained on a Universal diamond ATR top-plat.

GRAPHICAL OVERVIEW

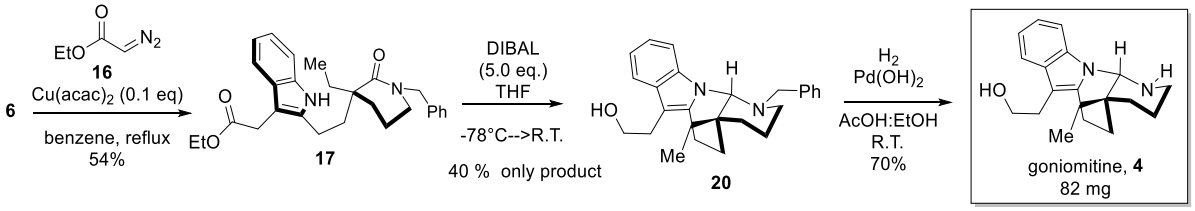
Synthetic sequence for the preparation of indole-valerolactam 6.

Experimental procedures found in pages 5 – 11.



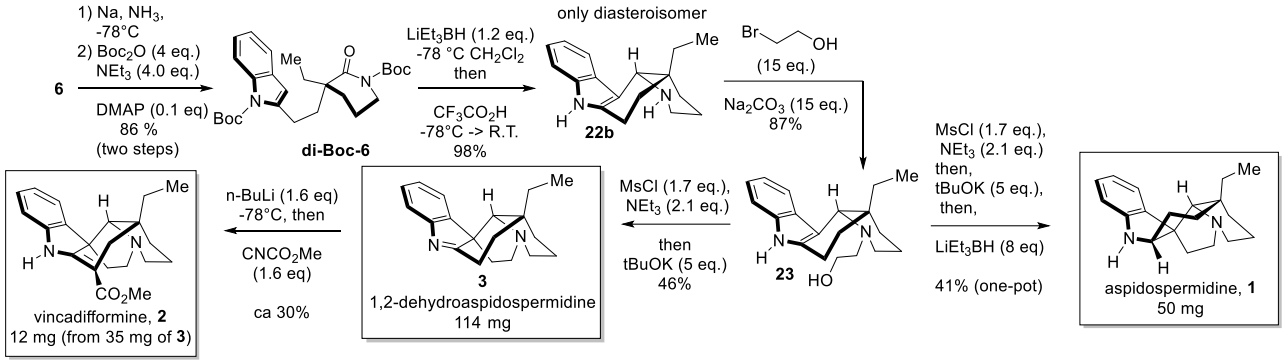
Synthetic sequence for the preparation of goniomitine (4) from indole-valerolactam 6.

Experimental procedures found in pages 12– 14.



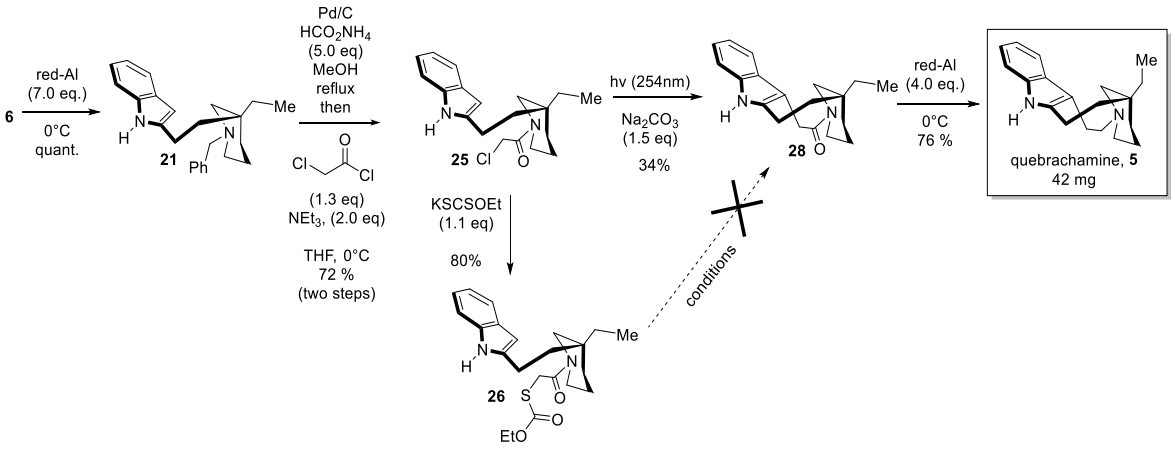
Synthetic sequence for the preparation of aspidospermidine (1), vincadifformine (2) and 1,2-dehydroaspidospermidine (3) from indole-valerolactam 6.

Experimental procedures found in pages 12 – 20.



Synthetic sequence for the preparation of quebrachamine (5) and xanthathe 26 from indole-valerolactam 6.

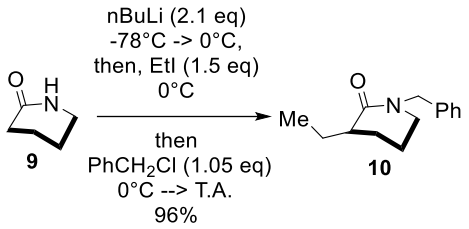
Experimental procedures found in pages 21 – 25.

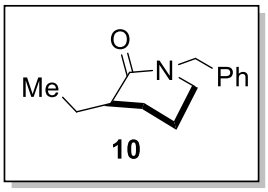


EXPERIMENTAL PROCEDURES

Intermediates for the synthesis of indole-valerolactam 6.

Valerolactam dialkylation





1-benzyl-3-ethylpiperidin-2-one

An anhydrous 500 mL round bottomed flask was charged with valerolactam (**9**, 5.0160 g, 50.0942 mmol, 1.0 eq.), then purged with nitrogen. Then, 167 mL (0.3 M) of freshly distilled THF were injected and valerolactam was readily dissolved. The flask was cooled in an ice-water bath for 20 minutes and then of n-BuLi 11M in hexane (9.6 mL, 105.1971 mmol, 2.1 eq.) was slowly added via syringe, and let to react maintaining the ice-water bath for 1 hour. Then, ethyl iodide was injected over a period of 5 min (11.84 g, 75.1413 mmol, 1.5 eq.) at 0 °C and allowed to react for 1 hour. The reaction mixture was then placed in an acetone/dry-ice bath and let chill for 15 min, then benzyl chloride (6.73 g, 52.5989 mmol) was slowly injected, the -78 °C bath was removed after 15 minutes and the mixture was allowed to reach room temperature for 3 hours. Then, the reaction was treated with 150 mL of saturated NH_4Cl solution, the phases were separated and the aqueous phase was back-extracted two times with EtOAc. All organic phases were put together and dried over Na_2SO_4, filtered, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (20% EtOAc/Hexane r.f. aprox: 0.35) to afford **10** (10.4505 g, 98% yield) as a pale yellow liquid.

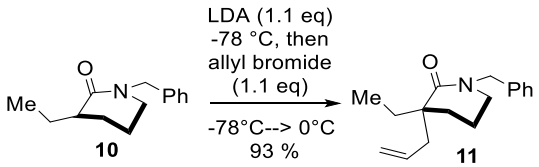
^{1}H NMR (300 MHz, Chloroform-d) δ 7.32 – 7.13 (m, 5H), 4.54 (s, 2H), 3.13 (dd, *J* = 7.1, 4.9 Hz, 2H), 2.37 – 2.16 (m, 1H), 2.93 – 1.73 (m, 3H), 1.70 – 1.45 (s, 3H), 0.93 (t, *J* = 7.5 Hz, 3H).

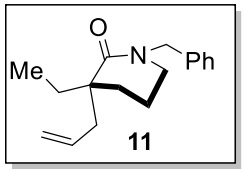
^{13}C NMR (75 MHz, Chloroform-d) δ 172.7, 137.7, 128.6, 128.0, 127.3, 50.3, 47.5, 43.0, 25.9, 25.0, 21.7, 11.6.

IR (cm^{-1}): 2932, 2868, 1631, 1491, 1447, 699.

HRMS: m/z (M+1) calculated for $C_{14}H_{20}NO$: 218.15448; found: 218.15459.

Enolate Allylation





3-allyl-1-benzyl-3-ethylpiperidin-2-one

An anhydrous 250 mL round bottomed flask was charged with freshly distilled N,N-diisopropylamine (3.7 mL, 2.6387 g, 25.9463 mmol, 1.1 eq.) and dissolved in 13 mL of freshly distilled THF (2.0 M), and chilled to -78 °C in an acetone/dry ice bath. Then, of n-BuLi 11M in hexane (2.4 mL, 25.9463 mmol, 1.1 eq.) was slowly added via syringe. The -78 °C bath was changed for an ice/water bath and the reaction was stirred for 20 minutes. Then, this LDA solution was chilled to -78 °C for 10 minutes and a solution of compound **10** (5.1258g, 23.5875 mmol, 1.0 eq.) in 62 mL of freshly distilled THF was slowly transferred via syringe under nitrogen, and let to react for 45 minutes at -78 °C. Then allyl bromide (2.3 mL, 3.24 g, 25.9463 mmol, 1.1 eq.) was slowly injected, and the reaction was allowed to reach room temperature over 3 hours. After the reaction was complete (as judged by TLC), it was treated with 150 mL of saturated NH_4Cl solution, the phases were separated and the aqueous phase was back-extracted two times with EtOAc. All organic phases were put together and dried over Na_2SO_4, filtered, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (10% EtOAc/Hexane, r.f. aprox: 0.35) to afford **11** (5.6460 g, 93% yield) as a colorless liquid.

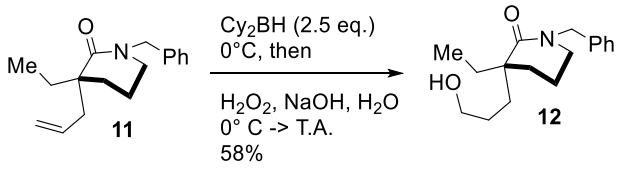
^{1}H NMR (300 MHz, Chloroform-d) δ 7.34 - 7.22 (m, 5H), 5.92 – 5.66 (m, 1H), 5.16 – 4.93 (m, 2H4.58 (d, J = 2.5 Hz, 2H) , 3.16 (ddd, J = 8.6, 4.4, 2.7 Hz, 2H), 2.55 (ddt, J = 13.6, 6.8, 1.4 Hz, 1H), 2.22 (ddt, J = 13.6, 8.0, 1.0 Hz, 1H), 1.89 – 1.62 (m, 6H), 1.53 (dq, J = 14.7, 7.4 Hz, 1H), 0.89 (t, J = 7.5 Hz, 3H).

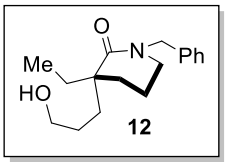
^{13}C NMR (75 MHz, Chloroform-d) δ 174.5, 137.8, 135.0, 128.6, 128.1, 127.3, 117.8, 50.6, 47.8, 45.3, 43.4, 31.6, 28.9, 19.8, 8.9.

IR (cm^{-1}): 2938, 2876, 1635, 1490, 1453, 1352, 1196, 913, 737, 701.

HRMS: m/z (M+1) calculated for $C_{17}H_{24}NO$: 258.18579; found 258.18583.

Hydroboration/oxidation





1-benzyl-3-ethyl-3-(3-hydroxypropyl)piperidin-2-one

A solution of $BH_3{\cdot}SMe_2$ (7.9 mL, 6.3547 g, 83.6480 mmol, 2.5 eq.) in 95 mL of freshly distilled THF, was chilled to 0 °C (ice/water bath), and then, cyclohexene (17.2 mL, 13.8805 g, 167.2761 mmol, 5.0 eq.) was slowly injected, and let it react for 1 hour at 0 °C. Then, a solution of alkene **11** (8.6114g, 33.4592 mmol, 1.0 eq.) in freshly distilled THF (50 mL) was slowly injected to the borane solution at 0 °C. The reaction mixture was allowed to reach room temperature overnight. The resulting solution is chilled to 0 °C (ice/water bath) and, very carefully, aqueous NaOH 2M (100 mL) was slowly added to the reaction flask (CAUTION: very exothermic reaction, gas evolution, use a well vented fume hood), followed by the slow and careful addition of aqueous 30% H_2O_2 (CAUTION: very exothermic reaction, gas evolution, use a well vented fume hood). The oxidation process was allowed to reach room temperature an proceeded for 24 hours. Then, the solids were filtrated, and the liquid phases were separated. The aqueous phase was extracted two times with EtOAc. All organic phases were put together and dried over Na_2SO_4, filtered, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (30 → 70% EtOAc/Hexane. 70% EtOAc/Hexane r.f. aprox: 0.35) to afford a colorless liquid which needed to be redisolved in EtOAc and washed with water, to obtain after drying and removal of the volatiles pure **12** (5.3444 g, 58% yield) as a colorless liquid.

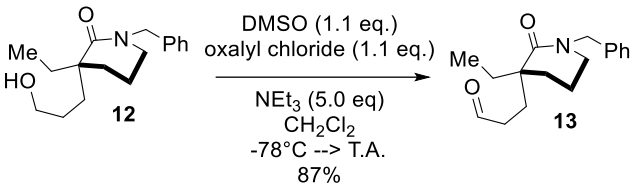
^{1}H NMR (300 MHz, Chloroform-d) δ 7.33 – 7.21 (m, 5H), 4.66 (d, J = 14.5 Hz, 1H), 4.48 (d, J = 14.5 Hz, 1H), 3.59 (m, 2H), 3.18 (m, 2H), 1.99 – 1.38 (m, 6H), 1.37 – 1.13 (m, 2H), 0.87 (t, J = 7.5 Hz, 3H).

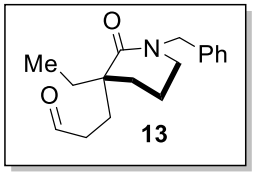
^{13}C NMR (75 MHz, Chloroform-d) δ 175.4, 137.6, 128.7, 128.2, 127.4, 62.9, 50.7, 47.8, 44.9, 35.6, 34.2, 31.9, 29.0, 27.8, 25.5, 24.2, 19.8, 8.7.

IR (cm^{-1}): 3405, 2938, 2868, 1610, 1491, 1449, 1196, 736, 700.

HRMS: m/z (M+1) calculated for $C_{17}H_{26}NO_2$: 276.19635; found 276.19698.

Swern Oxidation





3-(1-benzyl-3-ethyl-2-oxopiperidin-3-yl)propanal

A solution of anhydrous DMSO (1.51 mL, 1.66 g, 21.00 mmol, 1.1 eq.) in freshly distilled CH_2Cl_2 (45 mL) was cooled to -78 °C (acetone/dry ice) and oxalyl chloride (1.81 mL, 2.72 g, 21.00 mmol, 1.1 eq.) was slowly added via syringe. After 5 minutes of stirring at -78 °C, a solution of alcohol **12** (5.2593 g, 19. 098 mmol, 1.0 eq.) in freshly distilled CH_2Cl_2 (45 mL) was slowly added to the dimethyl chlorosulphonium solution maintaining the system at -78 °C and reacting for 15 minutes. Then triethylamine (13.4 mL, 9.8 g, 95.49 mmol, 5.0 eq.) was slowly added and the reaction was stirred for further 10 minutes at -78 °C, and then let reach room temperature for 30 minutes. When the reaction was complete (as judged by TLC), it was treated with 100 mL of saturated NH_4Cl solution, the phases were separated and the aqueous phase was back-extracted two times with CH_2Cl_2. All organic phases were put together and dried over Na_2SO_4, filtered, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (35% EtOAc/Hexane, r.f. aprox: 0.35) to afford **13** (4.590 g, 87 % yield) as a pale yellow liquid.

^{1}H NMR (300 MHz, Chloroform-d) δ 9.76 (t, J = 1.6 Hz, 1H), 7.34 - 7.20 (m, 5H), 4.64 (d, J = 14.5 Hz, 1H), 4.46 (d, J = 14.5 Hz, 1H), 3.18 (m, 2H), 2.67 – 2.38 (m, 2H), 2.02 - 1.71 (m, 6H), 1.63 – 1.49 (m, 2H), 0.87 (t, J = 7.5, 3H).

^{13}C NMR (75 MHz, Chloroform-d) δ 202.5, 174.1, 137.6, 128.7, 128.1, 127.4, 50.6, 47.8, 44.3, 39.8, 31.0, 30.2, 29.8, 19.6, 8.6.

IR (cm^{-1}): 2936, 2874, 1721, 1625, 1491, 1449, 1351, 1260, 1195, 955, 735, 700.

HRMS: m/z (M+1) calculated for $C_{17}H_{24}NO_2$: 274.18070; found 274.18065.

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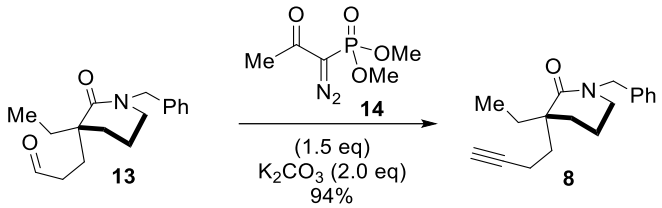
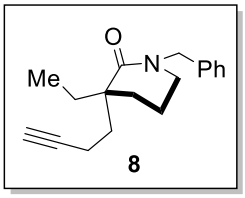
Ohira-Bestmann Homologation





1-benzyl-3-(but-3-yn-1-yl)-3-ethylpiperidin-2-one

NOTE: Ohira-Bestmann diazophosphonate **14** was prepared using a literature procedure.[1] To a solution of aldehyde **13** (4.4341 g, 16.2201 mmol, 1.0 eq.) in freshly distilled MeOH (200 mL), was added anhydrous K_2CO_3 (4.6741 g, 32.4403 mmol, 2.0 eq.) under nitrogen, and stirred vigorously for 10 minutes. Then, a solution of diazophophonate **14** (4.6741 g, 24.3302 mmol, 1.5 eq.) in freshly distilled MeOH (30 mL) was slowly added via syringe, and the reaction mixture was stirred overnight (12 hours aprox.). When the reaction was complete (as judged by TLC), the volatiles were removed under reduced pressure and the residue partitioned in EtOAc (150 mL) and water (150 mL), the aqueous layer was back-extracted two times with EtOAc. All organic phases were put together and dried over Na_2SO_4, filtered, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (15% EtOAc/Hexane, r.f. aprox: 0.35) to afford **8** (4.110 g, 94 % yield) as a colorless liquid.

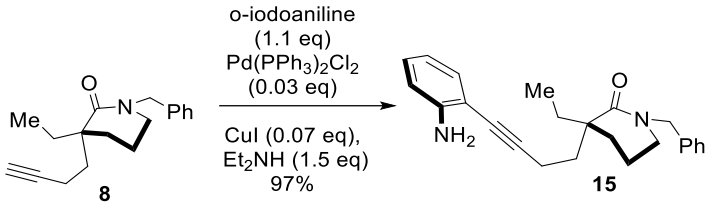
^{1}H NMR (300 MHz, Chloroform-d) δ 7.34 – 7.30 (m, 2H), 7.27 – 2.23 (m, 3H), 4.62 (d, J = 14.5 Hz, 1H), 4.53 (d, J = 14.5 Hz, 1H), 3.19 (t, J = 5.7 Hz, 2H), 2.25 (dddd, J = 9.1, 6.1, 3.6, 2.7 Hz, 2H), 2.01 (ddd, J = 13.6, 10.0, 6.4 Hz, 1H), 1.94 (t, J = 2.7 Hz, 1H), 1.85 - 1.71 (m, 6H), 1.56 (dq, J = 13.7, 7.4 Hz, 1H), 0.89 (t, J = 7.5 Hz, 3H).

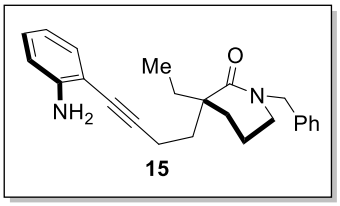
^{13}C NMR (75 MHz, Chloroform-d) δ 173.9, 137.6, 128.5, 128.0, 127.3, 84.8, 68.2, 50.5, 47.6, 44.8, 37.3, 31.0, 29.3, 19.7, 14.1, 8.6.

IR (cm^{-1}): 3296, 3234, 2937, 2874, 2116, 1626, 1490, 1448, 1352, 1258, 1193, 734, 799, 630.

HRMS: m/z (M+1) calculated for $C_{18}H_{24}NO$: 270.18579; found 270.18650.

Sonogashira Coupling





3-(4-(2-aminophenyl)but-3-yn-1-yl)-1-benzyl-3-ethylpiperidin-2-one

A solution of terminal alkyne **8** (3.3426 g, 12.4085 mmol, 1.0 eq.), and *o*-iodoaniline (2.6594 g, 13.6493 mmol, 1.1 eq.) in anhydrous DMF (38 mL), was degassed by the freeze-pump-thaw method (6 cycles, using an acetone/dry ice bath for freezing, and a room temperature water bath for thawing). Then, a mixture of $Pd(PPh_3)_2Cl_2$ (0.2666 g, 0.3723 mmol, 0.03 eq.) and CuI (0.1688 g, 0.8686 mmol, 0.07 eq.) was added under nitrogen, and the Et_2NH (2.94 mL, 1.3682 g, 18.6127 mmol, 1.5 eq.) was injected. The reaction was put in a pre-heathed oil bath at 50-55 °C and stirred for 2 hours. After the reaction was complete (as judged by TLC), the mixture was partitioned in EtOAc (150 mL) and satureated NH_4Cl (150 mL), and the organic layer was washed five times with water (100 mL). The organic phase was dried over Na_2SO_4, filtered, the solvent removed under reduced pressure and the residue purified by flash column chromatography (30% EtOAc/Hexane, r.f. aprox: 0.35) to afford **15** (4.430 g, 97 % yield) as a yellow syrup.

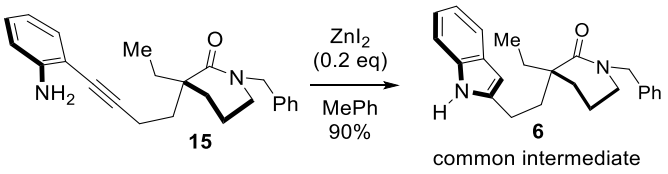
^{1}H NMR (300 MHz, Chloroform-d, rotamer mixture) δ 7.34 - 7.20 (m, 12H), 7.09 - 7.02 (m, 2H), 6.69 - 6.60 (m, 4H), 4.68 (d, J = 14.5 Hz, 1H), 4.62 (d, J = 14.5 Hz, 1H), 4.50 (d, J = 14.5 Hz, 1H), 4.45 (d, J = 14.5 Hz, 1H), 4.24 (br, 1H), 3.21 - 3.14 (m, 2H), 2.62 - 2.43 (m, 2H), 2.31 (t, J = 8.0 Hz, 1H), 2.19 - 2.09 (m, 2H), 1.91 - 1.67 (m, 10H),), 1.65 - 1.50 (m, 2H), 1.28 – 1.18 (m, 1H), 0.90 (t, J = 7.5 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H).

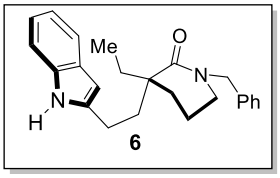
^{13}C NMR (75 MHz, Chloroform-d, rotamer mixture) δ 174.2, 174.0, 148.0, 137.7, 132.1, 129.0, 128.7, 128.1, 127.4, 117.8, 114.2, 108.8, 95.7, 50.6, 47.8, 45.0, 44.9, 37.8, 37.0, 31.5, 31.1, 29.3, 19.9, 19.7, 15.0, 8.8, 8.7.

IR (cm^{-1}): 3449, 3281, 2936, 2873, 1611, 1490, 1451, 1195, 734, 798.

HRMS: m/z (M+1) calculated for $C_{17}H_{24}NO_2$: 361.22799; found 361.22740.

Intramolecular alkyne hydro-amination





3-(2-(1*H*-indol-2-yl)ethyl)-1-benzyl-3-ethylpiperidin-2-one

To a solution of alkynilaniline **15** (6.1941 g, 17.1824 mmol, 1.0 eq.) in freshly distilled toluene (80 mL) was added ZnI_2 (1.0969 g, 3.4365 mmol) under nitrogen and heated to reflux for 1 hour. After the reaction was complete (as judged by TLC), the reaction was treated with water (100 mL), and the organic layer was dried over Na_2SO_4, filtered, the solvent removed under reduced pressure and the residue purified by flash column chromatography (30% EtOAc/Hexane, r.f. aprox: 0.35) to afford indole **6** (5.5747 g, 90 % yield) as a yellow syrup.

^{1}H NMR (300 MHz, Chloroform-d) δ 8.81 (br, 1H), 7.54 (d, J = 6.8 Hz, 1H), 7.36 – 7.22 (m, 6H), 7.17 – 6.99 (m, 2H), 6.23 (s, 1H), 4.70 (d, J = 14.6 Hz, 1H), 4.55 (d, J = 14.6 Hz, 1H), 3.23 (m, 2H), 2.88 (ddd, J = 14.4, 10.8, 6.0 Hz, 1H), 2.69 (ddd, J = 14.8, 10.7, 4.5 Hz, 1H), 2.23 (ddd, J = 13.7, 10.9, 4.5 Hz, 1H), 1.94 – 1.63 (m, J = 32.6 Hz, 8H), 1.28 (m, 1H), 0.93 (t, J = 7.5 Hz, 3H).

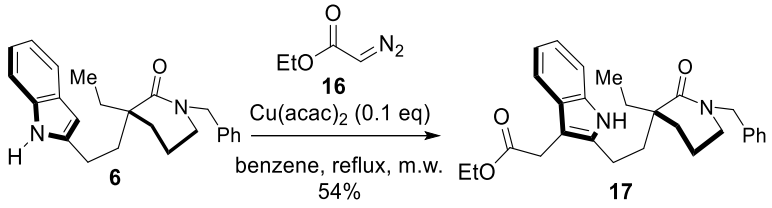
^{13}C NMR (75 MHz, Chloroform-d) δ 175.1, 140.2, 137.6, 136.3, 128.8, 128.1, 127.5, 120.9, 119.7, 119.4, 110.7, 99.1, 50.8, 47.9, 45.6, 38.2, 31.7, 29.2, 24.0, 19.7, 8.7.

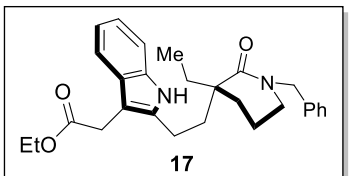
IR (cm^{-1}): 3270, 2939, 2871, 1609, 1491, 1454, 1348, 1286, 1198, 781, 738, 698.

HRMS: m/z (M+1) calculated for $C_{17}H_{24}NO_2$: 361.22799; found 361.22871.

Intermediates for the synthesis of Goniomitine (4), from indole-valerolactam 6.

Catalytic Indole C(3)-H carbene insertion





ethyl 2-(2-(2-(1-benzyl-3-ethyl-2-oxopiperidin-3-yl)ethyl)-1*H*-indol-3-yl)acetate

A solution of common intermediate **6** (0.3105 g, 0.8613 mmol, 1.0 eq.) in freshly distilled benzene (4.5 mL) in a CEM microwave vial, was degassed by the freeze-pump-thaw method (5 cycles), then $Cu(acac)_2$ (0.3105 g, 0.0861 mmol, 0.1 equiv.) was charged under nitrogen. Thereupon, ethyl diazoacetate 87% in CH_2Cl_2 (0.156 mL, 1.2920 mmol, 1.5 eq) was added via syringe, and the reaction was heated under microwave assistance at 85 °C for 1 hour. Then, another portion of ethyl diazoacetate 87% in CH_2Cl_2 (0.156 mL, 1.2920 mmol, 1.5 eq) was added via syringe, and the reaction was heated under microwave assistance at 85 °C for another 1 hour. Then, the volatiles were removed under reduced pressure, and the residue purified by flash column chromatography (25 % EtOAc/Hexane r.f. aprox: 0.30) to afford indoleacetate **17** (0.2076 g, 54 % yield) as a yellow syrup.

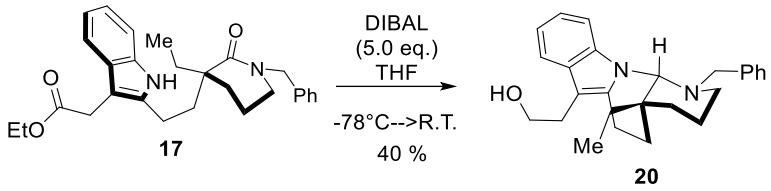
^{1}H NMR (400 MHz, Chloroform-d) δ 8.63 (s, 1H), 7.47 (d, J = 6.9 Hz, 1H), 7.25 – 7.15 (m, 6H), 7.05 – 6.98 (m, 2H), 4.61 (d, J = 14.6 Hz, 1H), 4.48 (d, J = 14.6 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.60 (s, 2H), 3.19 – 3.16 (m, 2H), 2.86 (ddd, J = 14.4, 10.4, 6.5 Hz, 1H), 2.52 (ddd, J = 14.5, 10.5, 4.4 Hz, 1H), 2.09 (ddd, J = 13.9, 10.4, 4.3 Hz, 1H), 1.81 – 1.68 (m, 6H), 1.61 (dd, J = 13.8, 7.5 Hz, 1H), 1.14 (t, J = 7.1 Hz, 3H), 0.83 (t, J = 7.5 Hz, 3H).

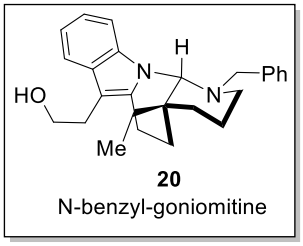
^{13}C NMR (100 MHz, Chloroform-d) δ 175.1, 172.1, 137.4, 135.3, 128.7, 127.9, 127.4, 121.1, 119.2, 118.2, 110.6, 103.7, 60.6, 50.7, 47.8, 45.8, 37.9, 31.6, 30.6, 29.1, 21.7, 19.6, 14.3, 8.5.

IR (cm^{-1}): 3275, 2936, 1729, 1609, 1491, 1458, 1261, 1194, 1160, 1030, 739, 700.

HRMS: m/z (M+1) calculated for $C_{28}H_{35}N_2O_3$: 447.26477; found: 447.26410.

Tandem ester reduction/iminium generation/cyclization





A solution of indoleacetate **17** (0.4039 g, 0.9044 mmol, 1.0 eq.) in freshly distilled THF (56 mL) was chilled to -78°C (acetone/dry ice bath) and then DIBAL 1M in heptane (5.0 mL, 4.9744 mmol, 5.5 eq.) was added dropwise and let react for 20 min at -78 °C. Then the cryogenic bat was removed and the reaction was allowed to reach room temperature for further 1.5 hours. When the reaction was complete (as judged by TLC), the reaction was cooled to 0 °C (ice/water bath) and was carefully quenched with aq. sat. potassium sodium tartrate (30 mL), the cold bath was removed and the reaction was stirred vigorously for 1 hour. The layers were separated and the aqueous phase was back-extracted twice with EtOAc. All organic phases were put together and dried over Na_2SO_4, filtered, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (r.f. aprox. 0.30, 20% EtOAc/hexane) to afford N-benzyl goniomitine (**20**) (0.1410 g, 40 % yield) as a colorless syrup.

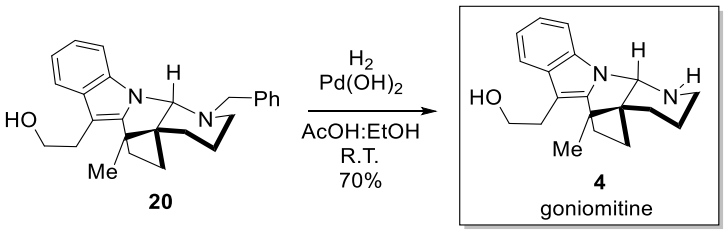
^{1}H NMR (400 MHz, Chloroform-d) δ 7.49 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.20 – 6.98 (m, 7H), 4.33 (s, 1H), 3.78 (t, J = 6.4 Hz, 2H), 3.58 (d, J = 13.4 Hz, 1H), 3.20 (ddd, J = 16.4, 9.5, 5.3 Hz, 1H), 3.00 -2.87 (m, 5H), 2.50 (ddd, J = 13.6, 9.5, 5.8 Hz, 1H), 2.18 (td, J = 12.1, 2.8 Hz, 1H), 1.89 – 1.76 (m, 1H), 1.75 - 1.67 (m, 1H), 1.54 - 1.41 (m, 4H), 1.38 - 1.23 (m, 2H), 0.98 -0.79 (m, 3H), 0.69 (t, J = 7.4 Hz, 3H).

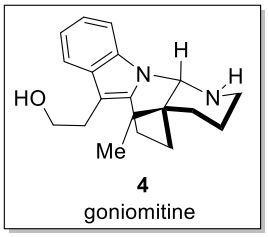
^{13}C NMR (100 MHz, Chloroform-d) δ 140.0, 137.4, 134.3, 128.4, 128.1, 127.9, 126.4, 120.4, 119.2, 117.9, 108.7, 105.5, 62.7, 57.7, 52.5, 38.5, 33.8, 30.9, 27.7, 24.2, 21.3, 18.3, 7.6.

IR (cm^{-1}): 3370, 2930, 1460, 1360, 1310, 1199, 1131, 1032, 734, 698.

HRMS: m/z (M+1) calculated for $C_{26}H_{33}N_2O$: 389.25929; found: 389.25914.

Benzylamine hydrogenolysis





To a solution of *N*-benzylamine **20** (0.1517 g, 0.3904 mmol, 1.0 eq.) in absolute ethanol (9 mL) and acetic acid (18 mL) was added $Pd(OH)_2/C$ (0.3034 g), then the system was purged with hydrogen gas and maintained with a hydrogen balloon for 2 hours. When the reaction was complete (as judged by TLC), the reaction was filtered through a celite pad, and the volatiles removed under reduced pressure. The residue was redisolved in CH_2Cl_2 and treated with aq. NaOH 1M until pH 10. The layers were separated and the aqueous phase was back-extracted twice with CH_2Cl_2. All organic phases were put together and dried over Na_2SO_4, filtered, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (r.f. aprox. 0.30, 5% MeOH/CH_2Cl_2) to synthetic goniomitine (**4**) (0.0815 g, 70 % yield) as a white semisolid. The analytical data matches the data in literature.[4]

^{1}H NMR (300 MHz, Chloroform-d) δ 7.52 (d, J = 7.9 Hz, 1H), 7.29 (m, 1H), 7.23 – 7.02 (m, 2H), 4.79 (s, 1H), 3.82 (s, 1H), 3.82 (t, J = 6.5 Hz, 2H), 3.08 - 2.98 (m, 2H), 2.97 – 2.90 (m, 2H), 2.90 – 2.74 (m, 2H), 2.51 (td, J = 12.9, 6.7 Hz, 1H), 1.94 - 1.84 (m, 1H), 1.84 – 1.40 (m, 8H), 1.20 (m, 2H), 0.94 – 0.82 (m, 3H).

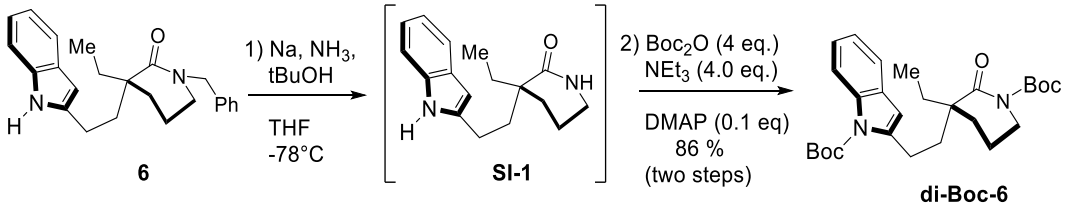
^{13}C NMR (75 MHz, Chloroform-d) δ 135.5, 132.8, 129.1, 120.6, 119.6, 118.2, 108.3, 106.0, 71.6, 62.7, 45.7, 35.2, 34.1, 28.7, 27.8, 21.7, 21.7, 18.6, 7.2.

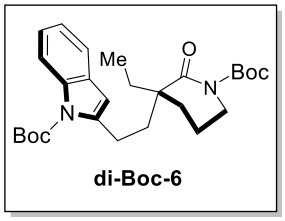
IR (cm^{-1}): 3300, 2925, 2853, 1460, 1356, 1309, 1190, 1113, 1043, 1014, 735.

HRMS: m/z (M+1) calculated for $C_{26}H_{33}N_2O$: 299.21234; found: 299.21104.

Intermediates for the synthesis of Aspidospermidine (1), Vincadifformine (2), 1,2-Dehydroaspidospermidine (3) from indole-valerolactam 6.

Debenzylation/N-Boc di-functionalization





tert-butyl 2-(2-(1-(*tert*-butoxycarbonyl)-3-ethyl-2-oxopiperidin-3-yl)ethyl)-1*H*-indole-1-carboxylate

A solution of common intermediate **6** (1.5542 g, 4.3114 mmol, 1.0 eq.) and anhydrous tBuOH (4.7 mL), in freshly distilled THF (110 mL) in a round bottomed two necked flask was chilled to -78 °C (acetone/dry ice bath), and then, freshly condensed liquid ammonia (77 mL) was slowly added to the reaction through one of the mouths under a positive pressure of nitrogen, and the system stirred at -78 °C for 10 minutes. Then, sodium metal in small pieces (0.5174 g, 21.5567 mmol, 5.0 eq.) was added to the reaction in a sole operation through one of the mouths of the flask under a positive pressure of nitrogen, and the reaction was vigorously stirred for 40 minutes. When **6** was consumed (as judged by TLC), the reaction was treated with solid NH_4Cl (3.12 g), the cryogenic bath was removed, the reaction was opened to the atmosphere and allowed to reach room temperature while the ammonia evaporated completely, under constant stirring in a well vented fume hood. Water (50 mL) was added, and the organic layer was separated. The aqueous layer was back-extracted with CH_2Cl_2 (30 mL X 2). All organic phases were put together and dried over Na_2SO_4, filtered, the solvent was removed under reduced pressure and the solid crude **SI-1** (1.1537 g) was subjected without further purification to the next step. Crude SI-1 was dissolved in CH_2Cl_2 (90 mL), and ditertbutyl dicarbonate (4.04 mL, 3.8407 g, 17.2456 mmol, 4.0 eq.) followed by triethylamine (2.42 mL, 1.763 g, 17.2456 mmol, 4.0 eq.) were added to the reaction flask, and heated to reflux without any moisture/oxygen excluding considerations for 15 hours. When the reaction was complete (as judged by TLC), water (50 mL) was added, the phases were separated and the aqueous phase was back-extracted two times with CH_2Cl_2. All organic phases were put together and dried over Na_2SO_4, filtered, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (10% EtOAc/Hexane r.f. aprox: 0.40) to afford **di-Boc-6** (1.7388 g, 86 % yield two steps) as a colorless syrup.

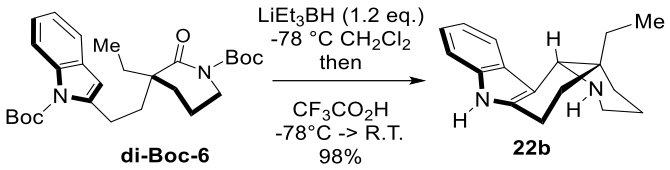
^{1}H NMR (300 MHz, Chloroform-d) δ 8.03 (d, J = 8.8 Hz, 1H), 7.45 - 7.42 (m, 1H), 7.25 - 7.14 (m, 2H), 6.38 (s, 1H), 3.64 (t, J = 5.2 Hz, 3H), 3.15 – 2.88 (m, 2H), 2.11 -1.46 (m, 8H), 1.68 (s, 9H), 1.51 (s, 9H), 0.92 (t, J = 7.5 Hz, 3H).

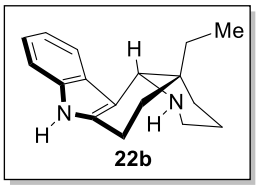
^{13}C NMR (75 MHz, Chloroform-d) δ 176.8, 154.0, 150.6, 142.5, 136.5, 129.4, 123.3, 122.6, 119.8, 115.6, 106.8, 83.7, 82.5, 48.2, 47.3, 36.5, 30.9, 30.6, 28.4, 28.1, 24.8, 20.2, 8.6.

IR (cm^{-1}): 2974, 2936, 2880, 1765, 1716, 1453, 1326, 1298, 1275, 1253, 1146, 1116, 1085, 851, 741.

HRMS: m/z (M+1) calculated for $C_{27}H_{39}N_2O_5$: 471.28590; found: 471.2861.

Iminium generation/ Diasteroselective C-3 indole cyclization Protocol





4a-ethyl-2,3,4,4a,5,6,7,11c-octahydro-1*H*-pyrido[3,2-*c*]carbazole

A solution of **di-boc-6** (1.7388 g, 3.6949 mmol, 1.0 eq.) in freshly distilled CH_2Cl_2 (37 mL) was chilled to -78 °C (acetone/dry ice bath), and $LiEt_3BH$ 1M in THF (4.44 mL, 4.44 mmol, 1.2 eq.) was slowly added via syringe, and let react for 30 min at -78 °C. Then, the system was opened and CF_3CO_2H (37 mL) was added slowly at -78 °C, and when the addition was complete, the reaction was allowed to reach room temperature and stirred overnight. Then, the volatiles were removed under reduced pressure, the residue redisolved in CH_2Cl_2 and treated with NaOH 1M until pH 10-11. the layers were separated and the aqueous phase was back-extracted two times with CH_2Cl_2. All organic phases were put together and dried over Na_2SO_4, filtered, the solvent was removed under reduced pressure to obtain, without any further purifications, pure carbazole **22b** (0.9359 g, 98%, r.f. aprox. 0.35, 25%acetone/hexane + 10% NEt_3) as a white solid. The analytical data matches the data in literature.[1]

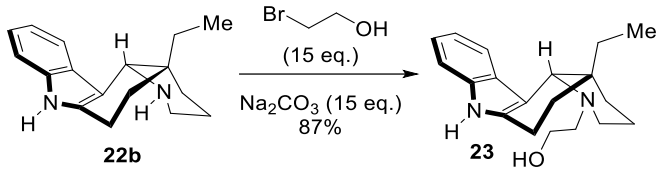
^{1}H NMR (300 MHz, Chloroform-d) δ 8.38 (s, br, 1H), 7.56 (m, 1H), 7.21 - 7.18 (m, 1H), 7.11 – 7.05 (m, 2H), 3.71 (s, 1H), 3.03 (d, J = 12.5 Hz, 1H), 2.76 (td, J = 12.3, 11.7, 3.4 Hz, 2H), 2.57 (dd, J = 8.4, 3.9 Hz, 3H), 2.47 – 2.13 (m, 1H), 1.81 (d, J = 13.0 Hz, 1H), 1.71 – 1.37 (m, 6H), 1.17 – 1.03 (m, 1H), 0.84 (t, J = 7.5 Hz, 3H).

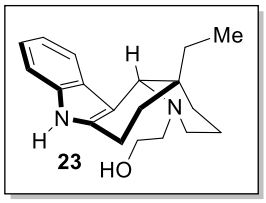
^{13}C NMR (75 MHz, Chloroform-d) δ 136.3, 134.6, 127.5, 120.9, 119.2, 117.6, 111.9, 110.7, 56.7, 46.2, 34.6, 34.2, 29.6, 24.2, 22.7, 20.1, 7.7.

IR (cm^{-1}): 3058, 2926, 2880, 1451, 1304, 1204, 1113, 898, 871, 734.

HRMS: m/z (M+1) calculated for $C_{17}H_{17}N_2$: 255.18612; found: 255.18615.

Amine hydroxyethylation





2-(4a-ethyl-2,3,4,4a,5,6,7,11c-octahydro-1*H*-pyrido[3,2-*c*]carbazol-1-yl)ethan-1-ol

To a solution of pyridocarbazole **22b** (0.8111 g, 3.1887 mmol, 1.0 eq.) in absolute ethanol (80 mL) was added 2-bromoethanol (3.55 mL, 6.2567 g, 47.8299 mmol, 15 eq.), followed by Na_2CO_3 (5.0695 g, 47.8299 mmol, 15 eq.) and was refluxed overnight with vigorous stirring. When the reaction was complete (as judged by TLC), the reaction was allowed to reach room temperature, the volatiles were removed under reduced pressure, the residue partitioned between EtOAc and water. The layers were separated and the aqueous phase was back-extracted two times with EtOAc. All organic phases were put together and dried over Na_2SO_4, filtered, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (r.f. aprox. 0.35, 25%acetone/hexane + 10% NEt_3) to afford hydroxyamine **23** (0.8280 g, 87 % yield) as a colorless syrup. The analytical data matches the data in literature.[2]

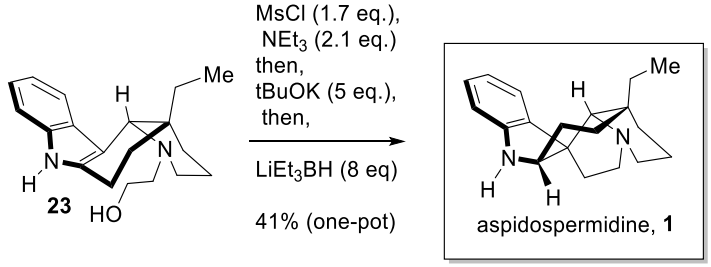
^{1}H NMR (300 MHz, Chloroform-d) δ 8.48 (s, br, 1H), 7.47 -7.44 (m, 1H), 7.19 -7.16 (m, 1H), 7.10 - 7.07 (m, 2H), 3.48 (m, 2H), 3.25 – 3.09 (m, 5H), 2.66 – 2.56 (m, 3H), 2.30 - 2.21 (m, 2H), 1.90 - 1.70 (m, 2H), 1.66 - 1.57 (m, 1H), 1.50 -1.34 (m, 2H), 1.22 - 1.12 (m, 1H), 0.99 – 0.87 (m, 1H), 0.74 (t, *J* = 7.4 Hz, 3H).

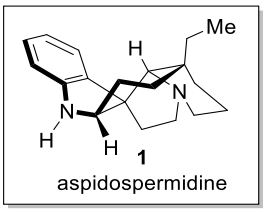
^{13}C NMR (75 MHz, Chloroform-d) δ 136.2, 135.8, 129.9, 120.8, 119.3, 117.7, 110.7, 110.1, 63.1, 56.0, 54.3, 52.5, 37.1, 34.8, 29.7, 24.3, 22.1, 20.3, 8.0.

IR (cm^{-1}): 3391, 3056, 2931, 2877, 2793, 1461, 1381, 1330, 1260, 1124, 1040, 742

HRMS: m/z (M+1) calculated for $C_{19}H_{27}N_2O$: 299.21234; found: 299.21242.

One-pot Mesilation/S_N2/imine reduction protocol





A solution of hydroxyamine **23** (0.1294 g, 0.4335 mmol, 1.0 eq.) in freshly distilled CH_2Cl_2 (3 mL) was chilled to approximately – 10 °C (ice/NaCl/water bath), then triethylamine (0.122 mL, 0.088 g, 0.8671 mmol, 2.0 eq.) was injected followed by methanesulfonyl chloride (0.064 mL, 0.0948 g, 0.8237, 1.9 eq.), and stirred at that temperature for 40 minutes. When the reaction was complete (as judged by TLC), t-BuOK 1M in THF was added (2.17 mL, 2.1675 mmol, 5.0 eq.) and the reaction was allowed to reach room temperature for 1.5 hours. When the reaction was complete (as judged by TLC), it was cooled to 0 °C (ice/water bath) and $LiEt_3BH$ 1M in THF was added (3.5 mL, 3.468 mmol, 8.0 eq.), and the reaction was allowed to reach room temperature for 1.0 hour. When the reaction was complete (as judged by TLC), it was quenched with 5 mL of aq. sat. NH_4Cl (5 mL), the layers were separated and the aqueous phase was back-extracted two times with EtOAc. All organic phases were put together and dried over Na_2SO_4, filtered, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (r.f. aprox. 0.30, 10% acetone/hexane + 10% NEt_3) to afford synthetic aspidospermidine **1** (0.0498 g, 41 % yield) as a white solid. The analytical data matches the data in literature.[2]

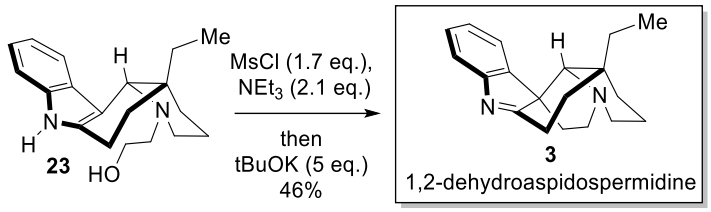
^{1}H NMR (400 MHz, Chloroform-d) δ 7.07 (d, J = 7.3 Hz, 1H), 7.01 (td, J = 7.6, 1.1 Hz, 1H), 6.72 (td, J = 7.4, 1.0 Hz, 1H), 6.63 (d, J = 7.6 Hz, 1H), 3.51 (s, br, 1H), 3.12 – 3.05 (m, 2H), 2.34 – 2.18 (m, 2H), 2.01 – 1.90 (m, 2H), 1.81 – 1.70 (m, 1H), 1.68 – 1.60 (m, 3H), 1.53 – 1.33 (m, 4H), 1.16 – 1.02 (m, 1H), 0.87 (dq, J = 14.5, 7.4 Hz, 1H), 0.64 (t, J = 7.5 Hz, 3H).

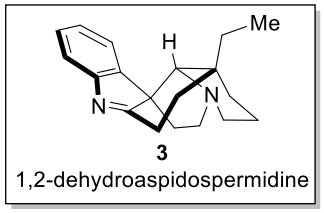
^{13}C NMR (100 MHz, Chloroform-d) δ 149.4, 135.7, 127.1, 122.8, 119.0, 110.3, 71.3, 65.7, 53.9, 53.4, 53.0, 38.8, 35.7, 34.5, 30.0, 28.1, 23.0, 21.8, 6.8.

IR (cm^{-1}): 3362, 3282, 2929, 2859, 2777, 2721, 1605, 1480, 1461, 1340, 1257, 1178, 1025, 903, 865, 740.

HRMS: m/z (M+1) calculated for $C_{19}H_{27}N_2$: 283.21742; found: 283.21753.

One-pot Mesilation/S_N2 protocol





A solution of hydroxyamine **23** (0.2925 g, 0.9800 mmol, 1.0 eq.) in freshly distilled CH_2Cl_2 (7 mL) was chilled to approximately -10 °C (ice/NaCl/water bath), then triethylamine (0.276 mL, 0.2003 g, 1.960 mmol, 2.0 eq.) was injected followed by methanesulfonyl chloride (0.145 mL, 0.2144 g, 1.8620 mmol, 1.9 eq.), and stirred at that temperature for 40 minutes. When the reaction was complete (as judged by TLC), t-BuOK 1M in THF was added (4.90 mL, 4.90 mmol, 5.0 eq.) and the reaction was allowed to reach room temperature for 1.5 hours. When the reaction was complete (as judged by TLC), it was quenched with 5 mL of aq. sat. NH_4Cl (10 mL), the layers were separated and the aqueous phase was back-extracted two times with EtOAc. All organic phases were put together and dried over Na_2SO_4, filtered, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (r.f. aprox. 0.30, 10% acetone/hexane + 10% NEt_3) to afford synthetic 1,2-dehydroaspidospermidine **3** (0.1143 g, 42 % yield) as a colorless semisolid. The analytical data matches the data in literature.[3]

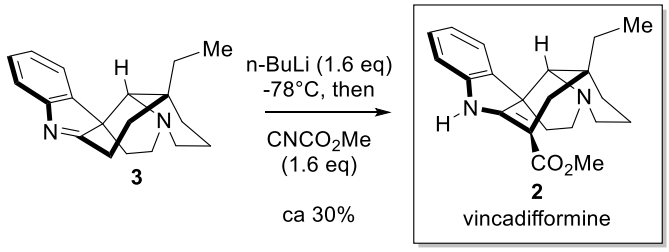
^{1}H NMR (300 MHz, Chloroform-d) δ 7.52 (d, J = 7.6 Hz, 1H), 7.17 (d, J = 7.4 Hz, 1H), 7.30 (t, J = 7.2 Hz, 1H), 7.17 (t, J = 7.4 Hz, 1H), 3.22 - 3.15 (m, 2H), 2.77 (t, J = 12.3 Hz, 1H), 2.79 (d, J = 10.7 Hz, 1H), 2.60 (ddd, J = 12.2, 8.3, 5.7 Hz, 1H), 2.52 - 2.41 (m, 2H), 2.25 – 2.11 (m, 3H), 1.98 – 1.75 (m, 1H), 1.72 – 1.27 (m, 3H), 1.03 (dd, J = 13.5, 4.8 Hz, 1H), 0.99 (dd, J = 13.5, 4.8 Hz, 1H), 0.78 – 0.54 (m, 2H), 0.50 (t, J = 7.1 Hz, 3H).

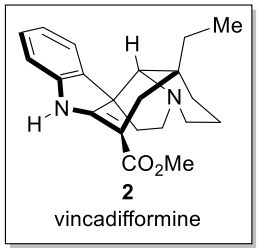
^{13}C NMR (75 MHz, Chloroform-d) δ 192.3, 154.5, 147.1, 127.4, 125.1, 121.0, 120.1, 79.0, 61.3, 54.6, 52.0, 36.5, 35.2, 33.2, 29.7, 27.2, 23.7, 22.0, 7.3.

IR (cm^{-1}): 2929, 2975, 2719, 1575, 1457, 1323, 1192, 739.

HRMS: m/z (M+1) calculated for $C_{19}H_{25}N_2$: 281.20177; found: 281.20183.

Imine α-carboxymethylation





A solution of 1,2-dehydroaspidospermidine (**3**) (0.0350 g, 0.1248 mmol, 1.0 eq.) in freshly distilled THF (1 mL) was chilled to -78 °C (dry ice/acetone bath), then nBuLi 2.5 M in hexanes (0.2 mL, 0.1977 mmol, 1.6 eq.) was added dropwise by the internal sides of the reaction flask, and stirred for 30 minutes at -78°C. Then MeOCOCN (Mander's reagent) was added (0.0160 mL, 0.0172 g, 0.1977 mmol, 1.6 eq.), the cryogenic bath was removed, and the reaction was allowed to reach room temperature for 30 minutes. Then the reaction was quenched with aq. sat. NH_4Cl, the layers were separated and the aqueous phase was back-extracted one more time with EtOAc. All organic phases were put together and dried over Na_2SO_4, filtered, the solvent was removed under reduced pressure and the residue purified by preparative TLC (r.f. aprox. 0.30, 10% trietylamine/hexane) to afford synthetic vincadiffomine (**2**) (0.0120 g, 30 % yield) as a colorless syrup. The analytical data matches the data in literature.[3]

^{1}H NMR (300 MHz, Chloroform-d) δ 8.90 (s, br, 1H), 7.12 (td, J = 7.7, 1.2 Hz, 1H), 6.85 (td, J = 7.5, 1.0 Hz, 1H), 6.79 (ddd, J = 7.8, 1.0, 0.6 Hz, 1H), 3.76 (s, 3H), 3.16 – 3.05 (m, 1H), 3.00 – 2.83 (m, 1H), 2.71 (d, J = 15.2 Hz, 1H), 2.61 – 2.49 (m, 1H), 2.48 – 2.33 (m, 1H), 2.27 (d, J = 15.1 Hz, 1H), 2.11 – 1.96 (m, 1H), 1.90 – 1.75 (m, 1H), 1.74 – 1.65 (m, 1H), 1.65 – 1.48 (m, 2H), 1.33 – 1.17 (m, 2H), 1.02 - 0.88 (m, 1H), 0.69 – 0.48 (m, 4H).

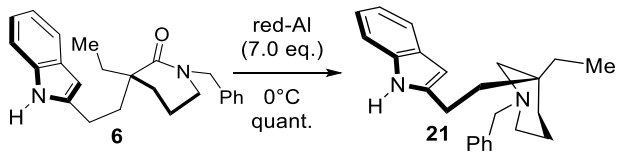
^{13}C NMR (75 MHz, Chloroform-d) δ 169.1, 167.8, 143.2, 137.9, 127.5, 120.5, 109.3, 92.6, 77.4, 77.2, 77.0, 76.6, 72.7, 55.5, 51.8, 51.0, 50.6, 45.2, 38.1, 32.8, 29.4, 25.7, 22.1, 7.1.

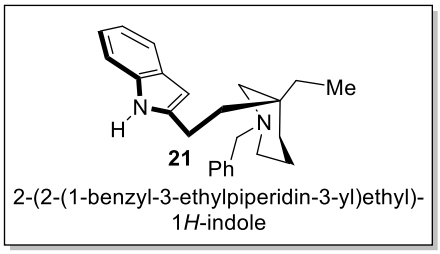
IR (cm^{-1}): 3361, 2930, 2768, 1673, 1605, 1477, 1460, 1435, 1278, 1253, 1206, 1236, 1155, 1124, 1110, 1043, 747

HRMS: m/z (M+1) calculated for $C_{21}H_{27}N_2O_2$: 339.20725; found: 339.20718.

Intermediates for the synthesis of quebrachamine (5), from indole-valerolactam 6.

Lactam reduction





2-(2-(1-benzyl-3-ethylpiperidin-3-yl)ethyl)-1*H*-indole

A solution of common intermediate **6** (1.7181 g, 4.7660 mmol, 1.0 eq.) in freshly distilled THF (100 mL) was cooled to 0 °C (ice/water bath) and then Red-Al 60% in MePh (10.9 mL, 33.3621 mmol, 7.0 eq.) was slowly added by the internal sides of the flask, and stirred for 1 hour. When the reaction was complete (as judged by TLC), the reaction was carefully quenched with aq. sat. potassium sodium tartrate (100 mL) at 0°C, the cold bath was removed and the reaction was stirred vigorously for 1 hour. The layers were separated and the aqueous phase was back-extracted twice with EtOAc. All organic phases were put together and dried over Na_2SO_4, filtered, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (r.f. aprox. 0.40, 20% acetone/hexane) to afford N-benzylamine **21** (1.6514 g, 100 % yield) as a colorless syrup.

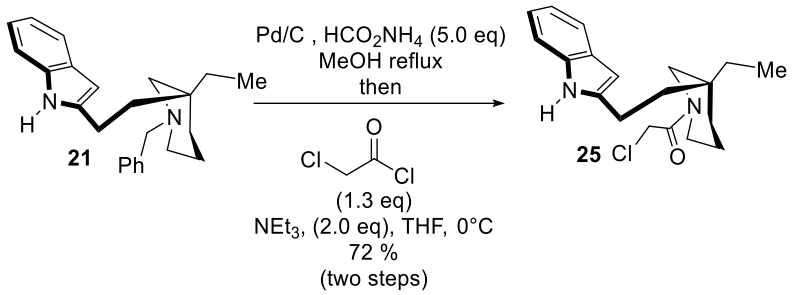
^{1}H NMR (300 MHz, Chloroform-d) δ 8.10 (s, br, 1H), 7.54 (d, J = 9.5 Hz, 1H), 7.39 – 7.25 (m, 6H), 7.18 – 7.02 (m, 2H), 6.24 (s, 1H), 3.52 (d, J = 13.4 Hz, 2H), 3.44 (d, J = 13.2 Hz, 1H), 2.66 – 2.44 (m, 3H), 2.34 – 2.22 (m, 2H), 2.03 - 1.89 (m, 2H), 1.74 – 1.57 (m, 3H), 1.59 – 1.24 (m, 5H), 0.82 (t, J = 7.6 Hz, 3H).

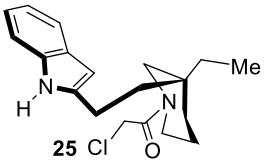
^{13}C NMR (75 MHz, Chloroform-d) δ 140.8, 136.0, 129.1, 129.0, 128.3, 127.9, 120.9, 119.8, 119.6, 110.4, 99.1, 63.5, 62.2, 55.1, 35.9, 34.0, 22.1, 22.0, 7.5.

IR (cm^{-1}): 3406, 2931, 1455, 1287, 1122, 780, 700, 738, 698.

HRMS: m/z (M+1) calculated for $C_{24}H_{31}N_2$: 347.24872; found: 347.24881.

Benzylamine hydrogenolysis and chloroacetamide synthesis





1-(3-(2-(1*H*-indol-2-yl)ethyl)-3-ethylpiperidin-1-yl)-2-chloroethan-1-one

To a solution of benzylamine **21** (0.500 g, 1.4430 mmol, 1.0 eq.) in methanol (16 mL) was added Pd/C (0.500 g), and then, ammonium formate (0.4550, 7.2147 mmol, 5.0 eq) was added in portions (CAUTION: Use a well vented hood. In some of the runs, the reaction catched fire at this point, regardless of the order of addition of the reagents. In the case of fire, the reaction flask was caped, which caused fire to put out quickly). The reaction mixture was heated to reflux for 1.5 hours and when the reaction was complete (as judged by TLC), the reaction was brought to room temperature, filtered through a celite pad, and the clear liquid filtrate concentrated under reduced pressure. This residue was purged with nitrogen, redissolved in anhydrous THF (36 mL), cooled to aprox. 0 °C (ice/water bath) and triethylamine (0.1770 g, 0.244 mL, 1.7316 mmol, 1.2 eq.) was added via syringe. Then chloroacetyl chloride (0.1995 g, 0.141 mL, 1.7316 mmol, 1.2 eq.) was added dropwise, and let react for 30 min at 0 °C. when the reaction was complete (as judged by TLC), the reaction was quenched with aq. sat. NH_4Cl (30 mL), the layers were separated and the aqueous phase was back-extracted twice with EtOAc. All organic phases were put together and dried over Na_2SO_4, filtered, the solvent was removed under reduced pressure to afford chlroacetamide **25** (0.3458 g, 72 % yield) as a colorless syrup.

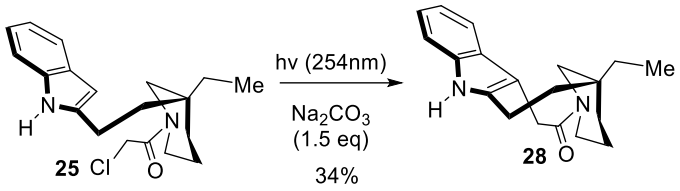
^{1}H NMR (300 MHz, Chloroform-d, rotamer mixture : 6*:1°) δ 8.80* (s, br, 1H), 8.54° (s, br, 1H), 7.54*,° (d, J = 8.2 Hz, 2H), 7.36*,° (d, J = 7.2 Hz, 2H), 7.16 – 7.04*,° (m, 4H), 6.26° (s, 1H), 6.23* (s, 1H) 4.19 – 4.04*,° (m, 6H), 3.62 - 3.52*,° (m, 2H), 3.21 - 3.12*,° (m, 2H), 2.80 – 2.60*,° (m, 6H), 1.71 - 1.36*,° (m, 12H), 1.33 – 1.16*,° (m, 2H), 0.93* (t, J = 7.5 Hz, 3H), 0.90° (d, J = 7.5 Hz, 3H) .

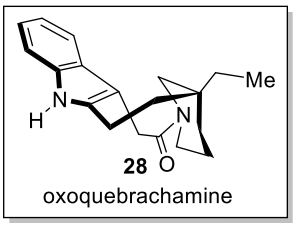
^{13}C NMR (75 MHz, Chloroform-d, rotamer mixture) δ 169.4, 166.2, 140.6, 139.6, 136.3, 136.2, 128.8, 121.2, 120.8, 119.8, 119.7, 119.3, 110.9, 110.7, 99.3, 98.9, 55.3, 50.5, 47.8, 43.4, 41.4, 41.2, 37.1, 36.4, 34.4, 33.6, 33.1, 31.1, 28.3, 27.0, 22.6, 22.0, 20.7, 7.6, 7.3.

IR (cm^{-1}): 3278, 2937, 2861, 1634, 1455, 1283, 1248, 782, 736.

HRMS: m/z (M+1) calculated for $C_{19}H_{26}N_2OCl$: 333.17337; found: 333.17342.

Witkop chloroacetamide photocyclization





In a quartz vessel, a solution of chloroacetamide **25** (0.1916 g, 0.5756 mmol, 1.0 eq.) in ethanol (30 mL) and water (5 mL) was treated with Na_2CO_3 (0.1220 g, 1.1513 mmol, 2.0 eq.) and then, nitrogen was bubbled to the solution for 15 minutes with constant stirring. Then, the quartz vessel was irradiated at 254 nm (300 W) for 5 hours (NOTE: the reaction was not complete at this time. However, extended irradiation caused complex mixtures and lower isolated yields). The solvent was removed under reduced pressure and the residue purified by flash column chromatography (r.f. aprox. 0.40, 50% EtOAc/hexane) to afford oxoquebrachamine **16** (0.0589g, 34 % yield) as a white semisolid.

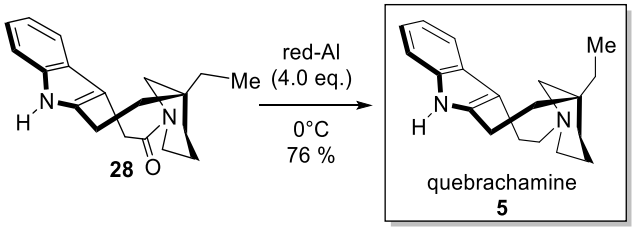
^{1}H NMR (300 MHz, Chloroform-d + Dimethylsulfoxide-d_6) δ 9.24 (s, br, 1H), 7.53 – 7.50 (m, 1H), 7.13 - 7.09 (m, 1H), 6.94 – 6.89 (m, 2H), 4.47 (d, J = 12.4 Hz, 1H), 4.32 (d, J = 14.0 Hz, 1H), 3.90 (d, J = 14.0 Hz, 1H), 3.42 (d, J = 14.0 Hz, 1H), 2.71 – 2.44 (m, 4H), 2.32 (td, J = 12.4, 2.8 Hz, 1H), 1.60 - 0.97 (m, 8H), 0.73 (t, J = 7.5 Hz, 3H).

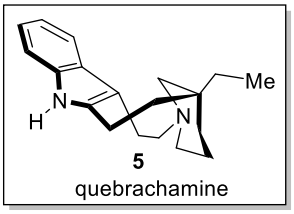
^{13}C NMR (75 MHz, Chloroform-d + Dimethylsulfoxide-d_6) δ 170.4, 138.6, 134.5, 129.6, 120.7, 119.3, 118.0, 110.4, 104.6, 53.7, 42.8, 38.7, 34.5, 32.1, 30.5, 29.7, 28.7, 20.7, 20.4, 7.3.

IR (cm^{-1}): 3234, 2926, 2857, 1599, 1466, 732, 699.

HRMS: m/z (M+1) calculated for $C_{19}H_{25}N_2O$: 297.19669; found: 333.17342.

Lactam reduction





A suspension of oxoquebrachamine **28** (0.0589 g, 0.1957 mmol, 1.0 eq.) in freshly distilled THF (7 mL) was cooled to 0 °C (ice/water bath) and then Red-Al 60% in MePh (0.255 mL, 0.7827 mmol, 4.0 eq.) was slowly added by the internal sides of the flask, and stirred for 2 hours (the starting solid dissolves as it reacts). When the reaction was complete (as judged by TLC), the reaction was carefully quenched with aq. sat. potassium sodium tartrate (7 mL) at 0°C, the cold bath was removed and the reaction was stirred vigorously for 1 hour. The layers were separated and the aqueous phase was back-extracted twice with EtOAc. All organic phases were put together and dried over Na_2SO_4, filtered, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (r.f. aprox. 0.35, 5% MeOH/CH_2Cl_2) to afford synthetic quebrachamine (**5**) (0.0418 g, 76 % yield) as a colorless semisolid. The analytical data matches the data in literature.[5]

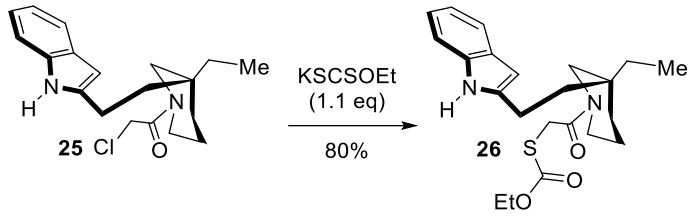
^{1}H NMR (300 MHz, Chloroform-d) δ 7.75 (s, br, 1H), 7.51 - 7.48 (m, 1H), 7.30 - 7.25 (m, 1H), 7.11 – 7.06 (m, 2H), 3.26 (d, J = 11.7, 1H), 2.99 – 2.78 (m, 2H), 2.74 – 2.63 (m, 2H), 2.51 – 2.20 (m, 4H), 1.97 – 1.88 (m, 1H), 1.66 – 1.46 (m, 4H), 1.36 – 1.95 (m, 5H), 0.85 (d, J = 7.6 Hz, 3H).

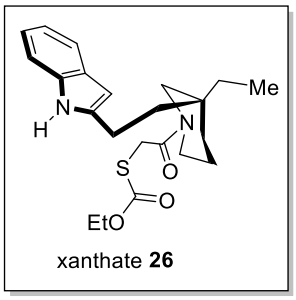
^{13}C NMR (75 MHz, Chloroform-d) δ 140.0, 134.9, 129.0, 120.3, 118.8, 117.5, 110.1, 108.8, 56.8, 55.2, 53.4, 37.2, 34.9, 33.6, 32.2, 22.8, 22.6, 22.1, 7.9.

IR (cm^{-1}): 3234, 2926, 2857, 1466, 732, 699.

HRMS: m/z (M+1) calculated for $C_{19}H_{27}N_2$: 283.21742; found: 283.21749.

Xanthate nucleophilic displacement





xanthate **26**

A solution of chloroacetamide **25** (0.1000 g, 0.1957 mmol, 1.0 eq.) in acetonitrile (4 mL) was treated with potassium ethyl xanthogenate (0.0359 g, 0.2153 mmol, 1.1 eq.) and stirred for 3 hours. When the reaction was complete (as judged by TLC), the reaction was concentrated in vacuo and the residue partitioned between ethyl acetate and water. The layers were separated and the aqueous phase was back-extracted twice with EtOAc. All organic phases were put together and dried over Na_2SO_4, filtered, the solvent was removed under reduced pressure and the residue purified by flash column chromatography to afford xanthate (**26**) (0.0418 g, 76 % yield) as a yellow liquid.

^{1}H NMR (300 MHz, Chloroform-d) δ 8.90 (s, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.12 – 7.00 (m, 2H), 6.18 (s, 1H), 4.70 - 4.62 (m, 1H), 4.61 - 4.51 (m, 1H), 4.48 – 4.36 (m, 2H), 4.32 (d, J = 15.4 Hz, 1H), 4.16 – 4.10 (m, 1H), 4.10 (d, J = 15.4 Hz, 1H), 3.91 (d, J = 13.1 Hz, 1H), 3.27 - 3.14 (m, 1H), 2.81 – 2.57 (m, 3H), 1.70 – 1.47 (m, 5H), 1.39 (t, J = 7.1 Hz, 3H), 1.32 – 1.12 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-d) δ 214.0, 166.1, 140.6, 136.3, 128.7, 120.6, 119.5, 119.1, 110.9, 98.8, 77.2, 70.9, 50.8, 47.9, 39.7, 37.2, 35.0, 32.9, 28.9, 22.8, 22.4, 13.9, 7.2.

HRMS: m/z (M+1) calculated for $C_{22}H_{31}N_2O_2S_2$: 419.18269; found: 419.18278.

References

1. a) Z. Li, S. Zhang, S. Wu, X. Shen, L. Zou, F. Wang, X. Li, F. Peng, H. Zhang, Z. Shao, *Angew. Chem. Int. Ed.* **2013**, 52, 4117; b) M. G. Banwell, D. W. Lupton, A. C. Willis, *Aust. J. Chem.* **2005**, 58, 722.

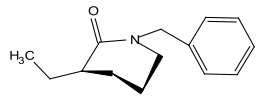
2. H. Ma, X. Xie, P. Jing, W. Zhanga, X. She, *Org. Biomol. Chem.* **2015**, 13, 5255.

3. S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. Macmillan, *Nature*, **2011**, 475, 183.

4. M. Mizutani, F. Inagaki, T. Nakanishi, C. Yanagihara, I. Tamai, C. Mukai, *Org. Lett.* **2011**, 12, 1796.

5. N. Wang, S. Du, D. Li, X. Jiang, *Org. Lett.* **2017**, 19, 3167

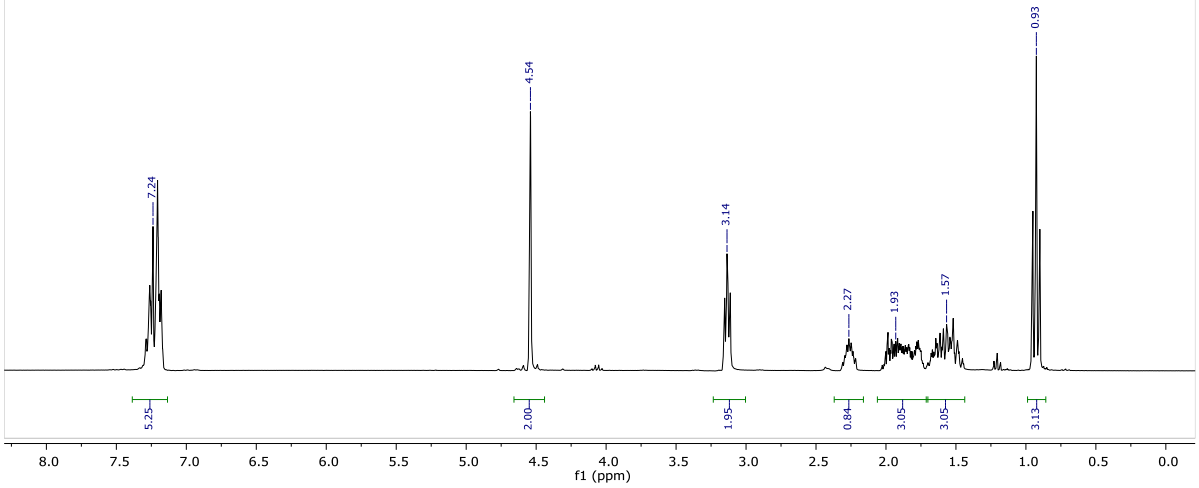
1H and 13C NMR

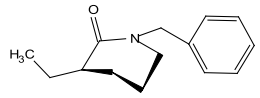


1-benzyl-3-ethylpiperidin-2-one

compound 10

^{1}H NMR (300 MHz, $CDCl_3$)

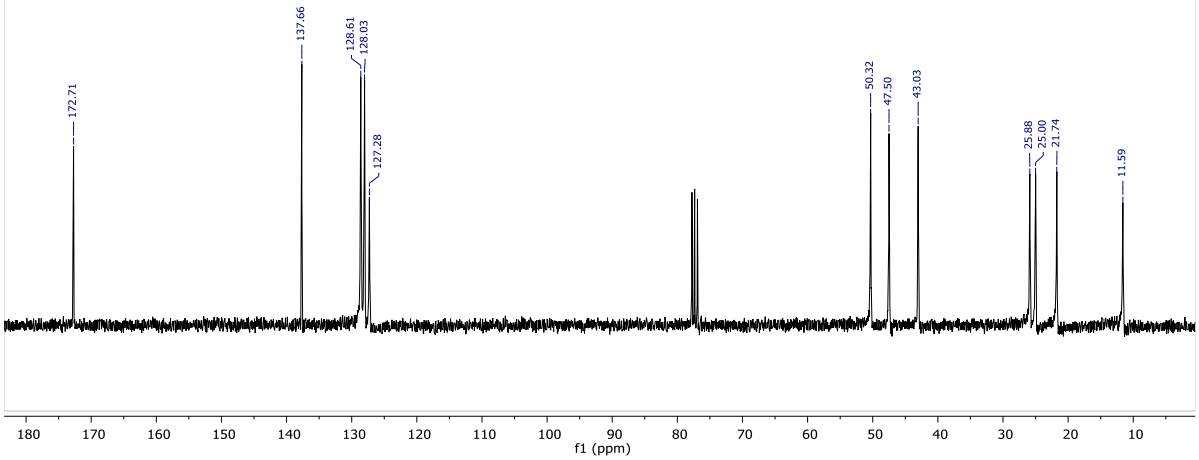


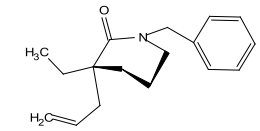


1-benzyl-3-ethylpiperidin-2-one

compound 10

^{13}C NMR (75MHz, $CDCl_3$)

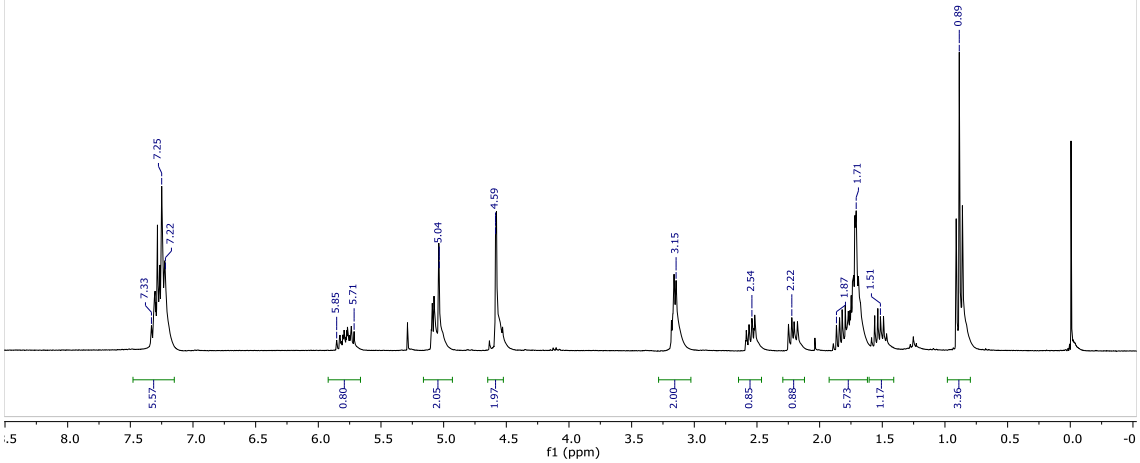


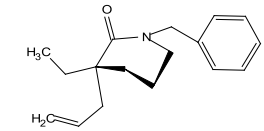


3-allyl-1-benzyl-3-ethylpiperidin-2-one

Compound 11

1H NMR (300MHz CDCl 3)

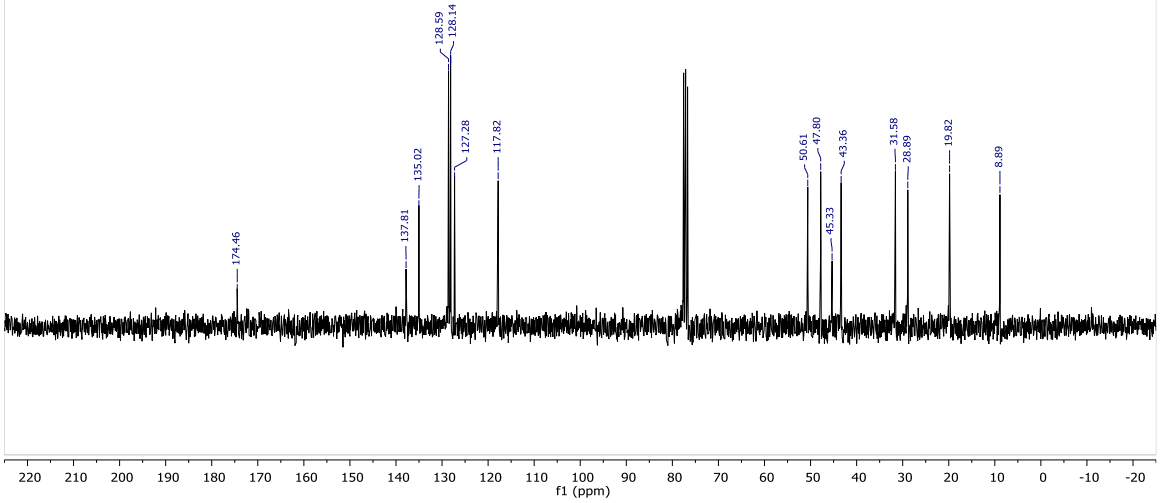


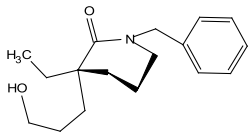


3-allyl-1-benzyl-3-ethylpiperidin-2-one

Compound 11

13C NMR (75 MHz CDCl 3)

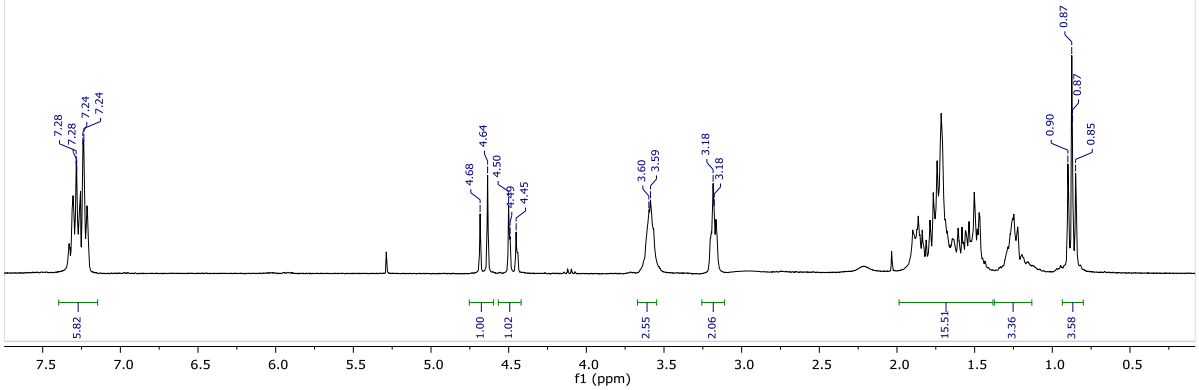


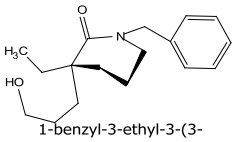


1-benzyl-3-ethyl-3-(3-hydroxypropyl)piperidin-2-one

Compound 12

^{1}H NMR (300MHz CDCl $_3$)

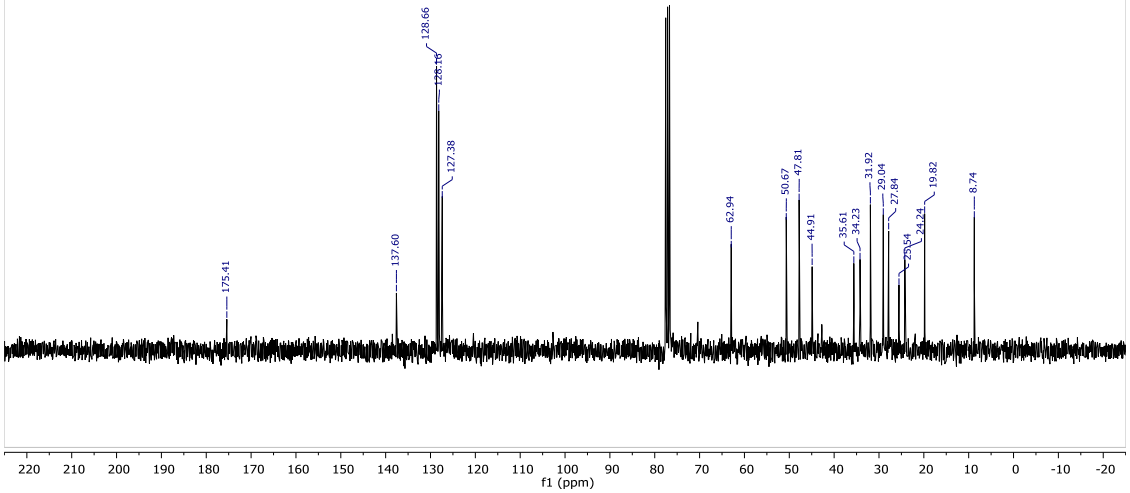


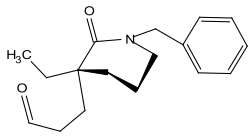


1-benzyl-3-ethyl-3-(3-hydroxypropyl)piperidin-2-one

Compound 12

^{13}C NMR (75 MHz CDCl $_3$)

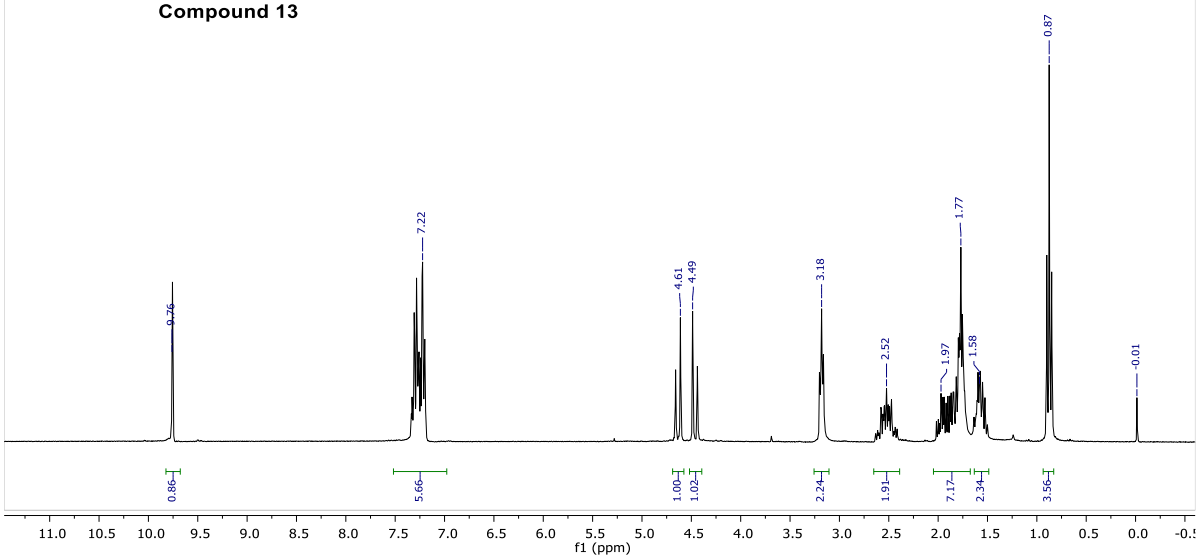


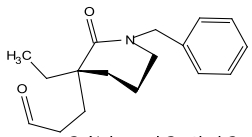


3-(1-benzyl-3-ethyl-2-oxopiperidin-3-yl)propanal

Compound 13

^{1}H NMR (300MHz CDCl $_3$)

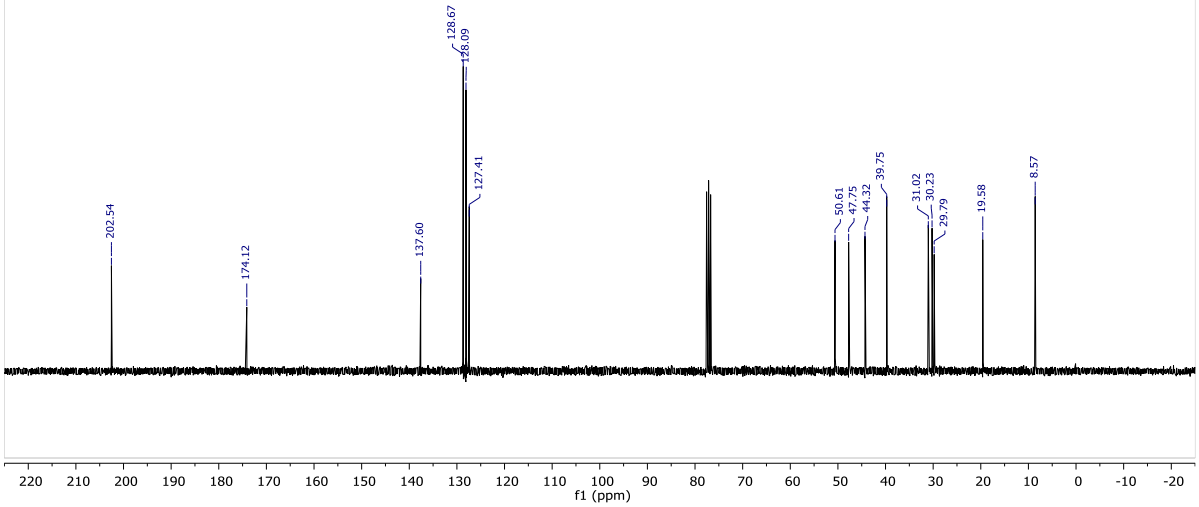


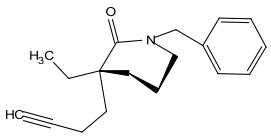


3-(1-benzyl-3-ethyl-2-oxopiperidin-3-yl)propanal

Compound 13

^{13}C NMR (75 MHz CDCl $_3$)

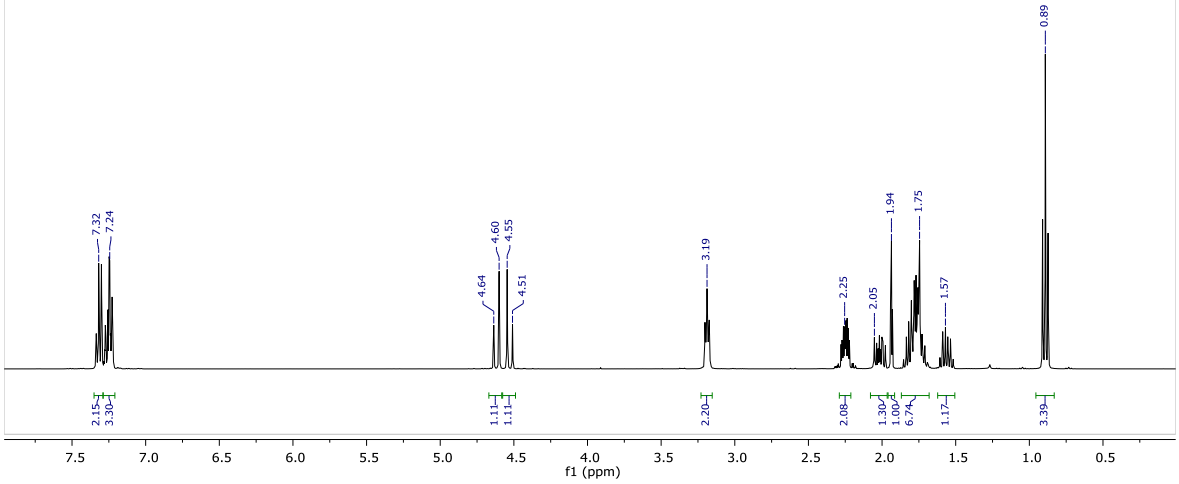


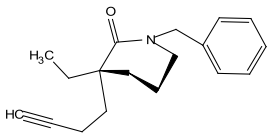


^{1}H NMR (400MHz CDCl $_3$)

1-benzyl-3-(but-3-yn-1-yl)-3-ethylpiperidin-2-one

Compound 8

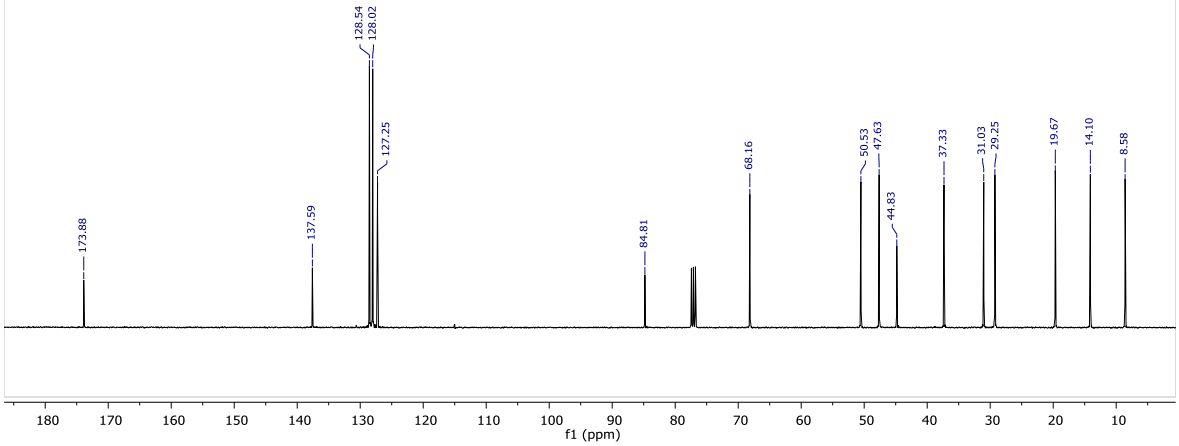


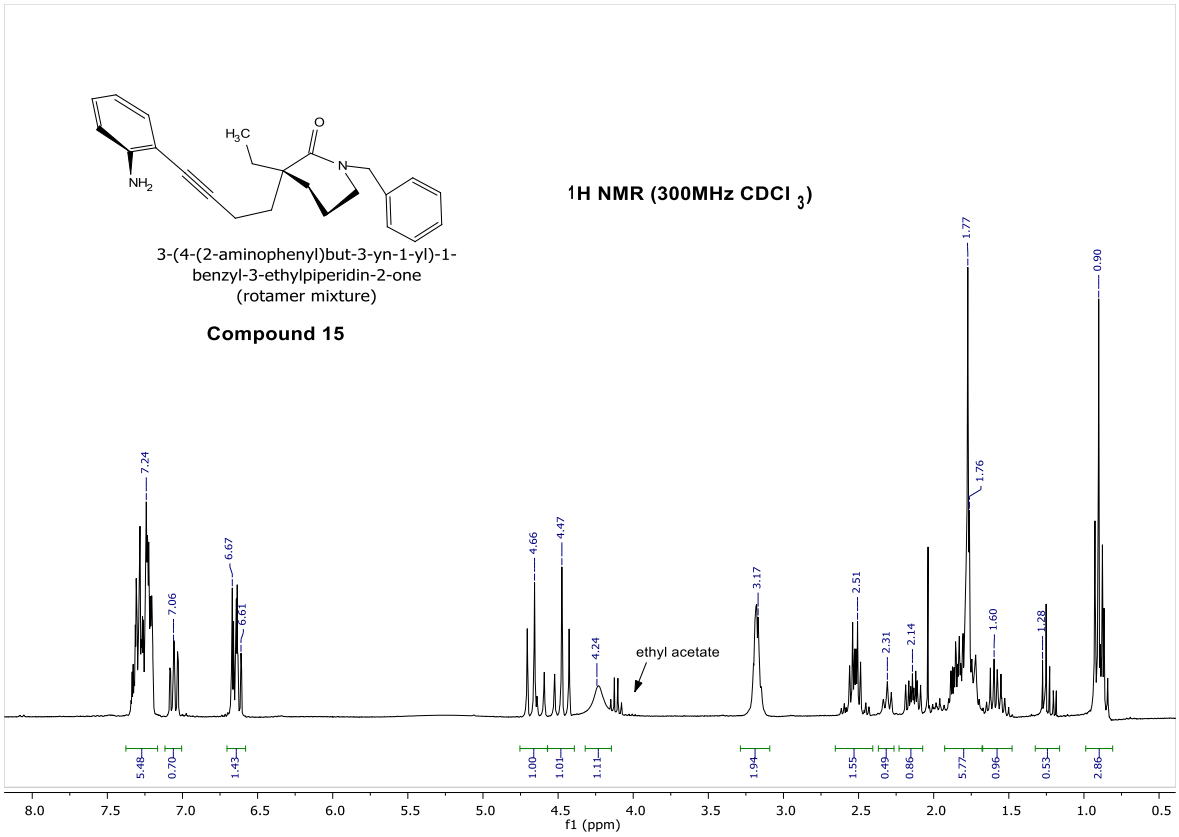


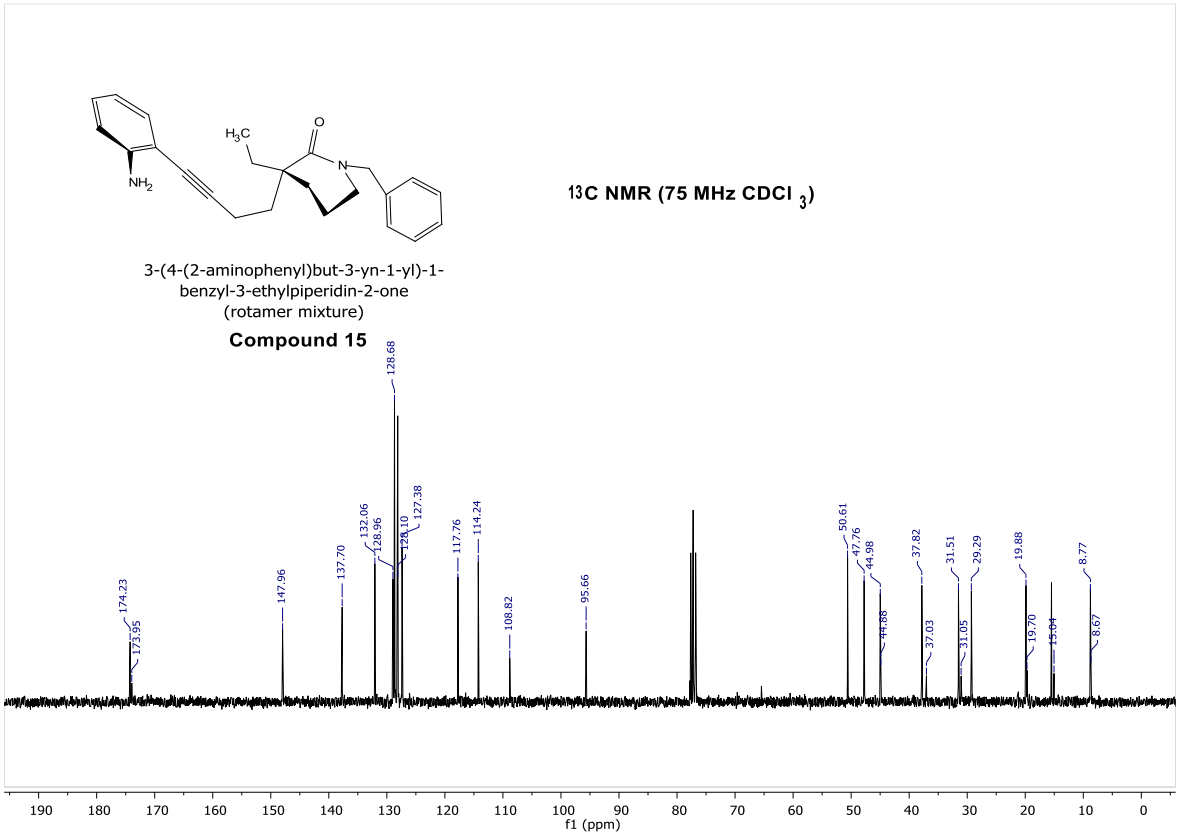
^{13}C NMR (100MHz CDCl $_3$)

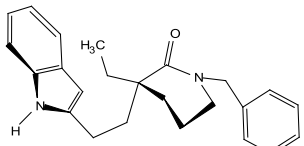
1-benzyl-3-(but-3-yn-1-yl)-3-ethylpiperidin-2-one

Compound 8




3-(4-(2-aminophenyl)but-3-yn-1-yl)-1-benzyl-3-ethylpiperidin-2-one
(rotamer mixture)
Compound 15
1H NMR (300MHz CDCl 3)
ethyl acetate
f1 (ppm)

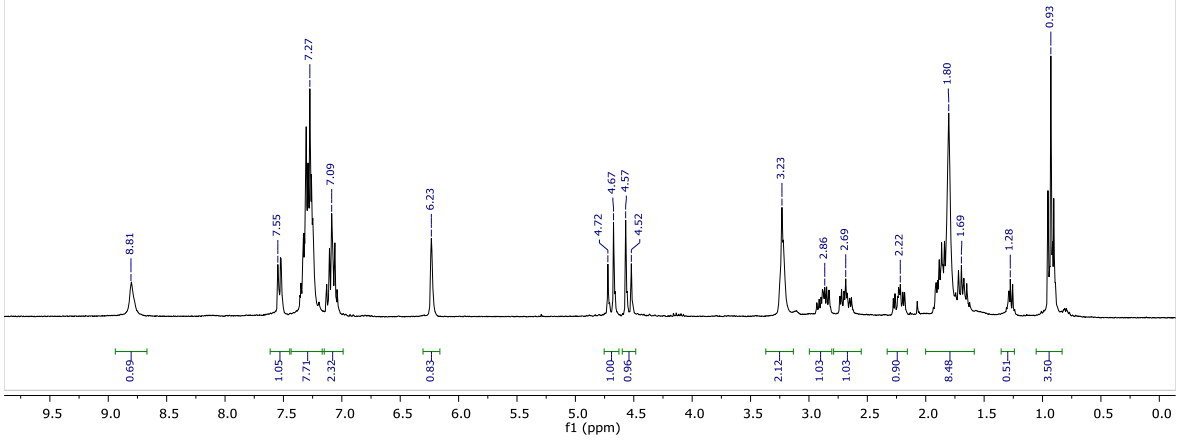

3-(4-(2-aminophenyl)but-3-yn-1-yl)-1-benzyl-3-ethylpiperidin-2-one
(rotamer mixture)
Compound 15
13C NMR (75 MHz CDCl 3)
f1 (ppm)

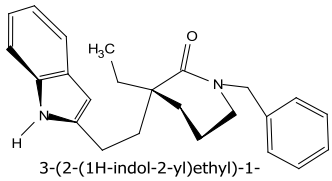


3-(2-(1H-indol-2-yl)ethyl)-1-benzyl-3-ethylpiperidin-2-one

Compound 6

1H NMR (300MHz CDCl 3)

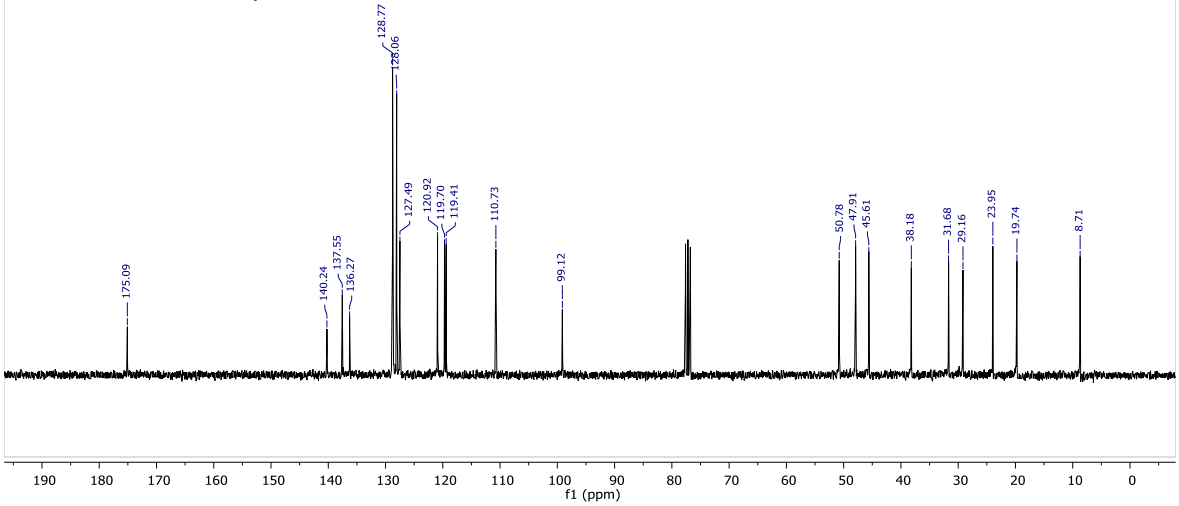


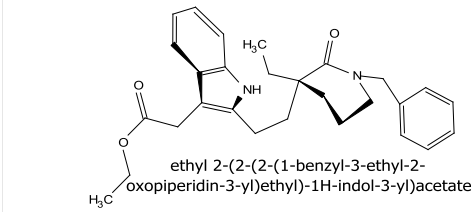


3-(2-(1H-indol-2-yl)ethyl)-1-benzyl-3-ethylpiperidin-2-one

Compound 6

13C NMR (75 MHz CDCl 3)

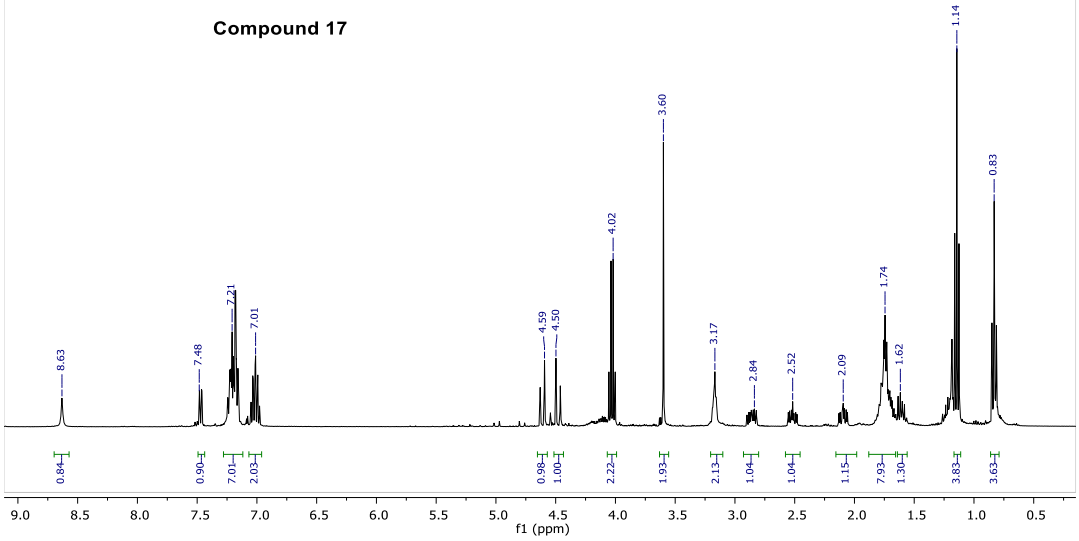


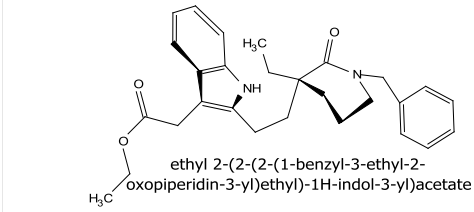


ethyl 2-(2-(2-(1-benzyl-3-ethyl-2-oxopiperidin-3-yl)ethyl)-1H-indol-3-yl)acetate

Compound 17

1H NMR (400 MHz CDCl 3)

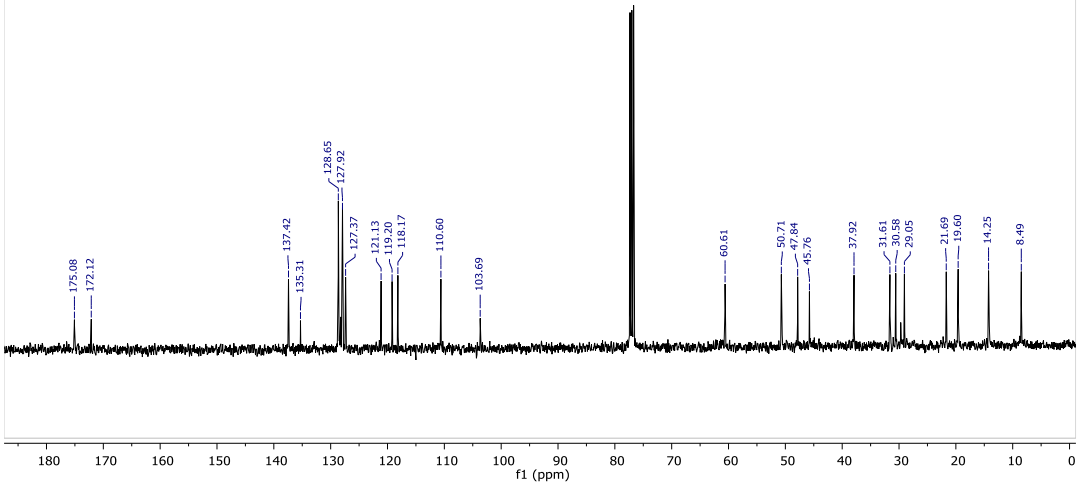


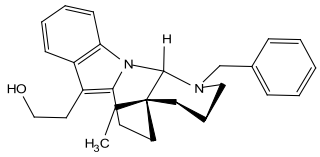


ethyl 2-(2-(2-(1-benzyl-3-ethyl-2-oxopiperidin-3-yl)ethyl)-1H-indol-3-yl)acetate

Compound 17

13C NMR (100 MHz CDCl 3)

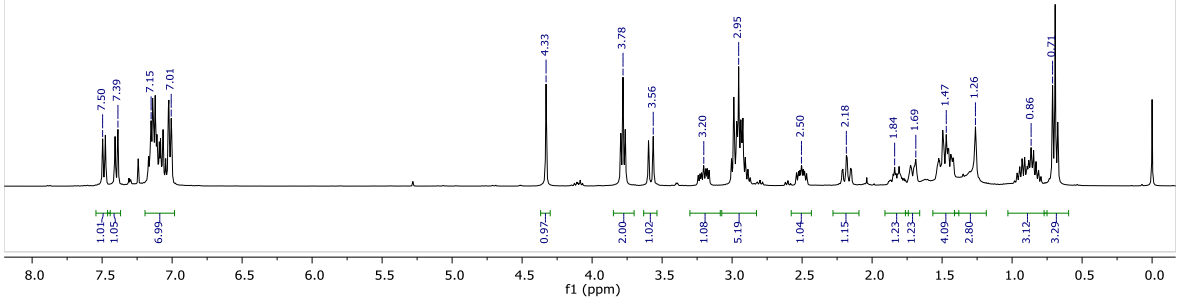


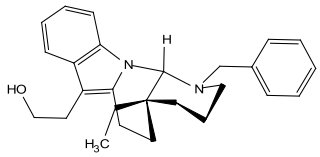


N-benzyl-goniomitine

Compound 20

^{1}H NMR (400 MHz CDCl $_3$)

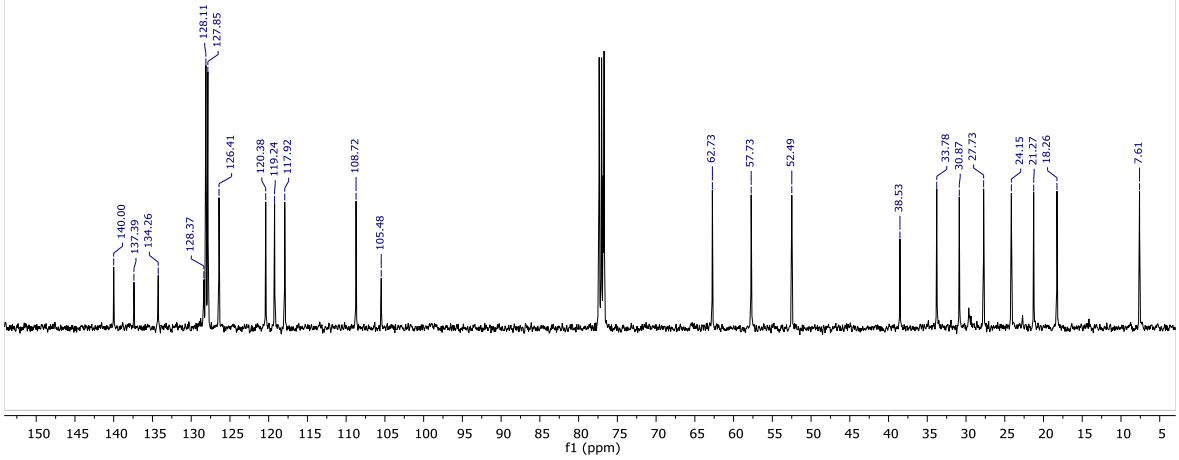


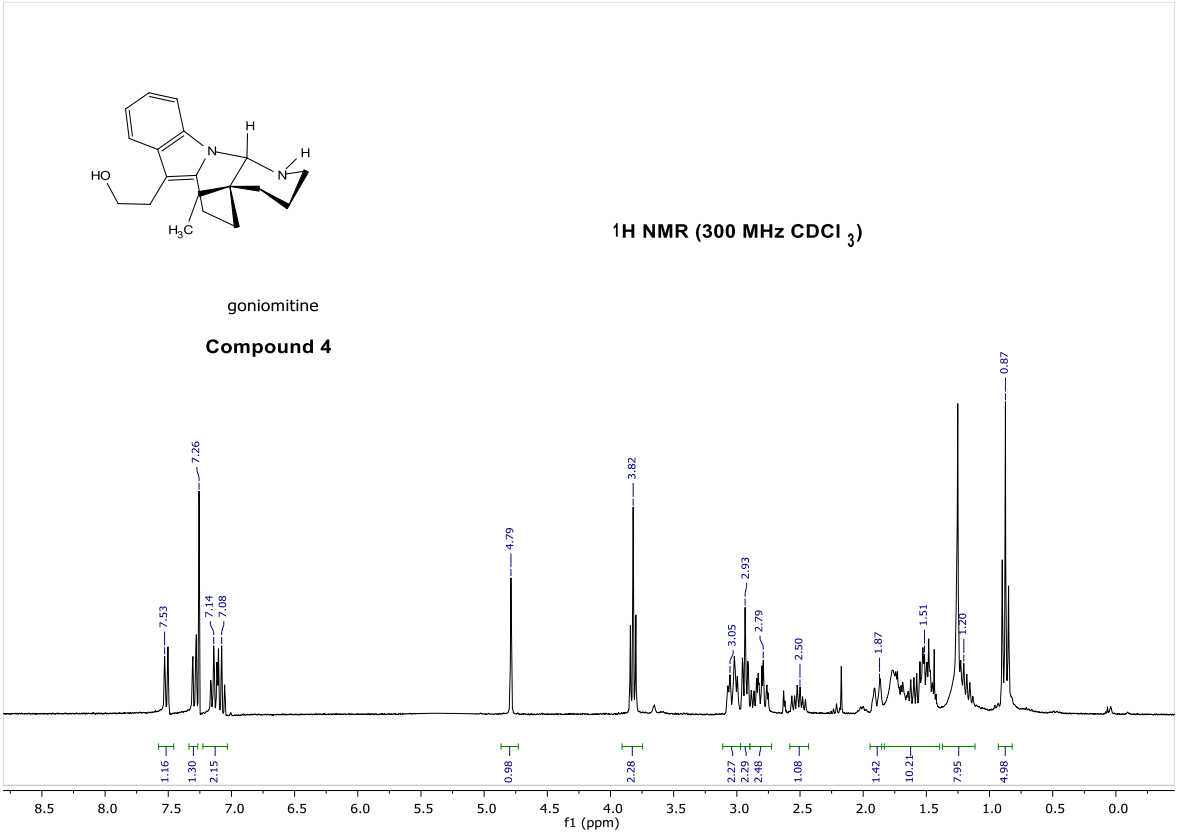


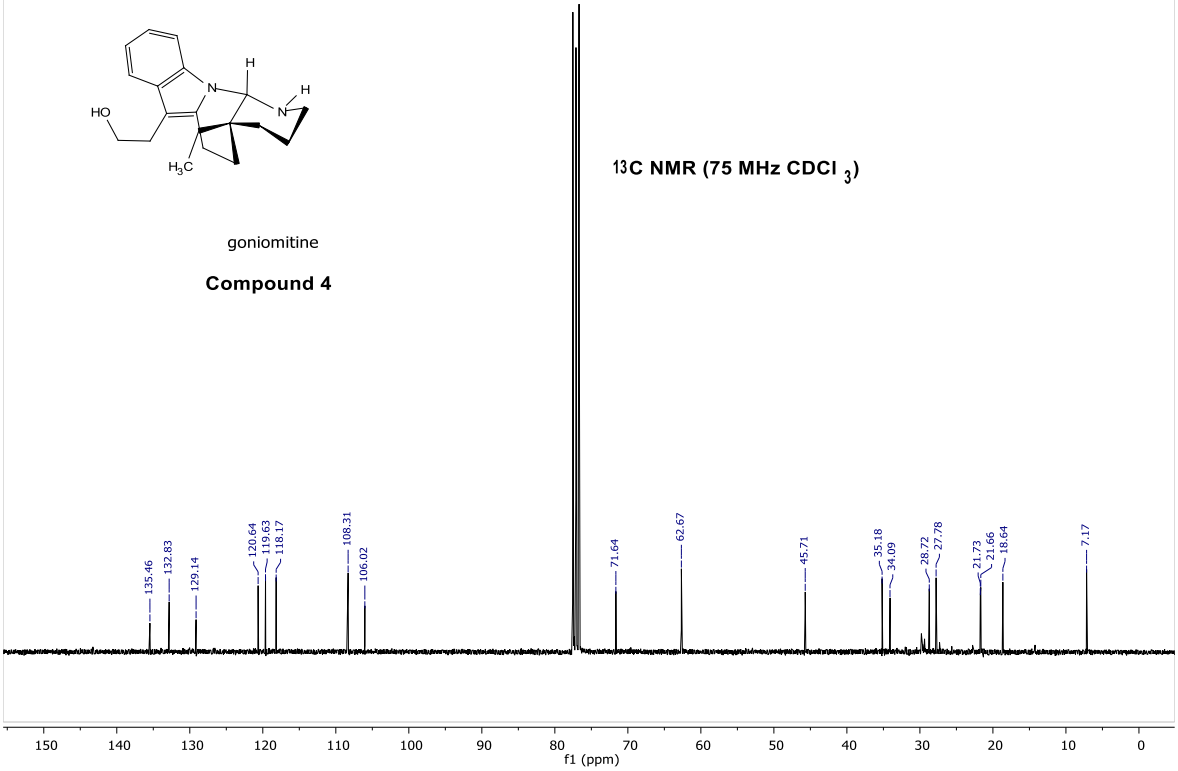
N-benzyl-goniomitine

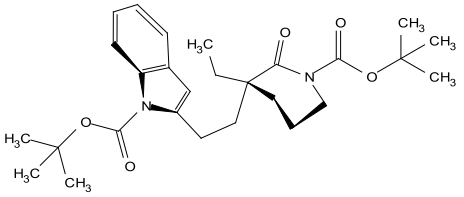
Compound 20

^{13}C NMR (100 MHz CDCl $_3$)




HO
H
N
H
N
H3C
1H NMR (300 MHz CDCl 3)
goniomitine
Compound 4
7.53
7.26
7.14
7.08
4.79
3.82
3.05
2.93
2.79
2.50
1.87
1.51
1.20
0.87
1.16
1.30
2.15
0.98
2.28
2.27
2.29
2.48
1.08
1.42
10.21
7.95
4.98
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

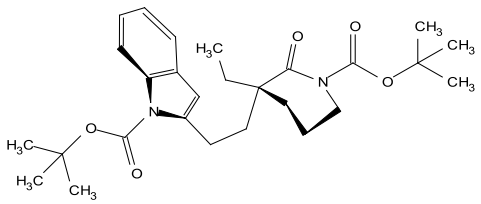

HO
H
N
H
N
H3C
13C NMR (75 MHz CDCl 3)
goniomitine
Compound 4
135.46
132.83
129.14
120.64
119.63
118.17
108.31
106.02
71.64
62.67
45.71
35.18
34.09
28.72
27.78
21.73
21.66
18.64
7.17
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



tert-butyl 2-(2-(1-(tert-butoxycarbonyl)-3-ethyl-2-oxopiperidin-3-yl)ethyl)-1H-indole-1-carboxylate

Compound di-Boc-6

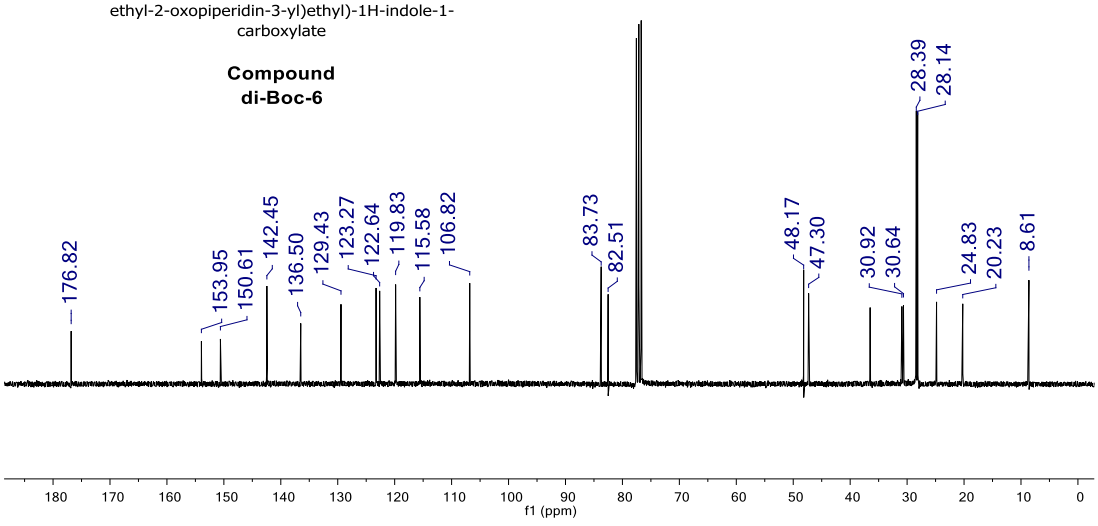
^{1}H NMR (300 MHz CDCl $_3$)

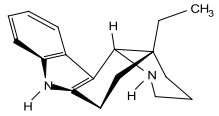


tert-butyl 2-(2-(1-(tert-butoxycarbonyl)-3-ethyl-2-oxopiperidin-3-yl)ethyl)-1H-indole-1-carboxylate

Compound di-Boc-6

^{13}C NMR (75 MHz CDCl $_3$)

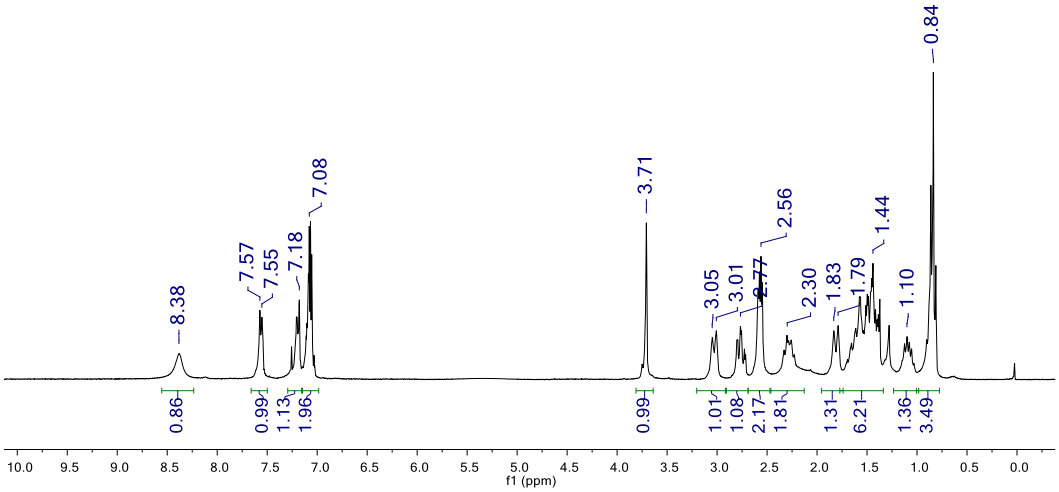


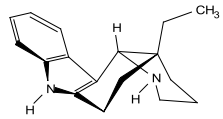


4a-ethyl-2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido[3,2-c]carbazole

Compound 22b

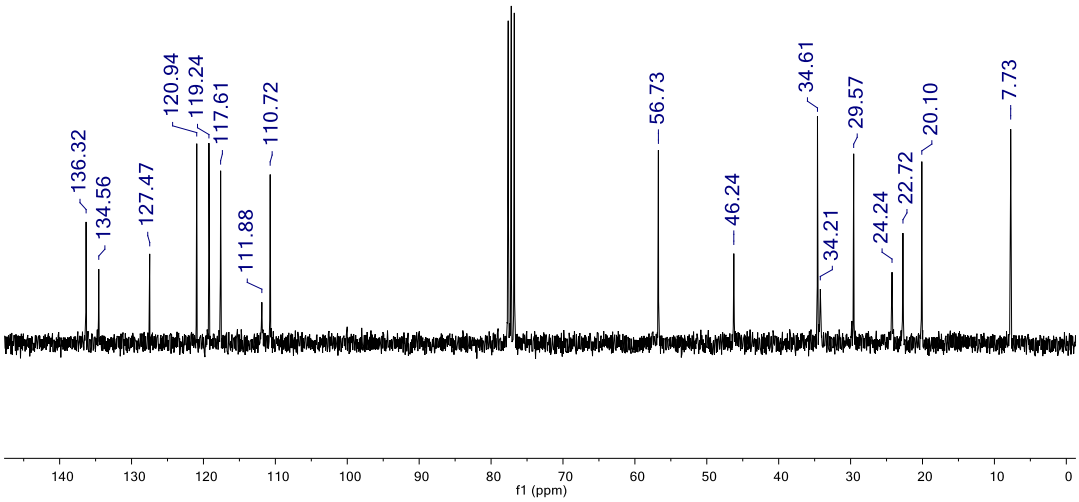
^{1}H NMR (300 MHz CDCl $_3$)

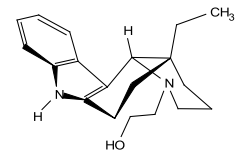




Compound 22b

^{13}C NMR (75 MHz CDCl $_3$)

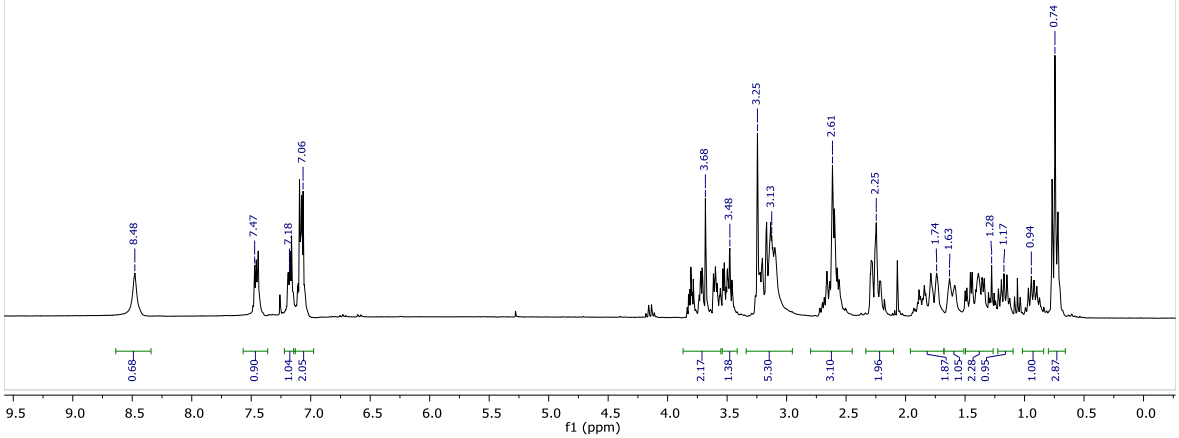


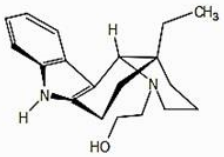


2-(4a-ethyl-2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido[3,2-c]carbazol-1-yl)ethan-1-ol

1H NMR (300 MHz CDCl 3)

Compound 23

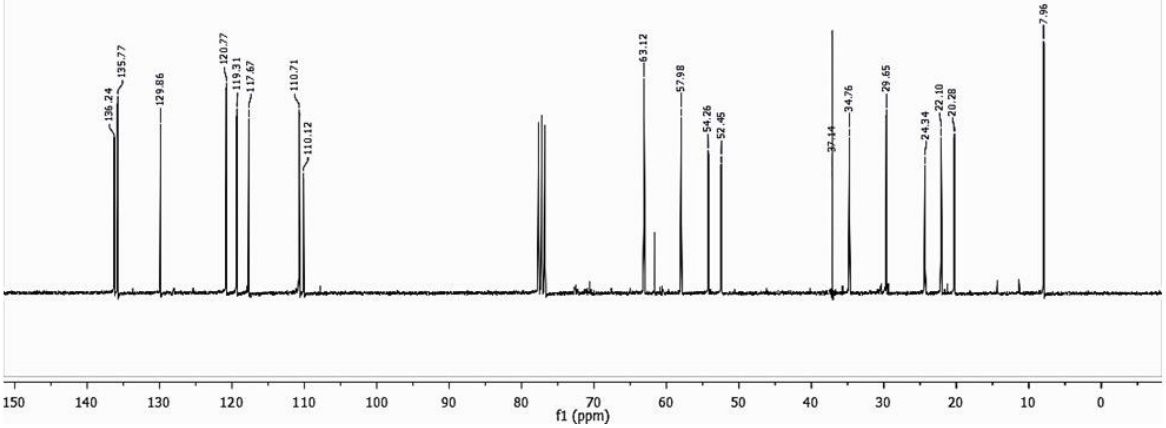


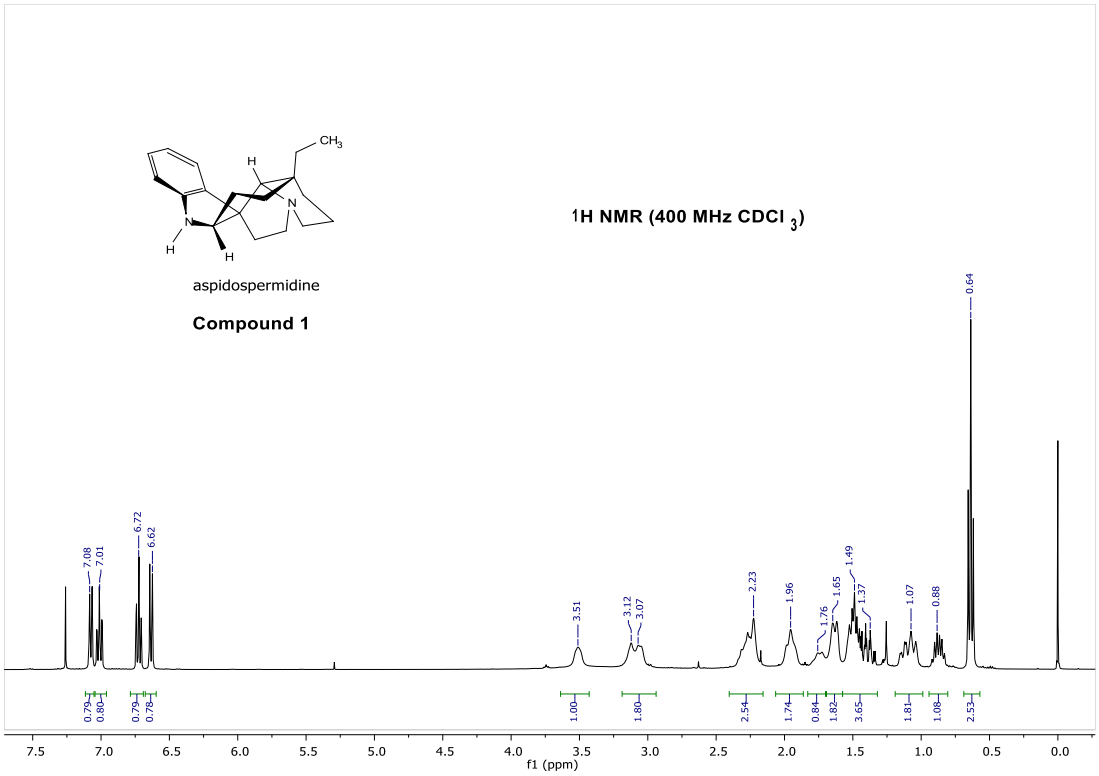


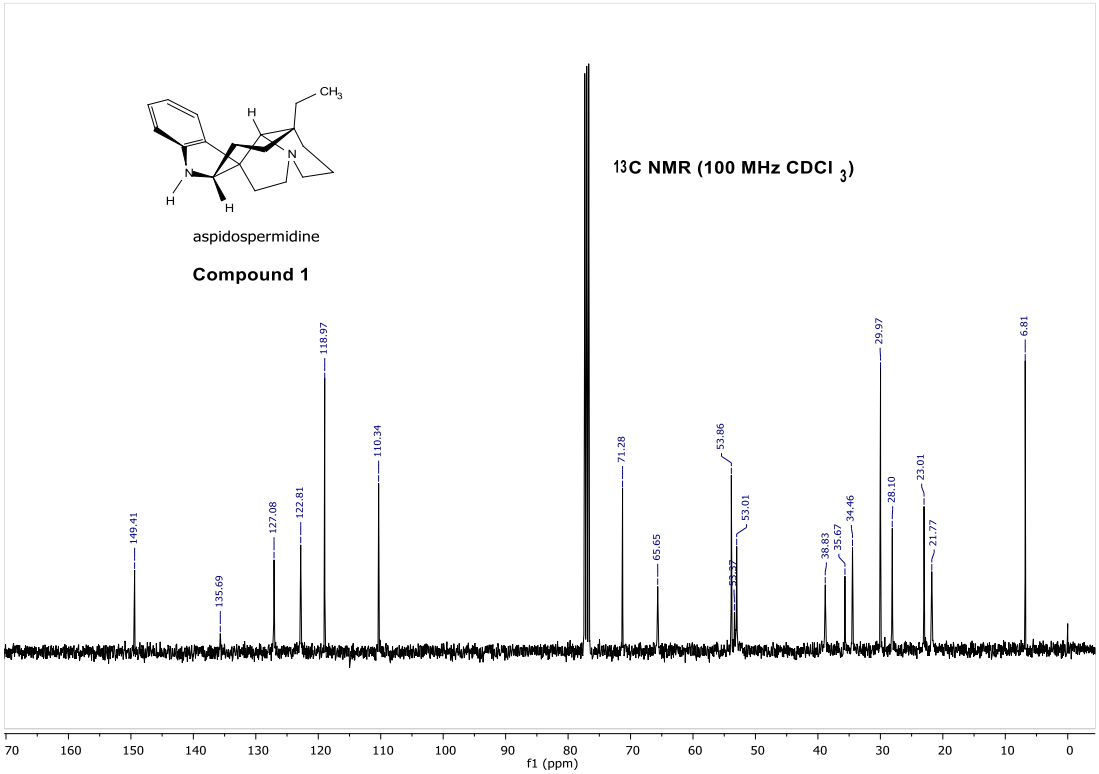
2-(4a-ethyl-2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido[3,2-c]carbazol-1-yl)ethan-1-ol

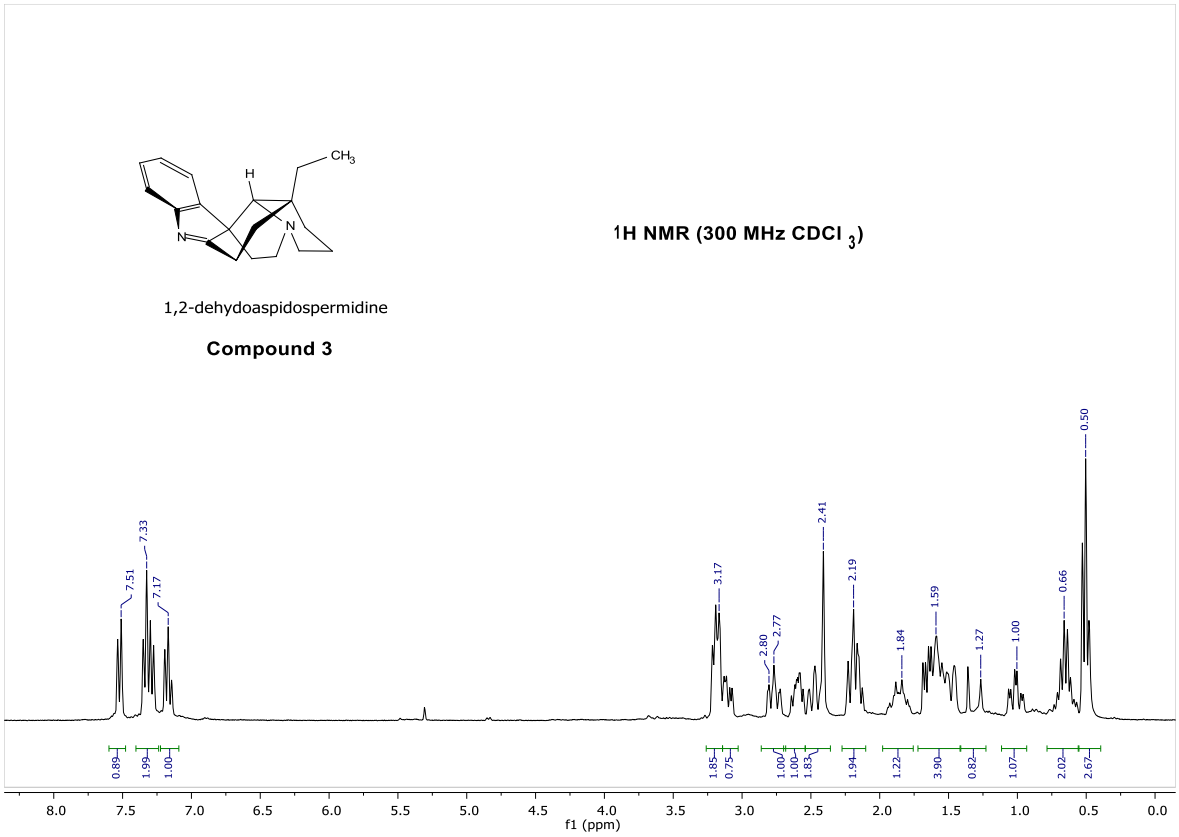
13C NMR (75 MHz CDCl3)

Compound 23




CH3
H
N
N
H
H
aspidospermidine
Compound 1
1H NMR (400 MHz CDCl 3)
7.08
7.01
6.72
6.62
3.51
3.12
3.07
2.23
1.96
1.76
1.65
1.49
1.37
1.07
0.88
0.64
0.79
0.80
0.79
0.78
1.00
1.80
2.54
1.74
0.84
1.82
3.65
1.81
1.08
2.53
f1 (ppm)

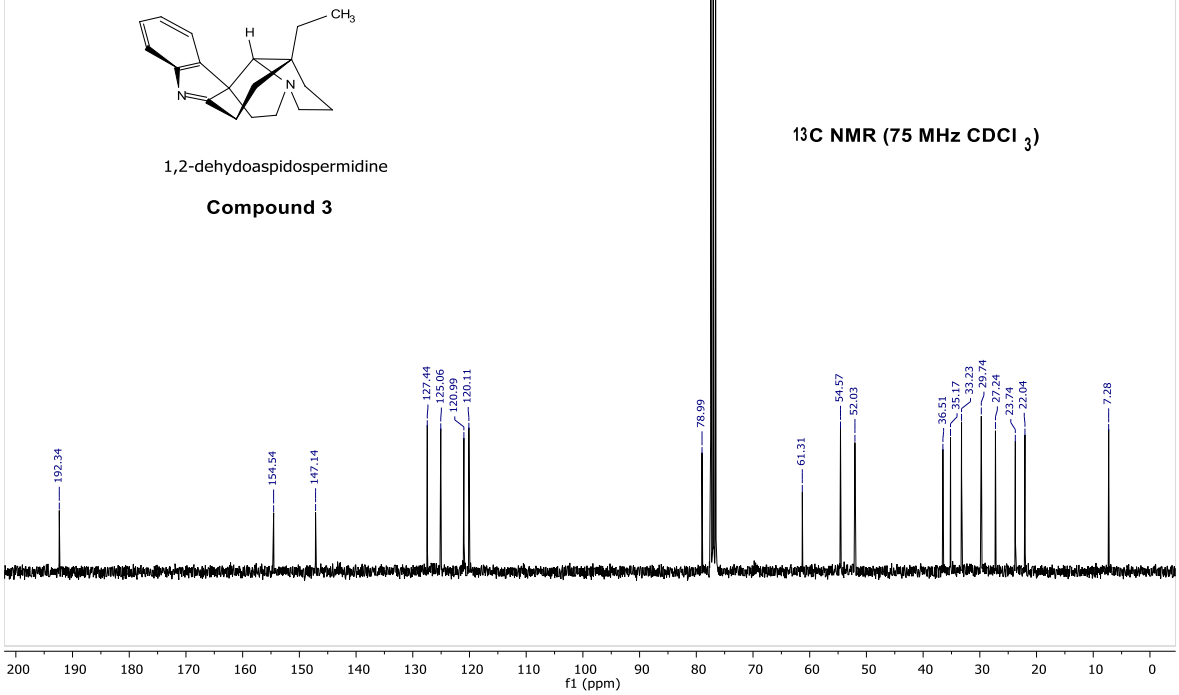

CH3
H
N
N
H
H
aspidospermidine
Compound 1
13C NMR (100 MHz CDCl 3)
149.41
135.69
127.08
122.81
118.97
110.34
71.28
65.65
53.86
53.01
53.27
38.83
35.67
34.46
29.97
28.10
23.01
21.77
6.81
f1 (ppm)



1,2-dehydoaspidospermidine

Compound 3

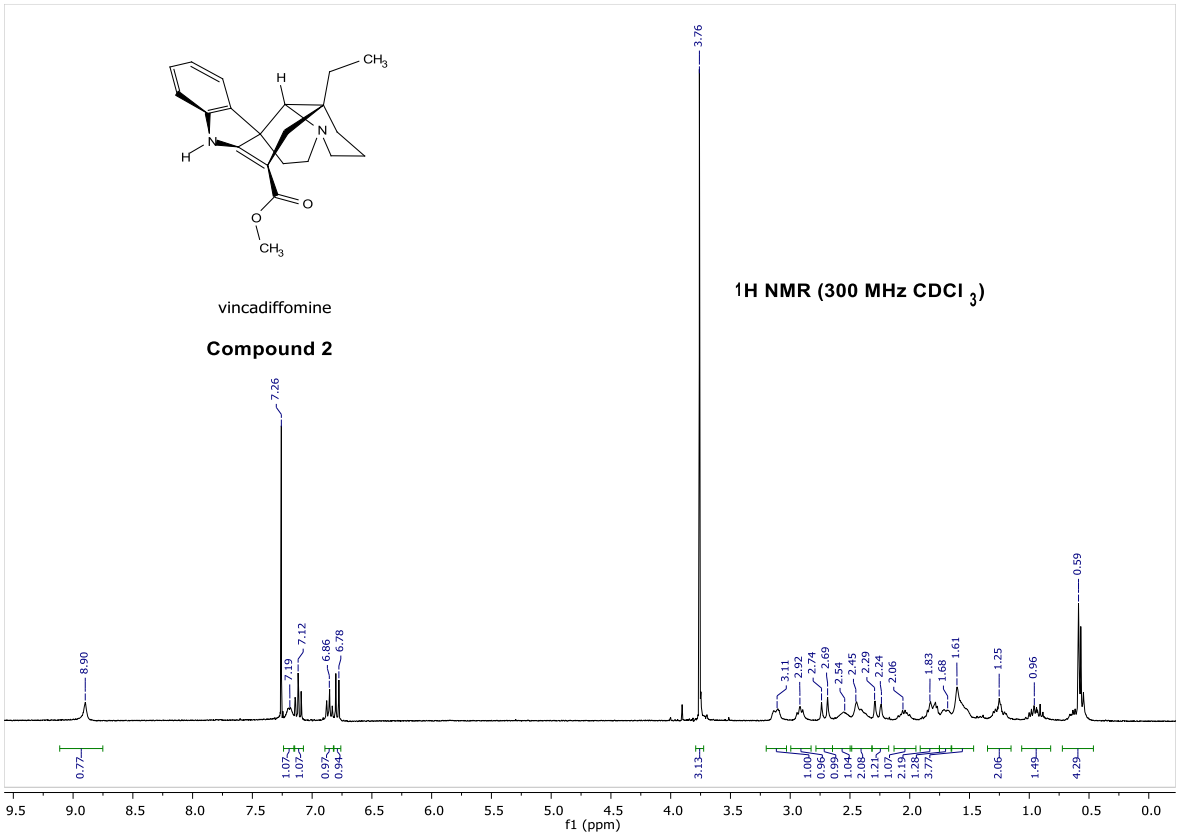
1H NMR (300 MHz CDCl 3)

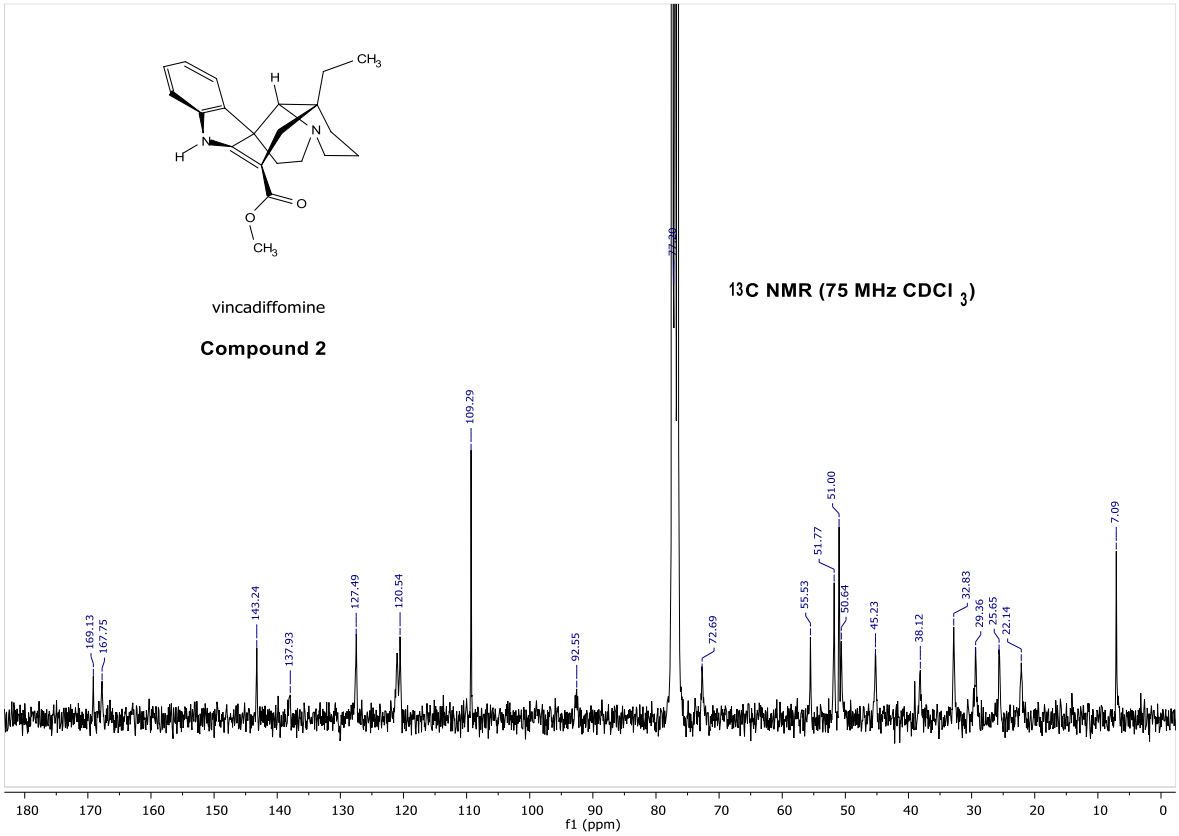


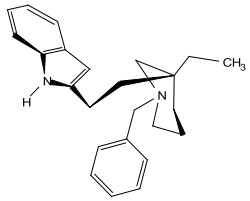
1,2-dehydoaspidospermidine

Compound 3

13C NMR (75 MHz CDCl 3)


vincadiffomine
Compound 2
1H NMR (300 MHz CDCl 3)
f1 (ppm)

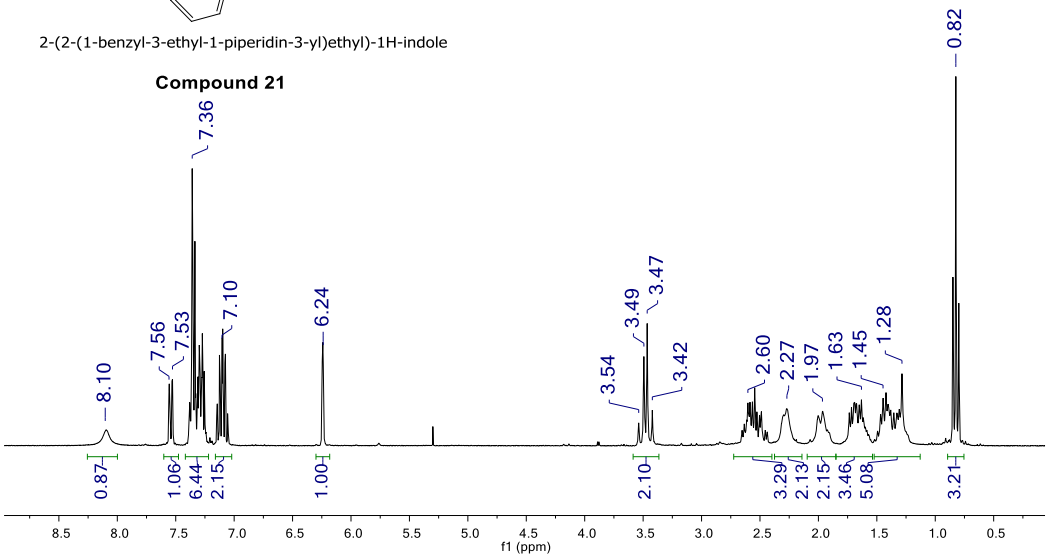

vincadiffomine
Compound 2
13C NMR (75 MHz CDCl 3)
f1 (ppm)

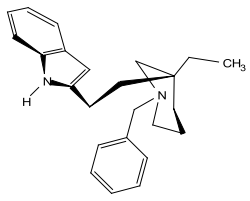


2-(2-(1-benzyl-3-ethyl-1-piperidin-3-yl)ethyl)-1H-indole

1H NMR (300 MHz CDCl 3)

Compound 21

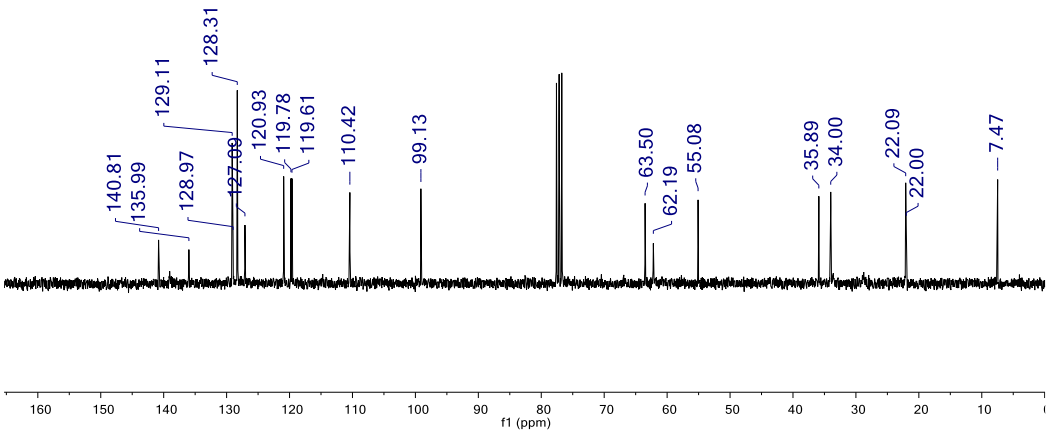


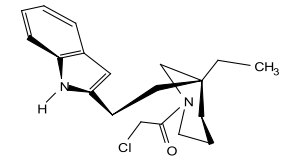


2-(2-(1-benzyl-3-ethyl-1-piperidin-3-yl)ethyl)-1H-indole

1H NMR (300 MHz CDCl 3)

Compound 21



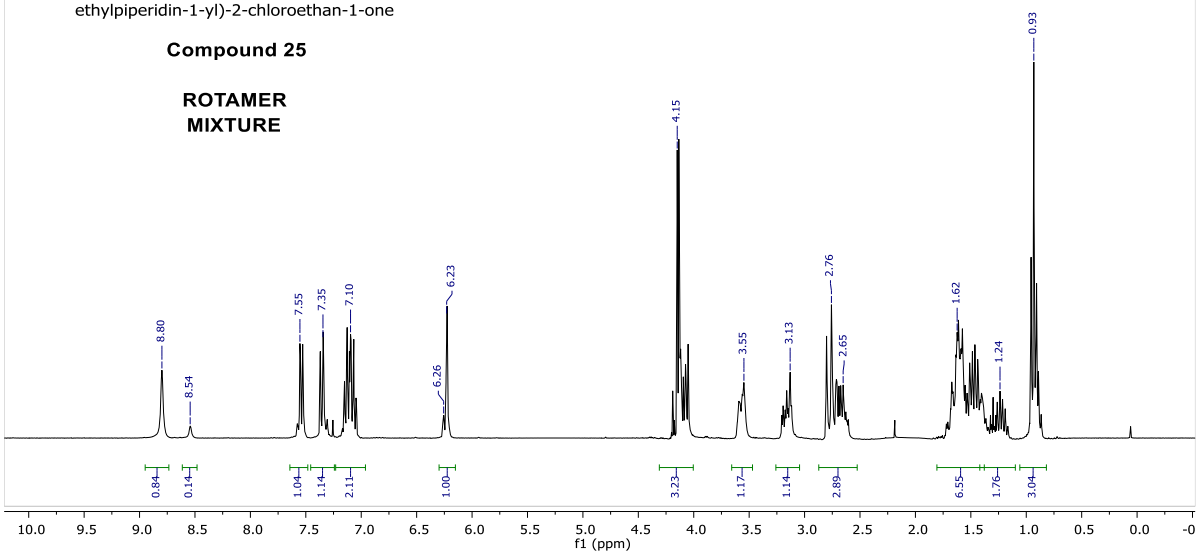


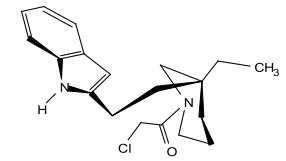
1-(3-(2-(1H-indol-2-yl)ethyl)-3-ethylpiperidin-1-yl)-2-chloroethan-1-one

Compound 25

ROTAMER MIXTURE

1H NMR (300 MHz CDCl 3)



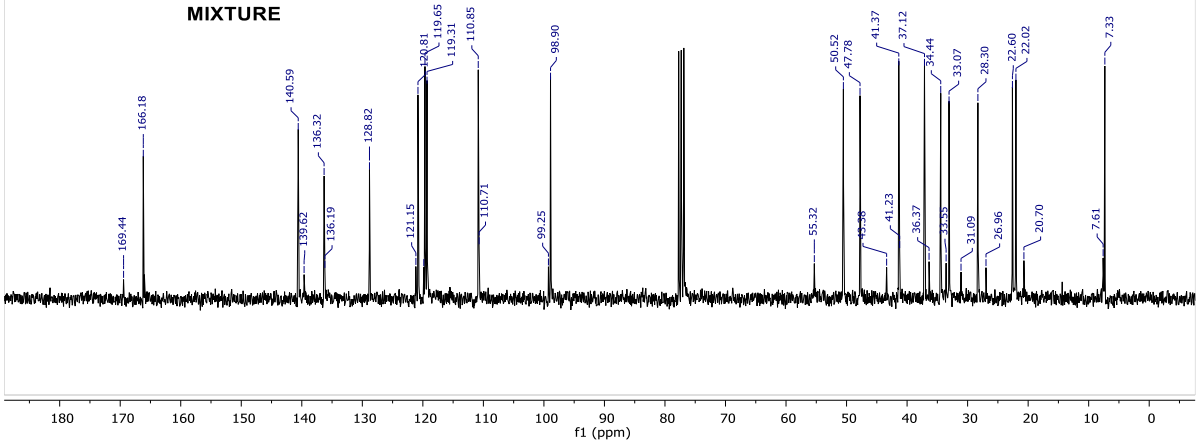


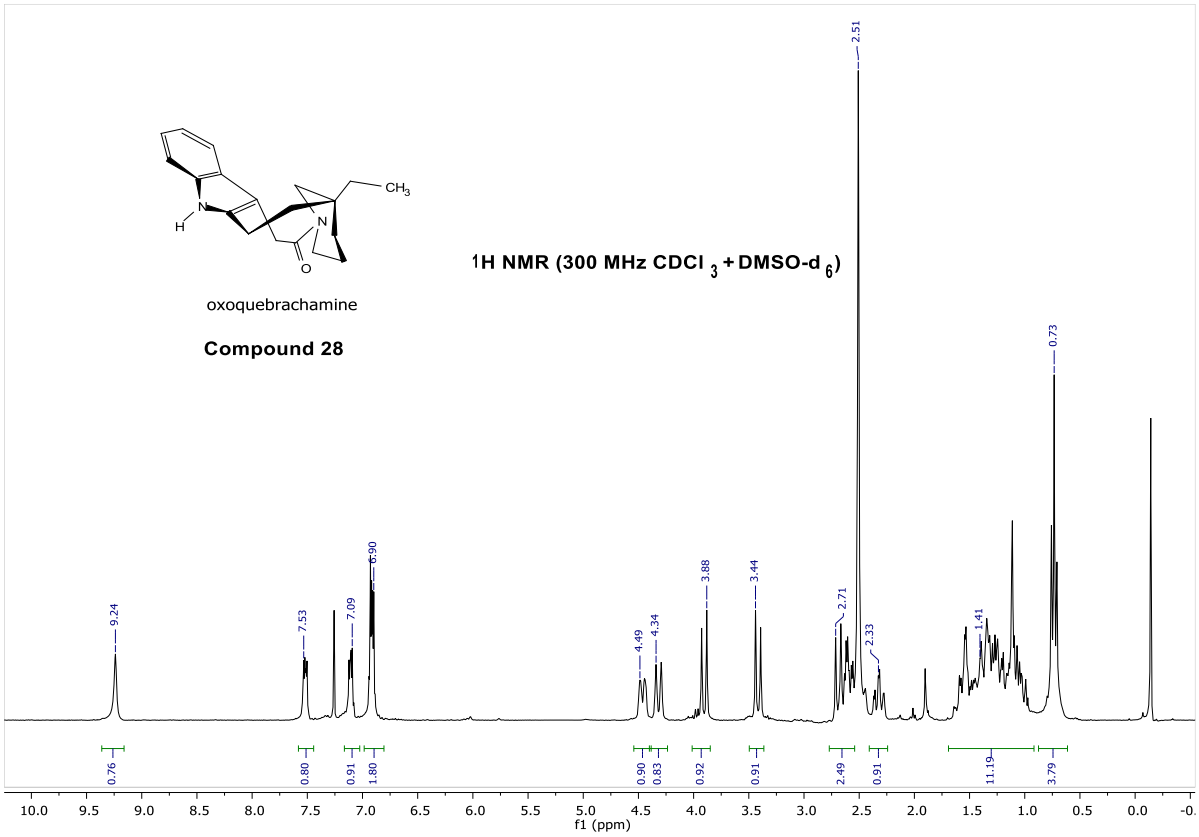
1-(3-(2-(1H-indol-2-yl)ethyl)-3-ethylpiperidin-1-yl)-2-chloroethan-1-one

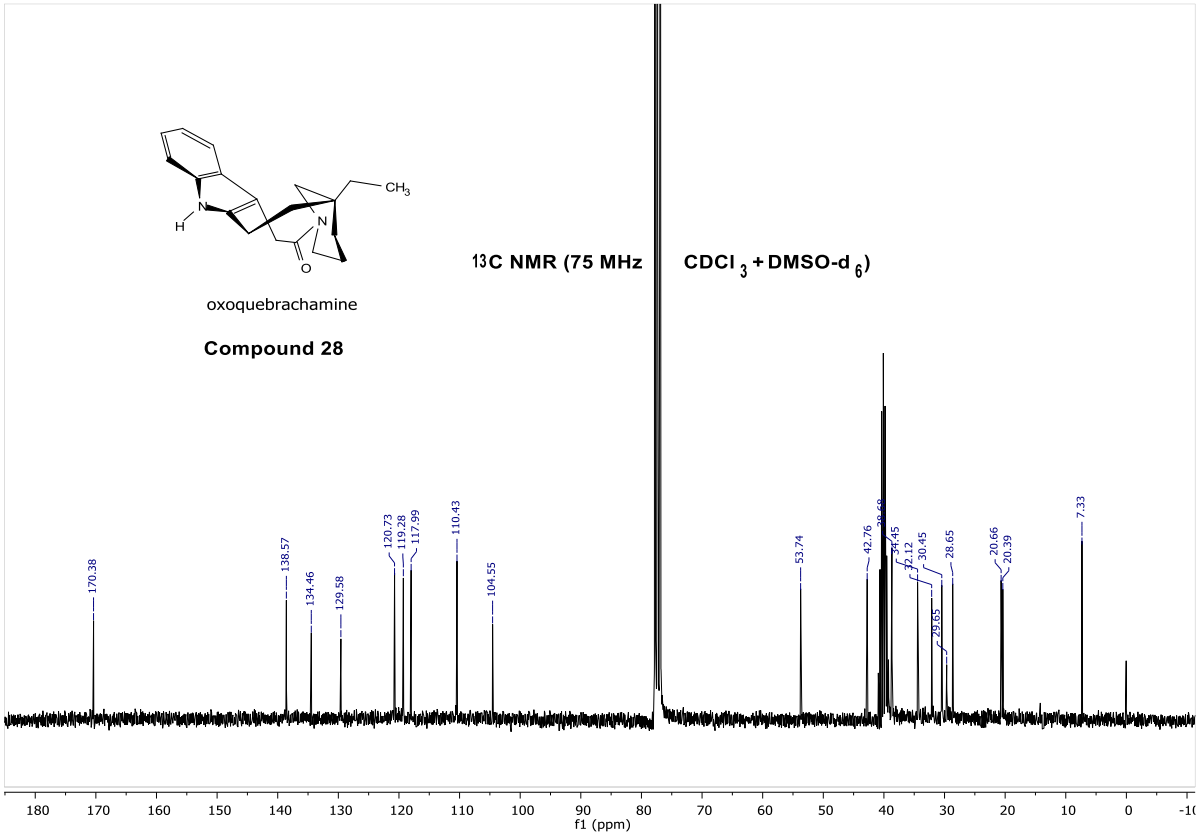
Compound 25

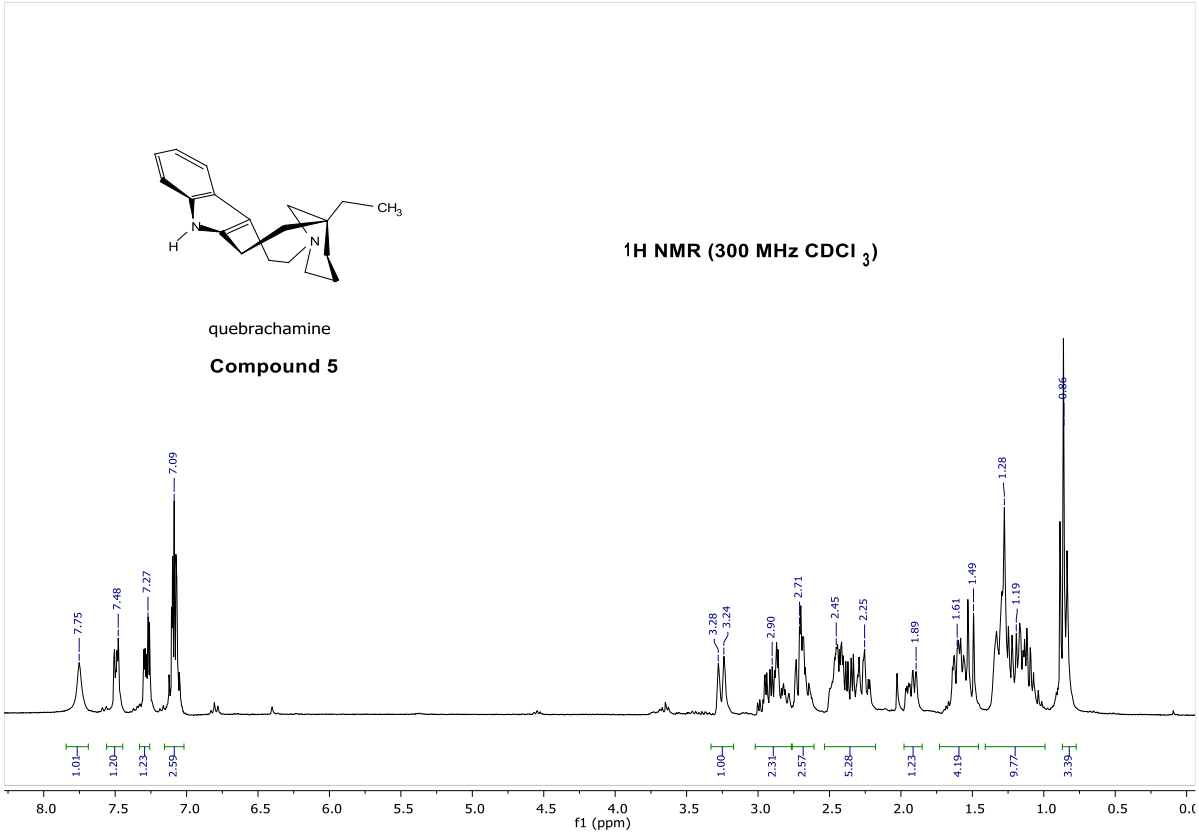
ROTAMER MIXTURE

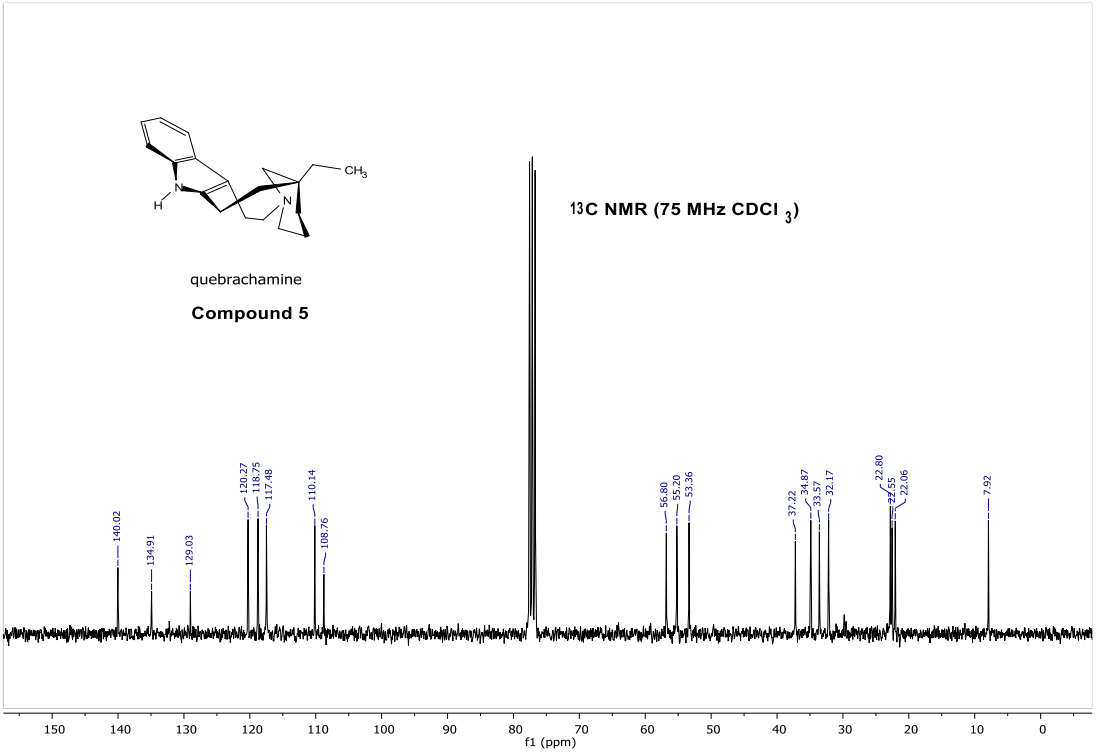
13C NMR (75 MHz CDCl 3)

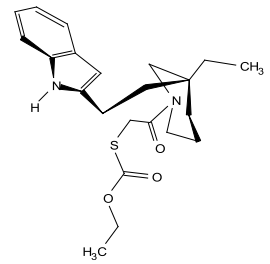



oxoquebrachamine
Compound 28
1H NMR (300 MHz CDCl 3 + DMSO-d 6)
f1 (ppm)


oxoquebrachamine
Compound 28
13C NMR (75 MHz CDCl 3 + DMSO-d 6)
f1 (ppm)


1H NMR (300 MHz CDCl 3)
quebrachamine
Compound 5
7.75
7.48
7.27
7.09
3.28
3.24
2.90
2.71
2.45
2.25
1.89
1.61
1.49
1.28
1.19
0.86
1.01
1.20
1.23
2.59
1.00
2.31
2.57
5.28
1.23
4.19
9.77
3.39
f1 (ppm)

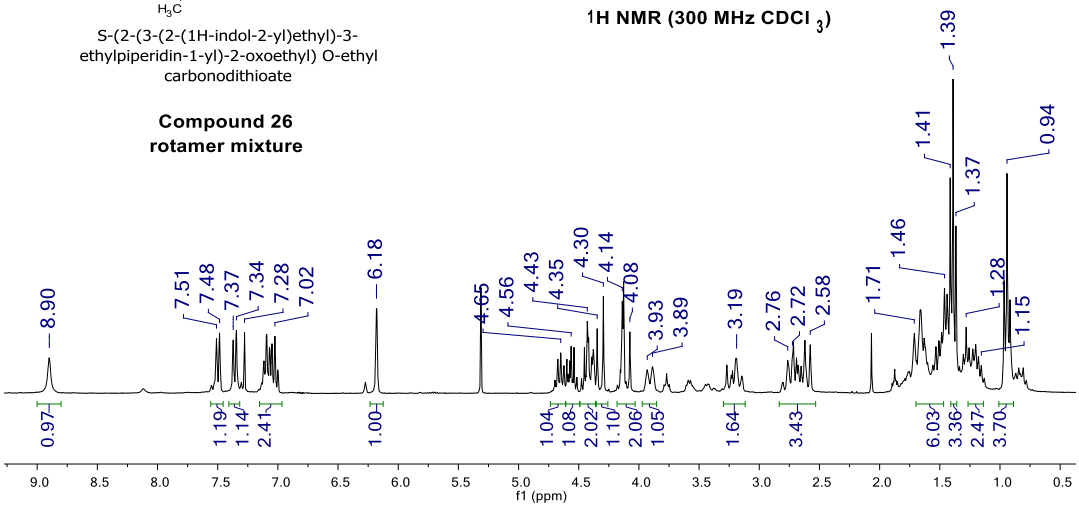

13C NMR (75 MHz CDCl 3)
quebrachamine
Compound 5
140.02
134.91
129.03
120.27
118.75
117.48
110.14
108.76
56.80
55.20
53.36
37.22
34.87
33.57
32.17
22.80
22.55
22.06
7.92
f1 (ppm)

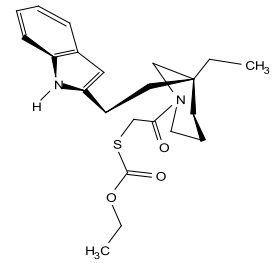


S-(2-(3-(2-(1H-indol-2-yl)ethyl)-3-ethylpiperidin-1-yl)-2-oxoethyl) O-ethyl carbonodithioate

Compound 26
rotamer mixture

^{1}H NMR (300 MHz CDCl $_3$)





S-(2-(3-(2-(1H-indol-2-yl)ethyl)-3-ethylpiperidin-1-yl)-2-oxoethyl) O-ethyl carbonodithioate

Compound 26
rotamer mixture

^{13}C NMR (300 MHz CDCl $_3$)