Electronic Supplementary Material (ESI) for Chemical Communications.

Supporting Information for

"Extension of hydrogen borrowing alkylation reactions for the total synthesis of (–)-γ-Lycorane"

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Contents

1. General Information

Reactions were carried out in standard glassware under an atmosphere of air unless stated otherwise. Room temperature (rt) refers to 20-25 °C. Temperatures of 0 °C were obtained using an ice/water bath. High temperatures were obtained using an oil bath equipped with a contact thermometer.

Diethyl ether, CH_2Cl_2, DMF, and tetrahydrofuran were purified by filtration through activated alumina columns employing the method of Grubbs *et al*.[1] All other solvents and reagents were used as supplied without prior purification. All other reagents were used directly as supplied by major chemical suppliers, or following purification procedures described by Perrin and Armarego.[2]

Thin layer chromatography was performed on Merck Kieselgel 60 F_{254} 0.25 mm pre-coated aluminium plates. Product spots were visualized under UV light (λ = 254 nm) and/or by staining with potassium permanganate solution. Flash chromatography was performed using VWR silica gel 60 (40-63 µm particle size) using head pressure by means of a nitrogen line.

NMR spectroscopy was carried out using Bruker 400 MHz or 500 MHz spectrometers in the deuterated solvent stated, using the residual non-deuterated solvent signal as an internal reference. Chemical shifts are quoted in ppm with signal splittings recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), sextet (sext), septet (sept), octet (oct), nonet (non) and multiplet (m). The abbreviation br denotes broad. Coupling constants, *J*, are measured to the nearest 0.1 Hz and are presented as observed.

Infrared spectra were recorded neat on a Bruker Tensor 27 spectrometer equipped with an attenuated total reflectance attachment with internal calibration. Absorption maxima (λ_{max}) are quoted in wavenumbers (cm^{-1}). The abbreviation br denotes broad.

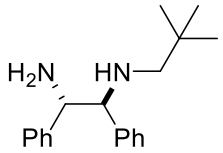
Electrospray ionisation (ESI) HRMS were recorded on a Thermo Exactive orbitrap spectrometer equipped with a Waters Equity LC system, with a flow rate of 0.2 mL/min using water:methanol:formic acid (10:89.9:0.1) as eluent. The system uses a heated electrospray ionisation (HESI-II) probe for ESI^+ and has a resolution of 50,000 FWHM under conditions for maximum sensitivity, with an accuracy of better than 5 ppm for 24 h following external calibration on the day of analysis. The mass reported is that containing the most abundant isotopes, with each value rounded to 4 decimal places and within 5 ppm of the calculated mass. Electron impact ionisation (EI) HRMS were performed on an Agilent 7200 quadrupole time of flight (Q-ToF) instrument equipped with a direct insertion probe supplied by Scientific Instrument Manufacturer (SIM) GmbH. Instrument control and data processing were performed using Agilent MassHunter software. The mass reported is that containing the most abundant isotopes, with each value to 4 decimal places and within 5 ppm of the calculated mass.

Optical rotations were recorded on a Schmidt Haensch Unipol L2000 polarimeter in a cell with a path length of 1 dm (using the sodium D line, 589 nm). Concentrations are reported in g/100 mL. Temperatures are reported in °C.

Chiral normal phase HPLC was performed on an Agilent 1260 Series HPLC unit equipped with UV-vis diode-array detector, fitted with the appropriate Daicel Chiralpak column (dimensions: 0.46 cm ø x 25 cm) along with the corresponding guard column (0.4 cm ø x 1 cm). Wavelengths (λ) are reported in nm, retention times (t_R) are reported in minutes and solvent flow rates are reported in mL min^{-1}.

2. Experimental Procedures

(1*S*,2*S*)-N^1-Neopentyl-1,2-diphenylethane-1,2-diamine, 4



4

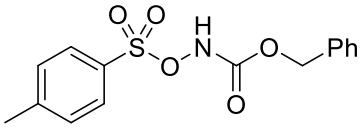
To a stirred solution of (1S,2S)-DPEN (182 mg, 0.86 mmol, 1.0 equiv.) in MeOH (2 mL) at rt was added pivaldehyde (103 µL, 0.95 mmol, 1.1 equiv.) and the reaction left to stir for 1 h. The reaction was then cooled to 0 °C and $NaBH_4$ (65 mg, 1.72 mmol, 2.0 equiv.) was added portion-wise. The reaction was then warmed to rt and stirred for 1.5 h before being quenched by the addition of water (10 mL). The precipitated solid was collected by filtration and air-dried at 80 °C overnight to give the desired amine **4** (218 mg, 77%) as a colourless, amorphous powder.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.25 – 7.06 (m, 10H), 3.97 (d, J = 7.0 Hz, 1H), 3.64 (d, J = 7.0 Hz, 1H), 2.17 (d, J = 11.2 Hz, 1H), 2.06 (d, J = 11.2 Hz, 1H), 0.85 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 143.8, 142.2, 128.2 (2C), 128.1 (2C), 127.9 (2C), 127.2 (2C), 127.0, 126.9, 70.6, 62.2, 60.2, 31.8, 27.9 (3C).

Data was consistent with that previously reported.[3]

Benzyl (tosyloxy)carbamate, SI-1



SI-1

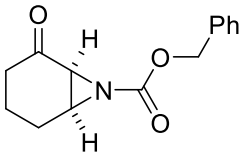
To a stirred solution of Na_2CO_3 (6.5 g, 60 mmol, 1.5 equiv.) in water (20 mL) was added hydroxylamine hydrochloride (3.2 g, 46 mmol, 1.15 equiv.), followed by a solution of benzyl chloroformate (5.63 mL, 40 mmol, 1.0 equiv.) in CH_2Cl_2. The reaction was stirred at rt for 4 h, after which the reaction was acidified to approximately pH 2 by the addition of conc. HCl, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product (5.88 g, 88%) as a colourless solid which was used without further purification. To a stirred solution of hydroxylamine (5.88 g, 35 mmol, 1.06 equiv.) and Et_3N (4.56 mL, 33 mmol, 1.0 equiv.) in THF (100 mL) at –15 °C was added TsCl (6.30 g, 33 mmol, 1.0 equiv.) in THF (50 mL) and the reaction left to stir for 30 min. Any precipitated solids were then filtered off and the filtrate concentrated *in vacuo* to give the crude product. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 67:33) gave the desired compound **SI-1** (7.99 g, 75%) as a colourless solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.85 – 7.80 (m, 2H), 7.35 – 7.32 (m, 2H), 7.28 – 7.16 (m, 5H), 5.02 (s, 2H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 155.4, 146.2, 134.6, 130.3, 129.9 (2C), 129.7 (2C), 128.9 (2C), 128.7 (2C), 128.5, 68.8, 22.0.

Data was consistent with that previously reported.[4]

Benzyl (1*S*,6*S*)-2-oxo-7-azabicyclo[4.1.0]heptane-7-carboxylate, 5



5

To a stirred solution of diamine catalyst **4** (1.13 g, 4 mmol, 0.2 equiv.), benzoic acid (2.44 g, 20 mmol, 1.0 equiv.), $NaHCO_3$ (8.4 g, 100 mmol, 5.0 equiv.), and protected hydroxylamine **SI-1** (6.42 g, 20 mmol, 1.0 equiv.) in $CHCl_3$ (200 mL) at rt was added 2-cyclohexen-1-one (5.82 mL, 60 mmol, 3.0 equiv.) and the reaction left to stir for 66 h. The reaction was then quenched by the addition of water (200 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting oil was purified by column chromatography (SiO_2, dry load, pentane:Et_2O, 70:30) to give the desired compound (–)-**5** (3.17 g, 64%, 98:2 er) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.42 – 7.29 (m, 5H), 5.14 (d, J = 0.9 Hz, 2H), 3.15 (dtd, J = 5.7, 2.3, 0.9 Hz, 1H), 2.99 (d, J = 5.8 Hz, 1H), 2.55 – 2.44 (m, 1H), 2.32 – 2.21 (m, 1H), 2.12 – 2.01 (m, 1H), 2.01 – 1.90 (m, 1H), 1.80 (dddd, J = 14.3, 11.0, 4.8, 2.2 Hz, 1H), 1.71 – 1.59 (m, 1H).

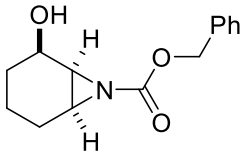
^{13}C NMR ($CDCl_3$, 100 MHz) δ = 203.8, 161.7, 135.5, 128.8 (2C), 128.7 (2C), 128.5, 68.8, 43.1, 40.8, 37.0, 22.7, 17.3.

$[\alpha]_D^{25}$ = – 79.5 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak AD with guard, 10.0 % IPA, 90.0 % hexane, 1.0 mL/min, 25 °C, λ = 210 nm, 10 µL injection, t_r(major) = 10.1 min, t_r(minor) = 8.7 min).

Data (including er) was consistent with that previously reported.[5]

Benzyl (1*S*,2*R*,6*S*)-2-hydroxy-7-azabicyclo[4.1.0]heptane-7-carboxylate, 6



6

To a stirred solution of aziridine (–)-**5** (2.45 g, 10 mmol, 1.0 equiv.) in MeOH (100 mL) at –17 °C was added $NaBH_4$ (0.76 g, 20 mmol, 2.0 equiv.) portion-wise and the solution left to stir for 2 h. The reaction was then quenched by the addition of sat. aq. NaHCO3, extracted with EtOAc, dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (SiO2, eluent load, pentane:Et_2O, 40:60) gave the desired compound **6** (1.9 g, 77%) as a waxy solid, and as a 2.3:1 mixture of alcohol diastereomers.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.41 – 7.28 (m, 7H), 5.14 (s, 2H), 5.12 (s, 0.8H), 4.11 (dt, J = 7.2, 5.0 Hz, 0.4H), 4.03 – 3.94 (m, 1H), 2.99 – 2.87 (m, 2H), 2.77 (ddd, J = 5.8, 4.3, 1.3 Hz, 0.4H), 2.66 (dd, J = 6.1, 0.9 Hz, 0.4H), 2.14 (ddd, J = 9.9, 4.6, 2.5 Hz, 1H), 2.05 – 1.91 (m, 0.8H), 1.91 – 1.68 (m, 2.4H), 1.60 – 1.34 (m, 3.4H), 1.34 – 1.14 (m, 1.8H).

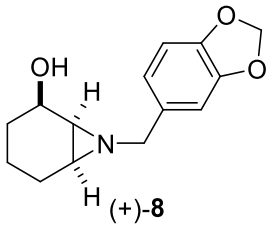
^{13}C NMR ($CDCl_3$, 100 MHz) δ = 165.6 (*minor*), 163.5 (*major*), 136.0 (*minor*), 135.9 (*major*), 128.7 (2C, *major*), 128.6 (2C, *minor*), 128.5 (2C, *major*), 128.5 (2C, *minor*), 128.4 (*minor*), 128.3 (*major*), 68.4 (*major*), 68.3 (*minor*), 66.0 (*minor*), 65.2 (*major*), 42.4 (*major*), 42.0 (*minor*), 40.2 (*major*), 38.2 (*minor*), 29.7 (*minor*), 29.6 (*major*), 23.5 (*minor*), 22.8 (*major*), 18.2 (*major*), 15.0 (*minor*).

IR ν_{max} (film)/cm^{-1} 3401, 2941, 1723, 1688, 1278, 1216, 1055, 752, 699.

HRMS (ESI^+) $C_{14}H_{17}O_3NNa$ requires 270.1101, found $[M+Na]^+$ 270.1101 (Δ 0.24 ppm).

M.p. 58 – 60 °C.

(1*S*,2*R*,6*S*)-7-(Benzo[d][1,3]dioxol-5-ylmethyl)-7-Azabicyclo[4.1.0]heptan-2-ol, 8



(+)-**8**

To a stirred solution of enantioenriched cyclic aziridine alcohol **6** (1.73 g, 7 mmol, 1.0 equiv.) in MeOH (30 mL) at rt was added K_2CO_3 (1.45 g, 10.5 mmol, 1.5 equiv.) and the reaction left to stir for 1 h. The reaction mixture was then passed through a short plug of silica, eluting with MeOH, to remove excess K_2CO_3 before being concentrated *in vacuo* to give a crude oil which was then dissolved in DMF (30 mL). To this mixture was added K_2CO_3 (2.42 g, 17.5 mmol, 2.5 equiv.) and piperonyl bromide **7** (3.00 g, 14 mmol, 2.0 equiv.) and the reaction left to stir at rt for 2.5 h. The reaction was then quenched by the addition of water (30 mL), extracted with EtOAc (3 × 30 mL) and washed with brine (3 × 50 mL) before being dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 50:50 to 30:70) gave the desired product (+)-**8** as a separable mixture of diastereomers in a 2.7:1 ratio (1.30 g, 75%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.88 (d, J = 3.7 Hz, 1H), 6.76 (d, J = 5.7 Hz, 2H), 5.94 (d, J = 2.7 Hz, 2H), 4.03 (t, J = 5.7 Hz, 1H), 3.94 (dq, J = 10.2, 5.2 Hz, 1H), 3.37 (t, J = 4.4 Hz, 1H), 2.38 – 2.28 (m, 1H), 2.02 (t, J = 5.8 Hz, 1H), 1.95 (t, J = 5.4 Hz, 1H), 1.81 (ddt, J = 15.1, 9.5, 5.4 Hz, 1H), 1.68 – 1.60 (m, 2H), 1.44 (ddtt, J = 15.3, 7.7, 5.2, 2.7 Hz, 1H), 1.18 (ddt, J = 11.0, 7.3, 4.3 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 147.8, 133.4, 121.2, 120.7, 108.7, 108.3, 101.1, 64.3, 64.1, 43.0, 42.1, 30.8, 23.9, 16.9.

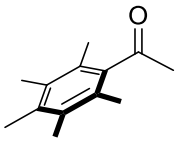
IR ν_{max} (film)/cm^{-1} = 3406, 2935, 1503, 1490, 1441, 1374, 1241, 1100, 1039, 927, 808.

HRMS (ESI$^+$) $C_{14}H_{18}O_3N$ requires 248.12812, found $[M+H]^+$ 248.12815 (Δ 0.16 ppm).

M.p. = 82 – 84 °C.

$[\alpha]_D^{25}$ = +19.0 (c = 1.00, $CHCl_3$).

1-(2,3,4,5,6-Pentamethylphenyl)ethan-1-one, 9



9

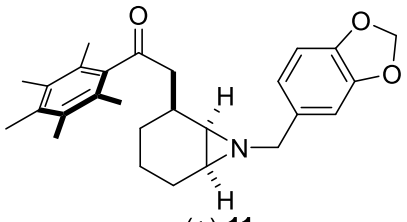
To a stirred solution of pentamethylbenzene (10.0 g, 67.6 mmol, 1.0 eq.) and acetyl bromide (5.48 mL, 74.3 mmol, 1.1 eq.) in CH_2Cl_2 (675 mL) at 0 °C was added $AlCl_3$ (11.25 g, 84.5 mmol, 1.25 eq.) portionwise. After stirring for 30 min, the reaction was poured into water (cooled with a water-ice bath) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers washed with sat. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 90:10) gave the desired compound **9** as a white solid (12.0 g, 93%) that may be recrystallised from hexane.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.46 (s, 3H), 2.24 (s, 3H), 2.19 (s, 6H), 2.14 (s, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 210.2, 141.1, 135.5, 133.2 (2C), 127.1 (2C), 33.3, 17.2 (2C), 16.8, 16.1 (2C).

The spectral data matched that previously reported in the literature.[6]

2-((1*R*,2*S*,6*S*)-7-(Benzo[d][1,3]dioxol-5-ylmethyl)-7-Azabicyclo[4.1.0]heptan-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one, 11



(+)-**11**

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added cyclic aziridine alcohol (+)-**8** 248 mg, 1.04 mmol), $[Cp^*IrCl_2]_2$ (11.1 mg, 0.013 mmol, 2.0 mol%), Ph* methyl ketone (132 mg, 0.696 mmol) and KOH (78.1 mg, 1.39 mmol) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and an argon balloon fitted. The vial was heated to the 85 °C in a preheated oil bath for 16 h. The mixture was cooled to rt, filtered through a SiO_2 plug (eluting with Et_2O) and concentrated in vacuo. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 80:20) gave a single diastereomer (+)-**11** (223 mg, 53%, 98:2 er) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.87 (s, 1H), 6.72 (s, 2H), 5.90 (d, J = 1.3 Hz, 1H), 5.83 (d, J = 1.3 Hz, 1H), 3.48 (d, J = 13.3 Hz, 1H), 3.10 (d, J = 13.4 Hz, 1H), 2.82 – 2.54 (m, 2H), 2.41 (dq, J = 12.4, 7.2, 6.3 Hz, 1H), 2.22 (s, 3H), 2.17 (s, 6H), 2.06 (s, 6H), 1.90 (dd, J = 6.5, 4.1 Hz, 1H), 1.70 (t, J = 6.0 Hz, 1H), 1.64 (s, 2H), 1.44 (dt, J = 7.2, 4.9 Hz, 2H), 1.28 – 1.01 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 211.8, 147.5, 146.3, 140.7, 135.2, 133.9, 133.0 (2C), 127.2 (2C), 121.0, 108.6, 107.9, 100.8, 64.4, 53.5, 50.4, 42.1, 39.8, 29.5, 26.5, 24.1, 20.8 (2C), 17.1, 16.7 (2C).

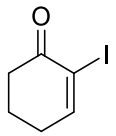
IR ν_{max} (film)/cm^{-1} = 2929, 1698, 1503, 1489, 1442, 1376, 1245, 1100, 1039, 928, 807.

HRMS (ESI^+) $C_{27}H_{34}O_3N$ requires 420.25332, found $[M+H]^+$ 420.25206 (Δ –3.04 ppm).

$[\alpha]_D^{25}$ = +20.0 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 5.0 % IPA, 95.0 % hexane, 1.0 mL/min, 25 °C, λ = 210 nm, 10 µL injection, t_r(major) = 8.0 min, t_r(minor) = 7.5 min).

2-Iodocyclohex-2-en-1-one, 12



12

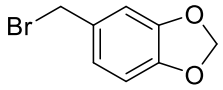
To a stirred solution of cyclohexenone (1.0 mL, 10 mmol, 1.0 equiv.) in THF-water (1:1, 50 mL) was added sequentially K_2CO_3 (1.66 g, 12 mmol, 1.2 equiv.), I_2 (3.8 g, 15 mmol, 1.5 equiv.) and DMAP (240 mg, 2.0 mmol, 0.2 equiv.) and the reaction left to stir for 1 h. The reaction mixture was then poured into EtOAc (100 mL), washed with sat. aq. $Na_2S_2O_3$ (2 × 100 mL), 0.1 M aq. HCl (200 mL) and brine. Drying over $MgSO_4$ and concentration *in vacuo* yielded crude **12**. Purification by column chromatography (SiO_2, dry load, pentane:EtOAc, 90:10) gave the desired compound **12** (1.44 g, 65%) as a pale yellow solid that slowly decomposed when stored at rt.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.77 (t, J = 4.5 Hz, 1H), 2.71 – 2.60 (m, 2H), 2.49 – 2.37 (m, 2H), 2.08 (tt, J = 6.3 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 192.4, 159.6, 104.0, 37.4, 30.1, 23.0.

Data was consistent with that previously reported.[7]

Piperonyl bromide, 7



7

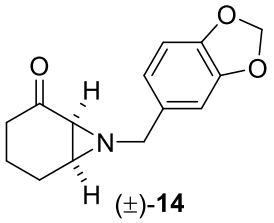
To a stirred solution of piperonyl alcohol (3.04 g, 20 mmol, 1.0 equiv.) in Et_2O (30 mL) at 0 °C was added PBr_3 (2.07 mL, 22 mmol, 1.1 equiv.) in Et_2O (25 mL) *via* a dropping funnel over the course of 15 min. After stirring for an additional 30 min, the reaction was quenched by the addition of water (50 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL) and the organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the desired product **7** (4.15 g, 97%) as a colourless solid without any additional purification.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.90 – 6.84 (m, 2H), 6.75 (dd, J = 7.8, 0.6 Hz, 1H), 5.97 (s, 2H), 4.46 (s, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 148.1, 148.0, 131.7, 122.9, 109.6, 108.5, 101.5, 34.3.

Data for **7** was consistent with that previously reported.[8]

(1*RS*,2*SR*,6*RS*)-7-(Benzo[d][1,3]dioxol-5-ylmethyl)-7-Azabicyclo[4.1.0]heptan-2-one, 14



(±)-**14**

2-Iodocyclohex-2-en-1-one **12** (2.21 g, 10 mmol), Cs_2CO_3 (3.87 g, 10 mmol), phenanthroline (1.8 g, 10 mmol) and piperonylamine (**13**) (1.87 mL, 15 mmol) were added sequentially to CH_2Cl_2 (75 mL) at rt and left to stir 4 h, after which another 0.5 equiv. of Cs_2CO_3 (1.93 g, 5 mmol) was added. After a further 4 h, 0.5 equiv. of phenanthroline (0.9 g, 5 mmol) were added and the reaction left to stir for 16 h. The resulting mixture was then diluted with CH_2Cl_2 (75 mL), washed with water (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 70:30) gave the desired product **14** (2.32 g, 95%) as a yellow oil.

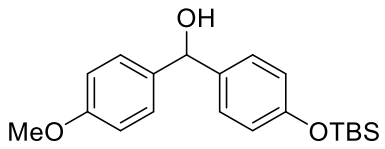
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.84 (s, 1H), 6.75 (t, J = 6.3 Hz, 2H), 5.94 (s, 2H), 3.66 (d, J = 13.4 Hz, 1H), 3.28 (d, J = 13.4 Hz, 1H), 2.54 – 2.38 (m, 1H), 2.29 (d, J = 2.9 Hz, 1H), 2.15 – 1.90 (m, 4H), 1.80 – 1.51 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 207.8, 147.8, 146.8, 132.4, 120.9, 108.4, 108.2, 101.1, 63.3, 46.4, 43.8, 37.2, 23.3, 18.9.

IR ν_{max} (film)/cm^{-1} = 2940, 1703, 1503, 1490, 1442, 1250, 1235, 1100, 1084, 1037, 927, 808.

HRMS (ESI^+) $C_{14}H_{16}O_3N$ requires 246.11247, found $[M+H]^+$ 246.11245 (Δ –0.05 ppm).

(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)(4-methoxyphenyl)methanol, 15



15

To a stirred solution of 4-hydroxybenzaldehyde (3.74 g, 20.0 mmol, 1.0 equiv.) in DMF (50 mL) at rt was sequentially added TBSCl (3.00 g, 20.0 mmol, 1.0 equiv.) and imidazole (1.63 g, 24.0 mmol, 1.2 equiv.), and the reaction left to stir for 1 h. The reaction was quenched by the addition of water (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were then washed with brine (3 × 50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give the desired product **SI-2** (4.72 g, 99%) that was used without further purification.

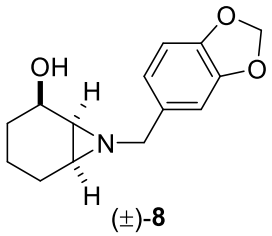
To a stirred solution of 4-bromoanisole (3.74 g, 20.0 mmol, 1.0 equiv.) in THF (90 mL) at –78 °C was added 2.5 M *n*BuLi in hexanes (8.0 mL, 20.0 mmol, 1.0 equiv.) dropwise and the reaction stirred for 2 h. 4-((*tert*-Butyldimethylsilyl)oxy)benzaldehyde **SI-2** (4.72 g, 20.0 mmol, 1.0 equiv.) in THF (5 mL) was added and the reaction warmed to rt over the course of 1.5 h. The reaction was quenched by the addition of water (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were then washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, CH_2Cl_2) gave the desired compound **15** (3.46 g, 50%) as a clear oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.27 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.2 Hz, 2H), 5.76 (d, J = 3.3 Hz, 1H), 3.79 (s, 3H), 0.97 (s, 9H), 0.18 (s, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 159.1, 155.2, 137.0, 136.5, 127.9 (2C), 127.8 (2C), 120.1 (2C), 113.9 (2C), 75.6, 55.4, 25.8, 18.3 (6C), -4.3 (2C).

Data was consistent with that previously reported.[9]

(1*RS*,2*SR*,6*RS*)-7-(Benzo[d][1,3]dioxol-5-ylmethyl)-7-Azabicyclo[4.1.0]heptan-2-ol, 8

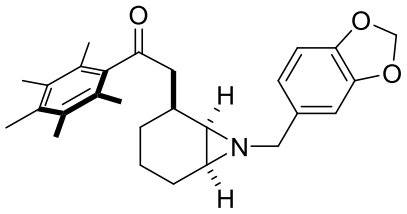


(±)-**8**

To a stirred solution of cyclic aziridine ketone **14** (980 mg, 4.00 mmol) in MeOH (20 mL) at 0 °C was added $NaBH_4$ portion-wise (3 × 181 mg, 3 × 4.80 mmol) and the reaction left to stir for 3 h until completion was indicated by TLC. After being quenched by the addition of water (20 mL), extraction with Et_2O (3 × 30 mL), drying with $MgSO_4$, and concentration *in vacuo* afforded the pure product (±)-**8** (989 mg, quant.) as a creamy solid.

Data matched that which was reported for the synthesis of enantioenriched (+)-**8**.

2-((1*RS*,2*SR*,6*SR*)-7-(Benzo[d][1,3]dioxol-5-ylmethyl)-7-Azabicyclo[4.1.0]heptan-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one, 11



(±)-**11**

Two-Step procedure

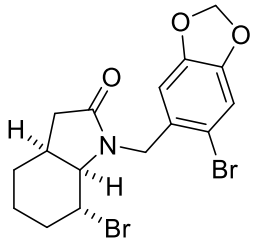
To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added (±)-**8** (147 mg, 0.594mmol), $[Cp^*IrCl_2]_2$ (6.3 mg, 0.0079 mmol, 2.0 mol%), Ph* methyl ketone (75.4 mg, 0.396 mmol) and KOH (44.5 mg, 0.793 mmol) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and an argon balloon fitted. The vial was heated to the required temperature (85 °C) in a preheated oil bath for 16 h. The mixture was cooled to rt, filtered through a SiO_2 plug (eluting with Et_2O) and concentrated in vacuo. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 80:20) gave a single diastereomer (±)-**11** (151 mg, 60%) as a yellow oil.

One-Step procedure using hydride donor 15

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added Cyclic aziridine ketone **14** (221 mg, 0.901 mmol), $[Cp^*IrCl_2]_2$ (9. 6 mg, 0.012 mmol, 2.0 mol%), Ph* methyl ketone (114 mg, 0.601 mmol) and KOH (67.4 mg, 1.20 mmol) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and an argon balloon fitted. The vial was heated to the required temperature (85 °C) in a preheated oil bath for 16 h. The mixture was cooled to rt, filtered through a SiO_2 plug (eluting with Et_2O) and concentrated in vacuo. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 80:20) gave a single diastereomer (±)-**11** (204 mg, 54%) as a yellow oil.

Data matched that which was reported for the synthesis of enantioenriched (+)-**11**.

(3a*S*,7*R*,7a*R*)-7-Bromo-1-((6-bromobenzo[d][1,3]dioxol-5-yl)methyl)octahydro-2H-indol-2-one, 16



16

Enantioenriched

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added cyclic aziridine ketone (+)-**11** (100 mg, 0.238 mmol) and CH_2Cl_2 (1.2 mL, 0.2 M) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and cooled to –17 °C (ice/NaCl bath). Following this, Br_2 (114 mg, 0.715 mmol) was added dropwise and the mixture stirred 15 min. The reaction was then quenched with *n*-BuOH (88.3 mg, 1.19 mmol), diluted with Et_2O (5 mL) and water (3 mL). The layers were separated, and the aqueous layer extracted with Et_2O three times. The combined organics were washed with sat. aq. $Na_2S_2O_3$, sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, dry load, Et_2O) gave the desired compound (–)-**16** (42 mg, 40%) as a yellow oil.

Racemic

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added cyclic aziridine ketone (±)-**11** (126 mg, 0.300 mmol) and CH_2Cl_2 (1.5 mL, 0.2 M) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and cooled to –17 °C (ice/NaCl bath). Following this, Br_2 (144 mg, 0.901 mmol) was added dropwise and the mixture stirred 15 min. The reaction was then quenched with *n*-BuOH (111 mg, 1.50 mmol), diluted with Et_2O (5 mL) and water (3 mL). The layers were separated, and the aqueous layer extracted with Et_2O three times. The combined organics were washed with sat. aq. $Na_2S_2O_3$, sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, dry load, Et_2O) gave the desired compound (±)-**16** (100 mg, 78%) as a pale brown oil.

Data for **16**

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.99 (s, 1H), 6.78 (s, 1H), 5.97 (q, J = 1.3 Hz, 2H), 4.86 (d, J = 15.6 Hz, 1H), 4.56 (d, J = 15.6 Hz, 1H), 4.23 (ddd, J = 8.8, 6.5, 3.8 Hz, 1H), 3.67 (t, J = 6.3 Hz, 1H), 2.63 (q, J = 7.2 Hz, 1H), 2.32 (qd, J = 16.4, 7.8 Hz, 2H), 1.93 – 1.37 (m, 6H).

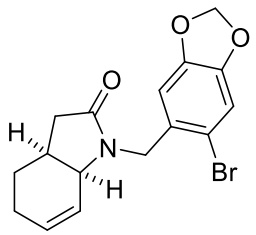
^{13}C NMR ($CDCl_3$, 100 MHz) δ = 175.7, 148.0, 147.8, 129.1, 113.8, 113.1, 109.9, 102.0, 63.7, 52.3, 45.7, 36.0, 34.0, 33.2, 26.5, 20.3.

IR ν_{max} (film)/cm^{-1} = 2931, 1689, 1502, 1478, 1407, 1235, 1190, 1110, 1036, 928, 729.

HRMS (ESI^+) $C_{16}H_{17}O_3N^{79}Br_2Na$ requires 451.94674, found $[M+Na]^+$ 451.94707 (Δ 0.72 ppm).

$[\alpha]_D^{25}$ = – 46.5 (c = 1.00, $CHCl_3$).

(3a*S*,7a*R*)-1-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-1,3,3a,4,5,7a-Hexahydro-2H-indol-2-one, SI-3



SI-3

Enantioenriched

To a stirred solution of dibromide **16** (161 mg, 0.375 mmol, 1.0 equiv.) in THF (3 mL) at rt was added 1M KO*t*BU in THF (413 µL, 0.413 mmol, 1.1 equiv.) and the reaction left to stir for 45 min. The reaction was then quenched by the addition of water (10 mL), extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (5 mL) and concentrated *in vacuo* to give a crude residue. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 50:50) gave the desired compound (–)-**SI-3** (131 mg, quant.) as a pale oil.

Racemic

To a stirred solution of dibromide **16** (50 mg, 0.116 mmol, 1.0 equiv.) in THF (1 mL) at rt was added 1M KO*t*BU in THF (130 µL, 0.130 mmol, 1.1 equiv.) and the reaction left to stir for 45 min. The reaction was then quenched by the addition of water (5 mL), extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (5 mL) and concentrated *in vacuo* to give a crude residue. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 50:50) gave the desired compound (±)-**SI-3** (40 mg, 99%) as a pale oil.

Data for **SI-3**

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.97 (s, 1H), 6.74 (s, 1H), 5.96 – 5.94 (m, 3H), 5.72 (ddt, J = 10.2, 3.6, 2.0 Hz, 1H), 4.75 (d, J = 15.6 Hz, 1H), 4.25 (d, J = 15.6 Hz, 1H), 3.85 (ddt, J = 5.1, 3.4, 1.8 Hz, 1H), 2.58 – 2.43 (m, 2H), 2.29 (td, J = 16.1, 15.5, 6.1 Hz, 1H), 2.15 – 1.88 (m, 2H), 1.76 – 1.51 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 174.6, 147.9, 132.0, 129.5, 123.4, 113.7, 112.8, 109.4, 102.0, 54.9, 44.1, 35.9, 31.2, 24.3, 22.4.

IR ν_{max} (film)/cm^{-1} = 2920, 2360, 1680, 1501, 1232, 1033, 729.

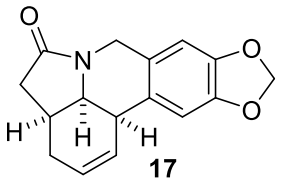
HRMS (ESI^+) $C_{16}H_{17}O_3N^{79}Br$ requires 350.0386 requires 270.1125, $[M+H]^+$ = 350.0388 (Δ = +0.44 ppm).

M.p. = 120 – 122 °C.

$[\alpha]_D^{25}$ = –1.4 (c = 1.00, $CHCl_3$).

Data was consistent with that previously reported.[10]

(3a*S*,3a^1*R*,12b*R*)-3a,4,7,12b-Tetrahydro-3H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-5(3a1H)-one, 17



17

Enantioenriched

A stirred solution of bromo alkene (–)-**SI-3** (105 mg, 0.3 mmol, 1.0 equiv.) in DMF (9 mL) at rt was sparged with N_2 for 1 h. This was followed by the sequential addition of PPh_3 (31 mg, 0.12 mmol, 40 mol%), $Pd(OAc)_2$ (13 mg, 0.06 mmol, 20 mol%), and *i*-PrNEt (183 µL, 0.6 mmol, 2.0 equiv.) and the reaction was heated to 155 °C for 20 h. The reaction was then quenched by the addition of water (10 mL), extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (3 × 5 mL) and concentrated *in vacuo* to give a crude residue. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 20:80) gave the desired compound (+)-**17** (49 mg, 60%) as a pale oil.

Racemic

A stirred solution of bromo alkene (±)-**SI-3** (140 mg, 0.4 mmol, 1.0 equiv.) in DMF (11 mL) at rt was sparged with N_2 for 1 h. This was followed by the sequential addition of PPh_3 (42 mg, 0.16 mmol, 40 mol%), $Pd(OAc)_2$ (18 mg, 0.08 mmol, 20 mol%), and *i*-PrNEt (244 µL, 0.8 mmol, 2.0 equiv.) and the reaction was heated to 155 °C for 16 h. The reaction was then quenched by the addition of water (10 mL), extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (3 × 5 mL) and concentrated *in vacuo* to give a crude residue. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 20:80) gave the desired compound (±)-**17** (69 mg, 64%) as a pale oil.

Data for **17**:

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.66 (s, 1H), 6.57 (s, 1H), 5.95 – 5.91 (m, 2H), 5.88 (ddt, J = 9.5, 6.5, 3.5 Hz, 1H), 5.64 (dtd, J = 9.5, 2.6, 1.3 Hz, 1H), 4.78 (d, J = 17.1 Hz, 1H), 4.11 (d, J = 17.1 Hz, 1H), 4.05 (dd, J = 8.1, 5.2 Hz, 1H), 3.28 (d, J = 2.6 Hz, 1H), 2.92 – 2.82 (m, 1H), 2.66 (ddd, J = 17.0, 9.6, 1.5 Hz), 2.19 (dddt, J = 16.1, 6.3, 3.8, 2.5 Hz, 1H), 2.14 – 2.07 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 174.4, 147.0, 146.9, 132.7, 129.8, 126.9, 124.4, 108.9, 106.2, 101.2, 56.7, 42.2, 38.9, 38.6, 29.2, 27.4.

IR ν_{max} (film)/cm^{-1} = 1674, 1483, 1035, 721, 694.

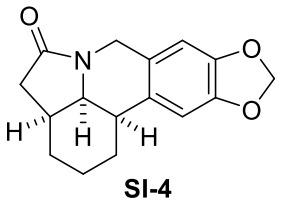
HRMS (ESI^+) $C_{16}H_{16}O_3N$ requires 270.1125, found [M+H]+ = 270.1124 (Δ = –0.16 ppm).

M.p. = 120 – 122 °C.

$[\alpha]_D^{25}$ = +68.8 (c = 1.00, $CHCl_3$).

Data was consistent with that previously reported.[11]

(3a*S*,3a1*R*,12b*R*)-2,3,3a,4,7,12b-Hexahydro-1H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-5(3a1H)-one, SI-4



SI-4

Enantioenriched

To a stirred solution of substrate (+)-**17** (48.9 mg, 0.182 mmol, 1.0 equiv.) in methanol (2.0 mL) was added 10% Pd/C (6.4 mg, 0.06 mmol, 0.3 equiv.) and hydrogen pressure was applied with a balloon for 16 h. The reaction mixture was filtered through Celite® using MeOH and the filtrate concentrated *in vacuo*, yielding the title compound (–)-**SI-4** (49.0 mg, 0.181 mmol, 99%) as colourless crystals.

Racemic

To a stirred solution of substrate (±)-**17** (68.8 mg, 0.256 mmol, 1.0 equiv.) in methanol (2.5 mL) was added 10% Pd/C (8.5 mg, 0.08 mmol, 0.3 equiv.) and hydrogen pressure was applied with a balloon for 16 h. The reaction mixture was filtered through Celite® using MeOH and the filtrate concentrated *in vacuo*, yielding the title compound (±)-**SI-4** (63.5 mg, 0.234 mmol, 92%) as colourless crystals.

Data for **SI-4**:

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.62 (s, 1H), 6.60 (s, 1H), 5.94 (d, J = 1.4 Hz, 1H), 5.92 (d, J = 1.4 Hz, 1H), 4.54 (d, J = 17.3 Hz, 1H), 4.33 (d, J = 17.3 Hz, 1H), 3.77 (t, J = 4.6 Hz, 1H), 2.75 (dt, J = 12.7, 4.4 Hz, 1H), 2.58 (dd, J = 16.1, 6.8 Hz, 1H), 2.49 – 2.37 (m, 1H), 2.09 (d, J = 16.1 Hz, 1H), 1.84 – 1.66 (m, 3H), 1.41 – 1.07 (m, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 175.8, 146.9, 146.8, 131.8, 123.5, 108.6, 106.8, 101.2, 55.9, 42.8, 40.4, 40.0, 33.1, 30.4, 28.0, 23.8.

IR ν_{max} (film)/cm^{-1} = 2360, 1675, 1482, 1035, 932, 847.

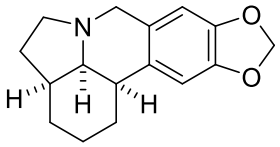
HRMS (ESI^+) $C_{16}H_{17}O_3NNa$ requires 294.1101, found $[M+Na]^+$ = 294.1100 (Δ = –0.27 ppm).

M.p. = 122 – 124 °C.

$[\alpha]_D^{25}$ = –70.6 (c = 1.00, $CHCl_3$).

Data was consistent with that previously reported.[10]

(–)-γ-Lycorane (1)



γ-lycorane (**1**)

Enantioenriched

Substrate **SI-4** (34.0 mg, 0.125 mmol, 1.0 equiv.) was dissolved in THF (50 mL) and placed under a nitrogen atmosphere. $LiAlH_4$ (19.1 mg, 0.502 mmol, 4.0 equiv.) was added portion-wise to the stirred solution at rt. The mixture was heated at reflux for 15 h, cooled to rt, and poured over sat. aq. Na_2SO_4 (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL), filtered, concentrated *in vacuo*, yielding the crude product. Purification by column chromatography (SiO_2; wet load; 94.5% CH_2Cl_2, 4% MeOH, 0.5% NEt_3), gave (–)-γ-lycorane (**1**) as a colourless solid (21.7 mg, 0.085 mmol, 68%, 99:1 er).

Racemic

Substrate **SI-4** (60.0 mg, 0.221 mmol, 1.0 equiv.) was dissolved in THF (10 mL) and placed under a nitrogen atmosphere. $LiAlH_4$ (33.6 mg, 0.885 mmol, 4.0 equiv.) was added portionwise to the stirred solution at rt. The mixture was heated at reflux for 15 h, cooled to rt, and poured over sat. aq. Na_2SO_4 (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 20 mL), filtered, concentrated *in vacuo*, yielding the crude product. Purification by column chromatography (SiO_2; wet load; 94.5% CH_2Cl_2, 4% MeOH, 0.5% Et_3N), gave (±)-γ-lycorane (**1**) as a pale green solid (41.0 mg, 0.159 mmol, 72%).

Data for γ-lycorane (**1**):

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.61 (s, 1H), 6.49 (s, 1H), 5.90 – 5.87 (m, 2H), 4.02 (d, J = 14.4 Hz, 1H), 3.39 (td, J = 9.2, 3.9 Hz, 1H), 3.22 (d, J = 14.3 Hz, 1H), 2.74 (dt, J = 12.1, 4.7 Hz, 1H), 2.38 (t, J = 5.0 Hz, 1H), 2.27 – 2.11 (m, 2H), 2.08-1.96 (m, 1H), 1.81 – 1.67 (m, 2H), 1.67 – 1.59 (m, 1H), 1.53 – 1.41 (m, 2H), 1.36 – 1.25 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 146.2, 145.8, 133.3, 127.4, 108.5, 106.4, 100.8, 63.1, 57.3, 53.9, 39.6, 37.5, 31.8, 30.5, 29.4, 25.3.

IR ν_{max} (film)/cm^{-1} = 2921, 1504, 1229, 1039, 867, 851.

HRMS (ESI^+) $C_{16}H_{20}O_2N$ requires 258.1489, found $[M+H]^+$ = 258.1490 (Δ = +0.63 ppm).

M.p. = 100 – 102 °C.

$[\alpha]_D^{25}$ = –39.3 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IB with guard, 0.5 % IPA, 99.5 % hexane, 1.0 mL/min, 25 °C, λ = 230 nm, 10 µL injection, t_r(major) = 14.6 min, t_r(minor) = 9.8 min).

Data was consistent with that previously reported.[10]

3. NMR Comparison Tables

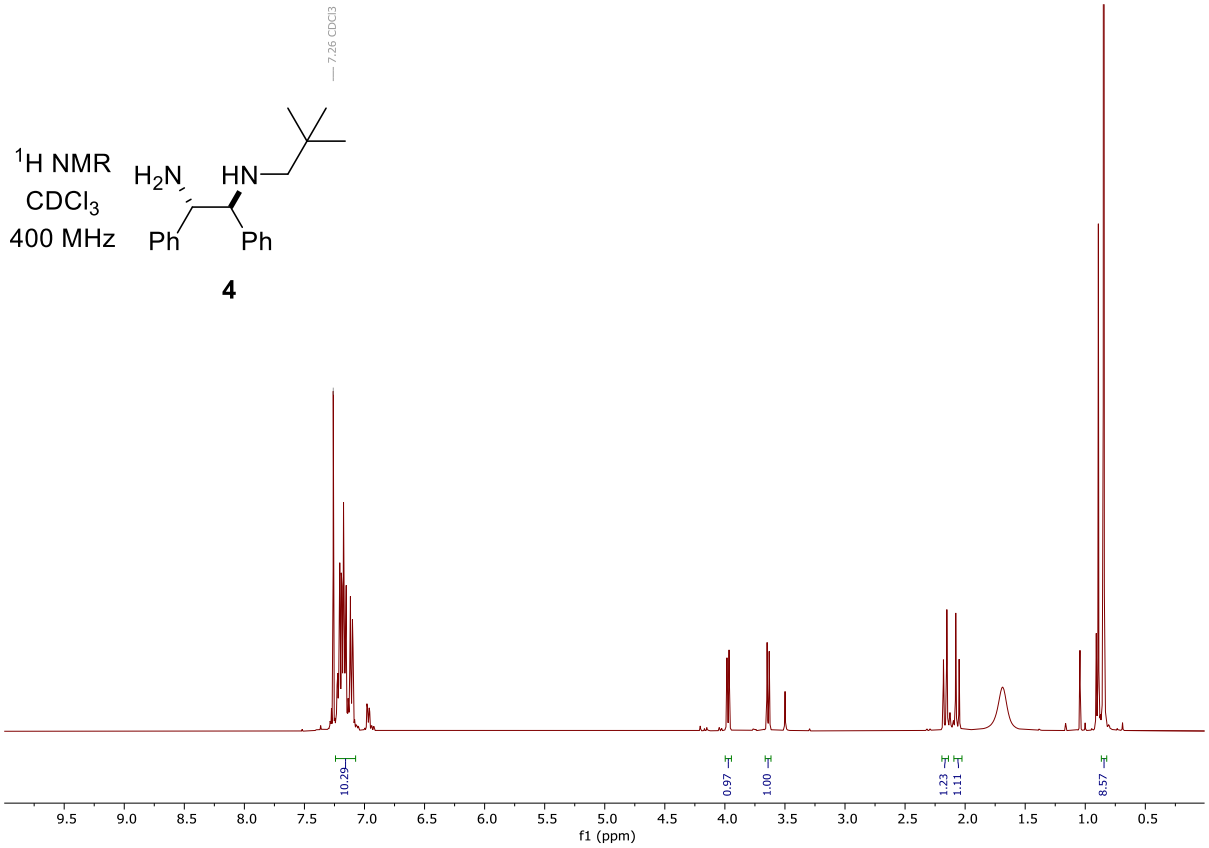
Table SI-1: ^{1}H NMR Comparison Table for Lycorane (**1**). Coupling constants in parentheses, in Hz.

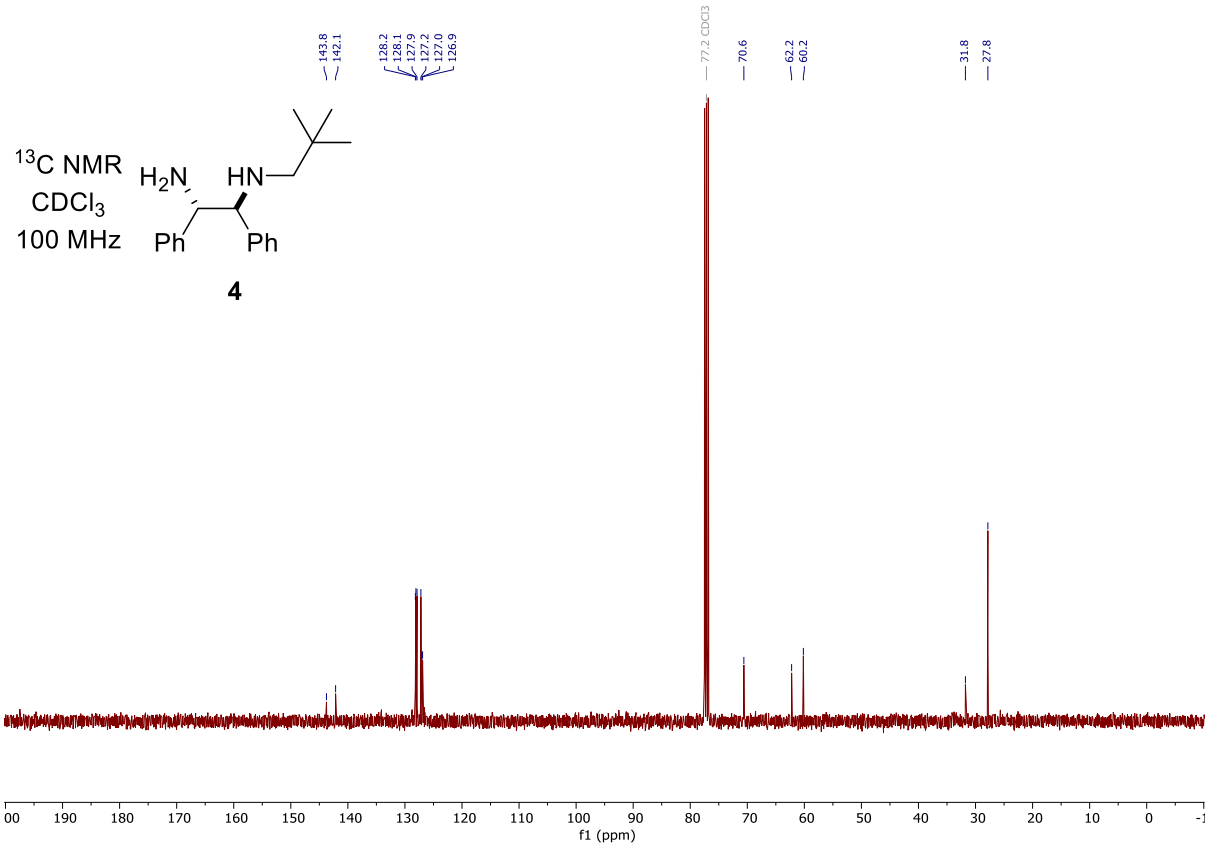
This Work (2022) ($CDCl_3$, 400 MHz)	Hilton (2017)[12] ($CDCl_3$, 400 MHz)	Baudin (2018)[13] ($CDCl_3$, 400 MHz)
6.61 s	6.61 s	6.61 s
6.49 s	6.49 s	6.49 s
5.90-5.87 m	5.89 d (1.3); 5.88 d (1.3)	5.90-5.86 m
4.02 d (14.4)	4.02 d (14.3)	4.01 d (14.4)
3.39 td (9.2, 3.9)	3.38 td (9.2, 3.9)	3.38 td (9.2, 3.9)
3.22 d (14.3)	3.21 d (14.3)	3.21 d (9.2, 3.9)
2.74 dt (12.1, 4.7)	2.74 dt (9.2, 3.9)	2.74 dt (12.0, 4.7)
2.38 t (5.0)	2.38 t (4.7)	2.38 t (4.8)
2.27-2.11 m	2.18 m	2.24-2.11 m
2.08-1.96 m	2.08-1.99 m	2.02 dddd (12.3, 10.9, 8.2, 3.9)
1.81-1.67 m	1.78-1.67 m	1.81-1.67 m
1.67-1.60 m	1.66-1.60 m	1.67-1.60 m
1.53-1.41 m	1.53-1.42 m	1.53-1.42 m
1.36-1.25 m	1.39-1.29 m	1.37-1.25 m

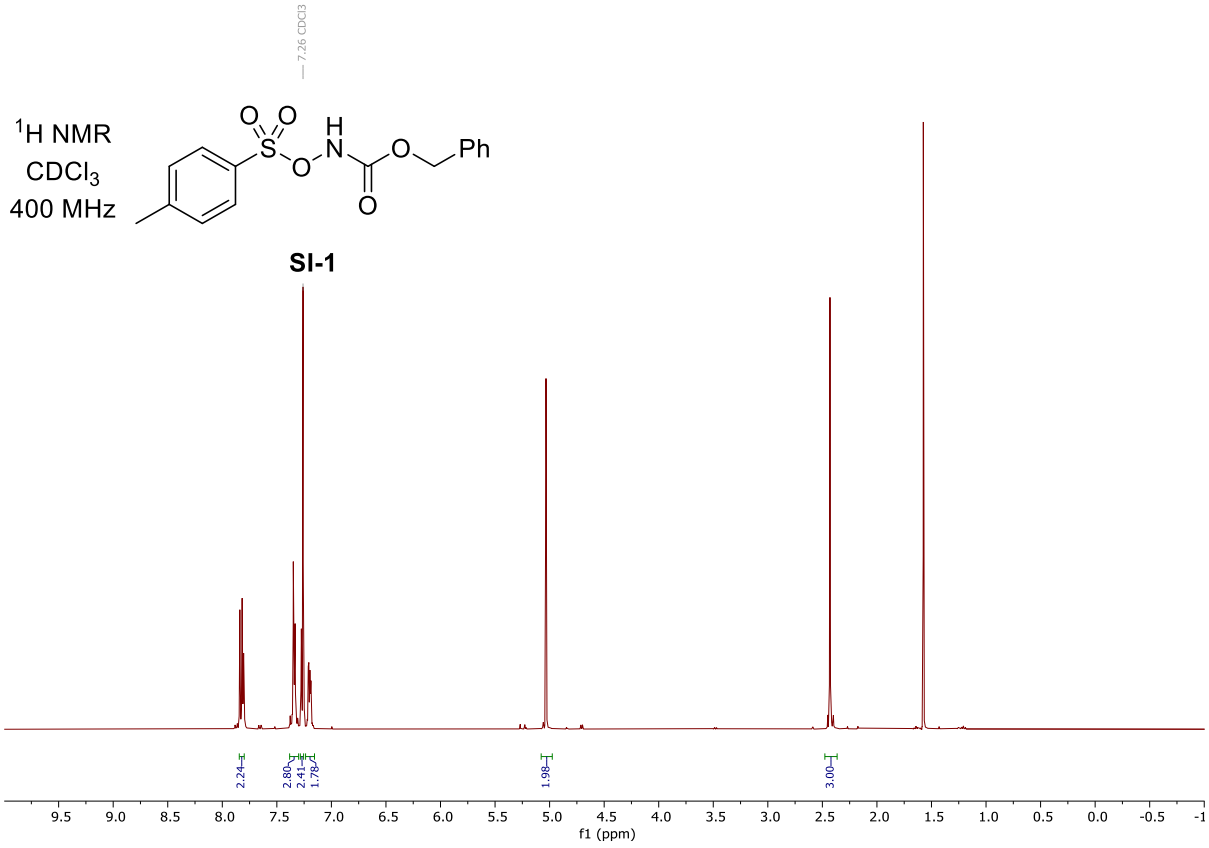
Table SI-2: ^{13}C NMR Comparison Table for γ-Lycorane (**1**).

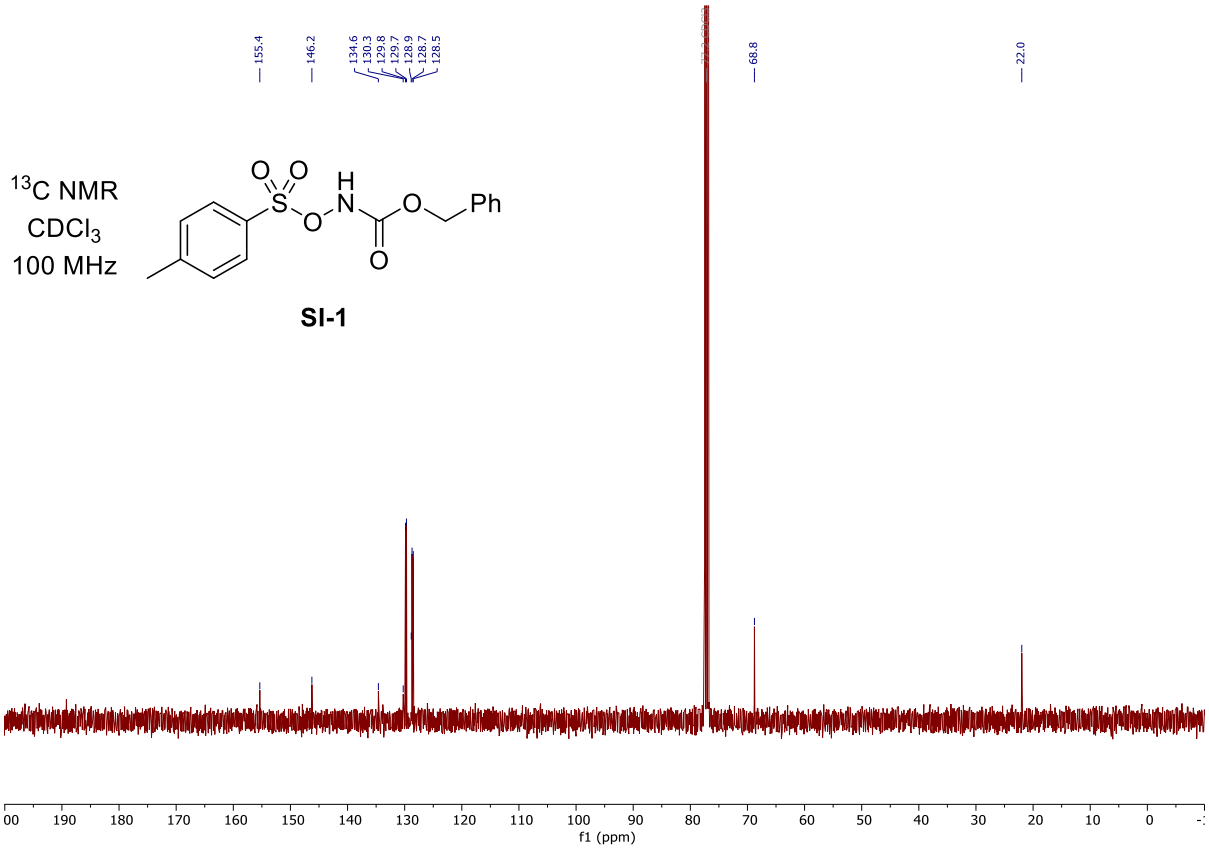
This Work (2022) ($CDCl_3$, 100 MHz)	Hilton (2017)[12] ($CDCl_3$, 100 MHz)		Baudin (2018) [13] ($CDCl_3$, 100 MHz)	
δ	δ	$\Delta\delta_C$	δ	$\Delta\delta_C$
146.2	146.1	–0.1	146.2	0
145.8	145.7	–0.1	145.8	0
133.3	133.2	–0.1	133.3	0
127.4	129.3	–0.1	127.4	0
108.5	108.3	–0.2	108.5	0
106.4	106.3	–0.1	106.4	0
100.8	100.7	–0.1	100.8	0
63.1	62.9	–0.2	63.1	0
57.3	57.1	–0.2	57.3	0
53.9	53.7	–0.2	53.9	0
39.6	39.5	–0.1	39.6	0
37.5	37.4	–0.1	37.5	0
31.8	31.7	–0.1	31.9	+0.1
30.5	30.4	–0.1	30.6	+0.1
29.4	29.3	–0.1	29.4	0
25.3	25.2	–0.1	25.4	+0.1

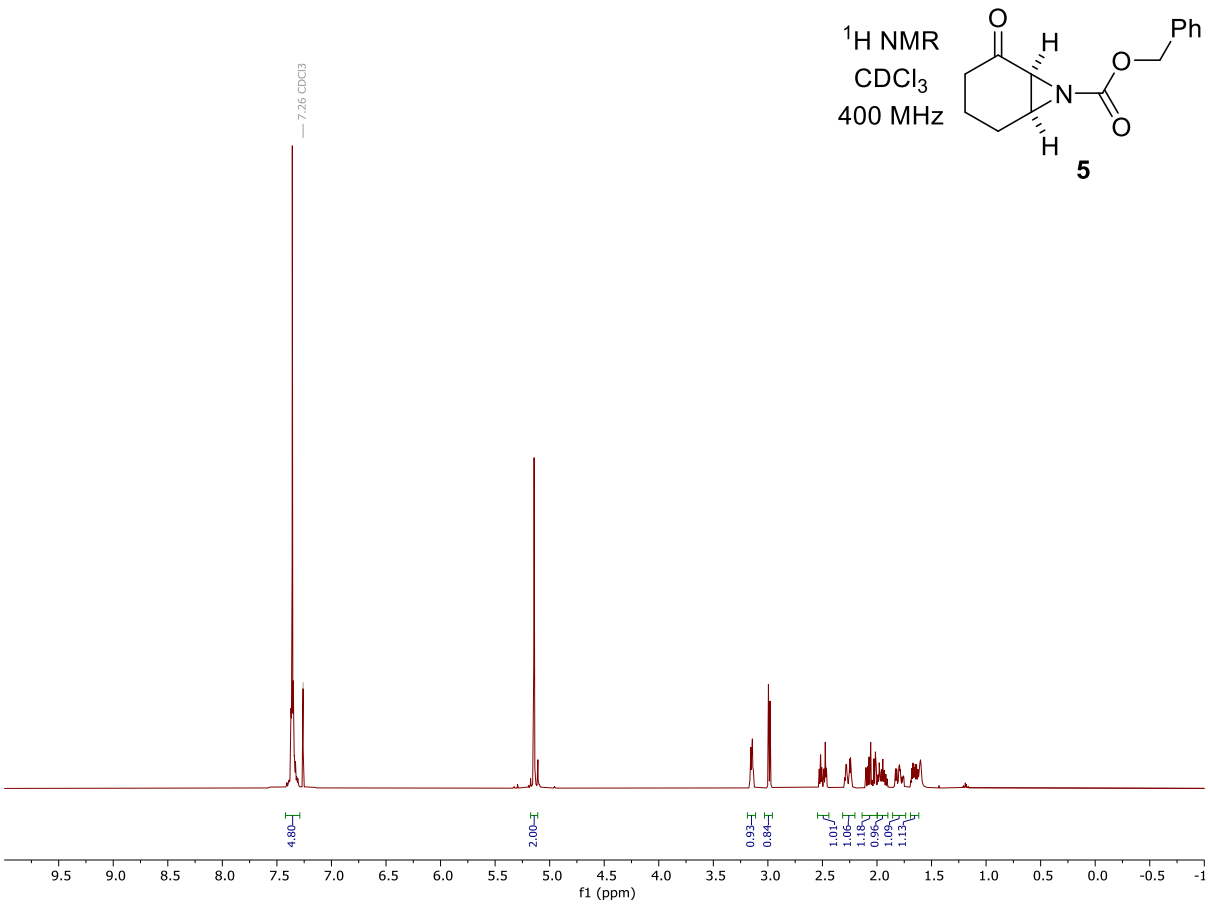
4. *NMR Spectra*

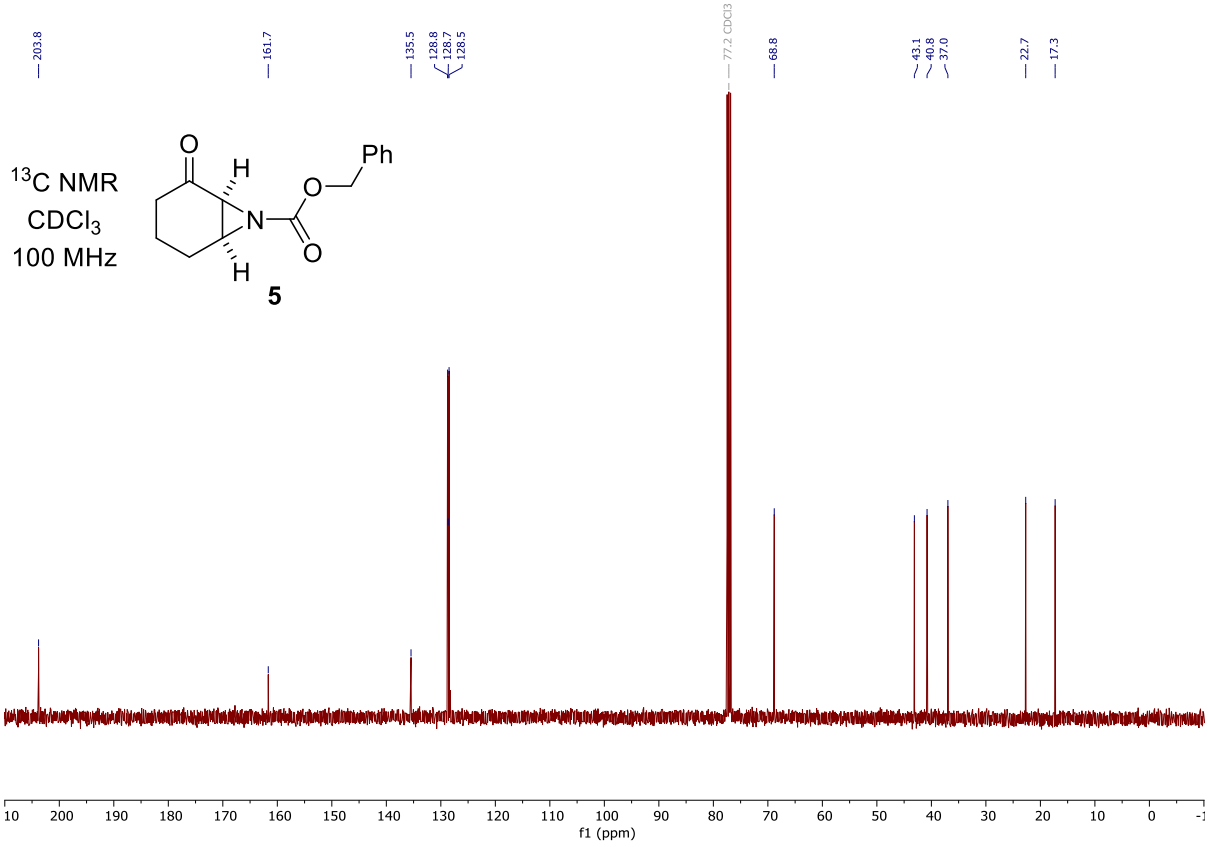


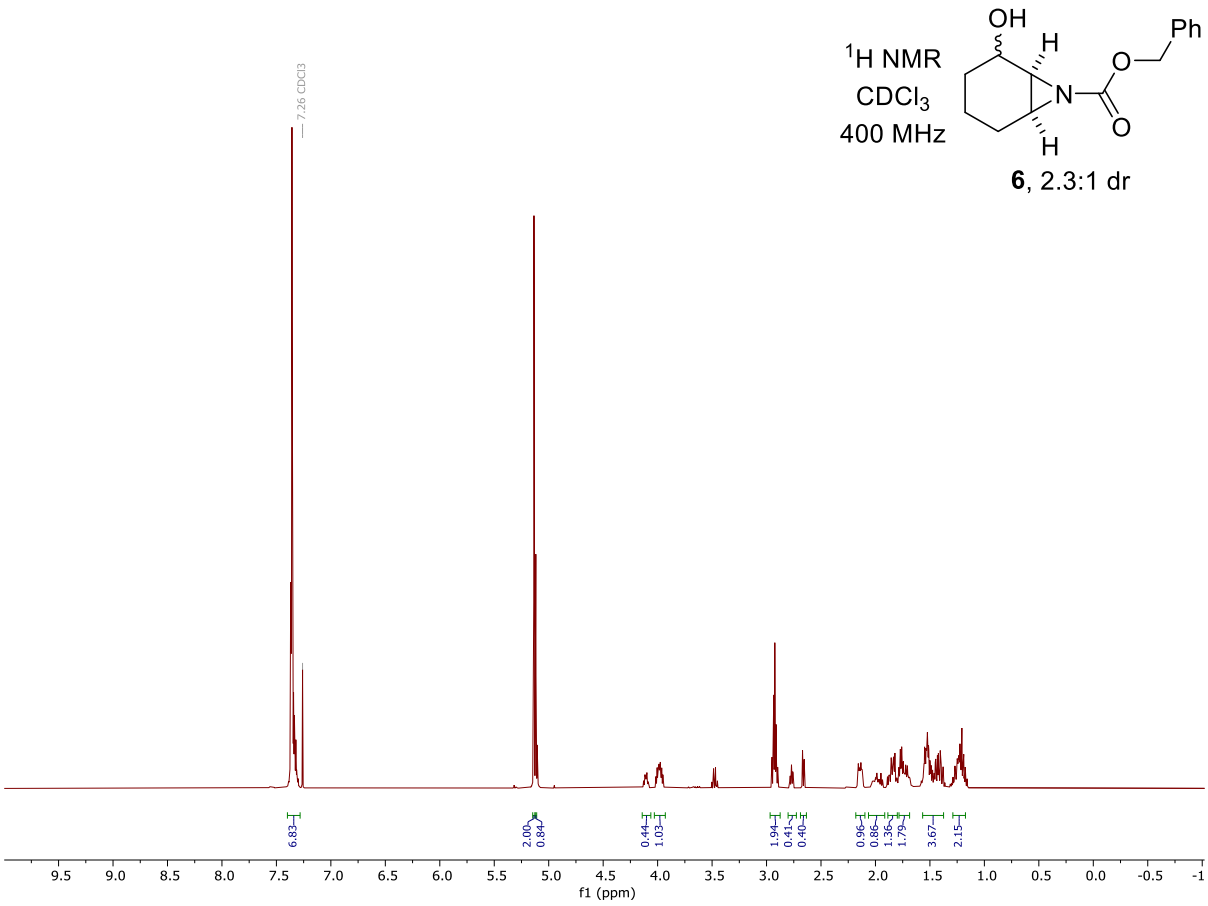


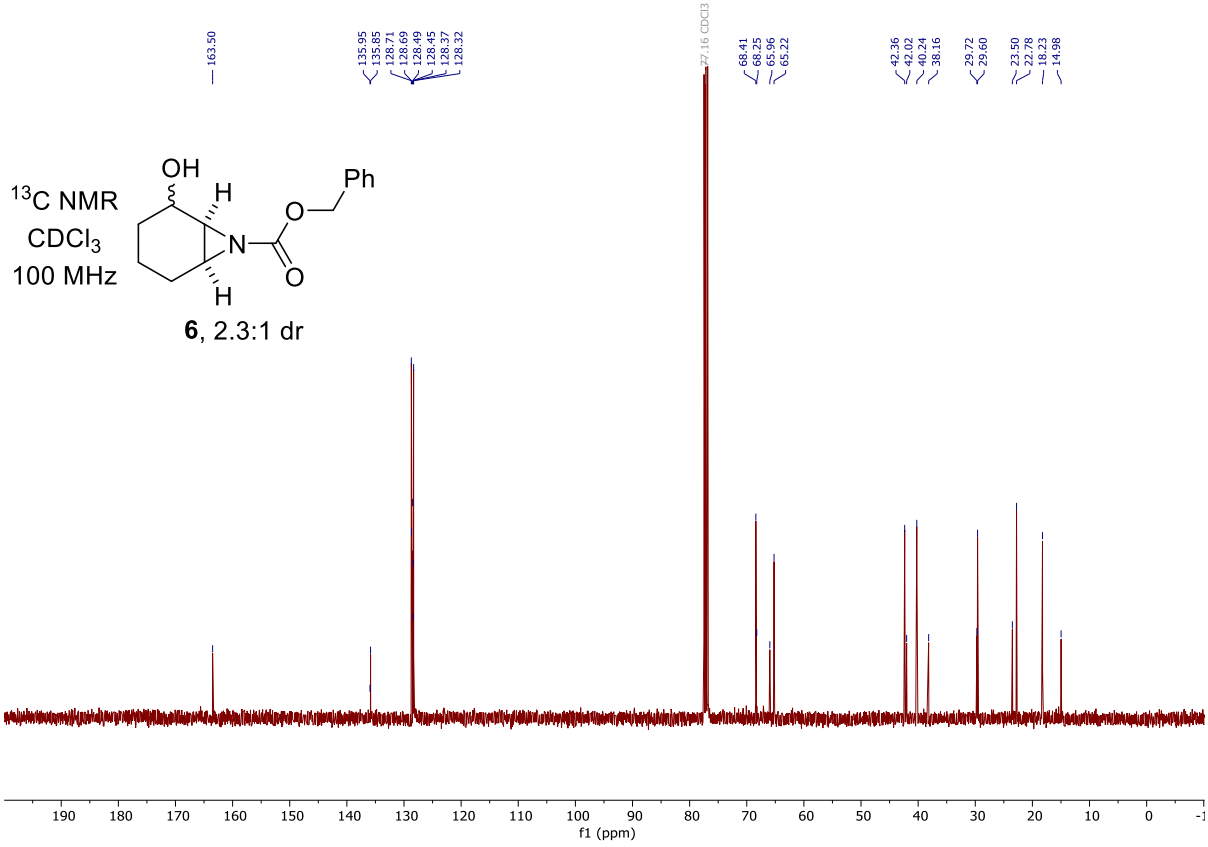

7.26 CDCl3
1H NMR
CDCl3
400 MHz
O
O
S
O
H
N
O
O
Ph
SI-1
2.24
2.80
2.41
1.78
1.98
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

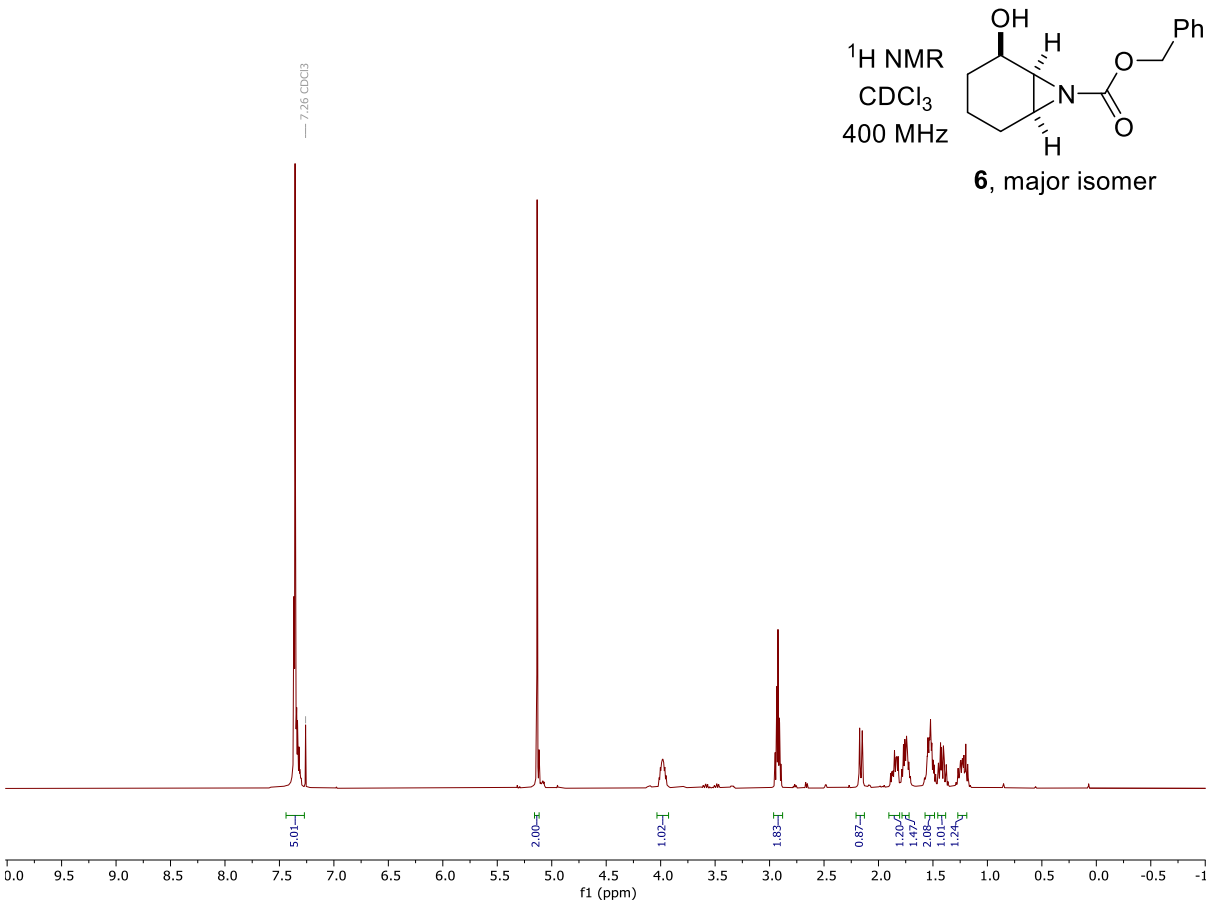

155.4
146.2
134.6
130.3
129.8
129.7
128.9
128.7
128.5
68.8
22.0
13C NMR
CDCl3
100 MHz
O
O
S
O
H
N
O
O
Ph
SI-1
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


^{1}H NMR
$CDCl_3$
400 MHz
5
7.26 CDCl3
4.80
2.00
0.93
0.84
1.01
1.06
1.18
0.96
1.09
1.13
f1 (ppm)

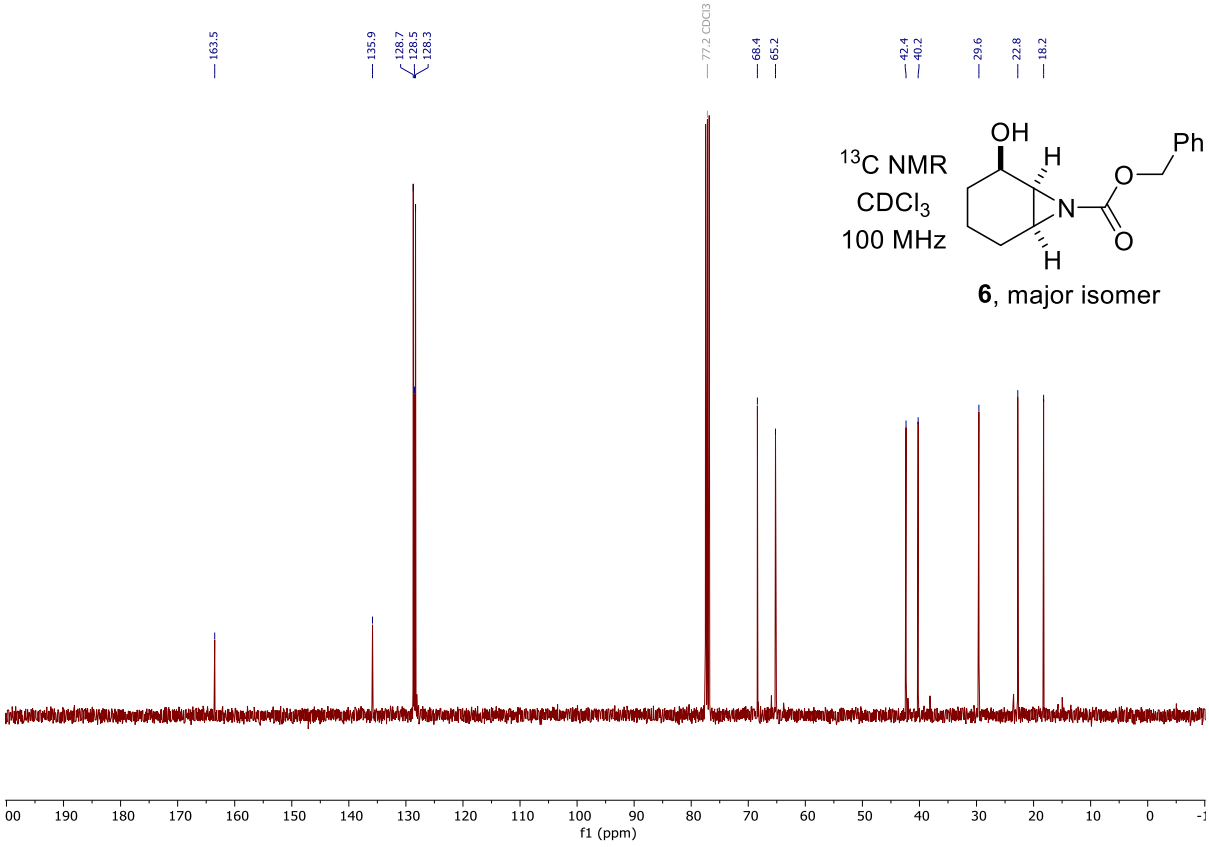

^{13}C NMR
$CDCl_3$
100 MHz
5
203.8
161.7
135.5
128.8
128.7
128.5
77.2 CDCl3
68.8
43.1
40.8
37.0
22.7
17.3
f1 (ppm)


^{1}H NMR
$CDCl_3$
400 MHz
OH
H
Ph
O
N
O
H
6, 2.3:1 dr
7.26 CDCl3
6.83
2.00
0.84
0.44
1.03
1.94
0.41
0.40
0.96
0.86
1.36
1.79
3.67
2.15
f1 (ppm)

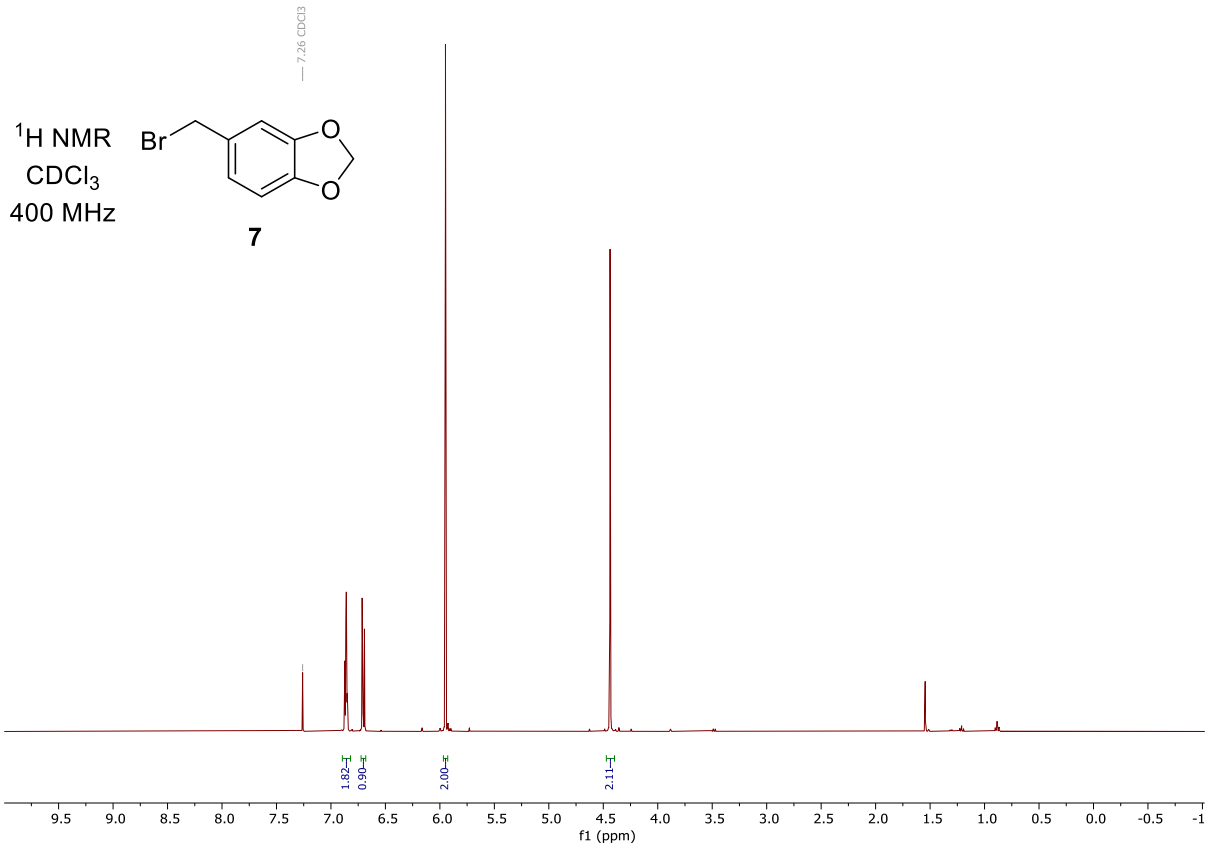

^{13}C NMR
$CDCl_3$
100 MHz
OH
H
Ph
O
N
O
H
6, 2.3:1 dr
163.50
135.95
135.85
128.71
128.69
128.49
128.45
128.37
128.32
77.16 CDCl3
68.41
68.25
65.96
65.22
42.36
42.02
40.24
38.16
29.72
29.60
23.50
22.78
18.23
14.98
f1 (ppm)

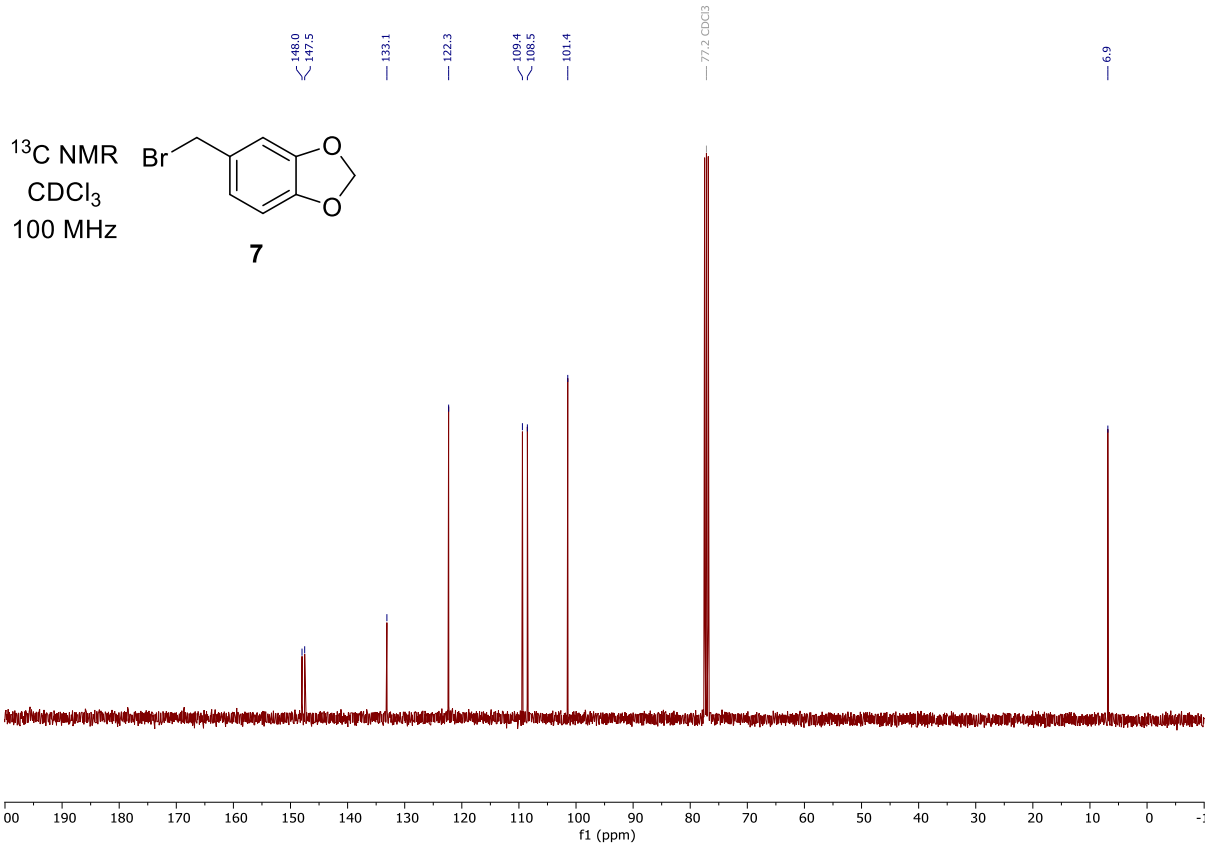


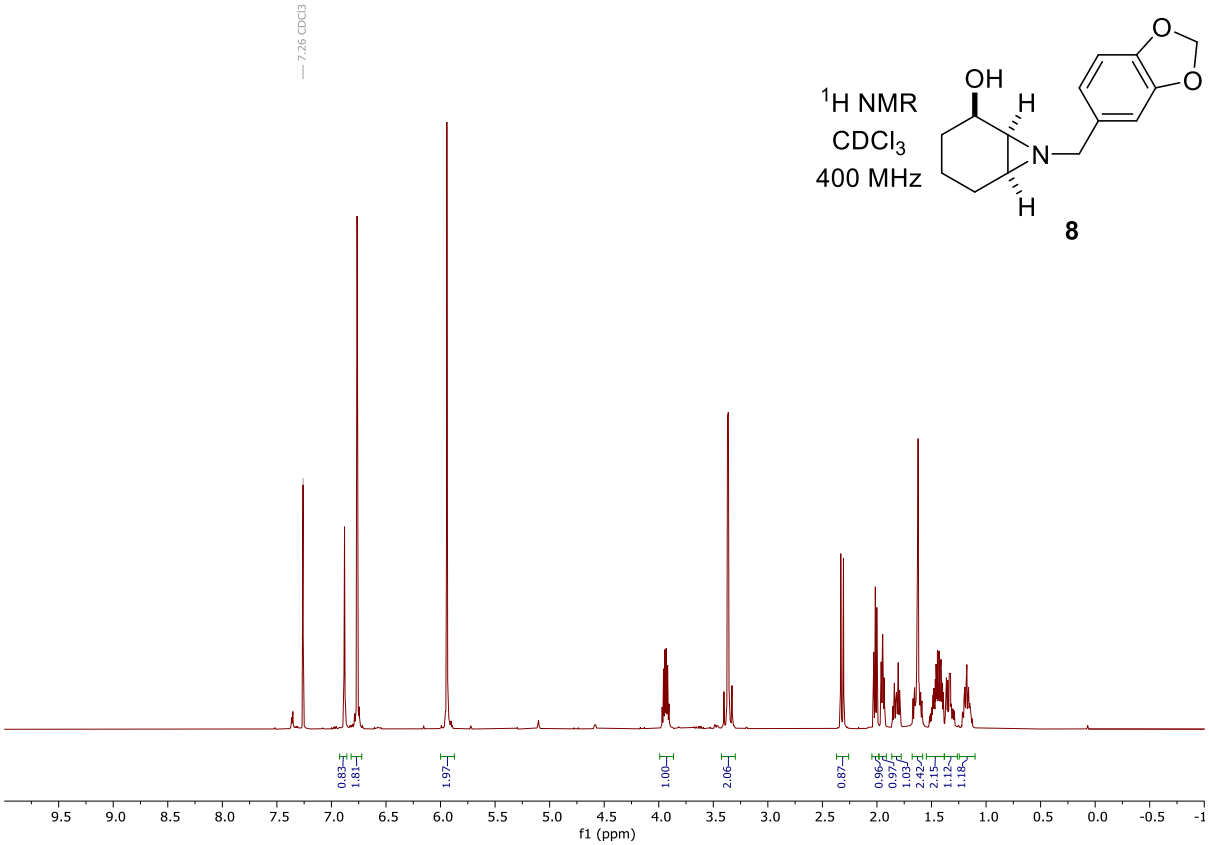
6, major isomer

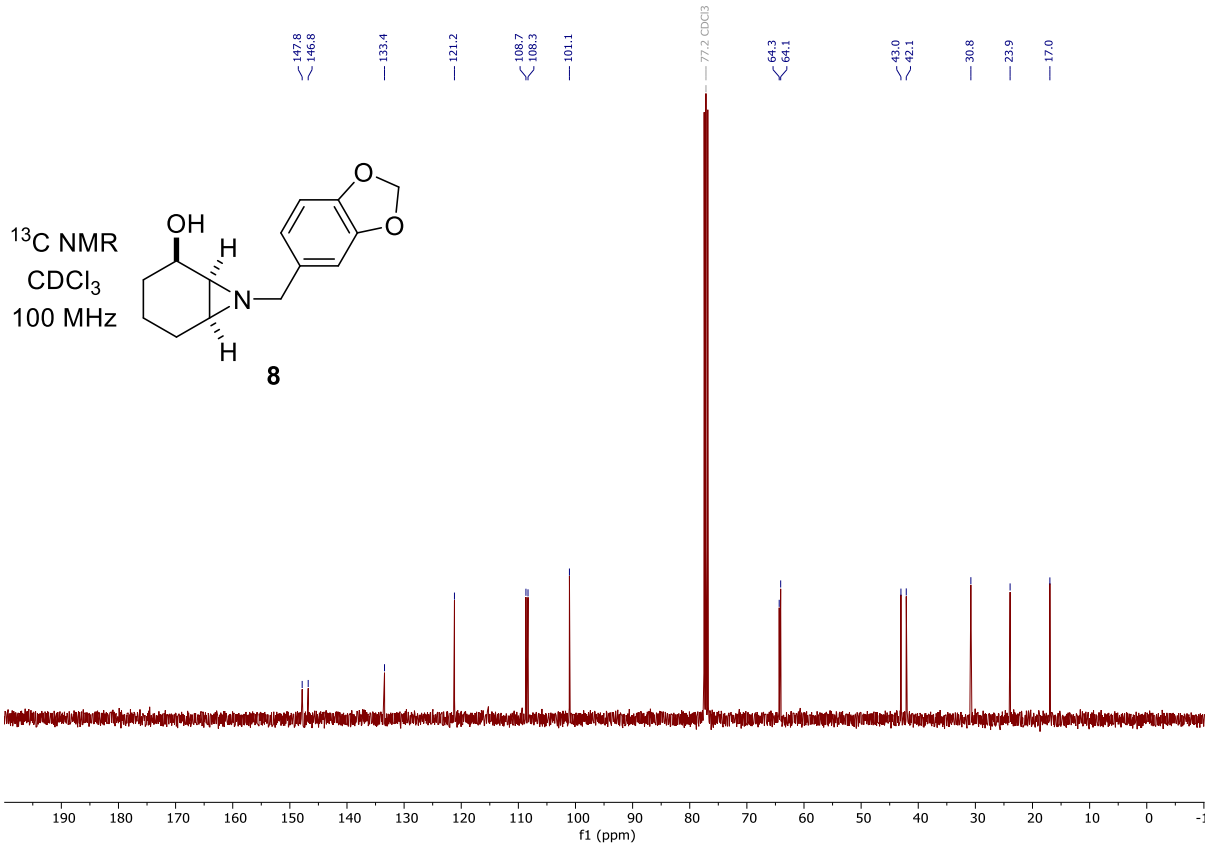


6, major isomer

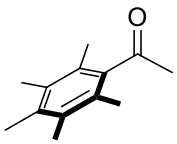

7.26 CDCl3
^{1}H NMR
$CDCl_3$
400 MHz
Br
O
O
7
1.82
0.90
2.00
2.11
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


148.0
147.5
133.1
122.3
109.4
108.5
101.4
77.2 CDCl3
6.9
^{13}C NMR
$CDCl_3$
100 MHz
Br
O
O
7
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.26 CDCl3
^{1}H NMR
$CDCl_3$
400 MHz
OH
H
N
H
O
O
8
0.83
1.81
1.97
1.00
2.06
0.87
0.96
0.97
1.03
2.42
2.15
1.12
1.18
f1 (ppm)

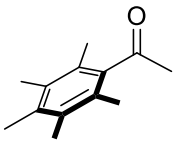

147.8
146.8
133.4
121.2
108.7
108.3
101.1
77.2 CDCl3
64.3
64.1
43.0
42.1
30.8
23.9
17.0
^{13}C NMR
$CDCl_3$
100 MHz
OH
H
N
H
O
O
8
f1 (ppm)

^{1}H NMR
$CDCl_3$
400 MHz

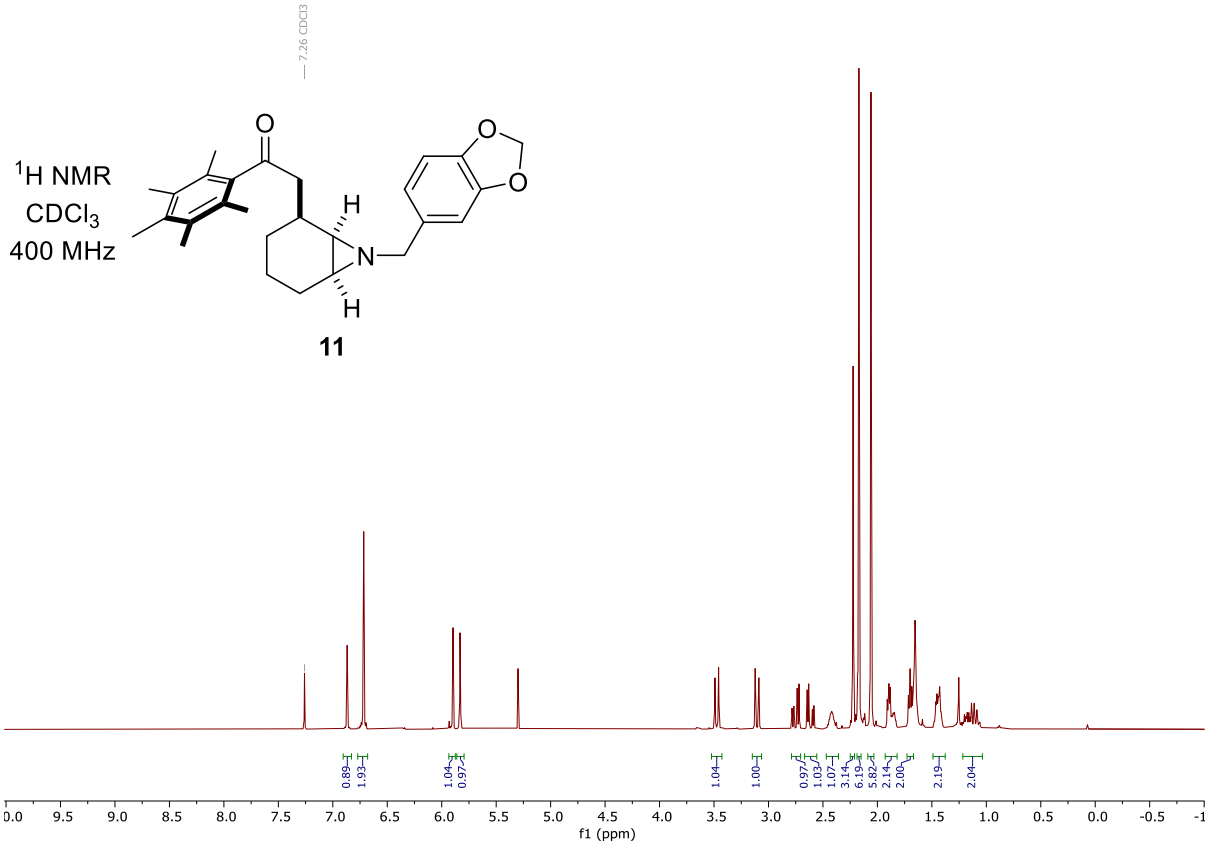


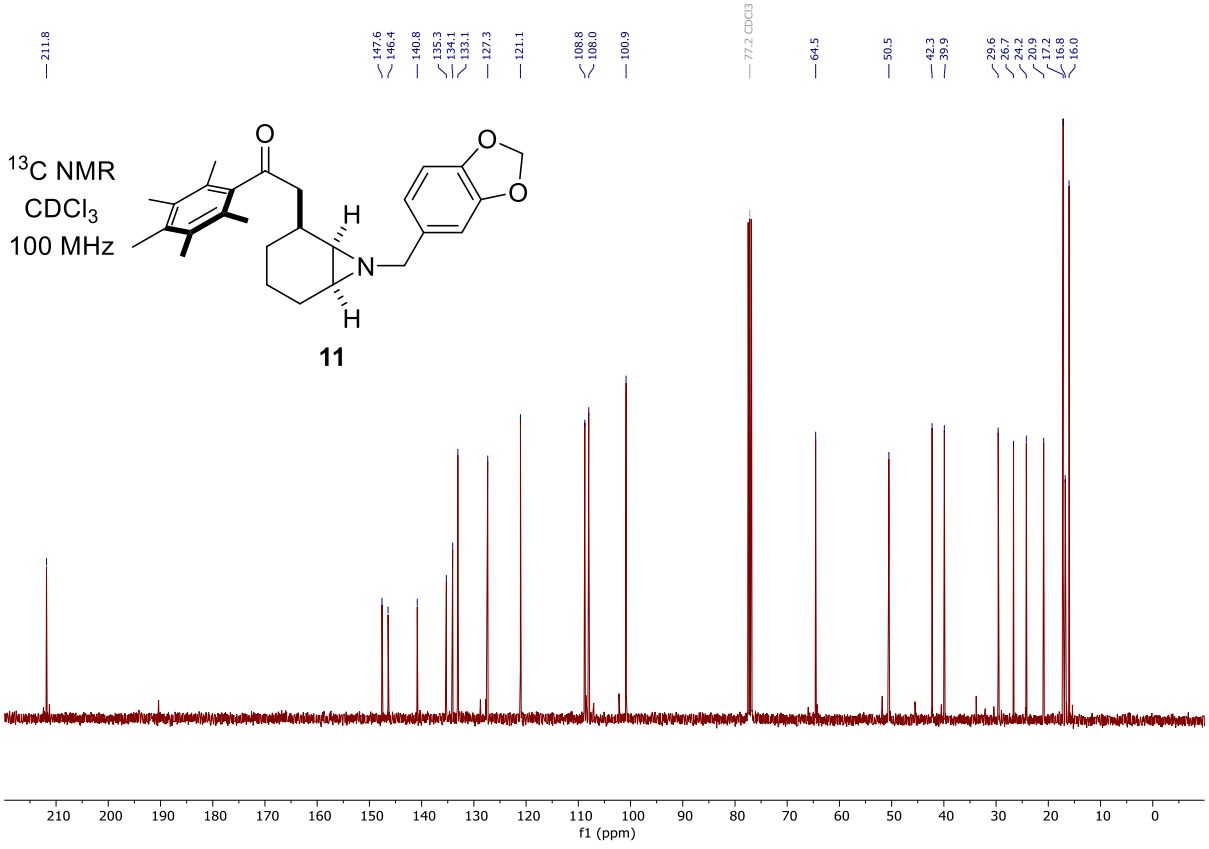
9

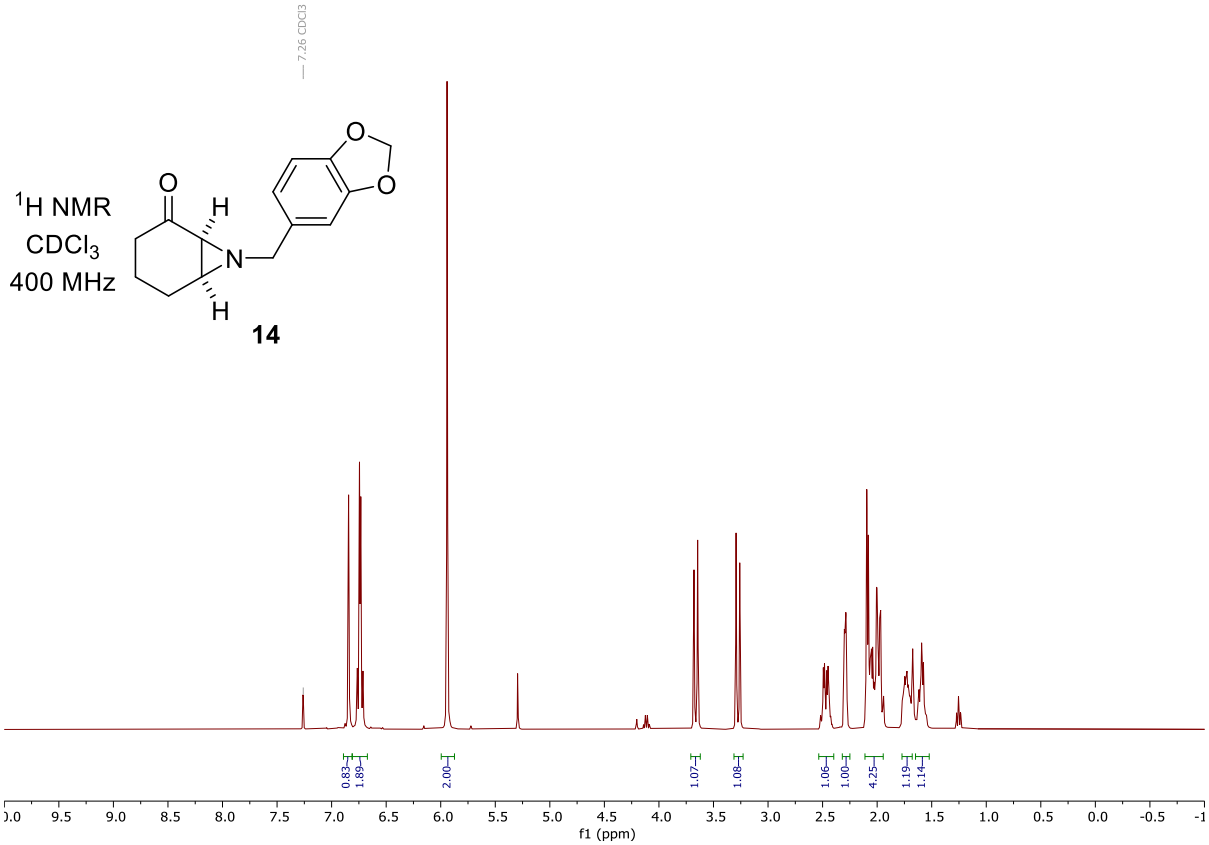
^{13}C NMR
$CDCl_3$
100 MHz

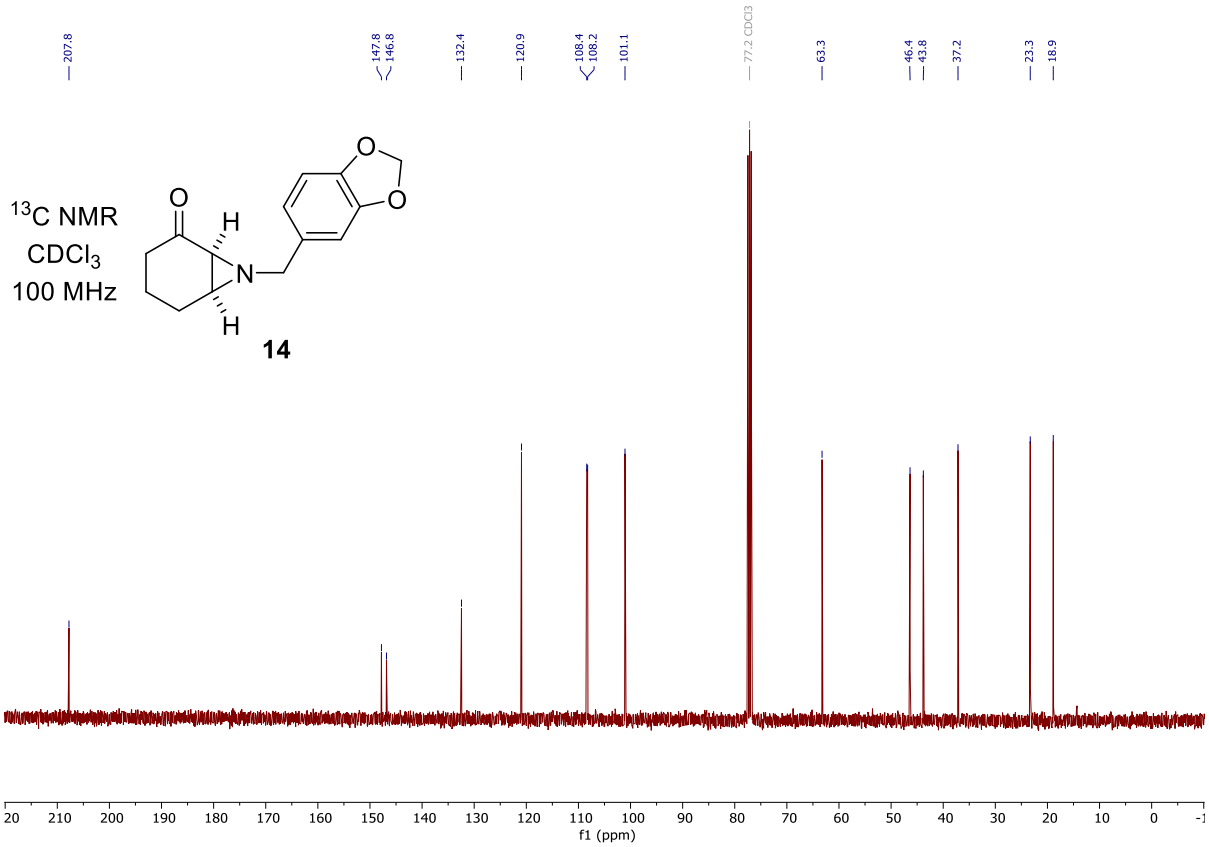


9

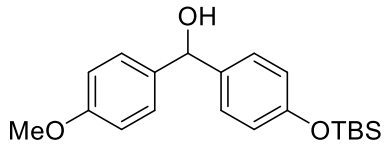

7.26 CDCl3
1H NMR
CDCl3
400 MHz
O
O
O
H
N
H
11
0.89
1.93
1.04
0.97
1.04
1.00
0.97
1.03
1.07
3.14
6.19
5.82
2.14
2.00
2.19
2.04
f1 (ppm)


211.8
147.6
146.4
140.8
135.3
134.1
133.1
127.3
121.1
108.8
108.0
100.9
77.2 CDCl3
64.5
50.5
42.3
39.9
29.6
26.7
24.2
20.9
17.2
16.8
16.0
13C NMR
CDCl3
100 MHz
O
O
O
H
N
H
11
f1 (ppm)


7.26 CDCl3
^{1}H NMR
$CDCl_3$
400 MHz
O
H
N
O
O
H
14
0.83
1.89
2.00
1.07
1.08
1.06
1.00
4.25
1.19
1.14
f1 (ppm)

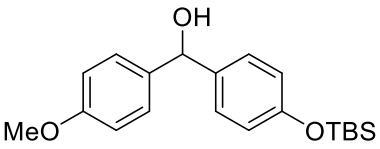

207.8
147.8
146.8
132.4
120.9
108.4
108.2
101.1
77.2 CDCl3
63.3
46.4
43.8
37.2
23.3
18.9
^{13}C NMR
$CDCl_3$
100 MHz
O
H
N
O
O
H
14
f1 (ppm)

^{1}H NMR
$CDCl_3$
400 MHz

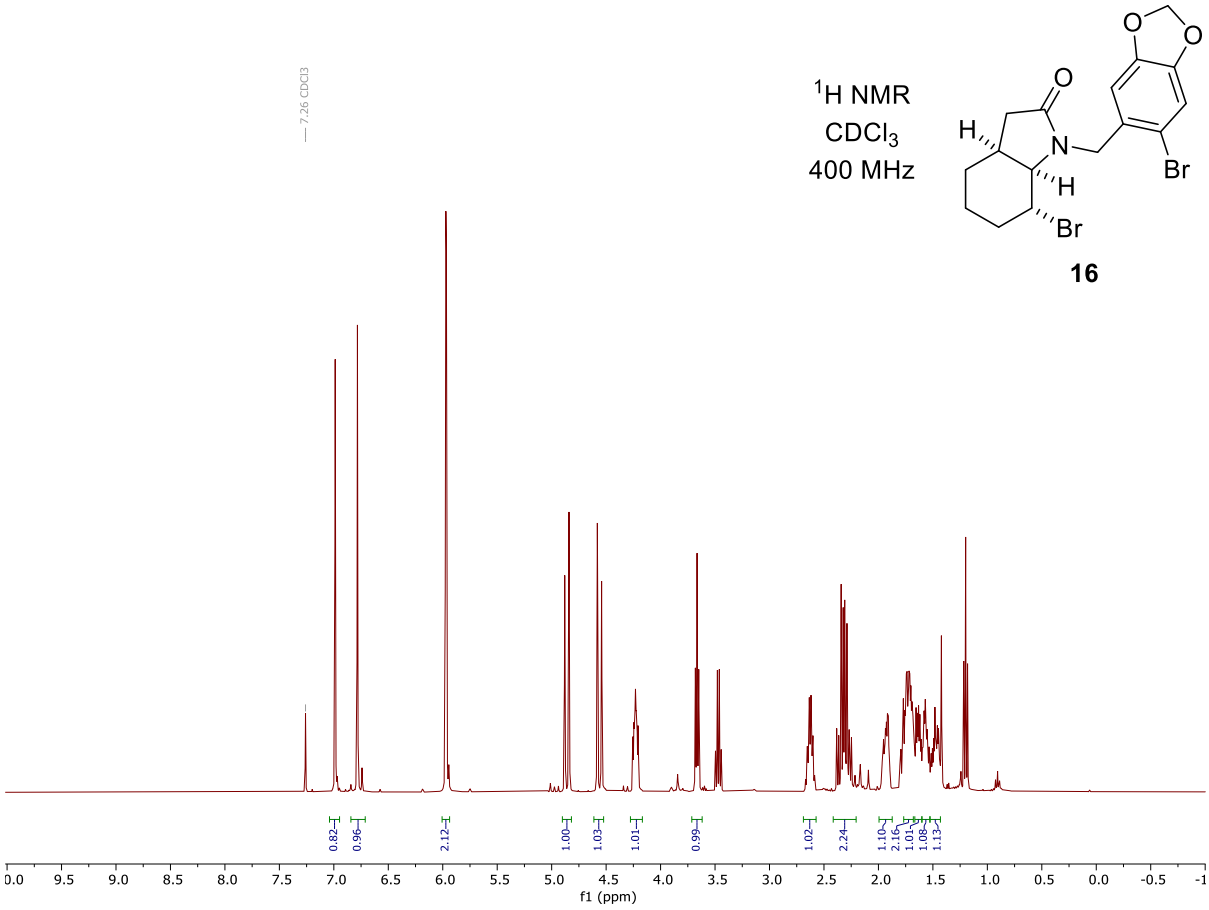


15

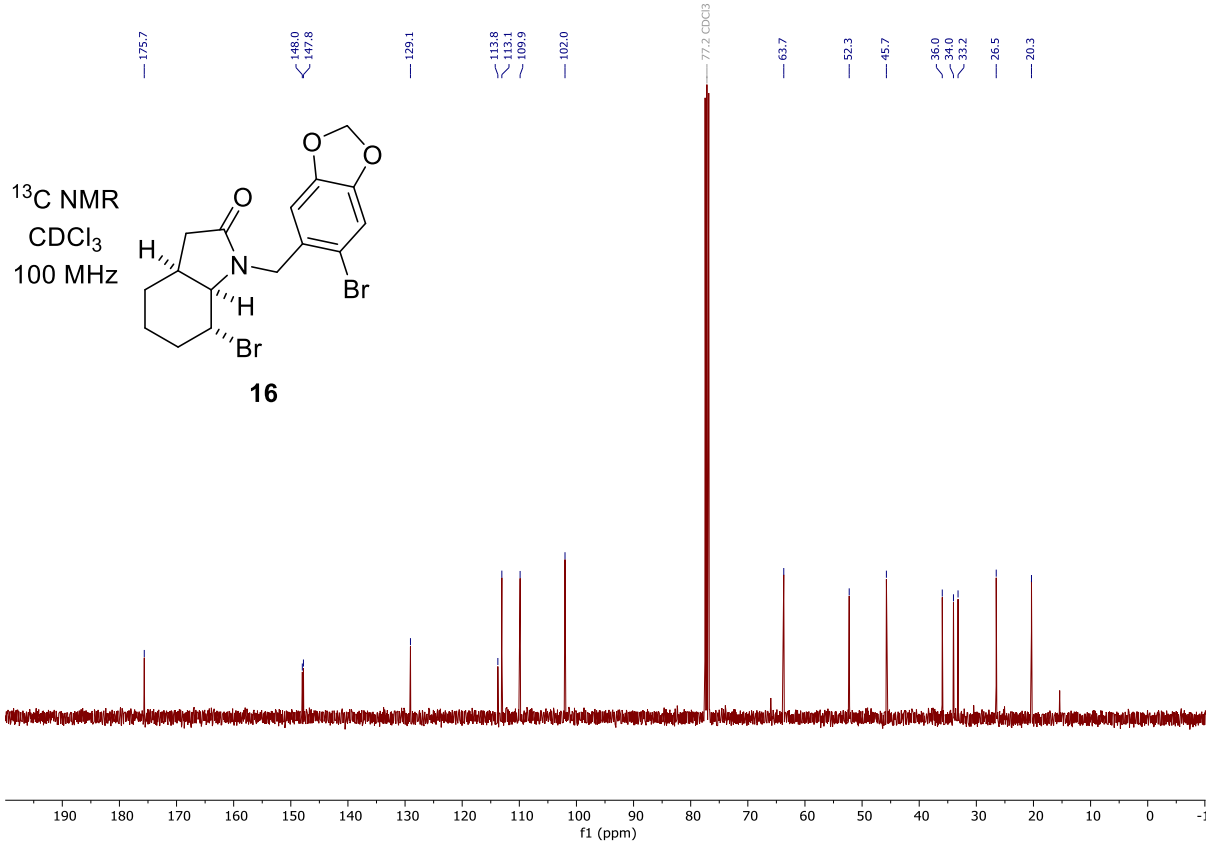
^{13}C NMR
$CDCl_3$
100 MHz



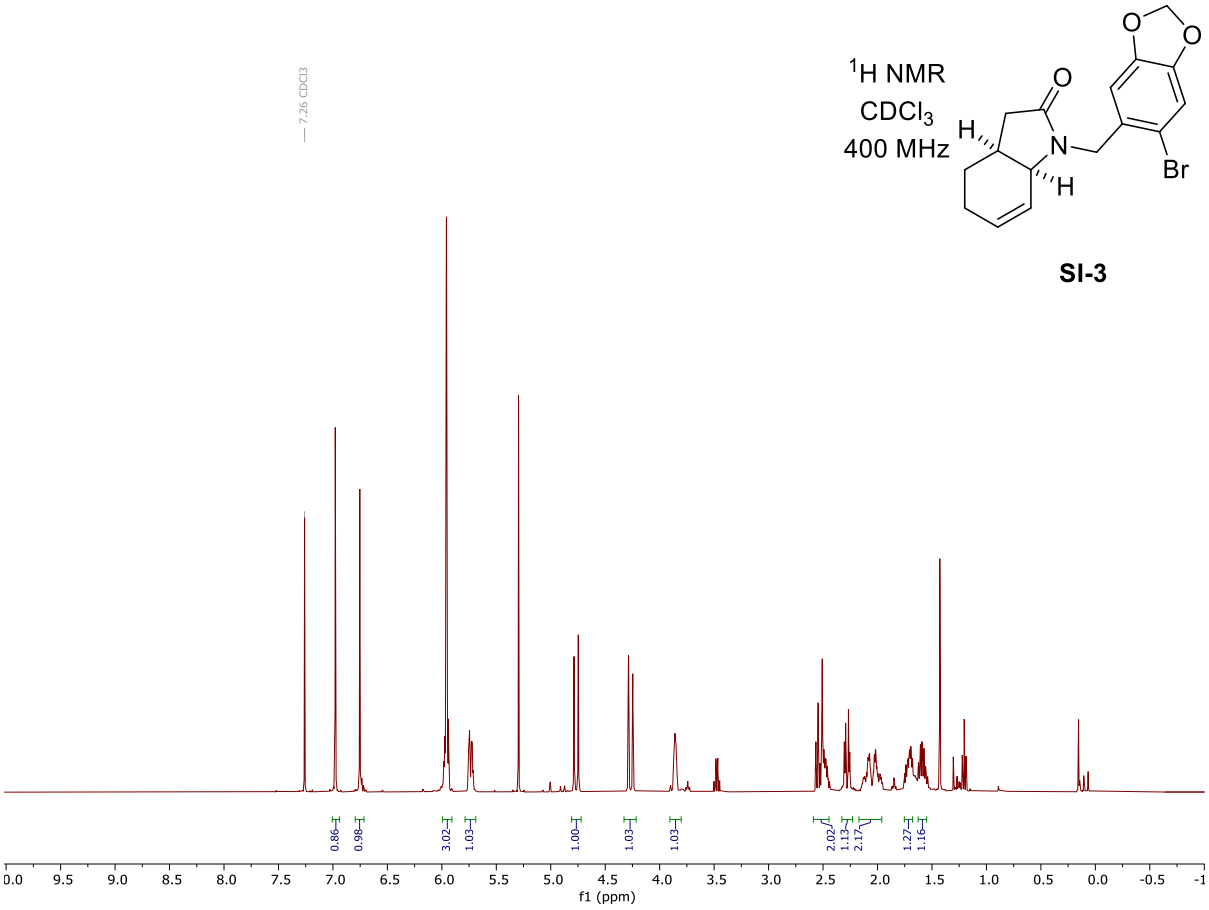
15


^{1}H NMR
$CDCl_3$
400 MHz
7.26 CDCl3
0.82
0.96
2.12
1.00
1.03
1.01
0.99
1.02
2.24
1.10
2.16
1.01
1.08
1.13
f1 (ppm)

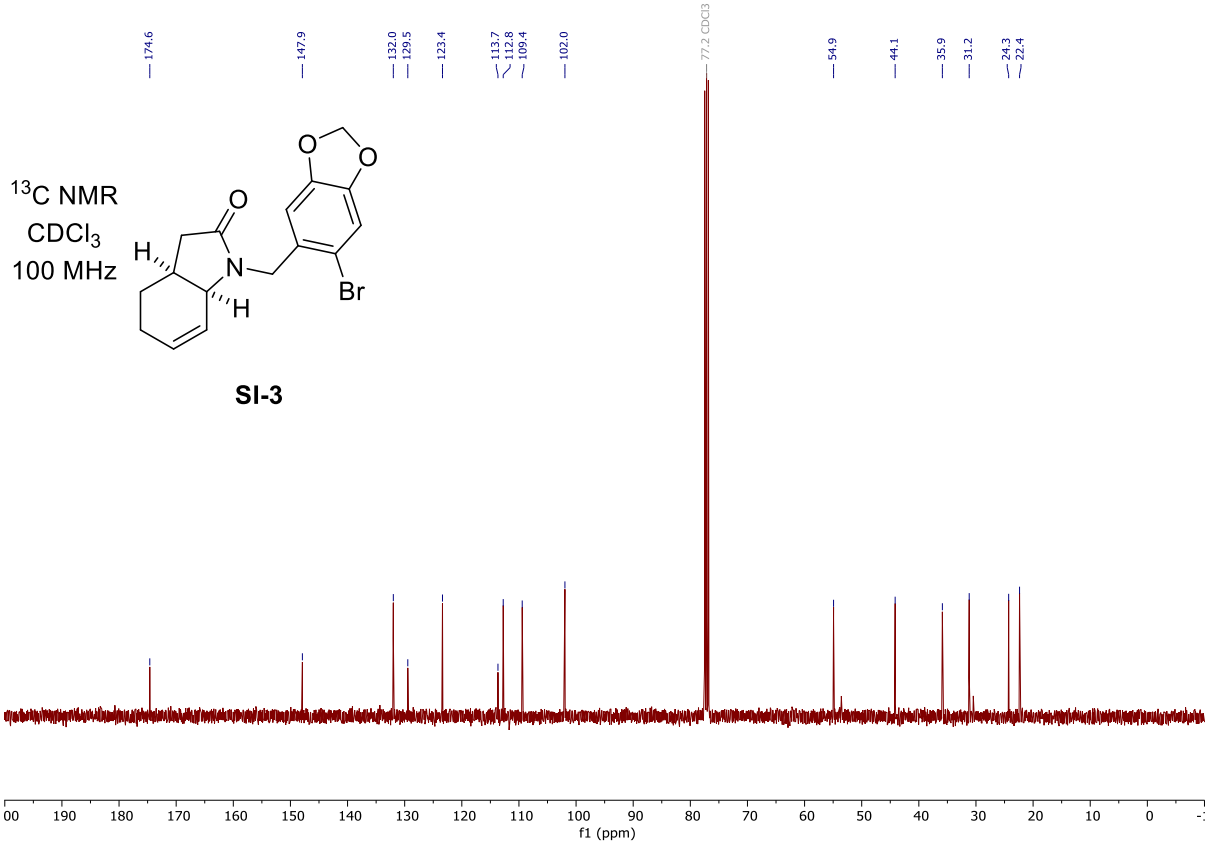
16


^{13}C NMR
$CDCl_3$
100 MHz
175.7
148.0
147.8
129.1
113.8
113.1
109.9
102.0
77.2 CDCl3
63.7
52.3
45.7
36.0
34.0
33.2
26.5
20.3
f1 (ppm)

16

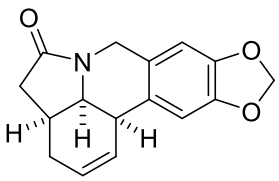

^{1}H NMR
$CDCl_3$
400 MHz
O
O
O
H
N
H
Br
7.26 CDCl3
0.86
0.98
3.02
1.03
1.00
1.03
1.03
2.02
1.13
2.17
1.27
1.16
f1 (ppm)

SI-3


^{13}C NMR
$CDCl_3$
100 MHz
O
O
O
H
N
H
Br
174.6
147.9
132.0
129.5
123.4
113.7
112.8
109.4
102.0
77.2 CDCl3
54.9
44.1
35.9
31.2
24.3
22.4
f1 (ppm)

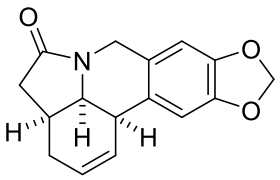
SI-3

^{1}H NMR
$CDCl_3$
400 MHz



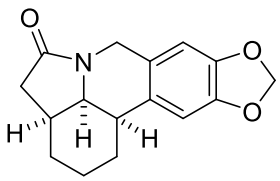
17

^{13}C NMR
$CDCl_3$
100 MHz

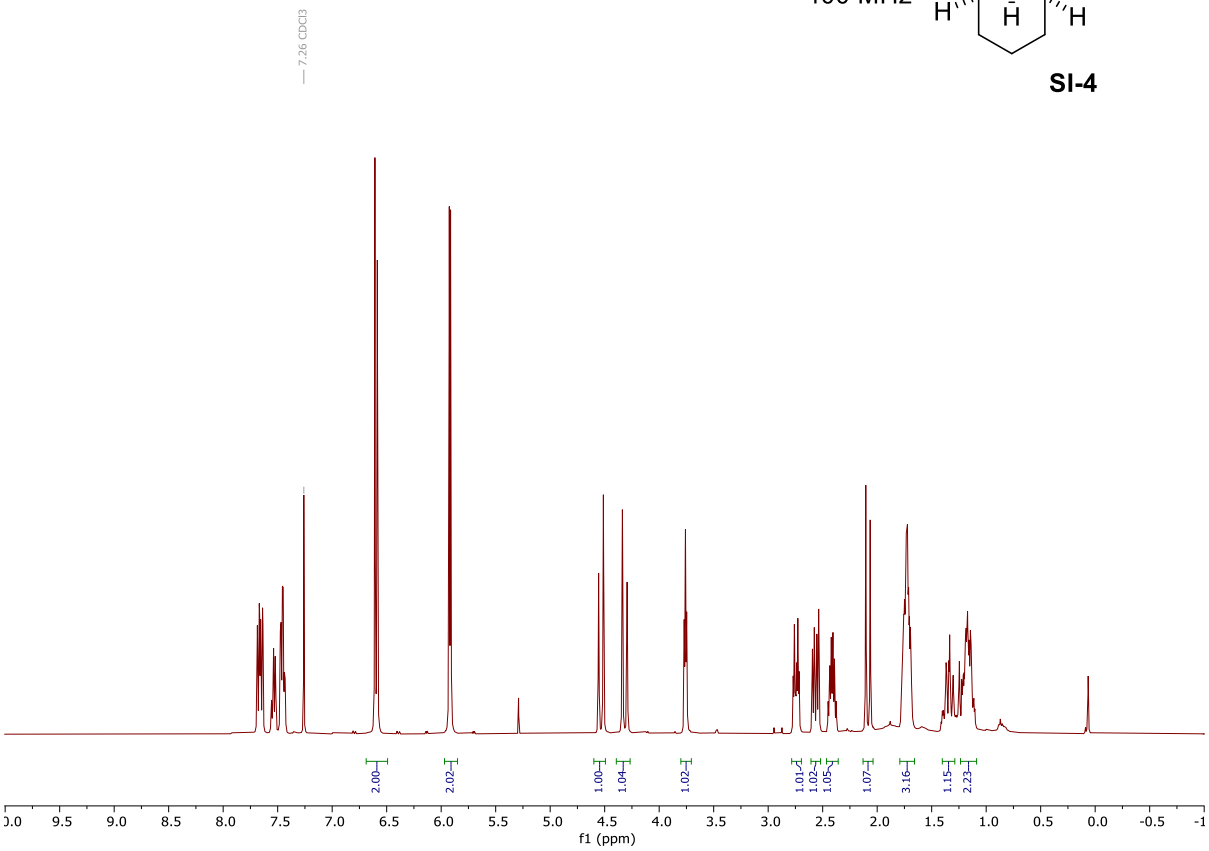


17

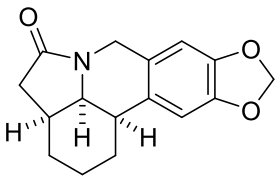
^{1}H NMR
$CDCl_3$
400 MHz



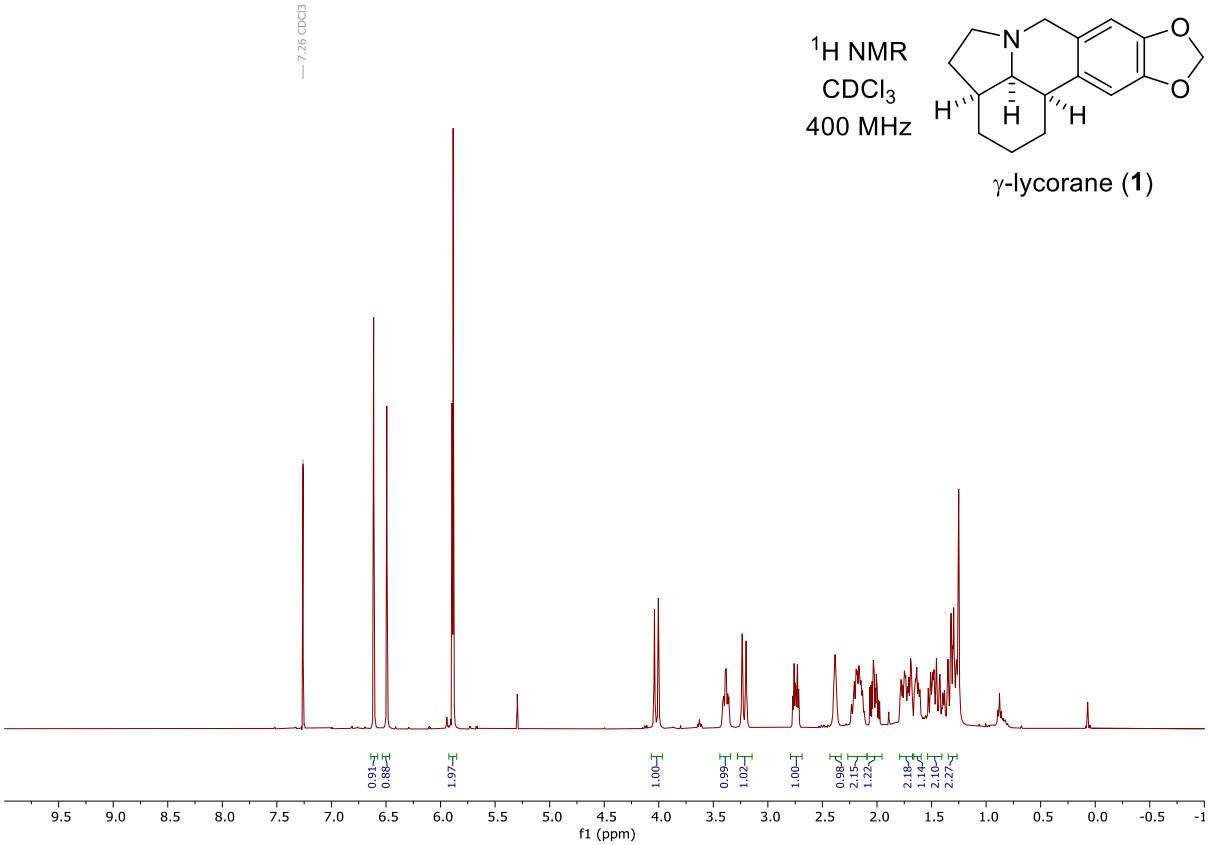
SI-4

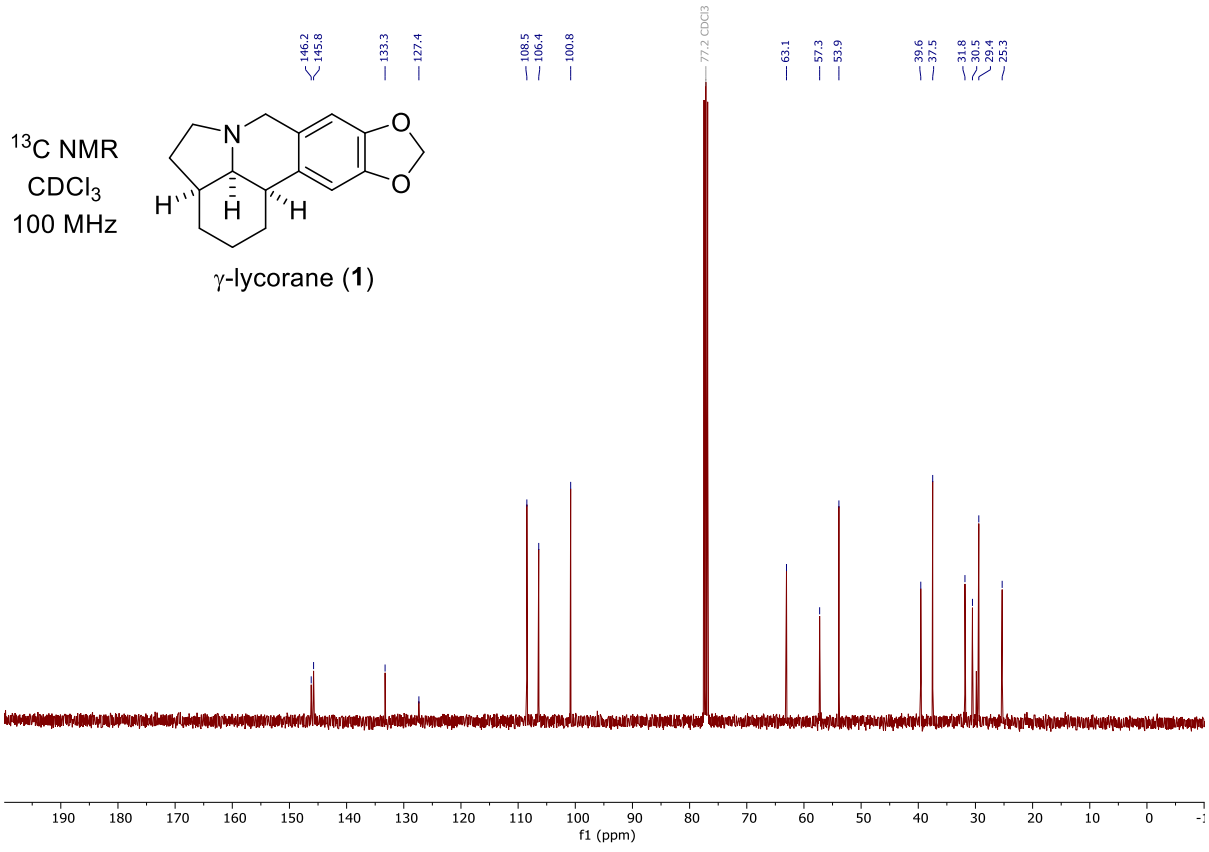


^{13}C NMR
$CDCl_3$
100 MHz

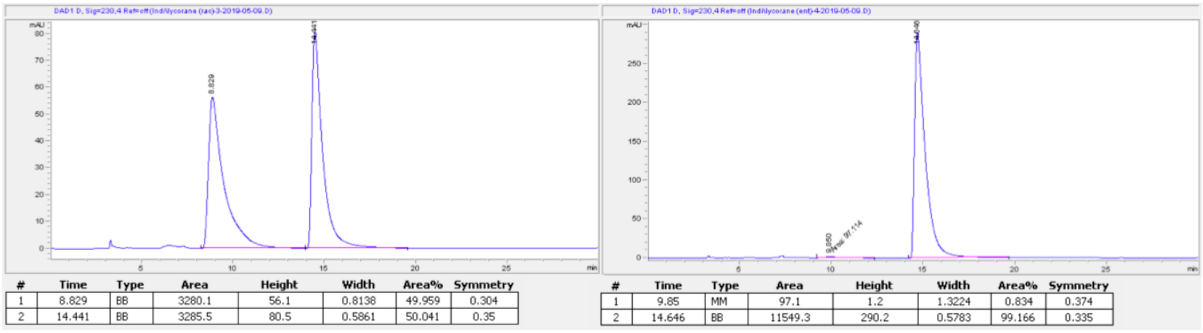


SI-4


7.26 CDCl3
^{1}H NMR
$CDCl_3$
400 MHz
γ-lycorane (**1**)
0.91
0.88
1.97
1.00
0.99
1.02
1.00
0.98
2.15
1.22
2.18
1.14
2.10
2.27
f1 (ppm)


146.2
145.8
133.3
127.4
108.5
106.4
100.8
77.2 CDCl3
63.1
57.3
53.9
39.6
37.5
31.8
30.5
29.4
25.3
^{13}C NMR
$CDCl_3$
100 MHz
γ-lycorane (**1**)
f1 (ppm)

5. *Chiral HPLC Traces*



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.829	BB	3280.1	56.1	0.8138	49.959	0.304
2	14.441	BB	3285.5	80.5	0.5861	50.041	0.35

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.85	MM	97.1	1.2	1.3224	0.834	0.374
2	14.646	BB	11549.3	290.2	0.5783	99.166	0.335

Figure SI-1: Chiral HPLC trace for racemic, and enantioenriched γ-lycorane (**1**)

6. *X-Ray Crystallographic Data*

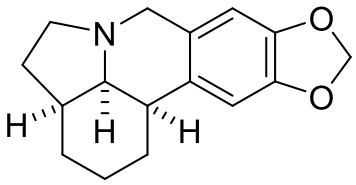
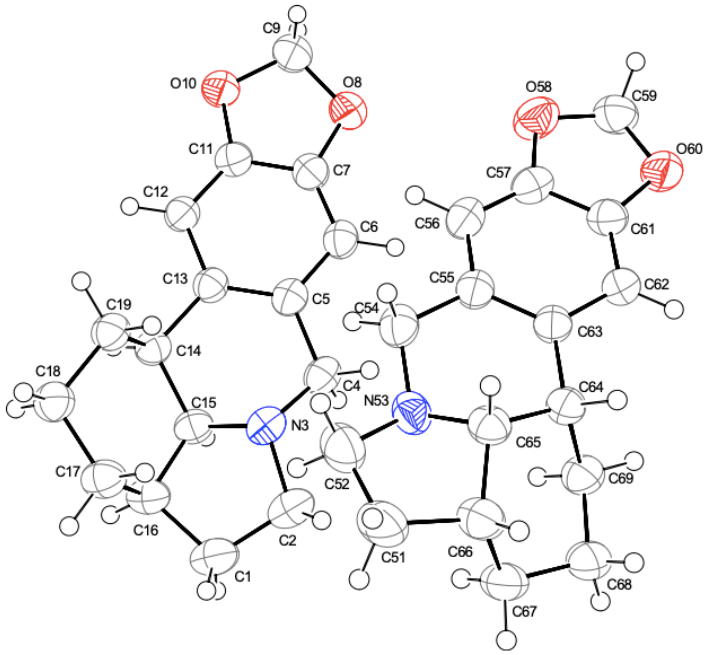


Table SI-3 Crystal data and structure refinement for γ-lycorane (**1**).

Identification code with CCDC	2151105	
Empirical formula	C16 H19 N O2	
Formula weight	257.33	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 9.5572(6) Å	α= 101.237(6)°.
	b = 12.2819(10) Å	β= 99.446(5)°.
	c = 12.4294(6) Å	γ = 110.609(7)°.
Volume	1295.68(17) $Å^3$	
Z	4	
Density (calculated)	1.319 Mg/m^3	
Absorption coefficient	0.689 mm^{-1}	
F(000)	551.996	
Crystal size	0.19 x 0.15 x 0.05 mm^3	
Theta range for data collection	3.748 to 76.818°.	
Index ranges	-12<=h<=12, -15<=k<=15, -15<=l<=15	
Reflections collected	21905	
Independent reflections	5401 [R(int) = 0.060]	
Completeness to theta = 75.281°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.97 and 0.74	

Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	5401 / 0 / 344
Goodness-of-fit on F^2	0.9945
Final R indices [I>2sigma(I)]	R1 = 0.0665, wR2 = 0.1943
R indices (all data)	R1 = 0.0839, wR2 = 0.2173
Largest diff. peak and hole	0.28 and -0.26 e.$Å^{-3}$



7. *References*

[1] A. B. Pangborn, M. A. Gairdello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics*, **1996**, *15*, 1518–1520.

[2] *Purification of Laboratory Chemicals*, 3rd edition. D.D. Perrin, W. L. F. Armarego, *Pergamon Press*, Oxford, **1988**.

[3] Y. Menjo, A. Hamajima, N. Sasaki, Y. Hamada, *Org. Lett.* **2011**, *13*, 5744–5747

[4] L. Qin, Z. Zhou, J. Wei, T. Yan, H. Wen, *Synth. Commun.* **2010**, *40*, 642–646.

[5] F. De Vincentiis, G. Bencivenni, F. Pesciaioli, A. Mazzanti, G. Bartoli, P. Galzerano, P. Melchiorre, *Chem.: Asian J.* **2010**, *5*, 1652–1656.

[6] P. Kiprof, J. Li, C. L. Renish, E. K. Kalombo, V. G. Young, *J. Organomet. Chem.* **2001**, *620*, 113–118.

[7] M. E. Krafft, J. W. Cran, *Synlett* **2005**, *2005*, 1263–1266.

[8] S. L. Drew, A. L. Lawrence, M. S. Sherburn, *Angew. Chem. Int. Ed.* **2013**, *52*, 4221–4224.

[9] N. S. Chandrakumar, B. B. Chen, M. Clare, B. N. Desai, S. W. Djuric, S. H. Docter, A. F. Gasiecki, R. A. Haack, C.-D. Liang, J. M. Miyashiro, et al., *LTA4 Hydrolase Inhibitors*, **2002**, EP1221441A2.

[10] M. Ikeda, S. Ohtani, T. Sato, H. Ishibashi, *Synthesis* **1998**, *1998*, 1803–1806.

[11] S. Nagumo, H. Takada, E. Yasui, Y. Sahara, Y. Chinen, H. Tanaka, Y. Morita, C. Kobiki, D. Narisawa, M. Mizukami, et al., *Heterocycles* **2011**, *83*, 555.

[12] A. Monaco, B. R. Szulc, Z. X. Rao, M. Barniol-Xicota, M. Sehailia, B. M. A. Borges, S. T. Hilton, *Chem. Eur. J.* **2017**, *23*, 4750.

[13] R. Rocaboy, D. Dailler, O. Baudoin, *Org. Lett.* **2018**, *20*, 772.