

Supporting information for

Enantioselective Access to Isoquinuclidines by Tropenone Desymmetrization and Homoallylic Radical Rearrangement: Synthesis of (+)-Ibogamine

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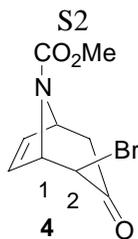
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- Preparative procedures and characterisation data for **4**, **7-15**, and (+)-**1**.
- Copies of ¹H and ¹³C NMR spectra of **4**, **8-15**, and (+)-**1**.

General Details

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under an atmosphere of argon. Syringes and needles for the transfer of reagents were dried at 140 °C and allowed to cool in a desiccator over P₂O₅ before use. THF was distilled from benzophenone ketyl; DMSO and NEt₃ from CaH₂; MeOH from Mg(OMe)₂; benzene, MeCN, and CH₂Cl₂ by passing through basic alumina. Air was dried by passing through CaCl₂. Reactions were monitored by TLC, using plates pre-coated with a 0.25 mm layer of silica containing a fluorescent indicator. Visualization of reaction components was achieved with 254 nm, and with a basic KMnO₄ dip. Organic layers were dried using MgSO₄ unless otherwise stated. Column chromatography was carried out on Kieselgel 60 (40-63 μm). Petroleum ether refers to the fraction of petroleum boiling between 30 °C and 40 °C. IR spectra were recorded as either KBr discs or thin films. Melting points were recorded on a Kofler hot block, and are uncorrected. ¹H and ¹³C NMR spectra of compounds were recorded in CDCl₃ at 25 °C unless otherwise stated. Chemical shifts are reported relative to CDCl₃ (δ_H 7.25) and CHCl₃ (δ_C (central line of t) 77.23) unless otherwise stated. Coupling constants (*J*) are given in Hz, multiplicities are given as multiplet (m), singlet (s), doublet (d), triplet (t), or quartet (q). COSY, HMQC, HMBC, and DEPT experiments were used to aid spectral assignments. Doubling of signals due to Boc rotamers was often observed: in these cases the word ‘and’ is used specifically to signify extra peaks and coupling constants arising from rotamers in the spectra.

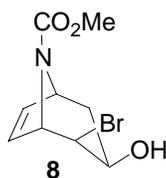


Preparation of and data for α -bromoketone **4**¹

To a stirred solution of the chiral lithium amide **6**² in THF (25 mL) [prepared from the corresponding amine (3.26 g, 12.5 mmol) and *n*-BuLi (2.5 M in hexane; 5.0 mL, 12.5 mmol) at -78 °C] was added HMPA (2.9 mL, 16.6 mmol) at -78 °C, and the resulting mixture was warmed to room temperature for 1 h; it was then cooled to -90 °C. To the cooled mixture were added Me₃SiCl (3.2 mL, 25.2 mmol) and then tropenone **3**³ (1.5 g, 8.3 mmol) in THF (10 mL) at -90 °C over 20 min; the reaction mixture was then stirred for 2 h at -90 °C. The reaction was quenched by the addition of saturated NaHCO₃ (30 mL) to the mixture, after which the aqueous layer was separated and extracted with Et₂O (3 × 15 mL). To the combined organic extracts were added cold dilute HCl solution (0.2 M, 20 mL), after which the aqueous layer was separated and the process repeated once. The remaining organic extract was then washed with saturated aq. NaHCO₃ (10 mL) and with brine (10 mL), then dried and evaporated to give the corresponding silylenol ether **7** as a pale yellow oil which was used in the next step without further purification. Basification of the remaining acidic aqueous layer (NaOH pellets) followed by extraction with ether (3 × 15 mL) and further purification by Kugelrohr distillation (bp 120 °C/ 0.8 mmHg) gave recovered chiral amine (2.9 g, ~90%).

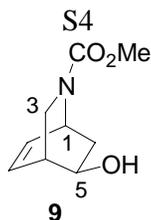
To a stirred solution of silylenol ether **7** in THF (20 mL) at 0 °C was added recrystallized NBS (1.63 g, 9.16 mmol) in one portion. The resulting solution was stirred at 0 °C for 10 min and then saturated aq. NH₄Cl (30 mL) and ether (30 mL) were added. The two layers were separated and the aqueous layer was extracted with ether (2 × 25 mL). The combined organic layers were washed with brine (20 mL), dried, concentrated *in vacuo*, and purified by column chromatography on silica with petroleum ether-EtOAc (8-2) as eluent to give a single diastereoisomer of α -bromoketone (+)-**4** (1.73 g, 80%, 80% ee) as a white solid. (+)-**4** was recrystallized twice from ether-petroleum ether to provide bromoketone **4** of >99% ee (969 mg, 45% yield from **4**) according to chiral GC analysis; *R*_f 0.36 (Et₂O); mp 29-30 °C; [α]_D²² +256.7 (*c* 1, CHCl₃) of a sample of >99% ee; ν_{\max} (KBr)/cm⁻¹ 3087, 2958, 1715, 1455, 1403, 1329, 1279, 1119, 986, 730; δ_{H} (400 MHz, CDCl₃): 6.38 (1H, br s, CH=), 6.20 (1H, br s, CH=), 5.14 and 5.03 (1H, br s, CHN), 4.95 (1H, br s, CHN), 4.00 (1H, br s, C(2)H), 3.71 (3H, s, OMe), 3.09 (1H, br d, *J* 16, C(4)H^{exo}), 2.35 (1H, d, *J* 16, C(4)H^{endo}), δ_{C} (100 MHz) 198.7 (C=O), 153.5 (NCO₂), 137.9 and 137.4 (CH=), 131.7 and 131.2 (CH=), 61.5 (CHN), 56.3 and 56.1 (CHN), 52.6 (OMe), 48.3 (C2), 43.1 and 42.8 (C4); *m/z* (CI⁺), 279 and 277 (M + NH₄⁺, 100%), (Found (ES⁺) M + NH₄⁺, 277.0184. C₉H₁₄BrN₂O₃ requires 277.0182).

GC analysis of **4** for ee determination: (CP Chirasil Dex-CD column using H₂ as a carrier flow). Program 100 °C to 160 °C at a rate of 0.5 °C/min, 1 mL/min, 3 mg/mL), $t_{r,min}$ = 115.1 min and $t_{r,maj}$ = 115.8 min.



Preparation of and data for bromohydrin **8**⁴

To a cold (−30 °C), stirred solution of α -bromoketone (+)-**4** (900 mg, 3.46 mmol, >99% ee) in 20 mL of 1:1 MeOH-THF was added NaBH₄ (197 mg, 5.19 mmol) in one portion. The reaction mixture was allowed to slowly warm up to room temperature over a period of 2 h [the reduction being sluggish from −30 °C to −15 °C; careful control of the temperature must be performed from −15 °C to 0 °C (where most of the reduction occurs) to avoid competitive reduction at C2]. The reaction mixture was then quenched with dilute aqueous HCl (1 M) until gas evolution ceased, then further diluted with EtOAc (20 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (4 × 25 mL). The combined organic layers were washed with saturated aq. NaHCO₃ (10 mL), dried, concentrated *in vacuo*, and purified by column chromatography on silica with petroleum ether-EtOAc (1-1) as eluent to give a single diastereoisomer of bromohydrin (+)-**8** (508 mg, 56%) as a viscous oil, which crystallized to a white solid on standing; R_f 0.33 (EtOAc); mp 56-58 °C; $[\alpha]_D^{22}$ +45.4 (*c* 0.5, CHCl₃), ν_{max} (KBr)/cm^{−1} 3418, 3080, 2995, 2927, 2854, 1695, 1455, 1109, 1006, 694, δ_H (400 MHz, CDCl₃): 6.20-6.15 (2H, m, CH=), 5.14 and 5.02 (1H, br s, CHN), 4.82 and 4.77 (1H, br s, CHN), 4.43-4.40 (1H, m, C(2)H), 3.85-3.80 (1H, m, C(3)H), 3.70 (3H, s, OMe), 2.09 (1H, br s, OH), 1.85-1.80 (1H, br dd, *J* 13 and 6, C(4)H), 1.67-1.62 (1H, m, C(4)H), δ_C (100 MHz) 153.8 (NCO₂), 134.9 and 134.1 (CH=), 130.5 and 129.7 (CH=), 64.5 (CHOH), 62.8 (CHN), 57.8 (C2), 57.2 and 56.8 (CHN), 52.5 and 52.4 (OMe), 31.3 and 31.1 (C4); m/z (CI⁺), 281 and 279 (M + NH₄⁺, 100%), (Found (ES⁺) M + NH₄⁺, 279.0337. C₉H₁₆BrN₂O₃ requires 279.0339).



Preparation of and data for dehydroisoquinuclidinol **9** from bromohydrin **8** (stoichiometric version)

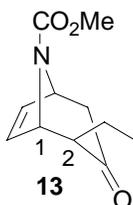
A solution of bromohydrin (+)-**8** (50 mg, 0.19 mmol) in toluene (5 mL) was stirred and heated under argon at 90 °C, and a solution of Bu₃SnH (43 μL, 0.23 mmol) and AIBN (1.6 mg, 5%) in toluene (5 mL) was added over 1 h via syringe pump. After a further 15 min, TLC analysis showed complete consumption of the starting material. The reaction mixture was cooled, washed with saturated aq. NaHCO₃ (10 mL) and extracted with EtOAc (10 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried, concentrated *in vacuo*, and purified by column chromatography on silica with petroleum ether-EtOAc (6-4) as eluent to give dehydroisoquinuclidinol (–)-**9** (26 mg, 75%) as a colorless oil; *R*_f 0.25 (EtOAc); [α]_D²² –125.4 (*c* 0.5, CHCl₃), *v*_{max}(neat)/cm^{–1} 3418, 3056, 2958, 2980, 1682; 1455, 1398, 1192, 1120, 1084, 768, 715, δ_H (400 MHz, CDCl₃): 6.45-6.31 (2H, m, CH=), 4.73 and 4.58 (1H, br s, C(1)H), 3.99-3.97 (1H, m, C(5)H), 3.83-3.78 (1H, m, C(3)H), 3.68 and 3.67 (3H, s, OMe), 2.92 and 2.87 (1H, d, *J* 10, C(3)H), 2.78-2.73 (1H, m, C(4)H), 2.31 (1H, br s, OH), 2.00-1.89 (1H, m, C(6)H), 1.64-1.55 (1H, m, C(6)H), δ_C (100 MHz) 155.8 (NCO₂), 134.0 and 133.4 (CH=), 132.5 and 132.1 (CH=), 65.2 (C5), 52.3 (OMe), 46.4 and 45.9 (C1), 40.3 and 40.1 (C3), 38.4 and 38.3 (C4), 36.9 (C6); *m/z* (CI⁺), 201 (M + NH₄⁺, 65%), 184 (M + H⁺, 100), (Found (ES⁺) M + H⁺, 184.0970. C₉H₁₄NO₃ requires 184.0968).

Preparation of dehydroisoquinuclidinol **9** from bromohydrin **8** (catalytic version)

To a stirred solution of (+)-**8** (400 mg, 1.53 mmol) in 10 mL of EtOH was added NaBH₄ (87 mg, 2.30 mmol), AIBN (25 mg, 0.15 mmol), and Bu₃SnCl (62 μL; 0.23 mmol) (effervescence occurred for 2 min) and the suspension was then heated to reflux for 30 min (ending of effervescence marked completion of the rearrangement). The suspension produced was evaporated under reduced pressure, and then diluted with EtOAc (20 mL) and quenched with aq. HCl (1 M, 5 mL). The two layers were separated and the aqueous layer was further extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL), dried, concentrated *in vacuo*, and purified by column chromatography on silica with petroleum ether-EtOAc (6-4) as eluent to give dehydroisoquinuclidinol (–)-**9** (230 mg, 82%).

Preparation of dehydroisoquinuclidinol **9** from α -bromoketone **4** (one pot)

To a cold ($-30\text{ }^{\circ}\text{C}$), stirred solution of (+)-**4** (900 mg, 3.47 mmol, $>99\%$ ee) in EtOH (20 mL) was added NaBH_4 (198 mg, 5.23 mmol) in one portion. The reaction mixture was slowly allowed to warm up to room temperature over a period of 2 h [the reduction being sluggish from $-30\text{ }^{\circ}\text{C}$ to $-15\text{ }^{\circ}\text{C}$; careful control of the temperature must be performed from $-15\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$ (where most of the reduction occurs) to avoid competitive reduction at C2]. To this reaction mixture was added NaBH_4 (198 mg, 5.23 mmol), AIBN (57 mg, 0.35 mmol), and Bu_3SnCl (0.141 mL; 0.52 mmol) (effervescence occurred for 2 min) and the suspension heated to reflux for 30 min (ending of effervescence marked completion of the rearrangement). The suspension produced was evaporated under reduced pressure, and then diluted with EtOAc (20 mL) quenched with aqueous HCl (1 M, 5 mL). The two layers were separated and the aqueous layer was extracted with EtOAc ($2 \times 20\text{ mL}$). The combined organic layers were washed with brine (10 mL), dried, concentrated *in vacuo*, and purified by column chromatography on silica with petroleum ether-EtOAc (6-4) as eluent to give dehydroisoquinuclidinol (–)-**9** (515 mg, 81%).

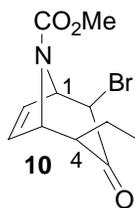


Preparation of and data for α -ethylketone **13**

To a stirred solution of the chiral lithium amide **6**² in THF (25 mL) [prepared from the corresponding amine (2.16 g, 8.3 mmol) and *n*-BuLi (2.5 M in hexane; 3.33 mL, 8.3 mmol) at $-78\text{ }^{\circ}\text{C}$] was added HMPA (1.93 mL, 11.1 mmol) at $-78\text{ }^{\circ}\text{C}$, and the resulting mixture was warmed to room temperature for 1 h; it was then cooled to $-90\text{ }^{\circ}\text{C}$. To the cooled mixture were added Me_3SiCl (2.13 mL, 16.6 mmol) and then tropenone **3**³ (1.0 g, 5.5 mmol) in THF (7 mL) at $-90\text{ }^{\circ}\text{C}$ over 20 min; the reaction mixture was then stirred for 2 h at $-90\text{ }^{\circ}\text{C}$. The reaction was quenched by the addition of saturated aq. NaHCO_3 (30 mL) to the mixture, after which the aqueous layer was separated and extracted with Et_2O ($3 \times 15\text{ mL}$). To the combined organic extracts were added cold dilute HCl solution (0.2 M, 20 mL), after which the aqueous layer was separated and the process repeated once. The remaining organic extract was then washed with saturated aq. NaHCO_3 (10 mL) and with brine (10 mL), then dried and evaporated to give the corresponding silylenol ether **7** as a pale yellow oil which was used in the next step without further purification. Basification of the remaining acidic aqueous layer (NaOH pellets) followed by extraction with ether ($3 \times 15\text{ mL}$) and further purification by Kugelrohr distillation (bp $120\text{ }^{\circ}\text{C}/0.8\text{ mmHg}$) gave recovered chiral amine (1.98 g, $\sim 92\%$).

Tetrabutylammonium triphenyldifluorosilicate (3.0 g, 5.5 mmol) and activated 4Å molecular sieves (flame dried for 5 min) (5 g) were placed under nitrogen in a 25 mL round bottom flask equipped with a septum, to which THF (10 mL) was added. To the resulting suspension, a solution of the above crude silylenol ether **7** and EtI (4.43 mL, 55.2 mmol) was slowly added over 5 min. The mixture was stirred for 30 min then filtered through a pad of celite and washed with Et₂O. The organic extract was then washed with saturated aq. NaHCO₃ (15 mL) and with brine (15 mL), then dried and evaporated to give a mixture of α-ethylketone **13** and starting material **3** as a yellow oil. Column chromatography on silica with petroleum ether-EtOAc (8-2) as eluent gave α-ethylketone (+)-**13**

(635 mg, 55%, 86% brsm) and recovered starting material **3** (360 mg); *R*_f 0.40 (Et₂O); [α]_D²² +82.4 (*c* 1, CHCl₃) of a sample of 80% ee (determined in the next transformation), *v*_{max}(KBr)/cm⁻¹ 3081, 2964, 2937, 2878, 1699, 1455, 1403, 1111, 981, 710; δ_H (400 MHz, CDCl₃): 6.17 and 6.15 (2 H, br s, CH=), 4.89 and 4.84 (1 H, br s, CHN), 4.84 and 4.75 (1 H, br s, CHN), 3.66 (3 H, s, OMe), 2.71-2.56 (1 H, m, C(4)H), 2.23 (1 H, d, *J* 17, C(4)H), 2.20-2.08 (1 H, m, C(2)H), 1.65-1.49 (2 H, m, CH₂Me), 0.94 (3 H, m, CH₃), δ_C (100 MHz) 208.7 (C=O), 153.8 (NCO₂), 134.5 (CH=), 133.9 (CH=), 58.5 (CHN), 57.8 (C2), 56.1 (CHN), 52.4 (OMe), 44.6 and 44.3 (C4), 23.1 (CH₂), 11.7 (CH₃); *m/z* (Cl⁺), 227 (M + NH₄⁺, 100%), 210 (75) (Found (ES⁺) M + NH₄⁺, 227.1387. C₁₁H₁₉N₂O₃ requires 227.1390).



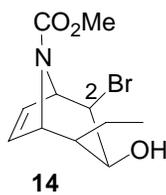
Preparation of and data for α-bromoketone **10**

A solution of *n*-BuLi (1.5 M in hexanes, 3.24 mL, 4.9 mmol) was added dropwise to a solution of *N,N*-diisopropylamine (0.69 mL, 4.9 mmol) in THF (15 mL) at -78 °C. After 10 min, the solution was removed from the cold bath for 5 min then recooled to -78 °C. Me₃SiCl (1.24 mL, 9.7 mmol) was then added dropwise followed by a solution of α-ethylketone (+)-**13** (680 mg, 3.2 mmol) in THF (5 mL). After 60 min, the reaction mixture was poured into an aq. solution of NaHCO₃ (20 mL) and extracted with ether (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried, and evaporated under reduced pressure to give the corresponding crude silylenol ether as a pale yellow oil which was used in the next step without further purification.

To a stirred solution of the above silylenol ether in THF (7 mL) at 0 °C was added NBS (636 mg, 3.6 mmol) in one portion. The resulting solution was stirred at 0 °C for 10 min and then poured into a saturated aq. NH₄Cl (20 mL) and ether (20 mL). The two layers were separated and the aqueous

layer was further extracted with ether (2×20 mL). The combined organic layers were washed with brine (15 mL), dried, and evaporated under reduced pressure to give a pale yellow oil. Purification by flash chromatography on silica with petroleum ether-EtOAc (8-2) as eluent gave a single diastereoisomer of α -bromoketone (–)-**10** (777 mg, 83%) as a white solid. (–)-**10** was recrystallized from ether-petroleum ether to provide (–)-**10** of 98% ee (560 mg, 60 % yield from **13**) according to chiral GC analysis; R_f 0.41 (Et₂O); mp 80 °C; $[\alpha]_D^{22}$ -156.1 (c 1, CHCl₃) of a sample of 98% ee; ν_{\max} (neat)/cm⁻¹ 2960, 2920, 2877, 1705, 1456, 1403, 1309, 1253, 1195, 1114, 1008, 721; δ_H (400 MHz, CDCl₃): 6.40 and 6.36(1 H, br s, CH=), 6.18 and 6.16 (1 H, br s; CH=), 5.14 and 5.04 (1 H, br s, CHN), 4.90 and 4.83 (1 H, br s, CHN), 3.92 (1 H, br s, C(2)H), 3.73 (3H, s, OMe), 2.33 (1H, br s, C(4)H), 1.97-1.85 (2 H, m, C4), 1.00 (3 H, t, *J* 7, CH₃); δ_C (100 MHz) 201.9 (C=O), 154.7 (NCO₂), 138.4 and 137.6 (CH=), 131.7 and 131.0 (CH=), 62.1 (CHN), 59.2 and 59.0 (CHN), 58.3 (C4), 52.8 (OMe), 46.8 (C2), 26.3 (CH₂), 12.1 (CH₃); m/z (CI⁺), 305 (M + NH₄⁺, 100%), 307 (90), 289 (50) (Found (ES⁺) M + NH₄⁺, 305.0494. C₁₁H₁₈BrN₂O₃ requires 305.0495).

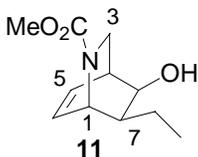
GC analysis of (–)-**10** for ee determination: (CP Chirasil Dex-CD column using H₂ as a carrier flow). Program 70 °C to 150 °C at a rate of 0.2 °C/min, 1 mL/min, 3 mg/mL), $t_{r,\min}$ = 225.5 min and $t_{r,\text{maj}}$ = 258.0 min.



Preparation of and data for bromohydrin **14**⁵

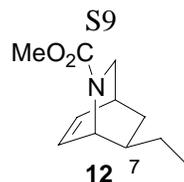
To a cold (–30 °C), stirred solution of α -bromoketone **10** (300 mg, 1.04 mmol.) in 8 mL of 1:1 MeOH-THF was added NaBH₄ (59 mg, 1.56 mmol) in one portion. The reaction mixture was allowed to slowly warm up to room temperature over a period of 2 h [the reduction being sluggish from –30 °C to –15 °C; careful control of the temperature must be performed from –15 °C to 0 °C (where most of the reduction occurs) to avoid competitive reduction at C2]. The reaction mixture was then quenched with dilute aqueous HCl (1 M) until gas evolution ceased, then further diluted with EtOAc (10 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (2×15 mL). The combined organic layers were washed with saturated aq. NaHCO₃ (10 mL), dried, concentrated *in vacuo*, and purified by column chromatography on silica with petroleum ether-EtOAc (6-4) as eluent to give a single diastereoisomer of bromohydrin **14** (236 mg, 78%) as a white solid; R_f 0.46 (EtOAc); mp 93 °C; δ_H (400 MHz, CDCl₃): 6.22-6.12 (2H, m, CH=), 5.11 and 5.01 (1H, br s, CHN), 4.92 and 4.84 (1H, br s, CHN), 4.34-4.32 (1H, m, C(2)H), 4.03 (1H, br s,

C(3)H), 3.70 (3H, s, OMe), 2.28 (1H, br s, OH), 1.78-1.65 (2H, m, C(4)H and CH₂), 1.64-1.53 (1H, m, CH₂), 1.05-0.97 (3H, m, CH₃), δ_{C} (100 MHz) 155.1 (NCO₂), 135.3 and 134.3 (CH=), 130.7 and 129.8 (CH=), 65.5 (C3), 63.6 and 63.5 (CHN), 59.4 and 59.1 (CHN), 56.4 (C2), 52.6 (OMe), 42.0 (C4), 18.5 (CH₂), 12.3 and 12.1 (CH₃); m/z (CI⁺), 309 and 307 (M + NH₄⁺, 80%), 290 and 292 (M + H⁺, 50), 227 (100), (Found (ES⁺) M + H⁺, 290.0387. C₁₁H₁₇BrNO₃ requires 290.0386).



Preparation of and data for dehydroisoquinuclidinol **11**⁶

To a cold (−30 °C), stirred solution of α -bromoketone (−)-**10** (505 mg, 1.75 mmol, 98% ee) in EtOH (15 mL) was added NaBH₄ (100 mg, 2.63 mmol) in one portion. The reaction mixture was slowly allowed to warm up to room temperature over a period of 2 h [the reduction being sluggish from −30 °C to −15 °C; careful control of the temperature must be performed from −15 °C to 0 °C (where most of the reduction occurs) to avoid competitive reduction at C2]. To this reaction mixture was added NaBH₄ (100 mg, 2.63 mmol), AIBN (28 mg, 0.18 mmol), and Bu₃SnCl (71 μ L; 0.26 mmol) (effervescence occurred for 2 min) and the suspension heated to reflux for 30 min (ending of effervescence marked completion of the rearrangement). The suspension produced was evaporated under reduced pressure, and then diluted with EtOAc (15 mL) quenched with aqueous HCl (1 M, 5 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (2 \times 15 mL). The combined organic layers were washed with brine (10 mL), dried, concentrated *in vacuo*, and purified by column chromatography on silica with petroleum ether-EtOAc (6-4) as eluent to give dehydroisoquinuclidinol (+)-**11** (515 mg, 78%) as a colorless oil which crystallized upon standing; R_f 0.25 (EtOAc); $[\alpha]_{\text{D}}^{22} +77.1$ (*c* 1, CHCl₃), mp 103 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ 3442, 2958, 1682; 1456, 1398, 1121, 1040, 767, 702, δ_{H} (400 MHz, CDCl₃) 6.48 and 6.42 (1H, br dd, *J* 8 and 8, CH=), 6.34 and 6.31 (1H, br dd, *J* 8 and 8, CH=), 4.66 and 4.51 (1H, d, *J* 6, C(1)H), 3.92 (1H, m, C(8)H), 3.70 (1H, m, C3(H)), 3.69 and 3.68 (3H, s, OMe), 2.88 and 2.82 (1H, d, *J* 11, C(3)H), 2.76-2.69 (1H, m, C(7)H), 1.75 (1H, s, OH), 1.66-1.52 (2H, m, C(4)H and CH₂), 1.33-1.22 (1H, m, CH₂), 1.02 and 0.98 (3H, t, *J* 7, CH₃); δ_{C} (100 MHz) 156.6 and 156.1 (NCO₂), 135.0 and 134.3 (CH=), 132.3 and 131.8 (CH=), 65.2 (C8), 52.3 (OMe), 48.5 and 48.0 (C1), 43.0 and 42.8 (C4), 40.3 and 40.1 (C3), 38.7 and 38.6 (C7), 19.8 and 19.7 (CH₂), 12.7 and 12.4 (CH₃); m/z (CI⁺), 229 (55%), 212 (M + H⁺, 100), (Found (ES⁺) M + H⁺, 212.1281. C₁₁H₁₈NO₃ requires 212.1281).

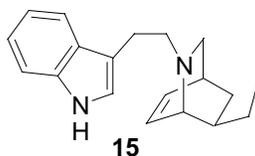


Preparation of and data for dehydroisoquinuclidine 12

Dehydroisoquinuclidinol (+)-**11** (205 mg, 0.97 mmol) was added to KH (391 mg of a 30% suspension, 2.92 mmol) in THF (10 mL) at 0 °C and the mixture was then stirred at room temperature for 20 min. The mixture was cooled to 0 °C and CS₂ (175 μL, 2.91 mmol) was added and the mixture stirred for 10 min at 0 °C. Finally, MeI (181 μL, 2.91 mmol) was added and the solution was stirred at room temperature for 20 min. The reaction was quenched with dropwise addition of water until effervescence had ceased and then the aq. layer extracted with Et₂O (2 × 15 mL). The combined extracts were dried, concentrated *in vacuo*, and purified by column chromatography on silica with petroleum ether-Et₂O (8-2) as eluent to give the corresponding xanthate

(252 mg, 86%) as a colorless oil, *R*_f 0.52 (Et₂O). The xanthate was not fully characterised, but was identified by a shift in the CH–O signal in the ¹H NMR spectrum from 3.92 to 5.71 ppm and the appearance of a 3H singlet at 2.55 and 2.54 (rotamers) assigned to SCH₃.

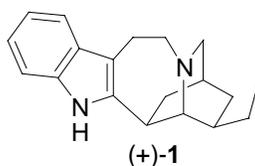
A mixture of xanthate (250 mg, 0.83 mmol), AIBN (14 mg, 0.08 mmol) and Bu₃SnH (269 μL, 1.00 mmol), in toluene (5 mL), was heated at reflux. After 60 min, the reaction mixture was allowed to cool, concentrated *in vacuo*, and purified by column chromatography on silica with petroleum ether-Et₂O (8-2) as eluent to give dehydroisoquinuclidine (+)-**12** (95 mg, 50% from alcohol (+)-**11**), *R*_f 0.62 (Et₂O); [α]_D²² +67.3 (*c* 1, CHCl₃); ν_{max}/cm⁻¹ 3053, 2957, 2874, 1700, 1449, 1395, 1112, 767, 702, δ_H (400 MHz, CDCl₃) 6.47 and 6.42 (1H, br dd, *J* 8 and 8, CH=), 6.34 and 6.30 (1H, br dd, *J* 8 and 8, CH=), 4.59 and 4.44 (1H, d, *J* 6, C(1)H), 3.67 and 3.66 (3H, s, OMe), 3.20 (1H, td, *J* 10 and 2, C(3)H), 2.98 and 2.94 (1H, dt, *J* 10 and 3, C(3)H), 2.70-2.61 (1H, m, C(4)H), 1.64 and 1.61 (1H, dt, *J* 10 and 3, C(8)H), 1.50-1.31 (3H, m, C(7)H and CH₂), 1.00 (1H, m, C(8)H), 0.95 and 0.92 (3H, t, *J* 7, CH₃); δ_C (100 MHz) 156.7 and 156.3 (NCO₂), 133.8 and 133.7 (CH=), 133.3 and 133.1 (CH=), 52.2 and 52.1 (OMe), 49.1 and 48.8 (C1), 48.4 and 48.1 (C3), 40.7 (C4), 30.8 and 30.6 (C7), 29.9 (C8), 27.5 and 27.4 (CH₂), 12.1 and 12.0 (CH₃); *m/z* (CI⁺), 196 (M + H⁺, 100%), (Found (ES⁺) M + H⁺, 196.1335. C₁₁H₁₈NO₂ requires 196.1332).



Preparation of and Data for dehydroisoquinuclidine 15

To a cold (0 °C), stirred solution of dehydroisoquinuclidine (+)-**12** (130 mg, 0.67 mmol) in CH₂Cl₂ (5 mL) was added Me₃SiI (379 μL, 2.67 mmol). After 5 min, the mixture was allowed to warm to rt, and left for 3 h. The reaction was then quenched with MeOH (2 mL) and concentrated *in vacuo* to produce the deprotected crude of dehydroisoquinuclidine which was used without purification for the following step.

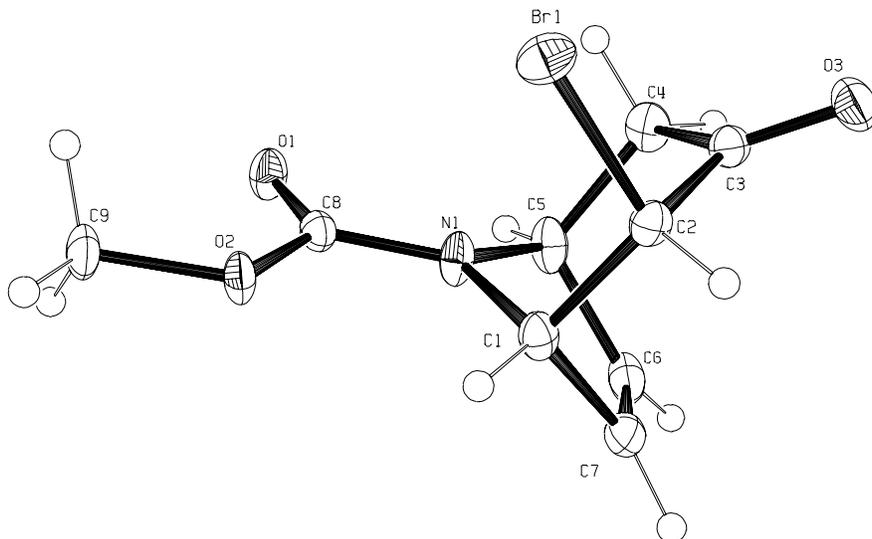
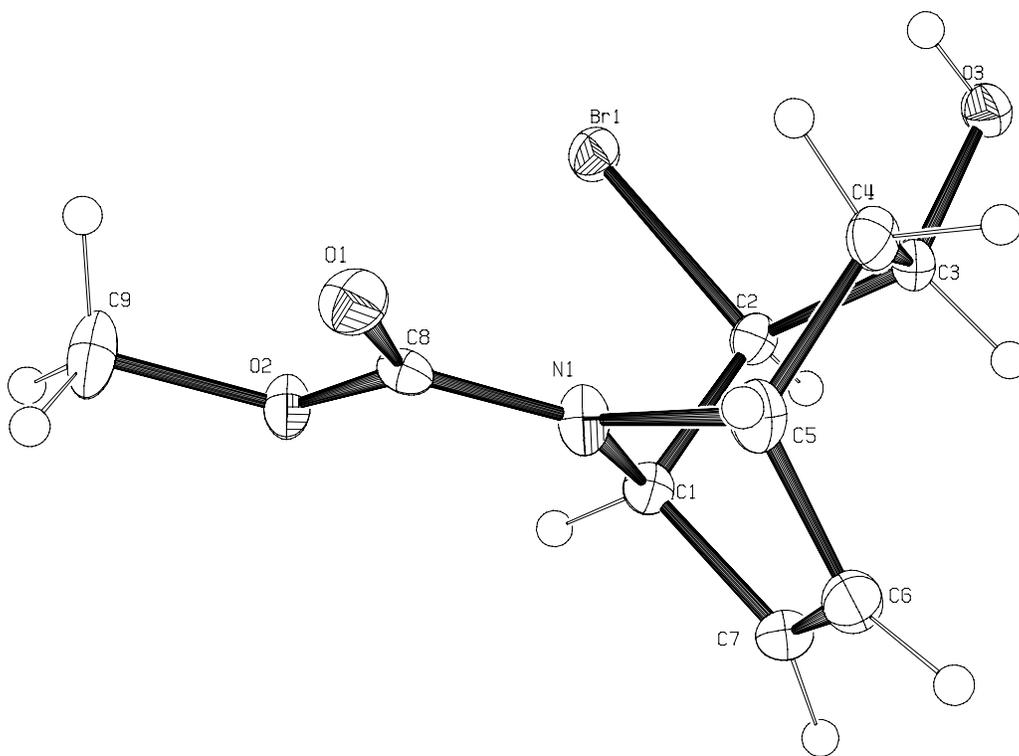
A suspension of NaHCO₃ (168 mg, 2.0 mmol) in anhydrous CH₃CN (3 mL) containing the above deprotected isoquinuclidine and tryptophyl bromide (149 mg, 0.67 mmol) was stirred at reflux for 14 h, then cooled to 25 °C, and poured into water (5 mL) and extracted with CHCl₃ (3 × 15 mL). The combined extracts were washed with water, dried, concentrated *in vacuo*, and purified by column chromatography on silica with CH₂Cl₂-MeOH (utilising a gradual increase in concentration from 0.5 to 2 % in MeOH) as eluent to give dehydroisoquinuclidine (+)-**15** (151 mg, 81%) as a pale brown oil, *R*_f 0.41 (CH₂Cl₂-MeOH, 4-1); [α]_D²² +9.9 (*c* 1, CHCl₃); *v*_{max}/cm⁻¹ 3418, 3042, 2934, 1619, 1456, 1353, 1225, 1092, 741,698; δ_H (400 MHz, CDCl₃) 8.04 (1H, br s, NH), 7.62 (1H, d, *J* 8, Ar), 7.36 (1H, d, *J* 8, Ar), 7.19 (1H, t, *J* 8, Ar), 7.12 (1H, d, *J* 8, Ar), 7.04 (1H, d, *J* 1, CHNH), 6.40 (1H, br dd, *J* 7 and 7, CH=), 6.34 (1H, br dd, *J* 7 and 7, CH=), 3.38 (1H, br s, C(1)H), 3.21 (1H, br d, *J* 8, C(3)H), 2.99-2.80 (3H, m, benzylic CH₂ of indole ring and 1H of N-CH₂ of tryptophyl group), 2.66-2.56 (1H, m, 1H of N-CH₂ of tryptophyl group), 2.49 (1H, br s, C(4)H), 2.01 (1H, br d, *J* 9, C(3)H), 1.72-1.59 (2H, m, CH₂), 1.56-1.49 (1H, m, C(8)H), 1.39-1.32 (1H, m, C(7)H), 0.99 (1H, br dd, *J* 12 and 3, C(8)H), 0.94 (3H, t, *J* 7, CH₃); δ_C (100 MHz) 136.1 (quaternary), 133.2 and 132.4 (CH=), 127.6 (quaternary), 121.8, 121.7 (indole ring), 119.1, 114.5 (quaternary), 111.1, 58.9 (NCH₂), 56.2 C(3), 55.9 C(1), 40.1 C(7), 31.4 (C4), 29.8 (C8), 27.2 (CH₂), 24.1 (CH₂ benzylic), 12.6 (CH₃); *m/z* (CI⁺), 281 (M + H⁺, 100%), (Found (ES⁺) M + H⁺, 281.2016. C₁₉H₂₅N₂ requires 281.2012).



Preparation of and data for (+)-ibogamine **1**

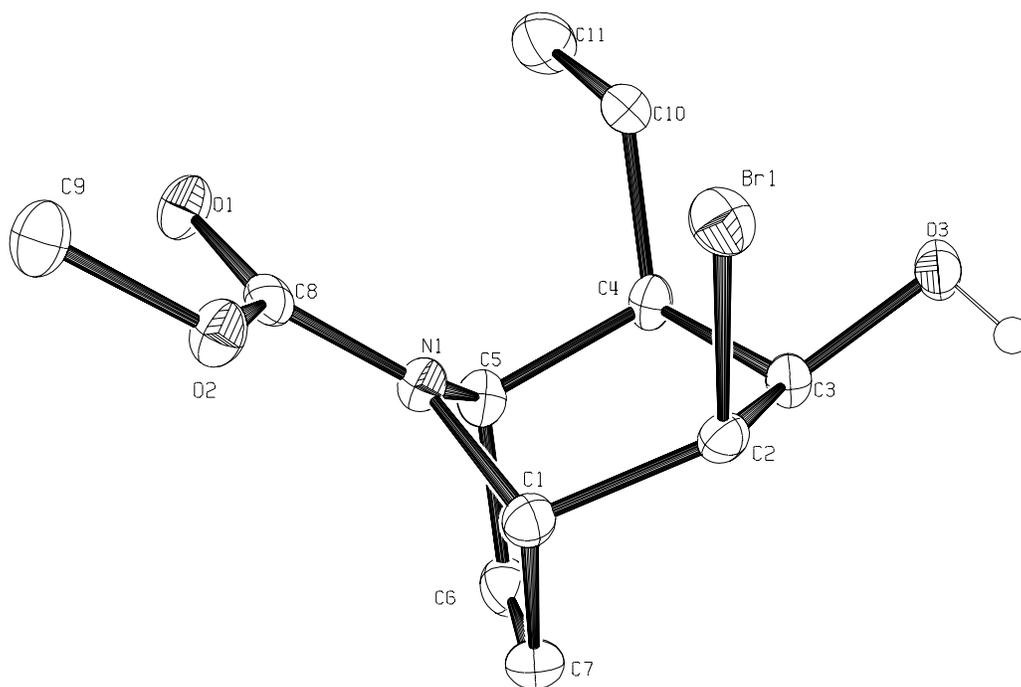
Bis(acetonitrile)palladium chloride (275 mg, 1.06 mmol) was slurried in CH₃CN (2 mL) and Et₃N (74 μL, 0.53 mmol) under an argon atmosphere. Silver tetrafluoroborate (413 mg, 2.12 mmol) was added and the orange heterogeneous mixture immediately became yellow. After 15 min, the dehydroisoquinuclidine (+)-**15** (150 mg, 0.53 mmol) in CH₃CN (2.5 mL) was added producing a deep red solution. This mixture was stirred 1 h at room temperature then heated at 65 °C for 12 h. The mixture was cooled to 0 °C, MeOH (2 mL) was added, followed by NaBH₄ (20 mg, 0.53 mmol) in portions. The solution was stirred for 1 h at 0 °C, water (1 mL) was added and the solution was

acidified with cold 3 N aq. HCl. The mixture was filtered through celite to remove palladium black, extracted with ether (30 mL) then basified with cold concentrated aqueous NH_4OH . The basic aqueous solution was extracted with ethyl acetate (3×25 mL). The organic extracts were combined, dried, concentrated *in vacuo*, and purified by column chromatography on silica with CH_2Cl_2 -MeOH (utilising a gradual increase in concentration from 0.5 to 2 % in MeOH) as eluent to give ibogamine (+)-**1** (37 mg, 25%) as a pale brown oil, which crystallised upon standing; R_f 0.51 (CH_2Cl_2 -MeOH, 4-1); mp 141-145 °C, $[\alpha]_D^{22}$ +42.2 (c 0.29, EtOH), lit.⁷ $[\alpha]_D^{23}$ -36.4 (CHCl_3), lit.⁸ $[\alpha]_D^{23}$ -45.8 (c 0.2, EtOH), $\nu_{\text{max}}/\text{cm}^{-1}$ 3400, δ_{H} (400 MHz, CDCl_3) 7.63 (1H, br s), 7.46 (1H, d, J 7), 7.36 (1H, d, J 8), 7.25-7.24 (1H, m), 7.12-7.06 (2H, m), 3.42-3.36 (1H, m), 3.34 (1H, ddd, J 16, 12 and 5), 3.19-3.13 (3H, m), 3.08-2.99 (2H, m), 2.95 (1H, ddd, J 11, 4 and 2), 2.88 (1H, br s), 2.73-2.66 (1H, m), 2.09-2.00 (1H, m), 1.86-1.78 (2H, m), 1.65 (2H, 2H, ddd, J 13, 7 and 4), 1.61-1.42 (2H, m); 1.22 (1H, m), 0.90 (3H, t, J 7), δ_{C} (63 MHz) 141.0, 134.7, 129.5, 121.2, 119.3, 117.9, 110.2, 108.9, 58.1, 54.5, 50.0, 41.6, 40.9, 33.8, 31.7, 27.5, 26.1, 20.3, 11.9; m/z (CI^+), 281 ($\text{M} + \text{H}^+$, 100%), (Found (ES^+) $\text{M} + \text{H}^+$, 281.2010. $\text{C}_{19}\text{H}_{25}\text{N}_2$ requires 281.2012).

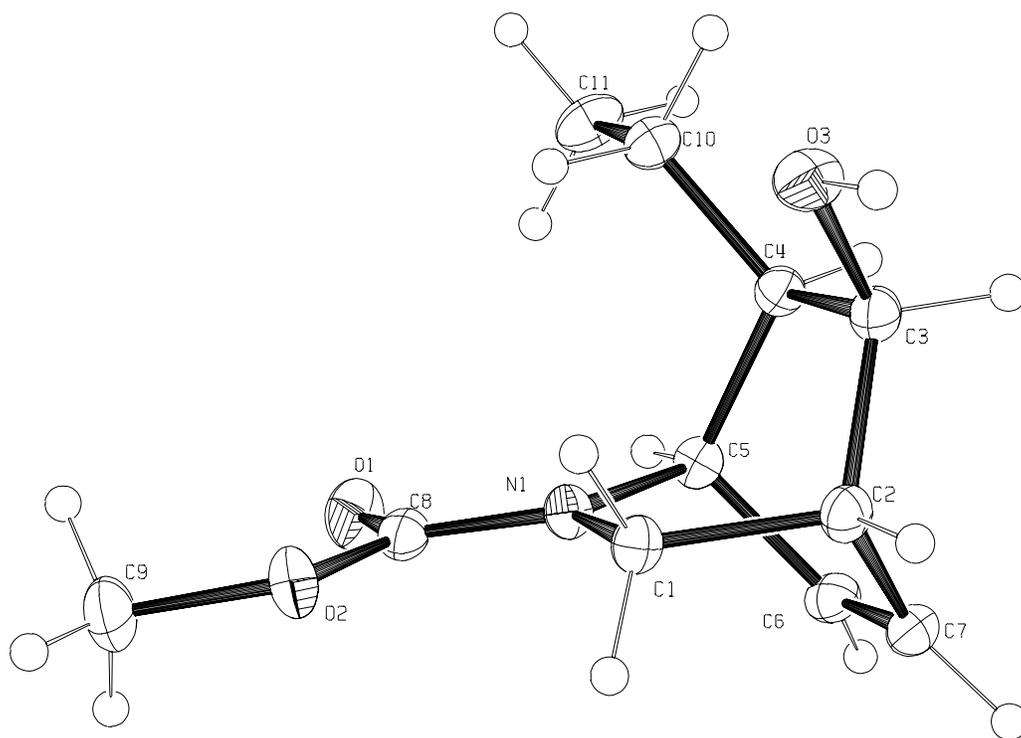
X-ray Data (ORTEPs shown at 40% probability)Methyl (1*S*,2*S*,5*S*)-2-bromo-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (**4**)¹Methyl 2-*exo*-bromo-3-*exo*-hydroxy-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (**8**)⁴

S13

Methyl 2-*exo*-bromo-4-*exo*-ethyl-3-*exo*-hydroxy-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (**14**)⁵

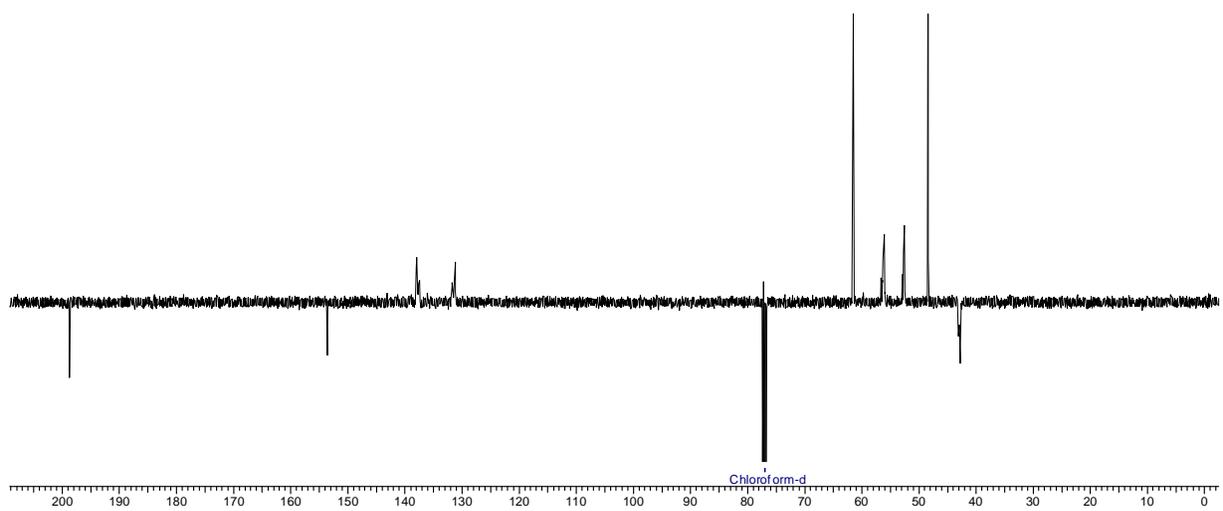
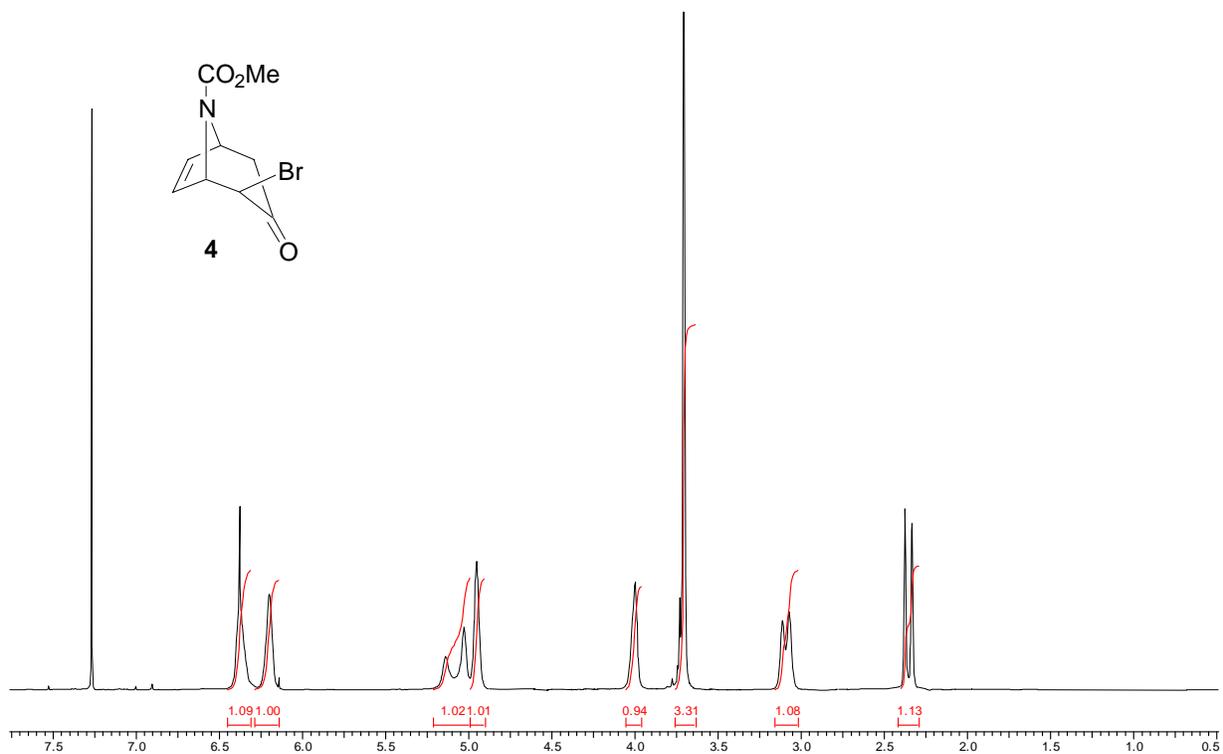


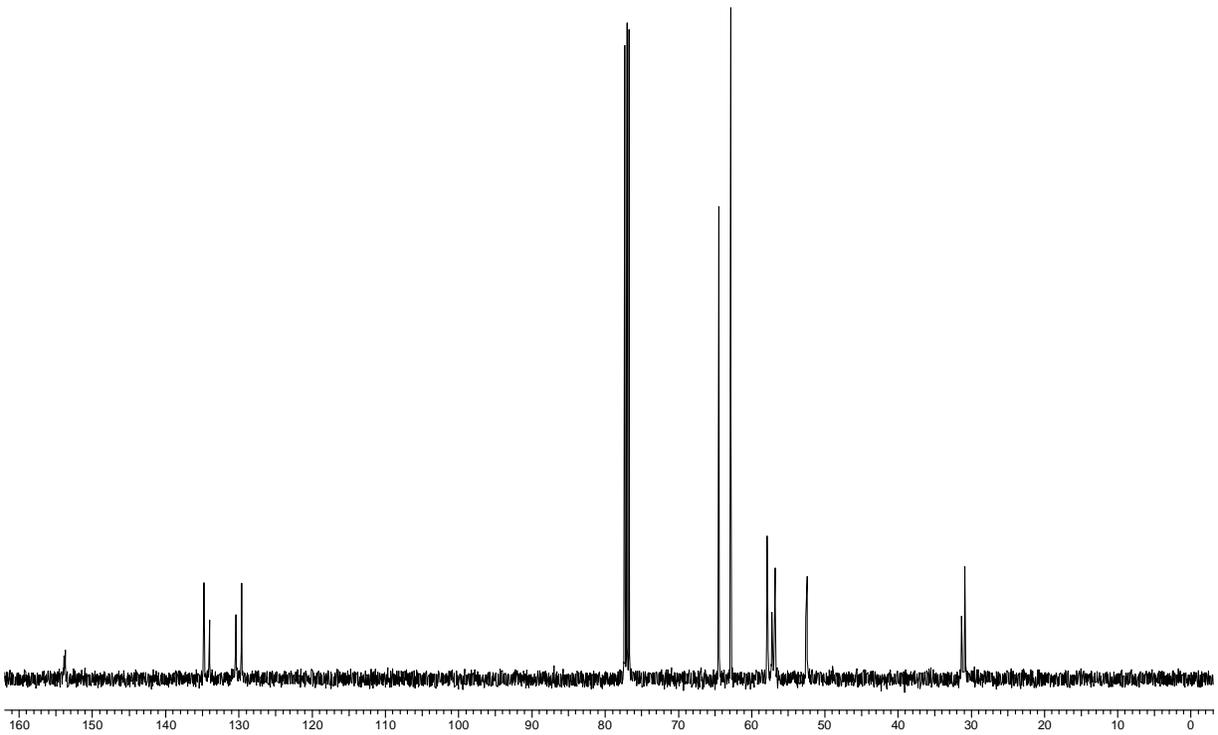
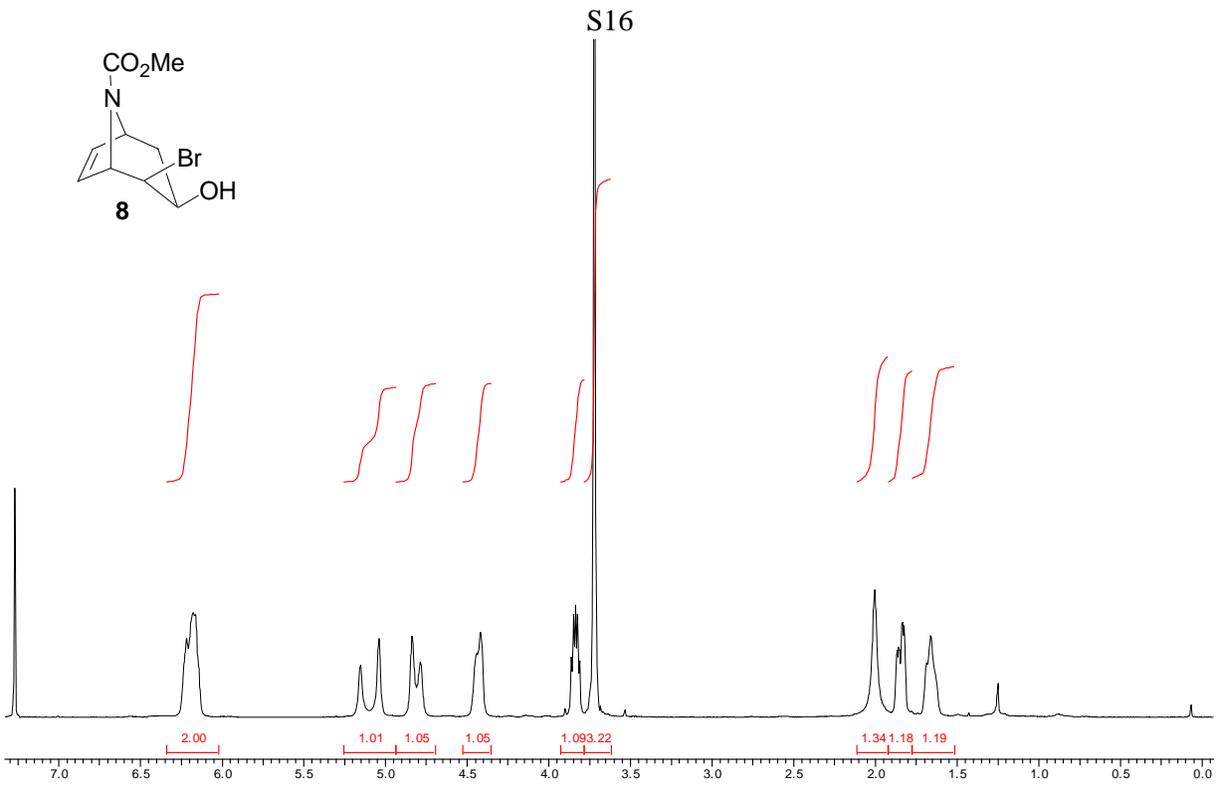
Methyl 7-*syn*-ethyl-8-*syn*-hydroxy-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (**11**)⁶



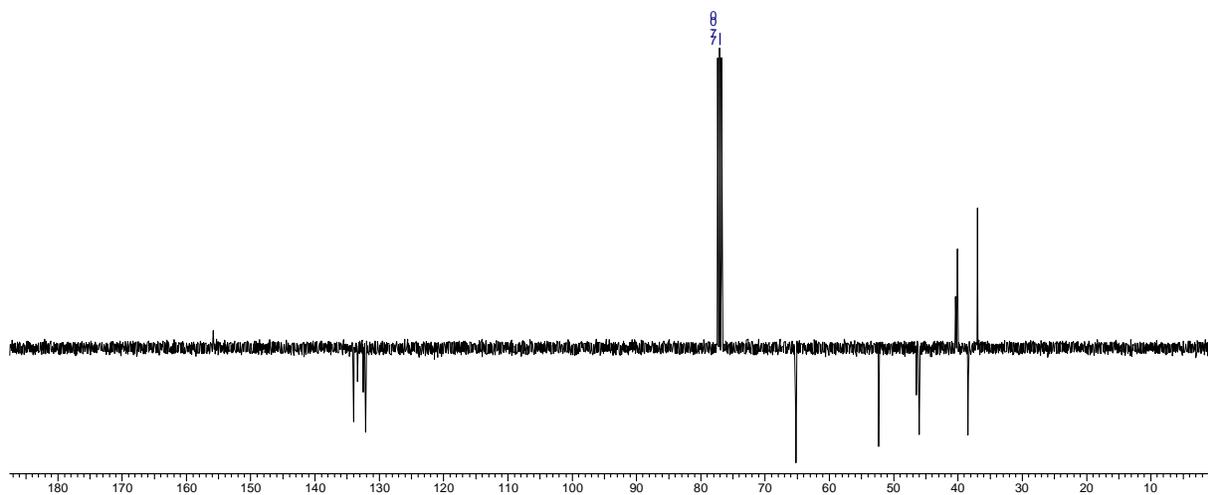
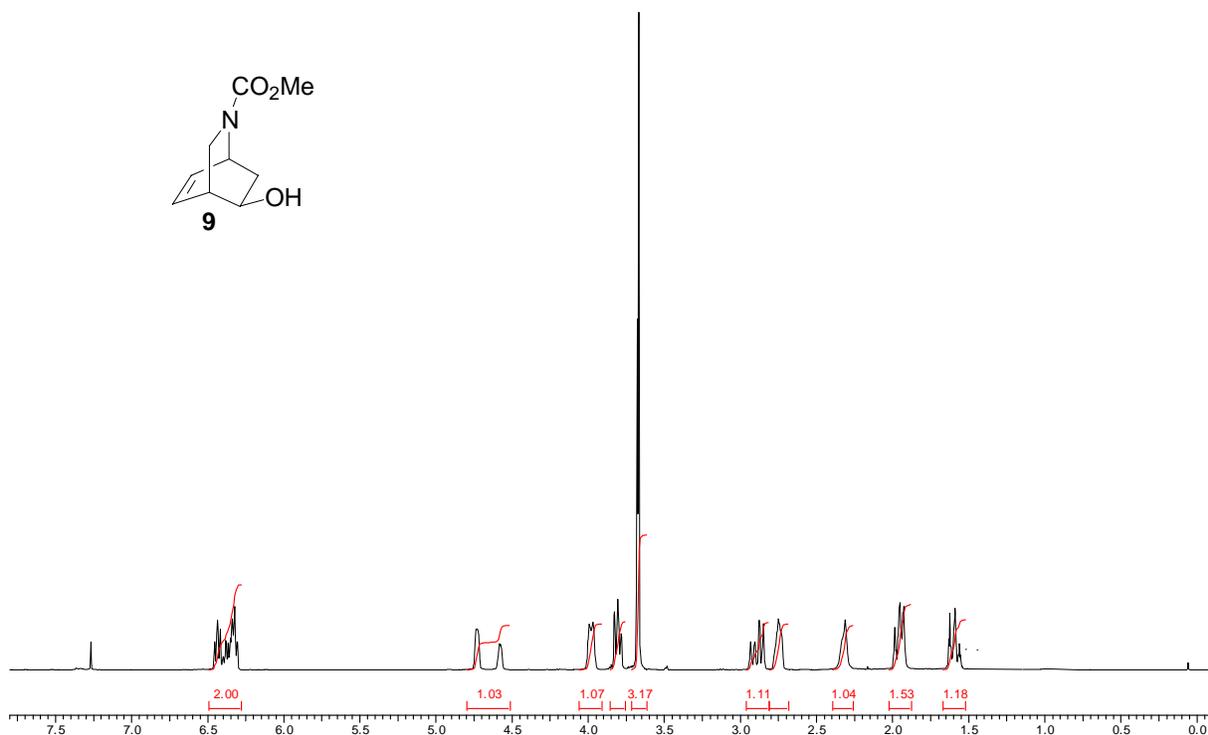
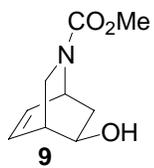
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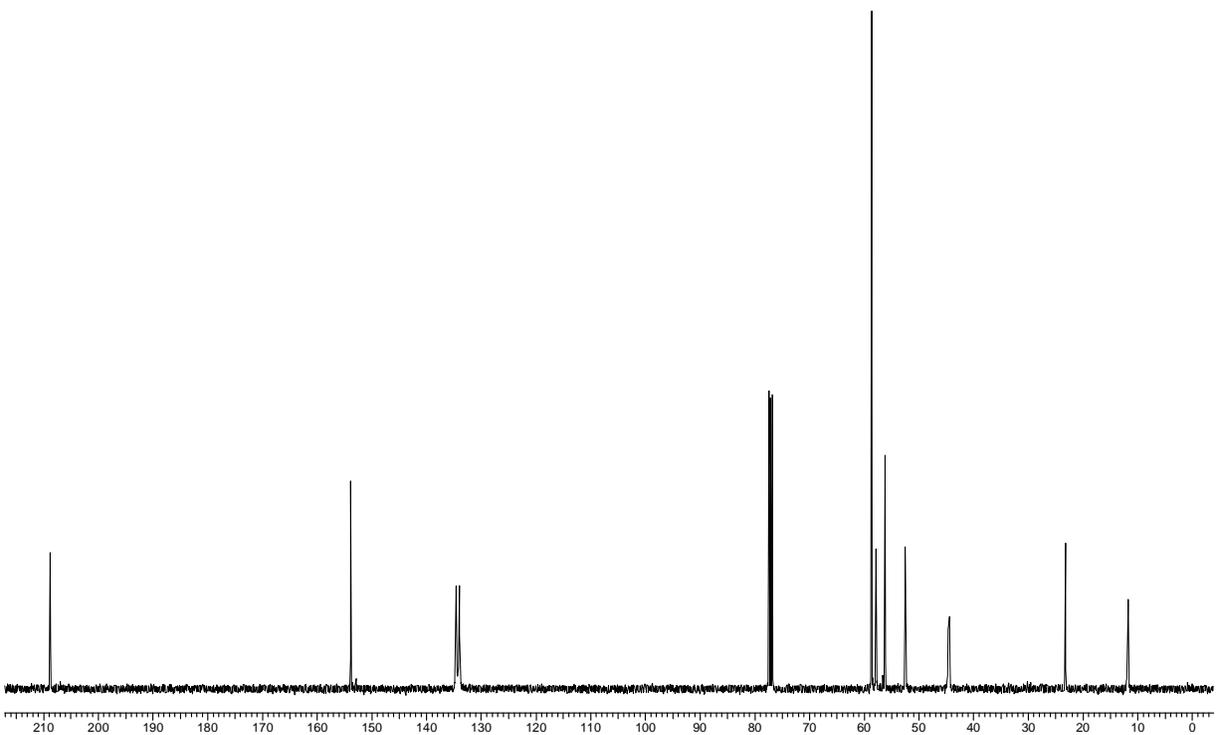
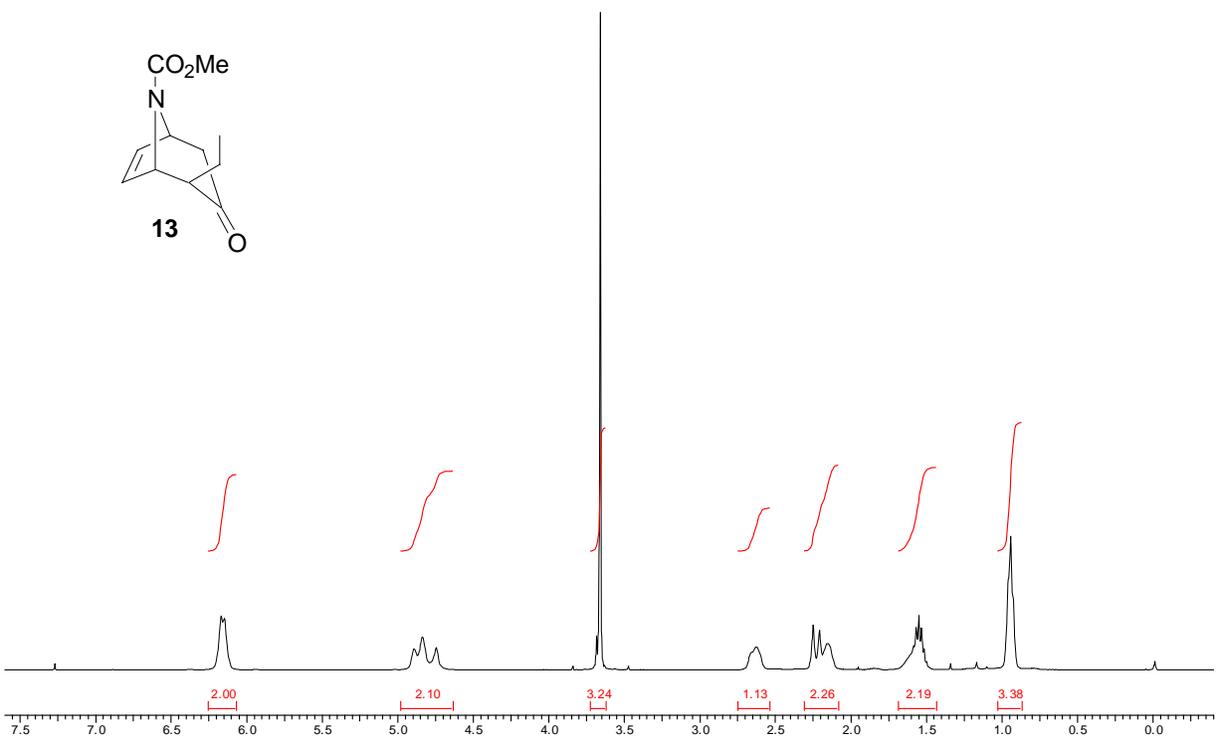
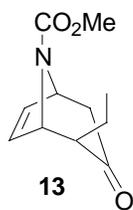




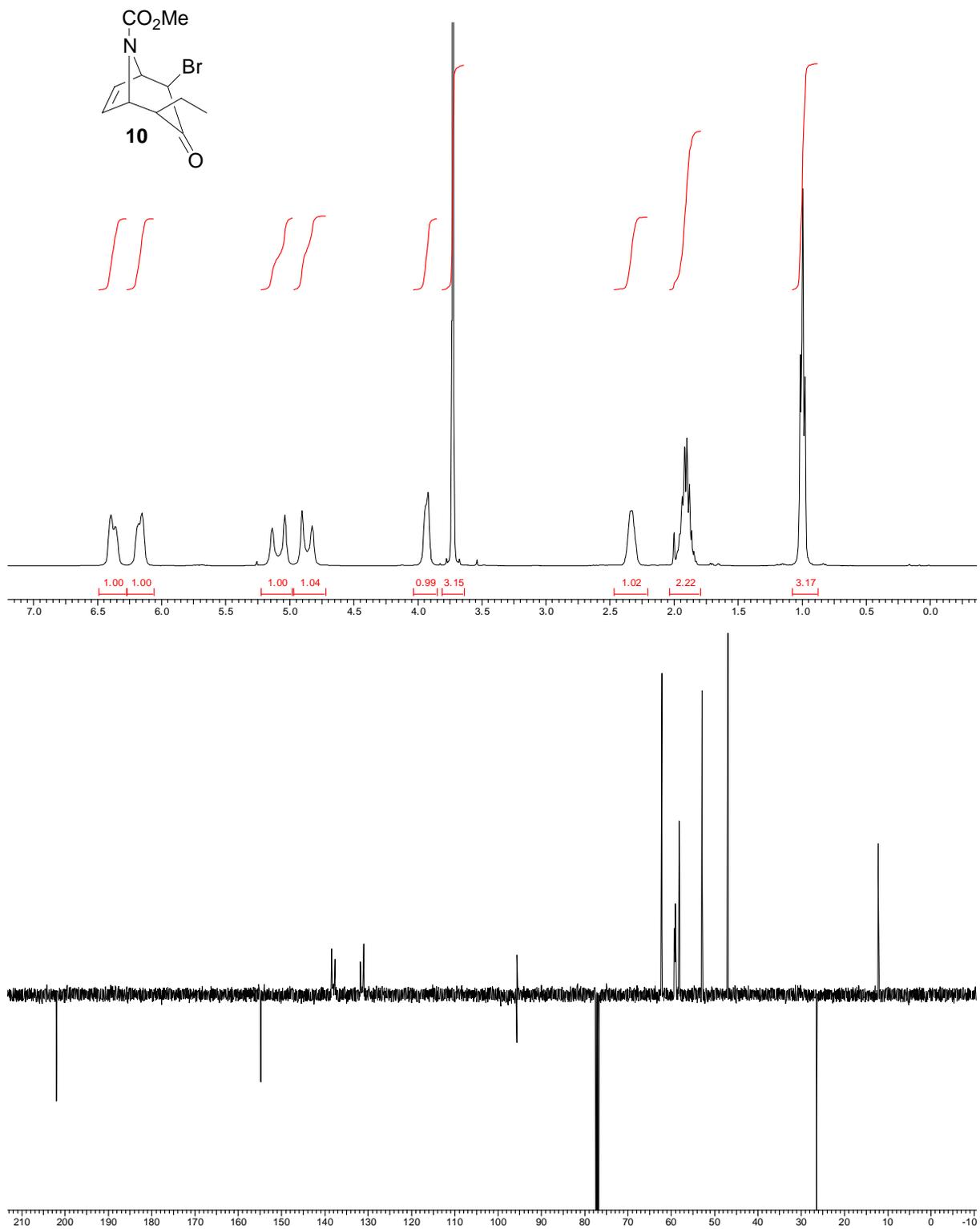
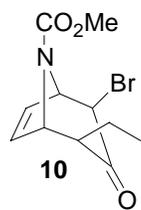
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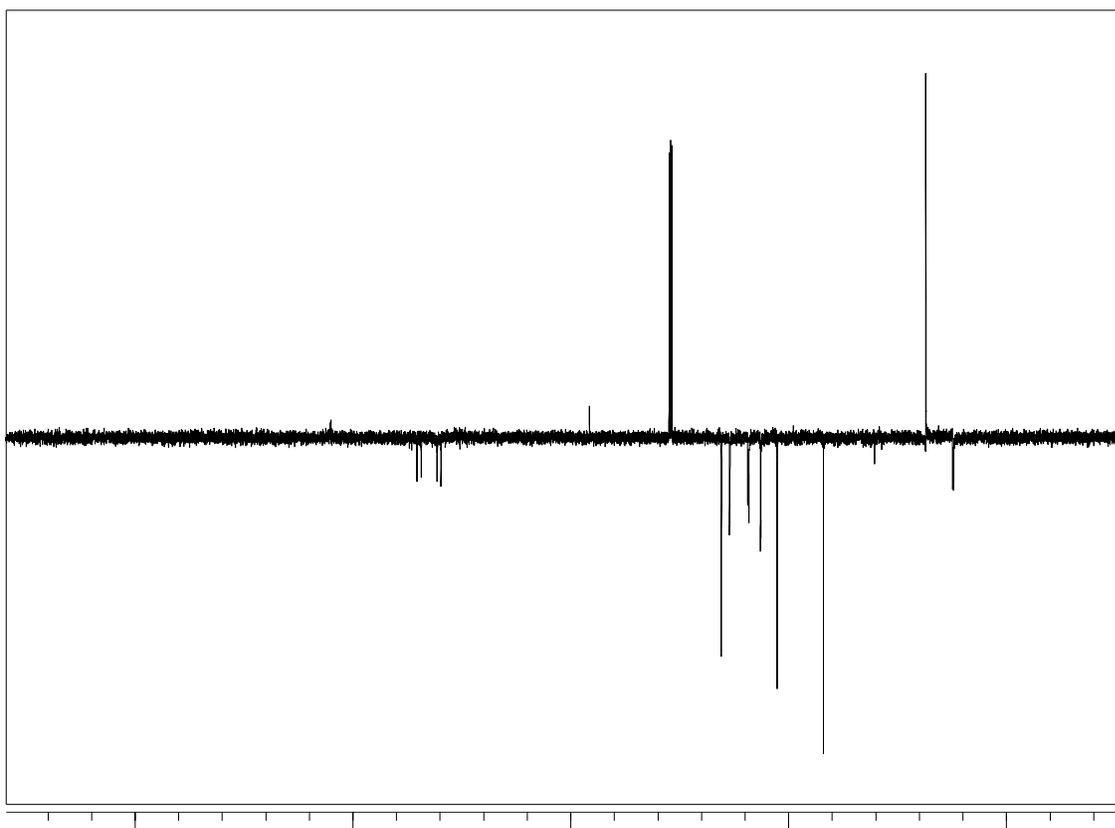
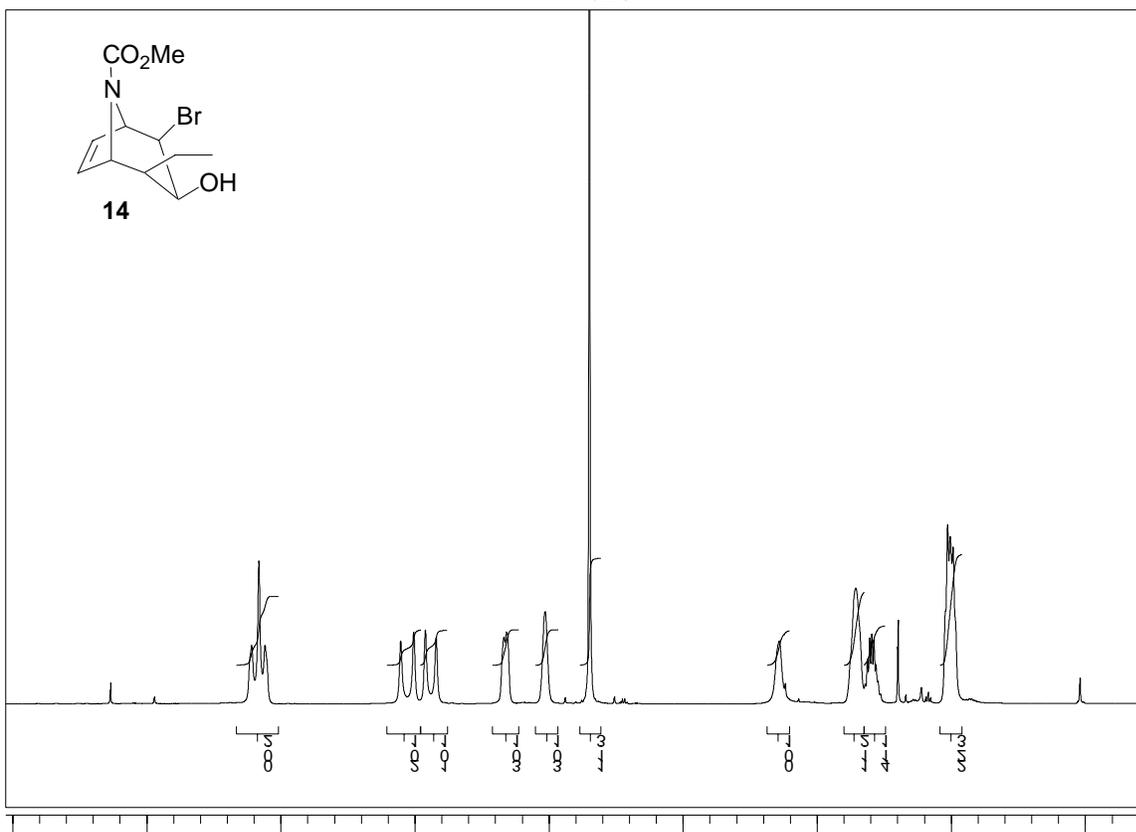


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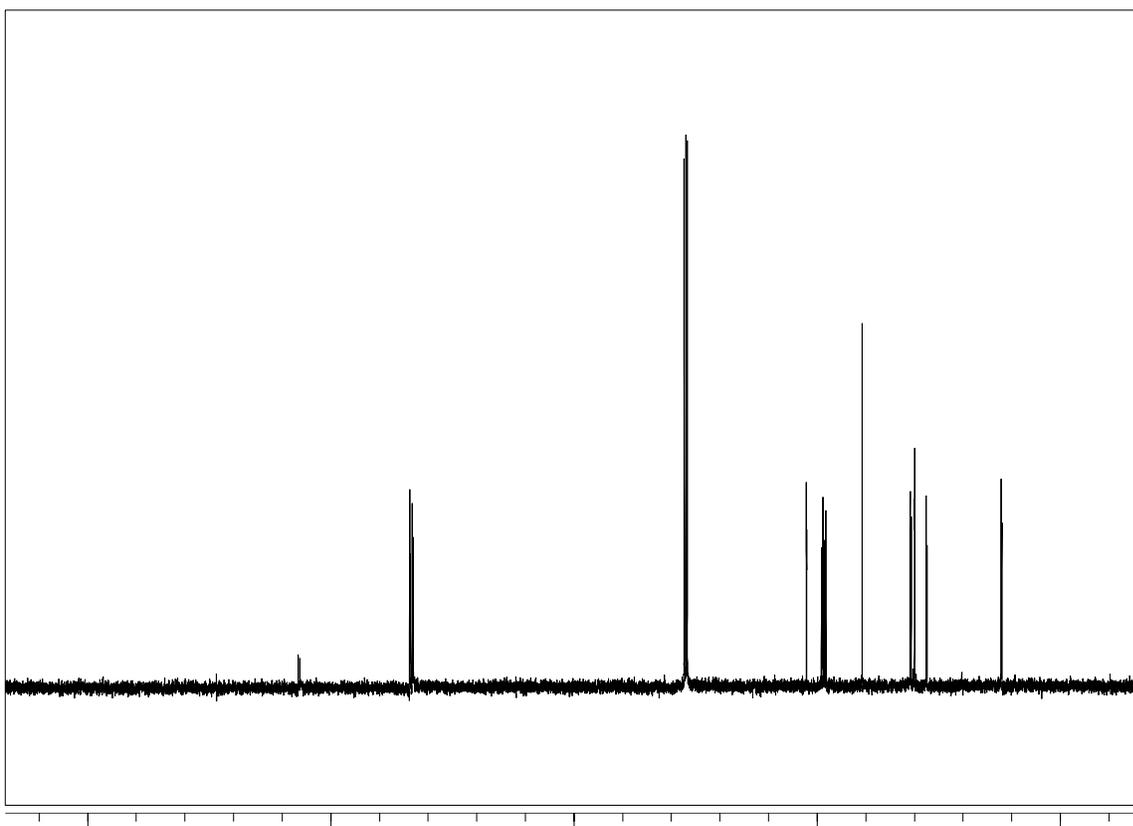
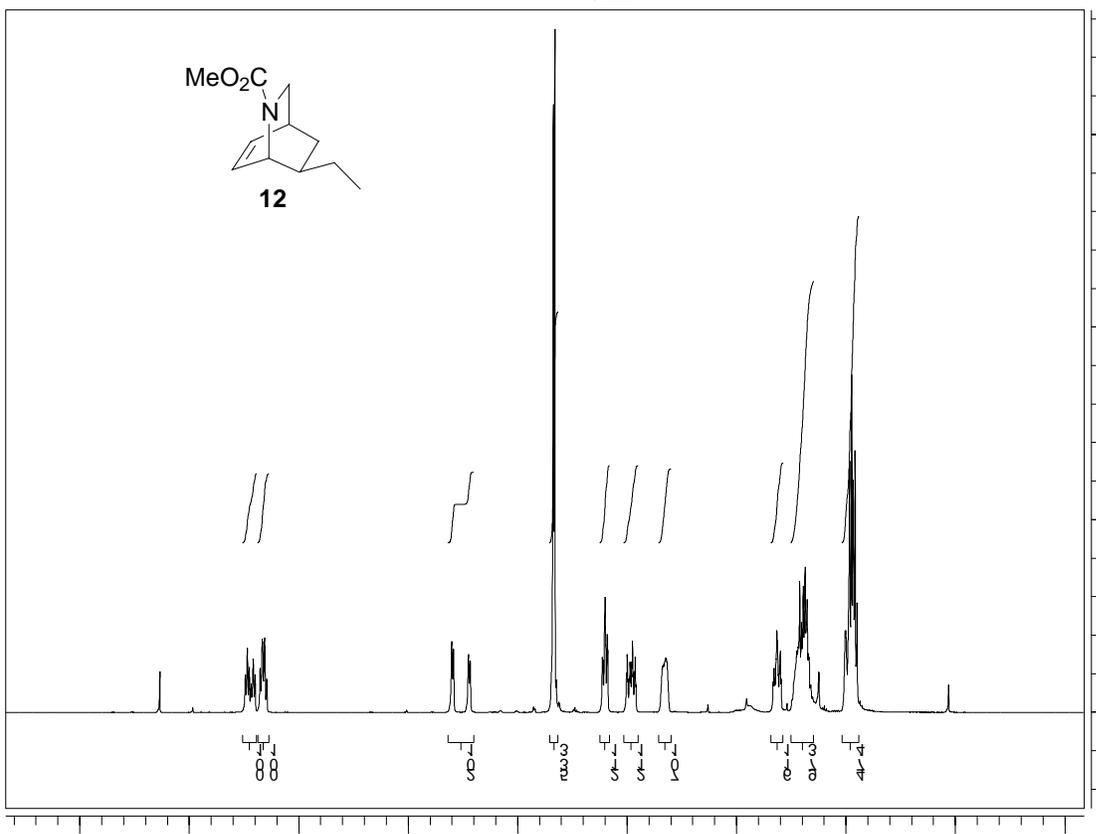


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S22



S23

