A Concise Total Synthesis of (–)-Quinocarcin via Aryne Annulation

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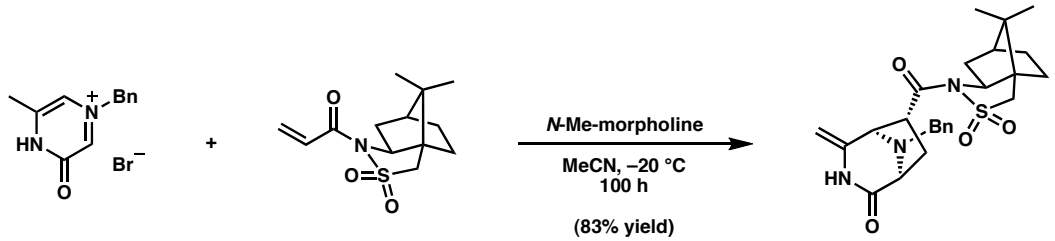
Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or ceric ammonium molybdate staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. Analytical chiral supercritical fluid chromatography was performed with a Berger Analytix SFC (Thar Technologies) using a Chiralcel OD-H column (250 mm x 4.6 mm, 5 μm particle size, 2.0 mL/min flow rate). Preparatory reverse-phase HPLC was performed on a Waters HPLC with a Waters Delta-Pak column (100 mm x 2 mm, 15 μm particle size, 1.5 mL/min flow rate) equipped with a guard, employing a variable gradient of methanol and water. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the Caltech Mass Spectral Facility. Optical rotations were measured on a Jasco P-1010 polarimeter using a 100 mm path-length cell.

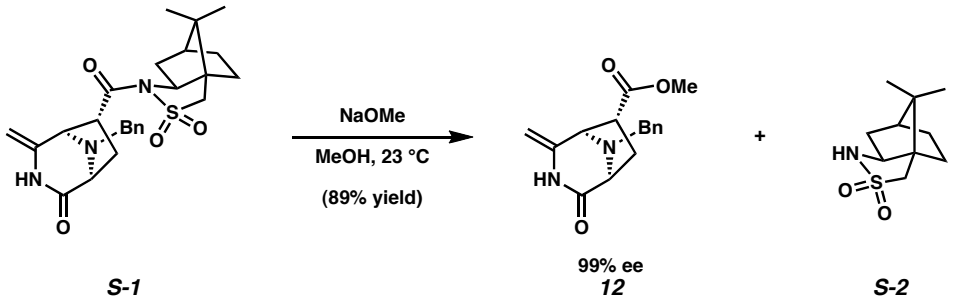
Experimental Procedures



13 ***14*** ***S-1***

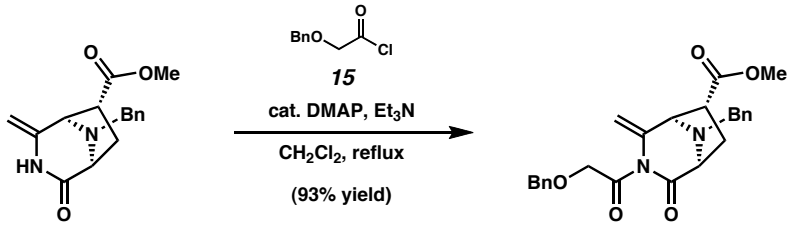
Diazabicycle S-1.[1,2] A flame-dried 1 L round-bottomed flask equipped with a stir bar was charged with oxidopyrazinium bromide **13** (12.70 g, 45.2 mmol) and acetonitrile (250 mL). The suspension was cooled to –20 °C in a Thermo Scientific NESLAB CB-80 cold bath. *N*-methylmorpholine (14.9 mL, 136 mmol) was added via syringe and the mixture was stirred until all solids had dissolved (10 min). A solution of acrylamide **14** (14.57 g, 54.1 mmol) in acetonitrile (350 mL) was then added and the reaction was maintained at –20 °C for 100 h. The reaction was then diluted cold in EtOAc (400 mL) and washed with water (2 x 300 mL). The combined aqueous layers were extracted with EtOAc (2 x 200 mL) and the combined organic layers were washed with brine (400 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude orange-yellow solid was filtered through a plug of silica (CH_2Cl_2 → 75:25 EtOAc/hexanes) to remove orange baseline material. Solvent was removed under reduced pressure to afford an off-white solid.[3] The crude solid was dissolved in a minimum amount of CH_2Cl_2 (240 mL), and to this solution was added hexanes (300 mL) while swirling until the first crystals were visible. The solution was then allowed to stand at 23 °C for 8 h. Filtration under vacuum provided diazabicycle **S-1** (14.85 g, 70% yield) as a white solid. The mother liquor was concentrated and the residue was resubmitted to recrystallization to provide additional diazabicycle **S-1** (2.75 g, 13% yield — 83% combined yield) as a white solid. R_f = 0.38 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (br s, 1H), 7.31–7.21 (comp m, 5H), 4.38 (d, *J* = 1.2 Hz, 1H), 4.32 (d, *J* = 1.2 Hz, 1H), 3.94 (d, *J* = 12.8 Hz, 1H), 3.89 (dd, *J* = 7.8, 4.6 Hz, 1H), 3.74 (d, *J* = 7.8 Hz, 1H), 3.68 (s, 1H), 3.59 (dd, *J* = 9.0, 3.9

Hz, 1H), 3.57 (d, *J* = 12.8 Hz, 1H), 3.41 (s, 2H), 3.06 (ddd, *J* = 13.4, 7.8, 3.9 Hz, 1H), 2.15 (dd, *J* = 13.4, 9.0 Hz, 1H), 2.06 (dd, *J* = 13.9, 7.8 Hz, 1H), 1.91–1.84 (comp m, 3H), 1.82 (dd, *J* = 4.2, 3.7 Hz, 1H), 1.43–1.32 (comp m, 2H), 0.92 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 171.3, 139.2, 138.2, 128.8, 128.5, 127.5, 94.0, 65.8, 63.4, 63.3, 53.3, 52.1, 49.2, 48.6, 47.9, 44.8, 38.5, 33.0, 31.3, 26.6, 20.8, 20.0; IR (Neat Film, NaCl) 3199, 2960, 1688, 1654, 1455, 1329, 1213, 1134, 853 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{32}N_3O_4S$ $[M+H]^+$: 470.2108, found 470.2136; $[\alpha]^{22}_D$ +100.72° (*c* 1.0, $CHCl_3$).



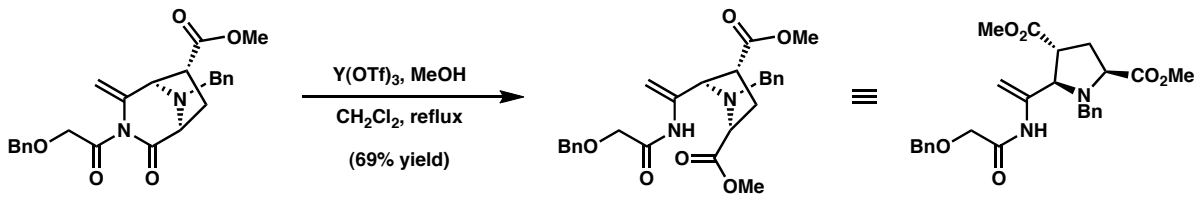
Ester 12. A flame-dried 500 mL round-bottomed flask equipped with a stir bar was charged with a 60% w/w suspension of NaH in mineral oil (1.32 g, 33.0 mmol). Methanol (200 mL) was slowly added with stirring at 23 °C under argon. **Warning:** vigorous gas evolution. The suspension was stirred until all solids had dissolved (15 min). A solution of diazabicycle **S-1** (5.07 g, 10.8 mmol) in CH_2Cl_2 (40 mL) was then added, and the reaction was maintained at 23 °C for 20 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl (250 mL) and extracted into EtOAc (3 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified via flash chromatography over silica gel (25:75 → 30:70 EtOAc/hexanes) to afford methyl ester **12** (2.75 g, 89% yield) as a white solid and sultam **S-2** (1.74 g, 75% yield) as a white crystalline solid. R_f = 0.45 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (br s, 1H), 7.35–7.29 (comp m, 4H), 7.28–7.24 (m, 1H), 4.33 (d, *J* = 1.2 Hz, 1H), 4.19 (d, *J* = 1.2,

1H), 4.02 (s, 1H), 3.82 (d, *J* = 13.4 Hz, 1H), 3.74 (s, 3H), 3.73 (d, *J* = 13.4 Hz, 1H), 3.62 (d, *J* = 7.3 Hz, 1H), 3.02 (dd, *J* = 9.8, 5.6 Hz, 1H), 2.66 (ddd, *J* = 13.2, 7.3, 5.6 Hz, 1H), (dd, *J* = 13.2, 9.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 171.6, 141.3, 137.9, 128.7, 128.6, 127.6, 91.7, 63.3, 62.5, 52.6, 52.5, 48.4, 33.5; IR (Neat Film, NaCl) 3202, 2953, 1737, 1684, 1656, 1454, 1318, 1200, 850 cm^{-1}; HRMS (FAB+) *m*/*z* calc'd for $C_{16}H_{19}N_2O_3$ $[M+H]^+$: 287.1396, found 287.1390; $[\alpha]^{26}_D$ –23.66° (*c* 1.0, $CHCl_3$). Analytical chiral SFC assay: Chiralcel OD-H column, 10:90 2-propanol:CO_2, 2.0 mL/min, λ = 254 nm, 40 °C isothermal method over 20 min. Racemic **12**: t_{fast} = 11.31 min (**(–)-12**, 49.9%), t_{slow} = 11.89 min (**(+)-12**, 50.1%). Enantio-enriched **12**: t_{fast} = 11.39 min (**(–)-12**, >99%) (the trace corresponding to **(+)-12** was below the threshold of detection).



Imide 16. A flame-dried 500 mL 3-neck round-bottomed flask equipped with a stir bar and a reflux condenser was charged with benzyloxyacetic acid (8.76 g, 52.8 mmol) and CH_2Cl_2 (140 mL). To this solution was added oxalyl chloride (4.53 mL, 51.9 mmol) and *N*,*N*-dimethylformamide (0.205 mL, 2.65 mmol). **Warning:** vigorous gas evolution. The reaction was maintained at 23 °C until bubbling had ceased (45 min). A solution of ester **12** (5.00 g, 17.5 mmol), triethylamine (7.9 mL, 56.7 mmol), and 4-dimethylaminopyridine (0.325 g, 2.66 mmol) in CH_2Cl_2 (35 mL) was then added dropwise via syringe over 5 min. The reaction was heated to 40 °C and maintained for 30 h. After cooling to room temperature, the solution was diluted in CH_2Cl_2 (200 mL) and washed with saturated aqueous NH_4Cl (200 mL), water (200 mL), and brine (200 mL). The organic layer was dried over $MgSO_4$ and

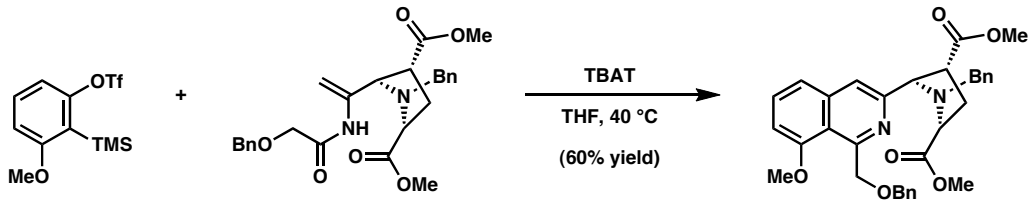
concentrated under reduced pressure. The crude orange residue was purified via flash chromatography over silica gel (15:85 → 25:75 EtOAc/hexanes) to afford imide **16** (7.06 g, 93% yield) as a colorless oil. R_f = 0.47 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.34 (comp m, 4H), 7.34–7.29 (comp m, 4H), 7.29–7.24 (comp m, 2H), 5.25 (d, *J* = 1.2 Hz, 1H), 4.65 (s, 2H), 4.59 (d, *J* = 1.2 Hz, 1H), 4.56 (d, *J* = 16.8 Hz, 1H), 4.49 (d, *J* = 16.8 Hz, 1H), 4.04 (s, 1H), 3.77 (d, *J* = 4.9 Hz, 2H), 3.74 (s, 3H), 3.68 (d, *J* = 7.1 Hz, 1H), 3.04 (dd, *J* = 9.8, 6.0 Hz, 1H), 2.62 (ddd, *J* = 13.4, 7.1, 6.0 Hz, 1H), 2.26 (dd, *J* = 13.4, 9.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 173.4, 172.1, 139.2, 137.4, 137.2, 128.8, 128.7, 128.6, 128.4, 128.3, 127.7, 99.8, 74.0, 72.9, 65.2, 64.7, 52.7, 52.7, 47.5, 32.7; IR (Neat Film, NaCl) 2952, 1736, 1634, 1454, 1200, 1117, 1028 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{27}N_2O_5$ $[M+H]^+$: 435.1920, found 435.1930; $[\alpha]^{21}_D$ –51.53° (*c* 1.0, $CHCl_3$).



16 ***11***

***N*-acyl enamine 11.** A flame-dried 500 mL 3-neck round-bottomed flask equipped with a stir bar and reflux condenser was charged with $Y(OTf)_3$ (2.59 g, 4.83 mmol) and CH_2Cl_2 (120 mL). The suspension was heated to 40 °C and a solution of imide **16** (2.05 g, 4.72 mmol) in CH_2Cl_2 (35 mL) was added. The mixture was maintained at 40 °C for 1 h, at which point MeOH (1.35 mL, 33.3 mmol) was added via syringe. The suspension immediately cleared and stirring was continued at 40 °C for an additional 30 min. After cooling to room temperature, the reaction was concentrated to a cloudy yellow oil containing yttrium salts, which was suspended in a minimum amount of CH_2Cl_2 (12 mL) and filtered through a plug of Celite. The filtrate was concentrated under reduced pressure and purified via flash chromatography over silica gel (25:75 → 40:60 EtOAc/hexanes) to yield *N*-acyl enamine **11** (1.52 g,

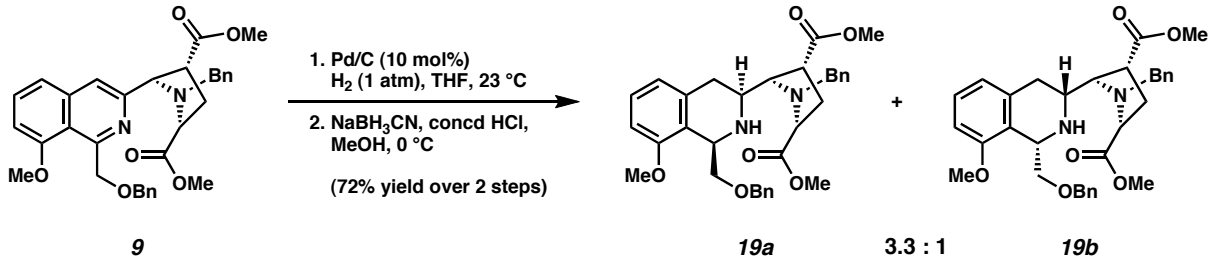
69% yield) as a pale yellow oil. R_f = 0.70 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (br s, 1H), 7.43 (d, *J* = 6.6 Hz, 2H), 7.39 (dd, *J* = 7.2, 6.6 Hz, 2H), 7.34, (tt, *J* = 7.2, 1.5 Hz, 1H), 7.29–7.22 (comp m, 5H), 6.01 (s, 1H), 4.76 (d, *J* = 1.2 Hz, 1H), 4.75 (d, *J* = 12.4 Hz, 1H), 4.71 (d, *J* = 12.4 Hz, 1H), 4.06 (s, 2H), 3.97 (d, *J* = 13.7 Hz, 1H), 3.69 (s, 3H), 3.65 (d, *J* = 9.0 Hz, 1H), 3.60 (d, *J* = 13.7 Hz, 1H), 3.56 (dd, *J* = 9.5, 4.2 Hz, 1H), 3.40 (s, 3H), 3.09 (dd, *J* = 9.5, 8.8 Hz, 1H), 2.33 (dt, *J* = 12.9, 9.8 Hz, 1H), 2.13 (ddd, *J* = 12.7, 8.3, 4.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 173.2, 169.5, 137.4, 137.3, 136.8, 129.7, 128.8, 128.5, 128.3, 128.2, 127.8, 101.7, 73.7, 72.2, 70.0, 63.2, 56.4, 52.4, 52.0, 47.6, 33.1; IR (Neat Film, NaCl) 3316, 2951, 1737, 1696, 1512, 1454, 1436, 1201, 1174, 1028 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{26}H_{31}N_2O_6$ $[M+H]^+$: 467.2182, found 467.2188; $[\alpha]^{25}_D$ –29.78° (*c* 1.0, $CHCl_3$).



17 ***11*** ***9***

Isoquinoline 9. A flame-dried 500 mL 3-neck round-bottomed flask equipped with a stir bar and reflux condenser was charged with tetra-*n*-butylammonium difluorotriphenylsilicate (5.45 g, 10.1 mmol) and THF (120 mL). A solution of *N*-acyl enamine **11** (2.35 g, 5.04 mmol) in THF (50 mL) was added at 23 °C, followed by silylaryl triflate **17**[4] (3.31 g, 10.1 mmol). The reaction was heated to 40 °C and maintained for 15 h, then cooled to room temperature and concentrated under reduced pressure. The yellow residue was purified via flash chromatography over silica gel (15:85 → 25:75 EtOAc/hexanes) to afford isoquinoline **9** (1.68 g, 60% yield) as a pale yellow oil. R_f = 0.65 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.55 (dd, *J* = 8.1, 7.8 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.34 (dd, *J* = 7.8, 7.1 Hz, 2H), 7.32–7.25 (comp m, 4H), 7.22 (dd, *J* = 7.6, 7.1 Hz, 2H), 7.15 (t, *J* = 7.3 Hz,

1H), 6.90 (d, *J* = 7.8 Hz, 1H), 5.32 (d, *J* = 12.5 Hz, 1H), 5.29 (d, *J* = 12.5 Hz, 1H), 4.78 (d, *J* = 11.7 Hz, 1H), 4.68 (d, *J* = 11.7 Hz, 1H), 4.52 (d, *J* = 6.1 Hz, 1H), 4.04 (d, *J* = 13.4 Hz, 1H), 3.96 (s, 3H), 3.79 (d, *J* = 13.4 Hz, 1H), 3.77 (dd, *J* = 9.5, 7.6 Hz, 1H), 3.61 (s, 3H), 3.51 (s, 3H), 3.31 (dt, *J* = 8.3, 6.1 Hz, 1H), 2.44 (ddd, *J* = 12.7, 8.3, 6.1 Hz, 1H), 2.26 (ddd, *J* = 12.7, 8.1, 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 174.5, 157.7, 156.4, 154.2, 140.0, 139.2, 137.9, 130.4, 129.8, 128.5, 128.4, 128.2, 127.6, 127.4, 120.3, 118.0, 106.7, 75.2, 73.0, 72.7, 65.3, 58.1, 55.9, 52.2, 51.9, 50.6, 45.0, 32.9; IR (Neat Film, NaCl) 2950, 1736, 1733, 1619, 1566, 1454, 1361, 1201, 1171 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{33}H_{35}N_2O_6$ $[M+H]^+$: 555.2490, found 555.2497; $[\alpha]^{24}_D$ –8.21° (*c* 1.0, $CHCl_3$).



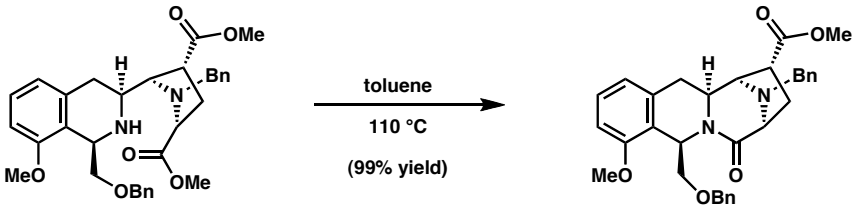
Tetrahydroisoquinolines 19a and 19b. A flame-dried 10 mL round-bottomed flask equipped with a stir bar was charged with 10% w/w palladium on carbon (0.019 g, 0.018 mmol) followed by a solution of isoquinoline **9** (0.100 g, 0.180 mmol) in THF (3.6 mL). The flask was purged with hydrogen and a hydrogen balloon was attached. The reaction was maintained at 23 °C for 6 h, then filtered through a plug of silica with 30:70 EtOAc/hexanes. Removal of the solvents under vacuum provided a 3.3:1 mixture of dihydroisoquinolines **18a** and **18b**[5] (not shown) (0.082 g), which was carried on without further purification. A flame-dried 5 mL round-bottomed flask equipped with a stir bar was charged with dihydroisoquinolines **18a** and **18b** (0.082 g, 0.148 mmol) in methanol (2.9 mL), and the solution was cooled to 0 °C. Concentrated hydrochloric acid (0.018 mL, 0.216 mmol) was added via syringe followed by $NaBH_3CN$ (0.046 g, 0.732 mmol) added in portions, allowing for bubbling to subside. The reaction was maintained at 0 °C for 15 min, and then quenched with saturated aqueous $NaHCO_3$ (1.5

mL) followed by CH_2Cl_2 (1.5 mL). The cloudy white mixture was vigorously stirred for 5 min, then 0.2 N NaOH was added dropwise until the mixture cleared (6 drops). The biphasic mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were washed with brine (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The yellow residue was purified via flash chromatography over silica gel (15:85 EtOAc/hexanes) to yield tetrahydroisoquinoline **19a** (0.055 g, 55% yield over 2 steps) as a clear colorless oil and tetrahydroisoquinoline **19b** (0.017 g, 17% yield over 2 steps) as a clear colorless oil.

Tetrahydroisoquinoline 19a. R_f = 0.38 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.3 Hz, 2H), 7.36–7.29 (comp m, 4H), 7.29–7.23 (comp m, 3H), 7.21 (dd, *J* = 7.3, 7.1 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 4.66 (d, *J* = 12.2 Hz, 1H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.47 (d, *J* = 7.1 Hz, 1H), 4.17 (dd, *J* = 8.8, 2.2 Hz, 1H), 3.99 (d, *J* = 13.9 Hz, 1H), 3.81 (d, *J* = 13.9 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.63 (dd, *J* = 8.3, 7.8 Hz, 1H), 3.46–3.33 (comp m, 4H), 3.38 (s, 3H), 2.98 (ddd, *J* = 11.2, 2.9, 2.7 Hz, 1H), 2.65 (dd, *J* = 14.7, 11.2 Hz, 1H), 2.55 (dd, *J* = 14.7, 2.7 Hz, 1H), 2.35 (ddd, *J* = 12.5, 7.1, 3.8 Hz, 1H), 2.27 (ddd, *J* = 12.7, 9.0, 8.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 174.4, 157.1, 139.4, 139.1, 138.7, 129.3, 128.4, 128.3, 127.8, 127.5, 127.4, 127.1, 124.4, 121.8, 108.2, 75.2, 73.1, 72.0, 66.8, 59.1, 55.3, 53.6, 53.4, 52.3, 51.8, 45.0, 42.9, 34.5, 34.0; IR (Neat Film, NaCl) 2949, 1734, 1731, 1584, 1470, 1255, 1198, 1170, 1074 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{33}H_{39}N_2O_6$ $[M+H]^+$: 559.2803, found 559.2814; $[\alpha]^{23}_D$ –52.71° (*c* 1.0, $CHCl_3$).

Tetrahydroisoquinoline 19b. R_f = 0.18 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.38–7.34 (comp m, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.19–7.14 (comp m, 3H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 4.72 (d, *J* = 12.2 Hz, 1H), 4.68 (d, *J* = 12.2 Hz, 1H), 4.62 (dd, *J* = 9.5, 2.2 Hz, 1H), 4.03 (d, *J* = 13.4 Hz,

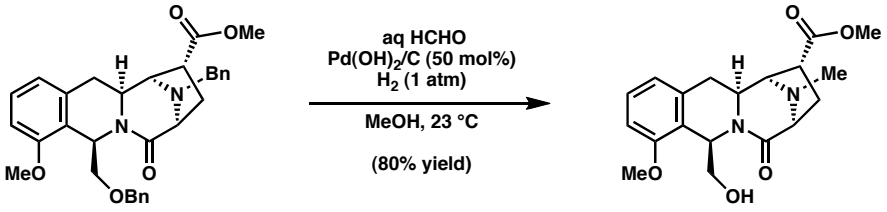
1H), 3.79 (d, *J* = 13.4 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.67–3.56 (comp m, 3H), 3.60 (d, *J* = 9.3 Hz, 1H), 3.39–3.32 (comp m, 2H), 3.38 (s, 3H), 3.30 (app dt, *J* = 8.1, 7.1 Hz, 1H), 2.60 (d, *J* = 7.6 Hz, 2H), 2.35–2.21 (comp m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 174.3, 156.6, 139.2, 138.2, 136.9, 129.8, 128.5, 128.3, 127.8, 127.6, 127.4, 123.8, 121.6, 107.7, 72.8, 71.5, 69.4, 66.8, 59.2, 55.4, 52.3, 51.8, 47.4, 42.7, 34.1, 32.4; IR (Neat Film, NaCl) 2949, 1733, 1588, 1454, 1257, 1198, 1171, 1074 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{33}H_{39}N_2O_6$ $[M+H]^+$: 559.2803, found 559.2825; $[\alpha]^{21}_D$ –17.00° (*c* 0.5, $CHCl_3$).



19a ***20***

Lactam 20. A flame-dried 20 mL scintillation vial equipped with a stir bar was charged with tetrahydroisoquinoline **19a** (0.075 g, 0.135 mmol) in toluene (5.4 mL). The vial was sealed with a teflon cap and the reaction was heated to 110 °C for 24 h. The reaction was then cooled to room temperature and the solvent was removed under reduced pressure. Purification via flash chromatography over silica gel (25:75 EtOAc/hexanes) provided tetracyclic lactam **20** (0.071 g, 99% yield) as a pale yellow oil. R_f = 0.61 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.22 (comp m, 9H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.07 (dd, *J* = 7.6, 2.4 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.74 (d, *J* = 7.3 Hz, 1H), 5.64 (t, *J* = 2.2 Hz, 1H), 4.32 (d, *J* = 12.0 Hz, 1H), 4.29 (d, *J* = 12.0 Hz, 1H), 4.25 (dd, *J* = 9.5, 3.2 Hz, 1H), 3.79 (s, 3H), 3.76 (dd, *J* = 12.4, 2.2 Hz, 1H), 3.73 (s, 3H), 3.72 (br s, 1H), 3.68 (d, *J* = 6.4 Hz, 1H), 3.60 (br s, 1H), 3.48 (dd, *J* = 9.5, 2.0 Hz, 1H), 3.25 (app t, *J* = 8.1 Hz, 1H), 3.12 (app t, *J* = 13.4 Hz, 1H), 2.66 (app dt, *J* = 6.6, 6.6 Hz, 1H), 2.44 (dd, *J* = 14.2, 2.2 Hz, 1H), 2.21 (dd, *J* = 13.2, 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 170.8, 155.9, 138.7, 138.6, 138.3, 128.9, 128.6, 128.5, 128.1, 127.8, 127.6,

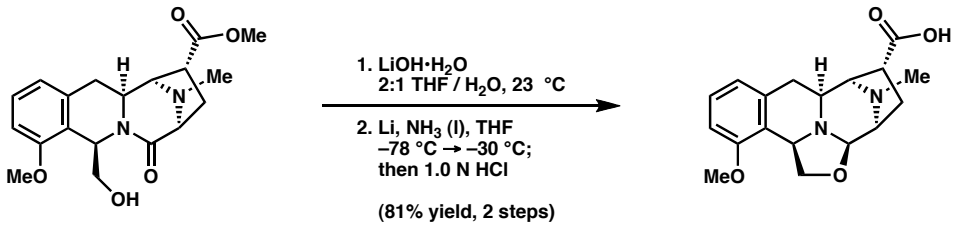
127.5, 123.2, 119.9, 108.9, 73.5, 70.9, 66.6, 65.2, 57.1, 55.5, 54.6, 52.4, 49.7, 41.2, 34.5, 32.4; IR (Neat Film, NaCl) 2950, 1735, 1654, 1474, 1437, 1265, 1208, 1099, 1069 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{32}H_{35}N_2O_5$ $[M+H]^+$: 527.2540, found 527.2543; $[\alpha]^{24}_D$ –85.60° (*c* 1.0, $CHCl_3$).



20 ***21***

***N*-Methyl amine 21.** A flame-dried 1 dram vial equipped with a stir bar and a septum-bearing screw cap was charged with moist 20% w/w $Pd(OH)_2$ on carbon (≤50% water) (0.062 g, 0.044 mmol) followed by a solution of lactam **20** (0.0435 g, 0.083 mmol) in MeOH (0.85 mL). The vial was purged with hydrogen and a hydrogen balloon was attached. The reaction was maintained at 23 °C for 20 h, at which point a 37% w/w aqueous solution of formaldehyde (0.310 mL, 4.14 mmol) was added via syringe. The reaction was maintained at 23 °C under hydrogen for an additional 20 h, and then filtered through a plug of Celite eluting with 10:90 MeOH/CH_2Cl_2. The solvent was removed under reduced pressure and the residue was purified via flash chromatography over silica (CH_2Cl_2 → 2:98 MeOH/CH_2Cl_2) to afford *N*-methyl amine **21** (0.024 g, 80% yield) as a solid white foam. R_f = 0.28 (10:90 MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 5.72 (dd, *J* = 5.6, 3.2 Hz, 1H), 3.91 (ddd, *J* = 11.3, 6.2, 2.9 Hz, 1H), 3.84 (s, 3H), 3.83 (app dt, *J* = 12.4, 2.4 Hz, 1H), 3.76 (s, 3H), 3.66 (dd, *J* = 1.5, 1.2 Hz, 1H), 3.60 (d, *J* = 6.4 Hz, 1H), 3.55 (ddd, *J* = 11.0, 5.6, 3.4 Hz, 1H), 3.31 (dd, *J* = 9.5, 6.6 Hz, 1H), 3.03 (dd, *J* = 5.6, 4.6 Hz, 1H), 2.96 (dd, *J* = 14.6, 12.7 Hz, 1H), 2.66 (app dt, *J* = 13.2, 6.6 Hz, 1H), 2.62 (dd, *J* = 14.6, 2.2 Hz, 1H), 2.48 (s, 3H), 2.39 (dd, *J* = 13.2, 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 173.5, 156.1, 137.5, 128.8, 121.8, 120.1, 109.3, 67.4, 67.3, 66.4, 55.7, 55.4, 52.7, 52.0, 41.6, 37.3, 34.8, 32.2; IR (Neat Film,

NaCl) 3404, 2951, 1733, 1638, 1474, 1436, 1264, 1204, 1064, 915 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{19}H_{24}N_2O_5$ $[M]^+$: 360.1685, found 360.1701; $[\alpha]^{22}_D$ –104.64° (*c* 1.0, $CHCl_3$).



21 ***Quinocarcin (1)***

Quinocarcin (1).[6] A flame-dried 15 mL round-bottomed flask equipped with a stir bar was charged with *N*-methyl amine **21** (36.4 mg, 0.101 mmol) in THF (2.7 mL). A solution of $LiOH·H_2O$ (0.0423 g, 1.01 mmol) in H_2O (1.35 mL) was added via syringe and the mixture was vigorously stirred at 23 °C for 3 h. Ethyl acetate (4 mL) was added and the solution was neutralized to pH 7 with 2.0 N HCl (4 drops). The biphasic mixture was transferred to a 50 mL round-bottomed flask and the solvents were removed under reduced pressure. The resulting cloudy white residue was dried under high vacuum for 6 h, and then suspended in THF (7 mL) and cooled to –78 °C. Ammonia (14 mL) was condensed into the flask using a cold finger at –78 °C and lithium metal (0.0401 g, 5.78 mmol) was added. The mixture turned dark blue and was vigorously stirred for 2 min. The –78 °C cold bath was replaced with a –30 °C cold bath ($MeCN/CO_2$) and stirring was continued for 15 min. The reaction was quenched by the addition of methanol (5 mL) down the side of the cold finger and stirred for an additional 5 min. Solid NH_4Cl (0.960 g, 17.9 mmol) was added in portions, the cold bath was removed, and the ammonia was evaporated under a stream of argon at room temperature. Water (10 mL) was added and the mixture was neutralized to pH 7 with 1.0 N HCl (10 mL). The solvents were removed under reduced pressure, and the resulting solids were dissolved in a minimum amount of water (1 mL) and filtered through a 5 g Sep-Pak C_{18} plug (H_2O → 50:50 $MeOH/H_2O$) to remove salts. The crude residue was purified via semi-preparative reverse-phase HPLC (20:80 → 70:30 $MeOH/H_2O$, t_R = 33 min) to afford quinocarcin (**1**)

(0.0269 g, 81% yield over 2 steps) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 7.17 (t, *J* = 7.8 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 4.57 (d, *J* = 2.9 Hz, 1H), 4.55 (dd, *J* = 7.3, 2.9 Hz, 1H), 4.07 (br s, 2H), 3.82 (s, 3H), 3.68 (dd, *J* = 10.7, 2.9 Hz, 1H), 3.43–3.33 (comp m, 2H), 3.39 (dd, *J* = 10.7, 7.3 Hz, 1H), 2.79–2.74 (m, 1H), 2.77 (s, 3H), 2.64 (dd, *J* = 14.6, 2.4 Hz, 1H), 2.64–2.60 (m, 1H), 2.46 (dd, *J* = 13.9, 10.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 179.5, 157.2, 137.6, 129.1, 124.0, 121.3, 110.0, 92.6, 73.2, 68.2, 66.9, 56.3, 55.9, 55.7, 42.8, 40.7, 32.9, 28.3; IR (Neat Film, NaCl) 3370, 2941, 1590, 1474, 1383, 1264, 1054 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{23}N_2O_4$ $[M+H]^+$: 331.1652, found 331.1669; $[\alpha]^{22}_D$ –31.57° (*c* 0.28, H_2O). The analytical data for the synthetic sample matched those for the natural sample in all respects.[7]

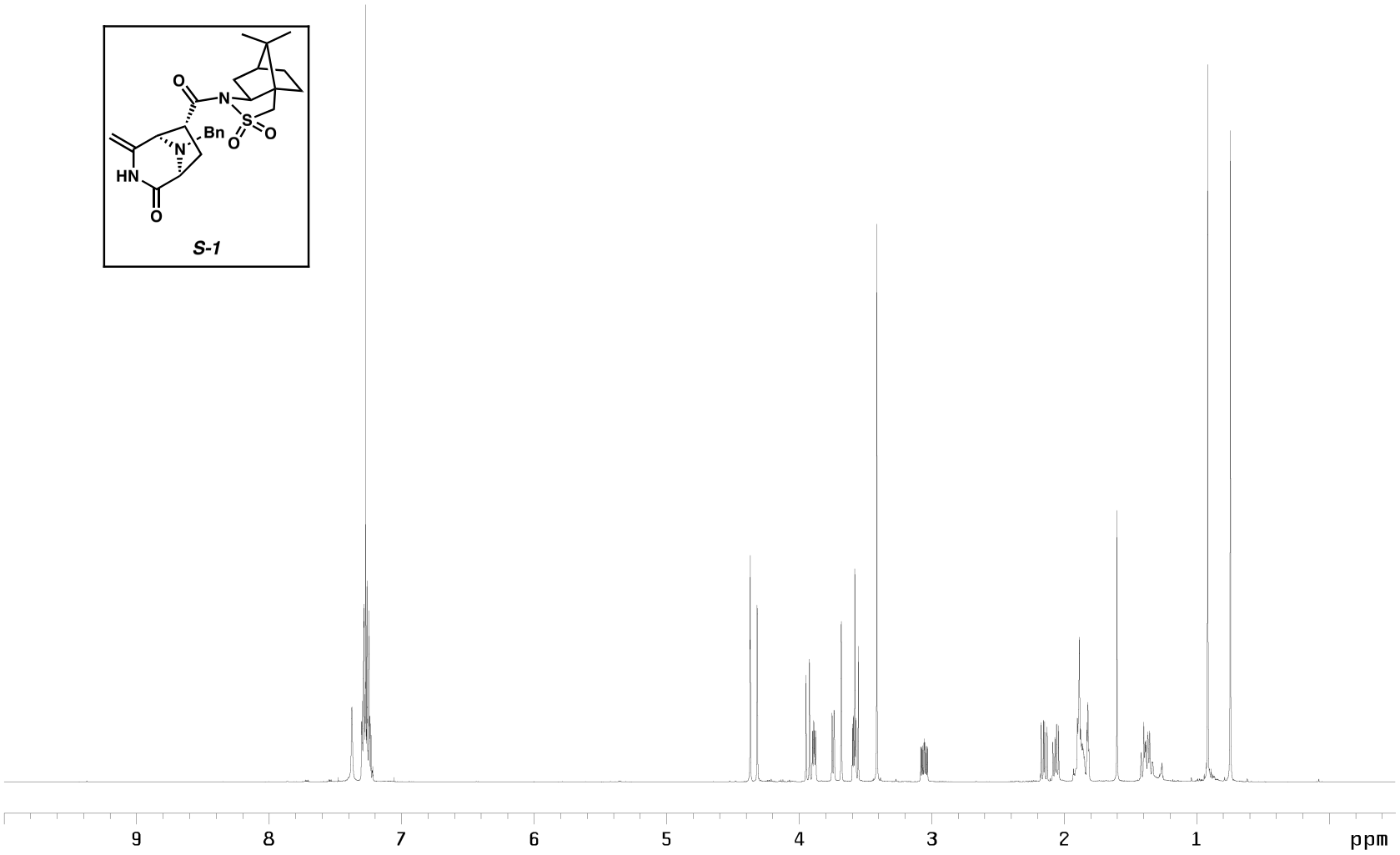


Figure 1.1. ^{1}H NMR (500 MHz, $CDCl_3$) of diazabicycle **S-1**

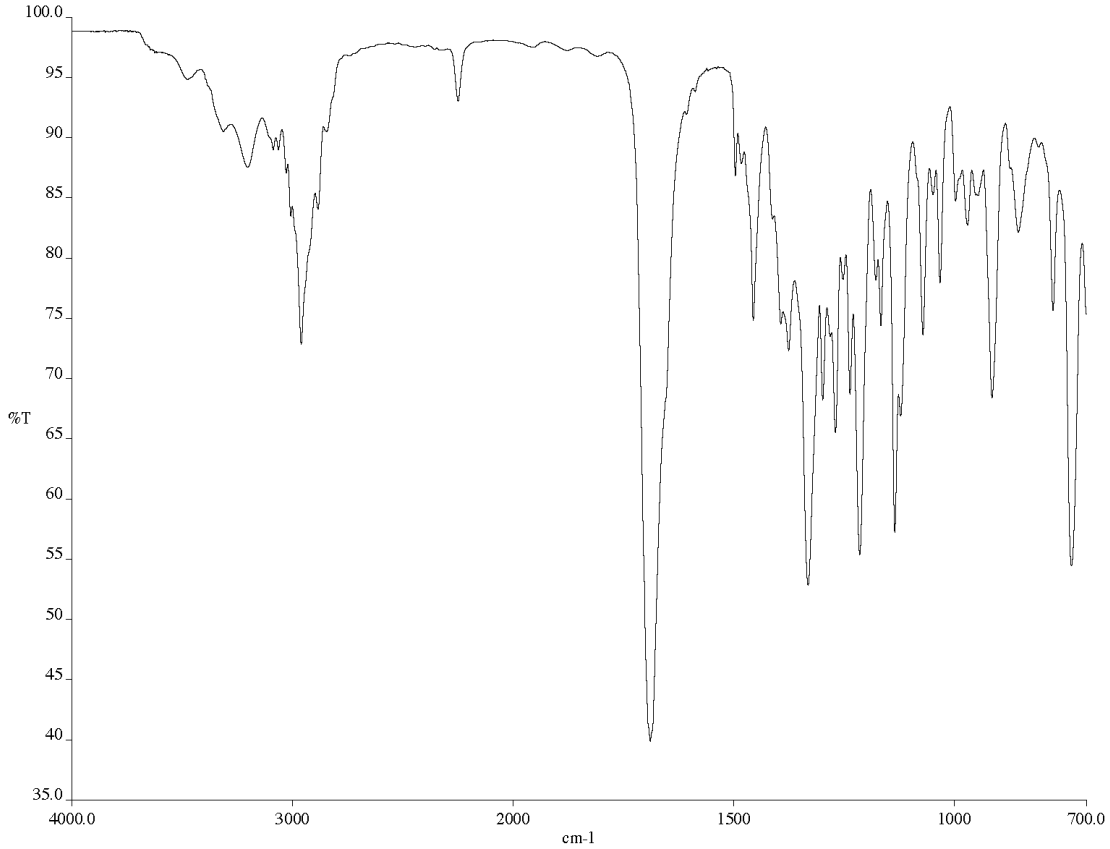


Figure 1.2. Infrared spectrum (thin film/NaCl) of diazabicycle **S-1**.

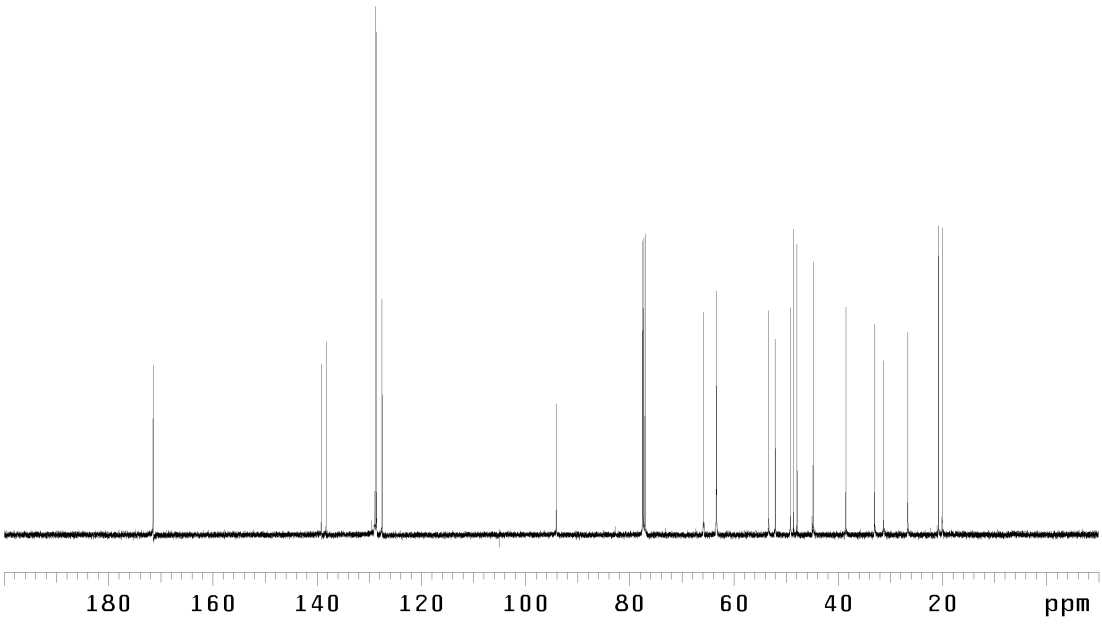


Figure 1.3 ^{13}C NMR (125 MHz, $CDCl_3$) of diazabicycle **S-1**.

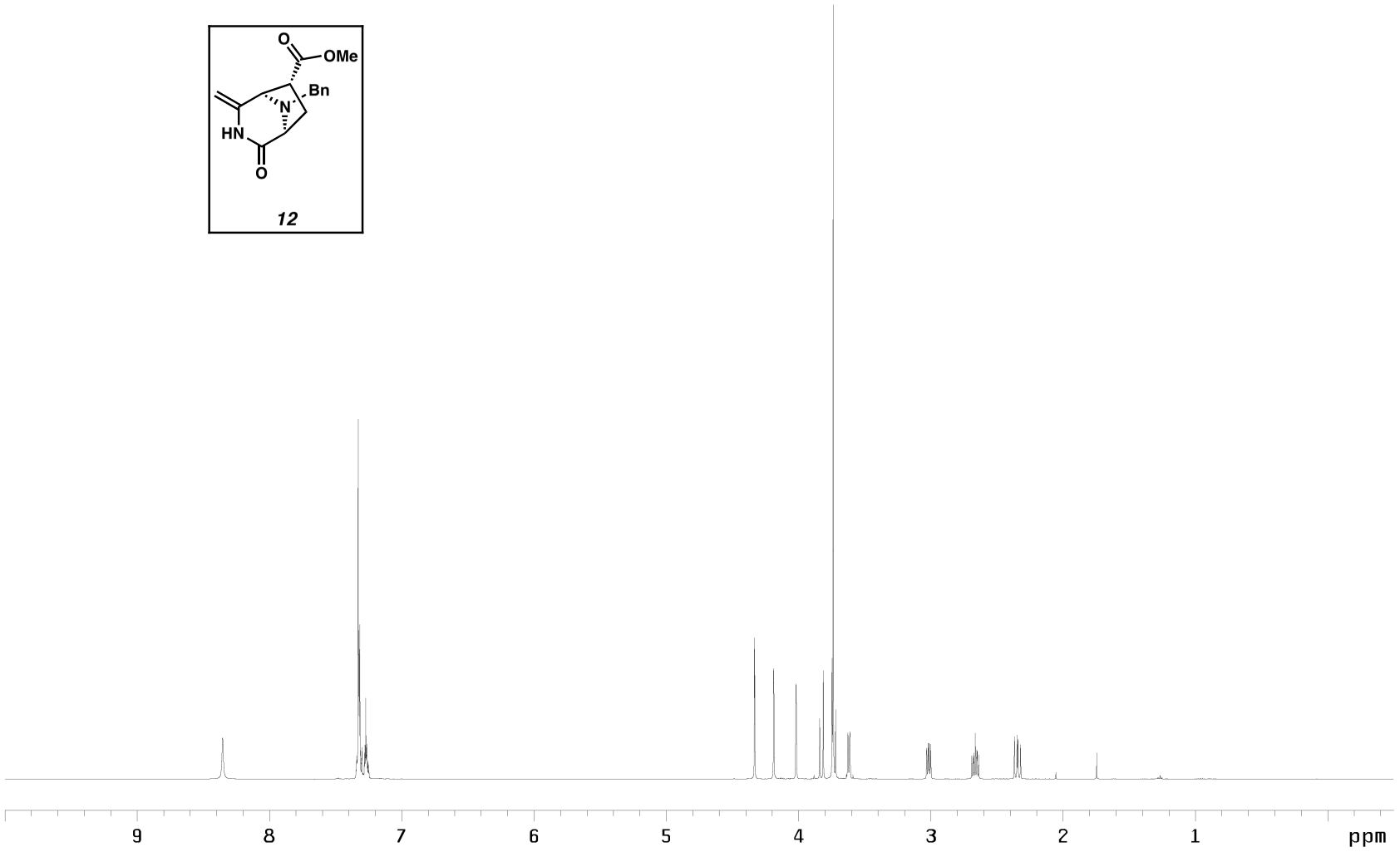


Figure 2.1. ^{1}H NMR (500 MHz, $CDCl_3$) of methyl ester **12**.

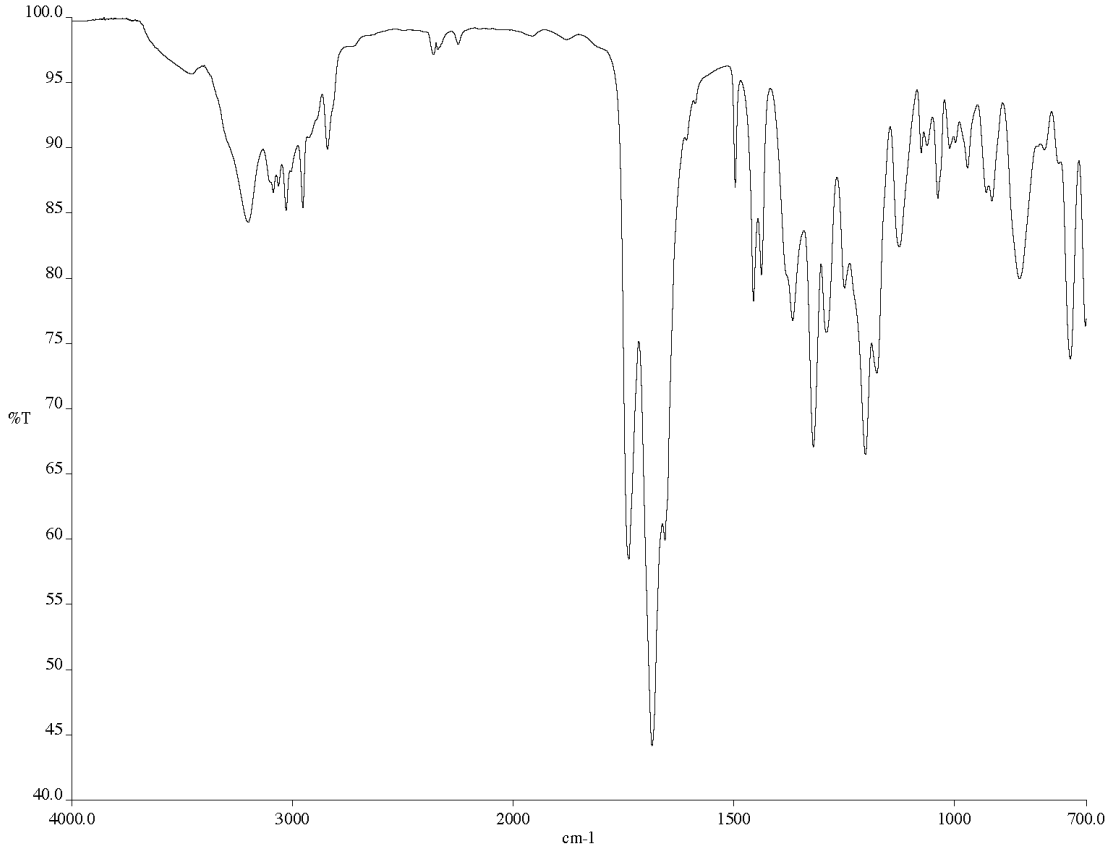


Figure 2.2. Infrared spectrum (thin film/NaCl) of methyl ester **12**.

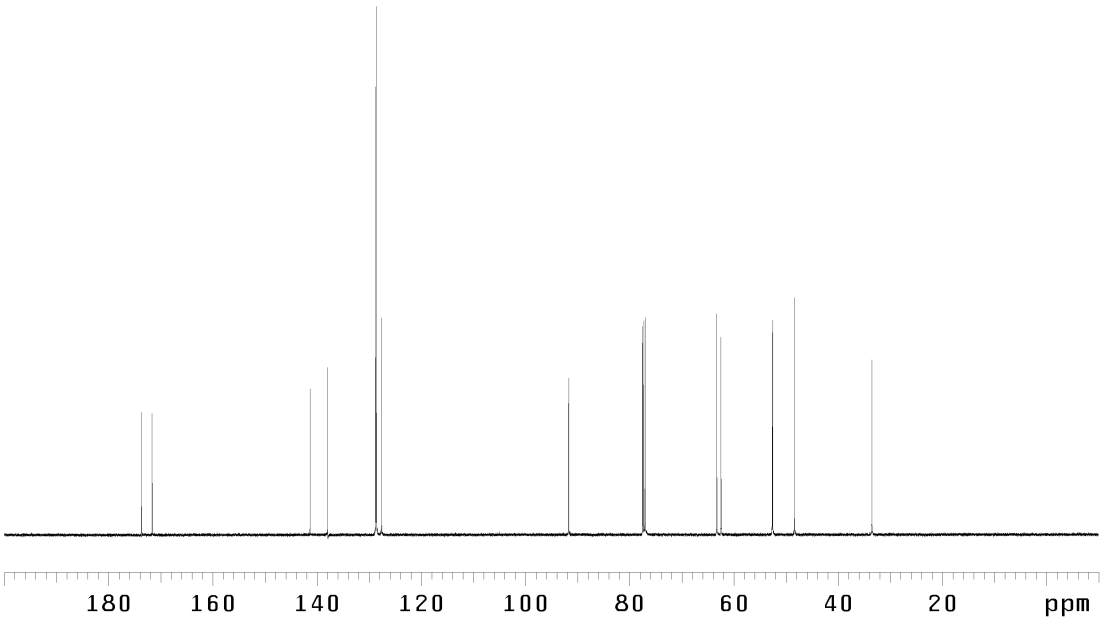


Figure 2.3. ^{13}C NMR (125 MHz, $CDCl_3$) of methyl ester **12**.

Figure 2.4. Chiral SFC traces for racemic methyl ester **12**.

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		Inj Volume	: 5 µl
Acq. Method	: C:\Chem32\1\DATA\KALLAN\KMA-ESTER 2008-09-28 16-41-01\KMA-CHIRAL S3C3 ISO10-20MIN-2.M		
Last changed	: 9/28/2008 3:34:13 PM by JST		
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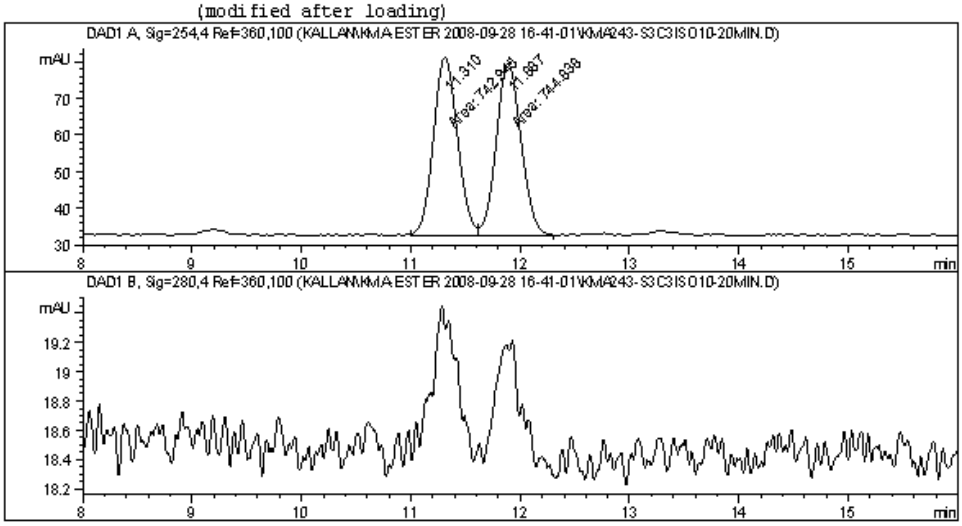

Area Percent Report

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Use Multiplier & Dilution Factor with ISTDs

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2	11.887	MM	0.2632	744.83813	47.16733	50.0636
Totals :				1487.78345	95.85054	

Figure 2.5. Chiral SFC trace for enantioenriched methyl ester **(–)-12** (>99% ee).

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                                                  Inj Volume : 5 µl
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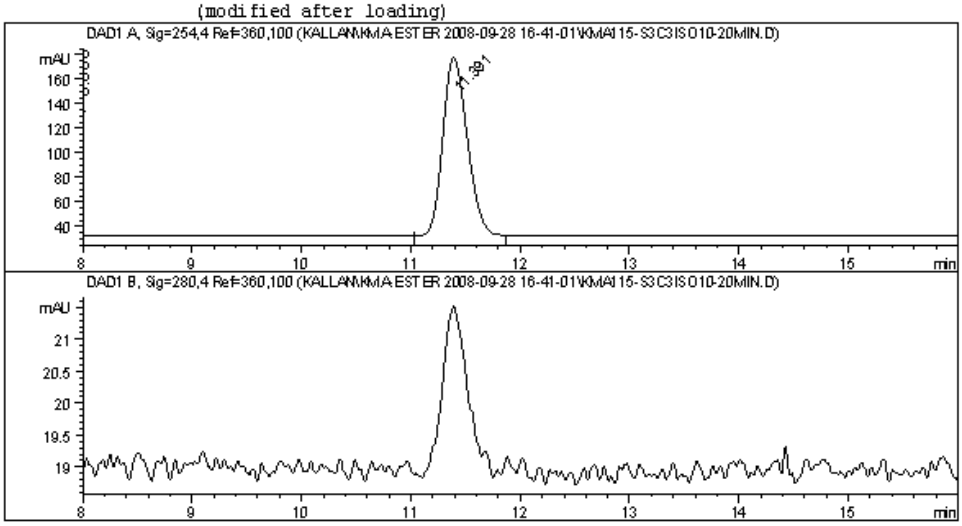


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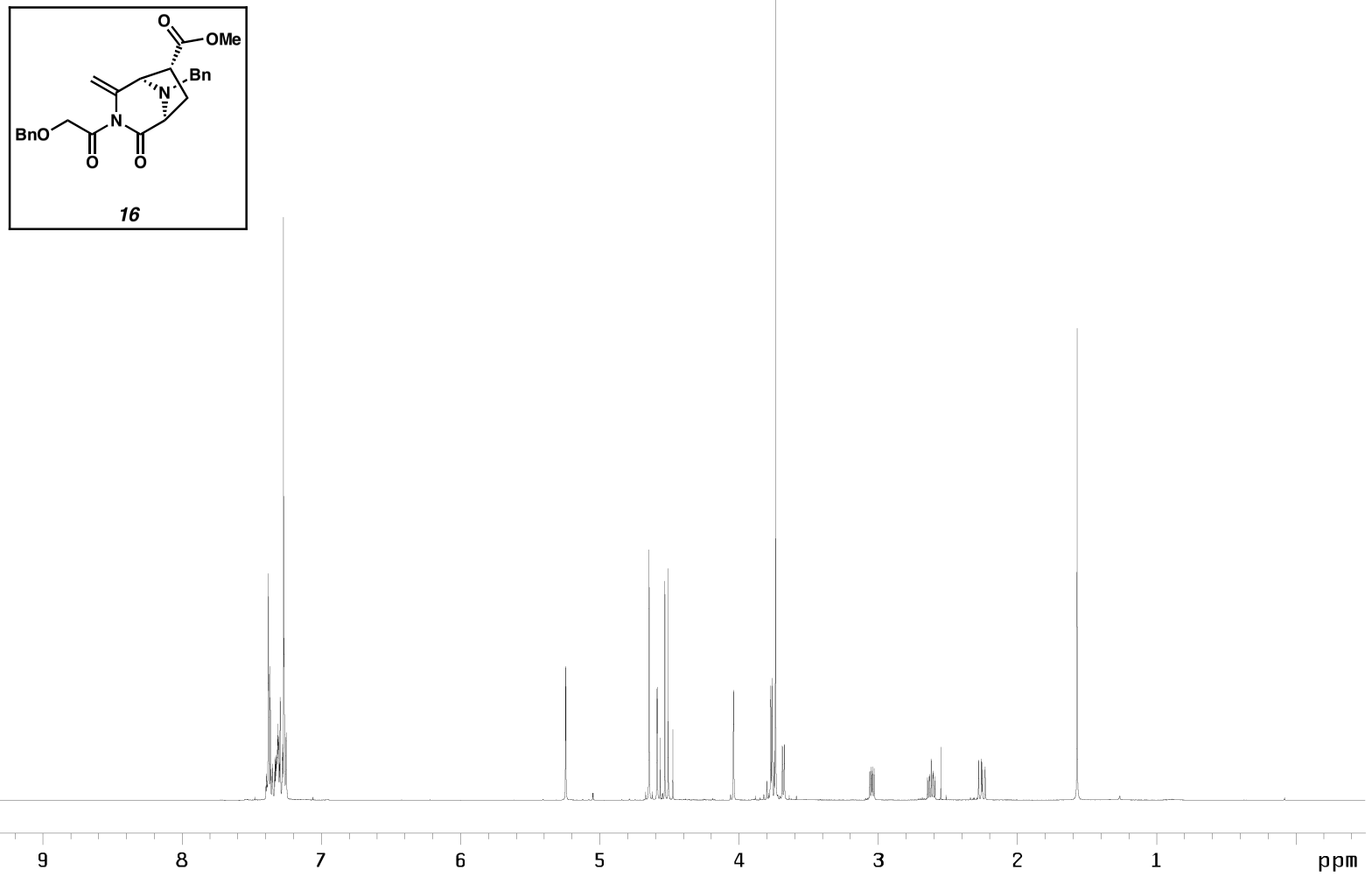

Figure 3.1. ^{1}H NMR (500 MHz, $CDCl_3$) of imide **16**.

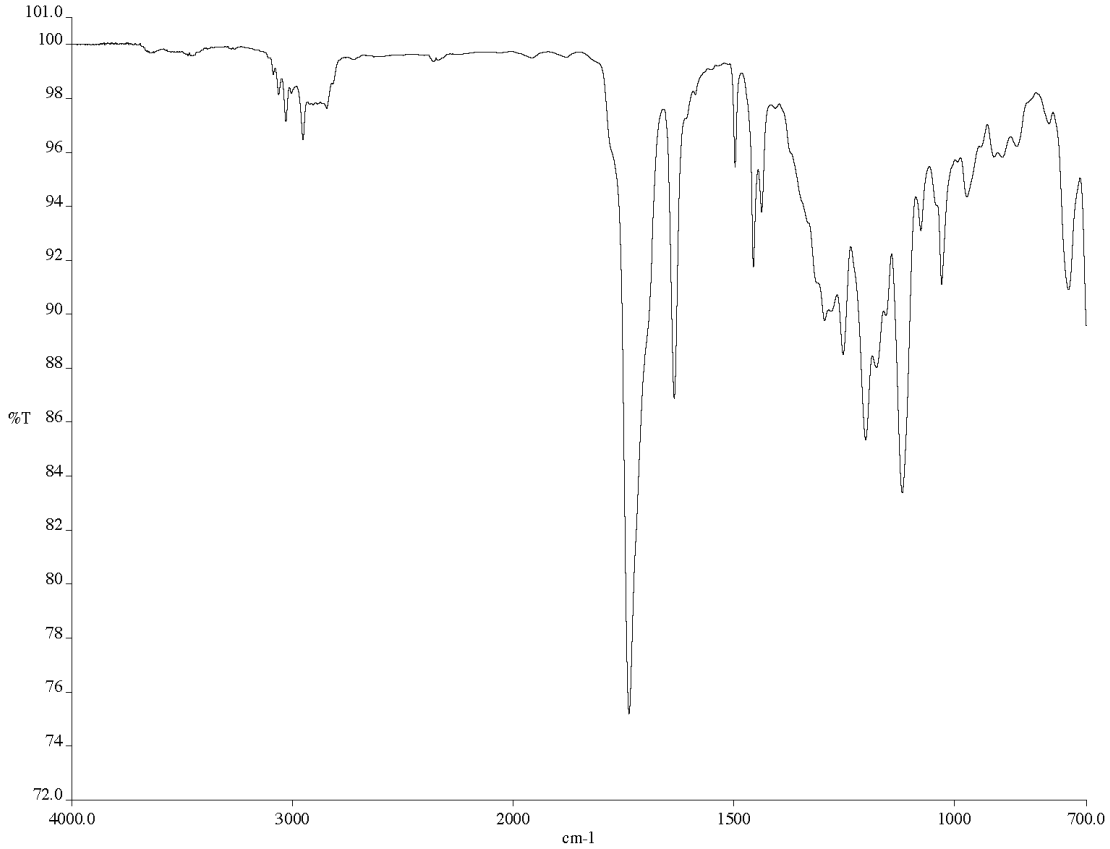

Figure 3.2. Infrared spectrum (thin film/NaCl) of imide **16**.

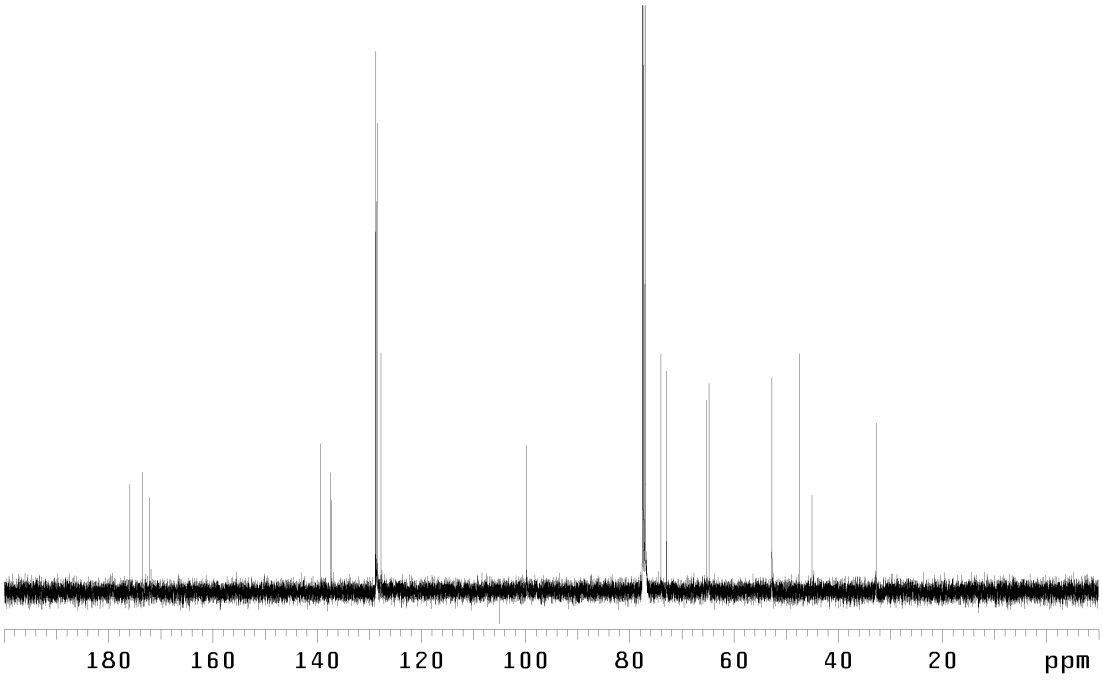

Figure 3.3. ^{13}C NMR (125 MHz, $CDCl_3$) of imide **16**.

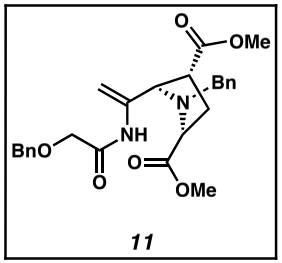

Figure 4.1. ^{1}H NMR (500 MHz, $CDCl_3$) of *N*-acyl enamine **11**.

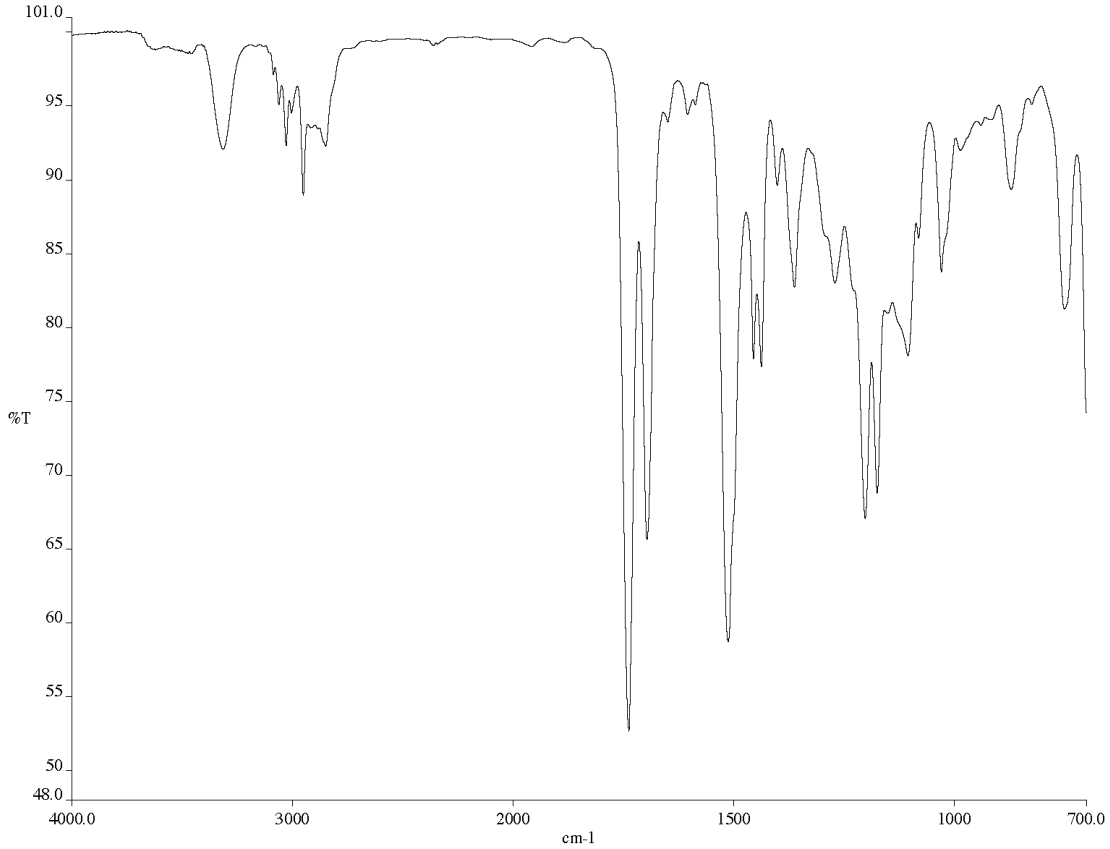

Figure 4.2. Infrared spectrum (thin film/NaCl) of *N*-acyl enamine **11**.

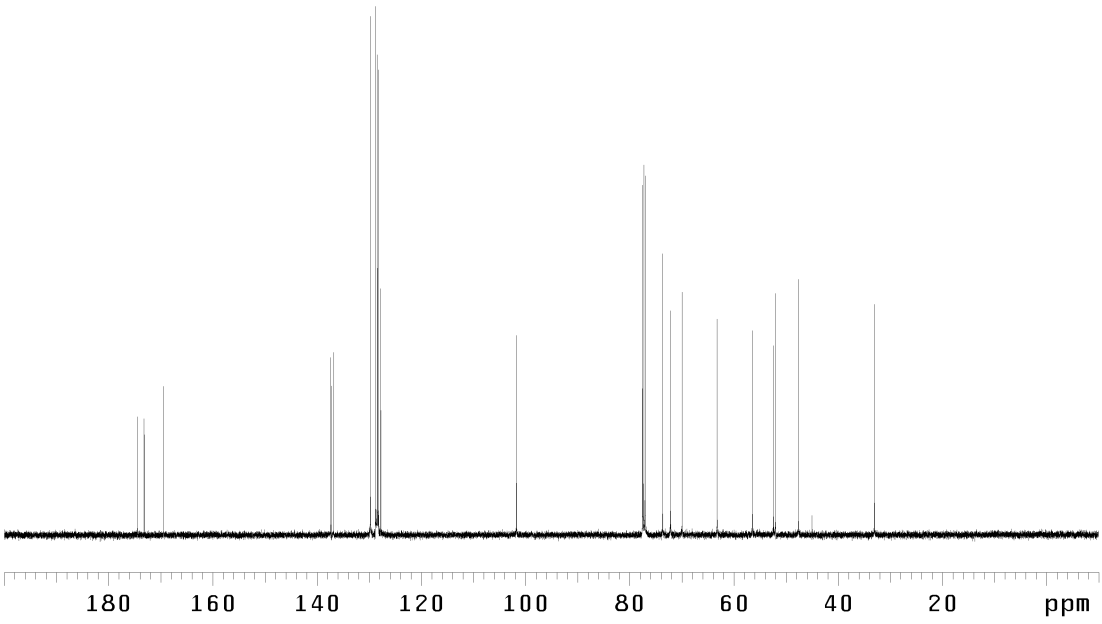

Figure 4.3. ^{13}C NMR (125 MHz, $CDCl_3$) of *N*-acyl enamine **11**.

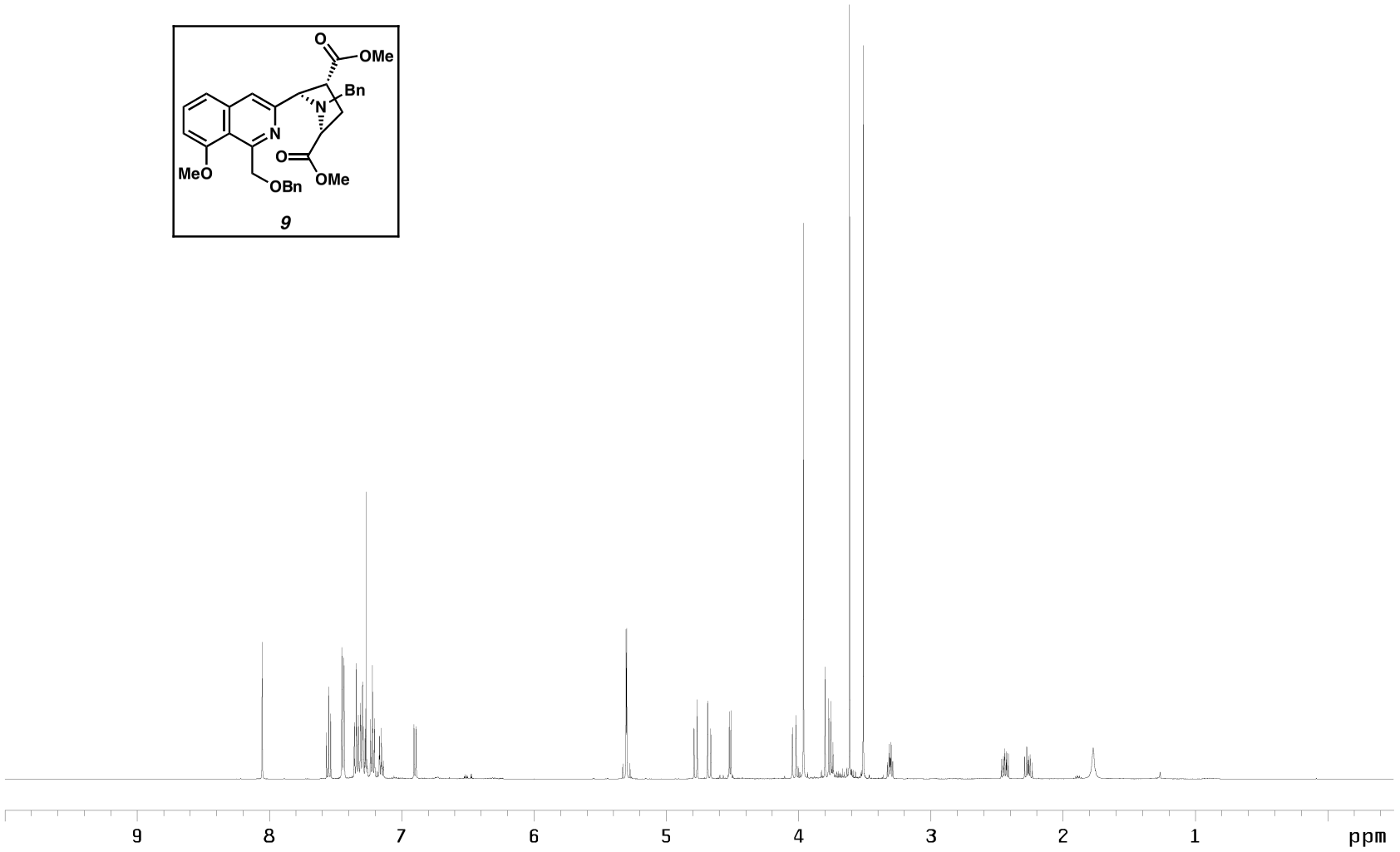

Figure 5.1. ^{1}H NMR (500 MHz, $CDCl_3$) of isoquinoline **9**.

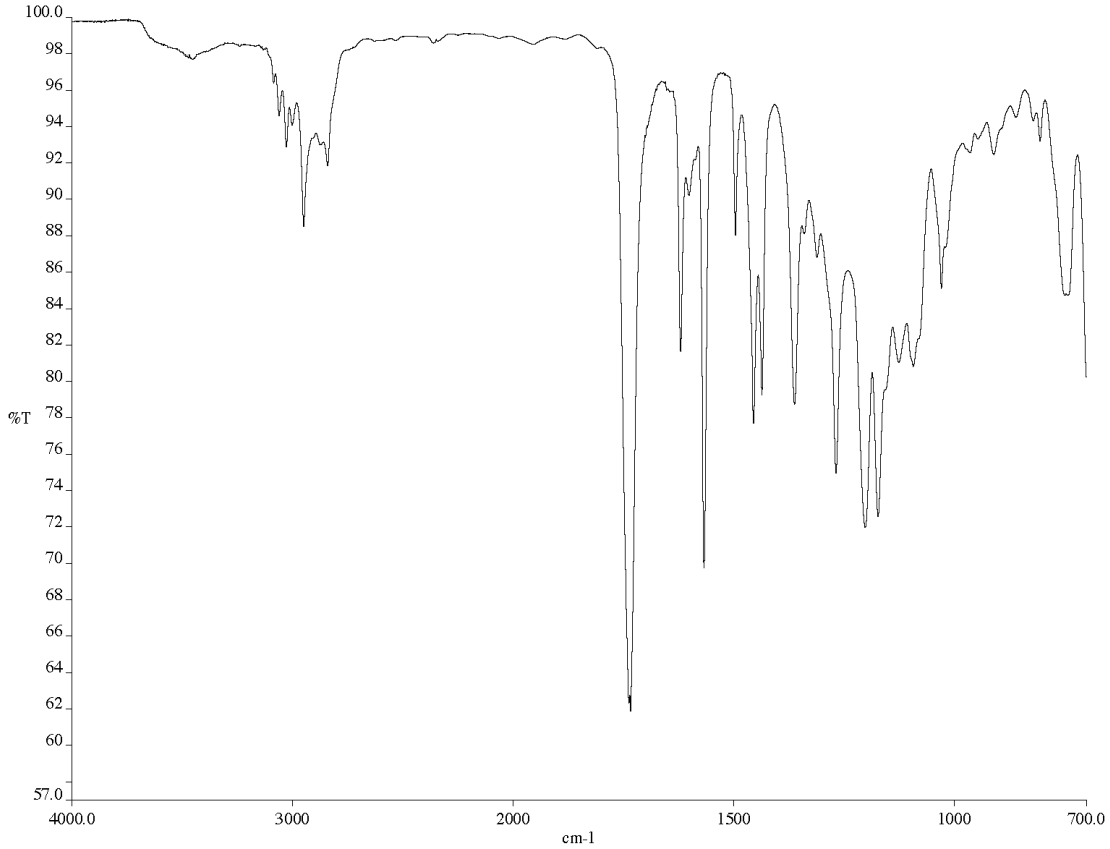

Figure 5.2. Infrared spectrum (thin film/NaCl) of isoquinoline **9**.

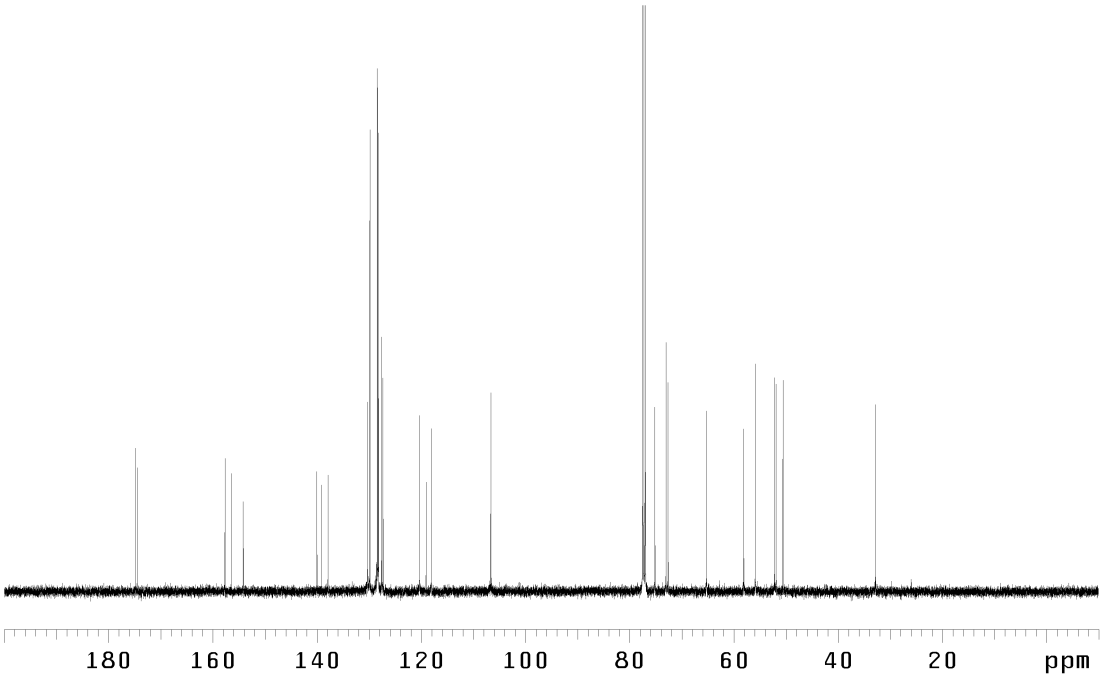

Figure 5.3. ^{13}C NMR (125 MHz, $CDCl_3$) of isoquinoline **9**.

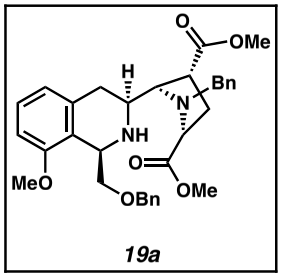

Figure 6.1. ^{1}H NMR (500 MHz, $CDCl_3$) of tetrahydroisoquinoline **19a**.

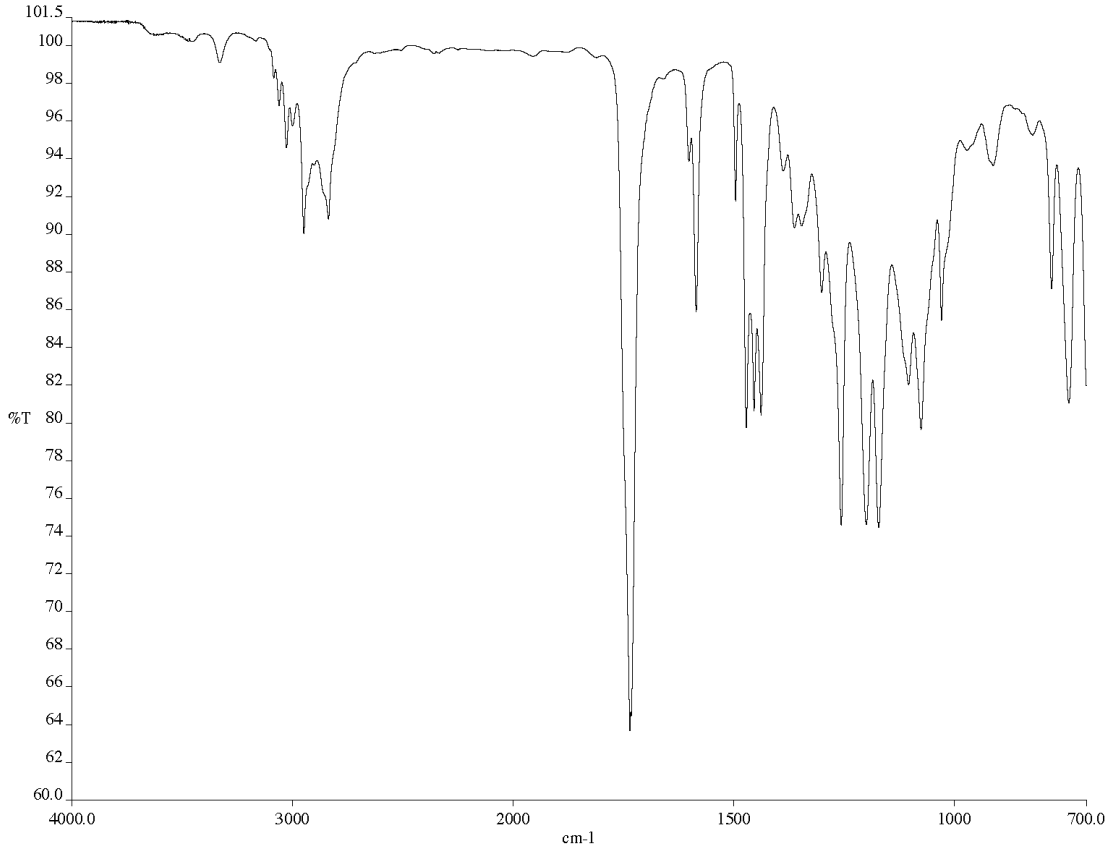

Figure 6.2. Infrared spectrum (thin film/NaCl) of tetrahydroisoquinoline **19a**.

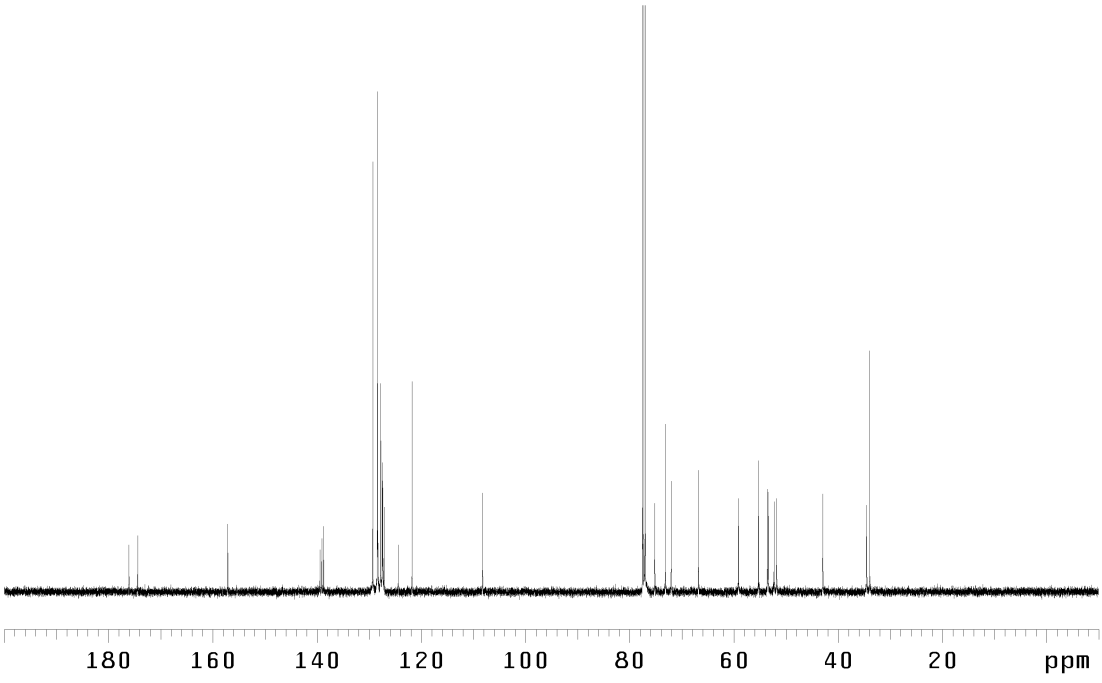

Figure 6.3. ^{13}C NMR (125 MHz, $CDCl_3$) of tetrahydroisoquinoline **19a**.

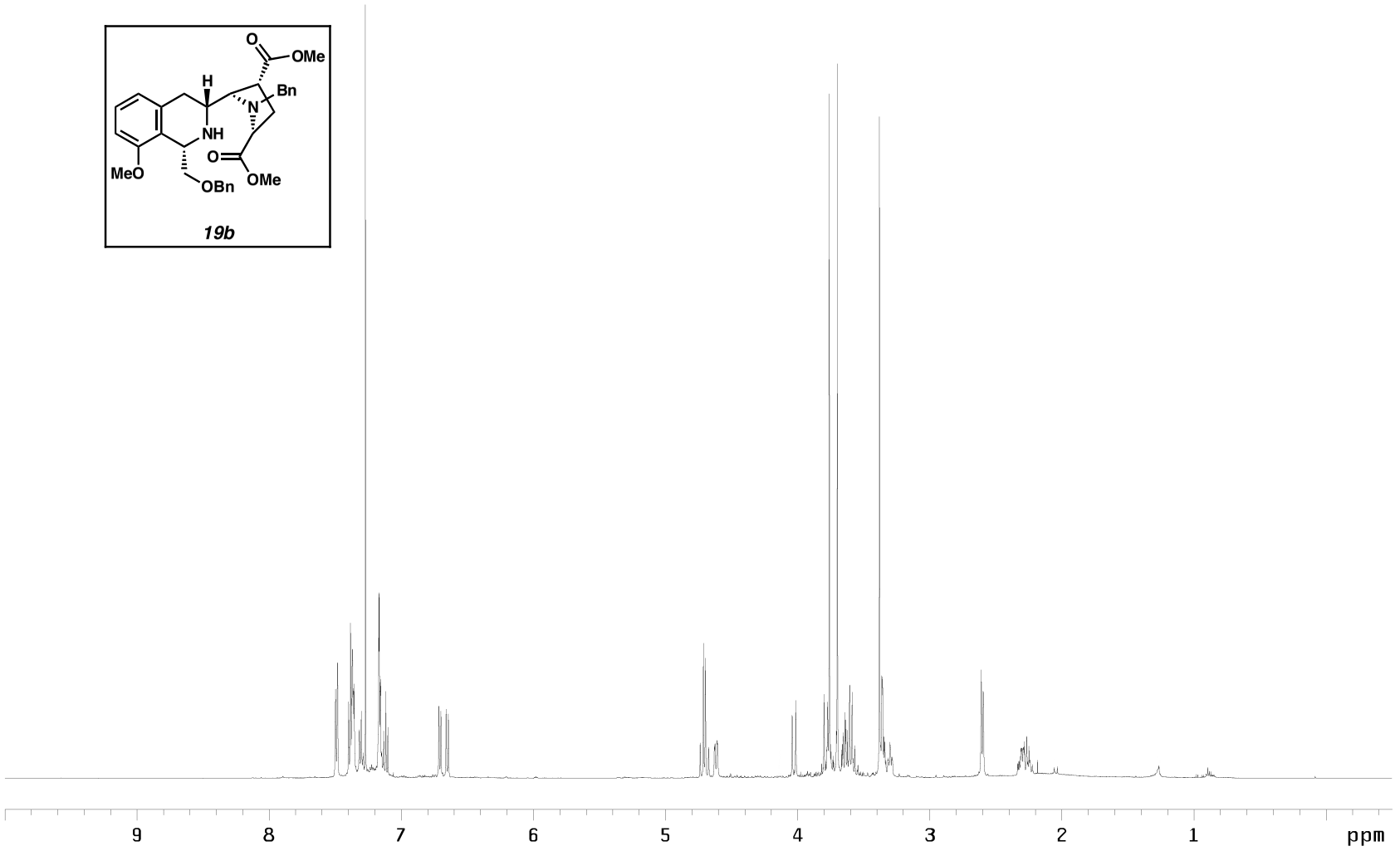

Figure 7.1. ^{1}H NMR (500 MHz, $CDCl_3$) of tetrahydroisoquinoline **19b**.

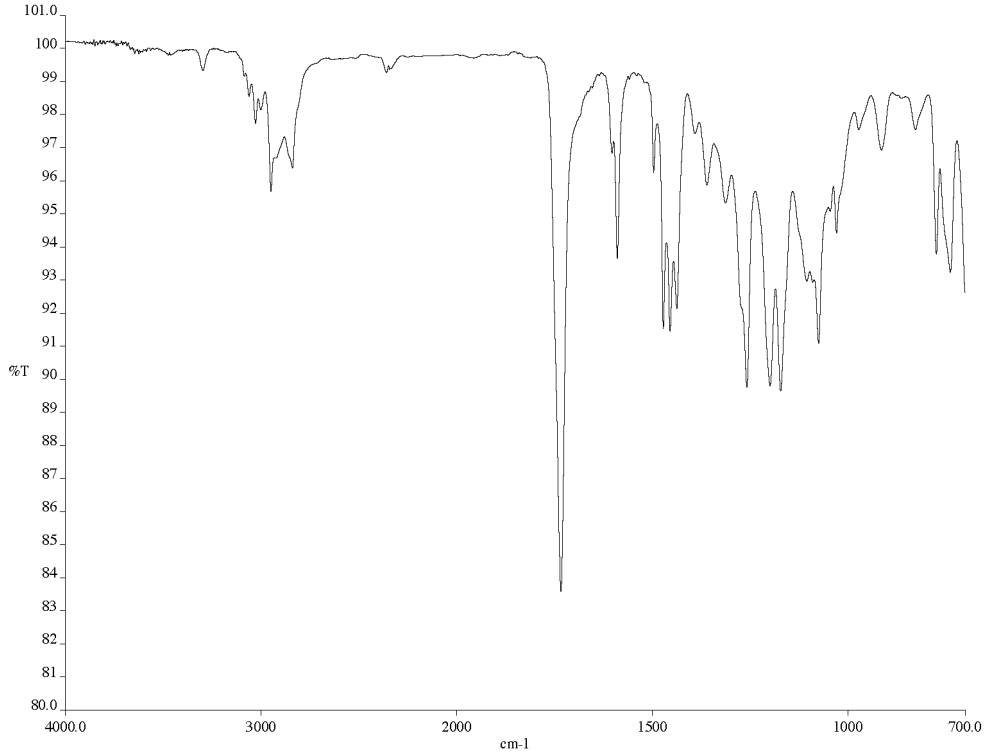

Figure 7.2. Infrared spectrum (thin film/NaCl) of tetrahydroisoquinoline **19b**.

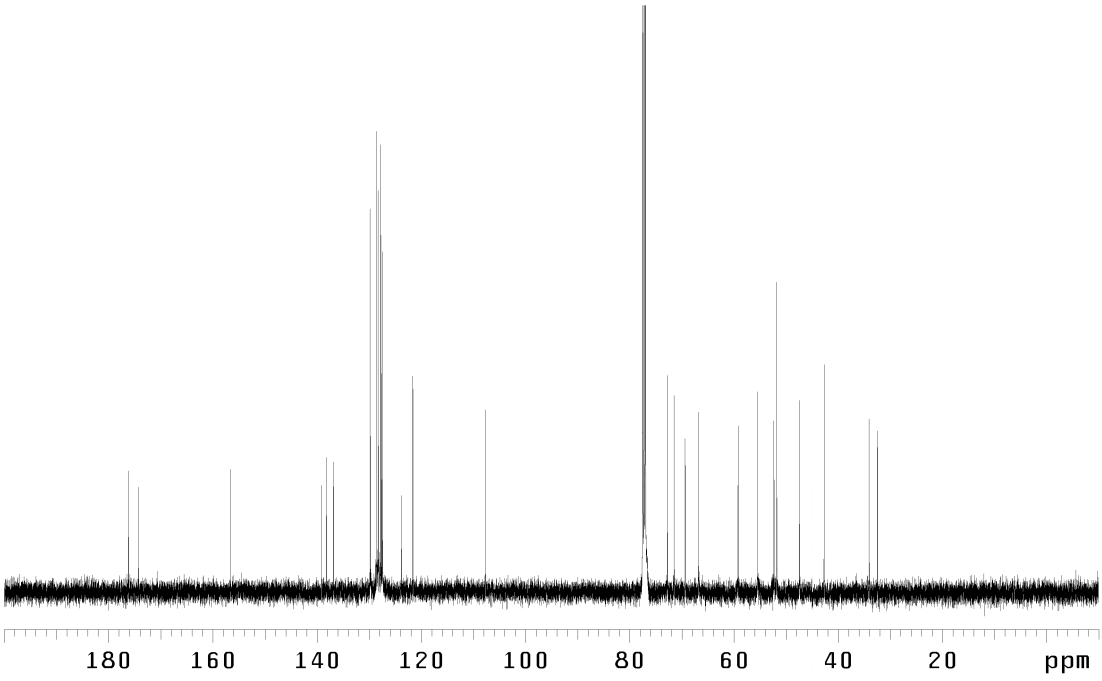

Figure 7.3. ^{13}C NMR (125 MHz, $CDCl_3$) of tetrahydroisoquinoline **19b**.

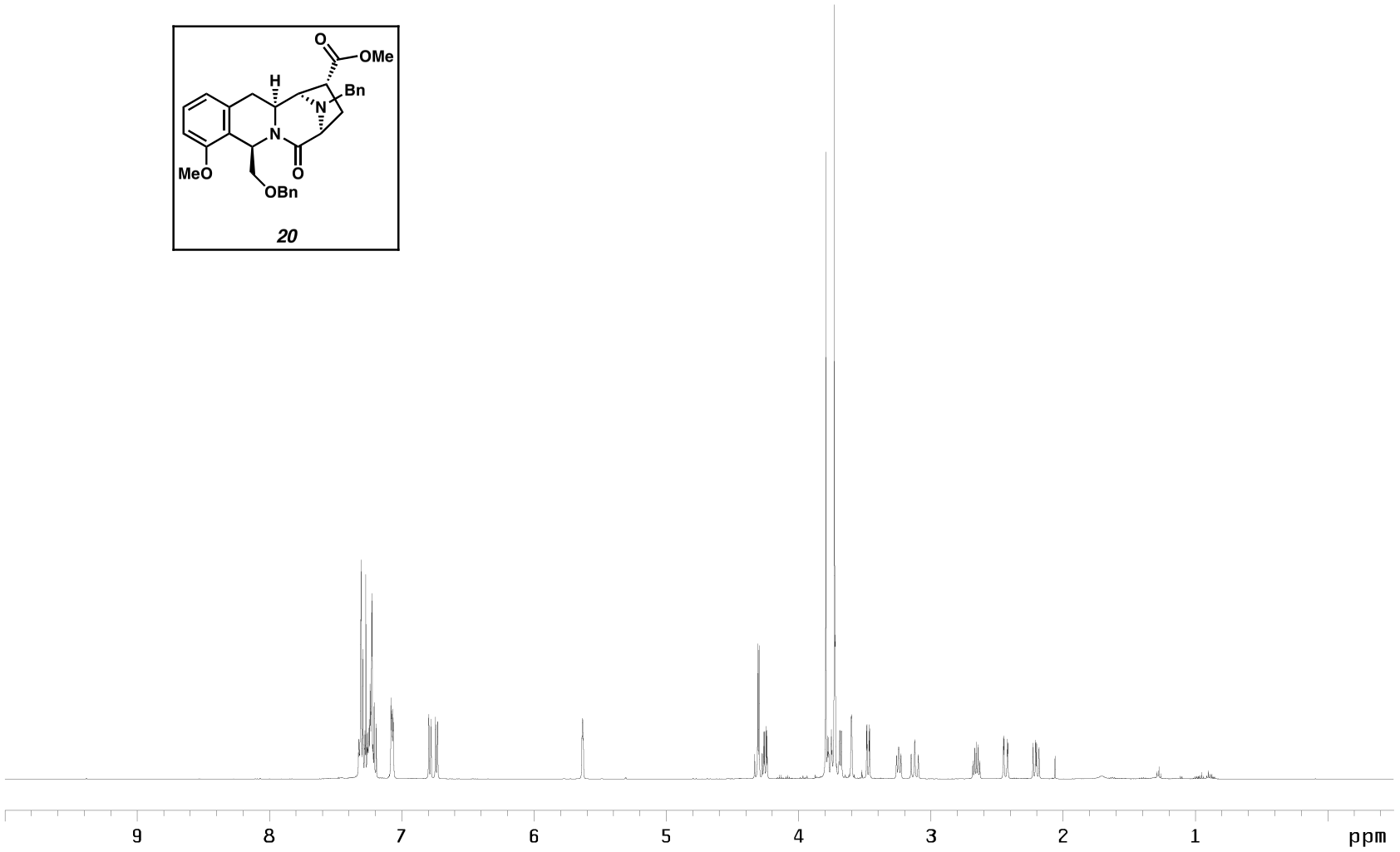

Figure 8.1. ^{1}H NMR (500 MHz, $CDCl_3$) of lactam **20**.

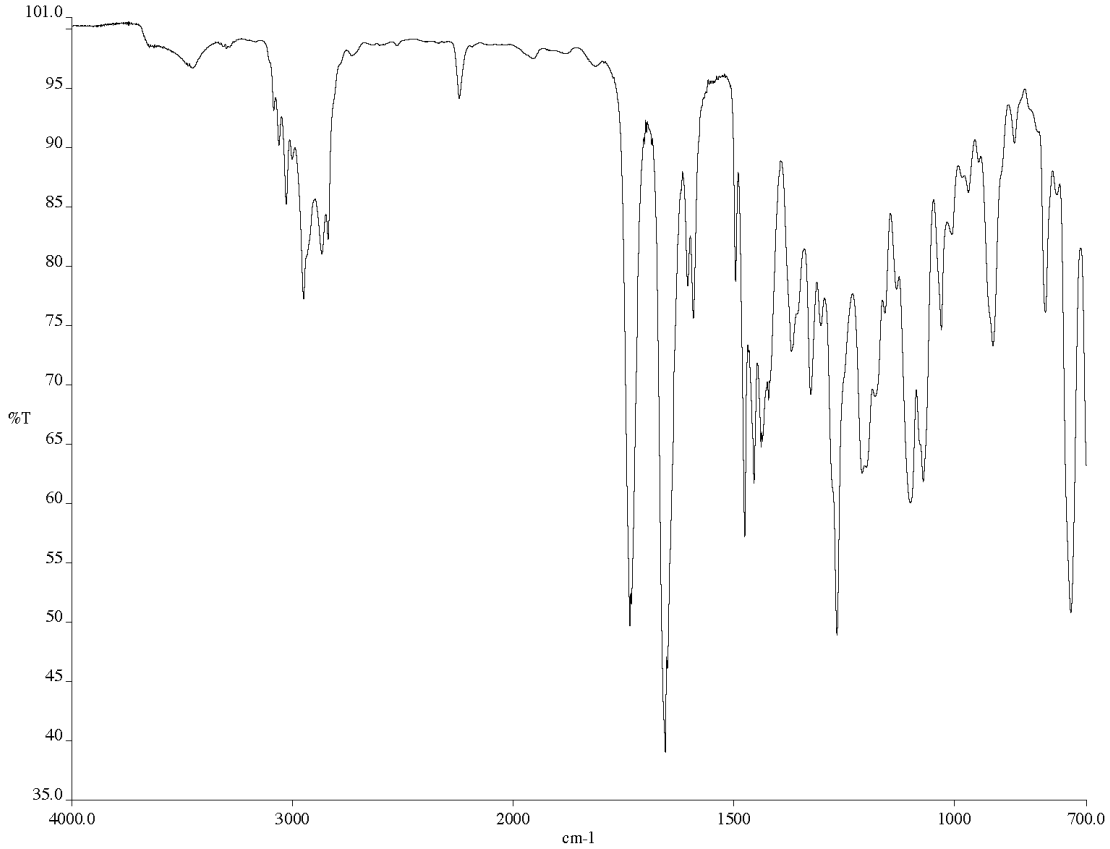

Figure 8.2. Infrared spectrum (thin film/NaCl) of lactam **20**.

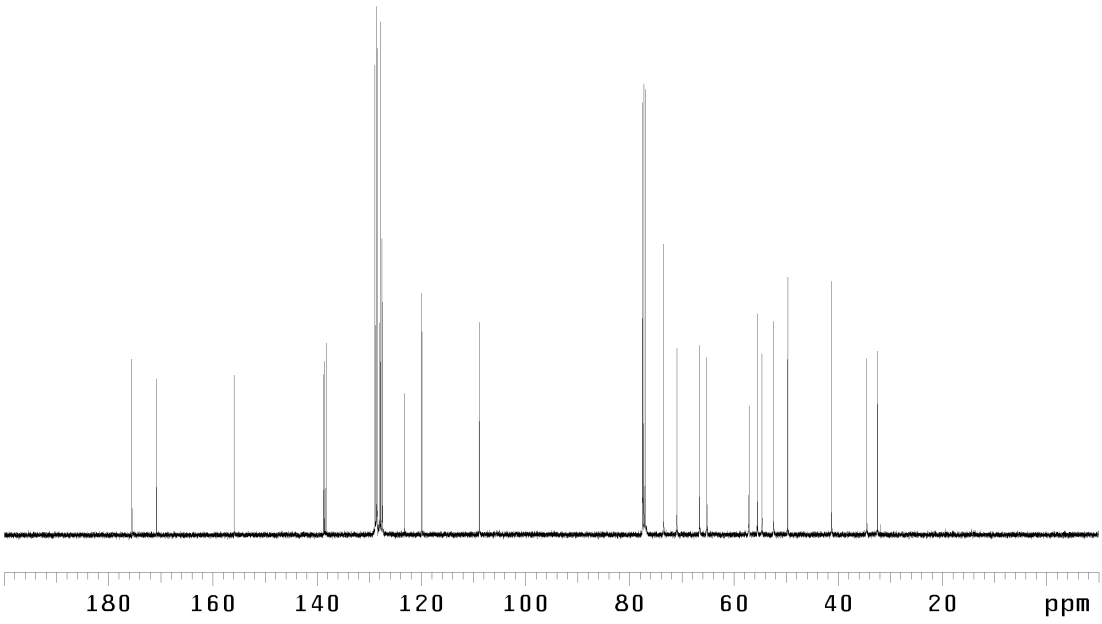

Figure 8.3. ^{13}C NMR (125 MHz, $CDCl_3$) of lactam **20**.

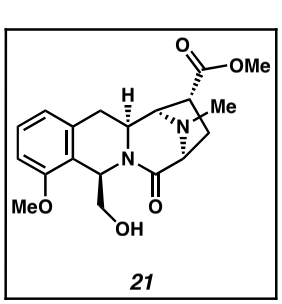

Figure 9.1. ^{1}H NMR (500 MHz, $CDCl_3$) of *N*-methyl amine **21**.

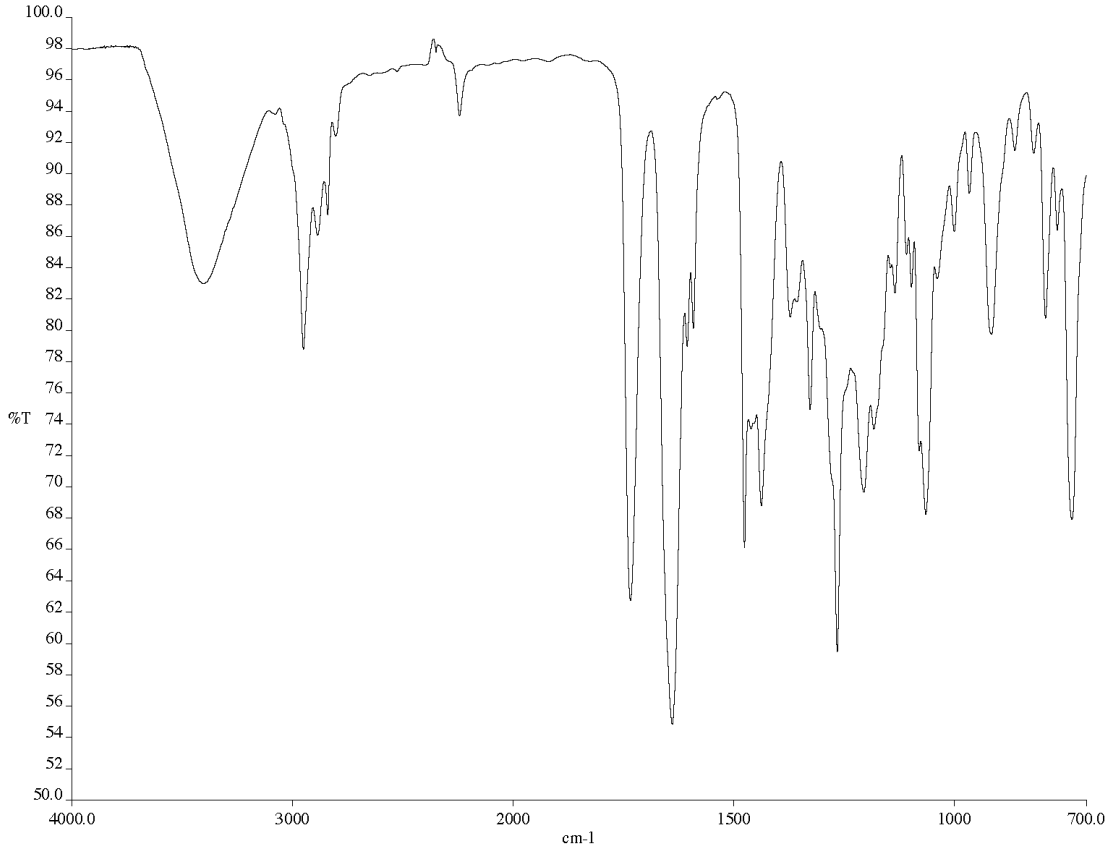

Figure 9.2. Infrared spectrum (thin film/NaCl) of *N*-methyl amine **21**.

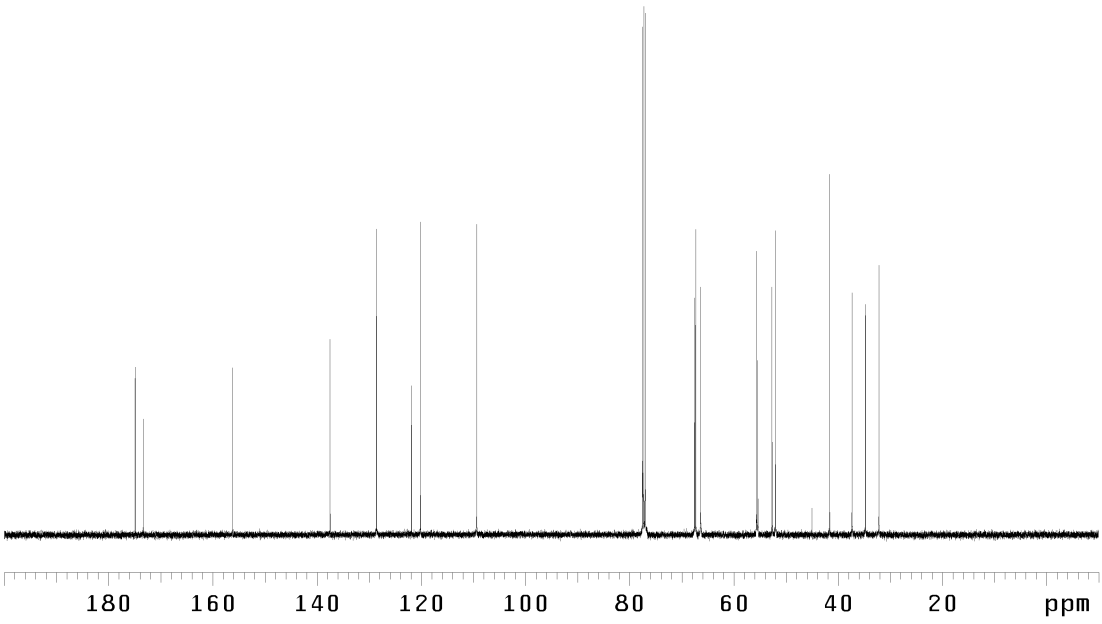

Figure 9.3. ^{13}C NMR (125 MHz, $CDCl_3$) of *N*-methyl amine **21**.

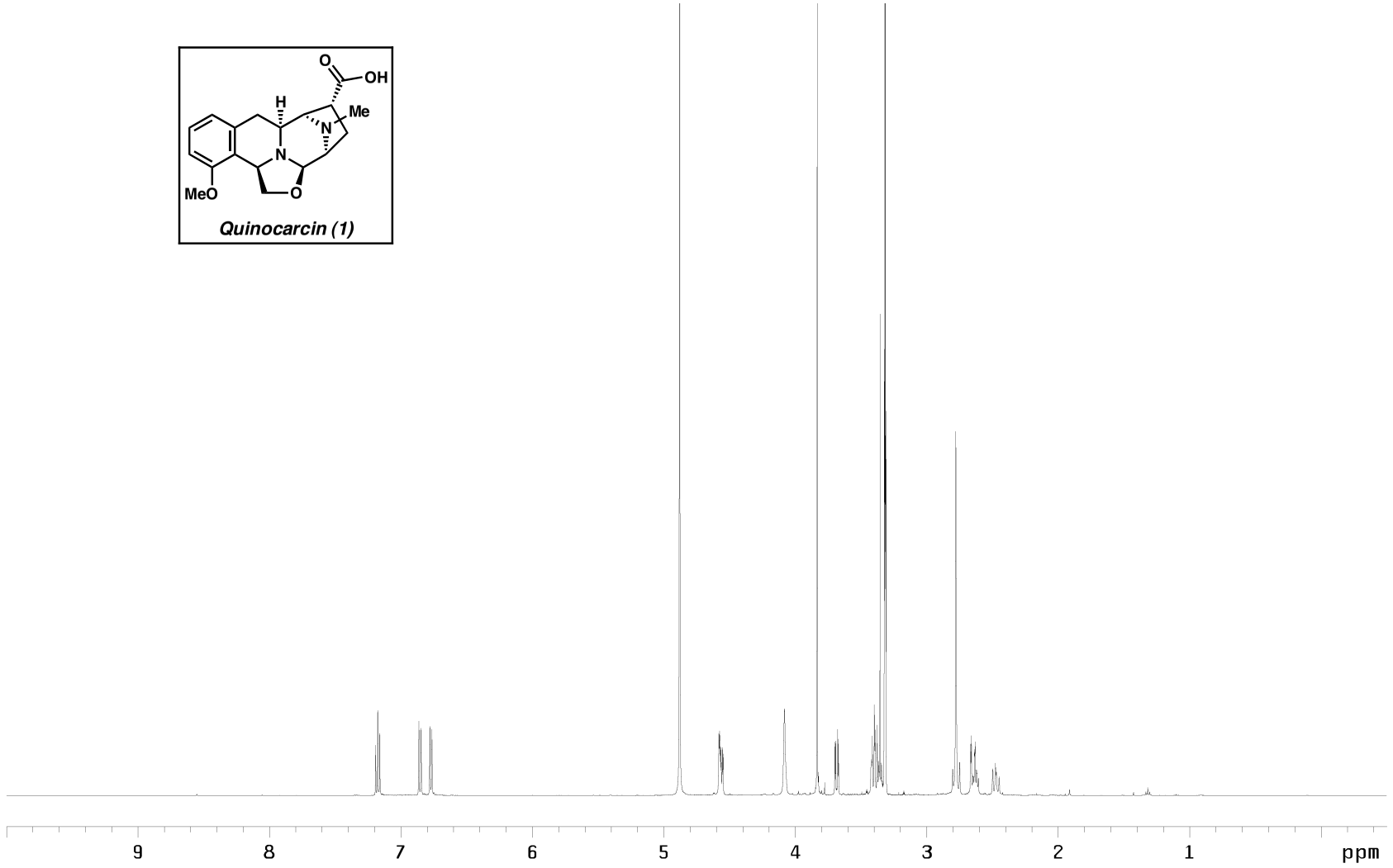

Figure 10.1. ^{1}H NMR (500 MHz, CD_3OD) of (–)-quinocarcin (**1**).

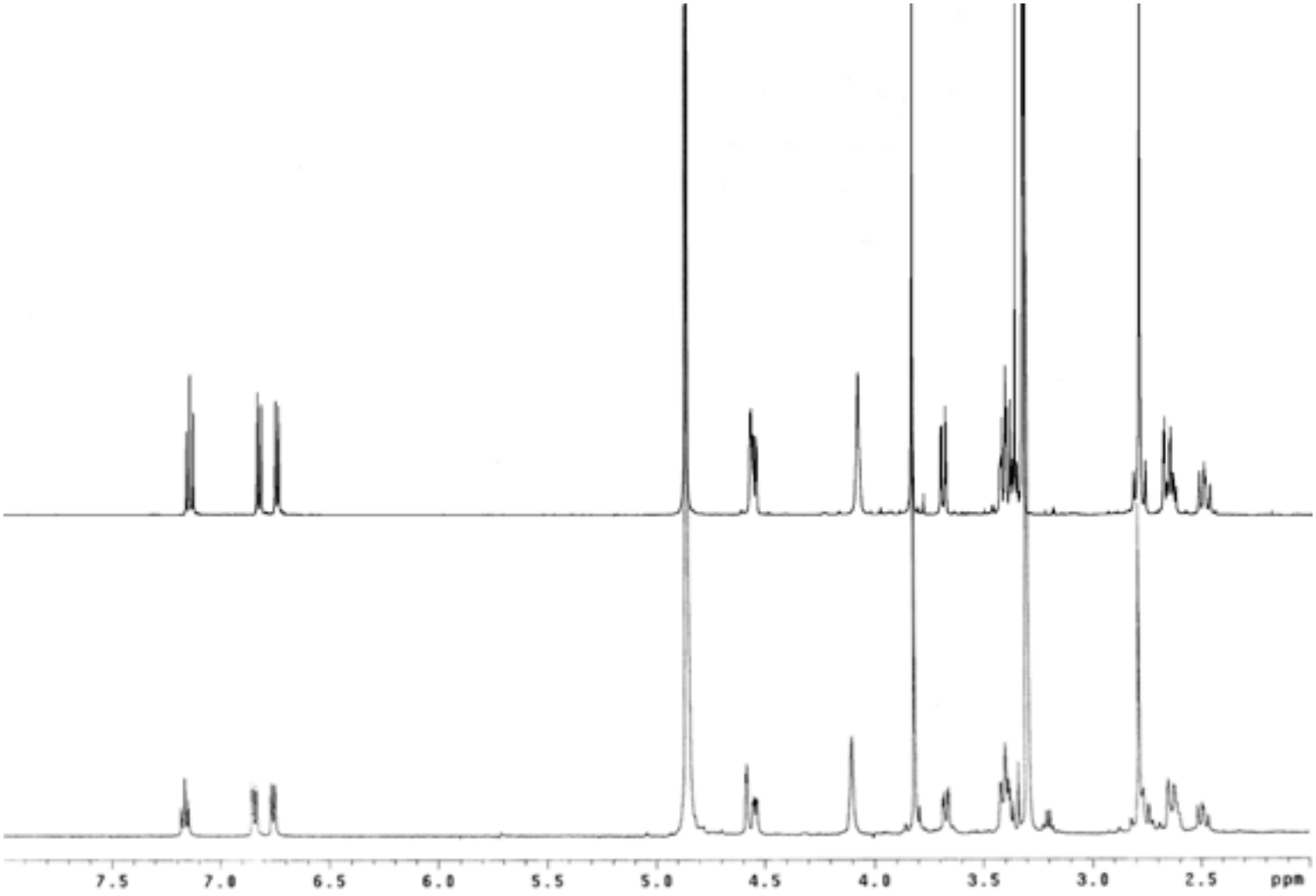

Figure 10.2. ^{1}H NMR comparison of synthetic (above) and natural (below) (–)-quinocarcin (**1**) (500 MHz, CD_3OD).

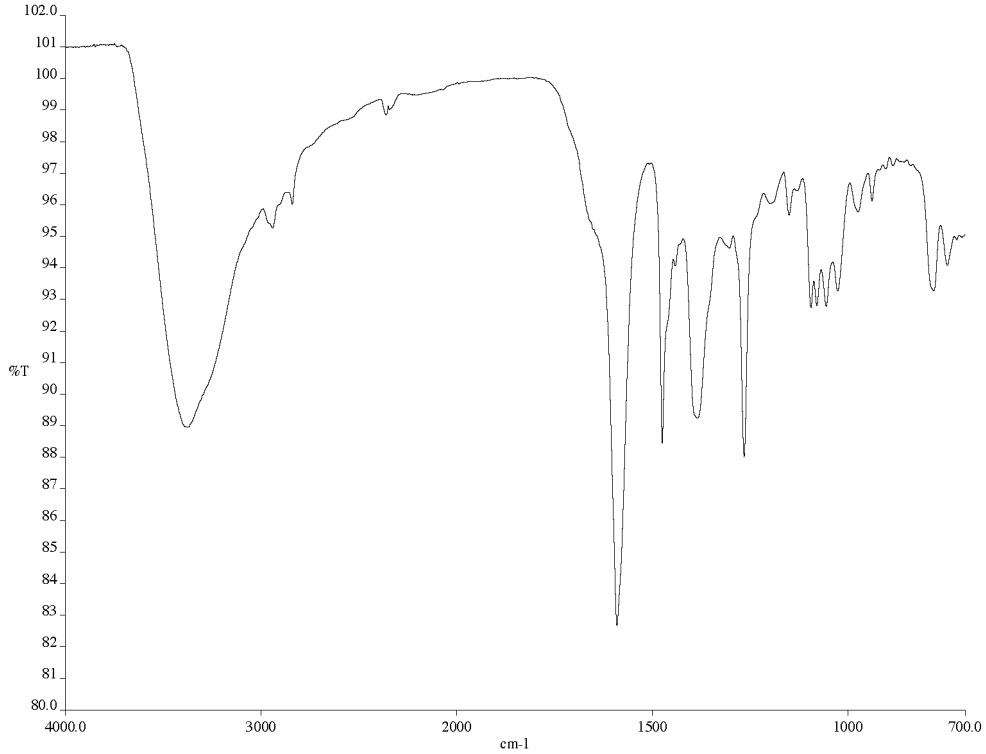

Figure 10.3. Infrared spectrum (thin film/NaCl) of quinocarcin (**1**).

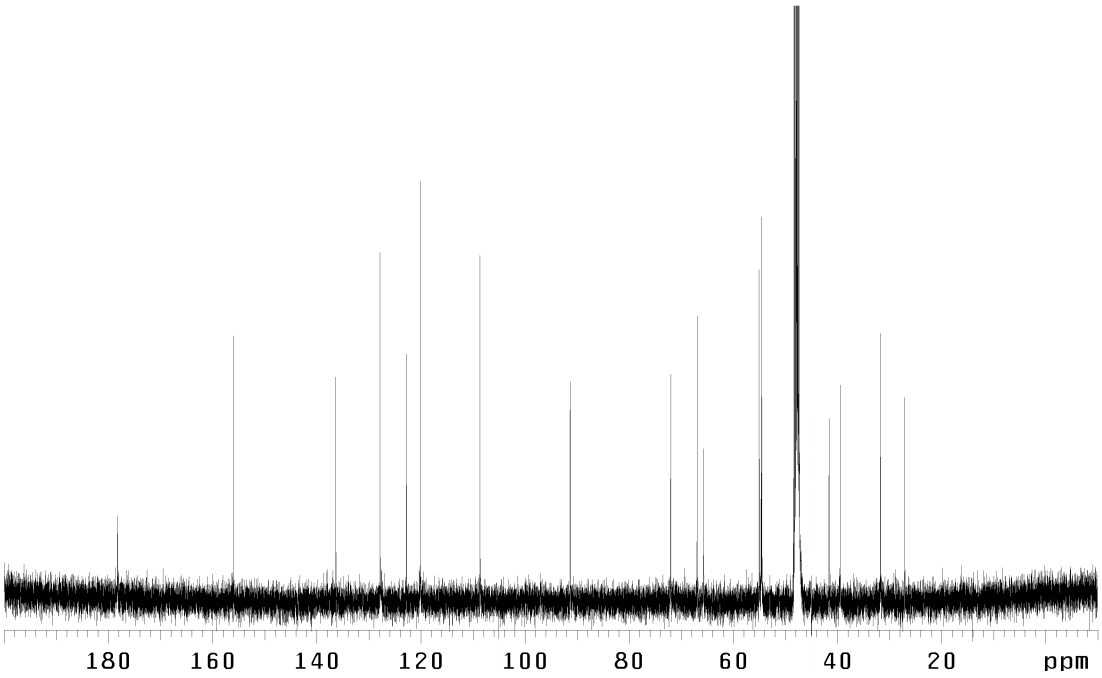

Figure 10.4. ^{13}C NMR (125 MHz, CD_3OD) of quinocarcin (**1**).

Supplemental Table 1. Comparison of ^{1}H NMR data for synthetic and natural quinocarcin.

Synthetic (ppm)	**Multiplicity**	**Natural[7] (ppm)**	**Multiplicity**
7.17	t	7.16	t
6.85	d	6.84	d
6.76	d	6.76	d
4.57	d	4.57	d
4.55	dd	4.54	dd
4.07	br s (2H)	4.08	br s (2H)
3.82	s (3H)	3.82	s (3H)
3.68	dd	3.67	dd
3.43–3.33	comp m (2H)	3.41–3.35	m (3H)
3.39	dd		
2.79–2.74	m	2.79–2.74	m
2.77	s (3H)	2.77	s (3H)
2.64	dd	2.64	dd
2.64–2.60	m	2.63–2.59	m
2.46	dd	2.47	dd

Supplemental Table 2. Comparison of ^{13}C NMR data for synthetic and natural quinocarcin.[8]

Synthetic (ppm)[a]	**Natural[7] (ppm)**[b]
179.5	174.9
157.2	157.2
137.6	137.0
129.1	129.1
124.0	123.8
121.3	121.3
110.0	110.0
92.6	92.1
73.2	72.3
68.2	67.9
66.9	66.8
56.3	56.3
55.9	55.9
55.7	53.4
42.8	40.6
40.7	40.3
32.9	32.5
28.3	27.3

[a] ^{13}C NMR data measured at 125 MHz in CD_3OD.
[b] ^{13}C NMR data measured at 100 MHz in CD_3OD.

References

(1) The fundamental reaction protocol for this dipolar cycloaddition is based on the pioneering work of Joule, see: (a) Kiss, M.; Russell-Maynard, J.; Joule, J. A. *Tetrahedron Lett*. **1987**, *28*, 2187–2190. (b) Allway, P. A.; Sutherland, J. K.; Joule, J. A. *Tetrahedron Lett*. **1990**, *31*, 4781–4782. (c) Yates, N. D.; Peters, D. A.; Allway, P. A.; Beddeoes, R. L.; Scopes, D. I. C.; Joule, J. A. *Heterocycles* **1995**, *40*, 331–347.

(2) The specific experimental procedure for this dipolar cycloaddition is based on the previous synthesis of (–)-lemonomycin completed in our labs, see: Ashley, E. R.; Cruz, E. G.; Stoltz, B. M. *J. Am. Chem. Soc*. **2003**, *125*, 15000–15001.

(3) ^{1}H NMR analysis shows this crude material to be an 11:1 mixture of diastereomeric cycloadducts. The major diastereomer (**S-1**) is purified via subsequent recrystallization.

(4) 3-Methoxy-2-(trimethylsilyl)phenyl triflate (**17**) is prepared in three steps from 3-methoxyphenol, see: Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Am. Chem. Soc*. **1999**, *121*, 5827–5828.

(5) The ratio of dihydroisoquinolines (i.e., **18a**:**18b**) was determined by ^{1}H NMR.

(6) The experimental procedure for the dissolving metal reduction is based on similar procedures carried out individually by Evans, Garner, and Zhu, see: (a) Evans, D. A.; Illig, C. R.; Saddler, J. C. *J. Am. Chem. Soc*. **1986**, *108*, 2478–2479. (b) Garner, P.; Ho, W. B.; Shin, H. *J. Am. Chem. Soc*. **1992**, *114*, 2767–2768. (c) Garner, P.; Ho, W. B.; Shin, H. *J. Am. Chem. Soc*. **1993**, *115*, 10742–10753. (d) Wu, Y.-C.; Liron, M.; Zhu, J. *J. Am. Chem. Soc*. **2008**, *130*, 7148–7152.

(7) Kwon, S.; Myers, A. G. *J. Am. Chem. Soc*. **2005**, *127*, 16796–16797.

(8) Fukuyama noted that the pH of the analytical solution had a dramatic effect on the chemical shifts in both the ^{1}H and ^{13}C NMR spectra of quinocarcin, accounting for observed differences between natural and synthetic spectra. See: Fukuyama, T.; Nunes, J. J. *J. Am. Chem. Soc*. **1988**, *110*, 5196–5198.