# CHAPTER THREE

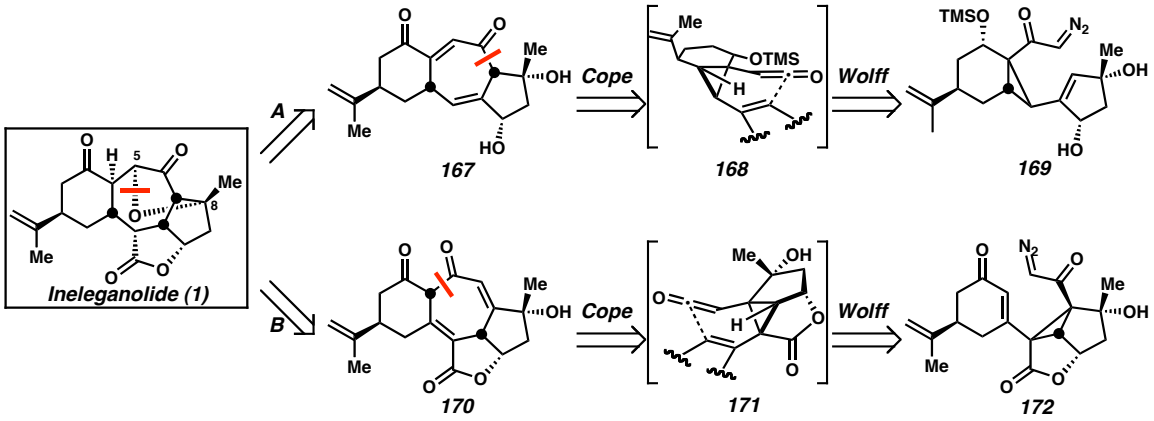
## Computational and Synthetic Validation of a Wolff/Cope Approach to the Synthesis of Ineleganolide

### 3.1 Retrosynthetic Analysis of Ineleganolide

Many of the most striking advances in synthesis today facilitate medium-ring synthesis, or enable asymmetric construction of a stereocenter. Ineleganolide is difficult to construct synthetically precisely because it centers around a cycloheptanone with six stereocenters, and contains an additional three stereocenters. We hoped to harness and develop cutting-edge technologies to surmount these synthetic challenges.

At the outset of this project, we planned to generate the seven-membered ring core of ineleganolide (**1**) through a Wolff/Cope rearrangement.[1,2] Initial retrosynthetic simplification of the C(8)–C(5) ether reveals two strategic Wolff/Cope disconnections. In the first case, retrosynthetic disconnection of the C(8)–C(5) ether would expose cycloheptadienone **167** (Scheme 3.1.1a), which would arise from a key Cope rearrangement of ketene **168**, formed in situ by Wolff rearrangement of α-diazoketone **169**. Alternatively, retrosynthetic simplification of the C(8)–C(5) ether would reveal cycloheptadienone **170**, which would be assembled from a Cope rearrangement of ketene **171**, generated in situ by Wolff rearrangement of α-diazoketone **172** (Scheme 3.1.1a).

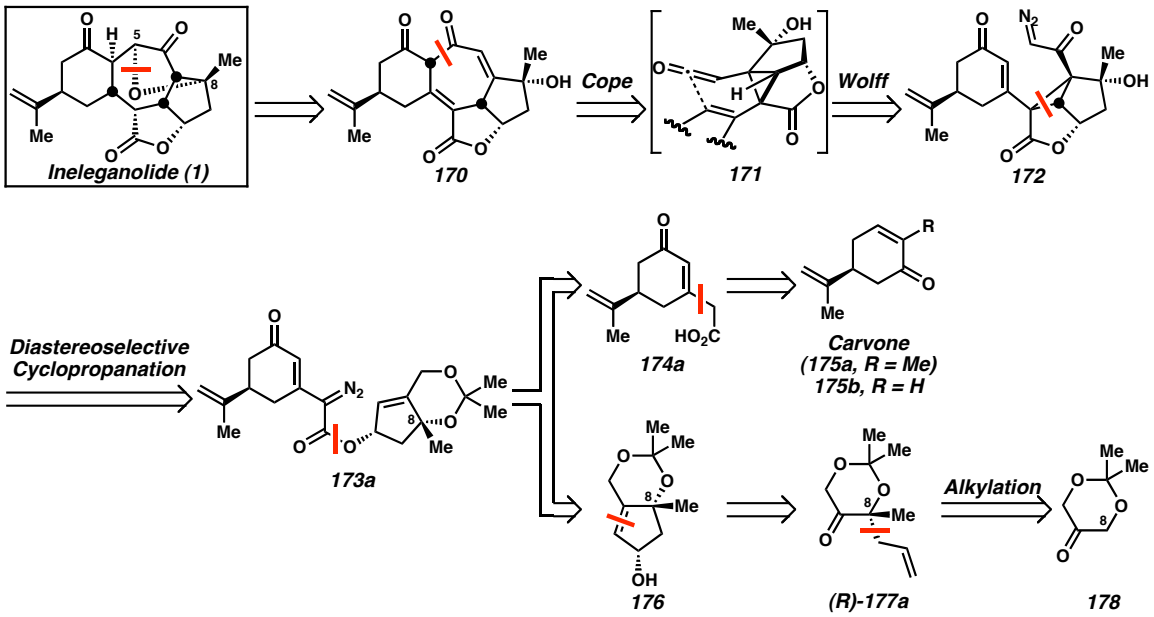
*Scheme 3.1.1* Our retrosynthetic analysis for ineleganolide




Our previous studies indicate that Wolff/Cope rearrangements are more efficient with [5–3]- than [6–3]-fused systems. While both routes are promising, we have only had time to pursue the latter of these opportunities. While the key Wolff/Cope rearrangement involves a [6–3]-fused backbone in path A, it proceeds from a [5–3]-fused system in path B. Thus, our efforts to date have focused on the latter of these opportunities.

Continuing with this analysis, cyclopropane **172** would arise diastereoselectively from vinyldiazoester **173**, which itself would be the product of coupling of carboxylic acid **174a** and alcohol **176** (Scheme 3.1.2). Carboxylic acid **174a** would be accessed from carvone (**175a**, via *des*-methyl carvone (**175b**)[3]). Embedded within alcohol **176** is a tertiary stereocenter at C(8), which we target through enantioselective alkylation starting from dioxanone **178**.

*Scheme 3.1.2* Retrosynthetic analysis for ineleganolide




## 3.2 Modeling the Key Wolff/Cope Rearrangement Computationally[i]

We have employed the detailed computational understanding[2] described in Chapter 2 to evaluate potential Wolff/Cope substrates for the synthesis of ineleganolide. In computational models of the formation of a simplified [6–7–5–5]-fused system **180a**, the gap between activation energies is restored to levels similar to those found for non-ketene Cope rearrangements at around 9.7 kcal/mol (Table 3.2.1). This gap is largely maintained with methyl substitution at the positions corresponding to C(8) and C(1) of ineleganolide (entries 2 and 3). Bis-substitution at the C(3) position with methyl, or methoxy substituents results in slightly smaller transition state energy differences, but maintains the transition state ordering (entries 4 and 5). Finally, the α,β-unsaturated

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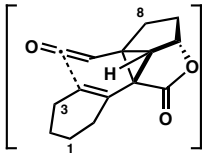
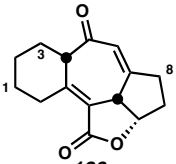
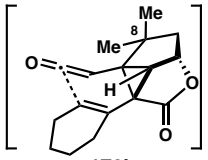
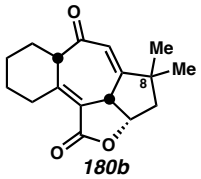
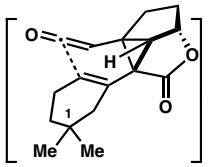
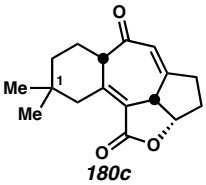
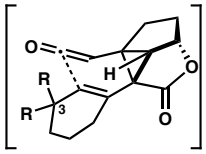
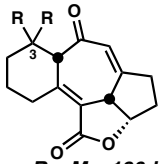
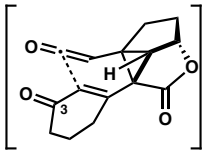
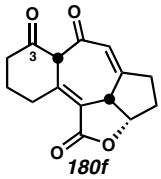
[i] These unpublished calculations were performed in collaboration with Julius Su, W. A. Goddard, III, and B. M. Stoltz.

substrate has an increased transition state energy gap of 17.5 kcal/mol (entry 6). The key Wolff/Cope rearrangement is predicted to work well with a broad range of desired substitution patterns.

*Table 3.2.1* Computational analysis of ketene-Cope rearrangement

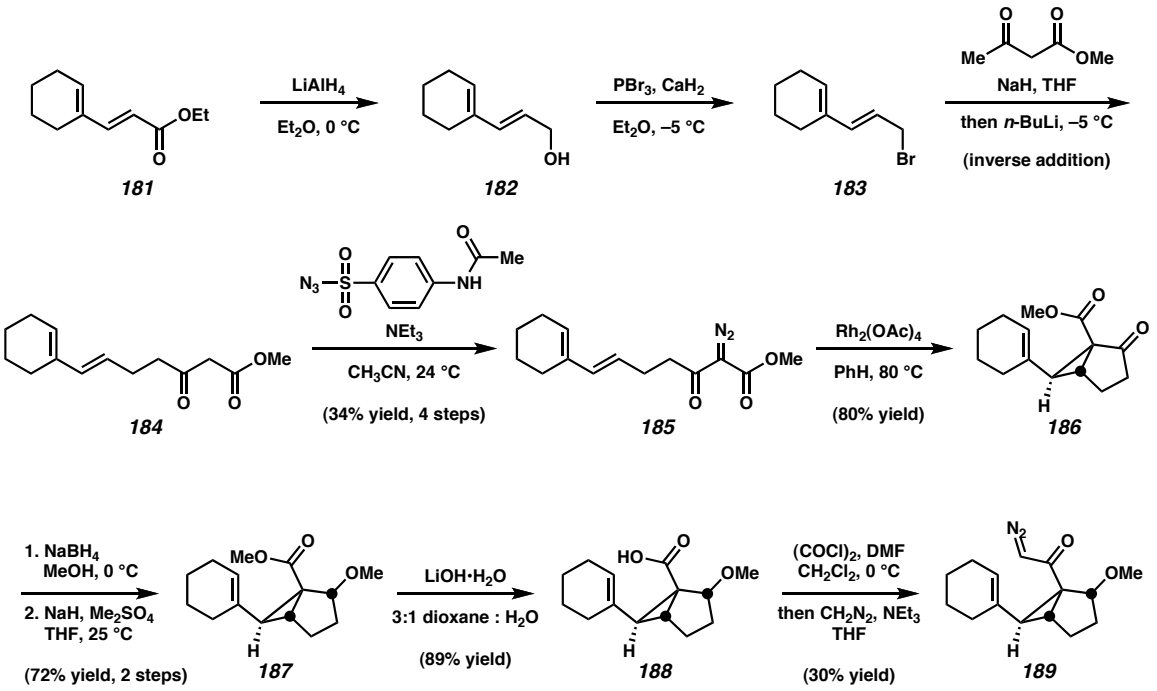
| entry | Wolff product | product | ΔΔG‡ (kcal/mol) |
|---|---|---|---|
| 1. |  |  | 9.7 |
| | *179a* | *180a* | |
| 2. |  |  | 9.7 |
| | *179b* | *180b* | |
| 3. |  |  | 9.4 |
| | *179c* | *180c* | |
| 4. |  |  | R = Me 6.9 |
| 5. | | | R = OMe 7.9 |
| | *R = Me, 179d* *R = OMe, 179e* | *R = Me, 180d* *R = OMe, 180e* | |
| 6. |  |  | 17.5 |
| | *179f* | *180f* | |

## 3.3 Modeling the Key Wolff/Cope Rearrangement Synthetically

At the outset of this project, the Wolff/Cope rearrangement had yet to provide a fused tricyclic framework. Although we were encouraged by the computational results, we sought an experimental model to provide a critical proof of principal for this key step. Thus we prepared model **189** from ester **181**[4] (Scheme 3.3.1). Ester **181** can be reduced with $LiAlH_4$ to form alcohol **182**, which is then converted to bromide **183**. Addition of the dianion of methyl malonate to bromide **183** provides ketoester **184**, which includes the majority of the carbon framework of the Wolff/Cope substrate. Subsequent diazotization forms α-diazoketoester **185**, and rhodium-mediated cyclopropanation

affords cyclopropane **186**. The methyl ether is installed through ketone reduction and alcohol methylation (e.g., **186** → **187**). Finally, methyl ester saponification, activation of the resulting acid as the acid chloride and diazomethane addition provide the requisite α-diazoketone (**189**), the targeted Wolff/Cope model substrate.

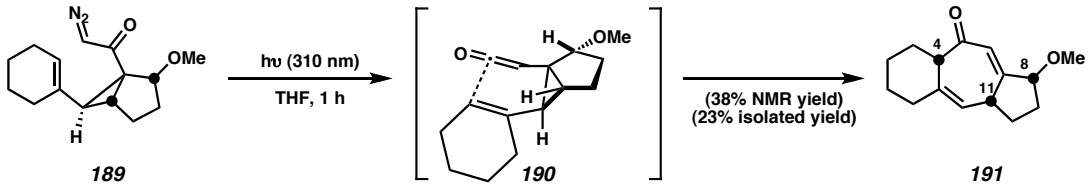
*Scheme 3.3.1* Preparation of a model for the key Wolff/Cope rearrangement




With the critical diazovinylcyclopropane **189** in hand, we began to investigate the key Wolff/Cope rearrangement (Scheme 3.3.2). To our delight, both sonochemical and photochemical conditions induce rearrangement of α-diazoketone **189** to [6–7–5] tricyclic framework **191** as a single diastereomer. The small scale photochemical reaction proceeds in 38% yield, with 23% yield of isolated product. Crude cycloheptadieneone **191** appears to be the sole product by $^{1}$H NMR analysis, but decomposes on exposure to air, silica gel, and organic bases. Due to this instability, the reaction has not been further optimized. The structure of cycloheptadieneone **191** has

been confirmed by extensive 1D and 2D $^{1}H$ and $^{13}C$ NMR analysis. Applying the norcembrane numbering system, NOESY analysis demonstrated coupling between H(4) and H(11), as well as H(11) and H(8), indicating that these protons are on the same face of the tricycle. Access to fused tricycle **191** lends credibility to our strategic approach to the asymmetric total synthesis of ineleganolide.

*Scheme 3.3.2* A successful model of the key Wolff/Cope rearrangement




## 3.4 Concluding Remarks

For the first time, we have demonstrated that the Wolff/Cope rearrangement is capable of delivering a fused tricyclic scaffold (e.g., **191**). Gaining synthetic access to fused tricycle **191** provides critical validation for our strategic approach to the synthesis of ineleganolide. This proof of principal is buttressed by computational calculations supporting the viability of a Wolff/Cope rearrangement to deliver a fused tetracyclic framework (e.g., **180**), a skeleton very similar to the one we expect to pursue in the total synthesis of ineleganolide (**1**).

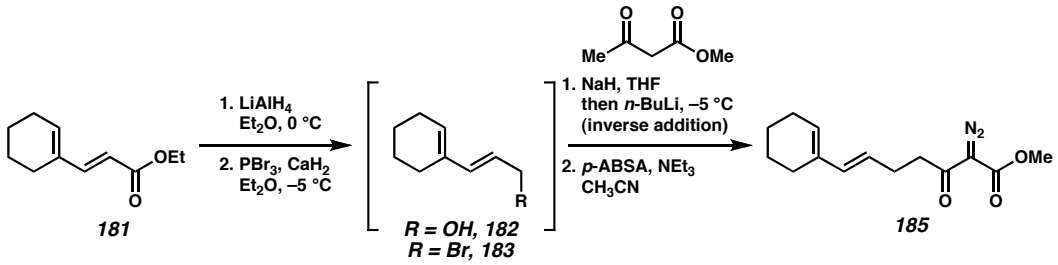
## 3.5 Experimental Section

### 3.5.1 Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Triethylamine ($NEt_3$) was distilled from sodium hydride immediately prior to use. Other commercial 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, anisaldehyde, or CAM staining. Florisil® (100–200 mesh) and ICN Silica gel (particle size 0.032–0.063 mm) were used for flash chromatography. Photochemical irradiation was performed in septum-sealed quartz tubes in a Luzchem® Photochemical reactor. High pressure liquid chromatography was completed using a Waters HPLC with two normal phase Waters 25 mm x 100 mm porasil columns (pore size = 15–25 μm) using a flow rate of 20 mL/min and Hexanes with a ramp of 0.25% EtOAc/min with visualization at 254 nm. $^{1}$H and $^{13}$C NMR spectra were collected on a Varian Mercury 300 (at 300 MHz and 75 MHz, respectively), on Varian Mercury 500 (at 500 MHz and 125 MHz, respectively), or on a Varian Mercury 600 (at 600 MHz, $^{1}$H only), 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). Spin multiplicity is described in short-hand: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. 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 wavenumbers ($cm^{-1}$). High resolution mass spectra were obtained from the Caltech Mass Spectral Facility. All reported procedures are modifications of protocols reported by Sarpong and Stoltz.[1]

### 3.5.2 Preparative Procedures



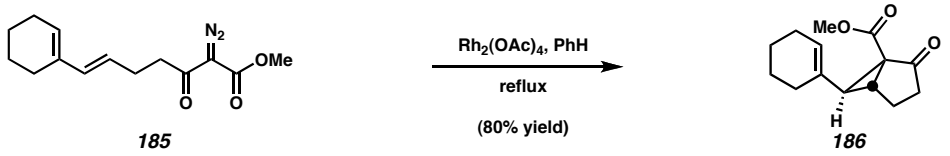

**α-Diazo-β-Keto Ester 185.** To a disperson of $LiAlH_4$ (1.247 g, 30.2 mmol) in $Et_2O$ (70 mL) at 0 ºC was added ester **181**[4] (7.900 g, 43.8 mmol) in $Et_2O$ (18 mL) over 22 minutes. After one hour, a Fieser[5] quench was performed: to the grey dispersion was added Celite, followed by $H_2O$ (1.2 mL, dropwise). After ten minutes, 15% NaOH (1.2 mL) was added, followed 10 minutes later by dropwise addition of $H_2O$ (3.6 mL). The mixture was allowed to warm to room temperature. The white precipitate was filtered and rinsed with $Et_2O$ (2 x 25 mL). The combined organics were dried over $Mg_2SO_4$, refiltered, and concentrated in vacuo to a yellow oil (5.398 g, 89% crude alcohol **182**).

To a 500 mL flask with a dispersion of $CaH_2$ (2.776 g, 65.7 mmol) in $Et_2O$ (70 mL) was added dropwise crude alcohol **182** (5.327 g) in $Et_2O$ (18 mL). The dispersion was wrapped in aluminum-foil and cooled to –5 ºC (ice-brine bath). To the flask was added $PBr_3$ (1.54 mL, 16.2 mmol) in $Et_2O$ (4.65 mL) over 3 minutes. After 70 minutes, the flask was allowed to warm to ambient temperature. After 30 minutes, the flask was then recooled to –5 ºC, and dry MeOH (0.15 mL) was added. After 15 minutes, the foil was removed. The mixture was then filtered through celite and partially concentrated in vacuo to a brown oil (containing bromide **183)**, which was diluted with THF (15 mL) and used without further purification.

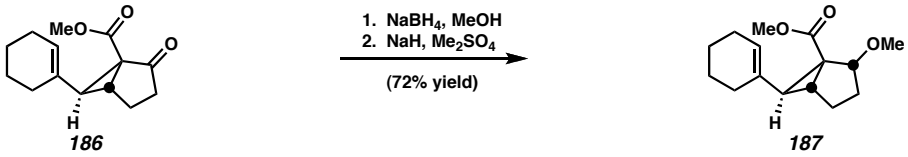
Methyl acetoacetate (5.7 mL, 53 mmol) was added dropwise to a dispersion of NaH (2.751 g, 68.8 mmol) in THF (100 mL) at ambient temperature, which generated a yellow solution. After 30 minutes, the flask was cooled to –5 ºC (ice-brine bath), and *n*-BuLi (2.4 M, 27 mL, 65 mmol) was carefully added in a stream down the side of the flask over less than a minute, forming a deep red solution. Immediately, crude bromide **183** (in 18 mL THF) was added dropwise over a minute, resulting in an orange solution. Stirring was continuted for 30 minutes, at which time the reaction was quenched by slow addition of saturated aq $NH_4Cl$ (65 mL), forming two yellow layers. The mixture was allowed to warm to room temperature. The layers were separated, and the aqueous layer was further washed with $Et_2O$ (5 x 30 mL). The combined organics were dried over $Na_2SO_4$, decanted and concentrated in vacuo to a yellow oil, which was purified by flash chromatography (1:6 EtOAc:hexanes eluent) to furnish ketoester **184** (4.84 g, 46.8% yield) as a yellow oil.

To a pale yellow solution of acetoacetate **184** (4.84 g) in $CH_3CN$ (100 mL) was added dropwise $NEt_3$ (5.7 mL, 41 mmol), and *para*-acetamidobenzenesulfonyl azide, *p*ABSA (6.397 g, 26.6 mmol). A white precipitate formed and stirring was continued for 30 minutes. The reaction was diluted with $Et_2O$ (50 mL), and filtered through celite, washing with $Et_2O$ (200 mL). The filtrate was concentrated to a yellow paste and purified by flash chromatography (1:6 EtOAc:hexanes eluent) to furnish α-diazo-β-keto ester **185** (5.38g, 34%) as a yellow oil. $R_f$ 0.47 (1:3 EtOAc:hexanes, UV(254nm)); $^1$H NMR (300 MHz, $CDCl_3$) δ 6.06 (d, J = 15.7, 1 H), 5.64 (s, 1 H), 5.54 (m, 1 H), 3.83 (s, 3 H), 2.94 (t, J = 7.5, 3 H), 2.41 (dd, J = 72, 14.6, 2H), 2.09 (s, 4H), 1.6 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 192.3, 162.0, 135.6, 134.7, 128.2, 124.5, 53.4, 40.4, 27.6, 26.0, 24.7,

22.8, 22.7; IR (neat) 2924, 2130, 1722, 1659, 1435, 1309, 1207 $cm^{-1}$; HRMS ($EI^+$) calc'd for $[C_{14}H_{18}N_2O_3]^+$: *m/z* 262.1318, found 262.1323.



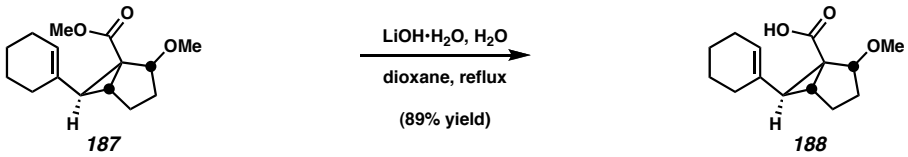

**Bicyclo[3.1.0] hexane 186.** A flask containing a solution of α-diazo-β-keto ester **185** (1.60 g, 6.10 mmol) and $Rh_2(OAc)_4$ (3 mg, 0.006 mmol) in benzene (245 mL) was heated and held at reflux (oil bath temperature of 93 ºC) for 12.3 hours. The green/yellow solution was removed from heat and concentrated in vacuo to a green oil (1.71 g). The oil was purified by flash chromatography (1:2 EtOAc:hexanes eluent) to yield cyclopropane **186** (1.15 g, 80% yield) as a white solid. $R_f$ 0.19 (1:3 EtOAc:hexanes, UV(254nm)); $^1$H NMR (300 MHz, $C_6D_6$) δ 5.42 (s, 1H), 3.41 (s, 1H), 2.52 (t, J = 5.5, 3H), 1.3–2.0 (m, 12H), 1.2 (m, 1H); $^{13}$C NMR (75 MHz, $C_6D_6$) δ 205.2, 166.3, 131.2, 125.7, 52.0, 47.0, 39.3, 33.5, 29.6, 29.4, 25.9, 23.5, 23.0, 21.2; IR (KBr) 2928, 2835, 1729, 1711, 1437, 1247$cm^{-1}$; HRMS ($EI^+$) calc'd for $[C_{14}H_{18}O_3]^+$: *m/z* 234.1256, found 234.1254.




**Methyl ether 187.** To a cooled solution (0 ºC) of cyclopropane **186** (0.466 g, 1.99 mmol) in bench methanol (28 mL, 0.07 M) was added sodium borohydride (0.105 g, 2.98 mmol), and gas evolution was observed. The reaction was stirred for 1 hour, and then quenched with 1N HCl (28 mL). The mixture was stirred while warming to room temperature over 2.5 hours. The reaction was extracted with ethyl acetate (250 mL), the

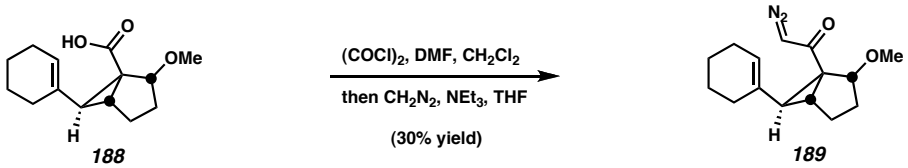
combined organics were washed with water (10 mL), followed by brine (20 mL), and then dried over sodium sulfate, filtered, and concentrated in vacuo to a yellow oil (0.563 g, crude alcohol), which was used without further purification.

To a 100 mL flask with a dispersion of NaH (60% dispersion in mineral oil, 0.796 g, 19.9 mmol) in THF (10 mL) was added dropwise the crude alcohol (yellow oil) in THF (10 mL), followed by dimethyl sulfate (0.38 mL). After 21 hours, the reaction was quenched by dropwise addition of saturated aq $NaHCO_3$ (15 mL). The aqueous layer was extracted with $Et_2O$ (3 x 10 mL), and the combined organics were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo to a yellow oil (0.783 g). The concentrate was purified by flash chromatography (6:1 Hexanes:EtOAc eluent) to yield methyl ether **187** (0.338 g, 72.5%) as a colorless oil. $R_f$ 0.64 (1:1 EtOAc:hexanes); $^1$H NMR (600 MHz, $C_6D_6$) δ 5.66 (t, J = 1.6 Hz, 1H), 4.50 (t, J = 7.5 Hz, 1H), 3.40 (s, 3H), 3.36 (s, 3H), 2.18–2.22 (m, 2H), 1.90–2.12 (m, 4H), 1.82 (m, 1H), 1.47–1.57 (m, 6H), 1.26 (m, 1H); $^{13}$C NMR (75 MHz, $C_6D_6$) δ 173.1, 132.7, 124.7, 82.6, 57.6, 51.6, 40.8, 35.1, 33.5, 30.0, 29.5, 25.5, 25.3, 23.1, 22.7; IR (neat) 2929, 2833, 1714, 1436, 1337, 1105 cm$^{-1}$; HRMS-EI calc'd for $[C_{15}H_{22}O_3]^+$: *m/z* 250.1569, found 250.1561.




**Carboxylic Acid 188.** A mixture of methyl ester **187** (0.124 g, 0.50 mmol), $H_2O$ (2.5 mL), bench dioxane (7.6 mL) and LiOH•$H_2O$ (0.145 g, 3.47 mmol) was warmed and held at reflux (in a 95 ºC oil bath). After 12 hours, the mixture was cooled to room temperature, diluted with $Et_2O$ (2 mL), and poured over 1 N HCl (7 mL). The aqueous

layer was extracted with $Et_2O$ (3 x 10 mL), and the combined organics were washed with brine (5 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuo to a yellow solid (0.156 g). The solid was purified by flash chromatography (1:2 EtOAc:hexanes eluent) to yield acid **188** (0.104 g, 89%) as a white solid. $R_f$ 0.58 (EtOAc, CAM); $^1$H NMR (300 MHz, $C_6D_6$) δ 5.65 (s, 1 H), 4.42 (t, J = 7, 1 H), 3.31 (s, 3H), 2.22 (m, 2H), 1.8–2.2 (m, 4H), 1.7 (m, 1 H), 1.4–1.6 (m, 5H), 1.2 (m, 2H); $^{13}$C NMR (75 MHz, $C_6D_6$) δ 132.9, 125.7, 82.5, 57.7, 41.5, 36.7, 35.2, 30.6, 30.0, 26.0, 25.6, 23.7, 23.2; IR (KBr) 2935, 2832, 2608, 1681, 1438, 1336, 1286, 1107 cm$^{-1}$; HRMS-EI calc'd for $[C_{14}H_{20}O_3]^+$: *m/z* 236.1413, found 236.1408.




**α-Diazoketone 189.** To a clear solution of acid (35 mg, 0.25 mmol) in $CH_2Cl_2$ (1.1 mL, 0.13 M) at 0 ºC was added $(COCl)_2$ (16 μL, 0.18 mmol, 1.2 equiv), followed by DMF (0.00013 M in $CH_2Cl_2$, 23 μL, 0.0003 mmol). After 6.5 hours, the reaction was judged complete by TLC (the acid chloride was added to a small amount of MeOH, and that solution was compared with starting material). The acid chloride was concentrated under reduced pressure to a yellow oil.

**Caution!** Diazomethane is potentially explosive and hazardous, and should be handled in a fume hood. To a solution of $CH_2N_2$ (Na°-dried over 8 min., 0.25 M in $Et_2O$, 3.5 mL, 0.88 mmol) at –5 ºC was added acid chloride in THF (1.1 mL), followed by $NEt_3$ (62 μL, 0.44 mmol, 3.0 equiv). After an additional 12 hours, the reaction was quenched by addition of saturated aq $NaHCO_3$ (2 mL). The two yellow phases were separated, and

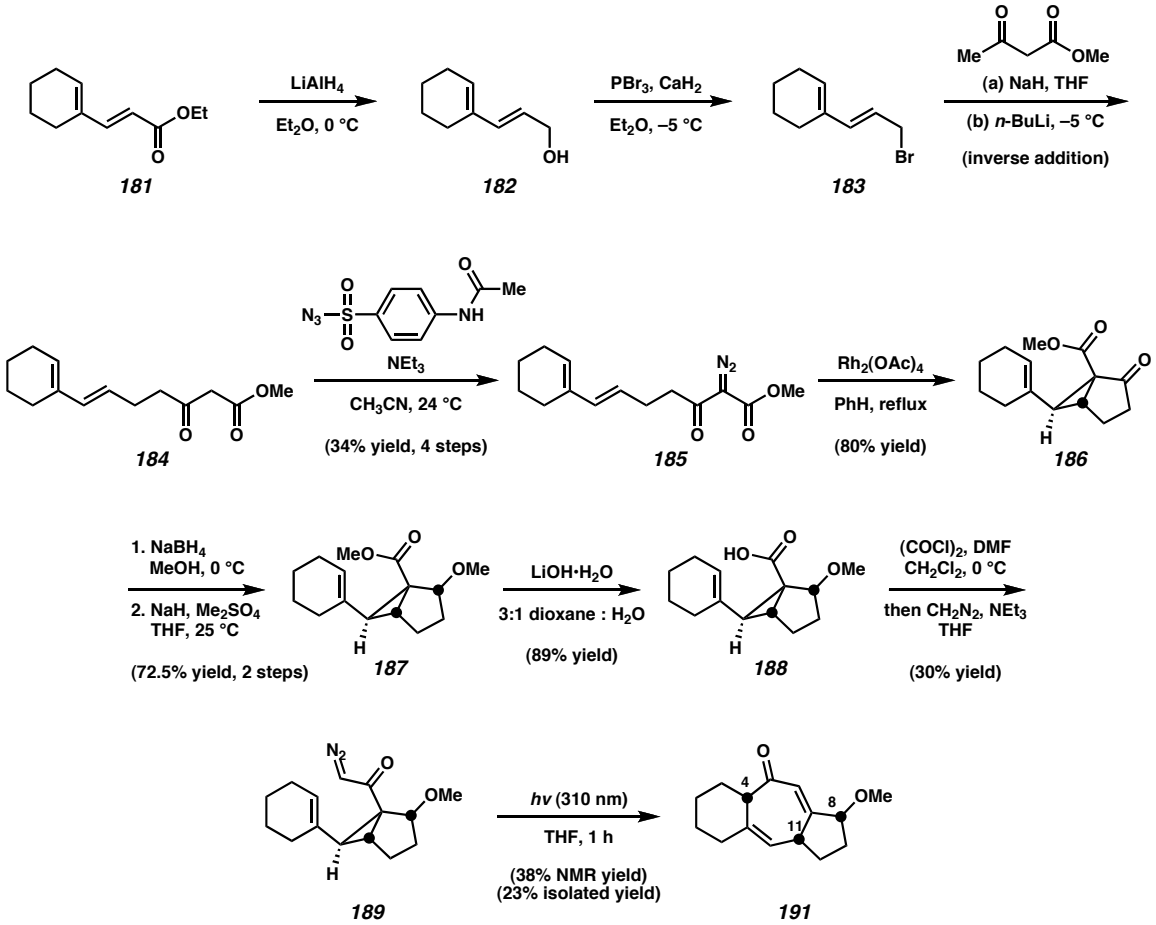
the aqueous layer was extracted with $Et_2O$ 6 x 7 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo to a yellow oil (80 mg), which was purified by flash chromatography (1:4 EtOAc:hexanes eluent) to yield α-diazoketone **189** (13 mg, 30% yield) as a yellow oil. $R_f$ 0.24 (1:8 EtOAc:hexanes, UV/Vis); $^1$H NMR (300 MHz, $C_6D_6$) δ 5.63 (m, 1H), 5.26 (s, 1 H), 3.99 (t, J = 7.7, 1H), 3.08 (s, 1H), 2.26 (m, 1H), 1.9–2.1 (m, 5 H), 1.66 (m, 1 H), 1.4–1.6 (m, 6H), 1.4 (m, 1H); $^{13}$C NMR (75 MHz, $C_6D_6$) δ 132.7, 125.8, 82.7, 57.1, 48.2, 35.7, 30.4, 30.3, 28.5, 26.0, 25.1, 23.6, 23.1; IR (neat) 3111, 2931, 2879, 2833, 2101, 1724, 1622, 1448, 1380, 1351, 1325, 1202, 1153, 1097 cm$^{-1}$; HRMS-EI calc'd for $[C_{15}H_{20}N_2O_2]^+$: *m/z* 260.1525, found 260.1518.


***189*** ***191***

**[6-7-5] Fused Tricycle 191.** In a tightly capped 10 mL quartz test-tube, a yellow solution of α-diazoketone **189** (19.5 mg, 0.0667 mmol) in THF (6.7 mL, 0.010 M) was irradiated (310 nm) for 1 hour. The solution was concentrated under reduced pressure to a yellow oil (19.2 mg), dissolved in $C_6D_6$ (0.1 mL) and transferred to an NMR tube. A solution of 1,4-bis(trimethylsilyl)benzene (0.1 M in $C_6D_6$, 31 μL, 0.0031 mmol) was added. The solution was further diluted with $C_6D_6$ (to 0.7 mL). $^1$H NMR showed 38% yield of the desired tricycle **43** based on the internal standard 1,4-bis(trimethylsilyl)benzene. The tricycle was dissolved in 20% EtOAc in hexanes and purified by high pressure liquid chromatography (0 to 15% EtOAc in hexanes over 60 minutes) to yield tricycle **191** (3.6 mg, 23% yield) as a clear oil. $R_f$ 0.33 (20:1

PhH:acetone; UV/Vis); $^{1}$H NMR (500 MHz, $C_6D_6$) δ 6.14 (dd, J = 2.93, 1 H), 5.40 (s, 1H), 3.60 (m, 1H), 3.50 (m, 1H), 3.17 (m, 1H), 2.98 (s, 3H), 2.46 (ddt, *J*=13.65, 5.86, 4.85, 1H), 2.05 (m, 1H), 1,96 (m, 1H), 1.62–1.81 (m, 4H), 1.49 (m, 2 H), 1.31–1.42 (m, 2H), 1.20 (m, 1H); $^{13}$C NMR (75 MHz, $C_6D_6$) δ 195.1, 164.6, 138.8, 131.1, 127.0, 84.4, 56.5, 52.1, 43.2, 32,0, 31.0, 30.0, 24.3, 23.8, 22.6; IR (neat) 2930.9, 2865.7, 2822.44, 1669.0, 1450.8, 1436.2, 1117,6, 1090.5, 842.9 $cm^{-1}$; HRMS ($EI^+$) calc'd for $[C_{15}H_{20}O_2]^+$: *m/z* 242.1463, found 242.1469.

### 3.6 Summary of Model System Synthesis



### 3.7 Notes and References

(1) Sarpong, R.; Su, J. T.; Stoltz, B. M. The Development of a Facile Tandem Wolff/Cope Rearrangement for the Synthesis of Fused Carbocyclic Skeletons *J. Am. Chem. Soc.* **2003**, *125*, 13624–13625.

(2) Su, J. T.; Sarpong, R.; Stoltz, B. M.; Goddard, W. A. III. Substituent Effects and Nearly Degenerate Transition States: Rational Design of Substrates for the Tandem Wolff/Cope Reaction. *J. Am. Chem. Soc.* **2004**, *126*, 24–25.

(3) Chen, J.; Marx, J. N. A Stereoselective Total Synthesis of (–)-Rishitin. *Tetrahedron Lett.* **1997**, *38*, 1889–1892.

(4) Piva, O.; Comesse, S. Tandem Michael–Wittig–Horner Reaction: One-Pot Synthesis of δ-Substituted α,β-Unsaturated Carboxylic Acid Derivatives — Application to a Concise Synthesis of (*Z*)- and (*E*)-Ochtoden-1-al. *Eur. J. Org. Chem.* **2000**, *2000*, 2417–2424.

(5) Fieser, L. F.; Fieser, M. Reagents for Organic Synthesis, John Wiley and Sons, Inc., New York **1967**, 584–595.

# APPENDIX THREE

## Spectra of Compounds Relevant to Chapter Three

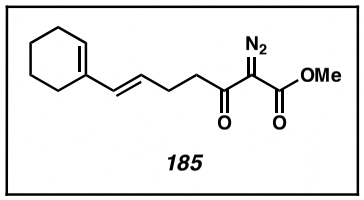






*Figure A3.1* $^{1}$H NMR (300 MHz, $CDCl_3$) of compound **185**

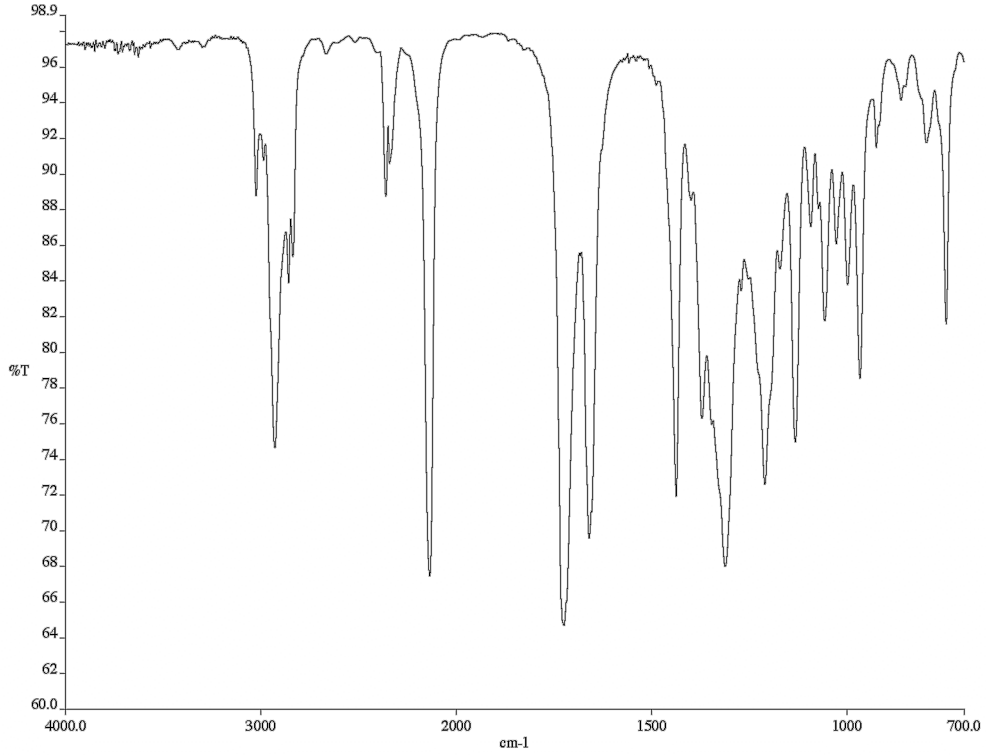



*Figure A3.2* Infrared spectrum (thin film/NaCl) of compound **185**

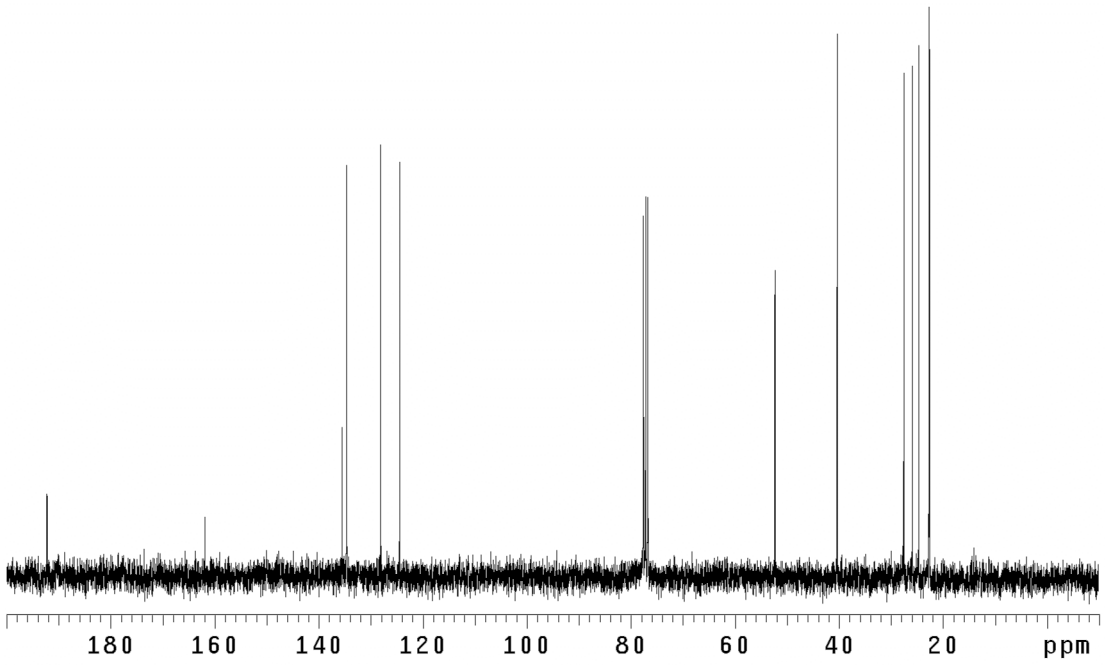



*Figure A3.3* $^{13}C$ NMR (75 MHz, $CDCl_3$) of compound **185**

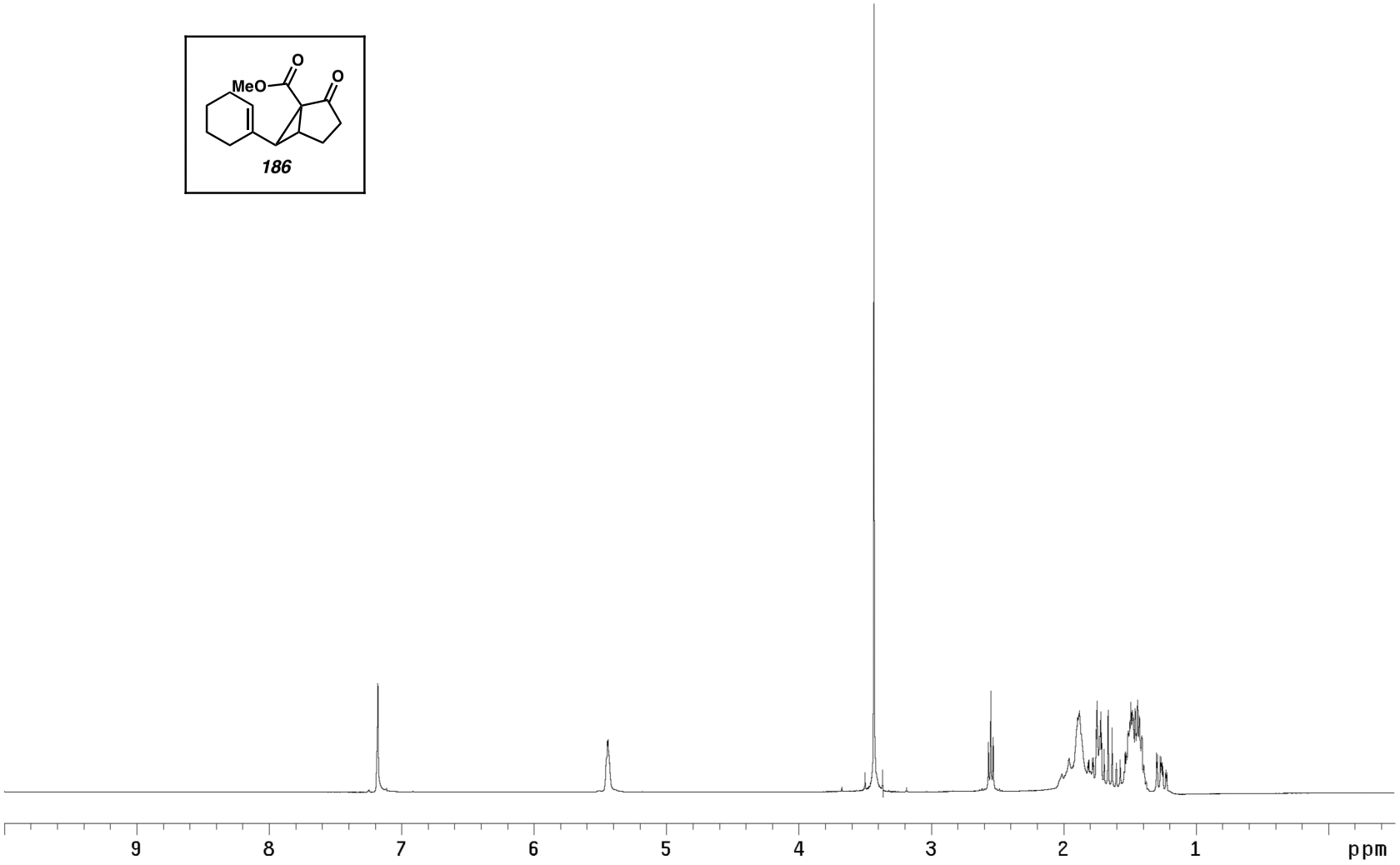



*Figure A3.4* $^{1}$H NMR (300 MHz, $C_6D_6$) of compound **186**

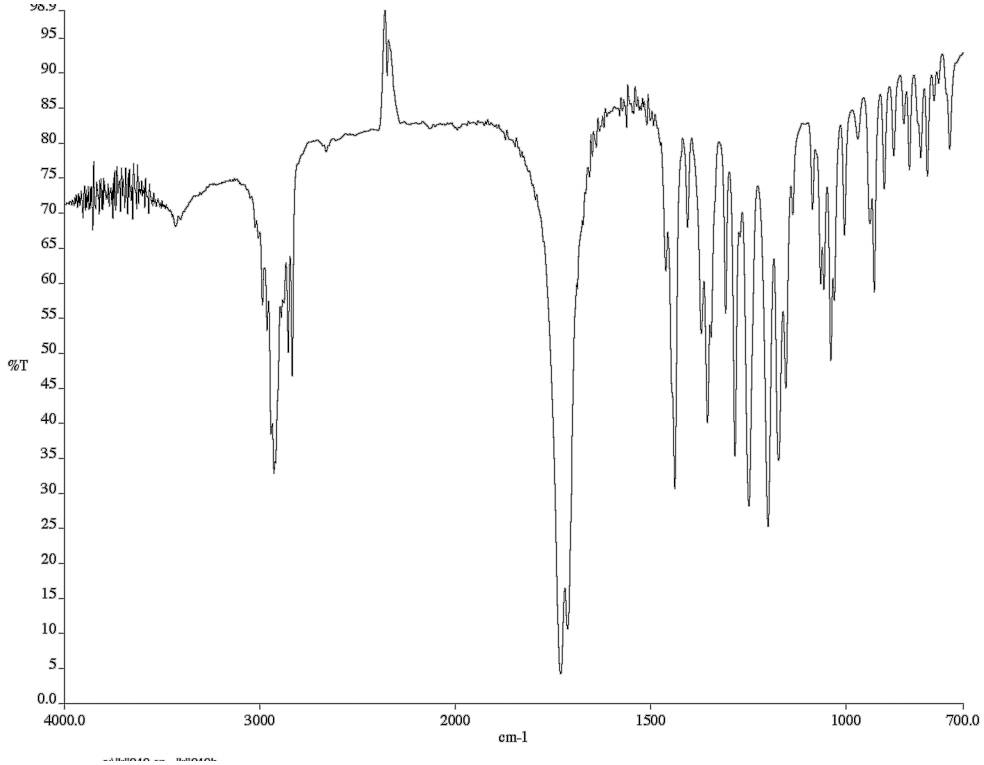



*Figure A3.5* Infrared spectrum (KBr pellet) of compound **186**

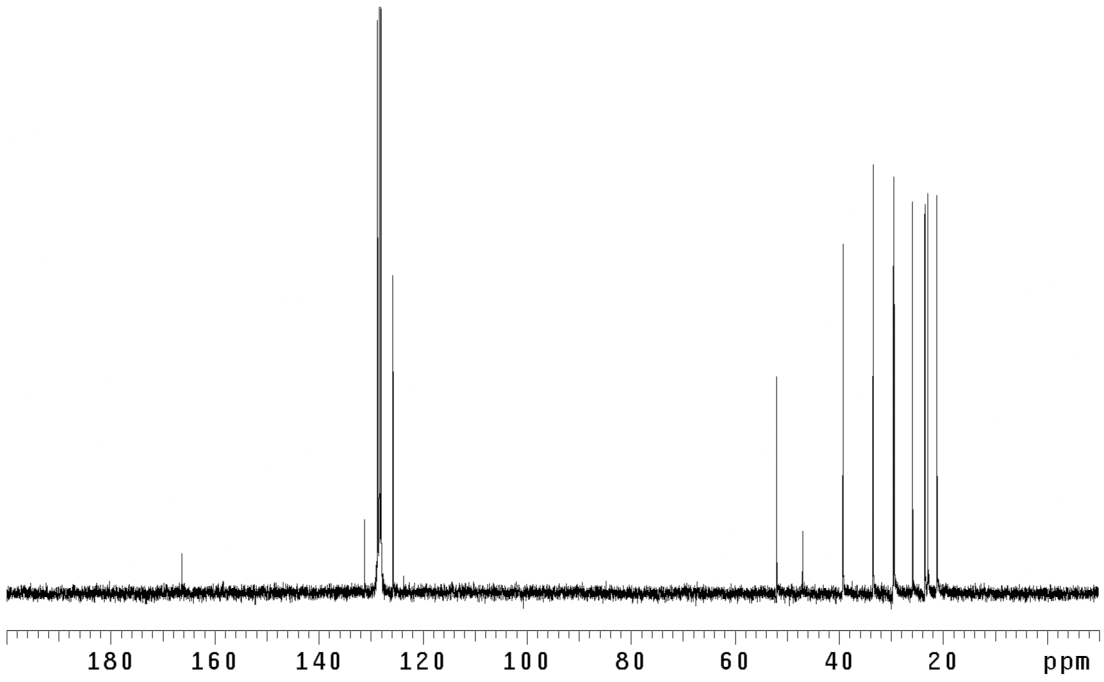



*Figure A3.6* $^{13}C$ NMR (75 MHz, $C_6D_6$) of compound **186**

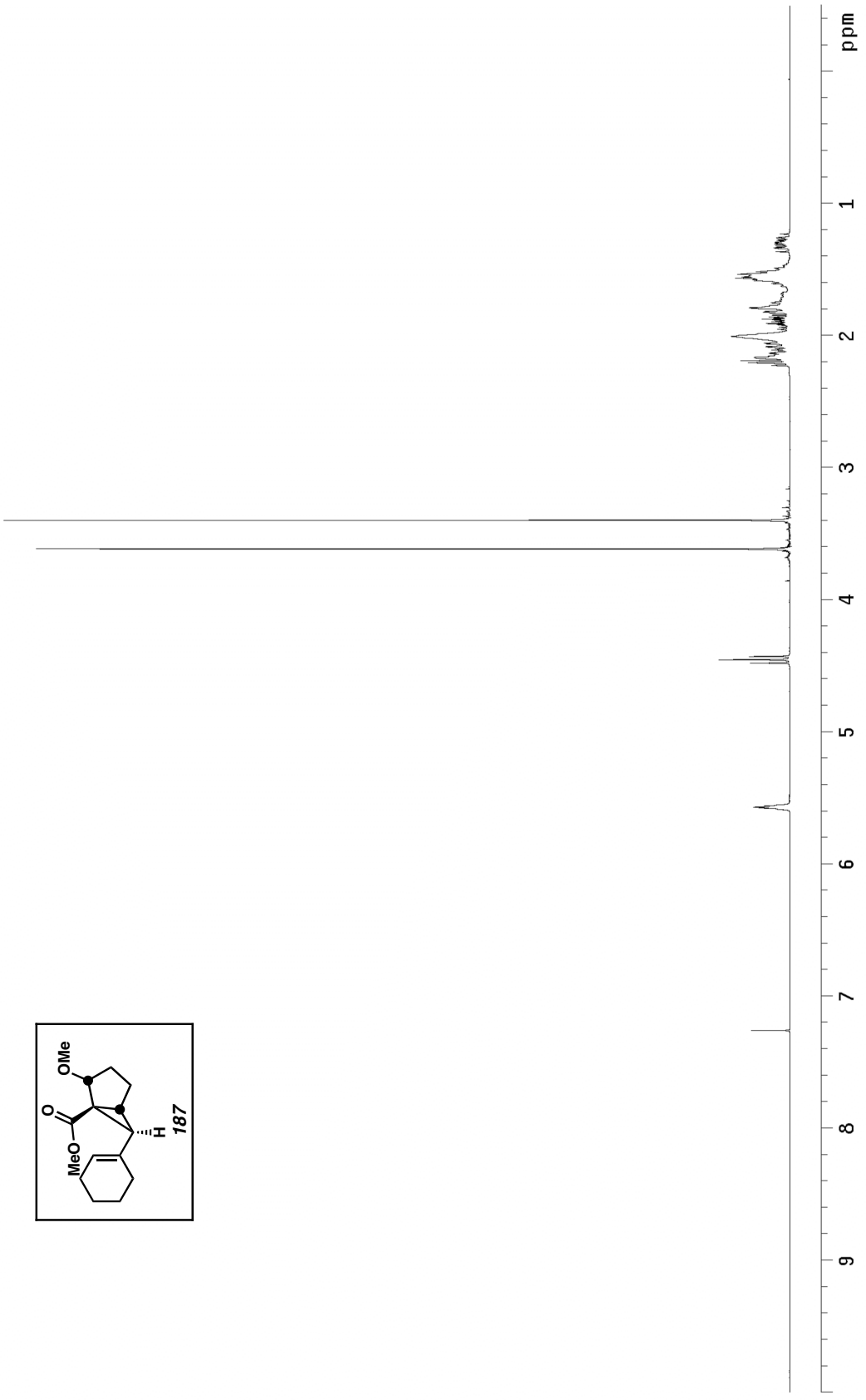



*Figure A3.7* $^{1}$H NMR (300 MHz, $CDCl_3$) of compound **187**

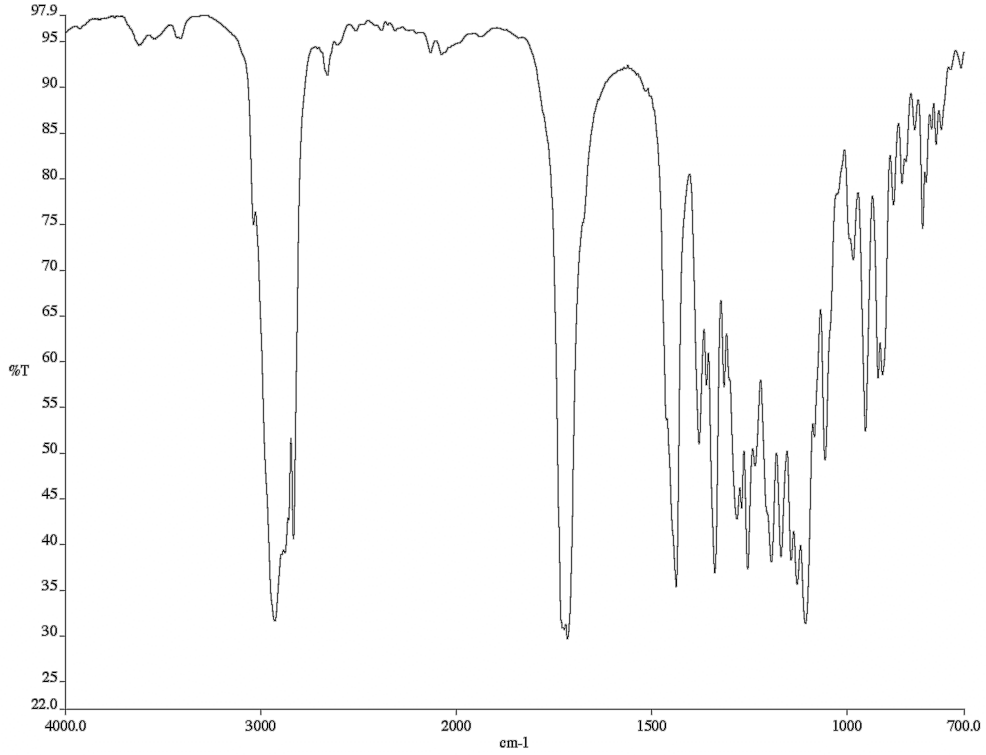



*Figure A3.8* Infrared spectrum (thin film/NaCl) of compound **187**

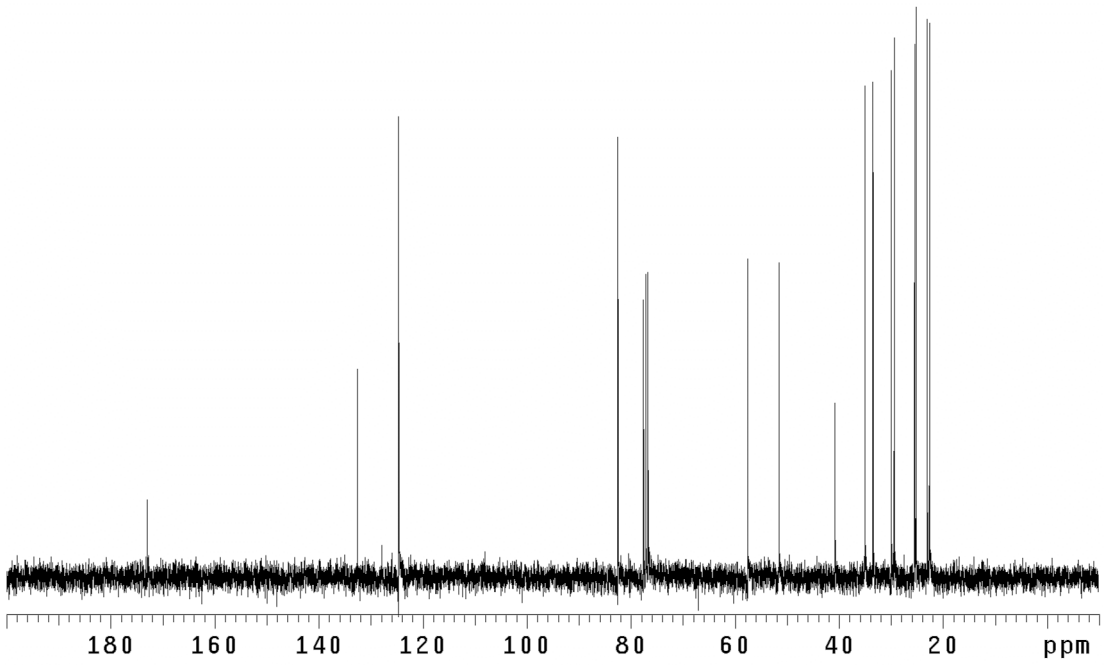



*Figure A3.9* $^{13}C$ NMR (75 MHz, $CDCl_3$) of compound **187**

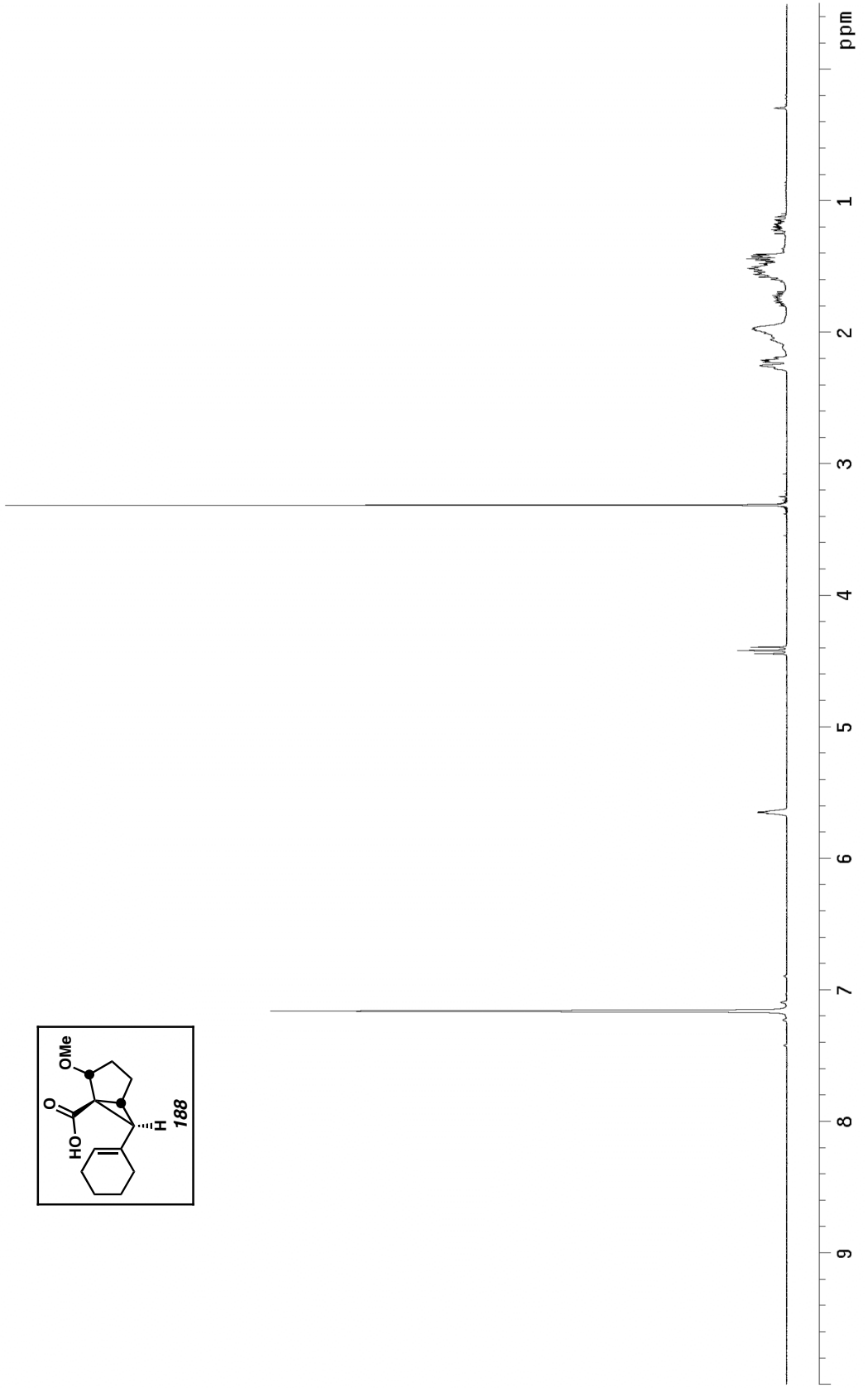



*Figure A3.10* $^{1}$H NMR (300 MHz, $C_6D_6$) of compound **188**

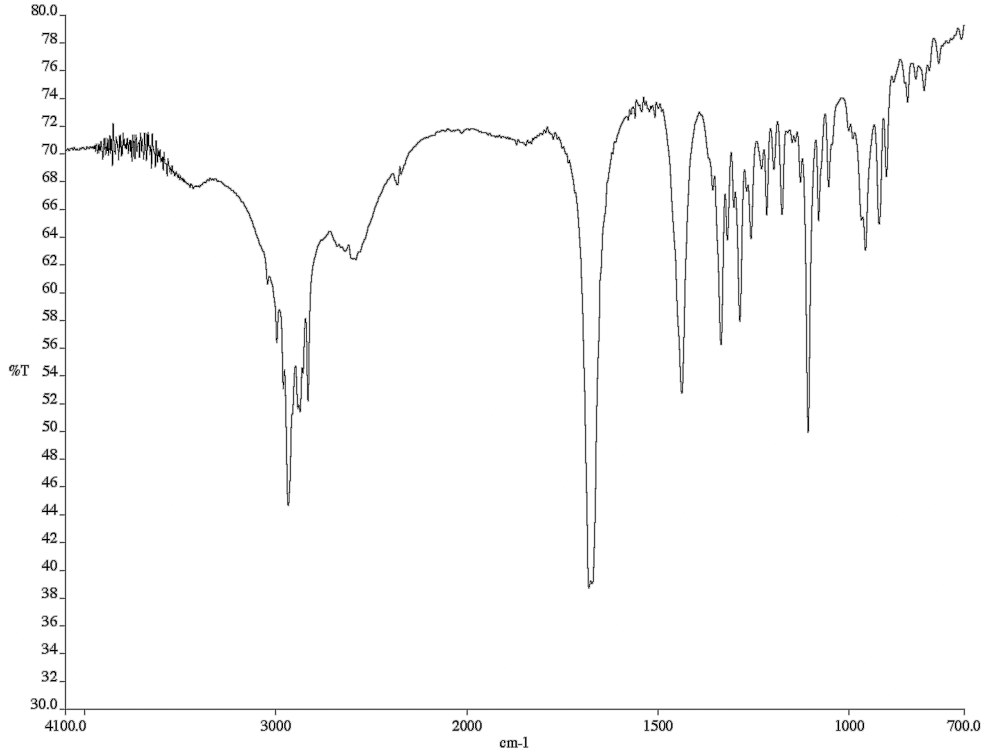



*Figure A3.11* Infrared spectrum (thin film/NaCl) of compound **188**

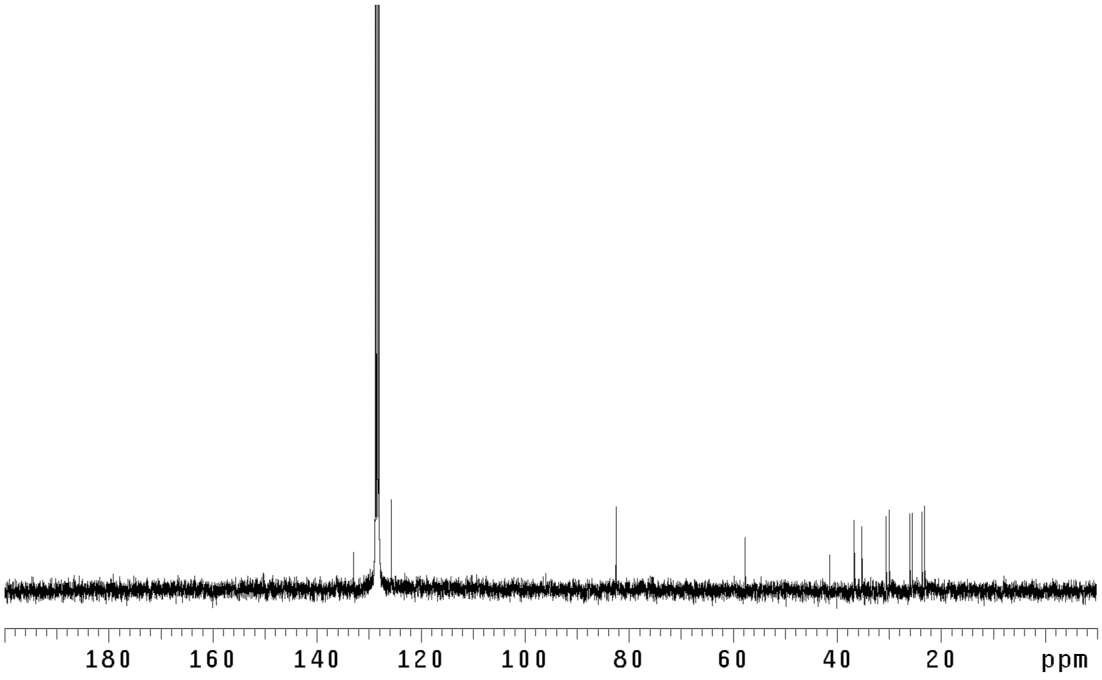



*Figure A3.12* $^{13}C$ NMR (75 MHz, $C_6D_6$) of compound **188**

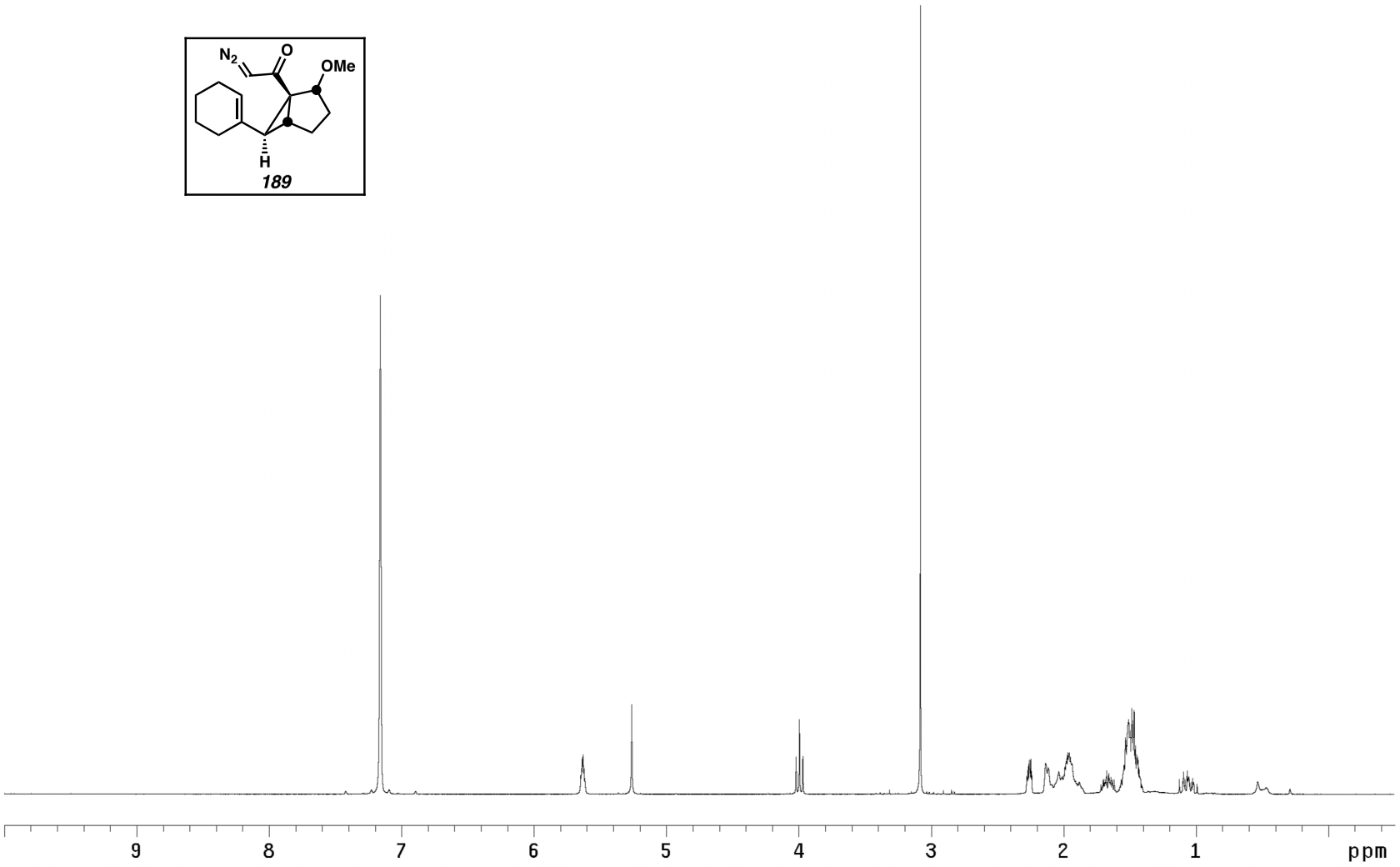



*Figure A3.13* $^{1}$H NMR (300 MHz, $C_6D_6$) of compound **189**

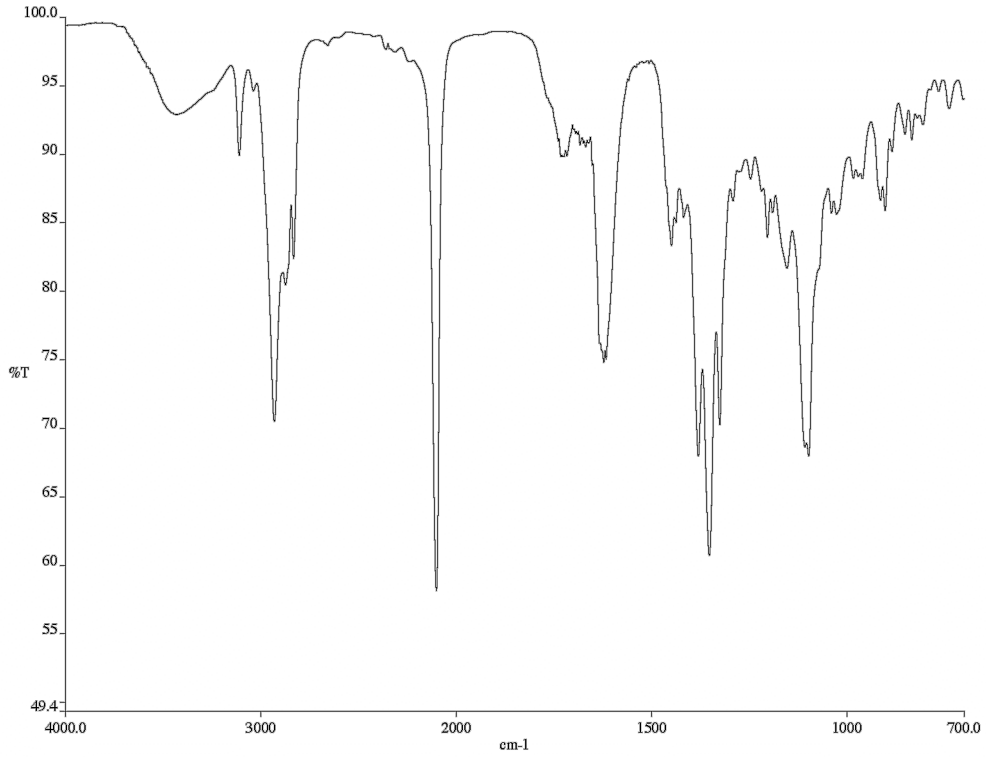



*Figure A3.14* Infrared spectrum (thin film/NaCl) of compound **189**

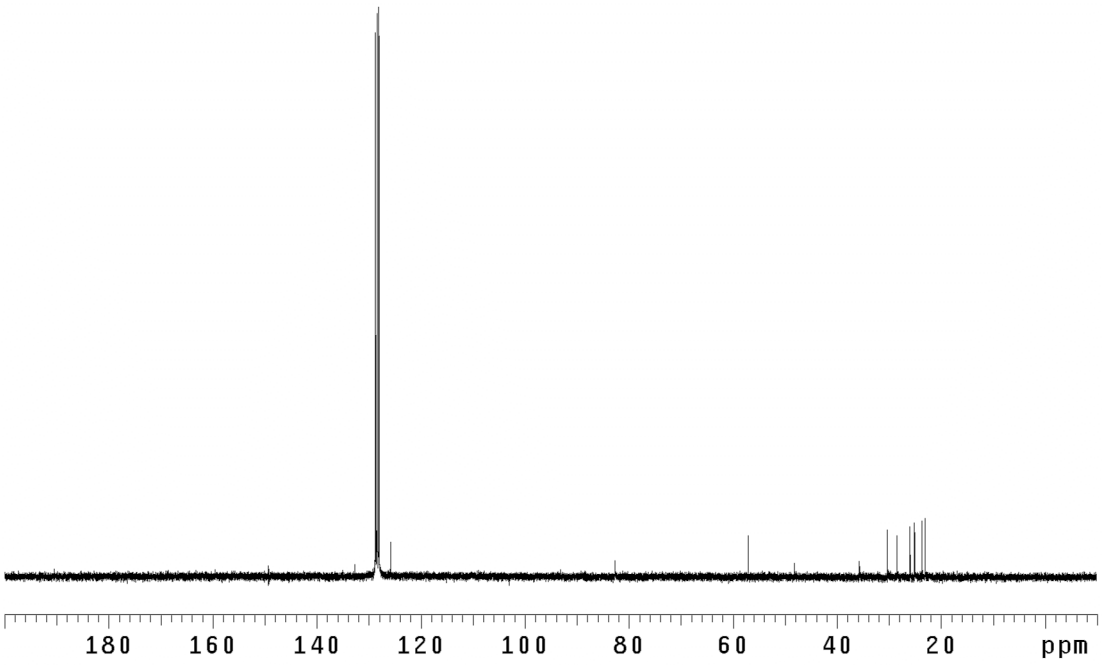



*Figure A3.15* $^{13}C$ NMR (75 MHz, $C_6D_6$) of compound **189**

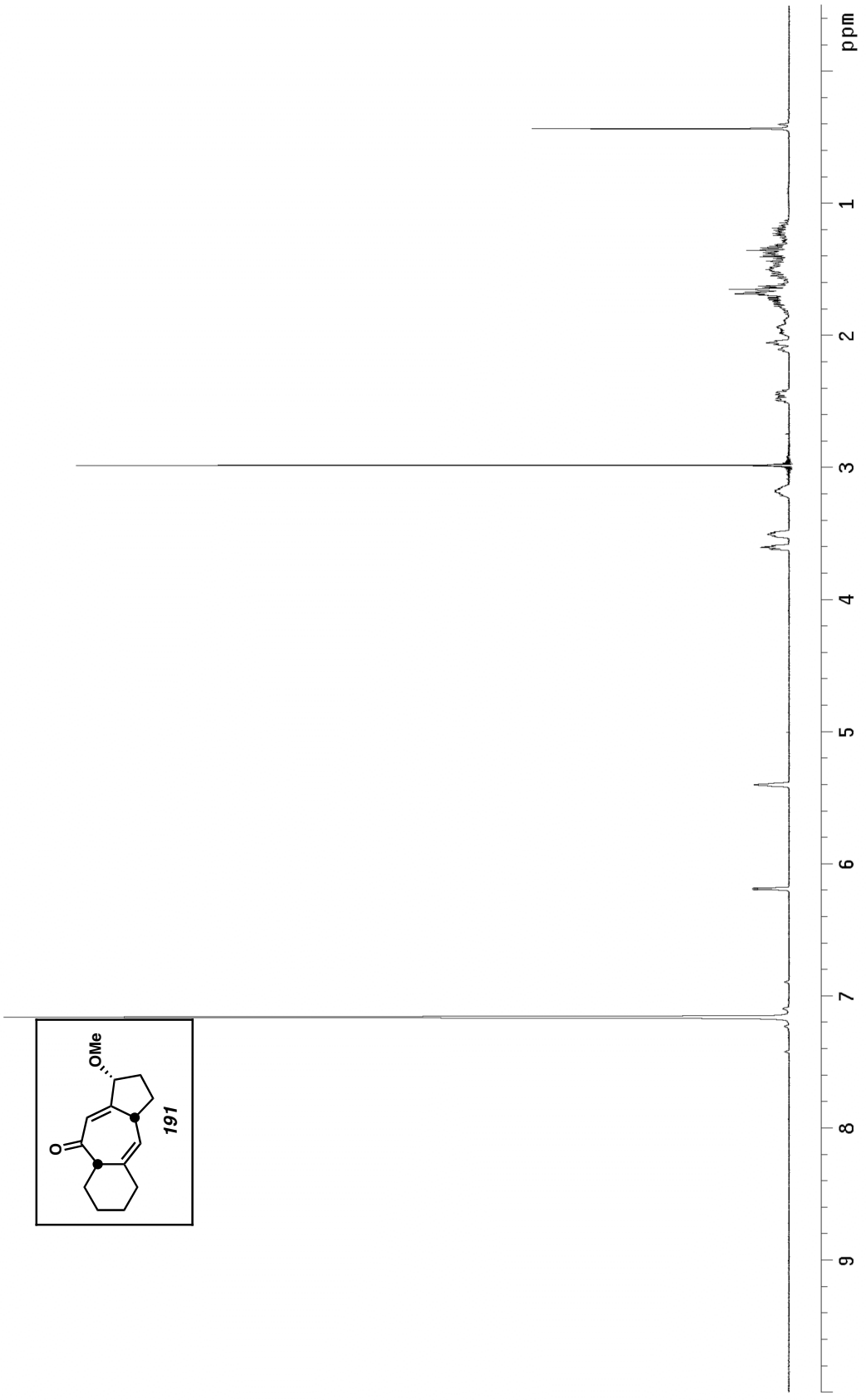



*Figure A3.16* $^{1}$H NMR (500 MHz, $C_6D_6$) of compound **191**

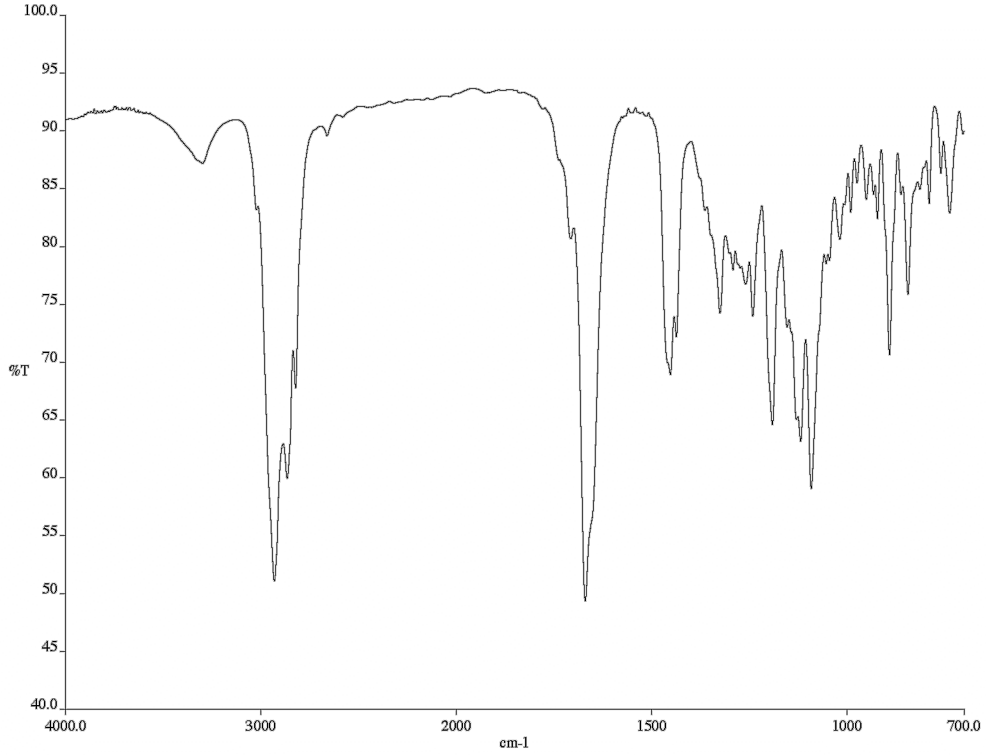



*Figure A3.17* Infrared spectrum (thin film/NaCl) of compound **191**

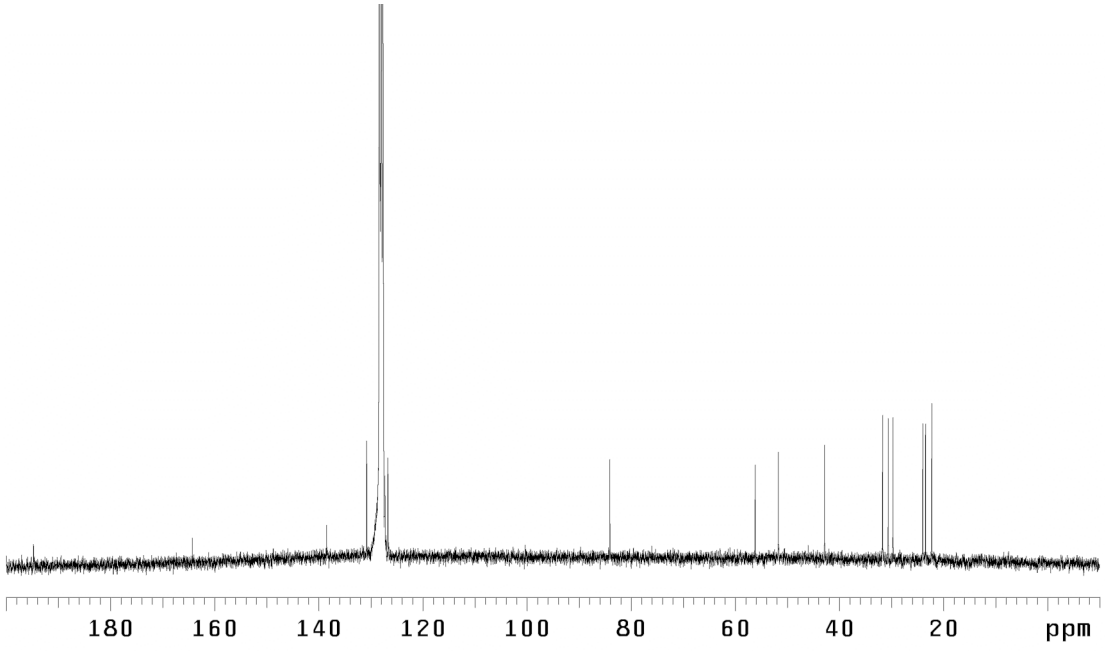



*Figure A3.18* $^{13}C$ NMR (125 MHz, $C_6D_6$) of compound **191**