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Supporting Information

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Carbonyl Ylide Cycloaddition Approach to Platensimycin

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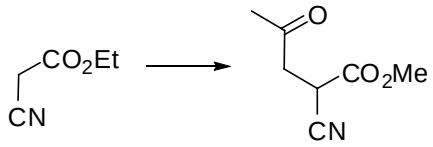
General Information

^{1}H- and ^{13}C-NMR spectra were obtained on a Bruker DPX-300 (300 MHz), a Bruker Avance-600 (600 MHz), or a Varian/Oxford As-500 (500 MHz) spectrophotometer. Chemical shift values were recorded as parts per million relative to tetramethylsilane as an internal standard unless otherwise indicated, and coupling constants in Hertz. Mass spectra were recorded on a JEOL JMS 600W spectrometer using electron impact (EI) or chemical ionization (CI) methods, and a JEOL JMS AX505WA spectrometer using fast atom bombardment (FAB) method. Significant fragments are reported in the following fashion: *m*/*z* (relative intensity).

The progress of reaction was checked on TLC plates (Merck 5554 Kiesel gel 60 F254), and the spots were visualized under 254 nm UV light and/or by charring after dipping the TLC plate into a vanillin solution (9.0 g of vanillin and 1.5 mL of concentrated sulfuric acid in 300 mL of methanol), a $KMnO_4$ solution (3 g of $KMnO_4$, 20 g of K_2CO_3, and 5 mL of 5% NaOH solution in 300 mL of water), or a phosphomolybdic acid solution (250 mg phosphomolybdic acid in 50 mL ethanol). Column chromatography was performed on silica gel (Merck 9385 Kiesel gel 60) using hexanes-EtOAc (v/v). The solvents were simple distilled unless otherwise noted.

Unless otherwise specified, all reactions were conducted under a slight positive pressure of dry nitrogen. The usual work-up refers to washing the quenched reaction mixture with brine, drying the organic extracts over anhydrous $MgSO_4$ and evaporating under reduced pressure using a rotary evaporator.

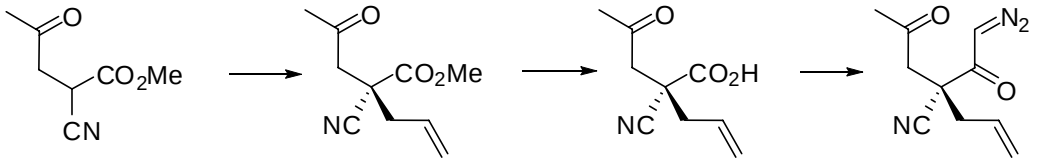
Solvents used in the reactions were dried under nitrogen atmosphere. THF was distilled from Na-benzophenone, and CH_2Cl_2 was distilled from P_2O_5. Benzene was washed with conc. H_2SO_4, distilled from Na-benzophenone, and stored over 4 Å molecular sieves. Et_2O was distilled from LAH. CH_3CN was distilled from CaH_2 and stored over 4 Å molecular sieves. Pyridine and TEA was distilled over KOH and stored over 4 Å molecular sieves.



3 **4**

Ester **4**

Ethyl cyanoacetate (**3**) (1.0 mL, 9.4 mmol) was added to a solution of sodium methoxide prepared from absolute methanol (10 mL) and sodium (220 mg, 9.6 mmol) at 0 ^{o}C. After 10 min stirring, chloroacetone (0.75 mL, 9.4 mmol) was added and the reaction mixture was stirred at r.t. for 3 h. After dilution with Et_2O (30 mL), the reaction mixture was cooled to 0 ^{o}C and treated with sat. NH_4Cl solution (30 mL). The aqueous phase was extracted with EtOAc (40 mL x 2) and the combined organic extracts were washed with 1 N HCl solution (saturated with NaCl, 20 mL x 2), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (hexanes-EtOAc, 2:1) to give ester **4** (1.3 g, 88%). R_f 0.21 (hexanes-EtOAc, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.97 (dd, J = 7.1, 5.4 Hz, 1 H), 3.84 (s, 3 H), 3.22 and 3.02 (ABX, J_{AB} = 18.4, J_{AX} = 7.1, J_{BX} = 5.4 Hz, 2 H), 2.26 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.5, 165.9, 116.1, 54.0, 42.2, 31.4, 29.6. IR (neat): ν_{max} = 3646, 2959, 2922, 2254, 1747, 1719, 1634, 1436, 1370, 1270, 1057, 826 cm^{-1}. MS *m*/*z* (CI, relative intensity): 156 (M^++1, 100), 155 (2), 152 (16), 139 (5), 124 (49), 75 (3). HRMS (CI): calcd. for $C_7H_{10}O_3N$ (M^++1) 156.0660, found 156.0659.



4 **4A** **5** **6**

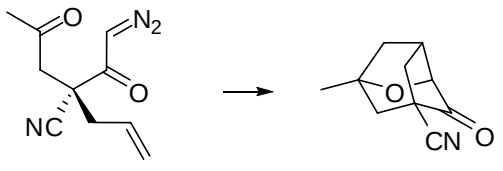
Diazoketone **6**

Ester **4** (1.0 g, 6.4 mmol) was added to a solution of sodium hydride (60% dispersion in mineral oil, 280 mg, 7.1 mmol) in THF (30 mL) at 0 ^{o}C. The mixture was stirred for 10 min before the addition of allyl bromide (0.67 mL, 7.7 mmol) and warmed to r.t. After 2 h, the reaction was quenched by addition of sat. NH_4Cl solution (20 mL), and the reaction mixture was extracted with Et_2O (100 mL x 2). The organic phase was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated.

Purification of the residue by flash column chromatography (hexanes-EtOAc, 3:1) gave methyl ester **4A** (1.3 g, quant.). R_f 0.35 (hexanes-EtOAc, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.77 - 5.88 (m, 1 H), 5.14 - 5.33 (m, 2 H), 3.84 (s, 3 H), 3.17 and 3.00 (ABq, J = 22.0 Hz, 2 H), 2.63 and 2.55 (ABX, J_{AB} = 16.4, J_{AX} = 8.8, J_{BX} = 9.0 Hz, 2 H), 2.20 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.0, 169.1, 130.2, 121.7, 118.6, 53.9, 49.1, 44.6, 41.3, 29.6.

Methyl ester **4A** (1.0 g, 5.1 mmol) was dissolved in MeOH (30 mL) and 1 N KOH solution (15 mL) was added to the solution at 0 ^{o}C. The reaction mixture was stirred for 10 min at r.t. and treated slowly with 2 N HCl (8 mL) at 0 ^{o}C. After extraction with EtOAc (100 mL x 2), the organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in toluene (10 mL) and evaporated to provide the crude acid **5** (930 mg, quant.) which was used in the next step without further purification.

TEA (0.93 mL, 6.6 mmol) was added to the solution of the crude acid **5** (930 mg, 5.1 mmol) in Et_2O (51 mL) at 0 ^{o}C and the mixture was treated with isobutyl chloroformate (0.79 mL, 6.1 mmol). After 30 min, an ethereal solution of diazomethane, which was prepared by the reaction of Diazald (6.6 g, 31 mmol) with KOH (6.6 g 118 mmol), was slowly added to the reaction mixture, and the mixture was allowed to warm to r.t. After stirring the reaction mixture for 4 h, the flask was cooled in an ice bath and excess diazomethane was decomposed by careful addition of acetic acid. The reaction mixture was filtered through a short column of silica gel with the aid of Et_2O and concentrated. The residue was purified by flash column chromatography (hexanes-EtOAc, 4:1) to provide diazoketone **6** (863 mg, 70%, two steps). R_f 0.45 (hexanes-EtOAc, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.07 (s, 1 H), 5.75 - 5.86 (m, 1 H), 5.19 - 5.35 (m, 2 H), 3.30 and 2.91 (ABq, J = 22.0 Hz, 2 H), 2.59 and 2.43 (ABX, J_{AB} = 16.3, J_{AX} = 8.4, J_{BX} = 9.3 Hz, 2 H), 2.18 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.2, 188.5, 130.1, 122.0, 120.2, 56.1, 49.1, 47.2, 41.6, 29.6.

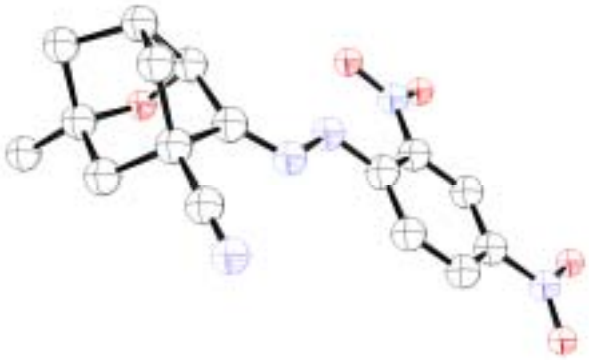


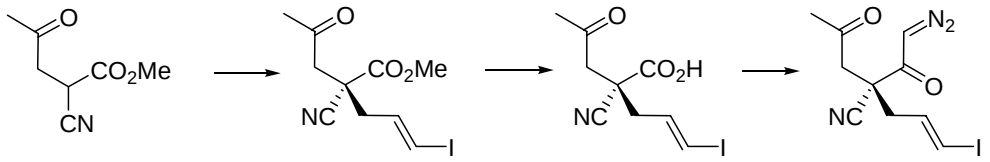
6 **8**

Ketone **8**

$Rh_2(TFA)_4$ (17 mg, 0.026 mmol) was added to a solution of diazoketone **6** (100

mg, 0.52 mmol) in CH_2Cl_2 (52 mL). After stirring for 10 h, the reaction mixture was filtered through a short column of silica gel with the aid of hexanes-EtOAc (1:1) to remove the catalyst, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes-acetone-CH_2Cl_2, 4:1:1) to provide ketone **8** (74 mg, 80%). R_f 0.20 (hexanes-acetone-CH_2Cl_2, 4:1:1). ^{1}H NMR (500 MHz, $CDCl_3$) of *the hydrate*: δ 4.26 (s, 1 H), 4.02 (d, J = 5.5 Hz, 1 H), 3.08 (s, 1 H), 2.84 (q, J = 6.2 Hz, 1 H), 2.46 - 2.53 (m, 1 H), 2.16 (dt, J = 13.6, 2.4 Hz, 1 H), 1.85 (d, J = 13.6 Hz, 1 H), 1.73 - 1.83 (m, 3 H), 1.33 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) of *the hydrate* : δ 119.7, 100.3, 82.3, 80.5, 46.3, 45.2, 41.3, 39.1, 37.7, 22.7. MS *m*/*z* (CI, relative intensity): 178 (M^++1, 100), 150 (96), 149 (36), 123 (13), 118 (5), 105 (4), 93 (8), 83 (3). HRMS (CI): calcd. for $C_{10}H_{12}O_2N$ (M^++1) 178.0868, found 178.0867. The X-ray diffraction structure of ketone **8** (as the dinitrophenylhydrazone): CCDC-669285.





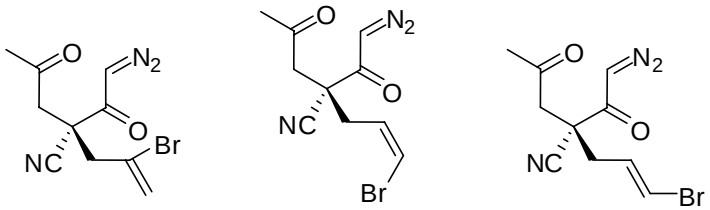
Diazoketone **13**

Ester **4** (1.0 g, 6.4 mmol) was added to a solution of sodium hydride (60% dispersion in mineral oil, 280 mg, 7.1 mmol) in THF (30 mL) at 0 °C. The mixture was stirred for 10 min before addition of (*E*)-iodoallyl iodide (2.3 g, 7.7 mmol) and warmed to r.t. After 2 h, the reaction was quenched by addition of sat. NH_4Cl solution (20 mL), and the reaction mixture was extracted with Et_2O (100 mL x 2). The organic

phase was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. Purification of the residue by flash column chromatography (hexanes-EtOAc, 3:1) gave methyl ester **4B** (2.0 g, 97%.). R_f 0.35 (hexanes-EtOAc, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.51 - 6.58 (m, 1 H), 6.40 (d, J = 14.4 Hz, 1H), 3.85 (s, 3 H), 3.15 and 3.00 (ABq, J = 18.1 Hz, 2 H), 2.61 and 2.57 (ABX, J_{AB} = 14.0, J_{AX} = 7.7, J_{BX} = 7.6 Hz, 2 H), 2.21 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.7, 168.5, 137.5, 118.2, 82.1, 54.1, 48.8, 44.1, 42.8, 29.6.

Methyl ester **4B** (2.0 g, 6.2 mmol) was dissolved in MeOH (30 mL) and 1 N KOH solution (15 mL) was added to the solution at 0 ^{o}C. The reaction mixture was stirred for 10 min at r.t. and treated slowly with 2 N HCl (8 mL) at 0 ^{o}C. After extraction with EtOAc (100 mL x 2), the organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in toluene (10 mL) and evaporated to provide the crude acid **4C** (1.9 g, quant.) which was used in the next step without further purification.

TEA (1.1 mL, 7.4 mmol) was added to the solution of the crude acid **4C** (1.9 g, 6.2 mmol) in THF (60 mL) at –20 ^{o}C and the mixture was treated with isobutyl chloroformate (1.1 mL, 6.8 mmol). After 30 min, an ethereal solution of diazomethane, which was prepared by the reaction of Diazald (8.0 g, 38 mmol) with KOH (8.0 g 143 mmol), was slowly added to the reaction mixture, and the mixture was allowed to warm to 0 ^{o}C. After stirring the reaction mixture for 4 h, excess diazomethane was decomposed by careful addition of acetic acid. The reaction mixture was filtered through a short column of silica gel with the aid of Et_2O and concentrated. The residue was purified by flash column chromatography (hexanes-EtOAc, 4:1) to provide diazoketone **13** (1.8 g, 88%, two steps). R_f 0.45 (hexanes-EtOAc, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.49 - 6.57 (m, 1 H), 6.41 (d, J = 14.5 Hz, 1 H), 6.07 (s, 1 H), 3.27 and 2.89 (ABq, J = 18.2 Hz, 2 H), 2.57 and 2.44 (ABX, J_{AB} = 13.9, J_{AX} = 7.6, J_{BX} = 7.9 Hz, 2 H), 2.18 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.8, 187.8, 137.5, 119.7, 82.4, 56.3, 48.9, 46.7, 43.3, 29.5. IR (neat): ν_{max} = 3427, 3113, 2924, 2240, 2118, 1714, 1633, 1361, 1159, 951 cm^{-1}. MS *m/z* (CI, relative intensity): 332 (M^++1, 100), 322 (14), 304 (39), 277 (22), 276 (11), 195 (13), 178 (22), 177 (37), 176 (39), 167 (11), 149 (57). HRMS (CI): calcd. for $C_{10}H_{11}O_2N_3I$ (M^++1) 331.9896, found 331.9897.



10 **11** **12**

Diazoketones **10, 11** and **12**

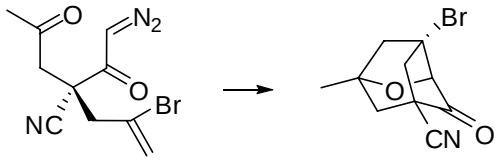
Other diazoketone derivatives were prepared from **4** following the procedure described above.

Reaction of **4** with 2,3-dibromo-1-propene provided diazoketone **10**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.16 (s, 1 H), 5.87 (s, 1 H), 5.75 (s, 1 H), 3.35 and 3.07 (ABq, J = 21.6 Hz, 2 H), 2.99 and 2.85 (ABq, J = 17.2 Hz, 2 H), 2.19 (s, 3 H).

Reaction of **4** with 1,3-dibromo-1-propene (1:1 *E*,*Z*-mixture) provided diazoketones **11** and **12**. Diazoketone **11**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.52 (d, J = 7.3 Hz, 1 H), 6.16 - 6.24 (m, 1 H), 6.09 (s, 1 H), 3.38 and 2.92 (ABq, J = 22.0 Hz, 2 H), 2.73 (d, J = 7.1, 2 H), 2.18 (s, 3 H). Diazoketone **12**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.33 (d, J = 13.6 Hz, 1 H), 6.16 - 6.24 (m, 1 H), 6.08 (s, 1 H), 3.28 and 2.90 (ABq, J = 21.6 Hz, 2 H), 2.58 and 2.45 (ABX, J_{AB} = 16.6, J_{AX} = 9.0, J_{BX} = 9.7 Hz, 2 H), 2.18 (s, 3 H).

General procedure for Rh-Catalyzed Cycloaddition

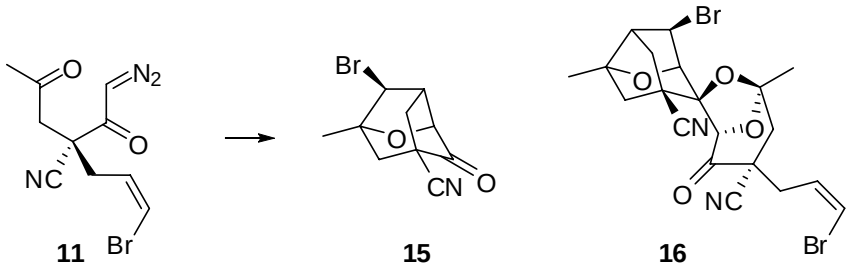
$Rh_2(OAc)_4$ was added to a solution of a diazoketone in CH_2Cl_2. After stirring for 10 h, the mixture was filtered through a short column of silica gel with the aid of hexanes-EtOAc (1:1) to remove the catalyst, and the filtrate was concentrated *in vacuo*. The products were separated by flash column chromatography.



10 **14**

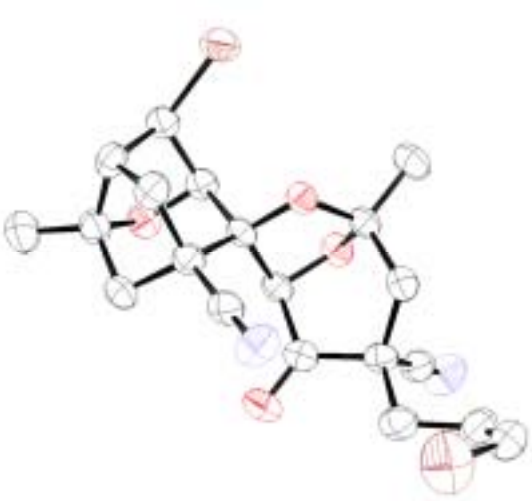
Ketone **14**

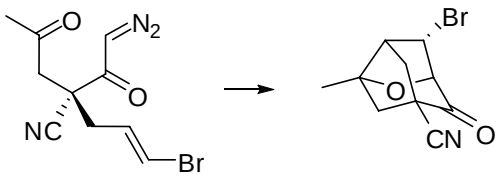
In the presence of 5 mol% $Rh_2(OAc)_4$, **10** (75 mg) was converted into ketone **14** (45 mg, 68%) as a mixture of the keto and hydrate forms after chromatographic separation (hexanes-acetone-CH_2Cl_2, 4:1:1). R_f 0.20 (hexanes-acetone-CH_2Cl_2, 4:1:1). ^{1}H NMR (500 MHz, $CDCl_3$) of *the hydrate*: δ 4.13 (s, 1 H), 3.03 (d, J = 11.7 Hz, 1 H), 2.36 (d, J = 11.7 Hz, 2 H), 2.26 - 2.32 (m, 1 H), 2.16 - 2.25 (m, 1 H), 1.83 (d, J = 13.6 Hz, 1 H), 1.37 (s, 3 H). MS *m*/*z* (CI, relative intensity): 256 (M^++1, 100), 230 (80), 229 (20), 228 (80), 178 (13), 176 (24), 149 (8), 148 (23). HRMS (CI): calcd. for $C_{10}H_{11}NO_2Br$ (M^++1) 255.9973, found 255.9972.



Ketone **15** and the Dimeric Ketal **16**

In the presence of 5 mol% $Rh_2(OAc)_4$, **11** (110 mg) was converted into ketone **15** (20 mg, 20%) as a mixture of keto and hydrate forms and a dimeric ketal **16** (39 mg, 20%) after chromatographic separation (hexanes-acetone-CH_2Cl_2, 4:1:1). Ketone **15**: R_f 0.20 (hexanes-acetone-CH_2Cl_2, 4:1:1). ^{1}H NMR (500 MHz, $CDCl_3$) of *the hydrate*: δ 4.12 (s 1 H), 4.08 (d, J = 5.4 Hz, 1 H), 3.95 (d, J = 6.1 Hz, 1 H), 2.99 (s, 1 H), 2.92 (q, J = 6.1 Hz, 1 H), 2.64 (d, J = 12.5 Hz, 1 H), 2.32 - 2.36 (m, 1 H), 2.30 (d, J = 13.9 Hz, 1 H), 2.03 (dt, J = 13.9, 2.20 Hz, 1 H), 1.31 (s, 3 H)). MS *m*/*z* (CI, relative intensity): 256 (M^++1, 100), 231 (23), 230 (43), 229 (30), 228 (44), 198 (15), 196 (14), 176 (12), 148 (11), 118 (20). HRMS (CI): calcd. for $C_{10}H_{11}NO_2Br$ (M^++1) 255.9973, found 255.9973. Ketal **16**: R_f 0.62 (hexanes-acetone-CH_2Cl_2, 4:1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.48 (d, J = 7.0 Hz, 1 H), 6.27 - 6.33 (m, 1 H), 4.95 (s, 1 H), 4.24 - 4.29 (m, 1 H), 3.94 (d, J = 2.9 Hz, 1 H), 3.11 (dd, J = 12.8, 2.93 Hz, 1 H), 3.01 and 2.93 (ABX, J_{AB} = 14.8, J_{AX} = 5.3, J_{BX} = 8.8 Hz, 2 H), 2.72 and 2.39 (ABq, J = 15.1 Hz, 2 H), 2.68 (dd, J = 12.9 Hz, 1 H), 2.51 (t, J = 6.4 Hz, 1 H), 2.08 (d, J = 12.9 Hz, 1 H), 2.07 (d, J = 12.5 Hz, 1 H), 1.81 (s, 3 H), 1.50 (s, 3 H). The X-ray diffraction structure of **16** : CCDC-669286.

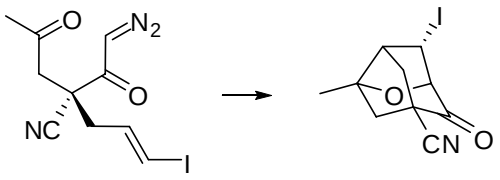




12 **17**

Ketone **17**

In the presence of 3 mol% $Rh_2(OAc)_4$, **12** (74 mg) was converted into ketone **17** (55 mg, 82%) as a mixture of keto and hydrate forms after chromatographic separation (hexanes-acetone-CH_2Cl_2, 4:1:1). R_f 0.20 (hexanes-acetone-CH_2Cl_2, 4:1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.47 (s, 1 H), 4.22 (s, 1 H), 3.03 (d, J = 7.0 Hz, 1 H), 2.77 (dd, J = 11.7, 2.9 Hz, 1 H), 2.55 (dd, J = 12.8, 7.3 Hz, 1 H), 2.31 (d, J = 11.7 Hz, 1 H), 2.17 (dd, J = 12.8, 2.9 Hz, 1 H), 1.73 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.2, 115.7, 88.4, 87.3, 53.7, 53.1, 52.6, 51.1, 44.4, 22.6. MS *m*/*z* (FAB, relative intensity): 256 (M^++1, 100), 231 (9), 230 (89), 229 (21), 228 (91), 227 (11), 176 (24), 148 (32), 118 (10), 106 (29), 59 (11). HRMS (CI): calcd. for $C_{10}H_{11}NO_2Br$ (M^++1) 255.9973, found 255.9971.

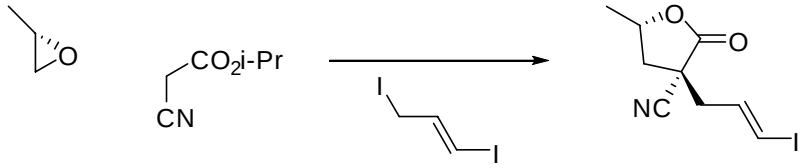


13 **20**

Ketone **20**

In the presence of 3 mol% $Rh_2(OAc)_4$, **13** (300 mg) was converted into ketone **20** (228 mg, 83%) as a mixture of keto and hydrate forms after chromatographic separation (hexanes-acetone-CH_2Cl_2, 4:1:1). R_f 0.20 (hexanes-acetone-CH_2Cl_2, 4:1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.43 (s, 1 H), 4.22 (s, 1 H), 3.05 (d, J = 7.1 Hz, 1 H), 2.75 (dd, J = 11.9, 3.1 Hz, 1 H), 2.47 (dd, J = 13.0, 7.1 Hz, 1 H), 2.32 (d, J = 12.0 Hz, 1 H), 2.22 (dd, J = 13.0, 3.2 Hz, 1 H), 1.77 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6, 115.9, 89.5, 87.5, 53.7, 53.5, 51.5, 46.8, 27.5, 23.1. IR (neat): ν_{max} = 3390, 2978, 2874, 2247, 1740, 1632, 1444, 1383, 1243, 1113, 1026, 825, 612 cm^{-1}. MS *m*/*z* (FAB, relative intensity): 304 (M^++1, 6), 289 (7), 273 (4), 219 (18), 194 (13), 176 (15), 154 (95), 136 (100), 107 (32), 90 (30), 77 (37). HRMS (FAB): calcd. for $C_{10}H_{11}O_2NI$ (M^++1) 303.9834, found 303.9824.

Enantioselective Synthesis

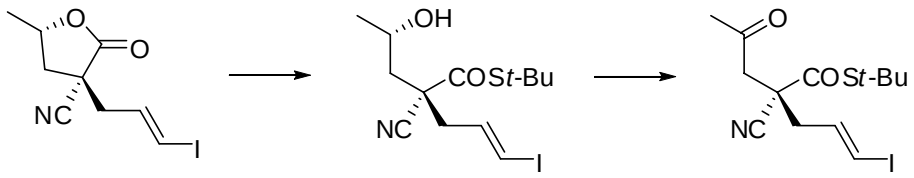


24 **23** **25**

Lactone **25**

Isopropyl cyanoacetate (**23**) (0.5 g, 3.9 mmol) was slowly added to a solution of sodium hydride (60% dispersion in mineral oil, 157 mg, 3.9 mmol) in THF (16 mL) at 0 ^{o}C. The mixture was stirred for 10 min before addition of (*S*)-propylene oxide (**24**, purchased from Aldrich, 0.27 mL, 3.9 mmol). After heating under reflux for 6 h, the mixture was cooled to r.t. and another portion of (*S*)-propylene oxide (0.27 mL, 3.9 mmol) was added to the mixture. The mixture was further refluxed for 6 h then cooled to 0 ^{o}C. (*E*)-Iodoallyl iodide (1.6 g, 5.4 mmol) in THF (3 mL) was slowly added to the mixture. After stirring at r.t. for 30 min, the mixture was diluted with Et_2O (200 mL) before addition of 1 N HCl (20 mL). The organic phase was washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (hexanes-EtOAc, 5:1) to give lactone **25** (726 mg, 63%). R_f 0.42 (hexanes-EtOAc, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.46 - 6.62 (m, 2 H), 4.60 - 4.73 (m, 1 H), 2.76 (dd, J = 14.2, 6.4 Hz, 1 H), 2.49 - 2.63 (m, 2 H), 2.37 (dd, J = 13.5, 7.6 Hz, 1 H), 1.54 (d, J = 6.1 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 137.0, 117.6, 83.1, 75.3, 43.3, 41.1, 39.4, 21.2. IR (neat): ν_{max} = 3056, 2983, 2932, 2320, 2248, 1778,

1607, 1449, 1387, 1346, 1199, 1047, 944 cm^{-1}. $[\alpha]^{25}_D$ –38.8 (*c* 0.41, $CHCl_3$).

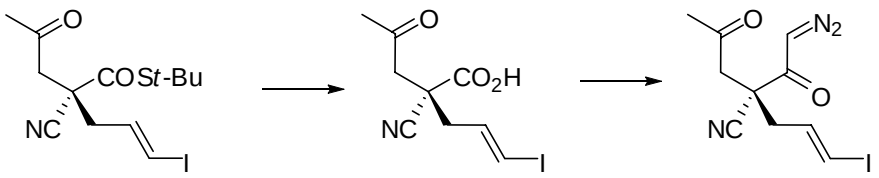


25 **25A** **26**

Thioester **26**

To a solution of trimethylaluminium (2 M in toluene, 5.1 mL, 10.2 mmol) in dry CH_2Cl_2 (12 mL) was carefully added 2-methyl-2-propanethiol (1.1 mL, 10.2 mmol) at 0 °C and the resultant mixture was allowed to warm to r.t. over 20 min and cooled again to 0 °C. A solution of lactone **25** (370 mg, 1.27 mmol) in CH_2Cl_2 (2 mL) was added and the mixture was stirred at 0 °C for 3 h. The mixture was cooled to –78 °C and quenched with Et_2O (40 mL) followed by careful addition of 1 N HCl (15 mL). The organic phase was washed with 1 N HCl (15 mL x 2), sat. $NaHCO_3$ (10 mL), and brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give relatively unstable alcohol **25A**, which was used in the next step immediately.

The crude alcohol **25A** was dissolved in CH_2Cl_2 (3 mL) and added to a solution of Dess-Martin periodinane (1.1 g, 2.6 mmol) in CH_2Cl_2 (6 mL) at 0 °C. After 2 h, the reaction mixture was treated with sat. $NaHCO_3$ solution (10 mL) and the aqueous phase was extracted with Et_2O (20 mL x 2). The combined organic phase was washed with brine (10 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (hexanes-EtOAc, 4:1) to give thioester **26** (443 mg, 92%, two steps). R_f 0.45 (hexanes-EtOAc, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.47- 6.59 (m, 1 H), 6.36 (d, J = 14.4 Hz, 1 H), 3.18 and 2.90 (ABq, J = 18.0 Hz, 2 H), 2.62 and 2.54 (ABX, J_{AB} = 13.8, J_{AX} = 7.8, J_{BX} = 7.6 Hz, 2 H), 2.19 (s, 3 H), 1.50 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.1, 194.7, 137.6, 118.7, 82.0, 50.7, 50.5, 48.7, 43.9, 29.8. IR (neat): ν_{max} = 2964, 2924, 2240, 1723, 1674, 1607, 1475, 1365, 1173, 925, 767 cm^{-1}. $[\alpha]^{25}_D$ –107.2 (*c* 1.03, $CHCl_3$).

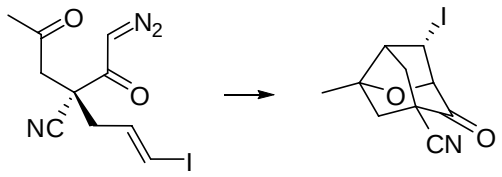


26 **4C** **13**

Diazoketone **13**

Thioester **26** (443 mg, 1.17 mmol) was dissolved in MeOH (6 mL) and 1 N KOH solution (2 mL) was added to the solution at 0 °C. The reaction mixture was stirred for 10 min at r.t. and treated slowly with 1 N HCl (3 mL) at 0 °C. After extraction with EtOAc (30 mL x 2), the organic phase was washed with brine (5 mL x 2), dried over $MgSO_4$, filtered and concentrated to provide the crude acid **4C** (360 mg, quant.) which was used in the next step without further purification.

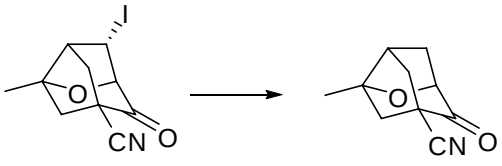
TEA (0.20 mL, 1.40 mmol) was added to the solution of the crude acid **4C** (360 mg, 1.17 mmol) in Et_2O (15 mL) at –20 °C and the mixture was treated with isobutyl chloroformate (0.17 mL, 1.29 mmol). After 30 min, an ethereal solution of diazomethane, which was prepared by the reaction of Diazald (1.5 g, 7.1 mmol) with KOH (1.5 g 27 mmol), was slowly added to the reaction mixture, and the mixture was allowed to warm to 0 °C. After stirring the reaction mixture for 4 h, excess diazomethane was decomposed by careful addition of acetic acid. The reaction mixture was filtered through a short column of silica gel with the aid of Et_2O and concentrated. The residue was purified by flash column chromatography (hexanes-EtOAc, 4:1) to provide enantiomerically enriched diazoketone **13** (337 mg, 88%, two steps). $[\alpha]^{25}_{D}$ −212.0 (*c* 0.50, $CHCl_3$).



13 **20**

Ketone **20**

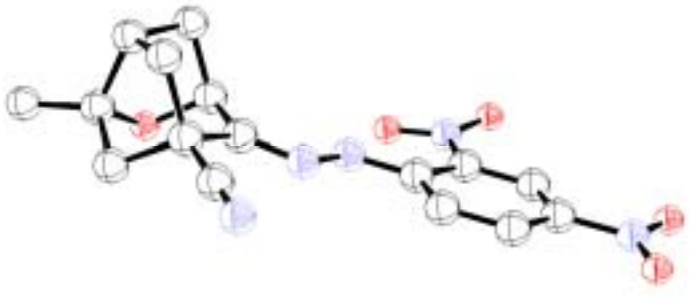
Enatiomerically enriched ketone **20** was prepared from diazoketone **13** following the procedure described above. $[\alpha]^{25}_{D}$ –90.5 (*c* 0.33, $CHCl_3$).

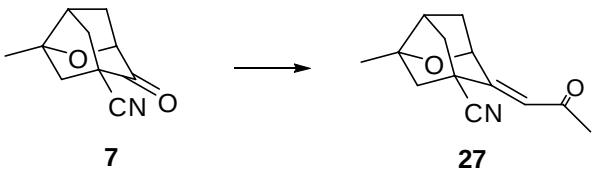


20 **7**

Ketone **7**

To a solution of hypophosphorous acid (50% aq. solution, 1.05 g, 7.95 mmol) in MeOH (25 mL), 1-ethylpiperidine (1.09 mL, 7.95 mmol) was slowly added at 0 ^{o}C. After 10 min, a solution of **20** (481 mg, 1.59 mmol) in MeOH (5 mL) was added to the solution, followed by the addition of Et_3B (1 M in hexanes, 3.2 mL, 3.2 mmol). The reaction mixture was warmed to r.t. and stirred 20 min before dilution with EtOAc (150 mL). The organic phase was washed with brine (30 mL x 2), dried over $MgSO_4$, filtered and concentrated. Flash column chromatography (hexanes-EtOAc, 1:1) provided ketone **7** (264mg, 94%) as a mixture of keto and hydrate forms. R_f 0.19 (hexanes-EtOAc, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40 (d, J = 4.8 Hz, 1 H), 2.68 - 2.73 (m, 2 H), 2.46 - 2.52 (m, 1 H), 2.33 (d, J = 11.7 Hz, 1 H), 2.28 - 2.31 (m, 1 H), 2.16 (dd, J = 12.1, 2.9 Hz, 1 H), 1.95 (d, J = 12.5 Hz, 1 H), 1.58 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.6, 116.4, 86.6, 83.5, 53.4, 52.4, 47.1, 44.1, 42.3, 22.0. IR (neat): ν_{max} = 3418, 2974, 2870, 2247, 1744, 1453, 1384, 1289, 1126, 1038, 833 cm^{-1}. MS *m*/*z* (FAB, relative intensity): 178 (M^++1, 19), 165 (10), 154 (24), 149 (14), 136 (38), 107 (32), 95 (40), 77 (42), 69 (64), 55 (100), 43 (83). HRMS (FAB): calcd. for $C_{10}H_{12}O_2N$ (M^++1) 178.0868, found 178.0874. $[\alpha]^{25}_D$ +7.2 (*c* 0.44, MeOH). The X-ray diffraction structure of ketone **7** (as the dinitrophenylhydrazone): CCDC-669284.

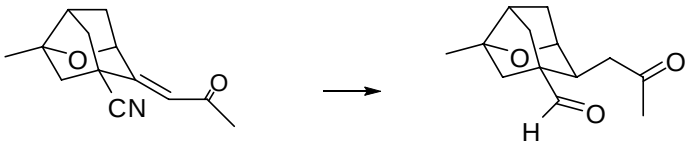




7 **27**

Enone **27**

Dimethyl 2-oxopropylphosphonate (0.23 mL, 1.7 mmol) was added to a stirred suspension of anhydrous LiCl (126 mg, 2.98 mmol) and DIPEA (0.39 mL, 2.2 mmol) in anhydrous MeCN (15 mL) at 0 °C. After 15 min, a solution of **7** (264mg, 1.49 mmol) in anhydrous MeCN (2 mL) was added to the mixture and the reaction mixture was stirred for 2 h at r.t. before dilution with Et_2O (100 mL). The organic phase was washed with brine (20 mL x 2), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (hexanes-EtOAc, 3:1) to give enone **27** (291 mg, 90%). R_f 0.75 (hexanes-EtOAc, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.44 (s, 1 H), 5.82 (d, J = 4.8 Hz, 1 H), 2.56 (t, J = 6.4 Hz, 1 H), 2.43 (dd, J = 11.2, 3.1 Hz, 1 H), 2.36 - 2.41 (m, 1 H), 2.29 (s, 3 H), 2.18 - 2.25 (m, 1 H), 2.15 (d, J = 11.4 Hz, 1 H), 2.02 (dd, J = 11.4, 3.3 Hz, 1 H), 1.82 (d, J = 11.7 Hz, 1 H), 1.47 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.4, 149.5, 121.5, 118.9, 86.2, 75.2, 53.5, 48.7, 46.0, 44.7, 43.0, 32.0, 22.4. IR (neat): ν_{max} = 3519, 2972, 2869, 2244, 1694, 1626, 1447, 1381, 1176, 1039, 960, 831 cm^{-1}. MS *m*/*z* (FAB, relative intensity): 218 (M^++1, 16), 200 (7), 155 (25), 154 (100), 138 (30), 137 (59), 136 (75), 124 (10), 120 (13), 107 (23), 89 (21). HRMS (FAB): calcd. for $C_{13}H_{16}O_2N$ (M^++1) 218.1181, found 218.1183. [α] $^{25}_D$ –1.0 (*c* 0.76, $CHCl_3$).

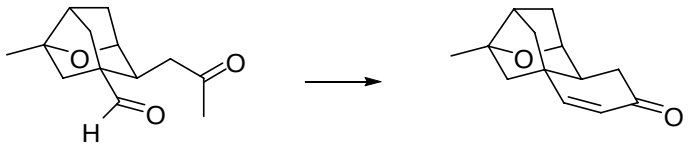


27 **28**

Aldehyde **28**

Dimethylphenylsilane (0.062 mL, 0.40 mmol) was added to a solution of enone **27** (73 mg, 0.34 mmol) and $(Ph_3P)_3RhCl$ (6.2 mg, 0.0067 mmol) in toluene (0.7 mL) at r.t. The reaction mixture was stirred for 1 h at 60 °C and cooled to –40 °C. After slow addition of DIBAL (1 M in toluene, 1 mL, 1 mmol), the reaction mixture was stirred for 1 h and carefully quenched by addition of AcOH-H_2O (1:1) solution (1.5 mL). The mixture was stirred vigorously at 0 °C for 1 h and diluted with EtOAc (15 mL). The mixture was washed with brine (5 mL x 2), dried over Na_2SO_4, filtered and concentrated. This crude mixture was dissolved in THF (2 mL) before dropwise addition of 2 N HCl (0.1 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and diluted with EtOAc (15 mL), washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (hexanes-acetone, 6:1) to give

aldehyde **28** (45 mg, 59%). R_f 0.40 (hexanes-acetone, 3:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.32 (s, 1 H), 4.24 (br. s., 1 H), 2.82 (br. s., 1 H), 2.62 (dd, *J* = 17.4, 4.9 Hz, 1 H), 2.35 (t, *J* = 6.6 Hz, 1 H), 2.18 (d, *J* = 7.8 Hz, 1 H), 2.15 (s, 3 H), 1.98 (dd, *J* = 11.1, 3.3 Hz, 1 H), 1.84 - 1.93 (m, 2 H), 1.79 (d, *J* = 11.7 Hz, 1 H), 1.65 - 1.71 (m, 2 H), 1.44 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.6, 202.8, 85.8, 79.0, 59.1, 48.0, 44.7, 42.7, 38.5, 37.8, 35.9, 30.4, 23.0. IR (neat): ν_{max} = 3411, 2964, 2715, 1714, 1452, 1379, 1168, 1099, 994, 935, 824, 687 cm^{-1}. $[\alpha]^{25}_D$ –27.6 (*c* 0.70, $CHCl_3$).

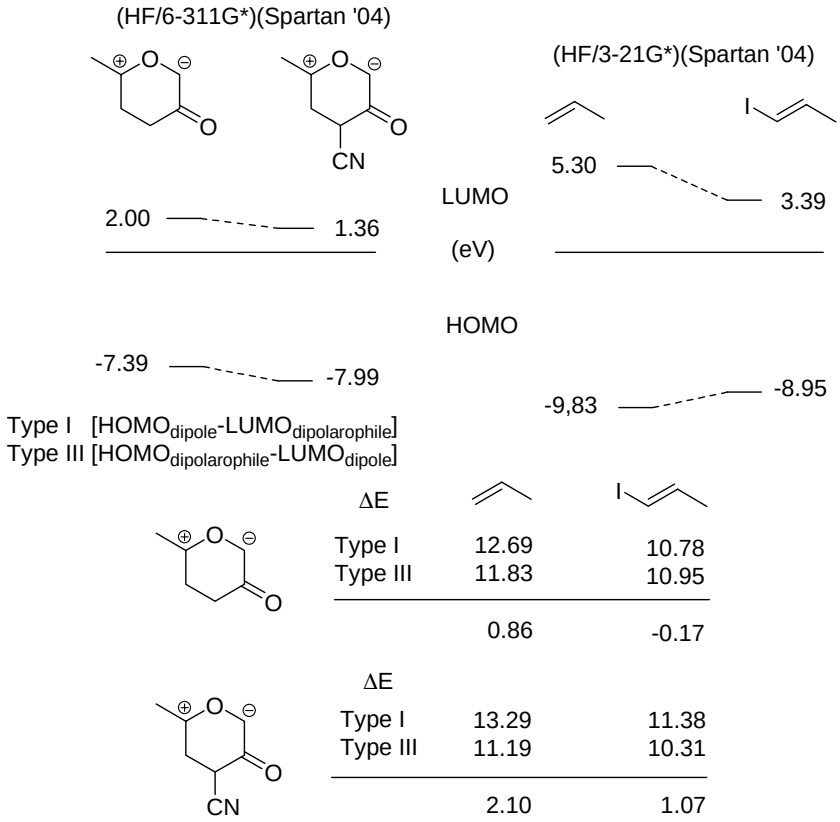


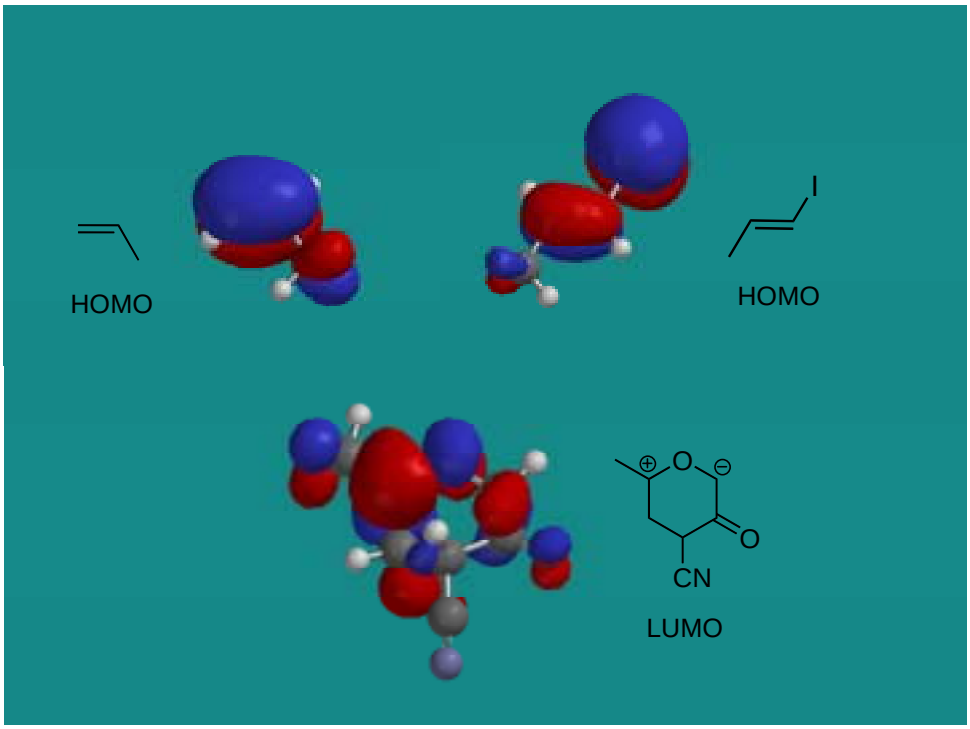
28 **2**

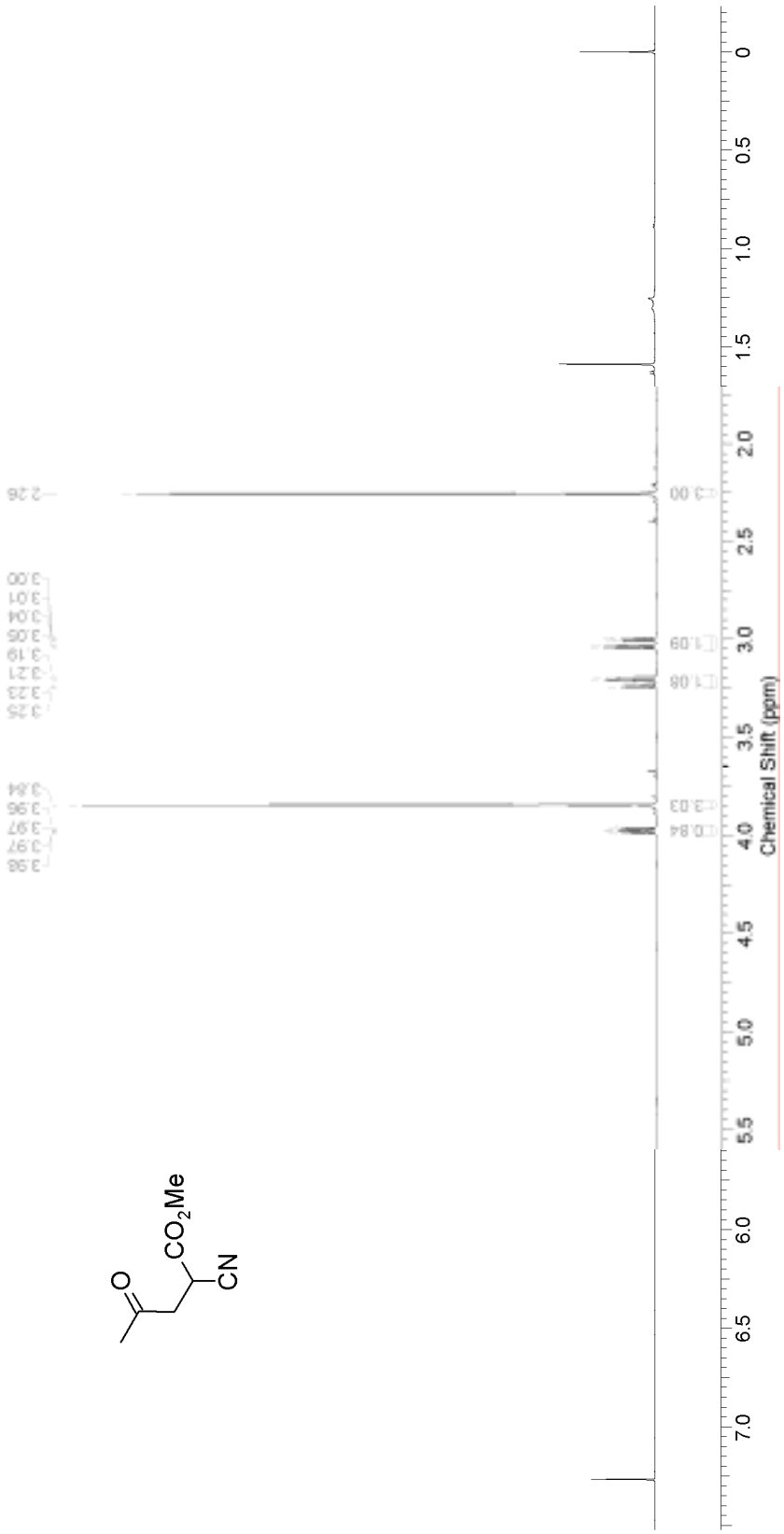
Cyclic enone **2**

p-TsOH monohydrate (10 mol%, 4 mg) was added to a solution of aldehyde **28** (49 mg, 0.22 mmol) in toluene (4 mL) and the mixture was heated under reflux for 2 h with concomitant removal of water (Dean-Stark trap). After cooling to r.t., the mixture was diluted with Et_2O (10 mL), washed with sat. $NaHCO_3$ solution (3 mL), dried over $MgSO_4$, filtered and concentrated. Flash column chromatography (hexanes-acetone, 6.5:1) provided cyclic enone **2** (43 mg, 96%). R_f 0.42 (hexanes-acetone, 3:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.62 (d, *J* = 10.3 Hz, 1 H), 5.94 (d, *J* = 10.3 Hz, 1 H), 4.16 (t, *J* = 3.3 Hz, 1 H), 2.27 - 2.44 (m, 4 H), 1.92 - 1.97 (m, 2 H), 1.89 (d, 1 H), 1.75 - 1.78 (m, 2 H), 1.66 (d, *J* = 11.0 Hz, 1 H), 1.45 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.1, 155.2, 128.9, 87.0, 79.0, 51.7, 46.2, 44.2, 42.7, 42.3, 37.9, 37.5, 23.1. IR (neat): ν_{max} = 3501, 2955, 2871, 1681, 1607, 1448, 1379, 1281, 1249, 1138, 1038, 821 cm^{-1}. MS *m*/*z* (CI, relative intensity): 205 (M^++1, 55), 154 (100), 136 (82), 135 (20), 107 (46), 91 (31), 81 (31), 69 (45), 55 (62), 43 (50), 41 (37), 29 (11). HRMS (FAB): calcd. for $C_{13}H_{17}O_2$ (M^++1) 205.1229, found 205.1231. $[\alpha]^{25}_D$ –22.8 (*c* 0.46, $CHCl_3$).

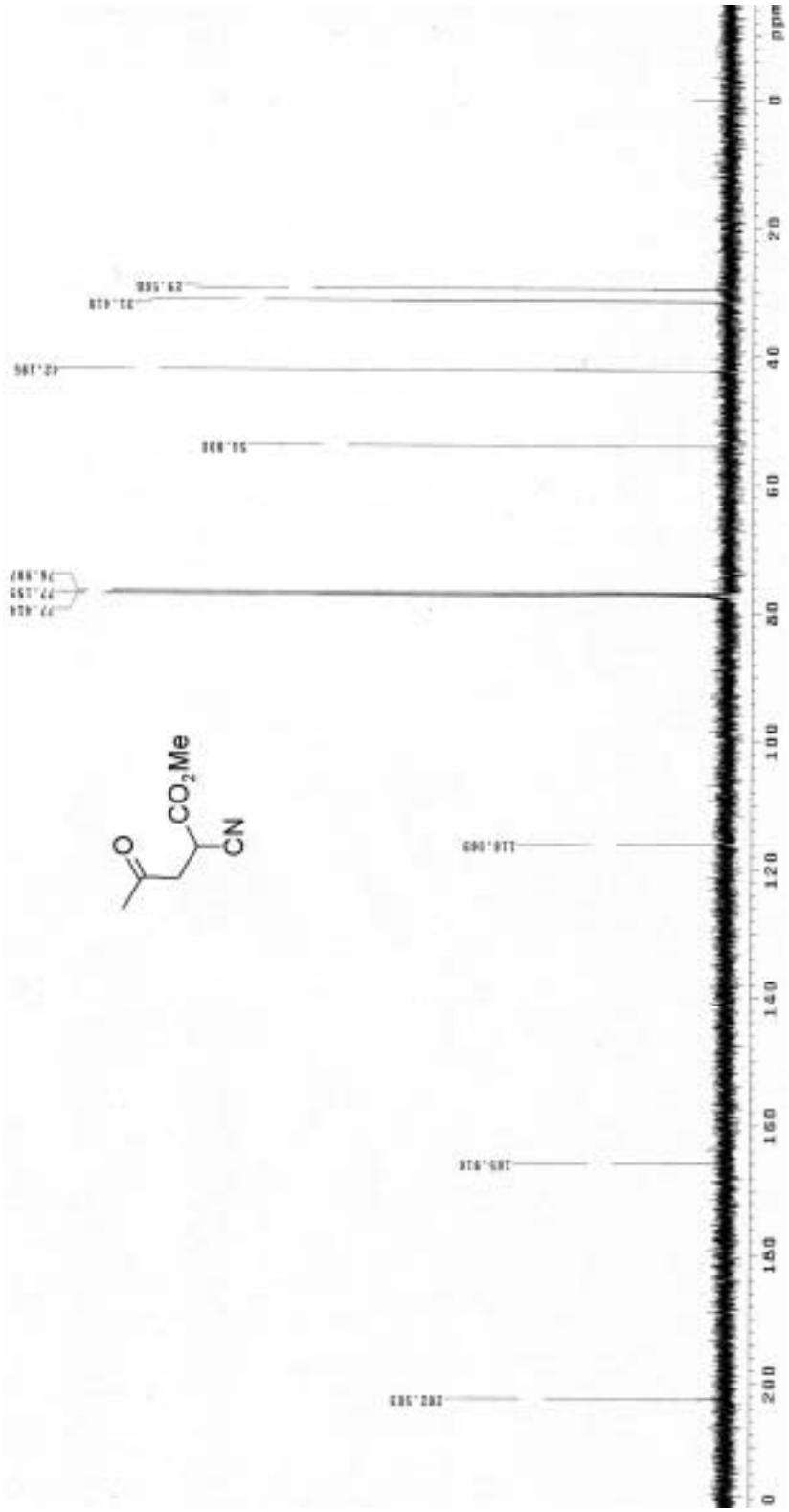
Frontier Orbital Calculations



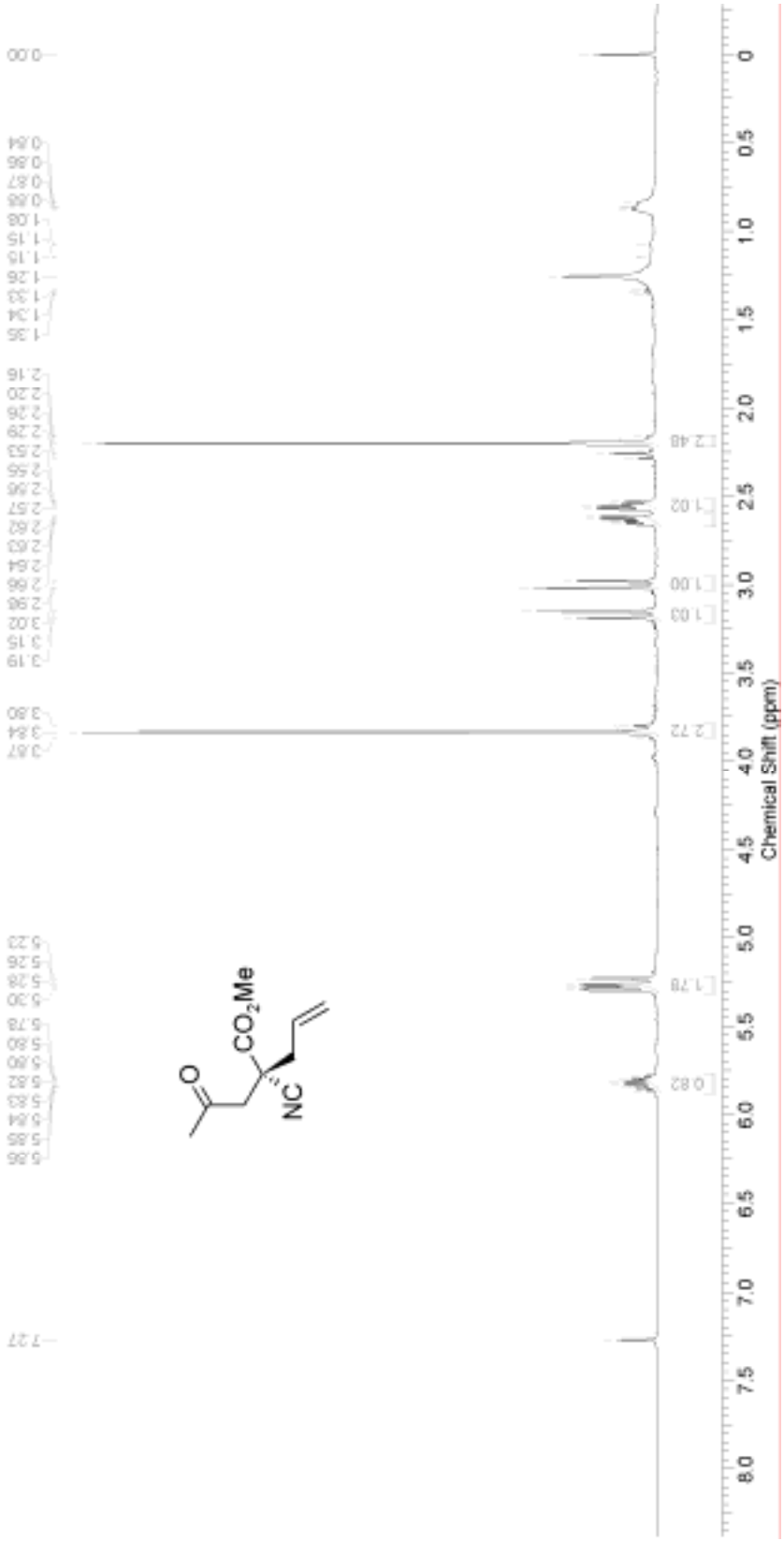




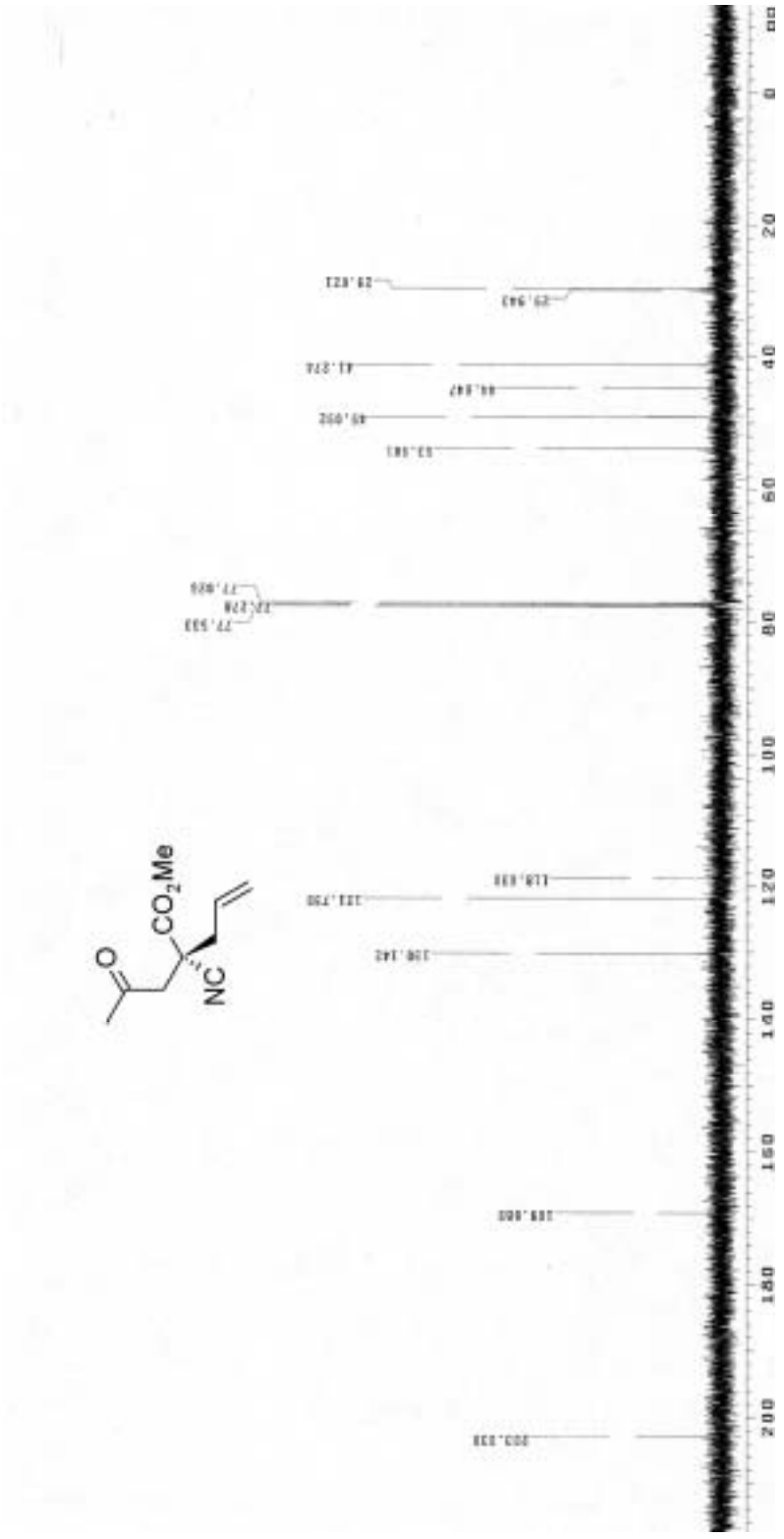
^{1}H-NMR (500 MHz, $CDCl_3$) of **4**



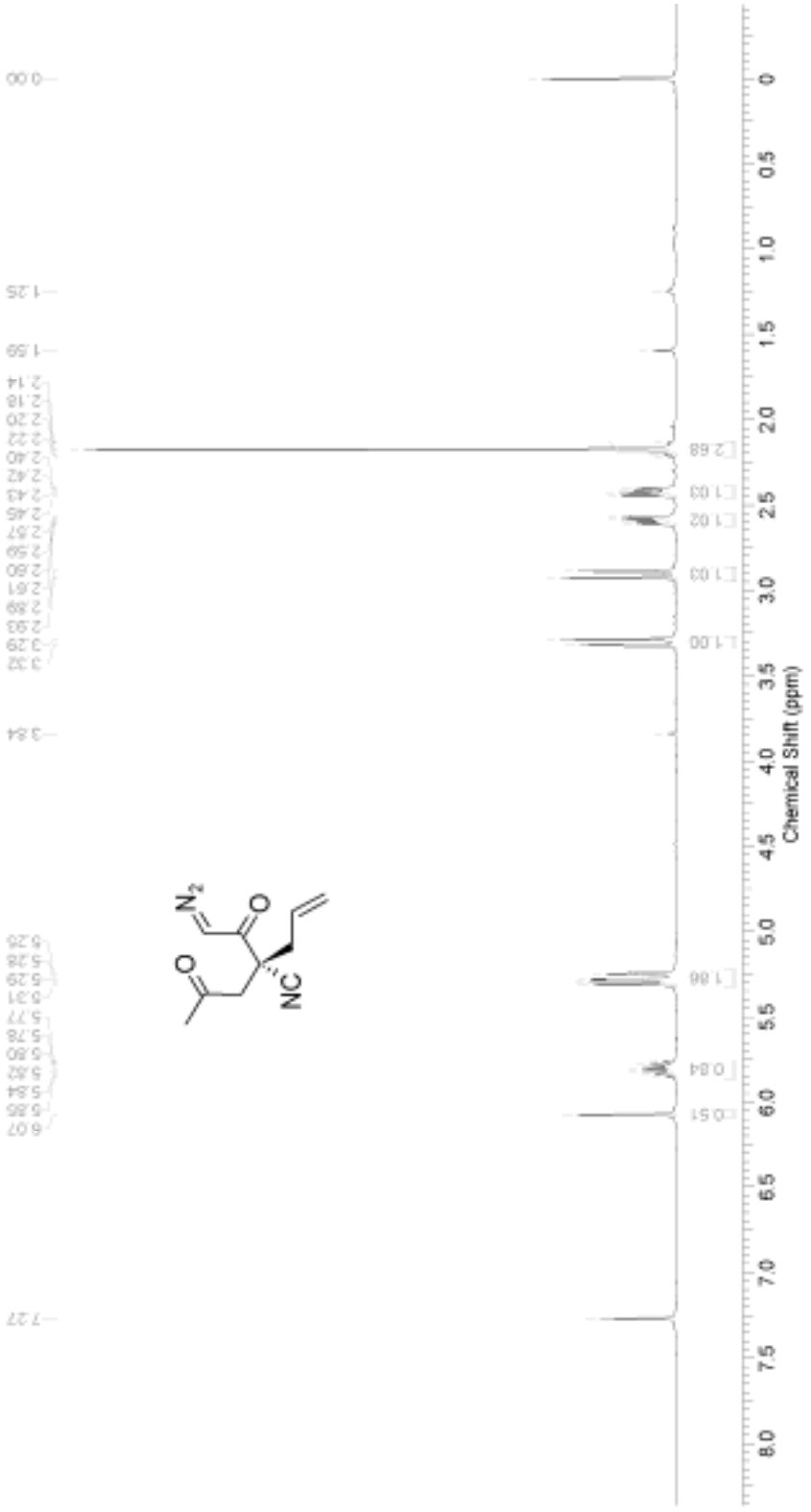
^{13}C-NMR (125 MHz, $CDCl_3$) of **4**



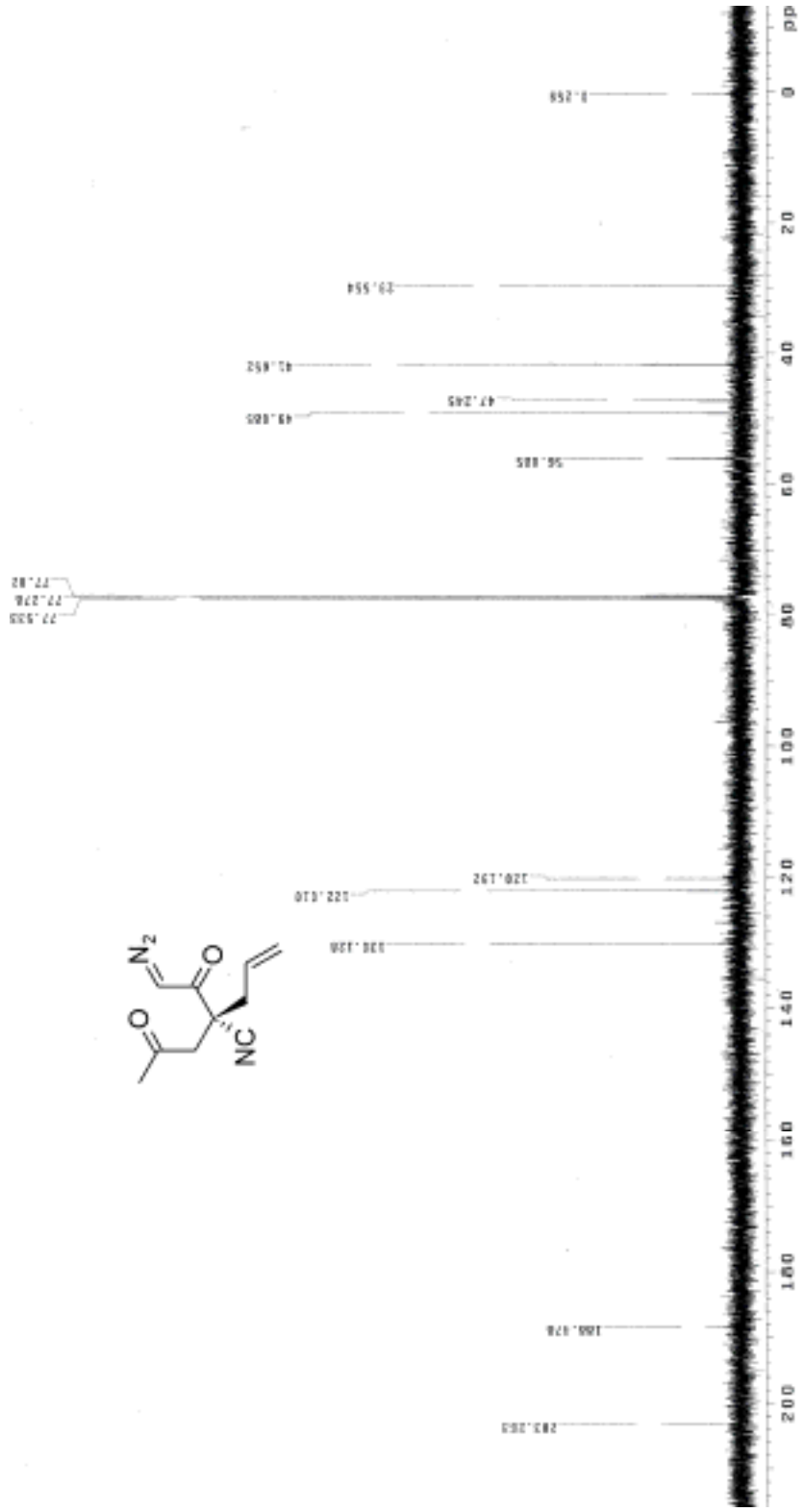
^{1}H-NMR (500 MHz, $CDCl_3$) of **4A**



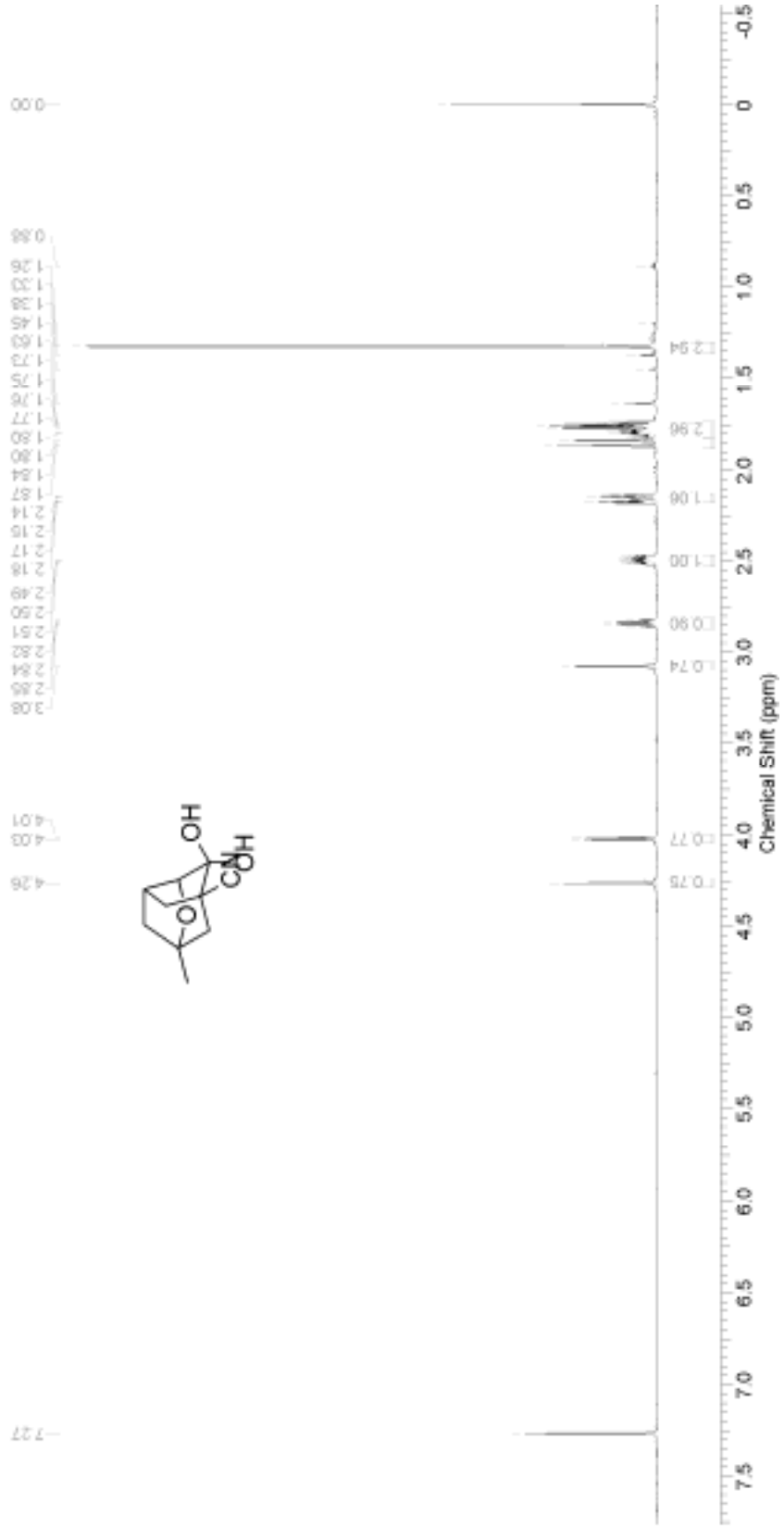
^{13}C-NMR (125 MHz, $CDCl_3$) of **4A**



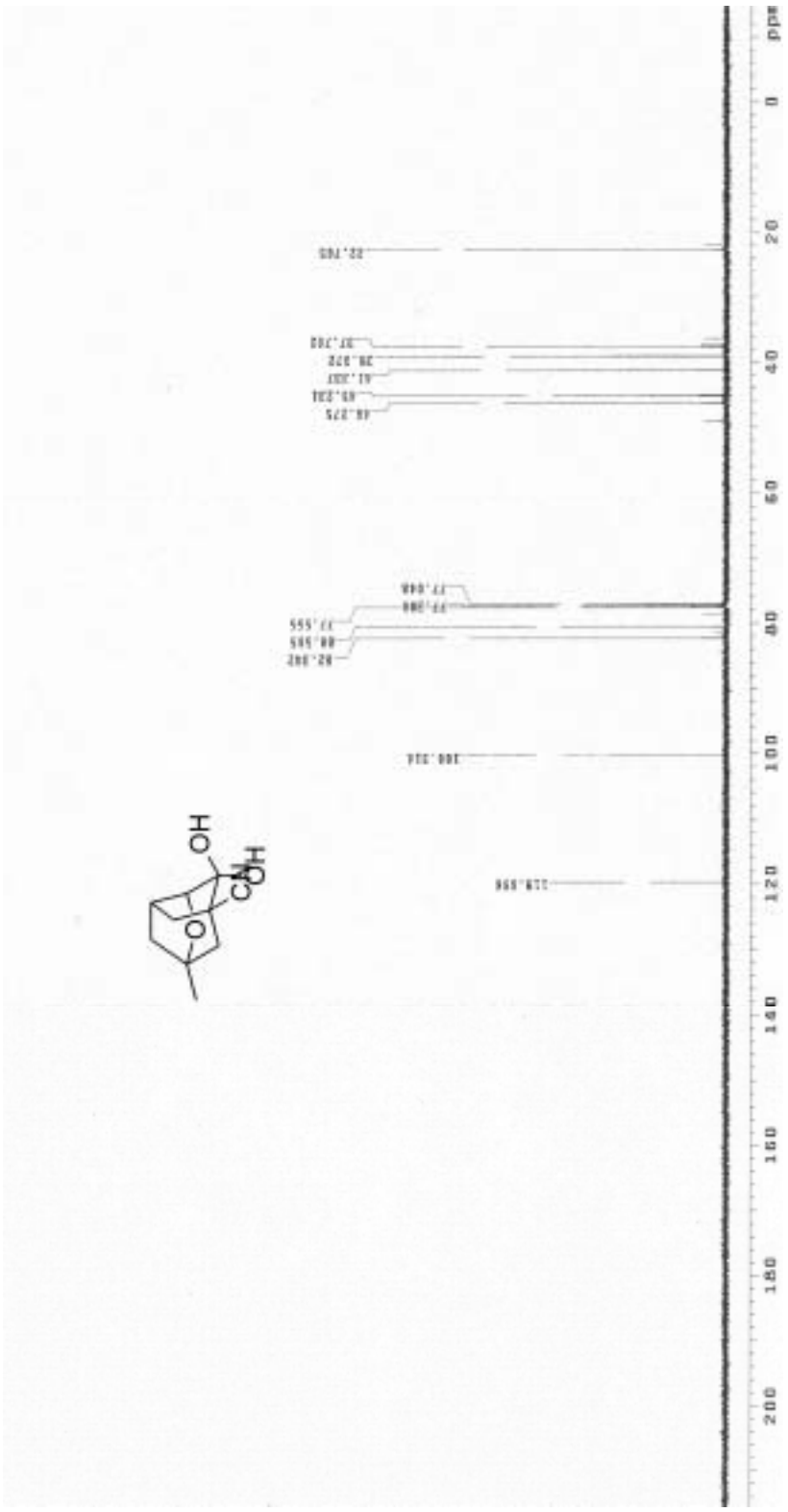
^{1}H-NMR (500 MHz, $CDCl_3$) of **6**



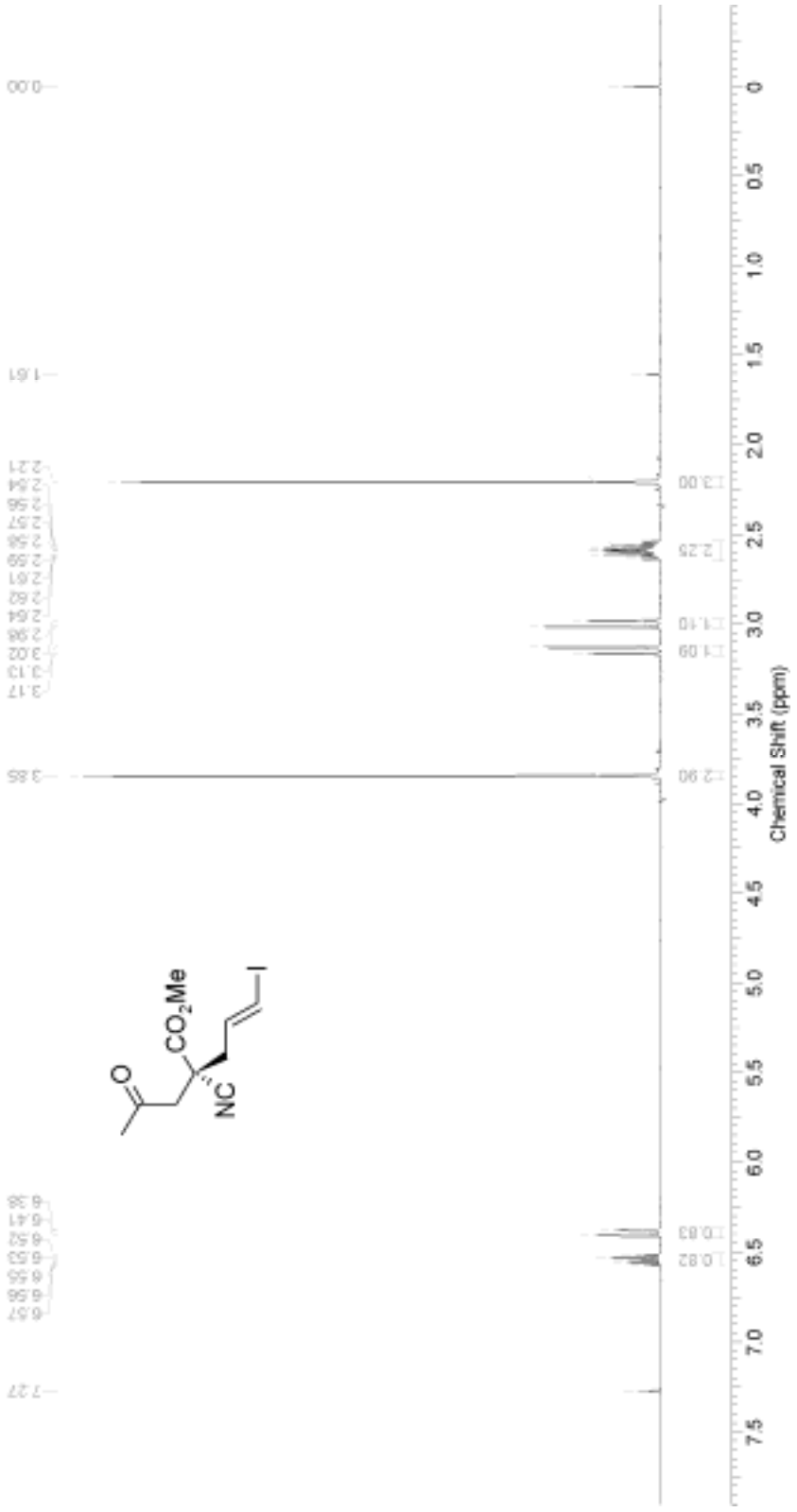
^{13}C-NMR (125 MHz, $CDCl_3$) of **6**



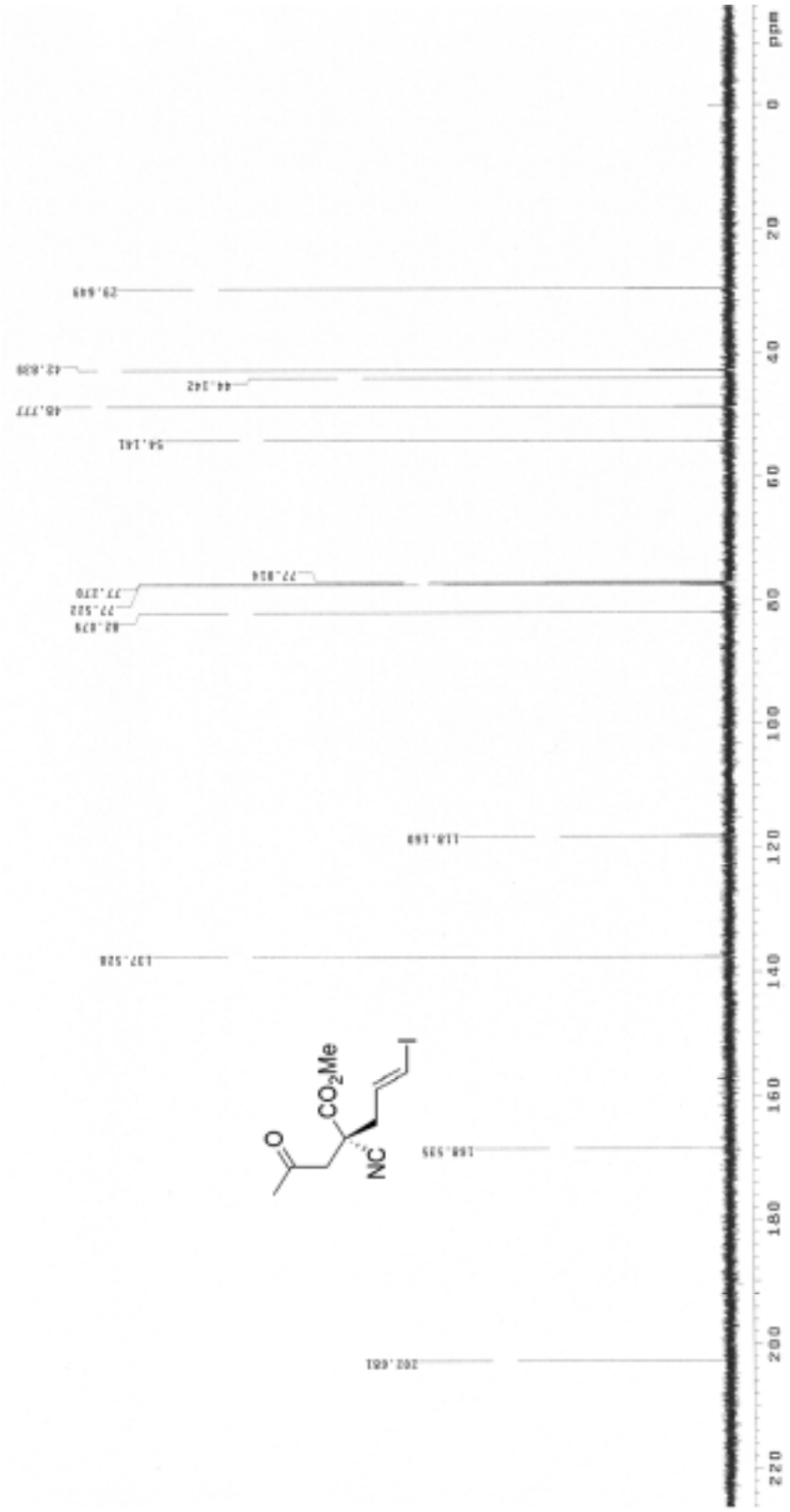
^{1}H-NMR (500 MHz, $CDCl_3$) of **8** (hydrate)



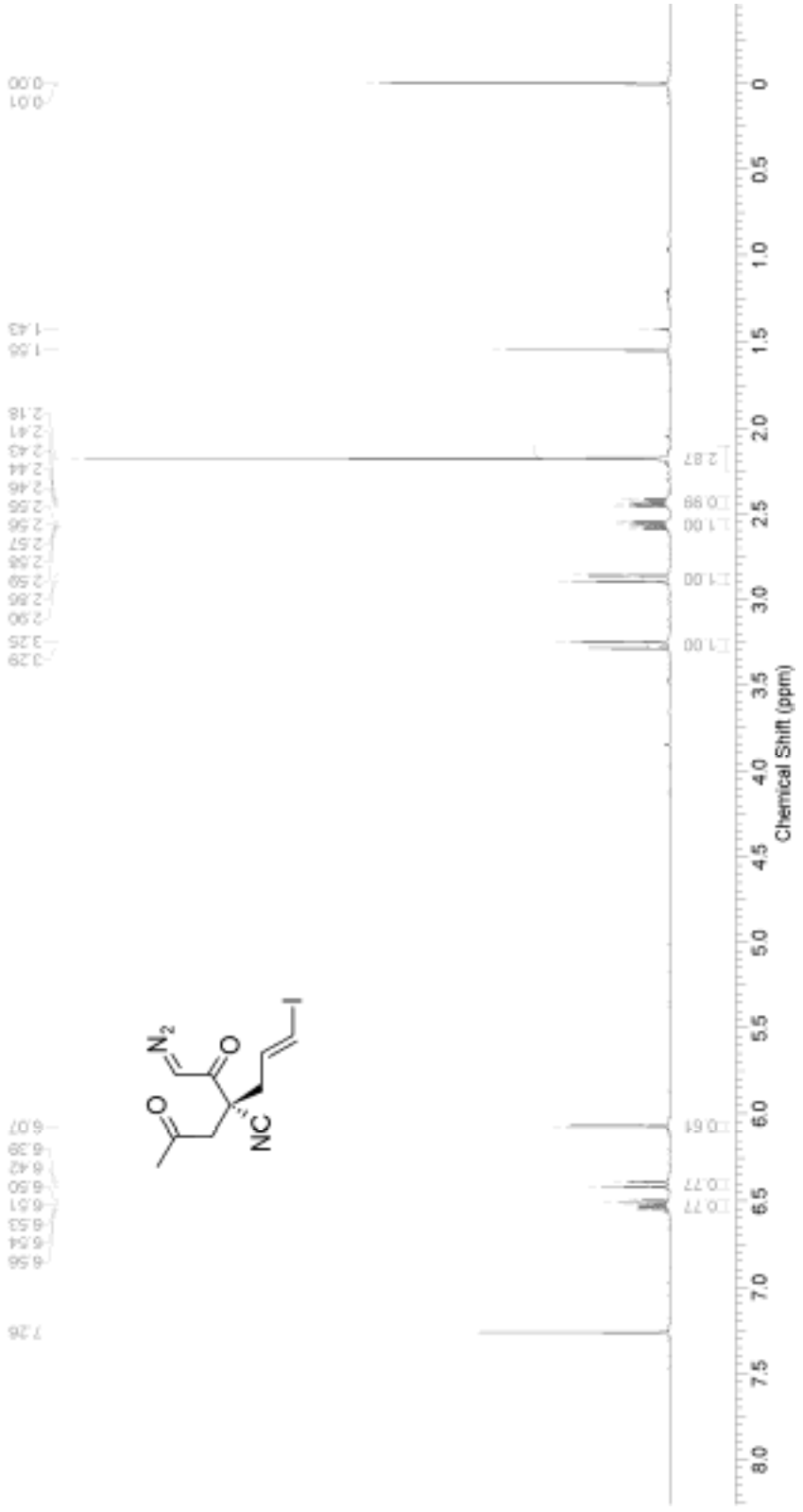
^{13}C-NMR (125 MHz, $CDCl_3$) of **8** (hydrate)



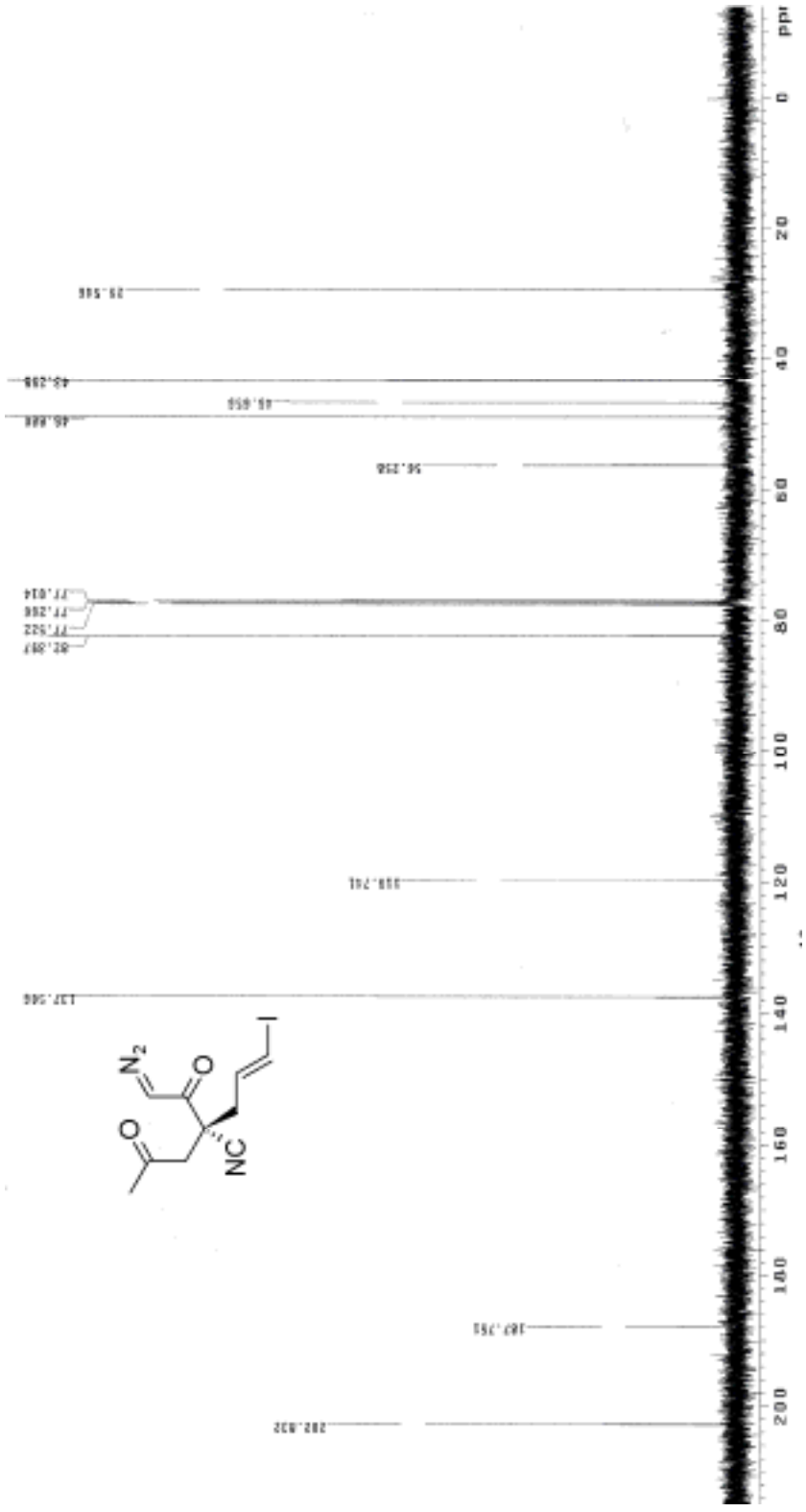
^{1}H-NMR (500 MHz, $CDCl_3$) of **4B**



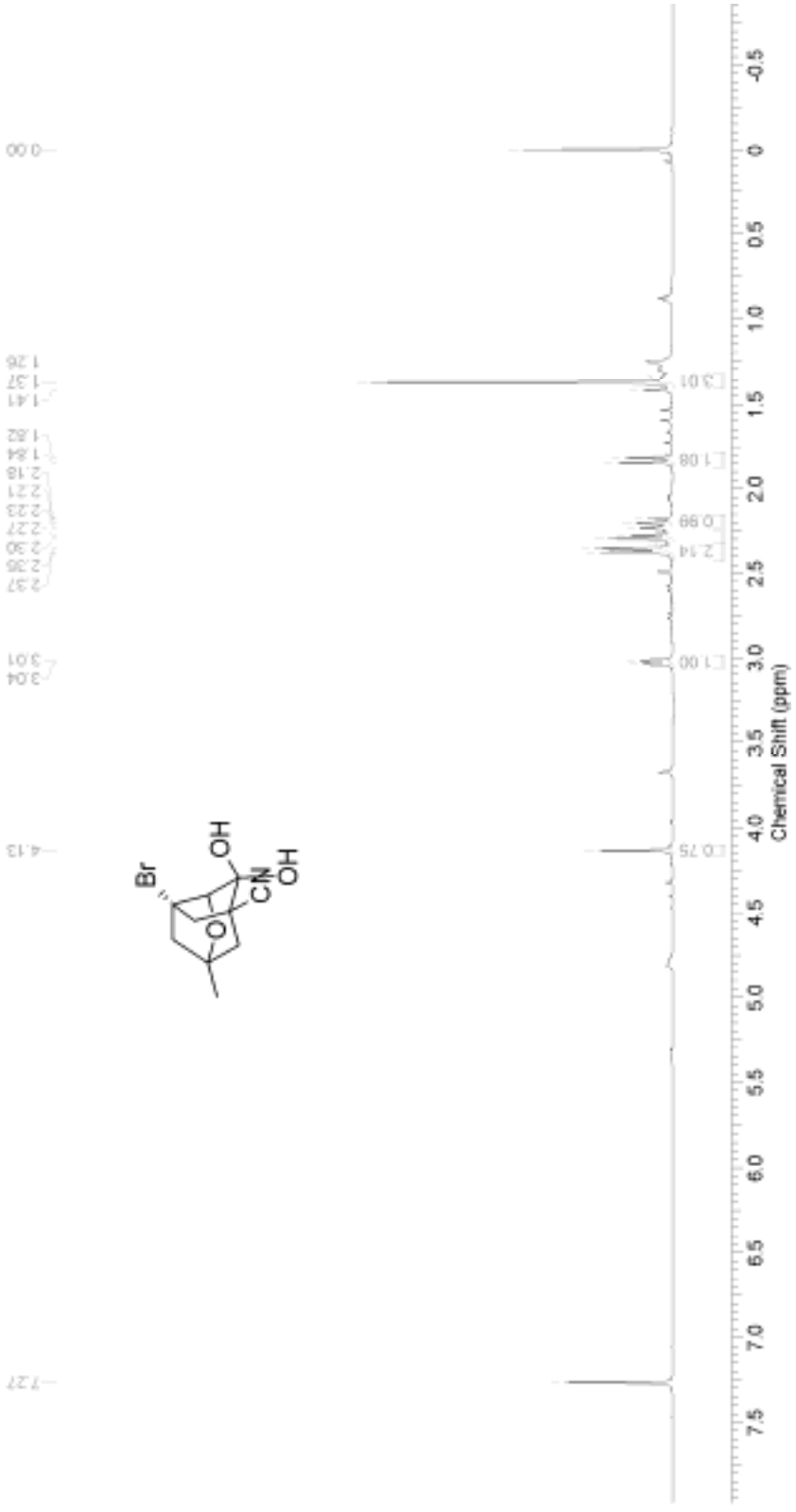
^{13}C-NMR (125 MHz, $CDCl_3$) of **4B**



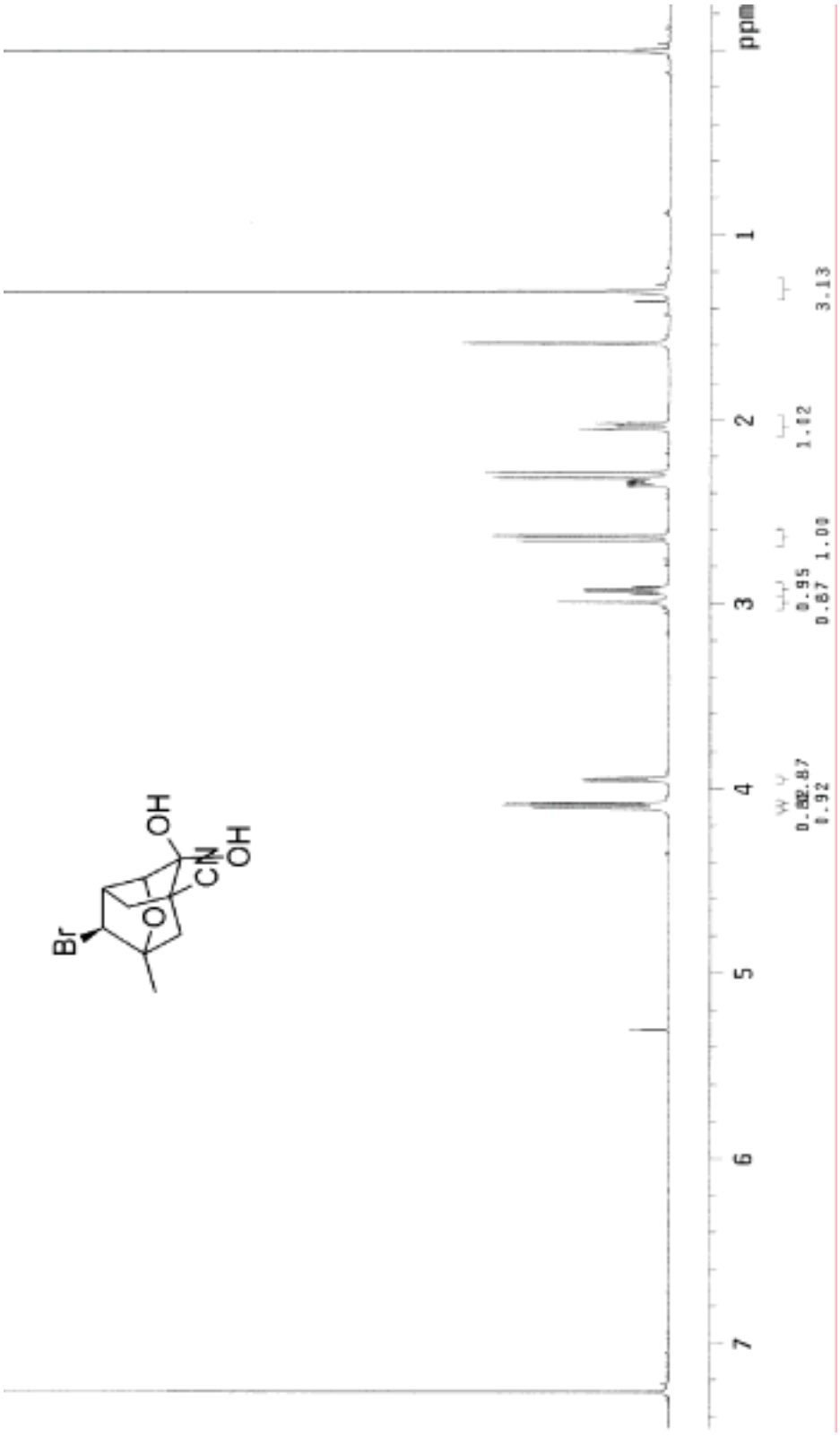
^{1}H-NMR (500 MHz, $CDCl_3$) of **13**



^{13}C-NMR (125 MHz, $CDCl_3$) of **13**

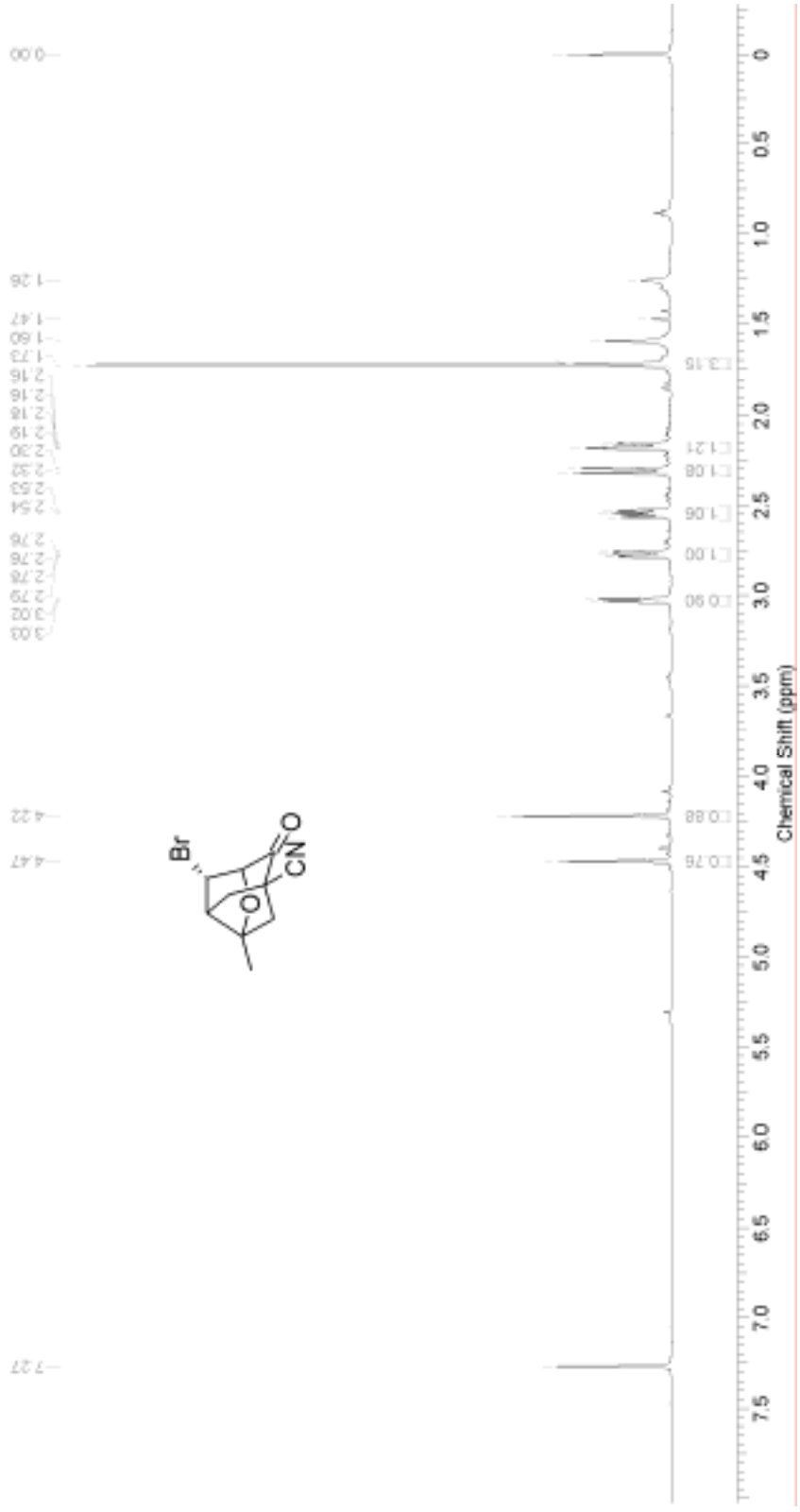


^{1}H-NMR (500 MHz, $CDCl_3$) of **14** (hydrate)

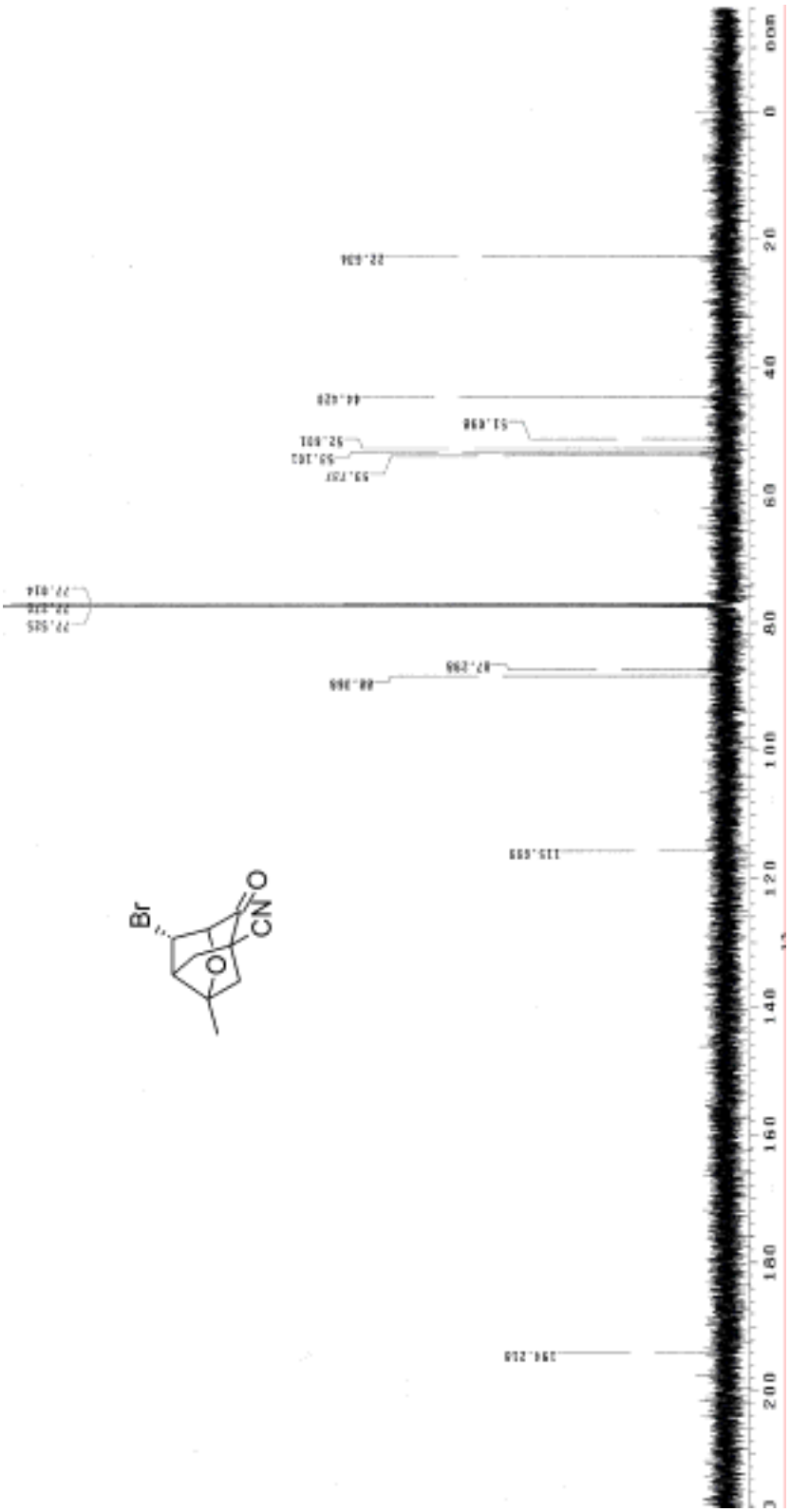


^{1}H-NMR (500 MHz, $CDCl_3$) of **15**

^{1}H-NMR (500 MHz, $CDCl_3$) of **16**

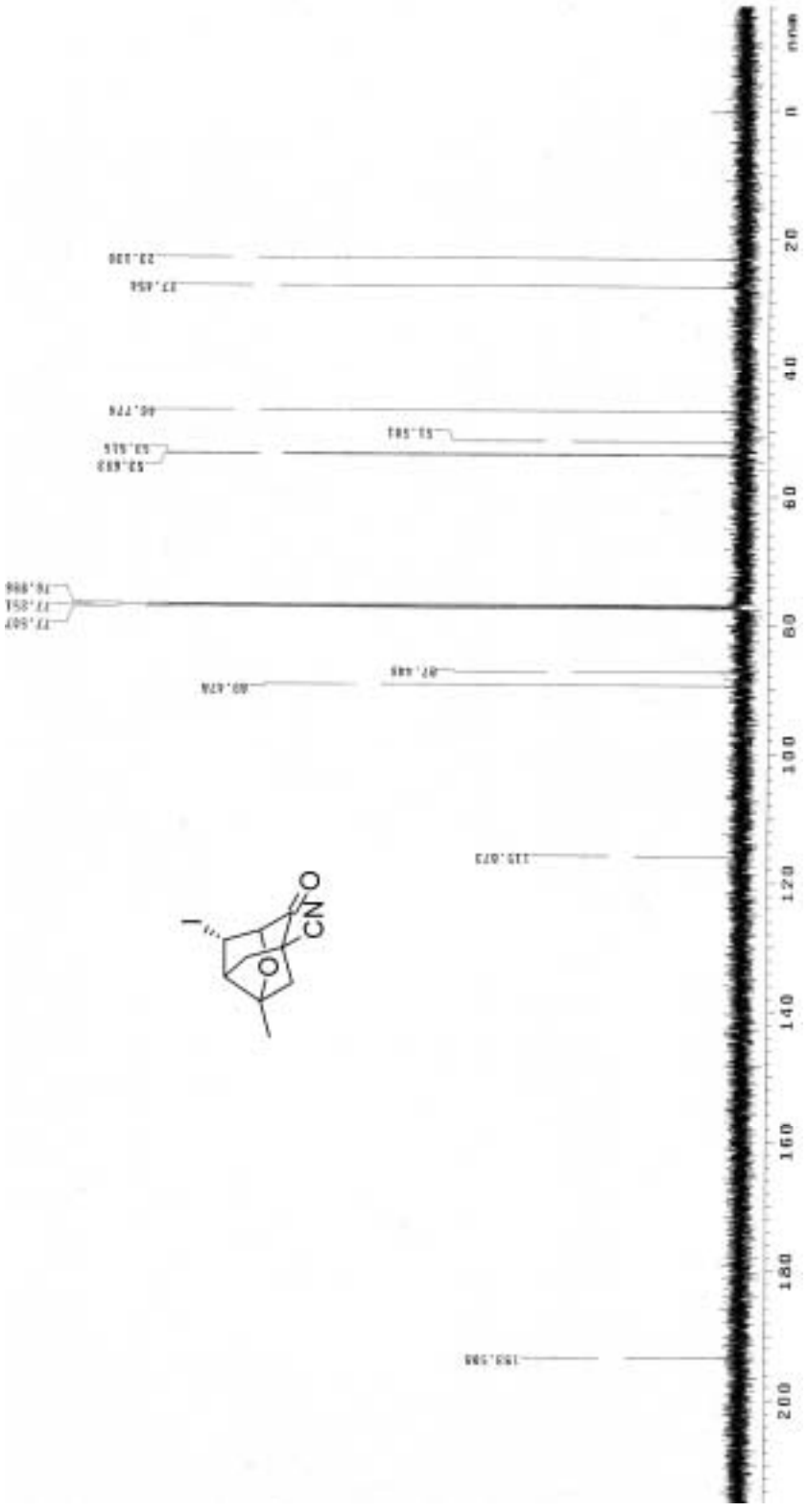


^{1}H-NMR (500 MHz, $CDCl_3$) of **17**

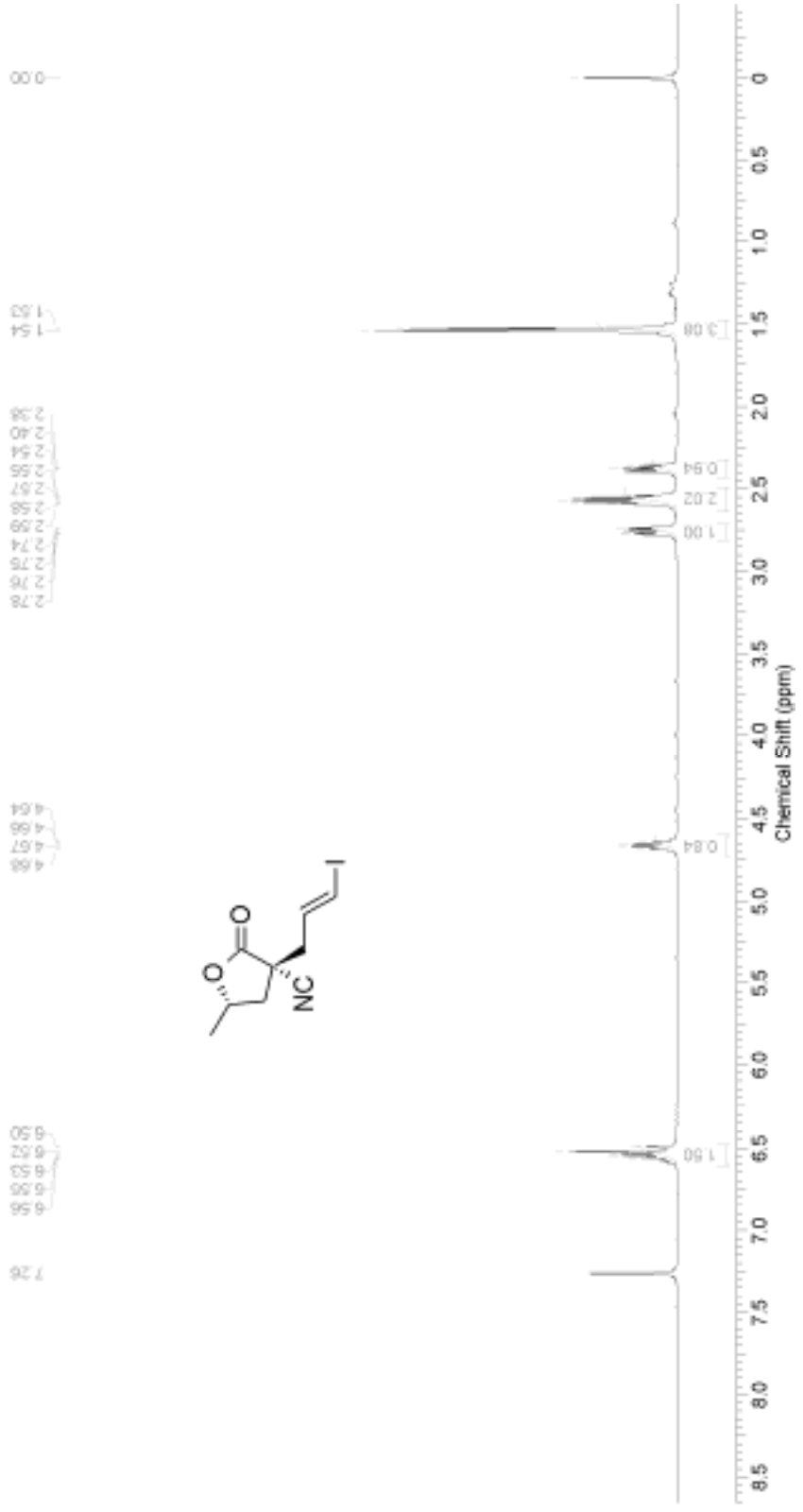


^{13}C-NMR (125 MHz, $CDCl_3$) of **17**

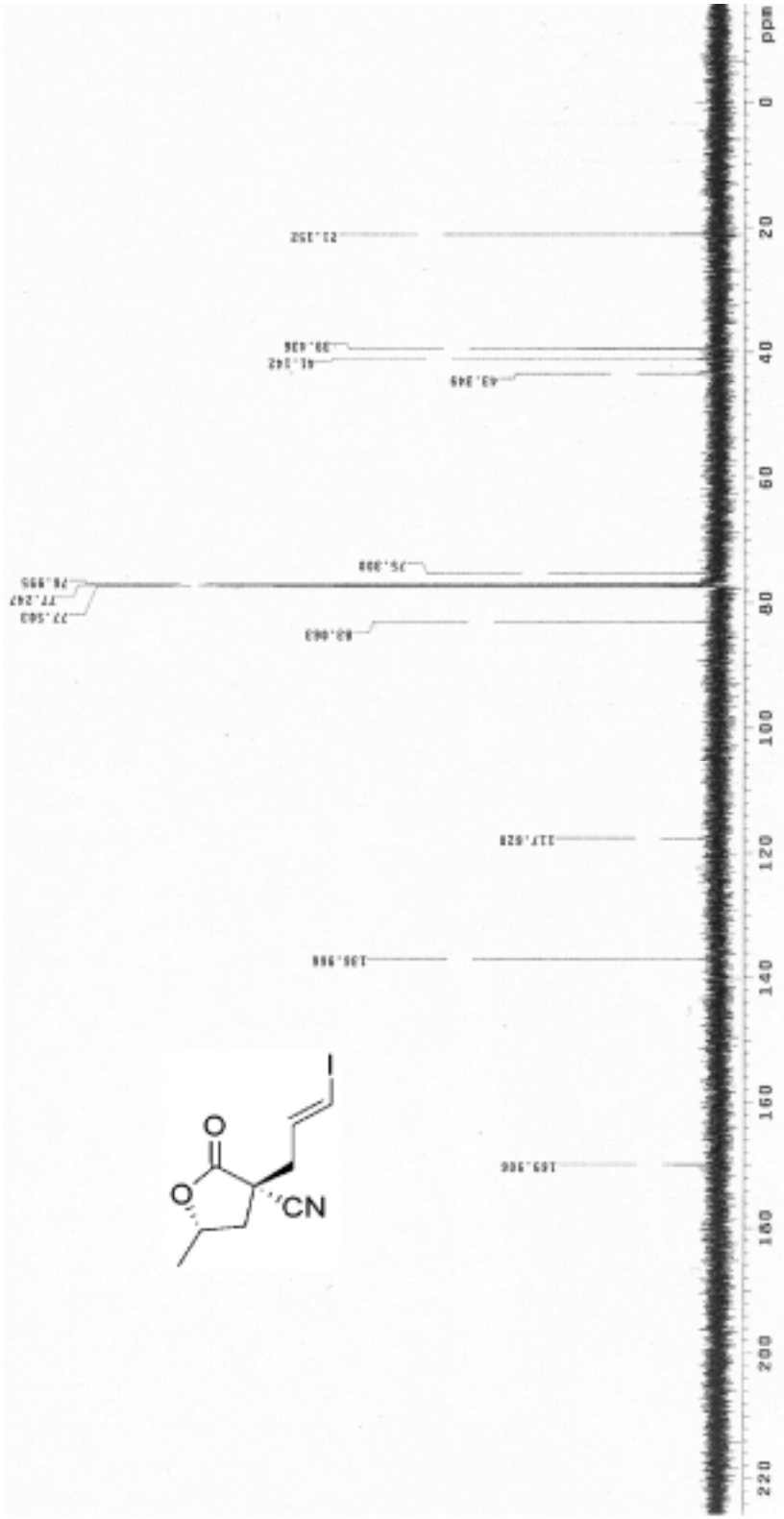
^{1}H-NMR (500 MHz, $CDCl_3$) of **20**



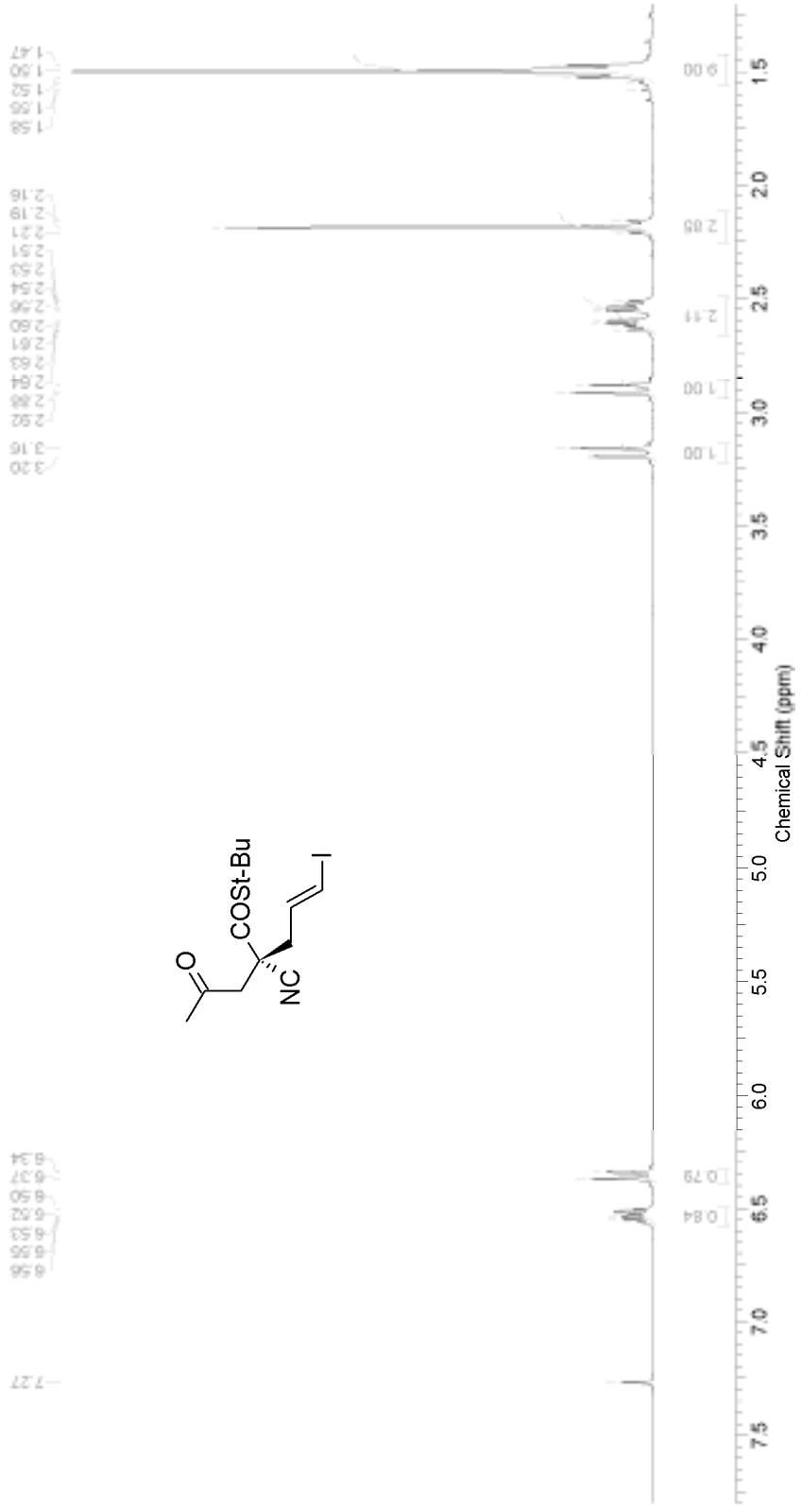
^{13}C-NMR (125 MHz, $CDCl_3$) of **20**



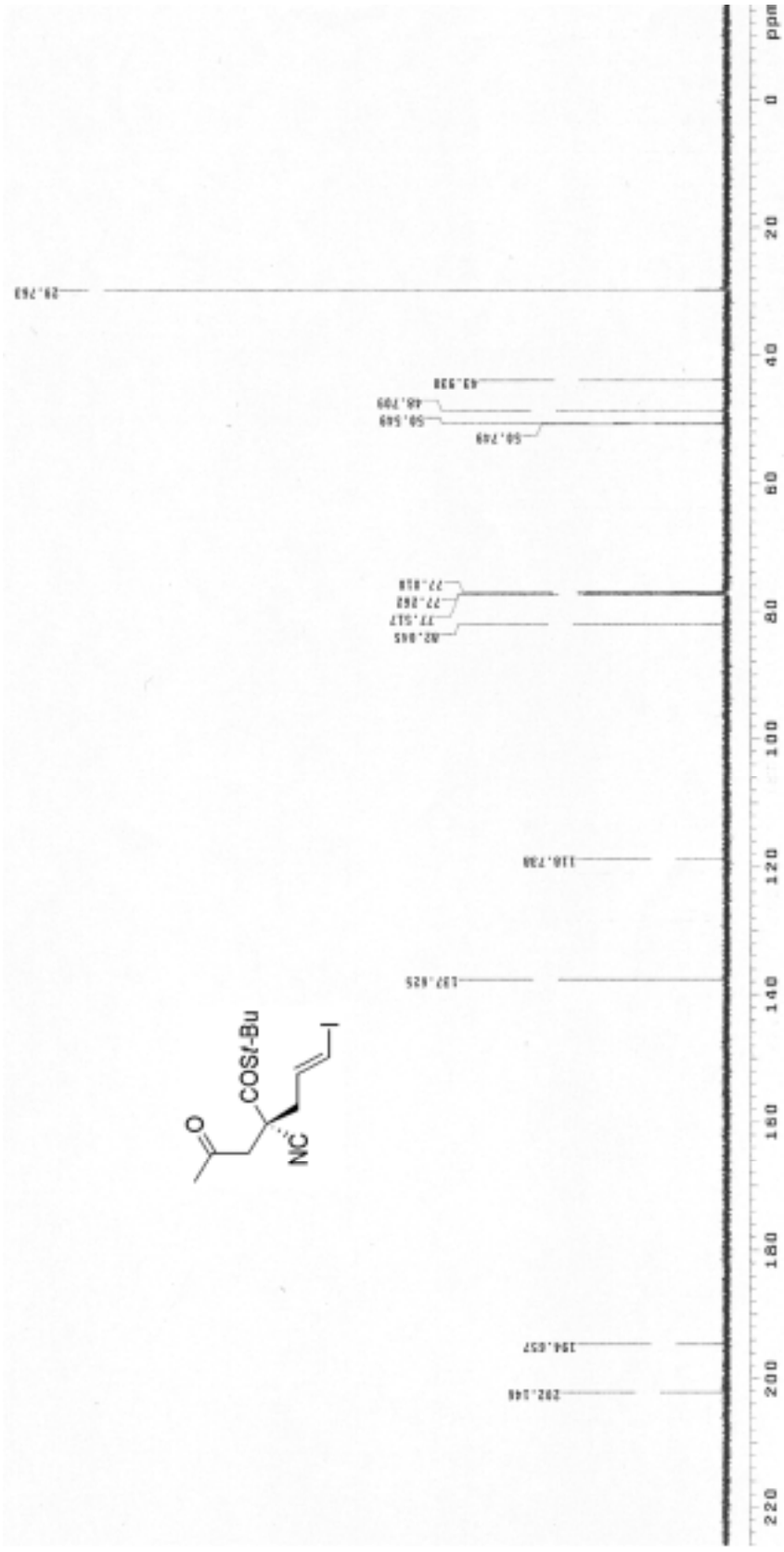
^{1}H-NMR (500 MHz, $CDCl_3$) of **25**



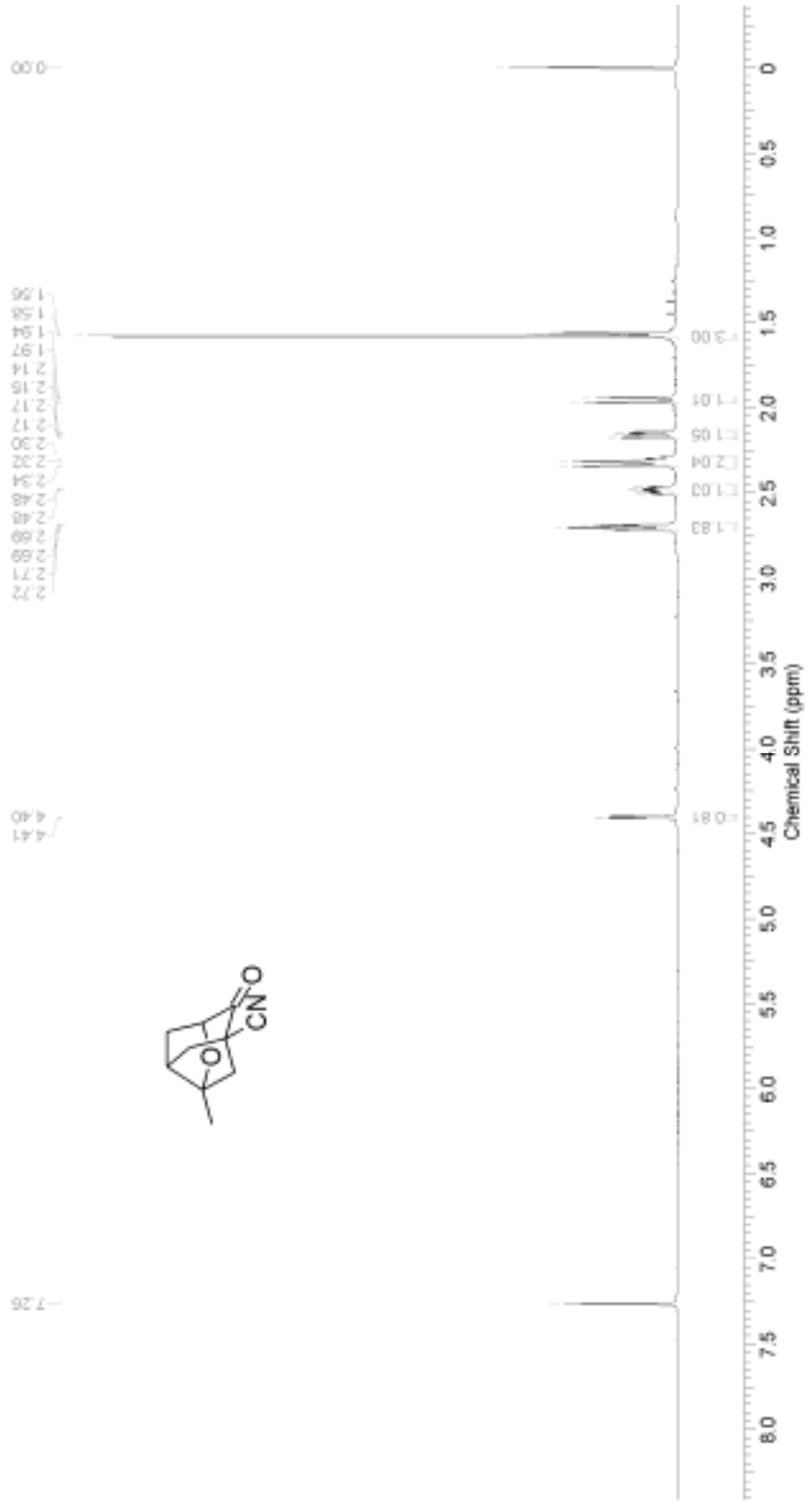
^{13}C-NMR (125 MHz, $CDCl_3$) of **25**



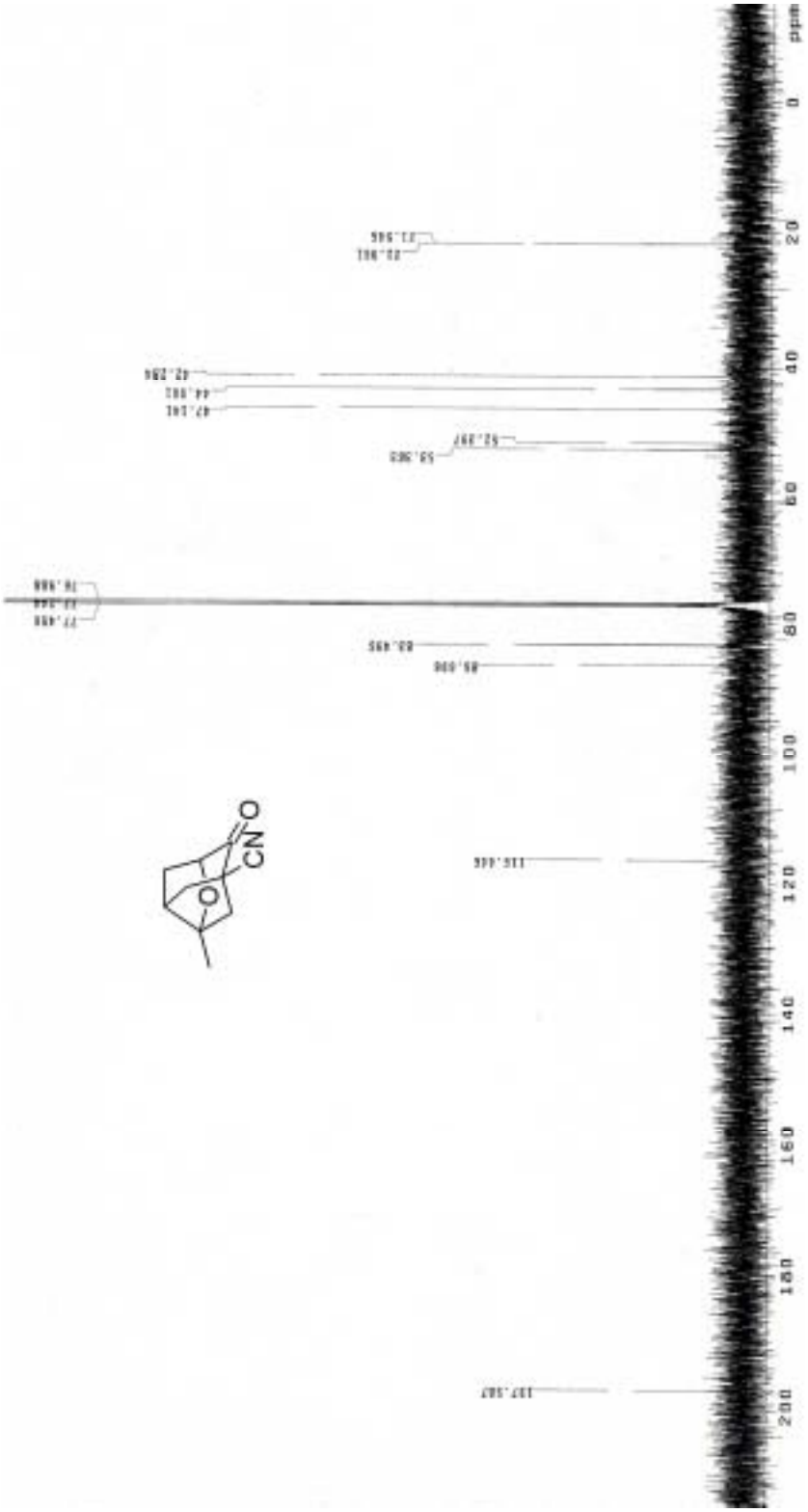
^{1}H-NMR (500 MHz, $CDCl_3$) of **26**



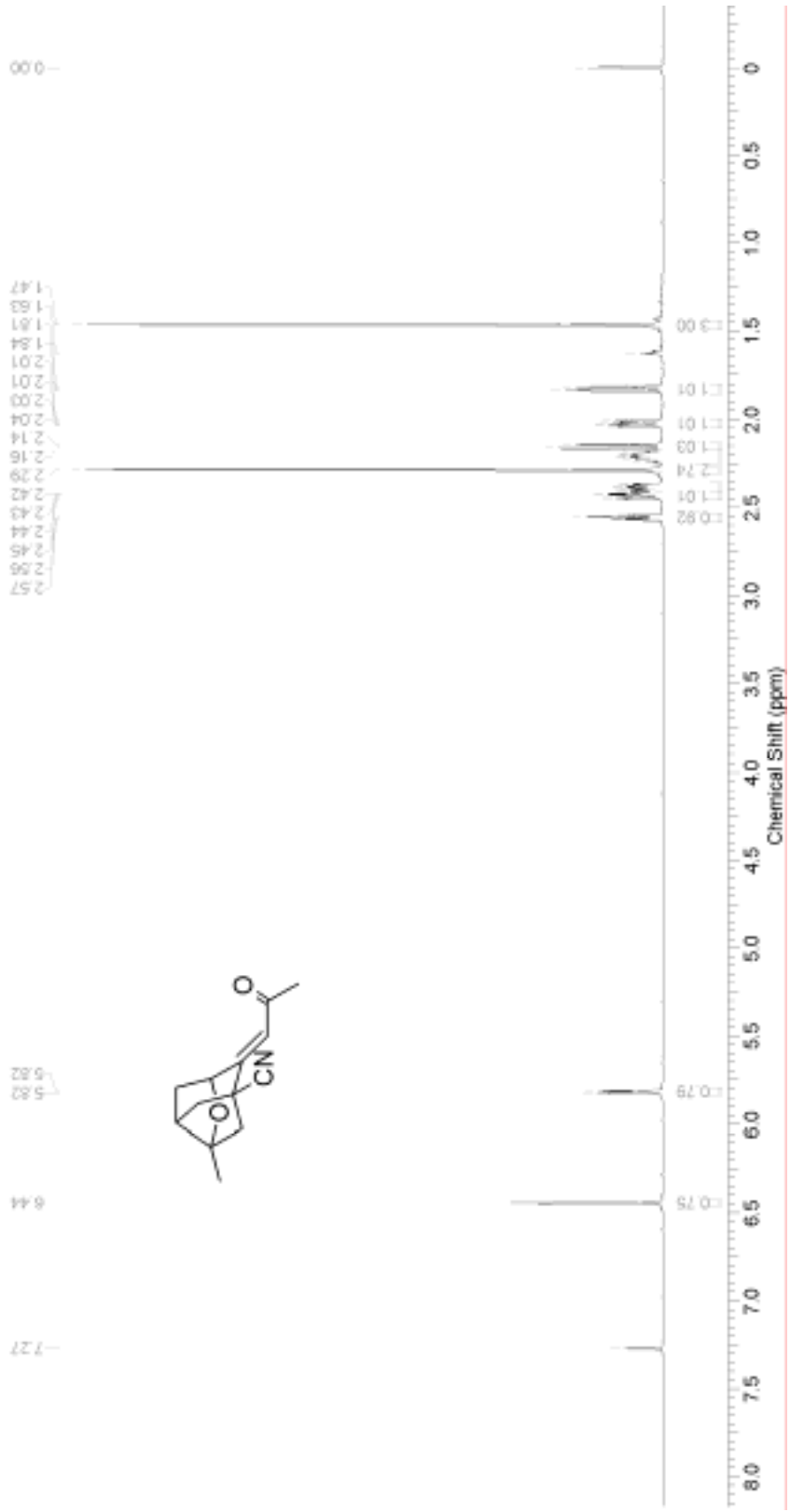
^{13}C-NMR (125 MHz, $CDCl_3$) of **26**



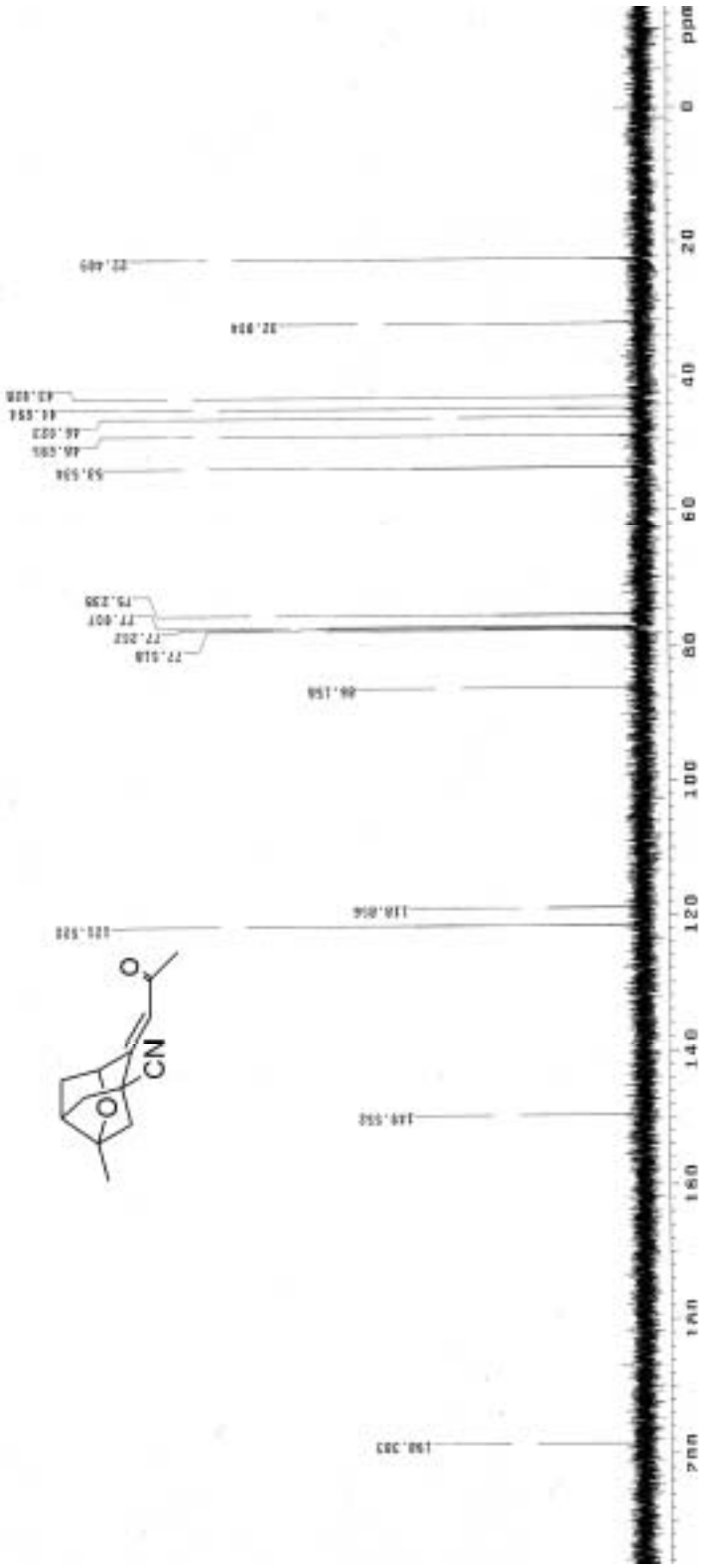
^{1}H-NMR (500 MHz, $CDCl_3$) of **7**



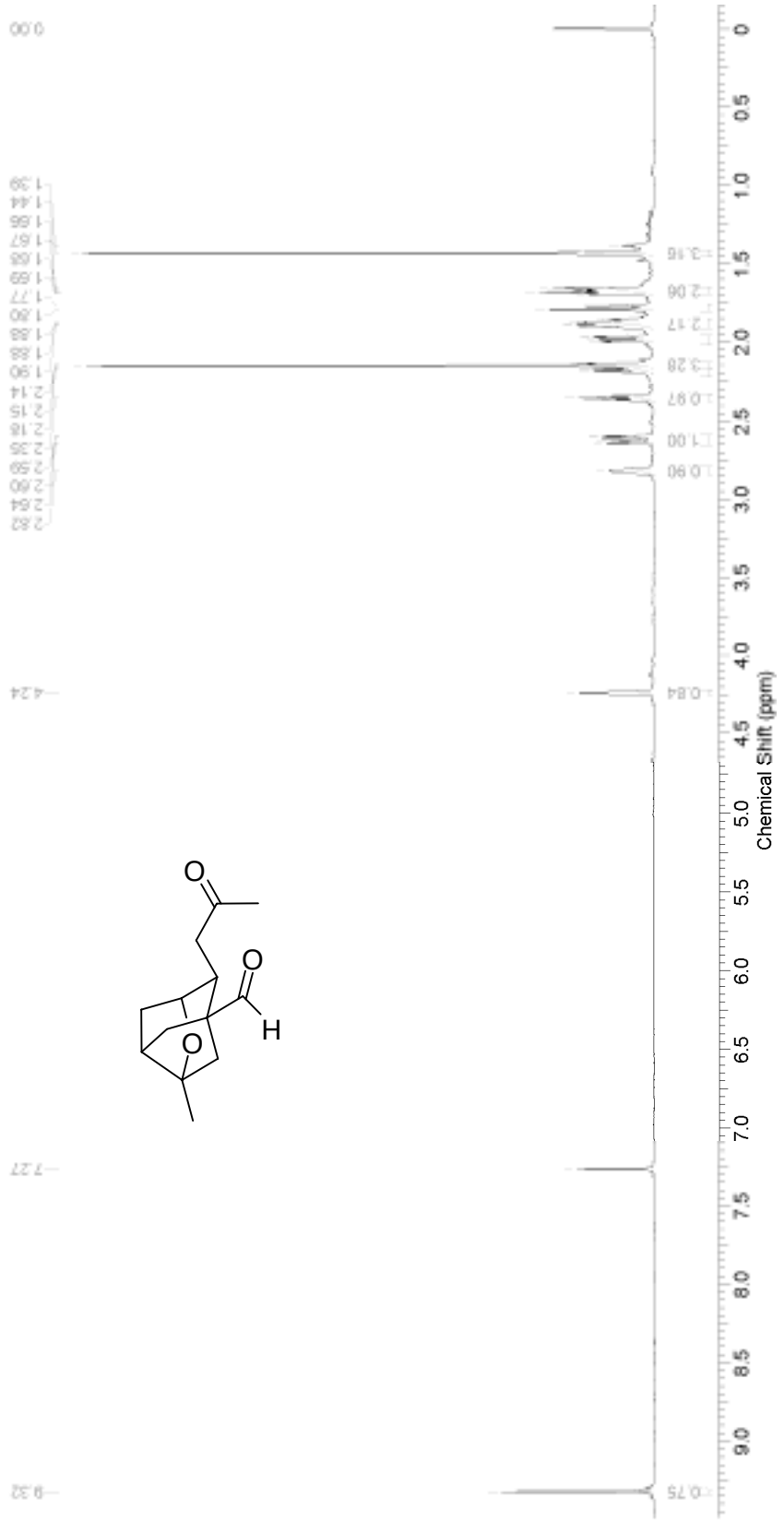
^{13}C-NMR (125 MHz, $CDCl_3$) of **7**



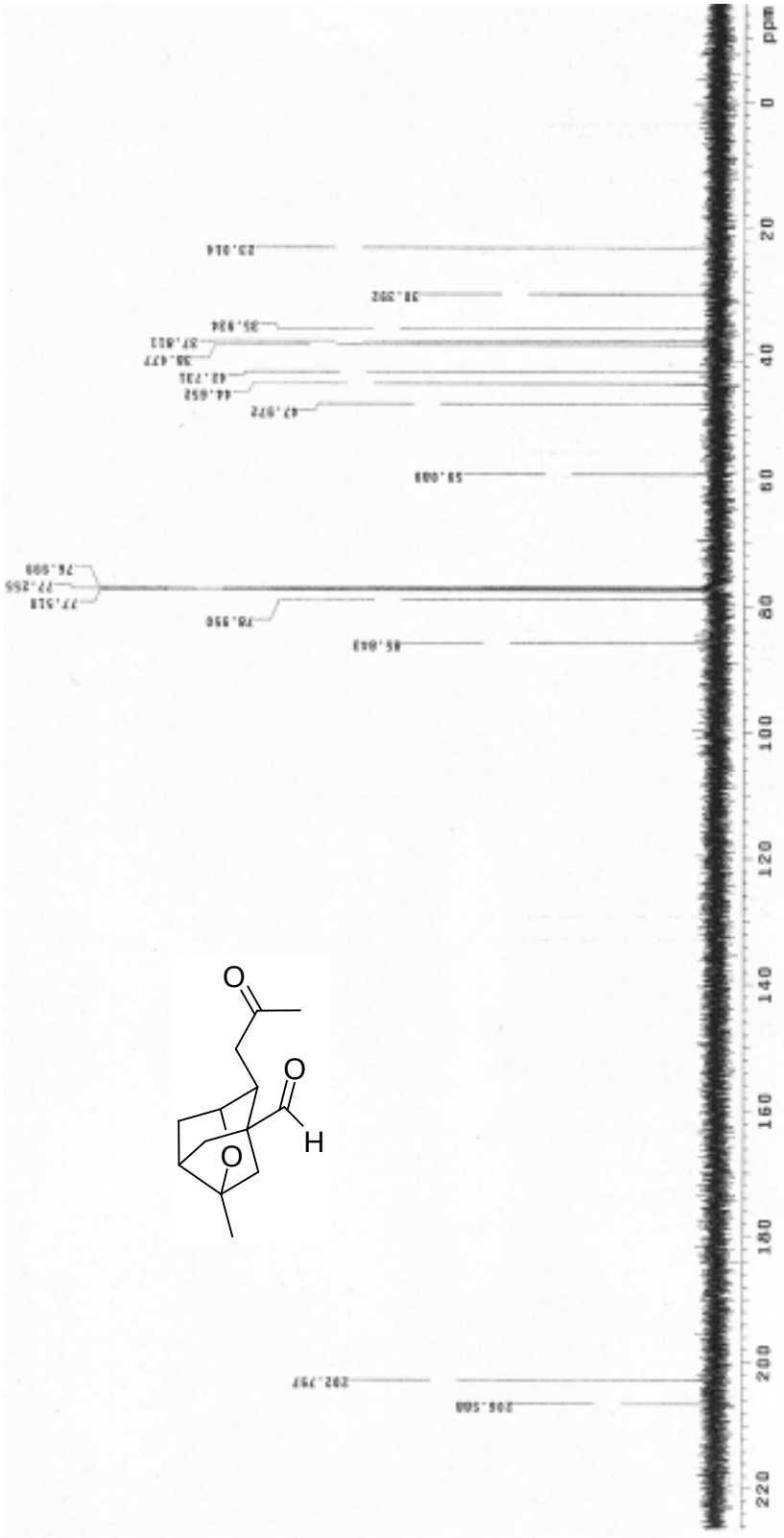
^{1}H-NMR (500 MHz, $CDCl_3$) of **27**



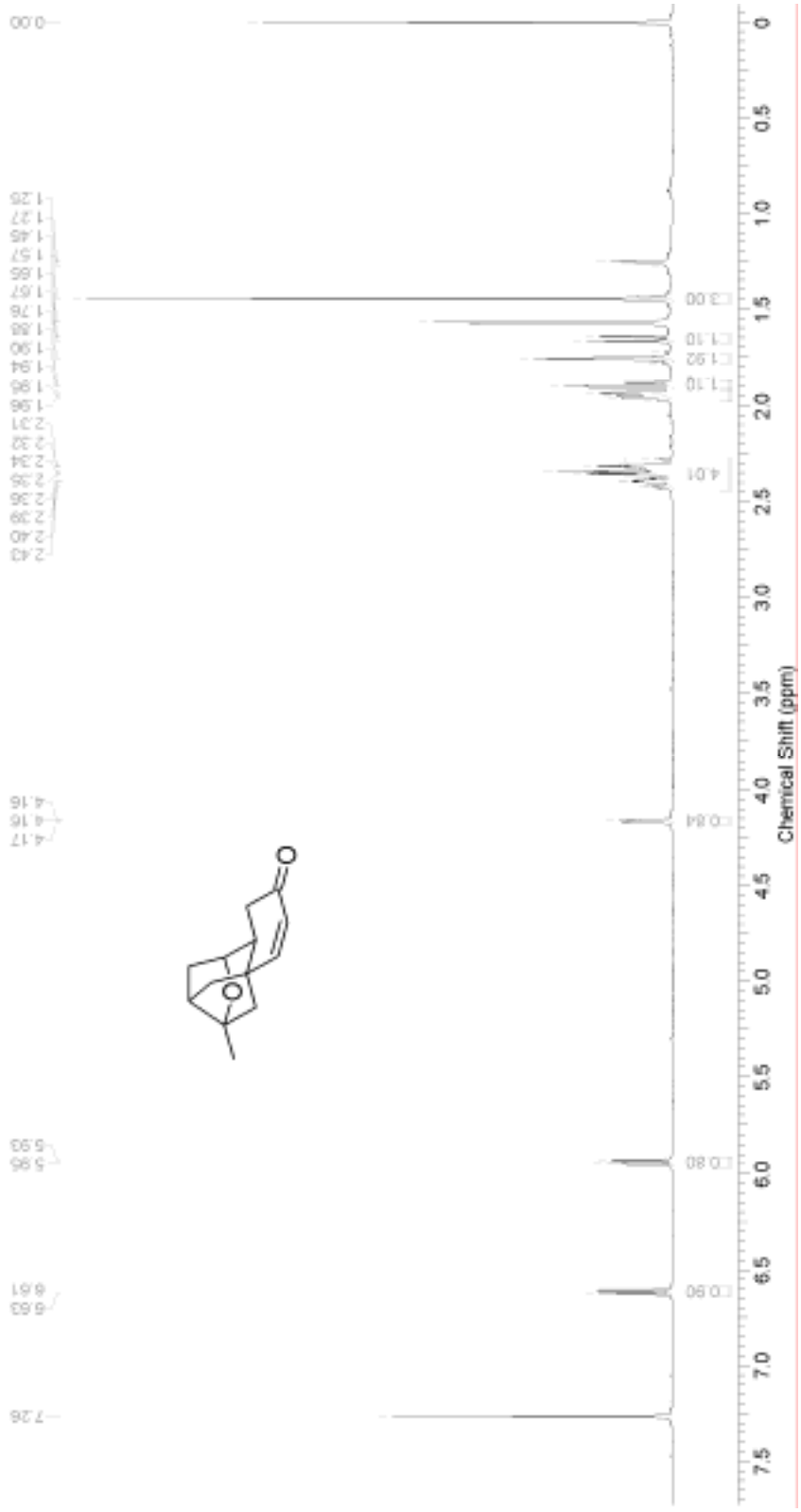
^{13}C-NMR (125 MHz, $CDCl_3$) of **27**



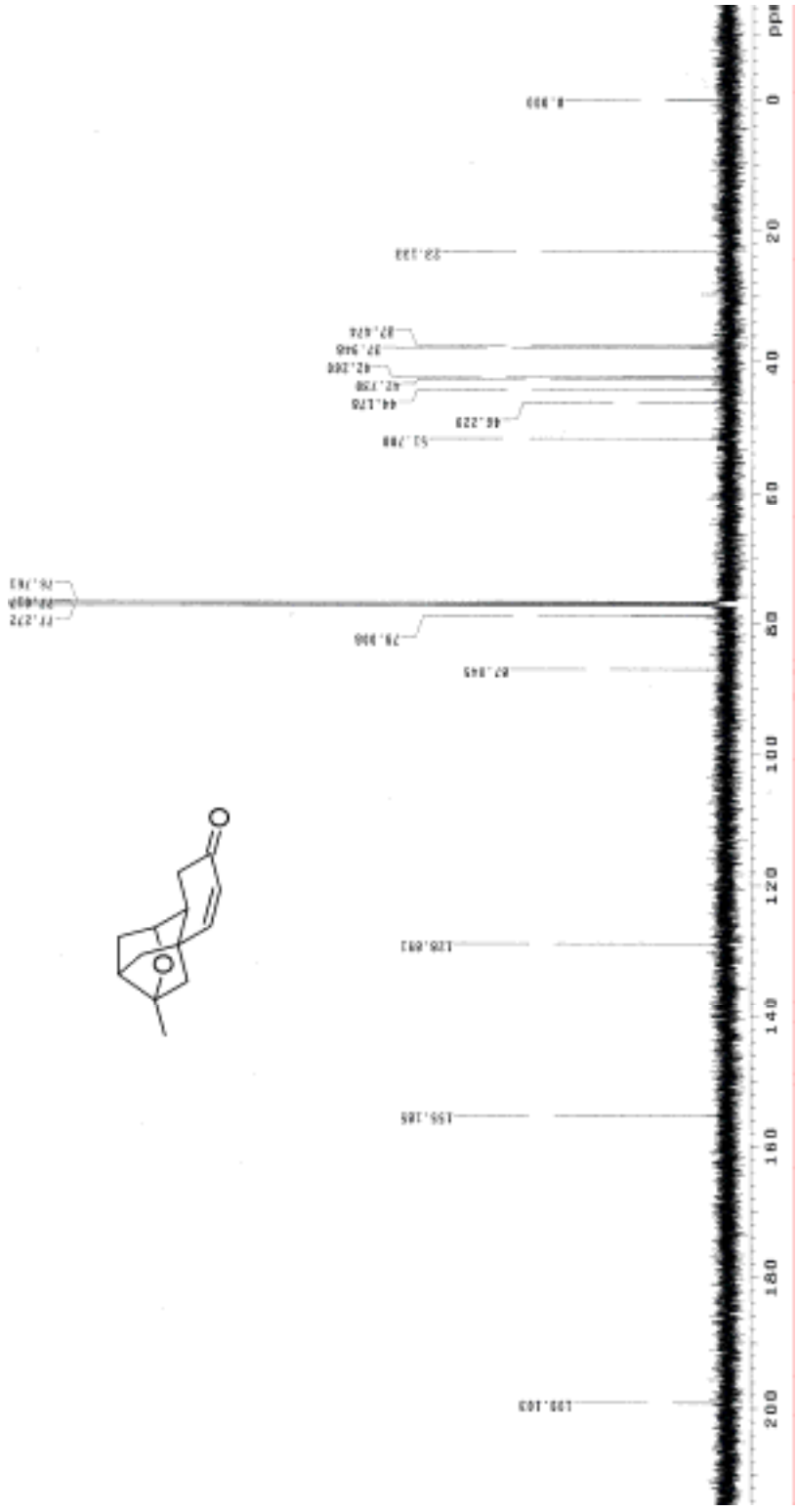
^{1}H-NMR (500 MHz, $CDCl_3$) of **28**



^{13}C-NMR (125 MHz, $CDCl_3$) of **28**



^{1}H-NMR (500 MHz, $CDCl_3$) of **2**



^{13}C-NMR (125 MHz, $CDCl_3$) of **2**