Stereochemical Control of Skeletal Diversity

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Supporting Information

Materials and Methods. All reagents were purchased from Aldrich with the exception of the ruthenium based olefin metathesis catalyst containing 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene, which was purchased from Strem and (*S*)-phenylglycinol, which was purchased from Fluka. Methylene chloride and tetrahydrofuran were passed through two activated alumina columns to remove impurities prior to use (as described in *Organometallics* **1996**, 15, 1518-1520). Except as otherwise indicated, reactions were carried out under nitrogen with dry, freshly distilled solvents. Triethylamine was distilled from calcium hydride.

All reactions were monitored by thin layer chromatography using 0.25 mm E. Merck precoated silica gel 60 (particle size 0.040-0.063 mm). Column chromatography performed using Merck 60 Å (230-400 mesh ASTM) silica gel. Yields refer to chromatographically and spectroscopically pure compounds, except as noted. Concentration refers to the removal of solvent using a Büchi rotary evaporator followed by use of a vacuum pump at approximately 1 torr.

Proton and carbon-13 NMR spectra were recorded on Varian Mercury 400, Varian Mercury 500 and Varian Unity/Inova 600 spectrometers. Proton and carbon-13 chemical shifts are reported in δ values relative to chloroform (7.26 ppm). 1D and 2D NMR experiments were configured using the GLIDE NMR software package VNMR 6.1B Software provided by Varian. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a JASCO DIP 370 digital polarimeter. High resolution mass spectra were obtained with JEOL AX-505 and JEOL SX-102 spectrometers.

X-Ray Crystallographic Data. All the crystal structure information for **(+/-)-1, 6, 8,** and **12** will be submitted to the Cambridge Crystal Structure Data Base following the instructions given by the Journal of Organic Letters.

Experimental Section

Tricyclic Cycloadduct (+/-) 1. Furfural (1.0 mL, 12.2 mmol) was dissolved in 20 mL of methanol. To this solution were added, 4-methoxybenzylamine (2.5 g, 18.3 mmol), fumaric acid monoethyl ester (2.6 g, 18.3 mmol), and benzyl isocyanide (1.5 mL, 12.2 mmol). The reaction was judged to be complete after 48 h based on TLC analysis. After removal of solvent, the crude reaction mixture was applied directly to a silica gel column. The reaction yielded an 11:1 mixture of diastereomers. The major isomer **1**, (R_f = 0.73, 2:1 ethyl acetate:hexanes) was separated by column chromatography (silica gel, 2:1 hexanes:ethyl acetate) from the minor isomer (R_f = 0.79, 2:1 ethyl acetate:hexanes). The major isomer was isolated as a pale yellow oil in 90% yield. **1** was recrystallized from ethyl acetate:hexanes (6:1). ^{1}H NMR ($CDCl_3$, 500 MHz). See spectral data for

assignment of the tricyclic lactam core. δ 7.33-7.28 (m, 3H), 7.21 (d, J = 2.2 Hz, 2H) 7.07 (d, J = 8.5 Hz, 2H), 6.97 (bs, NH); 6.80 (d, J = 8.0 Hz, 2H), 6.39 (d, J = 5.5 Hz, 1H), 6.28 (dd, J = 1.5, 6.0 Hz, 1H), 5.2 (dd, J = 1.5, 5.0 Hz, 1H), 4.84 (d, J = 15.5 Hz, 1H), 4.46-4.37 (qd, J = 6.0, 14.5 Hz, 2H), 4.12 (s, 1H), 4.10 (q, J = 7.0 Hz, 2H), 3.99 (d, J = 15.0 Hz, 1H), 3.76 (s, 3H), 3.40 (t, J = 4.0 Hz, 1H) 3.07 (d, J = 3.5 Hz, 1H) 1.24 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.3, 170.3, 166.9, 159.5, 137.7, 135.1, 134.4, 129.8, 129.0, 128.2, 128.0, 127.1, 114.5, 92.1, 80.4, 63.5, 61.5, 55.5, 50.7, 47.3, 45.9, 44.1, 14.4. HRMS (EI) calculated for $C_{27}H_{28}N_2O_6$ [M+H]: 477.2026, found: 477.2017.

Crystallographic data: orthorhombic single crystal (0.10 x 0.15 x 0.15 mm^3, Space group Pccn, Unit cell constants a = 17.972(1), b = 20.562(1), c = 13.0049(7) Å, α = 90 °, β = 90°, γ = 90°, V = 4805.8(5) Å^3, Z = 4, D_x = 1.317 g/cm^3). X-ray diffraction data were collected using a Bruker SMART CCD diffractometer equipped with an LT-2 low-temperature apparatus at 213 K. Data were measured using omega scans of 0.3° per frame for 30 seconds. A total of 1271 frames were collected with a maximum resolution of 0.75 Å. Cell parameters were retrieved using SMART software and refined using SAINT on all observed reflections. Data reduction was performed with SAINT and the structures are solved by the direct method using the SHELXS-97 program incorporated in SHELXTL-PC V 5.10 and refined by least squares method on F^2. The final agreement factors are $R(F)$ = 0.0610, Rw(F) = 0.1231.

Allyl Carboxylate *(+/-) 4*. The tricyclic cycloadduct **1**, (7.2 g, 15.1 mmol) was dissolved in 35 mL of THF. To this solution were added cesium hydroxide-monohydrate (4.1 g,

24.2 mmol) and allyl bromide (7.9 mL, 90.8 mmol). The reaction mixture was stirred at ambient temperature for 8 h. The reaction was quenched by the addition of 30 mL of 2 N HCl. The reaction mixture was diluted with water. The resultant solution was extracted three times with hexanes:ethyl acetate (1:1). The combined organic layers were washed twice with a saturated solution of sodium bicarbonate and brine. The organic layer was then dried over magnesium sulfate. After filtration over a short pad of silica gel, the organic solvent was removed yielding the crude allylation product as a pale brown oil. The crude material was carried forward without purification.

The crude allylation product (1.5 g, 2.8 mmol) was dissolved in 20 mL of THF. To this solution was added barium hydroxide-octahydrate (2.7 g, 8.5 mmol). The reaction mixture was stirred for 12 h at ambient temperature. The reaction was quenched by the addition of 20 mL of 2 N HCl. The resultant milky white solution was treated with hydrochloric acid until the pH of the reaction solution was adjusted to 2. A small volume of methanol (5 mL) was added to clarify the turbid aqueous solution. The aqueous solution was extracted five times with methylene chloride. The combined organic layers were washed with brine. The organic layer was then dried over magnesium sulfate and filtered over a short pad of silica gel. The residue was purified by flash chromatography (silica gel, 9:1 ethyl acetate:methanol) affording **(+/-)-4** (90% yield over both steps) as a pale yellow oil that foams under vacuum. ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum (mixture of rotamers). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.2, 166.6, 166.3, 159.2, 159.1, 136.6, 135.7, 135.1, 132.8, 131.9, 131.1, 129.5, 129.3, 129.0, 128.9, 128.9, 128.8, 128.6, 128.1, 128.0, 127.9, 126.7, 126.5, 120.0, 117.8, 114.2, 114.1, 91.7, 80.5, 80.4, 59.5, 59.4,

55.3, 55.20, 51.3, 49.4, 49.2, 48.9, 48.3, 46.4, 45.2. HRMS (EI) calculated for $C_{28}H_{28}N_2O_6$ [M+H]: 489.2026, found: 489.2026.

Typical Procedure for Synthesis of the *N*-(4-pentenoyl) Amino Alcohols

***N*-4-pentenoyl-(*1R,2R*)-pseudoephedrine.** To a solution of 4-pentenoic acid (2.4 g, 24.2 mmol), triethylamine (9.7 mL, 72.6 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) (5.1 g, 26.6 mmol), and dimethylaminopyridine (DMAP) (591 mg, 4.8 mmol) in CH_2Cl_2 was added (*1R,2R*)-pseudoephedrine (4.0 g, 24.2 mmol). The reaction mixture was stirred at ambient temperature for 12 h. After removal of the solvent in vacuo, the residue was purified by flash chromatography (silica gel, 1:1 hexanes:ethyl acetate) afforded 4-pentenoyl-(*1R,2R*)-pseudoephedrine (77%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) (mixture of rotamers). δ 7.38-7.35 (m, 4H), 7.29-7.26 (m, 1H), 5.89-5.83 (m, 1H), 5.56 (bt, J = 5.9 Hz, NH), 5.08 (dd, J = 1.5, 17.0 Hz, 1H), 5.03 (d, J = 1.5 Hz, 1H), 4.58 (t, J = 3.4 Hz, 1H), 4.56 (bs, OH), 4.01 (q, 1H) 2.93 (s, 1H), 2.83 (s, 2H), 2.48-2.33 (m, 4H), 1.1 (dd, J = 4.4 Hz, 2H), 0.99 (dd, J = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.6, 142.3, 137.8, 137.4, 128.6, 128.3, 128.3, 127.6, 126.9, 115.2, 115.0, 76.4, 75.4, 58.3, 33.5, 32.9, 32.5, 29.3, 29.0, 26.8, 15.3, 14.4; Low Res. EIMS [M+H] calculated for $C_{15}H_{21}NO_2$: 248.2, found 248.0.

***N*-4-pentenoyl-(*1S,2S*)-2-amino-3-methoxy-1-phenyl-1-propanol.** Yield: 64%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36-7.32 (m, 3H), 7.28-7.25 (m, 1H), 6.18 (d, J = 7.8 Hz, NH), 5.76-5.68 (m, 1H), 5.01 (dd, J = 1.5, 17.1 Hz), 5.0 (t, J = 3.4 Hz, 1H), 4.22-4.19 (m, 1H), 3.84 (d, J = 2.9 Hz, 1H), 3.44 (qd, J = 3.4, 9.8 Hz, 2H), 3.36 (s, 3H), 2.33-

2.29 (m, 2H), 2.27-2.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.1, 141.1, 136.8, 128.3, 127.6, 125.9, 115.5, 74.4, 73.4, 59.2, 54.6, 35.7, 29.5; EIMS $[M+H]^+$ calculated for $C_{15}H_{21}NO_3$: 264.3, found 264.1.

***N*-4-pentenoyl-(*S*)-1-phenyl-2-aminoethanol.** Yield: 67%, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (d, J = 4.4 Hz, 2H), 7.22-7.17 (m, 3H), 5.9 (bs, NH), 5.75-5.67 (m, 1H), 4.96 (dd, J = 1.5, 17.1 Hz, 1H), 4.91 (dd, J = 1.5, 10.2 Hz, 1H), 4.76-4.73 (m, 1H), 3.6 (dq, J = 2.9, 6.8 Hz, 1H), 3.43 (bs, 1H), 3.24 (qd, J = 1.5, 6.8 Hz, 2H), 2.27 (qd, J = 1.5, 7.8 Hz, 2H), 2.19 (t, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.8, 141.8, 136.8, 128.4, 127.7, 125.8, 115.6, 73.2, 47.4, 35.6, 29.5; EIMS $[M+H]^+$ calculated for $C_{13}H_{17}NO_2$: 220.1, found 219.9.

***N*-4-pentenoyl-(*S*)-1-aminopropanol.** Yield: 70%, pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.10 (bs, NH), 5.86-5.78 (m, 1H), 5.07 (dd, J = 1.5, 17.1 Hz, 1H), 5.01 (dd, J = 1.95, 10.3 Hz, 1H), 3.93-3.87 (m, 1H), 3.43 (dq, J = 2.9, 6.8 Hz, 2H), 3.13-3.07 (m, 1H), 2.9 (d, J = 4.4 Hz, 1H), (2.39 (qd, J = 1.5, 6.8 Hz, 2H), 2.30 (t, J = 7.3 Hz, 2H), 1.43 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.6, 136.7, 115.5, 66.9, 46.9, 35.6, 29.5, 20.7; EIMS $[M+H]^+$ calculated for $C_8H_{15}NO_2$: 158.1, found 157.9.

***N*-4-pentenyl-(*1S,2R*)-norephedrine**. Yield: 78 %, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38-7.26 (m, 5H), 5.87-5.79 (m, 1H), 5.56 (d, J = 5.9 Hz, NH), 5.08 (dd, J = 1.5, 17.0 Hz, 2H), 5.03 (dd, J = 1.5, 9.8 Hz, 2H), 4.85 (t, J = 3.4 Hz, 1H), 4.35 (dq, J = 2.9, 7.3 Hz, 1H), 3.54 (d, J = 4.4 Hz, 1H), 2.4 (q, J = 6.8 Hz, 2H), 2.9 (t, J = 1.5 Hz, 2H), 1.02

(d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.1, 140.7, 136.8, 128.1, 127.4, 126.3, 115.7, 51.0, 35.7, 29.5, 14.4; EIMS $[M+H]^+$ calculated for $C_{14}H_{19}NO_2$: 234.1, found 233.9.

***N*-4-pentenyl-2-amino-2-methyl-1-propanol.** Yield: 52%, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.85-5.77 (m, 1H) 5.56 (bs, NH), 5.07 (dd, J = 1.95, 17 Hz, 2H), 5.03 (dd, J = 1.0, 10.3 Hz, 2H), 4.87 (d, J = 5.9 Hz, OH), 3.57 (d, J = 5.9 Hz, 2H), 2.37 (dt, J = 6.8, 7.3 Hz, 2H), 2.25 (t, J = 7.8 Hz, 2H), 1.28 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4, 136.7, 115.8, 70.7, 56.1, 36.2, 29.7, 24.6.; EIMS $[M+H]^+$ calculated for $C_9H_{17}N0_2$: 172.1, found 171.9.

Typical Procedures for Synthesis of Metathesis Substrates

Protocol A: Metathesis substrates 2 and 3. Racemic **4** (1.7 g, 3.4 mmol) was dissolved in 10 mL of CH_2Cl_2. To this solution was added benzotriazol-1-yloxy-tris(dimethyl-amino)phosphoniumhexafluorophosphate (BOP) (1.7 g, 3.8 mmol), triethylamine (2.3 mL, 17.2 mmol), and dimethylaminopyridine (126 mg, 1.0 mmol), and 4-pentenyl-(*1R,2R*)-pseudoephedrine (851 mg, 2.5 mmol). The reaction was allowed to proceed at ambient temperature for 16 h. The deep purple reaction mixture was quenched by the addition of 10 mL of 2 N potassium hydroxide and water. The solution was extracted five times with hexanes:ethyl acetate (1:1). The combined organic layers were washed with twice with 2 N HCl, saturated sodium bicarbonate, and brine. The organic layer was then dried over magnesium sulfate and subsequently filtered over a short pad of silica gel. The residue left after removal of solvent in vacuo was purified by flash chromatography

(silica gel, 4:1 ethyl acetate:hexanes) affording **2** and **3** in a combined yield of 67%. The diastereomers were initially separated from unconsumed 4-pentenoyl-(*1R,2R*)-pseudoephedrine by flash chromatography (1.5:1, hexanes:ethyl acetate). Subsequently, the diastereomers (R_f = 0.81 & 0.75; 4:1 ethyl acetate:methylene chloride) were separated from one another by flash chromatography (silica gel, 5:1 methylene chloride:ethyl acetate). **2** was the less polar of the two diastereomeric products.

Protocol B: <u>Metathesis substrates 2 and 3</u>. Racemic **4** (1.0 g, 2.0 mmol,) was dissolved in 60 mL of dry methylene chloride and stirred at room temperature. To this flask was added 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) (575 mg, 3.0 mmol) and 4-(Dimethylamino)-pyridine (DMAP) (50 mg, 0.40 mmol) which were stirred for 30 min. *N*-4-pentenoyl-(*1R,2R*)-pseudoephedrine (760 mg, 3.0 mmol) was dissolved in 10 mL of dry methylene chloride and then added slowly to the flask containing (+/-)-4, EDC and DMAP (complete addition took 20 min). The reaction was monitored by TLC using a 2:1, methylene chloride:ethyl acetate mobile phase. Two product spots were visualized on the TLC plate using a Phosphomolybdic acid (PMA) stain. The R_f values of the newly formed diastereomers **2** and **3** were 0.47 and 0.40 respectively. Once all the starting material was consumed the mixture was concentrated under vacuum and loaded directly onto a silica gel column. Column chromatography was conducted using an isocratic 1:1, methylene chloride:ethyl acetate mobile phase and yielded compound **2** (47%) and compound **3** (45%).

Metathesis Substrate 2. Pale yellow oil, (R_f = 0.81, 4:1 ethyl acetate:methylene chloride). ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum (mixture of rotamers). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.0, 172.9, 172.7, 172.5, 169.2, 168.9, 168.9, 167.1, 167.1, 166.7, 159.1, 159.0, 137.6, 137.6, 136.8, 136.8, 136.7, 135.7, 135.5, 135.4, 135.3, 135.2, 133.6, 133.6, 133.4, 132.0, 131.9, 131.2, 129.4, 129.2, 129.2, 129.1, 129.0, 129.0, 128.9, 128.9, 128.6, 128.5, 128.4, 128.0, 128.0, 127.4, 127.3, 127.3, 127.2, 127.2, 127.1, 126.5, 126.5, 119.8, 119.7, 117.8, 115.5, 115.1, 114.1, 91.6, 91.7, 80.2, 80.1, 80.0, 76.3, 76.2, 59.0, 58.8, 55.6, 55.2, 55.2, 50.8, 50.7, 50.6, 49.5, 49.2, 48.8, 48.4, 47.0, 46.7, 44,9, 33.4, 33.2, 29.4, 29.0, 26.8, 15.4, 14.7; HRMS (EI) calculated for $C_{43}H_{47}N_3O_7$ [M+H]: 718.3493, found: 718.3492.

Metathesis Substrate 3. Pale yellow oil, (R_f = 0.75, 4:1 ethyl acetate:methylene chloride). ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.6, 173.0, 173.0, 172.9, 169.3, 169.3, 167.7, 166.0, 166.7, 159.2, 159.1, 137.7, 137.7, 137.6, 137.5, 137.3, 137.2, 136.7, 135.3, 135.0, 134.9, 134.4, 134.0, 133.3, 131.2, 129.6, 129.5, 129.4, 129.3, 129.2, 129.0, 128.9, 128.9, 128.8, 128.8, 128.8, 128.7, 128.6, 128.6, 128.1, 128.0, 128.0, 127.8, 127.5, 127.5, 127.4, 127.3, 127.3, 127.2, 127.2, 127.0, 127.0, 126.5, 119.7, 117.7, 115.1, 114.2, 114.1, 114.0, 91.8, 91.7, 91.6, 91.3, 80.0, 77.4, 76.7, 63.7, 63.1, 59.0, 58.9, 55.6, 55.3, 55.2, 55.2, 51.1, 50.6, 50.5, 50.3, 49.3, 49.1, 48.7, 48.3, 47.0, 46.6, 45.7, 44.9, 43.8, 33.2, 33.1, 32.9, 29.4, 29.0, 15.1, 14.3; HRMS (EI) calculated for $C_{43}H_{47}N_3O_7$ [M+H]: 718.3493, found: 718.3495.

Typical Procedure for Metathesis Reactions

12-5-5-7 fused ring macrocyle 5. To a solution of **2** (84 mg, 0.12 mmol) in CH_2Cl_2 (250 mL) was added the ruthenium based olefin metathesis catalyst containing 1,3-dimesityl-4, 5-dihydroimidazol-2-ylidene (10 mg, 0.012 mmol). The catalyst was added portion-wise (5 mol % catalyst every 6 h) until reaction was complete. The reaction mixture was stirred at 40 °C for 12 h. TLC analysis indicated that the reaction was complete. After quenching the reaction with ethyl vinyl ether and removal of the solvent, the residue was purified by flash chromatography (silica gel, 2:1 ethyl acetate:hexanes) to afford **5** (65%) as a brown solid (R_f = 0.47 ethyl acetate). ^{1}H NMR ($CDCl_3$, 600 MHz) See spectral data for complete assignment. δ 7.39-7.36 (m, 5H), 7.33-7.27 (m, 3H), 7.19 (d, *J* = 6.6 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.40 (td, *J* = 11.0, 39.0 Hz, 1H), 5.90 (t, *J* = 4.8 Hz, 1H), 5.85 (m, 2H), 5.65 (d, *J* = 10.8 Hz, 1H), 5.45 (m, 1H), 5.25 (d, *J* = 14.4 Hz, 1H), 5.13 (dd, *J* = 9.0, 15.6 Hz, 1H), 4.60 (d, *J* = 15.0 Hz, 1H), 4.56 (s, 1H), 4.52 (d, *J* = 14.4Hz, 1H), 4.43 (t, *J* = 7.2 Hz, 1H), 4.05 (d, *J* = 15.6 Hz, 1H), 3.99 (d, *J* = 14.4 Hz, 1H), 3.81 (s, 3H), 3.62 (d, *J* = 6.6 Hz, 1H), 3.25-3.16 (m, 1H), 2.98 (s, 3H), 2.84-2.80 (m, 1H), 2.77-2.73 (m, 1H), 2.35-2.19 (m, 2H), 0.83 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8, 171.7, 170.8, 168.1, 159.2, 136.9, 136.5, 134.1, 133.6, 133.1, 132.9, 130.1, 129.9, 129.7, 129.5, 129.3, 129.0, 128.9, 128.7, 128.5, 128.4, 127.9, 127.8, 127.5, 127.3, 125.1, 114.2, 84.0, 82.8, 82.4, 81.9, 78.4, 69.0, 67.5, 64.5, 55.3, 55.0, 54.6, 54.2, 53.5, 51.2, 53.5, 51.1, 50.0, 45.8, 45.6, 42.0, 41.1, 32.6, 30.4, 29.5, 29.0, 27.1, 14.6, 14.0; HRMS (EI) calculated for $C_{41}H_{43}N_3O_7$ [M+H]: 690.3179, found: 690.3167.

The structure of the fused ring product was proposed based on spectroscopic analogy to a previously described 7-5-5-7 fused ring product of related structure (Lee, D.; Sello, J. K.; Schreiber, S. L. *Org. Lett*, **2000**, *2*, 709- 712*). The spectra of both molecules share characeteristic olefinic protons signals. In particular. the spectra of these molecules have a characteristic doublet at 6.4 or 6.24 ppm that can be assigned as the olefinic hydrogen atom of the seven membered ring that is adjacent to the cycloadduct's quaternary center. In both cases, the doublet has a coupling constant of 10.7 Hz that is consistent with the proposed cis geometry of the olefin in the fused seven membered ring. Furthermore, both spectra share a multiplet at 5.8 ppm that can be assigned as the other three olefinic protons of the molecule. The proposed 12-5-5-7 fused structure was further validated by a series of 1D TOCSY NMR experiments. Moreover, the molecular mass of this molecule is consistent with the proposed fused ring structure. The structures of all other 12-5-5-7 fused ring compounds(**10**,**14**,**18** and **22**) were inferred by analogy to the NMR spectra of this molecule and by molecular mass.*

Bridged macrocycle 6. To a solution of **3** (80 mg, 0.11 mmol) in CH_2Cl_2 (250 mL) was added the ruthenium based olefin metathesis catalyst containing 1,3-dimesityl-4, 5-dihydroimidazol-2-ylidene (9 mg, 0.01 mmol). The catalyst was added portion-wise (5 mol % catalyst every 6 h) until reaction was complete. The reaction mixture was stirred at 40 °C for 16 h. After quenching the reaction with ethyl vinyl ether and removal of the solvent, the residue was purified by flash chromatography (silica gel, 2:1 ethyl acetate: hexanes) to afford **6** (87%) as a brown solid with an *E*/*Z* ratio of 10:1. (R_f = 0.83 ethyl acetate). The product was recrystallized from ethyl acetate:methylene chloride:hexanes

2:1:2 mixture. ^{1}H NMR ($CDCl_3$, 600 MHz). Data refers to the *Z* isomer. δ 7.45 (d, *J* = 7.2 Hz, 2H), 7.39-7.34 (m, 3H), 7.30 (t, *J* = 1.8 Hz, 3H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.94 (t, *J* = 3.6 Hz, 2H), 6.73 (d, *J* = 9.0 Hz, 2H), 6.53 (d, *J* = 4.8 Hz, 1H), 6.27 (d, *J* = 6.0 Hz, 1H), 5.81-5.73 (m, 2H), 5.62 (d, *J* = 10.8 Hz, 1H), 5.43-5.40 (dd, *J* = 6.0, 14.4 Hz, 1H), 5.31-5.27 (m, 1H), 5.25 (d, *J* = 3.0 Hz, 1H), 5.21 (d, *J* = 15.6 Hz, 1H), 4.55 (s, 1H), 5.53 (d, *J* = 16.8 Hz, 1H), 4.21 (d, *J* = 16.8 Hz, 1H), 3.81 (d, *J* = 15.0 Hz, 1H), 3.72 (s, 3H), 3.50 (t, *J* = 3.6 Hz, 1H), 3.04 (d, *J* = 3.0 Hz, 1H), 3.00 (dd, *J* = 6.6, 7.2 Hz, 1H), 2.94 (q, *J* = 13.2 Hz, 1H), 2.73 (s, 3H), 2.54-2.48 (ddt, *J* = 4.8, 5.4, 16.8 Hz, 1H), 2.35-2.31 (m, 1H), 2.03 (t, *J* = 13.8 Hz, 1H), 0.83 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4, 171.5, 170.0, 165.6, 159.2, 138.1, 138.0, 137.0, 135.2, 133.4, 129.7, 129.3, 129.1, 129.1, 128.4, 128.2, 127.7, 126.8, 123.5, 114.3, 91.6, 80.2, 77.4, 76.5, 59.0, 55.4, 50.8, 49.9, 48.9, 47.7, 45.1, 39.0, 33.7, 32.2, 29.9, 29.6, 28.6, 23.9, 22.9, 14.6; HRMS (EI) calculated for $C_{41}H_{43}N_3O_7$[M+H]: 690.3179, found: 690.3176.

Crystallographic data: orthorhombic single crystal (0.25 x 0.1 x 0.05 mm^3, Space group $P2_12_12_1$, Unit cell constants *a* = 8.260(1), *b* = 16.714(3), *c* = 26.608(6) Å, α = 90 °, β = 90°, γ = 90°, *V* = 3674(1) $Å^3$, *Z* = 4, D_x = 1.251 g/cm^3). X-ray diffraction data were collected using a Bruker SMART CCD diffractometer equipped with an LT-2 low-temperature apparatus at 213 K. Data were measured using omega scans of 0.3° per frame for 30 seconds. A total of 1271 frames were collected with a maximum resolution of 0.80 Å. Cell parameters were retrieved using SMART software and refined using SAINT on all observed reflections. Data reduction was performed with SAINT and the structures are solved by the direct method using the SHELXS-97 program incorporated in

SHELXTL-PC V 5.10 and refined by least squares method on F^2. The final agreement factors are $R(F) = 0.0534$, $Rw(F) = 0.1121$.

*The proposed structure of the bridged ring product was confirmed by x-ray crystallography. The structures of all other reported bridged rings (**8**, **12**, **16**, and **20**) were confirmed by x-ray crystallography or inferred by analogy to the proton NMR spectrum of this molecule.*

Allyl carboxylate (+)-4. To a solution of **2** (1.0 g, 1.4 mmol) in 15 mL of MeOH was added barium hydroxide-octahydrate (879 mg, 2.8 mmol). The reaction was stirred at ambient temperature for 12 h. The reaction was quenched by the addition of 2 N HCl. The pH of the reaction mixture was brought to 2 by the slow addition of hydrochloric acid. A small volume of methanol was added to this mixture to clarify the solution. The aqueous reaction mixture was extracted five times with methylene chloride. The combined organic layers were washed with brine. The resultant organic layer was dried with magnesium sulfate and filtered through a short pad of silica gel. After removal of the solvent in vacuo, the residue was purified by silica gel chromatography (3:1 ethyl acetate: hexanes to 9:1 ethyl acetate:methanol) yielding **(+)-4** in 90%. $[\alpha]^{20}_{D} = +0.63^{0}$ (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.2, 166.6, 166.3, 159.2, 159.1, 136.64, 135.7, 135.1, 132.8, 131.9, 131.1, 129.5, 129.3, 129.0, 128.9, 128.91, 128.8, 128.6, 128.1, 128.0, 127.9, 126.7, 126.5, 120.0, 117.8, 114.2, 114.1, 91.7, 80.5, 80.4, 59.5, 59.4, 55.3, 55.2, 51.3, 49.4, 49.2, 48.9, 48.3,

46.4, 45.2. The absolute stereochemistry of **(+)-4** could be inferred from the X-ray crystal information obtained on **8**, which was prepared from **(+)-4**.

Allyl carboxylate (-)-4. To a solution of **3** (676 mg, 0.94 mmol) in 15 mL of MeOH was added barium hydroxide-octahydrate (594 mg, 1.88 mmol). The reaction was stirred at ambient temperature for 12 h. The reaction was quenched by the addition of 2 N HCl. The pH of the reaction mixture was brought to 2 by the slow addition of hydrochloric acid. A small volume of methanol was added to this mixture to clarify the solution. The aqueous reaction mixture was extracted five times with methylene chloride. The combined organic layers were washed with brine. The resultant organic layer was dried with magnesium sulfate and filtered through a short pad of silica gel. After removal of the solvent in vacuo, the residue was purified by flash chromatography (silica gel, 3:1 ethyl acetate:hexanes to 9:1 ethyl acetate:methanol) yielding **(-)-4** in 93%. $[\alpha]^{20}_{D}$ = -0.440° (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.2, 166.6, 166.3, 159.2, 159.0, 136.7, 135.7, 135.1, 133.0, 131.9, 129.8, 129.5, 129.3, 129.0, 129.0, 128.9, 129.0, 128.6, 128.1, 128.0, 127.9, 126.7, 126.5, 119.7, 117.8, 114.2, 113.2, 91.7, 80.5, 80.2, 59.5, 59.4, 55.6, 55.2, 51.1, 49.5, 49.2, 48.9, 48.1, 46.7, 44.8. The absolute stereochemistry of **(-)-4** could be inferred from the X-ray crystal information obtained on **6**, which was prepared from **(-)-4**.

*The resolved acids, **(+)-4** and **(-)-4**, were used to prepare all reaction substrates. All metathesis reaction substrates were synthesized using conditions identical to those described for the preparation of **2** and **3**. Substrates **7**, **11**, **15**, and **19** were prepared from **(+)-4**. Substrates **9**, **13**, **17**, and **21** were prepared from **(-)-4**. Metathesis reactions were*

carried out as described above, at 0.0005 M and catalyzed by the ruthenium based olefin metathesis catalyst containing 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene.

Metathesis substrate 7. Yield: 54%. Pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ173.1, 172.1, 169.6, 167.1, 166.8, 159.2, 137.0, 136.9, 136.8, 135.8, 135.7, 135.2, 133.5, 133.4, 132.0, 131.2, 129.4, 129.2, 129.0, 128.9, 128.86, 128.7, 128.6, 128.1, 128.0, 127.2, 127.1, 126.9, 126.87, 126.6, 119.8, 117.9, 115.7, 114.1, 114.1, 91.5, 91.5, 80.0, 79.9, 75.7, 71.6, 59.0, 59.0, 55.3, 55.2, 52.9, 51.0, 49.5, 49.2, 48.8, 48.5; 47.0, 45.0, 35.8, 29.5; Low Res. EIMS [M+H] calculated for $C_{43}H_{47}N_3O_8$: 734.3, found: 734.3.

Bridged Macrocycle 8. Catalyst loading: 10 mol %. Reaction time: 12 h. Yield: 52% (R_f = 0.79 ethyl acetate). The product was recrystallized from ethyl acetate-methylene chloride. ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.2, 171.2, 169.8, 166.3, 158.9, 139.2, 137.0, 136.6, 135.4, 133.1, 129.6, 129.5, 129.0, 129.0, 128.8, 128.7, 128.4, 128.0, 127.7, 127.5, 127.2, 126.5, 124.2, 114.0, 94.2, 91.4, 80.2, 75.8, 70.8, 58.9, 58.7, 55.2, 55.1, 53.3, 50.6, 49.7, 47.4, 45.9, 44.9, 35.2, 29.6, 26.8. HRMS (EI) calculated for $C_{41}H_{43}N_3O_8$ [M+H]: 706.3128, found: 706.3150.

Crystallographic data: orthorhombic single crystal (0.10 x 0.12 x 0.12 mm^3, Space group $P2_12_12_1$, Unit cell constants a = 9.4799(5), b = 17.1466(9), c = 23.3272(13) Å, α = 90 °, β = 90°, γ = 90°, V = 3791.8(4) Å^3, Z = 4, D_x = 1.236 g/cm^3). X-ray diffraction data were collected using a Bruker SMART CCD diffractometer equipped with an LT-2 low-temperature apparatus at 213 K. Data were measured using omega scans of 0.3° per frame for 30 seconds. A total of 1271 frames were collected with a maximum resolution

of 0.75 Å. Cell parameters were retrieved using SMART software and refined using SAINT on all observed reflections. Data reduction was performed with SAINT and the structures are solved by the direct method using the SHELXS-97 program incorporated in SHELXTL-PC V 5.10 and refined by least squares method on F^2. The final agreement factors are $R(F) = 0.0718$, $Rw(F) = 0.1741$.

Metathesis substrate 9. Yield: 54 %. Pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.1, 172.1, 169.6, 167.1, 166.8, 159.2, 137.0, 136.9, 136.8, 135.8, 135.7, 135.2, 133.5, 133.4, 132.0, 131.2, 129.4, 129.2, 129.0, 128.9, 128.9, 128.7, 128.6, 128.1, 128.0, 127.2, 127.1, 126.9, 126.6, 119.8, 117.9, 115.7, 114.1, 114.1, 91.5, 91.5, 80.0, 79.9, 75.7, 71.6, 59.0, 59.0, 55.3, 55.2, 52.9, 51.0, 49.5, 49.2, 48.8, 48.5; 47.0, 45.0, 35.8, 29.5; Low Res. EIMS [M+H] calculated for $C_{43}H_{47}N_3O_8$: 734.3, found: 734.3.

12-5-5-7 fused macrocycle 10. Catalyst loading: 10 mol %, reaction time: 16 h, yield: 56% (R_f = 0.34 ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6, 171.3, 171.1, 168.1, 159.2, 136.8, 136.5, 133.6, 132.4, 130.0, 129.9, 128.9, 128.8, 128.6, 128.4, 127.7, 127.7, 127.6, 126.3, 114.2, 82.8, 81.5, 71.1, 69.0, 59.0, 55.2, 55.1, 54.2, 52.1, 51.1, 45.7, 41.9, 34.8, 27.1; HRMS (EI) calculated for $C_{41}H_{43}N_3O_8$ [M+H]: 706.3128, found: 706.3108.

Metathesis substrate 11. Yield: 63%. Pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4, 173.4, 171.9, 169.5, 166.9, 166.5,

159.1, 159.0, 137.0, 137.0, 136.9, 136.6, 135.2, 135.1, 133.3, 133.3, 131.8, 131.1, 129.3, 129.1, 128.9, 128.8, 128.7, 128.4, 128.1, 128.0, 128.0, 127.0, 126.9, 126.4, 126.3, 126.2, 119.8, 117.7, 115.5, 114.1, 114.0, 91.6, 91.5, 80.1, 80.1, 78.3, 59.1, 58.9, 55.2, 55.1, 51.3, 51.2, 49.4, 49.1, 48.8, 48.5, 48.4, 48.3, 46.5, 44.9, 35.5, 29.4, 14.8, 14.6; Low Res. EIMS [M+H] calculated for $C_{42}H_{45}N_3O_7$: 704.3, found: 704.3.

Bridged Macrocycle 12. Catalyst loading: 15 mol%, reaction time: 16 h, yield: 66% (R_f = 0.80 ethyl acetate). The product was recrystallized from methylene chloride- ethyl acetate. ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.1, 170.6, 168.5, 166.2, 159.0, 136.7, 135.4, 134.8, 133.9, 133.7, 129.6, 129.0, 128.8, 128.0, 127.5, 127.3, 126.5, 122.7, 114.1, 91.9, 81.1, 76.2, 59.1, 55.2, 50.9, 49.2, 48.0, 47.5, 47.3, 45.0, 33.8, 25.8, 18.8; HRMS (EI) calculated for $C_{40}H_{41}N_3O_7$ [M+H]: 676.3023, found: 676.3052.

Crystallographic data: orthorhombic single crystal (0.20 x 0.10 x 0.10 mm^3, Space group $P2_12_12_1$, Unit cell constants a = 13.6681(18), b = 14.992(2), c = 17.274(2) Å, α = 90 °, β = 90°, γ = 90°, V = 3539.6(8) Å^3, Z = 4, D_x = 1.268 g/cm^3). X-ray diffraction data were collected using a Bruker SMART CCD diffractometer equipped with an LT-2 low-temperature apparatus at 213 K. Data were measured using omega scans of 0.3° per frame for 30 seconds. A total of 1271 frames were collected with a maximum resolution of 0.75 Å. Cell parameters were retrieved using SMART software and refined using SAINT on all observed reflections. Data reduction was performed with SAINT and the structures are solved by the direct method using the SHELXS-97 program incorporated in

SHELXTL-PC V 5.10 and refined by least squares method on F^2. The final agreement factors are $R(F) = 0.0630$, $Rw(F) = 0.1433$.

Metathesis substrate 13. Yield: 60%, pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.2, 171.7, 169.4, 167.0, 166.7, 159.1, 159.0, 137.0, 136.7, 136.2, 136.1, 135.8, 135.8, 135.1, 133.10, 133.0, 131.9, 131.1, 129.4, 129.2, 128.9, 128.8, 128.8, 128.4, 128.2, 128.0, 128.0, 127.2, 127.1, 126.6, 126.5, 119.8, 117.7, 115.6, 114.1, 114.0, 91.6, 91.5, 80.4, 80.3, 78.0, 59.1, 58.93, 55.2, 55.1, 51.1, 49.4, 49.2, 48.7, 48.4, 47.8, 47.8, 46.8, 44.9, 35.8, 29.5, 15.8, 15.7; Low Res. EIMS [M+H] calculated for $C_{42}H_{45}N_3O_7$: 704.3, found: 704.3.

12-5-5-7 fused ring macrocycle 14. Catalyst loading: 15 mol %, reaction time: 26 h, yield: 46% (R_f = 0.36 ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.0, 171.3, 170.9, 167.7, 159.2, 137.0, 136.4, 133.8, 133.0, 129.9, 129.8, 129.5, 128.7, 128.6, 128.5, 127.9, 127.8, 127.6, 125.3, 114.3, 84.1, 82.1, 67.6, 55.3, 54.8, 53.6, 51.2, 49.4, 45.7, 42.0, 35.8, 29.2, 13.2; HRMS (EI) calculated for $C_{40}H_{41}N_3O_7$ [M+H]: 676.3023, found: 676.3051.

Metathesis substrate 15-Ph. Yield: 53%. Pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4, 172.7, 169.7, 166.9, 159.2, 137.4, 137.1, 136.7, 135.2, 135.1, 135.1, 133.3, 133.3, 131.8, 131.1, 129.4, 129.2, 129.0, 128.9, 128.8, 128.7, 128.6, 128.1, 128.0, 127.1, 126.5, 126.4, 117.8, 115.6, 114.1, 114.1, 91.6, 91.5, 80.1, 80.0, 76.0, 59.2, 59.0, 55.2, 55.18, 51.4, 51.3, 49.4, 49.2, 48.8, 48.3,

46.6, 45.0, 44.0, 43.9, 35.5, 29.4; Low Res. EIMS [M+H] calculated for $C_{42}H_{43}N_3O_7$: 690.3, found: 690.3.

Bridged Macrocycle 16-Ph. Catalyst loading: 15 mol %. Reaction time: 18 h. Yield: 51% (R_f = 0.63 ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.1, 171.4, 169.0, 166.2, 159.0, 136.8, 135.9, 135.5, 135.4, 133.7, 129.6, 129.4, 129.1, 128.98, 128.9, 128.5, 128.1, 127.2, 126.6, 126.5, 126.2, 125.9, 123.0, 114.2, 114.1, 91.8, 80.9, 72.5, 59.1, 55.2, 50.8, 49.4, 47.6, 47.3, 45.0, 43.7, 33.9, 26.1; HRMS (EI) calculated for $C_{40}H_{39}N_3O_7$ [M+H]: 662.2866, found: 662.2833.

Metathesis substrate 17-Ph. Yield: 60 %. Pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.2, 172.5, 169.6, 167.1, 159.2, 159.1, 137.1, 137.1, 136.9, 136.8, 136.0, 133.3, 133.3, 131.9, 131.2, 129.4, 129.2, 129.0, 128.9, 128.9, 128.7, 128.6, 128.1, 128.0, 127.2, 126.5, 126.3, 119.9, 117.8, 115.7, 114.1, 114.1, 91.6, 91.5, 80.3, 80.2, 75.4, 59.2, 59.0, 55.3, 55.2, 51.0, 49.5, 49.3, 48.8, 48.5, 46.9, 45.0, 44.0, 35.7, 29.4; Low Res. EIMS [M+H] calculated for $C_{41}H_{43}N_3O_7$: 690.3, found: 690.3.

12-5-5-7 fused ring macrocycle 18-Ph. Catalyst loading: 15 mol %, Reaction time: 18 h. Yield: 55% (R_f = 0.32 ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz) See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.1, 171.9, 170.8, 167.8, 159.2, 144.3, 137.2, 136.4, 133.3, 133.1, 129.9, 129.6, 129.3, 129.0, 128.8, 128.8, 128.7, 128.5, 127.8, 127.5, 126.5, 114.2,

83.7, 81.9, 75.3, 67.9, 55.3, 54.8, 53.7, 51.2, 48.3, 47.5, 45.7, 44.6, 42.0, 35.6, 28.8; HRMS (EI) calculated for $C_{39}H_{39}N_3O_7$ [M+H]: 662.2866, found: 662.2871.

Metathesis substrate 15-Me. Yield: 55%. Pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.3, 172.7, 170.1, 167.0, 166.7, 159.2, 159.0, 137.1, 136.7, 135.3, 135.2, 135.1, 133.5, 133.4, 131.9, 131.2, 129.4, 129.2, 129.0, 128.9, 128.8, 128.1, 128.0, 127.1, 127.0, 126.5, 119.9, 117.8, 115.6, 114.1, 114.1, 91.6, 91.5, 80.1, 80.0, 71.5, 59.2, 59.9, 55.2, 55.2, 51.5, 51.4, 49.5, 49.2, 48.9, 48.4, 46.7, 45.0, 43.5, 35.6, 29.5, 17.5; Low Res. EIMS [M+H] calculated for $C_{36}H_{41}N_3O_7$: 628.3, found: 628.2.

Bridged Macrocycle 16-Me. Catalyst loading: 15 mol %. Reaction time: 20 h. Yield: 52% (R_f = 0.43 ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.3, 173.2, 171.5, 169.5, 166.2, 158.9, 136.9, 136.1, 135.4, 133.4, 129.5, 129.4, 129.0, 128.1, 127.2, 126.5, 123.4, 114.0, 91.7, 80.8, 68.4, 58.9, 58.7, 55.2, 51.7, 50.6, 49.3, 47.1, 44.9, 43.4, 34.4, 26.7, 17.0, 15.7; HRMS (EI) calculated for $C_{34}H_{37}N_3O_7$ [M+H]: 600.2710, found: 600.2686.

Metathesis substrate 17-Me. Yield: 60%. Pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.3, 172.5, 170.0, 167.2, 166.8, 159.0, 137.0, 136.7, 135.8, 135.7, 135.1, 133.4, 131.9, 131.2, 129.5, 129.4, 129.2, 129.0, 128.9, 128.1, 128.04, 127.9, 127.1, 127.0, 126.5, 119.9, 117.9, 115.7, 114.2, 114.1, 114.08, 91.5, 91.5, 80.2, 80.1, 71.2, 59.2, 59.0, 55.2, 55.19, 51.0, 49.5, 49.3, 48.8, 48.5,

47.0, 45.0, 43.6, 35.7, 29.5, 17.5; Low Res. EIMS [M+H] calculated for $C_{36}H_{41}N_3O_7$: 628.3, found: 628.3.

12-5-5-7 fused ring macrocycle 18-Me. Catalyst loading: 15 mol %. Reaction time: 32 h. Yield: 48% (R_f = 0.20 ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.9, 172.0, 153.1, 149.8, 133.4, 131.7, 130.7, 130.1, 130.0, 129.7, 129.5, 129.4, 128.8, 128.5, 128.5, 127.8, 127.4, 114.1, 94.3, 84.1, 81.8, 76.4, 72.6, 70.4, 66.9, 55.3, 53.9, 52.3, 51.1, 45.5, 42.0, 37.3, 29.7, 25.4, 19.7, 17.8, 17.5; HRMS (EI) calculated for $C_{34}H_{37}N_3O_7$ [M+H]: 600.2710, found: 600.2686.

Metathesis substrate 19. To a solution of **(+)-4** (115 mg, 0.24 mmol) in CH_2Cl_2 were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) (52 mg, 0.3 mmol), triethylamine (0.100 mL, 0.7 mmol), dimethylaminopyridine (DMAP) (7 mg, 0.06 mmol), and (S)-phenylgycinol (32 mg, 0.24 mmol). The reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was quenched by the addition of 2 N potassium hydroxide and water. The solution was extracted five times with hexanes: ethyl acetate (1:1). The combined organic layers were washed with twice with 2 N HCl, saturated sodium bicarbonate, and brine. The organic layer was then dried over magnesium sulfate and subsequently filtered over a short pad of silica gel. The residue left after removal of solvent in vacuo was purified by flash chromatography (silica gel, 4:1 ethyl acetate:hexanes) affording the desired product in 75% yield.

The reaction product (56 mg, 0.09 mmol) was added to a solution containing 4-pentenoic acid (9 mg, 0.09 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) (21 mg,

0.11 mmol), triethylamine (0.04 mL, 0.3 mmol), and dimethylaminopyridine (DMAP) (2.2 mg, 0.02 mmol) dissolved in methylene chloride. After removal of solvent in vacuo, the crude reaction mixture was applied directly to a silica gel column. The title compound was isolated (3:1 ethyl acetate:hexanes) in 80% yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.9, 172.9, 169.8, 169.7, 167.0, 166.7, 159.2, 159.0, 138.2, 136.7, 136.7, 136.6, 135.2, 132.2, 131.9, 131.2, 129.4, 129.2, 129.0, 128.9, 128.8, 128.1, 128.0, 127.1, 127.0, 127.0, 126.7, 126.5, 119.9, 117.7, 115.5, 114.1, 91.1, 91.1, 80.4, 80.3, 66.0, 59.6, 59.5, 55.2, 55.2, 53.2, 53.1, 52.5, 49.4, 49.2, 48.9, 48.3, 45.0, 33.2, 28.6; Low Res. EIMS [M+H] calculated for $C_{41}H_{43}N_3O_7$: 690.3, found: 690.3.

Bridged Macrocycle 20. To a solution of **19** (49 mg, 0.07 mmol) in CH_2Cl_2 (150 mL) was added the ruthenium based olefin metathesis catalyst containing 1,3-dimesityl-4, 5-dihydroimidazol-2-ylidene (11 mg, 0.01 mmol). The catalyst was added portion-wise (5 mol % catalyst every 6 h) until reaction was complete. The reaction mixture was stirred at 40 °C for 12 h. TLC analysis indicated that the reaction was complete. After quenching the reaction with ethyl vinyl ether and removal of the solvent, the residue was purified by flash chromatography (silica gel, 2:1 ethyl acetate:hexanes) to afford **20** (63%) as a brown solid (R_f = 0.64, ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ173.6, 172.6, 170.6, 166.3, 159.0, 139.3, 137.9, 137.0, 136.5, 135.5, 131.6, 130.2, 129.8, 129.6, 129.2, 129.0, 128.9, 128.7, 128.4, 128.4, 128.1, 127.8, 127.5, 127.2, 126.9, 126.5, 124.2, 114.2, 114.1, 91.0, 81.0, 80.6, 76.7, 68.2, 66.0, 59.1, 55.9. 55.3, 55.2, 54.6, 53.9, 51.6, 51.5, 51.1, 50.8, 48.8, 46.5, 45.2,

33.2, 28.9, 27.1; HRMS (EI) calculated for $C_{39}H_{39}N_3O_7$ [M+H]: 662.2866, found: 662.2849.

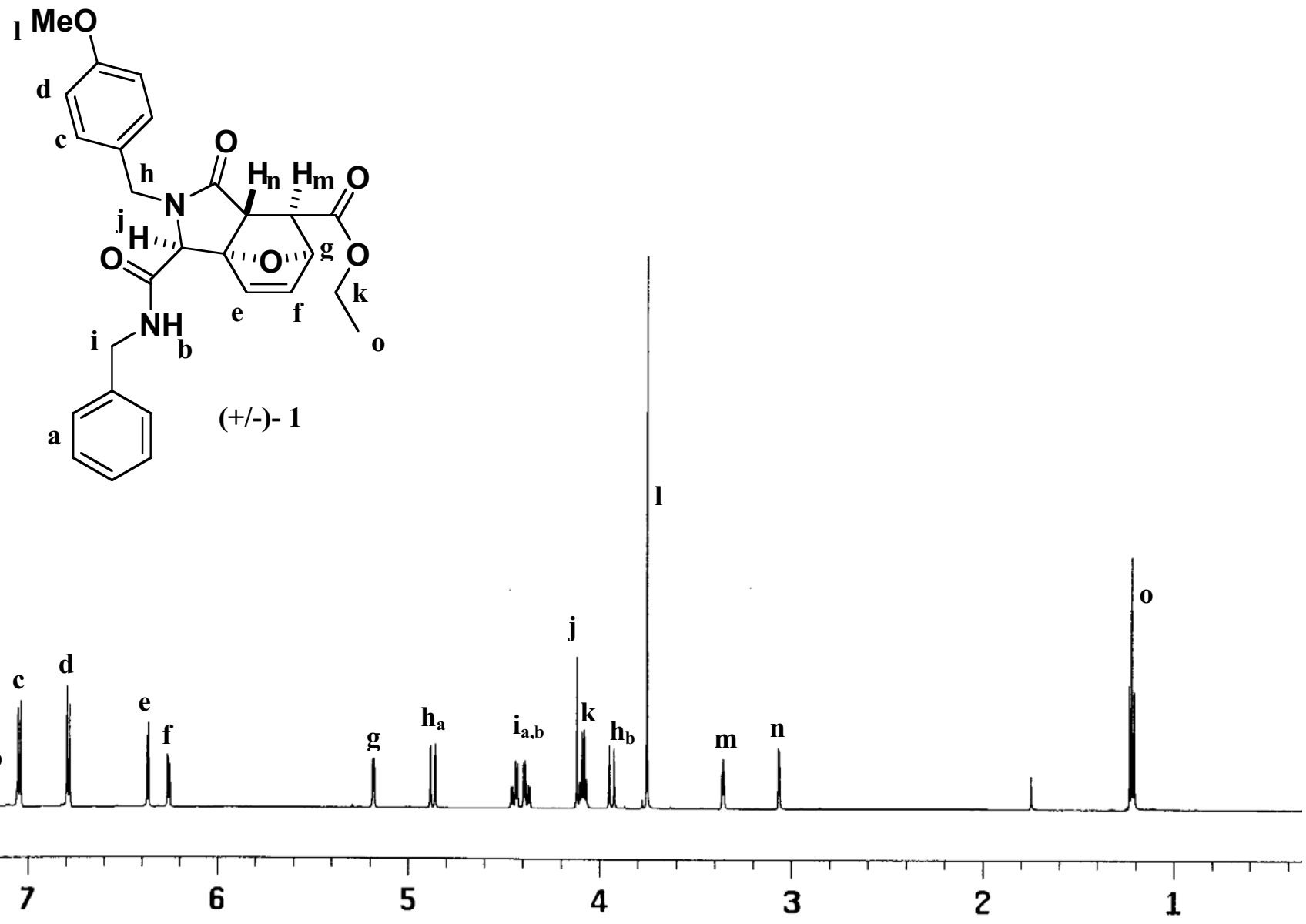
Metathesis substrate 21. To a solution of **(-)-4** (115 mg, 0.2 mmol) in CH_2Cl_2 were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) (52 mg, 0.3 mmol), triethylamine (0.100 mL, 0.7 mmol), dimethylaminopyridine (DMAP) (7 mg, 0.06 mmol), and (*S*)-phenylgycinol (32 mg, 0.2 mmol). The reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was quenched by the addition of 2 N potassium hydroxide and water. The solution was extracted five times with hexanes: ethyl acetate (1:1). The combined organic layers were washed twice with 2 N HCl, saturated sodium bicarbonate, and brine. The organic layer was then dried over magnesium sulfate and subsequently filtered over a short pad of silica gel. The residue left after removal of solvent in vacuo was purified by flash chromatography (silica gel, 4:1 ethyl acetate:hexanes) affording the desired product in 68%.

The reaction product (56 mg, 0.09 mmol) was added to a solution containing 4-pentenoic acid (9 mg, 0.08 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) (18 mg, 0.1 mmol), triethylamine (0.033 mL, 0.24 mmol), and dimethylaminopyridine (DMAP) (2 mg, 0.02 mmol) dissolved in methylene chloride. After removal of solvent in vacuo, the crude reaction mixture was applied directly to a silica gel column. The title compound was isolated (3:1 ethyl acetate:hexanes) in 82% yield. ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.9, 172.9, 169.6, 169.5, 167.0, 166.6, 159.2, 159.0, 137.8, 136.7, 136.6, 136.5, 135.2, 135.3, 132.2, 131.9, 131.1, 129.4, 129.2, 129.0, 128.9, 128.9, 128.9, 128.1, 127.9, 127.9, 127.1, 127.0, 126.5, 124.5, 120.9,

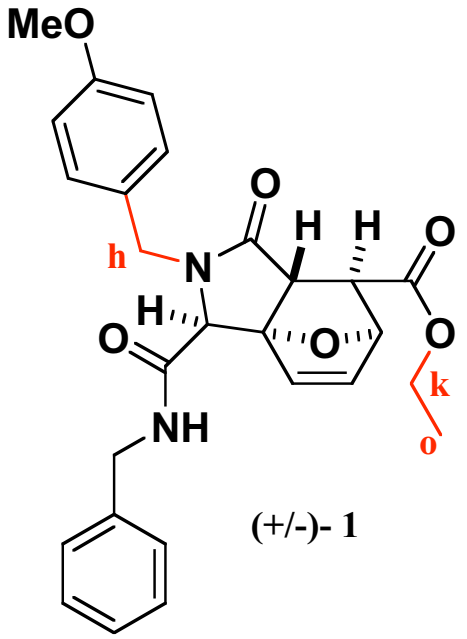
117.7, 115.6, 114.2, 114.2, 91.2, 91.1, 80.5, 80.4, 66.3, 59.7, 59.5, 55.2, 55.1, 53.3, 53.2, 52.3, 49.4, 49.2, 48.9, 48.3, 48.3, 48.2, 45.0, 33.3, 28.7; Low Res. EIMS [M+H] calculated for $C_{41}H_{43}N_3O_7$: 690.3, found: 690.3.

12-5-5-7 fused ring macrocycle 22. To a solution of **21** (37 mg, 0.06 mmol) in CH_2Cl_2 (120 mL) was added the ruthenium based olefin metathesis catalyst containing 1,3-dimesityl-4, 5-dihydroimidazol-2-ylidene (6.9 mg, 0.02 mmol). The catalyst was added portion-wise (5 mol % catalyst every 6 h) until reaction was complete. The reaction mixture was stirred at 40 °C for 22 h. TLC analysis indicated that the reaction was complete. After quenching the reaction with ethyl vinyl ether and removal of the solvent, the residue was purified by flash chromatography (silica gel, 2:1 ethyl acetate:hexanes) to afford **22** (76%) as a brown solid (R_f = 0.32 ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz). See spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.7, 172.8, 169.8, 168.1, 159.2, 148.4, 138.9, 137.4, 136.5, 133.9, 133.4, 131.3, 129.7, 129.5, 129.0, 128.7, 128.6, 128.5, 128.3, 127.8, 127.7, 126.8, 114.2, 83.9, 82.3, 76.7, 68.6, 66.6, 64.9, 64.6, 55.7, 55.3, 54.8, 54.6, 51.2, 47.3, 45.7, 42.1, 39.3, 33.6, 28.0; HRMS (EI) calculated for $C_{39}H_{39}N_3O_7$ [M+H]: 662.2866, found: 662.2870.

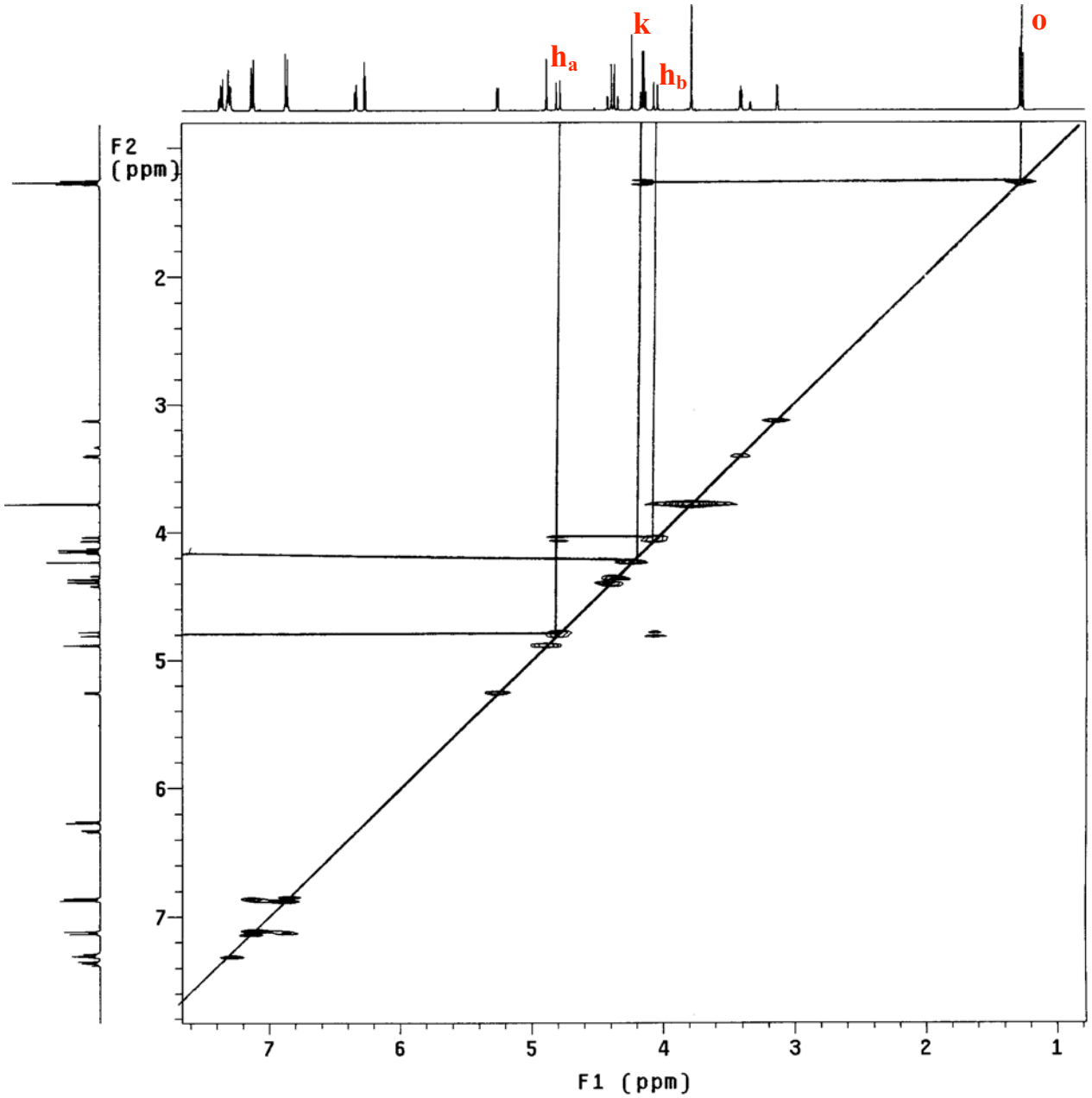
500 MHz in $CDCl_3$



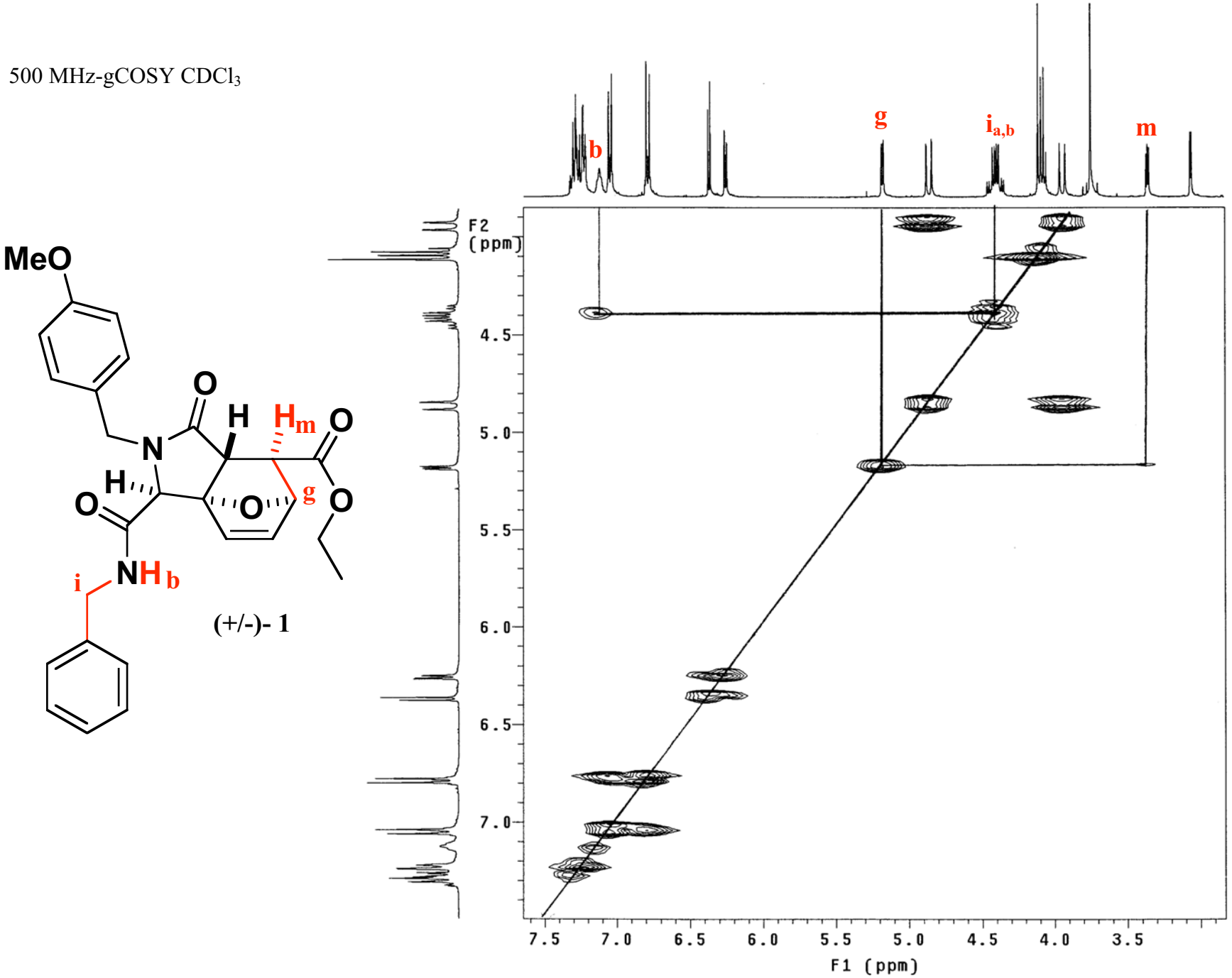
500 MHz-gCOSY $CDCl_3$

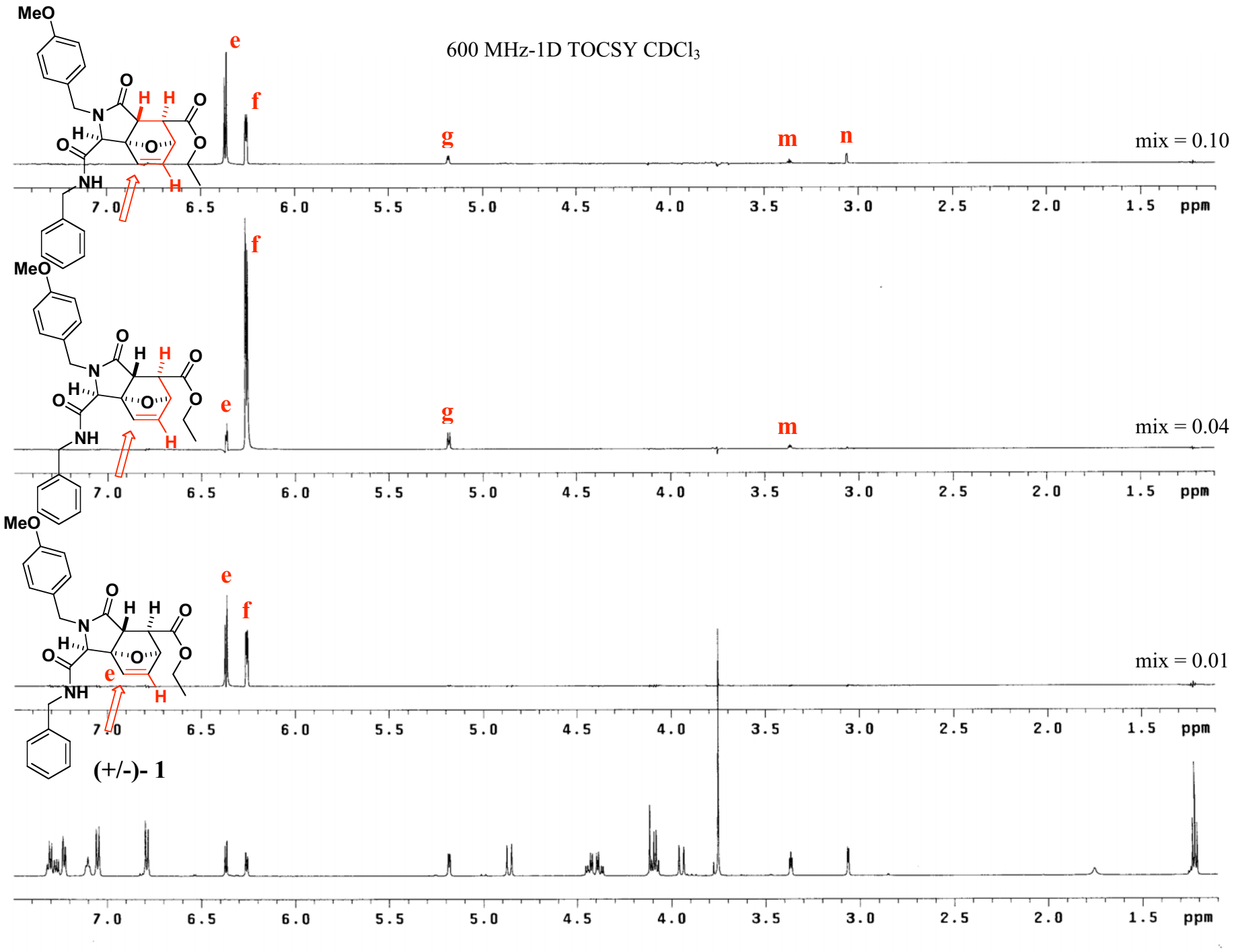


(+/-)- 1



500 MHz-gCOSY $CDCl_3$




600 MHz-1D TOCSY CDCl3
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e
f
g
m
n
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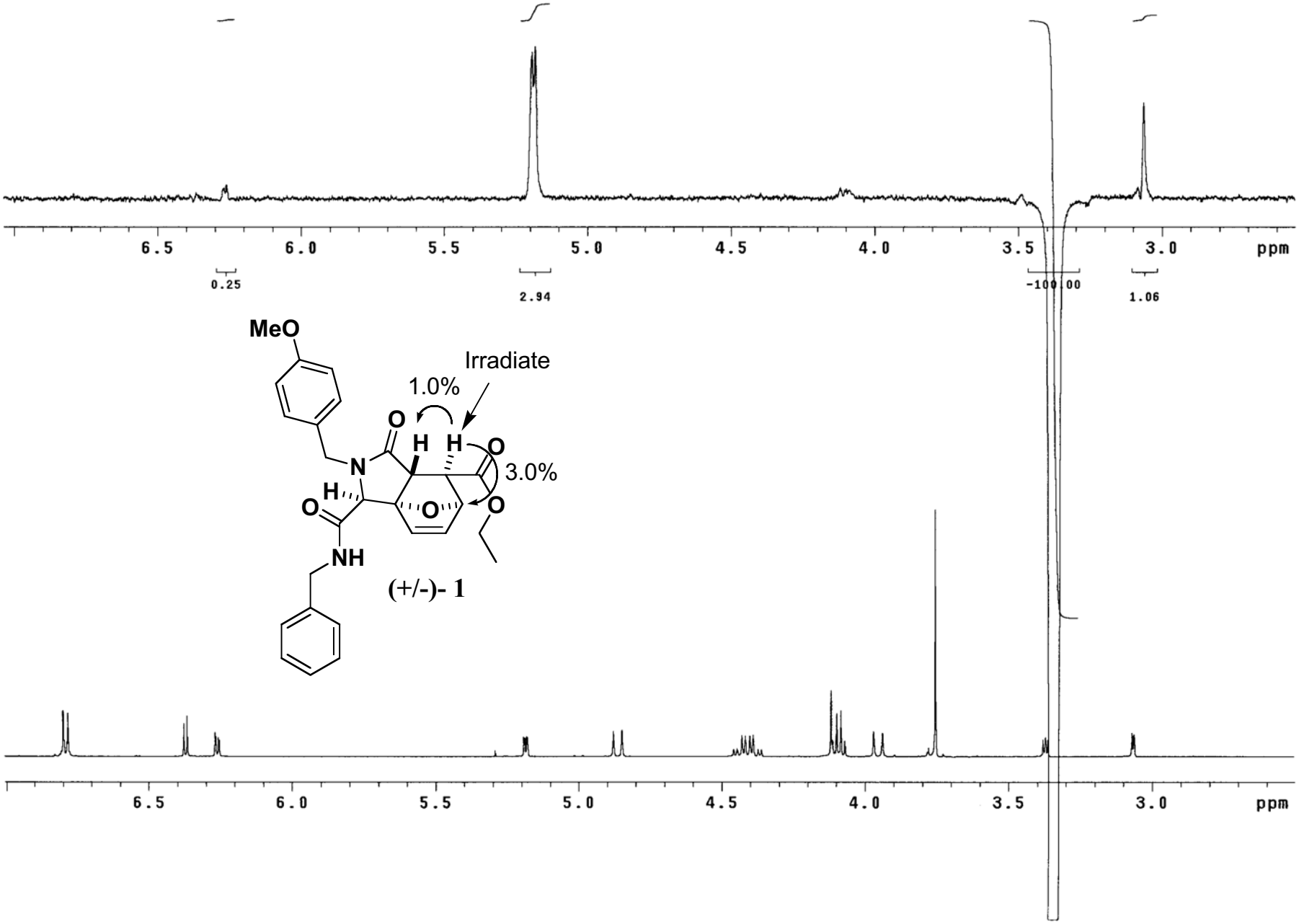
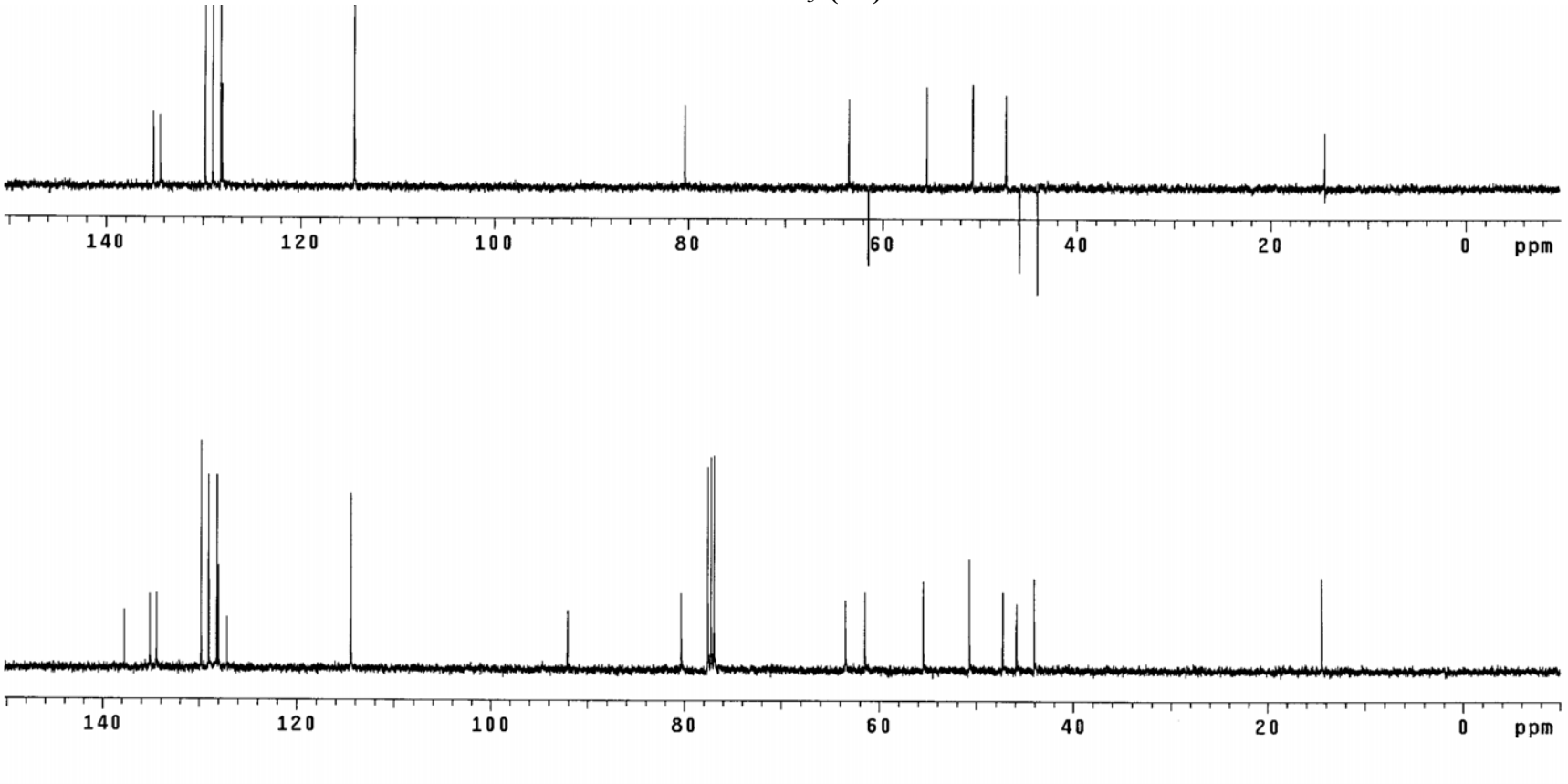
mix = 0.04
mix = 0.01
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
(+/-)- 1

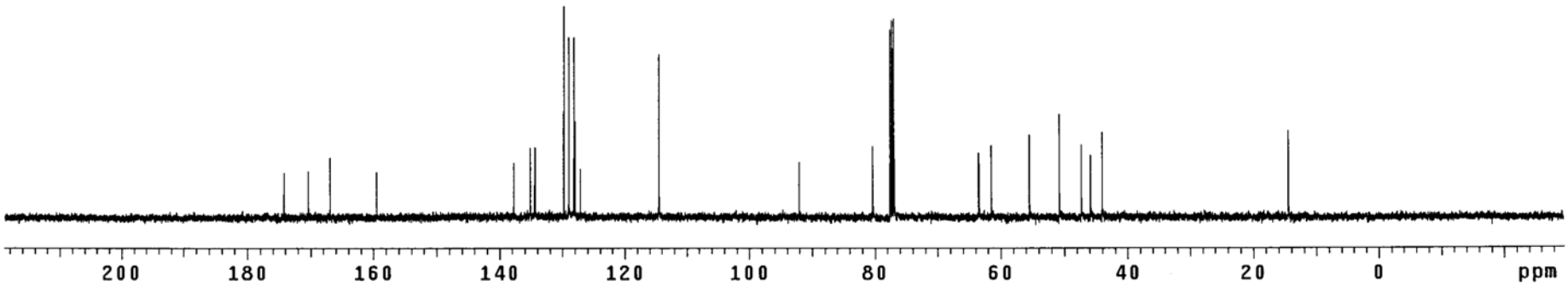
600 MHz-nOe $CDCl_3$



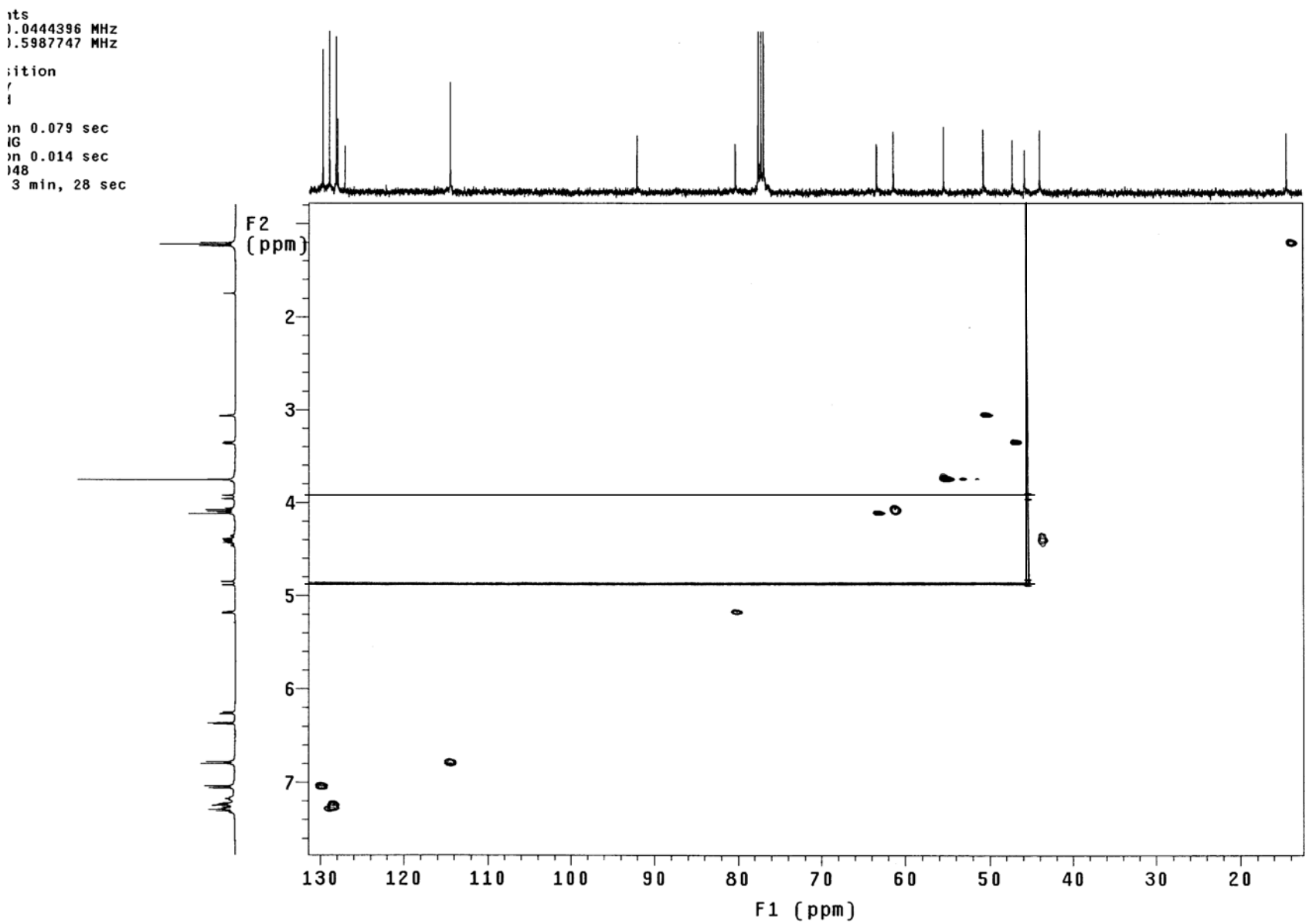
400 MHz-DEPT $CDCl_3$ **(+/-)-1**

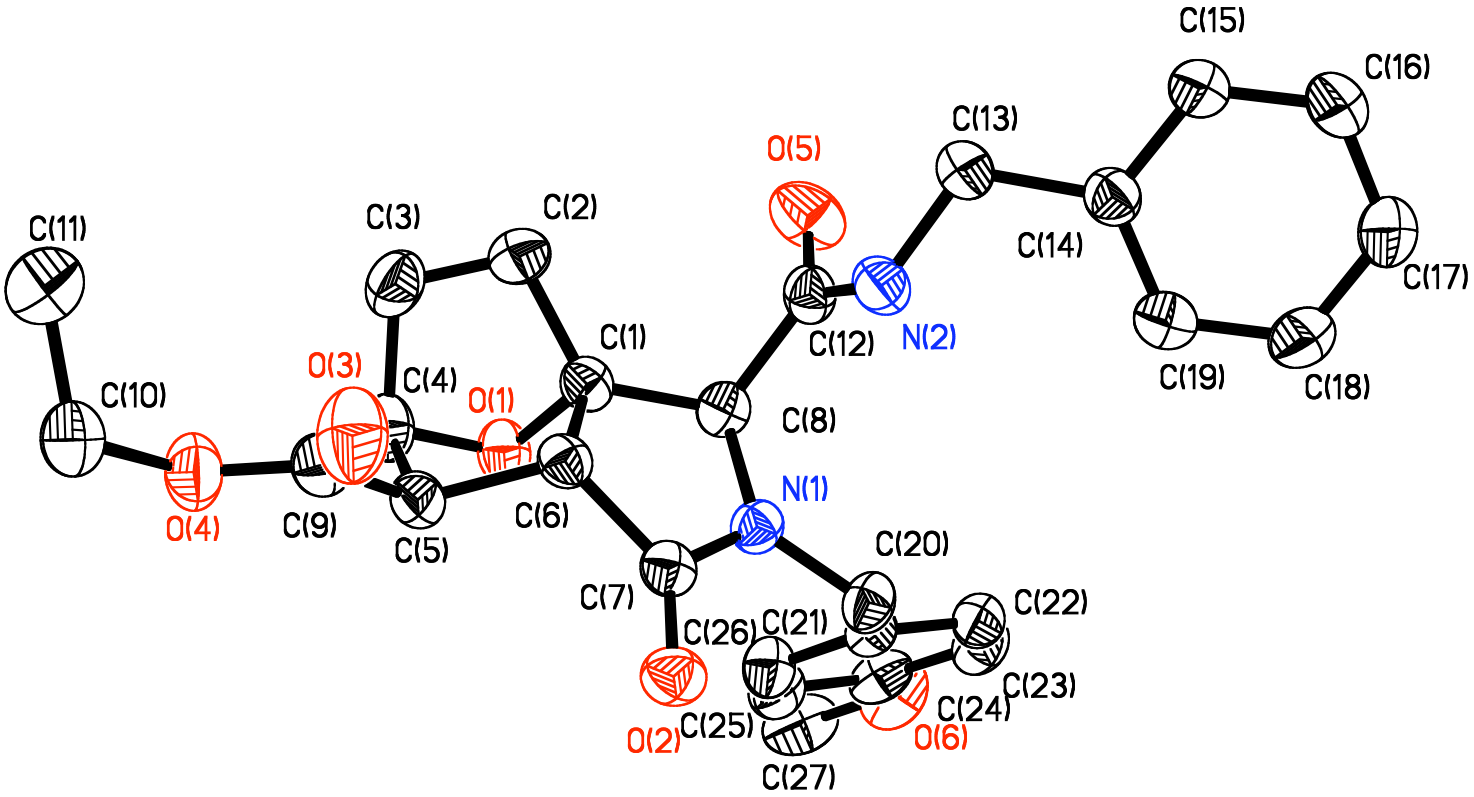


400 MHz-^{13}C $CDCl_3$ **(+/-)-1**



400 MHz-gHMQC $CDCl_3$ **(+/-)-1**




C(15)
C(16)
C(13)
O(5)
C(11)
C(3)
C(2)
C(14)
C(17)
C(1)
C(12)
N(2)
O(3)
C(4)
O(1)
C(19)
C(18)
C(10)
C(8)
N(1)
O(4)
C(9)
C(5)
C(6)
C(20)
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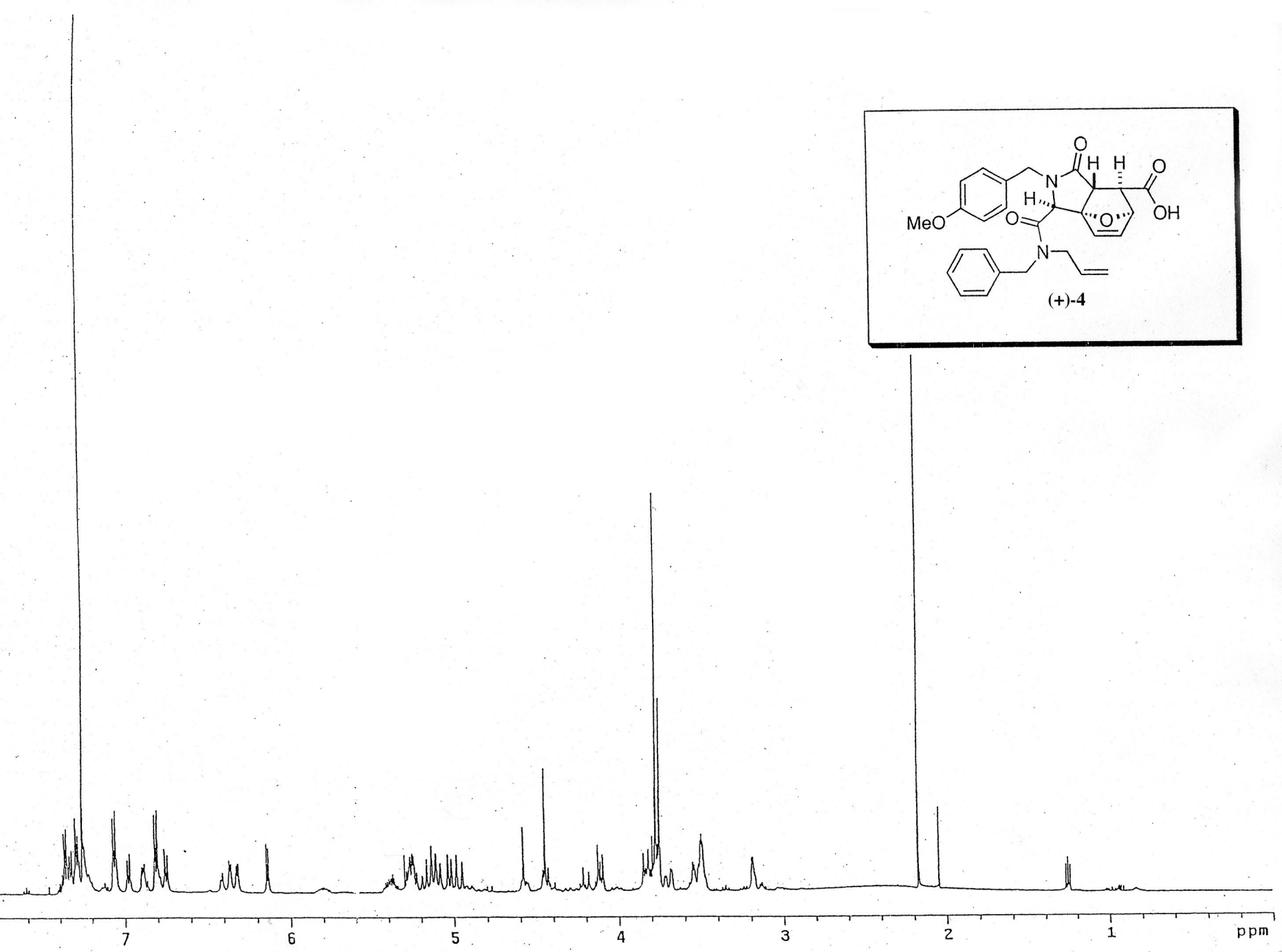
C(24)
O(2)
C(25)
O(6)
C(27)


MeO
O
H
H
O
N
H
O
O
OH
N
(+)-4
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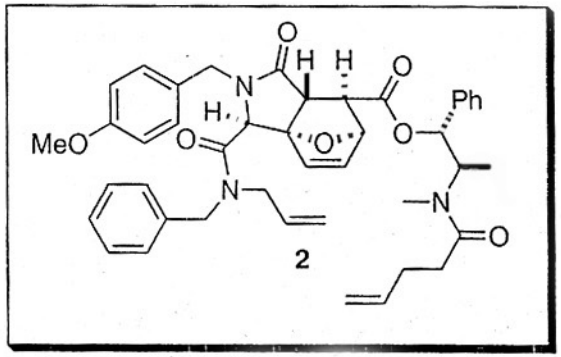
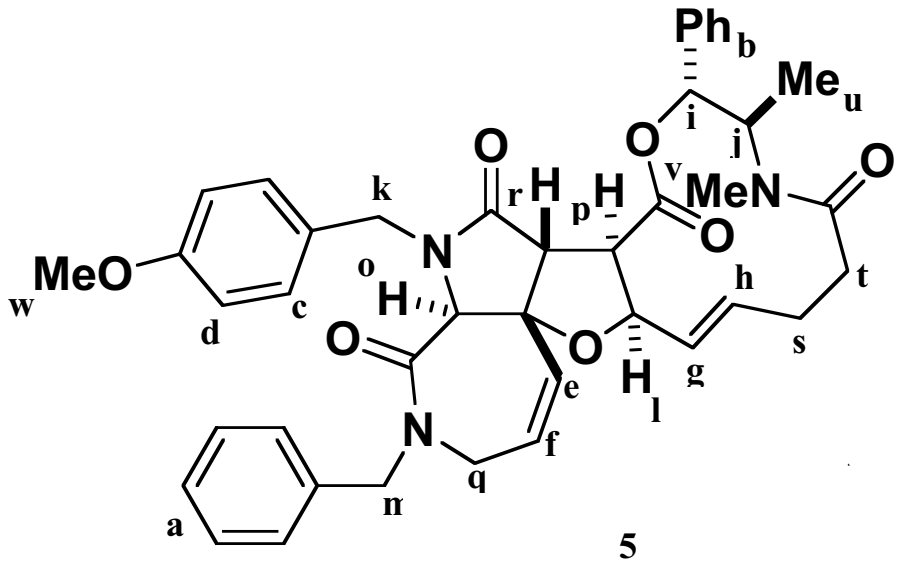
6
5
4
3
2
1
ppm


MeO
Ph
2

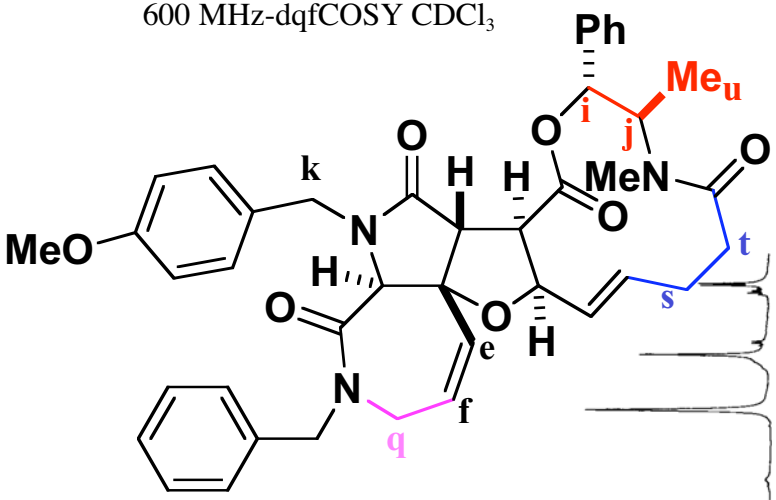
7
6
5
4
3
2
1
ppm

600 MHz $CDCl_3$



5

600 MHz-dqfCOSY $CDCl_3$



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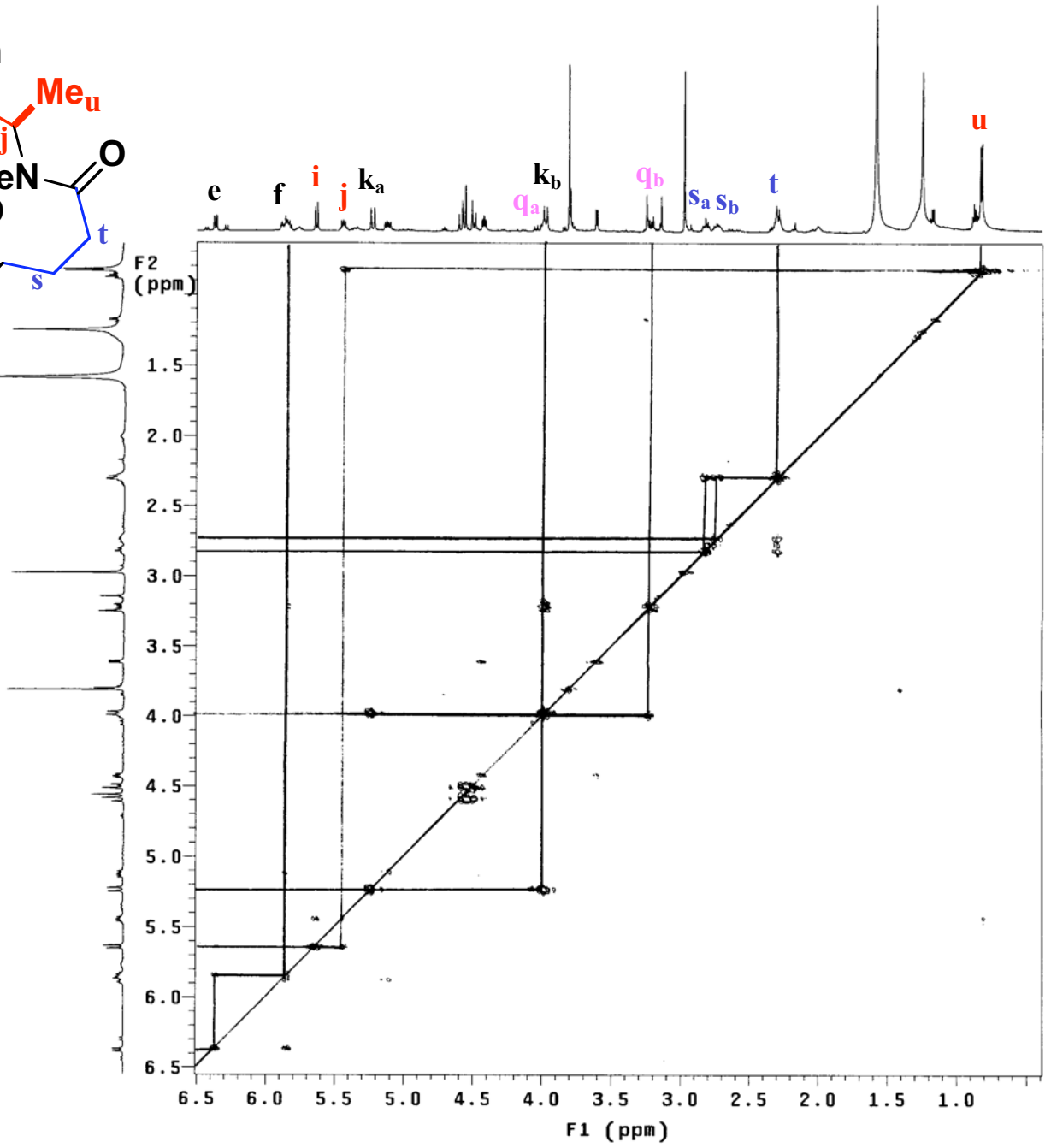
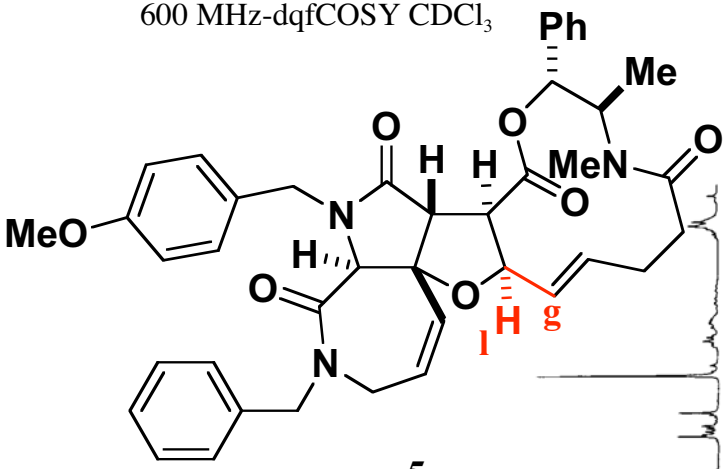


600 MHz-dqfCOSY $CDCl_3$



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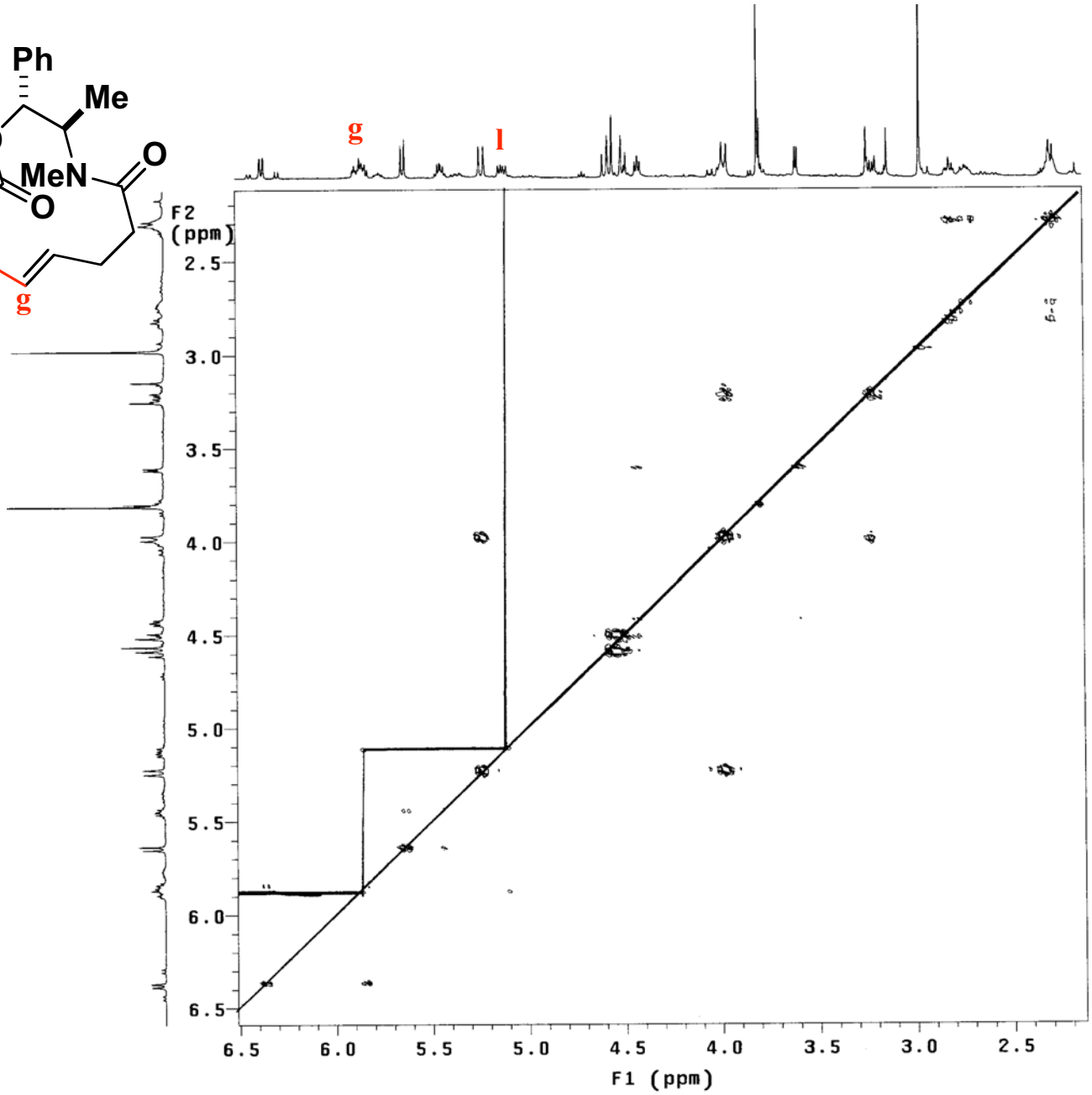
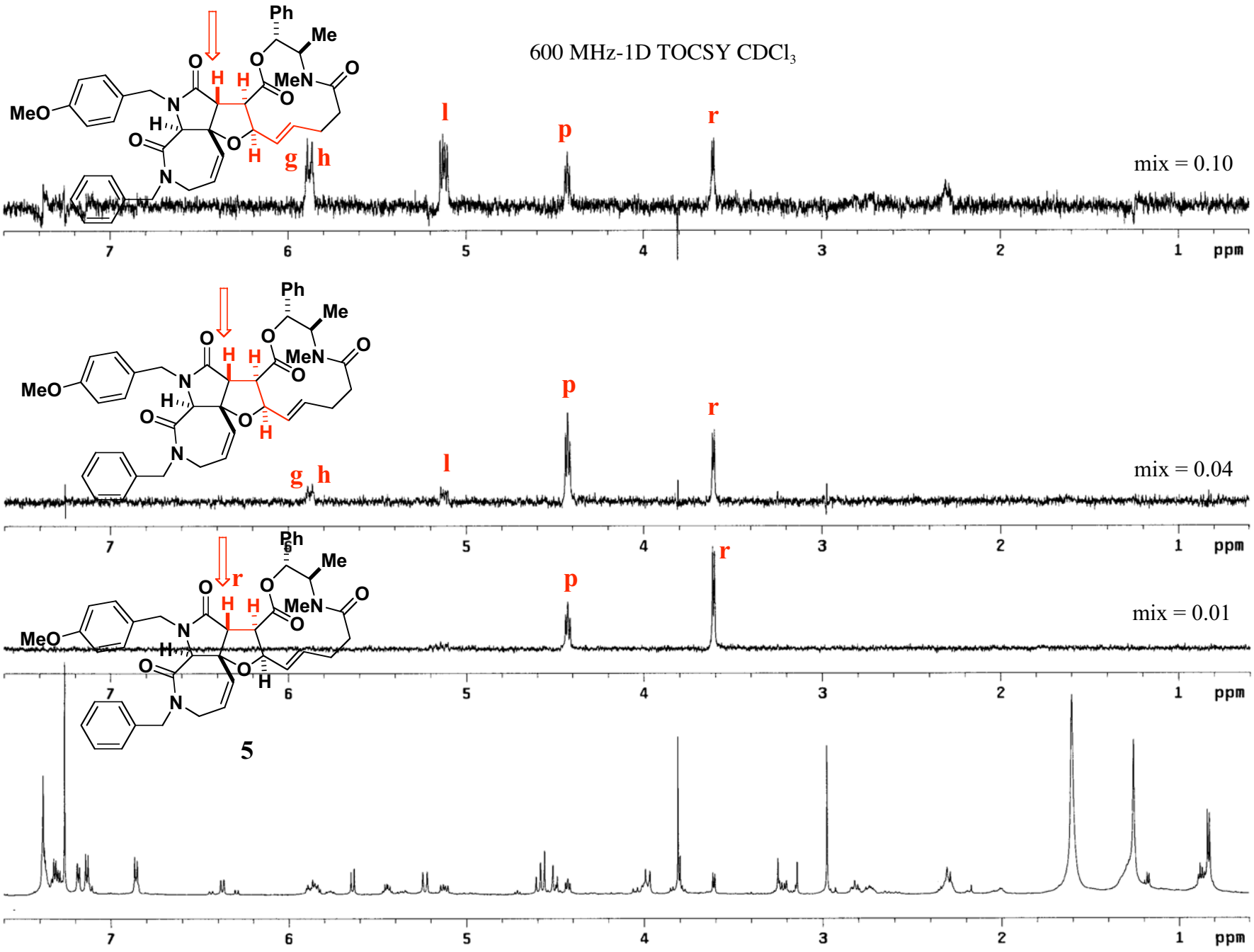
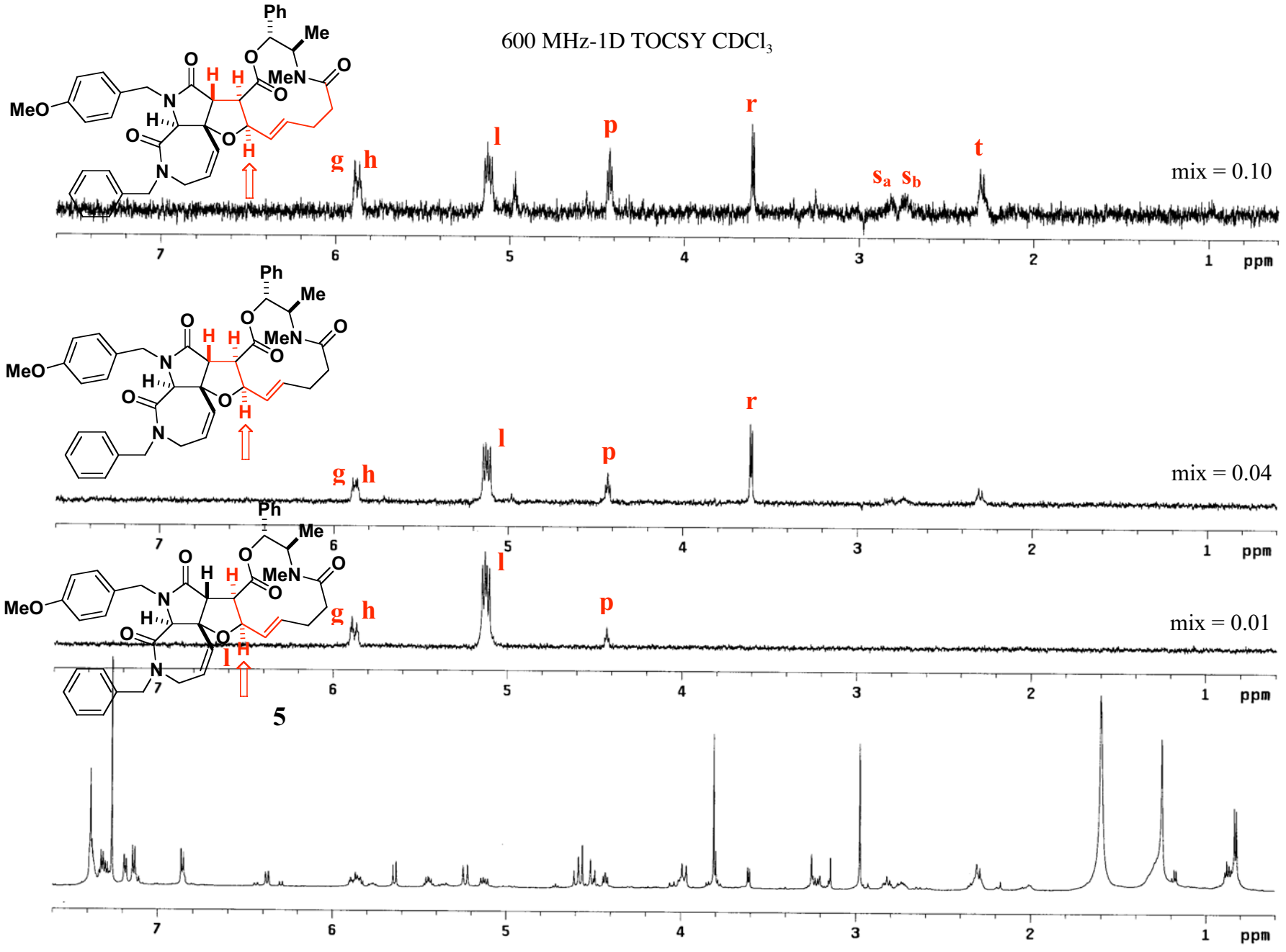
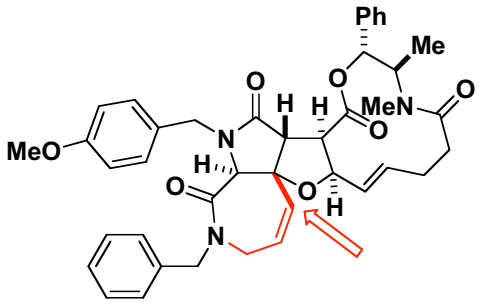


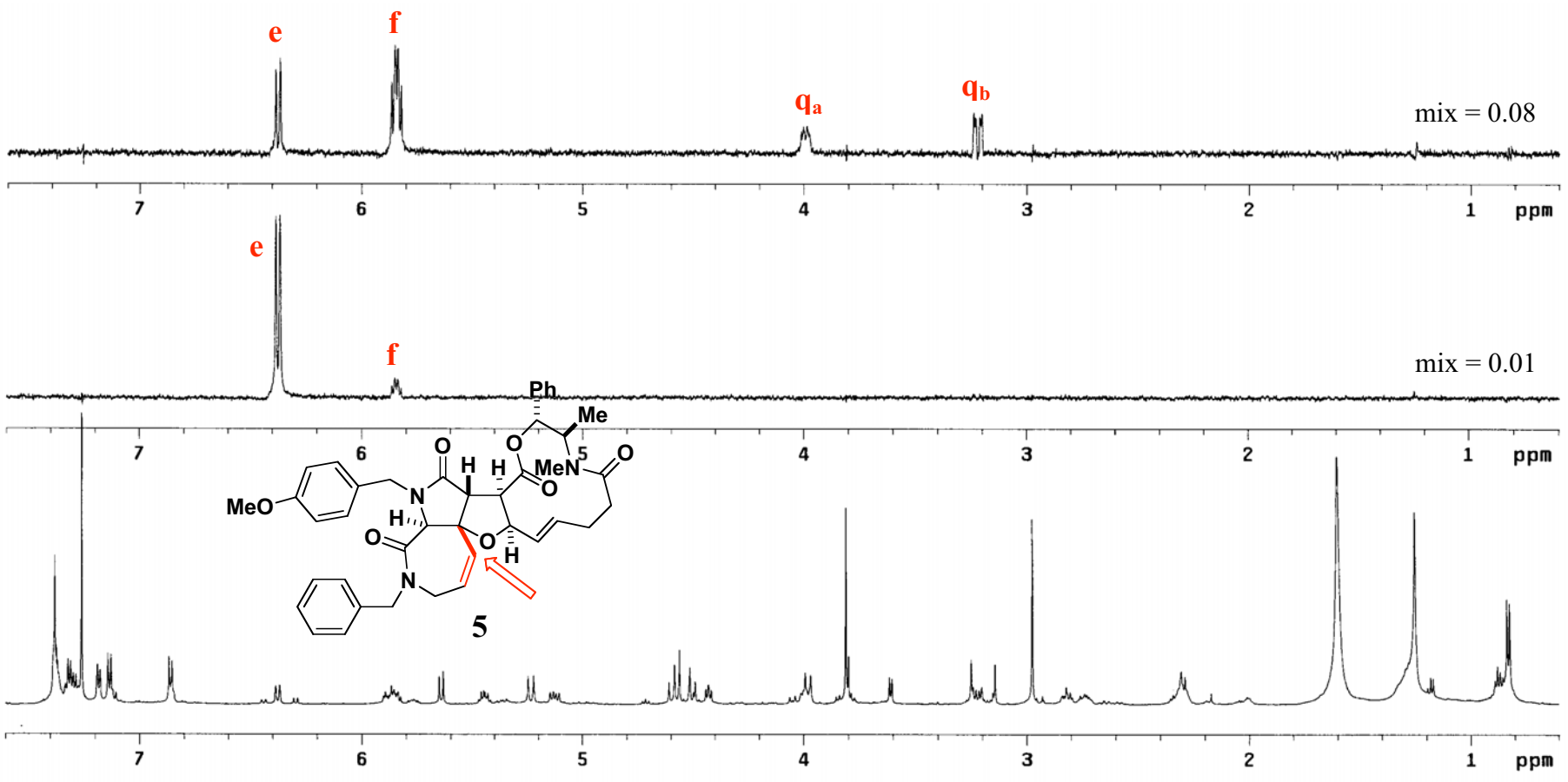

600 MHz-1D TOCSY CDCl3
Ph
Me
MeO
MeN
H
g
h
l
p
r
mix = 0.10
mix = 0.04
mix = 0.01
7
6
5
4
3
2
1
ppm
5


600 MHz-1D TOCSY CDCl3
MeO
Ph
Me
MeN
H
g
h
l
p
r
sa
sb
t
mix = 0.10
mix = 0.04
mix = 0.01
ppm
7
6
5
4
3
2
1

5

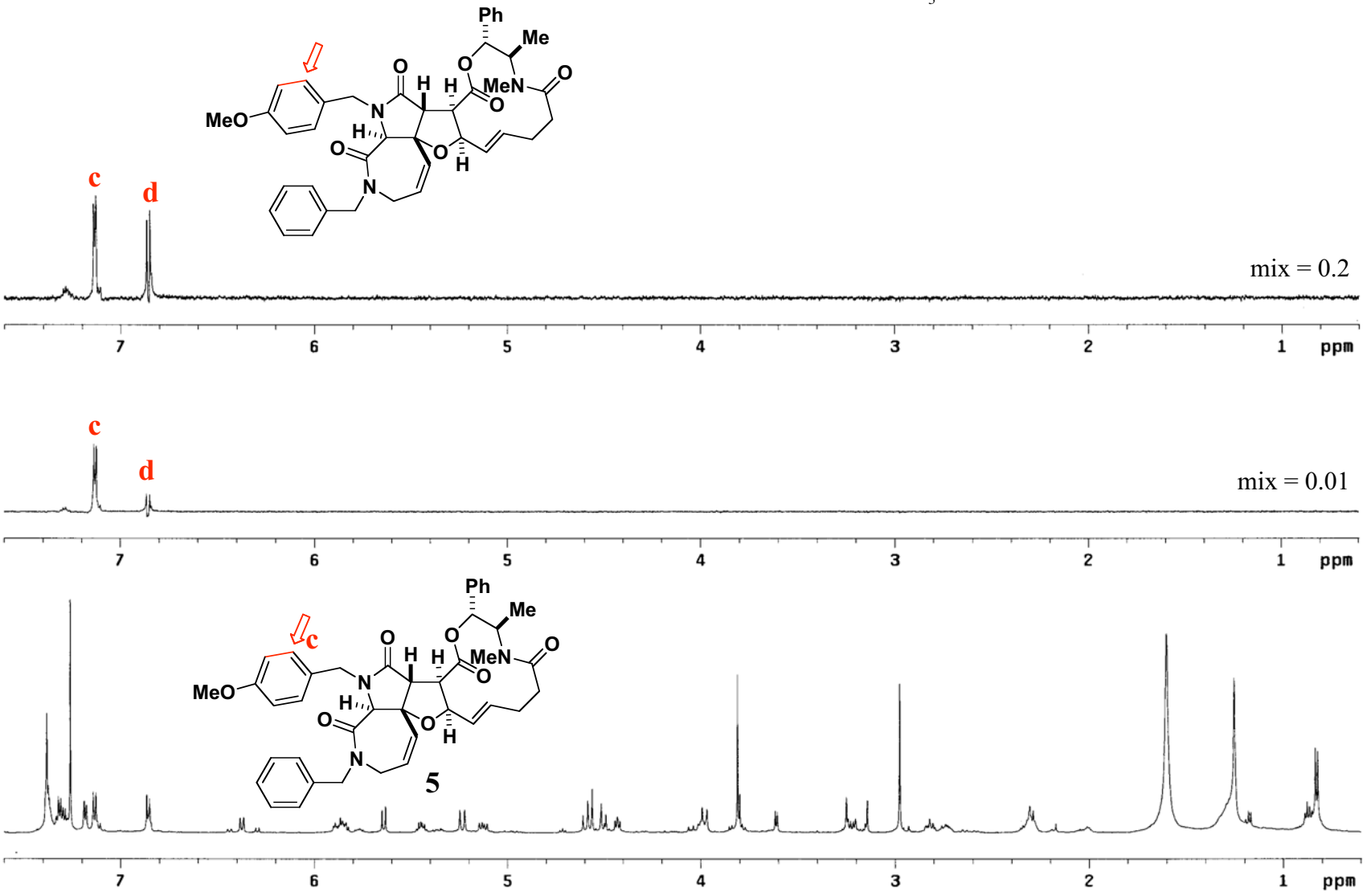


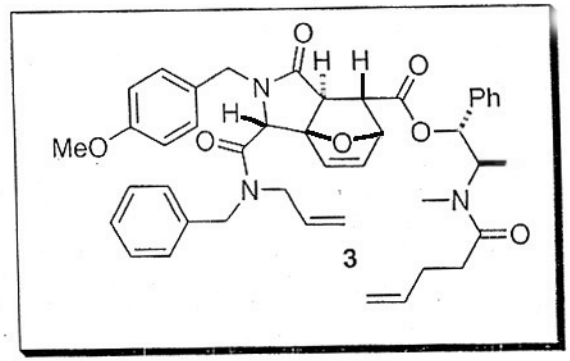
600 MHz-1D TOCSY $CDCl_3$

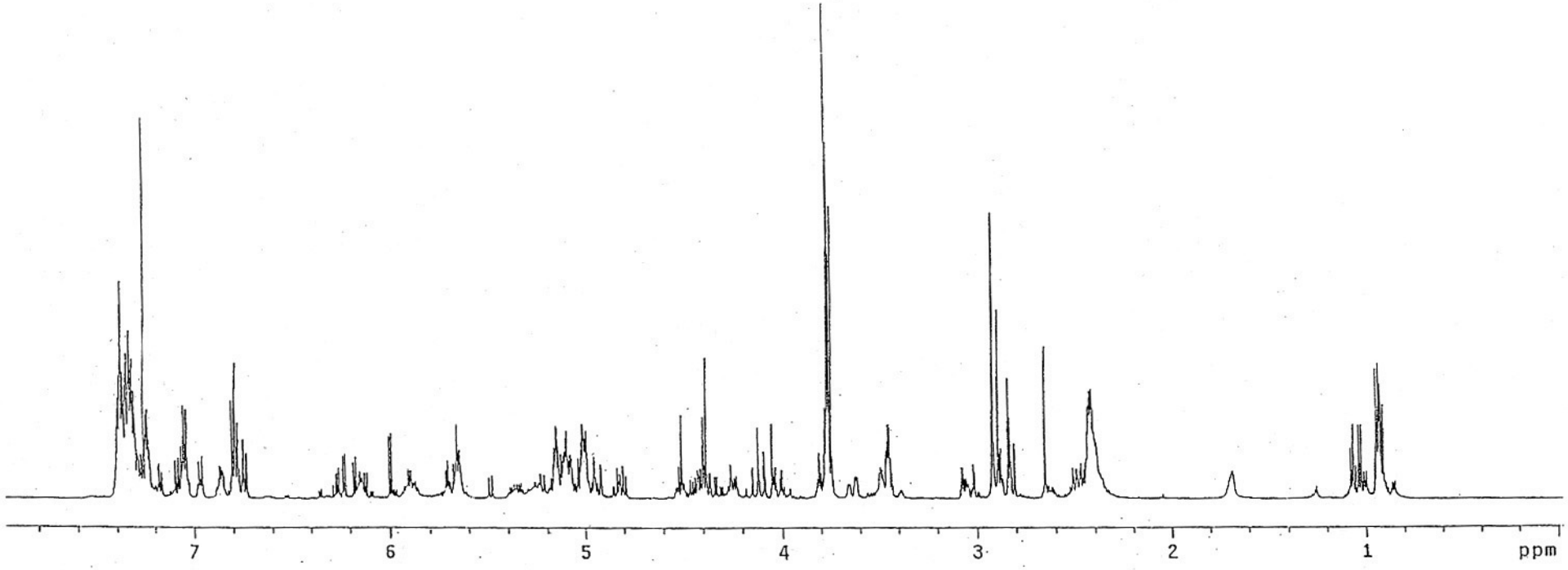


5

600 MHz-1D TOCSY $CDCl_3$

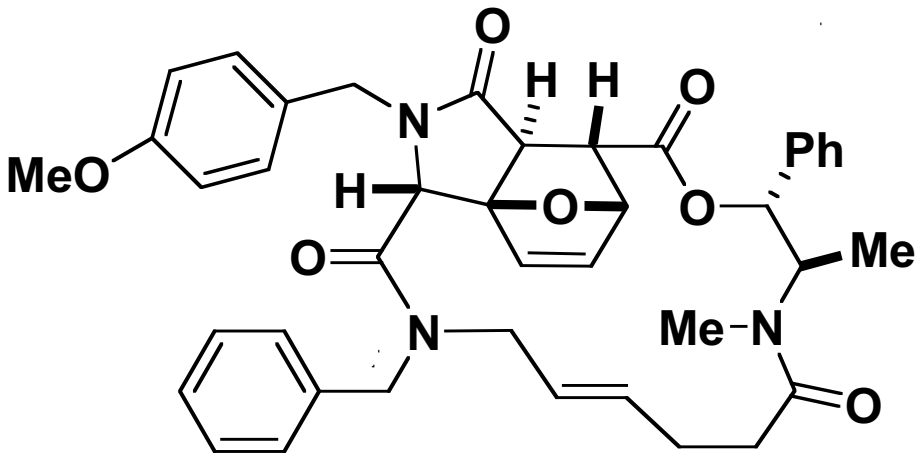



MeO
Ph
3

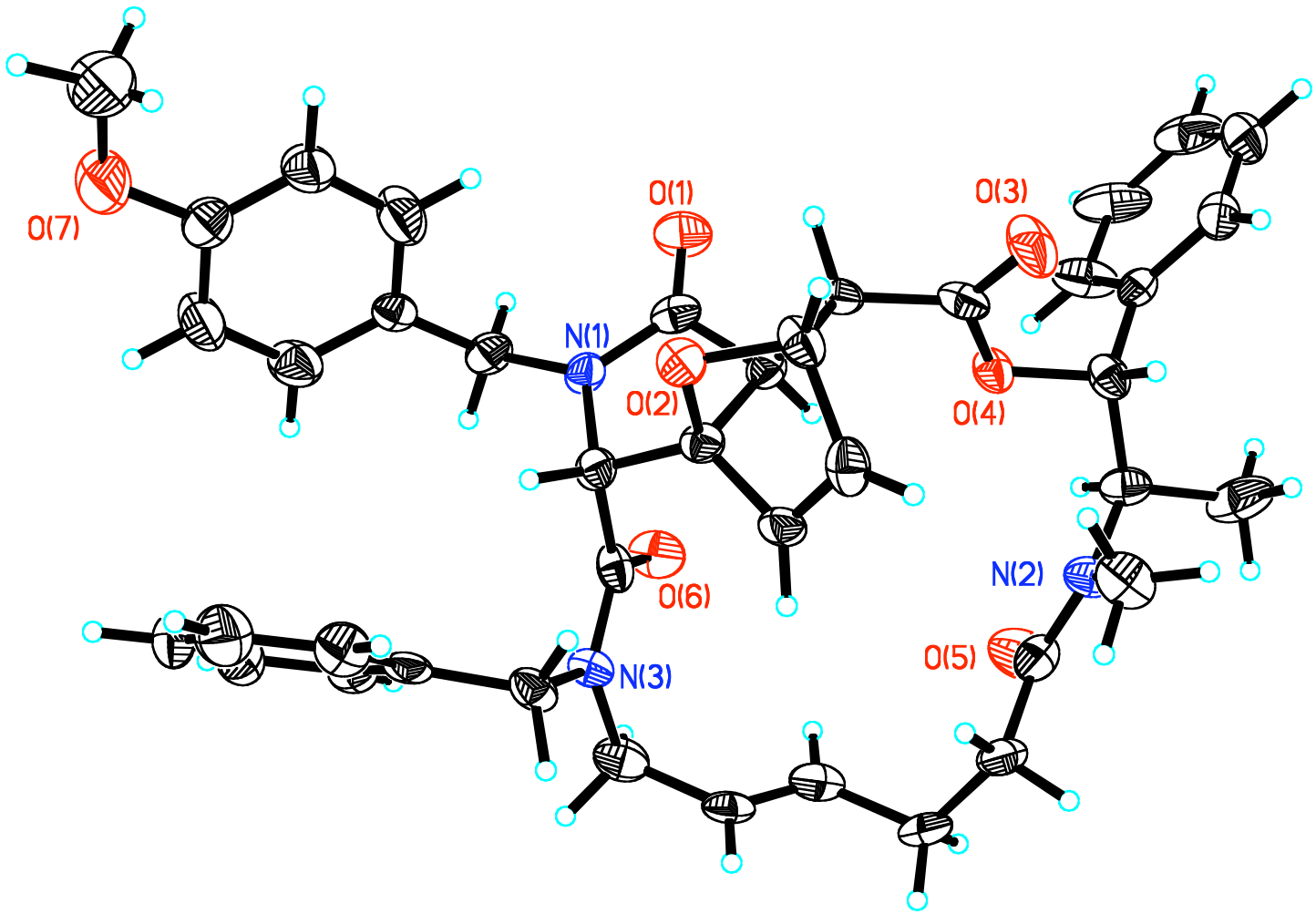

7
6
5
4
3
2
1
ppm

600 MHz-^{1}H NMR $CDCl_3$

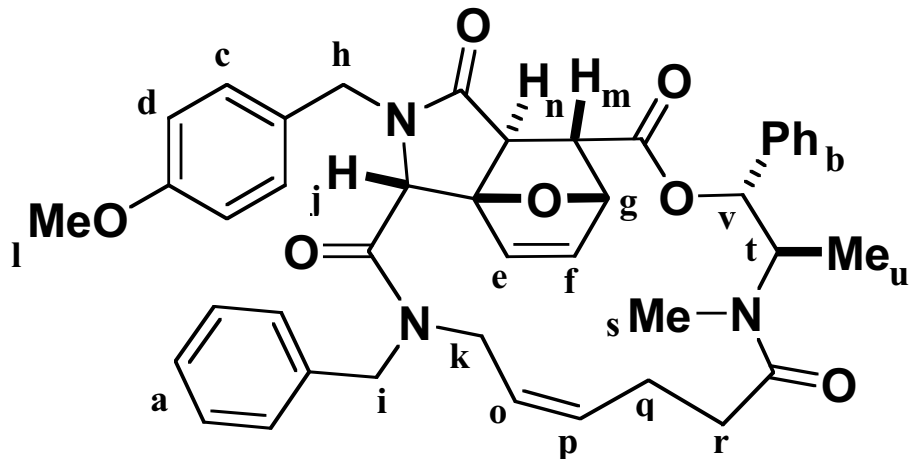
NMR obtained by dissolving crystals.



(*E*)-6

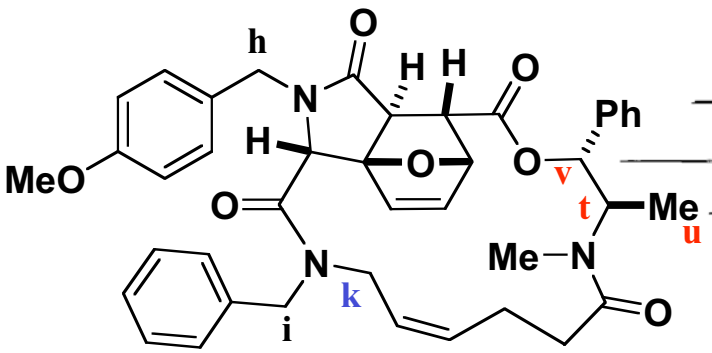

O(7)
O(1)
O(3)
N(1)
O(2)
O(4)
O(6)
N(2)
O(5)
N(3)

600 MHz-^{1}H NMR $CDCl_3$

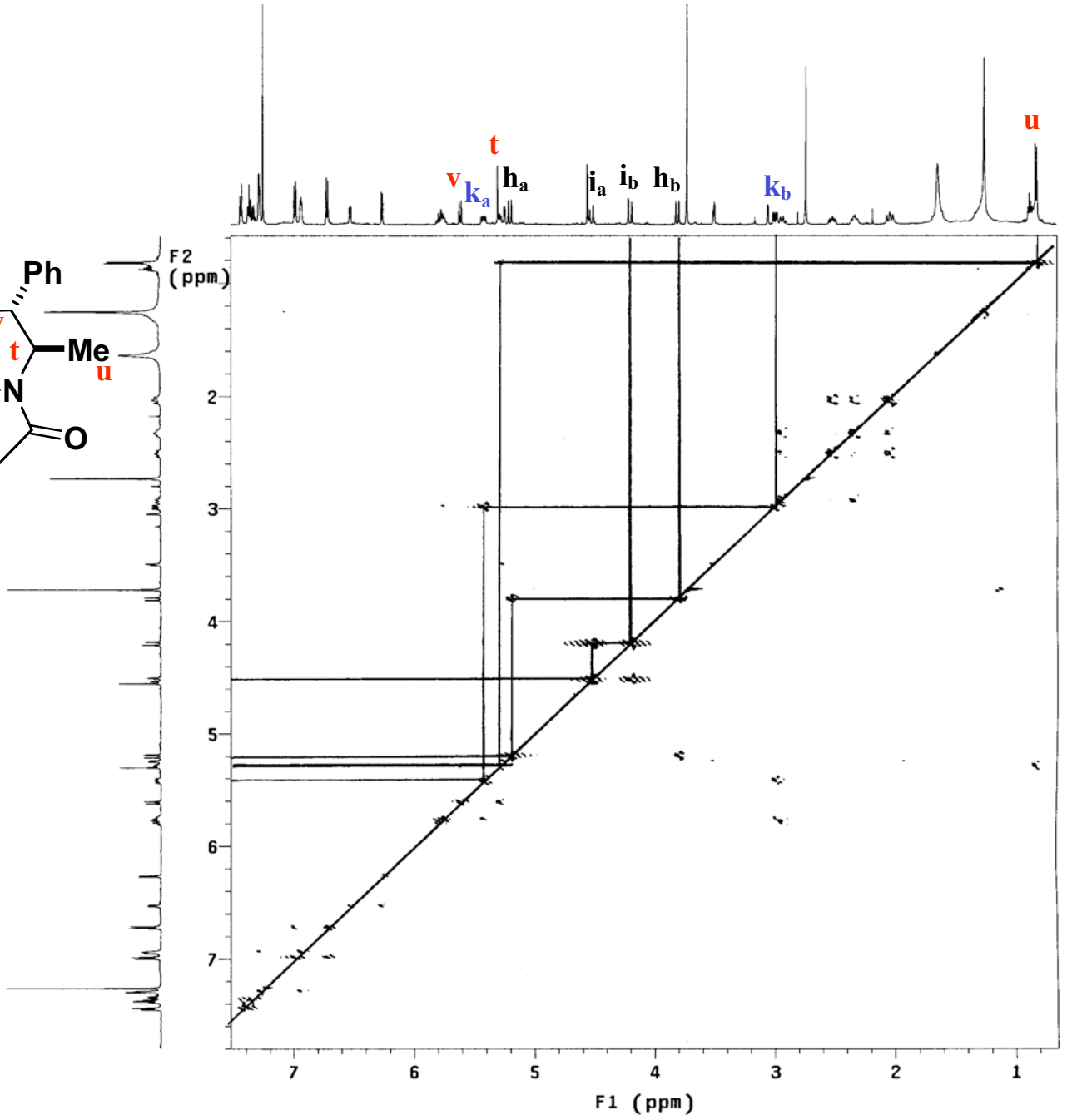


(*Z*)-6

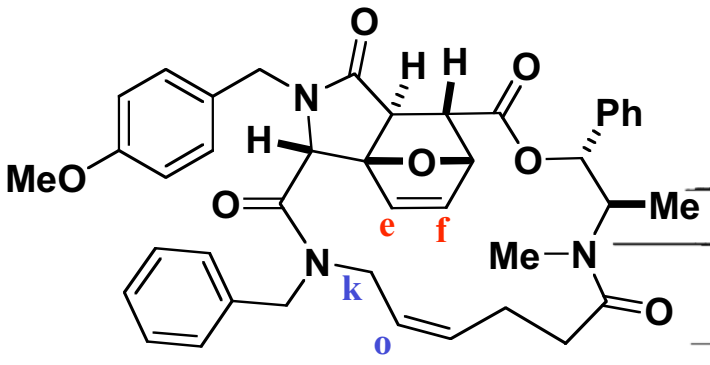
600 MHz-dqfCOSY $CDCl_3$



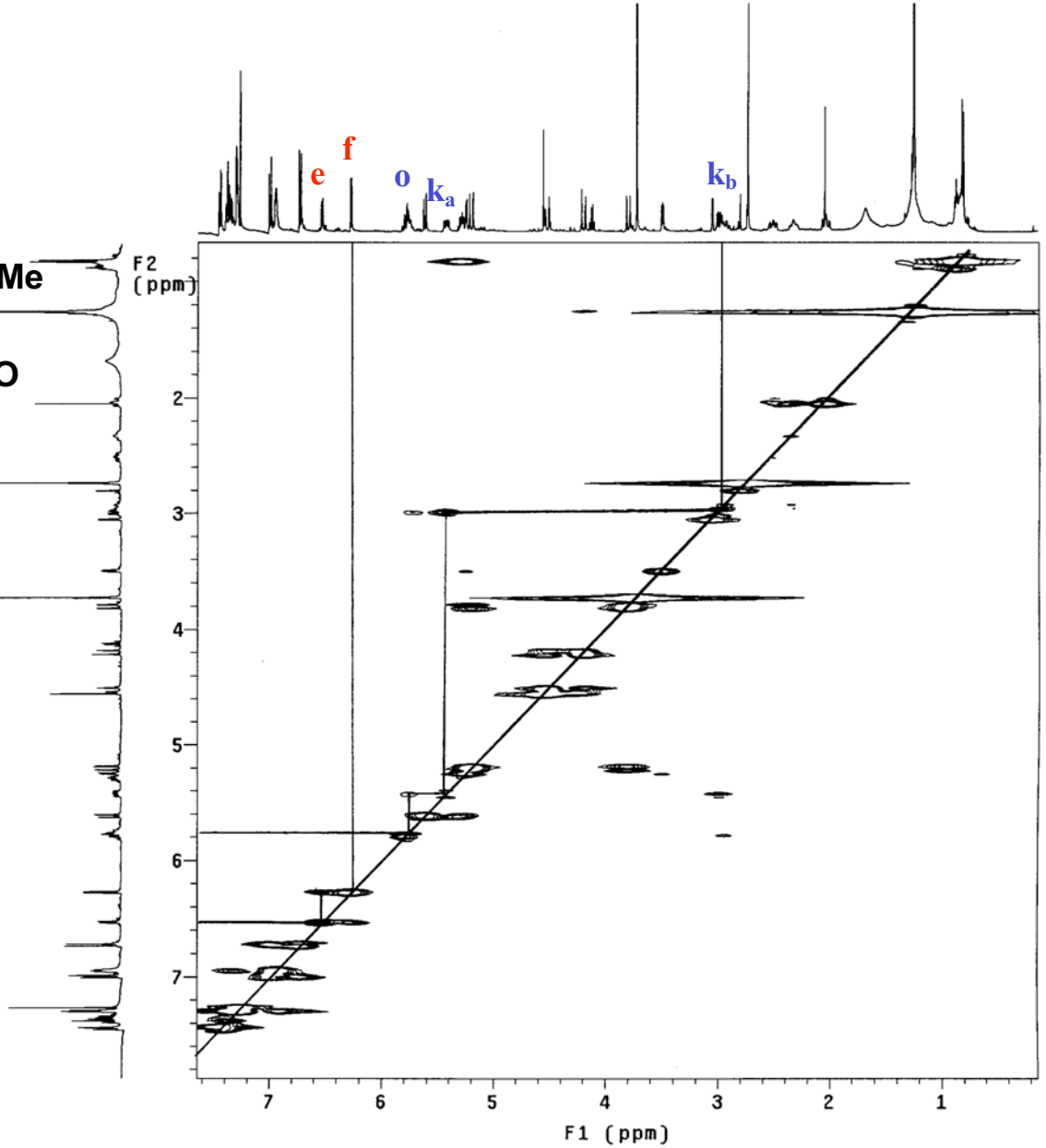
(*Z*)-6



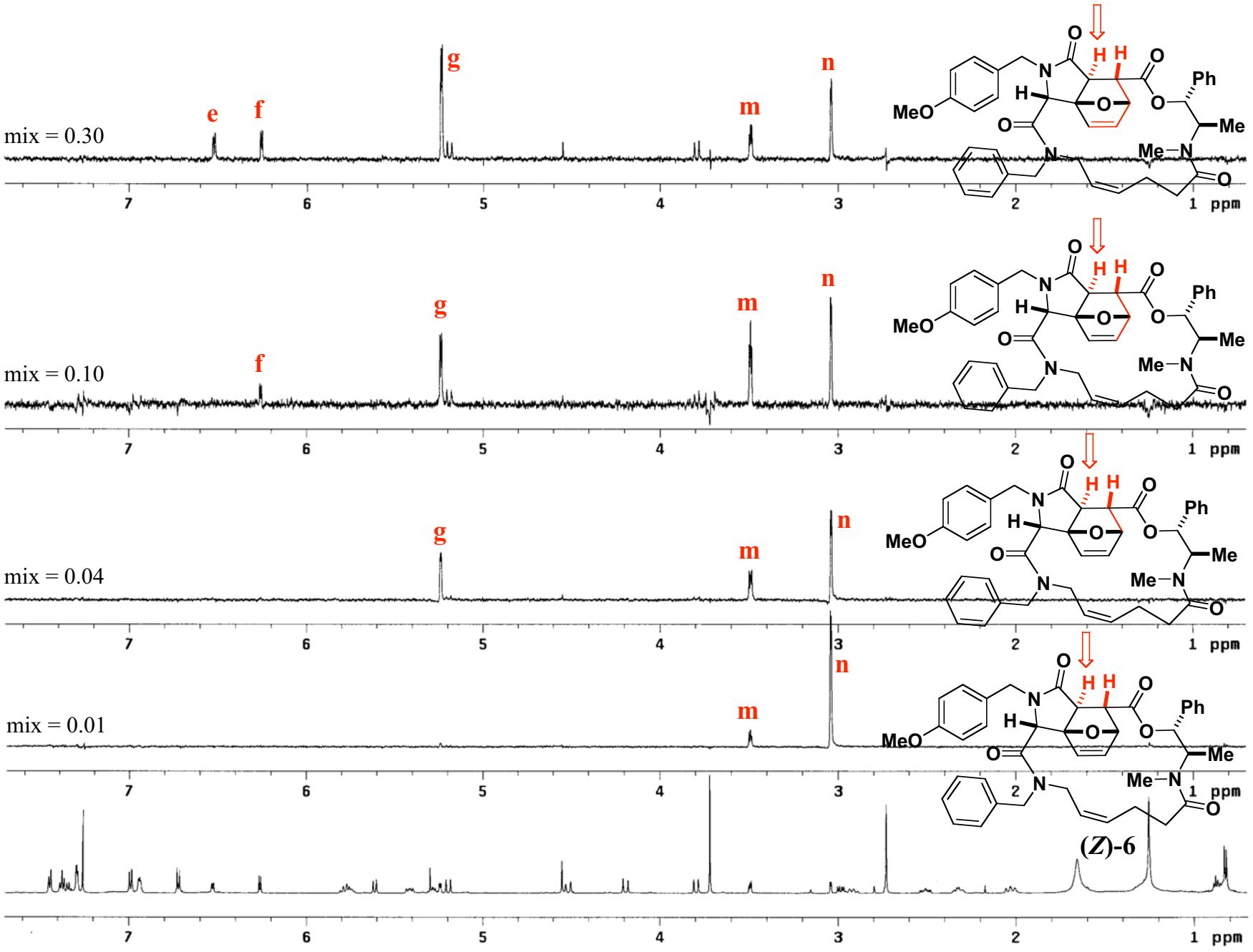
600 MHz-gCOSY $CDCl_3$



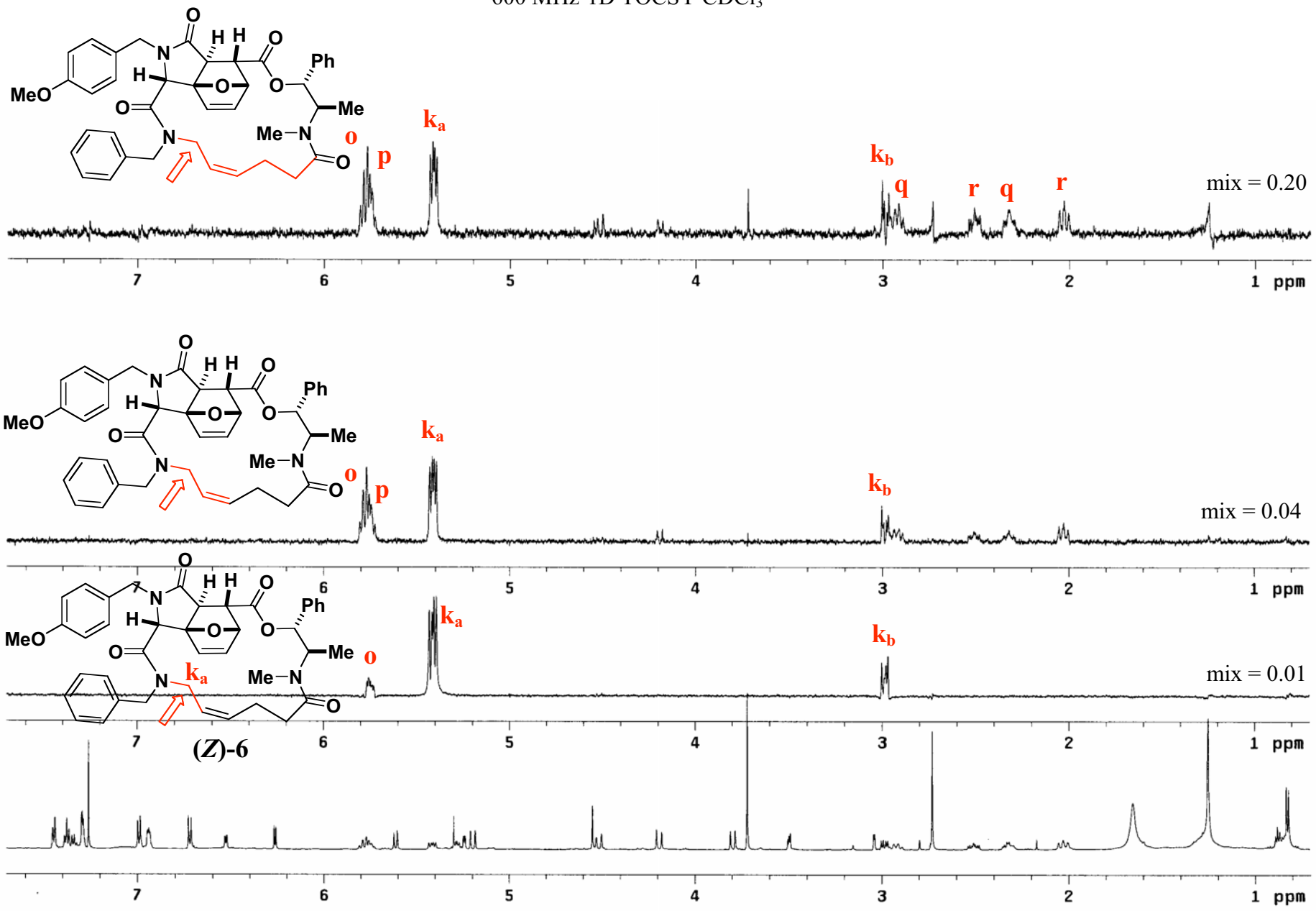
(*Z*)-6



600 MHz-1D TOCSY $CDCl_3$

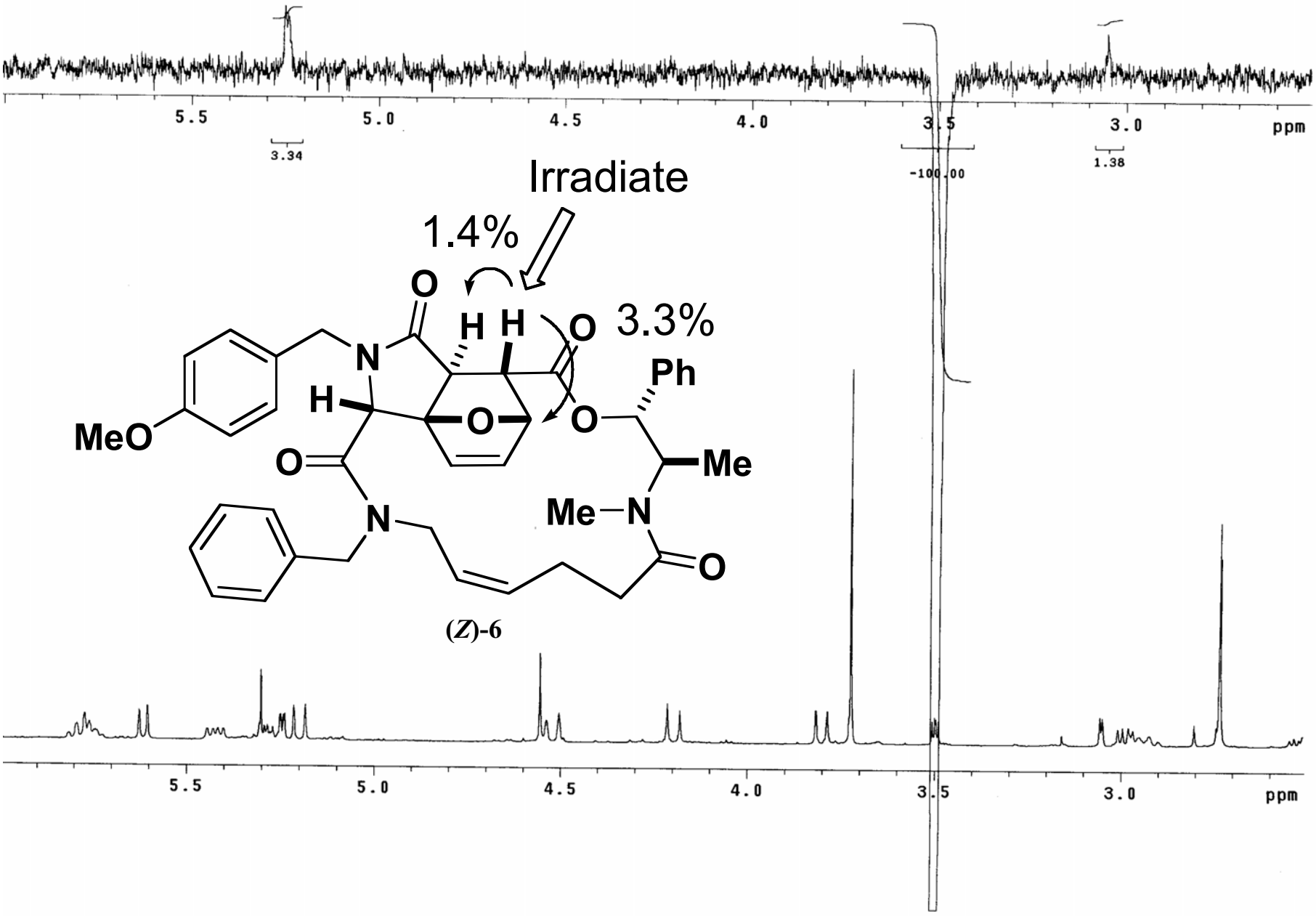


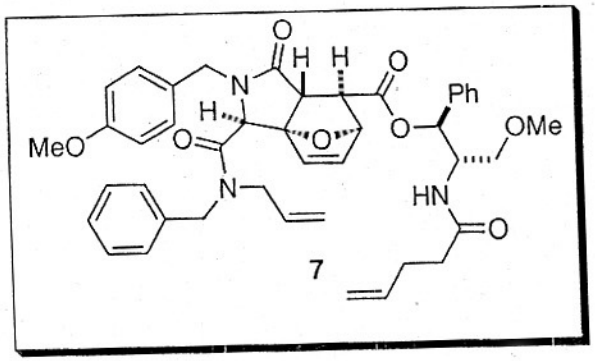
600 MHz-1D TOCSY $CDCl_3$



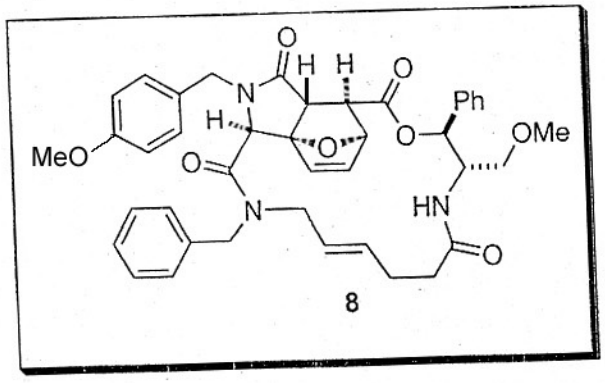
(*Z*)-6

600 MHz-nOe $CDCl_3$

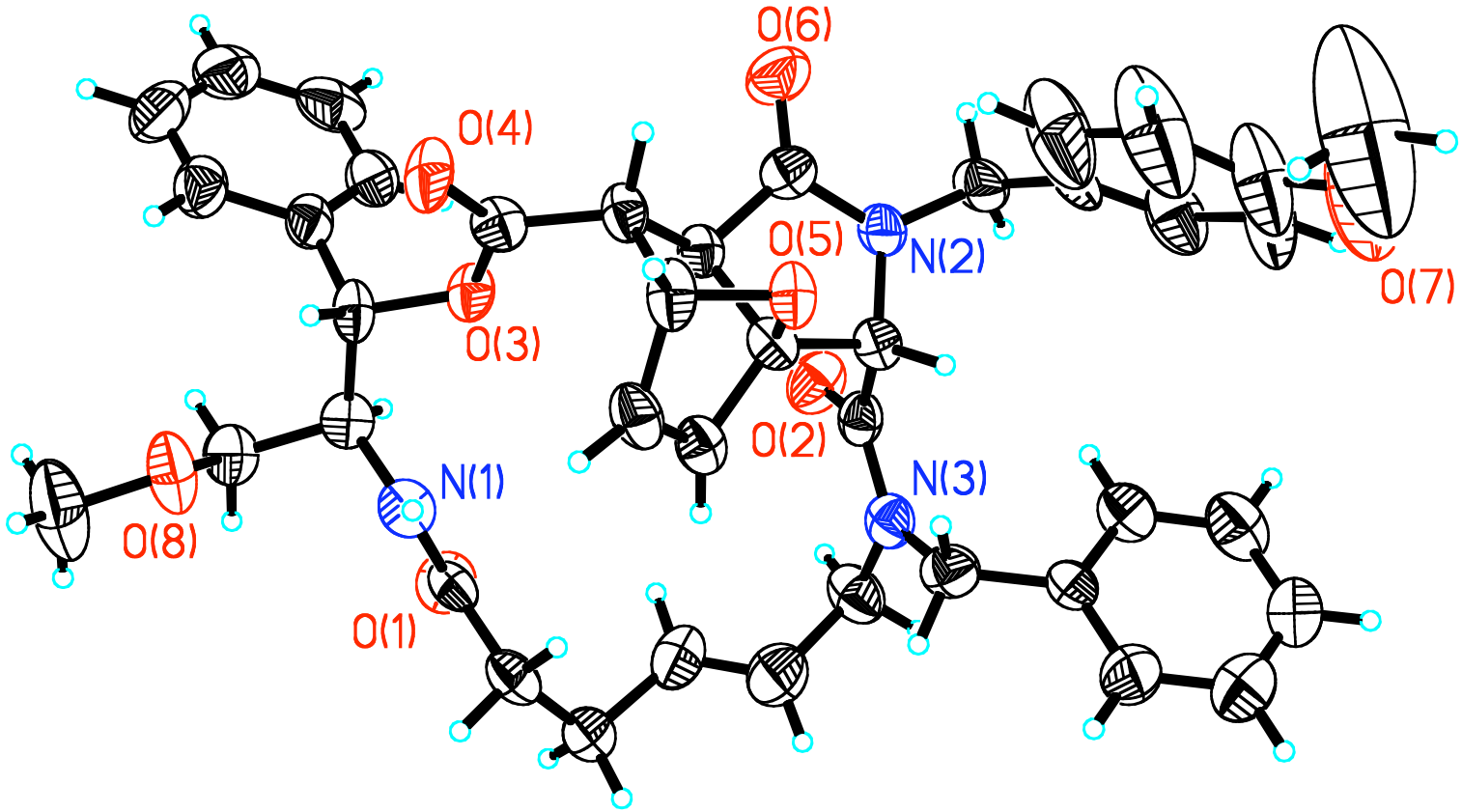


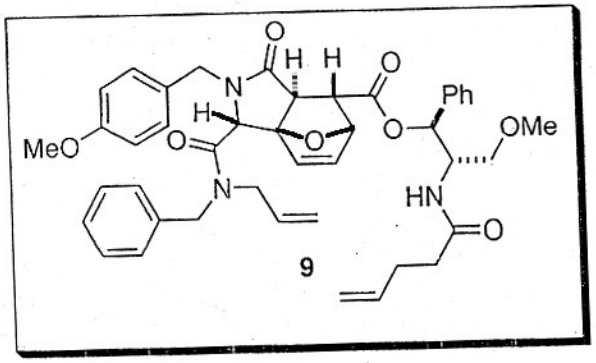

MeO
OMe
Ph
HN
7

7
6
5
4
3
2
1
ppm

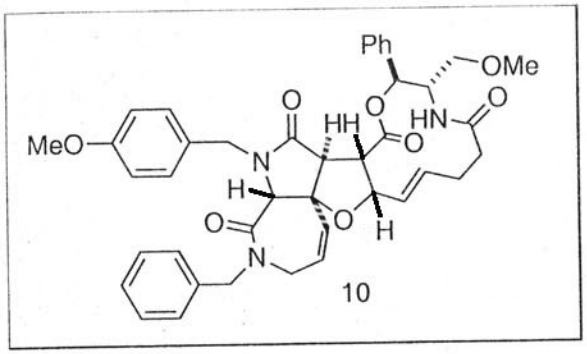


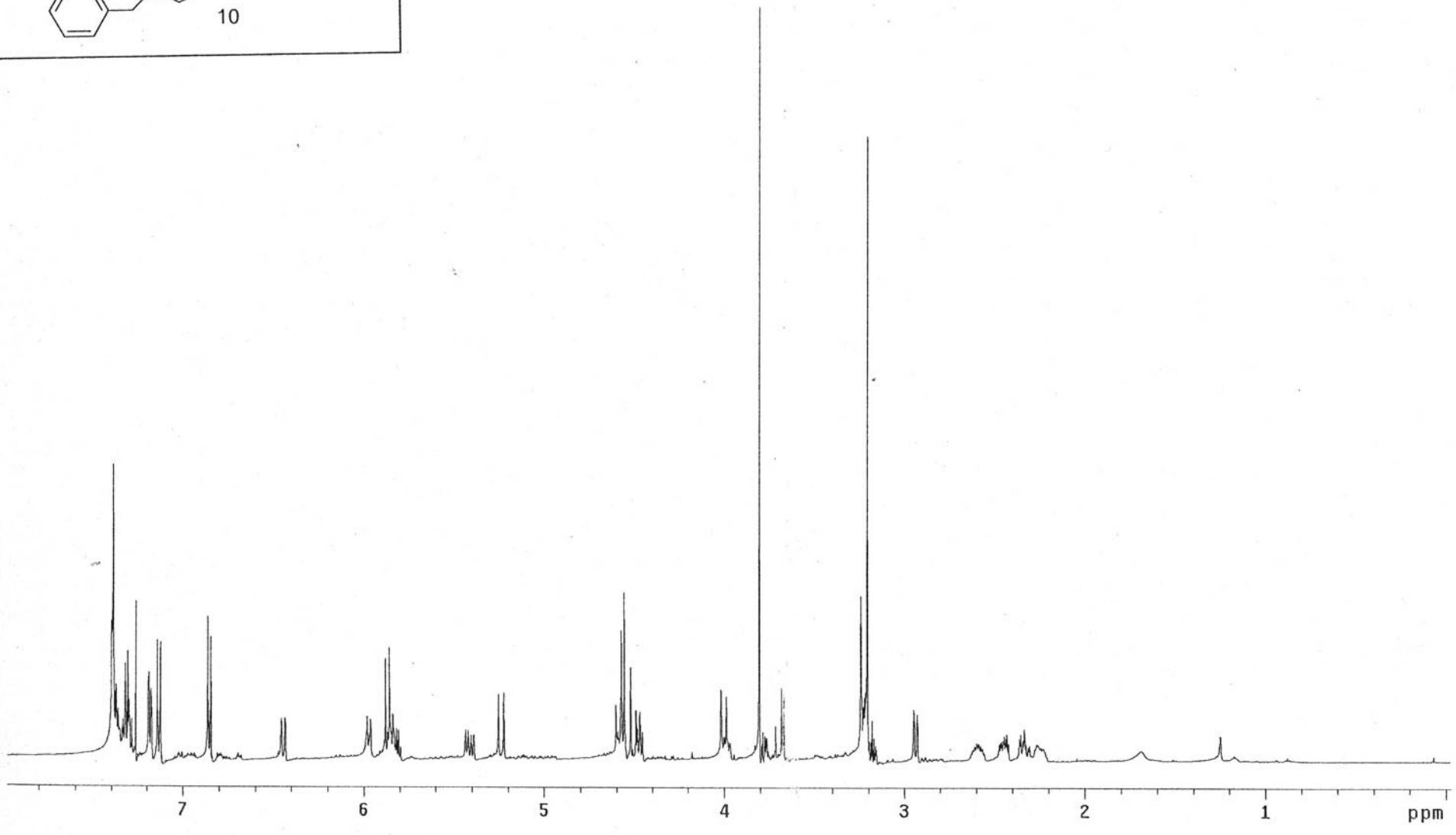
8


O(6)
O(4)
O(5)
N(2)
O(7)
O(3)
O(2)
N(1)
N(3)
O(8)
O(1)


MeO
OMe
Ph
HN
9

7
6
5
4
3
2
1
ppm


Ph
OMe
MeO
O
HH
O
HN
O
N
H
O
O
H
O
N
10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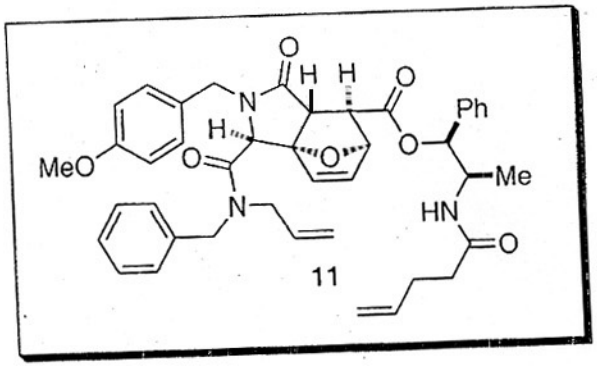
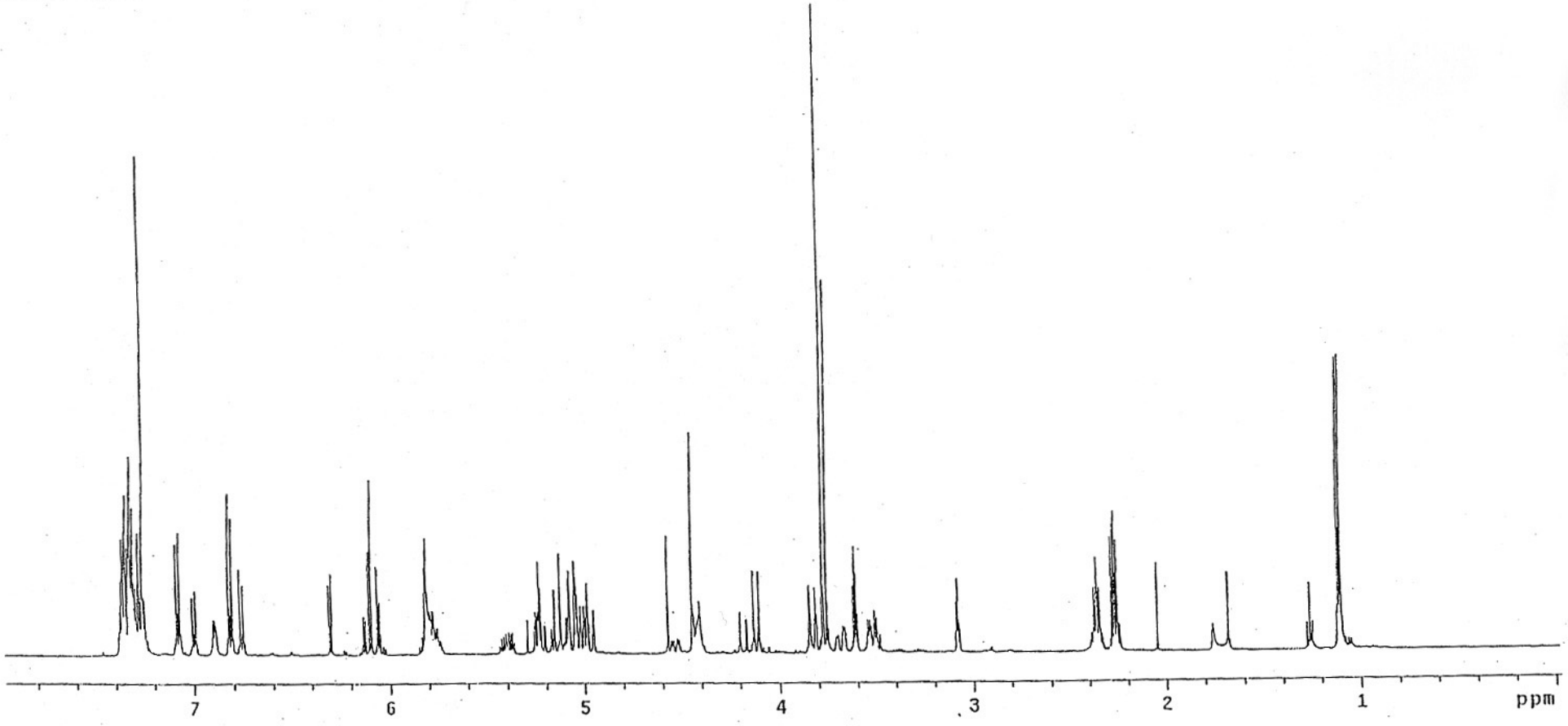
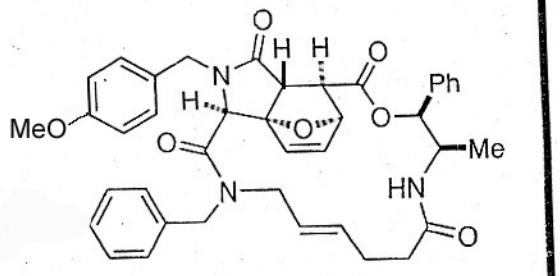


11





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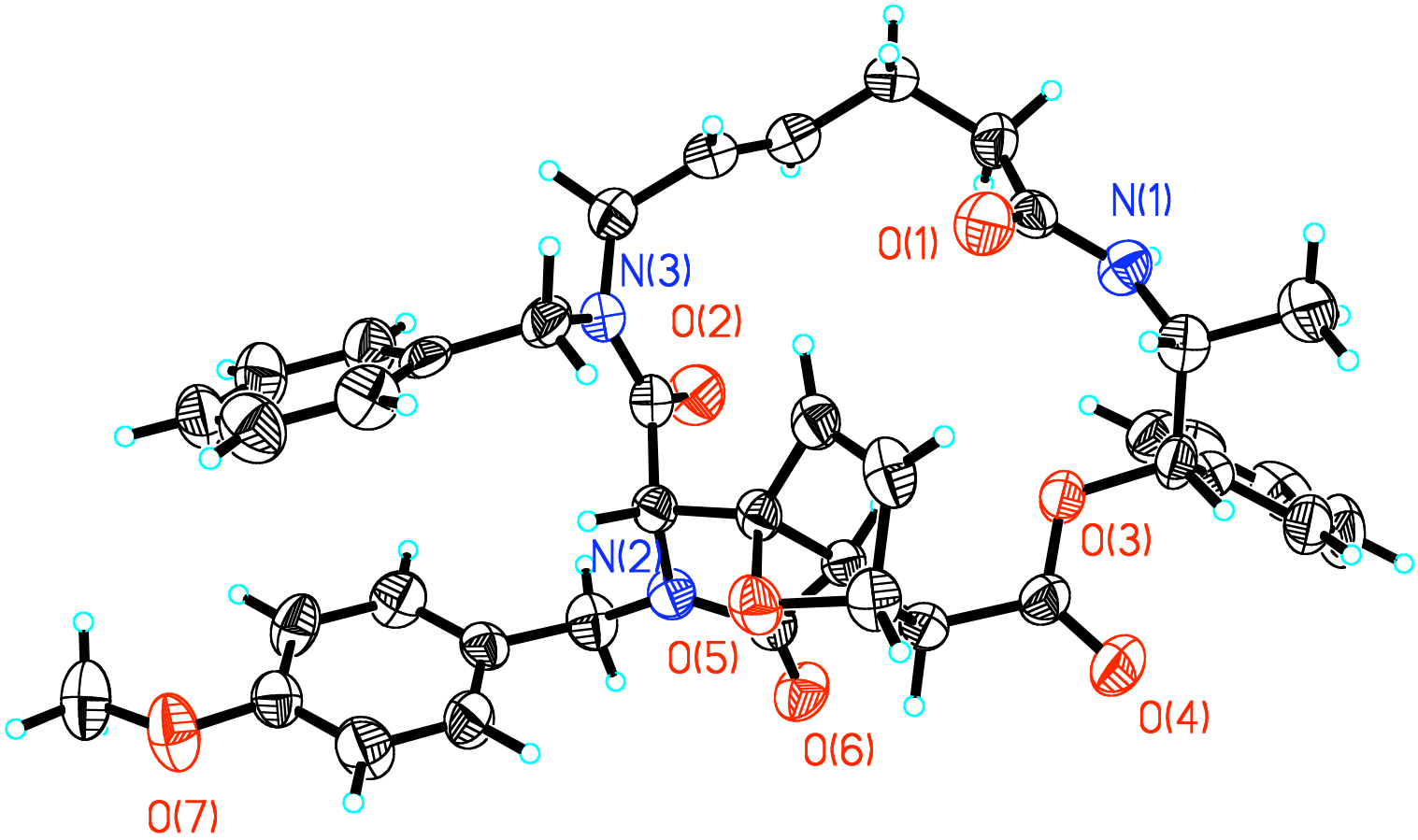
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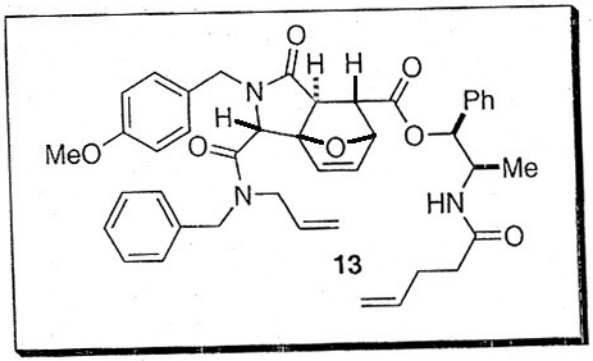
O(1)
N(3)
O(2)
O(3)
N(2)
O(5)
O(4)
O(6)
O(7)


MeO
Ph
Me
HN
13

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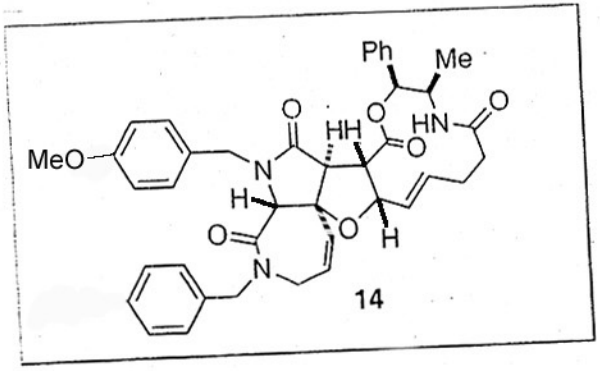
3
2
1
ppm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Me
MeO
HH
HN
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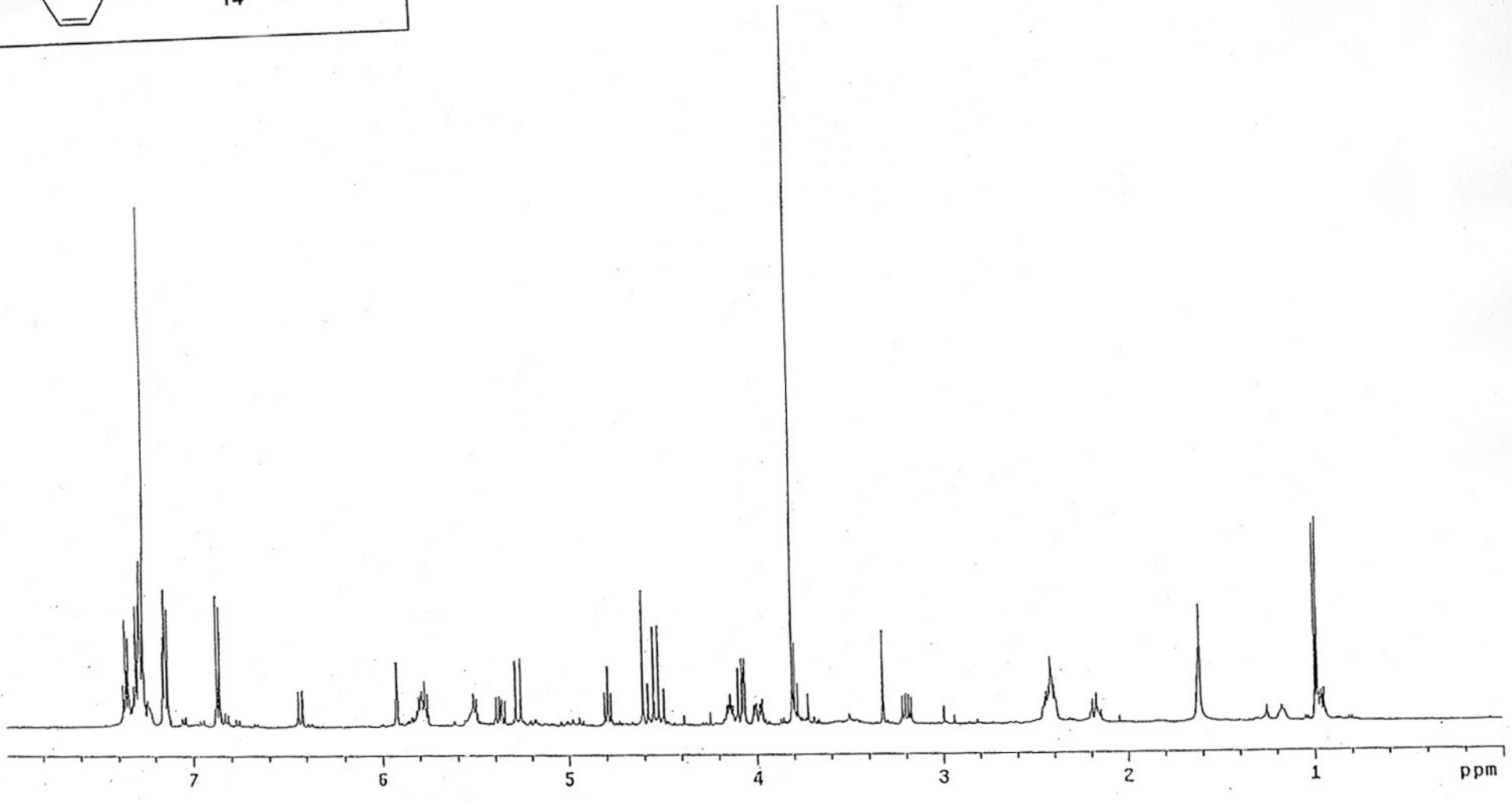
O
O
H
N
14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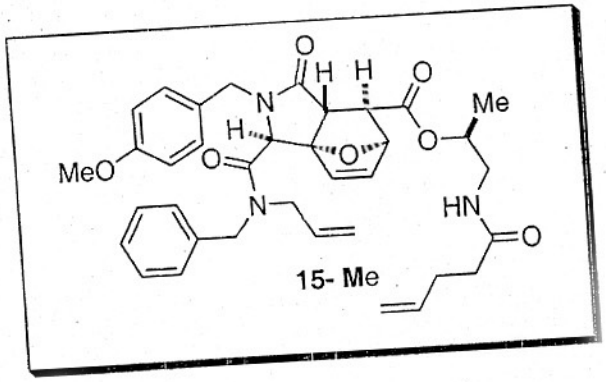
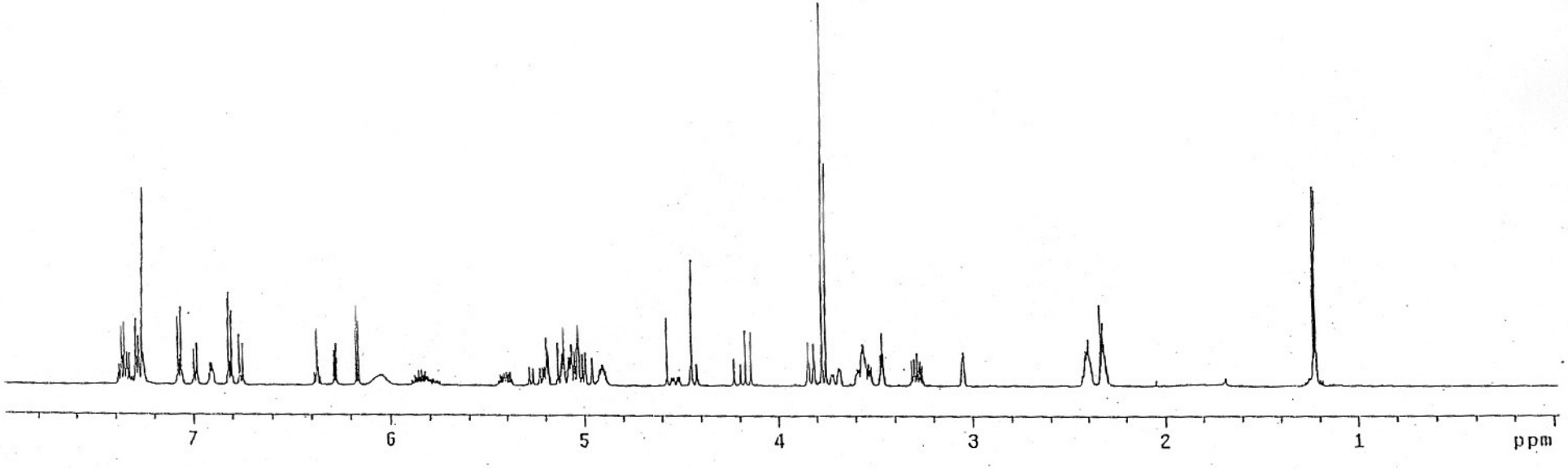

MeO
Me
HN
15- Me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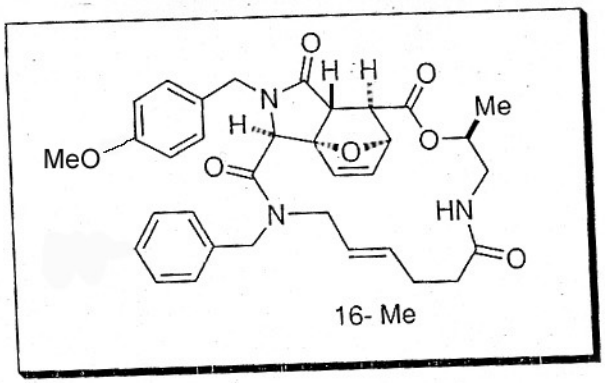
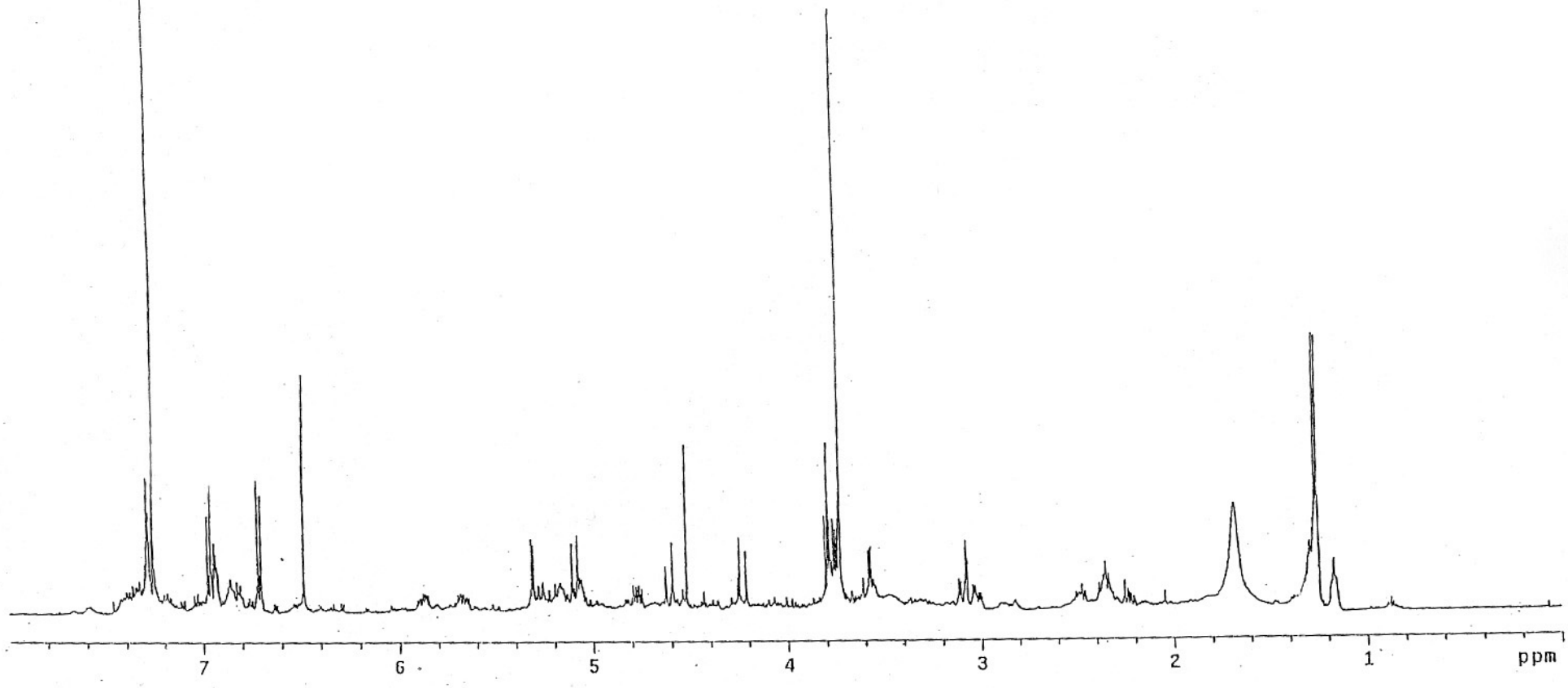
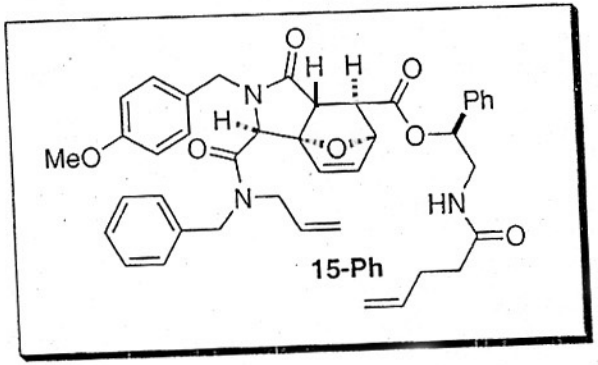


16- Me

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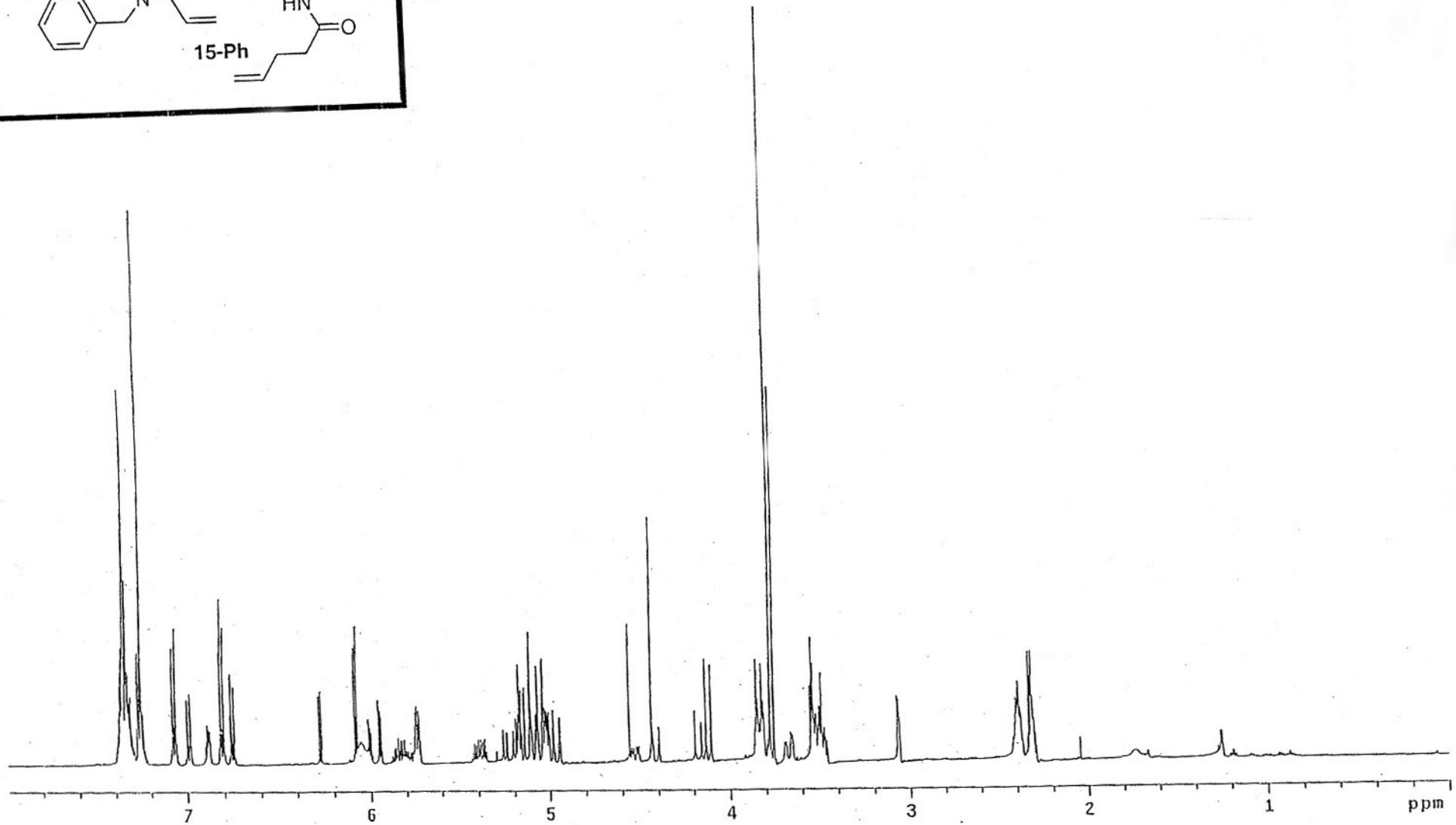
HN
15-Ph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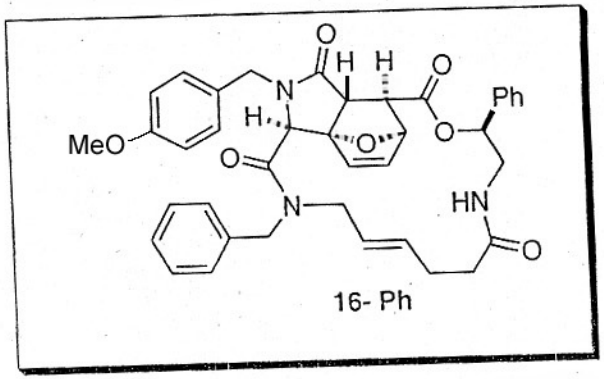
MeO
Ph
HN
16- Ph

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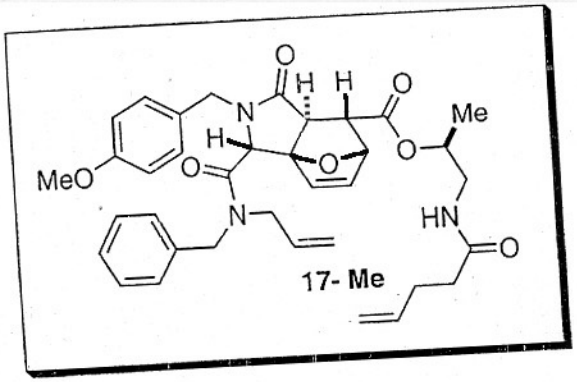
4
3
2
1
ppm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N
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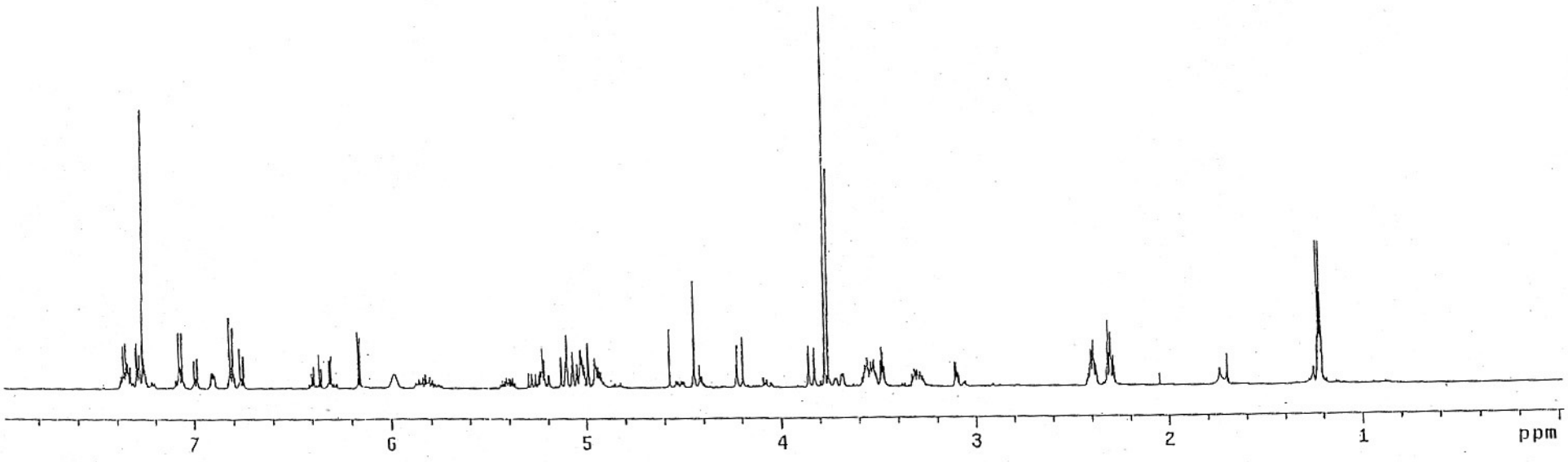
H
O
O
Me
O
O
N
HN
O
17- Me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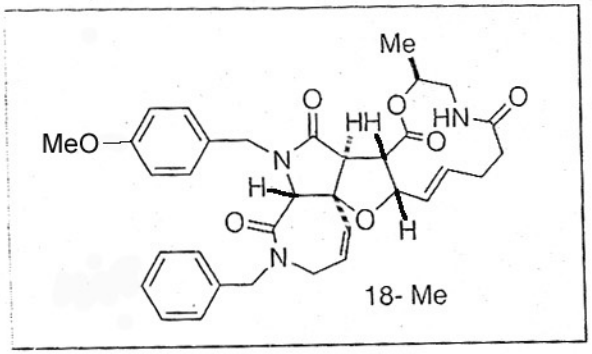
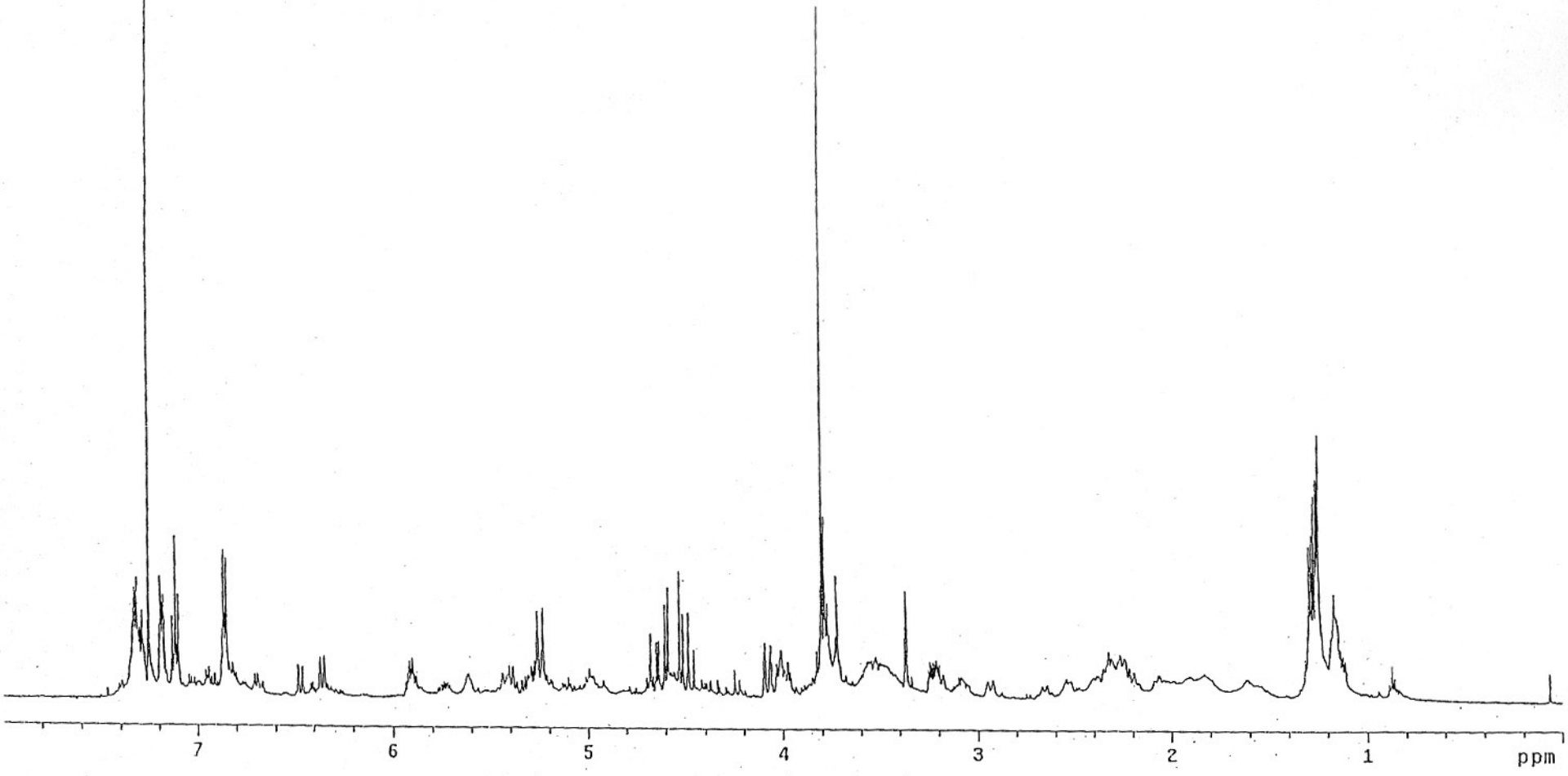

Me
MeO
O
HH
O
HN
O
N
O
H
O
O
H
N
18- Me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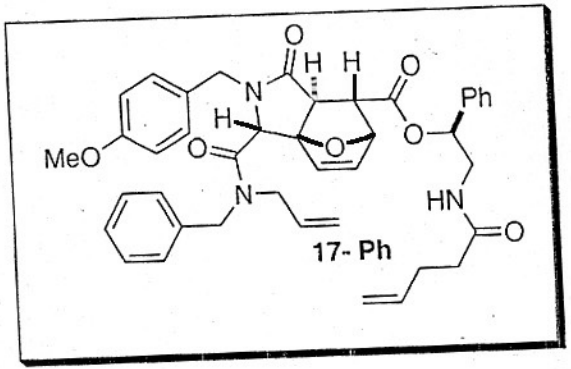
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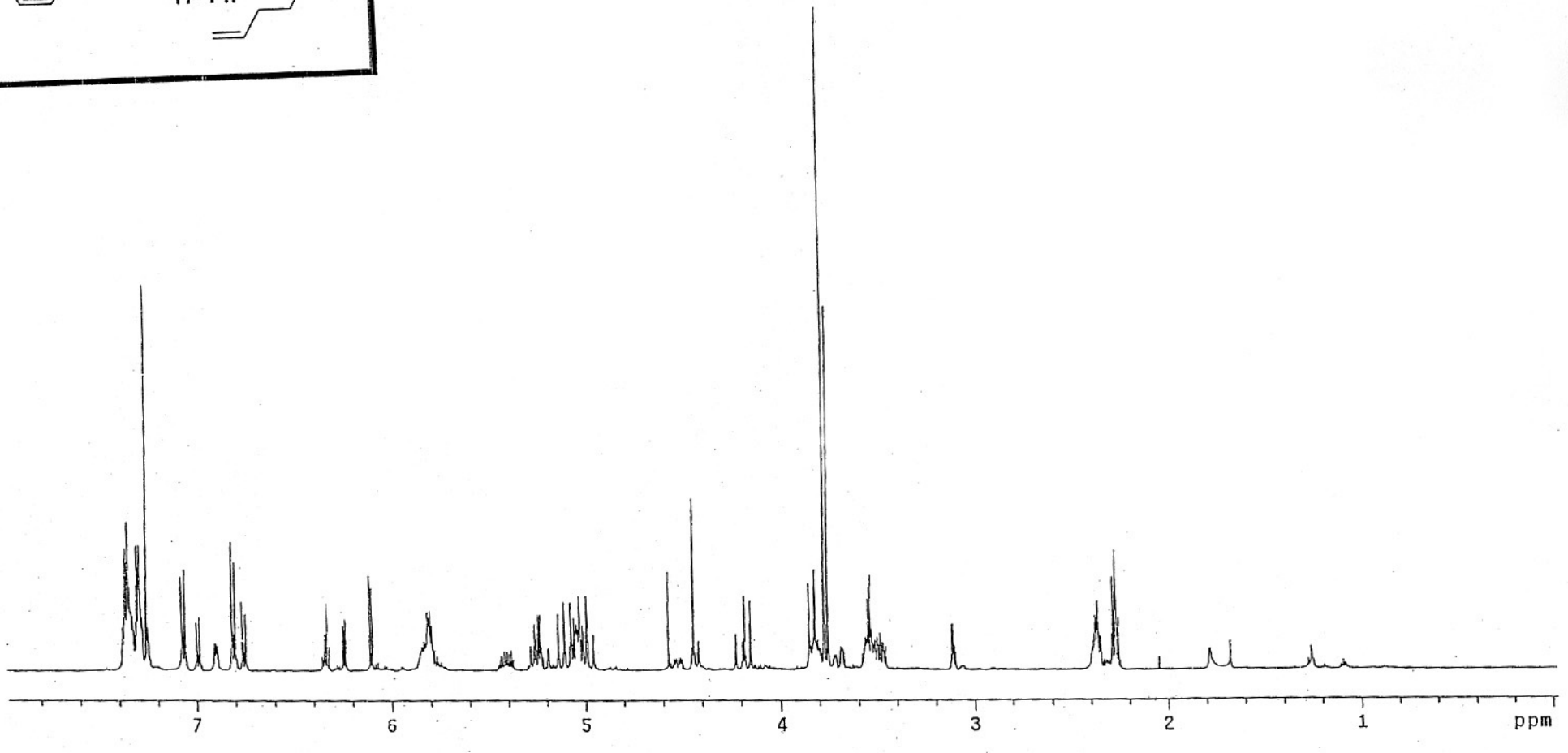
Ph
HN
17- Ph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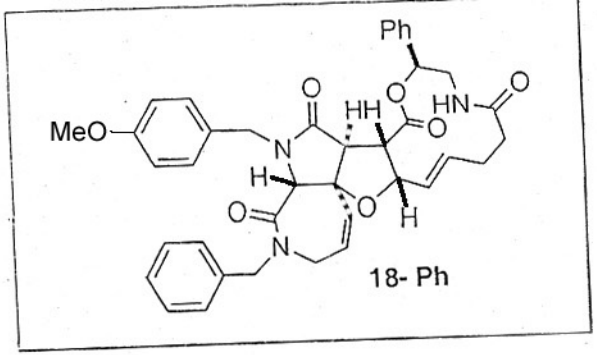
Ph
MeO
HH
HN
H
H
18- Ph

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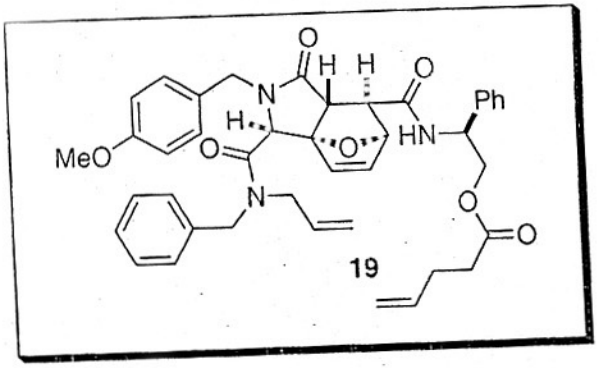
ppm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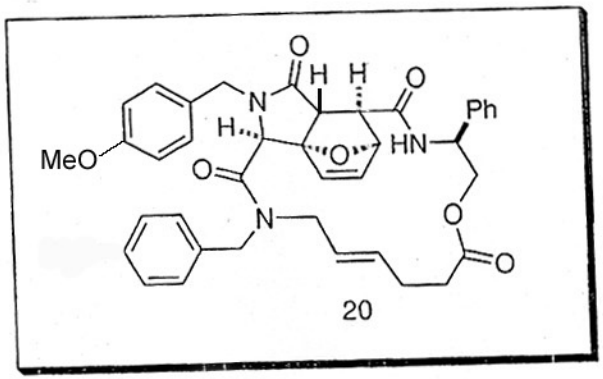
ppm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Ph
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N
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2
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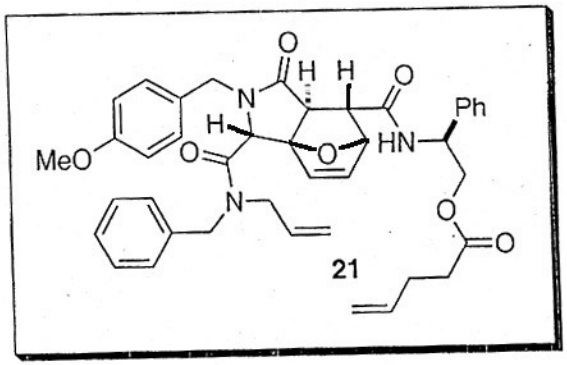
ppm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MeO
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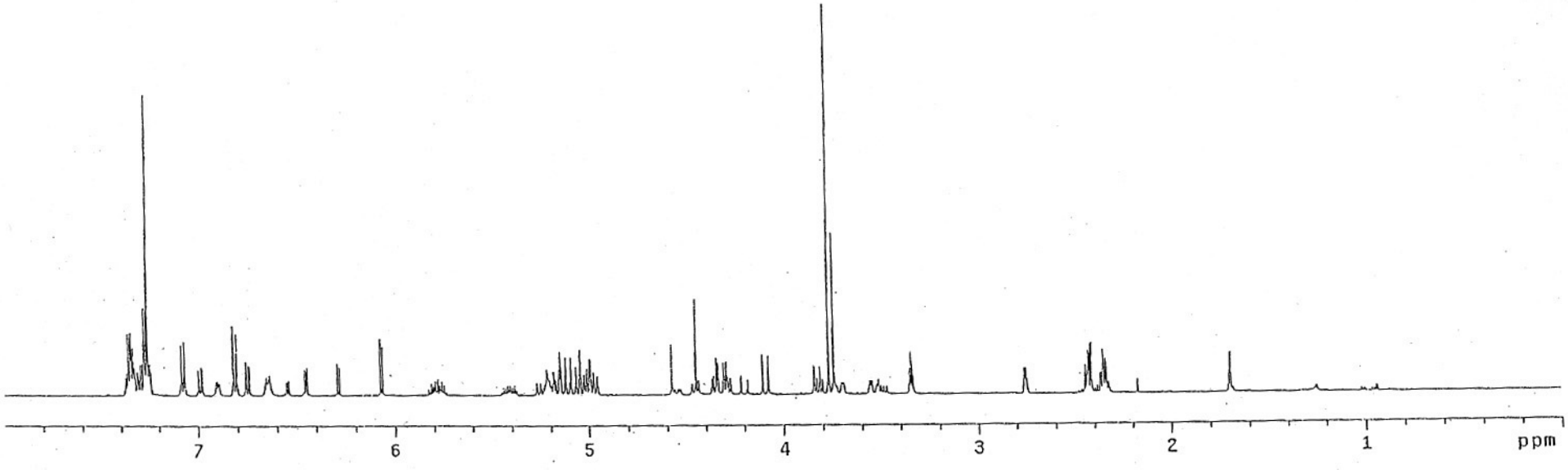
21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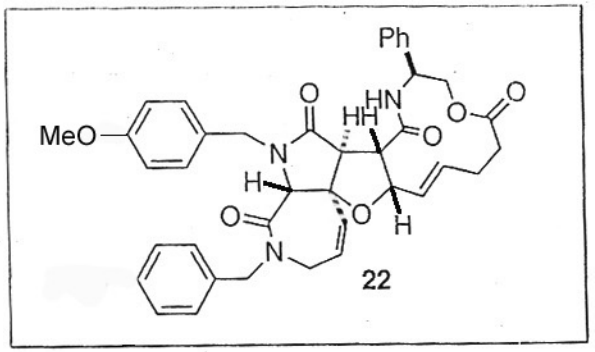
Ph
HN
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HH
MeO
N
H
O
O
H
N
22

7
6
5
4
3
2
1
ppm