Development of an Automated Microfluidic Reaction Platform for Multidimensional Screening: Reaction Discovery Employing Bicyclo[3.2.1]octanoid Scaffolds

Supporting Information

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General Information: ^{1}H NMR spectra were recorded at 400 MHz at ambient temperature with $CDCl_3$ as solvent unless otherwise stated. ^{13}C NMR spectra were recorded at 100.0 MHz at ambient temperature with $CDCl_3$ as solvent unless otherwise stated. Chemical shifts are reported in parts per million relative to $CDCl_3$ (^{1}H, δ 7.27; ^{13}C, δ 77.0). Data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, m = multiplet) and coupling constants are reported as values in hertz. All ^{13}C NMR spectra were recorded with complete proton decoupling. Infrared spectra were recorded on a FT-IR spectrophotometer. High-resolution mass spectra were obtained in the Boston University Chemical Instrumentation Center using a Q-TOF mass spectrometer. Analytical LC was performed on a UPLC with PDA, ELS and mass detectors. A BEH 2.1 x 50 mm 1.7 μM C18 column was used for analytical LC. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Otherwise, flash chromatography was performed using 200-400 mesh silica gel. Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. Acetonitrile, THF, and toluene were purified by passing through two packed columns of neutral alumina. All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted.

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I. Technical Design Notes

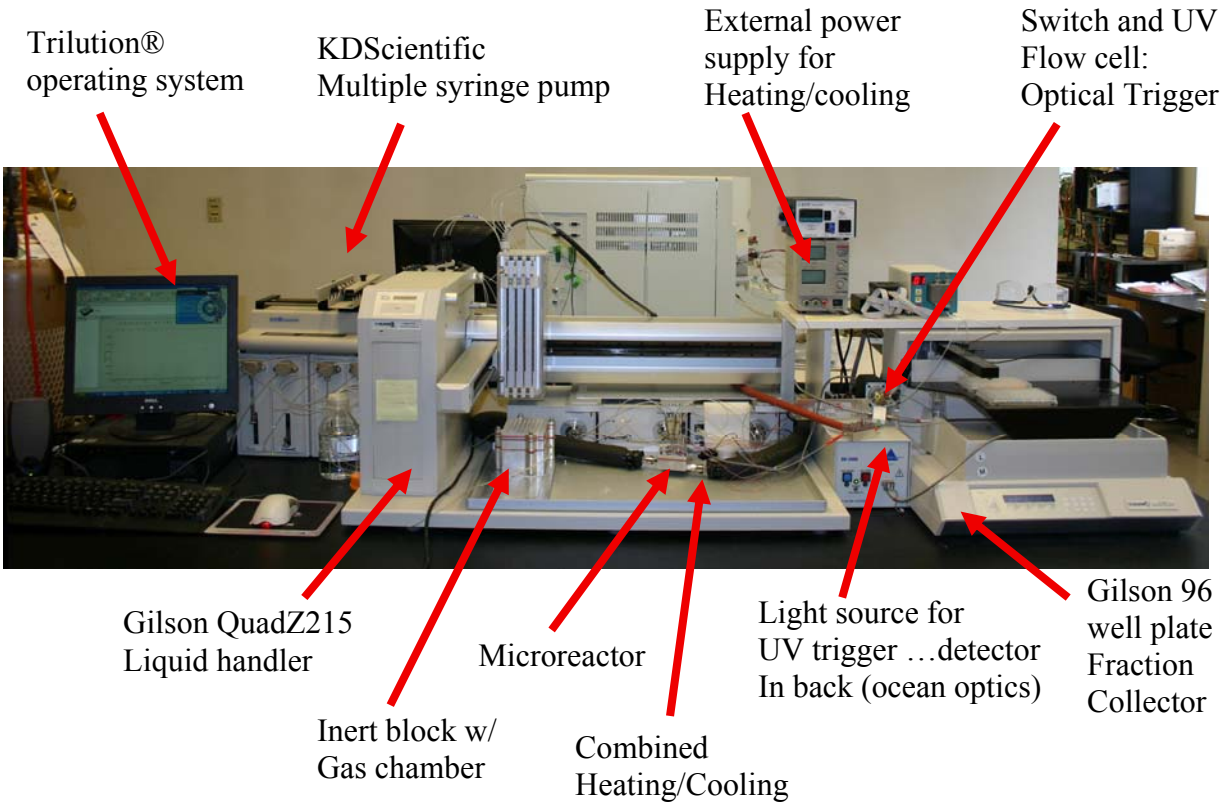


Figure S1. Automated microfluidic platform for reaction screening.

Microreactor Screening Platform Description and Capabilities

We have successfully assembled a microfluidics platform capable of conducting programmed reaction arrays (Figure S1). The ability to perform a series of specified reactions was made possible by the incorporation of a Gilson Quad-Z 215 liquid handler equipped with four independently controlled sample probes (Figure S2-A). In order to insure the ability to conduct a wide range of chemical transformations, we designed and fabricated a custom 96-well reagent aluminum block that could be mounted to the liquid handler bed (Figure S2-B, Figure S3). The block was designed to accommodate commercially available glass sleeves which are sealed silicon rubber septum (Figure S2-B). The integrity of the reagents within the block is maintained with the inclusion of an inert gas chamber that is mounted over the sample wells. The inert gas chamber also serves as a source of buffering atmosphere during reagent transfer by modifying the sampling routine to include the aspiration of inert gas on either side of the reagent (Figure S2-C). The flow for our fluidics platform is achieved using a KDScientific multiple syringe pump (Figure S2-D). The use of a multi-head syringe pump is a convenient way to obtain equal flow in the three inlet lines that lead form the injector to the reactor insuring proper alignment of the reactions pulses.

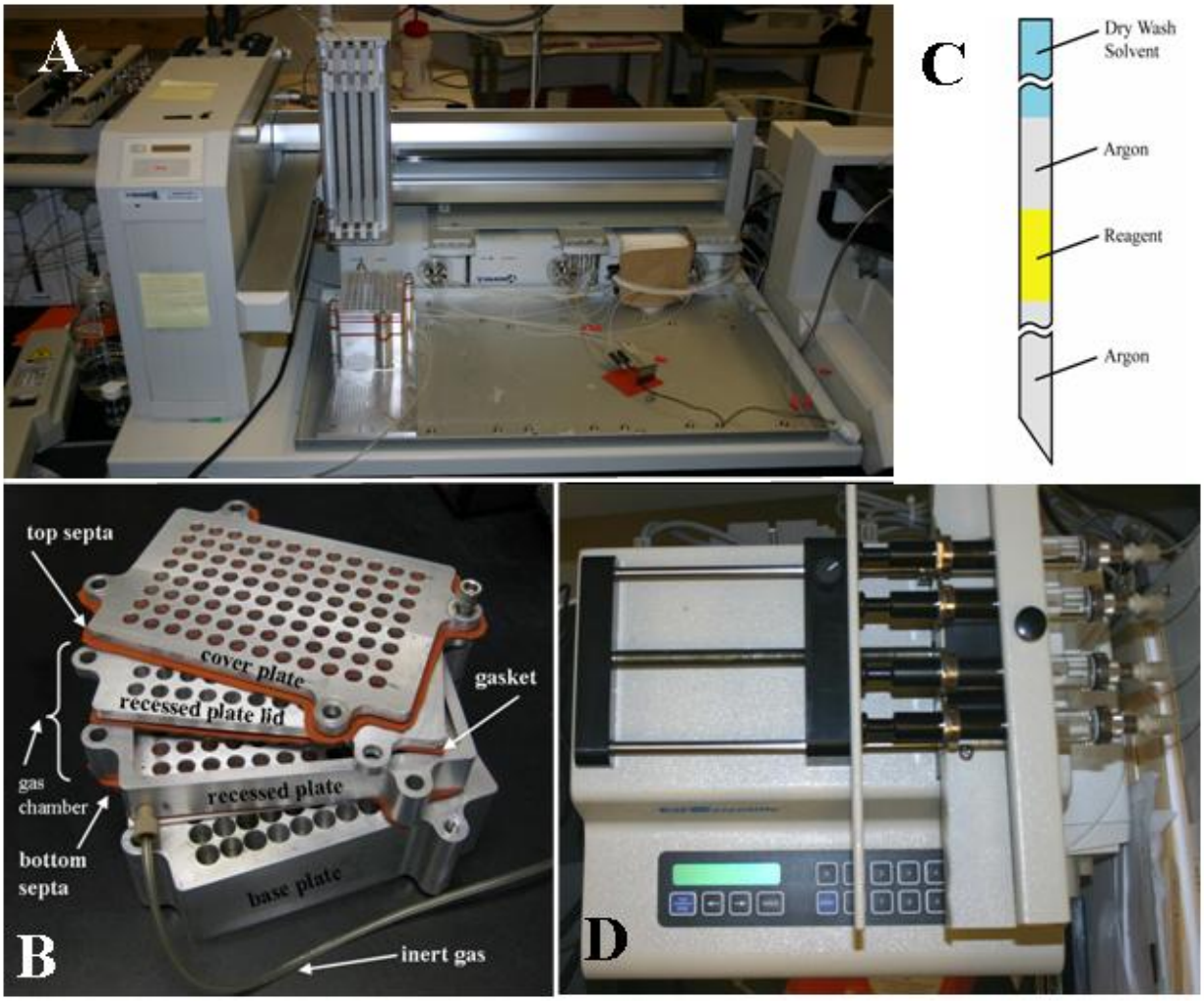


Figure S2: A) Gilson Quad-Z 215 liquid handler equipped with three independently controller sample probes, three Gilson 819 injection modules and two Gilson 402 syringe pumps. The liquid handling capabilities are controlled by Trilution ® software. **B)** Custom designed reagent block made out of aluminum consisting of a glass lined 96 well base plate that is cover by a layer of septa. The middle two plates make up the inert gas chamber that will have second layer of septa on top (between the gas chamber and the cover plate) to insure a tight seal around the gas chamber. The gas chamber is fitted with an inlet and outlet ports to allow a steady stream of argon through the chamber. The plate was designed to dock onto the liquid handing work space to accommodate the preexisting software. The reagent block was designed to receive glass sleeves commercially available form Water Inc. (HPLC vials). **C)** Illustration of the injection sequence showing how the regent is buffered on both sides by an inert atmosphere during reagent sampling and transfer maintaining its integrity. **D)** KD Scientific KDS220 Multi-Syringe Infusion Pump holds up to 10 syringes and delivers 40 lb of total force. The step size for advancement is 0.165 micron (1/16 step) offering steady flow and low flow rates. The minimum step rate is 1/100 sec allowing for flow rate as low as 1 μL/min which roughly corresponds to a reaction time of 25 min.

The microreactor is housed in a combined heating/cooling module equipped with a thermo electric device that is capable of heating and cooling (Figure S3, Figure S4). Utilizing a variable DC power supply (Figure S3-D), we were able to maintain reaction temperatures ranging from -30 to 100^{o}C. In order to reach reduced temperatures we utilized a heat sink to dissipate heat generated by the TE modules. The heat sink (not shown) is cooled by circulating coolant (Thermo NesLab RTE740 bath circulator), which can maintain temperatures as low as -40 ^{o}C.

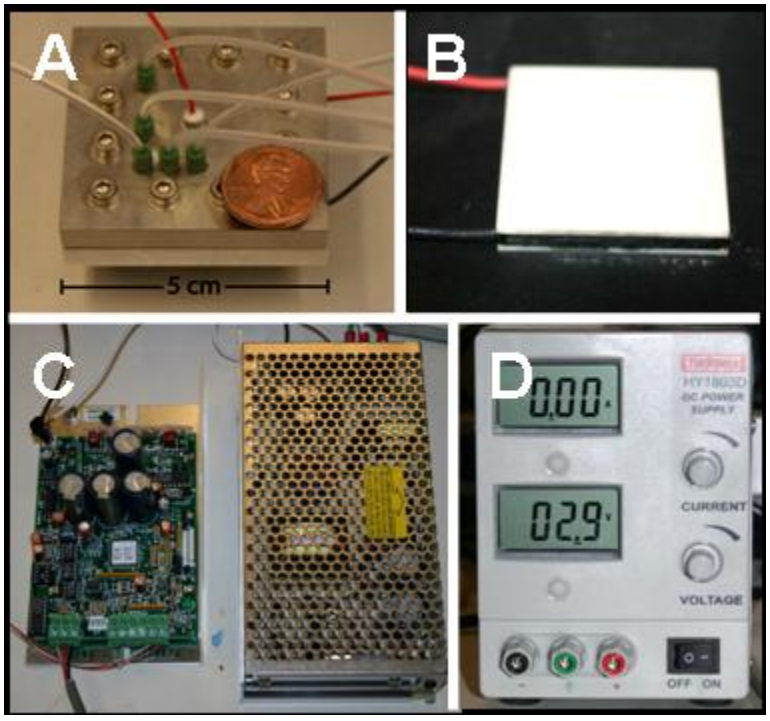


Figure S3. A) Combined heating/cooling stand. **B)** TE module capable of heating and cooling depending on the direction of current. These modules are reported to have a maximum ΔT = 70 ^{o}C (temp across top and bottom plate). The module is potted(sealed) to prevent moisture from condensing and freezing inside the module. The maximum temperature for the module is 150 ^{o}C and with a maximum power rating of 5 V/3amp (15W). They are available from TE Technology Inc. (part # VT-127-1.0-1.3-71P). **C)** Model TC-36-25 RS232 Temperature Controller (left) provides bi-directional temperature control for thermoelectric devices. The controller can be programmed directly through RS232 serial communication port. A power supply (12V, 8.4amp) is required to run temperature controller (right). These components are available from TE Technology Inc. **D)** The temperature controller in panel C potentiates power from an external DC power supply (TEKPower HY1803D). This is a variable power supply capable of regulating from 0 TO 18 V / 0 TO 3 Amps.

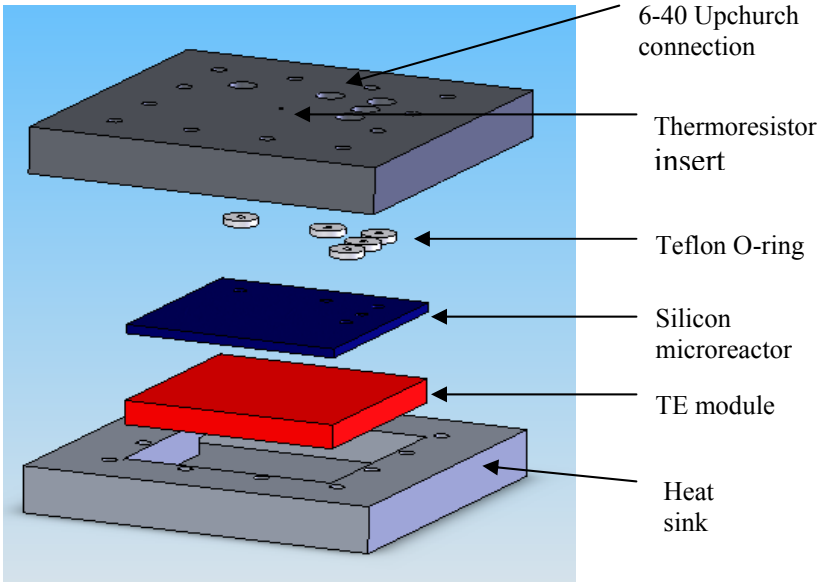


Figure S4. Compression packaging unit that houses microreactor and thermoelectric device used for heating/cooling. The compression packing method is a reversible packaging with decreased system volume in comparison with solder-based techniques[S1]. Fluidic connections to the microreactor were achieved with 6-40 Upchurch fittings and the fluidic seals on the microreactor were achieved by using Teflon O-rings.

It was observed that, when heating the reactor while continuously flowing solvent, gas bubbles appeared well below the boiling point for the solvent. This was attributed to the expansion of dissolved gas in the solvent. The formation of bubbles results in segmentation of solvent flow interfering with reaction pulses. To address this problem, we incorporated a custom designed vacuum degasser (Figure S5) that degasses the solvent lines leading to the three injectors and the quench solvent prior to entering the reactor. The degasser consists of a machined aluminum vacuum chamber with gas-permeable Teflon® AF tubing coiled within the chamber and a vacuum pump (Fisher Maxima* C plus Vacuum Pump M4C capable of pulling down to 1 x 10^{-4} torr). Although vacuum degassing the solvent prior to its entry into the reactor significantly reduced out gassing, it does not completely resolve the issue. To further address this problem, the use of a back pressure regulator is required.

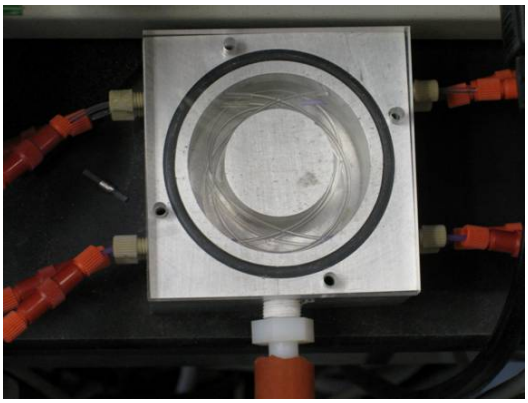


Figure S5. Vacuum degasser that consists of a machined aluminum vacuum chamber with gas-permeable Teflon® AF tubing coiled within the chamber.

[S1] Murphy, E.R.; Inoue, T.; Sahoo, H. R.; Zaborenko, N.; Jensen, K.F. *Lab on a Chip* **2007**, *7*, 1309.

The final components of the microfluidics system are involved in the collection of individual reactions for analysis. This was achieved by coupling an optical trigger to an analytical scale switch and a Gilson 96 well plate fraction collector (Figure S6). The occurrence of random gas bubbles flowing into the UV-flow cell resulted in substantial disruption the optically triggered collection. This was resolved with the incorporation of a second vacuum degassing device placed before the optical flow cell (Figure S7)

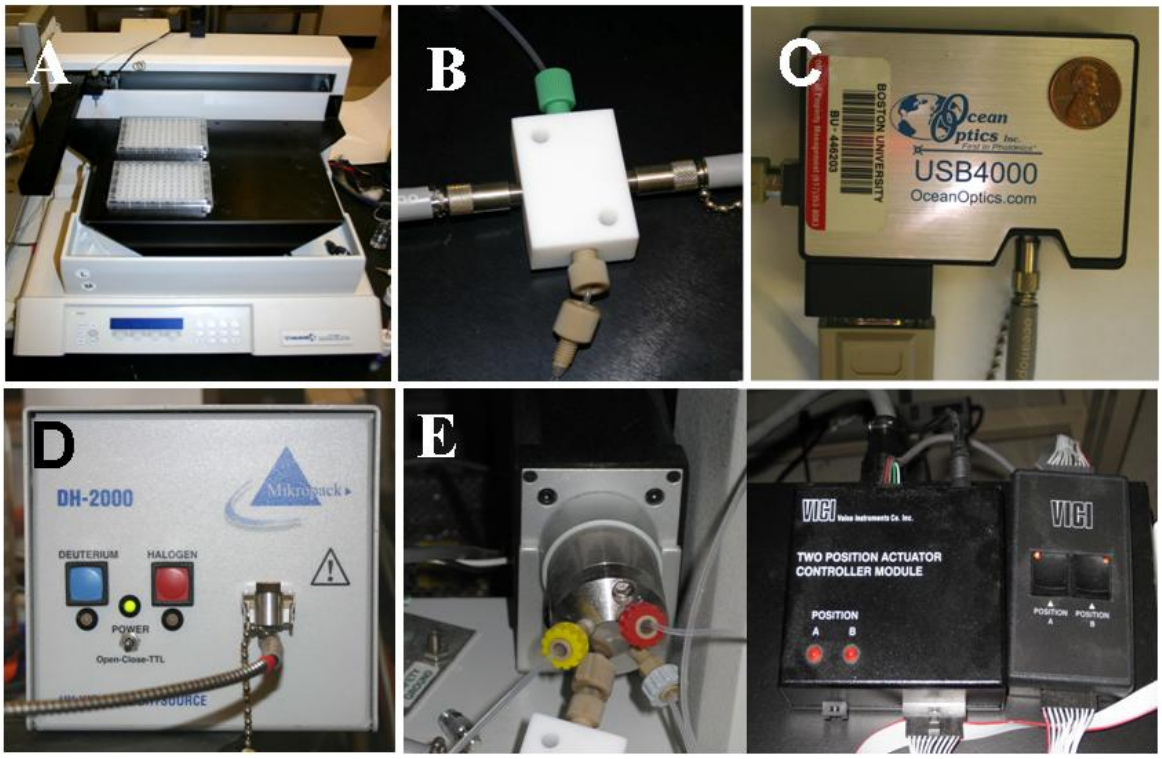


Figure S8. A) Gilson Fraction Collector FC204 which collects fraction into 96-wells. **B)** Z-path flow cell w/SMA 905, 10-mm path microliter volume, made out of Teflon, available from Ocean Optics Inc. **C)** USB4000 UV-Vis dectector capable of detecting in the range of 200-850 nm. Fiber optic cables (455 um Fiber extreme solarization-resistant). Items are available from Ocean Optics Inc. **D)** MikroPak DH2000-S-DUV light source with integrated shutter, provides light in the range of 190-2000 nm, also available from Ocean Optics Inc. **E)** VICI analytical scale four port switching value.

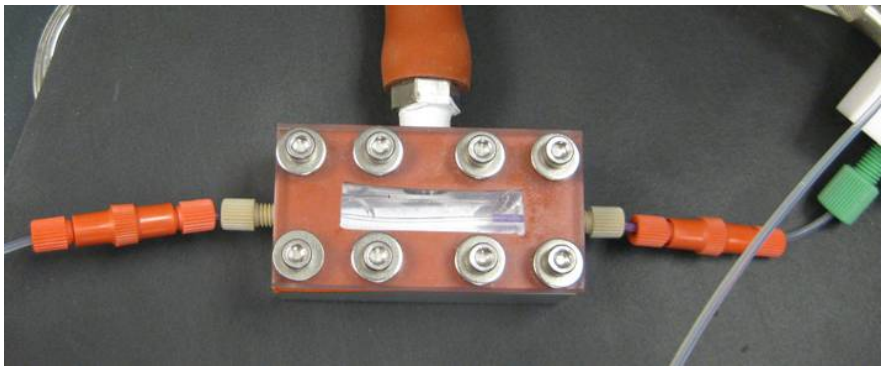


Figure S7. Vacuum degasser placed before the optical flow cell.

Maintaining Reliable Pulsed-Flow and Minimization of Dispersion

Our strategy for conducting reaction screens involved inserting reaction pulses into a continuous stream of solvent, thereby affecting a pulsed-flow. However, when we attempted the insertion of fluorescent dye pulses, we observed considerable dispersion. Since our efforts investigating other methods of segmentation were unsuccessful, our focus became minimization of pulse dispersion. The clear disadvantage to this segmentation strategy is the preponderance for sequential reaction pulses to merge if the reaction pulses are to close, resulting in reaction crossover. In order to prevent pulses from merging, we plumbed the system with minimal lengths of PTFE tubing (non-wetting surface) (Table S1) and incorporated programmed delays. We improve reaction throughput with the use of optically triggered collection which allowed for the collection of the most concentrated portion of the reaction pulse reducing the time delay needed between each reaction injection. The portion of the reaction pulse that crosses over with other pulses is simply discarded.

Table S1. Minimized volumes for all wetted surfaces. Total system volume is ~250 μL.

Location	length (cm)	ID (mm)	volume (μL)	Material type
each injection loop	8.3	0.25	8.1[a]	Teflon® HPFA
each inlet tubing	29.0	0.25	14.2	Teflon® HPFA
reactor	-	-	87.0	SiO_2
exit tubing	40.0	0.25	19.6	Teflon® HPFA
inline degasser tubing	10.5	0.81	54.1	Teflon® AF2400
tubing between degasses and UV/vis	4.5	0.25	2.2	Teflon® HPFA
UV/vis	1.0	1.5	17.7	Teflon®
tubing between UV/vis and switch	2.5	0.25	1.2	Teflon® HPFA

[a] Includes Rheodyne valve volume.

Microfluidic Reactor

The first design for a silicon-based microreactor was based on a device used previously used for synthetic chemistry.[S2,S3] The microreactor layout (Figure S8, left) consisted of 3 fluid inlets, followed by a 18 μL mixing zone and a 69 μL reaction zone. The flow then contacts an inlet quench flow, followed by a quench mixing zone before exiting through the outlet. The reactor was designed to be a versatile, multi-purpose fluidic device, usable for continuous-flow and pulse-flow applications. The design was intended to maximize mixing, minimize pressure drop, allow for flow visualization, and be chemically robust. T-mixers at the inlet zone are used to control and promote mixing of the reagents. The quench also includes a T-mixer and serpentine path to ensure good mixing and termination of the reaction.

[S2] Ratner, D. M.; Murphy, E. R.; Jhunjnunwala, M.; Snyder, D. A.; Jensen, K. F.; Seeberger, P. H. *Chem. Commun*. **2005**, *5*, 578.
[S3] Murphy, E.R.; Martinelli, J.R.; Zaborenko, N.; Buchwald, S.L.; Jensen, K.F. *Angew. Chem. Int. Ed. Engl*. **2007**, *46*, 1734.

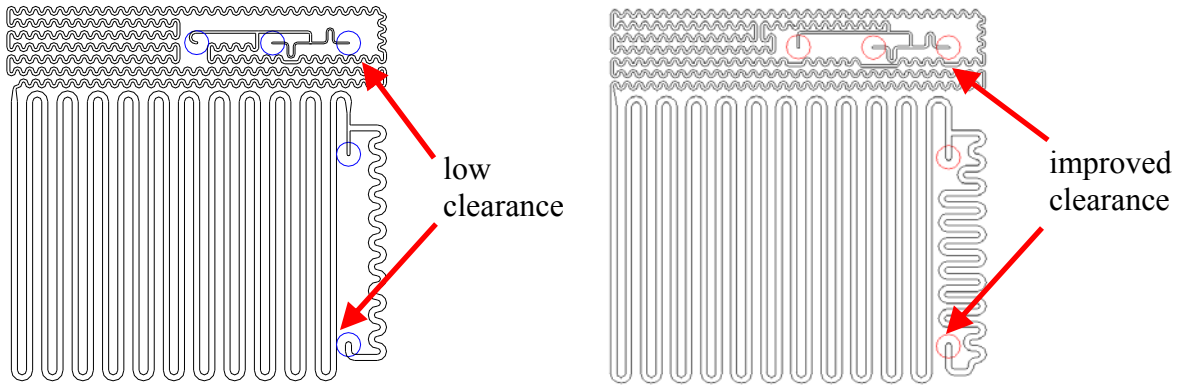


Figure S8: (left) Silicon reactor layout, version 1 (blue circles represent port holes) (right) Microreactor layout, version 2 (red circles represent drilled Pyrex ports).

The reactor layout design described (Figure A8, left) was initially intended to be used with ports etched through the silicon, rather than drilled in the Pyrex cap wafer. This design made precise alignment of Pyrex wafers difficult and caused high rates of reactor error. In such reactors, overlap between an active channel and the port hole led to the reaction flow mixing improperly or exiting the reactor prematurely without contacting the quench flow. Modifications were made to the reactor design to provide at least 100 μm clearance between the reactor ports and any channel (sufficient for microscope-aided alignment). Additionally, the mixing zone was further enhanced, inlet channels were altered to maintain proper flows and balanced resistances, the post-quench mixer was enlarged and enhanced, and the constriction in the lead-up to the quench inlet was removed in order to prevent clogging issues. The inlet channel widths were now 200 μm leading to the first T-mixer and 150 μm leading to the second one (Figure S8, right).

The microreactors were manufactured in MIT's Microsystems Technology Laboratories (MTL) using standard silicon processing techniques on 650 μm thick, 150 mm diameter silicon wafers. The channel patterns were defined using photolithography and etched using deep-reactive ion etching (a sidewall-passivating dry-etching technique that yields good feature resolution and vertical sidewalls) to a depth of ~350 μm. A ~3500 Å layer of wet oxide was grown to provide a glass interface for the reaction fluid, and the reactor wafer was capped with a Pyrex wafer (700 μm thick, 150 mm diameter, drilled with 1.6 mm diameter holes for each inlet and outlet) using anodic bonding (a bonding technique that creates covalent bonds between Pyrex's SiO_2 and the SiO_2 layer grown on the reactors). Electron-beam evaporation deposition of metal was used to pattern 5 mm diameter solder pads centered on each of the inlets and outlets on the Pyrex surface. 20 nm adhesion layer of chrome was deposited, followed by 200 nm of copper. The final wafers were diced into the 3cm x 3cm reactors. Fluidic connections to the chip were made via stainless steel tubing attached by lead-tin solder to the solder pads.

For screening application, it is necessary for three reagent pulses to enter the main channels simultaneously. The Hagen-Poiseuille Law was used to determine the pressure drops of fluid through the channels at the given channel geometry and size. Then, the necessary channel widths and lengths for the three inlet channels were calculated, such that the first two reagents enter the first T-mixer simultaneously, and the resulting stream enters the second T-mixer at the same time as the third inlet flow. The channel widths were then 118 μm wide for the first two inlets, 150 μm wide for the third inlet and the stream from the first T-mixer, 200 μm wide in the

mixing zone, and the reaction zone channels were 400 μm wide. Pressure gradients were simulated using FEMLAB, assuming 5 μL/min flow through each of the three inlets, and using water's fluid properties (Figure S9). It was shown that the pressures of the two streams entering the first T-mixer are equal, as are the pressures of the two streams entering the second T-mixer. Additionally, at those flow rates, which are in the upper range of the planned system use, the pressure drop within the reactor is less than 2 mmHg for single-phase liquid flow.

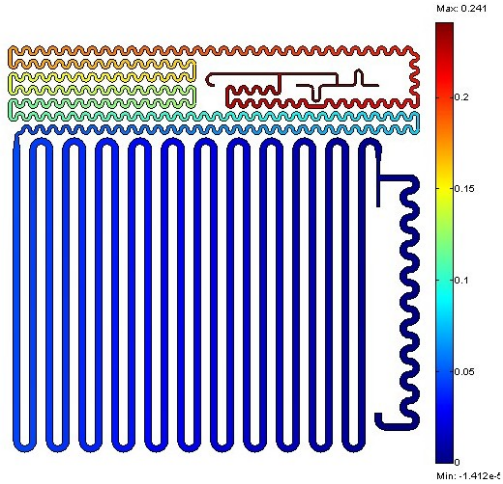


Figure S9: FEMLAB simulation of pressure gradient at fluid flow of 5 μL/min through each of the 3 inlets. The scale is from 0 to 0.241 kg/mm-s^2, or 0 to 1.81 mmHg. Model assumes physical properties of water.

The reactant mixing area consisted of a large number of semicircular channel lengths. Concentration gradients were simulated using FEMLAB, assuming 5 μL/min flow through each of the three inlets, 0.1 M concentration of a reagent in stream #2, and using water's fluid properties and typical diffusivity in water (Figure S10). It was found mixing better than 90% was achieved in the first 15% of the mixing zone.

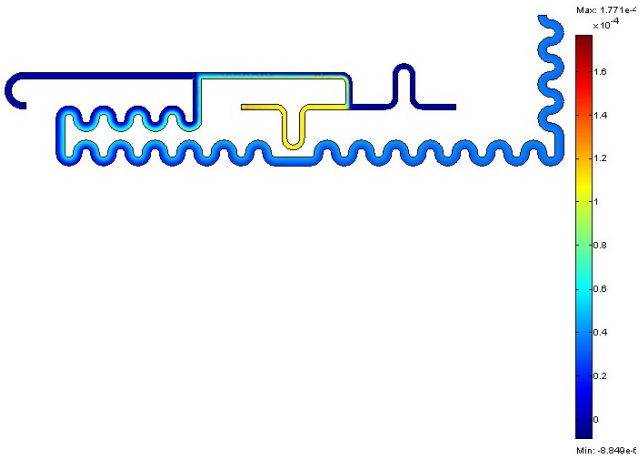
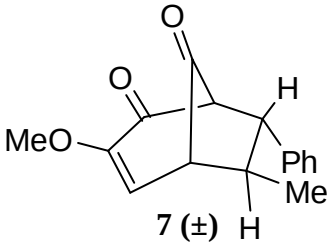


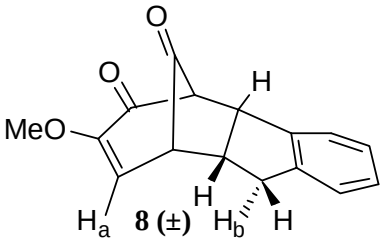
Figure S10: FEMLAB simulation of concentration gradient at fluid flow of 5 μL/min through each of the 3 inlets and 0.1 M of reagent in one of the streams. The gradient is from 0 to 1e-4 mol/m^3, or 0 to 0.1 M. Water was the assumed fluid, and typical water-soluble reagent diffusivity was used. Only the portion necessary for >90% mixing is shown.

II. Preparation of Bicyclo[3.2.1]octanoid substrates



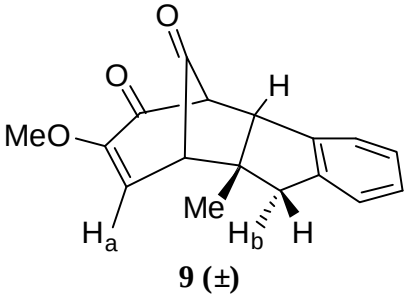
General procedure for synthesis of Bicyclo[3.2.1]octanoid substrates.

(1R,5R,6R,7R)-3-methoxy-6-methyl-7-phenylbicyclo[3.2.1]oct-3-ene-2,8-dione (±) (7). To a oven-dried vial was added dry (1*S*)-(+)-10-camphorsulfonic acid (CSA) (63 mg, 0.27 mmol) followed by anhydrous CH_3CN (3 mL), water (3.7 μL, 0.21 mmol), and β-*trans*-methylstyrene (70 μL, 0.54 mmol). To this mixture was added 3,4,4-trimethoxycyclohexa-2,5-dienone[S4] (50 mg, 0.27 mmol) dissolved in CH_3CN (1 mL). The reaction was stirred at rt for 1.5 h, quenched with triethylamine (38 μL) and stirred for 15 min. The solution was diluted with sat. $NaHCO_3$ and extracted with diethylether (x3). The organic layer was washed with brine (x1), dried over sodium sulfate, filtered, and evaporated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 20:80 EtOAc:petroleum ether) to afford **3** (43 %, 66 mg, 0.27 mmol) as clear/white crystals. m.p. = 140 - 142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2 H), 7.24 – 7.19 (m, 1 H), 7.05 (d, *J* = 8.6 Hz, 2 H), 6.48 (d, *J* = 8.6 Hz, 1 H), 3.81 (dd, *J* = 7.0, 2.0 Hz, 1 H), 3.72 (s, 3 H), 3.20 (t, *J* = 6.5 Hz, 1 H), 3.05 (dd, *J* = 8.6, 2.1 Hz, 1 H), 2.56 (qt, *J* = 6.7 Hz, 1 H), 1.26 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 190.3, 154.6, 138.0, 129.1, 128.6, 127.8, 118.1, 71.1, 56.0, 54.1, 49.6, 43.2, 21.7; IR (thin film) νmax 2962, 1761, 1684, 1606, 1456, 1363, 1245, 1223, 1153, 1103, 1036, 753, 701 cm^{-1}; HRMS calculated for $C_{16}H_{16}O_3Na$: 279.0997, found: 279.1022 (M+Na).



Bicyclo[3.2.1]octanoid (±) 8.

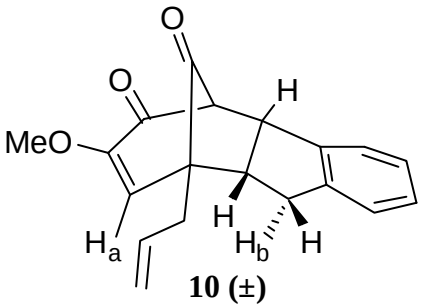
Product isolated as clear/white crystals (55 %, 38 mg, 0.15 mmol); m.p. = 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.04 (m, 4 H), 6.01 (d, *J* = 8.2 Hz, 1 H), 4.31 (t, *J* = 8.4 Hz, 1 H), 4.00 (dd, *J* = 8.4, 1.9 Hz, 1 H), 3.47 (ddd, *J* = 8.2, 4.2, 1.9 Hz, 1 H), 3.38 (s, 3 H), 3.33-3.25 (ovrlp m, 2 H), 2.94 (d, *J* = 14.6 Hz, 1 H); NOED (400 MHz, $CDCl_3$) irrad. δ 6.01 (H_a) 2 % enhancement at H_b, irrad. δ 2.94 (H_b) 2 % enhancement at H_a; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 190.3, 155.5, 144.0, 139.9, 128.0, 127.5, 126.3, 124.2, 113.4, 66.7, 55.9, 50.8, 46.9, 39.2, 34.1; IR (thin film) νmax 2934, 1761, 1685, 1605, 1457, 1220, 1127, 1092, 750 cm^{-1}; HRMS calculated for $C_{16}H_{14}O_3Na$: 277.0841, found: 277.0855 (M+Na).



Bicyclo[3.2.1]octanoid (±) 9.

Product isolated as clear/white crystals (70 %, 51 mg, 0.19 mmol); m.p. = 135 - 138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.10 (m, 2 H), 7.09 – 7.03 (m, 2 H), 6.04 (d, *J* = 8.3 Hz, 1 H), 4.02 (dd, *J* = 8.3, 1.8 Hz, 1 H), 3.77 (d, *J* = 8.3 Hz, 1 H), 3.35 (s, 3 H), 3.20 (d, *J* = 17.3 Hz, 1 H), 3.12 (dd, *J* = 8.3, 2.0 Hz, 1 H), 2.95 (d, *J* = 17.3 Hz, 1 H), 1.42 (s, 3 H); NOED (400 MHz, $CDCl_3$) irrad. δ 6.04 (H_a) 2 % enhancement at H_b, irrad. δ 3.20 (H_b) 3 % enhancement at H_a; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 190.3, 154.7, 143.8, 140.1, 128.0, 127.5, 126.2, 124.1, 114.2, 67.5, 58.1, 55.8, 55.1, 47.2, 42.5, 28.4; IR (thin film) νmax 2962, 2923, 1762, 1685, 1608, 1458, 1218, 1141, 749 cm^{-1}; HRMS calculated for $C_{17}H_{16}O_3Na$: 291.0997, found: 291.1026 (M+Na).

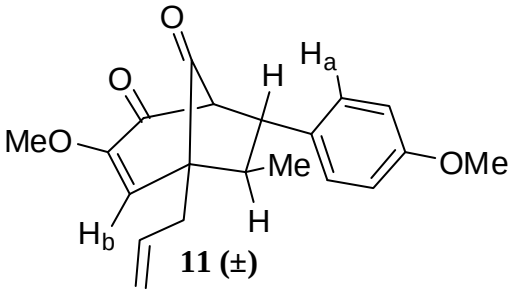
[S4]Clive, D.L.; Fletcher, S. P.; Liu, D. *J. Org. Chem.* **2004**, *69*, 3282.



10 (±)

Bicyclo[3.2.1]octanoid (±) 10.

Reaction was performed with 2-allyl-4,4,5-trimethoxycyclohexa-2,5-dienone[S4,S5] (60 mg, 0.27 mmol) dissolved in CH_3CN (1 mL) in place of 3,4,4-trimethoxycyclohexa-2,5-dienone. Product isolated as clear/white crystals (60 %, 48 mg, 0.16 mmol); m.p. = 164 - 167 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.04 (m, 4 H), 5.99 (ddt, 1 H, *J* = 17.3, 10.1, 1.4 Hz), 5.78 (s, 1 H), 5.26 (m, 2 H), 4.27 (app t, 1 H, *J* = 8.9 Hz), 4.02 (d, 1 H, *J* = 8.4 Hz), 3.34 (s, 3 H), 3.24 (dd, 1 H, *J* = 17.0, 9.8 Hz), 3.09 (dt, 1 H, *J* = 9.8, 2.7 Hz), 2.90 (dd, 1 H *J* = 17.0, 2.7 Hz), 2.59 (d, 1 H *J* = 8.1 Hz); NOED (400 MHz, $CDCl_3$) irrad. δ 5.78 (H_a) 2 % enhancement at H_b, irrad. δ 2.90 (H_b) 2 % enhancement at H_a; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 190.4, 154.8, 143.9, 139.8, 133.4, 127.9, 127.5, 126.3, 124.2, 119.7, 117.4, 66.6, 55.9, 55.8, 47.0, 44.3, 36.8, 34.0; IR (thin film) νmax 2929, 1761, 1691, 1603, 1457, 1148, 1114, 1091, 749 cm^{-1}; HRMS calculated for $C_{19}H_{18}O_3Na$: 317.1154, found: 317.1172 (M+Na).



11 (±)

Bicyclo[3.2.1]octanoid (±) 11.

Reaction was performed with 2-allyl-4,4,5-trimethoxycyclohexa-2,5-dienone[S4,S5] (60 mg, 0.27 mmol) dissolved in CH_3CN (1 mL) in place of 3,4,4-trimethoxycyclohexa-2,5-dienone. Product isolated as a clear oil (69 %, 61 mg, 0.19 mmol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.7 Hz, 2 H), 6.81 (d, *J* = 8.7 Hz, 2 H), 6.27 (s, 1 H), 5.95 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1 H), 5.28 (m, 2 H), 3.76 (d, *J* = 7.4 Hz, 2 H), 3.76 (s, 3 H), 3.68 (s, 3 H), 3.13 (dd, *J* = 7.2, 6.0 Hz, 1 H), 2.62 (dd, *J* = 14.8, 7.1 Hz, 1 H), 2.57 (qt, *J* = 6.4 Hz, 1 H), 2.45 (dd, *J* = 14.8, 7.1 Hz, 1 H), 1.15 (d, *J* = 7.0 Hz, 3 H); NOED (400 MHz, $CDCl_3$) irrad. δ 6.98 (H_a) 1 % enhancement at H_b, irrad. δ 6.27 (H_b) 1 % enhancement at H_a; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 190.4, 159.1, 153.7, 133.6, 130.0, 129.5, 122.1, 119.8, 114.4, 69.2, 55.9, 55.4, 55.2, 49.2, 45.1, 32.8, 18.3; IR (thin film) νmax 2960, 2935, 1758, 1695, 1610, 1514, 1457, 1252, 1182, 1151, 1034, 847 cm^{-1}; HRMS calculated for $C_{20}H_{22}O_4Na$: 349.1416, found: 349.1404(M+Na).

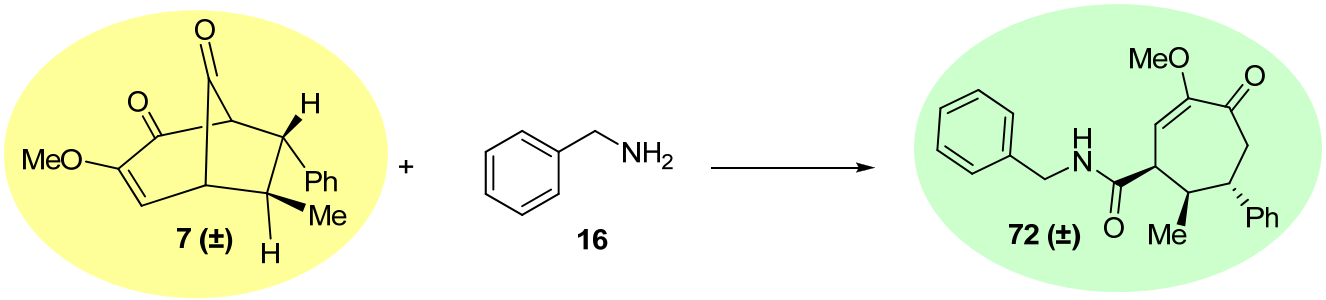
[S5] Van Otterlo, W. A. L.; Ngidi, E. L.; Kuzvidza, S.; Morgans, G. L.; Moleele, S. S.; de Koning, C. B. *Tetrahedron* **2005**, *61*, 9996.

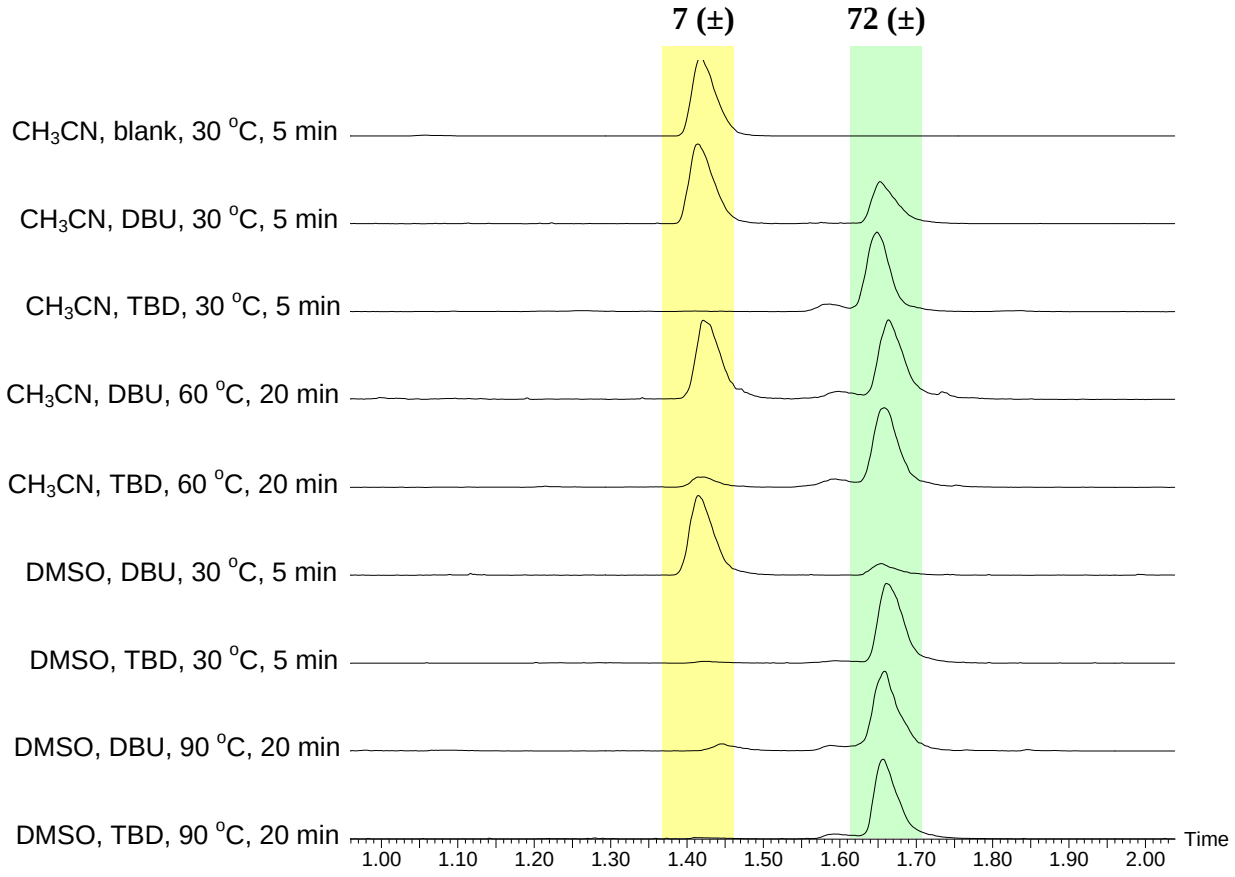
III. Analytical Reaction Screening and Profiling

General procedure for analytical reaction screening

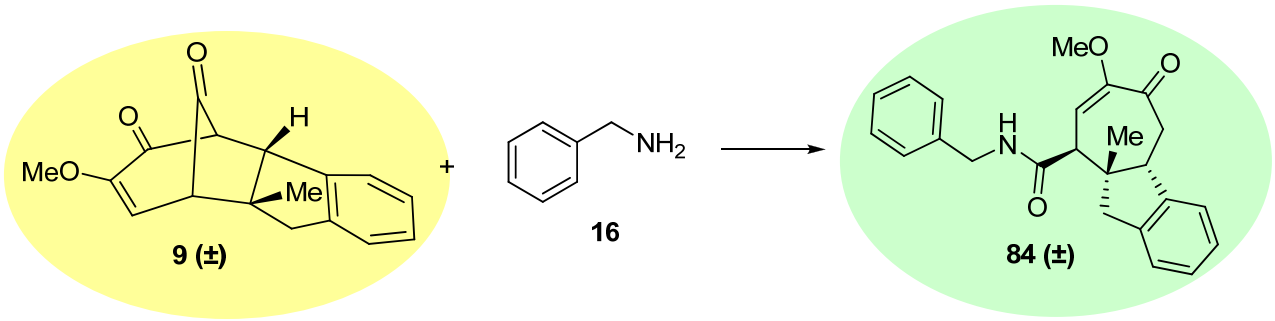
Stock solutions of substrate (0.125 M), reaction partner (0.25 M), and base (0.15 M) were prepared in DMSO or CH_3CN (anhydrous) while maintaining dry handling. The solutions were placed in a custom designed 96-well aluminum holding block fitted with oven dried glass sleeves. This was covered with an inert gas chamber and sealed. The block was attached to the microfluidics platform and a slow steady stream of argon was passed through the inert gas chamber. System parameters were first set to achieve 5 min reactions (microreactor residence time) at 30 ^{o}C. Longer reaction times at elevated reaction temperatures were achieved by decreasing the syringe pump flow rate and increasing the power supply to the TE heating module. Reactions were quenched on the microreactor by flowing acetic anhydride (10 % V/V in DMSO or CH_3CN) into the quench port. Individual reactions were collected into 96-well plates using optical detection. Each reaction was analyzed by UPLC/MS/ELSD (10-90 % CH_3CN, 2 min). Reactions affording >20% conversion to a major product were subsequently scaled up and isolated, using traditional bench chemistry methods, for further characterization. Sample reaction profiles are also provided in this section.

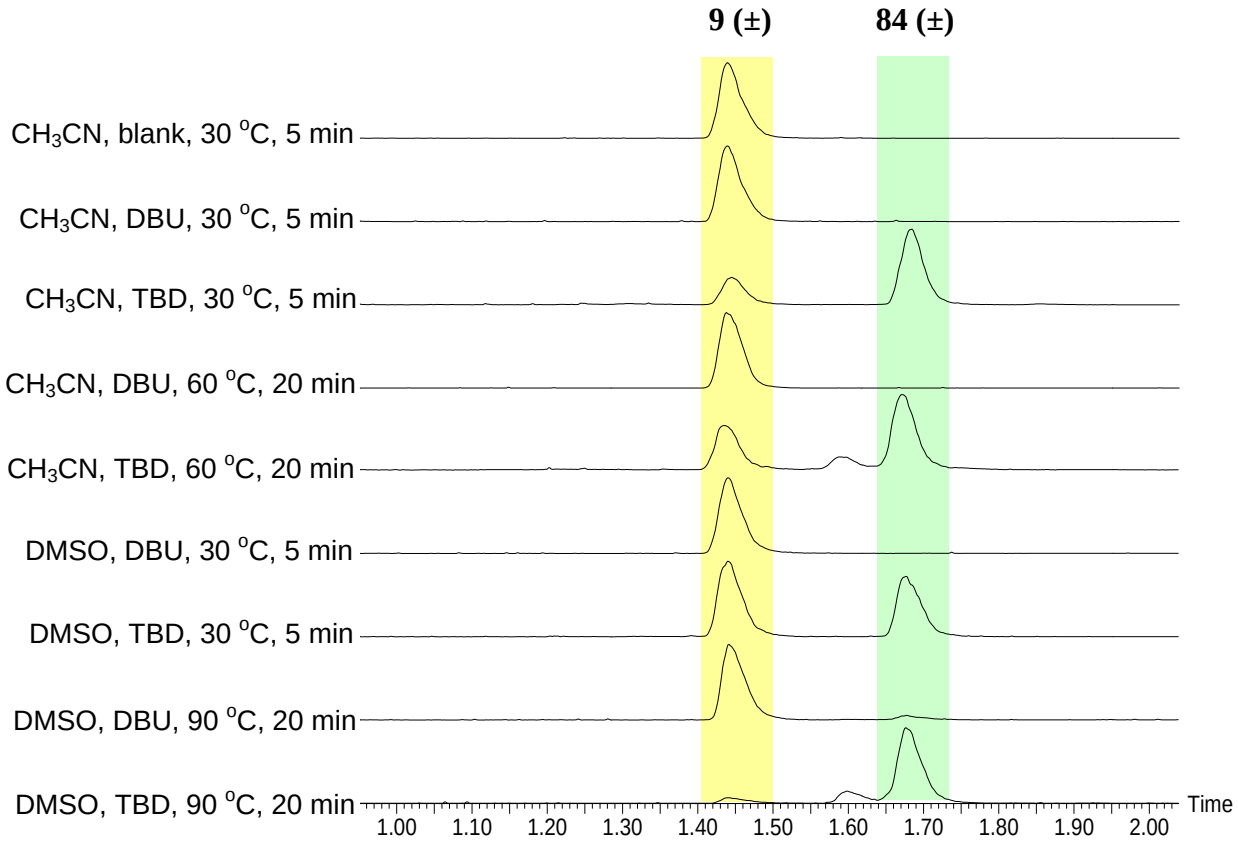
a) UPLC/ELSD Profile for substrate 7 and benzylamine (16)



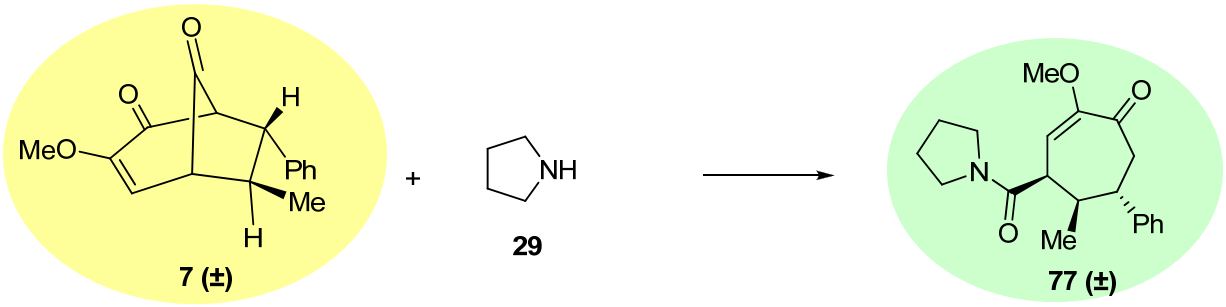


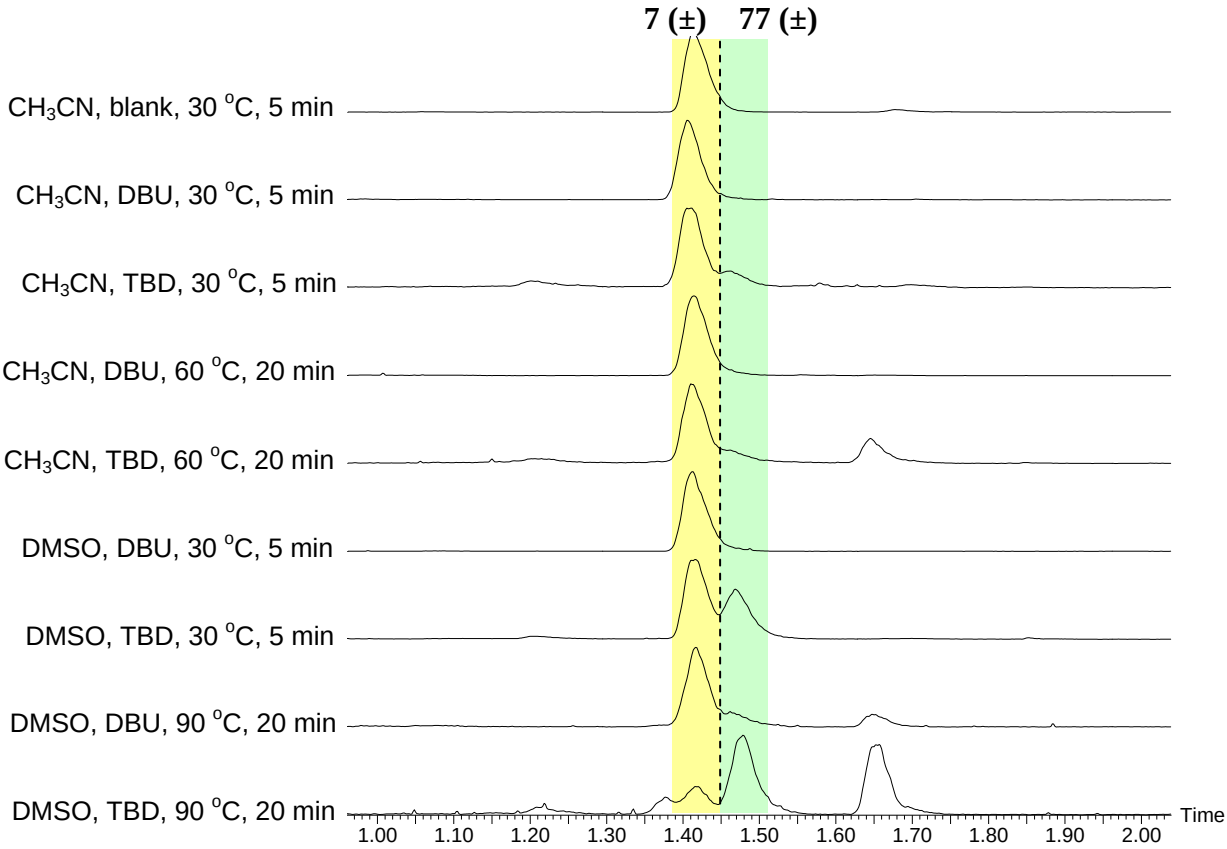
b) UPLC/ELSD Profile for substrate 9 and benzylamine (16)



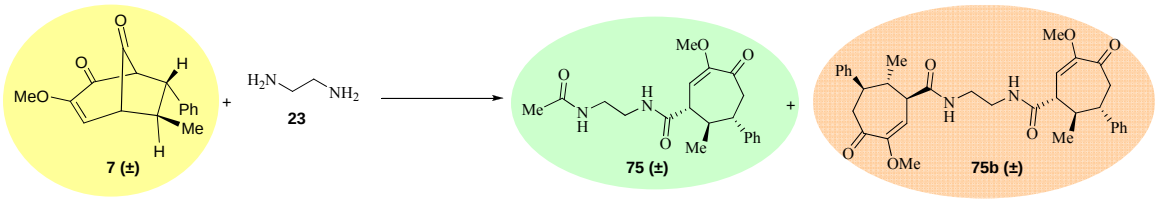


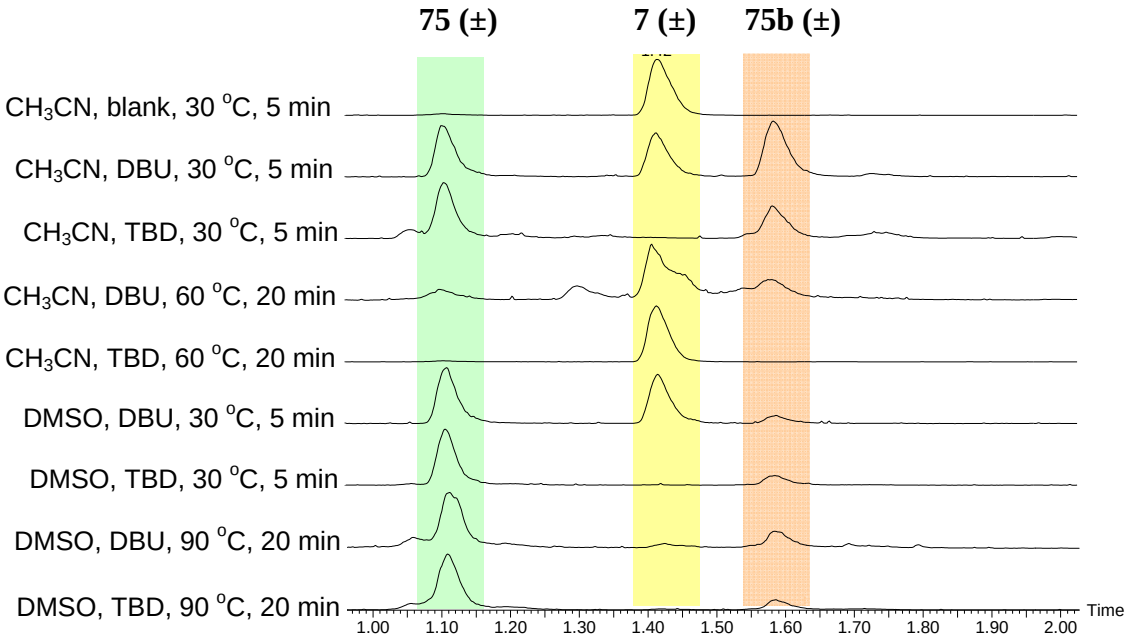
c) UPLC/ELSD Profile for substrate 7 and pyrrolidine (29)



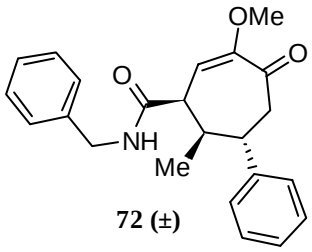


d) UPLC/ELSD Profile for substrate 7 and ethylenediamine (23)





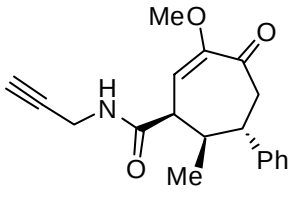
IV. Experimental Procedures and Characterization Data



72 (±)

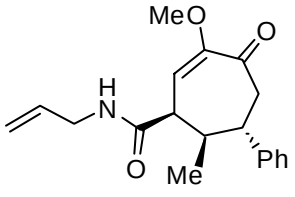
General procedure for synthesis of products 72-93 and 108-111.

(1R,6S,7R,E)-N-benzyl-3-methoxy-7-methyl-4-oxo-6-phenylcyclohept-2-enecarboxamide (±) (72). To an oven-dried 1 dram vial was added 3-methoxy-6-methyl-7-phenylbicyclo[3.2.1]oct-3-ene-2,8-dione (**7**) (40 mg, 0.16 mmol) and anhydrous CH_3CN (0.90 mL) followed by the addition of benzylamine (34 μL, 0.31 mmol). To this mixture was added DBU (28 μL, 0.19 mmol) in anhydrous CH_3CN (100 μL). The reaction was stirred at rt for 60 min under argon and quenched with the addition of acetic anhydride (44 μL, 0.47 mmol) in CH_3CN (400 μL). The reaction was filtered through a short plug of silica and washed with CH_3CN (2 mL x 3, until all product was eluted from the silica plug as indicated by TLC). The eluent was then evaporated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2:MeOH) to afford **72** as a mixture of diastereomers in 20:1 ratio (dr was estimated from crude UPLC/ELSD) (63 %, 36 mg, 0.098 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.21 (m, 8 H), 7.17 - 7.12 (m, 2 H), 6.20 (d, *J* = 6.1 Hz, 1 H), 5.95 (t, *J* = 5.3 Hz, 1 H), 4.50 (dd, *J* = 5.5, 4.1 Hz, 2 H), 3.73 (s, 3 H), 3.71 (ovrlp t, *J* = 5.7 Hz, 1 H), 3.02 (dd, *J* = 17.6, 11.9 Hz, 1 H), 2.80 (dd, *J* = 17.6, 1.2 Hz, 1 H), 2.60 (dd, *J* = 11.1, 9.8 Hz, 1 H), 2.26 - 2.14 (m, 1 H), 0.88 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 171.2, 152.8, 143.8, 137.9, 128.8, 128.7, 128.0, 127.7, 126.9, 107.6, 55.5, 48.1, 45.9, 45.0, 44.1, 43.0, 15.3; IR (thin film) νmax 3337, 2961, 2927, 1666, 1537, 1454, 1345, 1208, 1140, 701 cm^{-1}; HRMS calculated for $C_{23}H_{26}NO_3$: 364.1913, found: 364.1937 (M+H).



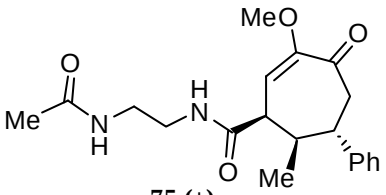
73 (±)

(1R,6S,7R,E)-N-(4-methoxybenzyl)-3-methoxy-7-methyl-4-oxo-6-phenyl cyclohept-2-enecarboxamide (±) (73). Purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2:MeOH). Product isolated as a mixture of diastereomers in 11:1 ratio (dr was estimated from crude UPLC/ELSD) (60 %, 29 mg, 0.094 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.22 (m, 3 H), 7.17 (d, *J* = 7.0 Hz, 2 H), 6.15 (d, *J* = 6.3 Hz, 1 H), 5.99 - 5.91 (m, 1 H), 4.11 (dt, *J* = 5.2, 2.7 Hz, 2 H), 3.73 (s, 3 H), 3.73 (ovrlp t, *J* = 5.7 Hz, 1 H), 3.06 (dd, *J* = 17.6, 12.1 Hz, 1 H), 2.83 (d, *J* = 17.2 Hz, 1 H), 2.61 (dd, *J* = 11.3, 9.4 Hz, 1 H), 2.31 - 2.19 (m, 2 H), 0.91 - 0.83 (s, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 171.2, 152.9, 143.8, 128.7, 127.7, 126.9, 107.3, 79.2, 71.8, 55.5, 48.1, 45.8, 44.8, 42.9, 29.5, 15.2; IR (thin film) νmax 3300, 2965, 1684, 1653, 1540, 1456, 1345, 1267, 1207, 1141, 736, 703 cm^{-1}; HRMS calculated for $C_{19}H_{21}NO_3Na$: 334.1419, found: 334.1377 (M+Na).



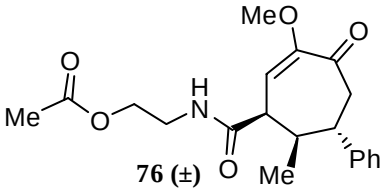
74 (±)

(1R,6S,7R,E)-N-(4-methoxybenzyl)-3-methoxy-7-methyl-4-oxo-6-phenyl cyclohept-2-enecarboxamide (±) (74). Purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2:MeOH). Product isolated as a mixture of diastereomers in 13:1 ratio (dr was estimated from crude UPLC/ELSD) (54 %, 26 mg, 0.084 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 - 7.22 (m, 3 H), 7.17 (d, *J* = 7.0 Hz, 2 H), 6.17 (d, *J* = 5.9 Hz, 1 H), 5.91 - 5.78 (m, 1 H), 5.75 (t, *J* = 5.3 Hz, 1 H), 5.20 (d, *J* = 17.2 Hz, 1 H), 5.15 (d, *J* = 9.8 Hz, 1 H), 3.95 (t, *J* = 5.3 Hz, 2 H), 3.75 - 3.68 (m, 4 H), 3.06 (dd, *J* = 17.2, 12.1 Hz, 1 H), 2.83 (d, *J* = 17.2 Hz, 1 H), 2.61 (dd, *J* = 11.3, 9.8 Hz, 1 H), 2.27 - 2.16 (m, 1 H), 0.88 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 171.3, 152.7, 143.9, 133.9, 128.7, 127.7, 126.9, 116.9, 107.9, 55.5, 48.1, 45.9, 44.9, 43.0, 42.3, 15.2; IR (thin film) νmax 3336, 2964, 1666, 1536, 1454, 1266, 1207, 1141, 736, 703 cm^{-1}; HRMS calculated for $C_{19}H_{23}NO_3Na$: 336.1576, found: 336.1614 (M+Na).



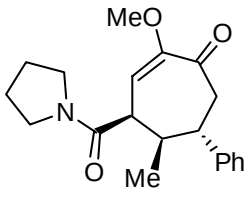
75 (±)

(1R,6S,7R,E)-N-(4-methoxybenzyl)-3-methoxy-7-methyl-4-oxo-6-phenylcyclohept-2-enecarboxamide (±) (75). Reaction was performed in CH_3CN (3 mL) with ethylenediamine (125 μL, 1.87 mmol) and quenched with acetic anhydride (350 μL, 3.74 mmol) in CH_3CN (1 mL). Purified by flash chromatography (SiO_2, 20:1 CH_2Cl_2:MeOH). Product isolated as a mixture of diastereomers in 14:1 ratio (dr was estimated from crude UPLC/ELSD) (65 %, 36 mg, 0.10 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 - 7.11 (m, 6 H), 6.37 (br. s., 1 H), 6.10 (d, *J* = 6.3 Hz, 1 H), 3.75 (t, *J* = 5.9 Hz, 1 H), 3.70 (s, 3 H), 3.46 - 3.30 (m, 4 H), 3.08 (dd, *J* = 17.6, 12.1 Hz, 1 H), 2.75 (d, *J* = 17.6 Hz, 1 H), 2.54 (dd, *J* = 11.7, 9.4 Hz, 1 H), 2.36 - 2.26 (m, 1 H), 1.92 (s, 3 H), 0.80 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 172.8, 171.9, 152.8, 143.9, 128.7, 127.8, 126.8, 107.7, 55.5, 48.2, 45.9, 44.7, 42.5, 40.7, 39.9, 23.1, 15.2; IR (thin film) νmax 3319, 1653, 1558, 1540, 1506, 1456, 1207, 1140. 731 cm^{-1}; HRMS calculated for $C_{20}H_{26}N_2O_4Na$: 381.1790, found: 381.1798 (M+Na).



76 (±)

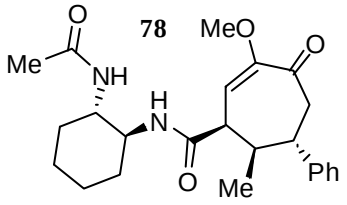
(1R,6S,7R,E)-N-(4-methoxybenzyl)-3-methoxy-7-methyl-4-oxo-6-phenylcyclohept-2-enecarboxamide (±) (76). Purified by flash chromatography (SiO_2, 20:1 CH_2Cl_2:MeOH). Product isolated as a mixture of diastereomers in 10:1 ratio (dr was estimated from crude UPLC/ELSD) (57 %, 32 mg, 0.089 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.29 (m, 3 H), 7.18 (d, *J* = 7.4 Hz, 2 H), 6.13 (d, *J* = 6.3 Hz, 1 H), 6.03 (t, *J* = 4.9 Hz, 1 H), 4.24 - 4.16 (m, 2 H), 3.73 (s, 3 H), 3.69 (t, *J* = 5.9 Hz, 1 H), 3.60 (dt, *J* = 9.8, 4.9 Hz, 2 H), 3.06 (dd, *J* = 17.6, 12.1 Hz, 1 H), 2.82 (d, *J* = 17.6 Hz, 1 H), 2.60 (dd, *J* = 11.9, 9.2 Hz, 1 H), 2.28 - 2.17 (m, 1 H), 2.04 (s, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 171.6, 171.3, 152.8, 143.8, 128.7, 127.7, 126.9, 107.6, 63.0, 55.5, 48.1, 45.8, 44.9, 42.8, 39.2, 20.8, 15.2; IR (thin film) νmax 3342, 2962, 1740, 1670, 1541, 1232, 1208, 1140, 1051, 703 cm^{-1}; HRMS calculated for $C_{20}H_{25}NO_5Na$: 382.1630, found: 382.1624 (M+Na).



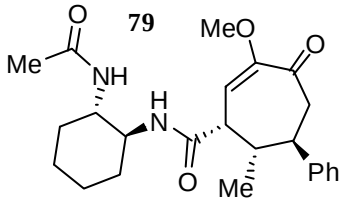
77 (±)

(1R,6S,7R,E)-N-(4-methoxybenzyl)-3-methoxy-7-methyl-4-oxo-6-phenylcyclohept-2-enecarboxamide (±) (77). Reaction was performed with TBD (26 mg, 1.9 mmol) in place of DBU. Purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2:MeOH). Product isolated as a mixture of diastereomers in 9:1 ratio (dr was estimated from crude UPLC/ELSD) (56 %, 29 mg, 0.087 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.22 (m, 3 H), 7.16 (d, *J* = 7.4 Hz, 2 H), 6.25 (d, *J* = 5.9 Hz, 1 H), 3.98 (t, *J* = 5.5 Hz, 1 H), 3.73 (s, 3 H), 3.67 - 3.40 (m, 4 H), 3.07 (dd, *J* = 17.6, 12.5 Hz, 1 H), 2.83 (d, *J* = 17.6 Hz, 1 H), 2.61 (dd, *J* = 11.7, 9.4 Hz, 1 H), 2.31 - 2.18 (m, 1 H), 2.06 - 1.97 (m, 2 H), 1.93 - 1.85 (m, 2 H), 0.88 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 170.1, 152.6, 144.2, 128.8, 127.6, 126.8, 109.2, 55.5, 48.1, 46.5, 46.0, 43.0, 40.3, 26.3, 24.1, 15.5; IR (thin film) νmax 2966, 1728, 1680, 1625, 1452, 1209, 1137, 733, 703 cm^{-1}; HRMS calculated for $C_{20}H_{25}NO_3Na$: 350.1732, found: 350.1714 (M+Na).

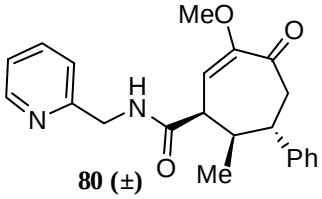
(1R,6S,7R,E)-N-(4-methoxybenzyl)-3-methoxy-7-methyl-4-oxo-6-phenylcyclohept-2-enecarbox amide (78) and (1S,6R,7S)-N-((1S,2S)-2-acetamidocyclohexyl)-3-methoxy-7-methyl-4-oxo-6-phenyl cyclohept-2-enecarboxamide (79). Reaction was performed in anhydrous CH_3CN (3 mL) with (1S,2S)-(+)-1,2-diaminocyclohexane (107 mg, 0.936 mmol) and quenched with acetic anhydride (175 μL, 1.87 mmol) in CH_3CN (1 mL). Purified by flash chromatography (SiO_2, 30:1 CH_2Cl_2:MeOH).



Product **78** was isolated as a mixture of diastereomers in >25:1 ratio (dr was estimated from crude UPLC/ELSD) (35 %, 22 mg, 0.055 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.28 (m, 2 H), 7.26 - 7.19 (m, 3 H), 6.73 (d, *J* = 6.6 Hz, 1 H), 6.11 (d, *J* = 5.9 Hz, 1 H), 5.64 (d, *J* = 7.8 Hz, 1 H), 3.73 (s, 3 H), 3.72 (ovrlp m, 1 H), 3.64 (t, *J* = 5.7 Hz, 1 H), 3.61 - 3.49 (m, 1 H), 3.05 (dd, *J* = 17.6, 12.1 Hz, 1 H), 2.77 (d, *J* = 17.6 Hz, 1 H), 2.53 (dd, *J* = 11.9, 9.2 Hz, 1 H), 2.26 (dt, *J* = 9.2, 6.4 Hz, 1 H), 2.20 (d, *J* = 13.3 Hz, 1 H), 1.97 (d, *J* = 10.6 Hz, 1 H), 1.82 - 1.71 (m, 2 H), 1.68 (s, 3 H), 1.40 - 1.13 (m, 4 H), 0.76 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 171.6, 171.5, 152.7, 143.8, 128.7, 127.9, 126.8, 107.6, 56.2, 55.5, 52.4, 48.3, 45.9, 44.8, 42.0, 32.5, 32.1, 24.8, 24.3, 23.1, 15.1; IR (thin film) νmax 3318, 2934, 1653, 1540, 1453, 1375, 1208, 1141, 735, 703 cm^{-1}; HRMS calculated for $C_{24}H_{33}N_2O_4$: 413.2440, found: 413.2427 (M+H); $[\alpha]^{25}_D$= +62.5 ($CHCl_3$).

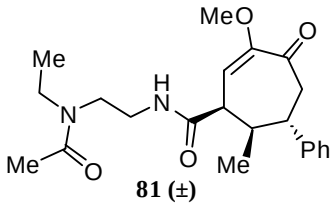


Product **79** was isolated as a mixture of diastereomers in >25:1 ratio (dr was estimated from crude UPLC/ELSD) (23 %, 15 mg, 0.036 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.28 (m, 2 H), 7.25 - 7.16 (m, 3 H), 6.63 (d, *J* = 7.0 Hz, 1 H), 6.11 (d, *J* = 6.3 Hz, 1 H), 5.66 (d, *J* = 8.2 Hz, 1 H), 3.72 (s, 3 H), 3.70 - 3.62 (m, 2 H), 3.60 (t, *J* = 5.9 Hz, 1 H), 3.09 (dd, *J* = 17.8, 12.3 Hz, 1 H), 2.80 (d, *J* = 17.6 Hz, 1 H), 2.56 (dd, *J* = 11.7, 9.4 Hz, 1 H), 2.23 (dq, *J* = 15.3, 6.5 Hz, 1 H), 2.10 (d, *J* = 12.9 Hz, 1 H), 1.97 (s, 4 H), 1.82 - 1.70 (m, 2 H), 1.40 - 1.21 (m, 4 H), 0.82 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 171.8, 171.4, 152.8, 143.8, 128.7, 127.8, 126.8, 107.5, 55.5, 55.4, 52.8, 48.1, 45.9, 44.9, 42.9, 32.3, 32.2, 24.8, 24.3, 23.4, 15.1; IR (thin film) νmax 3301, 2933, 1649, 1545, 1452, 1142, 735, 702 cm^{-1}; HRMS calculated for $C_{24}H_{33}N_2O_4$: 413.2440, found: 413.2457 (M+H); $[\alpha]^{25}_D$= -16.2 ($CHCl_3$).



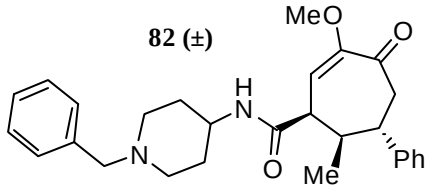
80 (±)

(1R,6S,7R,E)-N-(4-methoxybenzyl)-3-methoxy-7-methyl-4-oxo-6-phenyl cyclohept-2-enecarboxamide (±) (80). Purified by flash chromatography (SiO_2, 20:1 CH_2Cl_2:MeOH). Product isolated as a mixture of diastereomers in >25:1 ratio (dr was estimated from crude UPLC/ELSD) (55 %, 31 mg, 0.086 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.7 Hz, 1 H), 7.73 - 7.65 (m, 1 H), 7.36 - 7.16 (m, 7 H), 7.01 (br. s., 1 H), 6.19 (d, *J* = 5.9 Hz, 1 H), 4.67 (dd, *J* = 16.4, 5.1 Hz, 1 H), 4.57 (dd, *J* = 16.4, 4.7 Hz, 1 H), 3.83 (t, *J* = 5.7 Hz, 1 H), 3.74 (s, 3 H), 3.10 (dd, *J* = 17.6, 12.1 Hz, 1 H), 2.84 (d, *J* = 17.6 Hz, 1 H), 2.61 (dd, *J* = 12.3, 8.8 Hz, 1 H), 2.37 - 2.26 (m, 1 H), 0.85 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 171.5, 156.0, 152.8, 148.9, 143.9, 137.0, 128.7, 127.8, 126.8, 122.6, 122.4, 107.8, 55.5, 48.2, 45.9, 44.9, 44.6, 42.8, 15.3; IR (thin film) νmax 3336, 2962, 1675, 1624, 1540, 1437, 1206, 1140, 734, 703 cm^{-1}; HRMS calculated for $C_{22}H_{25}N_2O_3$: 365.1865, found: 365.1865 (M+H).



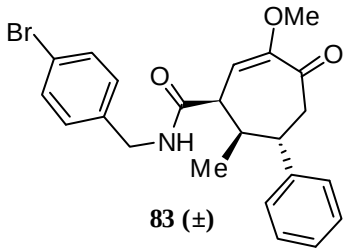
81 (±)

(1R,6S,7R)-N-(2-(N-ethylacetamido)ethyl)-3-methoxy-7-methyl-4-oxo-6-phenylcyclohept-2-enecarboxamide (±) (81). Purified by flash chromatography (SiO_2, 20:1 CH_2Cl_2:MeOH). Product isolated as a mixture of diastereomers in 10:1 ratio (dr was estimated from crude UPLC/ELSD) (45 %, 24 mg, 0.070 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 - 7.28 (m, 2 H), 7.26 - 7.18 (m, 3 H), 7.16 (br. s., 1 H), 6.12 (d, *J* = 5.9 Hz, 1 H), 3.73 (s, 3 H), 3.67 (d, *J* = 5.5 Hz, 1 H), 3.57 - 3.36 (m, 4 H), 3.32 (q, *J* = 7.3 Hz, 2 H), 3.07 (dd, *J* = 17.6, 12.1 Hz, 1 H), 2.78 (d, *J* = 17.2 Hz, 1 H), 2.56 (dd, *J* = 11.3, 9.4 Hz, 1 H), 2.29 (dq, *J* = 15.6, 6.1 Hz, 1 H), 2.01 (s, 3 H), 1.20 (t, *J* = 7.0 Hz, 3 H), 0.79 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 172.6, 172.0, 152.8, 144.0, 128.6, 127.8, 126.7, 107.8, 55.5, 48.3, 45.9, 44.8, 44.2, 44.0, 42.4, 40.3, 21.2, 15.3, 13.9; IR (thin film) νmax 3334, 2966, 1675, 1624, 1541, 1455, 1425, 1208, 1140, 734, 703 cm^{-1}; HRMS calculated for $C_{22}H_{30}N_2O_4Na$: 409.2103, found: 409.2082 (M+Na).



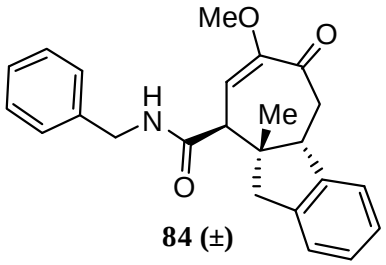
82 (±)

(1R,6S,7R,E)-N-(4-methoxybenzyl)-3-methoxy-7-methyl-4-oxo-6-phenylcyclohept-2-enecarboxamide (±) (82). Purified by flash chromatography (SiO_2, 20:1 CH_2Cl_2:MeOH). Product isolated as a mixture of diastereomers in >25:1 ratio (dr was estimated from crude UPLC/ELSD) (63 %, 44 mg, 0.098 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 - 7.20 (m, 8 H), 7.17 (d, *J* = 7.8 Hz, 2 H), 6.14 (d, *J* = 5.9 Hz, 1 H), 5.56 (d, 1 H), 3.92 - 3.78 (m, 1 H), 3.70 (s, 3 H), 3.64 (t, *J* = 5.7 Hz, 1 H), 3.48 (s, 2 H), 3.05 (dd, *J* = 17.6, 12.1 Hz, 1 H), 2.86 -2.74 (ovrlp m, 3 H), 2.57 (app t, *J* = 10.6 Hz, 1 H), 2.20 - 2.05 (m, 3 H), 1.96 - 1.82 (m, 2 H), 1.54 - 1.35 (m, 2 H), 0.83 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 170.6, 152.7, 143.9, 138.1, 129.0, 128.7, 128.2, 127.7, 127.1, 126.8, 107.9, 62.9, 55.4, 52.2, 52.1, 48.1, 47.0, 45.9, 44.8, 43.0, 32.2, 15.1; IR (thin film) νmax 3335, 2933, 1672, 1538, 1453, 1344, 1207, 1141, 736, 701 cm^{-1}; HRMS calculated for $C_{28}H_{35}N_2O_3$: 447.2648, found: 447.2646 (M+H).



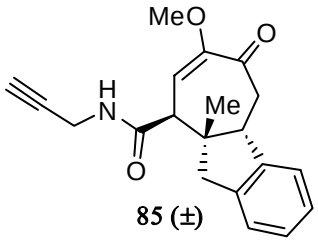
83 (±)

(1R,6S,7R,E)-N-(4-bromobenzyl)-3-methoxy-7-methyl-4-oxo-6-phenyl cyclohept-2-enecarboxamide (±) (83). Purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2:MeOH). Product isolated as a mixture of diastereomers in >25:1 ratio (dr was estimated from crude UPLC/ELSD) (65 %, 45 mg, 0.10 mmol). Characterization data for major diastereomer: Obtained clear crystals from ethyl acetate/hexane for x-ray analysis. m.p. = 205 - 207 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.2 Hz, 2 H), 7.34 - 7.20 (m, 3 H), 7.14 (t, *J* = 7.8 Hz, 4 H), 6.16 (d, *J* = 6.3 Hz, 1 H), 6.01 (t, *J* = 5.3 Hz, 1 H), 4.44 (d, *J* = 5.9 Hz, 2 H), 3.71 (s, 3 H), 3.70 (ovrlp t, *J* = 6.3 Hz, 1 H), 3.00 (dd, *J* = 17.6, 12.1 Hz, 1 H), 2.78 (d, *J* = 17.2 Hz, 1 H), 2.58 (dd, *J* = 11.2, 9.2 Hz, 1 H), 2.25 - 2.10 (m, 1 H), 0.84 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 171.3, 152.9, 143.7, 137.0, 131.9, 129.6, 128.8, 127.7, 126.9, 121.6, 107.3, 55.5, 48.0, 45.8, 45.0, 43.4, 43.0, 15.2; IR (thin film) νmax 3333, 2963, 1667, 1540, 1489, 1208, 1141, 1012, 736, 703 cm^{-1}; HRMS calculated for $C_{23}H_{24}BrNO_3Na$: 464.0837, found: 464.0866 (M+Na).



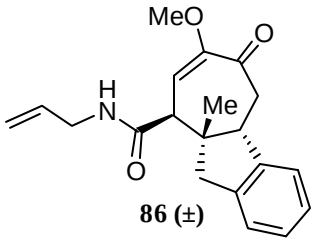
84 (±)

(1R,6S,7R,E)-N-(4-methoxybenzyl)-3-methoxy-7-methyl-4-oxo-6-phenylcyclohept-2-enecarboxamide (±) (84). Reaction was performed with TBD (26 mg, 1.9 mmol) in place of DBU. Purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2:MeOH). Product isolated as a mixture of diastereomers in 7:1 ratio (dr was estimated from crude UPLC/ELSD) (72 %, 40 mg, 0.11 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 - 7.30 (m, 5 H), 7.20 (d, *J* = 4.3 Hz, 3 H), 7.14 (br. s., 1 H), 6.14 (d, *J* = 5.9 Hz, 1 H), 5.96 (t, *J* = 5.1 Hz, 1 H), 4.60 (dd, *J* = 14.5, 5.5 Hz, 1 H), 4.52 (dd, *J* = 14.5, 5.5 Hz, 1 H), 3.70 (s, 3 H), 3.40 (d, *J* = 5.9 Hz, 1 H), 3.06 (d, *J* = 15.6 Hz, 1 H), 2.98 (dd, *J* = 11.7, 2.7 Hz, 1 H), 2.77 - 2.68 (m, 3 H), 1.15 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 171.3, 153.1, 143.3, 141.1, 137.9, 128.8, 128.0, 127.8, 127.4, 127.2, 124.9, 124.8, 111.9, 55.4, 51.0, 50.6, 48.7, 46.6, 44.4, 44.2, 23.4; IR (thin film) νmax 3334, 2930, 1673, 1622, 1537, 1455, 1206, 1155, 1137, 1119, 754, 734, 700 cm^{-1}; HRMS calculated for $C_{24}H_{26}NO_3$: 376.1913, found: 376.1919 (M+H).



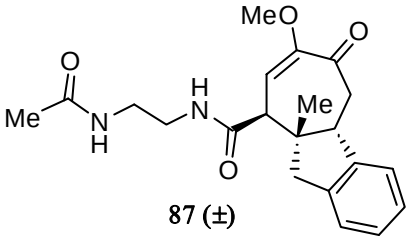
85 (±)

(1R,6S,7R,E)-N-(4-methoxybenzyl)-3-methoxy-7-methyl-4-oxo-6-phenyl cyclohept-2-enecarboxamide (±) (85). Reaction was performed with TBD (26 mg, 1.9 mmol) in place of DBU. Purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2:MeOH). Product isolated as a mixture of diastereomers in 8:1 ratio (dr was estimated from crude UPLC/ELSD) (65 %, 31 mg, 0.097 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 - 7.16 (m, 4 H), 6.09 (d, *J* = 5.9 Hz, 1 H), 5.95 - 5.88 (m, 1 H), 4.24 (ddd, *J* = 17.6, 5.5, 2.7 Hz, 1 H), 4.12 (ddd, *J* = 17.6, 5.1, 2.3 Hz, 1 H), 3.69 (s, 3 H), 3.43 (d, *J* = 5.9 Hz, 1 H), 3.12 (d, *J* = 15.6 Hz, 1 H), 2.99 (dd, *J* = 11.1, 3.3 Hz, 1 H), 2.83 (d, *J* = 15.6 Hz, 1 H), 2.80 - 2.72 (m, 2 H), 2.31 (t, *J* = 2.5 Hz, 1 H), 1.13 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 171.2, 153.1, 143.2, 141.1, 127.5, 127.3, 124.9, 124.9, 111.4, 79.2, 71.9, 55.5, 51.0, 50.4, 48.8, 46.6, 44.3, 29.5, 23.3; IR (thin film) νmax 3300, 2932, 1673, 1624, 1532, 1205, 1155, 1137, 1120, 736, 736 cm^{-1}; HRMS calculated for $C_{20}H_{21}NO_3Na$: 346.1419, found: 346.1440 (M+Na).



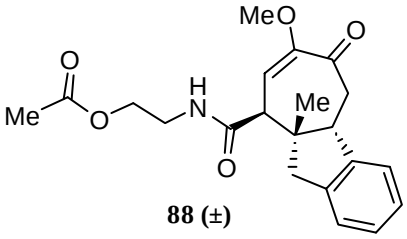
86 (±)

(1R,6S,7R,E)-N-(4-methoxybenzyl)-3-methoxy-7-methyl-4-oxo-6-phenyl cyclohept-2-enecarboxamide (±) (86). Reaction was performed with TBD (26 mg, 1.9 mmol) in place of DBU. Purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2:MeOH). Product isolated as a mixture of diastereomers in 7:1 ratio (dr was estimated from crude UPLC/ELSD) (76 %, 37 mg, 0.11 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 - 7.16 (m, 4 H), 6.12 (d, *J* = 5.5 Hz, 1 H), 5.98 - 5.84 (m, 1 H), 5.74 (br. s., 1 H), 5.28 (d, *J* = 18.0 Hz, 1 H), 5.23 (d, *J* = 10.6 Hz, 1 H), 4.11 - 3.90 (m, 2 H), 3.69 (s, 3 H), 3.40 (d, *J* = 5.9 Hz, 1 H), 3.11 (d, *J* = 15.2 Hz, 1 H), 2.99 (dd, *J* = 10.9, 3.1 Hz, 1 H), 2.85 - 2.70 (m, 3 H), 1.14 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 171.2, 153.1, 143.3, 141.1, 133.8, 127.5, 127.3, 124.9, 124.8, 117.2, 111.9, 55.4, 51.0, 50.6, 48.6, 46.7, 44.5, 42.4, 23.4; IR (thin film) νmax 3336, 2931, 1674, 1539, 1458, 1205, 1155, 1138, 1120, 756, 735 cm^{-1}; HRMS calculated for $C_{20}H_{24}NO_3$: 326.1756, found: 326.1796 (M+H).



87 (±)

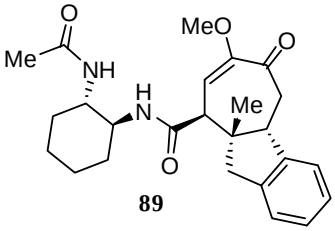
(1R,6S,7R,E)-N-(4-methoxybenzyl)-3-methoxy-7-methyl-4-oxo-6-phenylcyclohept-2-enecarboxamide (±) (87). Reaction was performed in CH_3CN (3 mL) with ethylenediamine (125 μL, 1.9 mmol) and with TBD (26 mg, 1.9 mmol) in place of DBU. The reaction was quenched with acetic anhydride (350 μL, 3.7 mmol) in anhydrous CH_3CN (1 mL). Purified by flash chromatography (SiO_2, 20:1 CH_2Cl_2:MeOH). Product isolated as a mixture of diastereomers in 9:1 ratio (dr was estimated from crude UPLC/ELSD) (53 %, 29 mg, 0.079 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 - 7.18 (m, 3 H), 7.18 - 7.14 (m, 1 H), 7.07 (br. s., 1 H), 6.29 (br. s., 1 H), 6.08 (d, *J* = 5.9 Hz, 1 H), 3.68 (s, 3 H), 3.54 - 3.41 (m, 5 H), 3.20 (d, *J* = 15.6 Hz, 1 H), 2.96 (dd, *J* = 10.7, 3.3 Hz, 1 H), 2.82 - 2.74 (m, 2 H), 2.69 (d, *J* = 15.6 Hz, 1 H), 2.02 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 172.5, 171.9, 153.0, 143.3, 141.3, 127.4, 127.2, 124.9, 124.8, 111.8, 55.4, 50.9, 50.4, 48.5, 46.7, 44.2, 41.1, 39.9, 23.4, 23.2; IR (thin film) νmax 3325, 2933, 1653, 1558, 1540, 1457, 1437, 1375, 1205, 1156, 1137, 1120, 735 cm^{-1}; HRMS calculated for $C_{21}H_{26}N_2O_4Na$: 393.1790, found: 393.1770 (M+Na).



88 (±)

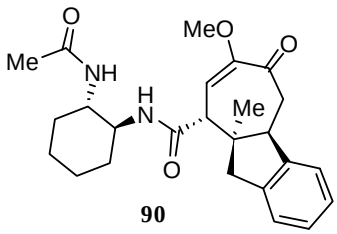
(1R,6S,7R,E)-N-(4-methoxybenzyl)-3-methoxy-7-methyl-4-oxo-6-phenylcyclohept-2-enecarboxamide (±) (88). Reaction was performed with TBD (26 mg, 1.9 mmol) in place of DBU. Purified by flash chromatography (SiO_2, 30:1 CH_2Cl_2:MeOH). Product isolated as a mixture of diastereomers in 10:1 ratio (dr was estimated from crude UPLC/ELSD) (68 %, 38 mg, 0.10 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 - 7.19 (m, 3 H), 7.19 - 7.14 (m, 1 H), 6.09 (d, *J* = 5.9 Hz, 2 H), 4.30 - 4.22 (m, 2 H), 3.79 - 3.71 (m, 1 H), 3.69 (s, 3 H), 3.62 - 3.51 (m, 1 H), 3.40 (d, *J* = 5.9 Hz, 1 H), 3.11 (d, *J* = 15.2 Hz, 1 H), 2.99 (dd, *J* = 10.0, 4.1 Hz, 1 H), 2.80 - 2.73 (m, 3 H), 2.13 (s, 3 H), 1.12 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 171.6, 171.2, 153.1, 143.3, 141.1, 127.5, 127.3, 125.0, 124.8, 111.6, 63.1, 55.5, 50.9, 50.5, 48.6, 46.7, 44.4, 39.2, 23.3, 20.9; IR (thin film) νmax 3348, 2958, 1739, 1678, 1546, 1556, 1368, 1232, 1206, 1155, 1138, 1120, 1052, 735 cm^{-1}; HRMS calculated for $C_{21}H_{25}NO_5Na$: 394.1630, found: 394.1630 (M+Na).

(1R,6S,7R,E)-N-(4-methoxybenzyl)-3-methoxy-7-methyl-4-oxo-6-phenylcyclohept-2-enecarbox amide (89) and **(4bR,9R,9aR)-N-((1S,2S)-2-acetamidocyclohexyl)-7-methoxy-9a-methyl-6-oxo-4b,5,6,9,9a,10-hexahydrobenzo[a]azulene-9-carboxamide (90).** Reaction was performed in anhydrous CH_3CN (3 mL) with (1S,2S)-(+)-1,2-diaminocyclohexane (107 mg, 0.936 mmol) and with TBD (26 mg, 1.9 mmol) in place of DBU. The reaction was quenched with acetic anhydride (175 μL, 1.87 mmol) in CH_3CN (1 mL). Purified by flash chromatography (SiO_2, 30:1 CH_2Cl_2:MeOH).



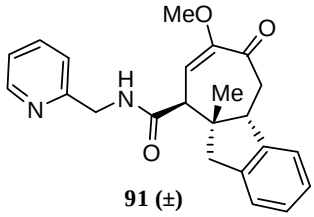
89

Product **89** was isolated as a mixture of diastereomers in >25:1 ratio (dr was estimated from crude UPLC/ELSD) (27 %, 17 mg, 0.040 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 2.7 Hz, 3 H), 7.14 (d, *J* = 5.9 Hz, 1 H), 6.48 (d, *J* = 6.6 Hz, 1 H), 6.02 (br. s., 1 H), 5.99 (d, *J* = 5.9 Hz, 1 H), 3.82 - 3.70 (m, 2 H), 3.69 (s, 3 H), 3.40 (d, *J* = 5.9 Hz, 1 H), 3.10 (d, *J* = 15.6 Hz, 1 H), 2.96 (dd, *J* = 8.6, 5.9 Hz, 1 H), 2.81 - 2.74 (m, 2 H), 2.58 (d, *J* = 15.6 Hz, 1 H), 2.25 - 2.16 (m, 1 H), 2.13 - 2.05 (m, 1 H), 2.03 (s, 3 H), 1.86 - 1.71 (m, 2 H), 1.42 - 1.21 (m, 4 H), 1.12 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 172.1, 170.7, 153.1, 143.3, 141.2, 127.4, 127.2, 124.9, 124.8, 111.6, 55.5, 54.7, 53.4, 51.0, 50.9, 48.4, 46.7, 44.0, 32.5, 32.2, 24.7, 24.5, 23.7, 23.5; IR (thin film) νmax 3311, 2931, 2856, 1652, 1540, 1457, 1375, 1205, 1154, 1118, 735 cm^{-1}; HRMS calculated for $C_{25}H_{32}N_2O_4Na$: 447.2260, found: 447.2212 (M+Na); $[\alpha]^{25}_D$= +67.5 ($CHCl_3$).



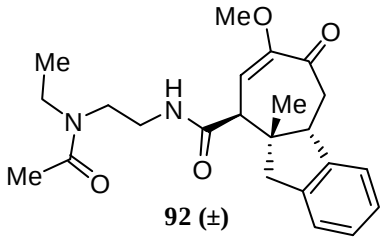
90

Product **90** isolated as a mixture of diastereomers in >25:1 ratio (dr was estimated from crude UPLC/ELSD) (24 %, 15 mg, 0.036 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 4 H), 6.82 (d, *J* = 6.6 Hz, 1 H), 6.14 (d, *J* = 5.9 Hz, 1 H), 5.73 (d, *J* = 7.4 Hz, 1 H), 3.85 - 3.71 (m, 2 H), 3.69 (s, 3 H), 3.36 (d, *J* = 5.9 Hz, 1 H), 3.20 (d, *J* = 15.6 Hz, 1 H), 2.95 (d, *J* = 10.9 Hz, 1 H), 2.82 - 2.68 (m, 3 H), 2.31 - 2.21 (m, 1 H), 2.04 - 1.98 (m, 1 H), 1.95 (s, 3 H), 1.82 (br. s., 2 H), 1.44 - 1.22 (m, 4 H), 1.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 171.7, 171.5, 152.9, 143.4, 141.2, 127.4, 127.2, 124.9, 111.7, 55.8, 55.4, 52.9, 51.0, 50.5, 48.6, 46.6, 44.6, 32.3, 32.2, 24.8, 24.4, 23.4; IR (thin film) νmax 3300, 2932, 2856, 1644, 1537, 1450, 1376, 1205, 1155, 1118, 735 cm^{-1}; HRMS calculated for $C_{25}H_{33}N_2O_4$: 425.2440, found: 425.2452 (M+H); $[\alpha]^{25}_{D}$= -74.7 ($CHCl_3$).



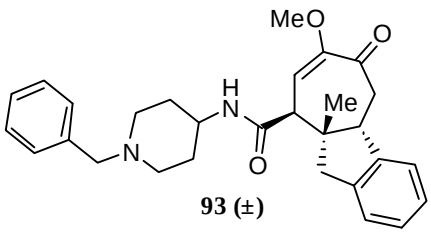
91 (±)

(1R,6S,7R,E)-N-(4-methoxybenzyl)-3-methoxy-7-methyl-4-oxo-6-phenyl cyclohept-2-enecarboxamide (±) (91). Reaction was performed with TBD (26 mg, 1.9 mmol) in place of DBU. Purified by flash chromatography (SiO_2, 20:1 CH_2Cl_2:MeOH). Product isolated as a mixture of diastereomers in 8:1 ratio (dr was estimated from crude UPLC/ELSD) (64 %, 36 mg, 0.095 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.7 Hz, 1 H), 7.84 - 7.77 (m, 1 H), 7.41 (d, *J* = 7.8 Hz, 1 H), 7.38 - 7.29 (m, 1 H), 7.24 - 7.12 (m, 5 H), 6.16 (d, *J* = 5.9 Hz, 1 H), 4.71 (t, *J* = 4.7 Hz, 2 H), 3.70 (s, 3 H), 3.60 (d, *J* = 5.9 Hz, 1 H), 3.25 (d, *J* = 15.6 Hz, 1 H), 2.99 (dd, *J* = 10.9, 3.1 Hz, 1 H), 2.85 - 2.72 (m, 3 H), 1.11 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 171.4, 155.5, 153.1, 148.9, 143.4, 141.3, 136.9, 127.4, 127.2, 124.9, 124.8, 122.6, 122.3, 111.9, 55.5, 51.1, 50.6, 48.7, 46.7, 44.6, 44.5, 23.4; IR (thin film) νmax 2931, 1676, 1623, 1539, 1478, 1459, 1437, 1204, 1154, 1138, 1120, 754, 734 cm^{-1}; HRMS calculated for $C_{23}H_{25}N_2O_3$: 377.1865, found: 377.1851 (M+H).



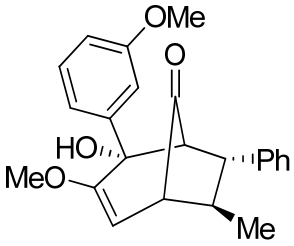
92 (±)

(4bS,9S,9aS)-N-(2-(N-ethylacetamido)ethyl)-7-methoxy-9a-methyl-6-oxo-4b,5,6,9,9a,10-hexahydrobenzo[a]azulene-9-carboxamide (±) (92). Reaction was performed with TBD (26 mg, 1.9 mmol) in place of DBU. Purified by flash chromatography (SiO_2, 20:1 CH_2Cl_2:MeOH). Product isolated as a mixture of diastereomers in 5:1 ratio (dr was estimated from crude UPLC/ELSD) (54 %, 29 mg, 0.080 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (br. s., 1 H), 7.24 - 7.11 (m, 4 H), 6.13 (d, *J* = 5.9 Hz, 1 H), 3.70 (s, 3 H), 3.63 - 3.57 (m, 2 H), 3.54 - 3.47 (m, 2 H), 3.44 - 3.36 (m, 3 H), 3.21 (d, *J* = 15.6 Hz, 1 H), 2.95 (dd, *J* = 11.7, 1.6 Hz, 1 H), 2.80 (d, *J* = 11.7 Hz, 1 H), 2.76 (d, *J* = 2.3 Hz, 1 H), 2.68 (d, *J* = 15.6 Hz, 1 H), 2.16 (s, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.09 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 172.4, 171.9, 152.9, 143.4, 141.4, 127.3, 127.1, 124.9, 124.8, 112.0, 55.4, 51.0, 50.4, 48.5, 46.7, 44.4, 44.3, 44.2, 40.5, 23.5, 21.3, 14.0; IR (thin film) νmax 3327, 2932, 1676, 1623, 1540, 1480, 1457, 1425, 1377, 1205, 1155, 1120, 734 cm^{-1}; HRMS calculated for $C_{23}H_{30}N_2O_4Na$: 421.2103, found: 421.2067 (M+Na).



93 (±)

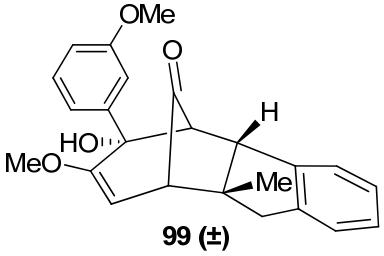
(1R,6S,7R,E)-N-(4-methoxybenzyl)-3-methoxy-7-methyl-4-oxo-6-phenylcyclohept-2-enecarboxamide (±) (93). Reaction was performed with TBD (26 mg, 1.9 mmol) in place of DBU. Purified by flash chromatography (SiO_2, 20:1 CH_2Cl_2:MeOH). Product isolated as a mixture of diastereomers in >25:1 ratio (dr was estimated from crude UPLC/ELSD) (49 %, 33 mg, 0.073 mmol). Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 - 7.31 (m, 4 H), 7.30 - 7.25 (m, 1 H), 7.24 - 7.14 (m, 4 H), 6.11 (d, *J* = 5.9 Hz, 1 H), 5.57 (d, *J* = 7.8 Hz, 1 H), 3.97 - 3.85 (m, 1 H), 3.68 (s, 3 H), 3.53 (s, 2 H), 3.34 (d, *J* = 5.5 Hz, 1 H), 3.08 (d, *J* = 15.6 Hz, 1 H), 2.97 (dd, *J* = 10.4, 3.7 Hz, 1 H), 2.93 - 2.83 (m, 2 H), 2.78 - 2.71 (m, 3 H), 2.23 - 2.11 (m, 2 H), 2.11 - 1.90 (m, 2 H), 1.63 - 1.47 (m, 2 H), 1.11 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 170.5, 153.0, 143.4, 141.0, 137.6, 129.2, 128.3, 127.5, 127.3, 127.2, 125.0, 124.8, 111.9, 62.8, 55.4, 52.2, 52.1, 50.9, 50.6, 48.6, 47.0, 46.6, 44.6, 32.3, 31.9, 23.4; IR (thin film) νmax 3329, 2930, 1676, 1646, 1540, 1205, 1155, 1120, 737, 700 cm^{-1}; HRMS calculated for $C_{29}H_{35}N_2O_3$: 459.2648, found: 459.2643 (M+H).



98 (±)

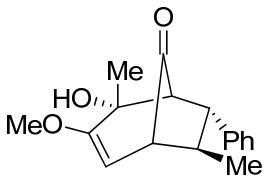
General procedure for synthesis of products 98-104 and 106.

(1R,4S,5S,6R,7R)-4-hydroxy-3-methoxy-4-(3-methoxyphenyl)-7-methyl-6-phenylbicyclo[3.2.1]oct-2-en-8-one (±) (98). To an oven-dried vial was added 3-methoxy-6-methyl-7-phenylbicyclo[3.2.1]oct-3-ene-2,8-dione (**7**) (40 mg, 0.16 mmol) and anhydrous THF (4.0 mL). The reaction mixture was cooled to 0 °C while under argon. To this mixture was added 1.0 M 3-methoxyphenylmagnesium bromide in THF (470 μL, 0.47 mmol) dropwise *via* syringe over 1 min while at 0 °C. The reaction was warmed to rt with continued stirring for 30 min. The reaction was cooled back down to 0 °C and quenched with the addition of water (20 μL). This mixture was warmed to rt, diluted with water (20 mL) and extracted into CH_2Cl_2 (15 mL x 3). The organic fractions were combined, washed with brine (20 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2:EtOAc) to afford **98** as an amorphous clear/white solid (96 %, 54 mg, 0.15 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.36 (m, 4 H), 7.33 - 7.27 (m, 1 H), 7.21 - 7.15 (m, 1 H), 6.83 - 6.81 (m, 1 H), 6.80 - 6.74 (m, 2 H), 5.39 (d, *J* = 7.4 Hz, 1 H), 3.74 (s, 3 H), 3.64 (s, 3 H), 3.09 (dd, *J* = 7.0, 5.9 Hz, 1 H), 2.94 (dd, *J* = 7.0, 1.6 Hz, 1 H), 2.88 - 2.78 (m, 1 H), 2.58 (dd, *J* = 7.4, 1.6 Hz, 1 H), 2.09 (s, 1 H), 1.07 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.7, 159.4, 155.4, 144.1, 140.6, 129.5, 128.9, 128.8, 127.2, 118.1, 113.2, 111.6, 99.5, 82.7, 63.6, 55.3, 55.1, 51.2, 50.4, 42.7, 21.5; IR (thin film) νmax 3552, 2958, 1750, 1600, 1584, 1484, 1455, 1434, 1289, 1250, 1227, 1150, 1095, 1079, 1032, 784, 701 cm^{-1}; HRMS calculated for $C_{23}H_{24}O_4Na$: 387.1572, found: 387.1587 (M+Na).



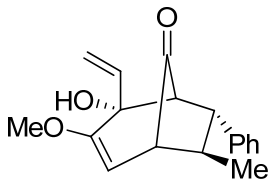
99 (±)

Tertiary alcohol (±) (99). Product was purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2:EtOAc) to afford **99** as an amorphous clear/tan solid (99 %, 58 mg, 0.16 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 - 7.50 (m, 1 H), 7.24 - 7.19 (m, 4 H), 6.94 - 6.90 (m, 1 H), 6.86 - 6.76 (m, 2 H), 5.09 (d, *J* = 7.5 Hz, 1 H), 3.78 (s, 3 H), 3.60 (d, *J* = 17.2 Hz, 1 H), 3.46 (d, *J* = 7.8 Hz, 1 H), 3.43 (s, 3 H), 3.11 (dd, *J* = 7.8, 2.0 Hz, 1 H), 2.80 (d, *J* = 17.2 Hz, 1 H), 2.62 (dd, *J* = 7.5, 2.0 Hz, 1 H), 2.47 (s, 1 H), 1.22 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 159.4, 155.6, 144.6, 144.1, 140.8, 128.9, 127.7, 127.5, 126.4, 125.2, 118.1, 113.1, 111.7, 96.6, 82.9, 60.9, 56.2, 55.2, 53.9, 47.4, 41.4, 29.1; IR (thin film) νmax 3546, 2952, 1750, 1600, 1483, 1457, 1435, 1288, 1249, 1228, 1147, 1037, 784, 746, 701 cm^{-1}; HRMS calculated for $C_{24}H_{24}O_4Na$: 399.1572, found: 399.1575 (M+Na).



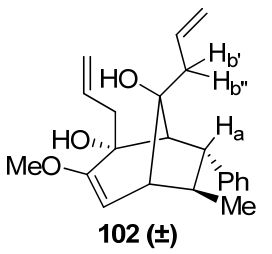
100 (±)

(1R,4R,5S,6R,7R)-4-hydroxy-3-methoxy-4,7-dimethyl-6-phenylbicyclo[3.2.1] oct-2-en-8-one (±) (100). Product was purified by flash chromatography (SiO_2, 30:1 CH_2Cl_2:EtOAc) to afford **100** as a white solid (95 %, 40 mg, 0.15 mmol). m.p. = 135 - 137 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.35 (m, 4 H), 7.31 - 7.27 (m, 1 H), 4.97 (d, *J* = 7.8 Hz, 1 H), 3.64 (s, 3 H), 3.13 (dd, *J* = 7.4, 5.1 Hz, 1 H), 2.86 (dd, *J* = 7.4, 2.0 Hz, 1 H), 2.82 - 2.74 (m, 1 H), 2.50 (dd, *J* = 7.8, 2.0 Hz, 1 H), 1.30 (s, 3 H), 1.07 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 158.2, 140.6, 129.2, 127.4, 95.4, 78.2, 62.7, 55.3, 51.4, 50.0, 42.4, 26.8, 21.7; IR (thin film) νmax 3566, 2958, 1750, 1635, 1456, 1373, 1230, 1147, 705 cm^{-1}; HRMS calculated for $C_{17}H_{20}O_3Na$: 295.1310, found: 295.1319 (M+Na).



101 (±)

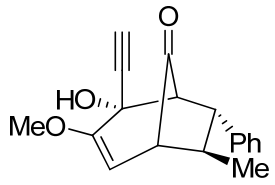
(1R,4R,5S,6R,7R)-4-hydroxy-3-methoxy-7-methyl-6-phenyl-4-vinylbicyclo [3.2.1]oct-2-en-8-one (±) (101). Product was purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2:EtOAc) to afford **101** as clear oil (91 %, 40 mg, 0.14 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.34 (m, 4 H), 7.31 - 7.27 (m, 1 H), 5.80 - 5.69 (m, 1 H), 5.16 (ovrlp d, *J* = 7.4 Hz, 1 H), 5.14 (ovrlp dd, *J* = 6.3, 1.2 Hz, 1 H), 5.11 (s, 1 H), 3.64 (s, 3 H), 3.13 (dd, *J* = 7.4, 5.1 Hz, 1 H), 2.86 (dd, *J* = 7.4, 1.6 Hz, 1 H), 2.84 - 2.78 (m, 1 H), 2.53 (dd, *J* = 7.4, 1.6 Hz, 1 H), 1.73 (s, 1 H), 1.07 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 155.7, 140.6, 138.8, 129.4, 129.0, 127.4, 114.8, 97.8, 80.5, 61.6, 55.4, 51.3, 50.1, 42.8, 21.7; IR (thin film) νmax 3561, 2957, 1748, 1636, 1455, 1228, 1152, 1098, 1031, 705 cm^{-1}; HRMS calculated for $C_{18}H_{20}O_3Na$: 307.1310, found: 307.1316 (M+Na).



102 (±)

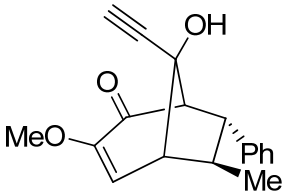
(1R,2R,5R,6R,7R,8S)-2,8-diallyl-3-methoxy-6-methyl-7-phenylbicyclo[3.2.1] oct-3-ene-2,8-diol (±) (102). Product was purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2:EtOAc) to afford **102** as an amorphous clear/white solid (98 %, 52 mg, 0.15 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 - 7.22 (m, 4 H), 7.20 - 7.13 (m, 1 H), 6.12 - 5.98 (m, *J* = 17.2, 10.1, 7.2, 7.2 Hz, 1 H), 5.91 - 5.77 (m, *J* = 17.4, 10.2, 7.1, 7.1 Hz, 1 H), 5.25 - 5.03 (m, 5 H), 3.56 (s, 3 H), 3.35 (dd, *J* = 9.2, 5.8 Hz, 1 H), 2.82 (dd, *J* = 5.8, 2.0 Hz, 1 H), 2.79 - 2.67 (ovrlp m, 2 H), 2.64 (d, *J* = 7.4 Hz, 2 H), 2.60 - 2.52 (m, 1 H), 2.38 (s, 1 H), 2.18 (dd, *J* = 7.8, 2.0 Hz, 1 H), 1.28 (s, 1 H), 1.18 (d, *J* = 7.0 Hz, 3 H); NOED (400 MHz, $CDCl_3$) irrad. δ 3.35 (H_a) 7 % enhancement at $H_{b'}$, 5 % enhancement at $H_{b''}$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 141.5, 134.7, 134.0, 128.7, 126.1, 118.5, 118.1, 99.8, 81.5, 77.6, 55.0, 53.2, 51.4, 49.1, 43.8, 43.4, 42.6, 20.6; IR (thin film) νmax 3566, 2954, 2928, 1638, 1450, 1373, 1223, 1153, 1065, 1033, 999, 912, 697 cm^{-1}; HRMS calculated for $C_{22}H_{28}O_3Na$: 363.1936, found: 363.1942 (M+Na).

(1R,4S,5S,6R,7R)-4-ethynyl-4-hydroxy-3-methoxy-7-methyl-6-phenylbicyclo[3.2.1]oct-2-en-8-one (±) (103) and **(1R,5R,6R,7R,8R)-8-ethynyl-8-hydroxy-3-methoxy-6-methyl-7-phenylbicyclo[3.2.1] oct-3-en-2-one (±) (104).** Product was purified by flash chromatography (SiO_2, 30:1 CH_2Cl_2:EtOAc) to afford **103** (60 %, 26 mg, 0.094 mmol) and **104** (30 %, 13 mg, 0.047 mmol).



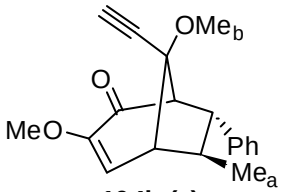
103 (±)

Characterization data for **103**: m.p. = 165-168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.31 (m, 4 H), 7.29 - 7.27 (m, 1 H), 5.13 (d, *J* = 7.4 Hz, 1 H), 3.71 (s, 3 H), 3.21 (dd, *J* = 7.4, 1.6 Hz, 1 H), 3.14 (dd, *J* = 7.4, 5.5 Hz, 1 H), 2.84 - 2.76 (m, 1 H), 2.60 (s, 1 H), 2.58 (dd, *J* = 7.4, 1.6 Hz, 1 H), 1.95 (s, 1 H), 1.09 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0, 154.4, 139.9, 129.4, 128.8, 127.3, 98.1, 82.6, 74.7, 73.6, 61.5, 55.8, 50.9, 49.8, 42.7, 21.7; IR (thin film) νmax 3536, 3277, 2960, 1751, 1645, 1455, 1228, 1150, 1097, 1080, 1031, 1018, 702 cm^{-1}; HRMS calculated for $C_{18}H_{19}O_3$: 283.1334, found: 283.1338 (M+H).



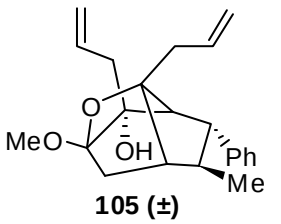
104 (±)

Characterization data for **104**: m.p. = 193-195 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 - 7.21 (m, 2 H), 7.19 - 7.14 (m, 1 H), 7.07 - 7.03 (m, 2 H), 6.33 (d, *J* = 8.2 Hz, 1 H), 3.68 (s, 3 H), 3.65 (t, *J* = 6.4 Hz, 1 H), 3.40 (dd, *J* = 6.6, 2.3 Hz, 1 H), 2.85 (dd, *J* = 8.2, 2.3 Hz, 1 H), 2.57 (s, 1 H), 2.50 - 2.41 (ovrlp m, 1 H), 2.45 (ovrlp s, 1 H), 1.38 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 153.5, 138.5, 128.5, 126.9, 120.6, 83.0, 79.6, 74.8, 70.7, 55.4, 53.2, 51.1, 46.6, 20.9; IR (thin film) νmax 3421, 3289, 2956, 2932, 1684, 1653, 1617, 1456, 1251, 1152, 740, 701 cm^{-1}; HRMS calculated for $C_{18}H_{18}O_3Na$: 305.1154, found: 305.1167 (M+Na).



104b (±)

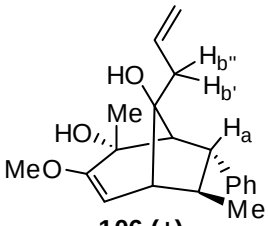
(1R,5R,6R,7R,8R)-8-ethynyl-3,8-dimethoxy-6-methyl-7-phenylbicyclo [3.2.1] oct-3-en-2-one (±) (104b). To an oven-dried 1 dram vial was added tertiary alcohol **103** (20 mg, 0.071 mmol) followed by the addition of anhydrous THF (1 mL) while under argon. To this mixture was added MeI (26 μL, 0.42 mmol). The reaction mixture was cooled to 0 °C and 60% NaH dispersion in mineral oil (4.2 mg, 0.11 mmol) was added with continued stirring at 0 °C for 1 h. The reaction was quenched with the addition of water (10 μL). The crude reaction was concentrated and purified by flash chromatography (SiO_2, 30:1 CH_2Cl_2:EtOAc) to afford **104b** as an amorphous clear/tan solid (80 %, 17 mg, 0.057 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 - 7.21 (m, 2 H), 7.19 - 7.14 (m, 1 H), 7.07 - 7.02 (m, 2 H), 6.31 (d, *J* = 8.6 Hz, 1 H), 3.68 (s, 3 H), 3.53 - 3.47 (ovrlp m, 2 H), 3.46 (s, 3 H), 2.95 (dd, *J* = 8.6, 2.3 Hz, 1 H), 2.49 - 2.40 (ovrlp m, 1 H), 2.44 (ovrlp s, 1 H), 1.33 (d, *J* = 7.0 Hz, 3 H); NOED (400 MHz, $CDCl_3$) irrad. δ 1.33 (Me$_a$) 2 % enhancement at Me$_b$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 153.8, 138.5, 128.5, 128.4, 126.9, 120.2, 85.3, 79.8, 76.2, 67.5, 55.4, 51.2, 51.1, 50.1, 46.6, 20.7; IR (thin film) νmax 2955, 1692, 1619, 1453, 1257, 1206, 1151, 1112, 1077, 736, 701 cm^{-1}; HRMS calculated for $C_{19}H_{20}O_3Na$: 319.1310, found: 319.1309 (M+Na).



105 (±)

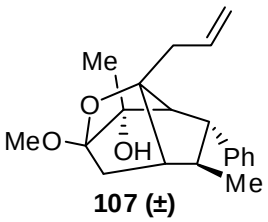
Polycyclic ketal (±) (105). To a 1 dram vial was added diol **102** (20 mg, 0.059 mmol) followed by the addition of THF (1 mL). The reaction mixture was heated to 50 °C for 8 h while stirring. The reaction was concentrated and purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2:EtOAc) to afford **105** as an amorphous clear/white solid (96 %, 19 mg, 0.056 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 - 7.27 (m, 4 H), 7.21 - 7.14 (m, 1 H), 6.02 - 5.89 (m, 1 H), 5.61 - 5.48 (m, 1 H), 5.20 - 5.12 (m, 2 H), 4.98 - 4.89 (m, 2 H), 3.45 (s, 3 H), 2.91 (dd, *J* = 9.6, 5.7 Hz, 1 H), 2.83 - 2.71 (m, 1 H), 2.59 (d, *J* = 7.0 Hz, 2 H), 2.48 (dd, *J* = 5.7, 1.6

Hz, 1 H), 2.32 - 2.14 (ovrlp m, 3 H), 2.07 - 1.96 (ovrlp m, 2 H), 1.24 (s, 1 H), 1.14 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 133.6, 133.4, 128.2, 128.1, 125.9, 119.7, 117.7, 109.7, 89.1, 81.4, 56.0, 52.5, 50.9, 49.5, 41.6, 40.6, 38.1, 36.2, 22.3; IR (thin film) νmax 2953, 1498, 1456, 1447, 1311, 1217, 1154, 1134, 1096, 1064, 1032, 994, 912, 697 cm^{-1}; HRMS calculated for $C_{22}H_{28}O_3Na$: 363.1936, found: 363.1944 (M+Na)



106 (±)

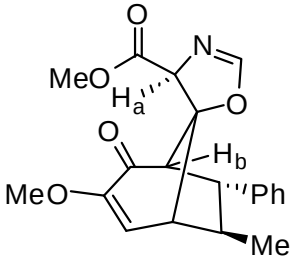
(1R,2R,5R,6R,7R,8S)-8-allyl-3-methoxy-2,6-dimethyl-7-phenylbicyclo [3.2.1]oct-3-ene-2,8-diol (±) (106). Product was purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2:EtOAc) to afford **106** as an amorphous clear/white solid (99 %, 23 mg, 0.073 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 - 7.27 (m, 4 H), 7.22 - 7.14 (m, 1 H), 6.14 - 6.00 (m, *J* = 17.1, 10.1, 7.1, 7.1 Hz, 1 H), 5.27 - 5.16 (m, 2 H), 5.05 (d, *J* = 7.8 Hz, 1 H), 3.57 (s, 3 H), 3.39 (dd, *J* = 9.2, 5.7 Hz, 1 H), 2.81 - 2.68 (m, 2 H), 2.65 - 2.58 (m, 1 H), 2.56 (dd, *J* = 5.7, 2.0 Hz, 1 H), 2.39 (s, 1 H), 2.21 (dd, *J* = 7.8, 2.0 Hz, 1 H), 1.45 (s, 3 H), 1.33 (s, 1 H), 1.18 (d, *J* = 7.0 Hz, 3 H); NOED (400 MHz, $CDCl_3$) irrad. δ 3.39 (H_a) 5 % enhancement at $H_{b'}$, 5 % enhancement at $H_{b''}$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 141.4, 133.9, 128.8, 127.9, 126.3, 118.1, 99.3, 81.2, 76.4, 58.7, 55.0, 51.7, 48.8, 43.2, 42.5, 29.0, 20.5; IR (thin film) νmax 2931, 2956, 1653, 1637, 1497, 1456, 1372, 1225, 1152, 1131, 1040, 1003, 912, 699 cm^{-1}; HRMS calculated for $C_{20}H_{26}O_3Na$: 337.1780, found: 337.1795 (M+Na).



107 (±)

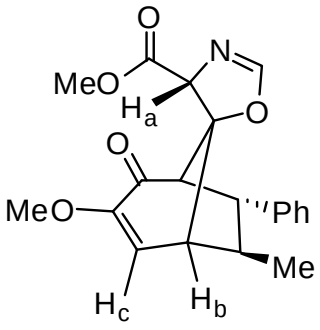
Polycyclic ketal (±) (107). To a 1 dram vial was added diol **106** (20 mg, 0.064 mmol) followed by the addition of THF (1 mL). The reaction mixture was heated to 50 °C for 8 h with continues stirring. The reaction was concentrated and purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2:EtOAc) to afford **107** as an amorphous clear/white solid (78 %, 16 mg, 0.050 mmol).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.28 (m, 4 H), 7.23 - 7.16 (m, 1 H), 6.03 - 5.89 (m, *J* = 16.1, 11.0, 7.2, 7.2 Hz, 1 H), 5.19 - 5.11 (m, 2 H), 3.43 (s, 3 H), 2.94 (dd, *J* = 9.0, 5.7 Hz, 1 H), 2.76 - 2.64 (m, 1 H), 2.57 (d, *J* = 7.0 Hz, 2 H), 2.49 (dd, *J* = 5.7, 1.6 Hz, 1 H), 2.22 (dd, *J* = 12.2, 11.4 Hz, 1 H), 1.99 (dd, *J* = 11.4, 1.6 Hz, 2 H), 1.21 (d, *J* = 7.4 Hz, 3 H), 1.20 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 133.6, 128.7, 127.0, 125.8, 117.7, 109.6, 88.5, 80.5, 58.6, 52.5, 50.2, 50.0, 41.6, 38.0, 35.7, 27.0, 23.0; IR (thin film) νmax 2952, 2927, 1456, 1219, 1159, 1106, 1063, 1044, 987, 908, 885, 698 cm^{-1}; HRMS calculated for $C_{20}H_{26}O_3Na$: 337.1780, found: 337.1789 (M+Na).

(1R,4'S,5R,5'R,6R,7R)-methyl 3-methoxy-7-methyl-4-oxo-6-phenyl-4'H-spiro[bicyclo[3.2.1] oct[2] ene-8,5'-oxazole]-4'-carboxylate (±) (108) and **(1R,4'R,5R,5'R,6R,7R)-methyl 3-methoxy- 7-methyl-4-oxo-6-phenyl-4'H-spiro[bicyclo[3.2.1]oct[2]ene-8,5'-oxazole]-4'-carboxylate (±) (109).** Purification by flash chromatography (SiO_2, 1:1 EtOAc:petroleum ether) afforded **108** (35 %, 19 mg, 0.055 mmol) and **109** (37 %, 21 mg, 0.058 mmol) as amorphous clear/white solids.



108 (±)

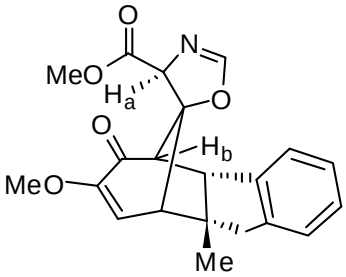
Characterization data for **108**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 - 7.22 (m, 2 H), 7.22 - 7.14 (m, 1 H), 7.08 - 7.00 (m, 3 H), 6.26 (d, *J* = 8.2, 1 H), 4.48 (s, 1 H), 3.71 (s, 3 H), 3.62 (s, 3 H), 3.51 (t, *J* = 6.4 Hz, 1 H), 3.39 (dd, *J* = 6.4, 2.0 Hz, 1 H), 3.15 (dd, *J* = 8.2, 2.0 Hz, 1 H), 2.53 (quin, *J* = 6.8 Hz, 1 H), 1.35 (d, *J* = 7.0 Hz, 3 H); NOED (400 MHz, $CDCl_3$) irrad. δ 4.48 (H_a) 3 % enhancement at H_b; irrad. δ 3.39 (H_b) 2 % enhancement at H_a; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 170.6, 156.2, 153.6, 138.0, 128.7, 128.3, 127.2, 121.2, 97.5, 70.9, 68.7, 55.4, 52.4, 51.4, 48.1, 46.6, 20.4; IR (thin film) νmax 2955, 2932, 1743, 1696, 1635, 1616, 1456, 1251, 1212, 1159, 1113, 971, 736, 701 cm^{-1}; HRMS calculated for $C_{20}H_{22}NO_5$: 356.1498, found: 356.1513 (M+H).



109 (±)

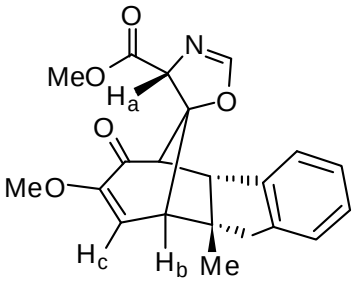
Characterization data for **109**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 - 7.21 (m, 2 H), 7.21 - 7.14 (m, 1 H), 7.11 (s, 1 H), 7.02 (d, *J* = 7.4 Hz, 2 H), 6.28 (d, *J* = 8.6 Hz, 1 H), 4.67 (d, *J* = 1.6 Hz, 1 H), 3.72 (s, 3 H), 3.56 (s, 3H), 3.56 (ovrlp t, *J* = 6.45 Hz, 1 H), 3.35 (dd, *J* = 6.6, 2.3 Hz, 1 H), 2.81 (dd, *J* = 8.4, 2.1 Hz, 1 H), 2.56 (d, *J* = 7.0 Hz, 1 H), 1.35 (d, *J* = 7.0 Hz, 3 H); NOED (400 MHz, $CDCl_3$) irrad. δ 4.67 (H_a) 3 % enhancement at H_b, 1 % enhancement at H_c; irrad. δ 2.81 (H_b) 2 % enhancement at H_a; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 169.0, 155.8, 154.5, 137.6, 128.6, 128.4, 127.2, 118.0, 97.3, 70.6, 65.1, 55.7, 52.3, 52.2, 51.5, 46.3, 20.5; IR (thin film) νmax 2955, 2932, 1745, 1692, 1632, 1615, 1244, 1207, 1176, 1162, 1138, 1103, 1009, 971, 734, 702 cm^{-1}; HRMS calculated for $C_{20}H_{22}NO_5$: 356.1498, found: 356.1522 (M+H).

Spirocycles (±) 110 and (±) 111. Purification by flash chromatography (SiO_2, 1:1 EtOAc:petroleum ether) afforded **110** (39 %, 21 mg, 0.058 mmol) and **111** (42 %, 23 mg, 0.063 mmol) as amorphous clear/white solids .



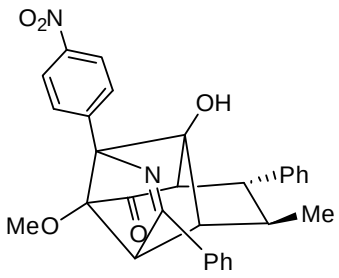
110 (±)

Characterization data for **110**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 - 7.08 (m, 3 H), 7.05 (d, *J* = 1.6 Hz, 1 H), 6.99 (d, *J* = 7.0 Hz, 1 H), 5.94 (d, *J* = 8.6 Hz, 1 H), 4.46 (d, *J* = 2.0 Hz, 1 H), 3.91 (d, *J* = 7.8 Hz, 1 H), 3.69 (s, 3 H), 3.55 (dd, *J* = 7.4, 2.3 Hz, 1 H), 3.37 (s, 3 H), 3.31 (dd, *J* = 8.2, 2.3 Hz, 1 H), 3.16 (d, *J* = 17.2 Hz, 1 H), 2.76 (d, *J* = 17.2 Hz, 1 H), 1.64 (s, 3 H); NOED (400 MHz, $CDCl_3$) irrad. δ 4.46 (H_a) 3 % enhancement at H_b; irrad. δ 3.55 (H_b) 2 % enhancement at H_a; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 170.5, 156.3, 152.4, 142.4, 140.0, 127.8, 127.1, 125.9, 124.2, 118.6, 98.5, 71.6, 65.8, 58.8, 55.2, 53.3, 52.4, 51.0, 44.9, 29.4; IR (thin film) νmax 2953, 2927, 1744, 1697, 1634, 1614, 1251, 1152, 1113, 972, 740 cm^{-1}; HRMS calculated for $C_{21}H_{22}NO_5$: 368.1498, found: 368.1473 (M+H).



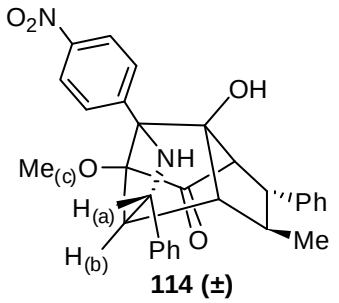
111 (±)

Characterization data for **111**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 - 7.07 (m, 4 H), 6.98 (d, *J* = 6.3 Hz, 1 H), 5.95 (d, *J* = 8.2 Hz, 1 H), 4.67 (d, *J* = 1.6 Hz, 1 H), 3.94 (d, *J* = 7.8 Hz, 1 H), 3.59 (s, 3 H), 3.54 (dd, *J* = 7.4, 2.3 Hz, 1 H), 3.48 (s, 3 H), 3.21 (d, *J* = 17.2 Hz, 1 H), 2.98 (dd, *J* = 8.6, 2.3 Hz, 1 H), 2.72 (d, *J* = 17.2 Hz, 1 H), 1.64 (s, 3 H); NOED (400 MHz, $CDCl_3$) irrad. δ 4.67 (H_a) 3 % enhancement at H_b, 2 % enhancement at H_c; irrad. δ 2.98 (H_b) 2 % enhancement at H_a; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 169.0, 155.8, 153.2, 142.2, 139.6, 127.9, 127.0, 126.3, 124.3, 116.0, 98.2, 71.7, 62.2, 59.9, 55.5, 54.9, 52.9, 52.2, 45.4, 29.7; IR (thin film) νmax 2952, 2927, 1745, 1696, 1635, 1615, 1266, 1205, 1148, 1107, 736 cm^{-1}; HRMS calculated for $C_{21}H_{22}NO_5$: 368.1498, found: 368.1501 (M+H).



113 (±)

Poylcyclic imine (±) 113. To a oven-dried 1 dram vial was added *N*-(4-nitrobenzyl)benzimidoyl chloride[S6] (**112**) (40 mg, 0.15 mmol), 3-methoxy-6-methyl-7-phenylbicyclo [3.2.1]oct-3-ene-2,8-dione (**7**) (25 mg, 0.097 mmol) and anhydrous toluene (2 mL) followed by the addition of triethylamine (30.0 μL, 0.215 mmol). The reaction was stirred at rt for 24 h while under argon. The reaction was then evaporated *in vacuo* and purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2:MeOH) to afford imine **113** as a pale yellow solid (44 %, 21 mg, 0.043 mmol). m.p. = 210 - 215 ^oC (dec); ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 9.0 Hz, 2 H), 7.98 (d, *J* = 7.0 Hz, 2 H), 7.85 (d, *J* = 9.0 Hz, 2 H), 7.64 - 7.48 (m, 3 H), 7.40 - 7.28 (m, 3 H), 7.22 (d, *J* = 7.4 Hz, 2 H), 3.81 (s, 1 H), 3.52 (dd, *J* = 10.6, 5.1 Hz, 1 H), 3.41 (s, 3 H), 2.70 (dd, *J* = 5.1, 2.3 Hz, 1 H), 2.42 (s, 1 H), 2.33 (ddd, *J* = 10.3, 6.9, 2.7 Hz, 1 H), 1.89 (t, *J* = 2.3 Hz, 1 H), 1.26 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 177.0, 147.5, 142.1, 136.8, 132.2, 130.5, 129.8, 129.2, 128.4, 128.2, 127.6, 127.3, 123.4, 103.2, 90.8, 88.4, 61.4, 57.4, 56.2, 56.1, 54.1, 40.9, 20.5; IR (thin film) νmax 2959, 1750, 1603, 1518, 1497, 1448, 1349, 1271, 1151, 910, 853, 732, 697 cm^{-1}; HRMS calculated for $C_{30}H_{27}N_2O_5$: 495.1920, found: 495.1915 (M+H).



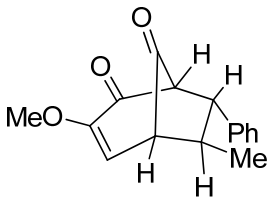
114 (±)

Polycyclic amine (±) 114. To an oven dried 1 dram vial was added polycyclic imine (**113**) (30 mg, 0.061 mmol) followed by the addition of MeOH (1 mL). Next was added $NaCNBH_3$ (46 mg, 0.73 mmol) and acetic acid (42 μL, 0.73 mmol). The reaction was capped and stirred at rt for 1 h. The reaction was extracted into CH_2Cl_2 (10 mL) and washed with water (10 mL x 2) then brine (10 mL). The organic portion was dried over Na_2SO_4 and evaporated *in vacuo*. The resulting residue was purified by flash chromatography (SiO_2, 20:1 CH_2Cl_2:MeOH) to afford amine **114** as a pale yellow solid (91 %, 28 mg, 0.056 mmol). m.p. = 225 - 230 ^oC (dec); ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.6 Hz, 2 H), 7.74 (d, *J* = 9.0 Hz, 2 H), 7.56 (d, *J* = 7.4 Hz, 2 H), 7.44 (t, *J* = 7.6Hz, 1 H), 7.37 - 7.21 (m, 5 H), 7.14 (d, *J* = 7.4 Hz, 2 H), 5.10 (d, *J* = 2.0 Hz, 1 H), 3.80 (s, 3 H), 3.23 (dd, *J* = 10.7, 5.3 Hz, 1 H), 2.81 (d, *J* = 3.1 Hz, 1 H), 2.66 (br. s., 1 H), 2.39 (dd, *J* = 5.1, 2.3 Hz, 1 H), 2.07 - 1.94 (m, 1 H), 1.89 (br. s., 1 H), 0.95 (d, *J* = 7.0 Hz, 3 H); NOED (400 MHz, $CDCl_3$) irrad. δ 5.10 (H_a) 3 % enhancement at Me_c, 5 % enhancement at H_b; irrad. δ 3.80 (Me_c) 2 % enhancement at H_a, 3 % enhancement at H_b; ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8, 147.5, 142.1, 139.2, 137.3, 129.0, 128.6, 128.3, 128.2, 127.3, 127.1, 127.0, 123.4, 95.2, 89.3, 79.7, 63.6, 61.0, 53.7, 53.0, 52.3, 50.6, 42.8, 20.3; IR (thin film) νmax 2959, 1744, 1602, 1521, 1496, 1456, 1349, 1152, 1031, 853, 754, 699 cm^{-1}; HRMS calculated for $C_{30}H_{29}N_2O_5$: 497.2076, found: 497.2063 (M+H).

[S6] Nair, V.; Sethumadhaven, D.; Nair, S. M.; Viji, S.; Rath, N. P. *Tetrahedron* **2002**, *58*, 3003.

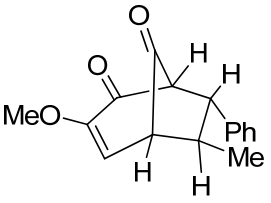
V. Select NMR Spectra

^{1}H NMR (400 MHz, $CDCl_3$)



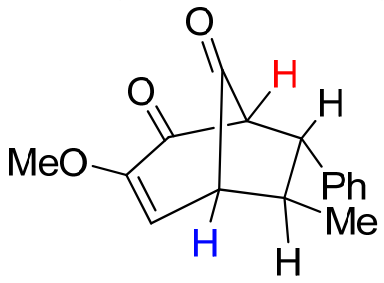
7 (±)

^{13}C NMR (100 MHz, $CDCl_3$)

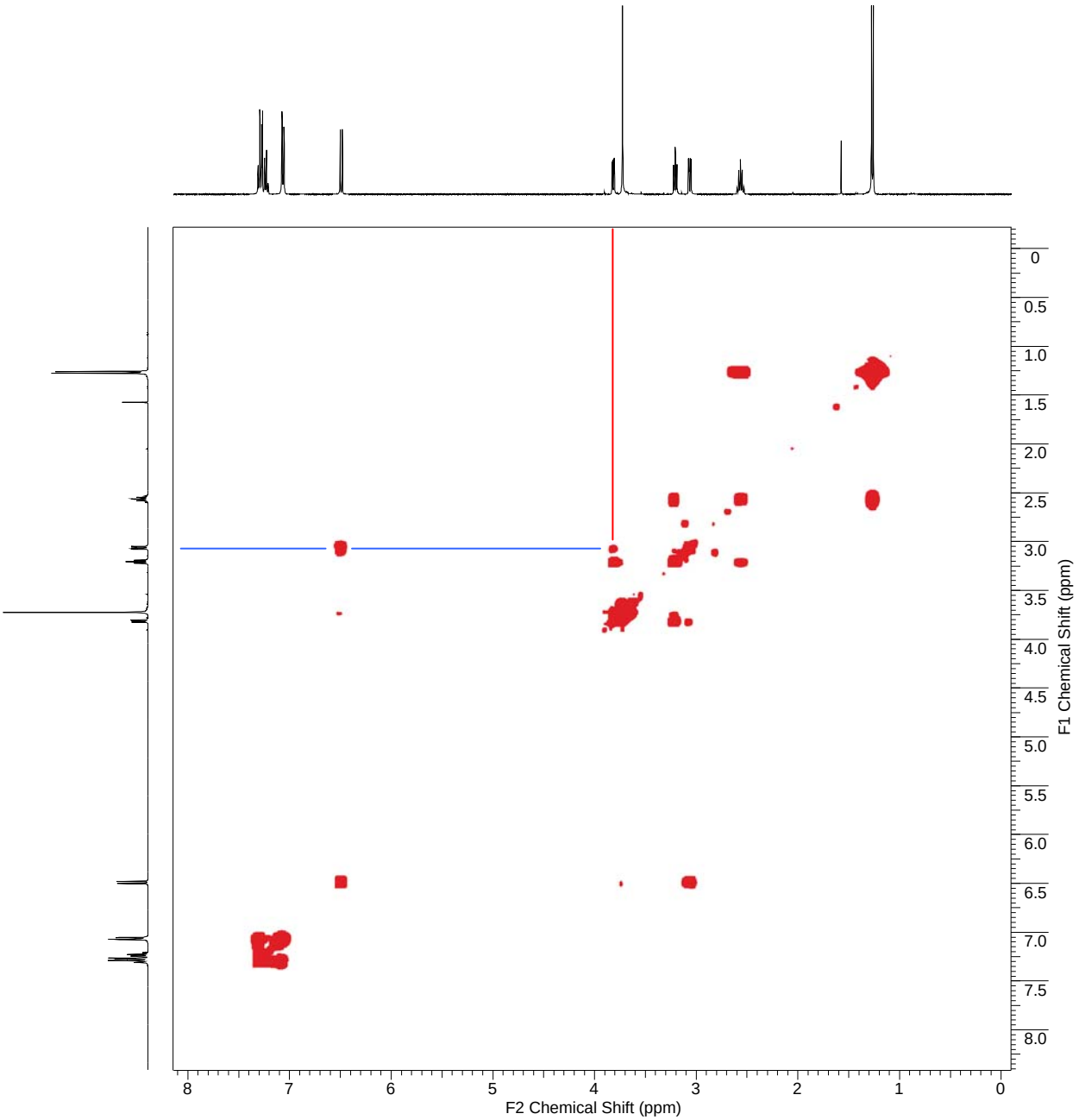


7 (±)

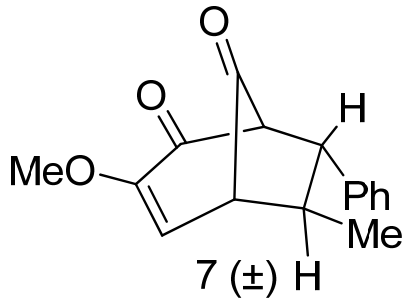
COSY (400 MHz, $CDCl_3$)

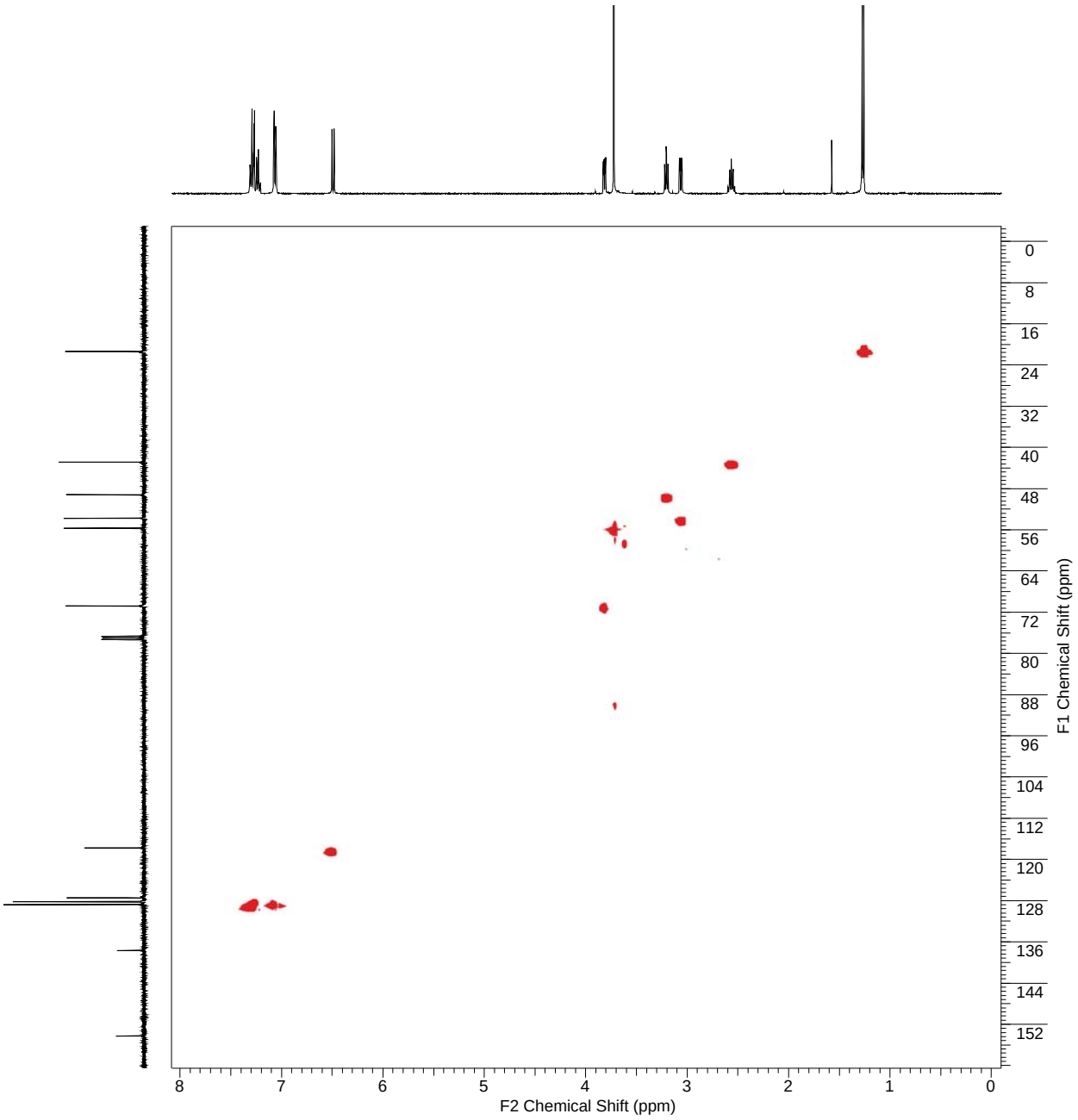


7 (±)

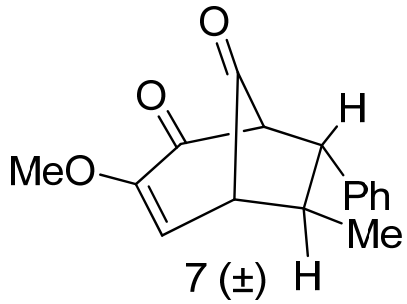


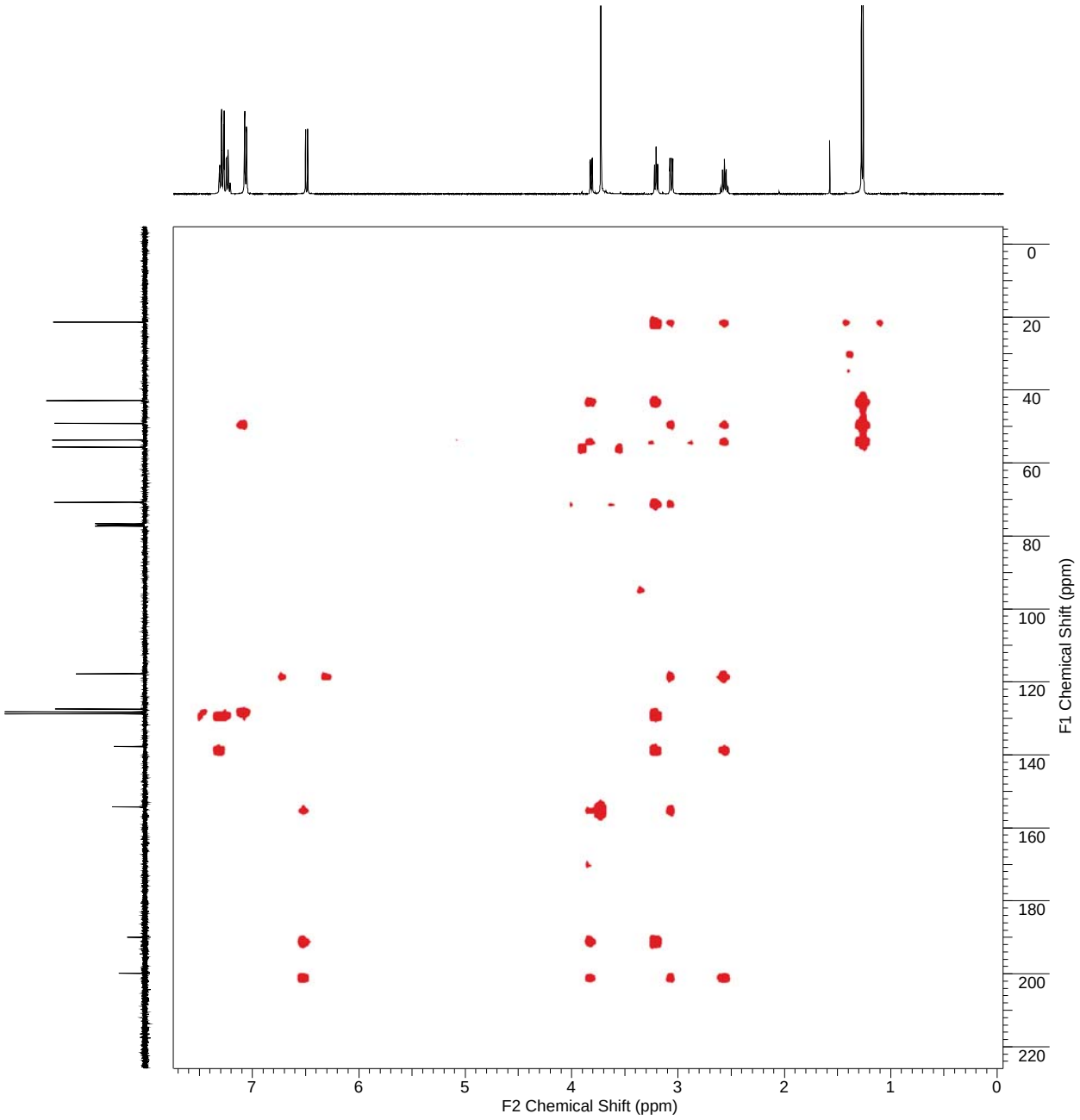
HMQC (100 MHz, $CDCl_3$)



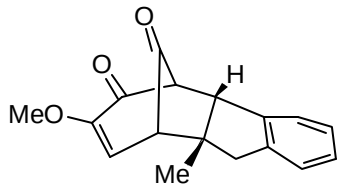


HMBC (100 MHz, $CDCl_3$)



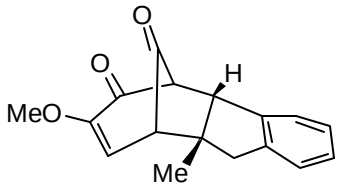


^{1}H NMR (400 MHz, $CDCl_3$)



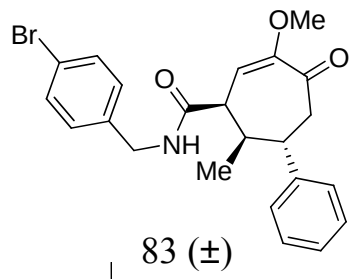
9 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



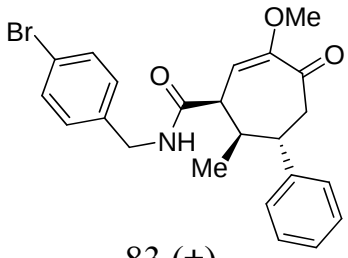
9 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



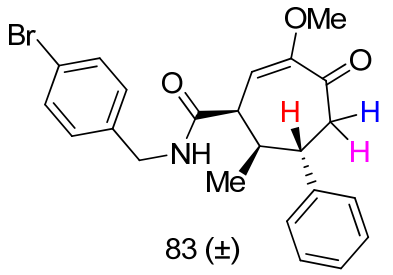
83 (±)

^{13}C NMR (100 MHz, $CDCl_3$)

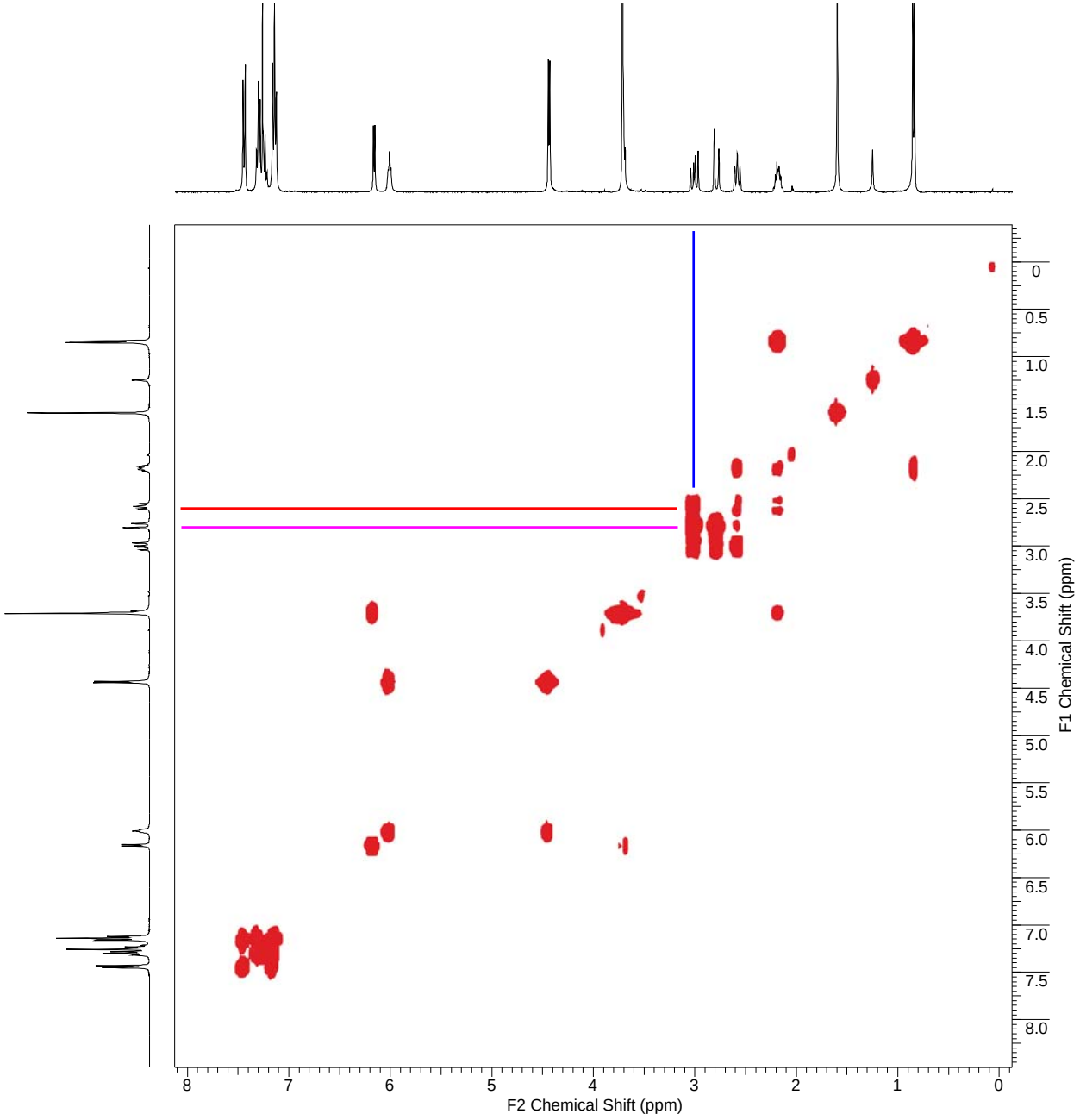


83 (±)

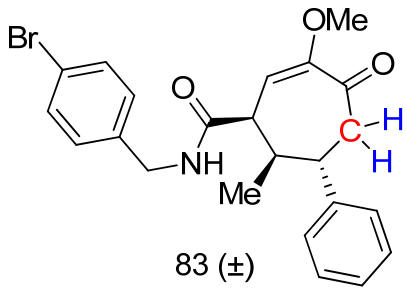
COSY (400 MHz, $CDCl_3$)



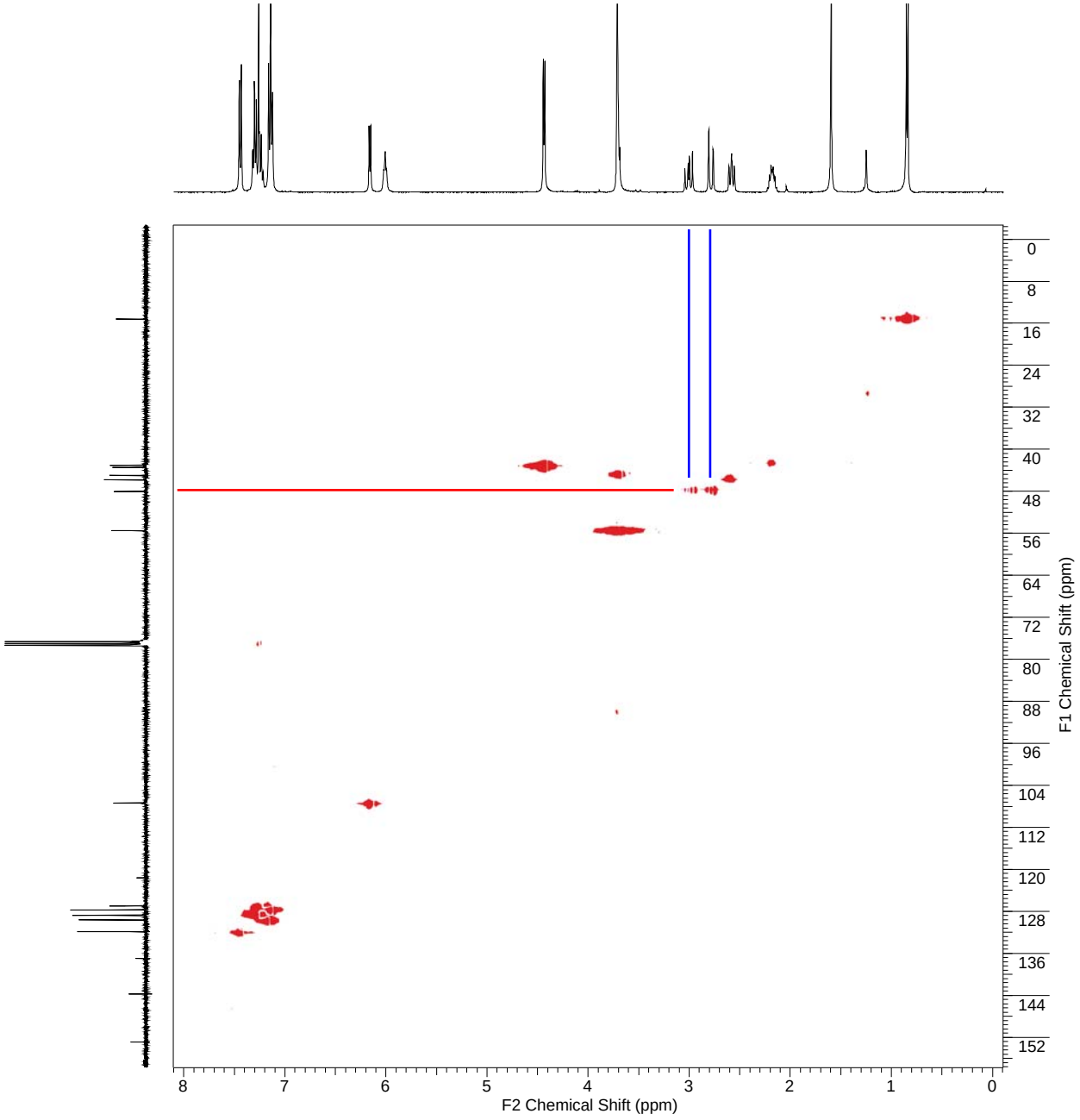
83 (±)



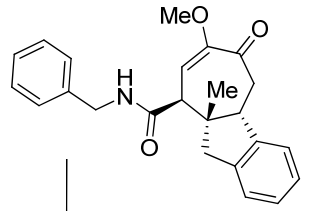
HMQC (100 MHz, $CDCl_3$)



83 (±)

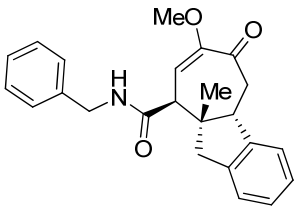


^{1}H NMR (400 MHz, $CDCl_3$)



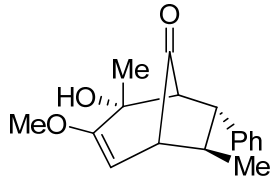
84 (±)

^{13}C NMR (101 MHz, $CDCl_3$)



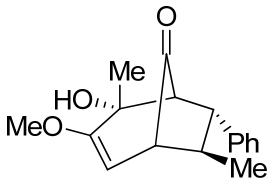
84 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



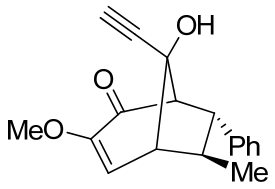
100 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



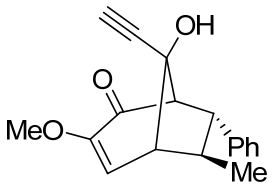
100 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



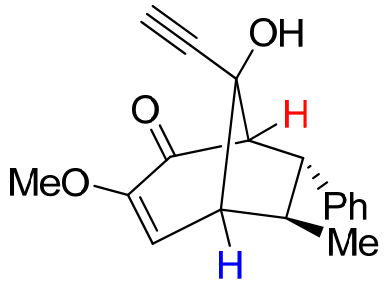
104 (±)

^{13}C NMR (100 MHz, $CDCl_3$)

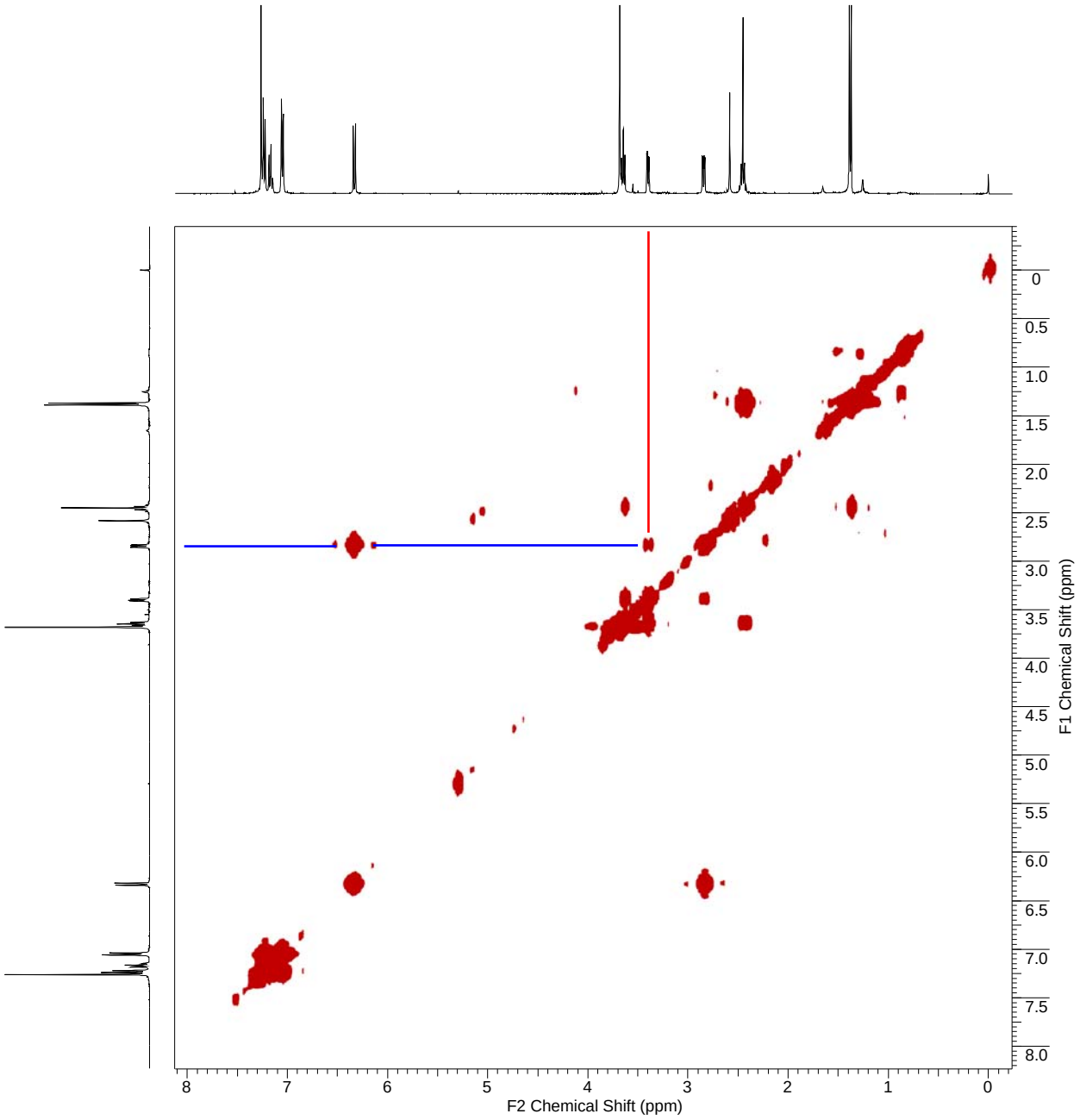


104 (±)

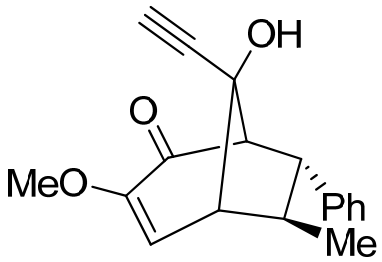
COSY (400 MHz, $CDCl_3$)



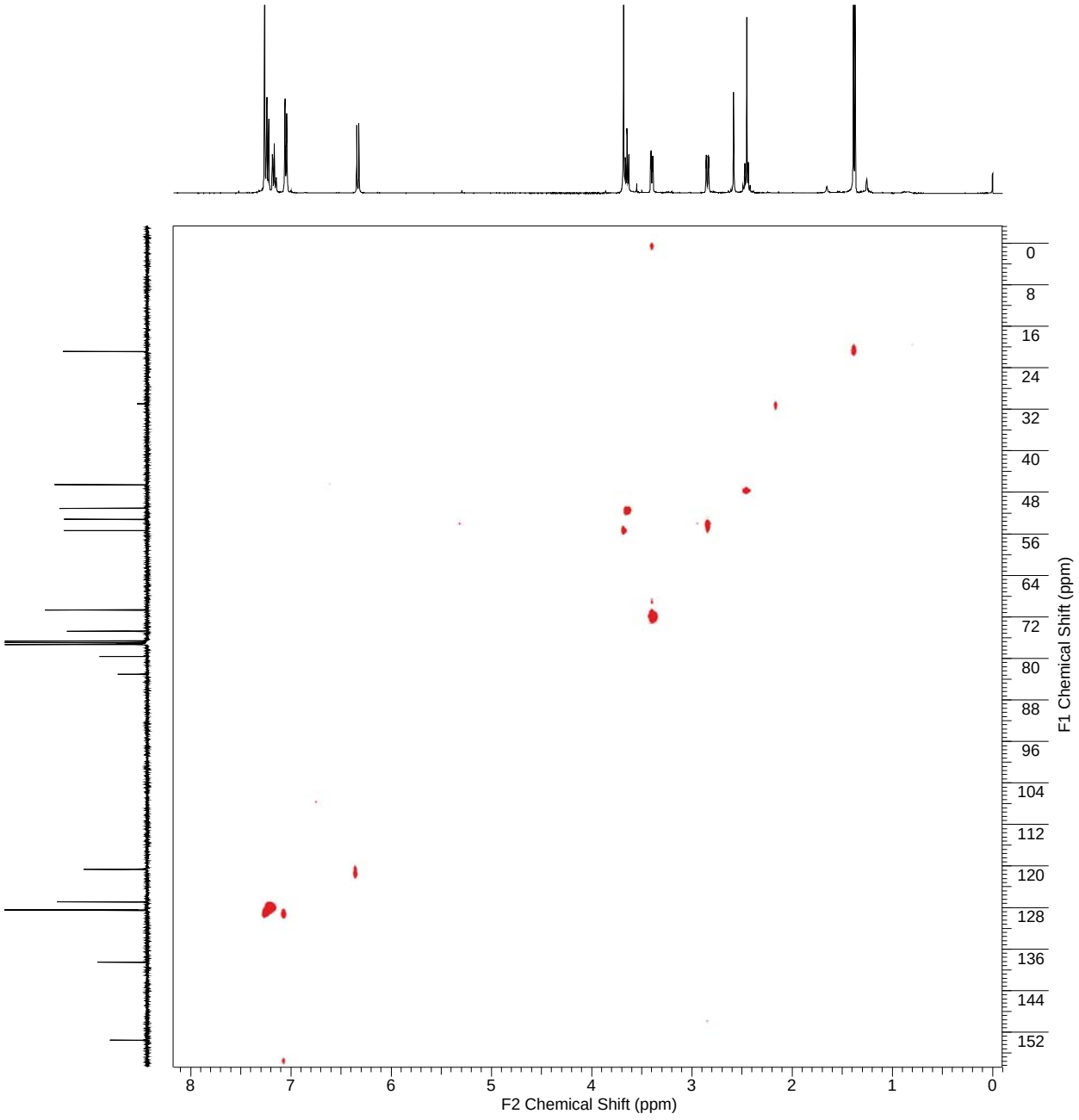
104 (±)



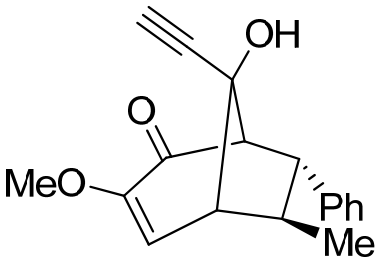
HMQC (100 MHz, $CDCl_3$)



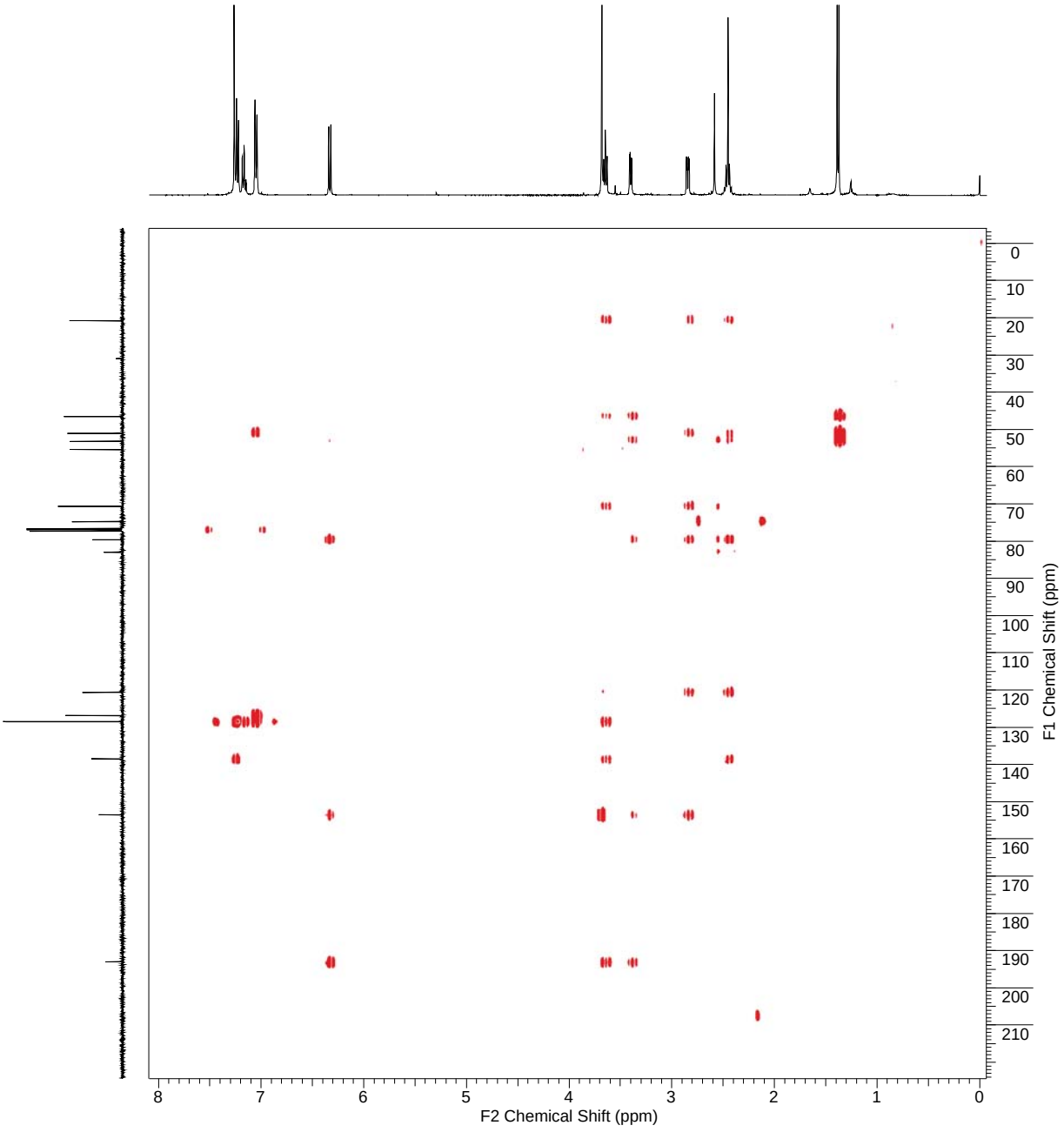
104 (±)



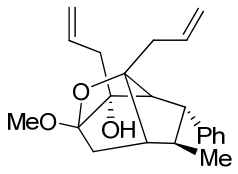
HMBC (100 MHz, $CDCl_3$)



104 (±)

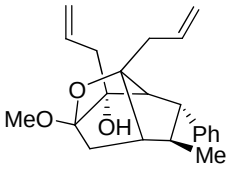


^{1}H NMR (400 MHz, $CDCl_3$)



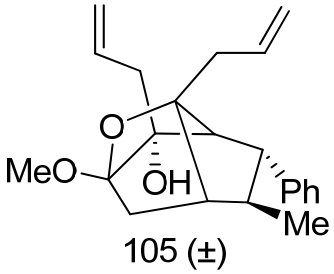
105 (±)

^{13}C NMR (100 MHz, $CDCl_3$)

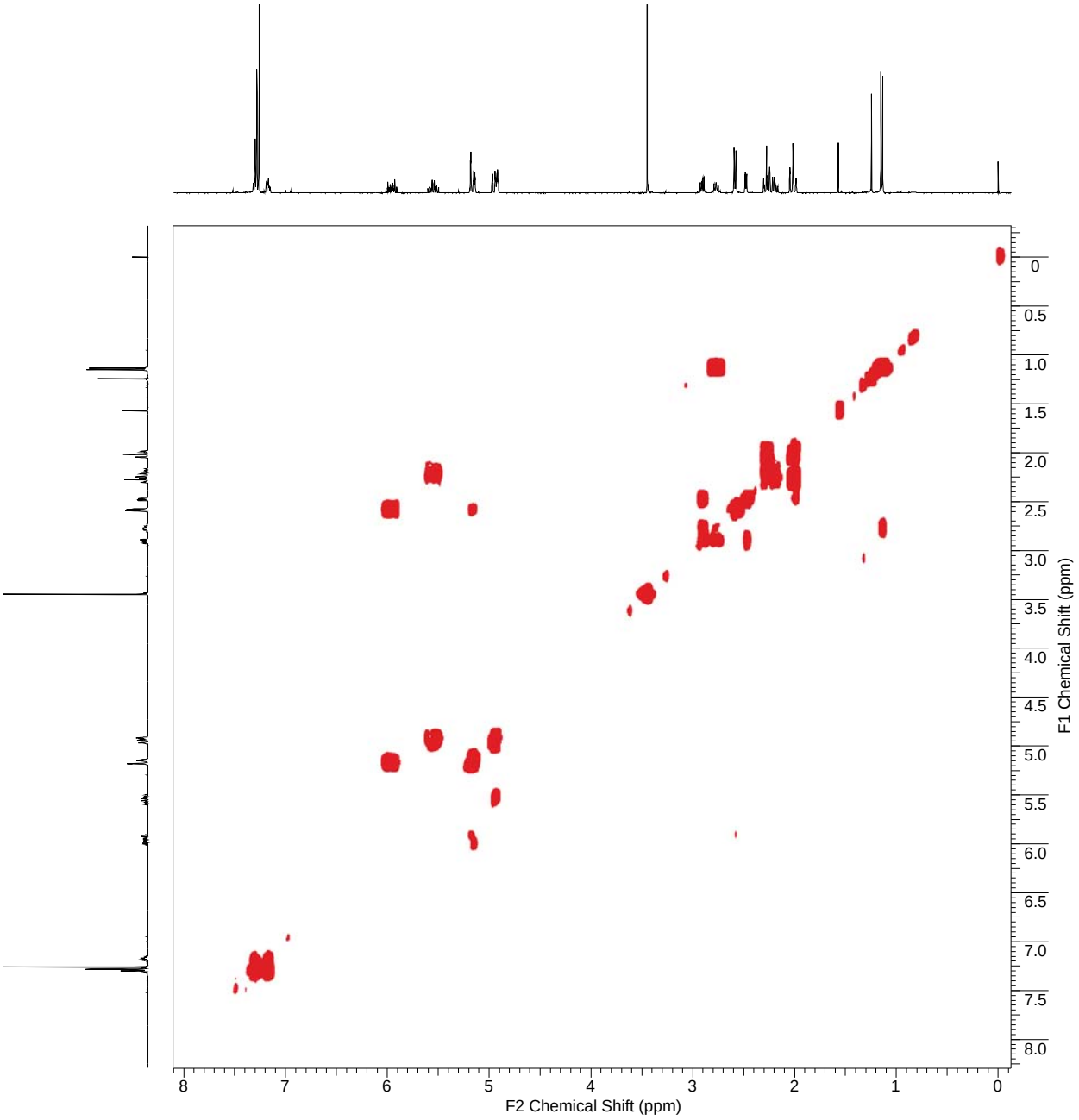


105 (±)

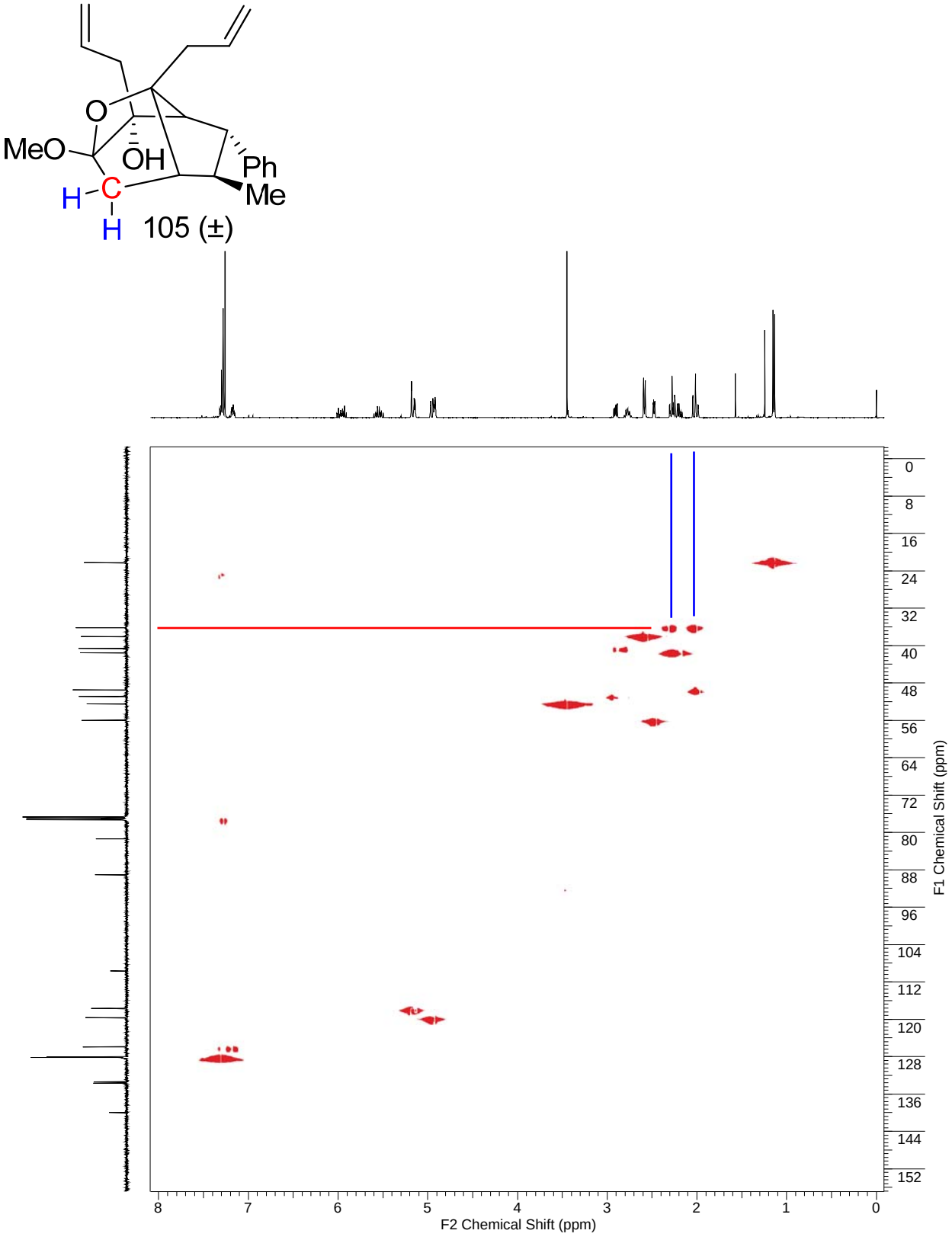
COSY (400 MHz, $CDCl_3$)



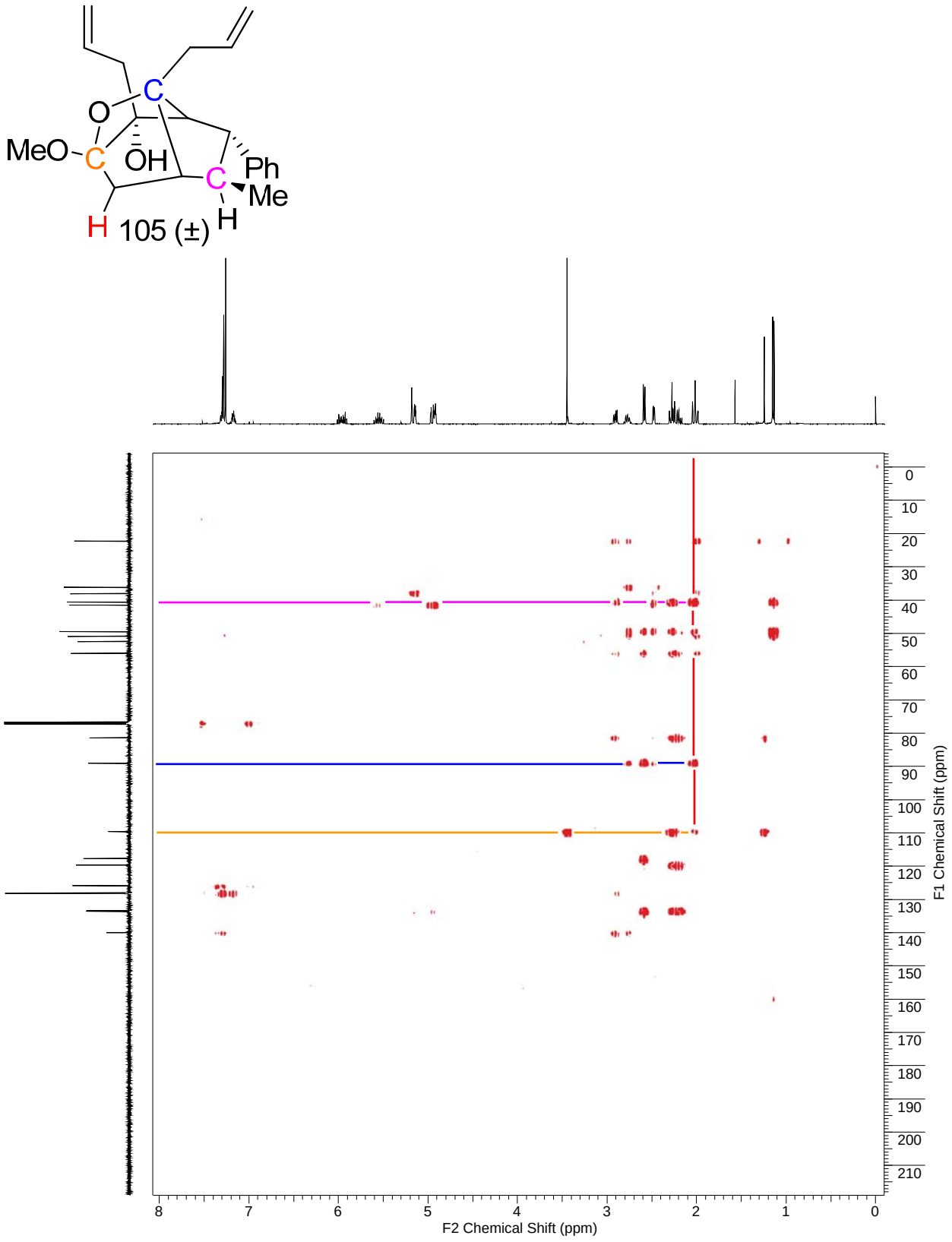
105 (±)



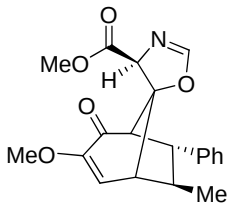
HMQC (100 MHz, $CDCl_3$)



HMBC (100 MHz, $CDCl_3$)

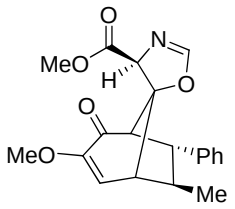


^{1}H NMR (400 MHz, $CDCl_3$)



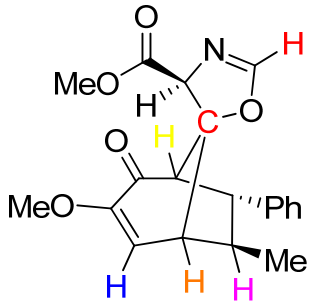
108 (±)

^{13}C NMR (101 MHz, $CDCl_3$)

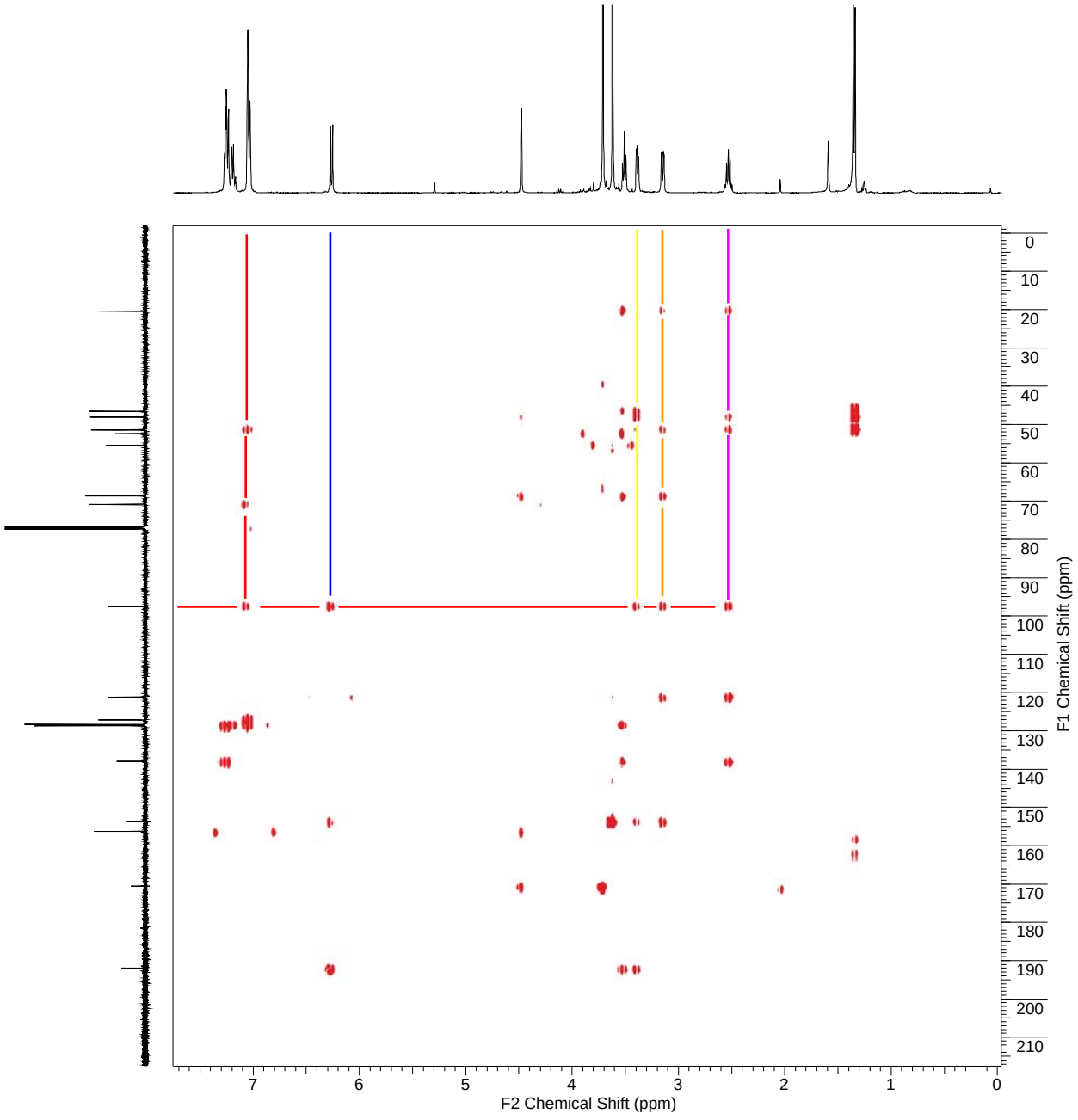


108 (±)

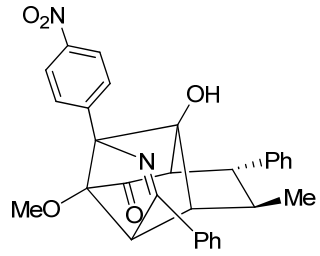
HMBC (100 MHz, $CDCl_3$)



108 (±)

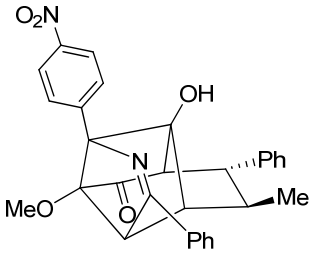


^{1}H NMR (400 MHz, $CDCl_3$)



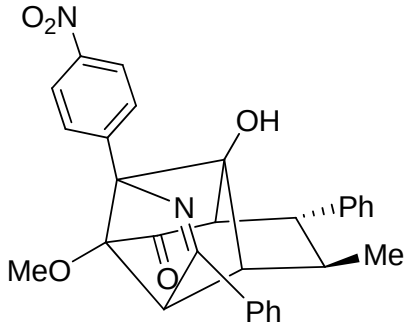
113 (±)

^{13}C NMR (101 MHz, $CDCl_3$)

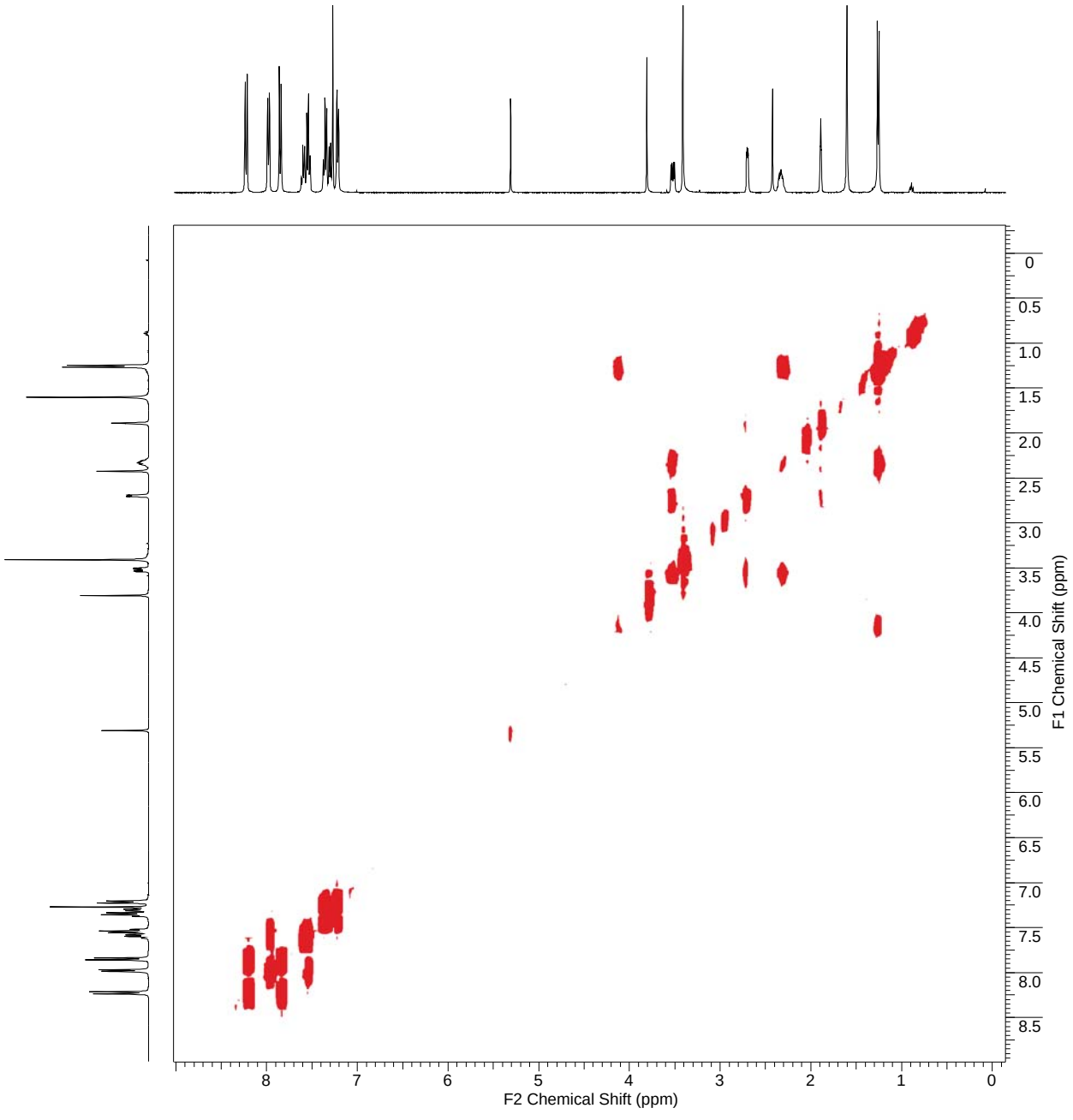


113 (±)

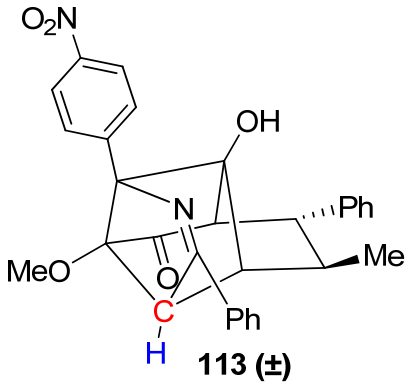
COSY (400 MHz, $CDCl_3$)



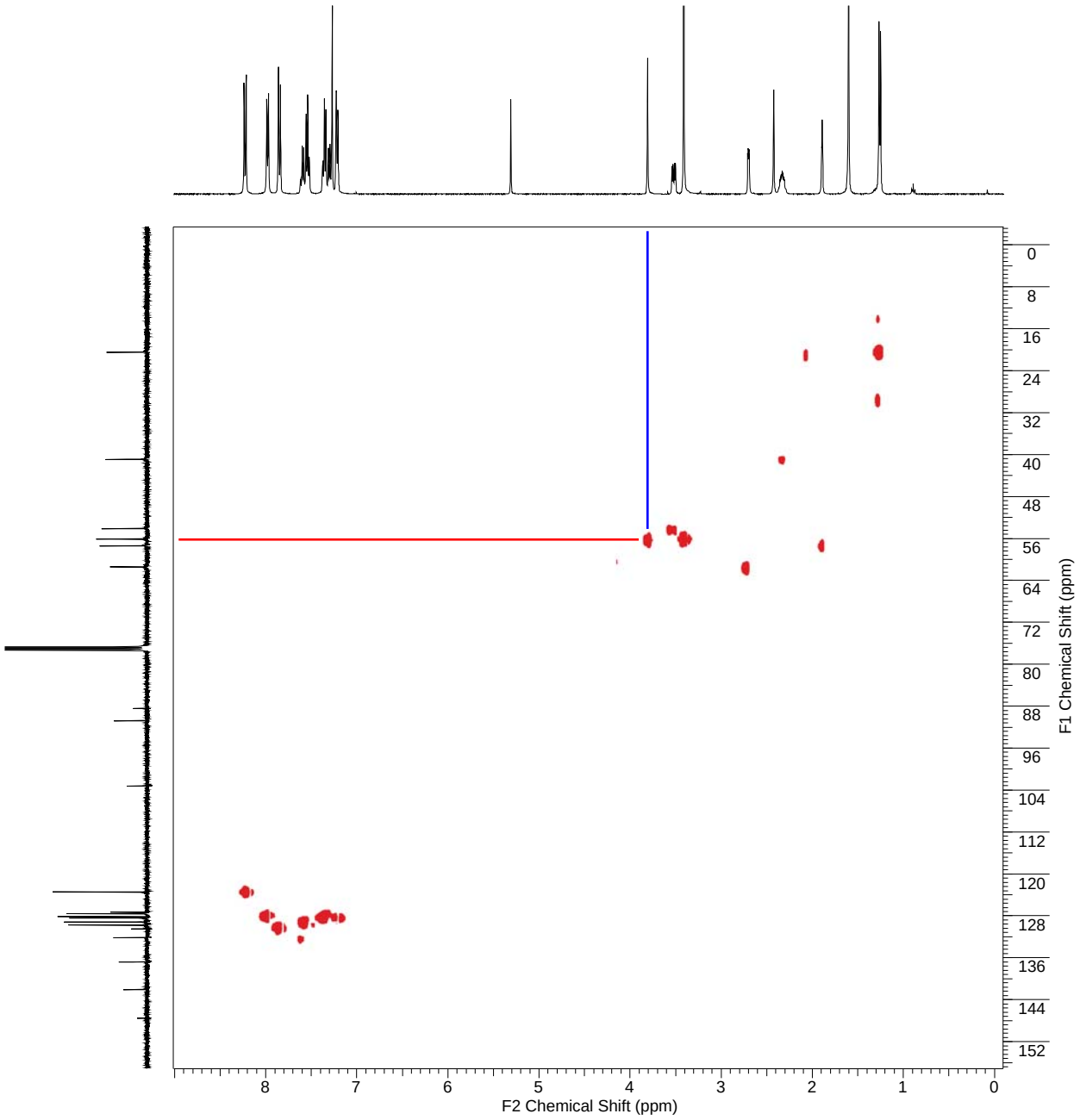
113 (±)



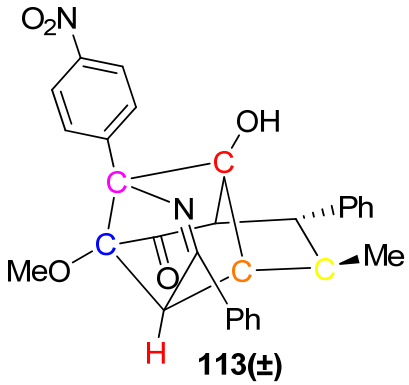
HMQC (100 MHz, $CDCl_3$)



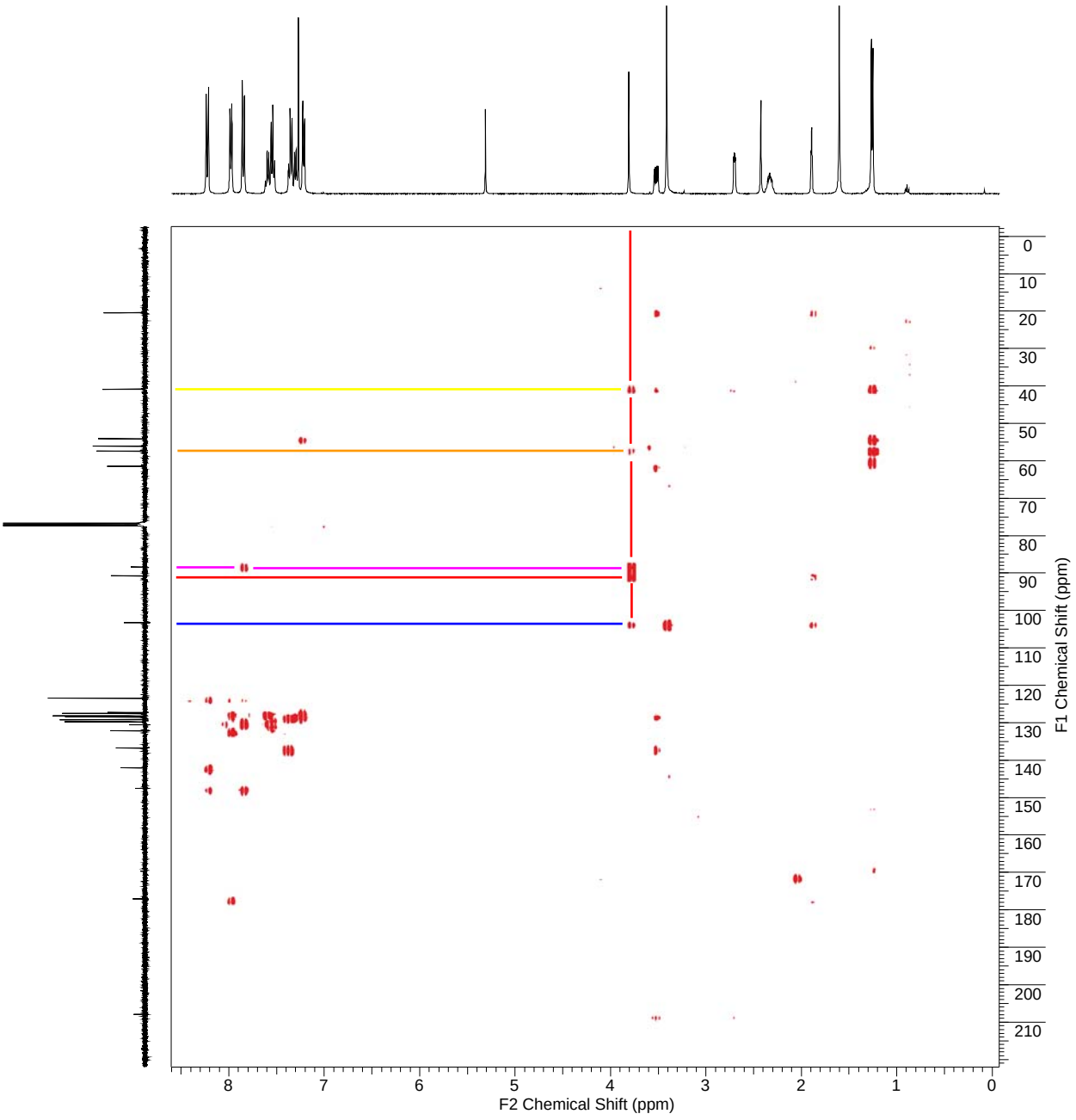
113 (±)



HMBC (100 MHz, $CDCl_3$)

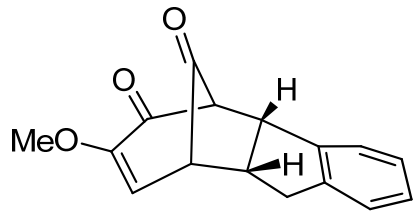


113(±)



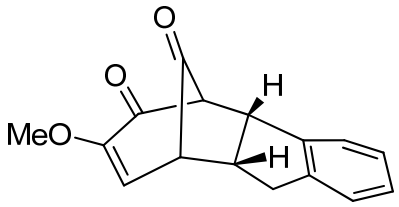
VI. Additional NMR Spectra

^{1}H NMR (400 MHz, $CDCl_3$)



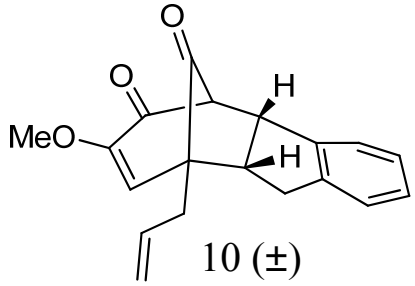
8 (±)

^{13}C NMR (100 MHz, $CDCl_3$)

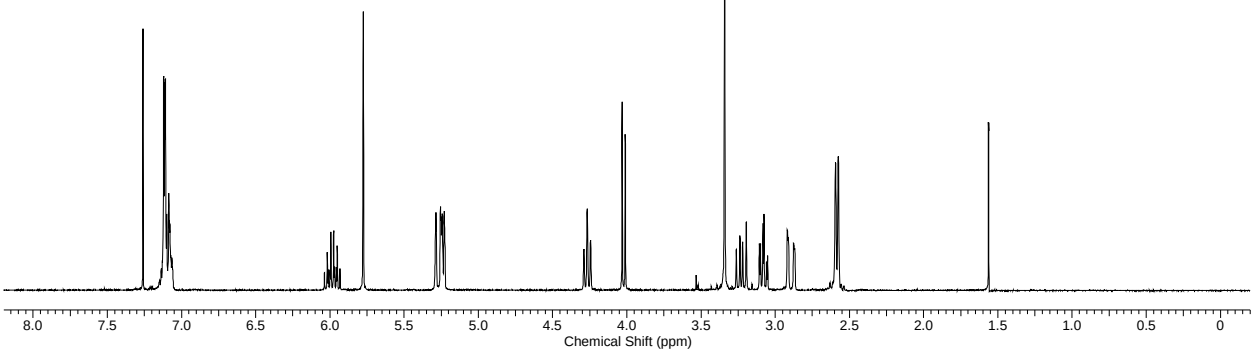


8 (±)

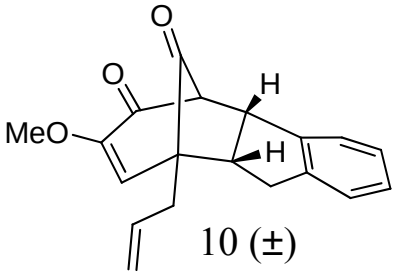
^{1}H NMR (400 MHz, $CDCl_3$)



10 (±)

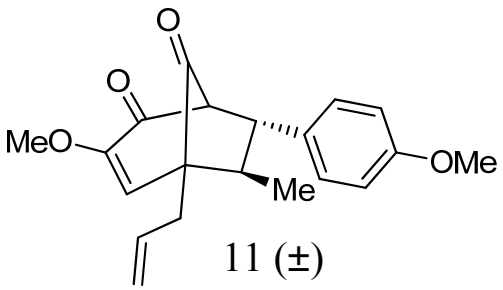


^{13}C NMR (100 MHz, $CDCl_3$)



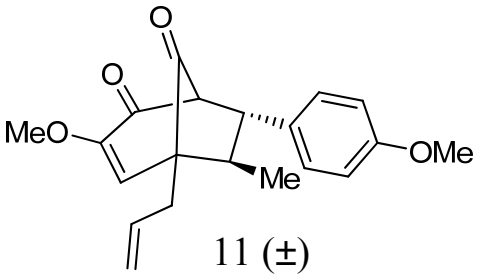
10 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



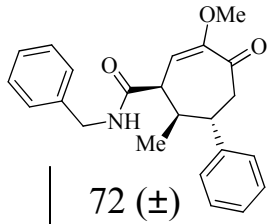
11 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



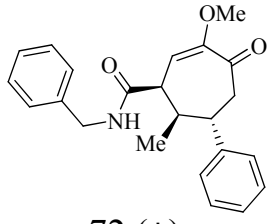
11 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



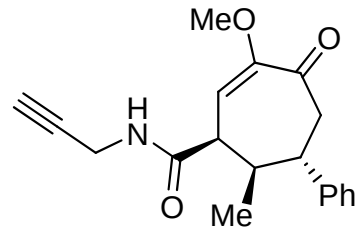
72 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



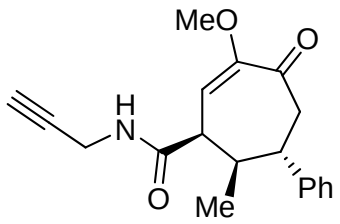
72 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



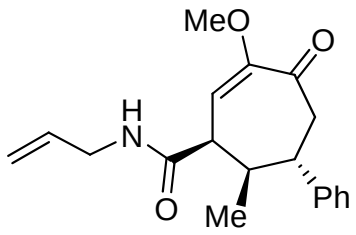
73 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



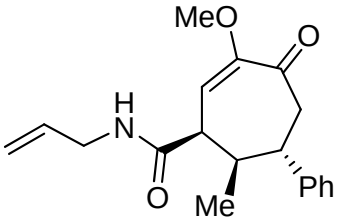
73 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



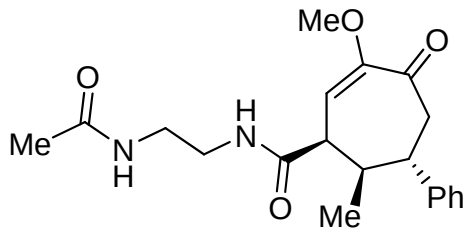
74 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



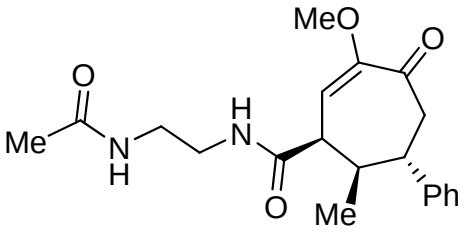
74 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



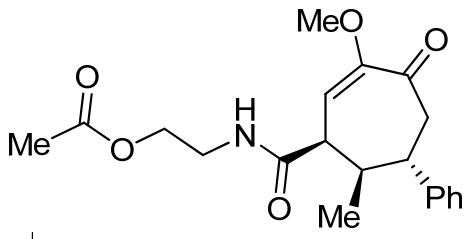
75 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



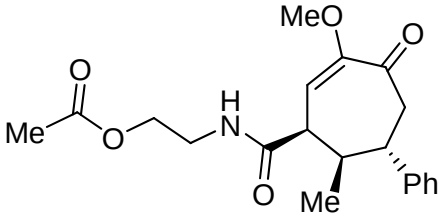
75 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



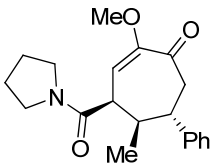
76 (±)

^{13}C NMR (100 MHz, $CDCl_3$)

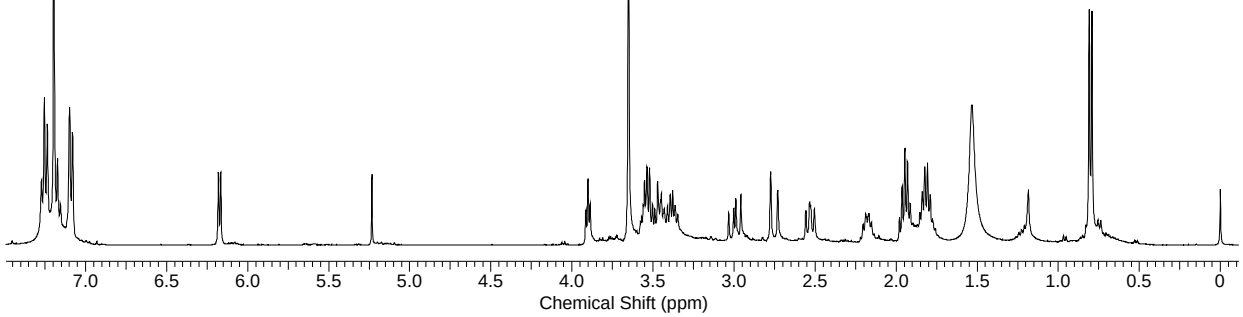


76

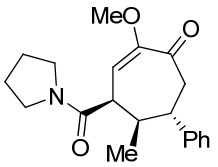
^{1}H NMR (400 MHz, $CDCl_3$)



77

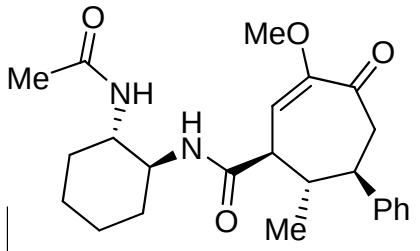


^{13}C NMR (100 MHz, $CDCl_3$)



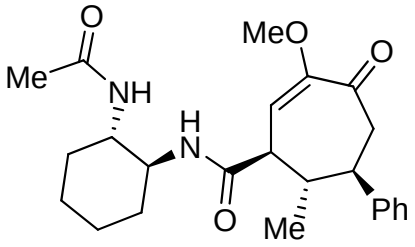
77

^{1}H NMR (400 MHz, $CDCl_3$)

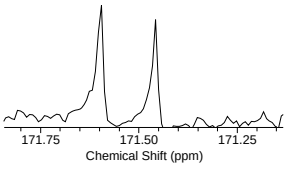


78 (±)

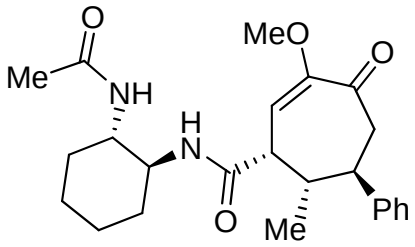
^{13}C NMR (100 MHz, $CDCl_3$)



78 (±)

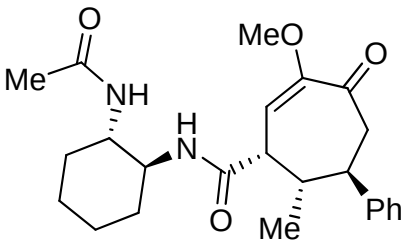


^{1}H NMR (400 MHz, $CDCl_3$)



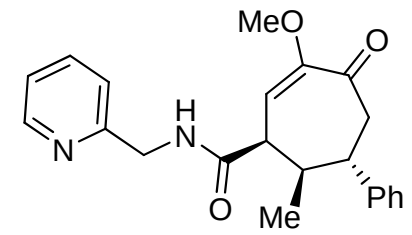
79 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



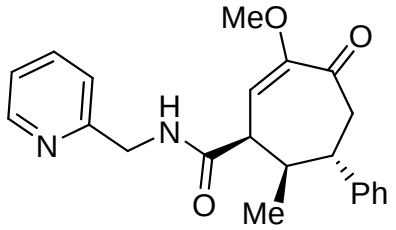
79 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



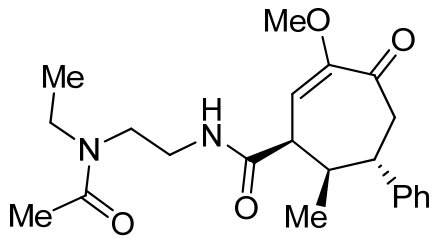
80 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



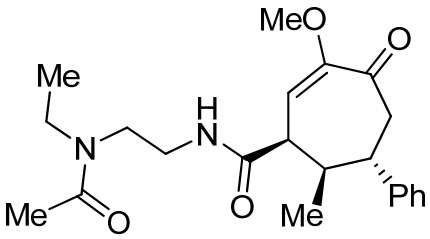
80 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



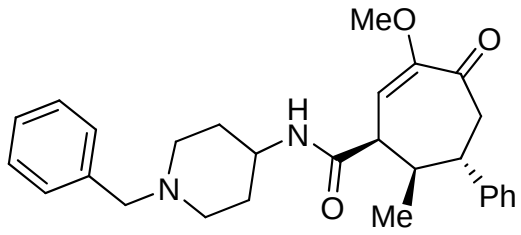
81 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



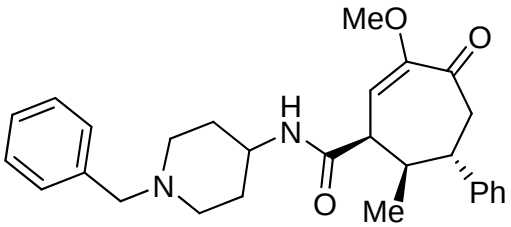
81 (±)

^{1}H NMR (400 MHz, $CDCl_3$)

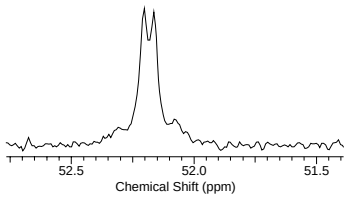


82 (±)

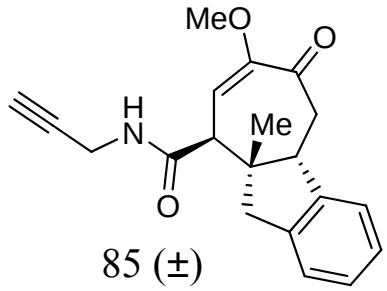
^{13}C NMR (100 MHz, $CDCl_3$)



82

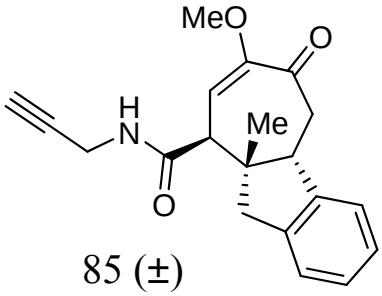


^{1}H NMR (400 MHz, $CDCl_3$)



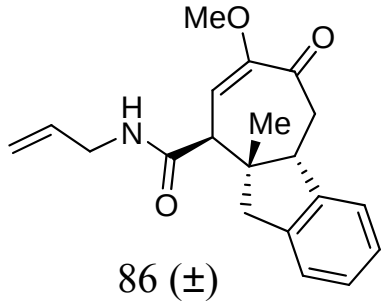
85 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



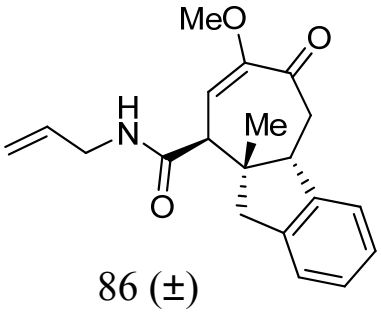
85 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



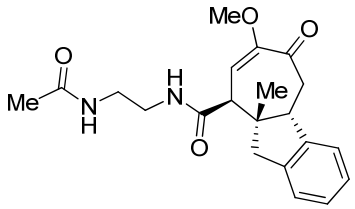
86 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



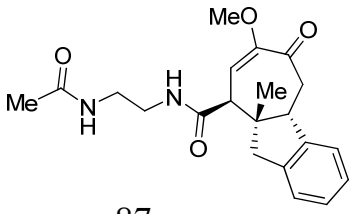
86 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



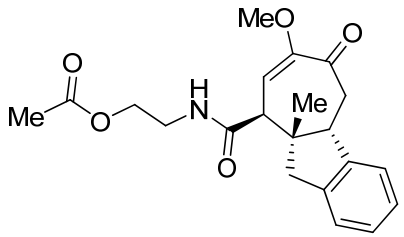
87

^{13}C NMR (100 MHz, $CDCl_3$)



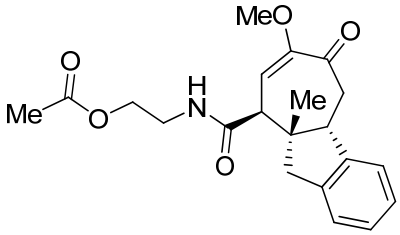
87

^{1}H NMR (400 MHz, $CDCl_3$)



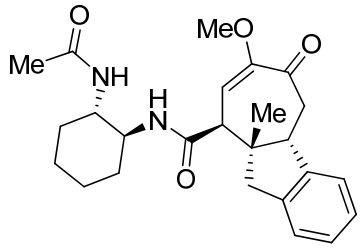
88 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



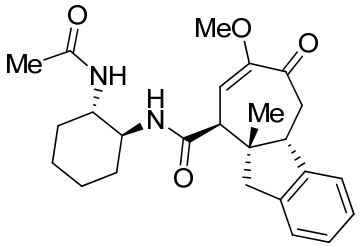
88 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



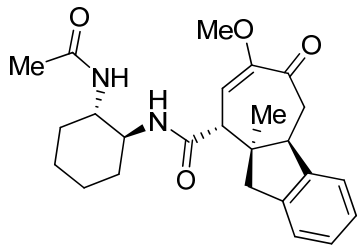
89 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



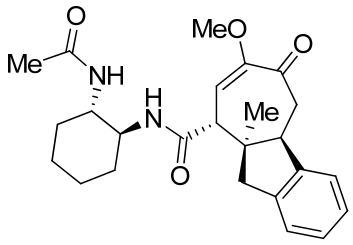
89 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



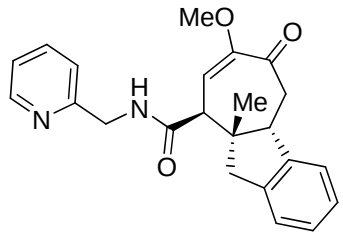
90 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



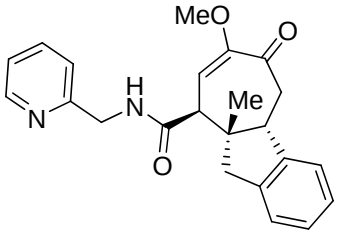
90

^{1}H NMR (400 MHz, $CDCl_3$)



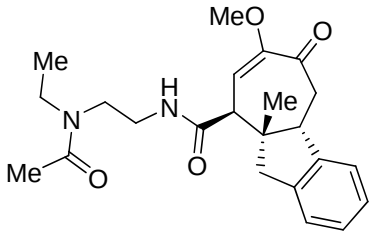
91 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



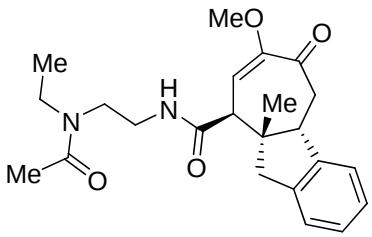
91 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



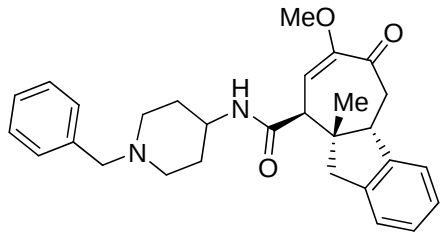
92 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



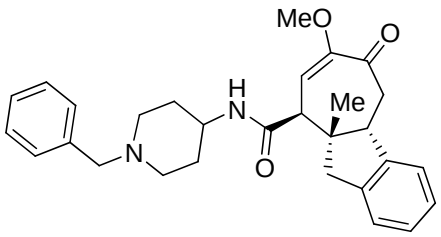
92 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



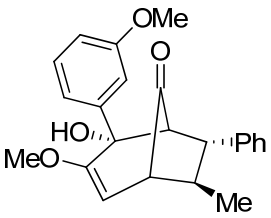
93 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



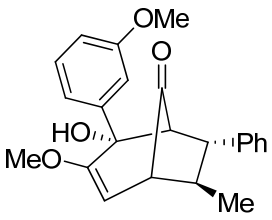
93 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



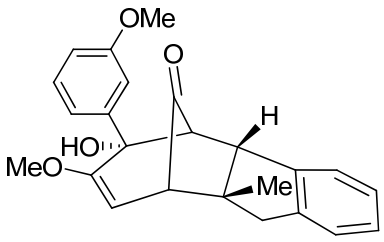
98 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



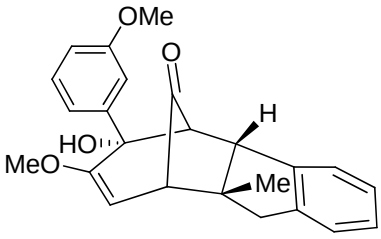
98 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



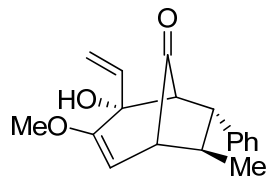
99 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



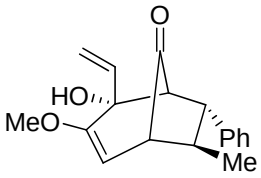
99 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



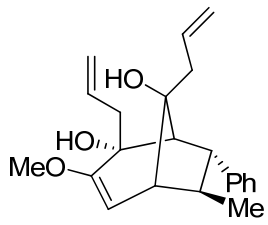
101 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



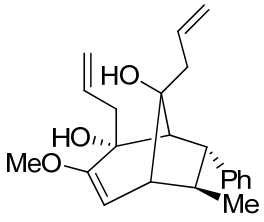
101 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



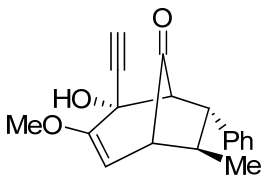
102 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



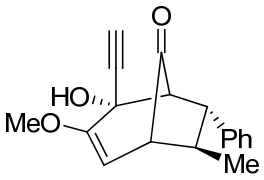
102 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



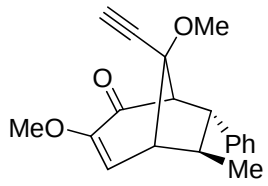
103 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



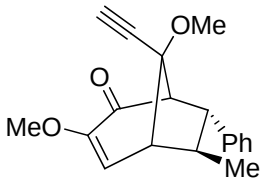
103 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



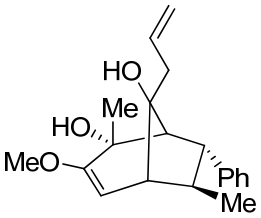
104b (±)

^{13}C NMR (100 MHz, $CDCl_3$)



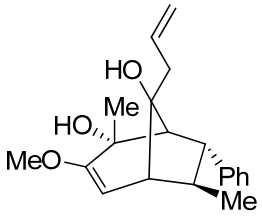
104b (±)

^{1}H NMR (400 MHz, $CDCl_3$)



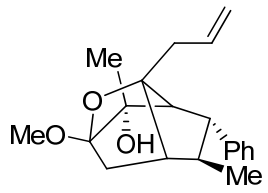
106 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



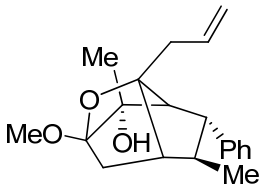
106 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



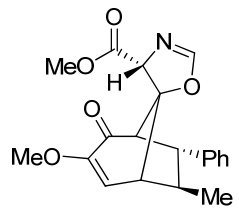
107 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



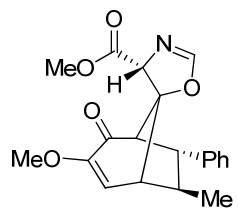
107 (±)

^{1}H NMR (400 MHz, $CDCl_3$)



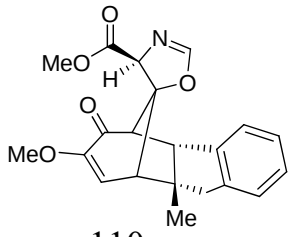
109

^{13}C NMR (100 MHz, $CDCl_3$)



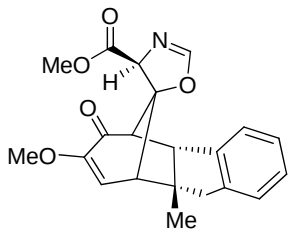
109

^{1}H NMR (400 MHz, $CDCl_3$)



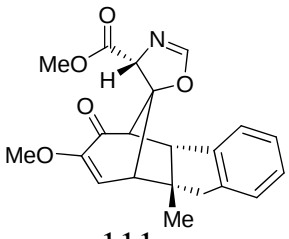
110

^{13}C NMR (100 MHz, $CDCl_3$)



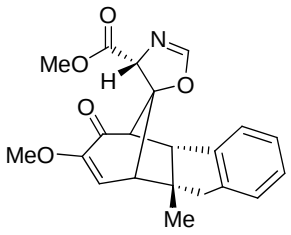
110

^{1}H NMR (400 MHz, $CDCl_3$)



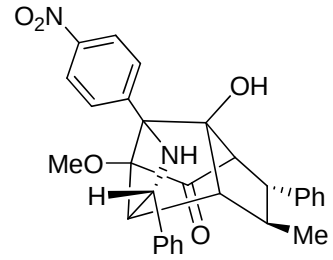
111

^{13}C NMR (100 MHz, $CDCl_3$)



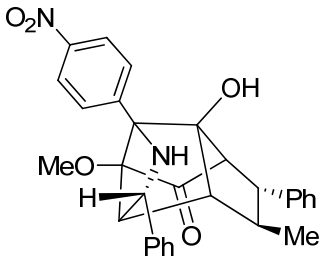
111

^{1}H NMR (400 MHz, $CDCl_3$)



114 (±)

^{13}C NMR (100 MHz, $CDCl_3$)



114 (±)

VII. *Ab initio* Modeling (Compounds 72, 77, and 82)

Conformational analysis (Molecular Operating Enviroment, MOE version 2005) followed by *ab initio* (B3LYP, 6-31g*) minimization (Chem3D, Games interface) of both possible diastereomers of amides **72, 77,** and **82** was performed to identify thermodynamically favored products. These results indicated that the major diastereomers (*syn* product) are thermodynamically favored by approximately 1-2 kcal/mol (Table A1). The ground state models also indicate that the weakly acidic α-amide hydrogen is not oriented with optimal geometry with the carbonyl for proton extraction (*syn* dihedral, Table S2, Figure S11).

Table S2. *Ab initio* results for amides **72**, **77**, and **82**.

compound	R	ΔE (*syn* - *anti*) (kcal)	*syn* dihedral (ϕ)
72	benzyl	-0.94	-167 ^{o}
77	pyrrolidine	-1.74	-177 ^{o}
82	N-benzyl-4-aminopiperidine	-0.76	-158 ^{o}

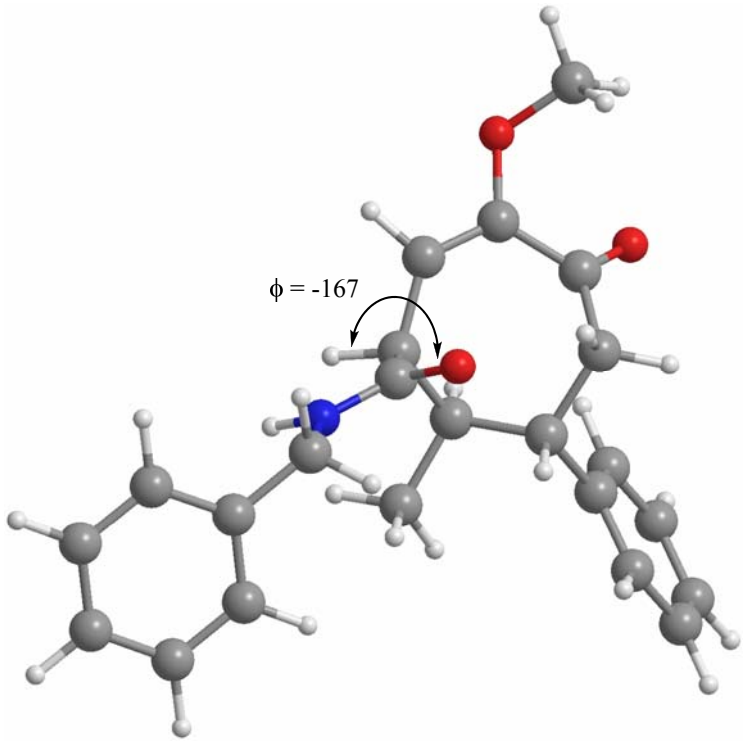


Figure S11. Minimized structure of compound **72** (*syn* product) illustrating dihedral of weakly acidic α-amide hydrogen

VIII. X-ray Crystallographic Data (Compounds 7, 83, 89, 100, and 113)

X-ray Crystal Structure of Compound 7:

Crystals of compound **7** suitable for x-ray analysis were obtained by dissolving the residue in a minimal amount of ethyl acetate and adding hexane very carefully as to produce two layers; the product crystallized as the layers diffused. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC # 725197). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)-1223-336-033;e-mail: deposit@ccdc.cam.ac.uk.

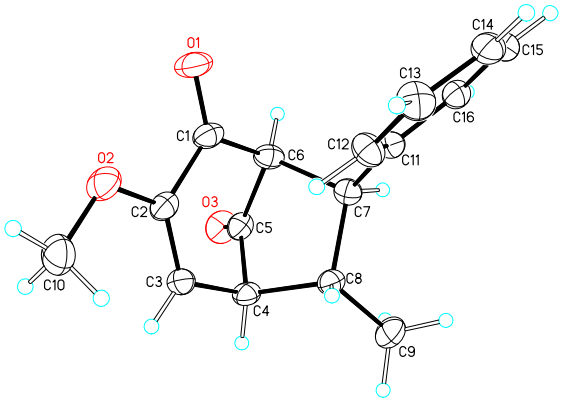


Table 1. Crystal data and structure refinement for **compound 7**.

Identification code	**compound 7**	
Empirical formula	C16 H16 O3	
Formula weight	256.29	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.5607(3) Å	α= 90°.
	b = 10.2164(5) Å	β= 90°.
	c = 17.0611(8) Å	γ = 90°.
Volume	1317.85(10) $Å^3$	
Z	4	
Density (calculated)	1.292 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	544	
Crystal size	0.60 x 0.50 x 0.30 mm^3	
Theta range for data collection	2.32 to 28.27°.	
Index ranges	-9<=h<=10, -13<=k<=10, -22<=l<=22	
Reflections collected	13655	

Independent reflections	1887 [R(int) = 0.0277]
Completeness to theta = 28.27°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9739 and 0.9488
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1887 / 0 / 236
Goodness-of-fit on F^2	1.031
Final R indices [I>2sigma(I)]	R1 = 0.0296, wR2 = 0.0786
R indices (all data)	R1 = 0.0314, wR2 = 0.0799
Absolute structure parameter	-0.9(11)
Largest diff. peak and hole	0.231 and -0.173 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for compound **7**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	6046(1)	4699(1)	638(1)	35(1)
O(2)	7863(1)	2484(1)	827(1)	31(1)
O(3)	10724(1)	6238(1)	-502(1)	32(1)
C(1)	7648(2)	4771(1)	660(1)	24(1)
C(2)	8799(2)	3610(1)	752(1)	23(1)
C(3)	10569(2)	3731(1)	745(1)	23(1)
C(4)	11441(1)	5058(1)	708(1)	22(1)
C(5)	10333(2)	5843(1)	136(1)	23(1)
C(6)	8604(2)	6074(1)	579(1)	23(1)
C(7)	9388(2)	6576(1)	1374(1)	21(1)
C(8)	11165(2)	5816(1)	1491(1)	21(1)
C(9)	12701(2)	6730(1)	1671(1)	33(1)
C(10)	8873(2)	1332(1)	994(1)	35(1)
C(11)	8133(2)	6571(1)	2063(1)	22(1)
C(12)	7745(2)	5432(1)	2476(1)	26(1)
C(13)	6611(2)	5464(1)	3122(1)	32(1)
C(14)	5870(2)	6636(2)	3361(1)	31(1)
C(15)	6213(2)	7769(1)	2947(1)	29(1)
C(16)	7338(2)	7737(1)	2299(1)	25(1)

X-ray Crystal Structure of Compound 83:

Crystals of compound **83** suitable for x-ray analysis were obtained by dissolving the residue in a minimal amount of ethyl acetate and adding hexane very carefully as to produce two layers; the product crystallized as the layers diffused. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC # 725198). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)-1223-336-033;e-mail: deposit@ccdc.cam.ac.uk.

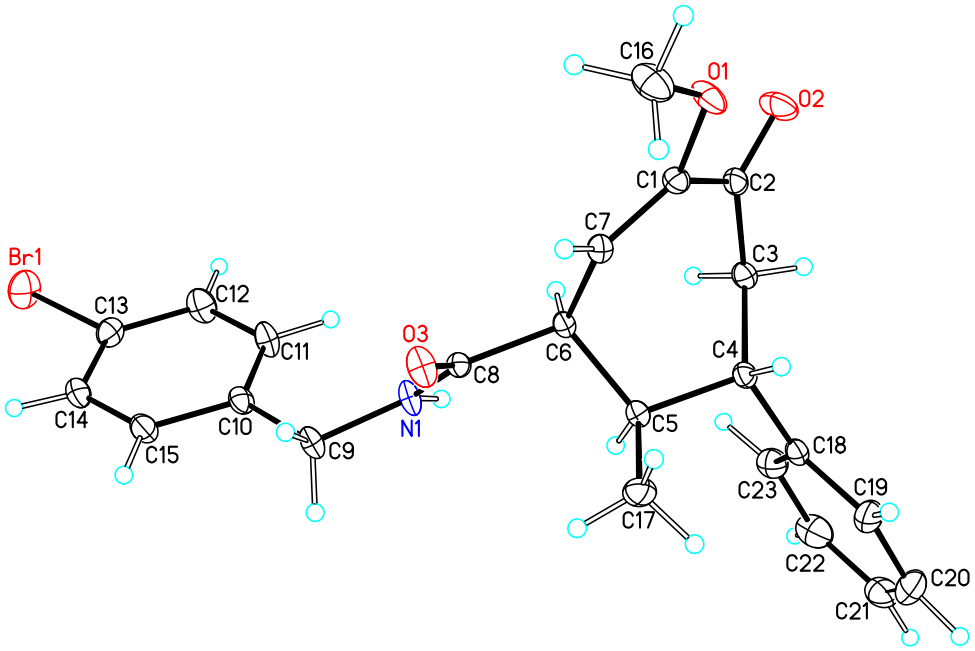


Table 1. Crystal data and structure refinement for **compound 83**.

Identification code	**compound 83**	
Empirical formula	C23 H24 Br N O3	
Formula weight	442.34	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 9.9135(4) Å	α= 90°.
	b = 17.8587(7) Å	β= 95.438(2)°.
	c = 11.2096(5) Å	γ = 90°.
Volume	1975.64(14) $Å^3$	
Z	4	
Density (calculated)	1.487 Mg/m^3	
Absorption coefficient	2.105 mm^{-1}	

F(000)	912
Crystal size	0.60 x 0.50 x 0.45 mm^3
Theta range for data collection	2.06 to 30.51°.
Index ranges	-14<=h<=14, -25<=k<=25, -16<=l<=15
Reflections collected	32437
Independent reflections	6017 [R(int) = 0.0313]
Completeness to theta = 30.51°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.4510 and 0.3648
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6017 / 0 / 349
Goodness-of-fit on F^2	1.039
Final R indices [I>2sigma(I)]	R1 = 0.0277, wR2 = 0.0688
R indices (all data)	R1 = 0.0380, wR2 = 0.0723
Largest diff. peak and hole	0.453 and -0.488 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **83**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	4095(1)	770(1)	7172(1)	26(1)
O(1)	9884(1)	2184(1)	16419(1)	20(1)
O(2)	10911(1)	3287(1)	15269(1)	23(1)
O(3)	9157(1)	97(1)	13504(1)	19(1)
N(1)	9436(1)	597(1)	11688(1)	15(1)
C(1)	10298(1)	2019(1)	15315(1)	14(1)
C(2)	11051(1)	2663(1)	14864(1)	14(1)
C(3)	12052(1)	2537(1)	13938(1)	14(1)
C(4)	12783(1)	1774(1)	14001(1)	13(1)
C(5)	11938(1)	1131(1)	13370(1)	12(1)
C(6)	10399(1)	1257(1)	13452(1)	12(1)
C(7)	10050(1)	1380(1)	14713(1)	13(1)
C(8)	9599(1)	592(1)	12898(1)	12(1)
C(9)	8752(1)	-17(1)	11030(1)	16(1)
C(10)	7653(1)	218(1)	10077(1)	15(1)

C(11)	7416(1)	953(1)	9710(1)	20(1)
C(12)	6364(1)	1131(1)	8842(1)	21(1)
C(13)	5555(1)	562(1)	8345(1)	17(1)
C(14)	5772(1)	-178(1)	8679(1)	18(1)
C(15)	6821(1)	-342(1)	9545(1)	17(1)
C(16)	9130(1)	1616(1)	16958(1)	24(1)
C(17)	12418(1)	371(1)	13870(1)	19(1)
C(18)	14134(1)	1823(1)	13471(1)	15(1)
C(19)	15296(1)	1521(1)	14071(1)	23(1)
C(20)	16525(1)	1534(1)	13559(1)	31(1)
C(21)	16599(1)	1853(1)	12447(1)	29(1)
C(22)	15453(1)	2155(1)	11838(1)	26(1)
C(23)	14225(1)	2140(1)	12344(1)	20(1)

X-ray Crystal Structure of Compound 89:

Crystals of compound **89** suitable for x-ray analysis were obtained by dissolving the residue in a minimal amount of methylene chloride and adding hexane very carefully as to produce two layers; the product crystallized as the layers diffused. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC # 725200). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)-1223-336-033;e-mail: deposit@ccdc.cam.ac.uk.

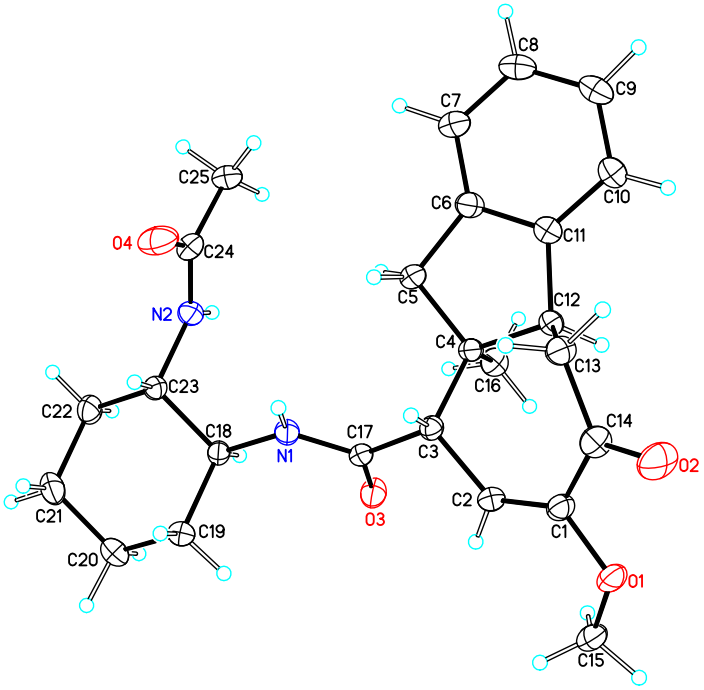


Table 1. Crystal data and structure refinement for **compound 89**.

Identification code	**compound 89**	
Empirical formula	C25 H36 N2 O6	
Formula weight	460.56	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.9036(3) Å	α= 90°.
	b = 12.6996(4) Å	β= 90°.
	c = 21.5174(8) Å	γ = 90°.
Volume	2433.02(14) $Å^3$	
Z	4	
Density (calculated)	1.257 Mg/m^3	
Absorption coefficient	0.089 mm^{-1}	

F(000)	992
Crystal size	0.35 x 0.30 x 0.25 mm^3
Theta range for data collection	1.86 to 30.51°.
Index ranges	-11<=h<=12, -12<=k<=18, -29<=l<=30
Reflections collected	18837
Independent reflections	4151 [R(int) = 0.0443]
Completeness to theta = 30.51°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9780 and 0.9694
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4151 / 0 / 442
Goodness-of-fit on F^2	1.025
Final R indices [I>2sigma(I)]	R1 = 0.0403, wR2 = 0.0952
R indices (all data)	R1 = 0.0520, wR2 = 0.1010
Absolute structure parameter	?
Largest diff. peak and hole	0.246 and -0.195 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **89**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	-3922(1)	-2475(1)	-2395(1)	25(1)
O(2)	-2303(2)	-1214(1)	-1741(1)	37(1)
O(3)	-3490(1)	-6119(1)	-1637(1)	24(1)
O(4)	1969(1)	-6885(1)	-179(1)	35(1)
N(1)	-1042(1)	-6253(1)	-1390(1)	18(1)
N(2)	-225(1)	-7675(1)	-419(1)	20(1)
C(1)	-3142(2)	-2927(1)	-1920(1)	21(1)
C(2)	-3094(2)	-3963(1)	-1819(1)	19(1)
C(3)	-2213(2)	-4532(1)	-1326(1)	17(1)
C(4)	-2772(2)	-4293(1)	-657(1)	17(1)
C(5)	-1670(2)	-4739(1)	-168(1)	23(1)
C(6)	-1781(2)	-3968(1)	362(1)	22(1)
C(7)	-1356(2)	-4090(1)	977(1)	28(1)
C(8)	-1570(2)	-3258(1)	1388(1)	30(1)

C(9)	-2185(2)	-2321(1)	1185(1)	28(1)
C(10)	-2604(2)	-2195(1)	566(1)	24(1)
C(11)	-2401(2)	-3028(1)	156(1)	20(1)
C(12)	-2803(2)	-3077(1)	-526(1)	18(1)
C(13)	-1731(2)	-2399(1)	-920(1)	22(1)
C(14)	-2366(2)	-2112(1)	-1548(1)	23(1)
C(15)	-4875(2)	-3151(1)	-2747(1)	30(1)
C(16)	-4357(2)	-4712(1)	-539(1)	23(1)
C(17)	-2303(2)	-5707(1)	-1468(1)	17(1)
C(18)	-985(2)	-7386(1)	-1502(1)	17(1)
C(19)	-594(2)	-7638(1)	-2178(1)	24(1)
C(20)	-584(2)	-8827(1)	-2286(1)	27(1)
C(21)	507(2)	-9368(1)	-1849(1)	29(1)
C(22)	167(2)	-9098(1)	-1174(1)	25(1)
C(23)	144(2)	-7913(1)	-1066(1)	18(1)
C(24)	697(2)	-7186(1)	-28(1)	24(1)
C(25)	140(2)	-7038(1)	622(1)	29(1)
O(1S)	-8289(1)	-5274(1)	-1085(1)	32(1)
O(2S)	-6326(1)	-5394(1)	-2054(1)	31(1)

X-ray Crystal Structure of Compound 100:

Crystals of compound **100** suitable for x-ray analysis were obtained by dissolving the residue in a minimal of amount ethyl acetate and adding hexane very carefully as to produce two layers; the product crystallized as the layers diffused at reduced temperature. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC # 725201). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk.

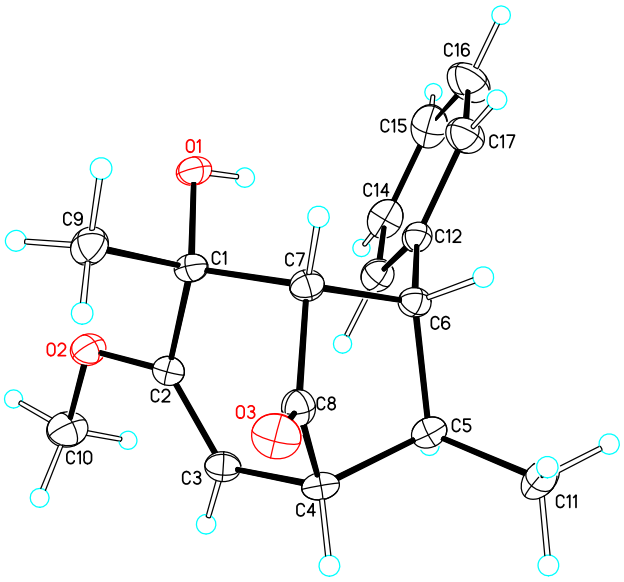


Table 1. Crystal data and structure refinement for compound **100**.

Identification code	compound **100**	
Empirical formula	C17 H20 O3	
Formula weight	272.33	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 6.6506(6) Å	α= 90°.
	b = 14.5039(14) Å	β= 97.781(3)°.
	c = 14.9477(12) Å	γ = 90°.
Volume	1428.6(2) $Å^3$	
Z	4	
Density (calculated)	1.266 Mg/m^3	
Absorption coefficient	0.086 mm^{-1}	

F(000)	584
Crystal size	0.50 x 0.35 x 0.20 mm^3
Theta range for data collection	1.97 to 28.28°.
Index ranges	-8<=h<=8, -19<=k<=19, -19<=l<=19
Reflections collected	14190
Independent reflections	3541 [R(int) = 0.0395]
Completeness to theta = 28.28°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9831 and 0.9585
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3541 / 0 / 261
Goodness-of-fit on F^2	1.086
Final R indices [I>2sigma(I)]	R1 = 0.0467, wR2 = 0.1058
R indices (all data)	R1 = 0.0657, wR2 = 0.1149
Largest diff. peak and hole	0.277 and -0.243 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **100**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	11090(2)	2995(1)	1075(1)	22(1)
O(2)	7639(2)	3230(1)	1845(1)	23(1)
O(3)	8496(2)	49(1)	848(1)	28(1)
C(1)	9815(2)	2218(1)	1180(1)	18(1)
C(2)	7651(2)	2503(1)	1264(1)	18(1)
C(3)	6021(2)	2074(1)	840(1)	19(1)
C(4)	6204(2)	1275(1)	198(1)	20(1)
C(5)	6613(2)	1612(1)	-741(1)	20(1)
C(6)	8914(2)	1883(1)	-592(1)	18(1)
C(7)	9779(2)	1534(1)	378(1)	18(1)
C(8)	8202(2)	813(1)	531(1)	20(1)
C(9)	10802(3)	1759(1)	2050(1)	25(1)
C(10)	5702(3)	3603(1)	1951(1)	30(1)
C(11)	6188(3)	863(1)	-1460(1)	29(1)
C(12)	9377(2)	2872(1)	-837(1)	19(1)
C(13)	8103(2)	3612(1)	-713(1)	23(1)

C(14)	8580(3)	4500(1)	-969(1)	28(1)
C(15)	10328(3)	4668(1)	-1347(1)	35(1)
C(16)	11607(3)	3943(1)	-1464(1)	40(1)
C(17)	11135(3)	3054(1)	-1218(1)	29(1)

X-ray Crystal Structure of Compound 113:

Crystals of compound **113** suitable for x-ray analysis were obtained by dissolving the residue in a minimal amount of ethyl acetate and adding hexane very carefully as to produce two layers; the product crystallized as the layers diffused. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC # 725199). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk.

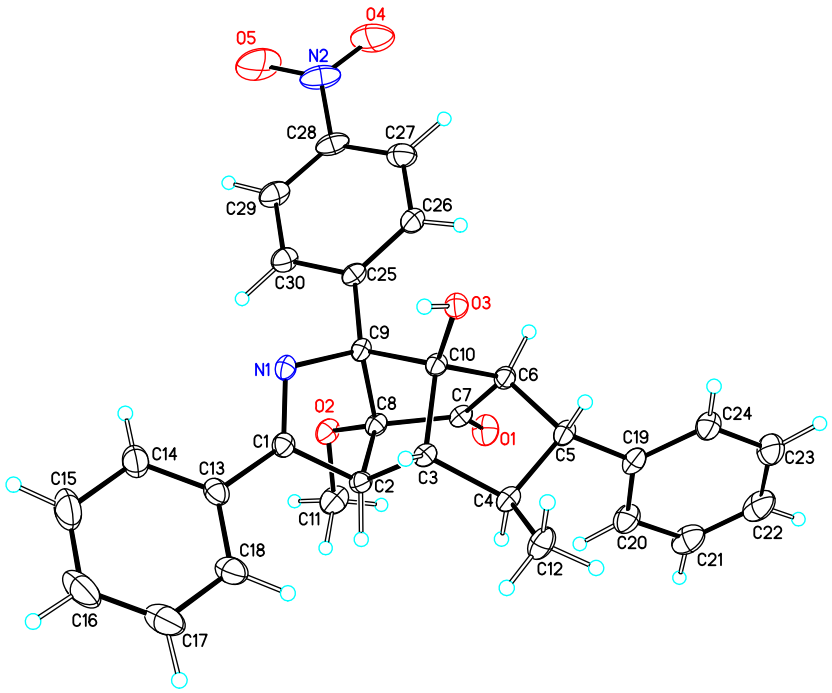


Table 1. Crystal data and structure refinement for compound **113**.

Identification code	compound **113**	
Empirical formula	C31 H28 Cl2 N2 O5	
Formula weight	579.45	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.4809(3) Å	α= 89.189(2)°.
	b = 15.1215(4) Å	β= 89.3230(10)°.
	c = 16.5157(4) Å	γ = 78.0290(10)°.
Volume	2804.51(12) $Å^3$	
Z	4	
Density (calculated)	1.372 Mg/m^3	

Absorption coefficient	0.276 mm^{-1}
F(000)	1208
Crystal size	0.60 x 0.50 x 0.40 mm^3
Theta range for data collection	1.23 to 28.28°.
Index ranges	-15<=h<=15, -20<=k<=19, -19<=l<=22
Reflections collected	60341
Independent reflections	13738 [R(int) = 0.0398]
Completeness to theta = 28.28°	98.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8978 and 0.8521
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	13738 / 9 / 965
Goodness-of-fit on F^2	1.049
Final R indices [I>2sigma(I)]	R1 = 0.0600, wR2 = 0.1536
R indices (all data)	R1 = 0.0859, wR2 = 0.1687
Largest diff. peak and hole	1.309 and -0.796 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **113**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	11442(1)	2171(1)	8321(1)	31(1)
O(2)	11281(1)	3786(1)	9226(1)	24(1)
O(3)	8907(1)	4414(1)	6775(1)	21(1)
O(4)	5193(1)	3253(1)	9885(1)	59(1)
O(5)	5543(1)	4249(2)	10716(1)	64(1)
N(1)	9842(1)	5315(1)	8296(1)	19(1)
N(2)	5781(1)	3789(1)	10109(1)	41(1)
C(1)	10927(1)	5347(1)	8139(1)	20(1)
C(2)	11622(1)	4436(1)	7865(1)	19(1)
C(3)	11075(1)	4353(1)	7022(1)	19(1)
C(4)	11778(1)	3581(1)	6498(1)	21(1)
C(5)	10975(1)	2891(1)	6461(1)	21(1)
C(6)	10266(1)	3064(1)	7262(1)	20(1)
C(7)	11012(1)	2895(1)	8025(1)	20(1)

C(8)	11018(1)	3810(1)	8407(1)	19(1)
C(9)	9746(1)	4360(1)	8198(1)	18(1)
C(10)	9873(1)	4101(1)	7278(1)	18(1)
C(11)	12497(2)	3383(1)	9418(1)	33(1)
C(12)	12121(2)	3902(1)	5669(1)	30(1)
C(13)	11402(1)	6176(1)	8140(1)	24(1)
C(14)	10913(2)	6885(1)	8645(1)	34(1)
C(15)	11402(2)	7652(1)	8656(2)	49(1)
C(16)	12352(2)	7720(2)	8155(2)	52(1)
C(17)	12832(2)	7025(1)	7654(2)	45(1)
C(18)	12373(2)	6250(1)	7651(1)	32(1)
C(19)	11572(2)	1925(1)	6288(1)	24(1)
C(20)	12626(2)	1492(1)	6651(1)	31(1)
C(21)	13136(2)	601(1)	6480(1)	38(1)
C(22)	12604(2)	132(1)	5932(1)	42(1)
C(23)	11569(2)	551(1)	5560(1)	40(1)
C(24)	11051(2)	1441(1)	5739(1)	30(1)
C(25)	8714(1)	4161(1)	8685(1)	21(1)
C(26)	7947(2)	3641(1)	8406(1)	28(1)
C(27)	7000(2)	3491(1)	8877(1)	32(1)
C(28)	6813(2)	3899(1)	9621(1)	29(1)
C(29)	7553(2)	4424(1)	9915(1)	31(1)
C(30)	8511(2)	4544(1)	9451(1)	26(1)
O(1A)	4604(1)	8416(1)	7024(1)	28(1)
O(2A)	6186(1)	7497(1)	5818(1)	23(1)
O(3A)	7592(1)	6432(1)	8502(1)	22(1)
O(4A)	4579(1)	3222(1)	7361(1)	48(1)
O(5A)	4835(1)	3239(1)	6063(1)	50(1)
N(1A)	8252(1)	6326(1)	6620(1)	19(1)
N(2A)	4875(1)	3565(1)	6729(1)	38(1)
C(1A)	8605(1)	7057(1)	6451(1)	19(1)
C(2A)	7722(1)	7875(1)	6748(1)	21(1)
C(3A)	7891(2)	7770(1)	7682(1)	22(1)
C(4A)	7327(2)	8608(1)	8183(1)	29(1)
C(5A)	6232(2)	8355(1)	8599(1)	26(1)
C(6A)	5952(1)	7615(1)	8049(1)	22(1)

C(7A)	5556(1)	7957(1)	7206(1)	21(1)
C(8A)	6543(1)	7550(1)	6614(1)	19(1)
C(9A)	7058(1)	6609(1)	7006(1)	18(1)
C(10A)	7182(1)	7019(1)	7865(1)	20(1)
C(11A)	5976(2)	8333(1)	5371(1)	30(1)
C(12A)	8185(2)	8859(2)	8787(2)	48(1)
C(13A)	9782(1)	7095(1)	6113(1)	23(1)
C(14A)	10412(2)	6389(1)	5646(1)	26(1)
C(15A)	11509(2)	6441(2)	5317(1)	37(1)
C(16A)	12005(2)	7182(2)	5469(1)	45(1)
C(17A)	11398(2)	7871(2)	5936(2)	44(1)
C(18A)	10281(2)	7839(1)	6253(1)	33(1)
C(19A)	5182(2)	9109(1)	8789(1)	30(1)
C(20A)	5019(3)	9968(2)	8462(2)	58(1)
C(21A)	4028(3)	10628(2)	8661(2)	67(1)
C(22A)	3193(2)	10444(2)	9188(1)	56(1)
C(23A)	3342(2)	9594(2)	9524(2)	61(1)
C(24A)	4338(2)	8936(2)	9332(2)	47(1)
C(25A)	6360(1)	5876(1)	6942(1)	20(1)
C(26A)	5870(2)	5522(1)	7611(1)	24(1)
C(27A)	5336(2)	4786(1)	7536(1)	28(1)
C(28A)	5320(2)	4404(1)	6789(1)	28(1)
C(29A)	5762(2)	4756(1)	6103(1)	29(1)
C(30A)	6269(2)	5497(1)	6184(1)	26(1)
Cl(1)	6708(1)	536(1)	6237(1)	82(1)
Cl(2)	7517(1)	2186(1)	6611(1)	63(1)
C(1S)	6753(3)	1362(2)	6951(2)	65(1)
Cl(3)	9209(2)	1121(1)	8686(1)	96(1)
Cl(4)	9706(1)	85(1)	7226(1)	69(1)
C(2S)	10302(5)	457(4)	8059(4)	90(2)
Cl(3')	9973(3)	576(3)	9034(2)	155(1)
Cl(4')	9880(5)	170(5)	7413(3)	198(2)
C(2S')	10726(7)	320(6)	8152(5)	74(3)