Catalytic Ring Expansions of Cyclic Alcohols Enabled by Proton-Coupled Electron Transfer

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Supporting Information

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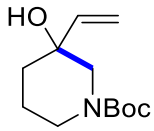
General Information

Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] All solvents were purified according to the method of Grubbs.[2] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using a water bath. Chromatographic purification of products was accomplished by flash chromatography on a Biotage Isolera One with cartridges containing Fluka 230–400 mesh silica gel. Thin-layer chromatography (TLC) was performed on Silicycle 250 μm silica gel plates. Visualization of the developed chromatogram was performed by irradiation with UV light or treatment with a solution of phosphomolybdic acid, ceric ammonium molybdate, *p*-anisaldehyde stains, and cobalt (II) thiocyanate followed by heating when necessary.[3] Yields refer to purified compounds unless otherwise noted.

All ^{1}H, NOESY, and ^{13}C{^{1}H} NMR spectra were recorded on Bruker Avance II 500 (500 and 126 MHz for ^{1}H and ^{13}C respectively), Bruker Avance III HD 400 (400 and 101 MHz for ^{1}H and ^{13}C respectively) instruments, and were referenced to residual protio-solvent signals: $CDCl_3$ at δ 7.26 and 77.16 ppm, and DMSO-d_6 at δ 2.50 and 39.52 ppm. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), broad peak (b), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, m = multiplet), coupling constant (Hz) and integration; data for ^{13}C NMR are reported in terms of chemical shift and no special nomenclature is used for equivalent carbons. In certain starting materials and products, the presence of the *N*-Boc group result in rotameric products, and for selected compounds, the NMR characterization issues were addressed by acquiring NMR spectral in DMSO-d_6 at 120 °C, otherwise, the characterizations of rotameric products were included. IR spectra were recorded on a Thermo Scientific Nicolet 6700 FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained at Princeton University Mass Spectrometry Facility using an Agilent 6210 TOF LC/MS (Electrospray Ionization, ESI) or an Agilent 7200 Q-TOF GC/MS (Electron Ionization, EI) or at Princeton University Proteomics and Mass Spectrometry Core Facility using a Thermo Scientific LTQ Orbitrap XL Mass Spectrometer (Electrospray Ionization, ESI).

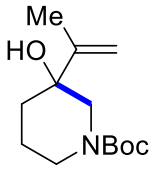
Bases were made in similar fashion as previous work.[4] In the case of tetrabutylphosphonium 2,2,2-trifluoroacetate base (TFA base), CF_3COOH was used as the acid of the reaction.

Synthesis of Starting Materials for n+2 Chemistry



***tert*-butyl 3-hydroxy-3-vinylpiperidine-1-carboxylate (1)**
The titled compound was synthesized by vinylation of *tert*-butyl 3-oxopiperidine-1-carboxylate.[5]

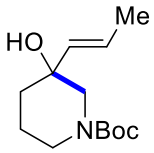
To an oven-dried 50-mL round-bottomed flask, charged with a stir bar, was added vinylmagnesium chloride (15.1 mmol, 3.00 eq., 9.5 mL, 1.6 M THF solution) under inert atmosphere. The solution was cooled to 0 °C, and a THF solution of *tert*-butyl 3-oxopiperidine-1-carboxylate (5.02 mmol, 1.00 eq., 1.00 g, 10 mL THF) was added in dropwise. The mixture was allowed to warm to r.t. and stirred for 14 h. Afterwards, the reaction was quenched with sat. aq. NH_4Cl (30 mL), extracted in Et_2O (20 mL, three times). The combined organic layers were washed with sat. aq. NaCl (40 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (5% to 28% EtOAc in hexanes) to obtain the titled compound (900.0 mg, 79% yield) as a colorless oil which slowly solidified to a white solid. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 5.91 (dd, *J* = 17.3, 10.9 Hz, 1H), 5.38 (dd, *J* = 17.4, 1.2 Hz, 1H), 5.16 (dd, *J* = 10.8, 1.2 Hz, 1H), 3.81 (dt, *J* = 13.2, 4.5 Hz, 1H), 3.66 (br, 1H), 3.14 – 2.89 (m, 2H), 1.96 – 1.74 (m, 2H), 1.74 –1.55 (m, 2H), 1.46 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 155.86, 142.30, 114.10, 79.98, 70.66, 53.27, 44.67, 35.78, 28.54, 21.36. **IR (neat):** 3434, 2967, 2936, 2662, 1668, 1431, 1464, 1267, 1165, 901, 701, 591 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{12}H_{21}NNaO_3$) requires *m/z* 250.14136, found *m/z* 250.14103.



***tert*-butyl 3-hydroxy-3-(prop-1-en-2-yl)piperidine-1-carboxylate (2)**
The titled compound was synthesized by isopropenylation of *tert*-butyl 3-oxopiperidine-1-carboxylate.[5]

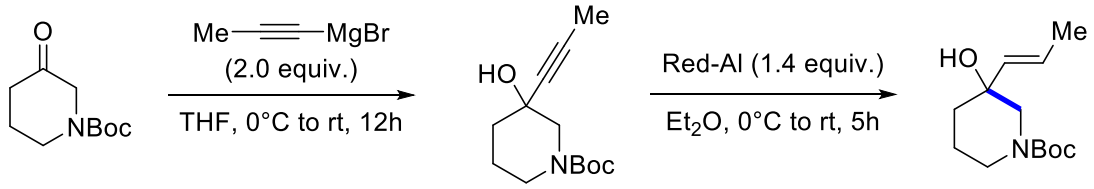
To an oven-dried 50-mL round-bottomed flask, charged with a stir bar, was added prop-1-en-2-ylmagnesium bromide (7.53 mmol, 3.00 eq., 15.0 mL, 0.5 M THF solution) under inert atmosphere. The solution was cooled to 0 °C, and a THF solution of *tert*-butyl 3-oxopiperidine-1-carboxylate (2.51 mmol, 1.00 eq., 0.500 g, 10 mL THF) was added in dropwise. The mixture was allowed to warm to r.t. and stirred for 18 h. Afterwards, the reaction was quenched with sat. aq. NH_4Cl (15 mL), extracted in Et_2O (15 mL, three times). The combined organic layers were washed with sat. aq. NaCl (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (5% to 28% EtOAc in hexanes) to obtain the titled compound (212mg, 35% yield) as a colorless oil which slowly solidified to a white solid. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 5.05 (s, 1H), 4.90 (s, 1H), 4.08 – 3.53 (m, 2H), 3.22 – 2.88 (m, 1H), 2.80 (ddd, *J* = 13.2, 11.7, 3.2 Hz, 1H), 2.06 – 1.78 (m, 4H), 1.78 – 1.63 (m, 2H), 1.54 – 1.48 (m, 1H), 1.46 (s, 9H). **^{13}C NMR (126 MHz,**

$CDCl_3$, mixture of rotamers) δ 155.30, 141.75, 111.16, 80.03, 72.47, 52.73, 49.55, 34.14, 28.57, 21.33, 19.04. **IR (neat):** 3434, 2964, 2940, 2868, 1665, 1439, 1310, 1274, 1151, 882, 768, 590 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{13}H_{23}NNaO_3$) requires *m/z* 264.15701, found *m/z* 264.15697.



***tert*-butyl (*E*)-3-hydroxy-3-(prop-1-en-1-yl)piperidine-1-carboxylate (3)**

The titled compound was synthesized by Red-Al® reduction of *tert*-butyl 3-hydroxy-3-(prop-1-yn-1-yl)piperidine-1-carboxylate, which was synthesized by propynylation of *tert*-butyl 3-oxopiperidine-1-carboxylate.[5,6]



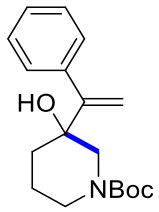
To an oven-dried 100-mL round-bottomed flask, charged with a stir bar, was added prop-1-yn-1-ylmagnesium bromide (20.08 mmol, 2.0 eq., 40 mL, 0.5 M THF solution) under inert atmosphere. The solution was cooled to 0 °C, and a THF solution of *tert*-butyl 3-oxopiperidine-1-carboxylate (10.0 mmol, 1.00 eq., 2.00 g, 20 mL THF) was added dropwise. The mixture was allowed to warm to r.t. and stirred for 12 h. Afterwards, the reaction was quenched with sat. aq. NH_4Cl (40 mL), extracted in Et_2O (30 mL, three times). The combined organic layers were washed with sat. aq. NaCl (40 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (10% to 40% EtOAc in hexanes) to obtain the *tert*-butyl 3-hydroxy-3-(prop-1-yn-1-yl)piperidine-1-carboxylate (1.85 g, 77% yield) as a pale yellow oil.

Data for *tert*-butyl 3-hydroxy-3-(prop-1-yn-1-yl)piperidine-1-carboxylate:

^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 3.75 – 2.99 (m, 4H), 2.56 – 1.92 (m, 1H), 1.89 – 1.55 (m, 6H), 1.45 (s, 9H).**^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 155.09, 81.06, 79.84, 66.20, 66.01, 55.03, 44.53, 43.25, 38.28, 28.56, 21.92, 15.42. **IR (neat)**: 3401, 2922, 2867, 1684, 1425, 1384, 1243, 1161, 1068, 870 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{13}H_{21}NNaO_3$) requires *m/z* 262.14136, found *m/z* 262.14160.

To an oven-dried 50-mL round-bottomed flask, charged with a stir bar, was added *tert*-butyl 3-hydroxy-3-(prop-1-yn-1-yl)piperidine-1-carboxylate (2.44 mmol, 1.00 eq., 584.0 mg). Under inert atmosphere, Et_2O (20 mL) was added, and the solution was cooled to 0 °C. At the same temperature, sodium bis(2-methoxyethoxy)aluminum hydride (3.42 mmol, 1.40 eq., 1.1 mL, 60% w/w toluene solution) was added slowly and dropwise. During the addition of reagent, hydrogen gas evolution was observed, and the solution slowly turned cloudy. The suspension was then allowed to warm up to r.t and stir for another 5 h. The mixture was then cooled to 0 °C and was

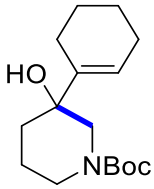
quenched by dropwise addition of sat. aq. NH_4Cl (5 mL). To the resulting mixture was added sat. aq. NH_4Cl (15 mL), aq. HCl (2 M, 10 mL) and Et_2O (20 mL). The aqueous layer was separated and then rinsed by Et_2O (20 mL, three times). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and evaporated to afford a colorless oil, which was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexanes) to obtain *tert*-butyl (*E*)-3-hydroxy-3-(prop-1-en-1-yl)piperidine-1-carboxylate (469.0 mg, 80% yield) as a a colorless oil. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 5.79 (dq, *J* = 15.5, 6.5 Hz, 1H), 5.52 (dq, *J* = 15.6, 1.7 Hz, 1H), 3.87 – 3.40 (m, 2H), 3.23 – 2.76 (m, 2H), 2.09 – 1.64 (m, 6H), 1.64 – 1.48 (m, 1H), 1.45 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 155.10, 135.29, 125.43+125.29, 79.88, 70.10, 53.98, 44.13 36.16, 28.56, 21.53, 18.07. **IR (neat):** 3426, 2932, 2868, 1666, 1369, 1364, 1242, 1151, 1062, 967, 766, 463 cm^{-1}. **HRMS (ESI)**: exact mass calculated for $[M+Na]^+$ ($C_{13}H_{23}NNaO_3$) requires *m/z* 264.15701, found *m/z* 264.15659.



***tert*-butyl 3-hydroxy-3-(1-phenylvinyl)piperidine-1-carboxylate (4)**

The titled compound was synthesized by the ketone insertion of (1-phenylvinyl)magnesium bromide to *tert*-butyl 3-oxopiperidine-1-carboxylate.[7]

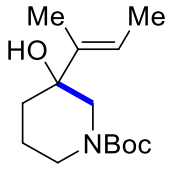
To an oven-dried 50-mL round-bottomed flask, charged with a stir bar, was added magnesium turnings (16.2 mmol, 2.30 eq., 393 mg) and a chip of iodine under inert atmosphere. THF (1 mL) was then added, and the brown mixture was vigorously stirred for 15 min. Two drops of neat (1-bromovinyl)benzene was then added to the mixture to initiate the reaction. The brown color of iodine faded, and the temperature increased significantly in about 2 min. At this point, a THF solution of (1-bromovinyl)benzene (15.5 mmol, 2.20 eq., 2 mL, 10 mL THF) was slowly added to the stirring mixture, and the resulting reaction mixture was stirred at r.t. for 2 h to afford a gray, cloudy mixture. The solution was cooled to 0 °C, and a THF solution of *tert*-butyl 3-oxopiperidine-1-carboxylate (7.03 mmol, 1.00 eq., 1.40 g, 10 mL THF) was added in dropwise. The mixture was allowed to warm to r.t. and stirred for 12 h. Afterwards, the reaction was quenched with sat. aq. NH_4Cl (50 mL), extracted in Et_2O (30 mL, three times). The combined organic layers were washed with sat. aq. NaCl (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (5% to 35% EtOAc in hexanes) to obtain the titled compound (393 mg, 18% yield) as a colorless oil which slowly solidified to a white solid. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 7.39 – 7.28 (m, 5H), 5.51 (br, 1H), 5.12 (br, 1H), 4.16 – 3.63 (m, 2H), 3.08 (br, 1H), 2.88 – 2.68 (m, 1H), 2.21 – 1.65 (m, 4H), 1.45 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 157.78, 156.58, 155.26, 140.50, 114.28, 113.79, 81.18, 80.64, 57.93, 57.01, 56.57, 49.54, 49.25, 28.50. **IR (neat):** 3420, 3052, 3004, 2974, 2927, 2867, 1666, 1425, 1390, 1317, 1240, 1147, 1003, 893, 770, 617 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{18}H_{25}NNaO_3$) requires *m/z* 326.17266, found *m/z* 326.17217.



***tert*-butyl 3-(cyclohex-1-en-1-yl)-3-hydroxypiperidine-1-carboxylate (5)**

The titled compound was synthesized by insertion of cyclohex-1-en-1-ylmagnesium bromide to *tert*-butyl 3-oxopiperidine-1-carboxylate.[7]

To an oven-dried 25-mL three-necked round-bottomed flask, charged with a stir bar and fitted with a condensor, was added magnesium turnings (6.60 mmol, 1.60 eq., 161 mg) and a chip of iodine under inert atmosphere. THF (4 mL) was then added, and the brown mixture was vigorously stirred for 15 min. Then, two drops of neat 1-bromocyclohex-1-ene was then added to the mixture to initialize the reaction. With gentle heating applied for 15 min by a heat gun, the brown color faded, the rest of neat 1-bromocyclohex-1-ene (6.21 mmol, 1.5 eq., 1.00 g) was slowly added. Upon completion, the reaction mixture was further stirred for 1.5 h at r.t. to obtain a gray, cloudy mixture, which was then cooled to 0 °C, and a THF solution of *tert*-butyl 3-oxopiperidine-1-carboxylate (4.14 mmol, 1.00 eq., 825 mg, 5 mL THF) was added dropwise. The mixture was allowed to warm to r.t. and stirred for another 12 h. The reaction was then quenched with sat. aq. NH_4Cl (25 mL), extracted in Et_2O (25 mL, three times). The combined organic layers were washed with sat. aq. NaCl (25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (5% to 35% EtOAc in hexanes) to obtain the titled compound (218 mg, 19% yield) as a colorless oil which slowly solidified to a white solid. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 5.89 – 5.73 (m, 1H), 3.98 – 3.56 (m, 2H), 3.02 (br, 1H), 2.82 (ddd, J = 13.2, 11.4, 3.3 Hz, 1H), 2.14 – 1.96 (m, 4H), 1.89 – 1.48 (m, 8H), 1.46 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 155.93, 140.63, 121.96, 79.89, 72.18, 60.25, 52.93, 34.03, 28.58, 25.33, 24.12, 23.12, 22.37, 21.45. **IR (neat):** 3425, 2925, 2856, 1680, 1424, 1390, 1296, 1242, 1147, 1006, 901, 765, 548 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{16}H_{27}NNaO_3$) requires *m/z* 304.18831, found *m/z* 304.18831.

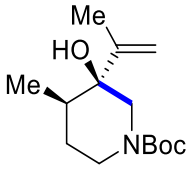


***tert*-butyl (*E*)-3-(but-2-en-2-yl)-3-hydroxypiperidine-1-carboxylate (6)**

The titled compound was synthesized by insertion of but-2-en-2-ylmagnesium bromide to *tert*-butyl 3-oxopiperidine-1-carboxylate.[7]

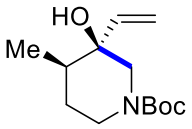
To an oven-dried 50-mL round-bottomed flask, charged with a stir bar, was added magnesium turnings (17.1 mmol, 1.70 eq., 415 mg) and a chip of iodine under inert atmosphere. THF (4 mL) was then added, and the brown mixture was vigorously stirred for 15 min. Then, two drops of neat (*E*)-2-bromobut-2-ene was then added to the mixture. The brown color faded, and the temperature increased significantly in about 2 min. At this point, a THF solution of (*E*)-2-bromobut-2-ene (15.5 mmol, 1.50 eq., 1.5 mL, 10 mL THF) was slowly added to the stirring mixture, and the resulting reaction mixture was stirred at r.t. for 2 h to afford a gray, cloudy mixture. The solution was cooled

to 0 °C, and a THF solution of *tert*-butyl 3-oxopiperidine-1-carboxylate (10.04 mmol, 1.00 eq., 2.0 g, 10 mL THF) was added in dropwise. The mixture was allowed to warm to r.t. and stirred for 12 h. Afterwards, the reaction was quenched with sat. aq. NH_4Cl (50 mL), extracted in Et_2O (30 mL, three times). The combined organic layers were washed with sat. aq. NaCl (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (5% to 35% EtOAc in hexanes) to obtain the titled compound (161.0 mg, 6% yield) as a colorless oil which slowly solidified to a white solid. Notably, the reaction also furnished small amount of the *Z* isomer, whose R_f value is slightly lower than the desired *E* isomer. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 5.63 (qq, *J* = 8.5, 1.6 Hz, 1H), 4.15–3.53 (m, 2H), 3.18–2.89 (m, 1H), 2.80 (ddd, *J* = 13.2, 11.6, 3.2 Hz, 1H), 1.89–1.76 (m, 2H), 1.74–1.66 (m, 4H), 1.63 (dd, *J* = 6.5, 1.8 Hz, 3H), 1.59–1.47 (m, 1H), 1.46 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 156.1, 138.30, 124.22, 79.94, 73.24, 52.50, 44.57+43.86, 34.09, 28.57, 21.49, 13.62, 12.20. **IR (neat):** 3431, 3008, 2976, 2926, 1669, 1424, 1364, 1270, 1147, 1004, 869, 766, 635 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{14}H_{25}NNaO_3$) requires *m/z* 278.17266, found *m/z* 278.17263.



***tert*-butyl (3*S**,4*R**)-3-hydroxy-4-methyl-3-(prop-1-en-2-yl)piperidine-1-carboxylate (7)**
The titled compound was synthesized by isopropenylation of *tert*-butyl 4-methyl-3-oxopiperidine-1-carboxylate.[5]

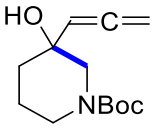
To an oven-dried 50-mL round-bottomed flask, charged with a stir bar, was added prop-1-en-2-ylmagnesium bromide (10.0 mmol, 2.04 eq., 20.0 mL, 0.5 M THF solution) under inert atmosphere. The solution was cooled to 0 °C, and a THF solution of *tert*-butyl 4-methyl-3-oxopiperidine-1-carboxylate (4.69 mmol, 1.00 eq., 1.00 g, 10 mL THF) was added in dropwise. The mixture was allowed to warm to r.t. and stirred for 12 h. Afterwards, the reaction was quenched with sat. aq. NH_4Cl (40 mL), extracted in Et_2O (30 mL, three times). The combined organic layers were washed with sat. aq. NaCl (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (5% to 35% EtOAc in hexanes) to obtain the titled compound (457.3 mg, 38% yield) as a white solid. Notably, the other diastereomer, which has a slightly lower R_f, was generated in a small quantity and was not recovered. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 5.14 (s, 1H), 4.97 (s, 1H), 4.12 (br, 1H), 3.84 (br, 1H), 2.87 (d, *J* = 13.7 Hz, 1H), 2.71 (br, 1H), 1.84–1.72 (m, 5H), 1.65–1.53 (m, 1H), 1.46 (s, 9H), 0.81–0.79 (m, 3H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 156.37, 147.16, 112.03, 80.05, 75.44, 53.87, 44.97, 35.94, 29.14, 28.55, 19.85, 14.82. **IR (neat):** 3465, 2972, 2962, 2921, 2851, 1660, 1429, 1364, 1164, 1027, 893, 647 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{14}H_{25}NNaO_3$) requires *m/z* 278.17266, found *m/z* 278.17275.



***tert*-butyl (3*S**,4*R**)-3-hydroxy-4-methyl-3-vinylpiperidine-1-carboxylate (8)**

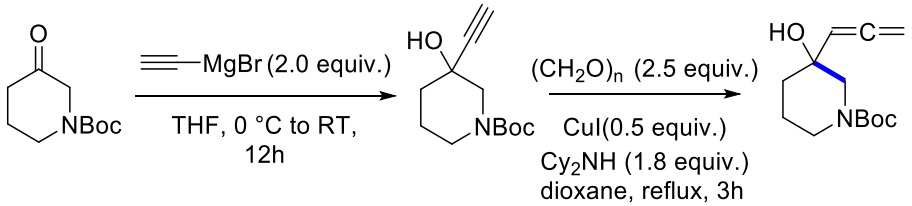
The titled compound was synthesized by vinylation of *tert*-butyl 4-methyl-3-oxopiperidine-1-carboxylate.[5]

To an oven-dried 50-mL round-bottomed flask, charged with a stir bar, was added vinylmagnesium chloride (9.38 mmol, 2.0 eq., 6.2 mL, 1.6 M THF solution) under inert atmosphere. The solution was cooled to 0 °C, and a THF solution of *tert*-butyl 4-methyl-3-oxopiperidine-1-carboxylate (4.69 mmol, 1.00 eq., 1.0 g, 10 mL THF) was added dropwise. The mixture was allowed to warm to r.t. and stirred for 12 h. Afterwards, the reaction was quenched with sat. aq. NH_4Cl (40 mL), extracted in Et_2O (30 mL, three times). The combined organic layers were washed with sat. aq. NaCl (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (5% to 35% EtOAc in hexanes) to obtain the titled compound (564.3 mg, 50% yield) as a colorless oil which solidified slowly to a white solid. In addition, the other diastereomer, which has a slightly lower R_f, was also recovered (320 mg, 28% yield) but was not used in the ring expansion reaction. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 5.98 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.36 (dd, *J* = 17.4, 1.4 Hz, 1H), 5.24 (dd, *J* = 11.0, 1.4 Hz, 1H), 4.15–3.76 (m, 2H), 3.05–2.67 (m, 2H), 1.74–1.53 (m, 3H), 1.44 (s, 9H), 0.89 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 153.65, 137.84, 115.03, 79.85, 73.36, 54.78, 52.78, 43.12, 40.72, 30.70, 28.55, 14.72. **IR (neat):** 3438, 2974, 2932, 2872, 1668, 1428, 1384, 1244, 1169, 898, 764, 640 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{13}H_{23}NNaO_3$) requires *m/z* 264.15701, found *m/z* 264.15673.



***tert*-butyl 3-hydroxy-3-(propa-1,2-dien-1-yl)piperidine-1-carboxylate (9)**

The titled compound was synthesized by Cu(I)-mediated homologation of *tert*-butyl 3-ethynyl-3-hydroxypiperidine-1-carboxylate,[8] which was synthesized by ethynylation of *tert*-butyl 3-oxopiperidine-1-carboxylate.



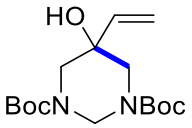
To an oven-dried 50-mL round-bottomed flask, charged with a stir bar, was added ethynylmagnesium bromide (11.2 mmol, 2.00 eq., 22.4 mL, 0.5 M THF solution) under inert atmosphere. The solution was cooled to 0 °C, and a THF solution of *tert*-butyl 3-oxopiperidine-1-carboxylate (5.62 mmol, 1.00 eq., 1.12 g, 10 mL THF) was added dropwise. The mixture was allowed to warm to r.t. and stirred for 12 h. Afterwards, the reaction was quenched with sat. aq.

NH_4Cl (20 mL), extracted in Et_2O (20 mL, three times). The combined organic layers were washed with sat. aq. NaCl (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexanes) to obtain the *tert*-butyl 3-ethynyl-3-hydroxypiperidine-1-carboxylate (1.01 g, 80% yield) as a colorless oil which solidified slowly to a white solid.

Data for *tert*-butyl 3-ethynyl-3-hydroxypiperidine-1-carboxylate

^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 3.91–3.05 (m, 4H), 2.97–2.23 (m, 2H), 2.05–1.52 (m, 4H), 1.45 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 154.92, 85.58, 80.09, 72.93, 65.97, 54.61, 53.57, 44.58, 43.14, 38.05, 37.37, 28.51, 21.78. **IR (neat):** 3308, 2975, 2930, 2860, 1954, 1663, 1424, 1365, 1243, 1150, 972, 877, 646 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{12}H_{20}NO_3$) requires *m/z* 226.14377, found *m/z* 226.14372.

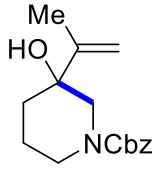
To an oven-dried 25-mL round-bottomed flask, charged with a stir bar and equipped with a condenser, was added paraformaldehyde (10.2 mmol, 2.5 eq., 305 mg) and *tert*-butyl 3-ethynyl-3-hydroxypiperidine-1-carboxylate (4.07 mmol, 1.0 eq., 917 mg). Under inert atmosphere, copper (I) iodide (2.03 mmol, 0.5 eq., 387 mg) was added. Then, dicyclohexylamine (7.32 mmol, 1.8 eq., 1.46 mL) and dioxane (6.8 mL) were added by syringes to afford a brown mixture. The mixture was stirred under reflux for 3 h. The reaction was complete as monitored by TLC and was then allowed to cool to r.t. and filtered to remove solid residue. The collected filtrate was transferred to a separatory funnel and was added water (20 mL) and CH_2Cl_2 (20 mL). After layer separation, the organic layer was collected, and the aqueous layer was extracted with CH_2Cl_2 (20 mL, three times). Organic layers were combined and was dried over anhydrous Na_2SO_4, filtered and evaporated to afford a crude yellow oil, which was purified by silica gel flash column chromatography twice (10% to 30% EtOAc in hexanes) to obtain the *tert*-butyl 3-hydroxy-3-(propa-1,2-dien-1-yl)piperidine-1-carboxylate (911.5 mg, 94% yield) as a pale yellow oil. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 5.32–5.26 (m, 1H), 4.96–4.85 (m, 2H), 4.01–2.80 (m, 5H), 2.27–1.49 (m, 4H), 1.45 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 206.57, 155.60, 96.78, 79.92, 78.76, 68.99, 53.61, 44.63, 43.56, 36.24, 28.55, 21.67. **IR (neat)**: 3406, 2974, 2930, 2858, 1954, 1684, 1421, 1364, 1269, 1242, 1160, 836, 764 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{13}H_{21}NNaO_3$) requires *m/z* 262.14136, found *m/z* 262.14104.



di-*tert*-butyl 5-hydroxy-5-vinyldihydropyrimidine-1,3(2H,4H)-dicarboxylate (10)
The titled compound was synthesized by vinylation[5] of di-*tert*-butyl 5-oxodihydropyrimidine-1,3(2*H*,4*H*)-dicarboxylate, the synthesis of which has been reported previously.[9]

To an oven-dried 25-mL round-bottomed flask, charged with a stir bar, was added vinylmagnesium chloride (5.59 mmol, 2.00 eq., 3.5 mL, 1.6 M THF solution) under inert atmosphere. The solution was cooled to 0 °C, and a THF solution of di-*tert*-butyl 5-oxodihydropyrimidine-1,3(2*H*,4*H*)-dicarboxylate (2.80 mmol, 1.00 eq., 840 mg, 10 mL THF) was added dropwise. The mixture was allowed to warm to r.t. and stirred for 12 h. Afterwards, the reaction was quenched with sat. aq. NH_4Cl (20 mL), extracted in Et_2O (20 mL, three times). The combined organic layers were washed

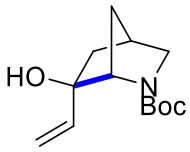
with sat. aq. NaCl (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexanes) to obtain the titled compound (640 mg, 70% yield) as a colorless oil, which solidified slowly to a white solid. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 5.84 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.72 (br, 1H), 5.50 (d, *J* = 17.3 Hz, 1H), 5.26 (d, *J* = 10.8 Hz, 1H), 4.29–3.66 (m, 3H), 3.08 (d, *J* = 13.7 Hz, 2H), 2.13 (br, 1H), 1.48 (s, 18H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 154.58, 138.70, 116.38, 80.85, 69.69, 57.02, 52.56, 28.42. **IR (neat):** 3406, 2974, 2930, 2858, 1954, 1684, 1421, 1391, 1364, 1269, 1242, 1150, 836, 764 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{16}H_{28}N_2NaO_5$) requires *m/z* 351.18904, found *m/z* 351.18920.



benzyl 3-hydroxy-3-(prop-1-en-2-yl)piperidine-1-carboxylate (11)

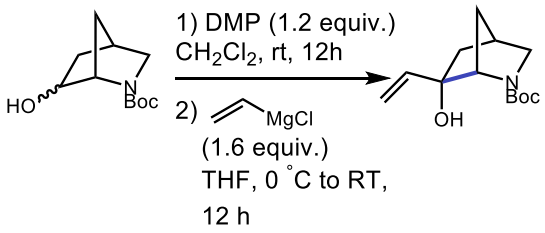
The titled compound was synthesized by isopropenylation of benzyl 3-oxopiperidine-1-carboxylate.[5]

To an oven-dried 50-mL round-bottomed flask, charged with a stir bar, was added prop-1-en-2-ylmagnesium bromide (7.00 mmol, 2.05 eq., 14.0 mL, 0.5 M THF solution). The solution was cooled to 0 °C, and a THF solution of benzyl 3-oxopiperidine-1-carboxylate (3.43 mmol, 1.00 eq., 800 mg, 10 mL THF) was added in dropwise. The mixture was allowed to warm to r.t. and stirred for 12 h. Afterwards, the reaction was quenched with saturated NH_4Cl solution (15 mL), extracted in Et_2O (15 mL, three times). The combined organic layers were washed with sat. aq. NaCl (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexanes) to obtain the titled compound (291 mg, 31% yield) as a colorless oil which slowly solidified to a white solid.**^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 7.39–7.33 (m, 4H), 7.33–7.28 (m, 1H), 5.15 (d, *J* = 2.3 Hz, 2H), 5.06 (s, 1H), 4.91 (t, *J* = 1.5 Hz, 1H), 4.24–3.78 (m, 2H), 3.09 (d, *J* = 14.0 Hz, 1H), 2.86 (t, *J* = 12.5 Hz, 1H), 1.96–1.44 (m, 7H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 155.56, 148.54, 136.91, 128.64, 128.13, 127.96, 111.32, 72.25, 67.34, 52.94, 44.51, 34.06, 21.25, 19.05. **IR (neat):** 3430, 2948, 2868, 1676, 1497, 1233, 1160, 898, 695, 604 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{16}H_{21}NNaO_3$) requires *m/z* 298.14136, found *m/z* 298.14114.



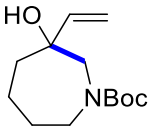
***tert*-butyl (1*S**,4*R**,6*S**)-6-hydroxy-6-vinyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (12)**

The titled compound was synthesized by vinylation of *tert*-butyl (1*S**,4*R**)-6-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate,[5] which was prepared by DMP oxidation of commercially available compound *tert*-butyl (1*S**,4*R**)-6-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate.[9]



To an oven-dried 50-mL round-bottomed flask, charged with a stir bar, was added a CH_2Cl_2 solution of *tert*-butyl 6-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate (4.69 mmol, 1.00 eq., 1.00 g in 20 mL CH_2Cl_2). Then, Dess-Martin periodinane (5.65 mmol, 1.20 eq., 2.40 g) was added in one portion. The resulting mixture was stirred at r.t. overnight. The reaction was then quenched by pouring into sat. $NaHCO_3$ aq. (30 mL), which was saturated by $Na_2S_2O_3$. After vigorously stirring for 45 min, a bilayer mixture was obtained, and the organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated to afford the desired ketone product (973.0 mg, 98%) as a white solid. The spectral data match with literature values.[10]

To an oven-dried 50-mL round-bottomed flask, charged with a stir bar, was added a THF solution of *tert*-butyl 6-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate (4.61 mmol, 1.00 eq., 973 mg, 20 mL THF). The solution was cooled to 0 °C, and the solution was dropwise added vinylmagnesium chloride (7.37 mmol, 1.60 eq., 4.6 mL, 1.6 M THF solution) under inert atmosphere. The mixture was stirred for 3 h at 0 °C. Afterwards, the reaction was quenched with sat. aq. NH_4Cl (30 mL), extracted in Et_2O (20 mL, three times). The combined organic layers were washed with sat. aq. NaCl (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (7% to 50% EtOAc in hexanes) to obtain the titled compound (744 mg, 68% yield) as a colorless oil. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 5.95 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.29 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.16–5.05 (m, 1H), 3.96 (d, *J* = 45.6 Hz, 1H), 3.35 (s, 1H), 3.11 (dd, *J* = 9.5, 1.3 Hz, 1H), 2.61–1.82 (m, 3H), 1.69–1.60 (m, 2H), 1.47 (s, 9H), 1.43–1.35 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 156.94, 142.32, 113.51, 113.13, 81.50, 79.75, 65.39, 64.05, 52.49, 52.15, 42.69, 37.23, 36.79, 28.63. **IR (neat):** 3425, 2974, 2882, 1675, 1403, 1159,1108, 878, 767, 562 cm^{-1}. **HRMS (EI):** exact mass calculated for $[M\text{-}Boc+H]^+$ ($C_8H_{13}NO$) requires *m/z* 139.09917, found *m/z* 139.09958.

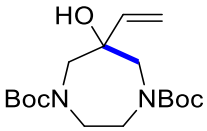


***tert*-butyl 3-hydroxy-3-vinylazepane-1-carboxylate (13)**

The titled compound was synthesized by vinylation of *tert*-butyl 3-oxoazepane-1-carboxylate.[5]

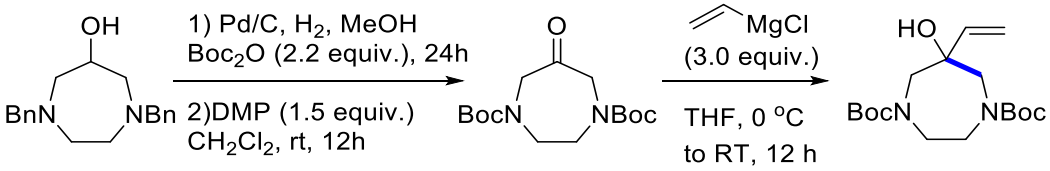
To an oven-dried 25-mL round-bottomed flask, charged with a stir bar, was added vinylmagnesium chloride (3.52 mmol, 3.00 eq., 2.4 mL, 1.6 M THF solution) under inert atmosphere. The solution was cooled to 0 °C, and a THF solution of *tert*-butyl 3-oxoazepane-1-carboxylate (1.17 mmol, 1.00 eq., 250 mg, 5 mL THF) was added in dropwise. The mixture was allowed to warm to r.t. and stirred for 12 h. Afterwards, the reaction was quenched with sat. aq. NH_4Cl (10 mL), extracted in Et_2O (15 mL, three times). The combined organic layers were washed with sat. aq. NaCl (15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexanes) to obtain the titled

compound (200 mg, 70% yield) as a colorless oil which slowly solidified to a white solid. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 5.98–5.82 (m, 1H), 5.45–5.29 (m, 1H), 5.09 (d, J = 10.7 Hz, 1H), 4.18 (s, 1H), 3.95–3.57 (m, 2H), 3.22–2.84 (m, 2H), 1.93–1.57 (m, 6H), 1.48 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 158.48, 142.87, 112.99, 80.50, 76.49, 56.79, 48.77, 40.72, 29.04, 28.54, 21.09. **IR (neat):** 3353, 2961, 2931, 2864, 1649, 1483, 1442, 1419, 1150, 919, 873, 779 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{13}H_{23}NNaO_3$) requires *m/z* 264.15701, found *m/z* 264.15710.



di-*tert*-butyl 6-hydroxy-6-vinyl-1,4-diazepane-1,4-dicarboxylate (14)

The titled compound was synthesized by a three-step sequence from known compound 1,4-dibenzyl-1,4-diazepan-6-ol.[11] 1,4-Dibenzyl-1,4-diazepan-6-ol was first converted to di-*tert*-butyl 6-hydroxy-1,4-diazepane-1,4-dicarboxylate under a one-pot reduction/Boc protection condition modified based on literature.[12] The oxidation of di-*tert*-butyl 6-hydroxy-1,4-diazepane-1,4-dicarboxylate by Dess-Martin periodinane delivered di-tert-butyl 6-oxo-1,4-diazepane-1,4-dicarboxylate.[9] The titled compound was then furnished by a final vinylation[5] of di-*tert*-butyl 6-oxo-1,4-diazepane-1,4-dicarboxylate.



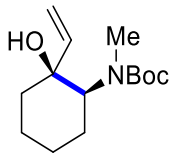
An oven-dried 50-mL round-bottomed flask, charged with a stir bar, was added 1,4-dibenzyl-1,4-diazepan-6-ol (0.675 mmol, 1.00 eq., 200 mg), di-*tert*-butyl decarbonate (1.48 mmol, 2.20 eq., 0.350 mL) and palladium on carbon (71.8 mg, 10 wt%). The flask was sealed and evacuated and refilled with nitrogen gas for three times. Then, MeOH (25 mL) was added. A hydrogen gas balloon was connected to the flask, and the evacuation and hydrogen gas refilling process was repeated for three times while stirring. The resulting mixture was stirred at r.t. for another 24 h under an atmospheric-pressure hydrogen. Then, the reaction mixture was filtered through a plug of Celite. The filter cake was rinsed by CH_2Cl_2 (10 mL, two times). The collected filtrate was concentrated under reduced pressure at 45 °C to afford di-*tert*-butyl 6-hydroxy-1,4-diazepane-1,4-dicarboxylate (200 mg, 94% yield) as a white solid. No further purification was conducted, and the crude material was carried on to next step.

An oven-dried 25-mL round-bottomed flask, charged with a stir bar, was added di-*tert*-butyl 6-hydroxy-1,4-diazepane-1,4-dicarboxylate (0.630 mmol, 1.00 eq., 200 mg) and Dess-Martin periodinane (0.950 mmol, 1.50 eq., 402 mg). Under inert atmosphere, CH_2Cl_2 (3 mL) was added. The solution was stirred at r.t. for 24 h and was then. diluted by Et_2O (10 mL). Quenched by 10% aq. $Na_2S_2O_3$ (40 mL), the mixture was stirred for 30 minutes. After layer separation, the organic layer was washed with 5% aq. Na_2CO_3 (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated to afford di-*tert*-butyl 6-oxo-1,4-diazepane-1,4-dicarboxylate (189 mg, 95% yield) as a white solid. No further purification was conducted, and the crude material was carried on to

next step. Spectral data of the crude match with literature values.[13]

To an oven-dried 10-mL round-bottomed flask, charged with a stir bar, was added vinylmagnesium chloride (1.86 mmol, 3.00 eq., 1.1 mL, 1.6 M THF solution) under inert atmosphere. The solution was cooled to 0 °C, and a THF solution of di-*tert*-butyl 6-oxo-1,4-diazepane-1,4-dicarboxylate (0.620 mmol, 1.00 eq., 195 mg, 3 mL THF) was added in dropwise. The mixture was allowed to warm to r.t. and stirred for 12 h. Afterwards, the reaction was quenched with sat. aq. NH_4Cl (20 mL), extracted in Et_2O (15 mL, three times). The combined organic layers were washed with sat. aq. NaCl (15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexanes) to obtain the titled compound (164 mg, 77% yield) as a colorless oil which slowly solidified to a white solid.

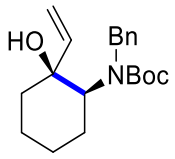
^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 5.95 (dd, *J* = 17.1, 10.7 Hz, 1H), 5.49 (d, *J* = 17.5 Hz, 1H), 5.15 (dd, *J* = 10.7, 1.7 Hz, 1H), 4.44–2.87 (m, 8H), 1.48 (br, 18H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 157.78, 156.58, 140.50, 114.28, 113.79, 81.18, 80.64, 77.55, 57.93, 57.01, 49.54, 49.25, 28.50. **IR (neat):** 3422, 2969, 2928, 1692, 1661, 1483, 1408, 1364, 1066, 768, 625 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{17}H_{30}N_2NaO_5$) requires *m/z* 365.20469, found *m/z* 365.20425.



***tert*-butyl ((1*S**,2*S**)-2-hydroxy-2-vinylcyclohexyl)(methyl)carbamate (15)**

The titled compound was synthesized by vinylation of *tert*-butyl methyl(2-oxocyclohexyl)carbamate, which was synthesized following a literature procedure.[5,14]

To an oven-dried 25-mL round-bottomed flask, charged with a stir bar, was added vinylmagnesium chloride (8.18 mmol, 2.00 eq., 5.5 mL, 1.6 M THF solution) under inert atmosphere. The solution was cooled to 0 °C, and a THF solution of *tert*-butyl methyl(2-oxocyclohexyl)carbamate (4.09 mmol, 1.00 eq., 930 mg, 10 mL THF) was added in dropwise. The mixture was allowed to warm to r.t. and stirred for 12 h. Afterwards, the reaction was quenched with sat. aq. NH_4Cl (20 mL), extracted in Et_2O (20 mL, three times). The combined organic layers were washed with sat. aq. NaCl (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (7% to 60% EtOAc in hexanes) to obtain the titled compound (413 mg, 40% yield) as a single diastereomer. The minor diastereomer, which had a slightly lower R_f, was contaminated with impurities and thus was not recovered. **^{1}H NMR (500 MHz, DMSO-d_6, 120 °C)** δ 5.89 (ddd, *J* = 17.4, 10.9, 1.9 Hz, 1H), 5.34–5.19 (m, 1H), 5.02–4.88 (m, 1H), 4.10 (s, 1H), 3.81 (dd, *J* = 12.7, 3.6 Hz, 1H), 2.79 (s, 3H), 2.05 (qd, *J* = 12.9, 4.2 Hz, 1H), 1.85–1.73 (m, 1H), 1.66 (dtd, *J* = 12.7, 8.4, 3.2 Hz, 1H), 1.58–1.50 (m, 1H), 1.50–1.24 (m, 12H). **^{13}C NMR (126 MHz, DMSO-d_6, 120 °C)** δ 154.10, 144.25, 110.56, 79.52, 73.21, 54.56, 38.13, 36.65, 27.55, 24.98, 24.50, 19.66. **IR (neat):** 3369, 2925, 2859, 1663, 1478, 1398, 1170, 1132, 970, 951, 767, 609 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{14}H_{25}NNaO_3$) requires *m/z* 278.17266, found *m/z* 278.17249.

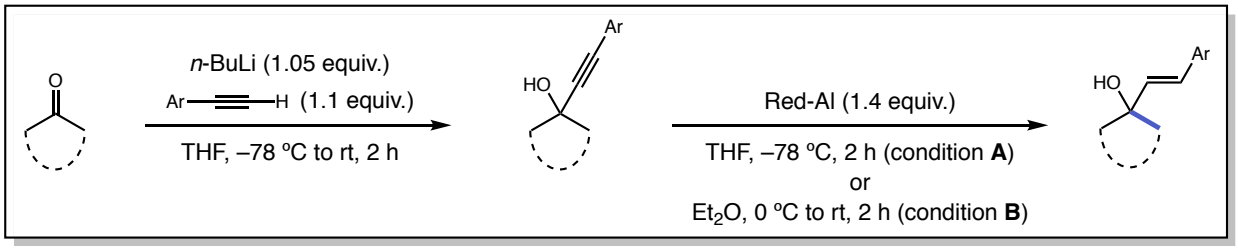


***tert*-butyl benzyl((1*S**,2*S**)-2-hydroxy-2-vinylcyclohexyl)carbamate (16)**

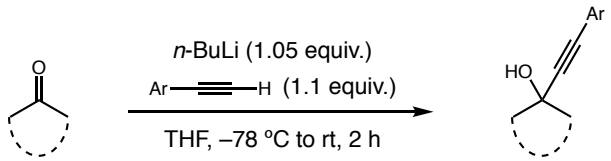
The titled compound was synthesized by vinylation of *tert*-butyl benzyl(2-oxocyclohexyl)carbamate, which was synthesized following a literature procedure.[5,15]

To an oven-dried 50-mL round-bottomed flask, charged with a stir bar, was added vinylmagnesium chloride (9.60 mmol, 2.10 eq., 6.0 mL, 1.6 M THF solution) under inert atmosphere. The solution was cooled to 0 °C, and a THF solution of tert-butyl *tert*-butyl benzyl(2-oxocyclohexyl)carbamate (4.61 mmol, 1.00 eq., 1.40 g, 20 mL THF) was added in dropwise. The mixture was allowed to warm to room temperature and stirred for 12 h. Afterwards, the reaction was quenched with sat. aq. NH_4Cl (20 mL), extracted in Et_2O (20 mL, three times). The combined organic layers were washed with sat. aq. NaCl (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (7% to 60% EtOAc in hexanes) to obtain the titled compound (242 mg, 16% yield) as a white solid. **^{1}H NMR (500 MHz, DMSO-d_6, 120 °C)** δ 7.37–7.10 (m, 5H), 5.93 (dd, J = 17.3, 10.8 Hz, 1H), 5.29 (dd, J = 17.2, 2.1 Hz, 1H), 4.98 (dd, J = 10.7, 2.1 Hz, 1H), 4.65 (d, J = 16.3 Hz, 1H), 4.53–4.35 (m, 2H), 3.87 (d, J = 10.5 Hz, 1H), 2.08–1.89 (m, 1H), 1.77–1.44 (m, 4H), 1.42–1.12 (m, 10H). **^{13}C NMR (126 MHz, DMSO-d_6, 120 °C)** δ 152.44, 144.29, 127.03, 126.12, 125.31, 110.84, 74.85, 69.76, 60.70, 48.15, 38.19, 27.37, 25.64, 25.11, 19.54. **IR (neat):** 3422, 2975, 2931, 2856, 2361, 2338, 1681, 1465, 1365, 1158, 970, 859, 569 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{20}H_{29}NNaO_3$) requires *m/z* 354.20396, found *m/z* 354.20383.

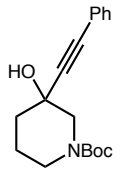
Synthesis of Starting Materials for n+1 Chemistry



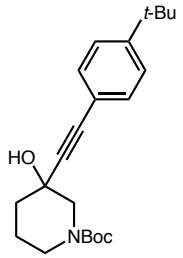
The starting materials for n+1 ring expansion were synthesized *via* alkynylation of ketone, followed by reduction of the corresponded α-alkynyl alcohol. Characterizations of α-alkynyl alcohols are iterated first.



General procedure for the alkynylation of ketone:[16]
To an oven-dried round-bottomed flask, charged with a stir bar, is added a THF solution of arylacetylene (1.10 eq. in 0.35 M THF). To the solution was added *n*-BuLi (1.05 eq., 1.6 M in hexanes) at –78 ºC. The mixture was stirred at same temperature for 30 min, and was then dropwise added a THF solution of ketone (1.00 eq. in 0.3 M THF). The resulting mixture was allowed to warm to room temperature and stirred for another 2 h. Afterwards, the reaction was quenched with sat. aq. NH_4Cl (20 mL), extracted in CH_2Cl_2 (20 mL, three times). The combined organic layers were washed with sat. aq. NaCl (20 mL), dried over $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (2% to 15% EtOAc in hexanes, unless otherwise noted) in hexanes to obtain the α-alkynyl alcohol.

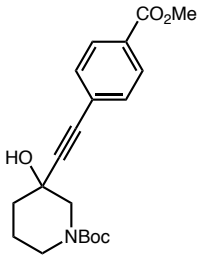


***tert*-butyl 3-hydroxy-3-(phenylethynyl)piperidine-1-carboxylate**
Prepared following the general procedure with phenylacetylene and *tert*-butyl 3-oxopiperidine-1-carboxylateto afford the titled compound as a white solid (2.55 g, 85%). **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 7.42–7.38 (m, 2H), 7.31–7.26 (m, 3H), 3.84–3.07 (m, 4H), 2.65 (br, 1H), 2.04–1.58 (m, 4H), 1.43 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers**) δ 155.46, 154.93, 131.86, 128.52, 128.33, 122.55, 90.73, 84.74, 79.96, 66.50, 54.86, 54.10, 44.56, 43.17, 38.33, 37.54, 28.51, 22.06. **IR (neat):** 3401, 2922, 2857, 1667, 1428, 1365, 1267, 1151, 899, 758 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{18}H_{24}NO_3$) requires *m/z* 302.17507, found *m/z* 302.17529.



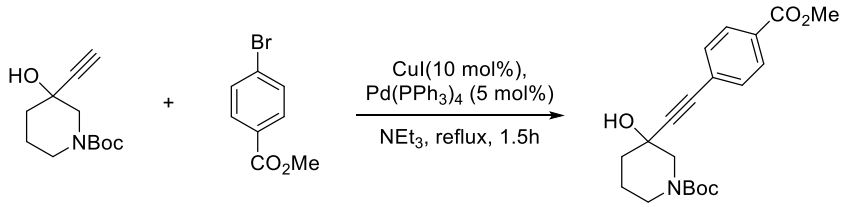
***tert*-butyl 3-((4-(*tert*-butyl)phenyl)ethynyl)-3-hydroxypiperidine-1-carboxylate**

Prepared following the general procedure with 4-*tert*-butylphenylacetylene and *tert*-butyl 3-oxopiperidine-1-carboxylateto afford the titled compound as a white solid (932 mg, 33%). **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 7.34 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 3.78–3.29 (m, 4H), 2.43 (br, 1H), 2.01–1.57 (m, 4H), 1.44 (s, 9H), 1.29 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers**) δ 154.94, 151.86, 131.60, 125.36, 119.44, 89.91, 84.98, 79.97, 66.55, 54.91, 54.17, 44.59, 43.22, 38.33, 37.50, 34.90, 31.28, 28.55, 21.97. **IR (neat):** 3405, 2953, 1678, 1440, 1364, 1269, 1156, 1074, 833, 759 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{22}H_{31}NNaO_3$) requires *m/z* 380.21961, found *m/z* 380.21948.



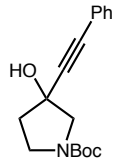
***tert*-butyl 3-hydroxy-3-((4-(methoxycarbonyl)phenyl)ethynyl)piperidine-1-carboxylate**

The titled compound was synthesized *via* Sonogashira coupling of *tert*-butyl 3-ethynyl-3-hydroxypiperidine-1-carboxylate with methyl 4-bromobenzoate following a literature procedure.[17]



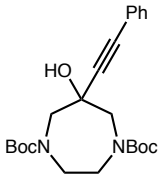
To an oven-dried 50-mL three-necked round-bottomed flask was charged with *tert*-butyl 3-ethynyl-3-hydroxypiperidine-1-carboxylate (6.00 mmol, 1.00 eq., 1.35 g), $Pd(PPh_3)_4$ (0.30 mmol, 5 mol%, 347 mg), and copper(I) iodide (0.60 mmol, 10 mol%, 114 mg) followed by triethylamine (38 mL). The flask was then purged with N_2 for 10 min before methyl 4-bromobenzoate (9.00 mmol, 1.50 eq., 1.94 g) was introduced. Purging with N_2 continued for 15 min and the resulting mixture was refluxed for 1.5 h. After cooling, the reaction mixture was filtered through a layer of Celite and the cake was washed with CH_2Cl_2. The filtrate was concentrated in vacuo and the crude residue was purified by silica gel flash column chromatography (5% to 50% EtOAc in hexanes) to furnish the titled compound (1.81g, 84%) as a pale yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 7.92 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 3.88 (s, 3H), 3.81 (m, 1H), 3.67 (br, 1H), 3.55–3.06 (m, 3H), 2.02 (m, 1H), 1.86–1.52 (m, 3H), 1.39 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 166.60, 155.31, 154.82, 131.73, 129.66, 129.45, 127.35, 93.88, 83.91, 80.01, 66.45, 54.71, 53.95, 52.33, 44.50, 43.14, 38.25, 37.49, 28.47, 22.13.

IR (neat): 3391, 2949, 2859, 1722, 1664, 1428, 1271, 1150, 1107, 972, 858, 768 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{20}H_{25}NNaO_5$) requires *m/z* 382.16249, found *m/z* 382.16226.



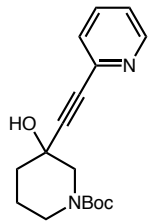
***tert*-butyl 3-hydroxy-3-(phenylethynyl)pyrrolidine-1-carboxylate**

Prepared following the general procedure with phenylacetylene and *tert*-butyl 3-oxopyrrolidine-1-carboxylateto afford the titled compound as a white solid (2.19 g, 76%). **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 7.42–7.40 (m, 2H), 7.33–7.28 (m, 3H), 3.74–3.51 (m, 4H), 3.01 (m, 1H), 2.28–2.21 (m, 2H), 1.46 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 154.65, 154.55, 131.83, 131.79, 128.76, 128.73, 128.44, 128.41, 122.25, 122.20, 89.08, 84.73, 79.80, 72.30, 71.48, 59.56, 59.31, 44.66, 44.26, 40.44, 40.06, 28.61. **IR (neat):** 3367, 2979, 2896, 1662, 1422, 1239, 1133, 936, 875, 762 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{17}H_{22}NO_3$) requires *m/z* 288.15942, found *m/z* 288.15931.



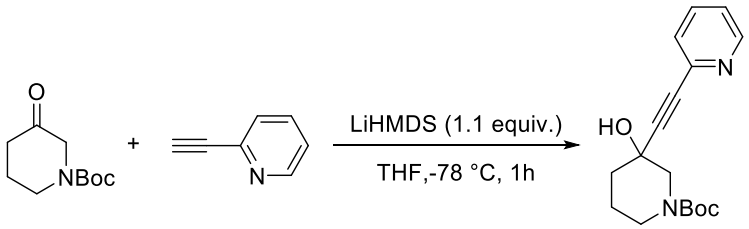
di-*tert*-butyl 6-hydroxy-6-(phenylethynyl)-1,4-diazepane-1,4-dicarboxylate

Prepared following the general procedure with phenylacetylene and di-*tert*-butyl 6-oxo-1,4-diazepane-1,4-dicarboxylate afford the titled compound as a pale yellow solid (693 mg, 82%). **^{1}H NMR (400 MHz, DMSO-d_6, 120 °C)** δ 7.39–7.31 (m, 5H), 5.38 (s, 1H), 4.04 (d, J = 14.0 Hz, 2H), 3.73–3.66 (m, 2H), 3.37–3.28 (m, 2H), 3.30 (d, J = 14.0 Hz, 2H), 1.38 (s, 18H). **^{13}C NMR (101 MHz, DMSO-d_6, 120 °C)** δ 154.07, 130.56, 127.52, 127.45, 122.28, 91.03, 83.75, 78.32, 69.36, 54.84, 45.49, 27.46. **IR (neat):** 3391, 2974, 2930, 1667, 1406, 1364, 1244, 1133, 1047, 865, 756 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{23}H_{32}N_2NaO_5$) requires *m/z* 439.22034, found *m/z* 439.22012.

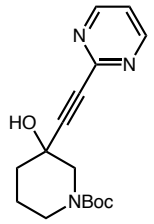


***tert*-butyl 3-hydroxy-3-(pyridin-2-ylethynyl)piperidine-1-carboxylate**

The titled compound was synthesized *via* alkynylation of *tert*-butyl 3-oxopiperidine-1-carboxylate with 2-ethynylpyridine using LiHMDS as a base following a literature procedure.[18]

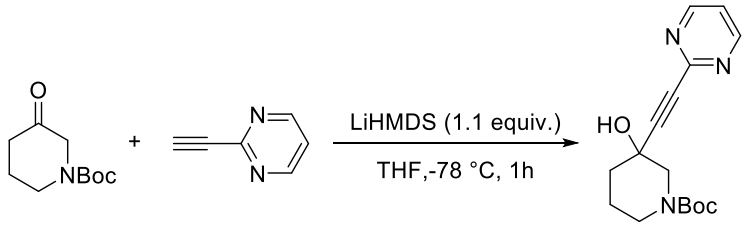


To an oven-dried 50-mL round-bottomed flask, charged with a stir bar, was added lithium bis(trimethylsilyl)amide (4.42 mmol, 1.10 eq., 739 mg) in a glove box and was then added THF (20 mL). At –78 °C, 2-ethynylpyridine (4.42 mmol, 1.10 eq., 0.45 mL) was added dropwise *by* a syringe. The resulting mixture was stirred at same temperature for 20 min to afford a yellow suspension. At –78 °C, a THF solution of *tert*-butyl 3-oxopiperidine-1-carboxylate (4.02 mmol, 1.00 eq., 0.800 g in 5 mL THF) was added dropwise. The mixture was stirred at same temperature for another 20 min. Afterwards, the reaction was quenched with sat. aq. NH_4Cl (20 mL), extracted in Et_2O (20 mL, three times). The combined organic layers were washed with sat. aq. NaCl (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (10% to 70% EtOAc in hexanes) to obtain the titled compound (762 mg, 63% yield) as a colorless, viscous oil. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 8.56 (d, *J* = 4.6 Hz, 1H), 7.63 (td, *J* = 7.7, 1.9 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.25–7.19 (m, 1H), 3.89–2.86 (m, 4H), 2.14–1.88 (m, 2H), 1.90–1.59 (m, 2H), 1.43 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 155.01, 149.99, 142.78, 136.34, 127.50, 123.22, 83.94, 80.02, 66.33, 60.55, 55.57, 53.87, 44.66, 43.24, 37.84, 28.53, 21.80. **IR (neat)** 3370, 2929, 2857, 1687, 1582, 1425, 1241, 1148, 974, 777 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{17}H_{23}N_2O_3$) requires *m/z* 303.17032, found *m/z* 303.17051.



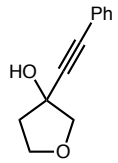
***tert*-butyl 3-hydroxy-3-(pyrimidin-2-ylethynyl)piperidine-1-carboxylate**

The titled compound was synthesized *via* alkynylation of *tert*-butyl 3-oxopiperidine-1-carboxylate with 2-ethynylpyrimidine using LiHMDS as a base following a literature procedure.[18]



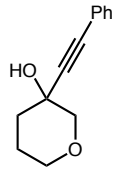
To an oven-dried 50-mL round-bottomed flask, charged with a stir bar, was added lithium bis(trimethylsilyl)amide (3.86 mmol, 1.10 eq., 647 mg) in a glove box and was then added THF (20 mL). At −78 °C, a THF solution of 2-ethynylpyrimidine (3.86 mmol, 1.10 eq., 402 mg in 3 mL THF) was added dropwise *by* a syringe. The resulting mixture was stirred at same temperature for 45 min to afford a yellow suspension. At −78 °C, a THF solution of *tert*-butyl 3-oxopiperidine-1-carboxylate (3.51 mmol, 1.00 eq., 700 mg in 5 mL THF) was added dropwise. The mixture was

stirred at same temperature for another 1 h. Afterwards, the reaction was quenched with sat. aq. NH_4Cl (20 mL), extracted in Et_2O (20 mL, three times). The combined organic layers were washed with sat. aq. NaCl (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (7% to 100% EtOAc in hexanes) to obtain the titled compound (730 mg, 69% yield) as a white solid. . **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** 8.72 (d, J = 5.0 Hz, 2H), 7.24 (t, J = 5.0 Hz, 1H), 4.05–2.30 (m, 5H), 2.03 (s, 2H), 1.89–1.77 (m, 1H), 1.68 (s, 1H), 1.44 (s, 9H).**^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 157.40, 155.03, 152.67, 120.24, 89.59, 83.29, 80.17, 66.23, 54.48, 44.77, 43.33, 37.47, 28.52, 21.37. **IR (neat):** 3244, 2980, 2946, 2864, 1683, 1565, 1476, 1408, 1241, 1072, 905, 649 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{16}H_{22}N_3O_3$) requires *m/z* 304.16557, found *m/z* 304.16559.



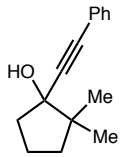
3-(phenylethynyl)tetrahydrofuran-3-ol

Prepared following the general procedure with phenylacetylene and tetrahydrofuran-3-one using 3% to 23% Et_2O in hexanes as flash silica gel chromatography eluent condition to afford the titled compound as a colorless oil (501 mg, 89%). **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 7.45–7.41 (m, 2H), 7.33–7.26 (m, 3H), 4.10 (m, 1H), 4.05–4.00 (m, 2H), 3.95 (d, J = 9.3 Hz, 1H), 3.12 (br, 1H), 2.42–2.27 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 131.72, 128.67, 128.39, 122.25, 88.78, 84.95, 80.02, 73.38, 67.76, 42.47. **IR (neat):** 3359, 2951, 2872, 1488, 1355, 1236, 1090, 1037, 940, 754, 689 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{12}H_{13}O_2$) requires *m/z* 189.09101, found *m/z* 189.09094.



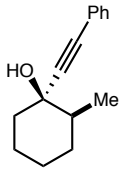
3-(phenylethynyl)tetrahydro-2*H*-pyran-3-ol

Prepared following the general procedure with phenylacetylene and dihydro-2*H*-pyran-3(4*H*)-one using 3% to 23% Et_2O in hexanes as flash silica gel chromatography eluent condition to afford the titled compound as a colorless oil (970 mg, 48%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.45–7.43 (m, 2H), 7.33–7.28 (m, 3H), 3.80–3.70 (m, 3H), 3.61 (m, 1H), 2.55 (br, 1H), 2.05–2.03 (m, 2H), 1.91 (m, 1H), 1.70 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 131.95, 128.67, 128.39, 122.39, 90.06, 85.07, 75.78, 68.07, 65.75, 36.56, 22.28. **IR (neat):** 3372, 2949, 2848, 1489, 1301, 1195, 1084, 922, 754, 690 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{13}H_{15}O_2$) requires *m/z* 203.10666, found *m/z* 203.10666.



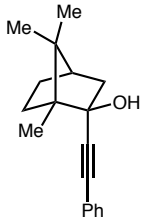
2,2-dimethyl-1-(phenylethynyl)cyclopentan-1-ol

The titled compound was prepared according to a literature procedure. Spectra are consistent with reported literature values.[19]



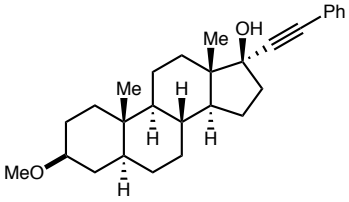
(1*R,2*S**)-2-methyl-1-(phenylethynyl)cyclohexan-1-ol**

The titled compound was prepared according to a literature procedure. Spectra are consistent with reported literature values.[20]



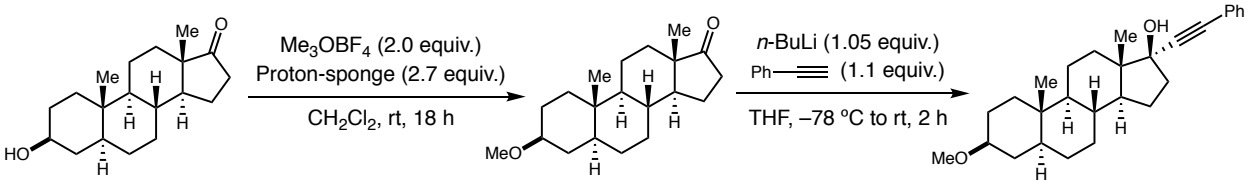
(1*R*,2*S*,4*R*)-1,7,7-trimethyl-2-(phenylethynyl)bicyclo[2.2.1]heptan-2-ol

The titled compound was prepared according to a literature procedure. Spectra are consistent with reported literature values.[21]



(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-methoxy-10,13-dimethyl-17-(phenylethynyl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-ol

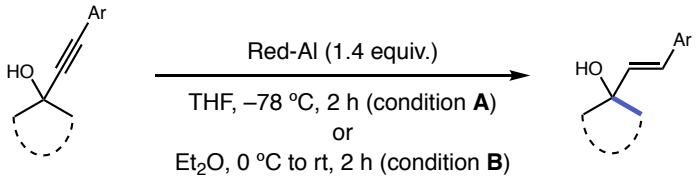
The titled compound was synthesized *via* methylation of *trans*-androsterone,[22] followed by alkynylation.



To a stirred solution of *trans*-androsterone (4.00 mmol, 1.00 eq., 1.16 g) and Proton-sponge® (10.8 mmol, 2.70 eq., 2.32 g) in CH_2Cl_2 (160 mL) was added trimethyloxonium tetrafluoroborate (8.00 mmol, 2.00 eq., 1.18 g) at room temperature. The mixture was stirred at same temperature for 18 h. The reaction was quenched by addition of sat. aq. NH_4Cl (20 mL), extracted in CH_2Cl_2 (20 mL, three times). The combined organic layers were washed with sat. aq. NaCl (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography to furnish methylated *trans*-androsterone (760 mg, 62%) as a white solid.

Data for (3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-3-methoxy-10,13-dimethylhexadecahydro-17*H*-cyclopenta[*a*]phenanthren-17-one: **^{1}H NMR (500 MHz, $CDCl_3$)** δ 3.33 (s, 3H), 3.12 (m, 1H), 2.42 (dd, *J* = 19.3, 8.8 Hz, 1H), 2.05 (m, 1H), 1.93–1.85 (m, 2H), 1.80–1.76 (m, 2H), 1.72 (dt, *J* = 13.2, 3.7 Hz, 1H), 1.68–1.62 (m, 2H), 1.57–1.44 (m, 2H), 1.37–1.17 (m, 7H), 1.08 (m, 1H), 1.00–0.91 (m, 2H), 0.85 (s, 3H), 0.81 (s, 3H), 0.68 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 221.54, 79.82, 55.70, 54.62, 51.57, 47.93, 44.90, 37.00, 36.08, 35.98, 35.17, 34.42, 31.69, 31.06, 28.66, 27.91, 21.90, 20.61, 13.94, 12.37. **IR (neat):** 2918, 2855, 1743, 1447, 1375, 1240, 1096, 1012, 932, 830 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{20}H_{33}O_2$) requires *m/z* 305.24751, found *m/z* 305.24747.

Following the general procedure, the alkynylation of methylated *trans*-androsterone with phenylacetylene afforded the titled compound as a white solid (803.8 mg, 82%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.46–7.42 (m, 2H), 7.34–7.29 (m, 3H), 3.34 (s, 3H), 3.12 (m, 1H), 2.35 (m, 1H), 2.08–1.96 (m, 2H), 1.77–1.17 (m, 16H), 1.07 (m, 1H), 0.99–0.86 (m, 2H), 0.88 (s, 3H), 0.82 (s, 3H), 0.68 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 131.80, 128.40, 128.32, 123.18, 93.07, 85.88, 80.49, 79.96, 55.68, 54.21, 50.87, 47.55, 44.90, 39.19, 37.06, 36.33, 36.02, 34.46, 33.17, 31.78, 28.86, 28.00, 23.39, 21.08, 13.16, 12.44. **IR (neat):** 3401, 2922, 2852, 1443, 1379, 1292, 1093, 1041, 911, 755, 690 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{28}H_{39}O_2$) requires *m/z* 407.29446, found *m/z* 407.29419.



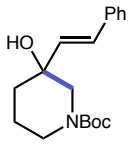
General procedure for the reduction of α-alkynyl alcohol:

Condition **A**[23]

To an oven-dried round-bottomed flask, charged with a stir bar, was added α-alkynyl alcohol (1.00 eq.) and THF. The solution was cooled to −78 °C and was added Red-Al® sodium bis(2-methoxyethoxy)aluminum hydride solution (1.40 eq.). The resulting mixture was stirred for another 2 h at same temperature. Afterwards, the reaction was quenched by slow addition of sat. aq. NH_4Cl at −78 °C. The resulting mixture extracted in Et_2O (20 mL, three times). The combined organic layers were washed with sat. aq. NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (2% to 15% EtOAc in hexanes, unless otherwise noted) to obtain the allylic alcohol.

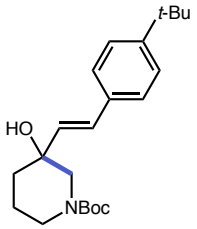
Condition **B**[6]

To an oven-dried round-bottomed flask, charged with a stir bar, was added α-alkynyl alcohol (1.00 eq.) and Et_2O. The solution was cooled to 0 °C and was added Red-Al® sodium bis(2-methoxyethoxy)aluminum hydride solution (1.40 eq.). The resulting mixture was allowed to warm to room temperature and stirred for another 2 h. Afterwards, the reaction was quenched by slow addition of sat. aq. NH_4Cl (15 mL) at 0 °C. The resulting mixture was extracted in Et_2O (20 mL, three times). The combined organic layers were washed with brine. The combined organic layers were then dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (2% to 15% EtOAc in hexanes, unless otherwise noted) to obtain the allylic alcohol.



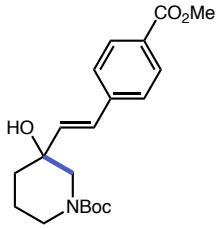
***tert*-butyl (*E*)-3-hydroxy-3-styrylpiperidine-1-carboxylate (17)**

Prepared following the general procedure (condition **B**) with *tert*-butyl 3-hydroxy-3-(phenylethynyl)piperidine-1-carboxylate to afford the titled compound as a white solid (2.17 g, 96%). **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 7.38–7.37 (m, 2H), 7.32–7.29 (m, 2H), 7.23 (m, 1H), 6.75 (d, J = 16.1 Hz, 1H), 6.25 (d, J = 16.1 Hz, 1H), 3.80–3.64 (m, 2H), 3.18–3.03 (m, 2H), 2.35 (br, 1H), 1.95–1.56 (m, 4H), 1.47 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 155.78, 136.82, 133.59, 129.21, 128.68, 127.75, 126.59, 80.02, 70.67, 54.27, 53.42, 44.74, 43.51, 36.34, 28.54, 21.47. **IR (neat):** 3406, 2951, 2854, 1650, 1433, 1248, 1156, 961, 837, 746 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{18}H_{25}NNaO_3$) requires *m/z* 326.17266, found *m/z* 326.17267.



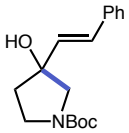
***tert*-butyl (*E*)-3-(4-(*tert*-butyl)styryl)-3-hydroxypiperidine-1-carboxylate (18)**

Prepared following the general procedure (condition **A**) with *tert*-butyl 3-((4-(*tert*-butyl)phenyl)ethynyl)-3-hydroxypiperidine-1-carboxylate to afford the titled compound as a white solid (681 mg, 71%). **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 7.34 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 16.1 Hz, 1H), 6.22 (d, *J* = 16.1 Hz, 1H), 3.96–3.44 (m, 2H), 3.35–2.88 (m, 2H), 2.13 (br, 1H), 1.86–1.56 (m, 4H), 1.47 (s, 9H), 1.31 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers**) δ 155.82, 150.95, 134.01, 132.78, 128.96, 126.32, 125.64, 80.03, 70.75, 54.24, 53.47, 44.84, 43.60, 36.36, 34.70, 31.41, 28.57, 21.47. **IR (neat):** 3455, 2961, 2864, 1669, 1424, 1267, 1151, 968, 902, 765 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{22}H_{33}NNaO_3$) requires *m/z* 382.23527, found *m/z* 382.23508.



***tert*-butyl (*E*)-3-hydroxy-3-(4-(methoxycarbonyl)styryl)piperidine-1-carboxylate (19)**

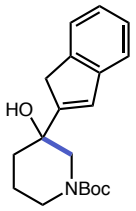
Prepared following the general procedure (condition **A**) with *tert*-butyl 3-hydroxy-3-((4-(methoxycarbonyl)phenyl)ethynyl)piperidine-1-carboxylate using 4% to 27% EtOAc in hexanes as flash silica gel chromatography eluent condition to afford the titled compound as a white solid (1.55 g, 93%). **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 6.79 (d, *J* = 16.0 Hz, 1H), 6.36 (d, *J* = 16.0 Hz, 1H), 3.90 (s, 3H), 3.82–3.53 (m, 2H), 3.17–2.84 (m, 2H), 2.36 (br, 1H), 1.91–1.66 (m, 4H), 1.46 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers**) δ 167.01, 156.04, 155.55, 141.35, 136.24, 130.05, 129.14, 128.40, 126.49, 80.19, 70.84, 54.20, 53.22, 52.24, 44.79, 43.52, 36.22, 28.53, 21.39. **IR (neat):** 3418, 2932, 2857, 1718, 1665, 1428, 1273, 1151, 1107, 969, 869, 762 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{20}H_{28}NO_5$) requires *m/z* 362.19620, found *m/z* 362.19613.



***tert*-butyl (*E*)-3-hydroxy-3-styrylpyrrolidine-1-carboxylate (20)**

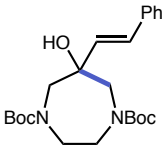
Prepared following the general procedure (condition **A**) with *tert*-butyl 3-hydroxy-3-(phenylethynyl)pyrrolidine-1-carboxylate to afford the titled compound as a white solid (1.14 g, 65%). **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 7.40–7.38 (m, 2H), 7.35–7.32 (m, 2H), 7.26 (m, 1H), 6.77 (dd, *J* = 16.1, 4.3 Hz, 1H), 6.32 (d, *J* = 16.1 Hz, 1H), 3.66–3.41 (m, 4H), 2.44 (m, 1H), 2.10–1.90 (m, 2H), 1.47 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers**) δ 154.84, 154.74, 136.40, 131.49, 129.56, 129.47, 128.75, 127.94, 126.64, 126.60,

79.62, 79.51, 78.68, 58.41, 58.08, 45.00, 44.59, 39.08, 38.64, 28.63. **IR (neat):** 3389, 2975, 2898, 1660, 1415, 1255, 1124, 971, 877, 750 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{17}H_{24}NO_3$) requires *m/z* 290.17507, found *m/z* 290.17500.



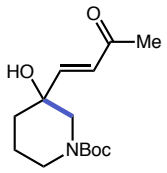
***tert*-butyl 3-hydroxy-3-(1*H*-inden-2-yl)piperidine-1-carboxylate (21)**
The titled compound was synthesized *via* Grignard addition of *tert*-butyl 3-oxopiperidine-1-carboxylate following a literature procedure.[7]

A flame-dried 250-mL three-necked round-bottomed flask was charged with a stir bar and magnesium turnings (24.0 mmol, 1.30 eq., 583 mg). The flask was then evacuated and refilled with argon. THF (40 mL) was added to the flask, and a THF (5 mL) solution of 2-bromoindene (20.0 mmol, 1.10 eq., 3.90 g) was added dropwise. The mixture was stirred at room temperature under argon atmosphere for 30 min and was then refluxed for another 1 h to complete the formation of the Grignard reagent. Afterwards, the solution was cooled to 0 ºC in an ice bath, and a THF (5 mL) solution of ketone (18.0 mmol, 1.00 eq., 3.59 g) was added dropwise. The reaction was allowed to warm to room temperature and stirred for another 12 h. The reaction was quenched by addition of sat. aq. NH_4Cl (30 mL), extracted in Et_2O (30 mL, three times). The combined organic layers were washed with sat. aq. NaCl (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a small volume. This crude was purified by silica gel flash column chromatography (2% to 15% EtOAc in hexanes, four times) to obtain the titled compound (2.34 g, 34% yield) as an orange solid. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 7.43 (d, *J* = 7.4 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.17 (td, *J* = 7.4, 1.2 Hz, 1H), 6.82 (s, 1H), 4.00–3.67 (m, 2H), 3.50 (d, *J* = 5.7 Hz, 2H), 3.30 (br, 1H), 3.02 (br, 1H), 2.34 (br, 1H), 1.98–1.78 (m, 4H), 1.47 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 156.09, 152.72, 144.51, 143.10, 127.03, 126.57, 124.78, 123.84, 121.10, 80.15, 70.53, 54.33, 53.54, 44.94, 43.68, 37.87, 36.17, 28.54, 21.46. **IR (neat):** 3418, 2928, 2857, 1663, 1425, 1243, 1147, 862, 751 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{19}H_{25}NNaO_3$) requires *m/z* 338.17266, found *m/z* 338.17233.

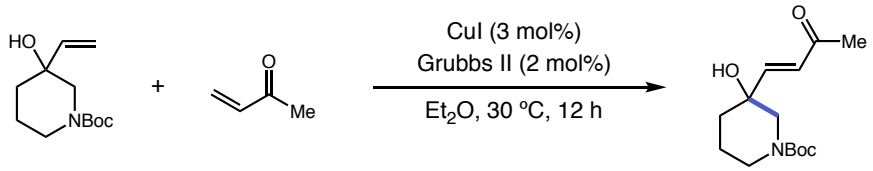


di-*tert*-butyl (*E*)-6-hydroxy-6-styryl-1,4-diazepane-1,4-dicarboxylate (22)
Prepared following the general procedure (condition **B**) with di-*tert*-butyl 6-hydroxy-6-(phenylethynyl)-1,4-diazepane-1,4-dicarboxylateto to afford the titled compound as a white solid (662 mg, 97%). **^{1}H NMR (400 MHz, DMSO-d_6, 120 °C)** δ 7.37 – 7.35 (m, 2H), 7.32 – 7.29 (m, 2H), 7.21 (m, 1H), 6.74 (d, *J* = 16.1 Hz, 1H), 6.33 (d, *J* = 16.1 Hz, 1H), 4.53 (s, 1H), 3.71 (d, *J* = 14.2 Hz, 2H), 3.68–3.59 (m, 2H), 3.46–3.38 (m, 2H), 3.33 (d, *J* = 14.2 Hz, 2H), 1.39 (s, 18H). **^{13}C NMR (101 MHz, DMSO-d_6, 120 °C)** δ 154.27, 136.83, 133.10, 127.66, 126.72, 126.37, 125.51, 78.46, 73.86, 55.05, 45.99, 27.42. **IR (neat):** 3419, 2975, 2930, 1688, 1408, 1364, 1245, 1139,

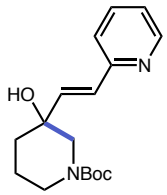
946, 862, 746 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{23}H_{34}N_2NaO_5$) requires *m/z* 441.23599, found *m/z* 441.23572.



(*E*)-*tert*-butyl 3-hydroxy-3-(3-oxobut-1-en-1-yl)piperidine-1-carboxylate (23)
The titled compound was synthesized *via* cross metathesis of *tert*-butyl 3-hydroxy-3-vinylpiperidine-1-carboxylate (**1**) with methyl vinyl ketone following a literature procedure.[24]

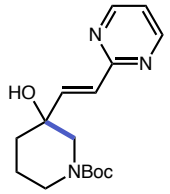


To an oven-dried 50-mL round-bottomed flask, charged with a stir bar and fitted with a condenser, is added *tert*-butyl 3-hydroxy-3-vinylpiperidine-1-carboxylate (**1**) (2.00 mmol, 1.00 eq., 455 mg) and Grubbs second generation catalyst (0.06 mmol, 0.03 eq., 11.4 mg). The system was then brought into a glove box and was added copper(I) iodide (0.04 mmol, 0.02 eq., 34.0 mg). The system was sealed and was brought out of glove box. Under N_2 atmosphere, Et_2O (20 mL) was added in one portion. The mixture was stirred for ~5 min and was then added methyl vinyl ketone (8.00 mmol, 4.00 eq., 670 μL) in one portion. The resulting mixture was stirred at 30 °C for 12h. Afterwards, the reaction mixture was concentrated to a small volume and was then purified by silica gel flash column chromatography (5% to 50% EtOAc in hexanes) to furnish the titled compound (390.0 mg, 72%) as a brown oil. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 6.76 (d, *J* = 15.9 Hz, 1H), 6.43 (d, *J* = 15.9, 1H), 4.00–3.48 (m, 2H), 3.23–2.84 (m, 2H), 2.42–2.06 (m, 4H), 1.88–1.52 (m, 4H), 1.46 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 198.47, 155.53 (br), 149.19, 129.00, 80.48, 70.78, 53.02, 52.64, 44.86, 43.08, 35.55, 28.52, 28.11, 21.03. **IR (neat):** 3418, 2975, 2932, 2861, 1667, 1423, 1364, 1251, 1209, 1151, 902, 765 cm^{-1}. **HRMS (EI):** exact mass calculated for $[M–Boc+H]^+$ ($C_9H_{15}NO_2$) requires *m/z* 169.10973, found *m/z* 169.10974.



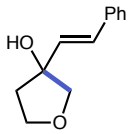
***tert*-butyl (*E*)-3-hydroxy-3-(2-(pyridin-2-yl)vinyl)piperidine-1-carboxylate (24)**
Prepared following the general procedure (condition **B** but instead used THF as a solvent) with *tert*-butyl 3-hydroxy-3-(pyridin-2-ylethynyl)piperidine-1-carboxylate using 7% to 60% EtOAc in hexanes as flash silica gel chromatography eluent condition to afford the titled compound as a viscous, a colorless oil (447 mg, 58%). **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 8.55 (d, *J* = 4.7 Hz, 1H), 7.63 (td, *J* = 7.6, 1.9 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 1H), 7.13 (ddd, *J* = 7.6, 4.7, 1.3 Hz, 1H), 6.88–6.71 (m, 2H), 4.00–3.58 (m, 2H), 3.12 (s, 1H), 2.92 (ddd, *J* = 13.9, 11.0, 3.3 Hz, 1H), 2.53–2.07 (m, 1H), 1.92–1.66 (m, 4H), 1.46 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 155.84 (br), 155.10, 149.67, 138.05, 136.81, 128.85, 122.56, 122.44, 80.12, 71.09,

54.19, 53.13, 44.97, 43.46, 36.00, 28.54, 21.24. **IR (neat)** 3406, 2974, 2930, 2857, 1668, 1586, 1426, 1242, 1149, 974, 902, 763 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{17}H_{24}N_2NaO_3$) requires *m/z* 327.17691, found *m/z* 327.16789.



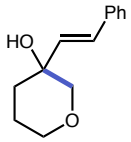
***tert*-butyl (*E*)-3-hydroxy-3-(2-(pyrimidin-2-yl)vinyl)piperidine-1-carboxylate (25)**

Prepared following the general procedure (condition **A**) with *tert*-butyl 3-hydroxy-3-(pyrimidin-2-ylethynyl)piperidine-1-carboxylate using 20% to 80% EtOAc in hexanes as flash silica gel chromatography eluent condition to afford the titled compound as a viscous, a colorless oil (550 mg, 75%). **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 8.69 (d, *J* = 4.9 Hz, 2H), 7.18 (d, *J* = 15.6 Hz, 1H), 7.11 (t, *J* = 4.9 Hz, 1H), 6.92 (d, *J* = 15.6 Hz, 1H), 4.09–3.53 (m, 2H), 3.32–2.78 (m, 2H), 2.54–1.99 (m, 1H), 1.95–1.78 (m, 2H), 1.76–1.66 (m, 1H), 1.63–1.53 (m, 1H), 1.46 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 164.44, 157.15, 156.15, 144.22, 128.72, 118.99, 80.09, 70.85, 53.55, 53.07, 44.80, 43.50, 35.88, 28.51, 21.17. **IR (neat)** 3399, 2973, 2930, 2857, 1666, 1554, 1414, 1150, 864, 767, 636, 550 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{16}H_{24}N_3O_3$) requires *m/z* 306.18122, found *m/z* 306.18123.



(*E*)-3-styryltetrahydrofuran-3-ol (26)

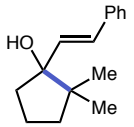
Prepared following the general procedure (condition **B**) with 3-(phenylethynyl)tetrahydrofuran-3-ol using 3% to 23% Et_2O in hexanes as flash silica gel chromatography eluent condition to afford the titled compound as a white solid (507 mg, 89%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.40–7.39 (m, 2H) 7.34–7.31 (m, 2H), 7.25 (m, 1H), 6.80 (d, *J* = 16.0 Hz, 1H), 6.32 (d, *J* = 16.0 Hz, 1H), 4.15 (m, 1H), 4.04 (td, *J* = 8.7, 3.5 Hz, 1H), 3.79 (d, *J* = 9.5 Hz, 1H), 3.75 (d, *J* = 9.5 Hz, 1H), 2.20 (m, 1H), 2.07 (m, 1H), 1.90 (br, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 136.51, 130.74, 129.45, 128.74, 127.84, 126.56, 80.90, 79.00, 67.94, 41.16. **IR (neat):** 3348, 2951, 2886, 1463, 1355, 1276, 1081, 1031, 971, 886, 753, 696 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{12}H_{15}O_2$) requires *m/z* 191.10666, found *m/z* 191.10663.



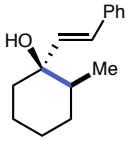
(*E*)-3-styryltetrahydro-2*H*-pyran-3-ol (27)

Prepared following the general procedure (condition **A**) with 3-(phenylethynyl)tetrahydro-2*H*-pyran-3-ol using 3% to 23% Et_2O in hexanes as flash silica gel chromatography eluent condition to afford the titled compound as a white solid (916 mg, quant.). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.40–7.39 (m, 2H), 7.33–7.30 (m, 2H), 7.24 (m, 1H), 6.76 (d, *J* = 16.1 Hz, 1H), 6.21 (d, *J* = 16.1 Hz, 1H), 3.92 (m, 1H), 3.59 (dd, *J* = 11.5, 1.5 Hz, 1H), 3.50–3.45 (m, 2H), 2.49 (br, 1H), 1.97 (m, 1H), 1.87–1.76 (m, 2H), 1.61 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 136.79, 132.16, 129.65, 128.67, 127.75, 126.56, 75.84, 69.97, 68.04, 34.88, 22.04. **IR (neat):** 3326, 2934, 2840, 1448,

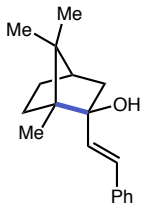
1307, 1201, 1080, 978, 929, 752, 696 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{13}H_{17}O_2$) requires *m/z* 205.12231, found *m/z* 205.12234.



(*E*)-2,2-dimethyl-1-styrylcyclopentan-1-ol (28)
Prepared following the general procedure (condition **B**) with 2,2-dimethyl-1-(phenylethynyl)cyclopentan-1-ol using 0% to 5% Et_2O in hexanes as flash silica gel chromatography eluent condition to afford the titled compound as a white solid (603 mg, 40%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.42–7.40 (m, 2H), 7.34–7.31 (m, 2H), 7.24 (m, 1H), 6.67 (d, *J* = 16.0 Hz, 1H), 6.39 (d, *J* = 16.0 Hz, 1H), 2.19 (m, 1H), 1.94–1.73 (m, 4H), 1.54 (m, 1H), 1.42 (s, 1H), 1.01 (s, 3H), 0.94 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 137.34, 132.97, 128.79, 128.68, 127.40, 126.49, 84.88, 46.83, 38.93, 38.46, 25.83, 21.35, 19.84. **IR (neat):** 3570, 2956, 2857, 1601, 1448, 1273, 1139, 979, 832, 754, 697 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}O$) requires *m/z* 217.15869, found *m/z* 217.15848.

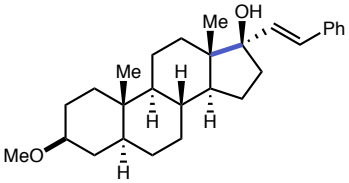


(1*R,2*S**)-2-methyl-1-((*E*)-styryl)cyclohexan-1-ol (29)**
Prepared following the general procedure (condition **B**) with (1*R**,2*S**)-2-methyl-1-(phenylethynyl)cyclohexan-1-ol using 0% to 3% Et_2O in hexanes as flash silica gel chromatography eluent condition to afford the titled compound as a white solid (559 mg, 82%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.43–7.41 (m, 2H), 7.35–7.32 (m, 2H), 7.24 (m, 1H), 6.73 (d, *J* = 16.1 Hz, 1H), 6.55 (d, *J* = 16.1 Hz, 1H), 1.91 (m, 1H), 1.78–1.65 (m, 5H), 1.62–1.49 (m, 2H), 1.38 (m, 1H), 1.28 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 137.46, 131.98, 128.99, 128.65, 127.39, 126.48, 75.19, 42.40, 40.21, 31.71, 25.20, 23.78, 15.69. **IR (neat):** 3406, 2925, 2854, 1597, 1447, 1334, 1028, 968, 743, 691 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}O$) requires *m/z* 217.15869, found *m/z* 217.15855.



(1*R*,2*S*,4*R*)-1,7,7-trimethyl-2-((*E*)-styryl)bicyclo[2.2.1]heptan-2-ol (30)
Prepared following the general procedure (condition **B**) with (1*R*,2*S*,4*R*)-1,7,7-trimethyl-2-(phenylethynyl)bicyclo[2.2.1]heptan-2-ol using 0% to 5% Et_2O in hexanes as flash silica gel chromatography eluent condition to afford the titled compound as a white solid (1.22 g, 68%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.41–7.40 (m, 2H), 7.34–7.31 (m, 2H), 7.23 (m, 1H), 6.63 (d, *J* = 16.1 Hz, 1H), 6.40 (d, *J* = 16.1 Hz, 1H), 2.12 (dt, *J* = 13.4, 3.8 Hz, 1H), 1.84–1.82 (m, 2H), 1.74 (m, 1H), 1.53 (s, 1H), 1.46–1.36 (m, 2H), 1.18 (s, 3H), 1.11 (m, 1H), 0.90 (s, 3H), 0.89 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 137.34, 136.24, 128.69, 127.77, 127.45, 126.56, 81.64, 53.55, 49.31,

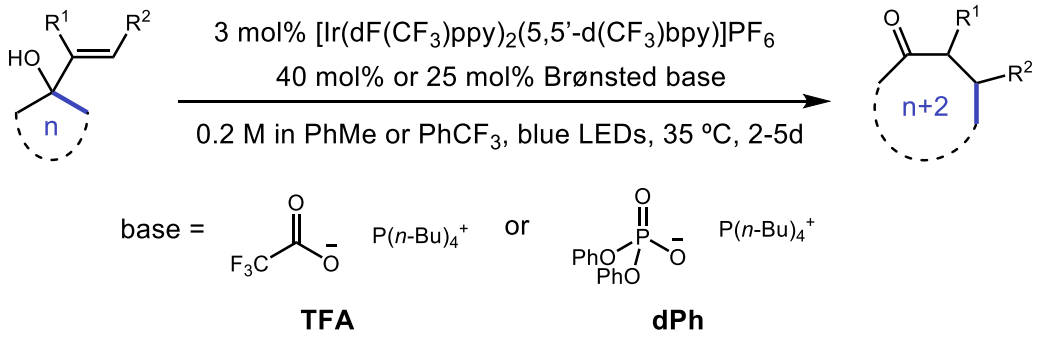
45.92, 45.74, 31.53, 27.09, 21.50, 21.11, 10.02. **IR (neat):** 3424, 2932, 2869, 1447, 1387, 1275, 1069, 968, 744, 690 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{18}H_{25}O$) requires *m/z* 257.18999, found *m/z* 257.18109.



(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*R*)-3-methoxy-10,13-dimethyl-17-((*E*)-styryl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-ol (31)

Prepared following the general procedure (condition **A**) with (3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-methoxy-10,13-dimethyl-17-(phenylethynyl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-ol using 2% to 10% Et_2O in hexanes as flash silica gel chromatography eluent condition to afford the titled compound as a white solid (539 mg, 67%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.42–7.41 (m, 2H), 7.34–7.31 (m, 2H), 7.24 (m, 1H), 6.52 (d, *J* = 16.1 Hz, 1H), 6.43 (d, *J* = 16.1 Hz, 1H), 3.33 (s, 3H), 3.10 (m, 1H), 2.07 (m, 1H), 1.93–1.85 (m, 2H), 1.73–1.62 (m, 4H), 1.60 (s, 1H), 1.55–1.16 (m, 11H), 1.03 (m, 1H), 0.94 (s, 3H), 0.94–0.80 (m, 2H), 0.80 (s, 3H), 0.57 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 137.37, 135.31, 128.72, 127.44, 127.35, 126.55, 84.30, 79.92, 55.68, 54.31, 50.49, 47.40, 44.98, 37.03, 37.00, 36.38, 36.01, 34.47, 32.67, 31.94, 28.89, 27.96, 23.83, 20.96, 14.43, 12.43. **IR (neat):** 3446, 2921, 2848, 1448, 1365, 1111, 970, 748, 690 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{28}H_{41}O_2$) requires *m/z* 409.31011, found *m/z* 409.31003.

Synthesis of Products



General Procedure A (n+2 Ring Expansion):

An oven-dried 2-dram vial, charged with a magnetic stir bar, was added substrate (0.500 mmol, 1.00 equiv) and [Ir(dF(CF_3)ppy)$_2$(5,5'-d(CF_3)bpy)]PF_6 (0.0150 mmol, 3.00 mol%, 17.2 mg), unless otherwise noticed. The vial was brought into a glove box where tetrabutylphosphonium 2,2,2-trifluoroacetate (0.200 mmol, 40.0 mol%, 74.5 mg) or tetrabutylphosphonium diphenyl phosphate (0.125 mmol, 25.0 mol%, 63.6 mg) was added. For when $PhCF_3$ was used as the reaction solvent, $PhCF_3$ (2.5 mL) were added at this point. The vial was then sealed with a Teflon septa and electric tape and removed from the glovebox. For when PhMe was used as the reaction solvent, dry PhMe (2.5 mL) was added by a syringe under N_2 atmosphere. The reaction was stirred at 35 ºC, which is the measured internal temperature using the reaction setup shown in **Figure S1** and irradiated with two Kessil lamps (Kessil H150B LED Grow Light) for 2 – 5 days. The reaction was then concentrated and purified by silica gel flash column chromatography. All preparative-scale reactions were run in duplicates, and the reported yield are the average yields of the two runs.

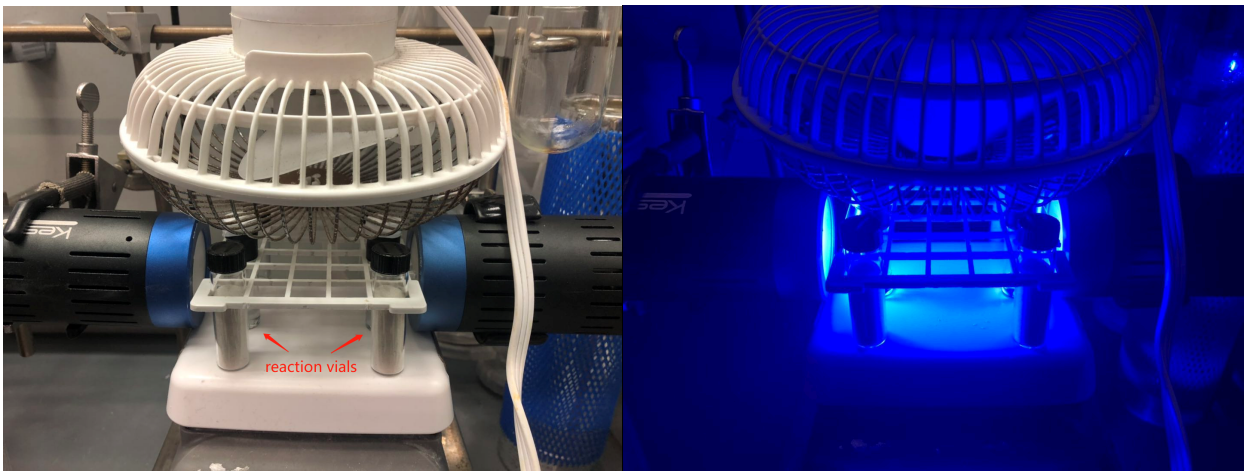


Figure S1. Lamps and fan setup examples. A test tube rack is used to hold the reaction vials.

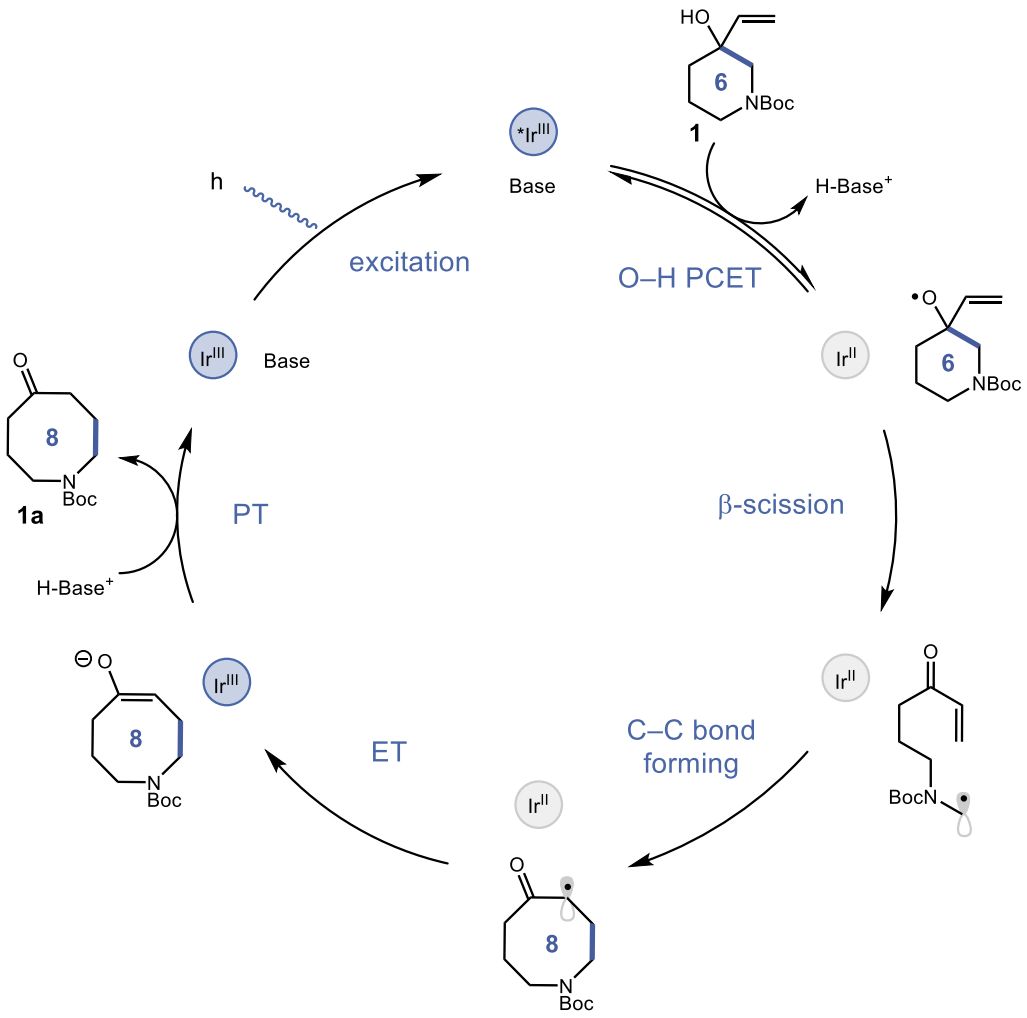
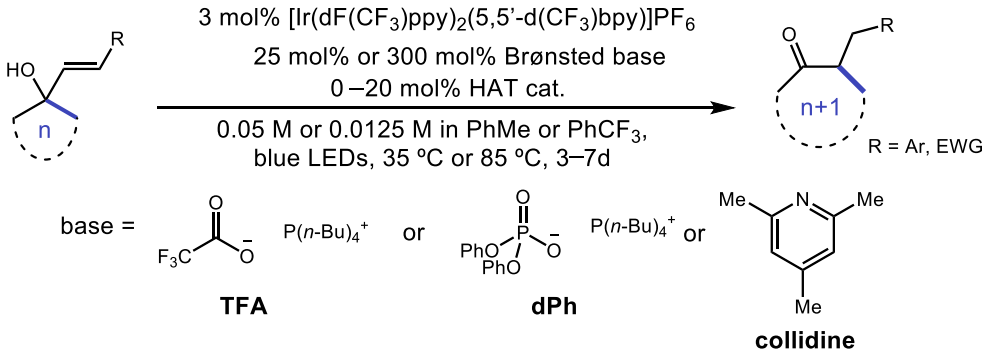


Figure S2. Proposed binary catalytic system for n+2 ring expansion



General Procedure B (n+1 Ring Expansion and n+2 Ring Expansion):

An oven-dried screw cap culture tube (16 × 125 mm or 28 × 139 mm) outfitted with a PTFE/silicone septum was charged with the relevant alcohol substrate (0.500 mmol, 1.00 equiv.) and $[Ir(dF(CF_3)ppy)_2(5,5'\text{-}d(CF_3)bpy)]PF_6$ (0.0150 mmol, 3.00 mol%, 17.2 mg). The culture tube was brought into a glove box, where tetrabutylphosphonium 2,2,2-trifluoroacetate (0.125 mmol, 25.0 mol%, 46.6 mg) or tetrabutylphosphonium diphenyl phosphate (0.125 mmol, 25.0 mol%, 63.6 mg) was weighed in. In the case of collidine base (1.50 mmol, 3.00 equiv., 198 μL), it was instead added *via* syringe after capping, outside the glovebox. For when $PhCF_3$ was used as the reaction solvent, $PhCF_3$ (10.0 mL) were added in the glovebox. The culture tube was then sealed with PTFE and electric tape and removed from the glovebox. For when PhMe was used as the reaction solvent, dry PhMe (10.0 mL or 40.0 mL) was added *via* a syringe under N_2 atmosphere. Lastly, 2,4,6-triisopropylbenzenthiol (TRIP-SH) or benzenethiol (0 mol% to 20 mol%) was added. The reaction was stirred at 35 ºC (with a fan to cool the reaction setup) or 85 ºC (without fan), which is the measured internal temperature using the reaction setup shown in **Figure S3** and irradiated with four Kessil lamps (Kessil H150B LED Grow Light) for 3 – 7 days. The reaction was then flushed through a plug of silica gel with acetone. The crude mixtures were concentrated and purified by flash column chromatography. All preparative-scale reactions were run in duplicates, and the reported yield are the average yields of the two runs.

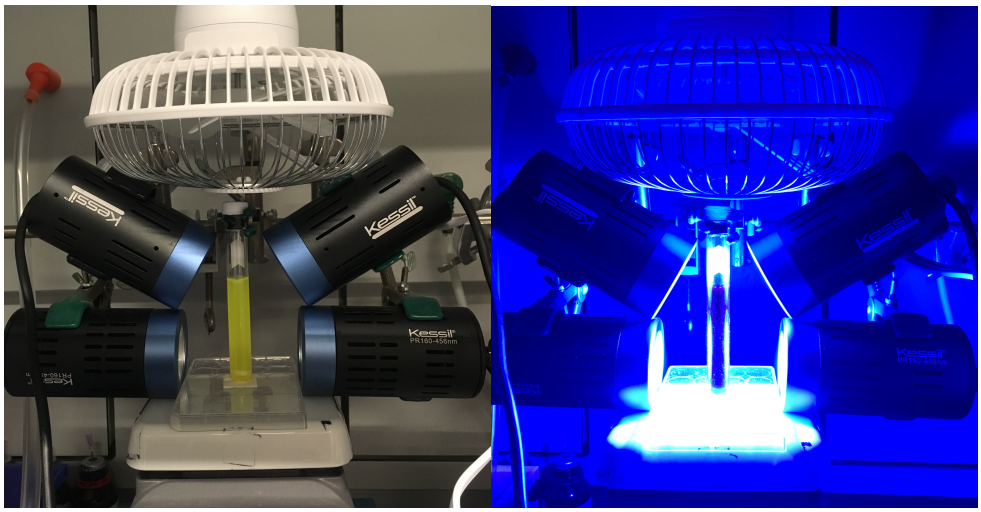


Figure S3. Lamps and fan setup examples. A clamp is used to hold the culture tube, and a riser can be used to align the bottom of the test tube with lights. This four-lamp configuration ensures even irradiation of the entire surface of the reaction vessel.

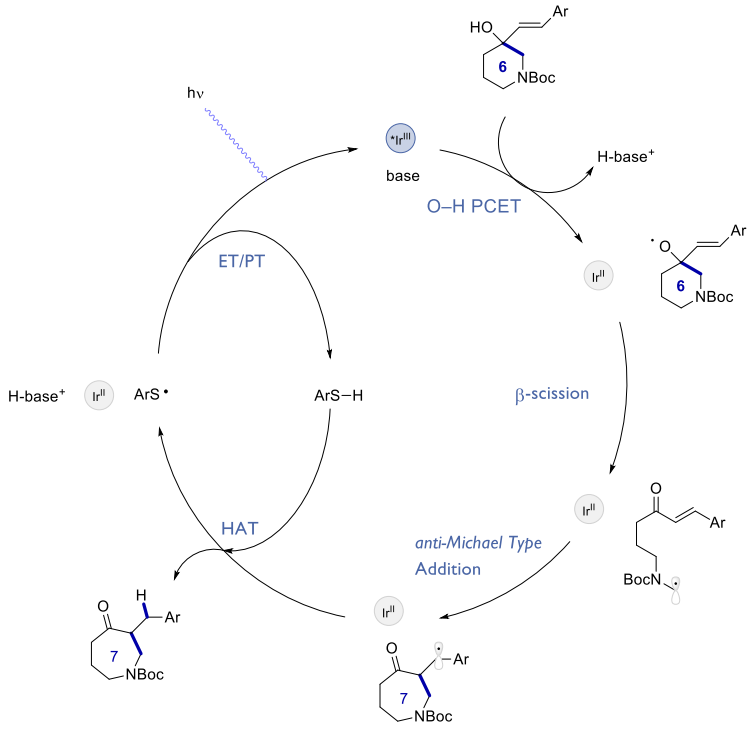


Figure S4. Proposed ternary catalytic system for n+1 ring expansion

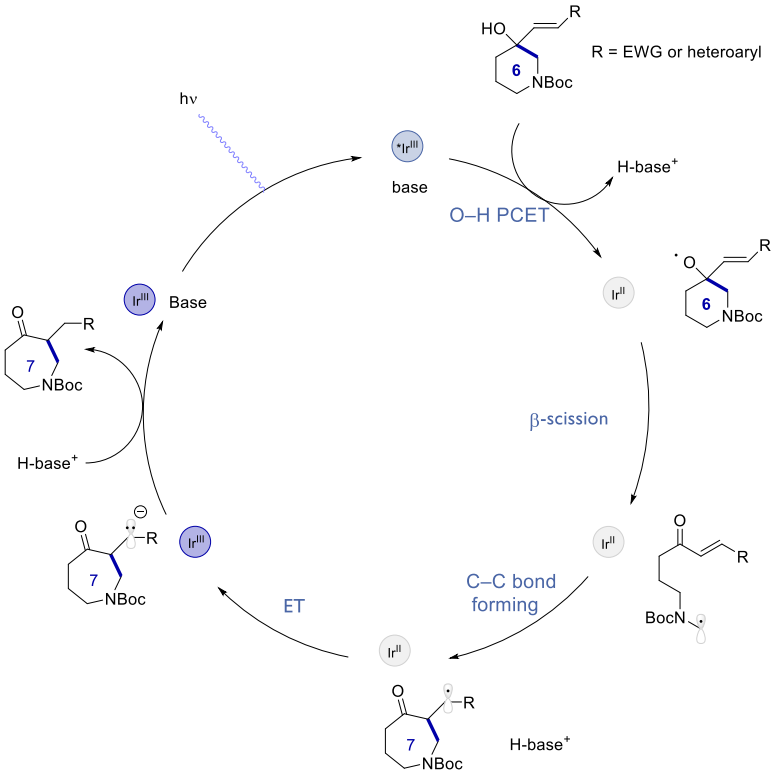
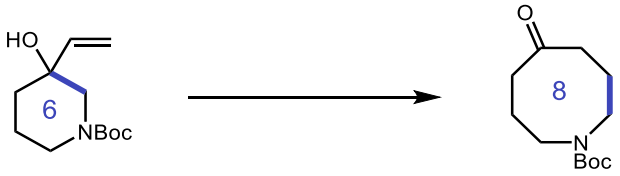


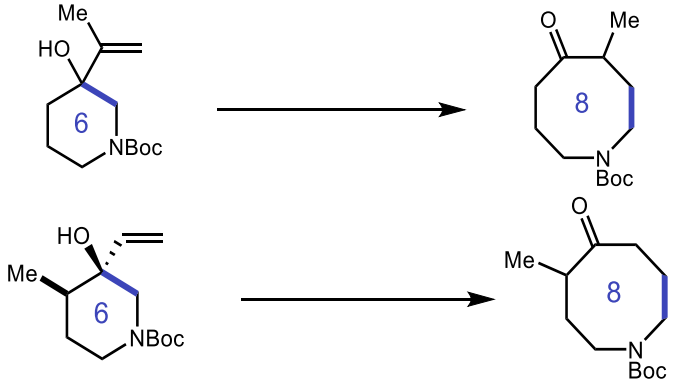
Figure S5. Proposed binary catalytic system for n+1 ring expansion (for **23a**-**25a**)

n+2 Ring Expansion



***tert*-butyl 5-oxoazocane-1-carboxylate (1a)**

The titled compound was prepared on 0.5 mmol scale following general procedure A with *tert*-butyl 3-hydroxy-3-vinylpiperidine-1-carboxylate (**1**) using PhMe solvent and TFA base and irradiated for 2 d. The crude material was purified by silica gel column chromatography (7% to 60% EtOAc in hexanes) to afford the titled compound as a pale yellow solid (95.4 mg, 84%). Spectra are consistent with reported literature values.[25]

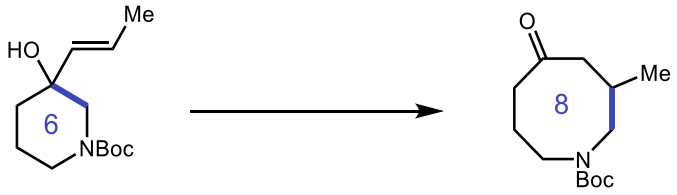


***tert*-butyl 4-methyl-5-oxoazocane-1-carboxylate (2a)**

The titled compound was prepared on 0.5 mmol scale following general procedure A with *tert*-butyl 3-hydroxy-3-(prop-1-en-2-yl)piperidine-1-carboxylate (**2**) using PhMe solvent and TFA base and irradiated for 3 d. The crude material was purified by silica gel column chromatography (7% to 60% EtOAc in hexanes) to afford the titled compound as a pale yellow solid (98.6 mg, 82%).

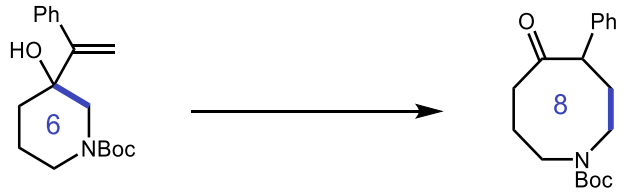
Alternatively, the titled compound was prepared on 0.5 mmol scale following general procedure A with *tert*-butyl 3-hydroxy-4-methyl-3-vinylpiperidine-1-carboxylate (**8**) using $PhCF_3$ solvent and TFA base and irradiated for 5 d. The crude material was purified by silica gel column chromatography (7% to 60% EtOAc in hexanes) to afford the titled compound as a pale yellow solid (74.8 mg, 62%).

^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 3.59–2.97 (m, 4H), 2.65–2.48 (m, 1H), 2.39–2.28 (m, 2H), 2.19–1.90 (m, 4H), 1.45 (s, 9H), 1.11–1.04 (m, 3H).**^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 215.95, 215.80, 155.44, 155.30, 80.17, 80.11, 47.52, 47.09, 45.70, 44.90, 43.67, 39.14, 37.64, 35.08, 33.42, 28.65, 28.39, 26.61, 16.01, 15.58. **IR (neat):** 2976, 2833, 1688, 1410, 1366, 1148, 776, 482 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{13}H_{23}NNaO_3$) requires *m/z* 264.15701, found *m/z* 264.15689.



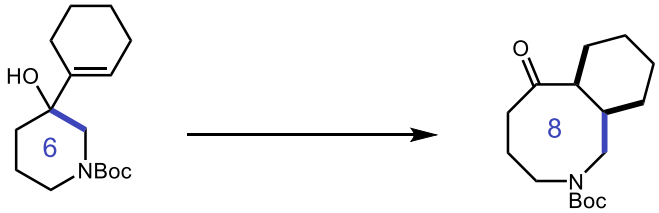
***tert*-butyl 3-methyl-5-oxoazocane-1-carboxylate (3a)**

The titled compound was prepared on 0.5 mmol scale following general procedure A with *tert*-butyl (E)-3-hydroxy-3-(prop-1-en-1-yl)piperidine-1-carboxylate (**3**) using PhMe solvent and TFA base and irradiated for 3 d. The crude material was purified by silica gel column chromatography (7% to 60% EtOAc in hexanes) to afford the titled compound as a pale yellow solid (95.0 mg, 79%). **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 3.86–2.52 (m, 5H), 2.49–2.14 (m, 5H), 1.94–1.81 (m, 1H), 1.44 (s, 9H), 0.97 (m, J = 8.2, 6.5 Hz, 3H).**^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 213.15, 155.54, 155.46, 80.31, 80.24, 54.40, 53.97, 48.80, 47.33, 47.94, 47.09, 41.67, 40.54, 35.02, 32.94, 28.63, 28.60, 27.43, 25.53, 19.02, 18.85. **IR (neat):** 2967, 2931, 2872, 1687, 1407, 1327, 1302, 1168, 1124, 897, 626 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{13}H_{23}NNaO_3$) requires *m/z* 264.15701, found *m/z* 264.15697.



***tert*-butyl 5-oxo-4-phenylazocane-1-carboxylate (4a)**

The titled compound was prepared on 0.5 mmol scale following general procedure A with *tert*-butyl 3-hydroxy-3-(1-phenylvinyl)piperidine-1-carboxylate (**4**) using $PhCF_3$ solvent and TFA base and irradiated for 5 d. The crude material was purified by silica gel column chromatography (7% to 60% EtOAc in hexanes) to afford the titled compound as a pale yellow solid (126 mg, 83%). **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 7.37–7.27 (m, 4H), 7.23 (m, 1H), 3.92–3.02 (m, 5H), 2.79–2.32 (m, 3H), 2.30–1.82 (m, 3H), 1.51–1.49 (m, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 211.96, 211.87, 155.47, 138.82, 138.17, 128.79, 128.70, 128.00, 127.82, 127.29, 127.26, 80.29, 80.25, 56.70, 55.15, 47.45, 47.12, 46.82, 45.98, 39.63, 37.14, 34.60, 31.80, 28.67, 28.60, 28.25, 26.37. **IR (neat):** 3031, 3008, 2969, 2934, 2862, 1689, 1475, 1404, 1362, 1288, 1183, 1106, 882, 770, 702, 641, 469 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{18}H_{25}NNaO_3$) requires *m/z* 326.17220, found *m/z* 326.17266.



***tert*-butyl 6-oxodecahydrobenzo[c]azocine-2(1*H*)-carboxylate(5a)**

The titled compound was prepared on 0.5 mmol scale following general procedure A with *tert*-butyl 3-(cyclohex-1-en-1-yl)-3-hydroxypiperidine-1-carboxylate (**5**) using $PhCF_3$ solvent and TFA base and irradiated for 5 d. The crude material was purified by silica gel column chromatography (7% to 60% EtOAc in hexanes) to afford the titled compound as a pale yellow solid (129 mg, 92%, d.r.>20:1 as judged by ^{1}H NMR analysis of the crude mixture). **^{1}H NMR (400 MHz, DMSO-d_6, 120 °C)** δ 3.97 (t, J = 13.6 Hz, 1H), 3.48 (dt, J = 14.1, 3.6 Hz, 1H), 2.97–2.87 (m, 2H), 2.73–2.63 (m, 1H), 2.30–2.15 (m, 2H), 2.01–1.93 (m, 1H), 1.81–1.15 (m, 19H). **^{13}C NMR (101 MHz, DMSO-d_6, 120 °C)** δ 211.65, 153.58, 78.09, 51.19, 46.55, 46.47, 36.13, 33.70, 27.56, 27.52, 27.36, 24.33, 19.97, 19.81. **IR (neat):** 2968, 2923, 2868, 2860, 1684, 1409, 1364, 1226, 1169, 699 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{16}H_{27}NNaO_3$) requires *m/z* 304.18831, found *m/z* 304.18851.

Crystal data of 5a (Figure S6): Compound **5a** was recrystallized from *n*-hexanes–dichloromethane at room temperature in 2 days. Formula $C_{16}H_{27}NO_3$, colorless, crystal dimensions 0.428 × 0.384 × 0.316 mm^3, monoclinic, space group *P* 1 2$_1$/*c*, *a* = 15.3169(12) Å, *b* = 8.6950(7) Å, *c* = 11.7020(9) Å, □ = 90º, □ = 102.1310(16)º, □ = 90º, *V* = 1523.68 Å^3, *Z* = 4, □$_{calc}$ = 1.227 g cm^{-3}, F(000) = 616, □(MoK□) = 0.083 mm^{-1}, *T* = 100 K. 47137 reflections collected, 6383 independent reflections with *I* > 2□(*I*) (2□$_{max}$ = 68.68º), and 184 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1 = 0.0421 and wR_2 = 0.1099. GOF = 1.063. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1900667. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Web page: http://www.ccdc.cam.ac.uk/].

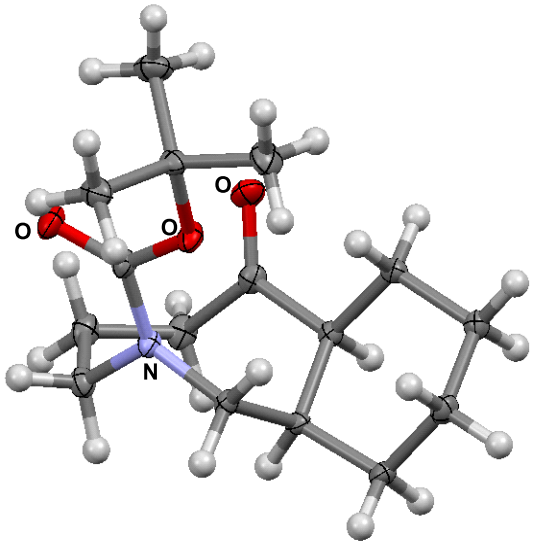
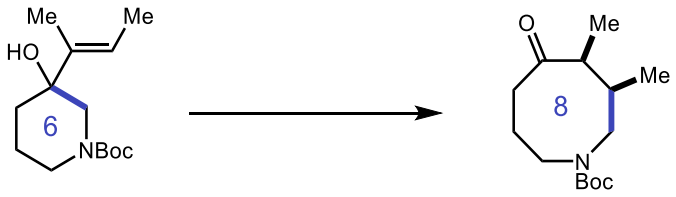


Figure S6. ORTEP drawing of 5a



***tert*-butyl 3,4-dimethyl-5-oxoazocane-1-carboxylate (6a)**

The titled compound was prepared on 0.5 mmol scale following general procedure A with *tert*-butyl (E)-3-(but-2-en-2-yl)-3-hydroxypiperidine-1-carboxylate (**6**) using $PhCF_3$ solvent and TFA base and irradiated for 5 d. The crude material was purified by silica gel column chromatography (7% to 60% EtOAc in hexanes) to afford the titled compound as a pale yellow solid (106 mg, 83%, d.r.>20:1 as judged by 1H NMR analysis of the crude mixture). **^{1}H NMR (400 MHz, DMSO-*d*$_6$, 120 °C)** δ 3.57–3.42 (m, 2H), 2.94–2.86 (m, 2H), 2.79–2.65 (m, 2H), 2.32 (qd, J = 6.8, 3.5 Hz, 1H), 2.20 (dddt, J = 13.8, 12.8, 11.9, 4.0 Hz, 1H), 2.01 (dddd, J = 12.0, 4.9, 3.9, 0.9 Hz, 1H), 1.77–1.69 (m, 1H), 1.40 (s, 9H), 0.97 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H). **^{13}C NMR (101 MHz, DMSO-*d*$_6$, 120 °C)** δ 211.97, 153.47, 78.09, 48.52, 48.50, 46.39, 36.36, 32.36, 27.58, 27.50, 15.35, 5.64. **IR (neat):** 2971, 2932, 1687, 1408, 1327, 1266, 1160, 762, 402 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{14}H_{25}NNaO_3$) requires *m/z* 278.17266, found *m/z* 278.17297.

Crystal data of 6a (Figure S7): Compound **6a** was recrystallized from *n*-hexanes–dichloromethane at room temperature for 1 days. Formula $C_{14}H_{25}NO_3$, colorless, crystal dimensions 0.39 × 0.26 × 0.22 mm^3, monoclinic, space group *P* 1 2$_1$/*c*, *a* = 12.5640 (5) Å, *b* = 9.2554(4) Å, *c* = 12.3410(5) Å, □ = 90º, □ = 91.5498 (12)º, □ = 90º, *V* = 1434.55(10) Å^3, *Z* = 1, □$_{calc}$ = 1.182 g cm^{-3}, F(000) = 560.0, □(CuK□) = 0.658 mm^{-1}, *T* = 100 K. 15321 reflections collected, 2620 independent reflections with *I* > 2□(*I*) (2□$_{max}$ = 140.1782º), and 168 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1 = 0.0337 and wR_2 = 0.0796. GOF = 1.034. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1900665. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Web page: http://www.ccdc.cam.ac.uk/].

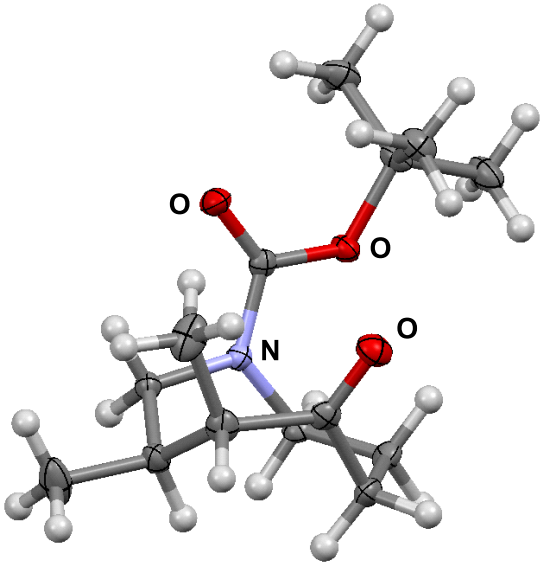
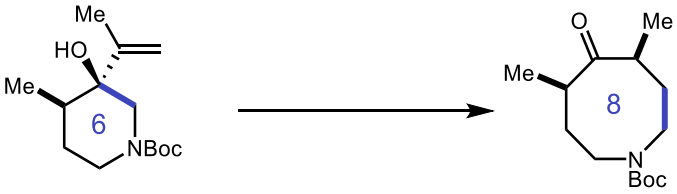


Figure S7. ORTEP drawing of 6a



***tert*-butyl 4,6-dimethyl-5-oxoazocane-1-carboxylate (7a)**

The titled compound was prepared on 0.5 mmol scale following general procedure A with *tert*-butyl 3-hydroxy-4-methyl-3-(prop-1-en-2-yl)piperidine-1-carboxylate (**7**) using $PhCF_3$ solvent and TFA base and irradiated for 5 d. The crude material was purified by silica gel column chromatography (7% to 60% EtOAc in hexanes) to afford the titled compound as a pale yellow solid (93.0 mg, 73%, d.r.>20:1 as judged by 1H NMR analysis of the crude mixture). **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 3.91 (m, 1H), 3.75 (m, 1H), 2.84–2.57 (m, 4H), 2.15–1.92 (m, 4H), 1.45 (s, 9H), 1.07 (d, J = 6.6 Hz, 6H).**^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 217.40, 155.10, 79.98, 45.39, 44.81, 43.04, 42.65, 35.17, 34.01, 28.55, 15.61, 15.26. **IR (neat):** 2973, 2930, 1687, 1408, 1364, 1247, 1149, 760, 444 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{14}H_{25}NNaO_3$) requires *m/z* 278.17266, found *m/z* 278.17261.

Crystal data of 6a (Figure S8): Compound **7a** was sublimated and condensed at room temperature for 3 weeks. Formula $C_{14}H_{25}NO_3$, colorless, crystal dimensions 0.390 × 0.168 × 0.164 mm^3, monoclinic, space group *C*1*c*1 (#9), a = 6.67270(10) Å, b = 17.8456(4) Å, c = 12.3622(3) Å, □ = 90º, □ = 98.4333(7)º, □ = 90º, V = 1456.15(5) $Å^3$, Z = 4, □$_{calc}$ = 1.165 g cm^{-3}, F(000) = 560, □(CuK□) = 0.648 mm^{-1}, T = 100 K. 2494 reflections collected, 10993 independent reflections with I > 2□(I) (2□$_{max}$ = 113.12º), and 168 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1 = 0.0222 and wR_2 = 0.0548.

GOF = 1.074. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1900666. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Web page: http://www.ccdc.cam.ac.uk/].

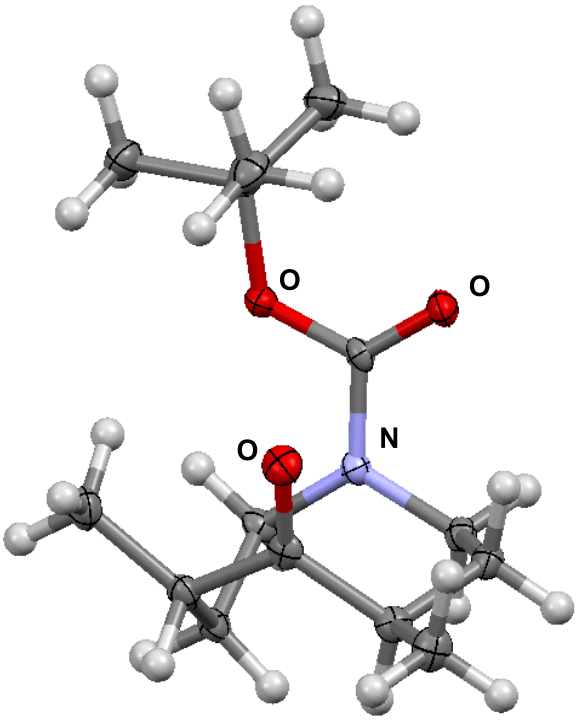
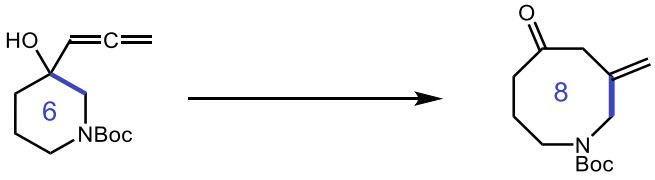


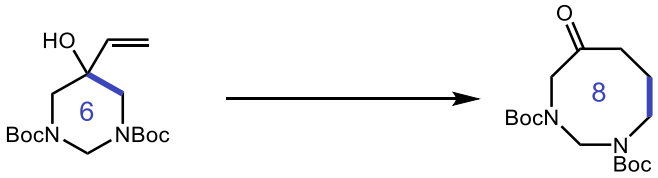
Figure S8. ORTEP drawing of 7a



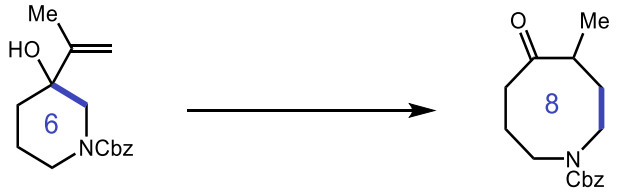
***tert*-butyl 3-methylene-5-oxoazocane-1-carboxylate (9a)**

The titled compound was prepared on 0.5 mmol scale following general procedure A with *tert*-butyl 3-hydroxy-3-(propa-1,2-dien-1-yl)piperidine-1-carboxylate (**9**) using PhMe solvent and TFA base and irradiated for 3 d. The crude material was purified by silica gel column chromatography (7% to 60% EtOAc in hexanes) to afford an inseparable mixture of starting material and the titled compound in 80% NMR yield. This mixture is then submitted to the following alcohol protection condition to remove the remaining starting material.[27]

To a 10-mL round-bottomed flask, charged with a stir bar, is added a *N*,*N*-dimethylformamide (3.0 mL) solution of the previously obtained mixture, followed by imidazole (51.0 mg, 0.75 mmol) and trimethylsilyl chloride (63.0 μL, 0.5 mmol). The resulting mixture is then stirred overnight under argon at room temperature. Afterwards, the reaction was quenched with sat. aq.NH_4Cl solution and then extracted by Et_2O for three times. The combined organic layers are dried over $MgSO_4$, filtered and concentrated to a small volume, then purified by silica gel flash column chromatography (7% to 60% EtOAc in hexanes) to afford the titled compound as a pale yellow solid (84.0 mg, 70%). The starting material is recovered as trimethylsilyl ether, which is less polar than the product. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 5.31–4.99 (m, 2H), 3.93 (m, 2H), 3.19 (m, 2H), 3.05 (s, 2H), 2.37 (t, *J* = 6.2 Hz, 2H), 2.13–1.95 (m, 2H), 1.45 (s, 9H).**^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 210.70, 210.26, 155.36, 154.54, 142.54, 118.35, 117.94, 80.41, 54.99, 54.05, 51.67, 51.51, 47.64, 47.57, 37.78, 37.06, 28.56, 28.52, 28.51, 27.86. **IR (neat):** 2972, 2931, 1689, 1406, 1393, 1244, 1183, 1027, 896, 766 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{13}H_{21}NNaO_3$) requires *m/z* 262.14136, found *m/z* 262.14122.

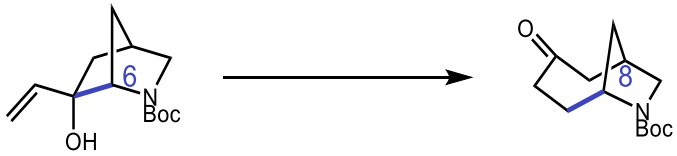


di-*tert*-butyl 5-oxo-1,3-diazocane-1,3-dicarboxylate (10a)
The titled compound was prepared on 0.5 mmol scale following general procedure A with di-*tert*-butyl 5-hydroxy-5-vinyldihydropyrimidine-1,3(2*H*,4*H*)-dicarboxylate (**10**) using PhMe solvent and TFA base and irradiated for 3 d. The crude material was purified by silica gel column chromatography (7% to 60% EtOAc in hexanes) to afford the titled compound as a white solid (115 mg, 70%). **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 5.06–4.83 (m, 2H), 4.05–3.61 (br, 2H), 3.26 (br, 2H), 2.36 (br, 2H), 2.10–1.94 (br, 2H), 1.51 (br, 9H), 1.44 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 212.88, 212.56, 154.54, 81.65, 81.57, 81.04, 61.09, 60.26, 59.38, 55.57, 55.28, 55.02, 54.79, 48.04, 47.87, 37.87, 37.64, 28.55, 28.48, 28.41. **IR (neat):** 2970, 2922, 1707, 1684, 1466, 1424, 1286, 1141, 894, 774, 525, 477 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{16}H_{28}N_2NaO_5$) requires *m/z* 351.18860, found *m/z* 351.18904.



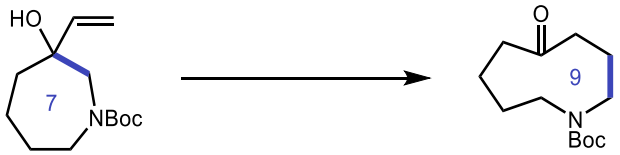
benzyl 4-methyl-5-oxoazocane-1-carboxylate (11a)
The titled compound was prepared on 0.5 mmol scale following general procedure A with benzyl 3-hydroxy-3-(prop-1-en-2-yl)piperidine-1-carboxylate (**11**) using $PhCF_3$ solvent and TFA base and irradiated for 5 d. The crude material was purified by silica gel column chromatography (7% to 60% EtOAc in hexanes) to afford the titled compound as a pale yellow solid (103 mg, 75%). **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 7.40–7.34 (m, 4H), 7.34–7.28 (m, 1H), 5.10 (s,

2H), 3.71–3.39 (m, 2H), 3.26–3.04 (m, 2H), 2.68–1.88 (m, 7H), 1.14–1.03 (m, 3H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 216.32, 216.25, 156.15, 156.01, 136.84, 136.80, 128.57, 128.20, 128.14, 128.06, 67.53, 67.51, 47.85, 47.34, 45.83, 45.69, 44.49, 43.69, 39.00, 38.02, 34.99, 33.50, 27.94, 26.36, 16.24, 15.71. **IR (neat):** 2931, 2871, 1690, 1446, 1414, 1345, 1123, 734, 696, 460 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{16}H_{22}NO_3$) requires *m/z* 276.15933, found *m/z* 276.15942.



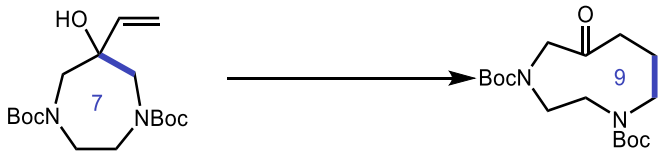
***tert*-butyl (1*R**,6*R**)-3-oxo-7-azabicyclo[4.2.1]nonane-7-carboxylate (12a)**

The titled compound was prepared on 0.5 mmol scale following general procedure B with 5 mol% Iridium photocatalyst loading and *tert*-butyl (1*S**,4*R**,6*S**)-6-hydroxy-6-vinyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (**12**) using 0.1 M $PhCF_3$ solvent and TFA base and irradiated for 6 d with one fan. The crude material was purified by silica gel column chromatography (7% to 60% EtOAc in hexanes) to afford the titled compound as a pale yellow solid (49.0 mg, 41%). **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 4.30–4.14 (m, 1H), 3.73–3.48 (m, 1H), 3.45–3.26 (m, 1H), 2.67–2.39 (m, 5H), 2.36–2.15 (m, 2H), 1.77–1.59 (m, 2H), 1.49–1.42 (m, 9H).**^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 212.09, 212.03, 154.24, 154.16, 79.76, 79.67, 56.09, 55.75, 54.04, 53.46, 50.93, 50.87, 39.00, 38.95, 35.85, 34.59, 32.23, 30.84, 30.65, 28.67, 28.64. **IR (neat):** 2966, 2883, 1687, 1390, 1364, 1161, 1109, 868, 762, 548 cm^{-1}. **HRMS (EI):** exact mass calculated for $[M]^+$ ($C_{13}H_{21}NO_3$) requires *m/z* 239.15159, found *m/z* 239.15177.



***tert*-butyl 5-oxoazonane-1-carboxylate (13a)**

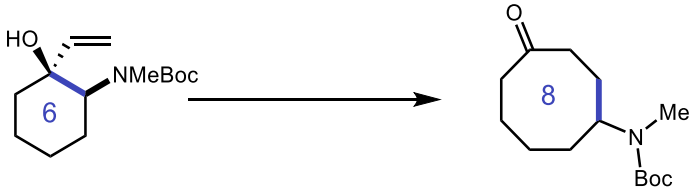
The titled compound was prepared on 0.5 mmol scale following general procedure A with *tert*-butyl 3-hydroxy-3-vinylazepane-1-carboxylate (**13**) using $PhCF_3$ solvent and TFA base and irradiated for 5 d. The crude material was purified by silica gel column chromatography (7% to 60% EtOAc in hexanes) to afford the titled compound as a pale yellow solid (58.0 mg, 48%). **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 3.28–2.99 (br, 4H), 2.47–2.37 (m, 4H), 2.16–2.01 (br, 2H), 1.93–1.86 (br, 2H), 1.79–1.63 (br, 2H), 1.53–1.42 (br, 9H).**^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 213.44, 212.99, 156.61, 156.23, 79.87, 52.07, 51.80, 50.27, 50.11, 45.80, 45.38, 38.68, 37.98, 28.58, 28.03, 27.12, 25.25, 24.68, 23.50. **IR (neat):** 2926, 2865, 1667, 1477, 1408, 1363, 1155, 1085, 776, 479 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{13}H_{24}NO_3$) requires *m/z* 242.17507, found *m/z* 242.17518.



di-*tert*-butyl 6-oxo-1,4-diazonane-1,4-dicarboxylate (14a)

The titled compound was prepared on 0.5 mmol scale following general procedure A with di-*tert*-butyl 6-hydroxy-6-vinyl-1,4-diazepane-1,4-dicarboxylate (**14**) using $PhCF_3$ solvent and TFA base and irradiated for 5 d. The crude material was purified by silica gel column chromatography (7% to 60% EtOAc in hexanes) to afford a mixture of starting material and the titled compound in 65% NMR yield. The mixture is then submitted to the following alcohol protection to remove the remaining starting material.[26]

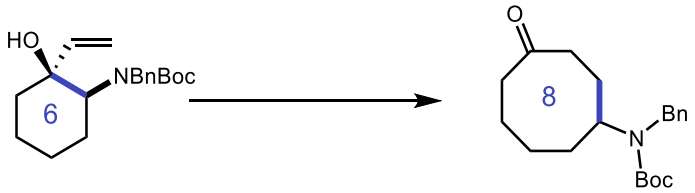
To a 10-mL round-bottomed flask, charged with a stir bar, is added a *N*,*N*-dimethylformamide (3.0 mL) solution of the previously obtained mixture, followed by imidazole (51.0 mg, 0.75 mmol) and trimethylsilyl chloride (63.0 μL, 0.5 mmol). The resulting mixture is then stirred overnight under argon at room temperature. Afterwards, the reaction was quenched with sat. aq. NH_4Cl solution and then extracted by Et_2O for three times. The combined organic layers are dried over $MgSO_4$, filtered and concentrated to a small volume, then purified by silica gel flash column chromatography (7% to 60% EtOAc in hexanes) to afford the titled compound as a pale yellow solid (99.0 mg, 58%). The starting material is recovered as trimethylsilyl ether, which is less polar than the product. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers)** δ 4.07–3.85 (m, 2H), 3.58–3.06 (m, 6H), 2.52–2.34 (br, 2H), 2.12–2.05 (br, 2H), 1.53–1.49 (m, 9H), 1.49–1.45 (m, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 209.10, 208.91, 207.75, 156.02, 155.64, 155.46, 154.84, 80.96, 80.78, 80.61, 80.50, 80.38, 61.92, 61.64, 61.33, 61.10, 53.84, 53.26, 52.56, 51.59, 49.67, 49.43, 49.20, 48.99, 37.38, 36.14, 35.96, 28.65, 28.61, 28.56, 28.43, 28.42, 27.48, 27.08, 26.28, 25.99. **IR (neat):** 2969, 2916, 1685, 1461, 1407, 1362, 1246, 1153, 1106, 952, 774, 511, 462 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{17}H_{30}N_2NaO_5$) requires *m/z* 365.20469, found *m/z* 365.20424.



***tert*-butyl methyl(4-oxocyclooctyl)carbamate (15a)**

The titled compound was prepared on 0.5 mmol scale following general procedure A with *tert*-butyl ((1*S**,2*S**)-2-hydroxy-2-vinylcyclohexyl)(methyl)carbamate (**15**) using $PhCF_3$ solvent and TFA base and irradiated for 5 d. The crude material was purified by silica gel column chromatography (7% to 60% EtOAc in hexanes) to afford the titled compound as a pale yellow solid (57.5 mg, 45%). **^{1}H NMR (500 MHz, DMSO-d_6, 120 °C)** δ 3.87 (ddt, *J* = 10.8, 7.8, 3.0 Hz, 1H), 2.70 (s, 3H), 2.56 (ddd, *J* = 13.3, 10.9, 3.9 Hz, 1H), 2.43–2.34 (m, 3H), 2.10–1.46 (m, 7H), 1.45–1.38 (m, 10H). **^{13}C NMR (126 MHz, DMSO-d_6, 120 °C)** δ 214.15, 153.94, 77.95, 54.95, 41.49, 38.22, 30.76, 30.09, 28.99, 27.65, 25.21, 23.65. **IR (neat):** 2931, 1683, 1447, 1391, 1384,

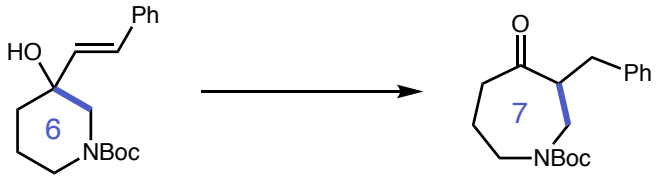
1319, 1138, 878, 771, 622 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{14}H_{26}NO_3$) requires *m/z* 256.19072, found *m/z* 256.19054.



***tert*-butyl benzyl(4-oxocyclooctyl)carbamate (16a)**

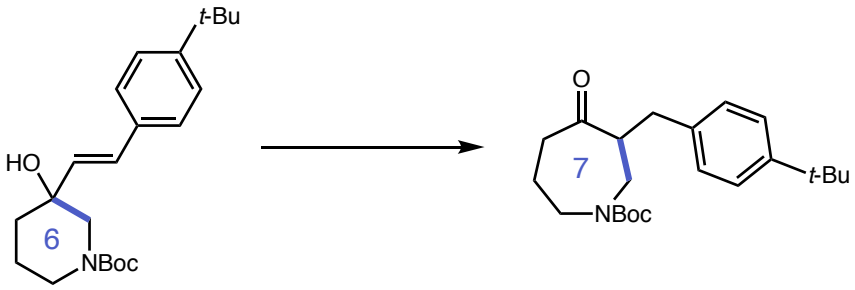
The titled compound was prepared on 0.5 mmol scale following general procedure A with *tert*-butyl benzyl((1*S**,2*S**)-2-hydroxy-2-vinylcyclohexyl)carbamate (**16**) using $PhCF_3$ solvent and dPh base and irradiated for 5 d. The crude material was purified by silica gel column chromatography (7% to 60% EtOAc in hexanes) to afford the titled compound as a pale yellow solid (91.1 mg, 55%). **^{1}H NMR (500 MHz, DMSO-*d*6, 100 °C)** δ 7.33 (t, *J* = 7.6 Hz, 2H), 7.28–7.21 (m, 3H), 4.45 (d, *J* = 15.9 Hz, 1H), 4.30 (d, *J* = 15.9 Hz, 1H), 3.63 (dd, *J* = 11.9, 7.4 Hz, 1H), 2.96 (s, 1H), 2.59–2.48 (m, 2H), 2.39–2.21 (m, 3H), 2.12 (dtd, *J* = 14.6, 11.2, 3.5 Hz, 1H), 1.96–1.77 (m, 2H), 1.69 (dddt, *J* = 18.7, 11.4, 7.5, 3.7 Hz, 1H), 1.61–1.45 (m, 2H), 1.45 (s, 9H). **^{13}C NMR (126 MHz, DMSO-*d*6, 100 °C)** δ 214.11, 154.18, 139.30, 127.56, 126.41, 126.04, 78.40, 56.85, 48.50, 41.71, 38.02, 31.91, 31.06, 27.59, 25.38, 23.04. **IR (neat):** 2931, 1682, 1445, 1391, 1352, 1139, 876, 841, 771, 622 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{20}H_{29}NNaO_3$) requires *m/z* 354.20396, found *m/z* 354.20395.

n+1 Ring Expansion



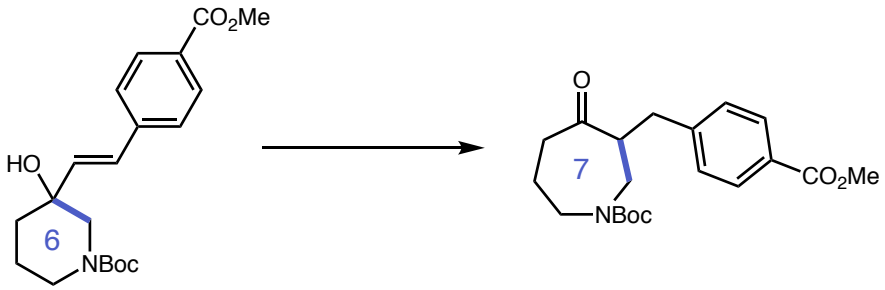
***tert*-Butyl 3-benzyl-4-oxoazepane-1-carboxylate (17a)**

The titled compound was prepared on 0.5 mmol scale following general procedure B with *tert*-butyl (*E*)-3-hydroxy-3-styrylpiperidine-1-carboxylate (**17**) using $PhCF_3$ (10 mL) solvent, TFA base (25 mol%), and TRIP-SH (5 mol%), and irradiated for 6 d at 35 ºC (with a fan to cool the reaction setup). The crude material was purified by silica gel column chromatography (2% to 18% EtOAc in hexanes) to afford the titled compound as a colorless oil (121 mg, 80%). **^{1}H NMR (400 MHz, DMSO-d_6, 120 °C)** δ 7.30–7.26 (m, 2H), 7.21–7.17 (m, 3H), 3.80 (dt, *J* = 14.1, 4.7 Hz, 1H), 3.72 (dd, *J* = 14.1, 5.2 Hz, 1H), 3.15–2.93 (m, 4H), 2.70–2.62 (m, 2H), 2.43 (m, 1H), 1.80–1.64 (m, 2H), 1.37 (s, 9H). **^{13}C NMR (101 MHz, DMSO-d_6, 120 °C)** δ 210.82, 153.33, 138.51, 128.02, 127.50, 125.32, 78.35, 52.99, 47.20, 46.81, 40.00, 34.43, 27.38, 24.08. **IR (neat):** 2974, 1686, 1467, 1412, 1242, 1155, 924, 757, 698 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{18}H_{26}NO_3$) requires *m/z* 304.19072, found *m/z* 304.19055.



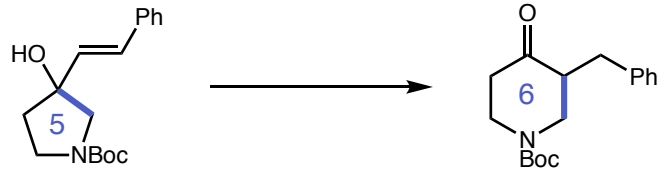
***tert*-Butyl 3-(4-(*tert*-butyl)benzyl)-4-oxoazepane-1-carboxylate (18a)**

The titled compound was prepared on 0.5 mmol scale following general procedure B with *tert*-butyl (*E*)-3-(4-(tert-butyl)styryl)-3-hydroxypiperidine-1-carboxylate (**18**) using PhMe (10 mL) solvent, TFA base (25 mol%), and TRIP-SH (5 mol%), and irradiated for 6 d at 85 ºC (without fan). The crude material was purified by silica gel column chromatography (2% to 14% EtOAc in hexanes) to afford the titled compound as a pale yellow oil (126 mg, 70%). **^{1}H NMR (400 MHz, DMSO-d_6, 120 °C)** δ 7.30 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 3.81 (dt, *J* = 14.0, 4.7 Hz, 1H), 3.72 (dd, *J* = 14.0, 5.3 Hz, 1H), 3.13–3.06 (m, 2H), 3.02–2.89 (m, 2H), 2.70–2.58 (m, 2H), 2.43 (m, 1H), 1.81–1.64 (m, 2H), 1.35 (s, 9H), 1.29 (s, 9H). **^{13}C NMR (101 MHz, DMSO-d_6, 120 °C)** δ 210.93, 153.31, 147.99, 135.36, 127.71, 124.22, 78.30, 53.07, 47.14, 46.81, 40.01, 33.88, 33.33, 30.46, 27.37, 24.01. **IR (neat):** 2962, 1689, 1465, 1412, 1241, 1159, 922, 770, 572 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{22}H_{34}NO_3$) requires *m/z* 360.25332, found *m/z* 360.25320.



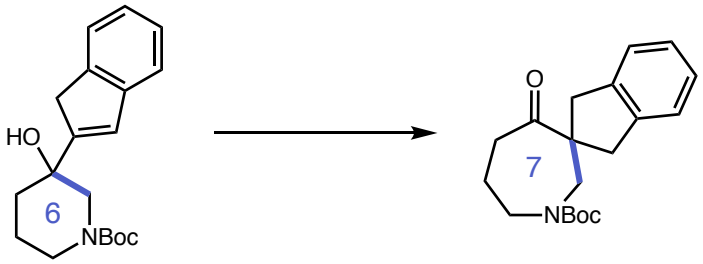
***tert*-Butyl 3-(4-(methoxycarbonyl)benzyl)-4-oxoazepane-1-carboxylate (19a)**

The titled compound was prepared on 0.5 mmol scale following general procedure B with *tert*-butyl (*E*)-3-hydroxy-3-(4-(methoxycarbonyl)styryl)piperidine-1-carboxylate (**19**) using PhMe (10 mL) solvent, TFA base (25 mol%), and TRIP-SH (5 mol%), and irradiated for 6 d at 85 ºC (without fan). The crude material was purified by silica gel column chromatography (4% to 27% EtOAc in hexanes) to afford the titled compound as a pale yellow oil (95.8 mg, 53%). **^{1}H NMR (400 MHz, DMSO-d_6, 120 °C)** δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 3.86 (s, 3H), 3.77 (dt, *J* = 14.1, 4.9 Hz, 1H), 3.71 (dd, *J* = 14.1, 4.9 Hz, 1H), 3.19–3.00 (m, 4H), 2.76 (m, 1H), 2.65 (m, 1H), 2.45 (m, 1H), 1.78–1.65 (m, 2H), 1.36 (s, 9H). **^{13}C NMR (101 MHz, DMSO-d_6, 120 °C)** δ 210.54, 165.54, 153.36, 144.36, 128.47, 128.36, 127.48, 78.45, 52.69, 50.95, 47.18, 46.65, 40.06, 34.28, 27.38, 23.97. **IR (neat):** 2950, 1687, 1610, 1467, 1412, 1274, 1159, 1103, 920, 765, 528 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+Na]^+$ ($C_{20}H_{27}NNaO_5$) requires *m/z* 384.17814, found *m/z* 384.17777.



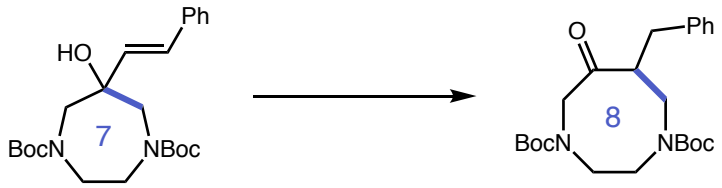
***tert*-Butyl 3-benzyl-4-oxopiperidine-1-carboxylate (20a)**

The titled compound was prepared on 0.5 mmol scale following general procedure B with *tert*-butyl (*E*)-3-hydroxy-3-styrylpyrrolidine-1-carboxylate (**20**) using $PhCF_3$ (10 mL) solvent, collidine base (3 equiv.), and TRIP-SH (20 mol%), and irradiated for 6 d at 35 ºC (with a fan to cool the reaction setup). The crude material was purified by silica gel column chromatography (2% to 18% EtOAc in hexanes) to afford the titled compound as a pale yellow solid (101 mg, 70%). **^{1}H NMR (400 MHz, DMSO-d_6, 120 °C)** δ 7.31–7.27 (m, 2H), 7.22–7.18 (m, 3H), 3.97–3.87 (m, 2H), 3.39 (m, 1H), 3.13–3.04 (m, 2H), 2.75 (m, 1H), 2.54–2.46 (m, 2H), 2.40 (dt, *J* = 14.9, 5.0 Hz, 1H), 1.40 (s, 9H). **^{13}C NMR (101 MHz, DMSO-d_6, 120 °C)** δ 207.06, 153.34, 138.59, 128.04, 127.52, 125.31, 78.69, 49.96, 46.47, 42.35, 39.32, 32.04, 27.40. **IR (neat):** 2977, 1683, 1496, 1415, 1238, 1157, 977, 855, 737, 550 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{17}H_{24}NO_3$) requires *m/z* 290.17507, found *m/z* 290.17532.



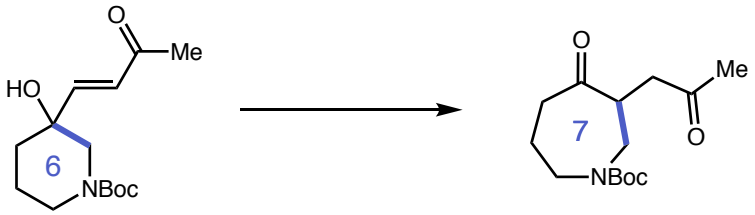
***tert*-Butyl 4-oxo-1',3'-dihydrospiro[azepane-3,2'-indene]-1-carboxylate (21a)**

The titled compound was prepared on 0.5 mmol scale following general procedure B with *tert*-butyl 3-hydroxy-3-(1H-inden-2-yl)piperidine-1-carboxylate (**21**) using $PhCF_3$ (10 mL) solvent, TFA base (25 mol%), and TRIP-SH (5 mol%), and irradiated for 6 d at 35 ºC (with a fan to cool the reaction setup). The crude material was purified by silica gel column chromatography (2% to 15% EtOAc in hexanes) to afford the titled compound as an inseparable mixture of the desired product and ~4% ring opened acyclic byproduct as judged by ^{1}H NMR analysis. This mixture is then purified by preparative SFC on a Chiralpak IC column (2 × 25 cm, conditions: 70 mL/min, 15% methanol, 220 nm, 1 mL/injection) to afford the titled compound as a white solid (120 mg, 76%).**^{1}H NMR (400 MHz, DMSO-d_6, 120 °C)** δ 7.27–7.15 (m, 4H), 4.10 (ddd, *J* = 11.6, 7.7, 4.3 Hz, 1H), 3.54–3.41 (m, 3H), 3.31 (dd, *J* = 16.2, 10.2 Hz, 1H), 3.12 (m, 1H), 2.97 (dd, *J* = 14.4, 11.4 Hz, 1H), 2.81 (dd, *J* = 16.2, 7.7 Hz, 1H), 2.70 (dt, *J* = 13.5, 7.7 Hz, 1H), 2.30 (dt, *J* = 13.5, 5.3 Hz, 1H), 2.08–2.00 (m, 2H), 1.46 (s, 9H). **^{13}C NMR (101 MHz, DMSO-d_6, 120 °C)** δ 210.88, 153.73, 142.99, 141.15, 126.42, 125.74, 124.05, 122.84, 78.45, 55.05, 50.60, 47.54, 46.68, 37.33, 30.06, 27.57, 25.13. **IR (neat):** 2971, 2930, 1686, 1477, 1406, 1364, 1226, 1157, 888, 749 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{19}H_{26}NO_3$) requires *m/z* 316.19072, found *m/z* 316.19058.



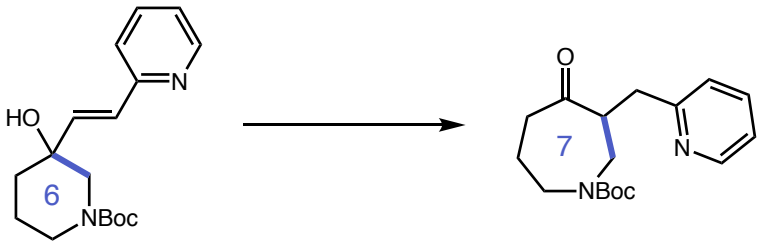
Di-*tert*-butyl 6-benzyl-7-oxo-1,4-diazocane-1,4-dicarboxylate (22a)

The titled compound was prepared on 0.5 mmol scale following general procedure B with di-*tert*-butyl (*E*)-6-hydroxy-6-styryl-1,4-diazepane-1,4-dicarboxylate (**22**) using PhMe (10 mL) solvent, TFA base (25 mol%), and TRIP-SH (5 mol%), and irradiated for 7 d at 85 ºC (without fan). The crude material was purified by silica gel column chromatography (2% to 18% EtOAc in hexanes) to afford the titled compound as a pale yellow solid (172 mg, 82%). **^{1}H NMR (400 MHz, DMSO-d_6, 120 °C)** δ 7.27–7.23 (m, 2H), 7.18–7.15 (m, 3H), 4.21 (d, *J* = 18.3 Hz, 1H), 4.10 (dt, *J* = 13.9, 4.6 Hz, 1H), 3.49 (dd, *J* = 12.9, 4.9 Hz, 1H), 3.42 (d, *J* = 10.6 Hz, 1H), 3.39–3.28 (m, 4H), 3.01–2.93 (m, 2H), 2.57 (dd, *J* = 14.1, 5.4 Hz, 1H), 1.40 (s, 9H), 1.36 (s, 9H). **^{13}C NMR (101 MHz, DMSO-d_6, 120 °C)** δ 211.86, 153.89, 153.19, 138.72, 128.00, 127.49, 125.30, 79.37, 78.90, 57.70, 50.73, 47.51, 46.94, 46.03, 33.50, 27.36, 27.24. **IR (neat):** 2974, 1688, 1453, 1413, 1236, 1150, 1041, 953, 770, 699 cm^{-1}. **HRMS (ESI):** exact mass calculated for [M+Na$^+$ ($C_{23}H_{34}N_2NaO_5$) requires *m/z* 441.23599, found *m/z* 441.23572.



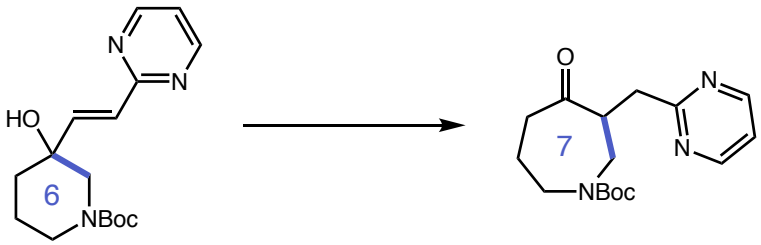
***tert*-Butyl 4-oxo-3-(pyridin-2-ylmethyl)azepane-1-carboxylate (23a)**

The titled compound was prepared on 0.5 mmol scale following general procedure B with *tert*-butyl (*E*)-3-hydroxy-3-(3-oxobut-1-en-1-yl)piperidine-1-carboxylate (**23**) using $PhCF_3$ (10 mL) solvent and TFA base (25 mol%), and irradiated for 3 d at 35 ºC (with a fan to cool the reaction setup). The crude material was purified by silica gel column chromatography (7% to 60% EtOAc in hexanes) to afford the titled compound as a pale yellow oil (88.5 mg, 66%). **^{1}H NMR (400 MHz, DMSO-d_6, mixture of rotamers)** δ 3.14–2.88 (m, 2H), 2.88–2.67 (m, 2H), 2.25 (dd, *J* = 17.8, 6.8 Hz, 1H), 2.14–1.91 (m, 3H), 1.60–1.49 (m, 4H), 1.22–1.00 (m, 2H), 0.84 (d, *J* = 3.8 Hz, 9H).**^{13}C NMR (101 MHz, DMSO-d_6, mixture of rotamers)** δ 211.82, 206.54, 206.28, 154.24, 153.88, 79.03, 78.93, 48.19, 48.07, 47.67, 47.50, 46.89, 46.31, 42.86, 42.83, 41.25, 41.08, 29.72, 27.96, 24.73, 24.68. **IR (neat)**: 3419, 2975, 2932, 2861, 1667, 1627, 1432, 1391, 1151, 980, 765 cm^{-1}. **HRMS (ESI)**: exact mass calculated for [M+H]$^+$ ($C_{14}H_{24}NO_4$) requires *m/z* 270.16998, found *m/z* 270.16961.



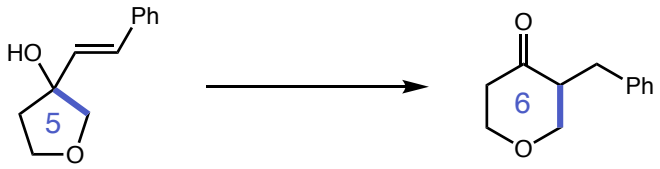
***tert*-Butyl 4-oxo-3-(pyridin-2-ylmethyl)azepane-1-carboxylate (24a)**

The titled compound was prepared on 0.5 mmol scale following general procedure B with *tert*-butyl (*E*)-3-hydroxy-3-(2-(pyridin-2-yl)vinyl)piperidine-1-carboxylate (**24**) using $PhCF_3$ (10 mL) solvent and TFA base (25 mol%), and irradiated for 6 d at 35 ºC (with a fan to cool the reaction setup). The crude material was purified by silica gel column chromatography (20% to 80% EtOAc in hexanes) to afford the titled compound as a pale yellow oil (117 mg, 77%). **^{1}H NMR (400 MHz, DMSO-d_6, 120 °C)** δ 8.46 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 7.66 (td, *J* = 7.7, 1.9 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.17 (dd, *J* = 7.5, 4.8 Hz, 1H), 3.80–3.71 (m, 2H), 3.34–3.03 (m, 4H), 2.93–2.81 (m, 1H), 2.69–2.55 (m, 1H), 2.55–2.39 (m, 1H), 1.79–1.68 (m, 2H), 1.37 (s, 9H). **^{13}C NMR (101 MHz, DMSO-d_6, 120 °C)** δ 210.75, 158.35, 153.43, 148.16, 135.44, 122.45, 120.51, 78.34, 51.24, 47.12, 46.79, 40.26, 36.67, 27.41, 23.90. **IR (neat)**: 2973, 2929,1685, 1435, 1142, 1244, 1154, 893, 751, 520 cm^{-1}. **HRMS (ESI)**: exact mass calculated for $[M+H]^+$ ($C_{17}H_{25}N_2O_3$) requires *m/z* 305.18597, found *m/z* 305.18596.



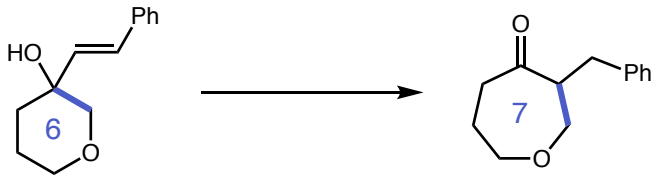
***tert*-Butyl 4-oxo-3-(pyridin-2-ylmethyl)azepane-1-carboxylate (25a)**

The titled compound was prepared on 0.5 mmol scale following general procedure B with (*E*)-*tert*-butyl 3-hydroxy-3-(pyrimidin-2-ylethynyl)piperidine-1-carboxylate (**25**) using $PhCF_3$ (10 mL) solvent and TFA base (25 mol%), and irradiated for 3 d at 35 ºC (with a fan to cool the reaction setup). The crude material was purified by silica gel column chromatography (7% to 100% EtOAc in hexanes) to afford the titled compound as an inseparable mixture of the desired product and ~8% n+2 ring expansion byproduct as judged by ^{1}H NMR analysis. This mixture is then purified by preparative SFC on a Lux Cellulose-4 column (2 × 25 cm, conditions: 70 mL/min, 20% isopropanol, 220 nm, 1 mL/injection) to afford the title compound as a white solid. (122 mg, 80%). **^{1}H NMR (400 MHz, DMSO-d_6, 120 °C)** δ 8.67 (d, *J* = 4.9 Hz, 2H), 7.27 (t, *J* = 4.9 Hz, 1H), 3.81–3.66 (m, 1H), 3.44–3.18 (m, 4H), 3.01 (dd, *J* = 15.3, 6.9 Hz, 1H), 2.71–2.59 (m, 1H), 2.58–2.49 (m, 1H), 1.84–1.69 (m, 1H), 1.38 (d, *J* = 1.0 Hz, 9H). **^{13}C NMR (101 MHz, DMSO-d_6, 120 °C)**) δ 210.42, 167.72, 156.19, 153.46, 118.17, 78.38, 50.24, 47.05, 46.69, 40.39, 37.93, 27.42, 23.74. **IR (neat)**: 3080, 2972, 2928, 2361, 2336, 1703, 1675, 1551, 1417, 1142, 921, 773 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{16}H_{24}N_3O_3$) requires m/z 306.18122, found m/z 306.18143.



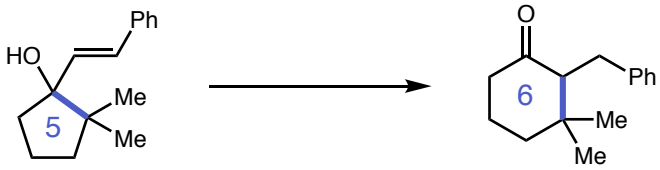
3-Benzyltetrahydro-4*H*-pyran-4-one (26a)

The titled compound was prepared on 0.5 mmol scale following general procedure B with (*E*)-3-styryltetrahydrofuran-3-ol (**26**) using PhMe (10 mL) solvent, collidine base (3 equiv.), and TRIP-SH (5 mol%), and irradiated for 6 d at 85 ºC (without fan). The crude material was purified by silica gel column chromatography (3% to 23% Et_2O in hexanes) to afford the titled compound as a pale yellow oil (70.4 mg, 74%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.29–7.26 (m, 2H), 7.20 (m, 1H), 7.16–7.15 (m, 2H), 4.17 (m, 1H), 4.03 (ddd, *J* = 11.3, 6.0, 1.3 Hz, 1H), 3.75 (td, *J* = 11.0, 3.5 Hz, 1H), 3.42 (dd, *J* = 11.3, 9.7 Hz, 1H), 3.21 (dd, *J* = 14.3, 5.1 Hz, 1H), 2.83 (m, 1H), 2.62 (m, 1H), 2.49–2.44 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 207.78, 138.90, 128.90 (2C), 128.58 (2C), 126.41, 72.16, 68.73, 53.02, 42.52, 31.81. **IR (neat):** 2966, 2851, 1710, 1453, 1368, 1219, 1149, 1099, 972, 735, 698, 571 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{12}H_{15}O_2$) requires *m/z* 191.10666, found *m/z* 191.10663.



3-Benzyloxepan-4-one (27a)

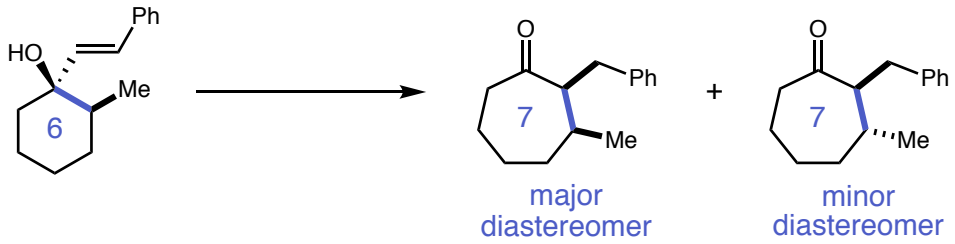
The titled compound was prepared on 0.5 mmol scale following general procedure B with (*E*)-3-styryltetrahydro-2*H*-pyran-3-ol (**27**) using PhMe (40 mL) solvent, dPh base (25 mol%), and TRIP-SH (10 mol%), and irradiated for 6 d at 85 ºC (without fan). The crude material was purified by silica gel column chromatography (3% to 23% Et_2O in hexanes) to afford the titled compound as a pale yellow oil (68.4 mg, 67%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.29–7.26 (m, 2H), 7.21–7.16 (m, 3H), 3.91 (m, 1H), 3.84 (dd, *J* = 13.0, 4.0 Hz, 1H), 3.69 (m, 1H), 3.54 (dd, *J* = 13.0, 7.6 Hz, 1H), 3.11 (dd, *J* = 13.9, 5.1 Hz, 1H), 2.93 (m, 1H), 2.70–2.58 (m, 3H), 1.92–1.78 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 212.90, 139.08, 129.18 (2C), 128.63 (2C), 126.48, 73.11, 70.31, 56.00, 42.32, 34.46, 26.55. **IR (neat):** 2922, 2852, 1699, 1453, 1370, 1251, 1118, 1083, 933, 752, 699, 503 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{13}H_{17}O_2$) requires *m/z* 205.12231, found *m/z* 205.12227.



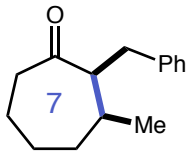
2-Benzyl-3,3-dimethylcyclohexan-1-one (28a)

The titled compound was prepared on 0.5 mmol scale following general procedure B with (*E*)-2,2-dimethyl-1-styrylcyclopentan-1-ol (**28**) using PhMe (10 mL) solvent, collidine base (3 equiv.), and

benzenethiol (10 mol%), and irradiated for 6 d at 85 ºC (without fan). The crude material was purified by silica gel column chromatography (0% to 5% Et_2O in hexanes) to afford the titled compound as a pale yellow solid (84.4 mg, 78%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.26–7.20 (m, 4H), 7.14 (m, 1H), 3.10 (dd, *J* = 13.8, 9.9 Hz, 1H), 2.58 (dd, *J* = 13.8, 2.2 Hz, 1H), 2.51 (dd, *J* = 9.9, 1.3 Hz, 1H), 2.33 (dtd, *J* = 12.8, 4.2, 1.3 Hz, 1H), 2.23 (m, 1H), 1.92 (m, 1H), 1.83 (m, 1H), 1.72 (td, *J* = 12.8, 4.2 Hz, 1H), 1.63 (m, 1H), 1.20 (s, 3H), 0.85 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 212.11, 142.22, 129.13, 128.33, 125.77, 63.46, 41.92, 40.57, 40.09, 30.07, 29.63, 23.44, 21.47. **IR (neat):** 2940, 1707, 1454, 1370, 1166, 1077, 934, 737, 695, 498 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}O$) requires *m/z* 217.15869, found *m/z* 217.15865.

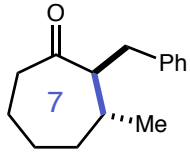


Prepared on 0.5 mmol scale following the general procedure B with (1*R**,2*S**)-2-methyl-1-((*E*)-styryl)cyclohexan-1-ol (**29**) using PhMe (40 mL) solvent, dPh base (25 mol%), and TRIP-SH (20 mol%), and irradiated for 6 d at 85 ºC (without fan). The crude material was purified by silica gel column chromatography (0% to 3% Et_2O in hexanes) to afford a 1.7:1 mixture of diastereomers as a pale yellow oil (75.7 mg, 70%). The diastereomers were separated by preparative SFC on a Chiralpak AD-H column (3 × 25 cm, conditions: 70 mL/min, 10% methanol, 220 nm, 1 mL/injection) and their stereochemistries were determined by NOESY analysis (see product NMR section).



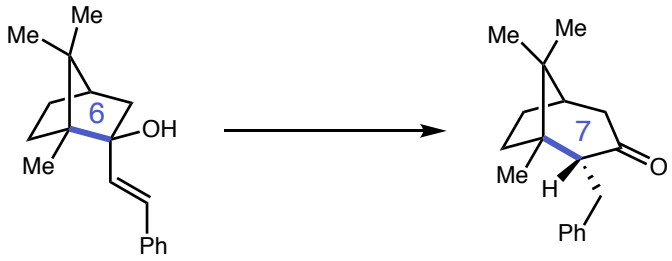
***cis*-2-Benzyl-3-methylcycloheptan-1-one (29a, major isomer)**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.26 (m, 2H), 7.20–7.16 (m, 3H), 3.18 (td, *J* = 7.0, 1.9 Hz, 1H), 3.12 (dd, *J* = 13.8, 6.7 Hz, 1H), 2.59 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.46 (m, 1H), 2.32 (m, 1H), 1.99 (m, 1H), 1.85 (m, 1H), 1.79–1.63 (m, 4H), 1.42 (m, 1H), 0.84 (d, *J* = 7.3 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 214.38, 140.97, 129.14, 128.43, 126.04, 56.82, 44.52, 37.60, 35.25, 32.61, 23.92, 23.76, 14.07. **IR (neat):** 3026, 2926, 1695, 1452, 1382, 1235, 1185, 1070, 930, 697 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}O$) requires *m/z* 217.15869, found *m/z* 217.15863.



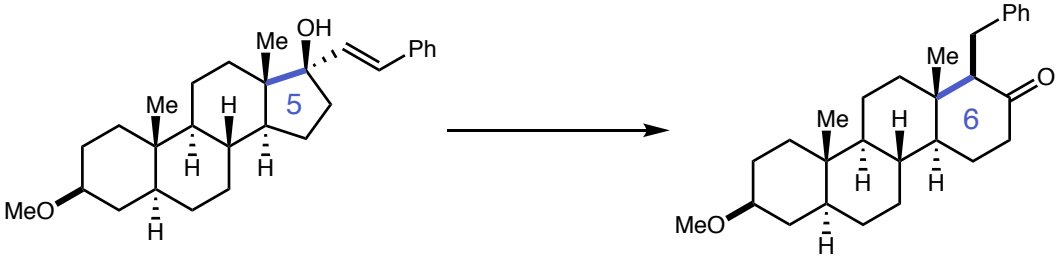
***trans*-2-Benzyl-3-methylcycloheptan-1-one (29a, minor isomer)**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.23 (m, 2H), 7.17 (m, 1H), 7.12–7.11 (m, 2H), 2.96 (dd, *J* = 13.8, 9.7 Hz, 1H), 2.86 (dd, *J* = 13.8, 4.3 Hz, 1H), 2.56 (td, *J* = 9.3, 4.3 Hz, 1H), 2.38 (m, 1H), 2.19 (m, 1H), 1.84–1.75 (m, 2H), 1.72–1.57 (m, 3H), 1.41 (m, 1H), 1.31 (m, 1H), 1.10 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 215.38, 139.88, 129.04, 128.46, 126.24, 61.11, 42.73, 37.13, 36.09, 35.38, 26.88, 25.28, 21.22. **IR (neat):** 3026, 2926, 1695, 1452, 1382, 1235, 1185, 1070, 930, 697 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}O$) requires *m/z* 217.15869, found *m/z* 217.15863.



(1*S*,2*R*,5*R*)-2-Benzyl-1,8,8-trimethylbicyclo[3.2.1]octan-3-one (30a)

The titled compound was prepared on 0.5 mmol scale following general procedure B with (1*R*,2*S*,4*R*)-1,7,7-trimethyl-2-((*E*)-styryl)bicyclo[2.2.1]heptan-2-ol (**30**) using PhMe (40 mL) solvent, dPh base (25 mol%), and TRIP-SH (20 mol%), and irradiated for 6 d at 85 ºC (without fan). The crude material was purified by silica gel column chromatography (0% to 5% Et_2O in hexanes) to afford the titled compound as a pale yellow solid (98.7 mg, 77%). The absolute configuration was determined by NOESY analysis (see product NMR section). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.29–7.25 (m, 4H), 7.16 (m, 1H), 3.33 (dd, *J* = 14.4, 6.5 Hz, 1H), 2.73 (dt, *J* = 15.8, 2.7 Hz, 1H), 2.67 (m, 1H), 2.51 (dd, *J* = 14.4, 3.3 Hz, 1H), 2.24 (dd, *J* = 15.8, 2.7 Hz, 1H), 2.03–1.94 (m, 2H), 1.71 (m, 1H), 1.52 (m, 1H), 1.36 (m, 1H), 1.18 (s, 3H), 1.03 (s, 3H), 1.02 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 212.19, 143.46, 128.97, 128.28, 125.50, 59.45, 49.91, 46.92, 45.86, 44.82, 31.13, 30.83, 27.48, 25.01, 19.22, 18.92. **IR (neat):** 2952, 1702, 1452, 1391, 1223, 1120, 1029, 740, 697, 554 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{18}H_{25}O$) requires *m/z* 257.18999, found *m/z* 257.19009.



(1*R*,4a*S*,4b*R*,6a*S*,8*S*,10a*S*,10b*S*,12a*S*)-1-Benzyl-8-methoxy-10a,12a-dimethylhexadecahydrochrysen-2(1*H*)-one (31a)

The titled compound was prepared on 0.5 mmol scale following general procedure B with (3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*R*)-3-methoxy-10,13-dimethyl-17-((*E*)-styryl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-ol (**31**) using PhMe (10 mL) solvent, collidine base (3 equiv.), and benzenethiol (20 mol%), and irradiated for 6 d at 85 ºC (without fan). The crude material was purified by silica gel column chromatography (2% to 10% Et_2O in hexanes) to afford the titled compound as a white solid (125 mg, 61%). The absolute configuration was determined by X-ray

crystallographic analysis (see **Figure S5** for details).**^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.23–7.18 (m, 4H), 7.12 (m, 1H), 3.34 (s, 3H), 3.17–3.08 (m, 2H), 2.53 (d, J = 13.7 Hz, 1H), 2.43 (d, J = 8.9 Hz, 1H), 2.34 (m, 1H), 2.21 (m, 1H), 2.13 (m, 1H), 2.01 (m, 1H), 1.92–1.89 (m, 2H), 1.78 (td, J = 13.1, 3.5 Hz, 1H), 1.69–1.66 (m, 2H), 1.42–1.17 (m, 9H), 1.07 (tt, J = 12.3, 3.0 Hz, 1H), 0.98–0.83 (m, 2H), 0.78 (s, 3H), 0.77 (m, 1H), 0.72 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 211.52, 142.77, 129.17 (2C), 128.20 (2C), 125.54, 79.75, 65.07, 55.64, 53.69, 51.46, 44.19, 42.96, 42.06, 38.91, 36.83, 35.92, 35.76, 34.21, 31.41, 28.78, 27.86, 27.84, 26.70, 21.03, 13.73, 12.28. **IR (neat):** 2927, 2849, 1702, 1447, 1385, 1172, 1102, 742, 699, 498 cm^{-1}. **HRMS (ESI):** exact mass calculated for $[M+H]^+$ ($C_{28}H_{41}O_2$) requires *m/z* 409.31011, found *m/z* 409.31003.

Crystal data of 31a (Figure S9): Compound **31a** was recrystallized from *n*-hexanes–dichloromethane at room temperature in 2 days. Formula $C_{28}H_{40}O_2$, colorless, crystal dimensions 0.32 × 0.25 × 0.20 mm^3, triclinic, space group *P*1 (#1), a = 6.7263(5) Å, b = 9.6206(7) Å, c = 10.0133(7) Å, α = 114.987(2)º, β = 102.242(2)º, γ = 94.169(2)º, V = 564.26(7) $Å^3$, Z = 1, ρ_{calc} = 1.202 g cm^{-3}, F(000) = 224, μ(MoKα) = 0.073 mm^{-1}, T = 100 K. 33508 reflections collected, 10387 independent reflections with $I > 2\sigma(I)$ ($2\theta_{max}$ = 71.24º), and 274 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1 = 0.0320 and wR_2 = 0.0876. GOF = 1.028. Flack x parameter = –0.02(17). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1900668. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Web page: http://www.ccdc.cam.ac.uk/].

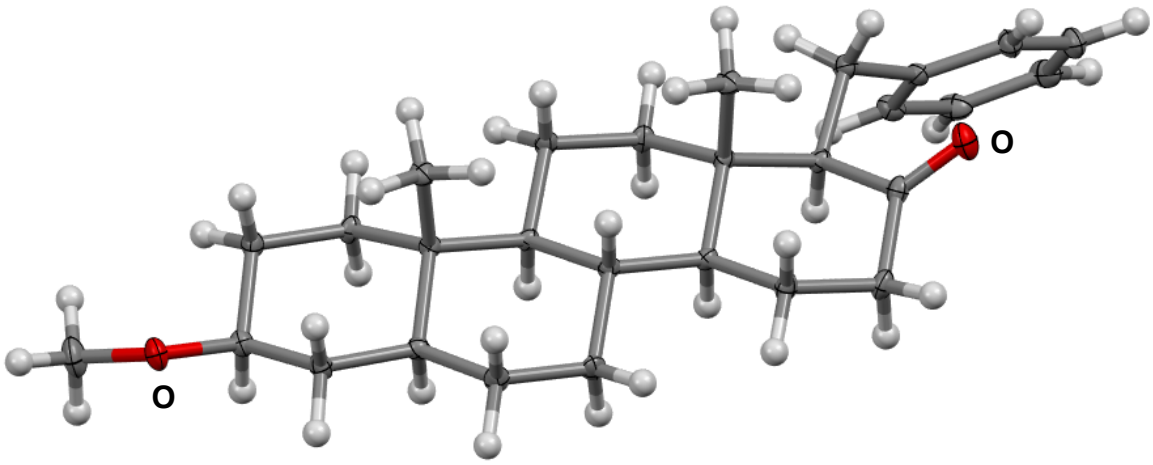
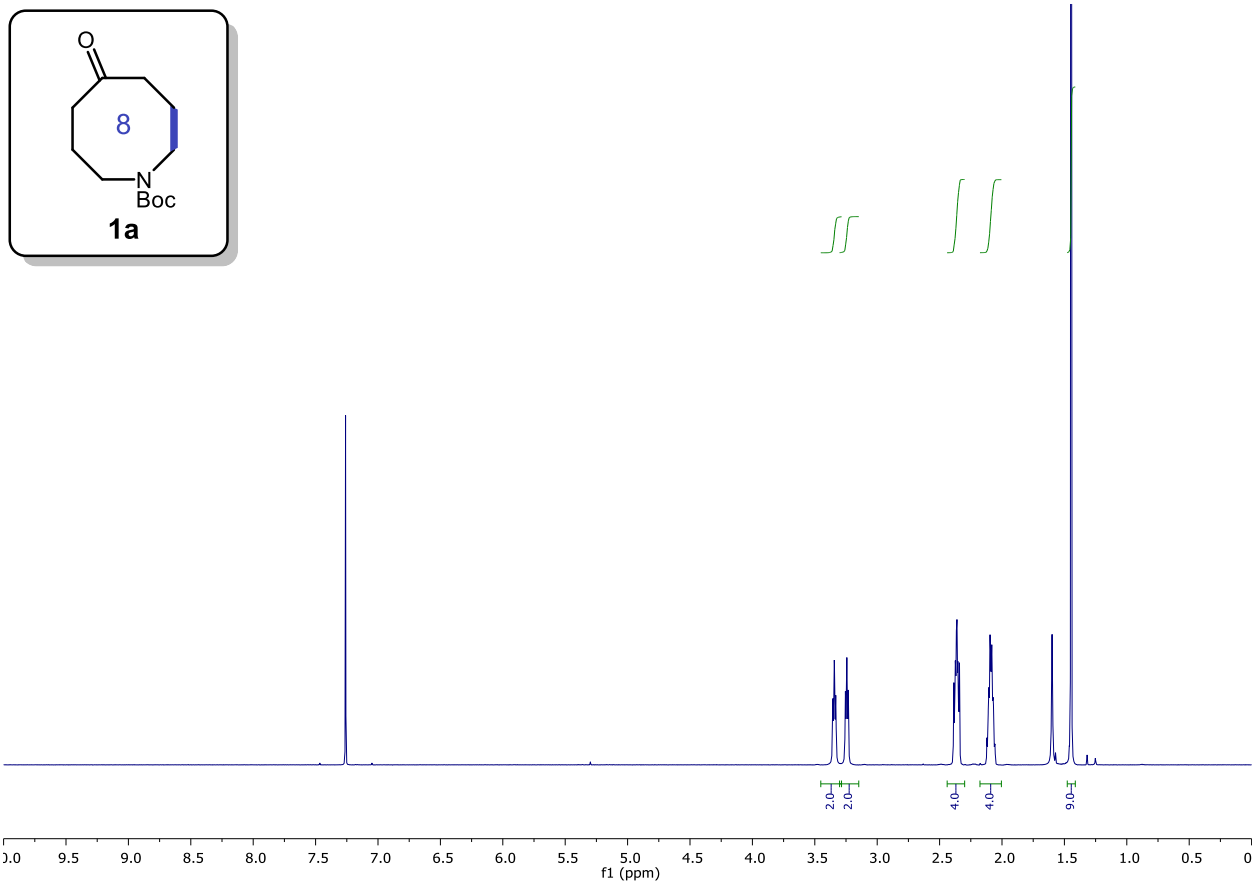
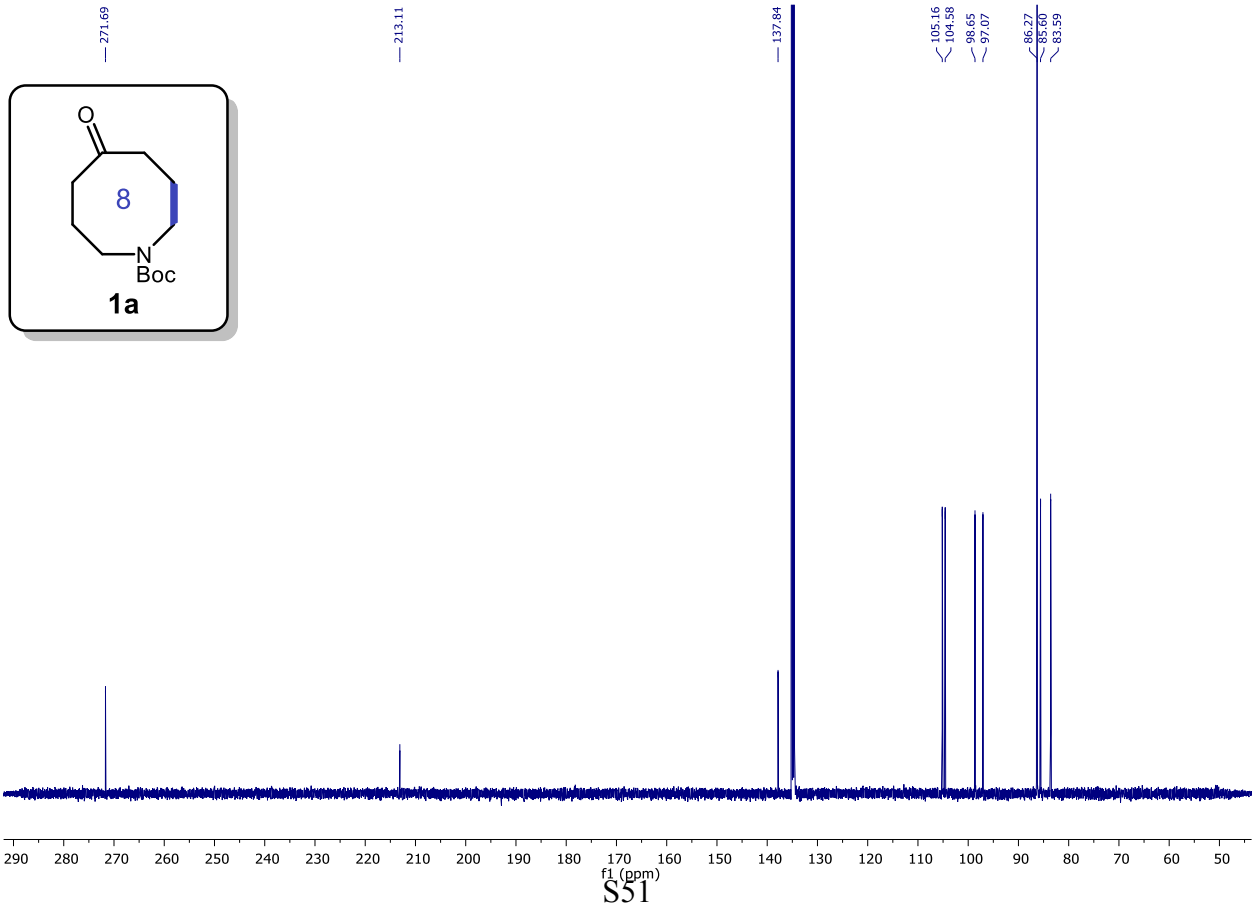
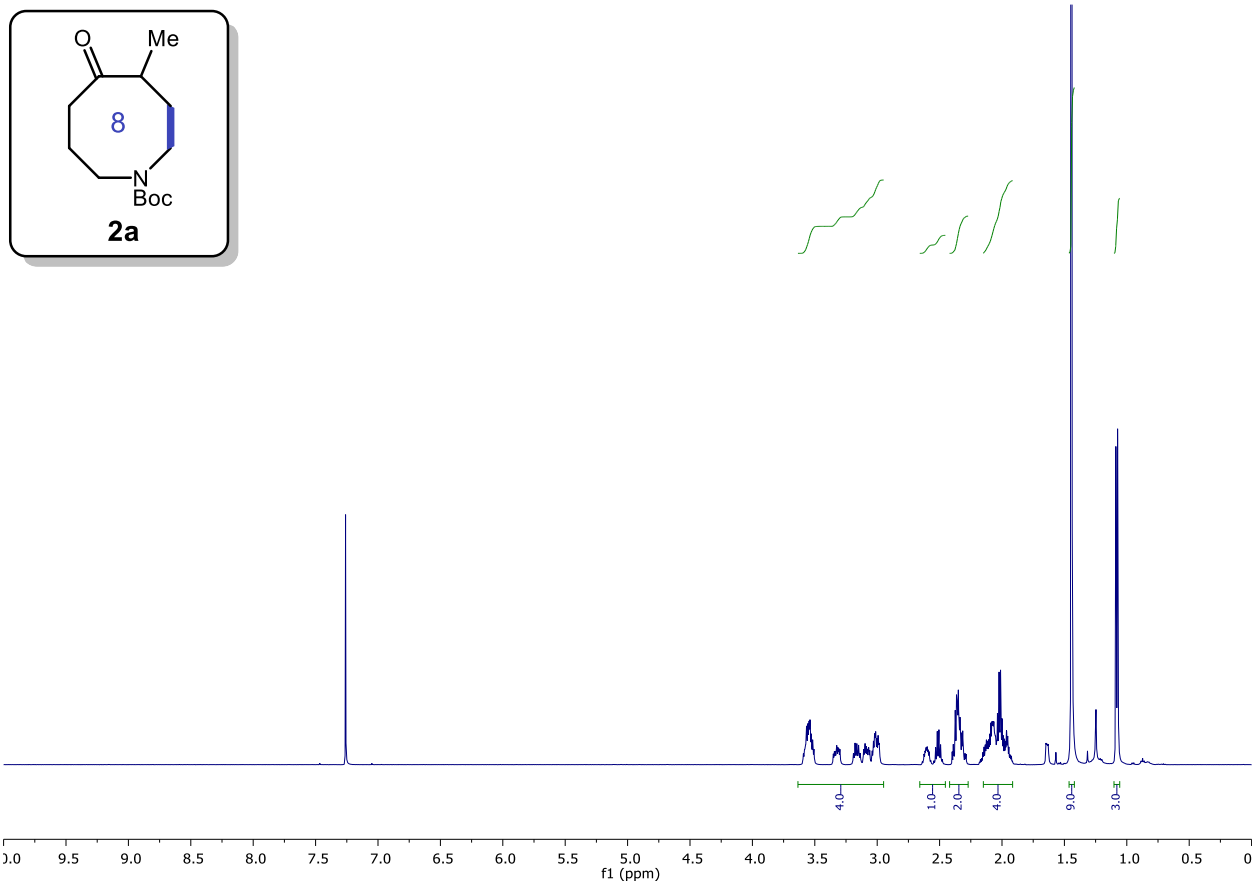


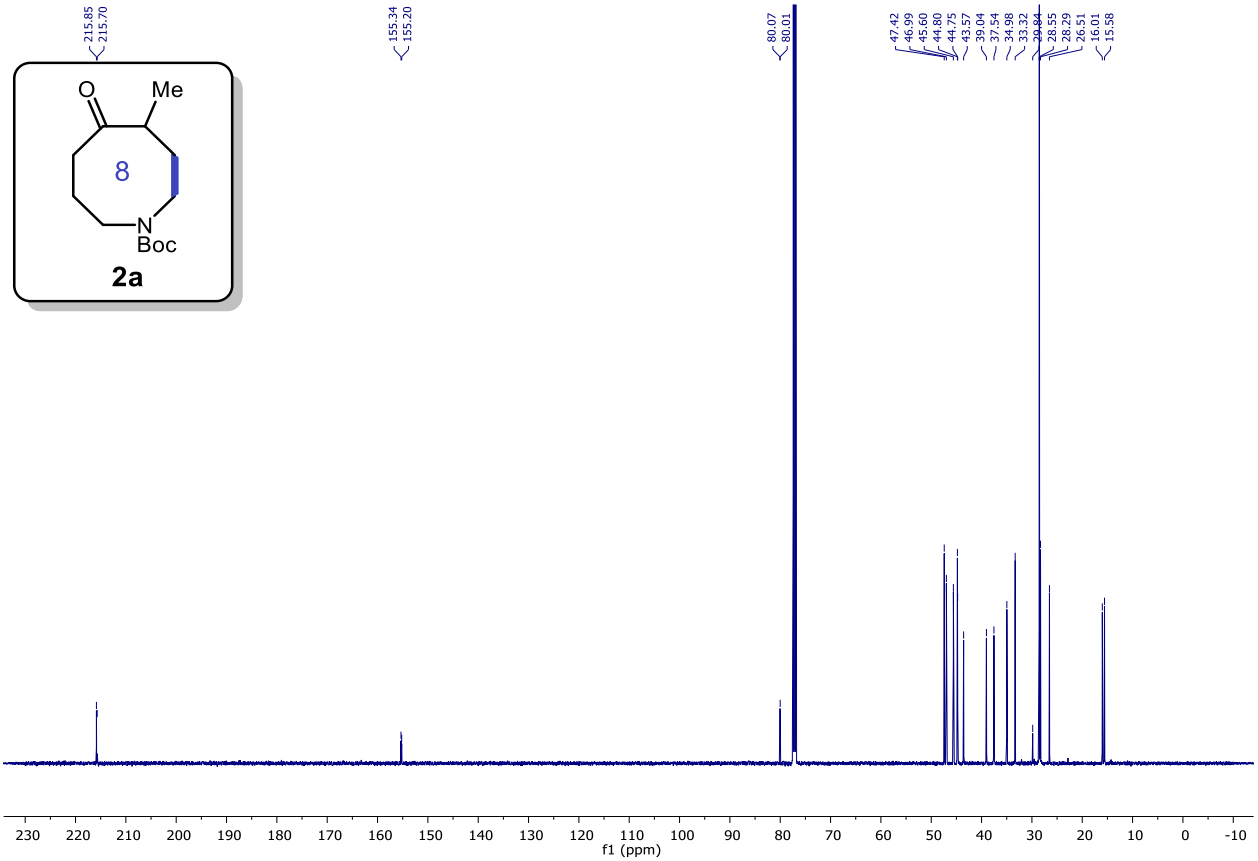
Figure S9. ORTEP drawing of 31a

^{1}H and ^{13}C NMR Spectra of Products






O
Me
8
N
Boc
2a
4.0
1.0
2.0
4.0
9.0
3.0
f1 (ppm)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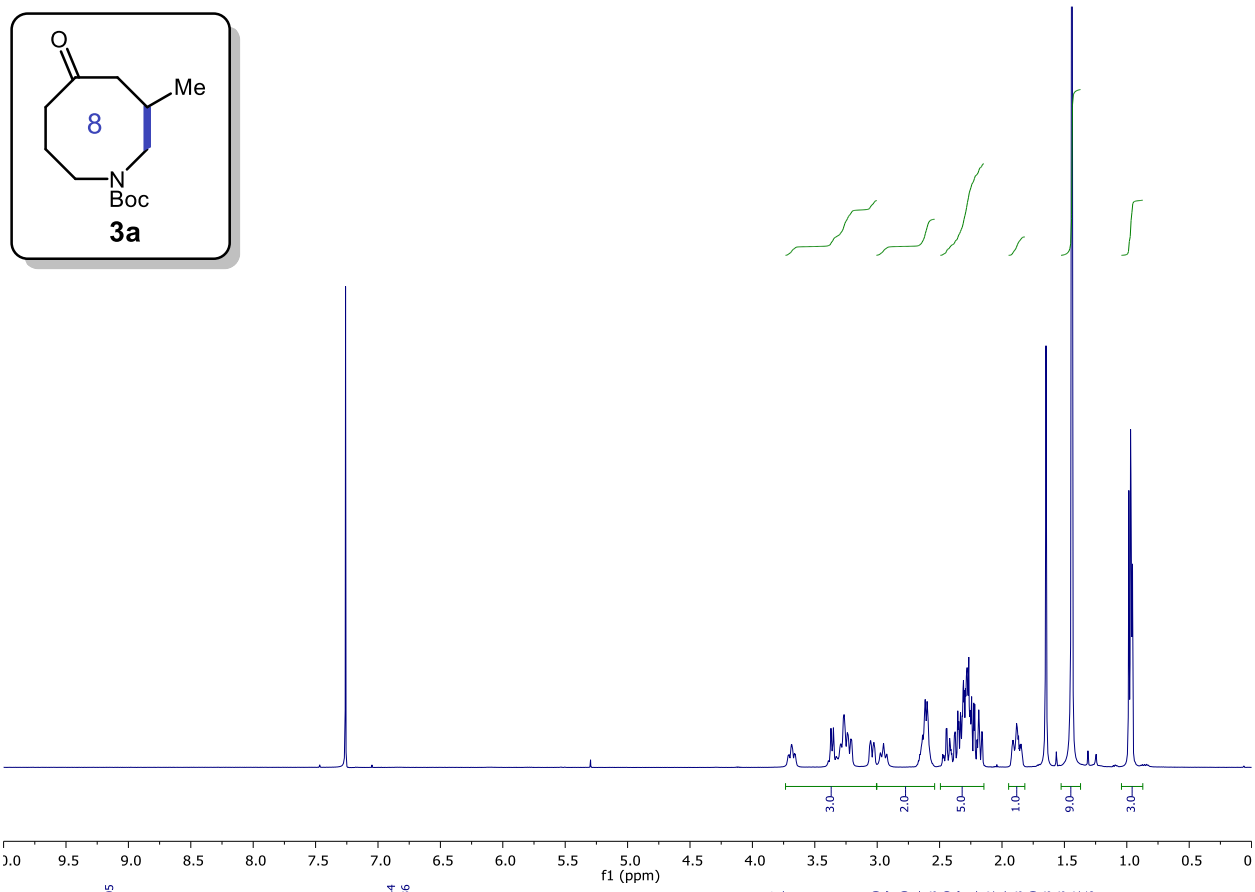
215.70
155.34
155.20
80.07
80.01
47.42
46.99
45.60
44.80
44.75
43.57
39.04
37.54
34.98
33.32
29.84
28.55
28.29
26.51
16.01
15.58
O
Me
8
N
Boc
2a
f1 (ppm)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Me
8
N
Boc
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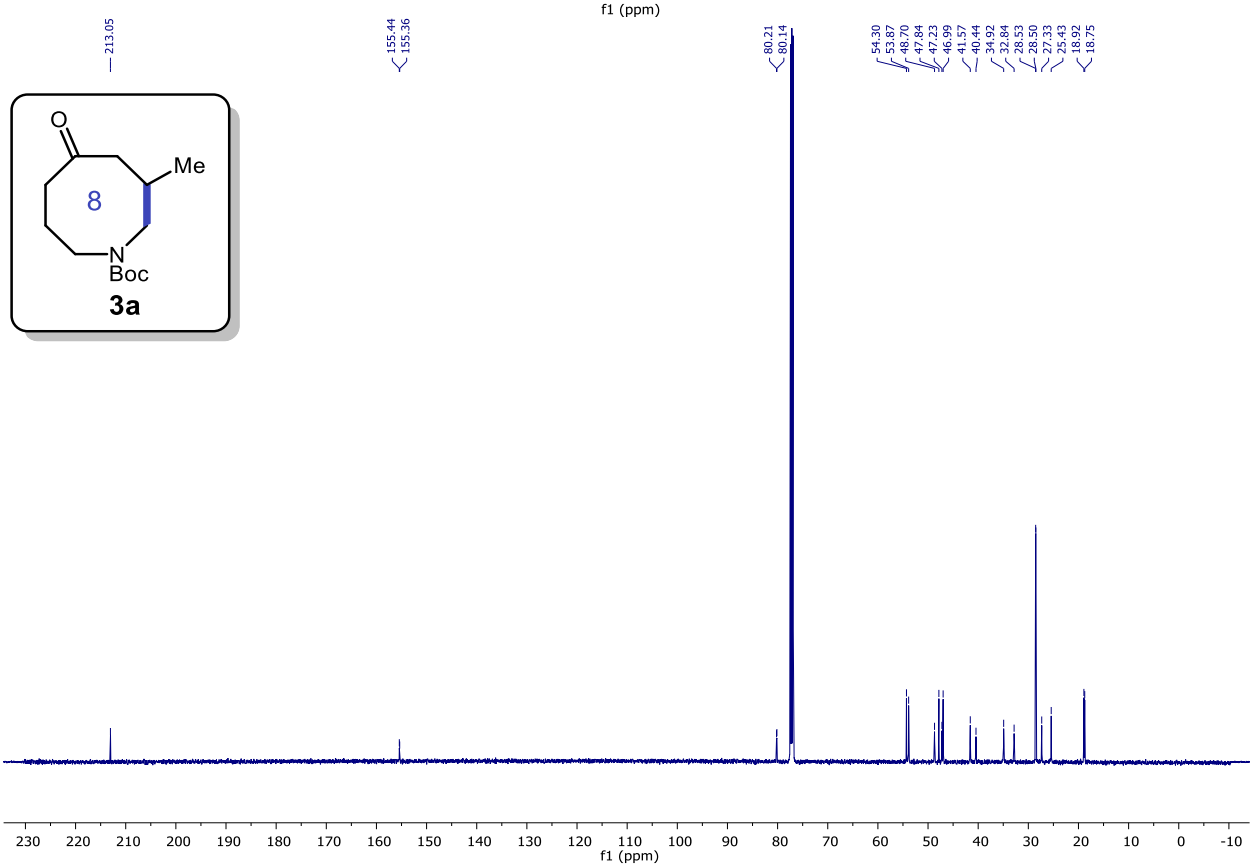
2.0
5.0
1.0
9.0
3.0
f1 (ppm)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155.36
80.21
80.14
54.30
53.87
48.70
47.84
47.23
46.99
41.57
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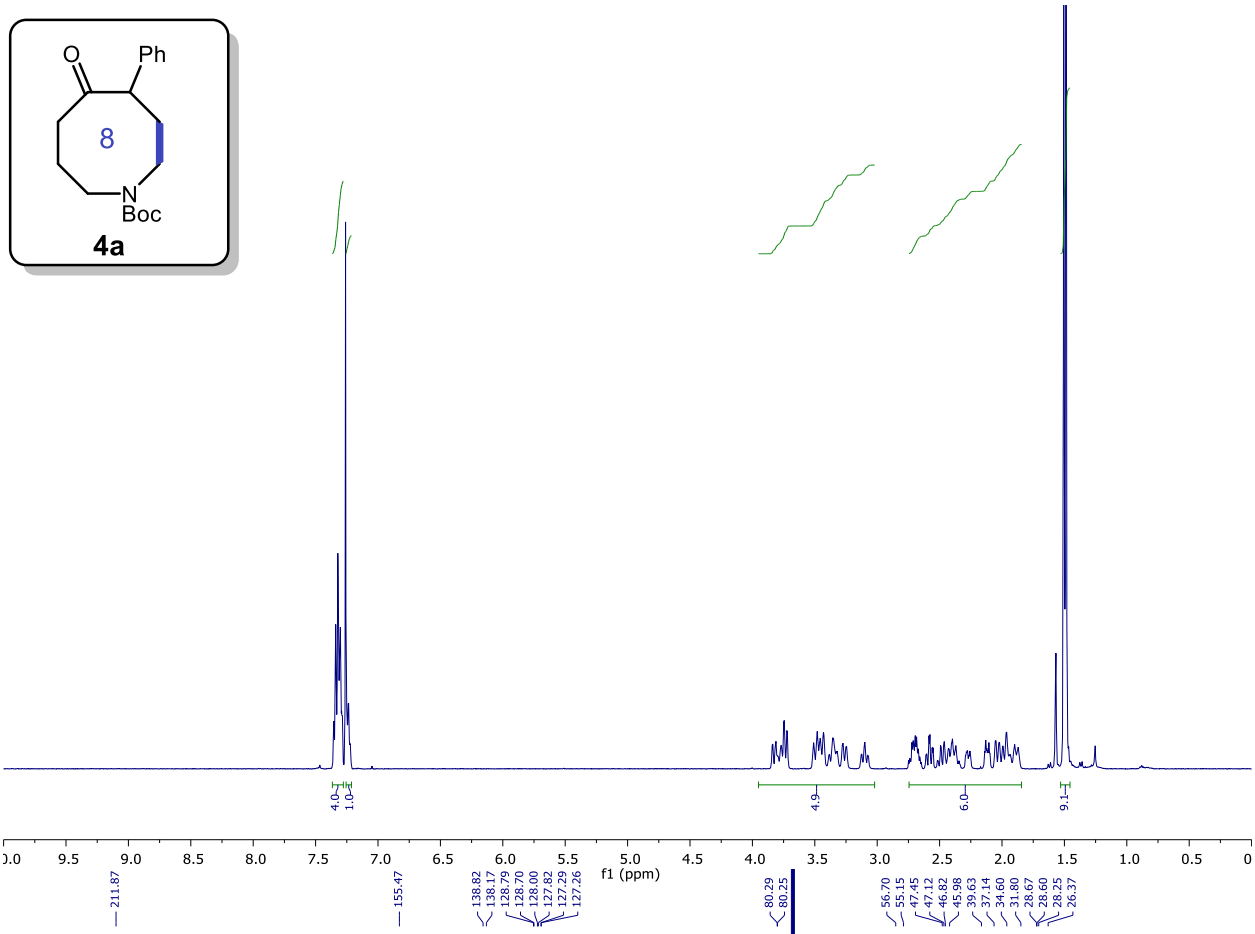
O
Me
8
N
Boc
3a
f1 (ppm)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Ph
8
N
Boc
4a
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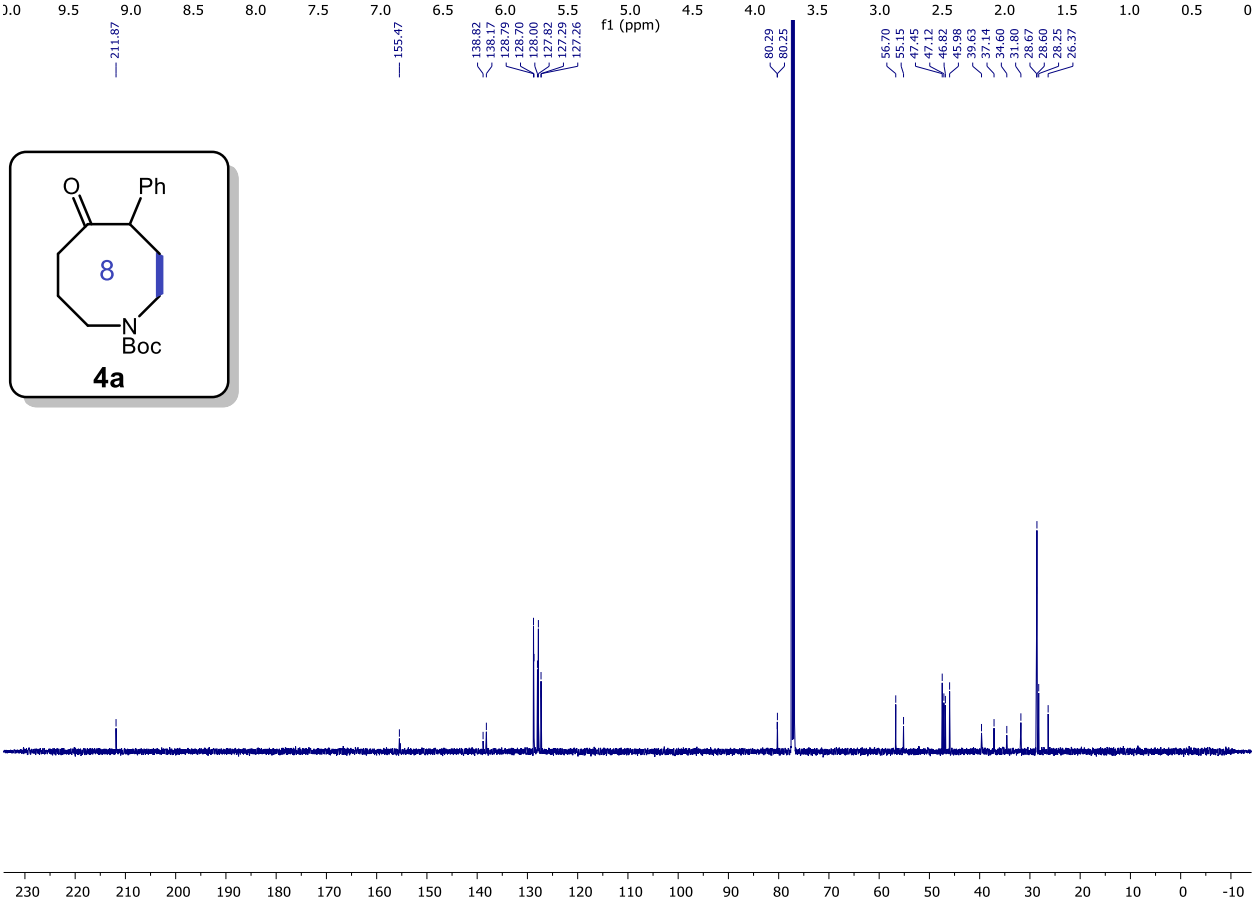
1.0
4.9
6.0
9.1
f1 (ppm)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138.17
128.79
128.70
128.00
127.82
127.29
127.26
80.29
80.25
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55.15
47.45
47.12
46.82
45.98
39.63
37.14
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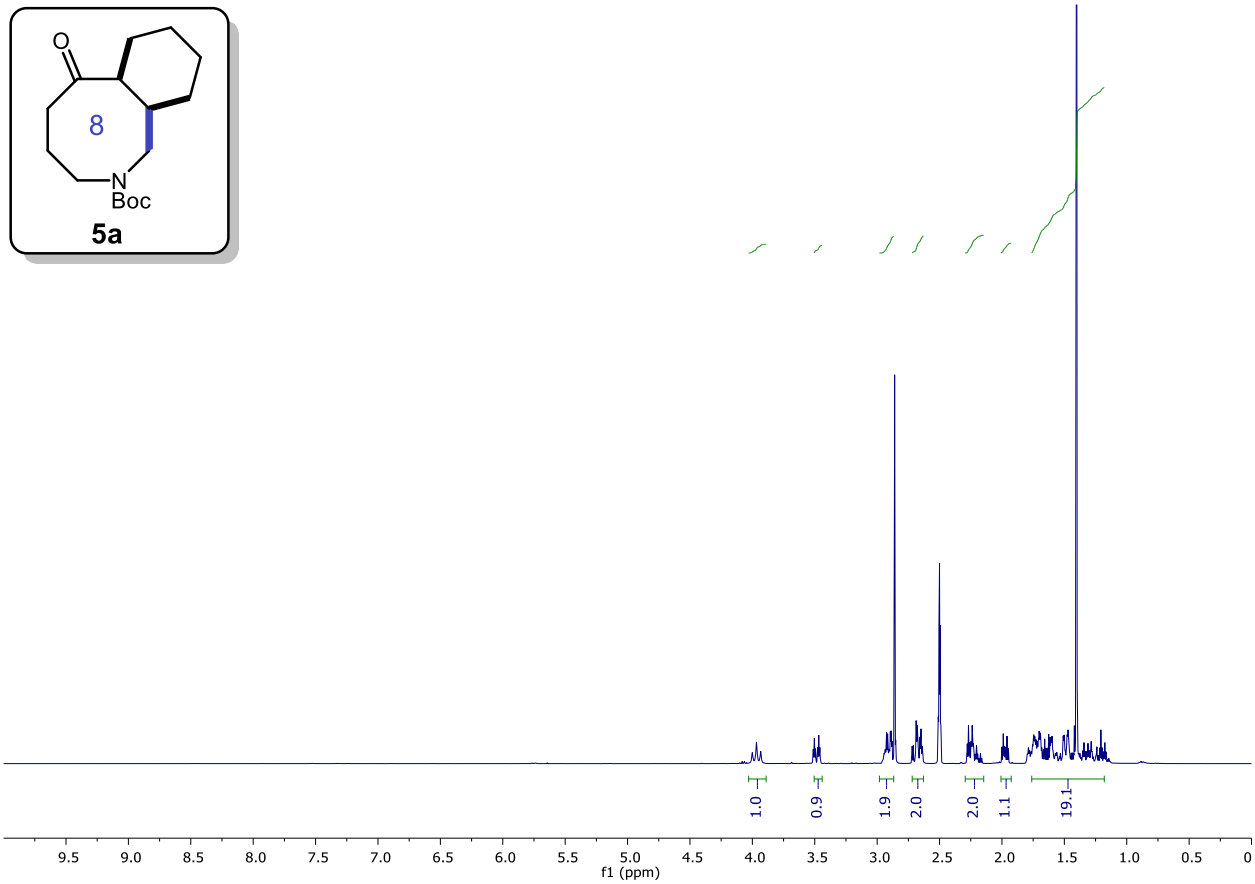
31.80
28.67
28.60
28.25
26.37
O
Ph
8
N
Boc
4a


O
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N
Boc
5a
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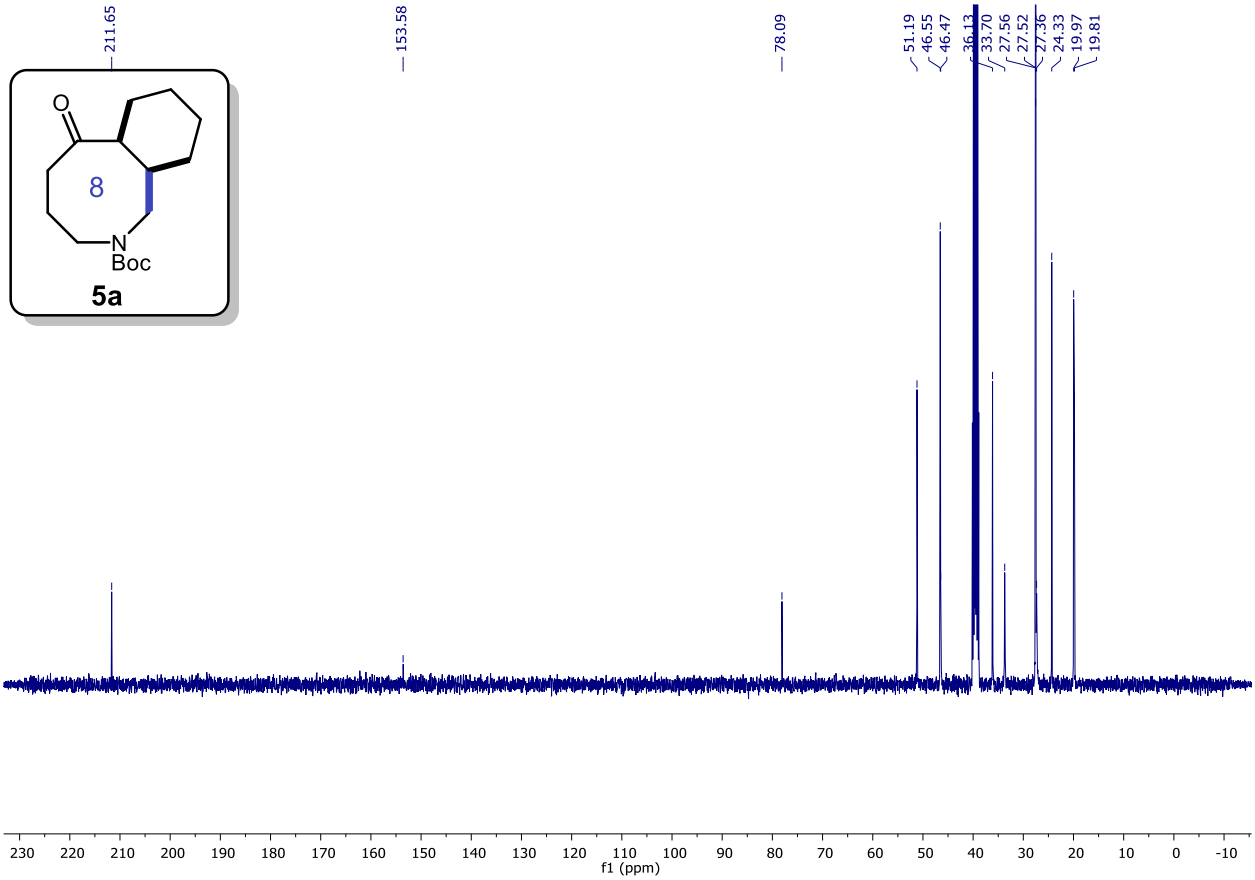
0.9
1.9
2.0
2.0
1.1
19.1
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)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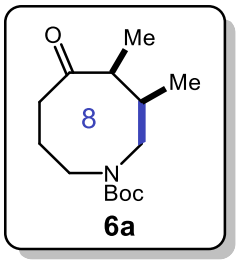
46.55
46.47
36.13
33.70
27.56
27.52
27.36
24.33
19.97
19.81
O
8
N
Boc
5a
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
Me
Me
8
N
Boc

6a

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1.0
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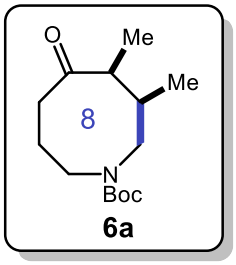
1.0
9.0
3.0
3.0
f1 (ppm)


O
Me
Me
8
N
Boc

6a

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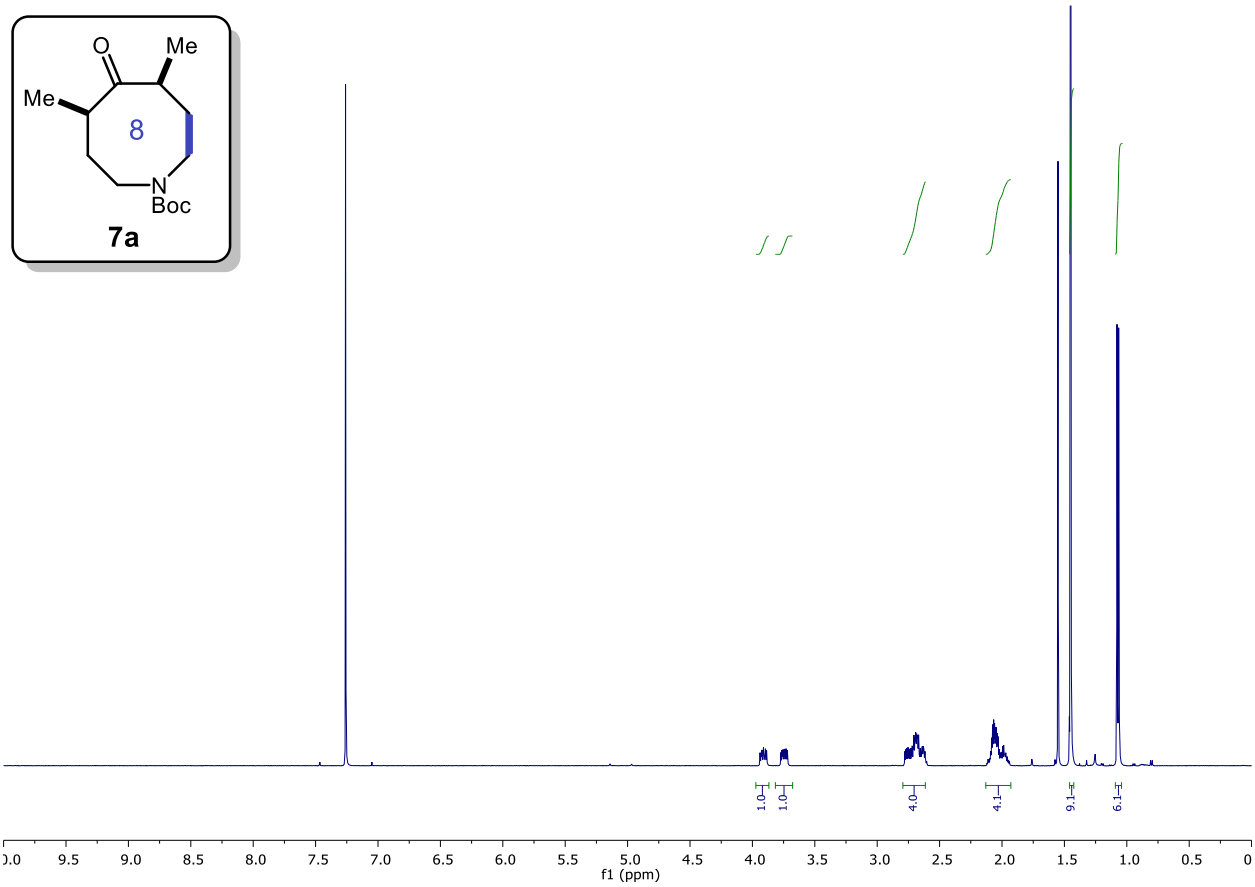
27.58
27.50
15.35
5.64
f1 (ppm)


O
Me
Me
8
N
Boc
7a
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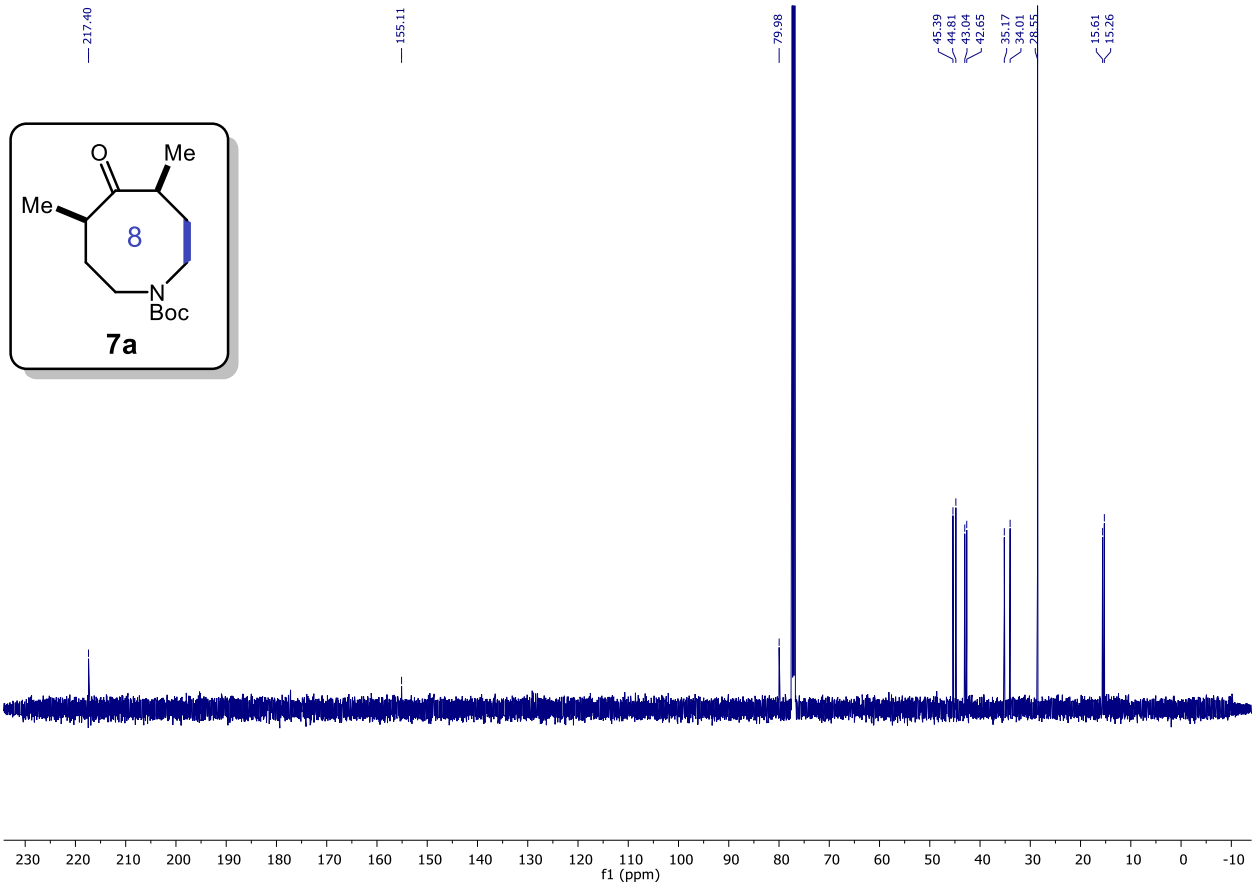
1.0
4.0
4.1
9.1
6.1
f1 (ppm)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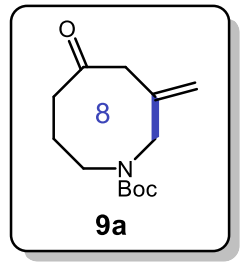
45.39
44.81
43.04
42.65
35.17
34.01
28.55
15.61
15.26
O
Me
Me
8
N
Boc
7a
f1 (ppm)


O
8
N
Boc

9a

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2.0
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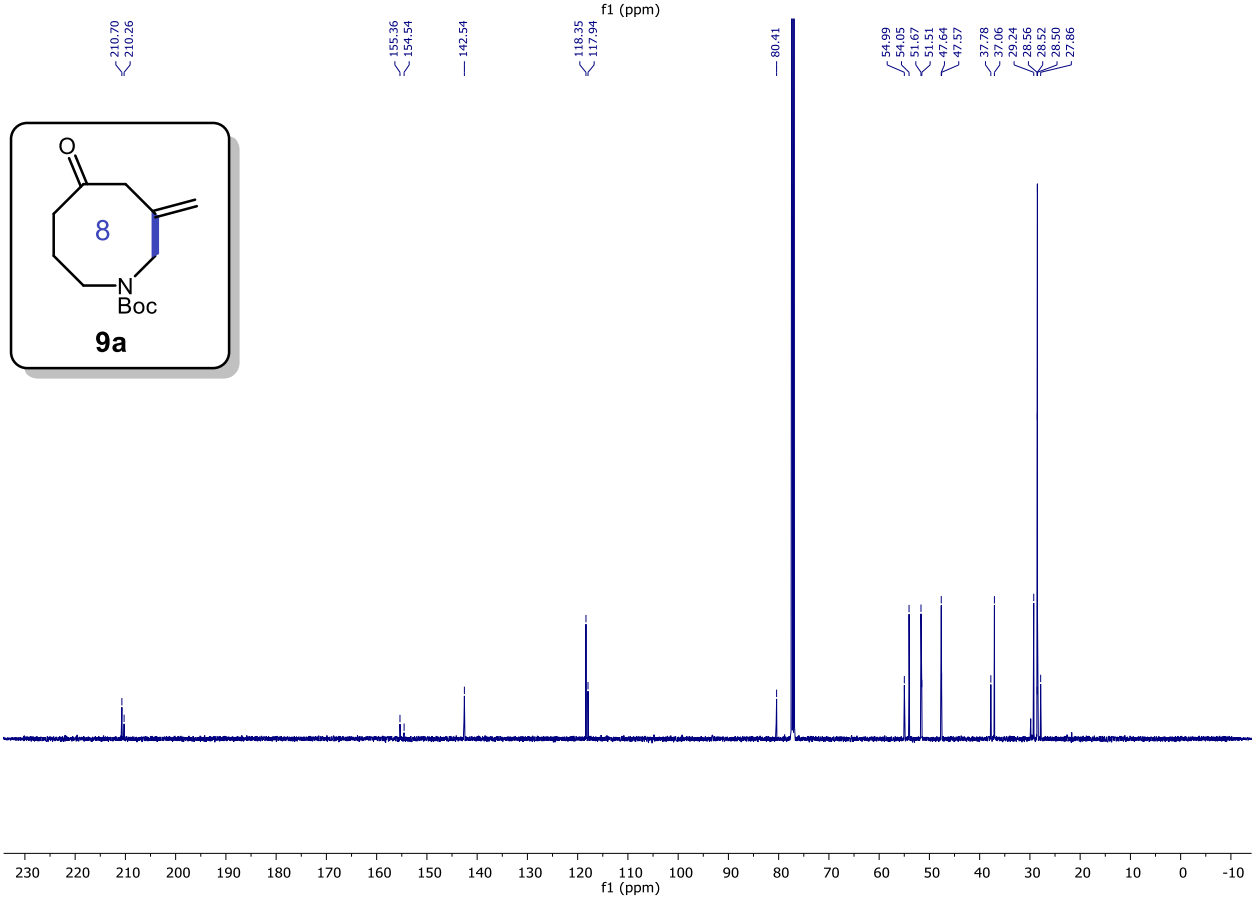
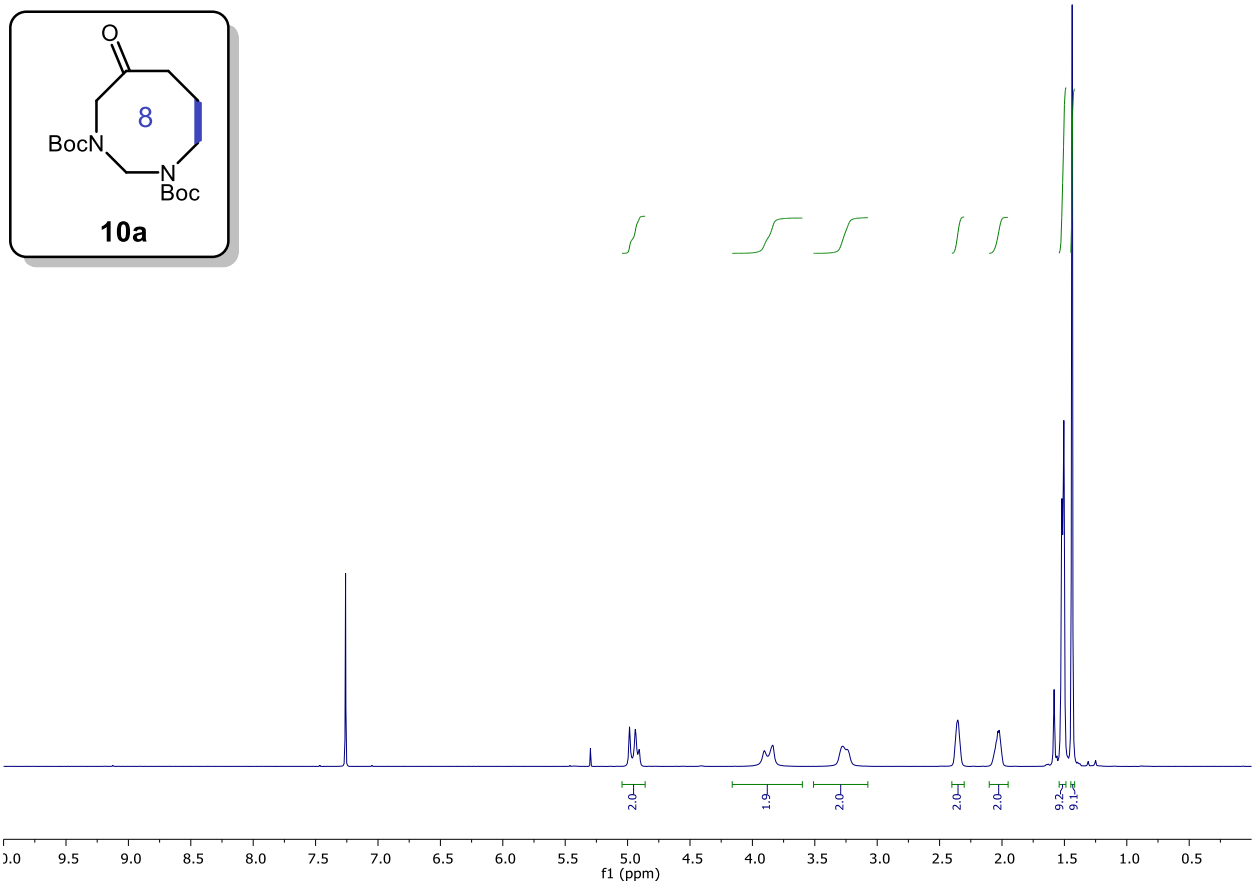
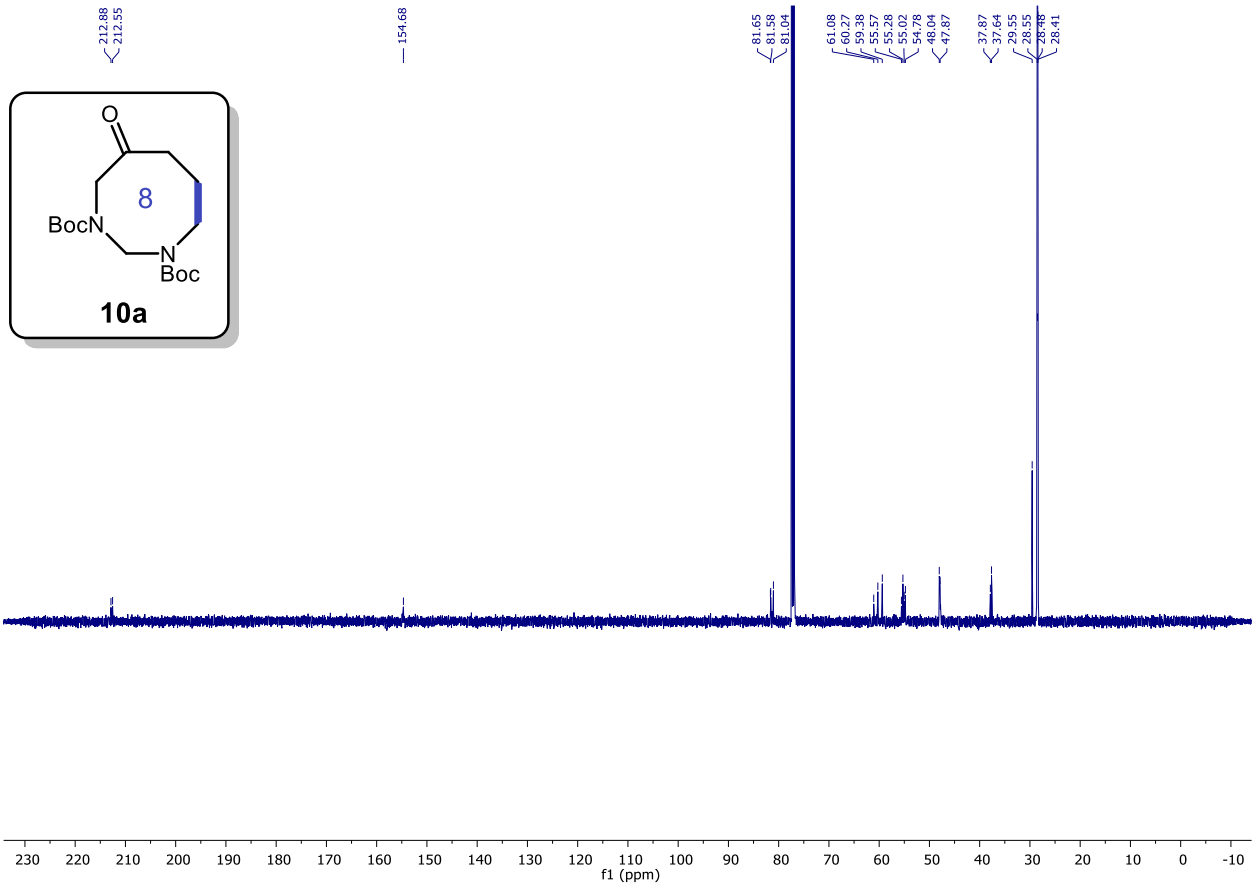
2.0
2.0
9.1
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)

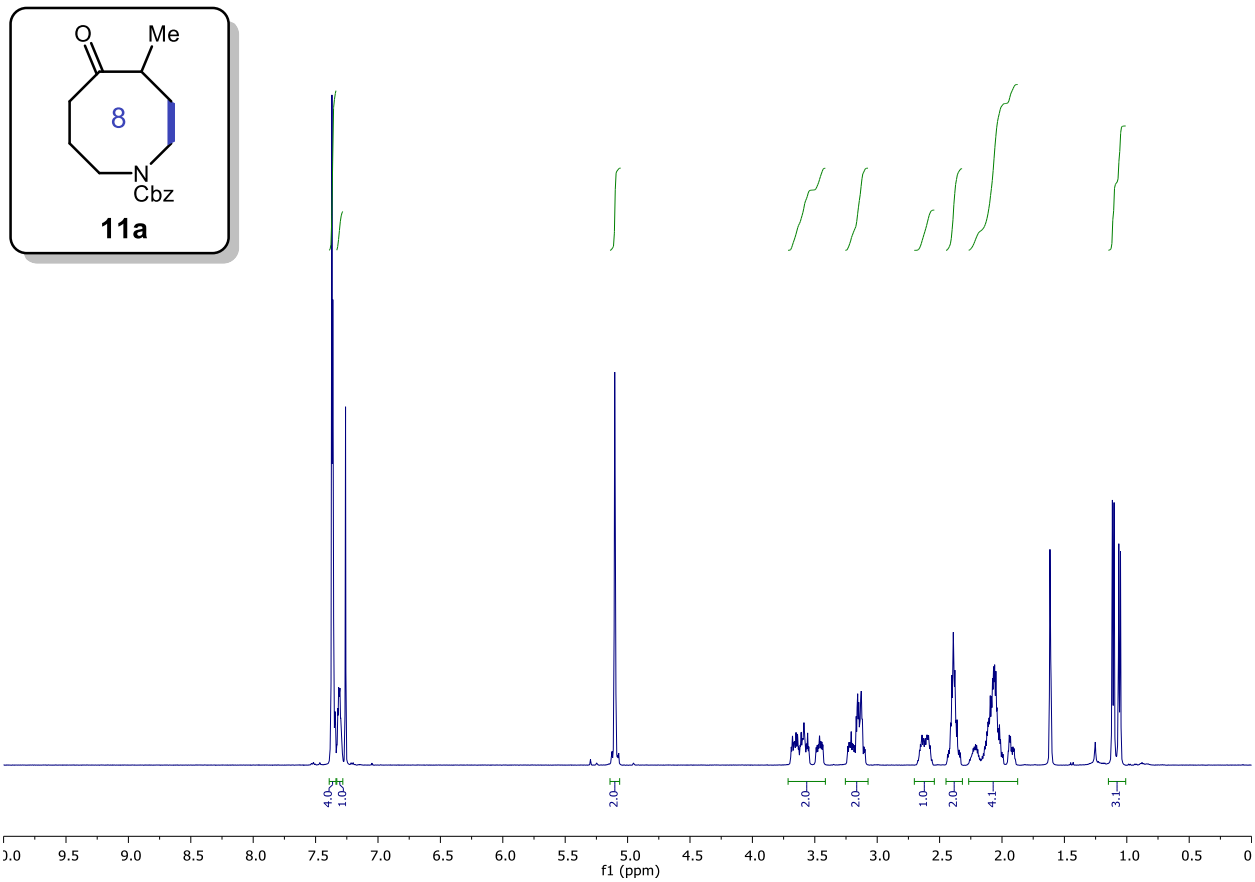

210.70
210.26
155.36
154.54
142.54
118.35
117.94
80.41
54.99
54.05
51.67
51.51
47.64
47.57
37.78
37.06
29.24
28.56
28.52
28.50
27.86
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

O
8
N
Boc

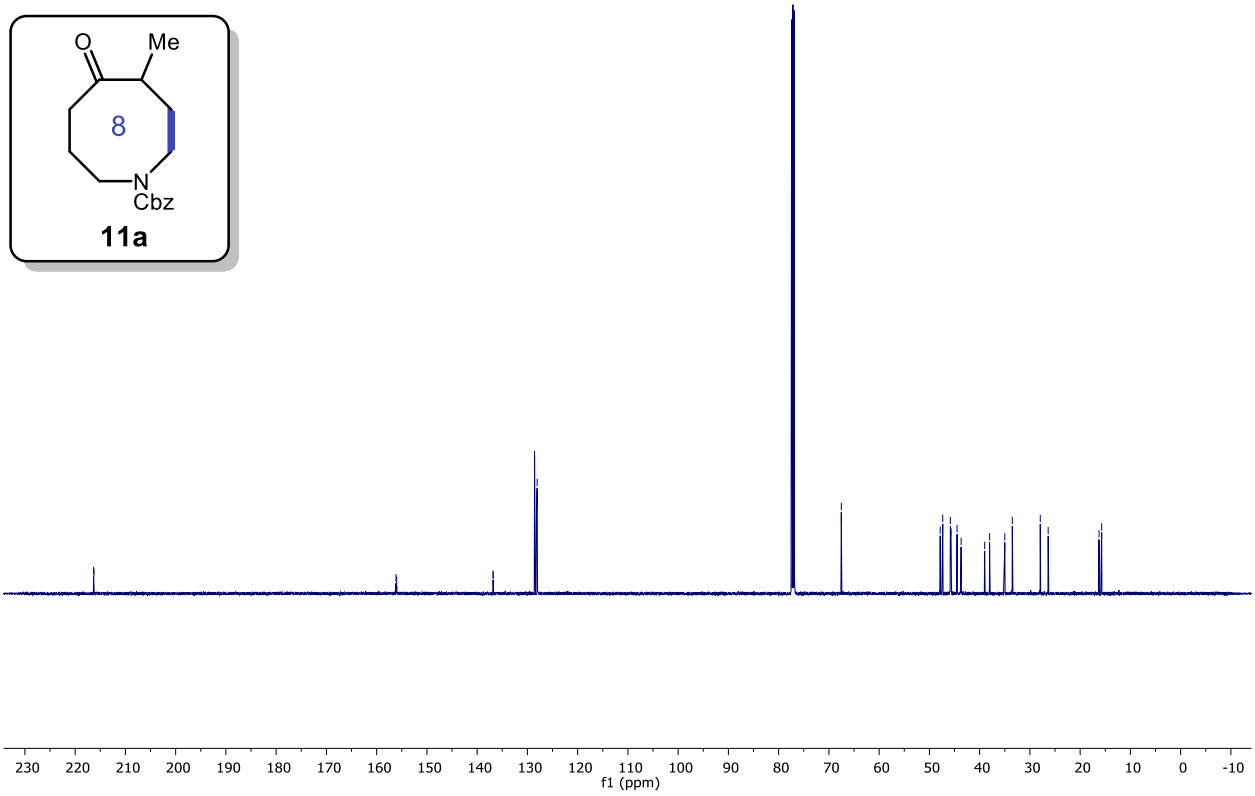
9a

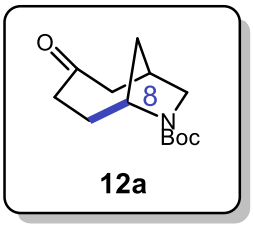

O
8
BocN
N
Boc
10a
2.0
1.9
2.0
2.0
2.0
9.2
9.1
f1 (ppm)


212.88
212.55
154.68
81.65
81.58
81.04
61.08
60.27
59.38
55.57
55.28
55.02
54.78
48.04
47.87
37.87
37.64
29.55
28.55
28.48
28.41
O
8
BocN
N
Boc
10a
f1 (ppm)


O
Me
8
N
Cbz
11a
4.0
1.0
2.0
2.0
2.0
1.0
2.0
4.1
3.1
f1 (ppm)

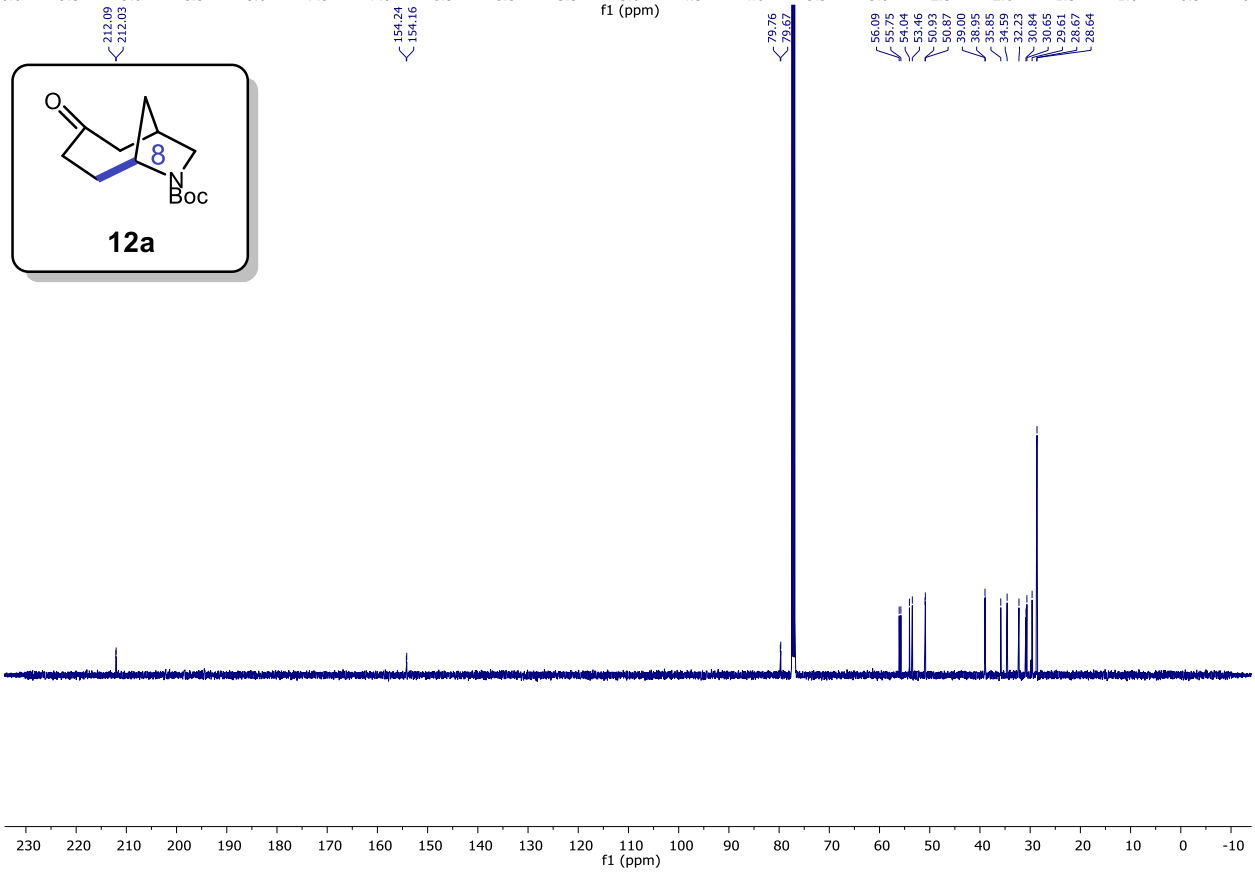

216.33
216.25
156.16
156.01
136.84
136.80
128.57
128.20
128.14
128.06
67.53
67.51
47.85
47.34
45.83
45.69
44.49
43.69
39.00
38.02
34.99
33.50
27.94
26.36
16.24
15.71


O
Me
8
N
Cbz
11a
f1 (ppm)


O
8
N
Boc

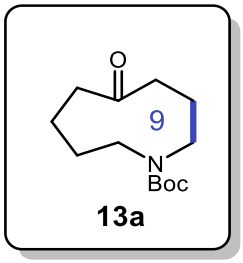
12a

1.0
1.0
1.0
5.1
2.1
1.6
9.1
f1 (ppm)


212.09
212.03
154.24
154.16
79.76
79.67
56.09
55.75
54.04
53.46
50.93
50.87
39.00
38.95
35.85
34.59
32.23
30.84
30.65
29.61
28.67
28.64
f1 (ppm)

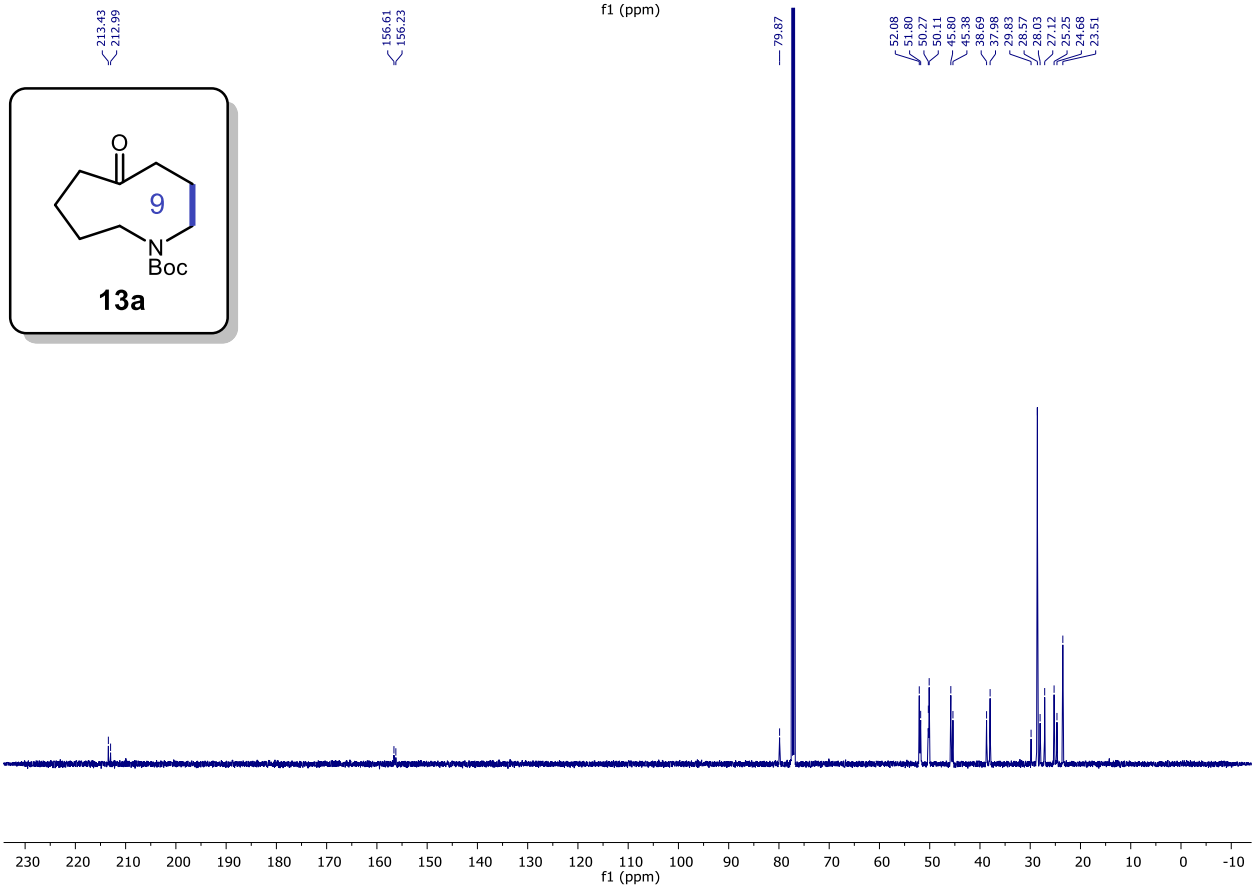
O
8
N
Boc

12a


O
9
N
Boc

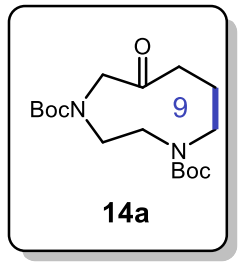
13a

4.0
4.0
2.0
2.0
2.0
9.1
f1 (ppm)


213.43
212.99
156.61
156.23
79.87
52.08
51.80
50.27
50.11
45.80
45.38
38.69
37.98
29.83
28.57
28.03
27.12
25.25
24.68
23.51
f1 (ppm)

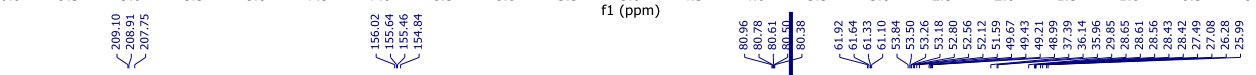
O
9
N
Boc

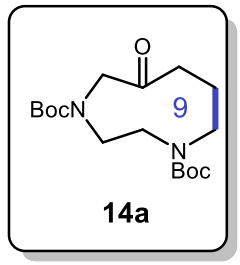
13a


O
BocN
9
N
Boc

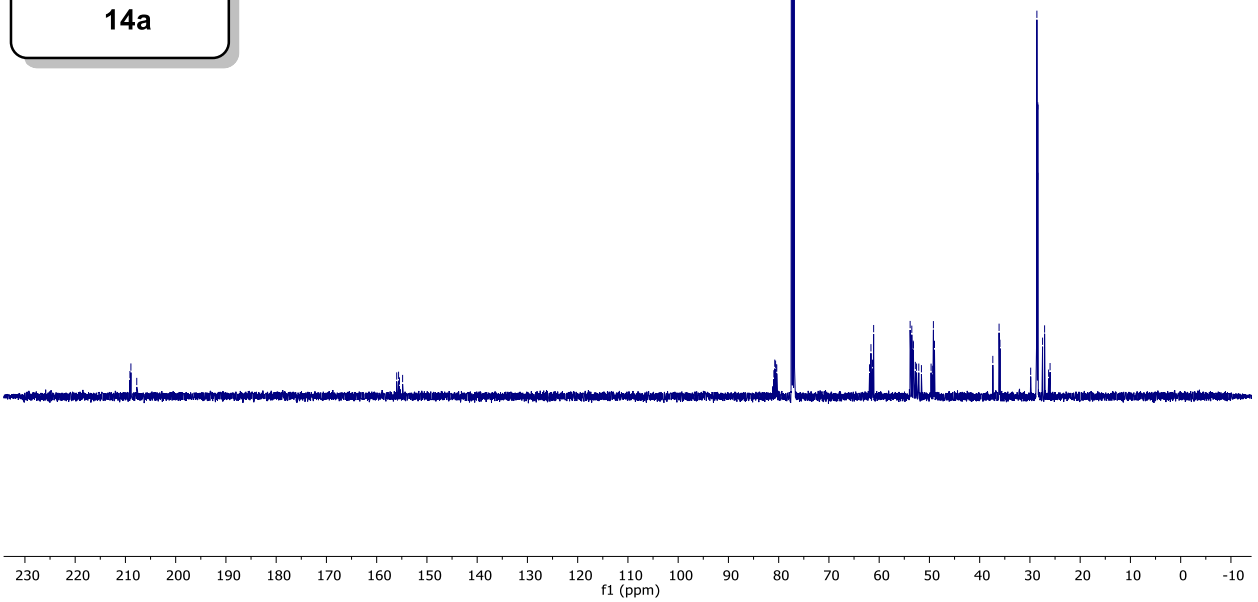
14a

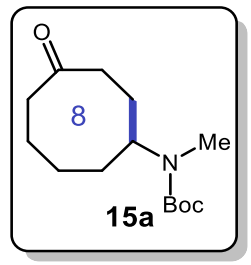
2.0
4.1
2.0
2.0
2.0
9.1
9.0
f1 (ppm)


209.10
208.91
207.75
156.02
155.64
155.46
154.84
80.96
80.78
80.61
80.50
80.38
61.92
61.64
61.33
61.10
53.84
53.50
53.26
53.18
52.80
52.56
52.12
51.59
49.67
49.43
49.21
48.99
37.39
36.14
35.96
29.85
28.65
28.61
28.56
28.43
28.42
27.49
27.08
26.28
25.99

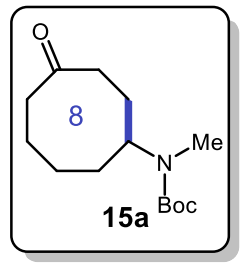

O
BocN
9
N
Boc

14a

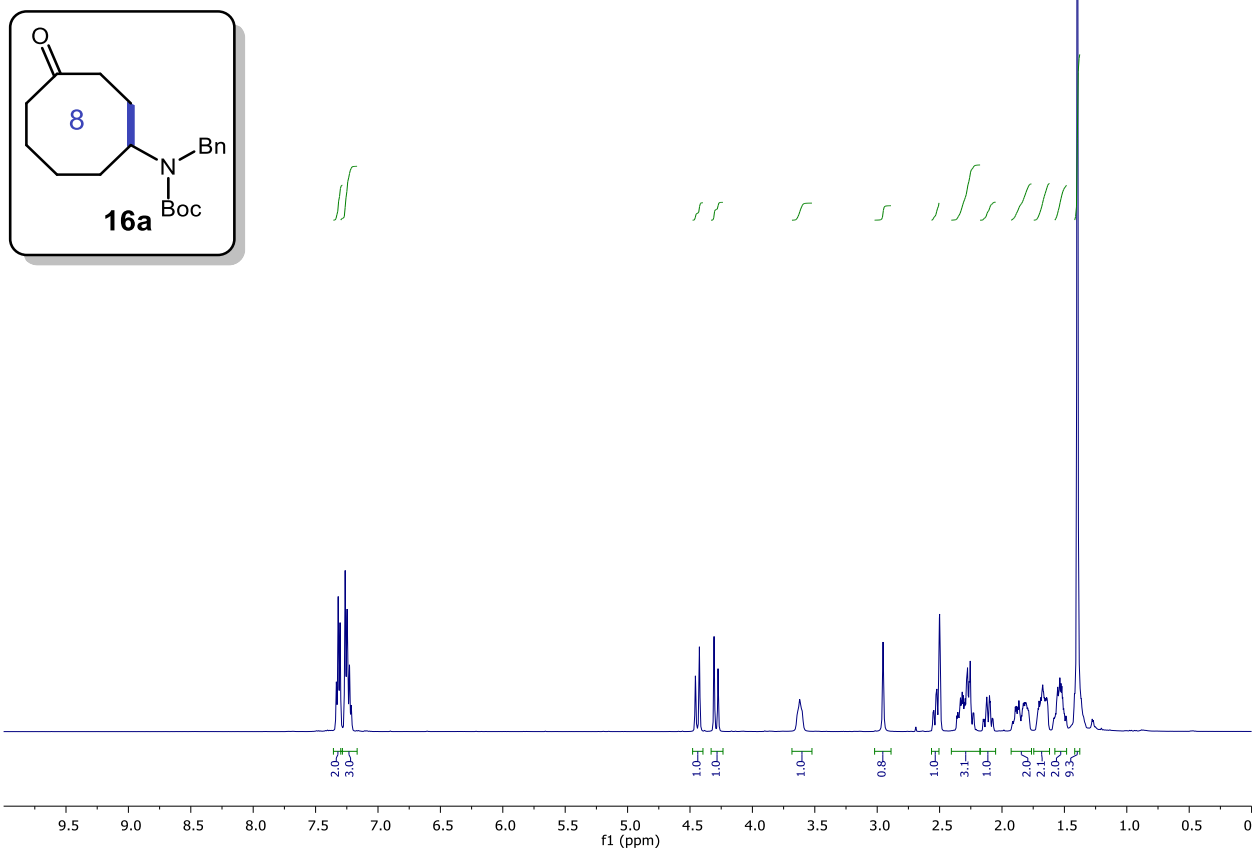

f1 (ppm)

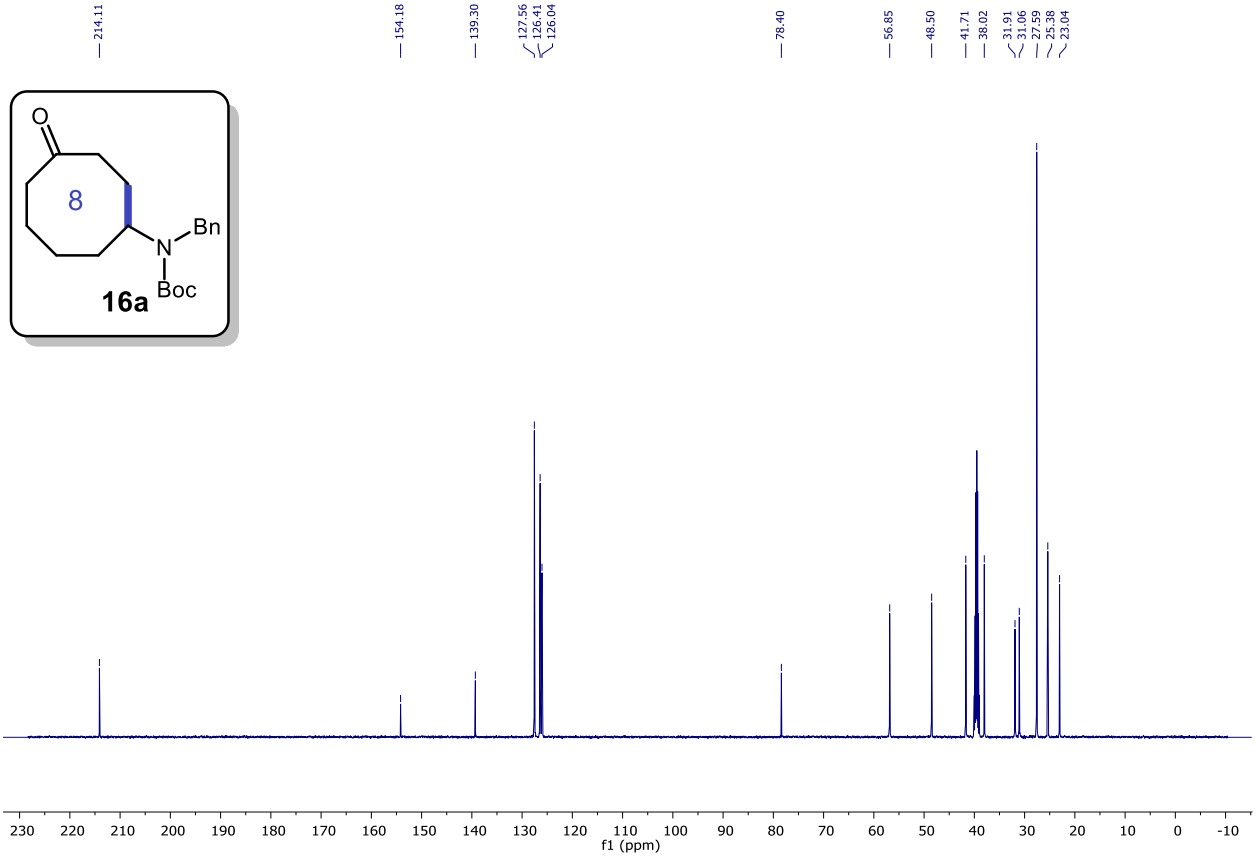

O
8
N
Me
Boc
15a

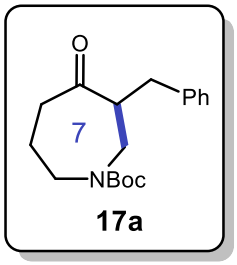
1.0
3.0
1.1
3.1
2.2
7.0
9.1
f1 (ppm)


O
8
N
Me
Boc
15a

214.16
153.95
77.96
54.96
41.50
38.23
30.77
30.10
29.00
27.66
25.22
23.66
f1 (ppm)


O
8
N
Bn
Boc
16a
2.0
3.0
1.0
1.0
1.0
0.8
1.0
3.1
1.0
2.0
2.1
2.0
9.3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)

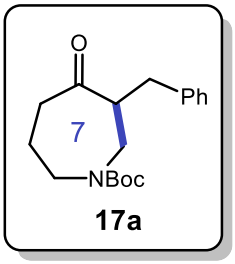

214.11
154.18
139.30
127.56
126.41
126.04
78.40
56.85
48.50
41.71
38.02
31.91
31.06
27.59
25.38
23.04
O
8
N
Bn
Boc
16a
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
Ph
7
NBoc

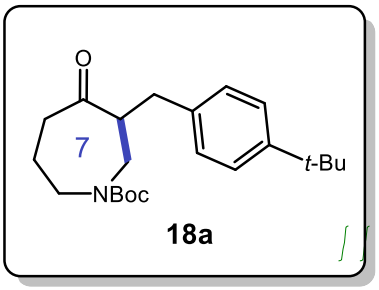
17a

1.9
3.0
0.9
1.0
4.0
2.0
1.0
2.0
9.1
f1 (ppm)


210.82
153.33
138.51
128.02
127.50
125.32
78.35
52.99
47.20
46.81
40.00
34.43
27.38
24.08


O
Ph
7
NBoc

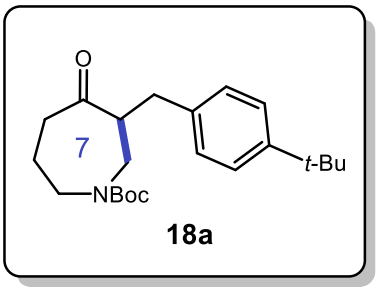
17a


O
7
NBoc
t-Bu

18a

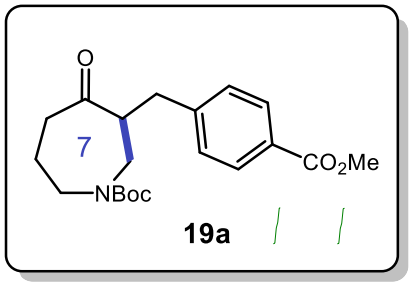
2.01
2.01
1.01
1.01
2.01
2.01
2.01
1.01
2.01
9.01
9.15
f1 (ppm)


210.93
153.31
147.99
135.36
127.71
124.22
78.30
53.07
47.14
46.81
40.01
33.88
33.33
30.46
27.37
24.01


O
7
NBoc
t-Bu

18a

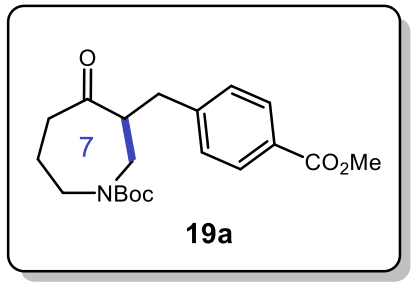
f1 (ppm)


O
7
NBoc
CO2Me

19a

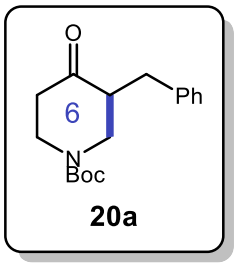
2.0
2.0
3.0
2.0
4.0
1.0
1.0
1.0
2.0
9.0
f1 (ppm)


210.54
165.54
153.36
144.36
128.47
128.36
127.48
78.45
52.69
50.95
47.18
46.65
40.06
34.28
27.38
23.97

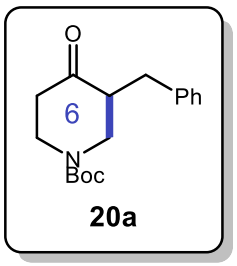

O
7
NBoc
CO2Me

19a

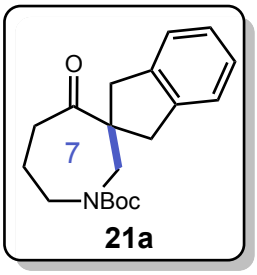
f1 (ppm)


O
6
Ph
N
Boc
20a

2.0
3.0
2.0
1.0
2.0
1.1
2.3
1.0
9.1
f1 (ppm)

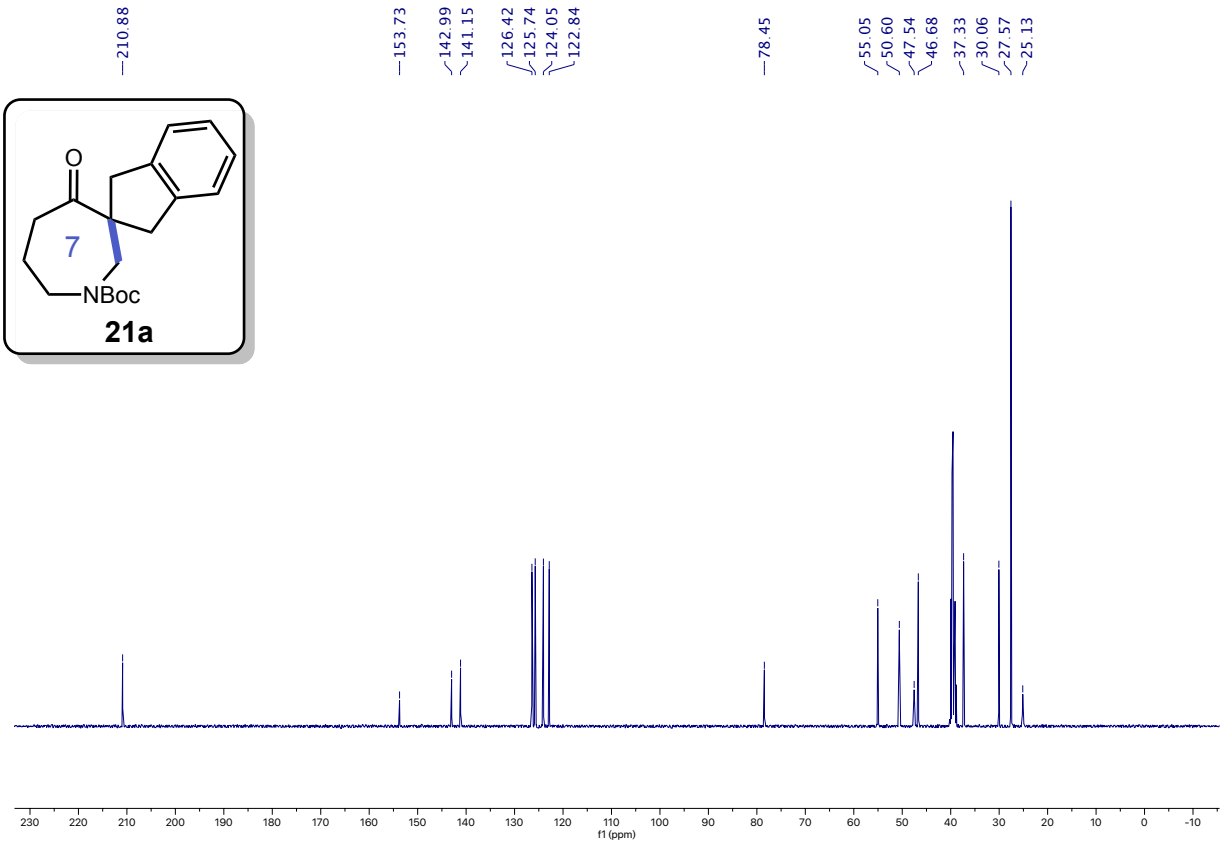

O
6
Ph
N
Boc
20a

207.06
153.34
138.59
128.04
127.52
125.31
78.69
49.96
46.47
42.35
39.32
32.04
27.40
f1 (ppm)


O
7
NBoc

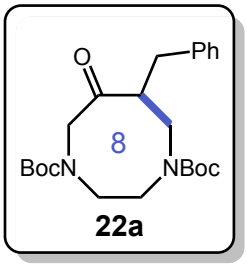
21a

4.0
1.0
3.0
1.0
1.0
1.0
1.0
1.0
1.0
2.0
9.0
f1 (ppm)


210.88
153.73
142.99
141.15
126.42
125.74
124.05
122.84
78.45
55.05
50.60
47.54
46.68
37.33
30.06
27.57
25.13
f1 (ppm)

O
7
NBoc

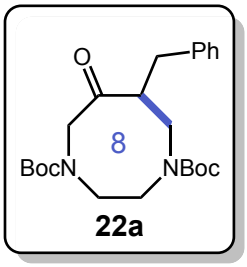
21a


O
Ph
8
BocN
NBoc

22a

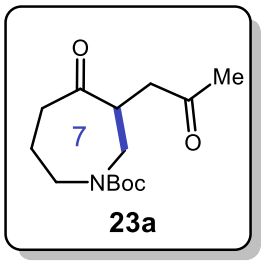
2.0
3.0
1.0
1.0
1.1
0.9
4.0
2.0
1.0
18.0
f1 (ppm)


211.86
153.89
153.19
138.72
128.00
127.49
125.30
79.37
78.90
57.70
50.73
47.51
46.94
46.03
33.50
27.36
27.24

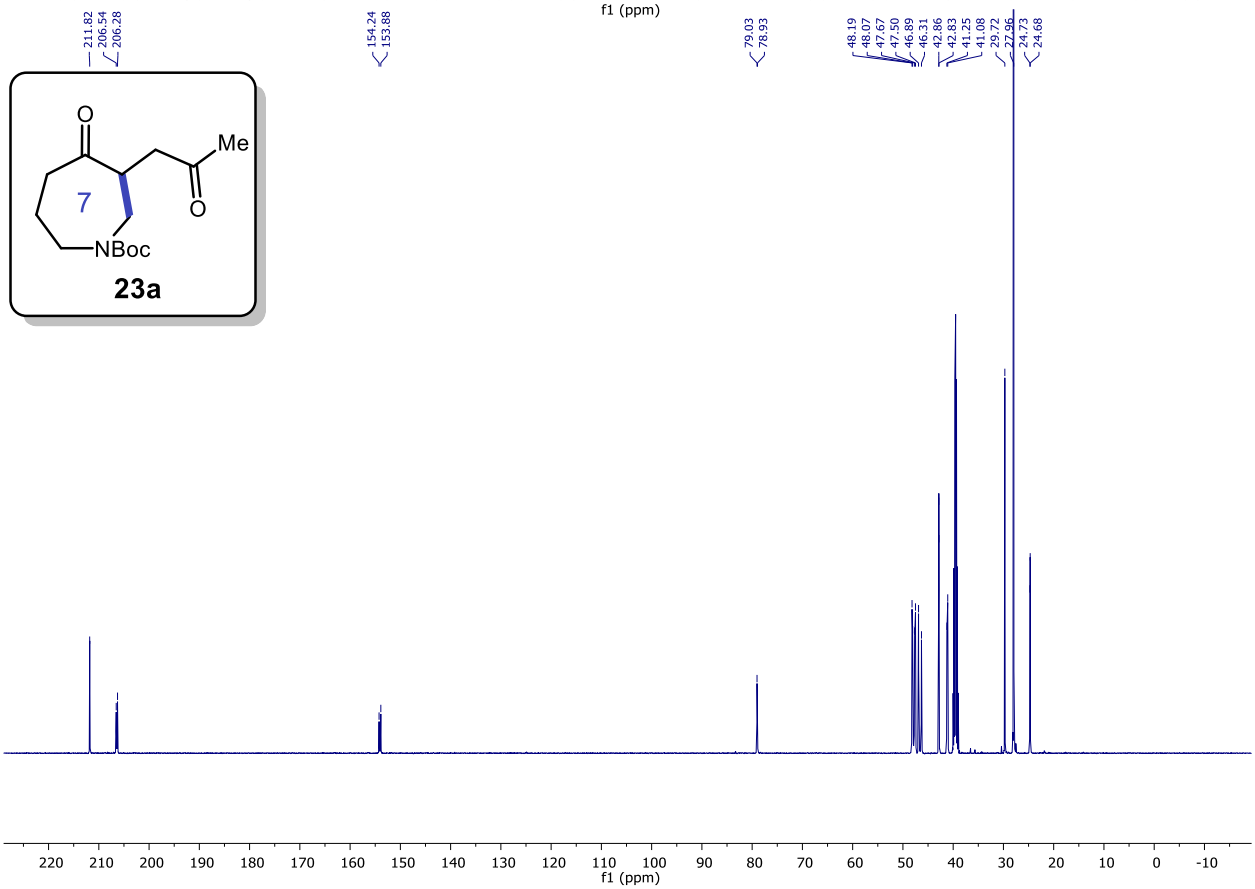

O
Ph
8
BocN
NBoc

22a

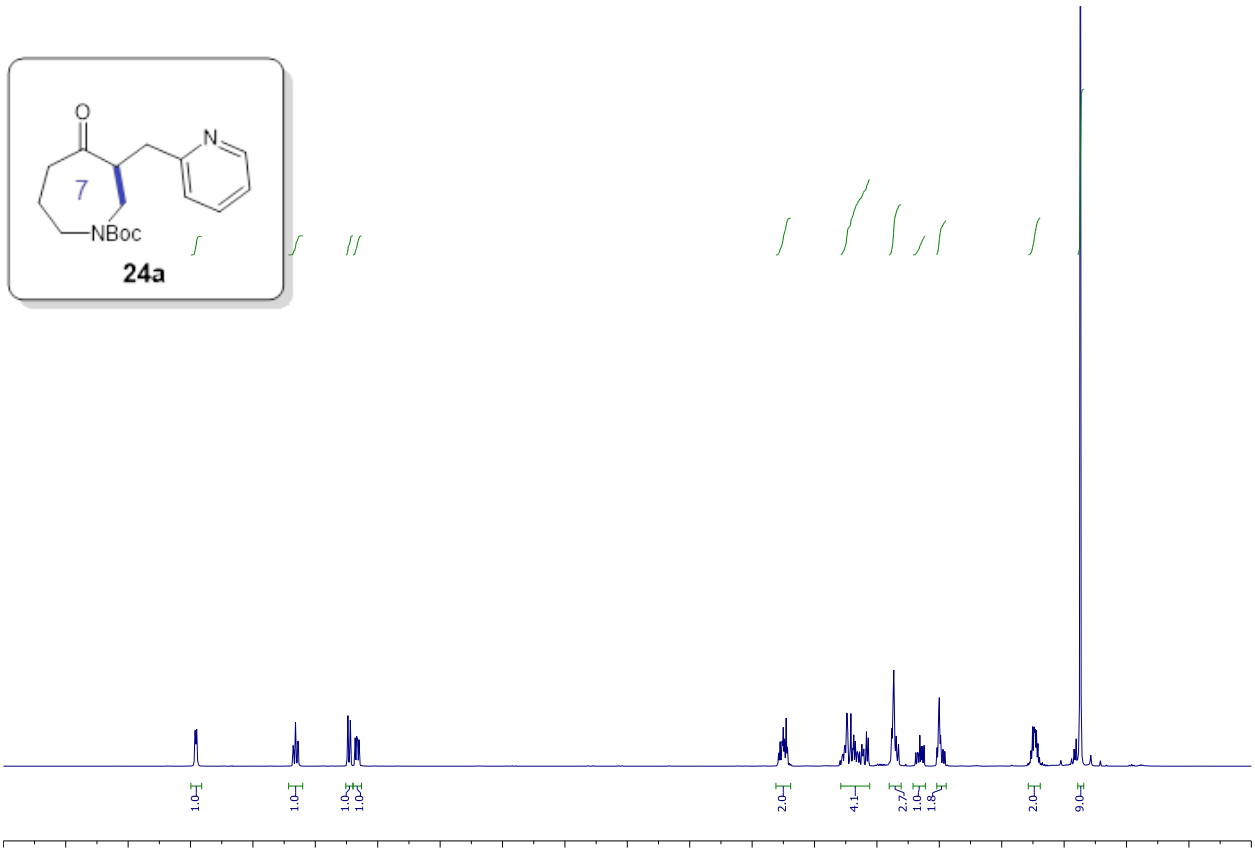
f1 (ppm)

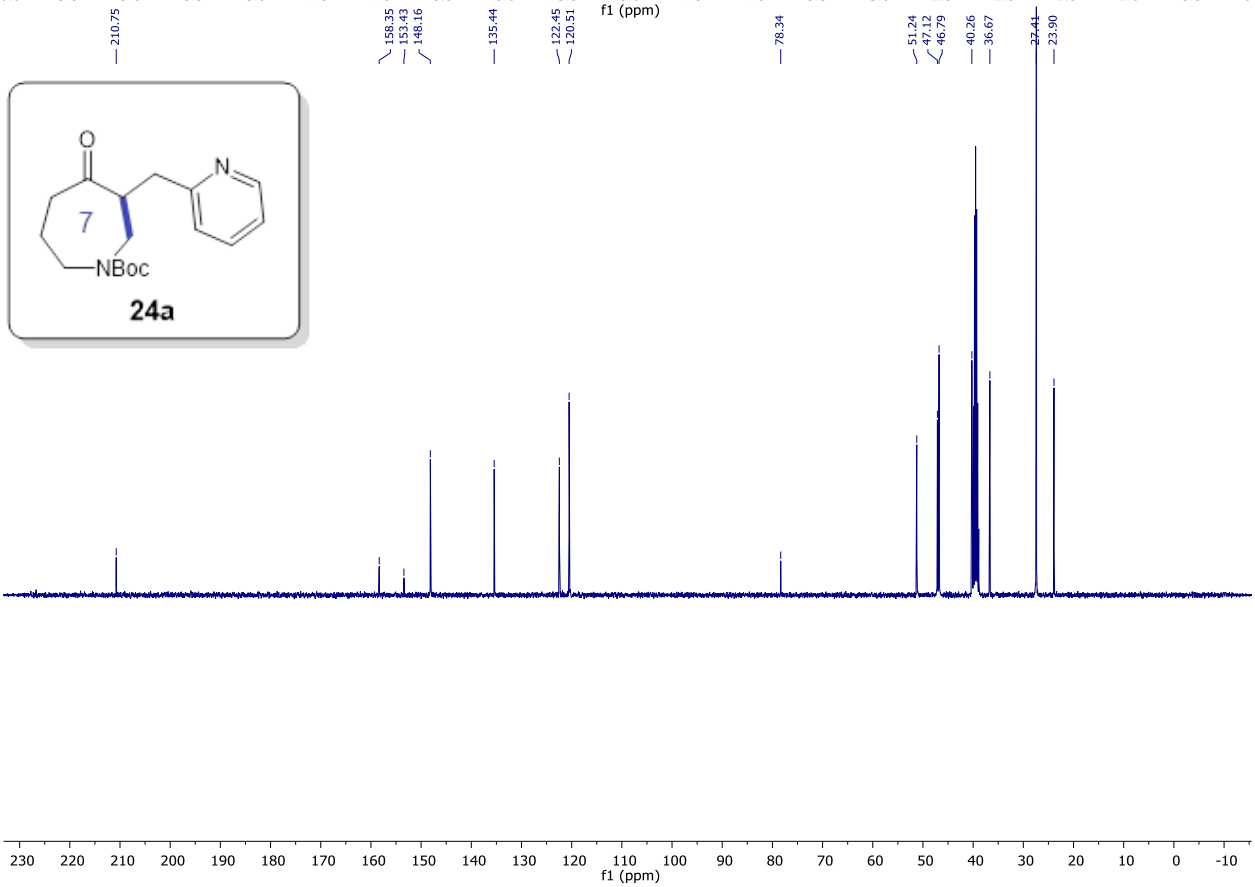


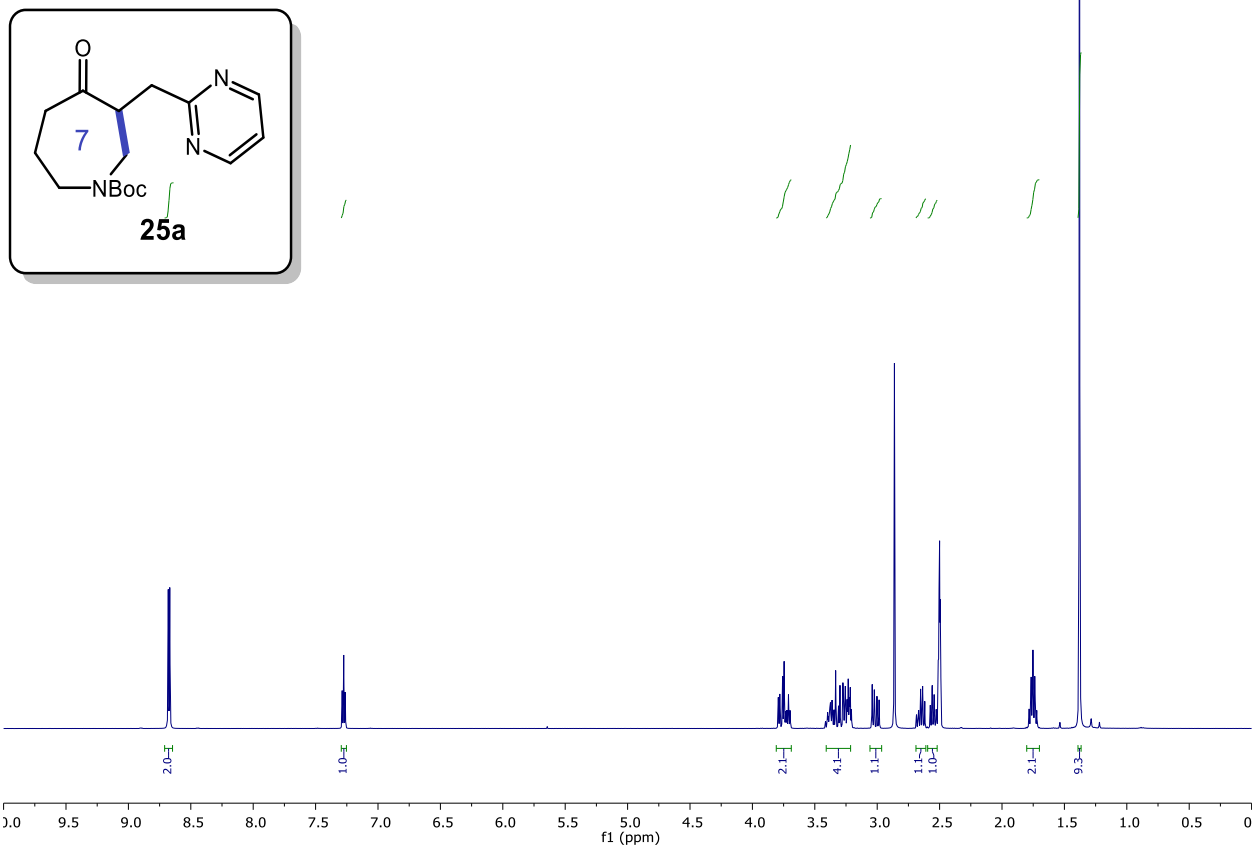
23a

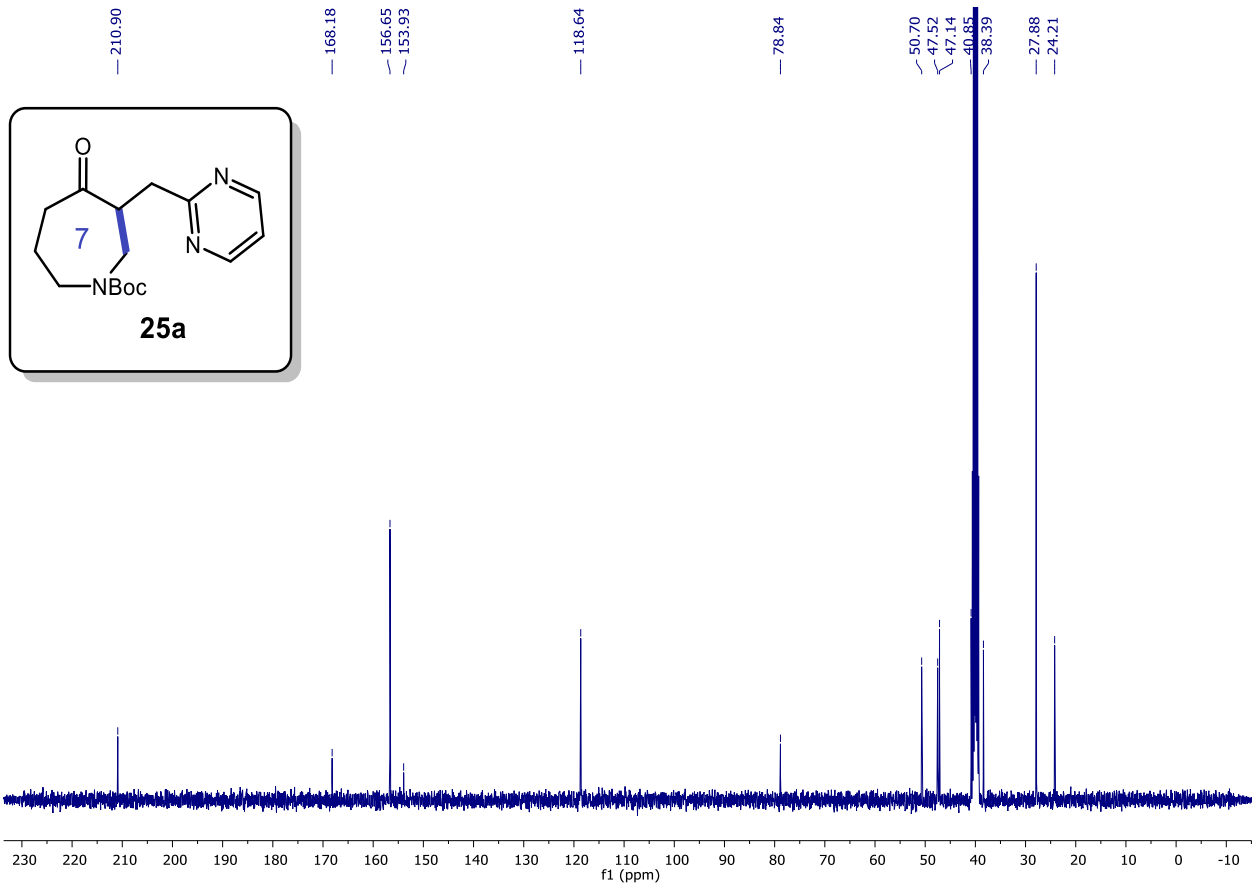


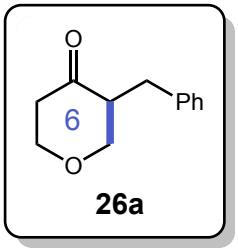
O
Me
7
O
NBoc
23a

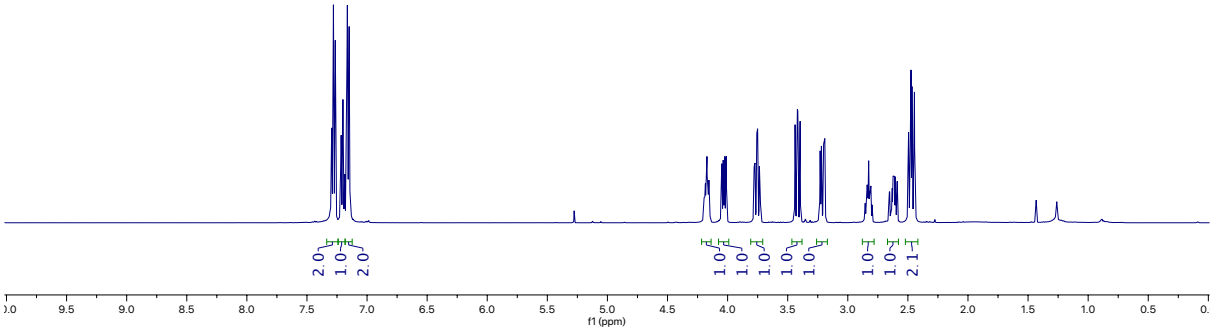

O
N
7
NBoc
24a
1.0
1.0
1.0
1.0
2.0
4.1
2.7
1.0
1.8
2.0
9.0
f1 (ppm)


210.75
158.35
153.43
148.16
135.44
122.45
120.51
78.34
51.24
47.12
46.79
40.26
36.67
27.41
23.90
O
N
7
NBoc
24a
f1 (ppm)

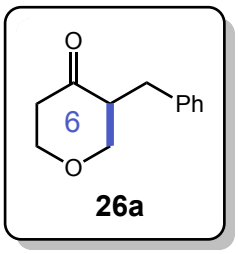

O
N
N
7
NBoc
25a
2.0
1.0
2.1
4.1
1.1
1.1
1.0
2.1
9.3
f1 (ppm)


210.90
168.18
156.65
153.93
118.64
78.84
50.70
47.52
47.14
40.85
38.39
27.88
24.21
O
N
N
7
NBoc
25a
f1 (ppm)

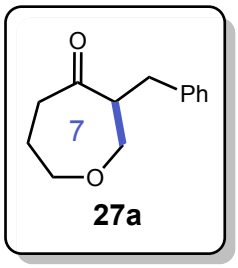

O
6
Ph
O
26a

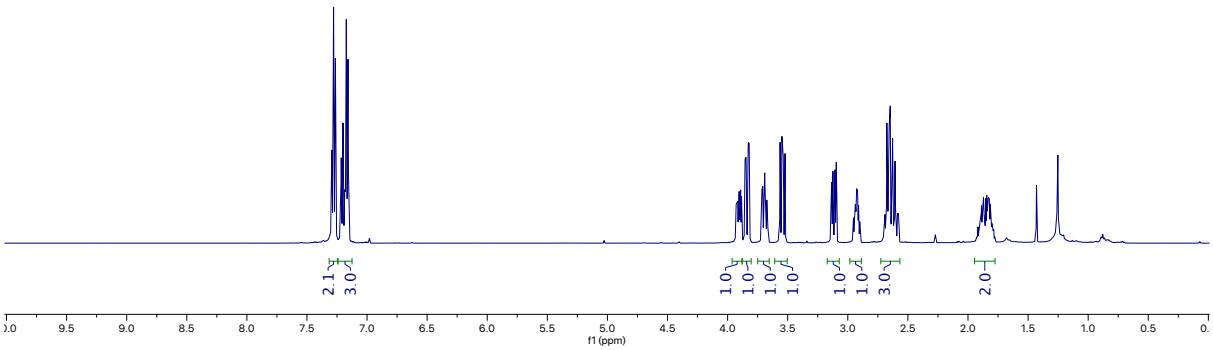

2.0
1.0
2.0
1.0
1.0
1.0
1.0
1.0
1.0
1.0
2.1
f1 (ppm)

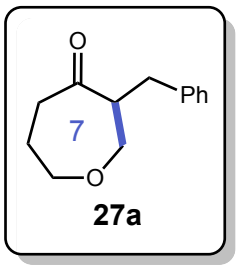

207.78
138.90
128.90
128.58
126.41
72.16
68.73
53.02
42.52
31.81

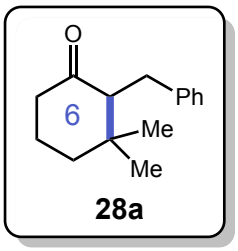

O
6
Ph
O
26a

f1 (ppm)


O
Ph
7
O
27a

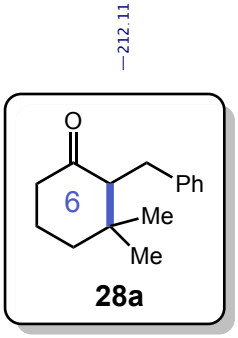

2.1
3.0
1.0
1.0
1.0
1.0
1.0
1.0
3.0
2.0
f1 (ppm)


212.90
139.08
129.18
128.63
126.48
73.11
70.31
56.00
42.32
34.46
26.55
O
Ph
7
O
27a
f1 (ppm)


O
6
Ph
Me
Me

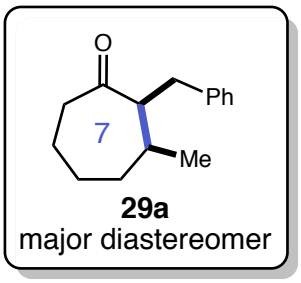
28a

4.0
1.0
1.0
1.0
1.0
1.0
1.0
1.0
1.1
1.1
1.4
3.0
3.0
f1 (ppm)


O
6
Ph
Me
Me

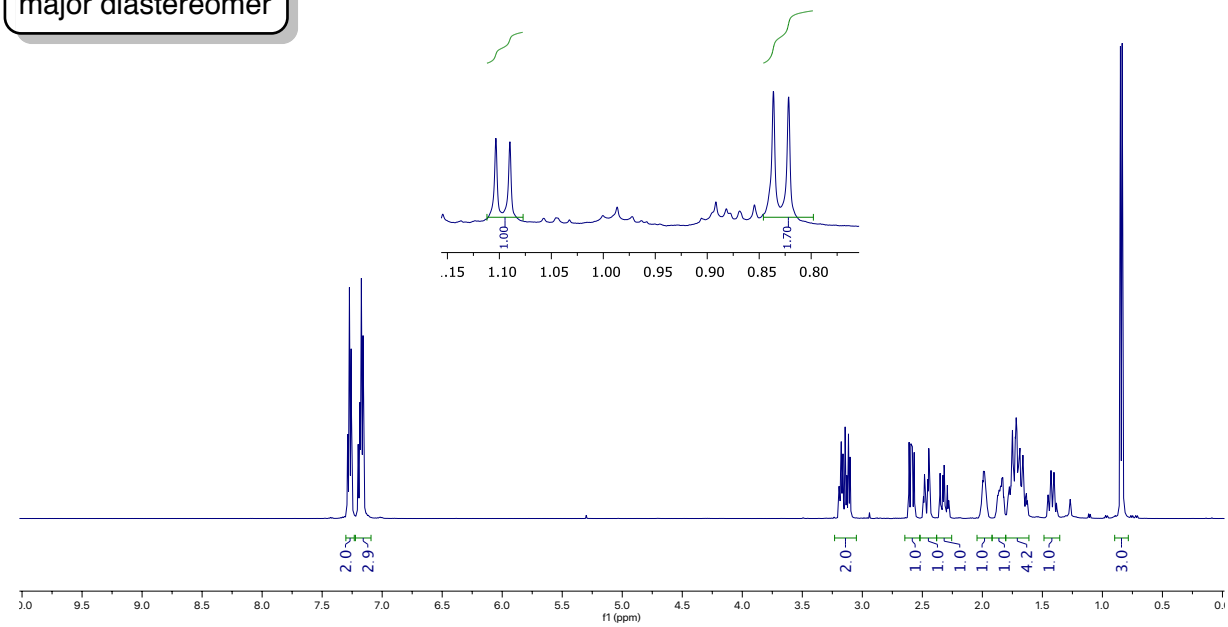
28a

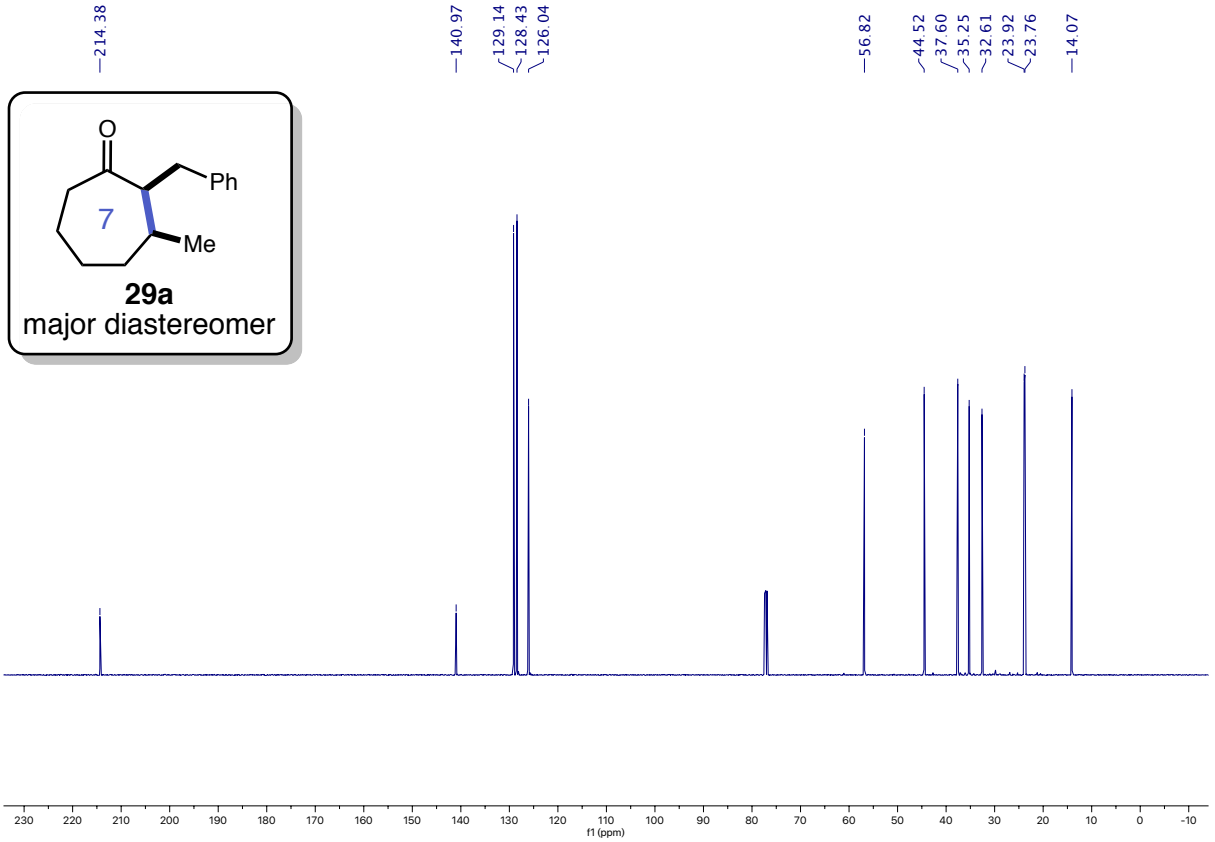
212.11
142.22
129.13
128.33
125.77
63.46
41.92
40.57
40.09
30.07
29.63
23.44
21.47
f1 (ppm)



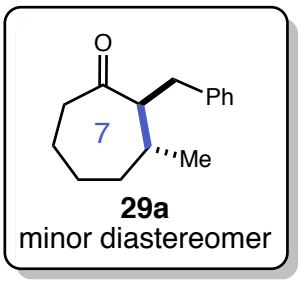
29a
major diastereomer

Crude in $CDCl_3$ at 500 MHz

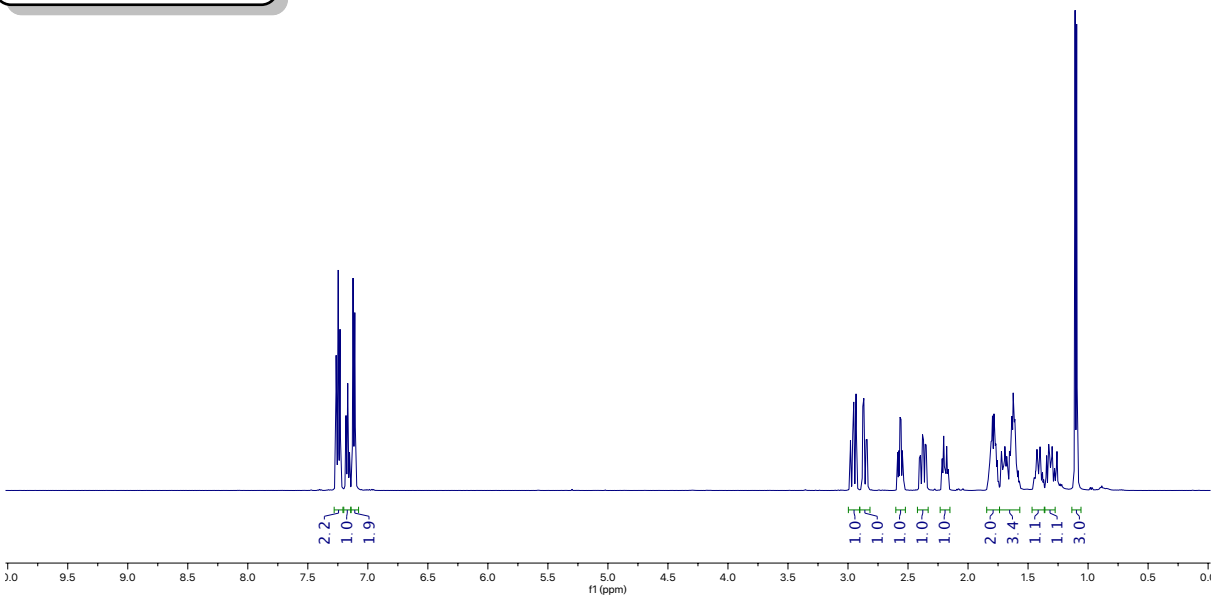


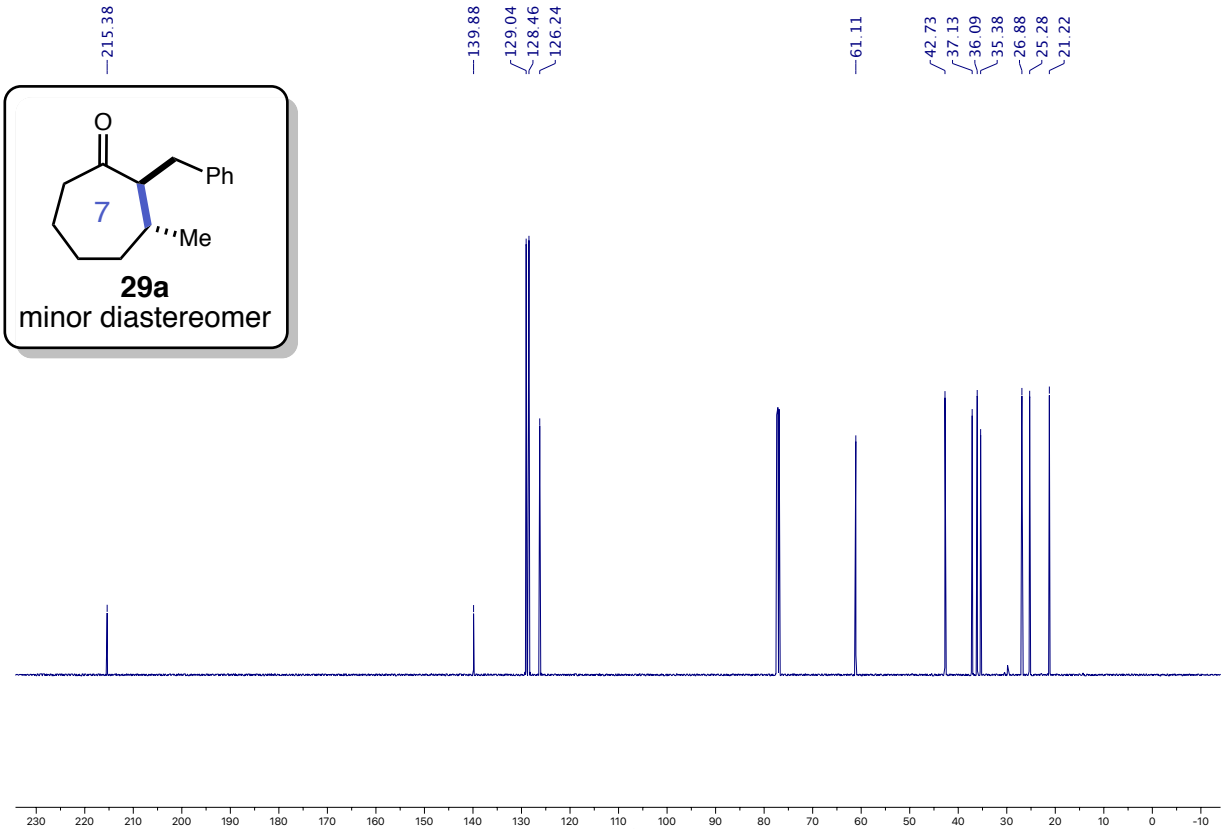


29a
major diastereomer



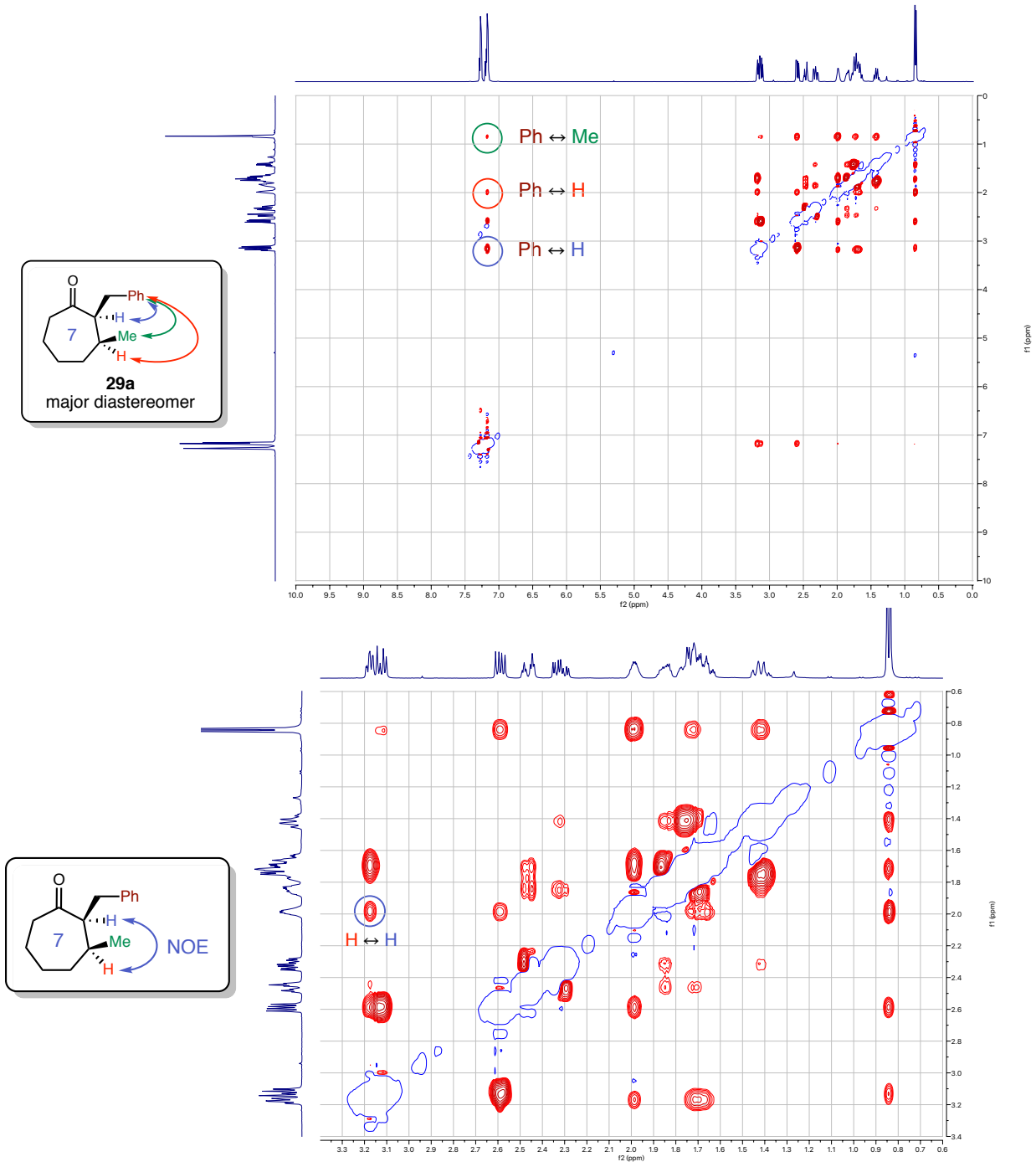
29a
minor diastereomer



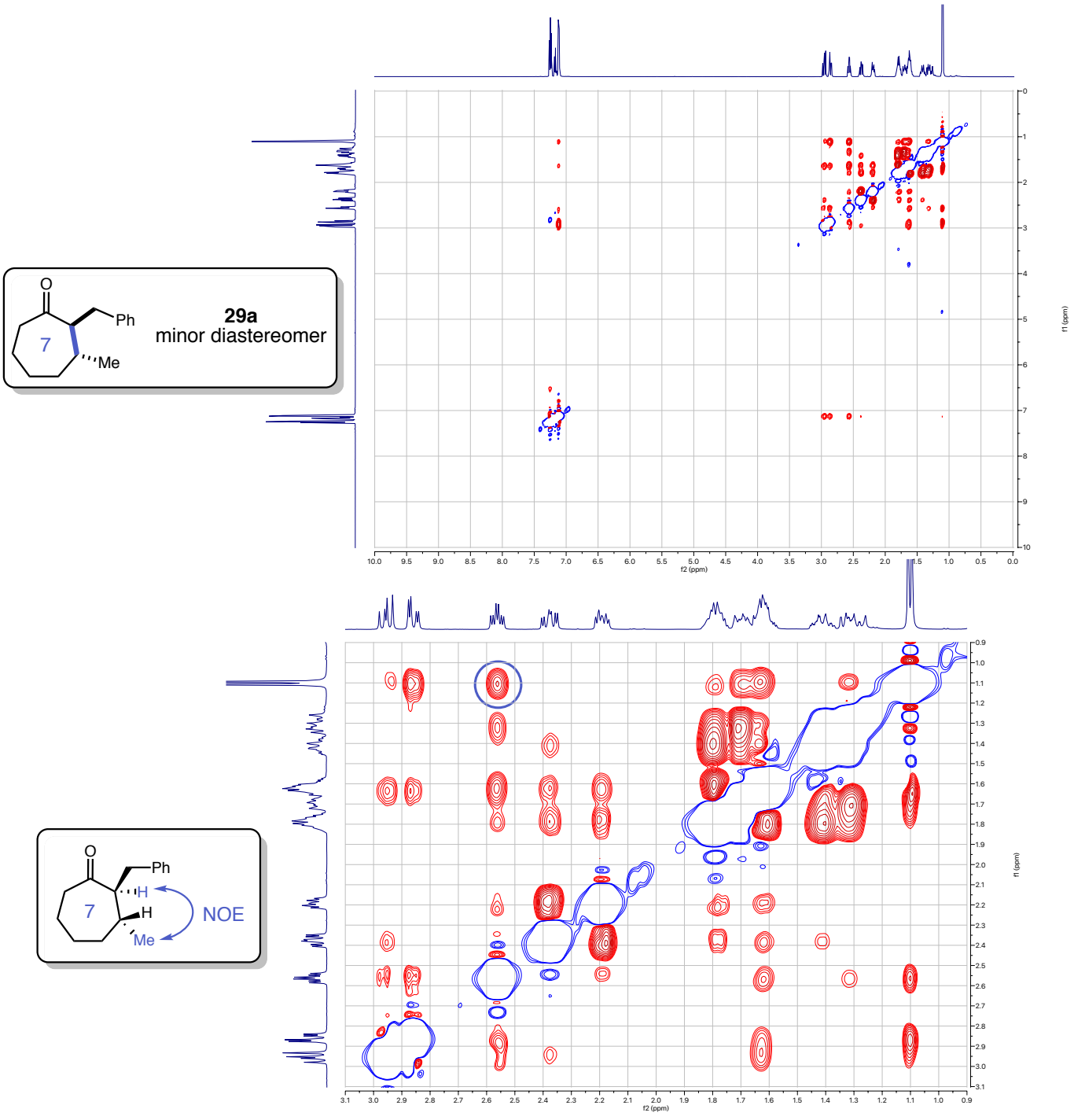


29a
minor diastereomer

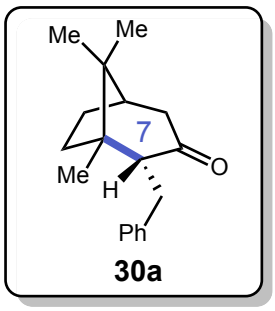
NOESY Analysis of 29a



NOESY analysis of **29a** (major diastereomer), annotated with important cross-peaks.
The α-proton (H) shows strong nuclear Overhauser effect (NOE) to the β-proton (H), but no NOE is observed between the α-proton (H) and Me. This evidence indicates that the benzyl group and methyl group in the major isomer are in a *cis* conformation.



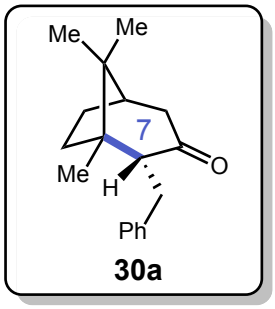
NOESY analysis of **29a** (minor diastereomer), annotated with important cross-peaks.
Unlike the NOESY of the *cis* isomer, the α-proton (H) shows strong NOE to the methyl group (Me). This evidence suggests a *trans* conformation for this minor isomer.


Me
Me
7
Me
H
O
Ph

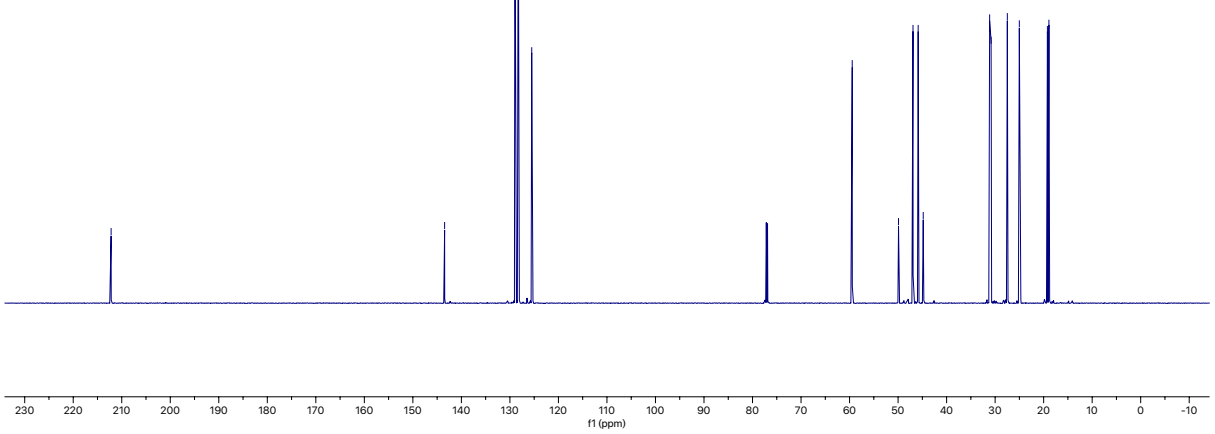
30a

3.9
1.0
1.0
1.0
1.0
1.0
2.0
1.1
1.0
1.0
3.0
6.0
f1 (ppm)

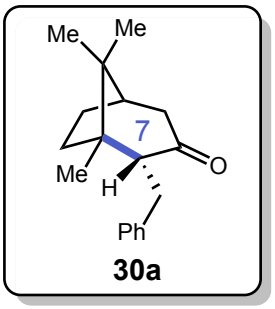

212.19
143.46
128.97
128.28
125.50
59.45
49.91
46.92
45.86
44.82
31.13
30.83
27.48
25.01
19.22
18.92


Me
Me
7
Me
H
O
Ph

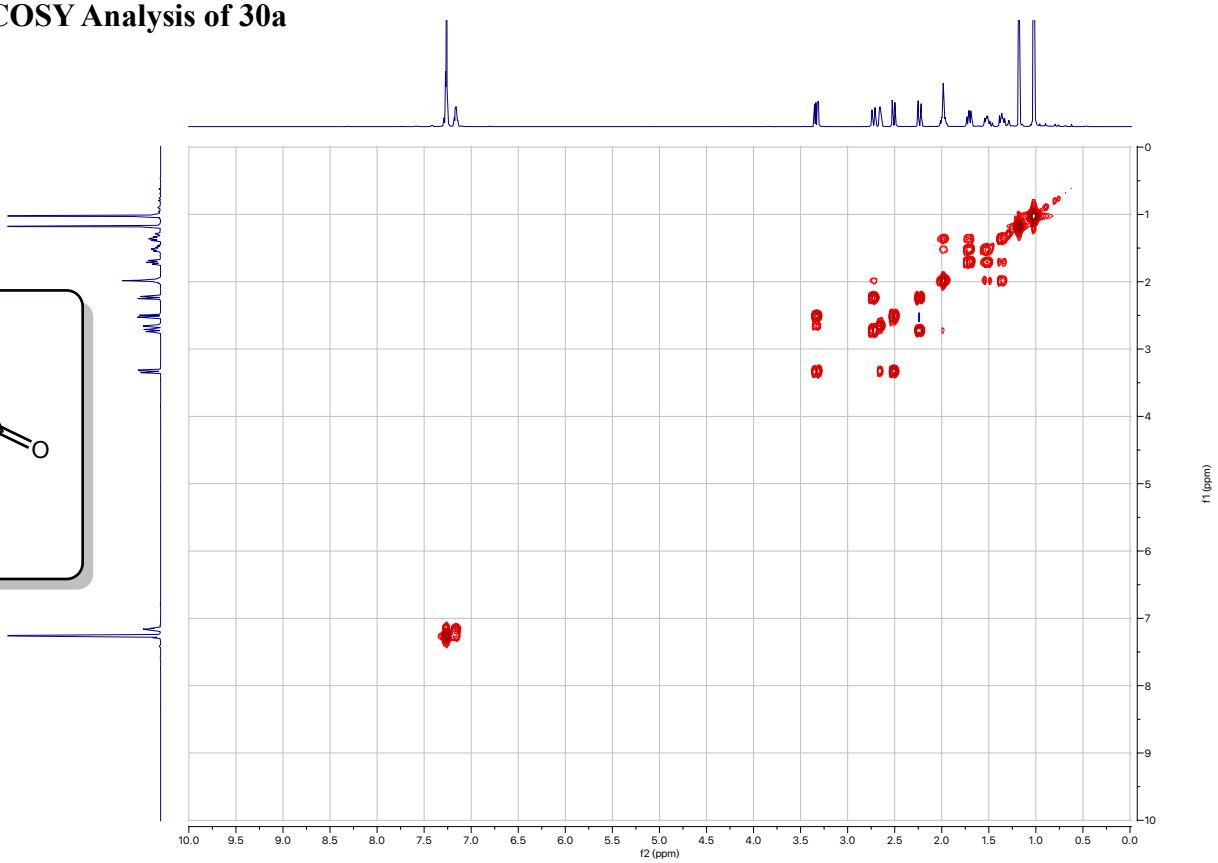
30a

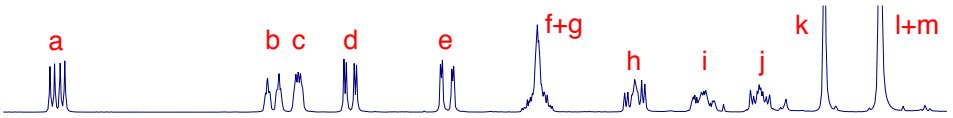

f1 (ppm)

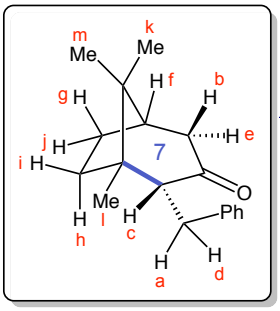
COSY Analysis of 30a

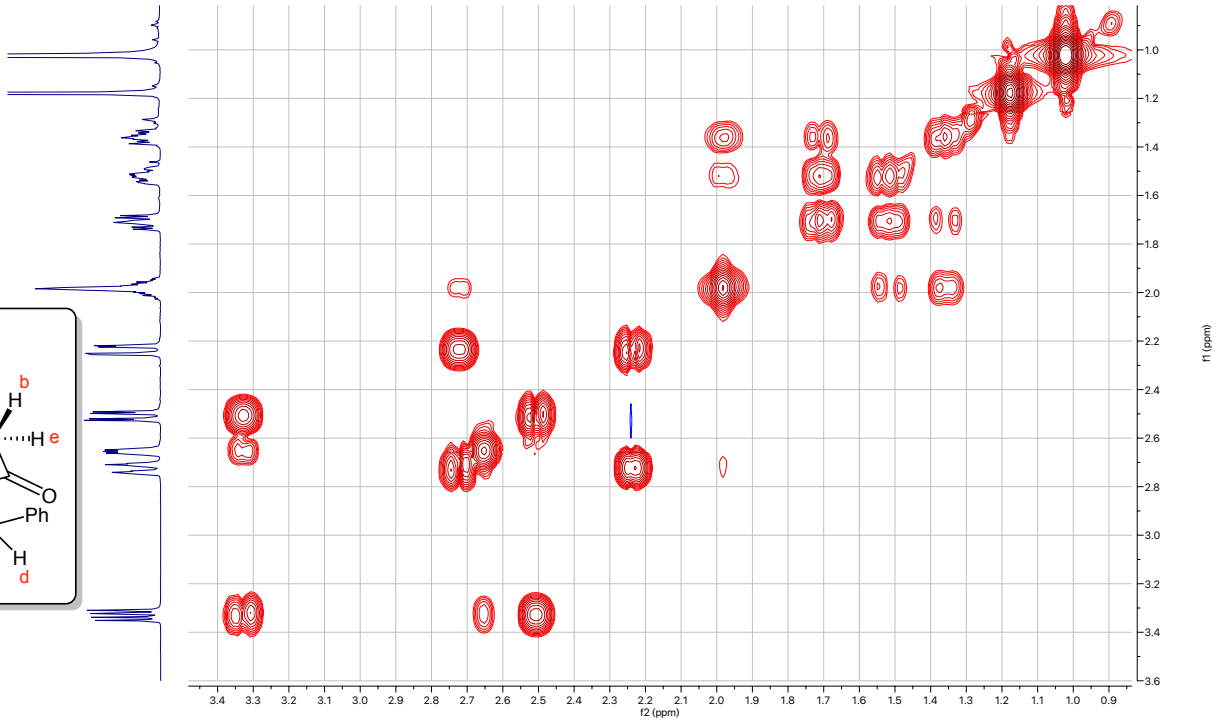


30a

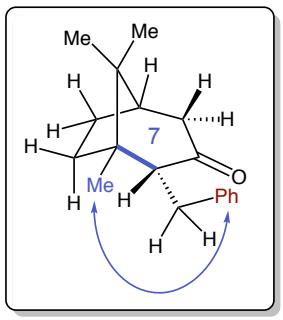


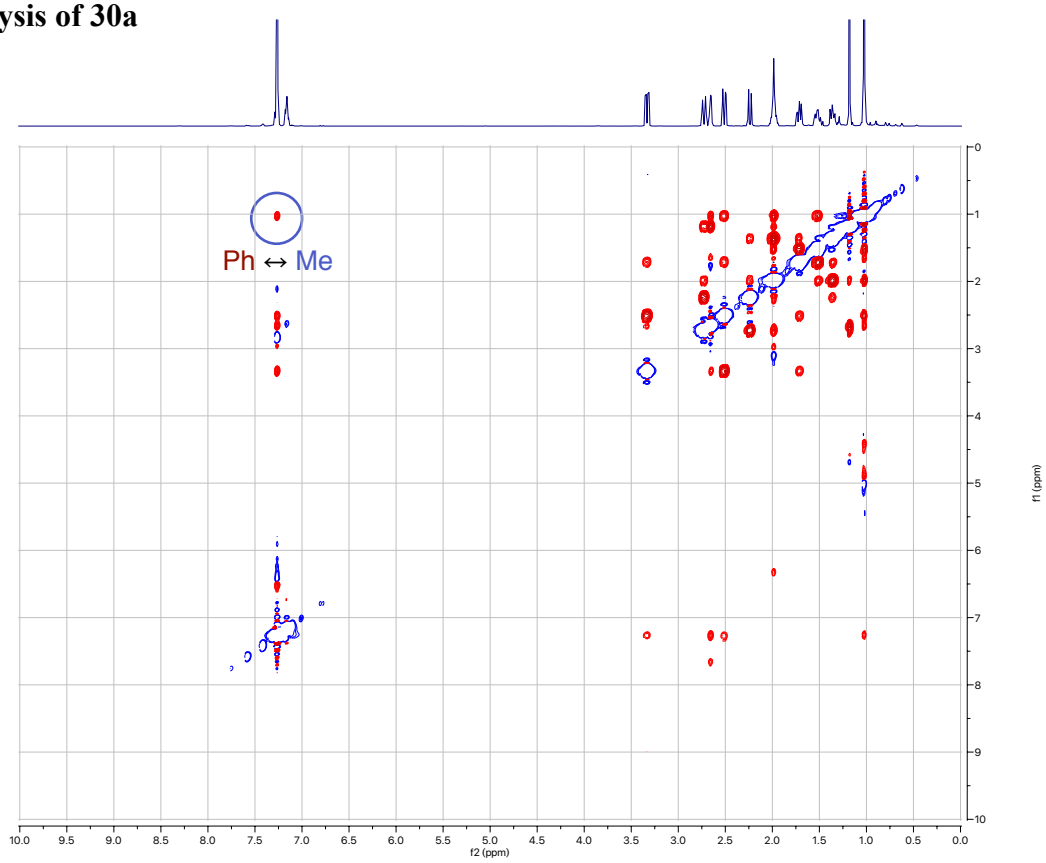


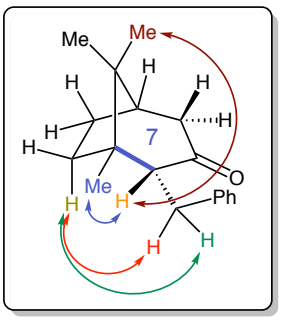


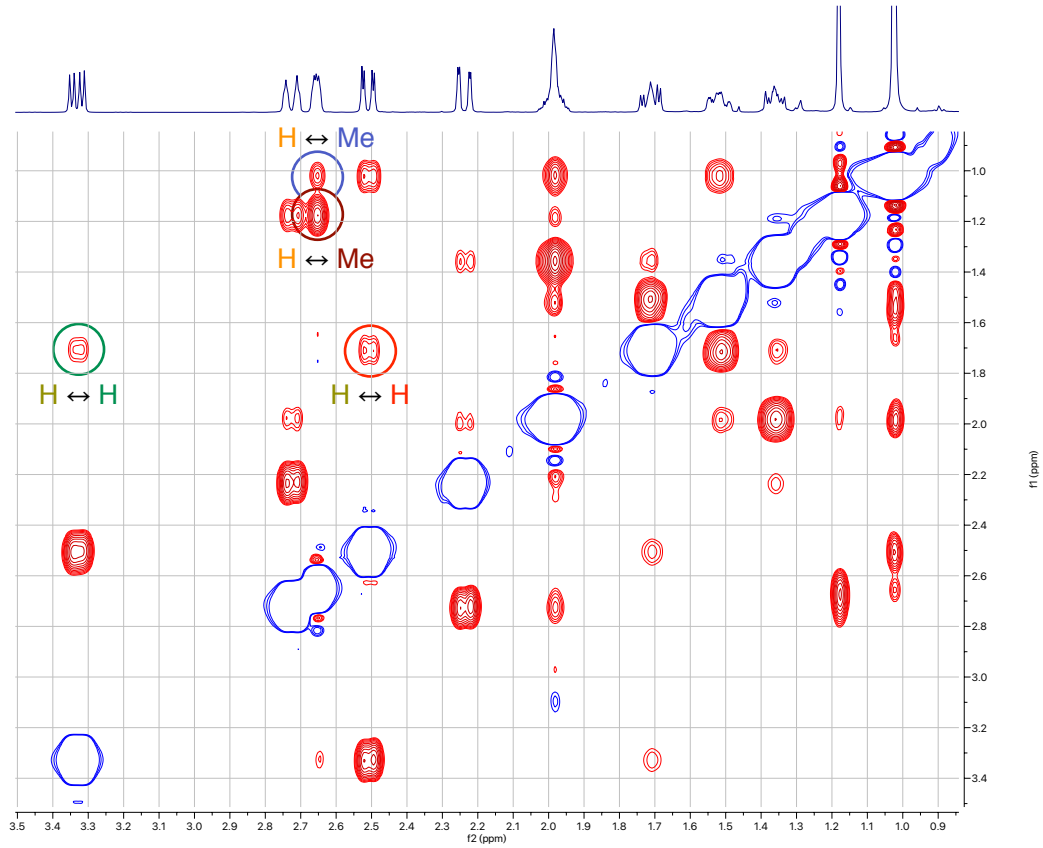


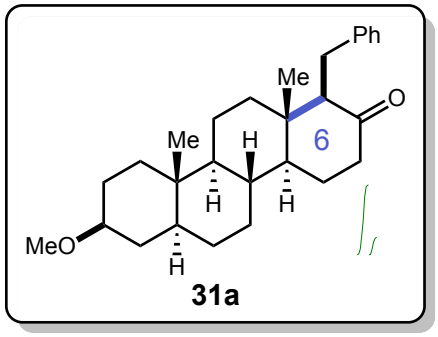
NOESY Analysis of 30a







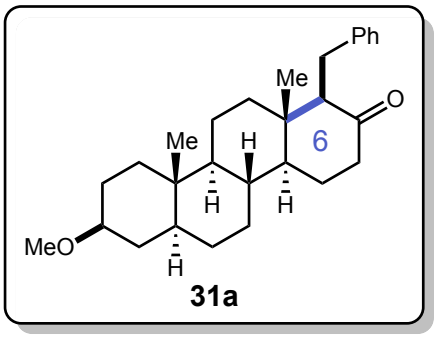



Ph
Me
O
Me
H
6
H
H
MeO
H

31a

4.0
1.0
3.0
2.0
1.0
1.0
1.0
1.0
1.0
2.0
1.1
2.0
9.1
1.0
2.0
4.0
3.0
f1 (ppm)


211.52
142.77
129.17
128.20
125.54
79.75
65.07
55.64
53.69
51.46
44.19
42.06
38.91
36.83
35.76
31.41
28.78
27.86
27.84
26.70
21.03
13.73


Ph
Me
O
Me
H
6
H
H
MeO
H

31a

f1 (ppm)

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[12]Hartman, George D. (Novira Therapeutics, Inc.) U.S. Patent 225355, May 14, 2015 (Location in patent: Paragraph 0413)

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