Convergent Synthesis of Stereodefined Exo-alkylidene-γ-Lactams from β-Halo Allylic Alcohols

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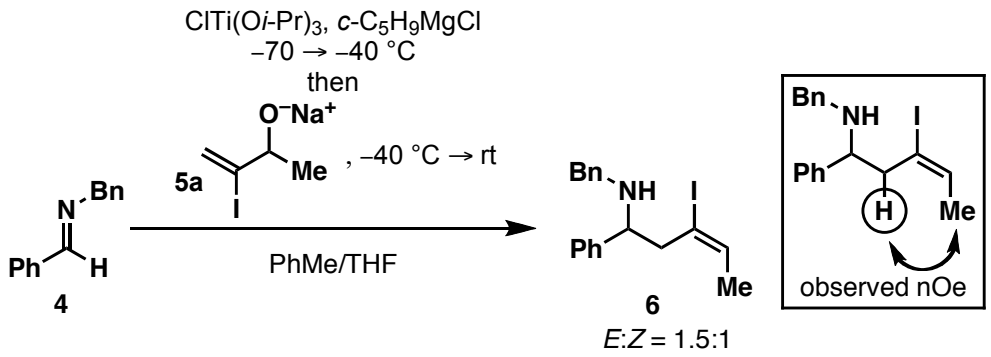
SUPPORTING INFORMATION:

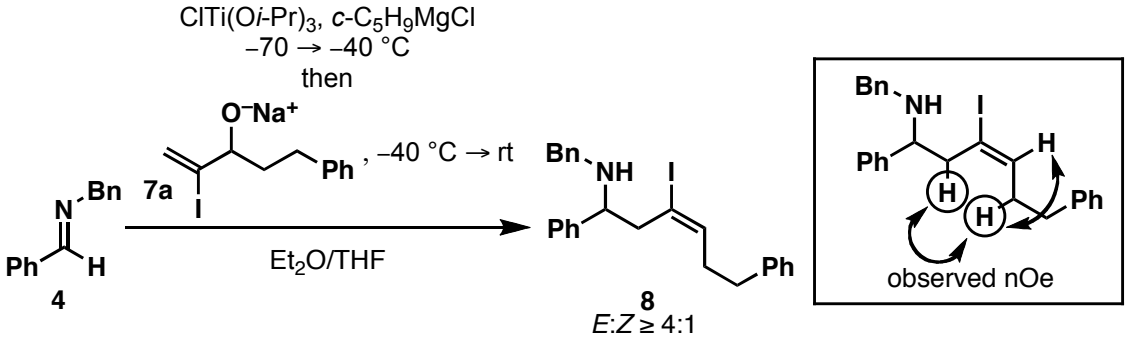
Experimental Procedures and Spectral Data

General. All reactions were conducted in flame-dried glassware under a nitrogen atmosphere with dry solvents, unless otherwise noted. Dry diethyl ether, tetrahydrofuran, toluene and dichloromethane were obtained by passing inhibitor-free, HPLC grade solvents through activated alumina columns. Triethylamine, and chlorotrimethylsilane were distilled from CaH_2 before use. Chlorotriisopropoxytitanium(IV) was purchased from Sigma-Aldrich Co. as a 1.0 M solution in hexanes and used as received, with no bottle being used more than one month after opening. Cyclopentylmagnesium chloride was purchased as solution in Et_2O, and titrated on a monthly basis.[1] Carbon monoxide was purchased from Praxair in research purity (99.99%). Imine **4**,[2] and alcohols **1**,[3] **2**,[4] **5**,[5] **7**,[6] **13**,[7] and **22**[8] were prepared according to literature procedures. Alcohols **16** and **19** were prepared from iodination of the cyclic enone[9] followed by reduction.[10] Alcohol **10** was prepared by adapting the procedure from alcohol **7**.[6] All other commercially available reagents were used as received. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 250 μm E. Merck silica gel plates (60F-254) and visualized using UV light or appropriate stains, including ninhydrin, *p*-anisaldehyde, ceric ammonium nitrate, and potassium permanganate. Silica gel for flash column chromatography was purchased from Silicycle (P60, particle size 40-63 μm). ^{1}H NMR data were recorded at 400 or 500 MHz using a AVANCE-400 or AM-500 instruments. ^{1}H NMR chemical shifts are reported relative to residual $CHCl_3$ (7.26 ppm) or TMS (0.00 ppm). ^{13}C NMR data were recorded at 100 or 126 MHz using a Bruker AVANCE-400 or AM-500 instruments. ^{13}C NMR chemical shifts were reported relative to the central line of CDCl3 (77.23 ppm). Infrared spectra were recorded using a Perkin Elmer Spectrum One FT-IR spectrometer. Low-resolution mass spectrometry was performed on a Waters Micromass® ZQTM instrument using electrospray ionization. High resolution mass spectrometry was performed by the University of Florida Mass Spectrometry Services. All compounds purified by chromatography were sufficiently pure for use in further experiments, unless indicated otherwise. Diastereoselectivity is reported from the ^{1}H NMR of the crude reaction mixture. Relative stereochemistry was defined using the R*/S* convention proposed by IUPAC.



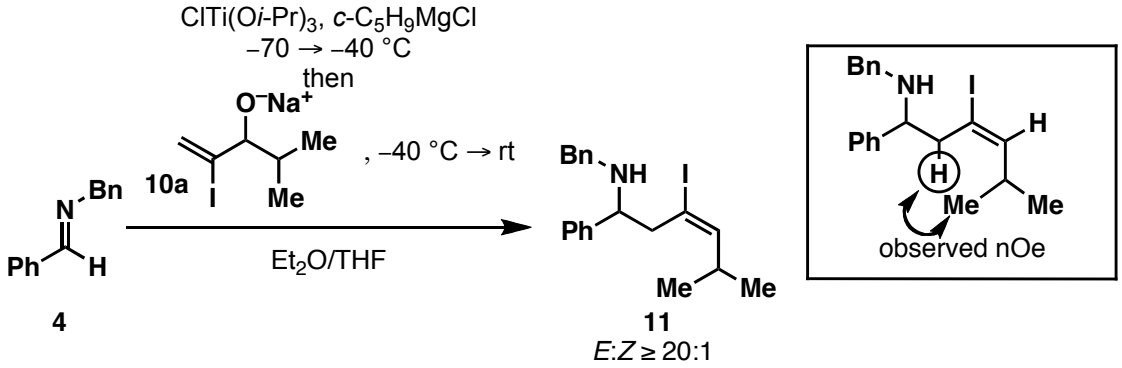
Synthesis of (*E*)-*N*-benzyl-3-iodo-1-phenylpent-3-en-1-amine 6: To a solution of imine **4** (451 μL, 473 mg, 2.42 mmol) and ClTi(O*i*-Pr)$_3$ (1.0 M in diethyl ether, 2.55 mmol) in toluene (10 ml) at –70 °C was added *c*-C_5H_9MgCl (2.00 M in diethyl ether, 5.09 mmol) in a drop-wise manner with a syringe. The orange-brown solution was slowly warmed to –40 °C over 30 minutes and stirred at –40 °C for a further 1.5 hours. A solution of sodium alkoxide **5a**, generated from the deprotonation of the corresponding alcohol (120 mg, 0.606 mmol) with NaH (60 % suspension, 30 mg, 0.76 mmol), in THF (2.5 mL) at 0 °C, was added in a drop-wise manner via Teflon cannula to the brown solution of imine–Ti complex at –40 °C. The reaction was allowed to warm to ambient temperature and stirred overnight. Next, saturated aqueous NH_4Cl (5 mL) was added and the resulting biphasic mixture was stirred rapidly for 15 minutes. The resulting solution was further diluted with saturated aqueous $NaHCO_3$ (150 mL) and extracted with ether (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/40→1/25 EtOAc/Hexanes) to yield haloallylic amine **6** as a colorless oil, (185 mg, 81%, *E*:*Z* = 1.5:1).

Data for *N*-benzyl-3-iodo-1-phenylpent-3-en-1-amine 6: ^{1}H NMR (400 MHz, $CDCl_3$) (*E*)-isomer: δ 7.47-7.19 (m, 10 H), 6.30 (q, *J* = 7.1 Hz, 1 H), 4.00 (dd, *J* = 7.6, 6.0 Hz, 1 H), 3.79 (d, *J* = 13.2 Hz, 1 H), 3.58 (d, *J* = 13.2 Hz, 1 H), 2.78 (dd, *J* = 14.2, 7.6 Hz, 1 H), 2.61 (dd, *J* = 14.2, 6.0 Hz, 1 H), 1.45 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) (*E*)-isomer: δ 142.8, 140.6, 138.7, 128.5, 128.4, 128.1, 127.5, 127.4, 126.9, 98.9, 77.4, 77.1, 76.8, 61.5, 51.7, 47.1, 16.6; IR (thin film, NaCl) 3027, 2917, 2848, 1602, 1494, 1455, 1114, 1027, 697 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{18}H_{21}IN$ $(M+H)^+$ 378.0713; found $(M+H)^+$ 378.0737.



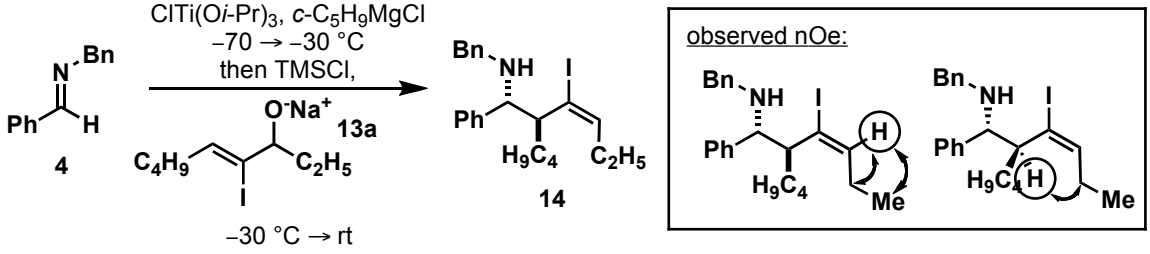
Synthesis of (*E*)-*N*-benzyl-3-iodo-1,6-diphenylhex-3-en-1-amine 8: To a solution of imine **4** (216 μL, 227 mg, 1.16 mmol) and ClTi(O*i*-Pr)$_3$ (1.0 M in diethyl ether, 1.22 mmol) in diethyl ether (4.5 mL) at –70 °C was added *c*-C_5H_9MgCl (1.94 M in diethyl ether, 2.44 mmol) in a drop-wise manner with a syringe. The orange-brown solution was slowly warmed to –40 °C over 30 minutes and stirred at –40 °C for a further 1.5 hours. A solution of sodium alkoxide **7a**, generated from the deprotonation of the corresponding alcohol (83 mg, 0.290 mmol) with NaH (60 % suspension, 15 mg, 0.363 mmol), in THF (1.2 mL) at 0 °C, was added in a drop-wise manner via Teflon cannula to the brown solution of imine–Ti complex at –40 °C. The reaction was allowed to warm to ambient temperature and stirred overnight. Next, saturated aqueous NH_4Cl (2.5 mL) was added and the resulting biphasic mixture was stirred rapidly for 15 minutes. The resulting solution was further diluted with saturated aqueous $NaHCO_3$ (50 mL) and extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/50→1/30 EtOAc/Hexanes) to yield haloallylic amine **8** as a colorless oil, (103 mg, 76%, *E*:*Z* ≥4:1).

Data for (*E*)-*N*-benzyl-3-iodo-1,6-diphenylhex-3-en-1-amine 8: ^{1}H NMR (400 MHz, $CDCl_3$) (*E*)-isomer: δ 7.42-7.31 (m, 2 H), 7.30-7.05 (m, 11 H), 6.97 (d, *J* = 7.1 Hz, 1 H), 6.17 (t, *J* = 7.4 Hz, 1 H), 3.91 (t, *J* = 6.8 Hz, 1 H), 3.59 (d, *J* = 13.2 Hz, 1 H), 3.49 (d, *J* = 13.2 Hz, 1 H), 2.64 (dd, *J* = 6.8, 14.2 Hz, 1 H), 2.51 (dd, *J* = 6.8, 14.2 Hz, 1 H), 2.43-2.23 (m, 2 H), 2.21-1.98 (dd, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) (*E*)-isomer: δ 143.5, 142.9, 141.1, 140.7, 128.7, 128.6, 128.5, 128.5, 128.3, 127.7, 127.6, 127.1, 126.2, 99.5, 61.6, 51.9, 47.7, 35.1, 33.0; IR (thin film, NaCl) 3026, 2947, 2857, 1603, 1494, 1454, 1028, 747, 698 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{25}H_{27}IN$ $(M+H)^+$ 468.1188; found $(M+H)^+$ 468.1188.



Synthesis of (*E*)-*N*-benzyl-3-iodo-5-methyl-1-phenylhex-3-en-1-amine 11: To a solution of imine **4** (93 μL, 98 mg, 0.500 mmol) and ClTi(O*i*-Pr)$_3$ (1.0 M in diethyl ether, 0.625 mmol) in diethyl ether (2.5 mL) at –70 °C was added *c*-C_5H_9MgCl (1.94 M in diethyl ether, 1.25 mmol) in a drop-wise manner with a syringe. The brown solution was slowly warmed to –40 °C over 30 minutes and stirred at –40 °C for a further 1.5 hours. A solution of sodium alkoxide **10a**, generated from the deprotonation of the corresponding alcohol (167 mg, 0.750 mmol) with NaH (60 % suspension, 38 mg, 0.94 mmol), in THF (2.5 mL) at 0 °C, was added in a drop-wise manner via Teflon cannula to the brown solution of imine–Ti complex at –40 °C. The reaction was allowed to warm to ambient temperature and stirred overnight. Next, saturated aqueous NH_4Cl (2.5 mL) was added and the resulting biphasic mixture was stirred rapidly for 15 minutes. The resulting solution was further diluted with saturated aqueous $NaHCO_3$ (50 mL) and extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/50→1/30 EtOAc/Hexanes) to yield haloallylic amine **11** as a colorless oil, (117 mg, 58%, *E*:*Z* ≥ 20:1).

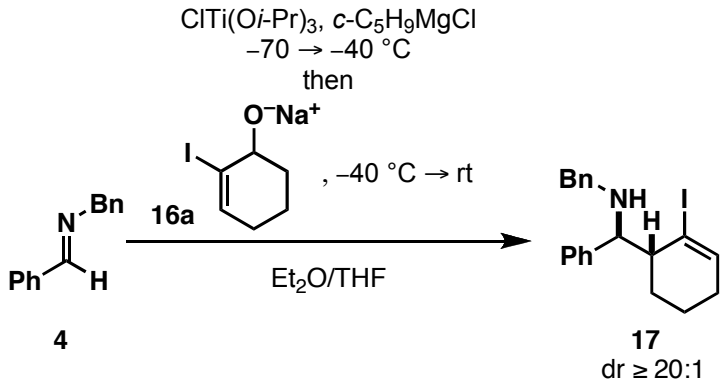
Data for (*E*)-*N*-benzyl-3-iodo-5-methyl-1-phenylhex-3-en-1-amine 11: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.33 (m, 2 H), 7.30-7.13 (m, 8 H), 5.98 (d, *J* = 10.0 Hz, 1 H), 3.93 (dd, *J* = 7.6, 6.1 Hz, 1 H), 2.67 (dd, *J* = 14.2, 7.6 Hz, 1 H), 2.56 (dd, *J* = 14.2, 6.1 Hz, 1 H), 2.36 (dtt, *J* = 10.0, 6.6, 6.6 Hz, 1 H), 0.82 (d, *J* = 6.6 Hz, 1 H), 0.55 (d, *J* = 6.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 143.0, 140.7, 128.7, 128.6, 128.3, 127.7, 127.6, 127.1, 97.1, 61.7, 52.0, 47.8, 31.2, 22.7, 22.3; IR (thin film, NaCl) 3026, 2959, 2866, 1492, 1453, 1004, 759, 699 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{20}H_{25}IN$ $(M+H)^+$ 406.1026; found $(M+H)^+$ 406.1038.



Synthesis of (1R*, 2S*, *E*)-*N*-benzyl-2-butyl-3-iodo-1-phenylhex-3-en-1-amine 14: To a solution of imine **4** (250 μL, 260 mg, 1.34 mmol) in toluene (2.8 mL) at room temperature was added $ClTi(O\textit{i}\text{-}Pr)_3$ (1.40 mmol, 1.0 M in hexanes). The reaction was then cooled to −70 °C and *c*-C_5H_9MgCl (2.28 M in ether, 2.80 mmol) was added in a drop-wise manner with a syringe. The mixture was warmed to −30 °C over 30 minutes and stirred for 2 hours at this temperature. Then freshly distilled TMSCl (160 μL, 137 mg, 1.27 mmol) was added and the reaction stirred at −30 °C for an additional 1hour. A solution of sodium alkoxide **13a**, prepared by the deprotonation of alcohol **13** (90 mg, 0.335 mmol) in THF (2.0 mL) at 0 °C with NaH (20 mg, 0.502 mmol, 60% dispersion in mineral oil) for 30 minutes, was added in a drop-wise manner to the brown solution of imine−Ti complex at −30 °C via Teflon cannula. An additional 3 mL of toluene was added to facilitate stirring. The mixture was allowed to warm to room temperature in the cooling bath and stir overnight. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (5.0 mL) followed by rapid stirring at room temperature for 15 minutes. The mixture was then diluted with saturated aqueous $NaHCO_3$ (50 mL) and extracted with ether (3 × 40 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (3→4% EtOAc/hexanes) to afford haloallylic amine **14** as a yellow oil (79 mg, 53%, dr ≥20:1). A portion of the product was purified a second time by column chromatography on silica gel (3% EtOAc/hexanes) to yield analytically pure **14**. See the transformation of **14→15**, and accompanying data for the assignment of relative stereochemistry.

Data for (1R*, 2S*, *E*)-*N*-benzyl-2-butyl-3-iodo-1-phenylhex-3-en-1-amine 14: ^1H NMR (500 MHz, $CDCl_3$) d 7.42-7.02 (m, 10H), 6.44 (t, J = 7.5 Hz, 1H), 3.46 (d, J = 13.4 Hz, 1H), 3.34 (d, J = 13.4 Hz, 1H), 3.27 (d, J = 9.3 Hz, 1H), 2.28-2.09 (m, 2H), 1.94-1.87 (m 1H), 1.77 (s (br), 1H), 1.14-0.90 (m, 7H), 0.83-0.59 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.6, 142.0, 140.9, 129.3, 128.5, 128.4, 128.4, 127.6, 126.9, 110.6, 66.4, 51.8,

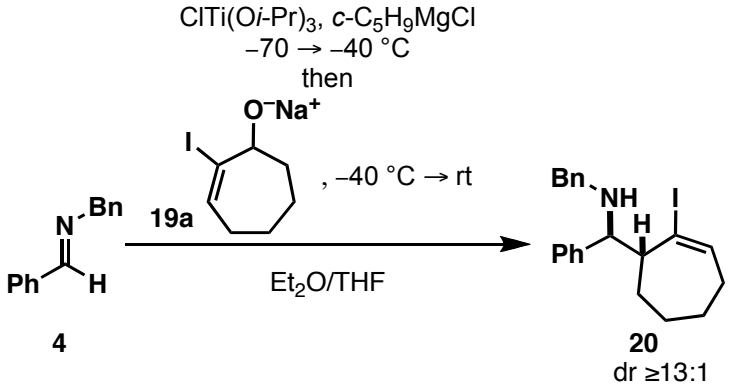
50.2, 31.1, 29.2, 25.6, 22.6, 14.1, 14.0; IR (thin film, NaCl) 3026, 2958, 2932, 2871, 2858, 1455, 1132, 756, 700 cm^{-1}; LRMS (ESI, H) *m/z* calc'd for $C_{23}H_{31}IN$ $(M + H)^+$ 448.2; found $(M+H)^+$ 448.2.



Synthesis of (*S)-*N*-benzyl-1-((*R**)-2-iodocyclohex-2-enyl)-1-phenylmethanamine 17:** To a solution of imine **4** (563 μL, 586 mg, 3.00 mmol) and ClTi(O*i*-Pr)$_3$ (1.0 M in diethyl ether, 3.75 mmol) in diethyl ether (12 mL) at –70 °C was added *c*-C_5H_9MgCl (2.00 M in diethyl ether, 7.50 mmol) in a drop-wise manner with a syringe. The brown solution was slowly warmed to –40 °C over 30 minutes and stirred at –40 °C for a further 1.5 hours. A solution of sodium alkoxide **16a**, generated from the deprotonation of the corresponding alcohol (1.01 g, 4.50 mmol) with NaH (60 % suspension, 225 mg, 5.63 mmol), in THF (15 mL) at 0 °C, was added in a drop-wise manner via Teflon cannula to the brown solution of imine–Ti complex at –40 °C. The reaction was allowed to warm to ambient temperature and stirred overnight. Next, saturated aqueous NH_4Cl (5 mL) was added and the resulting biphasic mixture was stirred rapidly. The resulting solution was further diluted with saturated aqueous $NaHCO_3$ (150 mL) and extracted with ether (3 × 150 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/40→1/30 EtOAc/Hexanes) to yield haloallylic amine **17** as a colorless oil, (811 mg, 67%, dr ≥ 20:1). See the transformation of **17→18,** and accompanying data for the assignment of relative stereochemistry.

Data for (*S)-*N*-benzyl-1-((*R**)-2-iodocyclohex-2-enyl)-1-phenylmethanamine 17:** ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.43 (m, 2 H), 7.37-7.22 (m, 8 H), 6.48 (dt, *J* = 1.5, 4.1 Hz, 1 H), 4.34 (d, *J* = 3.9 Hz, 1 H), 3.77 (d, *J* = 13.2 Hz, 1 H), 3.68 (d, *J* = 13.2 Hz, 1 H), 2.70-2.63 (m, 1 H), 1.92-1.77 (m, 2 H), 1.75-1.58 (m, 2 H), 1.29-1.20 (m, 1 H), 0.74-0.61

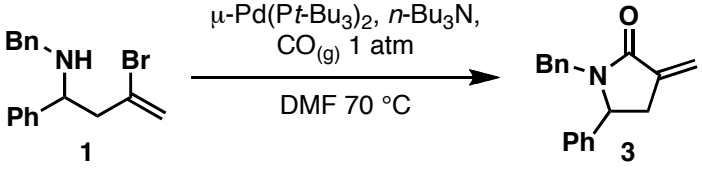
(m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 140.9, 140.8, 128.6, 128.4, 128.3, 128.2, 128.1, 127.3, 127.1, 103.0, 64.5, 52.1, 50.6, 29.4, 25.2, 18.2; IR (thin film, NaCl) 3027, 2934, 2867, 1602, 1494, 1454, 1115, 1028, 958, 732 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{20}H_{23}IN$ $(M+H)^+$ 404.0870; found $(M+H)^+$ 404.0834.



Synthesis of (*S)-*N*-benzyl-1-((*R**)-2-iodocyclohept-2-enyl)-1-phenylmethanamine 20:** To a solution of imine **4** (563 μL, 586 mg, 3.00 mmol) and $ClTi(O\textit{i}\text{-}Pr)_3$ (1.0 M in diethyl ether, 3.75 mmol) in diethyl ether (12 mL) at –70 °C was added *c*-C_5H_9MgCl (2.00 M in diethyl ether, 7.50 mmol) in a drop-wise manner with a syringe. The brown solution was slowly warmed to –40 °C over 30 minutes and stirred at –40 °C for a further 1.5 hours. A solution of sodium alkoxide **19a**, generated from the deprotonation of the corresponding alcohol (1.07 g, 4.50 mmol) with NaH (60 % suspension, 225 mg, 5.63 mmol), in THF (12 mL) at 0 °C, was added in a drop-wise manner via Teflon cannula to the brown solution of imine–Ti complex at –40 °C. The reaction was allowed to warm to ambient temperature and stirred overnight. Next, saturated aqueous NH_4Cl (5 mL) was added and the resulting biphasic mixture was rapidly stirred. The resulting red brown solution was further diluted with saturated aqueous $NaHCO_3$ (150 mL) and extracted with ether (3 × 150 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/25→1/20 EtOAc/Hexanes) to yield amine **20** as a colorless oil, (665 mg, 53%, dr ≥13:1). See the transformation of **20→21**, and accompanying data for the assignment of relative stereochemistry.

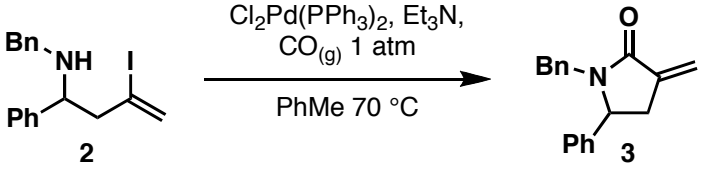
Data for (*S)-*N*-benzyl-1-((*R**)-2-iodocyclohept-2-enyl)-1-phenylmethanamine 20:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.18 (m, 10 H), 6.67 (dd, *J* = 8.8, 6.0 Hz, 1 H), 3.95 (d, *J* = 10.0 Hz, 1 H), 3.64 (d, *J* = 13.6 Hz, 1 H), 3.48 (d, *J* = 13.6 Hz, 1 H), 3.00 (ddd, *J*

= 10.0, 7.2, 3.6 Hz1 H), 2.10-1.76 (m, 3 H, (NH)), 1.75-1.18 (m, 5 H), 1.14-1.01 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 142.0, 140.8, 128.5, 128.4, 128.4, 128.4, 127.5, 126.9, 104.8, 64.6, 57.6, 51.6, 30.6, 26.7, 15.7; IR (thin film, NaCl) 3026, 2924, 2847, 1602, 1494, 1453, 1114, 1027, 735 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{21}H_{25}IN$ $(M+H)^+$ 418.1026; found $(M+H)^+$ 418.0988.

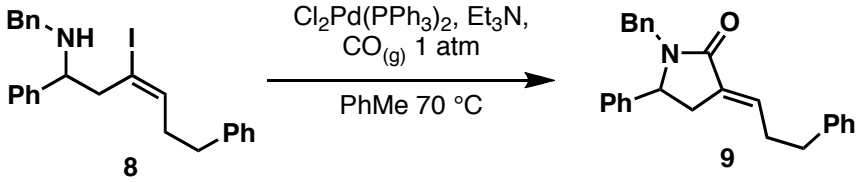


Synthesis of 1-benzyl-3-methylene-5-phenyl-2-pyrrolidinone 3: To a round bottom flask equipped with a reflux condenser was sequentially added amine **1** (79 mg, 0.250 mmol), DMF (2.5 mL), μ-Pd(P*t*-Bu$_3$)$_2$ (6 mg, 0.012 mmol) and *n*-Bu$_3$N (119 μL, 92 mg, 0.500 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C), and stirred for 12 hours. The reaction mixture was then allowed to cool to ambient temperature, diluted with EtOAc, filtered through cotton and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/7→1/5 EtOAc/Hexanes) to yield γ-lactam **3** as a white solid, (63 mg, 95%).

Data for 1-benzyl-3-methylene-5-phenyl-2-pyrrolidinone 3: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.23 (m, 6 H), 7.17-7.08 (m, 4 H), 6.15 (t, *J* = 2.4 Hz, 1 H), 5.40 (t, *J* = 2.4 Hz, 1 H), 5.19 (d, *J* = 14.8 Hz, 1 H), 4.40 (dd, *J* = 8.8, 4.0 Hz, 1 H), 3.54 (d, *J* = 14.8 Hz, 1 H), 3.14 (ddt, *J* = 17.2, 8.4, 2.4 Hz, 1 H), 2.64 (ddt, *J* = 17.2, 4.0, 2.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 140.9, 139.1, 136.3, 129.3, 129.2, 128.8, 128.7, 127.4, 127.8, 126.9, 116.4, 58.3, 44.9, 34.8; IR (thin film, NaCl) 3030, 2922, 2242, 1694, 1682, 1495, 1416, 922 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{18}H_{18}NO$ $(M+H)^+$ 264.1383; found $(M+H)^+$ 264.1382.



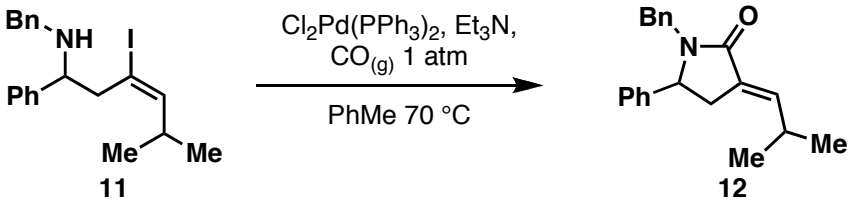
Synthesis of 1-benzyl-3-methylene-5-phenyl-2-pyrrolidinone 3: To a round bottom flask equipped with a reflux condenser was sequentially added amine **2** (230 mg, 0.630 mmol), toluene (6.3 mL), $Cl_2Pd(PPh_3)_2$ (22 mg, 0.031 mmol) and Et_3N (176 μL, 127 mg, 1.26 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C), and stirred for 12 hours. The reaction mixture was then allowed to cool to ambient temperature, diluted with EtOAc, filtered through cotton and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/7→1/5 EtOAc/Hexanes) to yield γ-lactam **3** as a white solid, (155 mg, 93%). NMR data was in accordance with that described for the transformation of **1→3**.



Synthesis of (*E*)-1-benzyl-5-phenyl-3-(3-phenylpropylidene)-2-pyrrolidinone 9: To a round bottom flask equipped with a reflux condenser was sequentially added amine **8** (54 mg, 0.115 mmol), toluene (1.2 mL), $Cl_2Pd(PPh_3)_2$ (4 mg, 5.75 μmol) and Et_3N (32 μL, 23 mg, 0.230 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C), and stirred for 12 hours. The reaction mixture was then allowed to cool to ambient temperature, diluted with EtOAc, filtered through cotton and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/10→1/7 EtOAc/Hexanes) to yield γ-lactam **9** as a white solid, (42 mg, 99%).

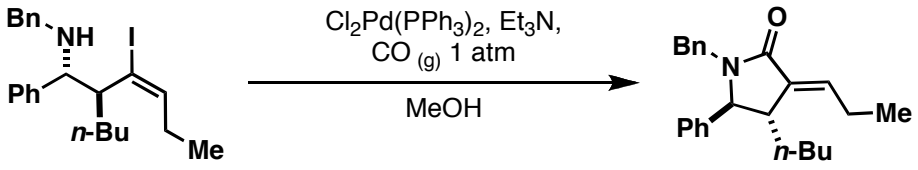
Data for (*E*)-1-benzyl-5-phenyl-3-(3-phenylpropylidene)-2-pyrrolidinone 9: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.23 (m, 3 H), 7.23-7.13 (m, 5 H), 7.12-7.06 (m, 3 H), 7.06-7.00 (m, 2 H), 7.00-6.95 (m, 2 H), 6.62-6.54 (m, 1 H), 5.09 (d, J = 14.6 Hz, 1 H), 4.24 (dd, J = 8.8, 3.7 Hz, 1 H), 3.40 (d, J = 14.6 Hz, 1 H), 2.86-2.74 (m, 1 H), 2.69 (t, J = 7.5

Hz, 2 H), 2.50 (dt, *J* = 7.5, 7.5 Hz, 2 H), 2.34-2.22 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 141.3, 136.6, 132.7, 131.6, 129.2, 128.8, 128.7, 128.6, 128.5, 128.3, 127.7, 126.9, 126.2, 58.4, 44.7, 34.9, 32.6, 31.5; IR (thin film, NaCl) 3028, 2923, 2856, 1694, 1682, 1603, 1494, 1455, 1435, 1246, 1029, 700 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{26}H_{26}NO$ $(M+H)^+$ 368.2009; found $(M+H)^+$ 368.2016.



Synthesis of (*E*)-1-benzyl-3-(2-methylpropylidene)-5-phenyl-2-pyrrolidinone 12: To a round bottom flask equipped with a reflux condenser was sequentially added amine **11** (54 mg, 0.160 mmol), toluene (1.6 mL), $Cl_2Pd(PPh_3)_2$ (6 mg, 0.008 mmol) and Et_3N (45 μL, 33 mg, 0.320 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C), and stirred for 12 hours. The reaction mixture was then allowed to cool to ambient temperature, diluted with EtOAc, filtered through cotton and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/10→1/7 EtOAc/Hexanes) to yield γ-lactam **12** as a white solid, (42 mg, 99%).

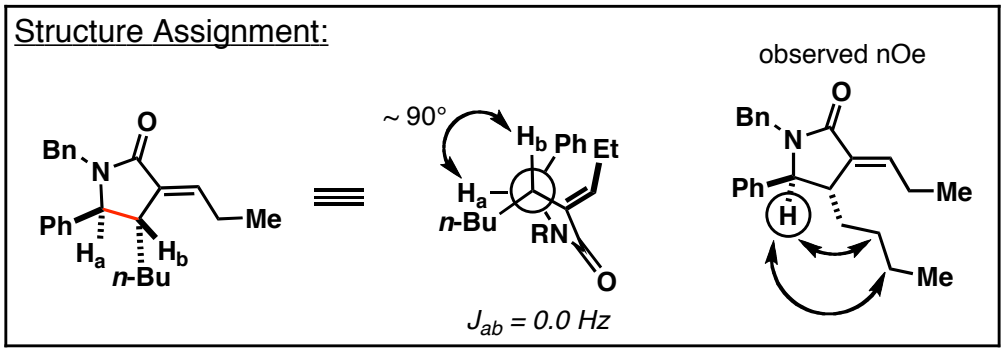
Data for (*E*)-1-benzyl-3-(2-methylpropylidene)-5-phenyl-2-pyrrolidinone 12: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.23 (m, 3 H), 7.23-7.13 (m, 5 H), 7.12-7.06 (m, 3 H), 7.06-7.00 (m, 2 H), 7.00-6.95 (m, 2 H), 6.62-6.54 (m, 1 H), 5.09 (d, *J* = 14.6 Hz, 1 H), 4.24 (dd, *J* = 8.8, 3.7 Hz, 1 H), 3.40 (d, *J* = 14.6 Hz, 1 H), 2.86-2.74 (m, 1 H), 2.69 (t, *J* = 7.5 Hz, 2 H), 2.50 (dt, *J* = 7.5, 7.5 Hz, 2 H), 2.34-2.22 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 141.3, 136.6, 132.7, 131.6, 129.2, 128.8, 128.7, 128.6, 128.5, 128.3, 127.7, 126.9, 126.2, 58.4, 44.7, 34.9, 32.6, 31.5; IR (thin film, NaCl) 3028, 2923, 2856, 1694, 1682, 1603, 1494, 1455, 1435, 1246, 1029, 700 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{21}H_{24}NO$ $(M+H)^+$ 306.1852; found $(M+H)^+$ 306.1862.

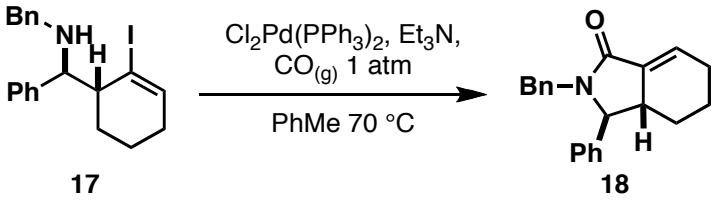


14 15

Synthesis of (4*S,5*S**,*E*)-1-benzyl-4-butyl-5-phenyl-3-propylidenepyrrolidin-2-one 15:** To a Schlenk tube was sequentially added amine **14** (80 mg, 0.178 mmol), MeOH (1.5 mL), $Cl_2Pd(PPh_3)_2$ (6 mg, 0.009 mmol), and triethylamine (100 μL, 72 mg, 0.712 mmol). The Schlenk tube was then cooled to −30 °C, evacuated (house-vac, 100 torr), and backfilled with 20 psig CO (evacuation and backfilling repeated three times) and placed in a preheated oil bath (70 °C) for 20 hours. The reaction was then diluted with H_2O, extracted with ether (3 x 50 mL), the combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/10→1/7 EtOAc/Hexanes) to yield lactam **15** as a colorless oil (41 mg, 66%).

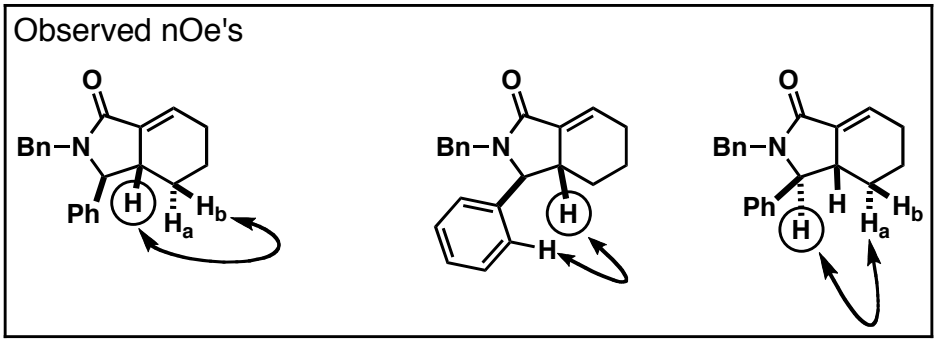
Data for (4*S,5*S**,*E*)-1-benzyl-4-butyl-5-phenyl-3-propylidenepyrrolidin-2-one 15:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.21 (m, 6H), 7.12-7.11 (m, 2H), 7.04-7.02 (m, 2H), 6.58 (td, *J* = 7.7, 1.9 Hz, 1H), 5.19 (d, *J* = 14.7 Hz, 1H), 3.96 (s, 1H), 3.43 (d, *J* = 14.7 Hz, 1H), 2.72-2.70 (m, 1H), 2.15-2.06 (m, 2H), 1.48-1.37 (m, 2H), 1.25-0.99 (m, 7H), 0.76 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 141.5, 136.7, 136.6, 134.5, 129.2, 128.8, 128.7, 128.1, 127.7, 126.5, 64.5, 44.7, 44.5, 35.1, 28.5, 22.8, 22.4, 14.0, 13.7; IR (thin film, NaCl) 3029, 2960, 2930, 2871, 2858, 1693, 1673, 1417, 1243, 739, 701 cm^{-1}; LRMS (EI, H) calcd for: $C_{24}H_{30}NO$ 348.2 *m/z* (M + H); found $(M + H)^+$ 348.2 *m/z*.

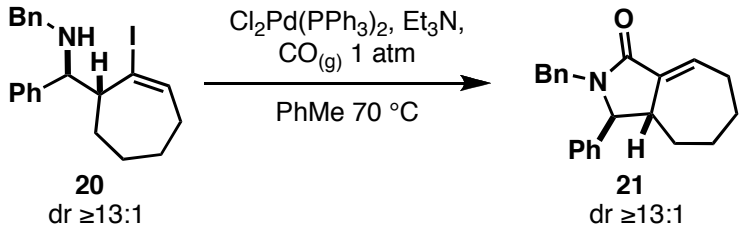




Synthesis of (3*S,3*S**)-2-benzyl-3-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-isoindol-1-one 18:** To a round bottom flask equipped with a reflux condenser was sequentially added amine **17** (169 mg, 0.420 mmol), toluene (4.2 mL), $Cl_2Pd(PPh_3)_2$ (14 mg, 0.021 mmol) and Et_3N (114 μL, 83 mg, 0.820 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C), and stirred for 12 hours. The reaction mixture was then allowed to cool to ambient temperature, diluted with EtOAc, filtered through cotton and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/10→1/5 EtOAc/Hexanes) to yield γ-lactam **18** as a white solid, (111 mg, 87%).

Data for (3*S,3*S**)-2-benzyl-3-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-isoindol-1-one 18:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 3 H), 7.18-7.10 (m, 3 H), 7.10-7.05 (m, 2 H), 6.94-6.86 (m, 2 H), 6.54 (dt, *J* = 3.3, 3.3 Hz, 1 H), 5.04 (d, *J* = 14.4 Hz, 1 H), 3.78 (d, *J* = 7.6 Hz, 1 H), 3.50 (d, *J* = 14.4 Hz, 1 H), 2.54-2.40 (m, 1 H), 2.28-2.14 (m, 1 H), 1.85-1.66 (m, 2 H), 1.43-1.26 (m, 1 H), 1.16-0.99 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 139.3, 136.5, 134.9, 129.0, 128.8, 128.5, 128.3, 127.6, 127.4, 66.7, 45.3, 44.4, 25.1, 24.8, 21.5; IR (thin film, NaCl) 3026, 2929, 2862, 1688, 1494, 1455, 1393, 1272, 736, 701 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{21}H_{22}NO$ $(M+H)^+$ 304.1696 *m/z* (M+H); found $(M+H)^+$ 304.1666.



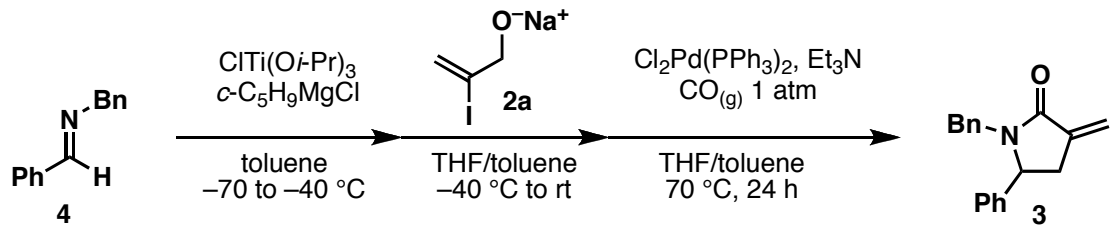


Synthesis of (3*S,3S*)-2-benzyl-3-phenyl3,3a,4,5,6,7-hexahydrocyclohepta-[*c*]-pyrrol-1(2*H*)-one 21:** To a round bottom flask equipped with a reflux condenser was sequentially added amine **20** (156 mg, 0.374 mmol), toluene (2.5 mL), $Cl_2Pd(PPh_3)_2$ (9 mg, 0.012 mmol) and Et_3N (70 μL, 50 mg, 0.500 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C), and stirred for 12 hours. The reaction mixture was then allowed to cool to ambient temperature, diluted with EtOAc, filtered through cotton and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/7→1/5 EtOAc/Hexanes) to yield γ-lactam **21** as a white solid, (109 mg, 92%, dr ≥13:1).

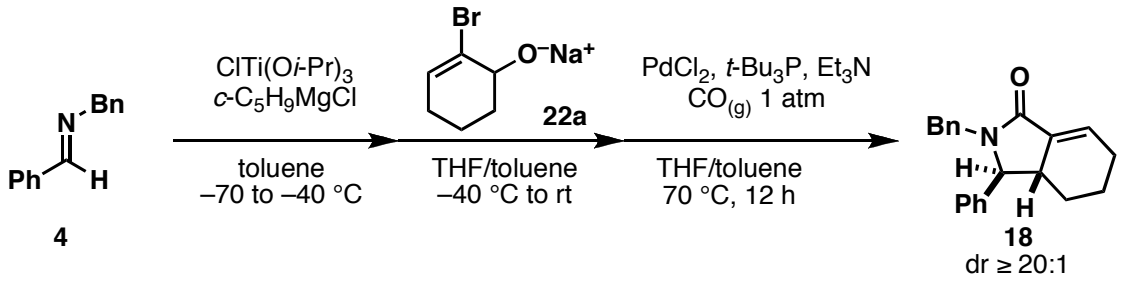
Data for (3*S,3*S**)-2-benzyl-3-phenyl-3,3a,4,5,6,7-hexahydrocyclohepta-[*c*]-pyrrol-1(2*H*)-one 21:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.12 (m, 6 H), 7.11-7.02 (m, 2 H), 7.00-6.93 (m, 2 H), 6.92-6.86 (m, 2 H), 5.07 (d, *J* = 14.4 Hz, 1 H), 3.75 (d, *J* = 5.6 Hz, 1 H), 3.44 (d, *J* = 14.4 Hz, 1 H), 2.70-2.60 (m, 1 H), 2.43-2.32 (m, 1 H), 2.16-2.02 (m, 1 H), 1.93-1.83 (m, 1 H), 1.79-1.67 (m, 2 H), 1.38-1.10 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 140.3, 138.1, 136.5, 135.3, 129.1, 128.8, 128.7, 128.6, 128.4, 127.5, 127.5, 66.0, 48.6, 44.8, 31.7, 30.3, 29.3, 27.4; IR (thin film, NaCl) 3030, 2920, 1695, 1668, 1494, 1415, 1271, 912, 730 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{22}H_{24}NO$ $(M+H)^+$ 318.1864; found $(M+H)^+$ 318.1864.

Relative stereochemistry for the major diastereomer was assigned in analogy to compound **18**.

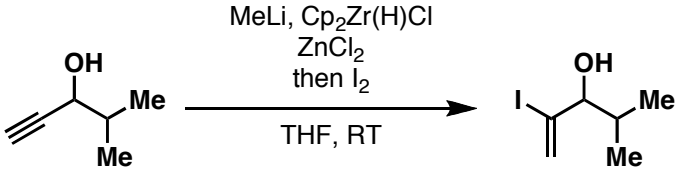
One Pot γ-Lactam Synthesis:



Synthesis of 1-benzyl-3-methylene-5-phenyl-2-pyrrolidinone 3: To a solution of imine **4** (372 μL, 0.391 g, 2.00 mmol) and ClTi(O*i*-Pr)$_3$ (1.0 M in diethyl ether, 2.50 mmol) in toluene (8.0 mL) at –70 °C was added *c*-C$_5$H$_9$MgCl (2.00 M in diethyl ether, 5.00 mmol) in a drop-wise manner with a syringe. The orange brown solution was slowly warmed to –40 °C over 30 minutes and stirred at –40 °C for a further 2 hours. A solution of sodium alkoxide **2a**, generated from the deprotonation of the corresponding alcohol (552 mg, 3.00 mmol) with NaH (60 % suspension, 150 mg, 3.75 mmol), in THF (8.0 mL) at 0 °C, was added in a drop-wise manner via Teflon cannula to the brown solution of imine–Ti complex at –40 °C. The reaction was allowed to warm to ambient temperature and stirred overnight. The following morning H_2O (180 μL, 180 mg, 10.0 mmol) was added and the reaction was rapidly stirred for 2 hours. To the reaction mixture was then added $Cl_2Pd(PPh_3)_2$ (14 mg, 0.020 mmol) and Et_3N (1.11 mL, 808 mg, 8.00 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C), and stirred for 24 hours. The reaction mixture was then allowed to cool to ambient temperature. The reaction mixture was diluted with EtOAc (25 mL), the solids ware removed by filtration through Celite™. The filtrate was further diluted with EtOAc (75 mL) and washed with 1 M HCl aq. (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was then dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/10→1/5 EtOAc/Hexanes) to yield γ-lactam **3** as a white solid, (363 mg, 69%). NMR data was in accordance with that described for the transformation of **1→3**.



Synthesis of (3*S*,3a*S*)-2-benzyl-3-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-isoindol-1-one 18: To a solution of imine **4** (74 μL, 78 mg, 0.400 mmol) and ClTi(O*i*-Pr)$_3$ (1.0 M in diethyl ether, 0.500 mmol) in toluene (1.6 mL) at –70 °C was added *c*-C_5H_9MgCl (2.00 M in diethyl ether, 1.00 mmol) in a drop-wise manner with a syringe. The orange-brown solution was slowly warmed to –40 °C over 30 minutes and stirred at –40 °C for a further 1.5 hours. A solution of sodium alkoxide **22a**, generated from the deprotonation of the corresponding alcohol (106 mg, 0.600 mmol) with NaH (60 % suspension, 30 mg, 0.750 mmol), in THF (1.6 mL) at 0 °C, was added in a drop-wise manner via Teflon cannula to the brown solution of imine-Ti complex at –40 °C. The reaction was allowed to warm to ambient temperature and stirred overnight. The following morning H_2O (36 μL, 36 mg, 2.00 mmol) was added and then rapidly stirred for 2 hours at ambient temperature. To the yellow solution of the reaction mixture was added $PdCl_2$ (1 mg, 0.008 mmol), *t*-Bu_3P (1.0 M toluene, 0.024 mmol) and Et_3N (223 μL, 161 mg, 1.60 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C), and stirred for 12 hours. The reaction vessel was then allowed to cool to ambient temperature. The reaction mixture was diluted with EtOAc (10 mL), the solids ware removed by filtration through celite. The filtrate was further diluted with EtOAc (75 mL) and washed with 1 M HCl aq. (75 mL), saturated aqueous $NaHCO_3$ (75 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/10→1/5 EtOAc/Hexanes) to yield γ-lactam **18** as a white solid, (89 mg, 73%, dr ≥20:1). NMR data was in accordance with that described for the transformation of **17→18**.



Synthesis of 2-iodo-4-methyl-1-penten-3-ol 10.

Alcohol **10** was prepared in accordance with the published procedure for directed hydrozirconation/iodination by Zhang, D.; Ready, J. M.[6]

The crude material was purified by column chromatography on silica gel (1/7→1/4 EtOAc/Hexanes) to yield haloallylic alcohol **10** as a colorless oil.

Data for 2-iodo-4-methyl-1-penten-3-ol 10: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (dd, *J* = 1.6, 0.8 Hz, 8 H), 5.84 (d, *J* = 1.6 Hz, 1 H), 3.08 (ddd, *J* = 7.2, 6.0, 0.8 Hz, 1 H), 1.77 (d, *J* = 6.0 Hz, 1 H), 1.75 (dqq, *J* = 7.2, 6.8, 6.4 Hz, 1 H), 0.96 (d, *J* = 6.4 Hz, 1 H), 0.78 (d, *J* = 6.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.4, 118.4, 83.6, 33.1, 19.4, 17.5; IR (thin film, NaCl) 3436 (br), 2921, 1729, 1463, 1260, 1021, 800, 735 cm^{-1}.

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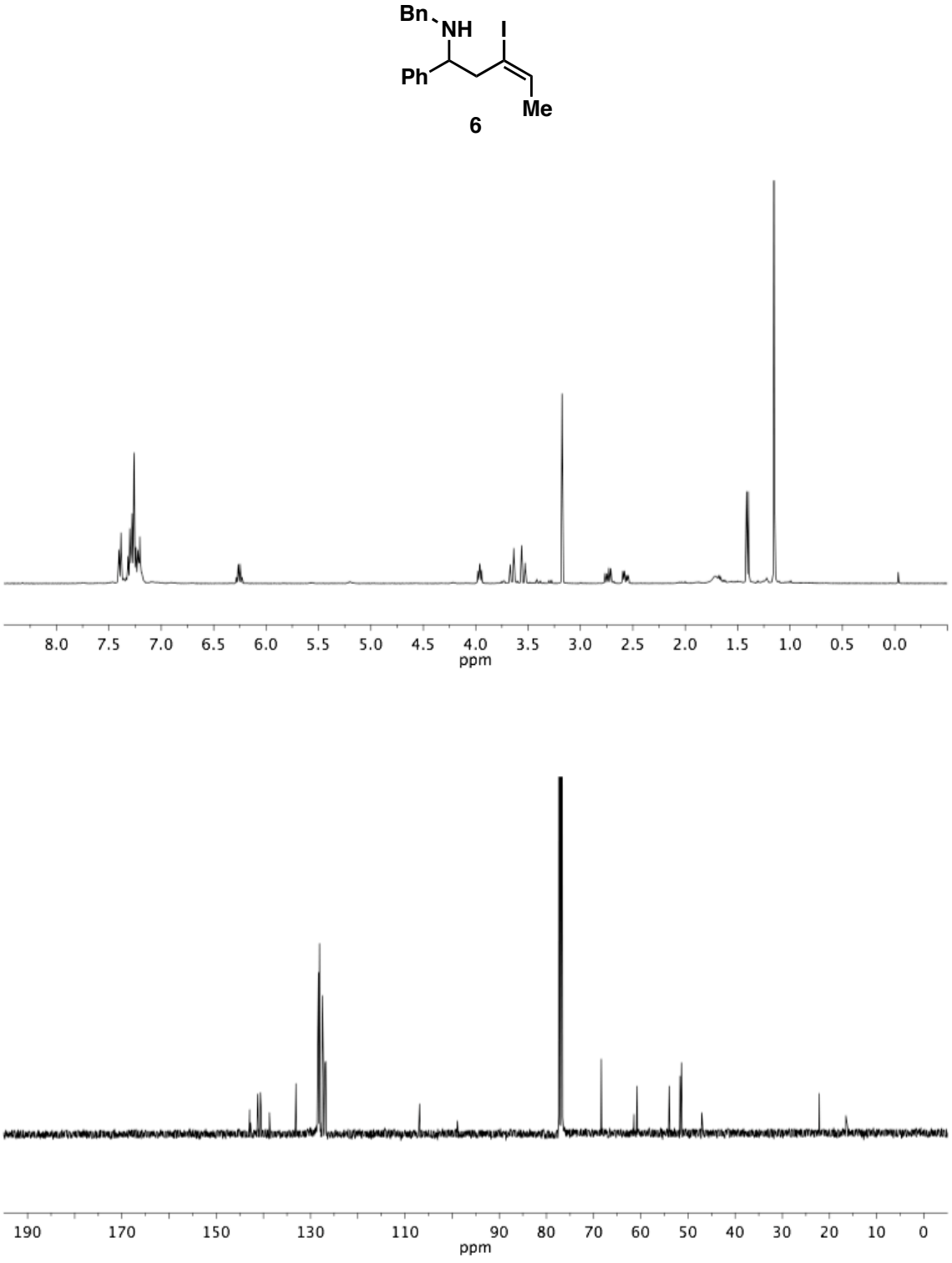
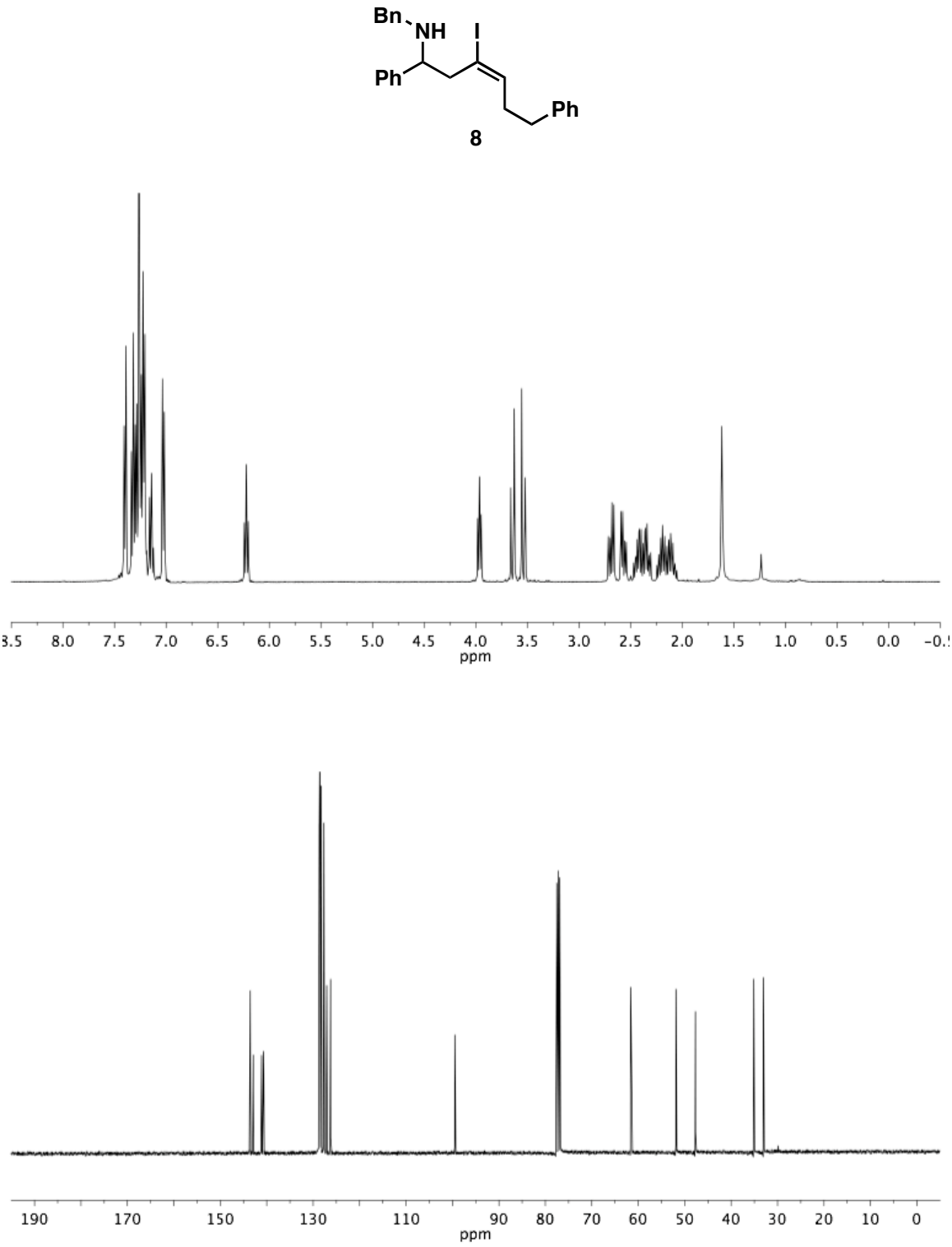
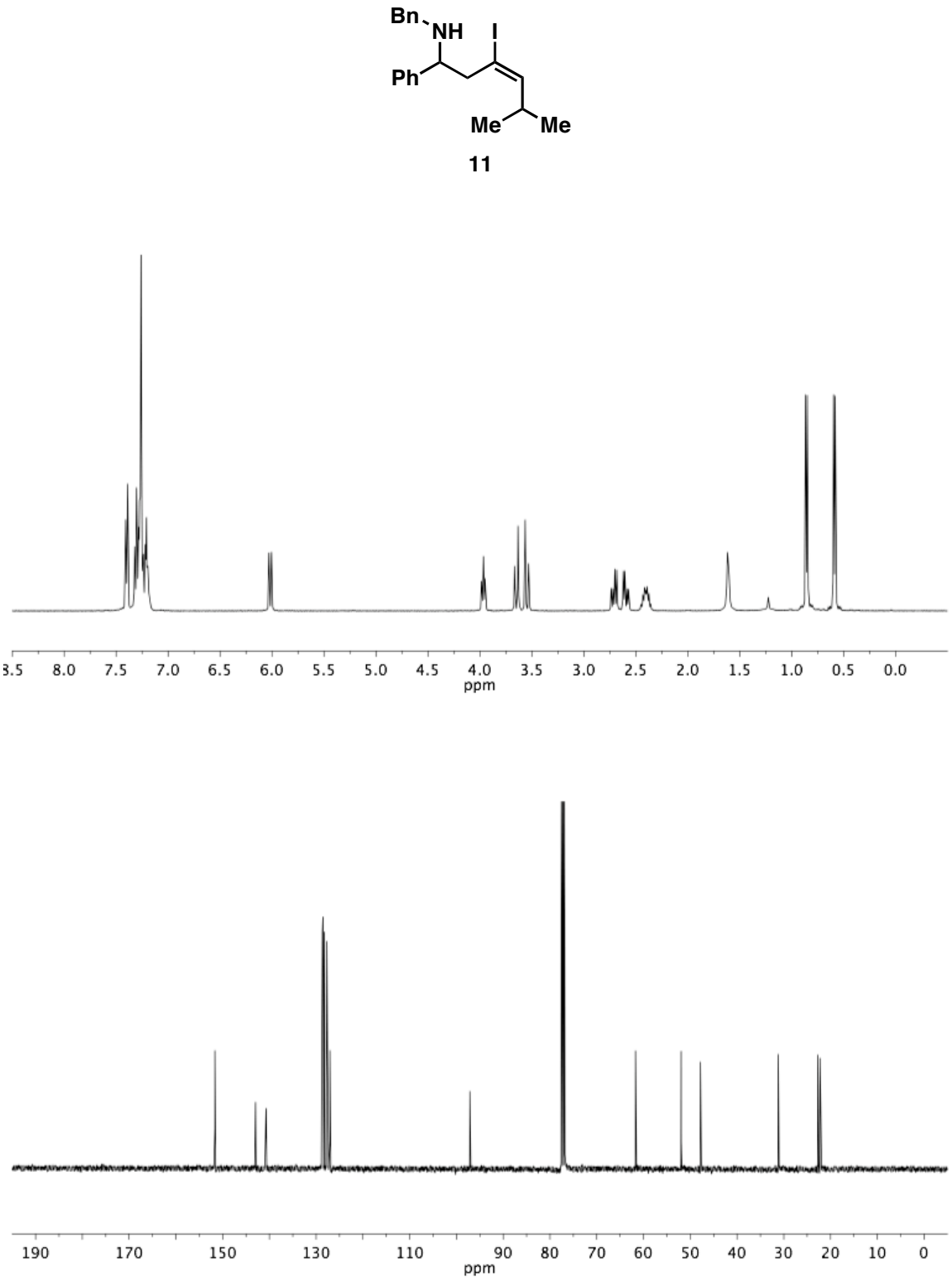


6

^{1}H NMR (400 Mhz) and ^{13}C NMR (100 Mhz) of compound **6**

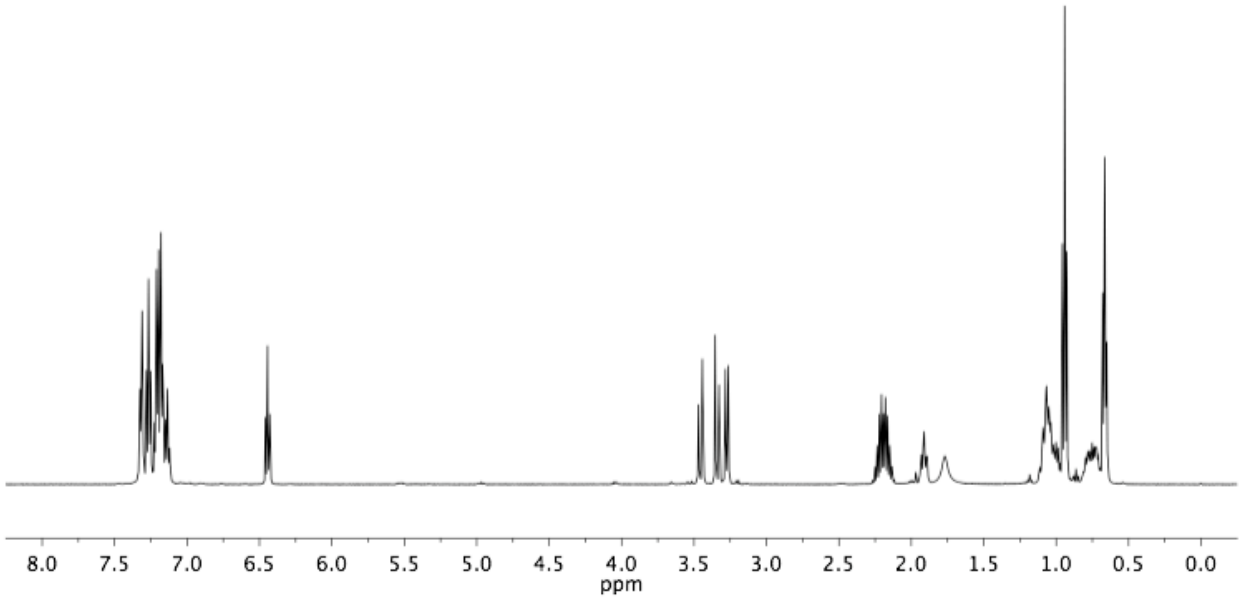


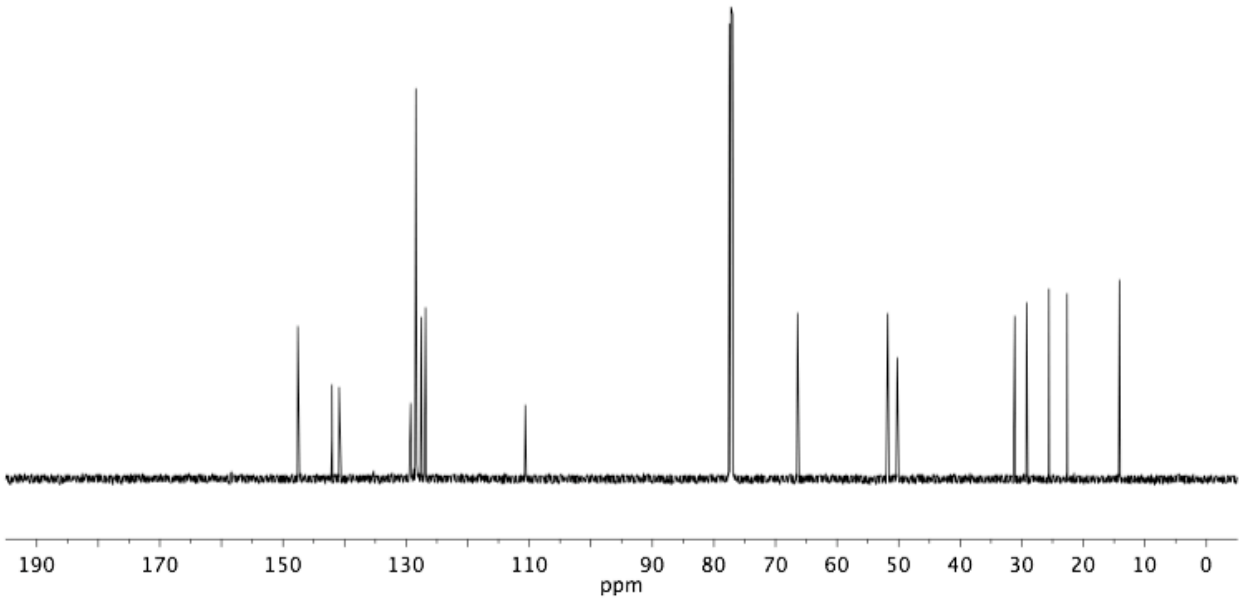
^{1}H NMR (400 Mhz) and ^{13}C NMR (100 Mhz) of compound **8**



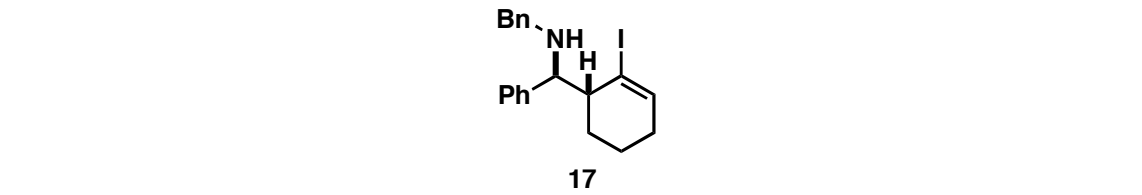
^{1}H NMR (400 Mhz) and ^{13}C NMR (100 Mhz) of compound **11**

14

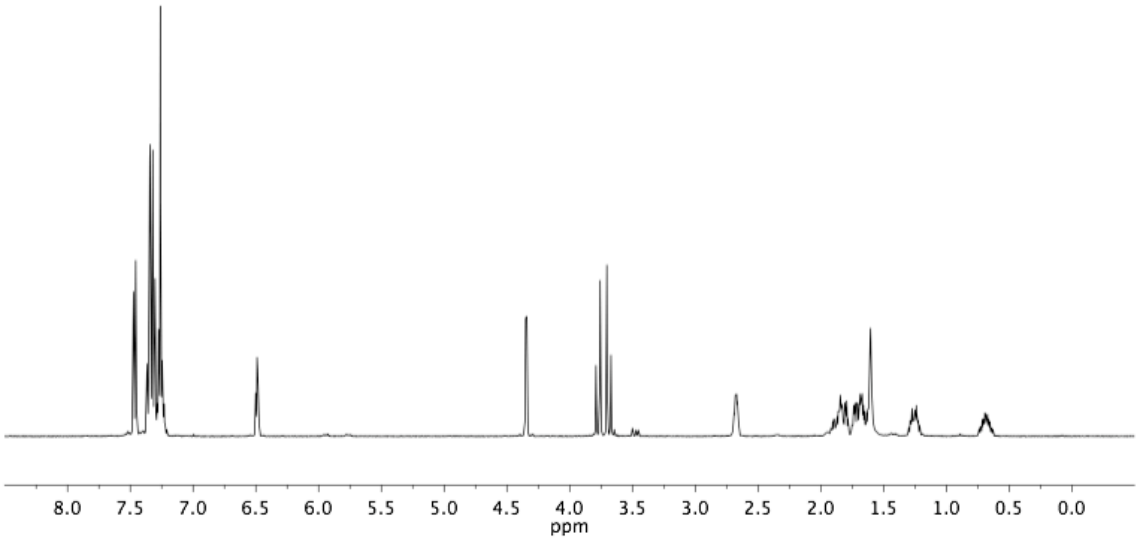


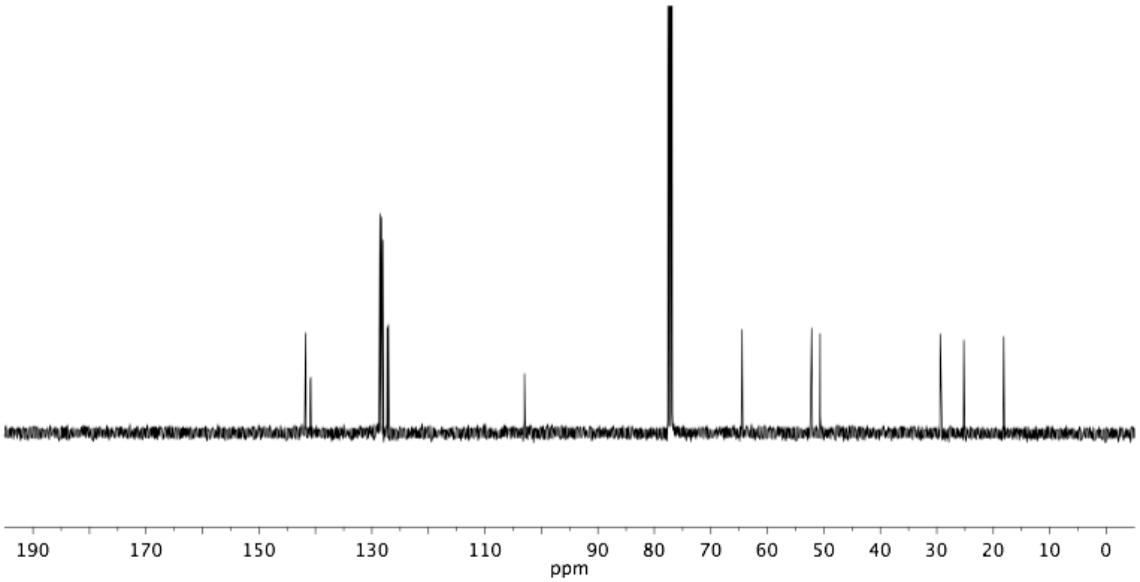


^{1}H NMR (500 Mhz) and ^{13}C NMR (126 Mhz) of compound **14**

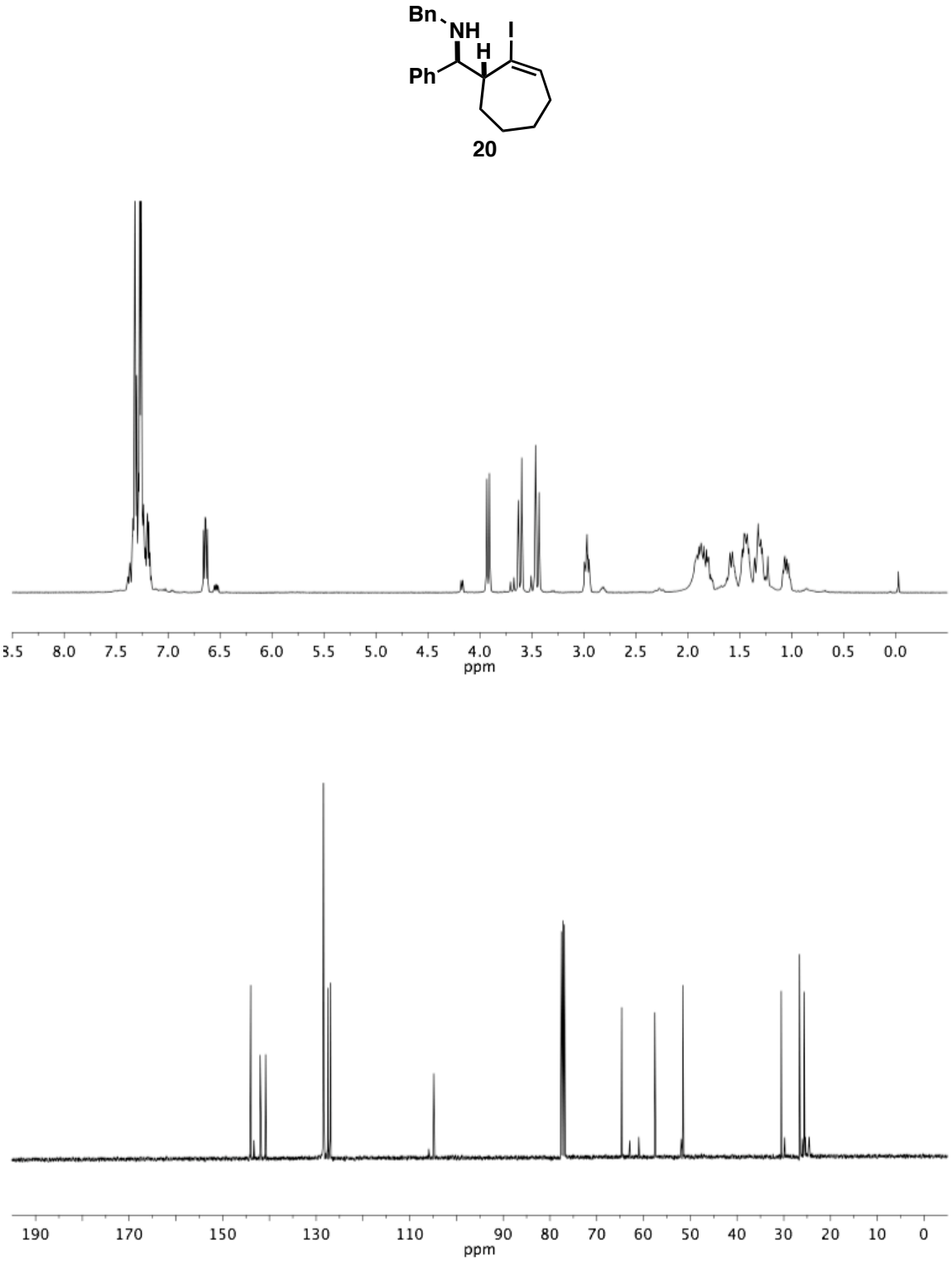


17

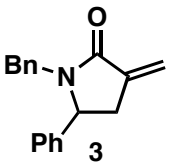




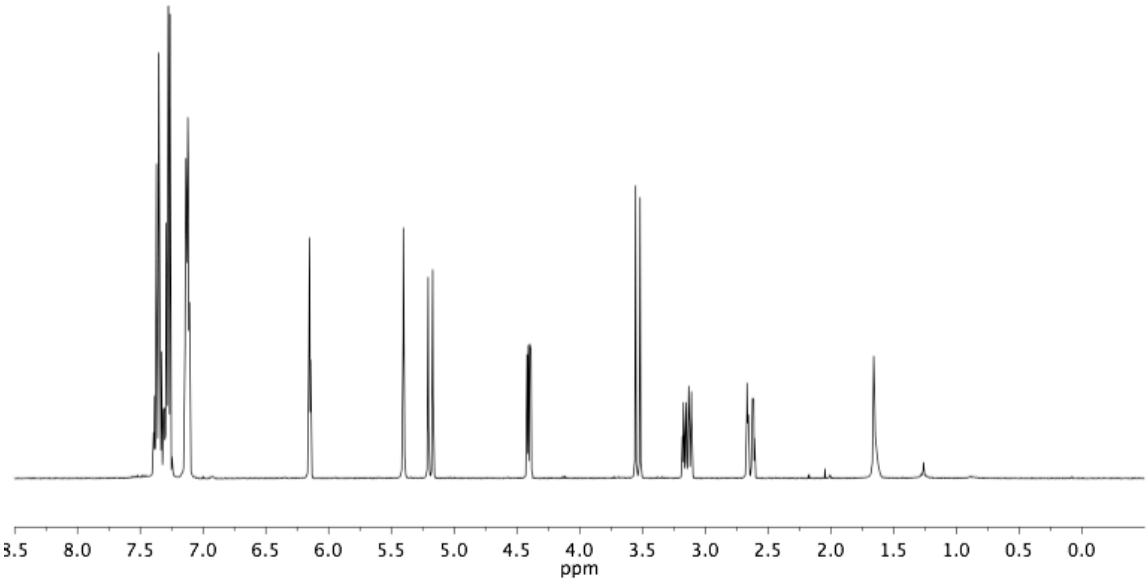
^{1}H NMR (400 Mhz) and ^{13}C NMR (100 Mhz) of compound **17**

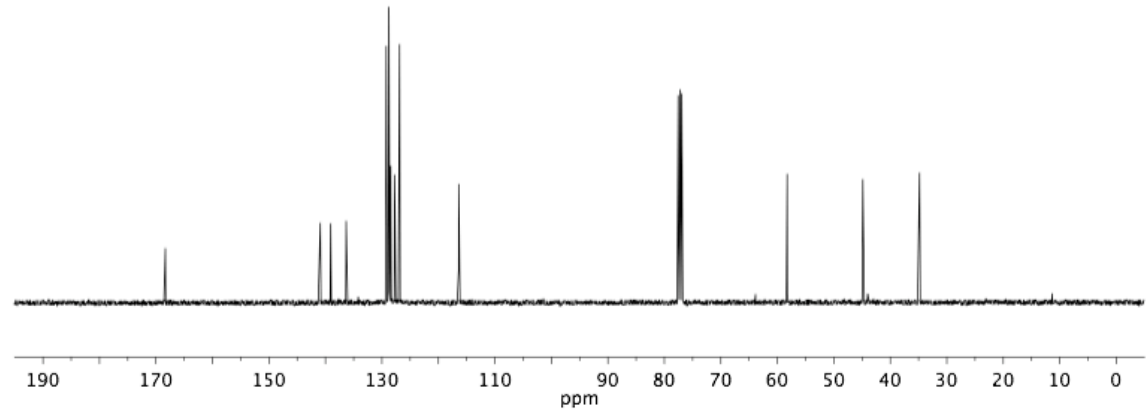


^{1}H NMR (400 Mhz) and ^{13}C NMR (100 Mhz) of compound **20**

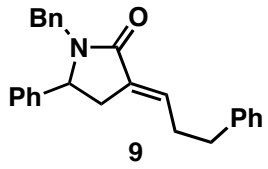


3

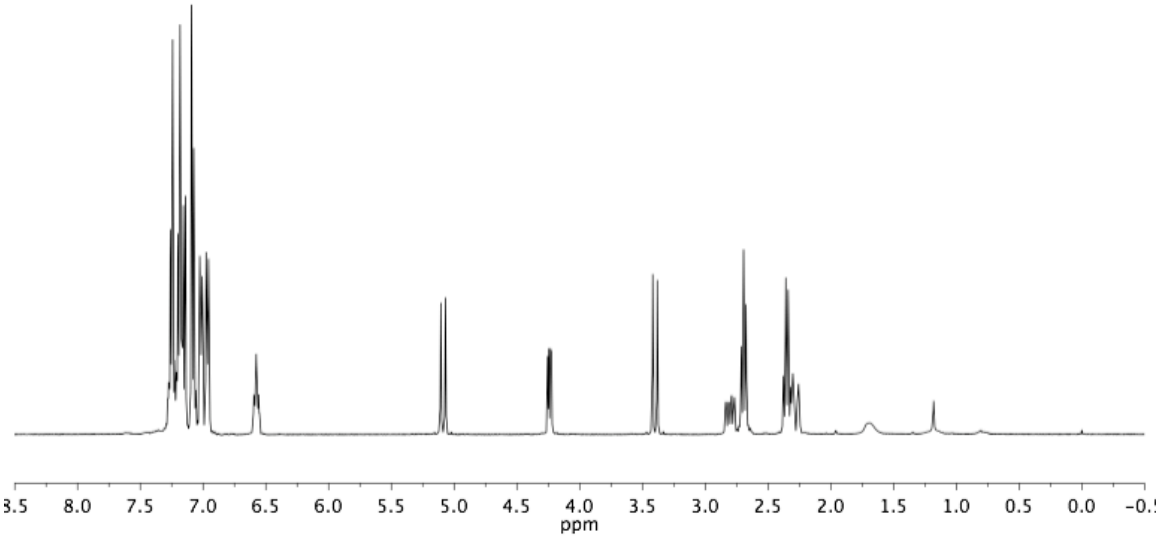


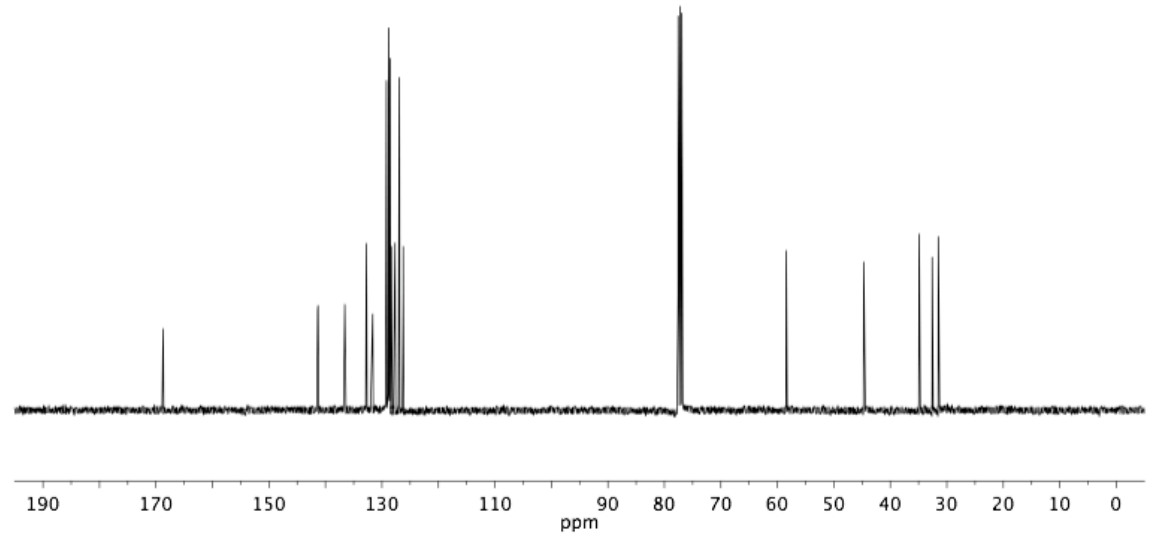


^{1}H NMR (400 Mhz) and ^{13}C NMR (100 Mhz) of compound **3**

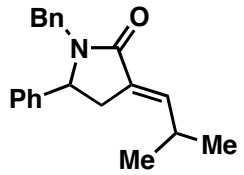


9

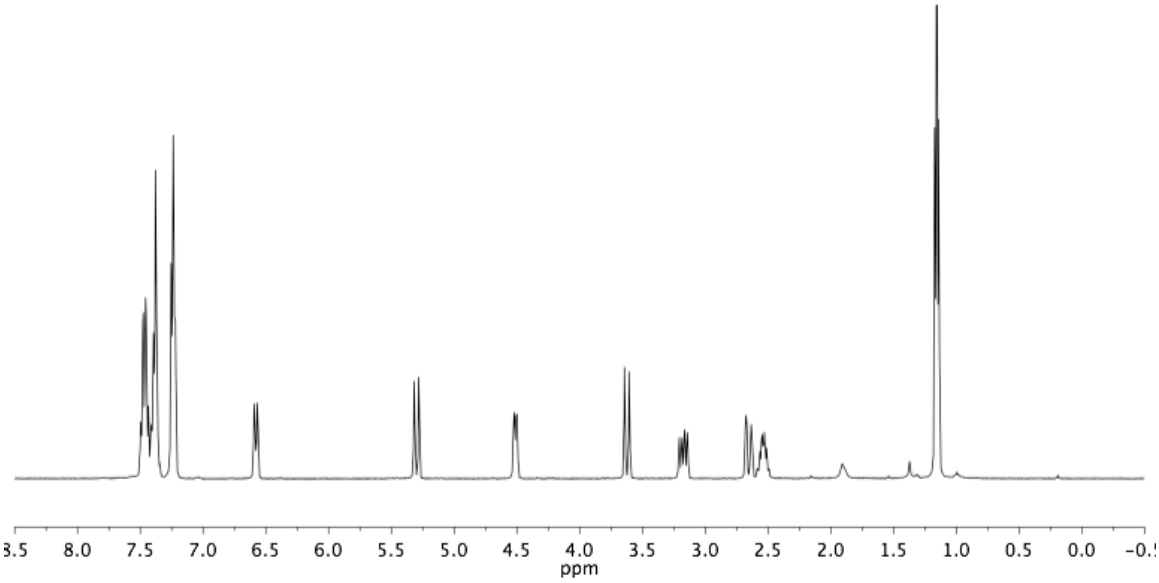


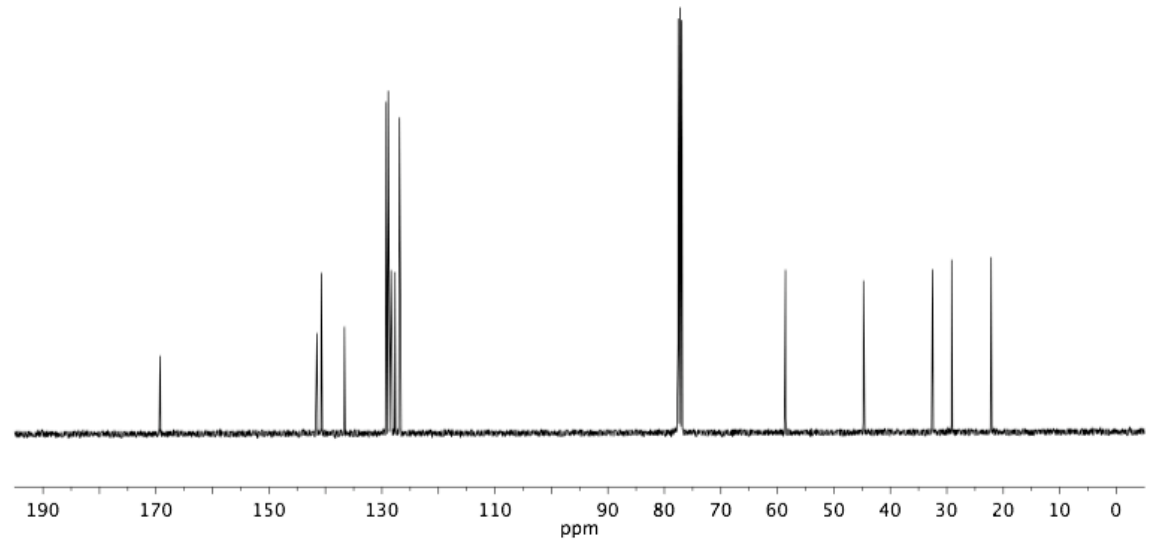


^{1}H NMR (400 Mhz) and ^{13}C NMR (100 Mhz) of compound **9**

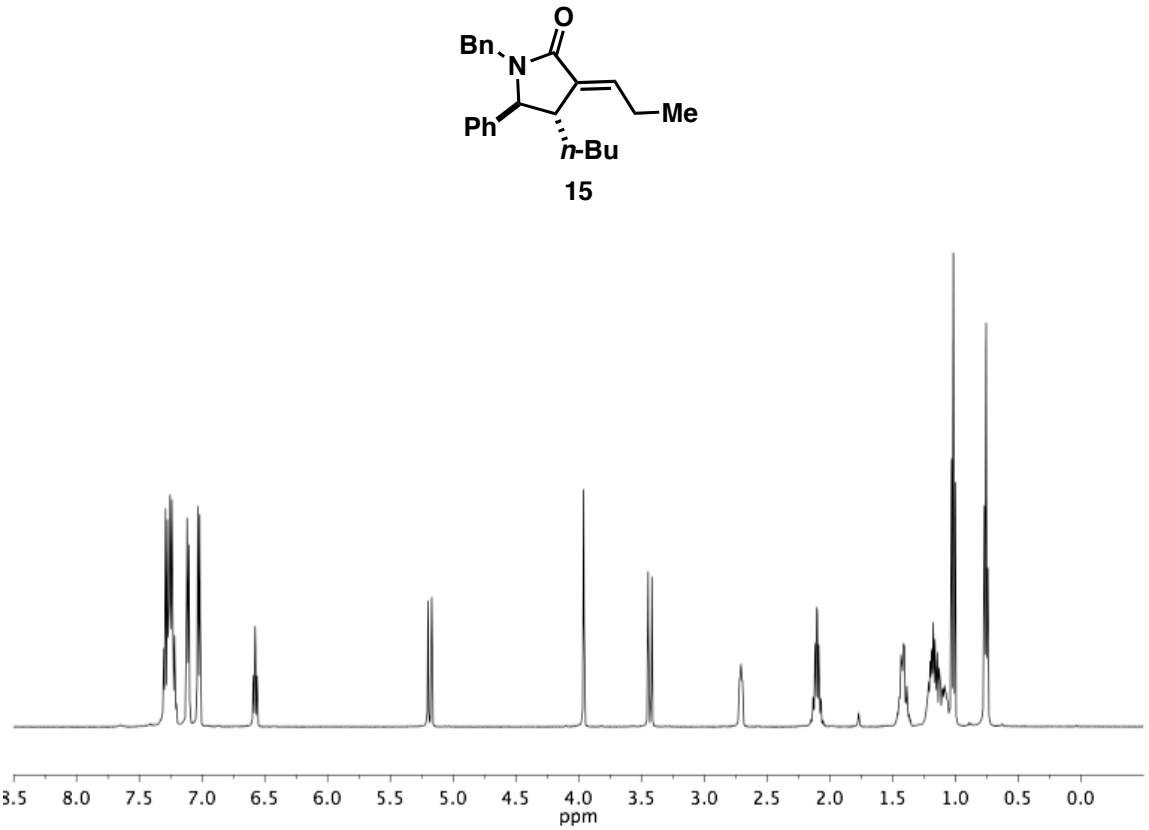


12

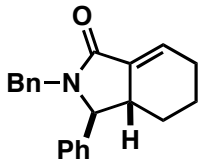




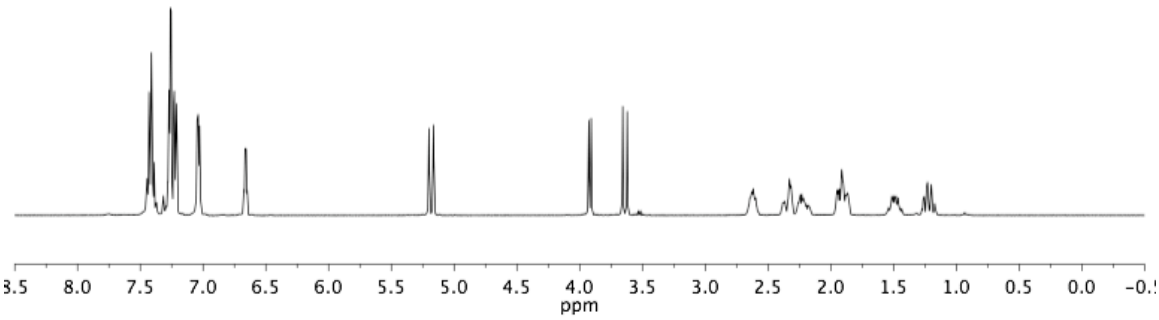
^{1}H NMR (400 Mhz) and ^{13}C NMR (100 Mhz) of compound **12**

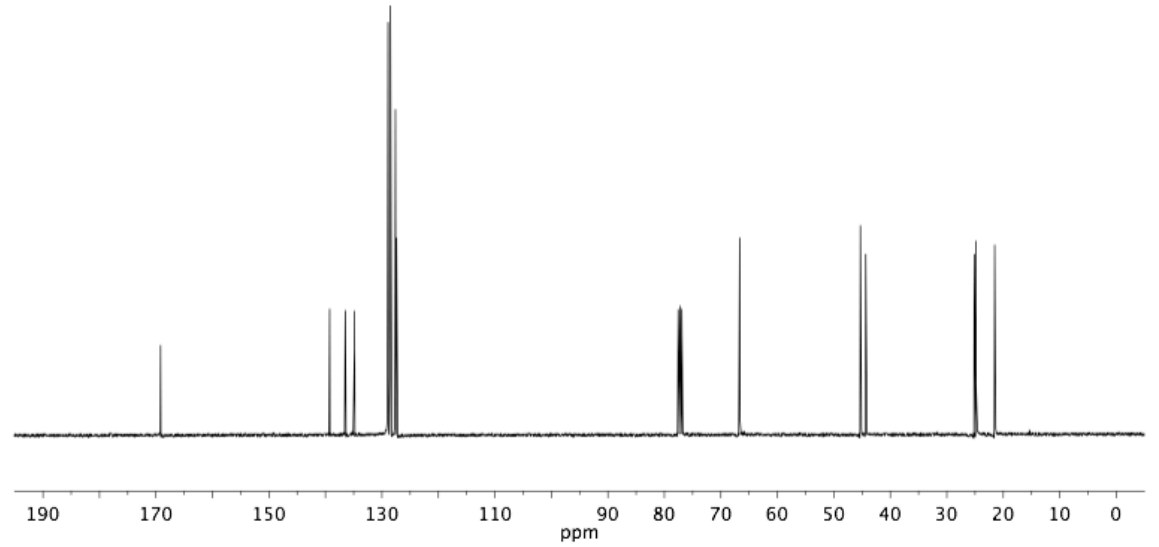


^{1}H NMR (500 Mhz) and ^{13}C NMR (126 Mhz) of compound **15**

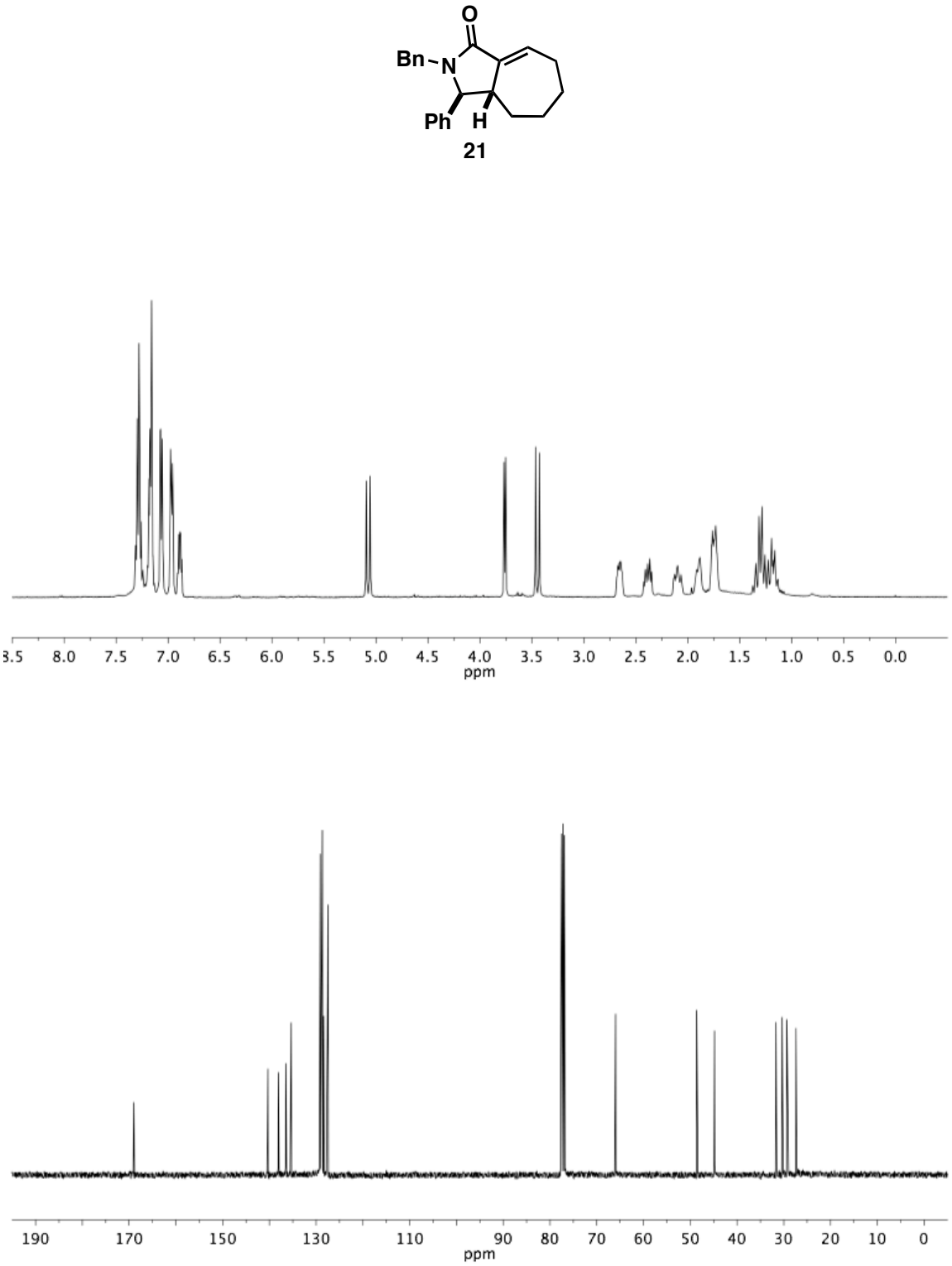


18





^{1}H NMR (400 Mhz) and ^{13}C NMR (100 Mhz) of compound **18**



^{1}H NMR (400 Mhz) and ^{13}C NMR (100 Mhz) of compound **21**