Supporting Information for

Sequential Cu(I)/Pd(0)-Catalyzed Multicomponent Coupling and Annulation Protocol for the Synthesis of Indenoisoquinolines

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General Experimental

Unless otherwise indicated, all NMR data were collected at room temperature in $CDCl_3$ with internal $CHCl_3$ as the reference (7.26 ppm for ^1H and 77.00 ppm for ^{13}C). IR spectra were measured in thin films on salt (NaCl) plates. Melting points are uncorrected and were taken in open capillary tubes. MS were measured under fast atom bombardment (FAB) or electron impact (EI) conditions. Analytical thin-layer chromatography (TLC) was carried out on commercial Merck silica gel 60 plates, 0.25 m thickness, with fluorescent indicator (F-254) or stained with aqueous $KMnO_4$ solution. Column chromatography was performed with 40-63 m silica gel (Sorbent). Methylene chloride, benzene, DMF and acetone were kept over 3Å (8-12 mesh) molecular sieves. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. Acetonitrile was distilled from CaH_2 and kept over 3Å (8-12 mesh) molecular sieves under an atmosphere of dry argon. *N*,*N*- Diisopropylethyl amine and triethyl amine were distilled from KOH and kept over 3Å (8-12 mesh) molecular sieves under an atmosphere of dry argon; other solvents were used as received. Unless otherwise specified, all reactions were carried out under an atmosphere of dry argon in oven-dried (at least 6 h at 140 ºC) glassware. Single crystals for X-ray analyses were obtained by recrystallization of the compounds from ethyl acetate/hexane. All imines **1** were prepared according to a modified literature procedure[1] by condensation of a 1:1 mixture of aldehyde and amine in benzene (65 °C) in the presence of activated 3 Å (8-12 mesh) molecular sieves for 4-6 h (monitored by ^1H NMR) followed by filtration through celite and removal of solvent under vacuum to afford pure imines. Ethyl 2-(tributylstannyl)acrylate[2] (**3a**), tributyl(prop-

1-en-2-yl)stannane[3] (**3b**) and tributyl(1-phenylvinyl)stannane[3] (**3c**) were prepared according to the indicated literature procedures. 2-Bromo-4,5-difluorobenzoyl chloride **2b** was prepared from 2-bromo-4,5-difluorobenzoic acid according to the literature procedure.[4] Other materials were used as received from commercial suppliers.

Ethyl 2-((*N*-benzyl-2-bromobenzamido)(4-methoxyphenyl)methyl)acrylate (4a) via the procedure described in Scheme 1. To a solution of *N*-benzyl-(4-methoxyphenyl)imine **1a** (0.225 g, 1.00 mmol, 1 equiv) and 2-bromobenzoyl chloride **2a** (0.260 g, 1.20 mmol, 1.2 equiv) in acetonitrile (3 mL) was added CuCl (0.0198 g, 0.200 mmol, 20 mol%). A solution of tributylvinyltin **3a** (0.585 g, 1.5 mmol, 1.5 equiv) in methylene chloride (6 mL) was added and the reaction mixture was heated to 45 °C for 6 h. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (15 mL), followed by the addition of solid KF (2 equiv) and a few drops of water. The mixture was stirred for 20 minutes and filtered through celite/silica pad. The filtrate was concentrated in vacuo and dried to give crude amide **4a**. The crude product was purified by flash chromatography over silica eluting with ethyl acetate/hexane (1: 3) to afford pure amide **4a** (0.415 g, 82%) as a colorless viscous oil: R_f = 0.47 (EtOAc/hexane 1 : 3); **^{1}H NMR** (400 MHz) □ 7.59 (q, *J* = 17.6 Hz, 8.0 Hz, 2 H), 7.40 – 7.34 (m, 3 H), 7.31 – 7.28 (m, 2 H), 7.10 – 7.08 (br m, 3 H), 7.02 (br d, *J* = 3.6 Hz, 2 H), 6.66 (d, *J* = 8.8 Hz, 1 H), 6.47 (s, 1 H), 6.29 (br s, 1 H), 5.73 (d, *J* = 23.2 Hz, 1 H), 4.65 (d, *J* = 5.6 Hz, 2 H), 3.90-3.84 (m, 2 H), 3.72 (s, 3 H), 0.97 (t, *J* = 7.2 Hz, 3 H); **^{13}C NMR** (125 MHz) □ 170.5, 167.5, 165.1, 159.4, 141.2, 137.9, 137.6, 133.3, 131.3, 130.5, 129.6, 128.7 (2 C), 127.9 (2 C), 127.6 (2 C), 127.0, 126.2, 119.3, 113.7 (2 C), 62.8, 60.8, 55.2, 44.2, 13.8; The ^{1}H and ^{13}C NMR spectra represent mixtures of rapidly interconverting amide

rotamers at room temperature. The major rotamer is represented in ^{1}H and ^{13}C NMR data given above. **IR** (neat, cm^{-1}): 1718 (s), 1645 (s); **HRMS** (ES^{+}) Calcd for $C_{27}H_{27}BrNO_4$ ($M+H^{+}$), 508.1124, found 508.1110.

(6a*R*,11a*S*)-Ethyl 6-benzyl-9-methoxy-5-oxo-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-c]isoquinoline-11a-carboxylate (5a) from 4a via the procedure described in Scheme 1. To a screw-sealable tube was added $Pd(OAc)_2$ (0.0013 g, 0.0059 mmol, 5 mol%) and sodium acetate (0.0097 g, 0.118 mmol, 1 equiv) followed by **4a** (0.060 g, 0.118 mmol, 1 equiv) in DMF (2 mL) under argon. The reaction mixture in the screw-capped sealed tube was stirred at 120 °C for 24 h. The reaction mixture was then diluted with ethyl acetate (25 mL) and the organic layer was washed three times with brine. The organic layer was dried ($MgSO_4$) and filtered through a celite/silica pad, and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography over silica eluting with ethyl acetate/hexanes (1 : 3) followed by trituration with hexane to afford indenoisoquinoline **5a** (0.0468 g, 93%) as a white powder: mp = 130-132 ºC (hexane); R_f = 0.43 (EtOAc/hexane 1 : 3); **^{1}H NMR** (400 MHz) □ 8.13 (d, *J* = 7.6 Hz, 1 H), 7.50-7.42 (m, 4 H), 7.36-7.30 (m, 4 H), 6.84 (d, *J* = 8.4 Hz, 1 H), 6.61 (s, 1 H), 6.60 (t, *J* = 8.4 Hz, 1 H), 5.50 (d, *J* = 14.4 Hz, 1 H), 5.36 (s, 1 H), 4.59 (d, *J* = 14.4 Hz, 1 H), 3.88 (dd, *J* = 14.0 Hz, 7.2 Hz, 2 H), 3.69 (s, 3 H), 3.60 (q, *J* = 33.2 Hz, 16.0 Hz, 2 H), 0.98 (t, *J* = 7.2 Hz, 3 H); **^{13}C NMR** (125 MHz) □ 172.2, 162.9, 159.9, 139.7, 137.7, 136.9, 132.9, 132.0, 129.5, 129.1 (2 C), 128.6, 128.5 (2 C), 127.9, 127.7, 126.7, 123.8, 112.8, 110.0, 65.6, 61.6, 57.6, 55.3, 51.5, 41.9, 13.8; **IR** (neat, cm^{-1}): 1728 (s), 1650 (s); **HRMS** (ES^{+}) Calcd for $C_{27}H_{26}NO_4$ ($M+H^{+}$), 428.1862, found 428.1865.

General Procedure for the Preparation of Indenoisoquinolines 5a-o described in Tables 1 and 2 (Method A). To a solution of imine (0.500 mmol, 1 equiv) and 2-bromobenzoyl chloride (0.600 mmol, 1.2 equiv) in acetonitrile (2 mL) was added CuCl (0.100 mmol, 20 mol%). A solution of tributylvinyltin (0.75 mmol, 1.5 equiv) in methylene chloride (4 mL) was added, and the reaction mixture was heated to 45 °C for 6 h. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (10 mL). Solid KF (2 equiv) and a few drops of water were added, and the mixture was stirred for 20 minutes. The resulting suspension was filtered through celite/silica, and the filtrate was concentrated in vacuo and dried to give crude amide **4**. $Pd(OAc)_2$ (0.025 mmol, 5 mol%) and sodium acetate (0.500 mmol, 1 equiv) were added into a screw-cap sealed tube, followed by the solution of crude amide **4** in DMF (2 mL), and an argon atmosphere was established in the reaction vessel. The reaction mixture in the screw-capped sealed tube was stirred at 120 °C for 24 h. The reaction mixture was then diluted with ethyl acetate and the organic layer was washed three times with brine. The organic layer was dried ($MgSO_4$), filtered through a celite/silica pad, and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography over silica eluting with with ethyl acetate/hexanes (1 : 3) followed by recrystallization from ethyl acetate/hexane or trituration with hexane to afford the corresponding indenoisoquinolines **5**.

(6a*R*,11a*S*)-Ethyl 6-benzyl-9-methoxy-5-oxo-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-c]isoquinoline-11a-carboxylate (5a) (Entry 1, Table 1): *N*-Benzyl-(4-methoxyphenyl)imine **1a** (0.113 g, 0.500 mmol), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol) and ethyl 2-(tributylstannyl)acrylate **3a** (0.293 g, 0.750 mmol) were treated

according to the general procedure described above to obtain crude amide **4a**. Crude amide **4a** was then dissolved in DMF (2 mL) and treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%) and sodium acetate (0.041g, 0.500 mmol, 1 equiv) according to the general procedure described above, eluting with EtOAc/hexane (1 : 3) followed by trituration with hexane to afford indenoisoquinoline **5a** (0.159 g, 75%) as a white powder. The analytical data for **5a** is presented above.

(6a*R*,11a*S*)-Ethyl 6-benzyl-9-methyl-5-oxo-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-c]isoquinoline-11a-carboxylate (5b) (Entry 2, Table 1): *N*-Benzyl-*p*-tolylimine **1b** (0.105 g, 0.500 mmol), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol) and ethyl 2-(tributylstannyl)acrylate **3a** (0.293 g, 0.750 mmol) were treated according to the general procedure described above to obtain crude amide **4b**. Crude amide **4b** was then dissolved in DMF (2 mL) and treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%) and sodium acetate (0.041 g, 0.500 mmol, 1 equiv) according to the general procedure described above, eluting with EtOAc/hexane (1 : 3) followed by trituration with hexane to afford indenoisoquinolines **5b** (0.141 g, 69%) as a white powder: mp = 124-126 ºC (hexane); R_f = 0.47 (EtOAc/hexane 1 : 3); **^{1}H NMR** (500 MHz) □ 8.18 (d, *J* = 8.0 Hz, 1 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 7.45 (t, *J* = 7.5 Hz, 1 H), 7.38 (t, *J* = 7.5 Hz, 2 H), 7.35-7.30 (m, 2 H), 6.91 (d, *J* = 7.0 Hz, 2 H), 6.90 (s, 1 H), 5.66 (d, *J* = 14.5 Hz, 1 H), 5.44 (s, 1 H), 4.65 (d, *J* = 14.0 Hz, 1 H), 3.94-3.90 (m, 2 H), 3.70 (dd, *J* = 31.0 Hz, 15.5 Hz, 2 H), 2.30 (s, 3 H), 1.01 (t, *J* = 7.0 Hz, 3 H); **^{13}C NMR** (125 MHz) □ 172.0, 162.7, 137.9 (2 C), 137.8, 137.2, 136.8, 131.8, 129.4, 128.9 (2 C), 128.4 (3 C), 127.8, 127.7, 127.5, 126.6, 124.9, 122.4, 65.8, 61.4, 57.3, 51.4, 41.5, 21.0, 13.6; **IR** (neat, cm^{-1}): 1728 (s), 1645 (s); **HRMS** (ES^+) Calcd for $C_{27}H_{26}NO_3$ ($M+H^+$), 412.1913, found 412.1903.

(6a*R*,11a*S*)-Ethyl 6-benzyl-5-oxo-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-c]isoquinoline-11a-carboxylate (5c) (Entry 3, Table 1): *N*-Benzyl-phenylimine (0.0975 g, 0.500 mmol) **1c**, 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol) and ethyl 2-(tributylstannyl)acrylate **3a** (0.293 g, 0.750 mmol) were treated according to the general procedure described above to obtain crude amide **4c**. Crude amide **4c** was then dissolved in DMF (2 mL) and treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%) and sodium acetate (0.041 g, 0.500 mmol, 1 equiv) according to the general procedure described above, eluting with EtOAc/hexane (1 : 3) followed by trituration with hexane to afford indenoisoquinoline **5c** (0.133 g, 67%) as a white powder: mp = 164-166 ºC (hexane); R_f = 0.50 (EtOAc/hexane 1 : 3); **^{1}H NMR** (500 MHz) □ 8.13 (dd, *J* = 8.0 Hz, 1.5 Hz, 1 H), 7.51 (d, *J* = 7.0 Hz, 1 H), 7. 48 (d, *J* = 8.0 Hz, 2 H), 7.45 (td, *J* = 7.5 Hz, 1.5 Hz,1 H), 7.37-7.29 (m, 4 H), 7.12-7.06 (m, 3 H), 6.91 (d, *J* = 8.0 Hz, 1 H), 5.63 (d, 14.5 Hz, 1 H), 5.43 (s, 1 H), 4.61 (d, 14.0 Hz, 1 H), 3.90-3.85 (m, 2 H), 3.66 (dd, *J* = 24.5 Hz, 16.0 Hz, 2 H), 0.98 (t, *J* = 7.0 Hz, 3 H); **^{13}C NMR** (125 MHz) □ 172.1, 162.9, 140.9, 137.9, 137.2, 136.7, 132.0, 129.5, 129.0 (2 C), 128.5 (3 C), 128.2, 127.9, 127.7, 127.2, 126.8, 124.3, 122.8, 66.1, 61.6, 57.4, 51.6, 41.7, 13.7; **IR** (neat, cm^{-1}): 1728 (s), 1650 (s); **HRMS** (ES^+) Calcd for $C_{26}H_{24}NO_3$ ($M+H^+$), 398.1756, found 398.1744.

(6a*R*,11a*S*)-Ethyl 6-benzyl-9-chloro-5-oxo-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-c]isoquinoline-11a-carboxylate (5d) (Entry 4, Table 1): *N*-Benzyl-(4-chlorophenyl)imine **1d** (0.1145 g, 0.500 mmol), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol) and ethyl 2-(tributylstannyl)acrylate **3a** (0.293 g, 0.750 mmol) were treated according to the general procedure described above to obtain crude amide **4d**. Crude amide **4d** was then dissolved in DMF (2 mL) and treated with $Pd(OAc)_2$ (0.0056 g, 0.025

mmol, 5 mol%) and sodium acetate (0.041 g, 0.500 mmol, 1 equiv) according to the general procedure described above, eluting with EtOAc/hexane (1 : 3) followed by trituration with hexane to afford indenoisoquinoline **5d** (0.105 g, 49%) as a white powder: mp = 143-145 ºC (hexane); R_f = 0.50 (EtOAc/hexane 1 : 3); **^{1}H NMR** (500 MHz) δ 8.12 (dd, *J* = 7.5 Hz, 1.5 Hz, 1 H), 7.49-7.43 (m, 4 H), 7.37-7.30 (m, 4 H), 7.04 (s, 1 H), 7.00 (dd, *J* = 8.0 Hz, 1.5 Hz, 1 H), 6.76 (d, *J* = 8.0 Hz, 1 H), 5.44 (d, *J* = 14.0 Hz, 1 H), 5.36 (s, 1 H), 4.79 (d, *J* = 14.0 Hz, 1 H), 3.90 (dd, *J* = 14.5 Hz, 7.5 Hz, 2 H), 3.61 (dd, *J* = 24.5 Hz, 16.0 Hz, 2 H), 1.00 (t, *J* = 7.0 Hz, 3 H); **^{13}C NMR** (125 MHz) δ 171.7, 162.8, 139.8, 139.5, 137.2 (2 C), 136.3, 133.8, 132.2, 129.1 (2 C), 128.7 (3 C), 128.2, 127.9, 127.5, 126.7, 124.7, 124.1, 65.7, 61.8, 57.6, 51.7, 41.4, 13.8; **IR** (neat, cm^{-1}): 1728 (s), 1650 (s); **HRMS** (ES^+) Calcd for $C_{26}H_{23}ClNO_3$ ($M+H^+$), 432.1366, found 432.1316.

***R*,11a*S*)-11a-Ethyl 9-methyl 6-benzyl-5-oxo-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-c]isoquinoline-9,11a-dicarboxylate (5e) (Entry 5, Table 1):** *N*-Benzyl-(4-methoxycarbonylphenyl)imine **1e** (0.1265 g, 0.500 mmol), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol) and ethyl 2-(tributylstannyl)acrylate **3a** (0.293 g, 0.750 mmol) were treated according to the general procedure described above to obtain crude amide **4e**. Crude amide **4e** was then dissolved in DMF (2 mL) and treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%), sodium acetate (0.041g, 0.500 mmol, 1 equiv) according to the general procedure described above, eluting with EtOAc/hexane (1 : 3) followed by trituration with EtOAc/hexane (1 : 39) to afford indenoisoquinoline **5e** (0.086 g, 38%) as a white solid: mp = 185-187 ºC (hexane); R_f = 0.37 (EtOAc/hexane 1 :

3); **^{1}H NMR** (500 MHz) □ 8.10 (dd, *J* = 8.0 Hz, *J* = 1.5 Hz, 1 H), 7.73 (s, 1 H), 7.72 (d, *J* = 7.5 Hz, 1 H), 7.50-7.47 (m, 3 H), 7.44 (td, *J* = 7.5 Hz, *J* = 1.5 Hz, 1 H), 7.38-7.30 (m, 4 H), 6.91 (d, *J* = 8.0 Hz, 1 H), 5.47 (d, *J* =14.5 Hz, 1 H), 5.42 (s, 1 H), 4.72 (d, *J* =14.0 Hz, 1 H), 3.91 (ddd, *J* =14.5 Hz, *J* = 7.5 Hz, *J* = 2.5 Hz, 2 H), 3.83 (s, 3 H), 3.67 (s, 2 H), 1.02 (t, *J* = 7.5 Hz, 3 H); **^{13}C NMR** (125 MHz) □ 171.8, 166.6, 162.8, 146.2, 138.3, 137.1, 136.2, 132.2, 130.3, 129.5, 129.2 (2 C), 129.1, 128.7 (3 C), 128.2, 127.9, 126.8, 125.6, 122.9, 66.2, 61.8, 57.7, 52.1, 51.8, 41.4, 13.8; **IR** (neat, cm^{-1}): 1722 (s), 1652 (s); **HRMS** (ES^+) Calcd for $C_{28}H_{26}NO_5$ ($M+H^+$), 456.1811, found 456.1827.

(6a*R*,11a*S*)-Ethyl 6-benzyl-8,9-dimethoxy-5-oxo-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-c]isoquinoline-11a-carboxylate (5f) (Entry 6, Table 1): *N*-Benzyl-(3, 4-dimethoxyphenyl)imine **1f** (0.1275 g, 0.500 mmol), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol) and ethyl 2-(tributylstannyl)acrylate **3a** (0.293 g, 0.750 mmol) were treated according to the general procedure described above to obtain crude amide **4f**. Crude amide **4f** was then dissolved in DMF (2 mL) and treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%) and sodium acetate (0.041 g, 0.500 mmol, 1 equiv) according to the general procedure described above eluting with EtOAc/hexane (1 : 3). The resulting off white solid was recrystallized from EtOAc/hexane (1 : 19) to afford indenoisoquinoline **5f** (0.176 g, 77%) as a white powder: mp = 127-129 ºC (hexane); R_f = 0.43 (EtOAc/hexane 1 : 3); **^{1}H NMR** (500 MHz) □ 8.12 (dd, *J* = 7.5 Hz, 1.5 Hz, 1 H), 7.57-7.54 (m, 3 H), 7.45 (td, *J* = 7.0 Hz, 1.5 Hz, 1 H), 7.39-7.35 (m, 4 H), 7.33-7.30 (m, 2 H), 6.54 (s, 1H), 6.05 (s, 1 H), 5.39 (s, 1 H), 5.42 (s, 1 H), 5.14 (d, *J* = 14.5 Hz, 1 H), 4.93 (d, *J* = 14.5 Hz, 1 H), 4.01-3.99 (m, 2 H), 3.74 (s, 3 H), 3.56 (s, 1 H), 3.50 (s, 1 H), 1.09

(t, J = 7.5 Hz, 3 H); **^{13}C NMR** (125 MHz) δ 172.2, 163.0, 149.1, 148.5, 137.9, 137.2, 132.1, 129.6, 129.5 (3 C), 129.3, 128.8 (2 C), 128.6, 128.0, 127.9, 126.7, 107.2, 106.2, 67.1, 61.6, 57.7, 55.9, 55.9, 55.8, 52.6, 41.5; **IR** (neat, cm^{-1}): 1726 (s), 1649 (s); **HRMS** (ES$^+$) Calcd for $C_{28}H_{28}NO_5$ (M+H$^+$), 458.1967, found 458.1953.

(6a*R*,11a*S*)-Ethyl 6-benzyl-5-oxo-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-c]isoquinolino[8,9-d][1,3]dioxole-11a-carboxylate (5g) (Entry 7, Table 1): *N*-Benzyl-(benzo[*d*][1,3]dioxole)imine **1g** (0.1195 g, 0.500 mmol), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol) and ethyl 2-(tributylstannyl)acrylate **3a** (0.293 g, 0.750 mmol) were treated according to the general procedure described above to obtain crude amide **4g**. Crude amide **4g** was then dissolved in DMF (2 mL) and treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%) and sodium acetate (0.041 g, 0.500 mmol, 1 equiv) according to the general procedure described above, eluting with EtOAc/hexane (1 : 3). The resulting white solid was recrystallized from EtOAc/hexane (1 : 19) to afford indenoisoquinoline **5g** (0.156 g, 71%) as an inseparable mixture of diastereomers (dr 4 : 1) as a colorless-white powder: mp = 143-145 ºC (hexane); R_f = 0.43 (EtOAc/hexane 1 : 3); **^{1}H NMR** (500 MHz) δ 8.14 (dd, J = 7.5 Hz, 1.5 Hz, 1 H), 7.50-7.43 (m, 4 H), 7.36-7.30 (m, 4 H), 6.53 (d, J = 8.5 Hz, 0.77 H), 6.52 (d, J = 8.5 Hz, 0.23 H), 6.46 (dd, J = 7.5 Hz, 1.5 Hz, 1 H), 5.86 (dd, J = 26.0 Hz, 1.5 Hz, 1.68 H), 5.85 (dd, J = 26.0 Hz, 1.5 Hz, 0.32 H), 5.58 (d, J = 14.5 Hz, 0.80 H), 5.44 (d, J = 14.5 Hz, 0.20 H), 5.31 (s, 1 H), 4.65 (d, J = 14.5 Hz, 0.20 H), 4.53 (d, J = 14.5 Hz, 0.80 H), 3.86 (dd, J = 14.0 Hz, 7.0 Hz, 2 H), 3.59 (dd, J = 49.0 Hz, 16.0 Hz, 2 H), 0.97 (t, J = 7.0 Hz, 3 H); **^{13}C NMR** (125 MHz) δ171.8, 162.8, 147.7 (147.8), 143.0, 137.2 (137.3), 136.6 (137.0), 136.1 (133.7), 132.1

(132.1), 129.0 (2 C) (129.1), 128.7 (128.6), 128.5 (2 C), 128.1 (2 C) (127.9), 127.7 (127.8), 126.7 (126.6), 118.2, 115.6, 107.3 (105.0), 101.2 (103.1), 65.8 (66.0), 61.7 (61.6), 57.6 (57.7), 51.5 (51.7), 37.4 (41.4), 13.7 (13.8) signals for the minor diastereomer are given in parentheses; **IR** (neat, cm^{-1}): 1728 (s), 1650 (s); **HRMS** (ES^+) Calcd for $C_{27}H_{24}NO_5$ ($M+H^+$), 442.1655, found 442.1640.

(6a*R*,11a*S*)-Ethyl 6-benzyl-8,9,10-trimethoxy-5-oxo-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-c]isoquinoline-11a-carboxylate (5h) (Entry 8, Table 1): *N*-Benzyl-(3, 4, 5-trimethoxyphenyl)imine **1h** (0.1425 g, 0.500 mmol), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol) and ethyl 2-(tributylstannyl)acrylate **3a** (0.293 g, 0.750 mmol) were treated according to the general procedure described above to obtain crude amide **4h**. Crude amide **4h** was then dissolved in DMF (2 mL) and treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%) and sodium acetate (0.041 g, 0.500 mmol, 1 equiv) according to the general procedure described above, eluting with EtOAc/hexane (1 : 3) followed by trituration with EtOAc/hexane (1 : 39) to afford indenoisoquinoline **5h** (0.156 g, 64%) as a white powder: mp = 135-137 ºC (EtOAc/hexane); R_f = 0.40 (EtOAc/hexane 1 : 3); **^{1}H NMR** (500 MHz) 8.13 (dd, *J* = 7.5 Hz, 1.5 Hz, 1 H), 7.58-7.54 (m, 3 H), 7.46 (td, *J* = 7.5 Hz, 1.5 Hz, 1 H), 7.39-7.31 (m, 4 H), 5.88 (s, 1 H), 5.36 (s, 1 H), 5.12 (d, *J* = 14.0 Hz, 1 H), 4.92 (d, *J* =14.5 Hz, 1 H), 3.99 (ddd, *J* = 14.5 Hz, 7.5 Hz, 2.0 Hz, 2 H), 3.78 (s, 3 H), 3.70 (s, 3 H), 3.69 (d, *J* = 15.5 Hz, 1 H), 3.48 (s, 3 H), 3.50 (d, *J* = 15.5 Hz, 1 H),1.09 (t, *J* = 7.0 Hz, 3 H); **^{13}C NMR** (125 MHz) 172.0, 163.0, 153.5, 149.2, 141.3, 137.9, 137.0, 136.4, 132.2, 129.7, 129.5 (2 C), 128.7 (2 C), 128.6, 128.0, 127.9, 126.7, 121.8, 102.3, 67.3, 61.7, 60.8, 60.5, 57.2, 56.0, 52.7, 38.2, 13.9; **IR** (neat, cm^{-1}): 1728 (s),

1650 (s); **HRMS** (ES^+) Calcd for $C_{29}H_{30}NO_6$ ($M+H^+$), 488.2073, found 488.2088.

(6a*R*,11a*S*)-Ethyl 6-benzyl-9-(dimethylamino)-5-oxo-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-c]isoquinoline-11a-carboxylate (5i) (Entry 9, Table 1): *N*-Benzyl-(4-N, N-dimethylphenyl)imine **5i** (0.119 g, 0.500 mmol), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol) and ethyl 2-(tributylstannyl)acrylate **3a** (0.293 g, 0.750 mmol) were treated according to the general procedure described above to obtain crude amide **4i**. Crude amide **4i** was then dissolved in DMF (2 mL) and treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%) and sodium acetate (0.041 g, 0.5 mmol, 1 equiv) according to the general procedure described above, eluting with EtOAc/hexane (1 : 3) followed by trituration with EtOAc/hexane (1 : 39) to afford indenoisoquinoline **5i** (0.130 g, 59%) as a white powder: mp = 125-127 ºC (EtOAc/hexane); R_f = 0.43 (EtOAc/hexane 1 : 3); **^{1}H NMR** (500 MHz) 8.13 (dd, *J* = 8.0 Hz, 1.5 Hz, 1 H), 7.50-7.42 (m, 4 H), 7.36-7.30 (m, 4 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 6.43 (s, 1 H), 6.42 (d, *J* = 8.0 Hz, 1 H), 5.58 (d, *J* = 14.5 Hz, 1 H), 5.35 (s, 1 H), 4.57 (d, *J* = 14.5 Hz, 1 H), 3.87 (q, *J* = 14.5 Hz, 7.5 Hz, 1 H), 3.64 (d, *J* = 15.5 Hz, 1 H), 3.54 (d, *J* = 15.5 Hz, 1 H), 2.85 (s, 6 H), 3.70 (s, 1 H), 0.97 (t, *J* = 7.0 Hz, 3 H); **^{13}C NMR** (125 MHz) 172.4, 162.9, 150.9, 139.4, 137.5, 137.3, 132.0, 129.5, 129.0 (2 C), 128.6, 128.5 (3 C), 127.8, 127.6, 126.7, 123.5, 111.3, 108.1, 65.7, 61. 5, 57.4, 51.4, 42.2, 40.6 (2 C), 13.8; **IR** (neat, cm^{-1}): 1726 (s), 1650 (s); **HRMS** (ES^+) Calcd for $C_{28}H_{29}N_2O_3$ ($M+H^+$), 441.2178, found 441.2146.

(6a*S*,10a*S*)-Ethyl-6-benzyl-5-oxo-5,6,6a,10-tetrahydro-10aH-thieno[3',2':4,5]cyclopenta[1,2-c]isoquinoline-10a-carboxylate (5j) (Entry 10, Table

1): *N*-Benzyl-(thiophen-2-yl)imine **1j** (0.1005 g, 0.500 mmol), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol) and ethyl 2-(tributylstannyl)acrylate **3a** (0.293 g, 0.750 mmol) were treated according to the general procedure described above to obtain crude amide **5j**. Crude amide **5j** was then dissolved in DMF (2 mL) and treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%) and sodium acetate (0.041 g, 0.500 mmol, 1 equiv) according to the general procedure described above eluting with EtOAc/hexane (1 : 3). The resulting light yellow solid was recrystallized from EtOAc/hexane (1 : 19) to afford heterocycle **5j** (0.149 g, 74%) as white crystals: mp = 131-133 ºC (EtOAc/hexane); R_f = 0.50 (EtOAc/hexane 1 : 3); **^{1}H NMR** (500 MHz) □ 8.22 (d, *J* = 8.0 Hz, 1 H), 7.57 (d, *J* = 8.0 Hz, 1 H), 7.52-7.48 (m, 3 H), 7.40-7.33 (m, 4 H), 7.09 (d, *J* = 5.0 Hz, 1 H), 6.65 (d, *J* = 5.0 Hz, 1 H), 5.47 (s, 1 H), 5.38 (d, *J* = 14.5 Hz, 1 H), 4.68 (d, *J* = 14.5 Hz, 1 H), 4.00-3.96 (m, 2 H), 3.55 (dd, *J* = 26.0 Hz, 15.5 Hz, 2 H), 1.03 (t, *J* = 7.0 Hz, 3 H); **^{13}C NMR** (125 MHz) □ 171.9, 162.1, 141.9, 139.6, 137.4, 136.7, 132.2, 129.6, 129.2 (2 C), 128.7, 128.6 (2 C), 128.3, 128.0, 127.8, 126.6, 121.8, 63.6, 61.7, 60.5, 50.5, 39.9,13.8; **IR** (neat, cm^{-1}): 1728 (s), 1650 (s); **HRMS** (ES^+) Calcd for $C_{24}H_{22}NO_3S$ ($M+H^+$), 404.1320, found 404.1324.

(6a*R*,11a*S*)-Ethyl 6-benzyl-3-methoxy-9-methyl-5-oxo-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-c]isoquinoline-11a-carboxylate (5k) (Entry 1, Table 2): *N*-Benzyl-(4-tolyl)imine **1b** (0.105 g, 0.500 mmol), 2-bromo-5-methoxybenzoyl chloride **2c** (0.149 g, 0.600 mmol) and ethyl 2-(tributylstannyl)acrylate **3a** (0.293 g, 0.750 mmol) were treated according to the general procedure described above to obtain crude amide **4k**. Crude amide **4k** was then dissolved in DMF (2 mL) and treated with $Pd(OAc)_2$ (0.0056 g, 0.025

mmol, 5 mol%) and sodium acetate (0.041 g, 0.500 mmol, 1 equiv) according to the general procedure described above, eluting with EtOAc/hexane (1 : 3) followed by trituration with EtOAc/hexane (1 : 39) to afford indenoisoquinoline **5k** (0.137 g, 62%) as a white solid: mp = 122-124 ºC (EtOAc/hexane); R_f = 0.47 (EtOAc/hexane 1 : 3); **^{1}H NMR** (500 MHz) 7.63 (d, *J* = 3.0 Hz, 1 H), 7.47 (d, *J* = 6.5 Hz, 2 H), 7.41 (d, *J* = 8.5 Hz, 1 H), 7.37-7.30 (m, 3 H), 6.98 (dd, *J* = 8.0 Hz, 3.0 Hz, 1 H), 6.88 (s, 1 H), 6.87-6.83 (m, 2 H), 5.56 (d, *J* = 14.5 Hz, 1 H), 5.37 (s, 1 H), 4.62 (d, *J* = 14.5 Hz, 1 H), 3.91-3.86 (m, 2 H), 3.79 (s, 3 H), 3.57 (dd, *J* = 32.0 Hz, 15.5 Hz, 2 H), 2.22 (s, 3 H), 0.99 (t, *J* = 7.0 Hz, 3 H); **^{13}C NMR** (125 MHz) 172.5, 162.8, 159.1, 138.1, 138.0, 137.3, 130.7, 129.1 (3 C), 128.9, 128.5 (2 C), 128.1, 127.9, 127.7, 125.1, 122.6, 119.8, 111.4, 66.0, 61.5, 56.8, 55.3, 51.8, 41.7, 21.2, 13.8; **IR** (neat, cm^{-1}): 1726 (s), 1649 (s); **HRMS** (ES^+) Calcd for $C_{28}H_{28}NO_4$ ($M+H^+$), 442.2018, found 442.2032.

(6a*R*,11a*S*)-Ethyl 6-benzyl-3,4-difluoro-9-methoxy-5-oxo-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-c]isoquinoline-11a-carboxylate (5l) (Entry 2, Table 2): *N*-Benzyl-(4-methoxyphenyl)imine **1a** (0.1125 g, 0.500 mmol), 2-bromo-4,5-difluorobenzoyl chloride **2b** (0.153 g, 0.600 mmol) and ethyl 2-(tributylstannyl)acrylate **3a** (0.293 g, 0.750 mmol) were treated according to the general procedure described above to obtain crude amide **4l**. Crude amide **4l** was then dissolved in DMF (2 mL) and treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%) and sodium acetate (0.041 g, 0.500 mmol, 1 equiv) according to the general procedure described above, eluting with EtOAc/hexane (1 : 3). The resulting white solid was recrystallized from EtOAc/hexane (1 : 19) to afford indenoisoquinoline **5l** (0.175 g, 76%) as a white solid: mp = 133-135 ºC (EtOAc/hexane); R_f = 0.47

(EtOAc/hexane 1 : 3); **^{1}H NMR** (500 MHz) □ 7.92 (t, *J* = 9.5 Hz, 1 H), 7.43 (d, *J* = 6.5 Hz, 2 H), 7.37-7.27 (m, 4 H), 6.82 (d, *J* = 8.5 Hz, 1 H), 6.62 (s, 1 H), 6.61 (d, *J* = 8.0 Hz, 1 H), 5.51 (d, *J* = 14.5 Hz, 1 H), 5.36 (s, 1 H), 4.57 (d, *J* = 14.5 Hz, 1 H), 3.93-3.86 (m, 2 H), 3.70 (s, 3 H), 3.62 (d, *J* = 15.5 Hz, 1 H), 3.42 (d, *J* = 15.5 Hz, 1 H), 1.01 (t, *J* = 7.0 Hz, 3 H); **^{13}C NMR** (125 MHz) □ 171.4, 161.1, 160.1, 153.8, 152.6 (dd, $J_{C\text{-}F}$ = 253.7 Hz, 13.7 Hz), 149.5 (dd, $J_{C\text{-}F}$ = 248.8 Hz, 12.5 Hz), 139.0, 137.0, 134.5 (q, $J_{C\text{-}F}$ = 2.25 Hz), 132.4, 129.0 (2 C), 128.7 (2 C), 127.0 (q, $J_{C\text{-}F}$ = 1.75 Hz), 123.7, 117.8 (d, $J_{C\text{-}F}$ = 18.5 Hz), 116.2 (d, $J_{C\text{-}F}$ = 18.5 Hz), 113.1, 110.1, 65.8, 62.0, 57.4, 55.3, 51.7, 42.0, 13.7; **IR** (neat, cm^{-1}): 1730 (s), 1654 (s); **HRMS** (ES$^+$) Calcd for $C_{27}H_{24}F_2NO_4$ (M+H$^+$), 464.1673, found 464.1671.

6a*S*,11a*R*)-6-Benzyl-9-methoxy-11a-methyl-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-c]isoquinolin-5-one (5m) (Entry 3, Table 2): *N*-Benzyl-(4-methoxyphenyl)imine **1a** (0.1125 g, 0.500 mmol), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol) and tributyl(prop-1-en-2-yl)stannane **3b** (0.248 g, 0.750 mmol) were treated according to the general procedure described above to obtain crude amide **4m**. Crude amide **4m** was then dissolved in DMF (2 mL) and treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%) and sodium acetate (0.041g, 0.500 mmol, 1 equiv) according to the general procedure described above, eluting with EtOAc/hexane (1 : 3) followed by trituration with hexane to afford indenoisoquinoline **5m** (0.126 g, 68%) as a white solid: mp = 129-131 ºC (hexane); R_f = 0.47 (EtOAc/hexane 1 : 3); **^{1}H NMR** (400 MHz) □ 8.10 (dd, *J* = 8.0 Hz, 3.0 Hz, 1 H), 7.43-7.37 (m, 3 H), 7.35-7.30 (m, 4 H), 7.23 (t, *J* = 8.0 Hz, 1 H), 7.05 (d, *J* = 14.0 Hz, 1 H), 6.61 (d, *J* = 6.8 Hz, 1 H), 6.60 (s, 1 H), 5.94 (d, *J* = 14.0 Hz, 1 H), 4.57

(s, 1 H), 4.28 (d, *J* = 14.4 Hz, 1 H), 3.69 (s, 3 H), 3.45 (d, *J* = 15.6 Hz, 1 H), 2.96 (d, *J* = 15.6 Hz, 1 H), 1.24 (s, 3 H); **^{13}C NMR** (125 MHz) □ 163.1, 159.5, 144.0, 141.4, 137.3, 134.6, 132.1, 128.7 (2 C), 128.6 (2 C), 128.5, 128.3, 127.7, 126.7, 125.0, 123.3, 112.2, 110.1, 68.0, 55.2, 50.7, 48.8, 44.0, 26.5; **IR** (neat, cm^{-1}): 1647 (s); **HRMS** (ES$^+$) Calcd for $C_{25}H_{24}NO_2$ (M+H$^+$), 370.1807, found 370.1808.

(6a*R*,11a*S*)-6-Benzyl-9-methoxy-11a-phenyl-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-c]isoquinolin-5-one (5n) (Entry 4, Table 2): *N*-Benzyl-(4-methoxyphenyl)imine **1a** (0.1125 g, 0.500 mmol), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol) and tributyl(1-phenylvinyl)stannane **3c** (0.295 g, 0.750 mmol) were treated according to the general procedure described above to obtain crude amide **4n**. Crude amide **4n** was then dissolved in DMF (2 mL) and treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%) and sodium acetate (0.041 g, 0.500 mmol, 1 equiv) according to the general procedure described above, eluting with EtOAc/hexane (1 : 4) followed by trituration with hexane to afford indenoisoquinoline **5n** (0.127 g, 59%) as a white solid: mp = 178-180 ºC (hexane); R_f = 0.47 (EtOAc/hexane 1 : 4); **^{1}H NMR** (500 MHz) □ 8.18 (d, *J* = 7.5 Hz, 1 H), 7.46-7.39 (m, 1 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 7.32 (t, *J* = 7.5 Hz, 1 H), 7.15-7.12 (m, 2 H), 7.07 (dd, *J* = 15.5 Hz, 8.0 Hz, 4 H), 7.02-6.99 (m, 3 H), 6.93 (d, *J* = 8.0 Hz, 2 H), 6.66 (s, 1 H), 6.64 (d, *J* = 9.0 Hz, 1 H), 5.73 (d, *J* = 14.5 Hz, 1 H), 5.11 (s, 1 H), 4.32 (d, *J* = 14.5 Hz, 1 H), 3.74 (s, 2 H), 3.72 (s, 3 H); **^{13}C NMR** (125 MHz) □ 163.3, 159.8, 143.4, 141.6, 140.8, 136.4, 133.7, 132.2, 129.9, 128.7 (2 C), 128.4 (2 C), 128.3 (2 C), 128.2 (2 C), 127.3, 127.2, 127.1 (2 C), 126.9, 126.8, 123.4, 112.6, 110.0, 56.6, 55.3, 50.9, 44.1; **IR** (neat, cm^{-1}): 1650 (s); **HRMS** (ES$^+$) Calcd for $C_{30}H_{26}NO_2$ (M+H$^+$), 432.1964,

found 432.1976.

(6a*S*,11a*R*)-6-Benzyl-9,11a-dimethyl-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-c]isoquinolin-5-one (5o) (Entry 5, Table 2): *N*-Benzyl-(4-tolyl)imine **1a** (0.105 g, 0.500 mmol), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol) and tributyl(prop-1-en-2-yl)stannane **3b** (0.248 g, 0.750 mmol) were treated according to the general procedure described above to obtain crude amide **4o**. Crude amide **4o** was then dissolved in DMF (2 mL) and treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%) and sodium acetate (0.041 g, 0.500 mmol, 1 equiv) according to the general procedure described above, eluting with EtOAc/hexane (1 : 4) to afford indenoisoquinoline **5o** (0.095 g, 54%) as a white waxy solid: mp = 63 ºC; R_f = 0.50 (EtOAc/hexane 1 : 3); **^{1}H NMR** (400 MHz) □ 8.07 (dd, *J* = 8.0 Hz, 1.5 Hz, 1 H), 7.40-7.37 (m, 3 H), 7.35-7.27 (m, 4 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.02 (d, *J* = 7.8 Hz, 1 H), 6.88-6.84 (m, 2 H), 5.95 (d, *J* = 14.4 Hz, 1 H), 4.55 (s, 1 H), 4.25 (d, *J* = 14.4 Hz, 1 H), 3.43 (d, *J* = 15.2 Hz, 1 H), 2.92 (d, *J* = 15.6 Hz, 1 H), 2.19 (s, 3 H), 1.21 (s, 3 H); **^{13}C NMR** (125 MHz) □ 163.2, 144.1, 139.9, 139.6, 137.5, 137.3, 132.1, 128.8 (2 C), 128.6 (3 C), 128.4, 127.7, 127.5, 126.7, 125.0, 124.9, 122.3, 68.2, 50.8, 48.7, 43.8, 26.6, 21.2; **IR** (neat, cm^{-1}): 1647 (s); **HRMS** (ES^+) Calcd for $C_{25}H_{24}NO$ ($M+H^+$), 354.1858, found 354.1868.

General Procedure for the Preparation of Indenoisoquinolines 5a, 5c and 5d via the Method B described in Table 1.

To a solution of imine (0.500 mmol, 1 equiv) and 2-bromobenzoyl chloride (0.600 mmol, 1.2 equiv) in acetonitrile (2 mL) was added CuCl (0.100 mmol, 20 mol%). A solution of

tributylvinyltin (0.75 mmol, 1.5 equiv) in methylene chloride (4 mL) was added, and the reaction mixture was heated to 45 °C for 6 h. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (10 mL). Solid KF (2 equiv) and a few drops of water were added and the mixture was stirred for 20 minutes. The resulting suspension was filtered through celite/silica and the filtrate was concentrated in vacuo and dried to give crude amides **4**. $Pd(OAc)_2$ (0.025 mmol, 5 mol%), sodium carbonate (0.500 mmol, 1 equiv) and tetra-*n*-butylammonium chloride (0.500 mmol, 1 equiv) were added into a screw-cap sealed tube, followed by the solution of crude amide **4** in DMF (2 mL), and an argon atmosphere was established in the reaction vessel. The reaction mixture in the screw-capped sealed tube was stirred at 120 °C for 36 h. The reaction mixture was then diluted with ethyl acetate and the organic layer was washed two times with brine. The organic layer was dried ($MgSO_4$) and filtered through a celite/silica pad and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography over silica eluting with ethyl acetate/hexanes (1 : 3) followed by recrystallization from ethyl acetate/hexane or trituration with hexane to afford the corresponding indenoisoquinolines **5**.

(6a*R*,11a*S*)-Ethyl 6-benzyl-9-methoxy-5-oxo-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-c]isoquinoline-11a-carboxylate (5a) (Entry 1, Table 1 via Method B): *N*-Benzyl-(4-methoxyphenyl)imine **1a** (0.113 g, 0.500 mmol), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol) and ethyl 2-(tributylstannyl)acrylate **3a** (0.293 g, 0.750 mmol) were treated according to the general procedure described above to obtain crude amide **4a**. Crude amide **4a** was then dissolved in DMF (2 mL) and treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%), sodium carbonate (0.053 g, 0.5 mmol, 1 equiv) and tetra-*n*-

butylammonium chloride (0.139 g, 0.5 mmol, 1 equiv) according to the general procedure described above, eluting with EtOAc/hexane (1 : 3) followed by trituration with hexane to afford indenoisoquinoline **5a** (0.151 g, 71%) as a white powder.

(6a*R*,11a*S*)-Ethyl 6-benzyl-5-oxo-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-c]isoquinoline-11a-carboxylate (5c) (Entry 3, Table 1 via Method B: *N*-Benzyl-phenylimine **1c** (0.0975 g, 0.500 mmol), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol) and ethyl 2-(tributylstannyl)acrylate **3a** (0.293 g, 0.750 mmol) were treated according to the general procedure described above to obtain crude amide **4c**. Crude amide **4c** was then dissolved in DMF (2 mL) and treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%), sodium carbonate (0.053 g, 0.500 mmol, 1 equiv) and tetra-*n*-butylammonium chloride (0.139 g, 0.500 mmol, 1 equiv) according to the general procedure described above, eluting the column with EtOAc/hexane (1 : 3) followed by trituration with hexane to afford indenoisoquinoline **5c** (0.034 g, 17 %) as a white powder.

(6a*R*,11a*S*)-Ethyl 6-benzyl-9-chloro-5-oxo-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-c]isoquinoline-11a-carboxylate (5d). (Entry 4, Table 1 via Method B): *N*-Benzyl-(4-chlorophenyl)imine **1d** (0.1145 g, 0.500 mmol), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol) and ethyl 2-(tributylstannyl)acrylate **3a** (0.293 g, 0.750 mmol) were treated according to the general procedure described above to obtain crude amide **4d**. Crude amide **4d** was then dissolved in DMF (2 mL) and treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%), sodium carbonate (0.053 g, 0.500 mmol, 1 equiv) and tetra-*n*-butylammonium chloride (0.139 g, 0.500 mmol, 1 equiv) according to the general procedure described above, eluting with EtOAc/hexane (1 : 4) followed by trituration

with hexane to afford indenoisoquinoline **5d** (0.024 g, 11 %) as a white powder.

***N*-Benzyl-2-bromo-*N*-(1-(4-methoxyphenyl)-3-phenylprop-2-ynyl)benzamide (7a) via the procedure described in Scheme 2:** A solution of *N*-benzyl-(4-methoxyphenyl)imine **1a** (0.225 g, 1.00 mmol, 1 equiv), 2-bromobenzoyl chloride **2a** (0.260 g, 1.20 mmol, 1.2 equiv) and phenyl acetylene **6a** (0.151 g, 1.500 mmol, 1.5 equiv) in acetonitrile (4 mL) was added to a suspension of CuCl (0.0198 g, 0.200 mmol, 20 mol%) in acetonitrile (4 mL) immediately followed by the addition of neat diisopropylamine (0.260 mL, 1.500 mmol, 1.5 equiv). The resulting bright yellow slurry was vigorously stirred for 1 h at room temperature. The reaction mixture was diluted with ethyl acetate (20 mL), filtered through a celite/silica pad and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography eluting with EtOAc/hexane (1 : 5) to afford amide **7a** (0.095 g, 54%) as an off-white fluffy solid: mp = 64-66 ^{o}C (hexane); R_f = 0.43 (EtOAc/hexane 1 : 4); **^{1}H NMR** (400 MHz) (the spectra represents amide rotamers rapidly interconverting at room temperature. The major rotamer is represented.) □ 7.68 (br d, *J* = 7.6 Hz, 1 H), 7.66-7.60 (m, 1 H), 7.50 (d, *J* = 8.8 Hz, 1 H), 7.43 (br t, *J* = 8.0 Hz, 1 H), 7.36-7.29 (m, 7 H), 7.27 (d, *J* = 6.4 Hz, 1 H), 7.11-7.03 (br m, 4 H), 6.93 (d, *J* = 7.2 Hz, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 5.79 (s, 0.3 H), 5.68 (s, 0.7 H), 4.73 (d, *J* = 16.8 Hz, 0.5 H), 4.41 (d, *J* = 16.8 Hz, 1.5 H), 3.75 (s, 2 H), 3.69 (s, 1 H); **^{13}C NMR** (125 MHz) □ 169.9 (169.5), 169.3, 159.6 (159.5), 137.7 (138.1), 133.3, 131.6 (131.5)(2 C), 130.6 (130.5), 129.8 (130.0) (2 C), 128.6 (2 C), 128.3 (2 C), 128.1, 127.9 (2 C), 127.5, 127.1, 126.8, 126.6, 122.0 (122.0), 119.4 (119.7), 113.8 (113.9) (2 C), 87.7 (87.9), 85.3 (85.2), 55.6, 55.3, 45.9 (46.7) signals for the minor

rotamer are given in parentheses; **IR** (neat, cm^{-1}): 1643 (s); **HRMS** (ES^+) Calcd for $C_{30}H_{25}BrNO_2$ ($M+H^+$), 510.1069, found 510.1066.

6-Benzyl-9-methoxy-11-phenyl-6,11-dihydro-5*H*-indeno[1,2-c]isoquinolin-5-one (8a) via the from 7a via the procedure described Scheme 2: To a screw-cap sealable tube was added $Pd(OAc)_2$ (0.0015 g, 0.0065 mmol, 5 mol%), sodium carbonate (0.011 g, 0.13 mmol, 1 equiv), and tetra-*n*-butylammonium chloride (0.036 g, 0.13 mmol, 1 equiv) followed by a solution of amide **7a** (0.066 g, 0.13 mmol, 1 equiv) in DMF (2 mL) under argon. The reaction mixture in the screw-capped sealed tube was stirred at 120 °C for 36 h. The reaction mixture was then diluted with ethyl acetate (25 mL) and the organic layer was washed three times with brine. The organic layer was dried ($MgSO_4$), filtered through a celite/silica pad and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography over silica eluting with ethyl acetate/hexanes (1 : 4) followed by trituration with hexane to afford indenoisoquinoline **8a** (0.051 g, 91%) as a white solid: mp = 209-211 °C (hexane); R_f = 0.40 (EtOAc/hexane 1 : 4); **^{1}H NMR** (500 MHz) □ 8.48 (d, *J* = 8.0 Hz, 1 H), 7.48-7.44 (m, 2 H), 7.37 (t, *J* = 7.5 Hz, 2 H), 7.33 (d, *J* = 7.2 Hz, 2 H), 7.30-7.28 (m, 3 H), 7.27-7.24 (m, 3 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 6.82 (s, 1 H), 6.70 (dd, *J* = 8.5 Hz, 2.5 Hz, 1 H), 5.92 (dd, *J* = 26.0 Hz, 17.0 Hz, 2 H), 5.01 (s, 1 H), 3.71 (s, 3 H); **^{13}C NMR** (125 MHz) □ 163.6, 159.4, 151.8, 141.9, 140.3, 136.7, 134.4, 132.4, 129.2, 129.1 (2 C), 128.9 (2 C), 128.6, 127.8 (2 C), 127.2, 127.1, 125.8 (2 C), 125.7, 123.9, 123.0, 122.6, 120.0, 112.6, 111.5, 55.4, 51.5, 47.9; **IR** (neat, cm^{-1}): 1647 (s), 1608 (s); **HRMS** (ES^+) Calcd for $C_{30}H_{24}NO_2$ ($M+H^+$), 430.1807, found 430.1789.

General Procedure for the Preparation of Indenoisoquinolines 8a-e described in Table 3. A solution of imine (0.500 mmol, 1 equiv), 2-bromobenzoyl chloride (0.600

mmol, 1.2 equiv) and phenyl acetylene (0.750 mmol, 1.5 equiv) in acetonitrile (3 mL) was added to a suspension of solid CuCl (0.100 mmol, 20 mol%) in acetonitrile (3 mL) followed by the addition of diisopropylamine (0.750 mmol, 1.5 equiv). The resulting bright yellow slurry was vigorously stirred for 1 h at room temperature. The reaction mixture was then diluted with ethyl acetate (20 mL), filtered through a celite/silica pad and the filtrate was concentrated in vacuo. Then the crude product was purified via a filtration through a short silica plug eluting with EtOAc/hexane (1 : 19) followed by EtOAc/hexane (1 : 4) removing the excess alkynes to afford the crude amides **7**. To a screw-cap sealable tube was added $Pd(OAc)_2$ (0.025 mmol, 5 mol%), sodium carbonate (0.500 mmol, 1 equiv) and tetra-*n*-butylammonium chloride (0.500 mmol, 1 equiv) followed by a solution of the crude amide **7** in DMF (2 mL) under argon. The reaction mixture in the screw-capped sealed tube was stirred at 120 °C for 36 h. The reaction mixture was then diluted with ethyl acetate (25 mL) and the organic layer was washed three times with brine. The organic layer was dried ($MgSO_4$), filtered through a celite/silica pad and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography over silica eluting with ethyl acetate/hexanes (1 : 4) followed by recrystallization with ethyl acetate/hexane or trituration with hexane to afford the corresponding indenoisoquinolines **8**.

6-Benzyl-9-methoxy-11-phenyl-6,11-dihydro-5*H*-indeno[1,2-c]isoquinolin-5-one (8a) (Entry 1, Table 3): A solution of *N*-benzyl-(4-methoxyphenyl)imine **1a** (0.1125 g, 0.500 mmol, 1 equiv), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol, 1.2 equiv) and phenyl acetylene **6a** (0.750 mmol, 1.5 equiv) in acetonitrile (3 mL) was treated with CuCl (0.1 mmol, 20 mol%) in acetonitrile (3 mL) and diisopropylamine (0.130 mL, 0.750

mmol, 1.5 equiv) according to the procedure described above. The resulting crude amide **7a** was then treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%), sodium carbonate (0.053 g, 0.500 mmol, 1 equiv) and tetra-*n*-butylammonium chloride (0.139 g, 0.500 mmol, 1 equiv) following the procedure described above to afford the crude indenoisoquinoline **8a**. The crude product was purified by flash column chromatography eluting with EtOAc/hexane (1 : 4) to afford a yellow oil, which was triturated with hexane to provide indenoisoquinoline **8a** (0.142 g, 66%) as an off-white solid: Analytical data for compound **8a** is presented above.

6-Benzyl-9-methyl-11-phenyl-6,11-dihydro-5*H*-indeno[1,2-c]isoquinolin-5-one (8b) (Entry 2, Table 3): A solution of *N*-benzyl-(4-tolyl)imine **1b** (0.105 g, 0.500 mmol, 1 equiv), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol, 1.2 equiv) and phenyl acetylene **6a** (0.0757 g, 0.750 mmol, 1.5 equiv) in acetonitrile (3 mL) was treated with CuCl (0.100 mmol, 20 mol%) in acetonitrile (3 mL) and diisopropylamine (0.130 mL, 0.750 mmol, 1.5 equiv) according to the procedure described above. The resulting crude amide **7b** was treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%), sodium carbonate (0.053 g, 0.500 mmol, 1 equiv) and tetra-*n*-butylammonium chloride (0.139 g, 0.500 mmol, 1 equiv) according to the procedure described above to afford the crude indenoisoquinoline **8b**. The crude product was purified by flash chromatography eluting with EtOAc/hexane (1 : 4). The resulting yellow oil was triturated with hexane to afford indenoisoquinoline **8b** (0.105 g, 51%) as a white powder: mp = 243-245 ºC (hexane); R_f = 0.40 (EtOAc/hexane 1 : 4); **^{1}H NMR** (500 MHz) □ 8.42 (d, *J* = 7.5 Hz, 1 H), 7.50-7.38 (m, 2 H), 7.31 (t, *J* = 8.5 Hz, 1 H), 7.28-7.17 (m, 9 H), 7.12 (d, *J* = 7.5 Hz, 2 H), 7.01 (s, 1 H), 6.91 (d, *J* = 8.0 Hz, 1 H), 5.83 (dd, *J* = 31.0 Hz, 16.5 Hz, 2 H), 4.95 (s, 1 H), 2.19

(s, 3 H); **^{13}C NMR** (125 MHz) □ 163.6, 149.8, 141.9, 140.3, 137.6, 136.7, 134.4, 133.2, 132.4, 129.2, 129.1 (2 C), 128.9 (2 C), 128.2, 127.8 (2 C), 127.2, 126.0, 125.9 (4 C), 124.3, 123.2, 121.6, 120.9, 51.5, 47.9, 21.3; **IR** (neat, cm^{-1}): 1647 (s); **HRMS** (ES^+) Calcd for $C_{30}H_{24}NO$ ($M+H^+$), 414.1858, found 414.1844.

6-Benzyl-10-phenyl-6,10-dihydro-5*H*-thieno[3',2':4,5]cyclopenta[1,2-*c*]isoquinolin-5-one (8c) (Entry 3, Table 3): A solution of *N*-benzyl-(thiophen-2-yl)imine **1j** (0.1005 g, 0.500 mmol), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol, 1.2 equiv) and phenyl acetylene **6a** (0.757 g, 0.075 mmol, 1.5 equiv) in acetonitrile (3 mL) was treated with CuCl (0.1 mmol, 20 mol%) in acetonitrile (3 mL) and diisopropylamine (0.130 mL, 0.750 mmol, 1.5 equiv) according to the procedure described above. The resulting crude amide **7c** was treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%), sodium carbonate (0.053g, 0.500 mmol, 1 equiv) and tetra-*n*-butylammonium chloride (0.139 g, 0.500 mmol, 1 equiv) according to the procedure described above to afford the crude heterocycle **8c**. The crude product was purified by flash chromatography eluting with EtOAc/hexane (1 : 4). The resulting white solid was recrystallized from EtOAc/hexane (1 : 19) to afford heterocycle **8c** (0.138 g, 68%) as white crystals: mp = 211-213 ºC (hexane); R_f = 0.43 (EtOAc/hexane 1 : 4); **^{1}H NMR** (500 MHz) □ 8.38 (d, *J* = 8.0 Hz, 1 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 7.27-7.23 (m, 3 H), 7.22-7.19 (m, 2 H), 7.18 (d, *J* = 7.5 Hz, 2 H), 7.16-7.12 (m, 4 H), 7.07 (d, *J* = 8.0 Hz, 2 H), 6.80 (d, *J* = 5.0 Hz, 1 H), 5.60 (s, 2 H), 4.86 (s, 1 H); **^{13}C NMR** (125 MHz) □ 162.8, 155.4, 140.5, 138.6, 136.0, 135.1, 134.8, 132.4, 129.3, 129.1 (2 C), 128.9, 128.6 (2 C), 127.6 (2 C), 127.4, 127.2, 126.7 (2 C), 125.3, 123.5, 122.3, 122.2, 121.8, 49.5, 49.1 **IR** (neat, cm^{-1}): 1645 (s); **HRMS** (ES^+) Calcd for $C_{27}H_{20}NOS$ ($M+H^+$), 406.1266, found 406.1260.

6-Benzyl-9-methoxy-11-p-tolyl-6,11-dihydro-5*H*-indeno[1,2-c]isoquinolin-5-one (8d) (Entry 4, Table 3): A solution of *N*-benzyl-(4-methoxyphenyl)imine **1a** (0.1005 g, 0.500 mmol), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol, 1.2 equiv) and *p*-tolyl acetylene **6b** (0.087 g, 0.750 mmol, 1.5 equiv) in acetonitrile (3 mL) was treated with CuCl (0.100 mmol, 20 mol%) in acetonitrile (3 mL) and diisopropylamine (0.130 mL, 0.750 mmol, 1.5 equiv) according to the procedure described above. The resulting crude amide **7d** was then treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%), sodium carbonate (0.053 g, 0.500 mmol, 1 equiv) and tetra-*n*-butylammonium chloride (0.139 g, 0.500 mmol, 1 equiv) according to the procedure described above to afford the crude indenoisoquinoline **8d**. The crude product was purified with flash chromatography eluting with EtOAc/hexane (1 : 3). The resulting white solid was triturated with hexane to afford indenoisoquinoline **8d** (0.139 g, 63%) as a white powder: mp = 185-187 ºC (hexane); R_f = 0.47 (EtOAc/hexane 1 : 3); **^{1}H NMR** (500 MHz) □ 8.49 (d, *J* = 8.0 Hz, 1 H), 7.49-7.46 (m, 2 H), 7.37 (t, *J* = 7.0 Hz, 1 H), 7.36 (d, *J* = 7.5 Hz, 2 H), 7.31-7.29 (m, 3 H), 7.27-7.25 (m, 1 H), 7.12–7.07 (m, 4 H), 6.83 (s, 1 H), 6.70 (dd, *J* = 8.5 Hz, 2.5 Hz, 1 H), 5.92 (dd, *J* = 27.0 Hz, 16.50 Hz, 2 H), 4.99 (s, 1 H), 3.72 (s, 3 H), 2.32 (s, 3 H); **^{13}C NMR** (125 MHz) □ 163.6, 159.4, 152.1, 141.7, 137.1, 136.8, 136.7, 134.5, 132.4, 129.8 (2 C), 129.1, 128.9 (2 C), 128.6, 127.6 (2 C), 127.1, 125.8 (2 C), 125.7, 123.9, 123.0, 122.6, 120.1, 112.5, 111.4, 55.4, 51.2, 47.8, 21.1; **IR** (neat, cm^{-1}): 1647 (s); **HRMS** (ES^+) Calcd for $C_{31}H_{26}NO_2$ ($M+H^+$), 444.1964, found 444.1956.

6-Benzyl-11-(4-fluorophenyl)-9-methoxy-6,11-dihydro-5*H*-indeno[1,2-c]isoquinolin-

5-one (8e) (Entry 5, Table 3): A solution of *N*-benzyl-(4-methoxyphenyl)imine **1a** (0.1005 g, 0.500 mmol), 2-bromobenzoyl chloride **2a** (0.130 g, 0.600 mmol, 1.2 equiv) and 1-ethynyl-4-fluorobenzene **6c** (0.090 g, 0.750 mmol, 1.5 equiv) in acetonitrile (3 mL) was treated with CuCl (0.100 mmol, 20 mol%) in acetonitrile (3 mL) and diisopropylamine (0.130 mL, 0.750 mmol, 1.5 equiv) according to the procedure described above. The resulting crude amide **7e** was then treated with $Pd(OAc)_2$ (0.0056 g, 0.025 mmol, 5 mol%), sodium carbonate (0.053 g, 0.500 mmol, 1 equiv) and tetra-*n*-butylammonium chloride (0.139 g, 0.500 mmol, 1 equiv) according to the procedure described above to afford the crude indenoisoquinoline **8e**. The crude product was purified by flash chromatography eluting with EtOAc/hexane (1 : 3). The resulting white solid was triturated with hexane to afford indenoisouqinoline **8e** (0.128 g, 57%) as a white powder: mp = 194-196 ºC (hexane); R_f = 0.47 (EtOAc/hexane 1 : 3); **^{1}H NMR** (500 MHz) □ 8.49 (d, *J* = 8.0 Hz, 1 H), 7.50-7.47 (m, 2 H), 7.39 (t, *J* = 8.0 Hz, 1 H), 7.36-7.33 (m, 2 H), 7.30-7.25 (m, 4 H), 7.16 (t, *J* = 7.0 Hz, 2 H), 7.00 (t, *J* = 8.5 Hz, 2 H), 6.80 (s, 1 H), 6.73 (dd, *J* = 8.0 Hz, 2.5 Hz, 1 H), 5.91 (q, *J* = 26.0 Hz, *J* = 16.5 Hz, 2 H), 4.99 (s, 1 H), 3.74 (s, 3 H); **^{13}C NMR** (125 MHz) □ 163.5, 161.9 (d, $J_{C\text{-}F}$ = 244.0 Hz), 159.5, 151.7, 141.9, 136.6, 135.9 (d, $J_{C\text{-}F}$ = 3.25 Hz), 134.3, 132.5, 129.3, 129.2 (2 C), 128.9 (2 C), 128.5, 127.2, 125.8 (3 C), 123.9, 122.8 (d, $J_{C\text{-}F}$ = 9.5 Hz, 2 C), 119.7, 116.0 (d, $J_{C\text{-}F}$ = 21.5 Hz, 2 C)), 112.6, 111.5, 55.4, 50.7, 47.8; **IR** (neat, cm^{-1}): 1647 (s); **HRMS** (ES^+) Calcd for $C_{30}H_{23}FNO_2$ ($M+H^+$), 448.1713, found 448.1722.

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X-ray Crystallographic Studies for $C_{24}H_{21}NO_3S$ (5j), $C_{30}H_{25}NO_2$ (5n) and $C_{27}H_{19}NOS$ (8c).

Colorless crystals of $C_{24}H_{21}NO_3S$ (**5j**) are, at 100(2) K, monoclinic, space group $P2_1/c$ – C_{2h}^5 (No. 14) (1) with **a** = 9.1318(5) Å, **b** = 12.3053(7) Å, **c** = 17.125(1) Å, β = 93.359(1)°, V = 1921.0(2) Å^3 and Z = 4 molecules {d_{calcd} = 1.395 g/cm^3; μ_a(MoKα) = 0.195 mm^{-1}}. Colorless crystals of $C_{30}H_{25}NO_2$ (**5n**) are, at 100(2) K, monoclinic, space group $P2_1/c$ – C_{2h}^5 (No. 14) with **a** = 10.1531(5) Å, **b** = 23.5585(11) Å, **c** = 9.4532(4) Å, β = 101.643(1)°, V = 2214.6(2) Å^3 and Z = 4 molecules {d_{calcd} = 1.294 g/cm^3; μ_a(MoKα) = 0.080 mm^{-1}}. Yellow plate-shaped crystals of $C_{27}H_{19}NOS$ (**8c**) are, at 100(2) K, triclinic, space group $P\bar{1}$ – C_i^1 (No. 2)[5] with **a** = 9.554(2) Å, **b** = 10.349(2) Å, **c** = 10.431(2) Å, α = 85.898(2)°, β = 79.880(3)°, γ = 78.751(3)° , V = 995.1(3) Å^3 and Z = 2 molecules {d_{calcd} = 1.353 g/cm^3; μ_a(MoKα) = 0.182 mm^{-1}}. Full hemispheres of diffracted intensities (1850 10-second frames with a ω scan width of 0.30°) were measured for single-domain specimens of **5j** and **5n** and a two-domain nonmerohedrally twinned specimen of **8c** using graphite-monochromated MoKα radiation (λ = 0.71073 Å) on a Bruker SMART

APEX CCD Single Crystal Diffraction System.[6] X-rays were provided for all three studies by a fine-focus sealed x-ray tube operated at 50kV and 30mA. Lattice constants were determined with the Bruker SAINT software package.[7] Since the major domain of **8c** accounted for 85% of the sample volume and very few reflections from the two domains overlapped, the structure of **8c** was solved and refined using just the data for the major domain.

Totals of 5590(**5j**), 6767(**5n**) and 5841(**8c**) unique integrated reflection intensities having 2□((MoK□)< 60.01°(**5j**), 2□((MoK□)< 61.07° (**5n**) or 61.11°(**8c**) resulted from the SAINT output; this represented a coverage which was 99.8% (**5j**), 99.8(**5n**) and 95.6%(**8c**) complete. The data for all three compounds were corrected empirically[8] for variable absorption effects using equivalent reflections; the relative transmission factors ranged from 0.938(**5j**), 0.928(**5n**) and 0.884 (**8c**) to 1.000. The Bruker software package SHELXTL was used to solve all three structures using "direct methods" techniques. All stages of weighted full-matrix least-squares refinement were conducted using F_o^2 data with the SHELXTL Version 6.10 software package.[9]

The final structural models for all three compounds incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. All hydrogen atoms were located in difference Fouriers and included in the structural model as independent isotropic atoms whose parameters were allowed to vary in least-squares refinement cycles.

For **5j**, a total of 346 parameters were refined using no restraints, 5590 data and weights of $w = 1/ [\sigma^2(F^2) + (0.0718\ P)^2 + 0.3424\ P]$, where $P = [F_o^2 + 2F_c^2] / 3$. Final agreement factors at convergence for **5j** are: R_1(unweighted, based on F) = 0.041 for

4943 independent absorption-corrected "observed" reflections having 2□(MoK□)< 60.01° and I>2□(I); R_1(unweighted, based on F) = 0.046 and wR_2(weighted, based on F^2) = 0.112 for all 5590 independent absorption-corrected reflections having 2□(MoK□)< 60.01°.

For **5n**, a total of 398 parameters were refined using no restraints, 6767 data and weights of w = 1/ [$\sigma^2(F^2)$ + (0.0817 P)^2 + 0.0895 P], where P = [F_o^2 + 2F_c^2] / 3. Final agreement factors at convergence for **5n** are: R_1(unweighted, based on F) = 0.043 for 5801 independent absorption-corrected "observed" reflections having 2□(MoK□)< 61.07° and I>2□(I); R_1(unweighted, based on F) = 0.049 and wR_2(weighted, based on F^2) = 0.122 for all 6767 independent absorption-corrected reflections having 2□(MoK□)< 61.07°.

For **8c**, a total of 347parameters were refined using no restraints, 5841 data and weights of or w = 1/ [$\sigma^2(F^2)$ + (0.0900 P)^2 + 0.4236 P] for **8c**, where P = [F_o^2 + 2F_c^2] / 3. Final agreement factors at convergence for **8c** are: R_1(unweighted, based on F) = 0.055 for 5312 independent absorption-corrected "observed" reflections having 2□(MoK□)< 61.11° and I>2□(I); R_1(unweighted, based on F) = 0.060 and wR_2(weighted, based on F^2) = 0.150 for all 5841 independent absorption-corrected reflections having 2□(MoK□)< 61.11°.

None of the compounds had shift/s.u. values greater than 0.000 in their final refinement cycles. The final difference maps for the three compounds had the following maxima and minima: 0.53 and -0.22 $e^-/Å^3$, for **5j**; : 0.45 and -0.22 $e^-/Å^3$, for **5n**; and 0.93 and -0.29 $e^-/Å^3$ for **8c**.

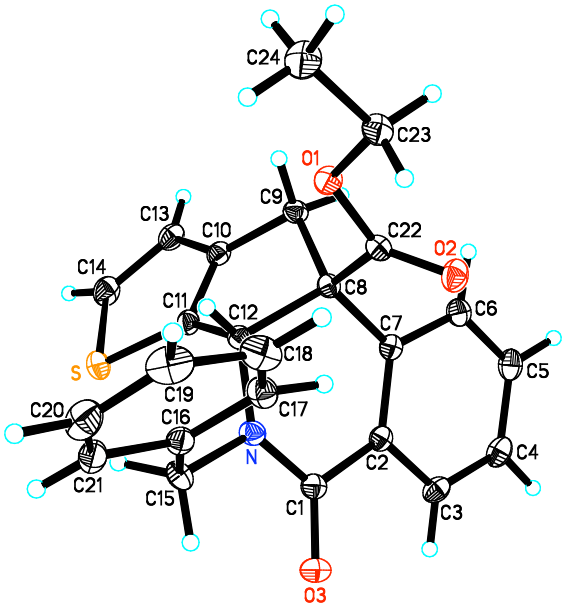


Figure S-1. Molecular structure of heterocycle **5j**. The thermal ellipsoids are drawn at 50% probability level.

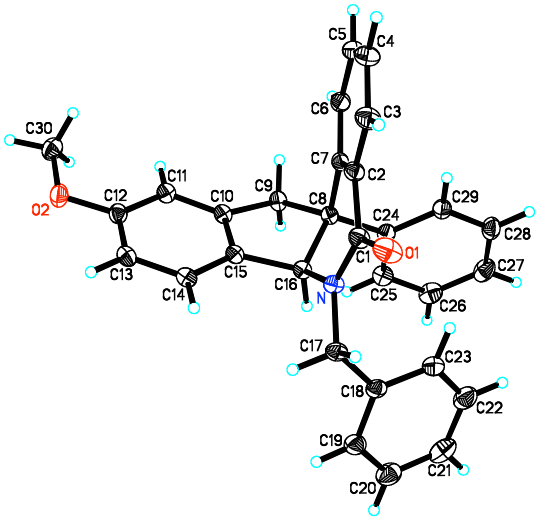


Figure S-2. Molecular structure of heterocycle **5n.** The thermal ellipsoids are drawn at

50% probability level.

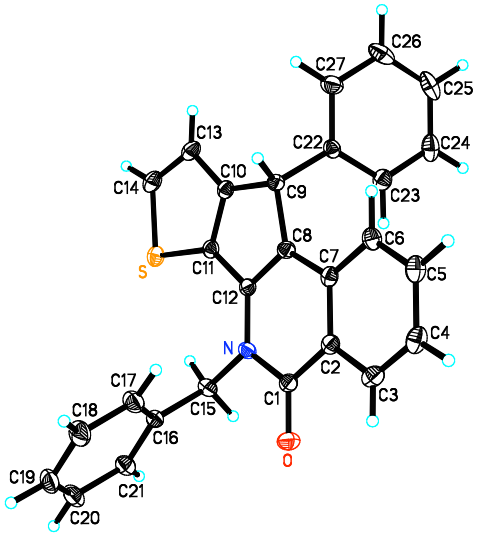


Figure S-3. Molecular structure of heterocycle **8c**. The thermal ellipsoids are drawn at 50% probability level.

Acknowledgment

The authors thank the National Science Foundation (grant CHE-0079282) and the University of Kansas for funds to purchase the x-ray instrument and computers.

References

5) International Tables for Crystallography, Vol A, 4th ed., Kluwer: Boston (1996).

6) Data Collection: SMART Software Reference Manual (1998). Bruker-AXS, 5465 E. Cheryl Parkway, Madison, WI 53711-5373 USA.

7) Data Reduction: SAINT Software Reference Manual (1998). Bruker-AXS, 6300 Enterprise Dr., Madison, WI 53719-1173, USA.

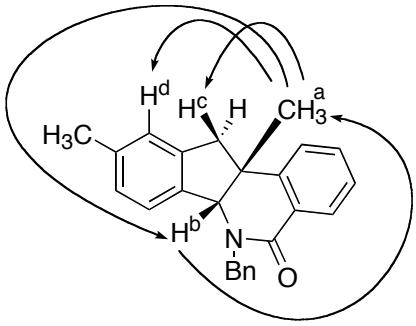
8) TWINABS Vers. 2008/1, Sheldrick, G.M. "Program for Absorption Correction of Twined Crystals", BRUKER AXS Inc., 5465 East Cheryl Parkway, Madison, WI 53711-5373 USA.

9) G. M. Sheldrick (2000). SHELXTL Version 6.10 Reference Manual. Bruker-AXS, 5465 E. Cheryl Parkway, Madison, WI 53711-5373 USA.

Structure Elucidation for the Single Diastereomers of Heterocycles 5, including the NOE studies on compound 5o.

The relative stereochemistry of the single diastereomers of isoquinolines **5a-i** and **5k-m** was assigned based on the analogy with the molecular structures of the heterocycle **5j** and **5n**, which were established via X-ray crystallographic analyses (vide supra). The analyses revealed that in both cases the hydrogen and the substituent (e.g. COOEt in **5j** and Ph in **5n**) at the ring junction were oriented *cis*.

To ascertain the relative stereochemistry of the indenoisoquinolines **5o** and **5m** bearing a methyl substituent at the ring junction, NOE ^{1}H NMR data were recorded for compound **5o**. Thus, irradiation of the signal for the methyl substituent at the ring junction (H^a 1.21 ppm (s, 3 H)) led to the enhancement in the signals of the proton at the ring junction (H^b 4.55 ppm (s, 1 H), one of the protons at the benzylic methylene group in the indene ring (H^c 2.92 (d, J = 15.6 Hz, 1 H)) and a weak increase in one signal in the aromatic region (H^d (7.35-7.27 ppm (m, 4 H)) (Figure S-4). Irradiation of the signal for the benzylic proton at the ring junction (H^b 4.55 ppm (s, 1 H)) resulted in the enhancement of the signal for the methyl group at the ring junction ((H^a 1.21 ppm (s, 3 H)) (Figure S-4). Thus, this data is consistent with the assignment of the relative stereochemistry for the indenoisoquinoline **5o** as shown in Table 2 and Figure S-4 with *the methyl group and hydrogen at the ring junction in the cis configuration*. The structure of the indenoisoquinoline **5m** (also bearing methyl substituent at the ring junction) was assigned in analogy to **5o**.



5o

NOE correlations

H^a (4.55 ppm (s, 1 H))

H^b (1.21 ppm (s, 3 H))

H^c (2.92 (d, J = 15.6 Hz, 1 H))

H^d (7.35-7.27 ppm (m, 4 H))

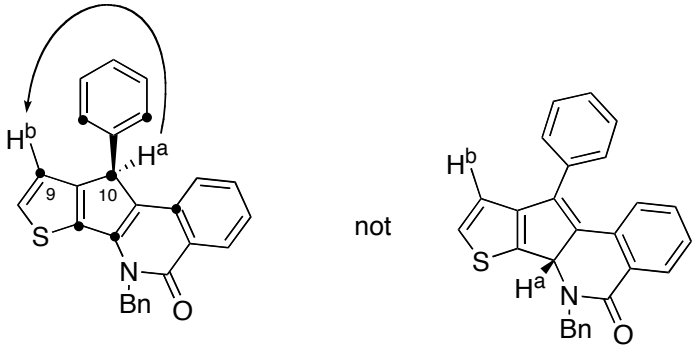
Figure S-4. NOE study on indenoisoquinoline **5o**

Structure Elucidation of the Single Diastereomers of Heterocycles 8, including 2D NMR and NOE studies on heterocycles 8c and 8d.

The goal of the structure elucidation studies was to establish the position of the double bond, whether it was in the five-membered ring of the indene, or at the ring junction. X-ray crystallographic analysis on the single crystals of the heterocycle **8c** established the position of the double bond at the ring junction (Figure S-5). Additional 2D NMR analyses (HSQC, HMBC) as well as NOE ^{1}H NMR studies were performed on heterocycles **8c** and **8d** to confirm that the double bond is positioned at the ring junction in the other members of the group of heterocycles **8** (Table 3).

To validate the protocol for the structure assignment, we have initially analyzed the spectral data for the heterocycle **8c**. The HSQC spectra indicated a cross peak

between 4.86 ppm (^{1}H NMR) and 49.5 ppm (^{13}C NMR) corresponding to the proton bonded to carbon C10 (Figure S-5). Inspection of the HMBC spectra revealed a series of three bond correlations **H**-C-C-**C** and a one-bond correlation between the proton at 4.86 ppm (H^a) and the carbons labeled with the black dot in the structure of **8c** in Figure S-5. These correlations include carbons signals at 122.3, 127.6 (2 C), 135.1, 138.6, 140.5 and 155.4. The DEPT spectra indicated that the signals at 135.1, 138.6, 140.5 and 155.4. represent quaternary carbons. The HSQC spectra indicated that carbons at 122.3 and 127.6 (2 C) are bonded to proton signals at 6.80 (d, J = 5.0 Hz, 1 H) (H^b) and 7.16-7.12 (m, 4 H), respectively. Only the C-H correlation between 122.3 ppm and 6.80 (d, J = 5.0 Hz, 1 H) could correspond to signals for carbon C9 and the corresponding proton H^b (Figure S-5). This correlation would NOT be present in the isomeric structure shown on the right (Figure S-5).



8c

NOE correlations

H^a (4.86 ppm (s, 1 H))

H^b (6.80 ppm (d, J = 5.0 Hz, 1 H))

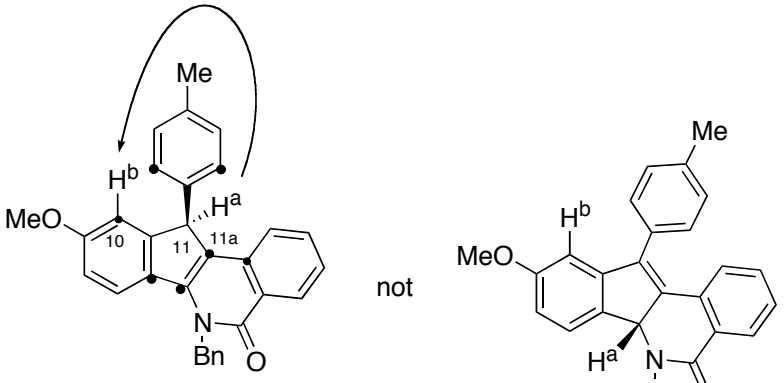
Figure S-5. NOE study on heterocycle **8c**

Next, we have recorded ^{1}H NMR NOE difference spectra, irradiating the proton H^{a} 4.86 ppm (s, 1 H) at C10. Enhancement of a signal for the proton H^{b} at 6.80 ppm (d, J = 5.0 Hz, 1 H) was observed. This data is in agreement with the structure of heterocycle **8c** as established by X-ray crystallographic analysis.

Next, an analogous protocol for structure elucidation was applied to the analysis of the 2D NMR and NOE data for indenoisoquinoline **8d**. Thus, the HSQC spectra indicated a cross peak between 4.99 ppm (^{1}H NMR) and 51.2 ppm (^{13}C NMR) corresponding to the proton bonded to carbon C11 (Figure S-6). Inspection of the HMBC spectra revealed a series of three bond correlations **H**-C-C-**C** and one two bond correlation (to carbon C 11a) between the proton at 4.99 ppm and the carbons labeled with the black dot in the structure of **8d** in Figure S-6. These correlations include carbons signals at 111.4, 120.1, 127.6 (2 C), 137.1, 141.7 and 152.1. The DEPT spectra indicated that the signals at 120.1, 137.1, 141.7 and 152.1 represent quaternary carbons. The HSQC spectra indicated that the carbons at 111.4 ppm and 127.6 (2 C) are bonded to proton signals at 6.83 (s, 1 H) and 7.12-7.07 (m, 4 H), respectively. Only the C-H correlation between 111.4 ppm and 6.83 (s, 1 H) could correspond to the signal for the carbon C10 and the corresponding proton H^{b} (Figure S-6). This correlation would NOT be present in the isomeric structure shown on the right (Figure S-6).

Next, we have recorded ^{1}H NMR NOE difference spectra, irradiating the proton H^{a} 4.99 ppm (s, 1 H) at C11. Enhancement of a signal for the proton H^{b} at 6.83 (s, 1 H) was observed. This data is in agreement with the structure of heterocycle **8d** as shown on the left side of Figure S-6, which analogous to the structure of heterocycle **8c**. This NOE correlation would NOT be present in the isomeric structure shown on the right due to the

distance between the protons H^a and H^b.



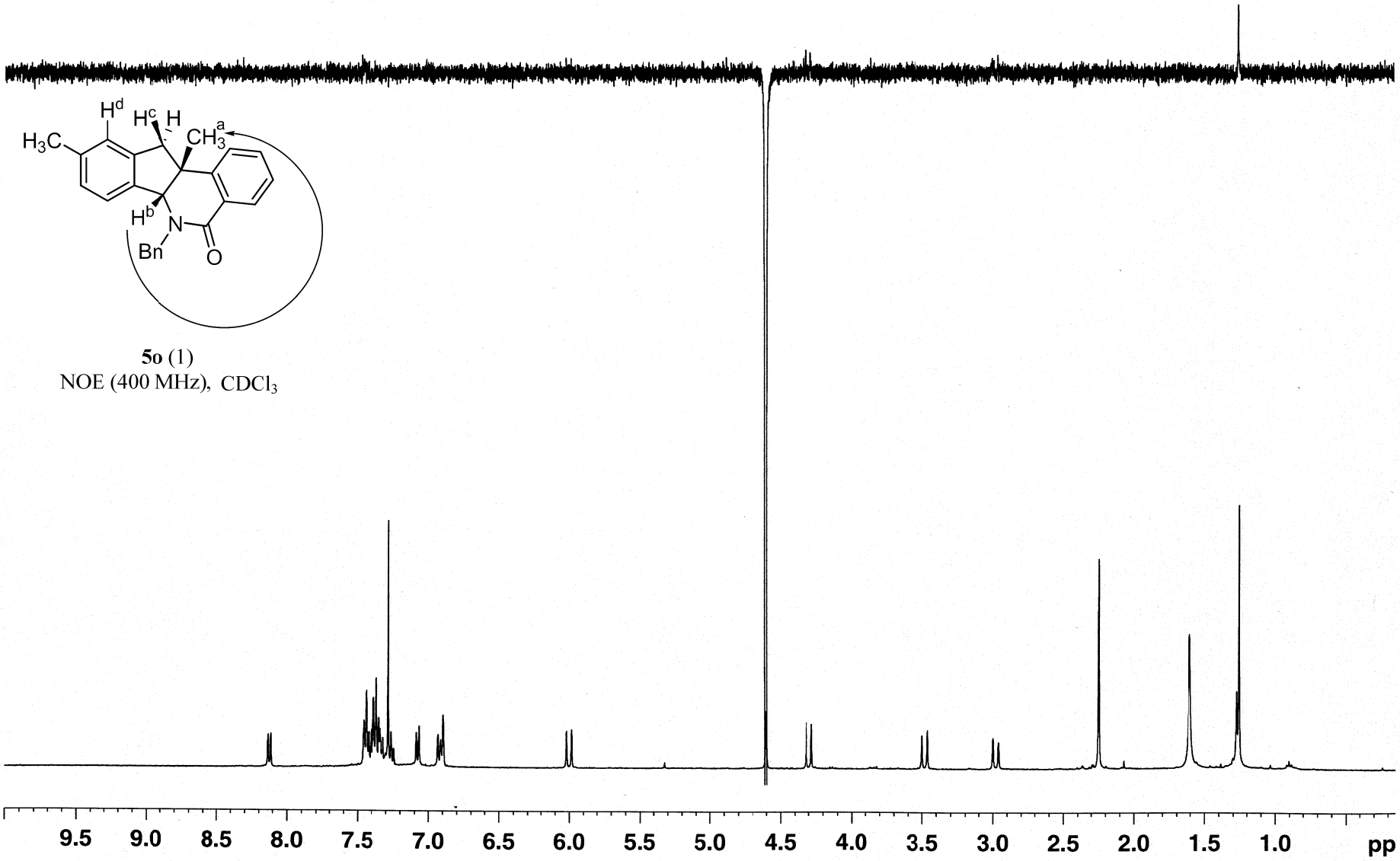
8d

NOE correlations

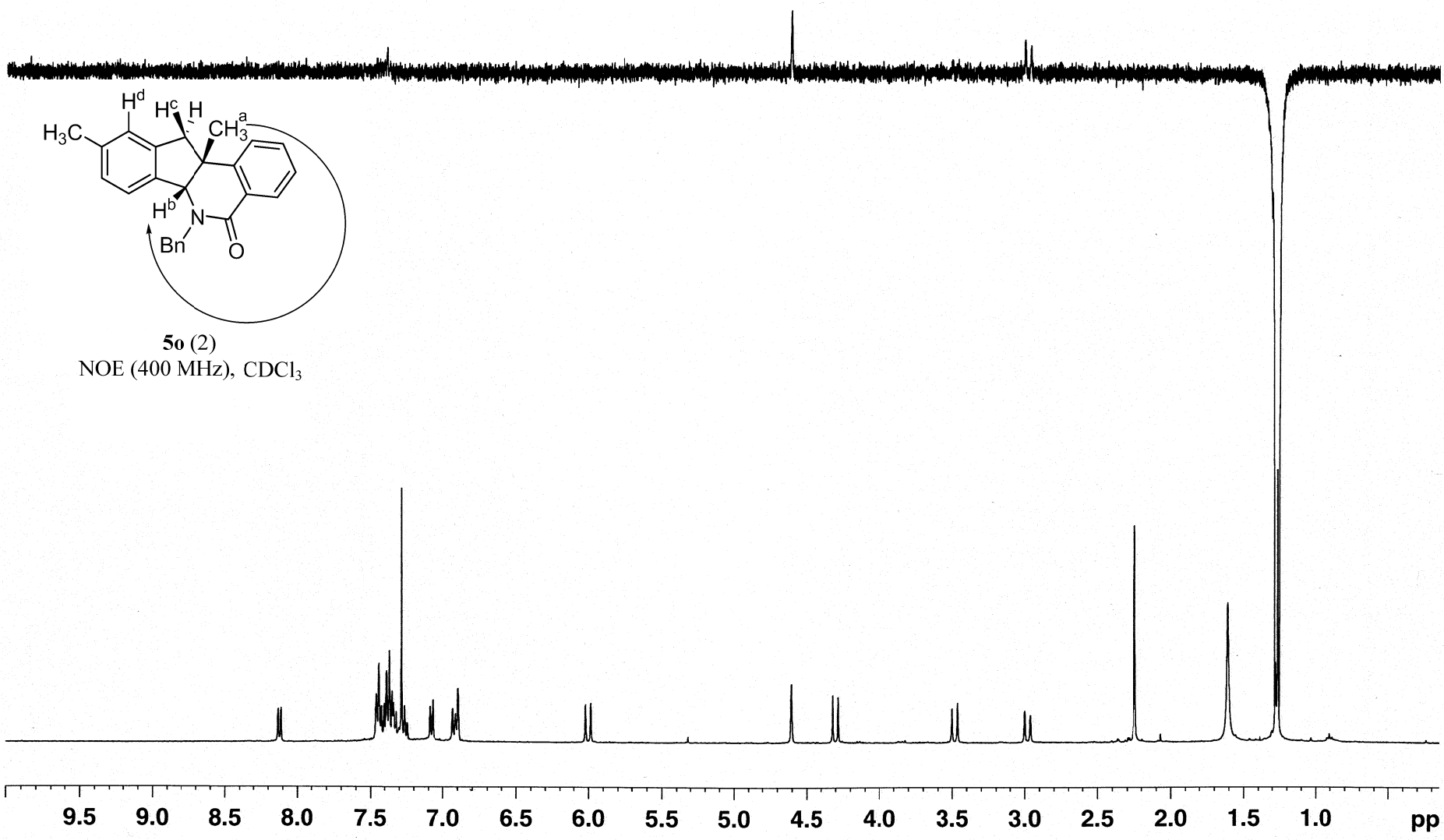
H^a (4.99 ppm (s, 1 H))

H^b (6.83 (s, 1 H))

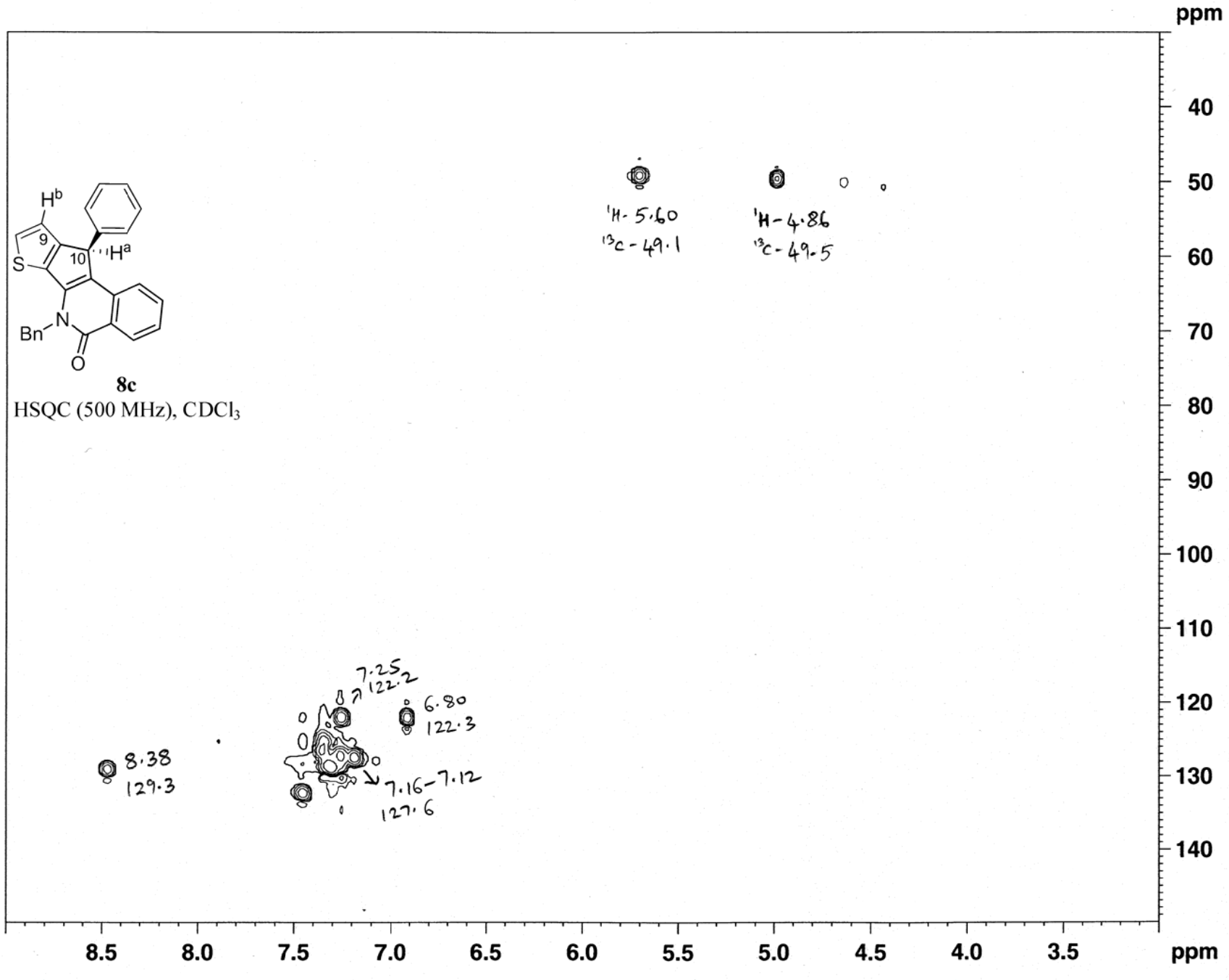
Figure S-6. NOE study on heterocycle **8d**



5o (1)
NOE (400 MHz), $CDCl_3$

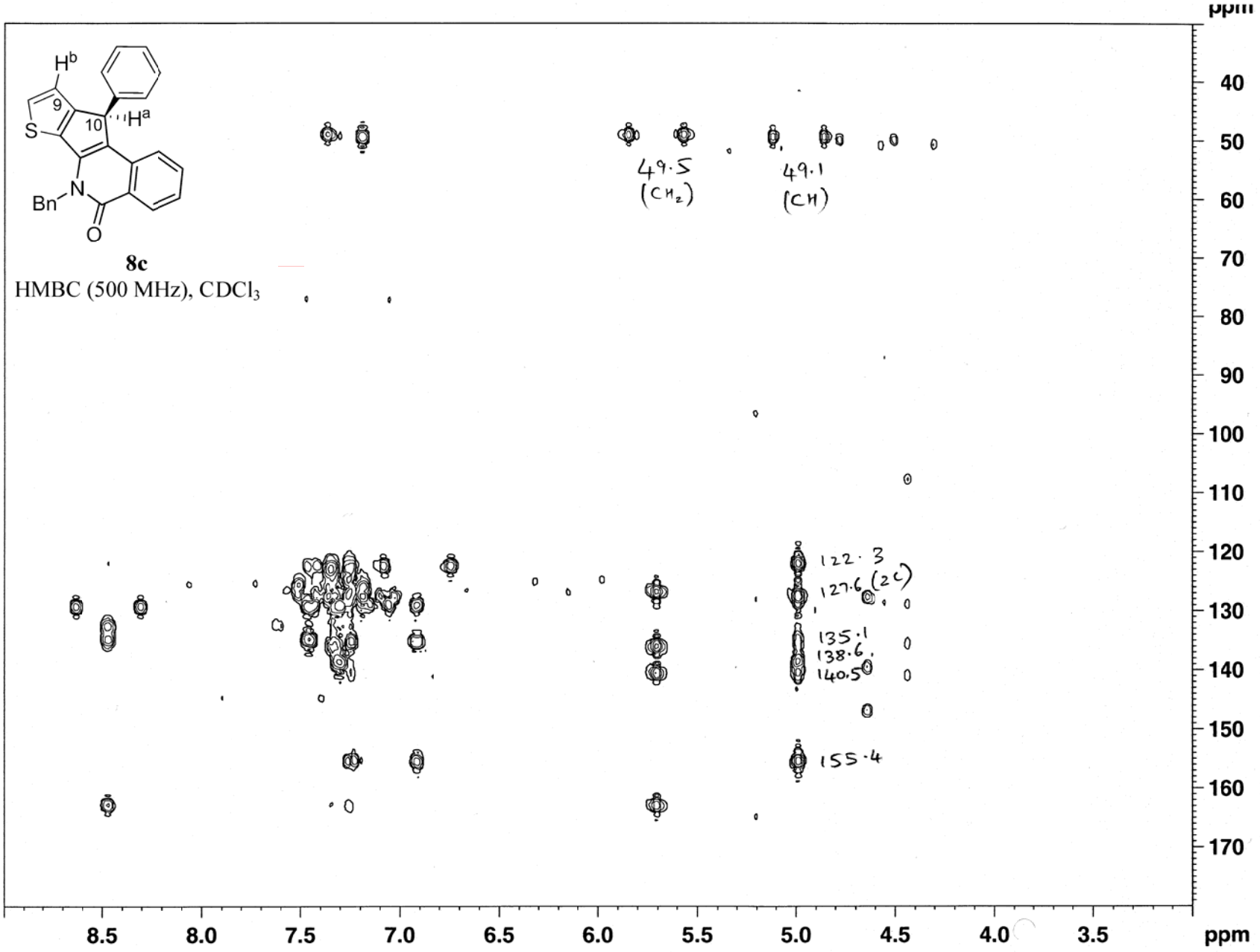


5o (2)
NOE (400 MHz), $CDCl_3$



8c

HSQC (500 MHz), $CDCl_3$


Hb
9
10
Ha
S
N
Bn
O
8c
HMBC (500 MHz), CDCl3
49.5
(CH2)
49.1
(CH)
122.3
127.6 (2C)
135.1
138.6
140.5
155.4
ppm
40
50
60
70
80
90
100
110
120
130
140
150
160
170
8.5
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7.5
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6.5
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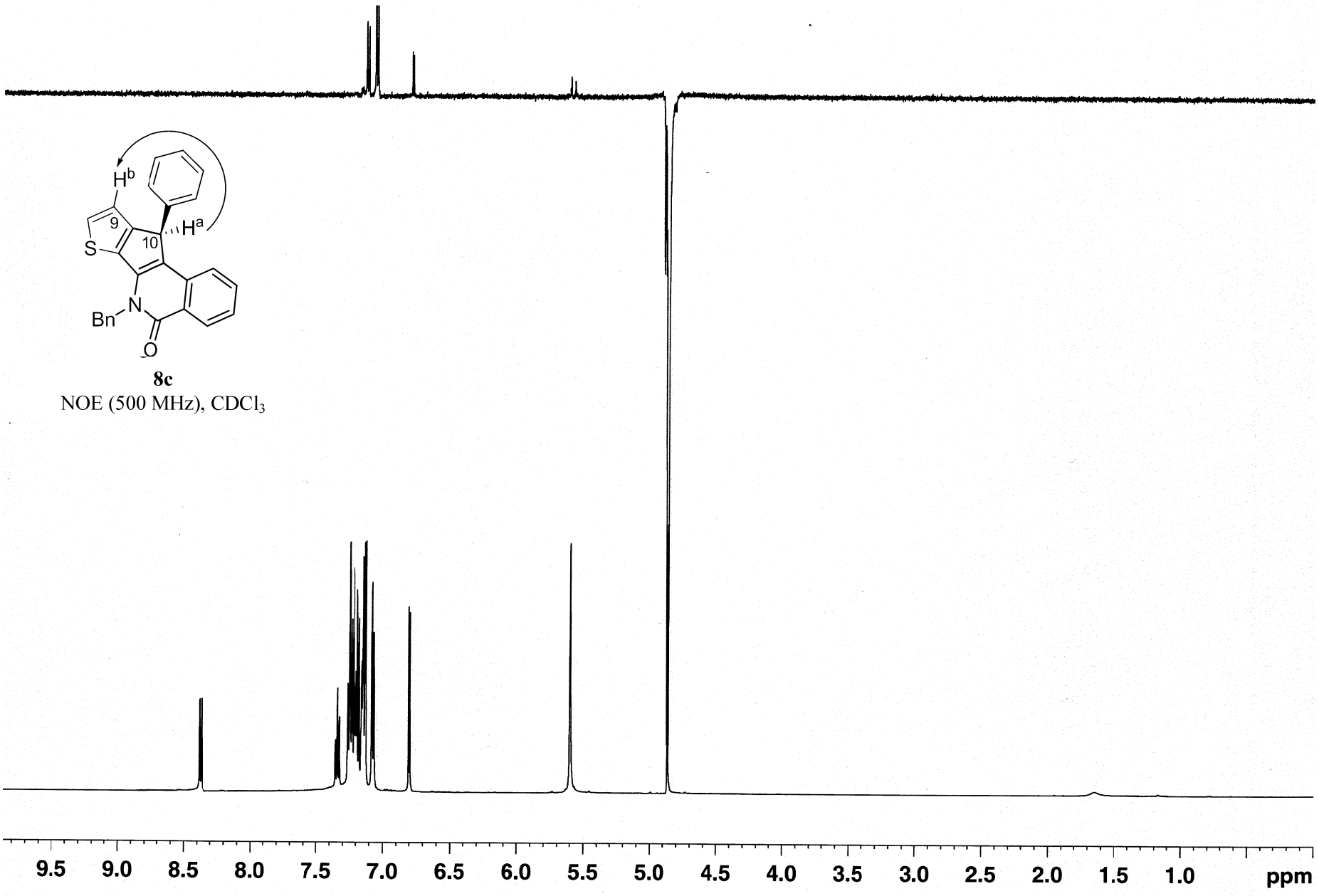
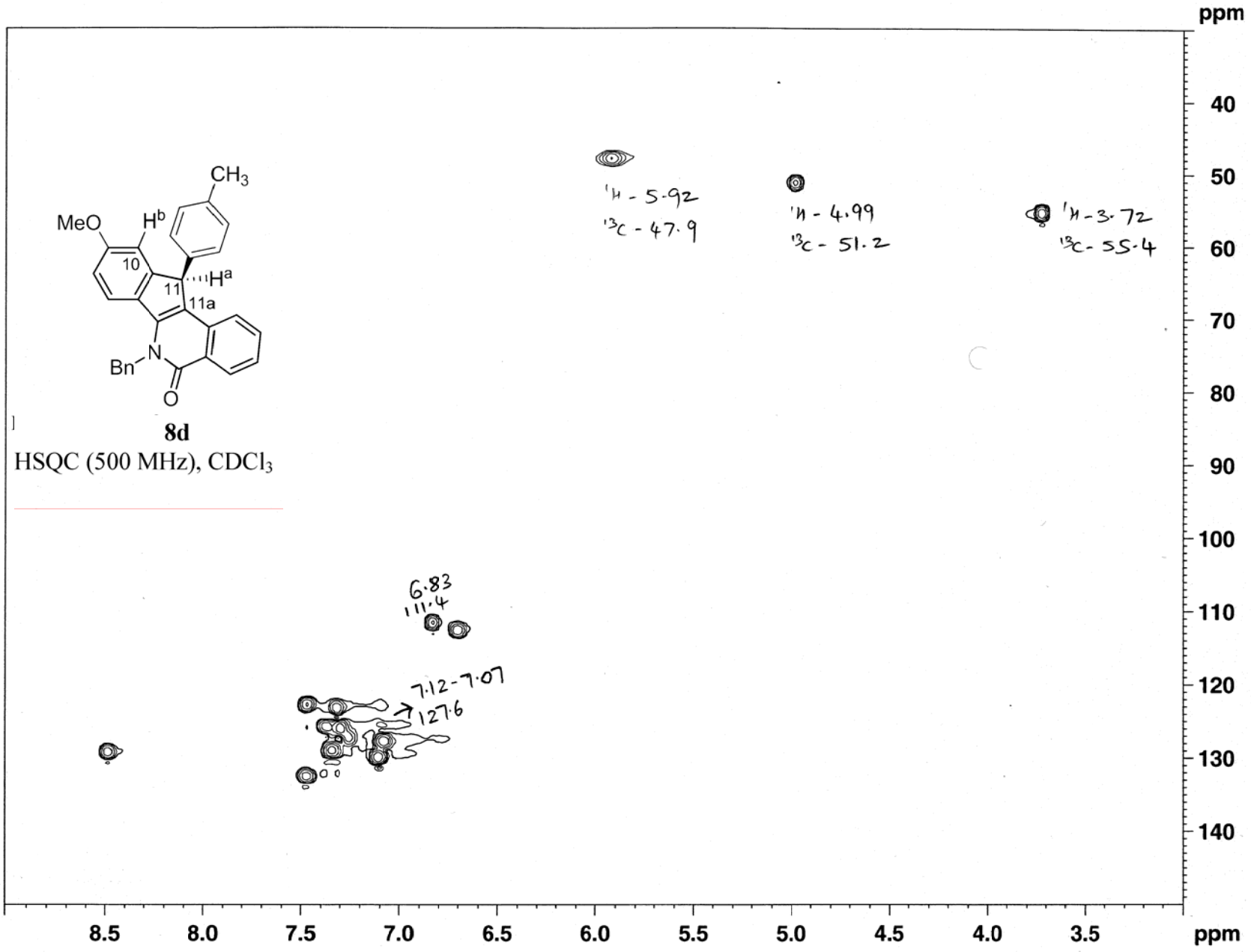
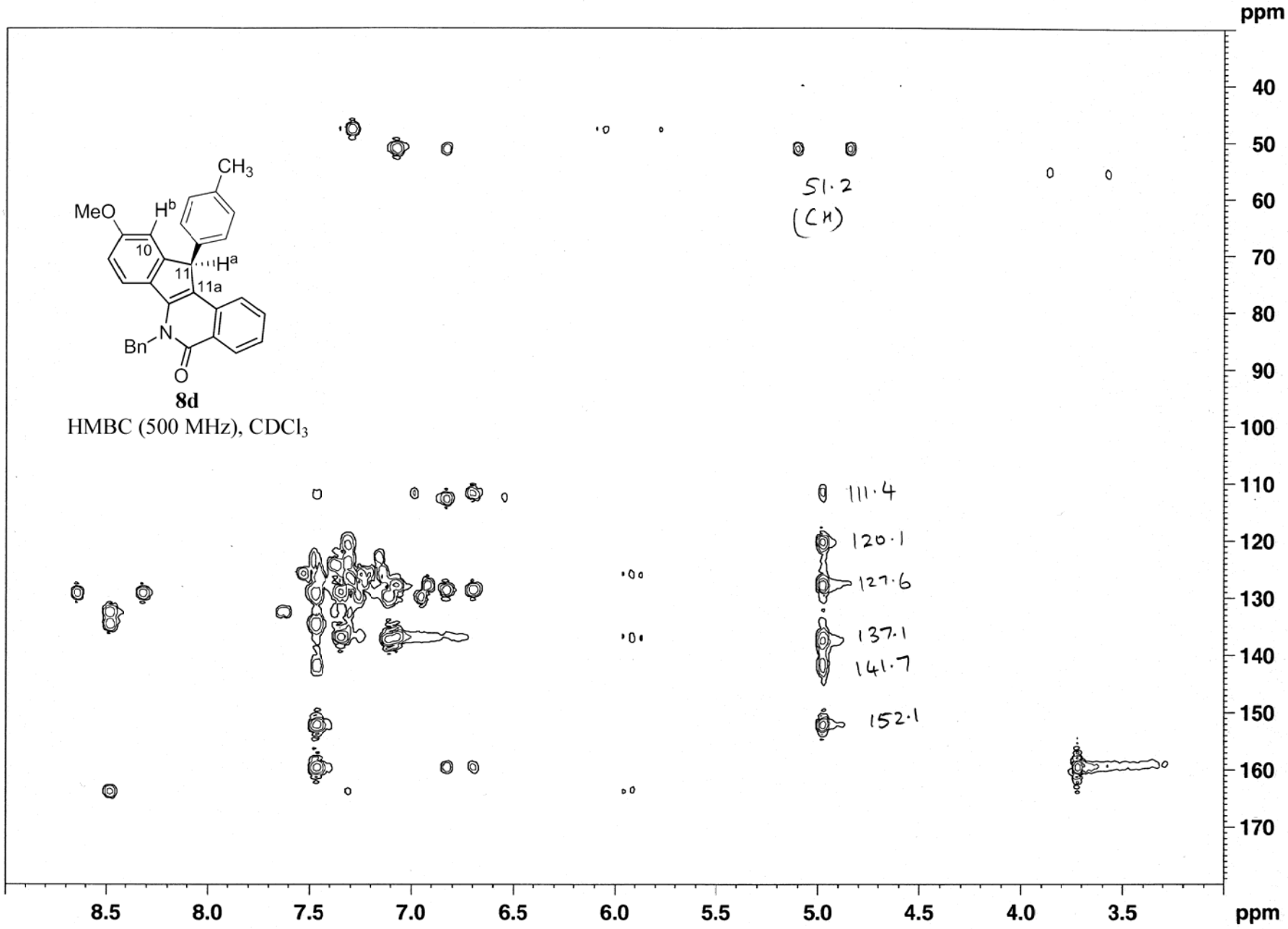
5.5
5.0
4.5
4.0
3.5
ppm



8c

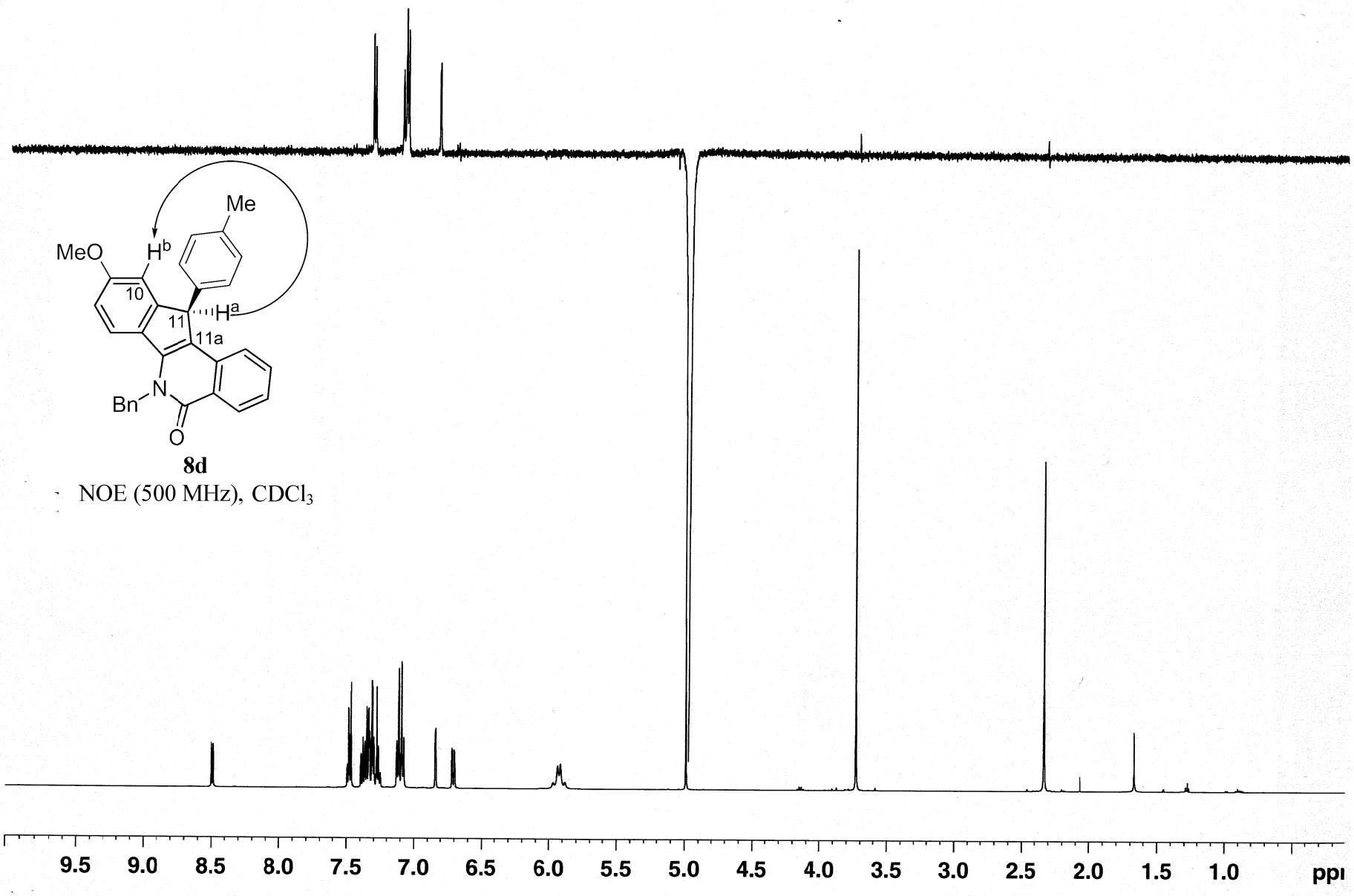
NOE (500 MHz), $CDCl_3$


ppm
40
50
60
70
80
90
100
110
120
130
140
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
MeO
H^b
CH_3
10
11
H^a
11a
N
Bn
O
8d
HSQC (500 MHz), $CDCl_3$
^1H - 5.92
^{13}C - 47.9
^1H - 4.99
^{13}C - 51.2
^1H - 3.72
^{13}C - 55.4
6.83
111.4
7.12-7.07
127.6



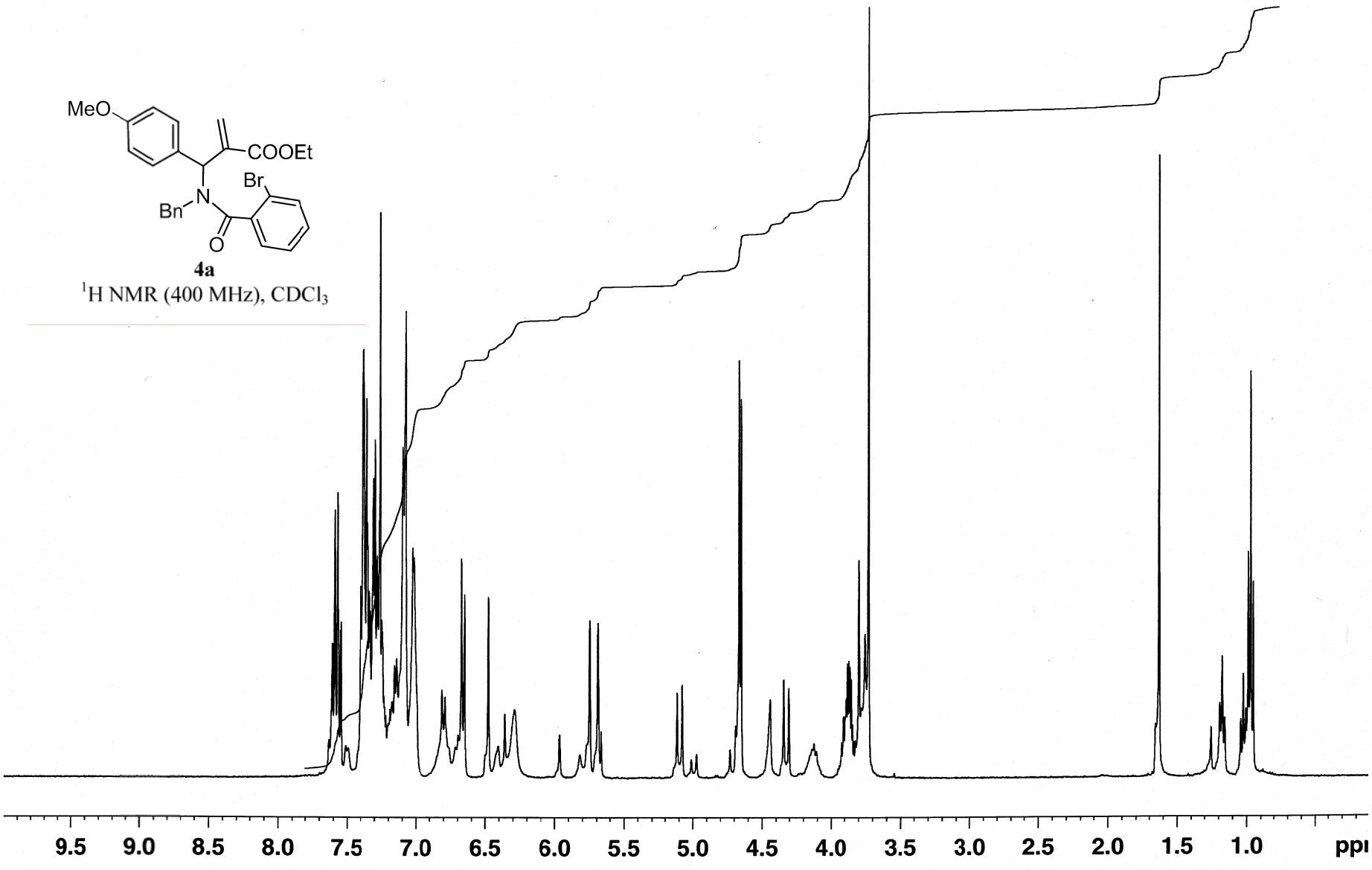
8d

HMBC (500 MHz), $CDCl_3$



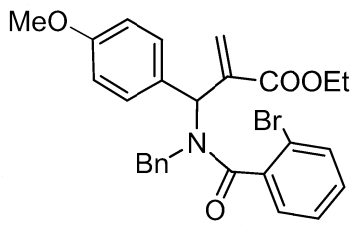
8d

NOE (500 MHz), $CDCl_3$



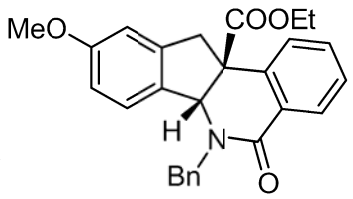
4a

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



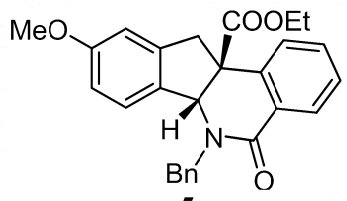
4a

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



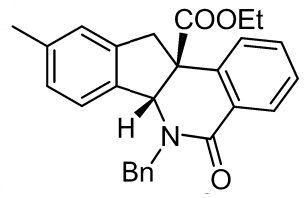
5a

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



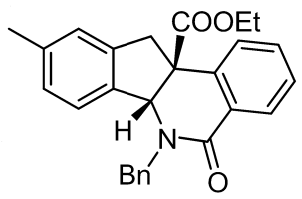
5a

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



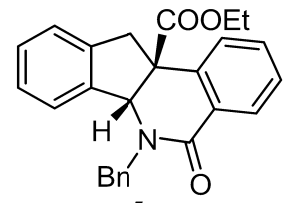
5b

^{1}H NMR (500 MHz), $CDCl_3$



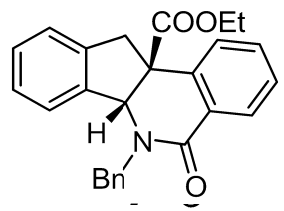
5b

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



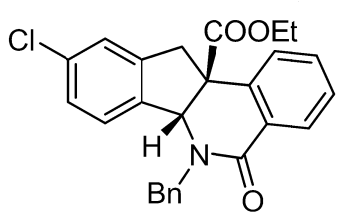
5c

^{1}H NMR (500 MHz), $CDCl_3$



5c

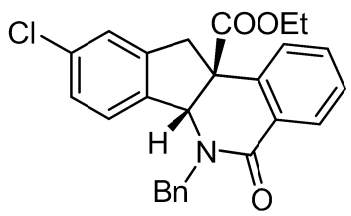
^{13}C NMR (125 MHz), $CDCl_3$



5d

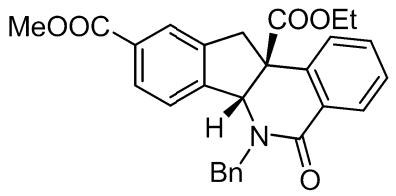
^{1}H NMR (500 MHz), $CDCl_3$

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 pp



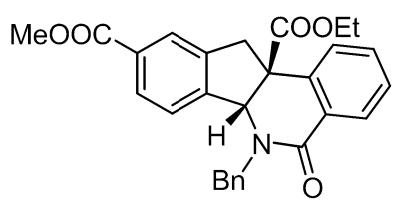
5d

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



5e

^{1}H NMR (500 MHz), $CDCl_3$



5e

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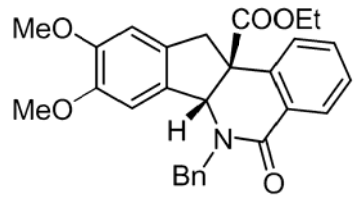
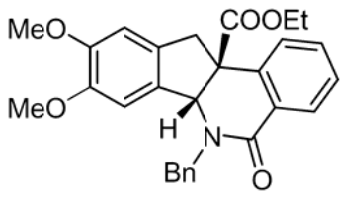


5f

^{1}H NMR (500 MHz), $CDCl_3$



5f

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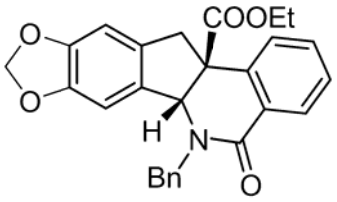
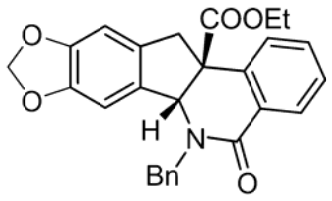


5g

^{1}H NMR (500 MHz), $CDCl_3$

dr 4 : 1



5g

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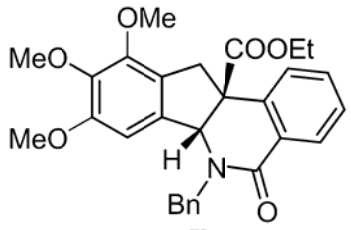
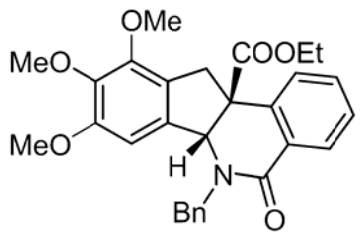
dr 4 : 1



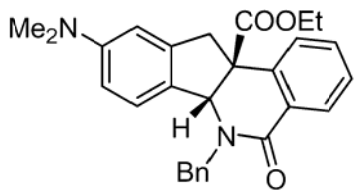
5h

^{1}H NMR (500 MHz), $CDCl_3$



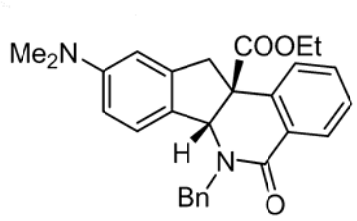
5h

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



5i

^{1}H NMR (500 MHz), $CDCl_3$



5i

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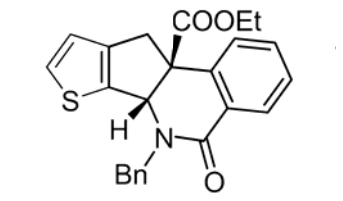

5j

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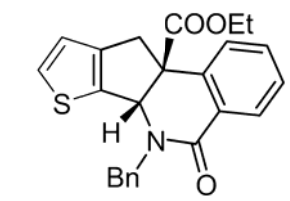

5j

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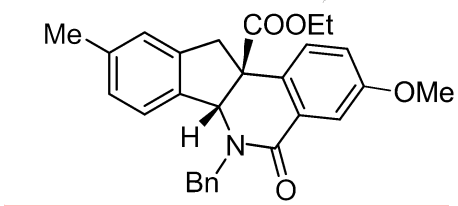
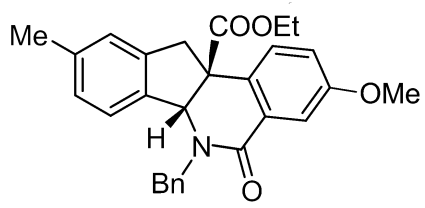


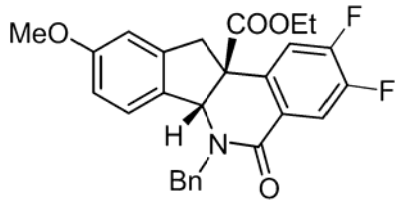
5k

^{1}H NMR (500 MHz), $CDCl_3$



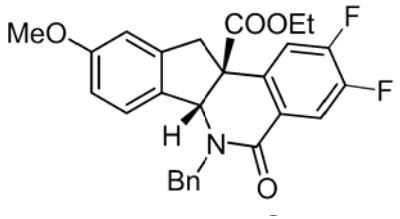
5k

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



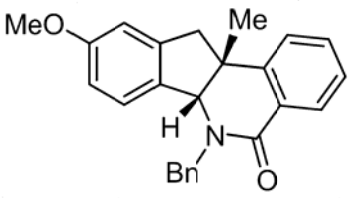
5l

^{1}H NMR (500 MHz), $CDCl_3$



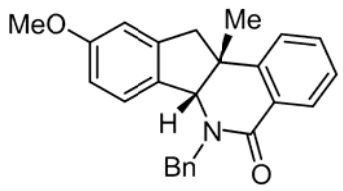
5l

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



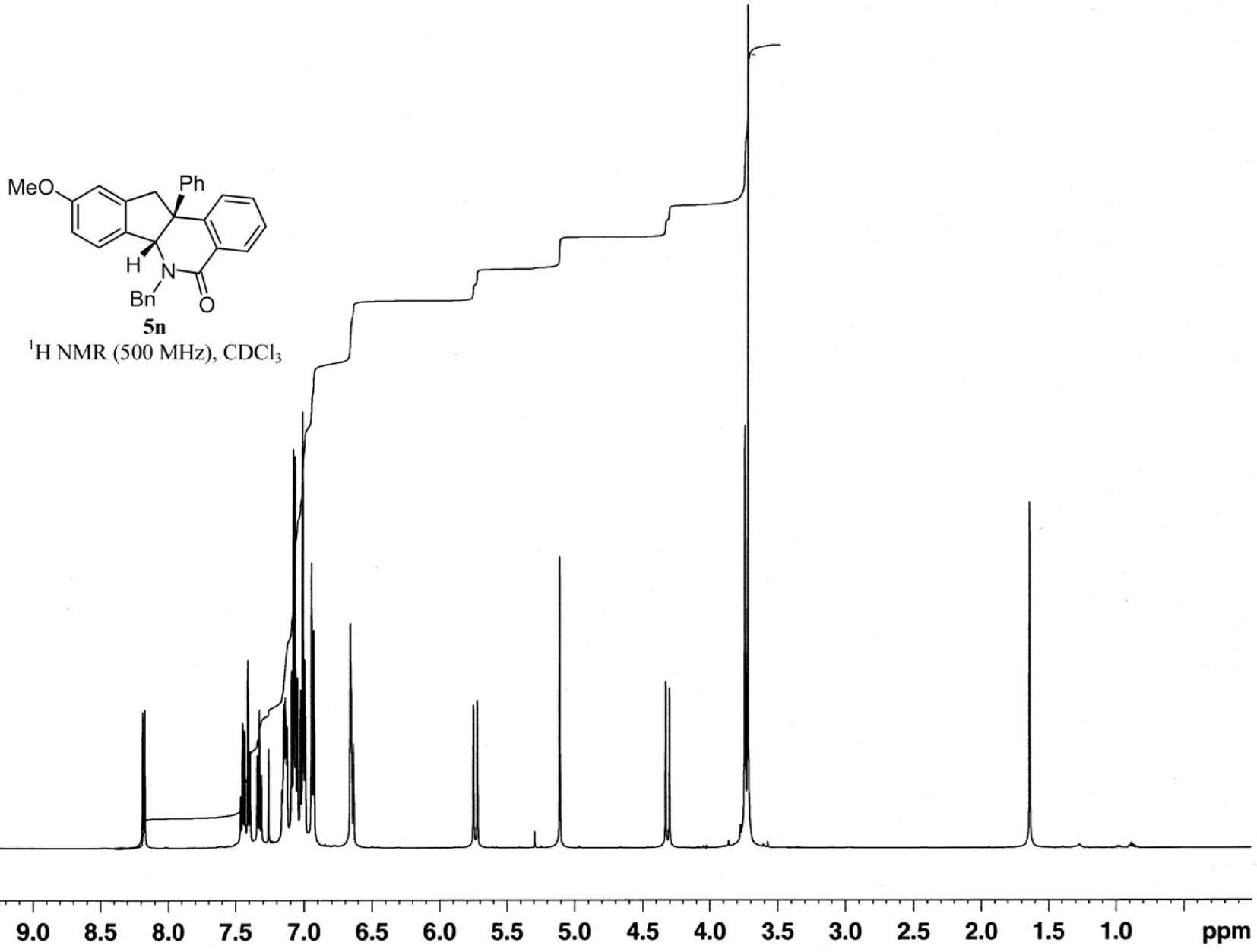
5m

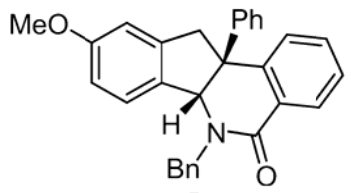
^{1}H NMR (400 MHz), $CDCl_3$



5m

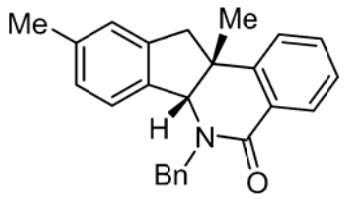
^{13}C NMR (125 MHz), $CDCl_3$


MeO
Ph
H
N
Bn
O
5n
^{1}H NMR (500 MHz), $CDCl_3$
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
ppm



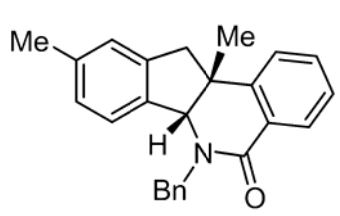
5n

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



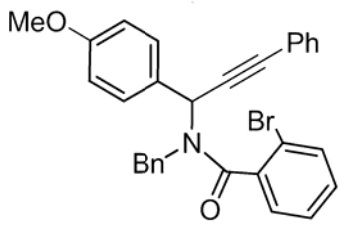
5o

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



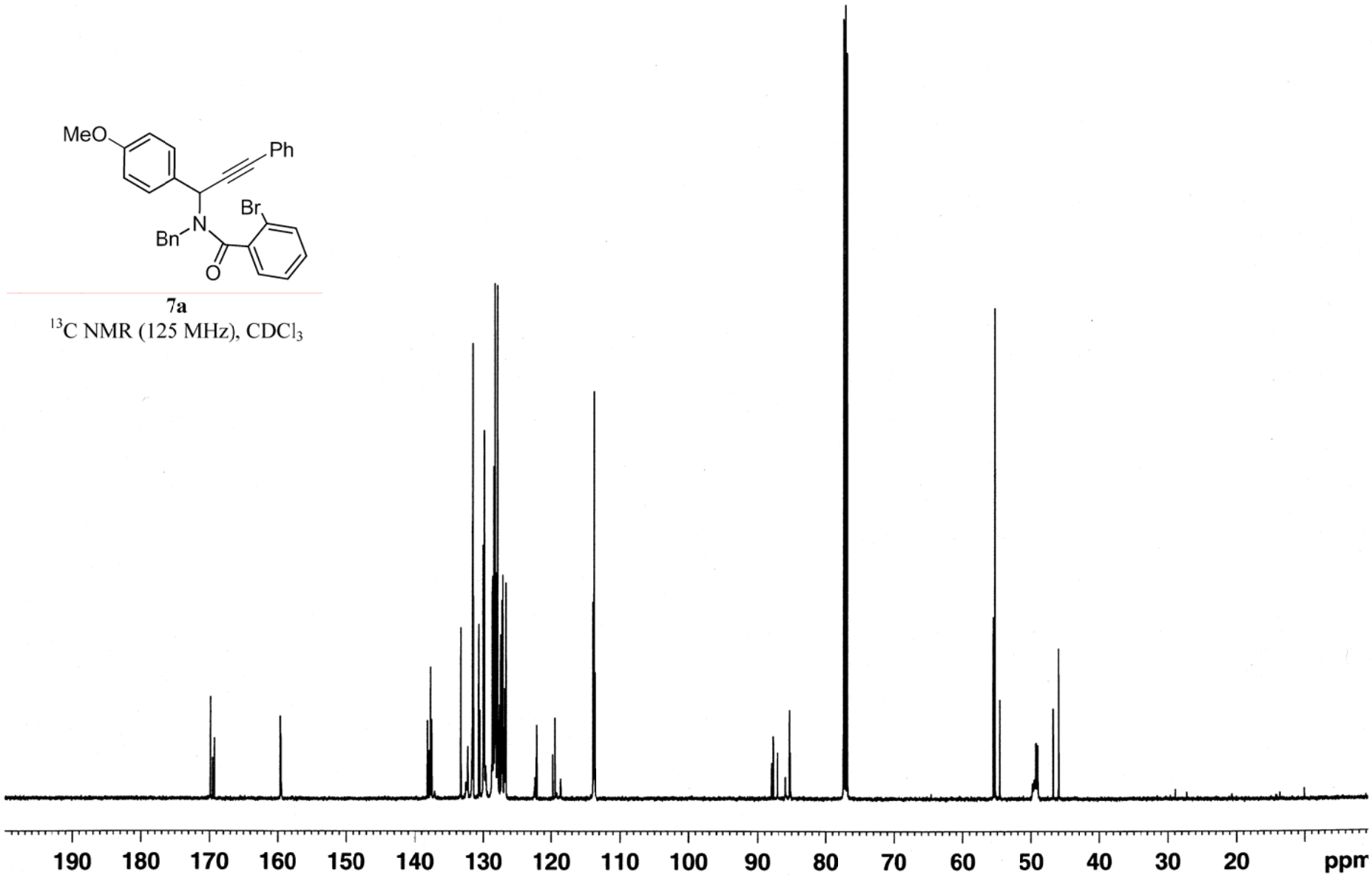
5o

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



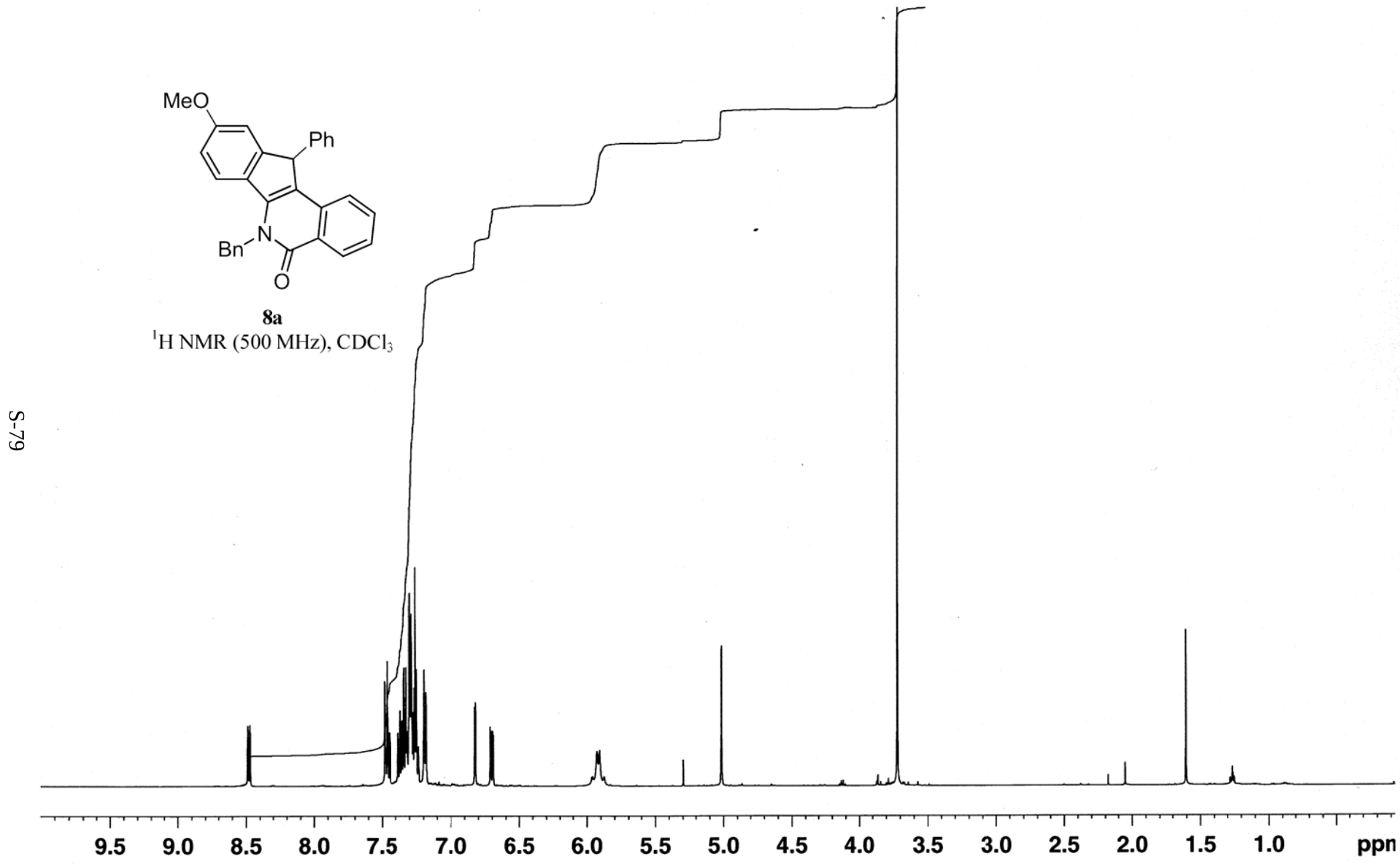
7a

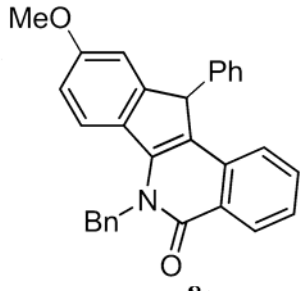
^{1}H NMR (400 MHz), $CDCl_3$



7a

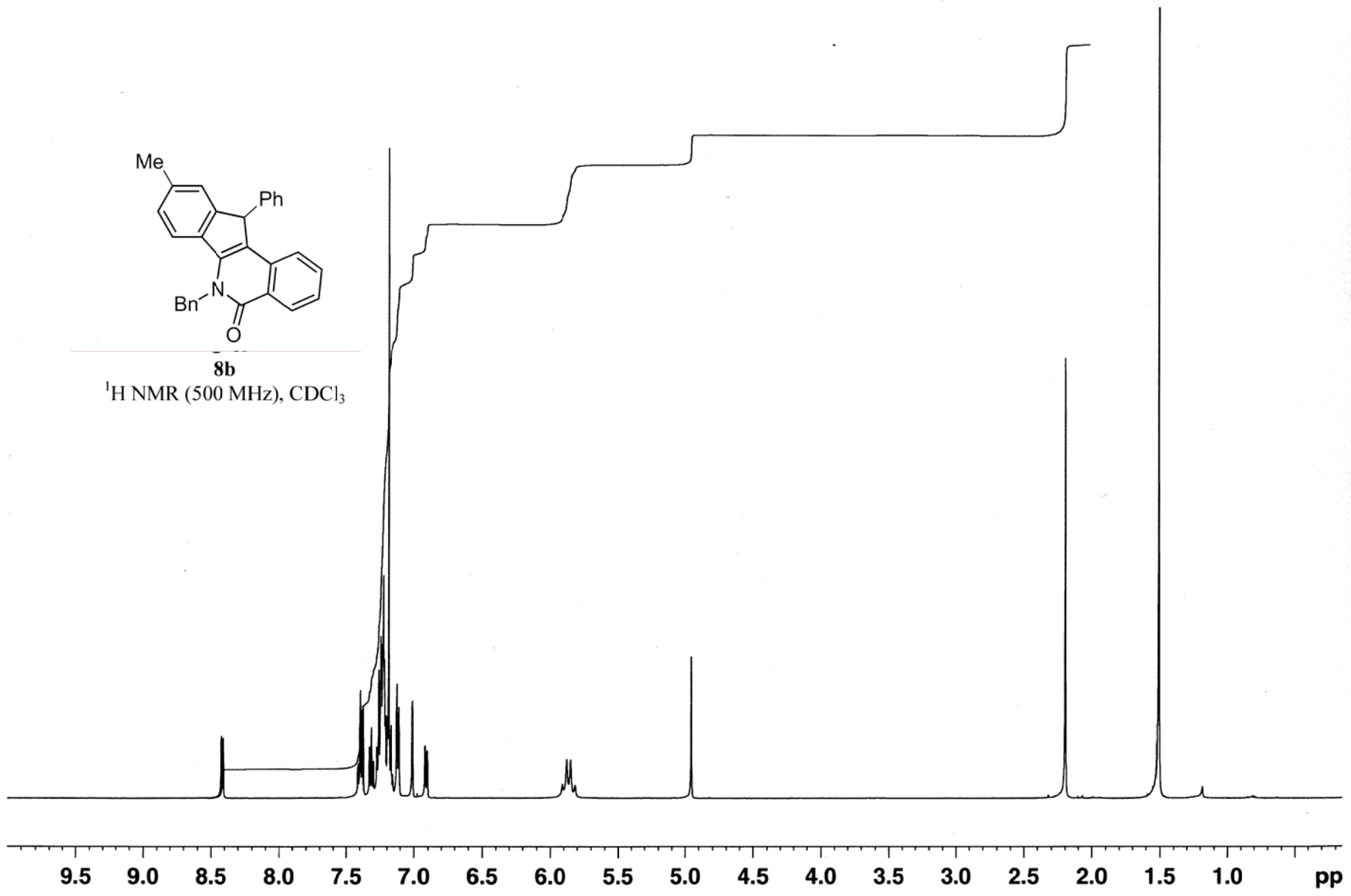
^{13}C NMR (125 MHz), $CDCl_3$


MeO
Ph
Bn
N
O
8a
^{1}H NMR (500 MHz), $CDCl_3$
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
ppm



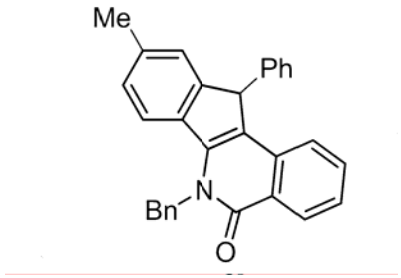
8a

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



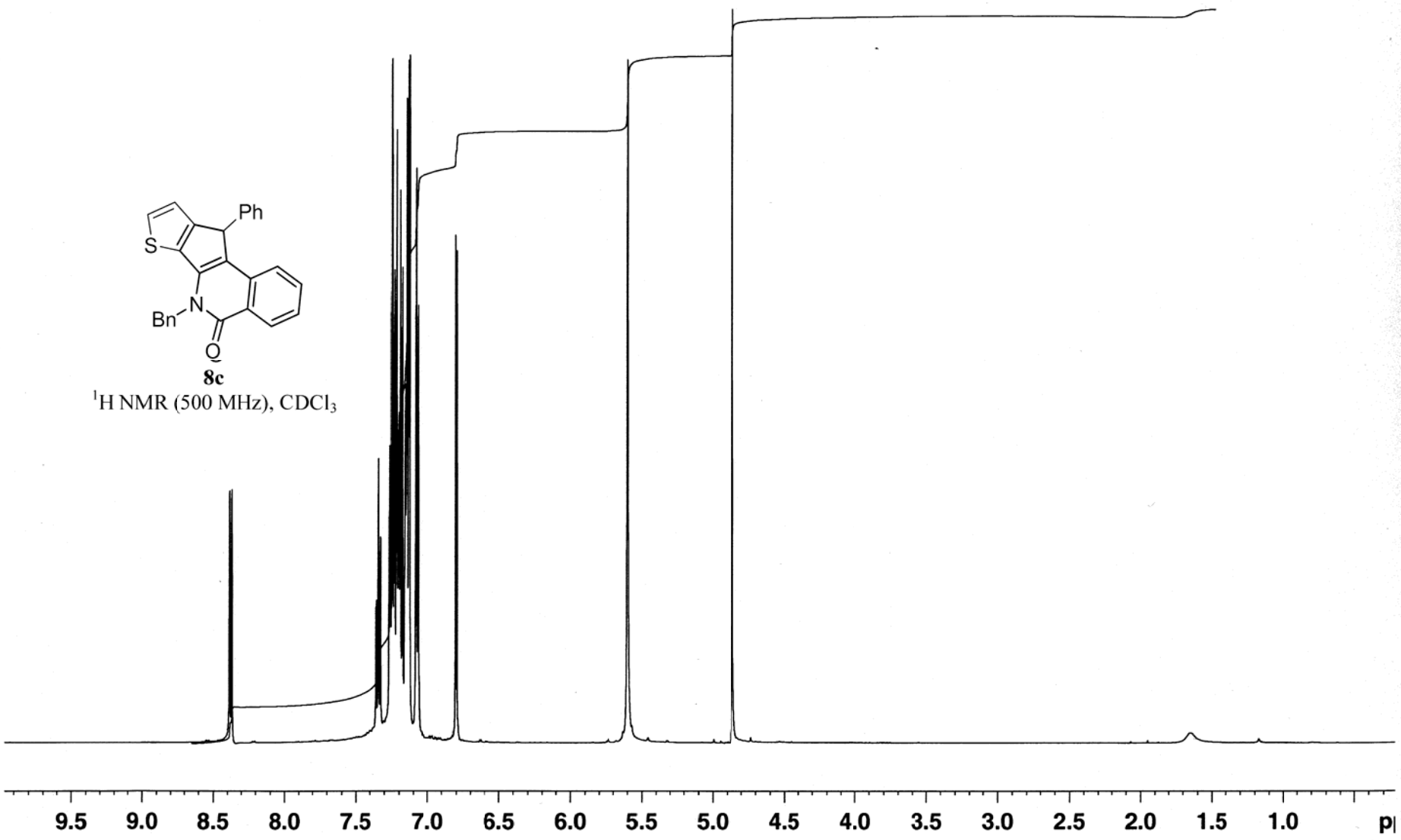
8b

^{1}H NMR (500 MHz), $CDCl_3$



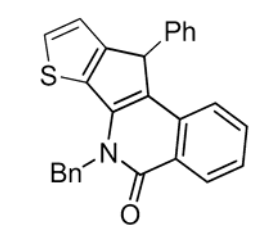
8b

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



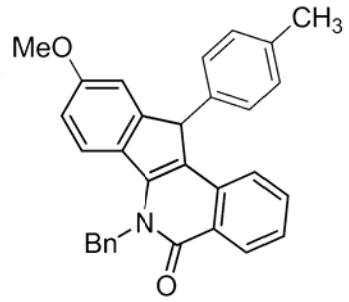
8c

^{1}H NMR (500 MHz), $CDCl_3$



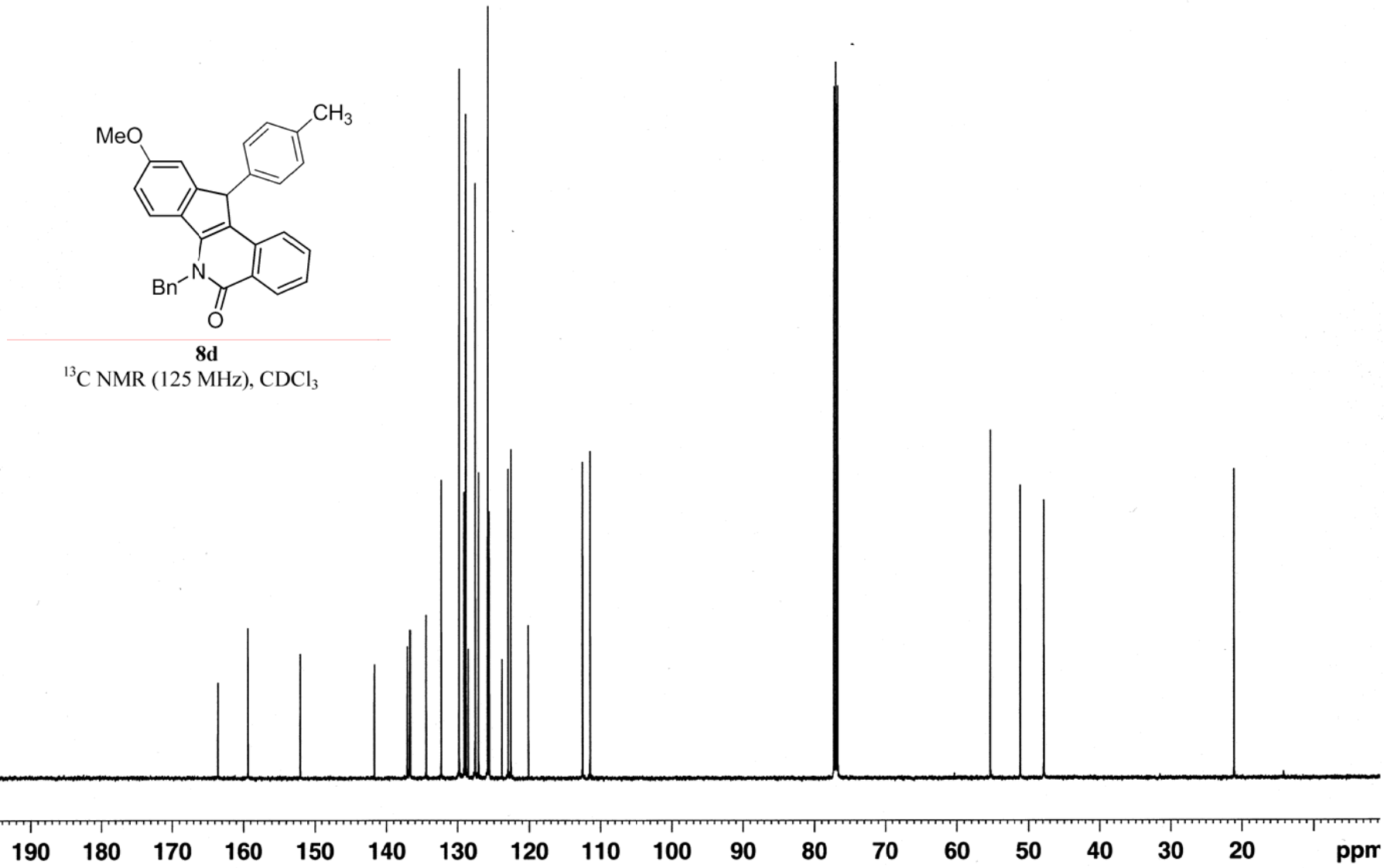
8c

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



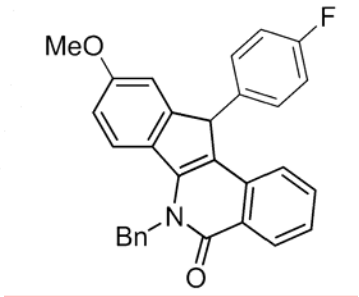
8d

^{1}H NMR (500 MHz), $CDCl_3$



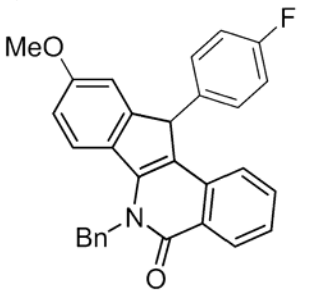
8d

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



8e

^{1}H NMR (500 MHz), $CDCl_3$



8e

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