A Diverging DOS Strategy Using an Allene-Containing Tryptophan Scaffold and a Library Design that Maximizes Biologically Relevant Chemical Space While Minimizing the Number of Compounds

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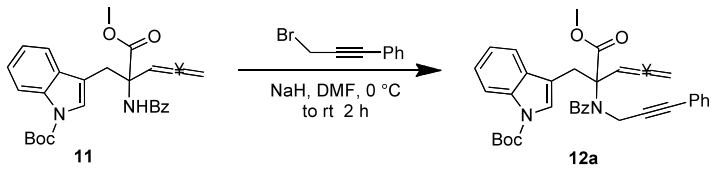
Supporting Information

Experimental

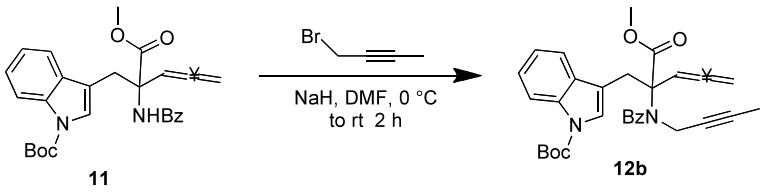
General Methods

Unless otherwise noted, all reactions were carried out under nitrogen atmosphere. All commercially available compounds were purchased and used as received, unless otherwise specified. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were purified by passing through alumina. Dichloromethane (CH_2Cl_2) was passed through alumina and Q5. Toluene and dichloroethane were freshly distilled from CaH_2 prior to use. Dimethyl formamide was distilled prior to use. Purification of the compounds by flash chromatography was performed by using silica gel (32-63 μm particle size, 60 Å pore size). TLC analyses were performed on EM Science Silica Gel 60 F_{254} plates (250 μm thickness). All ^{1}H NMR and ^{13}C NMR spectra were obtained on 300, 500, or 700 MHz Bruker Biospin NMR spectrometers with Topspin NMR software. Chemical shifts (δ) are reported relative to residual solvent resonances as indicated. All NMR spectra were obtained at room temperature unless otherwise specified. IR spectra were obtained using a Nicolet Avatar E.S.P. 360 FT-IR. EI mass spectrometry was performed on a Micromass Autospec high resolution mass spectrometer. The glassware was oven-dried or flame-dried.

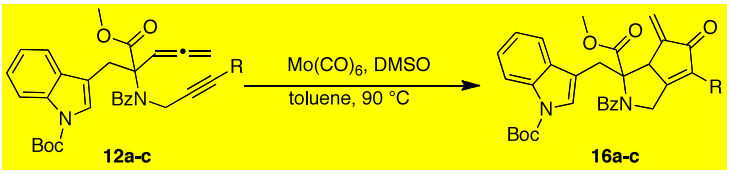


11 12a

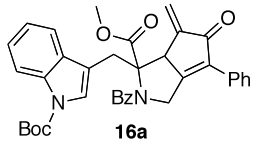
***tert*-Butyl 3-(2-(methoxycarbonyl)-2-(*N*-(3-phenylprop-2-yn-1-yl)benzamido)penta-3,4-dien-1-yl)-1*H*-indole-1-carboxylate (12a):** To a mixture of sodium hydride (87 mg of a 60% dispersion in mineral oil, 2.17 mmol) in dry DMF (6.0 mL) at 0 °C, was added a solution of **11** (500 mg, 1.08 mmol) in DMF (4.0 mL) via syringe and the mixture stirred for 30 min. 1-Bromo-3-phenyl-2-propyne (582 mg, 3.00 mmol) was added dropwise via syringe. The reaction mixture was stirred for 2 h at room temperature, until no starting material was evident by TLC. The reaction mixture was quenched with sat. NH_4Cl solution. The layers were separated and the aqueous layer extracted into ether (3x). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (30% ethyl acetate/hexanes) to afford **12a** (245 mg, 45%) as an amorphous, pale yellow solid. (R_f = 0.5, 40% ethyl acetate/hexanes). M.p.: 85-86 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02 (d, *J* = 7.5 Hz, 1H), 7.65 – 7.69 (m, 3H), 7.52 (s, 1H), 7.41 – 7.47 (m, 3H), 7.20 – 7.32 (m, 5H), 7.12 (d, *J* = 6.6 Hz, 2H), 6.02 (t, *J* = 6.6 Hz, 1H), 5.04 – 5.16 (m, 2H), 4.18 (A of an ABq, *J* = 14.7 Hz, 1H), 4.03 (s, 2H), 3.80 (s, 3H), 3.57 (B of an ABq, *J* = 14.7 Hz, 1H), 1.60 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 172.7, 171.4, 149.5, 135.8, 135.1, 131.6, 131.4, 130.5, 128.5, 128.4, 128.3, 127.5, 125.8, 124.3, 122.6, 122.2, 119.6, 115.2, 114.8, 91.3, 85.9, 84.5, 83.4, 79.5, 68.9, 52.5, 40.1, 29.03, 28.2. IR (thin film) ν 1740, 1642, 1446, 1368, 1258, 1164, 1090 cm^{-1}. MS [*m/z* + Na] (%) 597 (100), 575 (23), 527 (5). HRMS calculated for $C_{36}H_{34}N_2O_5Na$: 597.2365; found: 597.2354.



***Tert*-butyl-3-(2-(methoxycarbonyl)-2-(*N*-(but-2-ynyl)benzamido)penta-3,4-dienyl)-1*H*-indole-1-carboxylate) 12b**{*1, 0, 37*}**:** To a mixture of sodium hydride (108 mg of a 60% dispersion in mineral oil, 2.70 mmol) in DMF (6.8 mL), was added a solution of **11** (623 mg, 1.35 mmol) in DMF (4.5 mL) via cannula and the mixture stirred for 5 min. 1-Bromo-2-butyne (0.24 mL, 2.70 mmol) was added via syringe. After 2.5 h, sodium hydride (54 mg of a 60% dispersion in mineral oil, 1.35 mmol) was added to the mixture, in one portion, followed by 1-bromo-2-butyne (0.12 mL, 1.35 mmol) via syringe. The reaction mixture was stirred for another 30 min, until no starting material was evident by TLC. The reaction mixture was poured into water and diluted with ethyl acetate. The layers were separated and the aqueous layer extracted into ethyl acetate (4x). The combined organic layers were washed with water (1x) and brine (1x), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (10% to 30% ethyl acetate/hexanes) to afford **12b**{*1, 0, 37*} (500 mg, 72%) as an amorphous, light brown solid. (R_f = 0.67, 30% ethyl acetate/hexanes). M.p.: 66-67 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.14 (d, *J* = 7.2 Hz, 1H), 7.64 – 7.58 (m, 3H), 7.50 (s, 1H), 7.45 – 7.35 (m, 3H), 7.32 – 7.19 (m, 2H), 5.97 (t, *J* = 6.6 Hz, 1H), 5.11 – 4.98 (m, 2H), 4.14 (A of an ABq, *J* = 14.4 Hz, 1H), 3.78 – 3.76 (m, 5H), 3.51 (B of an ABq, *J* = 14.4 Hz, 1H), 1.66 (s, 9H), 1.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 172.3, 171.3, 149.6, 135.8, 135.2, 131.7, 130.3, 128.2, 127.4, 125.8, 124.2, 122.6, 119.8, 115.1, 115.0, 91.2, 83.5, 80.4, 79.1, 75.8, 69.1, 52.3, 39.7, 29.1, 28.2, 3.1; IR (thin film) ν 3058, 2980, 2949, 2228, 1958, 1735, 1640, 1453, 1369, 1259, 1157, 1085, 856, 742 cm^{-1}; MS *m/z* (%) 513 (11), 512 (36), 412 (49), 411 (25), 283 (67), 174 (78), 105 (100); EI-HRMS calcd for $C_{31}H_{32}N_2O_5$ *m/z* $[M]^+$ 512.2311; found 512.2307.

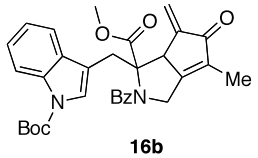


General procedure for $Mo(CO)_6$ mediated Pauson-Khand reaction: An oven dried 10 mL test tube with an attached septa was loaded with $Mo(CO)_6$ (1.5 eq). The test tube was evacuated with a needle under vacuum and filled with Argon (3x). A solution of allene-yne (1 eq) in dry toluene (1 ml) was added by syringe followed by the addition of dry DMSO (10 eq). The test tube was placed in a pre heated (90 °C) oil bath and the progress of the reaction was monitored by TLC. After completion the solution was passed through a pipette containing silica. The filtrate was concentrated and the crude material was purified by column chromatography using 20-40% ethyl acetate/hexanes.



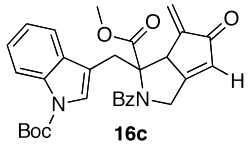
16a

***tert*-butyl-3-((2-benzoyl-1-(methoxycarbonyl)-6-methylene-5-oxo-4-phenyl-1,2,3,5,6,6a-hexahydrocyclopenta[*c*]pyrrol-1-yl)methyl)-1*H*-indole-1-carboxylate (16a)**: The general procedure for the $Mo(CO)_6$-mediated Pauson-Khand reaction was followed. The reaction was carried out with allene-yne **12a** (62.4 mg, 0.108 mmol), $Mo(CO)_6$ (39.6 mg, 0.15 mmol), DMSO (71 μL) and toluene (1 mL). The reaction was heated to 90 °C for 2 h. The crude product was purified by column chromatography using 20-40% ethyl acetate/hexanes. Compound **16a** was obtained in 65% Yield (39 mg) as a 3:1 mixture of two diastereomers. (R_f = 0.4, 40% ethyl acetate/hexanes). Major diastereomer was isolated as a pale yellow solid (28mg, 43%): M.p. 140-141 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.25 (d, *J* = 8.4 Hz, 1H), 7.61-7.63 (m, 2H), 7.49-7.52 (m, 3H), 7.38-7.45 (m, 2H), 7.31-7.35 (m, 5H), 7.23 (t, *J* = 7.2 Hz, 2H), 6.38 (d, *J* = 1.8 Hz, 1H), 5.85 (d, *J* = 1.2 Hz, 1H), 4.48 (A of an ABq, *J* = 15.3 Hz, 1H), 4.32 (d, *J* = 15.3 Hz, 2H), 4.14 (s, 1H), 3.70 (B of an ABq, *J* = 15.3 Hz, 1H), 3.62 (s, 3H), 1.68 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4, 171.1, 170.2, 164.1, 149.5, 141.1, 136.8, 135.4, 135.3, 131.6, 131.2, 130.3, 128.8, 128.6 (2C), 128.3, 127.7, 125.7, 124.8, 123.1, 118.9, 118.6, 115.4, 114.8, 84.0, 70.7, 52.4, 51.8, 50.3, 28.2, 27.4. IR (thin film) ν 1732, 1703, 1638, 1446, 1372, 1258, 1155 cm^{-1}. MS [*m/z* + Na] (%) 625 (100), 603 (19), 597 (37), 569 (18). HRMS calculated for $C_{37}H_{34}N_2O_6Na$: 625.2315; found: 625.2361.



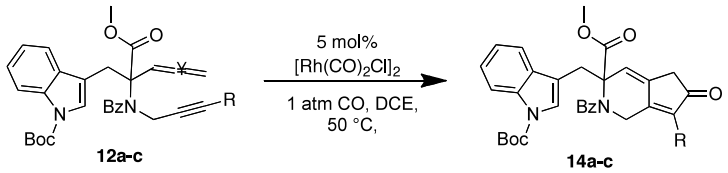
16b

***tert*-butyl-3-((2-benzoyl-1-(methoxycarbonyl)-4-methyl-6-methylene-5-oxo-1,2,3,5,6,6a-hexahydrocyclopenta[*c*]pyrrol-1-yl)methyl)-1*H*-indole-1-carboxylate (16b):** The general procedure for the $Mo(CO)_6$-mediated Pauson-Khand reaction was followed. The reaction was carried out with allene-yne **12b**(51.2 mg, 0.1 mmol), $Mo(CO)_6$ (39.6 mg, 0.15 mmol), DMSO(71 μL) and toluene (1 mL). The reaction was heated to 90 °C for 2 h. The crude product was purified by column chromatography using 30% ethyl acetate/hexanes. Compound **16b** was obtained in 74% Yield (40 mg) as a 4:1 mixture of two diastereomers. (R_f = 0.4, 40% ethyl acetate/hexanes). Major diastereomer was isolated as a white solid (27.1 mg, 50%): M.p. 189-190 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, *J* = 7.5 Hz, 1H), 7.42-7.62 (m, 7H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 6.24 (d, *J* = 2.1 Hz, 1H), 5.72 (s, 1H), 4.24-4.31 (m, 2H), 4.13-4.19 (m, 1H), 3.96 (bs, 1H), 3.61-3.66 (m, 1H), 3.63 (s, 3H), 1.68 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 171.0, 170.2, 162.8, 149.5, 140.6, 135.8, 135.2, 134.6, 131.6, 131.1, 128.6, 127.6, 125.6, 124.7, 123.0, 118.9, 117.5, 115.4, 114.8, 83.9, 71.2, 52.4, 50.7, 28.2, 27.6, 9.0. IR (thin film) ν 1736, 1634, 1450, 1376, 1254, 1164 cm^{-1}. MS [*m/z* + Na] (%) 563 (100), 527 (5). HRMS calculated for $C_{32}H_{32}N_2O_6Na$: 563.2158; found: 563.2191.



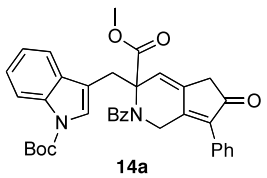
16c

***tert*-butyl-3-((2-benzoyl-1-(methoxycarbonyl)-6-methylene-5-oxo-1,2,3,5,6,6a-hexahydrocyclopenta[*c*]pyrrol-1-yl)methyl)-1*H*-indole-1-carboxylate (16c):** The general procedure for the $Mo(CO)_6$-mediated Pauson-Khand reaction was followed. The reaction was carried out with allene-yne **12c** (49.8 mg, 0.1 mmol), $Mo(CO)_6$ (39.6 mg, 0.15 mmol), DMSO (71 μL) and toluene (1 mL). The reaction was heated to 90 °C for 2 h. The crude product was purified by column chromatography using 20-30% ethyl acetate/hexanes. Compound **16c** was obtained in 65% Yield (34.2 mg) as a 3:1 mixture of two diastereomers. Major diastereomer was isolated as a pale yellow solid (22 mg, 42%). (R_f = 0.4, 40% ethyl acetate/hexanes). M.p. 110-111 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, *J* = 8.1 Hz, 1H), 7.57-7.59 (m, 2H), 7.43-7.54 (m, 4H), 7.34-7.40 (m, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 6.24 (d, *J* = 2.1 Hz, 1H), 6.07 (s, 1H), 5.74 (s, 1H), 4.25-4.31 (m, 2H), 4.13-4.18 (m, 1H), 4.05 (s, 1H), 3.62-3.68 (m, 1H), 3.66 (s, 3H), 1.67 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.3, 171.1, 170.3, 170.1, 149.5, 140.9, 135.6, 135.3, 131.5, 131.1, 128.6, 127.4, 126.2, 125.6, 124.8, 123.1, 118.8, 117.9, 115.4, 114.6, 84.0, 71.2, 52.4, 51.7, 28.2, 27.5. IR (thin film) ν 1740, 1711, 1642, 1454, 1372, 1254, 1160 cm^{-1}. MS [*m/z* + Na] (%) 549 (100). HRMS calculated for $C_{31}H_{30}N_2O_6Na$: 549.2002; found: 549.2020.



12a-c 14a-c

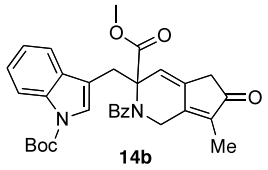
General procedure for $[Rh(CO)_2Cl]_2$ catalyzed Pauson-Khand reaction: An oven dried 10 mL test tube with an attached rubber septa was loaded with $[Rh(CO)_2Cl]_2$ (5 mol%). The test tube was evacuated with a needle under vacuum and filled with CO (3x). A solution of allene-yne (1 eq) in DCE (1 ml) was added by syringe. The test tube was placed in a pre heated (50 °C) oil bath and the progress of the reaction was monitored by TLC. After completion of the reaction the solution was concentrated and the crude material was purified by column chromatography using 30-40% ethyl acetate/hexanes.



14a

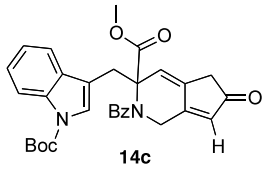
***tert*-butyl-3-((2-benzoyl-3-(methoxycarbonyl)-6-oxo-7-phenyl-2,3,5,6-tetrahydro-1*H*-cyclopenta[*c*]pyridin-3-yl)methyl)-1*H*-indole-1-carboxylate (14a):** The general procedure for the $[Rh(CO)_2Cl]_2$ catalyzed Pauson-Khand reaction was followed. The

reaction was carried out with allene-yne **12a** (57.4 mg, 0.1 mmol), $[Rh(CO)_2Cl]_2$ (2.0 mg, 0.005 mmol, 5 mol%), and DCE (1 mL). The reaction was heated to 60 °C for 2 h. The crude product was purified by column chromatography using 30% ethyl acetate/hexanes to afford the product **14a** (50.6 mg, 84%) as a pale yellow solid. (R_f = 0.4, 40% ethyl acetate/hexanes). M.p. 138-139 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, *J* = 7.8 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.41 (s, 1H), 7.38 – 7.27 (m, 5H), 7.19 – 7.24 (m, 5H), 6.96 – 6.99 (m, 2H), 5.99 (s, 1H), 4.60 (A of an ABq, *J* = 18.3 Hz, 1H), 4.39 (A of an ABq, *J* = 14.7 Hz, 1H), 3.85 (s, 3H), 3.51 (B of an ABq, *J* = 14.7 Hz, 1H), 3.48 (B of an ABq, *J* = 18.3 Hz, 1H), 3.20 (A of an ABq, *J* = 21.0 Hz, 1H), 3.08 (B of an ABq, *J* = 21.0 Hz, 1H), 1.61 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 171.9, 171.4, 154.6, 149.4, 137.2, 135.4, 134.7, 130.9, 130.0, 129.6, 128.7 (2C), 128.3 (2C), 126.5 (2C), 125.0, 123.2, 122.8, 119.5, 115.3, 115.0, 83.9, 66.0, 53.1, 45.2, 38.2, 29.5, 28.1. IR (thin film) ν 1736, 1711, 1642, 1450, 1368, 1262, 1155 cm^{-1}. MS [*m/z* + Na] (%) 625 (100), 603 (13), 570 (33). HRMS calculated for $C_{37}H_{34}N_2O_6Na$: 625.2315; found: 625.2261.



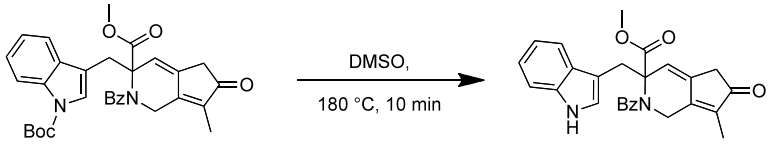
14b

***tert*-butyl-3-((2-benzoyl-3-(methoxycarbonyl)-7-methyl-6-oxo-2,3,5,6-tetrahydro-1*H*-cyclopenta[*c*]pyridin-3-yl)methyl)-1*H*-indole-1-carboxylate (14b):** The general procedure for the $[Rh(CO)_2Cl]_2$ catalyzed Pauson-Khand reaction was followed. The reaction was carried out with allene-yne **12b** (204 mg, 0.398 mmol), $[Rh(CO)_2Cl]_2$ (7.8 mg, 0.02 mmol, 5 mol%), and DCE (4 mL). The reaction was heated to 50 °C for 1 h. The crude product was purified by column chromatography using 40% ethyl acetate/hexanes to afford **14b**{*1, 0, 37*} (189 mg, 88%) as an amorphous, brown solid. (R_f = 0.09, 30% ethyl acetate/hexanes); M.p. 100-101 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, *J* = 8.1 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.42 – 7.27 (m, 5H), 7.24 – 7.19 (m, 3H), 5.81 (s, 1H), 4.35 (A of an ABq, *J* = 14.7 Hz, 1H), 4.33 (A of an ABq, *J* = 18.0 Hz, 1H), 3.82 (s, 3H), 3.43 (B of an ABq, *J* = 14.7 Hz, 1H), 3.21 (B of an ABq, *J* = 18.0 Hz, 1H), 3.02 (A of an ABq, *J* = 20.1 Hz, 1H), 2.91 (B of an ABq, *J* = 20.7 Hz, 1H), 1.62 (s, 9H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 171.9, 171.5, 154.7, 149.3, 136.2, 135.6, 135.1, 134.4, 130.8, 130.0, 128.6, 126.4, 124.8, 124.6, 122.7, 121.0, 119.6, 115.1, 115.1, 83.8, 65.8, 53.0, 44.7, 37.3, 29.4, 28.1, 7.9; IR (thin film) ν 3056, 2980, 2950, 1736, 1707, 1645, 1453, 1372, 1258, 1157, 1073, 736 cm^{-1}; MS *m/z* (%) 540 (69), 525 (30), 510 (19), 311 (46), 230 (35); EI-HRMS calcd for $C_{32}H_{32}N_2O_6$ *m/z* [M^+] 540.2260; found 540.2258.



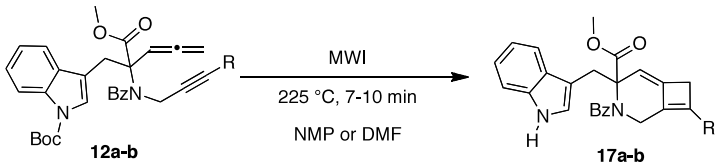
14c

***tert*-butyl-3-((2-benzoyl-3-(methoxycarbonyl)-6-oxo-2,3,5,6-tetrahydro-1*H*-cyclopenta[*c*]pyridin-3-yl)methyl)-1*H*-indole-1-carboxylate (14c):** The general procedure for the $[Rh(CO)_2Cl]_2$ catalyzed Pauson-Khand reaction was followed. The reaction was carried out with allene-yne **12c** (24 mg, 0.048 mmol), $[Rh(CO)_2Cl]_2$ (1.0 mg, 0.0025 mmol, 5.36 mol%), and DCE (0.5 mL). The reaction was heated to 50 °C for 2.5 h. The crude product was purified by column chromatography using 30% ethyl acetate/hexanes to afford the product **14c** (17.7 mg, 70%) as viscous oil. (R_f = 0.35, 40% ethyl acetate/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13 (d, *J* = 8.1 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.29 – 7.46 (m, 5H), 7.18 – 7.25 (m, 3H), 5.95 (d, *J* = 1.2 Hz, 1H), 5.69 (d, *J* = 1.5 Hz, 1H), 4.40 (A of an ABq, *J* = 18.3 Hz, 1H), 4.36 (A of an ABq, *J* = 14.7 Hz, 1H), 3.84 (s, 3H), 3.45 (B of an ABq, *J* = 15.6 Hz, 1H), 3.34 (B of an ABq, *J* = 18.3 Hz, 1H), 3.05 (A of an ABq, *J* = 21.0 Hz, 1H), 2.94 (B of an ABq, *J* = 21.0 Hz, 1H), 1.64 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 171.8, 171.2, 161.0, 149.3, 135.4, 135.3, 135.1, 130.7, 130.0, 128.7, 127.5, 126.4, 124.8, 124.7, 123.8, 122.7, 119.5, 115.2, 114.8, 83.9, 78.1 65.7, 53.1, 45.5, 37.8, 29.3, 28.1. IR (thin film) ν 1728, 1638, 1458, 1372, 1262, 1217, 1160 cm^{-1}. MS [*m/z* + Na] (%) 549 (100). HRMS calculated for $C_{31}H_{30}N_2O_6Na$: 549.2002; found: 549.2029.

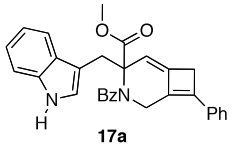


14b{*1, 0, 37*} **15**{*1, 0, 37*}

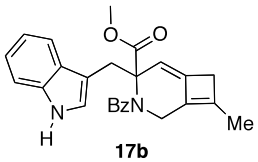
Heterocyclic bicyclo[4.3.0]nona-2,7-dien-1-one (15){*1, 0, 37*}**:** A solution of **14b**{*1, 0, 37*} (239 mg, 0.44 mol) in DMSO (4.4 mL) in a 10 mL round bottomed flask was placed into a silicone oil bath preheated to 180 °C for 15 min until no starting material was evident by TLC. The reaction mixture was cooled to room temperature and partitioned between water and ether. The layers were separated and the aqueous layer extracted with ether (2x). The combined organic layers were washed with water (3x) and brine (1x), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (50% to 60% ethyl acetate/hexanes) to afford **15**{*1, 0, 37*} (152 mg, 78%) as an amorphous, brown solid. (R_f = 0.38, 60% ethyl acetate/hexanes). M.p. 175-176 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.21 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.32 (m, 4H), 7.23 – 7.15 (m, 3H), 7.10 (dt, *J* = 6.9, 1.2 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 5.83 (s, 1H), 4.42 (A of an ABq, *J* = 14.7 Hz, 1H), 4.30 (A of an ABq, *J* = 17.7 Hz, 1H), 3.81 (s, 3H), 3.49 (B of an ABq, *J* = 14.7 Hz, 1H), 3.04 (A of and ABq, *J* = 21.6 Hz, 1H), 2.95 (B of an ABq, *J* = 17.7 Hz, 1H), 2.95 (B of an ABq, *J* = 21.6 Hz, 1H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 171.9, 171.7, 155.2, 135.9, 135.8, 135.6, 134.1, 129.9, 128.6, 128.0, 126.5, 123.6, 122.0, 121.5, 119.6, 119.2, 111.2, 109.8, 66.4, 52.8, 44.5, 37.4, 29.6, 7.7; IR (thin film) ν 3351, 3056, 2947, 2853, 1735, 1626, 1405, 1243, 1057, 740 cm^{-1}; MS *m/z* (%) 412 (32), 282 (42), 130 (74), 105 (100) ; EI-HRMS calcd for $C_{26}H_{24}N_2O_3$ *m/z* [M^+] 412.1787; found 412.1780.



General procedure for microwave assisted thermal [2 + 2] cycloaddition: A solution of allene-yne in dry NMP or DMF was heated under microwave irradiation in a Biotage Initiator microwave reactor at 225 °C for 7-10 min (Absorption level: very high; vial type: 2 – 5 mL; pre-stirring: 0; initial power: 0; approximate ramp time: 4 min). No starting material was evident by TLC after the described reaction time. The mixture was partitioned between ether and water and the layers were separated. The aqueous layer was extracted with ether (3x) and the combined organic layers were washed with water (3x) and brine (1x), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography using ethyl acetate/hexanes.

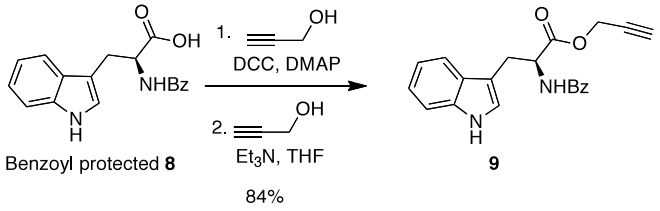


methyl-4-((1*H*-indol-3-yl)methyl)-3-benzoyl-8-phenyl-3-azabicyclo[4.2.0]octa-1(8),5-diene-4-carboxylate (17a): The general procedure for the microwave assisted thermal [2 + 2] cycloaddition was followed. The reaction was carried out with allene-yne **12a** (229.6 mg, 0.4 mmol) in dry NMP (4 mL) and heated to 225 °C for 10 min. The crude product was purified by column chromatography using 20-40% ethyl acetate/hexanes to afford the product **17a** (85 mg, 45%) as a yellow solid. (R_f = 0.2, 40% ethyl acetate/hexanes). M.p. 128-130 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (bs, 1H), 7.76 (d, *J* = 6.9 Hz, 1H), 7.29 – 7.35 (m, 5H), 7.12 – 7.22 (m, 6H), 7.01 (d, *J* = 2.1 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 2H), 5.36 (s, 1H), 4.47 (A of an ABq, *J* = 14.7 Hz, 1H), 4.16 (d, *J* = 17.4 Hz, 1H), 3.82 (s, 3H), 3.42 (B of an ABq, *J* = 14.7 Hz, 1H), 3.34-3.39 (m, 2H), 2.89 (td, *J* = 17.1 and 3.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 172.2, 137.5, 136.8, 135.8, 135.7, 133.7, 133.5, 129.3, 128.6, 128.55, 128.50, 127.9, 126.3, 126.2, 123.3, 121.9, 119.8, 119.6, 110.9, 110.6, 109.7, 66.4, 52.7, 44.7, 35.6, 30.0. IR (thin film) ν 1719, 1638, 1245 cm^{-1}. MS [*m/z* + Na] (%) 497 (95), 443 (20), 365 (38). HRMS calculated for $C_{31}H_{26}N_2O_3Na$: 497.1841; found: 497.1842.

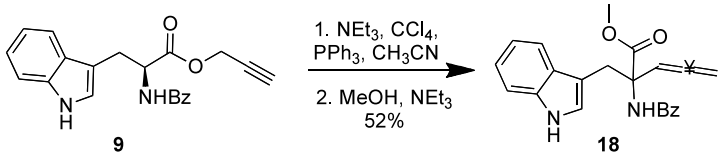


methyl-4-((1*H*-indol-3-yl)methyl)-3-benzoyl-8-methyl-3-azabicyclo[4.2.0]octa-1(8),5-diene-4-carboxylate (17b): The general procedure for the microwave assisted thermal [2 + 2] cycloaddition was followed. The reaction was carried out with allene-yne **12b** (503 mg, 0.98 mmol) in freshly distilled DMF (9.8 mL) and heated to 225 °C for 7 min. The

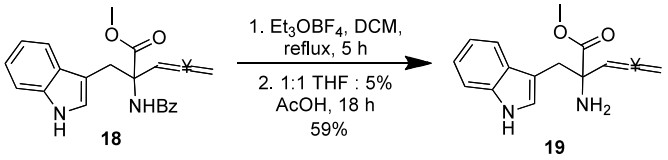
crude product was purified by column chromatography using 30% ethyl acetate/hexanes to afford the product **17b** (203 mg, 50%) as an amorphous brown solid. (R_f = 0.13, 30% ethyl acetate/hexanes). M.p. 91-92°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.46 (bs, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.34 – 7.26 (m, 4H), 7.20 – 7.07 (m, 4H), 7.01 (d, *J* = 1.2 Hz, 1H), 5.10 (s, 1H), 4.41 (A of an ABq, *J* = 14.7 Hz, 1H), 3.82 (s, 3H), 3.80 – 3.74 (m, 4H), 3.40 (B of an ABq, *J* = 14.7 Hz, 1H), 2.99 (m, 2H), 2.65 – 2.59 (m, 1H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 172.1, 138.9, 137.0, 136.4, 135.8, 134.4, 129.0, 128.6, 128.3, 126.2, 123.5, 121.7, 119.7, 119.3, 110.9, 110.5, 105.9, 66.1, 52.5, 43.7, 39.1, 30.0, 15.1; IR (thin film) ν 3351, 3056, 2947, 2853, 1735, 1626, 1405, 1243, 1057, 740 cm^{-1}; MS *m/z* (%) 412 (32), 282 (42), 130 (74), 105 (100) ; EI-HRMS calcd for $C_{26}H_{24}N_2O_3$ *m/z* [M$^+$] 412.1787; found 412.1780.



Prop-2-ynyl 2-(benzamido)-3-(1*H*-indol-3-yl)propanoate (9): To a solution of propargyl alcohol (1.73 mL, 29.7 mmol), dicyclohexylcarbodiimide (5.10 g, 24.7 mmol), and 4-(dimethylamino)pyridine (152 mg, 1.24 mmol) in CH_2Cl_2 (150 mL) was added a solution of benzoyl protected **8** (7.62 g, 24.7 mmol) in THF : CH_2Cl_2 (1 : 1) (82 mL) via cannula over 5-10 min. The resultant suspension was stirred for 16 h overnight until no starting material was evident by TLC. The mixture was filtered through a pad of silica gel (150 mL fritted funnel approximately half full) eluting with 250 mL of a 50% ethyl acetate/hexanes solution and the filtrate concentrated under vacuum. The residue was dissolved in THF (40 mL) and to this solution was added propargyl alcohol (0.87 mL, 12.4 mmol) and triethylamine (7 mL, 50.4 mmol). The solution was stirred for 1 h, when full conversion to the product from the intermediate oxazolidinone was observed by TLC. The reaction mixture was filtered through celite (150 mL fritted funnel approximately half full), eluting with ethyl acetate, and the filtrate concentrated under vacuum. The crude residue was chromatographed on silica gel (30% to 50% ethyl acetate/hexanes) to afford **9** (6.82 g, 84%) as an amorphous, brown solid. (R_f = 0.15, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.49 (bs, 1H), 7.68 (d, *J* = 7.2 Hz, 2H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.39 – 7.34 (m, 3H), 7.20 (dt, *J* = 6.9, 0.9 Hz, 1H), 7.09 (dt, *J* = 6.9, 0.9 Hz, 1H), 7.05 (d, *J* = 2.9 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 5.21 (dt, *J* = 7.8, 5.1 Hz, 1H), 4.77 (A of an ABq, d, *J* = 15.6, 2.4 Hz, 1H), 4.67 (B of an ABq, d, *J* = 15.6, 2.4 Hz, 1H), 3.49 (d, *J* = 5.1 Hz, 2H), 2.54 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 167.0, 136.1, 133.6, 131.7, 128.5, 127.6, 127.0, 123.1, 122.2, 119.7, 118.5, 111.4, 109.5, 77.1, 75.5, 53.5, 52.8, 27.4; IR (thin film) ν 3412, 3293, 3057, 2932, 2129, 1745, 1648, 1521, 1182, 743 cm^{-1}; MS *m/z* (%) 347 (15), 346 (64), 325 (13), 225 (29), 130 (100); EI-HRMS calcd for $C_{21}H_{18}N_2O_3$ *m/z* [M$^+$] 346.1317; found 346.1391.

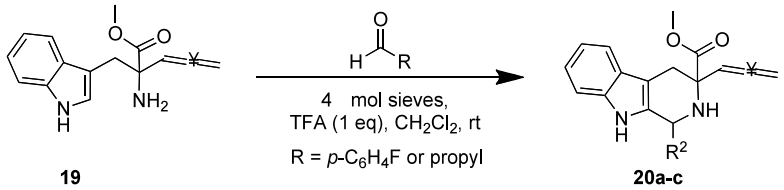


Methyl 2-((1*H*-indol-3-yl)methyl)-2-(benzamido)penta-3,4-dienoate (18): To a solution of propargyl ester **9** (6.33 g, 18.3 mmol) in freshly distilled CH_3CN (91 mL) was added triethylamine (10.7 mL, 76.7 mmol), carbon tetrachloride (6.2 mL, 64.0 mmol), and triphenylphosphine (14.7 g, 56.6 mmol). The reaction mixture was stirred for 20 h until no starting material was evident by TLC. The mixture was poured into a solution of ether : hexanes (350 mL : 100 mL) and the yellow/white solid precipitate was removed by vacuum filtration through celite (150 mL fritted funnel approximately half full). The filtrate was concentrated under vacuum and the residue dissolved in a solution of methanol (150 mL) and triethylamine (15 mL). The reaction mixture was stirred for another 20 h when TLC showed full conversion to the product and an impurity spot (R_f = 0.35, 30% ethyl acetate/hexanes). The solvent was removed under vacuum and the residue chromatographed on silica gel (25% ethyl acetate/ hexanes) to afford pure **18**(664 mg, ~10%), and **18** contaminated with triphenylphosphine oxide (> 8 g, mass ratio ~ 29% based upon isolated product. See below). The contaminated material was dissolved in ether and stored in a freezer (-20 °C) overnight. The mixture was filtered through celite (150 mL fritted funnel approximately half full) to remove precipitated triphenylphosphine oxide and the filtrate concentrated under vacuum. The residue was chromatographed on silica gel (40% to 50% ether/pentane) to afford pure **18** (2.35 g, 36%) as an amorphous, off-white solid. [Performing the reaction on 1.25 g of **9** affords 673 mg (52%) of **18** and the second triphenylphosphine oxide precipitation step was not necessary.] (R_f = 0.31, 30% ethyl acetate/hexanes). M.p. 67-68 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.49 (bs, 1H), 7.66 (d, *J* = 7.8 Hz, 2H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.49 – 7.44 (m 1H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 3.0 Hz, 1H), 6.96 (s, 1H), 5.79 (t, *J* = 6.6 Hz, 1H), 4.95 – 4.92 (m, 1H), 4.88 – 4.82 (m, 1H), 3.90 (A of an ABq, *J* = 14.7 Hz, 1H), 3.76 (s, 3H), 3.70 (B of an ABq, *J* = 14.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.1, 172.5, 166.6, 135.8, 134.5, 131.5, 128.5, 127.9, 126.9, 124.0, 121.8, 119.5, 118.8, 111.2, 109.2, 93.2, 79.7, 62.9, 52.9, 31.0; IR (thin film) ν 3404, 3325, 3057, 2950, 1958, 1736, 1655, 1515, 1484, 1248, 1099, 739 cm^{-1}; MS *m/z* (%) 361 (12), 360 (35), 255 (25), 240 (62), 239 (98), 105 (100); EI-HRMS calcd for $C_{22}H_{20}N_2O_3$ *m/z* [M^+] 360.1474; found 360.1471.



Methyl 2-((1*H*-indol-3-yl)methyl)-2-aminopenta-3,4-dienoate (19): To a solution of **18** (1.00 g, 2.77 mmol) in CH_2Cl_2 (2.8 mL) was added Et_3OBF_4 (9.90 mL of a 1.4 M

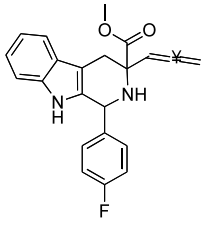
solution in CH_2Cl_2, 13.9 mmol).[1] The mixture was heated to reflux (cold finger) for 5 h when no starting material was evident by TLC (baseline iminium salt intermediate and impurity R_f = 0.78, 60% ethyl acetate/hexanes). The reaction mixture was cooled to room temperature then concentrated under vacuum. The residue was dissolved in THF (2.5 mL) and 5% aqueous acetic acid (2.5 mL) and stirred open to the atmosphere at room temperature for 16 h. The mixture was quenched with sat'd K_2CO_3 and stirred for 5 – 10 min then diluted with ethyl acetate and water. An emulsion forms that dissipates over ~ 5 min. The layers were separated and the aqueous layer was extracted with ethyl acetate (3x) and the combined organic layers were washed with brine (1x), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (20% to 40% to 80% ethyl acetate/hexanes) to afford **19** (421 mg, 59%) as a viscous, red/brown oil. Yields consistently ranged from 36% to 46% when using less than 1 g of starting benzamide **18**. (R_f = 0.08, 60% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.38 (bs, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.18 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.12 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.06 (d, *J* = 2.1 Hz, 1H), 5.62 (t, *J* = 6.6 Hz, 1H), 4.96 (d, *J* = 6.6 Hz, 2H), 3.69 (s, 3H), 3.46 (A of an ABq, *J* = 14.1 Hz, 1H), 3.14 (B of an ABq, *J* = 14.1 Hz, 1H), 1.92 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5, 175.5, 135.9, 128.0, 123.6, 122.0, 119.5, 119.2, 111.1, 110.0, 96.4, 79.4, 61.1, 52.4, 35.7; IR (thin film) ν 3365, 3176, 3057, 2950, 2872, 1956, 1732, 1242, 1203, 859, 744 cm^{-1}; MS *m/z* (%) 256 (74), 239 (37), 196 (16), 130 (100); EI-HRMS calcd for $C_{15}H_{16}N_2O_2$ *m/z* [M^+] 256.1212; found 256.1215.



19 **20a-c**

Allenic Tetrahydro-β-Carbolines 20a-c.

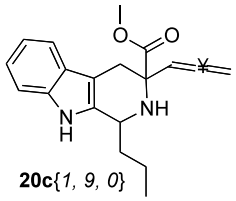
General Procedure A: Preparation of **20b**{1, 5, 0}.



20b{*1, 5, 0*}

[1] Meerwein's reagent (Et_3OBF_4) was prepared using a known procedure (Meerwein, H; Anderson, B. C.; Vogl, O. H.; McKusick, B. C. *Organic Syntheses* **1966**, *46*, 113). The solvent was removed from the salt under vacuum and the flask purged with argon and diluted to 1.4 M in CH_2Cl_2. The solution could be stored in a septum-sealed flask in a desiccator in the freezer (-20 °C) for 6-8 weeks without observable differences in reactivity. The flask was purged with argon between uses.

Methyl 1-(4-fluorophenyl)-2,3,4,9-tetrahydro-3-(propa-1,2-dienyl)-1*H*-pyrido[3,4-*b*]indole-3-carboxylate 20b{*1, 5, 0*}**:** To a solution of **19** (204 mg, 0.79 mmol) in CH_2Cl_2 (7.9 mL, use MeOH for formation of **20a**{*1, 2, 0*}, see below) was added and activated[2] powdered 4 Å molecular sieves (373 mg, 470 mg/mmol), *p*-fluorobenzaldehyde {*85*} (0.09 mL, 0.83 mmol), and trifluoroacetic acid (0.06 mL, 0.79 mmol). The reaction mixture was stirred for 3 h until no starting material was evident by TLC. The mixture was quenched with sat'd $NaHCO_3$ (~ 2 – 3 mL) and stirred for 5 min. (Alternatively, the molecular sieves can be removed by gravity filtration through filter paper prior to $NaHCO_3$ workup with no change in yield). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3x). The combined organic layers were washed with water (1x) and brine (1x), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (10% to 20% ethyl acetate hexanes; the residual *p*-fluorobenzaldehyde can be observed by UV on the TLC plate and removed) to afford **20b**{*1, 5, 0*} (200 mg, 70%) in a 2 : 1 mixture of diastereomers as an amorphous white solid. *Denotes minor diastereomer. (R_f = 0.44, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57 – 7.55 (m, 1H), 7.41 – 7.37 (m, 3H), 7.25 – 7.02 (m, 5H), *5.48 (t, *J* = 6.6 Hz, 0.3H), *5.43 (bs, 0.3H), 5.35 (t, *J* = 6.6 Hz, 0.7H), 5.24 (bs, 0.7H), *5.01 (d, *J* = 6.6 Hz, 0.7H), 4.95 – 4.89 (m, 0.7H), 4.76 – 4.70 (m, 0.7H), 3.83 (s, 2.1H), *3.66 (s, 0.9H), *3.64 (A of an ABq, d, *J* = 15.3, 2.7 Hz, 0.3H), 3.28 – 3.26 (m, 1.3H), *3.04 (B of an ABq, d, *J* = 15.3, 2.7 Hz, 0.3H), 2.80 (bs, 0.7H), *2.65 (bs, 0.3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, *206.9, *174.2, 173.5, 162.8 (d, J_{CF} = 245.3 Hz), *137.7 (d, J_{CF} = 3.0 Hz), 136.8 (d, J_{CF} = 3.0 Hz), *133.6, 133.4, 130.5 (d, J_{CF} = 8.3 Hz), *130.3 (d, J_{CF} = 8.3 Hz), 127.4, *127.0, 121.9, 119.5, *118.4, 118.2, 115.7 (d, J_{CF} = 21.0 Hz), 110.8, *107.9, 107.8, *95.5, 92.6, *79.6, 78.7, 77.2, *76.8, *62.4, 60.9, *55.1, 54.0, 52.6, *52.4, *29.9, 29.1; IR (thin film) ν 3391, 3057, 2951, 2847, 1952, 1732, 1604, 1508, 1253, 1224, 1153, 842, 742 cm^{-1}; MS *m/z* (%) 363 (11), 362 (45), 323 (9), 303 (52), 239 (81), 236 (100); EI-HRMS calcd for $C_{22}H_{19}FN_2O_2$ *m/z* $[M]^+$ 362.1431; found 362.1427.

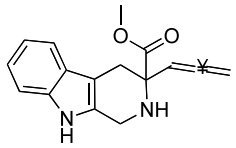


20c{*1, 9, 0*}

Methyl 2,3,4,9-tetrahydro-3-(propa-1,2-dienyl)-1-propyl-1*H*-pyrido[3,4-*b*]indole-3-carboxylate 20c{*1, 9, 0*}**:** According to General Procedure A, **19** (51 mg, 0.20 mmol), activated powdered 4 Å molecular sieves (93 mg, 470 mg/mmol), butyraldehyde (19 μL, 0.21 mmol), and trifluoroacetic acid (15 μL, 0.20 mmol) were reacted in CH_2Cl_2 (2 mL) for 50 min to afford **20c**{*1, 9, 0*} (41 mg, 68%) as a 2 : 1 mixture of diastereomers. The diastereomers were separated by chromatography on silica gel (25% ethyl acetate/hexanes). Major diastereomer (off-white solid, contains ~ 10% minor diastereomer by ^{1}H NMR): (R_f = 0.28, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 (bs, 1), 7.51 (d, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.5

[2] The powdered molecular sieves are activated by flame drying under vacuum (~ 3 torr) until the powder is free flowing and does not adhere to the walls of the flask (~ 2 – 3 min).

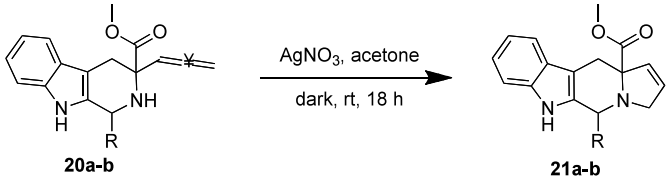
Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 5.25 (t, *J* = 6.5 Hz, 1H), 4.85 – 4.82 (m, 1H), 4.71 – 4.67 (m, 1H), 4.25 – 4.24 (m, 1H), 3.85 (s, 3H), 3.20 (A of an ABq, *J* = 15.5 Hz, 1H), 3.08 (B of an ABq, d, *J* = 15.5, 2.5 Hz, 1H), 2.57 (bs, 1H), 1.93 – 1.87 (m, 1H), 1.79 – 1.71 (m, 1H), 1.59 – 1.51 (m, 2H), 1.02 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 173.9, 136.2, 134.6, 127.6, 121.5, 119.4, 117.9, 110.7, 106.9, 92.8, 78.5, 60.4, 52.5, 48.4, 37.1, 29.5, 18.7, 14.1; IR (thin film) ν 3402, 3056, 2956, 2932, 2870, 1952, 1732, 1452, 1257, 1156, 852, 742 cm^{-1}; MS *m/z* (%) 311 (7), 310 (20), 267 (23), 239 (39), 207 (46), 180 (70), 119 (94); EI-HRMS calcd for $C_{19}H_{22}N_2O_2$ *m/z* [M^+] 310.1681; found 310.1691. Minor diastereomer (yellow oil, contains ~ 4% major diastereomer by ^{1}H NMR): (R_f = 0.34, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (bs, 1), 7.52 (d, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.17 – 7.09 (m, 2H), 5.48 (t, *J* = 6.5 Hz, 1H), 5.07 – 5.00 (m, 2H), 4.40 – 4.38 (m, 1H), 3.60 (s, 3H), 3.55 (A of an ABq, d, *J* = 15.0, 2.0 Hz, 1H), 2.87 (B of an ABq, d, *J* = 15.0, 2.0 Hz, 1H), 2.47 (bs, 1H), 1.88 – 1.82 (m, 1H), 1.77 – 1.68 (m, 1H), 1.58 – 1.51 (m, 2H), 1.02 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.9, 174.2, 136.2, 134.7, 127.2, 121.5, 119.43, 118.2, 110.6, 107.3, 95.7, 79.5, 61.8, 52.3, 49.7, 38.1, 29.9, 18.6, 14.1; IR (thin film) ν 3397, 3056, 2955, 2871, 1955, 1728, 1452, 1260, 1204, 857, 742 cm^{-1}.



20a{*1, 2, 0*}

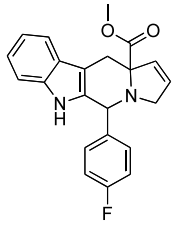
Methyl-2,3,4,9-Tetrahydro-3-(propa-1,2-dienyl)-1*H*-pyrido[3,4-*b*]indole-3-carboxylate 20a{*1, 2, 0*}**:** According to General Procedure I, **19** (57 mg, 0.22 mmol), activated powdered 4 Å molecular sieves (207 mg, 940 mg/mmol), formaldehyde (0.02 mL of a 37% aqueous solution, 0.26 mmol), and trifluoroacetic acid (16 μL, 0.22 mmol) were reacted in MeOH (5.5 mL) for 6 h to afford **20a**{*1, 2, 0*} (42 mg, 71%) as an amorphous brown solid. (R_f = 0.08, 60% ethyl acetate/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13 (bs, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.19 – 7.08 (m, 2H), 5.39 (t, *J* = 6.6 Hz, 1H), 5.00 – 4.94 (m, 1H), 4.92 – 4.86 (m, 1H), 4.25 (A of an ABq, *J* = 15.6 Hz, 1H), 4.12 (B of an ABq, *J* = 15.6 Hz, 1H), 3.71 (s, 3H), 3.37 (A of ABq, t, *J* = 15.3, 1.5 Hz, 1H), 3.01 (B of ABq, t, *J* = 15.3, 1.5 Hz, 1H), 2.49 (bs, 1H), minor inseparable impurities: 7.4 (d, *J* = 8.1 Hz, 0.19H), 5.33 (s, 0.26H), 3.19 (s, 0.39H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3, 173.9, 136.2, 131.0, 127.2, 121.4, 119.2, 117.8, 110.7, 106.7, 94.1, 79.2, 60.6, 52.4, 39.8, 29.7; IR (thin film) ν 3395, 3175, 3058, 2949, 2849, 1954, 1732, 1453, 1258, 857, 743 cm^{-1}; MS *m/z* (%) 268 (13), 267 (5), 239 (55), 143 (100); EI-HRMS calcd for $C_{16}H_{16}N_2O_2$ *m/z* [M^+] 268.1212; found 268.1210.

Tetracyclic Indolyl Pyrrolines 21a-b



20a-b **21a-b**

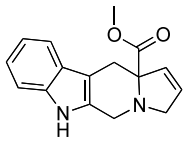
General Procedure B: Preparation of **21b**{*1, 5, 0*}



21b{*1, 5, 0*}

Methyl-5-(4-Fluorophenyl)-5,6,11,11a-tetrahydro-3*H*-indolizino[6,7-*b*]indole-11a-carboxylate 21b{*1, 5, 0*}**:** To a solution of allenic tetrahydro-β-carboline **20b**{*1, 5, 0*} (51 mg, 0.141 mmol, as a 2 : 1 mixture of diastereomers) in acetone (2.8 mL) in a septum-sealed 10 mL reaction vial wrapped in aluminum foil, was added silver nitrate (4.8 mg, 0.028 mmol, 20 mol%, weighed and transferred under low light). The reaction mixture was kept in a dark hood and stirred for 18 h until no starting material was evident by TLC (R_f = 0.51, 30% ethyl acetate/hexanes). The reaction mixture was diluted with CH_2Cl_2 and washed with sat'd $NaHCO_3$ (2x). The combined aqueous layers were extracted with CH_2Cl_2 (2x) and the combined organic layers dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (15% ethyl acetate/hexanes) to afford **21b**{*1, 5, 0*} (37 mg, 72%) as a 2 : 1 mixture of diastereomers as an amorphous yellow solid. An 83% yield of **21b**{*1, 5, 0*} was obtained when using 40 mol% silver nitrate under similar conditions. The diastereomers were separated via silica gel column chromatography (column diameter: 1.5 cm; silica gel height: 14.5 cm; 100% toluene; column progress followed by UV and $KMnO_4$ staining of the TLC plates). Major diastereomer (amorphous yellow solid, contains ~ 6% minor diastereomer by ^{1}H NMR): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61 (dd, J_{HF} = 5.4 Hz, J = 8.4 Hz, 2H), 7.57 – 7.53 (m, 1H), 7.40 – 7.35 (m, 1H), 7.25 – 7.20 (m, 1H), 7.17 – 7.09 (m, 4H), 6.02 (dt, J = 6.3, 1.8 Hz, 1H), 5.97 (dt, J = 6.3, 1.8 Hz, 1H), 5.04 (d, J = 1.5 Hz, 1H), 4.12 (A of an ABq, t, J = 13.8, 1.8 Hz, 1H), 3.84 (A of an ABq, J = 14.7 Hz, 1H), 3.80 (B of an ABq, t, J = 13.8, 1.8 Hz, 1H), 3.47 (s, 3H), 2.79 (B of an ABq, d, J = 14.7, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 162.5 (d, J_{CF} = 245.0 Hz), 136.8 (d, J_{CF} = 2.5 Hz), 136.0, 134.3, 131.1, 130.1 (d, J_{CF} = 7.5 Hz), 128.4, 126.9, 121.6, 119.6, 118.2, 115.6 (d, J_{CF} = 21.3 Hz), 111.0, 107.7, 74.9, 61.3, 59.9, 52.1, 29.3. Minor diastereomer (amorphous white solid, spectroscopically pure by ^{1}H NMR): ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.56 (ddd, J = 7.7, 1.4, 0.7 Hz, 1H), 7.37 (bs, 1H), 7.37 (dd, J_{HF} = 5.6 Hz, J = 8.4 Hz, 2H), 7.20 (ddd, J = 7.7, 1.4, 0.7 Hz, 1H), 7.14 – 7.10 (m, 2H), 7.03 (dd, J_{HF} = 9.1 Hz, J = 8.4 Hz, 2H), 6.11 (ddd, J = 6.3, 2.1, 1.4 Hz, 1H), 6.01 (ddd, J = 6.3, 2.1, 1.4 Hz, 1H), 5.51 (s, 1H), 3.73 – 3.71 (m, 1H), 3.70 (A of an ABq, d, J = 14.0, 1.4 Hz, 1H), 3.57 (s, 3H), 3.38 (B of an ABq, t, J = 13.3, 1.4 Hz, 1H), 2.99 (B of an ABq, d, J = 14.0, 2.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 162.6 (d, J_{CF} = 245 Hz),

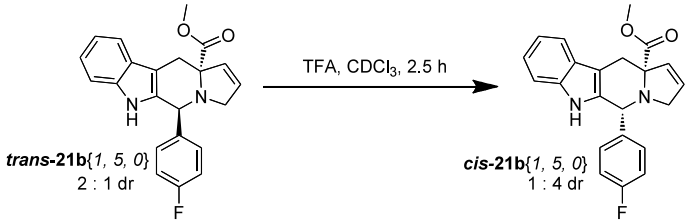
136.8, 136.6, 136.1, 132.1, 131.5, 130.3 (d, J_{CF} = 8.8 Hz), 127.1, 121.7, 119.4, 118.4, 115.6 (d, J_{CF} = 21.3 Hz), 110.8, 108.0, 74.0, 58.6, 54.3, 51.7, 29.5. (IR, MS, and HRMS analyses performed on the original 2 : 1 diastereomeric mixture.) IR (thin film) ν 3386, 3059, 2950, 2845, 2800, 1724, 1603, 1506, 1463, 1221, 1054, 840, 742 cm^{-1}; MS *m/z* (%) 362 (20), 331 (19), 303 (100), 236 (80); EI-HRMS calcd for $C_{22}H_{19}FN_2O_2$ *m/z* [M^+] 362.1431; found 362.1416.



21a{*1, 2, 0*}

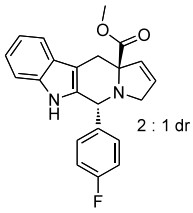
Methyl-5,6,11,11a-tetrahydro-3*H*-indolizino[6,7-*b*]indole-11a-carboxylate

21a{*1, 2, 0*}**:** According to General Procedure J, **20a**{*1, 2, 0*} (33.7 mg, 0.126 mmol) in acetone (2.5 mL), was reacted with silver nitrate (4.3 mg, 0.025 mmol) for 18 h. The crude residue was chromatographed on silica gel (25% ethyl acetate/hexanes) to afford **21a**{*1, 2, 0*} (18.9 mg, 56%) as an amorphous, white solid. (R_f = 0.46, 60% ethyl acetate/hexanes). M.p. 179-180 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (bs, 1), 7.51 (d, *J* = 7.5 Hz, 1H), 7.32 – 7.29 (m, 1H), 7.18 – 7.07 (m, 2H), 6.17 (dt, *J* = 6.0, 1.8 Hz, 1H), 6.02 (dt, *J* = 6.0, 1.8 Hz, 1H), 4.49 (A of an ABq, *J* = 14.4, 1.8 Hz, 1H), 4.10 (B of an ABq, *J* = 14.4 Hz, 1H), 3.99 (A of an ABq, t, *J* = 12.9, 1.8 Hz, 1H), 3.88 (B of an ABq, t, *J* = 12.9, 1.8 Hz, 1H), 3.61 (A of an ABq, d, *J* = 14.7, 2.1 Hz, 1H), 3.55 (s, 3H), 2.82 (B of an ABq, t, *J* = 14.7, 2.1 Hz, 1H), minor inseparable impurities: 5.40 (A of an ABq, *J* = 11.4 Hz, 0.15H), 5.35 (B of an ABq, *J* = 11.4 Hz, 0.15H), 3.21 (s, 0.18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 136.4, 132.5, 132.0, 131.4, 127.4, 121.4, 119.2, 118.0, 110.7, 107.5, 72.7, 56.9, 51.7, 43.7, 29.3; IR (thin film) ν 3392, 3144, 3060, 2947, 2878, 2845, 1726, 1448, 1170, 1027, 741 cm^{-1}; MS *m/z* (%) 268 (17), 253 (25), 209 (69), 143 (66), 117 (100); EI-HRMS calcd for $C_{16}H_{16}N_2O_2$ *m/z* [M^+] 268.1212; found 268.1210.

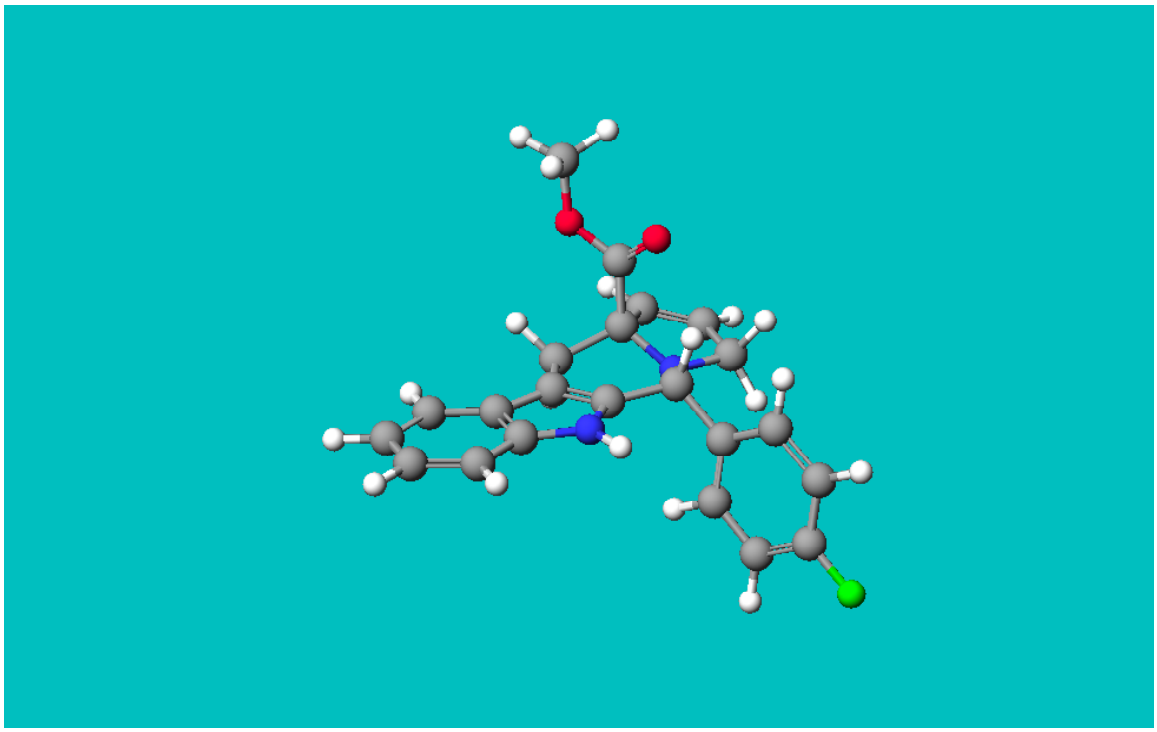


Thermodynamic Isomerization of *trans*-21b{*1, 5, 0*}**:** To a solution of ***trans*-21b**{*1, 5, 0*} (5.0 mg, 0.014 mmol, 2 : 1 mixture of diastereomers) in $CDCl_3$ (0.5 mL) in an NMR tube was added trifluoroacetic acid (3 μL, 0.034 mmol). The reaction was followed by ^{1}H NMR (peaks are broadened in the mixture due to TFA-amine salts). Analysis after 2.5 h indicated a reversal in the diastereomer ratio from 2 : 1 to 1 : 4 in favor of the major product isomer shown above. Analysis after 24 h showed the same ratio. The reaction mixture was diluted with ether and washed with sat'd $NaHCO_3$ (2x). The combined aqueous layers were extracted into ether (2x) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to afford crude ***cis*-21b**{*1, 5, 0*} (5.0 mg, 100%) as a 1 : 4 mixture of diastereomers. Subsequent reaction of the crude

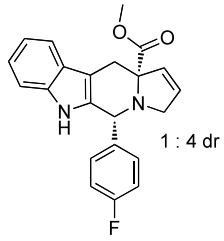
product with 6 μL trifluoroacetic acid in the same manner for an additional 24 h did not change the diastereomeric ratio. Spectral data for each isomer is provided above. The isomers shown are supported by modeling studies (see text for heats of formation and below for 3D models).



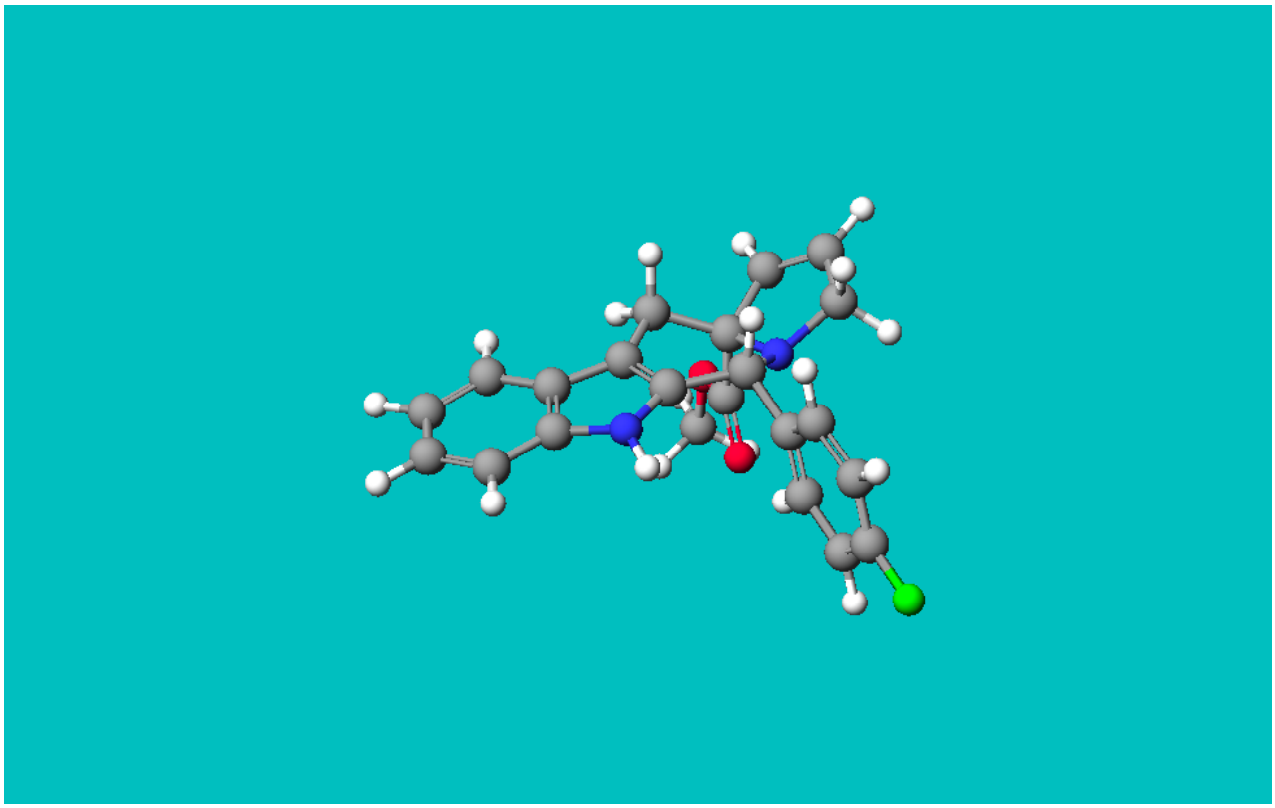
***trans*-21b**{*1, 5, 0*}



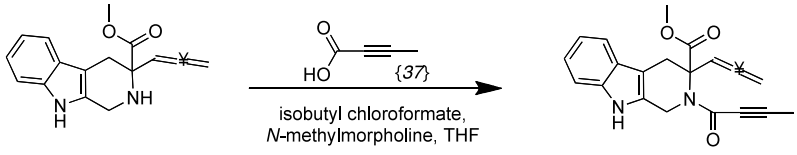
Cache Model of *trans*-21b{*1, 5, 0*}



***cis*-21b**{*1, 5, 0*}



Cache Model of *cis*-21b{*1, 5, 0*}

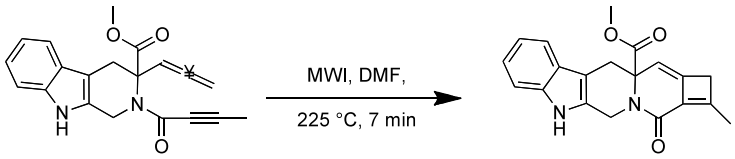


20a{*1, 2, 0*}

23a{*1, 2, 37*}

Methyl-2-(but-2-ynoyl)-2,3,4,9-tetrahydro-3-(propa-1,2-dienyl)-1*H*-pyrido[3,4-*b*]indole-3-carboxylate 23a{*1, 2, 37*}**:** To a solution of 2-butynoic acid (16 mg, 0.18 mmol) and *N*-methylmorpholine (51 μL, 0.46 mmol) in THF (1.8 mL) at 0 °C was added isobutyl chloroformate (24 μL, 0.18 mmol). The resultant white suspension was warmed to room temperature and stirred for 25 min. A solution of **20a**{*1, 2, 0*} (41 mg, 0.15 mmol) in THF (1.5 mL) was added via cannula and the mixture stirred for 20 h until no

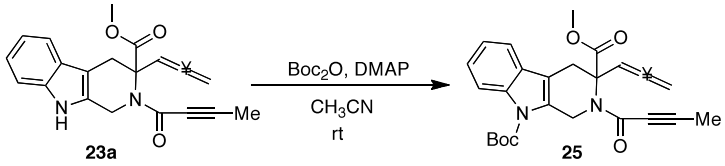
starting material was evident by TLC. The reaction mixture was quenched with sat'd $NaHCO_3$ and diluted with ethyl acetate. The layers were separated and the aqueous layer extracted into ethyl acetate (3x) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (30% ethyl acetate/hexanes) to afford **23a**{*1, 2, 37*} (37 mg, 72%) as an amorphous white solid. (R_f = 0.49, 60% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.34 (bs, 1), 7.48 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 5.46 (t, *J* = 6.6 Hz, 1H), 5.35 (A of an ABq, *J* = 16.2 Hz, 1H), 4.76 (dd, *J* = 11.7, 6.6 Hz, 1H), 4.72 (B of an ABq, *J* = 16.2 Hz, 1H), 4.52 (dd, *J* = 11.4, 6.6 Hz, 1H), 3.81 (s, 1H), 3.46 (A of an ABq, *J* = 15.9 Hz, 1H), 3.21 (B of an ABq, *J* = 15.9 Hz, 1H), 1.99 (s, 3H), minor inseparable impurities: 7.58 (dd, *J* = 7.5 Hz, 0.15H), 7.02 (s, 0.07H), 6.57 (s, 0.08H), 5.63 (t, 0.12H), 5.41 (s, 0.17H), 5.03 (m, 0.31H), 3.74 (s, 0.28H), 3.61 (s, 0.05H), 3.58 – 3.53 (m, 0.07H), 3.21 (m, 0.20H), 1.90 (s, 0.23H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 171.3, 155.9, 136.4, 128.8, 126.9, 121.9, 119.6, 118.0, 110.9, 107.6, 90.8, 90.7, 79.3, 73.4, 62.6, 52.6, 44.2, 26.9, 4.0; IR (thin film) ν 3057, 2949, 2855, 2236, 1958, 1739, 1628, 1395, 1257, 1044, 741 cm^{-1}; MS *m/z* (%) 335 (11), 334 (41), 275 (44), 192 (34), 174 (81), 143 (100); EI-HRMS calcd for $C_{20}H_{18}N_2O_3$ *m/z* [M^+] 334.1317; found 334.1323.



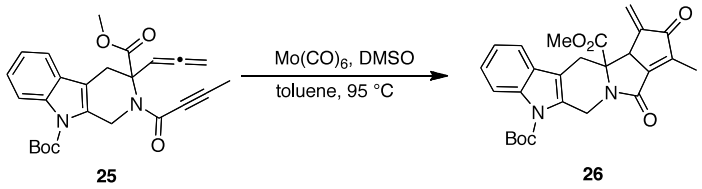
23a{*1, 2, 37*} **24**{*1, 2, 37*}

Fused Pentacyclic Indolyl bicyclo[4.2.0]octa-1,6-diene 24{*1, 2, 37*}**:** A solution of **23a**{*1, 2, 37*} (10.0 mg, 0.03 mmol) in freshly distilled DMF (0.3 mL) was heated under microwave irradiation in a Biotage Initiator microwave reactor at 225 °C for 7 min (Absorption level: very high; vial type: 0.2 – 0.5 mL; pre-stirring: 0; initial power: 0; dynamic deflector optimization: on; stir rate: 600; approximate ramp time: 4 min). An absence of starting material was observed by TLC after the described reaction time (R_f = 0.49 for both starting material and product, 60% ethyl acetate/hexanes; staining with PAA followed by a secondary water dip gives the product a green color and the starting material a brown/yellow color). The mixture was partitioned between ether and water and the layers were separated. The aqueous layer was extracted with ether (3x) and the combined organic layers were washed with water (3x) and brine (1x), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (30% ethyl acetate/hexanes) to afford **24**{*1, 2, 37*} (3.9 mg, 39%) as a white powder. (R_f = 0.49, 60% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.22 (bs, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 5.55 (A of an ABq, *J* = 17.5 Hz, 1H), 5.30 (s, 1H), 4.47 (B of an ABq, *J* = 17.5 Hz, 1H), 3.79 (A of an ABq, *J* = 15.3 Hz, 1H), 3.59 (s, 3H), 3.22 (A of an ABq, *J* = 16.5 Hz, 1H), 3.17 (B of an ABq, *J* = 16.5 Hz, 1H), 3.03 (B of an ABq, t, *J* = 15.3, 2.0 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 158.6, 153.3, 137.3, 136.6, 131.6, 129.5, 126.5, 121.9, 119.5, 118.1, 110.9, 106.4, 106.0, 70.7, 53.1, 40.4, 39.3, 32.9, 16.6;

IR (thin film) ν 3310, 2951, 2913, 2858, 1732, 1663, 1623, 1432, 1333, 1199, 1043, 743 cm^{-1}; MS *m/z* (%) 357 (93, M + 23Na), 335 (40).



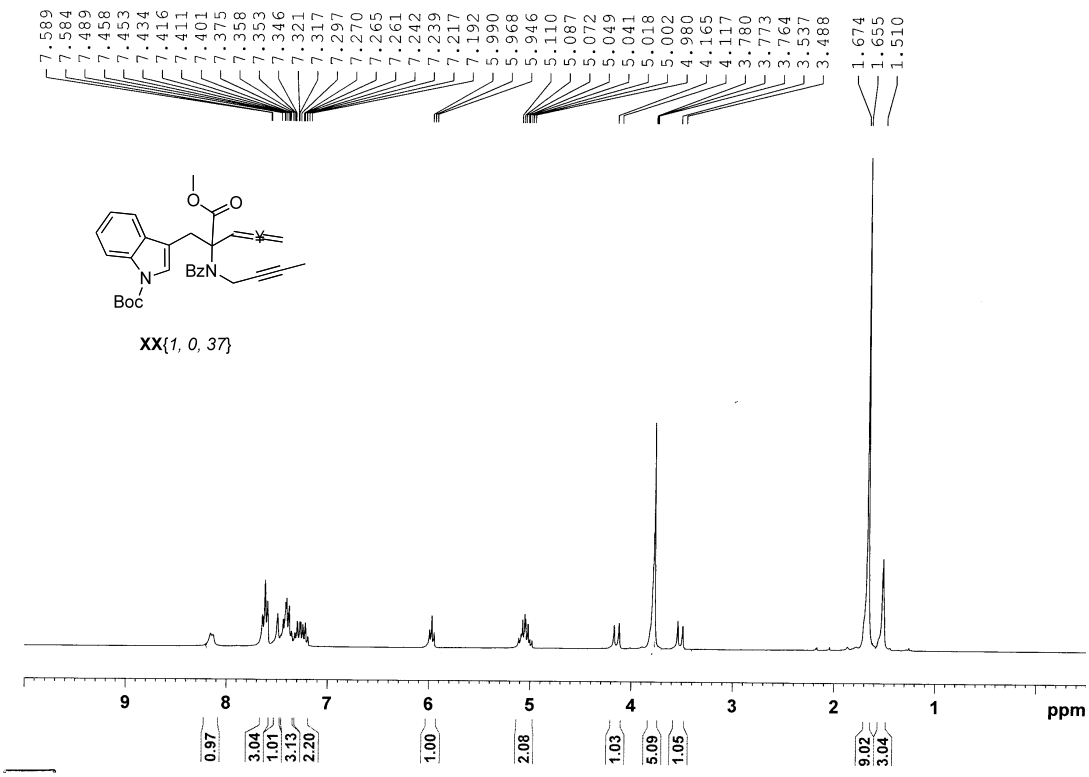
9-*tert*-butyl-3-methyl-2-(but-2-ynoyl)-3-(propa-1,2-dien-1-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-3,9(2*H*)-dicarboxylate (25): To a solution of allene-amide **23a** (60 mg, 0.179mmol) in 1.5 mL CH_3CN was added DMAP (2.2 mg, 0.018 mmol) and Boc_2O (41.5 mg, 0.19 mmol). The solution was stirred at room temperature for 45 min. Then the solution was diluted with ether and washed with saturated solution of $NaHSO_4$ followed by $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using 30% ethyl acetate/hexanes to afford the product **25** (60 mg, 77%) as a white solid. (R_f = 0.6, 50% ethyl acetate/hexanes). M.p. 152-153 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 6.9 Hz, 1H), 7.24 – 7.33 (m, 2H), 5.8 (A of an ABq, *J* = 18.0 Hz, 1H), 5.43 (s, 1H), 4.79-4.85 (m, 1H), 4.69 (B of an ABq, *J* = 18.0 Hz, 1H), 4.50-4.56 (m, 1H), 3.81 (s, 3H), 3.40 (A of an ABq, *J* = 15.9 Hz, 1H), 3.15 (B of an ABq, *J* = 16.5 Hz, 1H), 2.92 (s, 3H), 1.72 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 170.6, 155.9, 150.0, 135.7, 130.1, 128.8, 124.3, 122.9, 117.9, 115.3, 114.7, 90.4, 90.2, 84.2, 79.8, 73.3, 61.3, 52.7, 46.0, 28.2, 25.4, 4.0. IR (thin film) ν 1732, 1646, 1368, 1249, 1139 cm^{-1}. MS [*m/z* + Na] (%) 457 (100), 435 (25), 401 (40), 365 (50). HRMS calculated for $C_{25}H_{26}N_2O_5Na$: 457.1739; found: 457.1758.



7-*tert*-butyl-12a-methyl-3-methyl-1-methylene-2,4-dioxo-1,4,6,12,12a,12b hexahydrocyclopenta[1,2]indolizino[6,7-*b*]indole-7,12a(2*H*)-dicarboxylate (26): An oven dried 10 mL test tube was loaded with $Mo(CO)_6$ (27 mg, 0.103 mmol). The test tube was evacuated under vacuum and filled with Argon (3x). A solution of allene-amide (30 mg, 0.069 mmol) in dry toluene (1.4 ml) was added by syringe followed by the addition of dry DMSO (49 μL, 0.69 mmol). The solution was placed in a pre heated at 95 °C for 2 h. After completion the solution was passed through a pipette containing silica. The filtrate was concentrated and the crude material was purified by column chromatography using 40% ethyl acetate/hexanes to afford the product as a 1:1 mixture of two diastereomers in 73% (23.4 mg) yield as a viscous oil. (R_f = 0.55, 50% ethyl acetate/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (d, *J* = 8.1 Hz, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 7.51 (d, *J* = 6.6 Hz, 1H), 7.20-7.38 (m, 6H), 6.46 (d, *J* = 1.8 Hz, 1H), 6.34 (d, *J* = 2.1 Hz, 1H), 5.91 (s, 1H), 5.72 (d, *J* = 1.2 Hz, 1H), 5.59 (d, *J* = 17.4 Hz, 1H), 5.30 (d, *J*

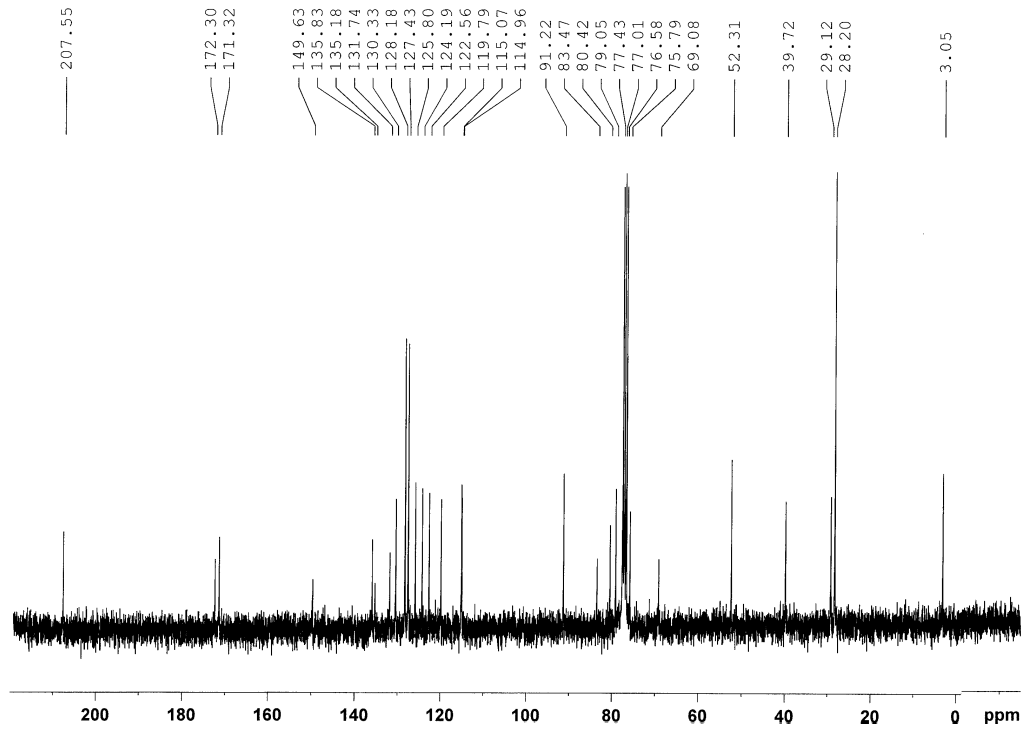
= 19.2 Hz, 1H), 4.72 (d, *J* = 18.3 Hz, 1H), 4.47 (d, *J* = 19.2 Hz, 1H), 4.11 (d, *J* = 15.0 Hz, 1H), 3.99-4.01 (m, 2H), 3.82 (s, 3H), 3.49 (s, 3H), 3.26 (d, *J* = 15.9 Hz, 1H), 3.07 (d, *J* = 15.3 Hz, 1H), 2.27 (d, *J* = 15.9 Hz, 1H), 2.18 (d, *J* = 3.0 Hz, 3H), 2.14 (d, *J* = 2.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.7, 195.4, 171.4, 168.6, 165.2, 163.8, 154.9, 153.8, 149.7, 149.6, 143.3, 141.8, 140.5, 139.7, 136.2, 135.7, 130.3, 128.9, 128.2, 127.8, 124.7, 124.6, 123.0, 122.8, 121.0, 120.7, 117.9, 117.7, 115.6, 115.5, 112.3, 111.6, 84.8, 84.7, 67.9, 65.6, 53.4, 53.1, 52.3, 48.2, 41.1, 40.0, 30.7, 28.2 (2C), 24.7, 9.1, 9.0. IR (thin film) ν 1732, 1707, 1368, 1139 cm^{-1}. MS [*m/z* + Na] (%) 485 (100), 447 (10), 407 (16), 230 (10). HRMS calculated for $C_{26}H_{26}N_2O_6Na$: 485.1689; found: 485.1669.

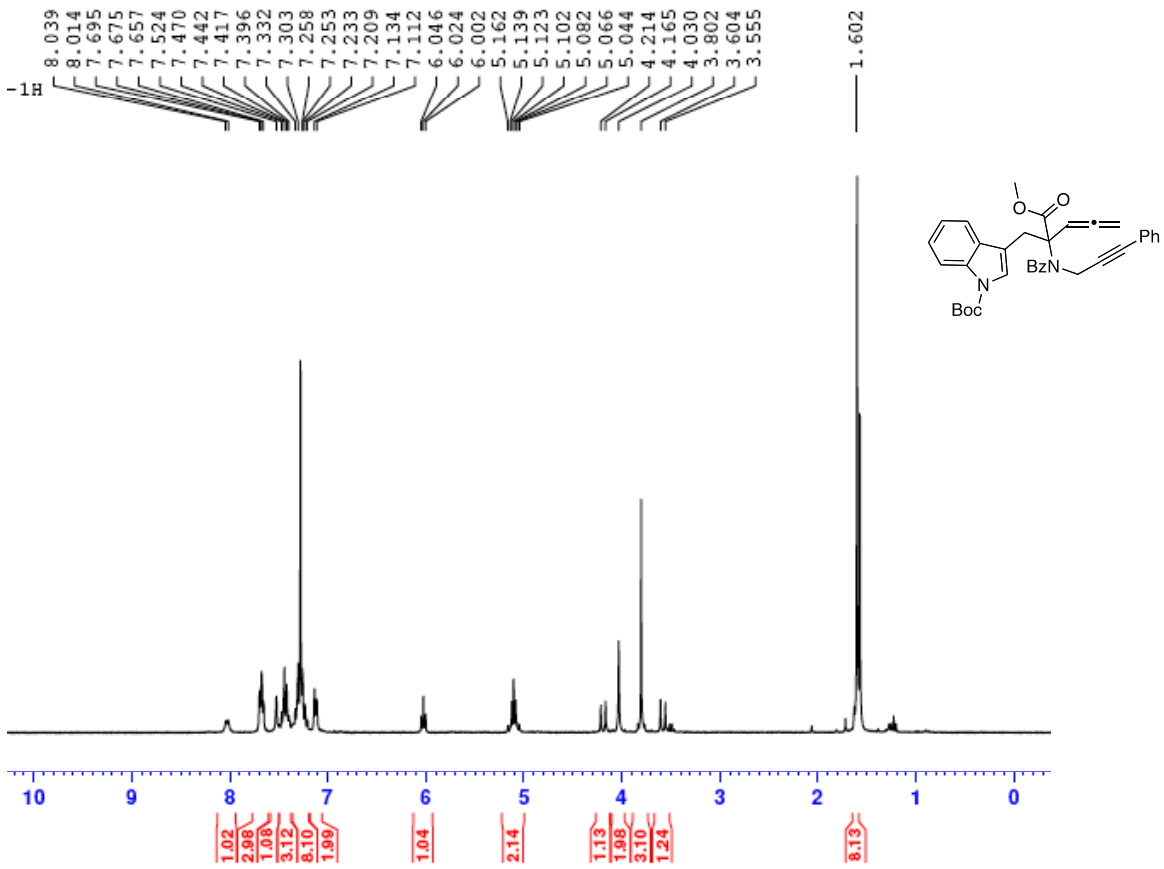
tp 432b.4-8-144 1H nmr301a 10/12/08



XX{*1, 0, 37*}

tp 432b.4-8-144 13C nmr300 10/12/08

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7.442
7.417
7.396
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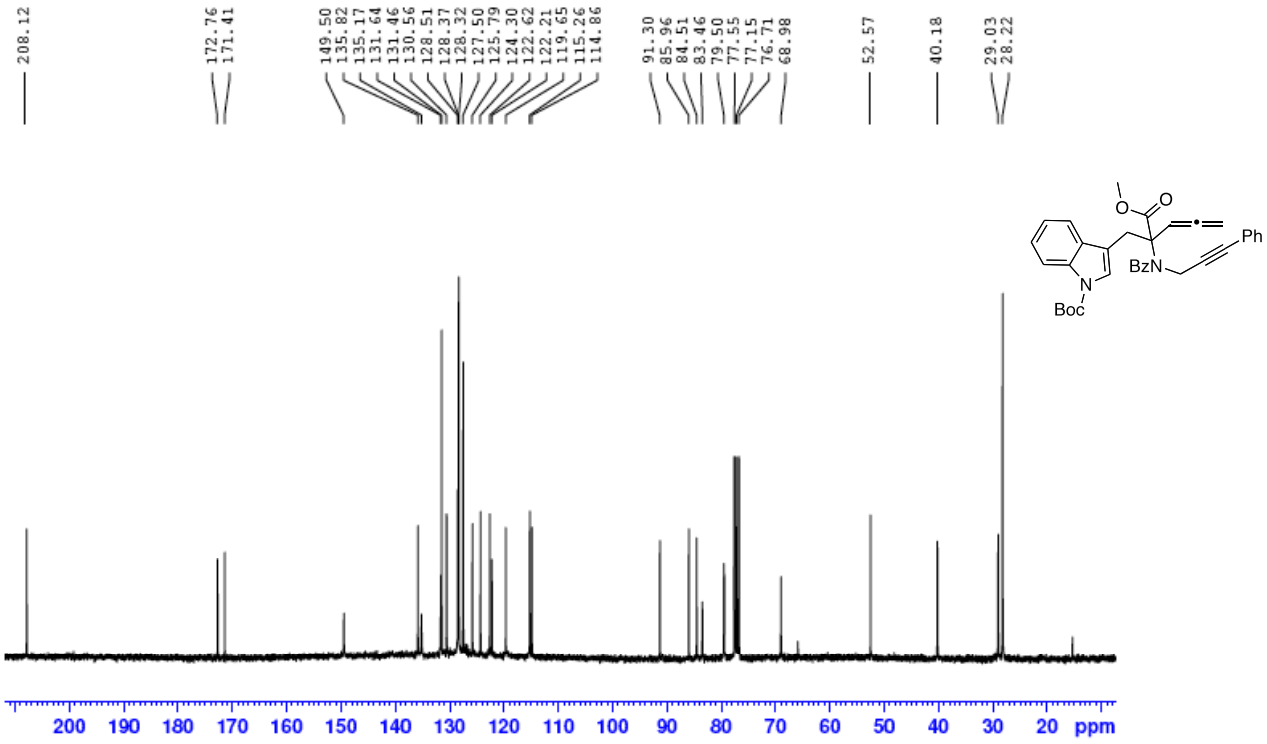
7.258
7.253
7.233
7.209
7.134
7.112
6.046
6.024
6.002
5.162
5.139
5.123
5.102
5.082
5.066
5.044
4.214
4.165
4.030
3.802
3.604
3.555
1.602
-1H
Ph
BzN
Boc
10
9
8
7
6
5
4
3
2
1
0
1.02
2.98
1.08
3.12
8.10
1.99
1.04
2.14
1.13
1.98
3.10
1.24
8.13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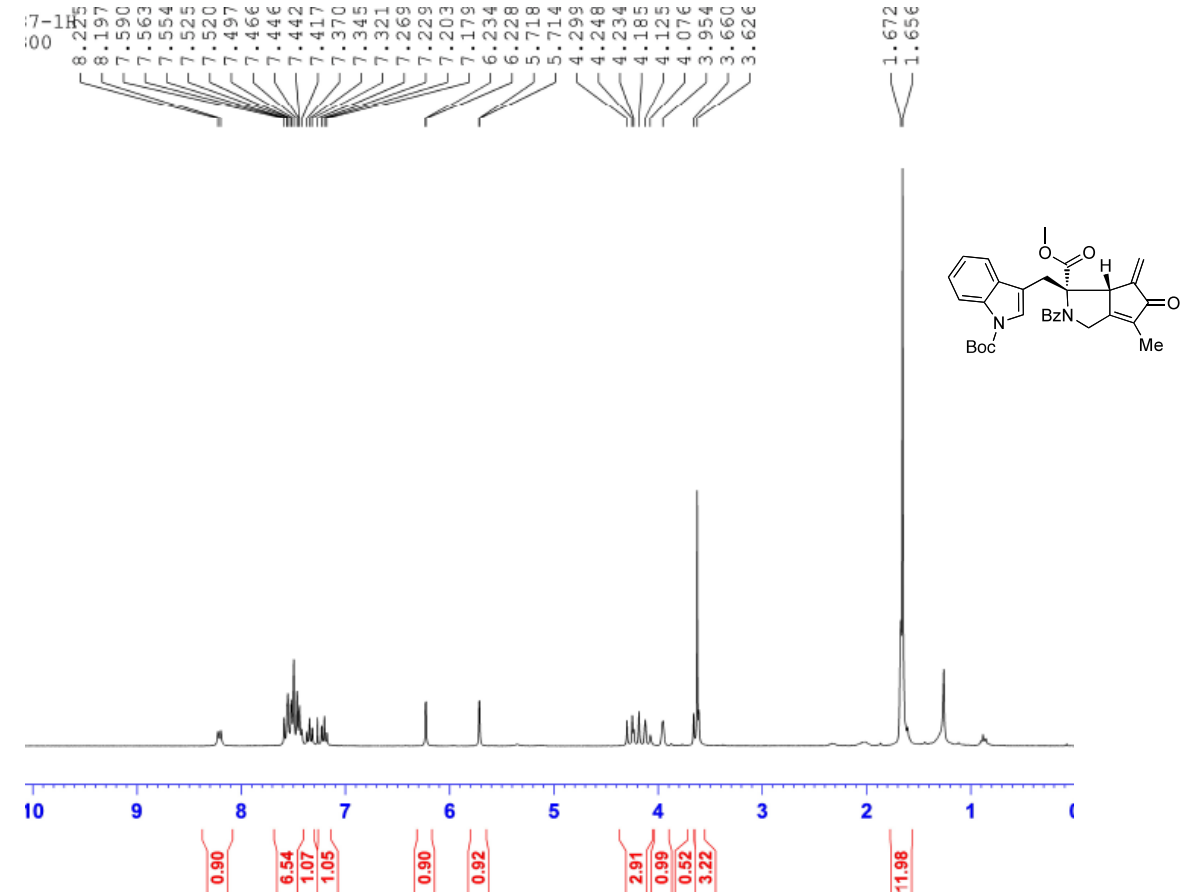
172.76
171.41
149.50
135.82
135.17
131.64
131.46
130.56
128.51
128.37
128.32
127.50
125.79
124.30
122.62
122.21
119.65
115.26
114.86
91.30
85.96
84.51
83.46
79.50
77.55
77.15
76.71
68.98
52.57
40.18
29.03
28.22
Ph
BzN
Boc
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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7.590
7.563
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7.525
7.520
7.497
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7.446
7.442
7.417
7.370
7.345
7.321
7.269
7.229
7.203
7.179
6.234
6.228
5.718
5.714
4.299
4.248
4.234
4.185
4.125
4.076
3.954
3.660
3.626
1.672
1.656
O
O
H
BzN
O
N
Boc
Me
10
9
8
7
6
5
4
3
2
1
0.90
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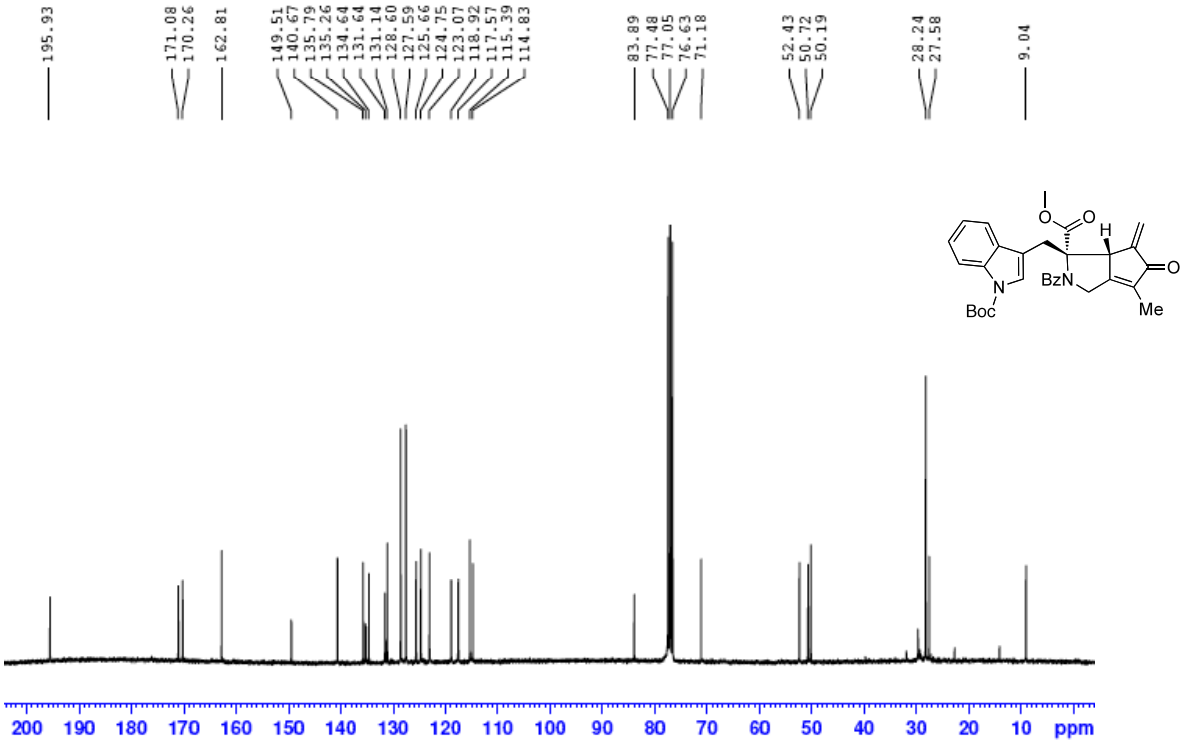
1.07
1.05
0.90
0.92
2.91
0.99
0.52
3.22
11.98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171.08
170.26
162.81
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140.67
135.79
135.26
134.64
131.64
131.14
128.60
127.59
125.66
124.75
123.07
118.92
117.57
115.39
114.83
83.89
77.48
77.05
76.63
71.18
52.43
50.72
50.19
28.24
27.58
9.04
O
O
H
BzN
O
N
Boc
Me
200
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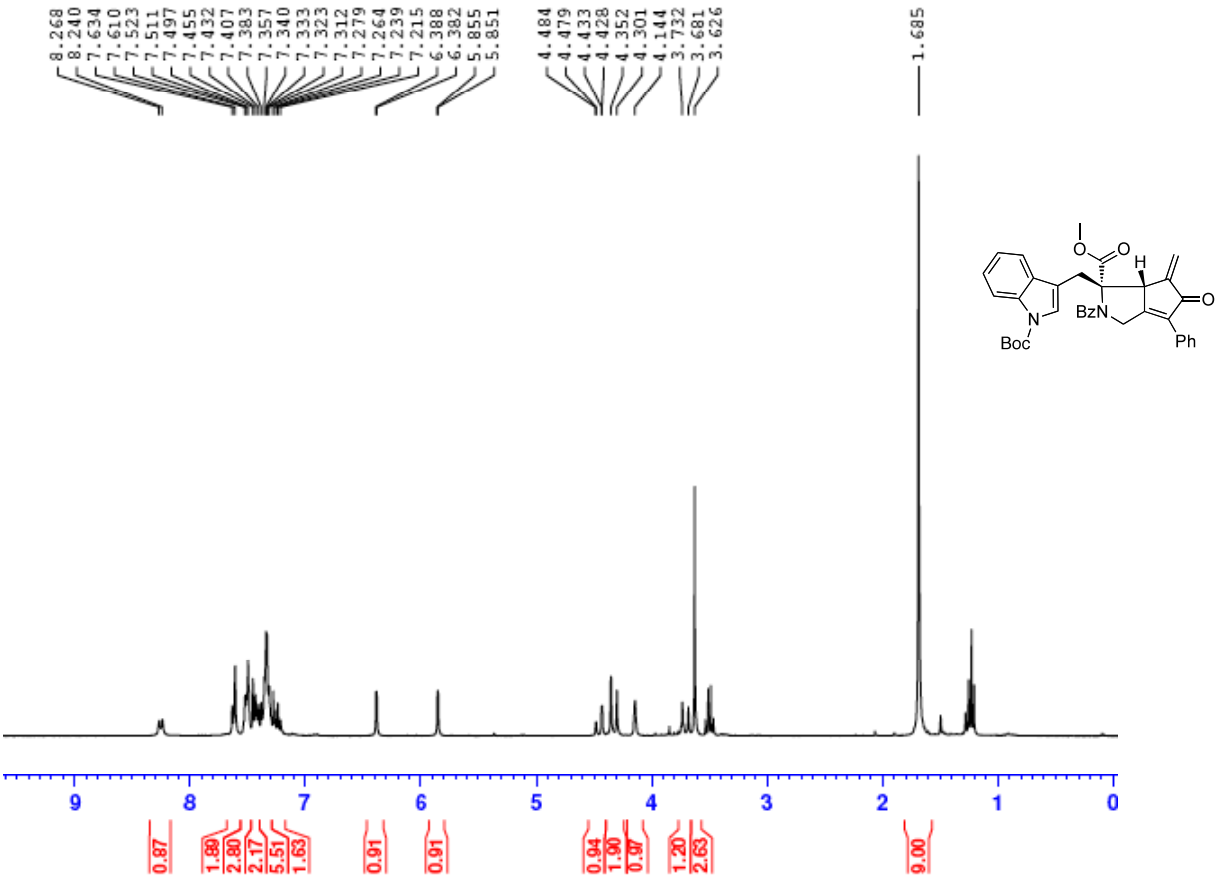
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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7.610
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7.511
7.497
7.455
7.432
7.407
7.383
7.357
7.340
7.333
7.323
7.312
7.279
7.264
7.239
7.215
6.388
6.382
5.855
5.851
4.484
4.479
4.433
4.428
4.352
4.301
4.144
3.732
3.681
3.626
1.685
0.87
1.80
2.80
2.17
5.51
1.63
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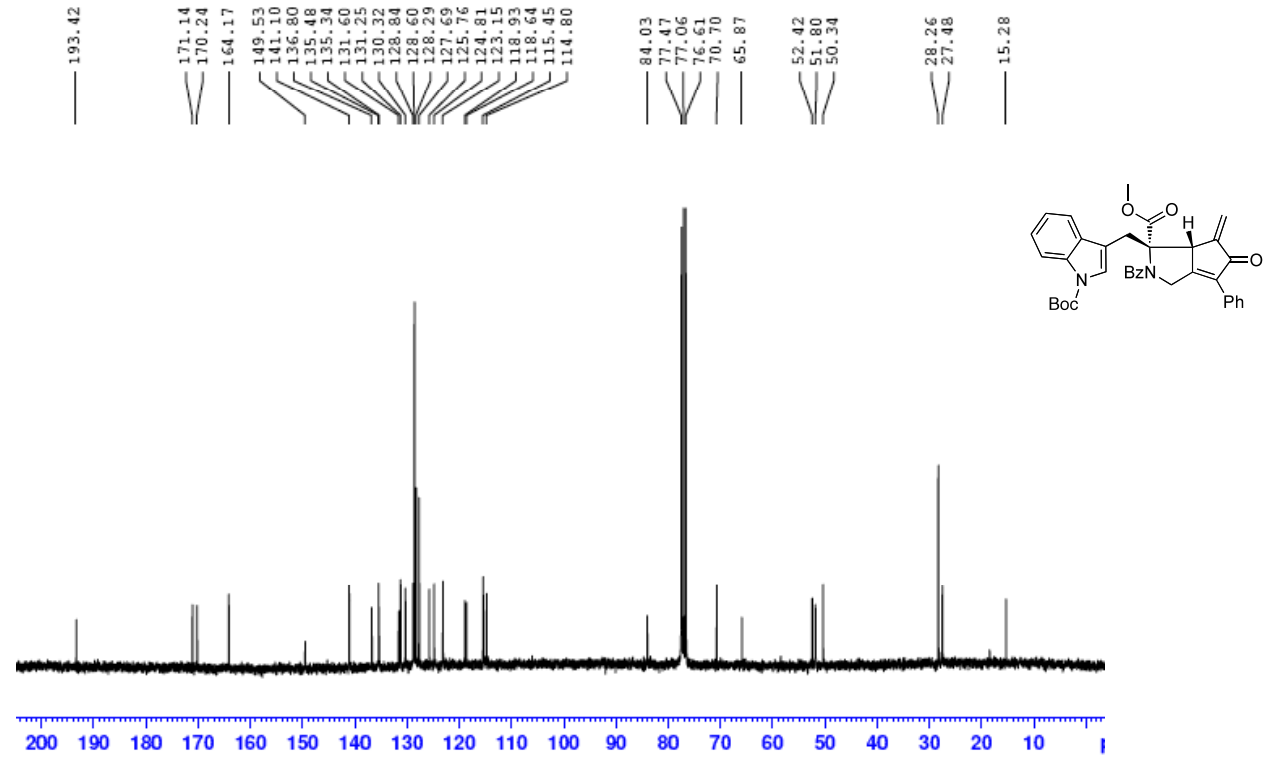
0.91
0.94
1.90
0.97
1.20
2.63
9.00
Boc
BzN
Ph


193.42
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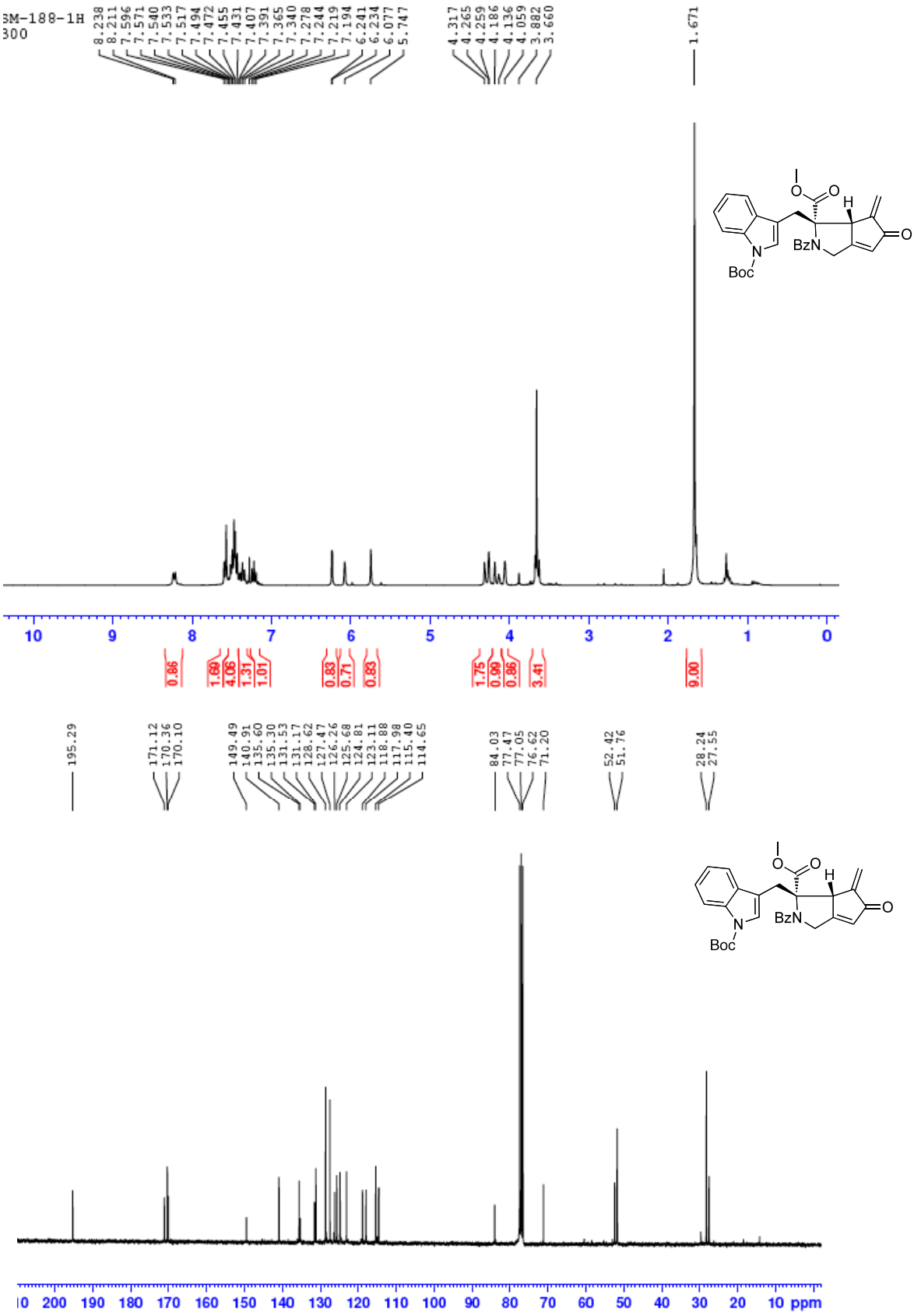
170.24
164.17
149.53
141.10
136.80
135.48
135.34
131.60
131.25
130.32
128.84
128.60
128.29
127.69
125.76
124.81
123.15
118.93
118.64
115.45
114.80
84.03
77.47
77.06
76.61
70.70
65.87
52.42
51.80
50.34
28.26
27.48
15.28
Boc
BzN
Ph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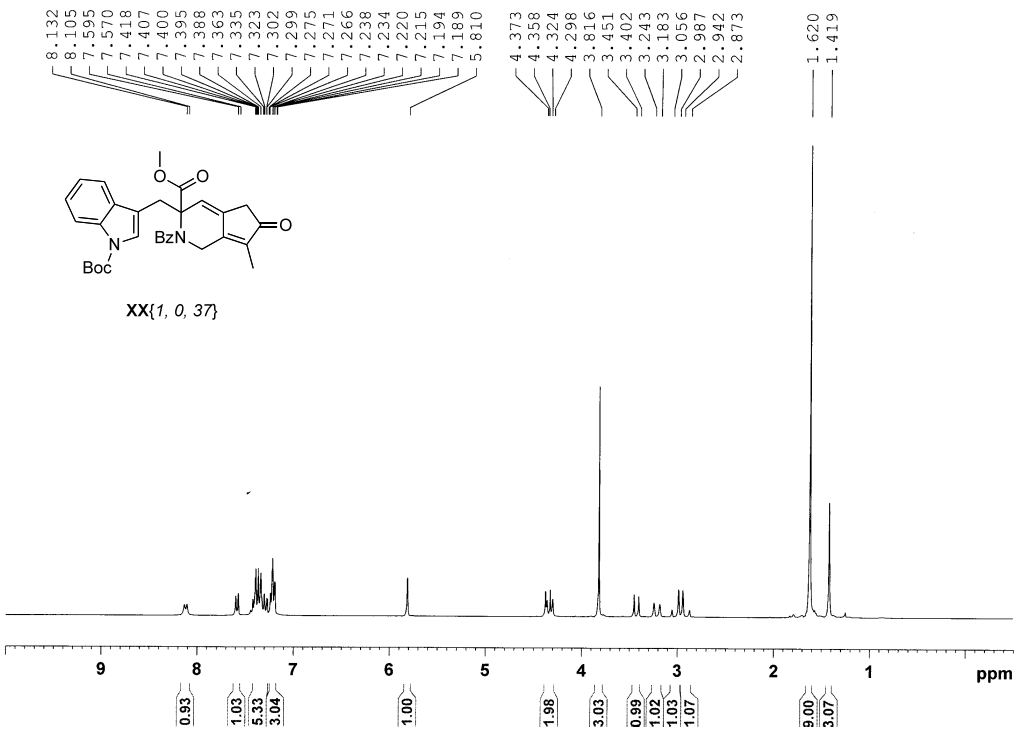
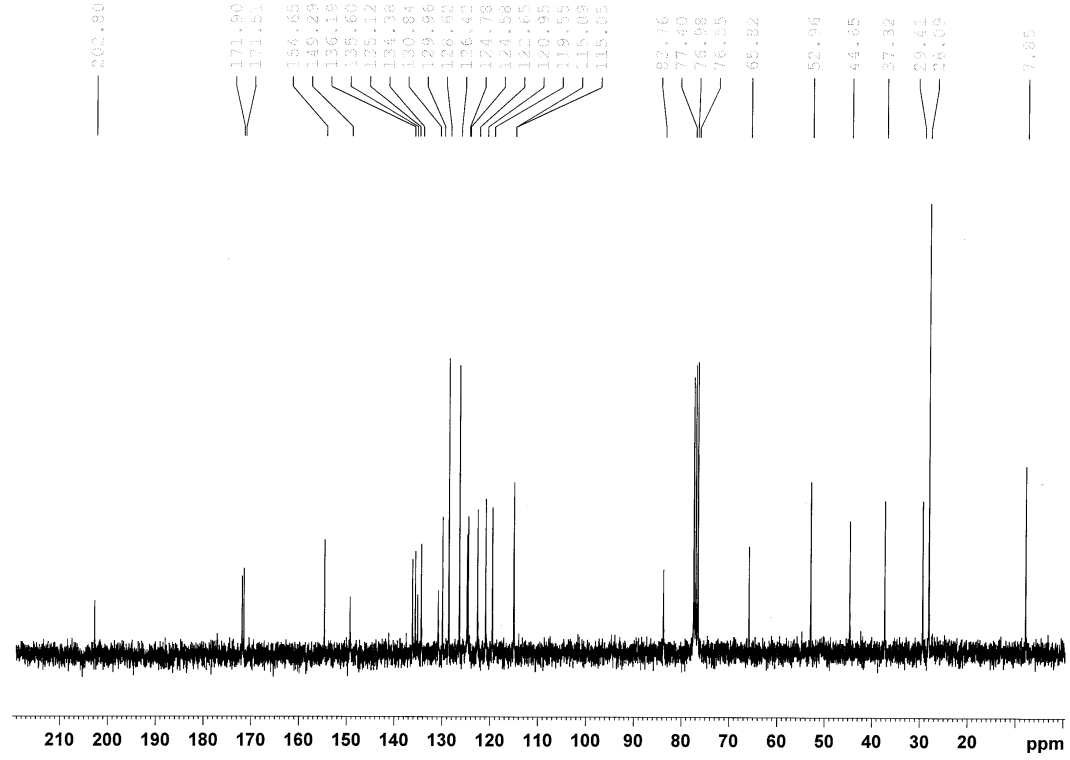
7.571
7.540
7.533
7.517
7.494
7.472
7.455
7.431
7.407
7.391
7.365
7.340
7.278
7.244
7.219
7.194
6.241
6.234
6.077
5.747
4.317
4.265
4.259
4.186
4.136
4.059
3.882
3.660
1.671
Boc
BzN
O
H
10 9 8 7 6 5 4 3 2 1 0
0.86
1.60
4.06
1.31
1.01
0.83
0.71
0.83
1.75
0.99
0.86
3.41
9.00
195.29
171.12
170.36
170.10
149.49
140.91
135.60
135.30
131.53
131.17
128.62
127.47
126.26
125.68
124.81
123.11
118.88
117.98
115.40
114.65
84.03
77.47
77.05
76.62
71.20
52.42
51.76
28.24
27.55
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

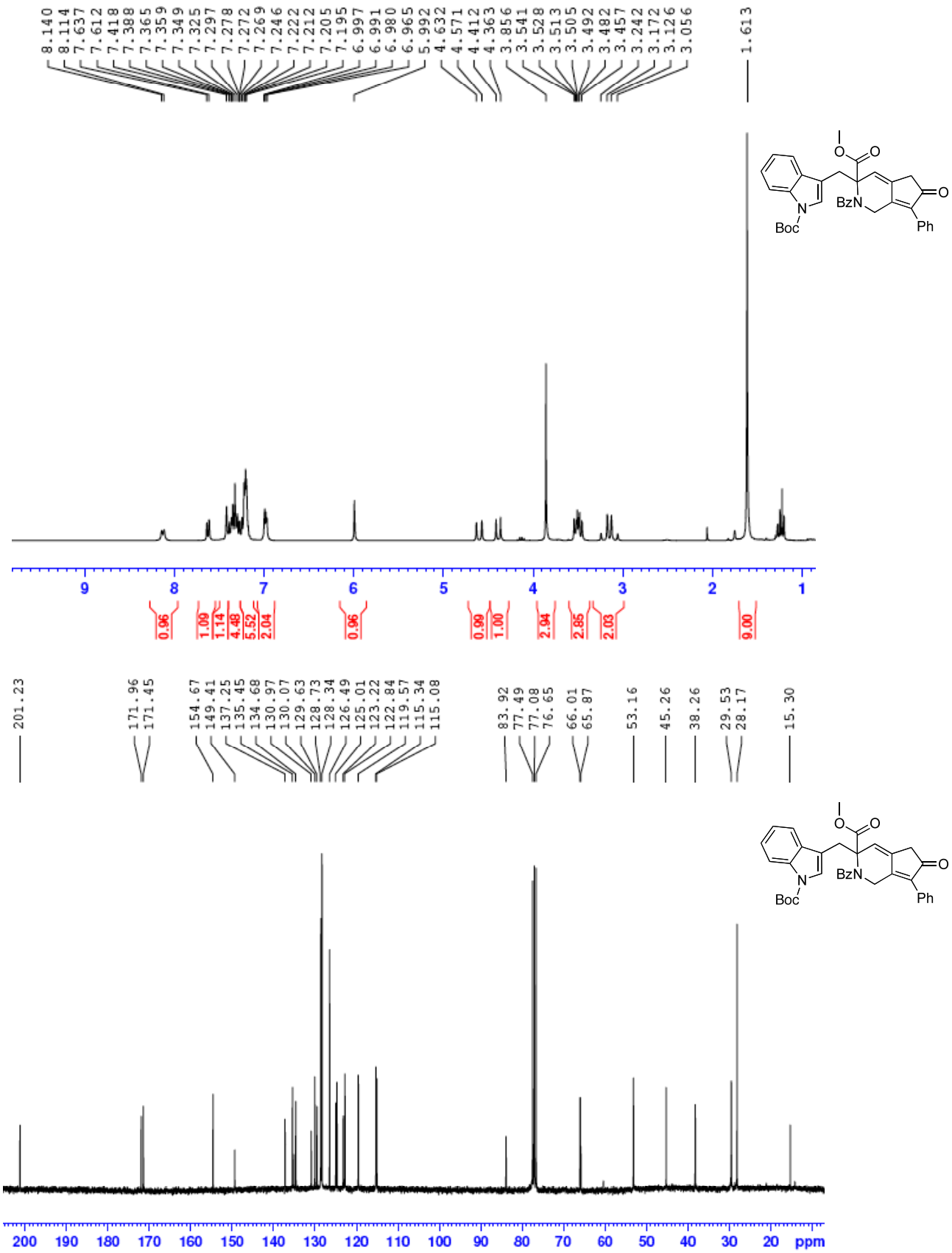
tp 440.2-8-1251H nmr301a 10/11/08



XX{*1, 0, 37*}

tp 440.2-8-125 13C nmr300 10/11/08

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7.365
7.359
7.349
7.325
7.297
7.278
7.272
7.269
7.246
7.222
7.212
7.205
7.195
6.997
6.991
6.980
6.965
5.992
4.632
4.571
4.412
4.363
3.856
3.541
3.528
3.513
3.505
3.492
3.482
3.457
3.242
3.172
3.126
3.056
1.613
O
O
O
N
Boc
BzN
Ph
9
8
7
6
5
4
3
2
1
0.96
1.09
1.14
4.48
5.52
2.04
0.96
0.99
1.00
2.94
2.85
2.03
9.00
201.23
171.96
171.45
154.67
149.41
137.25
135.45
134.68
130.97
130.07
129.63
128.73
128.34
126.49
125.01
123.22
122.84
119.57
115.34
115.08
83.92
77.49
77.08
76.65
66.01
65.87
53.16
45.26
38.26
29.53
28.17
15.30
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160
150
140
130
120
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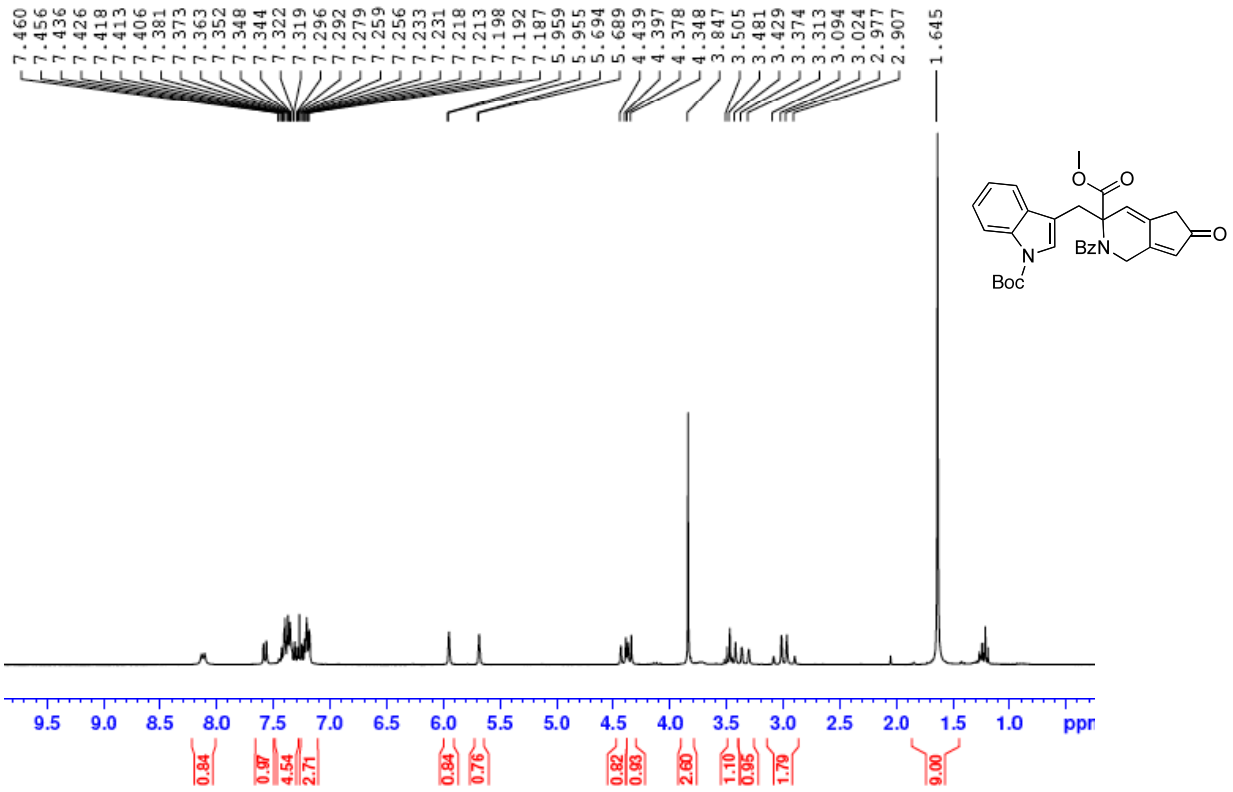
100
90
80
70
60
50
40
30
20
ppm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7.413
7.406
7.381
7.373
7.363
7.352
7.348
7.344
7.322
7.319
7.296
7.292
7.279
7.259
7.256
7.233
7.231
7.218
7.213
7.198
7.192
7.187
5.959
5.955
5.694
5.689
4.439
4.397
4.378
4.348
3.847
3.505
3.481
3.429
3.374
3.313
3.094
3.024
2.977
2.907
1.645
BzN
Boc
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
0.84
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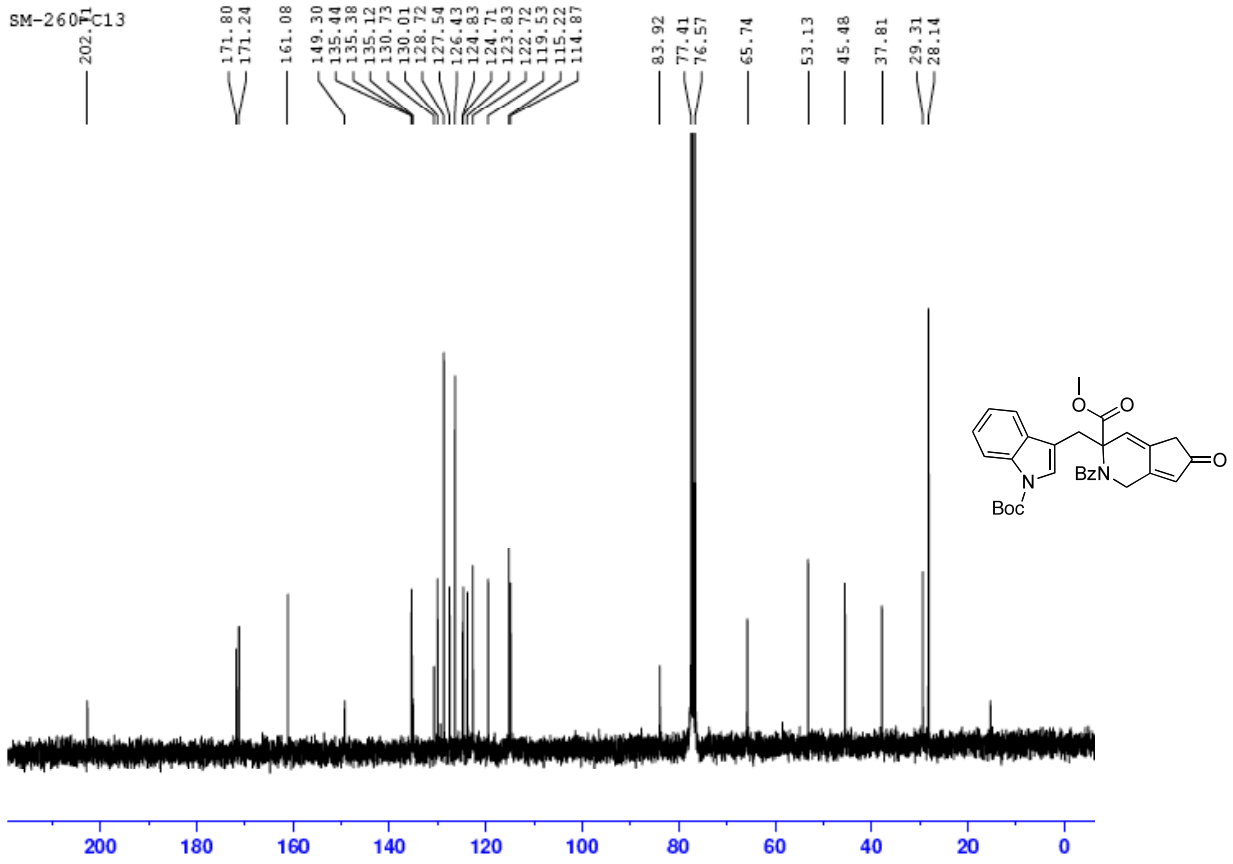
0.93
2.60
1.10
0.95
1.79
9.00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127.54
126.43
124.83
124.71
123.83
122.72
119.53
115.22
114.87
83.92
77.41
76.57
65.74
53.13
45.48
37.81
29.31
28.14
BzN
Boc
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160
140
120
100
80
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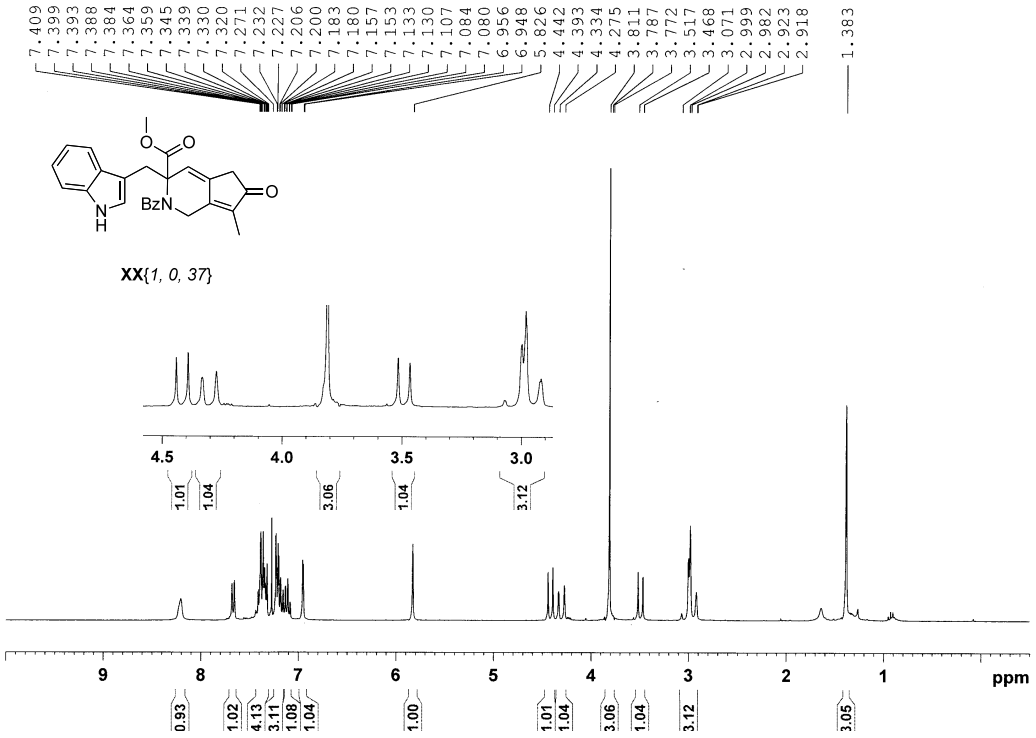
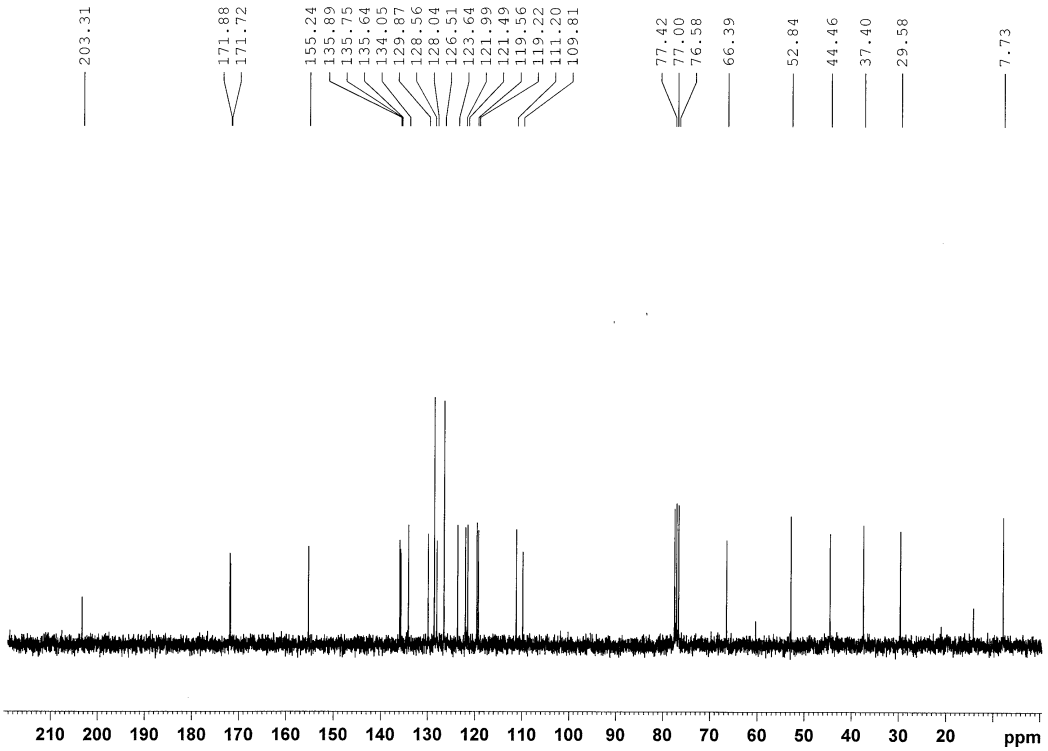
40
20
0

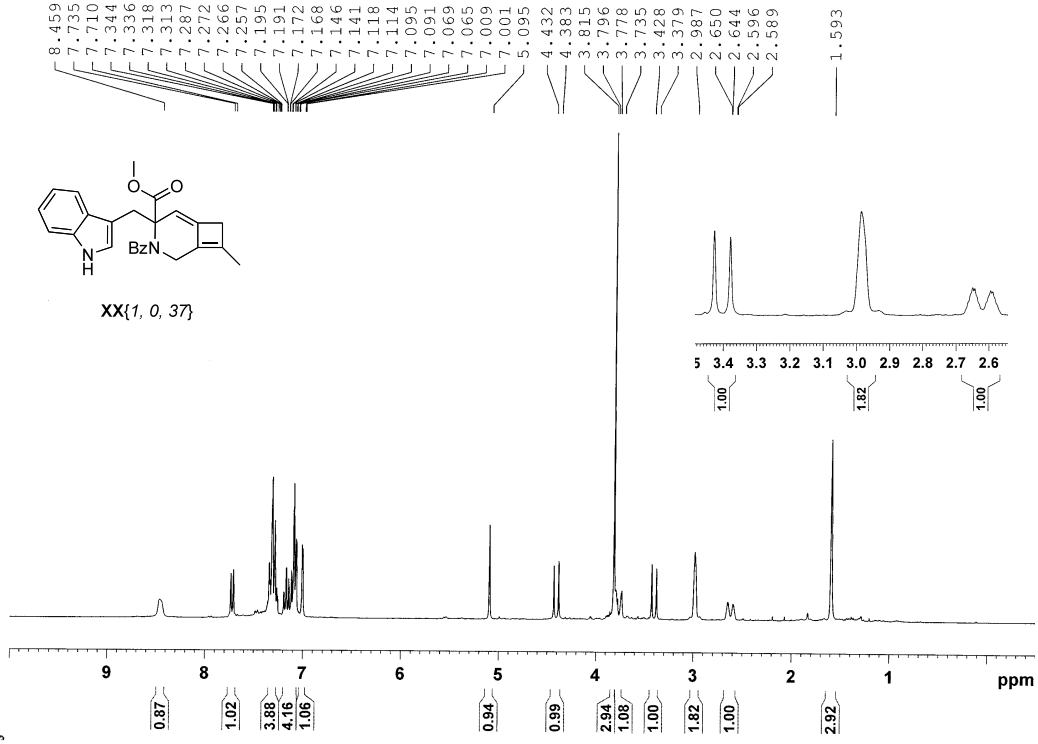
tp 441.5-8-145 1H nmr301a 10/11/08



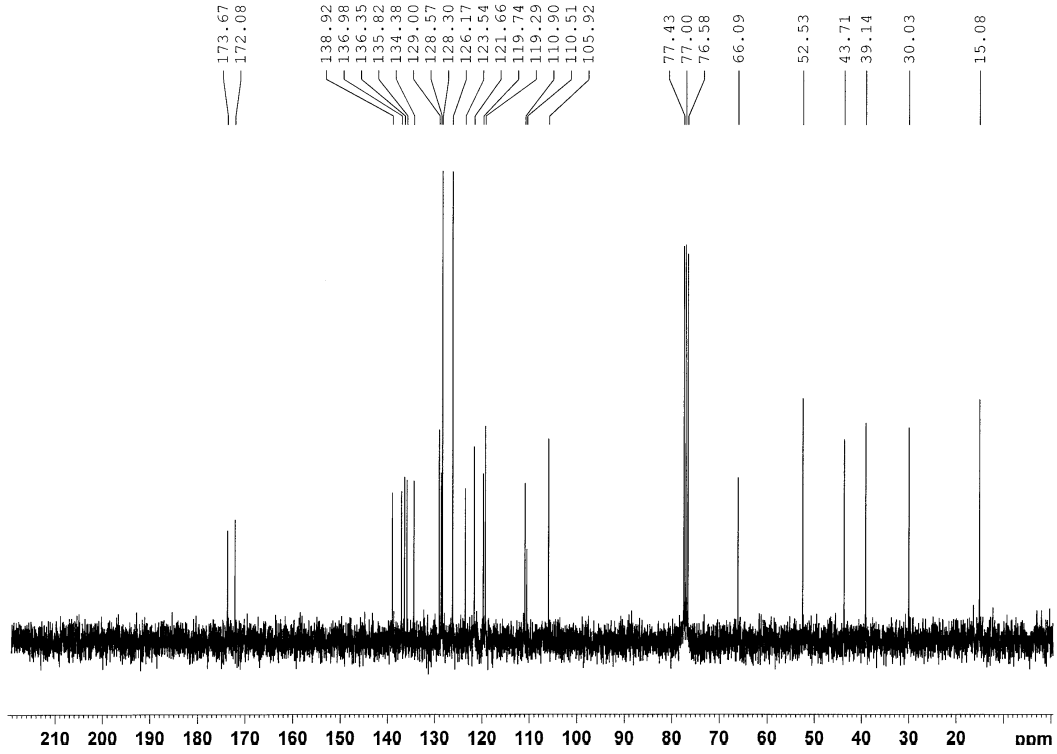
tp 441.6-8-152 13C CDCl3 nmr300 11/11/08

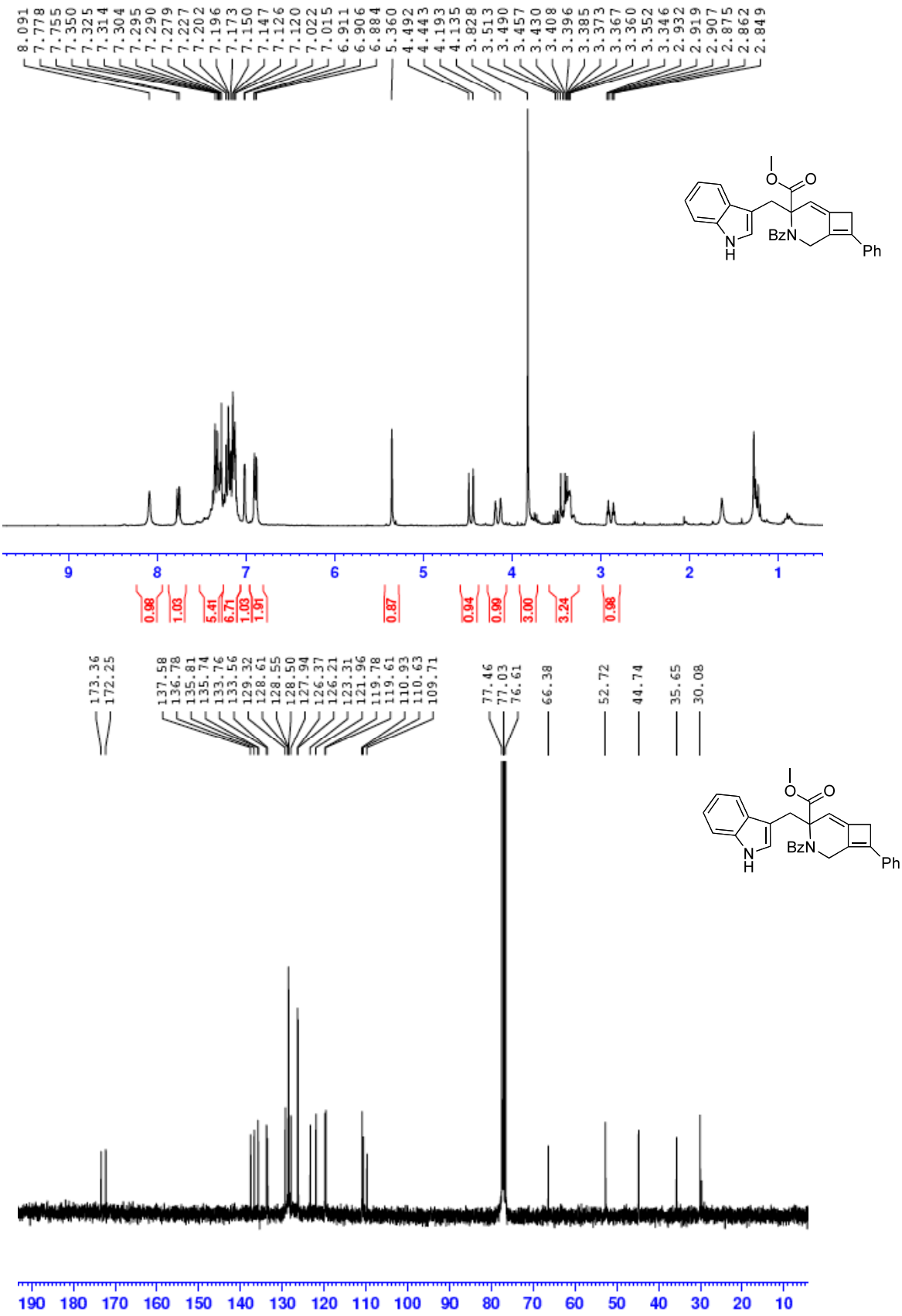


tp 436.4-8-158 1H CDCl3 nmr300 10/21/08



tp 436.4-8-158 13C CDCl3 nmr300 10/21/08

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7.279
7.227
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7.196
7.173
7.150
7.147
7.126
7.120
7.022
7.015
6.911
6.906
6.884
5.360
4.492
4.443
4.193
4.135
3.828
3.513
3.490
3.457
3.430
3.408
3.396
3.385
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3.346
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2.907
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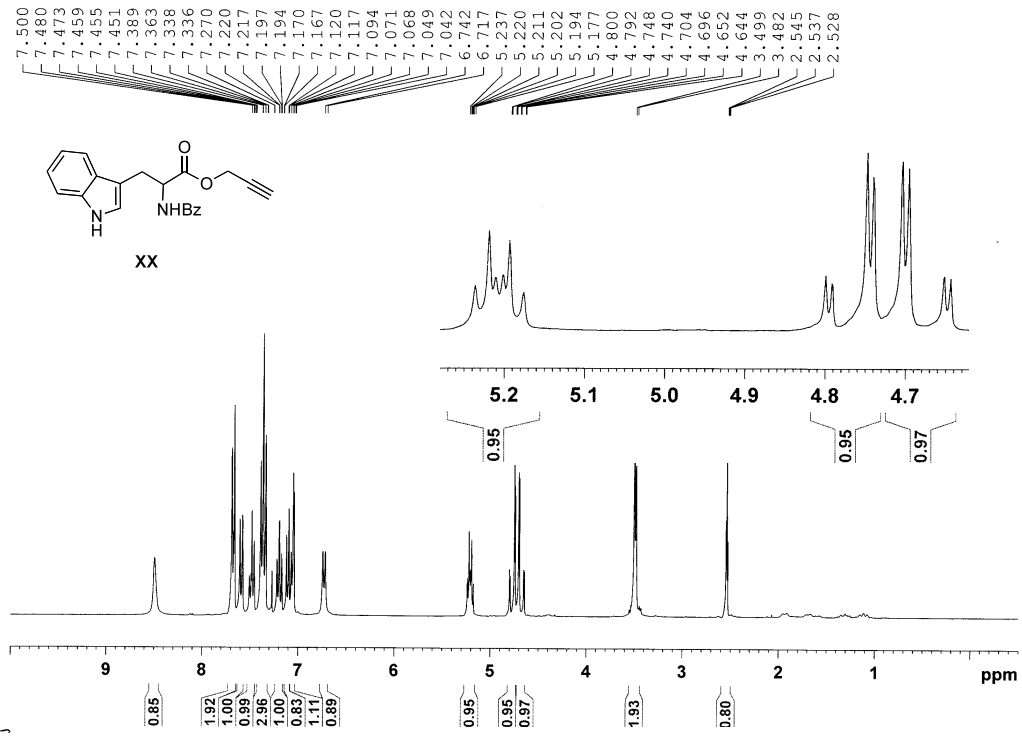
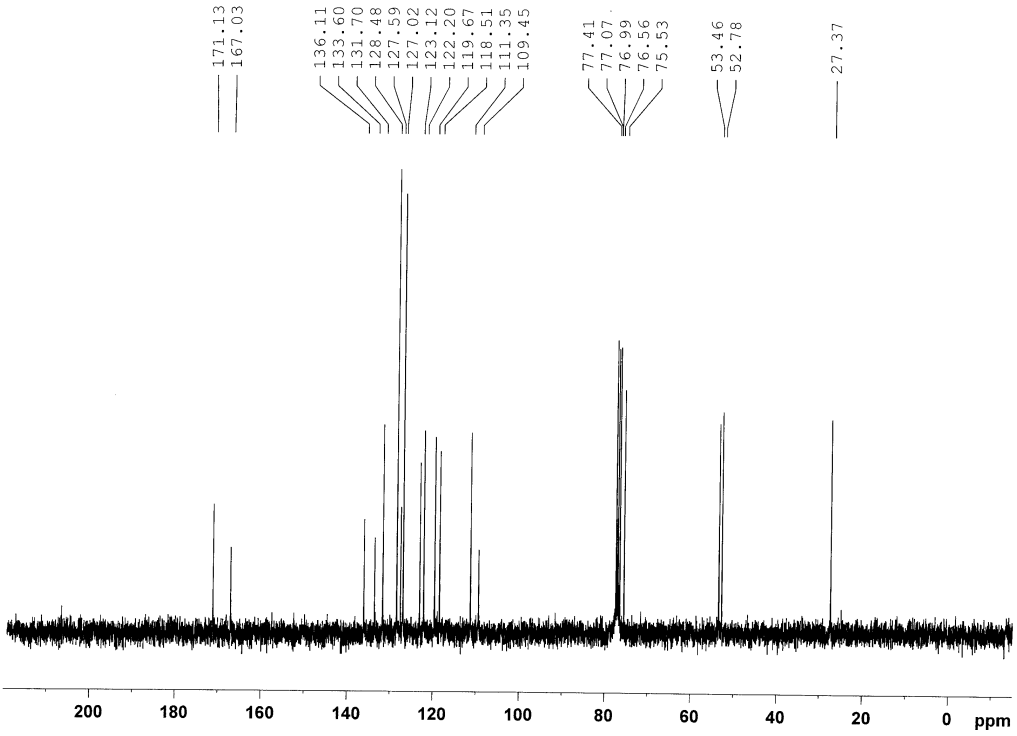
2.862
2.849
O
O
N
H
BzN
Ph
9
8
7
6
5
4
3
2
1
0.98
1.03
5.41
6.71
1.03
1.91
0.87
0.94
0.99
3.00
3.24
0.98
173.36
172.25
137.58
136.78
135.81
135.74
133.76
133.56
129.32
128.61
128.55
128.50
127.94
126.37
126.21
123.31
121.96
119.78
119.61
110.93
110.63
109.71
77.46
77.03
76.61
66.38
52.72
44.74
35.65
30.08
O
O
N
H
BzN
Ph
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

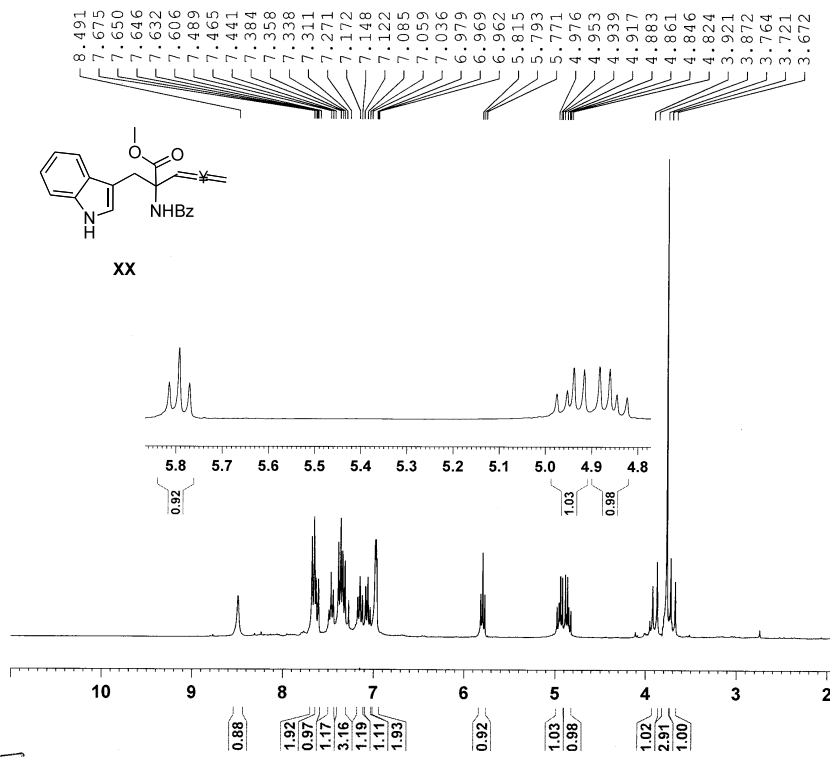
tp 411.4-8-90lH nmr301a 10/11/08



tp 411.4-8-90 13C nmr300 10/11/08

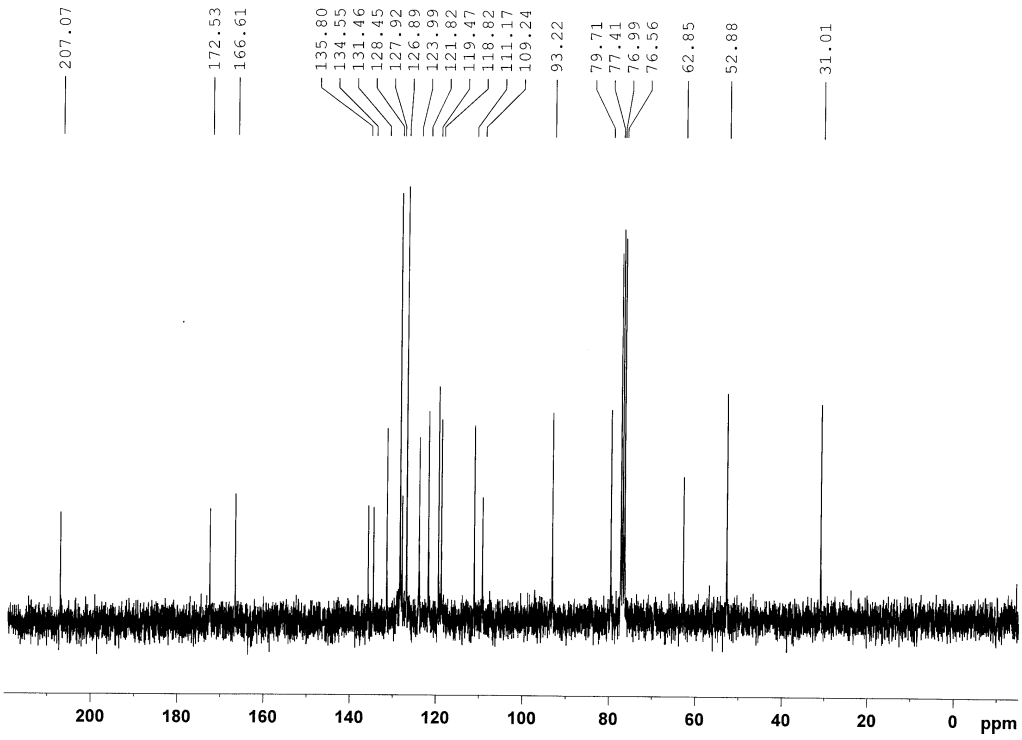


tp 420.3-8-92 nmr301a 10/11/08

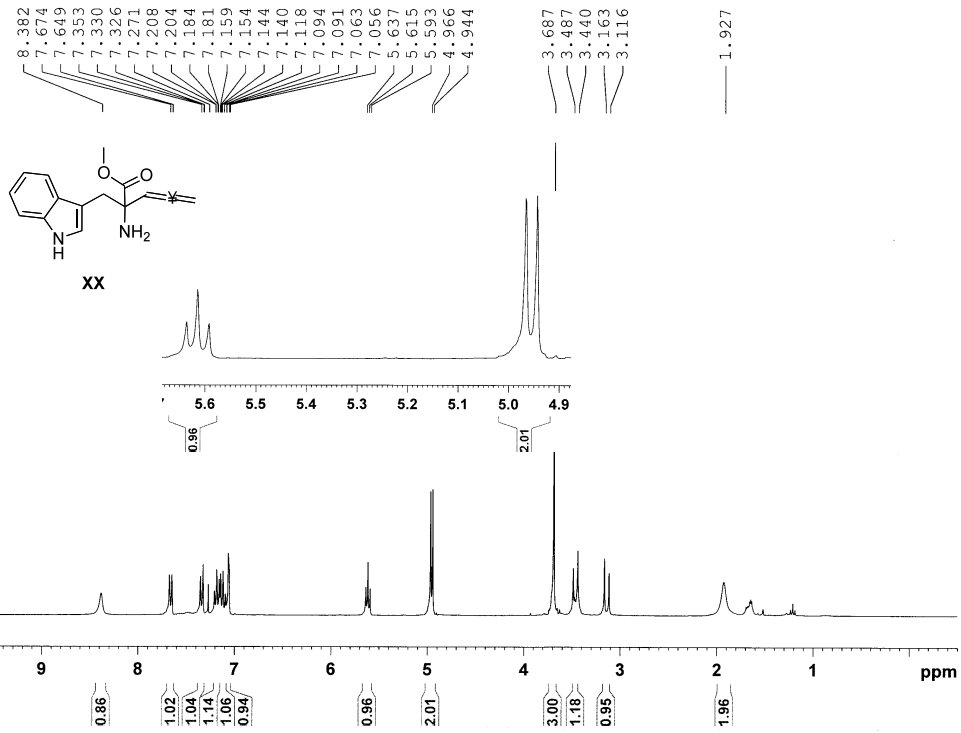


XX

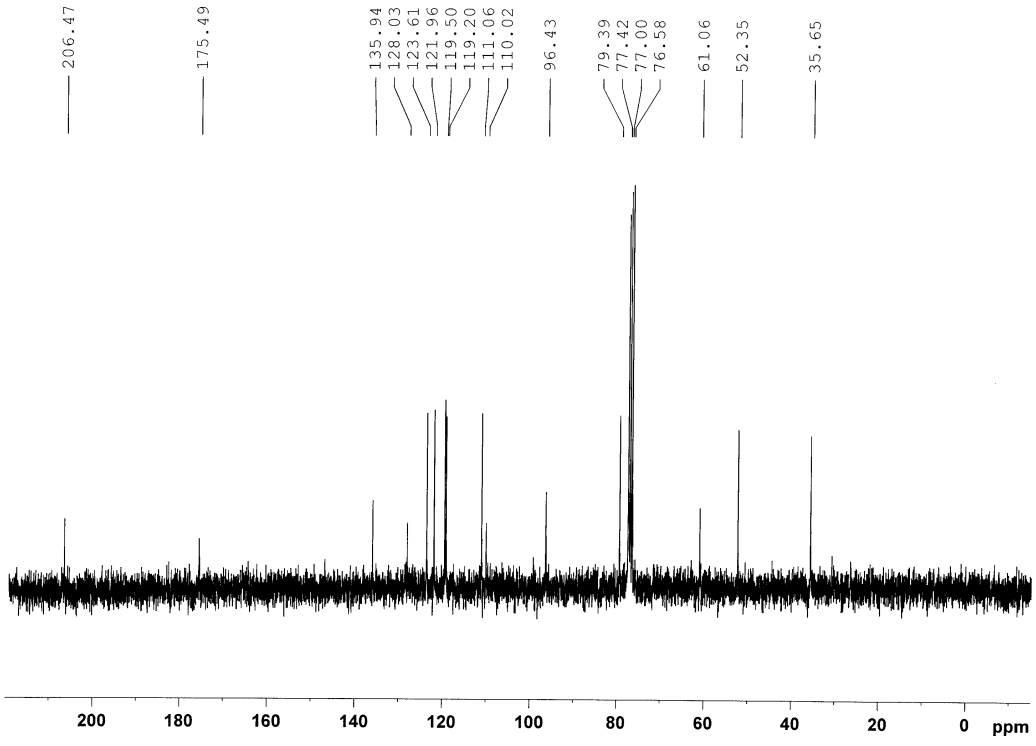
tp 420.3-8-92 13C nmr300 10/11/08



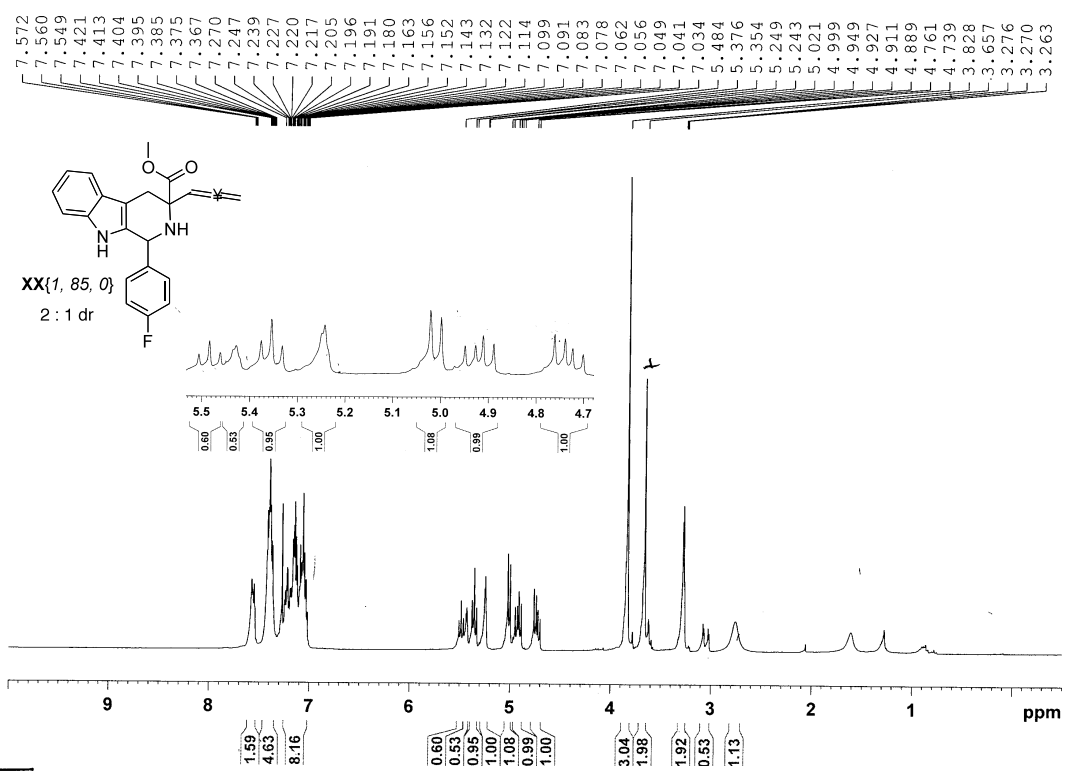
tp 419b.2-8-98 nmr301a 10/11/08



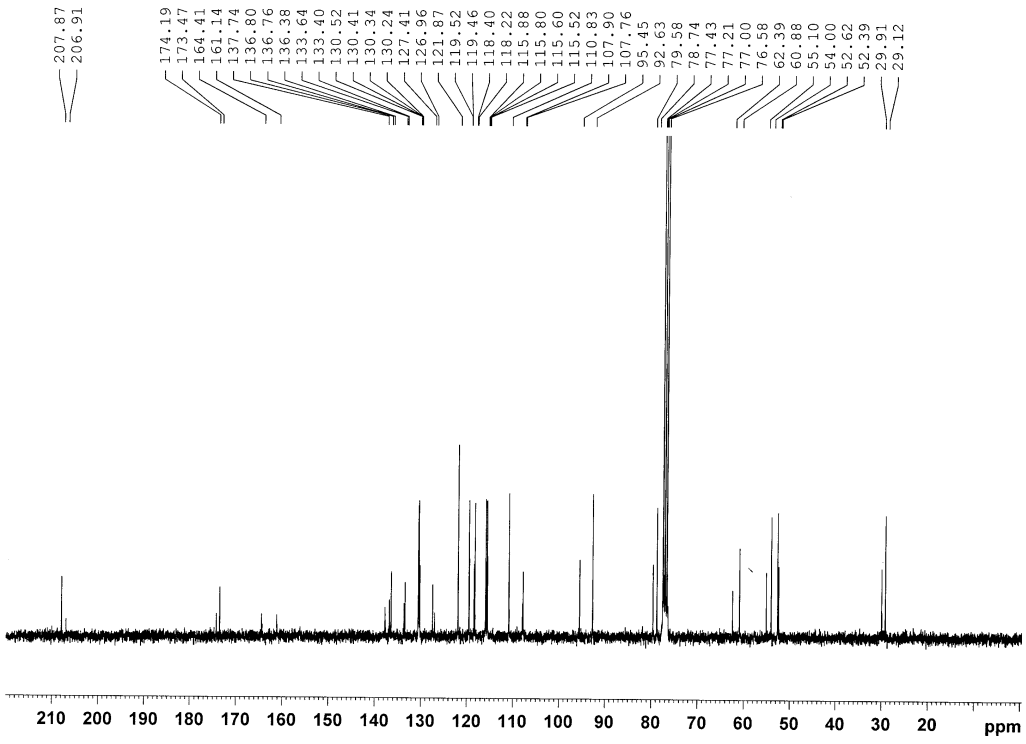
tp 419b.2-8-98 13C nmr300 10/11/08



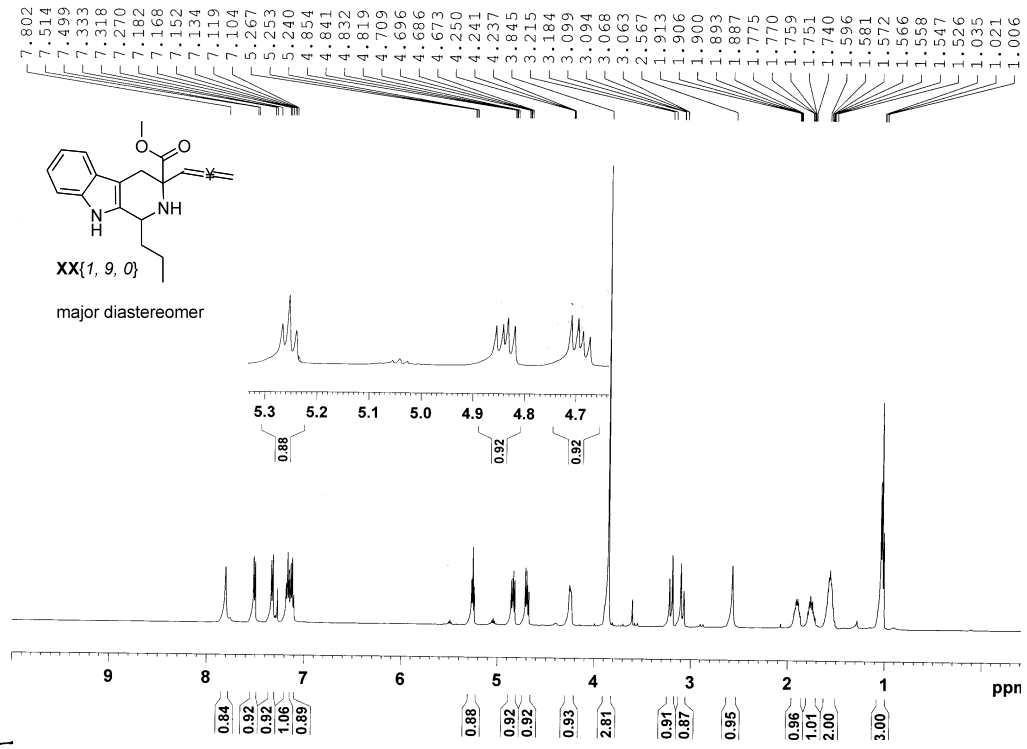
tp 428.1-8-102 1H CDCl3 nmr301a 8/23/08



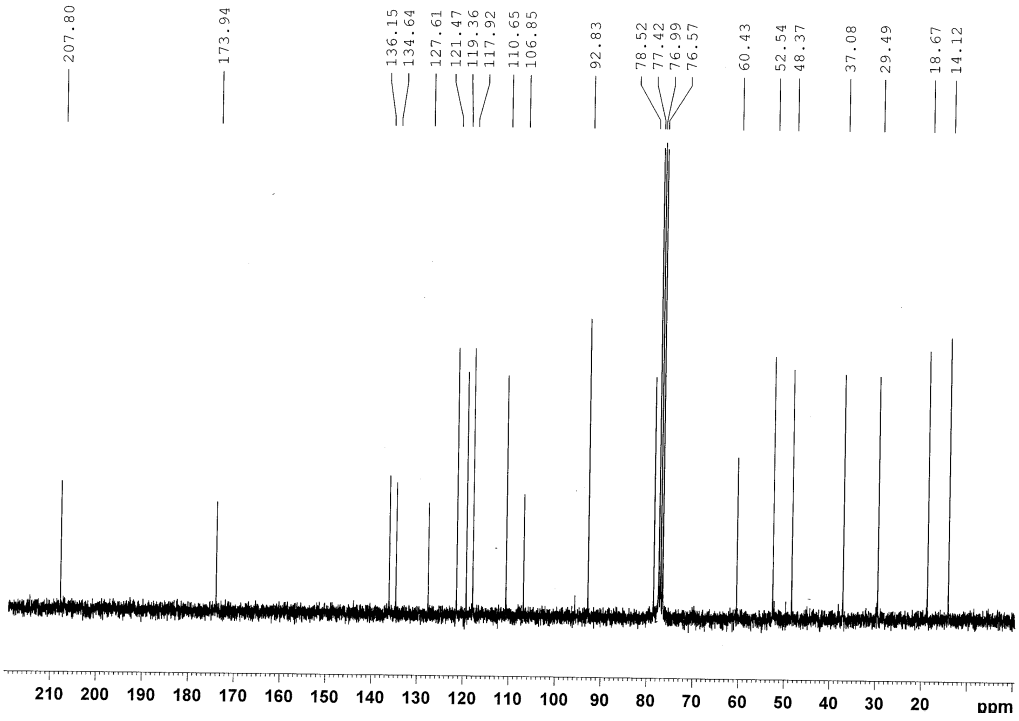
tp 428.1-8-102 13C CDCl3 nmr301a 8/23/08

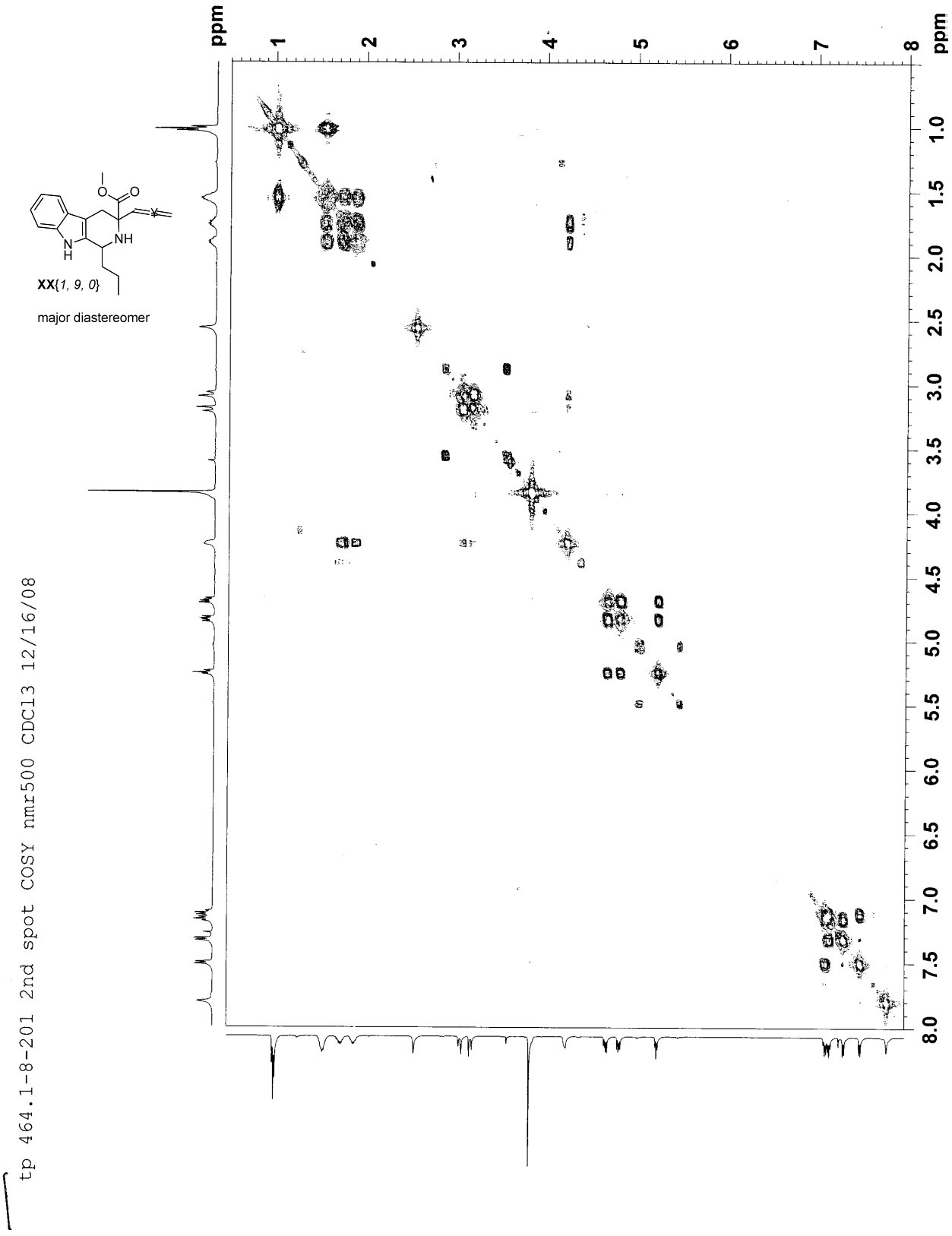


tp 464.1-8-201 2nd spot 1H nmr500 CDCl3 12/16/08

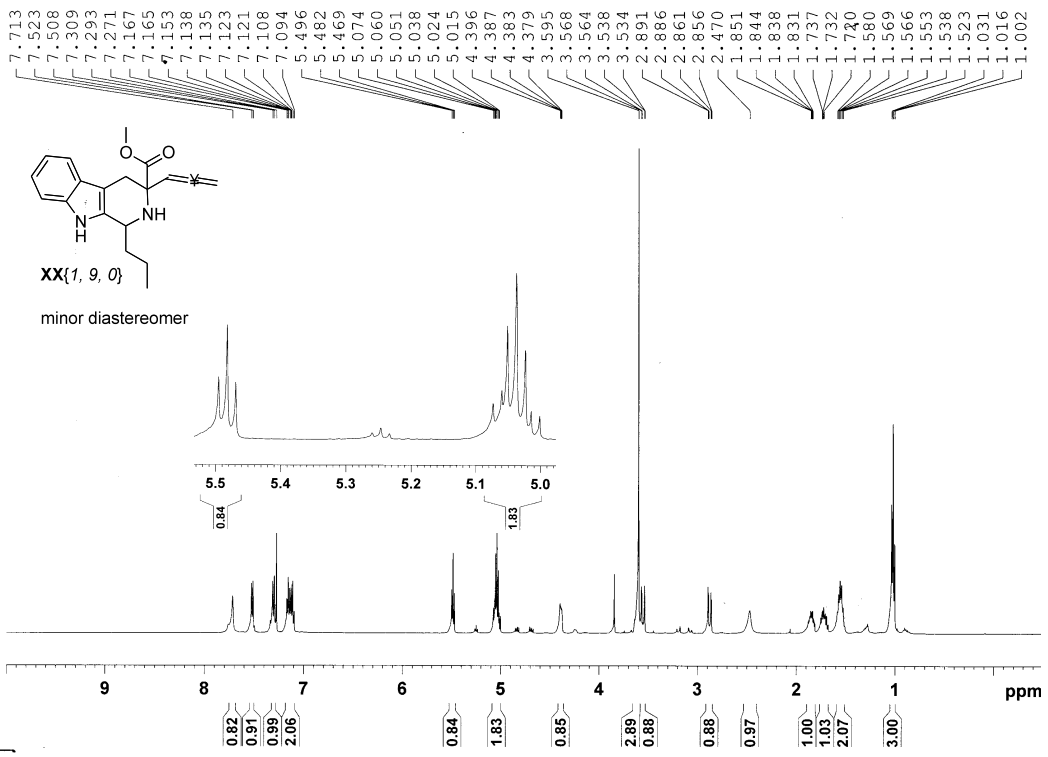


tp 464.1-8-201 2nd spot major diastereomer
13C CDCl3 nmr300 12/18/08

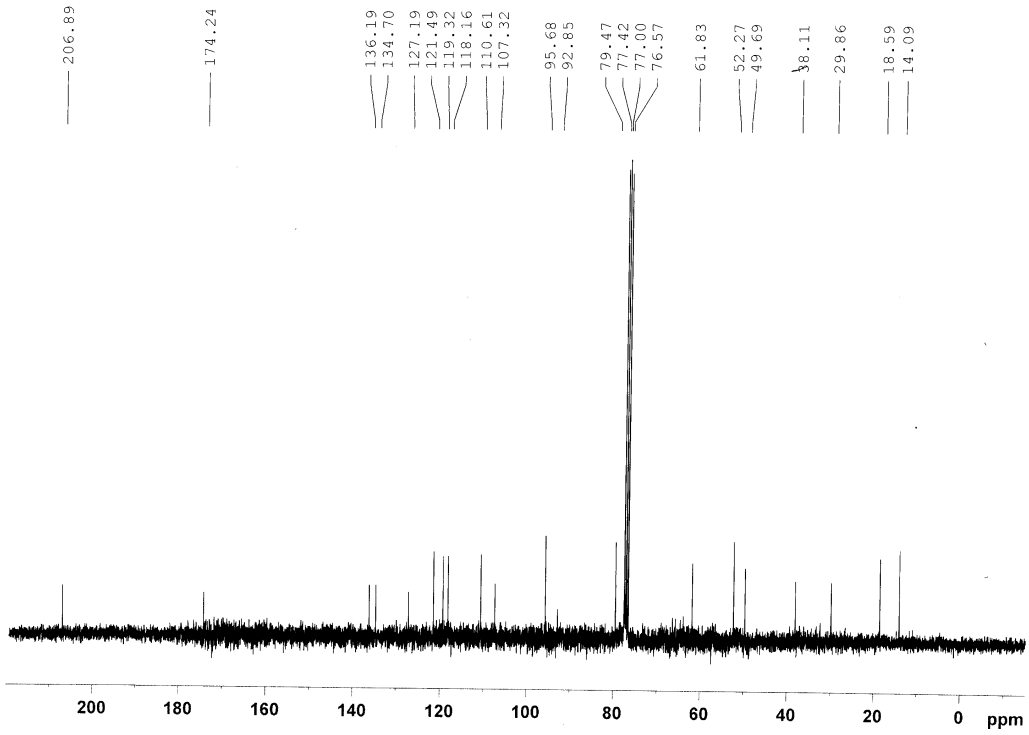


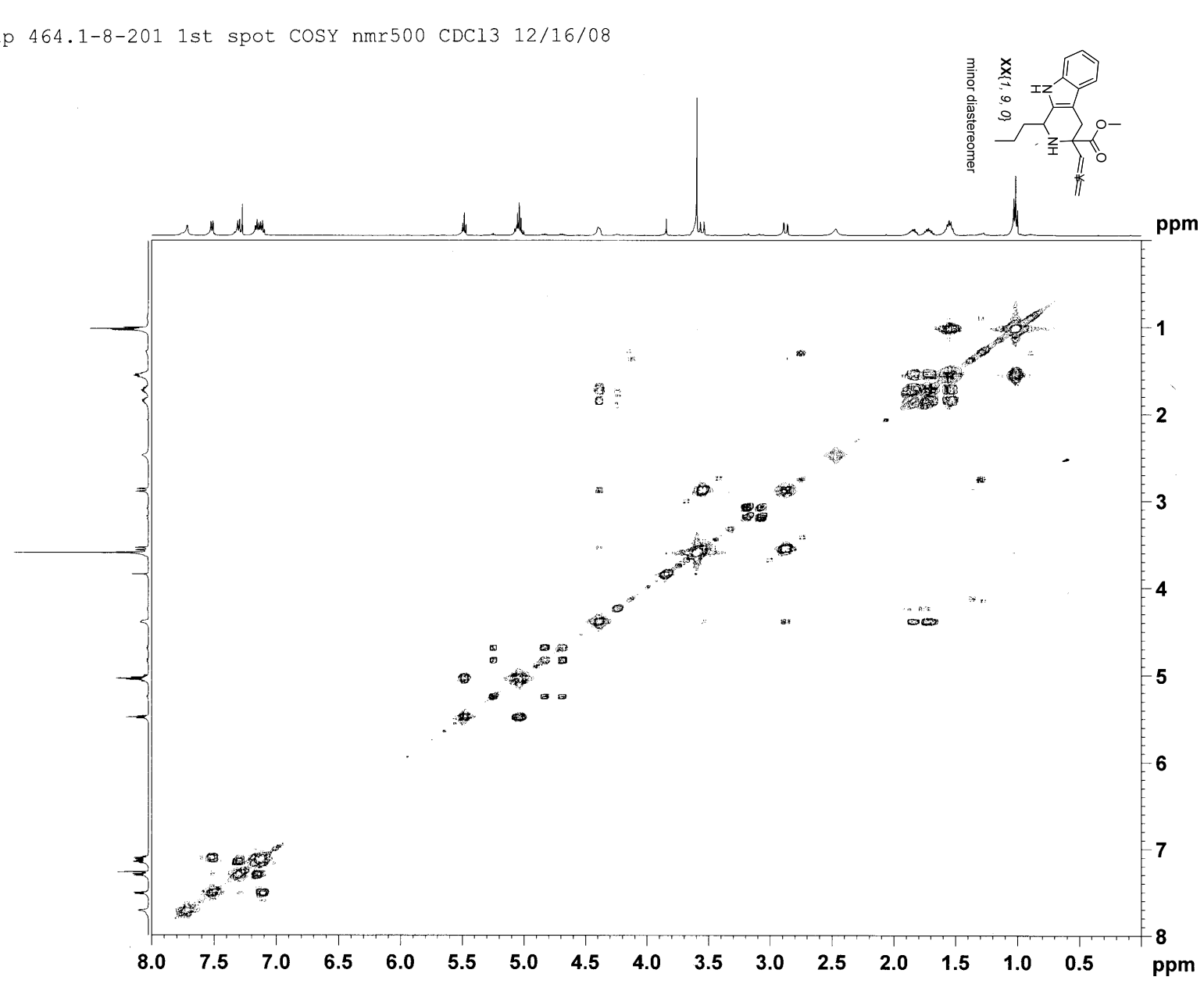

tp 464.1-8-201 2nd spot COSY nmr500 CDCl3 12/16/08
XX{1, 9, 0}
major diastereomer
ppm
ppm

tp 464.1-8-201 1st spot nmr500 CDCl3 12/16/08

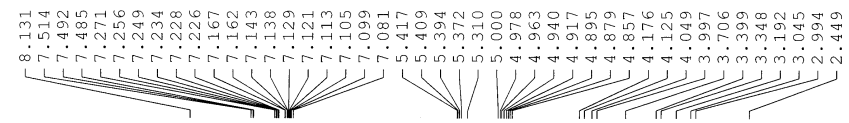


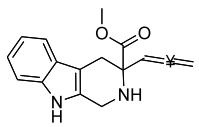
tp 464.1-8-201 1st spot (minor diastereomer)2
13C nmr301 12/18/08




tp 464.1-8-201 1st spot COSY nmr500 CDCl3 12/16/08
minor diastereomer
XX(1, 9, 0)
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

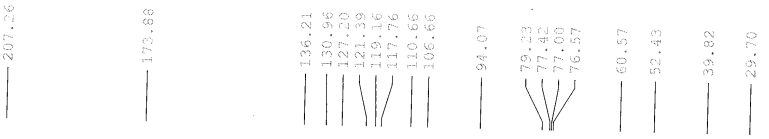
tp 429.3-4 1H CDCl3 nmr300 12/2/08

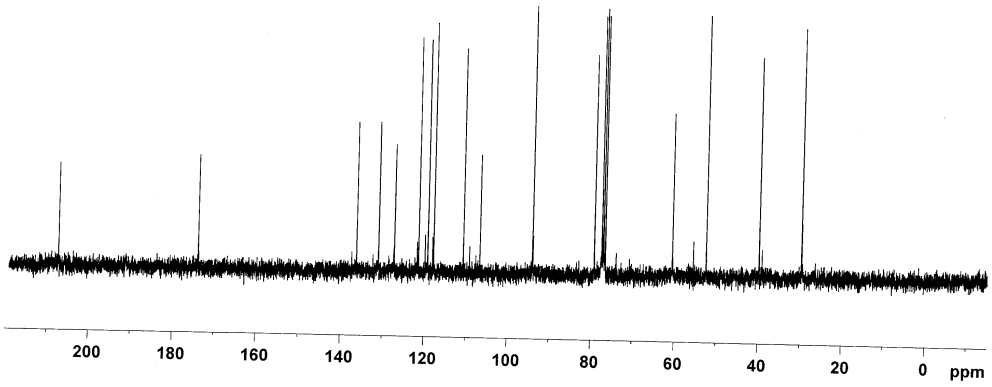




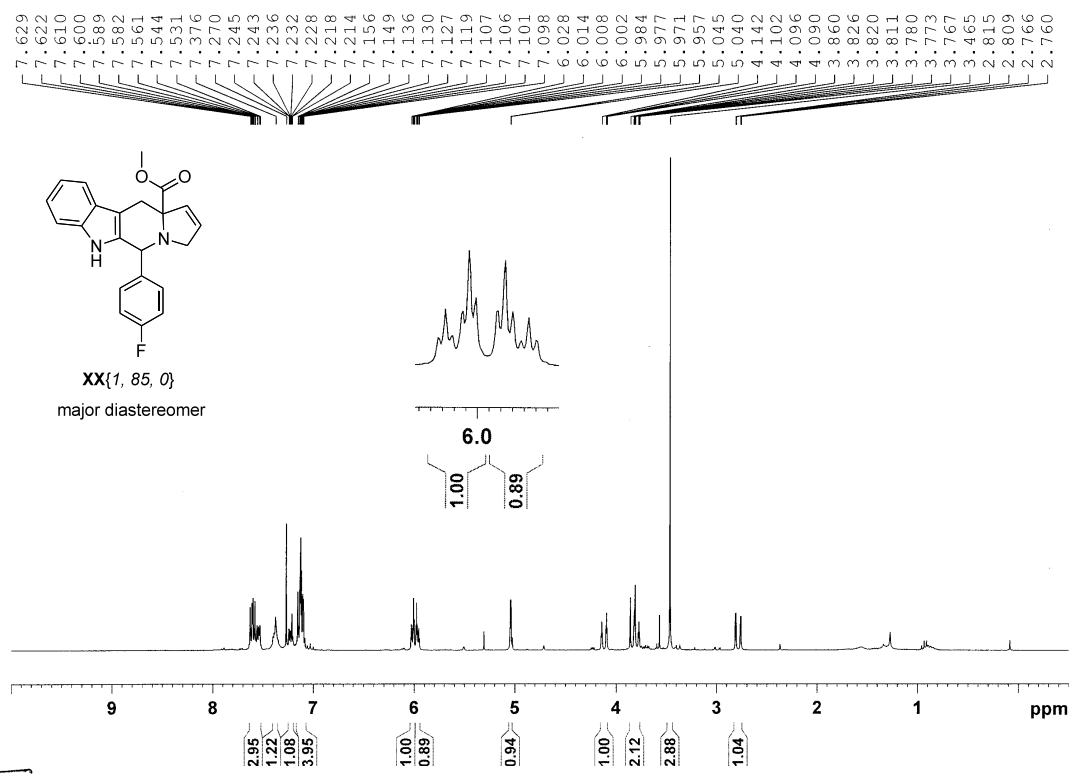
XX{*1, 2, 0*}

tp 429.3-4 13C CDCl3 nmr300 12/2/08

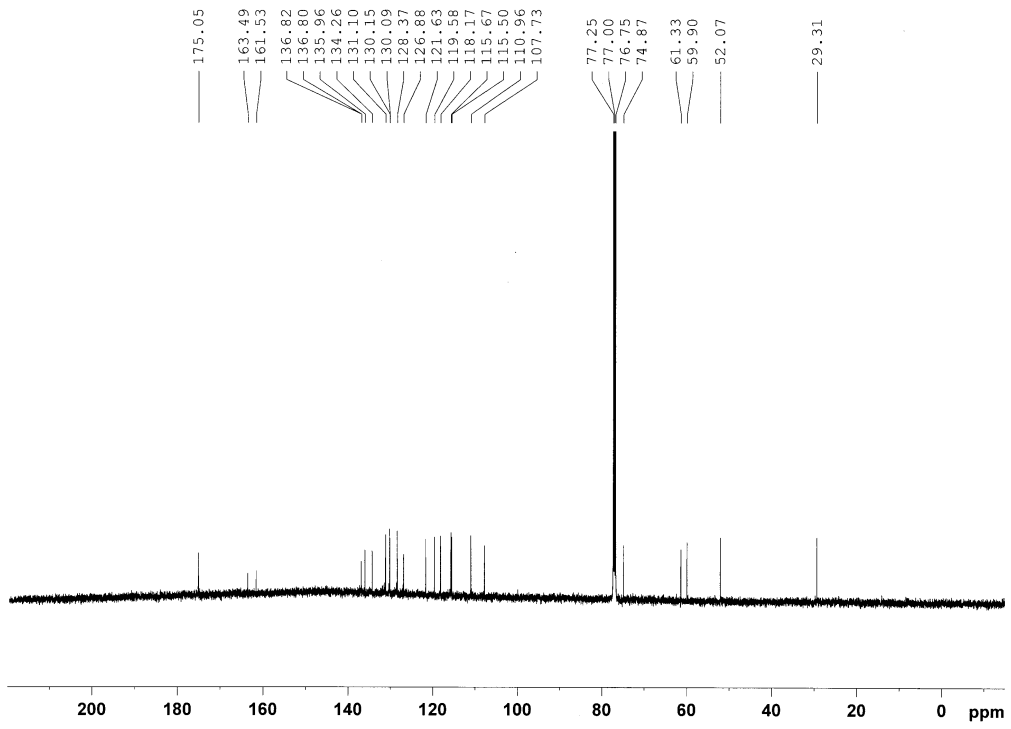




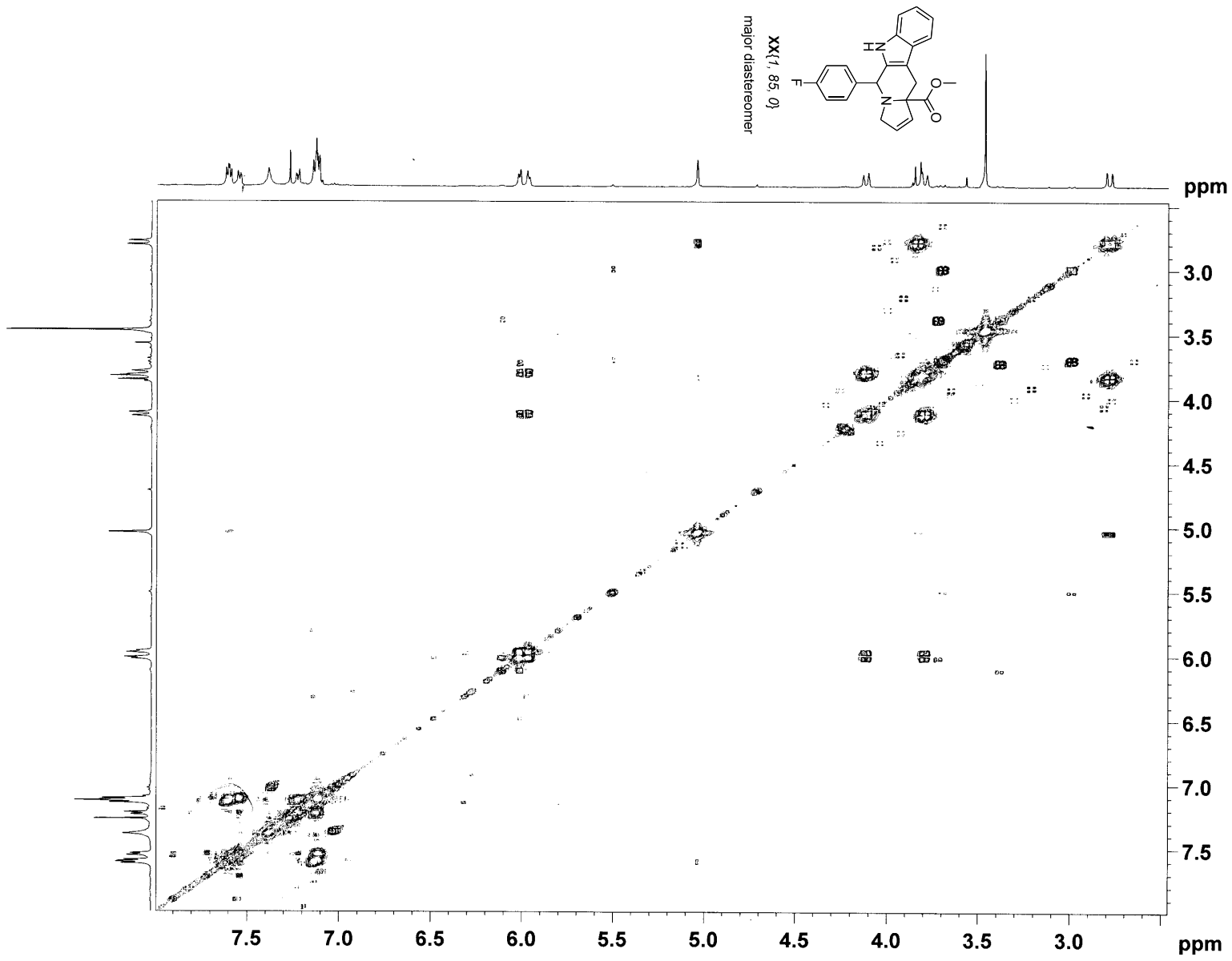
tp 452.3-8-189 final frxns nmr300 12/26/08



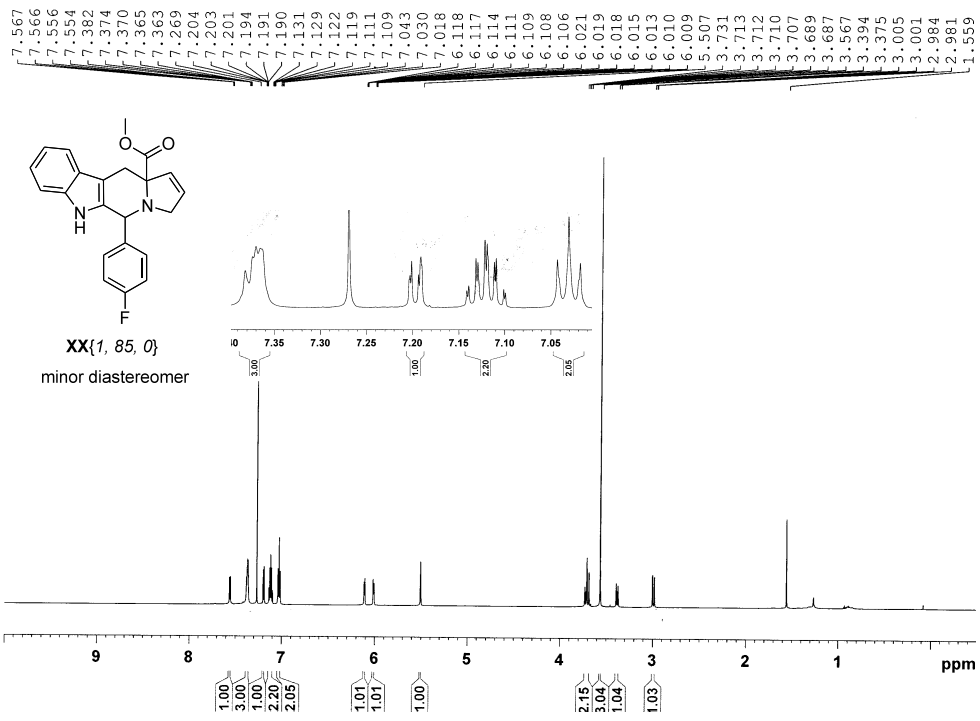
tp 452.3-8-189 2nd spot 13C CDCl3 nmr500 1/11/09



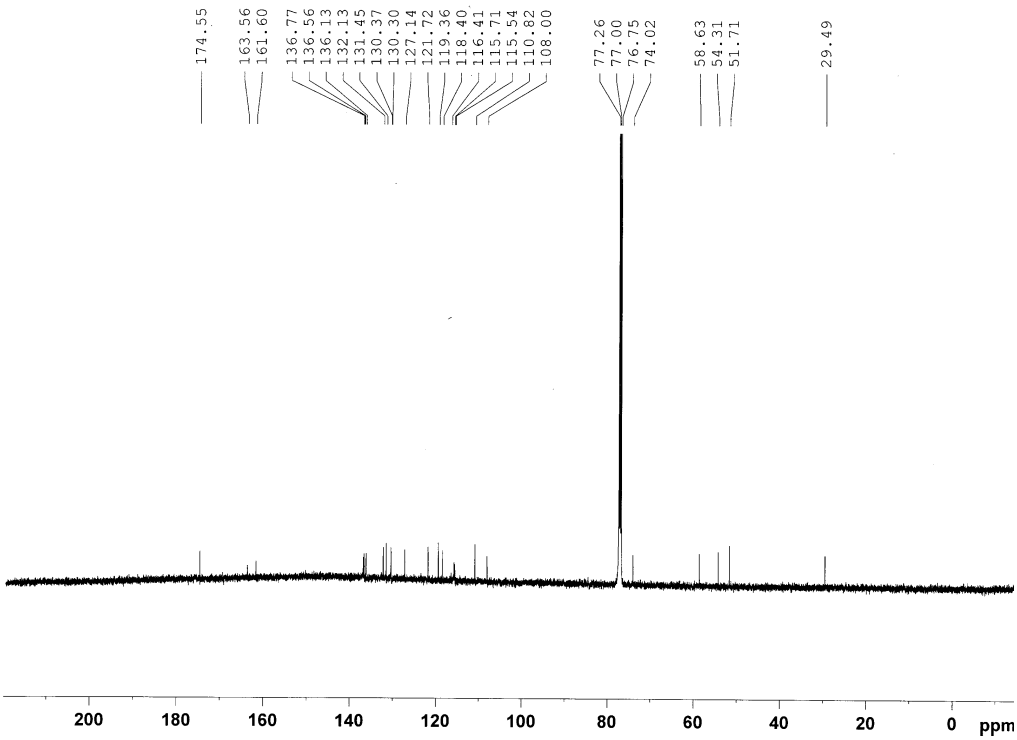
tp 452.3-8-189 2nd spot COSY CDCl3 nmr500 1/11/09

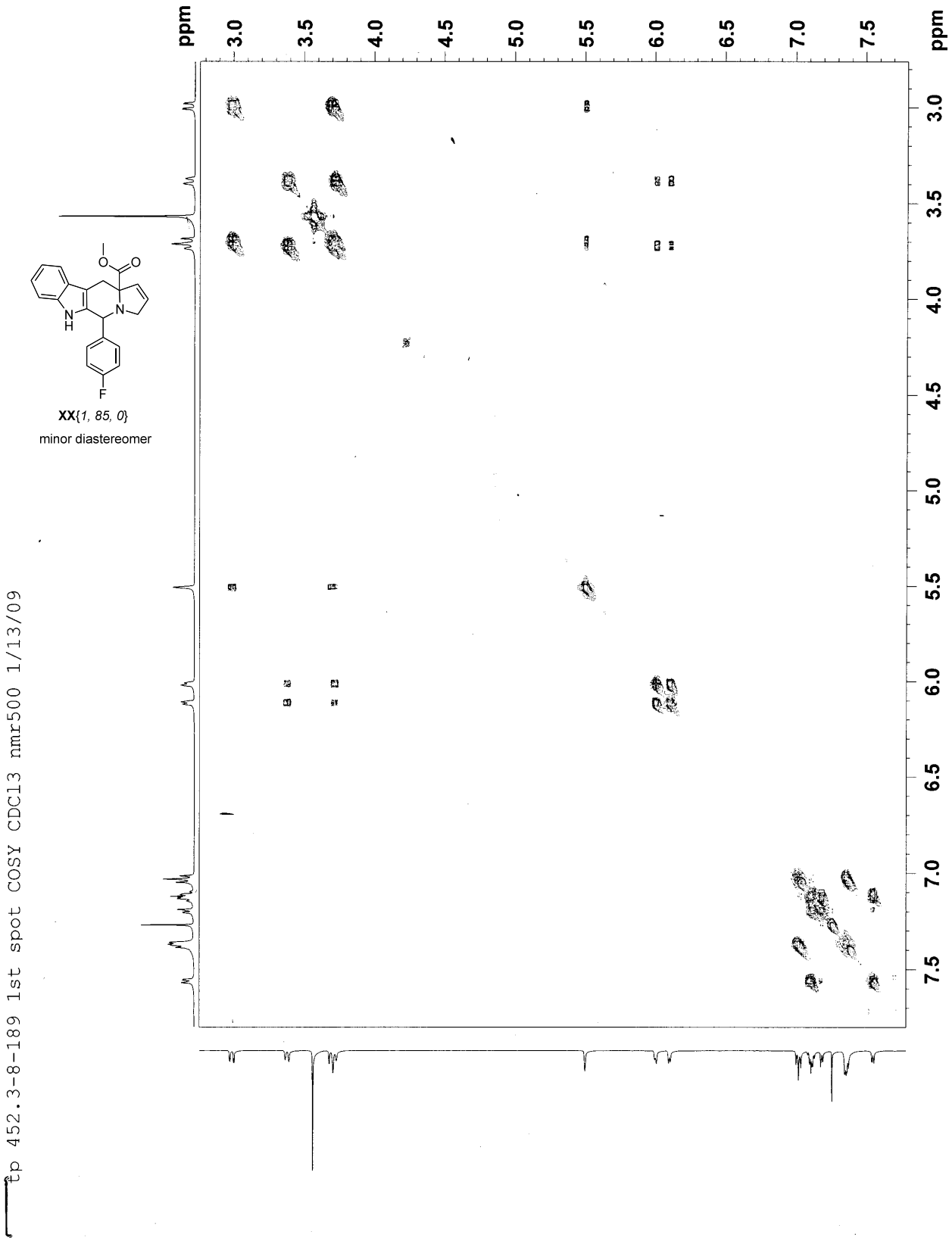


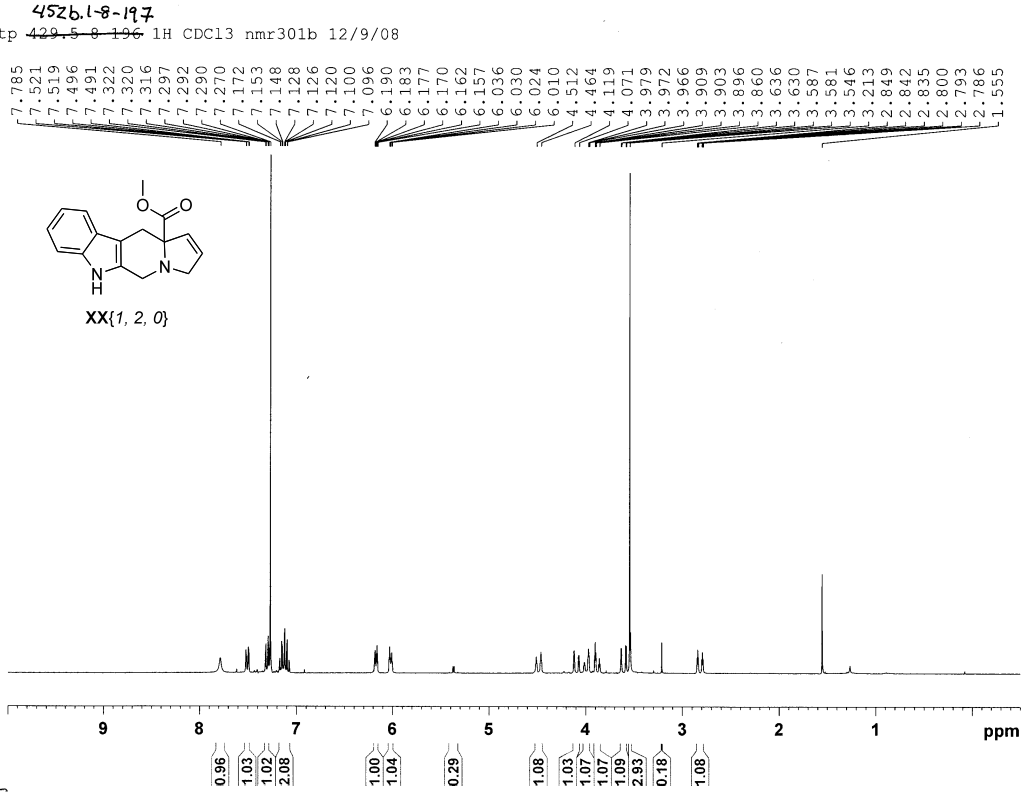
tp 452.3-8-189 1st frxns nmr700 1/14/09

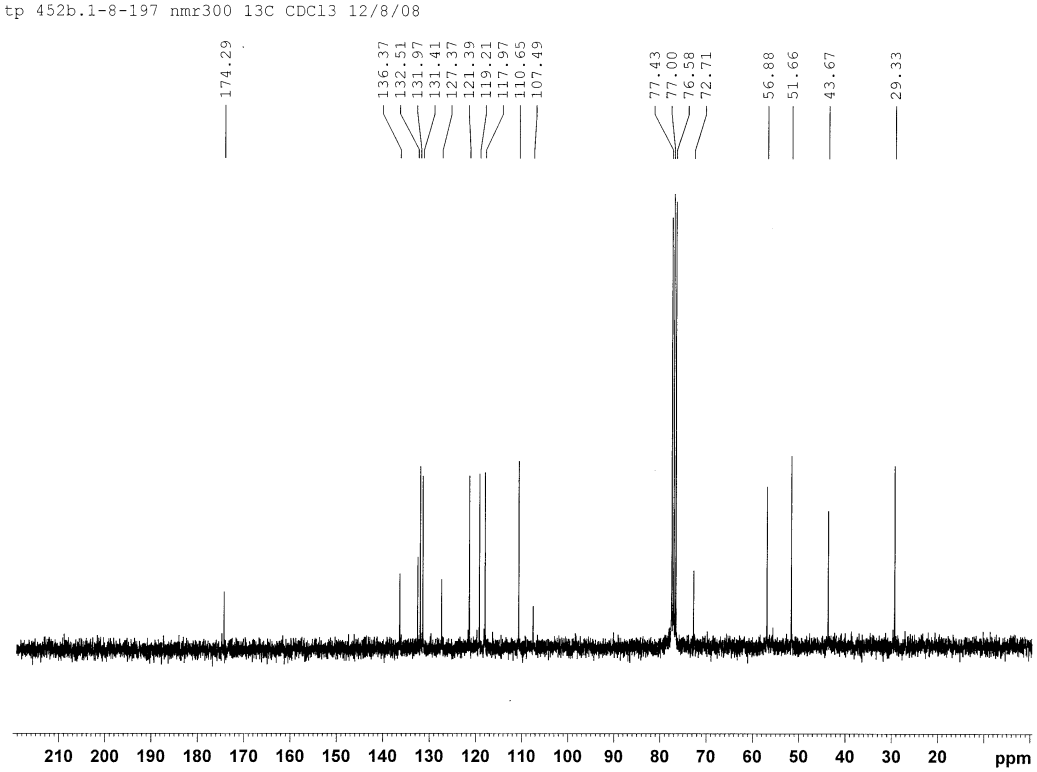


tp 452.3-8-189 1st spot 13C CDCl3 nmr500 1/13/09

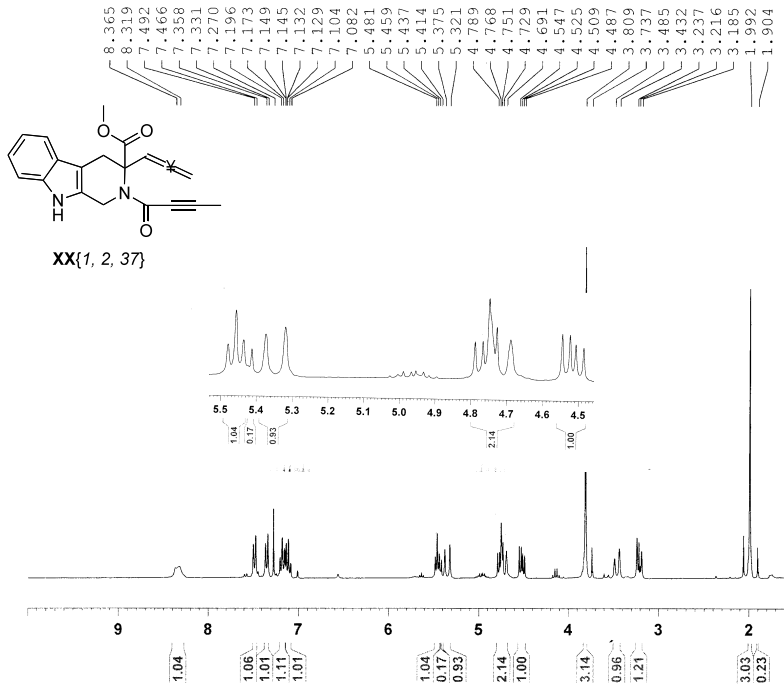



tp 452.3-8-189 1st spot COSY CDCl3 nmr500 1/13/09
XX{1, 85, 0}
minor diastereomer
ppm
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5


452b.1-8-197
tp 429.5-8-196 1H CDCl3 nmr301b 12/9/08
7.785
7.521
7.519
7.496
7.491
7.322
7.320
7.316
7.297
7.292
7.290
7.270
7.172
7.153
7.148
7.128
7.126
7.120
7.100
7.096
6.190
6.183
6.177
6.170
6.162
6.157
6.036
6.030
6.024
6.010
4.512
4.464
4.119
4.071
3.979
3.972
3.966
3.909
3.903
3.896
3.860
3.636
3.630
3.587
3.581
3.546
3.213
2.849
2.842
2.835
2.800
2.793
2.786
1.555
XX{1, 2, 0}
9
8
7
6
5
4
3
2
1
ppm
0.96
1.03
1.02
2.08
1.00
1.04
0.29
1.08
1.03
1.07
1.07
1.09
2.93
0.18
1.08

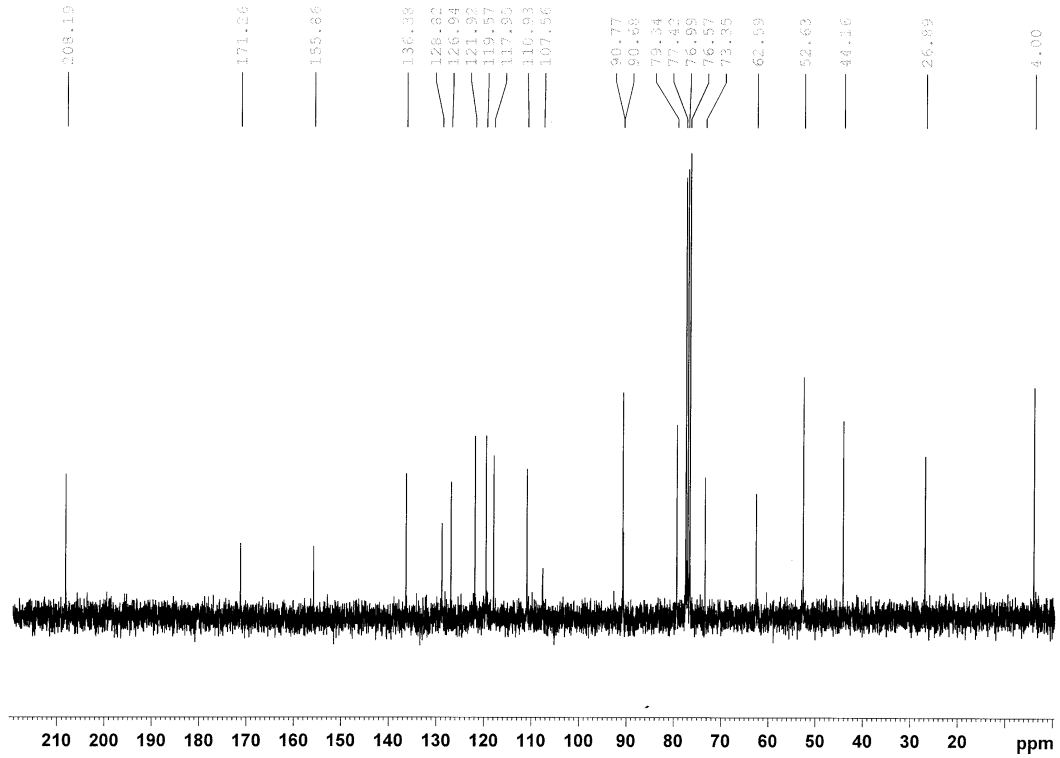

tp 452b.1-8-197 nmr300 13C CDCl3 12/8/08
174.29
136.37
132.51
131.97
131.41
127.37
121.39
119.21
117.97
110.65
107.49
77.43
77.00
76.58
72.71
56.88
51.66
43.67
29.33
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

tp 442b.2-8-199 1H CDCl3 nmr301 12/12/08

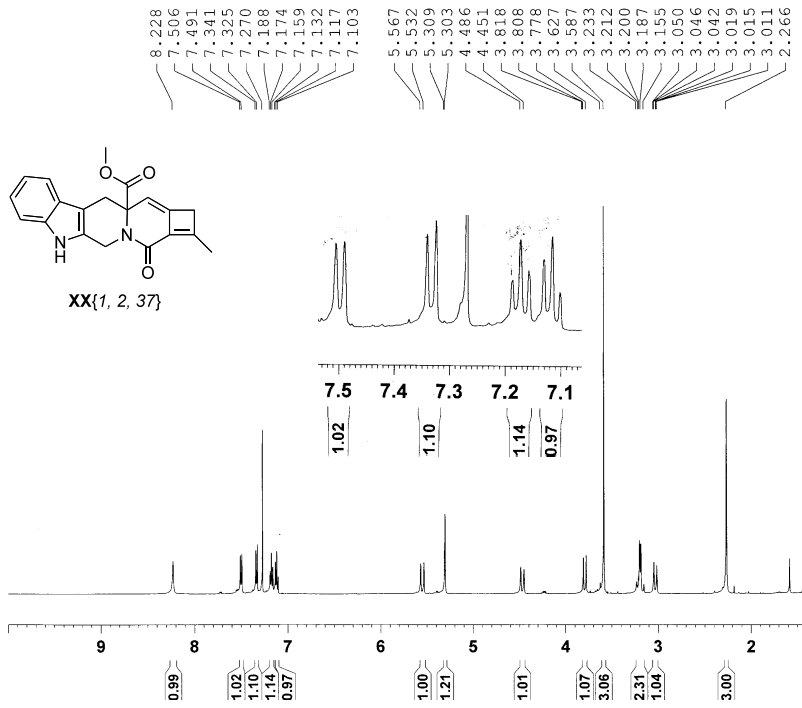


XX{*1, 2, 37*}

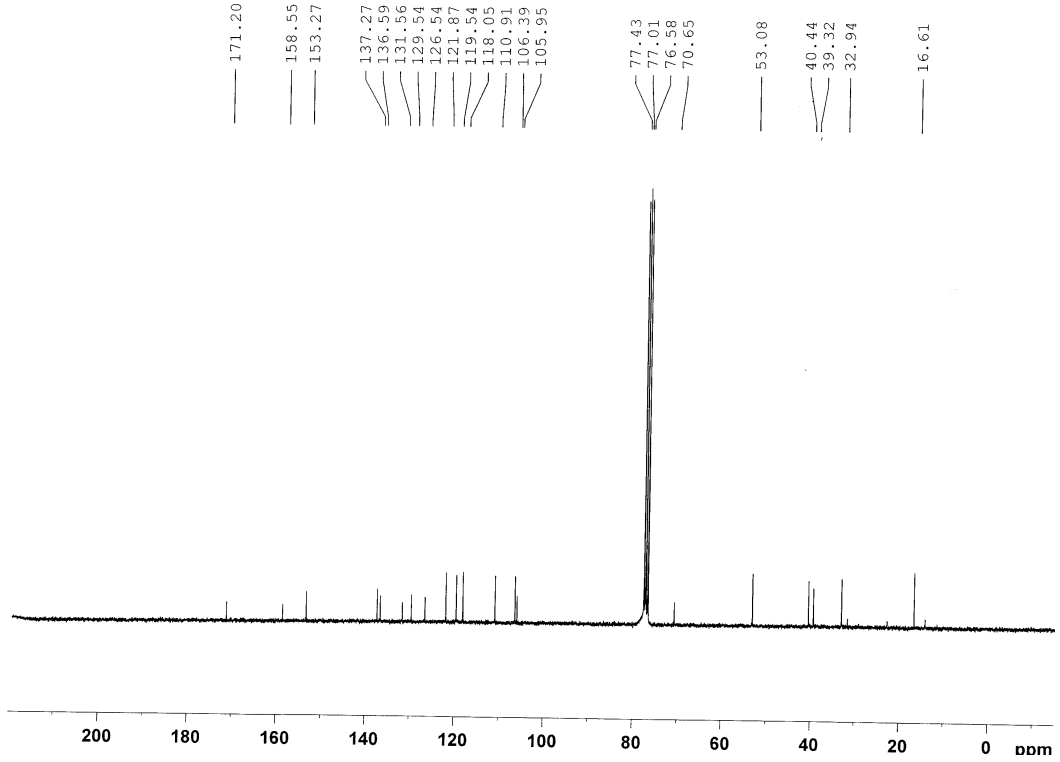
tp 442b.2-8-199 C13C CDCl3 nmr300 12/12/08

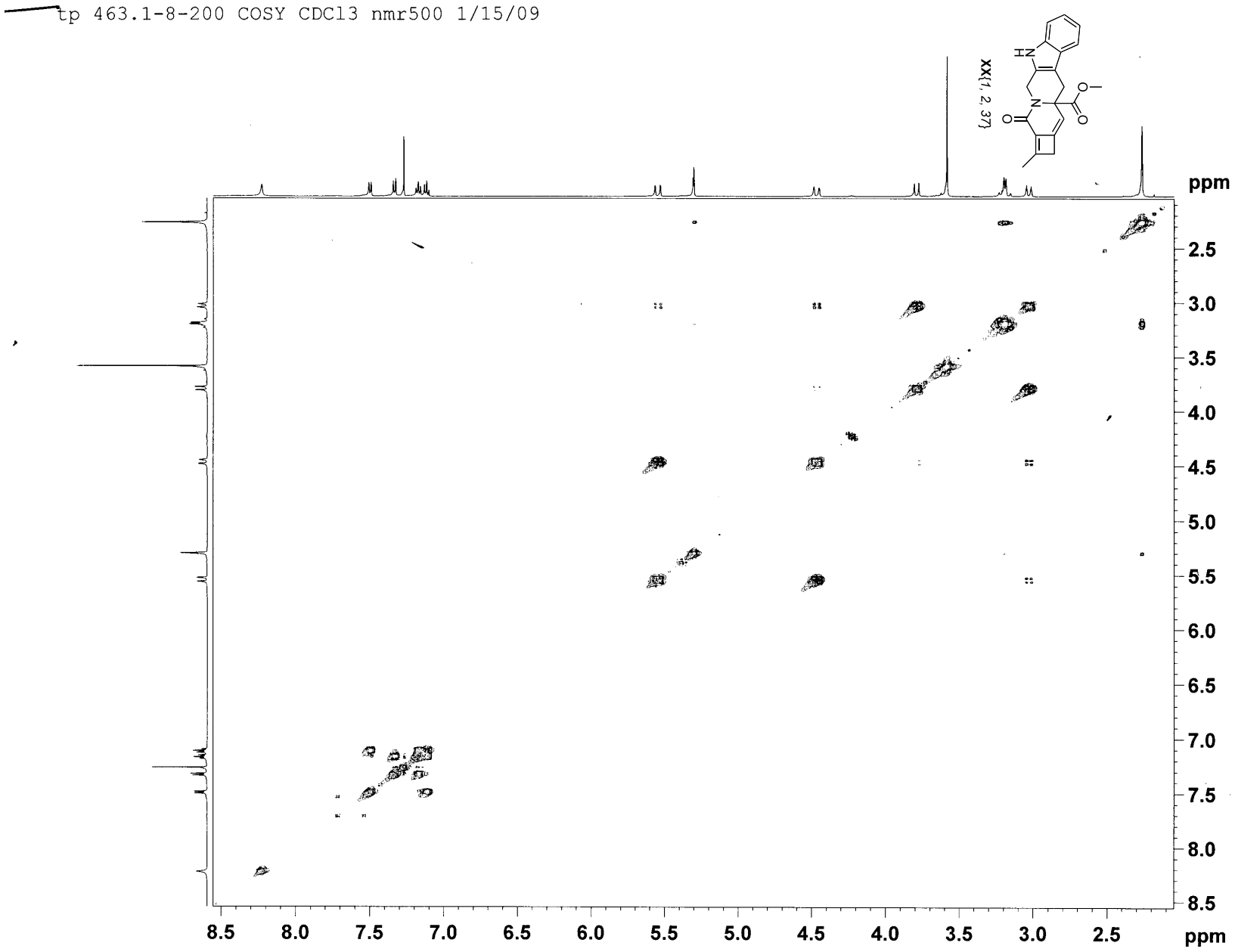


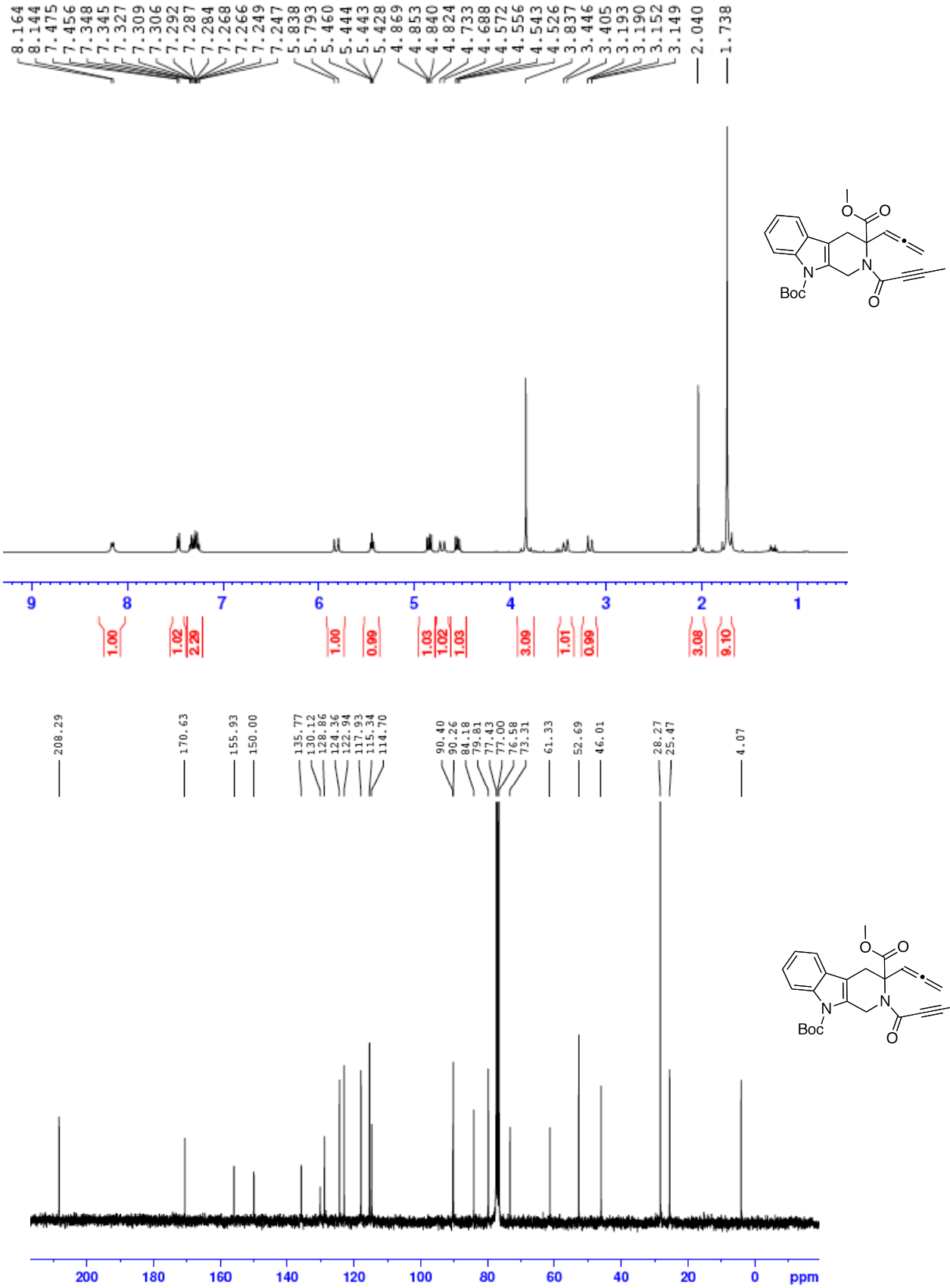
tp 463.1-8-200 1H CDCl3 nmr500 1/15/09

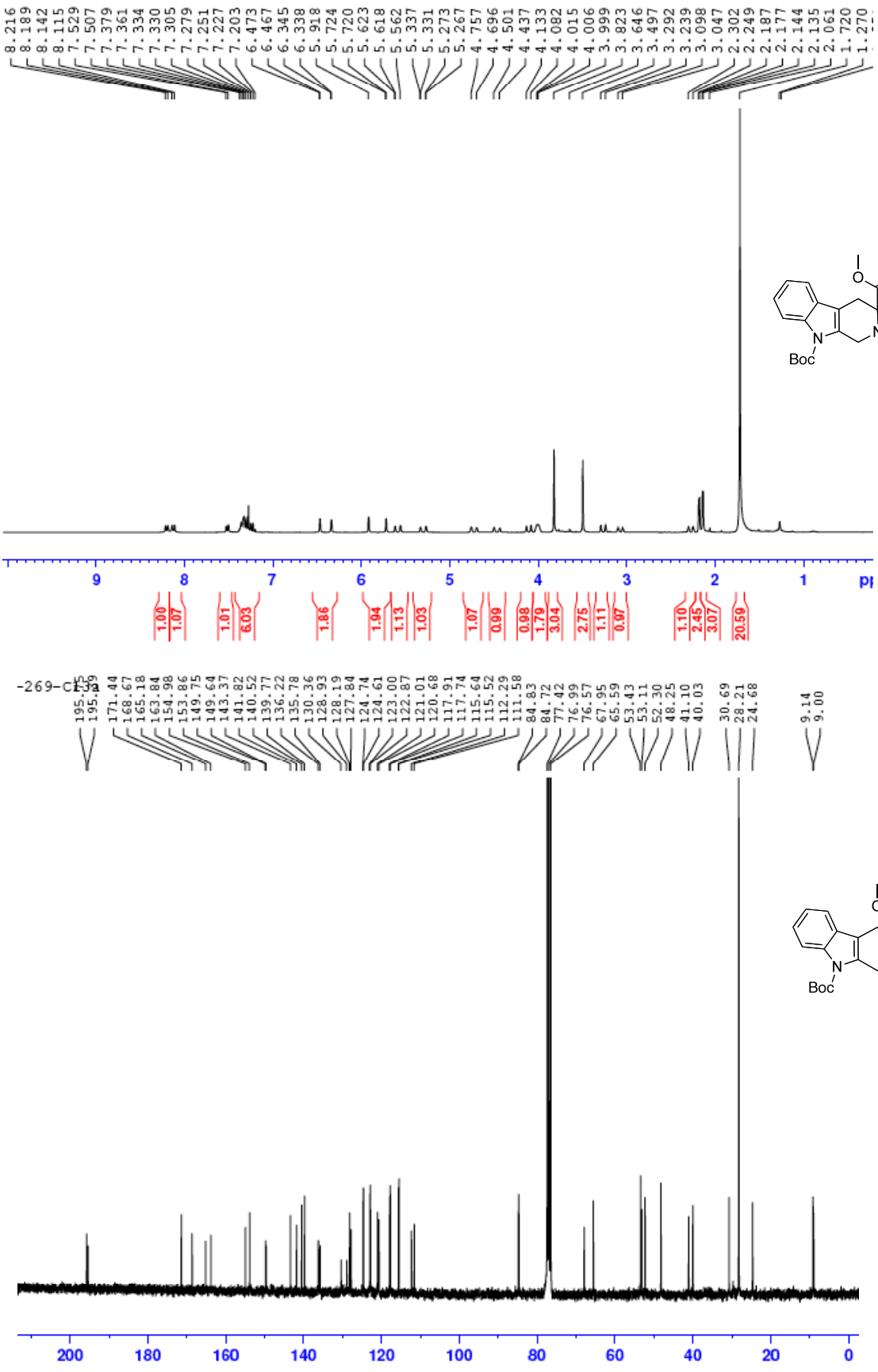


tp 463.2-8-207 13C CDCl3 nmr300 1/18/09




tp 463.1-8-200 COSY CDCl3 nmr500 1/15/09
XX{1, 2, 37}
ppm
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
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
ppm


8.164
8.144
7.475
7.456
7.348
7.345
7.327
7.309
7.306
7.292
7.287
7.284
7.268
7.266
7.249
7.247
5.838
5.793
5.460
5.444
5.443
5.428
4.869
4.853
4.840
4.824
4.733
4.688
4.572
4.556
4.543
4.526
3.837
3.446
3.405
3.193
3.190
3.152
3.149
2.040
1.738
Boc
1.00
1.02
2.29
1.00
0.99
1.03
1.02
1.03
3.09
1.01
0.99
3.08
9.10
208.29
170.63
155.93
150.00
135.77
130.12
128.86
124.36
122.94
117.93
115.34
114.70
90.40
90.26
84.18
79.81
77.43
77.00
76.58
73.31
61.33
52.69
46.01
28.27
25.47
4.07
Boc
ppm


8.216
8.189
8.142
8.115
7.529
7.507
7.379
7.361
7.334
7.330
7.305
7.279
7.251
7.227
7.203
6.473
6.467
6.345
6.338
5.918
5.724
5.720
5.623
5.618
5.562
5.337
5.331
5.273
5.267
4.757
4.696
4.501
4.437
4.133
4.082
4.015
4.006
3.999
3.823
3.646
3.497
3.292
3.239
3.098
3.047
2.302
2.249
2.187
2.177
2.144
2.135
2.061
1.720
1.270
O
O
N
O
O
Boc
Me
9
8
7
6
5
4
3
2
1
pp
1.00
1.07
1.01
6.03
1.86
1.94
1.13
1.03
1.07
0.99
0.98
1.79
3.04
2.75
1.11
0.97
1.10
2.45
3.07
20.59
-269-C13-a
195.45
195.39
171.44
168.67
165.18
163.84
154.98
153.86
149.75
149.64
143.37
141.82
140.52
139.77
136.22
135.78
130.36
128.93
128.19
127.84
124.74
124.61
123.00
122.87
121.01
120.68
117.91
117.74
115.64
115.52
112.29
111.58
84.83
84.72
77.42
76.99
76.57
67.95
65.59
53.43
53.11
52.30
48.25
41.10
40.03
30.69
28.21
24.68
9.14
9.00
O
O
N
O
O
Boc
Me
200
180
160
140
120
100
80
60
40
20
0

1. Construction of the virtual combinatorial library

Given a library design, a product scaffold structure and lists of building block reagents, the Legion package of Sybyl 8.0 was used to create reaction-based libraries.
We used the scaffold 4 as an illustration to demonstrate how to create the library.

a. Load molecule scaffold 4 with R-group substituted by hydrogens (Figure 1) into Sybyl workspace

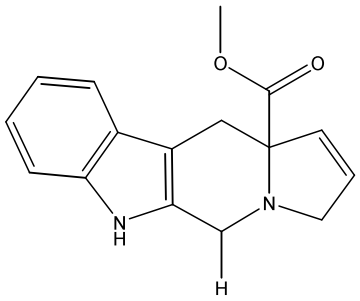


Figure 1. Scaffold 4 **with R-group substituted by hydrogens**

b. Retrieve reactants

In this step, the indole list (44 compounds) and aldehyde list (12 compounds) were loaded, and the variation sites among them were indicated as V1, V2, V3, and V4 in indoles (**Figure 2**) and V in aldehydes (**Figure 3**).

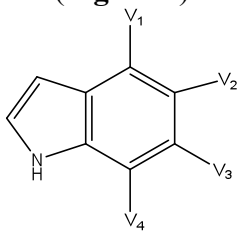


Figure 2. Variation sites among indole compounds

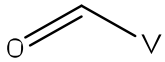


Figure 3. Variation site among aldehyde compounds

c. Map reactants to product

Each R group of reactant was attached on the atom in the product scaffold corresponding to its destination in the product, V1->X1, V2->X2, V3->X3, V4->X4 and V->Y (**Figure 4**).

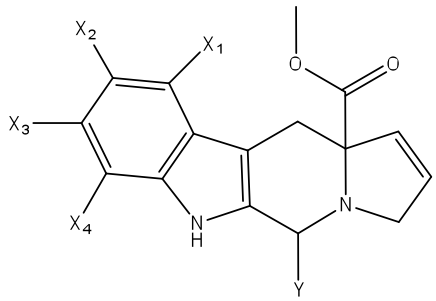


Figure 4. The substituted positions in scaffold 4

d. Build library

The Sybyl software will enumerate all the possible combinations to build the 528 (=44*12) products.

2. 2D fingerprint Tanimoto coefficient (Tc) calculation of MLSMR and 6 virtual libraries

Sybyl software includes a method to compare two UNITY databases based on their 2D fingerprints. Firstly, the fingerprints for MLSMR database and the virtual library were generated by the UNITY module of Sybyl software. Then these two databases are compared by the Database Comparison module (Figure 5). As shown in Figure 5, each time one of virtual libraries derived from the 6 scaffolds is set as reference database, and the SMR database is set as candidate database. This step yielded six histograms of the Tanimoto indices.

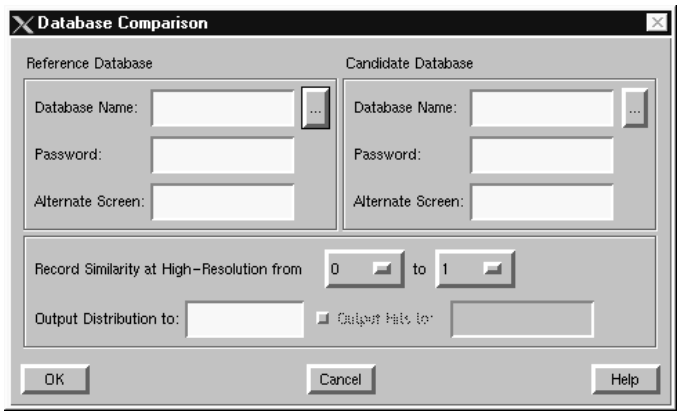


Figure 5. Database comparison interface of Sybyl software

3. Cell-Based BCUT Metrics Calculation and Diverse Subset Selection

Multidimensional chemistry space coordinates were calculated with DiverseSolutions (DVS) module of Sybyl software for each compound according to four main classes of atomic properties, including atomic Gasteiger−Huckel charge, polarity, hydrogen-bond donor, and hydrogen-bond acceptor attributes. Following is the detail.

a. Generate the properties files for MLSMR database and virtual libraries derived from the 6 scaffolds

In this step, each of compound databases was input in SDF format and the 2D H-suppressed BCUT descriptors were generated. Then these properties files were merged.

b. Generate chemical space with the merged properties file

In this step, three less correlated properties, names Bcut_gastchrg_burden_000.100_R_H, Bcut_tabpolar_burden_000.500_R_H and Bcut_haccept_burden_002.500_R_H, were selected as the coordinate axis.

c. Report chemistry space coordinates of these compounds.

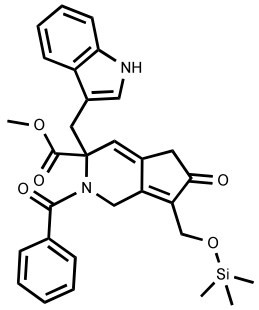
In this step, each of the properties was scaled to value 0-10. Each compound was mapped to a point in three dimension chem-space according to its properties. The coordinates of these derivatives of 6 scaffolds (11,748 compounds) together with the MLSMR database (327,000+ compounds) were plotted by the Xplottor module in DVS.

d. Generate the representative library by performing cell-based diverse subset selection from a compound source-file

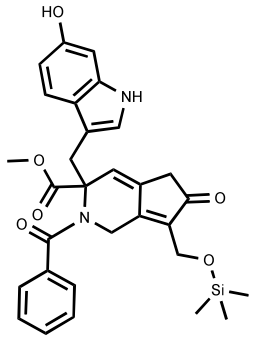
In this step, the compound source-file was designate to the merged derivatives of six scaffolds (11,748 compounds). The size of the produced representative library was set as

50. The result number of compounds retrieved by the Sybyl software was 53. The coordinates of these derivatives of 6 scaffolds together with the representative library (53 compounds, Chart 1) were also plotted by the Xplottor module in DVS.

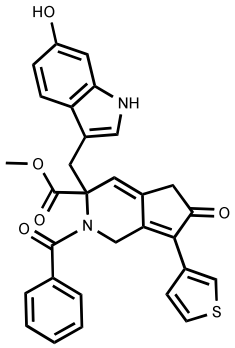
Scaffold 1



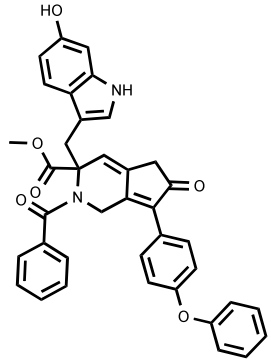
R1_1_R3_4



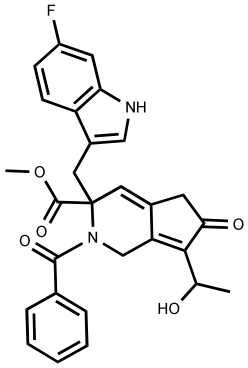
R1_11_R3_4



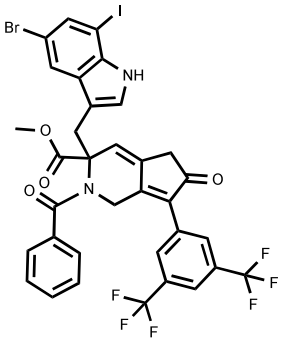
R1_11_R3_26



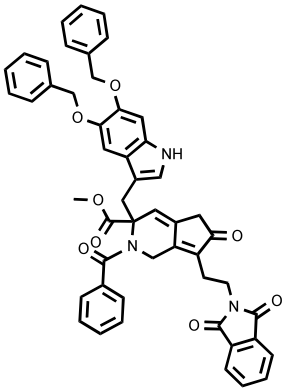
R1_11_R3_39



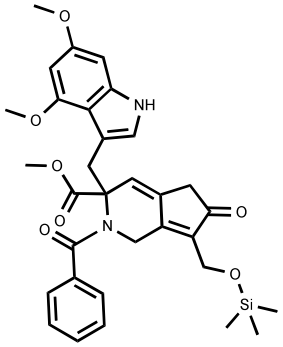
R1_15_R3_34



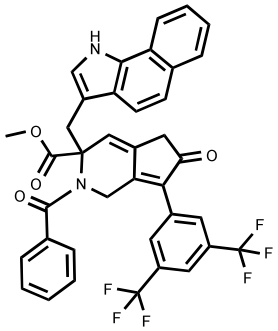
R1_34_R3_45



R1_35_R3_42

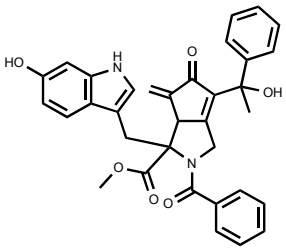


R1_39_R3_4



R1_33_R3_45

Scaffold 2



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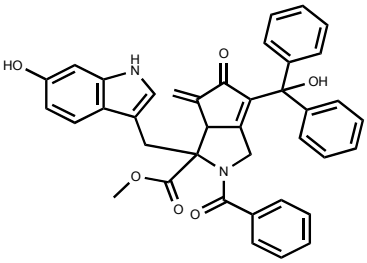
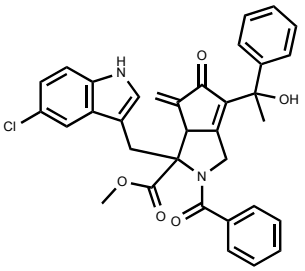
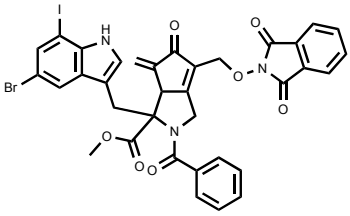


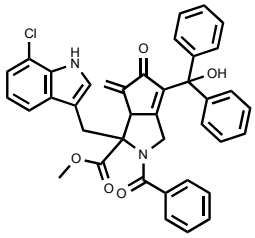
R1_11_R3_48



R1_24_R3_15



R1_34_R3_31



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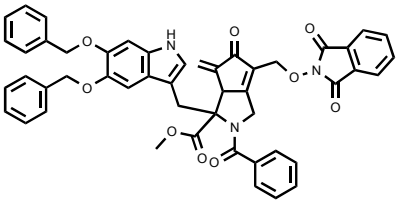
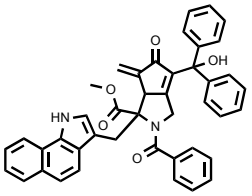
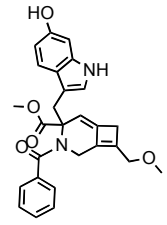


R1_35_R3_31

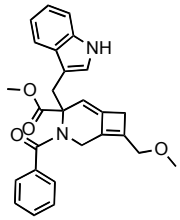


R1_33_R3_48

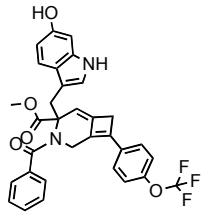
Scaffold 3



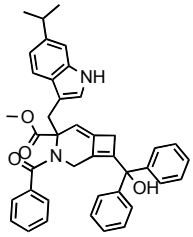
R1_11_R3_17



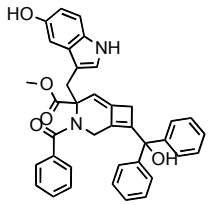
R1_1_R3_17



R1_11_R3_50



R1_30_R3_48



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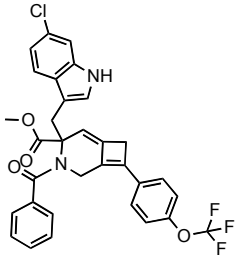

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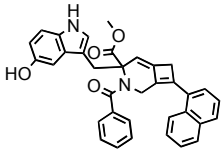
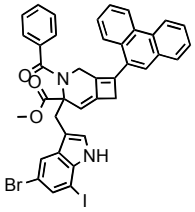
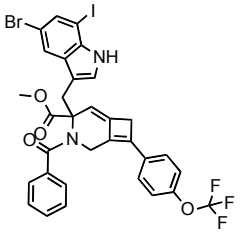


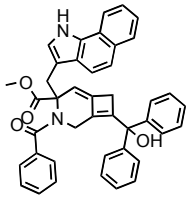
R1_12_R3_32



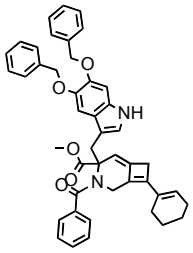
R1_34_R3_43



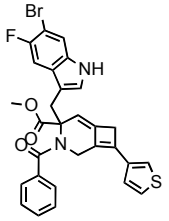
R1_34_R3_50



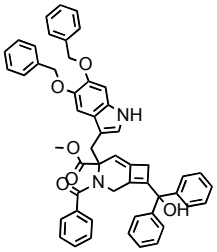
R1_33_R3_48



R1_35_R3_25

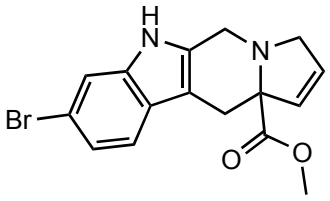


R1_42_R3_26

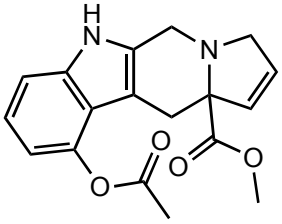


R1_35_R3_48

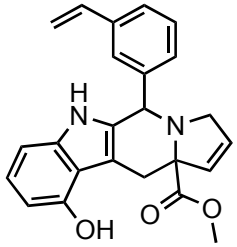
Scaffold 4



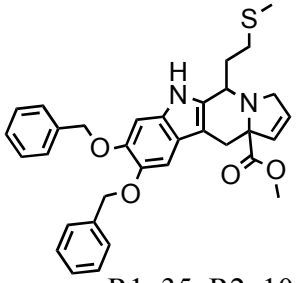
R1_17_R2_2



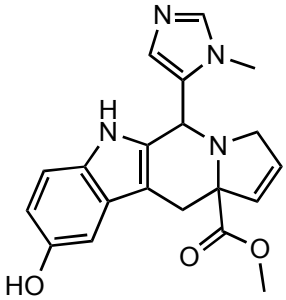
R1_37_R2_2



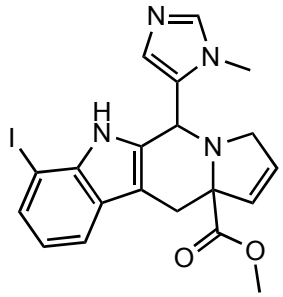
R1_10_R2_6



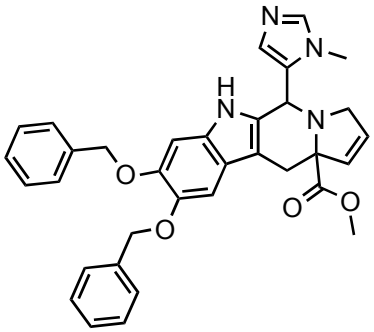
R1_35_R2_10



R1_12_R2_11

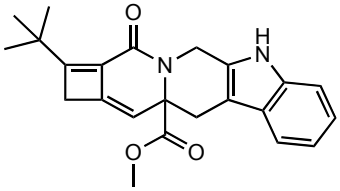


R1_18_R2_11

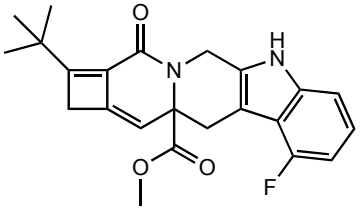


R1_35_R2_11

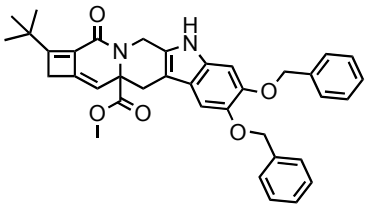
Scaffold 5



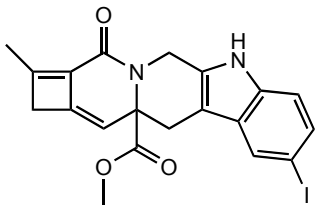
R1_1_R3_23



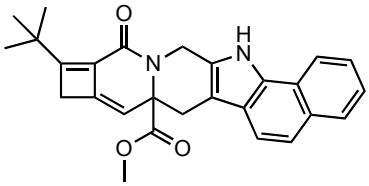
R1_14_R3_23



R1_35_R3_23

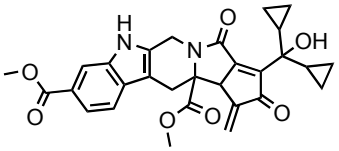


R1_26_R3_37

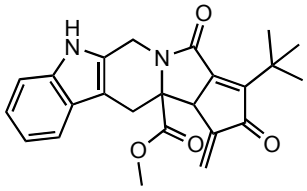


R1_33_R3_23

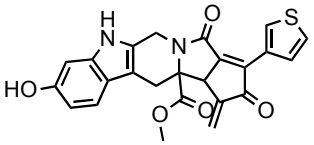
Scaffold 6



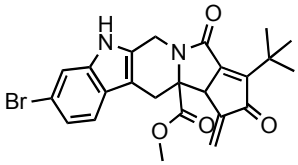
R1_6_R3_12



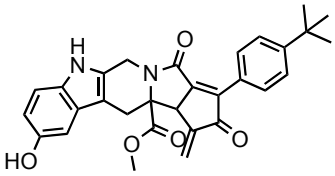
R1_1_R3_23



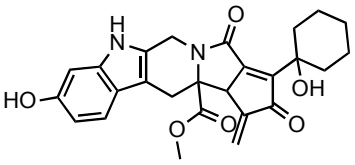
R1_11_R3_26



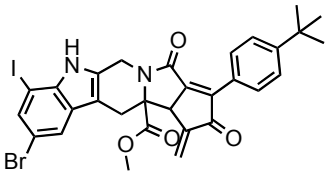
R1_17_R3_23



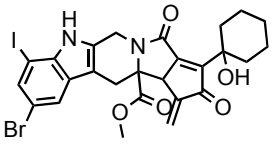
R1_12_R3_35



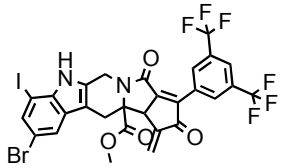
R1_11_R3_36



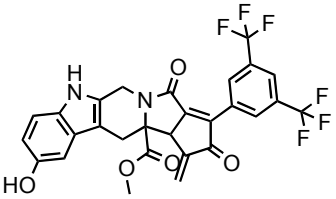
R1_34_R3_35



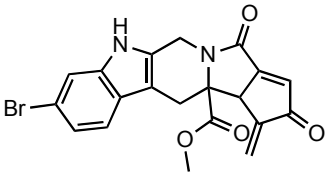
R1_34_R3_36



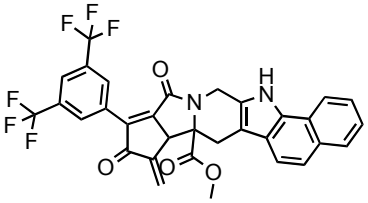
R1_34_R3_45



R1_12_R3_45



R1_17_R3_51



R1_33_R3_45