Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Face selective reduction of the exocyclic double bond in isatin derived spirocyclic lactones

Sandeep Rana,[a] and Amarnath Natarajan[a,b*]

[a]Eppley Institute for Cancer and Allied Diseases, University of Nebraska Medical Center, Omaha, NE, USA.

[b]Eppley Institute for Cancer and Allied Diseases and Department of Chemistry, University of Nebraska, Lincoln, NE, USA

Fax: 1-402-559-3793; Tel: 1-402-559-8270; E-mail: anatarajan@unmc.edu

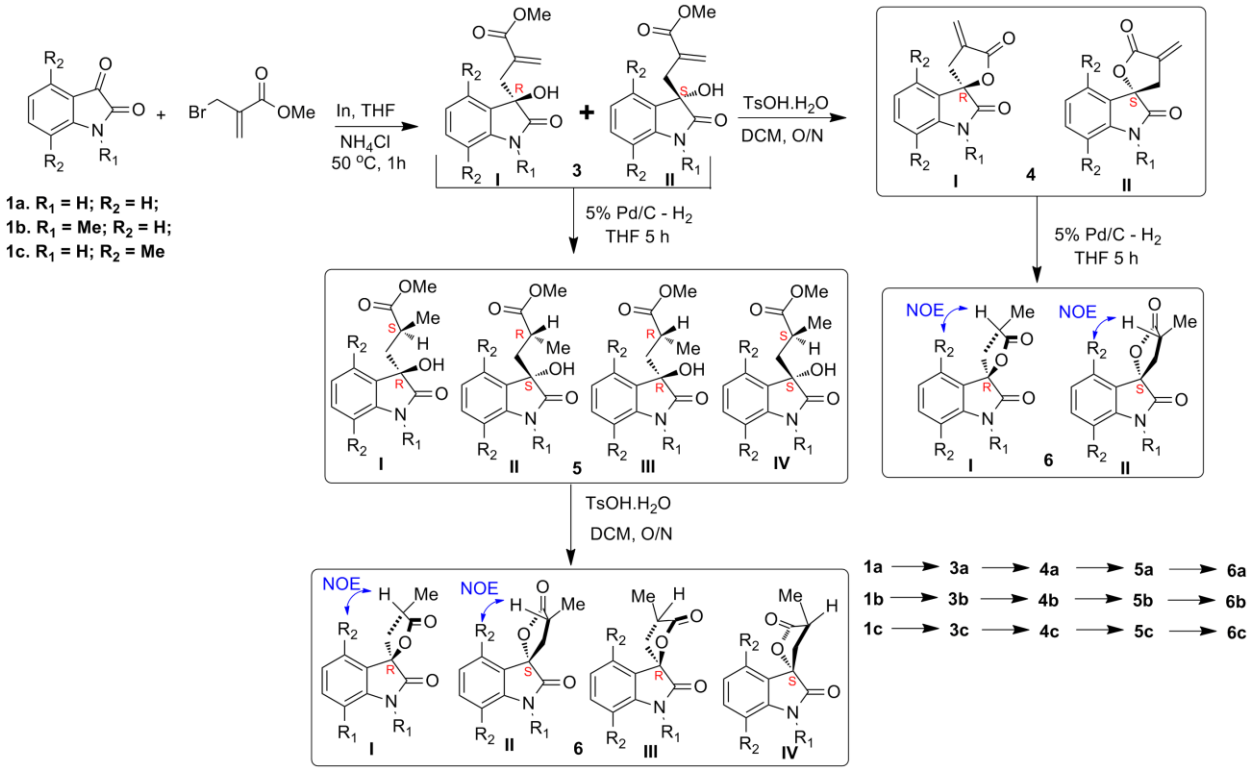
Contents

Supporting Experimental Methods

General methods

All reagents were purchased from commercial sources and were used without further purification. Flash chromatography was carried out on silica gel (200–400 mesh). Thin layer chromatography (TLC) were run on pre-coated EMD silica gel 60 F_{254} plates and observed under UV light at 254 nm and with basic potassium permanganate dip. Column chromatography was performed with silica gel (230-400 mesh, grade 60, Fisher scientific, USA). ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded in chloroform-d or DMSO-d_6 on a Varian-500 and Varian-600 spectrometer (DMSO-d_6 was 2.50 ppm for ^{1}H and 39.55 ppm for ^{13}C and $CDCl_3$ was 7.27 ppm for ^{1}H and 77.23 ppm for ^{13}C. Proton and carbon chemical shifts were reported in ppm relative to the signal from residual solvent proton and carbon. LC-MS for the compounds was generated on an Agilent 1200 series system with UV detector (214 nm and 254 nm) and an Agilent 6130 quadrupole mass detector. HRMS were carried our University of Nebraska at Lincoln Mass Spectrometry facility.

Experimental Section



General Procedure for Barbier-type reaction: In a dry round bottom flask equipped with a reflux condenser was taken indium metal powder (4.06 mmol, 2 eq) and ammonium chloride (4.06 mmol, 2 eq). To it was added a solution of methyl 2-(bromomethyl) acrylate (2.45 mmol, 1.2 eq) in dry THF (5 mL). The reaction mixture was heated at 50 °C for 15 minutes followed by addition of a solution of isatin/isatin derivatives (2.03 mmol, 1 eq) in 5 mL THF. Reaction mixture was heated at 50 °C with constant stirring for 30 minutes and reaction completion (disappearance of isatin) was monitored by thin layer chromatography using 50% ethyl acetate in hexane solvent. Following reaction completion, reaction mixture was cooled to room temperature and passed through silica gel to remove ammonium chloride and indium metal. Reaction solvent was evaporated under reduced pressure using rotavapor. Crude reaction mixture was dissolved in 0.1% HCl and extracted using ethyl acetate followed by washing with brine, and dried using magnesium sulfate. Crude mixture was column chromatographed using hexane and ethyl acetate gradient to obtain spirocyclic compound and acyclic compound respectively.

General procedure for the reduction reaction for spiro compounds: Taken spiro compound (0.11 mmol) in round bottom flask and added 4 mL of dry THF via syringe. To the reaction mixture was added Pd/C (5 mg, 5 % by weight on activated carbon) and nitrogen gas was bubbled though the reaction mixture for about 10 minutes. Reaction mixture was gently vacuumed and was kept under hydrogen atmosphere for 5 hours (*Note: Reaction was monitored by NMR spectroscopy as longer time leads to over reduction of carbonyl group of lactone*). After completion of reaction, mixture was passed through a bed of celite and column chromatographed using hexane and ethyl acetate gradient to obtained product as white solid.

General procedure for the reduction reaction for acyclic compounds: Taken acyclic compound (0.36 mmol) in round bottom flask and added 8 mL of dry THF via syringe. To the reaction mixture was added Pd/C (20 mg, 5 % by weight on activated carbon) and nitrogen gas was bubbled though the reaction mixture for about 10 minutes. Reaction mixture was gently vacuumed and was kept under hydrogen atmosphere for 24 hours. After completion of reaction, mixture was passed through a bed of celite and column chromatographed using hexane and ethyl acetate gradient to obtained product as colorless oil.

General procedure for the cyclization reaction of acyclic compounds: Taken acyclic compound (0.25 mmol, 1 eq.) in round bottom flask and added 5 mL of dichloromethane via syringe followed by addition of *p*-toluenesulfonic acid monohydrate salt (0.25 mmol, 1 eq.). Reaction mixture was stirred at room temperature for 12 h under nitrogen atmosphere. Completion of the reaction was monitored by thin layer chromatography. Crude mixture was washed with brine and extracted using dichloromethane, dried under magnesium sulfate and column chromatographed using hexane and ethyl acetate gradient to obtain desired product as white solid.

methyl 2-((3-hydroxy-2-oxindolin-3-yl)methyl)acrylate and methyl 2-((3-hydroxy-2-oxindolin-3-yl)methyl)acrylate 3a(I-II). White amorphous solid (360 mg, 82%): ^{1}H NMR ($CDCl_3$) δ 9.06 (s, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 6.99 (t, *J* = 7.0 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.20 (s, 1H), 5.58 (s, 1H), 3.60 (s, 3H), 3.13 (d, *J* = 13.5 Hz, 1H), 2.80 (d, *J* = 13.5 Hz, 1H); ^{13}C NMR δ 180.5, 168.2, 140.5, 134.2, 130.1, 130.0, 129.8, 125.0,

122.7, 110.8, 76.7, 52.3, 39.8.

4-methylene-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione and 4-methylene-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione 4a(I-II). White amorphous solid (58 mg, 15%): ^{1}H NMR ($CDCl_3$) δ 8.54 (s, 1H), 7.36 – 7.30 (m, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.42 (t, *J* = 2.5 Hz, 1H), 5.82 (t, *J* = 2.5 Hz, 1H), 3.34 (dt, *J* = 17.5 Hz, 3 Hz, 1H), 3.14 (dt, *J* = 17.5 Hz, 3.0 Hz, 1H); ^{13}C NMR δ 175.4, 169.1, 141.0, 132.8, 131.5, 127.2, 124.8, 124.0, 123.5, 111.0, 79.7, 36.6; IR (cm^{-1}) 2915, 2836, 1768, 1731, 1616, 1468, 1251, 1180, 1030; LCMS calcd for $C_{18}H_{13}NO_3$ m/z 215.0582, found: 216.05 (m + 1); HRMS (TOF MS EI^+) calcd for $C_{12}H_9NO_3$ m/z 215.0582, found: 215.0583

4-methyl-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dion and 4-methyl-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione 6a(I-II). Colorless gel (13 mg, 55%): ^{1}H NMR ($CDCl_3$) δ 8.32 (s, 1H), 7.34 – 7.29 (m, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 3.16 – 3.11 (m, 1H), 2.61 (dd, *J* = 13.0 Hz, 9.5 Hz, 1H), 2.41 (dd, *J* = 13.0 Hz, 9.5 Hz, 2H), 1.51 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 178.6, 175.4, 140.6, 131.2, 128.4, 124.3, 123.8, 110.9, 80.9, 38.8, 34.8, 16.6; IR (cm^{-1}) 1698, 1616, 1466, 1206, 749; LCMS calcd for $C_{18}H_{13}NO_3$ m/z 217.0739, found: 218.10 (m + 1); HRMS (TOF MS EI^+) calcd for $C_{12}H_{11}NO$ m/z 217.0739, found: 217.0742.

methyl 3-(3-hydroxy-2-oxindolin-3-yl)-2-methylpropanoate and methyl 3-(3-hydroxy-2-oxindolin-3-yl)-2-methylpropanoate and methyl 3-(3-hydroxy-2-oxindolin-3-yl)-2-methylpropanoate and methyl 3-(3-hydroxy-2-oxindolin-3-yl)-2-methylpropanoate 5a(I-IV) (2 inseparable set of compounds). Yellow gummy liquid (77 mg, 85%): ^{1}H NMR ($CDCl_3$) δ 8.18 (s, 1H), 8.12 (s, 1H) 7.40 (d, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 7.0 Hz, 1H), 7.26 - 7.23 (m, 2H), 7.08 - 7.05 (m, 2H), 6.89 - 6.86 (m, 2H), 4.03 (bs, 1H), 3.67 (s, 3H), 3.47 (s, 3H), 3.25 (bs, 1H), 2.99 - 2.92 (m, 1H), 2.62 - 2.52 (m, 3H), 1.88 - 1.83 (m, 2H), 1.16 - 1.14 (m, 6H); ^{13}C NMR δ 180.81, 180.8, 177.7, 177.1, 140.9, 140.5, 131.2, 130.0, 129.9, 129.8, 125.2, 124.2, 123.1, 123.0, 110.9, 76.4, 76.0, 52.1, 51.9, 41.6, 35.2, 34.9, 29.9, 19.4, 19.2. LCMS calcd for $C_{13}H_{15}NO_4$ m/z 249.1001, found: 249.10.

4-methyl-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione and 4-methyl-3*H*-spiro[furan-2,3'-

indoline]-2',5(4*H*)-dione and 4-methyl-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione and 4-methyl-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione 6a(I-IV) (2 inseparable set of compounds). White amorphous solid (20 mg, 92%): ^{1}H NMR ($CDCl_3$) δ 8.36 (bs, 1H), 8.22 (bs, 1H), 7.34 – 7.29 (m, 4H), 7.13 – 7.07 (m, 2H), 6.94 – 6.91 (m, 2H), 3.50 – 3.42 (m, 1H), 3.18 - 3.10 (m, 1H), 2.76 (dd, *J* = 13.0 Hz, 8.5 Hz, 1H), 2.61 (dd, *J* = 13.0 Hz, 9.5 Hz, 1H), 2.41 (dd, *J* = 13.0 Hz, 9.5.0 Hz, 1H), 2.16 (apparent triplet, *J* =12.5 Hz, 1H), 1.51 (d, *J* = 7.0 Hz, 3H), 1.40 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR δ 179.0, 178.7, 176.7, 176.0, 141.3, 140.7, 131.4, 131.2, 128.3, 126.7, 124.9, 124.2, 123.8, 123.8, 111.2, 110.9, 81.1, 80.8, 40.1, 38.7, 34.8, 34.4, 16.6, 15.7; LCMS calcd for $C_{12}H_{11}NO_3$ m/z 217.0739, found: 218.10 (m + 1).

1'-methyl-4-methylene-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione and 1'-methyl-4-methylene-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione 4b(I-II). White amorphous solid (58 mg, 26%): ^{1}H NMR ($CDCl_3$) δ 7.42 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.41 (t, *J* = 2.5 Hz, 1H), 5.80 (t, *J* = 2.5 Hz, 1H), 3.30 (dt, *J* = 17.0 Hz, 2.5 Hz 1H), 3.21 (s, 3H), 3.11 (dt, *J* = 17.0 Hz, 3.0 Hz, 1H); ^{13}C NMR δ 173.6, 169.1, 144.1, 133.0, 131.5, 126.9, 124.3, 123.8, 123.3, 109.1, 79.5, 36.5, 26.7; IR (cm^{-1}) 3040, 1768, 1721, 1610, 1466, 1371, 1261, 1123, 1092, 701; LCMS calcd for $C_{13}H_{11}NO_3$ m/z 229.0739, found: 230.10 (m + 1); HRMS (TOF MS EI^+) calcd for $C_{13}H_{11}NO_3$ m/z 229.0739, found: 229.0742.

1',4-dimethyl-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione and 1',4-dimethyl-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione 6b(I-II). White amorphous solid (30 mg, 60%): ^{1}H NMR ($CDCl_3$) δ 7.40 – 7.37 (dt, *J* = 8 Hz, 1.0 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 7.5 Hz, 1H), 3.23 (s, 3H), 3.17 – 3.08 (m, 1H), 2.57 (dd, *J* =13.0 Hz, 10.0 Hz, 1H), 2.39 (dd, *J* = 13.0 Hz, 9.5 Hz, 1H), 1.51 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR δ 178.6, 173.8, 143.7, 131.2, 128.0, 123.8, 123.7, 109.2, 80.8, 38.6, 34.9, 26.8, 16.6; IR (cm^{-1}) 3052, 2913, 1778, 1723, 1610, 1466, 1261, 1188, 1168, 1020, 991, 730, 700; LCMS calcd for $C_{13}H_{13}NO_3$ m/z 231.0895, found: 232.10 (m + 1); HRMS (TOF MS EI^+) calcd for $C_{13}H_{13}NO_3$ m/z 231.0895, found: 231.0890.

methyl 3-(3-hydroxy-1-methyl-2-oxindolin-3-yl)-2-methylpropanoate and methyl 3-(3-hydroxy-1-methyl-2-oxindolin-3-yl)-2-methylpropanoate and methyl 3-(3-hydroxy-1-methyl-2-oxindolin-3-yl)-2-methylpropanoate and methyl 3-(3-hydroxy-1-methyl-2-oxindolin-3-yl)-2-methylpropanoate 5b(I-IV) (2 inseparable set of compounds). Colorless gel (38 mg, 75%): ^{1}H NMR ($CDCl_3$) δ 7.42 – 7.30 (m, 4H), 7.10 – 7.07 (m, 2H), 6.83 – 6.82 (m, 2H), 4.06 (bs, 1H), 3.64 (s, 3H), 3.42 (s, 3H), 3.39 (bs, 1H), 3.18 (s, 3H), 3.16 (s, 3H), 2.86 – 2.80 (m, 1H), 2.59 – 2.43 (m, 3H), 1.91 – 1.85 (m, 2H), 1.14 – 1.11 (m, 6H); ^{13}C NMR δ 178.0, 177.8, 177.6, 176.8, 143.7, 143.2, 130.7, 130.0, 129.9, 129.3, 125.0, 123.8, 123.2, 123.1, 108.6, 76.0, 75.5, 52.2, 51.9, 41.9, 35.3, 35.0, 26.4, 26.3, 19.3, 19.2; LCMS calcd for $C_{14}H_{17}NO_4$ m/z 263.1158, found: 264.10 (m + 1).

1',4-dimethyl-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione and 1',4-dimethyl-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione and 1',4-dimethyl-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione and 1',4-dimethyl-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione 6b(I-IV) (2 inseparable set of compounds). Off-white solid (28 mg, 95%): ^{1}H NMR ($CDCl_3$) δ 7.42 – 7.30 (m, 4H), 7.16 – 7.09 (m, 2H), 6.88 – 6.85 (m, 2H), 3.52 – 3.47 (m, 1H), 3.23 (s, 3H), 3.20 (s, 3H), 3.15 - 3.08 (m, 1H), 2.70 (dd, *J* = 13.0 Hz, 9.0 Hz, 1H), 2.57 (dd, *J* = 13.0 Hz, 10.0 Hz, 1H), 2.29 (dd, *J* = 13.0 Hz, 9.5 Hz, 1H), 2.12 (apparent triplet, *J* = 13.0 Hz, 1H), 1.52 (d, *J* = 7.0 Hz, 3H), 1.39 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR δ 179.0, 178.6, 174.5, 173.8, 144.2, 143.7, 131.3, 131.1, 128.0, 126.4, 124.5, 123.8, 123.7, 123.7, 109.2, 109.0, 80.8, 80.4, 39.9, 38.6, 34.9, 34.5, 26.8, 26.5, 16.6, 15.7; LCMS calcd for $C_{13}H_{13}NO_3$ m/z 231.0895, found: 232.10 (m + 1);

1',4',7'-trimethyl-4-methylene-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione and 1',4',7'-trimethyl-4-methylene-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione 4c(I-II). White amorphous solid (38 mg, 96%): ^{1}H NMR ($CDCl_3$) δ 8.80 (s, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 6.44 (t, *J* = 2.5 Hz, 1H), 5.81 (t, *J* = 2.5 Hz, 1H), 3.32 – 3.22 (m, 2H), 2.23 (s, 3H) 2.22 (s, 3H); ^{13}C NMR δ 176.5, 169.5, 139.8, 133.7, 133.1, 132.5, 125.8, 124.2, 123.6, 117.9, 81.0, 34.4, 29.9, 17.5, 16.1; IR (cm^{-1}) 1768, 1725, 1599, 1282, 1262, 1243, 1152, 1028; LCMS calcd for $C_{14}H_{13}NO_3$ m/z 243.0895, found: 244.10 (m + 1); HRMS (TOF MS EI^{+}) calcd for $C_{14}H_{13}NO_3$ m/z 243.0895, found: 243.0895.

1',4,4',7'-tetramethyl-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione and 1',4,4',7'-tetramethyl-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione 6c(I-II) (67% yield). White amorphous solid 17 mg, 67%): ^{1}H NMR ($CDCl_3$) δ 9.16 (s, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 3.10 – 3.03 (m, 1H), 2.78 – 2.71 (m, 1H), 2.34 - 2.29 (m, 1H), 2.26 (s, 3H), 2.24 (s, 3H), 1.59 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR δ 179.7, 177.8, 139.8, 133.1, 132.3, 125.7, 125.2, 117.9, 82.6, 36.0, 35.2, 18.3, 17.5, 16.0; IR (cm^{-1}) 2920, 1778, 1721, 1594, 1453, 1260, 1193, 1019, 731; LCMS calcd for $C_{14}H_{15}NO_3$ m/z 245.1052, found: 246.10 (m + 1); HRMS (TOF MS EI^+)calcd for $C_{14}H_{15}NO_3$ m/z 245.1052, found: 245.1061.

1',4,4',7'-tetramethyl-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione and 1',4,4',7'-tetramethyl-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione and 1',4,4',7'-tetramethyl-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione and 1',4,4',7'-tetramethyl-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione 6c(I-IV) (2 inseparable set of compounds). White amorphous solid (12 mg, 74%): ^{1}H NMR ($CDCl_3$) δ 7.71 – 7.70 (m, 1H), 7.54 – 7.52 (m, 1H), 7.03 (d, *J* = 6.0 Hz, 1H), 6.78 (d, *J* = 6.5 Hz, 1H), 4.25 – 4.19 (m, 2H), 3.45 – 3.40 (m, 1H), 3.07 – 3.04 (m, 1H), 2.77 – 2.67 (m, 1H), 2.37 – 2.23 (m, 8H), 1.59 (d, J = 6.0 Hz, 3H), 1.40 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR δ 179.6, 179.2, 177.5, 177.2, 139.7, 139.5, 132.34, 132.29,131.1, 129.0, 125.8, 125.7, 125.2, 123.5, 117.8, 117.7, 82.5, 82.1, 37.5, 36.0, 35.2, 33.9, 18.3, 17.9,17.5, 16.0, 15.7, 15.2. LCMS calcd for $C_{14}H_{15}NO_3$ m/z 245.1052, found: 246.10 (m + 1);

LC-MS for the compounds was generated on an Agilent 1260 LC-MSD system with UV detector (214 nm and 254 nm) and an Agilent 6130 quadrupole mass detector.

Solvent A: 99.99% Water and 0.01% TFA

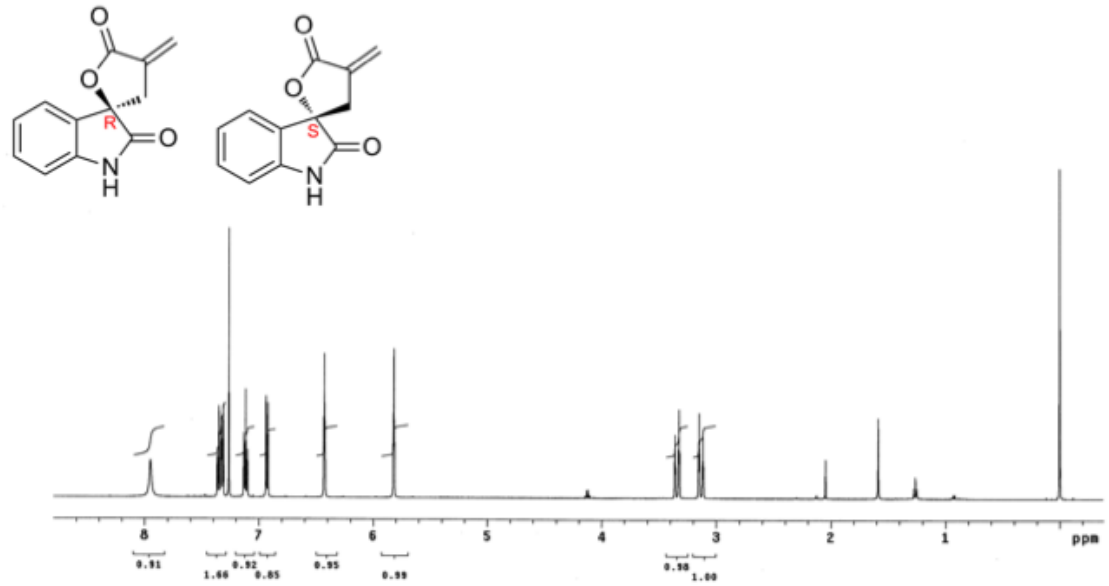
Solvent B: 99.99% CH3CN with 0.01% TFA

Method: 5 - 95% CH_3CN in 5 minutes, 40 psi, 300dC

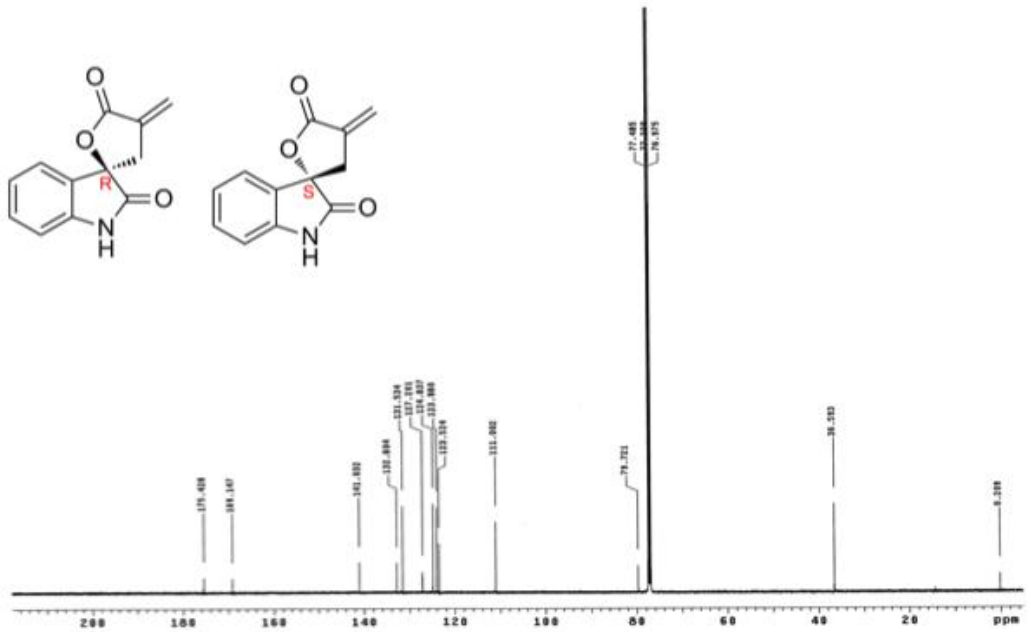
Column used: Zorbax 300SB-C18, Narrow-Bore 2.1 X 150mm 5 – micron (PN 883750-902

Compd	Retention time (min)
4a(I-II)	**2.70**
6a(I-II)	**2.67**
5a(I-IV)	**2.33 and 2.42**
6a(I-IV)	**2.66 and 2.82**
4b(I-II)	**2.96**
6b(I-II)	**2.94**
5b(I-IV)	**2.53 and 2.63**
6b(I-IV)	**2.95 and 3.10**
4c(I-II)	**3.50**
6c(I-II)	**3.52**
5c(I-IV)	**2.71 and 2.92**
6c(I-IV)	**3.52 and 3.58**

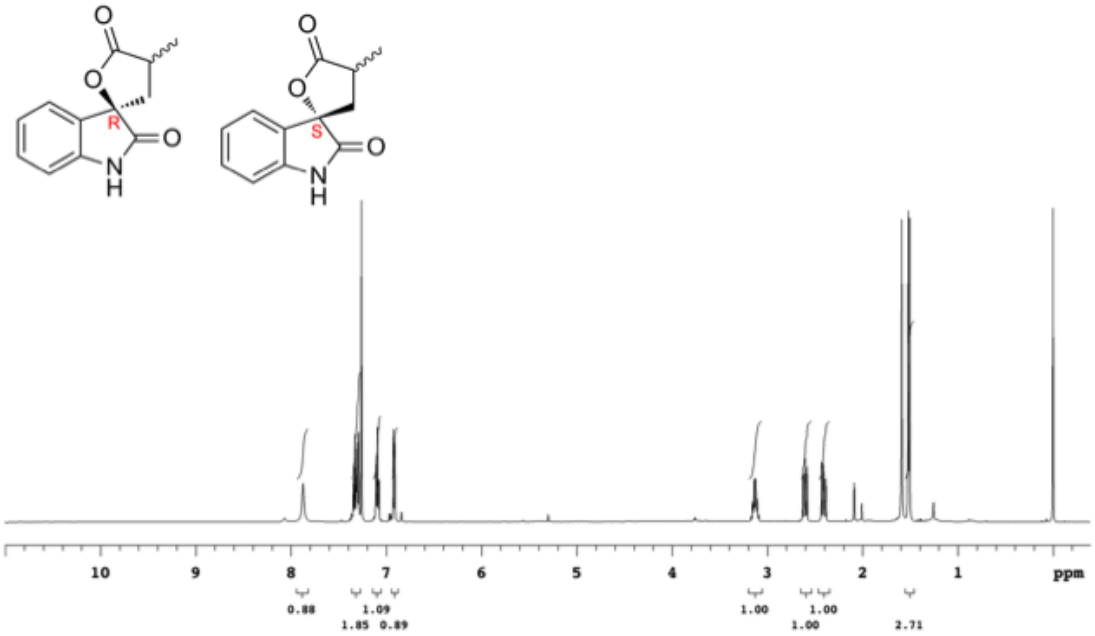
Compound 4a(I-II): ^{1}H-NMR



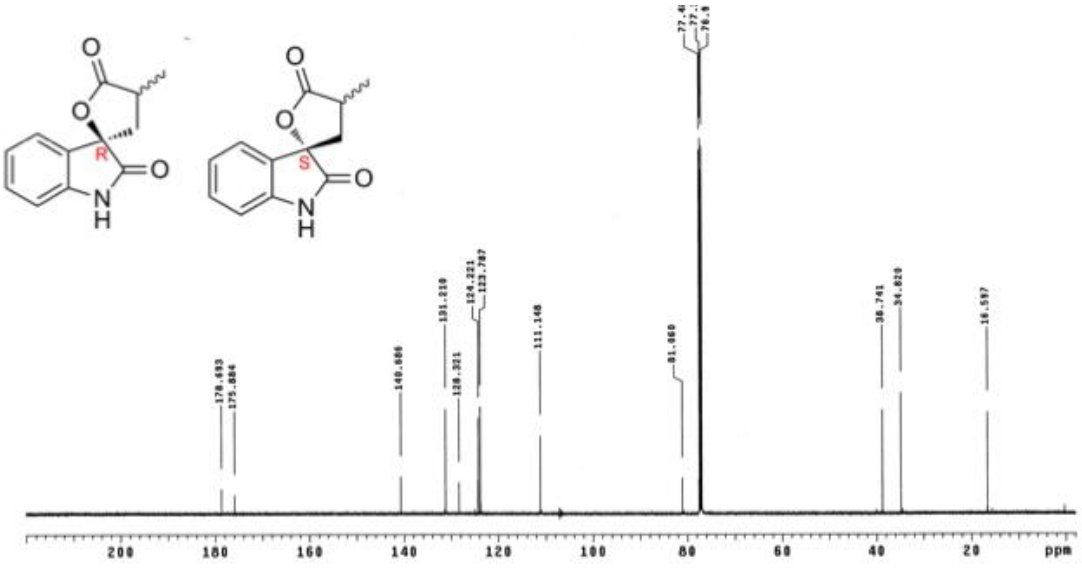
Compound 4a(I-II): ^{13}C-NMR



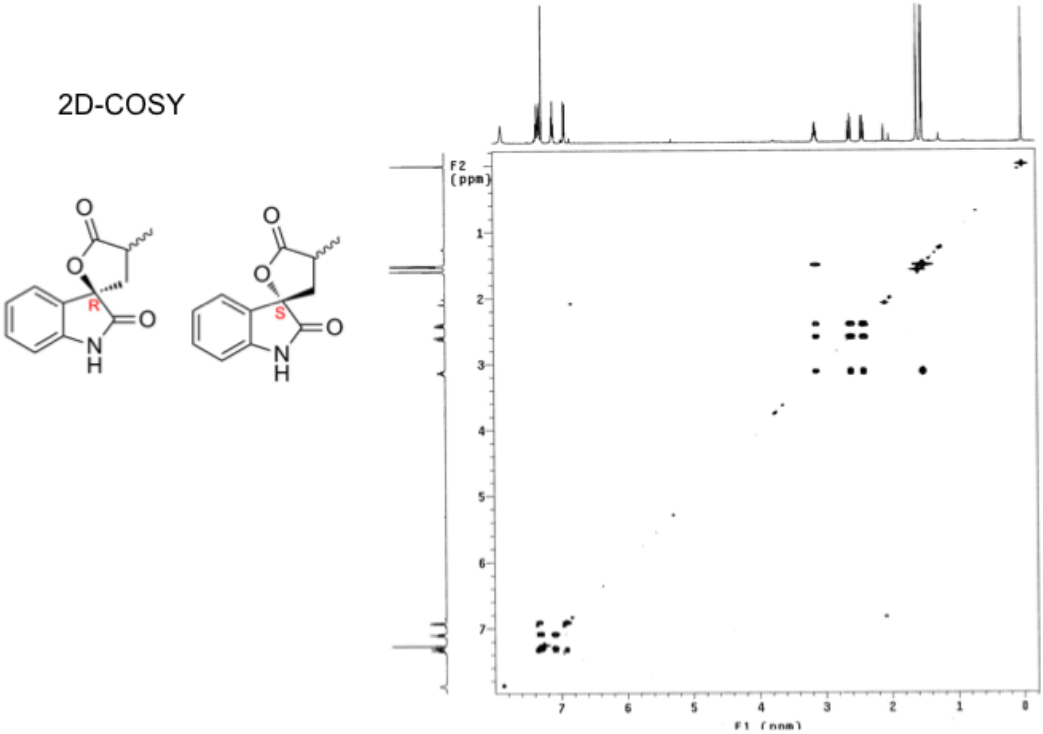
Compound 6a(I-II): ^{1}H-NMR



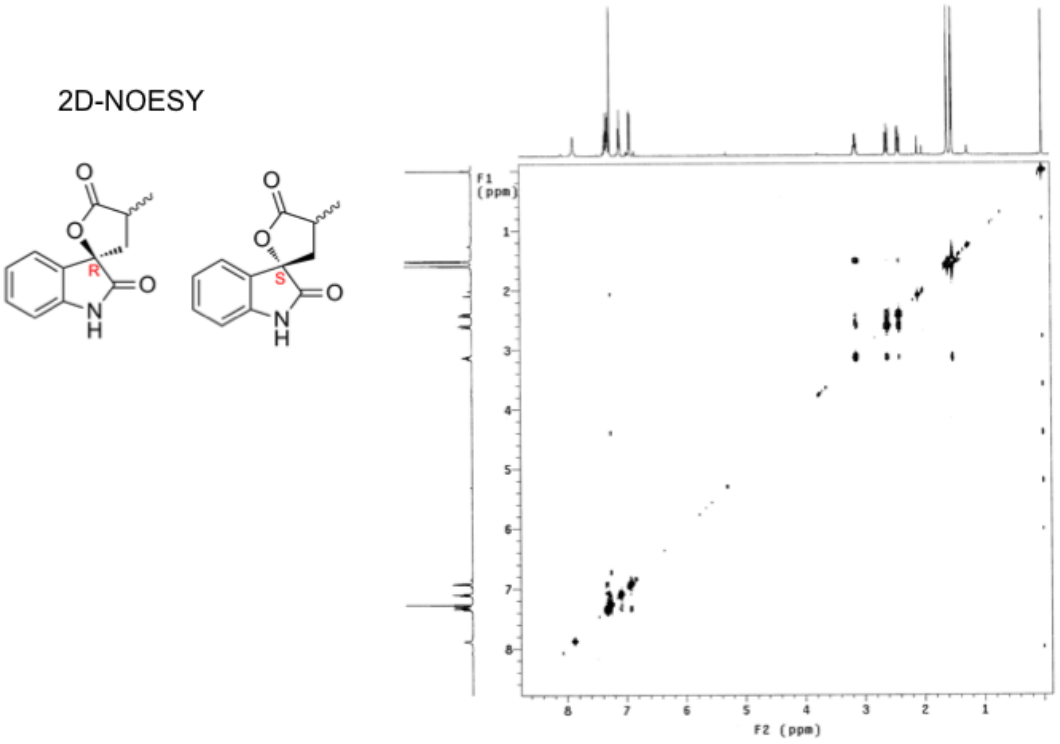
Compound 6a(I-II): ^{13}C-NMR



Compound 6a(I-II): gCOSY



Compound 6a(I-II): 2D-NOESY



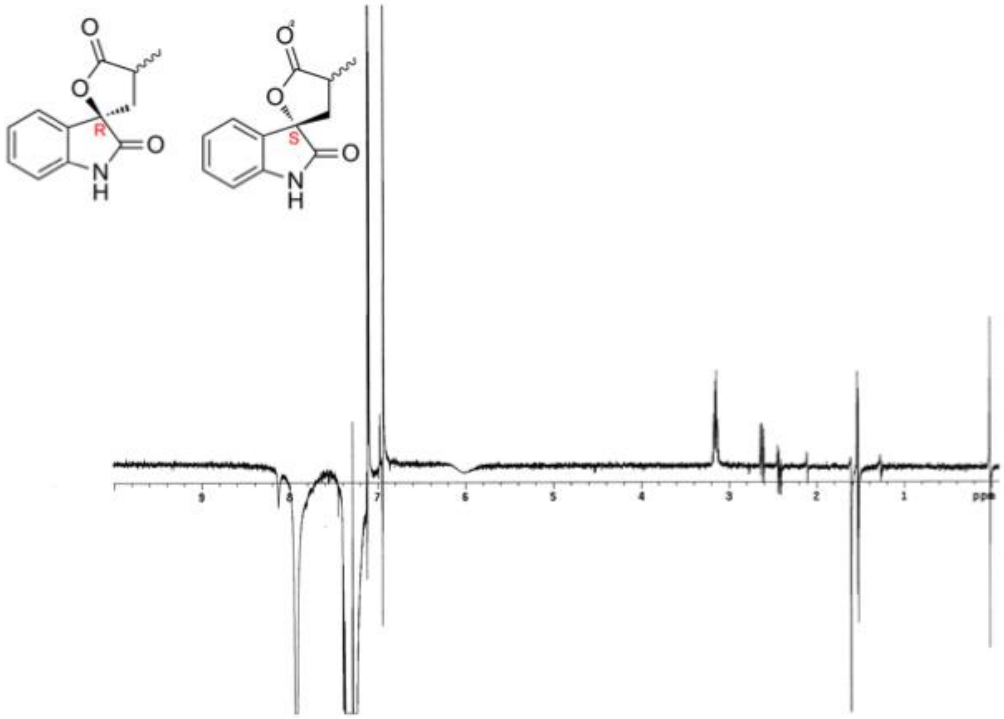
Compound 6a(I-II): 1D-NOE difference

Saturation Irradiation: 7.34 ppm

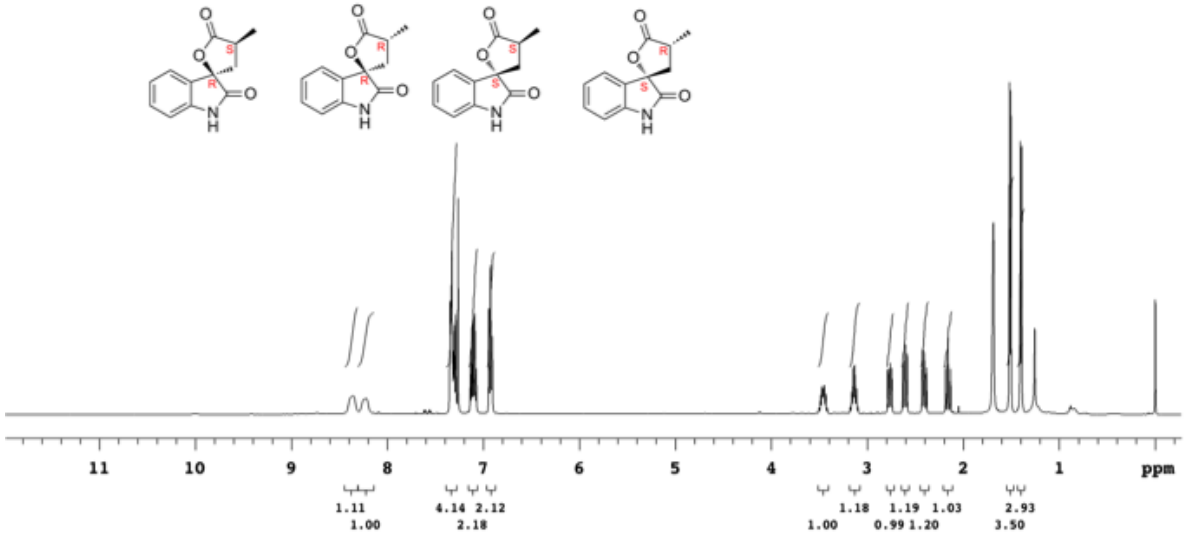
Saturation Selected Frequency: 1375.7

Selected Irradiation Power: -1

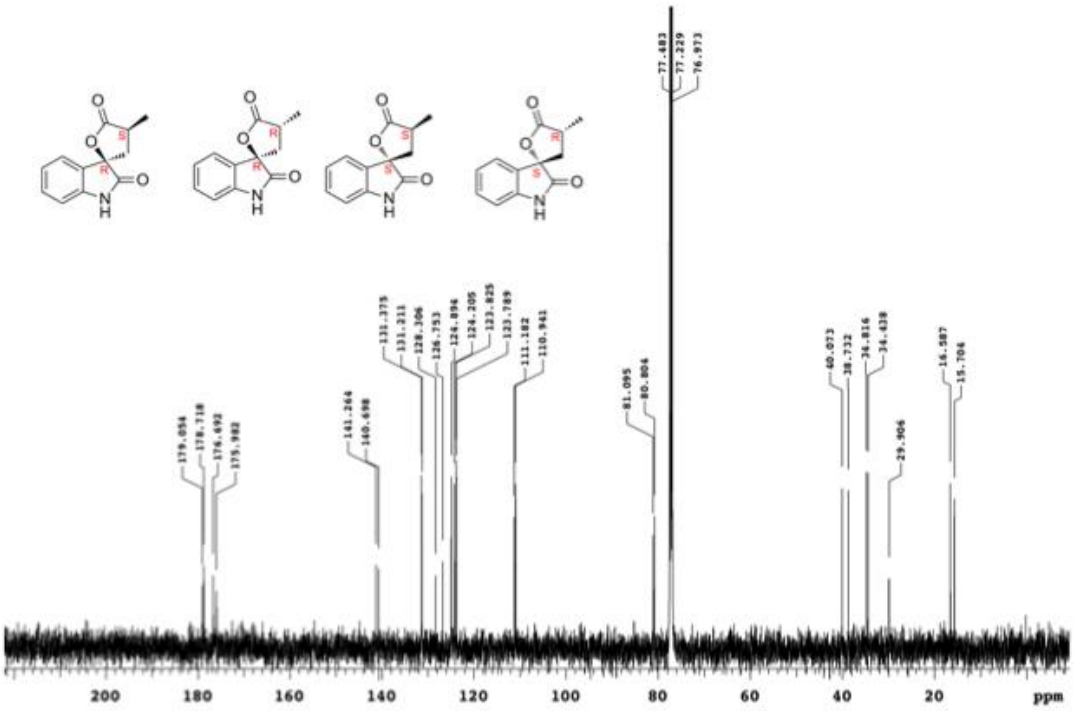
Exponential Line Broadening: 0 Hz



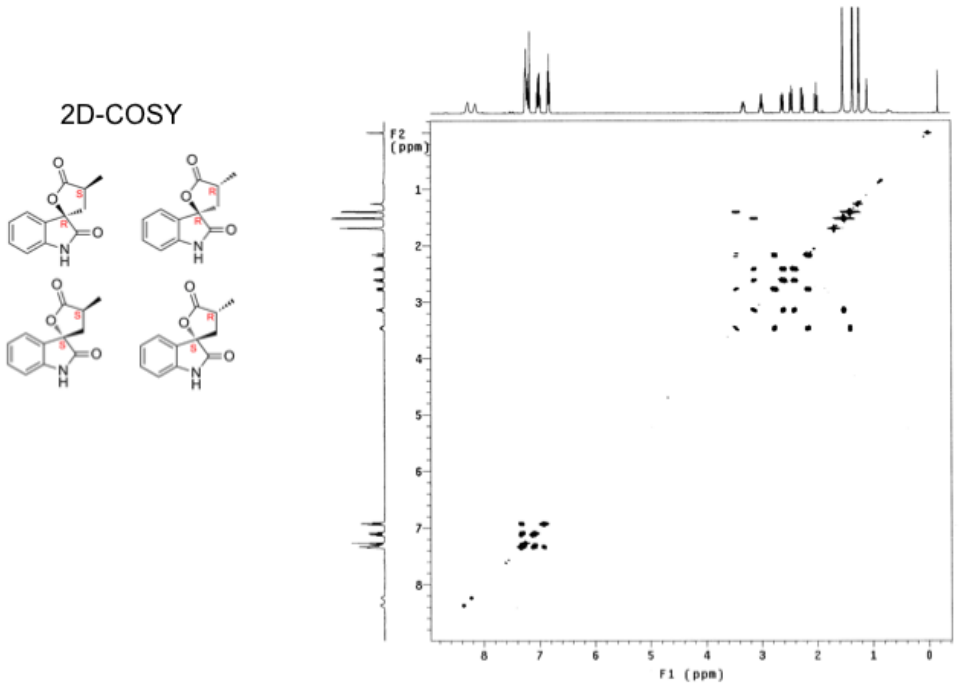
Compound 6a(I-IV): ^{1}H-NMR



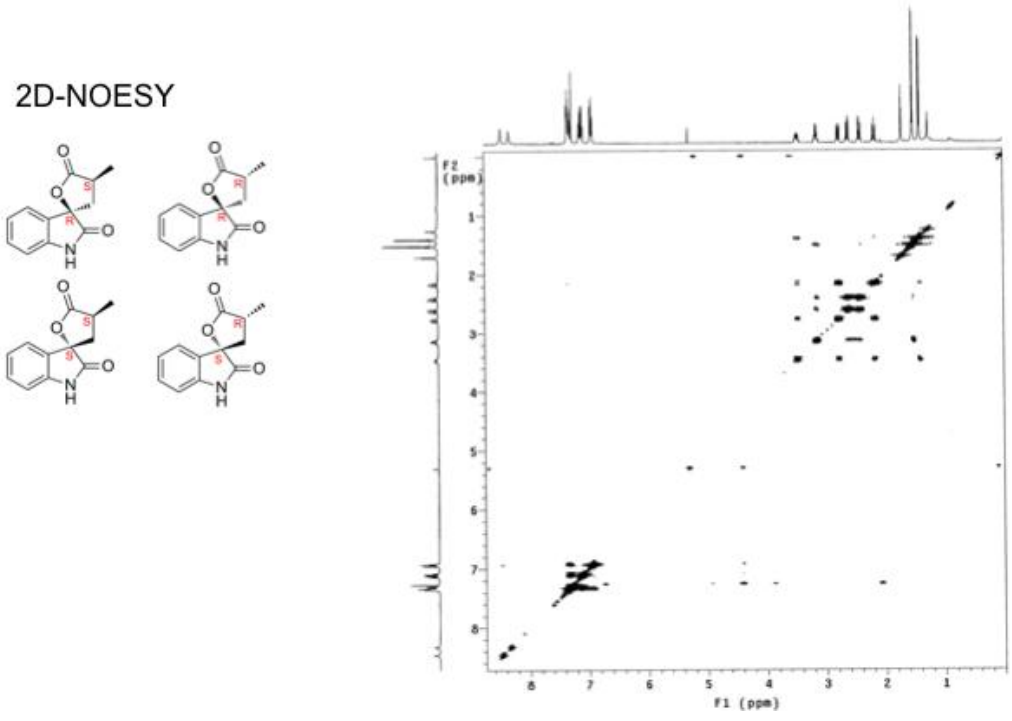
Compound 6a(I-IV): ^{13}C-NMR



Compound 6a(I-IV): gCOSY



Compound 6a(I-IV): NOESY



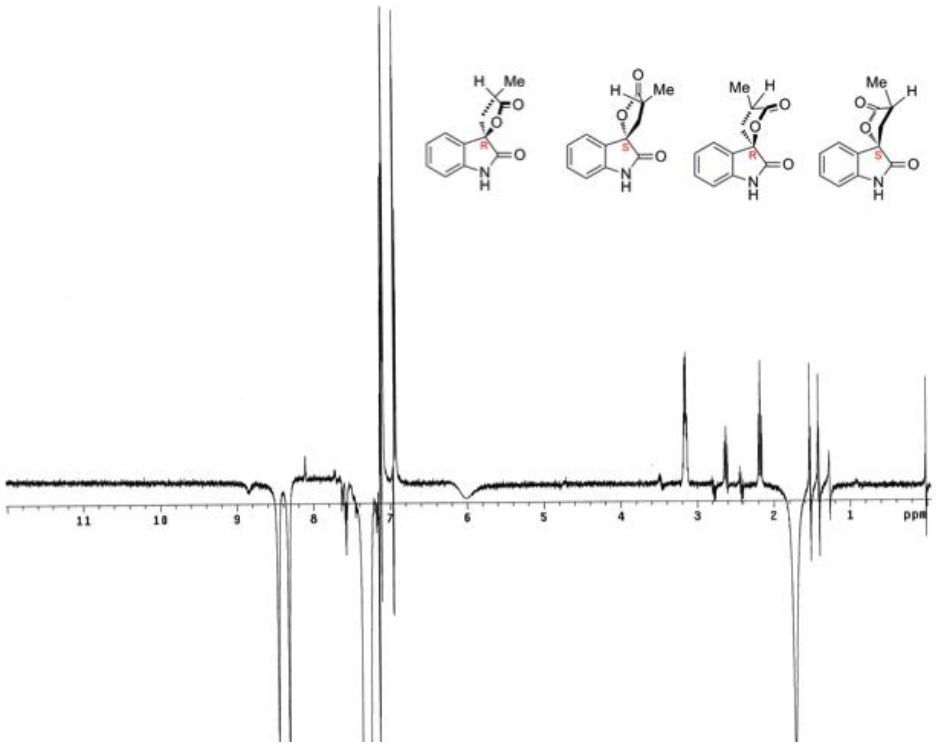
Compound 6a(I-IV): 1D- NOE difference

Saturation Irradiation: 7.3 ppm

Saturation Selected Frequency: 1374.0

Selected Irradiation Power: -1

Exponential Line Broadening: 0 Hz



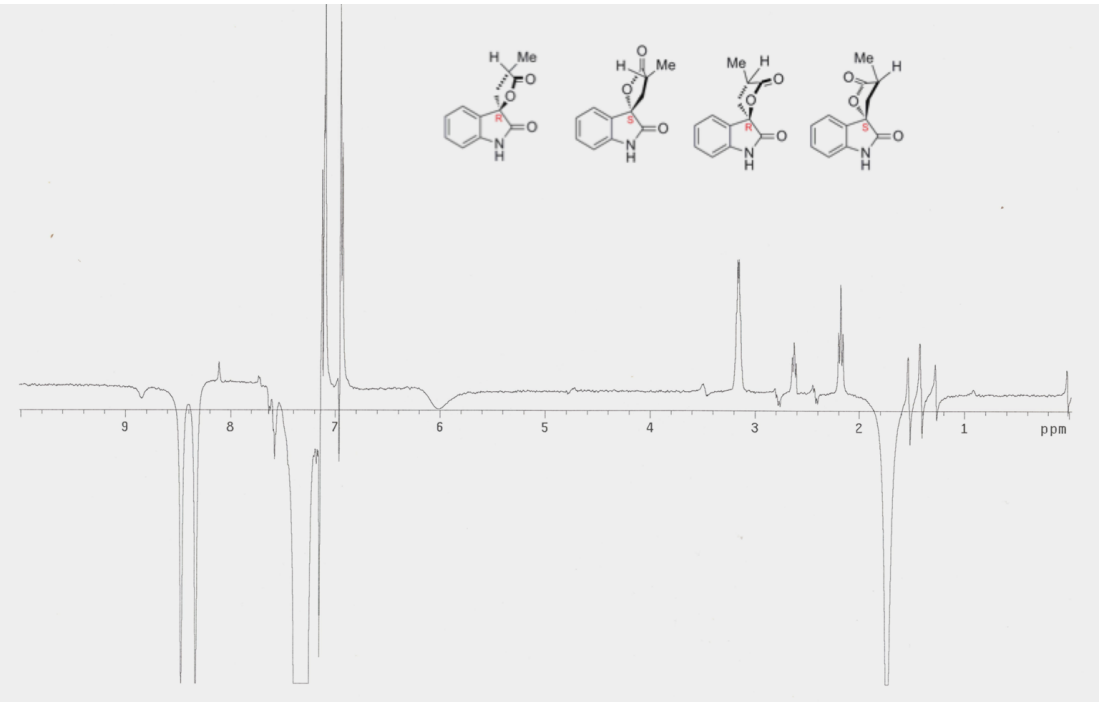
Compound 6a(I-IV): 1D- NOE difference

Saturation Irradiation: 7.3 ppm

Saturation Selected Frequency: 1374.0

Selected Irradiation Power: -1

Exponential Line Broadening: 3 Hz



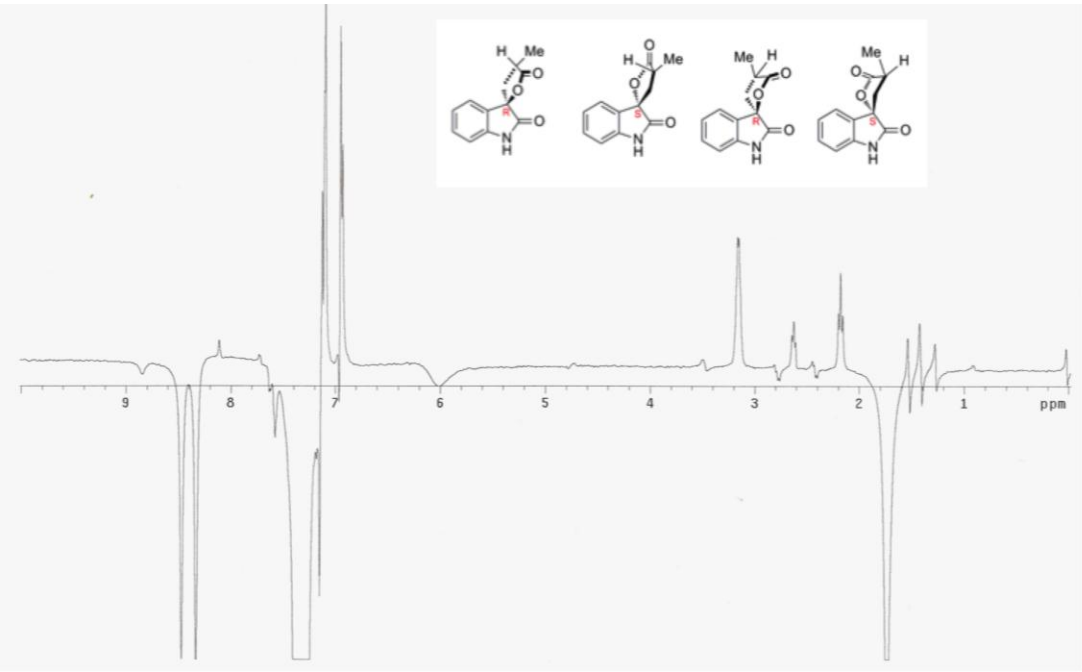
Compound 6a(I-IV): 1D- NOE difference

Saturation Irradiation: 7.3 ppm

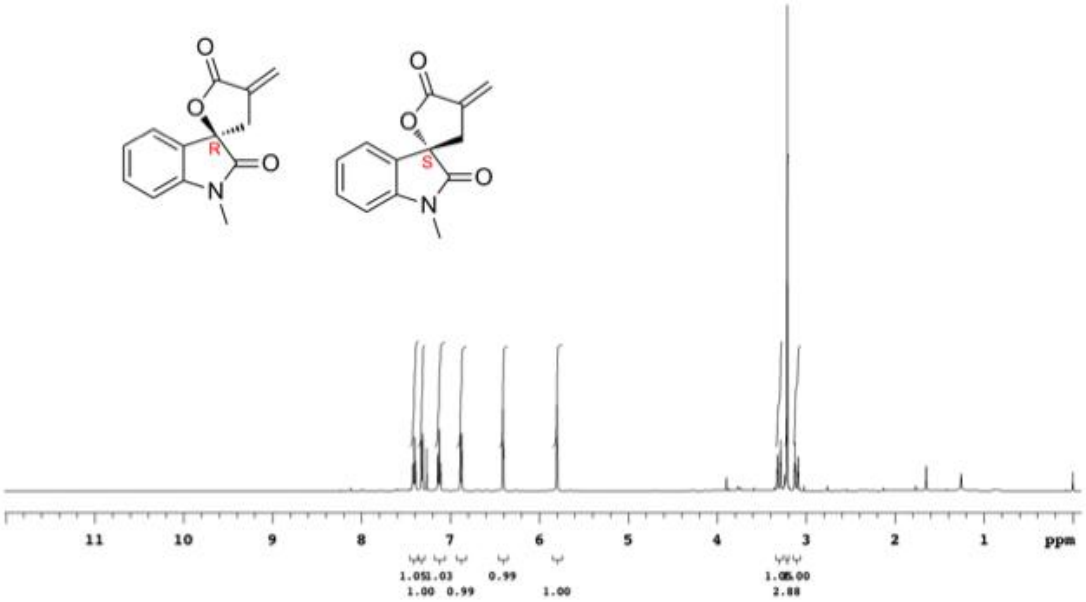
Saturation Selected Frequency: 1374.0

Selected Irradiation Power: -1

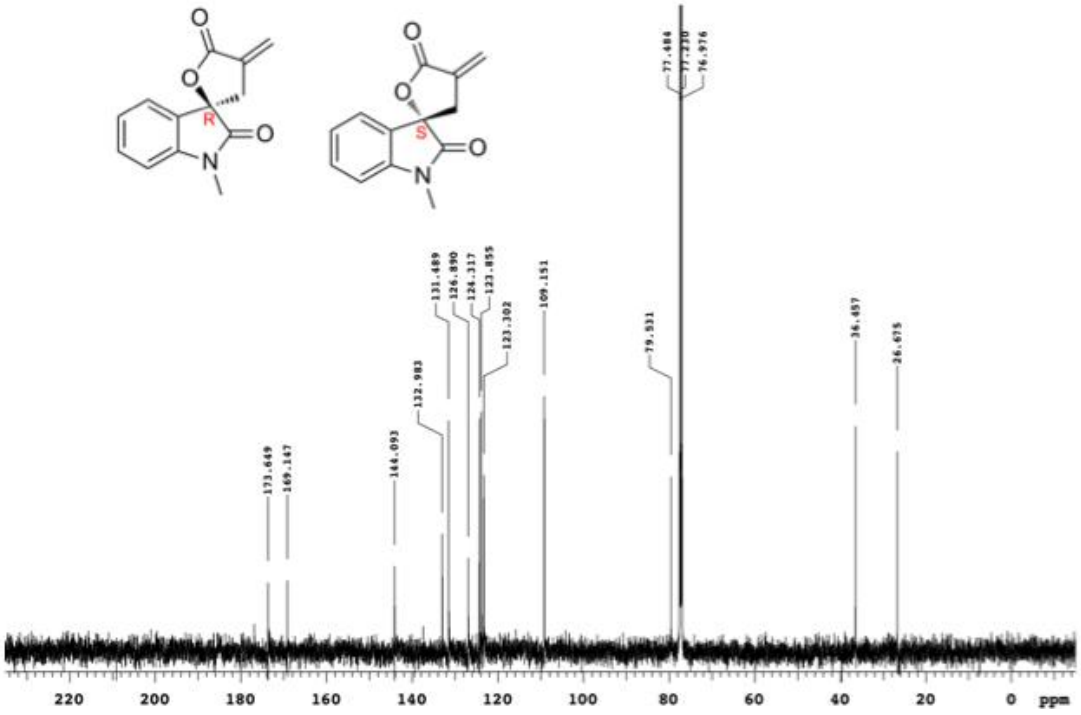
Exponential Line Broadening: 5 Hz



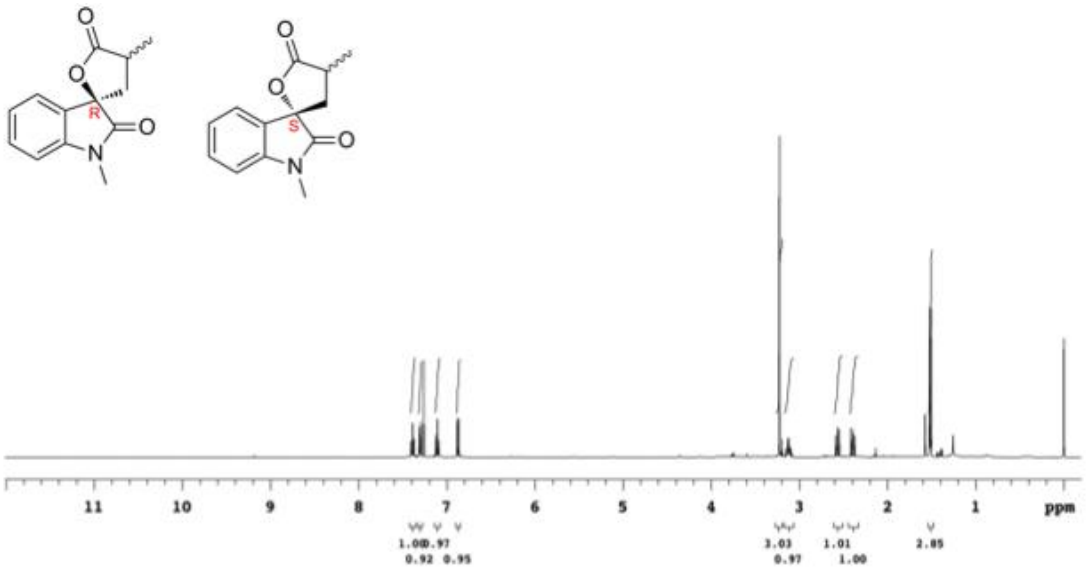
Compound 4b(I-II): ^{1}H-NMR



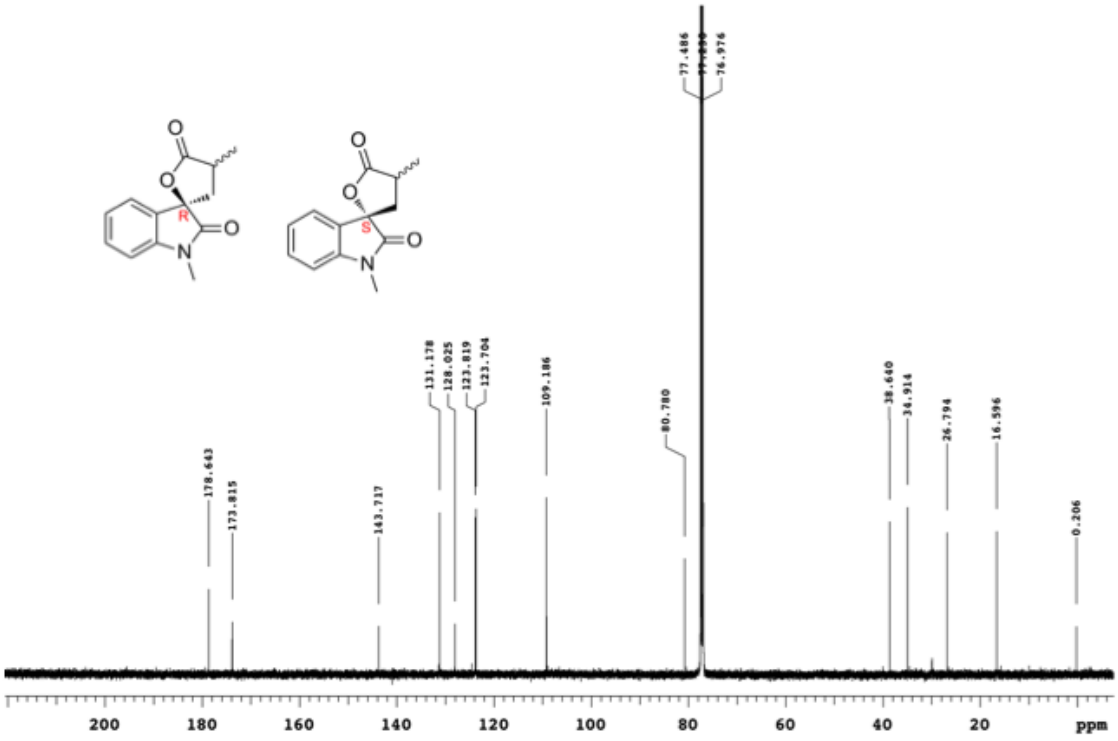
Compound 4b(I-II): ^{13}C-NMR



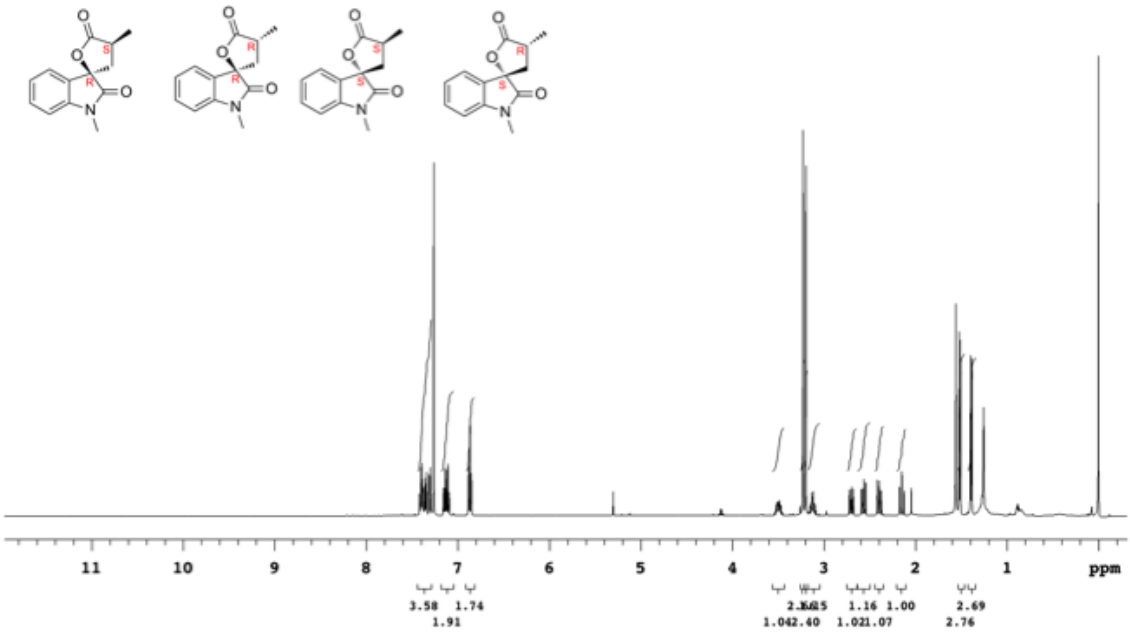
Compound 6b(I-II): ^{1}H-NMR



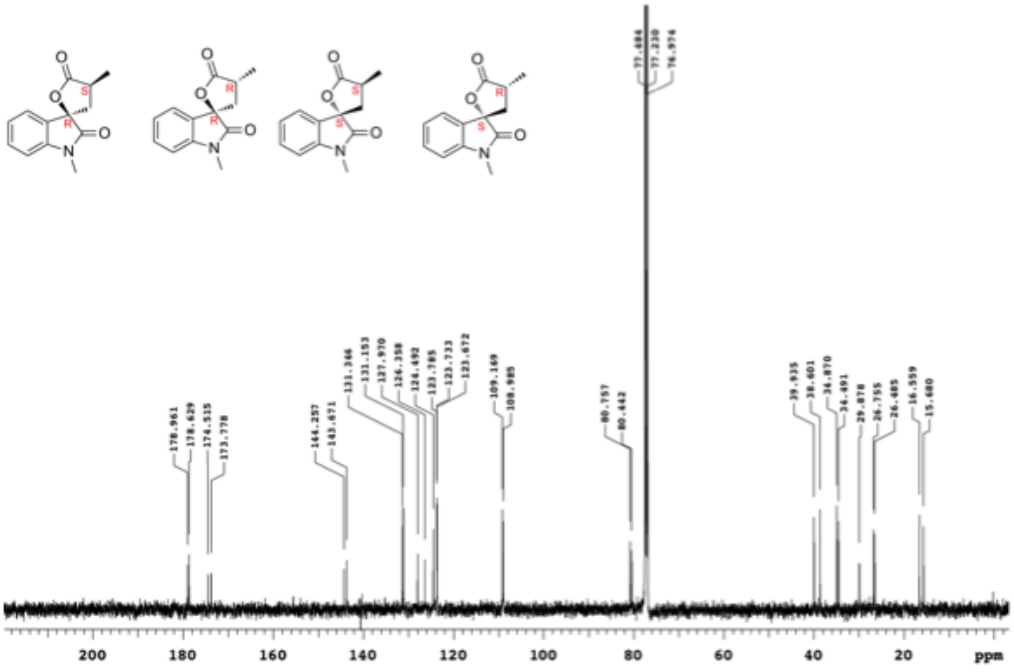
Compound 6b(I-II): ^{13}C-NMR



Compound 6b(I-IV): ^{1}H-NMR



Compound 6b(I-IV): ^{13}C-NMR



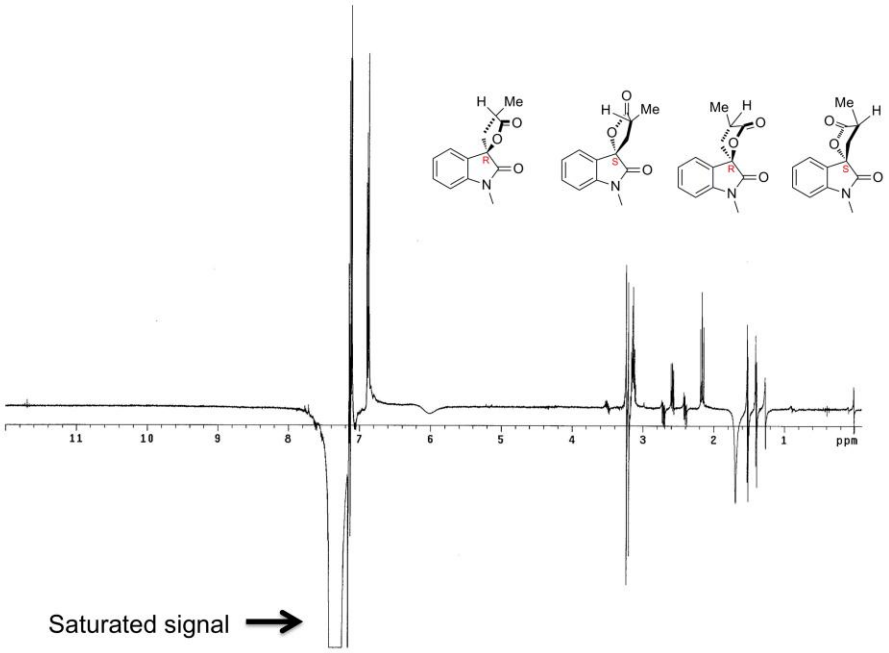
Compound 6b(I-IV): 1D-NOE difference

Saturation Irradiation: 7.34 ppm

Saturation Selected Frequency: 1375.7

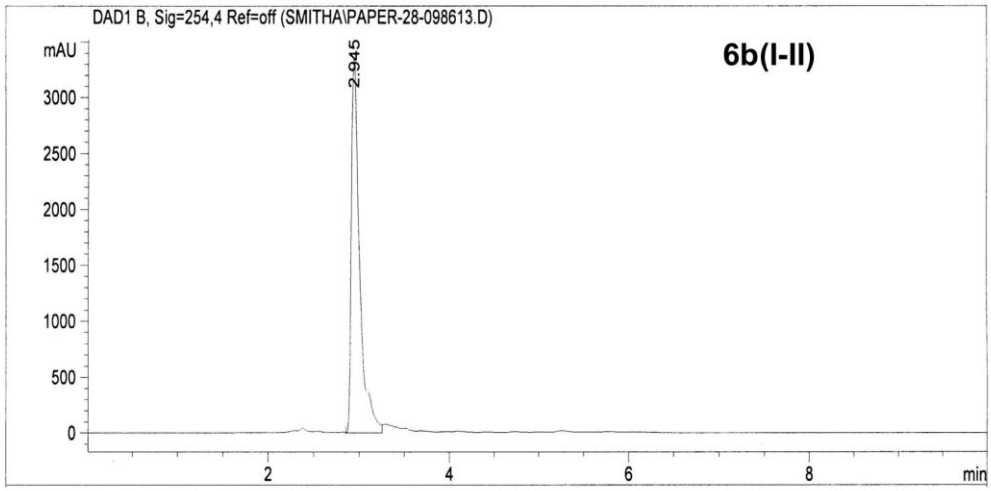
Selected Irradiation Power: -1

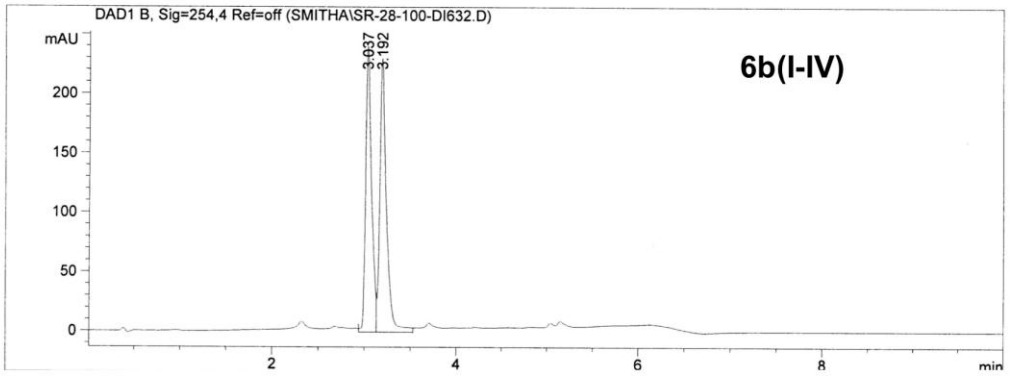
Exponential Line Broadening: 0 Hz



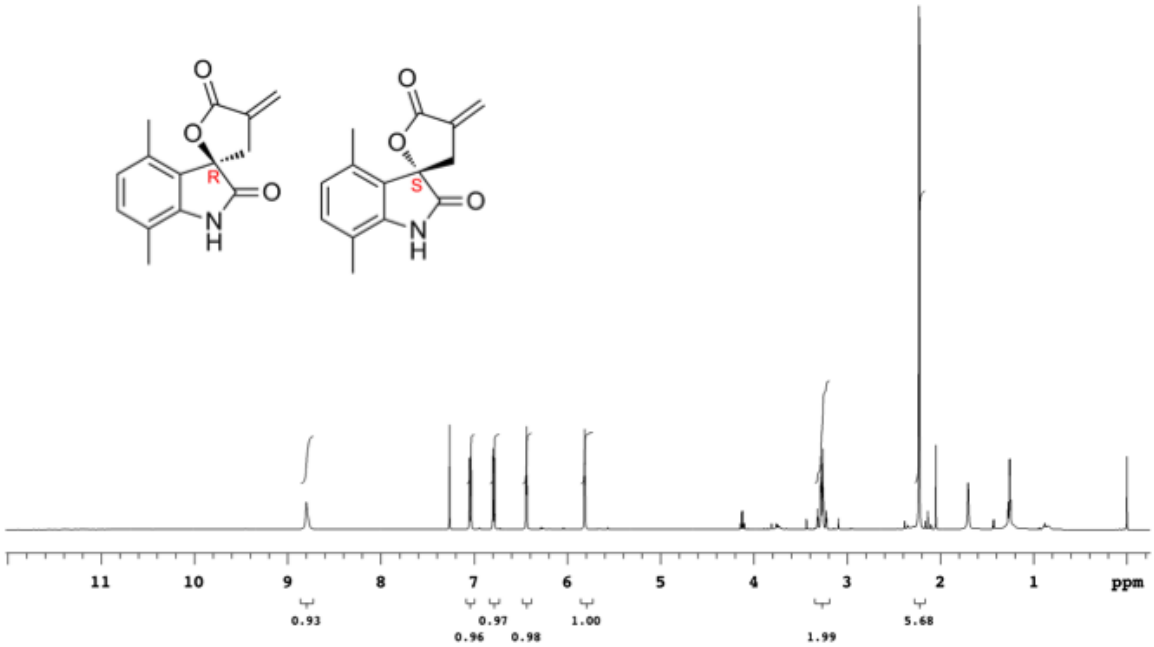
Representative LCMS trace for 6b(I-II) and 6b(I-IV)

```
1 ml/min; 5-95% ACN in 5 min; 9 L/min, 40 psi, 300dC

======================================================================
Acq. Operator   : SK
Acq. Instrument : Agilent 1260 LC-MSD-ELSD Syst   Location : Vial 2
Injection Date  : 10/29/2012 11:02:45 AM              Inj :   1
                                                Inj Volume : 10.000 µl
Acq. Method     : C:\CHEM32\1\METHODS\ORG CPD.M
Last changed    : 10/29/2012 10:30:45 AM by SK
Analysis Method : C:\CHEM32\1\METHODS\ORG CPD.M
Last changed    : 10/30/2012 10:27:09 AM by SK
                  (modified after loading)
Method Info     : Peptides Zorbax 300SB-C18

Sample Info     : 1 ml/min; 5-95% ACN in 5 min; 9 L/min, 40 psi, 300dC
```

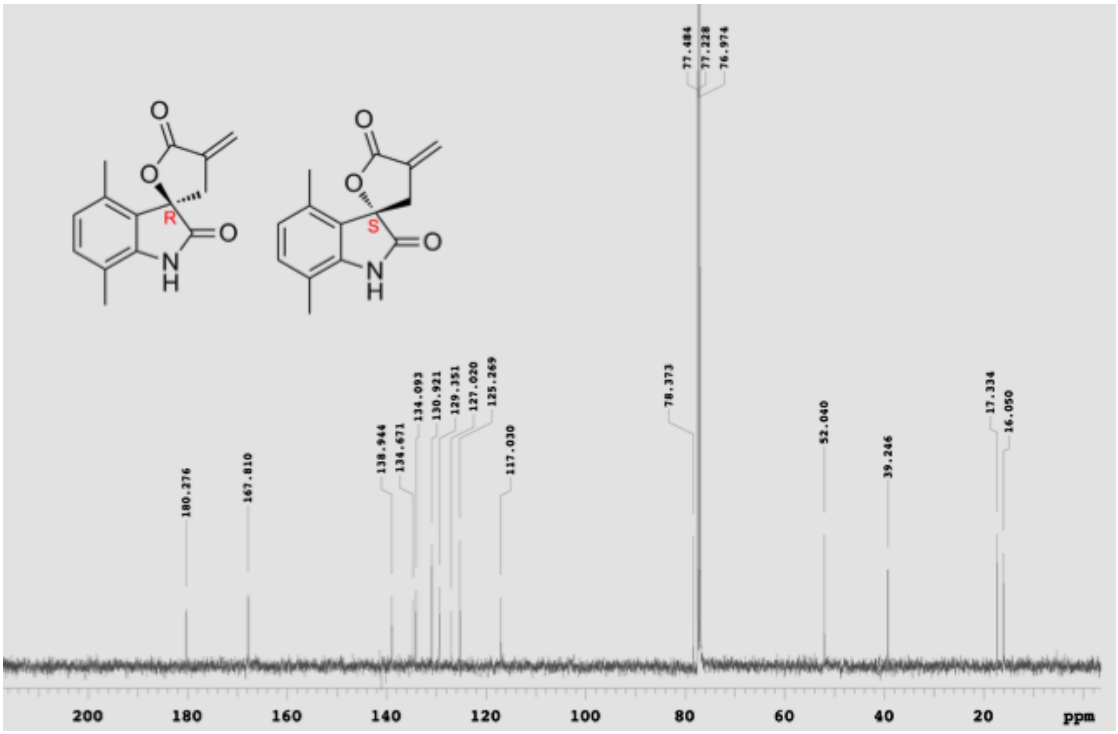




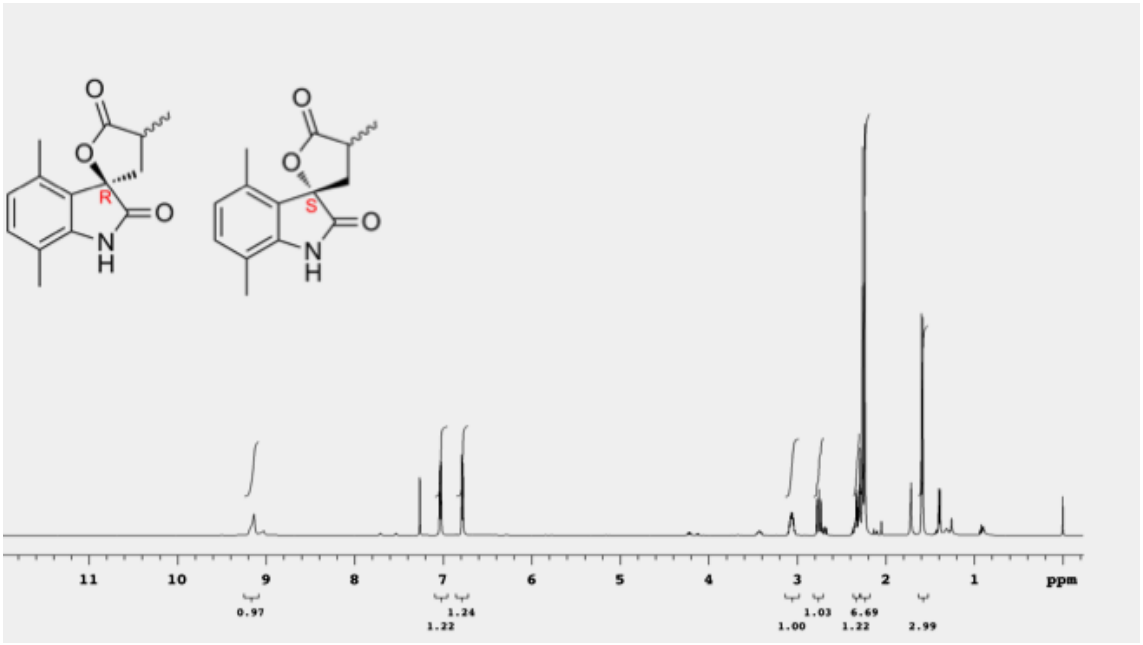
Compound 4c(I-II): ^{1}H-NMR



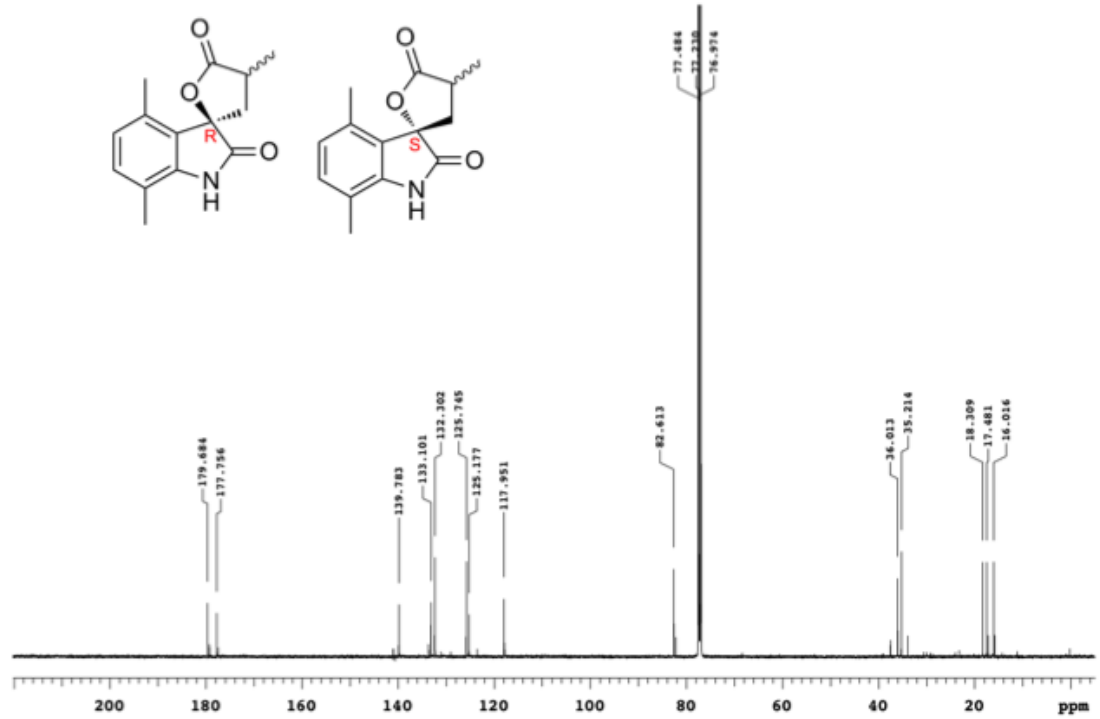
Compound 4c(I-II): ^{13}C-NMR



Compound 6c(I-II): ^{1}H-NMR



Compound 6c(I-II): ^{13}C-NMR



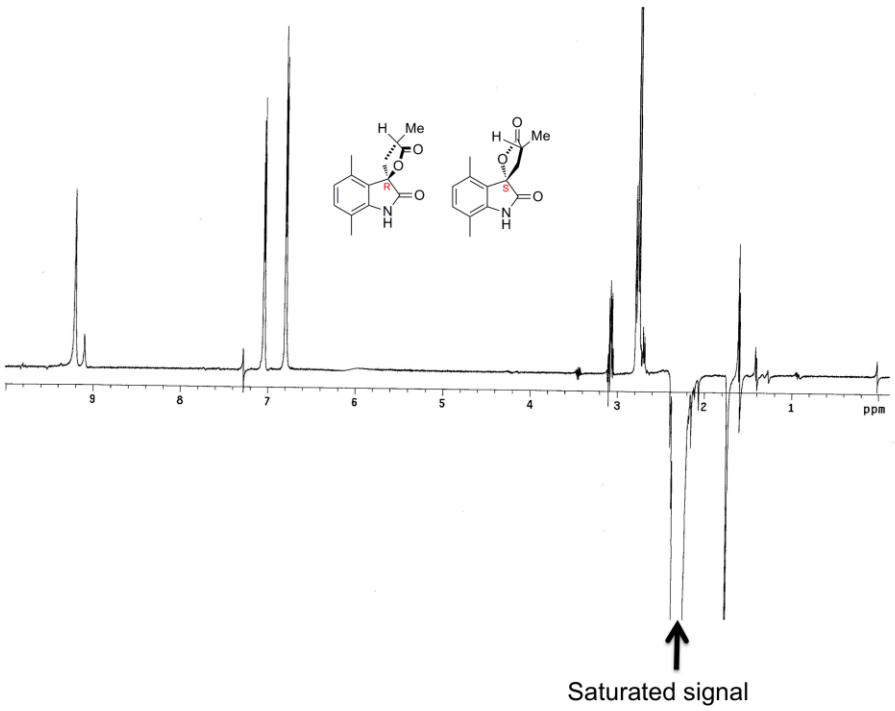
Compound 6c(I-II): 1D-NOE difference

Saturation Irradiation: 2.2 ppm

Saturation Selected Frequency: -1666.6

Selected Irradiation Power: -1

Exponential Line Broadening: 0 Hz



Compound 6c(I-IV): 1D-NOE difference

Saturation Irradiation: 2.2 ppm

Saturation Selected Frequency: -1678.2

Selected Irradiation Power: -1

Exponential Line Broadening: 0 Hz