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Utilization of whole cell mediated deracemization in a chemoenzymatic synthesis of enantiomerically enriched polycyclic chromeno[4,3-b] pyrrolidines

Thangavelu Saravanan [a], Sushital Jana [a], Anju Chadha*[, a, b]

[a]Laboratory of Bioorganic Chemistry, Department of Biotechnology, [b]National Centre for Catalysis Research, Indian Institute of Technology Madras, Chennai 600 036, India.

Tel.: +91 44 2257 4106; Fax: +91 44 2257 4102; E-mail address: anjuc@iitm.ac.in

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GENERAL METHODS

C. parapsilosis ATCC 7330 was purchased from ATCC Manassas, VA 201018, USA and maintained at 4°C in yeast malt agar medium that contained 5 g/L peptic digest of animal tissue, 3 g/L malt extract, 3 g/L yeast extract, 10 g/L dextrose and 20 g/L agar. The entire chemicals for media preparation were purchased locally. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400 and Bruker AVANCE III 500 MHz spectrometers. Chemical shifts are expressed in ppm values using TMS as an internal standard. Infrared spectra were recorded on a Shimadzu IR 470 instrument. Mass spectra were recorded on a Q TOF micro mass spectrometer. TLC was carried out on Kieselger 60 F254 aluminium sheets (Merck1.05554). All chemicals used were of analytical grade and distilled prior to use. HPLC analysis was carried out on Jasco PU-1580 liquid chromatograph with a PDA detector using Chiralcel OJ-H, OD-H, AD-H, OB-H (Daicel, 4.6*250mm) and Lux 5u Amylose-2 (Phenomenex, 4.6*250mm) chiral columns. Hexanes/2-propanol was used as the mobile phase. Optical rotations were determined on AutopalR digital polarimeter.X-ray crystallographic analysis was performed with a Bruker AXS Kappa APEX II single crystal CCD Diffractometer equipped with graphite-monochromated MoKα radiation (λ = 0.71073 Å) at room temperature.

EXPERIMENTAL PROCEDURES FOR SUBSTRATE SYNTHESIS

Synthesis of *rac*-aryl substituted propargyl alcohols by Sonogashira coupling (1a-1h)[1]

A mixture of aryl iodide (3.5 mmol), 10% Pd/C (0.12 mmol), PPh_3 (0.65 mmol,), CuI (0.16 mmol,) and 2-aminoethanol (0.6 mL) in H_2O (11 mL) was stirred at 35 ºC for 30 min under argon. To this the terminal alkyne (5.1 mmol) was added. The reaction mixture was stirred at 85 °C for 10-24h. The mixture was cooled to room temperature and ethyl acetate (60 mL) was added. After fitration of the reaction mixture through celite, the solvent was evaporated and crude residue was purified by column chromatography using hexane/ethyl acetate (95:05) as eluent to obtain a pure product in quantitative yield.

Synthesis of *rac*-alkyl substituted propargyl alcohols by Grignard reaction (1i-1n)[2]

To a dry two necked flask containing magnesium turnings (500 mg, 20.2 mmol) and I_2 (a few crystals) in THF (30 mL) were added several drops of ethyl bromide. Upon the initiation of the Grignard reaction, the remaining ethyl bromide (1.5 mL, 20.2 mmol) was added dropwise, which was followed by stirring until the magnesium disappeared. Phenylethyne (1.9 mL, 17.0 mmol) was added drop wise into the solution at 55 ◦C followed by stirring for 1.5 h at this temperature. Then the corresponding aldehyde (17.0 mmol) was added at 55◦C and the resulting mixture was stirred at this temperature for 2 h. The reaction mixture was then quenched with saturated NH_4Cl and extracted with Et_2O. The combined organic layer was washed sequentially with 5% HCl, sat. brine, and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent then silica gel column purification afforded the corresponding product.

***Rac*-4-phenylbut-3-yne-1,2-diol (1o)[3]**

To a solution of ethyl-2-oxo-4-phenylbut-3-ynoate (408mg, 2mmol) in ethanol (10 ml) $CeCl_3.7H2O$ (1.1g, 3mmol) was added at room temperature. After 5min stirring 2eq. of $NaBH_4$ (152mg, 4mmol) was added. The reaction was monitored by TLC, and after completion, excess alcohol was stripped off. The reaction mixture was quenched with dilute HCl and extracted with dichloromethane. The organic layer was dried, concentrated, purified by silica-gel column chromatography and afforded 4-phenylbut-3-yne-1,2-diol (68% yield)

***Rac*-ethyl 3-hydroxy-5-phenylpent-4-ynoate (1p)[4]**

*n*BuLi (5ml of a 1.67 M solution in hexane, 7 mmol) was added dropwise over 10 min to a solution of iPr_2NH (0.5 mL, 3.5 mmol) in THF (15 ml) at 0°C. After 30 min, the mixture was cooled to -78°C and ethyl acetate (7 mL, 7mmol) was added. After 1 h, a solution of 3-phenylpropynal (910 mg, 7 mmol) in THF (2 ml) was added dropwise over 5 min. After 15 min, the reaction was quenched at -78 °C by the addition of NH_4Cl solution (40 mL), and the resulting biphasic mixture was allowed to warm to rt. The two phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 10ml). The combined organic layer were washed with brine (40 ml), and dried over anhydrous Na_2SO_4, concentrated, purified by silica-gel column chromatography and afforded ethyl 3-hydroxy-5-phenyl-pent-4-ynoate (75%)

SPECTRAL DATA

(*R*)-4-phenylbut-3-yn-2-ol (2a)[5]

Yield 79 %; > 99% *ee*; pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): 1.55 (3H, d, *J*= 6.5 Hz), 2.14 (1H, d, *J*= 4.5 Hz), 4.76 (1H, m), 7.29-7.32 (3H, m), 7.41-7.44 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 24.3, 58.8, 84.0, 90.9, 122.6, 128.2, 128.3, 131.6; The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OJ-H column [hexanes/2-propanol = 95:05, 1.0 mL/min; retention times 12.7 (major) and 14.7 min (minor)]; $[\alpha]_D^{25}$ =+39.4 (c 1, $CHCl_3$).

(*R*)-4-*p*-tolylbut-3-yn-2-ol (2b)[6]

Yield 83%; > 99% *ee*; colorless solid; Mp 53-54 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 1.55 (3H, d, *J*= 6.5 Hz), 1.98 (1H, s) 2.34 (3H, s), 4.75 (1H, q, *J*= 6.5 Hz), 7.11 (2H, d, *J*= 8 Hz), 7.32 (2H, d, *J*= 8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 21.4, 24.4, 58.9, 84.1, 90.2, 119.5, 129.0, 131.6, 138.6; The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OJ-H column [hexanes/2-propanol = 95:05, 1.0 mL/min; retention times 16.0 (major) and 19.7 min (minor)]; $[\alpha]_D^{25}$ =+27.2 (c 0.5, Et_2O).

(*R*)-4-(4-methoxyphenyl)but-3-yn-2-ol (2c)[6]

Yield 81%; > 99% *ee*; pale yellow solid; Mp 45-46 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 1.54 (3H, d, *J*= 6.5 Hz), 2.21(1H, s) 3.76 (3H, s), 4.74 (1H, q, *J*= 6.5 Hz), 6.79 (2H, d, *J*= 8 Hz), 7.32 (2H, d, *J*= 8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 24.5, 55.4, 58.8, 84.0, 89.9, 114.1, 114.8, 131.4, 159.8; The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OB-H column [hexanes/2-propanol = 90:10, 1.0 mL/min; retention times 22.3 (major) and 27.6 min (minor)]; $[\alpha]_D^{25}$ =+27.2 (c 0.5, Et_2O).

(*R*)-4-(4-nitrophenyl)but-3-yn-2-ol(2d)[6]

Yield 72%; > 99% *ee*; pale yellow solid; Mp 118-119 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 1.57 (3H, d, *J*= 6.5 Hz), 2.02 (1H, d, *J*= 5.5 Hz), 4.79 (1H, m), 7.56 (2H, dt, *J*= 9 & 2 Hz), 8.17 (2H, dt, *J*= 9 & 2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 24.1, 58.8, 82.2, 96.2, 123.5, 129.5, 132.4, 147.2; The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OJ-H column [hexanes/2-propanol = 90:10, 1.0 mL/min; retention times 14.9 (minor) and 19.0 min (major)]; $[\alpha]_D^{25}$ =+42.7 (c 1, Et_2O).

(*R*)-4-(3-hydroxybut-1-ynyl)benzonitrile (2e)[7, 8]

Yield 76%; > 99% *ee*; pale yellow liqid; ^{1}H NMR (400 MHz, $CDCl_3$): 1.56 (3H, d, *J*= 6.8 Hz), 2.17 (1H, bs), 4.78 (1H, d, *J*= 6.8 Hz), 7.49 (2H, d, *J*= 8.4), 7.59(2H, d, *J*= 8.4); ^{13}C NMR (100 MHz, $CDCl_3$): 24.2, 58.8, 82.4, 95.4, 111.8, 118.4, 127.6, 132.0, 132.2; The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OJ-H column [hexanes/2-propanol = 90:10, 1.0 mL/min; retention times 14.0 (minor) and 15.2 min (major)]; $[\alpha]_D^{25}$ =+15.6 (c 1, $CHCl_3$).

(*R*)-4-(naphthalen-2-yl)but-3-yn-2-ol (2f)

Yield 75%; 27 % *ee*; colourless solid; Mp 98-99°C; ^{1}H NMR (500 MHz, $CDCl_3$): 1.60 (3H, d, *J*= 6.4 Hz), 2.02 (1H, s) 4.81 (1H, q, *J*= 6.5 Hz), 7.46-7.50 (3H, m), 7.76-7.82 (3H, m), 7.96 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 24.4, 59.0, 84.4, 91.3, 119.9, 126.5, 126.7, 127.7, 128.0, 128.4, 131.6, 132.8, 132.9; IR (ν, cm^{-1}): 3443, 3060, 2973, 2878, 2226, 1265, 1103, 801, 764, 712; HRMS: m/z, Calcd. Mass: 219.0780 [$(M + Na)^+$], Found: 219.0781 [$(M + Na)^+$]. The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OJ-H column

[hexanes/2-propanol = 90:10, 1.0 mL/min; retention times 25.1 min (major) and 29.2 min (minor)]; $[\alpha]_D^{25}$ =+2.2 (c 1, $CHCl_3$).

(*R*)-4-(biphenyl-4-yl)but-3-yn-2-ol (2g)[9]

Yield 72%; > 99% *ee*; colorless solid; Mp 128-129 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 1.58 (3H, d, *J*= 6.5 Hz), 2.01 (1H, d, 5 Hz), 4.79 (1H, m), 7.35–7.38 (1H, m), 7.43-7.45 (2H, m), 7.49–7.51 (2H, m), 7.54-7.56 (2H, m), 7.59–7. 60 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 24.4, 58.9, 83.9, 91.6, 121.5, 126.9, 127.0, 127.1, 127.6, 128.8, 132.1, 140.3, 141.1; The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OJ-H column [hexanes/2-propanol = 90:10, 1.0 mL/min; retention times 26.9 min (major) and 32.6 min (minor)]; $[\alpha]_D^{25}$ =- 15.3 (c 1, $CHCl_3$).

(*R*)-4-(9H-fluoren-2-yl)but-3-yn-2-ol (2h)

Yield 85%; 23 % *ee*; pale yellow solid; Mp 139-140°C; ^{1}H NMR (400 MHz, $CDCl_3$): 1.58 (3H, d, *J*= 6.4 Hz), 3.87 (2H, s) 4.79 (1H, d, *J*= 6.4 Hz), 7.31 (1H, td, *J* = 7.2 Hz & 1.2 Hz), 7.36-7.38 (1H, m), 7.45 (1H, dt, *J* = 8 Hz & 0.8 Hz), 7.58–7. 60 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 24.7, 36.9, 59.2, 84.9, 91.1, 119.9, 120.4, 120.8, 125.3, 127.1, 127.4, 128.5, 130.7, 141.1, 142.2, 143.3, 143.7; IR (ν, cm^{-1}): 3476, 2985, 2257, 1407, 829, 769, 733; HRMS: m/z, Calcd. Mass: 235.1117 [(M + H) $^+$], Found: 235.1113 [(M + H) $^+$]; The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OJ-H column [hexanes/2-propanol = 90:10, 1.0 mL/min; retention times 25.8 min (major) and 34.2 min (minor)]; $[\alpha]_D^{25}$ =+ 5.4 (c 1, $CHCl_3$).

(*R*)-1-phenylpent-1-yn-3-ol (2i)[10]

Yield 85%; 89% *ee*; pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): 1.08 (3H, t, *J*= 7.5 Hz), 1.77-1.89 (2H, m), 1.96 (1H, d, *J*= 4.5 Hz), 4.56 (1H, dd, *J* = 10.5 & 6 Hz), 7.29-7.32 (3H, m), 7.41-7.45 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 9.5, 31.0, 64.2, 84.9, 89.9, 122.7, 128.2, 128.3, 131.7; The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OD-H column [hexanes/2-propanol = 90:10, 1.0 mL/min; retention times 5.7 (major) and 11.5 min (minor)]; $[\alpha]_D^{25}$ =+5.8 (c 1, $CHCl_3$).

(*S*)-1-phenylhex-1-yn-3-ol (2j)[11]

Yield 82%; 62% *ee*; pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): 0.99 (3H, t, *J*= 7.5 Hz), 1.51-1.61(2H, m), 1.74-1.85 (2H, m), 1.96 (1H, bs), 4.61 (1H, t, *J* = 6.5Hz), 7.28-7.33 (3H, m), 7.41-7.45 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 13.7, 18.4, 40.0, 62.8, 84.8, 90.2, 122.7, 128.2, 128.3, 131.7; The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OD-H column [hexanes/2-propanol = 90:10, 1.0 mL/min; retention times 5.7 (minor) and 12.4 min (major)]; $[\alpha]_D^{25}$ =- 2.7 (c 1, $CHCl_3$).

(*S*)-1-phenylhept-1-yn-3-ol (2k)[12]

Yield 79%; 48% *ee*; pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): 0.94 (3H, t, *J*= 7.5 Hz), 1.26-1.47 (2H, m), 1.67-1.79 (2H, m), 1.74-1.85 (2H, m), 1.96 (1H, bs), 4.51 (1H, dd, *J* = 11.5 & 6.5 Hz), 7.21-7.25 (3H, m), 7.35-7.37 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 14.3, 22.3, 24.6, 38.0, 63.3, 85.7, 89.1, 122.8, 128.3, 128.3, 131.6; The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OD-H column [hexanes/2-propanol = 90:10, 1.0 mL/min; retention times 5.5 (minor) and 12.3 min (major)]; $[\alpha]_D^{25}$ =+ 1.2 (c 1, $CHCl_3$).

(*S*)-1-phenyloct-1-yn-3-ol (2l)[13]

Yield 81%; 40% *ee*; pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): 0.91 (3H, t, *J*= 7.0 Hz), 1.32-1.36 (4H, m), 1.49-1.57 (2H, m), 1.75-1.86 (2H, m), 4.58 (1H, dd, *J* = 12 & 6.6Hz), 7.28-7.44 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 14.0, 22.5, 24.9, 31.4, 37.9, 63.2, 84.9, 90.3, 122.8, 128.26, 128.3, 131.7; The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OD-H column [hexanes/2-propanol = 90:10, 1.0 mL/min; retention times 5.5 (minor) and 11.0 min (major)]; $[\alpha]_D^{25}$ =+ 1.6 (c 1, $CHCl_3$).

(*S*)-1-cyclohexyl-3-phenylprop-2-yn-1-ol (2m)[14]

Yield 72%; 20% *ee*; pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): 1.10-1.33 (6H, m), 1.62-1.94 (6H, m), 4.38 (1H, m), 7.29-7.32 (3H, m), 7.42-7.45 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 25.91, 25.93, 26.4, 28.2, 28.7, 44.4, 67.7, 85.7, 89.3, 122.8, 128.26, 128.29, 131.7; The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OD-H column [hexanes/2-propanol = 90:10, 1.0 mL/min; retention times 5.1 (minor) and 11.0 min (major)]; $[\alpha]_D^{25}$ =+ 1.9 (c 1, $CHCl_3$).

(*S*)-1,3-diphenylprop-2-yn-1-ol (2n)[14]

Yield 72%; 20% *ee*; pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): 2.39 (1H, bs), 5.70 (1H, s), 7.31-7.38 (4H, m), 7.40-7.43 (2H, m), 7.48-7.50 (2H, m), 7.62-7.64 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 65.1, 86.7, 88.7, 122.4, 126.7, 128.3, 128.4, 128.6, 128.7, 131.7, 140.6; The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OD-H column [hexanes/2-propanol = 90:10, 1.0 mL/min; retention times 10.4 (minor) and 18.5 min (major)]; $[\alpha]_D^{25}$ =-4.5 (c 2, $CHCl_3$).

(*S*)-4-phenylbut-3-yne-1,2-diol (2o)[15]

Yield 87%; > 99% *ee*; colorless solid; Mp 78-79°C; ^{1}H NMR (400 MHz, $CDCl_3$): 3.21 (2H, bs), 3.78 (1H, dd, *J* = 11.6 & 6.8 Hz), 3.84 (1H, dd, *J* = 11.6 & 3.6 Hz), 4.70 (1H, dd, *J* = 6.8 & 3.6 Hz), 7.27-7.33 (3H, m), 7.42-7.44 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 63.7, 66.5, 86.2, 86.5, 122.0, 128.3, 128.7, 131.7; The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OD-H column [hexanes/2-propanol = 95:05, 1.0 mL/min; retention times 40.6 (major) and 45.1 min (minor)]; $[\alpha]_D^{25}$ =+38.6 (c 1, $CHCl_3$).

(*S*)-ethyl 3-hydroxy-5-phenylpent-4-ynoate (2p)[16]

Yield 70%; > 99% *ee*; pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): 1.29 (3H, t,*J*= 7 Hz), 2.84 (2H, t, *J*= 6 Hz), 3.23 (1H, d, *J*= 6 Hz), 4.22 (2H, q, *J*= 7 Hz), 4.99 (1H, q, *J*= 6 Hz), 7.28-7.32 (3H, m), 7.41-7.43 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 14.2, 42.0, 59.3, 61.0, 85.1, 87.0, 122.2, 128.3, 128.6, 131.7, 171.3; The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OD-H column [hexanes/2-propanol = 90:10, 1.0 mL/min; retention times 9.5 (minor) and 12.4 min (major)]; $[\alpha]_D^{25}$ =- 2.8 (c 1, $CHCl_3$).

(S)-2-(4-phenylbut-3-yn-2-yloxy)benzaldehyde (4a)

Yield 72%; 91% *ee*; pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): 2.12 (3H, d, *J* = 6.4 Hz), 5.49 (1H, q, *J* = 6.4 Hz), 6.60 (1H, dd, *J* = 8 & 1.2 Hz) 7.35-7.39 (1H, m), 7.56-7.62 (4H, m), 7.66-7.69 (2H, m), 7.84-7.89 (1H, m) 8.16 (1H, dd, *J* = 7.6 & 1.6 Hz), 10.84 (1H, d, *J* =1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$):22,2, 65.6, 86.7, 87.2, 114.9, 121.5, 122.0, 125.8, 128.2, 128.3, 128.7, 131.7, 135.6, 160.0, 189.9; IR (ν, cm^{-1}): 3076, 2990, 1686, 1479, 1452, 1287, 1233, 757, 691; HRMS: m/z, Calcd. Mass: 273.0886 [(M + Na) $^+$], Found: 273.0894 [(M + Na) $^+$]. The

compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OD-H column [hexanes/2-propanol = 98:02, 1.0 mL/min, retention times 6.7 min (major) and 7.9 min (minor)]; $[\alpha]_D^{25}$ = +14.8 (c1, $CHCl_3$).

(4*S*)-methyl 1,4-dimethyl-3-phenyl-1,2,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2-arboxylate (6a)

Yield 39%; 91% *ee*; pale yellow liquid; ^{1}H NMR (400 MHz, CD_3OD): 0.98 (3H, d, *J* = 6.4 Hz), 2.79 (3H, s), 3.61 (3H, s), 4.96 (1H, dd, *J* = 5.2 & 1.2 Hz), 4.97 (1H, d, *J* = 5.2 Hz), 5.44 (1H, qt, *J* = 6.4 & 1.2Hz), 6.60 (1H, dd, *J* = 8 & 1.2 Hz) 7.06-7.08 (1H, m), 7.16-7.17 (1H, m), 7.18-7.19 (1H, m), 7.28-7.38 (4H, m) 7.41-7.43 (1H, m); ^{13}C NMR (100 MHz, CD_3OD): 19.7, 38.2, 52.2, 70.3, 74.1, 79.7, 119.9, 123.8, 125.7, 129.0, 129.4, 129.5, 129.8, 130.9, 132.4, 134.8, 143.0, 154.2, 173.0; IR (ν, cm^{-1}): 3061, 2978, 1735, 1482, 1452, 1387, 1286, 757, 700; HRMS: m/z, Calcd. Mass: 336.1594 [(M + H) $^+$], Found: 336.1601 [(M + H) $^+$]. The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL AD-H column [hexanes/2-propanol = 95:05, 1.0 mL/min, retention times 9.3 min (major) and 11.6 min (minor)]; $[\alpha]_D^{25}$ = +70.0 (c1, CH_3OH).

(4*S*)-methyl1,4-dimethyl-3-phenyl-1,2,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2-carboxylate (6b)

Yield 31%; 91% *ee*; viscous liquid; ^{1}H NMR (400 MHz, CD_3OD): 1.52 (3H, d, *J*= 6.8 Hz), 2.78 (3H, s), 3.64 (3H, s), 4.93 (1H, d, *J* = 4 Hz), 5.11 (1H, qd, *J* = 6.8 & 1 Hz), 5.13 (1H, d, *J* = 4Hz), 6.81 (1H, dd, *J* = 8.4 & 1.2 Hz) 6.98 (1H, td, *J* = 7.2 & 0.8 Hz), 7.17-7.18 (1H, m), 7.27-7.29 (2H, m), 7.35–7.37 (1H, m), 7.40-7.42 (2H, m); 7.43-7.45 (1H, m); ^{13}C NMR (100 MHz,

CD_3OD): 19.2, 38.3, 52.4, 66.2, 71.4, 78.5, 119.1, 122.4, 126.6, 128.6, 129.4, 129.8, 130.0, 130.9, 133.7, 134.8, 140.0, 153.8, 172.7; IR (ν, cm^{-1}): 2961,2352, 1727, 1485, 1452, 1387, 1217, 762, 700; HRMS: m/z, Calcd. Mass: 336.1594 [(M + H) $^+$], Found: 336.1598 [(M + H) $^+$]. The compound was resolved by HPLC analysis at 25°C, using a CHIRALCEL AD-H column [hexanes/2-propanol = 95:05, 1.0 mL/min, retention times 12.4 min (minor) and 18.0 min (major)]; $[\alpha]_D^{25}$ = -36.8 (c 0.5, CH_3OH).

(*S*)-methyl 1,4-dimethyl-3-phenyl-1,4-dihydrochromeno[4,3-b]pyrrole-2-carboxylate (7a)

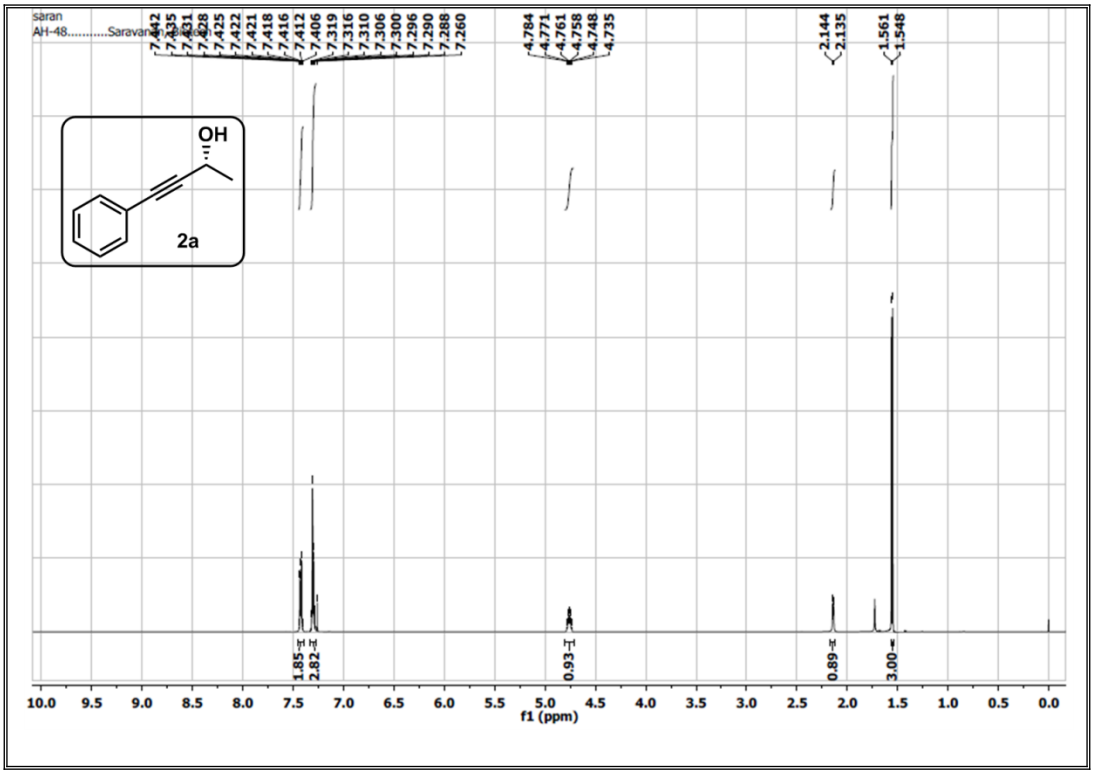
Yield 68%; 91% *ee*; colorless solid; Mp 128-129°C; ^{1}H NMR (400 MHz, $CDCl_3$): 1.21 (3H, d, *J*= 6.4 Hz), 3.54 (3H, s), 4.19 (3H, s), 5.29 (1H, q, *J* = 6.4 Hz), 7.00-7.01 (2H, m), 7.17-7.22 (1H, m), 7.24-7.27 (2H, m), 7.29–7.34 (1H, m), 7.35-7.39 (2H, m); 7.63 (1H, dd, *J* = 7.6 & 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 21.4, 35.5, 50.8, 71.2, 117.7, 118.6, 121.1, 121.4, 121.8, 122.5, 126.8, 127.7, 128.4, 128,7, 129.0, 129.6, 135.1, 153.1, 162.2; IR (ν, cm^{-1}): 3061, 2974, 1697, 1454, 1435, 752; HRMS: m/z, Calcd. Mass: 334.1438 [(M + H) $^+$], Found: 334.1428 [(M + H) $^+$]. The compound was resolved by HPLC analysis at 25°C, using a CHIRALCEL AD-H column [hexanes/2-propanol = 98:02, 1.0 mL/min, retention times 5.4 min (major) and 6.2 min (minor)]; $[\alpha]_D^{25}$ = -32.4 (c 0.5, CH_3OH).

(6S)-methyl 6-methyl-7-phenyl-6,7a,8,9,10,11a-hexahydrochromeno[3,4-b]pyrrolizine-7a-carboxylate (8) (inseparable diastereomers, 1.0 : 0.6 ratio)

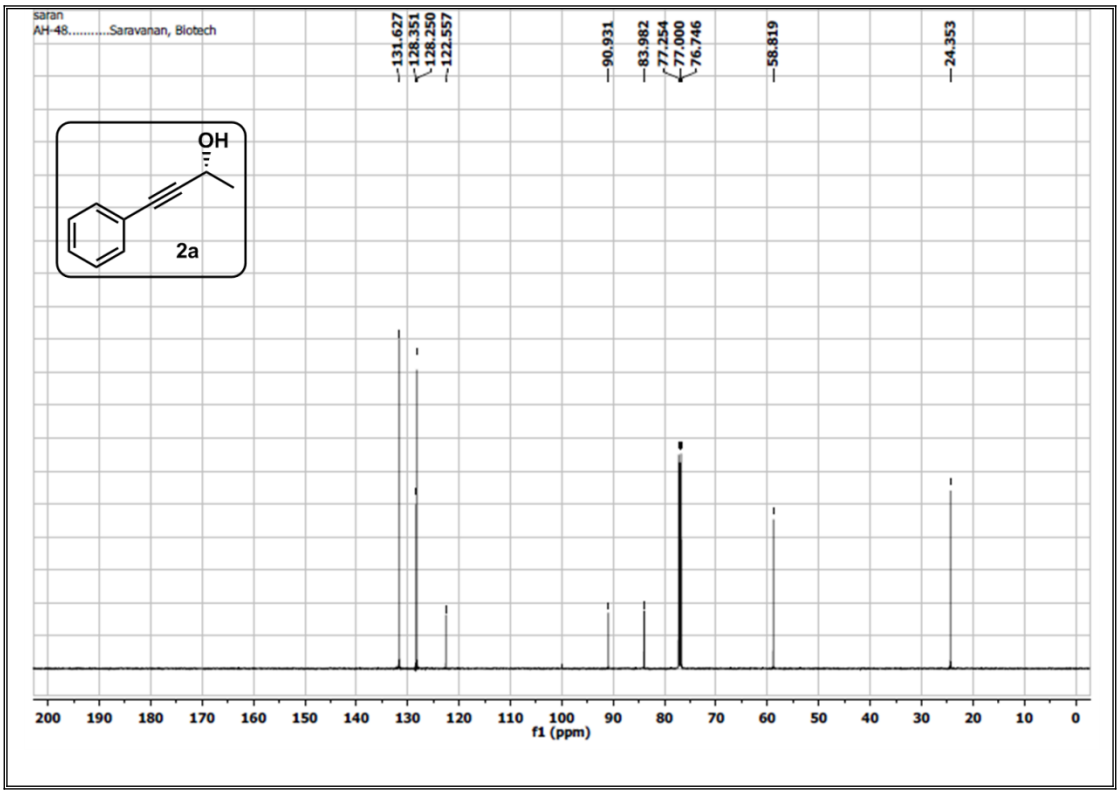
Yield 78%; 91% *ee*; pale yellow liquid; ^{1}H NMR (400 MHz, CD_3OD): 1.03 (3H, d, *J*= 6.4 Hz, major), 1.32 (2H, d, *J*= 6.4 Hz, minor), 1.73-1.80 (3.22H, m, major & minor), 1.85-1.92 (0.62H, m, minor), 2.01-2.07 (1H, m, major), 2.19-2.30 (2.63H, m, major & minor), 2.42-4.48 (0.6H,),

2.83-2.91 (1.6H, m, major & minor), 3.78 (3H, s, major), 3.80 (1.5H, s, minor), 4.72 (1H, qd, *J* = 6.4 & 0.8 Hz, major), 5.01 (0.5H, qd, *J* = 6.4 & 0.8 Hz, minor), 5.50 (0.53H, s,minor), 5.53 (1H, s,major), 6.79-6.84 (1.5H, m, major & minor), 6.95-7.00 (1.5H, m, major & minor), 7.13-7.20 (4.6H, m, major & minor), 7.36-7.42 (6.3H, m, major & minor); ^{13}C NMR (100 MHz, CD_3OD):19.0, 19.2, 25.7, 26.1, 32.9, 33.3, 52.3, 52.6, 53.0, 53.2, 63.5, 67.5, 71.6, 73.1, 87.4, 88.5, 118.3, 119.2, 122.0, 122.2, 122.4, 123.3, 129.2, 129.3, 129.8, 129.9, 130.0, 130.2, 130.7, 130.8, 131.1, 134.8, 135.8, 137.2, 137.7, 138.1, 138.3, 154.7, 157.5, 174.3, 174.8; IR (ν, cm^{-1}): 3055, 2986, 2928, 2306, 1734, 896, 754, 735, 725, 707; HRMS: m/z, Calcd. Mass: 362.1751 [(M + H) $^+$], Found: 362.1734 [(M + H) $^+$]. The compound was resolved by HPLC analysis at 25°C, using a phenomenex Lux 5u Amylose 2 column [hexanes/2-propanol = 95:05, 1.0 mL/min, retention times: **8a** major isomer 14.7 min (minor) and 17.7 min (major); **8b** minor isomer 11.8 min (major) and 13.7 min (major)]; $[\alpha]_D^{25}$ = -26.3 (c 2, CH_3OH).

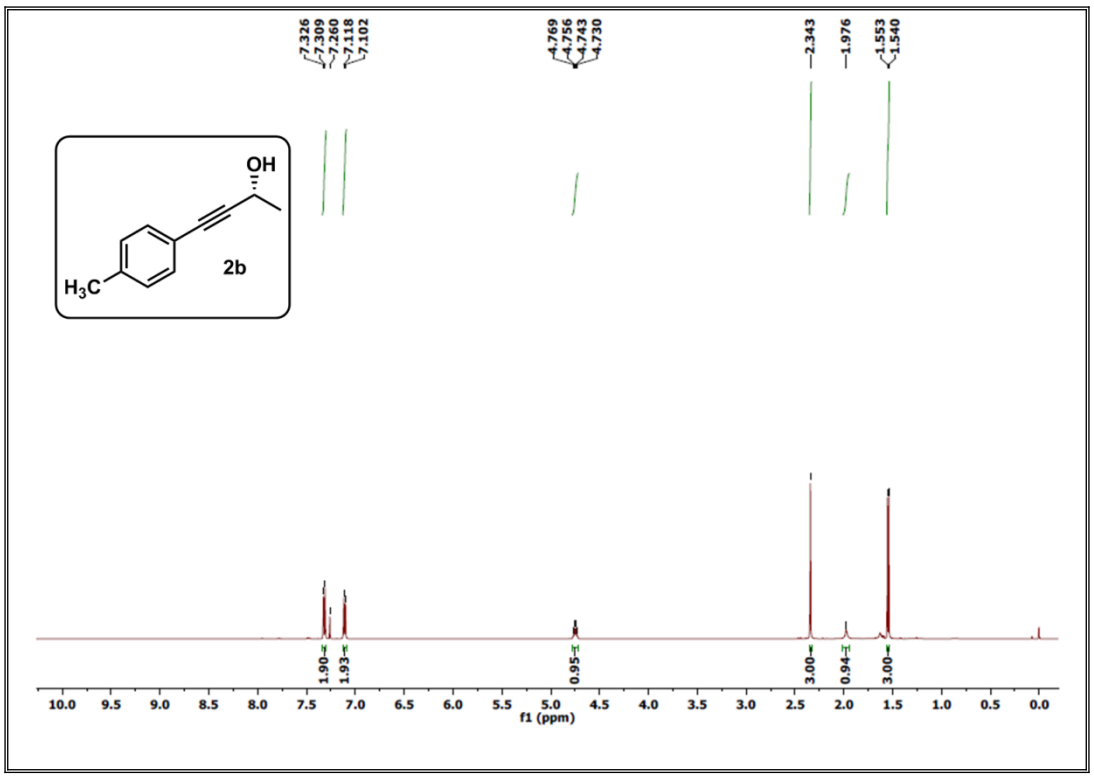
COPIES OF ^{1}H & ^{13}C NMR



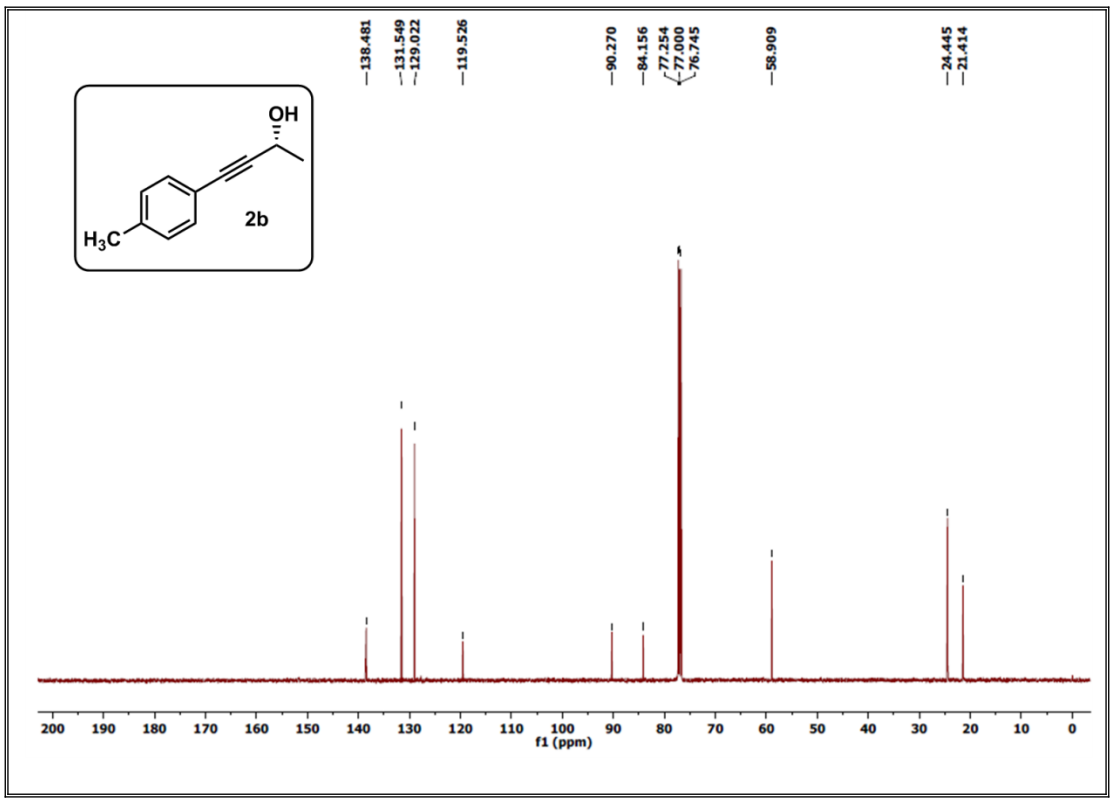
^{1}H NMR of **2a** (500 MHz, $CDCl_3$)



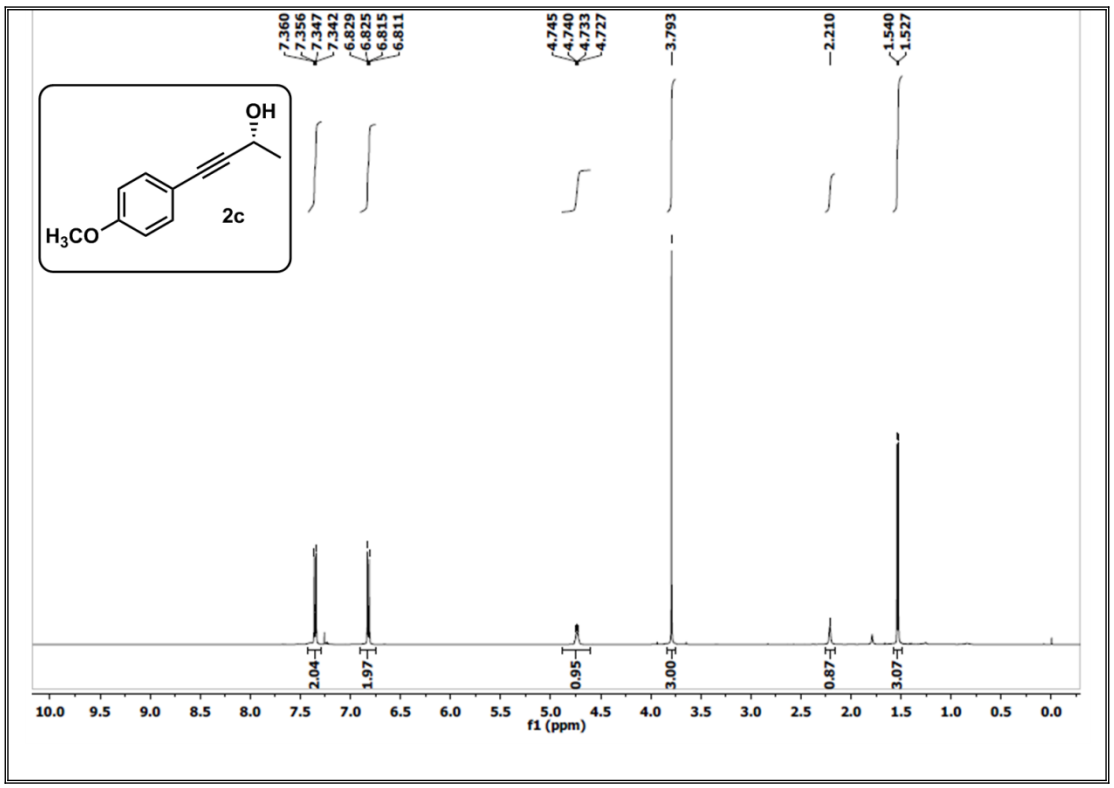
^{13}C NMR of **2a** (125 MHz, $CDCl_3$)



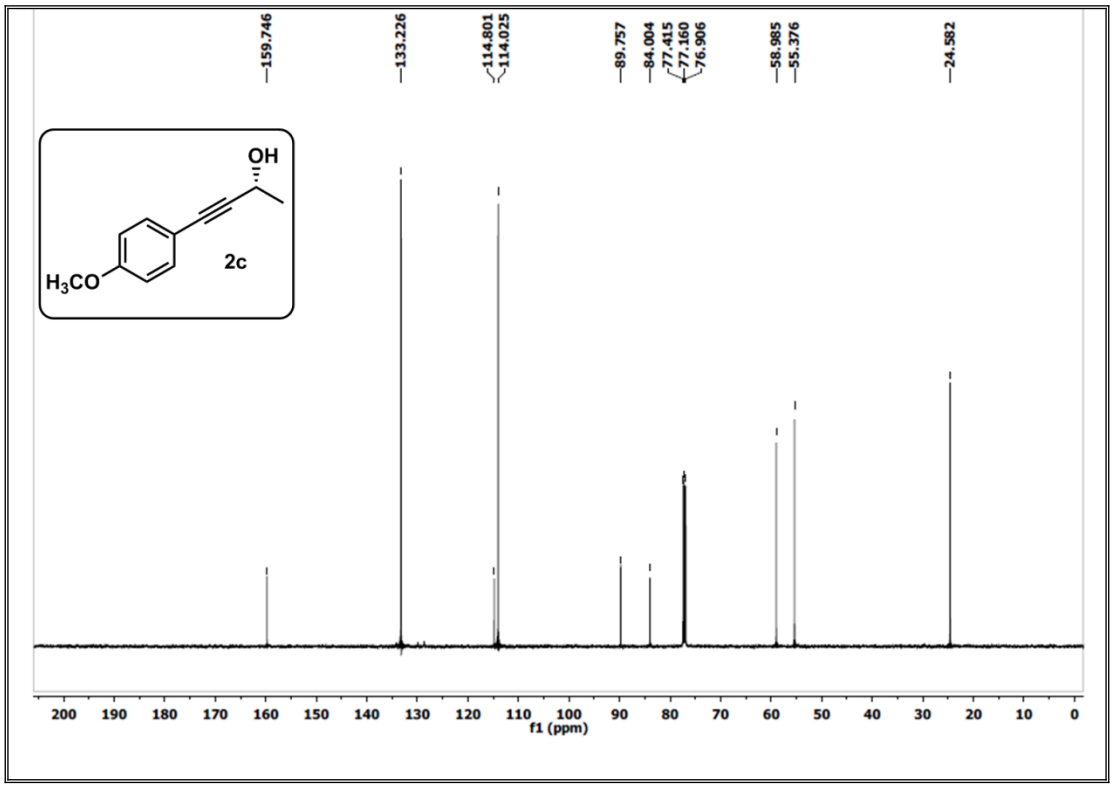
^{1}H NMR of **2b** (500 MHz, $CDCl_3$)



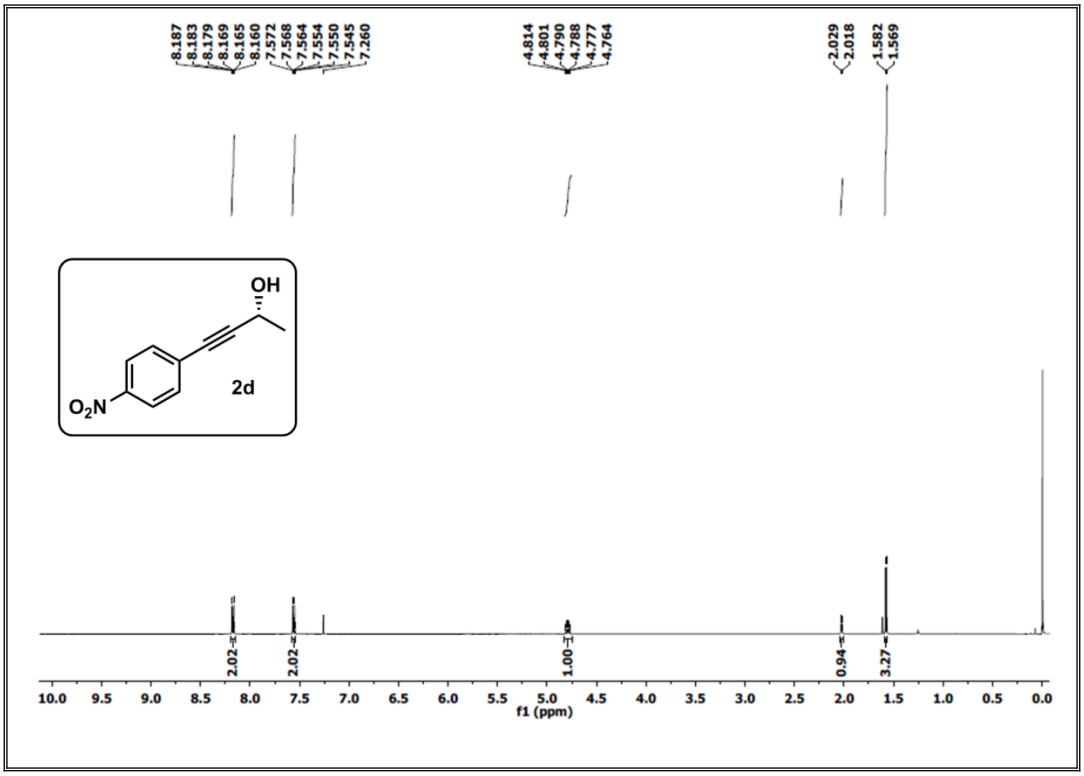
^{13}C NMR of **2b** (125 MHz, $CDCl_3$)



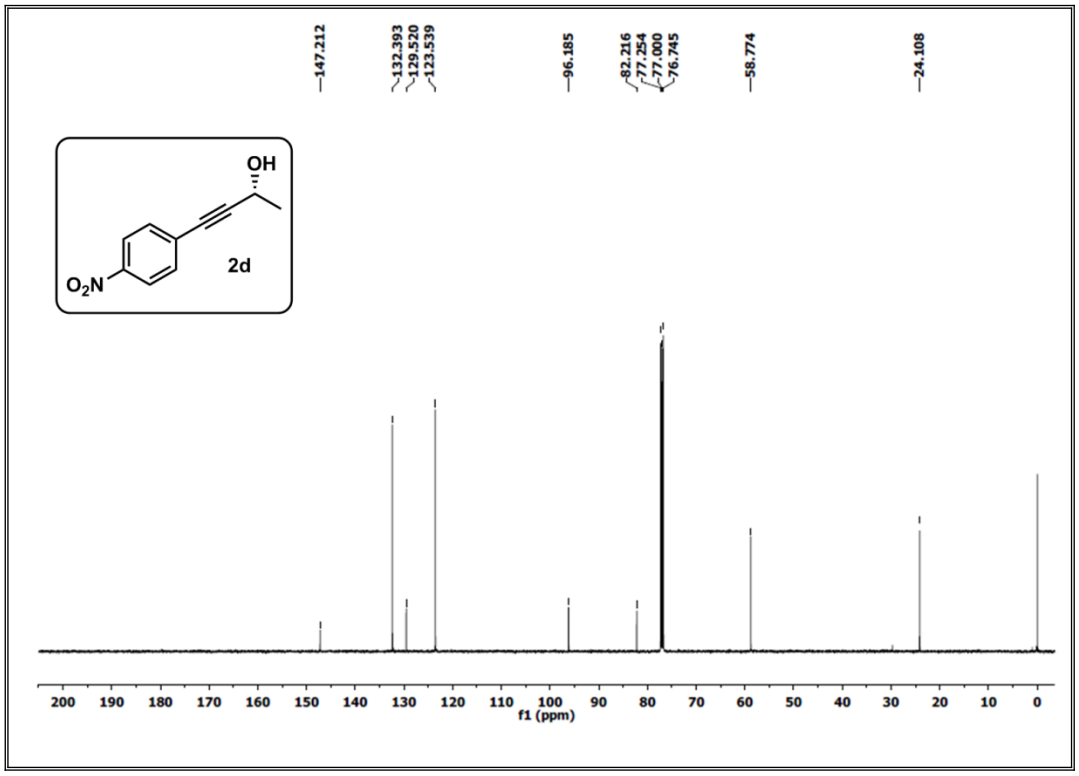
^{1}H NMR of **2c** (500 MHz, $CDCl_3$)



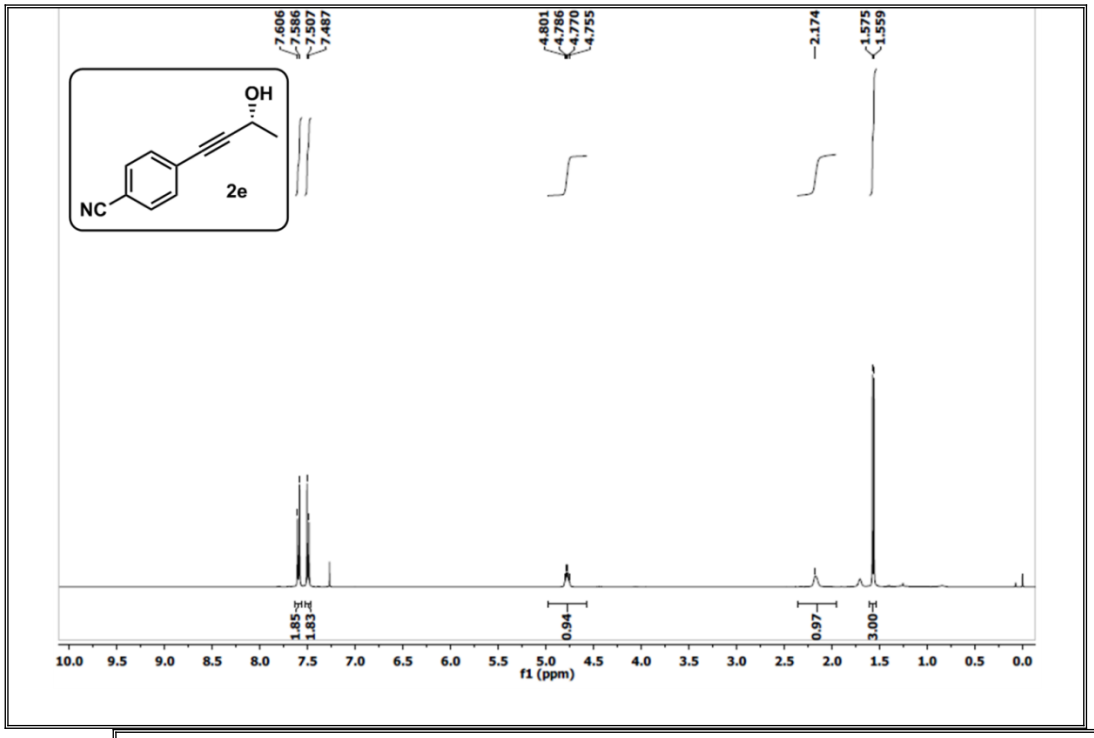
^{13}C NMR of **2c** (125 MHz, $CDCl_3$)



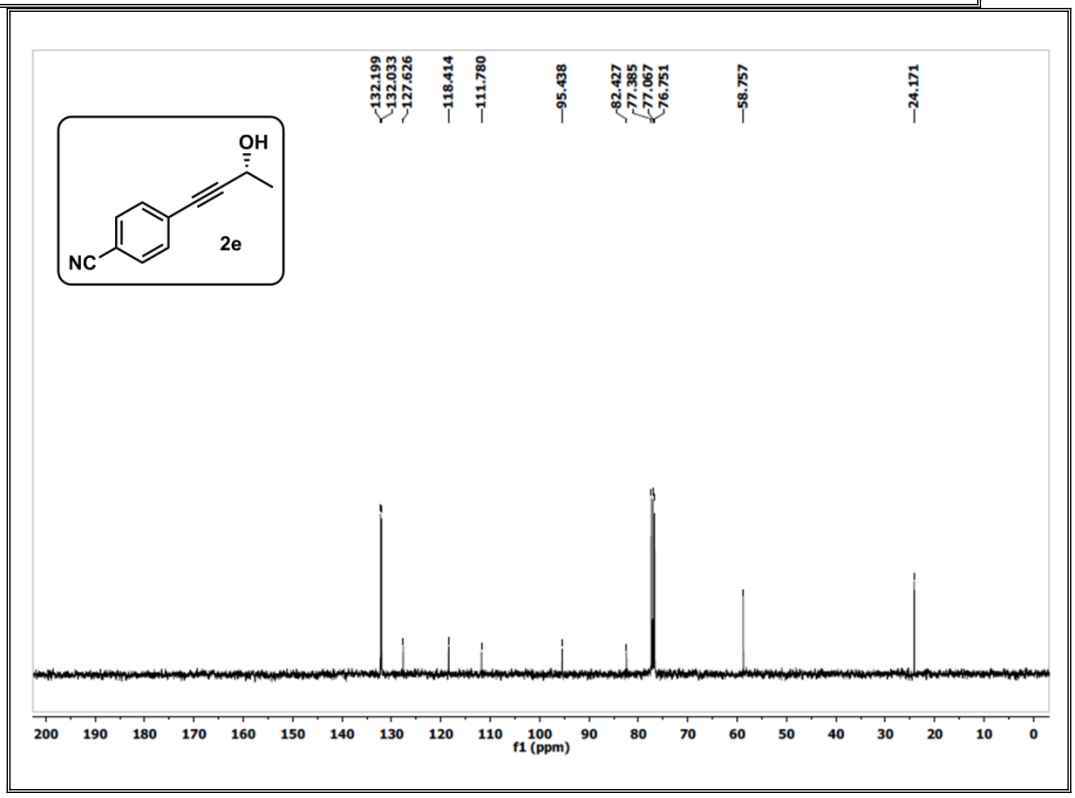
^{1}H NMR of **2d** (500 MHz, $CDCl_3$)



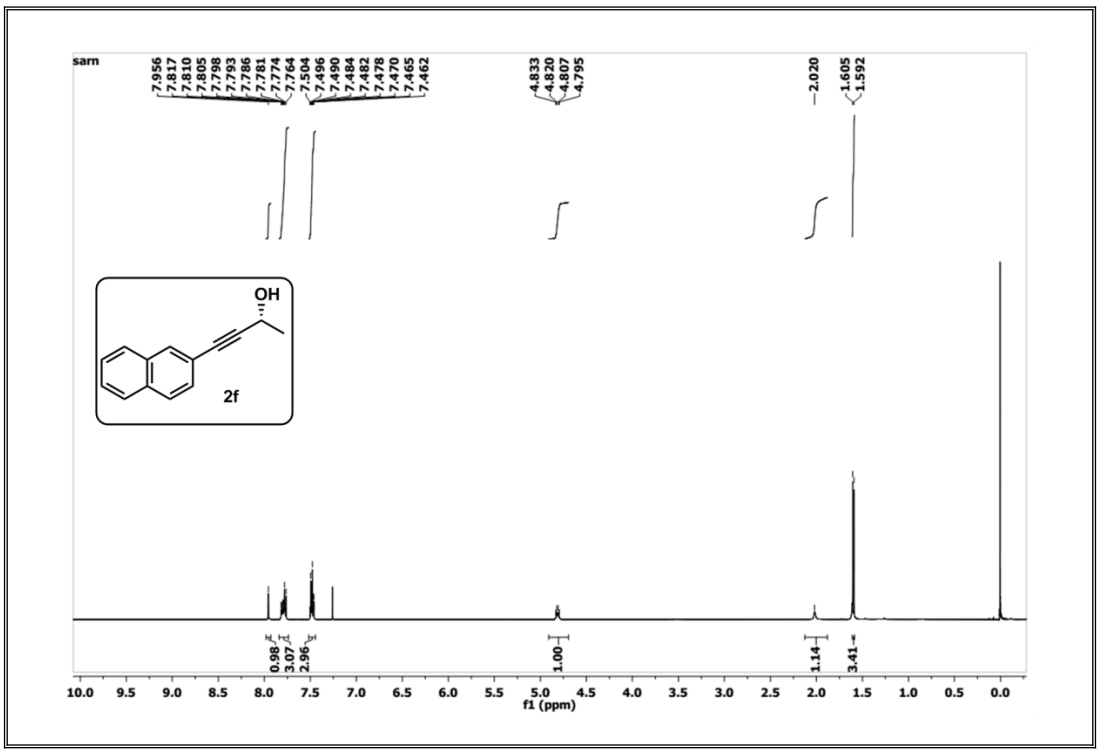
^{13}C NMR of **2d** (125 MHz, $CDCl_3$)



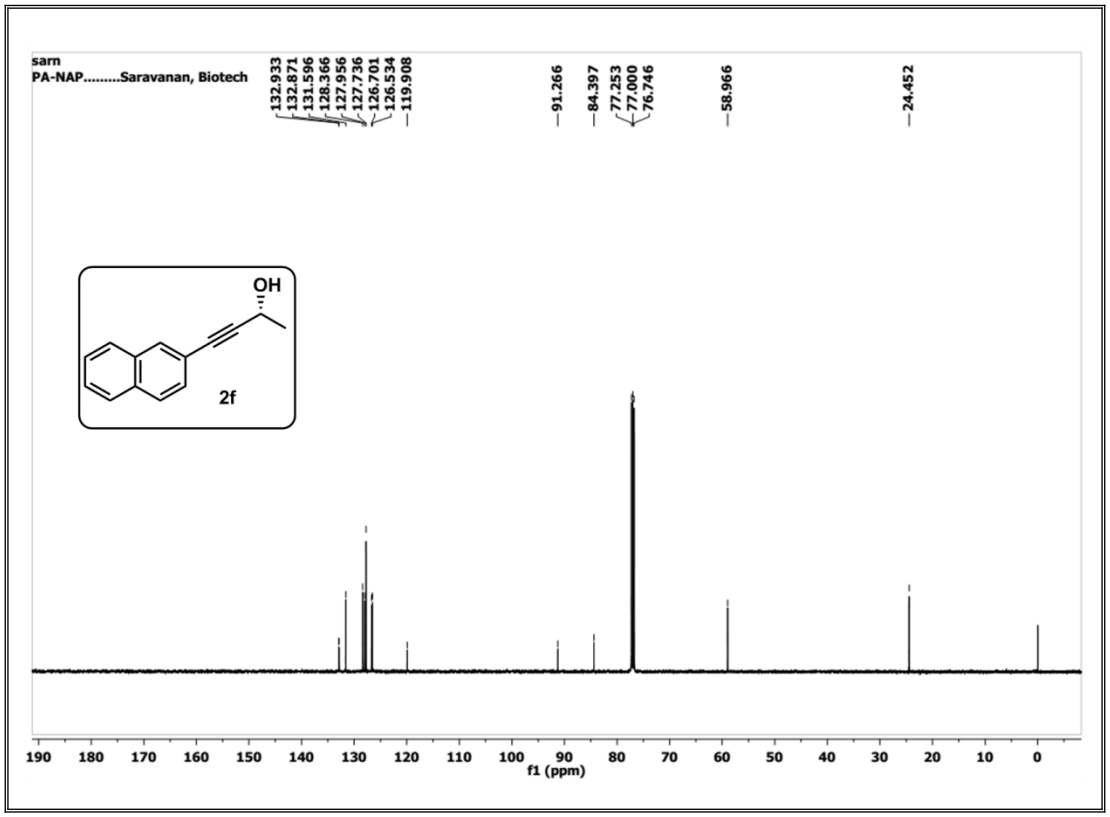
^{1}H NMR of **2e** (500 MHz, $CDCl_3$)



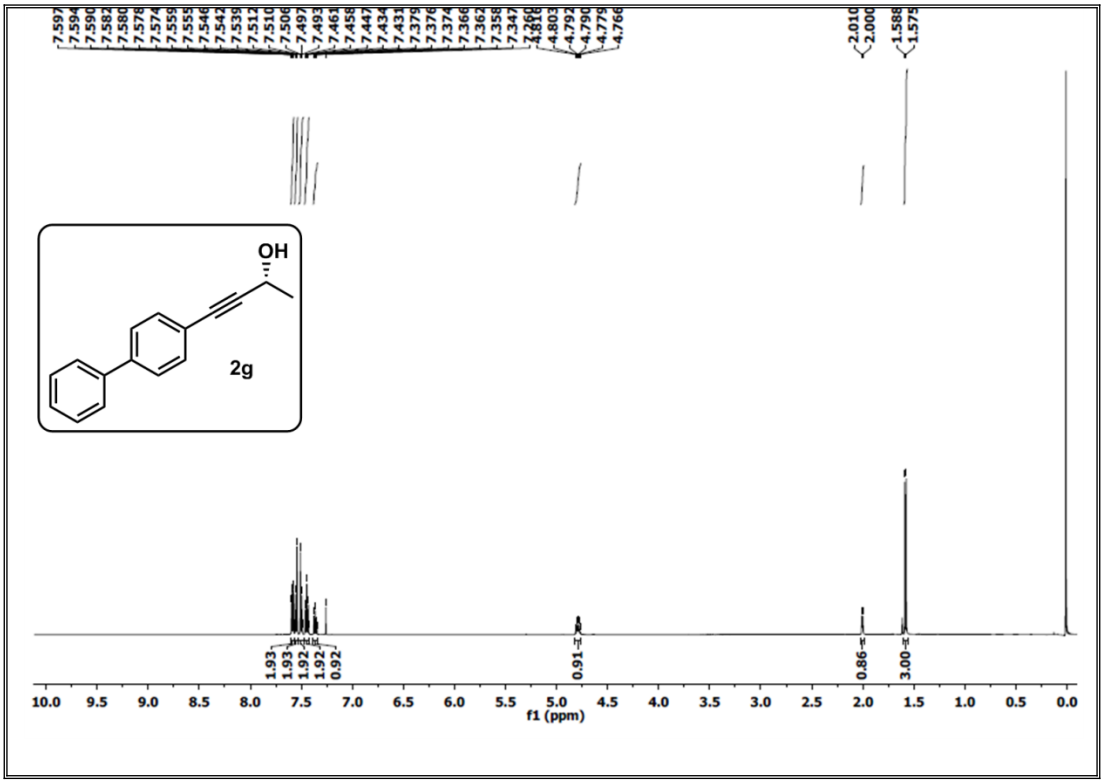
^{13}C NMR of **2e** (125 MHz, $CDCl_3$)



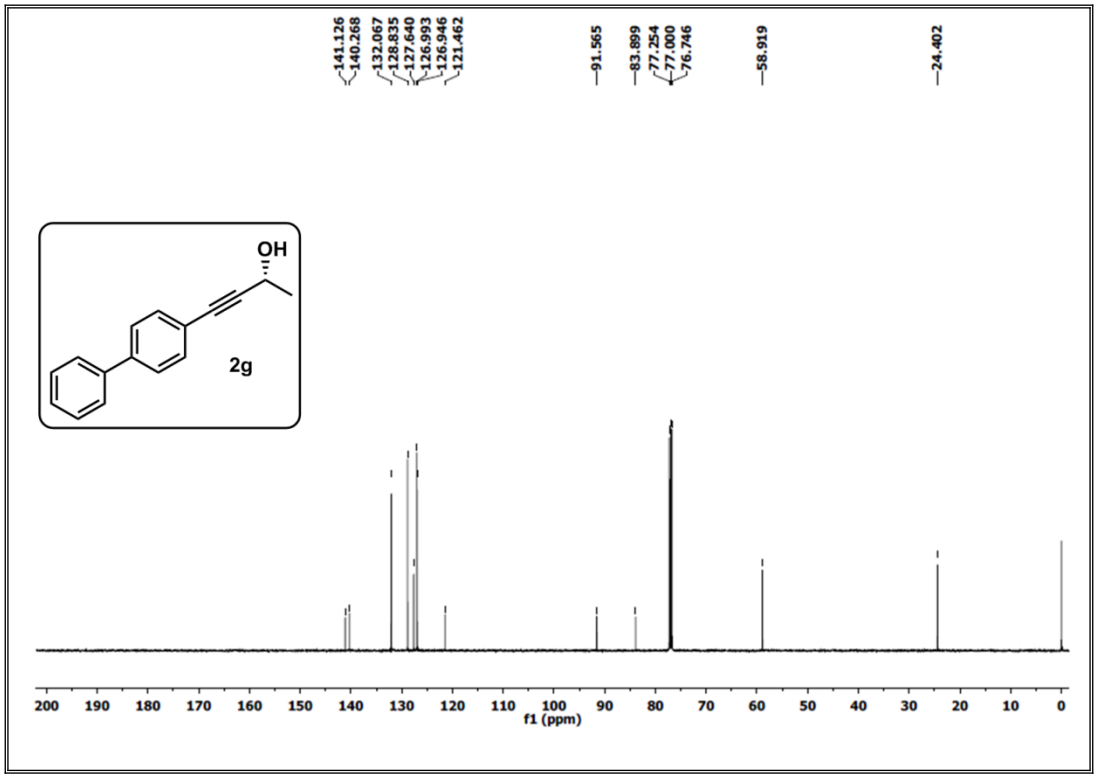
^{1}H NMR of **2f** (500 MHz, $CDCl_3$)



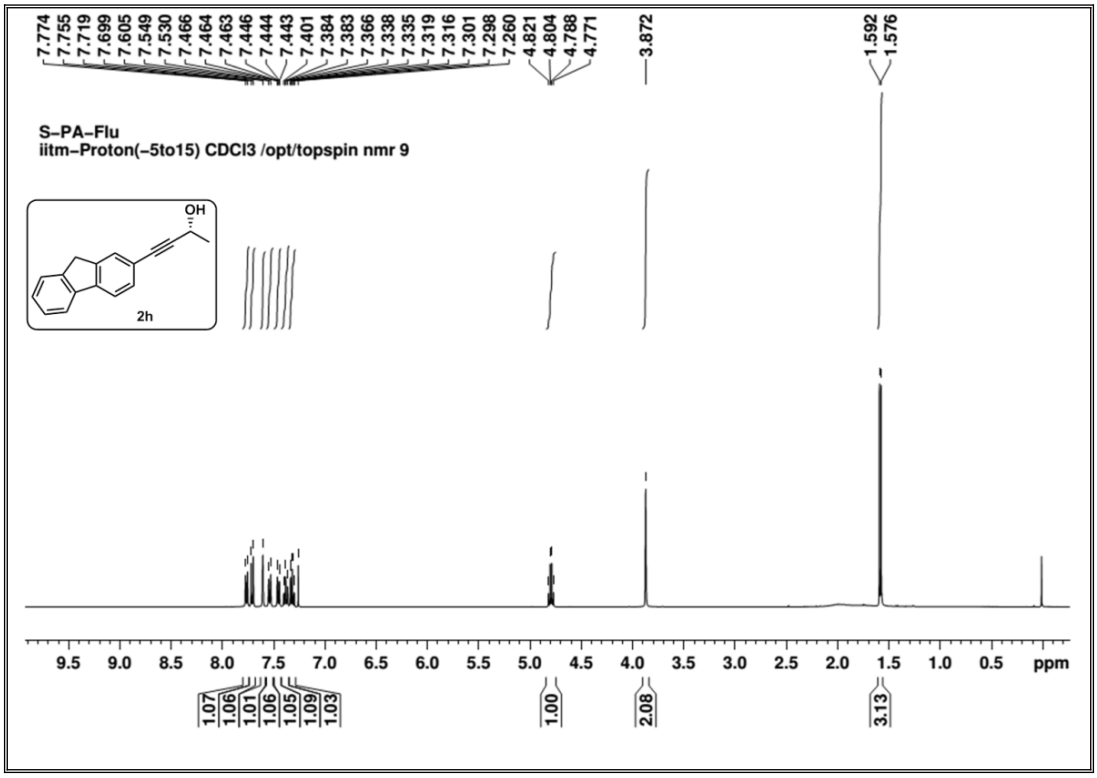
^{13}C NMR of **2f** (125 MHz, $CDCl_3$)



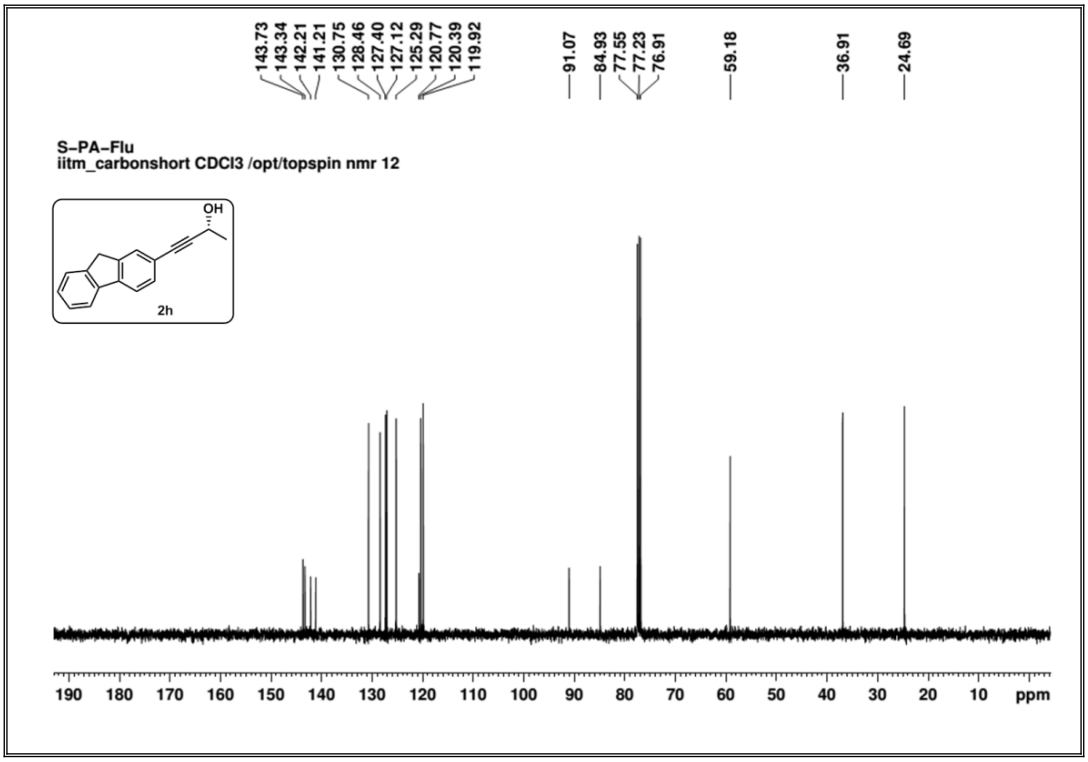
^{1}H NMR of **2g** (500 MHz, $CDCl_3$)



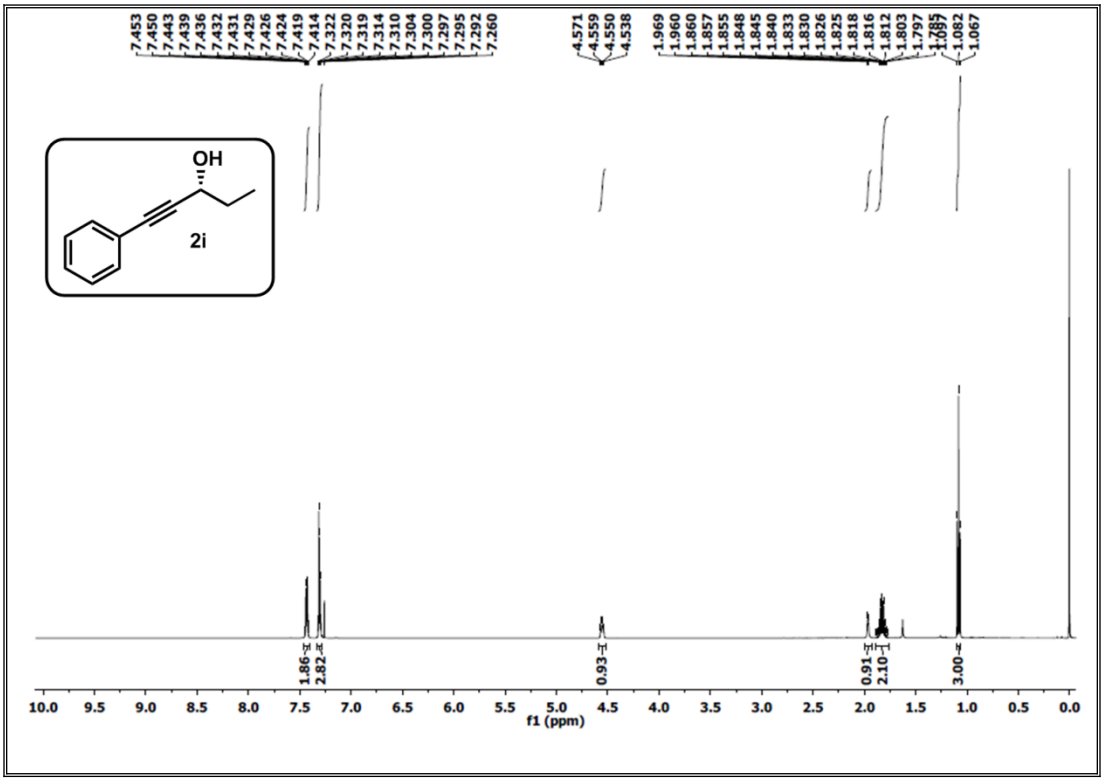
^{13}C NMR of **2g** (125 MHz, $CDCl_3$)



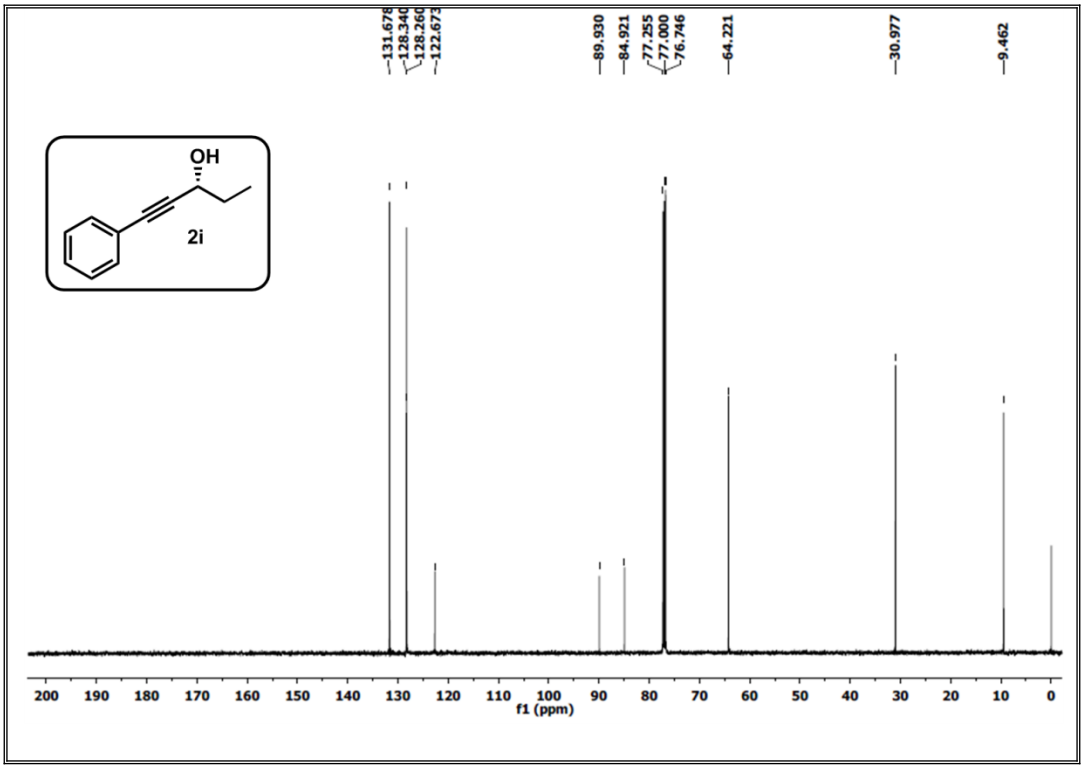
^{1}H NMR of **2h** (400 MHz, $CDCl_3$)



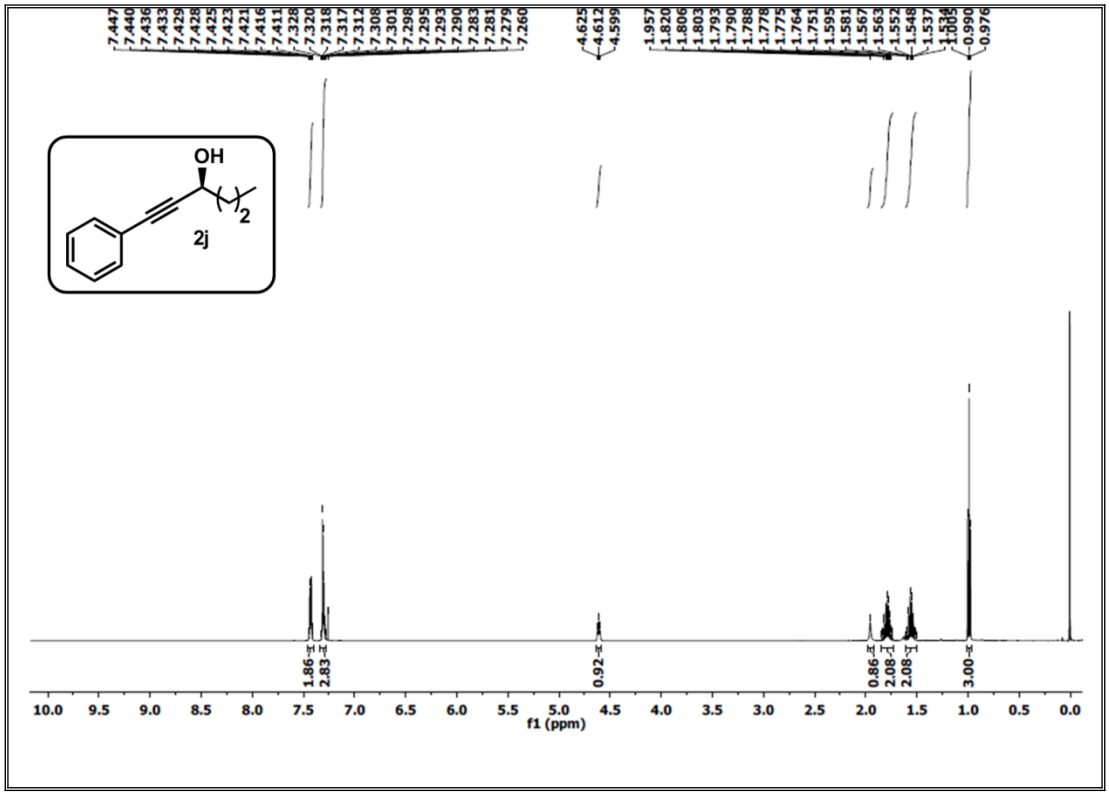
^{13}C NMR of **2h** (100 MHz, $CDCl_3$)



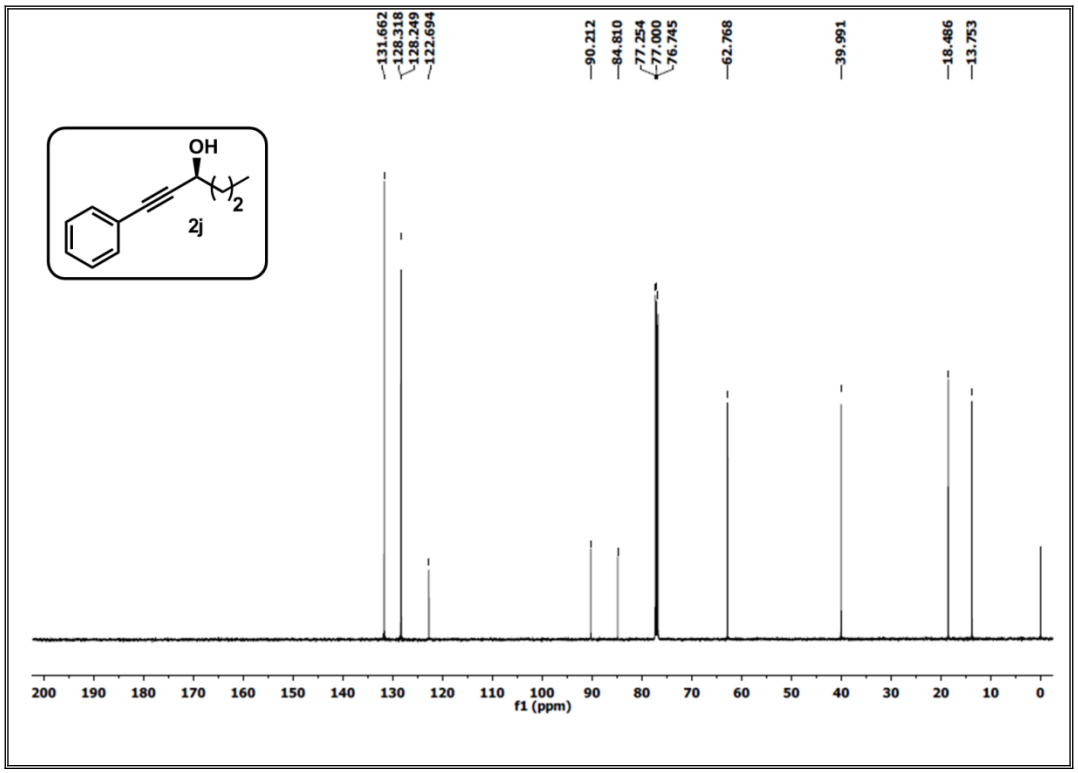
^{1}H NMR of **2i** (500 MHz, $CDCl_3$)



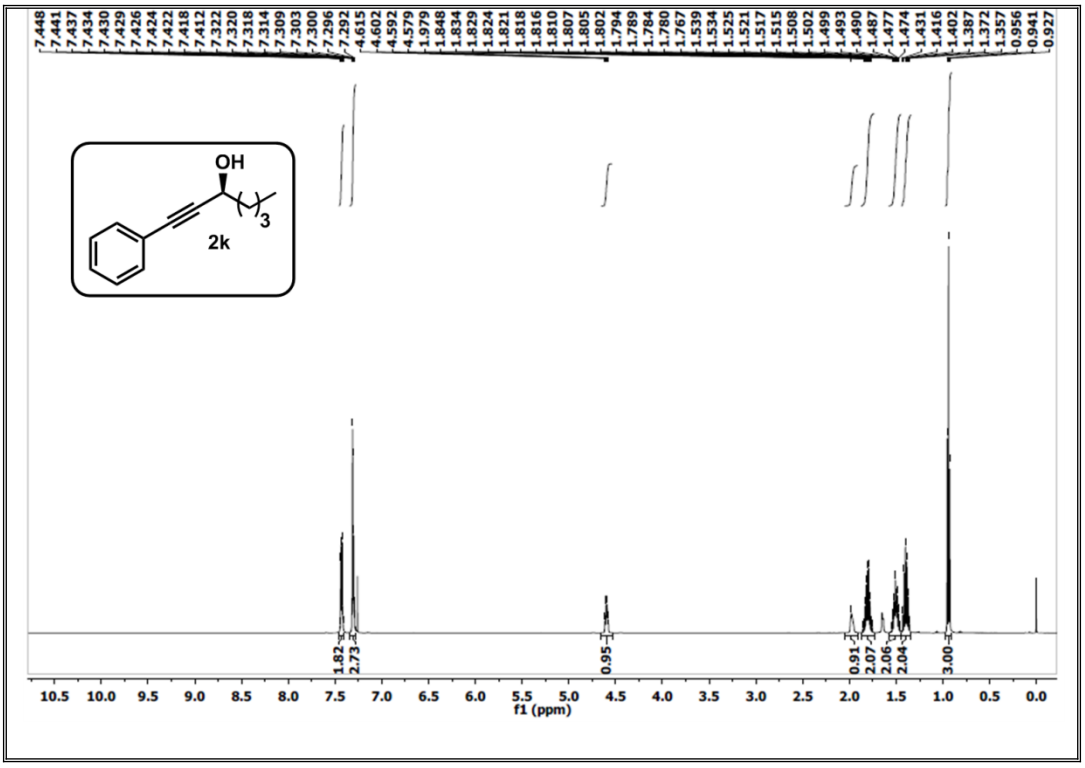
^{13}C NMR of **2i** (125 MHz, $CDCl_3$)



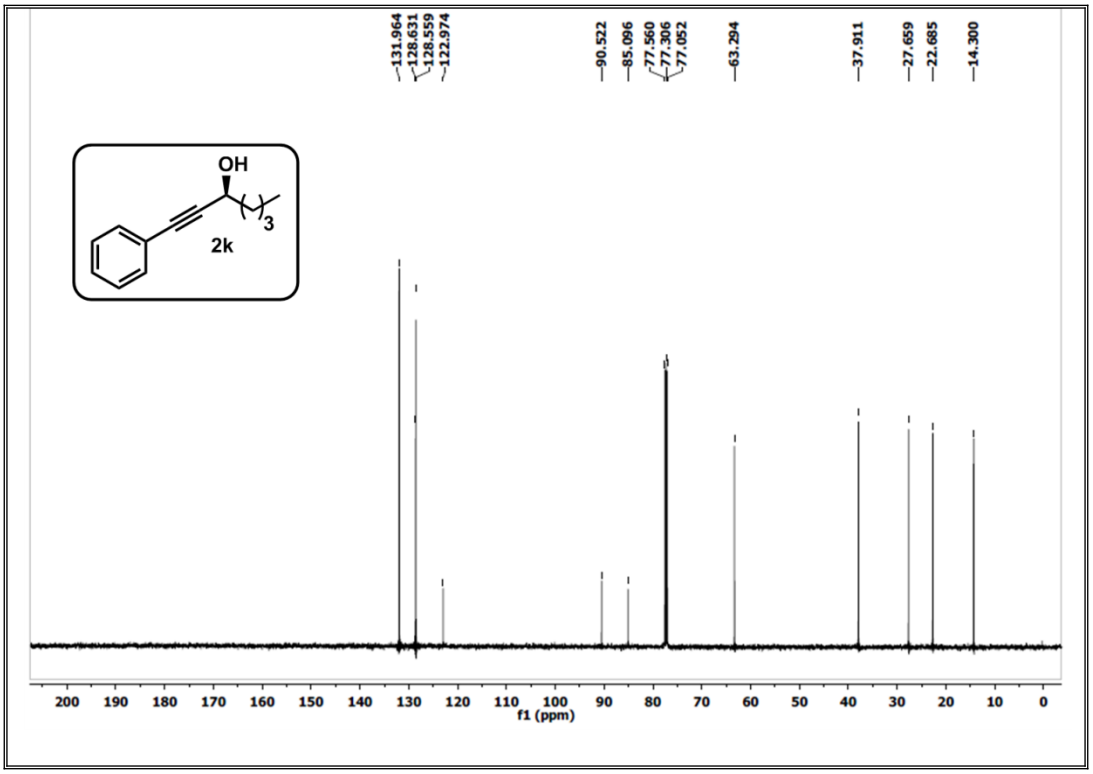
^{1}H NMR of **2j** (500 MHz, $CDCl_3$)



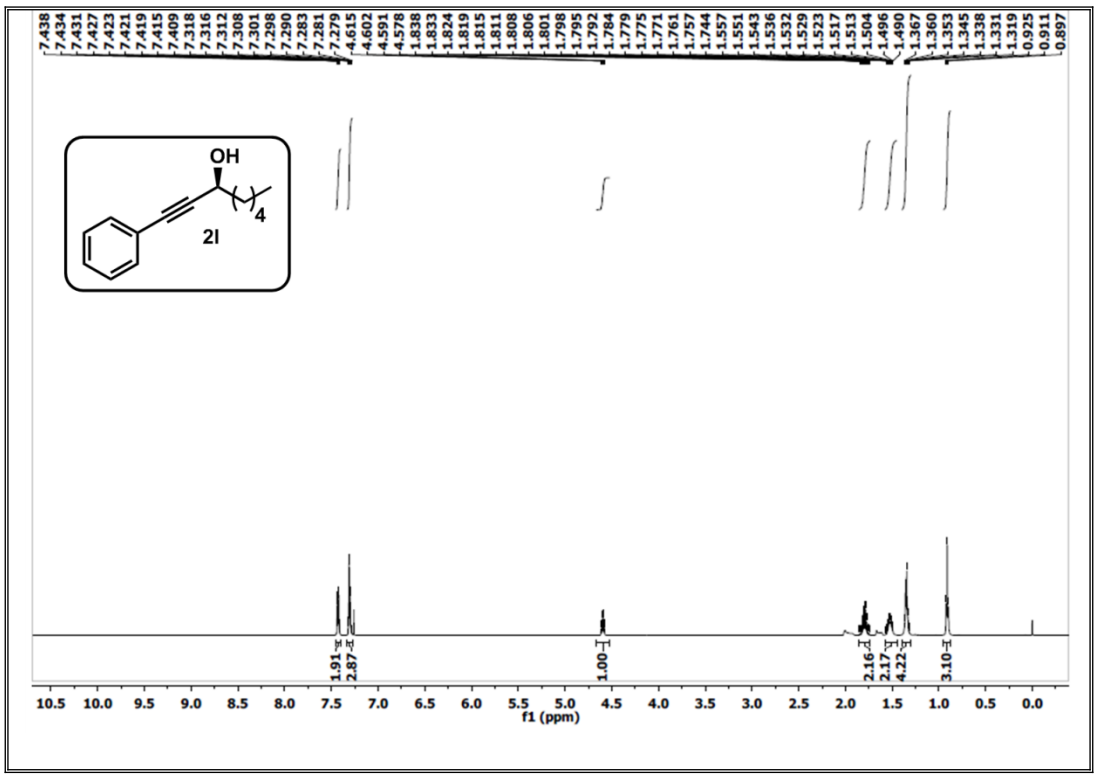
^{13}C NMR of **2j** (125 MHz, $CDCl_3$)



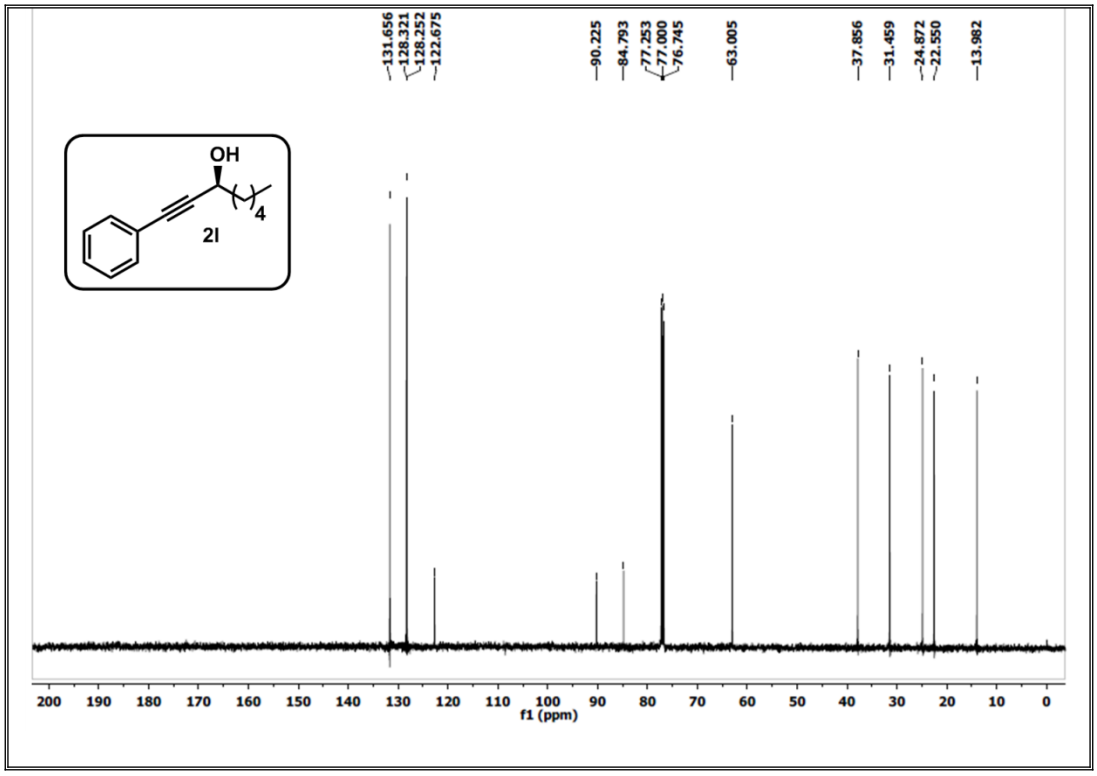
^{1}H NMR of **2k** (500 MHz, $CDCl_3$)



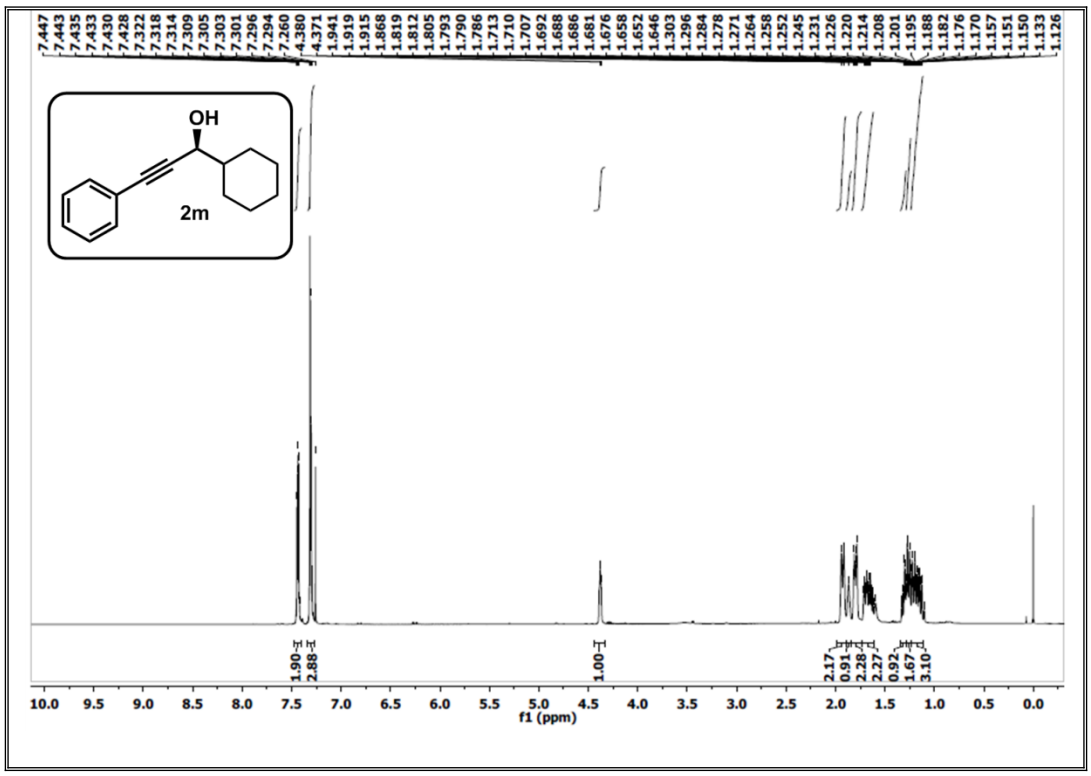
^{13}C NMR of **2k** (125 MHz, $CDCl_3$)



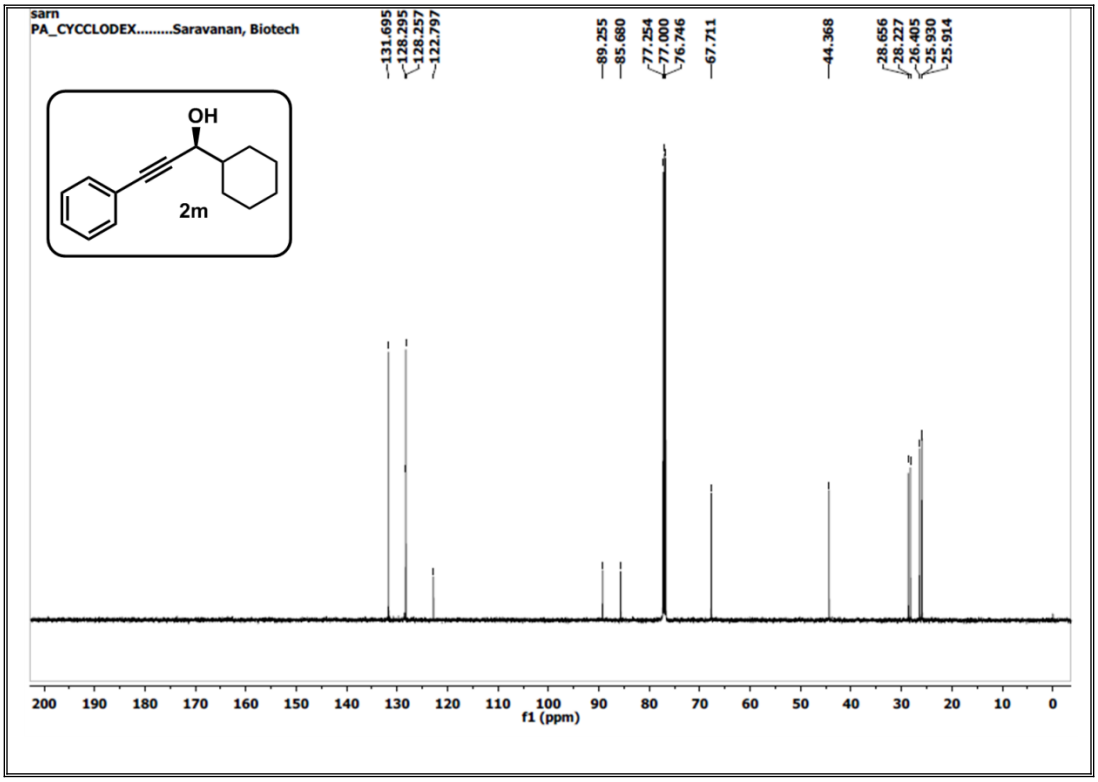
^{1}H NMR of **2l** (500 MHz, $CDCl_3$)



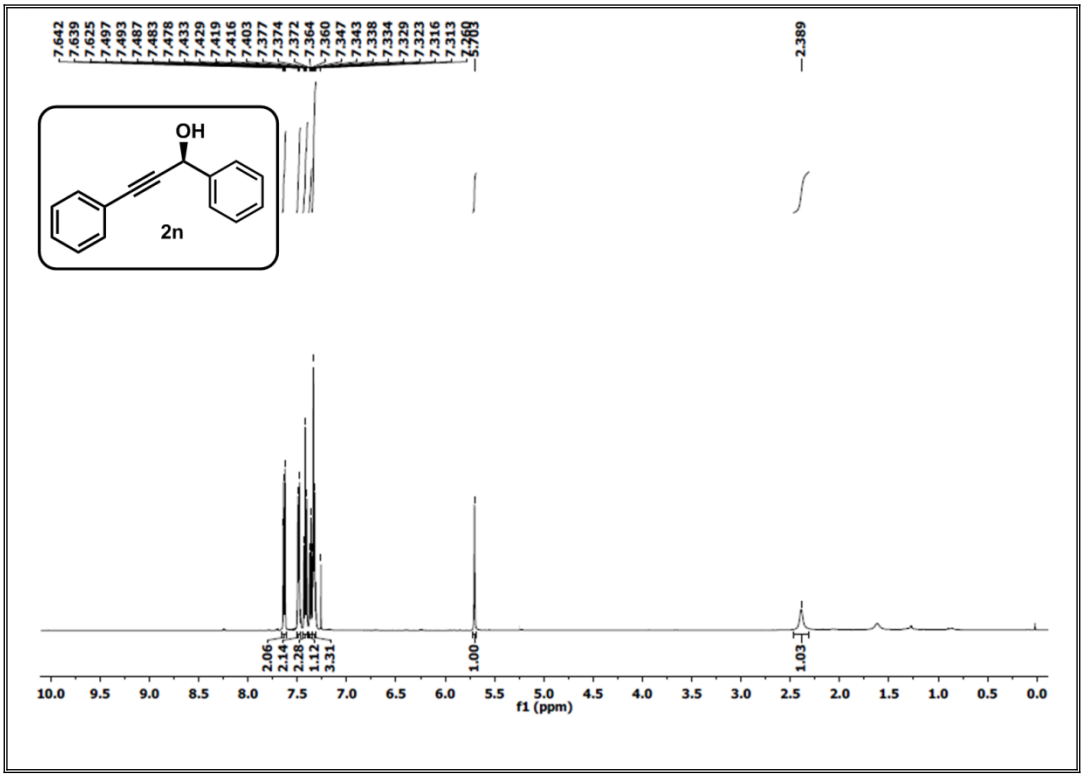
^{13}C NMR of **2l** (125 MHz, $CDCl_3$)



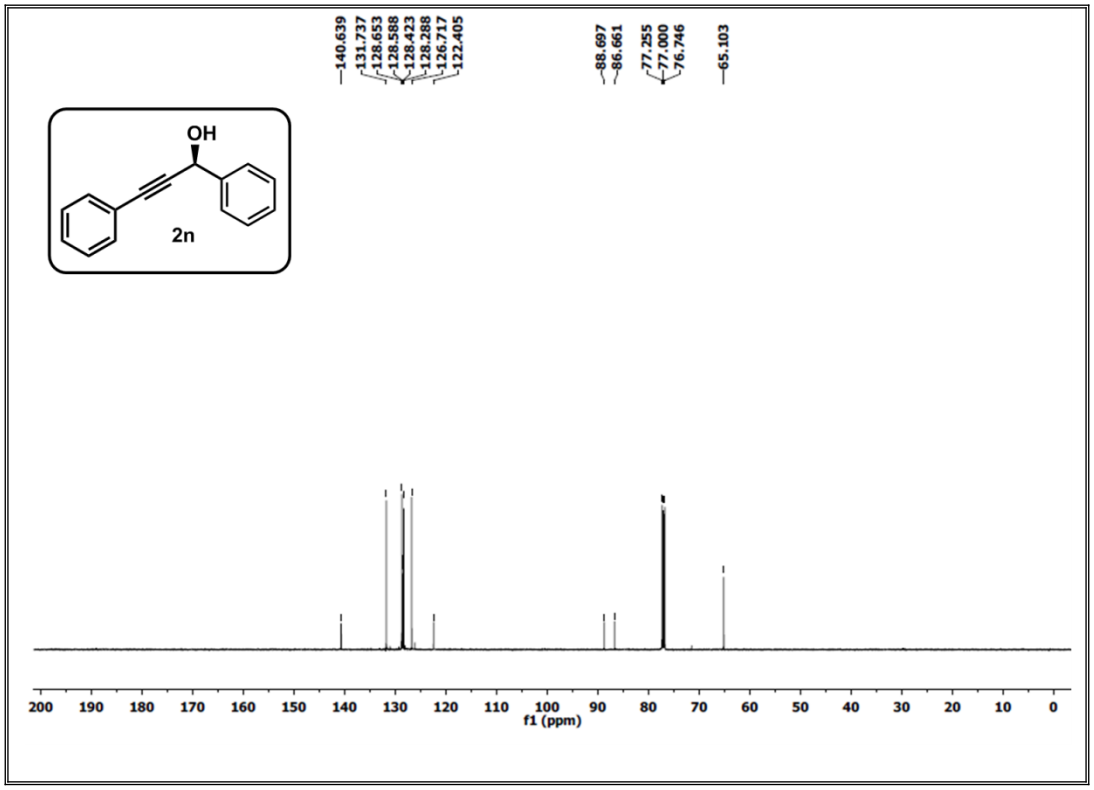
^{1}H NMR of **2m** (500 MHz, $CDCl_3$)



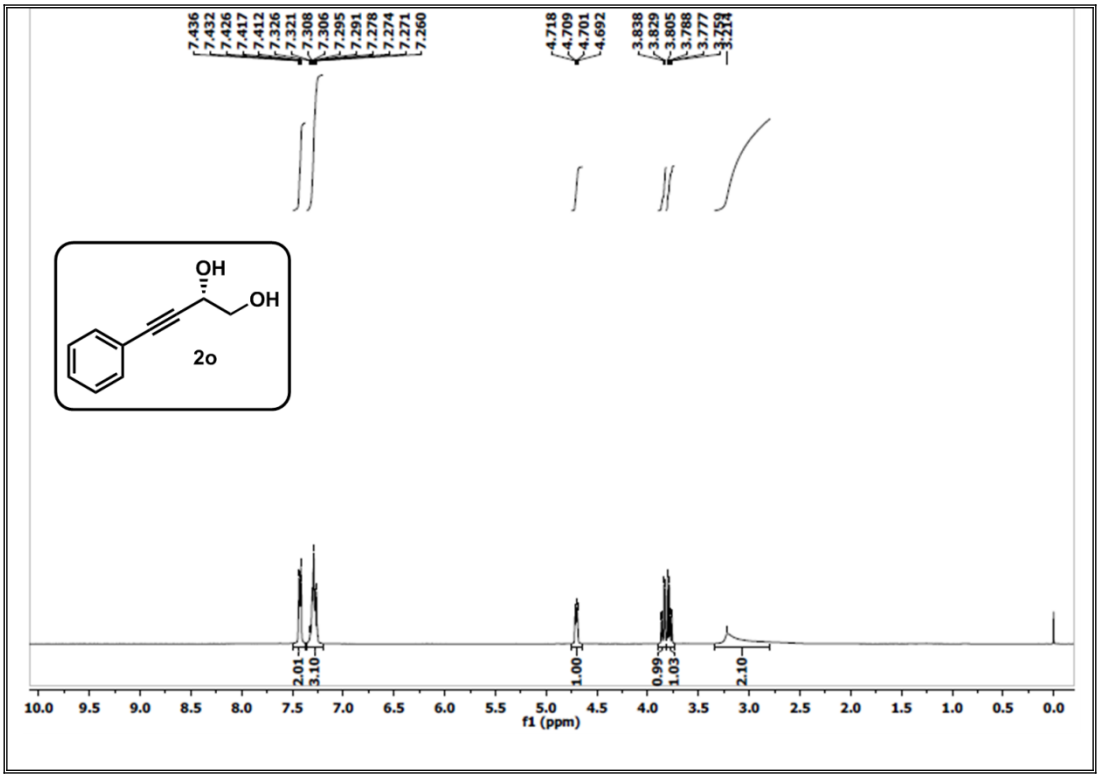
^{13}C NMR of **2m** (125 MHz, $CDCl_3$)



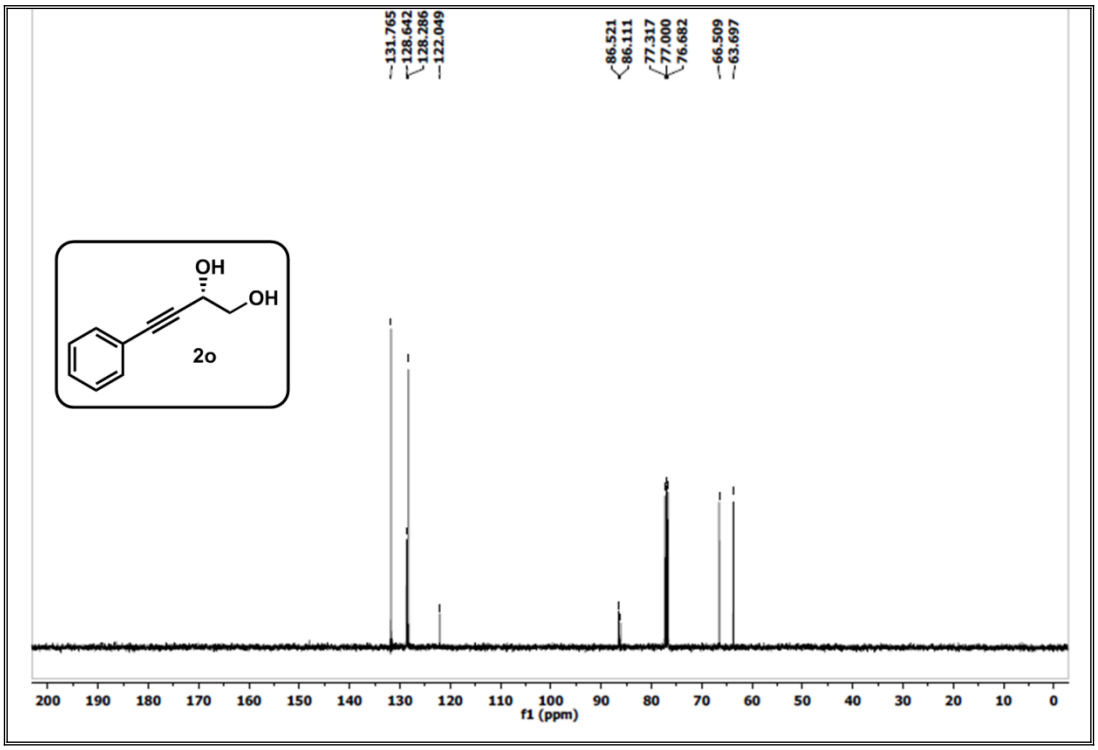
^{1}H NMR of **2n** (500 MHz, $CDCl_3$)



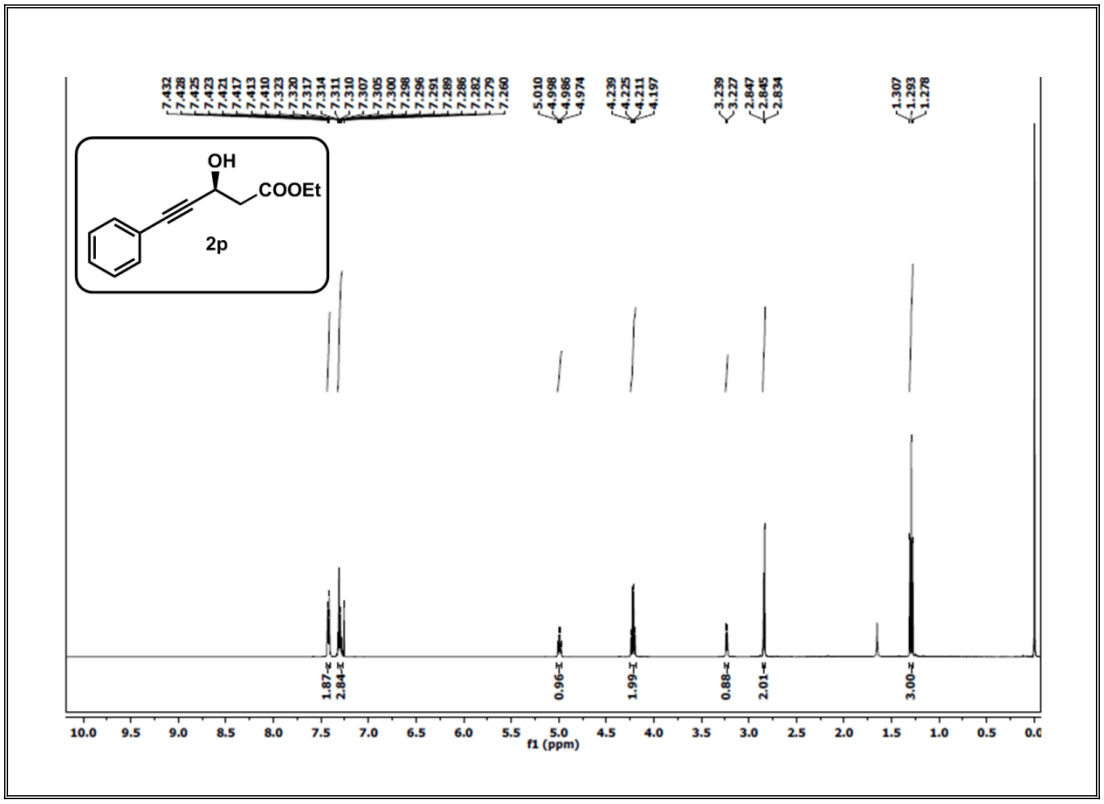
^{13}C NMR of **2n** (125 MHz, $CDCl_3$)



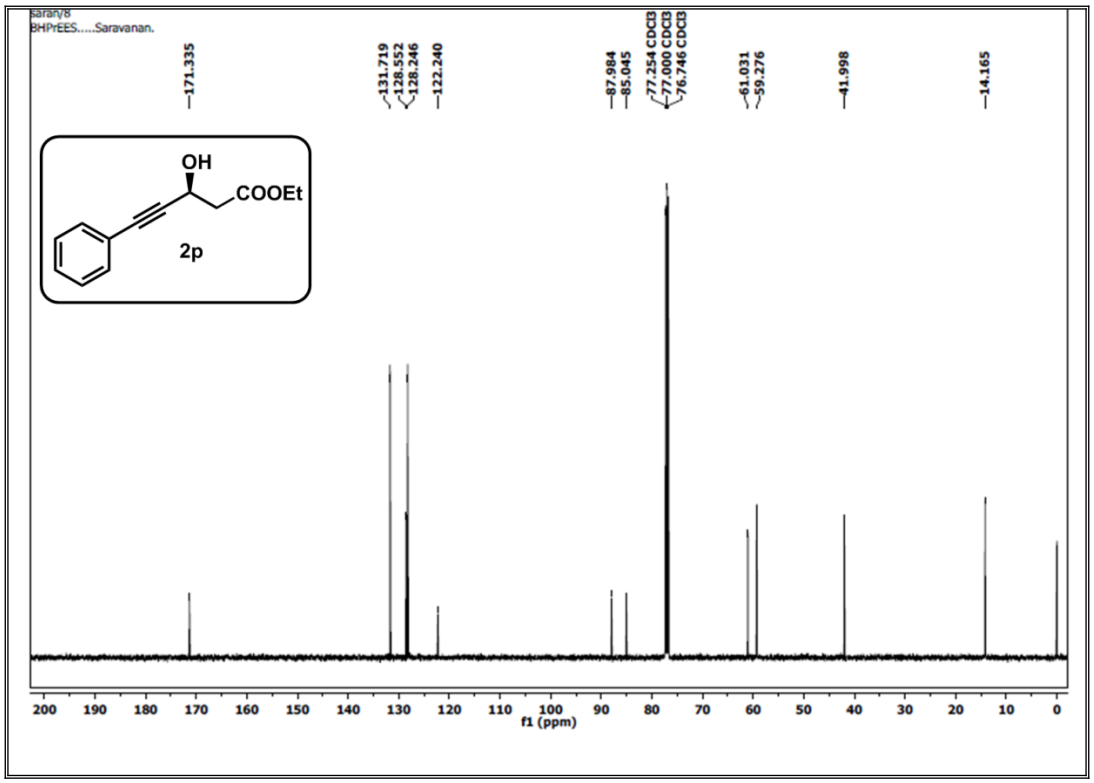
^{1}H NMR of **2o** (400 MHz, $CDCl_3$)



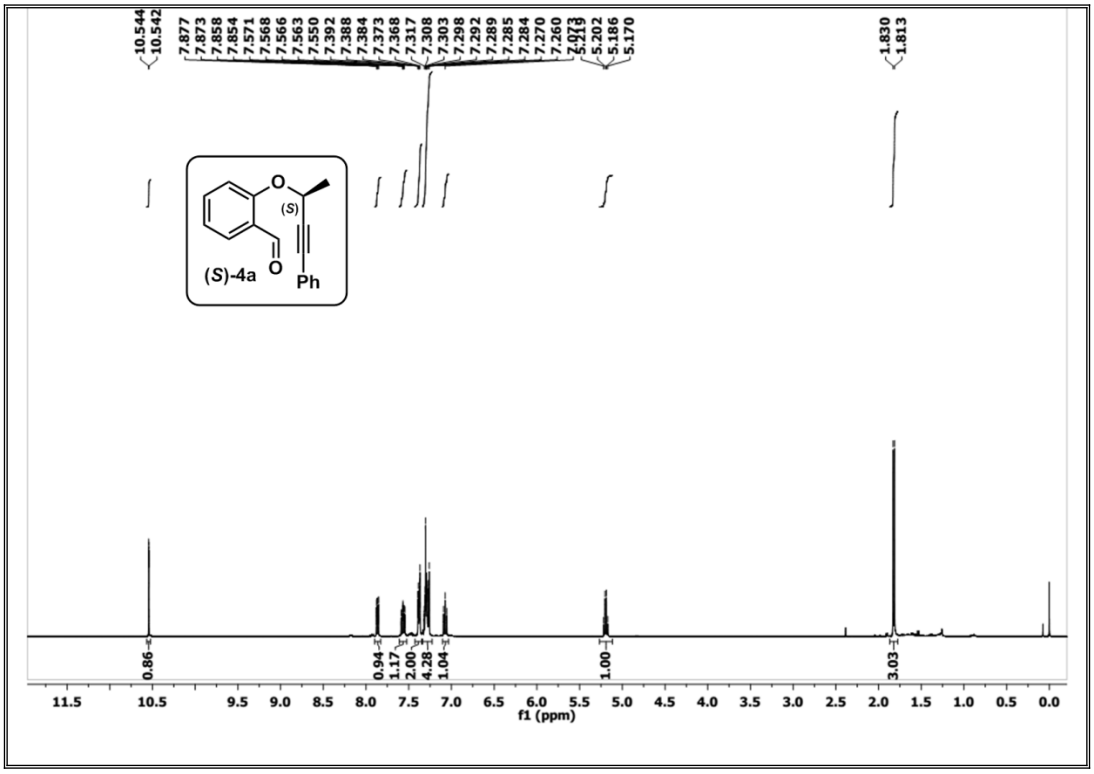
^{13}C NMR of **2o** (100 MHz, $CDCl_3$)



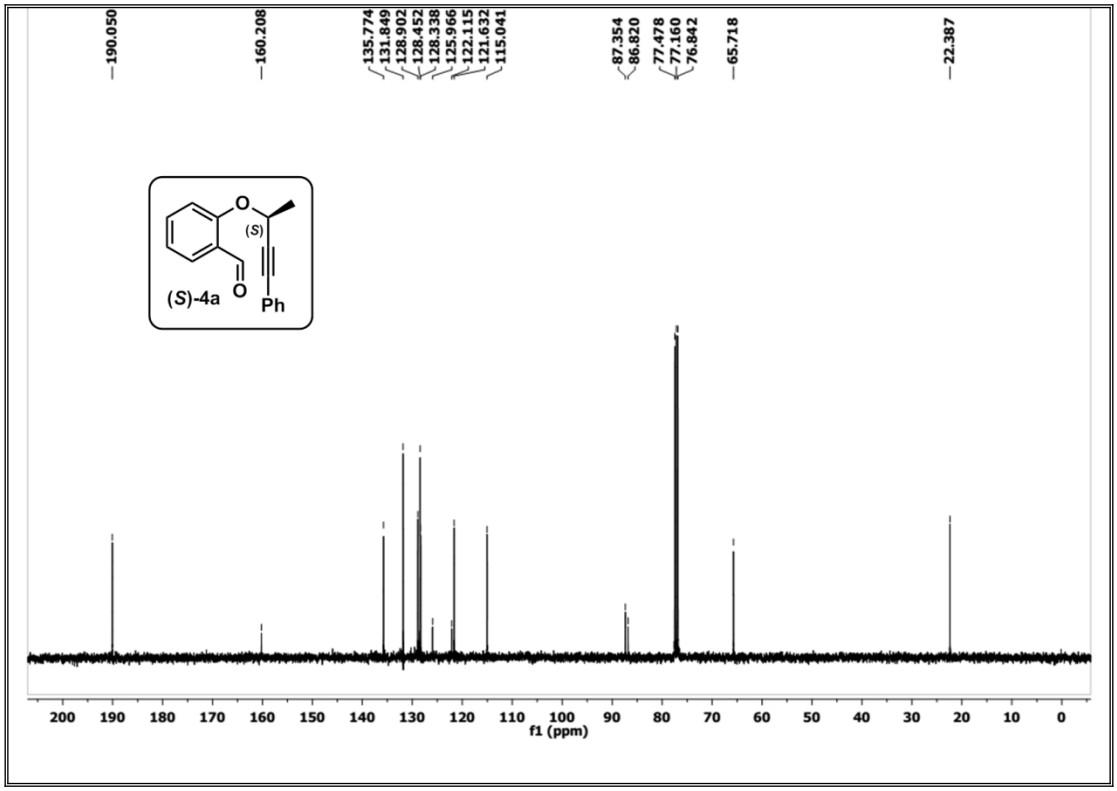
^{1}H NMR of **2p** (500 MHz, $CDCl_3$)



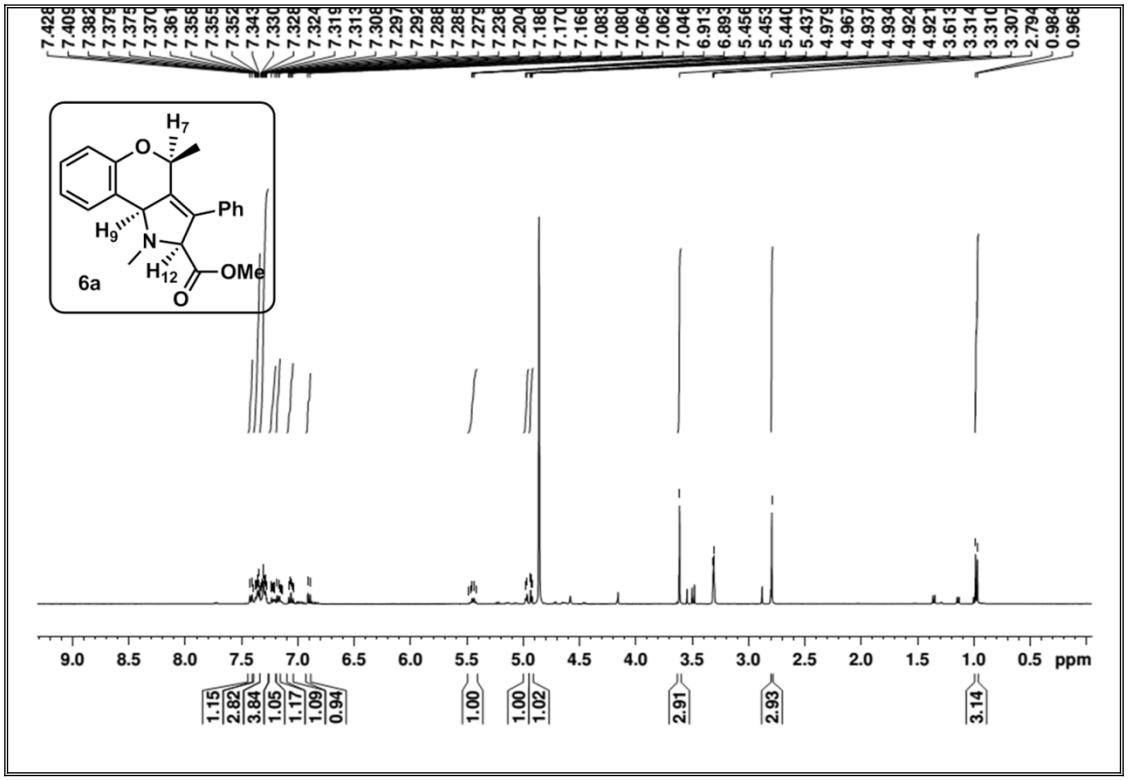
^{13}C NMR of **2p** (125 MHz, $CDCl_3$)



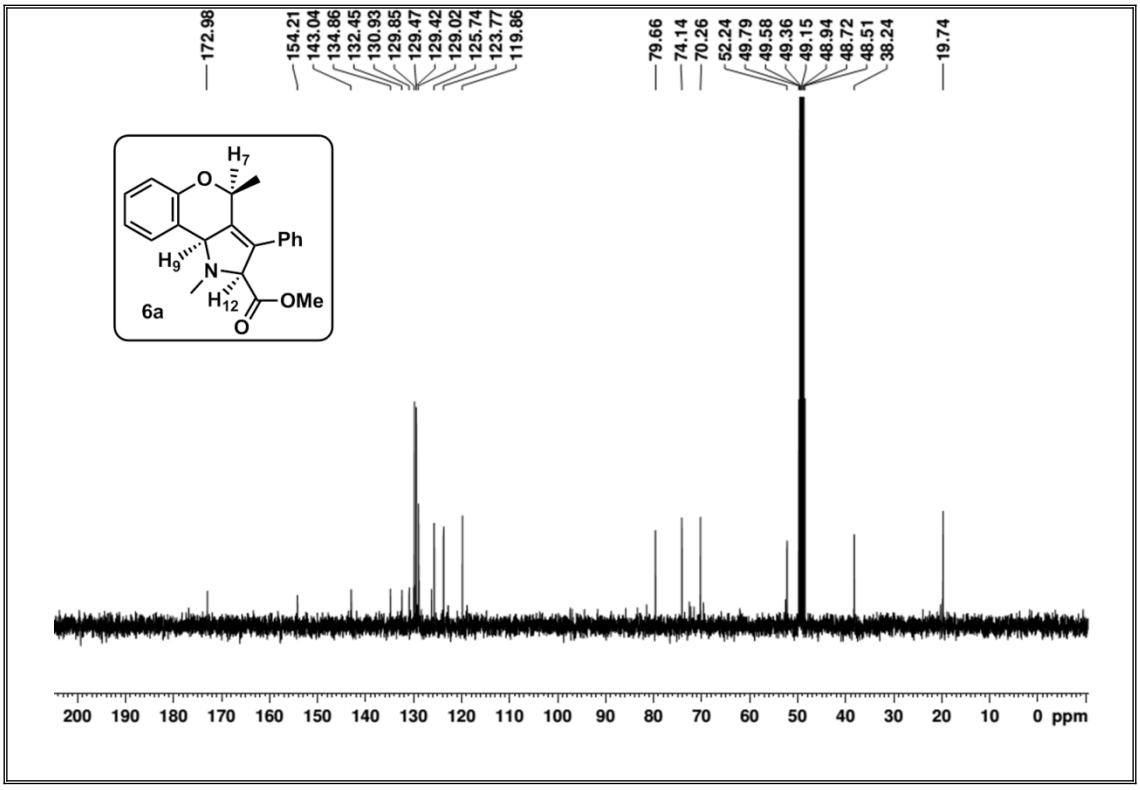
^{1}H NMR of **4a** (400 MHz, $CDCl_3$)



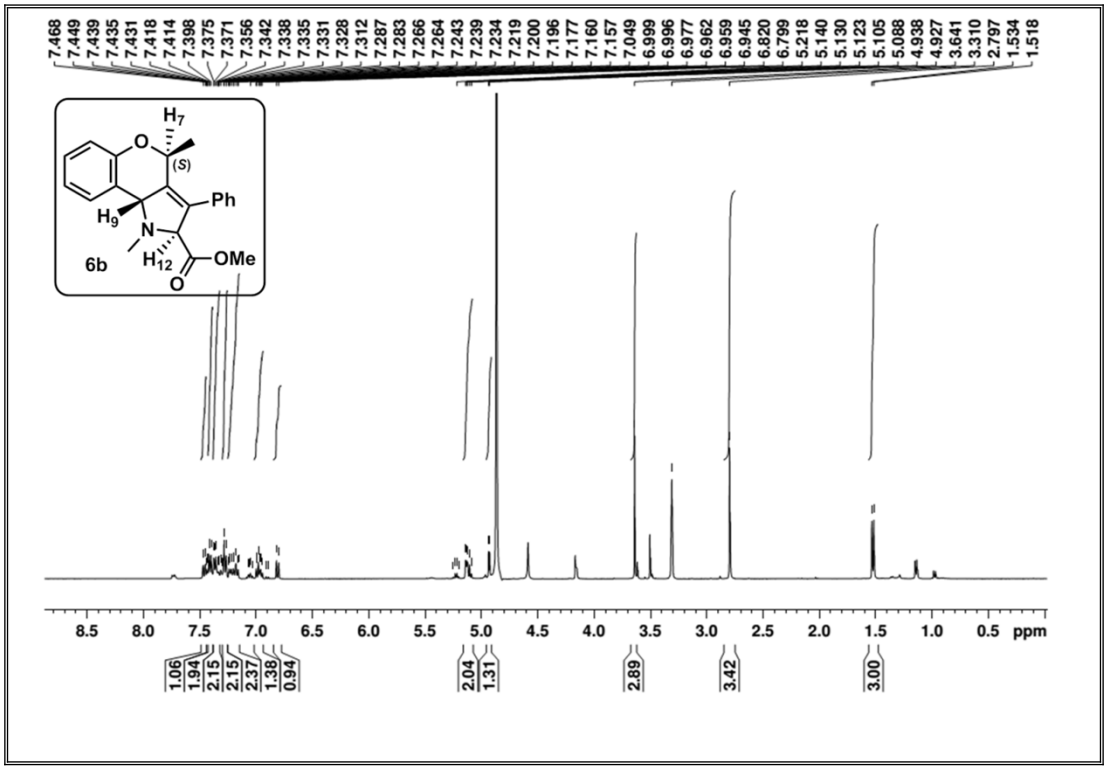
^{13}C NMR of **4a** (100 MHz, $CDCl_3$)



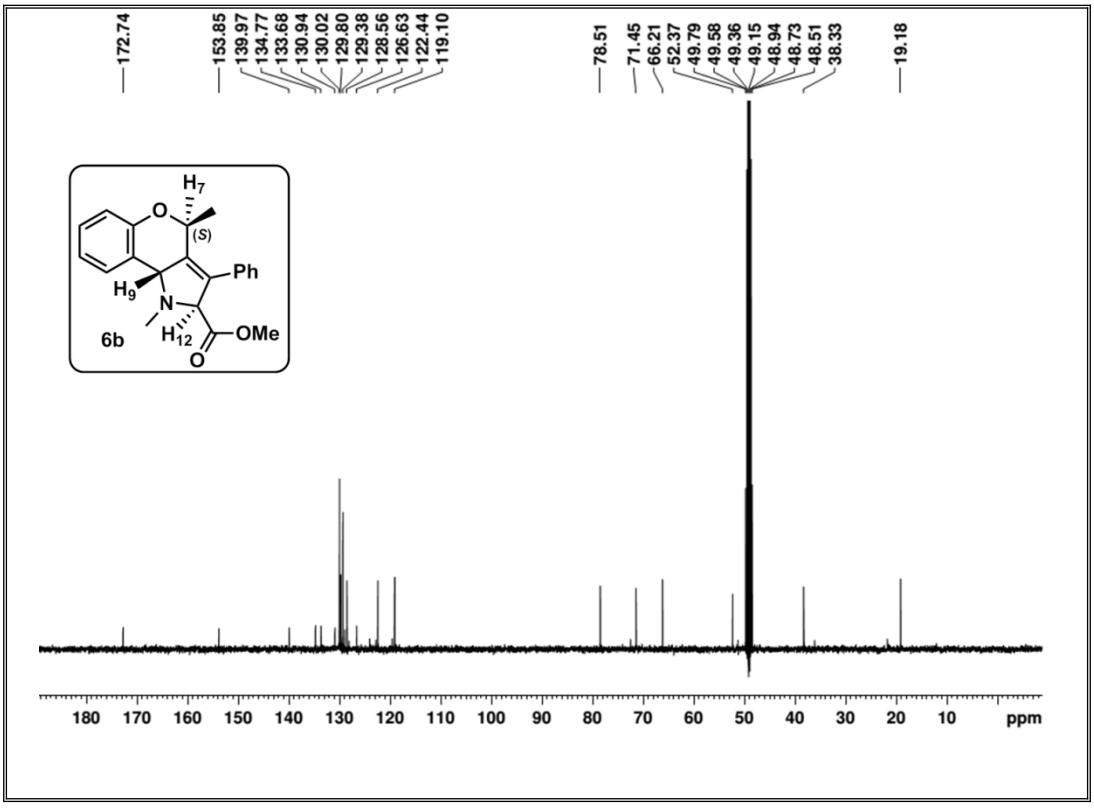
^{1}H NMR of **6a** (400 MHz, CD_3OD_3)



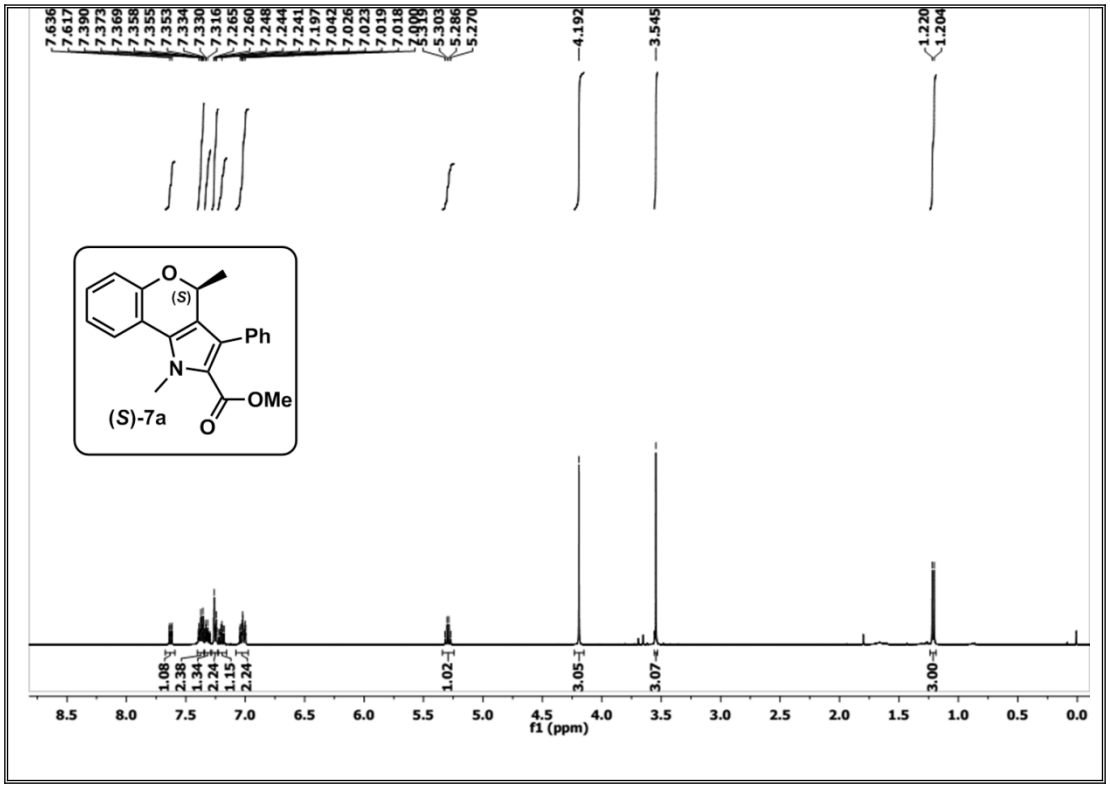
^{13}C NMR of **6a** (100 MHz, CD_3OD)



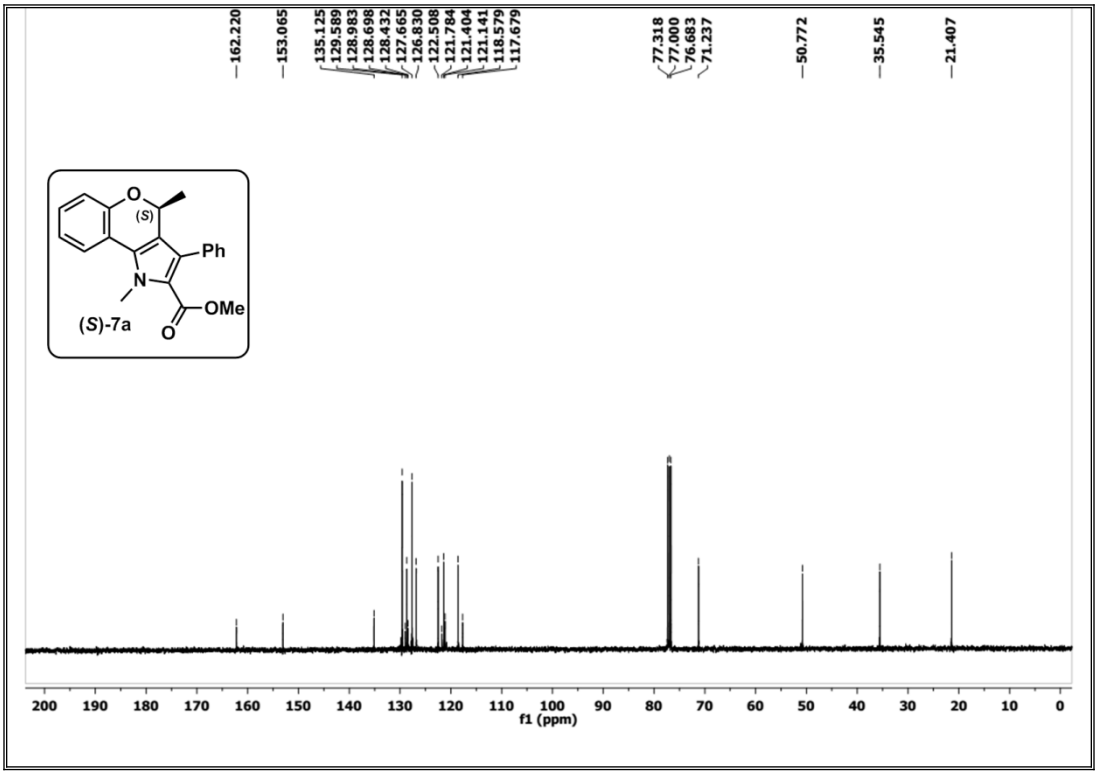
^{1}H NMR of **6b** (400 MHz, CD_3OD)



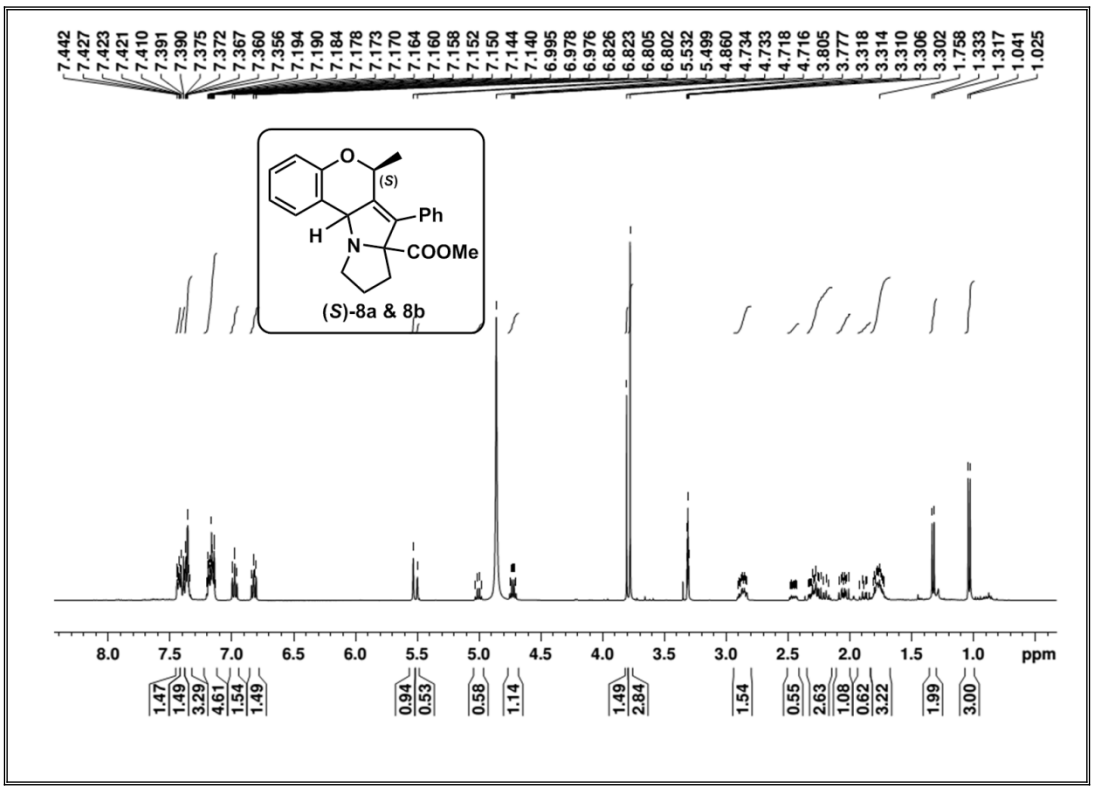
^{13}C NMR of **6b** (100 MHz, CD_3OD)



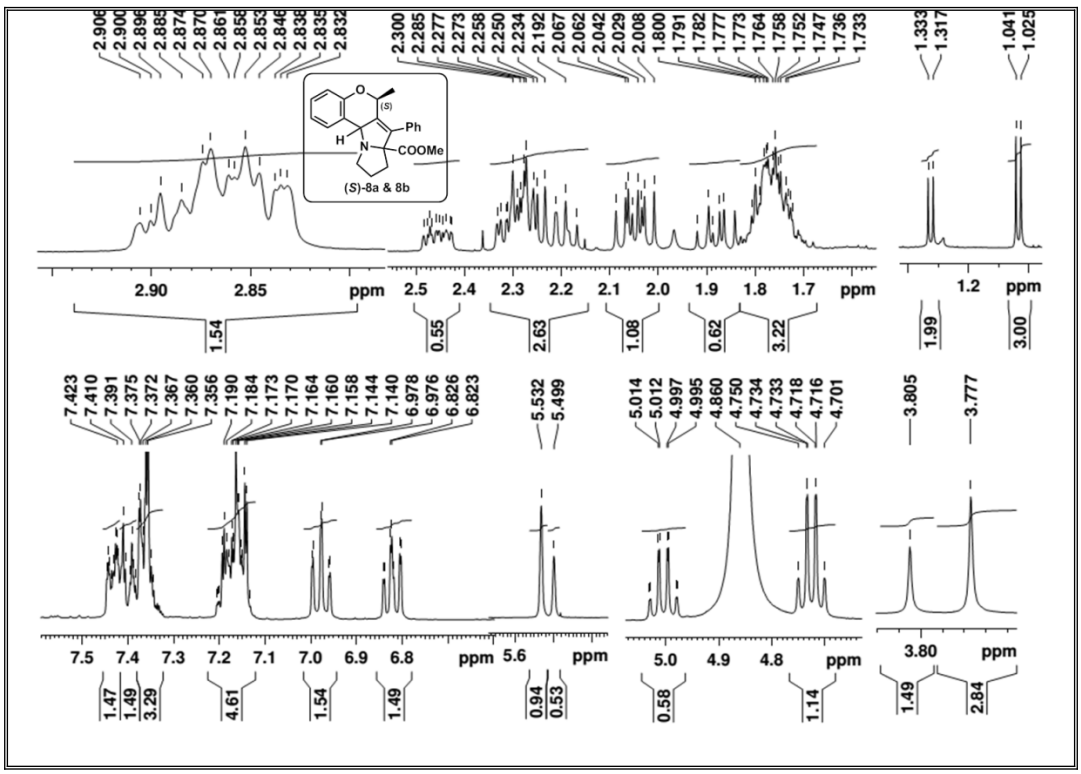
^{1}H NMR of **7a** (400 MHz, $CDCl_3$)



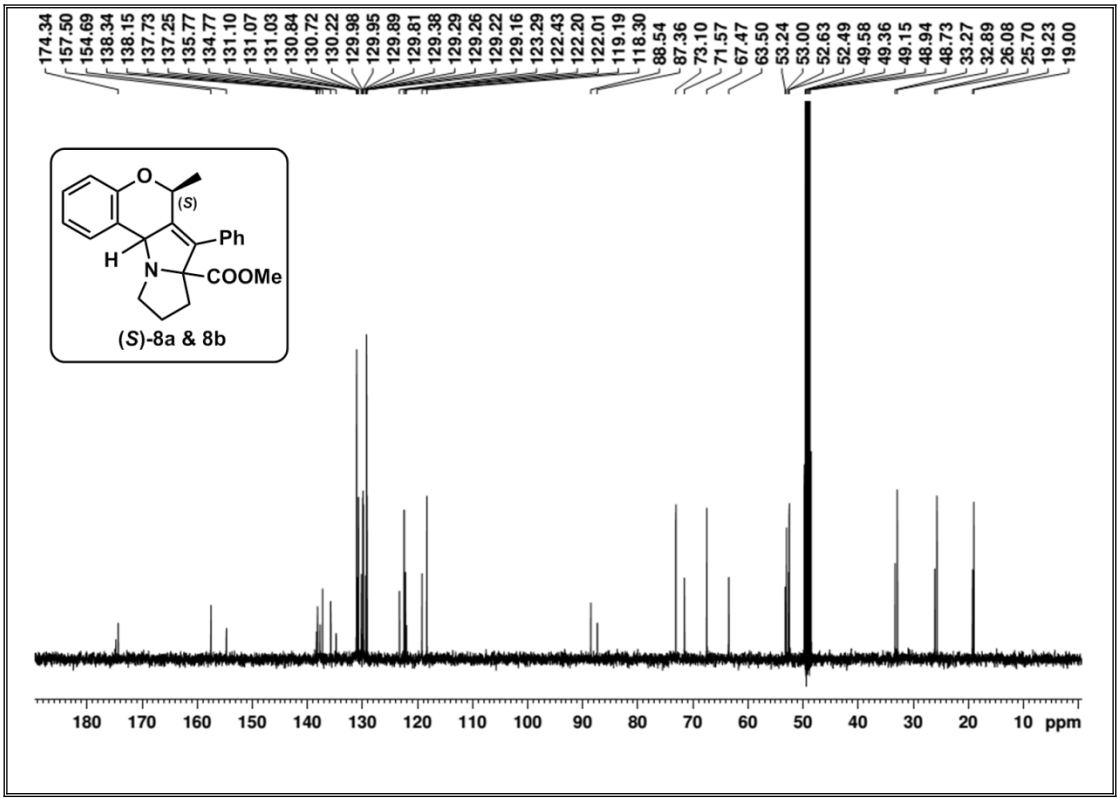
^{13}C NMR of **7a** (100 MHz, $CDCl_3$)



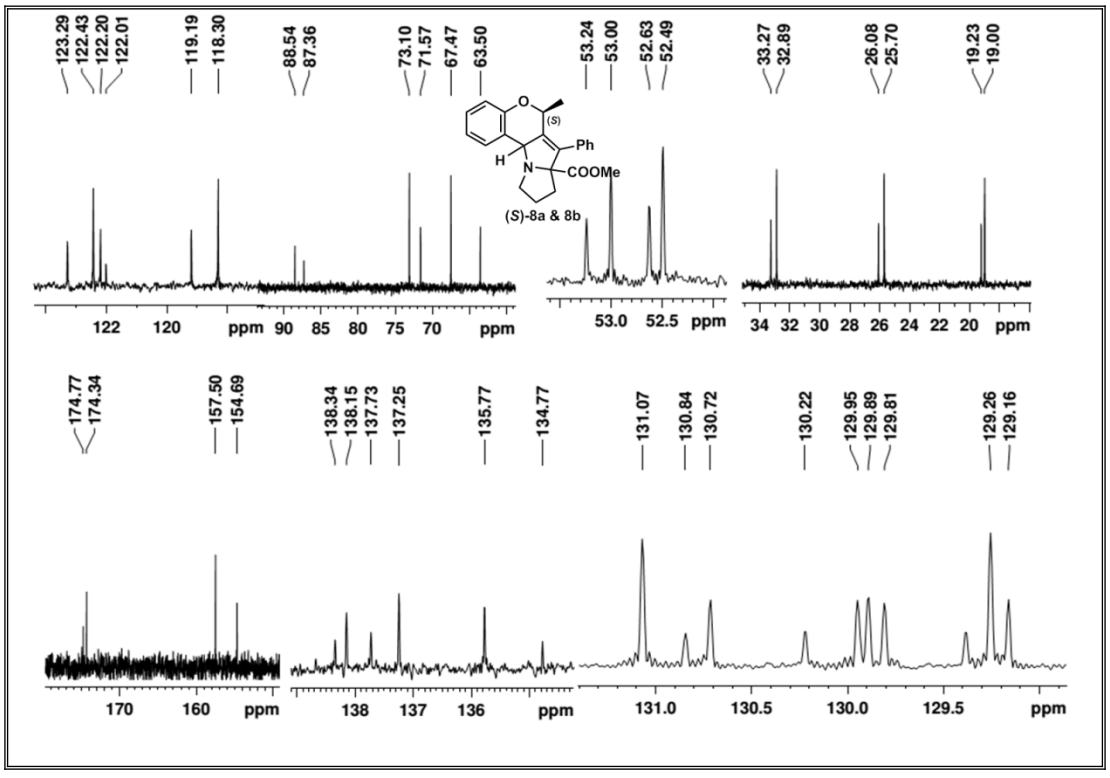
^{1}H NMR of **8a** & **8b** (400 MHz, CD_3OD)



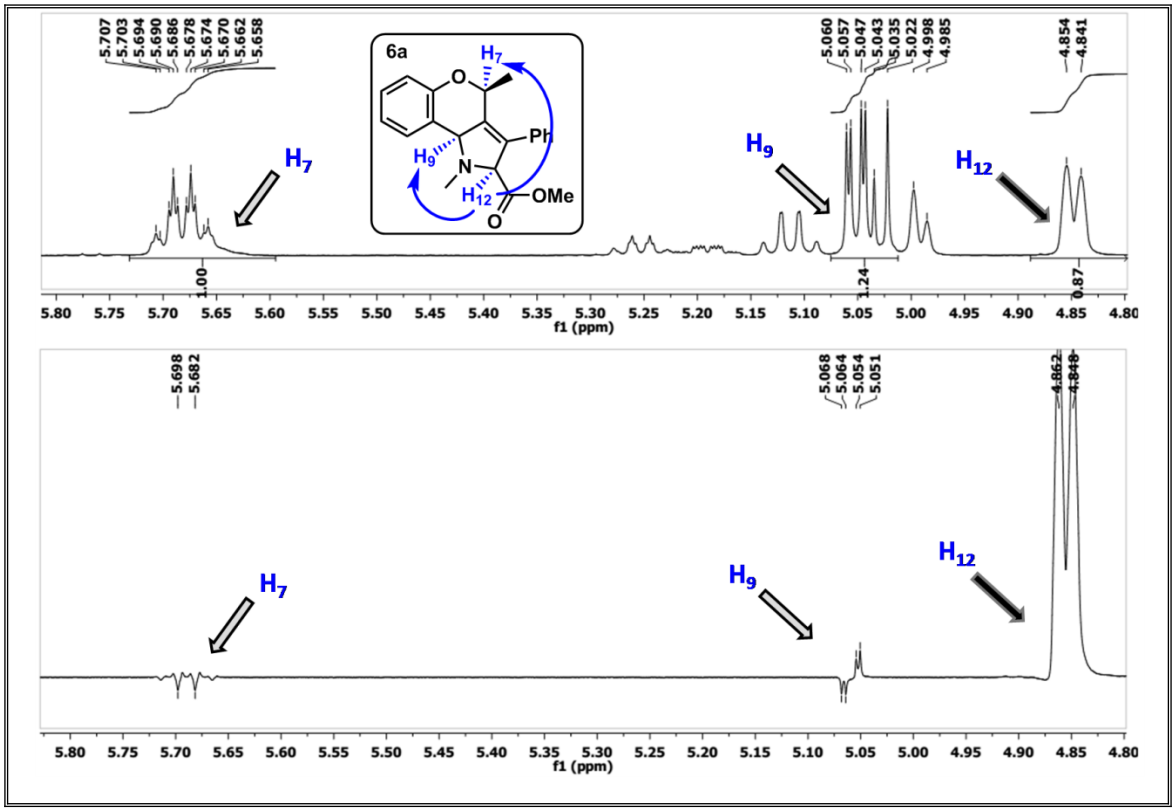
^{1}H NMR expansion of **8a** & **8b** (400 MHz, CD_3OD)



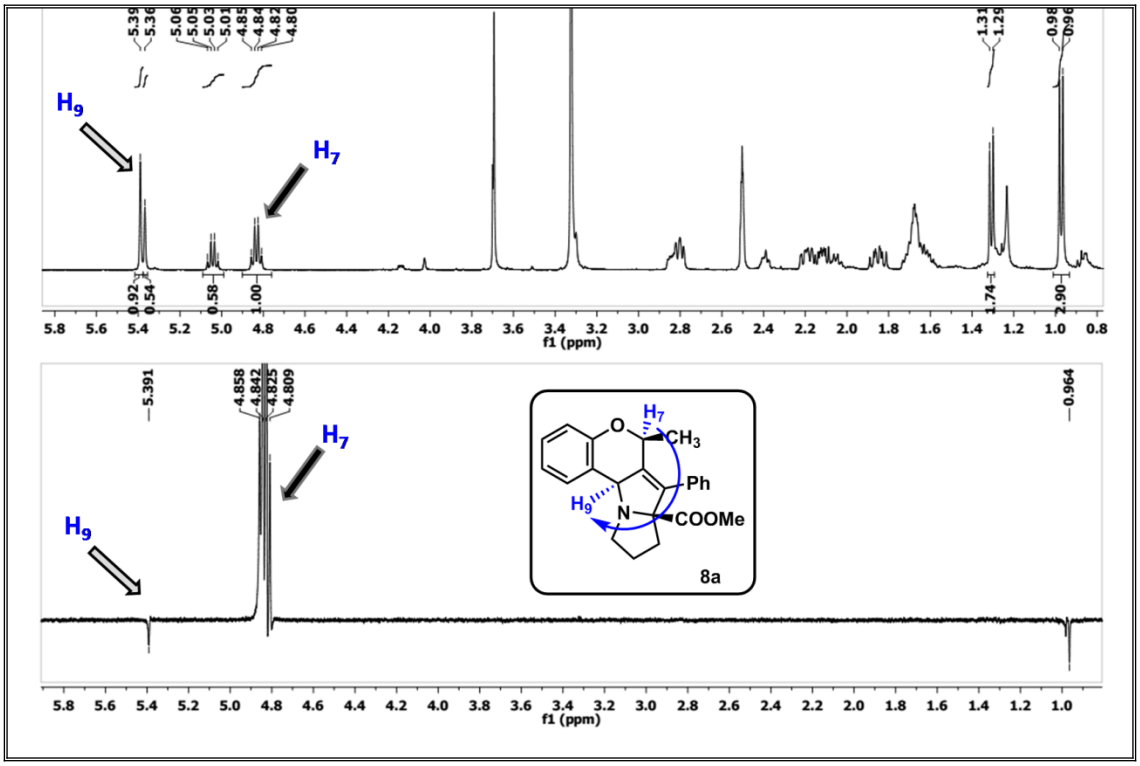
^{13}C NMR of **8a** & **8b** (100 MHz, CD_3OD)



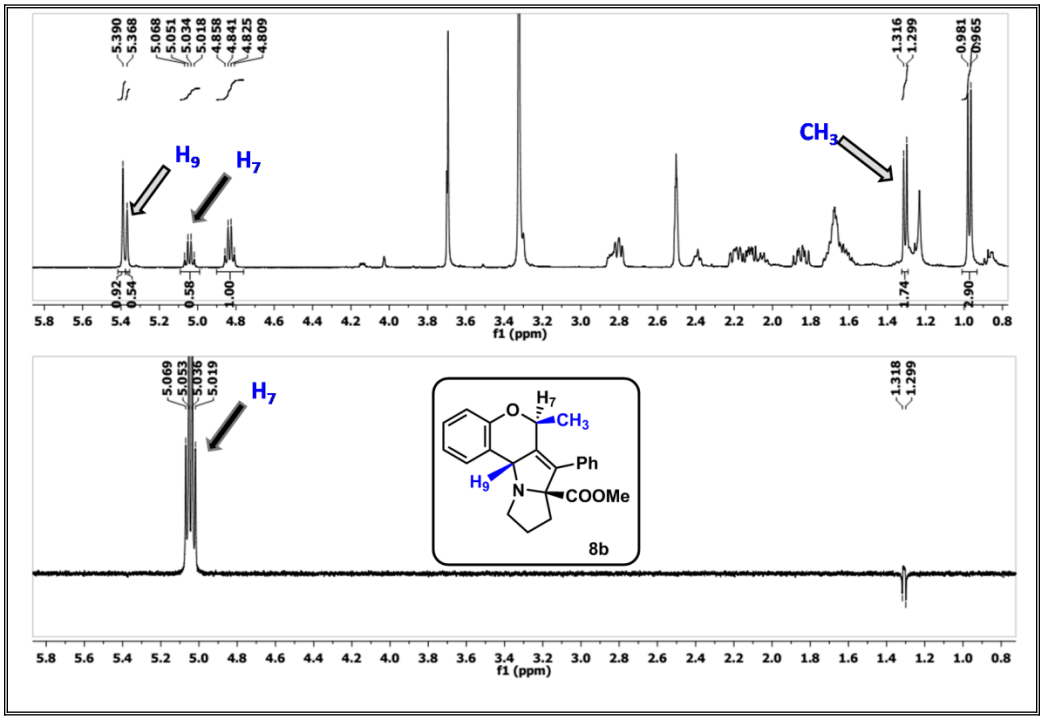
^{13}C NMR expansion of **8a** & **8b** (100 MHz, CD_3OD)



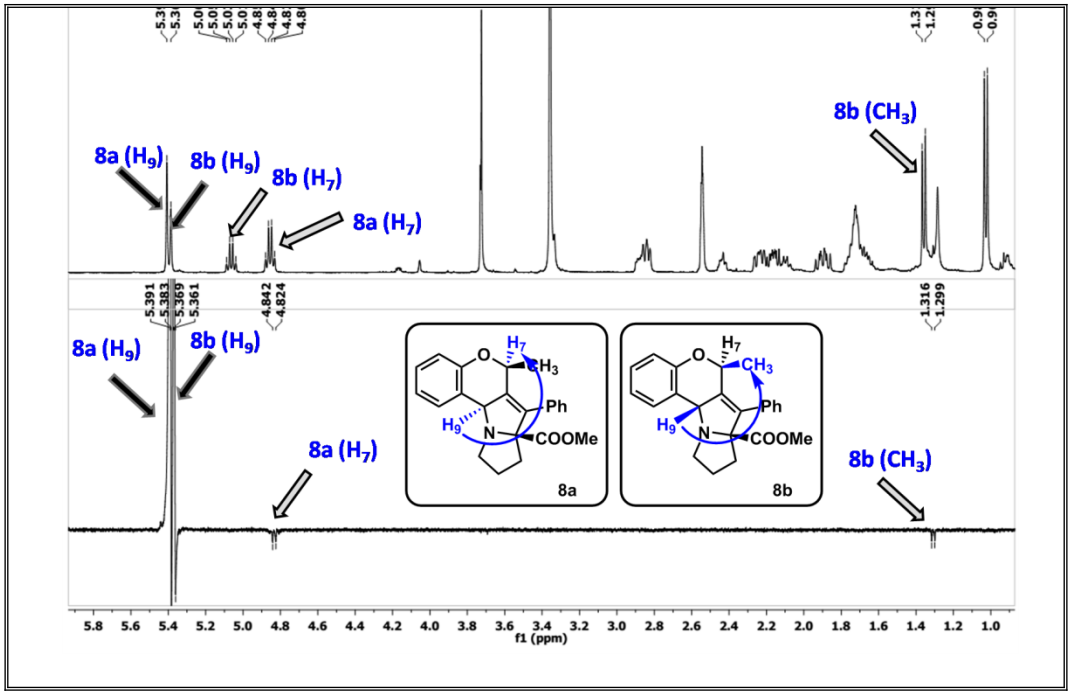
NOE spectra NMR of **6a** (400 MHz, DMSO-D6)



NOE spectra NMR of **8a** (400 MHz, DMSO-D6)

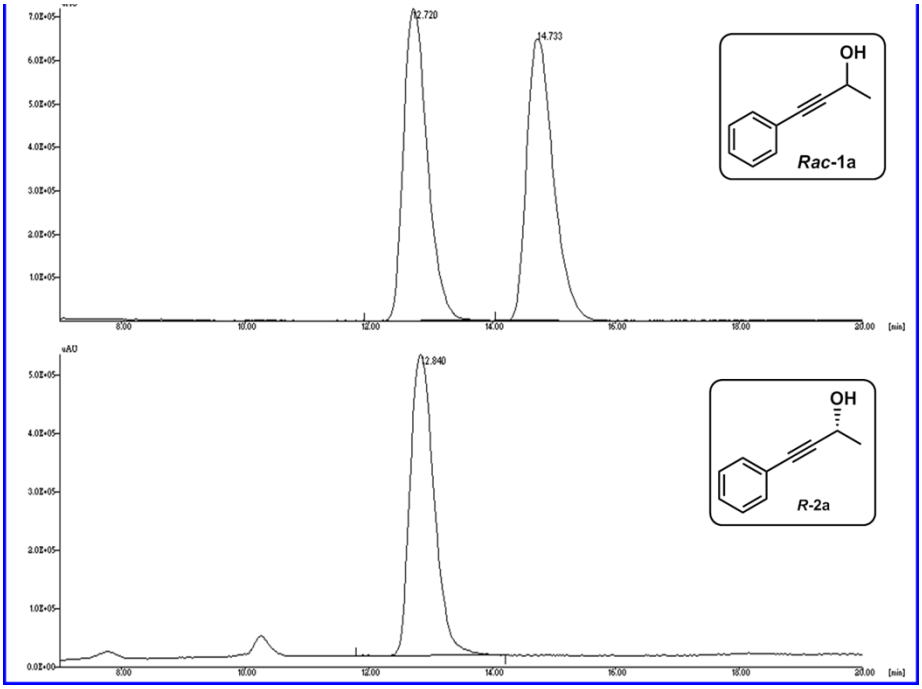


NOE spectra NMR of **8b** (400 MHz, DMSO-D6)

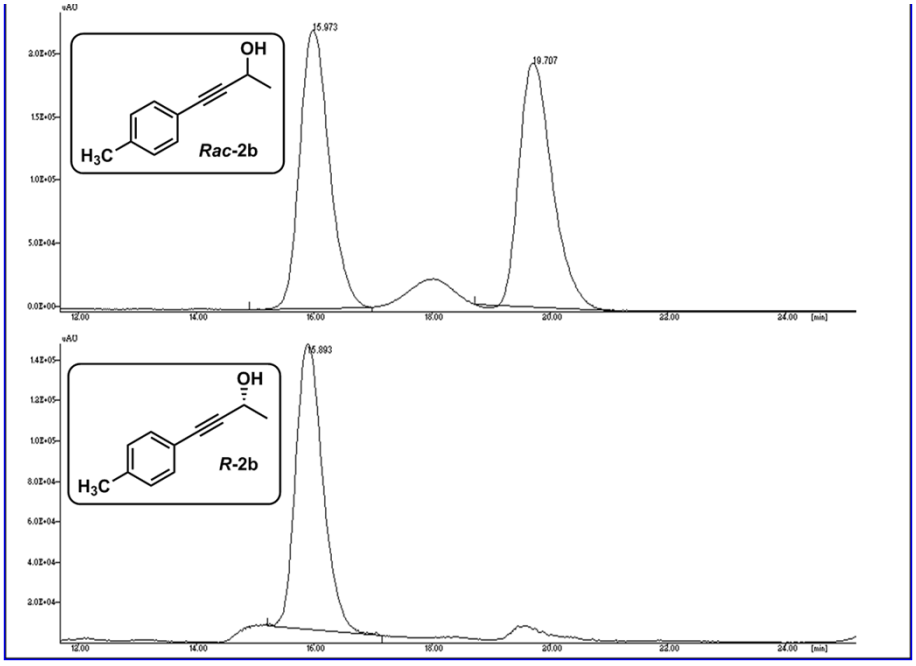


NOE spectra NMR of **8a** & **8b** (400 MHz, DMSO-D6)

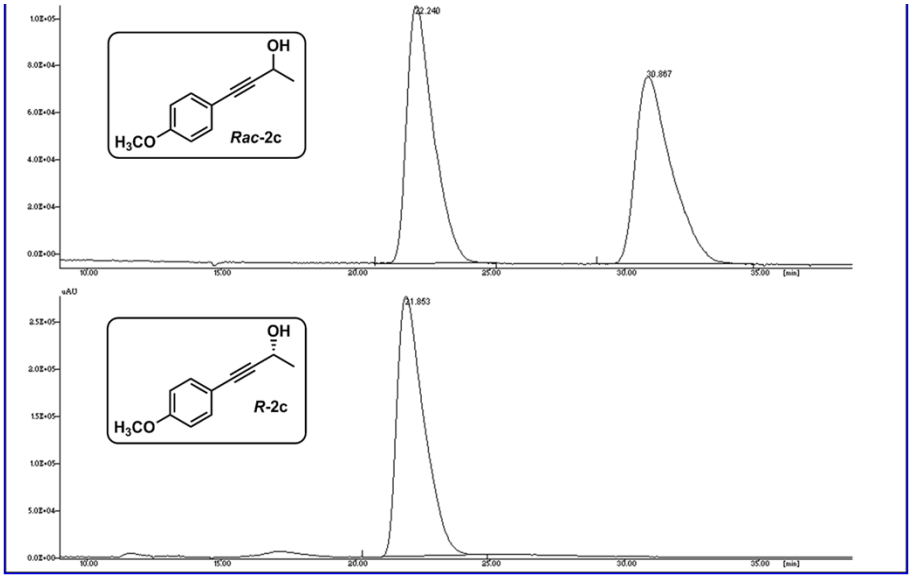
HPLC CHROMATOGRAM



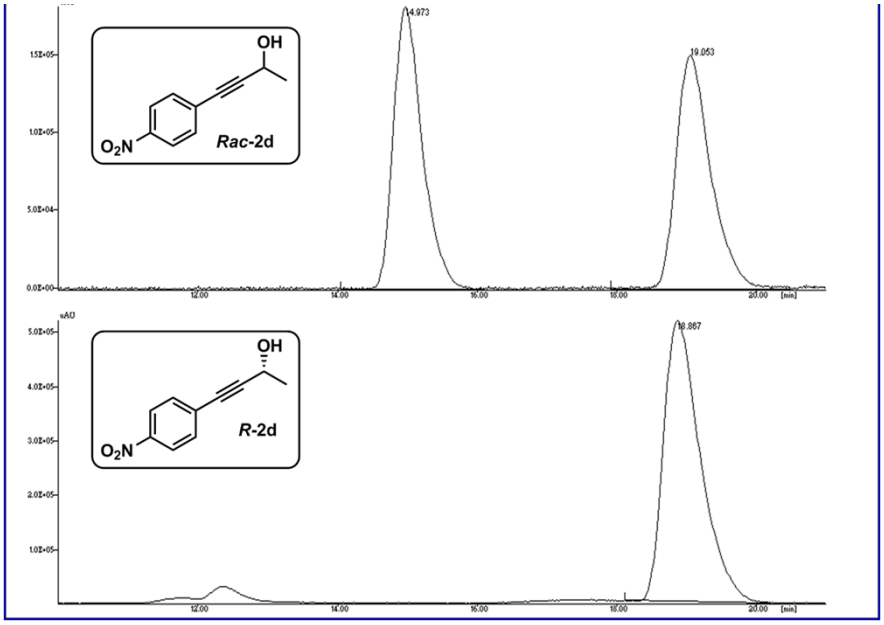
HPLC chromatogram of **2a**



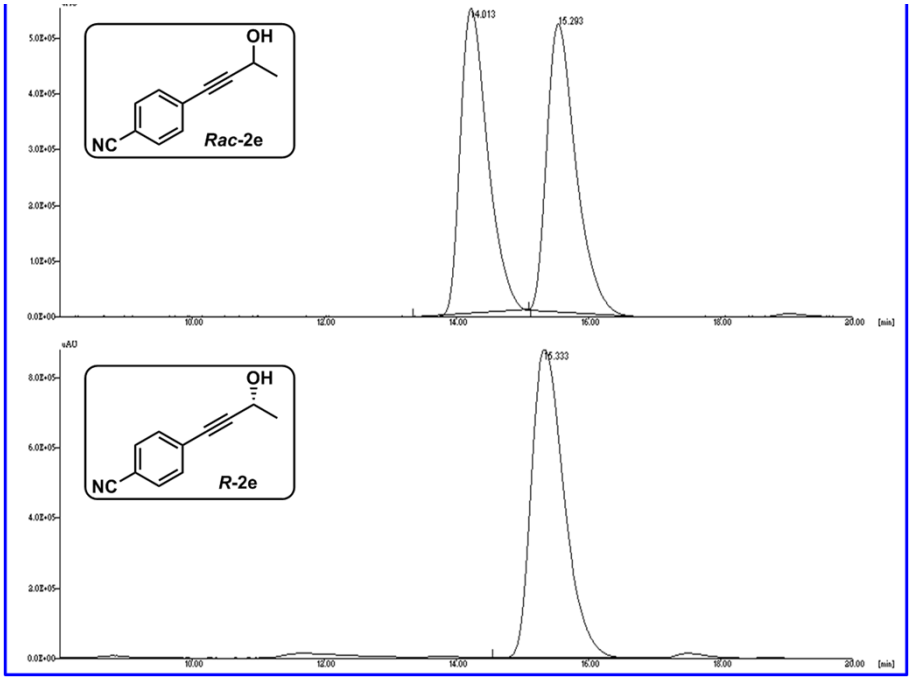
HPLC chromatogram of **2b**



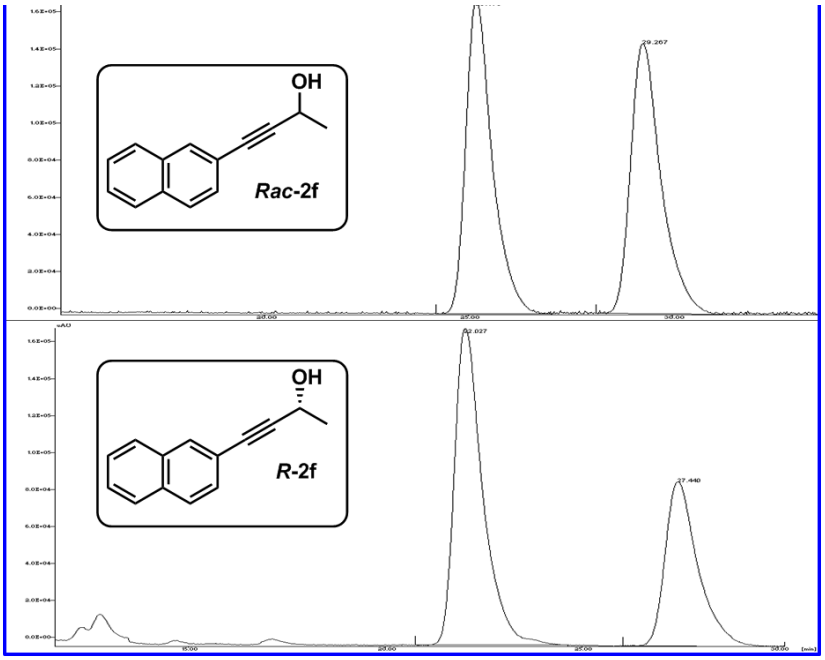
HPLC chromatogram of **2c**



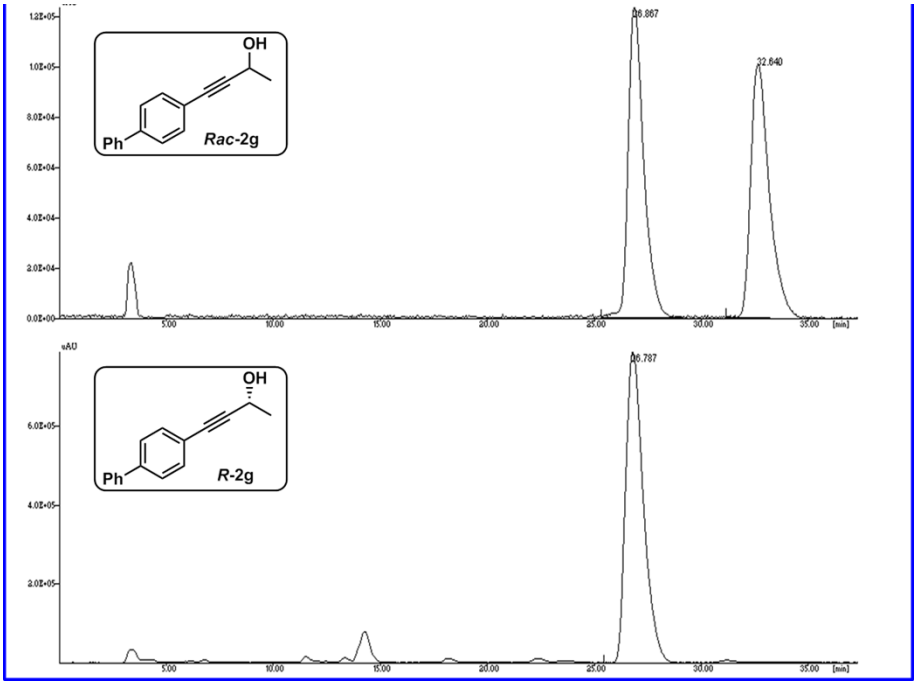
HPLC chromatogram of **2d**



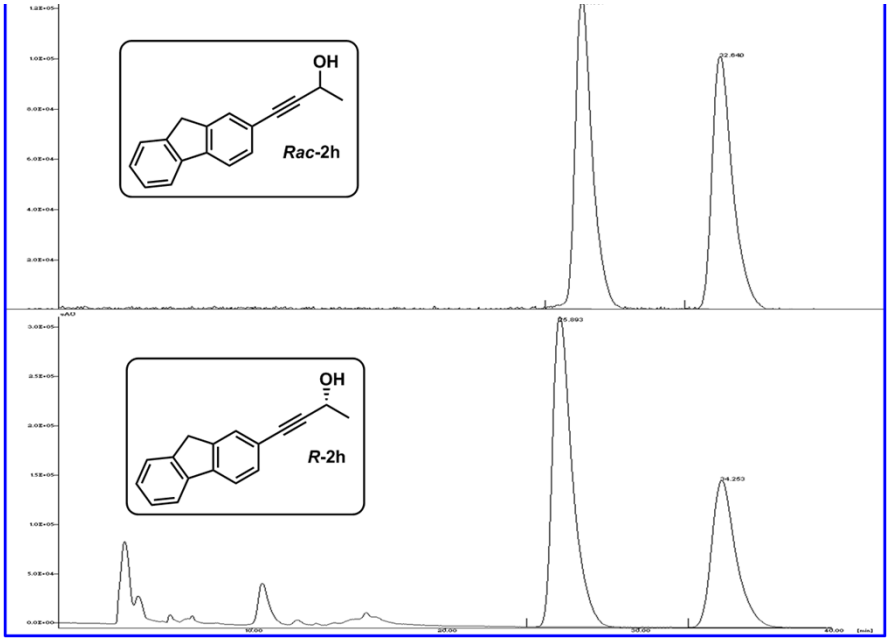
HPLC chromatogram of **2e**



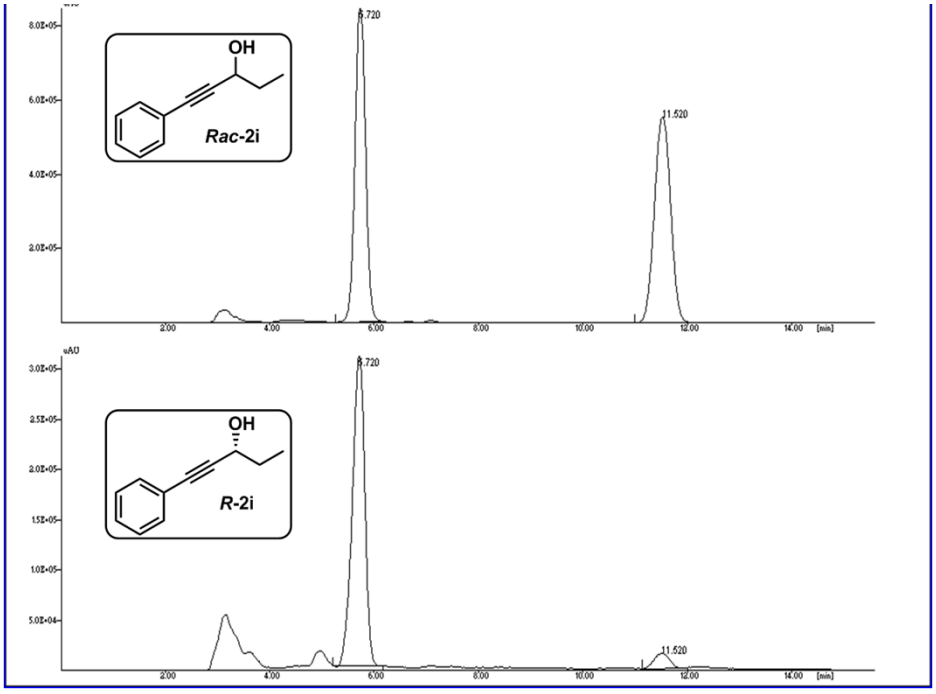
HPLC chromatogram of **2f**



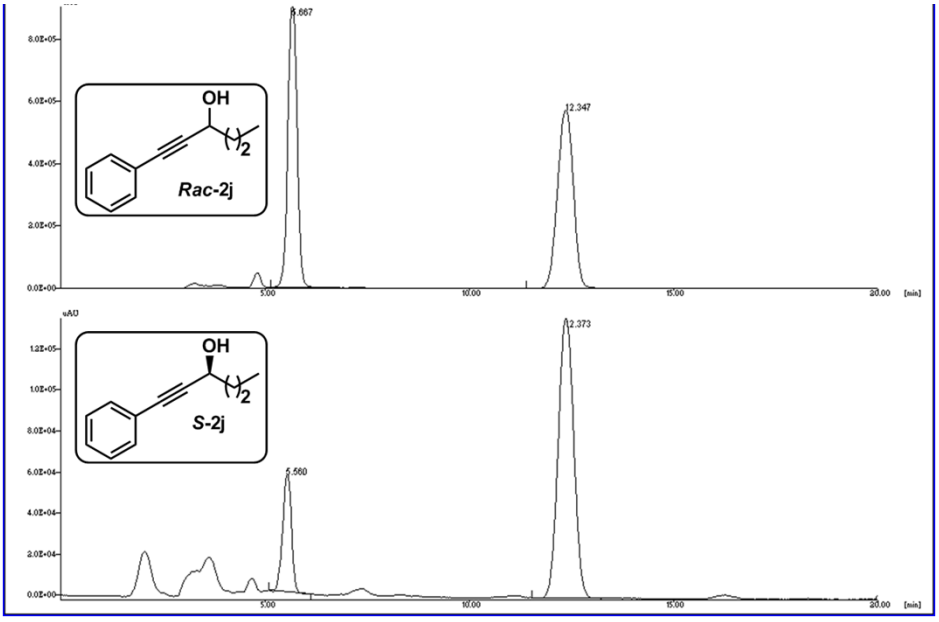
HPLC chromatogram of **2g**



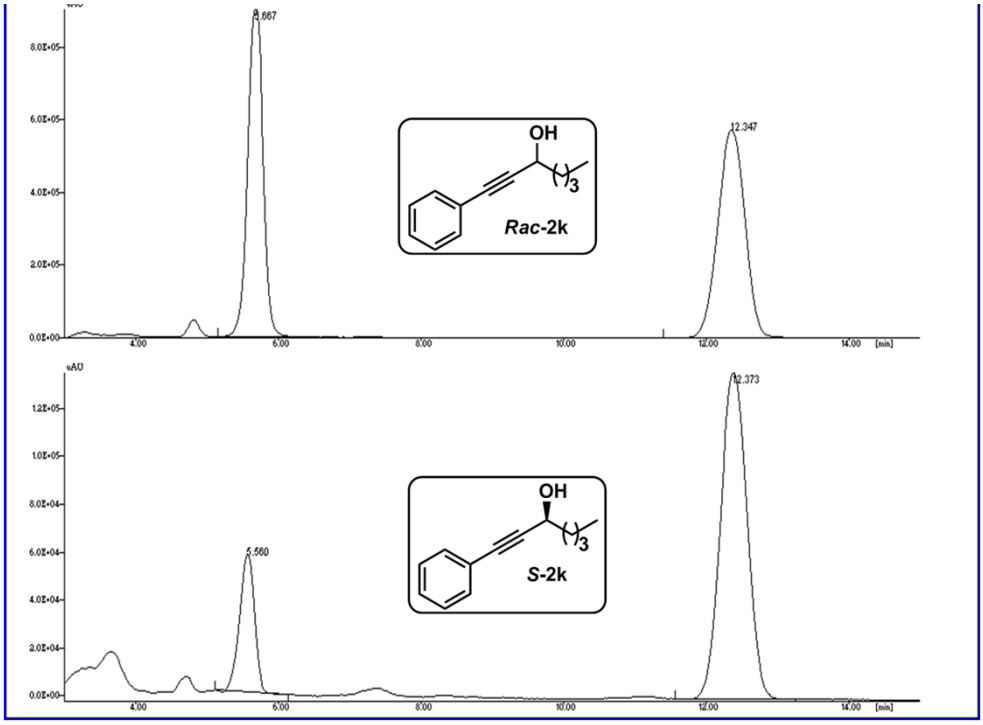
HPLC chromatogram of **2h**



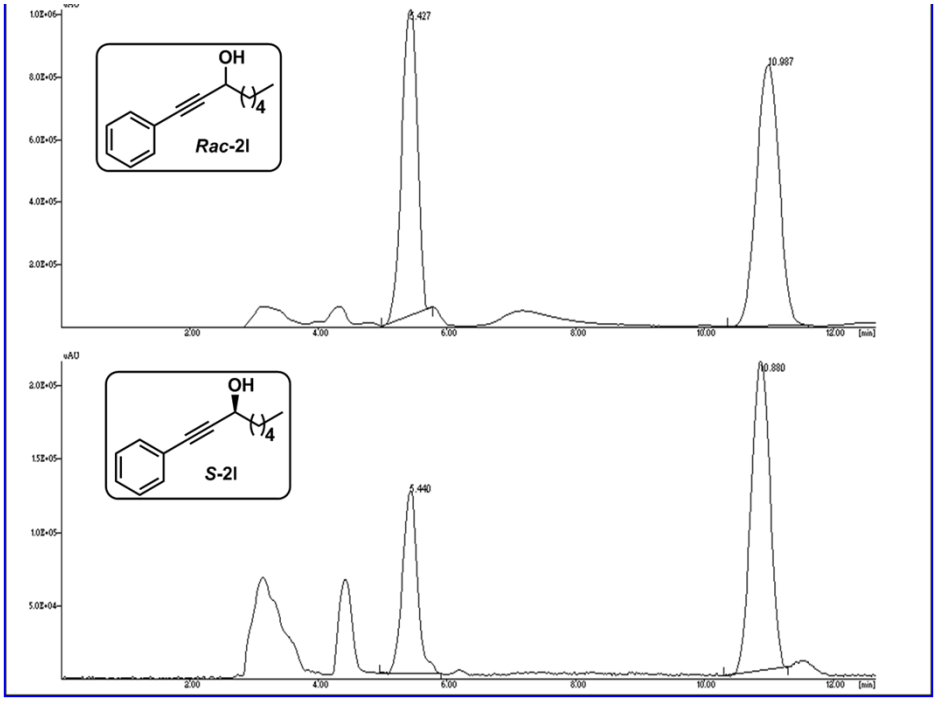
HPLC chromatogram of **2i**



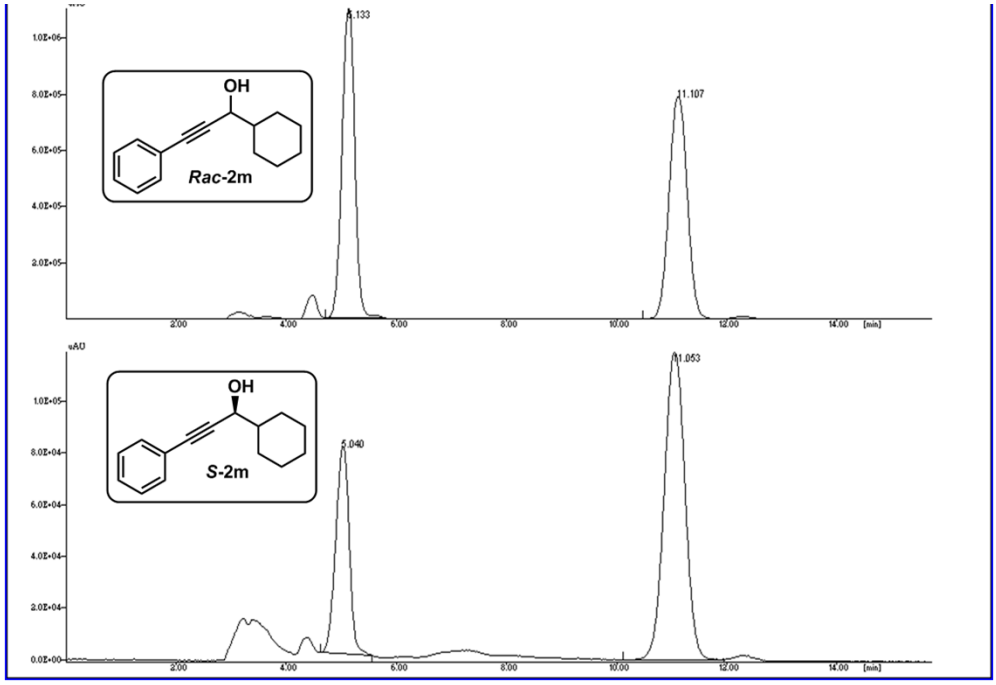
HPLC chromatogram of **2j**



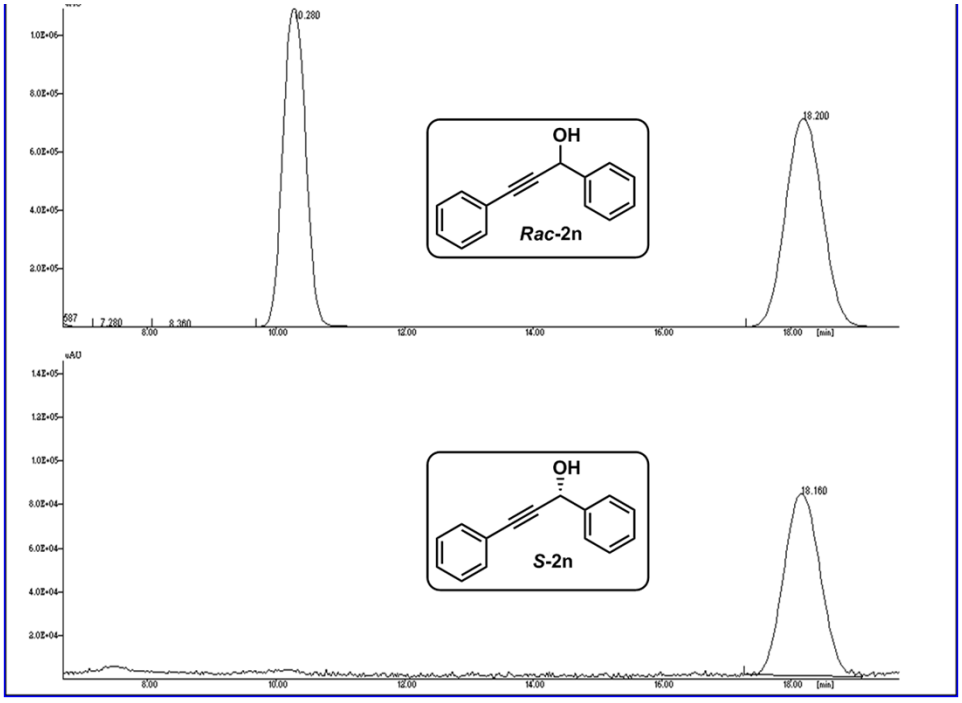
HPLC chromatogram of **2k**



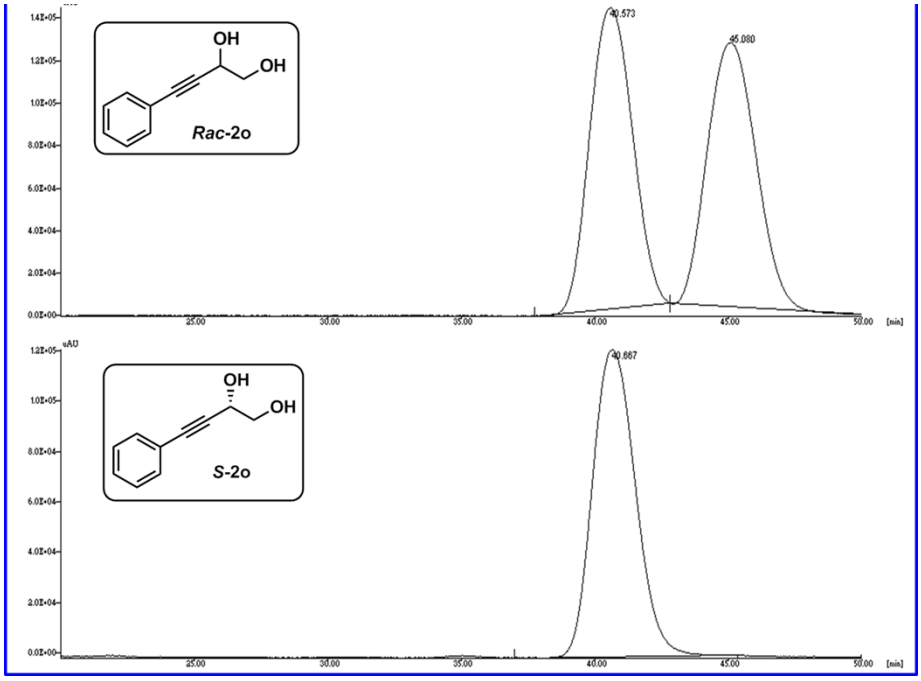
HPLC chromatogram of **2l**



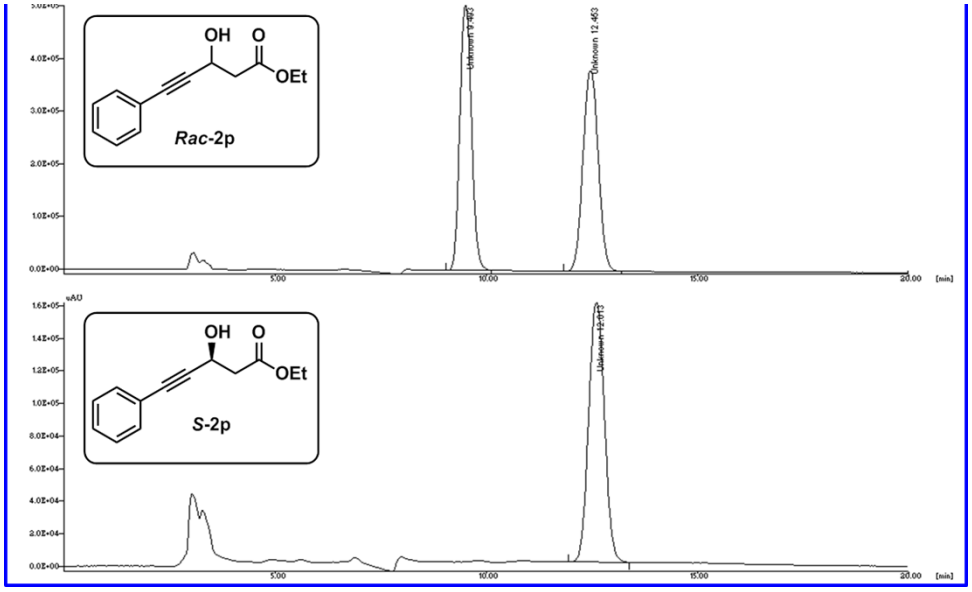
HPLC chromatogram of **2m**



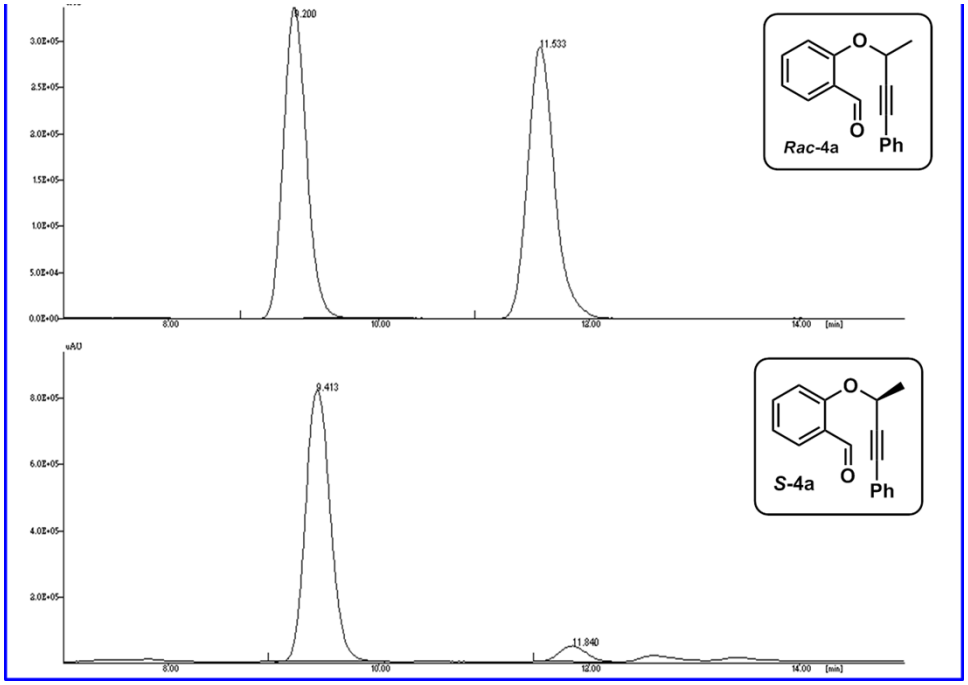
HPLC chromatogram of **2n**



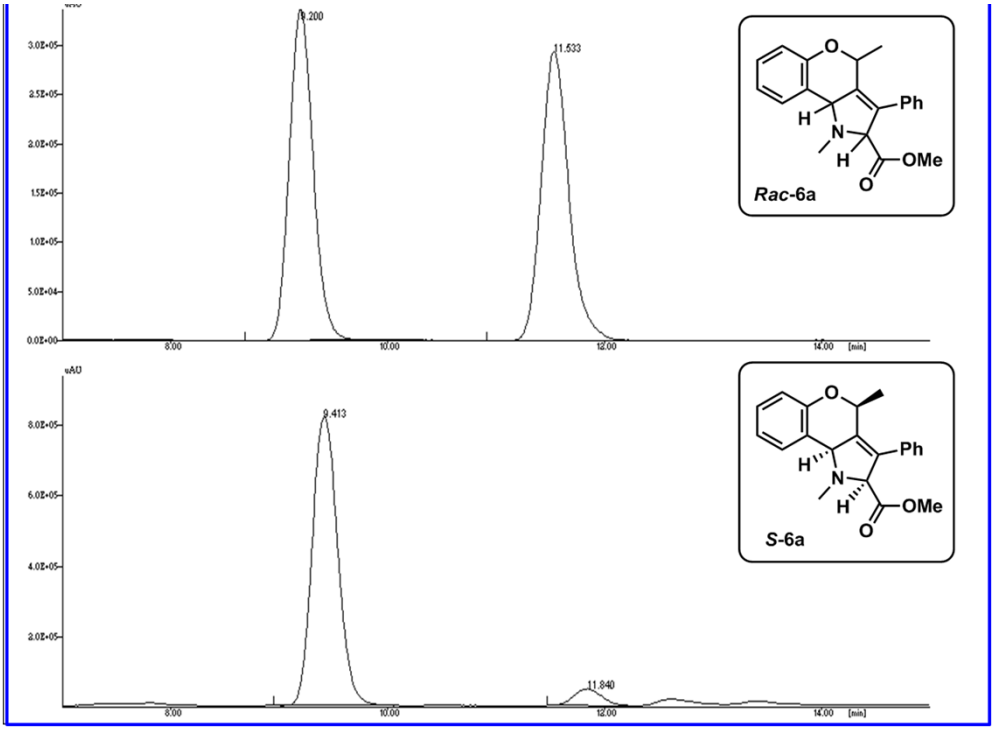
HPLC chromatogram of **2o**



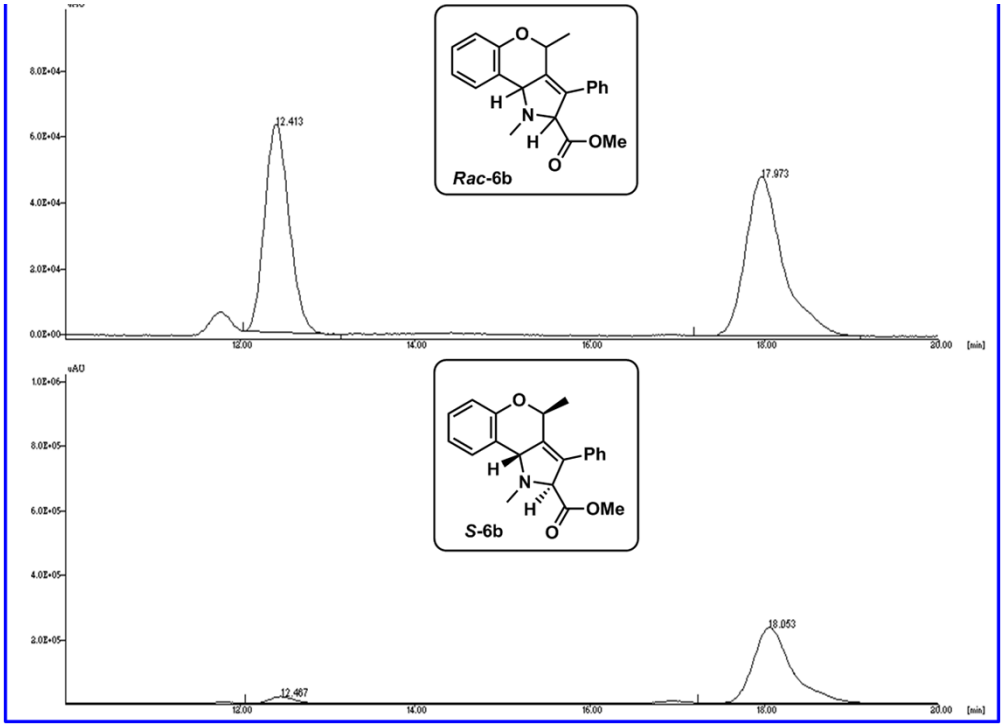
HPLC chromatogram of **2p**



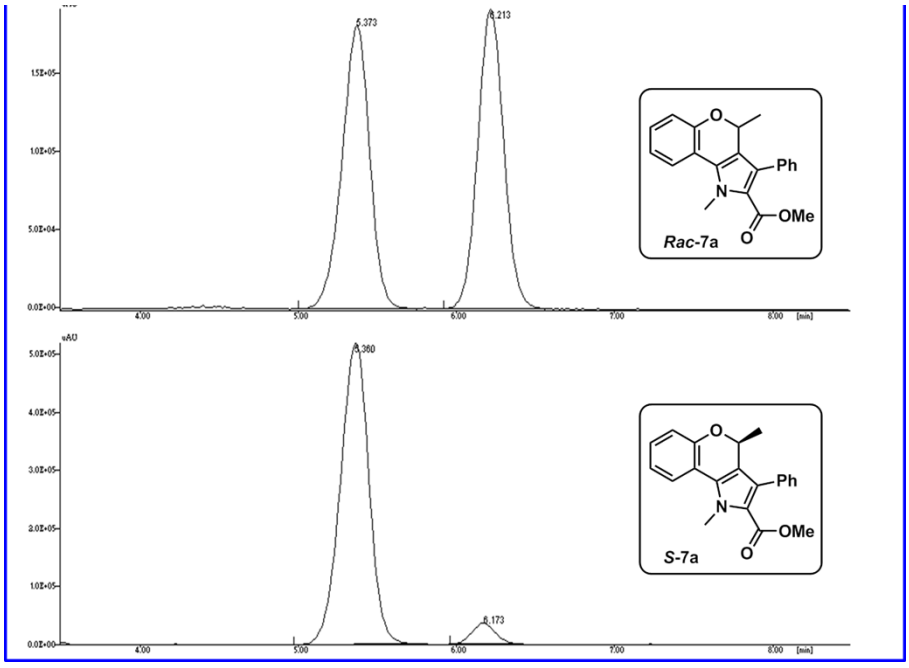
HPLC chromatogram of **4a**



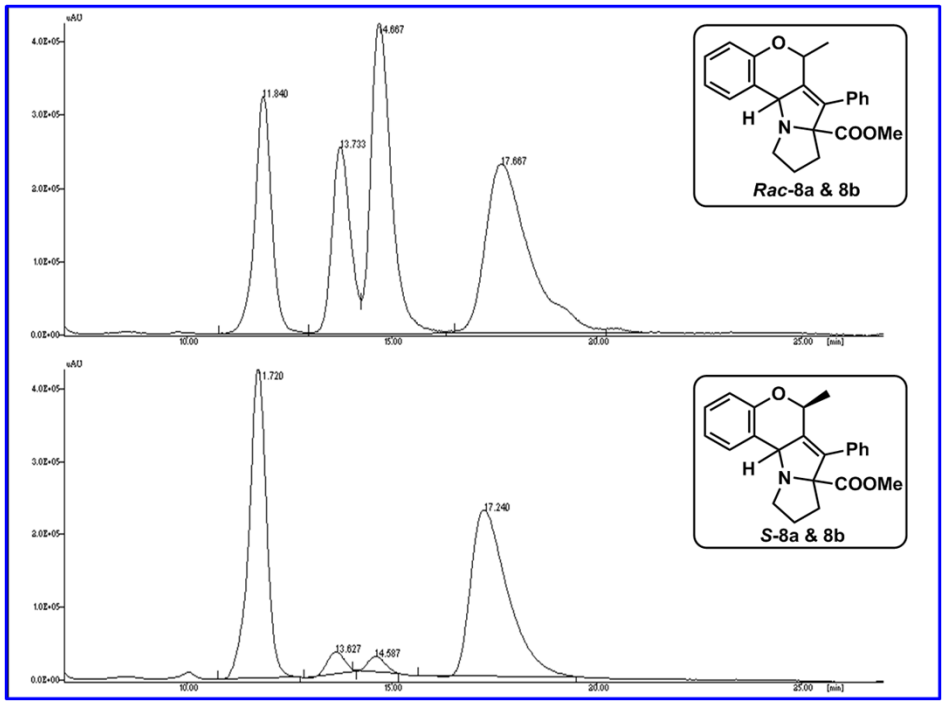
HPLC chromatogram of **6a**



HPLC chromatogram of **6b**



HPLC chromatogram of **7a**



HPLC chromatogram of **8**

CRYSTAL DATA & STRUCTURE REFINEMENT

Table 1 Crystal data and structure refinement for **6b**

Deposition number	CCDC 982489
Suitable solvent	Methanol
Identification code	**6b**
Empirical formula	C21 H21 N O3
Formula weight	335.39
Temperature	296(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P21/c
Unit cell dimensions	a = 10.7869(4) A alpha = 90 deg. b = 21.5015(8) A beta = 110.0980(10) deg. c = 8.1152(5) A gamma = 90 deg.
Volume	1767.58(14) A^3
Z, Calculated density	4, 1.260 Mg/m^3
Absorption coefficient	0.084 mm^-1
F(000)	712
Crystal size	0.40 x 0.35 x 0.35 mm
Theta range for data collection	2.22 to 26.00 deg.
Limiting indices	-13<=h<=13, -26<=k<=26, -10<=l<=10
Reflections collected / unique	27065 / 3467 [R(int) = 0.0267]
Completeness to theta	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9924 and 0.9527
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3467 / 0 / 227
Goodness-of-fit on F2	1.078
Final R indices [I>2sigma(I)]	R1 = 0.0463, wR2 = 0.1119
R indices (all data)	R1 = 0.0704, wR2 = 0.1318
Extinction coefficient	0.0045(13)
Largest diff. peak and hole	0.303 and -0.271 e.A^-3

Table 2 Crystal data and structure refinement for **7a**

Deposition number	CCDC 982490
Suitable solvent	Methanol
Identification code	**7a**
Empirical formula	C21 H19 N O3
Formula weight	333.37
Temperature	296(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, p-1
Unit cell dimensions	a = 8.0279(7) A alpha = 111.220(3) deg. b = 10.0480(8) A beta = 99.322(3) deg. c = 11.5774(9) A gamma = 101.074(3) deg.
Volume	826.55(12) A^3
Z, Calculated density	2, 1.339 Mg/m^3
Absorption coefficient	0.090 mm^-1
F(000)	352
Crystal size	0.40 x 0.15 x 0.10 mm
Theta range for data collection	2.26 to 24.99 deg.
Limiting indices	-9<=h<=9, -11<=k<=11, -13<=l<=13
Reflections collected / unique	23656 / 2915 [R(int) = 0.0379]
Completeness to theta	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9972 and 0.9582
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2915 / 0 / 230
Goodness-of-fit on F2	1.071
Final R indices [I>2sigma(I)]	R1 = 0.0376, wR2 = 0.0903
R indices (all data)	R1 = 0.0586, wR2 = 0.1072
Extinction coefficient	0.007(2)
Largest diff. peak and hole	0.180 and -0.148 e.A^-3

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