Supplementary Information

Catalytic Enantioselective Nucleophilic Addition of Ynamides to Aldehydes

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Contents:

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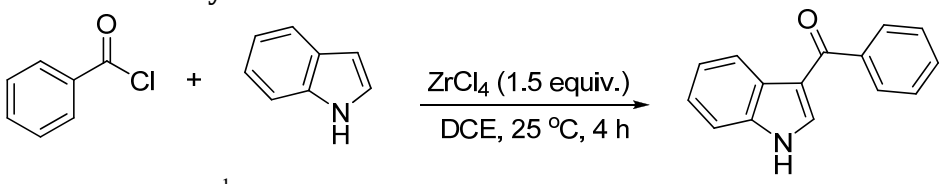
1. Synthetic Procedures

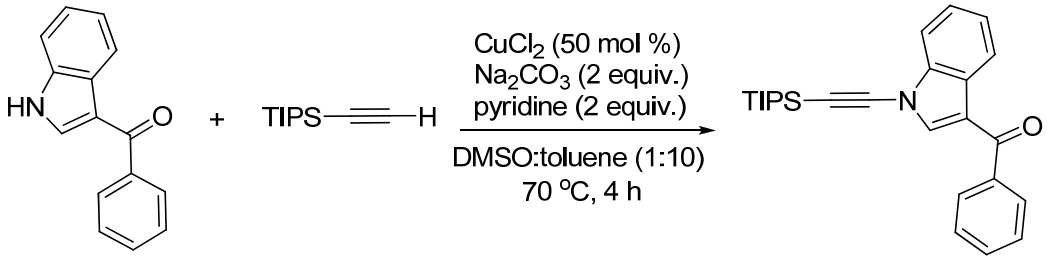
Commercially available reagents and solvents were used without further purification. Anhydrous solvents were used as purchased and not dried any further. Zinc triflate was dried at 120 °C under reduced pressure for 24 hours prior to use. Aldehydes were purified by column chromatography on silica gel prior to use unless noted otherwise. The catalytic asymmetric ynamide addition reaction was conducted using *N*,*N*-diisopropylethylamine from different vendors and essentially the same results were obtained. NMR spectra were obtained at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) in deuterated chloroform. Chemical shifts are reported in ppm relative to TMS. Reaction products were purified by column chromatography on silica gel (particle size 40-63 μm) as described below.

1.1. Ynamide Synthesis



3-Benzoylindole[1]

To a solution of indole (1.53 g, 13.1 mmol) in anhydrous 1,1-dichloroethane (15 mL) under nitrogen at 0 °C was added benzoyl chloride (1.40 g, 10.0 mmol) in anhydrous dichloromethane (15 mL) and zirconium tetrachloride (3.50 g, 15.0 mmol) in one portion. The bright yellow solution was stirred vigorously as it warmed to room temperature. After 4 hours the mixture was quenched with water (50 mL), transferred to a separatory funnel with acetone (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The resulting red solid was washed with acetone to give a light purple solid (1.33 g, 6.0 mmol 60% yield) which was used without further purification. ^{1}H NMR (400 MHz) δ = 8.58 (bs, 1H), 8.42 (m, 1H), 7.84 (m, 2H), 7.69 (d, *J* = 3.0 Hz, 1H), 7.56 (m, 1H), 7.52 – 7.42 (m, 3H), 7.37 – 7.30 (m, 2H). ^{13}C NMR (100 MHz) δ = 189.7, 140.7, 136.4, 133.4, 131.3, 128.8, 128.3, 126.4, 124.1, 122.8, 122.7, 117.4, 111.2.



1-(3-Benzoylindolyl)-2-(triisopropylsilyl)acetylene[2]

Copper(II) chloride (0.40 g, 3.0 mmol), sodium carbonate (1.27 g, 12.0 mmol), (triisopropylsilyl)acetylene (1.64 g, 9.0 mmol) and pyridine (0.95 g, 12.0 mmol) were combined in a round bottomed flask with toluene (50 mL) and a solution of 3-benzoylindole (1.33 g, 6.0 mmol) in DMSO (5 mL) was added. The resulting heterogeneous mixture was purged with dioxygen gas for approximately 10 minutes and stirred at 70 °C under oxygen for 4 hours. The crude mixture was concentrated by rotary evaporation. Unreacted 3-benzoylindol (0.49 g, 2.3 mmol, 38%) was recovered from a short silica plug (DCM/EtOAc) as a white solid. The crude product mixture was further purified by flash chromatography (30:1 hexanes:EtOAc) to give a colorless oil (1.15 g, 2.88 mmol, 48%). ^{1}H NMR (400 MHz) δ = 8.38 (d, *J* = 7.8 Hz, 1H), 7.86

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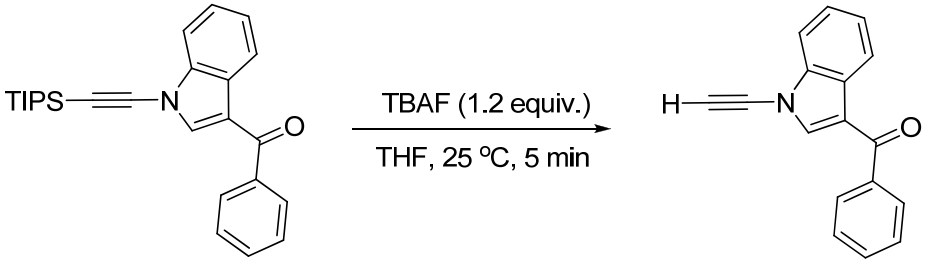
(d, *J* = 7.6 Hz, 2H), 7.68 (s, 1H), 7.61 – 7.54 (m, 2H), 7.54 – 7.47 (m, 2H), 7.44 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.40 (dd, *J* = 7.5, 7.4 Hz, 1H), 1.16 (s, 18H), 1.16 (s, 3H). ^{13}C NMR (100 MHz) δ = 190.5, 139.9, 138.7, 136.7, 131.8, 128.8, 128.5, 125.9, 125.2, 124.2, 123.0, 118.3, 111.3, 92.7, 71.3, 18.7, 11.3.



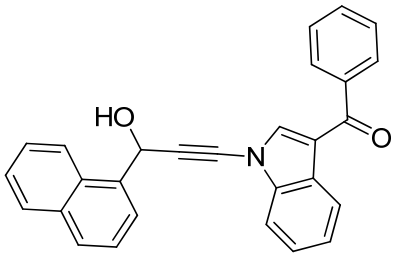
(3-Benzoylindolyl)acetylene

Tetrabutylammonium fluoride (1M THF, 3.5 mL) was added to a solution of 1-(3-benzoylindolyl)-2-(triisopropylsilyl)acetylene (1.15 g, 2.88 mmol) in dichloromethane (5 mL) and the mixture was stirred for 5 minutes at room temperature. The resulting solution was extracted with dichloromethane (3 x 30 mL) from H_2O. The concentrated crude residue was purified by column chromatography (40:30:1 CH_2Cl_2:hexanes:EtOAc) to give a white solid (0.68 g, 2.77 mmol, 95% yield) after solvents were removed by rotary evaporation at room temperature. ^{1}H NMR (400 MHz) δ = 8.38 (m, 1H), 7.85 (m, 2H), 7.69 (s, 1H), 7.64 – 7.54 (m, 2H), 7.50 (m, 2H), 7.47 – 7.36 (m, 2H), 3.18 (s, 1H). ^{13}C NMR (100 MHz) δ = 190.5, 139.7, 138.5, 136.7, 131.9, 128.8, 128.5, 125.9, 125.3, 124.3, 122.9, 118.6, 111.2, 72.7, 60.4. Anal. Calcd. For $C_{17}H_{11}NO_2$: C, 83.25; H, 4.52; N, 5.71. Found: C, 82.93; H, 4.59; N, 5.81. mp > 120 °C (decomp).

1.2. General Zinc Catalyzed Ynamide Addition Procedure

Zinc triflate (7.4 mg, 20 μmol), (1*R*,2*S*)-(-)-*N*-methylephedrine (3.9 mg, 22 μmol), 3-benzoyl-1-ethynylindole (50.0 mg, 0.20 mmol), aldehyde (0.30 mmol) and *N*,*N*-diisopropylethylamine (25.8 mg, 0.20 mmol) were dissolved in either toluene or a 1:1 toluene/hexane mixture (0.5 mL) under nitrogen atmosphere. The mixture was stirred at room temperature until completion as determined by ^{1}H NMR analysis. Solvents were evaporated under a stream of nitrogen and the crude residue was purified by flash chromatography or crystallization as described below.

2. Product Purification and Characterization



3-(1-Naphthyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

The reaction with 1-naphthaldehyde (52 mg, 0.33 mmol) was performed using the ynamide (55 mg, 0.22 mmol) in toluene (0.55 mL). After 18 hours, the precipitate was isolated from the yellow supernatant to give 81 mg (0.20 mmol, 92%, 96% ee) of a white solid. ^{1}H NMR (400 MHz) δ = 8.42 (d, *J* = 8.4 Hz, 1H), 8.37 (m, 1H), 7.96 – 7.87 (m, 3H), 7.83 (m, 2H), 7.67 (s, 1H), 7.64 – 7.47 (m, 7H), 7.44 – 7.36 (m, 2H), 6.45 (d, *J* = 5.6 Hz, 1H), 2.49 (d, *J* = 5.6 Hz, 1H).

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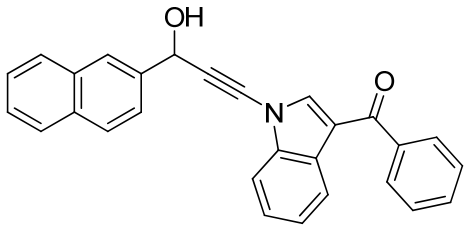
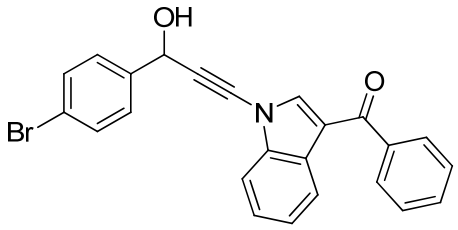
^{13}C NMR (100 MHz) δ = 190.5, 139.8, 138.6, 136.8, 135.3, 134.2, 131.9, 130.3, 129.7, 128.9, 128.8, 128.5, 126.7, 126.2, 126.0, 125.3, 124.6, 124.4, 123.8, 123.0, 118.7, 111.3, 71.8, 63.4. The ee was determined by HPLC on Chiralcel OD using hexanes:IPA (80:20) as the mobile phase at 1.0 mL/min, t_1 (minor) = 19.4 min, t_2 (major) = 27.1 min, α = 1.45. Anal. Calcd. For $C_{28}H_{19}NO_2$: C, 83.77; H, 4.77; N, 3.49. Found: C, 83.67; H, 4.63; N, 3.62. mp > 190 ^{o}C (decomp).



3-(2-Naphthyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

The reaction with 2-naphthaldehyde (52 mg, 0.33 mmol) was performed using the ynamide (55 mg, 0.22 mmol) in 1:1 toluene/hexane (0.55 mL). After 17 hours, the concentrated crude residue was purified by column chromatography (3% EtOAc, CH_2Cl_2) to give 83 mg (0.20 mmol, 92%, 90% ee) of a white solid. ^{1}H NMR (400 MHz) δ = 8.37 (m, 1H), 8.05 (s, 1H), 7.91 (d, *J* = 8.6 Hz, 1H), 7.87 (m, 2H), 7.84 – 7.78 (m, 2H), 7.73 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.62 (s, 1H), 7.60 – 7.44 (m, 6H), 7.43 – 7.34 (m, 2H), 5.96 (d, *J* = 5.9 Hz, 1H), 2.73 (d, *J* = 5.9 Hz, 1H).^{13}C NMR (100 MHz) δ = 190.6, 139.7, 138.5, 137.5, 136.9, 133.3, 133.2, 131.9, 128.9, 128.8, 128.5, 128.2, 127.7, 126.5, 126.0, 125.4, 125.3, 124.4, 124.2, 123.0, 118.7, 111.2, 76.8, 72.1, 64.9. The ee was determined by HPLC on Chiralpak IA using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min, t_1 (minor) = 19.8 min, t_2 (major) = 23.4 min, α = 1.21. Anal. Calcd. For $C_{28}H_{19}NO_2$: C, 83.77; H, 4.77; N, 3.49. Found: C, 83.41; H, 4.93; N, 3.57. mp 165-166 ^{o}C.



3-(4-Bromophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

The reaction with 4-bromobenzaldehyde (62 mg, 0.33 mmol) was performed using the ynamide (55 mg, 0.22 mmol) in toluene (0.55 mL). After 18 hours, a white precipitate was isolated and washed twice with hexanes (1 mL). Additional product was isolated from the concentrated supernatant by flash chromatography (5% EtOAc, CH_2Cl_2). The combined fractions gave 92 mg (0.21 mmol, 97%, 93% ee) of a white solid. ^{1}H NMR (400 MHz) δ = 8.38 (m, 1H), 7.84 (d, *J* = 7.4 Hz, 2H), 7.66 (s, 1H), 7.62 – 7.55 (m, 3H), 7.55 – 7.48 (m, 5H), 7.46 – 7.38 (m, 2H), 5.77 (d, *J* = 5.5 Hz, 1H), 2.37 (d, *J* = 5.5 Hz, 1H).^{13}C NMR (100 MHz) δ = 190.6, 139.6, 139.2, 138.5, 136.7, 132.0, 131.9, 128.8, 128.5, 128.2, 126.0, 125.4, 124.4, 123.0, 122.7, 118.8, 111.2, 76.8, 71.7, 64.1. The ee was determined by HPLC on Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min, t_1 (minor) = 12.4 min, t_2 (major) = 14.7 min, α = 1.23. Anal. Calcd. for $C_{24}H_{16}NO_2Br$: C, 66.99; H, 3.75; N, 3.26. Found: C, 66.93; H, 4.12; N, 3.14. mp 140 ^{o}C (decomp).

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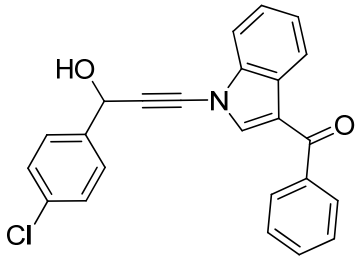
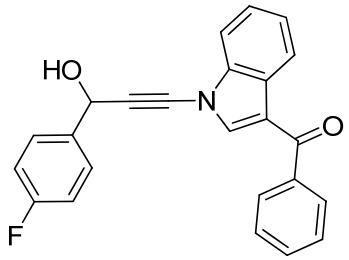


3-(4-Chlorophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

The reaction with 4-chlorobenzaldehyde (35 mg, 0.25 mmol) was performed using the ynamide (55 mg, 0.22 mmol) in 1:1 toluene-hexanes (0.55 mL). After 16 hours, the concentrated crude residue was purified by column chromatography (3% EtOAc, CH_2Cl_2) to give 78 mg (0.20 mmol, 92%, 95% ee) of a white solid. ^{1}H NMR (400 MHz) δ = 8.37 (m, 1H), 7.83 (m, 2H), 7.64 (s, 1H), 7.62 – 7.46 (m, 6H), 7.46 – 7.35 (m, 4H), 5.79 (d, *J* = 5.9 Hz, 1H), 2.48 (d, *J* = 5.9 Hz, 1H). ^{13}C NMR (100 MHz) δ = 190.5, 139.6, 138.6, 138.5, 136.7, 134.5, 131.9, 129.0, 128.8, 128.5, 127.8, 126.0, 125.3, 124.4, 123.0, 118.8, 111.1, 76.8, 71.7, 64.0. The ee was determined by HPLC on Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min, t_1 (minor) = 11.3 min, t_2 (major) = 13.2 min, α = 1.21. Anal. Calcd. For $C_{24}H_{16}ClNO_2$: C, 74.71; H, 4.18; N, 3.63. Found: C, 74.63; H, 4.15; N, 3.72. mp 166-167 ^{o}C.



3-(4-Fluorophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

The reaction with 4-fluorobenzaldehyde (39 mg, 0.31 mmol) was performed using the ynamide (50 mg, 0.20 mmol) in 1:1 toluene-hexanes (0.5 mL). After 18 hours, the concentrated crude residue was purified by column chromatography (2% EtOAc, CH_2Cl_2) to give 69 mg (0.19 mmol, 92%, 93% ee) of a white solid. ^{1}H NMR (400 MHz) δ = 8.34 (m, 1H), 7.79 (d, *J* = 7.8 Hz, 2H), 7.62 – 7.56 (m, 3H), 7.55 (s, 1H), 7.52 – 7.43 (m, 3H), 7.40 – 7.32 (m, 2H), 7.09 (dd, *J* = 8.6, 8.6 Hz, 2H), 5.78 (d, *J* = 5.8 Hz, 1H), 2.96 (d, *J* = 5.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.7, 162.8 (d, $J_{(C,F)}$ = 247.6 Hz), 139.6, 138.5, 136.8, 136.1 (d, $J_{(C,F)}$ = 3.2 Hz), 131.9, 128.8, 128.5, 128.3 (d, $J_{(C,F)}$ = 8.3 Hz), 125.9, 125.3, 124.4, 123.0, 118.7, 115.7 (d, $J_{(C,F)}$ = 21.8 Hz), 111.2, 71.9, 64.1. The ee was determined by HPLC on Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min, t_1 (minor) = 9.9 min, t_2 (major) = 11.4 min, α = 1.20. Anal. Calcd. For $C_{24}H_{16}FNO_2$: C, 78.04; H, 4.37; N, 3.79. Found: C, 77.75; H, 4.53; N, 3.88. mp 123-124 ^{o}C.

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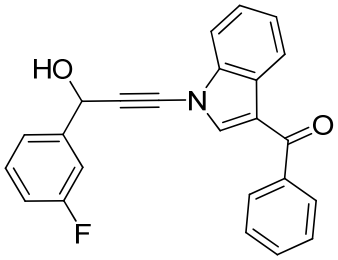
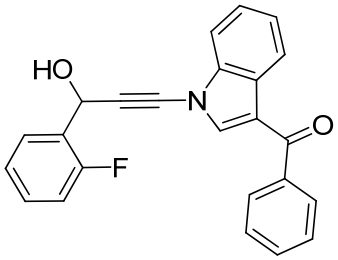


3-(3-Fluorophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

The reaction with 3-fluorobenzaldehyde (48 mg, 0.39 mmol) was performed using the ynamide (65 mg, 0.26 mmol) in 1:1 toluene-hexanes (0.65 mL). After 18.5 hours, the concentrated crude residue was purified by column chromatography (2% EtOAc, CH_2Cl_2) to give 84 mg (0.23 mmol, 87%, 88% ee) of a white solid. ^{1}H NMR (400 MHz) δ = 8.36 (m, 1H), 7.84 (d, *J* = 7.2 Hz, 2H), 7.65 (s, 1H), 7.63 – 7.46 (m, 4H), 7.46 – 7.38 (m, 4H), 7.35 (d, *J* = 9.9 Hz, 1H), 7.07 (m, 1H), 5.81 (d, *J* = 6.0 Hz, 1H), 2.47 (d, *J* = 6.0 Hz, 1H). ^{13}C NMR (100 MHz) δ = 190.8, 162.9 (d, $J_{(C,F)}$ = 246.8 Hz), 142.7 (d, $J_{(C,F)}$ = 7.0 Hz), 139.5, 138.4, 136.9, 132.0, 130.3 (d, $J_{(C,F)}$ = 8.1 Hz), 128.8 , 128.5 , 125.8, 125.3, 124.4, 122.9, 122.0 (d, $J_{(C,F)}$ = 3.1 Hz), 118.6, 115.4 (d, $J_{(C,F)}$ = 21.3 Hz), 113.5 (d, $J_{(C,F)}$ = 22.8 Hz), 111.1, 76.6 , 71.8 , 63.9 (d, $J_{(C,F)}$ = 2.1 Hz). The ee was determined by HPLC on Chiralpak IA using hexanes:EtOH (90:10) as the mobile phase at 1.5 mL/min, t_1 (minor) = 21.0 min, t_2 (major) = 22.5 min, α = 1.08. Anal. Calcd. For $C_{24}H_{16}FNO_2$: C, 78.04; H, 4.37; N, 3.79. Found: C, 77.64; H, 4.22; N, 3.87. mp > 136 °C (decomp).



3-(2-Fluorophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

The reaction with 2-fluorobenzaldehyde (42 mg, 0.34 mmol) was performed using the ynamide (50 mg, 0.20 mmol) in 1:1 toluene-hexanes (0.5 mL). After 13 hours, the concentrated crude residue was purified by column chromatography (2% EtOAc, CH_2Cl_2) to give 70.5 mg (0.19 mmol, 95%, 70% ee) of a white solid. ^{1}H NMR (400 MHz) δ = 8.35 (m, 1H), 7.81 (d, *J* = 7.4 Hz, 2H), 7.70 (ddd, *J* = 7.6, 7.6, 1.8 Hz, 1H), 7.58 (s, 1H), 7.57 – 7.44 (m, 4H), 7.42 – 7.31 (m, 3H), 7.21 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.11 (ddd, *J* = 10.5, 8.2, 1.2 Hz, 1H), 6.03 (d, *J* = 5.9 Hz, 1H), 2.98 (d, *J* = 5.9 Hz, 1H). ^{13}C NMR (100 MHz) δ = 190.7 , 160.0 (d, $J_{(C,F)}$ = 248.3 Hz), 139.7 , 138.5 , 136.9 , 131.9 , 130.5 (d, $J_{(C,F)}$ = 8.3 Hz), 128.8 , 128.5 , 128.1 (d, $J_{(C,F)}$ = 3.4 Hz), 127.6 (d, $J_{(C,F)}$ = 13.1 Hz), 125.9 , 125.3 , 124.6 (d, $J_{(C,F)}$ = 3.6 Hz), 124.4 , 122.9 , 118.7 , 115.9 (d, $J_{(C,F)}$ = 21.2 Hz), 111.2 , 76.3 , 71.1 , 59.3 (d, $J_{(C,F)}$ = 4.9 Hz). The ee was determined by HPLC on Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min, t_1 (minor) = 9.6 min, t_2 (major) = 11.4 min, α = 1.25. Anal. Calcd. For $C_{24}H_{16}FNO_2$: C, 78.04; H, 4.37; N, 3.79. Found: C, 78.17; H, 4.48; N, 3.93. mp 105-107 °C.

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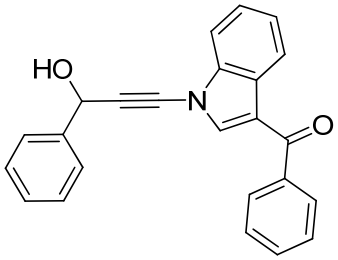
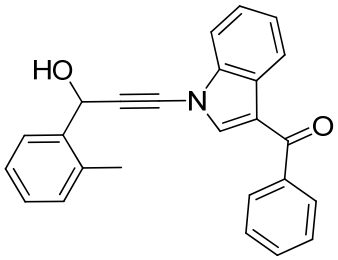


3-Phenyl-3-hydroxy-1-(3-benzoylindolyl)propyne

The reaction with benzaldehyde (63 mg, 0.59 mmol) was performed using the ynamide (65 mg, 0.26 mmol) in 1:1 toluene-hexanes (0.65 mL). After 18 hours, the concentrated crude residue was purified by column chromatography (1% EtOAc, CH_2Cl_2) to give 80 mg (0.23 mmol, 87%, 84% ee) of a white solid. ^{1}H NMR (400 MHz) δ = 8.34 (m, 1H), 7.78 (d, *J* = 7.9 Hz, 2H), 7.61 (d, *J* = 7.8 Hz, 2H), 7.58 – 7.52 (m, 2H), 7.52 – 7.31 (m, 8H), 5.78 (d, *J* = 6.0 Hz, 1H), 3.09 (d, *J* = 6.1 Hz, 1H). ^{13}C NMR (100 MHz) δ = 190.7, 140.3, 139.6, 138.5, 137.0, 131.9, 128.8, 128.6, 128.5, 126.5, 125.9, 125.2, 124.3, 122.9, 118.5, 111.2, 76.4, 72.2, 64.7. The ee was determined by HPLC on Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min, t_1 (minor) = 10.5 min, t_2 (major) = 12.8 min, α = 1.28. Anal. Calcd. For $C_{24}H_{17}NO_2$: C, 82.03; H, 4.88; N, 3.99. Found: C, 82.14; H, 4.94; N, 4.12. mp > 102 °C (decomp).



3-(2-Tolyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

The reaction with 2-tolyl aldehyde (47 mg, 0.39 mmol) was performed using the ynamide (65 mg, 0.26 mmol) in 1:1 toluene-hexanes (0.65 mL). After 15 hours, the concentrated crude residue was purified by column chromatography (2% EtOAc, CH_2Cl_2) to give 88 mg (0.24 mmol, 93%, 95% ee) of a white solid. ^{1}H NMR (400 MHz) δ = 8.38 (m, 1H), 7.84 (m, 2H), 7.73 (m, 1H), 7.66 (s, 1H), 7.62 – 7.54 (m, 2H), 7.50 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.46 – 7.37 (m, 2H), 7.33 – 7.27 (m, 2H), 7.23 (m, 1H), 5.96 (d, *J* = 5.7 Hz, 1H), 2.52 (s, 3H), 2.29 (d, *J* = 5.7 Hz, 1H). ^{13}C NMR (100 MHz) δ = 190.5, 139.8, 138.6, 138.0, 136.9, 135.7, 131.9, 131.0, 128.8, 128.8, 128.5, 126.5, 126.3, 126.0, 125.3, 124.4, 123.0, 118.7, 111.2, 76.5, 71.7, 62.6, 19.1. The ee was determined by HPLC on Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.0 mL/min, t_1 (minor) = 13.6 min, t_2 (major) = 16 min, α = 1.21. Anal. Calcd. For $C_{25}H_{19}NO_2$: C, 82.17; H, 5.24; N, 3.83. Found: C, 81.91; H, 5.27; N, 3.93. mp 144-147 °C.

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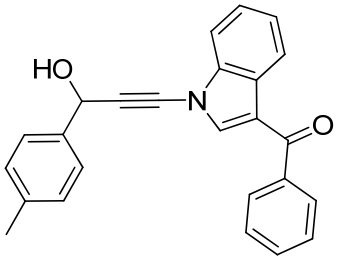
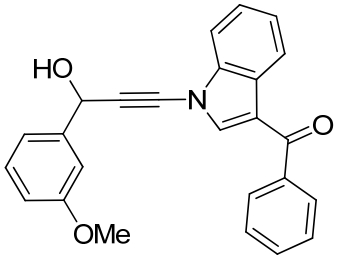


3-(4-Tolyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

The reaction with 4-tolyl aldehyde (48 mg, 0.40 mmol) was performed using the ynamide (65 mg, 0.26 mmol) in 1:1 toluene-hexanes (0.65 mL). After 20 hours, the concentrated crude residue was purified by column chromatography (2% EtOAc, CH_2Cl_2) to give 77 mg (0.21 mmol, 80%, 88% ee) of a white solid. ^{1}H NMR (400 MHz) δ = 8.38 (m, 1H), 7.84 (d, *J* = 6.8 Hz, 2H), 7.68 (s, 1H), 7.63 – 7.55 (m, 2H), 7.55 – 7.47 (m, 4H), 7.47 – 7.37 (m, 2H), 7.25 (d, *J* = 7.4 Hz, 2H), 5.77 (d, *J* = 6.0 Hz, 1H), 2.39 (s, 3H), 2.24 (d, *J* = 6.1 Hz, 1H). ^{13}C NMR (100 MHz) δ = 190.6, 139.8, 138.7, 138.6, 137.4, 136.9, 131.9, 129.5, 128.8, 128.5, 126.5, 126.0, 125.3, 124.3, 123.0, 118.6, 111.3, 76.4, 72.2, 64.7, 21.2. The ee was determined by HPLC on Chiralpak IA using hexanes:EtOH (90:10) as the mobile phase at 1.5 mL/min, t_1 (minor) = 23.0 min, t_2 (major) = 25.9 min, α = 1.14. Anal. Calcd. For $C_{25}H_{19}NO_2$: C, 82.17; H, 5.24; N, 3.83. Found: C, 81.77; H, 5.20; N, 3.90.



3-(3-Methoxyphenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

The reaction with 3-methoxybenzaldehyde (14 mg, 0.10 mmol) was performed using the ynamide (15 mg, 0.06 mmol) in 1:1 toluene-hexanes (0.15 mL). After 26 hours, the concentrated crude residue was purified by column chromatography (3% EtOAc, CH_2Cl_2) to give 21 mg (0.055 mmol, 92%, 87% ee) of a white solid. ^{1}H NMR (400 MHz) δ = 8.37 (m, 1H), 7.83 (d, *J* = 7.8 Hz, 2H), 7.64 (s, 1H), 7.62 – 7.53 (m, 2H), 7.50 (m, 2H), 7.45 – 7.37 (m, 2H), 7.35 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.23 – 7.14 (m, 2H), 6.91 (dd, *J* = 8.2, 2.5 Hz, 1H), 5.77 (d, *J* = 6.0 Hz, 1H), 3.84 (s, 3H), 2.47 (d, *J* = 6.1 Hz, 1H). ^{13}C NMR (100 MHz) δ = 190.6, 160.0, 141.8, 139.7, 138.5, 136.9, 131.9, 129.9, 128.8, 128.5, 126.0, 125.3, 124.4, 123.0, 118.7, 114.2, 112.1, 111.2, 76.6, 72.0, 64.7, 55.4. The ee was determined by HPLC on Chiralpak OD using hexanes:EtOH (85:15) as the mobile phase at 1.2 mL/min, t_1 (major) = 17.0 min, t_2 (minor) = 21.2 min, α = 1.29. Anal. Calcd. For $C_{25}H_{19}NO_3$: C, 78.72; H, 5.02; N, 3.67. Found: C, 78.49; H, 5.03; N, 3.71. mp 96-99 ^{o}C.

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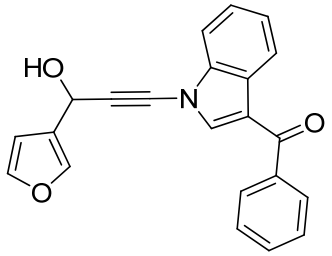
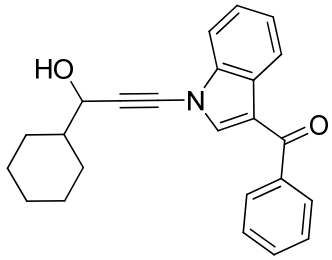


3-(3-Furyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

The reaction with 3-furanal (30 mg, 0.30 mmol) was performed using the ynamide (50 mg, 0.20 mmol) in 1:1 toluene-hexanes (0.5 mL). The aldehyde was used as purchased without further purification. After 21 hours, the concentrated crude residue was purified by column chromatography (2% EtOAc, CH_2Cl_2) to give 56 mg (0.16 mmol, 81%, 87% ee) of a white solid. ^{1}H NMR (400 MHz) δ = 8.36 (m, 1H), 7.82 (d, *J* = 6.9 Hz, 2H), 7.61 (m, 1H), 7.60 (s, 1H), 7.59 – 7.43 (m, 5H), 7.43 – 7.34 (m, 2H), 6.60 (dd, *J* = 1.8, 0.9 Hz, 1H), 5.74 (dd, *J* = 6.5, 1.0 Hz, 1H), 2.69 (d, *J* = 6.5 Hz, 1H) ^{13}C NMR (100 MHz) δ = 190.6, 143.9, 140.0, 139.6, 138.4, 136.8, 131.9, 128.8, 128.5, 126.1, 125.9, 125.3, 124.4, 122.9, 118.6, 111.1, 109.0, 75.2, 71.6, 57.5. The ee was determined by HPLC on Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min, t_1 (minor) = 11.0 min, t_2 (major) = 13.5 min, α = 1.29. Anal. Calcd. For $C_{22}H_{15}NO_3$: C, 77.41; H, 4.43; N, 4.10. Found: C, 77.23; H, 4.47; N, 4.17. mp > 118 °C (decomp).



3-Cyclohexyl-3-hydroxy-1-(3-benzoylindolyl)propyne

The reaction with cyclohexanecarboxaldehyde (44 mg, 0.39 mmol) was performed using the ynamide (65 mg, 0.26 mmol) in toluene (0.65 mL). After 15 hours, the concentrated crude residue was purified by column chromatography (2% EtOAc, CH_2Cl_2) to give 82 mg (0.23 mmol, 89%, 90% ee) of a colorless oil. ^{1}H NMR (400 MHz) δ = 8.38 (m, 1H), 7.83 (d, *J* = 6.9 Hz, 2H), 7.63 (s, 1H), 7.61 – 7.54 (m, 2H), 7.50 (dd, *J* = 7.4, 7.3 Hz, 2H), 7.46 – 7.35 (m, 2H), 4.49 (d, *J* = 5.8, 5.8 Hz, 1H), 2.11 (d, *J* = 5.7 Hz, 1H), 1.96 (m, 2H), 1.82 (m, 2H), 1.72 (m, 2H), 1.40 – 1.10 (m, 5H). ^{13}C NMR (100 MHz) δ = 190.6, 139.8, 138.6, 137.0, 131.9, 128.8, 128.5, 125.9, 125.2, 124.3, 122.9, 118.4, 111.2, 75.7, 72.1, 67.4, 44.2, 28.7, 28.4, 26.3, 25.9, 25.8. The ee was determined by HPLC on Chiralpak AD using hexanes:EtOH (90:10) as the mobile phase at 1.5 mL/min, t_1 (minor) = 9.5 min, t_2 (major) = 10.8 min, α = 1.18. Anal. Calcd. For $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.52; H, 6.54; N, 4.14.

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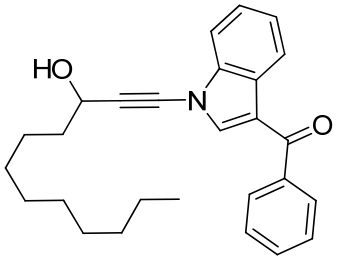
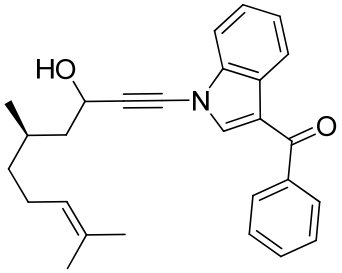


3-Nonyl-3-hydroxy-1-(3-benzoylindolyl)propyne

The reaction with decanal (66 mg, 0.42 mmol) was performed using the ynamide (65 mg, 0.26 mmol) in 1:1 toluene-hexanes (0.65 mL). After 13 hours, the concentrated crude residue was purified by column chromatography (1% EtOAc, CH_2Cl_2) to give 90 mg (0.23 mmol, 87%, 95% ee) of a colorless oil. ^{1}H NMR (400 MHz) δ = 8.36 (m, 1H), 7.79 (d, *J* = 7.8 Hz, 2H), 7.57 – 7.42 (m, 5H), 7.37 – 7.31 (m, 2H), 4.68 (q, *J* = 6.3 Hz, 1H), 2.90 (bs, 1H), 1.86 (m, 2H), 1.56 (m, 2H), 1.46 – 1.18 (m, 12H), 0.87 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz) δ = 190.7, 139.7, 138.4, 137.1, 131.9, 128.8, 128.4, 125.8, 125.1, 124.2, 122.8, 118.2, 111.1, 74.7, 73.4, 62.5, 37.9, 31.8, 29.51, 29.49, 29.3, 29.2, 25.3, 22.6, 14.1. The ee was determined by HPLC on Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min, t_1 (major) = 4.8 min, t_2 (minor) = 6.5 min, α = 1.71. Anal. Calcd. For $C_{27}H_{31}NO_2$: C, 80.76; H, 7.78; N, 3.49. Found: C, 80.61; H, 8.02; N, 3.57.



3-((2*R*)-2,6-Dimethylhept-5-enyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

The reaction with (*R*)-citronellal (46 mg, 0.30 mmol) was performed using the ynamide (50 mg, 0.20 mmol) in 1:1 toluene-hexanes (0.5 mL). After 3 hours, the concentrated crude residue was purified by column chromatography (1% EtOAc, CH_2Cl_2) to give 70.5 mg (0.18 mmol, 88%, 98% de) of a colorless oil.^{1}H NMR (400 MHz) δ = 8.38 (m, 1H), 7.82 (d, *J* = 6.9 Hz, 2H), 7.59 (s, 1H), 7.58 – 7.51 (m, 2H), 7.50 (dd, 7.6, 7.4 Hz, 2H), 7.42 – 7.34 (m, 2H), 5.10 (m, 1H), 4.76 (m, 1H), 2.26 (m, 1H), 2.10 – 1.75 (m, 5H), 1.65 (s, 3H), 1.60 (s, 3H), 1.42 (m, 1H), 1.26 (m, 2H), 0.99 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (100 MHz) δ = 190.6, 139.7, 138.5, 137.0, 131.8, 131.5, 128.8, 128.4, 125.9, 125.2, 124.4, 124.2, 122.9, 118.4, 111.1, 74.8, 73.6, 60.7, 45.3, 37.0, 29.1, 25.7, 25.3, 19.3, 17.7. The de was determined by HPLC on Chiralpak AD using hexanes:EtOH (92:8) as the mobile phase at 1.5 mL/min, t_1 (major) = 10.5 min, t_2 (minor) = 12.5 min, α = 1.25. Anal. Calcd. For $C_{27}H_{29}NO_2$: C, 81.17; H, 7.32; N, 3.51. Found: C, 81.20; H, 7.32; N, 3.51.

The reaction with (*R*)-citronellal (23 mg, 0.15 mmol) was also performed using (1*S*,2*R*)-(+)-*N*-methylephedrine and the ynamide (25 mg, 0.10 mmol) in 1:1 toluene-hexanes (0.1 mL). After 3 hours, the concentrated crude residue was purified by column chromatography (1% EtOAc, CH_2Cl_2) to give 22.5 mg (0.056 mmol, 56%, 73% de) of a colorless oil. ^{1}H NMR (400 MHz) δ = 8.38 (m, 1H), 7.83 (d, *J* = 7.0 Hz, 2H), 7.62 (s, 1H), 7.61 – 7.53 (m, 2H), 7.50 (dd, 7.6, 7.4 Hz, 2H), 7.45 – 7.35 (m, 2H), 5.10 (m, 1H), 4.77 (m, 1H), 2.10 (m, 1H), 2.08 – 1.98 (m, 2H), 1.92 –

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1.67 (m, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 1.44 (m, 1H), 1.26 (m, 2H), 0.99 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz) δ = 190.6, 139.8, 138.5, 137.0, 131.9, 131.5, 128.8, 128.5, 126.0, 125.2, 124.4, 124.3, 122.9, 118.5, 111.1, 75.1, 73.2, 61.3, 45.2, 37.0, 29.6, 25.7, 25.3, 19.7, 17.7. The de was determined by HPLC on Chiralpak AD using hexanes:EtOH (92:8) as the mobile phase at 1.5 mL/min, t_1 (minor) = 10.6 min, t_2 (major) = 12.4 min, α = 1.22.

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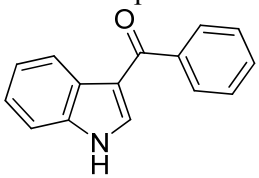
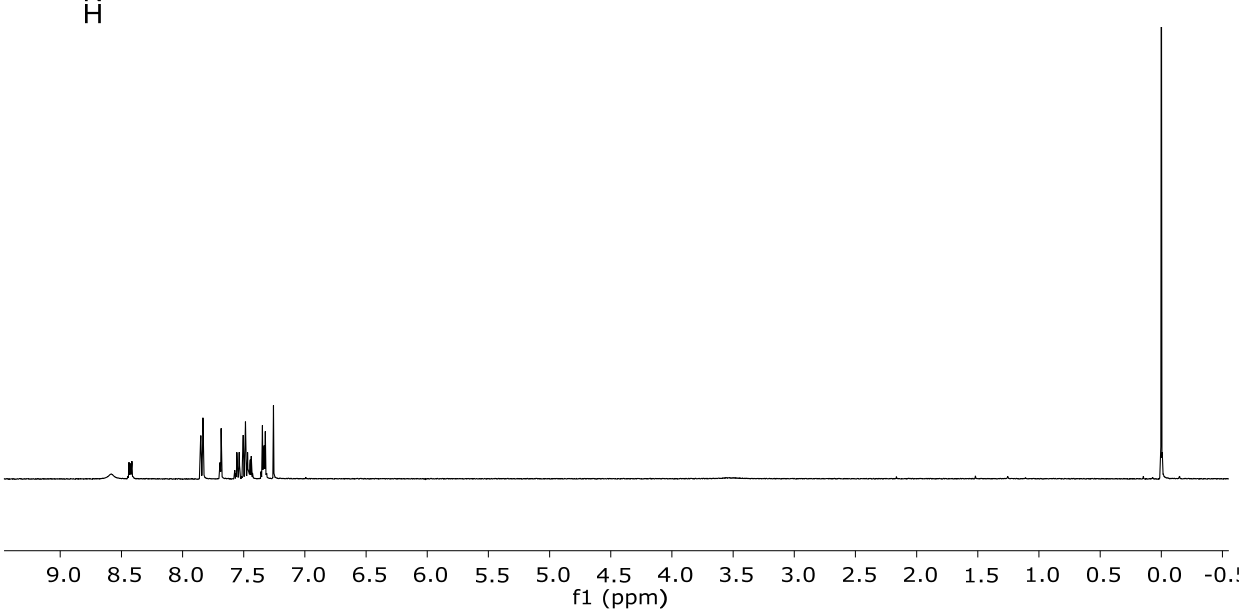
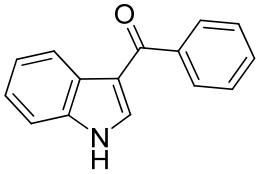
3. NMR Spectra

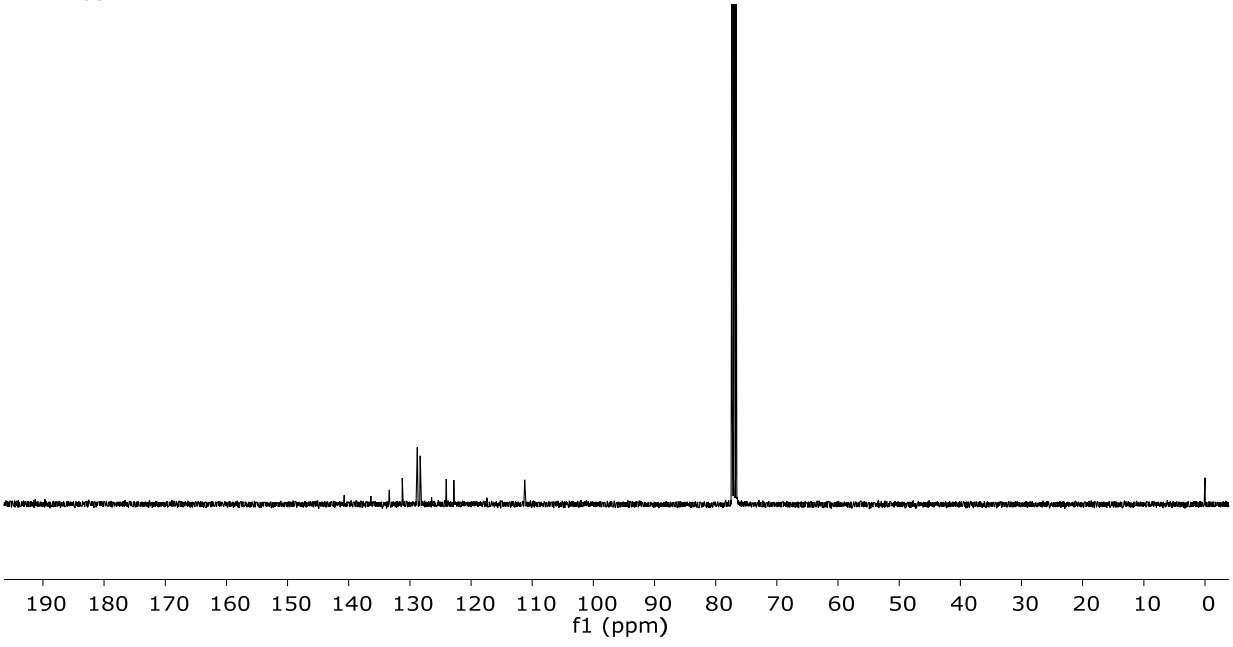
^{1}H NMR Spectrum of 3-Benzoylindole





^{13}C NMR Spectrum of 3-Benzoylindole





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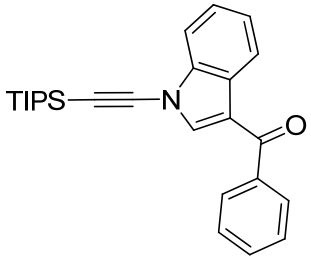
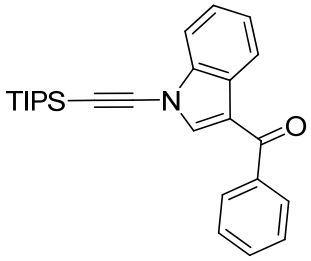
^{1}H NMR Spectrum of 1-(3-Benzoylindolyl)-2-(triisopropylsilyl)acetylene



^{13}C NMR Spectrum of 1-(3-Benzoylindolyl)-2-(triisopropylsilyl)acetylene



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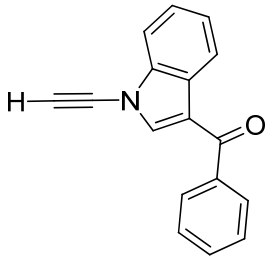
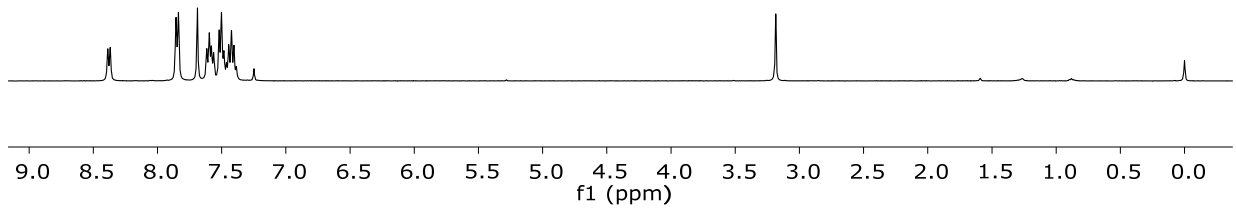
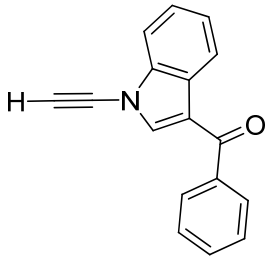
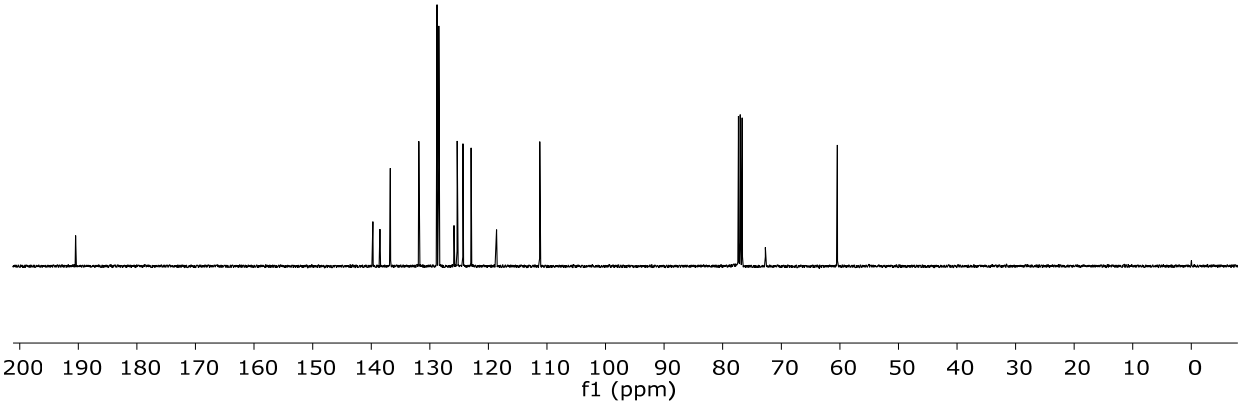
^{1}H NMR Spectrum of (3-Benzoylindolyl)acetylene





^{13}C NMR Spectrum of (3-Benzoylindolyl)acetylene





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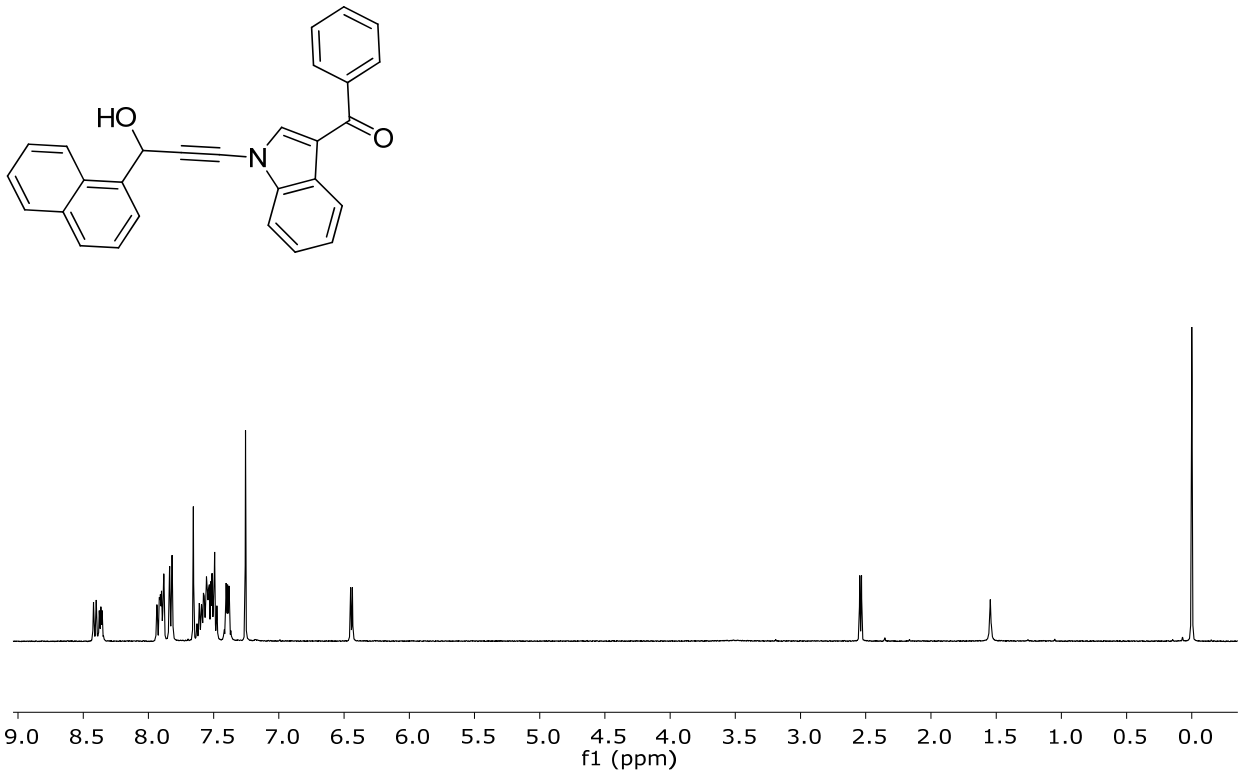
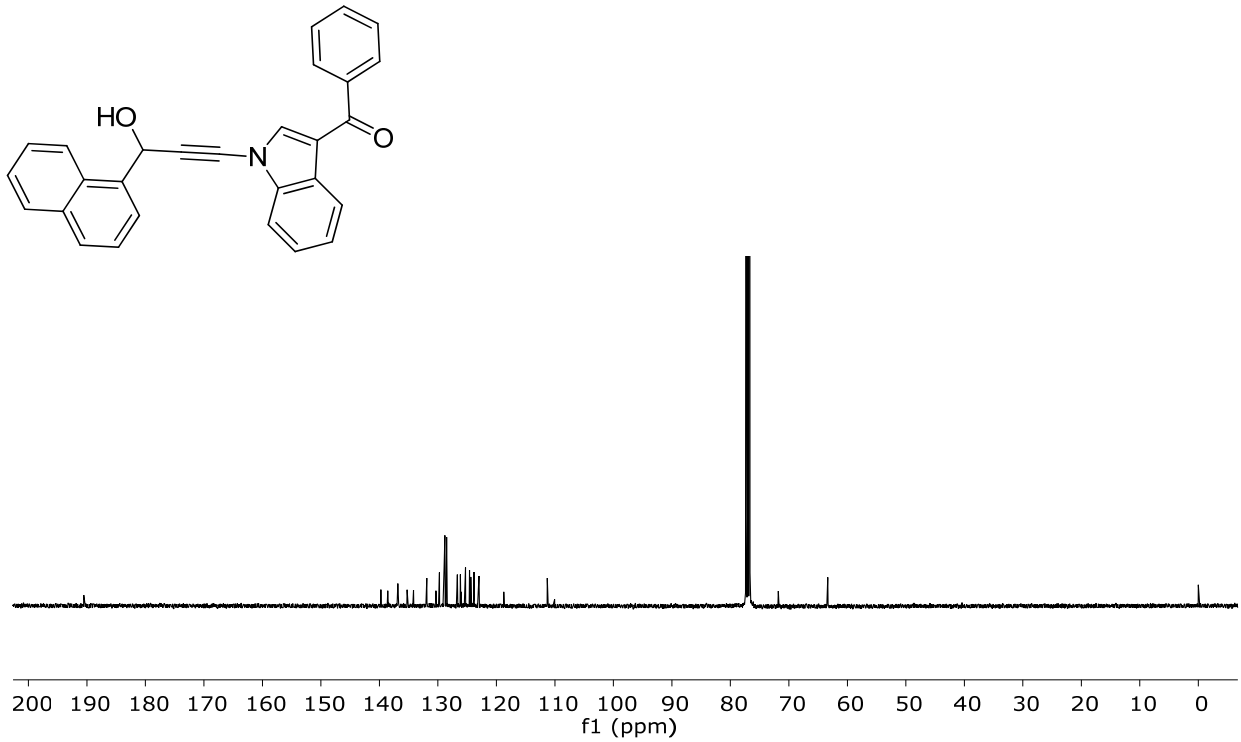
^{1}H NMR Spectrum of 3-(1-Naphthyl)-3-hydroxy-1-(3-benzoylindolyl)propyne



^{13}C NMR Spectrum of 3-(1-Naphthyl)-3-hydroxy-1-(3-benzoylindolyl)propyne



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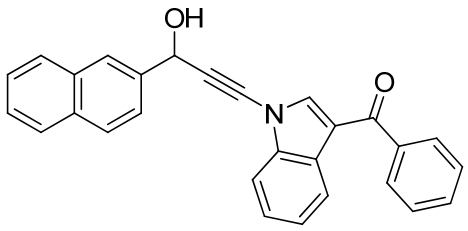
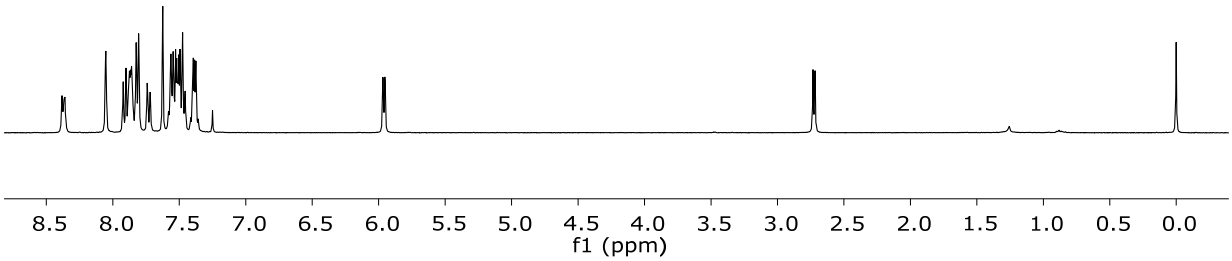
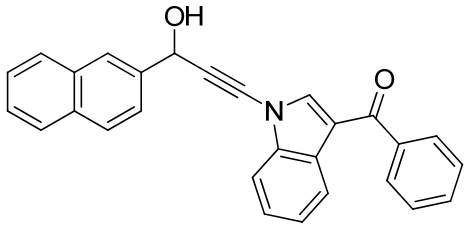
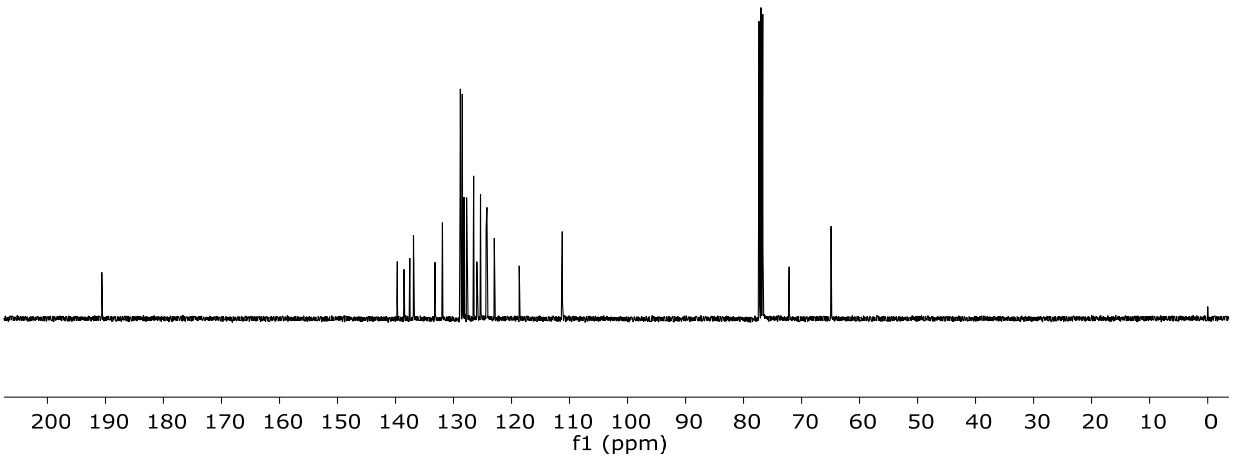
^{1}H NMR Spectrum of 3-(2-Naphthyl)-3-hydroxy-1-(3-benzoylindolyl)propyne





^{13}C NMR Spectrum of 3-(2-Naphthyl)-3-hydroxy-1-(3-benzoylindolyl)propyne





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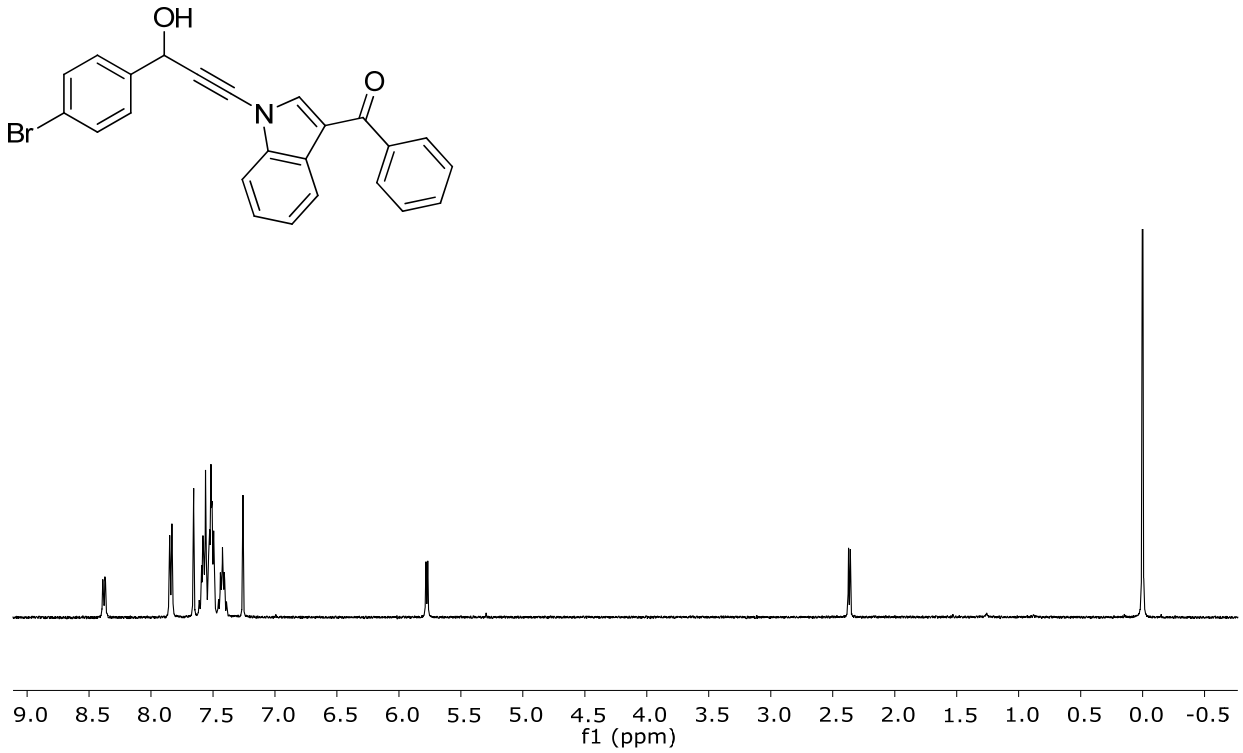
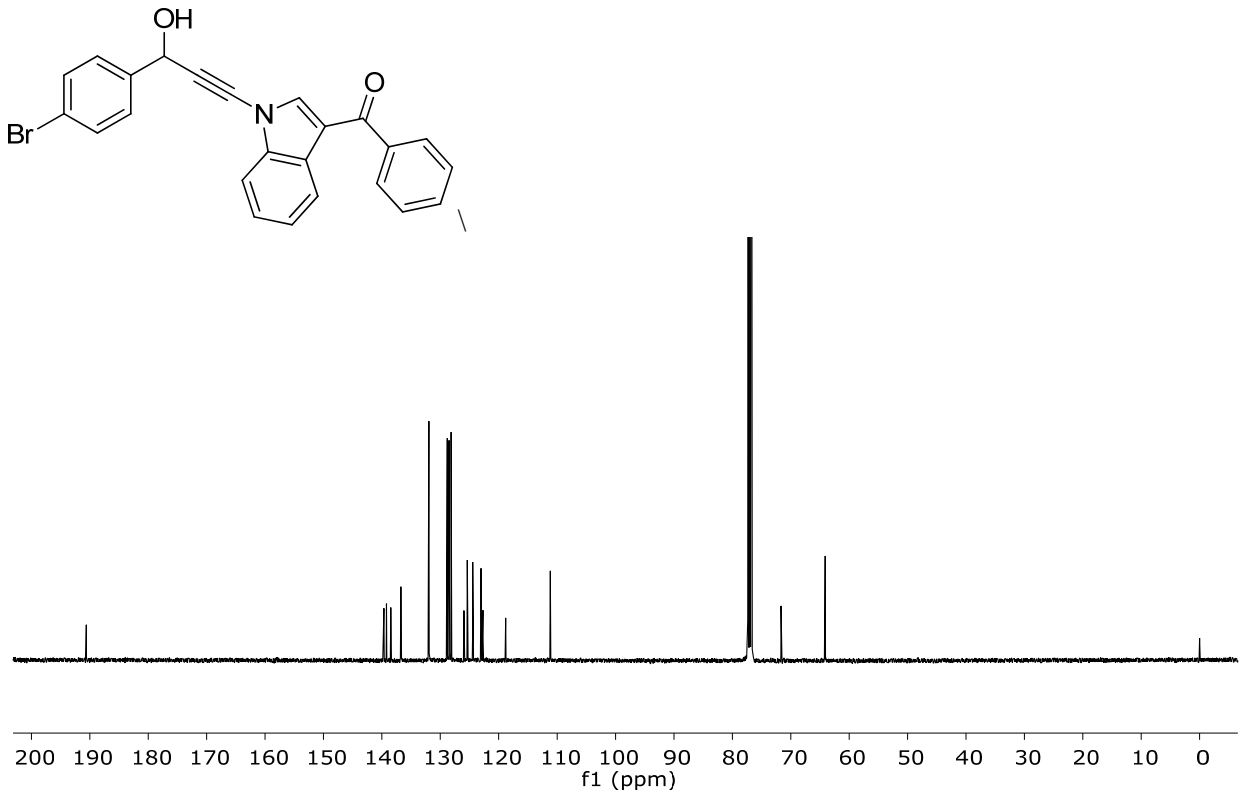
[1]H NMR Spectrum of 3-(4-Bromophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne



[13]C NMR Spectrum of 3-(4-Bromophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne



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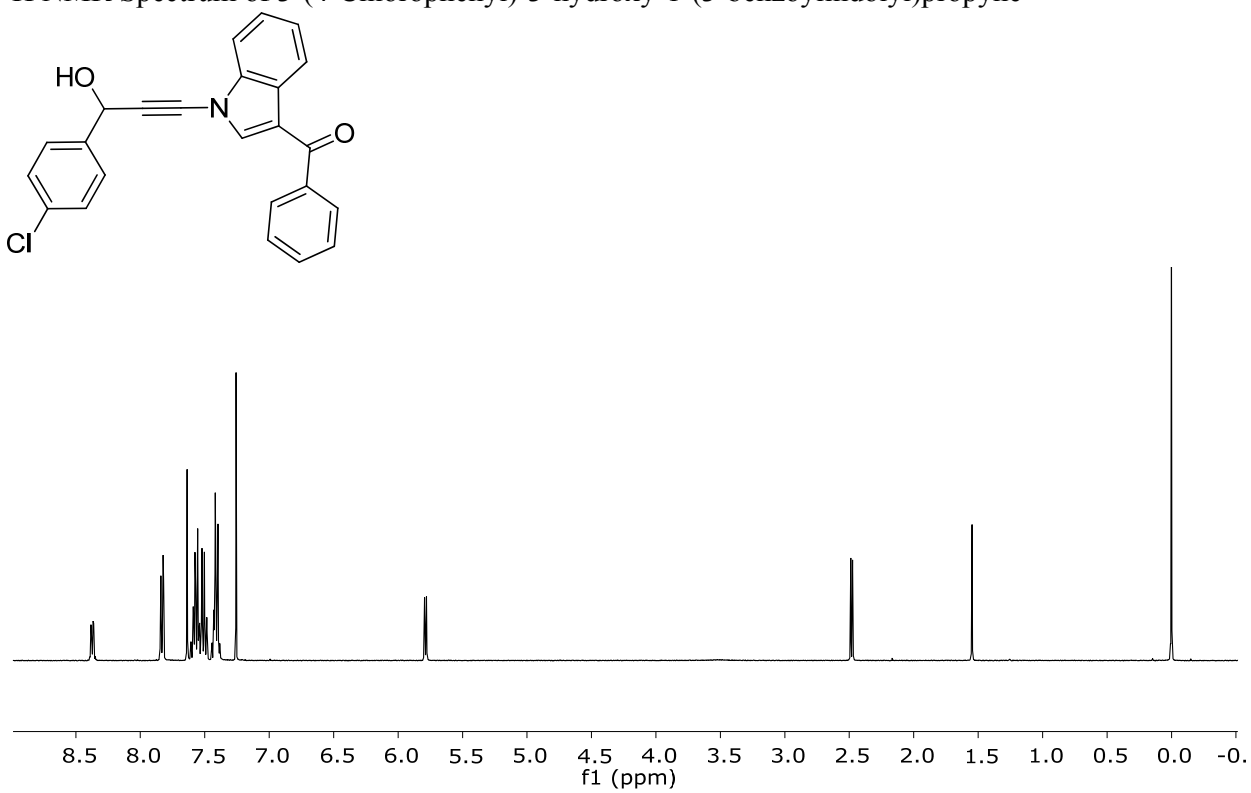
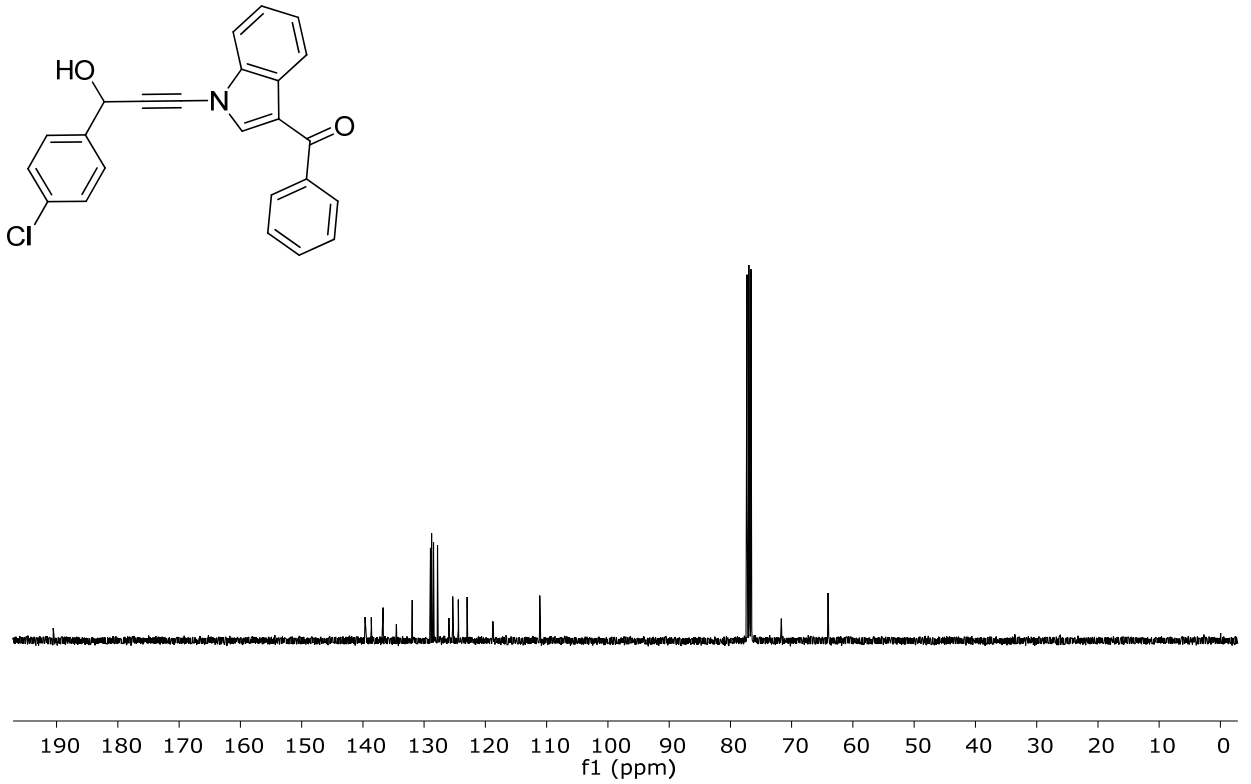
^{1}H NMR Spectrum of 3-(4-Chlorophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne



^{13}C NMR Spectrum of 3-(4-Chlorophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne



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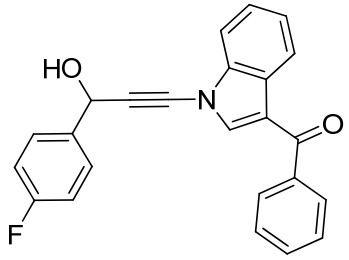
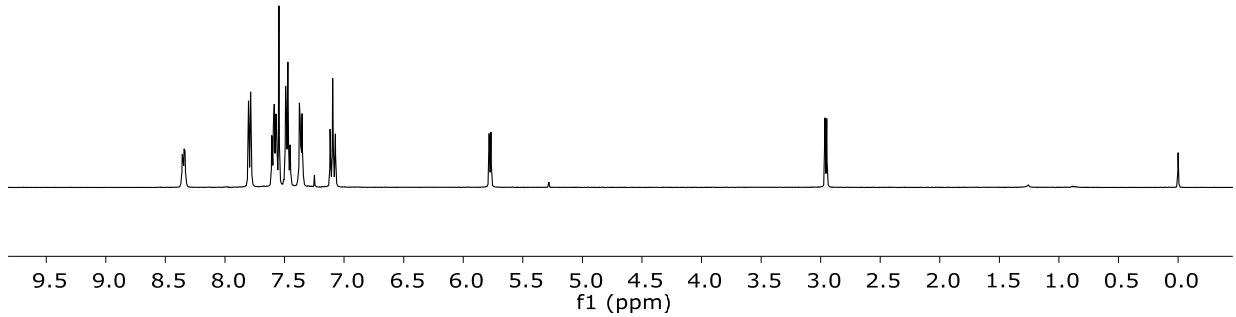
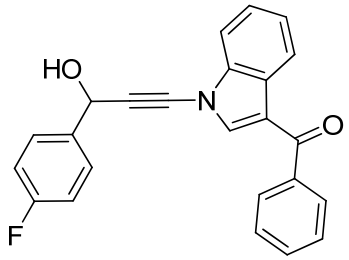
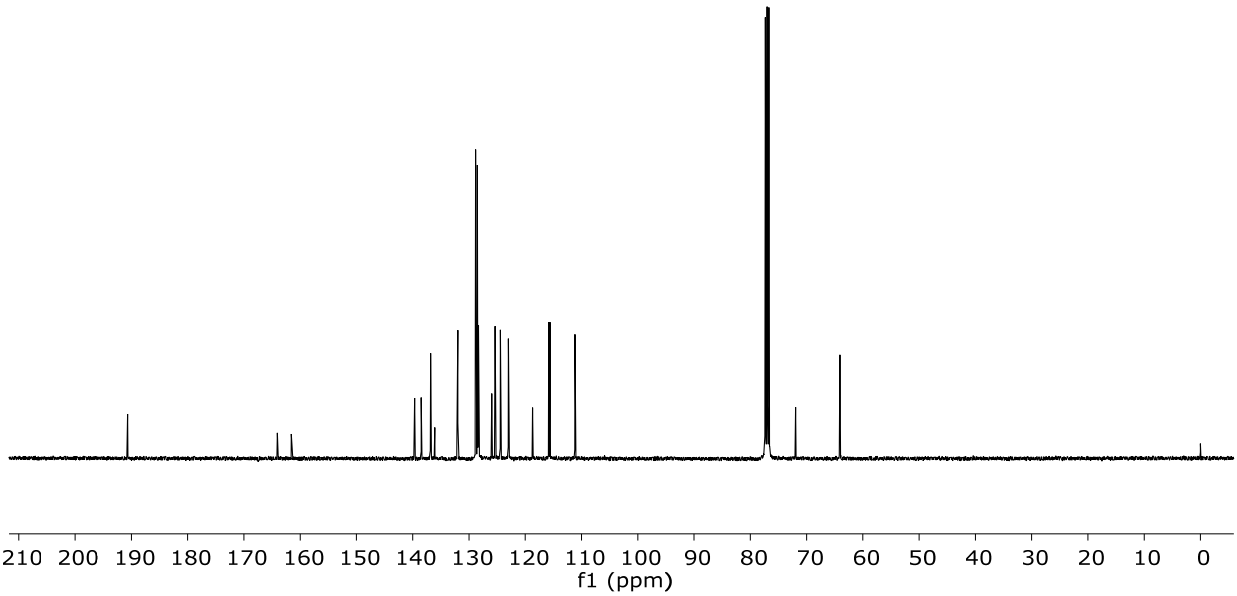
[1]H NMR Spectrum of 3-(4-Fluorophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne





[13]C NMR Spectrum of 3-(4-Fluorophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne





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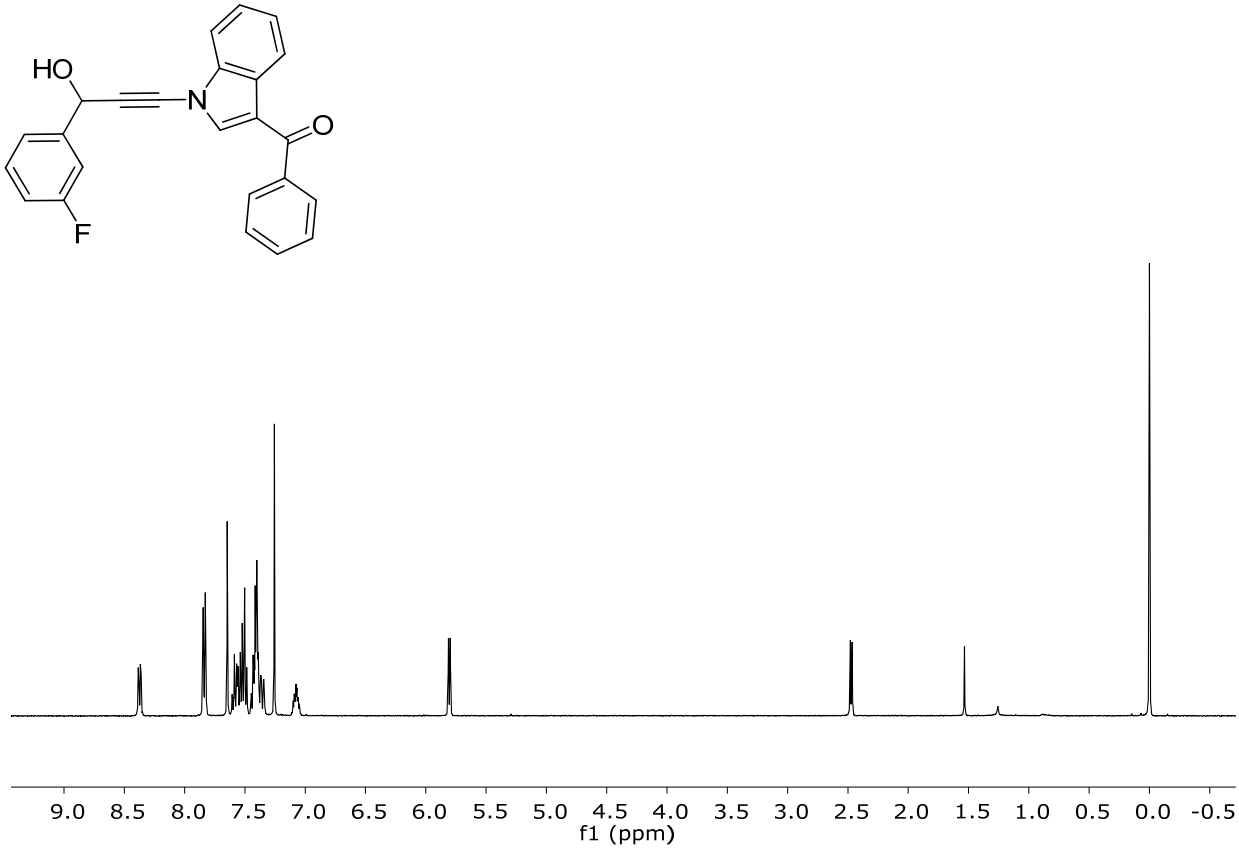
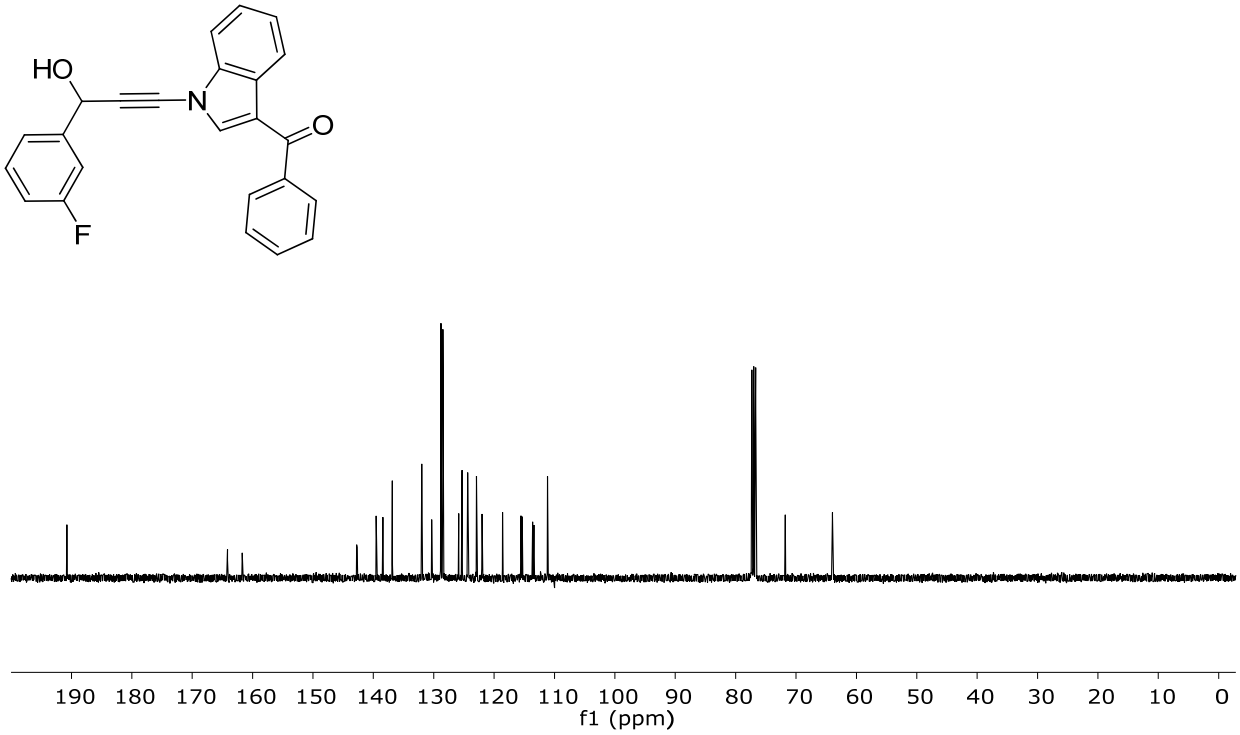
^{1}H NMR Spectrum of 3-(3-Fluorophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

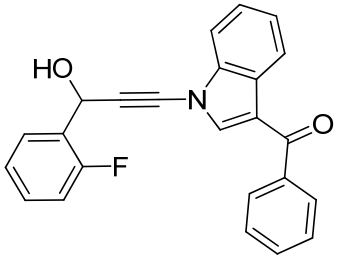


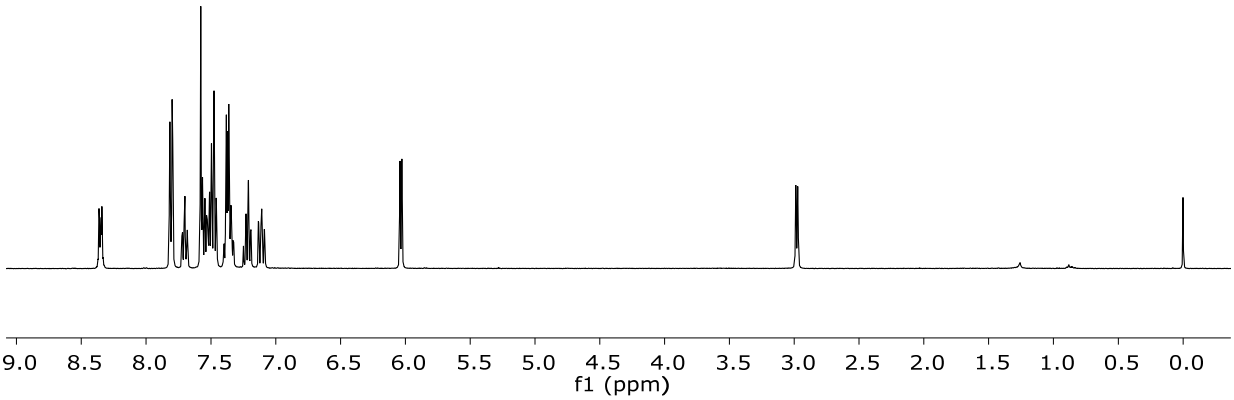
^{13}C NMR Spectrum of 3-(3-Fluorophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne



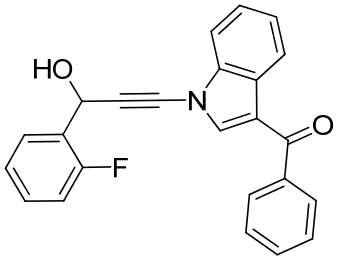
#

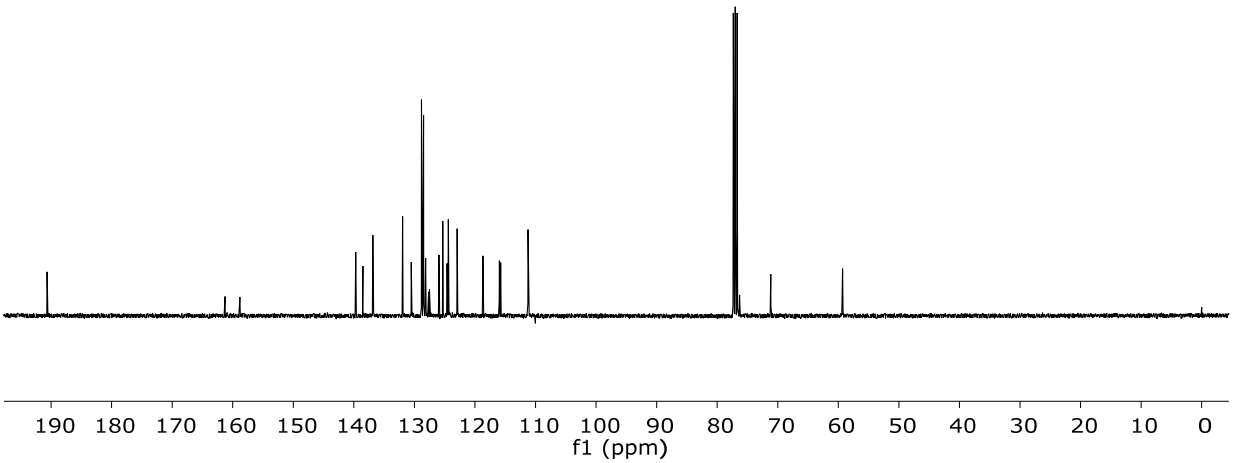
[1]H NMR Spectrum of 3-(2-Fluorophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne





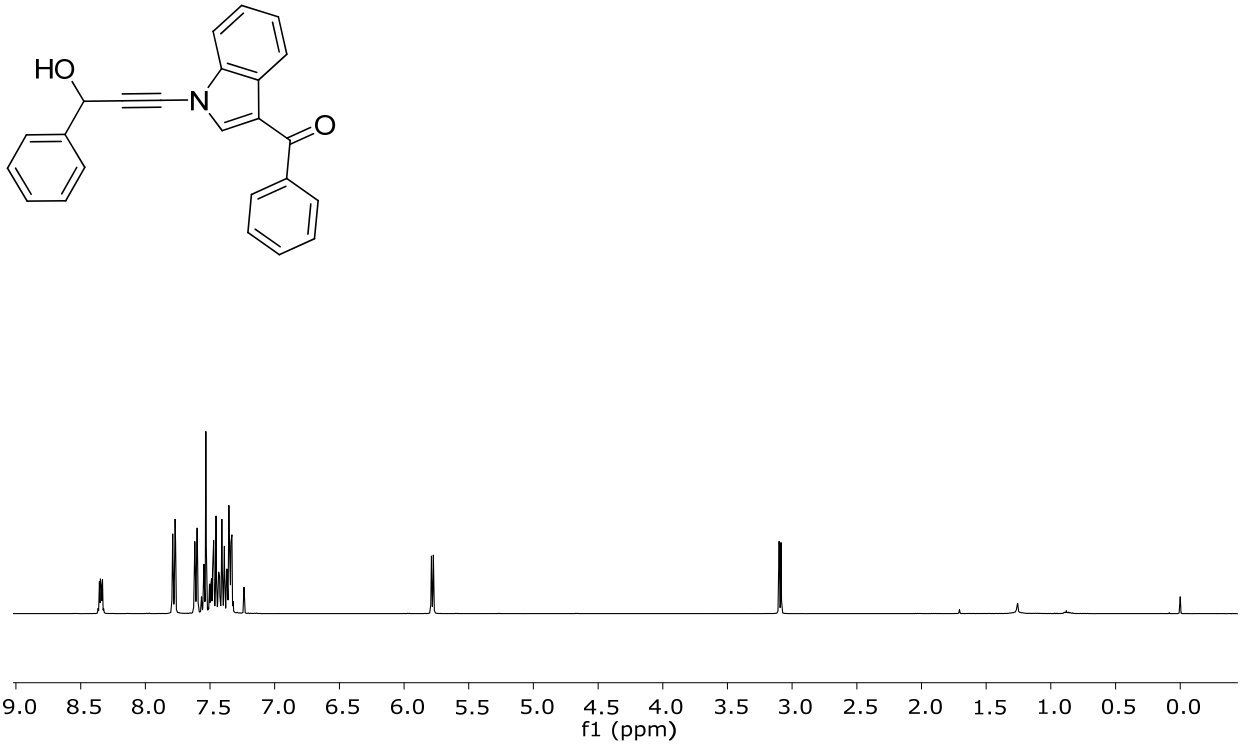
[13]C NMR Spectrum of 3-(2-Fluorophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne



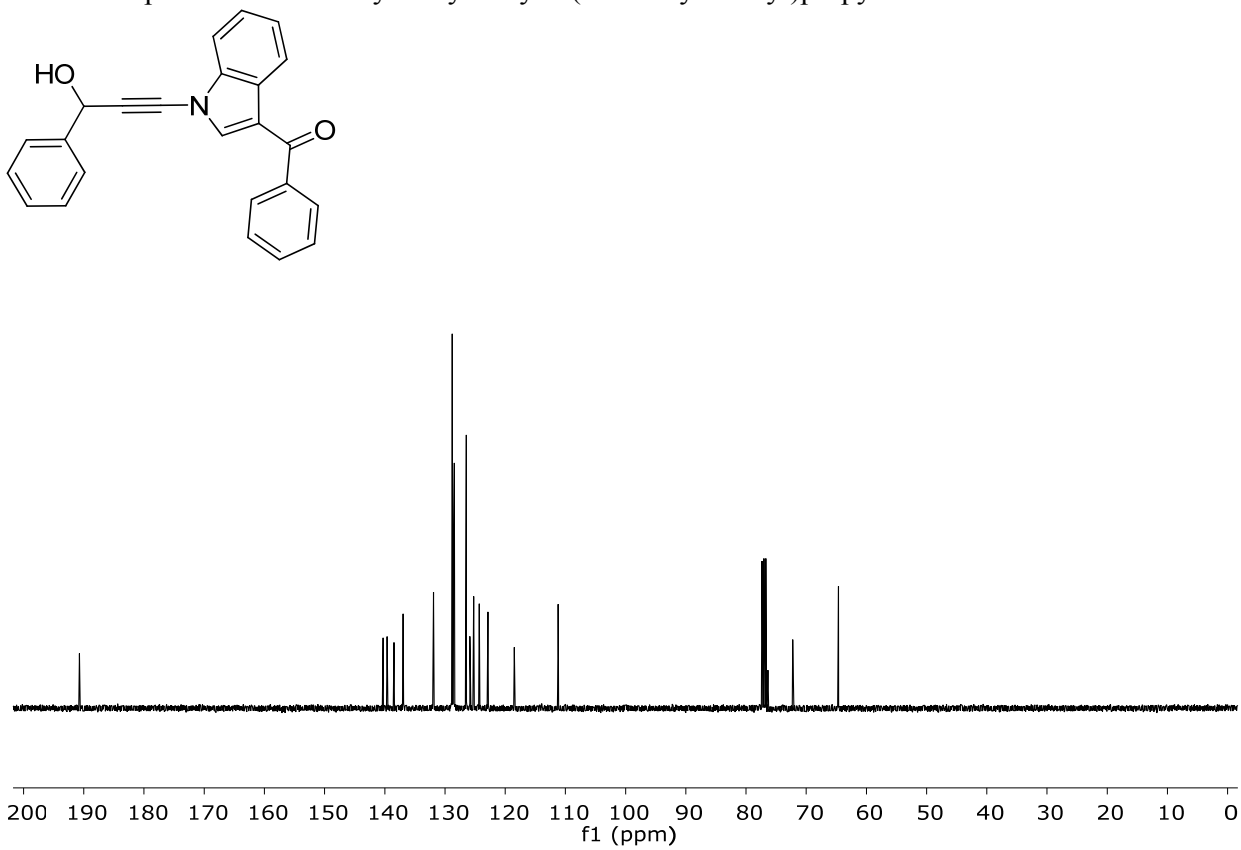


[1]H NMR Spectrum of 3-Phenyl-3-hydroxy-1-(3-benzoylindolyl)propyne

#

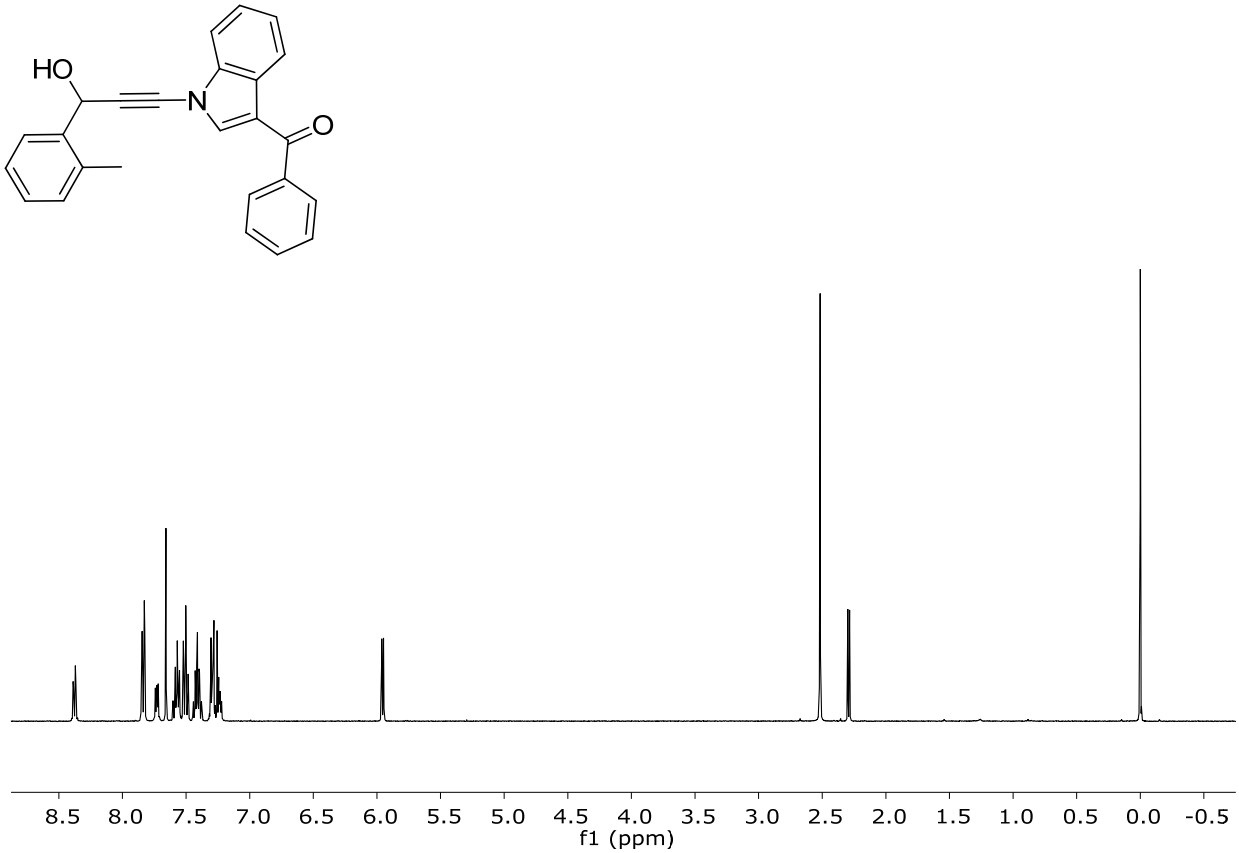


^{13}C NMR Spectrum of 3-Phenyl-3-hydroxy-1-(3-benzoylindolyl)propyne

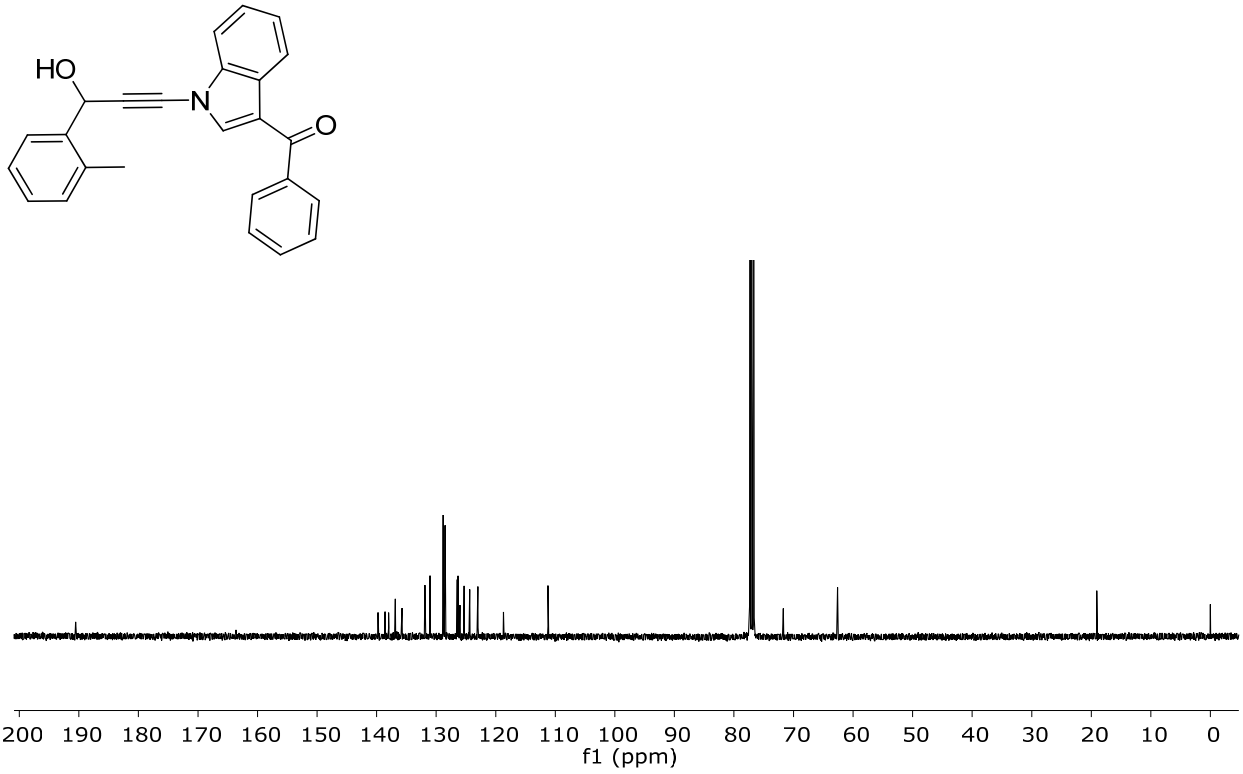


^{1}H NMR Spectrum of 3-(2-Tolyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

#



^{13}C NMR Spectrum of 3-(2-Tolyl)-3-hydroxy-1-(3-benzoylindolyl)propyne



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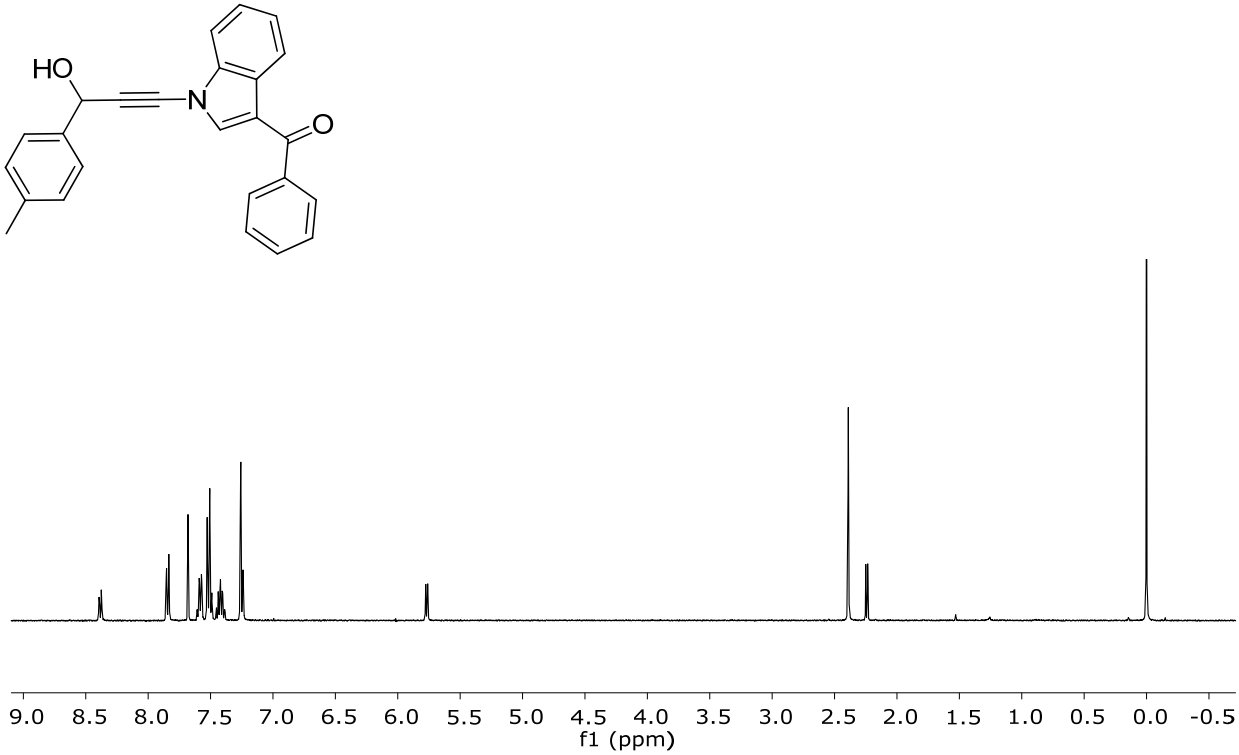
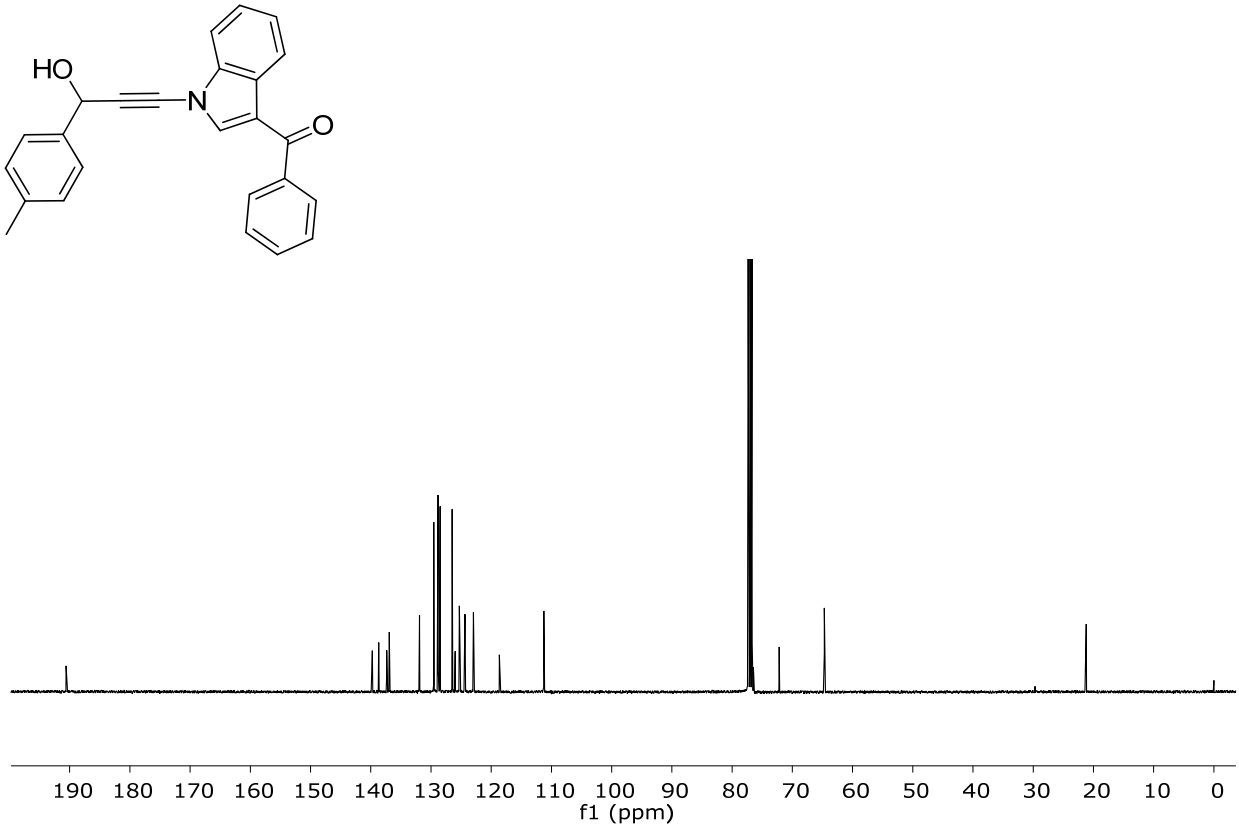
[1]H NMR Spectrum of 3-(4-Tolyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

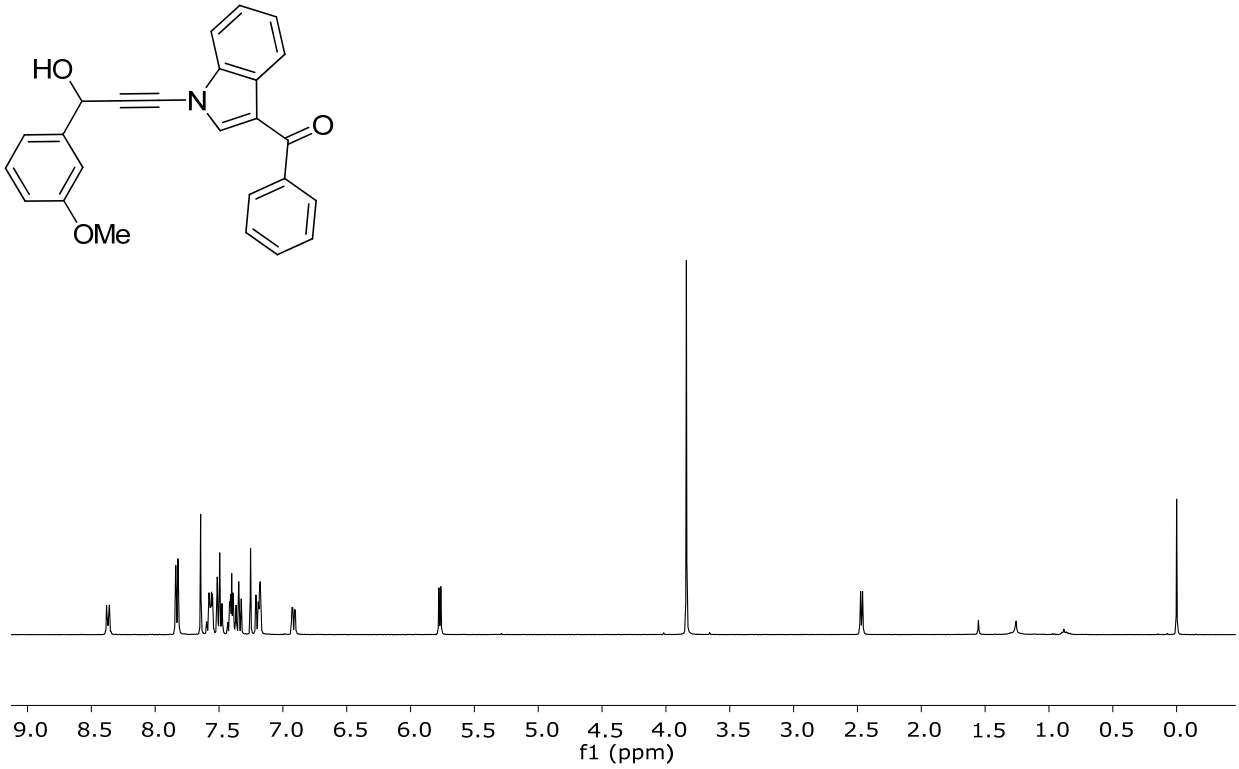


[13]C NMR Spectrum of 3-(4-Tolyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

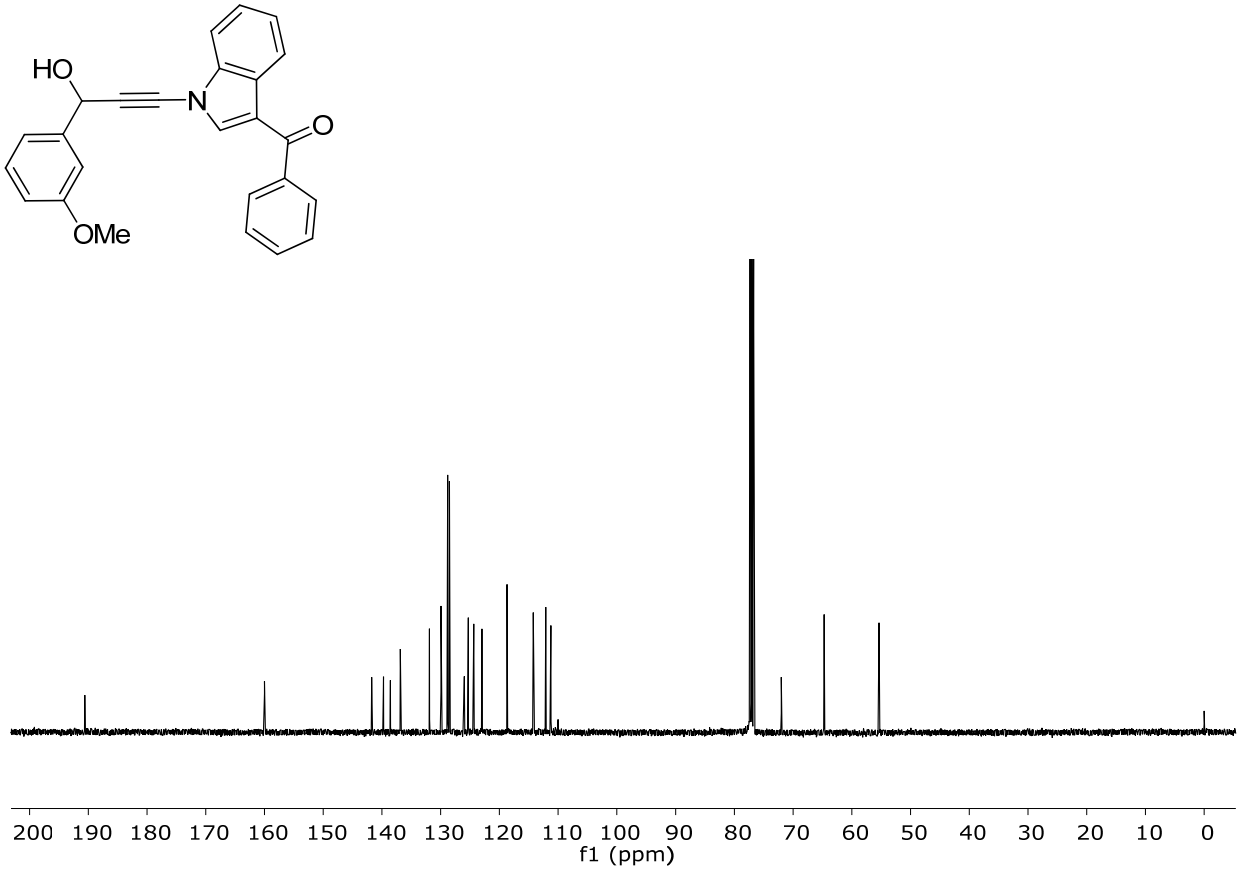


[1]H NMR Spectrum of 3-(3-Methoxyphenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

#

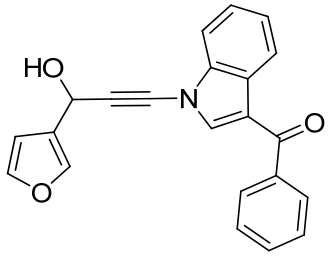


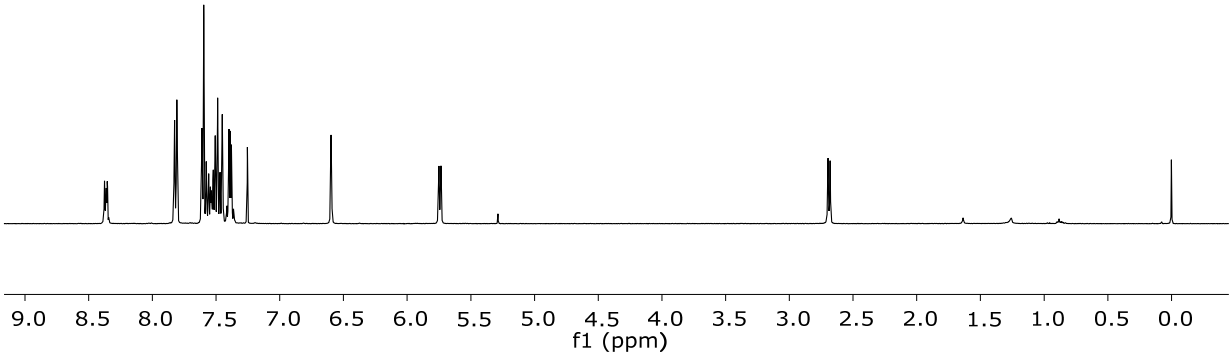
^{13}C NMR Spectrum of 3-(3-Methoxyphenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne



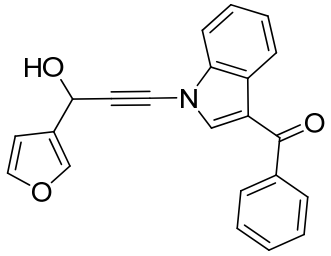
^{1}H NMR Spectrum of 3-(3-Furyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

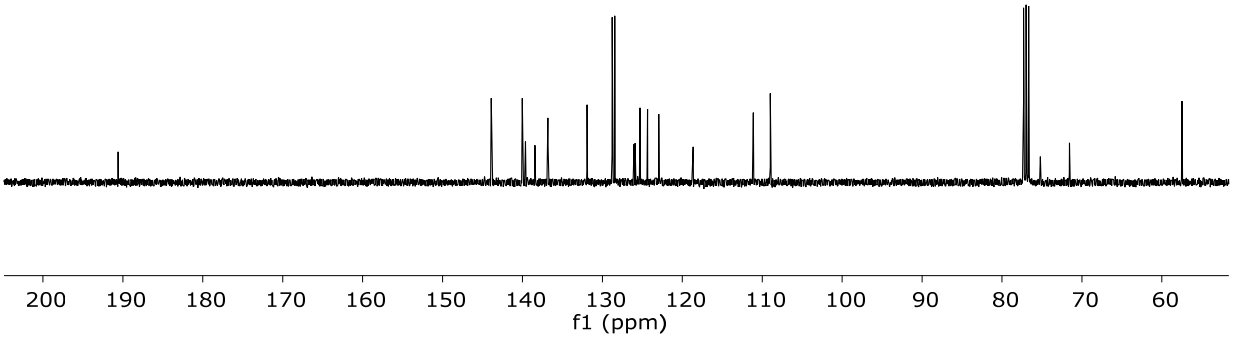
#





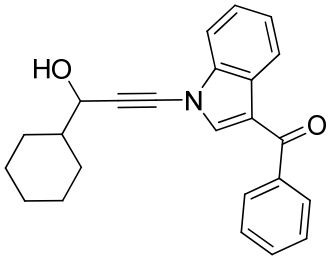
^{13}C NMR Spectrum of 3-(3-Furyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

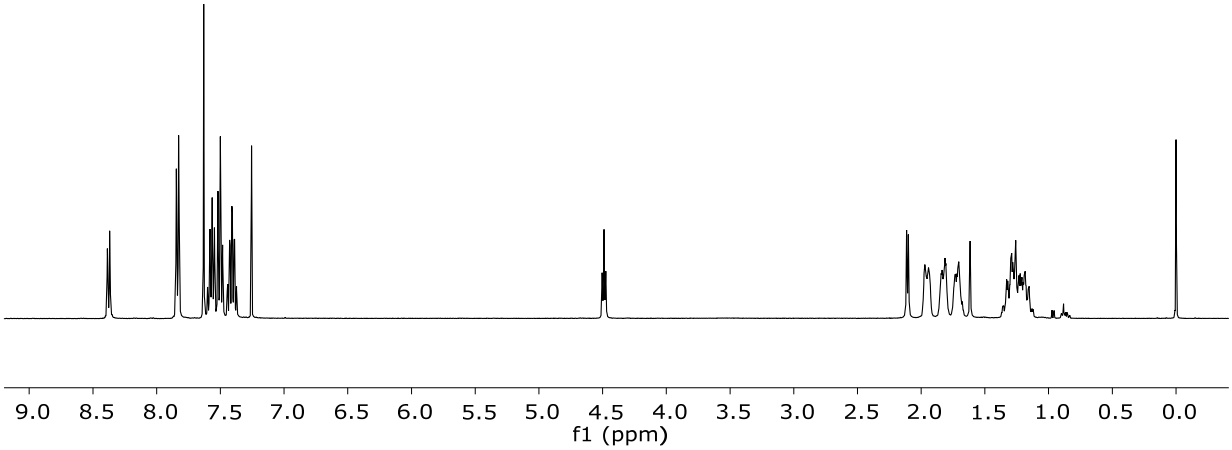




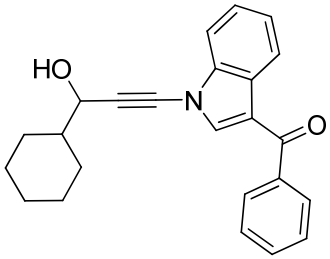
^{1}H NMR Spectrum of 3-Cyclohexyl-3-hydroxy-1-(3-benzoylindolyl)propyne

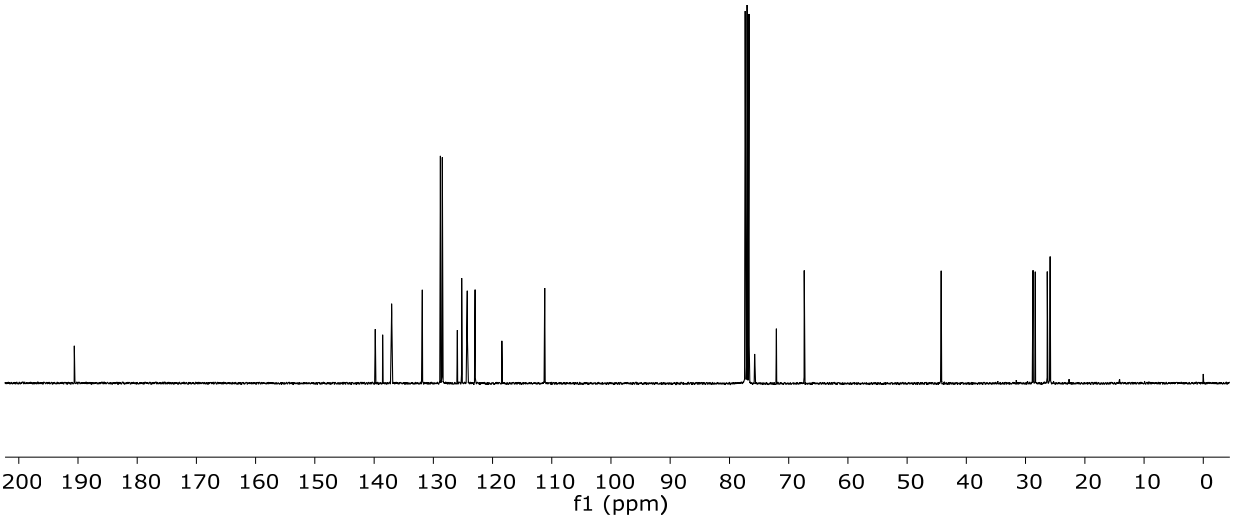
#





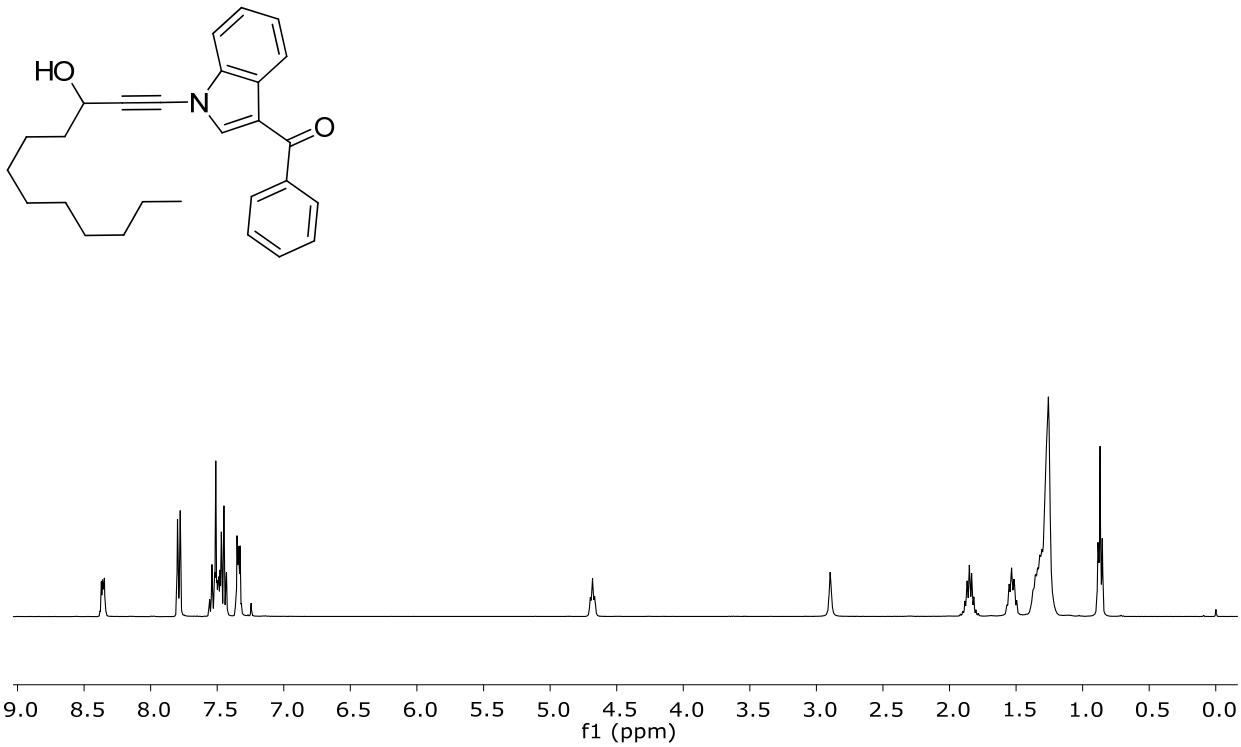
^{13}C NMR Spectrum of 3-Cyclohexyl-3-hydroxy-1-(3-benzoylindolyl)propyne



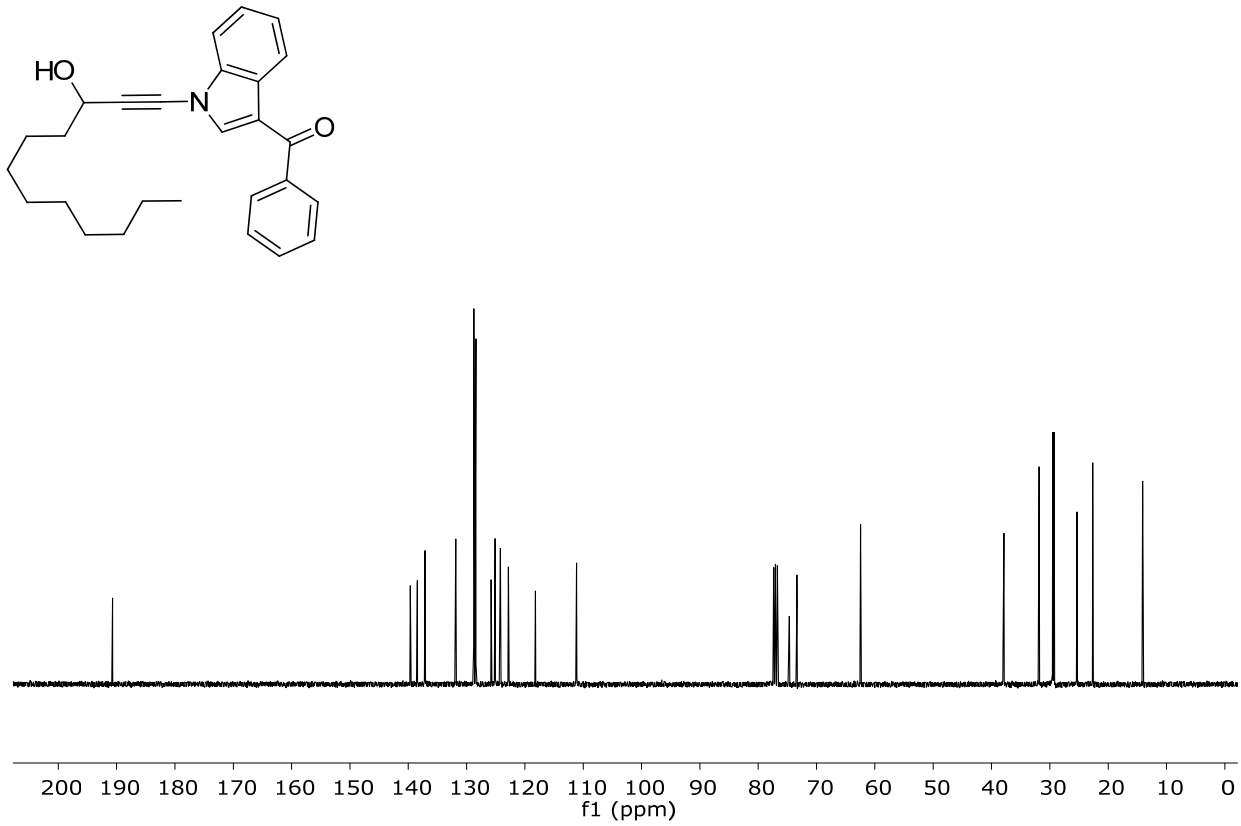


^{1}H NMR Spectrum of 3-Nonyl-3-hydroxy-1-(3-benzoylindolyl)propyne

#

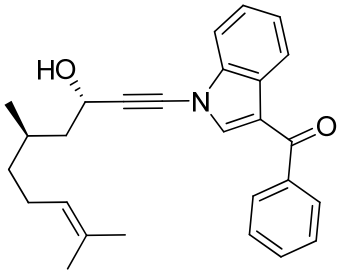


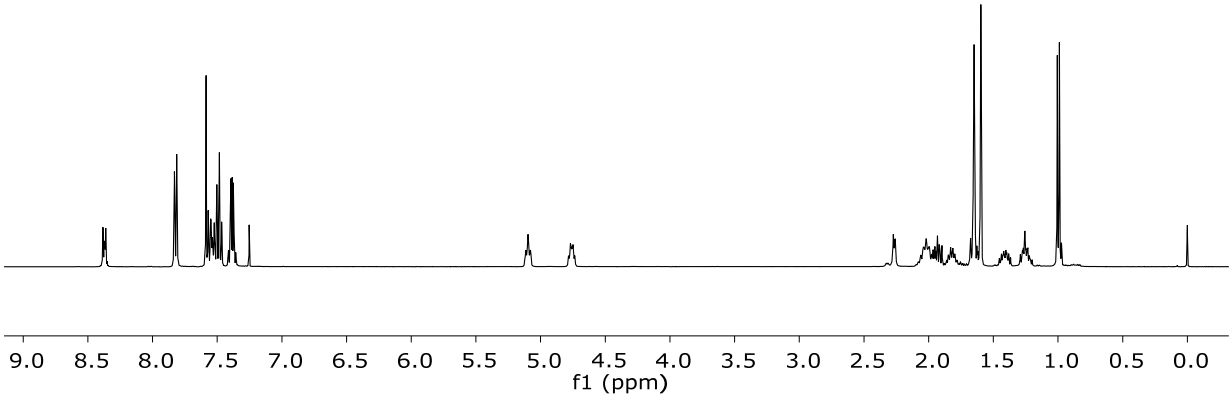
^{13}C NMR Spectrum of 3-Nonyl-3-hydroxy-1-(3-benzoylindolyl)propyne



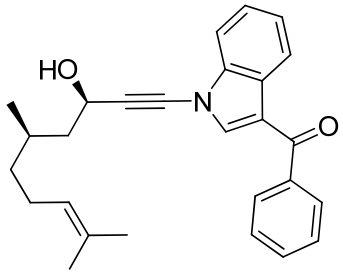
^{1}H NMR Spectrum of 3-((2*R*)-2,6-Dimethylhept-5-enyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

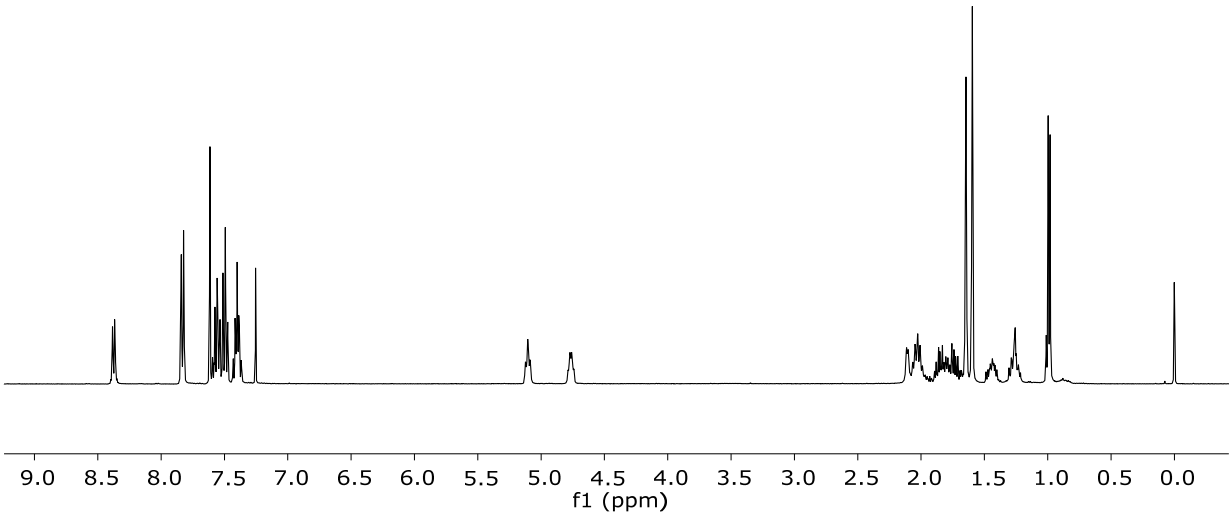
#





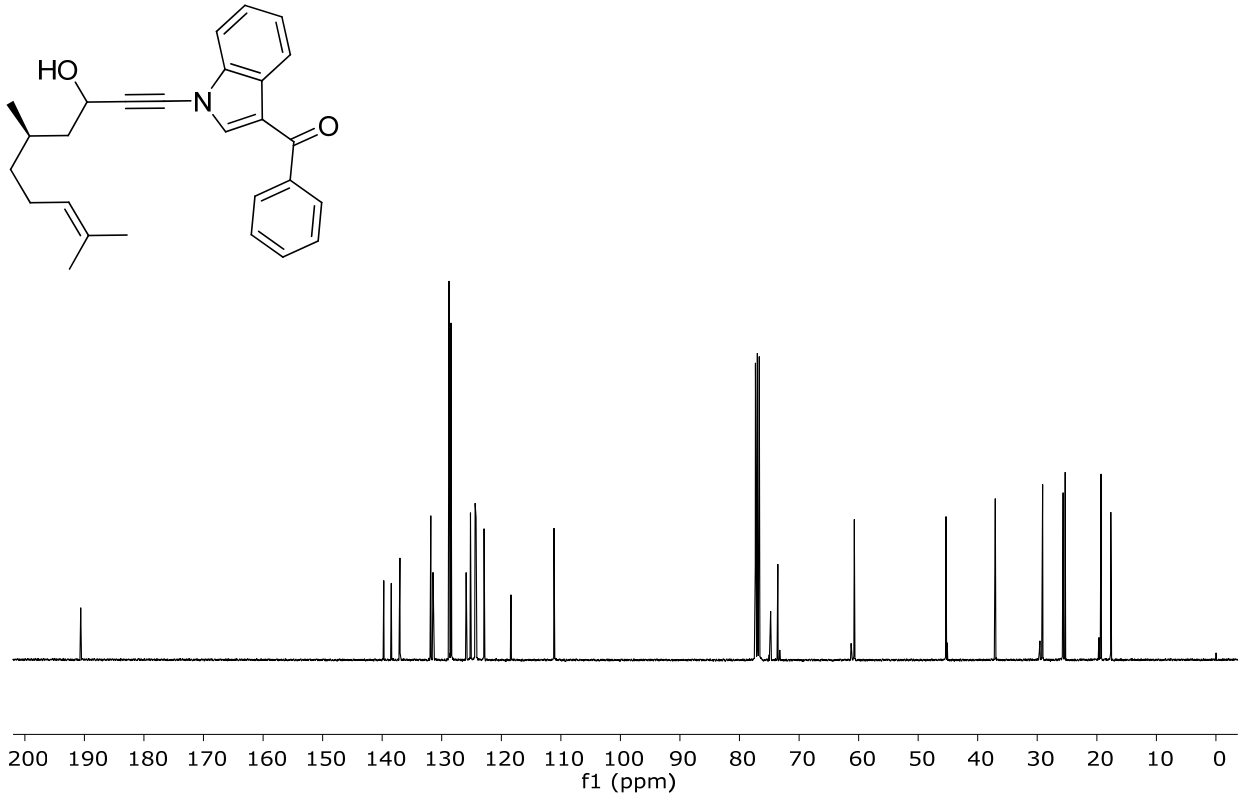
Reaction with (+)-NME



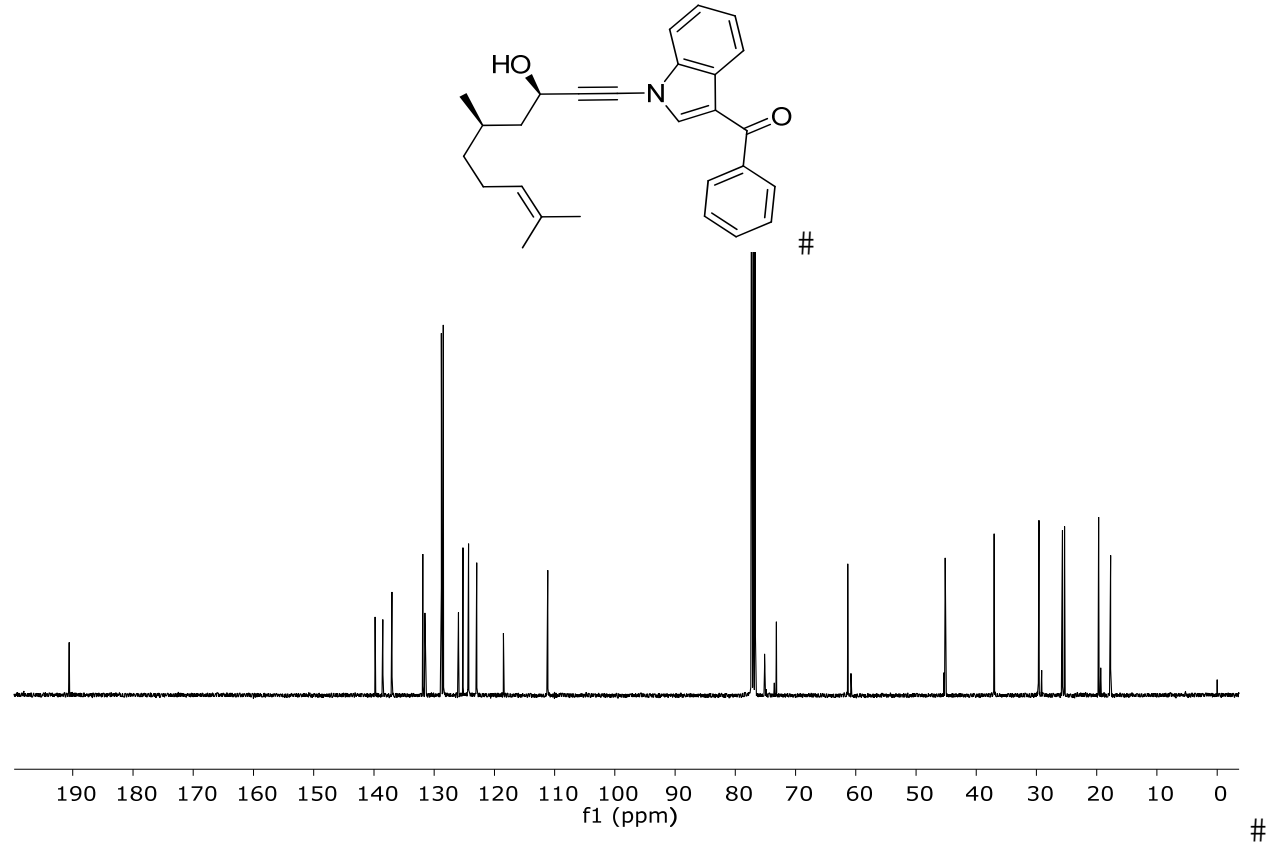


^{13}C NMR Spectrum of 3-((2*R*)-2,6-Dimethylhept-5-enyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

#



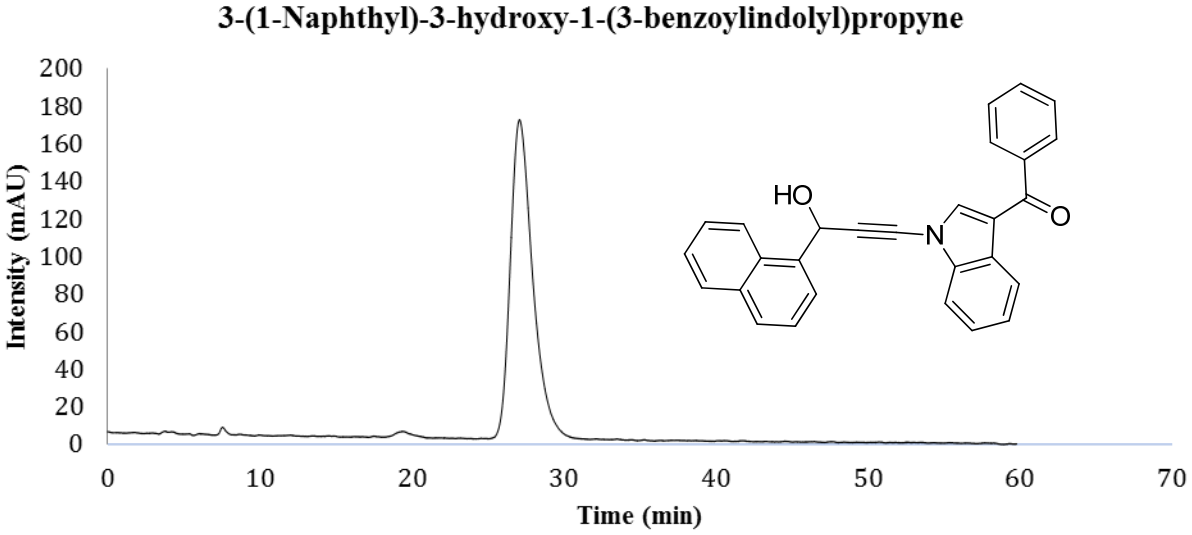
Reaction with (+)-NME



#

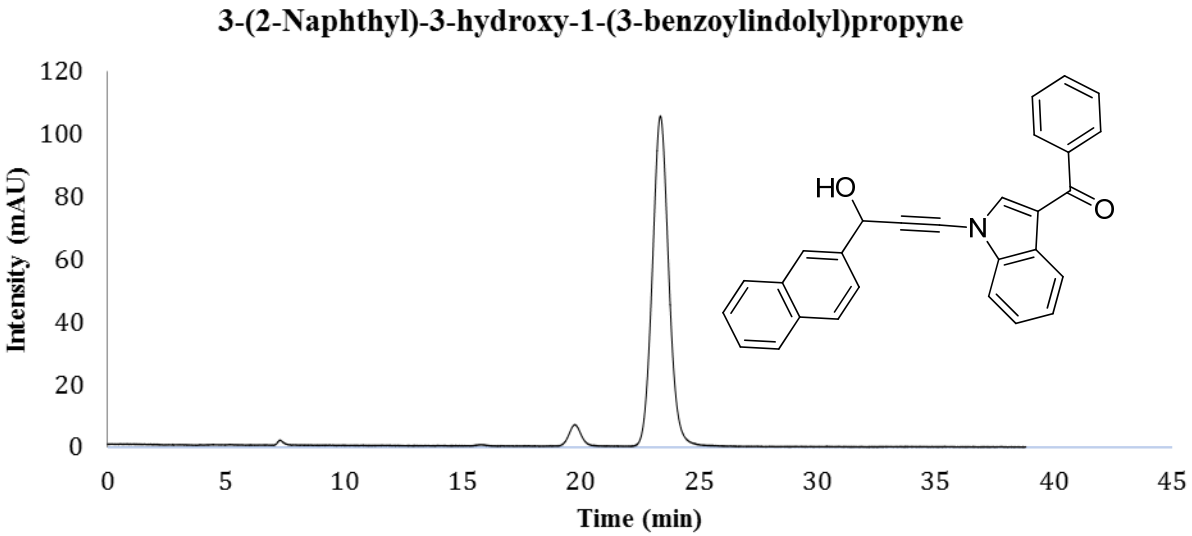
4. Chiral HPLC Chromatograms

#



Chiralcel OD using hexanes:IPA (80:20) as the mobile phase at 1.0 mL/min,
t_1 (minor) = 19.4 min, t_2 (major) = 27.1 min, α = 1.45

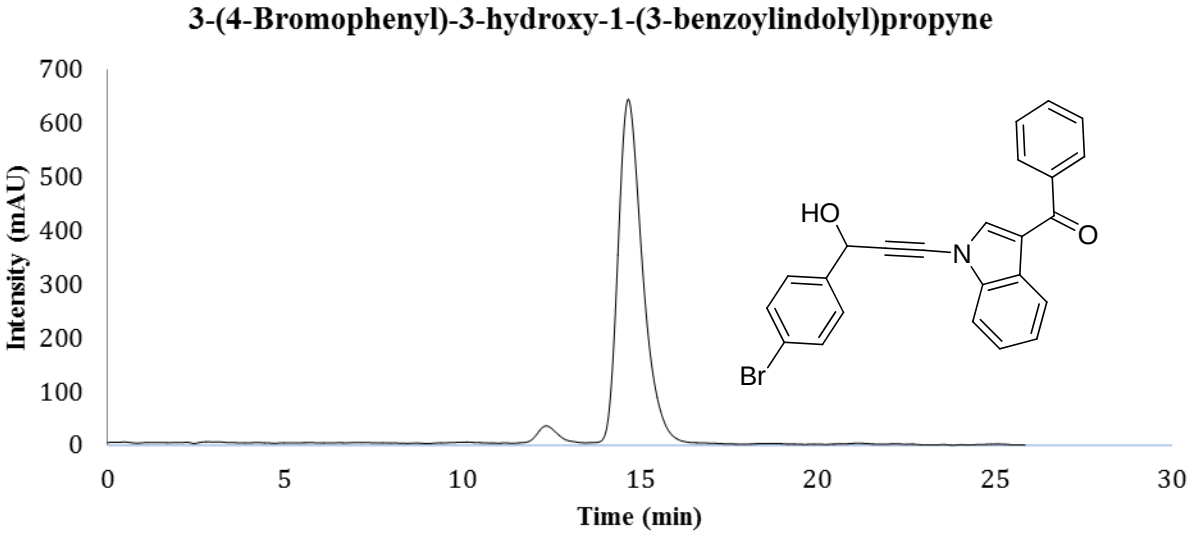
#



Chiralpak IA using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min,
t_1 (minor) = 19.8 min, t_2 (major) = 23.4 min, α = 1.21

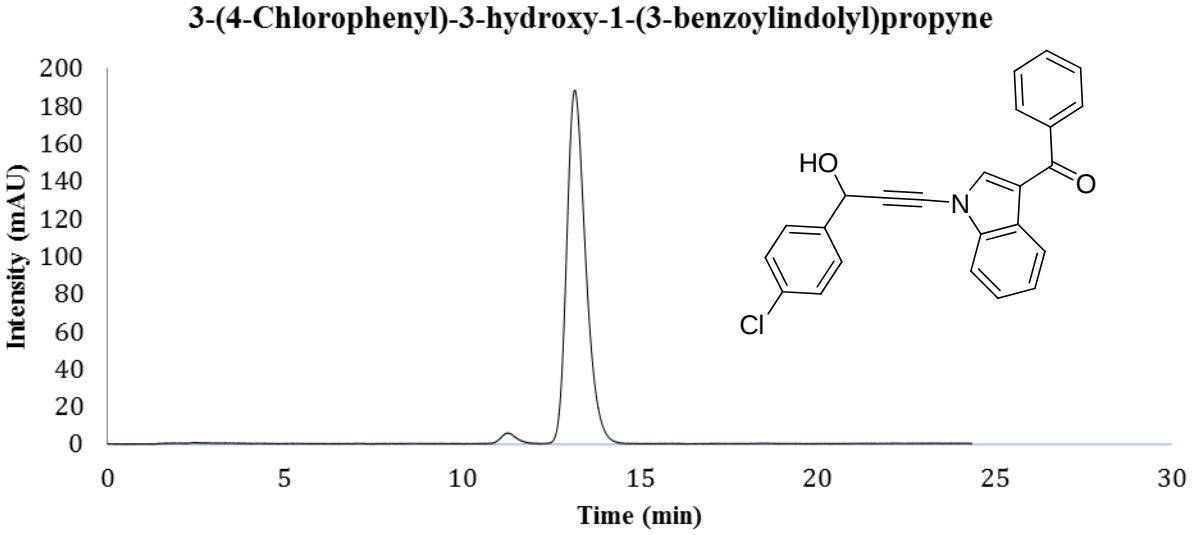
#

#



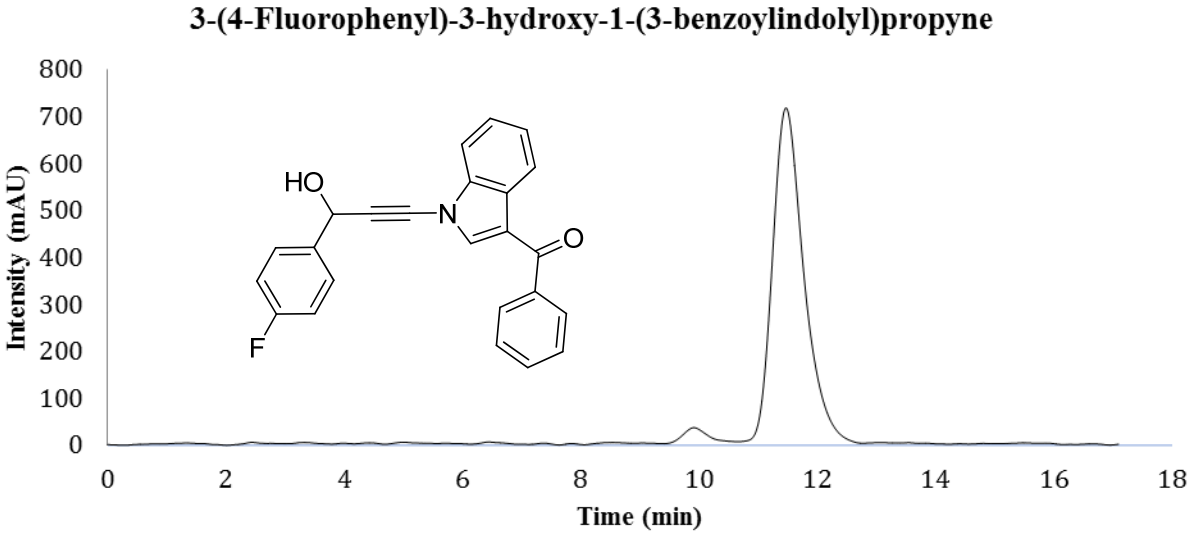
Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min, t_1 (minor) = 12.4 min, t_2 (major) = 14.7 min, α = 1.23

#

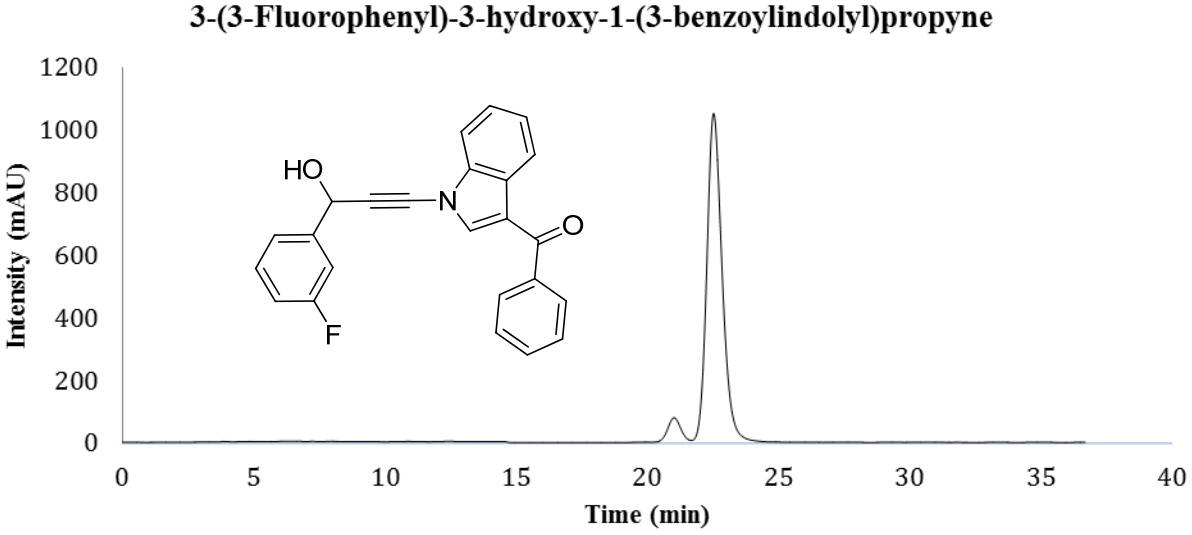


Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min, t_1 (minor) = 11.3 min, t_2 (major) = 13.2 min, α = 1.21

#

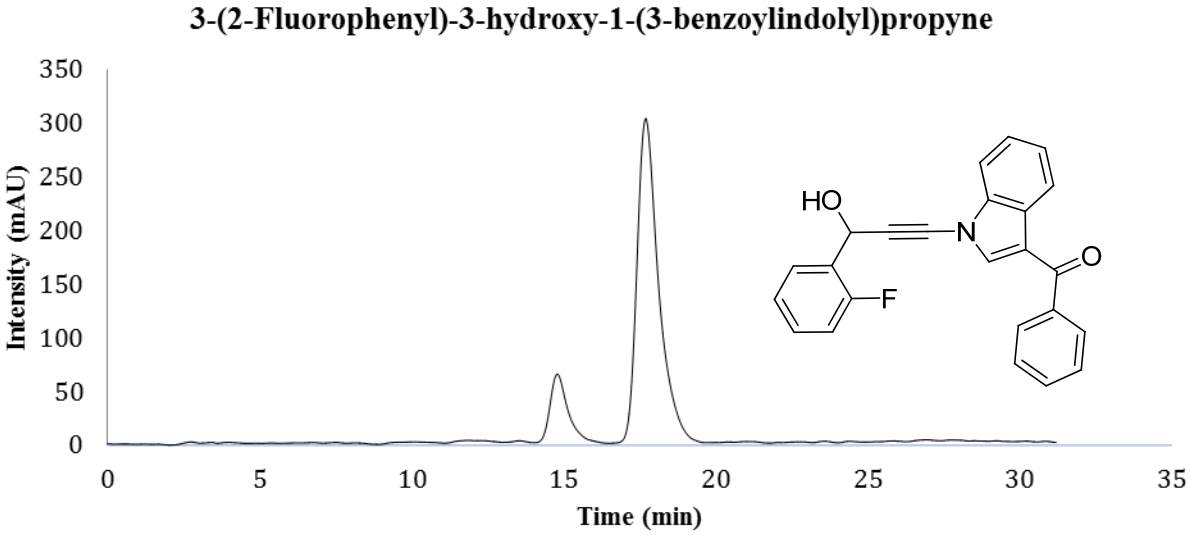


Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min,
t_1 (minor) = 9.9 min, t_2 (major) = 11.4 min, α = 1.20

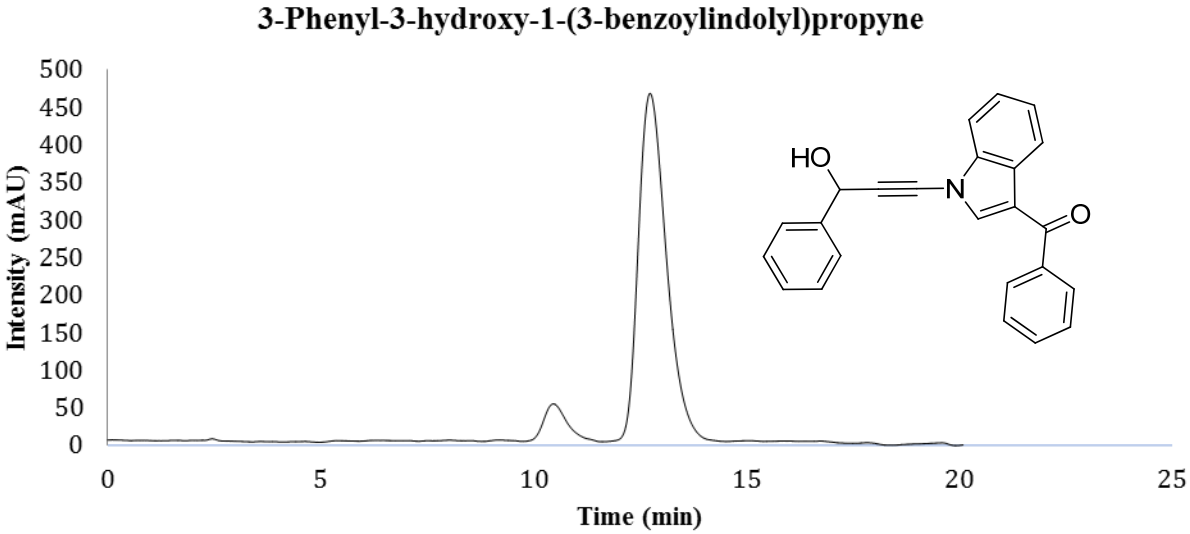


Chiralpak IA using hexanes:EtOH (90:10) as the mobile phase at 1.5 mL/min,
t_1 (minor) = 21.0 min, t_2 (major) = 22.5 min, α = 1.08

#

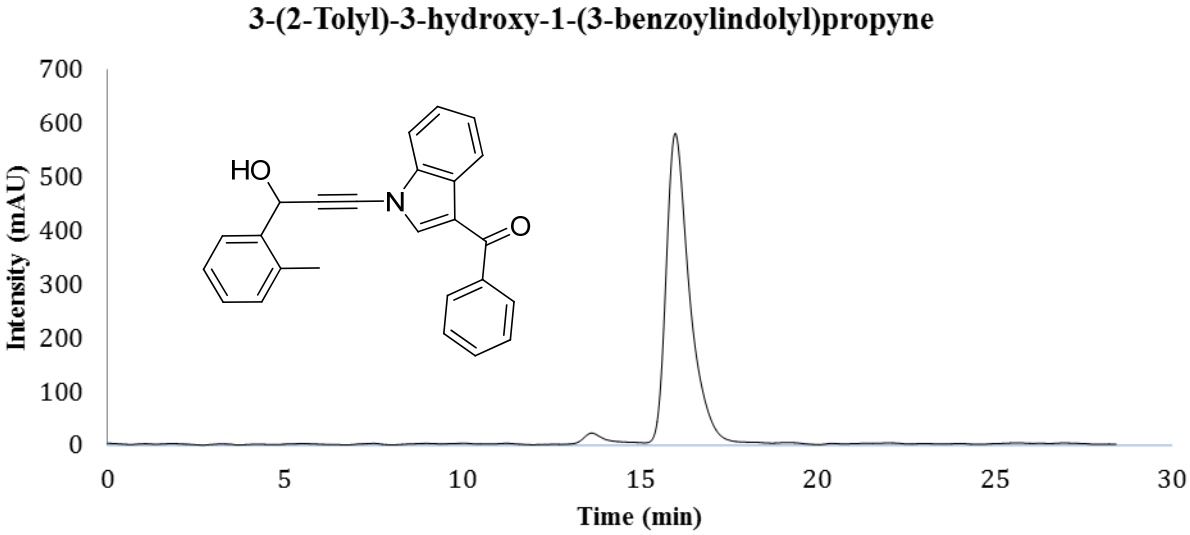


Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min,
t_1 (minor) = 9.6 min, t_2 (major) = 11.4 min, α = 1.25

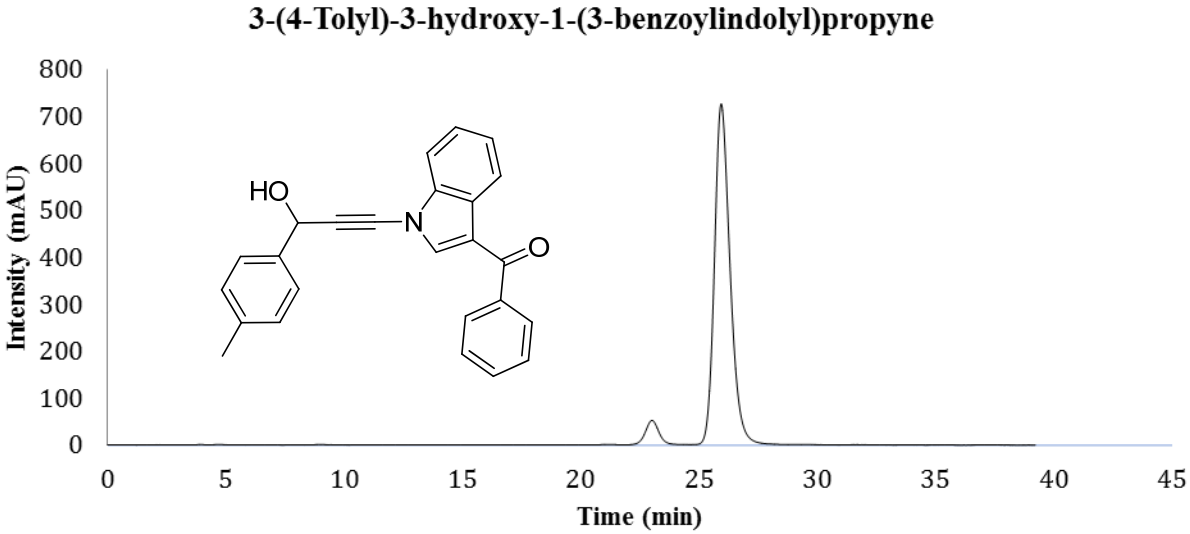


Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min,
t_1 (minor) = 10.5 min, t_2 (major) = 12.8 min, α = 1.28

#

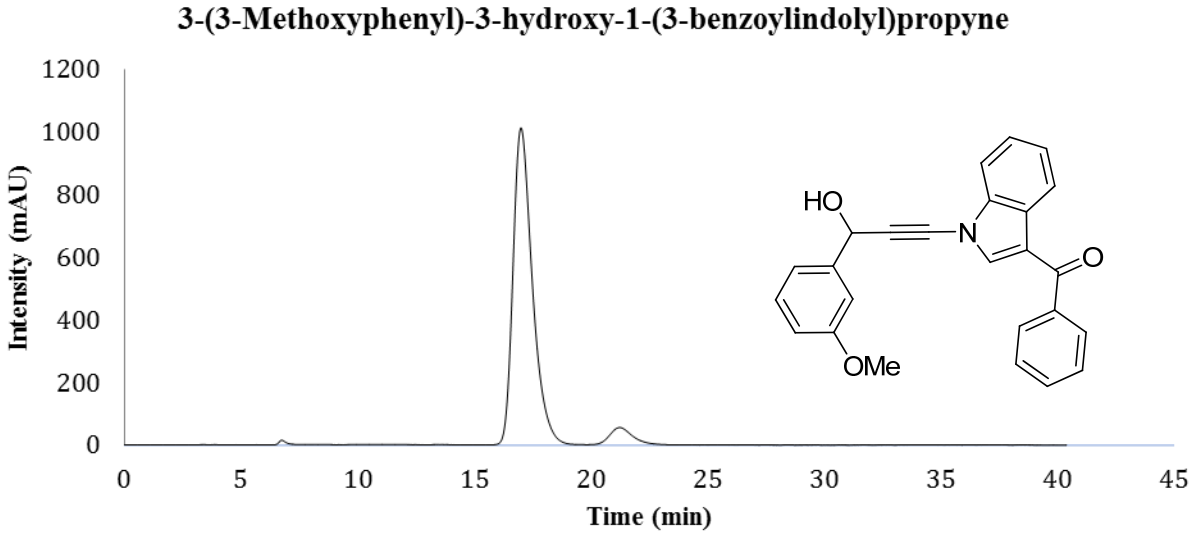


Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.0 mL/min,
t_1 (minor) = 13.6 min, t_2 (major) = 16 min, α = 1.21

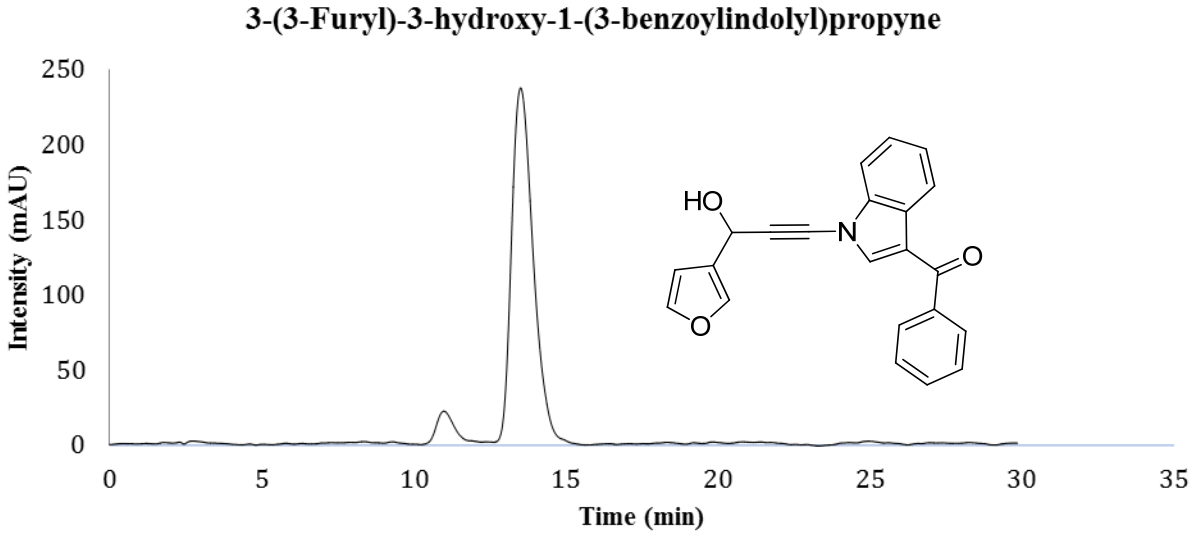


Chiralpak IA using hexanes:EtOH (90:10) as the mobile phase at 1.5 mL/min,
t_1 (minor) = 23.0 min, t_2 (major) = 25.9 min, α = 1.14

#

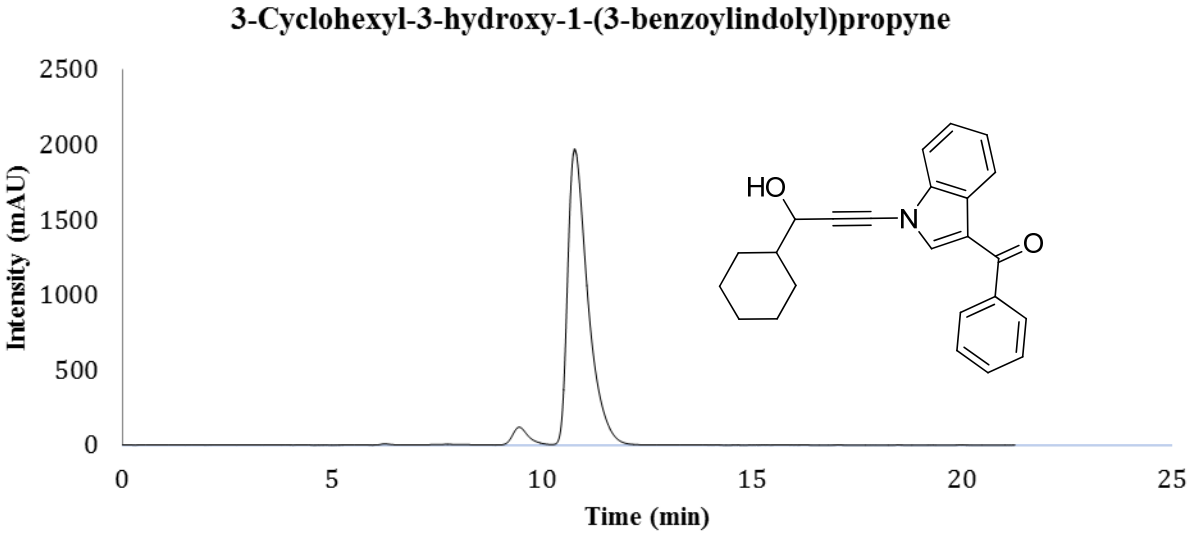


Chiralcel OD using hexanes:EtOH (85:15) as the mobile phase at 1.2 mL/min,
t_1 (major) = 17.0 min, t_2 (minor) = 21.2 min, α = 1.29



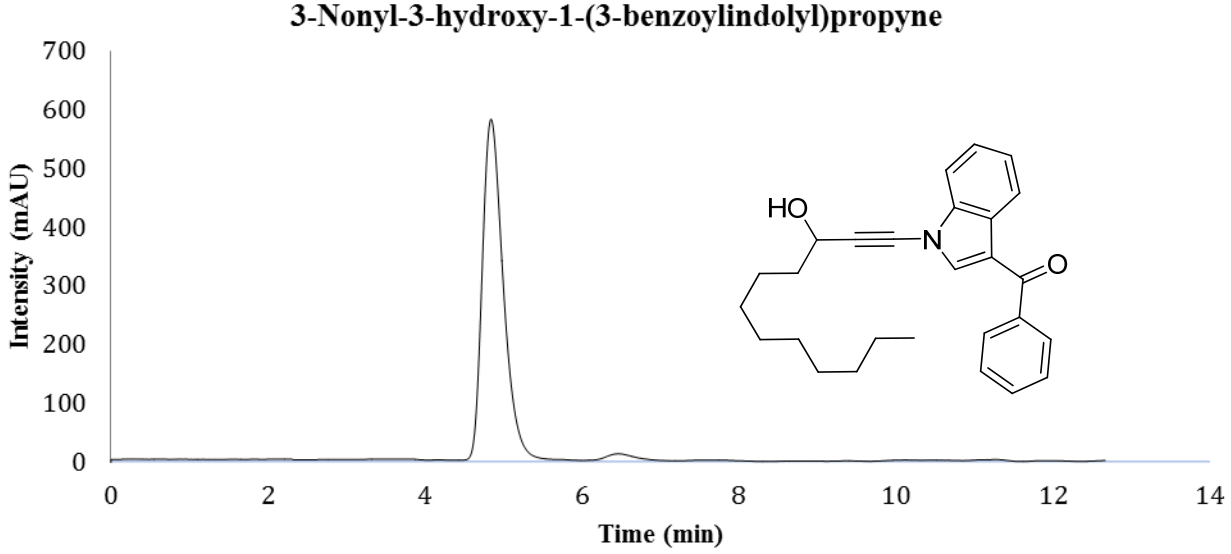
Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min,
t_1 (minor) = 11.0 min, t_2 (major) = 13.5 min, α = 1.29

#



Chiralpak AD using hexanes:EtOH (90:10) as the mobile phase at 1.5 mL/min, t_1 (minor) = 9.5 min, t_2 (major) = 10.8 min, $\alpha = 1.18$

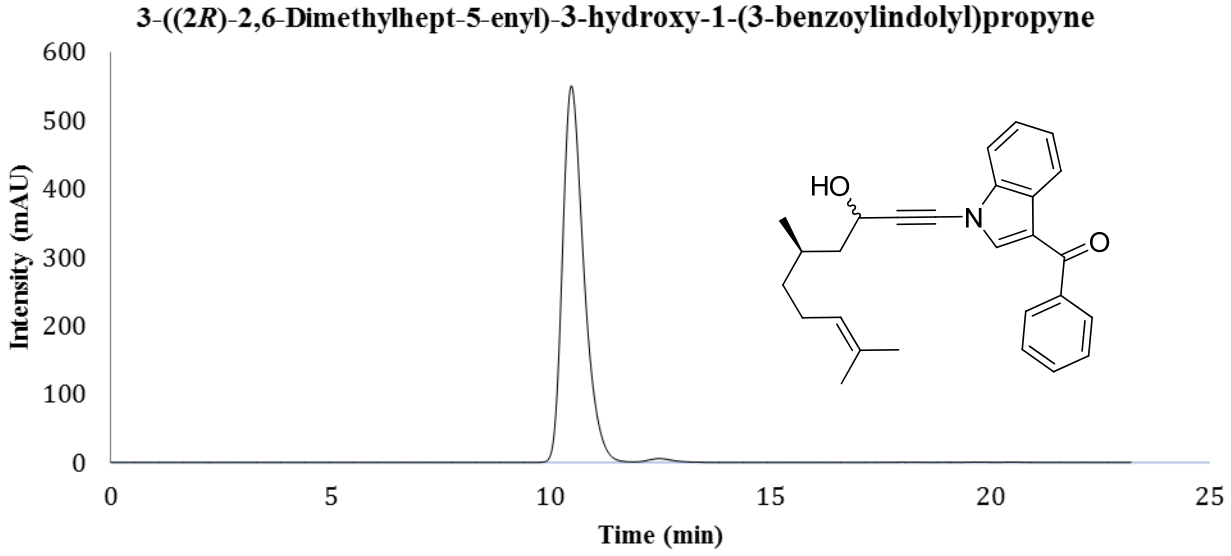
#
#
#
#



#

Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min, t_1 (major) = 4.8 min, t_2 (minor) = 6.5 min, $\alpha = 1.71$#

#



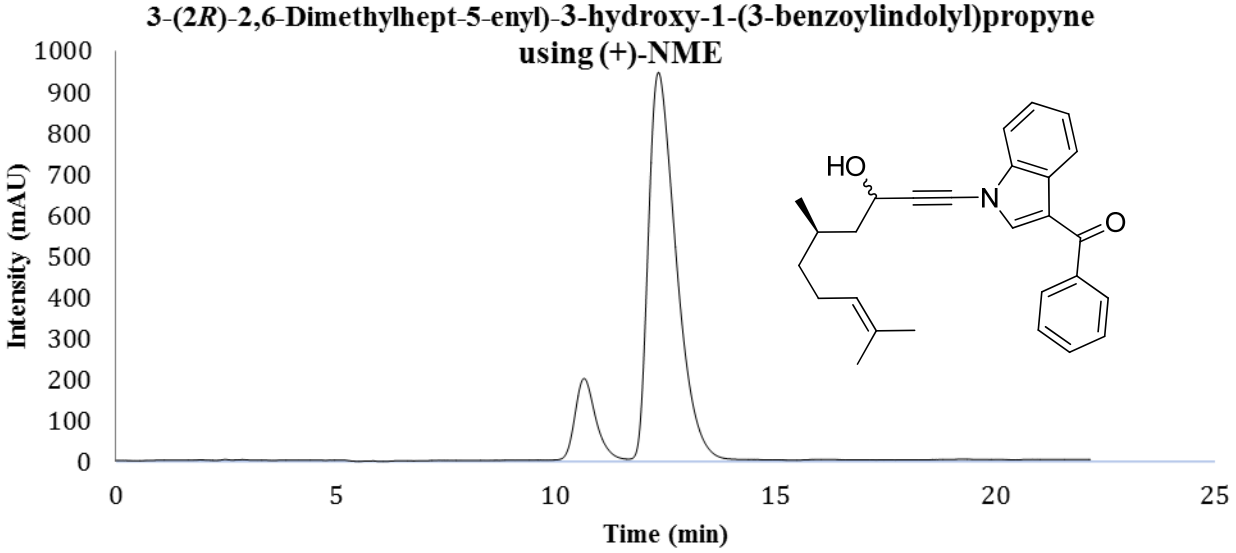
#

Chiralpak AD using hexanes:EtOH (92:8) as the mobile phase at 1.5 mL/min, t_1 (major) = 10.5 min, t_2 (minor) = 12.5 min, α = 1.25.

#

##

#

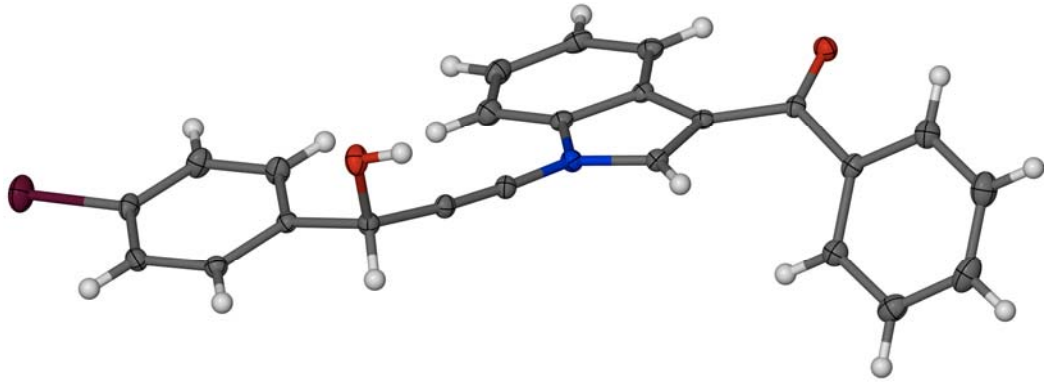


#

Chiralpak AD using hexanes:EtOH (92:8) as the mobile phase at 1.5 mL/min, t_1 (minor) = 10.6 min, t_2 (major) = 12.4 min, α = 1.22

#

5. Crystallographic Analysis



(3*S*)-3-(4-Bromophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

A single crystal was obtained by slow evaporation of a solution of the chiral alcohol in $CDCl_3$. Single crystal X-ray analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were integrated and corrected using the Apex 2 program. The structures were solved by direct methods and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameter. Crystal data: $C_{23}H_{16}NO_2Br$, M = 430.29, colorless rod, 1.4 x 4.4 x 5.0 mm^3, orthorhombic, space group $P2_12_1$, a = 6.6770(8), b = 13.3668(16), c = 21.243(3) Å, V = 1895.9(4) $Å^3$, Z = 4. Absolute structure parameter = 0.0194(73) (Flack, H. D. *Acta Cryst*. 1983, **A39**, 876-881).

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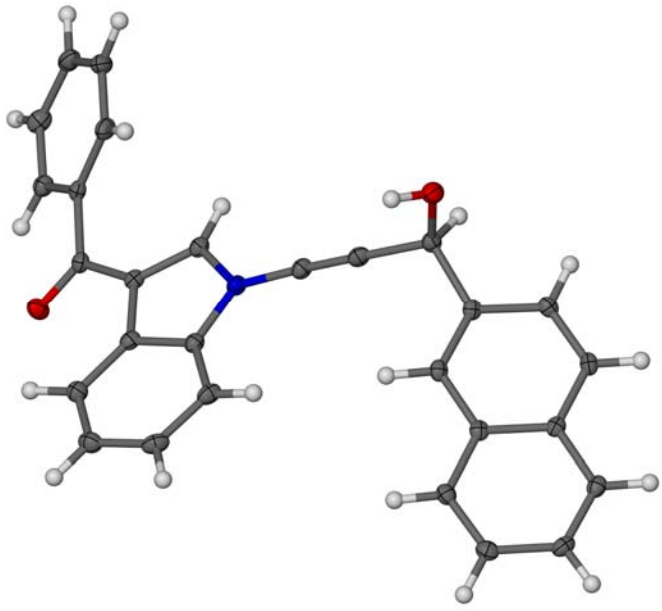

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3-(2-Naphthyl)-3-hydroxy-1-(3-benzoylindolyl)propyne

A single crystal was obtained by slow evaporation of a solution of the chiral alcohol in $CDCl_3$. Single crystal X-ray analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were integrated and corrected using the Apex 2 program. The structures were solved by direct methods and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were

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refined with anisotropic displacement parameter. Crystal data: $C_{28}H_{19}NO_2$, M = 401.16, colorless needle, 1.35 × 4.5 × 7.4 mm, monoclinic, space group $P2_1$, a = 8.0022(10), b = 7.1348(9), c = 16.892(2) Å, β = 92.7060(10) °C, V = 963.3(2) Å^3, Z = 2
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6. References

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2 Hamada, T.; Ye, Xuan; Stahl, S. S. *J. Am. Chem. Soc.* 2008, **130**, 833.

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