Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

A Highly Stereocontrolled Protocol to Prepare Pipecolic Acids Based on Heck and Cyclohydrocarbonylation Reactions

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Supporting Information

GENERAL EXPERIMENTAL DETAILS

All reagents were used as purchased from commercial suppliers without further purification. The reactions were carried out in oven dried or flamed vessels and performed under argon. Solvents were dried and purified by conventional methods prior use. Et_2O and THF were freshly distilled from sodium/benzophenone and dichloromethane was distilled from CaH_2. Toluene was distilled from sodium. Flash column chromatography was performed with Merck silica gel 60, 0.040-0.063 mm (230-400 mesh). PE refers to Petroleum Ether bp 60-80 °C. Merck aluminium backed plates pre-coated with silica gel 60 (UV254) were used for analytical and preparative thin layer chromatography and were visualized by staining with a $KMnO_4$ solution. NMR spectra were recorded at 400 MHz for ^1H and 100 MHz for ^{13}C. Conditions are specified for each spectrum (temperature 25 °C unless specified). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Chemical shifts (δ) are given in ppm relative to the resonance of their respective residual solvent peak, $CHCl_3$ (7.27 ppm, ^1H; 77.16 ppm, the middle peak, ^{13}C). High and low resolution mass spectroscopy analyses were recorded by electrospray ionization. Melting points were determined in open capillary tubes and are uncorrected. Specific rotations were measured with a 10 cm cell with a Na 589 nm filter: values are given in $10^{-1}deg.cm^3.g^{-1}$. Hydroformylation reactions under classical heating and hydrogenolysis reactions were carried out in a stainless steel bench-top autoclave equipped with the gas addition kit heated with an oil bath. Temperature measured with an internal thermocouple probe. MW heated reaction

were carried out with a CEM Discover oven equipped (when required) with the gas addition kit. Caution: The handling of H_2/CO needs special safety equipments.

(*R*)-Ethyl 2-((1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-ylamino)pent-4-enoate (4a) General procedure. Ethyl glyoxylate (0.103 g, 1.0 mmol) and (1*R*, 2*S*)-1-amino-2-indanol **1** (0.149 g, 1.0 mmol) in dry CH_2Cl_2 (10 mL) were stirred at rt in the presence of anhydrous Na_2SO_4 for 12 h. The solvent was evaporated and dry MeOH (10 mL) added followed by allyl bromide (0.363 g, 3.0 mmol) and Indium powder 0.228 g, 2.0 mmol). The reaction was vigorously stirred (magnetic stirring) at rt until all the metal dissolved (≈3 h). The reaction mixture was diluted with 10% aqueous $NaHCO_3$ and extracted with EtOAc. The organic layers were combined, washed with brine, dried over dry Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel, eluting with PE:EtOAc (8:2 to 6:4) to give compound **4a** (0.184 g, 67% yield) as a yellow oil. R_f: 0.8 (PE/EtOAc 7:3). ^{1}HNMR ($CDCl_3$, 400 MHz,) δ 7.02 (m, 4H), 6.13 (m, 1H), 5.13 (m 2H), 4.51 (d, J = 6 Hz, 1H), 4.16 (m, 2H), 3.43 (m, 1H), 3.25 (m, 1H), 2.31 (m, 2H), 1.99 (m, 1H), 1.61 (m, 1H), 1.26 (t, J = 6. Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$)) δ ^{13}C NMR (100 MHz,) δ 18.7, 34.1, 37.0, 55.9, 60.3, 62.8, 79.2, 114.9, 123.3, 126.4, 127.8, 128.9, 137.1, 138.5, 143.3, 174.8. ES/MS: m/z 276 $[M + 1]^+$. HRMS (EI) calcd for $C_{16}H_{22}NO_3^+$ $[M + 1]^+$: 276.1600, found 276.1599.

(*R*)-*tert*-Butyl 2-((1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-ylamino)pent-4-enoate (4b). The crude was purified by column chromatography on silica gel, eluting with PE:EtOAc (8:2 to 6:4), to give compound **4b** (0.221 g, 73% yield) as a yellow solid. M.p 87-89 °C. R_f: 0.8 (PE/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-6.92 (m, 4H), 6.01 (m, 1H), 5.80 (m, 1H), 5.12-5.10 (m, 2H), 3.46 (m, 1H), 3.16-3.14 (m,1H), 2.96 (m, 2H), 2.36 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 38.3, 39.7, 60.7, 65.2, 70.3, 81.8, 118.6, 123.9, 125.5, 126.8, 128.2, 133.3, 141.3, 173.9. ES/MS: m/z 304 $[M + 1]^+$. Anal calcd for $C_{18}H_{25}NO_3$ C, 71.26; H, 8.31; N, 4.62; O, 15.82. Found C, 71.21; H, 8.30; N, 4.59.

(2R,3S)-*tert*-Butyl 2-((1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-ylamino)-3-methyl-pent-4-enoate (4c). The product was purified by column chromatography on silica gel, eluting with PE:EtOAc (8:2 to 6:4) to give compound **4c** (0.225 g, 71% yield) as a yellow oil. R_f: 0.5 (PE/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$)) δ 7.15 – 6.80 (m, 4H), 5.71 (m, 1H), 5.20 (d, J = 10 Hz, 1H), 5.03 (d, J = 17 Hz, 1H), 4.51 (d, J = 6 Hz, 1H), 3.93 (d, J = 7 Hz, 1H), 3.30 (m, 1H), 2.01 (m, 2H), 1.63 (m, 1H), 1.44 (s, 9H), 1.07 (d, J = 6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 28.5, 33.9, 37.0, 63.6, 67.8, 80.1, 82.5, 114.4, 122.5, 126.2, 127.1,

128.1, 128.7, 136.0, 137.0, 137.1, 172.3. ES/MS: m/z 318 $[M + 1]^+$. HRMS (EI) calcd for $C_{19}H_{27}NO_3Na^+$ $[M + Na]^+$: 340.1888, found 340.1887.

(*R*,*E*)-*tert*-Butyl-2-((1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-ylamino)-5-phenylpent-4-enoate (6), general procedure. In the a 8 mL vial of a CEM Discovery microwave oven the starting alkene **4b** (200 mg, 0.66 mmol) was dissolved in DMF (0.5 mL) followed by Et_3N (100 mg, 1 mmol), iodobenzene (134 mg, 0.66 mmol) and Pd catalyst **5** (3.6 mg, 0.006 mmol) under N_2 atmosphere. After 3 cycles of vacuum/nitrogen the yellow solution obtained was heated at 120 °C for 20 minutes with the maximum power set to 200 W and max internal pressure 180 psi. After cooling, H_2O (2 mL) was added and the resulting mixture was extracted with EtOAc (2 x 5 mL). The organic layers were combined, washed with brine, dried over dry Na_2SO_4, filtrated and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel, eluting with PE:EtOAc (8:2 to 7:3), to give compound **6** (137 mg, 55% yield) as a yellow oil. Rf: 0.4 (PE/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (bs, 1H), 7.30-7.16 (m, 8H), 6.42 (d, J = 15.6 Hz, 1H), 6.19-6.12 (m, 1H), 4.39 (bs, 1H), 4.07 (d, J = 4 Hz, 1H), 3.48 (t, J = 6.4 Hz, 1H), 3.01 (m, 2H), 2.43 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 39.8, 61.1, 65.5, 70.3, 82.1, 124.2, 124.8, 126.3, 126.7, 127.0, 127.6, 128.8, 137.2, 141.0, 173.5. ES/MS: 380 $[M + 1]^+$. HRMS (EI) calcd for $C_{24}H_{30}NO_3^+$ $[M + 1]^+$: 380.2226, found 380.2224.

Ethyl (2R,E)-2-[(1R,2S)-2-hydroxy-1-indanylamino]-5-phenyl-4-pentenoate (7). The product was purified by flash chromatography on silica gel, eluting with PE:EtOAc (7:3 to 6:4), to give compound **7** (134 mg, 56% yield) as a pale yellow oil. Rf: 0.4 (PE/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 3H), 7.20 (m, 5H), 7.06 (m, 1H), 6.94 (m, 1H), 6.60 (d, J = 15 Hz, 1H), 6.09 (m, 1H), 4.56 (m, 1H), 4.27 (d, J = 5 Hz, 1H), 4.16 (q, J = 7 Hz, 2H), 3.50 (m, 1H), 3.09 (d, J = 10 Hz, 1H), 2.98 (d, J = 10 Hz, 1H), 2.37 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 33.9, 40.8, 61.7, 62.0, 63.0, 78.0, 125.6, 126.0, 127.2, 127.7, 127.8, 128.0, 133.3, 137.4, 137.6, 137.7, 137.7, 138.5, 138.5, 176.5. Anal calcd for $C_{22}H_{25}NO_3$ C, 75.19; H, 7.17; N, 3.99; O, 13.66. Found C 75.10; H, 7.15; N, 3.95.

(2*R*,3S,*E*)-*tert*-Butyl-2-((1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-ylamino)-3-methyl-5-phenylpent-4-enoate (8). The product was purified by flash chromatography on silica gel, eluting with PE:EtOAc (7:3 to 6:4), to give compound **8** (150 mg mg, 58% yield) as a waxy material. Rf: 0.3 (PE/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$)) δ 7.35 (m, 8H), 7.06 (d, J = 7 Hz, 1H), 6.94 (t, J = 7 Hz, 1H), 6.11 (d, J = 16 Hz, 1H), 5.68 (dd, H 0 16, 8 Hz, 1 H), 4.56 (m, 1H), 4.28 (d, J = 5 Hz, 1H), 3.99 (m, 1H), 3.05 (AB part of an ABX system, 2H), 2.03 (m, 1H), 1.50 – 1.31 (m, 9H), 1.19 (t, J 0 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 28.1, 37.2, 63.2, 66.5, 78.2, 79.7, 125.1, 125.5, 125.8, 128.1, 129.1, 129.3, 129.3, 129.4, 137.0,

139.0, 171.1. Anal calcd for $C_{25}H_{31}NO_3$ C, 76.30; H, 7.94; N, 3.56; O, 12.20 Found C, 76.22; H, 7.92; N, 3.53.

(4R,E)-4-[(1R,2S)-2-Hydroxy-1-indanylamino]-1-hydroxy-7-(p-methoxyphenyl)-2,2-dimethyl-6-hepten-3-one (9). The product was purified by flash chromatography on silica gel, eluting with PE:EtOAc (9:1 to 6:4), to give compound **9** (162 mg mg, 60% yield) as a waxy material. Rf: 0.3 (PE/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$)) δ 7.15 (m, 6H), 6.80 (m, 2H), 6.58 (d J 0 16 Hz, 1H), 6.10 (m, 1H), 4.51 (m, 1H), 3.78 (s, 3H), 3.41 (m, 1H), 3.28 (m, 1H), 2.38 (m, 2H), 1.99 (m, 1H), 1.62 (m, 1H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 28.1, 37.3, 51.9, 61.1, 63.2, 66.5, 78.2, 125.1, 125.5, 126.9, 129.1, 129.3, 129.4, 129.4, 137.0, 139.0, 148.7, 171.1. Anal calcd for $C_{25}H_{31}NO_4$ C, 73.32; H, 7.63; N, 3.42; O, 15.63 Found C, 73.27; H, 7.60; N, 3.39.

(1*R*,2*S*)-1-((*S*,*E*)6-(2-Nitrophenylhex-5-en-3-ylamino)-2,3,dihydro-1*H*-inden-2-ol (10). The crude was purified by column chromatography on silica gel, eluting with PE:EtOAc (9:1 to 7:3) to give compound **9** (60% yield) as a yellow oil. R_f: 0.6 (PE/EtOAc 8:2). Diastereomeric ratio: 91:9. Data related to the major isomer. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.86 (d, J = 8.0 Hz, 2H), 7.51(m, 5H) 7.30 (m, 7H), 6.26 (m, 1H), 4.32 (bs, 1H), 4.19 (d, J = 4.8 Hz, 2H), 2.80-2.05 (m, 8H) ^{13}C NMR (100 MHz, $CDCl_3$)) δ 147.6, 142.3, 141.5, 141.2, 133.0, 132.5, 128.6, 128.5, 128.3, 128.2, 127.7, 126.8, 126.1, 125.7, 124.4, 123.6, 71.1, 64.1, 56.9, 39.6, 38.5, 36.4, 32.3. HRMS (EI) calcd for $C_{27}H_{29}N_2O_3^+$ $[M + 1]^+$: 429.2178, found 429.2177.

(1*R*,2*S*)-1-((*S*,*E*)-6-(4-fluorophenyl)-1-phenylhex-5-en-3-ylamino)-2,3-dihydro-1*H*-inden-2-ol (11). The crude was purified by column chromatography on silica gel, eluting with PE:EtOAc (9:1 to 7:3) to give compound **11** (52% yield) as a yellow oil. R_f: 0.7 (PE/EtOAc 8:2). Diastereomeric ratio: 91:9. Data related to the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$)) δ ^{1}H NMR (400 MHz,) δ 7.32-7.07 (m, 12 H), 6.94 (m, 1H), 6.53 (d, J = 16 Hz, 1H), 6.01 (m, 1H), 4.47 (m, 1H), 4.17 (d, J = 6 Hz, 1H), 3.65 (m, 1H), 3.18 – 2.84 (m, 2H), 2.71 (m, 2H), 2.21 (m, 2H), 1.74 (m, 2H). ^{13}C NMR (100MHz, $CDCl_3$) δ 160.9, 142.6, 141.6, 141.3, 133.5, 131.7, 128.5, 128.3, 128.1, 127.6, 127.5, 126.8, 126.5, 126.1, 125.7, 123.6, 115.5, 115.3, 71.1, 64.1, 57.0, 39.6, 38.5, 36.4, 32.4. HRMS (EI) calcd for $C_{27}H_{29}FNO^+$ $[M + 1]^+$: 402.2233, found 402.2234.

(1*R*,2*S*)-1-(*S*,*E*)-6-(1*H*-Indol-5-yl)-1-phenylhex-5-en-3-ylamino)-2,3-dihydro-1*H*-inden-2-ol (12). The crude was purified by column chromatography on silica gel, eluting with PE:EtOAc (9:1 to 7:3) to give compound **12** (50% yield) as a yellow oil. R_f: 0.7 (PE/EtOAc 8:2). Diastereomeric ratio: 91:9. Data related to the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (bs, 1H), 7.60 (s, 1H), 7.28 (m, 10H), 6.60 (d, J = 15 Hz, 1H), 6.50 (s, 1H), 6.22 (m, 1H), 4.37 (m, 1H), 4.24 (m, 1H), 3.03 (m, 4H), 2.79 (m, 3H), 2.53 (m, 2H), 1.99 (m,

2H). δ ^{13}C NMR (100MHz, $CDCl_3$) δ 142.7 (C), 141.8 (C), 141.3 (C), 135.4 (C), 134.1 (C), 129.5 (CH), 128.5 (CH), 128.4 (CH), 128.1 (2 x CH), 126.9 (2 x CH), 126.0 (2 x CH), 125.7 (CH), 124.7 (C), 123.7 (CH), 123.5 (CH), 120.3 (CH), 118.7 (CH), 111.2 (CH), 102.7 (CH), 71.2 (CH), 64.0 (CH), 57.2 (CH), 39.6 (CH_2), 38.5 (CH_2), 36.3 (CH_2), 32.5 (CH_2). HRMS (EI) calcd for $C_{29}H_{31}N_2O^+$ $[M + 1]^+$: 423.2436, found 423.2427.

(1*R*,2*S*)-1-((*S*,*E*)-6-(4-Methylphenyl)-1-phenylhex-5-en-3-ylamino)-2,3-dihydro-1*H*-inden-2-ol (13). The crude was purified by column chromatography on silica gel, eluting with PE:EtOAc (9:1 to 7:3) to give compound **13** (65% yield) as a yellow oil. R_f: 0.7 (PE/EtOAc 8:2). Diastereomeric ratio: 91:9. Data related to the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 9H), 7.05 (m, 2H), 6.80 (m, 2H), 6.51 (d, J = 16 Hz, 1H), 6.10 (m, 1H), 4.45 (m, 1H), 3.77 (s, 3H), 3.02 (m, 2H), 2.72 (m, 1H), 1.90 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9 (C), 142.6 (C), 141.7 (C), 141.3 (C), 132,3 (CH), 130.2 (3 x CH), 128.5 (CH), 128.3 (CH), 128.1 (C), 127.2 (CH), 126.8 (2 x CH), 126.0 (C), 125.7 (CH), 124.4 (CH), 123.6 (CH), 114.0 (2 x CH), 71.2 (CH), 60.0 (CH), 57.1 (CH_3), 55.3 (CH), 39.6 (CH_2), 38.5 (CH_2), 36.3 (CH_2), 32.4 (CH_2). HRMS (EI) calcd for $C_{28}H_{32}NO_2^+$ $[M + 1]^+$: 414.2433, found 414.2435.

(1*R*,2*S*)-1-((*S*,*E*)-1,6-Diphenylhex-5-en-3-ylamino)-2,3-dihydro-1*H*-inden-2-ol (14). The crude was purified by column chromatography on silica gel, eluting with PE:EtOAc (8:2 to 7:3), to give compound **8** (58% yield) as a yellow oil. Rf: 0.4 (petrol/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 6.82 (m, 14H), 6.51 (d, J = 15 Hz, 1H), 6.01 (m, 1H), 4.48 (m, 1H), 4.16 (d, J = 5 Hz, 1H), 3.65 (m, 1H), 2.95 (AB part of an ABX system, 2H), 2.70 (m, 2H), 2.19 (m, 2H), 1.70 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$)) δ 29.3, 34.2, 35.6, 36.8, 59.8, 63.5, 79.7, 120.1, 122.1, 122.7, 123.0, 123.1, 123.2, 123.3, 124.5, 124.6, 125.0, 125.4, 127.1, 131.1, 135.3, 135.9, 135.9, 136.2, 139.8. ES/MS: m/z 384 $[M + 1]^+$. HRMS (EI) calcd for $C_{27}H_{30}NO^+$ $[M + 1]^+$: 384.2327, found 384.2322.

(1*R*,2*S*)-1-((3*S*,4*S*,*E*)-4-Methyl-1,6-diphenylhex-5-en-3-ylamino)-2,3-dihydro-1*H*-inden-2-ol (15) The crude was purified by column chromatography on silica gel, eluting with PE:EtOAc (8:2 to 7:3) to give compound **14** (58% yield) as a yellow oil. R_f: 0.5 (PE/EtOAc 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 6.94 (m, 14H), 6.02 (d, J = 15 Hz, 1H), 5.63 (m, 1H), 4.48 (m, 1H), 4.16 (d, J = 5 Hz, 1H), 3.55 (m, 1H), 2.96 (m, 2H), 2.72 (m, 2H), 1.75 (m, 3H), 0.98 (d, J = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 33.1, 33.9, 39.5, 40.6, 62.3, 65.1, 71.3, 123.6, 125.8, 126.2, 126.8, 127.1, 128.2, 128.4, 128.6, 130.4, 133.1, 137.6, 141.4, 141.8, 142.8. ES/MS: m/z 398 $[M + 1]^+$. HRMS (EI) calcd for $C_{28}H_{32}NO^+$ $[M + 1]^+$: 398.2483, found 398.2480.

(1*R*,2*S*)-1-((*S*,*E*)-1-Phenylhexadec-1-en-4-ylamino)-2,3-dihydro-1*H*-inden-2-ol (16) The crude was purified by column chromatography on silica gel, eluting with PE:EtOAc (8:2 to 7:3) to give compound **7** (57% yield) as a yellow oil. Rf: 0.7 (PE/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 10H), 6.42 (d, J = 15 Hz, 1H), 6.19 (m, 1H), 4.40 (m, 1H), 4.28 (m, 1H), 3.02 (m, 2H), 2.44 (m, 1H), 1.63 (m, 1H), 1.24 (m, 22H), 0.86 (t, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 20.7, 22.5, 24.0, 27.6, 28.2, 28.5, 28.9, 33.9, 36.4, 42.4, 59.5, 62.9, 79.7, 123.8, 125.8, 126.5, 127.1, 127.7, 128.1, 129.2, 129.4, 132.1, 135.0, 136.2, 137.0. ES/MS: m/z 448 $[M + 1]^+$. HRMS (EI) calcd for $C_{31}H_{46}NO^+$ $[M + 1]^+$: 488.3579, found 488.3580.

(1*R*,2*S*)-1-((3*S*,4*S*,*E*)-3-Methyl-1-phenylhexadec-1-en-4-ylamino)-2,3- dihydro-1*H*-inden-2-ol (17) The crude was purified by column chromatography on silica gel, eluting with PE:EtOAc (8:2 to 7:3) to give compound **17** (51% yield) as a yellow oil. R_f: 0.6 (PE/EtOAc 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 9H), 6.92 (m 2H), 6.02 (d, J = 16. Hz, 1H), 5.60 (m, 1H), 4.48 (m, 1H), 4.22 (m, 1H), 3.62 (m, 1H), 3.24 (m, 1H), 2.81 (m, 1H), 1.26 (m, 23H), 1.04 – 0.61 (m, 6H). ^{13}C NMR (100 MHz,) δ 14.2, 22.4, 24.0, 25.2, 25.2, 27.5, 27.6, 28.1, 28.3, 29.0, 31.5, 36.4, 42.4, 59.5, 62.9, 80.9, 123.8, 125.8, 126.5, 127.1, 127.7, 128.1, 129.2, 129.4, 132.0, 135.0, 136.2, 137.0, 137.1, 148.6. ES/MS: m/z 462$[M+1]^+$. HRMS(EI) calcd for $C_{32}H_{48}NO^+$ $[M+1]^+$: 462.3736, found 462.3735.

Ethyl (1R,2S,3R,7S,9S)-8-oxa-2-azatetracyclo[7.7.0.02,7.011,16]hexadeca-11(16),12,14-triene-3-carboxylate (18) General procedure for CHC . In a stainless steel autoclave under a N_2 inert atmosphere, a solution containing $[Rh(acac)(CO)_2]$ (1.87 mg, 0.0072 mmol) and BIPHEPHOS (11.3 mg, 0.014 mmol.) in dry THF (0.5 mL), was added to a solution of **4a** (100 mg, 0.36 mmol) in dry THF (1 mL). The autoclave was flushed with H_2/CO (1:1) followed by N_2 for three times. Then, the autoclave was filled with 7 bar of H_2/CO (1:1) and heated to 70 °C with stirring for 12 h. After cooling to room temperature the internal pressure was slowly and carefully released. The reaction mixture was then concentrated under reduced pressure to give an oil. The crude was purified by column chromatography on silica gel, eluting with PE:EtOAc (8:2 to 6:4) to give compound **18** (69 mg, 67% yield) as a yellow oil. R_f: 0.6 (PE/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 1H), 7.17 (m, 3H), 4.83 (t, J = 6.0 Hz, 1H), 4.55 (m, 1H), 4.25 (m, 2H), 3.25 (m, 1H), 3.16 (m, 1H), 3.04 (m, 1H), 1.90 (m, 3H), 1.62 (m, 4H), 1.30 (t, J = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 17.8, 25.7, 28.7, 39.7, 61.0, 61.9, 75.9, 87.5, 124.3, 126.2, 127.2, 128.4, 139.9, 142.5, 173.8. ES/MS: m/z 288 $[M + 1]^+$. Anal calcd for $C_{17}H_{21}NO_3$ C, 71.06; H, 7.37; N, 4.87; O, 16.70, Found C, 71.00; H, 7.35; N, 4.84.

Tetracyclic oxazolidine 19 The crude was purified by column chromatography on silica gel, eluting with PE:EtOAc (8:2 to 6:4) to give compound **19** (63 mg 56% yield) as a yellow solid.

M.p. 96-98 °C. R_f: 0.7 (PE/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (m, 1H), 7.18 (m, 3H), 4.86 (t, J = 6.0 Hz, 1H), 4.61 (d, J = 6 Hz, 1H), 4.21 (m,1H), 3.15 (m, 3H), 1.94 (m, 2H), 1.60 (m, 13H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 25.7, 28.2, 28.6, 39.7, 62.2, 75.6, 75.9, 81.0, 87.8, 124.3, 126.3, 127.2, 128.3, 128.3, 140.2, 142.5, 173.0.ES/MS: m/z 316 $[M + 1]^+$. Anal calcd for $C_{19}H_{25}NO_3$ C, 72.35; H, 7.99; N, 4.44; O, 15.22. Found C, 72.40; H, 7.97; N, 4.46.

Tetracyclic oxazolidine 20 The crude was purified by column chromatography on silica gel, eluting with PE:EtOAc (9:1 to 7:3) to give compound **20** (69 mg, 58% yield) as a yellow solid. M.p. 87-94 °C. R_f: 0.6 (PE/EtOAc 8:2). Diastereomeric ratio: 50:50. The two isomers were not separable by chromatography. Data related to the mixture. ^{1}H NMR (400 MHz, $CDCl_{3,}$) δ 7.65 (d, J = 6.0 Hz, 1H), 7.23-7.13 (m, 3H), 4.77 (t, J = 5.6 Hz, 1H), 4.53 (d, J = 5.2 Hz, 1H), 4.31 (s, 1H), 3.29 (d, J = 3.6 Hz, 1H), 3.22-3.18 (m, 1H), 3.15-3.01 (m, 1H), 2.31-2.89 (m, 1H), 2.31-1.89 (m, 1H), 1.87-1.79 (m, 4H).

Tetracyclic oxazolidine 21 The crude was purified by column chromatography on silica gel, eluting with PE:EtOAc (9:1 to 7:3) to give compound **21** (67 mg, 56% yield) as a waxy material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 8H), 6.92 (m, 1H), 4.17 (t, J = 7 Hz, 1H), 3.79 (m, 1H), 2.72 (m, 4H), 2.49 (m, 1H), 2.08 (m, 1H), 1-93-1.39 (m, 3H),1.42 (m, 1H), 1.19 (m, 1H), 0.87 (d, J = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 27.3, 28.5, 32.9, 33.2, 33.7, 39.7, 58.7, 73.8, 83.5, 89.9, 121.4, 123.4, 123.9, 124.3, 127.1, 127.3, 134.3, 136.5, 144.5. Anal calcd for $C_{23}H_{27}NO$ C, 82.84; H, 8.16; N, 4.20; O, 4.80. Found C, 82.79; H, (.14; N, 4.17.

Tetracyclic oxazolidine 22 The crude was purified by column chromatography on silica gel, eluting with PE:EtOAc (9:1 to 7:3) to give compound **22** (87 mg, 62% yield) as a white solid. M.p. 98-100 °C. R_f: 0.7 (PE/EtOAc 8:2). Diastereomeric ratio: 95:5. Data related to the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.05 (m, 8H), 6.92 (m, 1H), 4.44 (m, 1H), 3.90 (m, 1H), 3.68 (m, 2H), 2.82 (m, 2H), 2.41 (m, 2H), 2.10 (m, 1H), 1.76 (m, 1H), 1.55 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 128.8, 128.3, 128.1, 128.0, 127.2, 126.5, 126.3, 126.0, 124.3, 90.6, 81.2, 76.0, 75.0, 61.9, 42.9, 39.6, 29.2, 28.2, 23.6. HRMS (EI) calcd for $C_{25}H_{30}NO_3^+$ $[M + 1]^+$: 392.2226, found 392.2225.

Tetracyclic oxazolidine 23 The crude was purified by column chromatography on silica gel, eluting with PE:EtOAc (9:1 to 7:3) to give compound **21** (82 mg, 58% yield) as a waxy material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 13H), 6.90 (m, 1H), 4.34 (m, 1H), 3.80 (d, J = 6.3 Hz, 1H), 3.63 (m, 1H), 3.10 (bs, 1H), 2.84 (m, 4H), 2.45 (d, J = 15 Hz, 1H), 2.39 – 1.40 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 32.6, 36.3, 39.7, 40.4, 43.4, 59.8, 72.2, 82.9, 90.3, 123.8, 124.3, 124.8, 125.0, 125.6, 126.3, 126.5, 134.6, 135.7, 140.2, 145.2. Anal calcd for $C_{28}H_{29}NO$ C, 85.02; H, 7.39; N, 3.54; O, 4.05. Found C, 84.99; H, 7.40; N, 3.56.

Tetracyclic oxazolidine 24 The product was prepared following general procedure but charging the autoclave with 30 bar of syngas and using $(EtO)_3P$ (3 mg, 0.018 mmol) as ligand instead of BIPHEPHOS. The crude was purified by column chromatography on silica gel, eluting with PE:EtOAc (9:1 to 7:3) to give compound **24** (84 mg, 58% yield) as a white solid. M.p. 65-67 °C. R_f: 0.7 (PE/EtOAc 8:2). Diastereomeric ratio: 85:15. Data related to the major isomer obtained after purification via preparative tlc. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 – 6.69 (m, 14H), 4.66 (d, J = 6 Hz, 1H), 3.82 (m, 1H), 3.62 (t, J = 6.4 Hz, 1H), 3.11 (m, 1H), 2.93 (m, 1H), 2.71 (m, 3H), 2.51 (m, 1H), 2.24 (m, 1H), 1.65 (m, 3H), 1.28 (m, 1H), 0.90 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 20.7, 26.1, 28.2, 28.3, 30.4, 42.2, 51.9, 52.1, 83.1, 112.6, 124.3, 125.5, 125.8, 126.7, 127.5, 128.2, 129.0, 129.2, 129.4, 135.2, 148.7. HRMS (EI) calcd for $C_{29}H_{32}NO^+$ $[M + 1]^+$: 410.2484, found 410.2485.

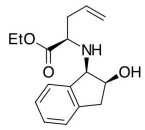
2*R*,6*R*)-*tert*-Butyl-6-isobutyl-1-((1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)piperidine-2-carboxylate (28). General procedure for oxazolidine ring opening.

To a solution of product **19** (50 mg, 0.17 mmol) in dry Et_2O (0.1 M), a solution of Grignard reagent in Et_2O (20 eq. freshly prepared from *i*-BuBr (1 g, 7 mmol) and Mg turning (168 mg, 7 mmol) and Et_2O (10 mL) at 0 °C was added. The reaction mixture was stirred at room temperature under N_2 for 3 h. H_2O was added and the resulting mixture was extracted with Et_2O. The organic layers were combined, washed with brine, dried over dry Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography on silica gel, eluting with PE:EtOAc (8:2 to 6:4) to give compound **28** (46 mg, 73% yield) as a yellow oil. The product was obtained a disatereomeric 65 : 35 mixture. An analytical sample was isolated by preparative tlc. R_f: 0.7 (PE/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 2H), 7.04 (m, 1H), 6.86 (m, 1H), 4.81 (m, 1H), 3.91 (m, 1H), 3.97 (m, 1H), 3.02 (m, 2H), 2.56 (m, 1H), 2.05 (m, 1H), 1.84 – 1.49 (m, 7H), 1.36 (s, 9H), 1.16 (m, 2H), 0.82 (d, J = 7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 23.1, 25.3, 27.8, 27.8, 32.6, 35.1, 48.4, 58.9, 64.2, 71.5, 81.1, 81.9, 125.9, 127.1, 128.2, 135.9, 139.5, 169.9. ES/MS: m/z 332 $[M + 1]^+$. HRMS (EI) calcd for $C_{23}H_{36}NO_3^+$ $[M + 1]^+$: 374.2695, found 374.2691.

(2*R*,5*R*,6*R*)-*tert*-Butyl-1-((1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-3-yl)-6-butyl-5-phenylpiperidine-2-carboxylate (29) . The product was purified by column chromatography on silica gel, eluting with PE:EtOAc (8:2 to 6:4), to give compound **29** (51 mg, 67% yield) as a yellow oil. The product was obtained a disatereomeric 75 : 25 mixture. An analytical sample was isolated by preparative tlc. Rf: 0.8 (PE/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 6.65 (m, 9H), 4.85 (m, 1H), 4.00 (m, 1H), 3.81 (d, J = 8 Hz, 1H), 3.37 (m, 1H), 3.08 (m, 2H), 2.77 (m, 1H), 1.85 (m, 6H), 1.38 (s, 13H), 0.90 (bt, J = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 26.6, 28.1, 31.6, 32.9, 41.6, 51.9, 70.4, 83.7, 91.4, 128.7, 128.8, 129.1, 129.4, 136.2, 137.0. HRMS (EI) calcd for $C_{29}H_{40}NO_3^+$ $[M + 1]^+$: 450.3008, found 450.3009.

(2*R*,6*S*)-6-Isobutylpiperidine-2-carboxylic acid (30), general procedure. A solution of ring opened oxazolidine (37 mg, 0.1 mmol) and $Pd(OH)_2/C$ (1 mg of a 10% dispersion of Pd)) in absolute methanol (0.5 mL) was stirred in a vial inserted into an autoclave under 10 bar of H_2 at room temperature for 24 h. Then the catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was dissolved in a solution of CH_2Cl_2/TFA 4:1 (0.5 mL) and stirred at room temperature for 1 hour. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography eluting with CH_2Cl_2:MeOH (10:0 to 9:1) to give compound **30** (14 mg, 80% yield) as a colourless oil. R_f: 0.6 (CH_2Cl_2:MeOH 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (m, 1H), 2.63 (m, 1H), 2.19 (m, 1H), 1.84-1.57 (m, 5H), 1.49 (m, 2H), 1.21. (m, 1H), 0.84 (bd, J = 7Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 21.0, 22.6, 24.2, 30.1, 33.6, 48.1, 52.1, 59.8, 172.9. ES/MS: m/z 199 $[M + 1]^+$. Analysis performed on the CF_3CO_2H salt. Calcd for $C_{12}H_{20}F_3NO_4$: C, 48.16%, H, 6.74%, O, 21.38. Found C, 48.0; H, 6.70, N, 21.35.

(2*R*,5*R*,6*R*)-*tert*-butyl-6-butyl-5-phenylpiperidine-2-carboxylate (31) The product was purified by column chromatography on silica gel, eluting with CH_2Cl_2:MeOH (9:1 to 6:4) to give compound **31** (16 mg, 63% yield) as a yellow oil. Rf: 0.5 (PE/EtOAc 7:3). ^{1}H NMR: ($CDCl_3$, 400 MHz,) δ 7.19 (m, 5H), 3.72 (m, 1H), 3.12 (m, 1H), 2.50 (m, 1H), 1.92 (m, 10H), 0.90 (bt, J = 7 Hz, 3H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 15.5, 22.8, 28.0, 28.7, 29.0, 33.0, 33.9, 59.6, 61.5, 127.8, 128.4, 128.7, 128.7, 137.1, 137.1, 172.7. Analysis performed on the CF_3CO_2H salt. Calcd for $C_{18}H_{24}F_3NO_4$ C, 57.59; H, 6.44; N, 3.73; O, 17.05. Found C, 57.62; H, 6,42; N, 3.71.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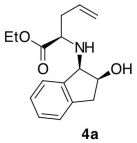
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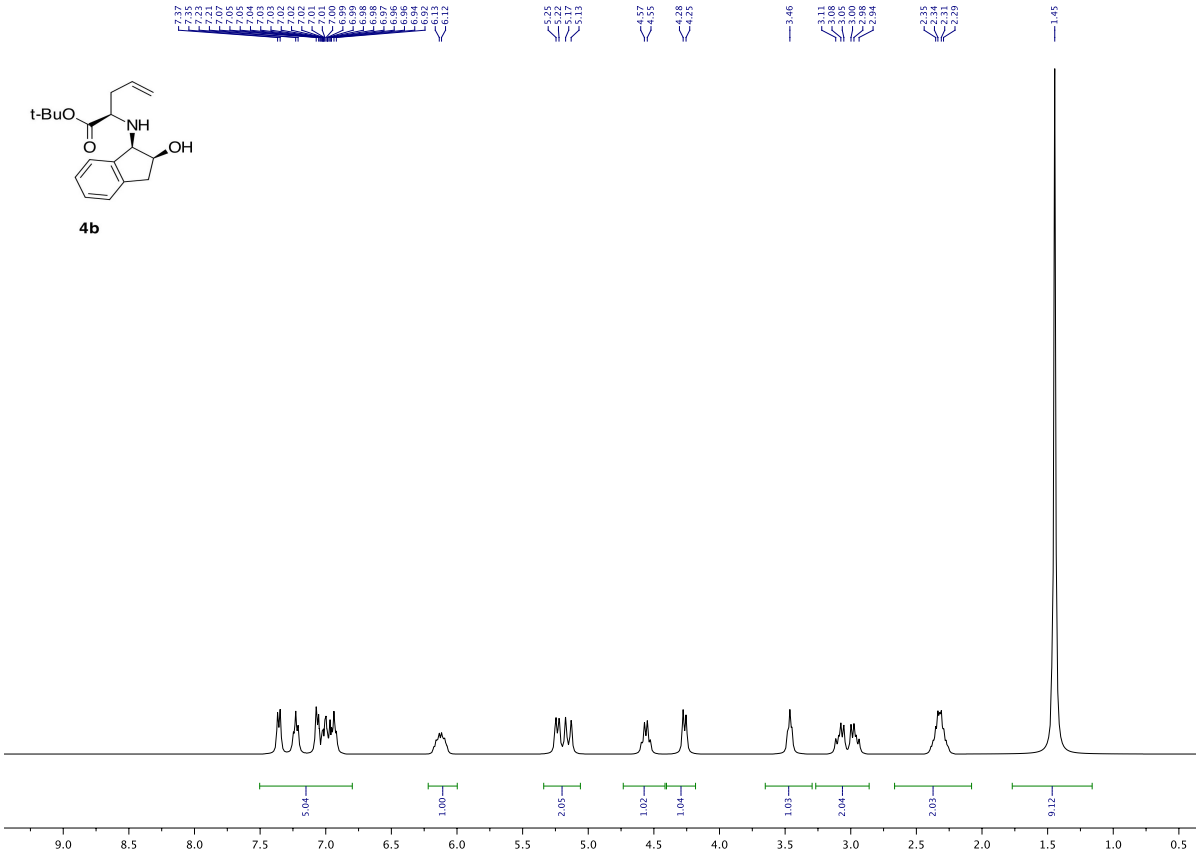
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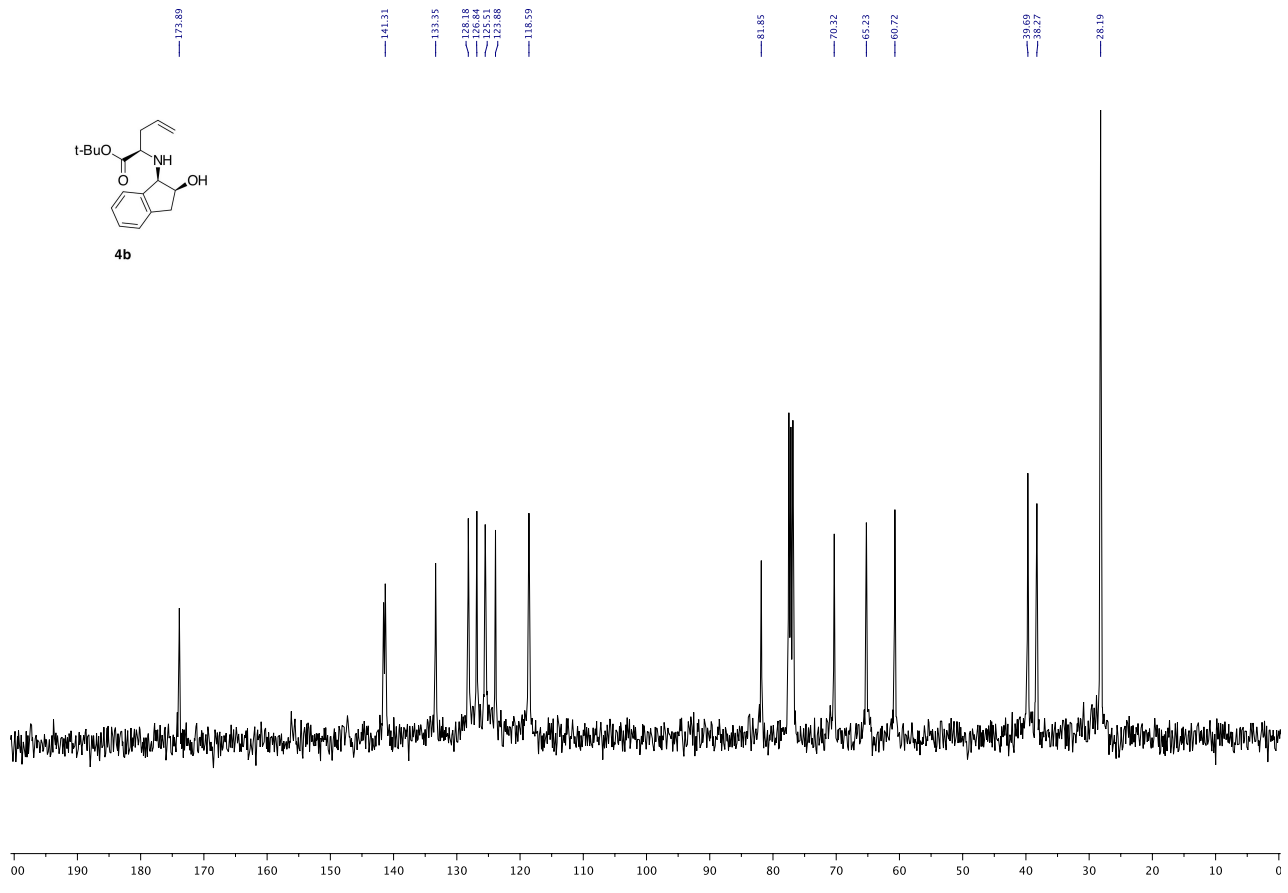
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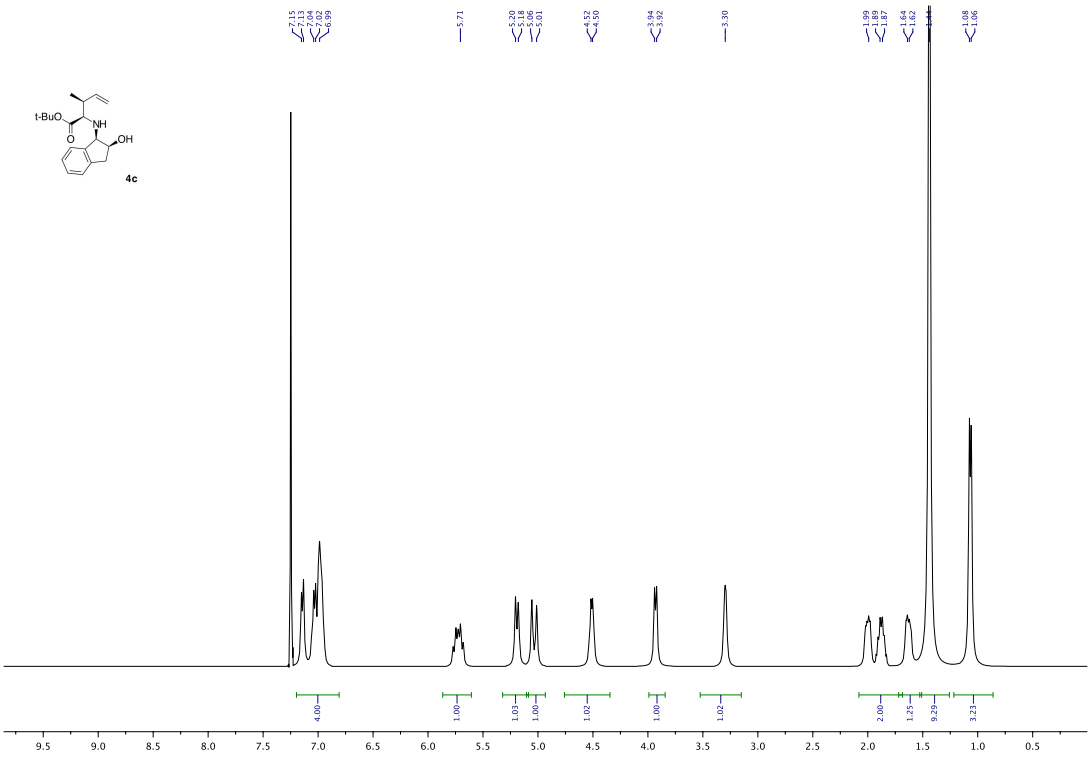
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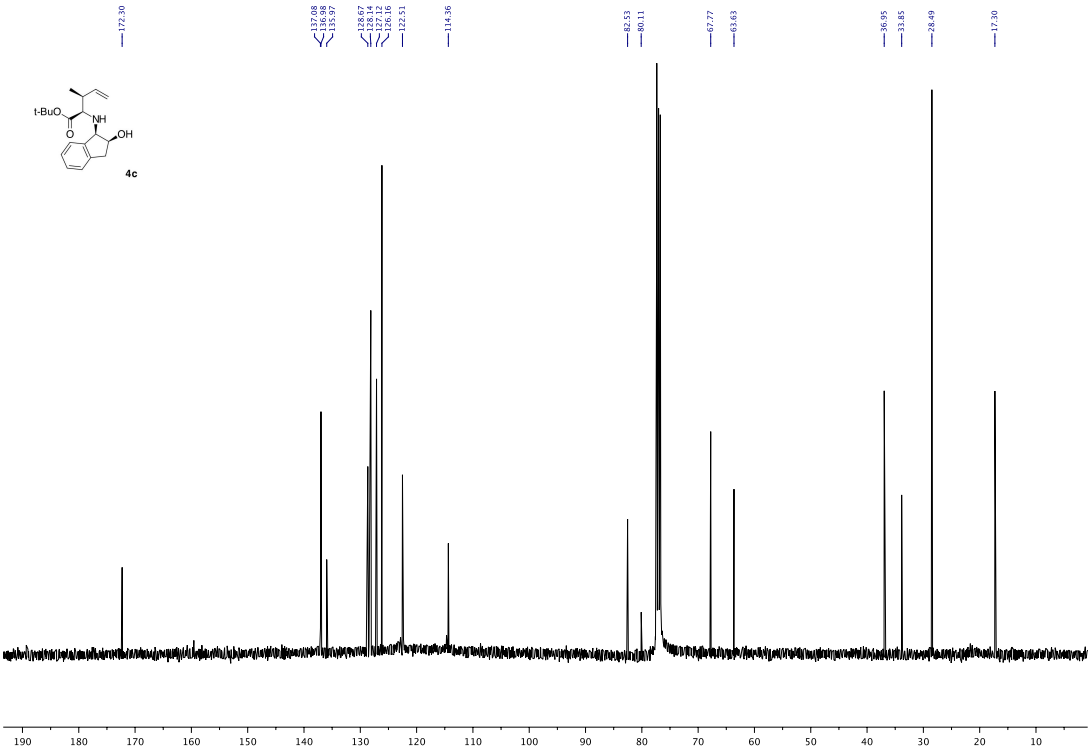
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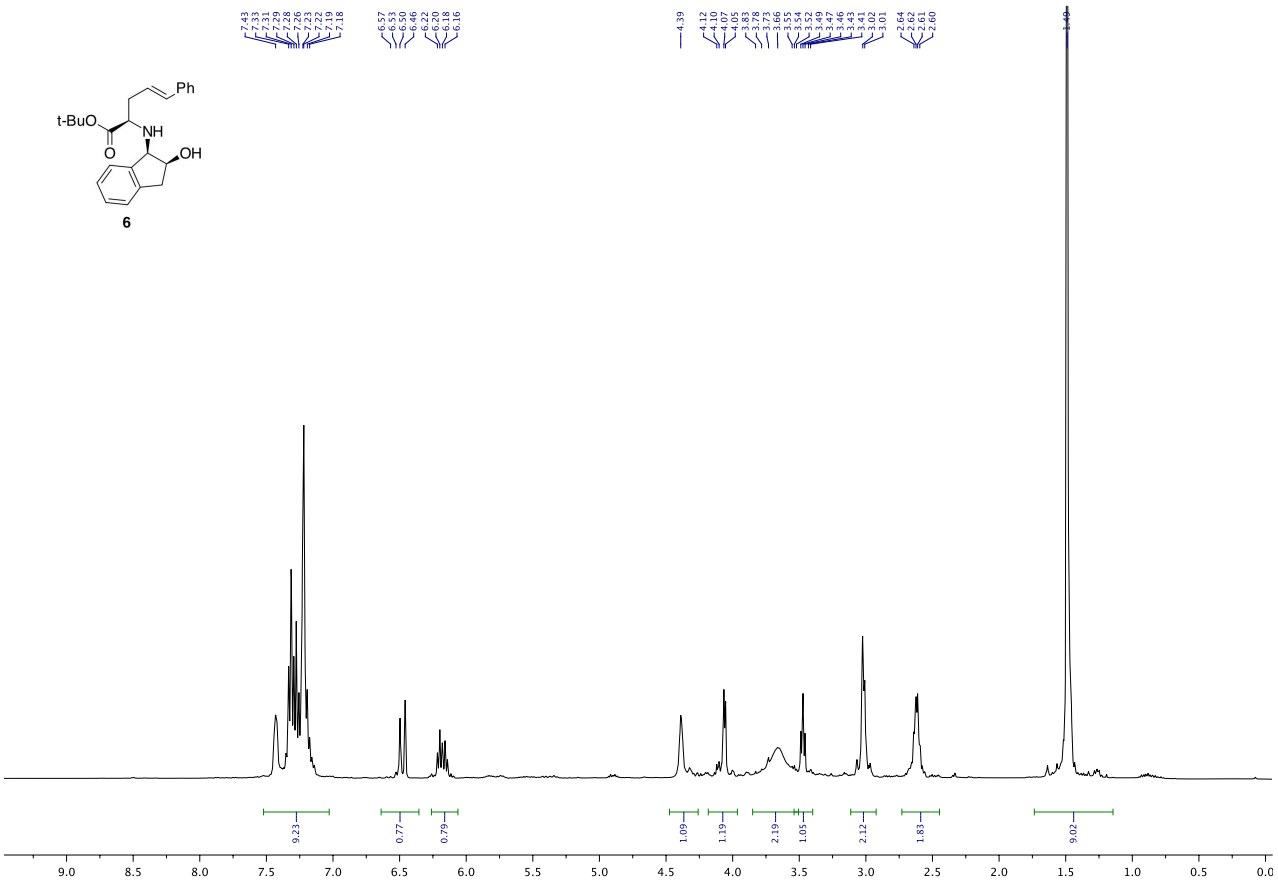
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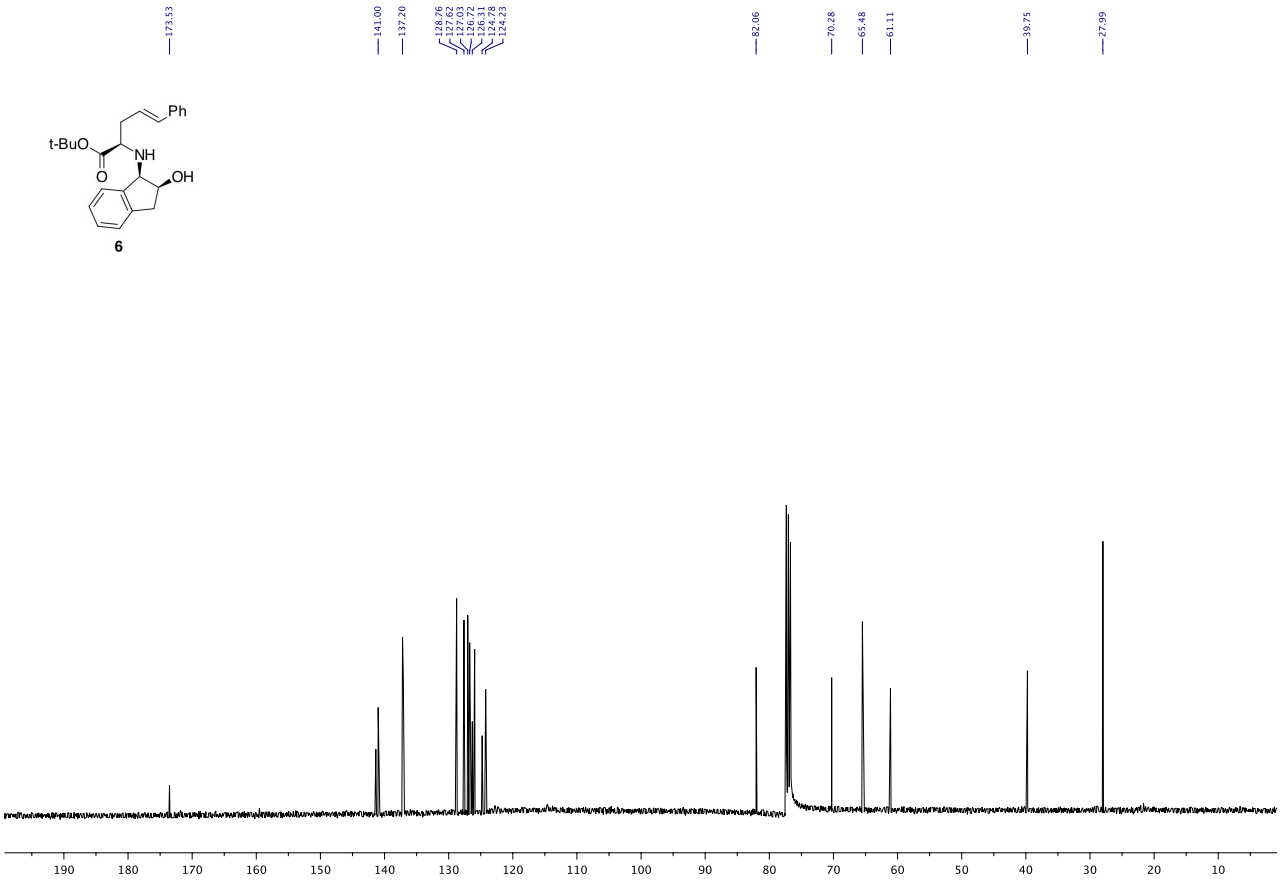
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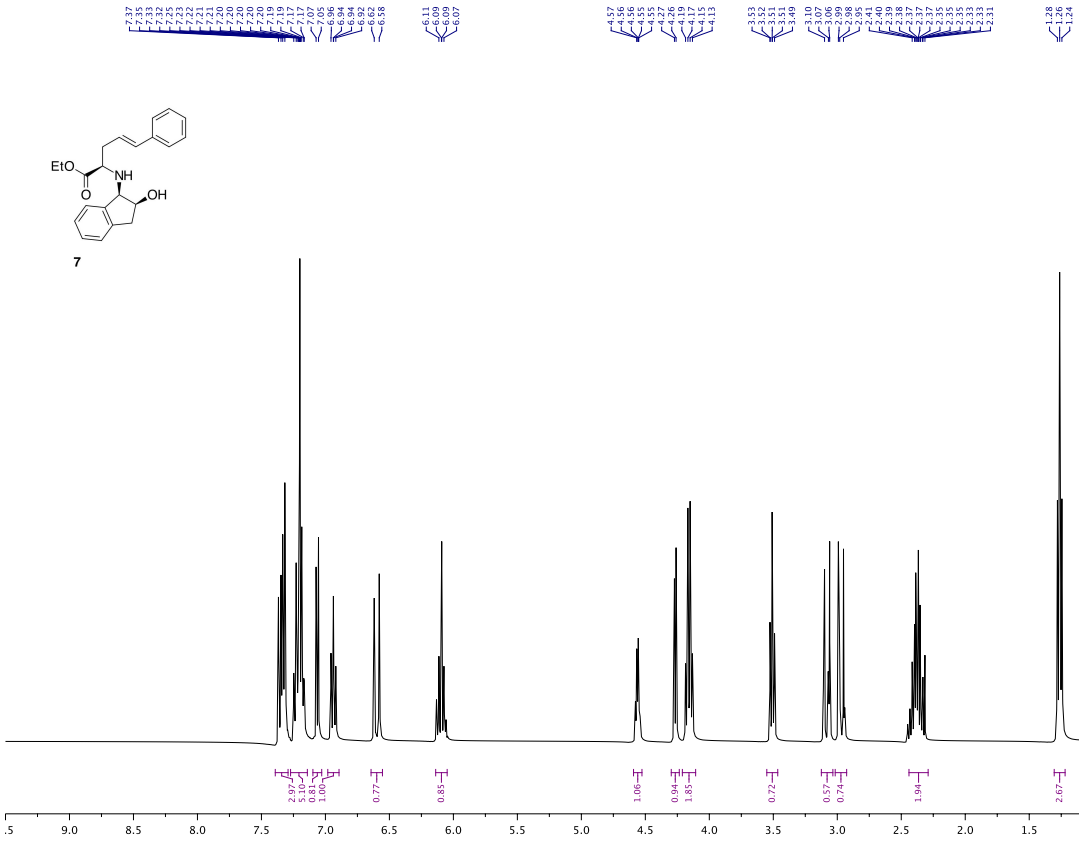
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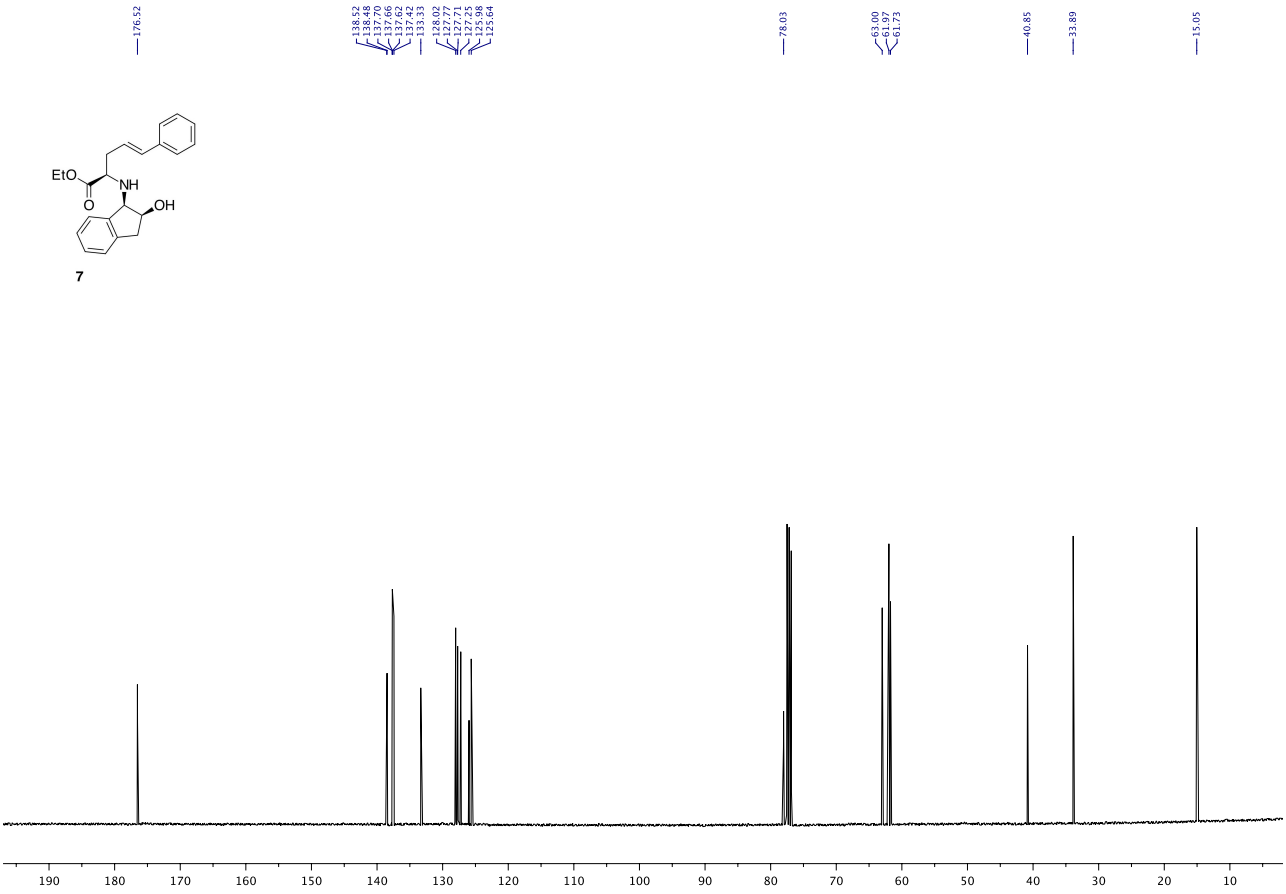
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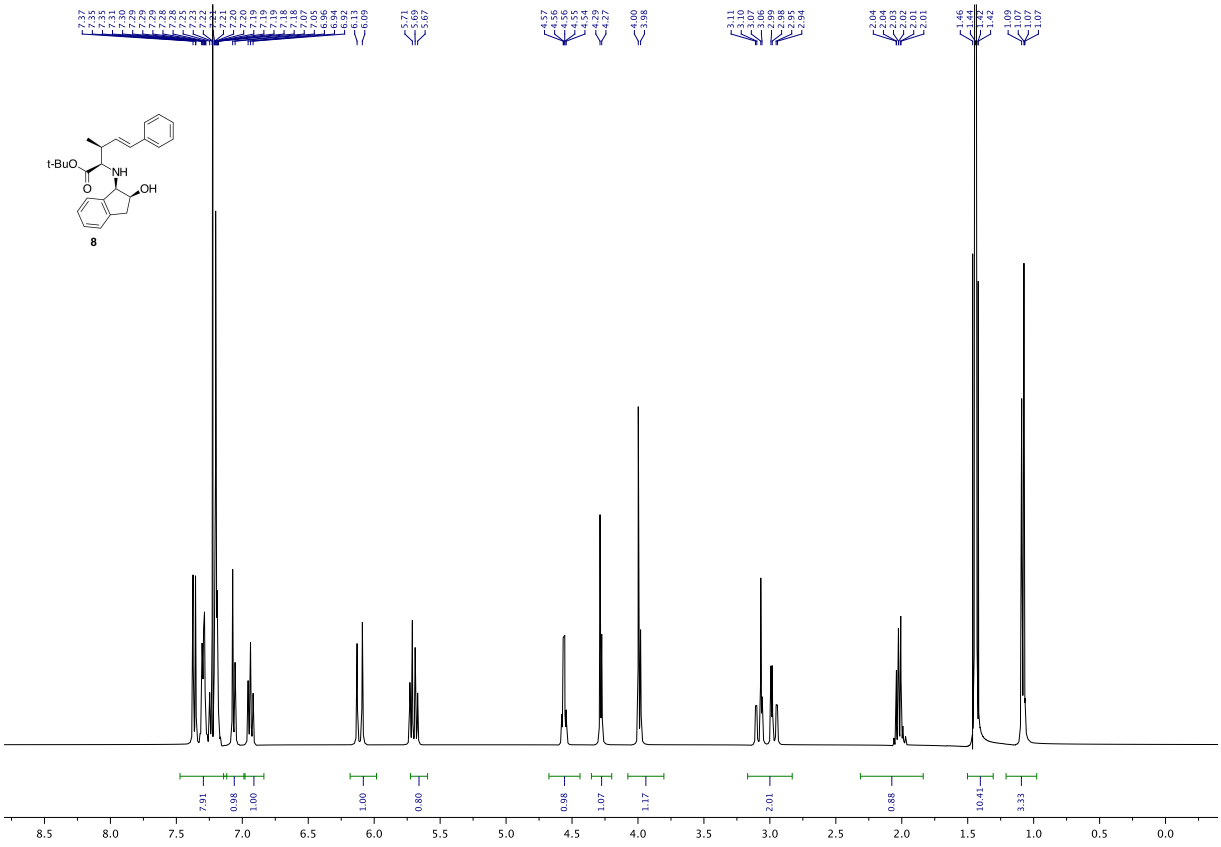
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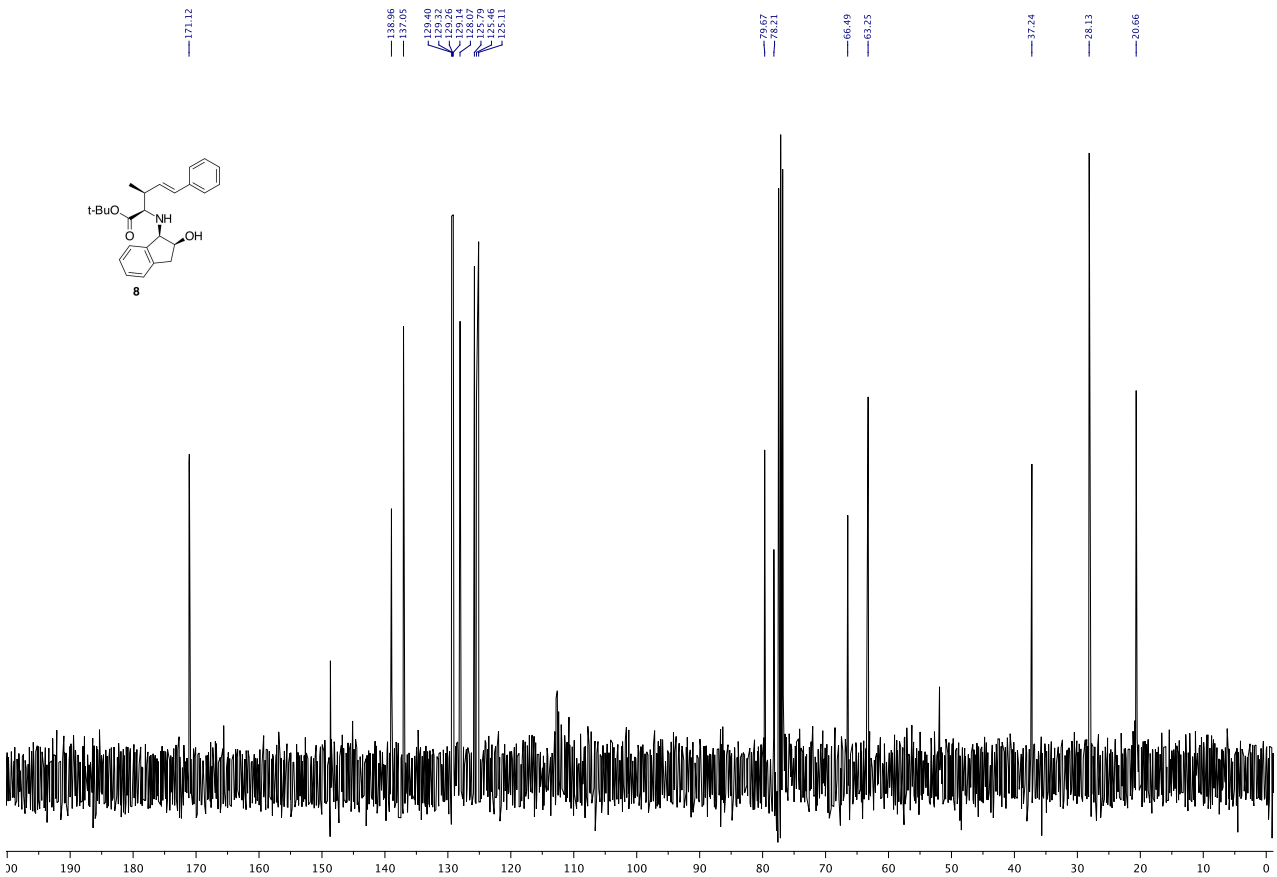
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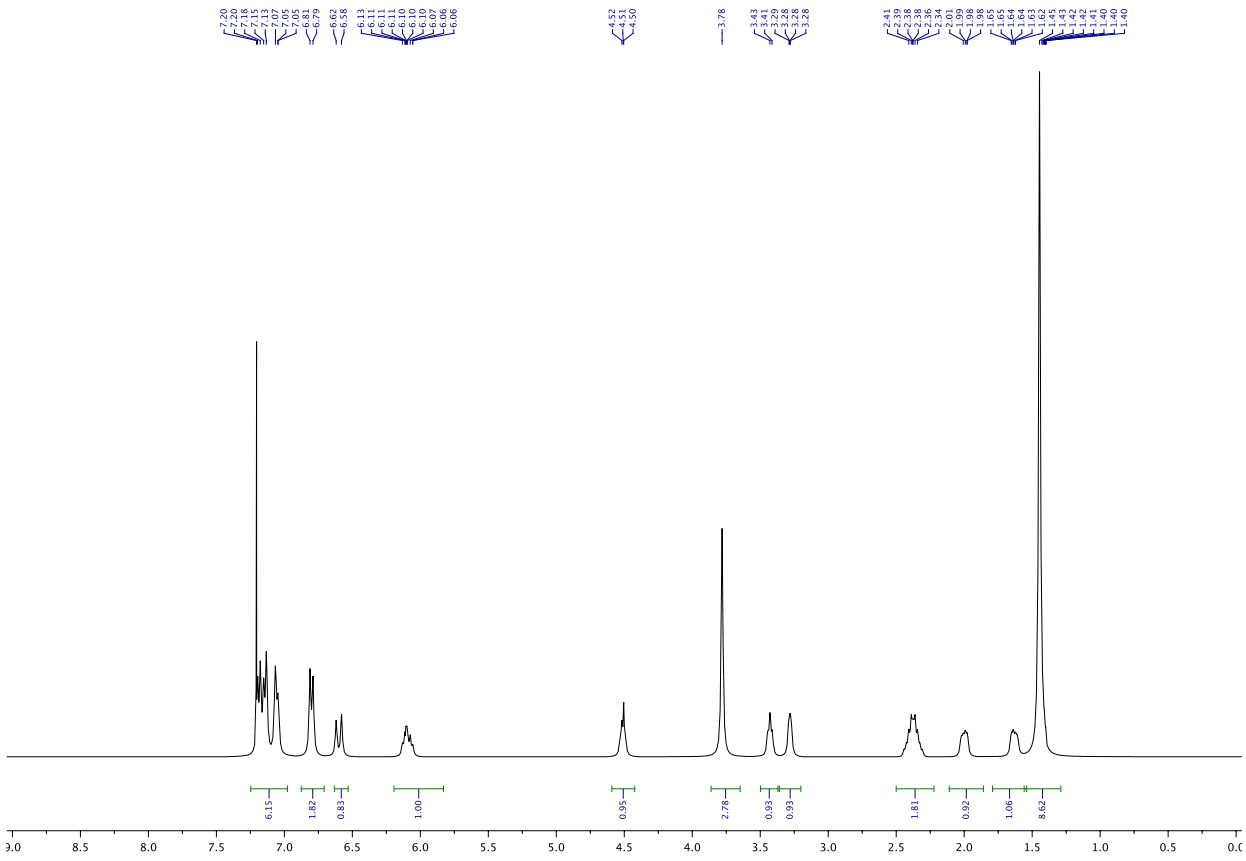
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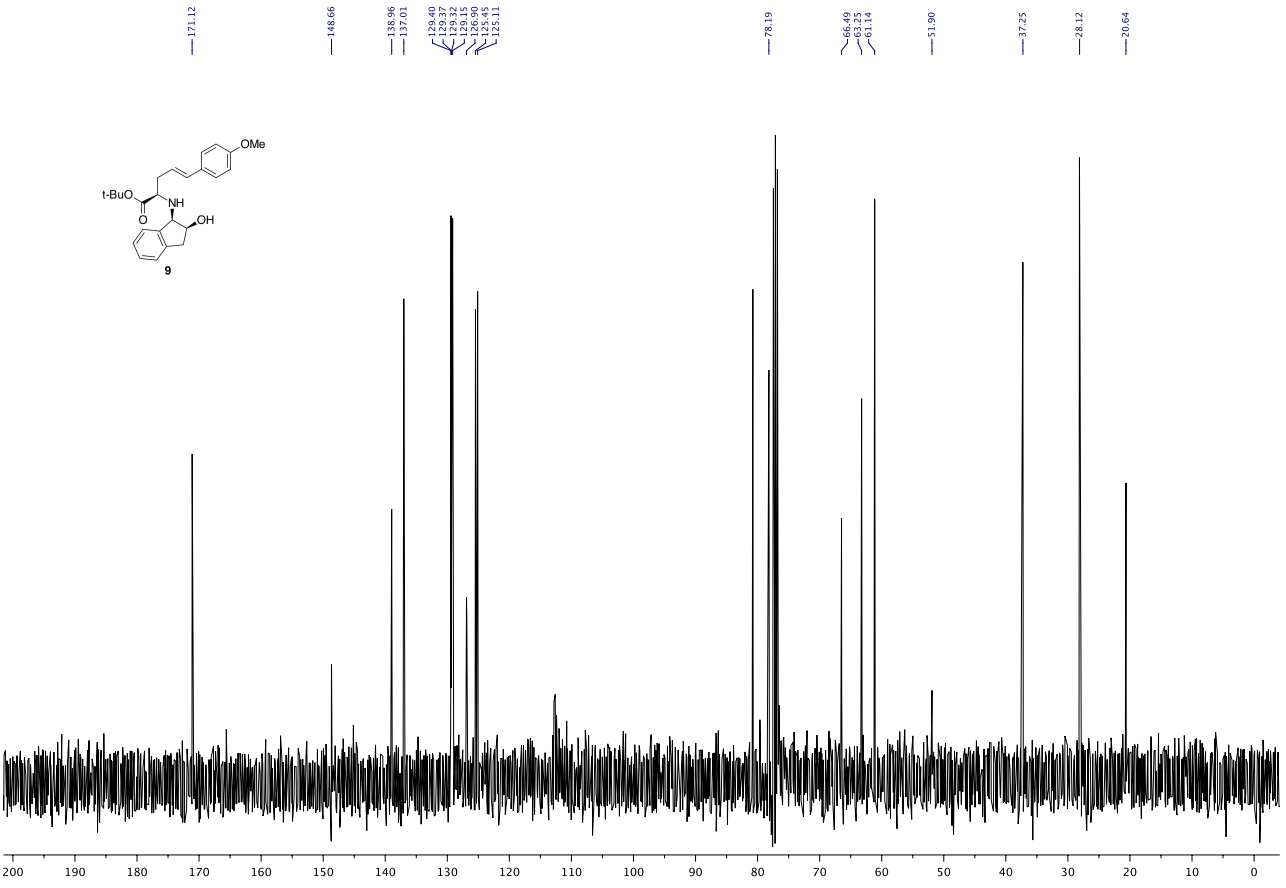
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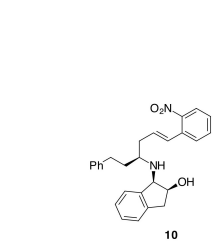

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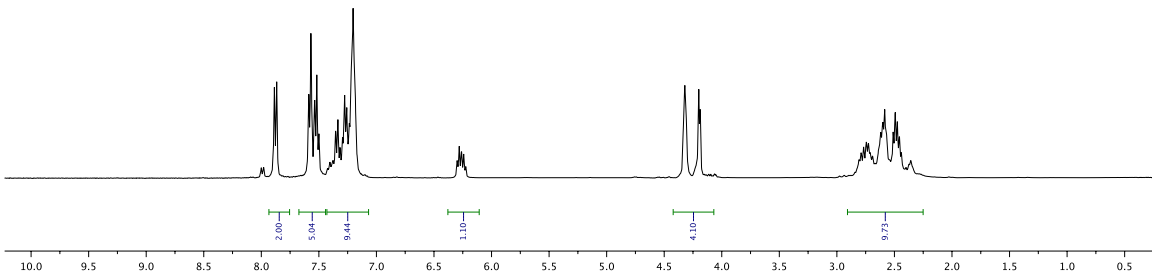

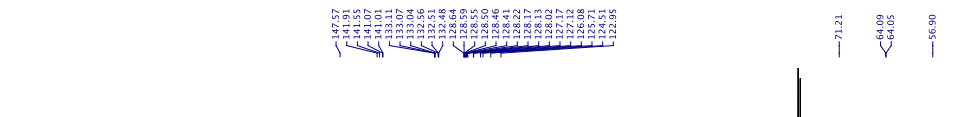

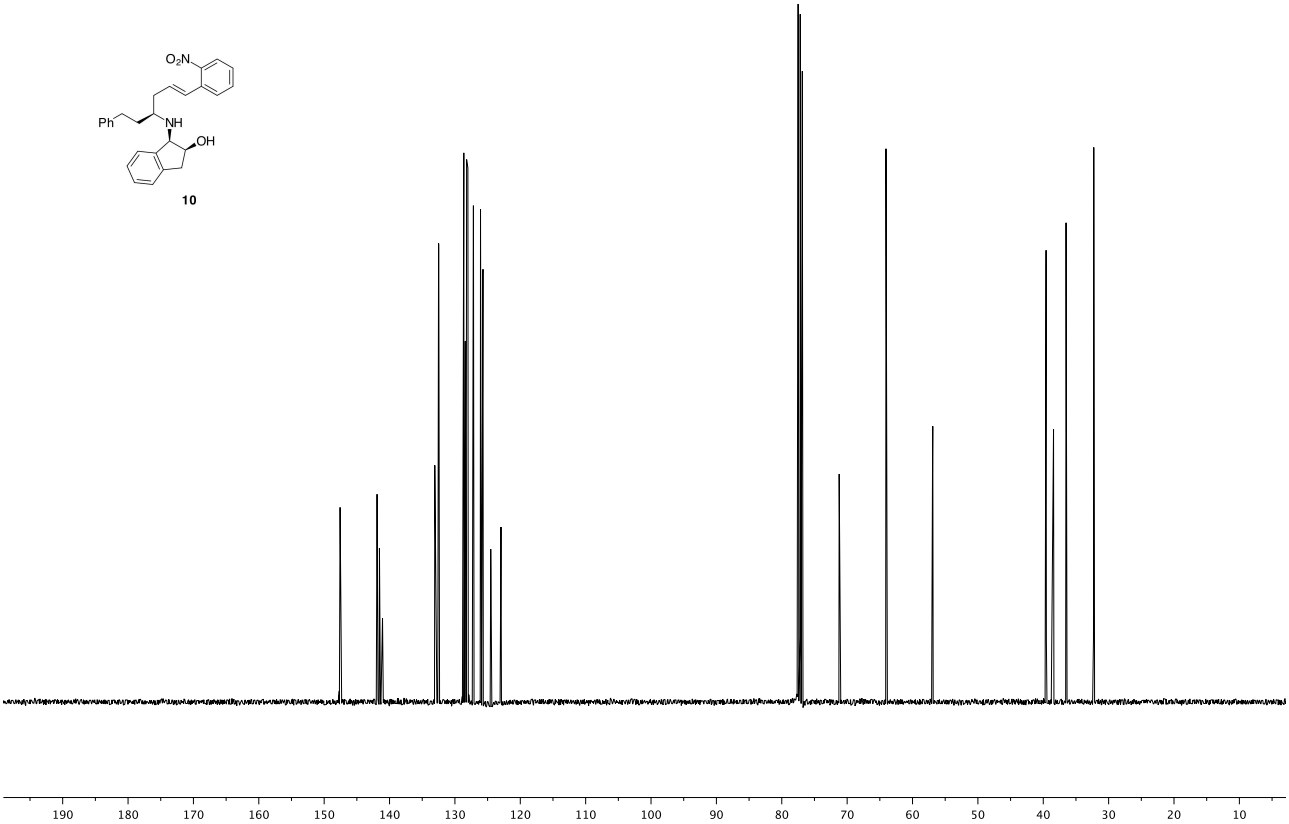

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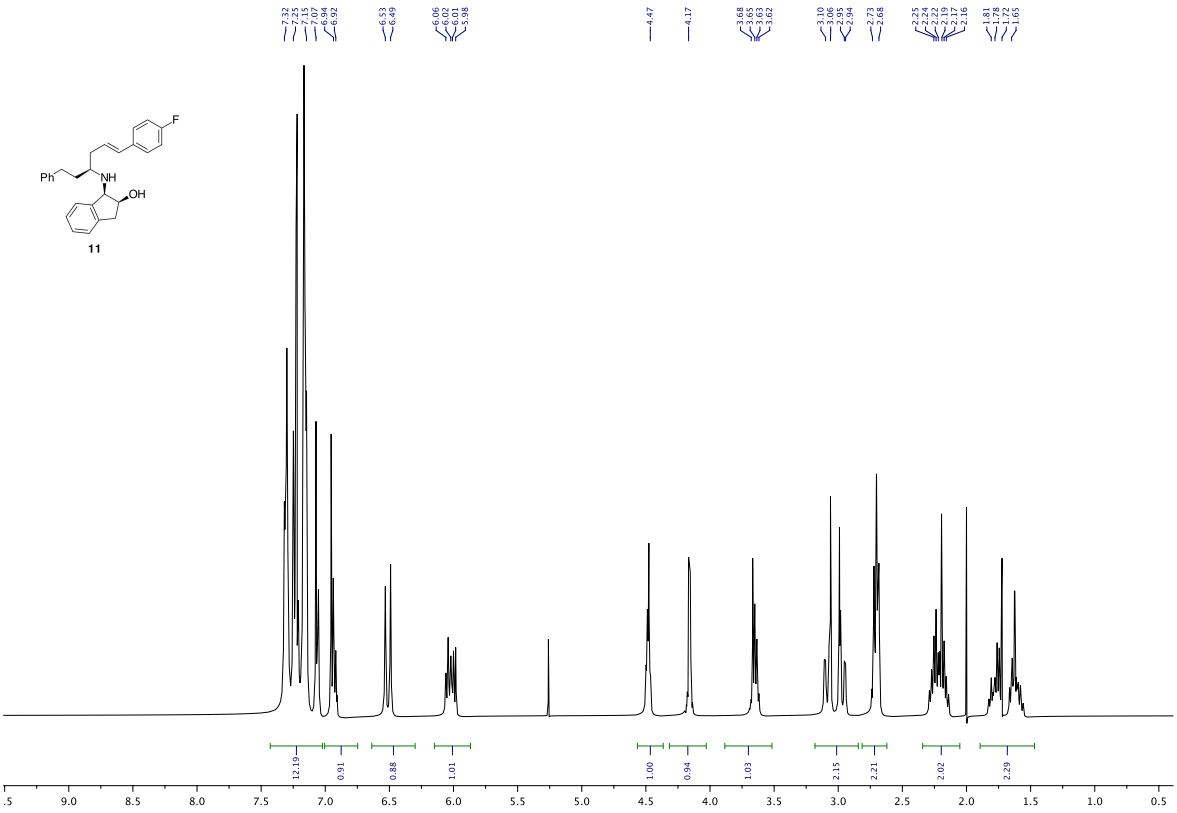
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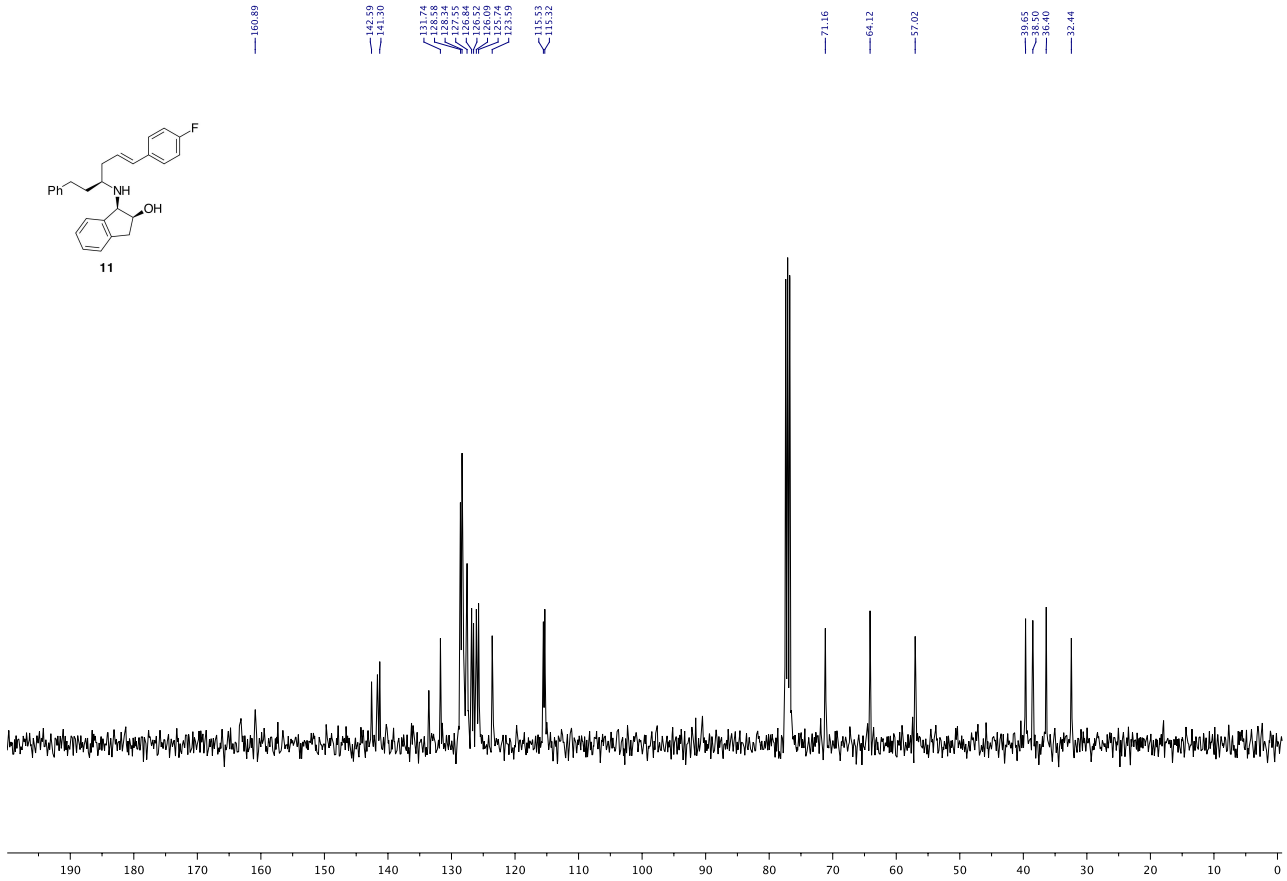
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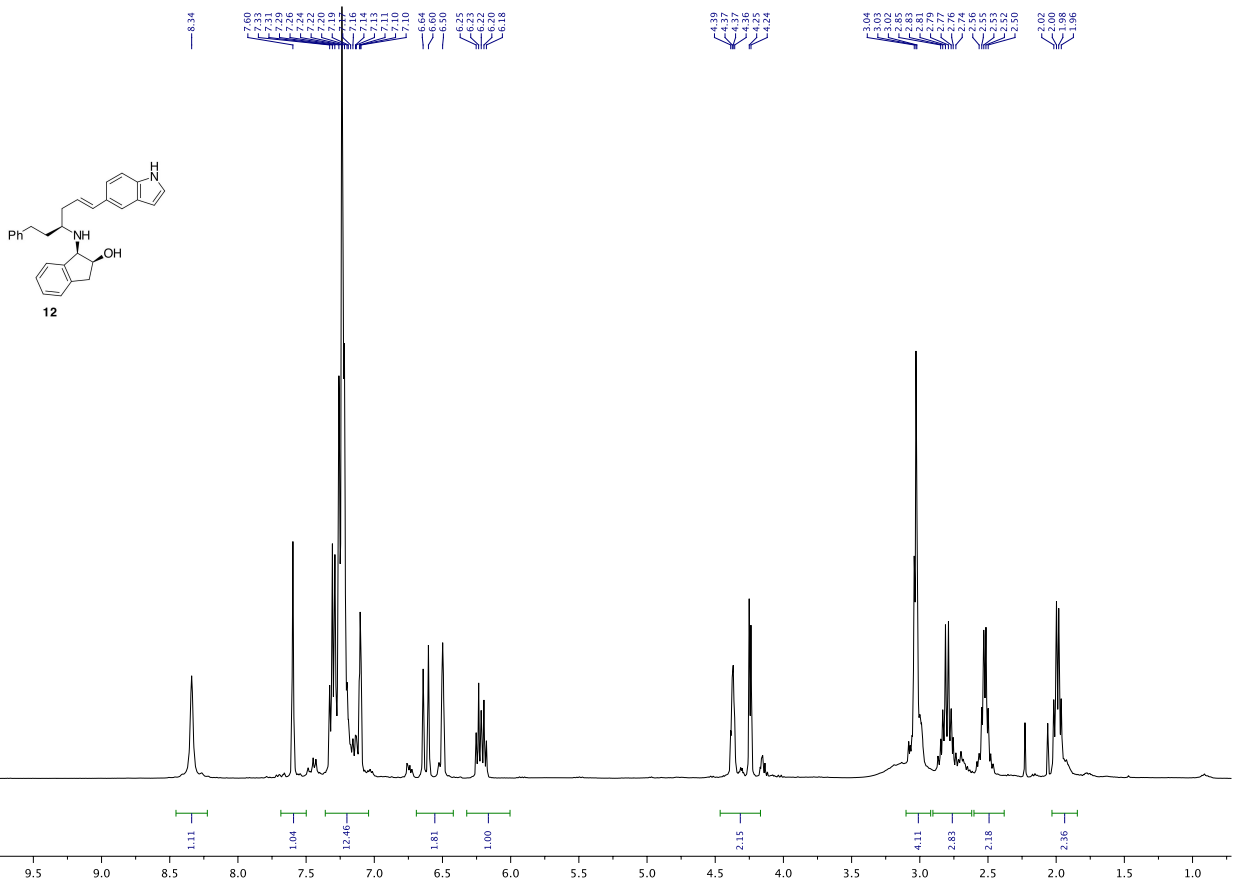
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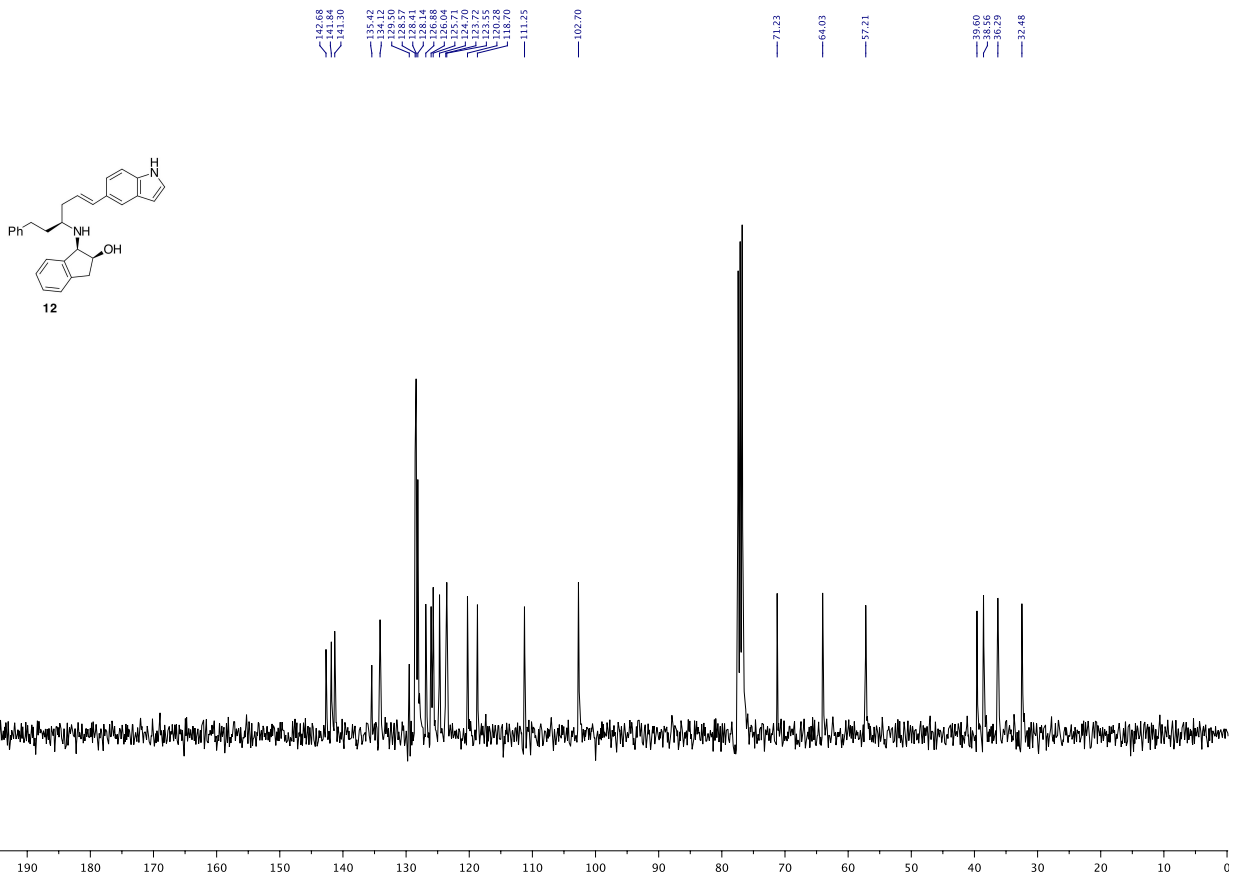
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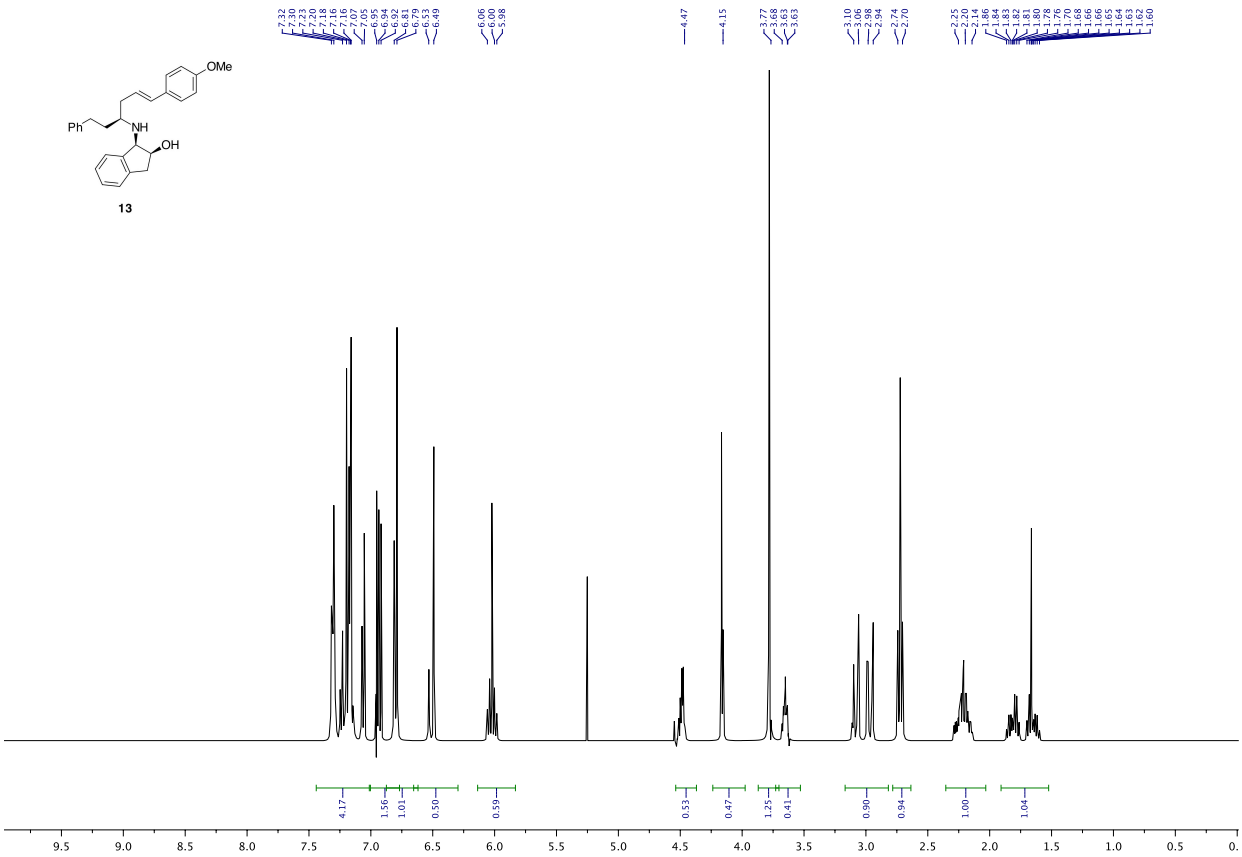
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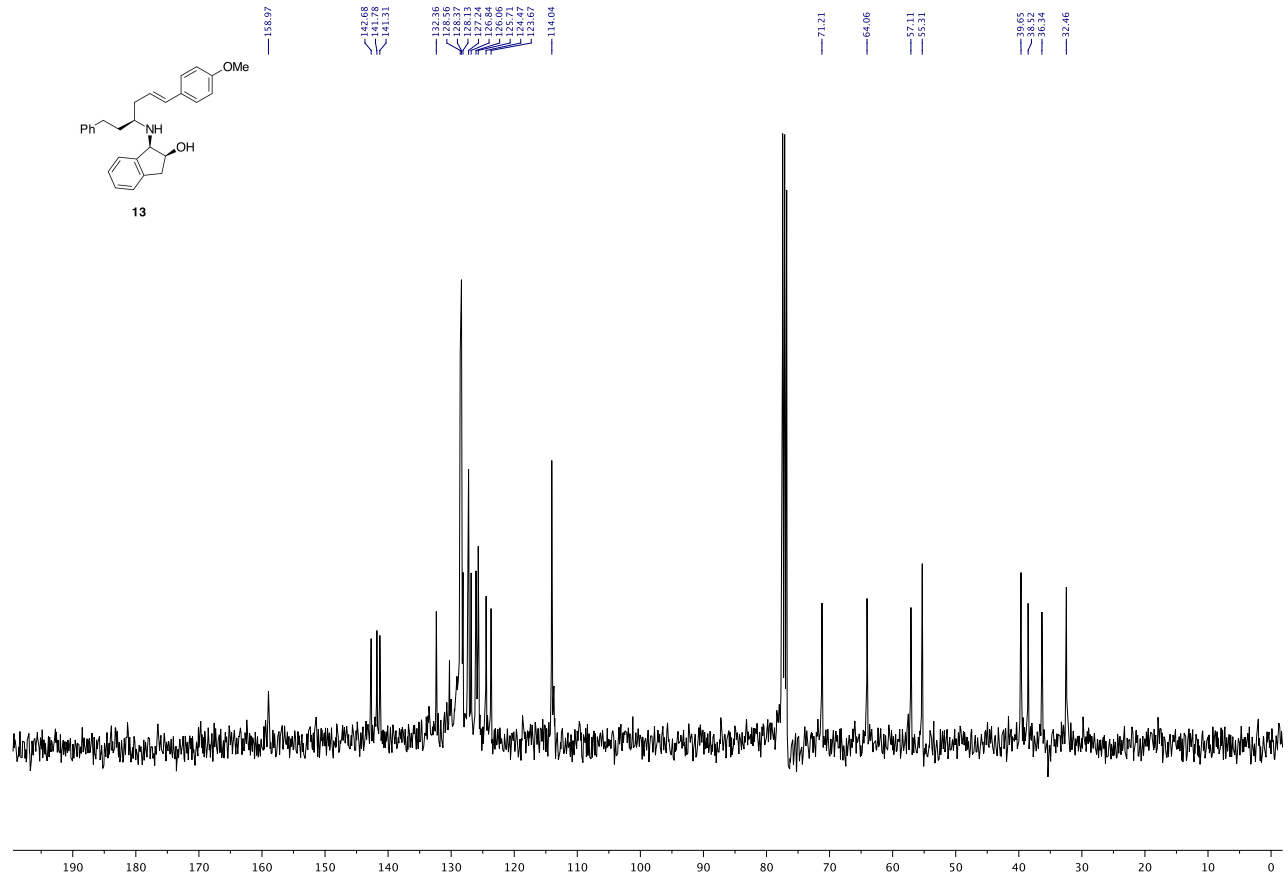
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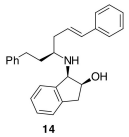
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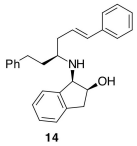
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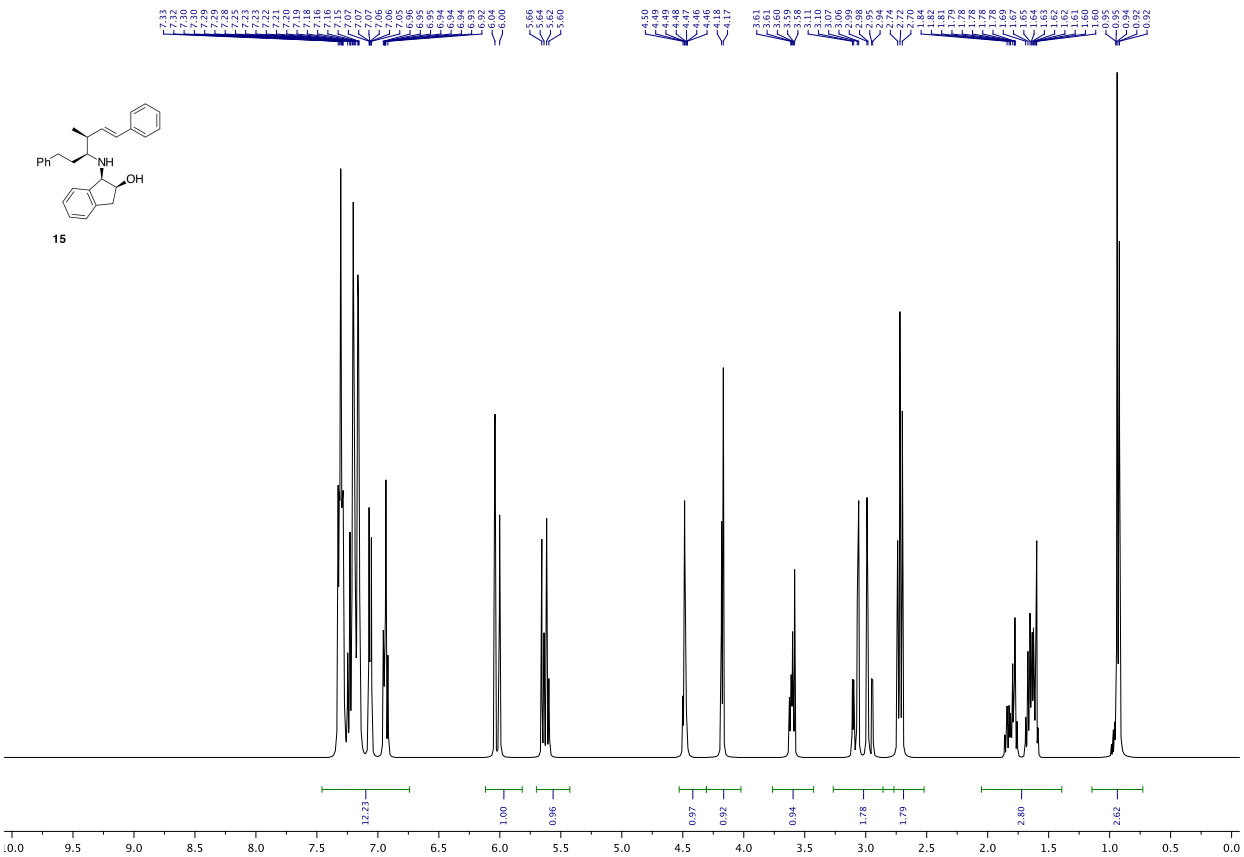
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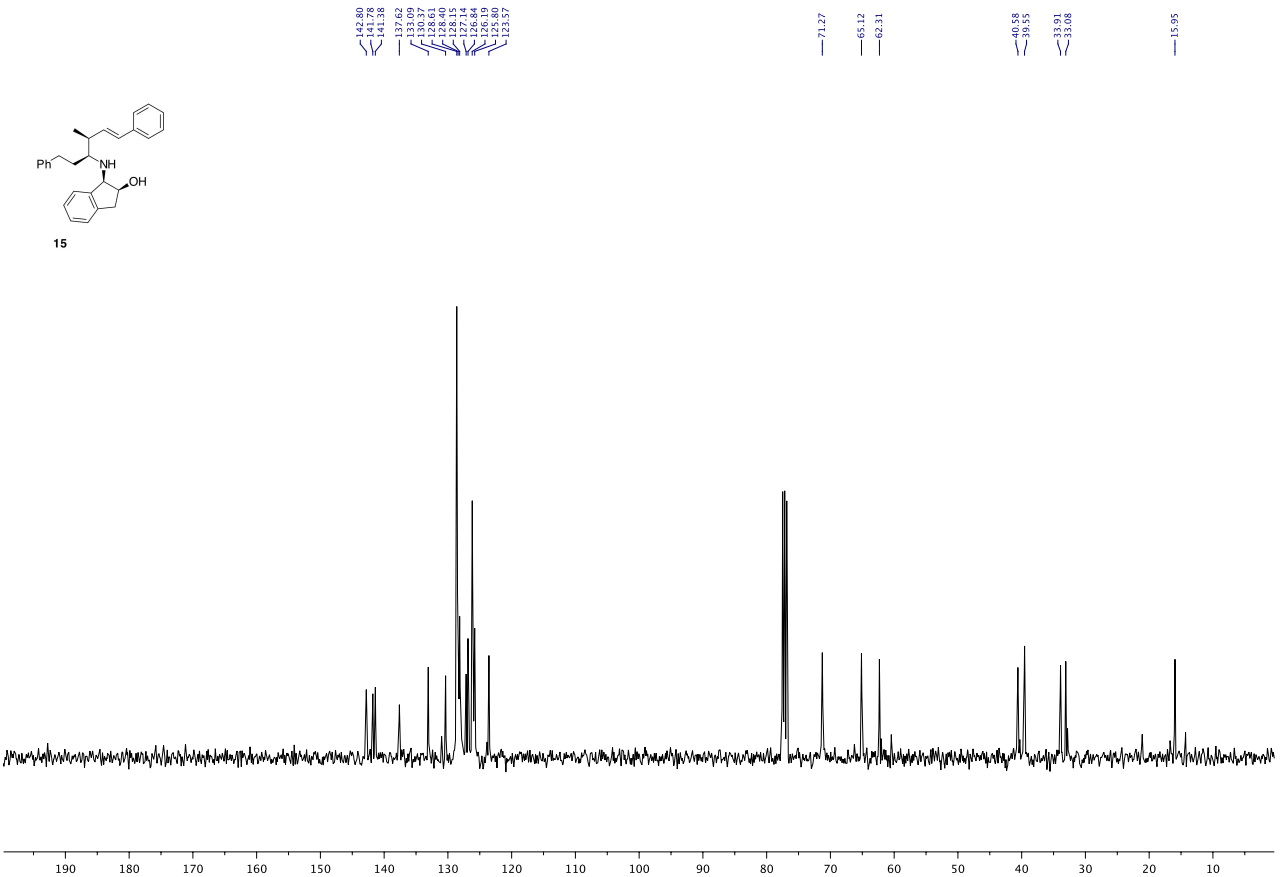
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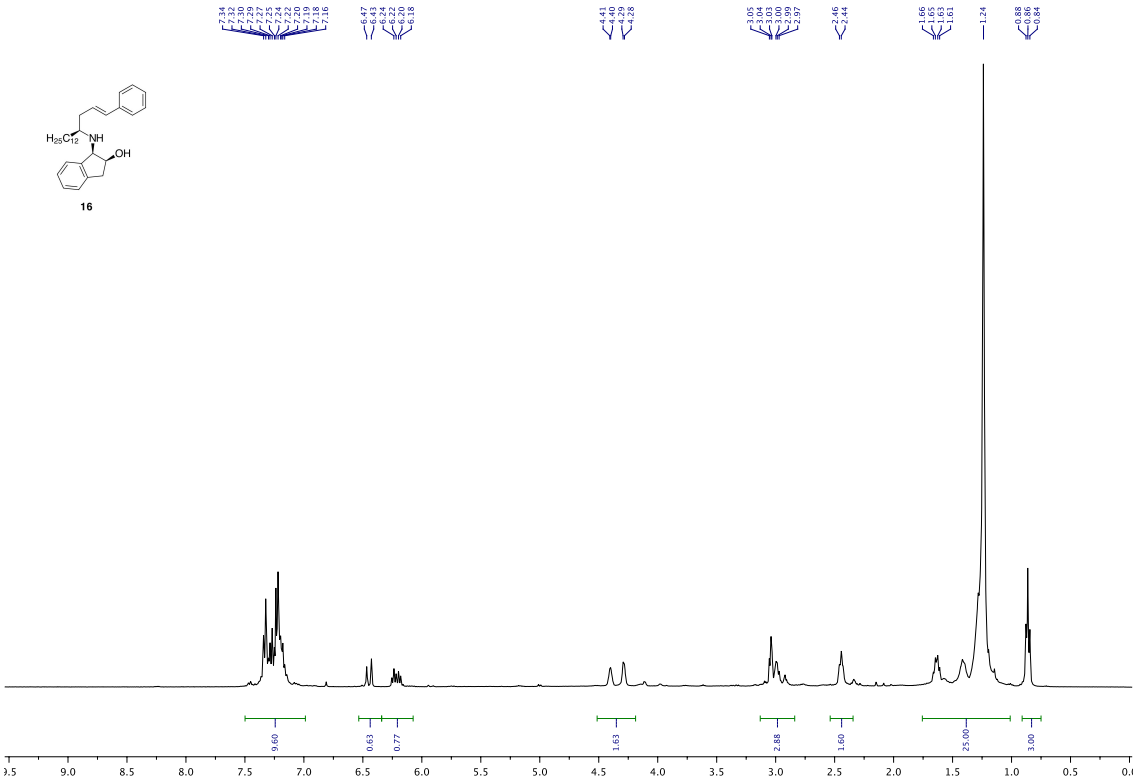
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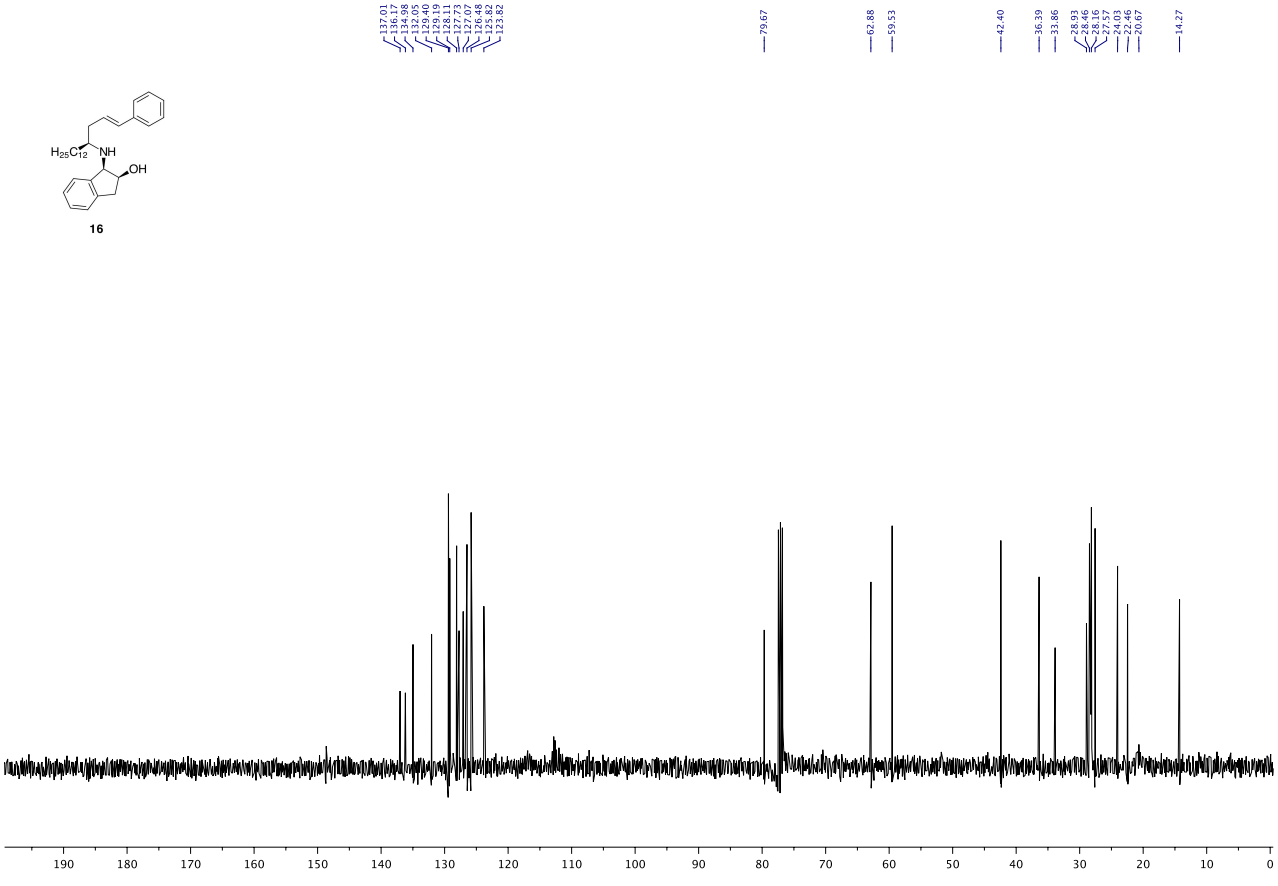
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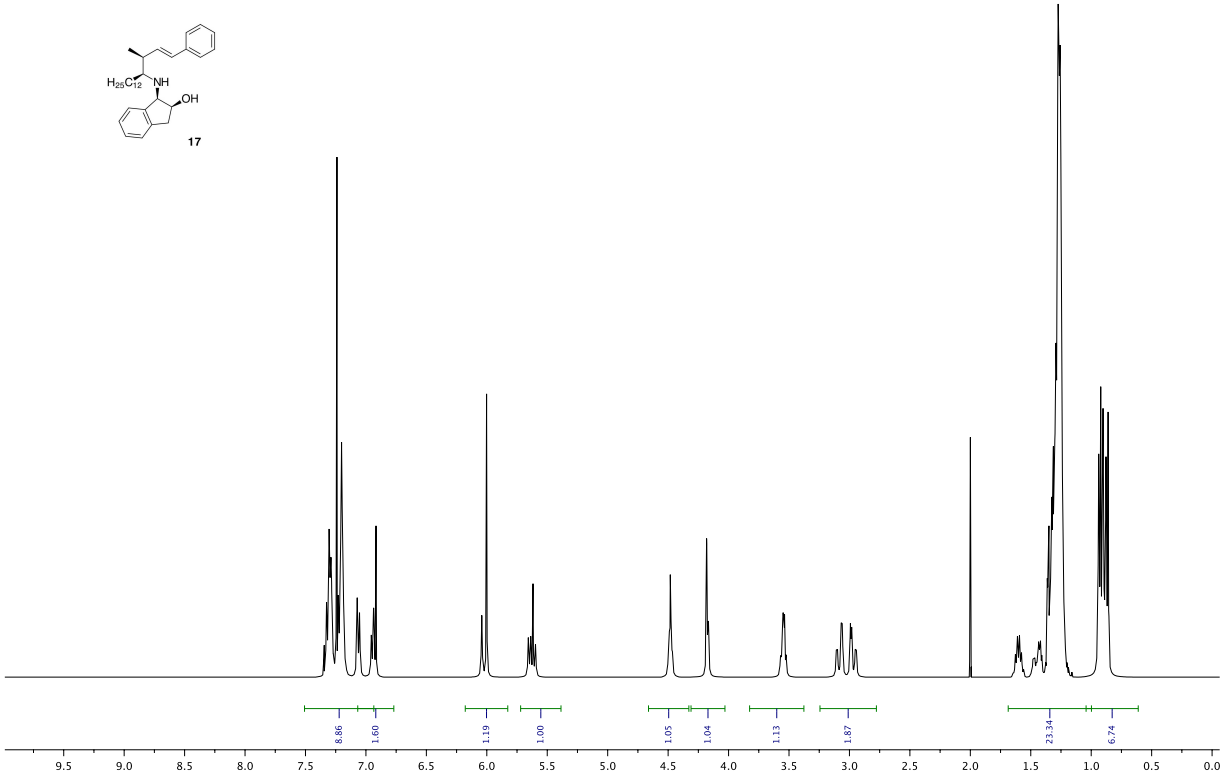
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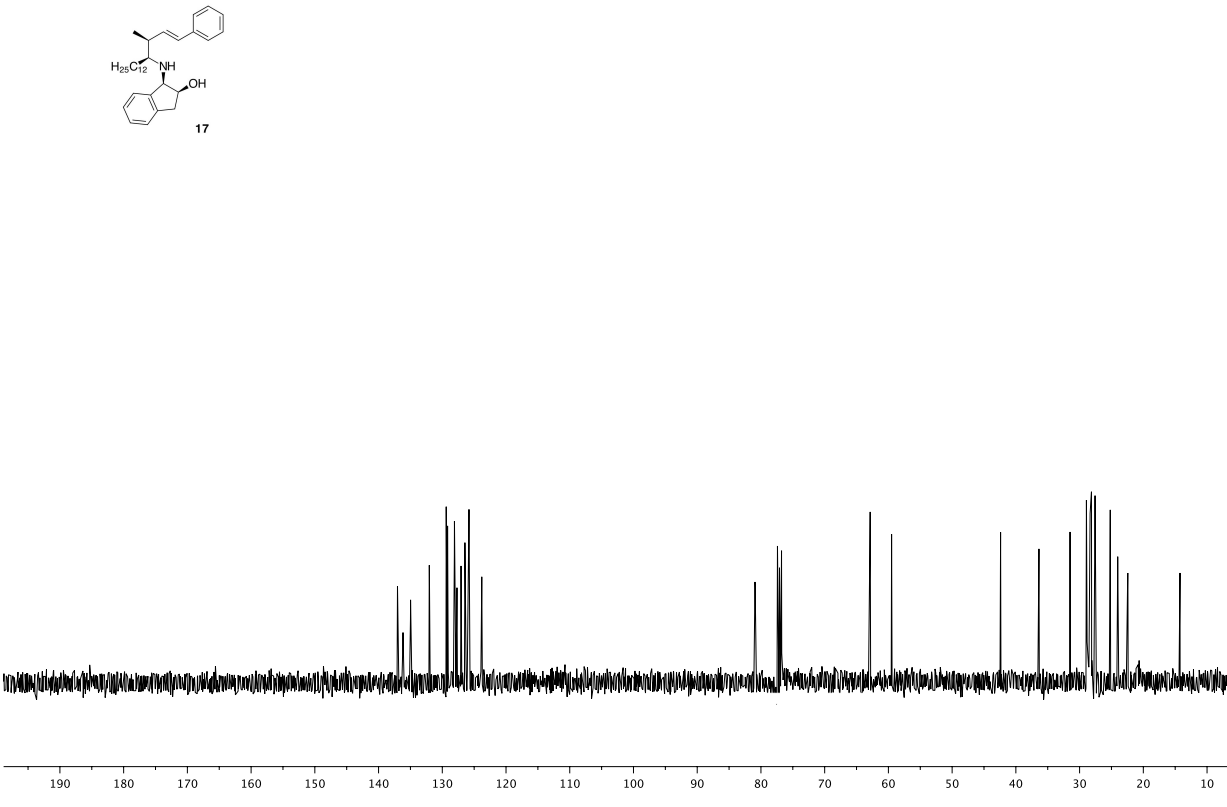
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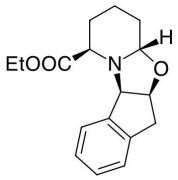
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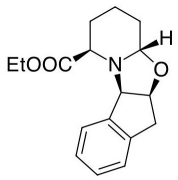
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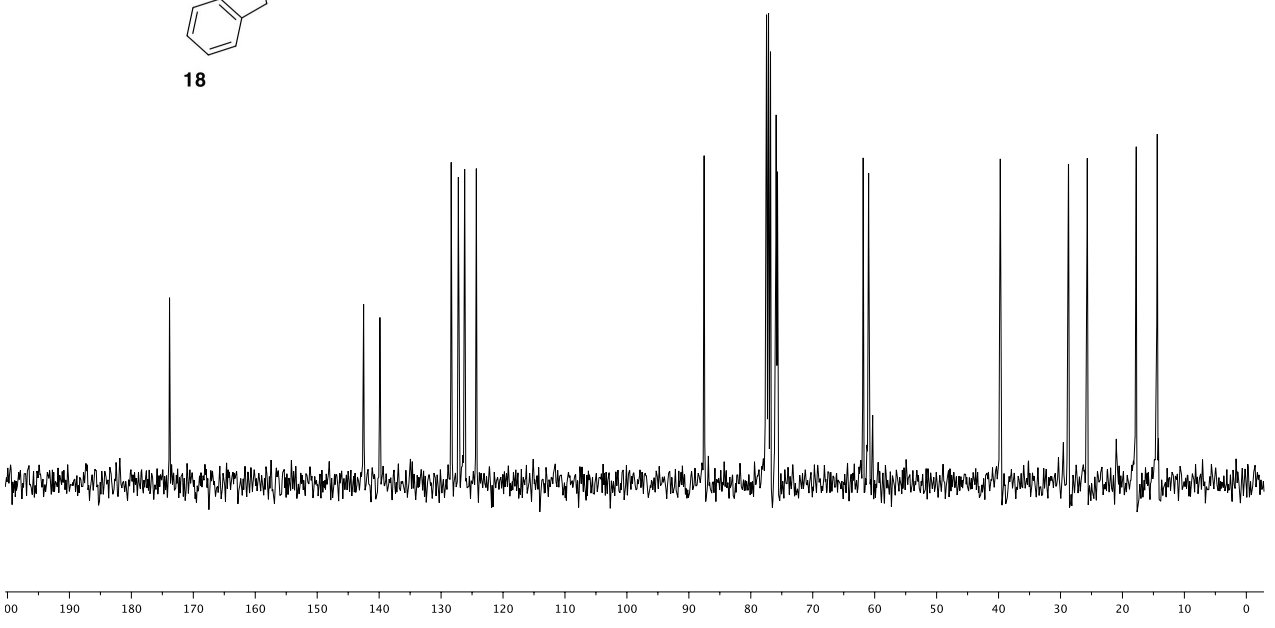
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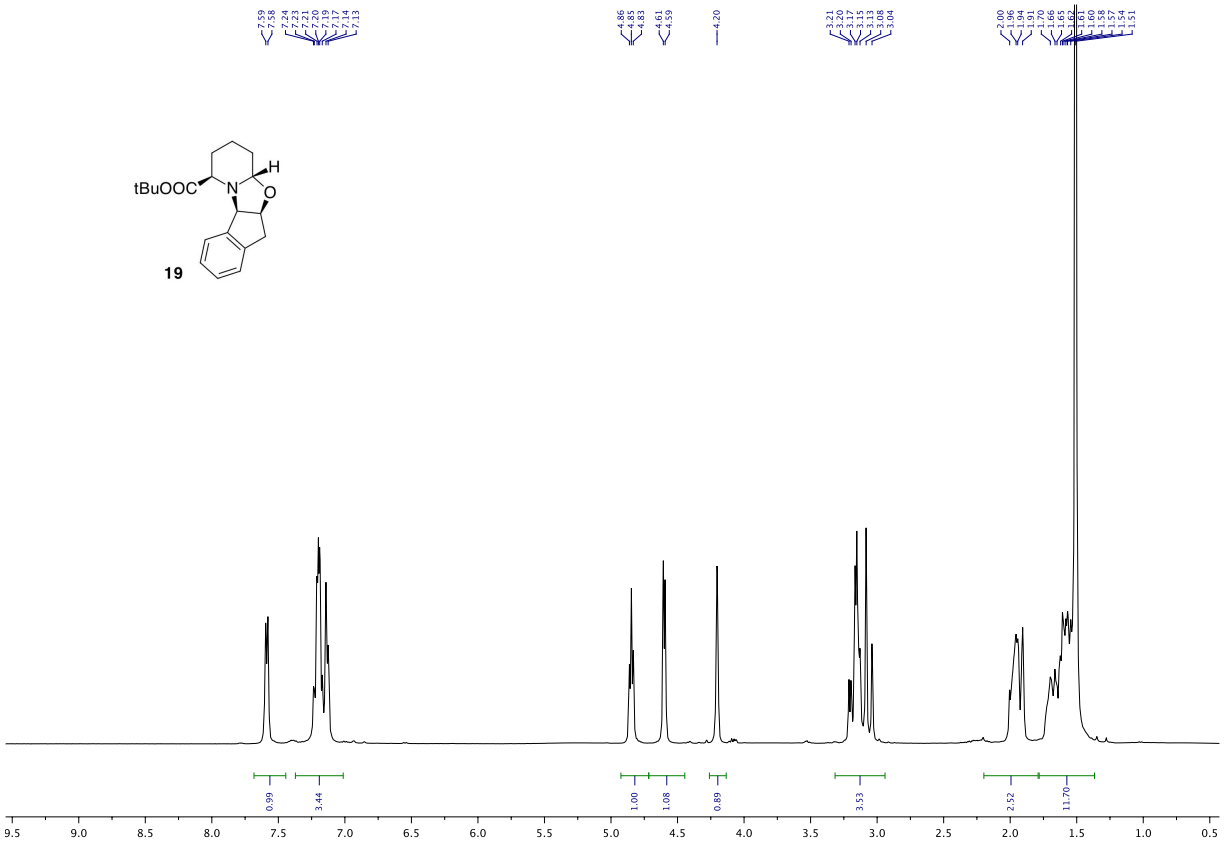
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3.15
3.13
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3.04
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1.91
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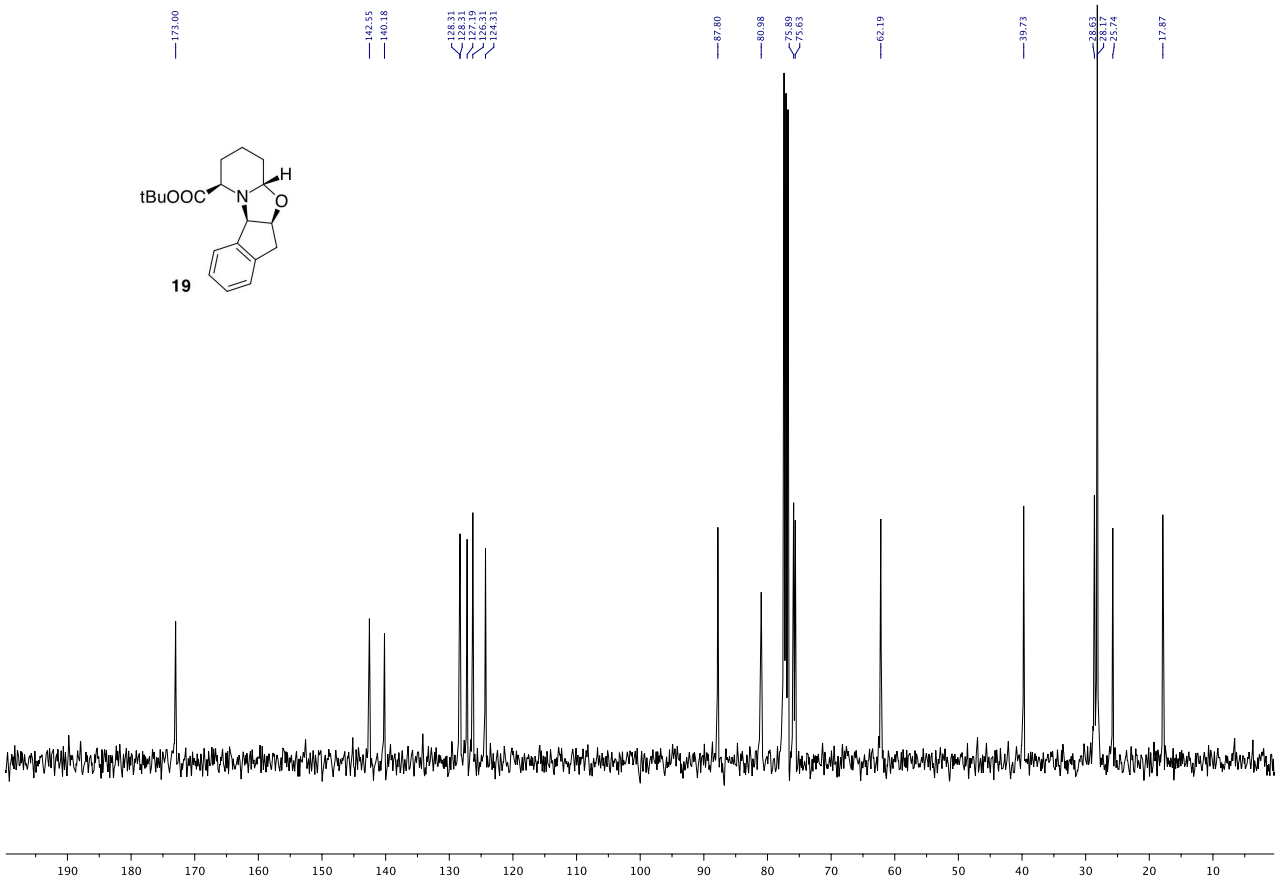
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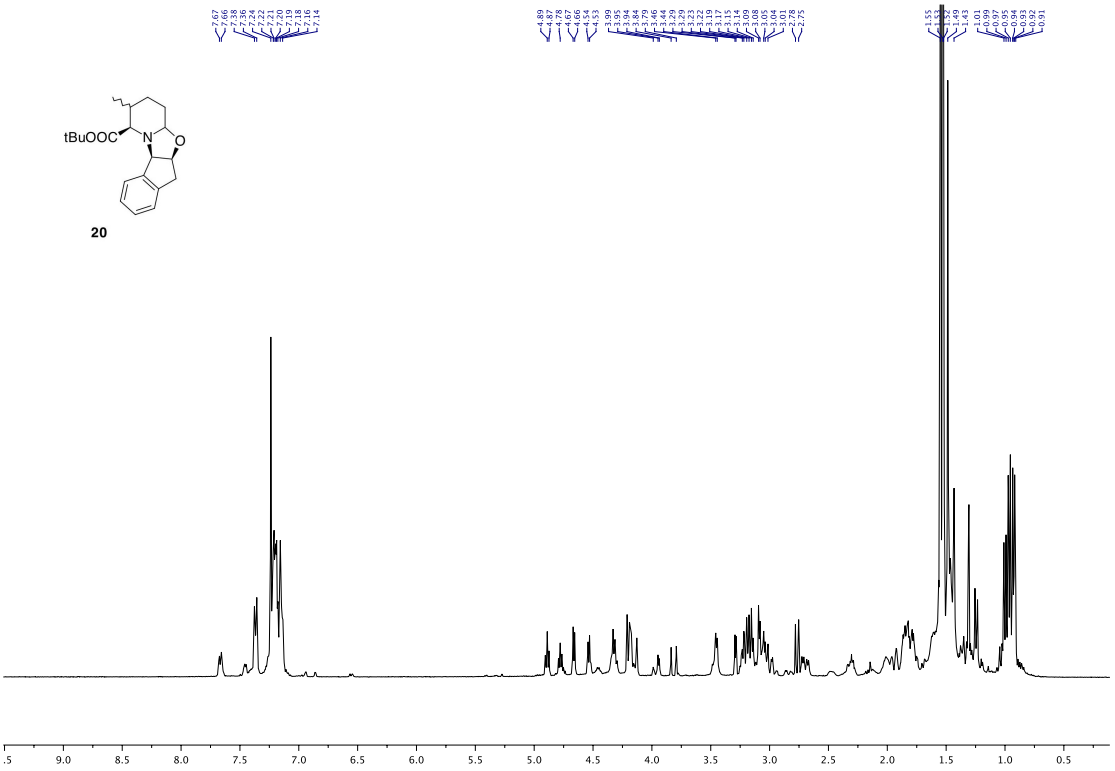
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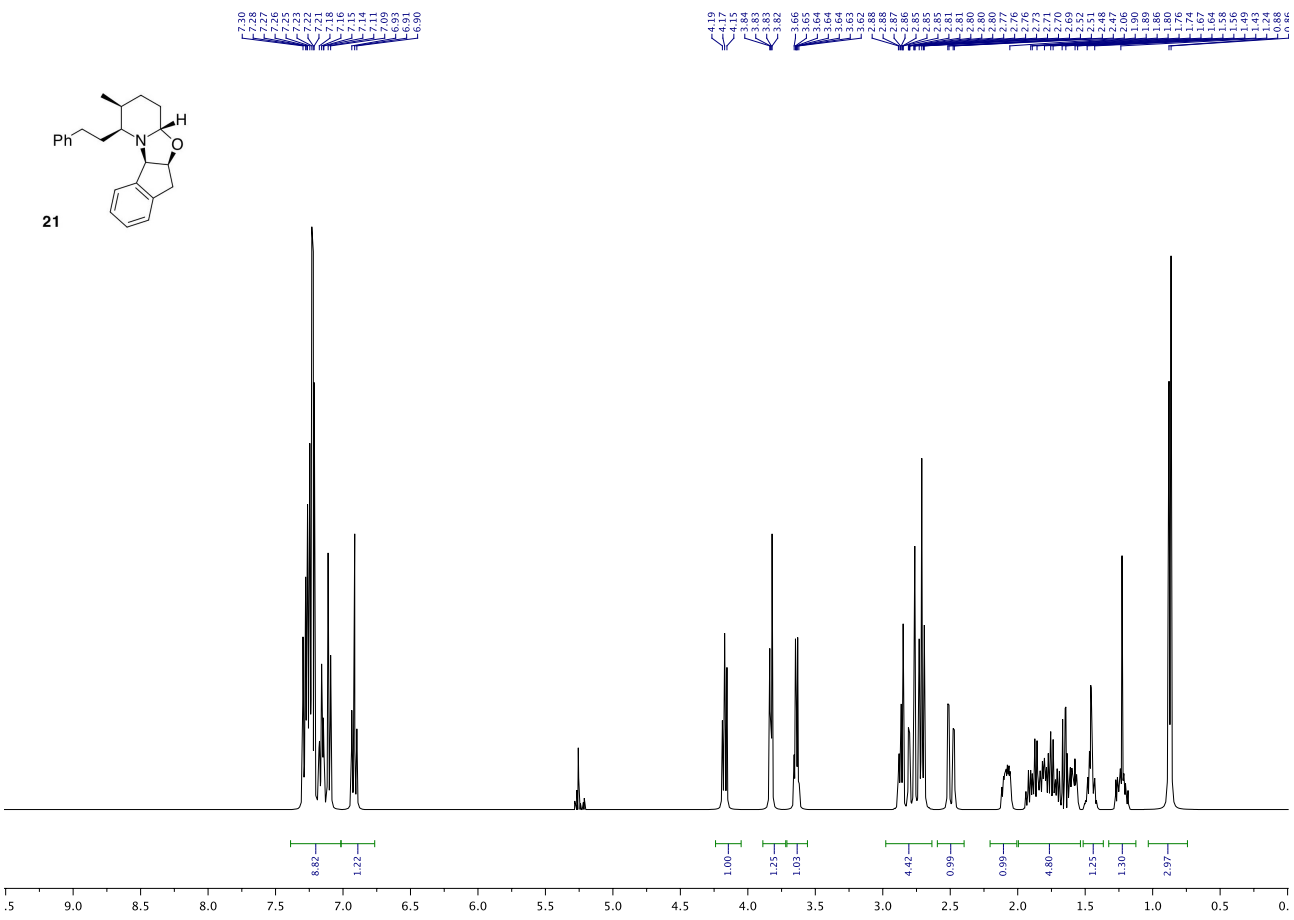
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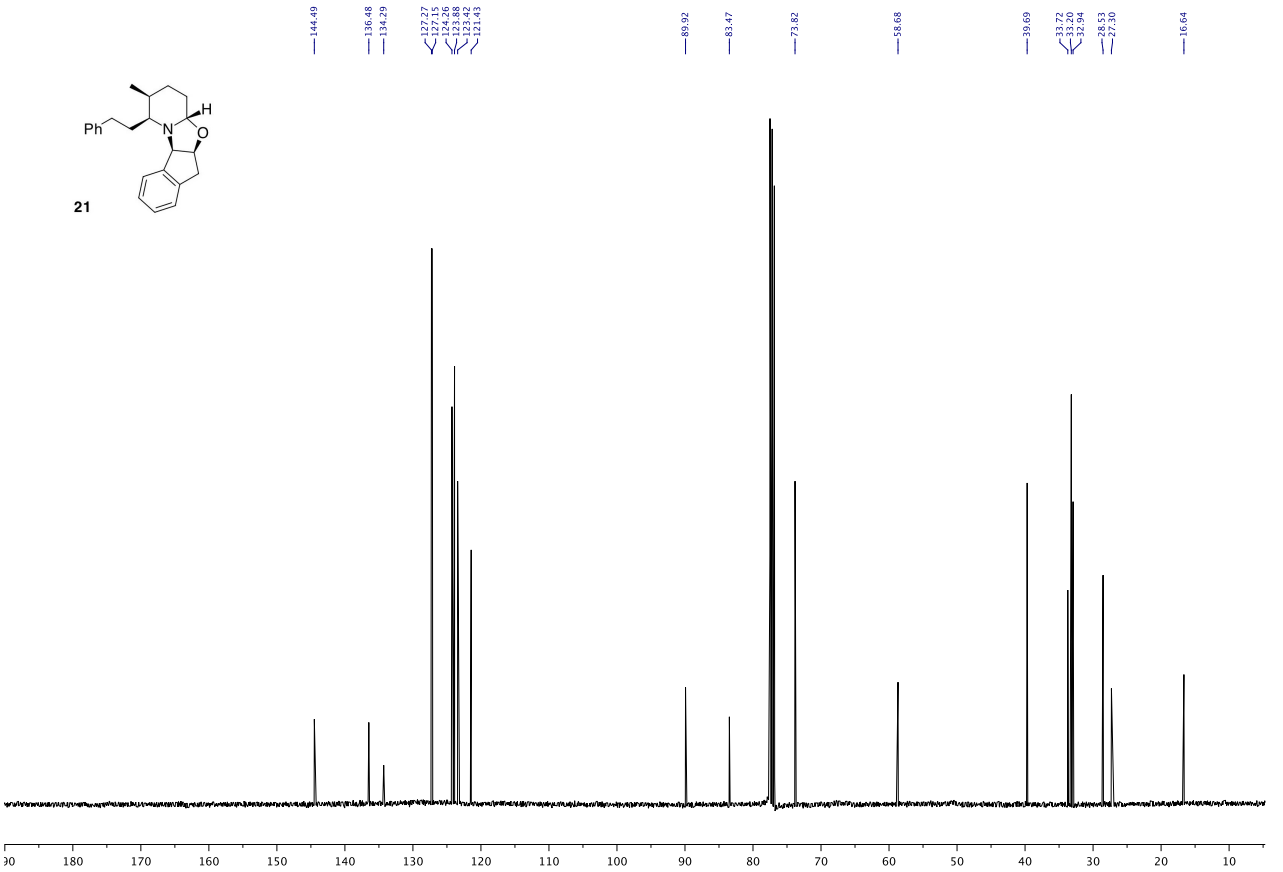
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32.94
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27.30
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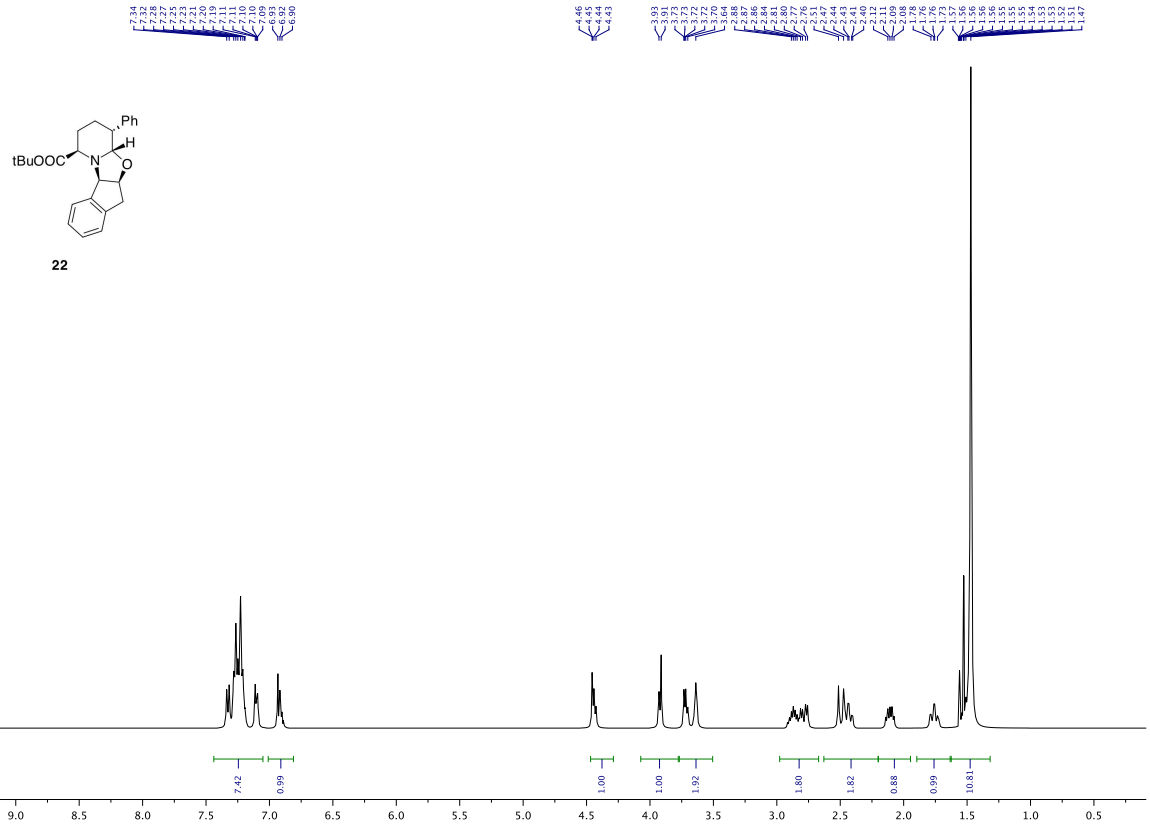
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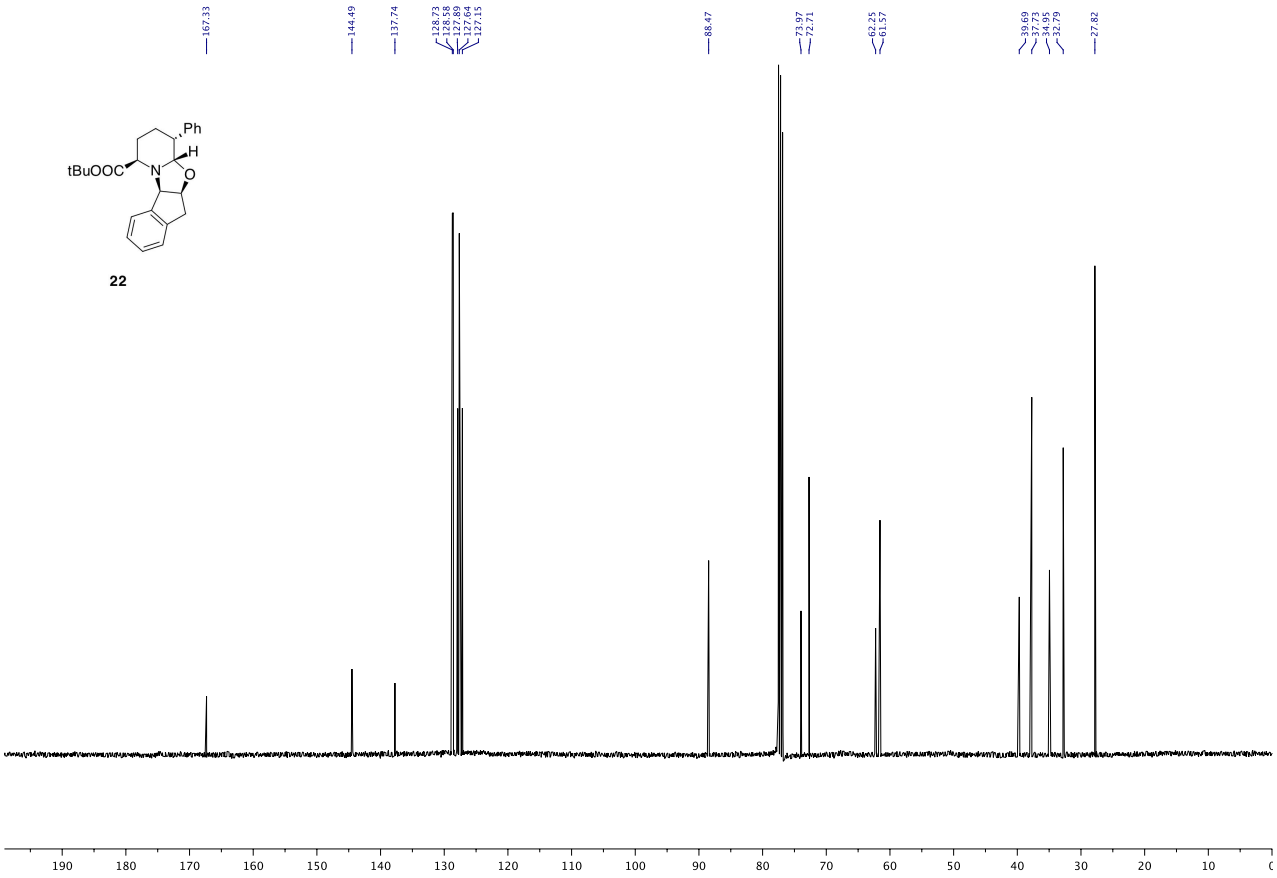
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34.95
32.79
27.82
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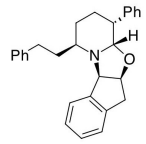
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0.81
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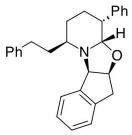
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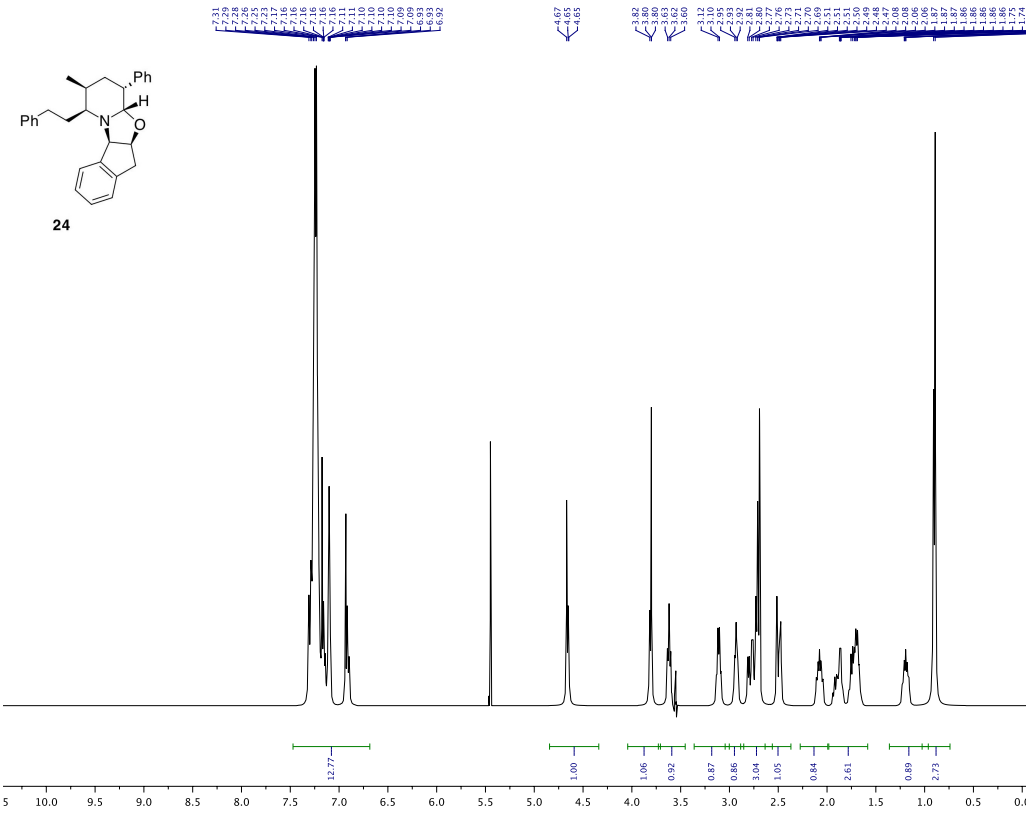
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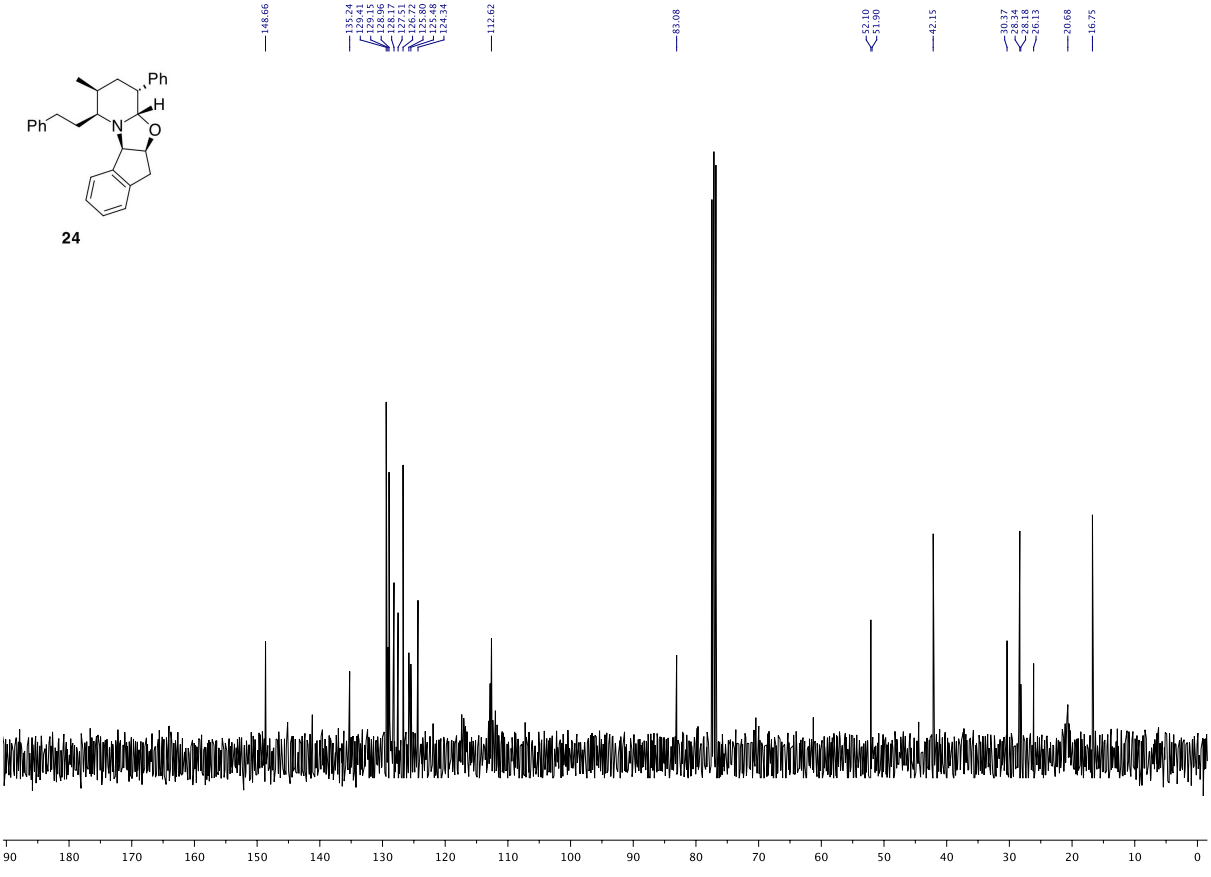
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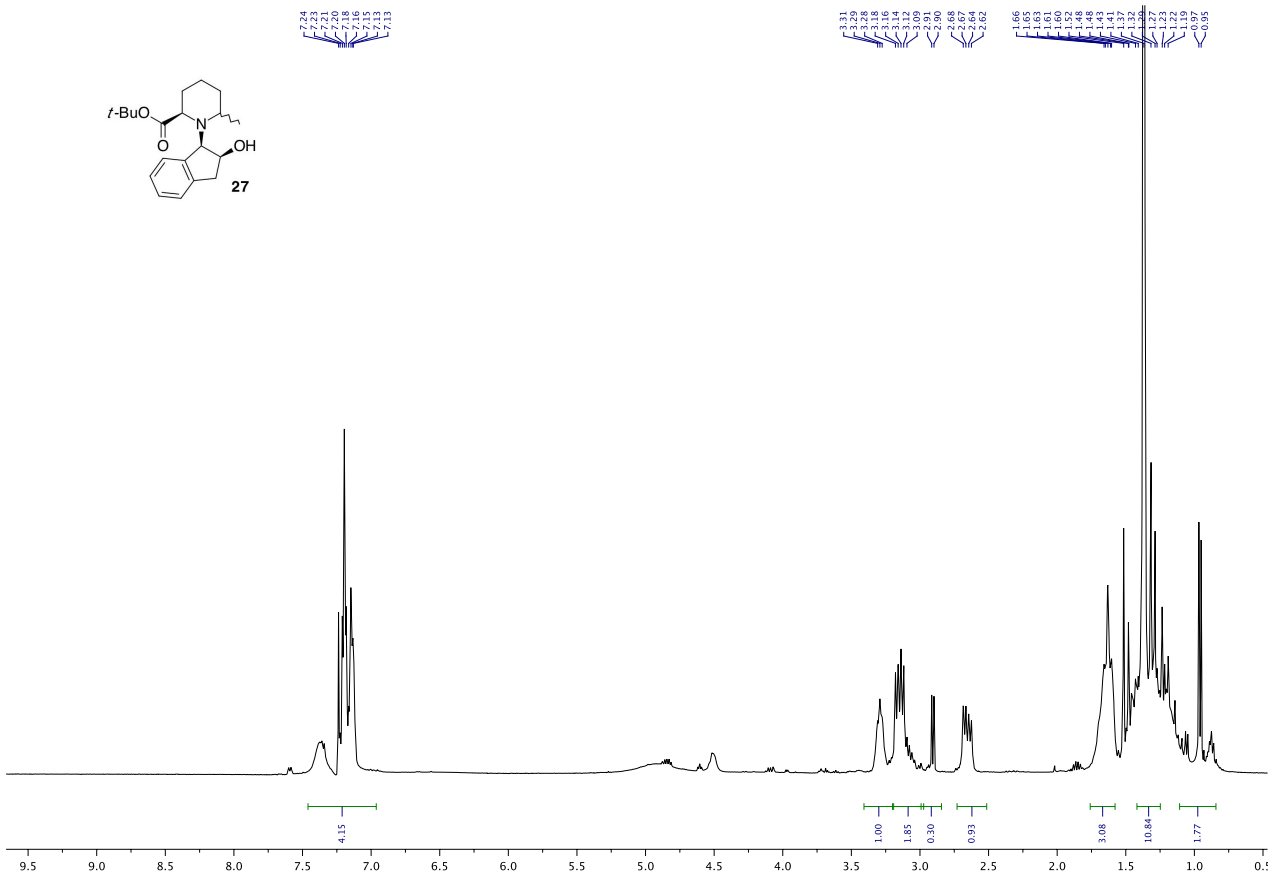
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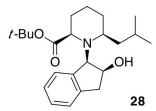

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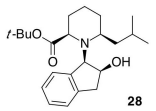

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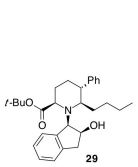
t-BuO
Ph
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OH
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29

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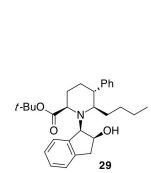
t-BuO
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OH
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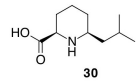
HO
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N
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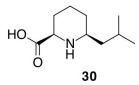
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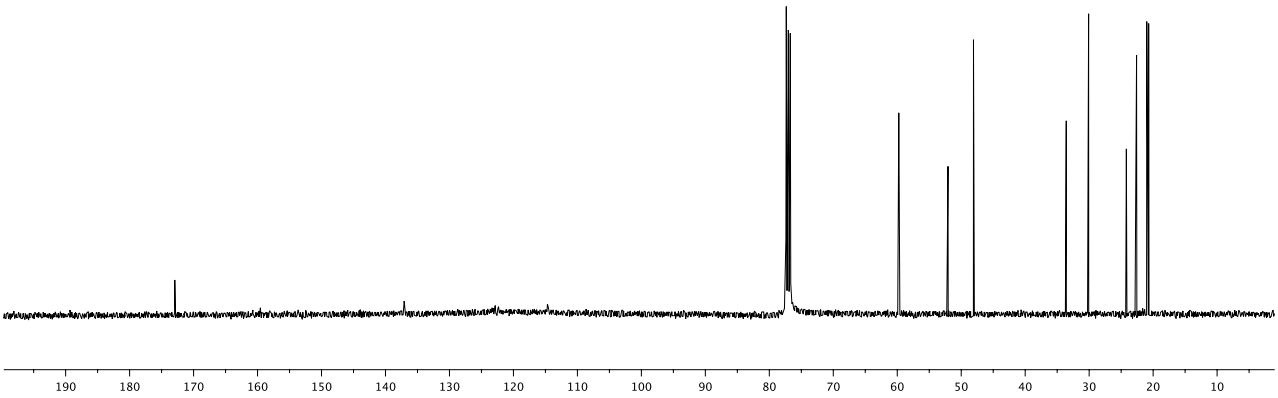
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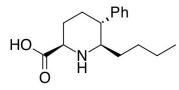
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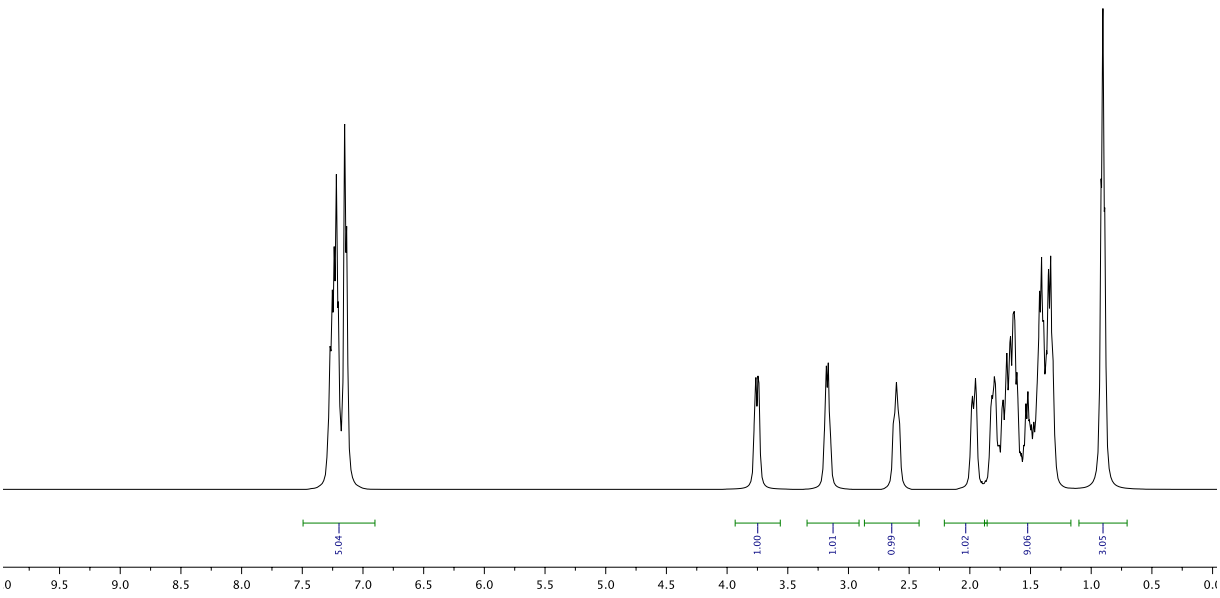
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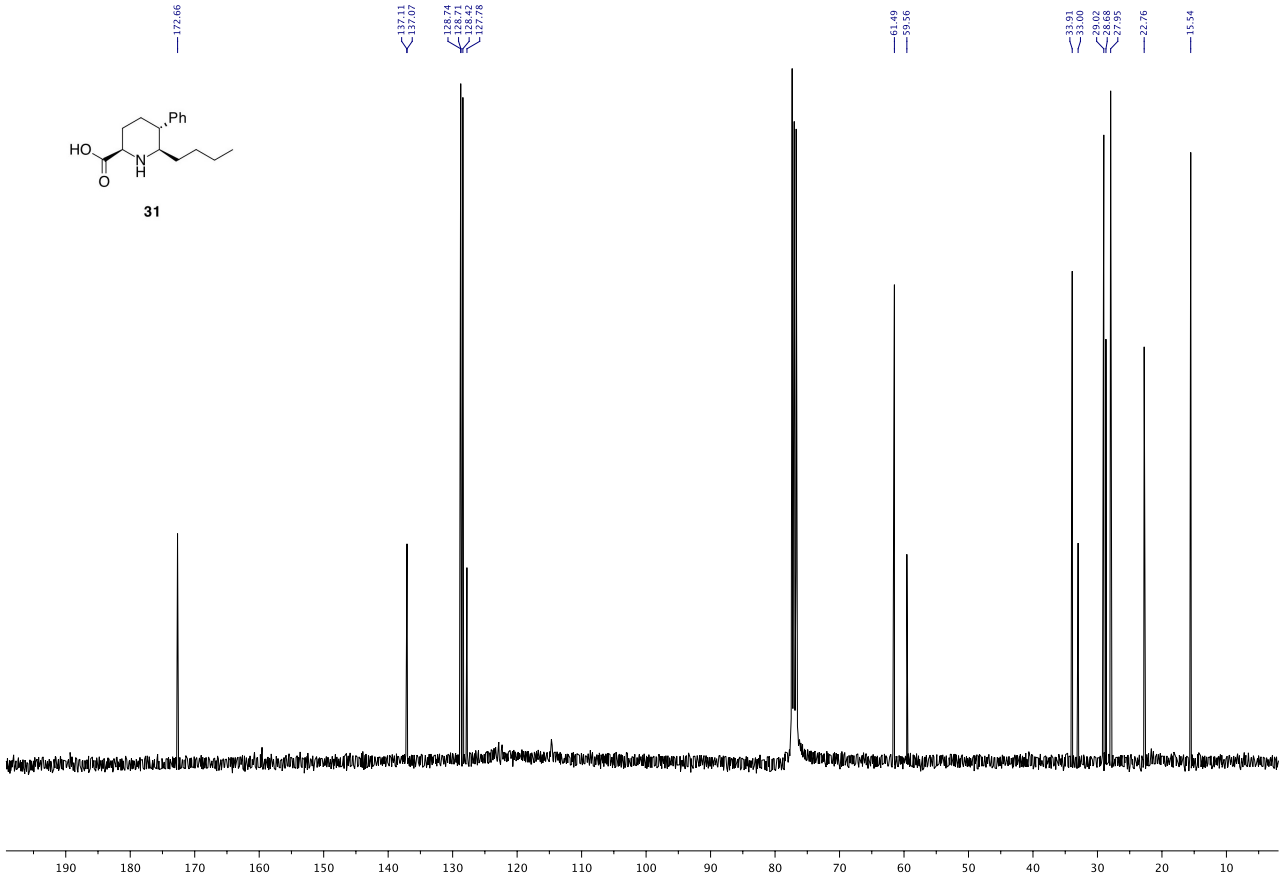
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Ph
HO
N
H
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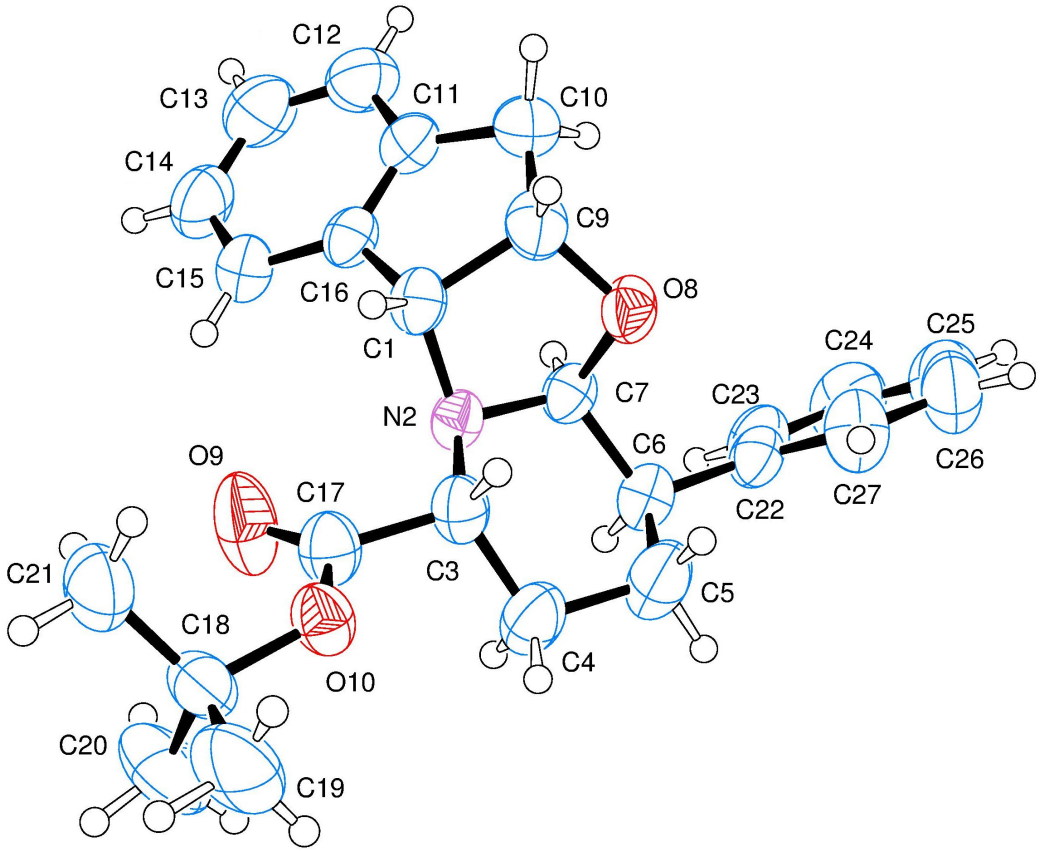
31



ORTEP diagram of compound **22**. The X-ray coordinates have been deposited at the Cambridge Crystallographic Data Centre, CCDC 1045261