Supplemental Information

180° Unidirectional Bond Rotation in a Biary Lactone Artificial Molecular Motor Prototype

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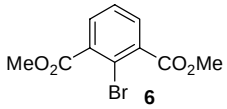
General methods

All starting materials were purchased from Aldrich Chemical Company, Alfa-Aesar, or TCI America Co. and used without further purification. Dichloromethane was distilled from CaH_2 before use. Tetrahydrofuran was distilled from Na and benzophenone before use. Other reagent grade solvents were used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 300 (75) MHz or 500 (125) MHz instrument. Qualitative transient ^{1}H NOESY-1D spectroscopic experiments were performed on a Varian Inova 500 MHz instrument. Chemical shifts are reported in parts per million (ppm), referenced to the appropriate residual solvent peak. Melting points were determined on a Laboratory Devices Meltemp II. FT-IR spectroscopy was performed on a Nicolet Magna IR 550 spectrometer as either liquid films on NaCl plates or as KBr pellets. Low resolution APCI mass spectrometry was performed on an Agilent 1100 Series LC-MS using a positive scan with low fragmentation to determine the molecular ion. X-ray crystal structures were performed on a Bruker Smart Apex 2540. Analytical TLC was performed on Kieselgel 60 F254 aluminum sheets. Spots were observed by exposure to 254 nm UV light or phosphomolybdic acid dip (PMA). Column chromatography was performed on silica gel 40-64 mesh (Silicycle) using technical grade solvents. Preparative TLC was performed on 20 × 20 cm 500 μ silica gel plates (Techware) with UV 254 nm visualization.

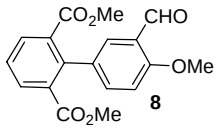
Synthetic Procedures



6

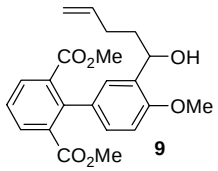
Dimethyl 2-bromoisophthalate (6). Commercially purchased (TCI) 2-bromo-*m*-xylene (9.4 g, 50 mmol) was added to a 100 mL mixture of 1:1 *t*-BuOH:H_2O. $KMnO_4$ (34.0 g, 213 mmol) and 34 g of Celite was then added and the mixture was refluxed for 16 hrs. After cooling to rt, the reaction mixture was filtered over Celite and concentrated to 1/3 volume under reduced pressure. Concentrated HCl was then carefully added until the product precipitated as a white solid. The solids were filtered and dried overnight in a vacuum dessicator yielding 8.0 g of crude product. This was not purified further and was carried on directly to the next step. ^{1}H NMR (300 MHz, d^6-DMSO): δ 7.68 (d, J = 7.5 Hz, 2H); 7.51 (t, J = 8.1 Hz, 1H). ^{13}C NMR (75 MHz, d^6-DMSO): δ 168.0, 136.9, 130.9, 128.0, 116.4. The crude product was added to 60 mL of methanol. 2 mL of concentrated H_2SO_4 was then carefully added and the reaction mixture was refluxed for 16 hours. After cooling to rt, the reaction was diluted with 50 mL of H_2O and extracted with 3 × 50 mL of Et_2O. The organic extracts were washed with 50 mL sat. of $NaHCO_3$ and 50 mL of brine. The organics were dried with $MgSO_4$, filtered, and the solvents were evaporated under reduced pressure to afford a crude oily product. Purification was achieved by vacuum distillation to afford 6.5 g of a clear colorless oil (48%, two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71

(d, J = 7.8 Hz, 2H), 7.41 (t, J = 7.5 Hz, 1H), 3.95 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 135.5, 132.5, 127.3, 119.3, 52.9. IR (liquid film) ν_{max}: 2953, 1736, 1284 cm^{-1}.



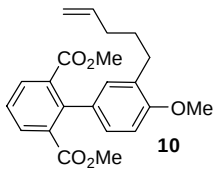
8

3'-Formyl-4'-methoxymethyl-biphenyl-2,6-dicarboxylic acid dimethyl ester (8). Aryl halide **6** (1.3 g, 4.8 mmol) was added to commercially purchased (Aldrich) 3-formyl-4-methoxyphenylboronic acid (860 mg, 4.8 mmol), Na_2CO_3 (451 mg, 4.8 mmol), tetrabutylammonium bromide (386 mg, 1.2 mmol), and $Pd(OAc)_2$ (10 mg, 0.4 mol %) in 20 mL of distilled H_2O. The flask was affixed with a reflux condenser was then placed into a 150 ºC oil bath and refluxed for 30 minutes. The cooled mixture was extracted with 4 × 25 mL of EtOAc. The organics were combined and washed with 25 mL of 5% NaOH, 25 mL of 5% HCl, 25 mL of brine, dried with Na_2SO_4, and the solvents were removed under reduced pressure. The product was isolated (1.4 g, 88%) by recrystallizing in 95% EtOH to afford white crystals. mp = 108-111 °C. R_f (1:1 EtOAc:hexane) 0.42. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.47 (s, 1H), 7.95 (d, J = 7.8 Hz, 2H), 7.51-7.41 (m, 3H), 7.01 (d, J = 9.0 Hz, 1H), 3.96 (s, 3H), 3.62 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.7, 167.7, 161.2, 140.8, 136.3, 132.9, 132.5, 131.6, 128.4, 127.7, 124.0, 110.9, 55.8, 52.4. IR (KBr) ν_{max}: 2953, 1734, 1671, 1284, 1247 cm^{-1}.



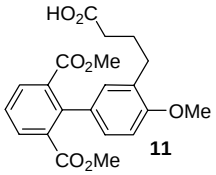
9

3'-(1-Hydroxy-pent-4-enyl)-4'-methoxy-biphenyl-2,6-dicarboxylic acid dimethyl ester (9). Mg turnings (1.80 g, 72.8 mmol) were added to an oven dried flask and was flushed with a N_2 stream for 30 minutes. Anhydrous THF (75 mL) was then added, followed by a dropwise addition of 4-bromo-1-butene (2.50 mL, 26.4 mmol) over a 30 min period. The mixture was then stirred at rt for 2 hrs. Biaryl aldehyde **8** (1.80 g, 72.8 mmol) was dissolved in 50 mL of anhydrous THF in a separate oven dried flask and purged with a N_2 stream for 30 min. The mixture was cooled in an ice bath and the Grignard reagent was added dropwise to **8** over 45 min. The reaction was stirred in an ice bath for 3 hrs after which 50 mL of sat. NH_4Cl was added dropwise. The layers were separated and the aqueous layer was extracted with 3 × 50 mL of Et_2O. The combined organics were dried with Na_2SO_4, filtered, and the solvents were removed under reduced pressure to yield a yellow oil. The crude product was purified by column chromatography (9:1 CH_2Cl_2:EtOAc → 3:1 CH_2Cl_2:EtOAc) to yield 2.6 g (82%) of a clear oil. R_f (9:1 CH_2Cl_2:EtOAc) 0.51. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, J = 8.1 Hz, 2H), 7.45 (t, J = 7.5 Hz, 1H), 7.14-7.09 (m, 2H), 6.88 (d, J = 8.4 Hz), 5.90-5.79 (m, 1H), 5.07-4.87 (m, 3H), 3.89 (s, 3H), 3.60 (s, 6H), 2.21-2.10 (m, 2H), 1.92-1.84 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 156.0, 141.2, 138.7, 133.4, 131.7, 131.3, 128.3, 127.5, 127.2, 114.8, 109.8, 70.4, 55.4, 52.3, 36.5, 30.3. IR (liquid film) ν_{max}: 3516, 3074, 2950, 1732, 1283, 1248 cm^{-1}.



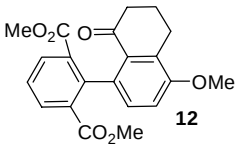
10

4'-Methoxy-3'-pent-4-enyl-biphenyl-2,6-dicarboxylic acid dimethyl ester (10). Biaryl alcohol **9** (2.4 g, 6.3 mmol) was dissolved in 50 mL of anhydrous CH_2Cl_2 in an oven dried flask, then purged under a N_2 stream for 30 minutes. The solution was cooled in an ice bath and trifluoroacetic acid (3.00 mL, 37.7 mmol) was added followed by triethylsilane (2.50 mL, 15.7 mmol). The reaction was stirred in a ice bath for 1.5 hrs after which it was diluted with 25 mL of toluene and the solvent removed under reduced pressure. The resulting yellow oil was taken up in 50 mL of Et_2O and washed with 25 mL of sat. $NaHCO_3$ and 25 mL of brine. The organics were dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure yielding a clear oil. The crude product was purified by column chromatography (3:1 CH_2Cl_2:hexane → CH_2Cl_2) to yield 2.04 g (88%)of a clear oil. R_f (1:1 hexane:EtOAc) 0.60. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, J = 7.8 Hz, 2H), 7.45 (t, J = 7.5 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.98 (s, 1H), 6.84 (d, J = 8.1 Hz, 1H), 5.90-5.81 (m, 1H), 5.07-4.94 (m, 2H), 3.86 (s, 3H), 3.60 (s, 6H), 2.64 (t, J = 7.5 Hz, 2H), 2.10 (dt, J = 6.9 Hz, 7.8 Hz, 2H), 1.68 (quin, J = 7.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 157.0, 141.3, 139.0, 133.6, 131.5, 130.8, 130.1, 127.0, 114.6, 109.5, 55.3, 52.3, 33.6, 29.7, 29.2. IR (liquid film) ν_{max}: 2998, 2949, 1733, 1285, 1244 cm^{-1}.



11

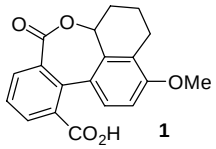
3'-(3-Carboxy-propyl)-4'-methoxy-biphenyl-2,6-dicarboxylic acid dimethyl ester (11). Biaryl alkene **10** (2.0 g, 5.5 mmol) was dissolved in 30 mL of DMF. A 0.1 M solution of OsO_4 in *t*-BuOH (550 µL, 0.55 mmol) was added and the solution was stirred 5 min. The solution was cooled in an ice bath and Oxone (13.5 g, 22.0 mmol) was added in six equal portions over 1 hr. The reaction was stirred for 3 hrs in an ice bath. 12 g of Na_2SO_3 was then added over the course of 30 min and the reaction was stirred for 1 hr. 50 mL of 5% HCl was then added and the reaction mixture was extracted with 3 × 50 mL of Et_2O. The organics were combined and washed with 2 × 50 mL of brine, dried over $MgSO_4$, and the solvents removed under reduced pressure. Purification by column chromatography (1:1 EtOAc:hexane) yielded 1.4 g (67%) of a white solid. R_f (1:1 hexane:EtOAc) 0.43. mp = 101-103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, J = 7.5 Hz, 2H), 7.45 (t, J = 7.8 Hz, 1H), 7.04 (dd, J = 8.4 Hz, 2.1 Hz, 1H), 6.96 (d, J = 2.1 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 3.85 (s, 3H), 3.61 (s, 6H), 2.69 (t, J = 7.2 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H), 1.94 (quin, 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.6, 168.8, 157.0, 141.3, 133.6, 131.7, 130.9, 130.4, 128.9, 127.4, 127.1, 109.6, 55.3, 52.4, 33.4, 29.5, 24.8. IR (KBr) ν_{max}: 3224, 2947, 1733, 1708, 1286, 1244 cm^{-1}.



12

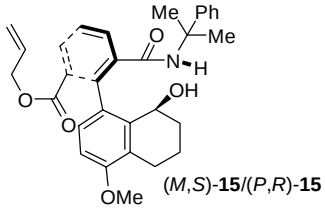
2-(4-Methoxy-8-oxo-5,6,7,8-tetrahydro-naphthalen-1-yl)-isophthalic acid dimethyl ester (12). Biaryl acid **11** (870 mg, 2.25 mmol) was dissolved in 20 mL of anhydrous CH_2Cl_2 in an oven dried flask. The solution was then purged under a N_2 stream for 30 minutes and placed in an ice bath. Oxalyl chloride (300 µL, 3.38 mmol) and 1 drop of anhydrous DMF were added and the flask was stirred while warming to rt for 1.5 hr. The solvent and excess oxalyl chloride were then evaporated under reduce pressure to afford a yellow oil. The crude acid chloride was dissolved in 20 mL of anhydrous CH_2Cl_2 and $AlCl_3$ (300 mg, 2.25 mmol) was added at rt and the solution was stirred for 4 hrs under a N_2 atmosphere. 20 mL of 5% HCl was added dropwise to the reaction mixture and the layers were separated. The aqueous layer was extracted with 3 × 25 mL of Et_2O and the organics were dried with

$MgSO_4$, filtered, and the solvents evaporated under reduced pressure to yield a reddish-brown oil. Purification by column chromatography (1:2 EtOAc:hexane) yielded a 373 mg (45%) of a white solid. R_f (1:1 hexane:EtOAc) = 0.58. mp = 121-124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 3.88 (s, 3H), 3.58 (s, 6H), 2.98 (t, *J* = 6.0 Hz, 2H), 2.54 (t, *J* = 6.0 Hz, 2H), 2.11 (quin, *J* = 6.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.9, 167.4, 156.1, 133.4, 133.2, 132.7, 130.9, 127.3, 126.3, 112.7, 55.6, 52.1, 39.6, 23.6, 22.6. IR (KBr) ν_{max}: 2951, 1740, 1682, 1281, 1245 cm^{-1}.



1

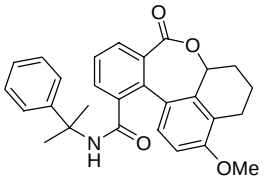
3-Methoxy-8-oxo-4,5,6,6a-tetrahydro-8H-7-oxa-benzo[4,5]cyclohepta[1,2,3-de]naphthalene-12-carboxylic acid ((*S*)-1/(*R*)-1). Biaryl tetralone **12** (420 mg, 1.14 mmol) was added to a 20 mL mixture of 3:1 MeOH:H_2O. LiOH (817 mg, 34 mmol) was added and the reaction was stirred for 8 hrs at rt. 5% HCl was then added until the pH = 4 and the aqueous was extracted with 3 × 25 mL of EtOAc. The combined organics were washed with 25 mL sat. $NaHCO_3$, dried over $MgSO_4$, filtered and the solvents evaporated under reduced pressure. The crude product was obtained as a white powder and carried on directly to the next step with no further purification. ^{1}H NMR (300 MHz, d^6-acetone): 8.04 (d, *J* = 7.8 Hz, 2H), 7.53 (t, *J* = 8.1 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), (d, *J* = 8.4 Hz, 1H), 3.96 (s, 3H), 2.92 (t, *J* = 6.0 Hz, 2H), 2.45 (t, *J* = 7.2 Hz, 2H), 2.06 (m, 2H). The crude product was dissolved in 20 mL of MeOH and cooled in an ice bath. $NaBH_4$ (433 mg, 11.4 mmol) was added in small portions, as gas evolution permitted. The reaction was stirred for 4 hrs and 5% HCl was carefully added until the pH = 4. The reaction was then extracted with 3 × 25 mL of EtOAc. The combined organics were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to yield a white solid. This crude material was then dissolved in 10 mL of TFA and the resulting purple solution was stirred for 1 hr. The reaction was diluted with 30 mL toluene and the solvents were removed under reduced pressure. The crude off-white solid was then purified using column chromatography (1% AcOH in 1:1 EtOAc:hexane → 1% AcOH in EtOAc) to yield 273 mg (74% for three steps) of white solid. mp = 251-254 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 8.01 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.18 (d, *J* = 8.7 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 1H), 5.25 (s, 1H), 3.86 (s, 3H), 3.06 (d, *J* = 12.9 Hz, 1H), 2.45-2.36 (m, 2H), 2.05-1.93 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 157.8, 139.5, 137.9, 134.5, 134.0, 133.3, 131.3, 129.2, 128.4, 127.6, 126.2, 110.1, 72.3, 55.7, 28.1, 22.6, 17.2. IR (KBr) ν_{max}: 3308, 2953, 1711, 1677, 1247 cm^{-1}. APCI-MS *m / z* (relative intensity, ion): 325.1 (100%, M + H$^+$). X-ray crystal structure was determined.[1]



(*M*,*S*)-**15**/(*P*,*R*)-**15**

Allyl-2-(8-hydroxy-4-methoxy-5,6,7,8-tetrahydronaphthalen-1-yl)-3-((2-phenylpropan-2-yl)carbamoyl)benzoate ((*M*,*S*)-15/(*P*,*R*)-15). Cumylamine (223 µL, 1.55 mmol) was dissolved in 10 mL anhydrous CH_2Cl_2 in an oven dried flask. The solution was purged with an N_2 stream for 15 minutes. A 2.0 M solution of trimethylaluminum in toluene (775 µL, 1.55 mmol) was then added via syringe and the resulting solution was stirred for 20 min. Racemic lactone **(*S*)-1/(*R*)-1** (100 mg, 0.31 mmol) was then added and the reaction flask was equipped with a N_2 flushed reflux condenser. The

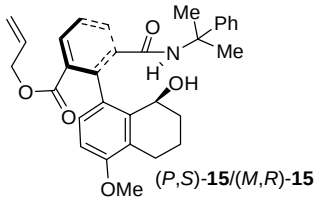
reaction was refluxed under a N_2 atmosphere for 16 hours. The reaction was cooled to rt and 10 mL of 1M HCl was carefully added dropwise, as gas evolution allowed, to the reaction mixture. The layers were separated and the aqueous was extracted with 3 × 15 mL of Et_2O. The combined organics were dried with Na_2SO_4, filtered and the solvents removed under reduced pressure to yield a white-yellow crude solid (155 mg) containing **(*M*,*S*)-13/(*P*,*R*)-13** which was carried on directly to the next step. ^{1}H NMR (300 MHz, d^6-acetone): δ 8.44 (s, 1H), 7.93 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.66 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.22-7.09 (m, 5H), 6.91 (d, *J* = 8.7 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 4.78 (s, 1H), 3.91 (s, 3H), 2.92 (d, *J* = 18.0 Hz, 1H), 2.48-2.33 (m, 1H), 2.02-1.86 (m, 2H), 1.74-1.46 (m, 2H), 1.34 (s, 6H). ^{13}C NMR (125 MHz, d^6-acetone): δ 169.2, 168.9, 158.2, 148.8, 142.4,139.4, 138.1, 133.3, 132.9, 132.1, 131.1, 129.0, 128.4, 127.0, 126.9, 126.1, 109.3, 65.0, 56.7, 56.2, 32.1, 29.2, 24.5, 17.2. APCI-MS *m / z* (relative intensity, ion): 460.2 (17%, M + H$^+$), 442.2 (100%, M – OH$^-$). The crude solid was dissolved in 4 mL of DMF. K_2CO_3 (64 mg, 0.46 mmol) and allyl bromide (31 µL, 0.37 mmol) were added and the solution was stirred for 1 hr. The reaction mixture was diluted with 40 mL of EtOAc and washed with 2 × 10 mL of H_2O and 2 × 10 mL of brine. The organics were dried with Na_2SO_4, filtered and the solvents removed under reduced pressure to yield a yellow oil. Purification with preparative thin layer chromatography (3:1 hexanes:EtOAc) yielded 111 mg of a white solid (72% yield for two steps). mp = 128-131 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.76 (dd, *J* = 6.0 Hz, 1.5 Hz, 1H) 7.49 (s, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.25-7.14 (m, 3H), 7.10-7.07 (m, 2H), 6.95 (d, *J* = 8.1 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 5.66-5.56 (m, 1H), 5.54-5.12 (m, 2H), 4.71 (d, *J* = 3.3 Hz, 1H), 4.48 (dd, *J* = 6.0 Hz, 1.8 Hz, 2H), 3.89 (s, 3H), 2.94 (d, *J* = 17.1 Hz, 1H), 2.51-2.45 (m, 1H), 2.16 (d, *J* = 3.6 Hz, 1H), 1.83-1.68 (m, 3H), 1.42 (s, 3H), 1.36 (s, 3H). ^{1}H NOESY-1D (500 MHz, $CDCl_3$): δ 4.71 (BnH) [nOe: 7.48 (weak, NH), 2.16 (strong, OH), 1.80-1.70 (strong, CH)], 7.48 (NH) [nOe: 7.94 (strong, ArH), 7.08 (weak, ArH), 2.16 (medium, OH), 1.42 (medium, CH_3), 1.36 (medium, CH_3)]. ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.1, 167.1, 157.1, 146.9, 140.4, 138.4, 135.8, 132.0, 131.8, 131.6, 131.2, 130.7, 128.2, 127.6, 127.3, 126.5, 118.6, 108.6, 65.8, 64.9, 55.9, 55.6, 31.4, 29.2, 28.0, 23.4, 16.2. IR (KBr) ν_{max}: 3320, 3227, 3057, 2936, 1739, 1705, 1646, 1560, 1249 cm^{-1}. APCI-MS *m / z* (relative intensity, ion): 482.2 (100%, M – OH$^-$).



(*S*)-**14**/(*R*)-**14**

3-Methoxy-8-oxo-4,5,6,6a-tetrahydro-8H-7-oxa-benzo[4,5]cyclohepta[1,2,3-de]naphthalene-12-carboxylic acid (1-methyl-1-phenyl-ethyl)-amide ((*S*)-14/(*R*)-14). Cumylamine (223 µL, 1.55 mmol) was dissolved in 10 mL anhydrous CH_2Cl_2 in an oven dried flask. The solution was purged over a N_2 stream for 15 minutes. A 2.0 M solution of trimethylaluminum in toluene (775 µL, 1.55 mmol) was then added via syringe and the resulting solution was stirred for 20 min. Racemic lactone **1** (100 mg, 0.31 mmol) was then added and the reaction flask was equipped with a N_2 flushed reflux condenser. The reaction was refluxed under a N_2 atmosphere for 16 hours. The reaction was cooled to rt and 10 mL of 1M HCl was carefully added dropwise, as gas evolution allowed, to the reaction mixture. The layers were separated and the aqueous was extracted with 3 × 15 mL of Et_2O. The combined organics were dried with Na_2SO_4, filtered and the solvents removed under reduced pressure to yield a white-yellow crude solid (155 mg) containing **(*M*,*S*)-13/(*P*,*R*)-13** which was carried on directly to the next step. ^{1}H NMR (300 MHz, d^6-acetone): δ 8.44 (s, 1H), 7.93 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.66 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.22-7.09 (m, 5H), 6.91 (d, *J* = 8.7 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 4.78 (s, 2H), 3.91 (s, 3H), 2.92 (d, *J* = 18.0 Hz, 1H), 2.48-2.33 (m, 1H), 2.02-1.86 (m, 2H), 1.74-1.46 (m, 2H), 1.34 (s, 6H). ^{13}C NMR (125 MHz, d^6-acetone): δ 169.2, 168.9, 158.2, 148.8, 142.4, 139.4,

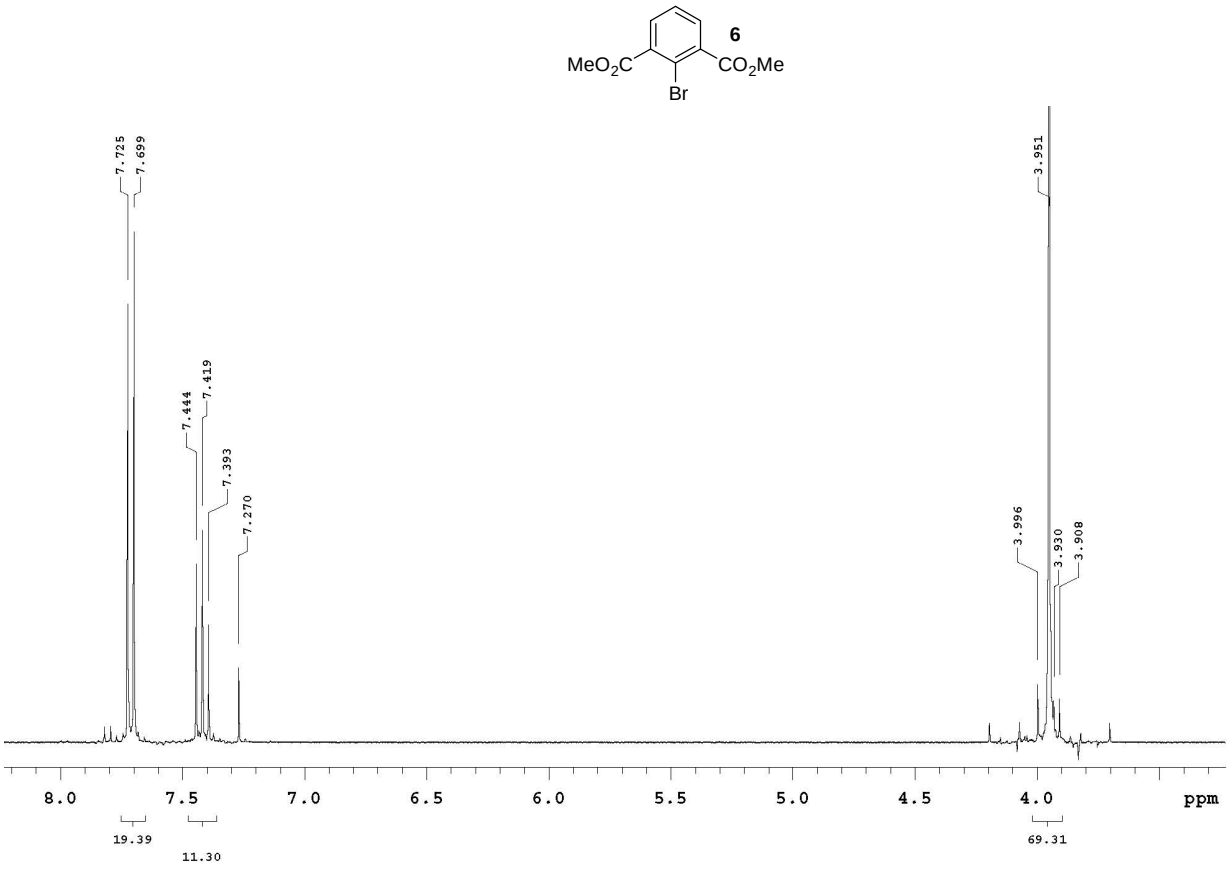
138.1, 133.3, 132.9, 132.1, 131.1, 129.0, 128.4, 127.0, 126.9, 126.1, 109.3, 65.0, 56.7, 56.2, 32.1, 29.2, 24.5, 17.2. APCI-MS *m / z* (relative intensity, ion): 460.2 (17%, M + H^+), 442.2 (100%, M – OH^-). 1,3-Dicyclohexylcarbodiimide (128 mg, 0.310 mmol), *N*,*N*-dimethylaminopyridine (114 mg, 0.930 mmol), and *N*,*N*-dimethylaminopyridine hydrochloride (98 mg, 0.620 mmol) were dissolved in an oven dried and N_2 flushed flask and dissolved in 25 mL anhydrous chloroform. The crude product was dissolved 8 mL of anhydrous THF and added to the reaction flask. The mixture was stirred at reflux for 2 hrs under an N_2 atmosphere. The reaction was cooled to rt, diluted with 2 mL MeOH and 2 mL AcOH, and stirred for 15 minutes. The solvent volume was reduced to approximately 5 mL under a reduced pressure, crude mixture was taken up in 20 mL Et_2O, and filtered through a pad of celite. The celite was wash once with 20 mL Et_2O. The organics were combined and the solvent was removed under reduced pressure to yield a white oily solid. The product was purified with preparative thin layer chromatography (1:1 EtOAc:Hexane) to yield 102 mg (75% two steps) of white solid. mp = 98-103 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 7.5 Hz, 1.2 Hz, 1H), 7.76 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.29-7.24 (m, 3H), 7.15 (d, *J* = 7.5 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 1H), 5.91 (s, 1H), 5.16 (s, 1H), 3.88 (s, 3H), 3.09 (d, *J* = 16.5 Hz, 1H), 2.55-2.34 (m ,2H), 2.01 (s, 1H), 1.98-1.81 (m, 3H), 1.79 (s, 3H), 1.65 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 168.3, 157.7, 146.8, 138.0, 135.4, 133.5, 132.6, 132.5, 132.4, 129.4, 128.6, 128.1, 127.7, 127.1, 126.2, 125.0, 110.3, 72.1, 56.8, 55.7, 28.9, 28.3, 27.1, 22.7, 17.3. δ IR (KBr) ν_{max}: 3318, 2934, 2852, 1714, 1647, 1532, 1308, 1262 cm^{-1}. APCI-MS *m / z* (relative intensity, ion): 442.2 (100%, M + H^+).



(*P*,*S*)-**15**/(*M*,*R*)-**15**

Allyl-2-(8-hydroxy-4-methoxy-5,6,7,8-tetrahydronaphthalen-1-yl)-3-((2-phenylpropan-2-yl)carbamoyl)benzoate ((*P*,*S*)-15/(*M*,*R*)-15). Amide **(*S*)-14/(*R*)-14** (100 mg, 0.23 mmol) was suspended in 15 mL MeOH and 5 mL H_2O. LiOH (55 mg, 2.3 mmol) was added and the suspension was stirred for 16 hrs. The solvent was evaporated under reduced pressure and the resulting solid was partitioned between 20 mL EtOAc and 20 mL 5% HCl. The layers were separated and the aqueous was extracted with 2 × 15 mL of EtOAc. The combined organics were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The resulting crude white solid containing **(*P*,*S*)-13/(*M*,*R*)-13** was not purified further and carried through directly to the next step. The crude white solid was dissolved in 5 mL DMF. K_2CO_3 (48 mg, 0.34 mmol) and allyl bromide (23 µL, 0.28 mmol) was added and the solution was stirred for 1 hr. The reaction mixture was diluted with 40 mL of EtOAc and washed with 2 × 10 mL of H_2O and 2 × 10 mL of brine. The organics were dried with Na_2SO_4, filtered and the solvents removed under reduced pressure to yield a yellow oil. Purification with preparative thin layer chromatography (9:1 CH_2Cl_2:EtOAc) yielded 52 mg of a colorless oil (45% two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.90 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H) 7.52 (t, *J* = 7.8 Hz, 1H), 7.26-7.18 (m, 3H), 7.08-7.05 (m, 2H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 5.87-5.78 (m, 1H), 5.53 (s, 1H), 5.33-5.33 (m, 2H), 4.63-4.59 (m, 3H), 3.83 (s, 3H), 3.61 (s, 1H), 3.03 (dd, *J* = 18.3 Hz, 5.4 Hz, 1H), 2.49-2.37 (m, 1H), 2.08-1.97 (m, 2H), 1.79-1.49 (m, 2H), 1.46 (s, 3H), 1.29 (s, 3H). ^{1}H NOESY-1D (500 MHz, $CDCl_3$): δ 4.63 (BnH) [nOe: 5.56 (medium, NH), 3.42 (strong, OH), 2.03 (strong, CH), 1.60-1.49 (strong, CH)], 5.56 (NH) [nOe: 8.02 (weak, ArH), 7.10 (medium, ArH), 6.91 (medium, ArH), 4.63 (medium, BnH), 1.49 (strong, CH_3), 1.33 (strong, CH_3)]. ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.0, 166.1, 157.9, 146.4, 137.9, 132.9, 132.7, 131.5, 131.3, 130.6, 128.4, 128.1, 126.8, 126.4, 124.8, 119.4, 108.9, 66.6, 64.1, 56.1, 55.5, 29.9, 29.0, 28.0, 16.0. APCI-MS *m / z* (relative intensity, ion): 482.2 (100%, M – OH^-).

NMR Spectra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6.5
6.0
5.5
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4.5
4.0
ppm
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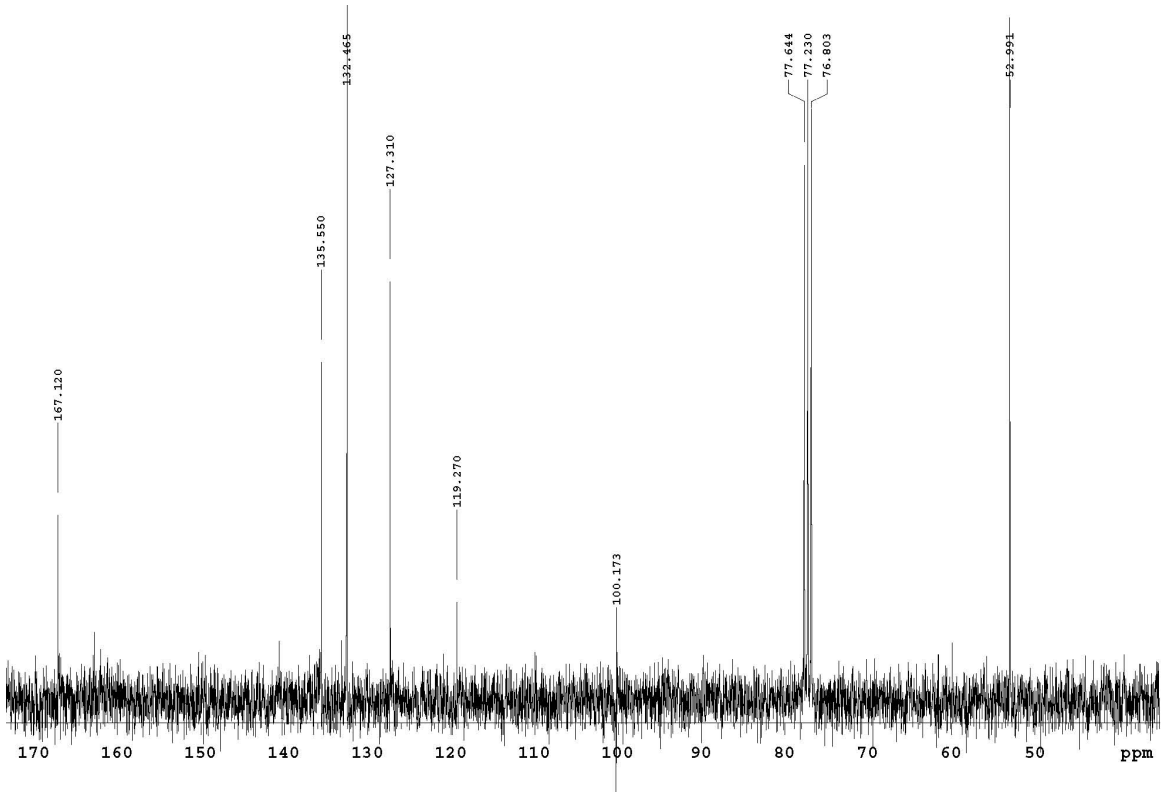
11.30
69.31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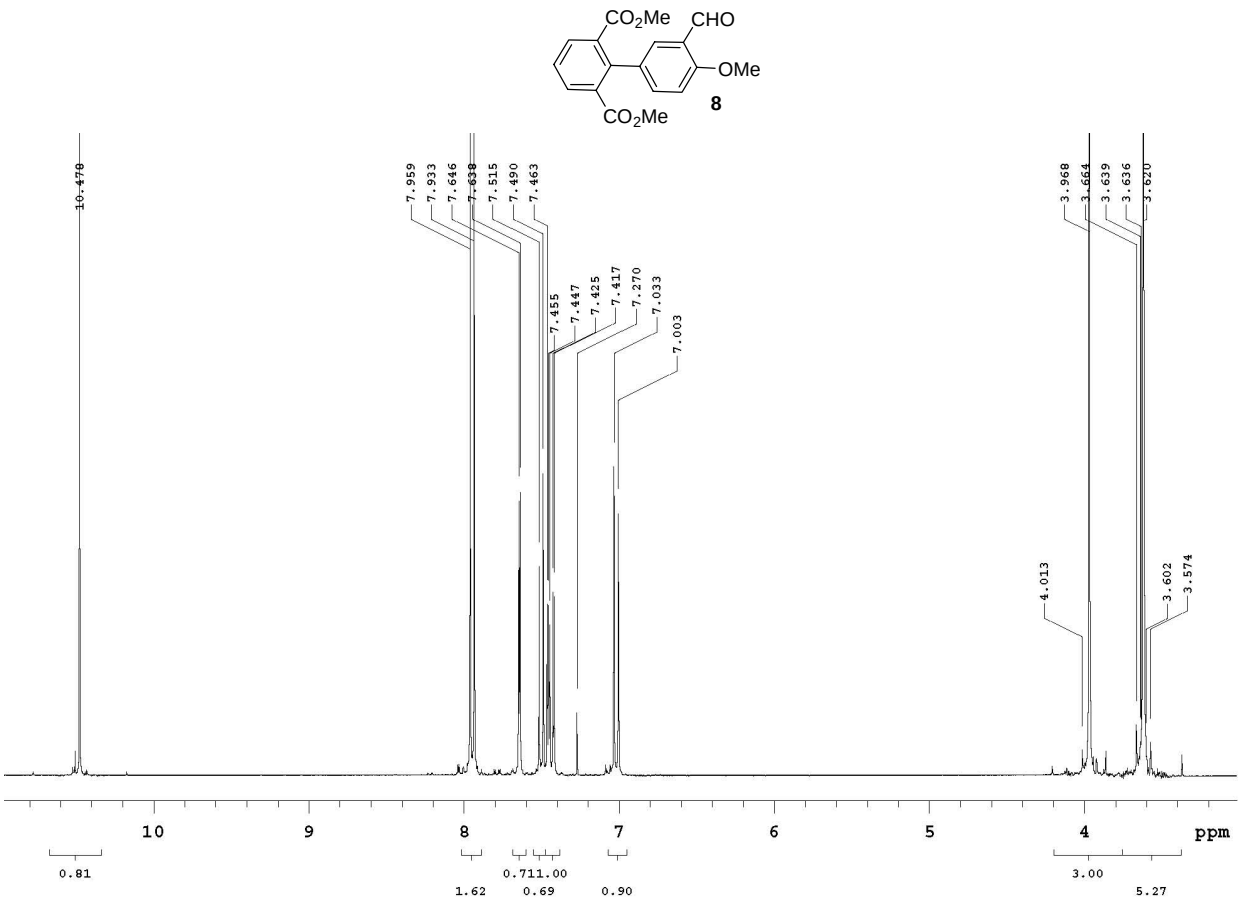
120
110
100
90
80
70
60
50
ppm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OMe
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7.417
7.270
7.033
7.003
4.013
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3.636
3.620
3.602
3.574
10
9
8
7
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5
4
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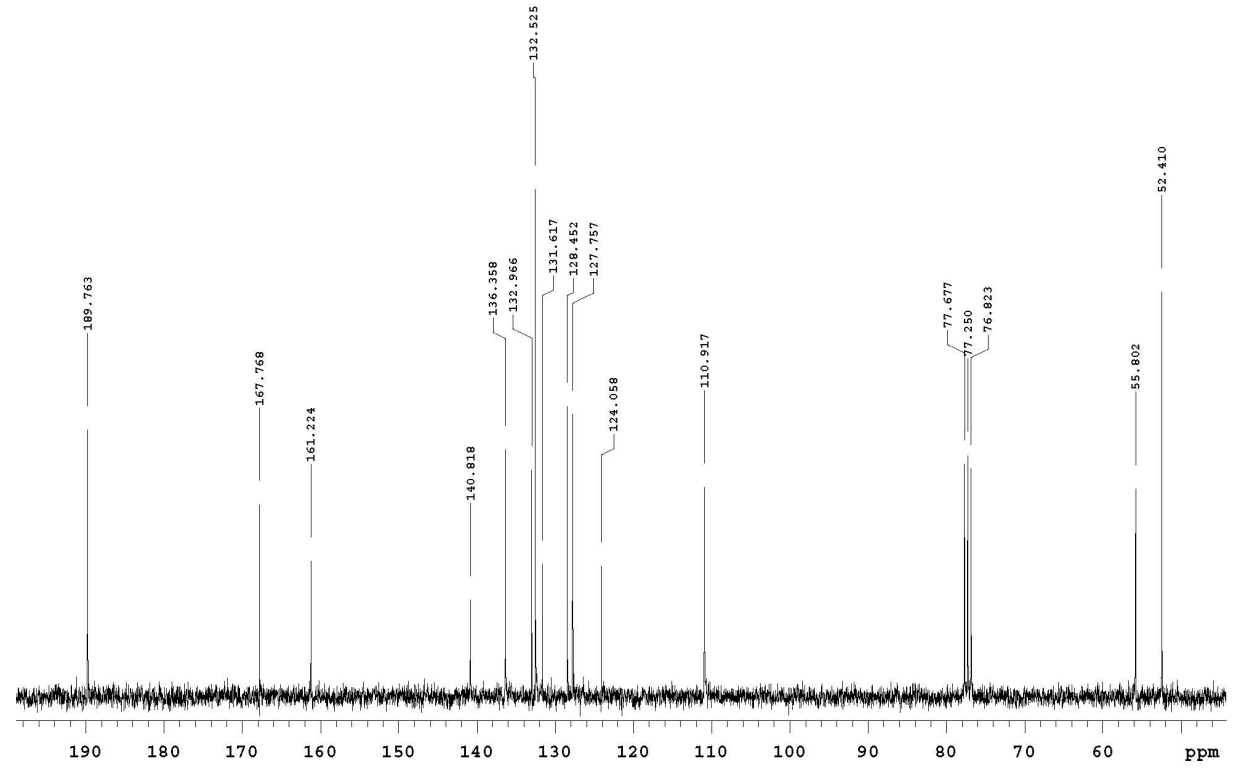
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131.617
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77.250
76.823
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180
170
160
150
140
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120
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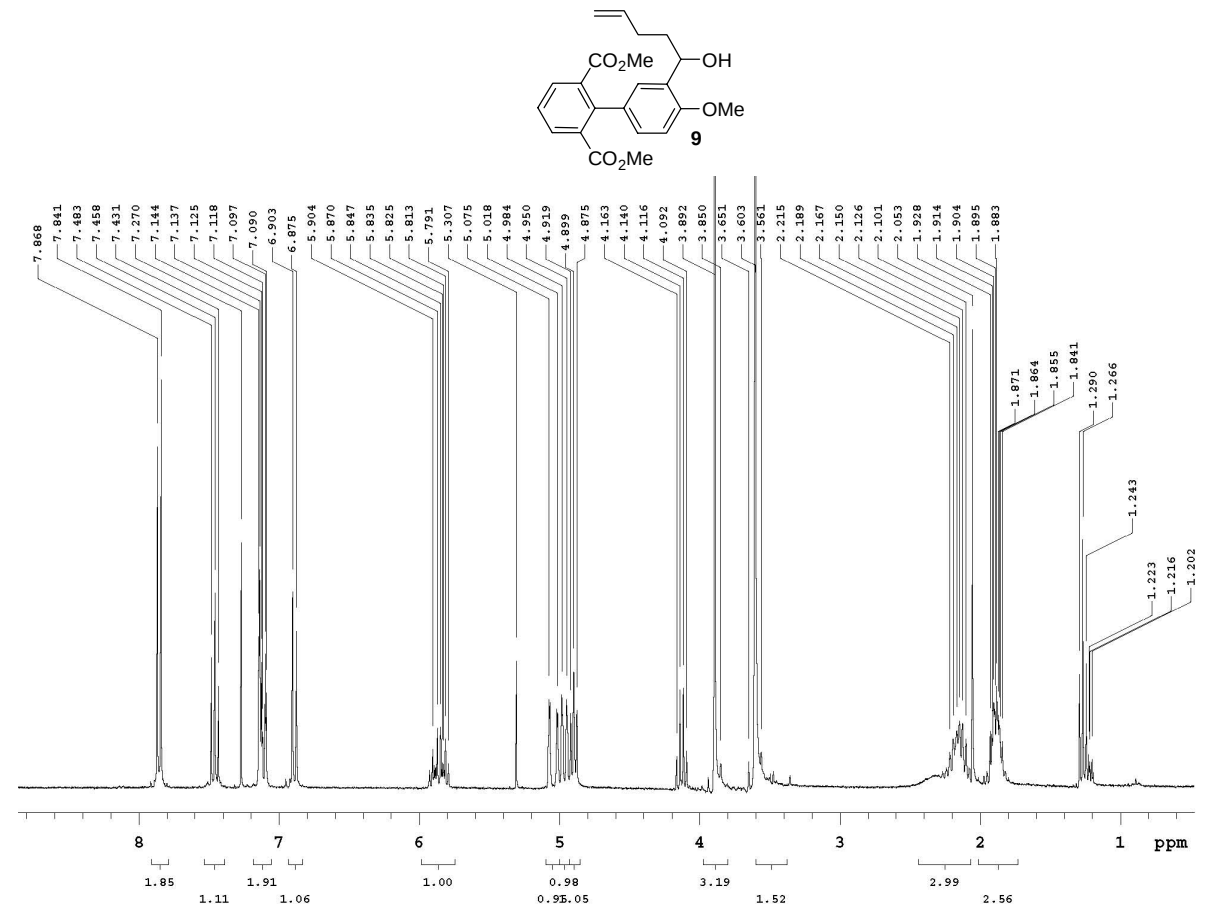
90
80
70
60
ppm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OH
OMe
CO2Me
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7.118
7.097
7.090
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6.875
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3.850
3.651
3.603
3.561
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1.914
1.904
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1.871
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1.855
1.841
1.290
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1.216
1.202
8
7
6
5
4
3
2
1
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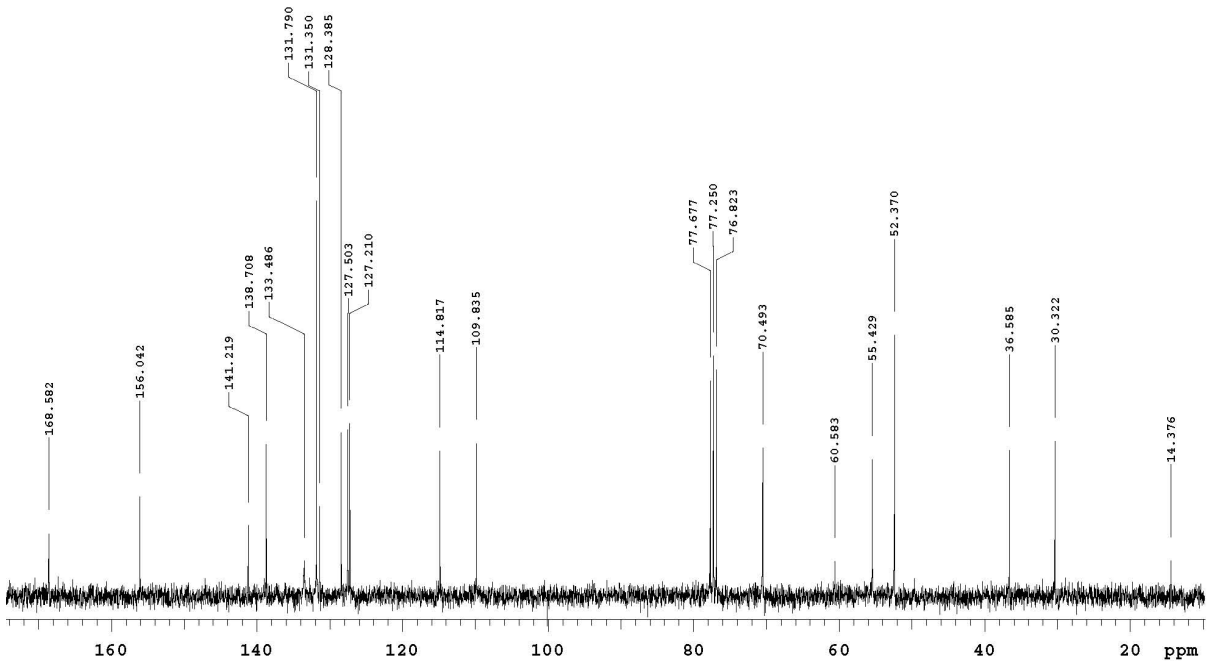
2.99
2.56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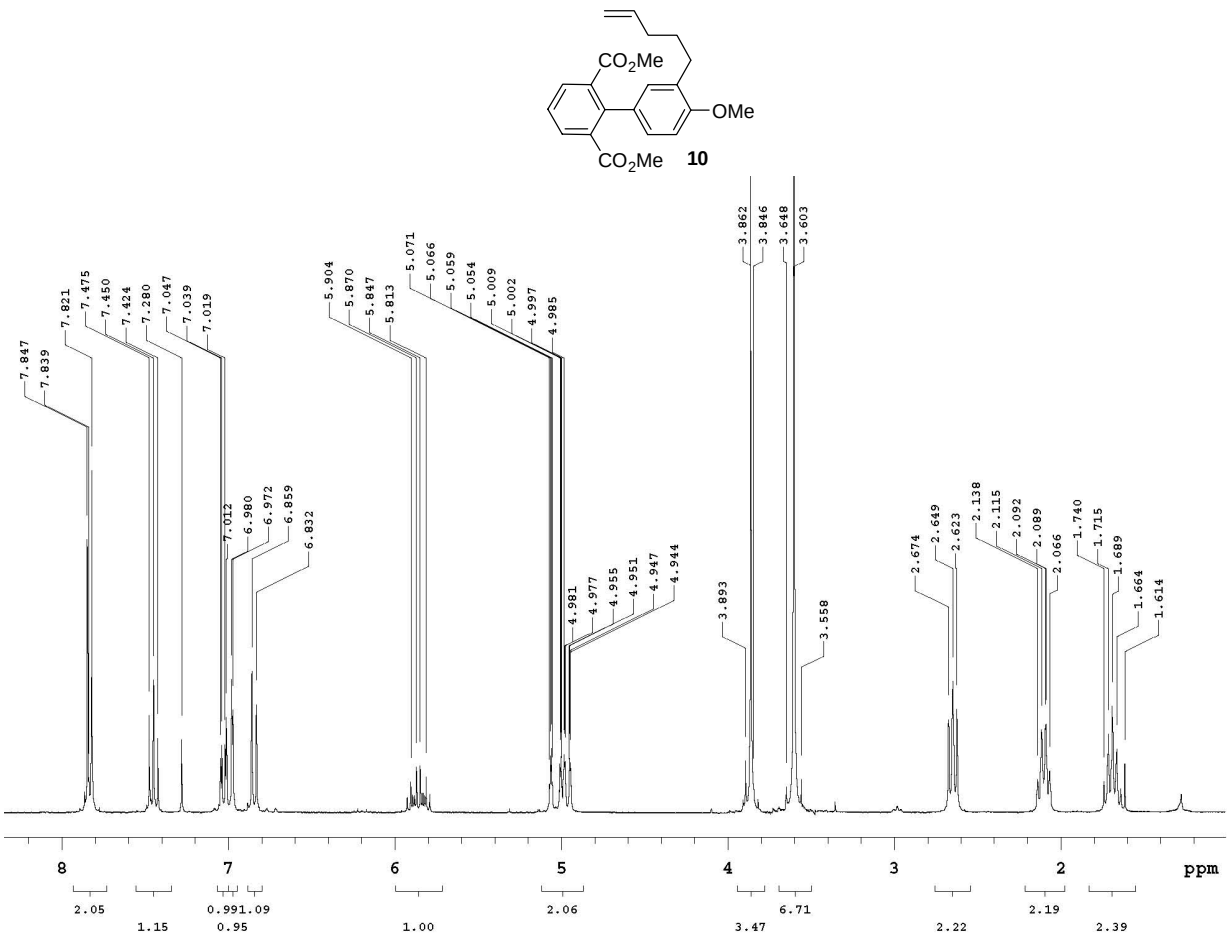
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OMe
CO2Me
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7.424
7.280
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7.039
7.019
5.904
5.870
5.847
5.813
5.071
5.066
5.059
5.054
5.009
5.002
4.997
4.985
3.862
3.846
3.648
3.603
7.012
6.980
6.972
6.859
6.832
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4.977
4.955
4.951
4.947
4.944
3.893
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1.664
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8
7
6
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4
3
2
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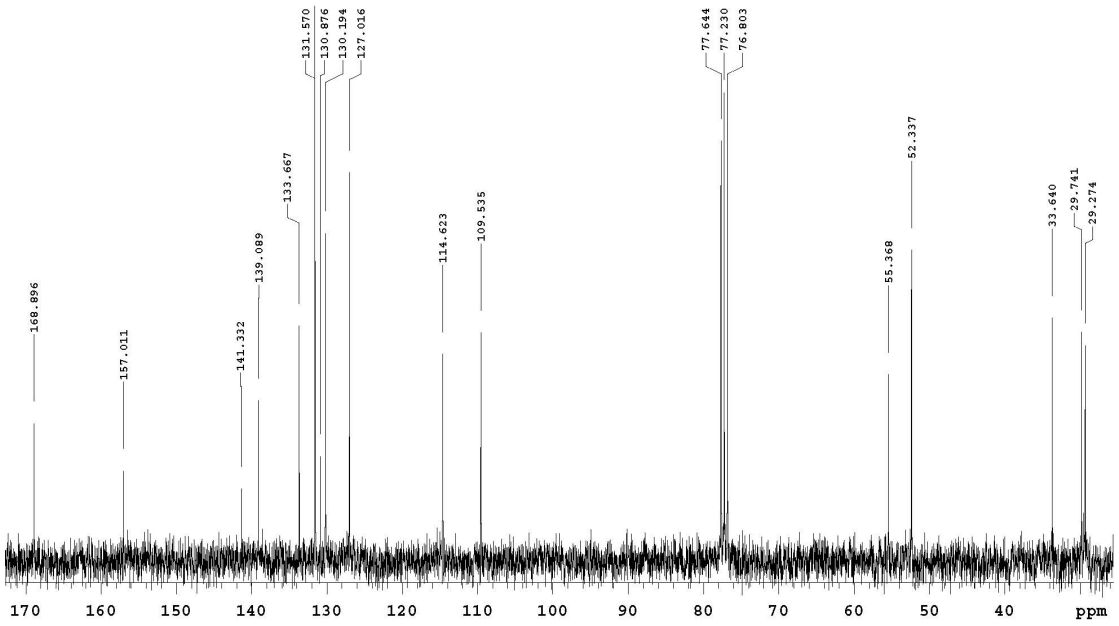
2.39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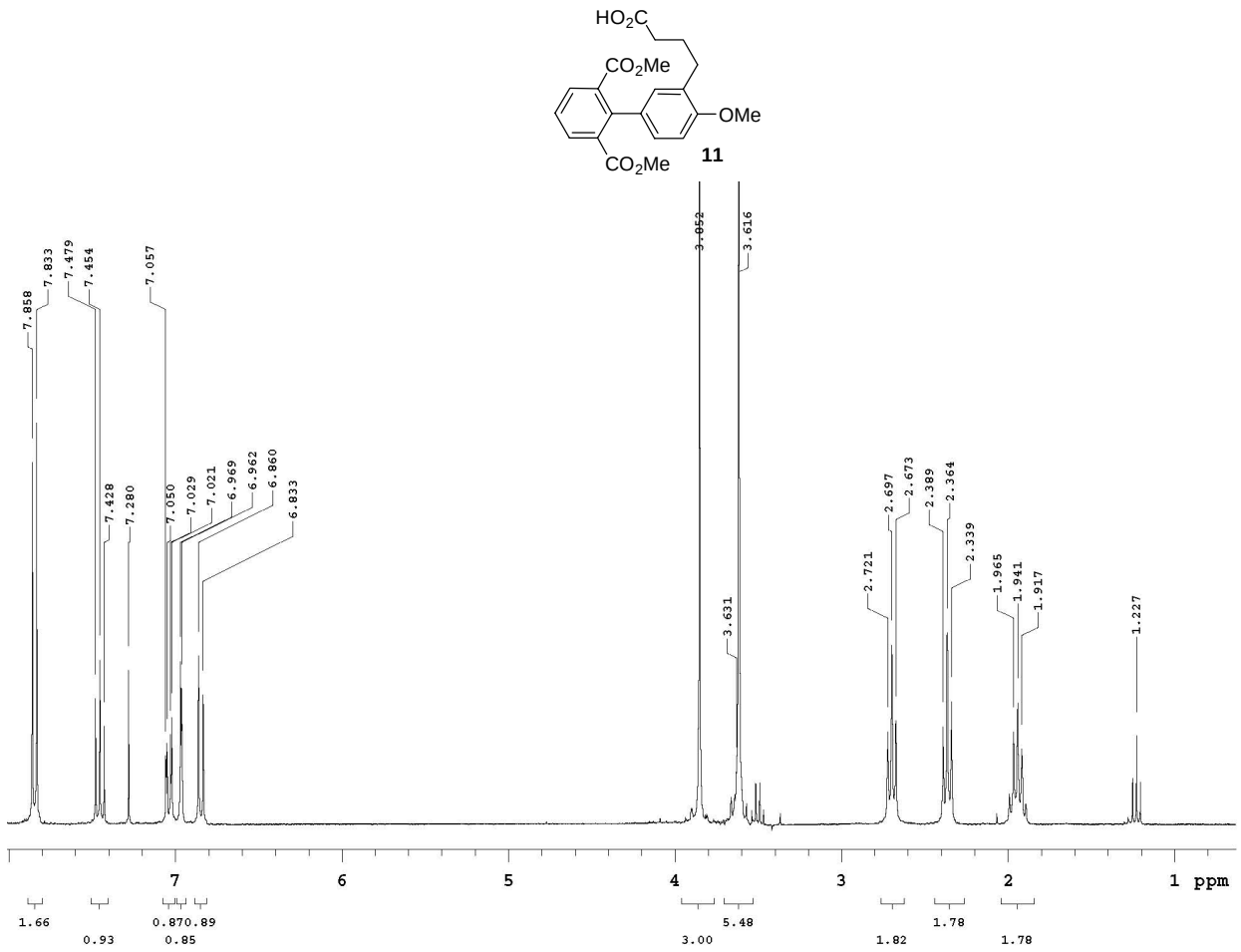
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7.021
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3.616
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5
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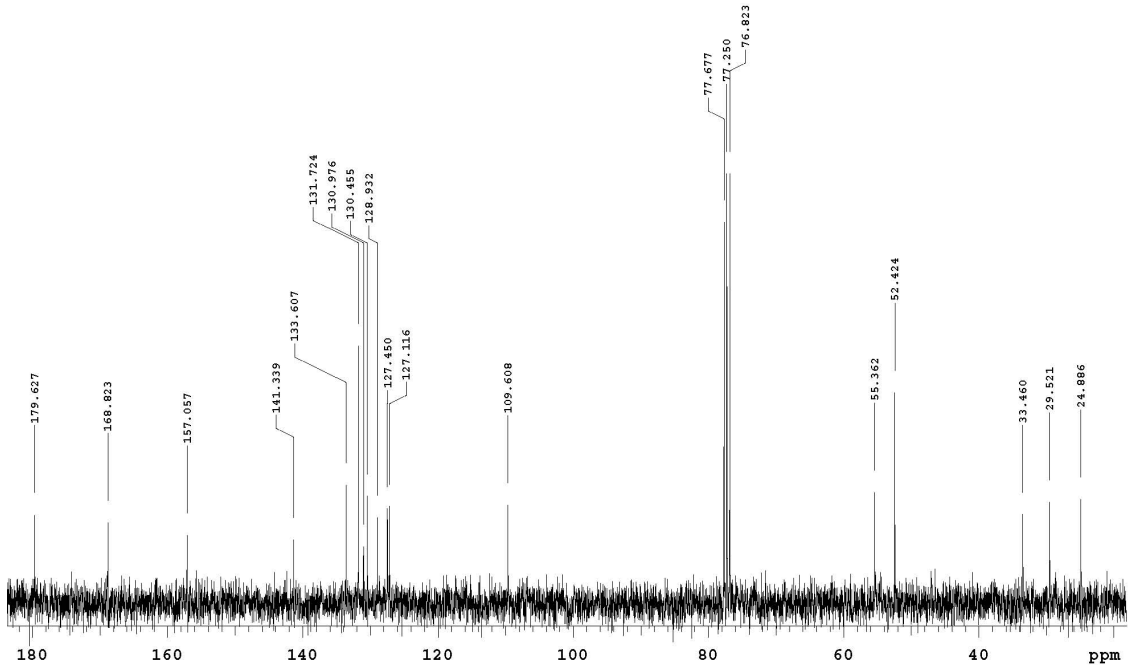
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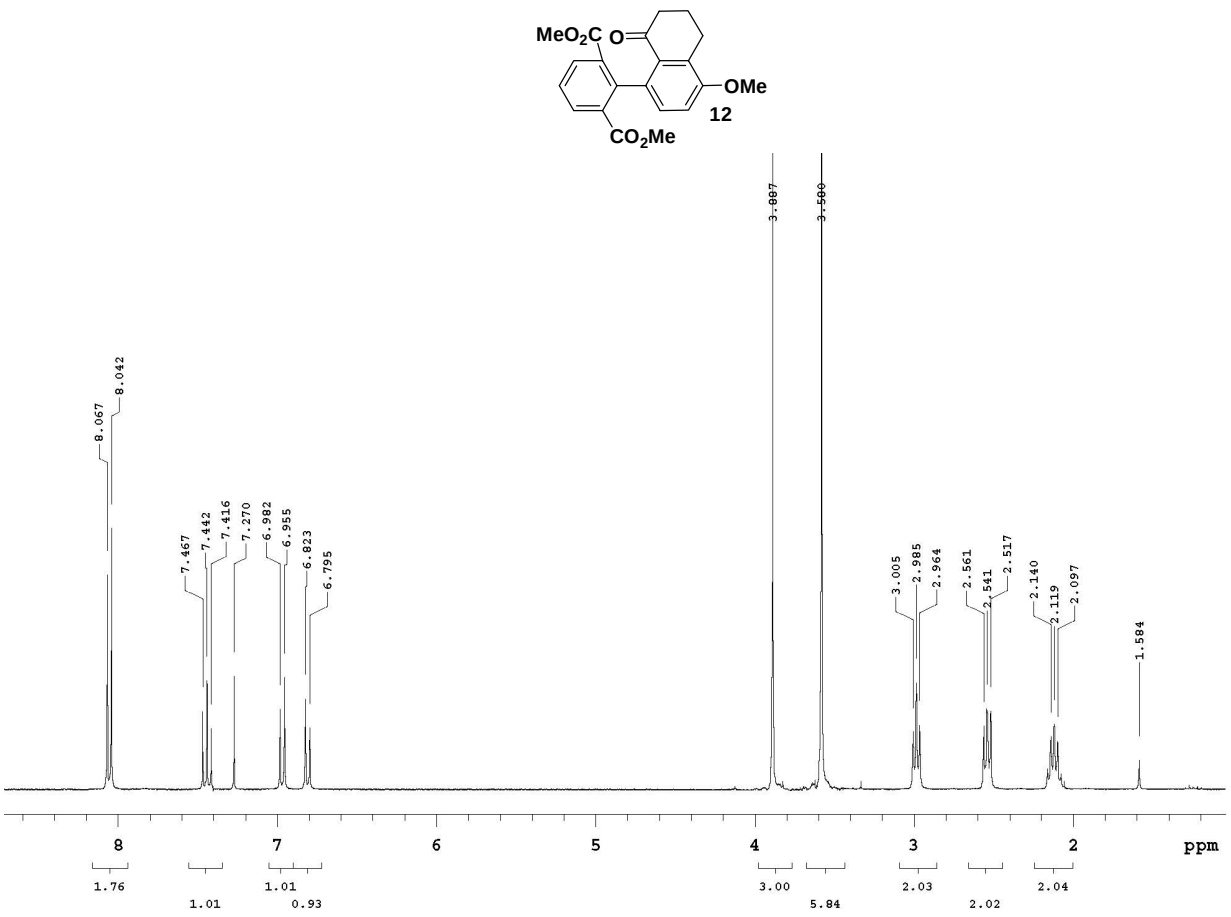
ppm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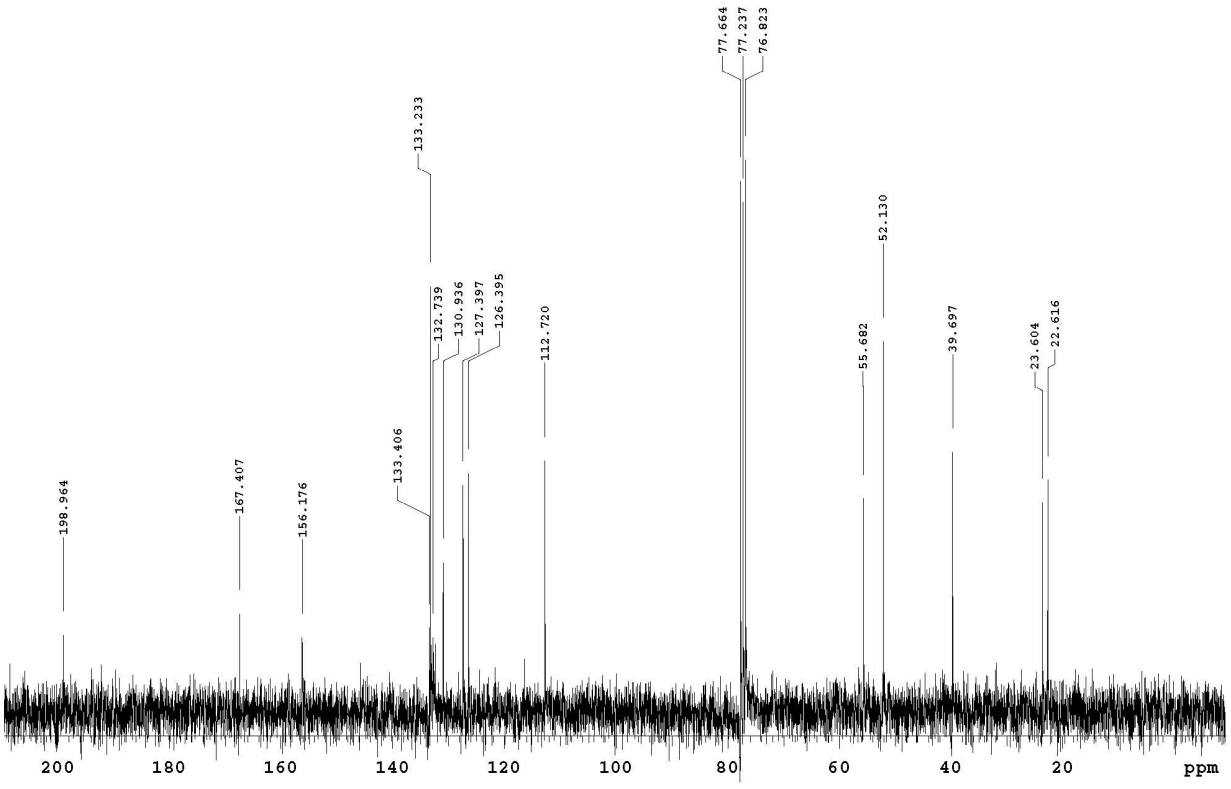
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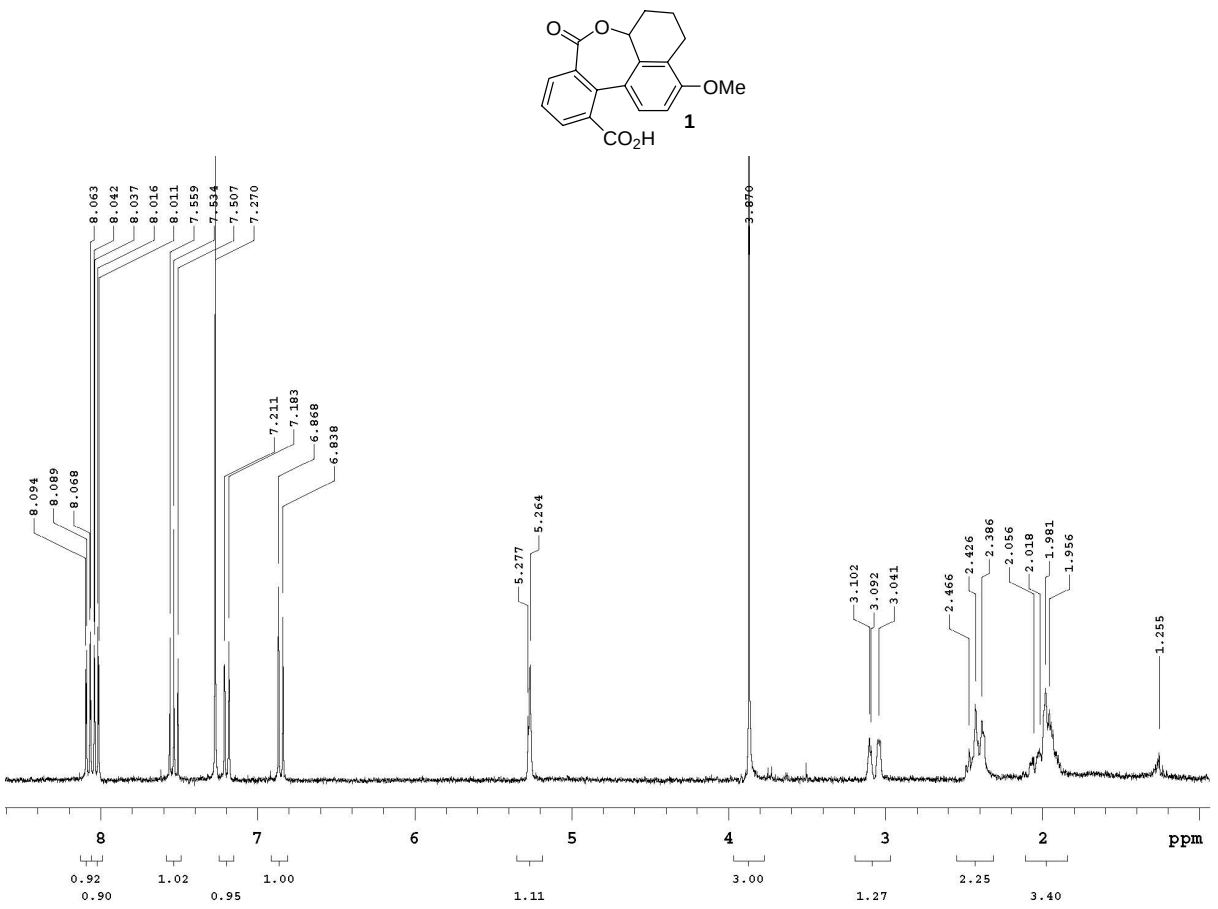
20
ppm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2.018
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7
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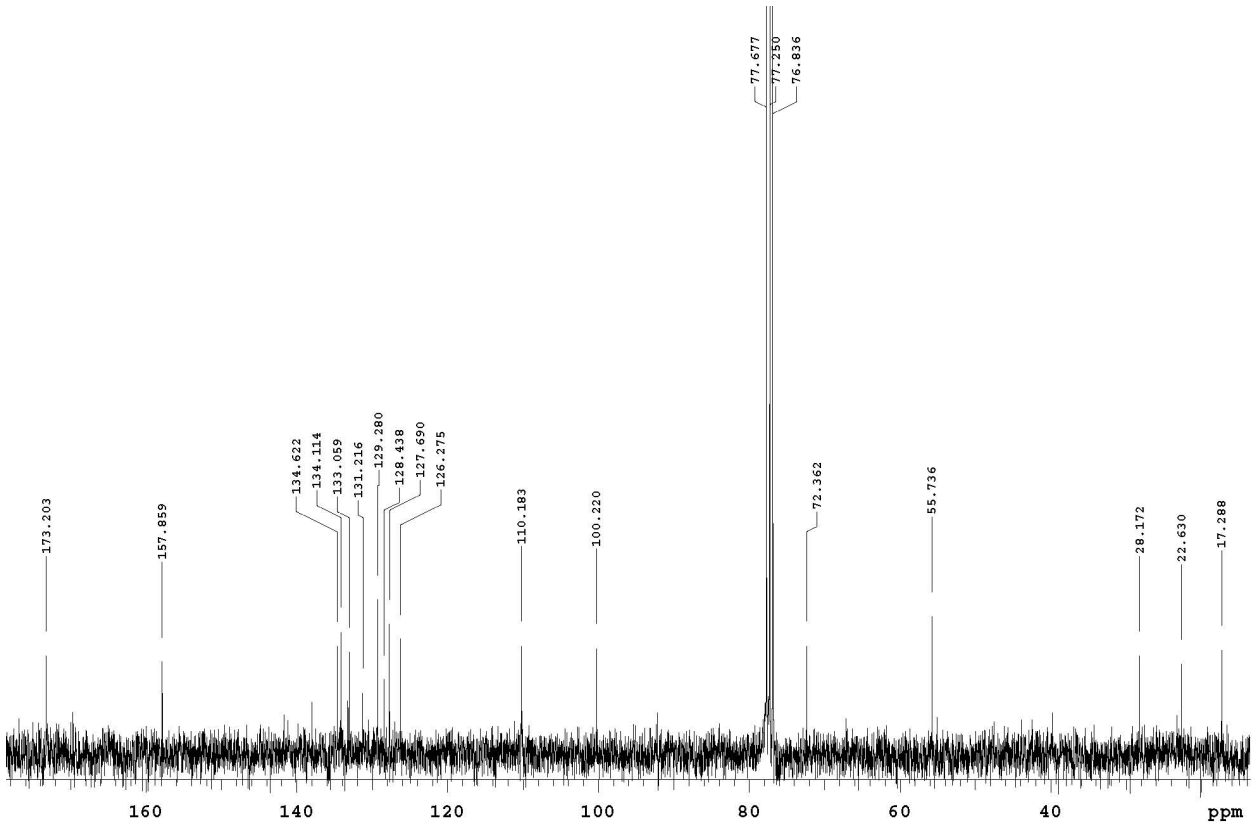
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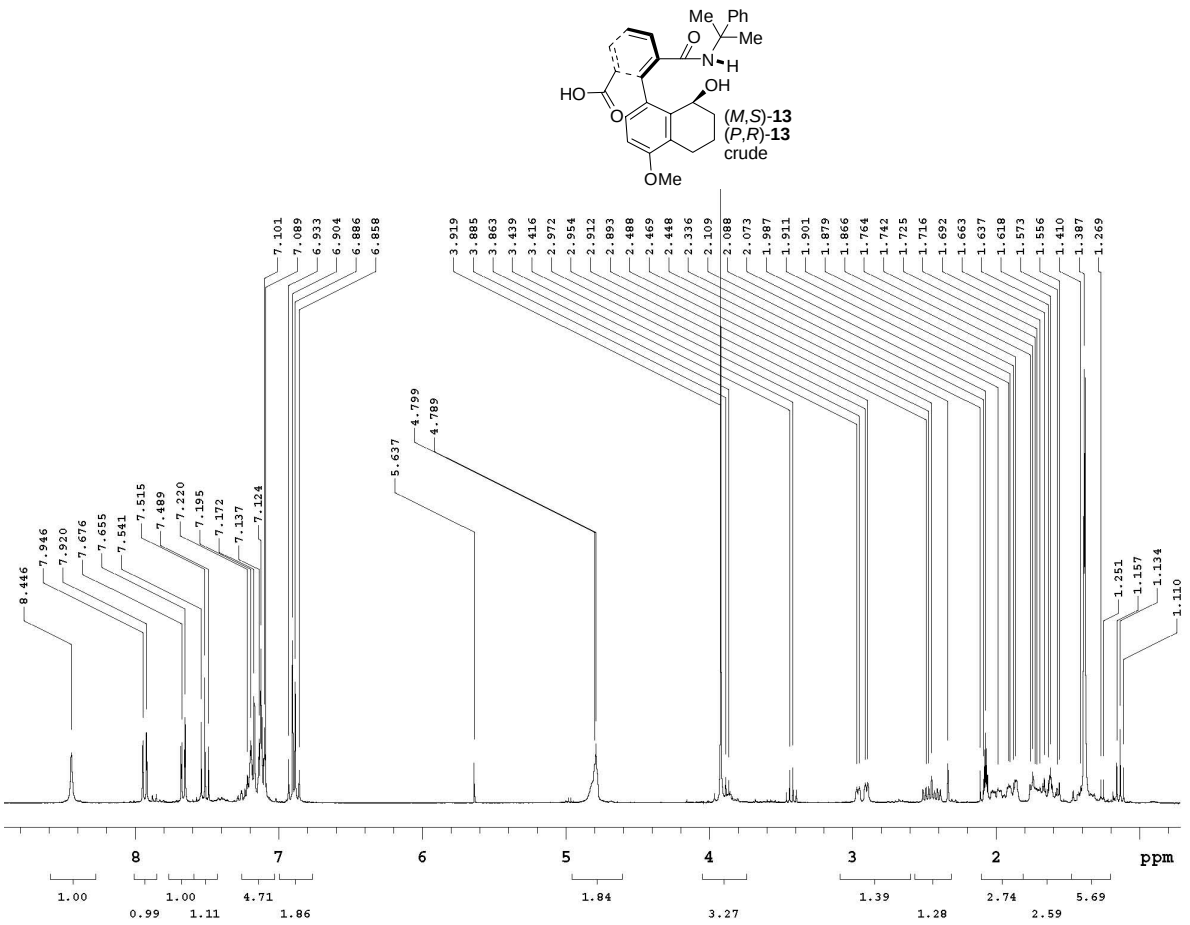
ppm


Me Ph
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O
N
H
HO
OH
O
OMe
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(P,R)-13
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7.920
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7.655
7.541
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7.195
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7.124
7.101
7.089
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6.904
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5.637
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4.789
3.919
3.885
3.863
3.439
3.416
2.972
2.954
2.912
2.893
2.488
2.469
2.448
2.336
2.109
2.088
2.073
1.987
1.911
1.901
1.879
1.866
1.764
1.742
1.725
1.716
1.692
1.663
1.637
1.618
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1.269
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7
6
5
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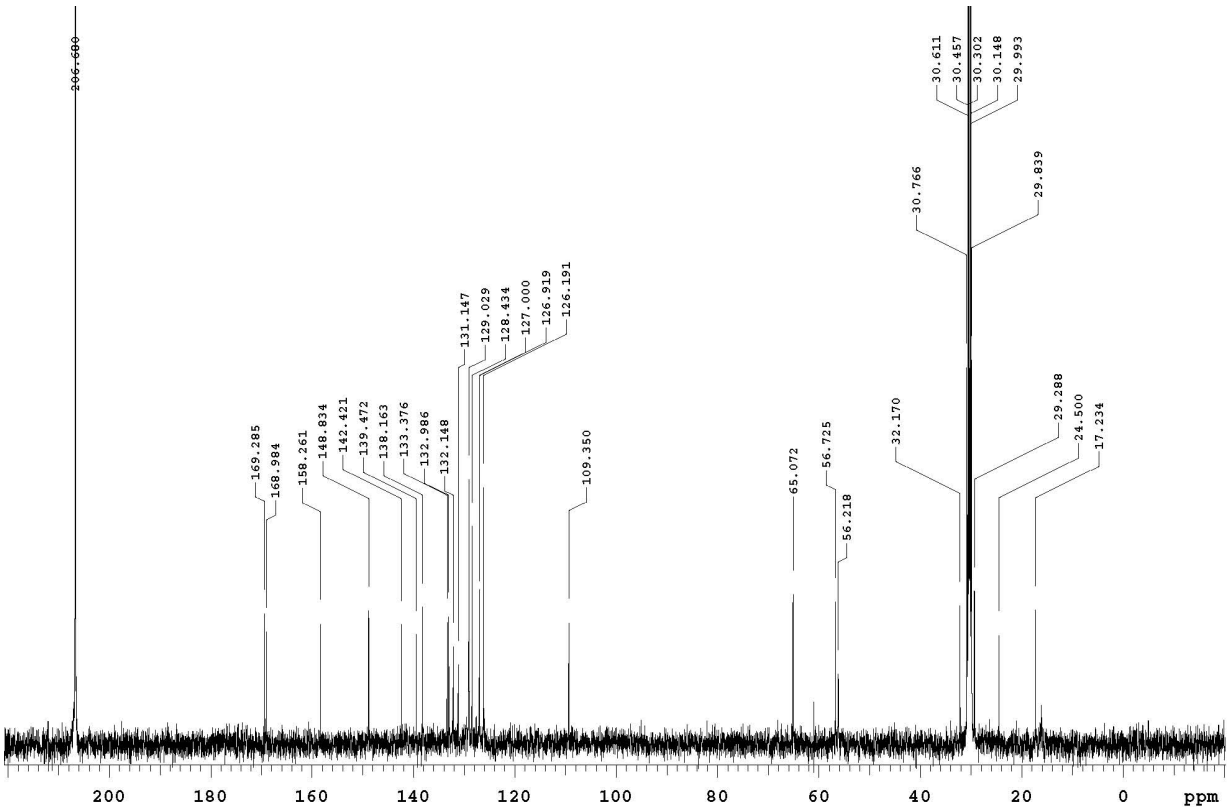
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127.000
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126.191
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56.725
56.218
32.170
30.766
30.611
30.457
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30.148
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120
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60
40
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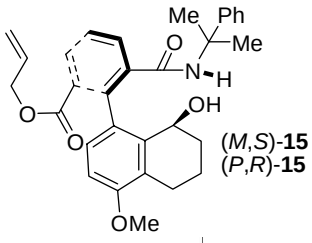
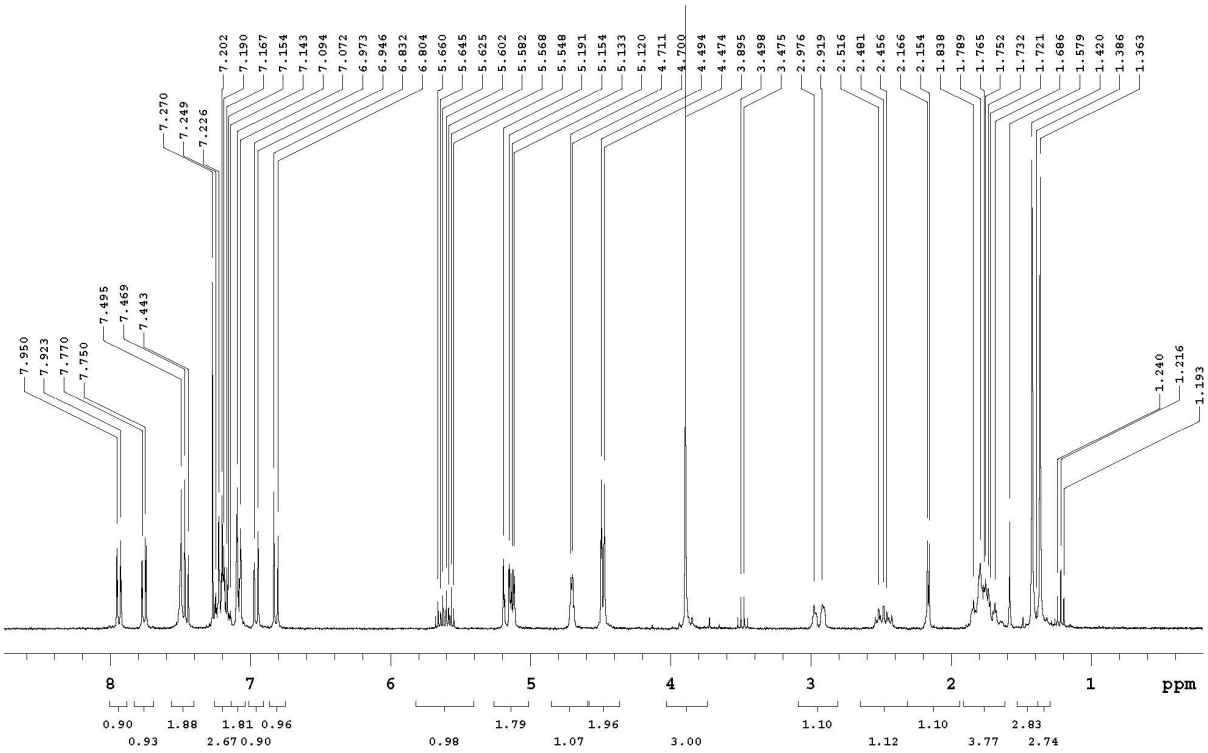
0
ppm


Me
Ph
Me
O
N
H
OH
O
O
OMe

(*M*,*S*)-**15**
(*P*,*R*)-**15**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7.770
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7.469
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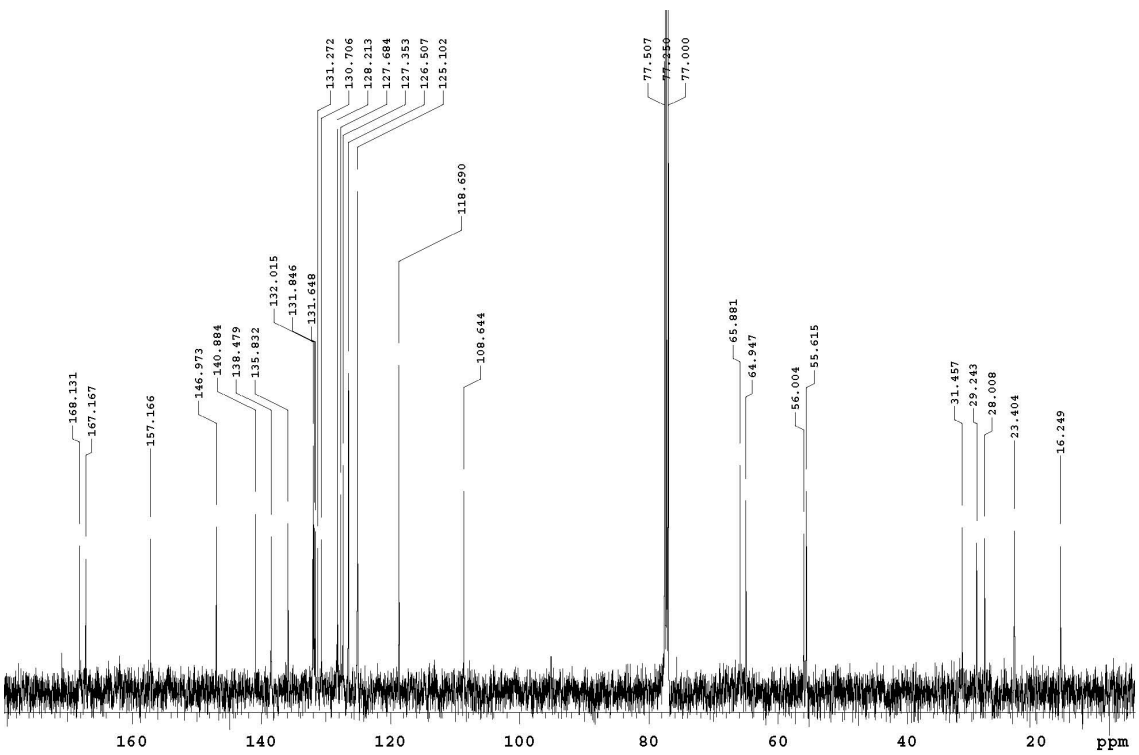
7.167
7.154
7.143
7.094
7.072
6.973
6.946
6.832
6.804
5.660
5.645
5.625
5.602
5.582
5.568
5.548
5.191
5.154
5.133
5.120
4.711
4.700
4.494
4.474
3.895
3.498
3.475
2.976
2.919
2.516
2.481
2.456
2.166
2.154
1.838
1.789
1.765
1.752
1.732
1.721
1.686
1.579
1.420
1.386
1.363
1.240
1.216
1.193
8
7
6
5
4
3
2
1
ppm
0.90
1.88
1.81
0.96
0.93
2.67
0.90
0.98
1.79
1.96
1.07
3.00
1.10
1.10
1.12
3.77
2.83
2.74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167.167
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128.213
127.684
127.353
126.507
125.102
118.690
108.644
77.507
77.250
77.000
65.881
64.947
56.004
55.615
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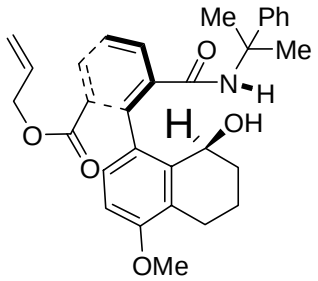
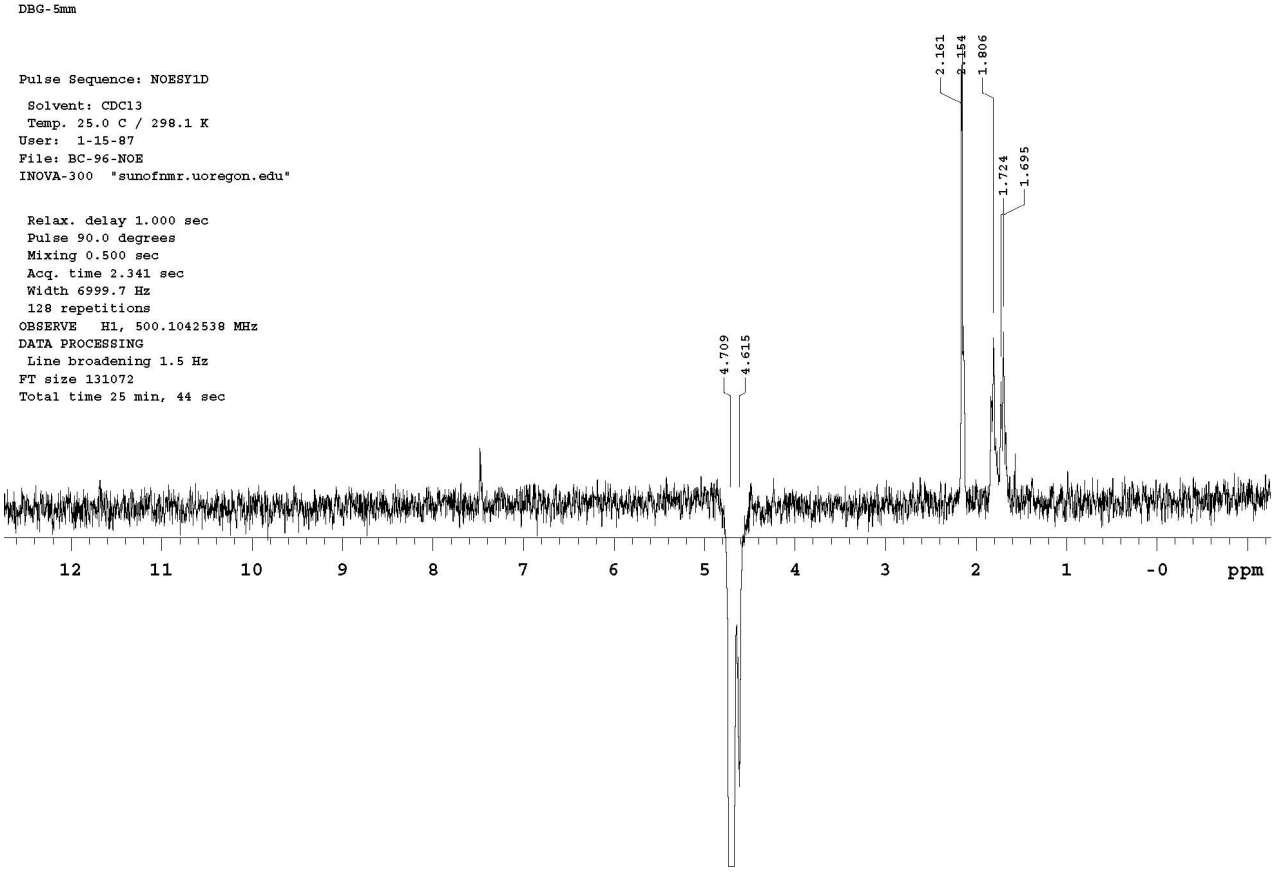
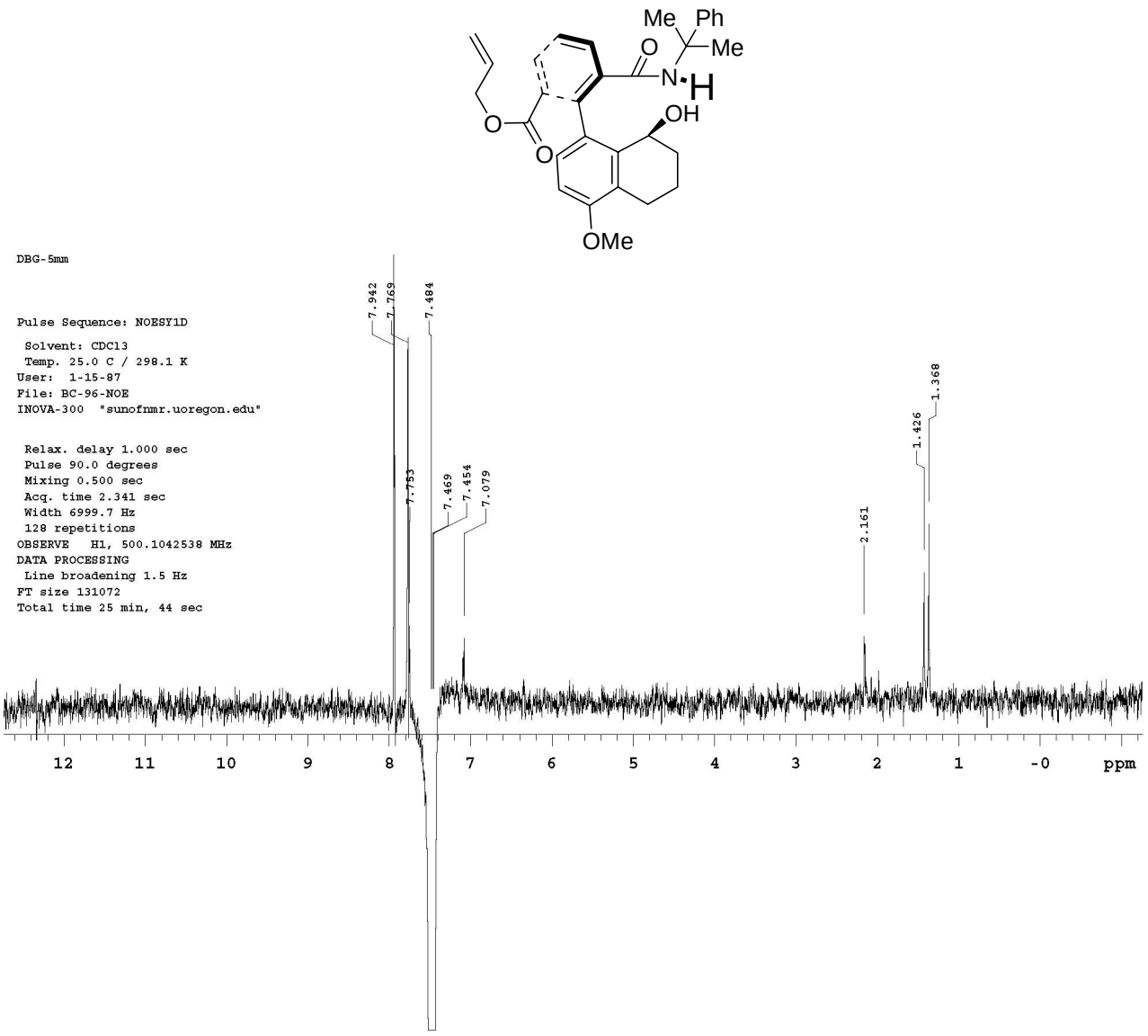
29.243
28.008
23.404
16.249
160
140
120
100
80
60
40
20
ppm

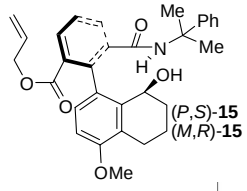




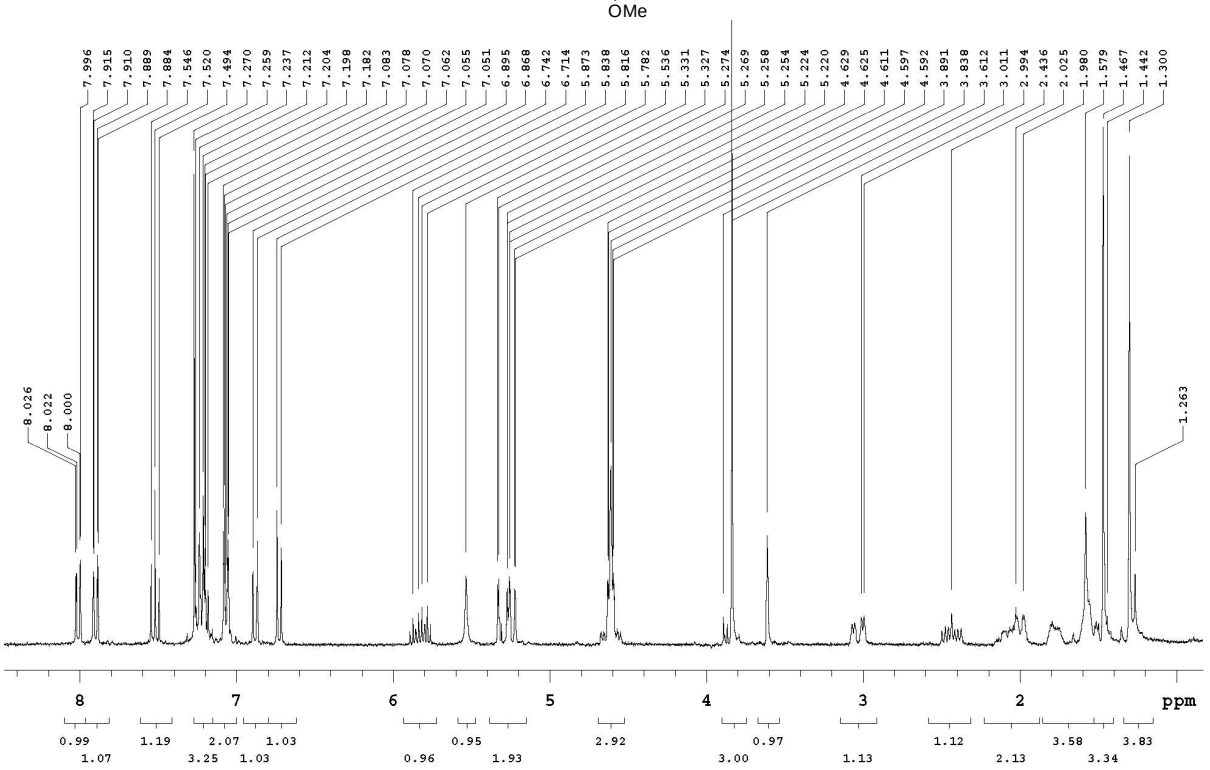
diastereomer	chemical shift (ppm), assignment	nOe chemical shift (ppm)	nOe assignment
(*M*,*S*)-**15**/(*P*,*R*)-**15**	4.71, BnH	7.48	NH
		2.16	OH
		1.80	CH_2
		1.72	CH_2



diastereomer	chemical shift (ppm), assignment	nOe chemical shift (ppm)	nOe assignment
(*M*,*S*)-**15**/(*P*,*R*)-**15**	7.48, NH	7.94	ArH
		7.08	ArH
		2.16	OH
		1.42	CH_3
		1.36	CH_3


Me
Ph
Me
O
N
H
OH
O
O
OMe

(*P*,*S*)-**15**
(*M*,*R*)-**15**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7.083
7.078
7.070
7.062
7.055
7.051
6.895
6.868
6.742
6.714
5.873
5.838
5.816
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5.327
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5.269
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5.254
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4.629
4.625
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3.891
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3.612
3.011
2.994
2.436
2.025
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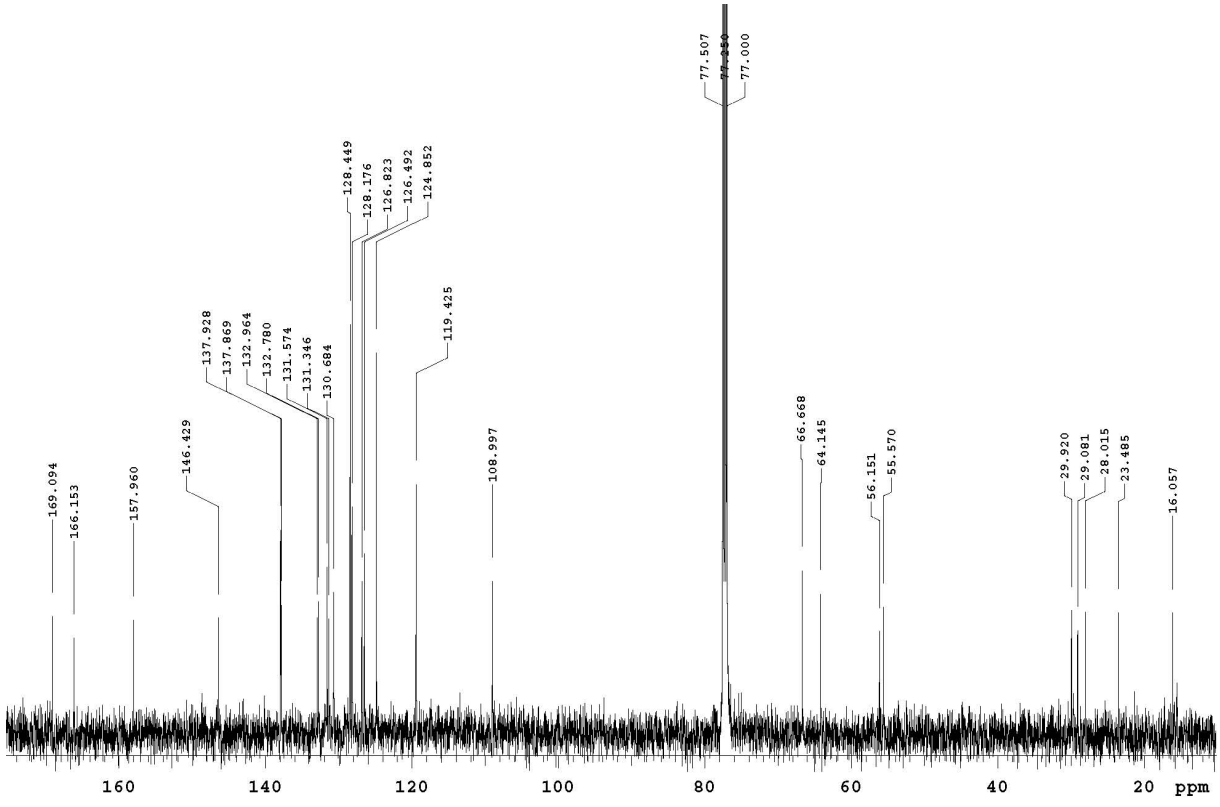
1.300
8.026
8.022
8.000
1.263
8
7
6
5
4
3
2
ppm
0.99
1.19
2.07
1.03
0.95
2.92
0.97
1.12
3.58
3.83
1.07
3.25
1.03
0.96
1.93
3.00
1.13
2.13
3.34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132.780
131.574
131.346
130.684
146.429
108.997
169.094
166.153
157.960
66.668
64.145
56.151
55.570
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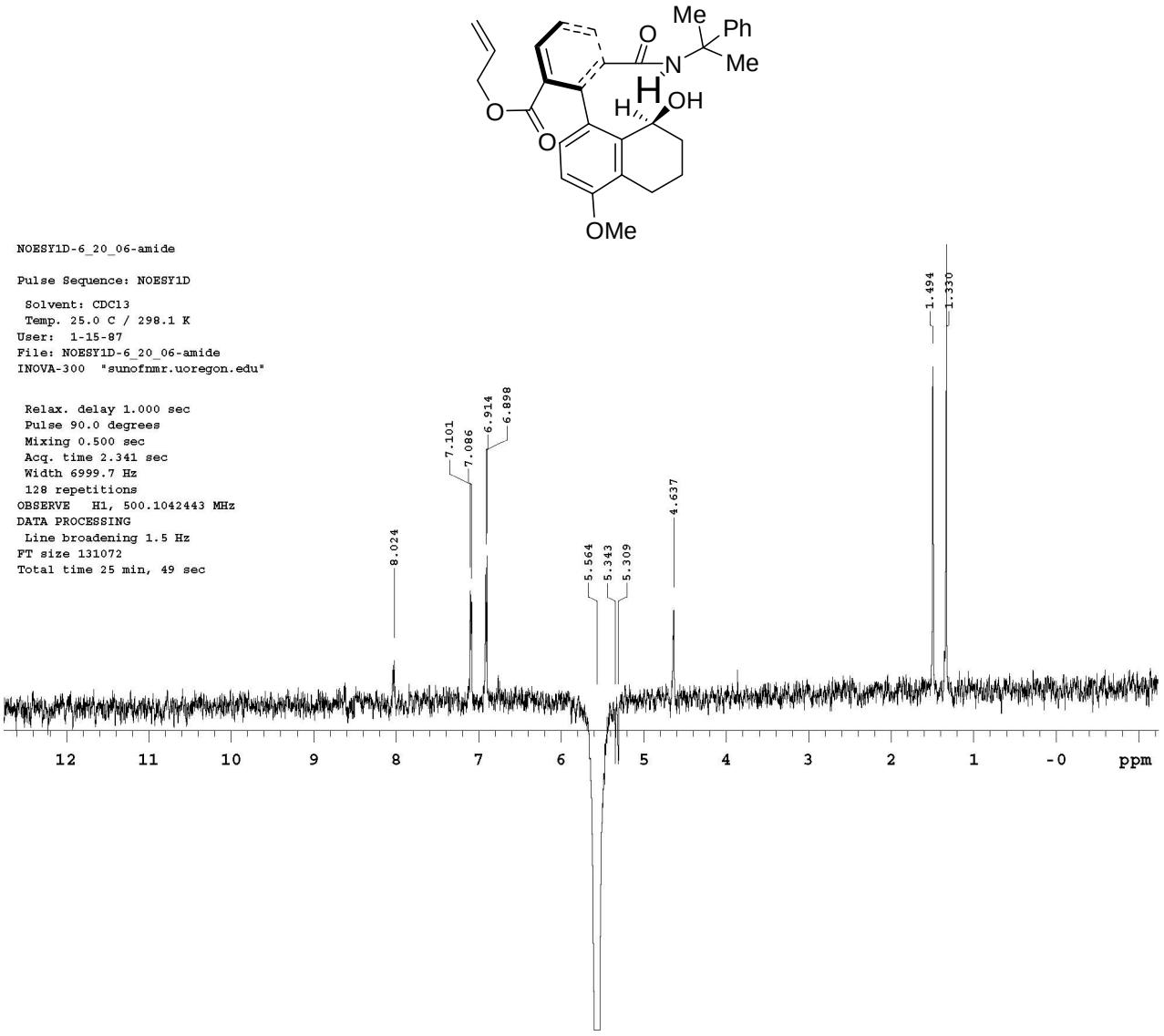
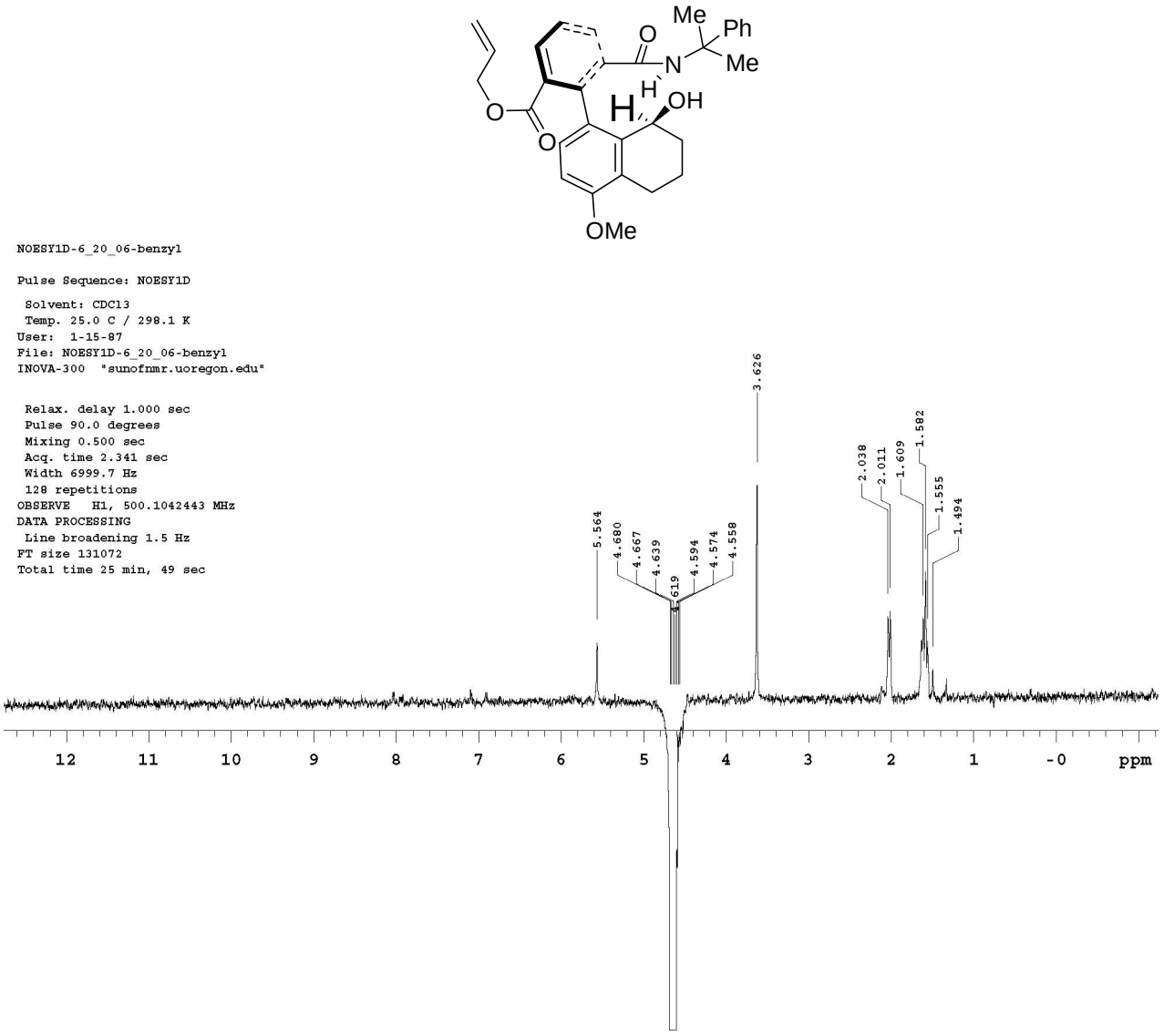
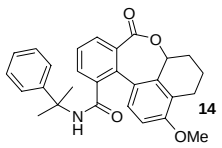
28.015
23.485
16.057
160
140
120
100
80
60
40
20
ppm



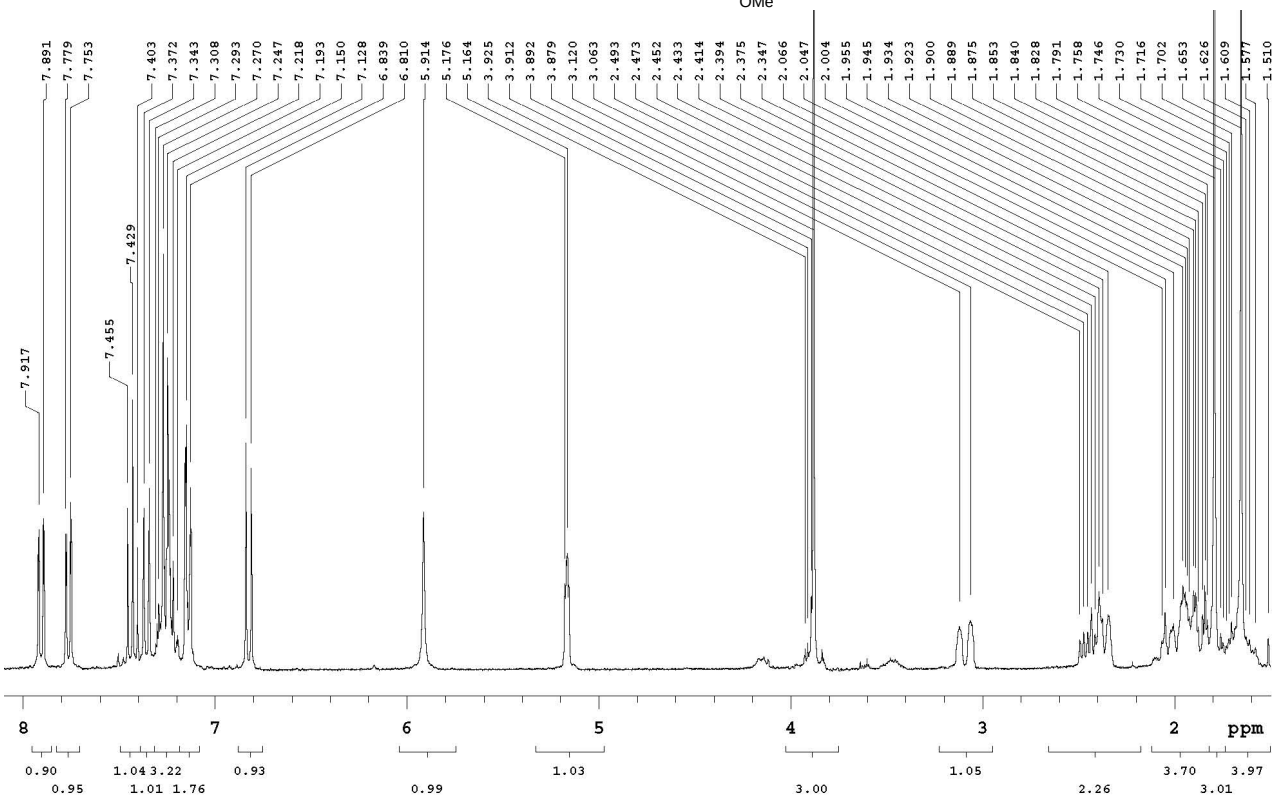
diastereomer	chemical shift (ppm), assignment	nOe chemical shift (ppm)	nOe assignment
(*P*,*S*)-**15**/(*M*,*R*)-**15**	5.56, NH	8.02	ArH
		7.10	ArH
		6.91	ArH
		4.63	BnH
		1.49	CH_3
		1.33	CH_3



diastereomer	chemical shift (ppm), assignment	nOe chemical shift (ppm)	nOe assignment
(*P*,*S*)-**15**/(*M*,*R*)-**15**	4.63, BnH	5.56	NH
		3.42	OH
		2.03	CH_2
		1.60-1.49	CH_2


O
O
N
H
O
OMe

14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7.308
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7.247
7.218
7.193
7.150
7.128
6.839
6.810
5.914
5.176
5.164
3.925
3.912
3.892
3.879
3.120
3.063
2.493
2.473
2.452
2.433
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2.394
2.375
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2.066
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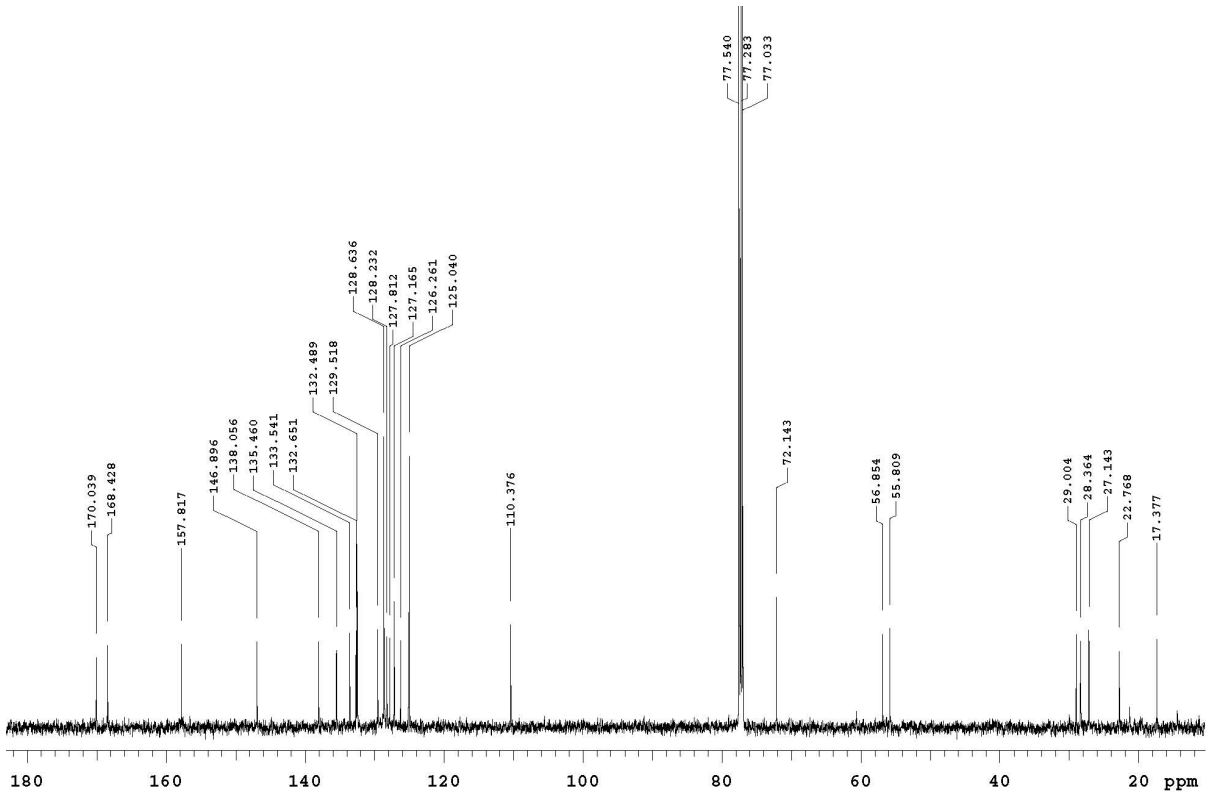
2.004
1.955
1.945
1.934
1.923
1.900
1.889
1.875
1.853
1.840
1.828
1.791
1.758
1.746
1.730
1.716
1.702
1.653
1.626
1.609
1.577
1.510
8
7
6
5
4
3
2
ppm
0.90
0.95
1.04
3.22
1.01
1.76
0.93
0.99
1.03
3.00
1.05
2.26
3.70
3.97
3.01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129.518
128.636
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127.165
126.261
125.040
110.376
77.540
77.283
77.033
72.143
56.854
55.809
29.004
28.364
27.143
22.768
17.377
180
160
140
120
100
80
60
40
20
ppm

References

1. CCDC 620132 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).