Supporting Information

Pd-catalyzed Acyl C–O Bond Activation for Selective Ring-opening of α-Methylene-β-lactones with Amines

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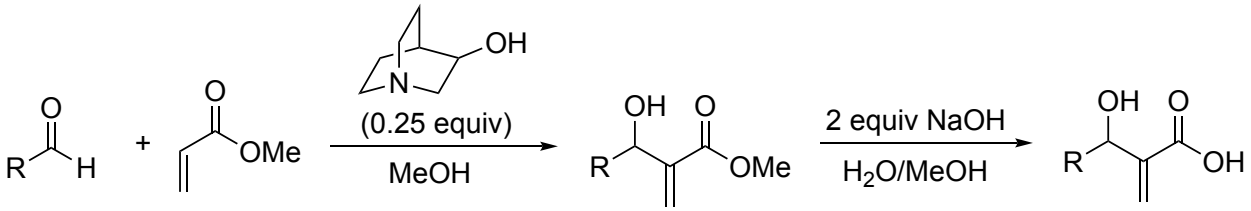
I. General Information

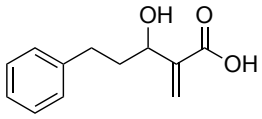
Commercially available reagents were used without further purification. All ^{1}H NMR experiments were recorded using a 300, 400 or 500 MHz spectrometer. All ^{13}C NMR experiments were recorded using a 100 or 125 MHz spectrometer. Chemical shifts (δ) are given in ppm, and coupling constants (*J*) are given in Hz. The 7.26 resonance of residual $CHCl_3$ for proton spectra and the 77.23 ppm resonance of $CDCl_3$ for carbon spectra were used as internal references. High-resolution mass spectra (HRMS) were obtained on a microTOF instrument. Unless otherwise stated, reaction progress was monitored by thin layer chromatography (TLC) performed on glass plates coated with silica gel UV254. Visualization was achieved by ultraviolet light (254 nm), 0.5% $KMnO_4$ in 0.1 M aq NaOH solution and/or 5% phosphomolybdic acid in ethanol. Column chromatography was performed using silica gel, 40 microns flash silica.

II. Preparation of α-methylene-β-hydroxyacids

General procedure for the preparation of α-methylene-β-hydroxyacids[1]



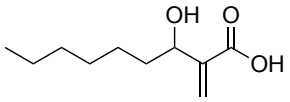
Methylacrylate (2 equiv) was added to a solution of aldehyde (1 equiv), MeOH (0.75 equiv), and quinuclidinol (0.25 equiv), and the mixture was stirred at rt. The reaction progress was monitored by ^{1}H NMR over a period of 2–3 d until >95% conversion. The reaction mixture was concentrated *in vacuo* to remove MeOH and excess methylacrylate. Aq 2.0 M NaOH (2 equiv) was added dropwise to the resulting crude mixture dissolved in MeOH (half the volume of NaOH solution). This was stirred for 2 d or until complete saponification. The progress of the reaction was monitored by ^{1}H NMR analysis or TLC. The reaction mixture was concentrated *in vacuo* to remove MeOH. The resulting aq solution was acidified using 10% aq HCl until pH 1 to 2. This was extracted with Et_2O (same volume as aq solution) three times. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.



7a

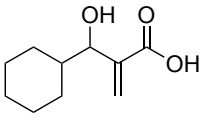
3-Hydroxy-2-methylene-5-phenylpentanoic acid (7a). The general procedure was followed using hydrocinnamaldehyde (4.00 g, 30.0 mmol), and the reaction mixture was stirred for 2 d. ^{1}H NMR analysis of the crude reaction mixture showed 95% conversion. Hydrolysis was complete in 2 d. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 70:30) gave **7a** as a white solid (3.65 g, 59% over two steps):[1] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.18 (m,

5H), 6.43 (s, 1H), 5.95 (s, 1H), 4.47 (dd, *J* = 7.4, 5.5 Hz, 1H), 2.89-2.67 (m, 2H), 2.09–1.98 (m, 2H)



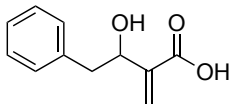
7b

3-Hydroxy-2-methylenenonanoic acid (7b). The general procedure was followed using heptaldehyde (3.40 g, 30.0 mmol), and the reaction mixture was stirred for 2 d. Hydrolysis was complete in 2 d. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 80:20) gave **7b** as a white solid (2.50 g, 50% over two steps):[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (s, 1H), 5.91 (s, 1H), 4.42 (t, *J* = 7.2 Hz, 1H), 1.75–1.60 (m, 2H) ,1.51–1.20 (m, 8H), 0.95–0.81 (m, 3H).



7c

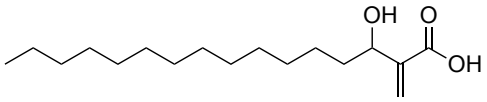
3-Cyclohexyl-3-hydroxy-2-methylenepropanoic acid (7c). The general procedure was followed using cyclohexanecarboxaldehyde (1.30 g, 11.6 mmol), and the reaction mixture was stirred for 2 d. Hydrolysis was complete in 2 d. Cmpd **7c** was obtained as a crude oil and carried to the next step with no further purification:[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (s, 1H) 5.83 (s, 1H) 4.11 (d *J* = 7.1 Hz, 1H) 1.97–1.93 (m, 1H) 1.75–1.56 (m, 6H) 1.24–0.96 (m, 4H).



7d

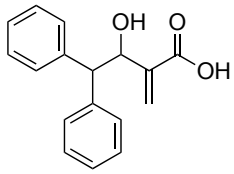
3-Hydroxy-2-methylene-4-phenylbutanoic acid (7d). The general procedure was followed using phenyl acetaldehyde (2.28 g, 19.0 mmol), and the reaction mixture was stirred for 3 h. Hydrolysis was complete in 1 day. Purification by flash chromatography on silica gel (petroleum

ether/EtOAc, 80:20) gave **7d** as a thick pale yellow oil (0.90 g, 23% over two steps):[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.19 (m, 5H), 6.41 (s, 1H), 5.94 (s, 1H), 4.45 (s, 1H) , 2.69 (m, 3H).



7e

3-Hydroxy-2-methylenehexadecanoic acid (7e). The general procedure was followed using tetradecanal (2.98 g, 15.0 mmol), and the reaction mixture was stirred for 2 d. Hydrolysis was complete in 2 d. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 85:15) gave **7e** as a white solid (3.20 g, 75% over two steps):[4] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (s, 1H), 5.91 (s, 1H), 4.43 (dd, *J* = 6.5, 6.5 Hz, 1H), 1.68−1.66 (m, 2H), 1.43−1.41 (m, 1H), 1.30−1.26 (m, 22H), 0.90 (t, *J* = 6.9 Hz, 3H).

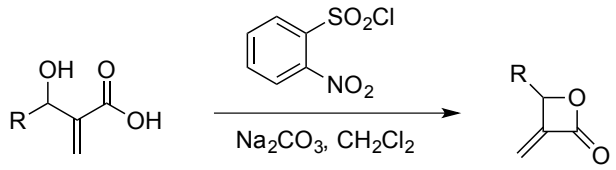


7f

3-Hydroxy-2-methylene-4,4-diphenylbutyric acid (7f). The general procedure was followed using diphenylacetaldehyde (2.94 g, 15.0 mmol), and the reaction mixture was stirred for 2 d. Hydrolysis was complete in 2 d. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 75:25) gave **7f** as a white foam (3.30 g, 83% over two steps):[5] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 10H), 6.29 (s, 1H), 5.71 (s, 1H), 5.23 (d, *J* = 8.0 Hz, 1H), 4.38 (d, *J* = 8.0 Hz, 1H).

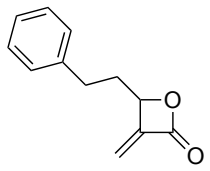
III. Preparation of α-methylene-β-lactones

General procedure for the preparation of α-methylene-β-lactones[1]



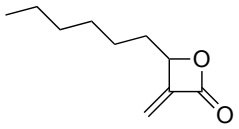
7 **1**

Na_2CO_3 (10 equiv) was added to α-methylene-β-hydroxyacids **7** (1 equiv) in DCM (5 mL DCM/mmol of acid), and the reaction mixture was stirred at rt. After 30 min, *o*-nosyl chloride (2 equiv) was added, and the resulting suspension was stirred at rt for 2 d or until complete conversion. The progress of the reaction was monitored by TLC or ^{1}H NMR analysis. The reaction mixture was diluted with DCM (10 volumes) and H_2O (5 volumes) and stirred for 15 min. The organic layer was separated, and the aq layer was extracted with DCM (3 x 5 volumes). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification was done by flash chromatography on silica gel to afford α-methylene-β-lactones **1**.



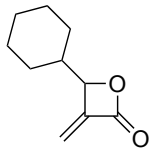
1a

4-(2-Phenylethyl)-3-methyleneoxetan-2-one (1a). The general procedure was followed using 3-hydroxy-2-methylene-5-phenylpentanoic acid (**7a**) (2.90 g, 14.1 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc 95:5) provided **1a** as a colorless oil (1.70 g, 65%):[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.31 (m, 2H), 7.27–7.22 (m, 3H), 5.86 (dd, *J* = 2.0, 2.0 Hz, 1H), 5.33 (dd, *J* = 1.7, 1.7 Hz, 1H), 4.97 (dddd, *J* = 6.4, 6.4, 1.7, 1.7 Hz, 1H), 2.87–2.71 (m, 2H), 2.19–2.12 (m, 2H).



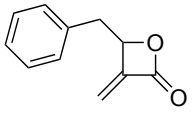
1b

4-Hexyl-3-methyleneoxetan-2-one (1b). The general procedure was followed using 3-hydroxy-2-methylenenonanoic acid (**7b**) (2.90 g, 14.1 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc 94:6) provided **1b** as a colorless oil (1.85 g, 78%): IR (neat): 2955, 2929, 2859, 1813, 1206, 1077 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.39 (dd, *J* = 1.6, 1.6 Hz, 1H), 4.92 (dddd, *J* = 6.6, 6.6, 1.8, 1.8 Hz, 1H), 1.80 (m, 2H), 1.46–1.37 (m, 2H), 1.33–1.24 (m, 6H), 0.84 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 146.5, 114.9, 79.7, 33.4, 31.6, 29.0, 24.6, 22.5, 14.1; HRMS (ESI) calcd for $C_{10}H_{17}O_2$ $(M + H)^+$ *m/z* 169.1229, found 169.1217.



1c

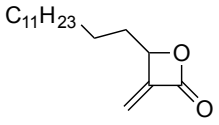
4-Cyclohexyl-3-methyleneoxetan-2-one (1c). The general procedure was followed using 3-cyclohexyl-3-hydroxy-2-methylenepropanoic acid (**7c**) (1.40 g, 5.20 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc 95:5) provided **1c** as a colorless oil (0.67 g, 77%):[2] ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (dd, *J* = 1.7, 1.7 Hz, 1H), 5.42 (dd, *J* = 1.7, 1.7 Hz, 1H), 4.69 (ddd, *J* = 7.1, 1.7, 1.7 Hz, 1H), 1.87–1.10 (m, 11H).



1d

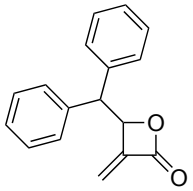
4-Benzyl-3-methyleneoxetan-2-one (1d). The general procedure was followed using 3-hydroxy-2-methylene-4-phenylbutanoic acid (**7d**) (900 mg, 4.68 mmol). Purification by flash

chromatography on silica gel (petroleum ether/EtOAc 94:4) provided **1d** as a pale yellow oil (244 mg, 30%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.23 (m, 5H), 5.89 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.23 (dd, *J* = 1.6, 1.6 Hz, 1H), 5.14 (dddd, *J* = 6.8, 6.8, 1.6, 1.6 Hz, 1H), 3.29 (dd, *J* = 14.1, 6.8 Hz, 1H), 3.05 (dd, *J* = 14.1, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 145.8, 134.8, 129.5, 128.9, 127.5, 116.2, 79.0, 39.7; HRMS (ESI) calcd for $C_{11}H_{10}O_2$ $(M + H)^+$ *m/z* 175.0759, found 175.0742.



1e

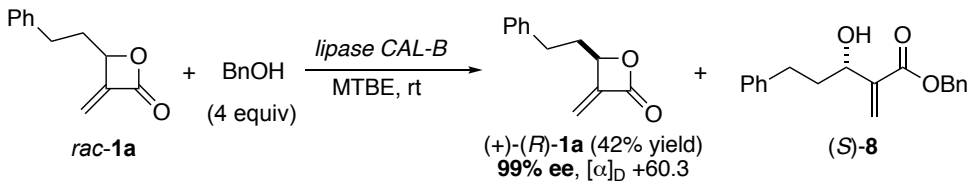
3-Methylene-4-tridecyloxetan-2-one (1e). The general procedure was followed using 3-hydroxy-2-methylenehexadecanoic acid (**7e**) (2.50 g, 9.25 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc 98:2) provided **1e** as a colorless oil (1.60 g, 65%):[4] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 1.9, 1.9 Hz, 1H), 5.39 (dd, *J* = 1.7, 1.7 Hz, 1H), 4.92 (dddd, *J* = 6.5, 6.5, 1.6, 1.6 Hz, 1H), 1.81 (m, 2H), 1.46–1.40 (m, 2H), 1.33–1.22 (m, 20H), 0.84 (t, *J* = 6.6 Hz, 3H).



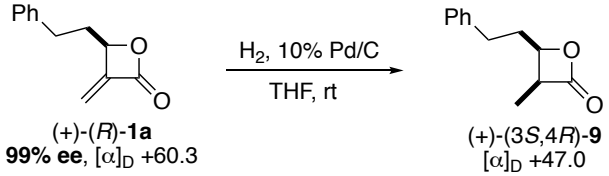
1f

4-Benzhydryl-3-methyleneoxetan-2-one (1f). The general procedure was followed using 3-hydroxy-2-methylene-4,4-diphenylbutyric acid (**7f**) (1.4 g, 5.2 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc 95:5) provided **1f** as a white solid (0.95 g, 73%):[5] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.23 (m, 10H), 5.74 (dd, *J* = 2.0, 1.4 Hz, 1H), 5.53 (ddd, *J* = 9.6, 2.0, 1.4 Hz, 1H), 4.72 (dd, *J* = 2.0, 1.4 Hz, 1H), 4.20 (d, *J* = 9.6, 1H).

Preparation of β-lactone (+)-(*R*)-1a[6]



Determination of absolute configuration:

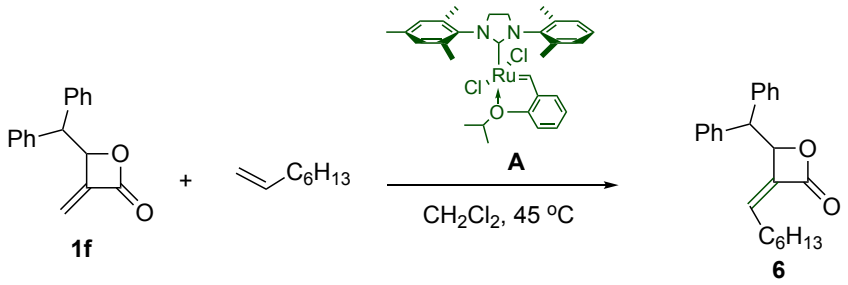


(*4R*)-4-(2-Phenylethyl)-3-methyleneoxetan-2-one [(*R*)-1a]. Lipase CAL-B (lipase acrylic resin from *Candida Antarctica;* 19 mg) was added to a solution of 4-(2-phenylethyl)-3-methyleneoxetan-2-one (*rac*-**1a**) (190 mg, 1.0 mmol) and benzyl alcohol (4 mmol) in MTBE (5 mL). The resulting suspension was stirred at rt, and conversion was monitored by ^{1}H NMR. After 24 h, ~50% conversion was obtained. Percent conversion was estimated based on the ratio of unreacted **1a** and product **8**. The reaction mixture was passed through a pad of Celite and washed with MTBE (3 x 5 mL). The filtrate was dried (Na_2SO_4) and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel (hexanes/EtOAc 95:5) and gave (*R*)-**1a** as a colorless oil (79 mg, 42%):[1] $[\alpha]^{20}_D$ = (+)-60.3 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.31 (m, 2H), 7.27–7.22 (m, 3H), 5.86 (dd, *J* = 2.0, 2.0 Hz, 1H), 5.33 (dd, *J* = 1.7, 1.7 Hz, 1H), 4.97 (dddd, *J* = 6.4, 6.4, 1.7, 1.7 Hz, 1H), 2.87–2.71 (m, 2H), 2.19–2.12 (m, 2H); 99% ee, retention time 7.7 min (major) and 8.7 min (minor) on Chiralpak AY3 (5% IPA/hexane, 1.0 mL/min). The absolute configuration was determined by reduction of **1a** to cmpd **9**.[7]

(3*S*,4*R*)-3-Methyl-4-(2-phenylethyl)oxetan-2-one (9). Cmpd (+)-(*R*)-**1a** (47 mg, 0.25 mmol) and 10% Pd on carbon (0.0075 mmol, 8 mg) were mixed in dry THF (2 mL) under a N_2 atmosphere. The reaction vessel was purged with H_2 for 10 min. The reaction mixture was stirred at rt for 2 h under a balloon filled with H_2. The crude mixture was filtered through a pad of

Celite. The Celite was washed with DCM (3 x 3 mL), and the filtrate was concentrated to give a pale yellow oil. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 92:8) afforded **9** as a pale yellow oil (41 mg, 88%):[7] $[\alpha]^{20}_D$ = (+)-47.0 (*c* = 1.00, $CHCl_3$) [lit.[8] $[\alpha]^{20}_D$ = (–)-47.2 (*c* = 2.04, $CHCl_3$) for *ent*-**9**]; ^{1}H NMR (400 MHz, $CDCl_3$) 7.38−7.24 (m, 5H), 4.57 (ddd, *J* = 4.5, 4.5, 4.5 Hz, 1H), 3.74 (dq, *J* = 14.6, 7.4 Hz, 1H), 2.90 (ddd, *J* = 14.2, 5.3, 5.3 Hz, 1H), 2.73 (m, 1H), 2.06 (m, 2H), 1.28 (d, *J* = 7.7 Hz, 3H).

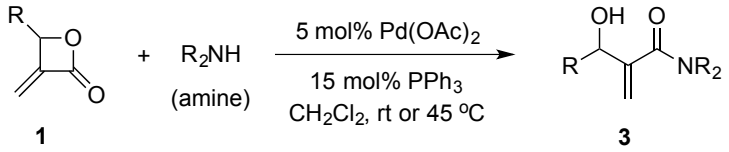
Preparation of β-lactone 6[5]



4-Benzhydryl-3-heptylideneoxetan-2-one (6). 1-Octene (168 mg, 1.5 mmol) was added to a solution of 4-benzhydryl-3-methyleneoxetan-2-one (**1f**) (250 mg, 1.0 mmol) under N_2 in DCM (4 mL). Cat **A** (5 mol %) was added, and the resultant solution was heated at reflux. The reaction was monitored by ^{1}H NMR. Upon consumption (~20 h) of **1f**, the solution was cooled and concentrated, and the brown residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 99:1). Lactone **6** was obtained as a clear oil (309 mg, 92%, *Z* isomer): ^{1}H NMR (400 MHz, $CDCl_3$) for the major isomer: δ 7.37–7.28 (m, 7H), 7.26–7.22 (m, 3H), 5.48 (d, *J* = 9.2 Hz, 1H), 5.18 (ddd, *J* = 8.1, 8.1, 1.0 Hz, 1H), 4.20 (d, *J* = 9.2 Hz, 1H), 2.45–2.30 (m, 2H), 1.33–1.21 (m, 8H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 140.0, 139.6, 139.0, 136.1, 129.0, 128.8, 128.5, 127.8, 127.3, 79.1, 55.1, 31.6, 29.2, 28.8, 28.7, 22.7, 14.2; HRMS (ESI) calcd for $C_{23}H_{27}O_2$ $(M + H)^+$ *m/z* 335.2011, found 335.1982.

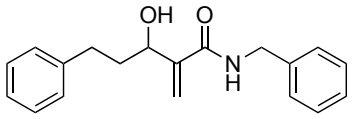
IV. Pd-catalyzed amidation of α-methylene-β-lactones

General procedure for the Pd-catalyzed amidation of α-methylene-β-lactones with amines



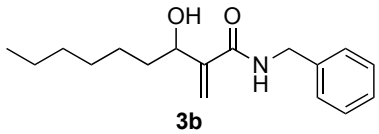
1 **3**

Anhydrous DCM (0.25 mL) was added to a reaction tube containing 5 mol % $Pd(OAc)_2$ (0.005 mmol, 1.1 mg) and 15 mol % PPh_3 (0.015 mmol, 4.0 mg) and stirred for 20 min at rt. The α-methylene-β-lactone (1.0 equiv, 0.1 mmol) in DCM (0.25 mL) was added via syringe, followed by the amine (1.1 equiv., 0.11 mmol; for aryl amines, 2-4 equiv. were used). The reaction mixture was stirred for 24 h at rt or 45 °C. The reaction mixture was filtered through a short pad of silica which was rinsed with DCM (2 x 2 mL). The crude mixture was concentrated *in vacuo* and purified by column chromatography on silica gel. [See **3f** for a 1.0 mmol scale reaction]



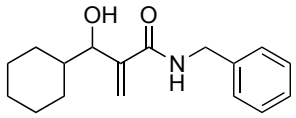
3a

***N*-Benzyl-3-hydroxy-2-methylene-5-phenylpentanamide (3a).** The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one (**1a**) and benzylamine, and the reaction was performed at 45 °C. Purification by column chromatography on silica gel (hexanes/EtOAc 70:30) provided **3a** as a pale yellow solid (29 mg, 98%): mp 96–97 °C; IR (neat) 3307 (br), 3027, 2925, 2855, 1715, 1654, 1605, 1535, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.18 (m, 7H), 7.13–7.09 (m, 3H), 6.64 (br s, 1H), 5.71 (s, 1H), 5.38 (s, 1H), 4.45 (dd, *J* = 14.8, 5.8 Hz, 1H), 4.41 (dd, *J* = 14.8, 5.7 Hz, 1H), 4.31 (dd, *J* = 7.9, 5.7 Hz, 1H), 3.08 (br s, 1H), 2.71 (ddd, *J* = 14.2, 9.6, 6.0 Hz, 1H), 2.59 (ddd, *J* = 15.9, 9.2, 6.7 Hz, 1H), 2.03–1.94 (m, 1H), 1.93–1.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 145.7, 141.7, 138.2, 129.0, 128.7, 128.6, 128.0, 127.8, 126.2, 120.1, 73.4, 43.7, 37.5, 32.3; HRMS (ESI) calcd for $C_{19}H_{22}NO_2$ $(M + H)^+$ *m/z* 296.1651, found 296.1664.



3b

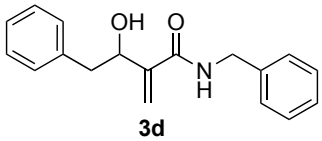
***N*-Benzyl-3-hydroxy-2-methylenenonanamide (3b).** The general procedure was followed using 4-hexyl-3-methyleneoxetan-2-one (**1b**) and benzylamine, and the reaction was performed at rt. Purification by column chromatography on silica gel (hexanes/EtOAc 70:30) provided **3b** as a white solid (27 mg, 98%): mp 77–78 ^{o}C; IR (neat) 3389 (br), 2954, 2926, 2856, 1654, 1609, 1536, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.33 (m, 2H), 7.30–7.28 (m, 3H), 6.83 (br s, 1H), 5.80 (s, 1H), 5.45 (s, 1H), 4.52 (dd, *J* = 14.9, 5.7 Hz, 1H), 4.48 (dd, *J* = 14.9, 5.7 Hz, 1H), 4.36 (dd, *J* = 12.5, 6.2 Hz, 1H), 2.94 (d, *J* = 5.5 Hz, 1H), 1.71–1.60 (m, 2H), 1.40–1.27 (m, 8H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 145.8, 138.3, 129.0, 127.9, 127.8, 120.1, 74.3, 43.7, 36.0, 31.9, 29.3, 26.1, 22.8, 14.3; HRMS (ESI) calcd for $C_{17}H_{26}NO_2$ $(M + H)^+$ *m/z* 276.1964, found 276.1961.



3c

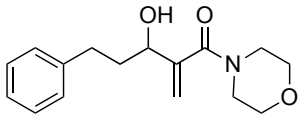
***N*-Benzyl-3-cyclohexyl-3-hydroxy-2-methylenepropanamide (3c).** The general procedure was followed using 4-cyclohexyl-3-methyleneoxetan-2-one (**1c**) and benzylamine, and the reaction was performed at rt. Purification by column chromatography on silica gel (hexanes/EtOAc 70:30) provided **3c** as a yellowish solid (24 mg, 89%): mp 82–83 ^{o}C; IR (neat) 3306 (br), 2923, 2851, 1654, 1609, 1537, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.31 (m, 2H), 7.28–7.26 (m, 3H), 7.00 (br s, 1H), 5.82 (s, 1H), 5.37 (s, 1H), 4.52 (dd, *J* = 14.9, 5.8 Hz, 1H), 4.48 (dd, *J* = 14.9, 5.8 Hz, 1H), 3.97 (dd, *J* = 8.1, 6.1 Hz, 1H), 3.28 (d, *J* = 6.1 Hz, 1H), 2.04–2.01 (m, 1H), 1.76–1.50 (m, 5H), 1.23–1.13 (m, 3H), 0.99–0.81 (m, 2H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 168.2, 144.5, 138.3, 128.9, 127.8, 127.7, 121.5, 80.0, 43.5, 42.2, 30.0, 29.5, 26.5, 26.1, 26.0; HRMS (ESI) calcd for $C_{17}H_{24}NO_2$ $(M + H)^+$ *m/z* 274.1807, found 274.1813.



3d

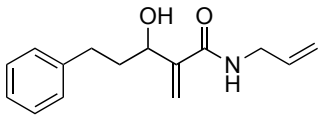
***N*-Benzyl-3-hydroxy-2-methylene-4-phenylbutanamide (3d).** The general procedure was followed using 4-benzyl-3-methyleneoxetan-2-one (**1d**) and benzylamine, and the reaction was performed at rt. Purification by column chromatography on silica gel (hexanes/EtOAc 70:30) provided **3d** as a pale yellow solid (21 mg, 76%): mp 102–104 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.16 (m, 10H), 6.72 (br s, 1H), 5.77 (s, 1H), 5.42 (s, 1H), 4.62 (m, 1H), 4.53 (d, *J* = 5.7 Hz, 2H), 3.06–2.94 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 144.6, 138.2, 137.9, 129.6, 128.9, 128.6, 127.8, 127.6, 126.7, 120.8, 74.7, 43.5, 42.9; HRMS (ESI) calcd for $C_{18}H_{20}NO_2$ $(M + H)^+$ *m/z* 282.1494, found 282.1482.



3e

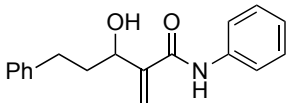
***N*-(3-Hydroxy-2-methylene-5-phenyl)pentanoylmorpholine (3e).** The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one (**1a**) and morpholine, and the reaction was performed at rt. Purification by column chromatography on silica gel (hexanes/EtOAc 60:40) provided **3e** as a pale yellow oil (25 mg, 92%): IR (neat) 3386 (br), 2922, 2855, 1643, 1604, 1436, 1069, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 3H), 7.21–7.19 (m, 2H), 5.50 (s, 1H), 5.18 (s, 1H), 4.32 (ddd, *J* = 12.9, 6.4, 6.4 Hz, 1H), 3.65 (br s, 8H), 3.05 (d, *J* = 6.3 Hz, 1H), 2.85 (ddd, *J* = 14.2, 7.6, 7.6 Hz, 1H), 2.71 (ddd, *J* = 14.4, 7.9, 7.9 Hz, 1H), 1.94–1.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 145.1, 141.7, 128.7, 128.7,

126.2, 116.4, 77.43, 73.2, 67.1, 37.8, 32.3; HRMS (ESI) calcd for $C_{16}H_{22}NO_3$ $(M + H)^+$ *m/z* 276.1600, found 276.1617.



3f

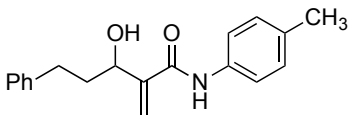
***N*-Allyl-3-hydroxy-2-methylene-5-phenylpentanamide (3f).** The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one (**1a**) (188 mg, 1.0 mmol) and allylamine (63 mg, 1.1 mmol), and the reaction was performed at rt. Purification by column chromatography on silica gel (hexanes/EtOAc 70:30) provided **3f** as a pale yellow solid (220 mg, 90%): mp 74–75 ^oC; IR (neat) 3306 (br), 2922, 2860, 1655, 1605, 1531, 921, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.26 (m, 3H), 7.20–7.17 (m, 2H), 6.53 (br s, 1H), 5.90–5.81 (m, 1H), 5.78 (s, 1H), 5.45 (s, 1H), 5.20 (dddd, *J* = 17.2, 1.6, 1.6, 1.6 Hz, 1H), 5.16 (dddd, *J* = 10.3, 1.4, 1.4, 1.4 Hz, 1H), 4.37 (ddd, *J* = 7.8, 5.8, 5.8 Hz, 1H), 3.95–3.92 (m, 2H), 3.23 (d, *J* = 6.0 Hz, 1H), 2.79 (ddd, *J* = 14.0, 5.9, 5.9 Hz, 1H), 2.68 (ddd, *J* = 14.1, 6.7, 6.7 Hz, 1H), 2.10–2.01 (m, 1H), 1.99–1.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 145.7, 141.7, 134.0, 128.7, 128.6, 126.2, 120.0, 116.8, 73.4, 42.0, 37.5, 32.3; HRMS (ESI) calcd for $C_{15}H_{20}NO_2$ $(M + H)^+$ *m/z* 246.1494, found 246.1521.



3g

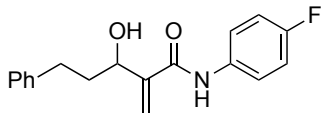
3-Hydroxy-2-methylene-*N*-phenyl-5-phenylpentanamide (3g). The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one (**1a**) (19 mg, 0.10 mmol) and aniline (41 mg, 0.44 mmol), and the reaction was performed at 45 ^oC. Purification by column chromatography on silica gel (hexanes/EtOAc 70:30) provided **3g** as a pale yellow solid (26 mg,

92%): mp 126–128 °C; IR (neat) 3306 (br), 3305, 2924, 2860, 1650, 1618, 1522, 747, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.60 (br s, 1H), 7.57–7.55 (m, 2H), 7.36–7.26 (m, 4H), 7.21–7.11 (m, 4H), 6.01 (s, 1H), 5.54 (s, 1H), 4.48 (dd, *J* = 7.8, 7.8 Hz, 1H), 2.94 (br s, 1H), 2.84–2.76 (m, 1H), 2.75–2.68 (m, 1H), 2.18–2.08 (m, 1H), 2.07–1.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 145.6, 141.4, 137.8, 129.3, 128.7, 126.3, 124.8, 122.1, 120.4, 73.6, 37.3, 32.3; HRMS (ESI) calcd for $C_{18}H_{20}NO_2$ $(M + H)^+$ *m/z* 282.1494, found 282.1498.



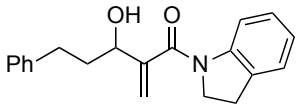
3h

3-Hydroxy-*N*-(4-methylphenyl)-2-methylene-5-phenylpentanamide (3h). The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one (**1a**) (19 mg, 0.10 mmol) *p*-toluidine (24 mg, 0.22 mmol), and the reaction was performed at 45 °C. Purification by column chromatography on silica gel (hexanes/EtOAc 70:30) provided **3h** as a pale yellow solid (28 mg, 96%): mp 113–115 °C; IR (neat) 3286 (br), 3026, 2921, 2861, 1658, 1597, 1513, 813, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (br s, 1H), 7.44–7.42 (m, 2H), 7.30–7.26 (m, 2H), 7.21–7.17 (m, 3H), 7.14–7.12 (m, 2H), 5.98 (s, 1H), 5.50 (s, 1H), 4.45 (dd, *J* = 7.9, 5.8 Hz, 1H), 3.19 (br s, 1H), 2.83–2.67 (m, 2H), 2.32 (s, 3H), 2.16–2.07 (m, 1H), 2.05–1.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 145.6, 141.4, 135.2, 134.5, 129.7, 128.7, 128.7, 126.2, 121.9, 120.5, 73.5, 37.4, 32.3, 21.1; HRMS (ESI) calcd for $C_{19}H_{22}NO_2$ $(M + H)^+$ *m/z* 296.1651, found 296.1681.



3i

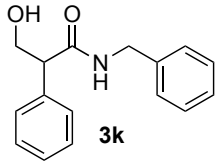
3-Hydroxy-*N*-(4-fluorophenyl)-2-methylene-5-phenylpentanamide (3i). The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one (**1a**) (19 mg, 0.10 mmol) and 4-fluoroaniline (50 mg, 0.44 mmol), and the reaction was performed at 45 °C. Purification by column chromatography on silica gel (hexanes/EtOAc 70:30) provided **3i** as a pale yellow solid (24 mg, 80%): mp 78–79 °C; IR (neat) 3293 (br), 2926, 2859, 1660, 1611, 1540, 1508, 832, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 7.54–7.49 (m, 2H), 7.31–7.26 (m, 2H), 7.21–7.18 (m, 3H), 7.04–6.99 (m, 2H), 6.03 (s, 1H), 5.52 (s, 1H), 4.47 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.05 (br s, 1H), 2.84–2.66 (m, 2H), 2.18–1.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 159.7 (d, J_{C-F} = 243 Hz), 145.2, 141.3, 133.8, 128.7, 128.7, 126.3, 122.5, 122.2 (d, J_{C-F} = 7.9 Hz), 115.9 (d, J_{C-F} = 22.5 Hz), 73.5, 37.4, 32.3; HRMS (ESI) calcd for $C_{19}H_{19}FNO_2$ $(M + H)^+$ *m/z* 300.1400, found 300.1417.



3j

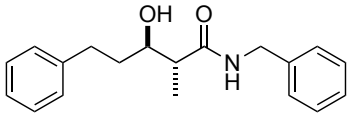
***N*-(3-Hydroxy-2-methylene-5-phenyl)-pentanoylindoline (3j).** The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one (**1a**) (19 mg, 0.10 mmol) and indoline (52 mg, 0.44 mmol), and the reaction was performed at 45 °C. Purification by column chromatography on silica gel (hexanes/EtOAc 60:40) provided **3j** as a light brown thick oil (28 mg, 90%, contains ~6% indoline as impurity): IR (neat) 3404 (br), 2922, 1641, 1618, 1481, 1408, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (br s, 1H), 7.29–7.26 (m, 3H), 7.22–7.15 (m, 5H), 7.06 (dd, *J* = 7.4, 7.4 Hz, 1H), 5.62 (s, 1H), 5.42 (s, 1H), 4.44 (dd, *J* = 6.6, 6.6 Hz, 1H), 4.17–4.04 (m, 2H), 3.22 (br s, 1H), 3.14 (dd, *J* = 14.9, 8.2 Hz, 1H), 3.07 (dd, *J* = 14.9, 8.2 Hz,

1H), 2.94–2.87 (m, 1H), 2.77–2.70 (m, 1H), 2.01 (dd, *J* = 7.7, 7.7 Hz, 1H), 1.99 (dd, *J* = 7.7, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 147.2, 142.4, 141.9, 132.6, 128.7, 128.6, 127.6, 126.1, 125.1, 124.6, 117.8, 116.9, 73.1, 50.8 (br), 38.0, 32.4, 28.3 (br); HRMS (ESI) calcd for $C_{20}H_{22}NO_2$ $(M + H)^+$ *m/z* 308.1651, found 308.1662.



3k

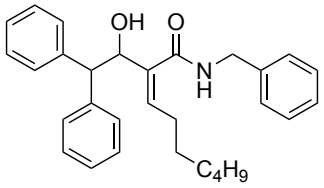
***N*-Benzyl-3-hydroxy-2-phenylpropanamide (3k).** The general procedure was followed using 3-phenyloxetan-2-one[9] (**4**) and benzylamine, and the reaction was performed at rt. Purification by column chromatography on silica gel (hexanes/EtOAc 60:40) provided **3k** as a white solid (25 mg, 96%): mp 116–118 °C; IR (neat) 3276 (br), 3030, 2924, 1638, 1548, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (m, 8H), 7.18–7.16 (m, 2H), 5.82 (br s, 1H), 4.43 (dd, *J* = 14.9, 5.8 Hz, 1H), 4.43 (dd, *J* = 14.9, 5.8 Hz, 1H), 4.18 (dd, *J* = 11.0, 8.8 Hz, 1H), 3.80 (dd, *J* = 11.0, 4.3 Hz, 1H), 3.70 (dd, *J* = 8.7, 4.5 Hz, 1H), 3.44 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 138.0, 136.8, 129.4, 128.9, 128.7, 128.2, 127.7, 127.7, 65.3, 54.6, 43.7; HRMS (ESI) calcd for $C_{16}H_{18}NO_2$ $(M + H)^+$ *m/z* 256.1338, found 256.1349.



3l

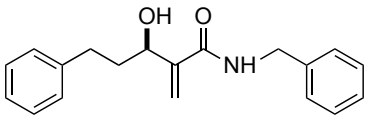
(*2R*,3R)-*N*-Benzyl-3-hydroxy-2-methyl-5-phenylpentanamide (3l).** The general procedure was followed using *trans*-3-methyl-4-(2-phenylethyl)-oxetan-2-one[10] (**5**) and benzylamine, and the reaction was performed at rt (2 d). Purification by column chromatography on silica gel (hexanes/EtOAc 60:40) provided **3l** as a white solid (24 mg, 82%): mp 133–135 °C; IR (neat) 3293 (br), 2914, 1643, 1549, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.24 (m, 7H), 7.20–

7.16 (m, 3H), 6.17 (br s, 1H), 4.43 (d, *J* = 2.5 Hz, 1H), 4.41 (d, *J* = 2.5 Hz, 1H), 3.63 (ddd, *J* = 5.4, 5.4, 5.4, 1H), 3.40 (br s, 1H), 2.86 (ddd, *J* = 14.2, 7.4, 7.4 Hz, 1H), 2.67 (ddd, *J* = 13.9, 8.0, 8.0 Hz, 1H), 2.26 (dq, *J* = 7.1, 5.2 Hz, 1H), 1.82–1.76 (m, 2H), 1.26 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 142.2, 138.2, 128.9, 128.7, 128.6, 127.9, 127.8, 126.1, 73.5, 46.2, 43.5, 37.6, 32.4, 15.9; HRMS (ESI) calcd for $C_{19}H_{24}NO_2$ $(M + H)^+$ *m/z* 298.1807, found 298.1813.



3m

***N*-Benzyl-4,4-diphenyl-2-heptylidene-3-hydroxybutanamide (3m).** The general procedure was followed using 4-benzhydryl-3-heptylideneoxetan-2-one (**6**) (290 mg, 0.87 mmol) and benzylamine (102 mg, 0.95 mmol), and the reaction was performed at 45 ^{o}C. Purification by column chromatography on silica gel (hexanes/EtOAc 80:20) provided **3m** as a pale yellow oil (344 mg, 90%, *Z* isomer): IR (neat) 3323 (br), 2954, 2926, 2856, 1660, 1601, 746, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) for the major isomer: δ 7.37–7.28 (m, 9H), 7.22–7.08 (m, 6H), 5.93 (dd, *J* = 5.3, 5.3 Hz, 1H), 5.30 (dd, *J* = 10.4, 7.6 Hz, 1H), 4.89 (dd, *J* = 10.0, 5.4 Hz, 1H), 4.49 (dd, *J* = 14.6, 5.9 Hz, 1H), 4.45 (dd, *J* = 14.6, 5.9 Hz, 1H), 4.16 (d, *J* = 10.0 Hz, 1H), 3.09 (d, *J* = 5.4 Hz, 1H), 2.09–2.04 (m, 2H), 1.26–1.00 (m, 8H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 142.0, 141.5, 138.3, 138.1, 135.8, 129.0, 128.9, 128.8, 128.8, 128.6, 128.3, 127.9, 127.0, 126.8, 78.9, 57.4, 43.6, 31.8, 29.3, 29.3, 28.9, 22.7, 14.3; HRMS (ESI) calcd for $C_{30}H_{36}NO_2$ $(M + H)^+$ *m/z* 442.2746, found 442.2770.

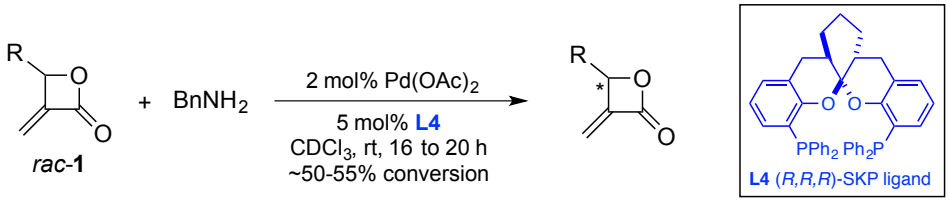


(+)-(*R*)-**3a**
99% ee

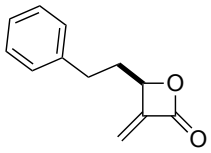
(3*R*)-*N*-Benzyl-3-hydroxy-2-methylene-5-phenylpentanamide [(*R*)-3a]. Anhydrous DCM (0.25 mL) was added to a reaction tube containing 5 mol % $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and 15 mol % PPh_3 (4.0 mg, 0.015 mmol), and the solution was stirred for 20 min at rt. (*R*)-4-(2-Phenylethyl)-3-methyleneoxetan-2-one [(*R*)-**1a**] (19 mg, 0.1 mmol) in DCM (0.25 mL) was added via syringe, followed by benzylamine (12 mg, 0.11 mmol). The reaction mixture was stirred for 24 h at 45 ^{o}C. The reaction mixture was filtered through a short pad of silica which was rinsed with DCM (2 x 2 mL). The crude mixture was concentrated *in vacuo* and purified by column chromatography on silica gel (hexanes/EtOAc 70:30) and gave (*R*)-**3a** as a pale yellow solid (27 mg, 92%): $[\alpha]^{20}_{D}$ = (+)-24.8 (*c* = 1.00, $CHCl_3$); mp 96–97 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.18 (m, 7H), 7.13–7.09 (m, 3H), 6.64 (br s, 1H), 5.71 (s, 1H), 5.38 (s, 1H), 4.45 (dd, *J* = 14.8, 5.8 Hz, 1H), 4.41 (dd, *J* = 14.8, 5.7 Hz, 1H), 4.31 (dd, *J* = 7.9, 5.7 Hz, 1H), 3.08 (br s, 1H), 2.71 (ddd, *J* = 14.2, 9.6, 6.0 Hz, 1H), 2.59 (ddd, *J* = 15.9, 9.2, 6.7 Hz, 1H), 2.03–1.94 (m, 1H), 1.93–1.84 (m, 1H); 99% ee, retention time 12.2 min (major) and 13.2 min (minor) on Chiralcel OJ (2% IPA/hexane, 1.5 mL/min).

V. Pd-catalyzed kinetic resolution of α-methylene-β-lactones

General procedure for the Pd-catalyzed kinetic resolution of α-methylene-β-lactones with benzylamine.

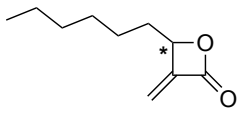


Deuterated chloroform (0.50 mL) was added to a reaction tube containing 2 mol % $Pd(OAc)_2$ (0.004 mmol, 1.0 mg) and 5 mol % **L4** (0.010 mmol, 6.6 mg), and the solution was stirred for 20 min at rt. The α-methylene-β-lactone (1.0 equiv, 0.2 mmol) in $CDCl_3$ (0.50 mL) was added via syringe, followed by the amine (1.0 equiv, 0.2 mmol). The reaction mixture was stirred at rt for 16 to 20 h until 50–55% conversion was reached. The reaction was monitored by ^1H NMR analysis. The reaction mixture was filtered through a short pad of silica, which was rinsed with DCM (2 x 2 mL). The crude mixture was concentrated *in vacuo* and purified by column chromatography on silica gel.



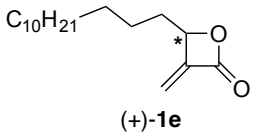
(R)-(+)-**1a**

(4*R*)-4-(2-Phenylethyl)-3-methyleneoxetan-2-one ([*R*]-[+]-1a). The general procedure was followed using racemic **1a** (38 mg, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc 95:5) provided (*R*)-(+)-**1a** as a colorless oil (16 mg, 43%):[1] $[\alpha]^{20}_D$ = (+)-40.3 (*c* = 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.31 (m, 2H), 7.27–7.22 (m, 3H), 5.86 (dd, *J* = 2.0, 2.0 Hz, 1H), 5.33 (dd, *J* = 1.7, 1.7 Hz, 1H), 4.97 (dddd, *J* = 6.4, 6.4, 1.7, 1.7 Hz, 1H), 2.87–2.71 (m, 2H), 2.19–2.12 (m, 2H); 68% ee, retention time 7.7 min (major) and 8.7 min (minor) on Chiralpak AY3 (5% IPA/hexane, 1.0 mL/min).



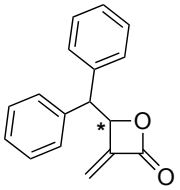
(+)-**1b**

4-Hexyl-3-methyleneoxetan-2-one ([+]1b). The general procedure was followed using racemic **1b** (34 mg, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc 94:4) provided (+)-**1b** as a colorless oil (13 mg, 38%): $[\alpha]^{20}_{D}$ = (+)-40.1 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.39 (dd, *J* = 1.6, 1.6 Hz, 1H), 4.92 (dddd, *J* = 6.6, 6.6, 1.8, 1.8 Hz, 1H), 1.80 (m, 2H), 1.46–1.37 (m, 2H), 1.33–1.24 (m, 6H), 0.84 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 146.5, 114.9, 79.7, 33.4, 31.6, 29.0, 24.6, 22.5, 14.1; 72% ee, retention time 5.5 min (minor) and 6.8 min (major) on Chiralpak AY3 (5% IPA/hexane, 0.5 mL/min).



(+)-**1e**

3-Methylene-4-tridecyloxetan-2-one ([+]-1e). The general procedure was followed using racemic **1e** (53 mg, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc 98:2) provided (+)-**1e** as a colorless oil (21 mg, 40%):[4] $[\alpha]^{20}_{D}$ = (+)-37.0 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 1.9, 1.9 Hz, 1H), 5.39 (dd, *J* = 1.7, 1.7 Hz, 1H), 4.92 (dddd, *J* = 6.5, 6.5, 1.6, 1.6 Hz, 1H), 1.81 (m, 2H), 1.46–1.40 (m, 2H), 1.33–1.22 (m, 20H), 0.84 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 146.6, 114.8, 79.7, 33.4, 32.0, 29.8, 29.7, 29.7, 29.6, 29.5, 29.5, 29.3; 56% ee, retention time 10.1 min (major) and 10.8 min (minor) on Chiralpak AY3 (5% IPA/hexane, 0.5 mL/min).



(+)-**1f**

4-Benzhydryl-3-methyleneoxetan-2-one ([+]-1f). The general procedure was followed using racemic **1f** (0.2 mmol, 50 mg). Purification by column chromatography on silica gel (petroleum ether/EtOAc 95:5) provided (+)-**1f** as a white solid (19 mg, 37%):[5] $[\alpha]^{20}_{D}$ = (+)-51.4 (*c* = 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.23 (m, 10H), 5.74 (dd, *J* = 2.0, 1.4 Hz, 1H), 5.53 (ddd, *J* = 9.6, 2.0, 1.4 Hz, 1H), 4.72 (dd, *J* = 2.0, 1.4 Hz, 1H), 4.20 (d, *J* = 9.6, 1H); 74% ee, retention time 6.5 min (major) and 7.1 min (minor) on Chiralpak AY3 (5% IPA/hexane, 1.0 mL/min).

VI. References

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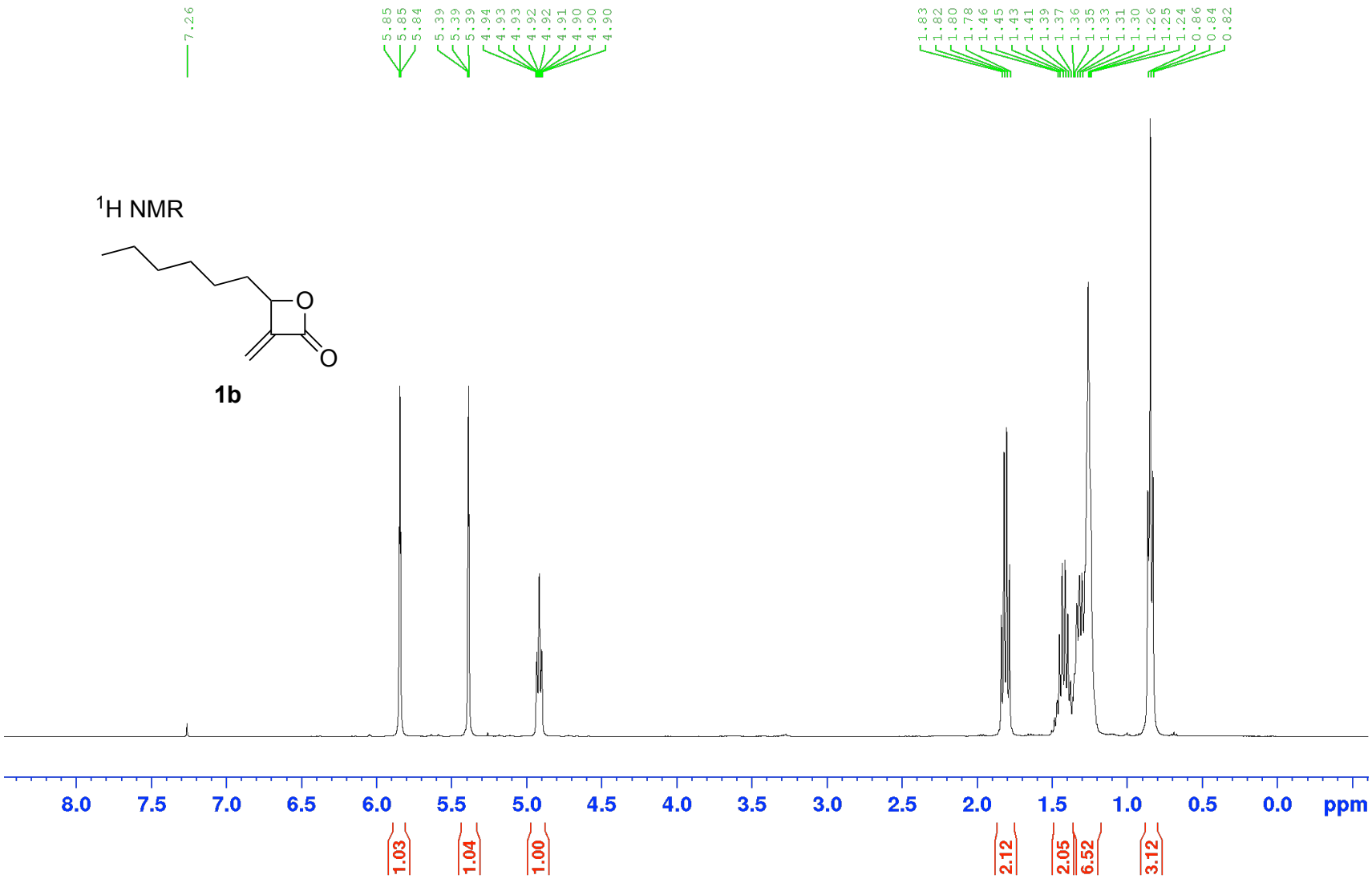
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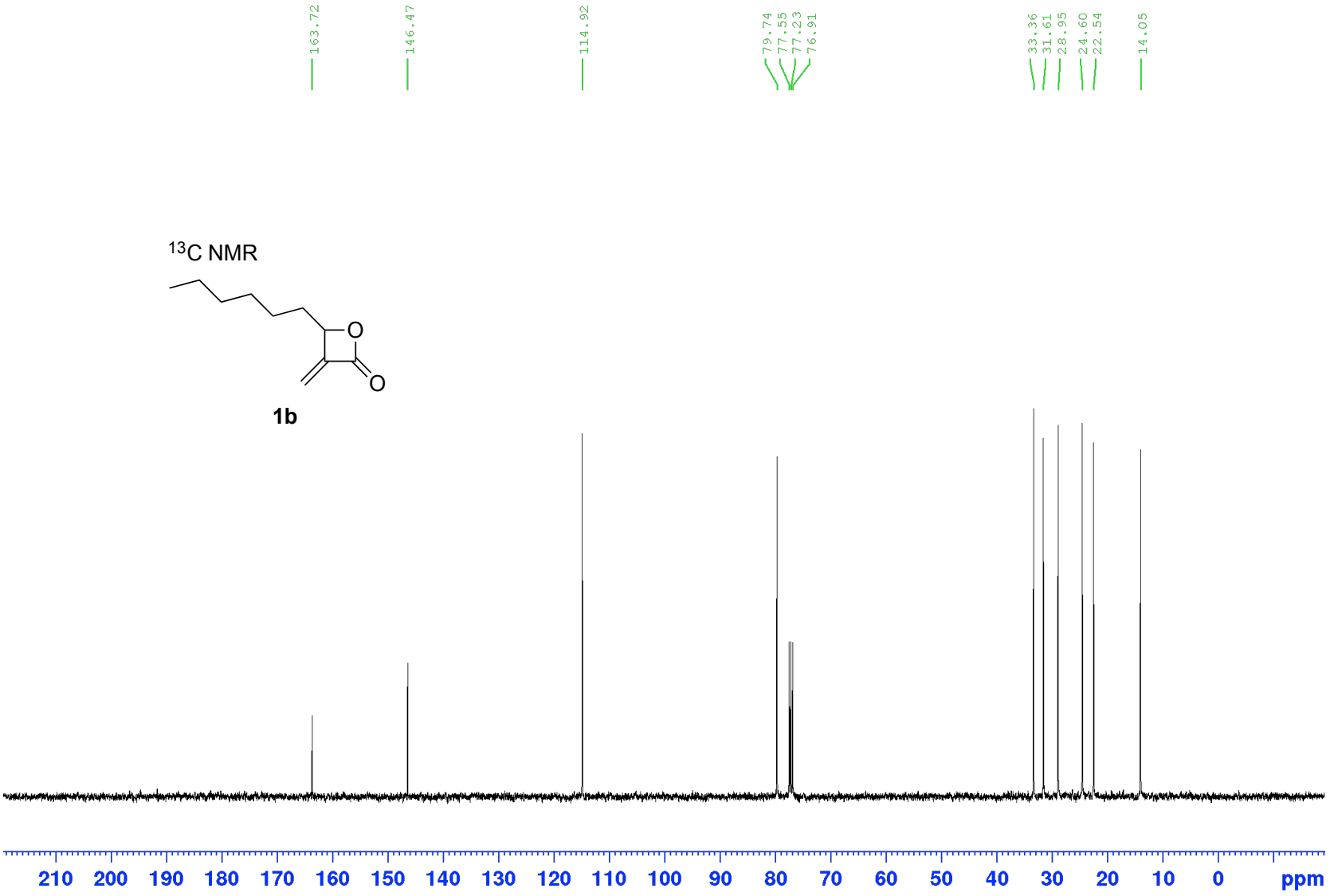
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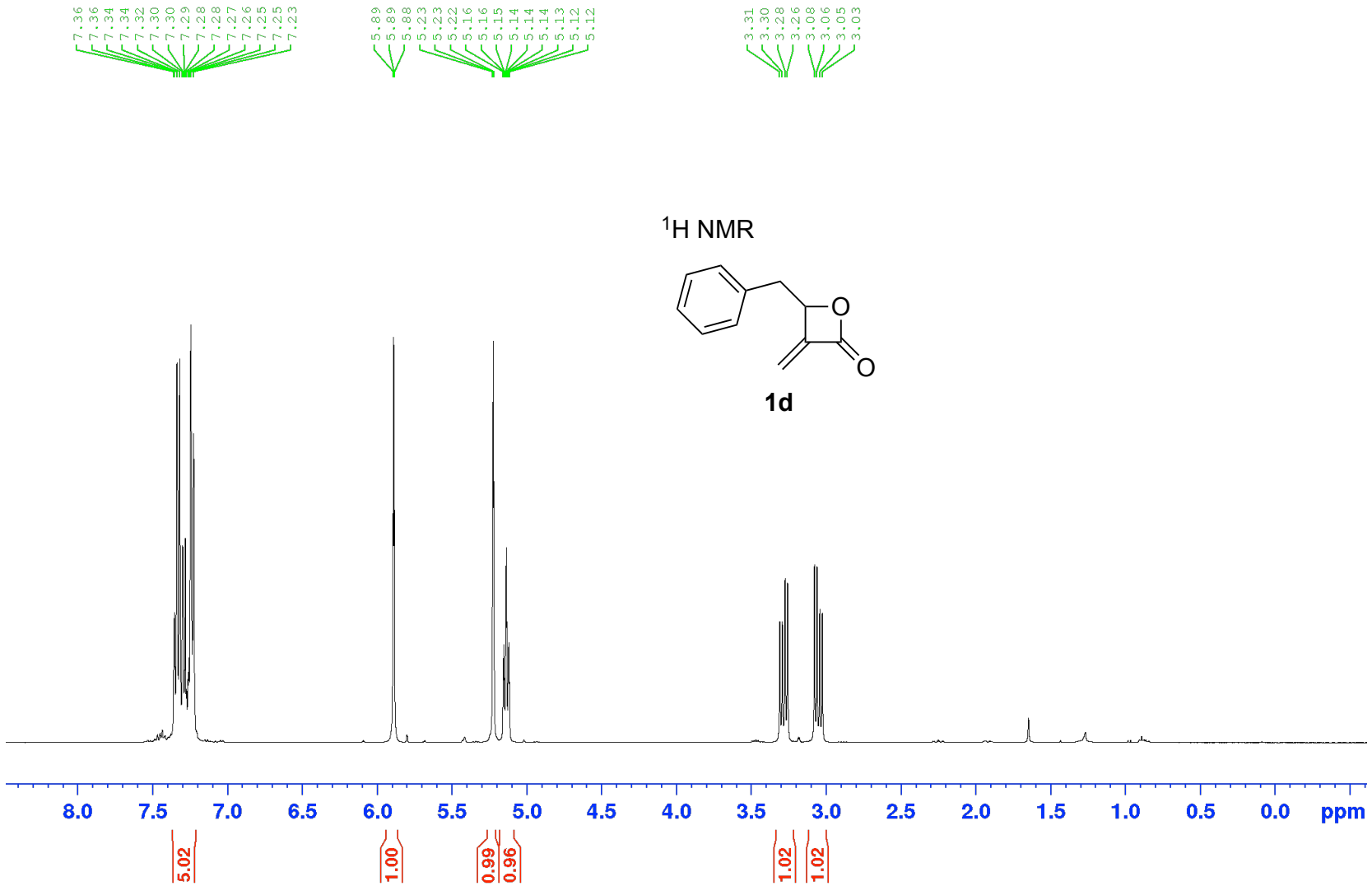
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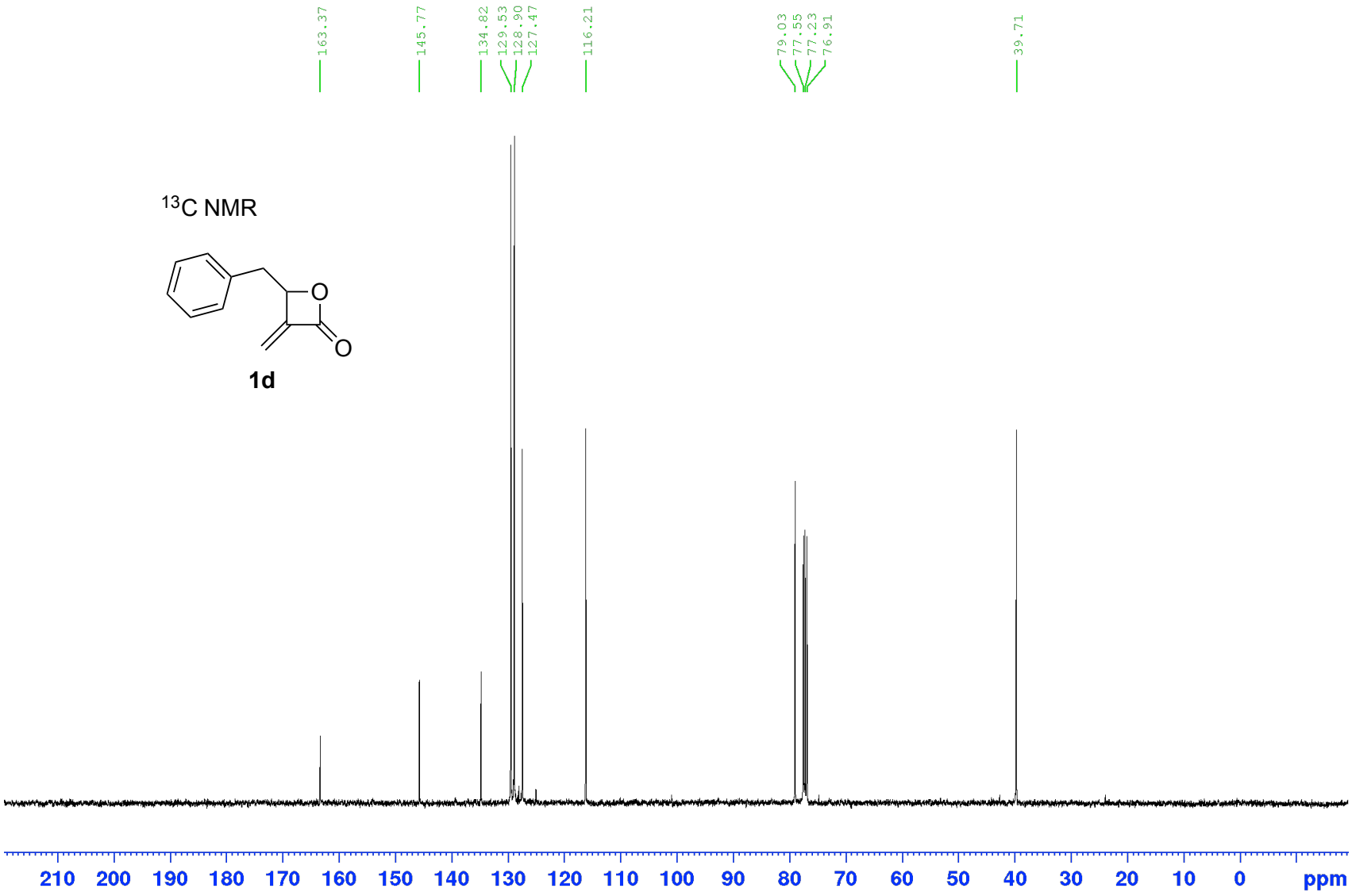
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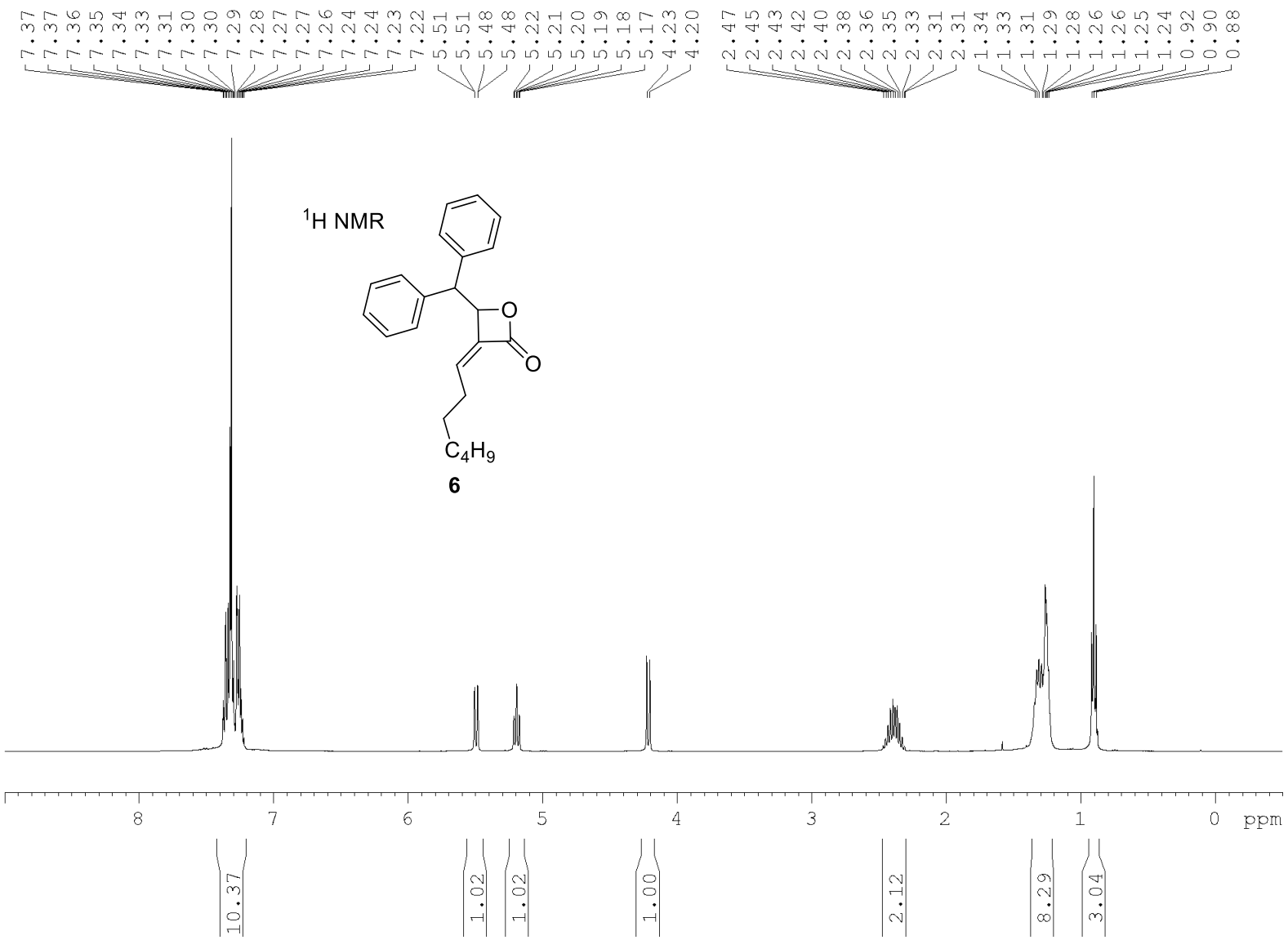
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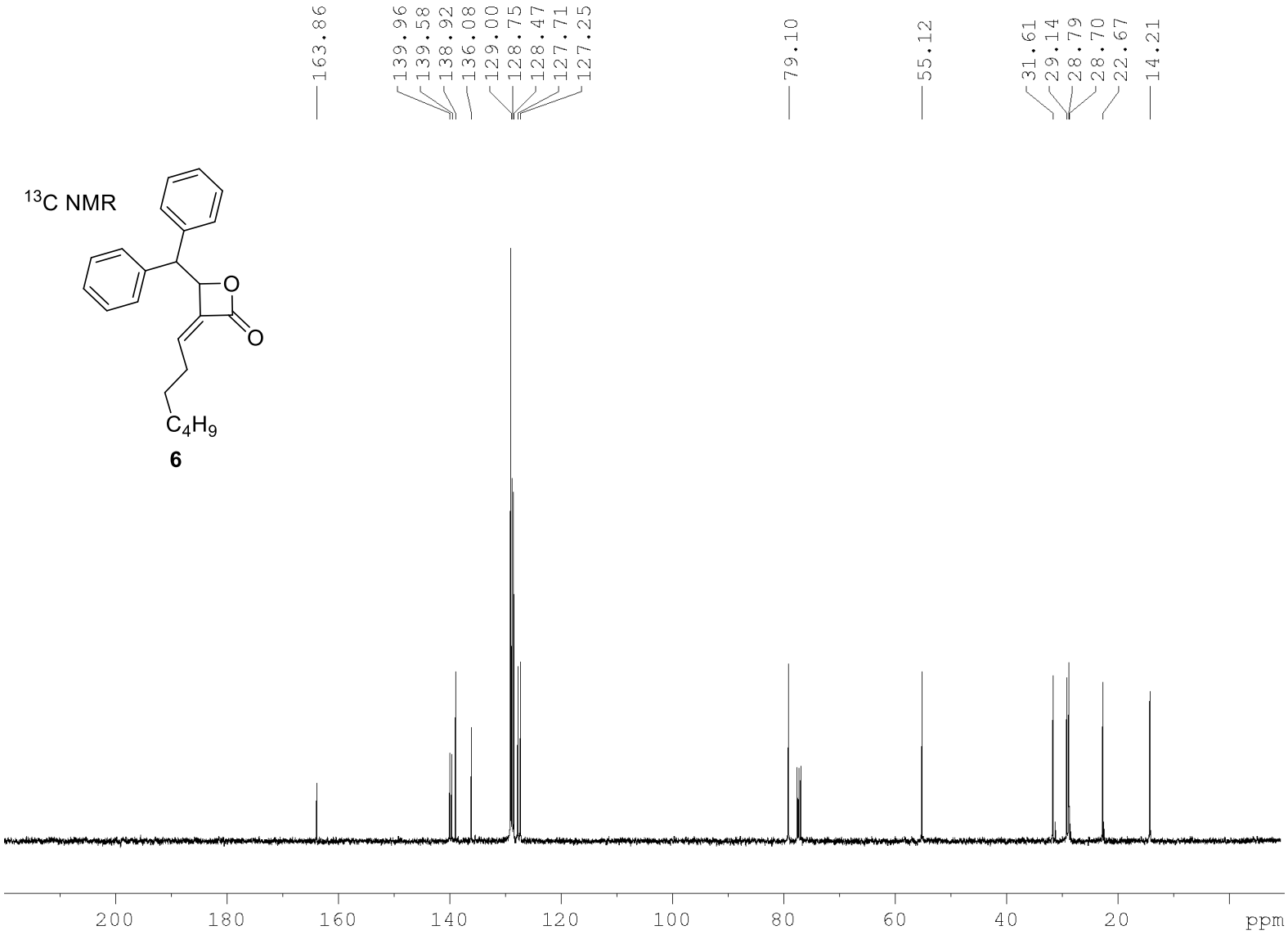
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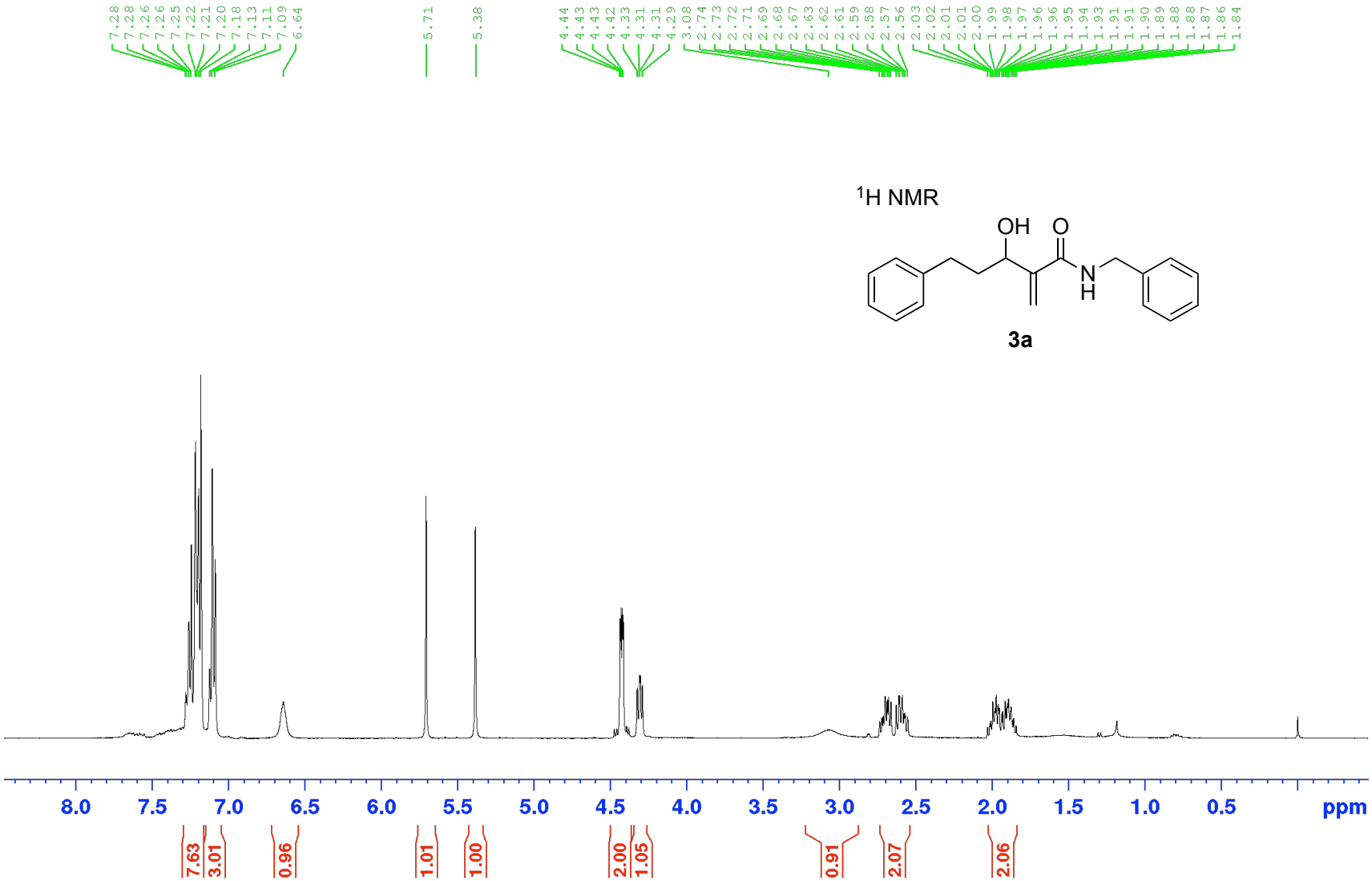
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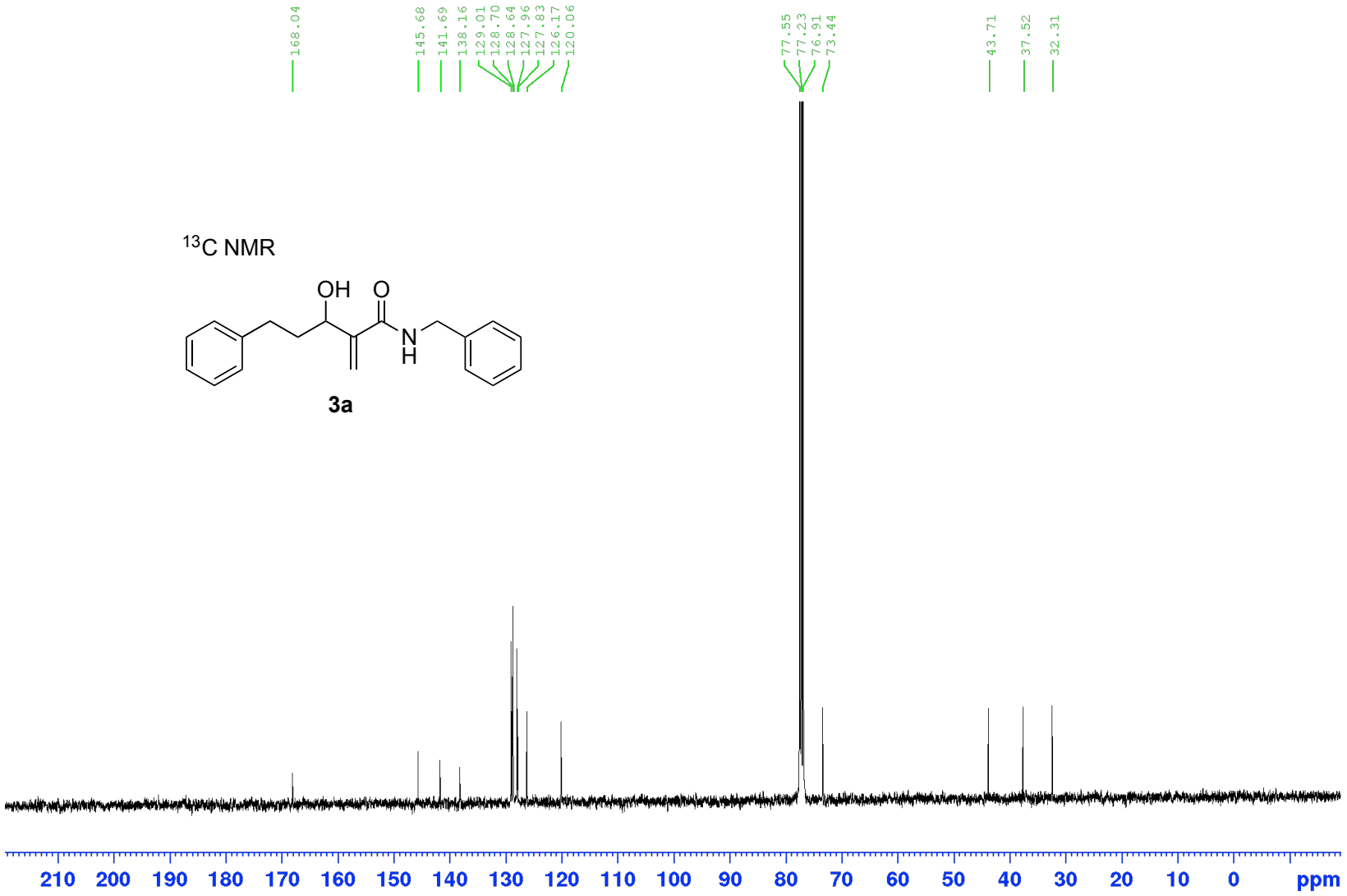
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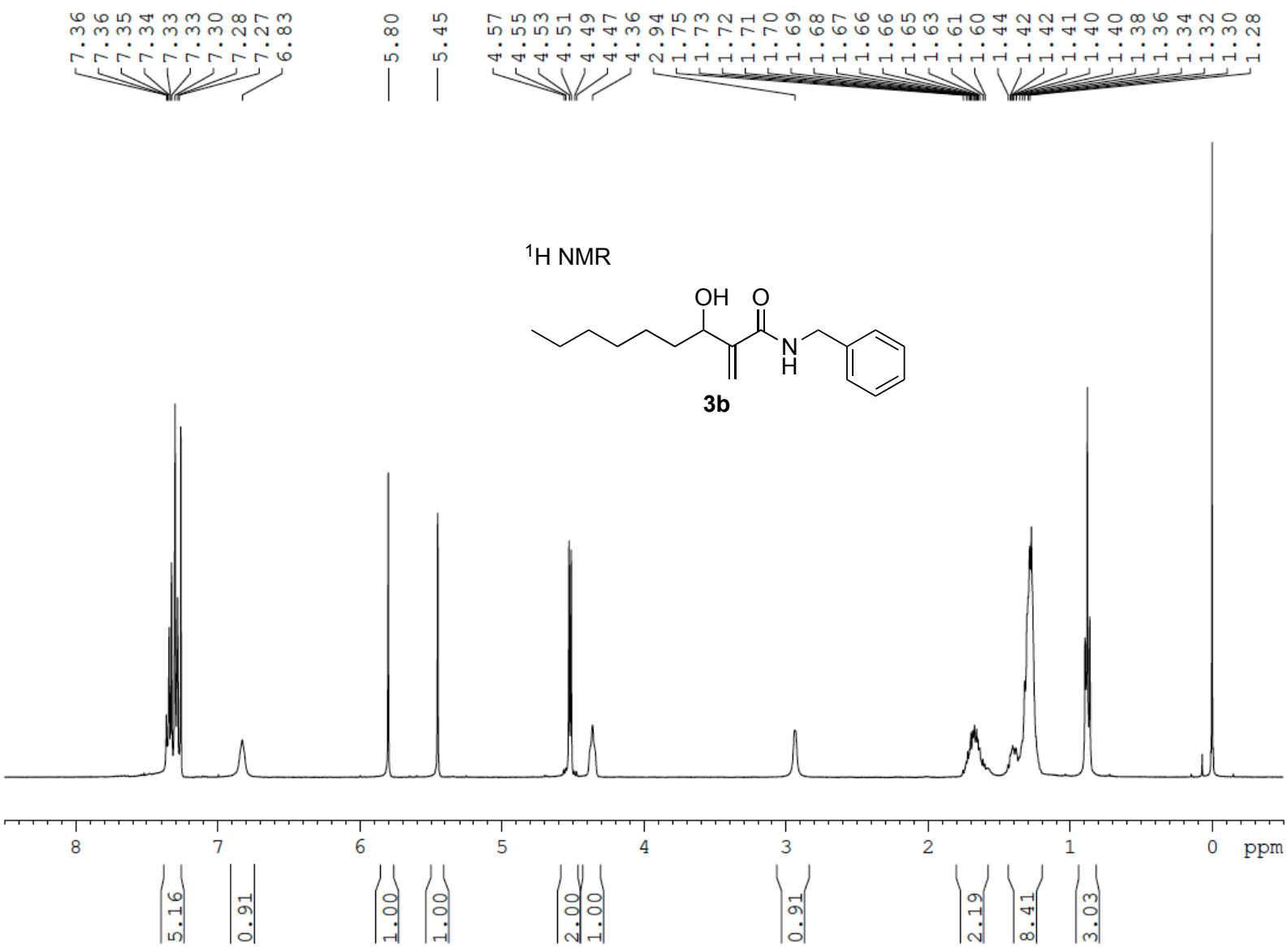
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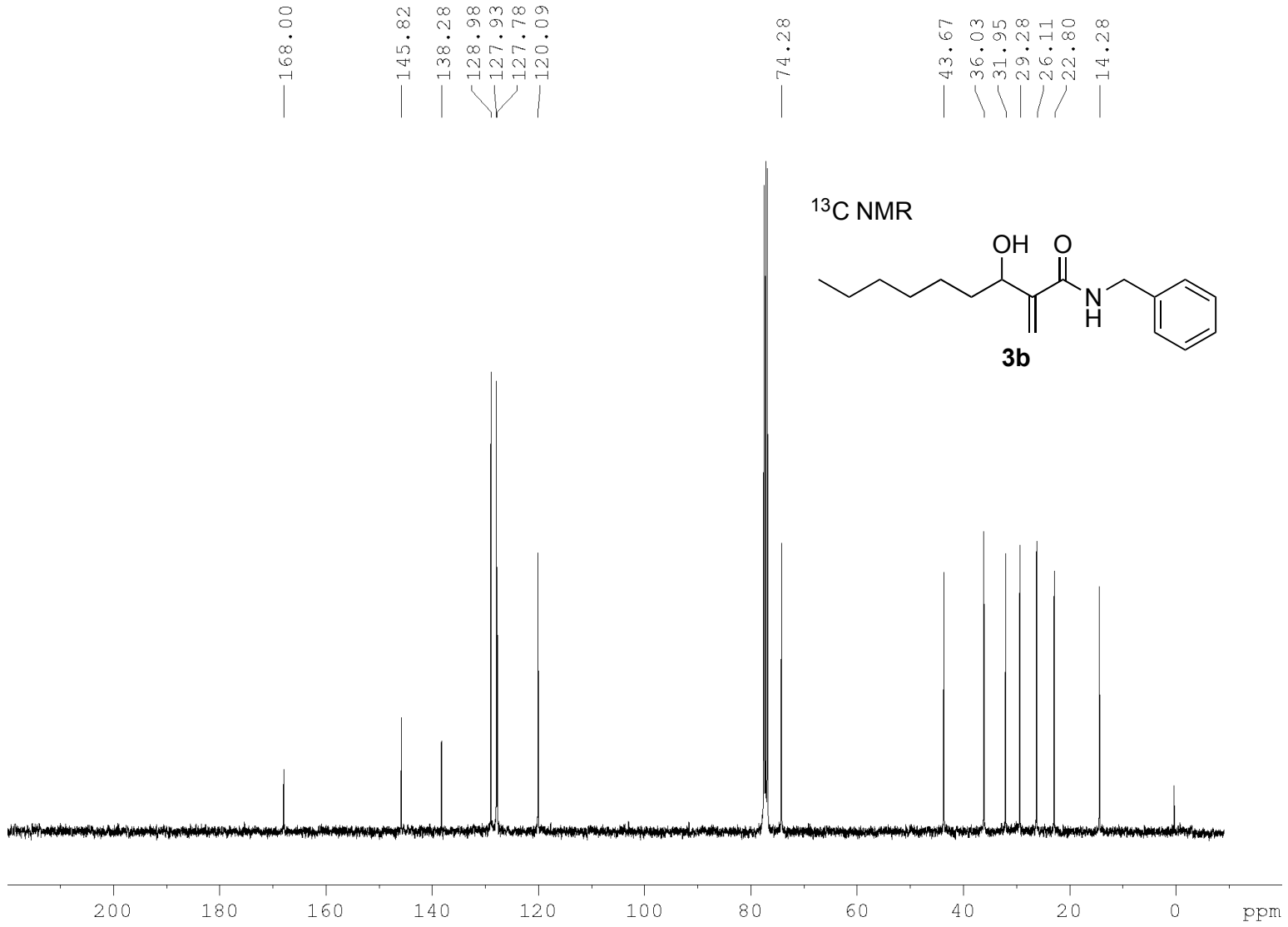
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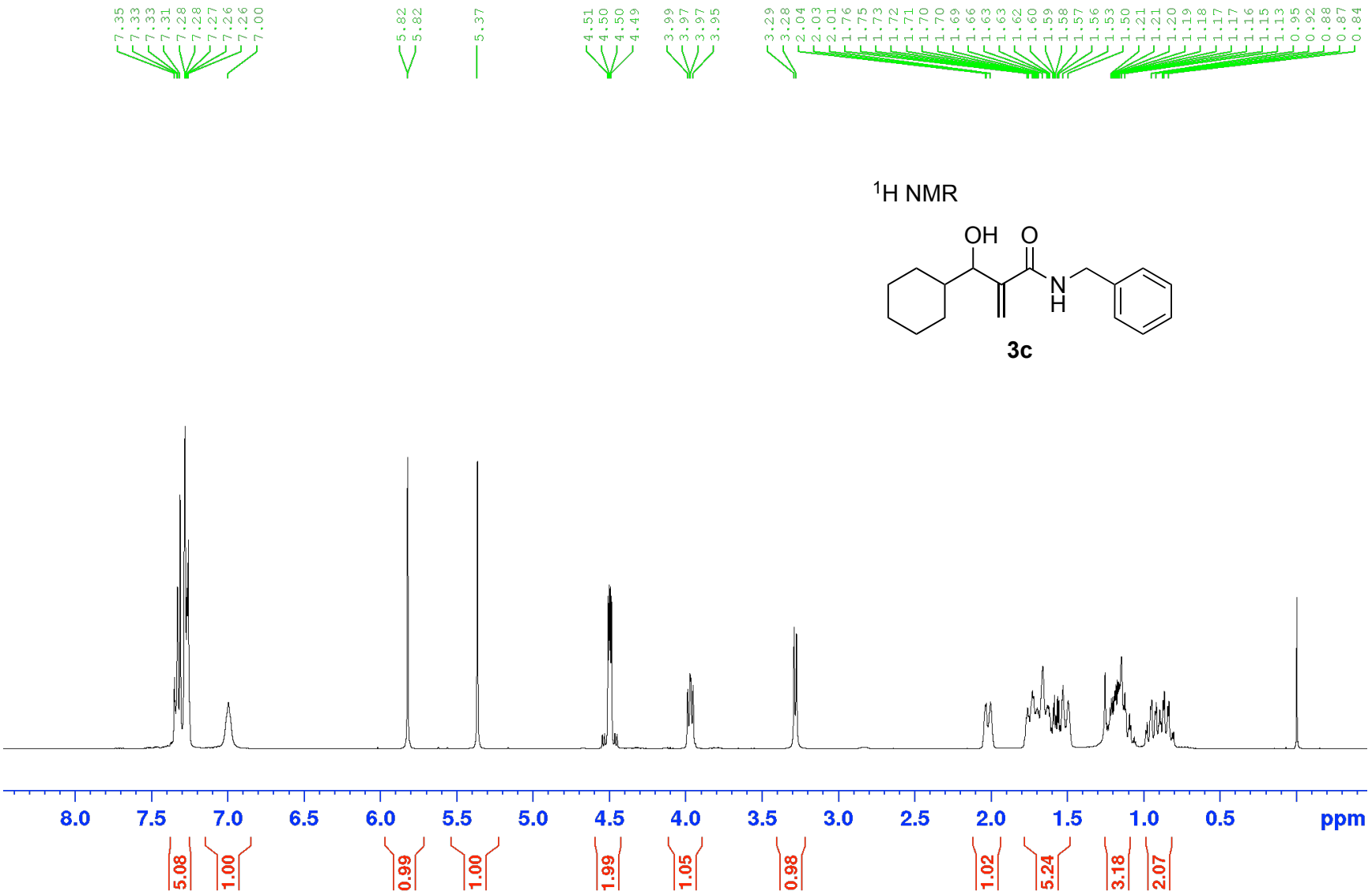
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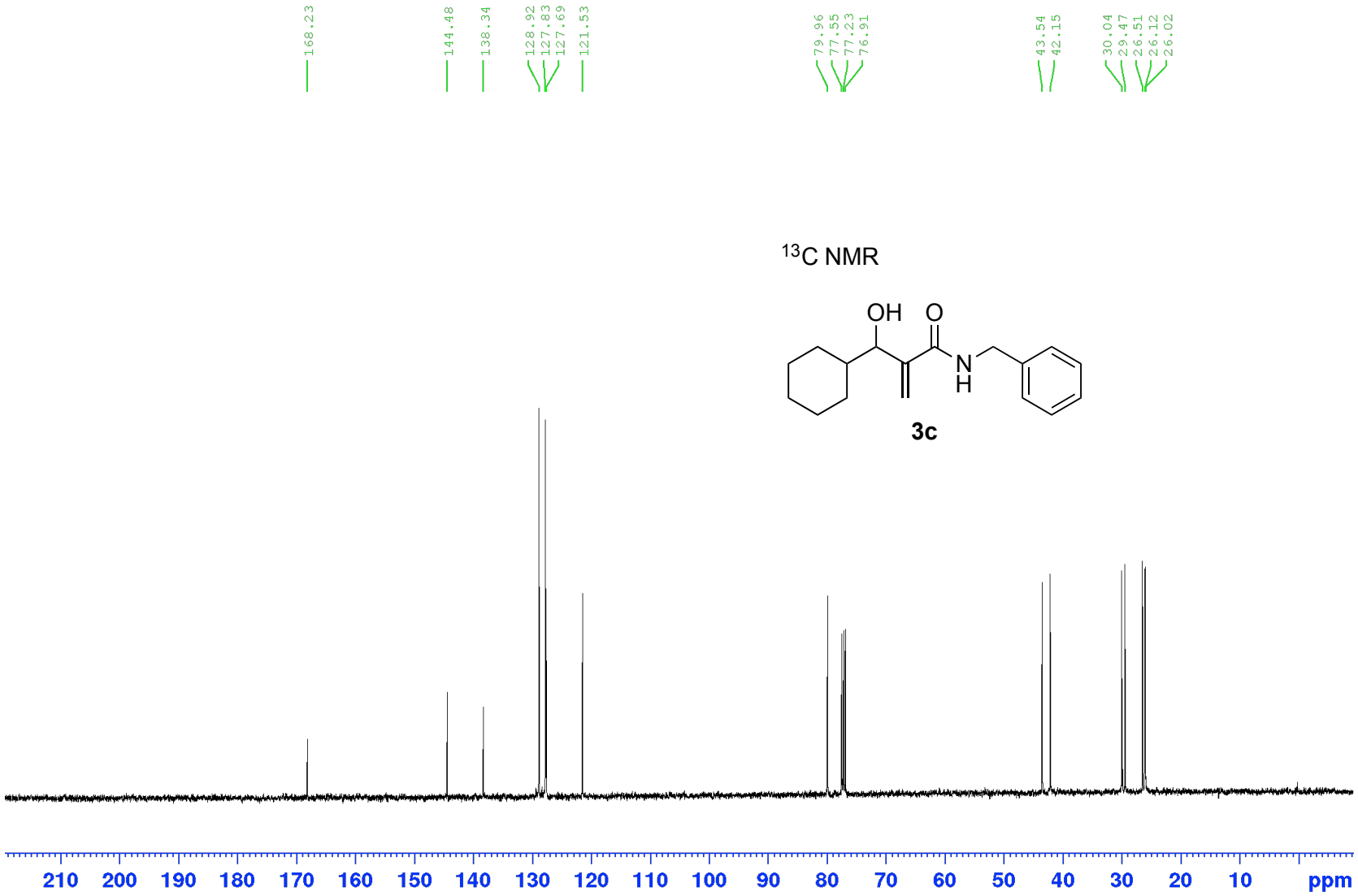
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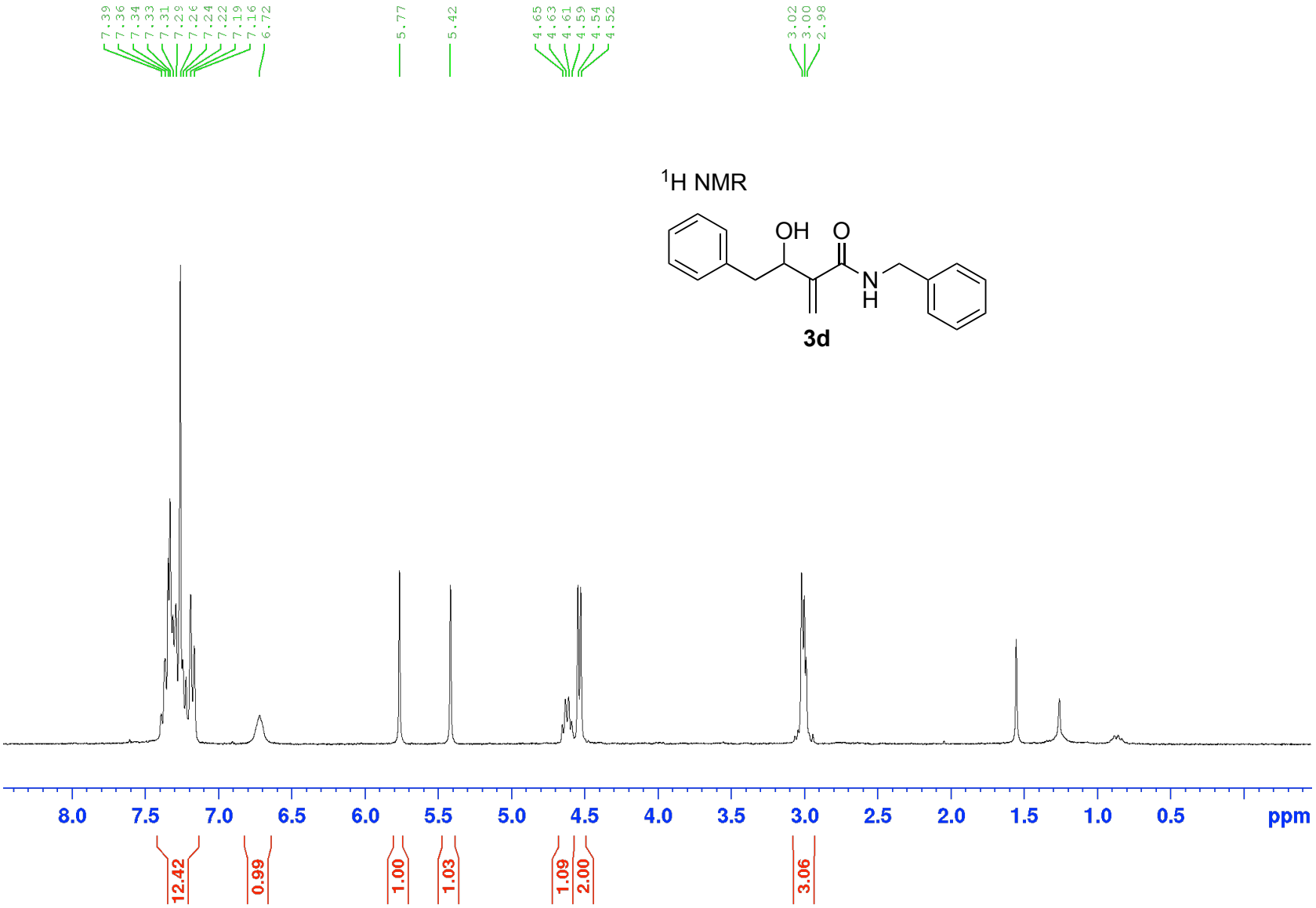
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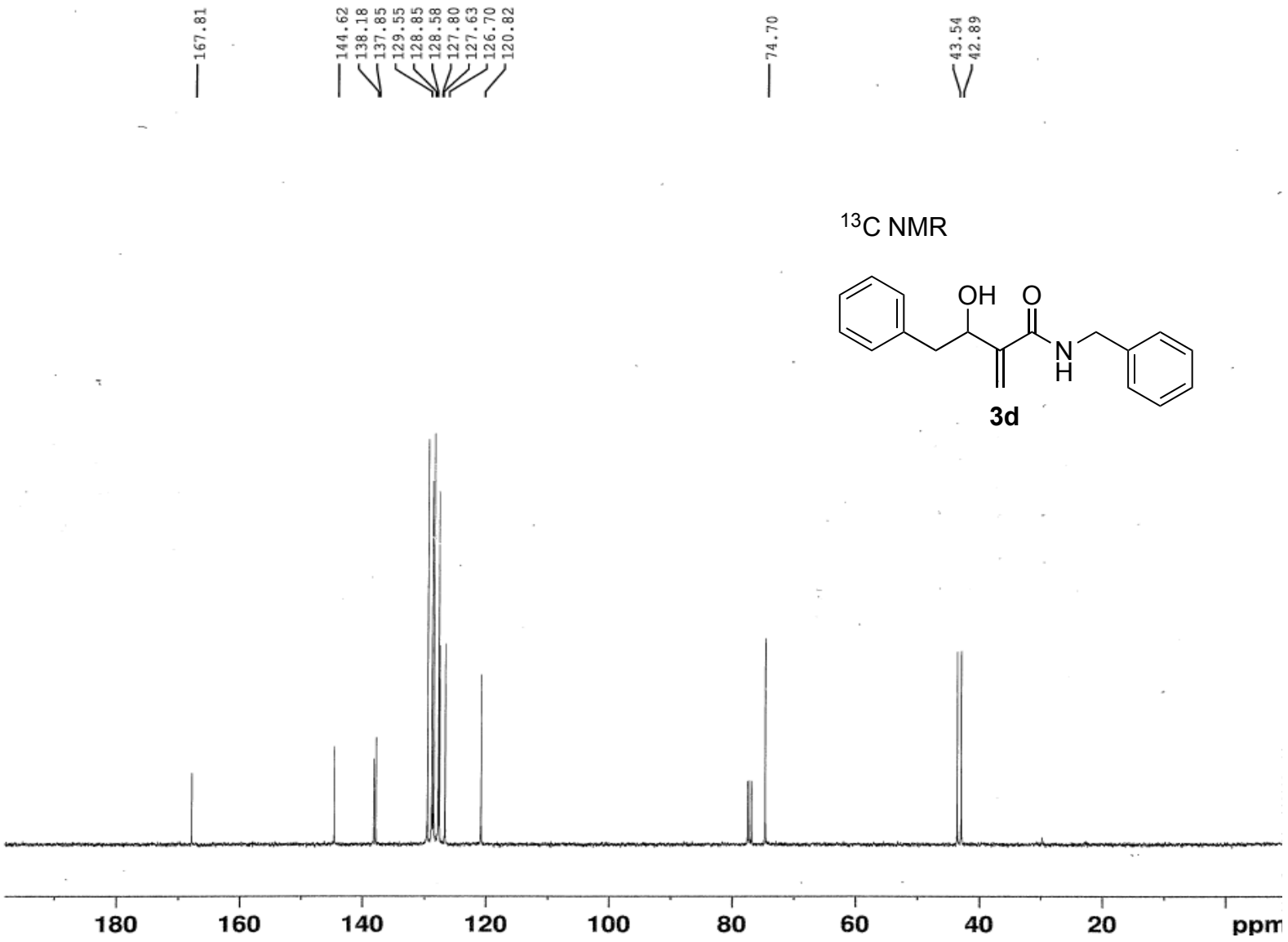
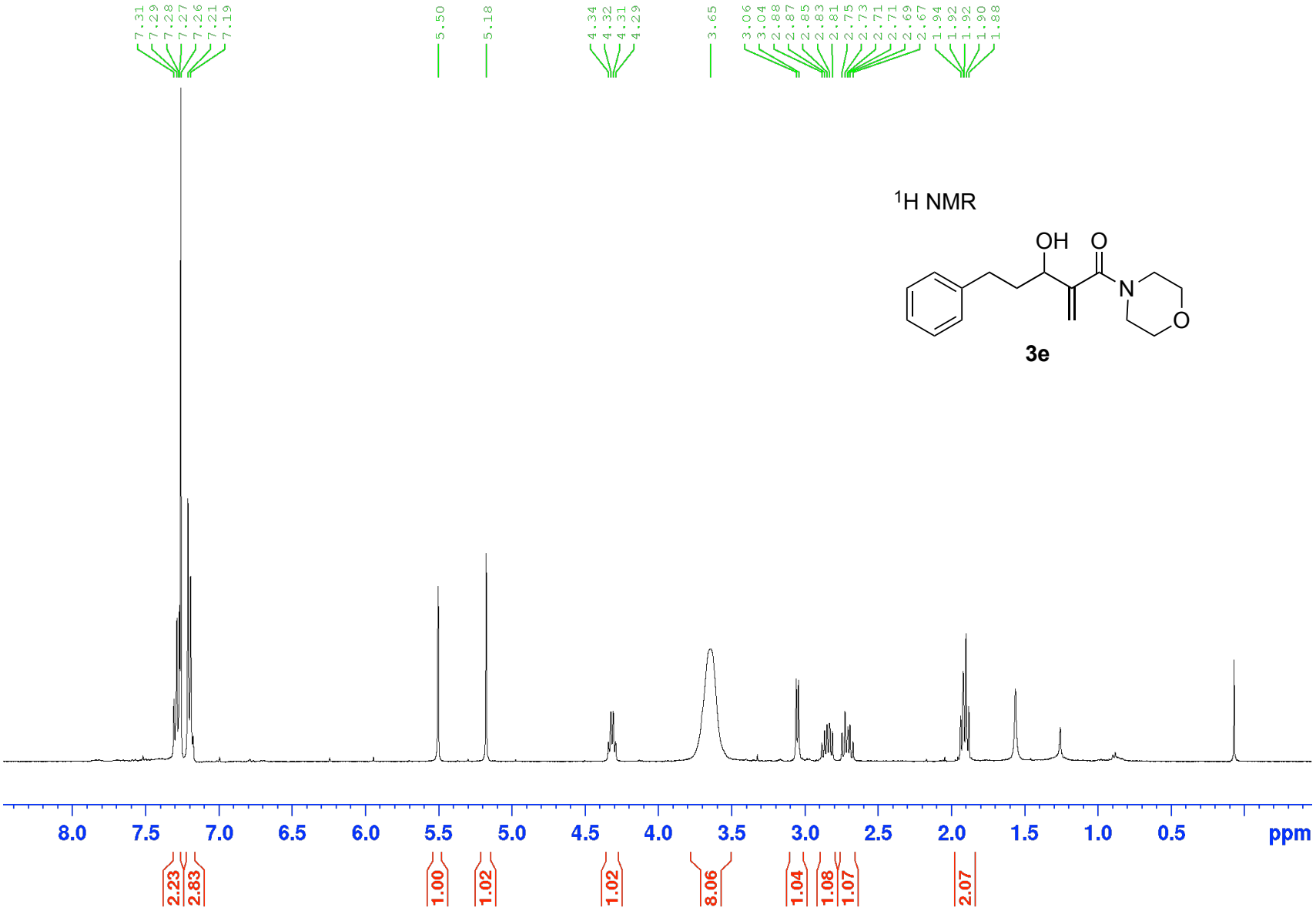
5.42
4.65
4.63
4.61
4.59
4.54
4.52
3.02
3.00
2.98
1H NMR
OH
O
N
H
3d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
12.42
0.99
1.00
1.03
1.09
2.00
3.06


167.81
144.62
138.18
137.85
129.55
128.85
128.58
127.80
127.63
126.70
120.82
74.70
43.54
42.89
180
160
140
120
100
80
60
40
20
ppm

^{13}C NMR

OH
O
N
H

3d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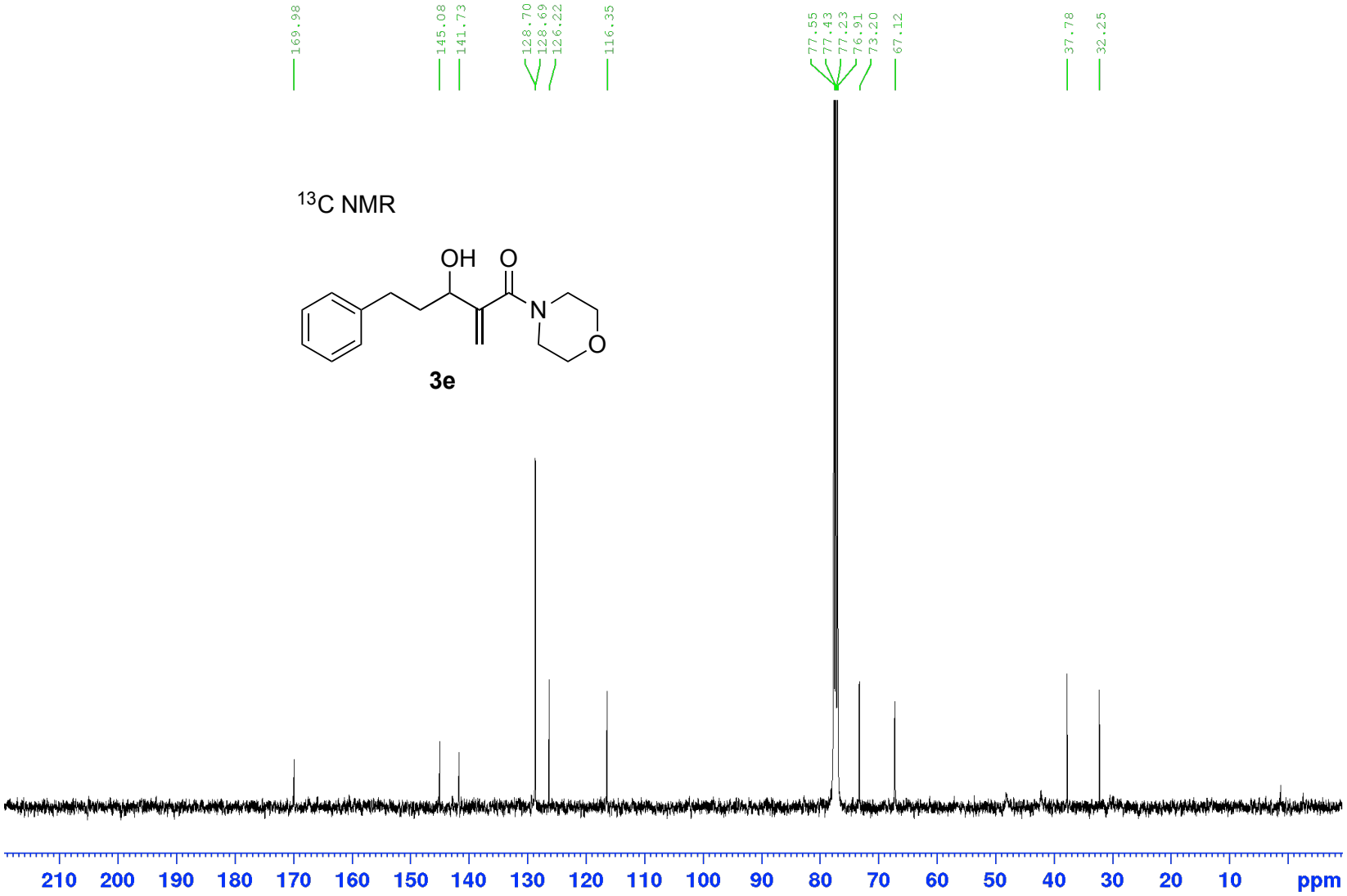
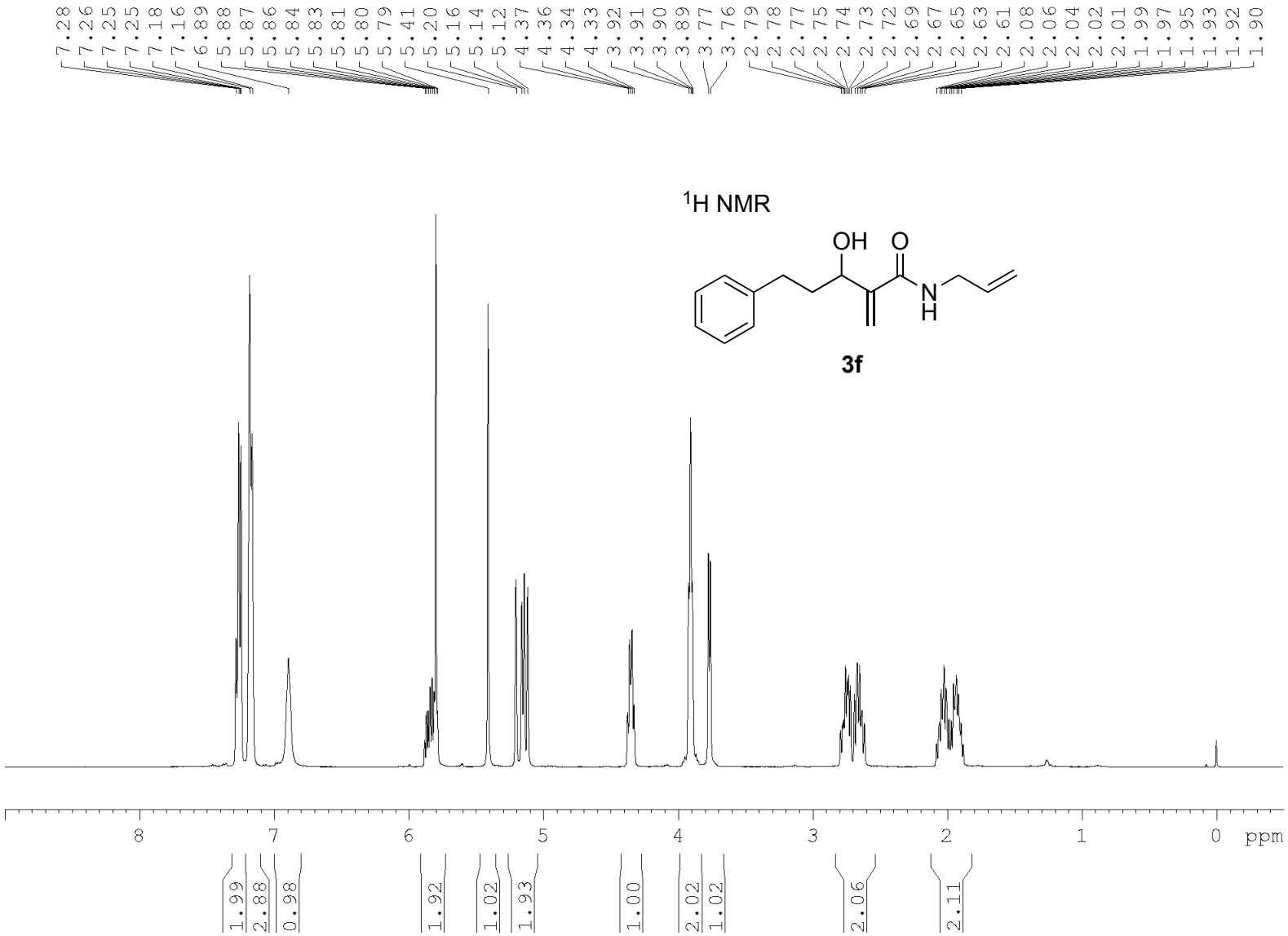
7.29
7.28
7.27
7.26
7.21
7.19
5.50
5.18
4.34
4.32
4.31
4.29
3.65
3.06
3.04
2.88
2.87
2.85
2.83
2.81
2.75
2.73
2.71
2.71
2.69
2.67
1.94
1.92
1.92
1.90
1.88
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.23
2.83
1.00
1.02
1.02
8.06
1.04
1.08
1.07
2.07

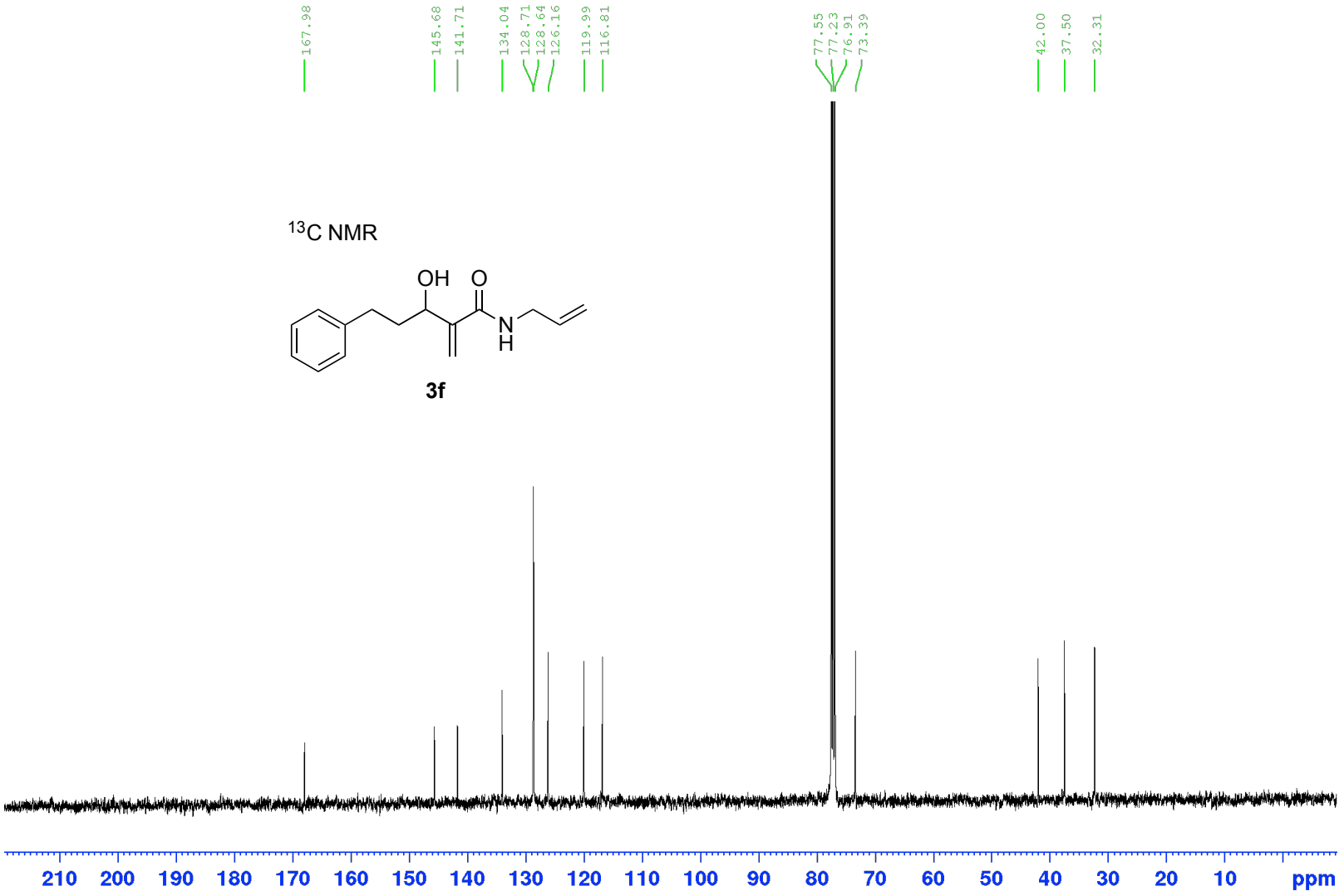
^{1}H NMR

OH
O
N
O

3e


169.98
145.08
141.73
128.70
128.69
126.22
116.35
77.55
77.43
77.23
76.91
73.20
67.12
37.78
32.25
13C NMR
OH
O
N
O
3e
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


7.28
7.26
7.25
7.25
7.18
7.16
6.89
5.88
5.87
5.86
5.84
5.83
5.81
5.80
5.79
5.41
5.20
5.16
5.14
5.12
4.37
4.36
4.34
4.33
3.92
3.91
3.90
3.89
3.77
3.76
2.79
2.78
2.77
2.75
2.74
2.73
2.72
2.69
2.67
2.65
2.63
2.61
2.08
2.06
2.04
2.02
2.01
1.99
1.97
1.95
1.93
1.92
1.90
1H NMR
OH
O
N
H
3f
8
7
6
5
4
3
2
1
0
ppm
1.99
2.88
0.98
1.92
1.02
1.93
1.00
2.02
1.02
2.06
2.11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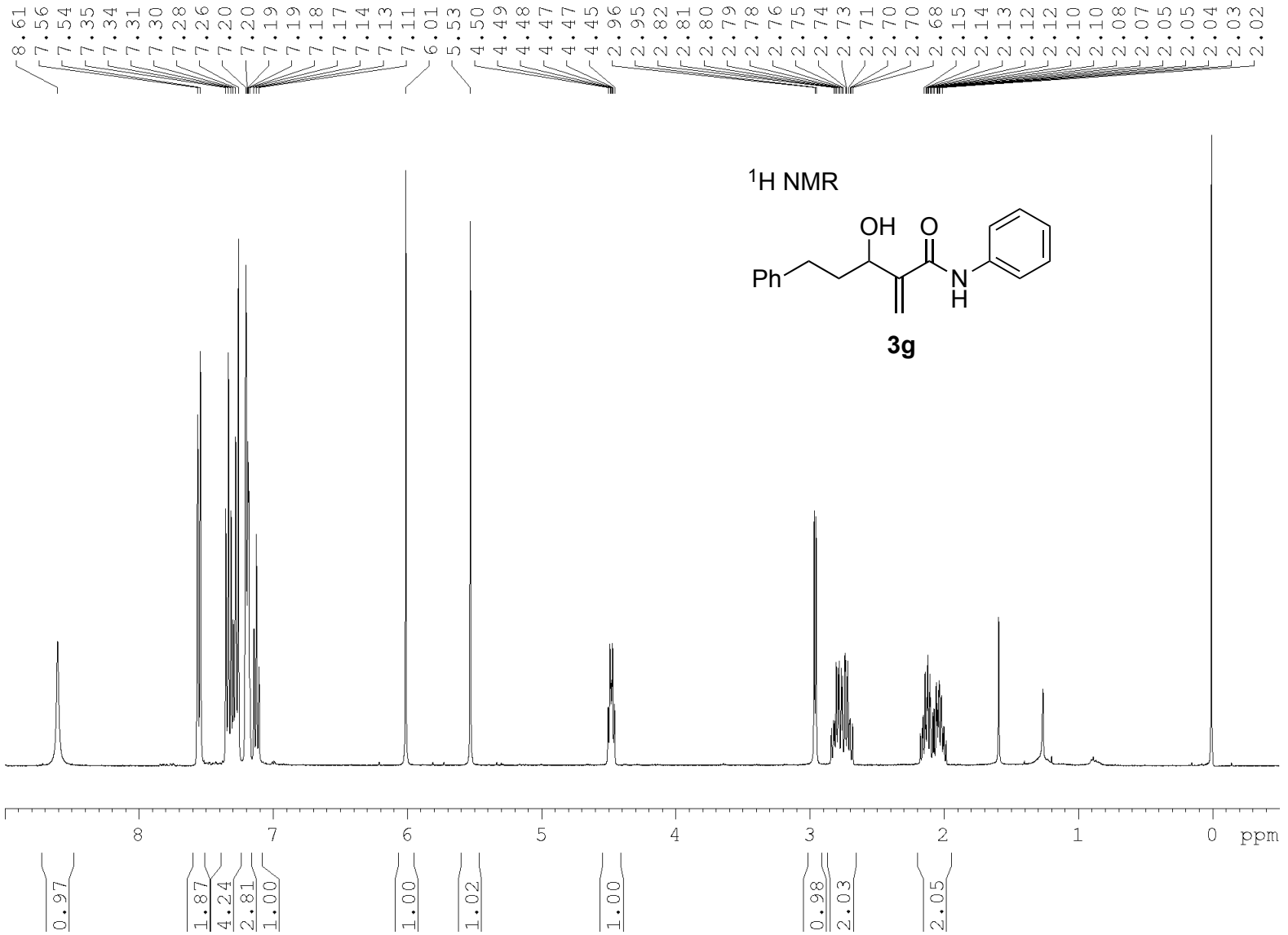
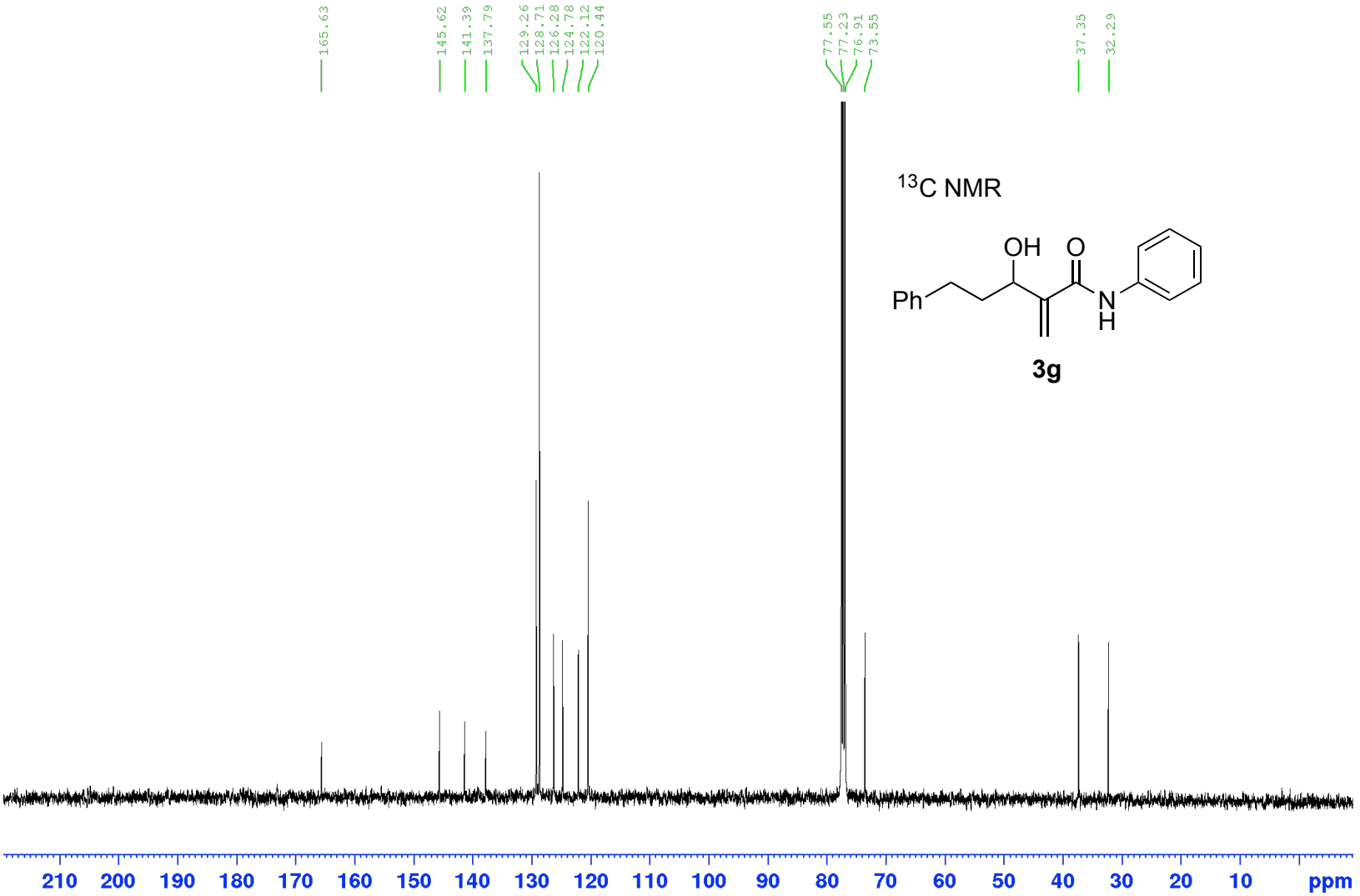
145.68
141.71
134.04
128.71
128.64
126.16
119.99
116.81
77.55
77.23
76.91
73.39
42.00
37.50
32.31
13C NMR
OH
O
N
H
3f
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


8.61
7.56
7.54
7.35
7.34
7.31
7.30
7.28
7.26
7.20
7.20
7.19
7.19
7.18
7.17
7.14
7.13
7.11
6.01
5.53
4.50
4.49
4.48
4.47
4.47
4.45
2.96
2.95
2.82
2.81
2.80
2.79
2.78
2.76
2.75
2.74
2.73
2.71
2.70
2.70
2.68
2.15
2.14
2.13
2.12
2.12
2.10
2.10
2.08
2.07
2.05
2.05
2.04
2.03
2.02
1H NMR
OH
O
Ph
N
H
3g
8
7
6
5
4
3
2
1
0
ppm
0.97
1.87
4.24
2.81
1.00
1.00
1.02
1.00
0.98
2.03
2.05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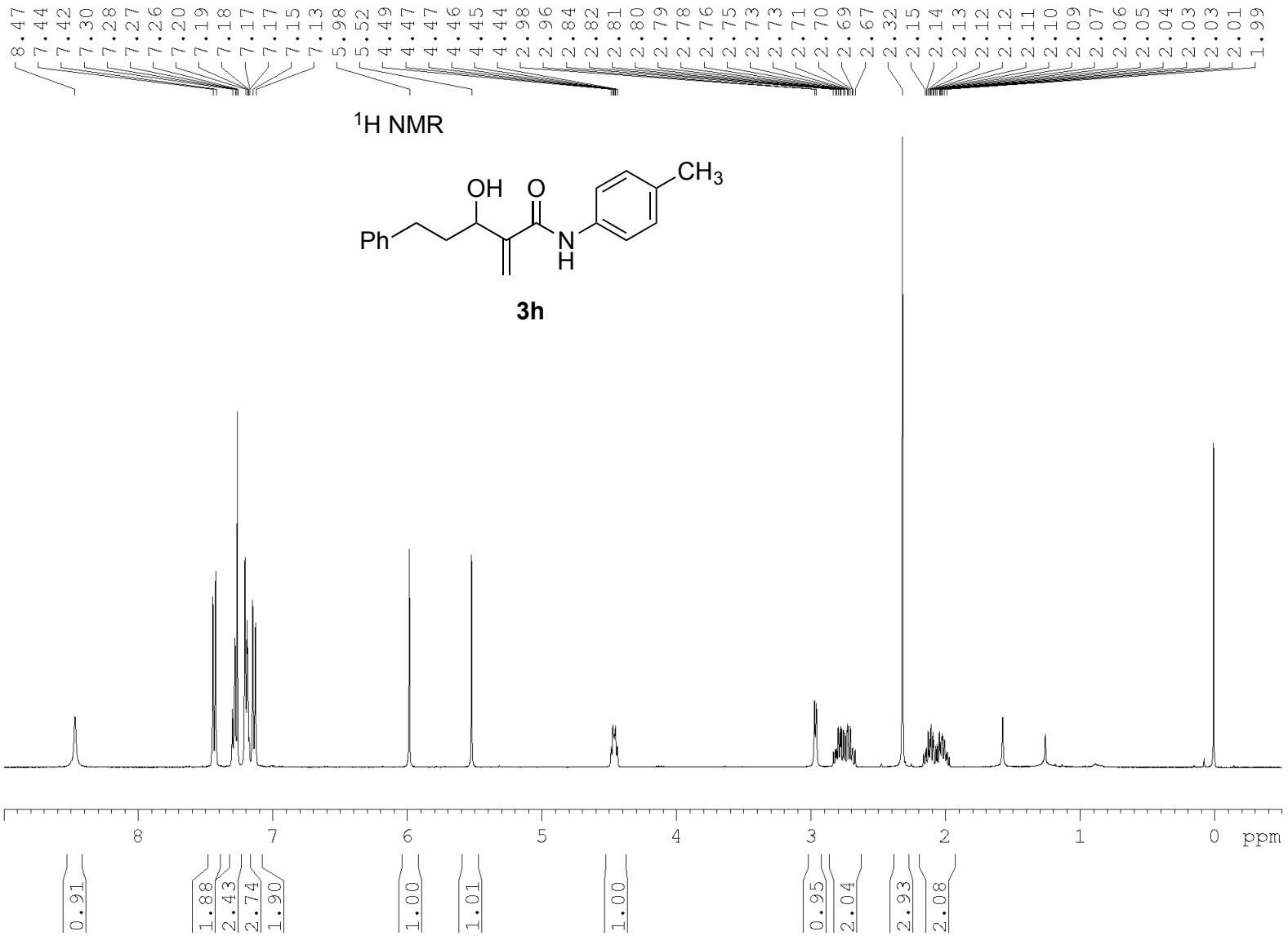
145.62
141.39
137.79
129.26
128.71
126.28
124.78
122.12
120.44
77.55
77.23
76.91
73.55
37.35
32.29
13C NMR
OH
O
Ph
N
H
3g
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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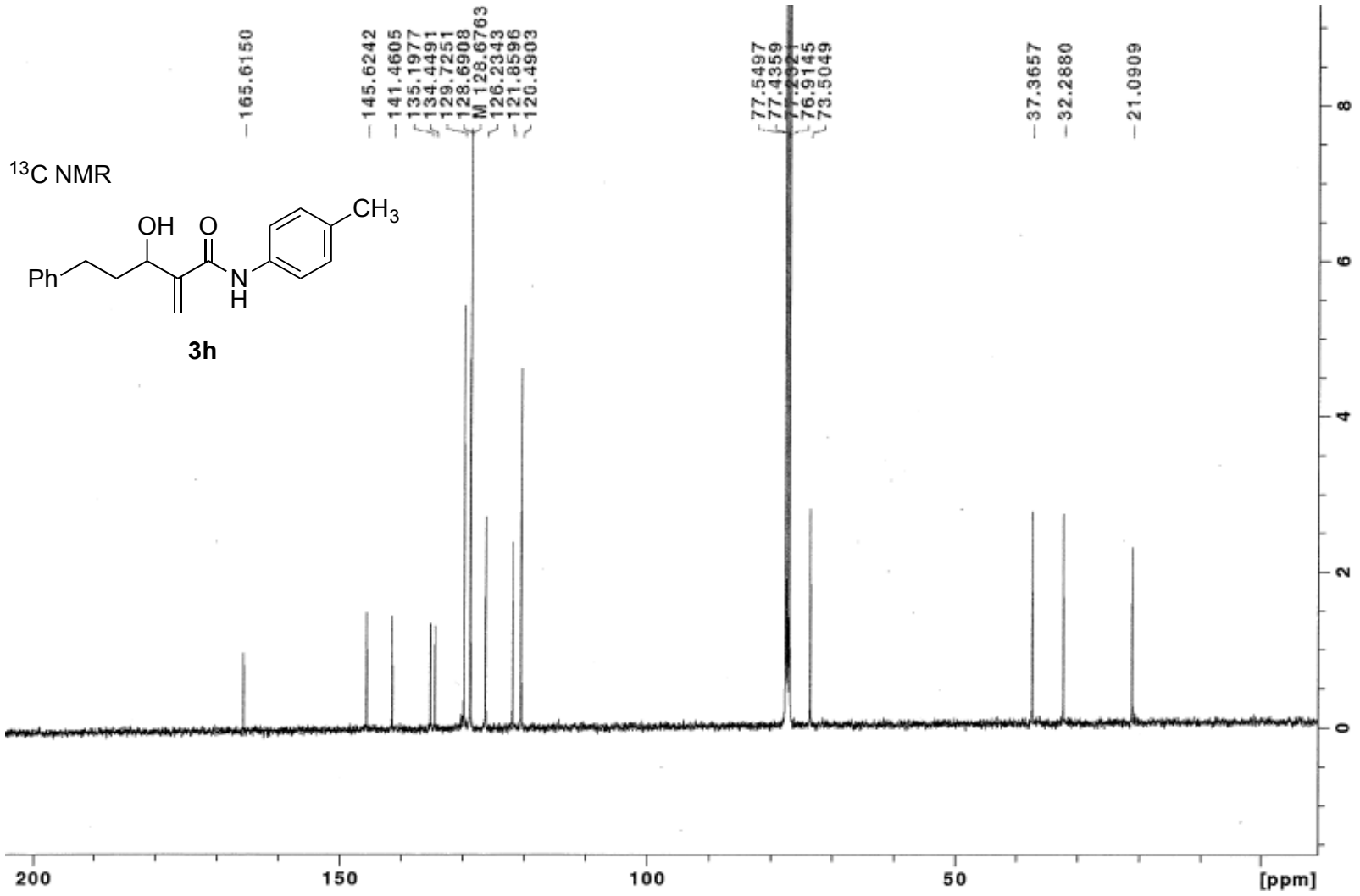
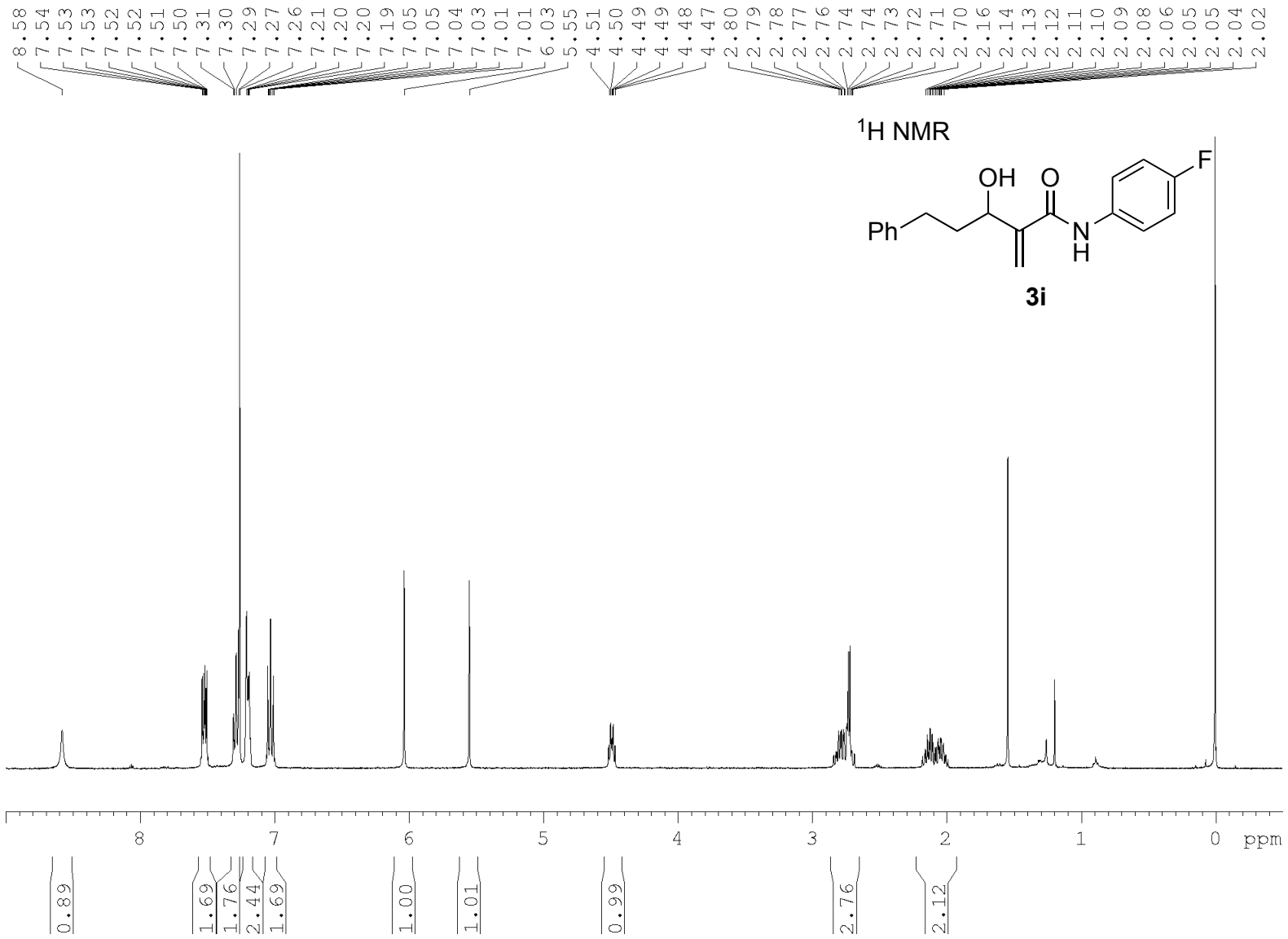
7.44
7.42
7.30
7.28
7.27
7.26
7.20
7.19
7.18
7.17
7.17
7.15
7.13
5.98
5.52
4.49
4.47
4.47
4.46
4.45
4.44
2.98
2.96
2.84
2.82
2.81
2.80
2.79
2.78
2.76
2.75
2.73
2.73
2.71
2.70
2.69
2.67
2.32
2.15
2.14
2.13
2.12
2.12
2.11
2.10
2.09
2.07
2.06
2.05
2.04
2.03
2.03
2.01
1.99
1H NMR
OH
O
CH3
Ph
N
H
3h
8
7
6
5
4
3
2
1
0
ppm
0.91
1.88
2.43
2.74
1.90
1.00
1.01
1.00
0.95
2.04
2.93
2.08


^{13}C NMR
OH
O
N
H
Ph
CH$_3$
3h
165.6150
145.6242
141.4605
135.1977
134.4491
129.7251
128.6908
M 128.6763
126.2343
121.8596
120.4903
77.5497
77.4359
76.9145
73.5049
37.3657
32.2880
21.0909
200
150
100
50
[ppm]
0
2
4
6
8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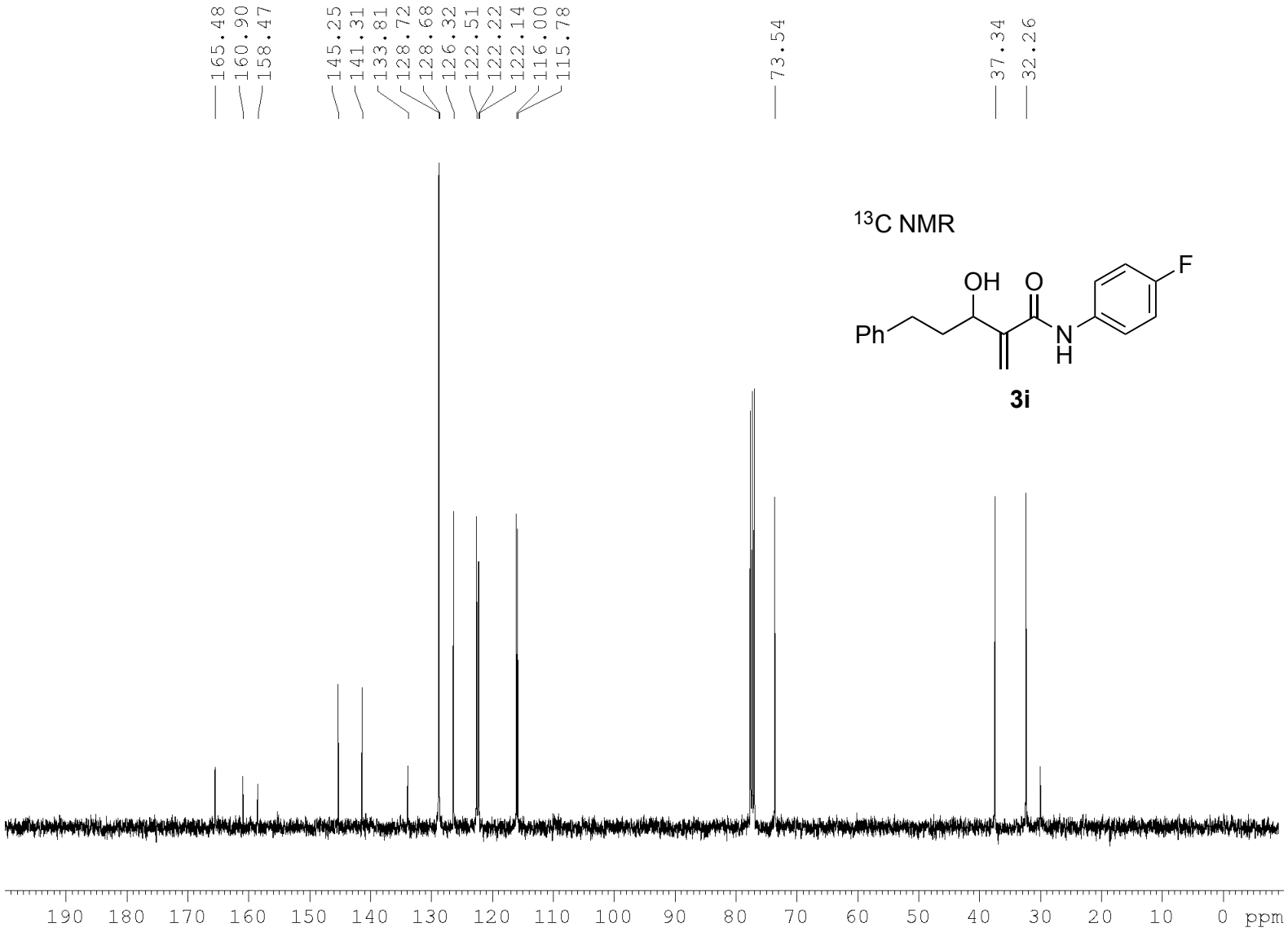
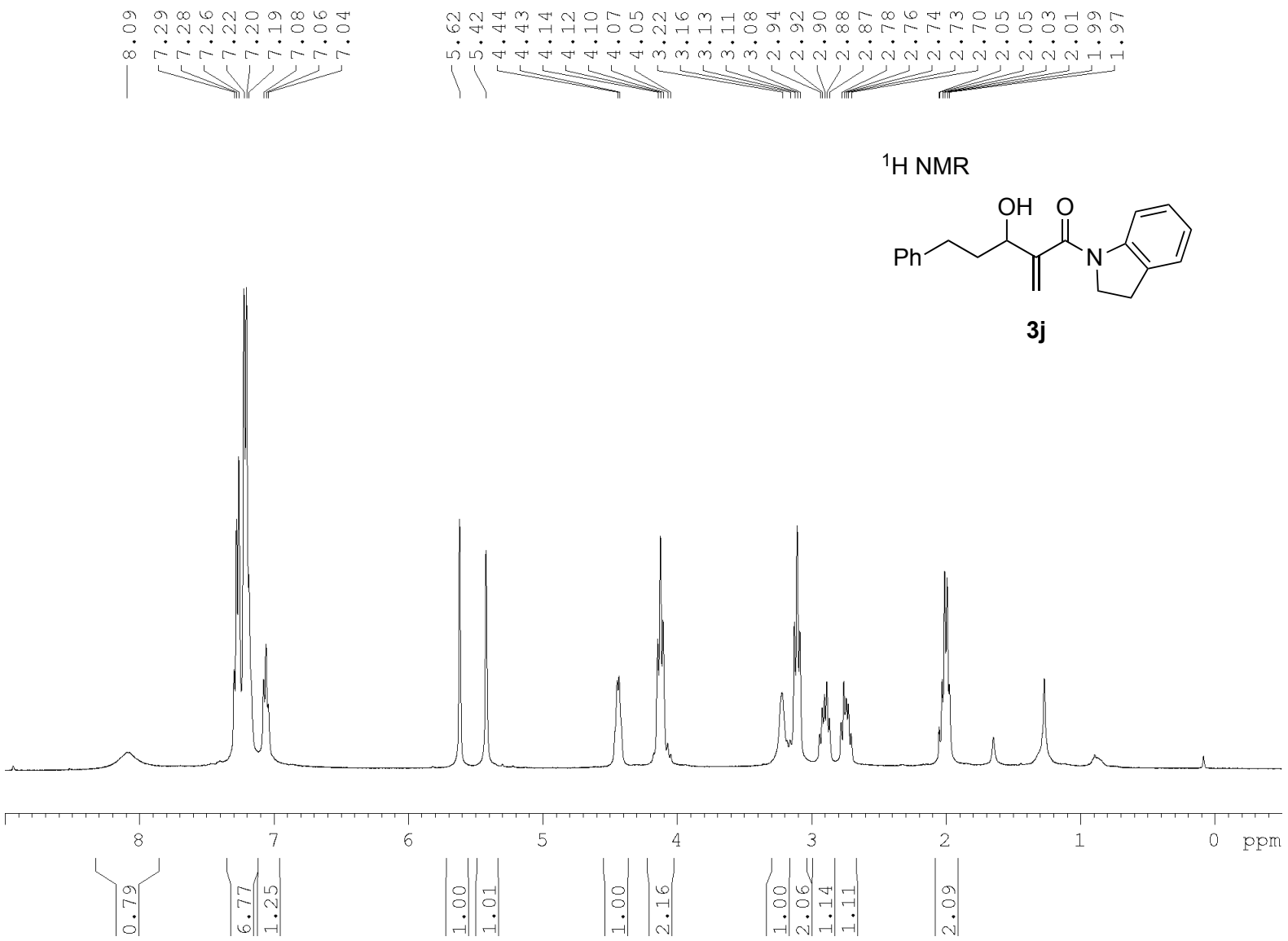
7.54
7.53
7.53
7.52
7.52
7.51
7.50
7.31
7.30
7.29
7.27
7.26
7.21
7.20
7.20
7.19
7.05
7.05
7.04
7.03
7.01
7.01
6.03
5.55
4.51
4.50
4.49
4.49
4.48
4.47
2.80
2.79
2.78
2.77
2.76
2.74
2.74
2.73
2.72
2.71
2.70
2.16
2.14
2.13
2.12
2.11
2.10
2.09
2.08
2.06
2.05
2.05
2.04
2.02
1H NMR
OH
O
F
Ph
N
H
3i
8
7
6
5
4
3
2
1
0
ppm
0.89
1.69
1.76
2.44
1.69
1.00
1.01
0.99
2.76
2.12

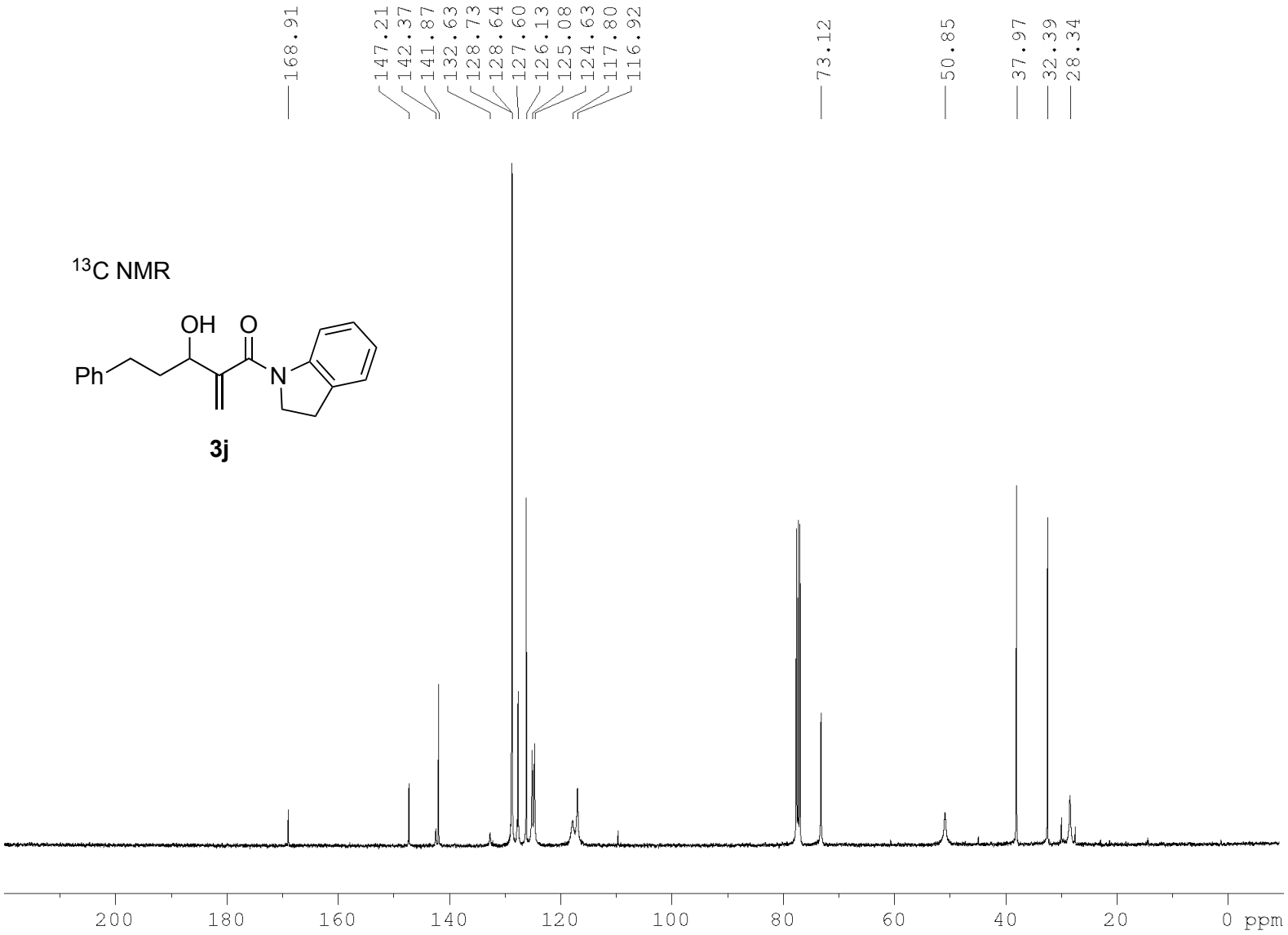

165.48
160.90
158.47
145.25
141.31
133.81
128.72
128.68
126.32
122.51
122.22
122.14
116.00
115.78
73.54
37.34
32.26
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

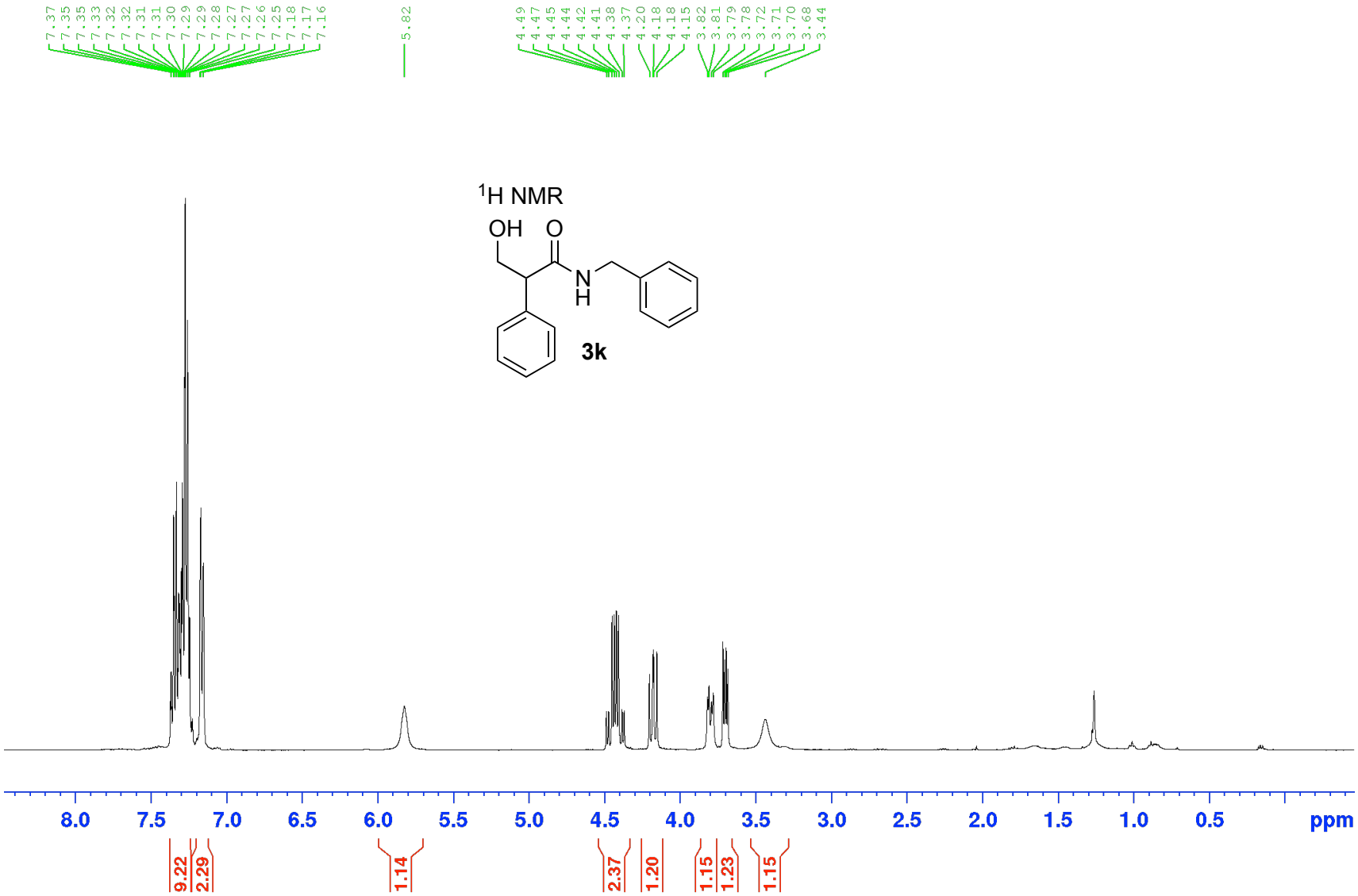
^{13}C NMR

OH
O
F
Ph
N
H

3i


8.09
7.29
7.28
7.26
7.22
7.20
7.19
7.08
7.06
7.04
5.62
5.42
4.44
4.43
4.14
4.12
4.10
4.07
4.05
3.22
3.16
3.13
3.11
3.08
2.94
2.92
2.90
2.88
2.87
2.78
2.76
2.74
2.73
2.70
2.05
2.05
2.03
2.01
1.99
1.97
1H NMR
OH
O
Ph
N
3j
8
7
6
5
4
3
2
1
0
ppm
0.79
6.77
1.25
1.00
1.01
1.00
2.16
1.00
2.06
1.14
1.11
2.09


168.91
147.21
142.37
141.87
132.63
128.73
128.64
127.60
126.13
125.08
124.63
117.80
116.92
73.12
50.85
37.97
32.39
28.34
13C NMR
OH
O
Ph
N
3j
200
180
160
140
120
100
80
60
40
20
0 ppm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7.35
7.33
7.32
7.32
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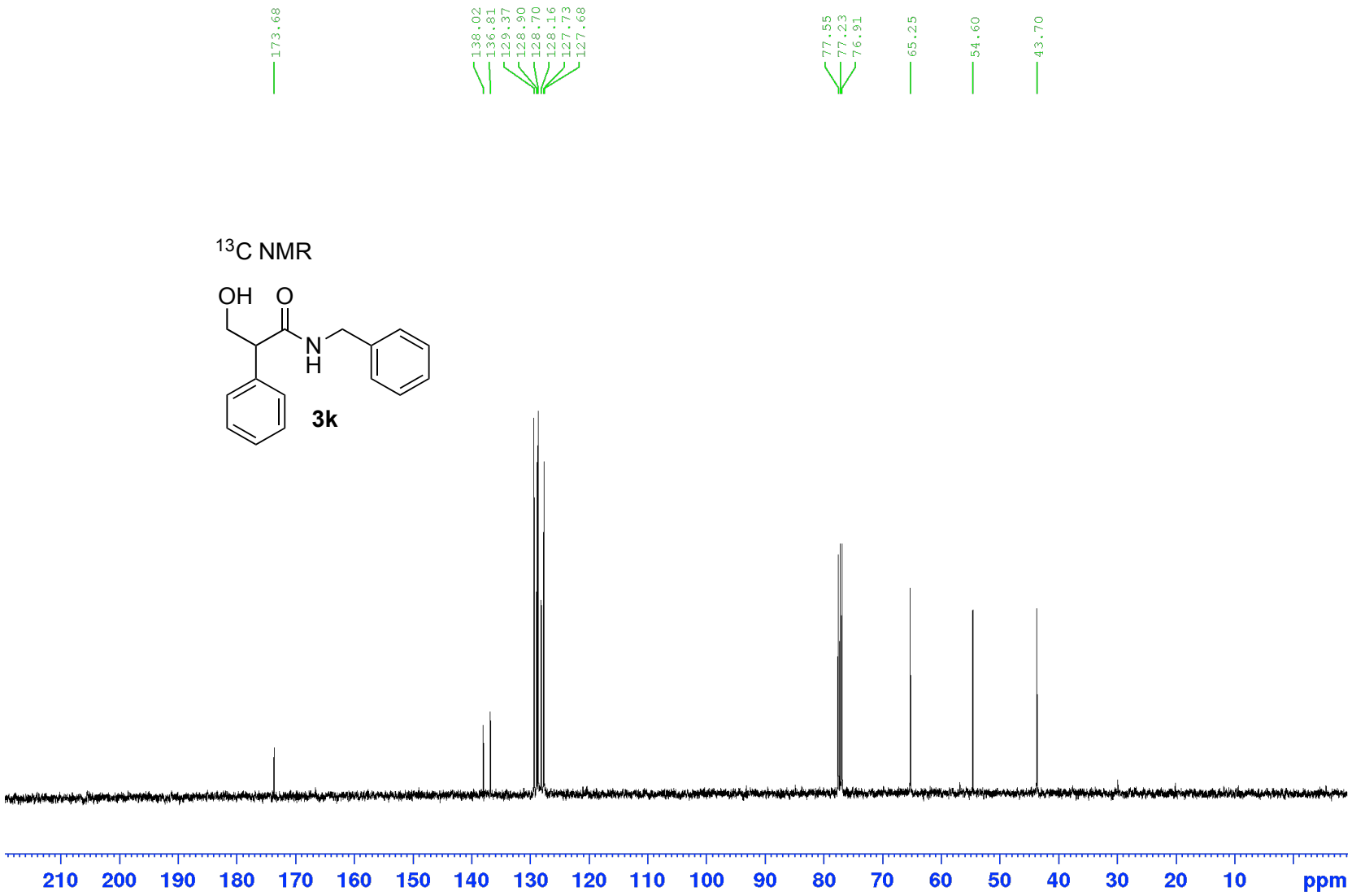
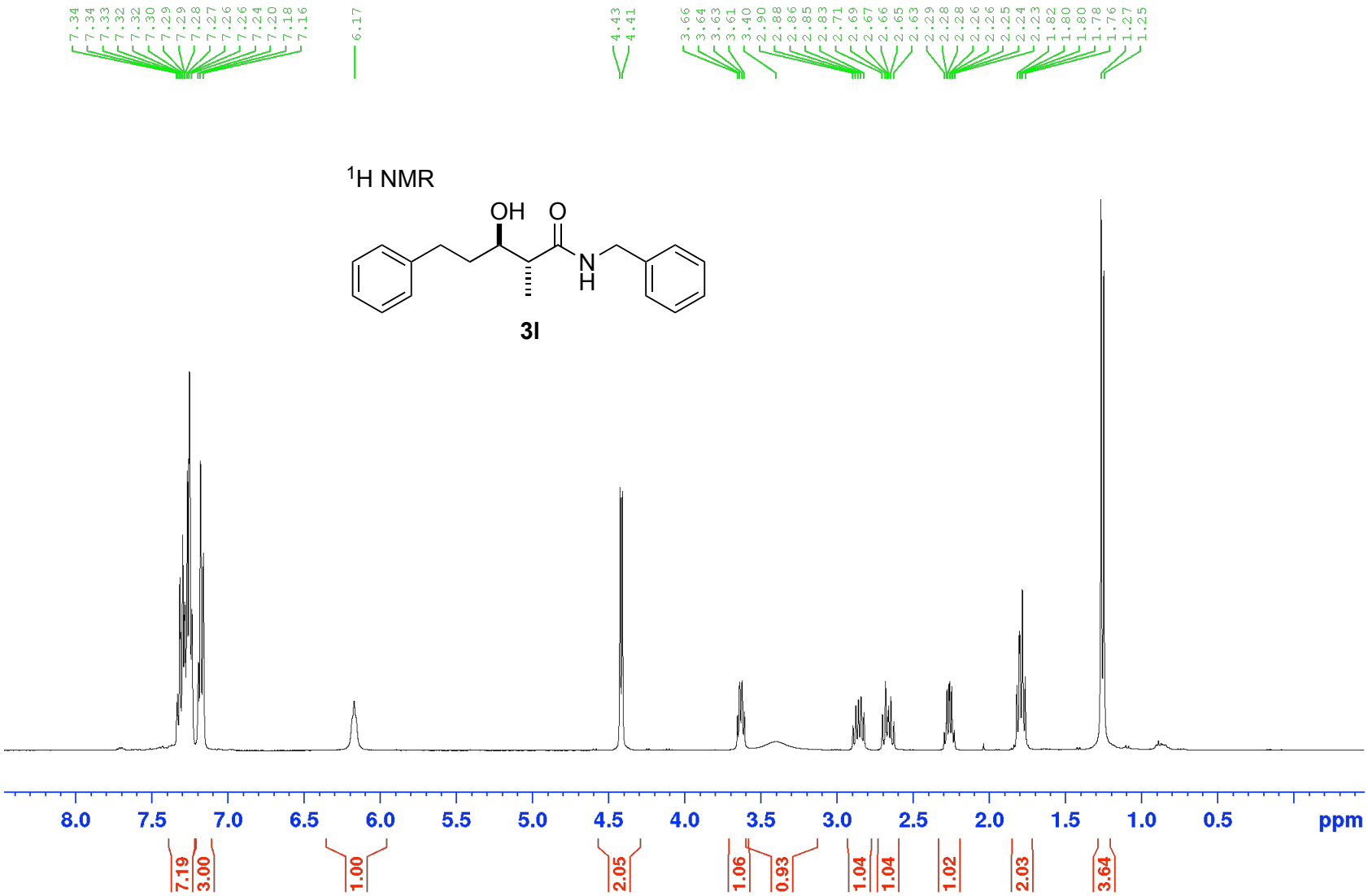
7.30
7.29
7.29
7.28
7.27
7.27
7.26
7.25
7.18
7.17
7.16
5.82
4.49
4.47
4.45
4.44
4.42
4.41
4.38
4.37
4.20
4.18
4.18
4.15
3.82
3.81
3.79
3.78
3.72
3.71
3.70
3.68
3.44
1H NMR
OH
O
N
H
3k
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
9.22
2.29
1.14
2.37
1.20
1.15
1.23
1.15


173.68
138.02
136.81
129.37
128.90
128.70
128.16
127.73
127.68
77.55
77.23
76.91
65.25
54.60
43.70
13C NMR
OH
O
N
H
3k
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


7.34
7.34
7.33
7.32
7.32
7.30
7.29
7.29
7.28
7.27
7.26
7.26
7.24
7.20
7.18
7.16
6.17
4.43
4.41
3.66
3.64
3.63
3.61
3.40
2.90
2.88
2.86
2.85
2.83
2.71
2.69
2.67
2.66
2.65
2.63
2.29
2.28
2.28
2.26
2.26
2.25
2.24
2.23
1.82
1.80
1.80
1.78
1.76
1.27
1.25
1H NMR
OH
O
N
H
3l
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
7.19
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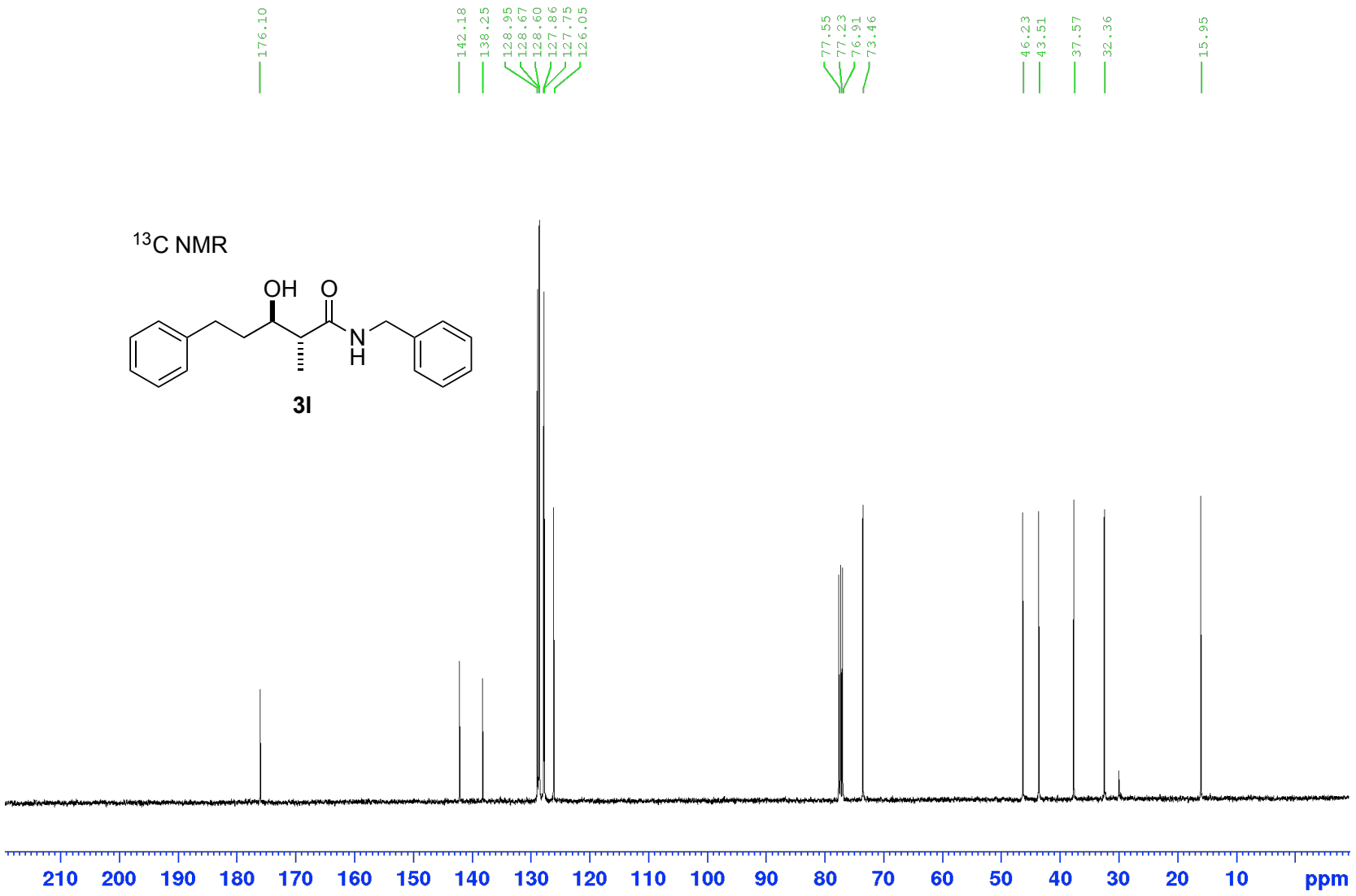
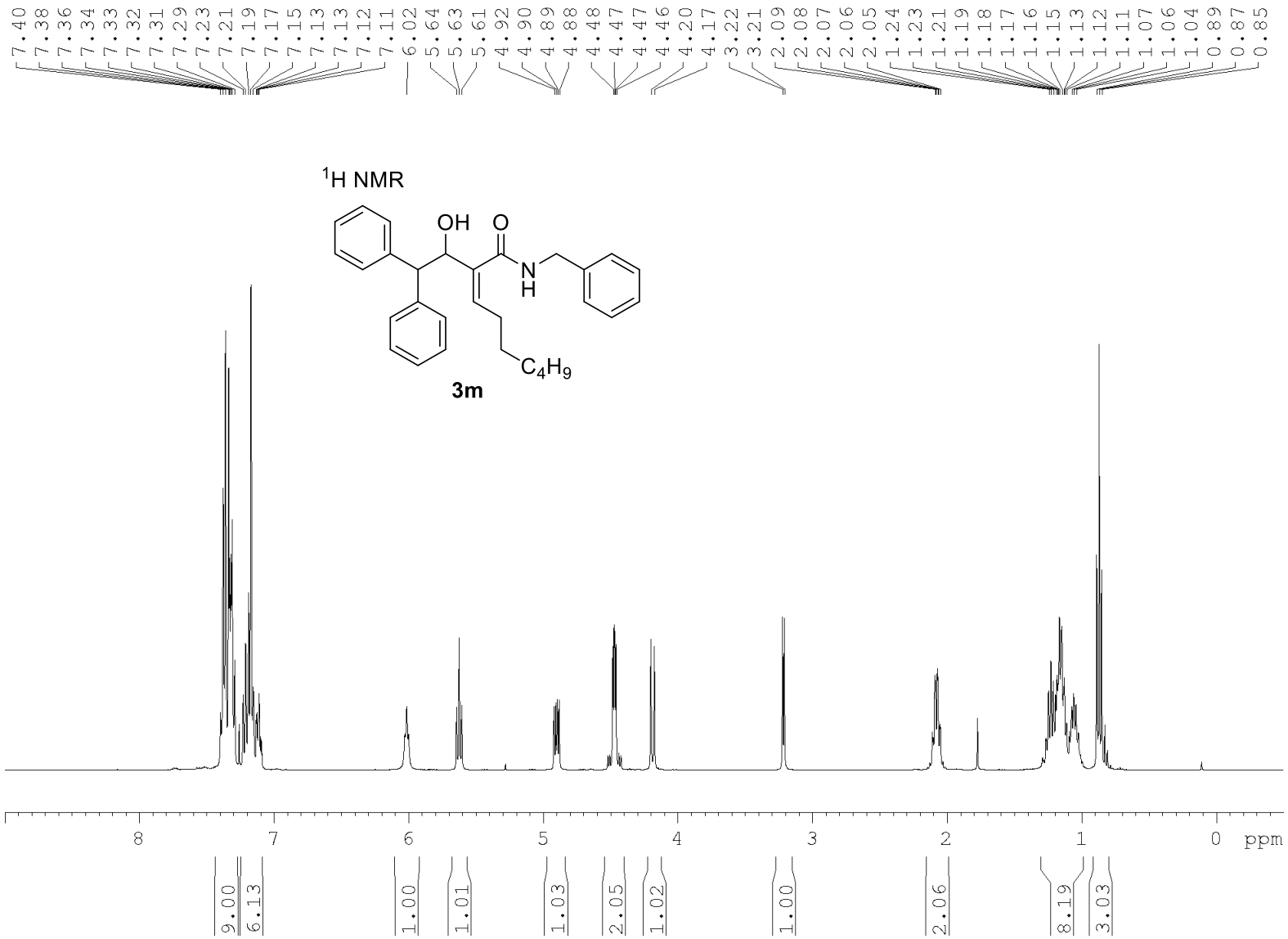
1.00
2.05
1.06
0.93
1.04
1.04
1.02
2.03
3.64


176.10
142.18
138.25
128.95
128.67
128.60
127.86
127.75
126.05
77.55
77.23
76.91
73.46
46.23
43.51
37.57
32.36
15.95
13C NMR
OH
O
N
H
3l
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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7.23
7.21
7.19
7.17
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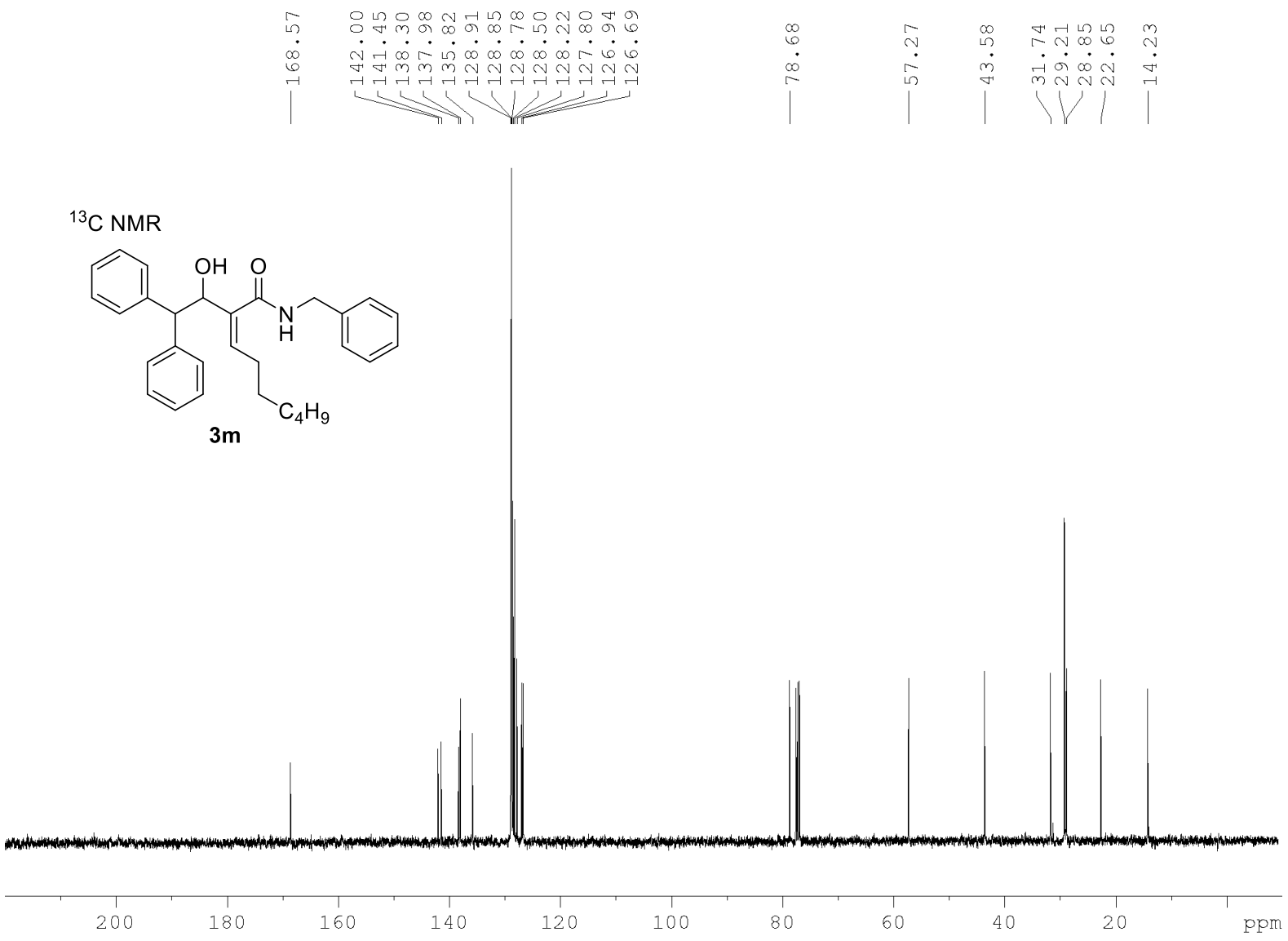
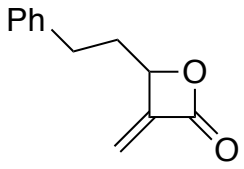
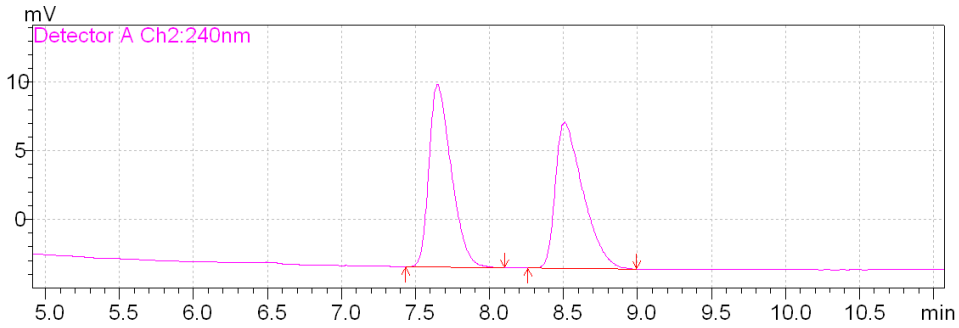
7.13
7.13
7.12
7.11
6.02
5.64
5.63
5.61
4.92
4.90
4.89
4.88
4.48
4.47
4.47
4.46
4.20
4.17
3.22
3.21
2.09
2.08
2.07
2.06
2.05
1.24
1.23
1.21
1.19
1.18
1.17
1.16
1.15
1.13
1.12
1.11
1.07
1.06
1.04
0.89
0.87
0.85
1H NMR
OH
O
N
H
C4H9
3m
8
7
6
5
4
3
2
1
0
ppm
9.00
6.13
1.00
1.01
1.03
2.05
1.02
1.00
2.06
8.19
3.03


168.57
142.00
141.45
138.30
137.98
135.82
128.91
128.85
128.78
128.50
128.22
127.80
126.94
126.69
78.68
57.27
43.58
31.74
29.21
28.85
22.65
14.23
13C NMR
OH
O
N
H
C4H9
3m
200
180
160
140
120
100
80
60
40
20
ppm

VIII. Chiral HPLC Traces of Enantioenriched Compounds



rac-**1a**

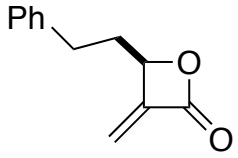


PeakTable

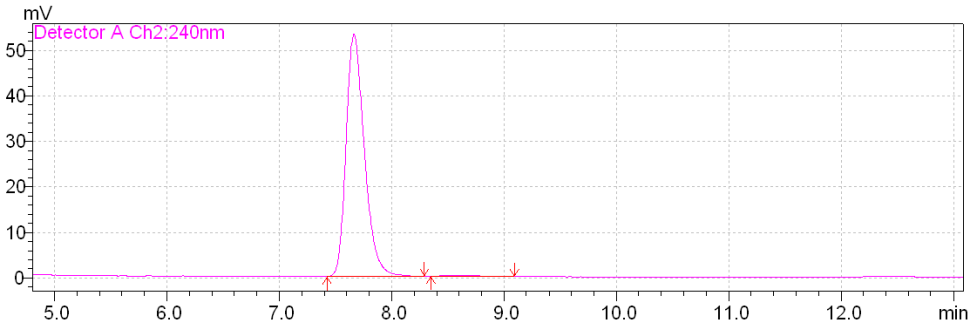
Detector A Ch2 240nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.647	139909	13317	50.122	55.617
2	8.506	139226	10628	49.878	44.383
Total		279135	23945	100.000	100.000

Method: Chiralpak AY3 (Particle size: 3 um; column size: 4.6 x 250 mm)
5.0% IPA/hexane; 1.0 mL/min



(+)-(*R*)-**1a**
99% ee

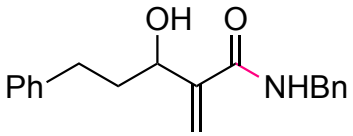


PeakTable

Detector A Ch2 240nm

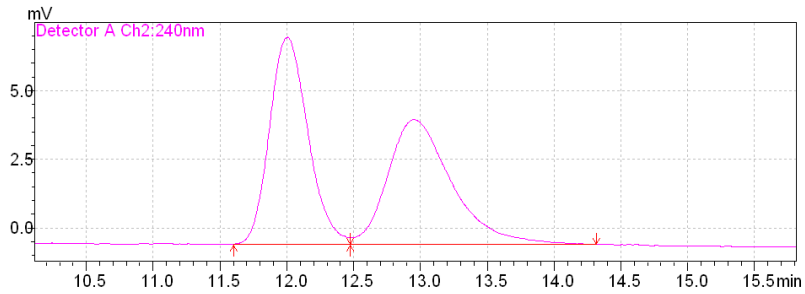
Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.663	602159	53267	99.325	99.660
2	8.566	4090	182	0.675	0.340
Total		606249	53449	100.000	100.000

Method: Chiralpak AY3 (Particle size: 3 um; column size: 4.6 x 250 mm)
5.0% IPA/hexane; 1.0 mL/min



rac-**3a**

-

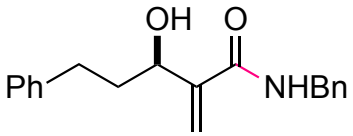


PeakTable

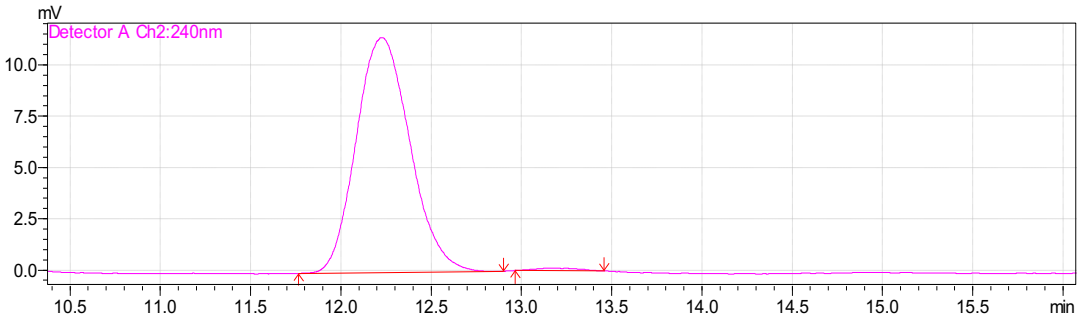
Detector A Ch2 240nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.003	151325	7555	49.951	62.394
2	12.949	151623	4553	50.049	37.606
Total		302948	12108	100.000	100.000

Method: Chiralcel OJ (Particle size: 3 um; column size: 4.6 x 250 mm)
2.0% IPA/hexane; 1.5 mL/min



(+)-(*R*)-**3a**
99% ee

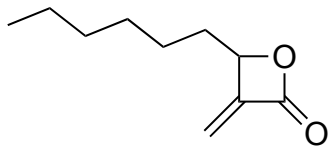


PeakTable

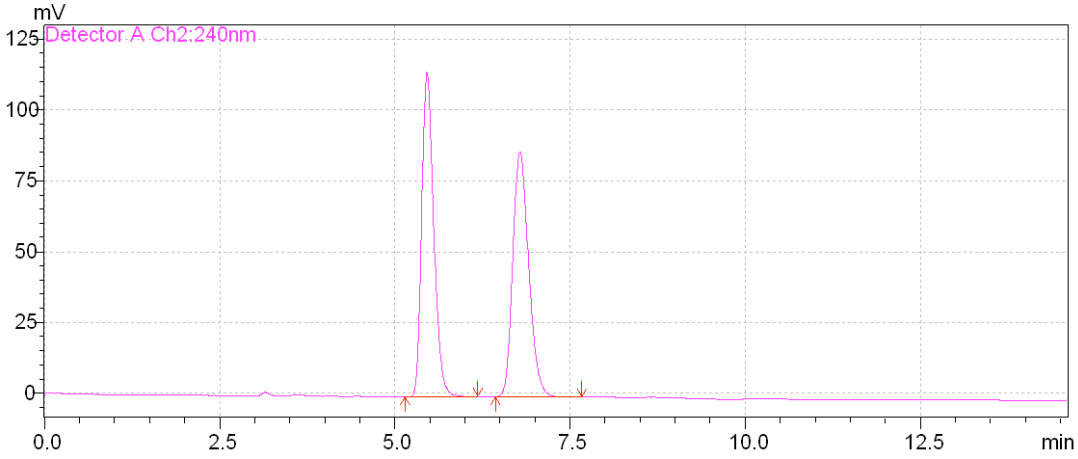
Detector A Ch2 240nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.224	237876	11461	99.626	99.361
2	13.182	893	74	0.374	0.639
Total		238769	11534	100.000	100.000

Method: Chiralcel OJ (Particle size: 3 um; column size: 4.6 x 250 mm)
2.0% IPA/hexane; 1.5 mL/min



rac-**1b**

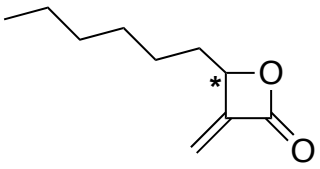


PeakTable

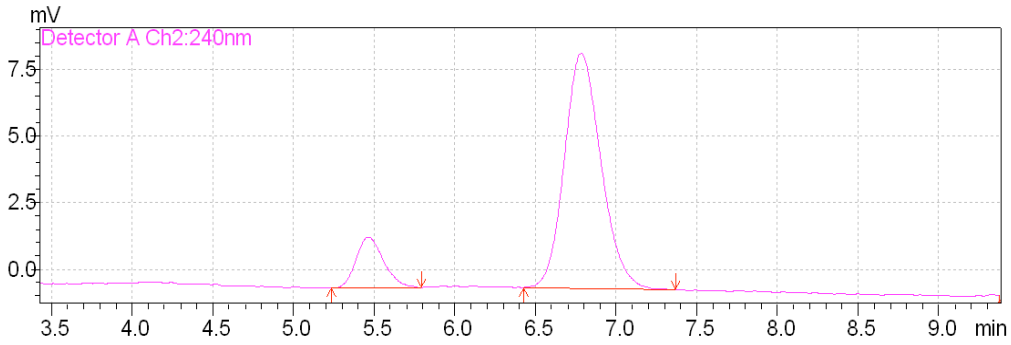
Detector A Ch2 240nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.456	1370855	114447	50.033	56.991
2	6.784	1369060	86369	49.967	43.009
Total		2739916	200816	100.000	100.000

Method: Chiralpak AY3 (Particle size: 3 um; column size: 4.6 x 250 mm)
5.0% IPA/hexane; 1.0 mL/min



(+)-1b
72% ee

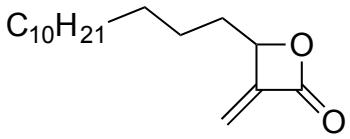


PeakTable

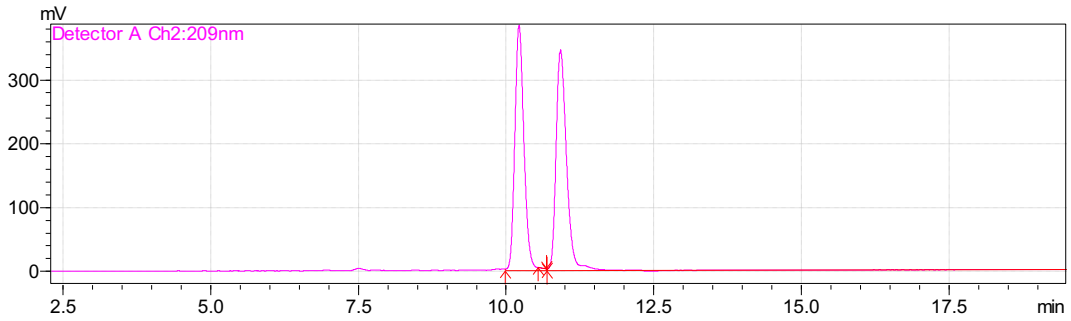
Detector A Ch2 240nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.463	22509	1902	13.880	17.748
2	6.784	139655	8816	86.120	82.252
Total		162164	10719	100.000	100.000

Method: Chiralpak AY3 (Particle size: 3 um; column size: 4.6 x 250 mm)
5.0% IPA/hexane; 1.0 mL/min

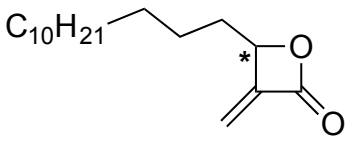


rac-**1e**

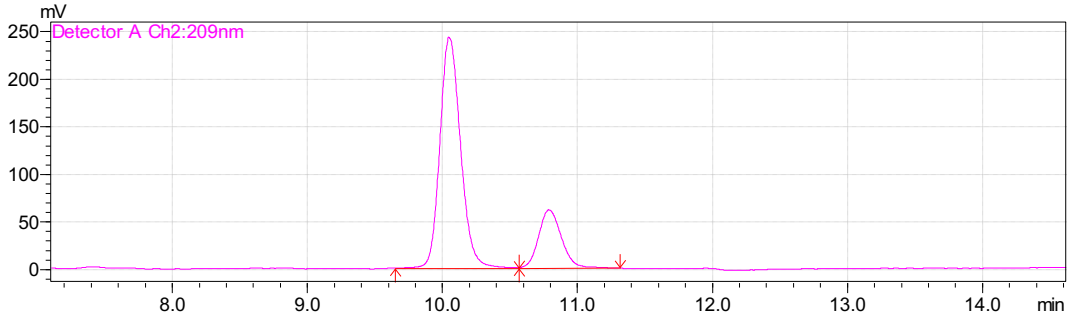


Retention time		Area	Height	% Area
RT10.120	10.120	4153842	383727	50.3263
RT10.882	10.882	4100737	345173	49.6829

Method: Chiralpak AY3 (Particle size: 3 um; column size: 4.6 x 250 mm)
5.0% IPA/hexane; 0.5 mL/min

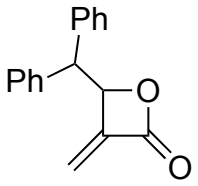


(+)-1e
56% ee

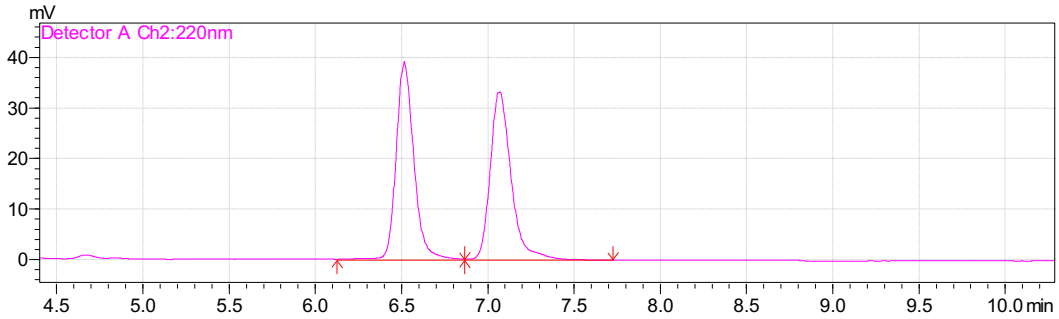


Retention time		Area	Height	% Area
RT10.068	10.068	2613948	243431	78.3454
RT10.788	10.788	722495	61480	21.6546

Method: Chiralpak AY3 (Particle size: 3 um; column size: 4.6 x 250 mm)
5.0% IPA/hexane; 0.5 mL/min

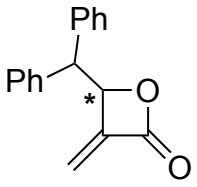


rac-**1f**

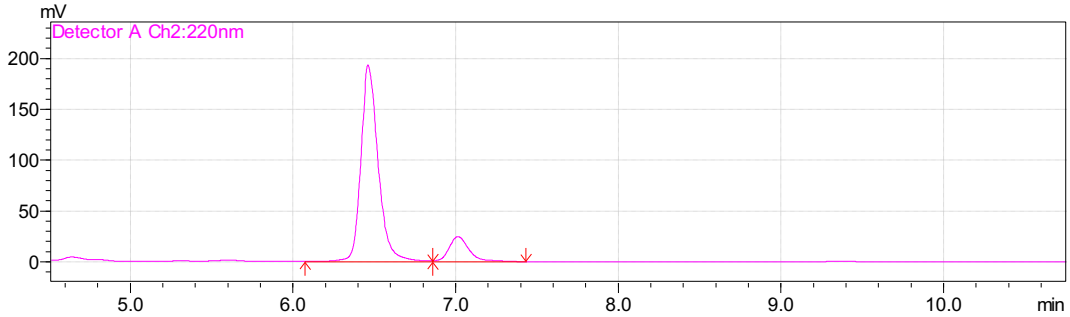


Retention time		Area	Height	% Area
RT6.514	6.514	283650	38926	50.1704
RT7.067	7.067	281724	33203	49.8296

Method: Chiralpak AY3 (Particle size: 3 um; column size: 4.6 x 250 mm)
5.0% IPA/hexane; 1.0 mL/min



(+)-**1f**
74% ee



Retention time	Area	Height	% Area
RT6.462	1431262	193060	87.0550
RT7.013	212827	24595	12.9450

Method: Chiralpak AY3 (Particle size: 3 um; column size: 4.6 x 250 mm)
5.0% IPA/hexane; 1.0 mL/min