

Supporting Information for:

“Asymmetric hydroformylation of *Z*-enamides and enol esters with rhodium-BisDiazaphos catalysts”

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I. General:

All manipulations were carried out under nitrogen using standard Schlenk, high vacuum, and glovebox techniques. Ethyl acetate, hexane, dichloromethane and anhydrous DMF were obtained from Sigma-Aldrich. Dichloro(*p*-cymene)Ru(II) dimer and Ru(COD)(2-methylallyl)₂ were purchased from Alfa Aesar. Dicyclohexylphosphinobutane, *tris*-(*p*-Cl-C₆H₄) phosphine, DMAP, and all alkynes, carboxylic acids, and primary amides were purchased from Sigma-Aldrich. Unless mentioned below, all chemicals were purchased and used without further purification. Enol esters^{1,2} and enamides³ were prepared by literature methods and purified by silica column chromatography prior to use (see section II). Bisdiazaphospholane ligands were prepared as reported in literature.⁴ [Rh(acac)(CO)₂] was used as received from Dow Chemical and stored in a N₂-filled glovebox. 1:1 CO:H₂ was purchased from Airgas. THF and toluene were either distilled from sodium/benzophenone ketyl under N₂ or dried by safety columns prior to use. Alkynes were degassed prior to use by either three freeze-pump-thaw cycles or sparging with N₂. Flash chromatography was performed on Silicycle Siliaflash P60 silica gel (40-63μm, 230-400 mesh). Chiral HPLC analysis was performed on a Gilson analytical HPLC with Chiralpak IA, IB, IC, and ID columns. Chiral super critical fluid chromatography (SFC) analysis was performed on a Berger SFC with Chiracel OJ-H or AD-H columns. Optical rotations were measured at room temperature using a 1 mL cell with a 0.5 dm path length on a Randolph digital polarimeter. Absolute configuration was determined by optical rotation for (-)(2*S*)-

¹ Gooßen, L. J.; Paetzold, J.; Koley, D. *Chem. Commun.* **2003**, 706-707.

² Doucet, H.; Martin-Vaca, B.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1995**, 60, 7247-7255.

³ Gooßen, L. J.; Salih, K. S. M.; Blanchot, M. *Angew. Chem. Int. Ed.* **2008**, 47, 8492.

⁴ Adint, T.T.; Wong, G.W.; Landis, C.R. *J. Org. Chem.* **2013**, 78 4231-4238.

(benzoyloxy)heptanal, (S)-1-oxoheptan-2-yl 4-methoxybenzoate, (S)-1-oxo-5-phenylpentan-2-yl acetate, (-)(S)*N*-(1-Formyl-2-phenylethyl) benzamide, 2,2,2-Trifluoro-*N*-[(1*S*)-1-formyl-2-phenylethyl]acetamide and assigned by analogy for other reported aldehydes. All pressures given are gauge pressures unless otherwise noted.

NMR spectra were recorded at ambient temperature on Varian Mercury-300, Inova-500 or Unity-500 and Bruker AC-300, Avance III 400, or Avance III 500 spectrometers. ^1H and ^{13}C NMR chemical shifts were referenced to tetramethylsilane if present or residual solvent. ^{31}P and ^{19}F NMR chemical shifts were referenced to TMS in the proton spectrum using the unified scale. ^1H NMR splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), apparent (ap), broad (br). First-order splitting patterns were assigned on the basis of the multiplet. Splitting patterns that could not be interpreted are designated as multiplet (m) or broad (br). Mass spectra were collected on a Waters (Micromass) LCT® for electrospray ionization experiments with a sample cone voltage of 20.

II. Synthesis and characterization of (*Z*)- enol ester and enamide substrates

All enol ester substrates were prepared according to procedures slightly modified from the reported procedures, as reported below.

General procedure for the synthesis of enol esters (Method 1)¹

An oven-dried Schlenk flask equipped with a magnetic stir bar and carboxylic acid (1 eq, 5 mmol) was brought into a N_2 glove box. A vial was charged with $[\text{Ru}(\text{p-cumene})\text{Cl}_2]_2$ (1 mol%, 0.05 mmol), $\text{P}(\text{p-Cl-C}_6\text{H}_4)_3$ (3 mol%, 0.15 mmol), DMAP (4 mol%, 0.20 mmol), dry toluene (15 mL) and transferred to the Schlenk flask via a Pasteur pipette, followed by 1-hexyne (1.3 eq, 6.5 mmol) via a syringe. In a fume hood, the flask was immersed in a silicone oil bath and stirred for 16 h at 60°C under N_2 . When reaction complete, the solution was allowed to cool down at room temperature for 30 min, then passed through a plug of silica gel and washed with dichloromethane. The solvent was removed in vacuo and the product was purified via silica gel flash chromatography with hexane/ethyl acetate as eluents. The enol ester was filtered through a plug of silica prior to hydroformylation.

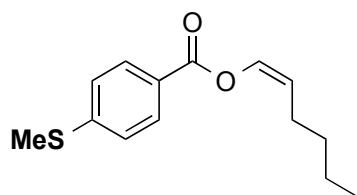
General procedure for the synthesis of enol esters (Method 2)²

An oven-dried Schlenk flask equipped with a magnetic stir bar and carboxylic acid (1 eq, 10 mmol) was brought into a N_2 glove box. A vial was charged with $\text{Ru}(\text{2-methallyl})_2$ -bis(diphenylphosphino)butane (1 mol%, 0.1 mmol) and solvent (5 mL) and transferred to the Schlenk flask via a Pasteur pipette. Degassed 4-Phenyl-1-butyne (1 eq, 10 mmol) was added via a syringe in a fume hood. The flask was immersed in a silicone oil bath and stirred for 24h under N_2 . When reaction complete, the solution was allowed to cool down at room temperature for 30 min, then passed through a plug of silica gel and washed with dichloromethane. The solvent was removed in vacuo and the product was purified via silica gel flash chromatography with hexane/ethyl acetate as eluents. The enol ester was filtered through a plug of silica prior to hydroformylation.

General procedure for the synthesis of enamides

All enamide substrates were prepared according to a procedure slightly modified from the reported procedure, as reported below. Their spectroscopic properties match those previously reported,⁵ or are reported below.

In an oven-dried Schlenk flask inside a nitrogen-filled glovebox, *bis*(2-methallyl)(COD)ruthenium(II) (5%, 0.25 mmol), 1,4-*bis*(dicyclohexylphosphino)butane (6%, 0.30 mmol), ytterbium triflate (4%, 0.20 mmol), and amide (5.0 mmol) were combined, and anhydrous DMF (15 mL) was added. On a Schlenk line, degassed alkyne (10.0 mmol) was added via syringe, followed by N₂-sparged H₂O (0.540 mL, 30 mmol). The resulting solution was stirred for 6-18h in a 60 °C oil bath, then poured into a saturated aqueous sodium bicarbonate solution (150 mL). This mixture was extracted with ethyl acetate (3x60 mL), the combined organics were washed with water (5x50 mL) and brine (1x50 mL), dried over magnesium sulfate, filtered, and the volatiles were removed by rotary evaporation. The dark brown oil was purified by column chromatography on silica gel with 9:1 Hexane/EtOAc. Two or more columns were frequently necessary for clean product isolation.



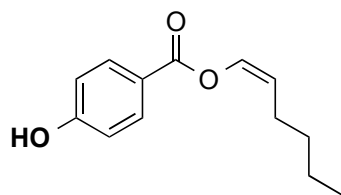
(Z)-hex-1-en-1-yl 4-(methylthio)benzoate

Prepared according to method 1. Product purified by silica gel flash chromatography (10:1 hexane/ethyl acetate) to afford a yellow oil in 72% isolated yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.5 Hz, 2H), 7.33 – 7.20 (m, 3H), 5.05 – 4.93 (m, 1H), 2.53 (s, 3H), 2.35 – 2.23 (m, 2H), 1.48 – 1.33 (m, 4H), 0.93 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 163.39, 146.26, 134.17, 130.15, 125.46, 124.98, 114.72, 31.38, 24.36, 22.26, 14.80, 13.93.

HRMS (ESI-TOF) *m/z*: [M]⁺ calcd for C₁₄H₁₈O₂S 250.1023; found 250.1019.



(Z)-hex-1-en-1-yl 4-hydroxybenzoate

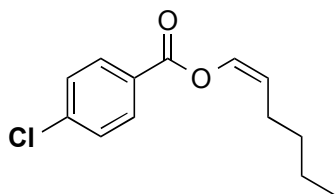
Prepared according to method 1. Reaction refluxed in THF. Product purified by silica gel flash chromatography (5:1 hexane/ethyl acetate) to afford a dark yellow oil in 40% isolated yield.

¹H NMR (500 MHz, Chloroform-*d*) δ 8.08 – 7.96 (m, 2H), 7.24 – 7.21 (m, 1H), 6.97 – 6.83 (m, 2H), 4.98 (tdd, *J* = 7.5, 6.4, 1.3 Hz, 1H), 2.31 – 2.24 (m, 2H), 1.46 – 1.34 (m, 4H), 0.93 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 164.10, 160.95, 134.09, 132.33, 121.30, 115.56, 114.98, 31.34, 24.34, 22.24, 13.90.

⁵ -Butyl, -(CH₂)₂Ph, -(CH₂)₃Cl, -CH₂Cy, and Ph substituted benzamides were reported in: Gooßen, L. J.; Salih, K. S. M.; Blanchot, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 8492. (Z)-*N*-(5-cyanopent-1-en-1-yl)benzamide was reported in: Honjo, T.; Phipps, R.J.; Rauniyar, V.; Toste, F.D.; *Angew. Chem. Int. Ed.* **2012**, *51*, 9684-9688.

HRMS (ESI-TOF) m/z : $[M]^+$ calcd for $C_{13}H_{16}O_3$ 220.1094; found 220.1095.



(Z)-hex-1-en-1-yl 4-chlorobenzoate

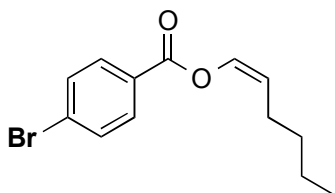
Prepared according to method 1. Product purified by silica gel flash chromatography (10:1 hexane/ethyl acetate) to afford a yellow oil in 26% isolated yield.

Characterization data agrees with previously reported results.⁶

¹H NMR (400 MHz, Chloroform-*d*) δ 8.19 – 7.92 (m, 2H), 7.57 – 7.38 (m, 2H), 7.31 – 7.17 (m, 1H), 5.13 – 4.94 (m, 1H), 2.36 – 2.21 (m, 2H), 1.51 – 1.27 (m, 4H), 0.93 (d, J = 7.0 Hz, 3H).

¹³C NMR (126 MHz, $CDCl_3$) δ 162.79, 139.93, 134.03, 131.22, 128.92, 127.90, 115.22, 31.30, 24.35, 22.23, 13.90.

HRMS (ESI-TOF) m/z : $[M]^+$ calcd for $C_{13}H_{15}ClO_2$ 238.0756; found 238.0759.



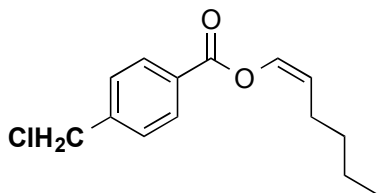
(Z)-hex-1-en-1-yl 4-bromobenzoate

Prepared according to method 1. Product purified by silica gel flash chromatography (10:1 hexane/ethyl acetate) to afford a yellow oil in 22% isolated yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.01 – 7.90 (m, 2H), 7.69 – 7.57 (m, 2H), 7.23 (dt, J = 6.4, 1.6 Hz, 1H), 5.03 (td, J = 7.5, 6.3 Hz, 1H), 2.33 – 2.21 (m, 2H), 1.49 – 1.30 (m, 4H), 0.93 (t, J = 7.0 Hz, 3H).

¹³C NMR (126 MHz, $CDCl_3$) δ 162.92, 134.02, 131.91, 131.33, 128.62, 128.36, 115.24, 31.29, 24.35, 22.23, 13.89.

HRMS (ESI-TOF) m/z : $[M]^+$ calcd for $C_{13}H_{15}BrO_2$ 282.0250; found 282.0252.



(Z)-hex-1-en-1-yl 4-(chloromethyl)benzoate

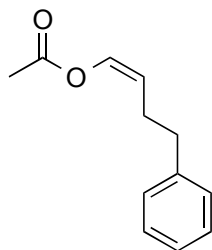
Prepared according to method 1. Product purified by silica gel flash chromatography (10:1 hexane/ethyl acetate) to afford a light yellow oil in 15% isolated yield.

¹H NMR (500 MHz, Chloroform-*d*) δ 8.13 – 8.07 (m, 2H), 7.54 – 7.47 (m, 2H), 7.25 (dt, J = 6.3, 1.6 Hz, 1H), 5.02 (td, J = 7.5, 6.3 Hz, 1H), 4.63 (s, 2H), 2.35 – 2.25 (m, 2H), 1.48 – 1.33 (m, 4H), 0.93 (t, J = 7.1 Hz, 3H).

¹³C NMR (126 MHz, $CDCl_3$) δ 162.05, 141.72, 133.07, 129.26, 128.39, 127.59, 114.07, 44.27, 30.28, 23.31, 21.20, 12.86.

HRMS (ESI-TOF) m/z : $[M]^+$ calcd for $C_{14}H_{17}ClO_2$ 252.0912; found 252.0903.

⁶ Das, U.K.; Bhattacharjee, M. *J. Organomet. Chem.* **2012**, 700, 78-82.



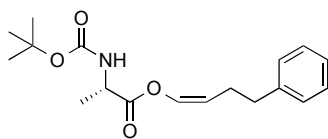
(Z)-4-phenylbut-1-en-1-yl acetate

Prepared according to method 2, using 2 mol% catalyst loading. Reaction run in hexane at 40°C for 24 h. Product purified by silica gel flash chromatography (10:1 hexane/ethyl acetate) to afford a clear oil in 75% isolated yield.

¹H NMR (500 MHz, Chloroform-*d*) δ 7.31 – 7.27 (m, 2H), 7.20 (d, *J* = 7.3 Hz, 2H), 7.01 (dt, *J* = 6.4, 1.4 Hz, 1H), 4.90 (td, *J* = 7.4, 6.2 Hz, 1H), 2.70 (t, *J* = 7.7 Hz, 2H), 2.54 – 2.40 (m, 2H), 2.11 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 168.04, 141.55, 134.39, 128.43, 128.31, 125.95, 112.97, 35.35, 26.21, 20.72.

HRMS (ESI-TOF) *m/z*: [M]⁺ calcd for C₁₂H₁₄O₂ 190.0989; found 190.0990.



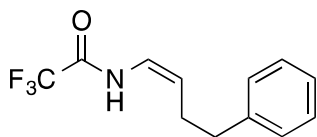
(S,Z)-4-phenylbut-1-en-1-yl 2-((tert-butoxycarbonyl)amino)propanoate

Prepared according to method 2. Reaction ran in toluene for 24 h at 75°C. Product purified by silica gel flash chromatography (10:1 hexane/ethyl acetate) to afford a light orange oil in 55% isolated yield.

¹H NMR (500 MHz, Chloroform-*d*) δ 7.31 – 7.24 (m, 2H), 7.23 – 7.14 (m, 3H), 7.00 (d, *J* = 6.3 Hz, 1H), 5.03 (d, *J* = 8.0 Hz, 1H), 4.96 (td, *J* = 7.4, 6.2 Hz, 1H), 4.37 (h, *J* = 6.3, 5.2 Hz, 1H), 2.69 (t, *J* = 7.6 Hz, 2H), 2.54 – 2.42 (m, 2H), 1.44 (s, 9H), 1.39 (d, *J* = 7.2 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 170.47, 155.04, 141.37, 134.29, 128.44, 125.98, 113.96, 80.01, 53.43, 49.04, 35.23, 28.30, 26.22, 18.47.

HRMS (ESI-TOF) *m/z*: [M+NH₄]⁺ calcd for C₁₈H₂₅NO₄ 337.2122; found 337.2119.



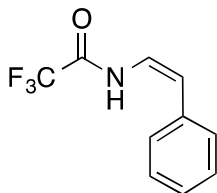
20% yield. Yellow oil.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.12 (m, 6H), 6.57 (t, *J* = 9.7 Hz, 1H), 5.12 (ap. q, *J* = 8.2 Hz, 1H), 2.74 (t, *J* = 7.1 Hz, 2H), 2.36 (ap. q, *J* = 7.3 Hz, 2H).

¹⁹F NMR (377 MHz, CDCl₃) δ -75.64 (Z isomer), -75.87 (E isomer).

¹³C NMR (101 MHz, CDCl₃) δ 154.22 (q, *J* = 37.8 Hz), 140.79, 128.80, 128.43, 126.51, 119.67, 115.63, 115.49 (q, *J* = 287 Hz), 34.96, 28.23.

HRMS (EI) *m/z*: [M•]⁺ Calcd for C₁₂H₁₂F₃NO 243.0866; found 243.0857.



69% yield (after two flash column chromatography purifications). Yellow oil.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.31 (br s, 1H), 7.49 – 7.39 (m, 2H), 7.39 – 7.29 (m, 1H), 7.30 – 7.25 (m, 2H), 6.90 (dd, *J* = 10.9, 9.4 Hz, 1H), 6.10 (d, *J* = 9.4 Hz, 1H).

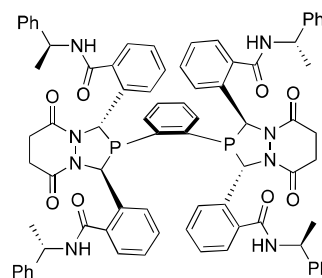
¹⁹F NMR (377 MHz, CDCl₃) δ -75.81.

¹³C NMR (101 MHz, CDCl₃) δ 154.57 (q, *J* = 38 Hz), 134.13, 129.57, 128.16, 127.93, 119.46, 115.78, 115.69 (q, *J* = 287 Hz), 77.16.

HRMS (EI) m/z: [M^{•+}] Calcd for C₁₀H₈F₃NO 215.0553; found 215.0551.

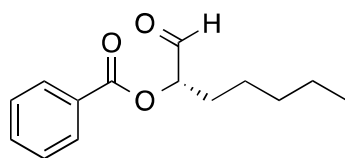
III. General method for hydroformylation.

Inside a N₂-purged glovebox, an oven-dried 15mL Ace Glass pressure bottle equipped with a magnetic stir bar was charged with THF stock solutions of Rh(acac)(CO)₂ and bisdiazaphospholane ligand **1** using 1000μL and 200μL Eppendorf® pipets. The pressure bottle was attached to a pressure reactor and removed from the glovebox, placed in a fume hood, subjected to 5 pressurization (140 psi)/depressurization (15 psi) cycles with syngas to ensure replacement of the dinitrogen atmosphere with syngas, then filled to the appropriate syngas pressure. The solution was allowed to stir at high speed to ensure gas mixing for 30-60 min in an oil bath at the reaction temperature. The reaction vessel was then removed from the oil bath and allowed to cool for 5 minutes, then the pressure was reduced to <10 psig and the olefin was injected with a gas-tight syringe with a 12" needle. Solid olefins were injected as a solution in THF. Reactions were run at 0.8-1.3 M final concentration of olefin. The reaction was then re-pressurized to the reaction pressure after additional pressurization/depressurization cycles and replaced in the oil bath. Upon completion of the reaction, the pressure bottle was removed from the oil bath, allowed to cool to room temperature, and vented in a fume hood. NMR spectra are initially obtained of the crude reaction mixture by adding acetone-d₆, MeOD, or CDCl₃ directly to the reaction mixture. NMR yields were determined by addition of a solution of internal standard (1,3,5-trimethoxybenzene or mesitylene) in NMR solvent and acquiring spectra with a sufficiently long delay. Enantiomeric excess of the branched hydroformylation product was determined by chiral SFC or HPLC.



1 (S,S,S)-BisDiazaphos

IV. Data for enol ester AHF



(-)(2S)-(Benzoyloxy)heptanal:

Yield 1.09g (92.0%), 97% ee, colorless oil.

[α]_D²⁰ = -14.7, c = 1.24 in CHCl₃. Lit. [α]_D²⁰ = -31.1 (c = 1.41, CH₂Cl₂).⁷

¹H NMR (400 MHz, Chloroform-*d*) δ 9.57 (d, *J* = 1.0 Hz, 1H), 8.12 – 7.88 (m, 2H), 7.53 (tt, *J* = 7.5, 1.2 Hz, 1H), 7.44 – 7.37 (m, 2H), 5.15 (ddd, *J* = 8.1, 4.9, 1.0 Hz, 1H), 1.96 – 1.73 (m, 2H), 1.49 – 1.39 (m, 2H), 1.32 – 1.21 (m, 4H), 0.90 – 0.74 (m, 3H).

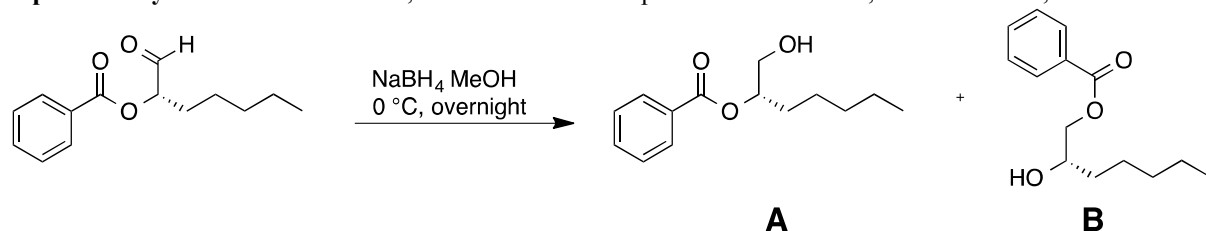
¹³C NMR (101 MHz, CDCl₃) δ 198.59, 166.19, 133.55, 129.87, 129.24, 128.55, 78.83, 31.45, 28.90, 24.70, 22.40, 13.96.

Enantiomeric excess was determined to be 97% by chiral SFC analysis, after NaBH₄ reduction in MeOH at 0 °C. The reduction conditions afford a mixture of two alcohol isomers, **A** and **B**, after partial migration of the benzoyl protecting group from the secondary alcohol to the primary alcohol (identified by HMBC and COSY experiments).

⁷ Chattopadhyay, A.; Mamdapur, V.R. *J. Org. Chem.* **1995**, *60*, 585-587.

The four peaks observed by SFC are due to the two enantiomers of each isomer. $t_r = 4.40$ min (isomer **A**, (*S*)), $t_r = 5.53$ min (isomer **B**, (*R*)), $t_r = 6.0$ min (isomer **B**, (*S*)), $t_r = 6.23$ min (isomer **A**, (*R*)).

Separation by SFC: Chiralcel AD-H, MeOH modifier ramp 5-50% over 10 min, 3 mL/min flow, $\lambda = 233$ nm.



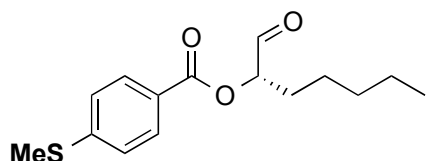
Alcohol isomers:

A: (S)-1-hydroxyheptan-2-yl benzoate

$^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 8.09 – 8.04 (m, 2H), 7.61 – 7.54 (m, 1H), 7.47 – 7.41 (m, 2H), 5.20 – 5.12 (m, 1H), 3.83 (dd, $J = 12.1, 3.4$ Hz, 1H), 3.76 (dd, $J = 12.1, 6.2$ Hz, 1H), 1.81 – 1.66 (m, 2H), 1.66 – 1.27 (m, 6H), 0.93 – 0.83 (m, 3H).

B: (S)-2-hydroxyheptyl benzoate (rearranged)

$^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 8.08 – 8.01 (m, 2H), 7.56 (tt, $J = 7.5, 1.2$ Hz, 1H), 7.47 – 7.39 (m, 2H), 4.38 (dd, $J = 11.4, 3.2$ Hz, 1H), 4.22 (dd, $J = 11.4, 7.1$ Hz, 1H), 4.02 – 3.94 (m, 1H), 1.61 – 1.52 (m, 2H), 1.52 – 1.27 (m, 6H), 0.89 (t, $J = 6.9$ Hz, 3H).



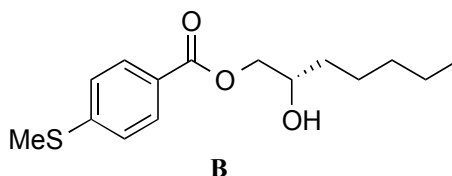
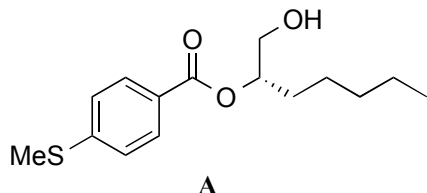
(S)-1-oxoheptan-2-yl 4-(methylthio)benzoate

Crude hydroformylation mixture filtered through a plug of silica and washed with dichloromethane. 84% isolated yield, yellow oil.

$^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 9.63 (d, $J = 0.9$ Hz, 1H), 7.99 (d, $J = 8.5$ Hz, 2H), 7.28 (d, $J = 8.5$ Hz, 2H), 5.19 (ddd, $J = 8.2, 5.0, 1.0$ Hz, 1H), 2.53 (s, 3H), 2.05 – 1.79 (m, 2H), 1.63 – 1.45 (m, 2H), 1.44 – 1.23 (m, 4H), 0.92 – 0.87 (m, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 198.70, 165.94, 146.44, 130.13, 125.20, 124.98, 78.72, 31.45, 28.90, 24.70, 22.40, 14.82, 13.96.

Enantiomeric excess was determined to be 90% by chiral HPLC analysis, after NaBH_4 reduction in MeOH at room temperature for 16 h, followed by addition of sat. aq. NH_4Cl solution, extraction with dichloromethane and drying over MgSO_4 . The reduction conditions afford a mixture of two alcohol isomers, **A** and **B**, after partial migration of the benzoyl protecting group from the secondary alcohol to the primary alcohol, as well as a transesterification by-product in the presence of MeOH. The mixture of alcohols was purified by silica gel flash chromatography (2:1 hexanes/ethyl acetate) prior to HPLC analysis.



Alcohol isomers:

A: (S)-1-hydroxyheptan-2-yl 4-(methylthio)benzoate

$^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 7.92 – 7.82 (m, 2H), 7.22 – 7.14 (m, 2H), 5.10 – 5.03 (m, 1H), 3.74 (dd, $J = 12.1, 3.3$ Hz, 1H), 3.67 (dd, $J = 12.1, 6.2$ Hz, 1H), 2.44 (s, 3H), 2.21 (s, 1H), 1.73 – 1.55 (m, 2H), 1.54 – 1.12 (m, 6H), 0.90 – 0.74 (m, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 165.83, 144.68, 128.82, 125.19, 123.86, 75.33, 63.96, 30.59, 29.62, 23.99, 21.43, 13.76, 12.93.

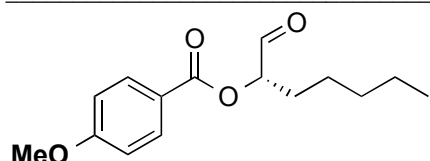
B: (S)-2-hydroxyheptyl 4-(methylthio)benzoate (rearranged)

^1H NMR (500 MHz, Chloroform-*d*) δ 7.92 – 7.82 (m, 2H), 7.22 – 7.14 (m, 2H), 4.29 (A of ABX, ap dd, J = 11.4, 3.2 Hz, 1H), 4.18 – 4.10 (m, 1H), 3.93 – 3.86 (m, 1H), 2.44 (s, 3H), 2.21 (br, 1H), 1.54 – 1.12 (m, 8H), 0.90 – 0.74 (m, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 165.47, 144.79, 128.90, 124.90, 123.86, 69.11, 68.12, 32.41, 30.72, 24.06, 21.53, 13.75, 12.98.

HRMS (ESI-TOF) m/z : $[\text{M}]^+$ calcd for $\text{C}_{15}\text{H}_{22}\text{O}_3\text{S}$ 282.1285; found 282.1290.

Separation by HPLC: CHIRALPAK 1A (AD-H), 3% iPrOH/hexanes, 0.9 ml/min, ambient temperature, 220 nm, t_R (A): 31.5 min (major, (S)), 36.7 min (minor, (R)), t_R (B): 44.7 min (major, (S)), 51.6 min (minor, (R))



(S)-1-oxoheptan-2-yl 4-methoxybenzoate

Crude hydroformylation mixture filtered through a plug of silica and washed with dichloromethane. 85% isolated yield, yellow oil.

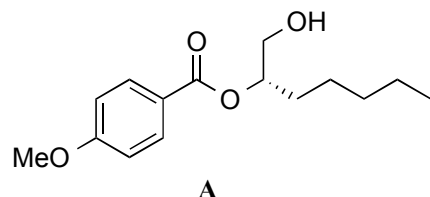
^1H NMR (500 MHz, Chloroform-*d*) δ 9.63 (d, J = 1.0 Hz, 1H), 8.06 (d, J = 8.9 Hz, 2H), 7.05 – 6.84 (d, J = 8.9 Hz, 2H), 5.17 (ddd, J = 8.2, 4.9, 1.0 Hz, 1H), 3.88 (s, 3H), 2.02 – 1.79 (m, 2H), 1.55 – 1.45 (m, 2H), 1.40 – 1.15 (m, 4H), 1.05 – 0.74 (m, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 198.97, 165.91, 163.83, 131.94, 121.54, 113.80, 78.54, 55.50, 31.44, 28.93, 24.68, 22.38, 13.94.

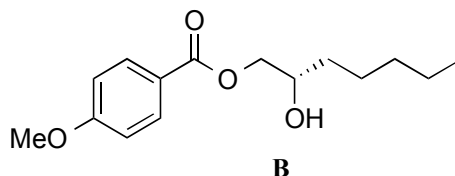
HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{20}\text{O}_4$ 265.1435; found 265.1438.

$[\alpha]_D^{20} = -19.4$, $c = 1.00$ in EtOH. Lit. $[\alpha]_D^{20} = -20.6$ ($c = 1.00$, EtOH) for 1,2-Heptanediol.⁸ Optical rotation and assignment of absolute configuration were determined by reduction of the aldehyde with LiAlH_4 in dry THF at 0°C warming to room temperature for 24 h total reaction time, followed by slow addition of MeOH, sat. aq. NH_4Cl and extraction with ethyl acetate of the resulting 1,2-Heptanediol.

Enantiomeric excess was determined to be 96% by chiral HPLC analysis, after NaBH_4 reduction in MeOH at room temperature for 6 h, followed by addition of sat. aq. NH_4Cl solution, extraction with dichloromethane and drying over MgSO_4 . The reduction conditions afford a mixture of two alcohol isomers, **A** and **B**, after partial migration of the benzoyl protecting group from the secondary alcohol to the primary alcohol.



A



B

Alcohol isomers:

A: (S)-1-hydroxyheptan-2-yl 4-methoxybenzoate

^1H NMR (500 MHz, Chloroform-*d*) δ 7.96 – 7.89 (m, 2H), 6.87 – 6.81 (m, 2H), 5.10 – 4.99 (m, 1H), 3.77 (s, 1H), 3.75 – 3.64 (m, 2H), 2.39 (br, 1H), 1.72 – 1.55 (m, 2H), 1.52 – 1.16 (m, 6H), 0.87 – 0.75 (m, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 166.77, 163.47, 131.71, 122.57, 113.62, 76.15, 65.03, 55.43, 31.65, 30.72, 25.05, 22.48, 13.98.

B (S)-2-hydroxyheptyl 4-methoxybenzoate (rearranged)

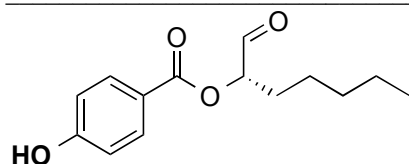
⁸ Egri, G.; Baitz-Gacs, E.; Poppe, L. *Tetrahedron: Asymmetry* **1996**, 5, 1437-1448.

¹H NMR (500 MHz, Chloroform-*d*) δ 7.96 – 7.89 (m, 2H), 6.87 – 6.81 (m, 2H), 4.27 (A of ABX, ap dd, *J* = 11.5, 3.2 Hz, 1H), 4.11 (B of ABX, ap dd, *J* = 11.4, 7.1 Hz, 1H), 3.94 – 3.84 (X of ABX, m, 1H), 3.77 (s, 1H), 2.39 (br, 1H), 1.52 – 1.16 (m, 8H), 0.87 – 0.75 (m, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 166.54, 163.50, 131.71, 122.29, 113.65, 70.17, 69.01, 55.43, 33.46, 31.78, 25.12, 22.58, 14.02.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₅H₂₂O₄ 267.1591; found 267.1599.

Separation by HPLC: CHIRALPAK 1A (AD-H), 5% iPrOH/hexanes, 0.8 ml/min, ambient temperature, 254 nm, *t_R* (A): 20.3 min (major, (*S*)), 23.6 min (minor, (*R*)), *t_R* (B): 26.0 min (major, (*S*)), 28.7 min (minor, (*R*)).



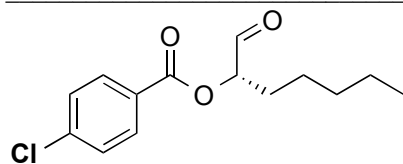
(Z)-hex-1-en-1-yl 4-hydroxybenzoate

Crude hydroformylation mixture filtered through a plug of silica and washed with dichloromethane. 82% isolated yield, dark yellow oil stored under dinitrogen.

¹H NMR (500 MHz, Chloroform-*d*) δ 9.64 (s, 1H), 8.00 (d, *J* = 7.9 Hz, 2H), 7.00 – 6.81 (m, 2H), 6.31 (broad s, 1H), 5.19 (dd, *J* = 8.3, 4.8 Hz, 1H), 2.04 – 1.79 (m, 2H), 1.57 – 1.45 (m, 2H), 1.40 – 1.29 (m, 4H), 0.96 – 0.87 (m, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 198.12, 165.16, 159.65, 131.24, 120.29, 114.43, 77.64, 30.40, 27.83, 23.66, 21.34, 12.90.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₄H₁₈O₄ 251.1278; found 251.1280.



(S)-1-oxoheptan-2-yl 4-chlorobenzoate

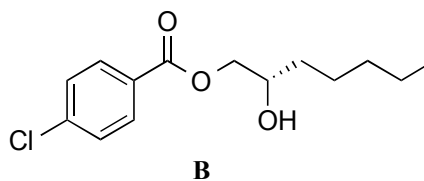
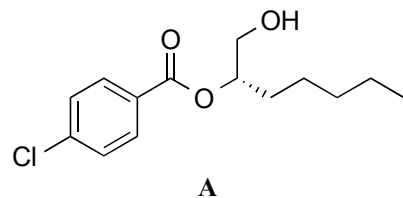
Crude hydroformylation mixture filtered through a plug of silica and washed with dichloromethane. 88% isolated yield, yellow oil.

¹H NMR (500 MHz, Chloroform-*d*) δ 9.63 (d, *J* = 0.8 Hz, 1H), 8.15 – 7.97 (m, 2H), 7.53 – 7.39 (m, 2H), 5.23 (dd, *J* = 8.3, 4.7 Hz, 1H), 2.04 – 1.81 (m, 2H), 1.63 – 1.43 (m, 2H), 1.34 (dtp, *J* = 7.4, 5.0, 2.6 Hz, 4H), 1.00 – 0.85 (m, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 198.07, 165.29, 140.06, 131.24, 128.92, 127.69, 79.00, 31.43, 28.78, 24.70, 22.38, 13.95.

HRMS (ESI-TOF) *m/z*: [M]⁺ calcd for C₁₄H₁₇ClO₃ 268.0861; found 268.0851.

Enantiomeric excess was determined to be 96% by chiral HPLC analysis, after NaBH₄ reduction in MeOH at room temperature for 6 h, followed by addition of sat. aq. NH₄Cl solution, extraction with dichloromethane and drying over MgSO₄. The reduction conditions afford a mixture of two alcohol isomers, **A** and **B**, after partial migration of the benzoyl protecting group from the secondary alcohol to the primary alcohol. Another by-product was detected in the region 3.4–3.73 ppm in ¹HNMR, tentatively assigned as a diol formed upon reduction of the ester group. The mixture was purified by silica gel flash chromatography (3:1 hexanes/ethyl acetate) prior to HPLC analysis.



Alcohol isomers:

A: (S)-1-hydroxyheptan-2-yl 4-chlorobenzoate

¹H NMR (500 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.2 Hz, 2H), 7.45 – 7.39 (m, 2H), 5.22 – 5.11 (m, 1H), 3.87 – 3.73 (m, 2H), 1.81 – 1.64 (m, 2H), 1.60 – 1.17 (m, 6H), 0.94 – 0.83 (m, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 165.07, 138.53, 130.03, 127.71, 127.61, 75.66, 63.80, 30.58, 29.57, 23.99, 21.43, 12.93.

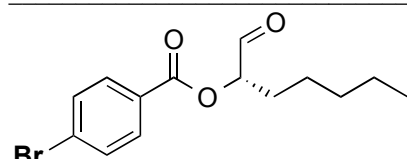
B: (S)-2-hydroxyheptyl 4-chlorobenzoate (rearranged)

¹H NMR (500 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.2 Hz, 2H), 7.45 – 7.39 (m, 2H), 4.43 – 4.33 (m, 1H), 4.23 (ap dd, *J* = 11.5, 7.1 Hz, 1H), 4.03 – 3.93 (m, 1H), 1.60 – 1.17 (m, 8H), 0.94 – 0.83 (m, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 164.90, 138.62, 130.02, 127.76, 127.32, 69.05, 68.36, 32.43, 30.72, 24.06, 21.54, 12.99.

HRMS (ESI-TOF) *m/z*: [M]⁺ calcd for C₁₄H₁₉ClO₃ 270.1018; found 270.1026.

Separation by HPLC: CHIRALPAK 1A (AD-H), 2% iPrOH/hexanes, 0.6 ml/min, ambient temperature, 254 nm, *t_R* (A): 48.4 min (major, (S)), 55.3 min (minor, (R)).

**(S)-1-oxoheptan-2-yl 4-bromobenzoate**

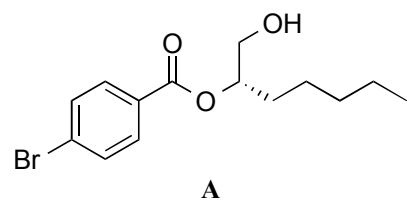
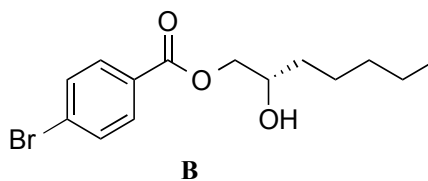
Crude hydroformylation mixture filtered through a plug of silica and washed with dichloromethane. 82% isolated yield, yellow oil.

¹H NMR (500 MHz, Chloroform-*d*) δ 9.63 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 5.23 (ddd, *J* = 8.0, 5.0, 0.8 Hz, 1H), 2.02 – 1.75 (m, 2H), 1.56 – 1.44 (m, 2H), 1.40 – 1.28 (m, 4H), 0.98 – 0.81 (m, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 196.98, 164.38, 130.87, 130.29, 127.70, 127.09, 77.97, 30.37, 27.72, 23.65, 21.33, 12.89.

HRMS (ESI-TOF) *m/z*: [M]⁺ calcd for C₁₄H₁₇BrO₃ 312.0356; found 312.0364.

Enantiomeric excess was determined to be 92% by chiral SFC analysis, after NaBH₄ reduction in MeOH at room temperature for 6 h, followed by addition of sat. aq. NH₄Cl solution, extraction with dichloromethane and drying over MgSO₄. The reduction conditions afford a mixture of two alcohol isomers, **A** and **B**, after partial migration of the benzoyl protecting group from the secondary alcohol to the primary alcohol. Another by-product was detected, tentatively assigned as transesterification product in the presence of MeOH.

**A****B****Alcohol isomers:****A: (S)-1-hydroxyheptan-2-yl 4-bromobenzoate**

¹H NMR (500 MHz, Chloroform-*d*) δ 7.97 – 7.85 (m, 2H), 7.62 – 7.55 (m, 2H), 5.23 – 5.11 (X of ABX, m, 1H), 3.83 (A of ABX, ap dd, *J* = 12.1, 3.2 Hz, 1H), 3.76 (B of ABX, ap dd, *J* = 12.1, 6.2 Hz, 1H), 1.85 – 1.63 (m, 2H), 1.62 – 1.16 (m, 6H), 0.97 – 0.80 (m, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 165.17, 130.71, 130.16, 128.64, 128.07, 75.69, 63.84, 30.58, 29.55, 23.99, 21.43, 12.94.

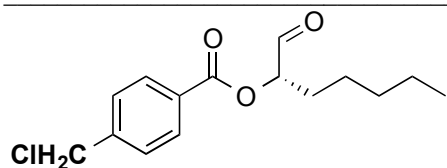
B: (S)-2-hydroxyheptyl 4-bromobenzoate (rearranged)

¹H NMR (500 MHz, Chloroform-*d*) δ 7.97 – 7.85 (m, 2H), 7.62 – 7.55 (m, 2H), 4.38 (A of ABX, ap dd, *J* = 11.4, 3.2 Hz, 1H), 4.28 – 4.18 (B of ABX, m, 1H), 4.02 – 3.94 (m, 1H), 1.62 – 1.16 (m, 8H), 0.97 – 0.80 (m, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 165.00, 130.76, 130.15, 128.63, 127.79, 69.06, 68.40, 32.43, 30.71, 24.05, 21.54, 12.99.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₄H₁₉BrO₃ 315.0591; found 315.0589.

Separation by SFC: Chiralcel OJ-H, 4% modifier, 4 ml/min, methanol, 50°C, 150 bar, t_R (**A**): 5.0 min (major, (S)), 6.5 min (minor, (R)), t_R (**B**): 7.3 min (minor, (R)), 9.8 min (major, (S)).



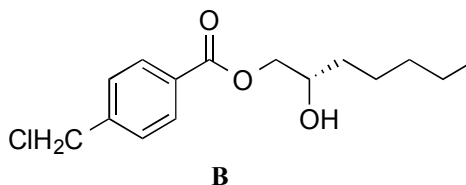
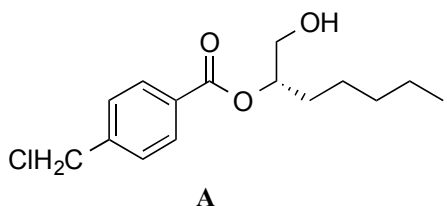
(S)-1-oxoheptan-2-yl 4-(chloromethyl)benzoate

Crude hydroformylation mixture filtered through a plug of silica and washed with dichloromethane. 78% isolated yield, yellow oil.

^1H NMR (400 MHz, Chloroform-*d*) δ 9.63 (d, J = 0.9 Hz, 1H), 8.13 – 8.06 (m, 2H), 7.53 – 7.47 (m, 2H), 5.23 (dd, J = 8.2, 4.9 Hz, 1H), 4.63 (s, 2H), 2.02 – 1.83 (m, 2H), 1.57 – 1.45 (m, 2H), 1.40 – 1.30 (m, 4H), 0.95 – 0.86 (m, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 198.31, 161.54, 142.94, 130.31, 129.18, 128.66, 78.92, 45.30, 31.43, 28.83, 24.70, 22.39, 13.96.

Enantiomeric excess was determined to be 92% by chiral HPLC analysis, after NaBH_4 reduction in MeOH at room temperature for 6 h, followed by addition of sat. aq. NH_4Cl solution, extraction with dichloromethane and drying over MgSO_4 . The reduction conditions afford a mixture of two alcohol isomers, **A** and **B**, after partial migration of the benzoyl protecting group from the secondary alcohol to the primary alcohol. The mixture was purified by silica gel flash chromatography (3:1 hexanes/ethyl acetate) prior to HPLC analysis.



Alcohol isomers:

A: (S)-1-hydroxyheptan-2-yl 4-(chloromethyl)benzoate

^1H NMR (500 MHz, Chloroform-*d*) δ 8.05 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 5.23 – 5.12 (m, 1H), 4.62 (s, 2H), 3.84 (ap dd, J = 12.1, 3.3 Hz, 1H), 3.77 (ap dd, J = 12.1, 6.3 Hz, 1H), 2.09 (s, 1H), 1.83 – 1.64 (m, 2H), 1.62 – 1.22 (m, 6H), 0.95 – 0.83 (m, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 166.40, 142.45, 130.16, 130.12, 128.52, 76.60, 64.98, 45.34, 31.62, 30.62, 25.02, 22.47, 13.97.

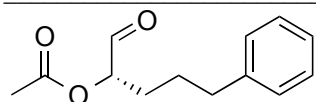
B: (S)-2-hydroxyheptyl 4-(chloromethyl)benzoate (rearranged)

^1H NMR (500 MHz, Chloroform-*d*) δ 8.09 – 8.02 (m, 2H), 7.47 (d, J = 8.1 Hz, 2H), 4.62 (s, 2H), 4.39 (A of ABX, ap dd, J = 11.4, 3.1 Hz, 1H), 4.23 (B of ABX, ap dd, J = 11.4, 7.1 Hz, 1H), 4.04 – 3.94 (m, 1H), 2.09 (br s, 1H), 1.62 – 1.22 (m, 8H), 0.95 – 0.83 (m, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 166.22, 142.51, 130.10, 129.86, 128.54, 70.14, 69.34, 45.32, 33.45, 31.76, 25.09, 22.57, 14.02.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{21}\text{ClO}_3$ 285.1252; found 285.1249.

Separation by HPLC: CHIRALPAK 1A (AD-H), 5% iPrOH/hexanes, 0.8 ml/min, ambient temperature, 254 nm, t_R (**A**): 20.3 min (major, (S)), 23.6 min (minor, (R)), t_R (**B**): 26.0 min (major, (S)), 28.7 min (minor (R)).



(S)-1-oxo-5-phenylpentan-2-yl acetate

Crude hydroformylation mixture filtered through a plug of silica and washed with dichloromethane. 88% isolated yield, yellow oil.

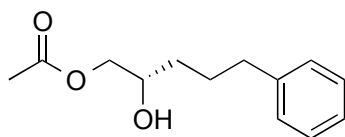
¹H NMR (400 MHz, Chloroform-*d*) δ 9.50 (d, J = 0.8 Hz, 1H), 7.32 – 7.25 (m, 2H), 7.24 – 7.14 (m, 3H), 5.01 (dd, J = 7.5, 4.3 Hz, 1H), 2.69 – 2.62 (m, 2H), 2.17 (s, 3H), 1.92 – 1.70 (m, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 198.18, 170.59, 141.31, 128.46, 128.37, 126.07, 78.13, 35.38, 28.17, 26.67, 20.62.

HRMS (ESI-TOF) m/z : [M+H]⁺ calcd for C₁₃H₁₆O₃ 221.1173; found 221.1174.

$[\alpha]_D^{20}$ = –0.8, c = 1.00 in CHCl₃. Lit. $[\alpha]_D^{RT}$ = –0.9 (c = 1.00, CHCl₃) for 5-Phenyl-1,2-Pentanediol, $[\alpha]_D^{20}$ = –13.6 (c = 1.00, CHCl₃) for (S)-4-Phenyl-1,2-Butanediol.⁹ Optical rotation and assignment of absolute configuration were determined by reduction of the aldehyde with LiAlH₄ in dry THF at 0°C warming to room temperature for 24 h total reaction time, followed by slow addition of MeOH, sat aq. NH₄Cl and extraction with ethyl acetate of the resulting 5-Phenyl-1,2-Pentanediol.

Enantiomeric excess was determined to be 93% by chiral HPLC analysis, after NaBH₄ reduction in MeOH at room temperature for 5 h, followed by addition of sat. aq. NH₄Cl solution, extraction with dichloromethane and drying over MgSO₄. The reduction conditions afford a mixture of two alcohol isomers, **A** and **B**, after partial migration of the benzoyl protecting group from the secondary alcohol to the primary alcohol. The mixture was purified and the two isomers separated by silica gel flash chromatography (3:1 hexanes/ethyl acetate) prior to HPLC analysis.



Alcohol isomer:

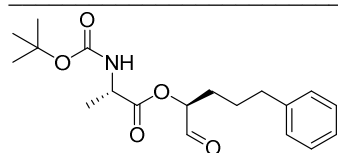
(S)-2-hydroxy-5-phenylpentyl acetate (rearranged):

¹H NMR (500 MHz, Chloroform-*d*) δ 7.30 – 7.24 (m, 2H), 7.20 – 7.15 (m, 3H), 4.11 (A of ABX, ap dd, J = 11.4, 3.0 Hz, 1H), 3.93 (B of ABX, ap dd, J = 11.4, 7.4 Hz, 1H), 3.88 – 3.81 (m, 1H), 2.64 (t, J = 7.6 Hz, 2H), 2.22 (d, J = 4.3 Hz, 1H), 2.07 (s, 3H), 1.88 – 1.75 (m, 1H), 1.74 – 1.62 (m, 1H), 1.54 – 1.47 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 171.26, 142.01, 128.42, 128.36, 125.86, 69.75, 68.71, 35.72, 32.83, 27.17, 20.91.

HRMS (ESI-TOF) m/z : [M+H]⁺ calcd for C₁₃H₁₈O₃ 223.1329; found 223.1329.

Separation by HPLC: CHIRALPAK 1D, 6% iPrOH/hexanes/0.1% TFA, 0.6 ml/min, ambient temperature, 220 nm, t_R : 31.3min (major, (S)), 38.8 min (minor, (R)).



(S)-(S)-1-oxo-5-phenylpentan-2-yl 2-((tert-butoxycarbonyl)amino)propanoate

Reaction mixture filtered through a pad of celite and washed with DCM. 83% isolated yield, orange oil.

¹H NMR (400 MHz, Chloroform-*d*) δ 9.48 (s, 1H), 7.34 – 7.25 (m, 2H), 7.24 – 7.13 (m, 3H), 5.09 (dd, J = 7.6, 4.5 Hz, 1H), 5.02 (d, J = 7.8 Hz, 1H), 4.47 – 4.35 (m, 1H), 2.66 (dd, J = 8.0, 6.0 Hz, 2H), 1.48 (d, J = 7.2 Hz, 3H), 1.44 (s, 9H).

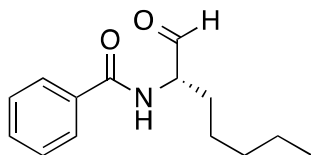
¹³C NMR (126 MHz, CDCl₃) δ 197.26, 173.14, 155.14, 141.19, 128.45, 128.38, 126.05, 80.00, 78.54, 49.12, 35.31, 28.29, 27.96, 26.50, 18.55.

HRMS (ESI-TOF) m/z : [M+H]⁺ calcd for C₁₉H₂₇NO₅ 350.1962; found 350.1953.

Enantiomeric excess was determined to be 92% by integration of aldehyde signals in crude ¹H NMR.

⁹ a. Kadyrov, R.; Koenigs, R. M.; Brinkmann, C.; Voigtlaender, D.; Rueping, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 7556-7559. b. Martynow, J. G.; Józwiak, J.; Szelejewski, W.; Achmatowicz, O.; Kutner, A. et al. *Eur. J. Org. Chem.* **2007**, 689-703.

V. Data for enamide AHF



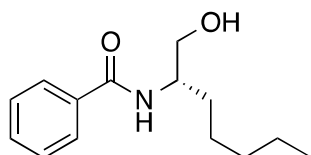
2-benzamido-heptanal.

Started with 100 mg enamide, 100% conversion.

¹H NMR (400 MHz, Chloroform-*d*) δ 9.67 (s, 1H), 7.91 – 7.76 (m, 2H), 7.58 – 7.49 (m, 1H), 7.49 – 7.37 (m, 2H), 6.86 (d, *J* = 6.9 Hz, 1H, *NH*), 4.76 (q, *J* = 6.6 Hz, 1H), 2.13 – 1.97 (m, 1H), 1.82 – 1.70 (m, 1H), 1.51 – 1.20 (m, 6H), 0.96 – 0.80 (m, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 199.46, 167.41, 133.80, 131.88, 128.66 (2C), 127.10 (2C), 59.24, 31.60, 29.09, 24.86, 22.42, 13.96.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₄H₂₀NO₂ 234.1489; found 234.1492.



Alcohol: (*S*)-*N*-(1-hydroxyheptan-2-yl)benzamide

¹H NMR (400 MHz, Chloroform-*d*) δ 7.82 – 7.69 (m, 2H), 7.51 – 7.43 (m, 1H), 7.42 – 7.32 (m, 2H), 6.61 (d, *J* = 8.3 Hz, 1H, *NH*), 4.12 (m, 1H, *X of ABX*), 3.78 – 3.70 (m, 1H, *A of ABX*), 3.70 – 3.60 (m, 1H, *B of ABX*), 3.50 (br s, 1H, *OH*), 1.70 – 1.51 (m, 2H), 1.46 – 1.33 (m, 2H), 1.34 – 1.22 (m, 4H), 0.95 – 0.80 (m, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 168.35, 134.50, 131.61, 128.61, 127.09, 65.37, 52.33, 31.80, 31.36, 25.98, 25.95, 22.63, 14.12.

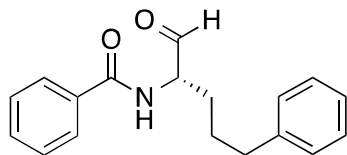
HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₄H₂₂NO₂ 236.1646; found 236.1638.

Separation by SFC: 85% *ee*.

Chiralcel OJ-H, 50 °C, 150 bar, MeOH modifier 2% for 1 min, then ramp to 8% over 6 min, hold 20 min, 2 mL/min flow, λ = 210 nm. *t_r* = 14.8 min (*S*), 16.9 min (*R*).

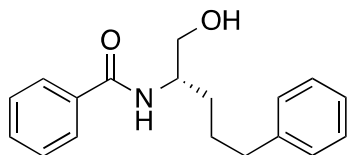
Separation by HPLC: 84% *ee*.

Chiralpak IA, 8% 2-propanol / 92% hexane, 1 mL/min flow, ambient temperature, λ = 254 or 220 nm. *t_r* = 8.5 min (*S*), 11.4 min (*R*).



2-benzamido-5-phenylpentanal.

Started with 104 mg of enamide. 87% conversion, 81.1% yield (aldehyde).



Alcohol: (S)-N-(1-hydroxy-5-phenylpentan-2-yl)benzamide

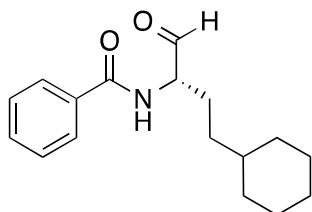
¹H NMR (500 MHz, Chloroform-*d*) δ 7.73 (d, *J* = 7.7 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 7.4 Hz, 2H), 7.21 – 7.11 (m, 3H), 6.46 (d, *J* = 8.4 Hz, 1H), 4.23 – 4.08 (m, 1H, *X of ABX*), 3.79 – 3.68 (m, 1H, *A of ABX*), 3.68 – 3.57 (m, 1H, *B of ABX*), 3.10 (t, *J* = 5.0 Hz, 1H, OH), 2.74– 2.54 (m, 2H), 1.78– 1.68 (m, 2H), 1.68 – 1.55 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 168.28, 142.02, 134.42, 131.69, 128.66, 128.52, 128.48, 127.08, 125.98, 65.41, 52.08, 35.74, 30.94, 28.08.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₈H₂₂NO₂ 284.1646; found 284.1652.

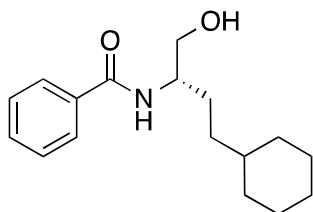
Separation by HPLC: 90% *ee*.

Chiralpak IA, 8% 2-propanol / 92% hexane, 1 mL/min flow, ambient temperature, λ=254 or 220 nm. *t_r* = 10.2 min (major, *S*), 13.4 min (*R*).



2-benzamido-4-cyclohexylbutanal.

80% conversion, 78% isolated yield (alcohol). Started with 150 mg enamide, isolated 131.9 mg alcohol.



Alcohol: (S)-N-(4-cyclohexyl-1-hydroxybutan-2-yl)benzamide

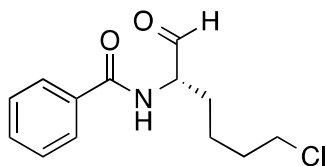
¹H NMR (400 MHz, Chloroform-*d*) δ 7.81 – 7.72 (m, 2H), 7.50 (ddt, *J* = 8.7, 6.3, 1.2 Hz, 1H), 7.42 (tt, *J* = 6.7, 1.6 Hz, 2H), 6.37 (d, *J* = 7.9 Hz, 1H, *NH*), 4.16 – 4.05 (m, 1H, *X of ABX*), 3.78 (app. dd, *J* = 11.1, 3.5 Hz, 1H, *A of ABX*), 3.67 (app. dd, *J* = 11.0, 5.4 Hz, 1H, *B of ABX*), 2.96 (br. s, 1H, OH), 1.79 – 1.51 (m, 7H), 1.34 – 1.05 (m, 6H), 0.96 – 0.79 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 168.26, 134.43, 131.60, 128.60 (2C), 126.99 (2C), 65.72, 52.67, 37.62, 33.84, 33.34, 33.29, 28.69, 26.62, 26.33 (2C).

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₇H₂₆NO₂ 276.1959; found 276.1956.

Separation by HPLC: 84% *ee*.

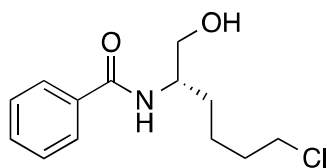
Chiralpak IA, 8% 2-propanol / 92% hexane, 1 mL/min flow, ambient temperature, λ=254 or 220 nm. *t_r* = 8.5 min (major, *S*), 12.6 min (*R*).



Aldehyde: 2-Benzamido-6-chlorohexanal.

79% conversion, 68% isolated yield. Started with 67 mg of enamide. Isolated alcohol as a yellow oil, 52 mg.

¹H NMR (400 MHz, Chloroform-*d*) δ 9.69 (s, 1H), 7.88 – 7.77 (m, 2H), 7.57 – 7.50 (m, 1H), 7.50 – 7.41 (m, 2H), 6.85 (d, *J* = 6.8 Hz, 1H), 4.78 (td, *J* = 6.9, 5.5 Hz, 1H), 3.54 (td, *J* = 6.4, 2.1 Hz, 2H), 2.18 – 2.04 (m, 1H), 1.95 – 1.72 (m, 3H), 1.69 – 1.48 (m, 2H).



Alcohol: (S)-N-(6-chloro-1-hydroxyhexan-2-yl)benzamide

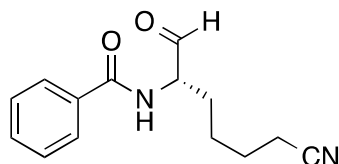
¹H NMR (500 MHz, Chloroform-*d*) δ 7.78 – 7.74 (m, 2H), 7.48 (tt, *J* = 7.5, 1.4 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 6.53 (d, *J* = 8.3 Hz, 1H), 4.21 – 4.09 (m, 1H, *X* of ABX), 3.82 – 3.73 (m, 1H, *A* of ABX), 3.69 (dt, *J* = 10.7, 4.6 Hz, 1H, *B* of ABX), 3.54 (t, *J* = 6.5 Hz, 2H), 3.08 (t, *J* = 4.9 Hz, 1H, *OH*), 1.89 – 1.73 (m, 2H), 1.73 – 1.61 (m, 2H), 1.61 – 1.47 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 168.28, 134.41, 131.76, 128.71 (2C), 127.09 (2C), 65.23, 51.93, 44.90, 32.32, 30.63, 23.54.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₃H₁₉ClNO₂ 256.1099; found 256.1096.

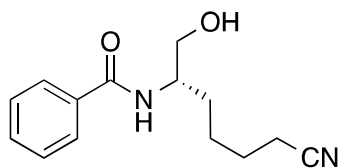
Separation by HPLC: 92% *ee*.

Chiralpak IA, 8% 2-propanol / 92% hexane, 1.2 mL/min flow, ambient temperature, λ=254 or 220 nm. *t_r* = 9.2 min (major, *S*), 15.0 min (*R*).



Aldehyde: 2-Benzamido-6-cyanoheptanal.

100% conversion.



Alcohol: (S)-N-(6-cyano-1-hydroxyhexan-2-yl)benzamide

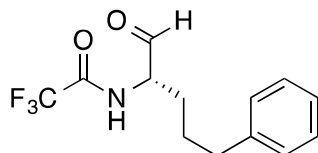
¹H NMR (400 MHz, Chloroform-*d*) δ 7.81 – 7.73 (m, 2H), 7.53 – 7.47 (m, 1H), 7.45 – 7.39 (m, 2H), 6.54 (d, *J* = 8.3 Hz, 1H), 4.22 – 4.07 (m, 1H, *X* of ABX), 3.82 – 3.66 (m, 2H, *AB* of ABX), 2.89 (br. s, 1H), 2.35 (t, *J* = 6.7 Hz, 2H), 1.79 – 1.62 (m, 4H), 1.62 – 1.49 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 168.13, 134.35, 131.86, 128.78 (2C), 127.10 (2C), 119.72, 77.16, 65.13, 51.53, 30.65, 25.36, 25.21, 17.21.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₄H₁₉N₂O₂ 247.1442; found 247.1438.

Separation by HPLC: 94% *ee*.

Chiralpak IA, 10% 2-propanol / 90% hexane, 1.2 mL/min flow, ambient temperature, λ=254 or 220 nm. *t_r* = 13.4 min (major, *S*), 24.1 min (*R*).

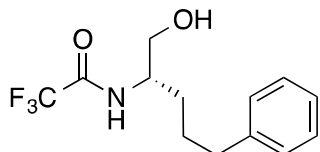


Aldehyde: (S)-2,2,2-trifluoro-N-(1-oxo-5-phenylpentan-2-yl)acetamide

100% conversion, 91% crude yield. Started from 100 mg enamide, isolated 103.4 mg alcohol.

¹H NMR (400 MHz, Chloroform-*d*) δ 9.49 (s, 1H), 8.30 (d, *J* = 8.7 Hz, 1H, NH), 7.31 – 7.21 (m, 2H), 7.21 – 7.06 (m, 3H), 4.52 (td, *J* = 8.4, 4.9 Hz, 1H), 2.77 – 2.54 (m, 2H), 1.77 – 1.56 (m, 4H).

¹⁹F NMR (377 MHz, CDCl₃) δ -75.73.



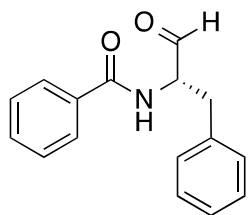
Alcohol: (S)-2,2,2-trifluoro-N-(1-hydroxy-5-phenylpentan-2-yl)acetamide

¹H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.24 (m, 2H), 7.23 – 7.13 (m, 3H), 6.51 (d, *J* = 8.4 Hz, 1H), 4.12 – 3.98 (m, 1H, X of ABX), 3.73 (app. dd, *J* = 11.0, 3.6 Hz, 1H, A of ABX), 3.67 (app. dd, *J* = 11.1, 4.1 Hz, 1H, B of ABX), 2.71 – 2.57 (m, 2H), 1.80 (br s, 1H), 1.75 – 1.54 (m, 4H).

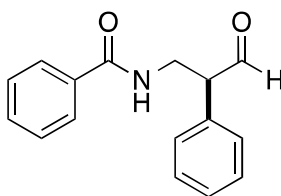
¹³C NMR (126 MHz, Chloroform-*d*) δ 157.38 (q, *J* = 37.0 Hz), 141.66, 128.60 (2C), 128.52 (2C), 126.16, 116.01 (q, *J* = 288.0 Hz), 63.83, 51.74, 35.57, 30.40, 27.75.

¹⁹F NMR (377 MHz, CDCl₃) δ -75.83.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₃H₁₇F₃NO₂ 276.1206; found 276.1198.



α (major)



β (minor)

Aldehyde, alpha: N-(1-Formyl-2-phenylethyl) benzamide

86.3% conversion, 81.2% isolated yield (aldehyde), 6.3:1 α:β.

Characterization data are consistent with literature report.¹⁰

¹H NMR (400 MHz, Acetone-*d*₆) δ 9.73 (s, 1H), 8.08 (s, 1H), 7.85 (dd, *J* = 7.5, 1.7 Hz, 2H), 7.58 – 7.50 (m, 1H), 7.50 – 7.41 (m, 2H), 7.35 – 7.23 (m, 4H), 7.24 – 7.15 (m, 1H), 4.64 (ddd, *J* = 9.5, 7.3, 4.8 Hz, 1H), 3.36 (dd, *J* = 14.1, 4.8 Hz, 1H), 3.09 (dd, *J* = 14.1, 9.6 Hz, 1H).

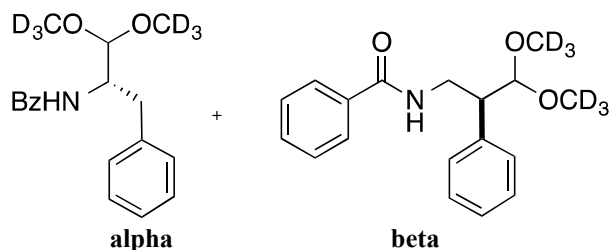
HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₆H₁₆NO₂ 254.1176; found 254.1170.

[α]_D²⁰ = -103.1, *c* = 1.29 in EtOH. Lit. [α]_D^{RT} = -109 (*c* = 3.00, EtOH) for *N*-(1-Formyl-2-phenylethyl) benzamide (aldehyde, alpha).¹¹ Pure *N*-(1-Formyl-2-phenylethyl) benzamide can be separated from the minor regioisomer by addition of CDCl₃ to the crude hydroformylation mixture and filtration of the resulting white solid (the alpha regioisomer).

When the NMR is taken in methanol-*d*₄ (to obtain accurate b:l ratios), the dimethoxyacetal forms spontaneously:

¹⁰ Pan, H.; Xie, Y.; Liua, M.; Shi, Y. *RSC Adv.* **2014**, *4*, 2389-2392.

¹¹ Silver, M. S.; Haskell, J. H. *J. Med. Chem.* **1989**, *32*, 1253-1259.

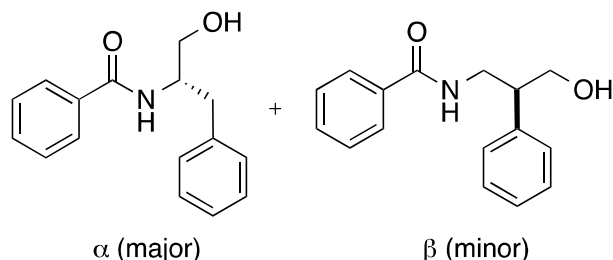


Dimethoxyacetal, alpha: (*S*)-*N*-(1,1-dimethoxy-3-phenylpropan-2-yl)benzamide

¹H NMR (500 MHz, Methanol-*d*₄) δ 7.74 – 7.67 (m, 2H), 7.52 – 7.35 (m, 3H), 7.34 – 7.20 (m, 4H), 7.18 – 7.12 (m, 1H), 4.66 (t, *J* = 3.4 Hz, 1H), 4.47 – 4.32 (m, 1H), 3.13 (app. ddd, *J* = 13.1, 7.7, 4.7 Hz, 1H), 2.92 (app. ddd, *J* = 14.8, 9.9, 6.1 Hz, 1H).

Dimethoxyacetal, beta: *N*-(3,3-dimethoxy-2-phenylpropyl)benzamide

¹H NMR (500 MHz, Methanol-*d*₄) δ 7.76 – 7.10 (m, 10H), 4.81 (d, *J* = 4.5 Hz, 1H, acetal H), 3.94 – 3.82 (m, 1H, *A* of *ABX*), 3.79 – 3.70 (m, 1H, *B* of *ABX*), 3.29 – 3.21 (m, 1H, *X* of *ABX*).



Alcohol, Alpha insertion: (*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)benzamide

¹H NMR (500 MHz, Methanol-*d*₄) δ 7.76 – 7.71 (m, 2H), 7.52 (tt, *J* = 7.4, 1.1 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.33 – 7.25 (m, 4H), 7.19 (tt, *J* = 6.9, 1.6 Hz, 1H), 4.36 (dq, *J* = 8.5, 5.7 Hz, 1H), 3.67 (d, *J* = 5.5 Hz, 2H), 3.04 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.88 (dd, *J* = 13.7, 8.5 Hz, 1H).

¹³C NMR (126 MHz, MeOD) δ 170.35, 139.97, 136.00, 132.49, 130.34 (2C), 129.42 (2C), 129.36 (2C), 128.27 (2C), 127.33, 64.29, 54.96, 49.00, 37.99.

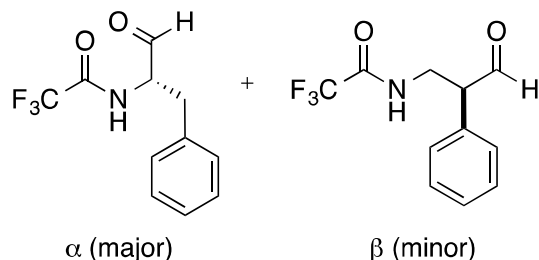
Alcohol, Beta insertion: *N*-(3-hydroxy-2-phenylpropyl)benzamide

¹H NMR (400 MHz, Methanol-*d*₄) δ 7.68 (dd, *J* = 7.2, 1.6 Hz, 2H), 7.53 – 7.45 (m, 2H), 7.44 – 7.36 (m, 2H), 7.33 – 7.21 (m, 4H), 3.82 (d, *J* = 6.4 Hz, 2H), 3.77 (dd, *J* = 13.5, 7.2 Hz, 1H), 3.63 (dd, *J* = 13.7, 7.9 Hz, 1H), 3.23 – 3.11 (m, 1H).

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₆H₁₈NO₂ 256.1333; found 256.1342.

Separation by HPLC: 98.3% *ee* α, 31.9% *ee* β.

Chiralpak IA, 8% 2-propanol / 92% hexane, 1 mL/min flow, ambient temperature, λ=220 nm. *t*_r (alpha isomer) = 11.5 min (major, *S*), 13.9 min (minor, *R*). *t*_r (beta isomer) = 19.3 min (minor), 21.8 min (major).



Aldehyde, alpha: 2,2,2-Trifluoro-*N*-[(1*S*)-1-formyl-2-phenylethyl]acetamide

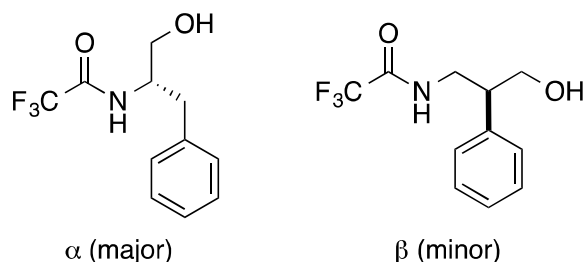
100% conversion, 65.5% isolated yield (alcohol).

Characterization data are consistent with literature report.¹²

¹H NMR (400 MHz, CDCl₃) δ 9.64 (s, 1H), 7.50 – 7.09 (m, 5H), 7.02 (br. s, 1H), 4.82 (app. q, *J* = 6.6 Hz, 1H), 3.30 (dd, *J* = 14.2, 5.5 Hz, 1H), 3.22 (dd, *J* = 14.2, 7.2 Hz, 1H).

¹⁹F NMR (377 MHz, CDCl₃) δ -75.86 (alpha), -76.05 (beta).

[α]_D²⁰ = -10.0, *c* = 1.7 in acetone for 12.3:1 α:β mixture of 2,2,2-trifluoro-*N*-(1-hydroxy-3-phenylpropan-2-yl)acetamide and 2,2,2-trifluoro-*N*-(3-hydroxy-2-phenylpropyl)acetamide. Lit. [α]_D^{RT} = -18.1 (*c* = 2.00, acetone).¹³



Alcohol, alpha: (S)-2,2,2-trifluoro-*N*-(1-hydroxy-3-phenylpropan-2-yl)acetamide

Characterization data agrees with literature reports.¹⁴

¹H NMR (400 MHz, Methanol-*d*₄) δ 7.38 – 7.13 (m, 5H), 4.17 (dq, *J* = 8.7, 5.9 Hz, 1H), 3.60 (qd, *J* = 11.2, 5.7 Hz, 2H), 2.96 (dd, *J* = 13.8, 5.9 Hz, 1H), 2.75 (dd, *J* = 13.8, 8.9 Hz, 1H).

¹⁹F NMR (377 MHz, MeOD) δ -77.17.

Alcohol, beta: 2,2,2-trifluoro-*N*-(3-hydroxy-2-phenylpropyl)acetamide

¹H NMR (400 MHz, Methanol-*d*₄) δ 7.34 – 7.15 (m, 5H), 3.76 (dd, *J* = 6.5, 2.4 Hz, 2H), 3.67 (dd, *J* = 13.4, 6.7 Hz, 1H), 3.60 – 3.52 (m, 1H), 3.10 (dq, *J* = 8.5, 6.7 Hz, 1H).

¹⁹F NMR (377 MHz, Methanol-*d*₄) δ -77.37.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₁H₁₃F₃NO₂ 248.0893; found 248.0897.

Separation by HPLC: 90% *ee* α, 54% *ee* β.

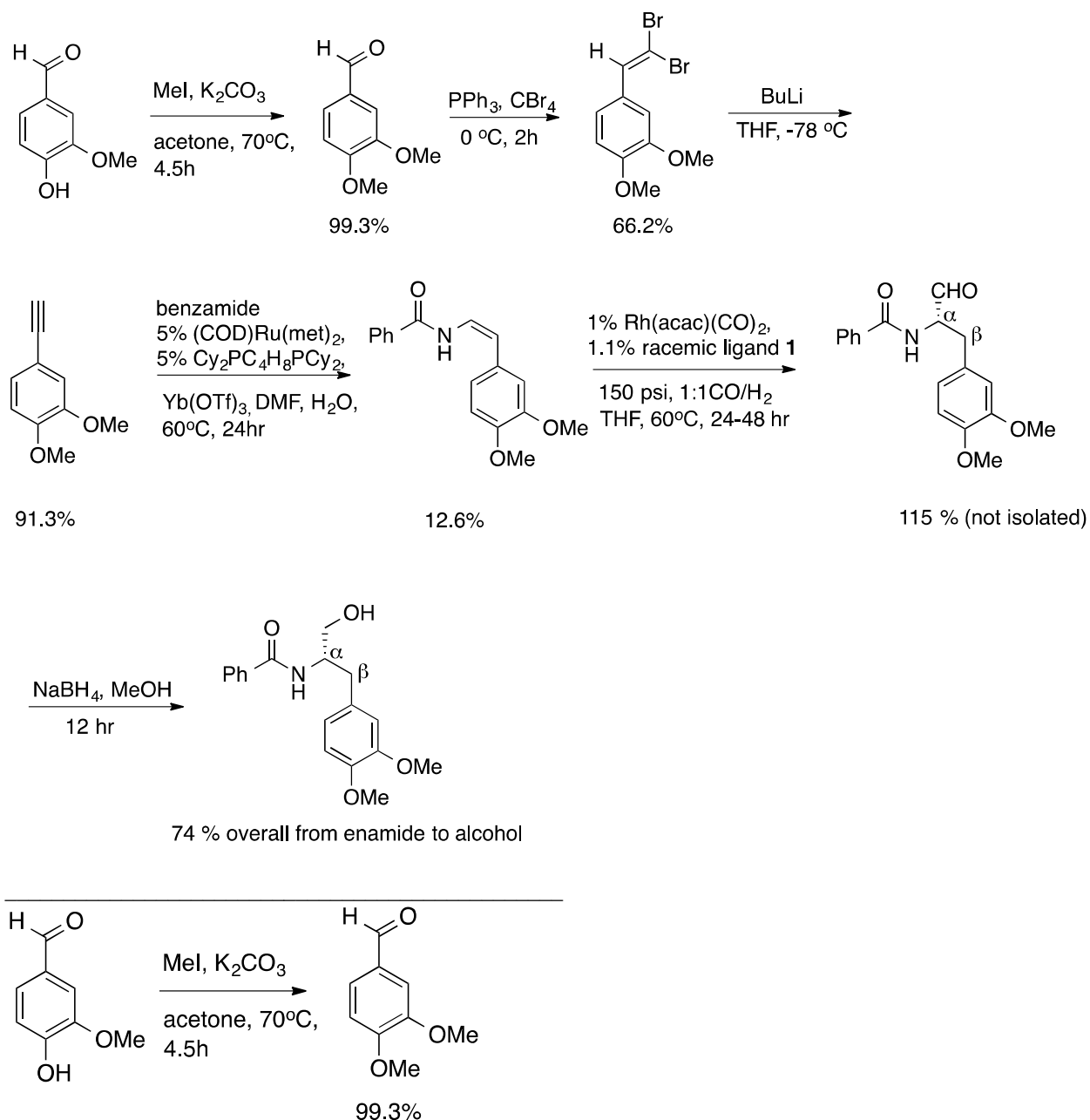
Chiralpak IA, 5% 2-propanol / 95% hexane, 1 mL/min flow, ambient temperature, λ=220 nm. *t*_r (alpha isomer) = 8.2 min (major, *S*), 9.5 min (minor, *R*). *t*_r (beta isomer) = 12.9 min (major), 14.1 min (minor).

¹² Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.*, **1999**, *121*, 8401–8402.

¹³ Jiang, H.; Sun, L.; Yuan, S.; Lu, W.; Wan, W.; Zhu, S.; Hao, J. *Tetrahedron* **2012**, *13*, 2858–2862.

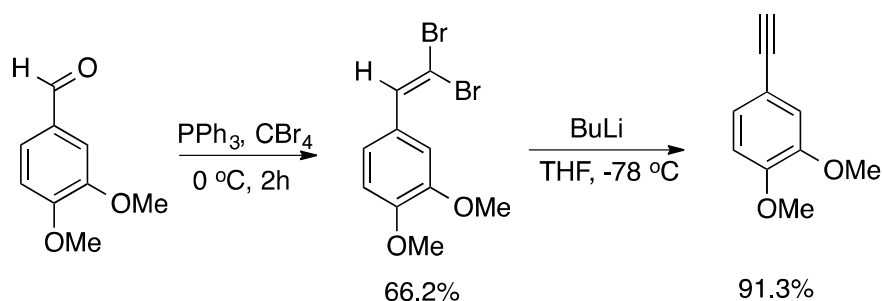
¹⁴ Jiang, H.; Yan, L.; Xu, M.; Lu, W.; Cai, Y.; Wan, W.; Yao, J.; Wu, S.; Zhu, S.; Hao, J. *J. Org. Chem.* **2013**, *78*, 4261–4269.

VI. Synthesis of L-DOPA precursor



Methylation: 12.172 g (80 mmol) of vanillin was added into 130 mL of acetone, and the mixture was warmed to 60°C to dissolve the vanillin. Then 11.222 g (80 mmol) of K_2CO_3 and 8 mL (120 mmol) of MeI were added, and the mixture was stirred at $60\text{--}70^\circ\text{C}$ overnight (17 hours) under reflux. The reaction mixture was filtered and the solids washed with acetone, then the filtrate was concentrated under vacuum to yield the desired product, which was further purified by flash column chromatography, to give 13.2 g (99.3% yield) of pure product. Characterization data are consistent with previously reported results.¹⁵

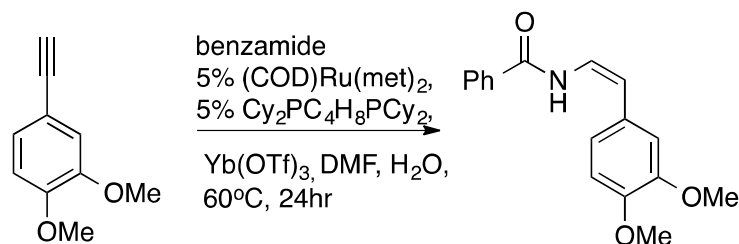
¹⁵Liu, X.; Xia, Q.; Zhang, Y.; Chen, C.; Chen, W. *J. Org. Chem.* **2013**, *78*, 8531–8536.



Corey-Fuchs:

1) To a solution of the methylated aldehyde (6.646g, 40 mmol) in dry DCM, triphenylphosphine (20.983g, 80mmol) was added. The mixture was cooled to 0 °C, and a solution of carbon tetrabromide (14.592g, 44 mmol) in dry DCM was added dropwise. The reaction mixture was allowed to gradually warm up to room temperature and stirred for another two hours after reaching room temperature. The reaction mixture was quenched with water, and the organic layer was separated and washed with brine. The crude mixture was dried over magnesium sulfate, filtered, concentrated under vacuum, and purified by flash column chromatography to give the dibromoethene derivative (8.521g, 66.2%). Characterization data are consistent with previously reported results.¹⁶

2) *n*BuLi (26.46 mL of 2.5 M solution in hexane, 66.15 mmol) was added dropwise to a solution of the dibromoethene derivative (8.521g, 26.46 mmol) in dry THF at -78 °C. The resulting solution was stirred at -78 °C for 1h, and then gradually warmed to room temperature. The reaction was quenched using saturated aqueous NH₄Cl, and the mixture was extracted with EtOAc. The organic layer was washed with water (x1) and brine (x1). After drying over magnesium sulfate and concentration under vacuum, the crude product was purified by column chromatography to yield alkyne (3.915g, 91.3%). Characterization data are consistent with previously reported results.¹⁶



12.6%

Enamide formation: The enamide was synthesized by the general procedure reported above, starting from 3.915g (24.17 mmol) of the alkyne. After the typical extractive workup and removal of the solvent under vacuum, the crude mixture was left overnight. Upon standing, the desired product precipitated out, and the dark liquid impurities were dissolved in EtOAc (the product does not dissolve in EtOAc). The product was separated using filtration, and the solids were washed with EtOAc. The product was recrystallized from a mixture of DCM and hexane

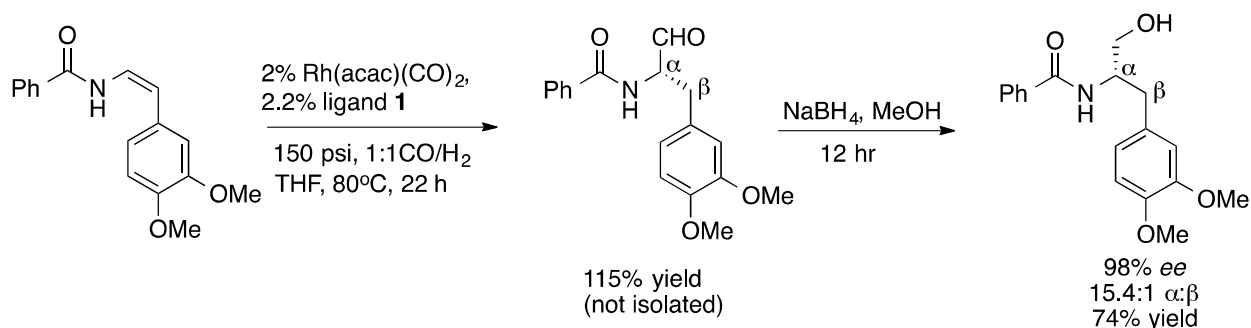
¹⁶Rosiak, A.; Frey, W.; Christoffers, J. *Eur. J. Org. Chem.* **2006**, 4044–4054.

four times to yield 0.8624g of light green crystals (12.6% yield). Characterization data are consistent with previously reported results.¹⁷

¹H NMR (500 MHz, Chloroform-*d*) δ 8.37 (d, *J* = 11.0 Hz, 1H), 7.80 – 7.73 (m, 2H), 7.58 – 7.50 (m, 1H), 7.50 – 7.41 (m, 2H), 7.16 (dd, *J* = 11.1, 9.4 Hz, 1H), 6.94 (d, *J* = 2.1 Hz, 2H), 6.83 (d, *J* = 1.5 Hz, 1H), 5.85 (d, *J* = 9.4 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 164.19, 149.51, 148.13, 133.41, 132.15, 128.87, 128.51, 127.02, 121.75, 119.99, 111.73, 111.29, 110.94, 55.98, 55.93.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₇H₁₇NO₃ 284.1282; found 284.1279.



AHF and reduction: 0.5 mL of 20 mM Rh(acac)(CO)₂ solution in THF was combined with 1.1 mL of 20 mM ligand solution in THF with about 50% potency. The mixture was stirred in a pressure bottle under 150 psi of syngas (1:1 H₂/CO) at 70–80 °C for 1 hr, then the entire mixture was removed via syringe and injected into another pressure bottle containing 0.1418g (0.5 mmol) of the olefin. The mixture was pressurized to 155 psi of syngas, submerged in an 80 °C oil bath, and stirred at a high rate to ensure sufficient gas-liquid mixing for 22 hours. The crude mixture was passed through a short pad of silica, rinsed with THF. Then the mixture was concentrated in vacuum to give the aldehyde (>100% crude yield).

The crude aldehyde was dissolved in MeOH, and excess NaBH₄ was added to the solution at 0 °C, and the resulting mixture was stirred overnight. The crude material was purified using small-scale flash column chromatography (60% EtOAc in hexane) to give 0.116g of the alcohol product (74% yield from enamide).

Aldehyde:

¹H NMR (500 MHz, 3:1 Toluene-*d*₈:CDCl₃) δ 9.39 (s, 1H), 7.64 (d, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 2H), 6.62 (d, *J* = 5.1 Hz, 1H), 6.59 – 6.51 (m, 3H), 4.61 (q, *J* = 6.1 Hz, 1H), 3.59 (s, 4H), 3.55 (s, 3H), 3.13 – 2.99 (m, 2H).

¹³C NMR (126 MHz, 3:1 Toluene-*d*₈:CDCl₃) δ 198.95, 167.39, 149.71, 148.80, 134.21, 132.23, 129.05 (2C), 128.64, 127.50 (2C), 121.84, 113.13, 111.88, 60.79, 56.027, 55.961, 34.86.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₈H₁₉NO₄ 314.1387; found 314.1392.

Alcohol:

¹H NMR (500 MHz, Chloroform-*d*) δ 7.71 – 7.66 (m, 2H), 7.52 – 7.46 (m, 1H), 7.45 – 7.37 (m, 2H), 6.83 – 6.76 (m, 3H), 6.46 (d, *J* = 7.4 Hz, 1H), 4.42 – 4.25 (m, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.82 – 3.68 (m, 2H), 2.95 (d, *J* = 7.2 Hz, 2H), 2.91 (br. s, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 168.15, 149.25, 148.01, 134.38, 131.85, 131.82, 130.18, 128.75, 127.03, 121.37, 112.40, 111.46, 64.35, 56.04, 55.99, 53.48, 36.70.

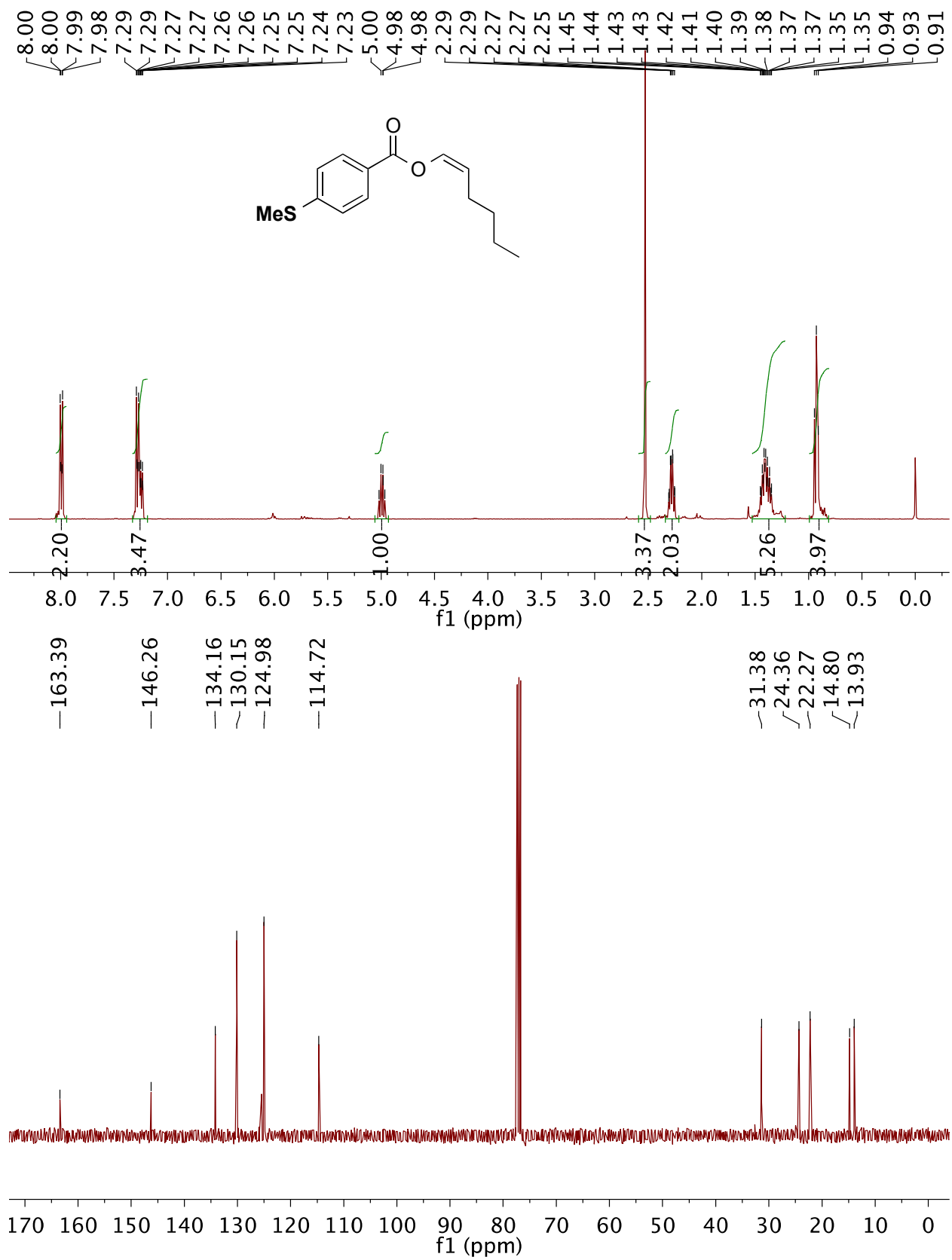
HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₈H₂₁NO₄ 316.1544; found 316.1550.

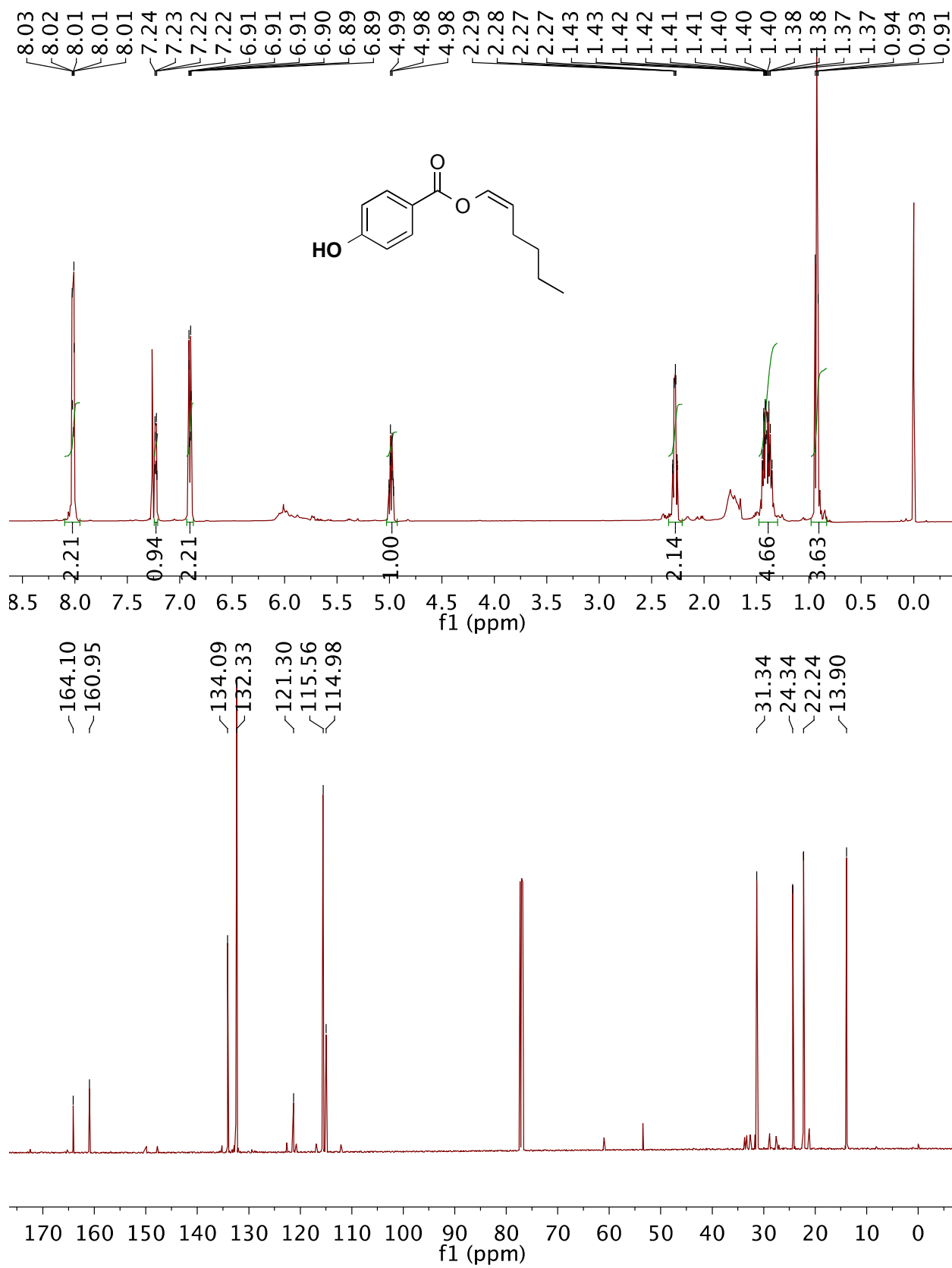
Separation by HPLC:

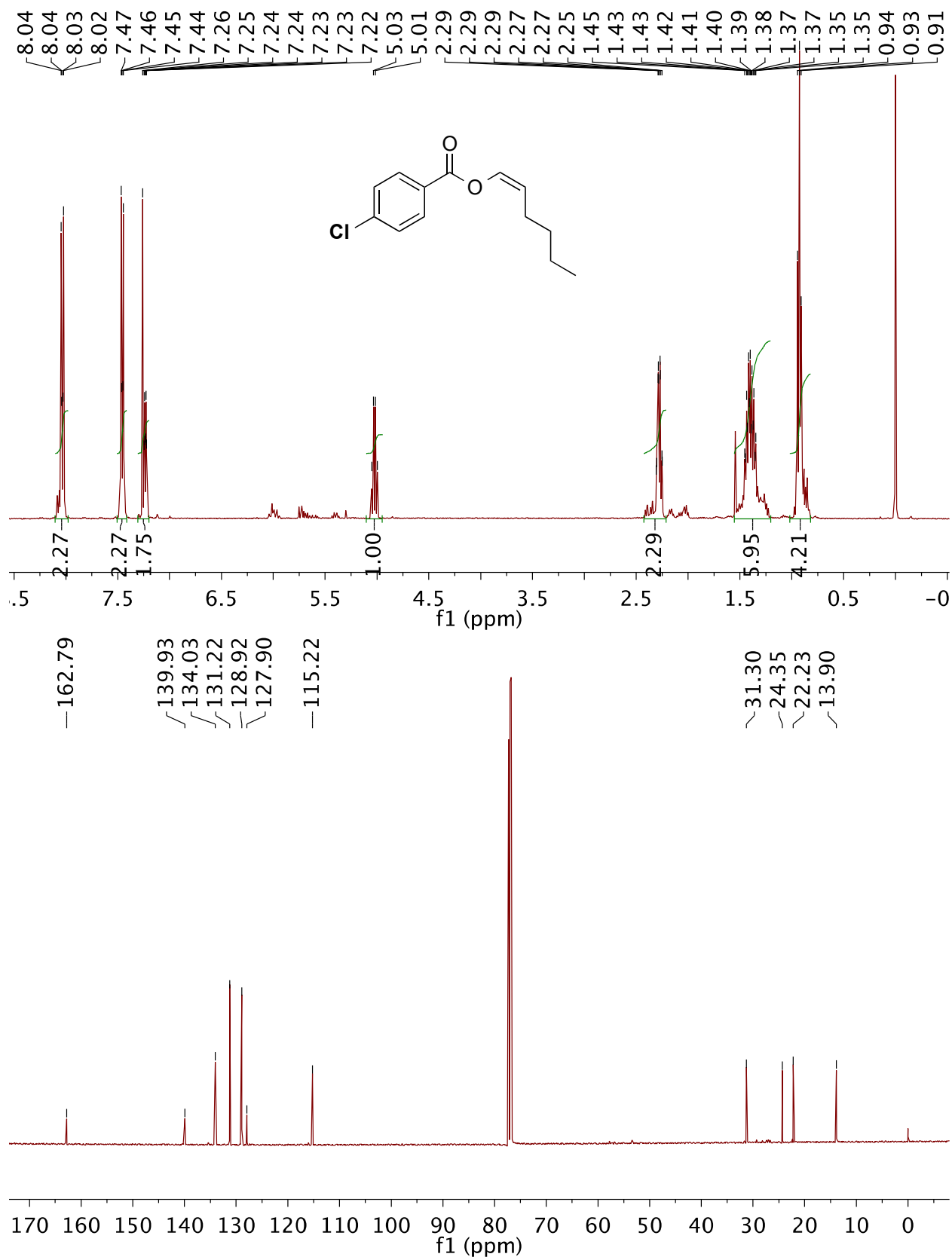
¹⁷Wendlandt, A.E.; Stahl, S.S.; *Org. Biomol. Chem.*, **2012**, *10*, 3866.

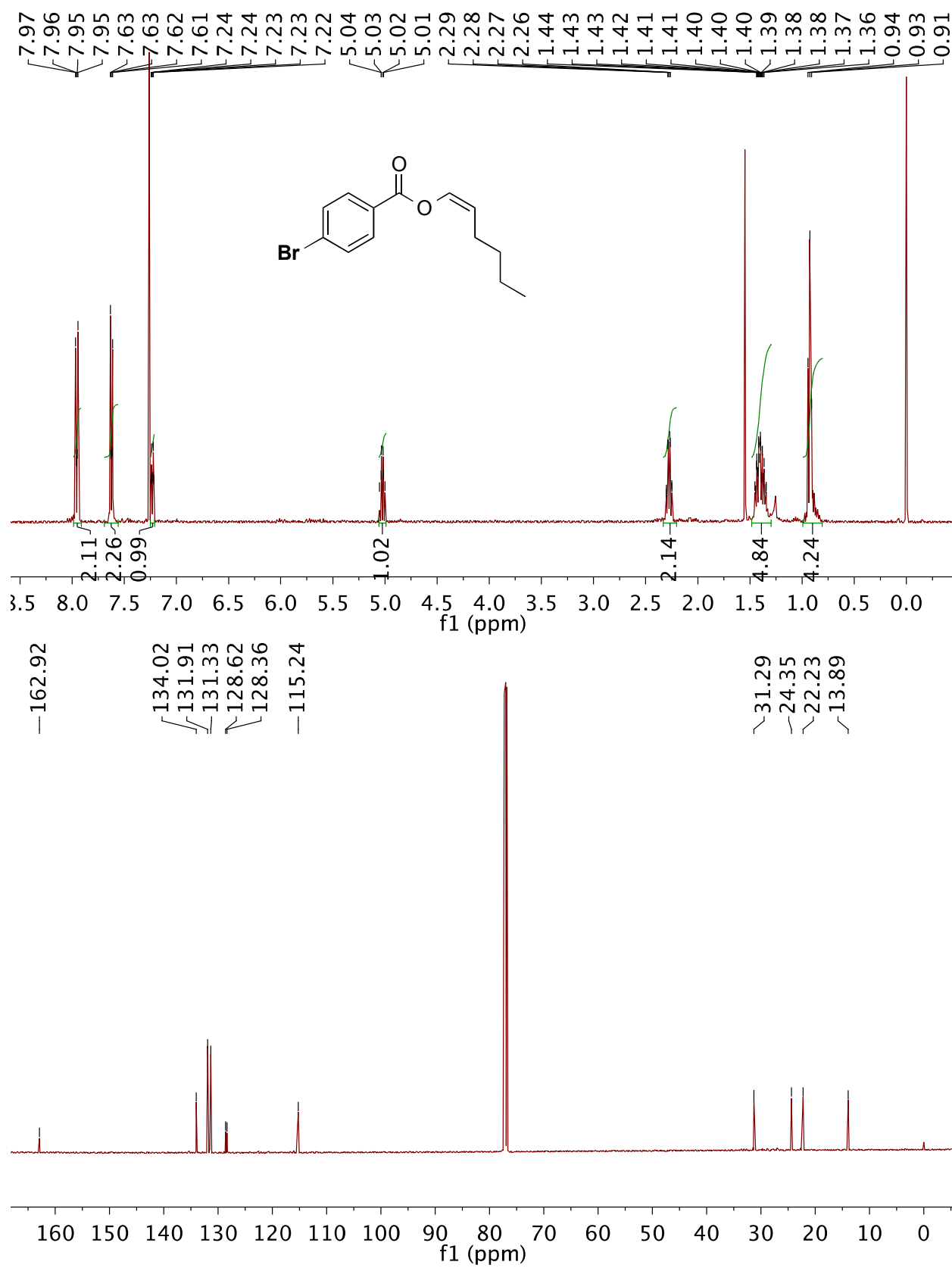
Chiralpak IA, 10% 2-propanol / 90% hexane, 1.2 mL/min flow, ambient temperature, $\lambda=220$ nm. t_r (alpha isomer) = 12.7 min (major, *S*), 15.7 min (minor, *R*). t_r (beta isomer) = 23.5 min (minor), 24.9 min (major).

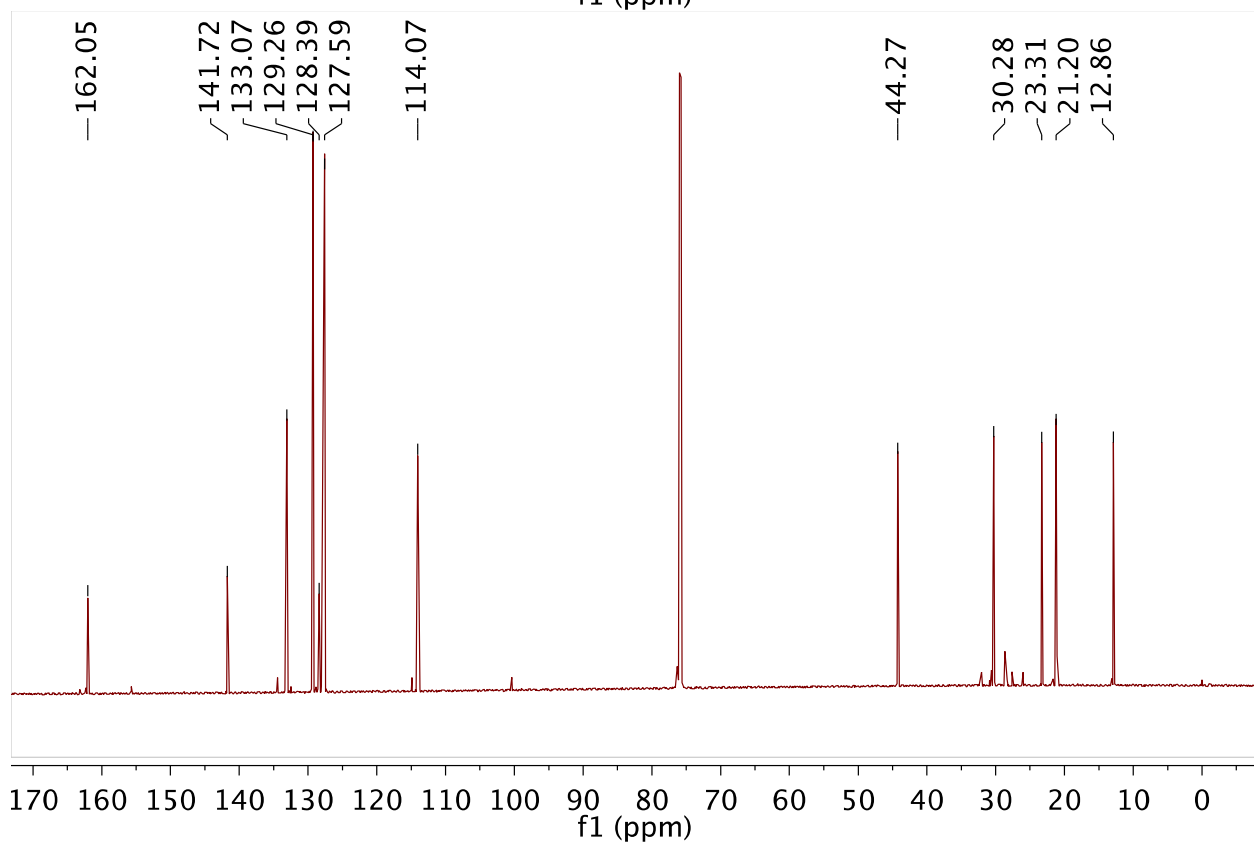
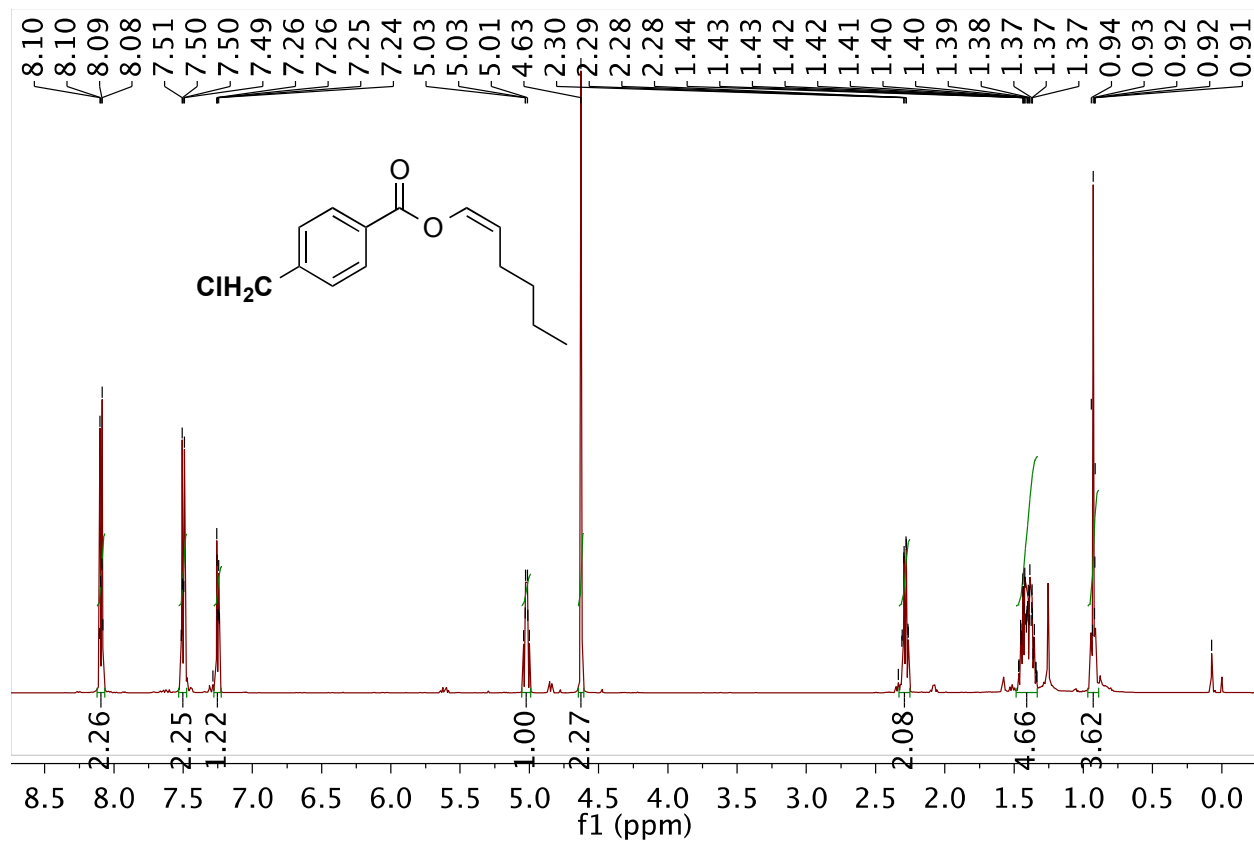
VI. NMR spectra

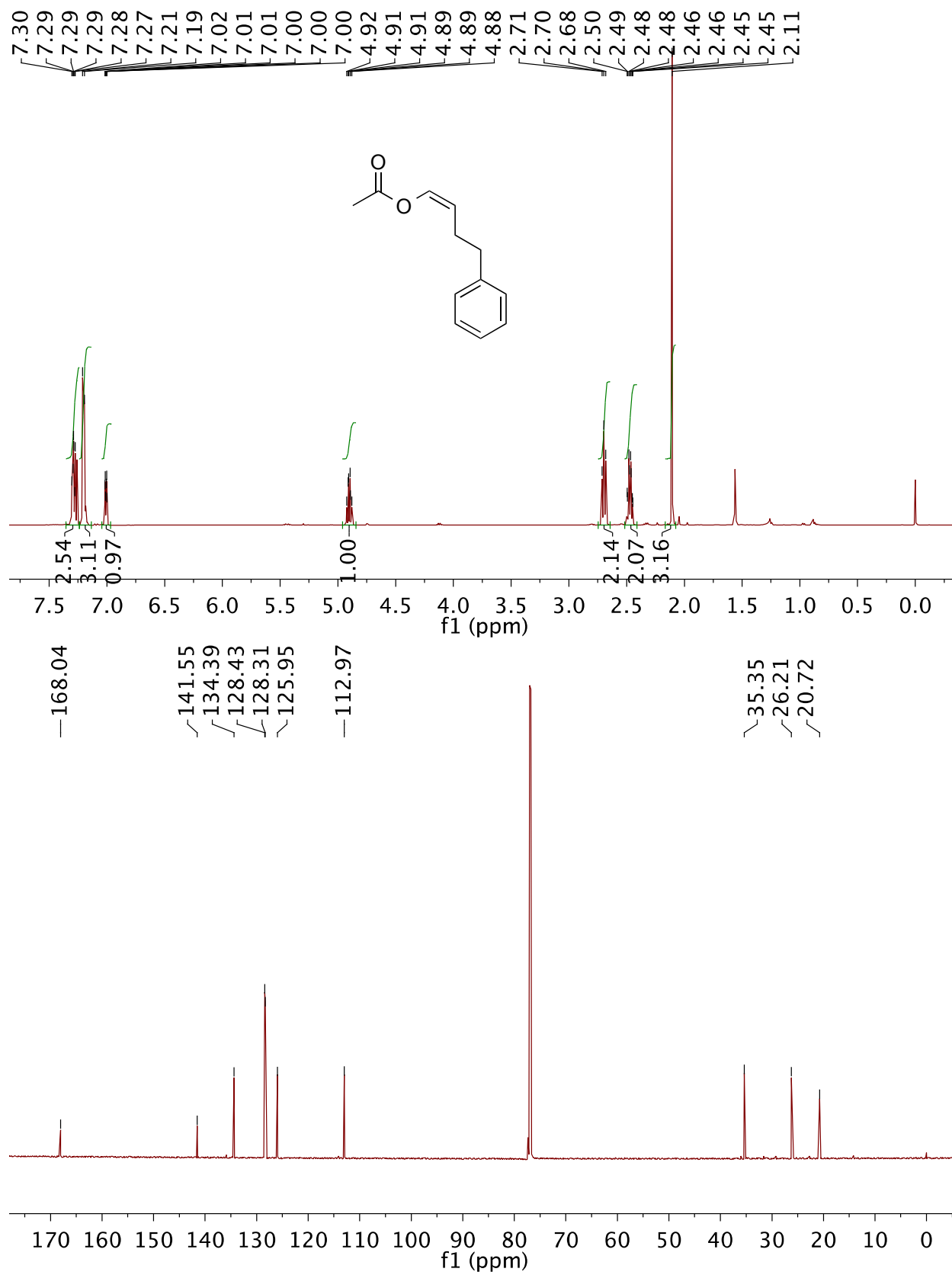


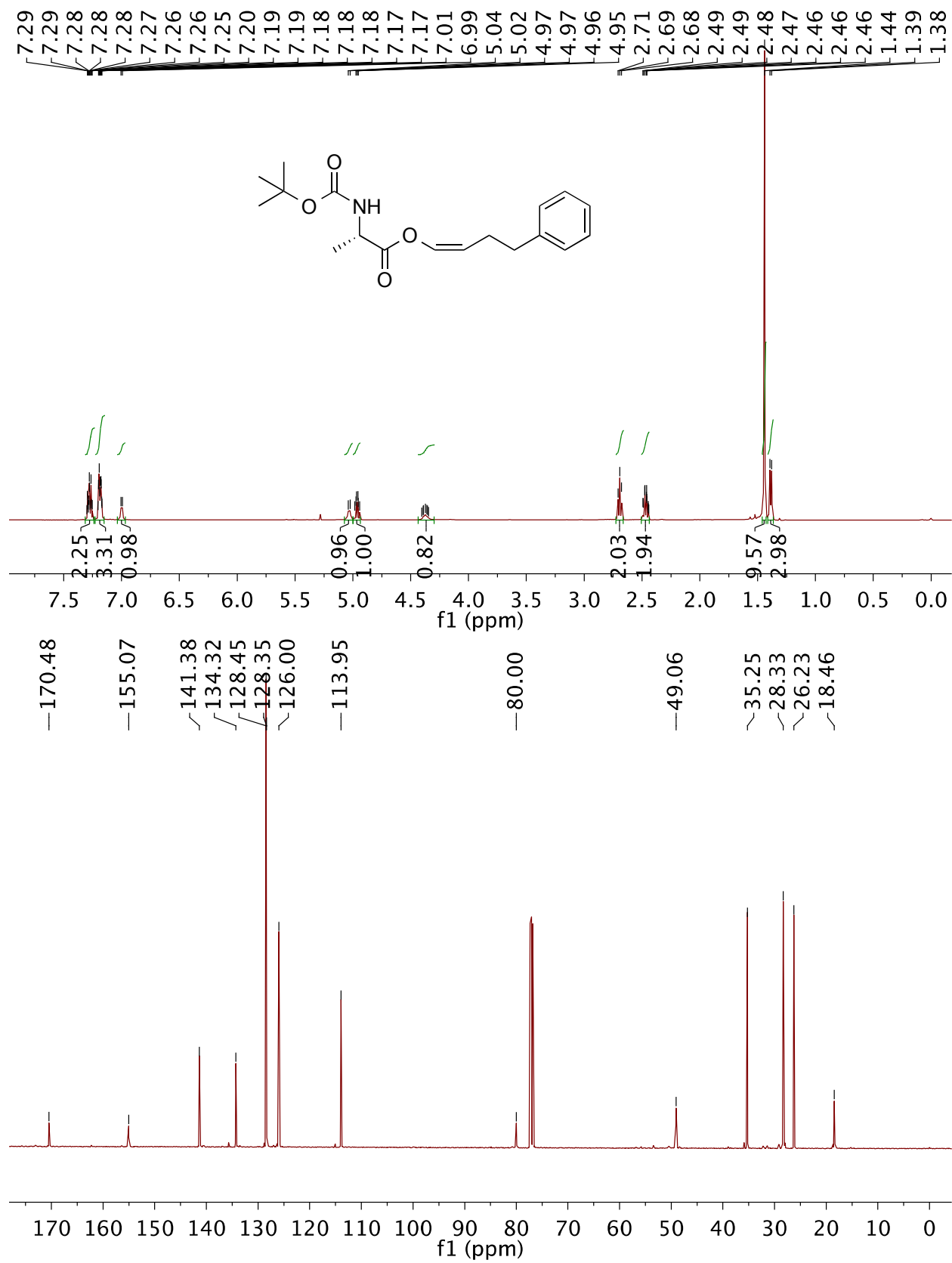


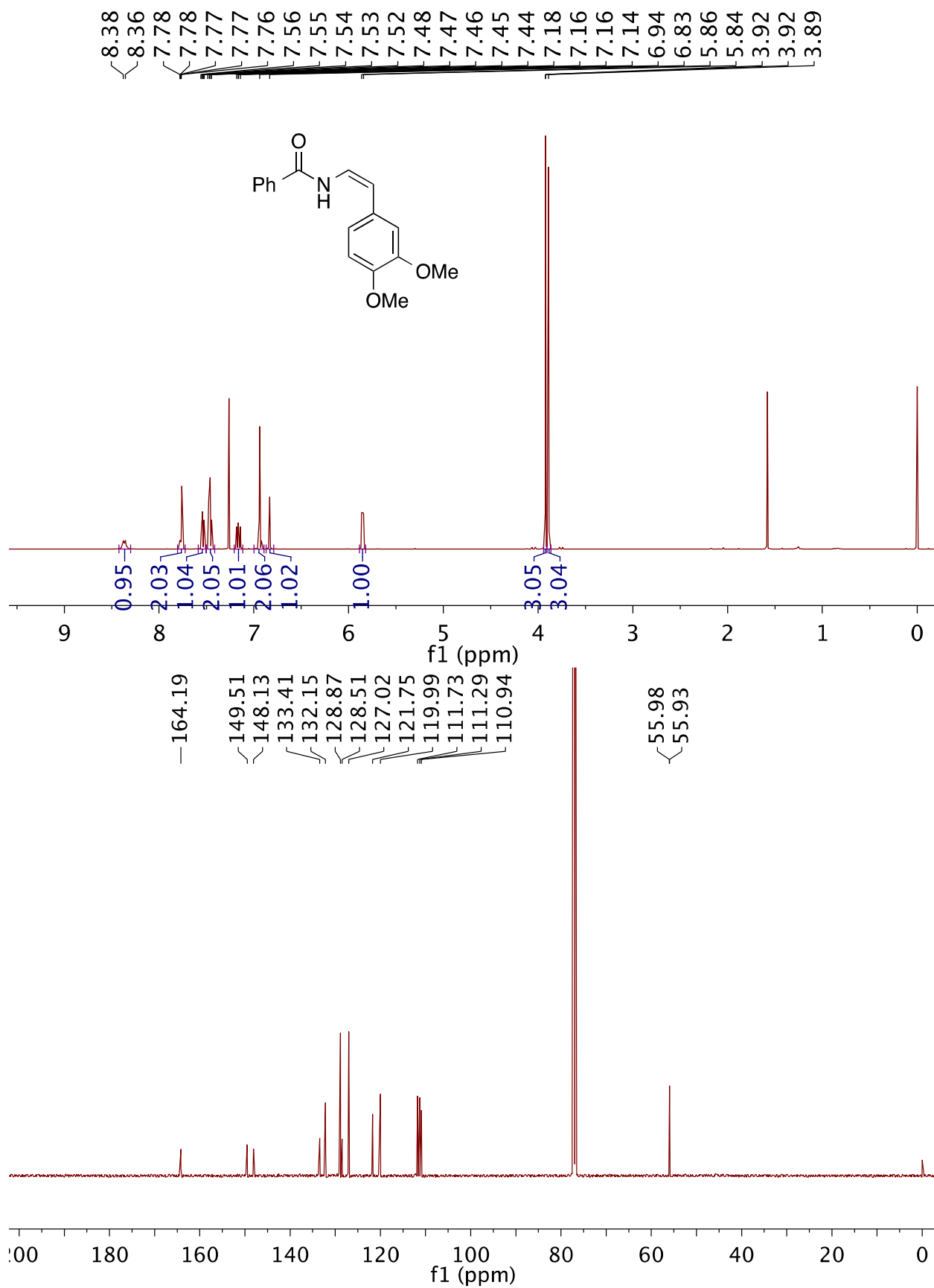


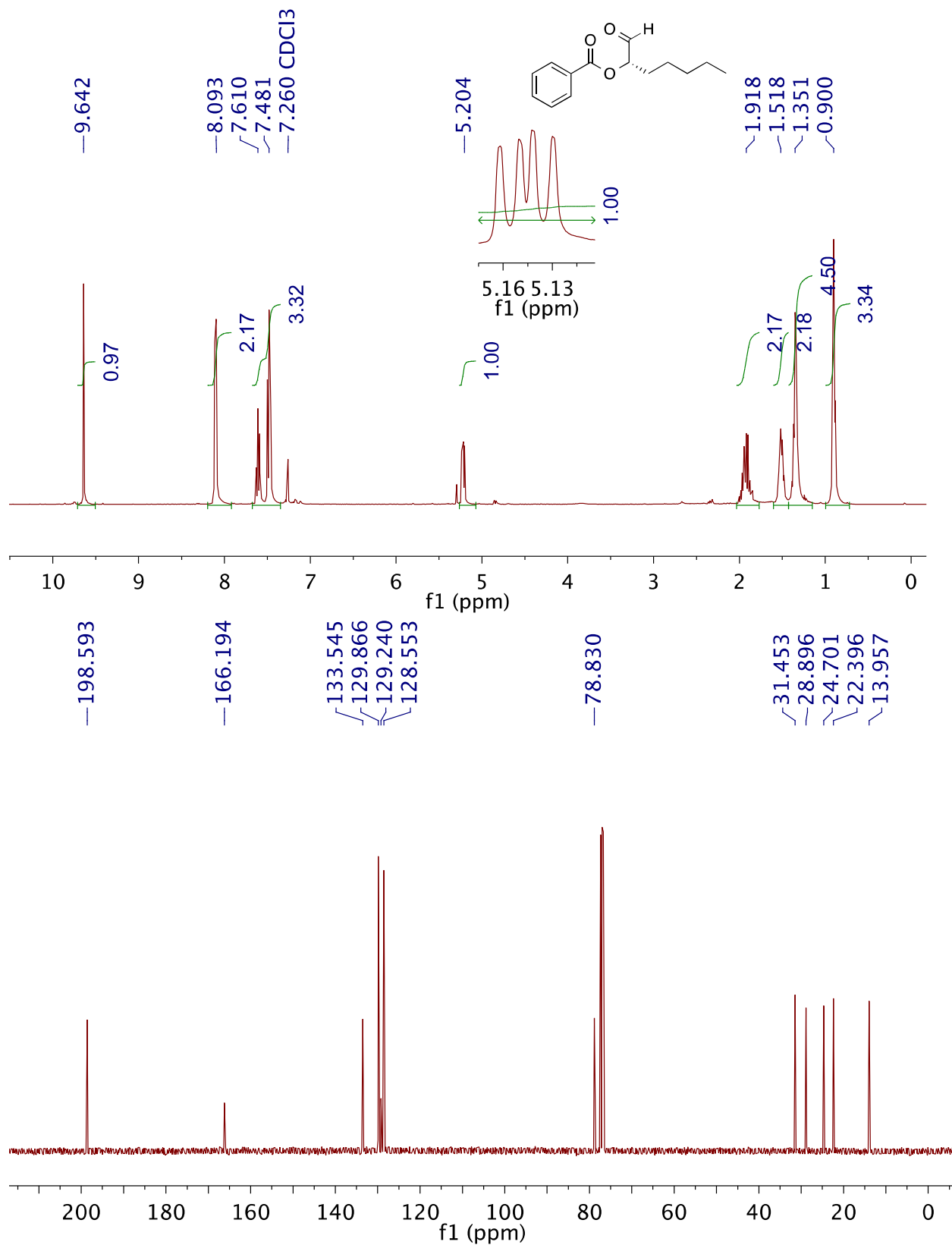


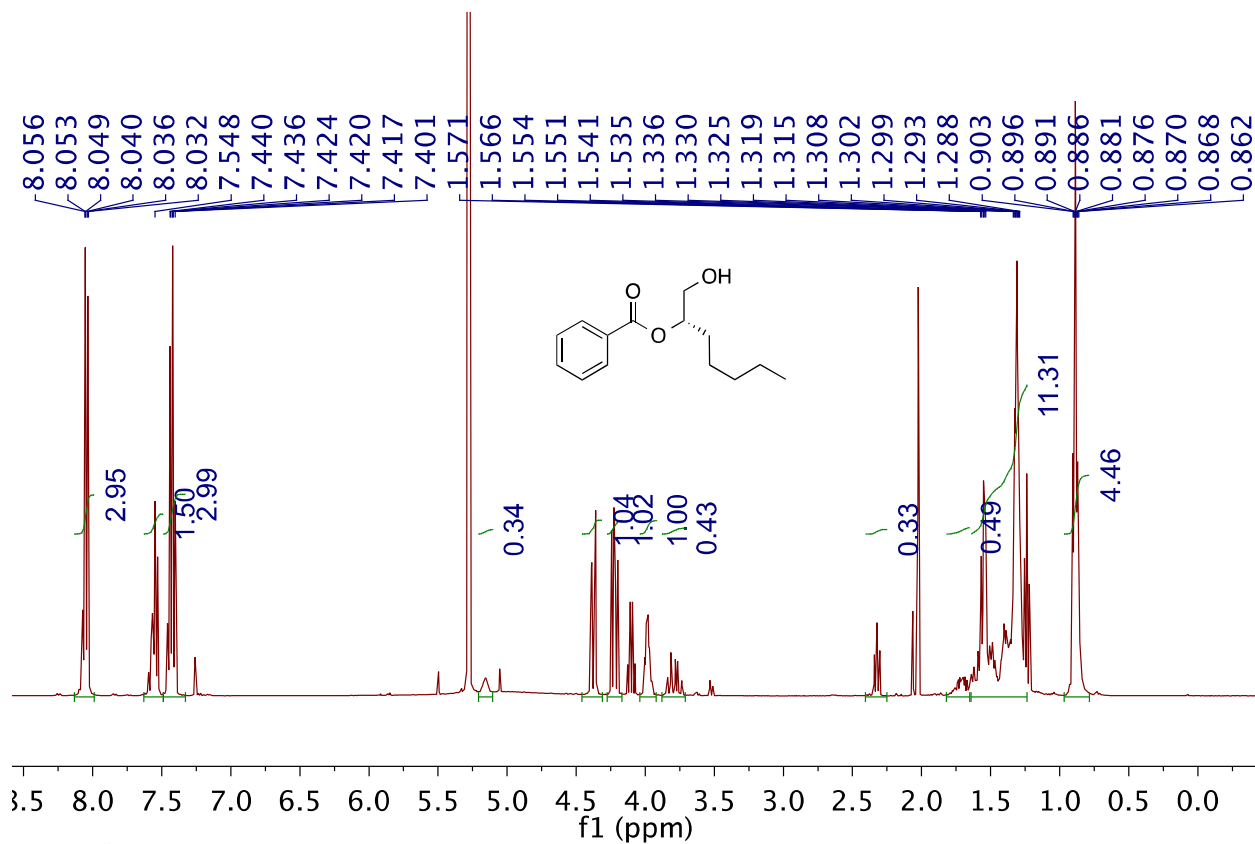




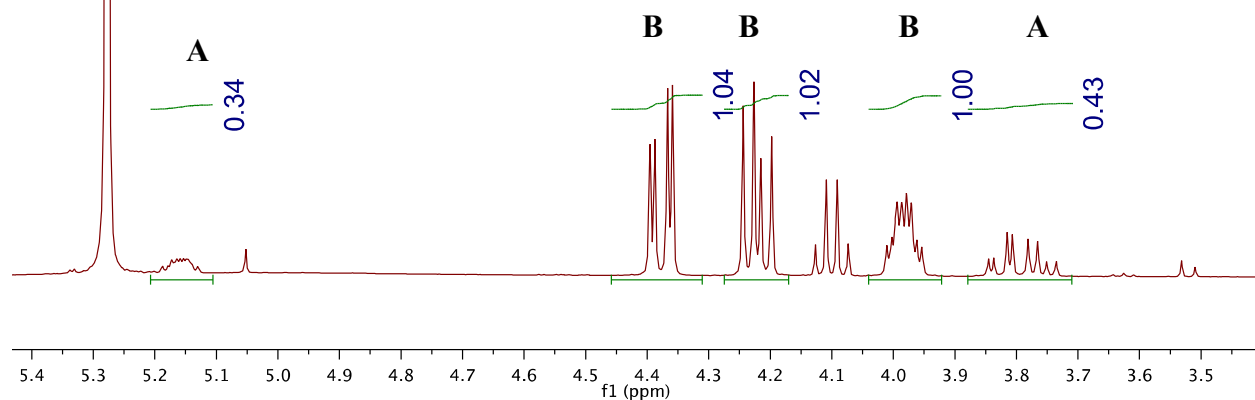
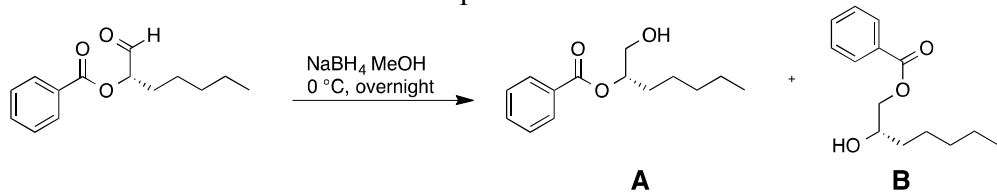


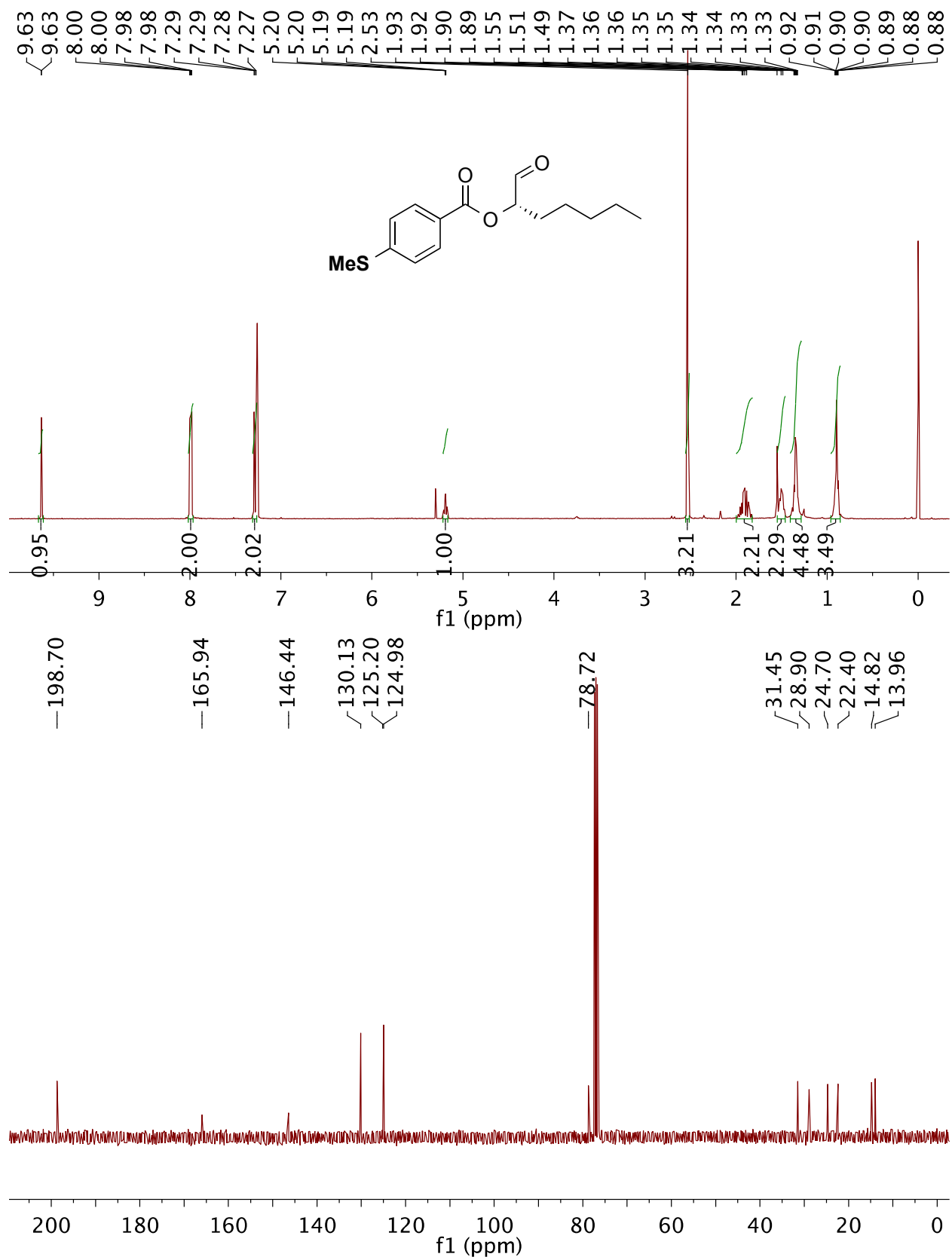


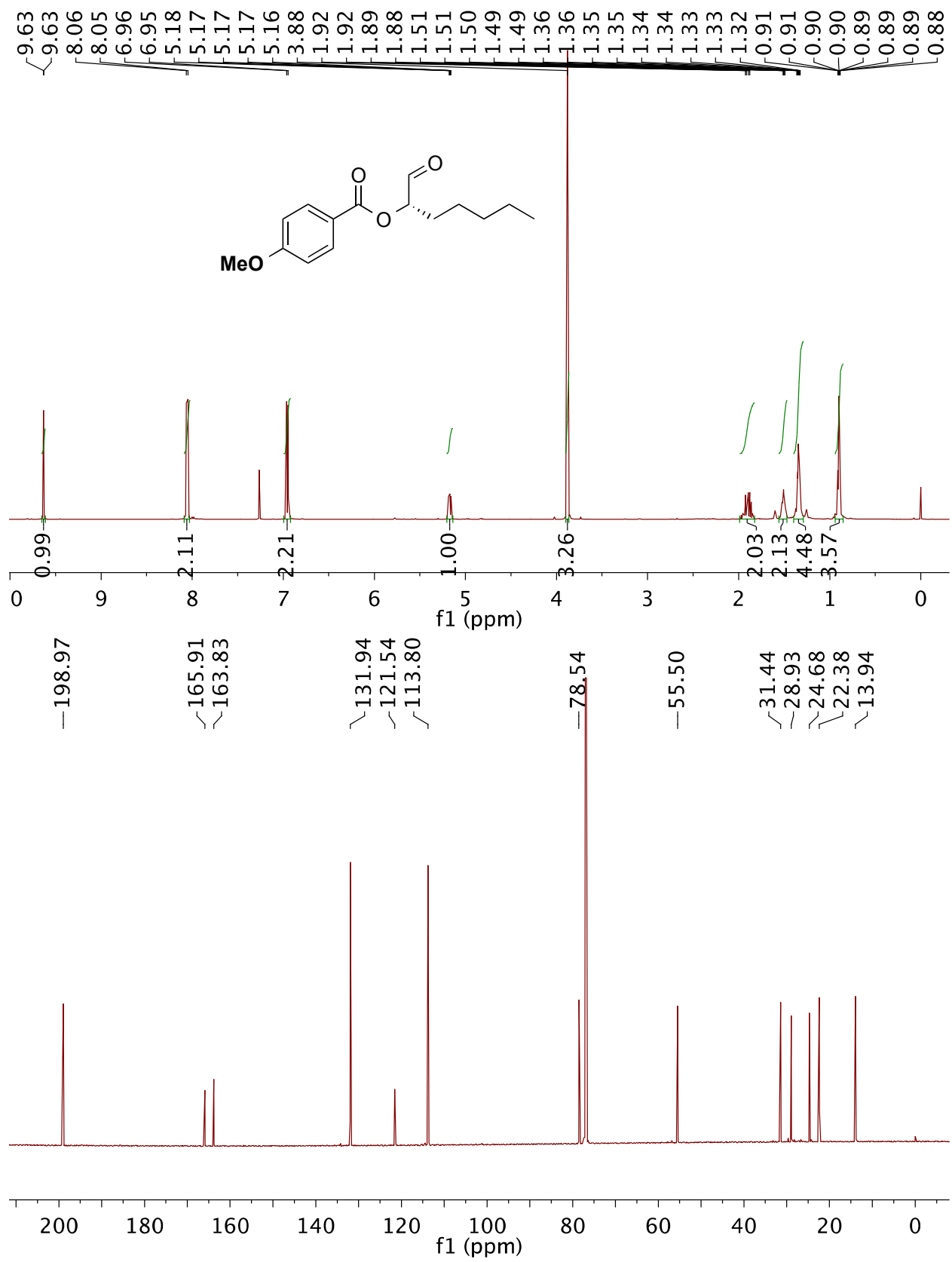


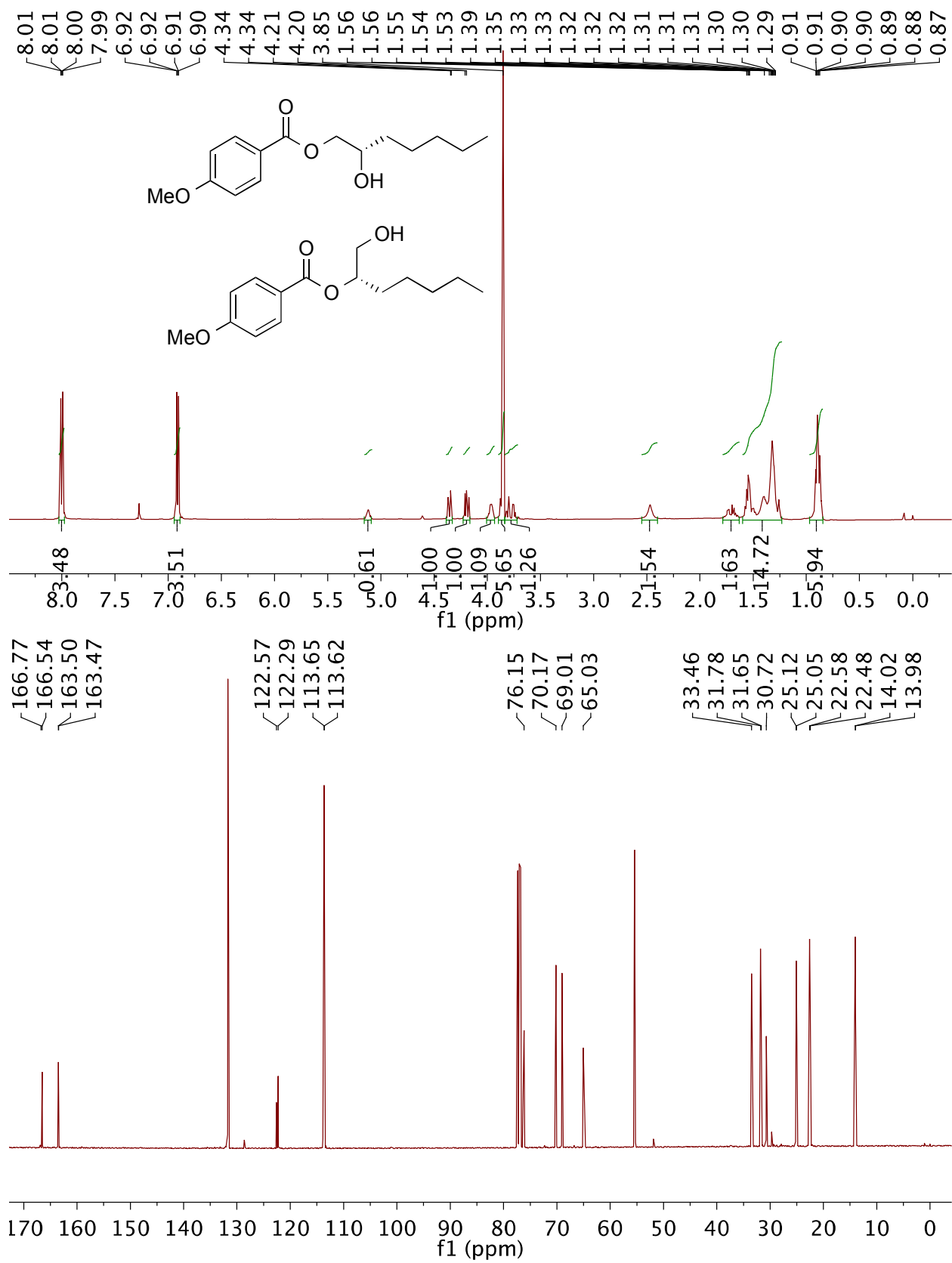


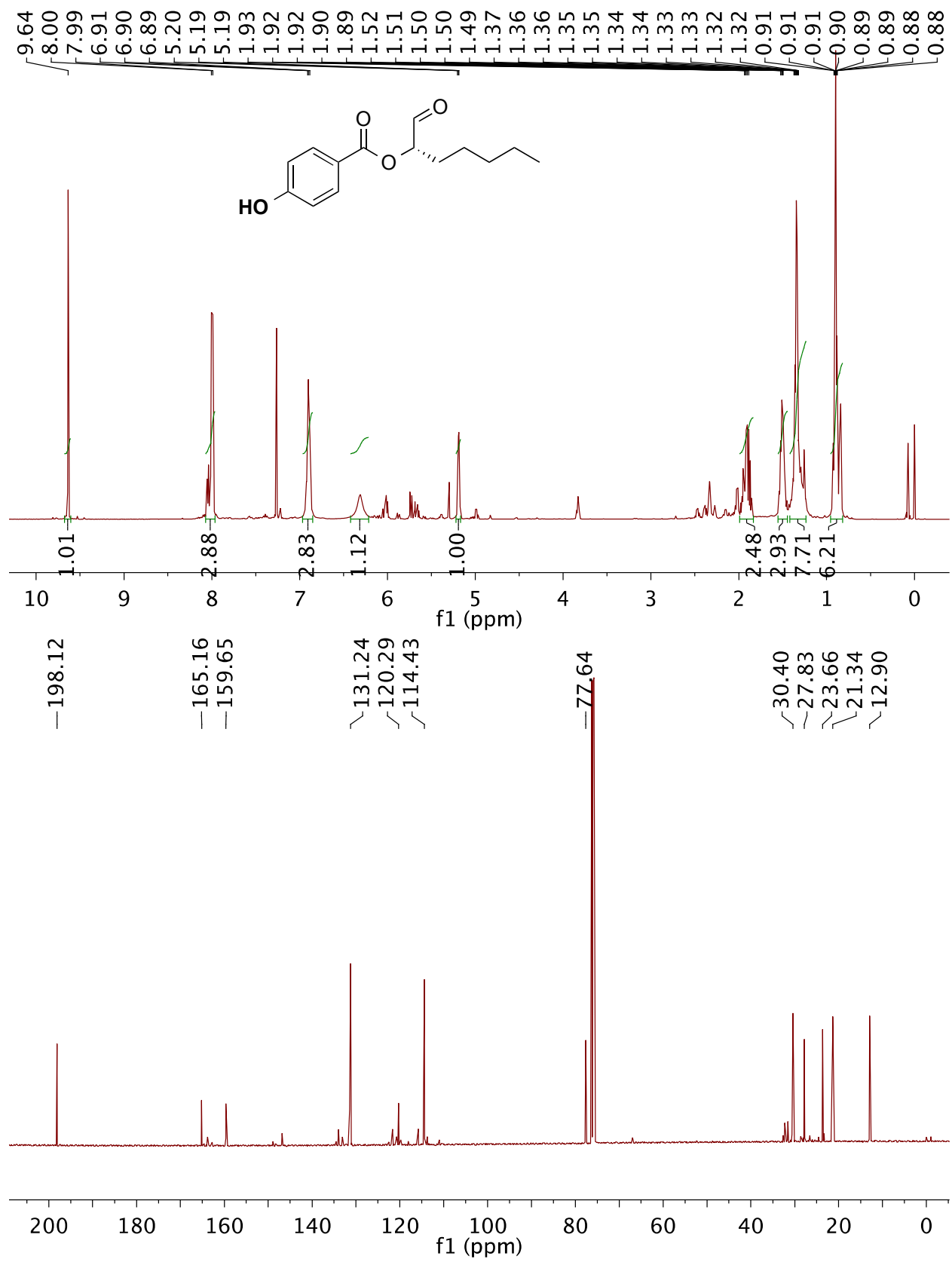
Detail of alcohol isomers in above spectrum:

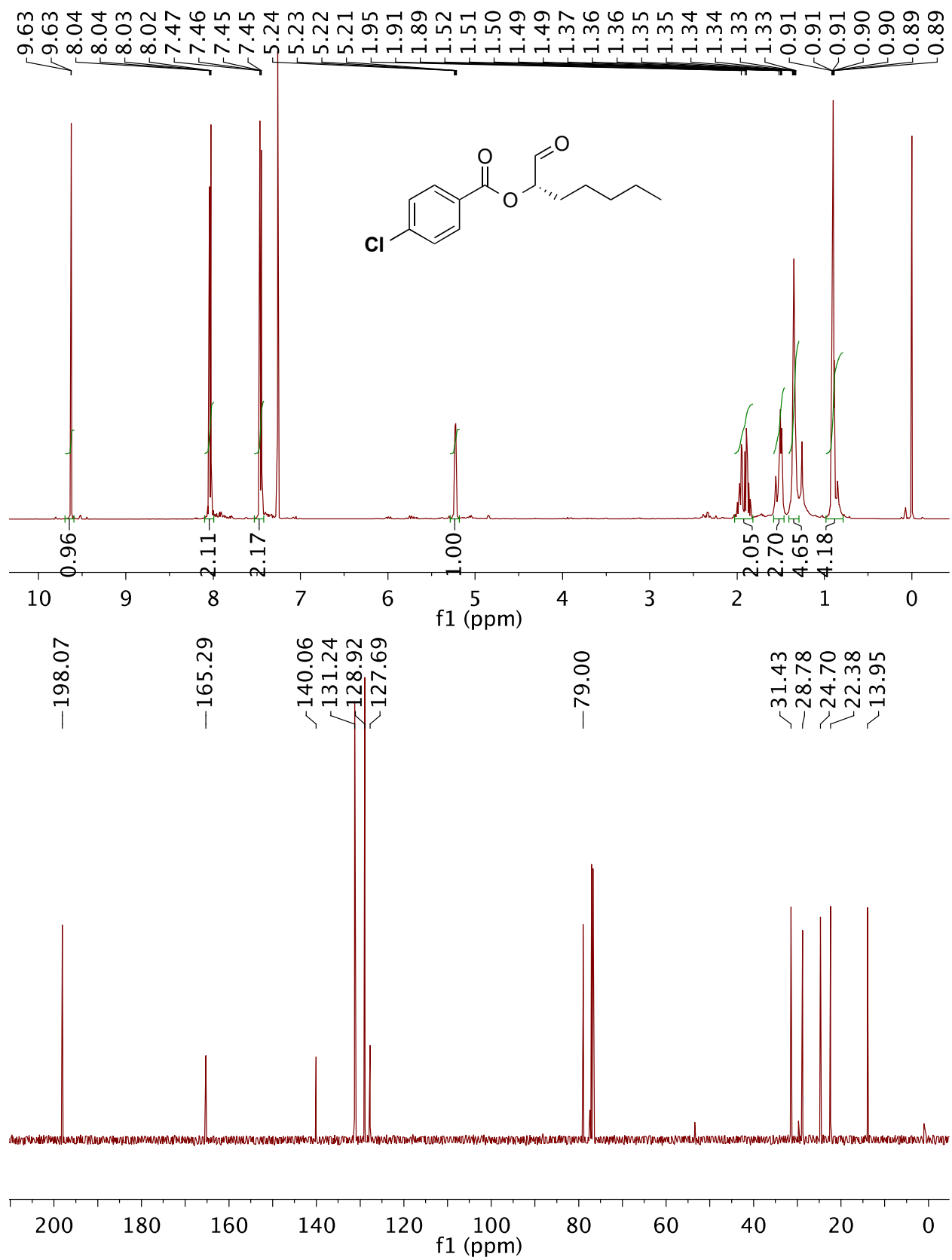


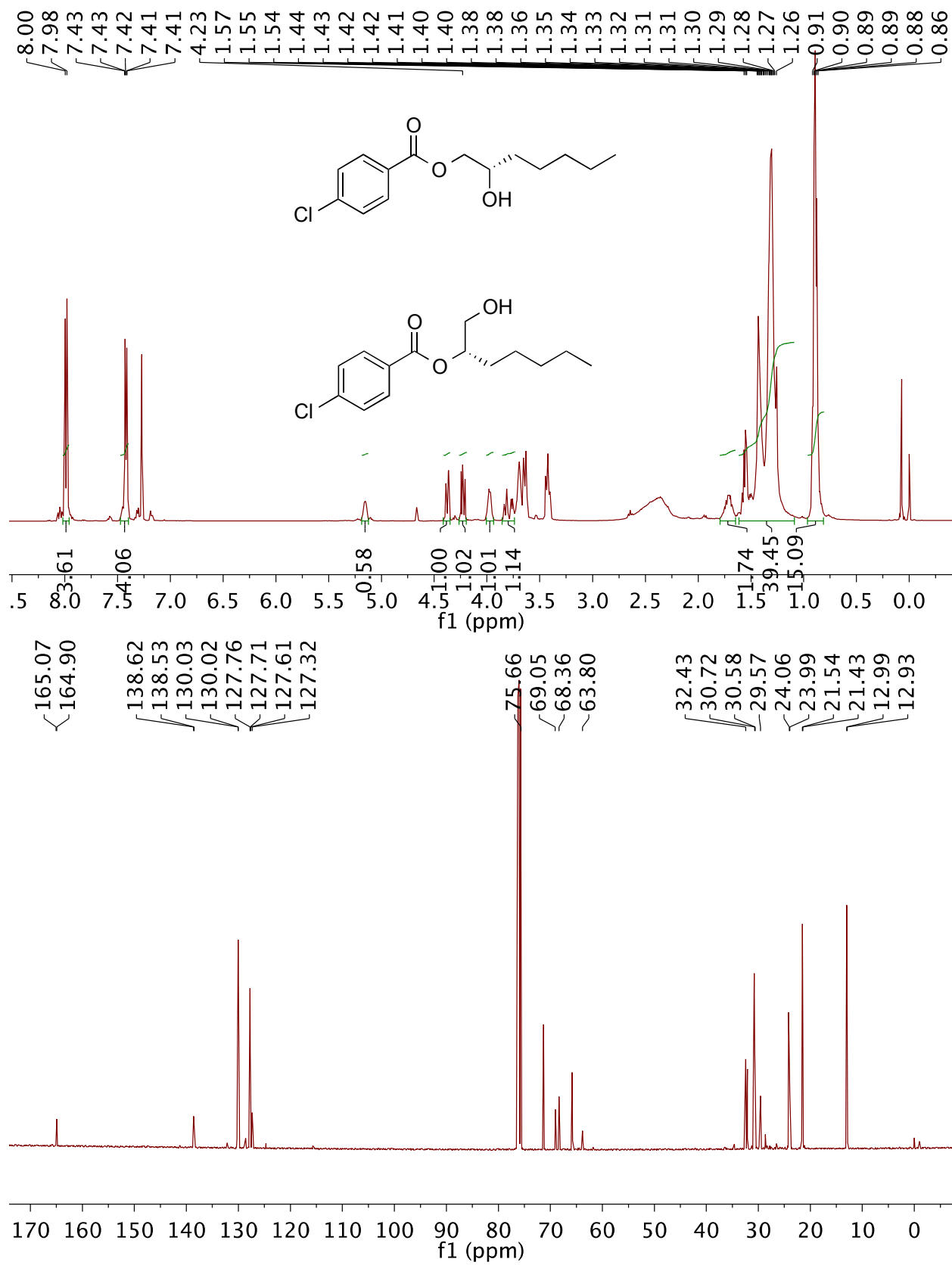


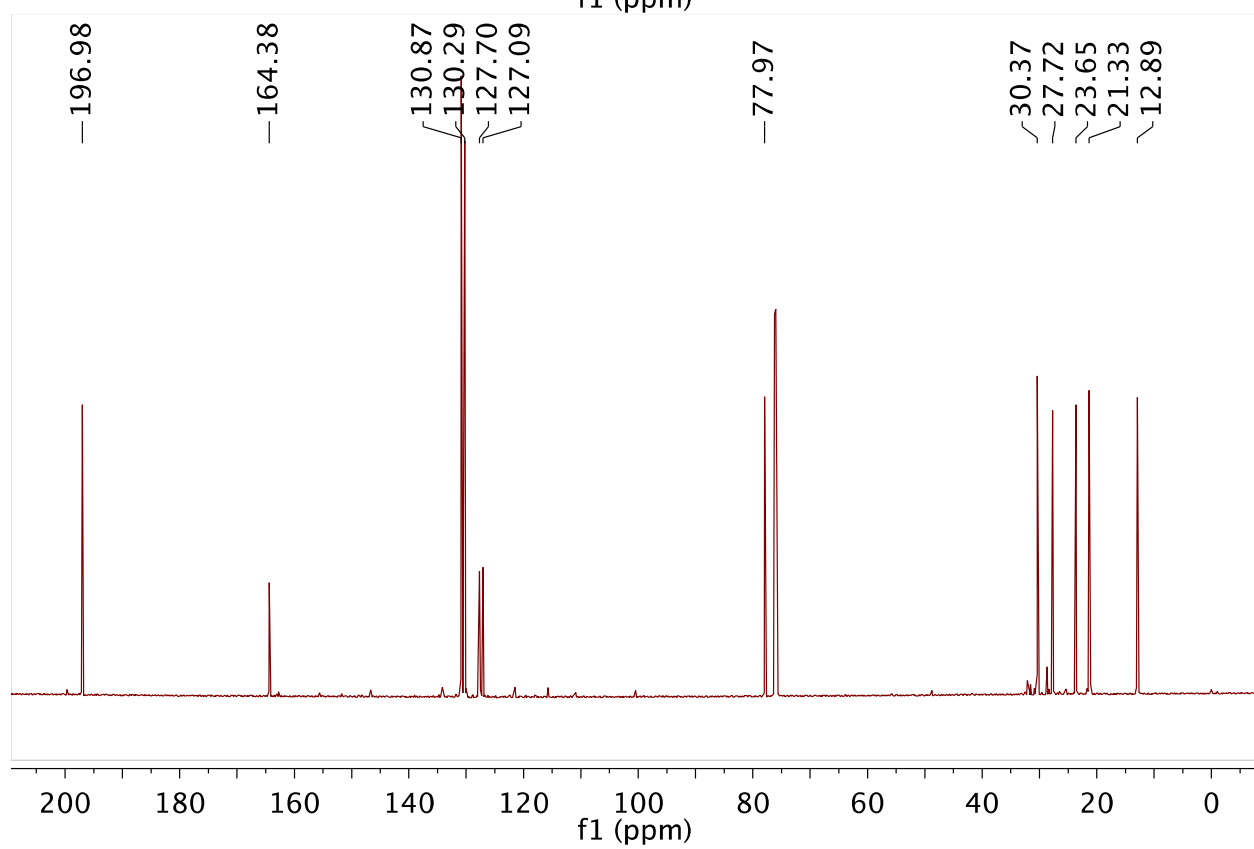
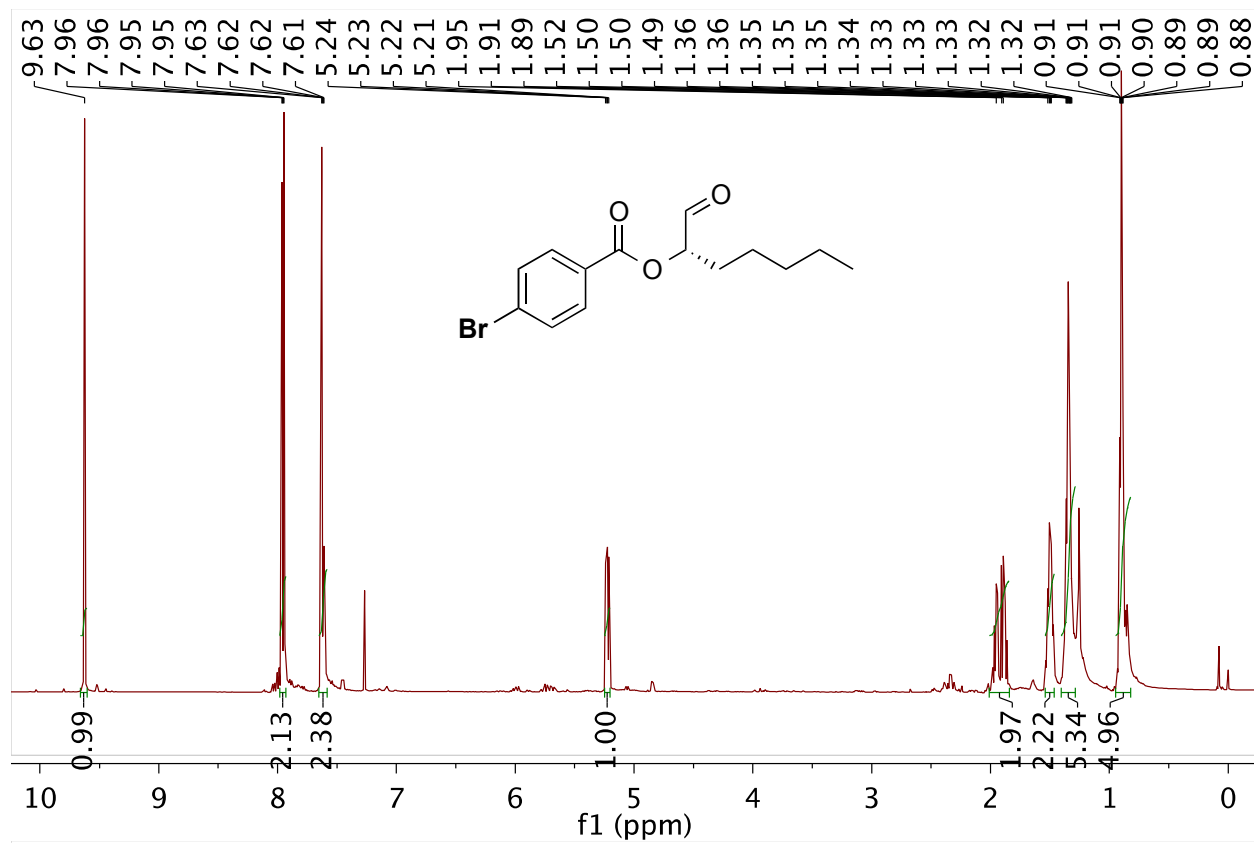


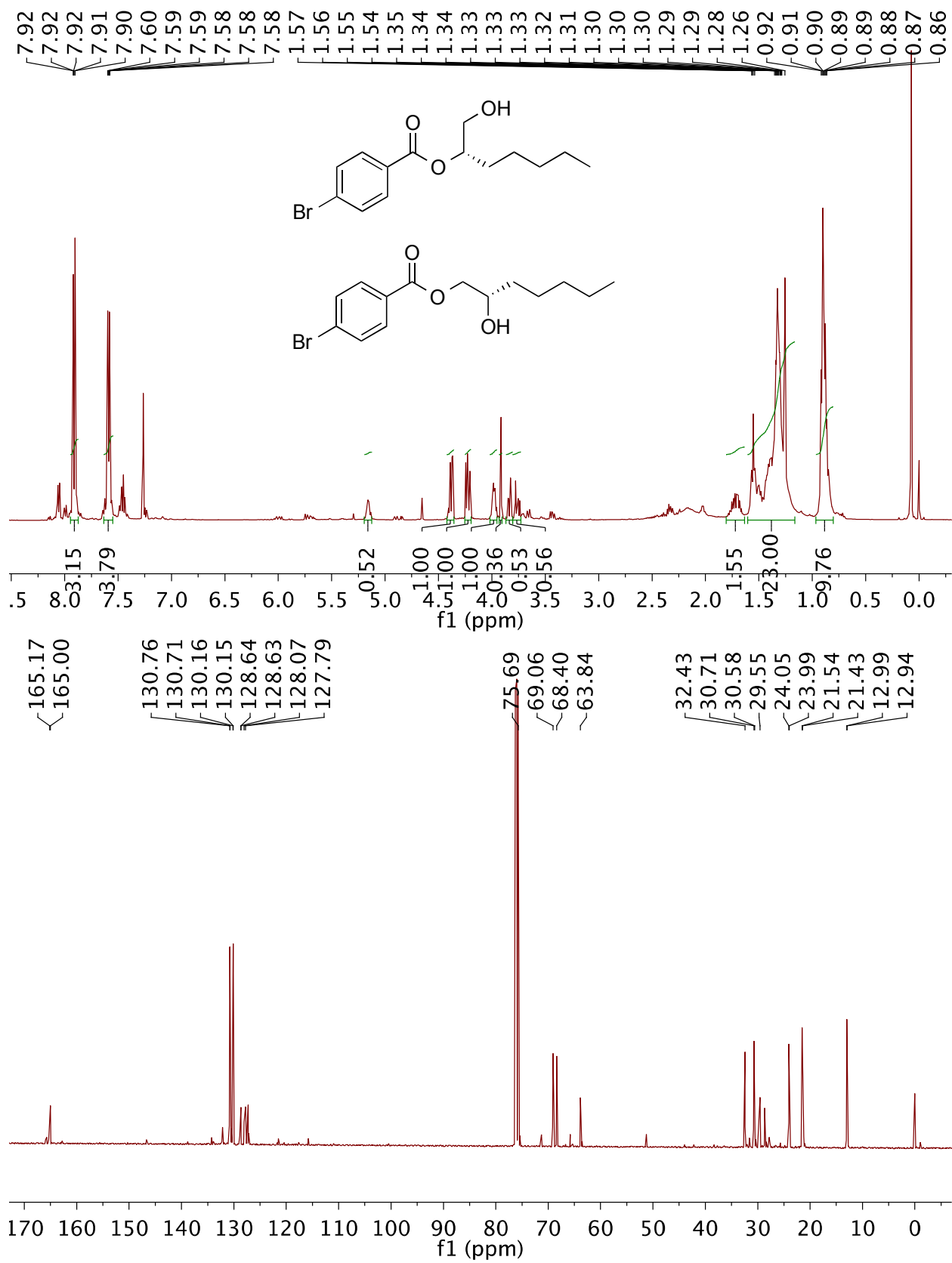


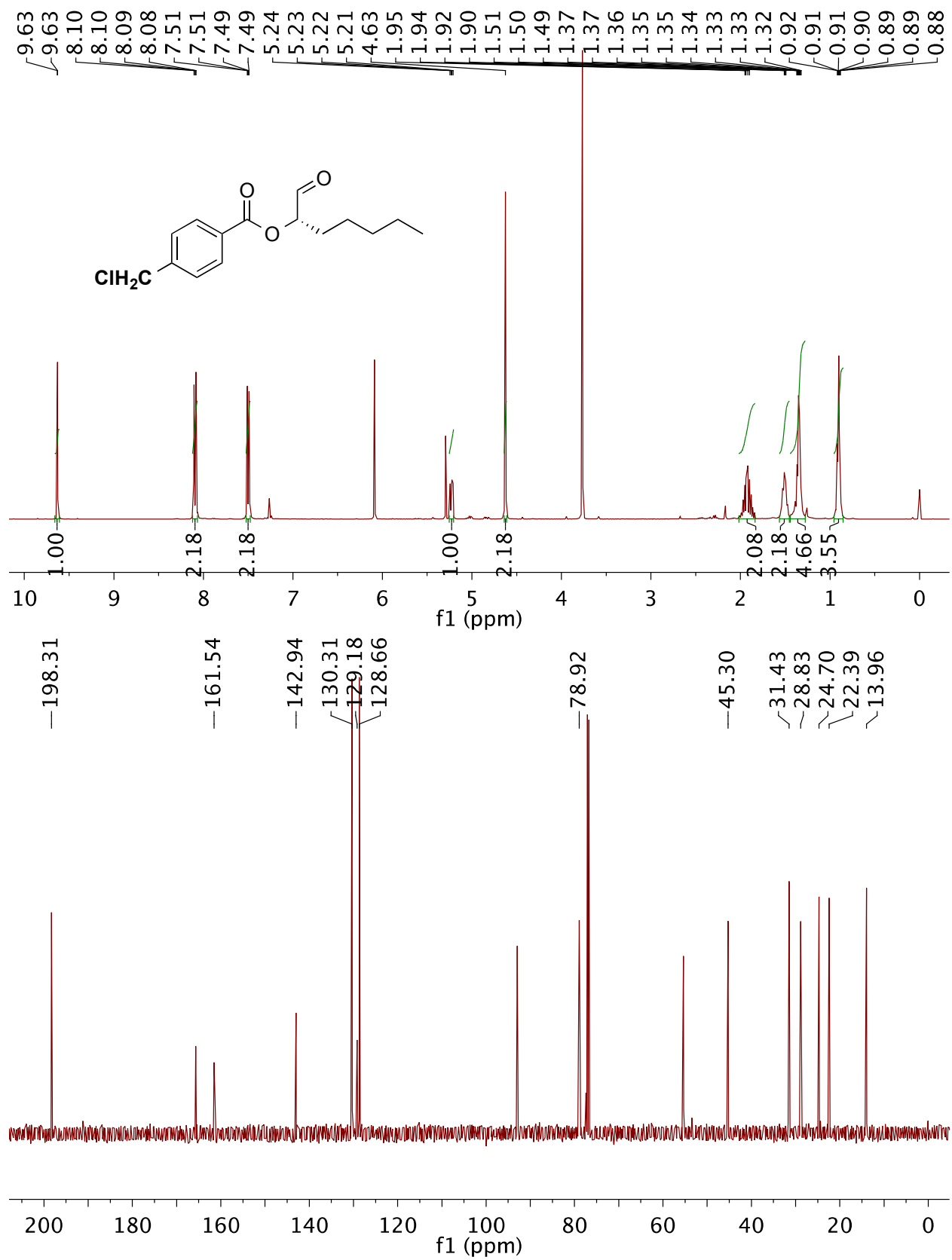


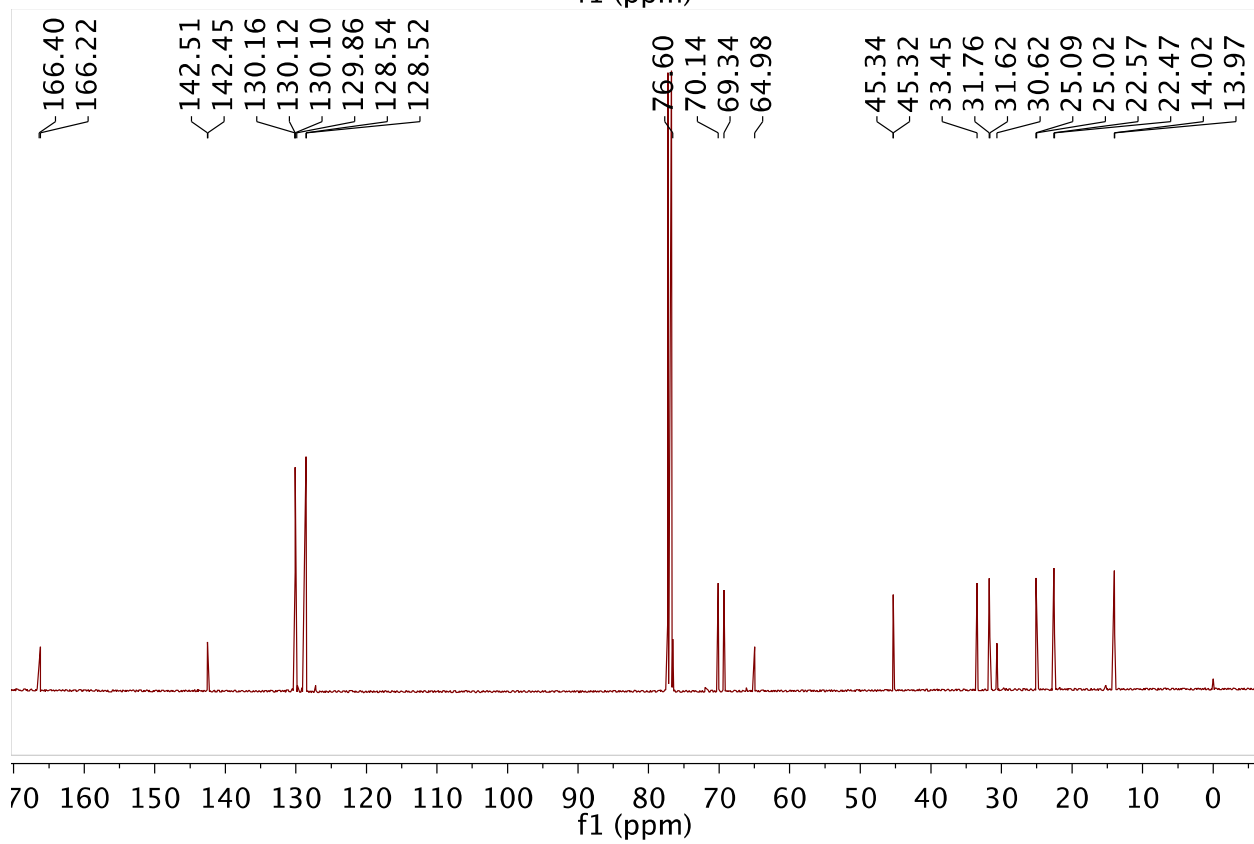
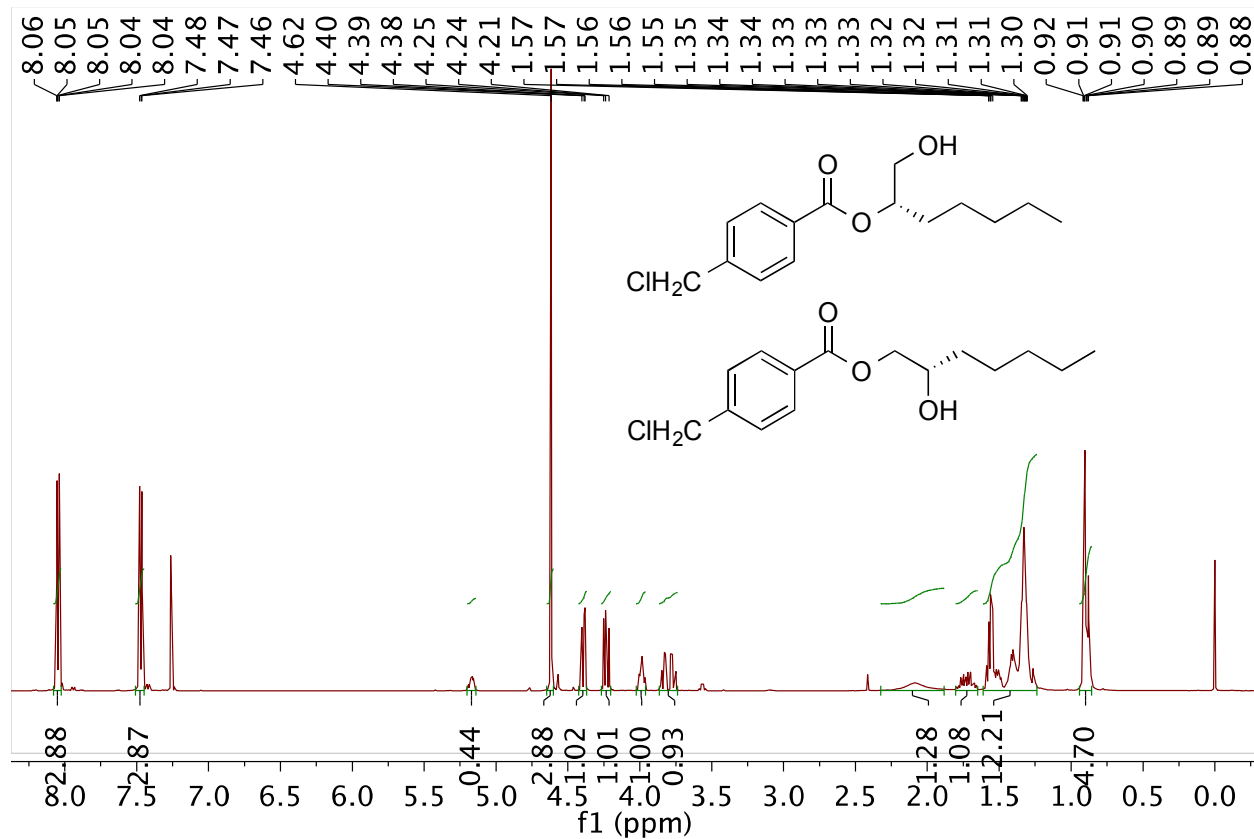


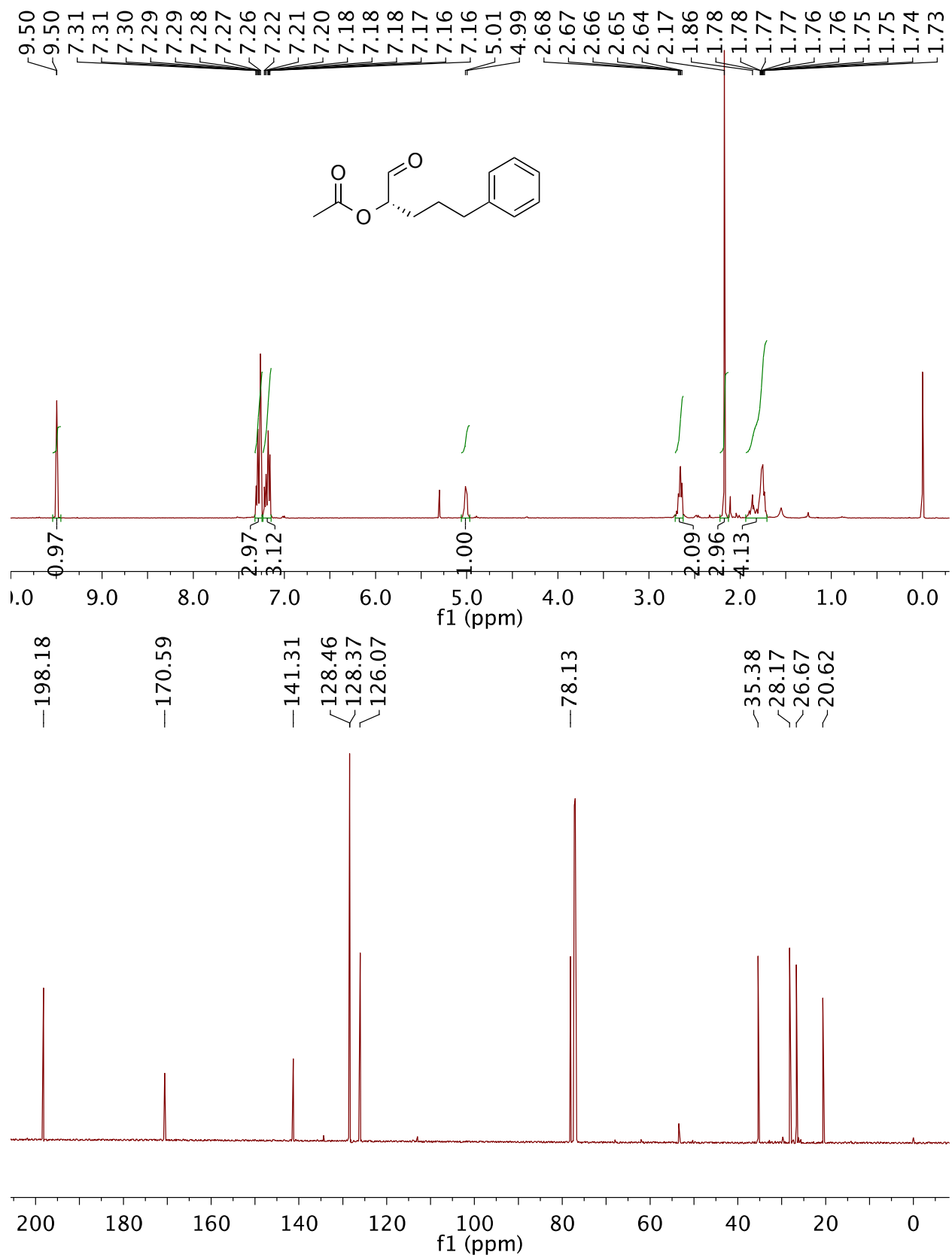


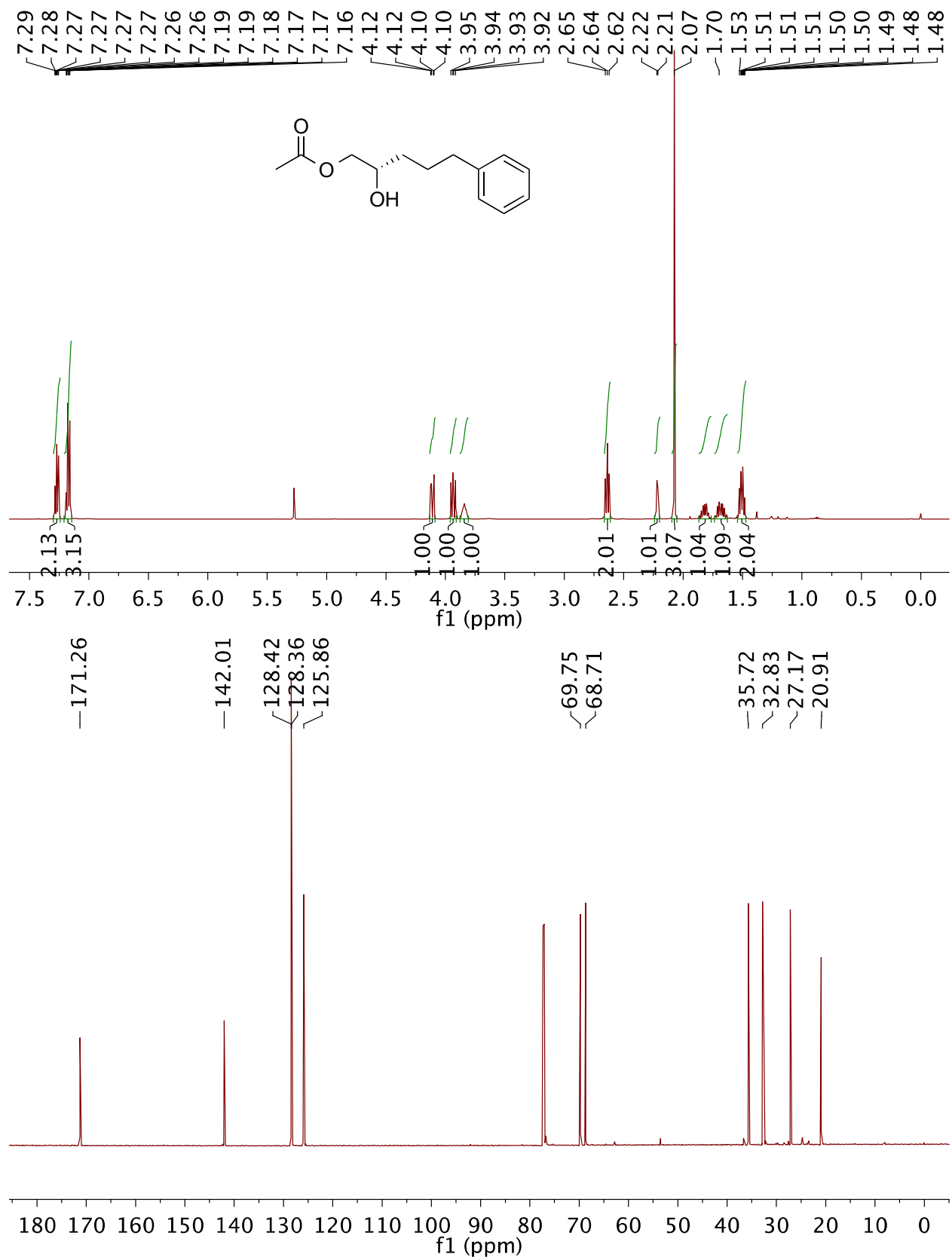


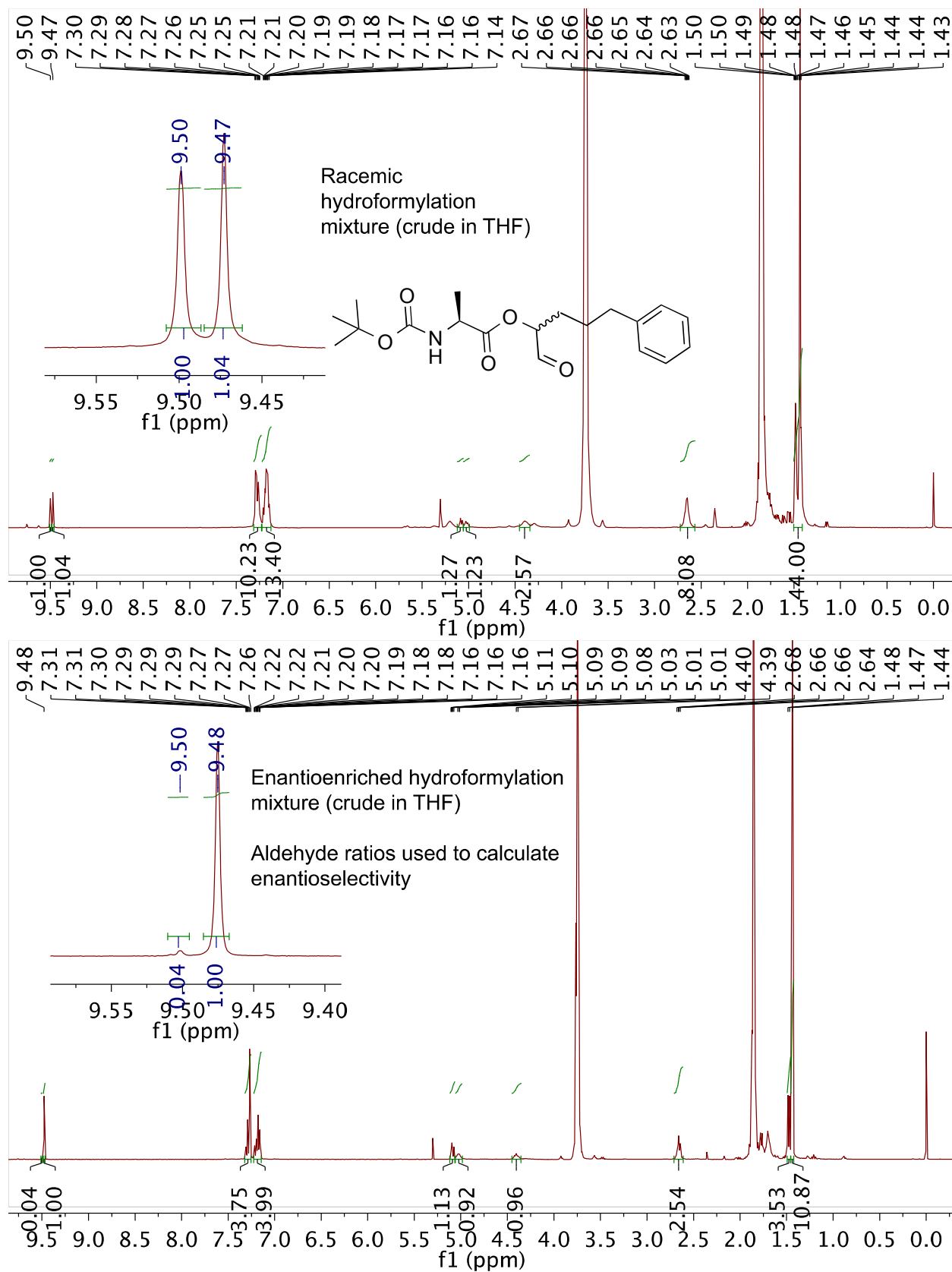


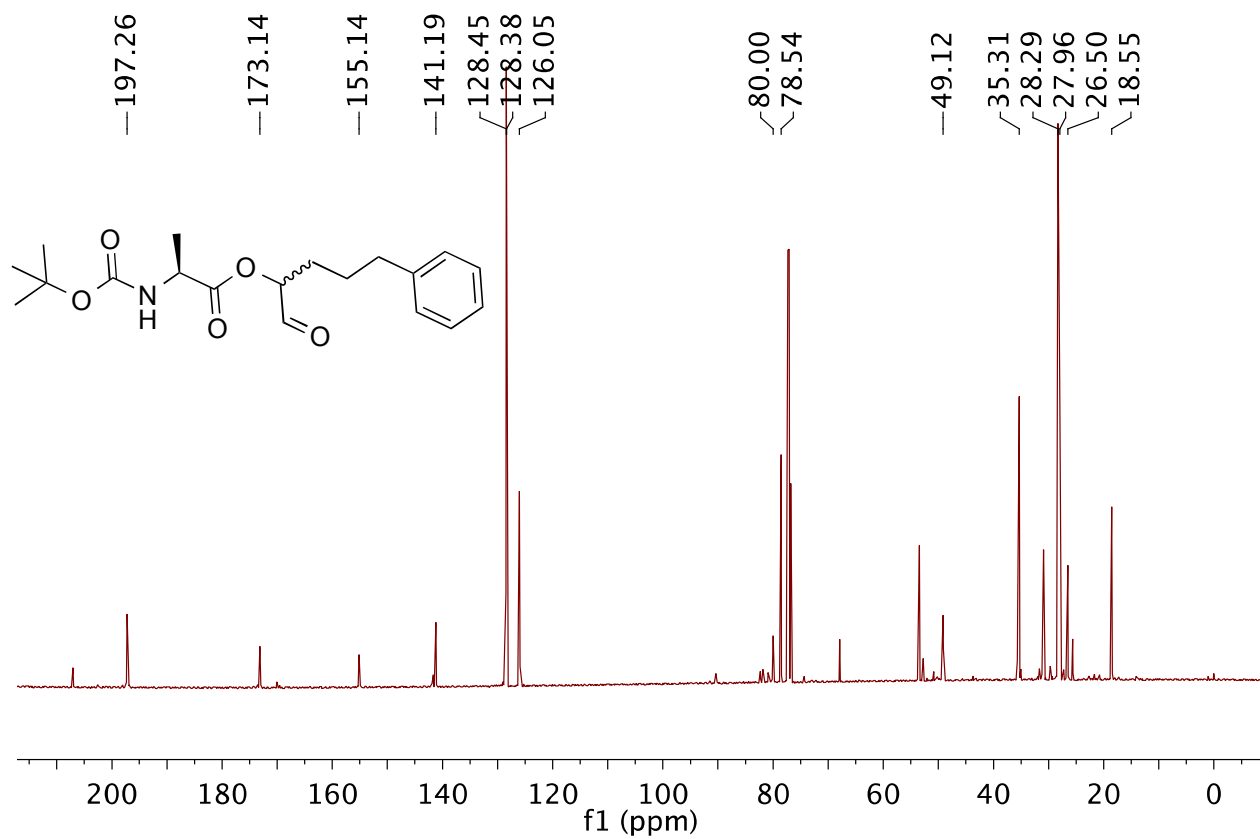


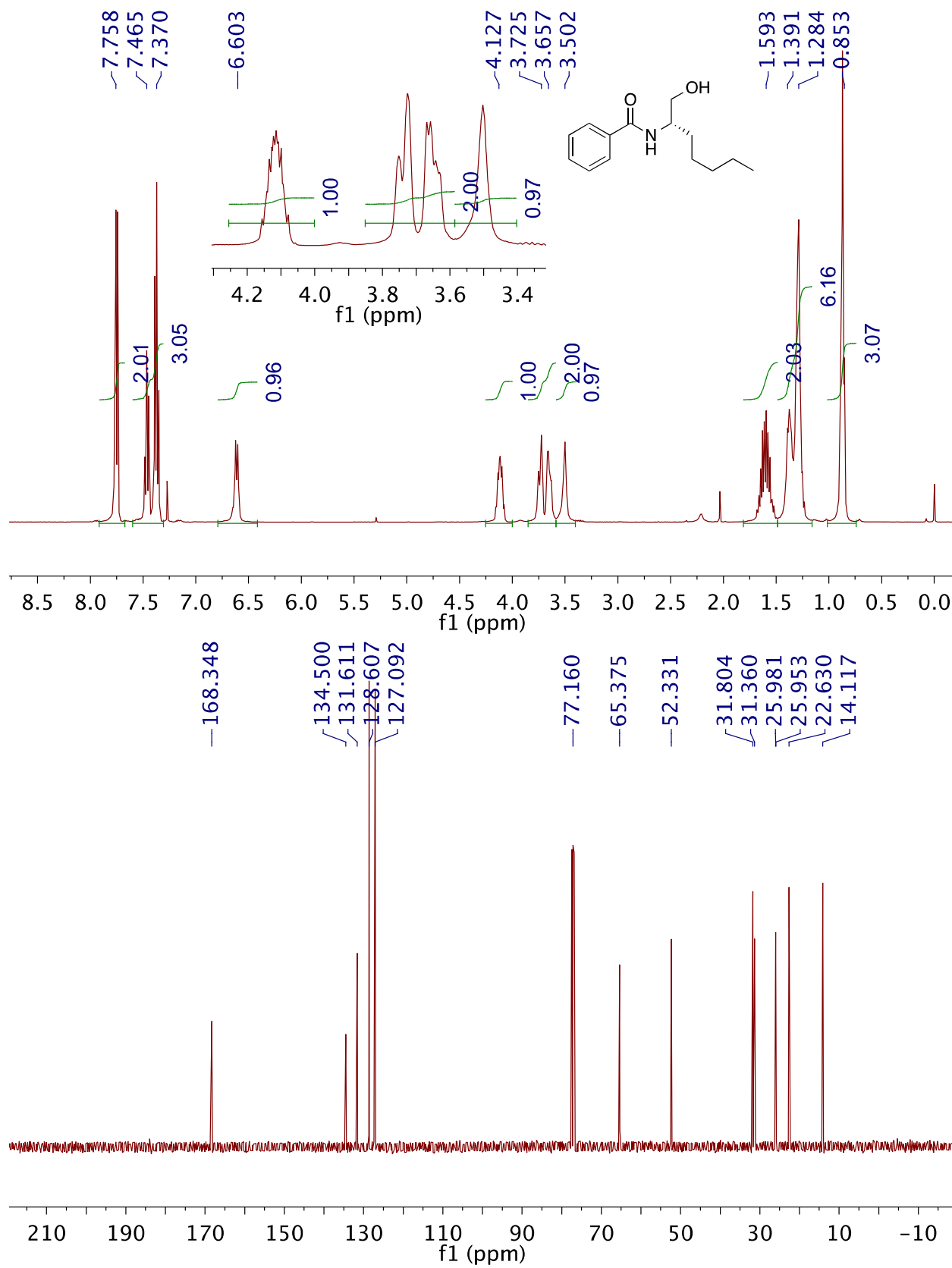


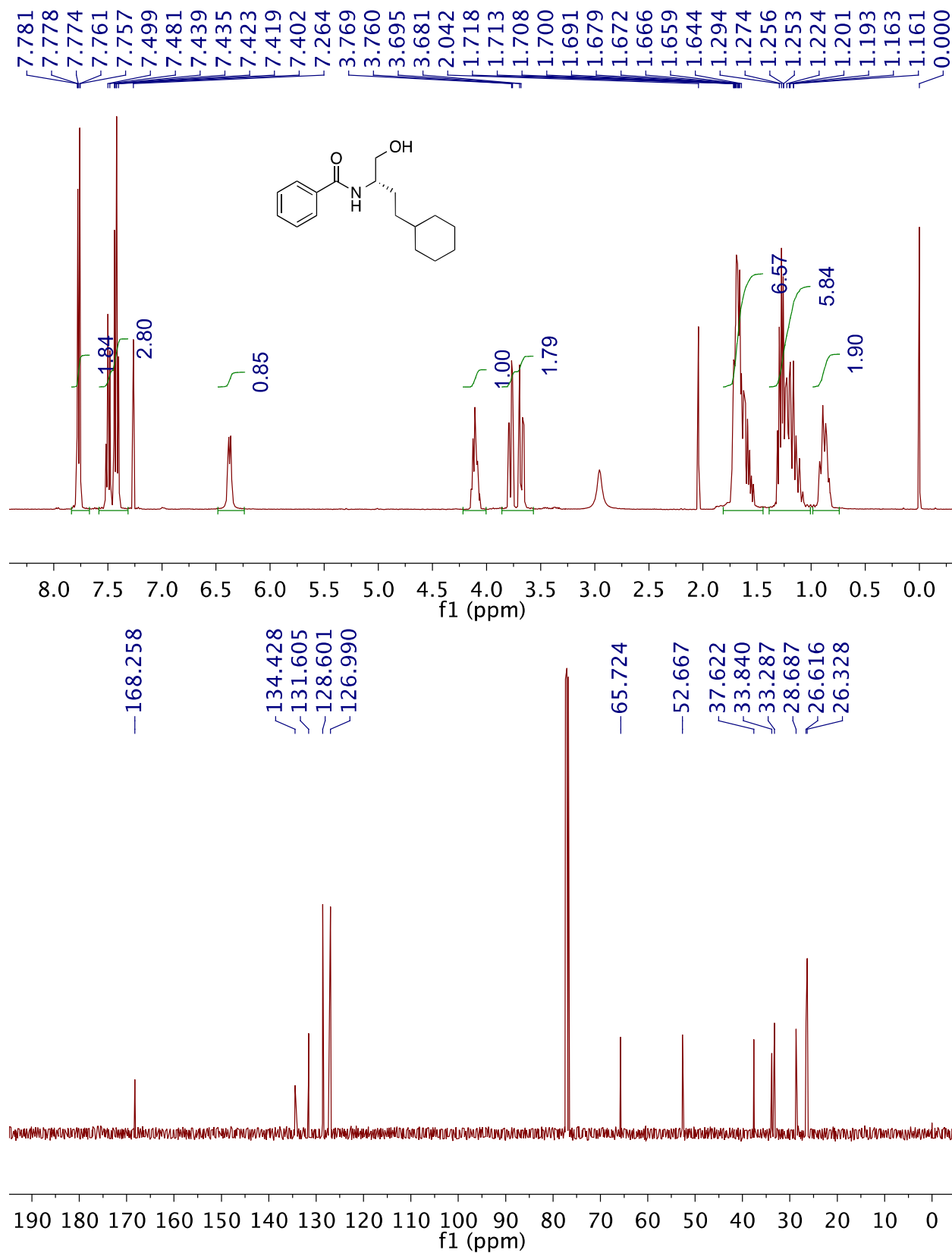


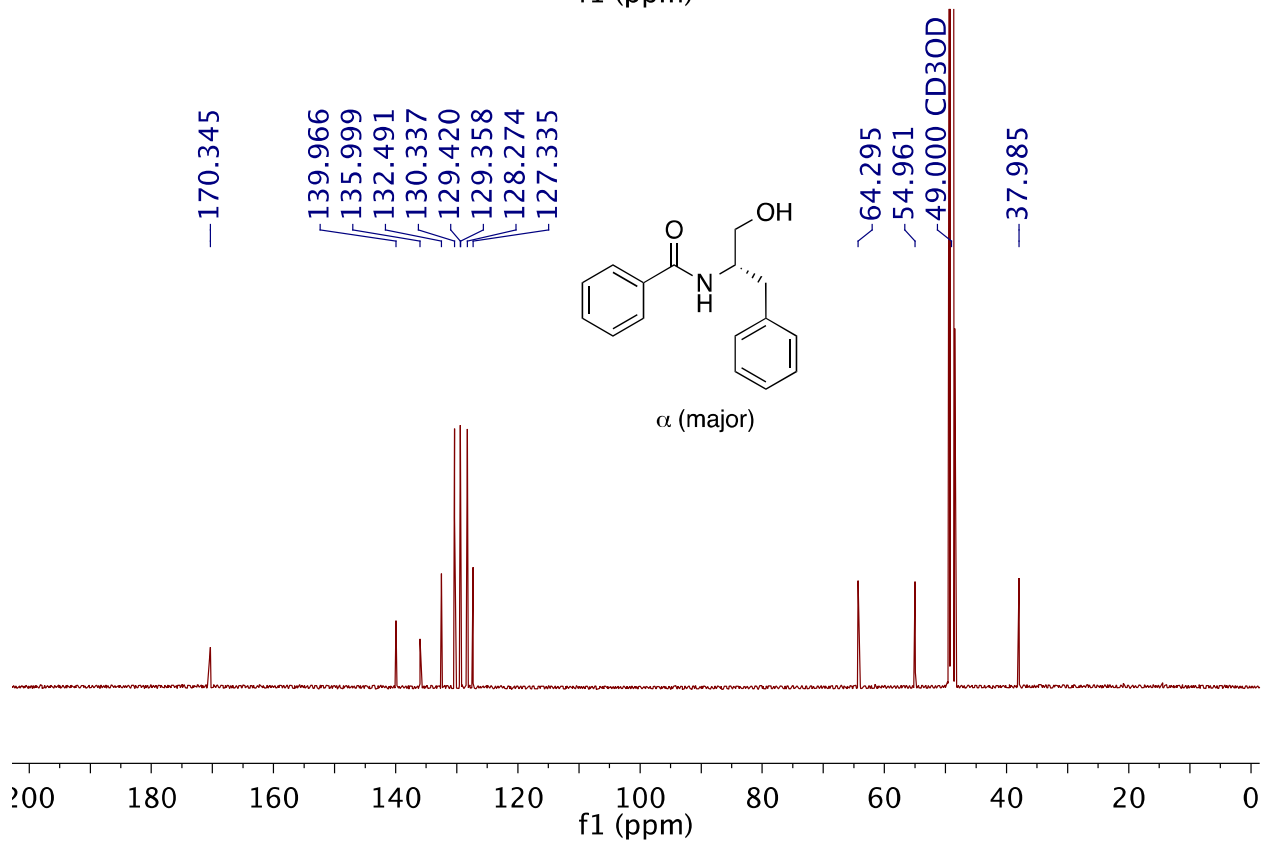
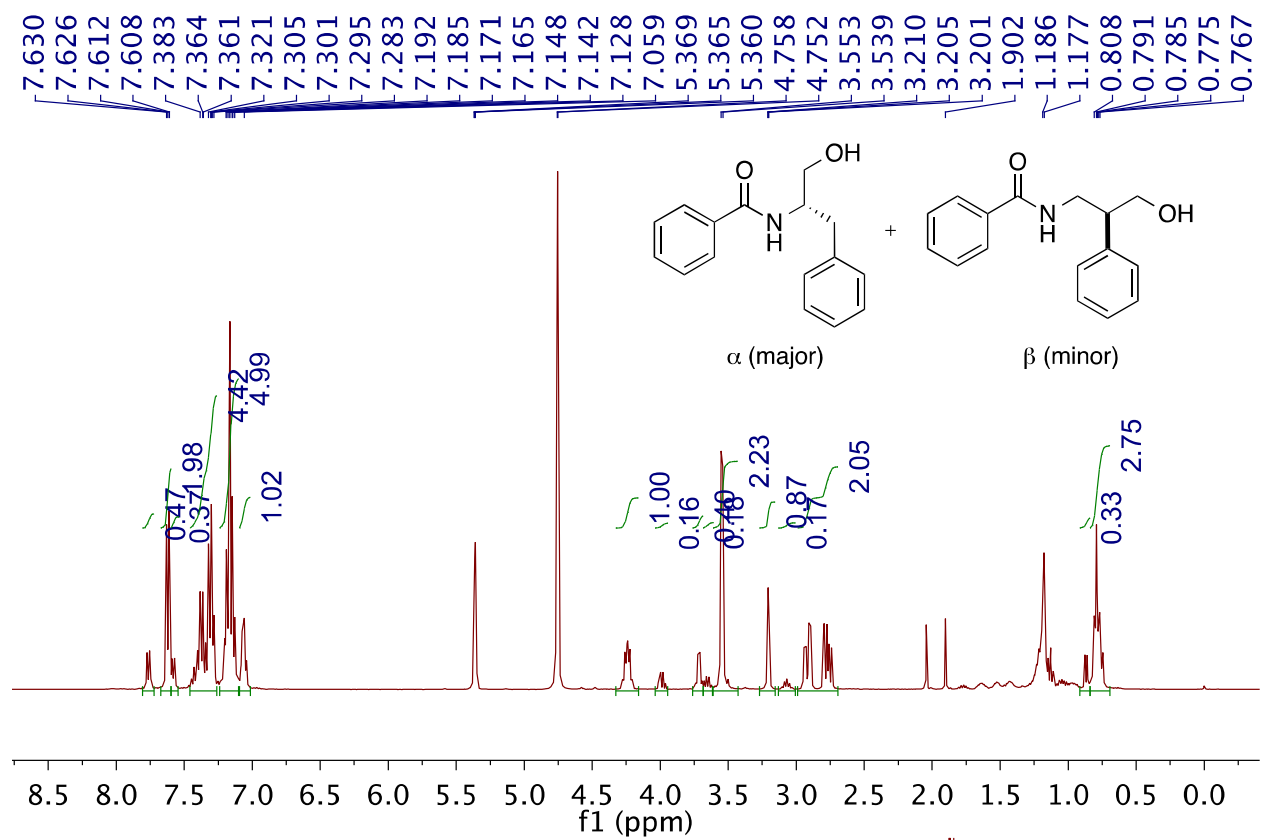


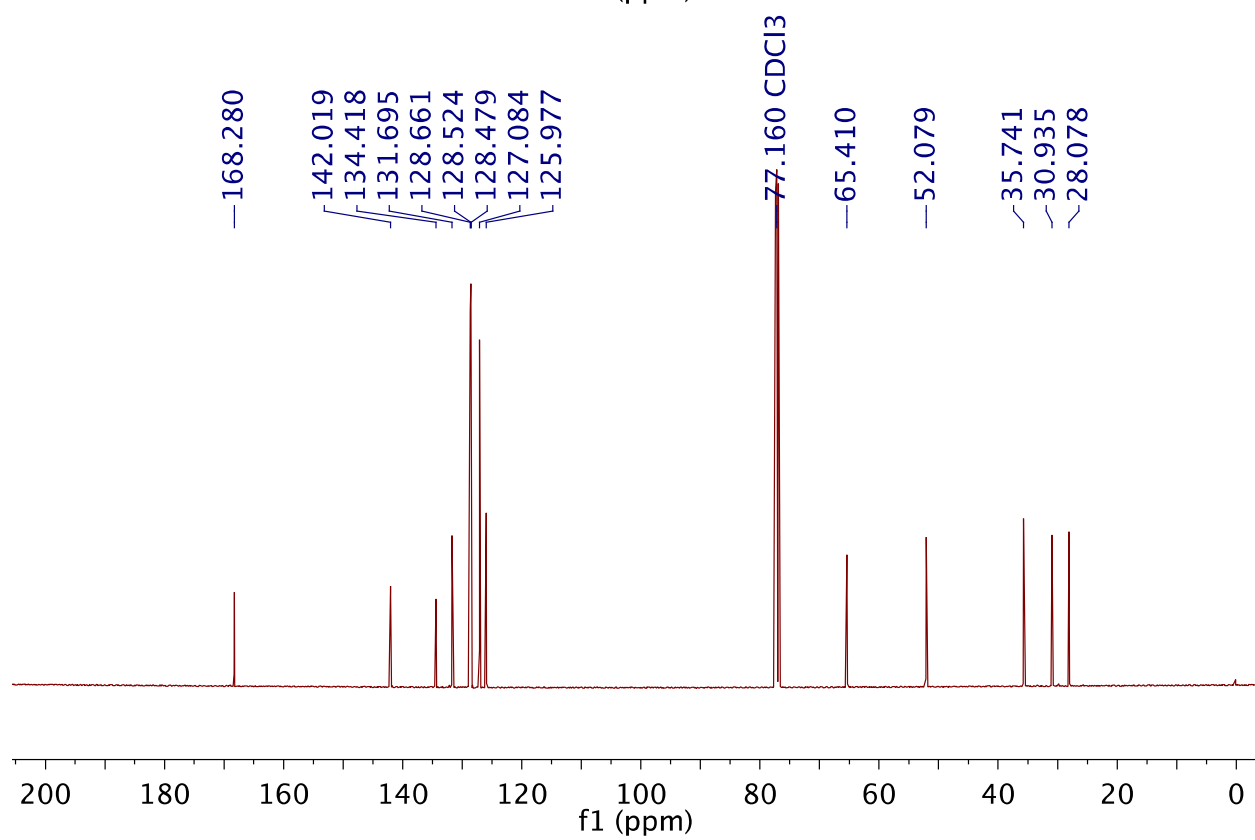
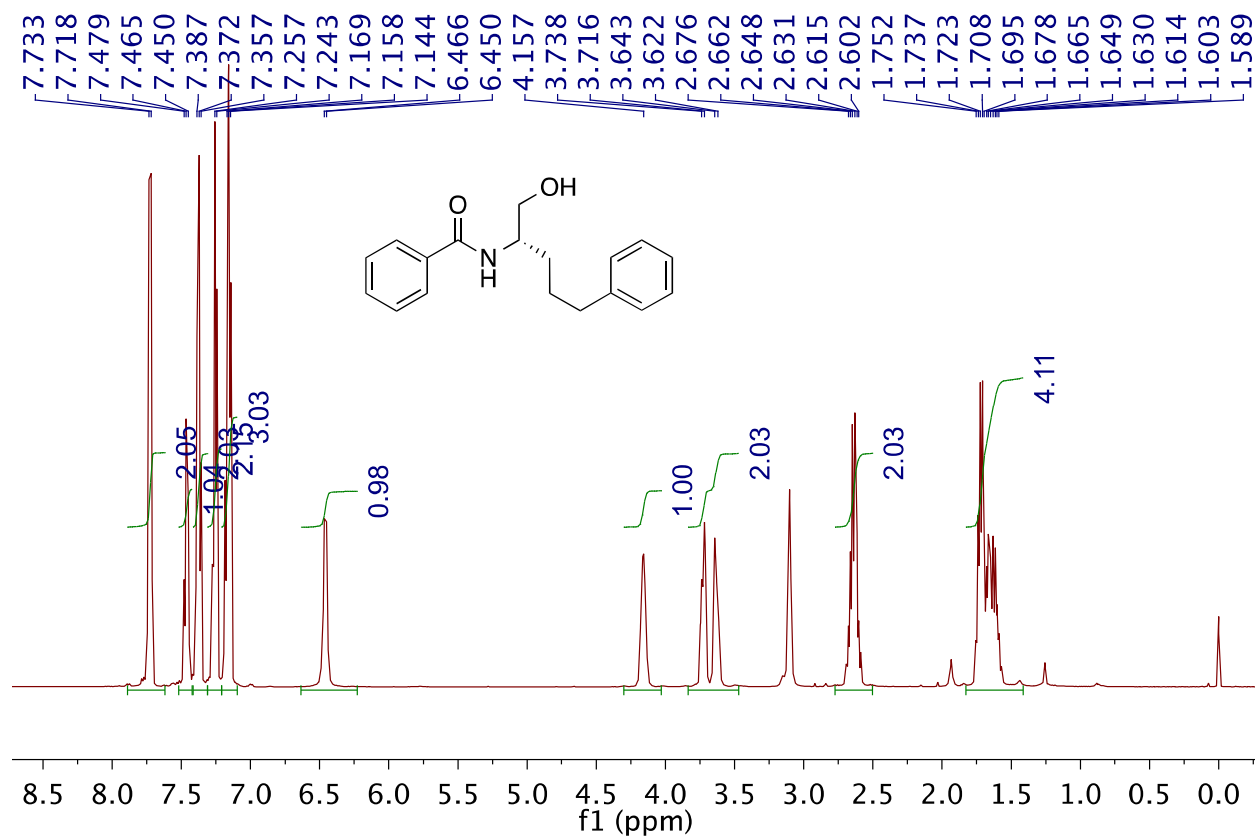


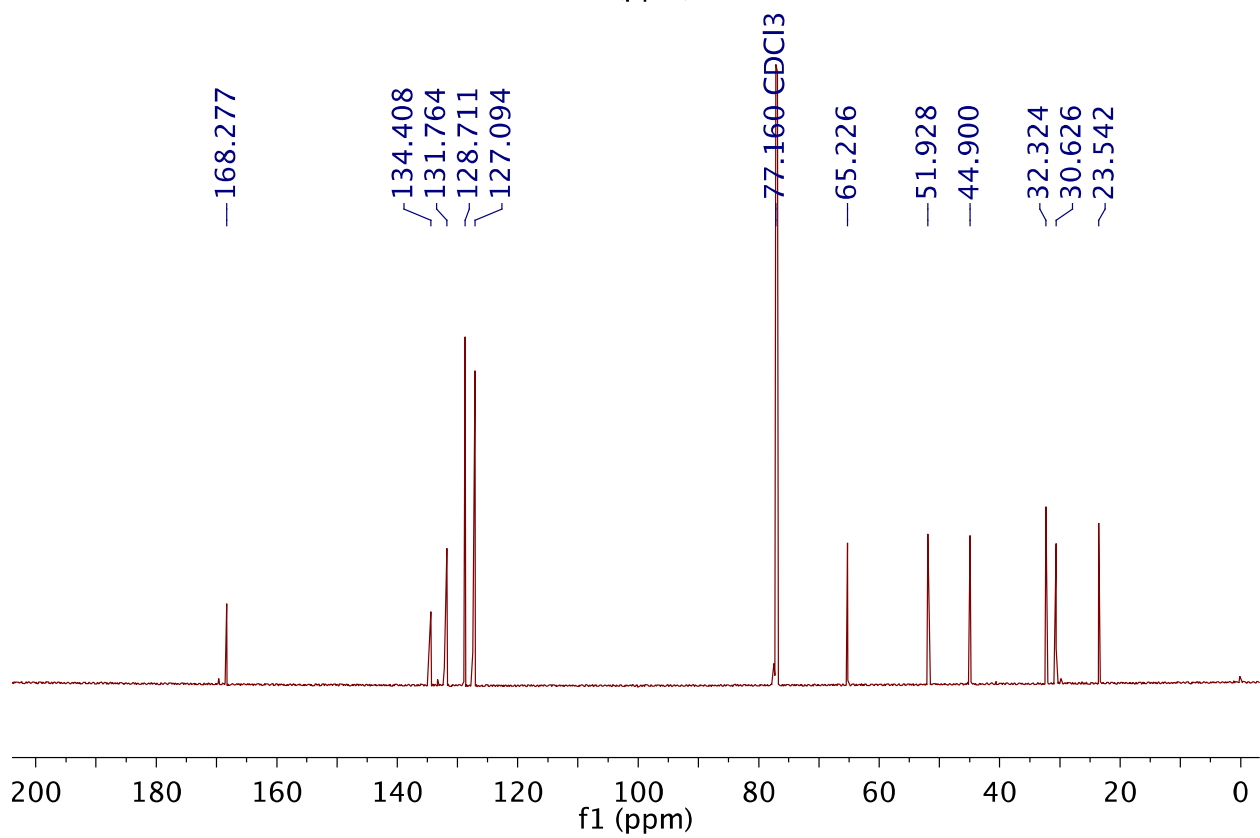
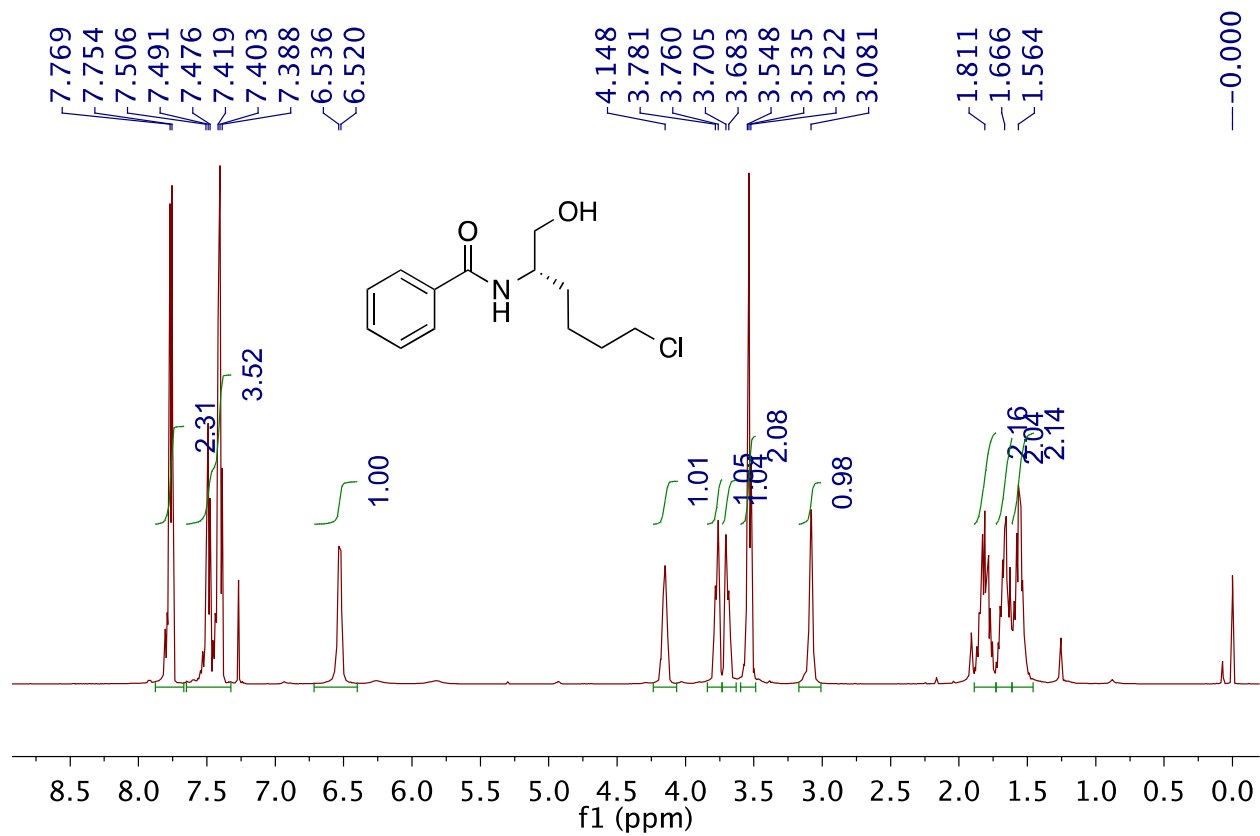


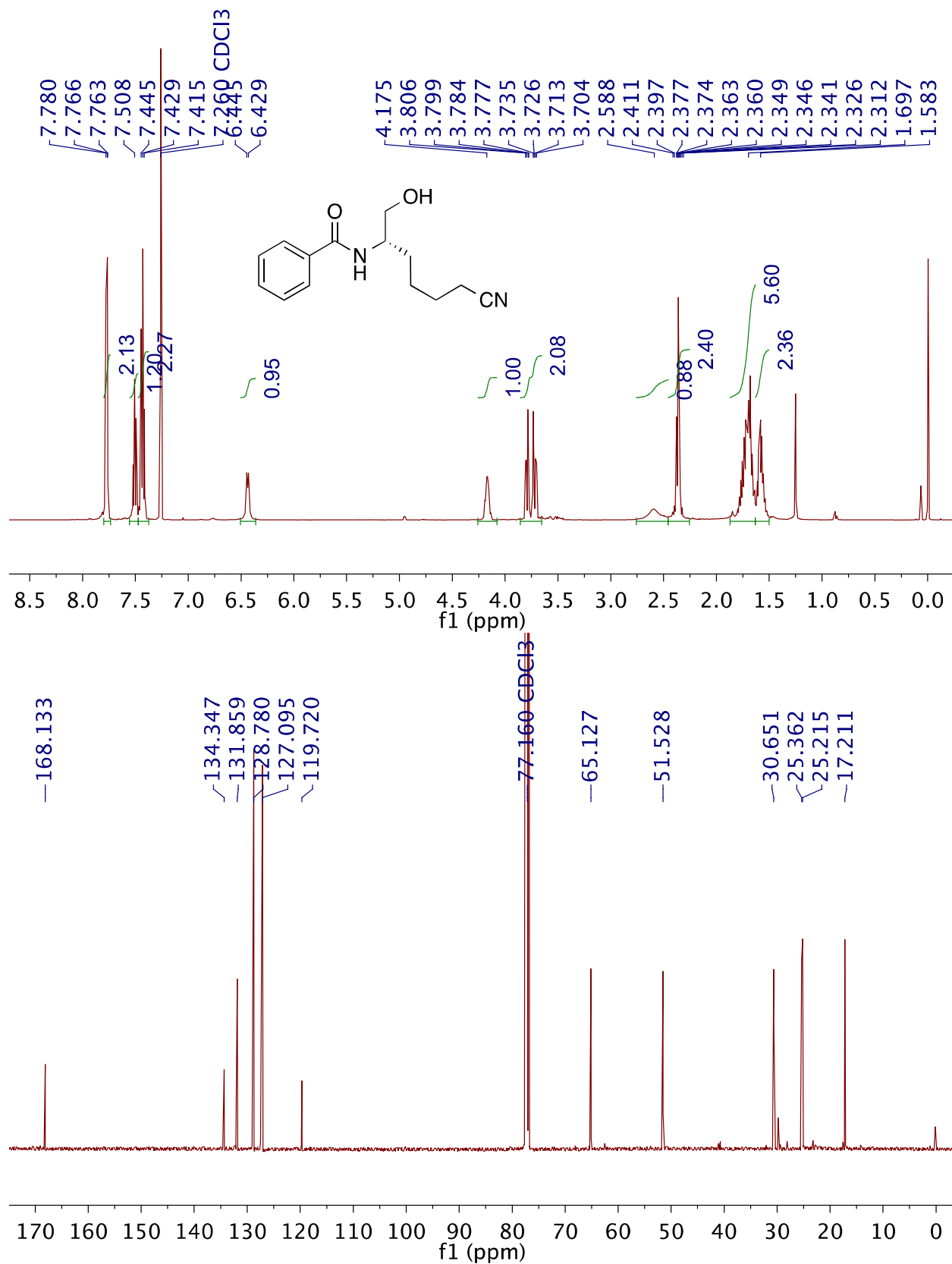


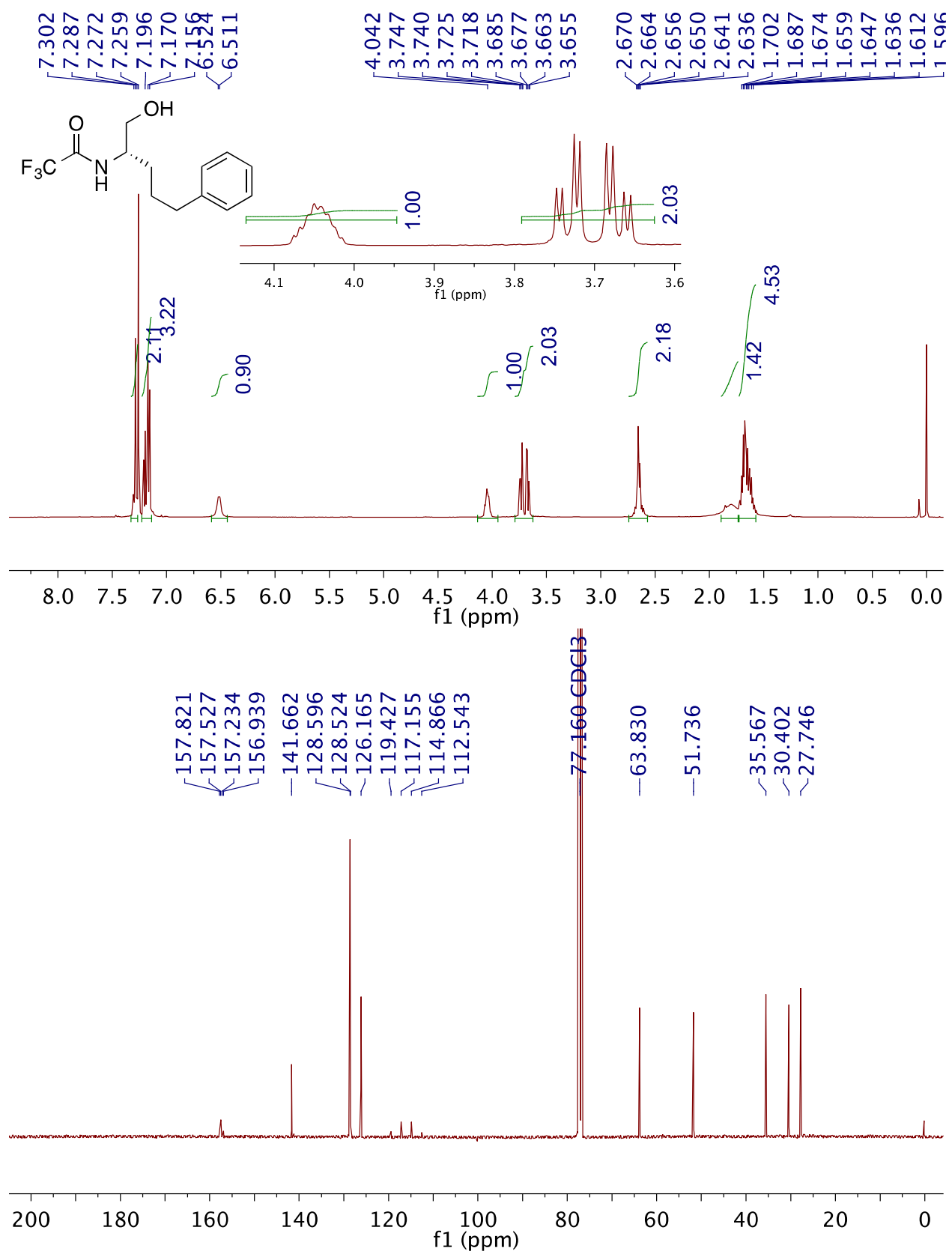


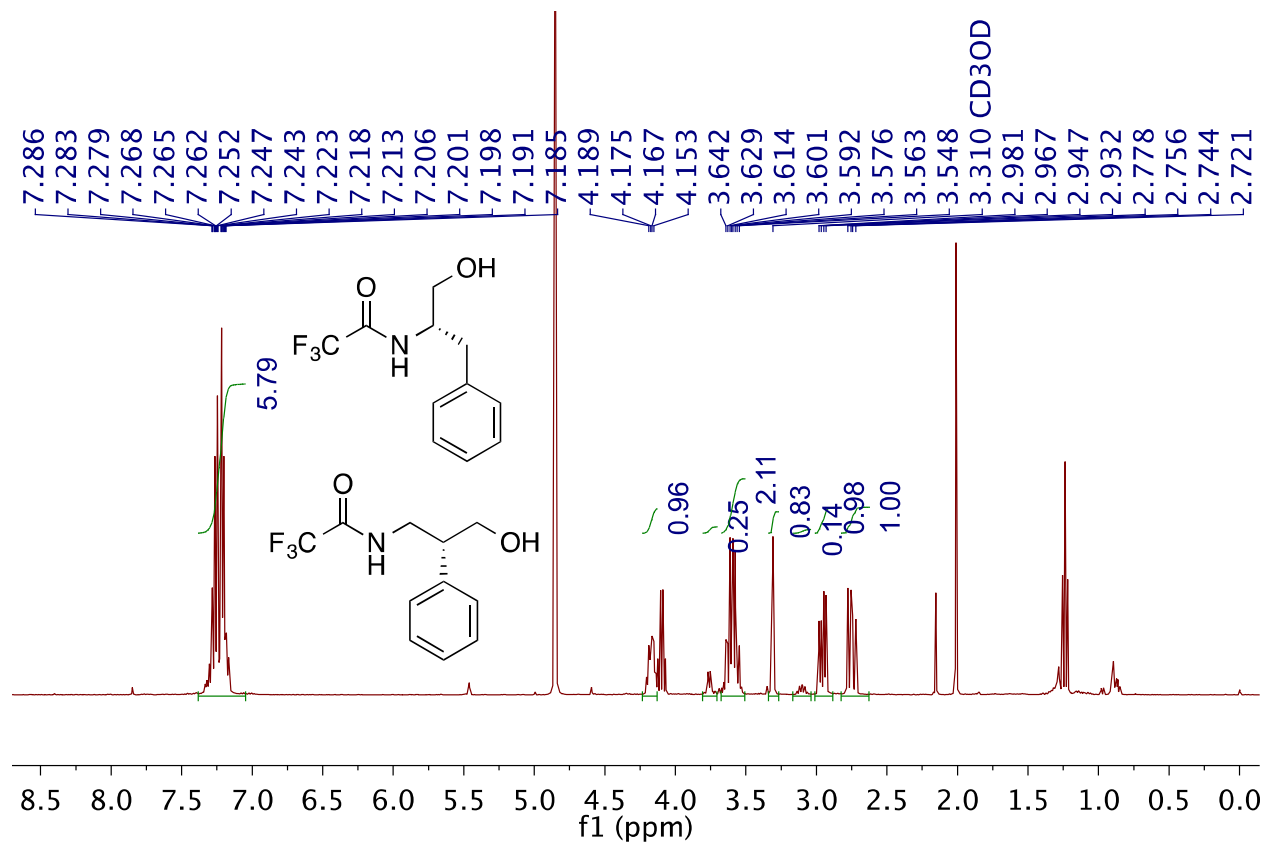


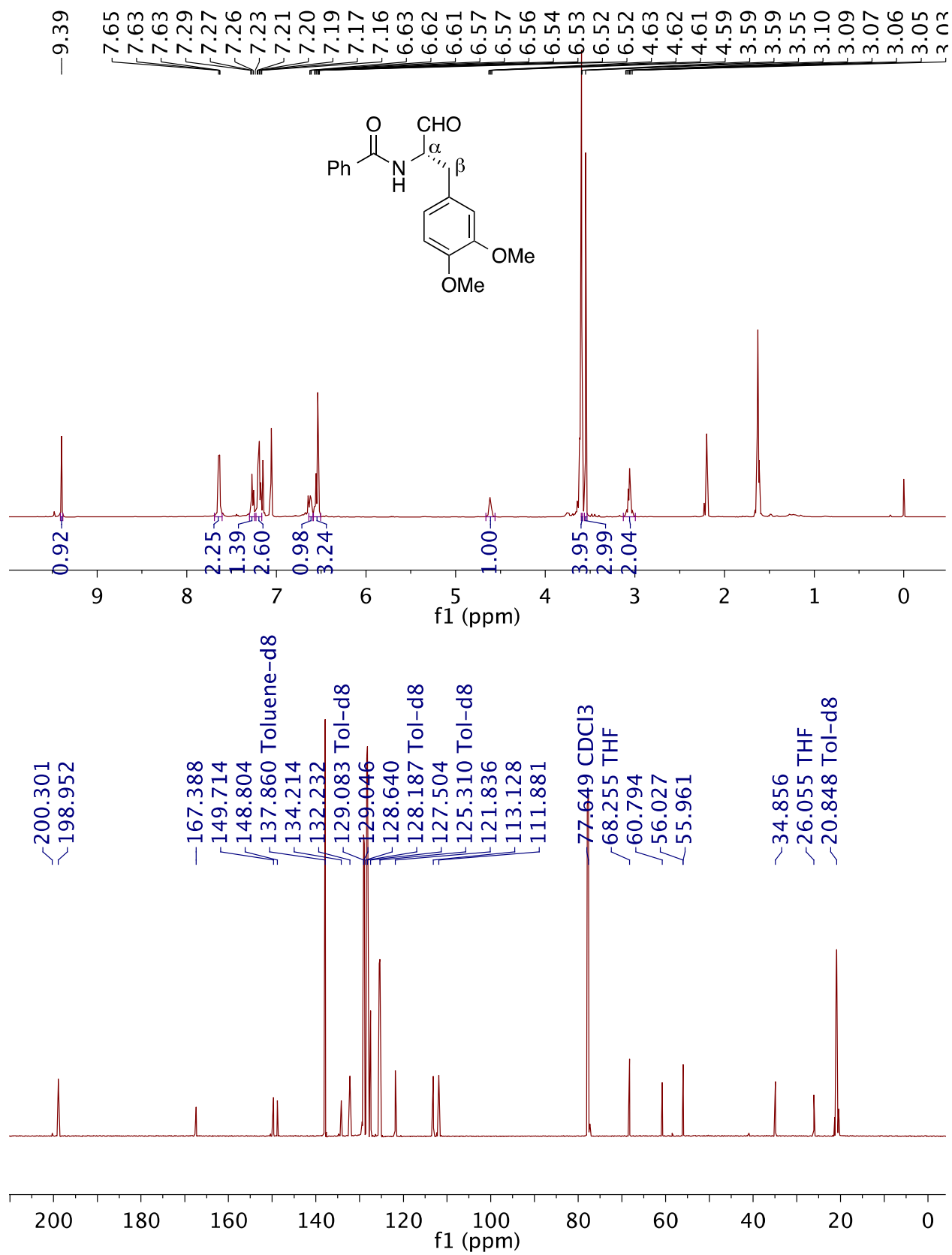






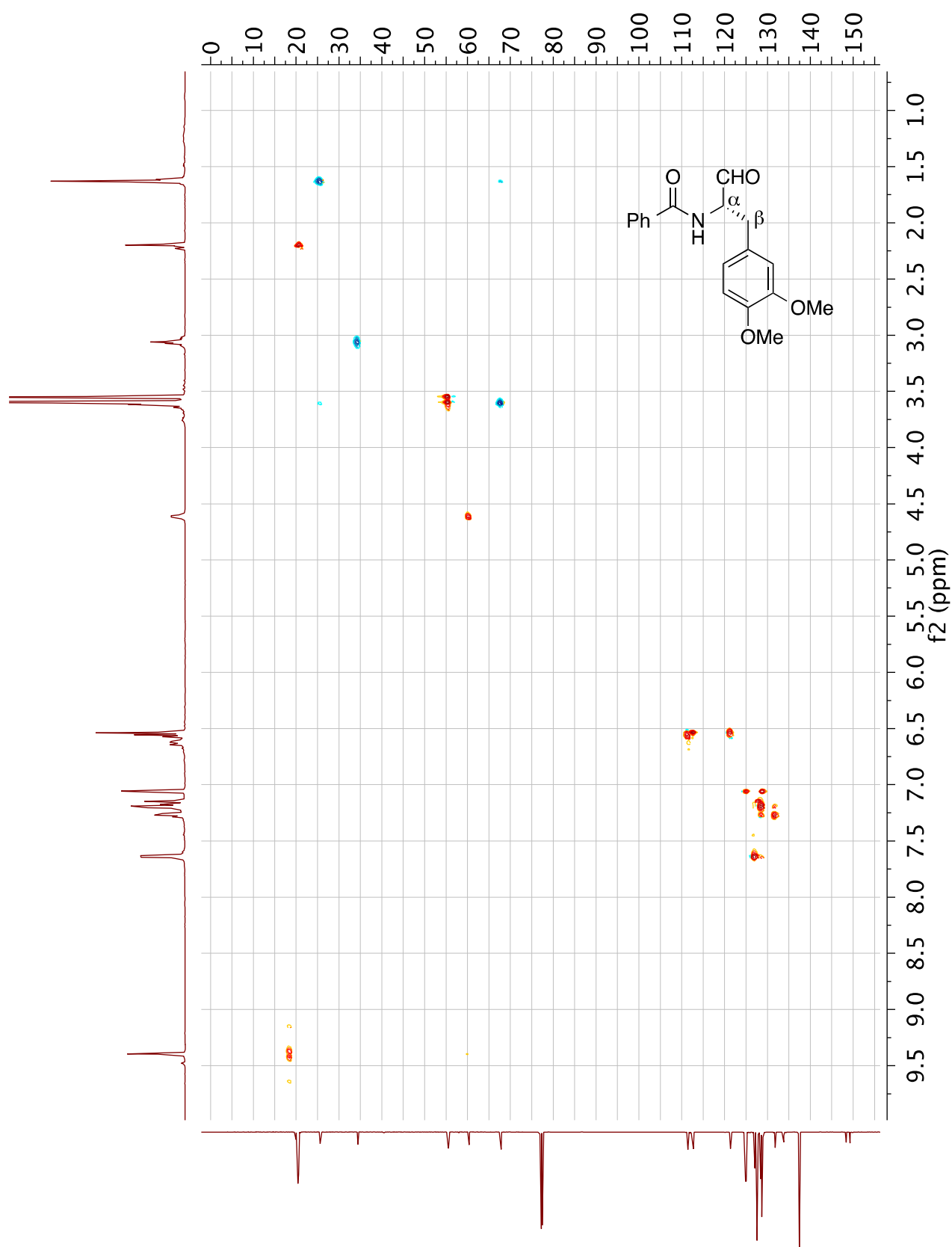


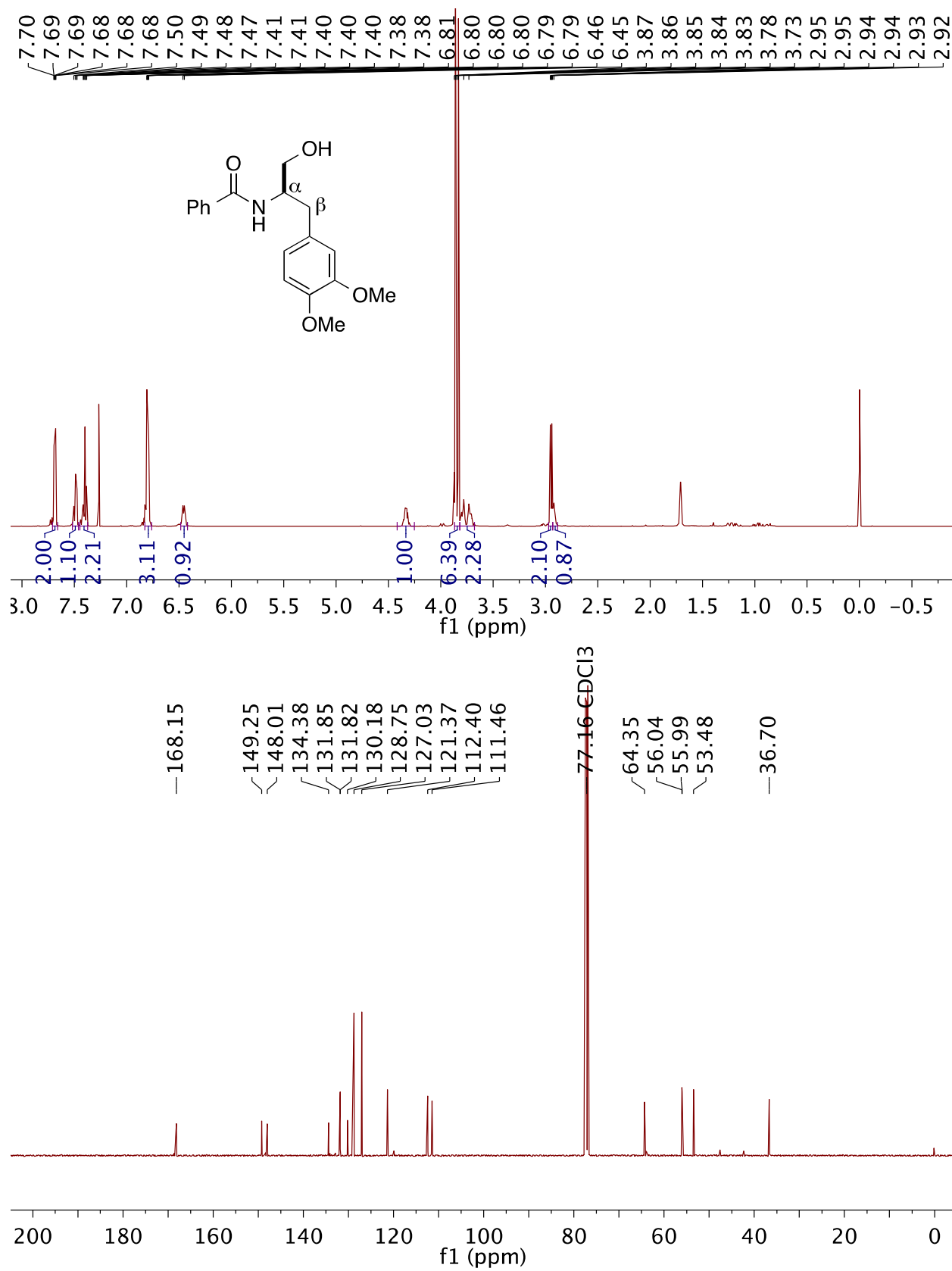


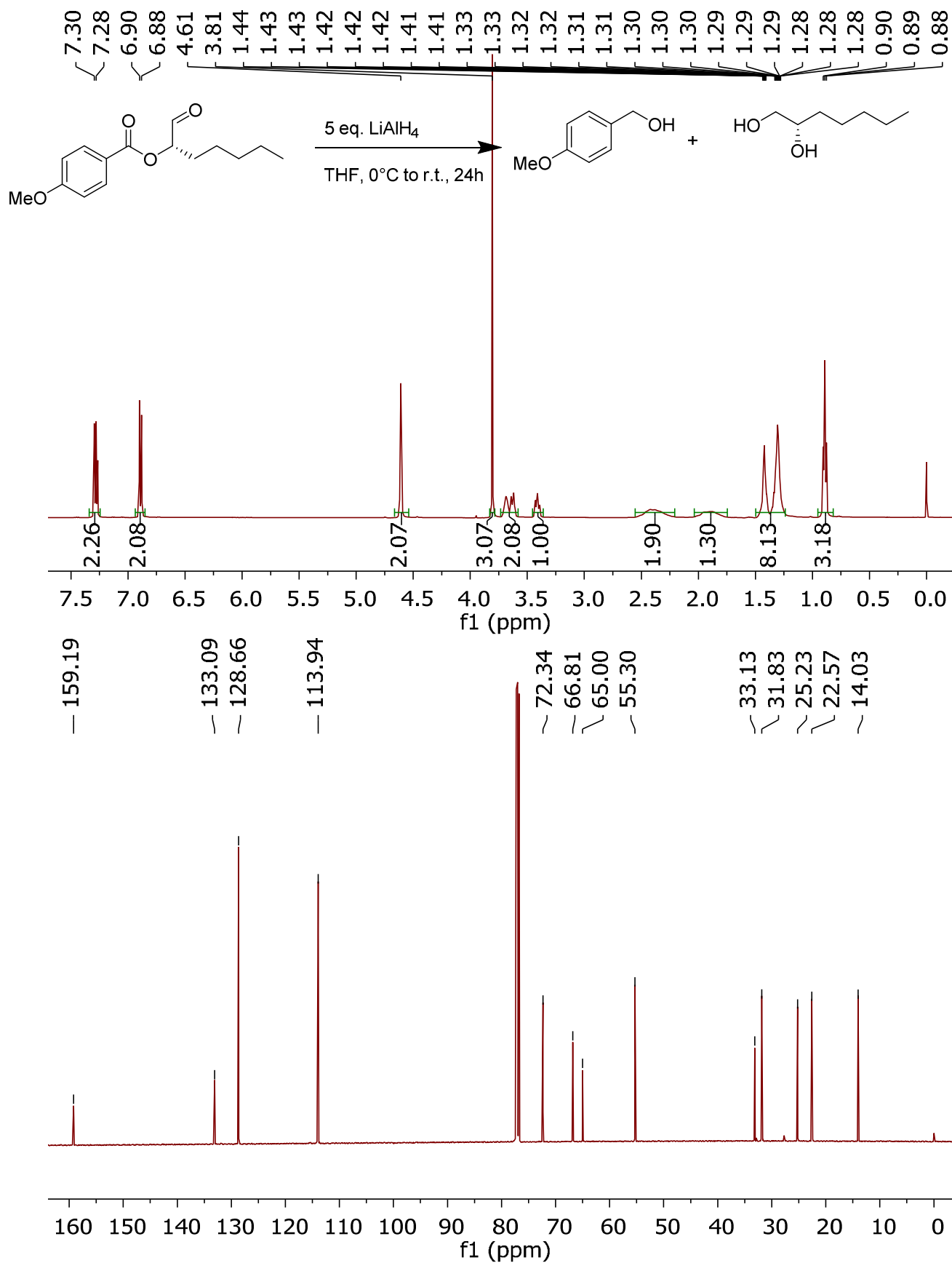


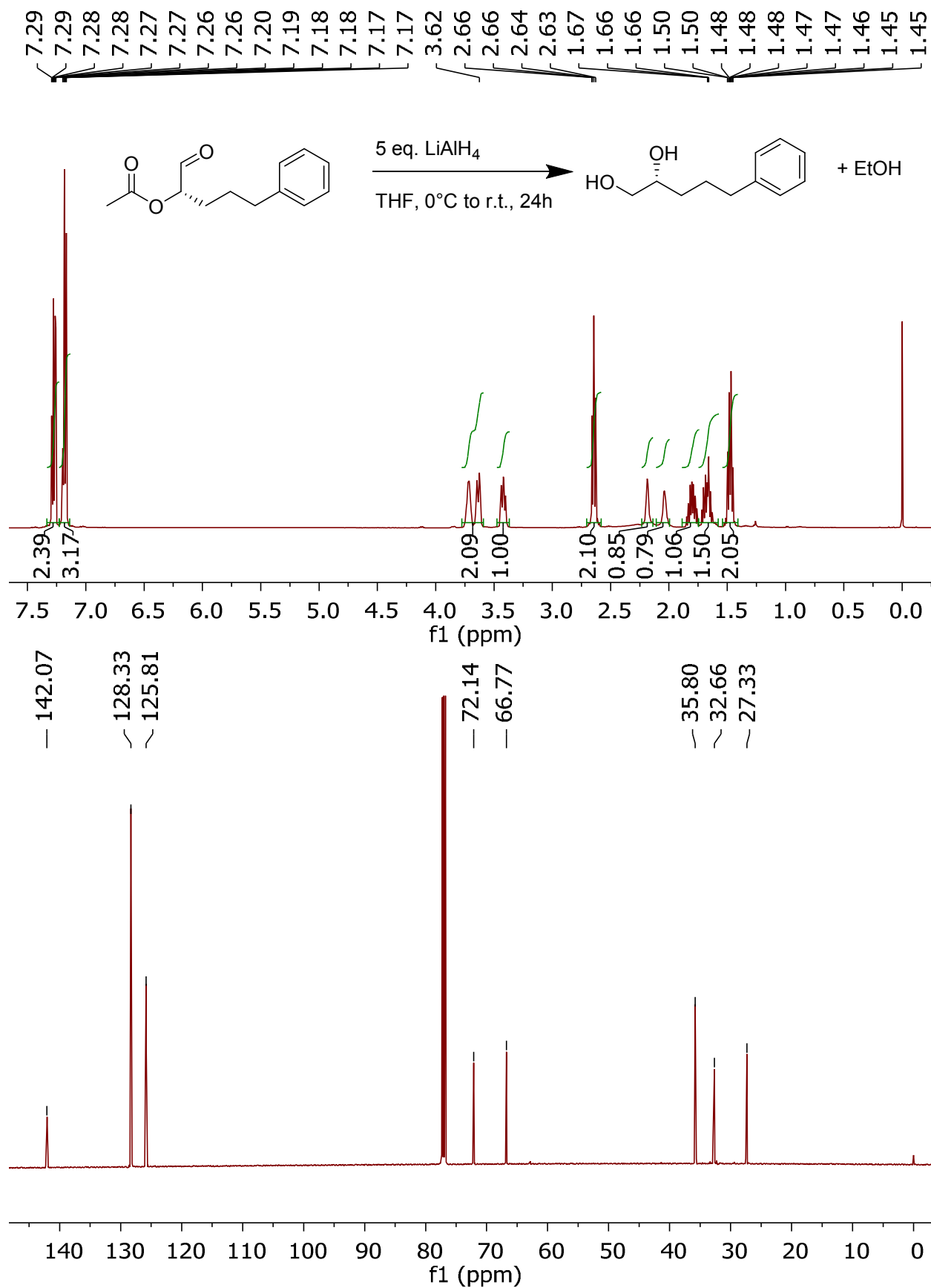
HSQC of the aldehyde to identify isomers

(μdd) τ_f

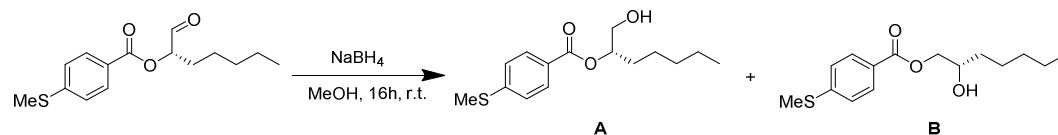






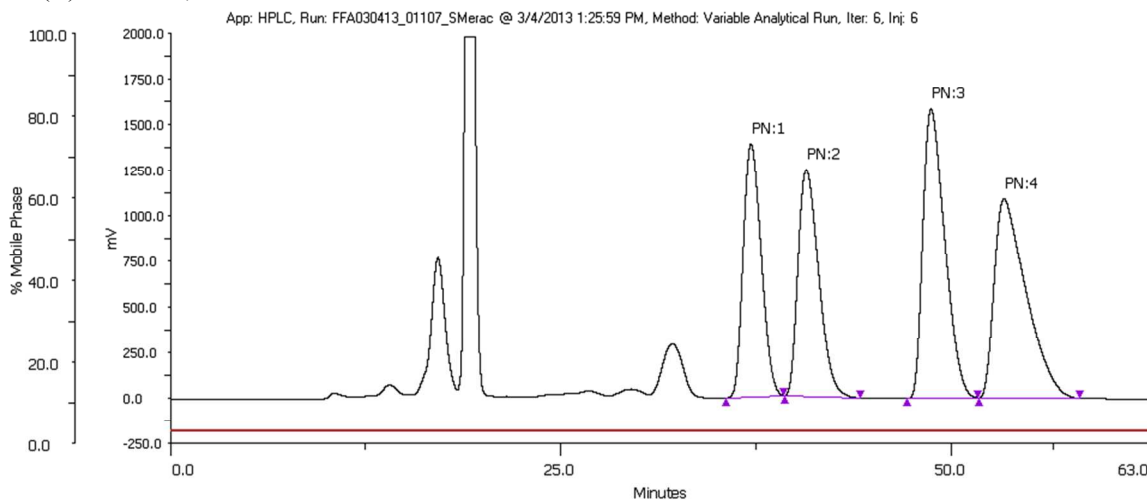


VII. HPLC and SFC traces

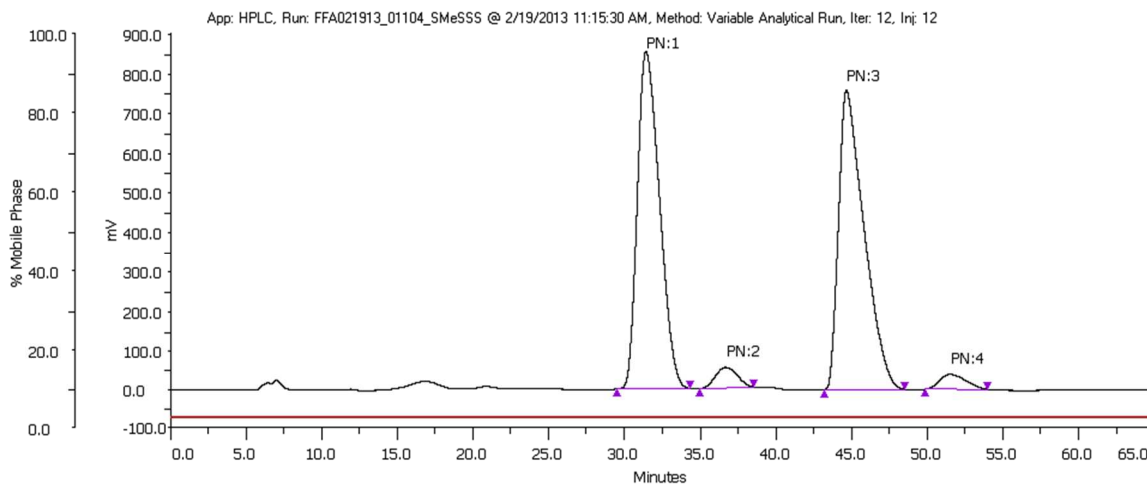


Resolution by HPLC:

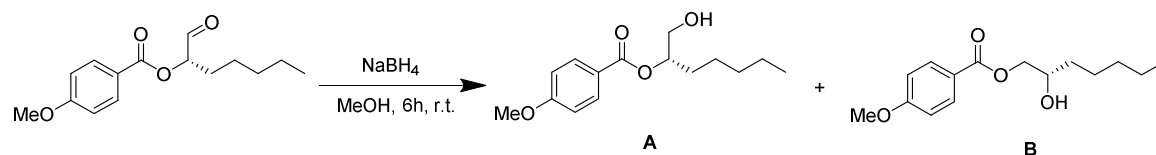
Racemic run: CHIRALPAK 1A (AD-H), 3% iPrOH/hexanes, 0.9 ml/min, 220 nm, t_R (**A**): 37.2 min, 40.8 min, t_R (**B**): 48.8 min, 53.4 min



Chiral run: CHIRALPAK 1A (AD-H), 3% iPrOH/hexanes, 0.9 ml/min, 220 nm, t_R (**A**): 31.5 min, 36.7 min, t_R (**B**): 44.7 min, 51.6 min, 90% ee

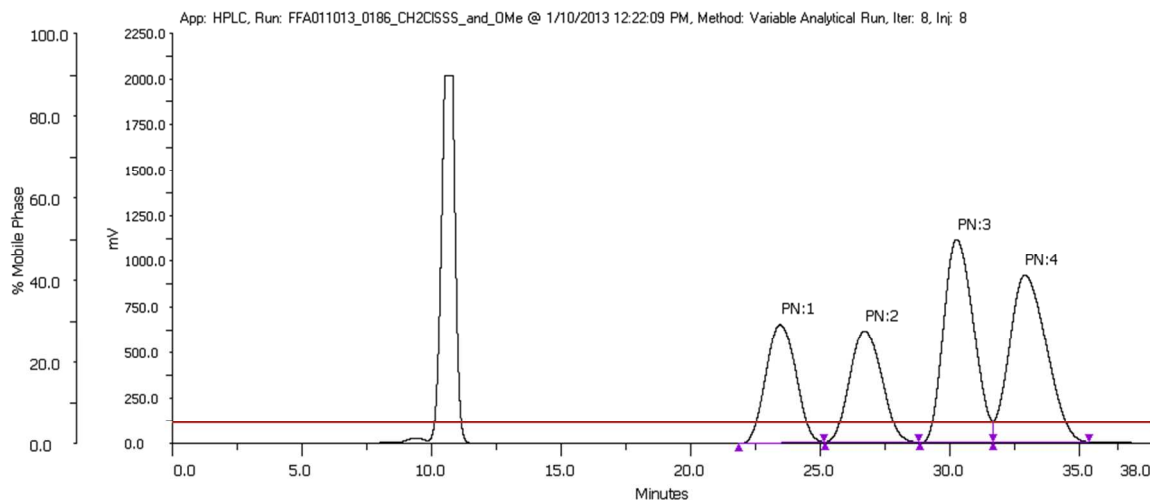


Peak Number (PN)	isomer	t_R (min)	Area (uVmin x100)	% Area
1	A	31.5	144958230.8322	46.905
2	A	36.7	8599526.6365	2.783
3	B	44.7	148067052.4987	47.911
4	B	51.6	7419669.9993	2.401

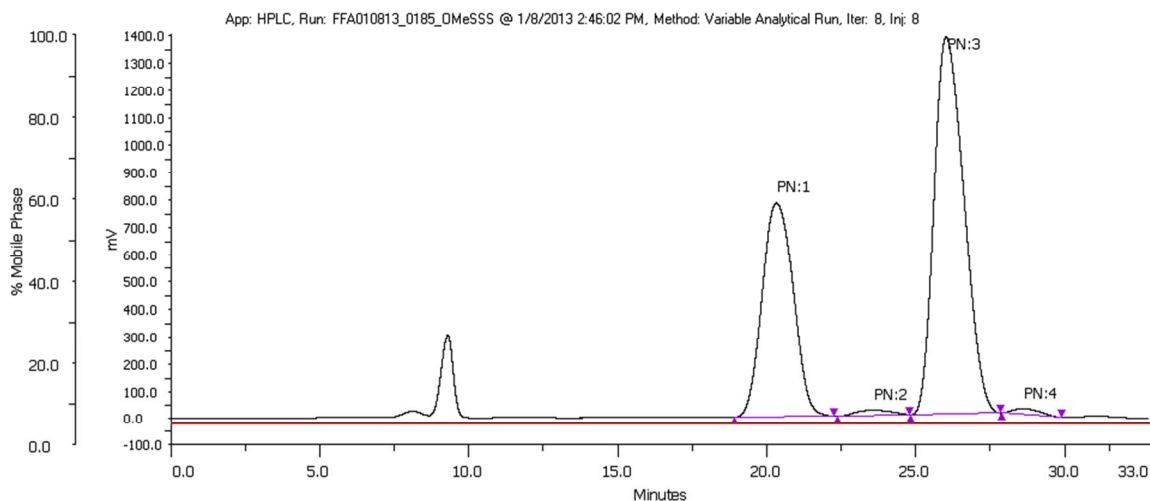


Resolution by HPLC:

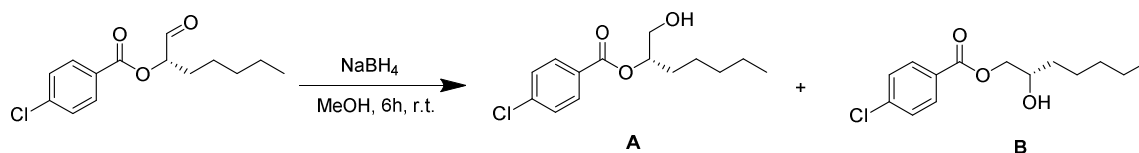
Racemic run: CHIRALPAK 1A (AD-H), 5% iPrOH/hexanes, 0.7 ml/min, 254 nm, t_R (**A**): 23.5 min, 26.8 min, t_R (**B**): 30.3 min, 33.0 min



Chiral run: CHIRALPAK 1A (AD-H), 5% iPrOH/hexanes, 0.8 ml/min, 254 nm, t_R (**A**): 20.3 min, 23.6 min, t_R (**B**): 26.0 min, 28.7 min, 96% ee

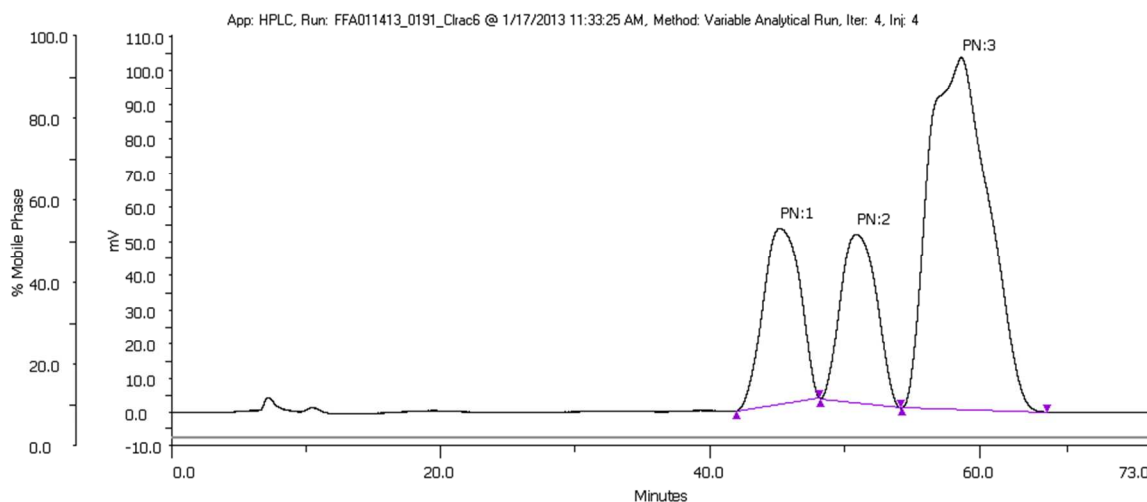


Peak Number (PN)	isomer	t_R (min)	Area (uVmin x100)	% Area
1	A	20.3	94911962.1362	36.417
2	A	23.6	2720385.831	1.044
3	B	26.1	160681660.8333	61.653
4	B	28.7	2308812.7922	0.886

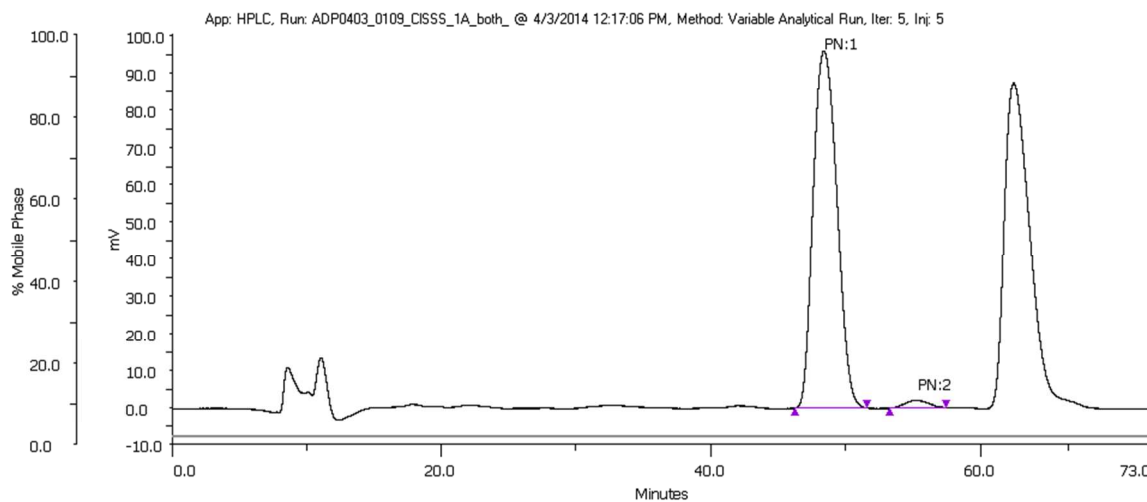


Resolution by HPLC:

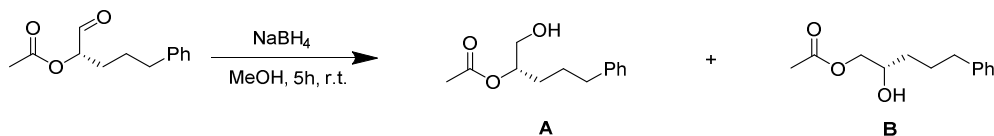
Racemic run: CHIRALPAK 1A (AD-H), 2% iPrOH/hexanes, 0.6 ml/min, 254 nm, t_R (**A**): 45.1 min, 51.0 min, t_R (**B**, unresolved): 58.7min



Chiral run: CHIRALPAK 1A (AD-H), 2% iPrOH/hexanes, 0.6 ml/min, 254 nm, t_R (**A**): 48.4 min, 55.3 min, 96% ee

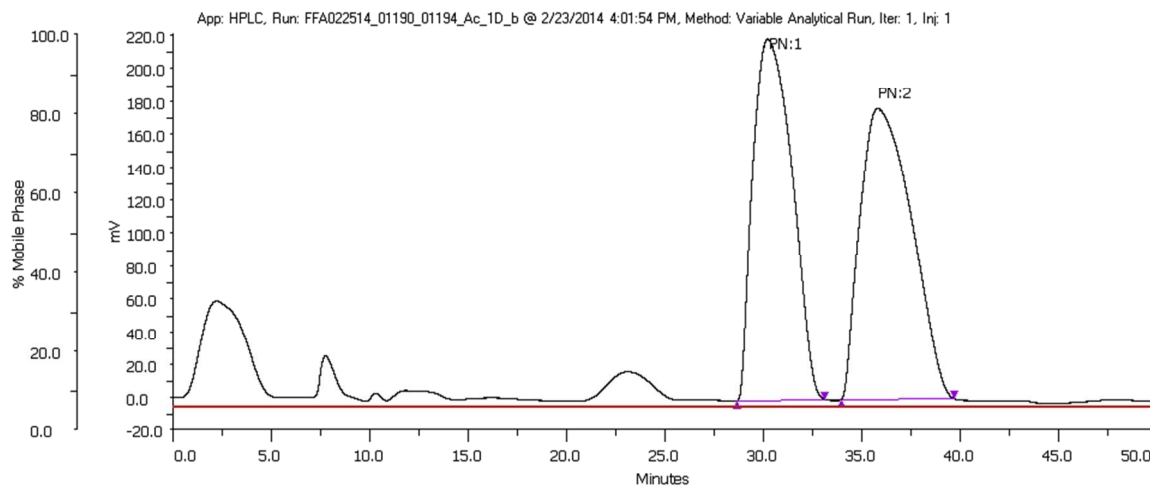


Peak Number (PN)	isomer	t_R (min)	Area (uVmin x100)	% Area
1	A	48.4	19554047.9174	98.008
2	A	55.3	397457.6244	1.992

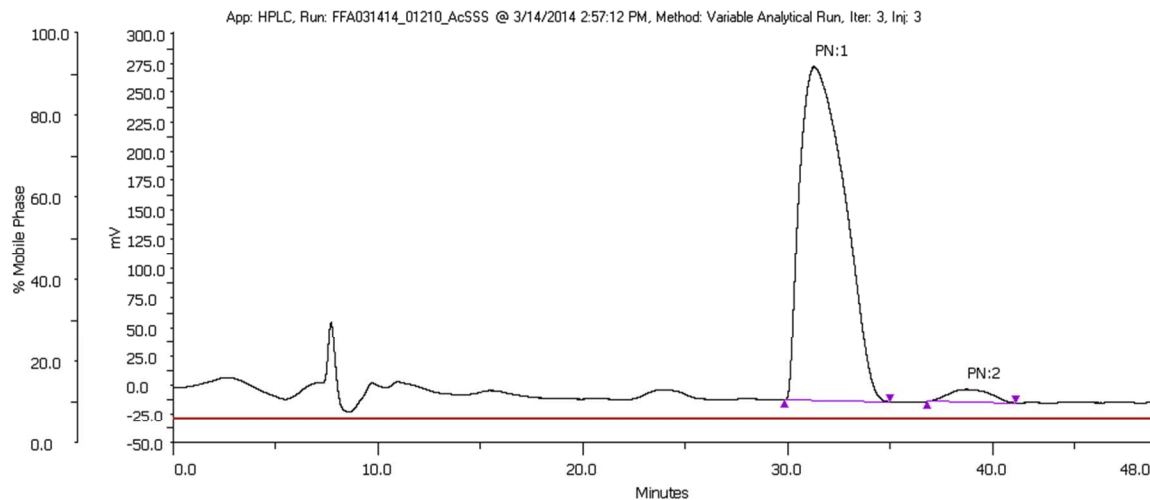


Resolution by HPLC:

Racemic run: CHIRALPAK 1D, 6% iPrOH/hexanes, 0.6 ml/min, 220 nm, t_R (**B**): 30.3 min, 35.9 min

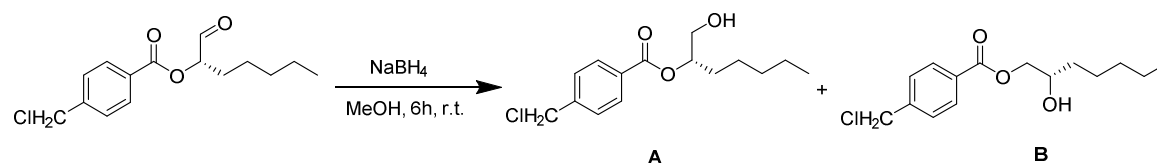


Chiral run: CHIRALPAK 1D, 6% iPrOH/hexanes/0.1% TFA, 0.6 ml/min, 220 nm, t_R (**B**): 31.3min, 88.8 min, 93%ee



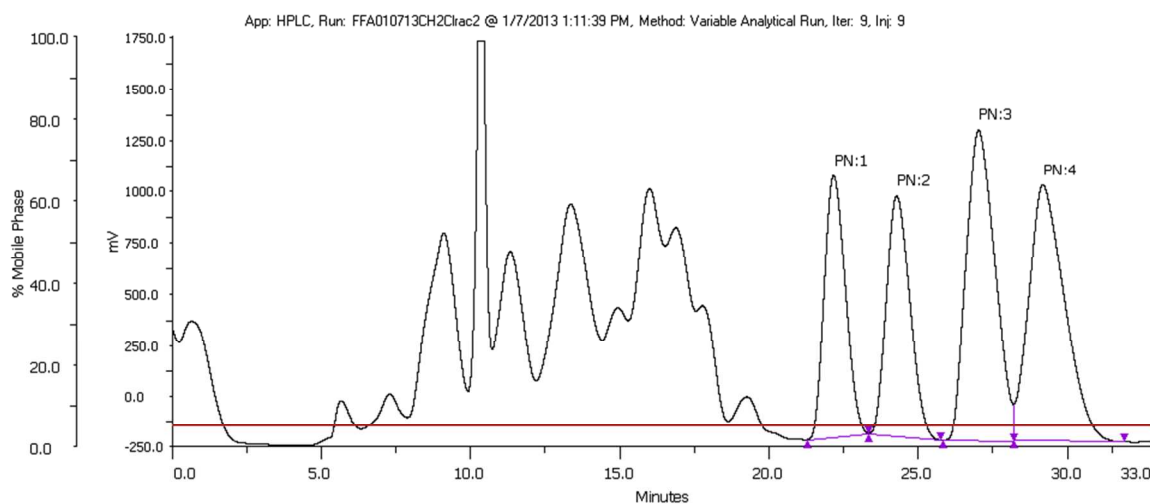
Enantioenriched run shows no **A** isomer because sample was purified before HPLC and only **B** isomer was collected.

Peak Number (PN)	isomer	t_R (min)	Area (uVmin x100)	% Area
1	B	31.3	71835284.9266	96.533
2	B	38.8	2579833.1423	3.467

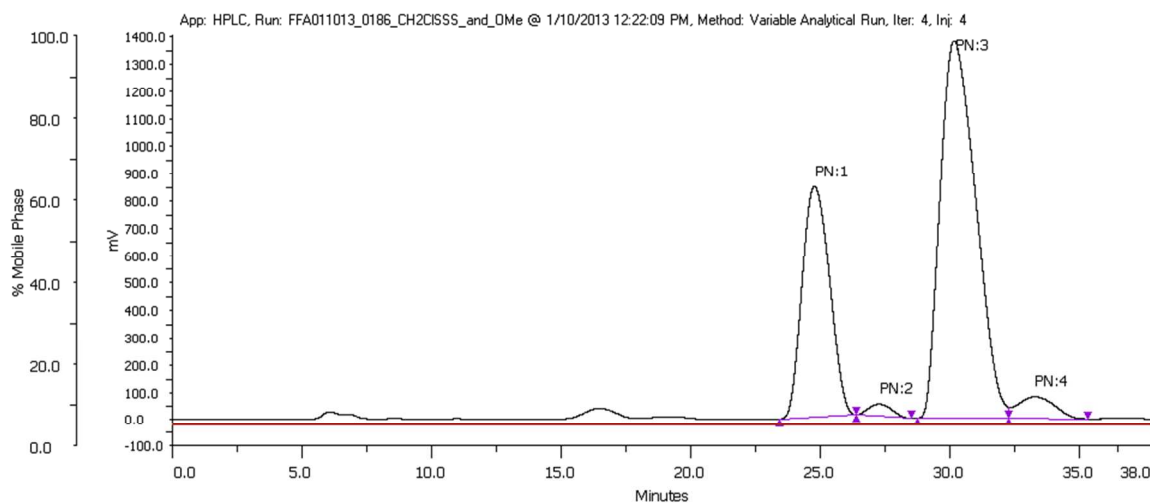


Resolution by HPLC:

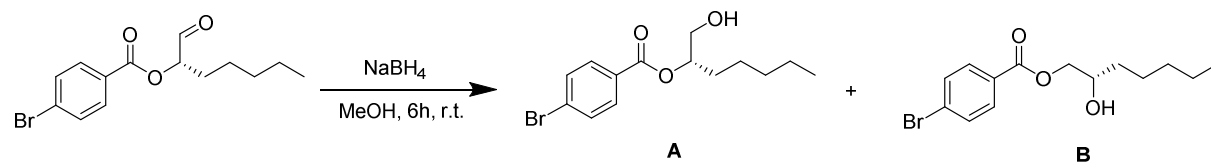
Racemic run: CHIRALPAK 1A (AD-H), 5% iPrOH/hexanes, 0.7 ml/min, 254 nm, t_R (**A**): 23.5 min, 26.8 min, t_R (**B**): 30.3 min, 33.0 min



Chiral run: CHIRALPAK 1A (AD-H), 5% iPrOH/hexanes, 0.8 ml/min, 254 nm, t_R (**A**): 20.3 min, 23.6 min, t_R (**B**): 26.0 min, 28.7 min, 92% ee

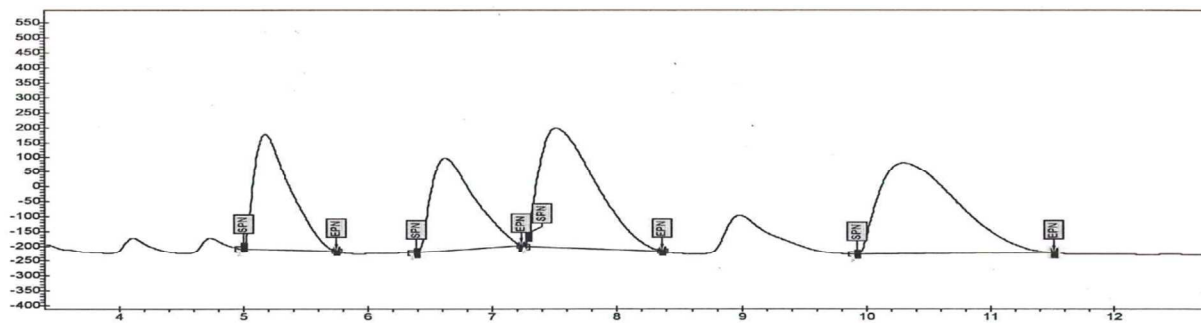


Peak Number (PN)	isomer	t_R (min)	Area (uVmin x100)	% Area
1	A	24.8	103527229.1501	30.298
2	A	27.3	4598088.8746	1.346

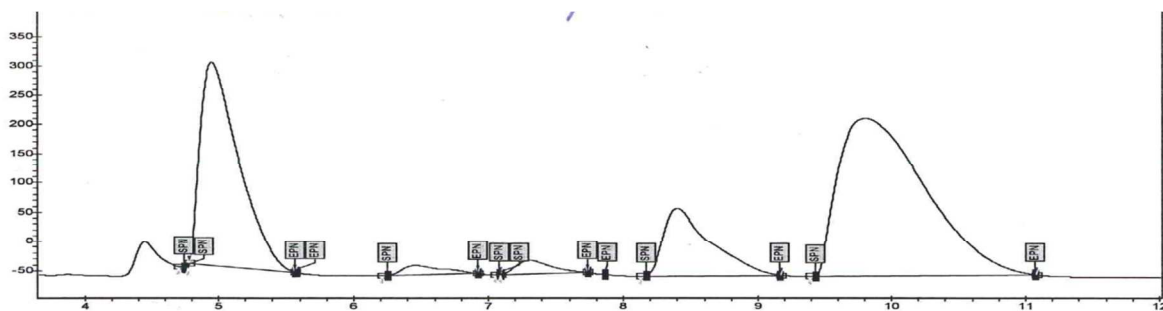


Resolution by SFC:

Racemic run: OJ-H, 4% modifier, 4 ml/min, methanol, 50°C, t_R (**A**): 5.2 min, 6.6 min, t_R (**B**): 7.5 min, 10.3 min



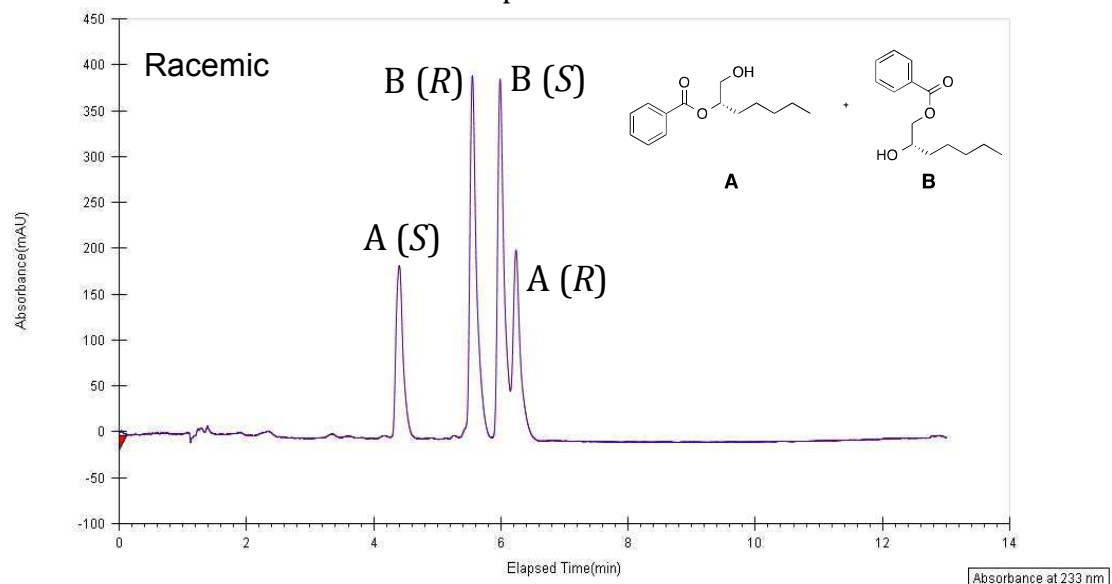
Chiral run: OJ-H, 4% modifier, 4 ml/min, methanol, 50°C, t_R (**A**): 5.0 min, 6.5 min, t_R (**B**): 7.3 min, 9.8 min, 92% ee



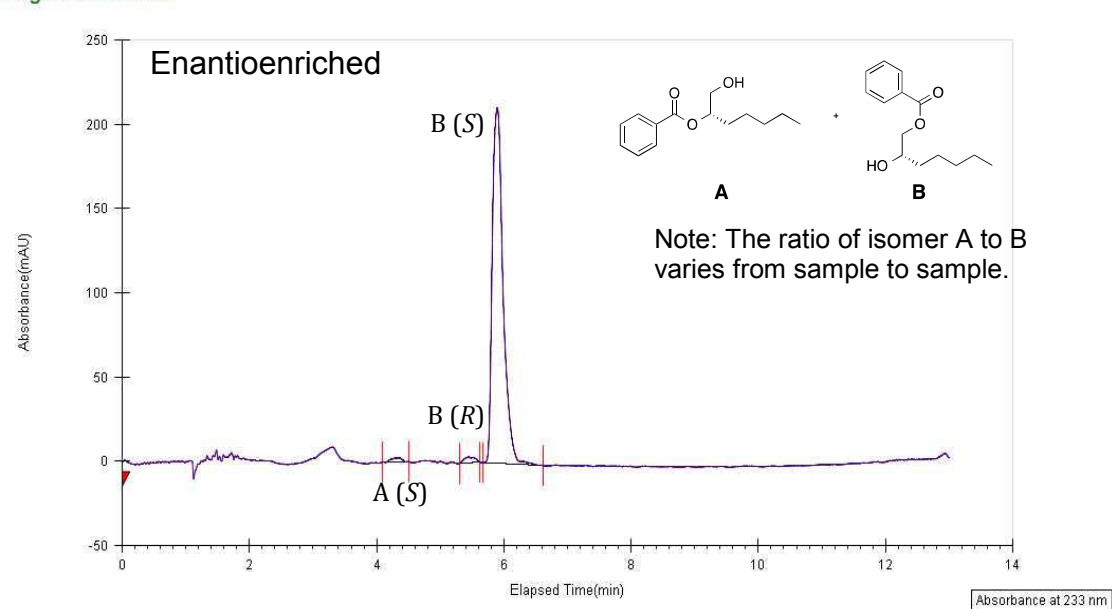
t_R (min)	isomer	Area (uVmin)	% Area
5.0	A	115.7	23.651
6.5	A	5.6	1.143
7.3	B	6.9	1.414
9.81	B	203.1	41.535

Single Absorbance

SFC Separation:



Single Absorbance



General Info

Log Author

Log Date 11/30/2013 5:46:05 PM

Report By current_User

Report Date 12/12/2013

Method Name Gradient_5_50_3flow.met

Notes

Injection Info

Inj Vol 10

Solvent MeOH

Column AD-H

Sample MLA2276r

Well location P1: 1E

Temp 35

Flow 3

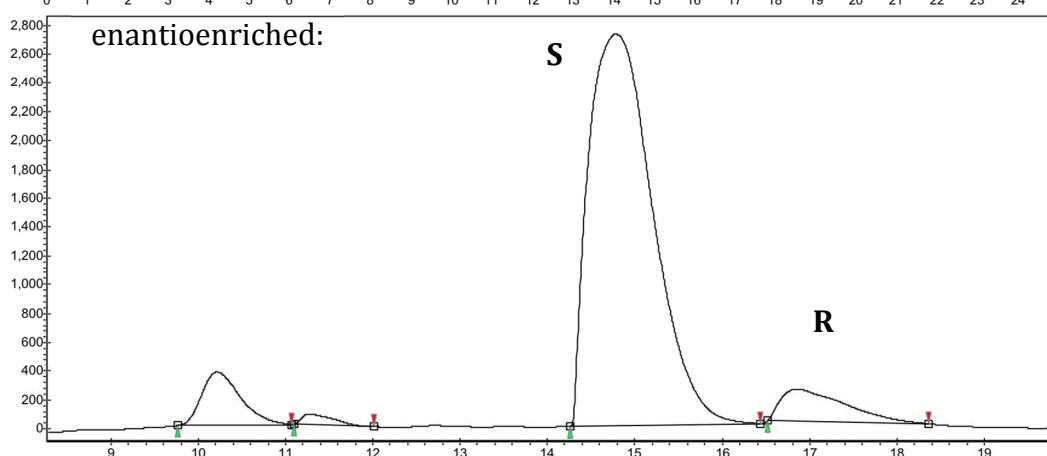
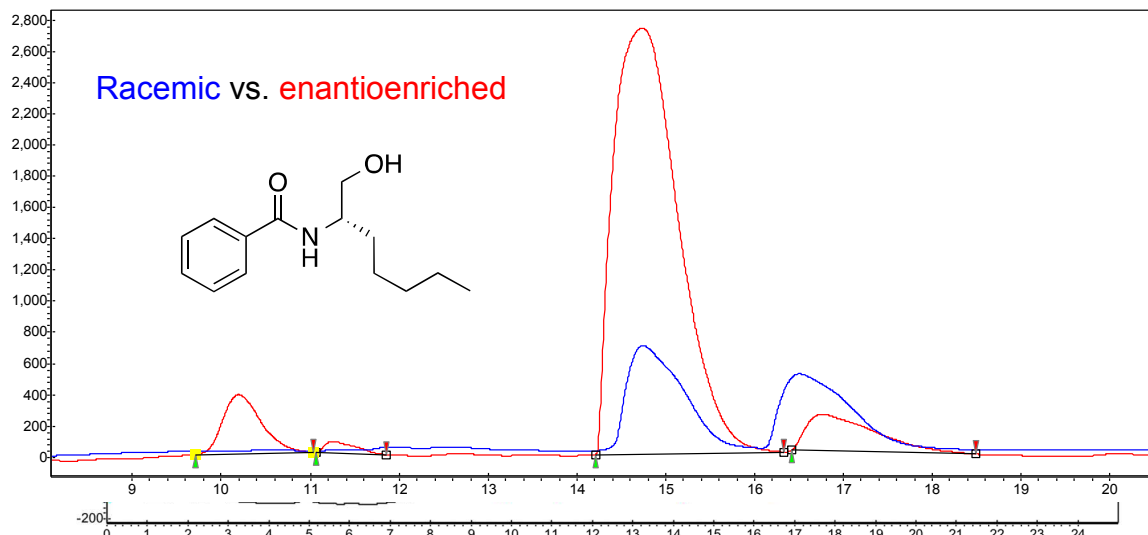
% Modifier 5

Pressure 100

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	1.0416	26.525	4.36	2.3412	0.0041
2	1.6264	41.4194	5.45	3.5302	0.0051
3	97.332	2478.6963	5.9	210.691	0.0055
Total:	100	2546.6407			

SFC separation:



#	Name	Start [Min]	Time [Min]	End [Min]	RT Offset [Min]	Quantity [% Area]	Height [μV]	Area [μV.Min]	Area [%]
1	UNKNOWN	9.77	10.21	11.07	0.00	6.89	366.1	187.5	6.886
4	UNKNOWN	11.10	11.28	12.01	0.00	1.12	74.4	30.6	1.122
2	UNKNOWN	14.26	14.78	16.44	0.00	84.94	2714.9	2313.1	84.937
3	UNKNOWN	16.52	16.86	18.36	0.00	7.05	224.6	192.1	7.055

Total 100.00 3380.0 2723.3 100.000
 MLA2085r_22 10/12/12 method MLAgredientC3_2to8mod_2flow_50C.METH

Column: 3 (OJ-H)

Temp: 50C

Pressure: 150 bar

Flow: 2mL/min

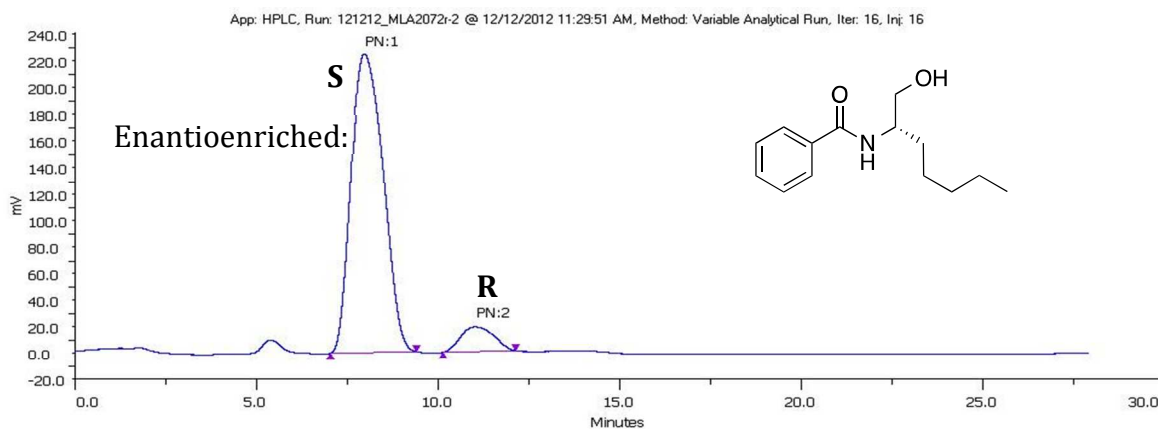
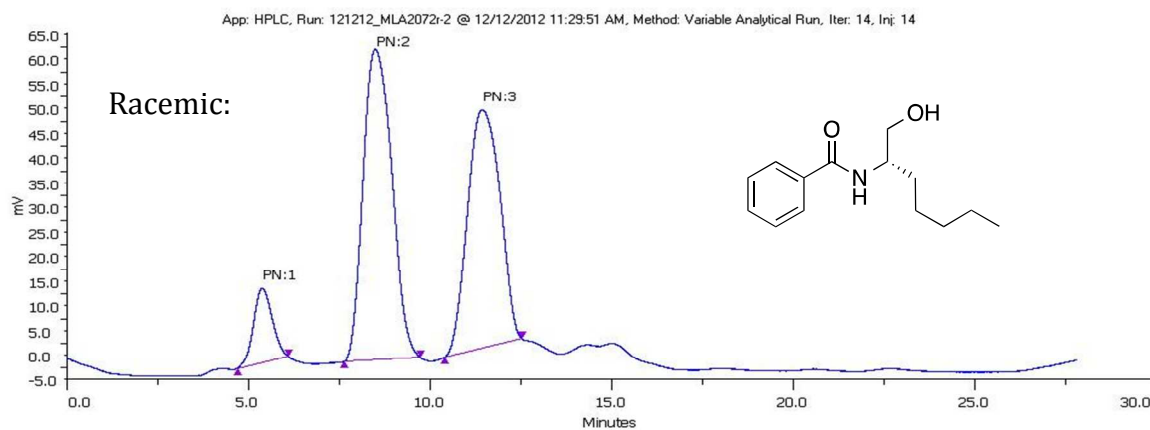
210 nm Detection

MeOH modifier in CO2

Modifier Program:

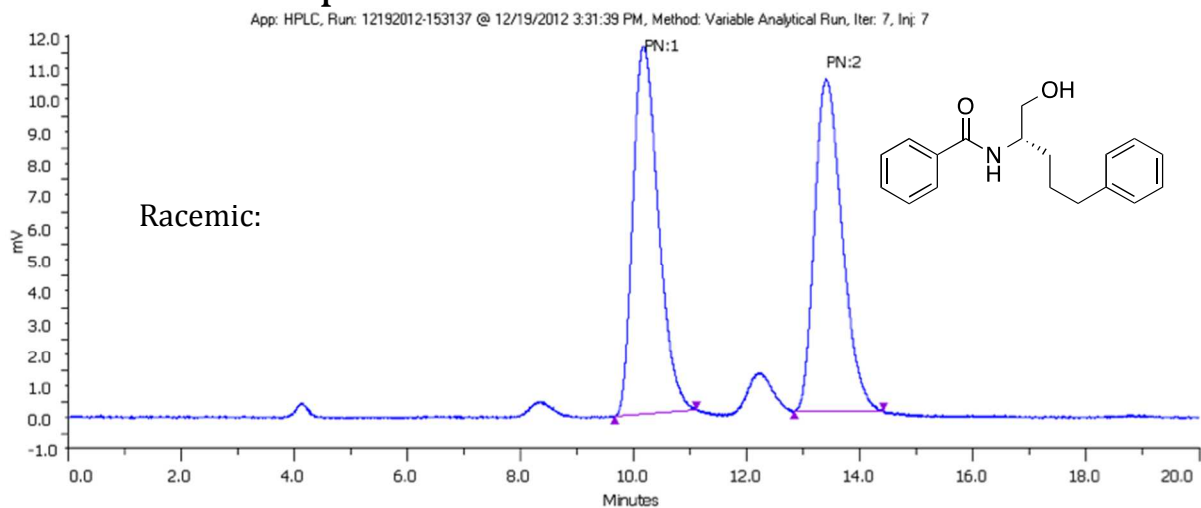
Rate	final	hold (min)
0	2	1
1	8	20
1	8	EOR

HPLC separation:

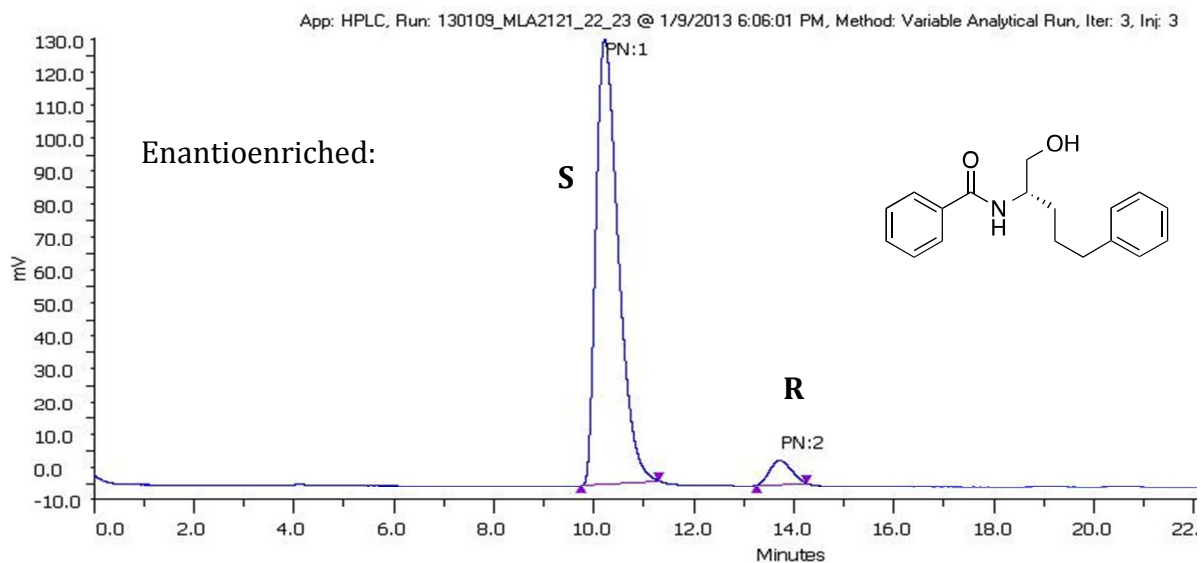


Peak Name	Retention Time (min)	Area (uVmin x100)	Area %
1	7.98	23098779.1658	92.214
2	11.026	1950412.4969	7.786

HPLC separation:

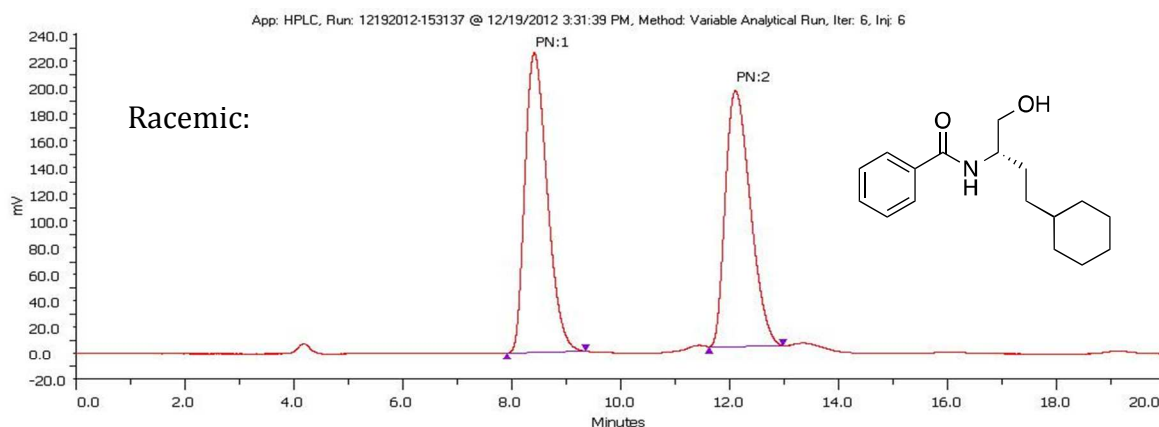


*Note that scales are different on the enantioenriched vs racemic traces.

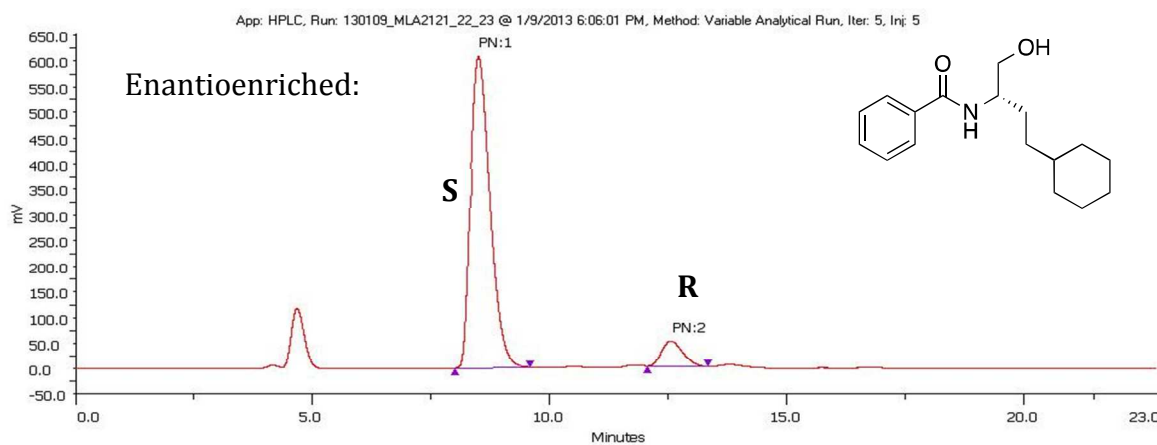


Peak Name	Retention Time (min)	Area (uVmin x100)	Area %
1	10.229	6971986.2537	95.077
2	13.728	361028.7597	4.923

HPLC separation:

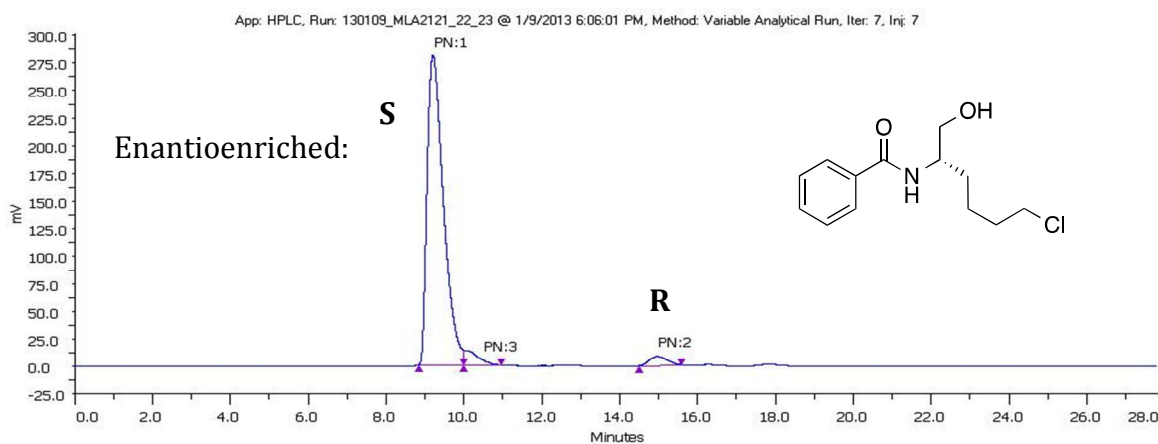
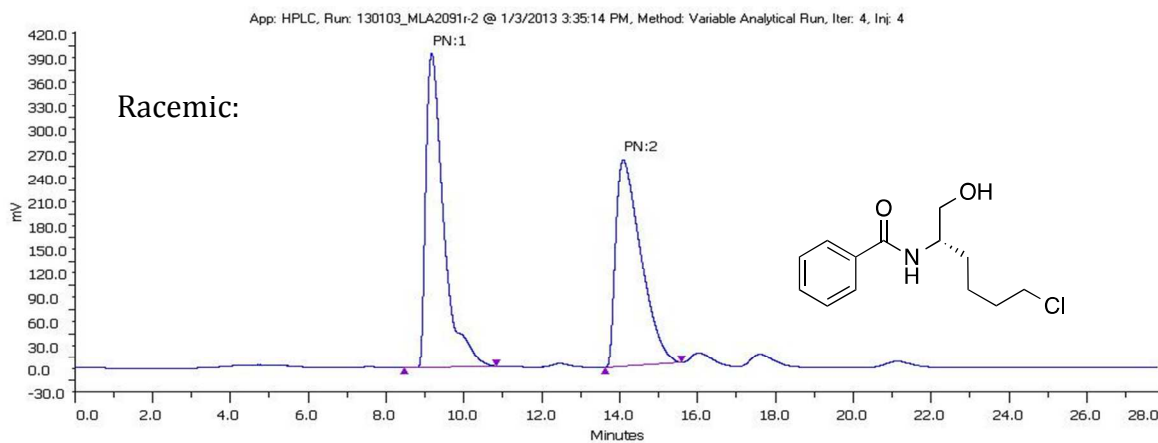


*Note that scales are different on the enantioenriched vs racemic traces.



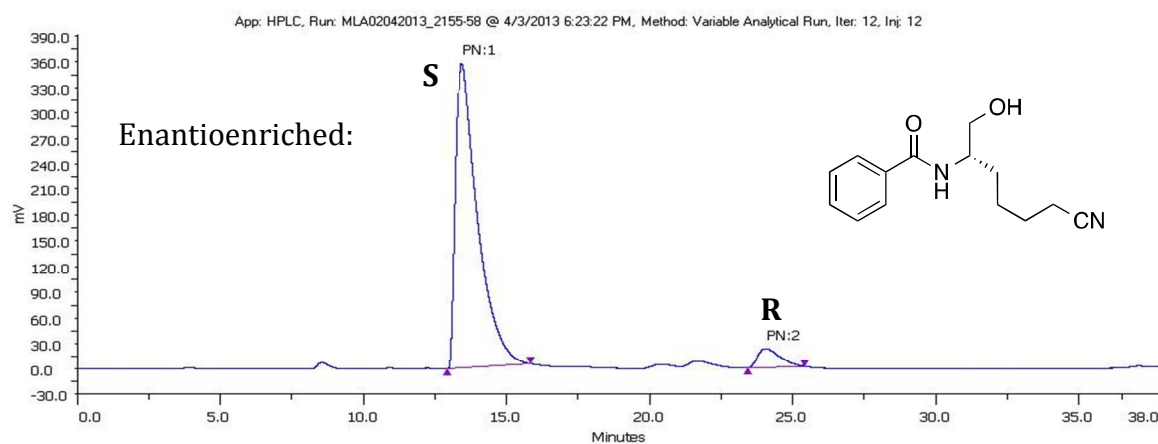
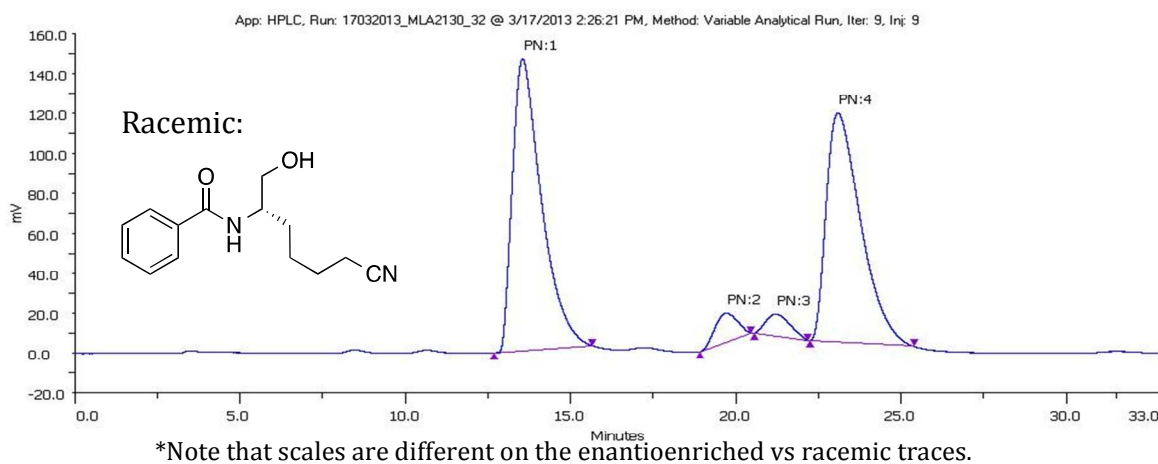
Peak Name	Retention Time (min)	Area (uVmin x100)	Area %
1	8.509	28931946.6674	91.896
2	12.571	2551569.1691	8.104

HPLC separation:



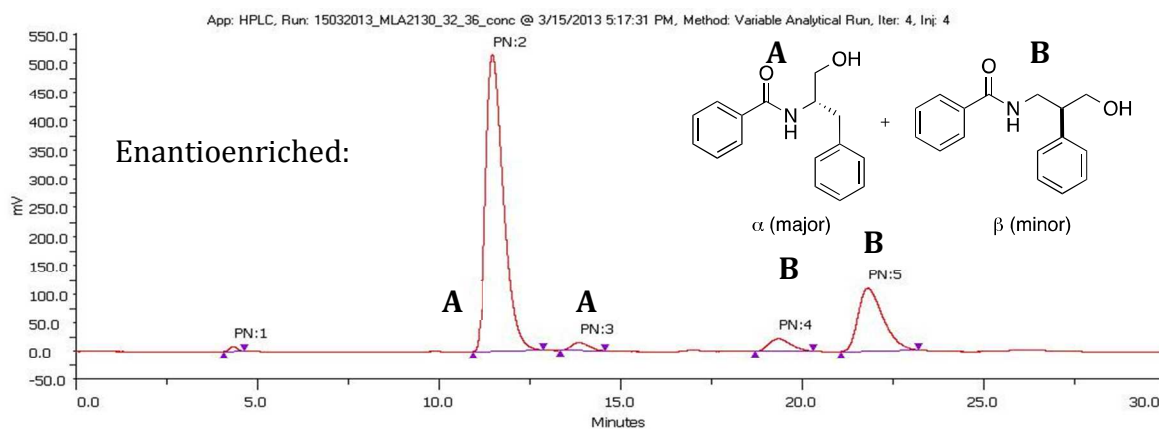
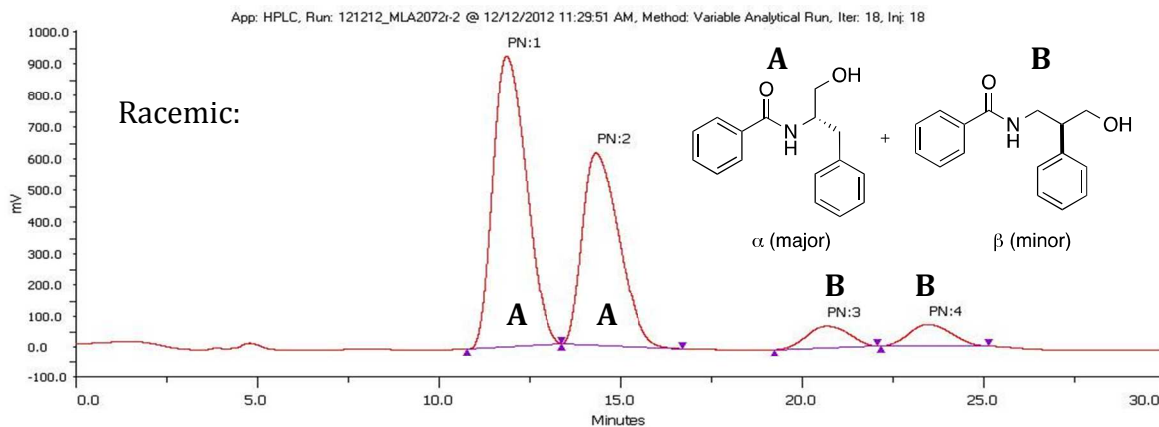
Peak Name	Retention Time (min)	Area (uVmin x100)	Area %
1	9.216	13707290.7953	93.202
2	14.983	441835.835	3.004
3 (impurity)	10.014	557908.081	3.793

HPLC separation:



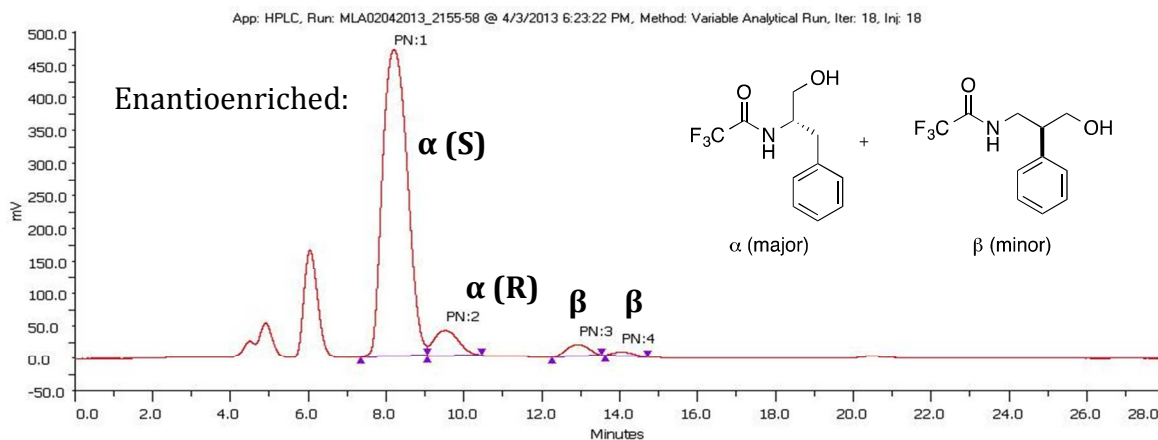
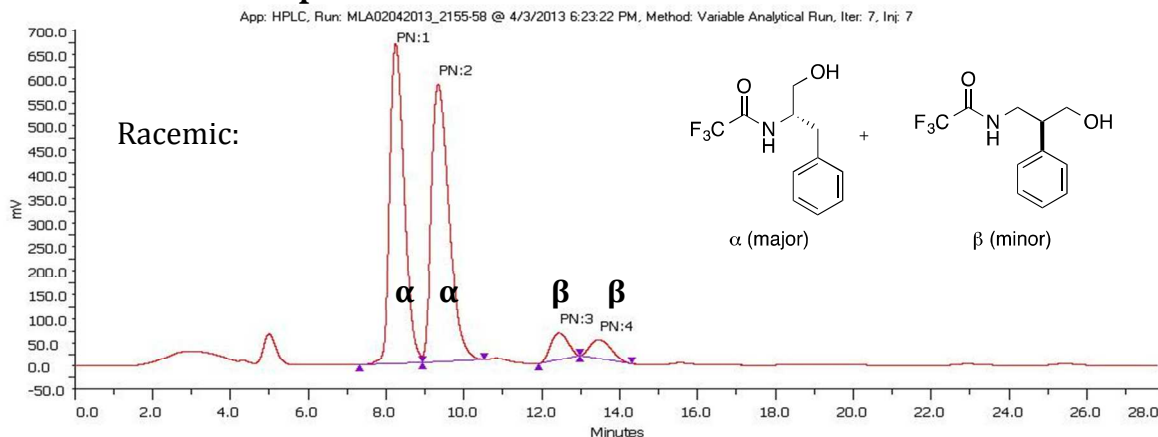
Peak Name	Retention Time (min)	Area (uVmin x100)	Area %
1	13.446	31690445.414	93.997
2	24.071	2024017.91	6.003

HPLC separation:



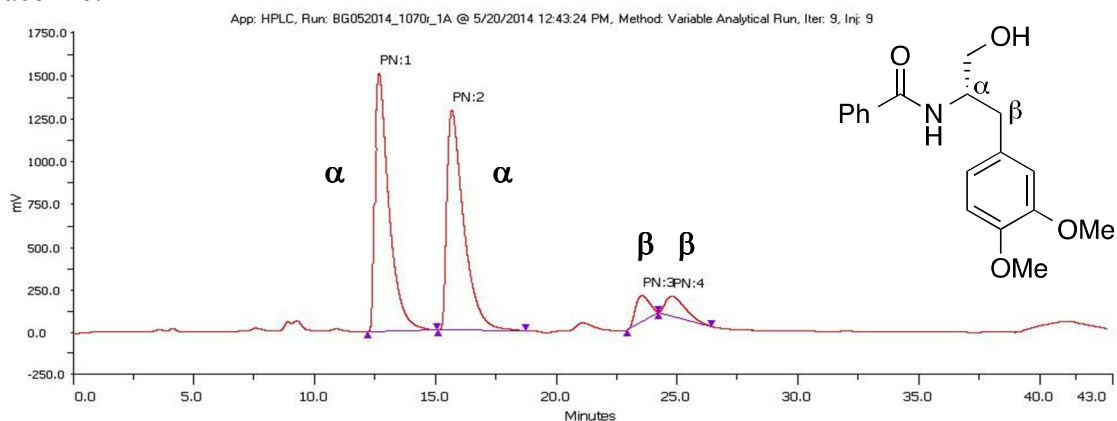
Peak Name	Retention Time (min)	Area (uVmin x100)	Area %
2	11.483	29252597.4926	72.508
3	13.885	768988.3313	1.906
4	19.352	1472231.6663	3.649
5	21.825	8638956.6561	21.413

HPLC separation:

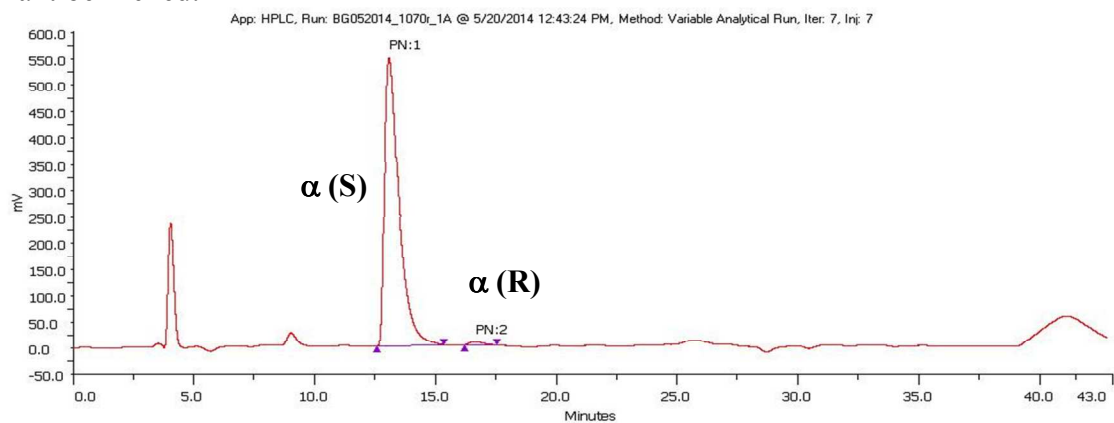


Peak Name	Retention Time (min)	Area (uVmin x100)	Area %
1	8.211	34620060.4828	88.619
2	9.528	2875018.0774	7.359
3	12.898	1206989.9988	3.09
4	14.11	364094.1667	0.932

Racemic:



Enantioenriched:



Enantioenriched run shows no β isomer because sample was purified before HPLC and only α isomer was collected.

Retention Time (min)	Area (uVmin x100)	Area %
13.092	37901592.4973	98.899
16.678	422008.3301	1.101