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Supporting Information

69451 Weinheim, Germany

Water-Compatible Iminium Activation: Organocatalytic Michael Reactions of Carbon Centered Nucleophiles with Enals

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Supporting Information

Contents

1. General information:

All reactions were carried out in water with efficient magnetic stirring. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 75 MHz respectively. The chemical shifts are reported in ppm relative to $CDCl_3$ ($\delta = 7.26$) for ^{1}H NMR and relative to the central resonances of $CDCl_3$ ($\delta = 77.0$) for ^{13}C NMR. Purification of reaction products was carried out by flash column chromatography using ROCC silica gel 60 (0.040-0.063mm, 230-400 mesh). Visualization was accomplished with a solution of Phosphomolybdic acid (1 g) in 100 ml of ethanol (limited lifetime), followed by heating. Analytical high performamce liquid chromatography (HPLC) was performed on waters 600E chromatographs, equipped with diode array UV detector, using Daicel Chiralpak IB, AD-H, AS-H and AD columns. Optical rotations were recorded on a Perkin Elmer polarimeter. MS spectra were recorded on an ESI-ion trap Mass spectrometer (Agilent 1100 series LC/MSD, SL model).

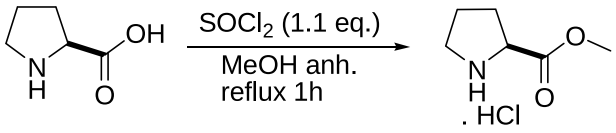
2. Materials.

All solvents were of p.a. quality and were dried by standard procedures prior to use if necessary. Unless otherwise specified, materials were obtained from commercial sources and used without purification. α,β-Unsaturated aldehydes were prepared following the procedure described in the literature.[1] Cinnamaldehyde and crotonaldehyde were purified by distillation before usage and stored in the fridge at -30ªC under nitrogen.

3. Experimental procedures and characterizations.

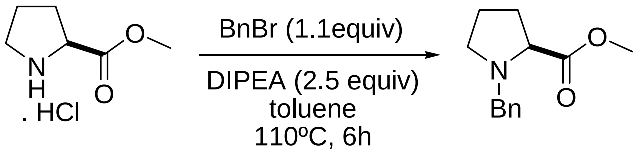
3.1. General description of the preparation of catalysts 1-8.

3.1.1. Preparation of (S)-methyl pyrrolidine-2-carboxylate hidrochloride[2]



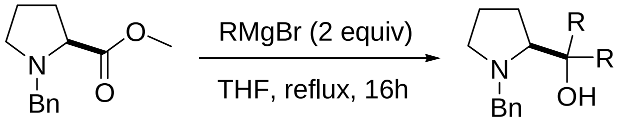
$SOCl_2$ (4.0 mL, 55 mmol) was added during 5 minutes at 0ºC to a mixture of L-proline (5.757 g, 50 mmol) in 35ml of anhydrous MeOH and afterwards stirred at reflux for 1h. Methanol and excess of $SOCl_2$ were evaporated under reduced pressure and the yellow oil obtained was used in the following step without further purification. Yield: 8.275 g (100%).

3.1.2. Preparation of (S)-methyl 1-benzylpyrrolidine-2-carboxylate[3]



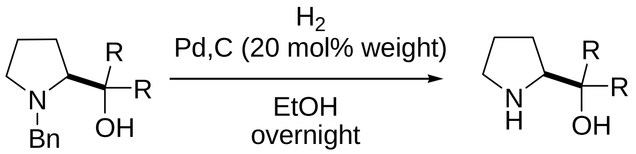
To a cooled solution, 0-5ºC, of (S)-methyl pyrrolidine-2-carboxylate hydrochloride (8.275 g, 50 mmol) and DIPEA (26.1ml; 150 mmol) in 50ml of toluene was slowly added benzylbromide (6.5 mL, 55 mmol). The reaction mixture was further stirred for 6h at 110ºC. The reaction was quenched with saturated sodium bicarbonate solution (40 mL) and the product was extracted with ethyl acetate (2x40 ml). The organic phase was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure, remaining a brown oil. The product was used in the following step without further purification. Yield: 10.298g (94%).

3.1.3. Preparation of dialkyl-(1-benzylpyrrolidin-2-yl)methanol[4]



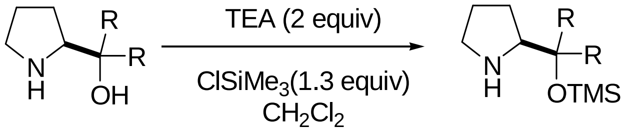
(S)-methyl 1-benzylpyrrolidine-2-carboxylate (4.38 g, 20 mmol) in THF (40 mL) was cooled at 0ºC and the corresponding alkylmagnesium bromide (60 mmol) was added dropwise over 10 min. The reaction mixture was further stirred overnight at room temperature. The reaction was quenched with saturated ammonium chloride solution (30 mL). The supernatant liquid was collected leaving behind a white precipitate which was extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the product obtained was used in the following step without further purification.

3.1.4. Preparation of dialkyl-(S)-pyrrolidin-2-yl-methanol



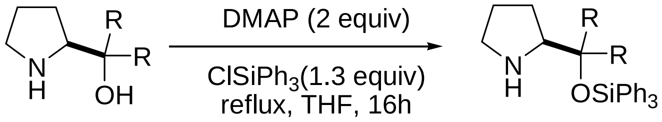
The crude dialkyl-(1-benzylpyrrolidin-2-yl)methanol (3.15vmmol) was disolved in 4 mL of ethanol and palladium, (10 wt. % on activated carbon, 20% mol % weight) was added. The reaction mixture was stirred under hydrogen atmosphere (1 atm) at room temperature overnight. The solution was filtered over celite in a Büchner funnel and the solvent evaporated under reduced pressure. The crude obtained was purified by column chromatography.

3.1.5. Preparation of dialkyl-2-((trimethylsilyloxy)methyl) pyrrolidine



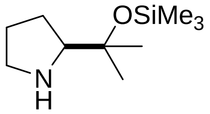
Trimethylsilyl chloride (39 mmol, 7.06 mL, 1.3 eq) was added dropwise to a solution of dialkyl-(S)-pyrrolidin-2-ylmethanol (30 mmol)and triethylanamine (8.4 mL, 60 mmol) in anhydrous CH_2Cl_2 (60 ml) at 0ºC. Then the reaction mixture was stirred at room temperature for 1h. The mixture was washed with water (2 x 100 mL), saturated $NaHCO_3$ (1 x 100 mL) and extracted with CH_2Cl_2 (2x 50 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash column chromatography (CH_2Cl_2/MeOH 95:5) and subsequent washing with $NaHCO_3$ (sat. sol.) or by a simple distillation.

3.1.6. Preparation of dialkyl-2-((Triphenylsilyloxy)methyl) pyrrolidine



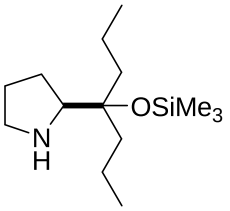
The dialkyl-(S)-pyrrolidin-2-ylmethanol (6 mmol) in anhydrous THF (12 mL) was added to a solution of DMAP (1.46 g, 12 mmol) and triphenylsilyl choride (3.11 g, 10.5 mmol) in THF (12 mL). Then the reaction was stirred at reflux overnight. The mixture was washed with water (2x 25 mL), saturated $NaHCO_3$ (1 x 25 mL) and extracted with CH_2Cl_2 (2x 25 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash column chromatography (CH_2Cl_2/MeOH 95:5) and subsequent washing with $NaHCO_3$ (sat. sol.)or by a simple distillation.

(s)-2-(2-(Trimethylsilyloxy)propan-2-yl)pyrrolidine (1)



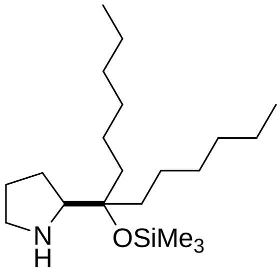
The catalyst compound was prepared from (S)-methyl 1-benzylpyrrolidine-2-carboxylate according to general procedure using methylmagnesium bromide (3.0M solution in diethyl ether). Overall yield over three steps: 53%. $[\alpha]_D^{25}$ = +10.4 (c=1, CH_2Cl_2). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 3.07-2.98 (m, 1H, -C$\underline{H}$-CH$_2$-), 2.88-2.77(m, 2H, -$\underline{H}$C$\underline{H}$-NH), 1.75-1.65 (m, 3H, CH2-$\underline{H}$CH-C$\underline{H_2}$-CH-), 1.54-1.47 (m, 1H,-CH$_2$-HC$\underline{H}$-CH$_2$-CH), 1.30(s, 3H, C$\underline{H_3}$), 1.22 (s, 3H, CH_3), 0.12 (s, 9H, -OSiMe$_3$). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 74.87, 69.30, 47.25, 28.24, 27.47, 26.56, 26.12, 2.45. MS: $C_{10}H_{23}NOSi$ 202.0 $[M]^+$.

(s)-2-(4-(Trimethylsilyloxy)heptan-4-yl)pyrrolidine (2)



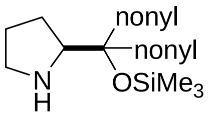
The catalyst compound was prepared from (S)-methyl 1-benzylpyrrolidine-2-carboxylate according to general procedure using propylmagnesium bromide. Overall yield over three steps: 55%. $[\alpha]_D^{25}$ = -20.8 (c =1, CH_2Cl_2). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 3.05-3.00 (m, 1H, -CH-CH2-), 2.91-2.88 (m, 1H,-HCH-NH), 2.77-2.72(m, 1H, -HCH-NH), 1.74-1.61 (m, 5H, CH2- CH2-CH_3), 1.57-1.49 (m, 2H,-CH2-CH2-CH3), 1.47-1.40(m, 1H,-CH2-CH2-CH_3), 1.33-1.23 (m, 4H,-CH2-CH2-CH-), 0.90 (t, 6H, J=7.2 Hz, CH_2-CH_3), 0.12 (s, 9H, -$OSiMe_3$). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 79.69, 66.09, 47.10, 40.56, 40.38, 26.09, 26.03, 17.51, 17.36, 14.77, 14.68, 2.88. MS: $C_{14}H_{31}NOSi$ 258.1 $[M]^+$.

(s)-2-(7-(Trimethylsilyloxy)tridecan-7-yl)pyrrolidine (3)



The catalyst compound was prepared from (S)-methyl 1-benzylpyrrolidine-2-carboxylate according to general procedure using hexylmagnesium bromide (2.0M solution in diethyl ether). Overall yield over three steps: 59%. b.p.= 175° (0.8 torr). $[\alpha]_D^{25}$ = -15.6 (c 1, CH_2Cl_2). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 3.01-2.98 (m, 1H, -CH-CH2-): 2.88-2.85 (m, 1H, -HCH-NH), 2.72-2.70 (m, 1H, -HCH-NH), 1.66-1.58 (m, 5H,C- CH2- CH_2-, HCH-CH2-CH-), 1.54-1.38 (m, 3H,-CH2-HCH-CH-), 1.30-1.24(m, 16H,), 0.87-1.86 (m, 6H), 0.09(s, 9H, -$OSiMe_3$). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 79.84, 66.14, 47.17, 38.12, 37.89, 31.12, 30.00, 26.14, 26.08, 24.23, 24.06, 22.66, 22.62, 14.02, 2.97. MS: $C_{20}H_{43}NOSi$ 342.3 $[M]^+$.

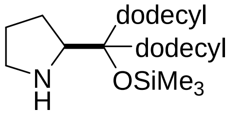
(s)-2-(10-(Trimethylsilyloxy)nonadecan-10-yl)pyrrolidine (4)



The catalyst compound was prepared from (S)-methyl 1-benzylpyrrolidine-2-carboxylate according to general procedure using nonylmagnesium bromide (1.0M solution in diethyl ether). Overall yield over three steps: 48%. $[\alpha]_D^{25}$ = -

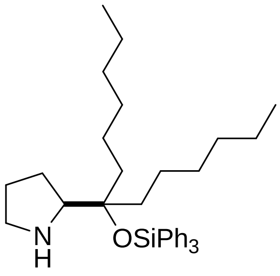
20.2 (c= 1, CH_2Cl_2. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 3.19-3.16(m, 1H), 3.13-3.02 (m, 2H), 1.86-1.75(m, 3H), 1.70-1.59 (m, 4H), 1.52-1.39 (m, 1H), 1.38-1.21 (m, 20H), 0.92-0.88(m, 6H), 0.15(s, 9H). ^{13}C-RMN (75 MHz, $CDCl_3$) δ:79.65, 66.29, 47.19, 38.14, 37.78, 31.90, 30.37, 30.38, 29.62, 29.56, 29.53, 29.29, 26.09, 25.88, 24.18, 24.10, 22.67, 14.07, 2.97. MS: $C_{26}H_{55}NOSi$ 426.4 $[M]^+$.

2-(13-(trimethylsilyloxy)pentacosan-13-yl)pyrrolidine (5)



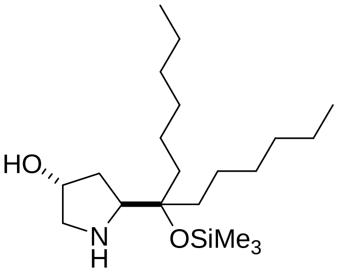
The catalyst compound was prepared from (S)-methyl 1-benzylpyrrolidine-2-carboxylate according to general procedure using dodecylmagnesium bromide (1.0M solution in diethyl ether). Overall yield over three steps: 63%. $[\alpha]_D^{25}$ = -9.0 (c= 1, CH_2Cl_2). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 3.04-3.00(m, 1H), 2.90-2.88 (m, 1H), 2.78-2.72(m, 1H), 1.68-1.27 (m, 48H), 0.92-0.88 (t, 6H, J= 7.0 Hz), 0.12 (s, 9H). ^{13}C-RMN (75 MHz, $CDCl_3$) δ:79.84, 66.1, 47.2, 38.1, 37.9, 31.9, 30.3, 29.6, 29.5, 29.3, 26.1, 26.0, 24.2, 24.0, 22.7, 14.8, 3.0. MS: $C_{32}H_{67}NOSi$.

(s)-2-(7-(Triphenylsilyloxy)tridecan-7-yl)pyrrolidine (6)



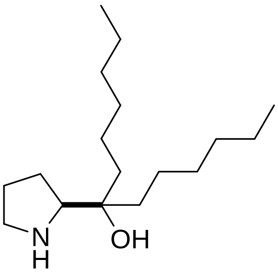
The catalyst compound was prepared from (S)-methyl 1-benzylpyrrolidine-2-carboxylate according to general procedure using hexylmagnesium bromide (2.0M solution in diethyl ether). Overall yield over three steps: 74%. b.p.= 295° (0.28 torr). $[\alpha]_D^{25}$ = -2.5 (c 1, CH_2Cl_2). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 7.73,-7-67 (m, 6H, Ar): 7.45-7.31 (m, 9H, Ar), 3.17-3.01(m, 1H, -CH-CH2-), 2.95-2.78 (m, 1H, -HCH-NH-), 2.77-2.63(m, 1H, -HCH-NH-), 1.74-1.53 (m, 4H), 1.38-0.96 (m, 20H), 0.84 (t, 6H, J= 6.4 Hz). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 135.57, 129.45, 127.58, 82.51, 66.03, 46.96, 38.36, 37.54, 31.70, 29.77, 26.40, 25.88, 24.10, 23.77, 22.62, 14.06. MS: $C_{35}H_{49}NOSi$ 528.3 $[M]^+$.

(3R,5S)-5-(7-(trimethylsilyloxy)tridecan-7-yl)pyrrolidin-3-ol (7)



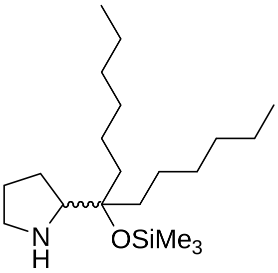
The catalyst compound was prepared from *trans*-4-Hydroxy-L-proline according to general procedure. Overall yield over five steps: 26%. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 4.42 (m, 1H), 3.36 (dd, J= 10.0, 5.0 Hz, 1H), 3.21 (dd, J= 15.0, 5.0 Hz), 2.90 (d, J= 15 Hz, 1H), 1.80-1.25 (m, 22H), 0.91 (m, 6H), 0.14 (s, 9H). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 79.24, 71.7, 64.1, 55.2, 38.1, 37.4, 35.8, 31.8, 31.6, 29.9, 29.8, 24.0, 23.9, 22.6, 22.5, 14.0, 2.91. MS: $C_{20}H_{43}NO_2Si$ 358.3 $[M]^+$.

(S)-7-(pyrrolidin-2-yl)tridecan-7-ol (8)



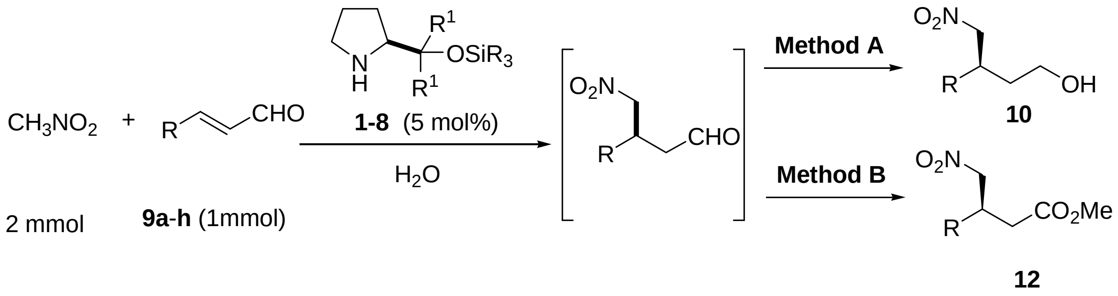
The catalyst compound was prepared from (S)-methyl 1-benzylpyrrolidine-2-carboxylate according to general procedure using hexylmagnesium bromide (2.0M solution in diethyl ether). Overall yield over two steps: 85%. $[\alpha]_D^{25}$ = -11.4 (c 0.5, CH_2Cl_2). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 3.11-3.08(m, 1H, -C$\underline{H}$-CH2-): 3.00-2.90 (m, 2H, -$\underline{H}$C$\underline{H}$-NH-), 1.81-1.65(m, 4H), 1.51-1.37 (m, 20H), 0.89 (t, 6H, J=6.5Hz). ^{13}C-RMN (75 MHz, $CDCl_3$) δ:73.44, 64.15, 46.55, 37.84, 35.07, 31.82, 31.75, 30.06, 30.03, 26.00, 25.25, 23.63, 23.38, 22.60, 13.99. MS: $C_{17}H_{35}NO$ 270.2 $[M]^+$.

3.2. Preparation of Catalyst 6-Rac:



Catalyst **6**-Rac was synthesized following the same experimental procedure as for catalyst **6** but using as starting material D-L-Proline.

3.3. General procedure for the Michael addition of nitromethane.

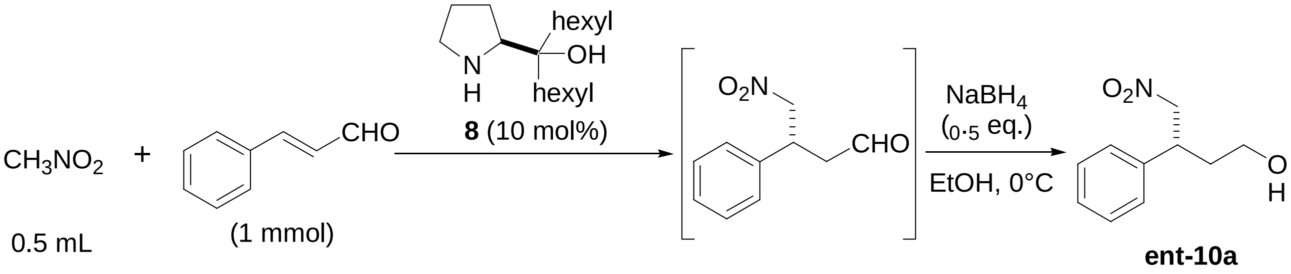


To a mixture of freshly prepared catalyst **1-8** (0.05 mmol, 5 mol%) the α,β–unsaturated aldehyde **9a-h** (1 mmol), water (1 mL), were added nitromethane (2 mmol, 110 μL) and benzoic acid (6.1 mg,0.05 mmol, 5 mol%). The mixture was stirred at room temperature for the specified time and then was elaborated as follow: **METHOD A** (derivatization to alcohols): To a cooled solution (ice-brine bath, –5 °C) of $NaBH_4$ (18.9 mg, 0.5 mmol) in EtOH (3 mL) the solution of the above reaction mixture in EtOH (5 mL) was added, dropwise. The reaction was stirred at the same temperature for 20 min (TLC: EtOAc/Hex 1:1) and afterwards quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was evaporated and the crude compound was purified by flash chromatography (eluent: EtOAc/Hex 1:2). **METHOD B** (derivatization to carboxylic methyl esters): The crude reaction (≈1.0 mmol) was dissolved in a mixture of MeOH (5.0 mL), CH_3CN (5.0 mL), and water (5.0 mL). The solution was cooled down to 0 °C and KH_2PO_4 (380 mg, 2.77 mmol) and $NaClO_2$ (225 mg, 2.10 mmol) were added. After the injection of H_2O_2 (35% solution, 3.0 mL), the mixture was warmed up to RT and stirred for 2 h. The pH was adjusted to 3 with 1M HCl and saturated Na_2SO_3 solution (20 mL) was added.

The resulting mixture was extracted with CH_2Cl_2 (3 x 30 mL), the combined organic layers were washed with 30 mL water, and dried over $MgSO_4$. The organic layer was concentrated in vacuum and the residue was dissolved in 5.0 mL toluene and 15.0 mL methanol.

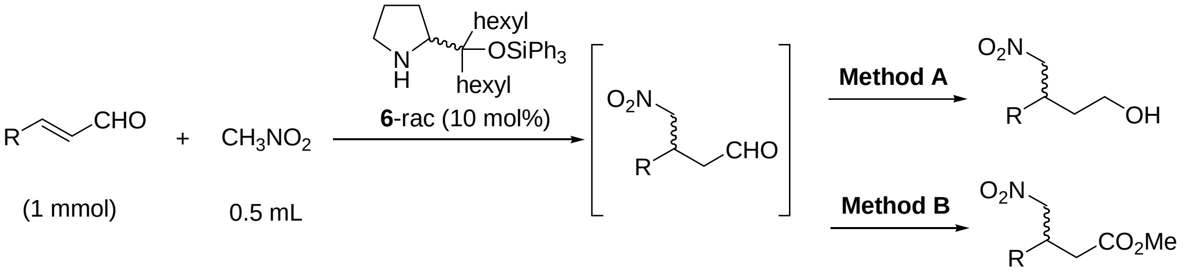
Trimethylsilyl diazomethane (0.5 mL, 1 mmol, 2.0 M in n-hexane) was added dropwise. The solution was stirred for additional 10 min and quenched with four drops of concentrated AcOH. The solvents were evaporated under vacuum. The crude product was subjected to FC on silica gel.

3.3.1. Synthesis of (R)-4-nitro-3-phenylbutan-1-ol (ent-10a) using catalyst 8.



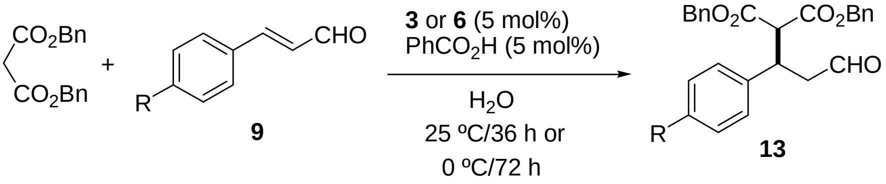
To a mixture of **8** (0.1 mmol, 0.1 equiv., 10 mol %) and α,β-unsaturated aldehyde **9a** (1.0 mmol, 132 mg, 126 μL) was added 0.5 mL of nitromethane. The reaction mixture was stirred for 18 h at room temperature and then the solvent was evaporated under vacuum. To a cooled solution (-5°C) of $NaBH_4$ (9.45 mg, 0.25 mmol, 0.5 eq.) in EtOH (10 mL) a solution of the reaction mixture in EtOH (5 mL) was added, dropwise. The reaction was stirred at 0 °C for 20 min (TLC: AcOEt/Hex 1:1) and afterwards quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was finally evaporated and the crude compound was purified by flash chromatography (eluent: AcOEt/Hex 1:2).

3.3.2. General procedure for the synthesis of racemic adducts.



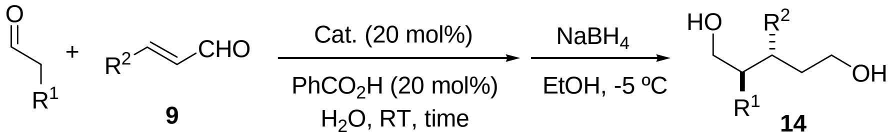
To a mixture of **6**-rac (0.1 mmol, 0.1 equiv., 10 mol %) and α,β-unsaturated aldehyde **9a-i** (1.0 mmol) was added 0.5 mL of nitromethane and benzoic acid (6.1 mg, 0.05 mmol, 5 mol%). The reaction mixture was stirred for 18 h at room temperature and then the solvent was evaporated under vacuum. The subsequent derivatization to the alcohol and ester products was carried out following the general procedure described above for the optically active products.

3.4. General procedure for the Michael addition of malonates



To a mixture of catalyst **3-6** (0.04 mmol, 0.04 equiv., 5 mol %),α,β-unsaturated aldehyde **9a-b** (1.0 mmol, 1.25 equiv.), and H_2O (1.0 mL) were added successively dibenzyl malonate (200 μL, 0.8 mmol, 1.0 equiv.) and benzoic acid (4.88 mg, 0.04 mmol, 4 mol%). The reaction mixture was stirred at the specified temperature until consumption of starting malonate (TLC) and the water evaporated under vacuum pump. Et_2O was added and then filtered through 1-2 cm bed of silica gel. The solvent was finally evaporated and the crude compound was purified by flash chromatography (eluent: AcOEt/Hex 1:10). Physical and spectroscopic data are in agreement with literature values.[5]

3.5. Amine catalyzed Michael addition of aldehydes to enals (14)



To a mixture of catalyst **6** (105.4 mg, 0.4 mmol, 0.4 equiv., 20 mol %), the α,β–unsaturated aldehyde **9** (2 mmol), and water (2 mL), were added propionaldehyde or pentanal (6 mmol) and benzoic acid (48.4 mg, 0.4 mmol, 20 mol%), the resulting emulsion was stirred at room temperature for the specify time. Once compound **9** was consumed (TLC), the reaction mixture was quenched with 1 N HCl (20 mL), and the resulting mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layers were then washed successively with saturated $NaHCO_3$ (1 x 20 mL) and brine (2 x 20 mL) and dried over anhydrous $MgSO_4$.

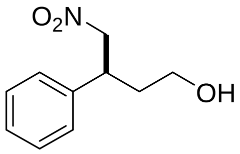
To a cooled solution (-5°C) of $NaBH_4$ (76.5 mg, 2.0 mmol) in EtOH (5 mL) a solution of the reaction mixture in EtOH (5 mL) was added, slowly and dropwise. The reaction was stirred at 0 ^{o}C for 20 min (TLC: AcOEt/Hex 1:1) and afterwards quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was finally evaporated and the crude compound was purified by flash chromatography (eluent: AcOEt/Hex 1:2).

The racemic adducts were obtained using pyrrolidine as catalyst following otherwise identical procedure.

The relative configuration of adducts 14 was determined to be *anti.*[6]

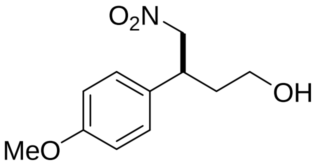
3.6. Data of adducts:

4-Nitro-3 phenylbutan-1-ol (10a)



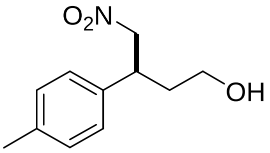
The title compound was prepared from nitromethane (2 mmol) and cinnamaldehyde (1 mmol) according to the general procedure A. Yield: 136 mg, 0.70 mmol, 70%. $[\alpha]_D^{25}$ = -13.7 (c 0.5, CH_2Cl_2, 96% ee). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 7.38-7.24 (m, 5H, Ar), 4.71-4.61 (m, 2H, $\underline{H}$CH-NO_2), 3.75-3.71 (m, 1H, $\underline{H}$CHOH), 3.67-3.62 (m, 1H, HC$\underline{H}$OH), 3.54-3.50(m, 1H, Ar-C$\underline{H}$), 2.02-1.96 (m, 2H, CH-$\underline{H}$C$\underline{H}$-CH_2). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 138.92, 129.06, 127.54, 80.64, 59.94, 41.15, 35.71. The enantiomeric excess was determined by HPLC with Chiralpack IB column at 220nm (hexane/^{i}PrOH in the ratio of 90/10, flow rate = 0.5 mL/min tr=35.72 min, tr=41.26 major). MS: $C_{10}H_{13}NO_3$ 218.1 $[M+Na]^+$.

4-Nitro-3 phenylbutan-1-ol (10b)



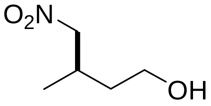
The title compound was prepared from nitromethane (2 mmol) and (E)-3-(4-methoxyphenyl)acrylaldehyde (1 mmol) according to de general procedure A. Yield: 179 mg, 0.71 mmol, 71%. $[\alpha]_D^{25}$ = -22.8 (c 0.5, CH_2Cl_2, 96% ee). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 7.14 (d, 2H, J= 8.7 Hz, Ar), 6.87 (d, 2H, J= 8.7 Hz, Ar) 4.62 (dd, 1H, J= 12.2, 7.2 Hz, $\underline{H}$CH-NO_2), 4.55 (dd, 1H, J = 12.2, 8.4 Hz, HC$\underline{H}$-NO_2), 3.79 (s, 3H, OC$\underline{H}_3$), 3.65-3.61 (m, 2H, $\underline{H}$C$\underline{H}$OH), 3.53-3.47(m, 1H, Ar-C$\underline{H}$), 1.97-1.87 (m, 2H, CH-$\underline{H}$C$\underline{H}$-CH_2). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 159.11, 130.71, 128.54, 80.89,77.00, 76.58, 59.96, 55.26, 40.43, 35.73. The enantiomeric excess was determined by HPLC with Chiralpack IB column at 220nm (hexane/^{i}PrOH in the ratio of 98/2, flow rate = 0.5 mL/min tr=109.7 min, tr=115.8 major). MS: $C_{11}H_{15}NO_4$ 248.0 $[M+Na]^+$.

4-Nitro-3-p- tolylbutan-1-ol (10c)



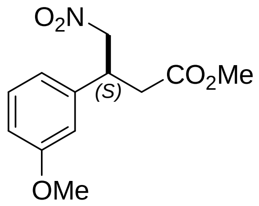
The title compound was prepared from nitromethane(2 mmol) and (E)-3-p-tolylacrylaldehyde (1 mmol) according to de general procedure A. Yield: 139 mg, 0.66 mmol, 66%. $[\alpha]_D^{25}$ = -14.7 (c 0.5, CH_2Cl_2, 97% ee). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 7.16 (d, 2H, J= 5.8 Hz, Ar), 7.10 (d, 2H, J= 5.8Hz, Ar), 4.63 (dd, 1H, J_1= 12.2, 7.2Hz, $\underline{H}CH\text{-}NO_2$), 4.57 (dd, 1H, J = 12.2, 8.3 Hz, $HC\underline{H}\text{-}NO_2$), 3.68-3.59 (m, 2H, $C\underline{H}_2OH$), 3.51-3.47 (m, 1H, $C\underline{H}CH_2$), 2.32 (s, 3H, $Ar\text{-}C\underline{H_3}$), 1.99-1.86 (m, 2H, $CH\text{-}\underline{H}C\underline{H}\text{-}CH_2$). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 137.34, 135.77, 129.65, 127.33, 80.72, 59.85, 40.73, 35.64, 20.95. The enantiomeric excess was determined by HPLC with Chiralpack IB column at 220nm (hexane/^{i}PrOH in the ratio of 90/10, flow rate = 0.5 mL/min tr=27.4 min, tr=28.9 major). MS: $C_{11}H_{15}NO_3$ 232.0 $[M+Na]^+$.

3-Methyl-4-nitrobutan-1-ol (10d)



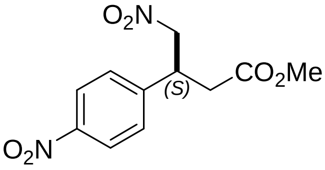
The title compound was prepared from nitromethane (2 mmol) and crotonaldehyde (1 mmol) according to the general procedure A. Yield: 80 mg, 0.60 mmol, 60%. $[\alpha]_D^{25}$ = +2.8 (c 1, CH_2Cl_2, 87% ee). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 4.45(dd, 1H, J= 11.8, 6.2 Hz, $\underline{H}CHNO_2$), 4.28 (dd, 1H, J= 11.8, 7.8 Hz, $HC\underline{H}NO_2$), 3.89-3.66 (m, 2H, $\underline{H}C\underline{H}OH$), 2.60-2.44(m, 1H, $CH\text{-}CH_3$), 1.74-1.45 (m, 2H, $CH\text{-}C\underline{H}_2\text{-}CH_2\text{-}$), 1.07 (d, 3H, J= 6.8 Hz). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 81.52, 60.01, 36.23, 29.92, 17.24. The enantiomeric excess was determined by HPLC analysis of the 2-naphthoyl derivative (Chiralpack AD-H column at 254nm (hexane/^{i}PrOH in the ratio of 95/5, flow rate = 0.5 mL/min tr=46.46 min, tr=48.8 major). MS: $C_5H_{11}NO_3$ 156.0 $[M+Na]^+$.

(S)-methyl 3-(3-methoxyphenyl)-4-nitrobutanoate (12e)



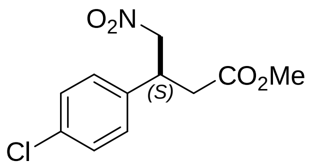
The title compound was prepared from nitromethane (2 mmol) and (E)-3-(3-methoxyphenyl)acrylaldehyde (1 mmol) according to de general procedure B. Yield: 144 mg, 0.57 mmol, 57%. $[\alpha]_D^{25}$ = -23.8 (c 0.5, CH_2Cl_2, 95% ee). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 7.29-7.24 (m, 1H, Ar), 6.85-6.77 (m, 2H, Ar), 4.68 (m, 2H), 3.97 (m, 1H), 3.81 (s, 3H), 3.66 (s, 3H), 2.78 (d, J= 7.5 Hz, 2H). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 171.0, 160.0, 139.9, 130.1, 119.4, 113.5, 113.1, 79.3, 55.2, 51.9, 40.2, 37.5. The enantiomeric excess was determined by HPLC with Chiralpack IB column at 220nm (hexane/^{i}PrOH in the ratio of 80/20, flow rate = 1.0 mL/min tr=13.0 min, tr=21.8 major). MS: $C_{12}H_{15}NO_5$ $[M+Na]^+$.

(S)-Methyl-4-nitro-3-(4-nitrophenyl)butanoate (12f)



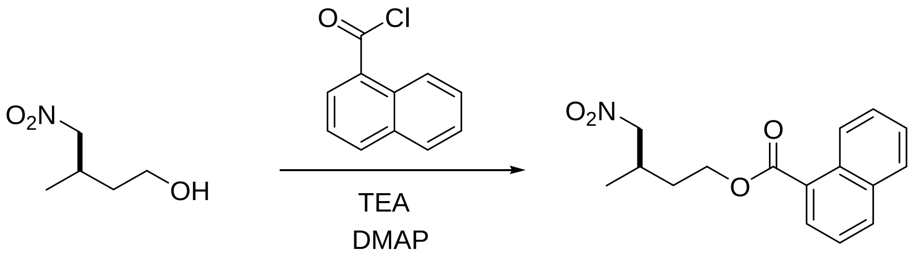
The title compound was prepared from nitromethane (2 mmol) and (E)-3-(4-nitrophenyl)acrylaldehyde (1 mmol) according to de general procedure B. Yield: 158 mg, 0.60 mmol, 60%. $[\alpha]_D^{25}$ = -7.6 (c 1, CH_2Cl_2, 98 % ee). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 8.21 (d, 2H, J= 8.7 Hz, Ar), 7.43 (d, 2H, J= 8.7 Hz, Ar), 4.79 (dd, 1H, J= 13.0, 6.5 Hz, $\underline{H}CH\text{-}NO_2$), 4.68 (dd, 1H, J= 13.0, 8.3 Hz, $HC\underline{H}\text{-}NO_2$), 4.17-4.01 (m, 1H, $C\underline{H}\text{-}Ar$), 3.65 (s, 3H,$COO\text{-}CH_3$), 2.81 (m, 2H, $C\underline{H}_2\text{-}CH_2\text{-}C\underline{H_3}$).^{13}C-RMN (75 MHz, $CDCl_3$) δ:170.35, 147.73, 145.61, 128.47, 124.29, 78.53, 52.18, 39.83, 37.07. The enantiomeric excess was determined by HPLC with Chiralpack AD-H column at 254nm (hexane/^{i}PrOH in the ratio of 90/10, flow rate = 0.5 mL/min tr=43.2 min, tr=49.8 major). MS: $C_{11}H_{12}N_2O_6$ 245.8 $[M-NO_2+Na]^+$.

(S)-Methyl 3-(4-chlorophenyl)-4-nitrobutanoate (12g)



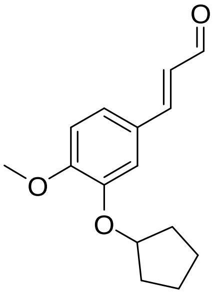
The title compound was prepared from nitromethane (2 mmol) and (E)-3-(4-chlorophenyl)acrylaldehyde (1 mmol) according to de general procedure B. Yield: 179 mg, 0.69 mmol, 69%. $[\alpha]_D^{25}$ = -9.1 (c 0.5, CH_2Cl_2, 95 % ee). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 7.33 (d, 2H, J= 8.5 Hz, Ar), 7.17 (d, 2H, J= 8.5 Hz, Ar), 4.73 (dd, J= 12.6, 6.9 Hz), 4.62 (dd, J= 12.6, 6.9 Hz), 3.98 (m, 1H), 3.64 (s, 3H), 2.80-2.71 (m, 2H). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 170.8, 136.8, 134.0, 129.3, 128.7, 79.1, 52.0, 39.6, 37.4. The enantiomeric excess was determined by HPLC with Chiralpack IB column at 220nm (hexane/^{i}PrOH in the ratio of 90/10, flow rate = 0.5 mL/min τ_1 = 30.7 min. (minor enantiomer); τ_2 = 35.4 min. (major enantiomer). MS: $C_{11}H_{12}ClNO_4$ 280.0 $[M+Na]^+$.

3.7. Derivatization of 3-Methyl-4-nitrobutan-1-ol with naphthoyl cloride



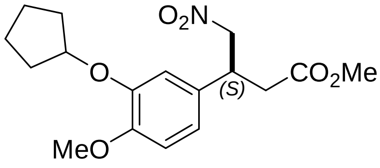
119mg (1mmol) of 3-Methyl-4-nitrobutan-1-ol were solved in 2 mL of dry dichloromethane and 0.42 mL of triethylamine (3 mmol, 6eq) was added at room temperature. At the same temperature 0.30 mL (2 mmol, 4 eq) of 1-napthoyl chloride was dropped followed of 6mg (0.05 mmol) of dimethylaminopyridine. The mixture was stirred at room temperature for 3h and then quenched with 2 mL of distilled water. The product was extracted with 3 x 10 mL of dichloromethane and the organic phase was washed with a solution of saturated NH_4Cl and $NaHCO_3$. The organic phase was then dried with magnesium sulphate and evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate 90:10) obtaining the compound as a pale yellow solid (yield: 249.9mg, 87 %).

3.8. (E)-3-(3-(Cyclopentyloxy)-4-methoxyphenyl)acrylaldehyde (9h)



The title compound was prepared using Heck reaction from 4-bromo-2-(cyclopentyloxy)-1-methoxybenzene (1.13 g, 4.16 mmol) according to the general literature procedure.[1] Yield: 0.90 g, 3.64 mmol, 87%. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 9.66 (d, 1H, J= 7.6 Hz, CHO), 7.40 (d, 1H, J= 15.8 Hz), 7.17-6.88 (m, 3H), 6.60 (dd, 1H, J= 15.8, 7.6 Hz), 4.81 (m, 1H), 3.90 (s, 3H), 2.18-1.57 (m, 8H). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 193.2, 152.9, 152.8, 147.8, 126.7, 126.3, 122.9, 113.5, 111.5, 80.5, 55.8, 32.6, 23.8.

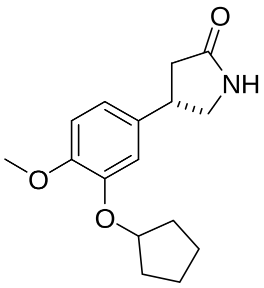
(S)-Methyl 3-(3-(cyclopentyloxy)-4-methoxyphenyl)-4-nitrobutanoate (12h)



The title compound was prepared from nitromethane (2 mmol) and (E)-3-(3-(cyclopentyloxy)-4-methoxyphenyl)acrylaldehyde (1 mmol) according to de general procedure B. Overall Yield: 209 mg, 0.62 mmol, 62 %. $[\alpha]_D^{25}$ = -18.3 (c 1, $CHCl_3$, 98 % ee). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 6.82-6.73 (m, 3H, Ar-H), 4.76 (m, 1H, CH), 4.70 (dd, 1H, J= 12.4, 7.2 Hz), 4.61 (dd, 1H, J= 12.4, 7.0 Hz), 3.90 (m, 1H), 3.82 (s, 3H), 3.64 (s, 3H), 2.75 (d, 2H, J= 7.2 Hz), 1.95-1.57 (m, 8H). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 171.26, 149.82, 147.91, 1430.58, 119.24, 114.54, 112.42, 80.62, 79.64, 56.03, 51.88, 39.81, 37.71, 32.75, 23.99. HPLC: Daicel Chiralpak IB, hexane/2-propanol (90/10), flow rate = 0.5 mL/min (τ_1 = 33.6

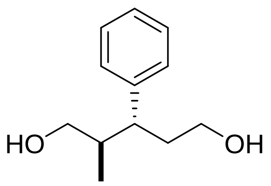
min. (minor enantiomer); τ_2 = 36.1 min. (major enantiomer)). MS: $C_{17}H_{23}NO_6$ 360.1 $[M+Na]^+$.

3.9. (S)-4-(3-(Cyclopentyloxy)-4-methoxyphenyl)pyrrolidin-2-one: (S)-(+)- Rolipram



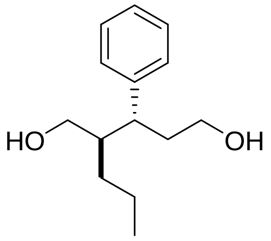
(S)-methyl 3-(3-(cyclopentyloxy)-4-methoxyphenyl)-4-nitrobutanoate (100 mg, 0.29mmol) was disolved in 5 ml of ethanol and palladium, 10 wt. % on activated carbon (20mg, 20% mol % weight) was added. The reaction mixture was stirred under hydrogen atmosphere (1 atm) at room temperature overnight. The solution was filtered over Celite in a Büchner funnel and the solvent evaporated under reduced pressure. The crude obtained was purified by column chromatography (SiO_2 eluent: AcOEt). Yield: 57.5 mg, 0.208 mmol, 72%. mp 133-136 ºC. $[\alpha]_D^{25}$ = +26.2 (c 0.6, MeOH, 98% *ee*). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 6.83-6.75 (m, 3H, Ar-H), 5.72 (m, 1H, NH), 4.75 (m, 1H, CH), 3.81 (s, 3H), 3.75 (m, 1H), 3.63 (m, 1H), 3.37 (t, J= 7.9 Hz, 1H), 2.69 (dd, J= 16.8, 8.7 Hz, 1H), 2.44 (dd, J= 16.8, 8.7 Hz, 1H), 1.95-1.58 (m, 8H). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 177.3, 149.3, 148.0, 134.6, 118.8, 114.0, 112.4, 80.7, 56.2, 49.6, 40.0, 37.9, 32.8, 24.0.

(2R,3R)-2-methyl-3-phenylpentane-1,5-diol 14a



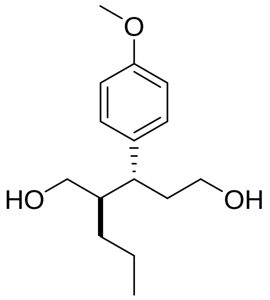
Yield: 240 mg, 1.24 mmol, 62%. $[\alpha]_D^{25}$ = +10.7 (c 1, CH_2Cl_2, dr≥99 *anti*, 98% *ee*). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 7.32-7.18 (m, 5H, Ar), 3.50 (m, 1H), 3.45 (dd, J= 10.0, 5.0 Hz, 1H), 3.39 (m, 1H), 3.27 (dd, J= 10.0, 5.0 Hz, 1H), 2.69 (m, 1H), 2.10 (m, 1H), 1.86 (m, 2H), 1.58 (b, 2H), 1.06 (d, J= 5.0 Hz, 3H). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 143.5, 128.5, 128.2, 126.4, 66.3, 61.3, 44.6, 41.3, 34.8, 14.8. HPLC: Daicel Chiralpak AS-H, hexane/2-propanol/Etanol (97/1/2), flow rate = 0.5 mL/min (anti, τ_1 = 31.8 min. (major enantiomer); τ_2 = 36.4 min. (minor enantiomer)).

(2R,3R)-3-phenyl-2-propylpentane-1,5-diol 14b



Yield: 244 mg, 1.10 mmol, 55 %. $[\alpha]_D^{25}$ = +9.6 (c 1, CH_2Cl_2, dr$\geq$99 *anti,* 97% *ee*). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 7.39-7.19 (m, 5H, Ar), 3.52 (m, 1H), 3.50 (dd, J= 15.0, 5.0 Hz, 1H), 3.41 (m, 1H), 3.36 (dd, J= 15.0, 5.0 Hz, 1H), 2.82 (m, 1H), 2.10 (m, 1H), 1.88 (m, 1H), 1.72 (m, 1H), 1.58 (b, 2H), 1.35 (m, 4H), 0.93 (d, J= 5.0 Hz, 3H). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 143.5, 128.5, 128.3, 126.4, 63.3, 61.5, 45.9, 43.4, 35.5, 30.9, 20.3, 14.43. HPLC: Daicel Chiralpak AS-H, hexane/2-propanol/Etanol (97/1/2), flow rate = 0.5 mL/min (anti, τ_1 = 39.1 min. (major enantiomer); τ_2 = 43.3 min. (minor enantiomer)).

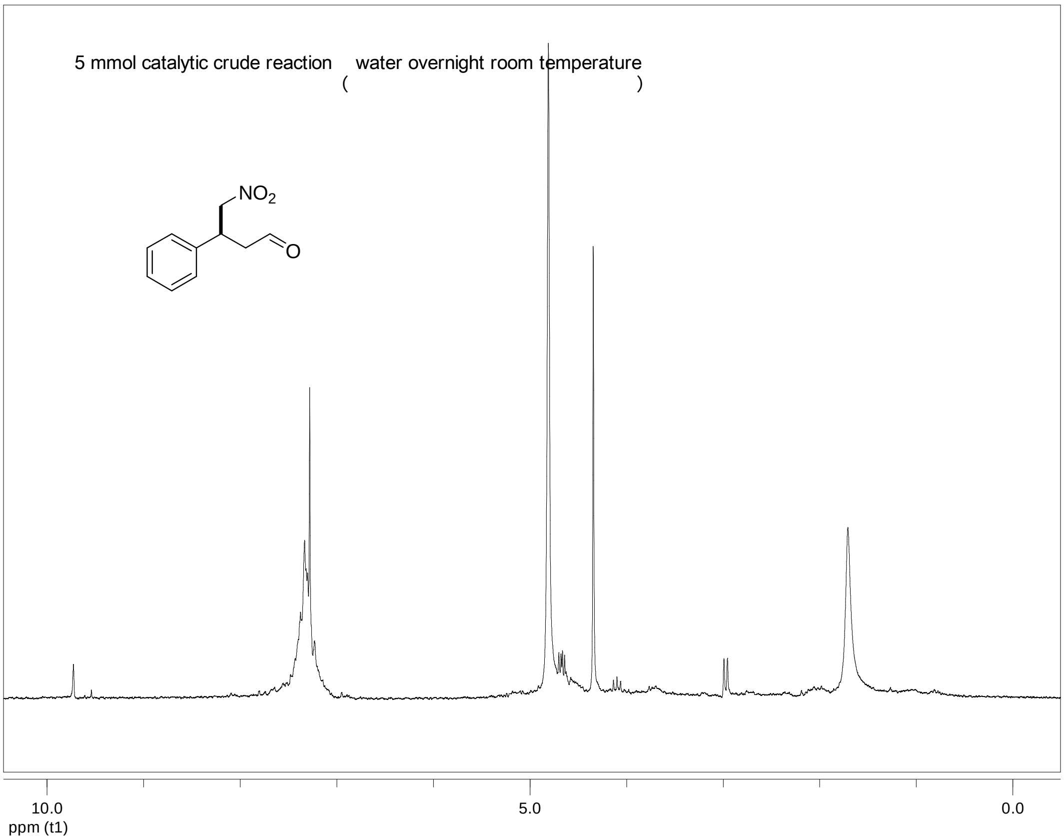
(2R,3R)-3-(4-methoxyphenyl)-2-propylpentane-1,5-diol 14c

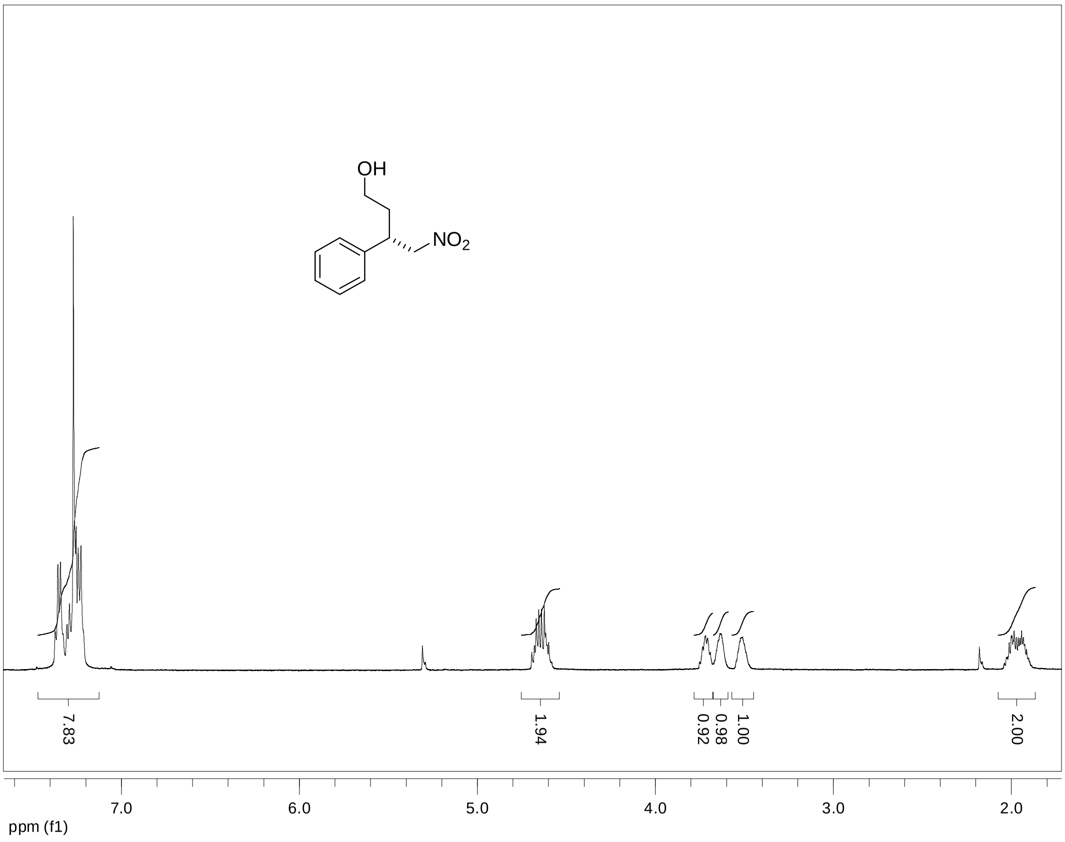


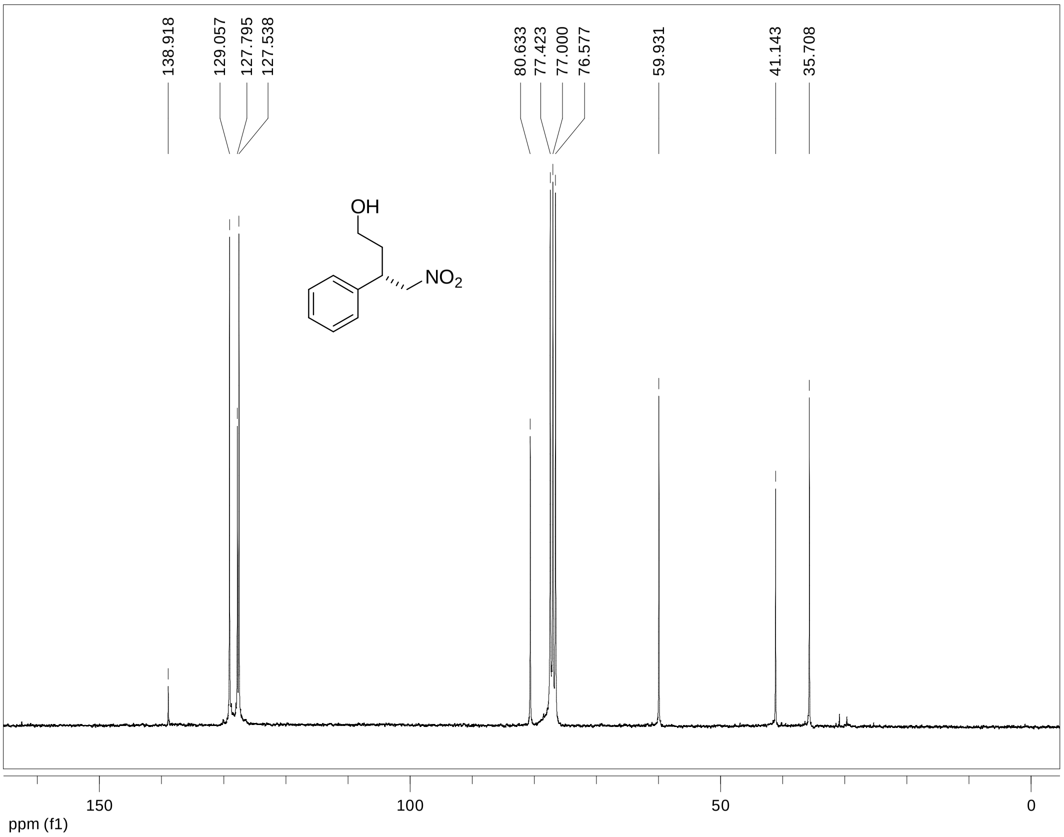
Yield: 92 mg, 0.42 mmol (in a 1 mmol scale), 42%. $[\alpha]_D^{25}$ = +15.2 (c 1, CH_2Cl_2, dr$\geq$99 *anti,* 98% *ee*). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 7.11(d, J= 10.0 Hz, 2H), 6.85 (d, J= 10.0 Hz, 2H), 3.80 (s, 3H), 3.52 (m, 1H), 3.50 (dd, J= 10.0, 5.0 Hz, 1H), 3.41 (m, 1H), 3.37 (dd, J= 10.0, 5.0 Hz, 1H), 2.76 (m, 1H), 2.08 (m, 1H), 1.84(m, 2H), 1.67(b, 2H), 1.34(m, 4H), 0.91 (t, J= 5.0 Hz, 3H). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 158.2, 135.1, 129.1, 114.0, 63.3, 61.5, 55.2, 46.0, 42.6, 35.7, 31.0, 20.4, 14.4. HPLC: Daicel Chiralpak AS-H, hexane/2-propanol/Etanol (90/6/4), flow rate = 1.0 mL/min (anti, τ_1 = 10.0 min. (major enantiomer); τ_2 = 12.3 min. (minor enantiomer)).

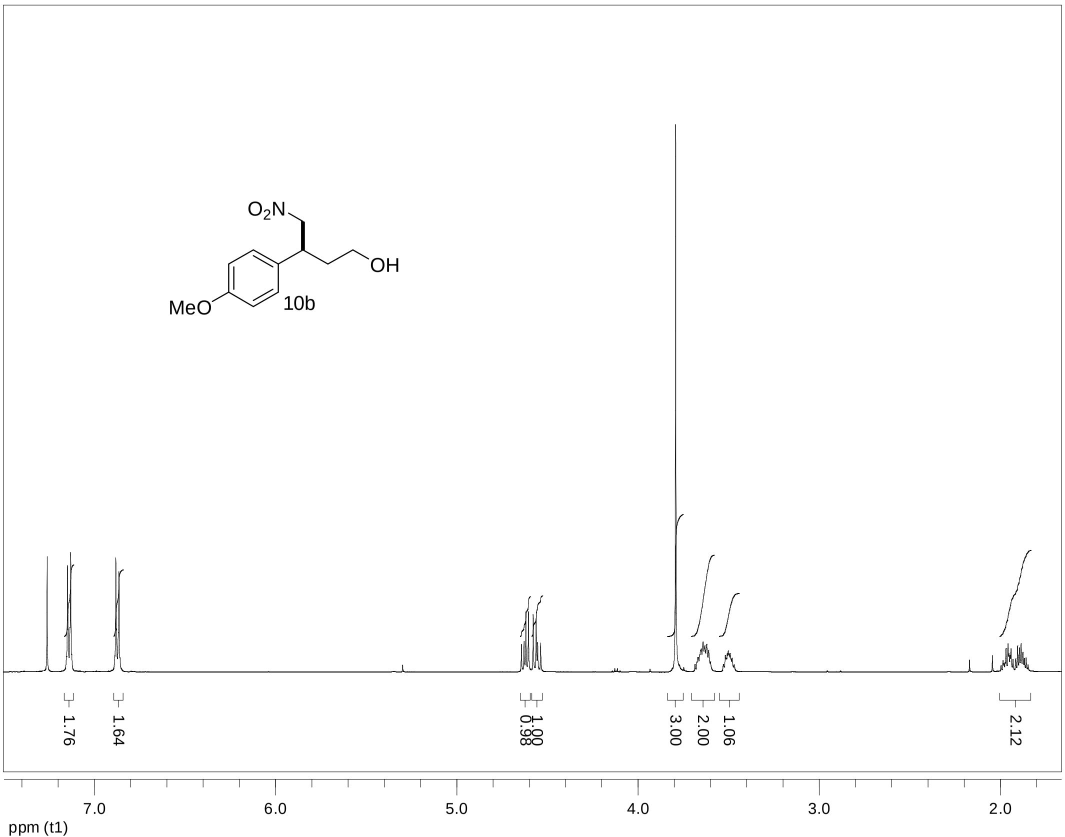
4. Selected ^{1}H and ^{13}C NMR Spectra

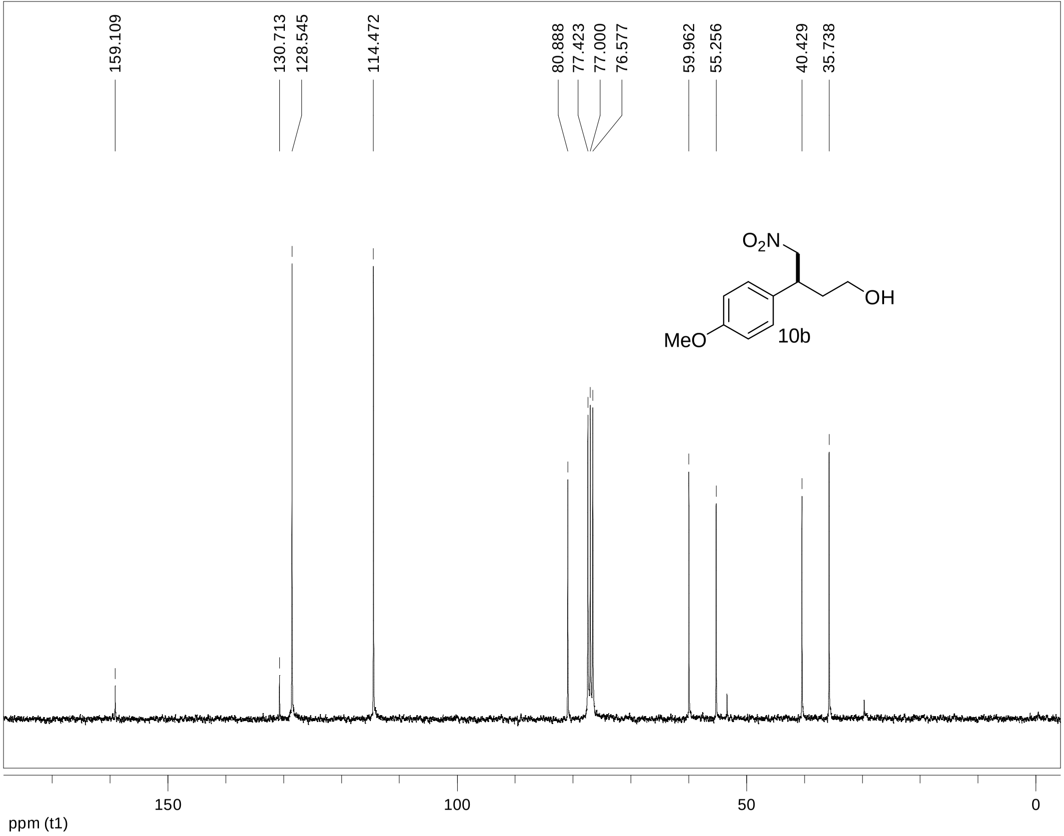
Below the ^{1}H-NMR spectra of the crude compound from the reaction between nitromethane and cinnamaldehyde before the reduction step is shown (reaction carried out at 5mmol scale)

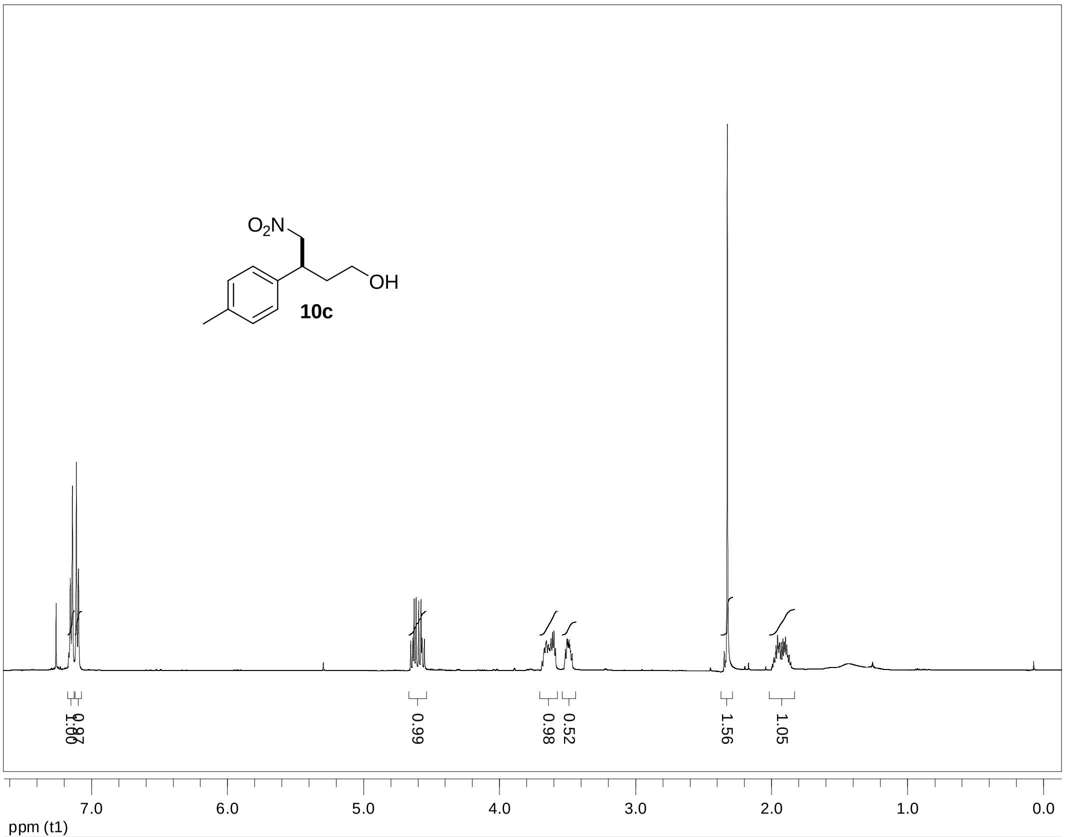


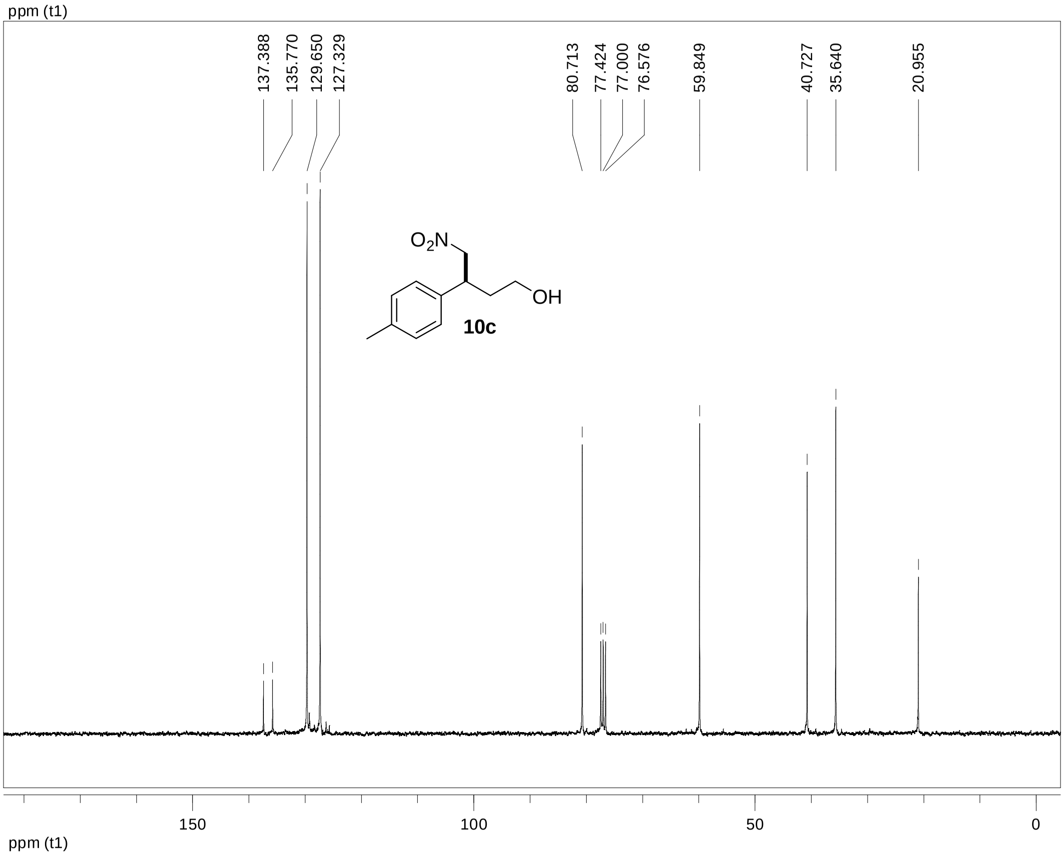

OH
NO2
7.83
1.94
0.92
0.98
1.00
2.00
7.0
6.0
5.0
4.0
3.0
2.0
ppm (f1)

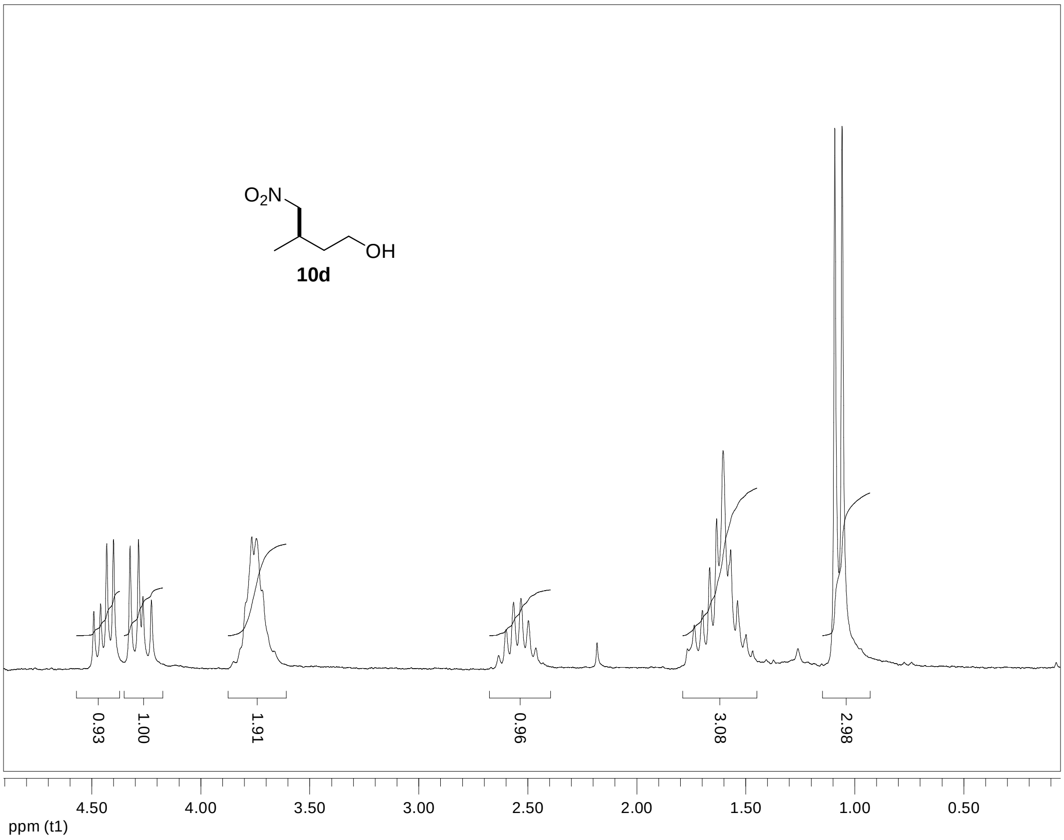

138.918
129.057
127.795
127.538
80.633
77.423
77.000
76.577
59.931
41.143
35.708
OH
NO2
150
100
50
0
ppm (f1)

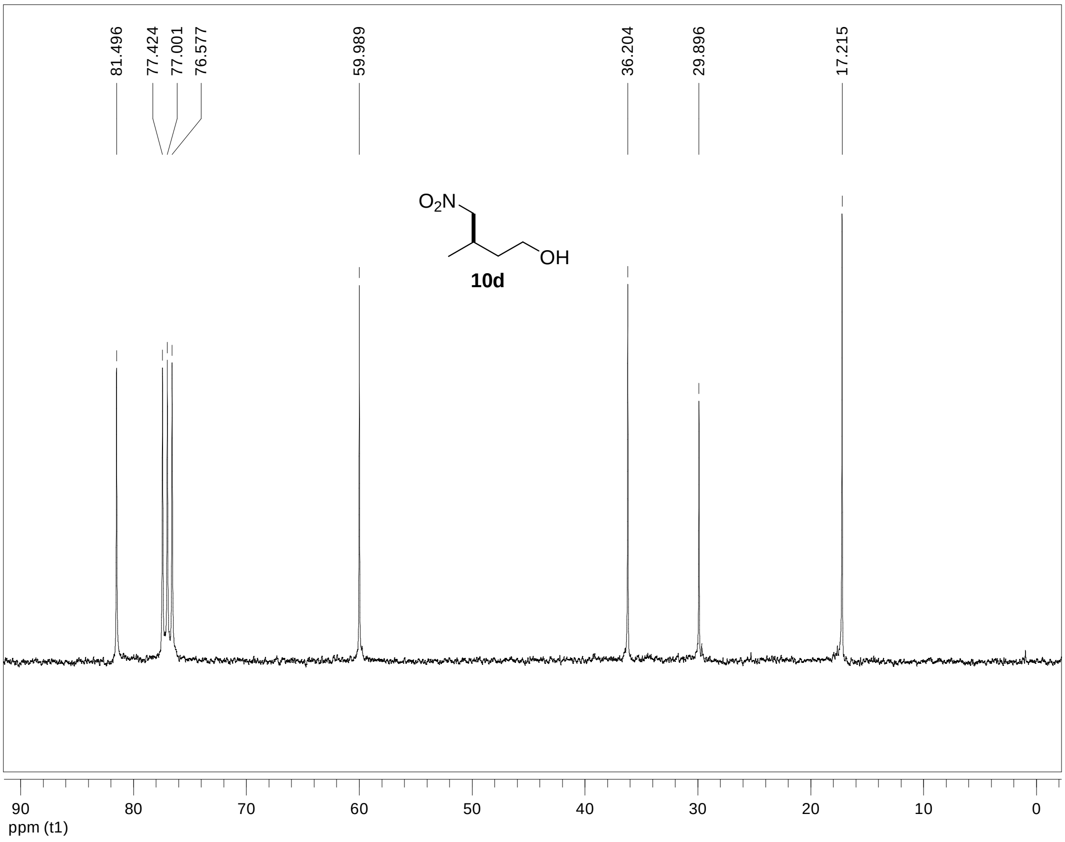

O2N
OH
MeO
10b
1.76
1.64
0.98
1.00
3.00
2.00
1.06
2.12
7.0
6.0
5.0
4.0
3.0
2.0
ppm (t1)

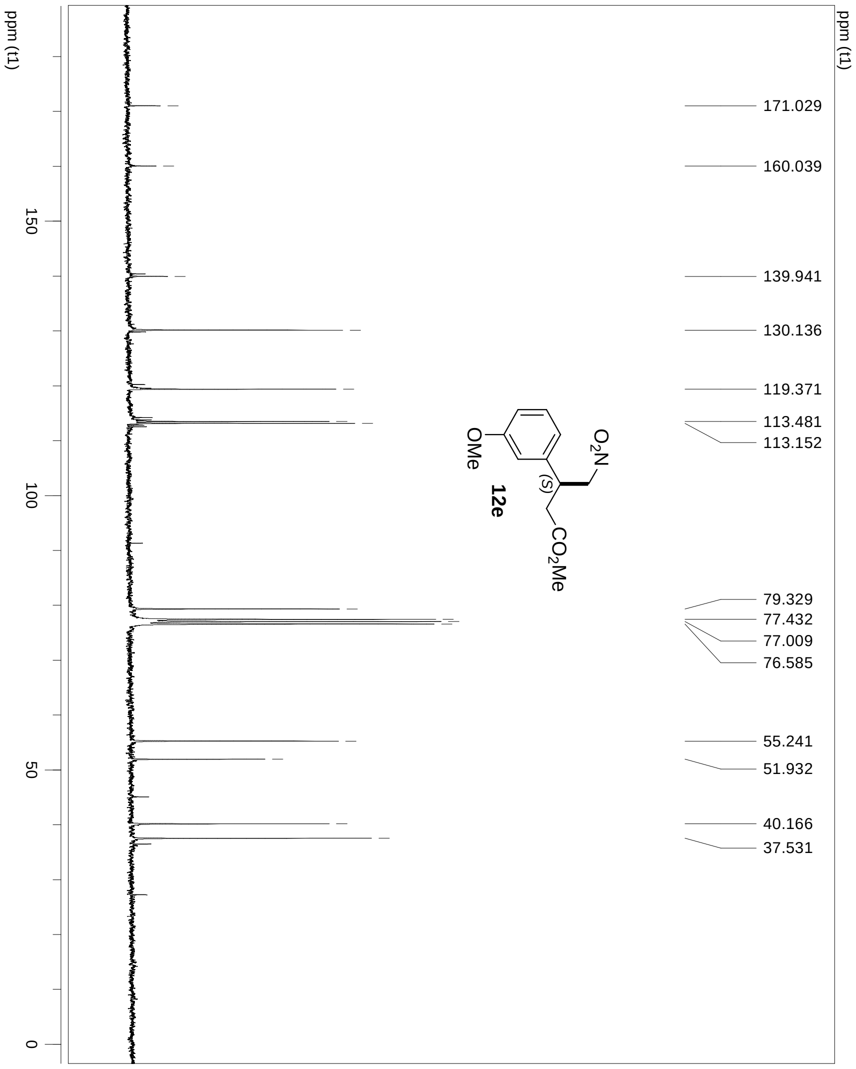

159.109
130.713
128.545
114.472
80.888
77.423
77.000
76.577
59.962
55.256
40.429
35.738
O2N
OH
MeO
10b
150
100
50
0
ppm (t1)


O2N
OH
10c
1.00
0.97
0.99
0.98
0.52
1.56
1.05
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

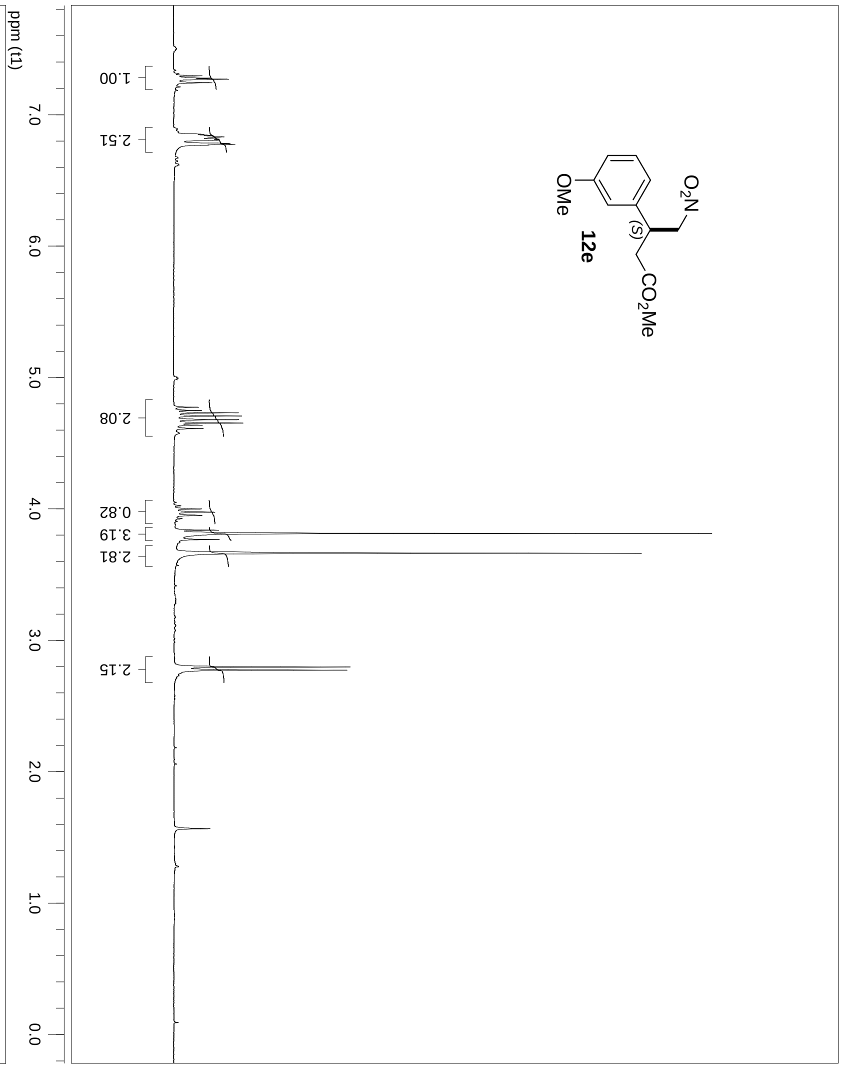

137.388
135.770
129.650
127.329
80.713
77.424
77.000
76.576
59.849
40.727
35.640
20.955
O2N
OH
10c
150
100
50
0
ppm (t1)


O_2N
OH
10d
0.93
1.00
1.91
0.96
3.08
2.98
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
ppm (t1)

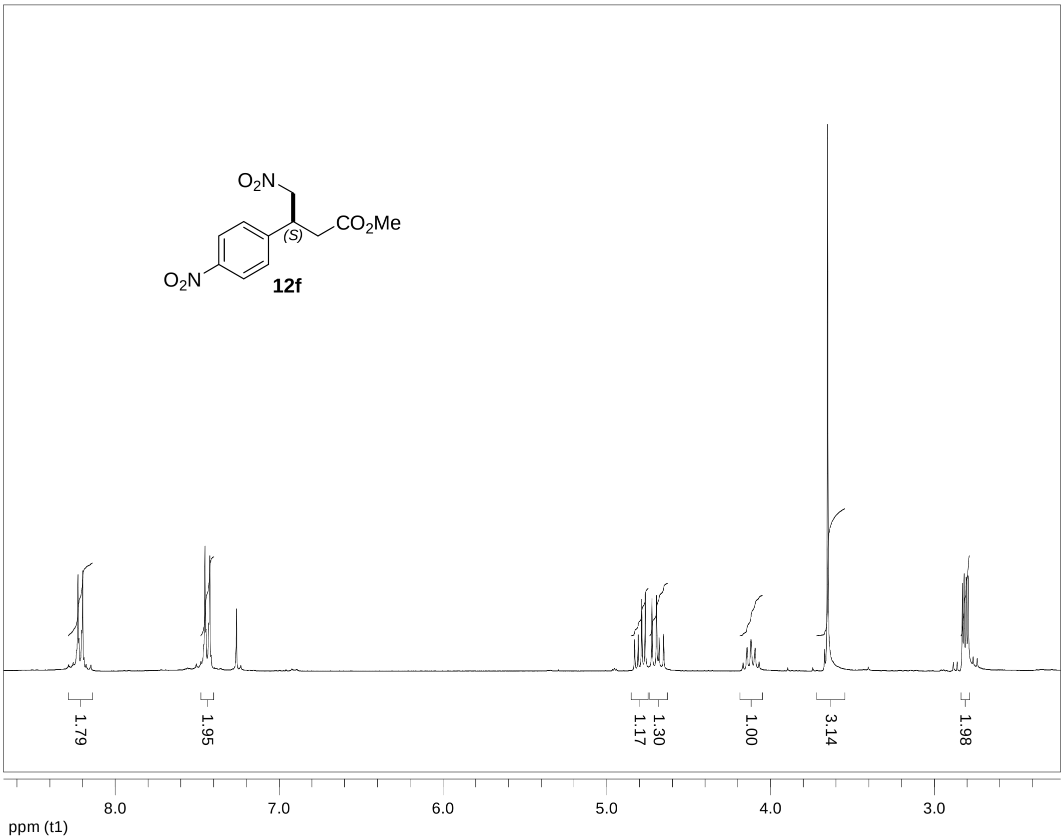

81.496
77.424
77.001
76.577
59.989
36.204
29.896
17.215
O_2N
OH
10d
90
80
70
60
50
40
30
20
10
0
ppm (t1)

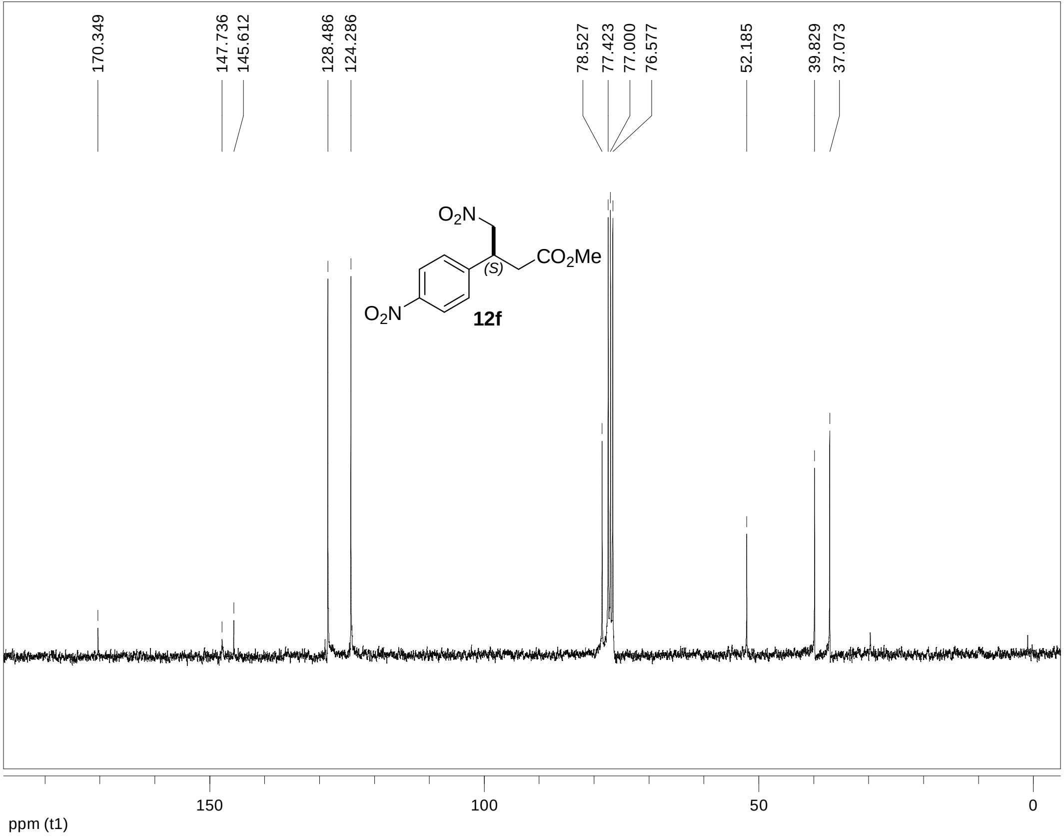

ppm (t1)
150
100
50
0
171.029
160.039
139.941
130.136
119.371
113.481
113.152
79.329
77.432
77.009
76.585
55.241
51.932
40.166
37.531
O2N
(S)
CO2Me
OMe

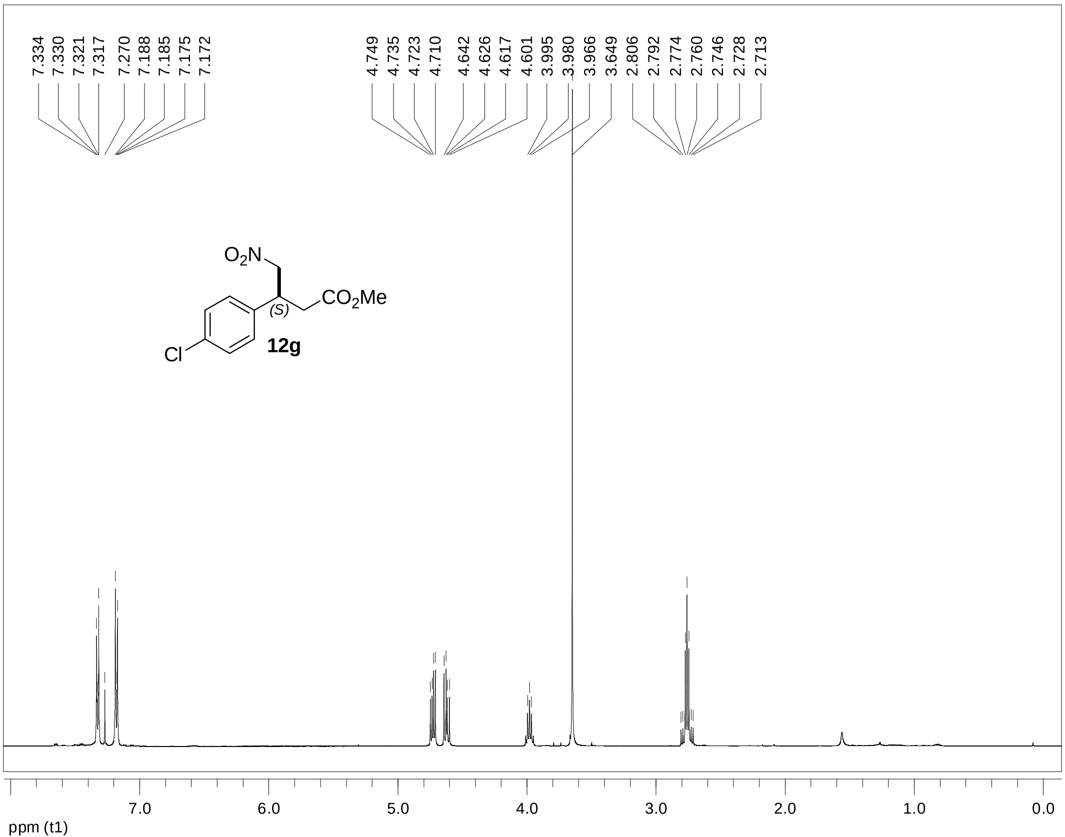
12e

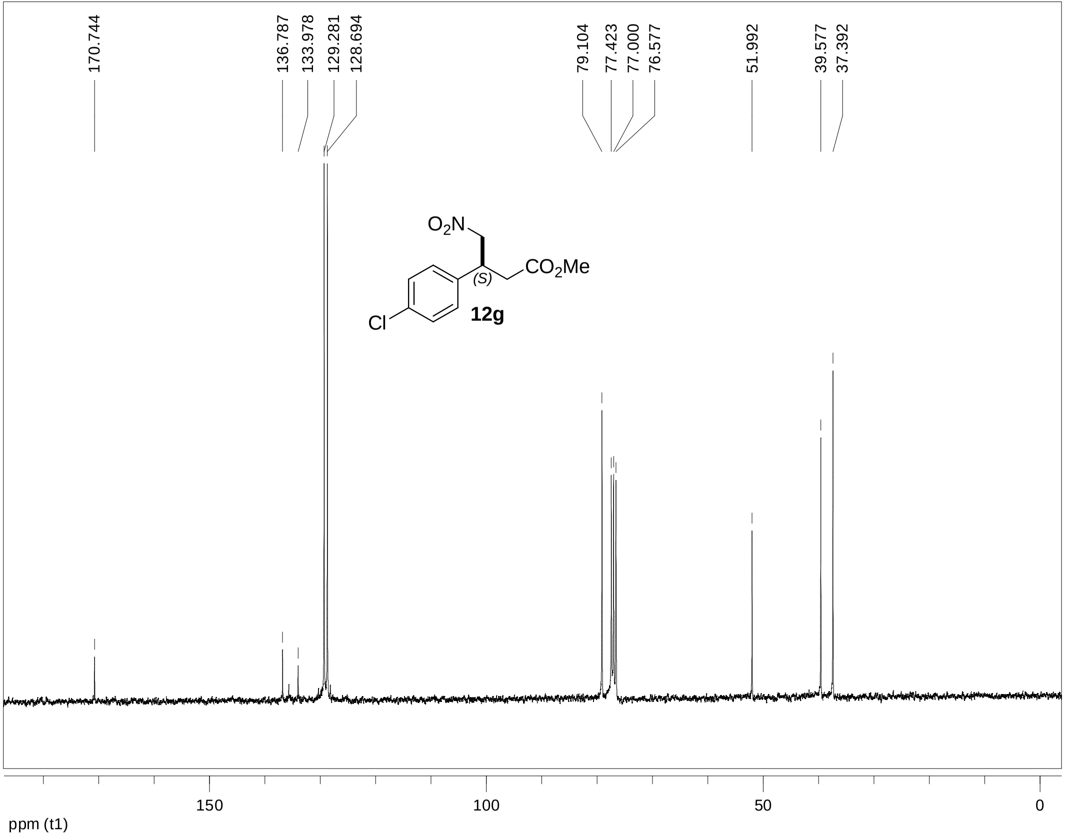

ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
1.00
2.51
2.08
0.82
3.19
2.81
2.15
O2N
(S)
CO2Me
OMe

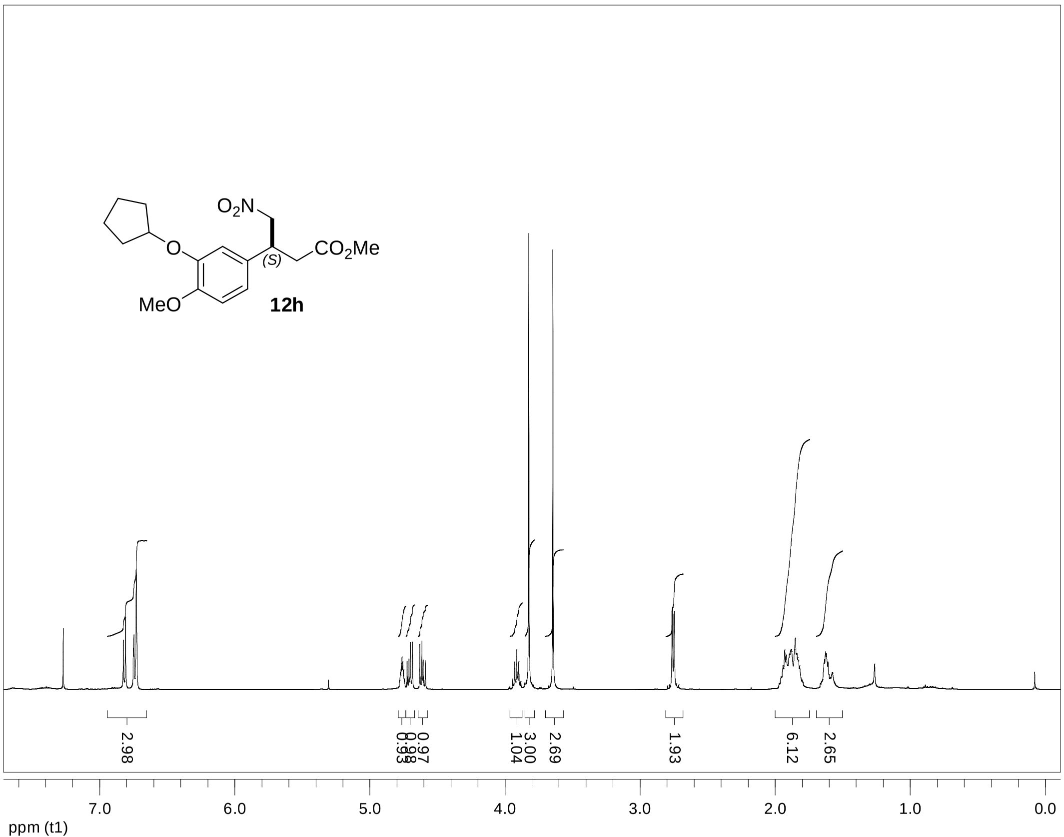
12e

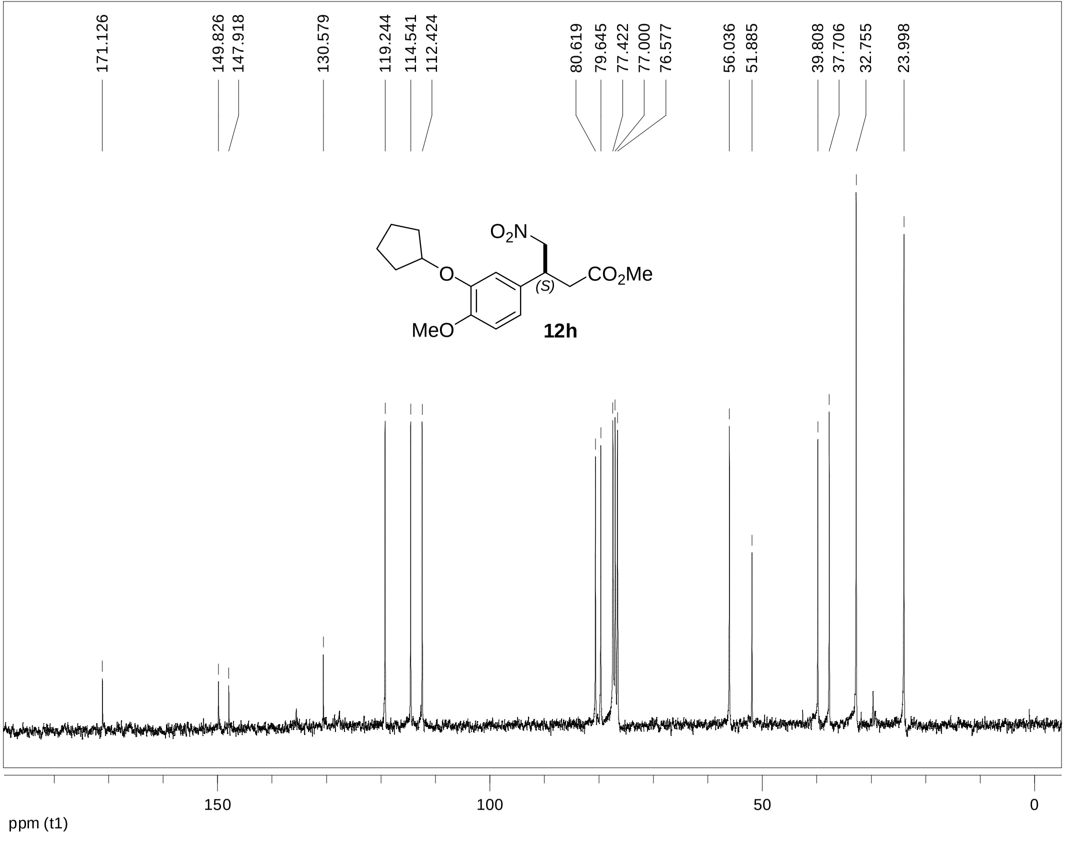

O2N
(S)
CO2Me
O2N
12f
1.79
1.95
1.17
1.30
1.00
3.14
1.98
8.0
7.0
6.0
5.0
4.0
3.0
ppm (t1)

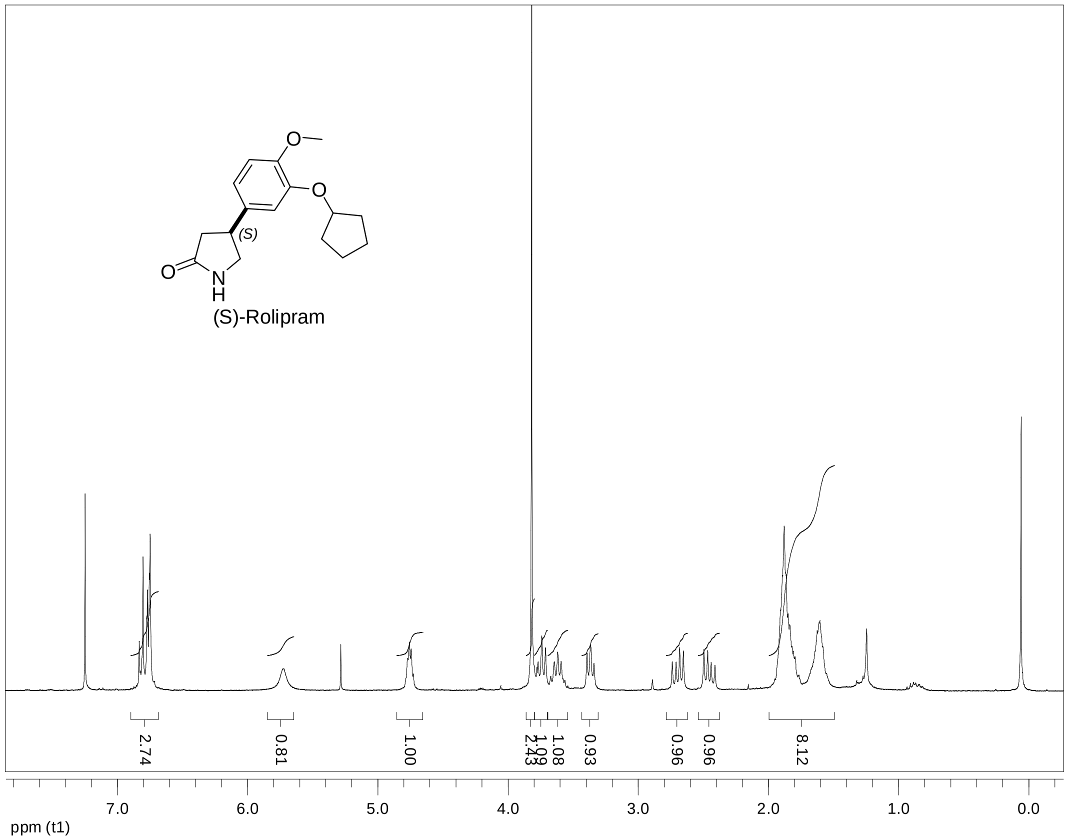

170.349
147.736
145.612
128.486
124.286
78.527
77.423
77.000
76.577
52.185
39.829
37.073
O2N
(S)
CO2Me
O2N
12f
150
100
50
0
ppm (t1)

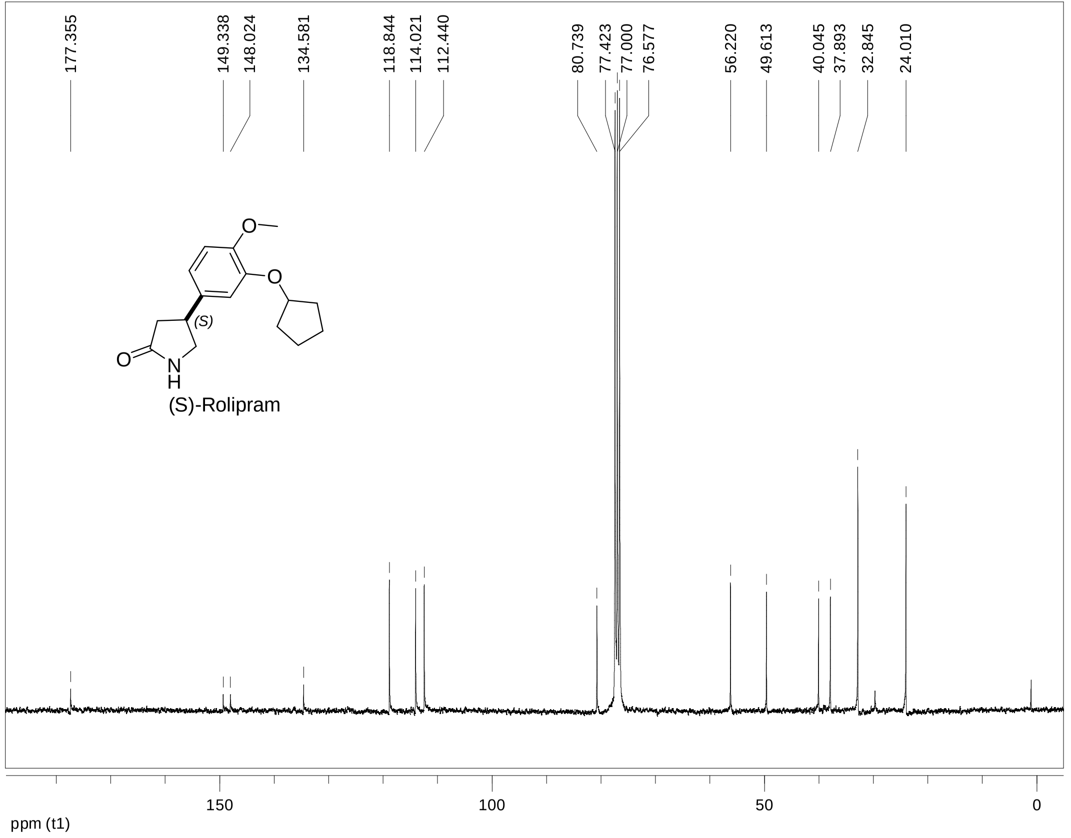

7.334
7.330
7.321
7.317
7.270
7.188
7.185
7.175
7.172
4.749
4.735
4.723
4.710
4.642
4.626
4.617
4.601
3.995
3.980
3.966
3.649
2.806
2.792
2.774
2.760
2.746
2.728
2.713
O2N
(S)
CO2Me
Cl
12g
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

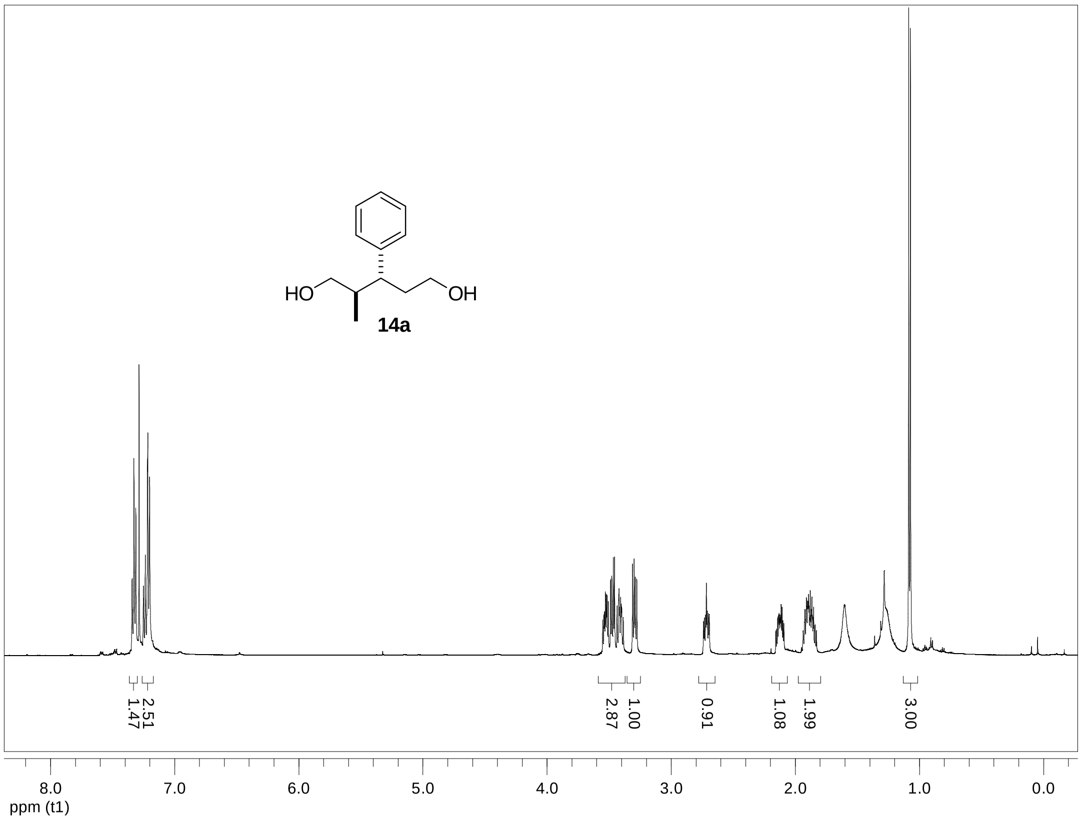

170.744
136.787
133.978
129.281
128.694
79.104
77.423
77.000
76.577
51.992
39.577
37.392
O2N
(S)
CO2Me
Cl
12g
150
100
50
0
ppm (t1)


O2N
CO2Me
(S)
MeO
O
12h
2.98
0.93
0.98
0.97
1.04
3.00
2.69
1.93
6.12
2.65
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

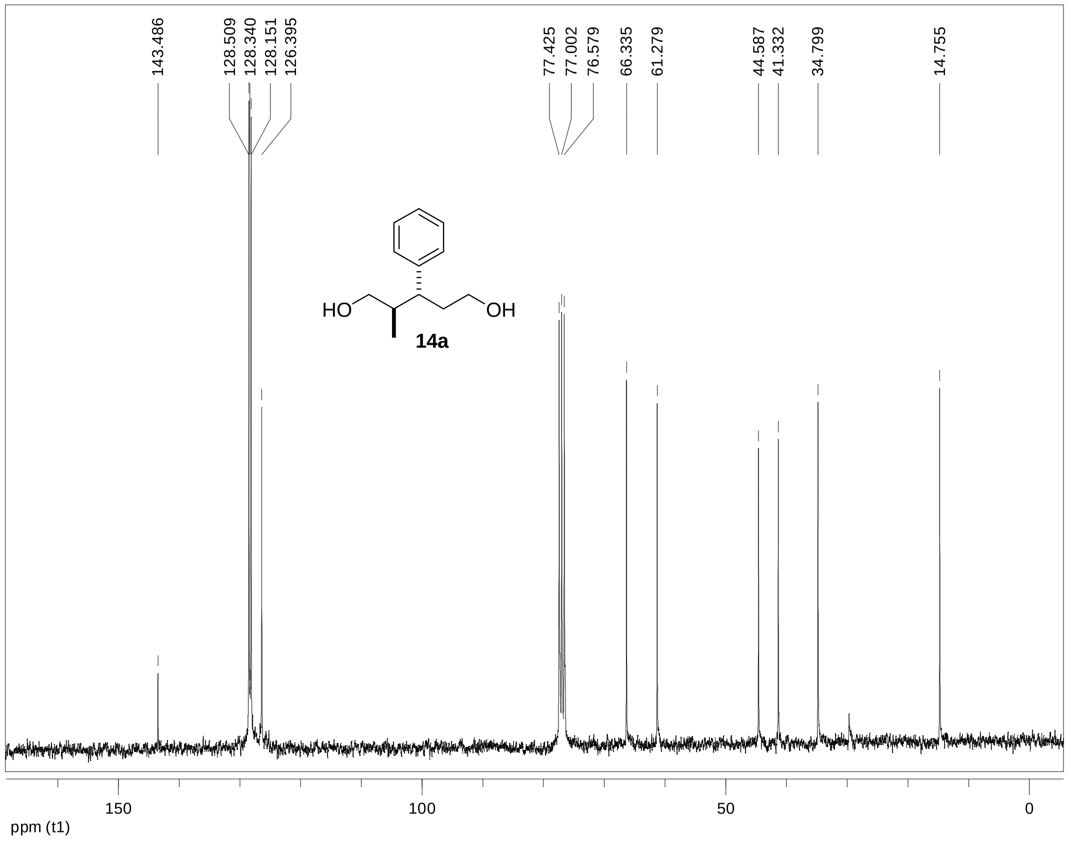

171.126
149.826
147.918
130.579
119.244
114.541
112.424
80.619
79.645
77.422
77.000
76.577
56.036
51.885
39.808
37.706
32.755
23.998
O2N
CO2Me
(S)
MeO
O
12h
150
100
50
0
ppm (t1)


(S)
O
N
H
O
O
(S)-Rolipram
2.74
0.81
1.00
2.43
1.09
1.08
0.93
0.96
0.96
8.12
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

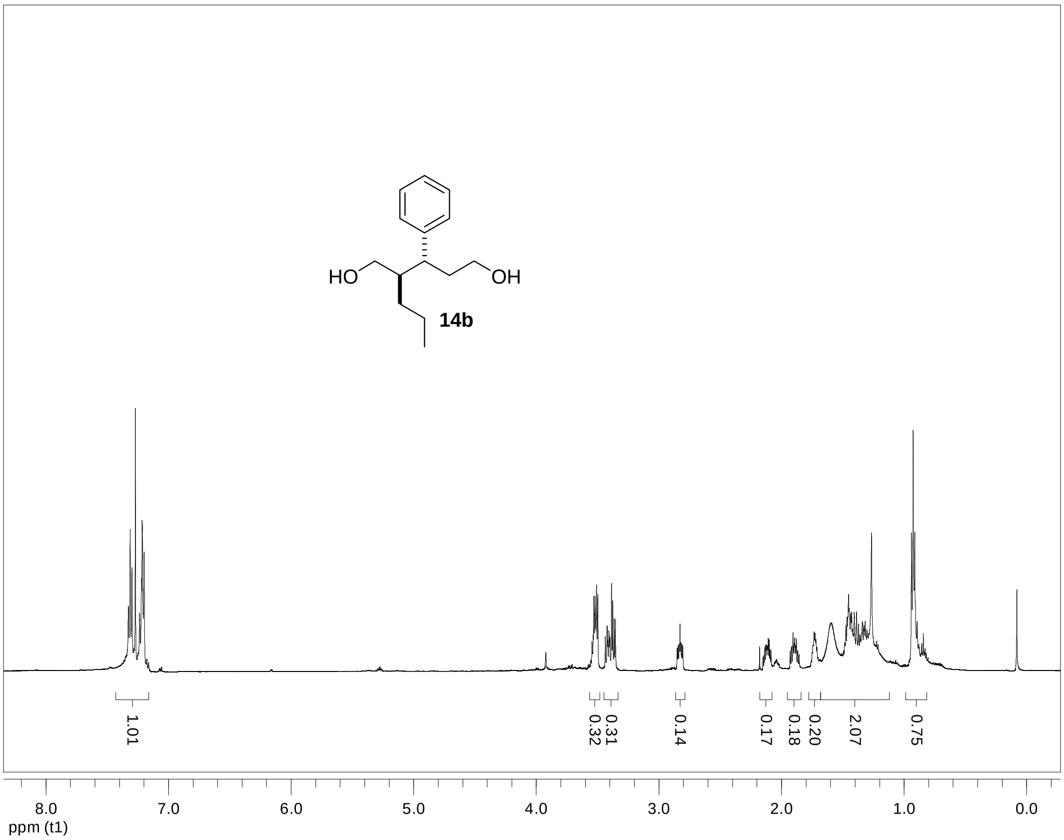

177.355
149.338
148.024
134.581
118.844
114.021
112.440
80.739
77.423
77.000
76.577
56.220
49.613
40.045
37.893
32.845
24.010
(S)
O
N
H
O
O
(S)-Rolipram
150
100
50
0
ppm (t1)

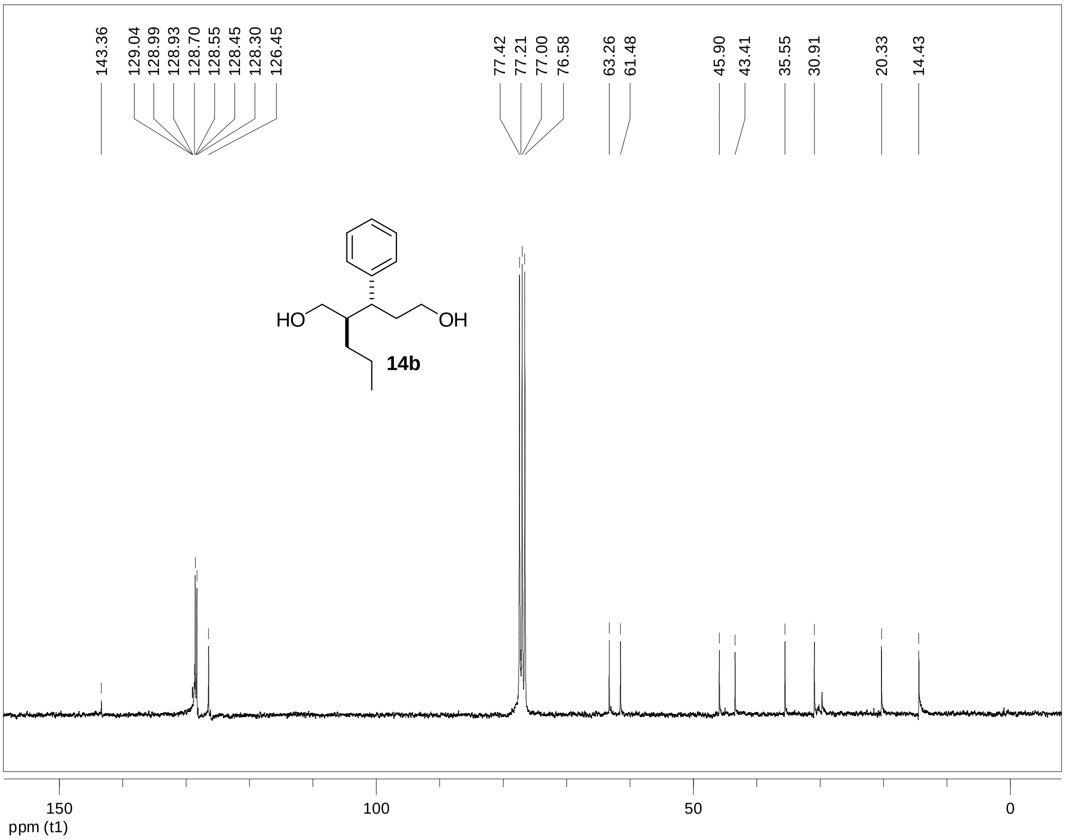


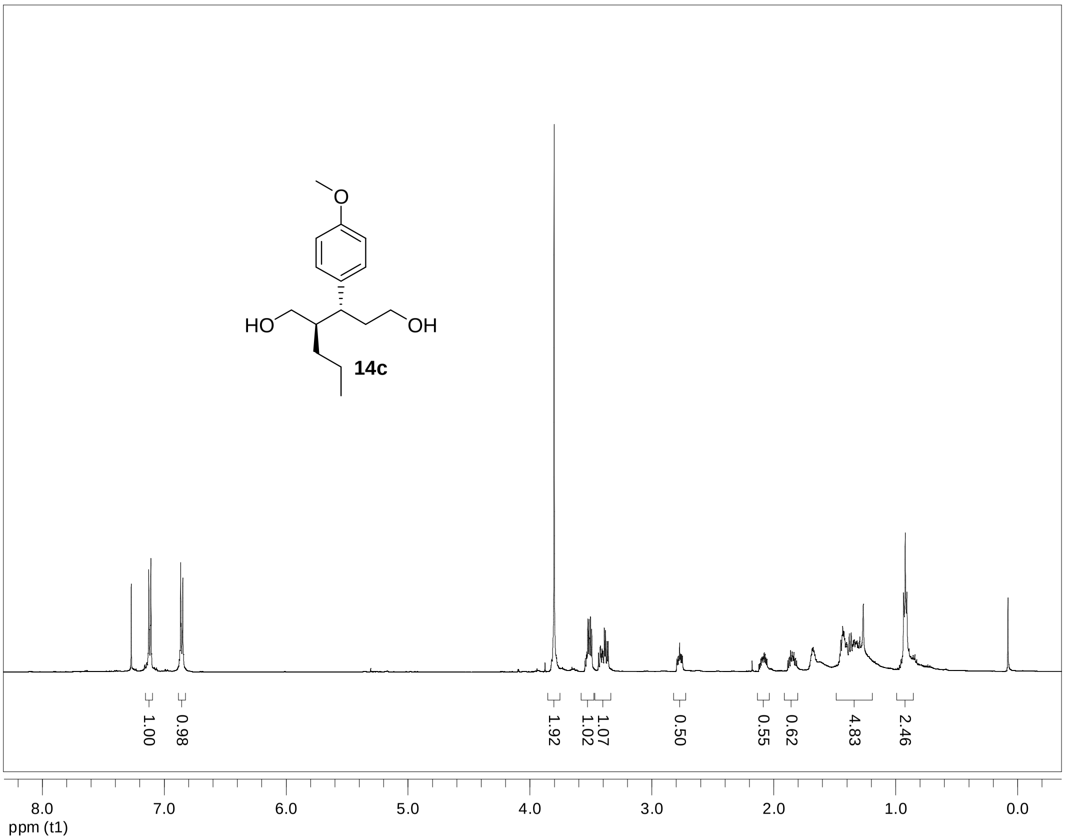
HO
OH
14a
1.47
2.51
2.87
1.00
0.91
1.08
1.99
3.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)



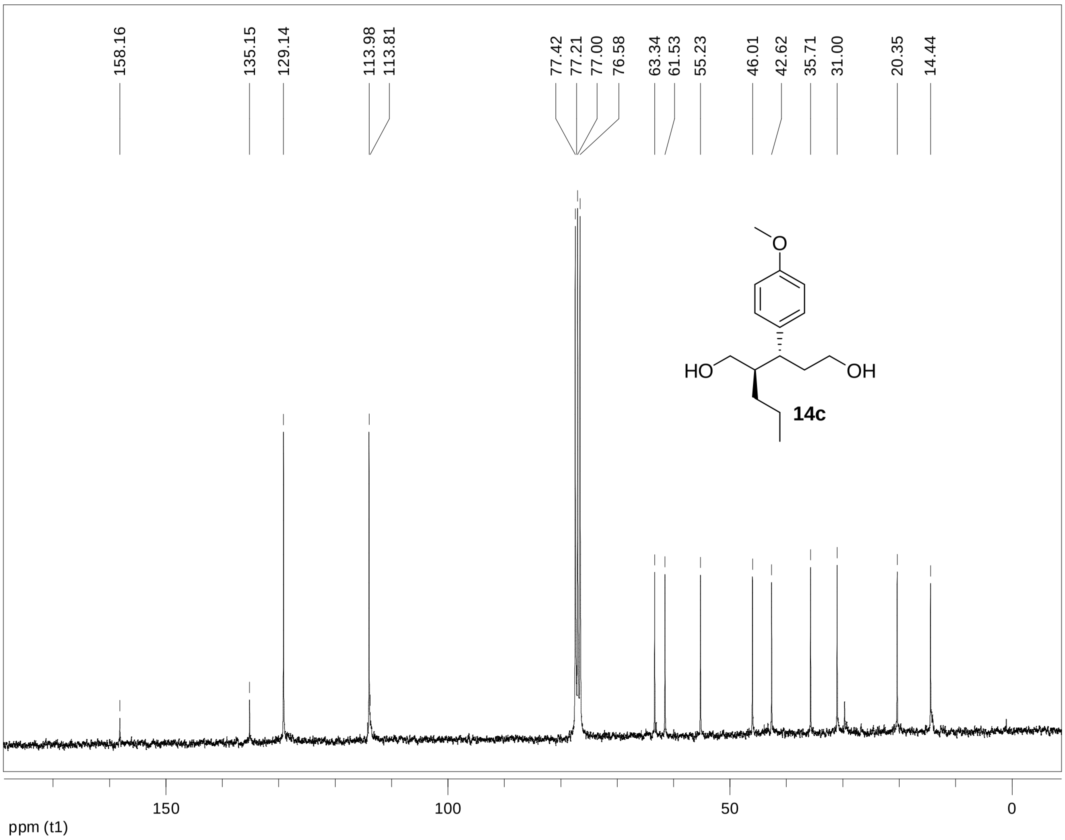
143.486
128.509
128.340
128.151
126.395
77.425
77.002
76.579
66.335
61.279
44.587
41.332
34.799
14.755
HO
OH
14a
150
100
50
0
ppm (t1)


HO
OH
14b
1.01
0.32
0.31
0.14
0.17
0.18
0.20
2.07
0.75
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


143.36
129.04
128.99
128.93
128.70
128.55
128.45
128.30
126.45
77.42
77.21
77.00
76.58
63.26
61.48
45.90
43.41
35.55
30.91
20.33
14.43
HO
OH
14b
150
100
50
0
ppm (t1)



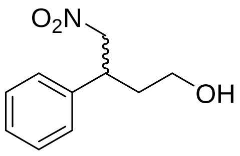
HO
OH
O
14c
1.00
0.98
1.92
1.02
1.07
0.50
0.55
0.62
4.83
2.46
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)



158.16
135.15
129.14
113.98
113.81
77.42
77.21
77.00
76.58
63.34
61.53
55.23
46.01
42.62
35.71
31.00
20.35
14.44
HO
OH
O
14c
150
100
50
0
ppm (t1)

5. HPLC Chromatograms of selected compounds.

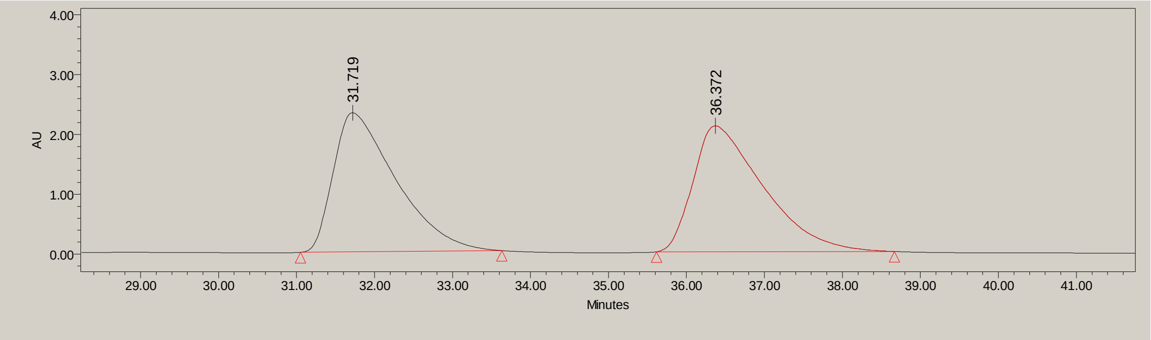
Chiralpak IB, 90:10 hexane:^{i}PrOH, 0.5mL/min, λ=220nm

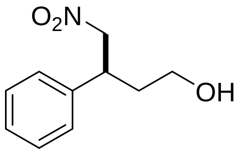


rac-**10a**

Processed Channel Descr.: PDA 217.1 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 217.1 nm	31.719	129613430	49.73	2325665
2	PDA 217.1 nm	36.372	131044031	50.27	2103710

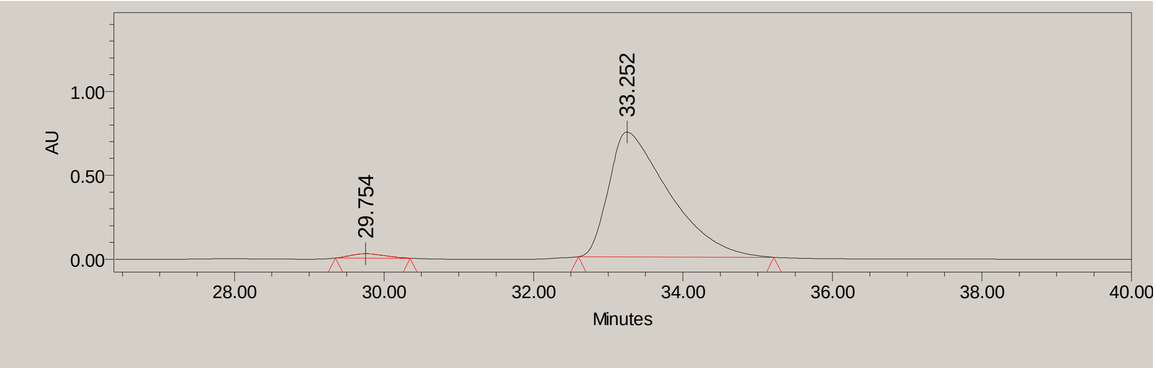




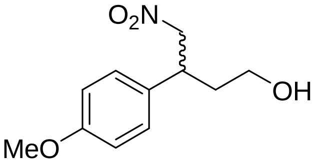
10a

Processed Channel Descr.: PDA 228.1 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 228.1 nm	29.754	824560	1.94	26541
2	PDA 228.1 nm	33.252	41639791	98.06	743751

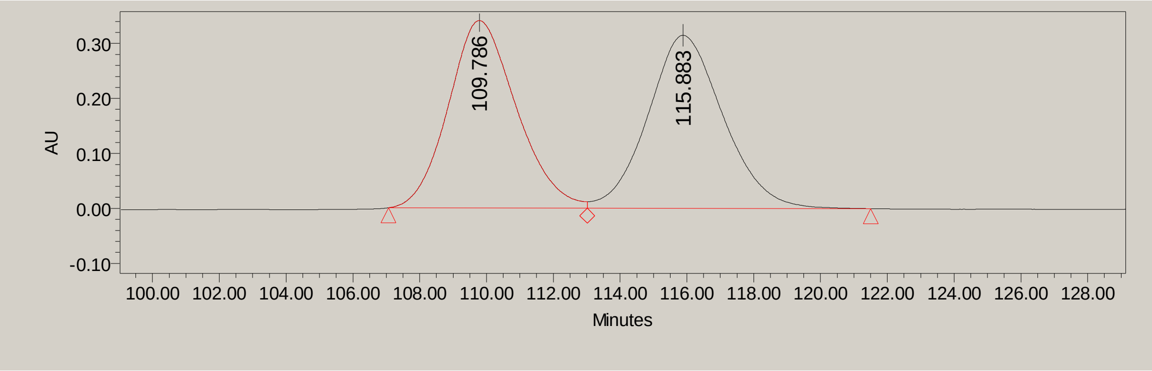


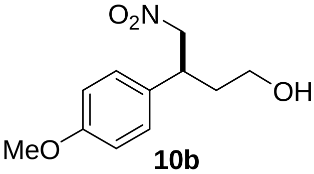
Chiralpak IB, 98:2 hexane:^{i}PrOH, 0.5mL/min, λ=220nm



rac-**10b**

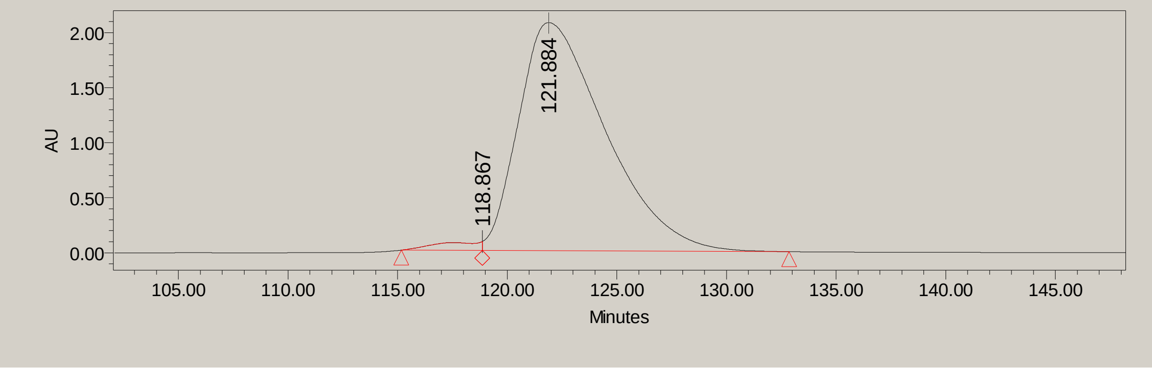
	RT	Area	% Area	Height
1	109.786	48343331	49.48	340907
2	115.883	49365937	50.52	314657



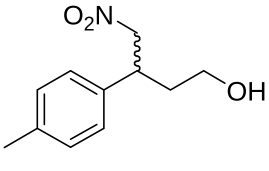


10b

	RT	Area	% Area	Height
1	118.867	10868331	1.87	81127
2	121.884	570481320	98.13	2074235



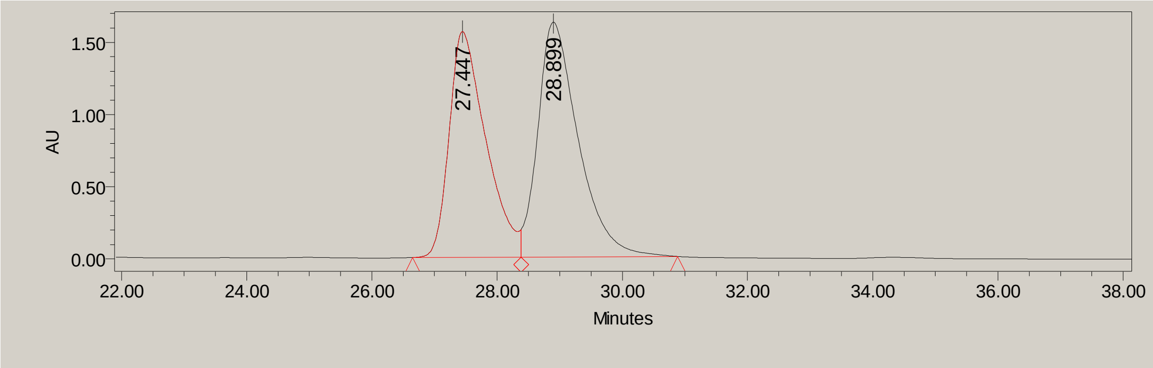
Chiralpak IB, 90:10 hexane:^{i}PrOH, 0.5mL/min, λ=220nm

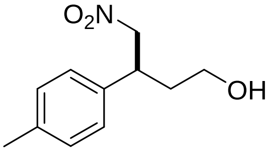


rac-**10c**

Processed Channel Descr.: PDA 220.2 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 220.2 nm	27.447	63602455	46.63	1564103
2	PDA 220.2 nm	28.899	72790630	53.37	1626695

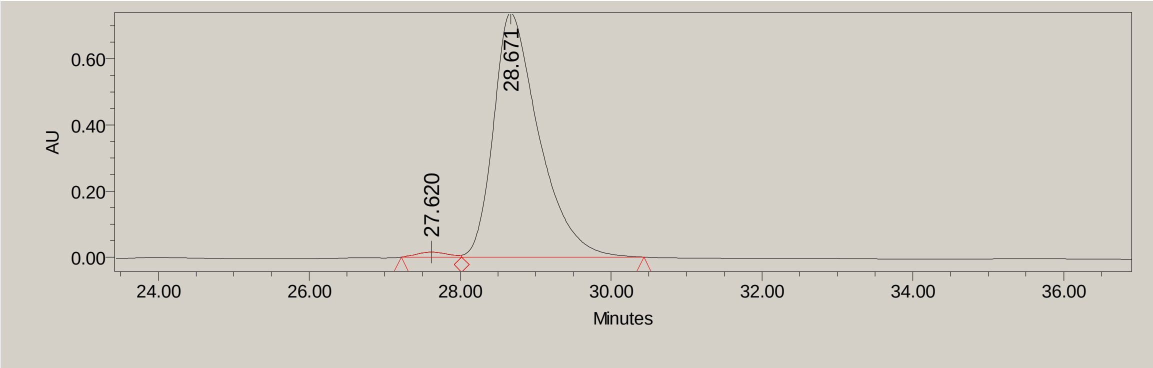




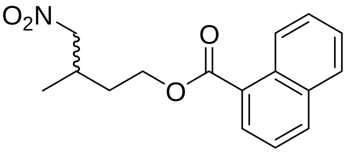
10c

Processed Channel Descr.: PDA 224.4 nm

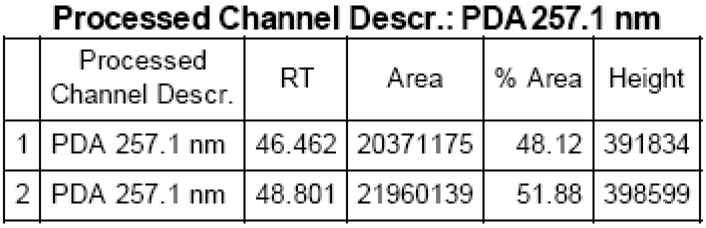
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 224.4 nm	27.620	431040	1.38	15055
2	PDA 224.4 nm	28.671	30803139	98.62	739075



Chiralpak AD-H, 95:5 hexane:^{i}PrOH, 0.5mL/min, λ=254nm

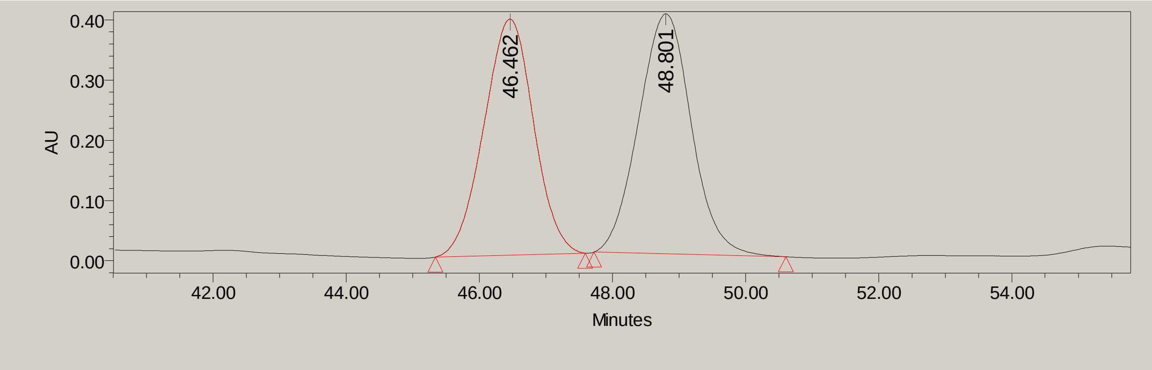


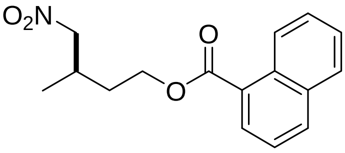
From rac-**10d**



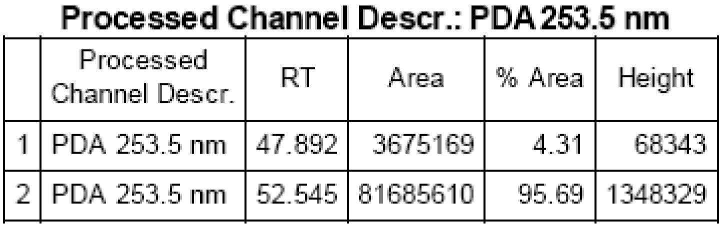
Processed Channel Descr.: PDA 257.1 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 257.1 nm	46.462	20371175	48.12	391834
2	PDA 257.1 nm	48.801	21960139	51.88	398599



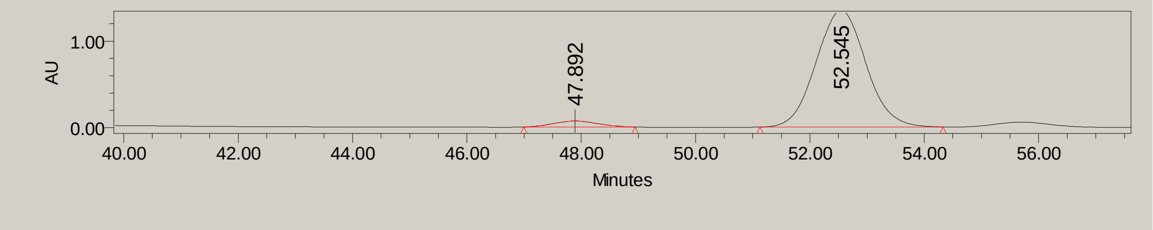


10d

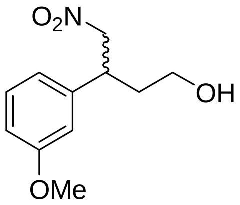


Processed Channel Descr.: PDA 253.5 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 253.5 nm	47.892	3675169	4.31	68343
2	PDA 253.5 nm	52.545	81685610	95.69	1348329



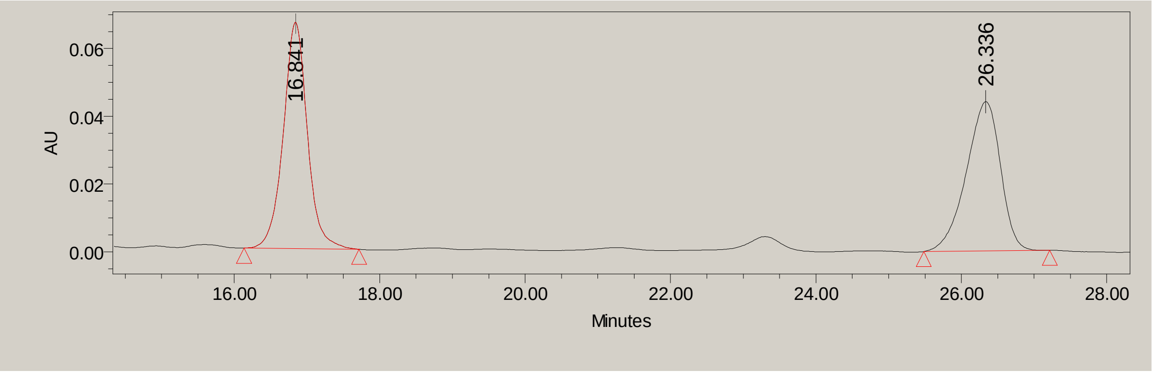
Chiralpak IB, 90:10 hexane:^{i}PrOH, 0.5mL/min, λ=220nm

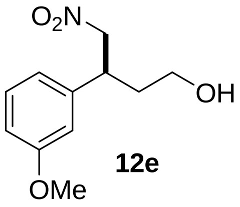


rac-**12e**

Processed Channel Descr.: PDA 227.1 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 227.1 nm	16.841	1538712	51.62	66951
2	PDA 227.1 nm	26.336	1441954	48.38	44083

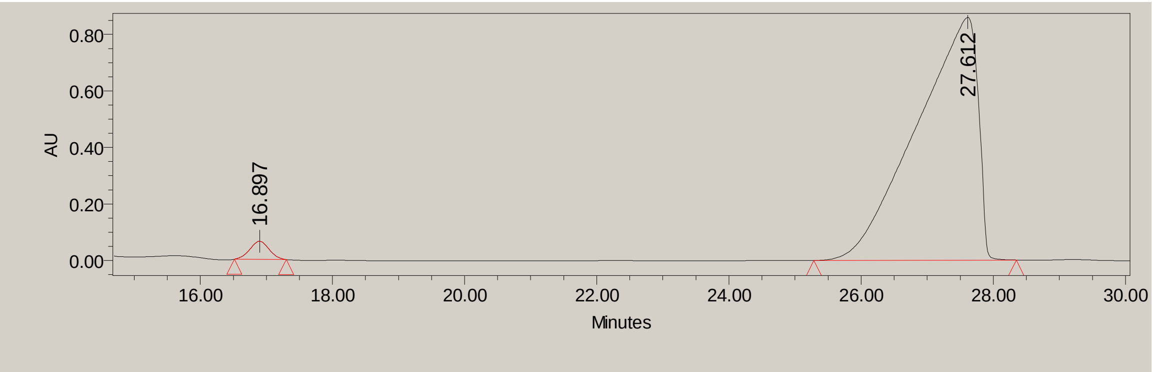




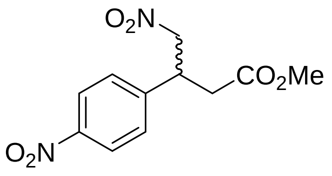
12e

Processed Channel Descr.: PDA 218.4 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 218.4 nm	16.897	1297227	2.28	63913
2	PDA 218.4 nm	27.612	55516524	97.72	860029



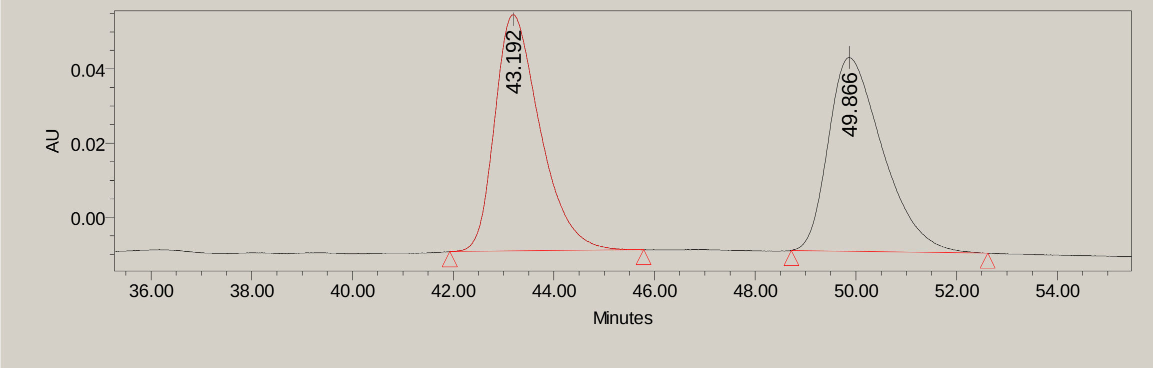
Chiralpak AD-H, 90:10 hexane:^{i}PrOH, 1mL/min, λ=254nm

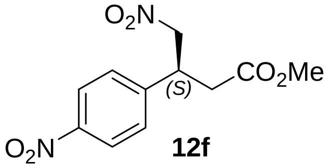


rac-**12f**

Processed Channel Descr.: PDA 261.8 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 261.8 nm	43.192	3987824	50.40	63741
2	PDA 261.8 nm	49.866	3924191	49.60	52250

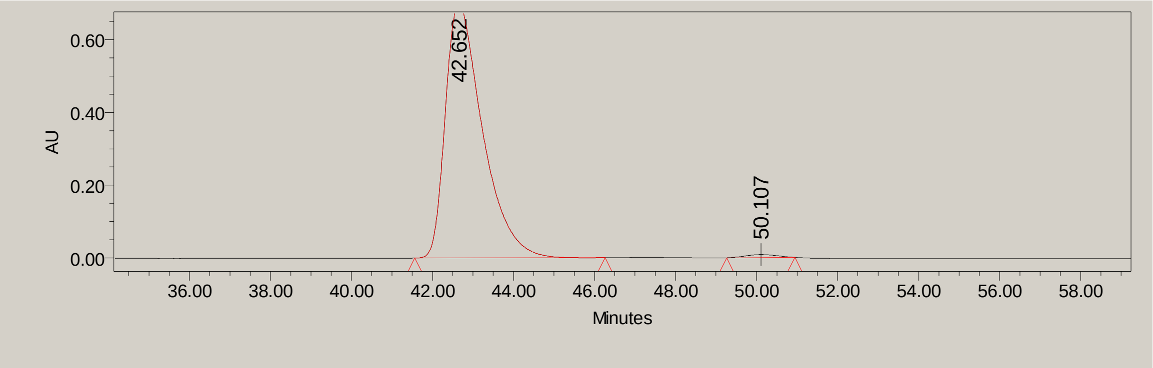




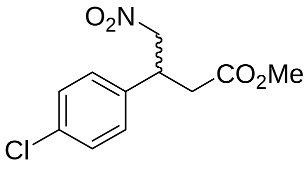
12f

Processed Channel Descr.: PDA 257.6 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 257.6 nm	42.652	44395654	99.01	699513
2	PDA 257.6 nm	50.107	444242	0.99	8164



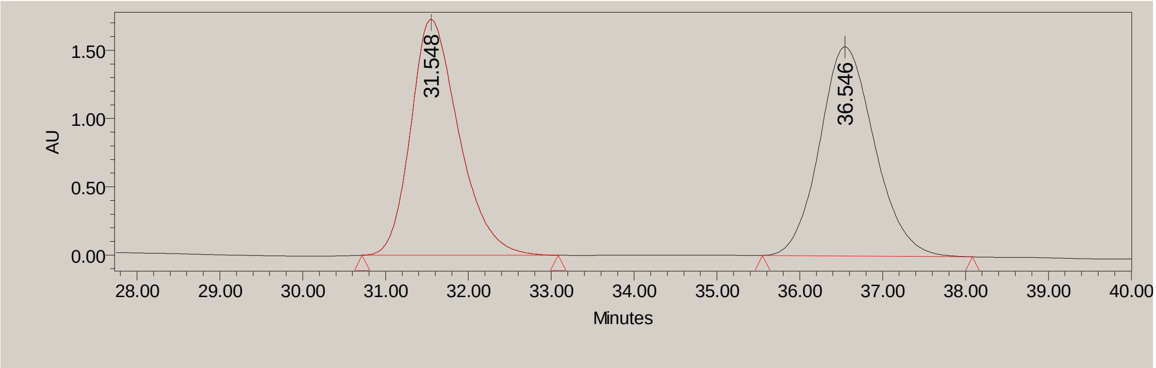
Chiralpak IB, 90:10 hexane:^{i}PrOH, 0.5mL/min, λ=220nm

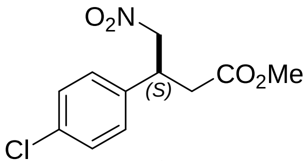


rac-**12g**

Processed Channel Descr.: PDA 220.3 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 220.3 nm	31.548	69661173	49.63	1727480
2	PDA 220.3 nm	36.546	70697708	50.37	1531820

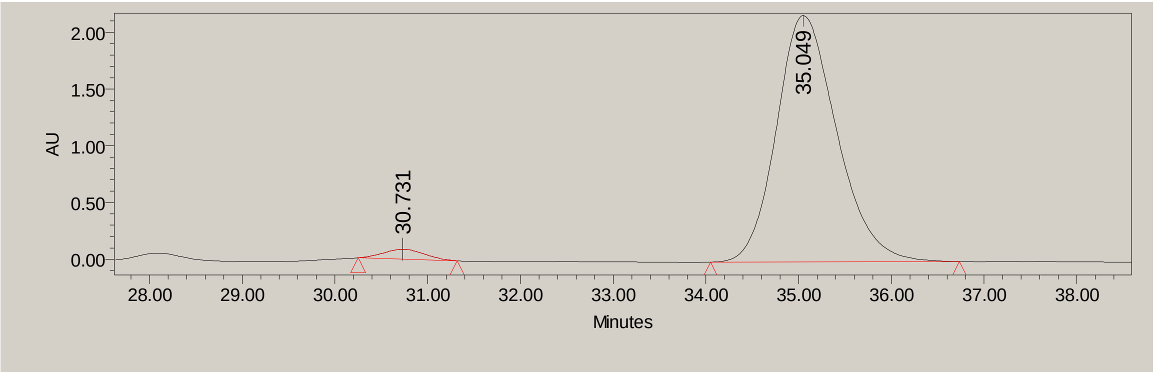




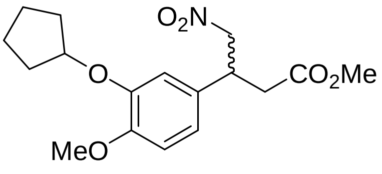
12g

Processed Channel Descr.: PDA 217.3 nm

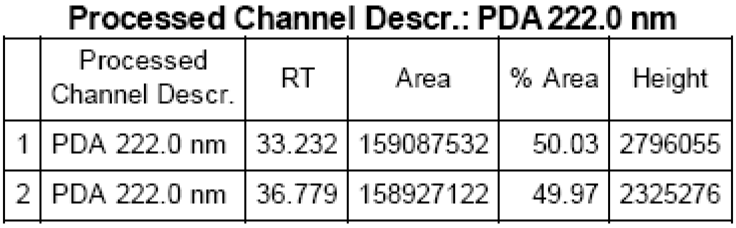
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 217.3 nm	30.731	2678207	2.65	87036
2	PDA 217.3 nm	35.049	98368539	97.35	2171406



Chiralpak IB, 90:10 hexane:^{i}PrOH, 0.5mL/min, λ=220nm

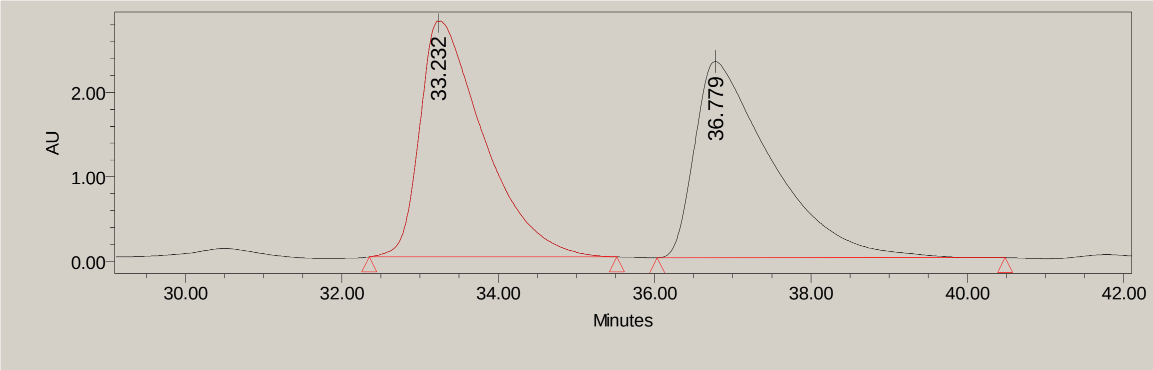


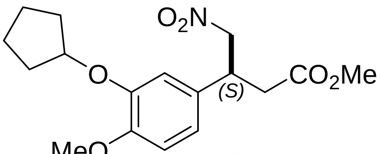
rac-**12h**



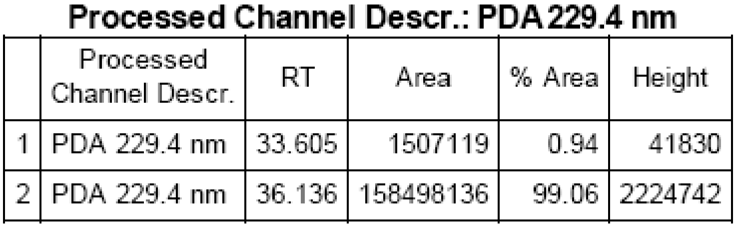
Processed Channel Descr.: PDA 222.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 222.0 nm	33.232	159087532	50.03	2796055
2	PDA 222.0 nm	36.779	158927122	49.97	2325276



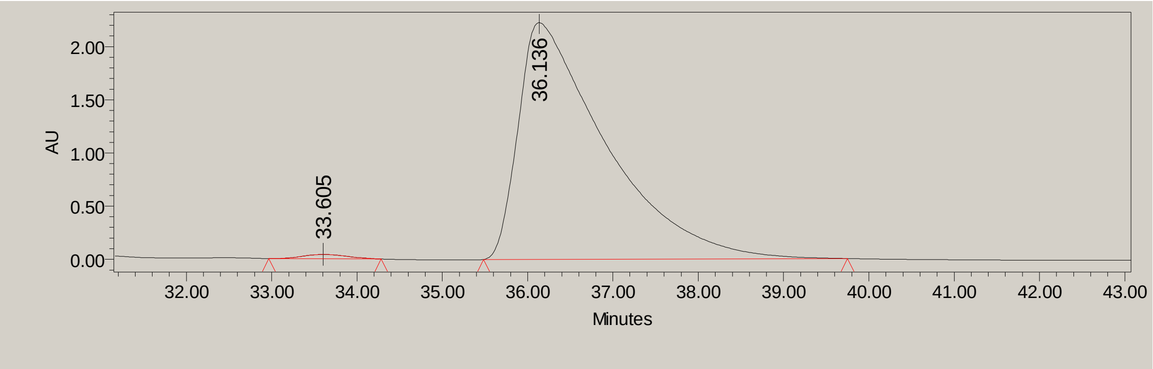


12h

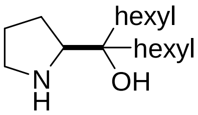


Processed Channel Descr.: PDA 229.4 nm

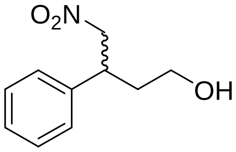
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 229.4 nm	33.605	1507119	0.94	41830
2	PDA 229.4 nm	36.136	158498136	99.06	2224742



Using catalyst:



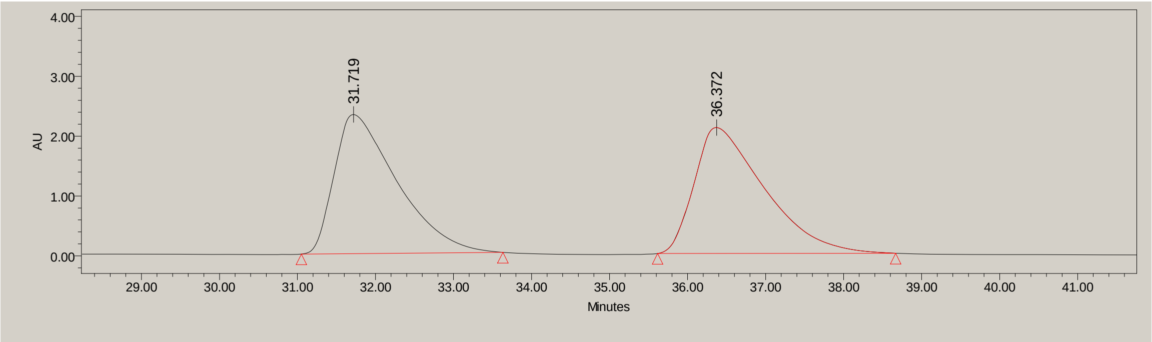
Chiralpak IB, 90:10 hexane:^{i}PrOH, 0.5mL/min, λ=220nm

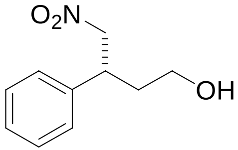


rac-**10a**

Processed Channel Descr.: PDA 217.1 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 217.1 nm	31.719	129613430	49.73	2325665
2	PDA 217.1 nm	36.372	131044031	50.27	2103710

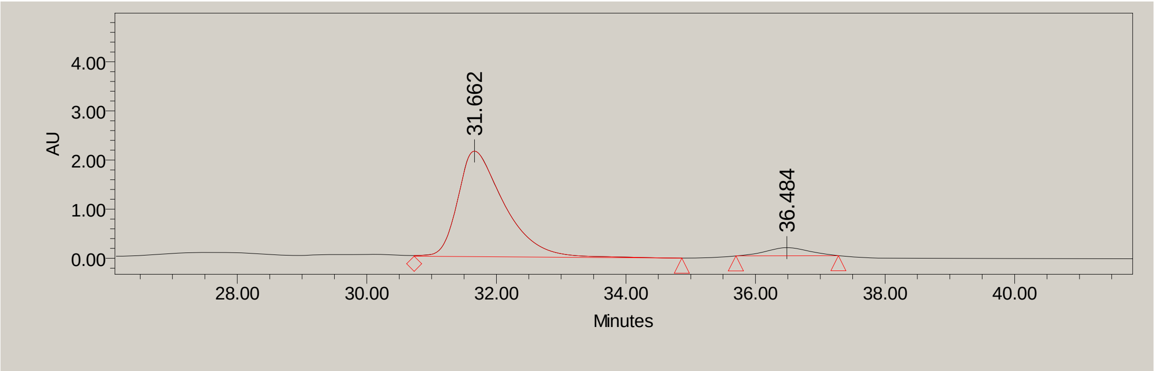




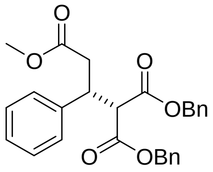
ent-10a

Processed Channel Descr.: PDA 210.1 nm

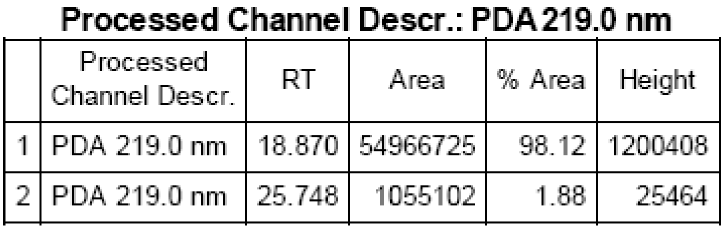
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 210.1 nm	31.662	107526011	93.42	2149842
2	PDA 210.1 nm	36.484	7575761	6.58	165897



Chiralpak AD, 80:20 hexane:*i*PrOH, 1mL/min, λ=220nm[5]

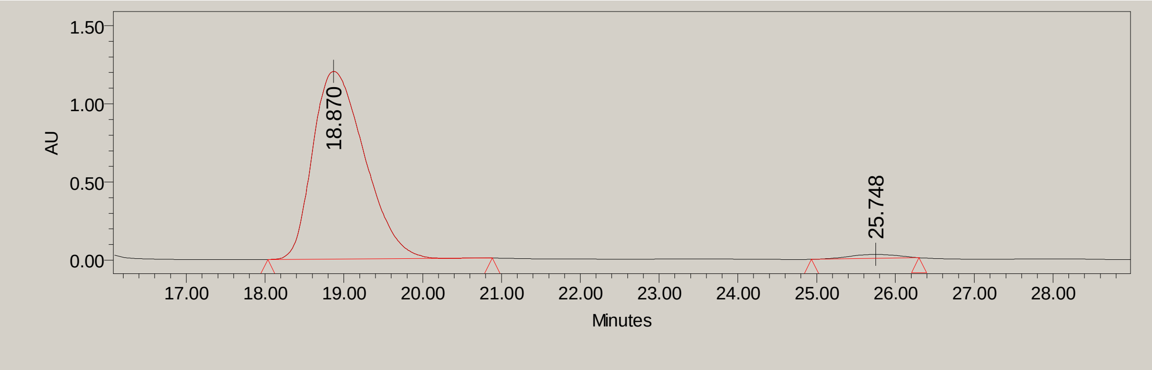


13a

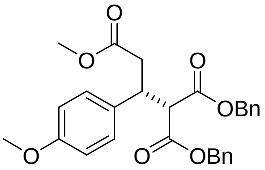


Processed Channel Descr.: PDA 219.0 nm

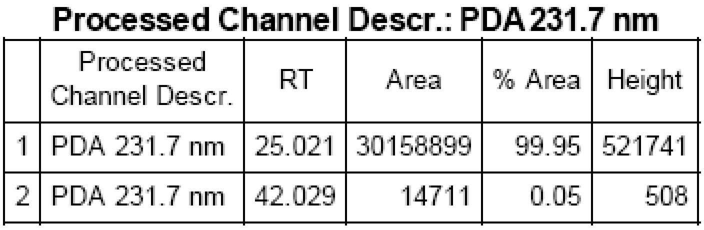
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 219.0 nm	18.870	54966725	98.12	1200408
2	PDA 219.0 nm	25.748	1055102	1.88	25464



Chiralpak AD, 80:20 hexane:*i*PrOH, 1mL/min, λ=220nm

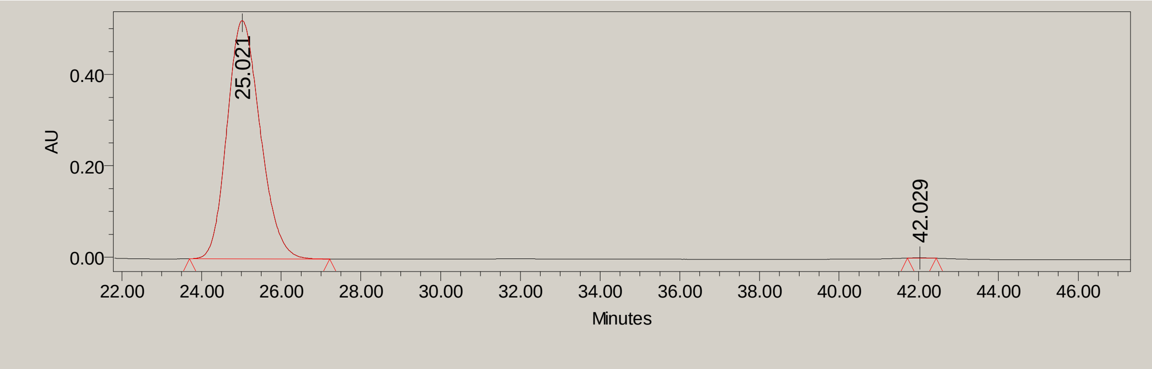


13b

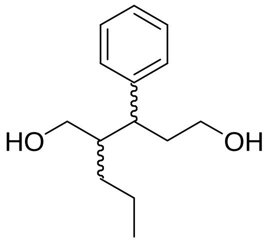


Processed Channel Descr.: PDA 231.7 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 231.7 nm	25.021	30158899	99.95	521741
2	PDA 231.7 nm	42.029	14711	0.05	508



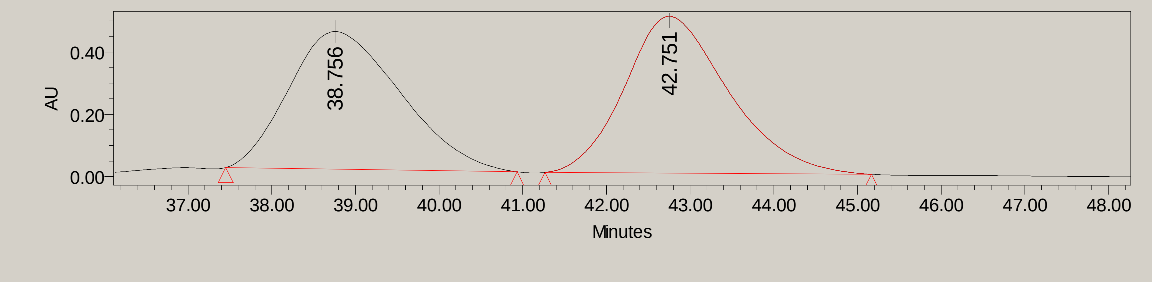
Chiralpak AS-H, 97:1:2 hexane:*i*PrOH:EtOH, 1mL/min, λ=209.8nm

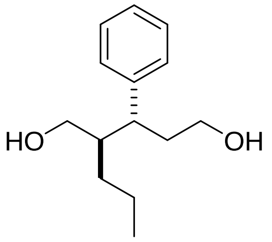


rac anti-**14b**

Processed Channel Descr.: PDA 209.8 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 209.8 nm	38.756	41090612	48.59	442221
2	PDA 209.8 nm	42.751	43473829	51.41	503991

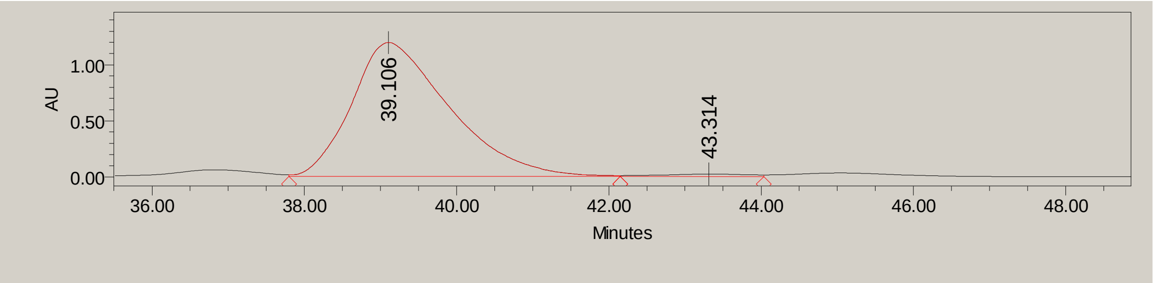




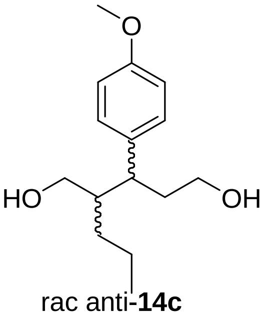
14b

Processed Channel Descr.: PDA 209.8 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 209.8 nm	39.106	106681934	98.35	1195454
2	PDA 209.8 nm	43.314	1792383	1.65	22088



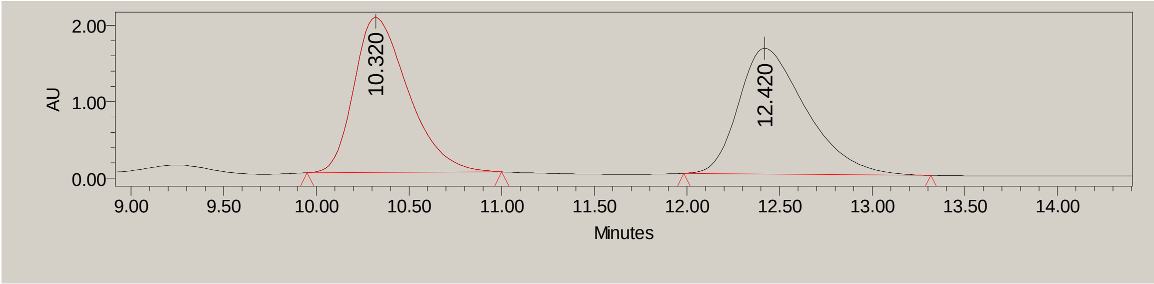
Chiralpak AS-H, 90:6:4 hexane:*i*PrOH:EtOH, 1mL/min, λ=228nm

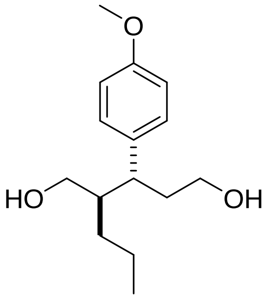


rac anti-**14c**

Processed Channel Descr.: PDA 228.6 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 228.6 nm	10.320	41232285	49.74	2030035
2	PDA 228.6 nm	12.420	41659925	50.26	1646428

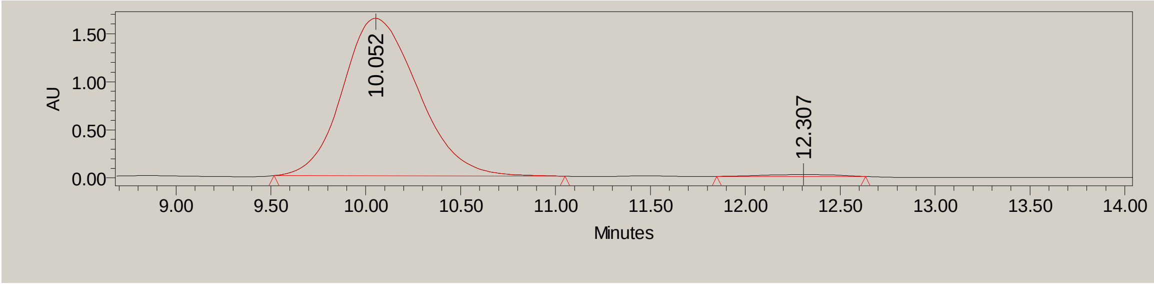




14c

Processed Channel Descr.: PDA 221.6 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 221.6 nm	10.052	45281806	98.84	1638843
2	PDA 221.6 nm	12.307	533079	1.16	20081



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