Supplementary Material (ESI) for Chemical Communications

Supplementary Information

Highly enantioselective addition of ketones to nitroolefins catalyzed by new thiourea-amine bifunctional organocatalysts

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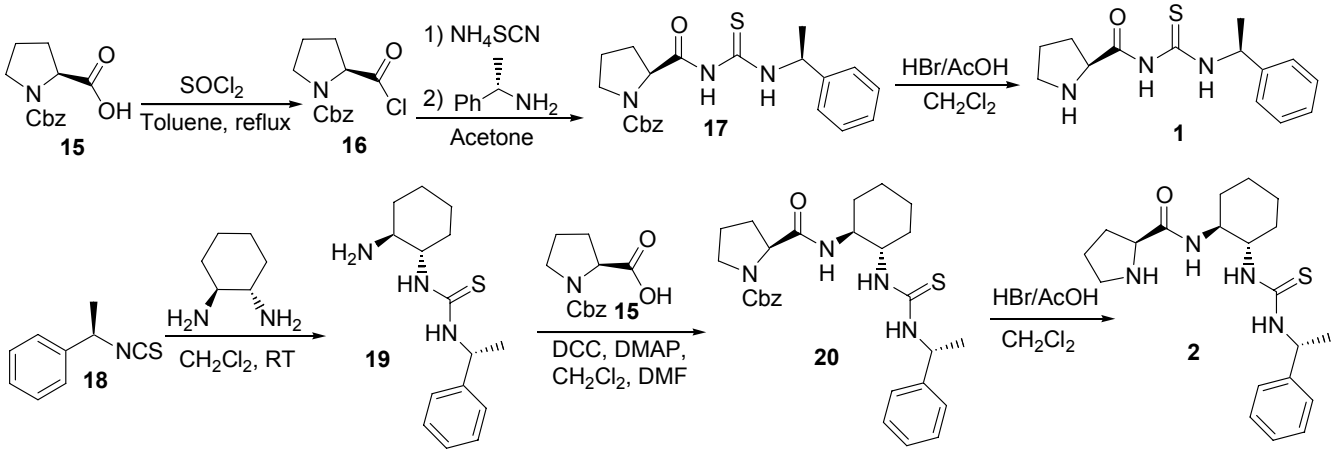
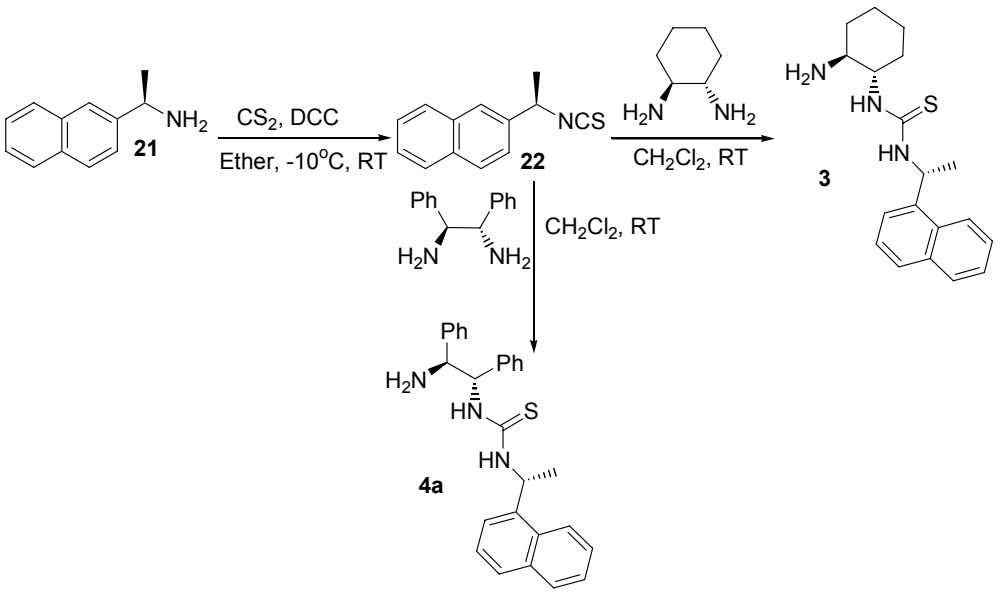
General: All solvents were purified by standard procedures and distilled prior to use. Reagents obtained from commercial sources were used without further purification. TLC chromatography was performed on precoated aluminium silica gel SIL G/UV_{254} plates (Marcherey, Nagel & Co.) or silica gel 60-F_{254} precoated glass plates (Merck). ^1H NMR spectra were recorded with Varian Unity 300. EI mass spectra were measured with a Finnigan MAT 95: Alpha AXP DEC station 3000-300LX; ESI mass spectra were recorded with a LCQ Finnigan spectrometer. High-resolution mass spectra were measured with a Bruker APEX IV 7T FT-ICR instrument. A Perkin-Elmer 241 polarimeter was used for optical rotation measurements.





Compound 16: To a solution of N-(benzyloxycarbonyl)-(*S*)-proline (**15**) (1.76 g, 7.06 mmol, 1eq) in dry toluene (20 ml) at room temperature was added dropwise an excess of $SOCl_2$ (1 ml, 1.64 g, 2 eq). The reaction mixture was stirred for 2 h at 80°C under nitrogen atmosphere. Evaporation of the solvent gave 1.89 g of product **16** as a light yellow oil and was used without further purification.

Compound 17: To a solution of ammonium thiocyanate (538.00 mg, 7.07 mmol, 1 eq) in anhydrous acetone (3 ml) under a nitrogen atmosphere, was dropwise added compound **16** (1.89 g, 7.06 mmol, 1 eq). The mixture was stirred for 20 min at 60°C and then a solution of (*S*)-α-methylbenzylamine (856.74 mg, 7.07 mmol, 901 ml, 1eq) in acetone (1.5 ml) was added dropwise. After the reaction mixture was stirred for 2 h at 65°C, it was poured into water (15 ml) and extracted with methylene chloride (3 x 15 ml). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness under reduced pressure. Purification of the residue by column chromatography (EtOAc / hexane, 1:1) afforded 886 mg (31%) of **17** as an yellow solid. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.50-1.53 (d, *J* = 7.2 Hz, 3H), 1.53-1.91 (m, 3H), 2.21-2.31 (m, 1H), 3.28-3.45 (m, 2H), 4.5 (m, 1H), 4.94-5.07 (m, 2H), 5.41-5.51 (q, *J* = 7.2 Hz, 1H), 7.10-7.31 (m, 3H), 7.32-7.37 (m, 7H), 10.89 (br. s, 1H, NH), 11.42 (br. s, 1H, NH) ppm. ESI-MS (positive ion): *m/z* = 434.1 $[M + Na]^+$, 844.7 $[2M + Na]^+$. ESI-MS (negative ion): *m/z* = 410.1 $[M - H]^-$.

Compound 1: HBr/ HOAc (200 µl, 33% HBr-HOAc) was dropwise added to a solution of **17** (100.00 mg, 0.24 mmol) in methylene chloride (1 ml) at 0°C. After stirring of the reaction mixture at 0°C for 30 min, and at room temperature for 1 hour, dry ether (2 ml) was added to precipitate the amine hydrobromide formed. The supernatant liquid was decanted and the solid was filtered and washed with ether. The product was then dissolved in water (1 ml) and treated with saturated

aqueous sodium bicarbonate to give the oil, which was extracted with ethyl acetate. The organic layer is then dried and concentrated under reduced pressure. Purification of the residue by column chromatography (EtOAc / hexane, 1:1) afforded 45.00 mg (67%) of **1** as a dark yellow solid. $[\alpha]^{20}_{D}$ = -54.5° (c = 0.33, $CHCl_3$). ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.51-1.53 (d, *J* = 6.6 Hz, 3H), 1.60-1.66 (m, 2H), 1.75-1.76 (m, 1H), 1.99-2.02 (m, 1H), 2.74-2.79 (m, 1H), 2.87-2.92 (m, 1H), 3.74-3.79 (dd, *J* = 9.0, 5.1 Hz, 1H), 5.44 (m, 1H), 7.29-7.38 (m, 5H), 10.82 (br, s, 1H) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 21.31, 25.91, 29.59, 46.49, 53.96, 59.91, 126.11, 127.30, 128.55, 141.91, 176.53, 178.01 ppm. EI-MS (70 eV); m/z (%): 277.2 (11) [M^+], 105.1 (20), 70.1 (100). ESI-MS (positive ion): *m/z* = 278.1 $[M + H]^+$. ESI-MS (negative ion): *m/z* = 276.1 $[M - H]^-$. HRMS (ESI): calcd. for $C_{14}H_{19}N_3OS$ $[M + H]^+$ 278.13216; found 278.13218.

Compound 19: (*R*)-1-Phenylethylisothiocyanate (**18**) (1.43 g, 8.75 mmol) was added over a period of 1 h to a stirred solution of (S,S)-1,2-diaminocyclohexane (1 g, 8.75 mmol) in dry dichloromethane (17 mL). The reaction mixture was stirred for a further 2 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on SiO_2 (EtOAc / EtOH, 3:1) to give **19** as a yellow solid in 61% (1.48 g). $[\alpha]_D^{20}$ = -92.5 (c = 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 0.99-1.26 (m, 4H), 1.41 (d, *J* = 6.6 Hz, 3H), 1.54-1.62 (m, 2H), 1.76-1.83 (m, 1H), 1.94-1.99 (m, 1H), 2.41-2.49 (m, 1H), 3.68-3.69 (m, 1H), 5.42-5.49 (m, 1H), 7.17-7.35 (m, 5H) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 22.30, 24.29, 24.42, 31.37, 34.40, 52.21, 54.20, 59.43, 125.97, 126.48, 128.12, 144.39, 181.57 ppm. ESI-MS (positive ion): *m/z* = 278.1 $[M + H]^+$, 554.9 $[2M + H]^+$. ESI-MS (negative ion): *m/z* = 276.1 $[M - H]^-$. HRMS (ESI): calcd. for $C_{15}H_{23}N_3S$ $[M + H]^+$ 278.16854; found 278.16866.

Compound 20: To a solution of **15** (0.70 g, 2.8 mmol, 1.3 eq), DMAP (52.90 mg, 0.43 mmol, 0.2 eq) and DCC (714.67 mg, 3.46 mmol, 1.6 eq) in CH_2Cl_2/DMF (2:1) was added compound **19** (600 mg, 2.16 mmol, 1 eq). The reaction mixture was stirred for 2 hours at ambient temperature. The urea which precipitated was removed by filtration. The organic layer was washed with saturated aqueous NH_4Cl (3 ml), water (3 ml) and brine and dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on SiO_2 (EtOAc / pentane, 4:1) to give **20** in 72% (795 mg) yield. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.05-1.31 (m, 6H), 1.35-1.38 (d, *J* = 7.2 Hz, 3H), 1.50-1.76 (m, 7H), 1.89-2.05 (m, 1H), 3.27-3.34 (m, 1H), 3.52-3.55 (m, 1H), 4.00-4.11 (m, 1H), 4.89-5.05 (m, 2H), 5.38-5.42 (m, 1H), 6.9 (br. s, 1NH), 7.12-7.54 (m, 10H), 7.98 (br. s, 2NH) ppm. ESI-MS (positive ion): *m/z* = 531.2 $[M + Na]^+$.

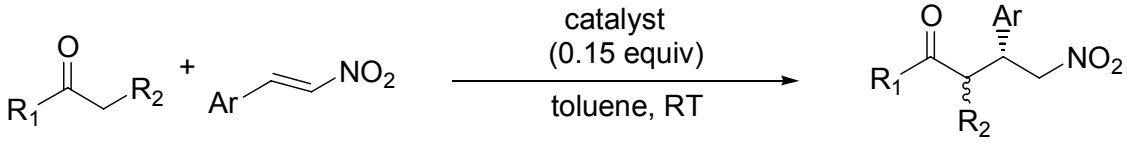
Compound 2: This compound was prepared from **20** by the same procedure as described above for **1**, to give **2** as a yellow solid in 83% (395 mg) yield. $[\alpha]^{20}_D$ = -80.0 (c = 0.42, $CHCl_3$). ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.13-1.24 (m, 5H), 1.36-1.38 (d, *J* = 6.0 Hz, 3H), 1.48-1.52 (m, 2H), 1.56-1.62 (m, 2H), 1.77-1.79 (m, 2H), 1.81-2.05 (m, 1H), 2.51-2.73 (m, 2H), 3.16-3.30 (m, 1H), 3.48-3.54 (m, 1H), 4.10-4.12 (m, 1H), 5.35-5.37 (m, 1H), 7.05 (br. s, NH), 7.16-7.42 (m, 5H), 7.78-7.90 (br. s, 2 NH) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 21.50, 23.74, 23.78, 24.81, 29.63, 31.35, 31.42, 45.94, 51.81, 52.08, 56.02, 59.94, 125.47, 125.95, 127.50, 143.88, 173.53, 181.42 ppm. ESI-MS (positive ion): *m/z* = 375.2 $[M + H]^+$, 398.2 $[M + Na]^+$, 748.9 $[2M + H]^+$, 770.9 $[2M + Na]^+$. HRMS (ESI): calcd. for $C_{20}H_{30}N_4OS$ $[M + H]^+$ 375.22131; found 375.22136.

Compound 22: To a solution of (R)-1-(1-naphtyl)ethylamine (**21**) (1 g, 5.8 mmol, 1 eq) in dry ether (5 ml) at –10 °C were added CS_2 (2.23 ml) and DCC (1.2 g, 5.8 mmol, 1 eq). The reaction mixture was allowed to warm slowly to room temperature over a period of 3 h and then was stirred for a further 12 h at room temperature. The thiourea which precipitated was removed by filtration and the solvent was subsequently removed under vacuum. The residue was taken up in ether and more of the thiourea was able to be removed by filtration. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on SiO_2 (EtOAc / hexane, 1:9) to give **22** (1.18 g, 95 %) as a colourless liquid. $[\alpha]^{20}_D$ = -126.0° (c = 0.592, acetone); ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.76-1.78 (d, *J* = 6.6 Hz, 3H), 6.02-6.09 (q, *J* = 6.7 Hz, 1H), 7.54-7.67 (m, 4H), 7.93-8.01 (m, 2H), 8.11-8.14 (d, *J* = 9 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 22.97, 53.34, 122,66, 122.94, 125.43, 125.99, 126.69, 128.72, 128.78, 129.17, 133.37, 135.36 ppm. EI-MS (70 eV); m/z (%): 213.1 (18) [M^+], 155.2 (100).

Compound 3: This compound was prepared from **22** and (S,S)-1,2-diaminocyclohexane in a manner analogous to **19** and was obtained as a light yellow solid in 71% (560 mg) yield. $[\alpha]^{20}_D$ = -124.1° (c = 0.61, $CHCl_3$). ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.12-1.26 (m, 5H), 1.53-1.61 (d, *J* = 6.9 Hz, 3H), 1.77-1.80 (m, 1H), 1.95-1.99 (m, 1H), 2.37-2.45 (m, 1H), 2.8-2.85 (m, 1H), 3.74-3.75 (m, 1H), 6.18-6.25 (q, *J* = 6.9 Hz, 1H), 7.20-7.23 (br. s, 1H, NH), 7.48-7.58 (m, 4H), 7.82-7.85 (d, *J* = 9.0 Hz, 1H), 7.90-7.95 (m, 1H), 8.12-8.19 (m, 1H) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 21.01, 24.22, 24.39, 31.32, 34.23, 54.31, 59.30, 122.55, 123.47, 125.35, 125.53, 126.03, 127.30, 128.49, 130.59, 133.36, 139.82, 181.5 ppm. ESI-MS (positive ion): *m/z* = 328.1 $[M + H]^+$, 654.9 $[2M + H]^+$. HRMS (ESI): calcd. for $C_{19}H_{25}N_3S$ $[M + H]^+$ 328.18419; found 328.18425.

Compound 4a: This compound was prepared from **22** and (1*S*,2*S*)-(-)-1,2-diphenylethylenediamine in a manner analogous to **19** and was isolated as a light yellow solid in 80% (850 mg) yield. $[\alpha]^{20}_{D}$ = -128.4° (c = 0.162, $CHCl_3$). ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.50-1.52 (d, *J* = 6.0 Hz, 3H), 1.65 (s, br, 2H, NH_2), 4.25 (br. s, 1H), 5.5 (br. s, 1H), 6.05 (br. s, 1H), 7.18-7.32 (m, 11H), 7.50-7.54 (m, 4H), 7.81(br. s, 1H), 7.91 (br. s, 1H), 8.12-8.14 (m, 1H), 8.22 (br. s, NH) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 20.64, 21.11, 40.04, 59.37, 62.50, 122.20, 123.27, 125.30, 125.45, 126.06, 126.52, 126.57, 126.79, 127.2, 127.04, 127.16, 127.60, 127.88, 128.43, 130.45, 133.30, 139.89, 143.11 ppm. ESI-MS (positive ion): *m/z* = 426.1 $[M + H]^+$, 850.9 $[2M + H]^+$. HRMS (ESI): calcd. for $C_{27}H_{27}N_3S$ $[M + H]^+$ 426.19985; found 426.19981.

Asymmetric Michael addition of ketones to nitroolefins



General procedure: To a stirred solution of catalyst (0.15 equiv) in toluene (0.5 mL) and ketone (10 equiv) at room temperature, was added water (2 equiv), acetic acid (0.15 equiv) and, after 5 minutes, nitroolefin (1 equiv). The reaction mixture was stirred at room temperature for the appropriate time. The solvent was evaporated and the residue was purified by TLC or chromatography on SiO_2-column (hexane/ethyl acetate, 1:1) to afford the desired product. The enantiomeric excess of the product was determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

Compounds **7**,[1,2] **11**,[2-4] **12** [2,3] and **13**[2,6,7] are known and our spectroscopic data are in agreement with published data. Relative and absolute configuration of the products **11-13** was determined by comparison with literature data: **11**,[2-4] **12** [2,3] and **13**[2,6,7]. The stereochemistry of γ-nitroketones **8-10** has been tentatively assigned by comparison to analogous compound **7**.

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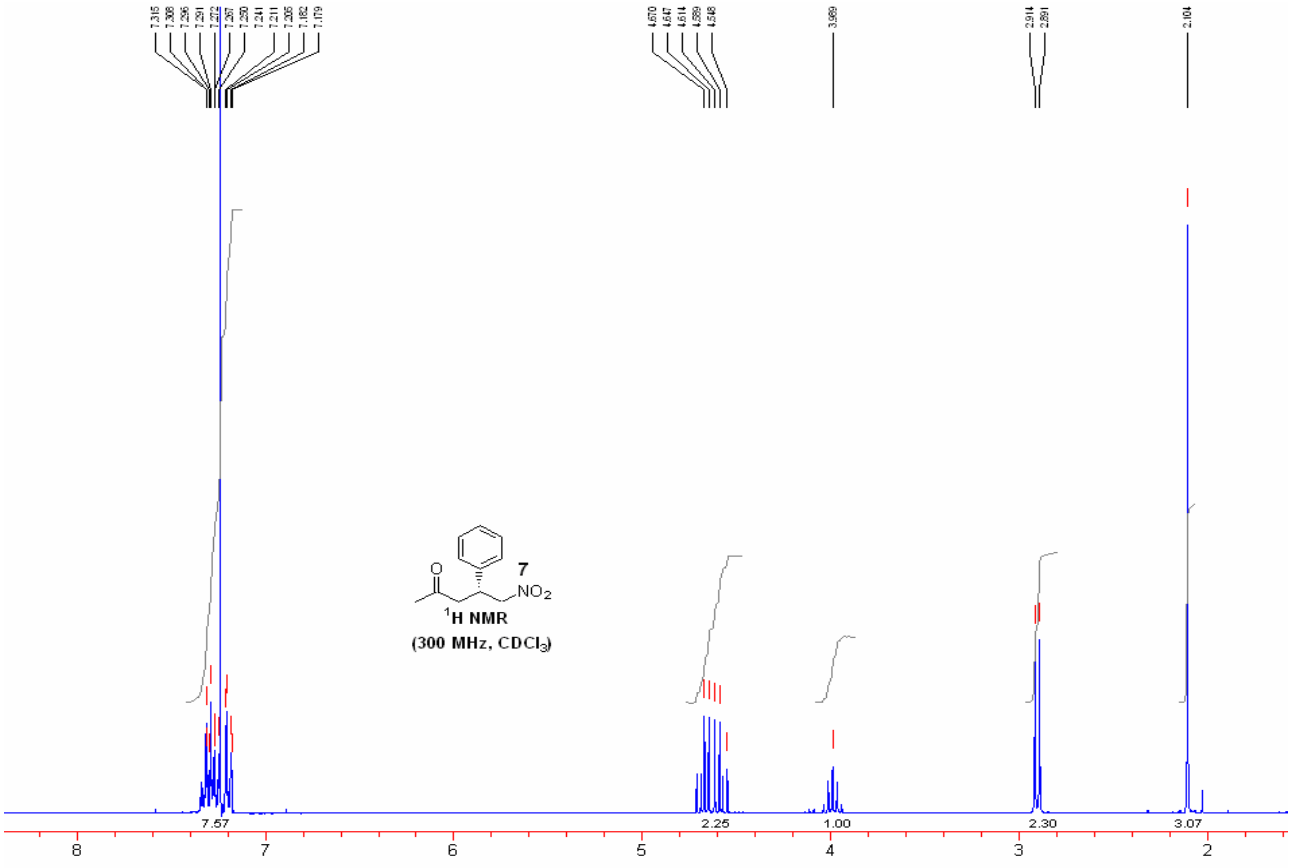

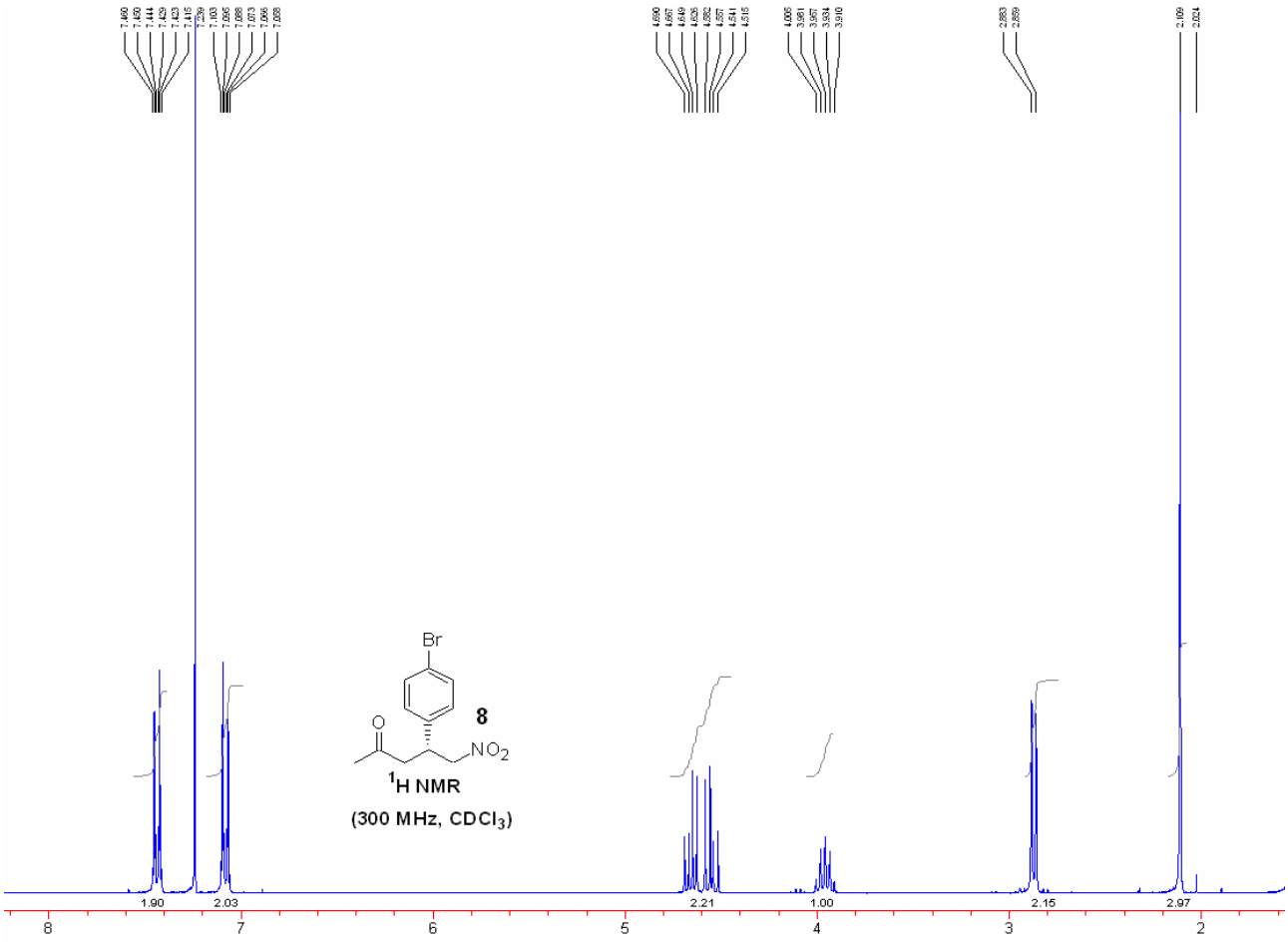
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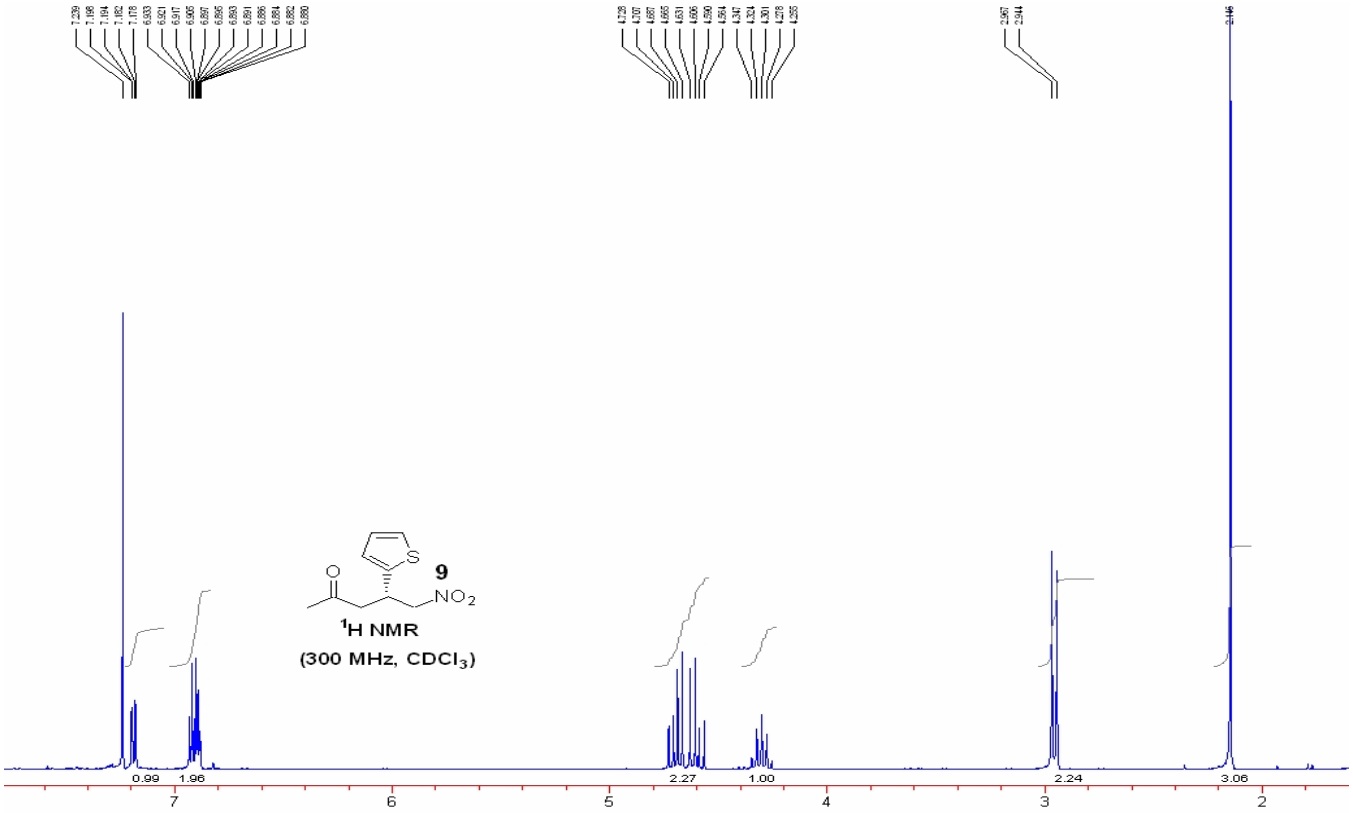
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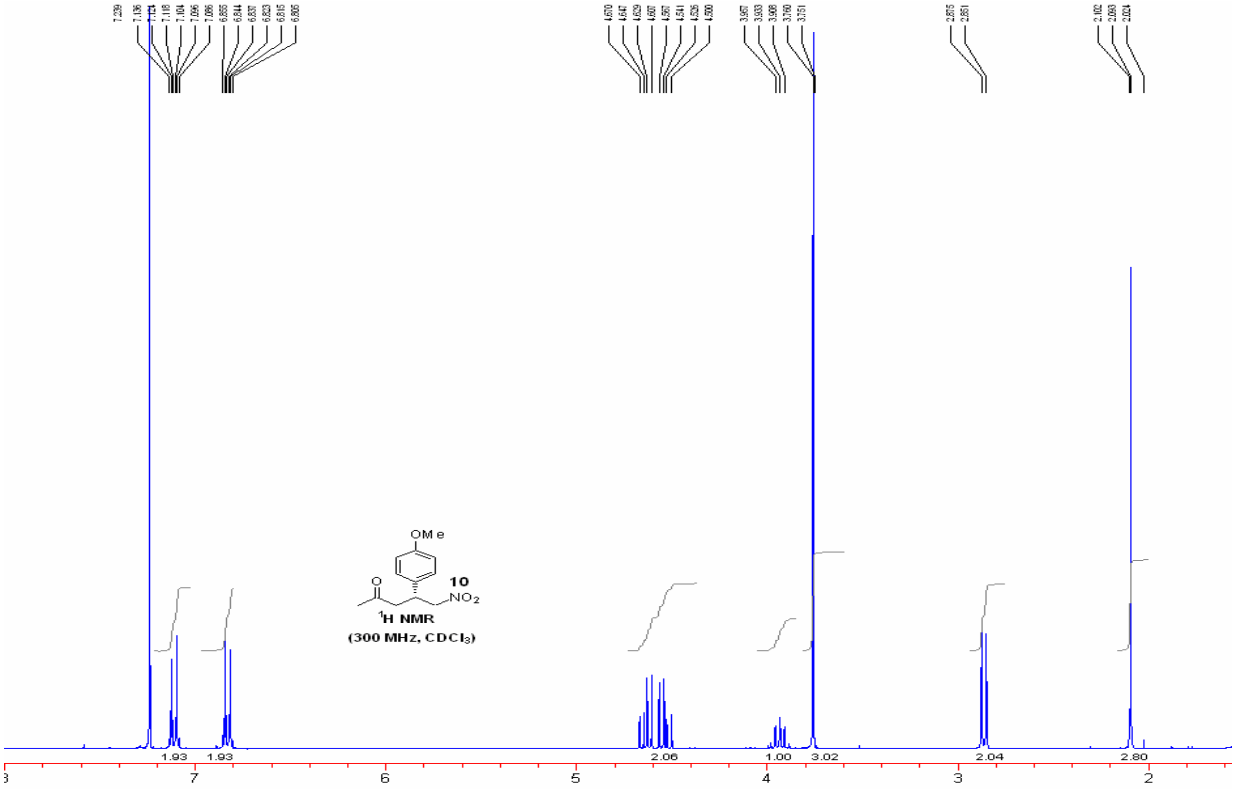
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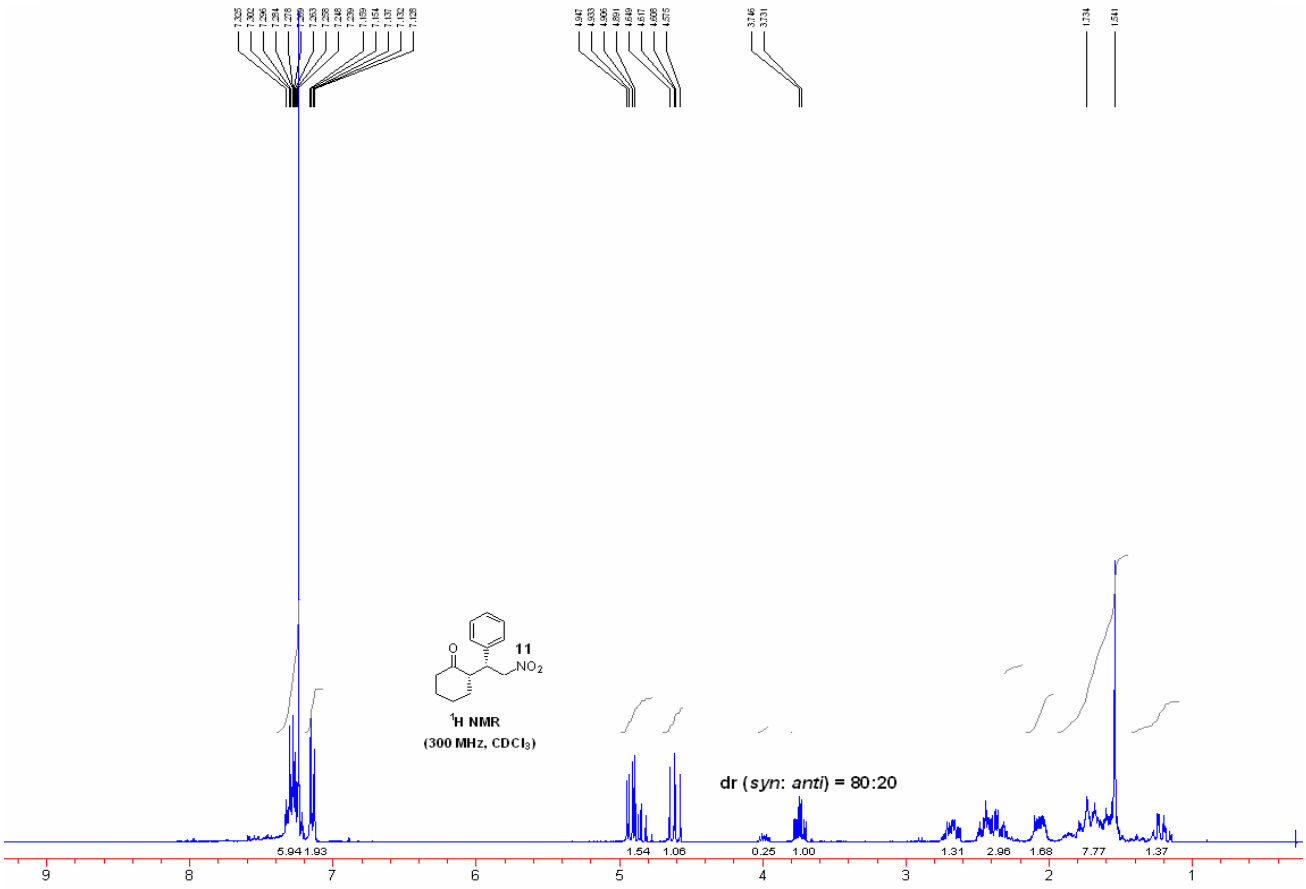
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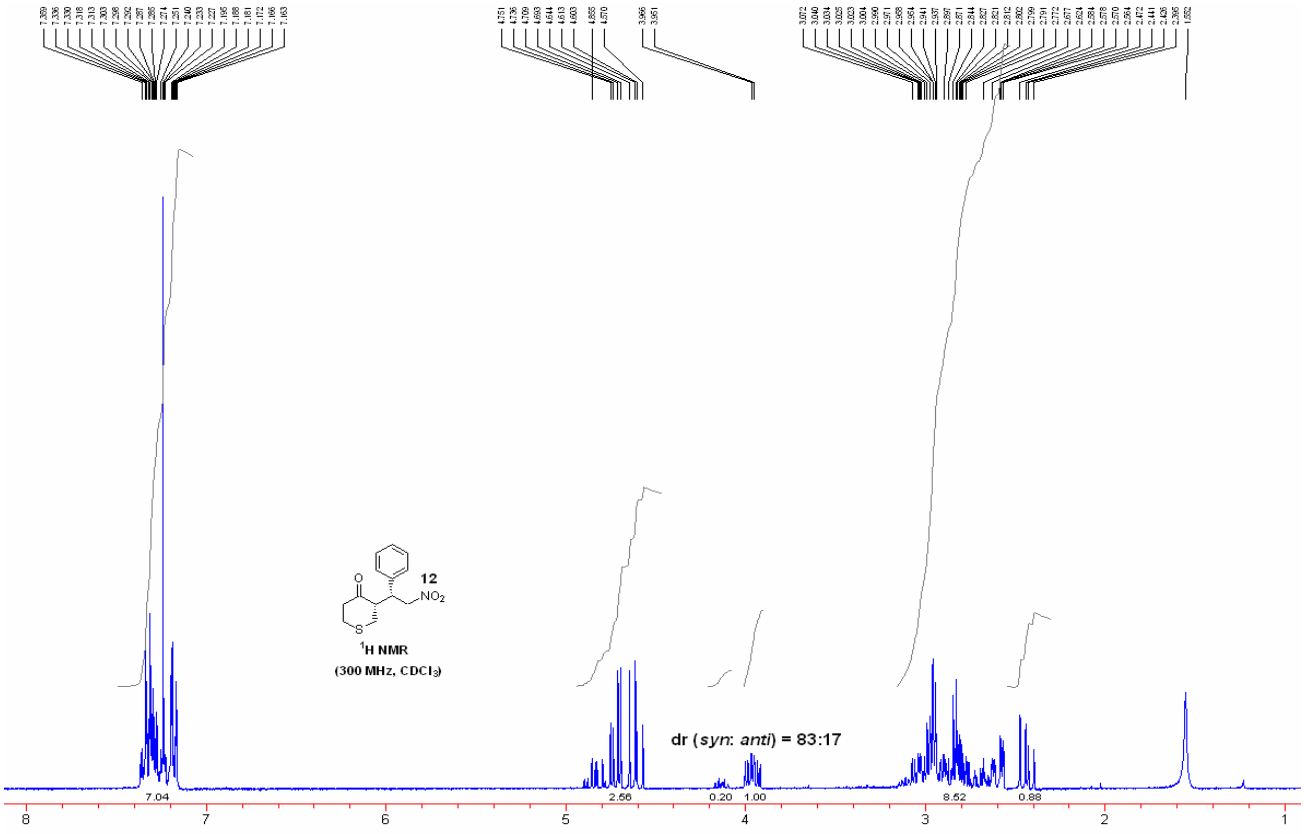

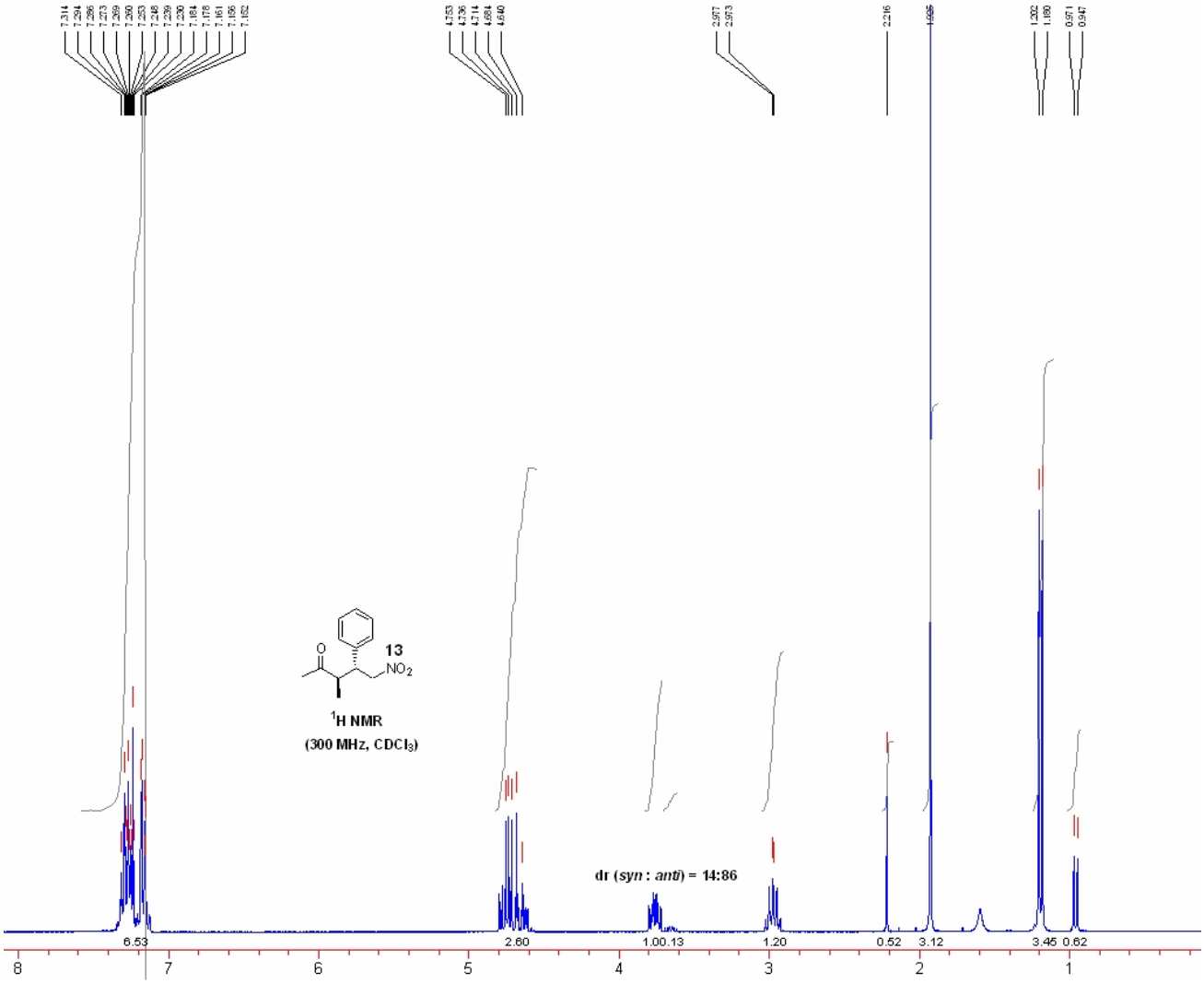

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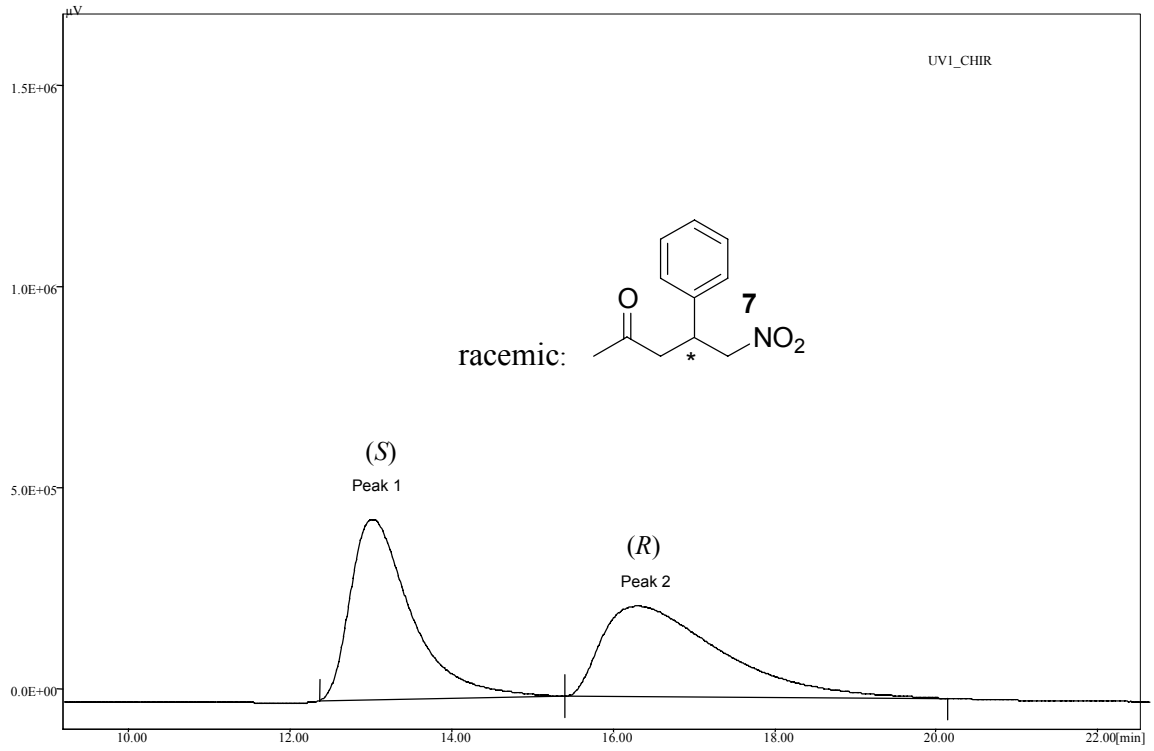

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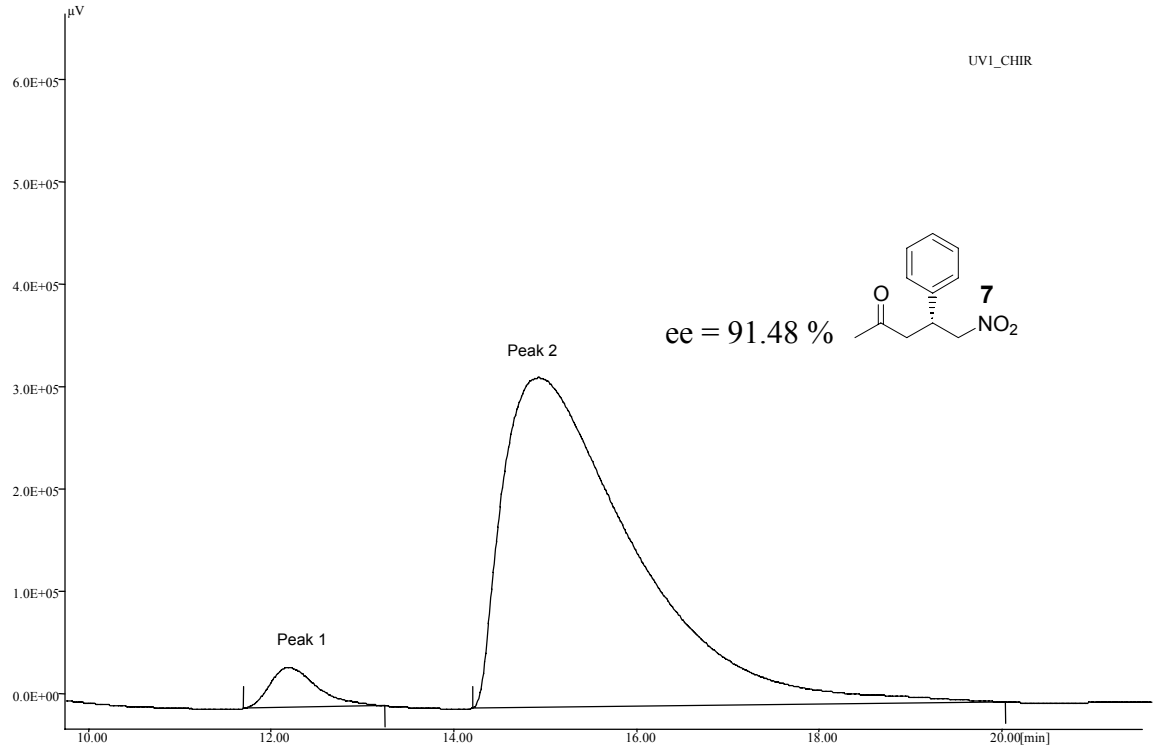

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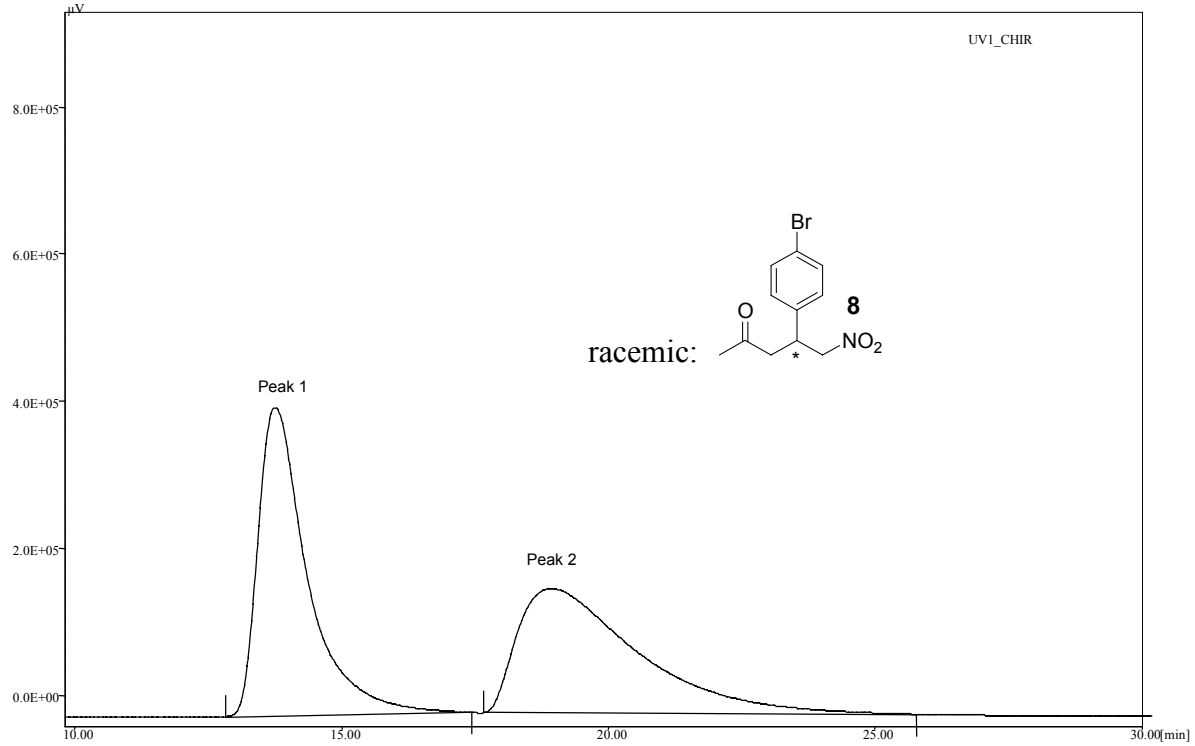

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Total Area of Peak = 52308631.50

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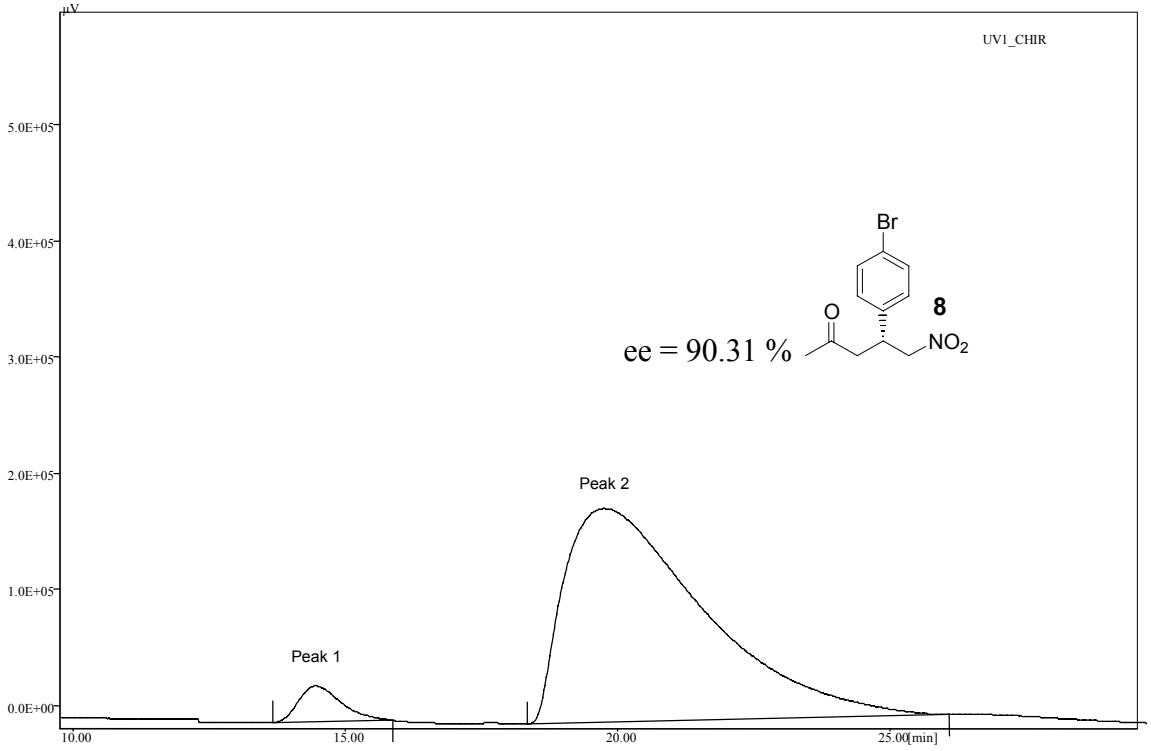

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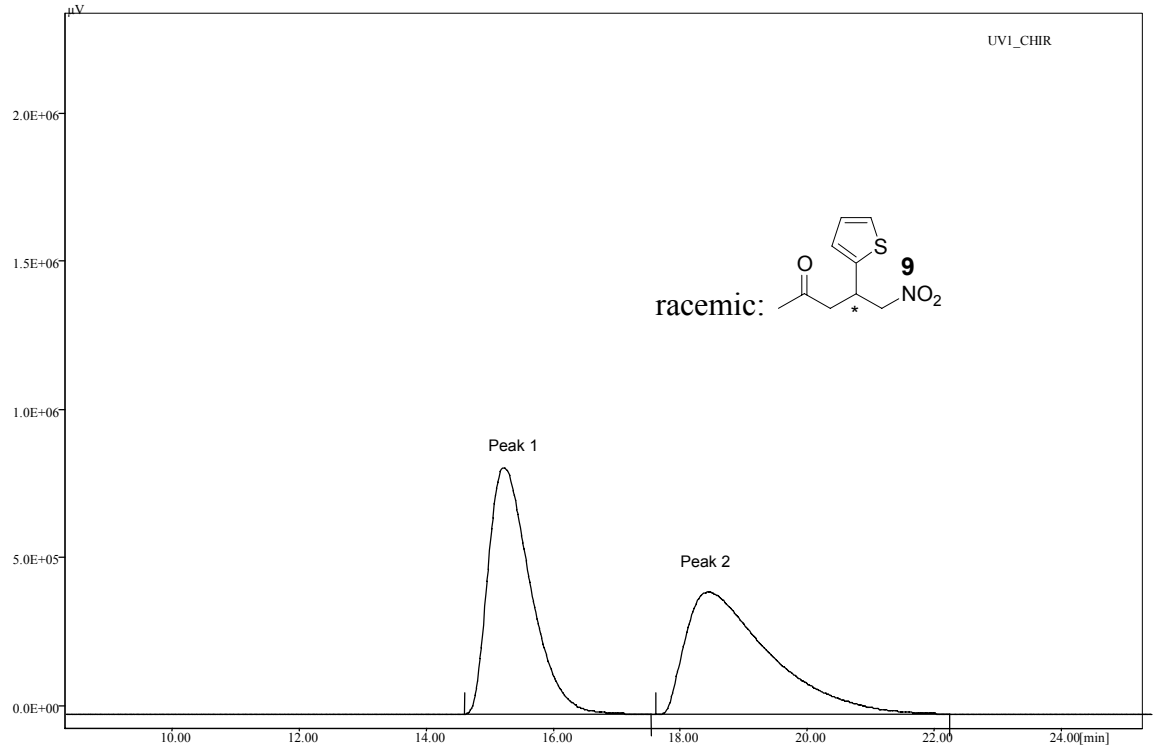

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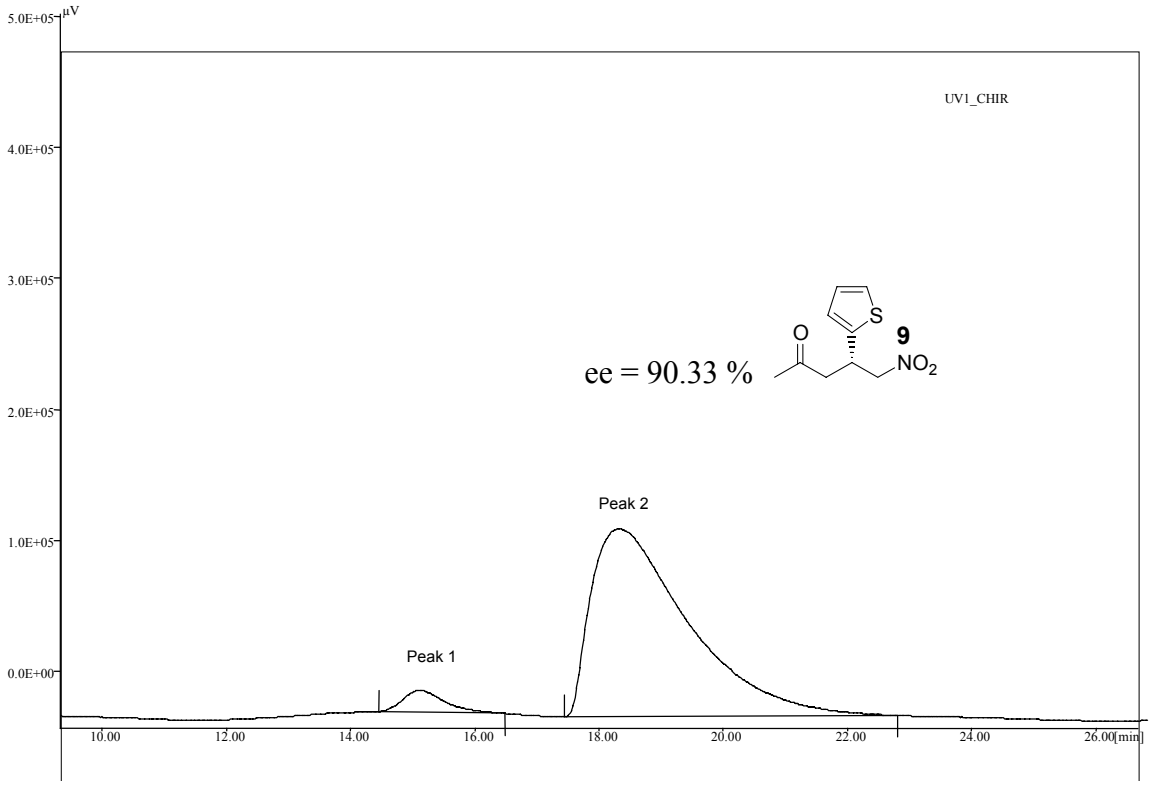

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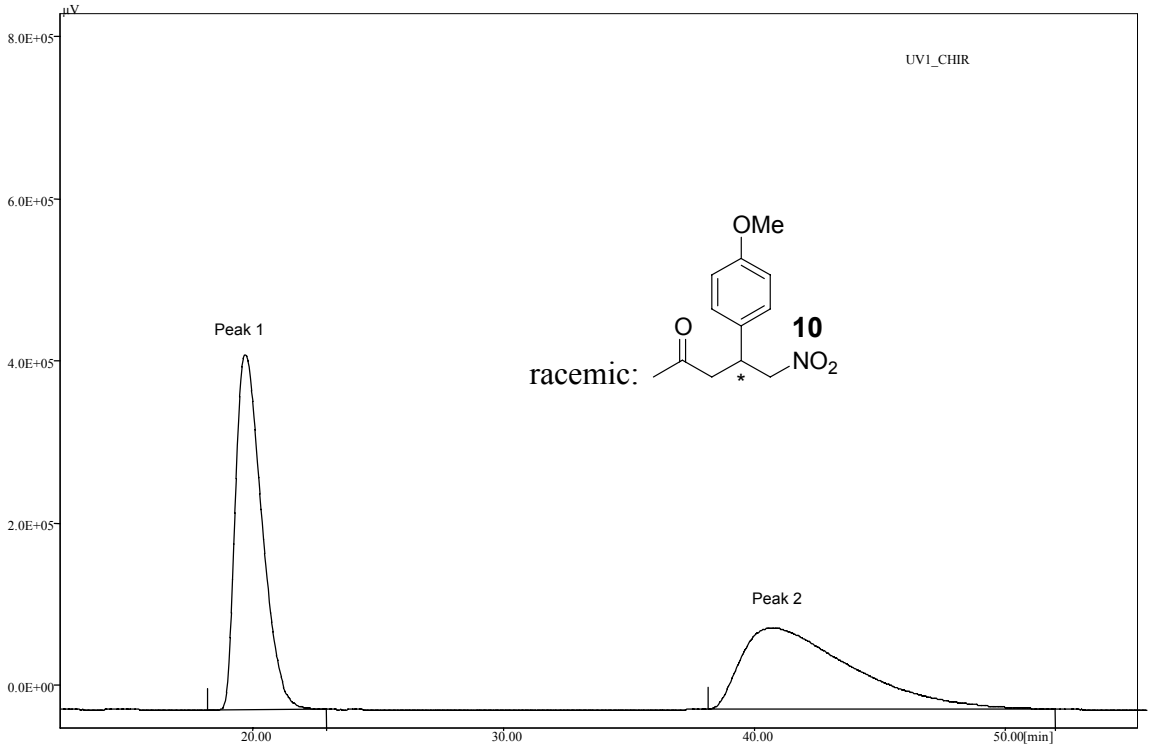

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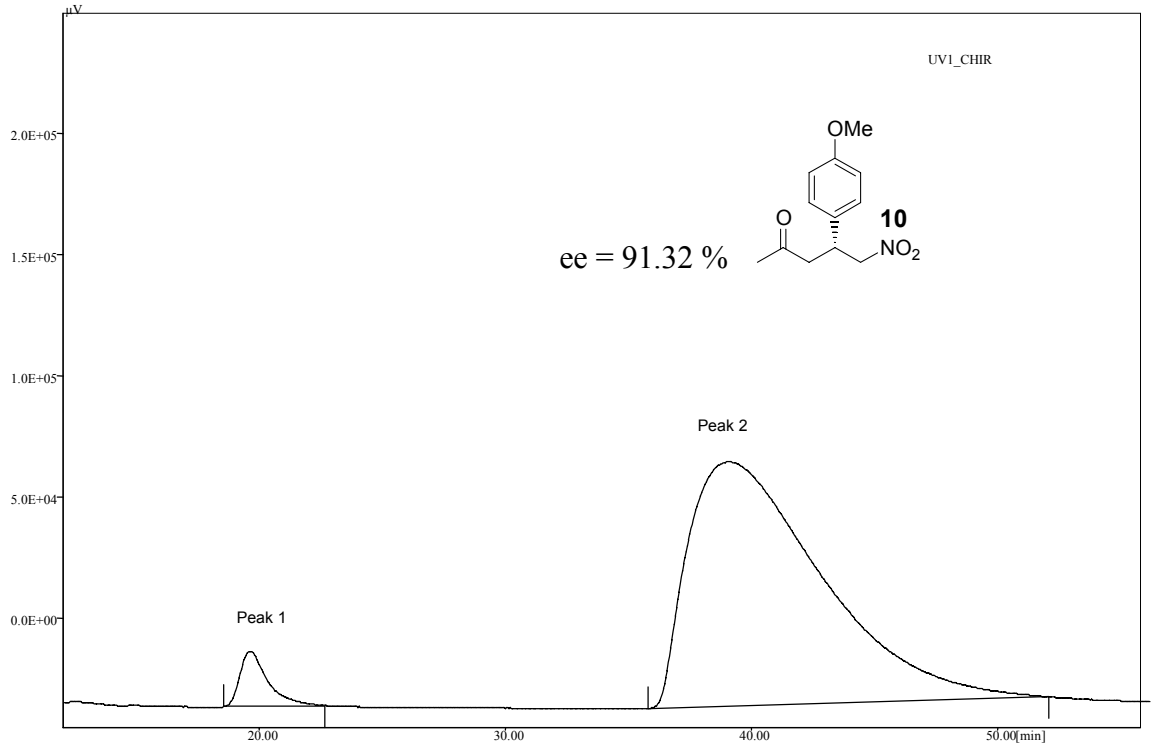
Total Area of Peak = 61042973.00

n-Hexane / 2-Propanol = 65 : 35, flow rate 1ml /min, λ = 210nm:

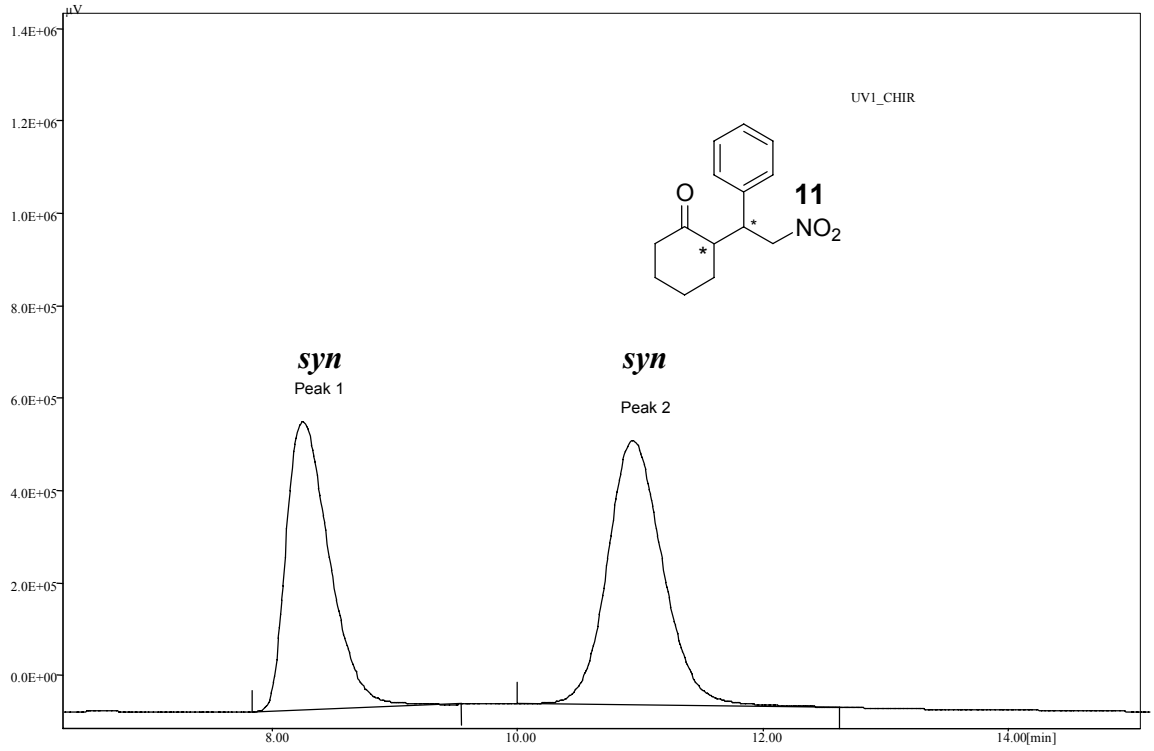


File name : W158-5001.CH3
Control Method : 65_35_1

#	Name	Rt	Area	%Area
1	Peak 1	19,59	1771690,999	4,505
2	Peak 2	38,81	37553990,004	95,495

Total Area of Peak = 39325681.00

n-Hexane / 2-Propanol = 65 : 35, flow rate 1ml /min, λ = 210nm:

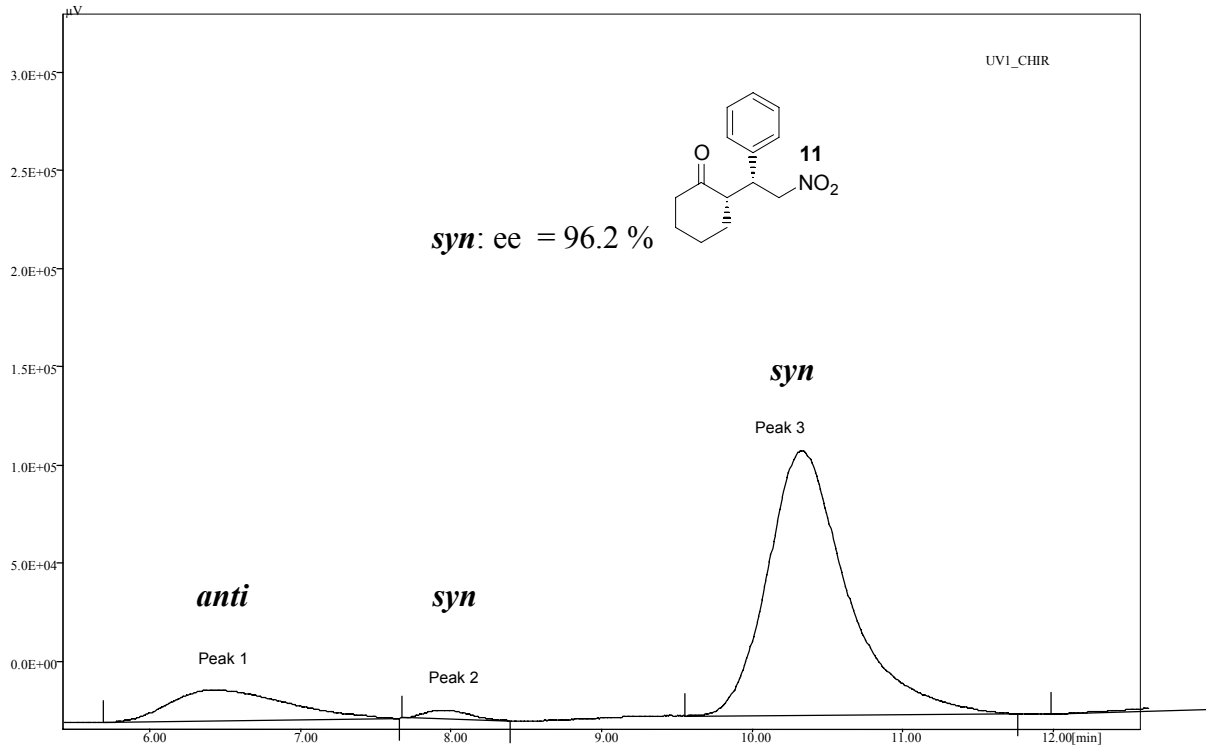


File name : DY50-5001.CH3
Control Method : 65_35_1

#	Name	Rt	Area	%Area
1	Peak 1	8,23	14924240,500	46,056
2	Peak 2	10,90	17480325,000	53,944

Total Area of Peak = 32404565.50

n-Hexane / 2-Propanol = 65 : 35, flow rate 1ml /min, λ = 210nm:

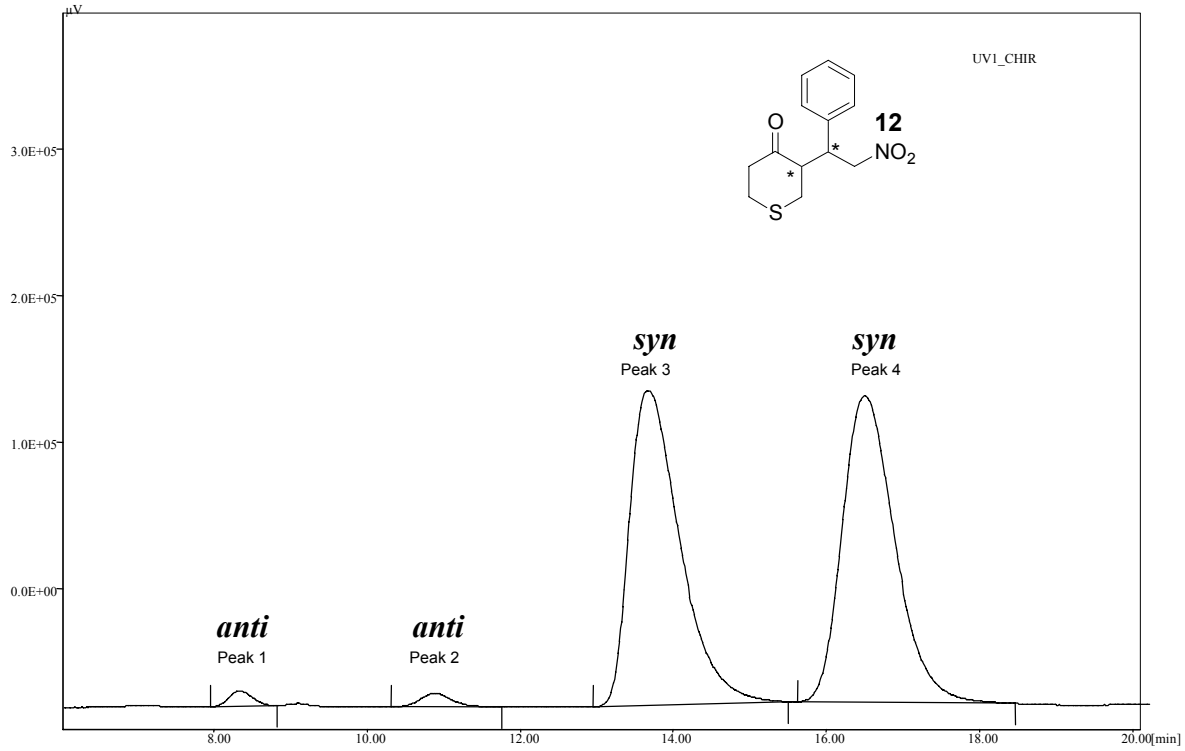


File name : W160-5001.
Control Method : 65_35_1

#	Name	Rt	Area	%Area
1	Peak 1	6,41	836394,750	13,922
2	Peak 2	7,92	95127,000	1,583
3	Peak 3	10,29	4910319,500	81,733

Total Area of Peak = 6007751.75

n-Hexane / 2-Propanol = 65 : 35, flow rate 1ml /min, λ = 210nm:

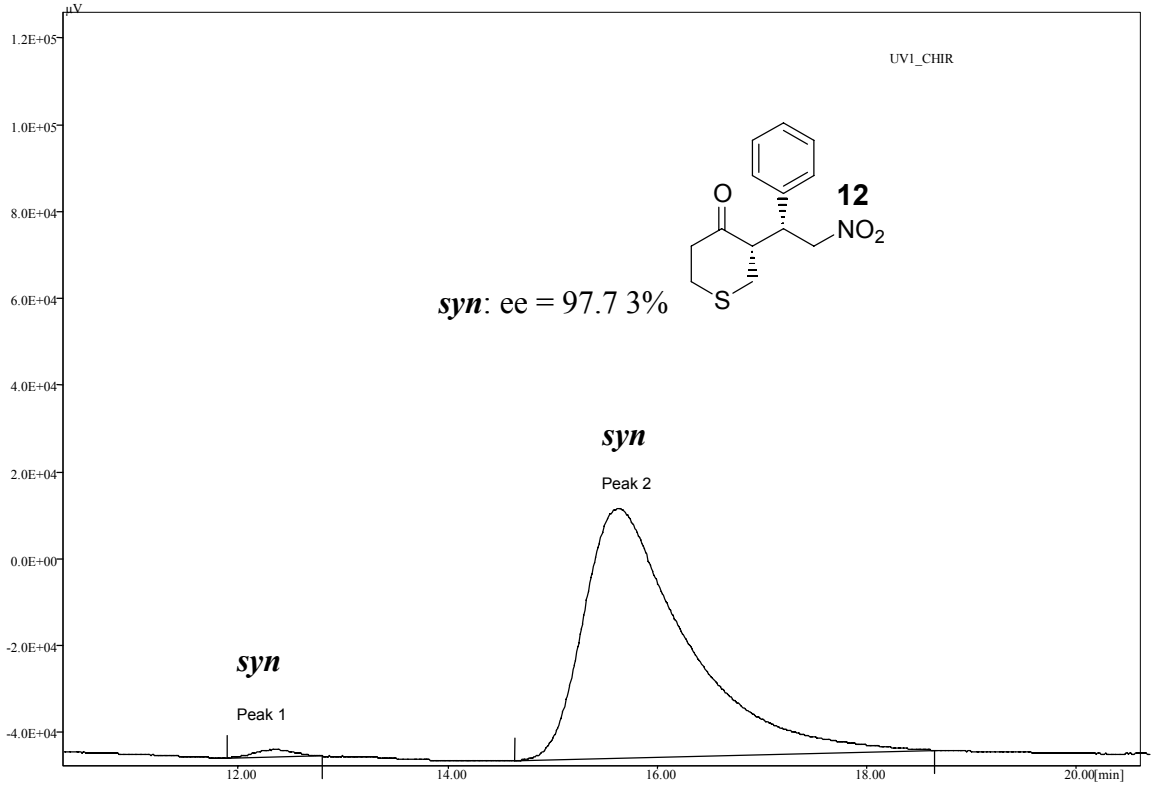


File name : DY49-5001
Control Method : 65_35_1

#	Name	Rt	Area	%Area
1	Peak 1	8,32	218656,250	1,101
2	Peak 2	10,86	262687,000	1,322
3	Peak 3	13,60	9613460,250	48,388
4	Peak 4	16,40	9772635,499	49,189

Total Area of Peak = 19867439.00

n-Hexane / 2-Propanol = 65 : 35, flow rate 1ml /min, λ = 210nm:

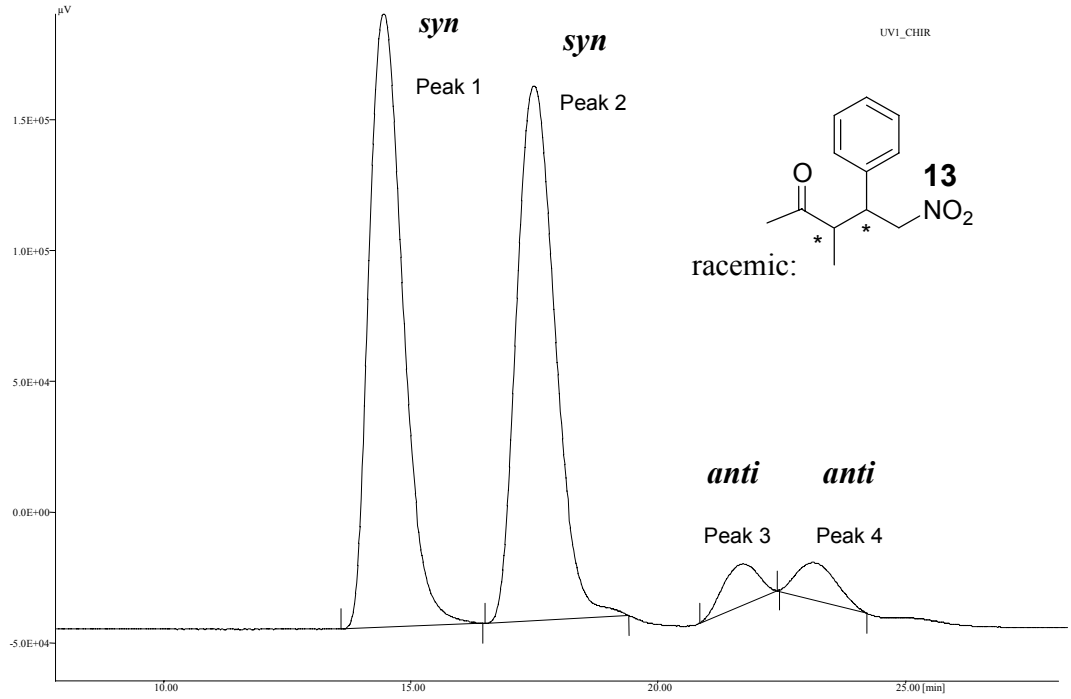


File name : W166-5001.CH3
Control Method : 65_35_1

#	Name	Rt	Area	%Area
1	Peak 1	12,32	44709,500	1,136
2	Peak 2	15,58	3889612,500	98,864

Total Area of Peak = 3934322.00

n-Hexane / 2-Propanol = 90 : 10, flow rate 1ml /min, λ = 210nm:

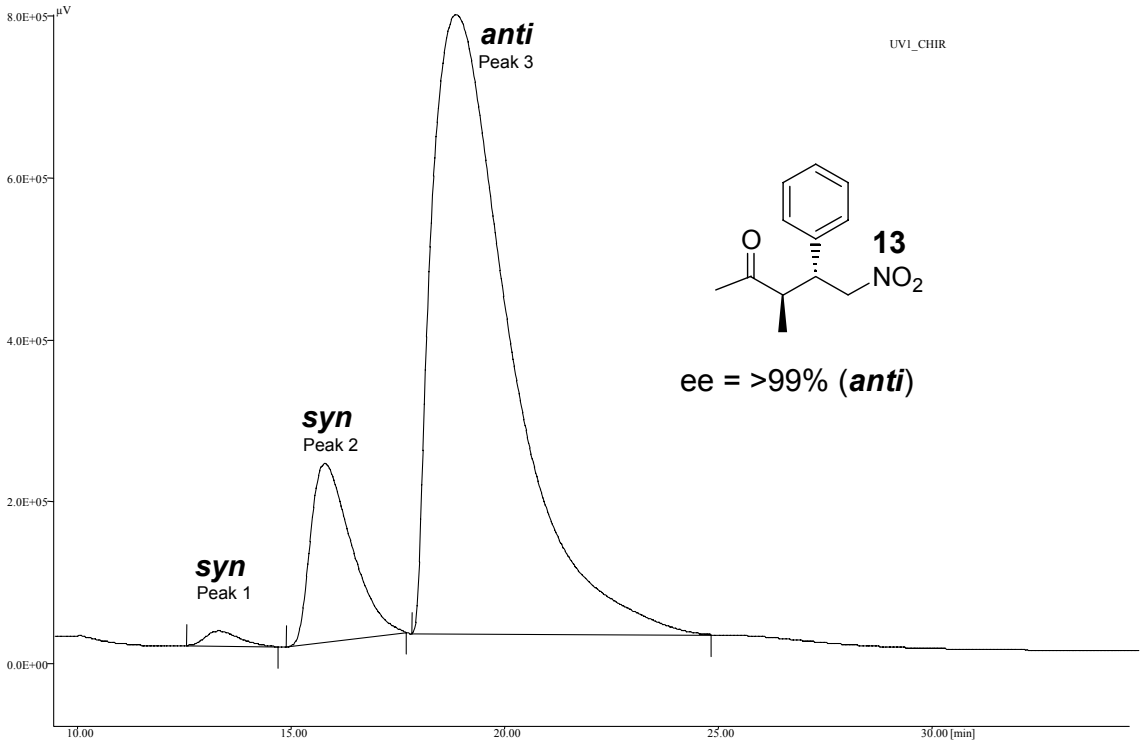


File name : DY555003.CH3
Control Method :90-10-1M

#	Name	Rt	Area	%Area
1	Peak 1	14,38	10881549,500	46,84
2	Peak 2	17,39	10755176,999	46,30
3	Peak 3	21,60	790241,750	3,40
4	Peak 4	22,98	801878,500	3,45

Total Area of Peak = 23228846.75

n-Hexane / 2-Propanol = 90 : 10, flow rate 1ml /min, λ = 210nm:

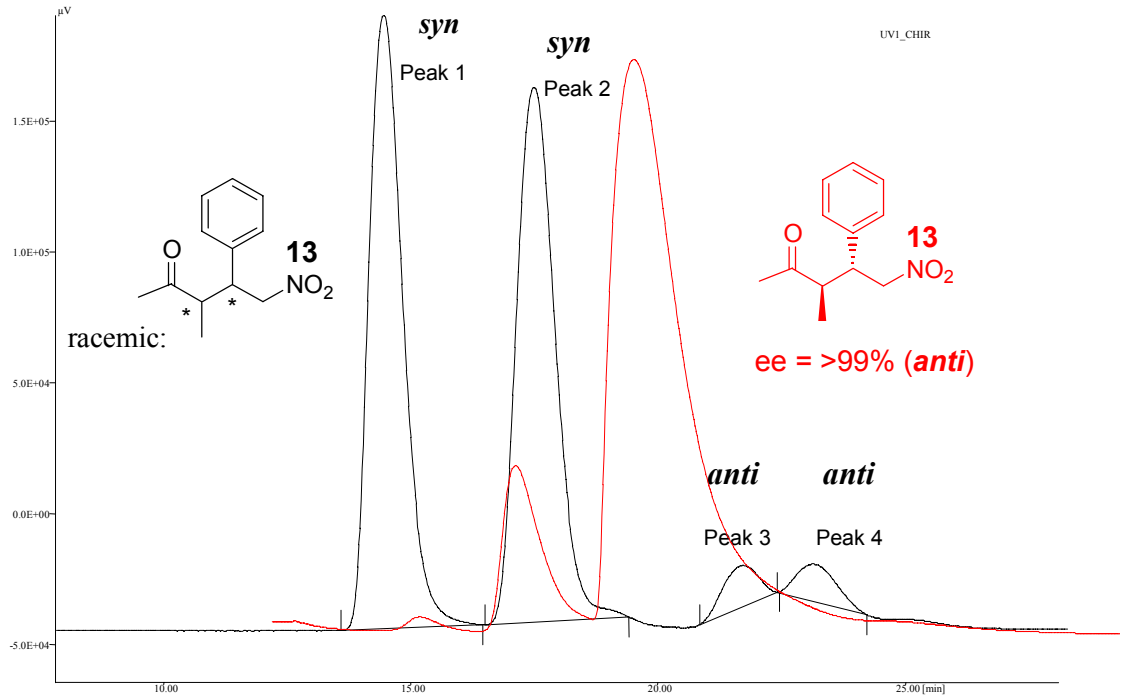


File name : W2435003.CH3
Control Method :90-10-1M

#	Name	Rt	Area	% Area
1	Peak 1	13,26	993024,750	0,90
2	Peak 2	15,72	14232402,750	12,88
3	Peak 3	18,77	95310326,998	86,23

Total Area of Peak = 110535754.50

n-Hexane / 2-Propanol = 90 : 10, flow rate 1ml /min, λ = 210nm:



ESI-MS experiment for the enamine intermediate 4a´: