Supporting information

Picolylamine as an Organocatalyst Template for Highly Diastereo- and Enantioselective Aqueous Aldol Reactions

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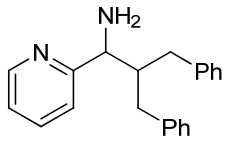
General Information: Commercial reagents were used as received from Sigma-Aldrich. Routine monitoring of reactions were performed by thin-layer chromatography (TLC) using precoated plates of silica gel 60 F_{254} and visualized under ultraviolet irradiation (254 nm). Column chromatography separations were performed by with silica gel 60 (0.040-0.063 mm). Petroleum ether with a boiling point range of 60-80 °C was used. Organic extracts were dried over anhydrous sodium sulfate. Evaporation of solvent was performed at reduced pressure. Chemical shifts (δ) were reported in parts per million (ppm) downfield from tetramethylsilane (TMS= 0) or relative to $CHCl_3$ (7.26 ppm) for ^1H NMR. Multiplicities are abbreviated as: (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet). Coupling constants are expressed in Hz. FT-IR spectra were obtained on Nicolet Avatar 370 thermonicolet spectrometer. MS data was measured on a Bruker Daltonics HCT Ultra. HRMS were recorded on a Brukar micrOTOF instrument with an ionization potential of 70 eV with ESI positive mode. The enantiomeric excess was determined by HPLC using a Chiralpak AS-H or OD-H column with *n*-heptane and *i*-propanol as eluents.

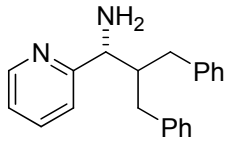


rac-**2**

Procedure for the Synthesis of Racemic PicAm (2)

A mixture of hydroxylammonium chloride (3.0 equiv, 3.33 g, 48.0 mmol) and Et_3N (3.0 equiv, 6.69 mL, 48.0 mmol) in EtOH (53 mL) was stirred at room temperature for 30 min.[1] The corresponding ketone (1.0 equiv, 4.82 g, 16.0 mmol) was then added. After heating under reflux for 8 h, the solvent was removed by rotary evaporation and the residue was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give the crude oxime as a brown oil. Without further purification, the crude oxime (1.0 equiv, 5.06 g, 16.0 mmol) was added to EtOH (70 mL) with NH_4OAc (1.3 equiv, 1.64g, 20.8 mmol) and NH_4OH (59 mL, 25% v/v in H_2O). This solution was heated at reflux and zinc powder (5.0 equiv, 5.05 g, 80.0 mmol) was added portion wise over 2 h every 15 min. After refluxing for an additional 8 h, the reaction mixture was cooled to room temperature and concentrated

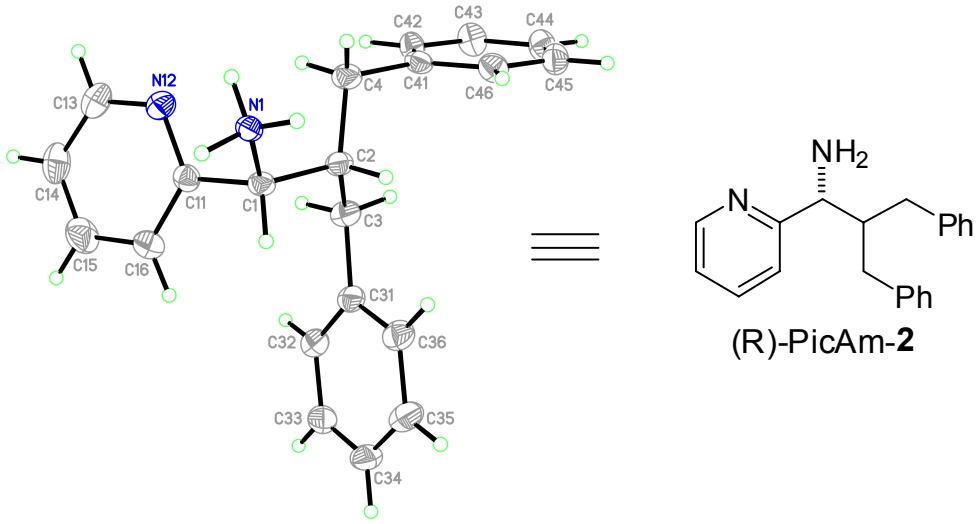
NaOH was added until reaching a pH of 12. After filtration through celite and washing with diethyl ether, the layers were separated. The aqueous layer was further extracted with Et_2O. The organic phases were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated. After column chromatography, EtOAc/pet ether (1:4), racemic PicAm (**2**) was afforded as a pure viscous oil (65% yield).[1]



(R)-PicAm **2**

Resolution of Racemic PicAm (2)

To a stirred solution of unnatural tartaric acid, (S,S)-D-tartaric acid (0.50 equiv, 1.59 g, 10.6 mmol), in a boiling mixture of THF/CH_3CN 1:5 (180 mL), was added racemic PicAm (**2**) (1.0 equiv, 6.4 g, 21.2 mmol).[2] The mixture was gently refluxed (~70 ^oC) for 1 h. During this time some precipitation of the salt may occur and is normal. The precipitated salt color, in the solution, is brown. The oil bath was then turned off. In this way the solution was allowed to come to room temperature over ~1 h. After stirring for an additional 1-2 h at room temperature the precipitate was filtered giving 5.14 g of off-white to brown colored solid. This material was crystallized a total of four more times but now from EtOH/H_2O (95:5 vol-to-vol ratio). The EtOH used was Sigma-Aldrich cat. # 32205. Each EtOH/H_2O crystallization was performed by dissolving the salt into the minimum volume of 95% ethanol sufficient to dissolve the salt at 70 ^oC. This was followed by gentle reflux for 1 h, then cooling to 25 ^oC in a controlled manner over 1 h. This was followed by 2 h of stirring at 25 ^oC, followed by filtration. Repeat three more times. After the five resolutions (1 with THF/CH_3CN and 4 with EtOH/H_2O), high vacuum drying furnished the (R)-PicAm **2** salt as a white powder (26% weight recovery, 2.10 g, 99% ee) [Note: salt ratio undetermined]. Before use in reactions, the salt was first converted to the corresponding free amine by addition to EtOAc (75 mL) and NaOH (75 ml, 0.5 M). Further extraction (EtOAc, 50 mL x 2) of the basic aqueous layer, was followed by organic extract combination and concentration (Rot Vap) providing the free amine [(R)-PicAm **2**] as an oil. This free amine was then dissolved in MeOH and unnatural tartaric acid ((S,S)-D-tartaric acid, 1.0 equiv) was added, this 1:1 salt of (R)-PicAm **2** was used for the reactions as indicated. The absolute configuration was determined by x-ray analysis of the 1:1 salt. The absolute configuration of D-tartaric acid is known, (S,S), and relative to this PicAm **2** was of the R configuration.



We thank Dr. Michael Bolte (Institute for Inorganic Chemistry, J.-W.-Goethe-Universität, Frankfurt/Main, Germany) for paid X-ray crystal structure service.

The ee of PicAm-**2** was determined by chiral HPLC (Chiral OD-H, *i*-PrOH/heptane 5/95, flow rate = 1 mL/min, λ = 254 nm): t_{major}= 10.4 min, t_{minor} = 13.8 min.
Free amine (R)-PicAm **2**: ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.78 (br s, 2H), 2.45-2.50 (m, 2H), 2.57-2.62 (m, 2H), 2.70-2.76 (m, 1H), 3.97 (d, *J* = 3.66 Hz, 1H), 7.02-7.26 (m, 12H), 7.54-7.58 (m, 1H), 8.55 (d, *J* = 5.04 Hz, 1H); ^{13}C NMR (400MHz, $CDCl_3$) (ppm): 34.5, 36.8, 49.2, 56.6, 121.6, 125.7, 125.8, 128.2, 128.3, 129.0, 129.1, 136.0, 141.0, 148.7, 163.9. FT-IR (R)-PicAm Naphthalenesulfonic acid salt: (KBr), ν_{max}: 3441, 3025, 2924, 1593, 1495, 1473, 1181, 1042 cm^{-1}; MS (EI), *m/z* (relative intensity): 325 $[M+Na]^+$, 100%), 286 [M- NH_2] 19.5%; HRMS (ESI-TOF) calculated for $C_{21}H_{22}N_2$ $[M+H]^+$ 303.1856; found: 303.1868.

General Procedure for Racemic Aldol Formation (3-12)
The following procedure can be used to synthesize all of the racemic aldol products shown in this manuscript. To a solution of water and methanol 4.0 mL (1:1 v/v) was added 2-picolylamine (0.40 mmol), aldedyde (2.0 mmol, 1.0 equiv), and ketone (1.5 to 3.3 equiv). This stirred at room temperature for 12-24 h, TLC was used to determine complete reaction. R_f values for each compound can be found in the experimental procedures found below for all enantioenriched aldol products. The reactions were quenched with a saturated solution of NH_4Cl (20-25mL) and the resulting mixture was extracted with EtOAc (30 mL x 2). The combined organic layers were separated, dried over anhydrous sodium sulfate, evaporated to give the crude aldol product. Column chromatography on silica gel using EtOAc/pet ether (1:9) gave the pure aldol product (70-90% yield). Although not examined further in this manuscript, tetrahydro-4H-thiopyran-4-one (see main text, Scheme 1, X= S), also readily provided the racemic aldol product under these conditions. Although all reactions were by-product free, this was not true for benzaldehyde, not examined in this manuscript, which afforded the expected

aldol product and ~20 % of the corresponding elimination product under the above noted conditions.

General Procedure for Enantioselective Aldol Reaction (compounds 3-12)
Four general reaction conditions were found to be optimal depending on the ketone examined. The limiting reagent was the aldehyde, which was always used at the 0.50 mmol scale:

Catalyst mixture A: The 2,4-dinitrobenzenesulfonic acid (2,4-DNBSA) salt of (S)-PicAm **2** (MW=550.58, 13.8 mg, 0.025 mmol, 5.0 mol%)

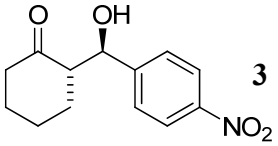
Catalyst mixture B: The 1-naphthalenesulfonic acid (1-NSA) salt of (R)-PicAm **2** (MW=510.65, 12.8 mg, 0.025 mmol, 5.0 mol%).

Catalyst mixture C: The 1:1 salt of (S,S)-D-tartaric acid (unnatural tartaric acid) and (R)-PicAm **2** (MW=452.50, 11.3 mg, 0.025 mmol, 5.0 mol%). Sodium dodecylbenezenesulfonate (NaDBSA) (MW= 348.48, 8.7 mg, 0.025 mmol, 5.0 mol%) was additionally added.

Catalyst mixture D: The 1:1 salt of (R,R)-L-tartaric acid (natural tartaric acid) and (S)-PicAm **2** (MW=452.50, 11.3 mg, 0.025 mmol, 5.0 mol%). Sodium dodecylbenezenesulfonate (NaDBSA) (MW= 348.48, 8.7 mg, 0.025 mmol, 5.0 mol%) and 2,4-dinitrobenzenesulfonic acid (2,4-DNBSA) (MW=248.17, 6.2 mg, 0.025 mmol, 5 mol%) were additionally added.

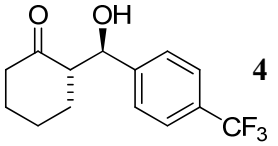
One of the above catalyst mixtures (A, B, C, or D) was added to distilled water or brine (1.0 mL, 0.5 M). The ketone (1.66 mmol, 3.3 equiv) and aldehyde (0.5 mmol, 1.0 equiv) were then added. This mixture was stirred and heated at 45 ^{o}C for the indicated reaction time. [NOTE: extension of the indicated reaction times can be detrimental to the diastereoselectivity (α-keto epimerization), do not extend the reaction time.] The reaction was quenched by simply adding water (10 mL) and EtOAc (10 mL). The resulting aqueous layer was extracted a total of three times with EtOAc (10 mL x 3). The combined organic extracts were dried (Na_2SO_4), evaporated (Rot Vap), and then exposed to high vacuum for 1 h. The resulting crude product was examined by ^{1}H NMR to determine the dr. The crude material was then purified by column chromatography (EtOAc/ petroleum ether). [Note: During column chromatography almost all of the aldol products epimerize. The α-keto-product epimerization likely occurs via enol induced processes on the acidic silica gel. Attempts to 'neutralize' the silica gel using eluent doped with Et_3N or pretreatment of the silica gel with NH_4OH treated solvent were helpful but did not completely and satisfactorily suppress the noted epimerization. As a consequence ^{1}H NMR data obtained after chromatography shows a lower dr than before chromatography.] The after chromatography ^{1}H NMR data supplied here is only provided to confirm the purity of the aldol products. The chromatography purified aldol products were then examined by HPLC to determine their *ee*. The relative and absolute configurations of the products were determined by comparison with the known ^{1}H NMR

data and by direct comparison with the literature available HPLC data for aldol products **3-11**, while product **12** is reported here for the first time.



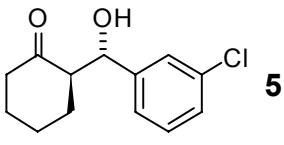
3

2-(hydroxy(4-nitrophenyl)methyl)cyclohexanone (3)[3]
Catalyst mixture A was used. The reaction medium was brine.
4-Nitrobenzaldehyde: 75.5 mg, 0.50 mmol, 1.00 equiv
Cyclohexanone: 0.17 mL, 1.65 mmol, 3.30 equiv
Reaction time: 16 h; flash column chromatography: (EtOAc/Pet ether = 10:90); yield: 92%; The ee was determined by chiral HPLC (Chiral OD-H, *i*-PrOH/heptane 5/95, flow rate = 1 mL/min, λ = 210 nm): t_{major}= 24.2 min, t_{minor}= 36.5 min, ee = 99%, dr = 22:1 (*anti*/*syn*), R_f= 0.29 EtOAc/pet ether (2:3).
^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.26-1.41 (m, 1H), 1.54-1.66 (m, 3H), 1.82 (m, 1H), 2.10 (m, 1H), 2.36-2.49 (m, 1H), 2.53-2.61 (m, 2H), 4.11 (br s, 1H), 4.90 (d, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 2H), 8.23 (d, *J* = 8.6 Hz, 2H).



4

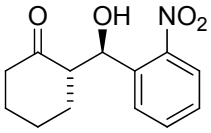
2-((4-(trifluoromethyl)phenyl)(hydroxy)methyl)cyclohexanone (4)[4,5]
Catalyst mixture A was used. The reaction medium was water.
4-(Trifluoromethyl)benzaldehyde: 67 uL, 0.50 mmol, 1.00 equiv. Note this aldehyde was stored over crucible crushed KOH.
Cyclohexanone: 0.17 mL, 1.65 mmol, 3.30 equiv
Reaction time: 22 h; flash column chromatography (EtOAc/Pet ether = 7:93); yield: 88%; The ee was determined by chiral HPLC (Chiral OD-H, *i*-PrOH/heptane 5/95, flow rate = 0.5 mL/min, λ = 219 nm): t_{major}= 23.5 min, t_{minor}= 30.7 min, ee = 99%, dr = 12:1 (*anti/syn*), R_f= 0.31 EtOAc/pet ether (1:4).
^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.25-1.39 (m, 1H), 1.48-1.73 (m, 3H), 1.79-1.83 (m, 1H), 2.07-2.14 (m, 1H), 2.35-2.39 (m, 1H), 2.46-2.51 (m, 1H), 2.57-2.64 (m, 1H), 4.05 (s, 1H), 4.84 (d, J = 8.6 Hz, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.1 Hz, 2H).



5

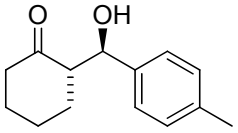
2-((3-chlorophenyl)(hydroxy)methyl)cyclohexanone (5)[6]
Method C was used. The reaction medium was water.
3-Chlorobenzaldeyde: 56 uL, 0.50 mmol, 1.00 equiv
Cyclohexanone: 0.17 mL, 1.65 mmol, 3.30 equiv
Reaction time: 40 h; flash column chromatography (EtOAc/pet ether = 7:93); yield: 82%; The ee was determined by chiral HPLC (Chiral OD-H, *i*-PrOH/heptane 5/95, flow rate =

1 mL/min, λ = 210 nm): t_{major}= 14.1 min, t_{minor}= 10.9 min, ee = 95%, dr = 5.5:1 (*anti/syn*), R_f= 0.36 EtOAc/pet ether (1:4).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20–1.30 (m, 1 H), 1.43–1.75 (m, 4 H), 1.99–2.07 (m, 1 H), 2.23–2.55 (m, 3 H), 3.93 (s, 1 H), 4.70 (d, *J* = 8.7 Hz, 1 H), 7.08–7.23 (m, 4 H).



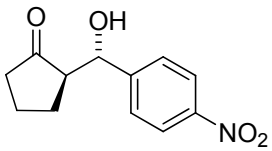
6

2-(hydroxy(2-nitrophenyl)methyl)cyclohexanone (6)[7]
Catalyst mixture A was used. The reaction medium was water.
2-Nitrobenzaldehyde: 75.5 mg, 0.50 mmol, 1.00 equiv
Cyclohexanone: 0.17 mL, 1.65 mmol, 3.30 equiv
Reaction time: 20 h; flash column chromatography (EtOAc/Pet ether = 10:90); yield: 84%; The ee was determined by chiral HPLC (Chiral OD-H, *i*-PrOH/heptane 5/95, flow rate = 1 mL/min, λ = 210 nm): t_{major}= 14.9 min, t_{minor}= 18.9 min, ee = 98%, dr = 30:1 (*anti/syn*), R_f= 0.43 EtOAc/pet ether (2:3).
^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.53-1.82 (m, 4H), 1.83-1.86 (br d, *J* = 12.1 Hz, 1H), 1.2.04-2.12 (m, 1H), 2.30-2.38 (m, 1H), 2.42-2.48 (m, 1H), 2.73-2.80 (m, 1H), 4.04 (br s, 1H), 5.44 (d, *J* = 8.4 Hz, 1H), 7.40-7.45 (m, 1H), 7.61-7.65 (m, 1H), 7.75-7.77 (m, 1H), 7.82-7.84 (m,1H).



7

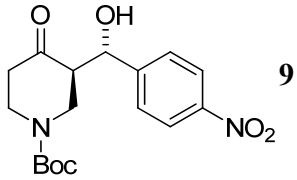
2-(hydroxy(p-tolyl)methyl)cyclohexanone (7)[7]
Catalyst mixture A was used. The reaction medium was brine.
p-Tolylaldehyde: 58 uL, 0.50 mmol, 1.00 equiv
Cyclohexanone: 0.17 mL, 1.65 mmol, 3.30 equiv
Reaction time: 24 h; flash column chromatography (EtOAc/Pet ether = 3:97); yield: 55%; The ee was determined by chiral HPLC (Chiral AS-H, *i*-PrOH/heptane 5/95, flow rate = 0.5 mL/min, λ = 210 nm): t_{major}= 22.5 min, t_{minor}= 26.9 min, ee = 96%, dr = 8:1 (*anti/syn*), R_f= 0.52 EtOAc/pet ether (2:3).
^{1}H NMR (400 MHz, $CDCl_3$) (ppm):1.18-1.38 (m, 1H), 1.50-1.70 (m, 3H), 1.72-1.82 (m, 1H), 2.03-2.14 (m, 1H), 2.34 (s, 3H), 2.35 (td, *J* = 13.2, 6.0 Hz, 1H), 2.43-2.51 (m, 1H), 2.54-2.66 (m, 1H), 3.91 (d, *J* = 2.7 Hz, 1H) 4.75 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.18 (dd, *J* = 17.1, 8.4 Hz, 4H).



8

2-(hydroxy(4-nitrophenyl)methyl)cyclopentanone (8)[4,8]
Catalyst mixture B was used. The reaction medium was water.
4-Nitrobenzaldeyde: 75.5 mg, 0.50 mmol, 1.00 equiv
Cyclopentanone: 0.14 mL, 1.65 mmol, 3.30 equiv

Reaction time: 16 h; flash column chromatography (EtOAc/Pet ether = 7:93); yield: 81%. The ee was determined by chiral HPLC (Chiral AS-H, *i*-PrOH/heptane 20/80, flow rate = 0.5 mL/min, λ = 254 nm): t_{major}= 31.5 min, t_{minor}= 41.1 min, ee = 92%, dr = 1.2:1 (*anti/syn*), R_f= 0.43 EtOAc/pet ether (2:3). The *syn*-diasteromer had an ee of 89%.
^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.54-2.02 (m, 4H), 2.27-2.45 (m, 3H), 4.76 (s, 1H), 4.84 (d, *J* = 9.2 Hz, 1H), 7.50-7.55 (m, 2H), 8.19-8.23 (m, 2H).

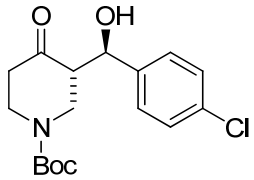


9

***tert*-Butyl 3-(hydroxy(4-nitrophenyl)methyl)-4-oxopiperidine-1-carboxylate (9)**[9]
Catalyst mixture C was used. The reaction medium was water.
4-Nitrobenzaldeyde: 75.5 mg, 0.50 mmol, 1.00 equiv
Tert-butyl 4-oxopiperidine-1-carboxylate: 328 mg, 1.65 mmol, 3.30 equiv
Reaction time: 33 h; flash column chromatography (EtOAc/Pet ether = 7:93); yield: 82%. The ee was determined by chiral HPLC (Chiral AS-H, *i*-PrOH/heptane 5/95, flow rate = 1 mL/min, λ = 280 nm): t_{major} = 45.1 min, t_{minor} = 51.1 min, ee = 98%, dr = 16:1 (*anti/syn*).

Catalyst mixture D was also examined. The reaction medium was brine.
4-Nitrobenzaldeyde: 75.5 mg, 0.50 mmol, 1.00 equiv
Tert-butyl 4-oxopiperidine-1-carboxylate: 328 mg, 1.65 mmol, 3.30 equiv
Reaction time: 35 h; flash column chromatography (EtOAc/Pet ether = 7:93); yield: 81%; ee = 96%, dr = 33:1

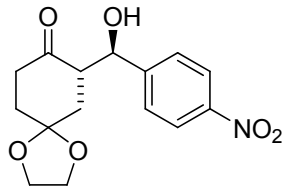
R_f= 0.26 EtOAc/pet ether (2:3).
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (br s, 9H), 2.52 (br s, 2H), 2.76 (br s, 1H), 2.93 (t, *J* = 11.8 Hz , 1H), 3.27 (br s, 2H), 3.85 (br s, 2H), 4.18 (br s, 1H), 4.96 (d, *J* = *7.8* Hz, 1H, *anti*), 5.48 (br s, 1H, *syn*), 7.56 (d, *J* = *7.2* Hz, 2H), 8.24 (d, *J* = 7.0 Hz, 2H).



10

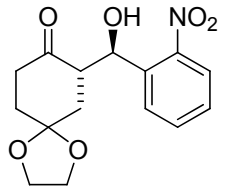
tert-butyl 3(hydroxy-(4-chlorophenyl) methyl)-4-oxopiperidine-1-carboxylate (10)[10]
Catalyst mixture A was used. The reaction medium was brine.
4-Chlorobenzaldeyde: 70.0 mg, 0.50 mmol, 1.00 equiv
Tert-butyl 4-oxopiperidine-1-carboxylate: 328 mg, 1.65 mmol, 3.30 equiv
Reaction time: 48 h; flash column chromatography: (EtOAc/Pet ether = 10:90); yield: 55 %; The ee was determined by chiral HPLC (Chiral AS-H, *i*-PrOH/heptane 5/95, flow rate = 0.5 mL/min, λ = 254 nm): t_{major}= 30.0 min, t_{minor}= 38.3 min, ee = >99%, dr = 66:1 (*anti/syn*), R_f= 0.22 EtOAc/pet ether (2:3).

^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.40 (br s, 9H), 2.47-2.53 (m, 2H), 2.72 (br1H), 2.83-2.89 (t, *J* = 11.2 Hz, 1H), 3.27 (br, 1H), 3.73 (br, 2H), 4.13 (s, 1H), 4.82 (d, *J* = 8.8 Hz, 1H), 7.25-7.35 (m, 4H).



11

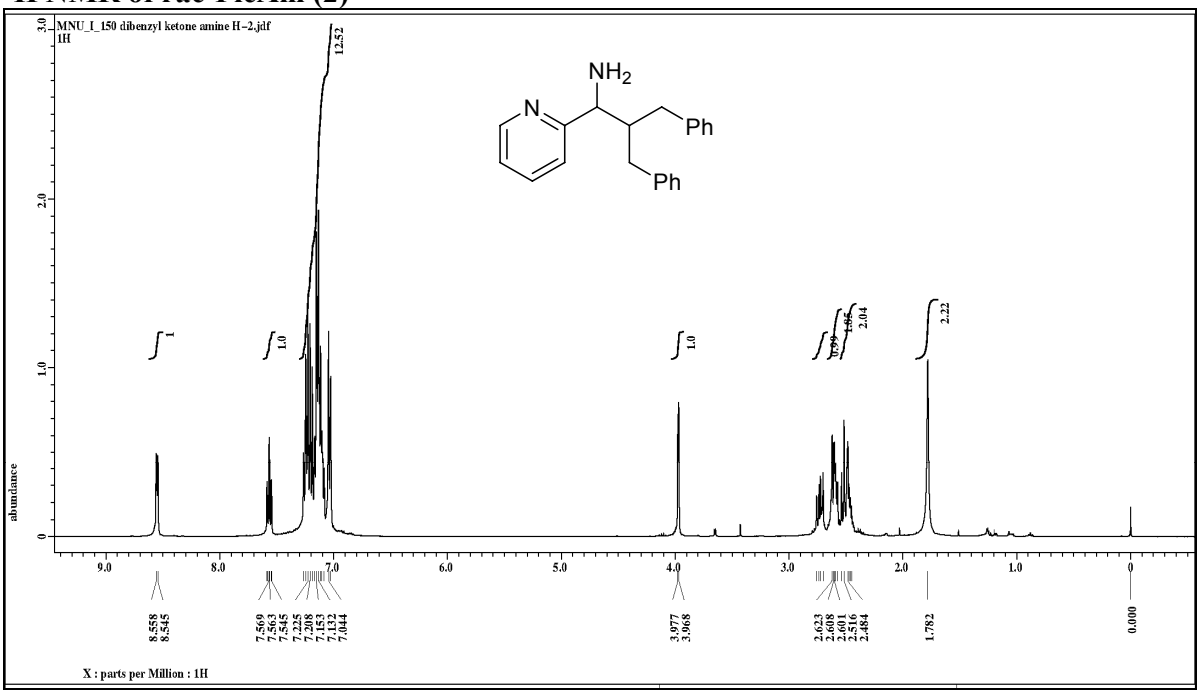
7-[Hydroxy-(4-nitro-phenyl)-methyl]-1,4-dioxa-spiro-[4.5]decan-8-one (11)[11]
Catalyst mixture A was used. The reaction medium was brine. Two equiv of the ketone were used for this reaction.
4-Nitrobenzaldeyde: 75.5 mg, 0.50 mmol, 1.00 equiv
1,4-Cyclochexanedione-monoethylenacetal: 156 mg, 1.00 mmol, 2.00 equiv
Reaction time: 21 h; flash column chromatography: (EtOAc/Pet ether = 5:95); yield: 91%; The ee was determined by chiral HPLC (Chiral AS-H, *i*-PrOH/heptane 20/80, flow rate = 1 mL/min, λ = 280 nm): t_{minor}= 25.6 min, t_{major}= 40.6 min, ee = 98%, dr = >65:1 (*anti/syn*), R_f= 0.20 EtOAc/pet ether (2:3).
^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.48–1.54 (m, 1H), 1.69–1.74 (m, 1H), 1.92–2.13 (m, 2H), 2.44-2.50 (m, 1H), 2.71-2.77 (m, 1H), 2.95-3.03 (m, 1H), 3.85–3.99 (m, 4H), 4.03 (d, J = 3.1 Hz, 1H), 4.94 (dd, J = 3.1, 8.1 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 8.19 (d, J = 8.4 Hz, 2H).



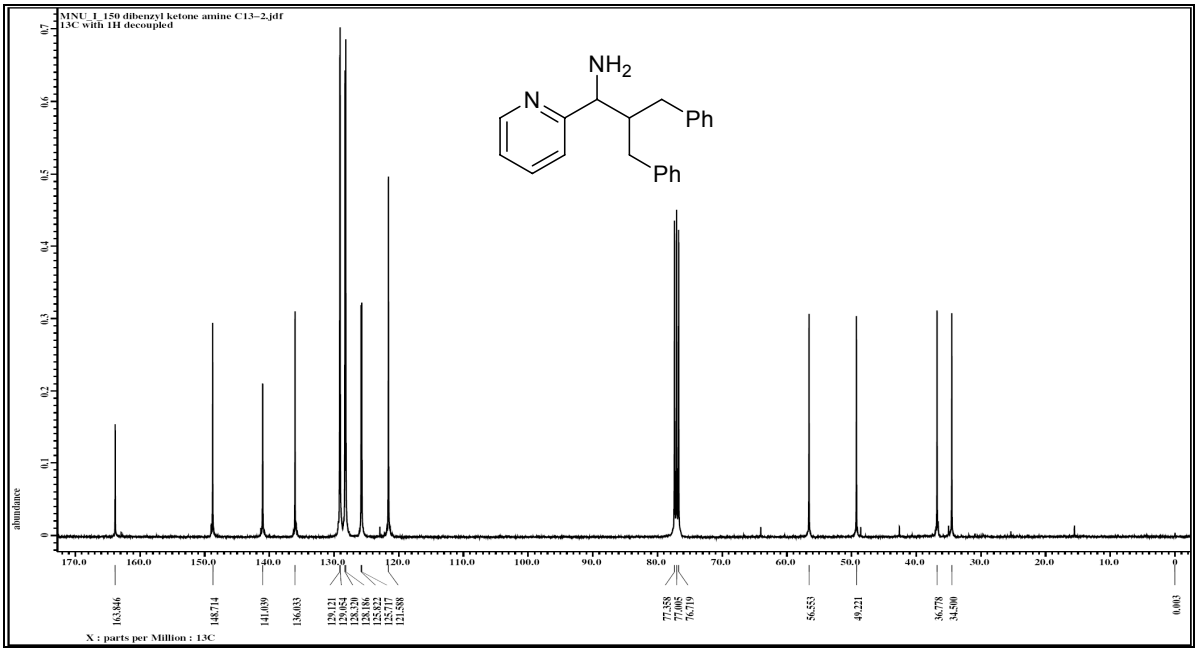
12

7-[Hydroxy-(2nitro-phenyl)-methyl]-1,4-dioxa-spiro-[4.5]decan-8-one (12)
Catalyst mixture A was used. The reaction medium was brine.
2-Nitrobenzaldeyde: 75.5 mg, 0.50 mmol, 1.00 equiv
1,4-Cyclochexanedione-monoethylenacetal: 257 mg, 1.65 mmol, 3.30 equiv
Reaction time: 38h; flash column chromatography: (EtOAc/Pet ether = 5:95); yield: 80; The ee was determined by chiral HPLC (Chiral AS-H, *i*-PrOH/heptane 20/80, flow rate = 1 mL/min, λ = 280 nm): t_{minor}= 24.3 min, t_{major}= 29.3 min, ee = 91%, dr = 18:1 (*anti/syn*), R_f= 0.23 EtOAc/pet ether (2:3).
^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.69-1.75 (m, 1H), 1.96–2.07 (m, 3H), 2.42–2.54 (m, 1H), 2.64-2.81 (m, 1H), 3.11-3.19 (m, 1H), 3.89-4.01 (m, 4H), 5.43–5.45 (d, J = 6.87 Hz, 1H), 7.42-7.48 (m, 1H), 7.67-7.74 (m, 1H), 7.75-7.76 (m, 1H), 7.85-7.94 (m, 1H),
^{13}C NMR (400MHz, $CDCl_3$) (ppm): 34.1, 37.6, 38.6, 52.9, 64.3, 64.6, 69.1, 106.7, 124.0, 128.3, 128.8, 133.1, 136.2, 148.3, 212.9. FT-IR (KBr), ν_{max}: 3431, 2961, 1703, 1524, 1360, 1120, 1009 cm^{-1} ; MS (EI), *m/z* (relative intensity): 330 $[M+Na]^+$, 100%), 312[M- H_2O] 7.5 %; HRMS (ESI-TOF) calculated for $C_{15}H_{17}NO_6$ $[M+Na]^+$ 330.0948; found: 330.0932.

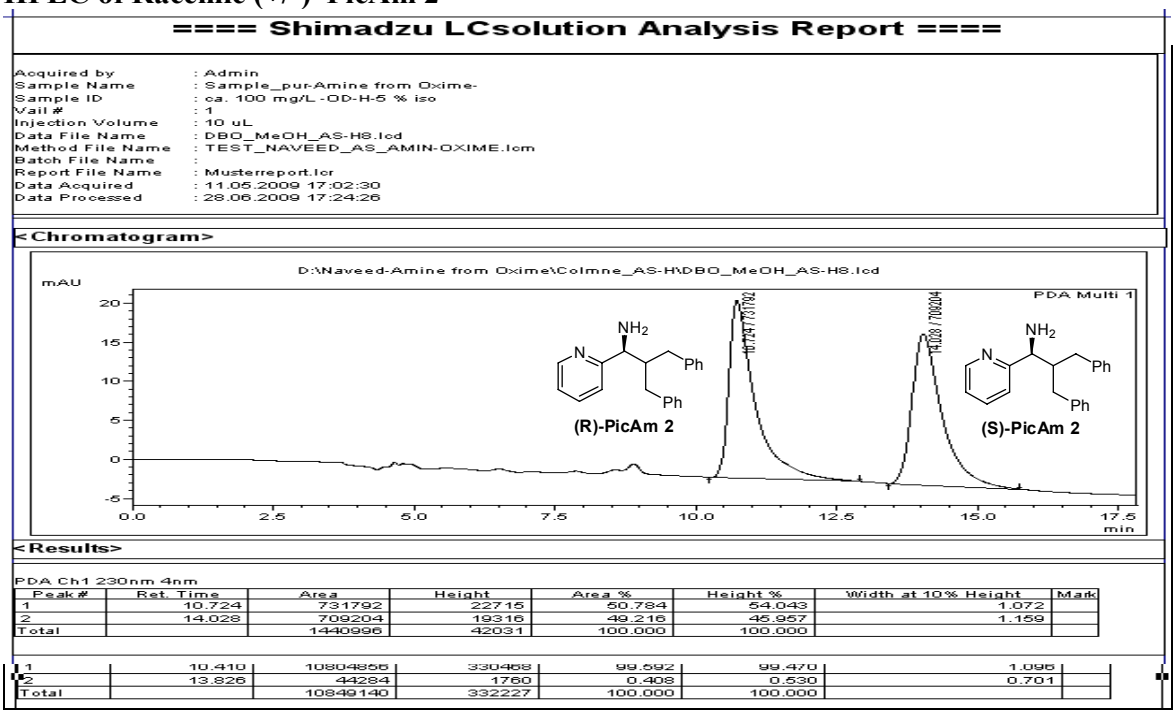
^{1}H NMR of rac-PicAm (2)



^{13}C NMR of rac-PicAm (2)



HPLC of Racemic (+/-) PicAm 2



HPLC of Racemic 2-(hydroxy(4-nitrophenyl)methyl)cyclohexanone (3)

==== Shimadzu LCsolution Analysis Report ====

Acquired by	: Admin
Sample Name	: Naveed
Sample ID	: 200 mg/ L
Vail #	: 1
Injection Volume	: 10 uL
Data File Name	: Aldol-cyclohexanone racemic.lcd
Method File Name	: ODH-Aldol-5% iPrOH.lcm
Batch File Name	:
Report File Name	: Musterreport.lcr
Data Acquired	: 05.07.2009 19:53:21
Data Processed	: 05.07.2009 21:55:10

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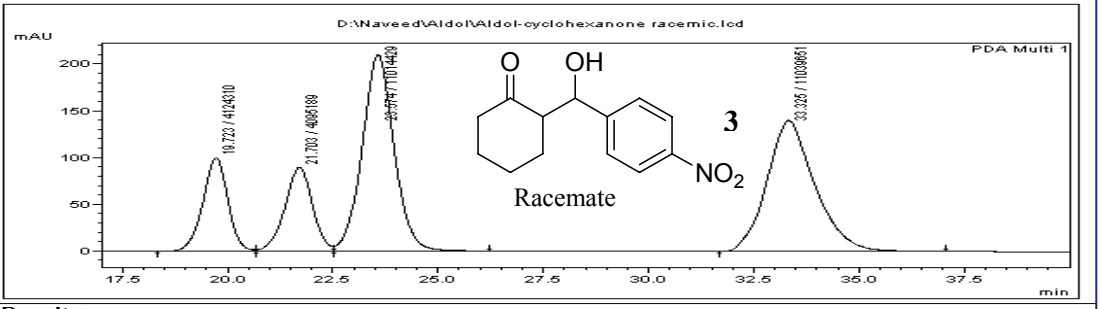

<Results>

PDA Ch1 210nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	19.723	4124310	99829	13.623	18.507	1.224	
2	21.703	4095189	89573	13.527	16.606	1.371	V
3	23.574	11014429	209828	36.383	38.899	1.571	V
4	33.325	11039651	140186	36.466	25.989	2.438	
Total		30273579	539415	100.000	100.000		

HPLC of 2-(hydroxy(4-nitrophenyl)methyl)cyclohexanone (3)
(after column chromatography with silica gel)

==== Shimadzu LCsolution Analysis Report ====

Acquired by	: Admin
Sample Name	: AB_II_2_cc
Sample ID	: AB_II_2_cc
Vail #	: 1
Injection Volume	: 10 uL
Data File Name	: AB_II_2_cc.lcd
Method File Name	: ODH 5% 1 ml Nav cat.lcm
Batch File Name	:
Report File Name	: Musterreport.lcr
Data Acquired	: 01.01.2010 19:13:29
Data Processed	: 01.01.2010 19:59:06

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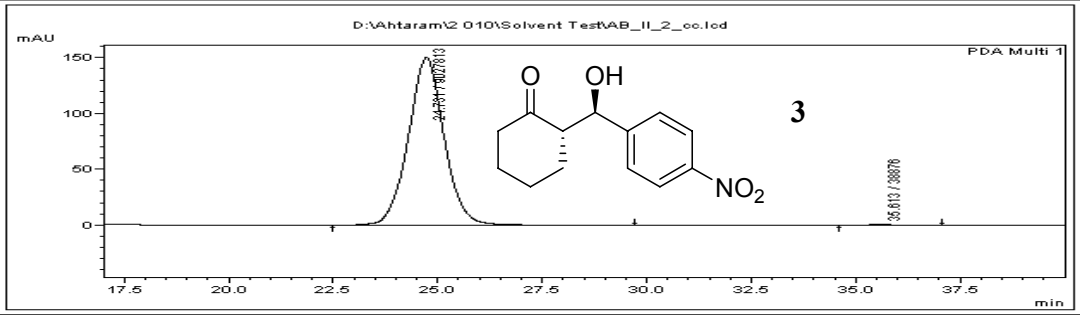
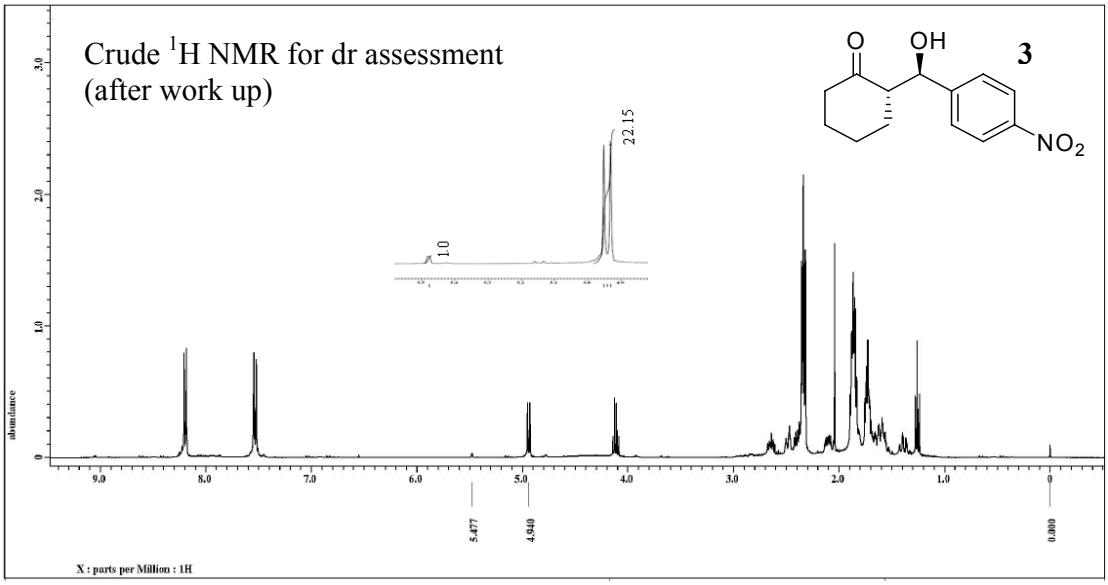


<Results>

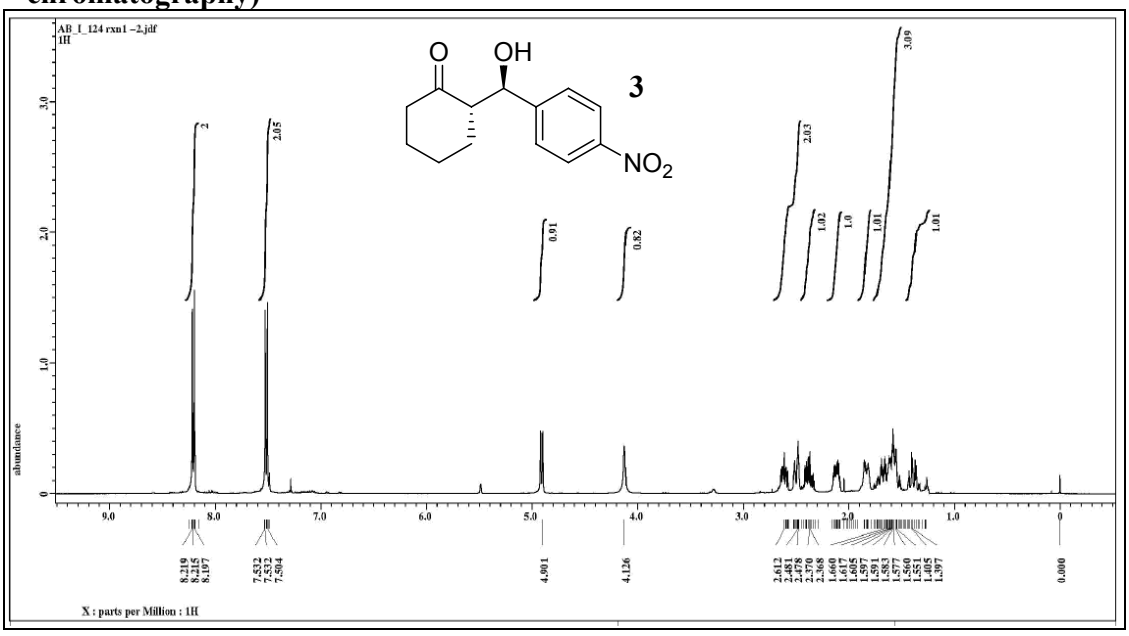
PDA Ch1 210nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	24.731	9027813	150581	99.571	99.624	1.782	
2	35.613	38876	568	0.429	0.376	1.825	
Total		9066689	151150	100.000	100.000		

Crude ^{1}H NMR of 2-(hydroxy(4-nitrophenyl)methyl)cyclohexanone (3)



^{1}H NMR of 2-(hydroxy(4-nitrophenyl)methyl)cyclohexanone (3) (after chromatography)



HPLC of Racemic 2-((4-(trifluoromethyl)phenyl)(hydroxy)methyl) cyclohexanone (4)

==== Shimadzu LCsolution Analysis Report ====

Acquired by	: Admin
Sample Name	: CH+4-CF3Ben racemic test 27Nov
Sample ID	: CH+4-CF3Ben racemic test 27Nov
Vail #	: 1
Injection Volume	: 10 uL
Data File Name	: CH+4-CF3Ben racemic test 27Nov1.lcd
Method File Name	: ODH 5% 0.5 ml.lcm
Batch File Name	:
Report File Name	: Musterreport.lcr
Data Acquired	: 26.11.2009 21:30:13
Data Processed	: 27.11.2009 00:44:36

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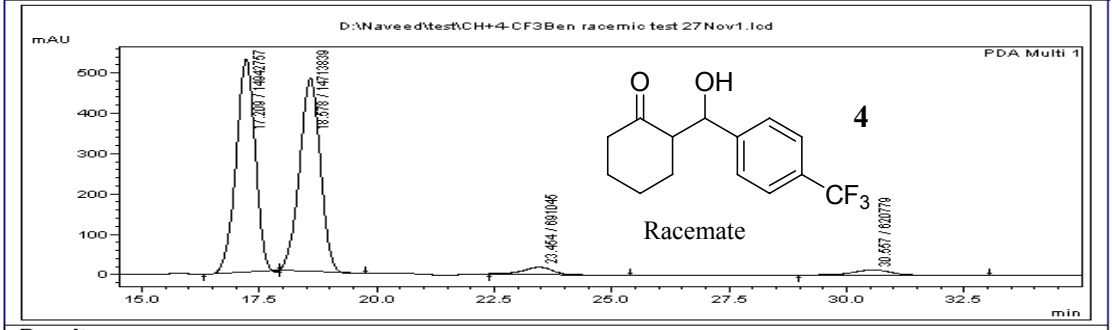

<Results>

PDA Ch1 217nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	17.209	14942757	527647	48.252	50.932	0.831	
2	18.578	14713839	478448	47.512	46.183	0.902	
3	23.464	691046	17434	2.231	1.683	1.204	
4	30.557	620779	12451	2.005	1.202	1.524	
Total		30968421	1035979	100.000	100.000		

HPLC of 2-((4-(trifluoromethyl)phenyl)(hydroxy)methyl) cyclo- hexanone (4)
(after column chromatography with silica gel)

==== Shimadzu LCsolution Analysis Report ====

Acquired by	: Admin
Sample Name	: MNU_II_103_CC major spot
Sample ID	: MNU_II_103_CC major spot
Vail #	: 1
Injection Volume	: 10 uL
Data File Name	: MNU_II_103_CC major spot.lcd
Method File Name	: ODH 5% 0.5 ml.lcm
Batch File Name	:
Report File Name	: Musterreport.lcr
Data Acquired	: 03.12.2009 20:42:13
Data Processed	: 09.12.2009 17:56:26

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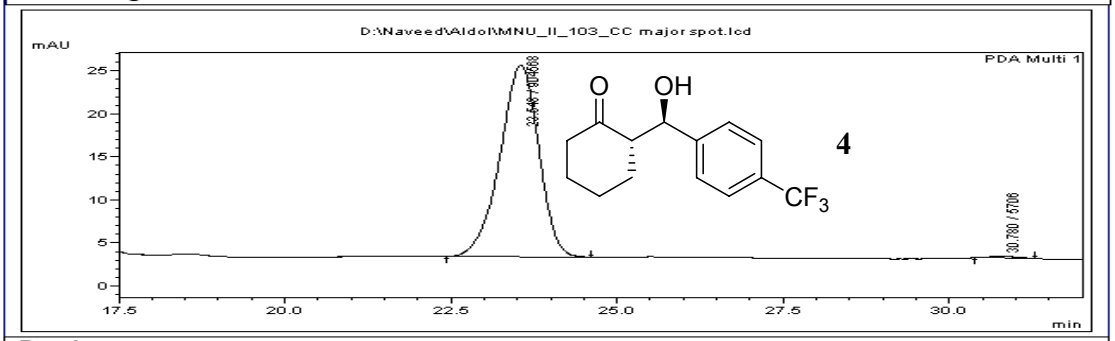
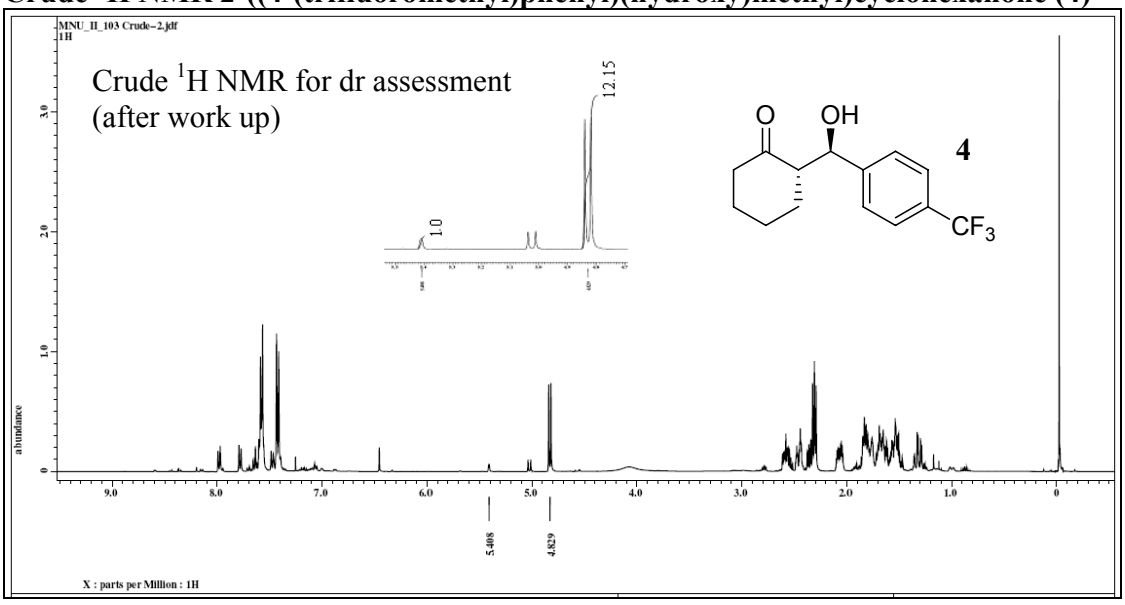


<Results>

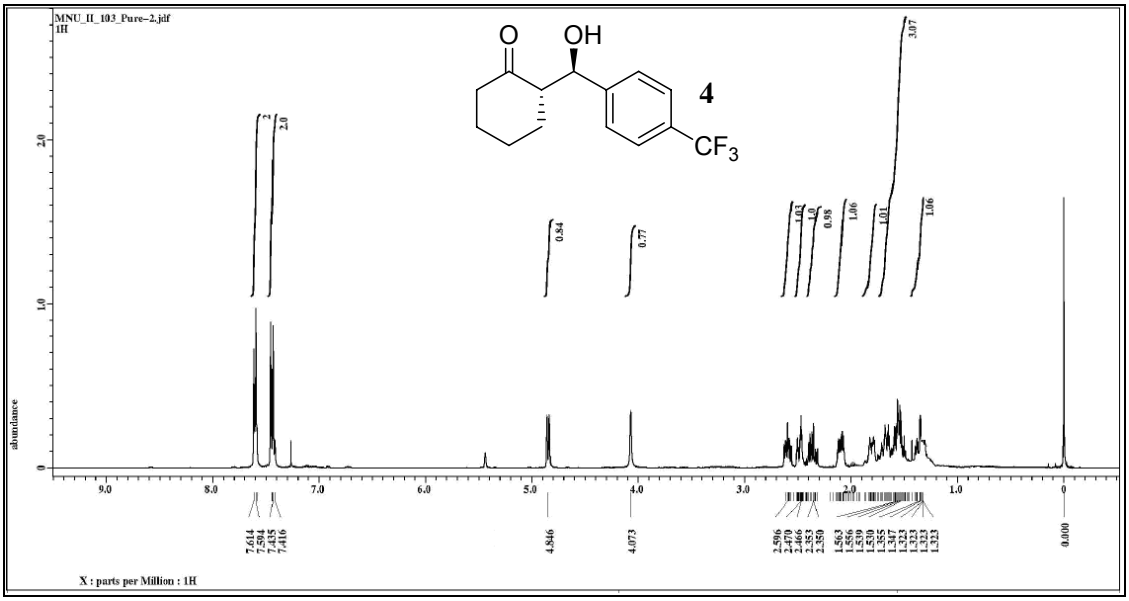
PDA Ch1 219nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	23.548	904568	22266	99.373	99.222	1.193	
2	30.780	5706	175	0.627	0.778	0.823	
Total		910274	22440	100.000	100.000		

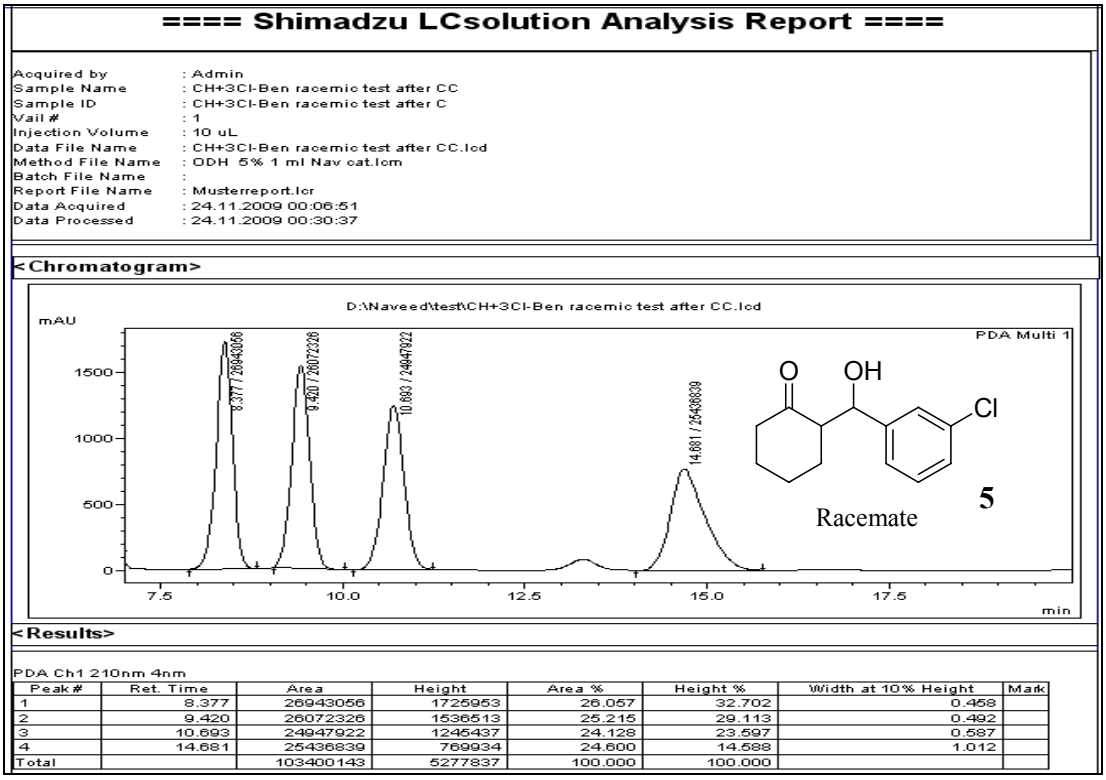
Crude ^{1}H NMR 2-((4-(trifluoromethyl)phenyl)(hydroxy)methyl)cyclohexanone (4)



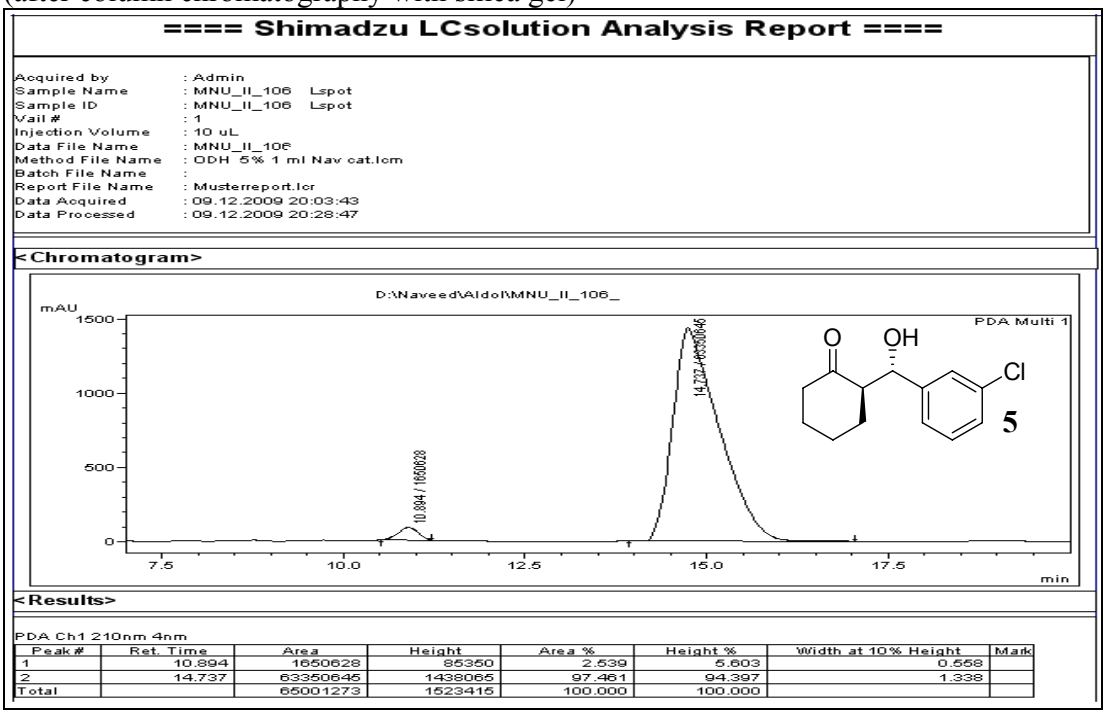
^{1}H NMR 2-((4-(trifluoromethyl)phenyl)(hydroxy)methyl)cyclohexanone (4) (after chromatography)



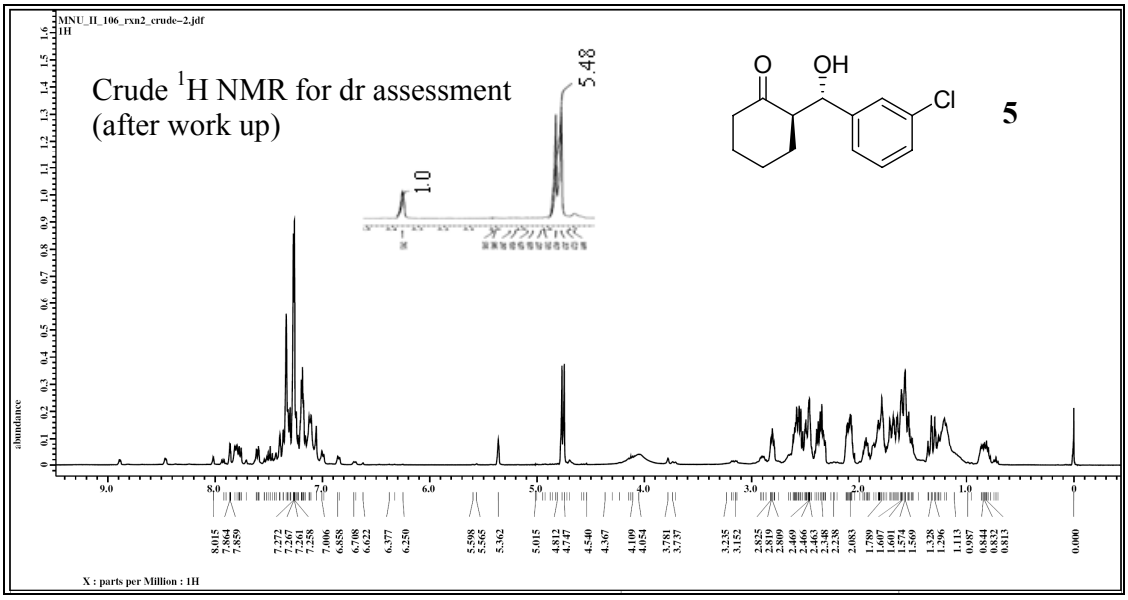
HPLC of Racemic 2-((3-chlorophenyl)(hydroxy)methyl)cyclohexanone (5)



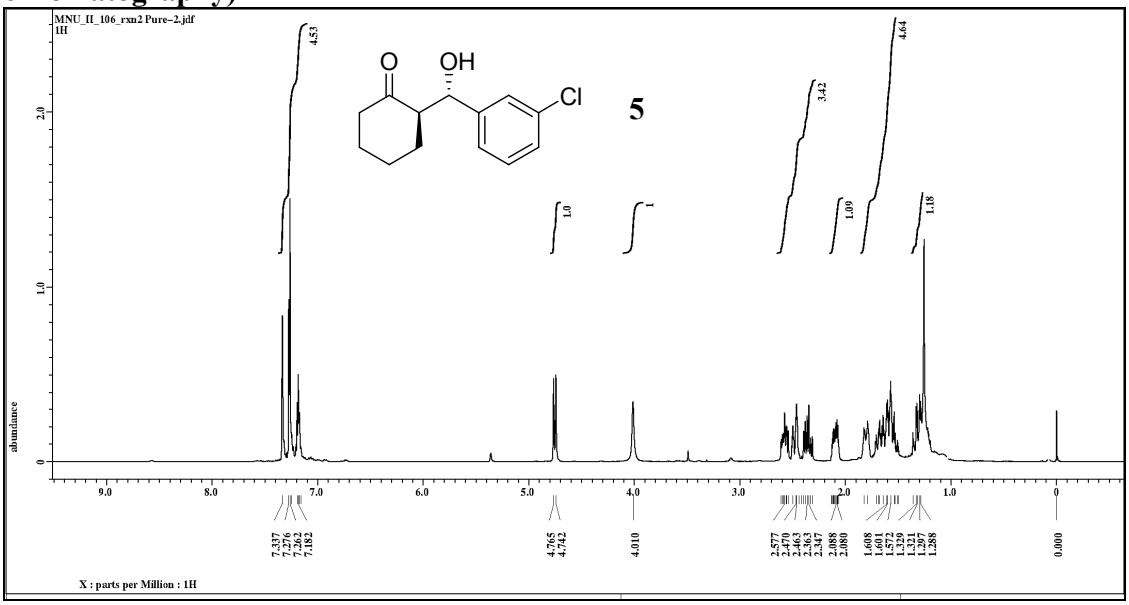
HPLC of 2-((3-chlorophenyl)(hydroxy)methyl)cyclohexanone (5)
(after column chromatography with silica gel)



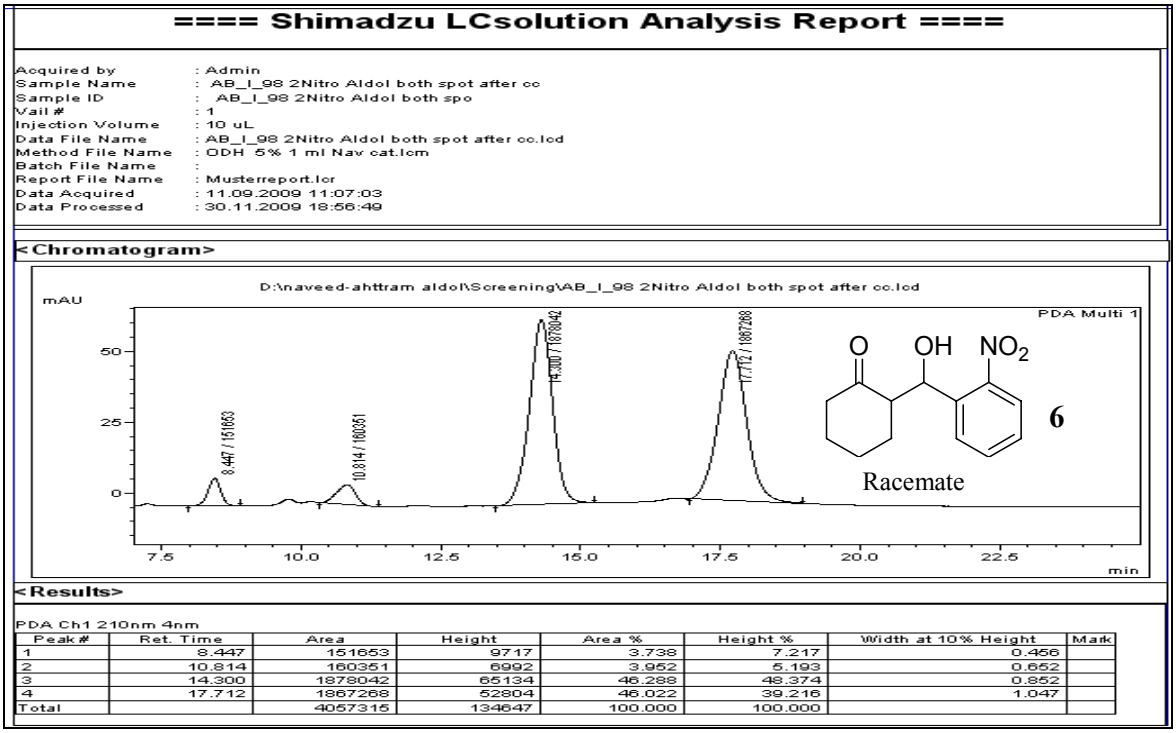
Crude ^{1}H NMR 2-((3-chlorophenyl)(hydroxy)methyl)cyclohexanone (5)



^{1}H NMR 2-((3-chlorophenyl)(hydroxy)methyl)cyclohexanone (5) (after chromatography)



HPLC of Racemic 2-(hydroxy(2-nitrophenyl)methyl)cyclohexanone (6)



==== Shimadzu LCsolution Analysis Report ====

Acquired by : Admin
Sample Name : AB_I_98 2Nitro Aldol both spot after cc
Sample ID : AB_I_98 2Nitro Aldol both spo
Vail # : 1
Injection Volume : 10 uL
Data File Name : AB_I_98 2Nitro Aldol both spot after cc.lcd
Method File Name : ODH 5% 1 ml Nav cat.lcm
Batch File Name :
Report File Name : Musterreport.lcr
Data Acquired : 11.09.2009 11:07:03
Data Processed : 30.11.2009 18:56:49

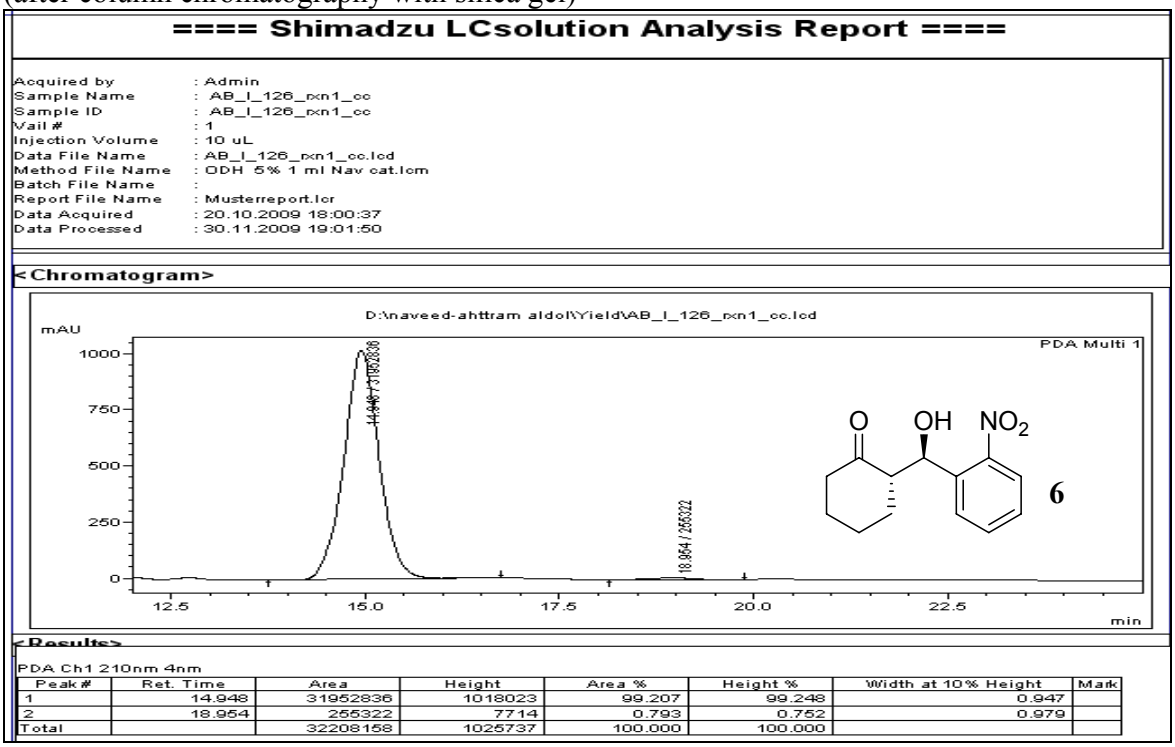
<Chromatogram>

<Results>

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	8.447	151653	9717	3.738	7.217	0.456	
2	10.814	160351	5992	3.952	5.193	0.652	
3	14.300	1878042	65134	46.288	48.374	0.852	
4	17.712	1867268	52804	46.022	39.216	1.047	
Total		4057315	134647	100.000	100.000		

HPLC of 2-(hydroxy(2-nitrophenyl)methyl)cyclohexanone (6)
(after column chromatography with silica gel)



==== Shimadzu LCsolution Analysis Report ====

Acquired by : Admin
Sample Name : AB_I_126_pxn1_cc
Sample ID : AB_I_126_pxn1_cc
Vail # : 1
Injection Volume : 10 uL
Data File Name : AB_I_126_pxn1_cc.lcd
Method File Name : ODH 5% 1 ml Nav cat.lcm
Batch File Name :
Report File Name : Musterreport.lcr
Data Acquired : 20.10.2009 18:00:37
Data Processed : 30.11.2009 19:01:50

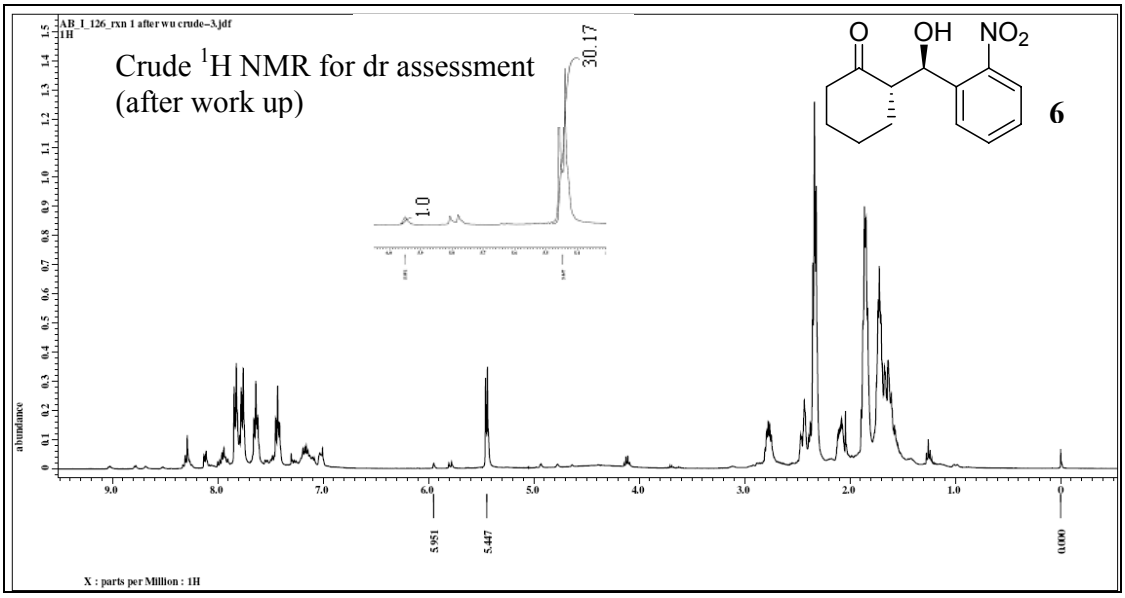
<Chromatogram>

<Results>

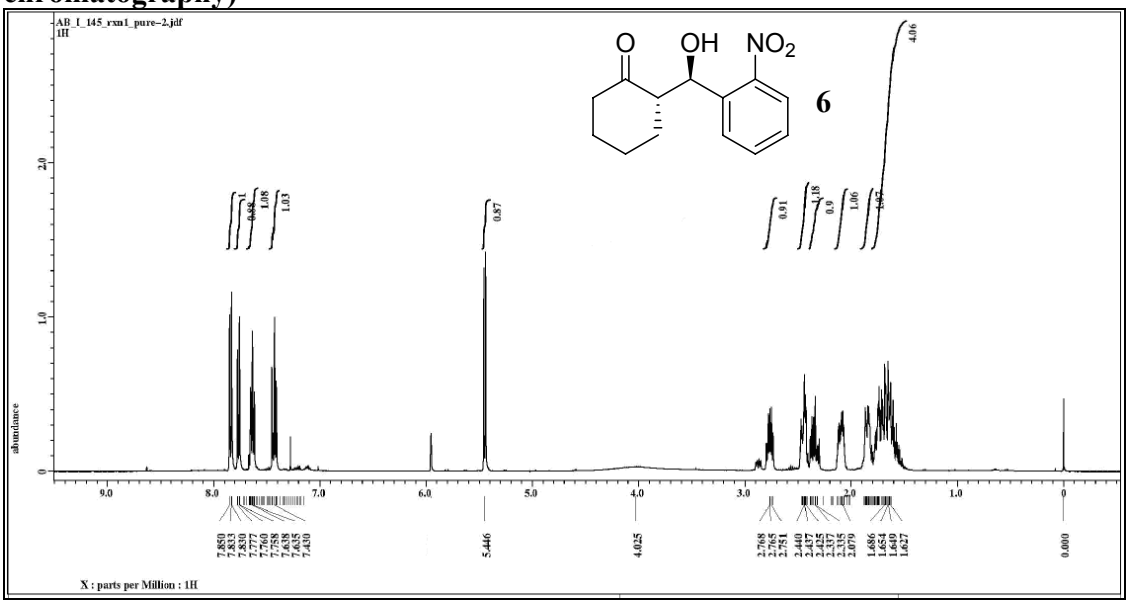
PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	14.948	31952836	1018023	99.207	99.248	0.947	
2	18.954	255322	7714	0.793	0.752	0.979	
Total		32208158	1025737	100.000	100.000		

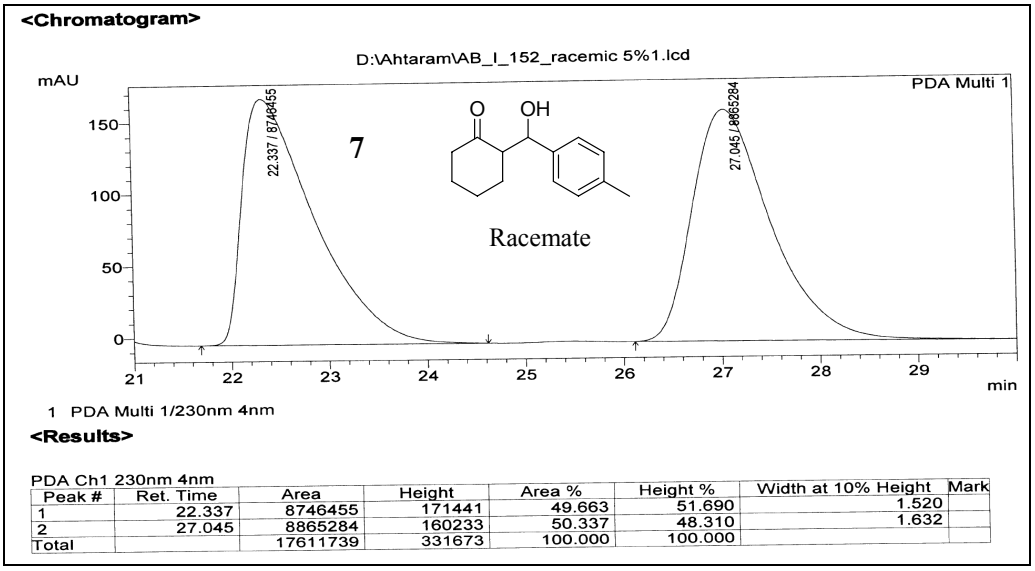
Crude ^{1}H NMR 2-(hydroxy(2-nitrophenyl)methyl)cyclohexanone (6)



^{1}H NMR 2-(hydroxy(2-nitrophenyl)methyl)cyclohexanone (6) (after chromatography)



HPLC of Racemic 2-(hydroxy(p-tolyl)methyl)cyclohexanone (7)

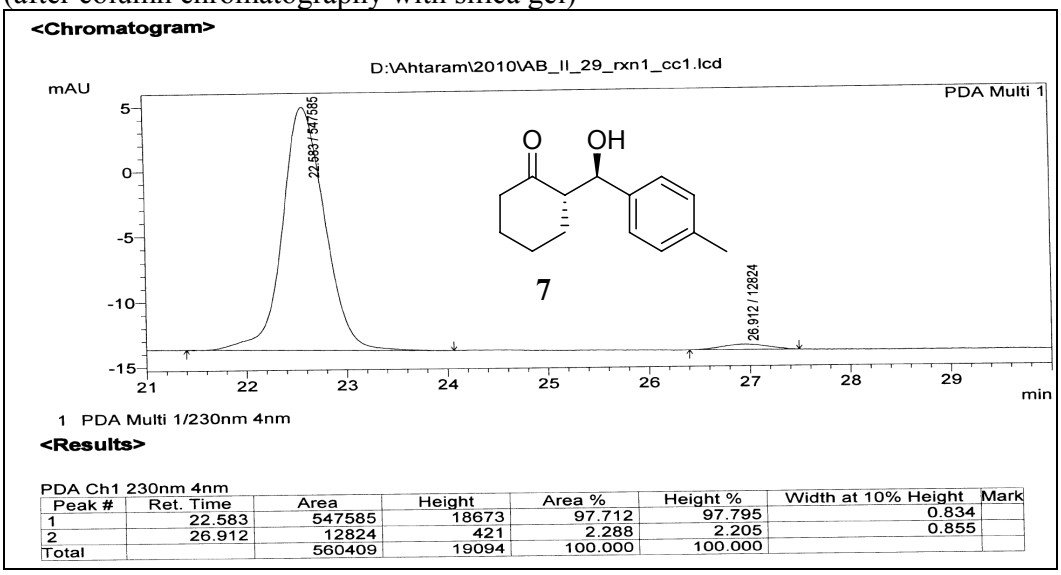


<Results>

PDA Ch1 230nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	22.337	8746455	171441	49.663	51.690	1.520	
2	27.045	8865284	160233	50.337	48.310	1.632	
Total		17611739	331673	100.000	100.000		

HPLC of 2-(hydroxy(p-tolyl)methyl)cyclohexanone (7)
(after column chromatography with silica gel)

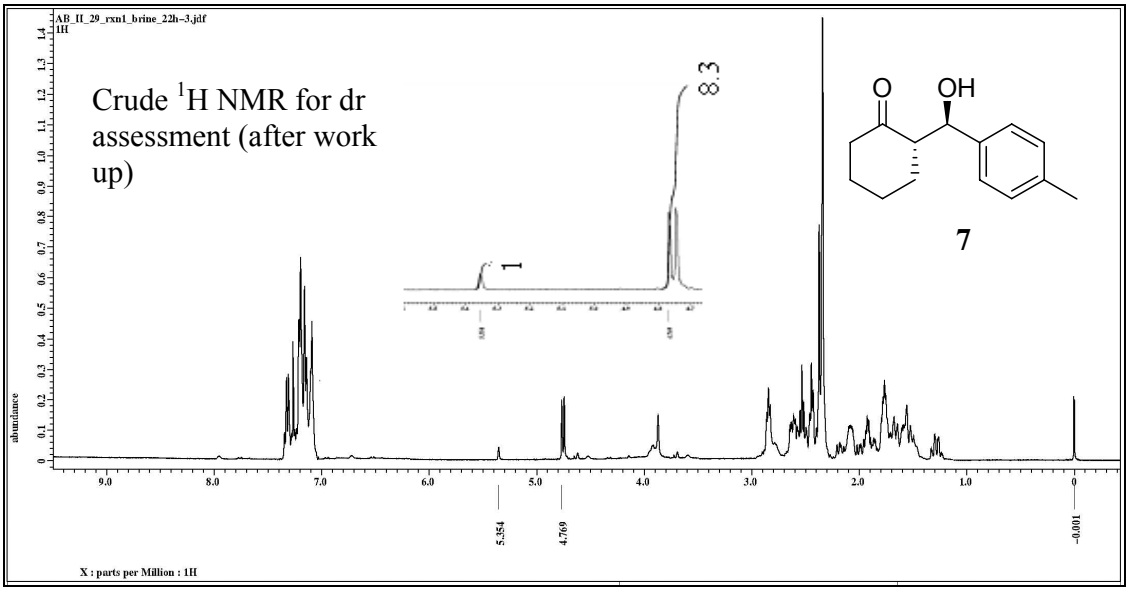


<Results>

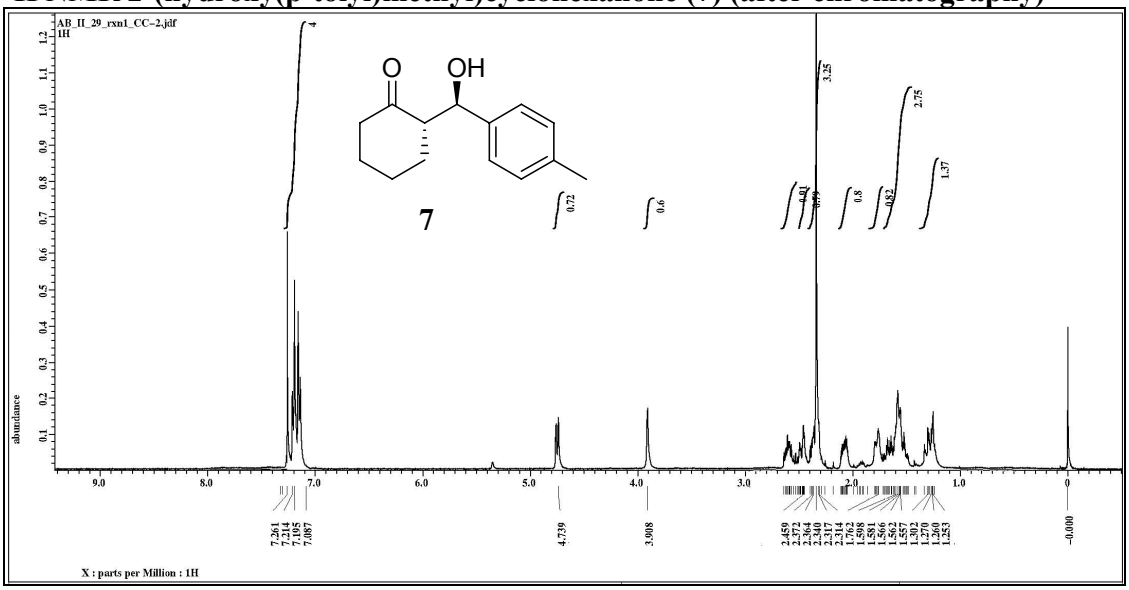
PDA Ch1 230nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	22.583	547585	18673	97.712	97.795	0.834	
2	26.912	12824	421	2.288	2.205	0.855	
Total		560409	19094	100.000	100.000		

Crude ^{1}H NMR 2-(hydroxy(p-tolyl)methyl)cyclohexanone (7)



^{1}H NMR 2-(hydroxy(p-tolyl)methyl)cyclohexanone (7) (after chromatography)

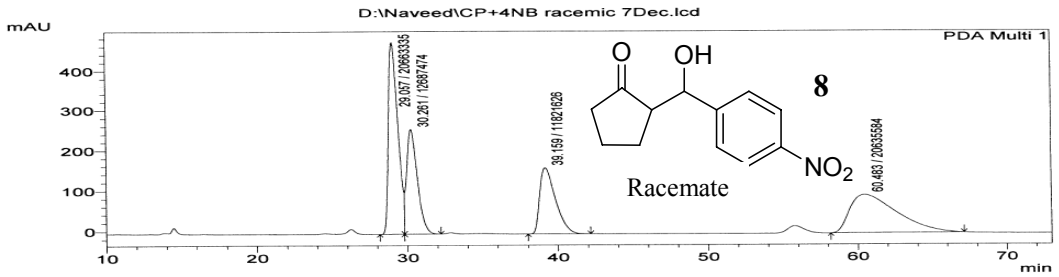


HPLC of Racemic 2-(hydroxy(4-nitrophenyl)methyl)cyclopentanone (8)

==== Shimadzu LCsolution Analysis Report ====

Acquired by : Admin
Sample Name : CP+4NB racemic 7Dec
Sample ID : CP+4NB racemic 7Dec
Vail # : 0
Injection Volume : 10 uL
Data File Name : CP+4NB racemic 7Dec.lcd
Method File Name : method cycpent+4nitro 20%IsoPr 0.5ml.lcm
Batch File Name :
Report File Name : Musterreport.lcr
Data Acquired : 07.12.2009 20:15:01
Data Processed : 08.12.2009 11:06:20
Diese Probe heißt: CP+4NB racemic 7Dec

<Chromatogram>



1 PDA Multi 1/280nm 4nm

<Results>

PDA Ch1 280nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	29.057	20663335	477560	31.399	48.003	0.000	
2	30.261	12687474	259431	19.280	26.077	0.000	V
3	39.159	11821626	163411	17.964	16.426	2.096	
4	60.483	20635584	94449	31.357	9.494	6.319	
Total		65808019	994851	100.000	100.000		

HPLC of 2-(hydroxy(4-nitrophenyl)methyl)cyclopentanone (8)
(after column chromatography with silica gel)

==== Shimadzu LCsolution Analysis Report ====

Acquired by : Admin
Sample Name : MNU_II_104
Sample ID : MNU_II_104
Vail # : 0
Injection Volume : 10 uL
Data File Name : MNU_II_104
Method File Name : method cycpent+4nitro 20%IsoPr 0.5ml.lcm
Batch File Name :
Report File Name : Musterreport.lcr
Data Acquired : 05.12.2009 22:21:47
Data Processed : 06.12.2009 00:43:07
Diese Probe heißt: MNU_II_104

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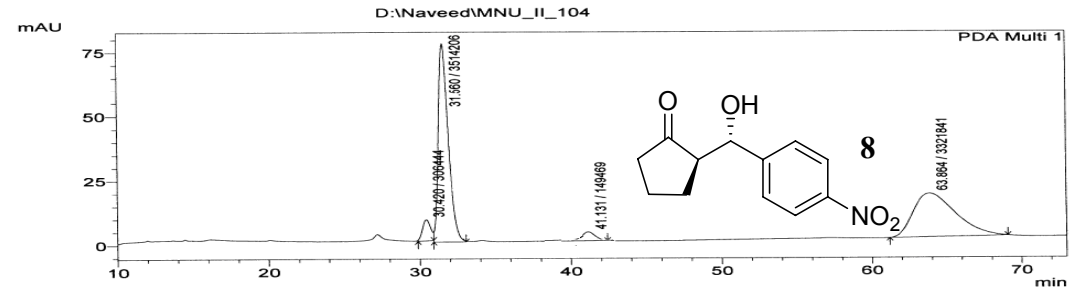


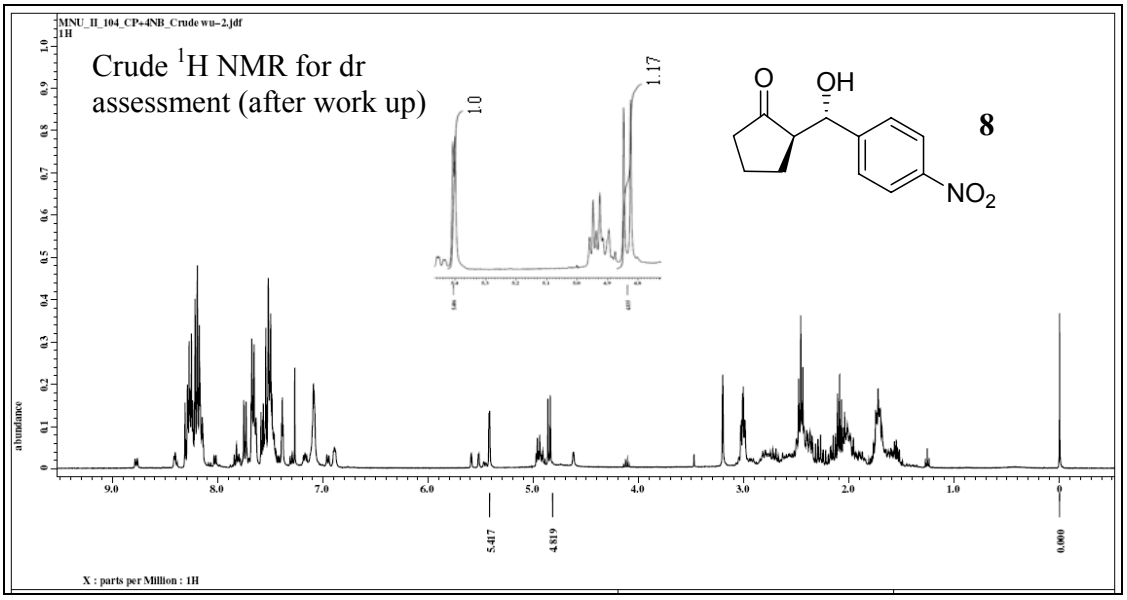
1 PDA Multi 1/254nm 4nm

<Results>

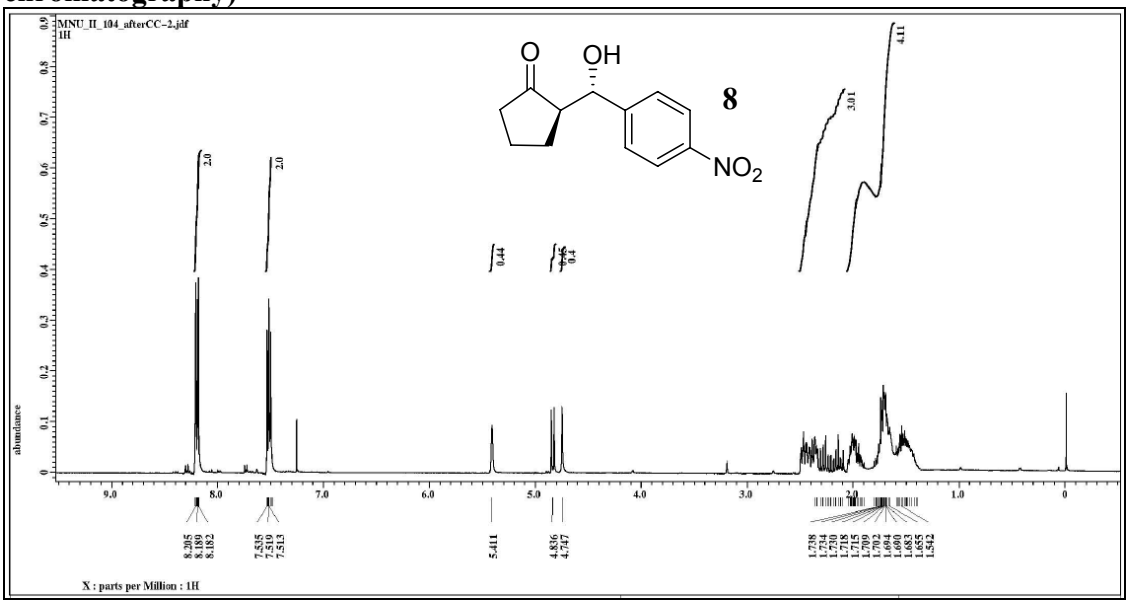
PDA Ch1 254nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	30.420	306444	8217	4.202	7.804	0.000	
2	31.560	3514206	77258	48.193	73.381	1.351	
3	41.131	149469	2801	2.050	2.660	1.503	
4	63.864	3321841	17008	45.555	16.154	5.655	
Total		7291960	105283	100.000	100.000		

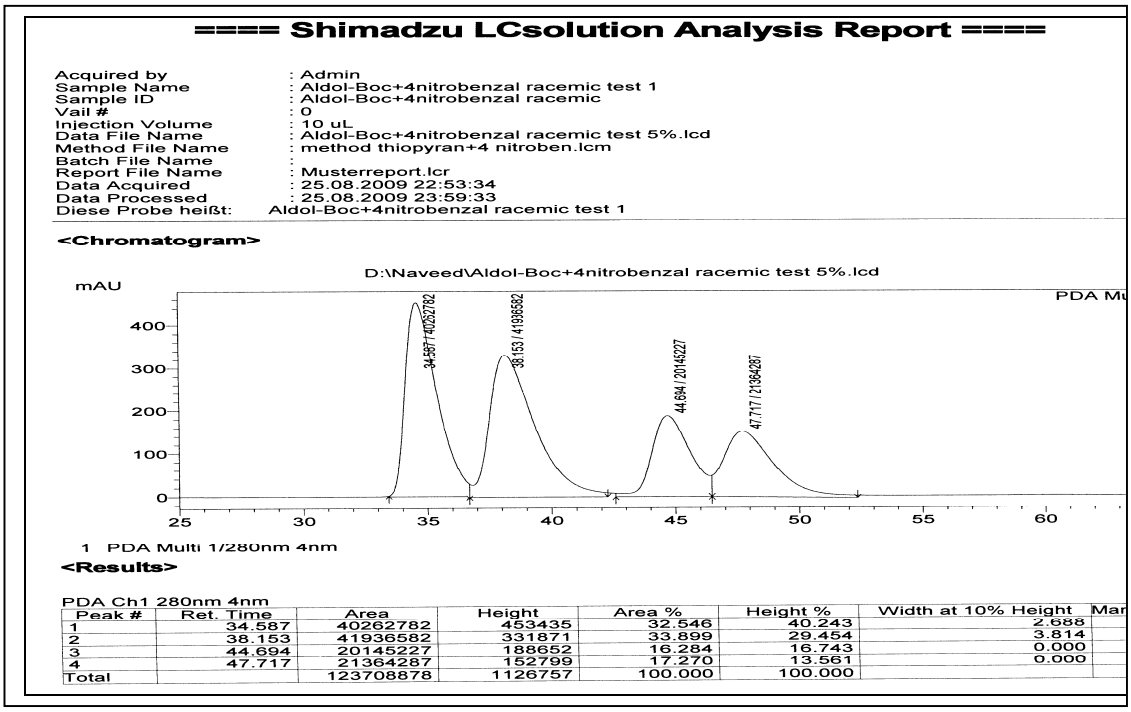
Crude ^{1}H NMR 2-(hydroxy(4-nitrophenyl)methyl)cyclopentanone (8)



^{1}H NMR 2-(hydroxy(4-nitrophenyl)methyl)cyclopentanone (8) (after chromatography)



HPLC of Racemic *Tert*-butyl 3-(hydroxy(4-nitrophenyl)methyl)-4-oxopiperidine -1-carboxylate (9)



==== Shimadzu LCsolution Analysis Report ====

Acquired by : Admin
Sample Name : Aldol-Boc+4nitrobenzal racemic test 1
Sample ID : Aldol-Boc+4nitrobenzal racemic
Vail # : 0
Injection Volume : 10 uL
Data File Name : Aldol-Boc+4nitrobenzal racemic test 5%.lcd
Method File Name : method thiopyran+4 nitroben.lcm
Batch File Name :
Report File Name : Musterreport.lcr
Data Acquired : 25.08.2009 22:53:34
Data Processed : 25.08.2009 23:59:33
Diese Probe heißt: Aldol-Boc+4nitrobenzal racemic test 1

<Chromatogram>

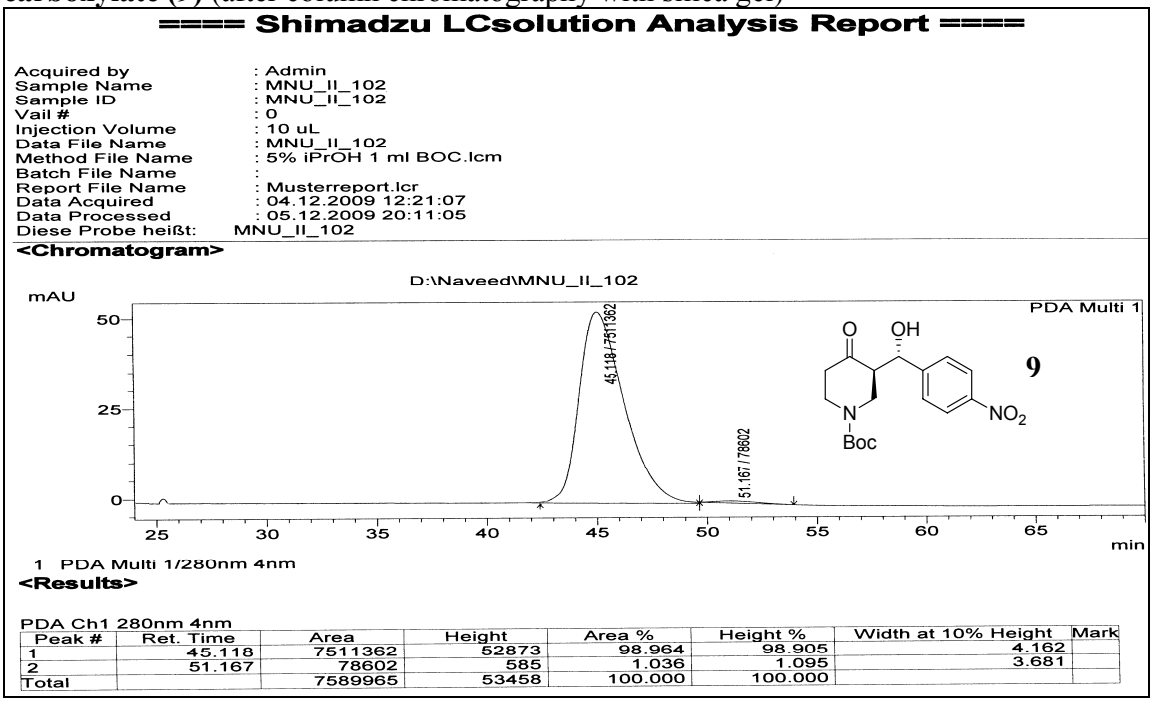
1 PDA Multi 1/280nm 4nm

<Results>

PDA Ch1 280nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mar
1	34.587	40262782	453435	32.546	40.243	2.688	
2	38.153	41936582	331871	33.899	29.454	3.814	
3	44.694	20145227	188652	16.284	16.743	0.000	
4	47.717	21364287	152799	17.270	13.561	0.000	
Total		123708878	1126757	100.000	100.000		

HPLC of *tert*-Butyl 3-(hydroxy(4-nitrophenyl)methyl)-4-oxopiperidine-1-carboxylate (9) (after column chromatography with silica gel)



==== Shimadzu LCsolution Analysis Report ====

Acquired by : Admin
Sample Name : MNU_II_102
Sample ID : MNU_II_102
Vail # : 0
Injection Volume : 10 uL
Data File Name : MNU_II_102
Method File Name : 5% iPrOH 1 ml BOC.lcm
Batch File Name :
Report File Name : Musterreport.lcr
Data Acquired : 04.12.2009 12:21:07
Data Processed : 05.12.2009 20:11:05
Diese Probe heißt: MNU_II_102

<Chromatogram>

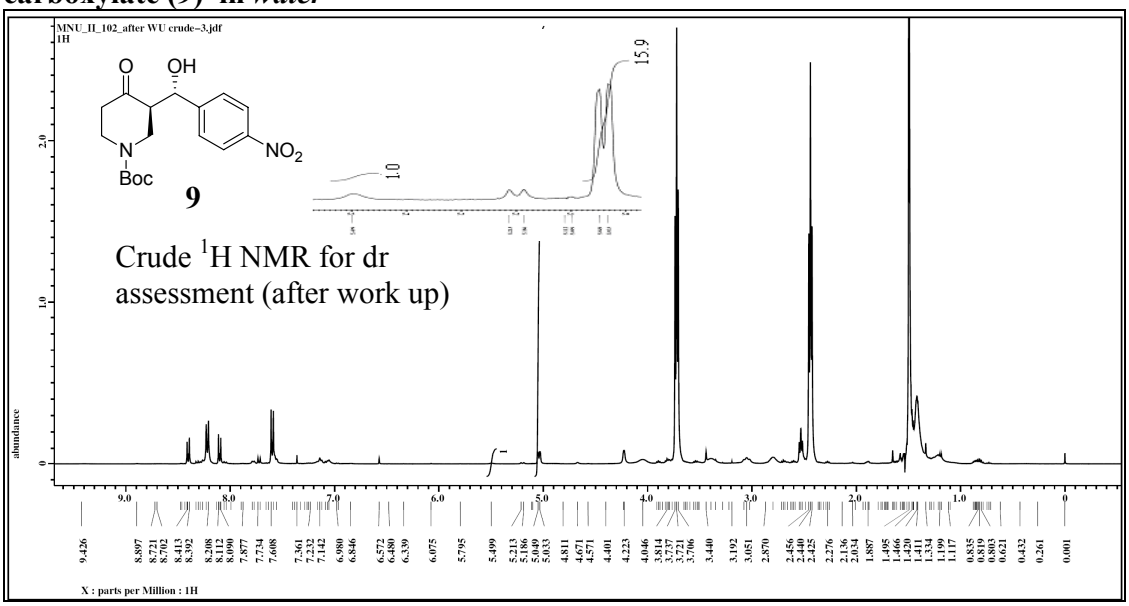
1 PDA Multi 1/280nm 4nm

<Results>

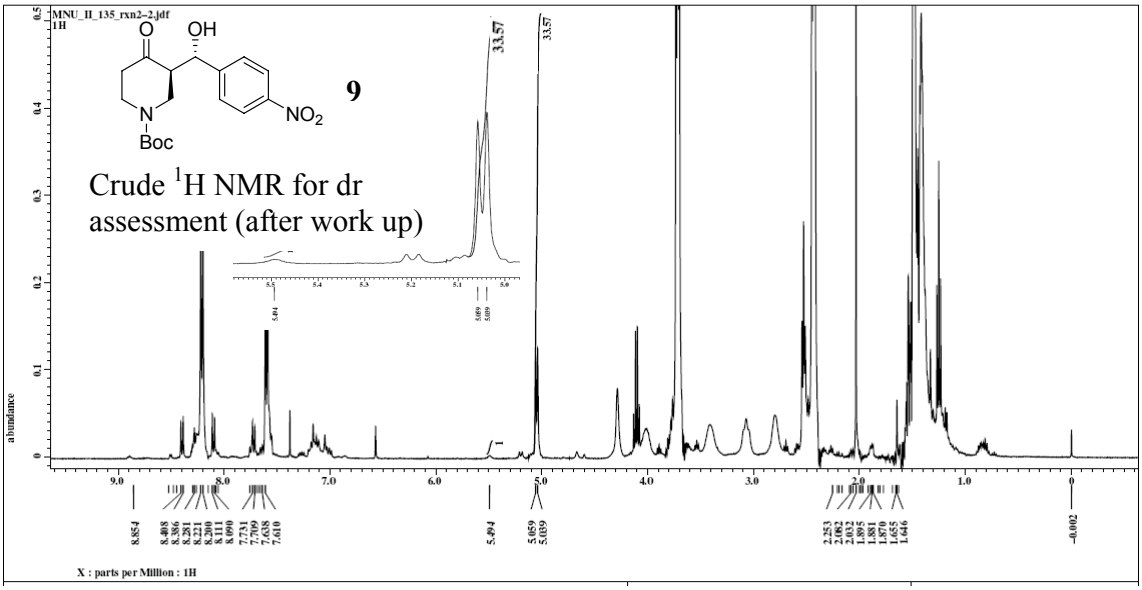
PDA Ch1 280nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	45.118	7511362	52873	98.964	98.905	4.162	
2	51.167	78602	585	1.036	1.095	3.681	
Total		7589965	53458	100.000	100.000		

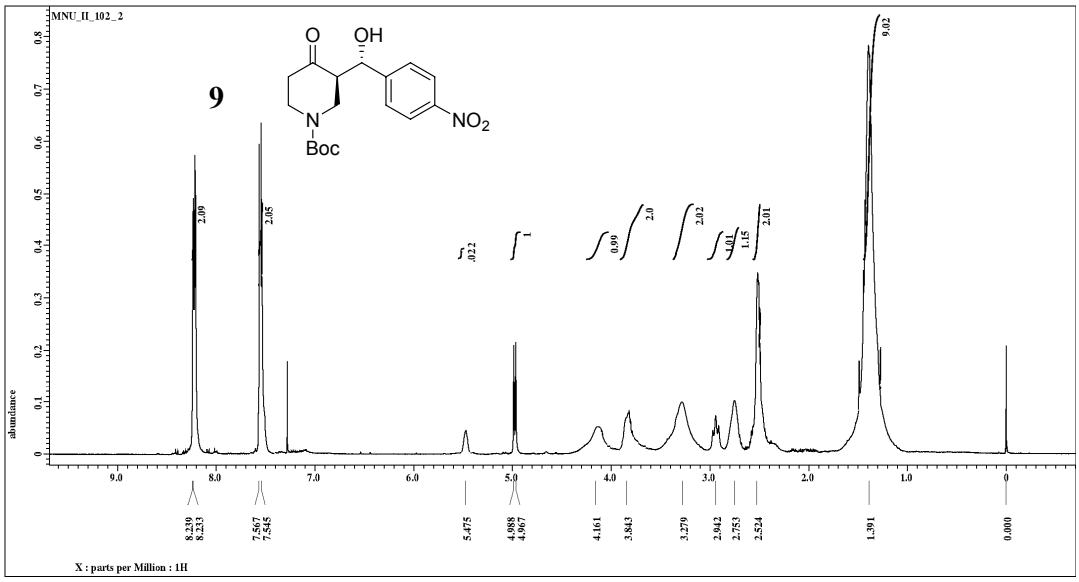
Crude ^{1}H NMR *tert*-butyl 3-(hydroxy(4-nitrophenyl)methyl)-4-oxopiperidine-1-carboxylate (9) in *water*



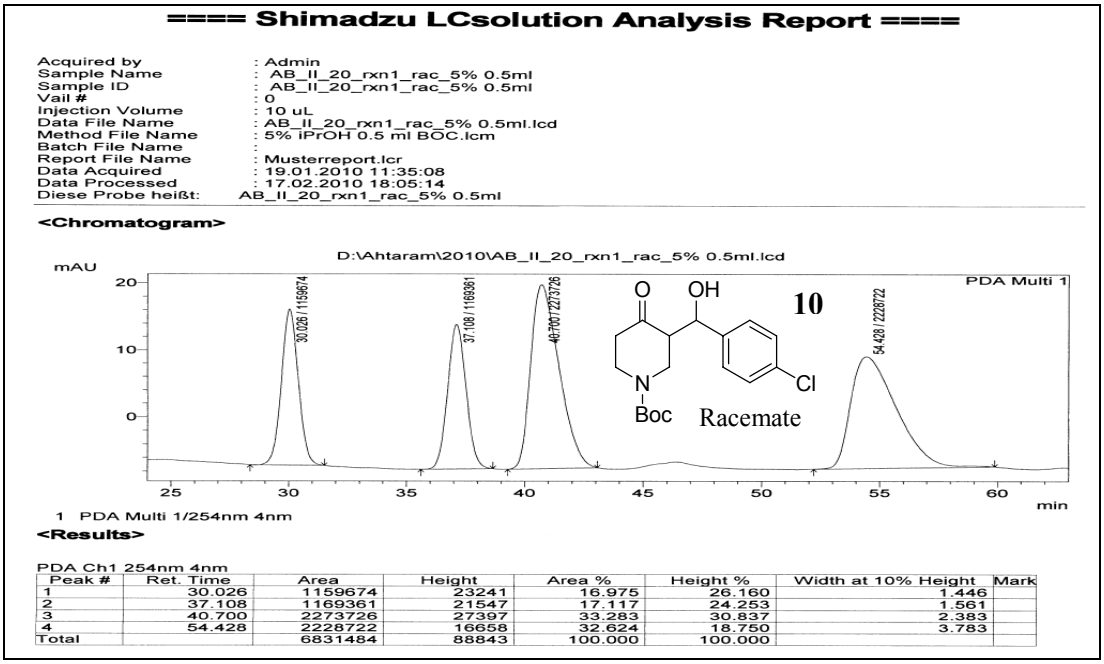
Crude ^{1}H NMR *tert*-butyl 3-(hydroxy(4-nitrophenyl)methyl)-4-oxopiperidine-1-carboxylate (9) in *brine*



^{1}H NMR *tert*-butyl 3-(hydroxy(4-nitrophenyl)methyl)-4-oxopiperidine-1-carboxylate (9) (after chromatography)

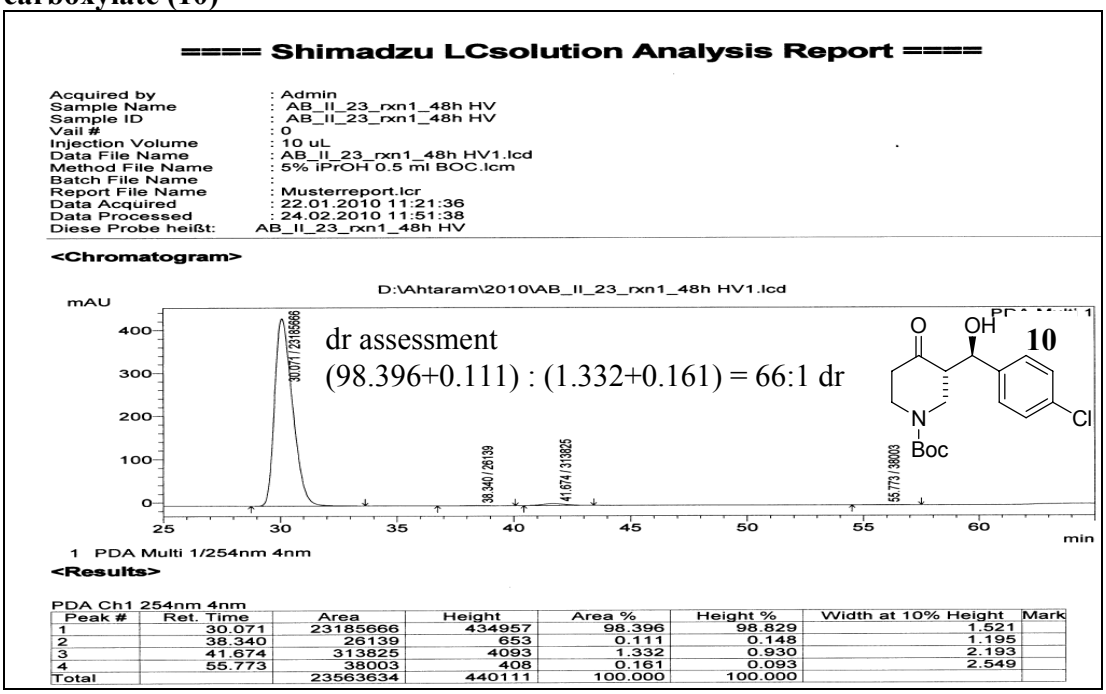


HPLC of Racemic *tert*-butyl 3-((4-chlorophenyl)(hydroxy)methyl)-4-oxopiperidine-1-carboxylate (10)



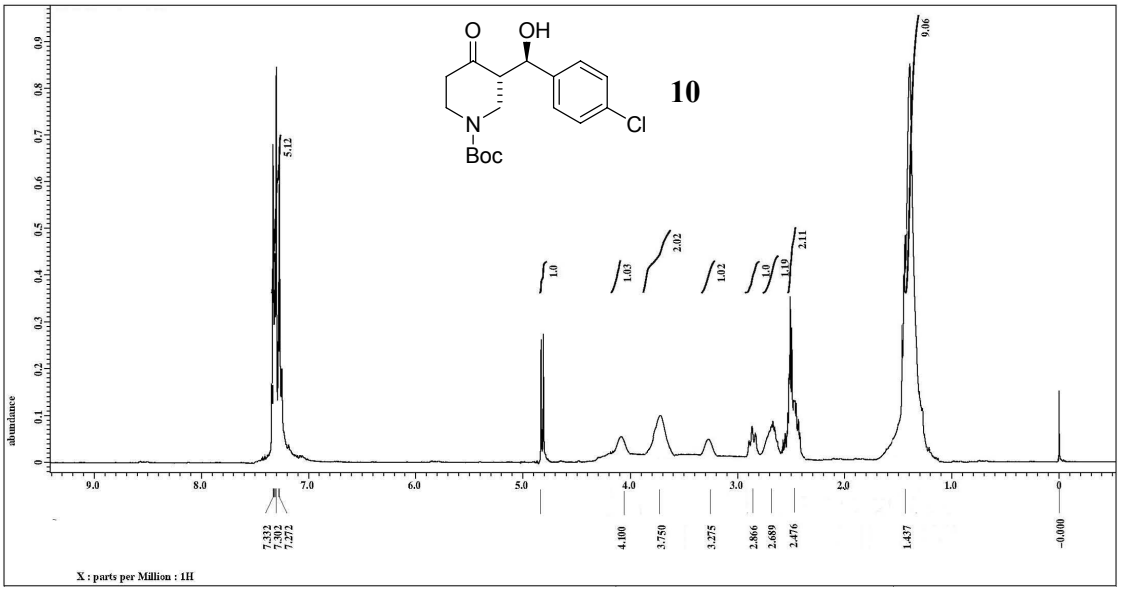
Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	30.026	1159674	23241	16.975	26.160	1.446	
2	37.108	1169361	21547	17.117	24.253	1.561	
3	40.700	2273726	27397	33.283	30.837	2.383	
4	54.428	2228722	16658	32.624	18.750	3.783	
Total		6831484	88843	100.000	100.000		

Crude HPLC of *tert*-butyl 3-((4-chlorophenyl)(hydroxy)methyl)-4-oxopiperidine-1-carboxylate (10)

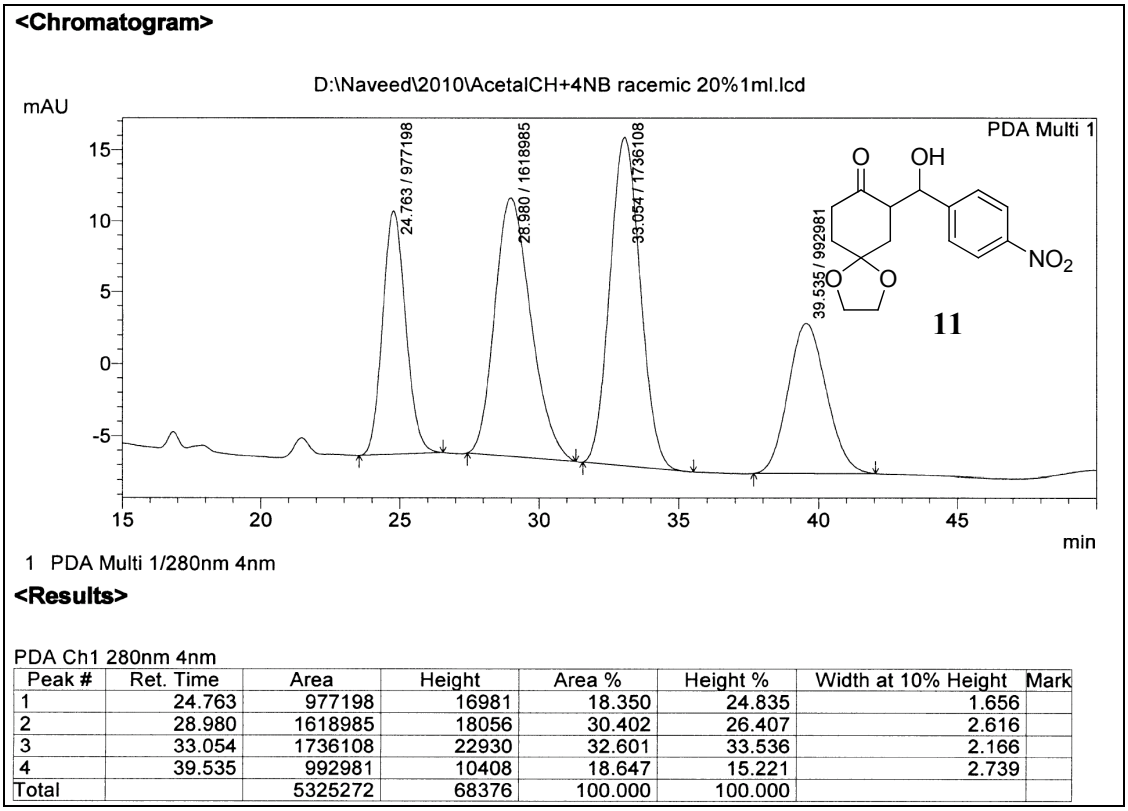


Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	30.071	23185666	434957	98.396	98.829	1.521	
2	38.340	26139	653	0.111	0.148	1.195	
3	41.674	313825	4093	1.332	0.930	2.193	
4	55.773	38003	408	0.161	0.093	2.549	
Total		23563634	440111	100.000	100.000		

^{1}H NMR *tert*-butyl 3-((4-chlorophenyl)(hydroxy)methyl)-4-oxopiperidine-1-carboxylate (after chromatography)



HPLC of Recemic 7-[Hydroxy-(4-nitro-phenyl)-methyl]-1,4-dioxa-spiro-[4.5]decan-8-one (11)

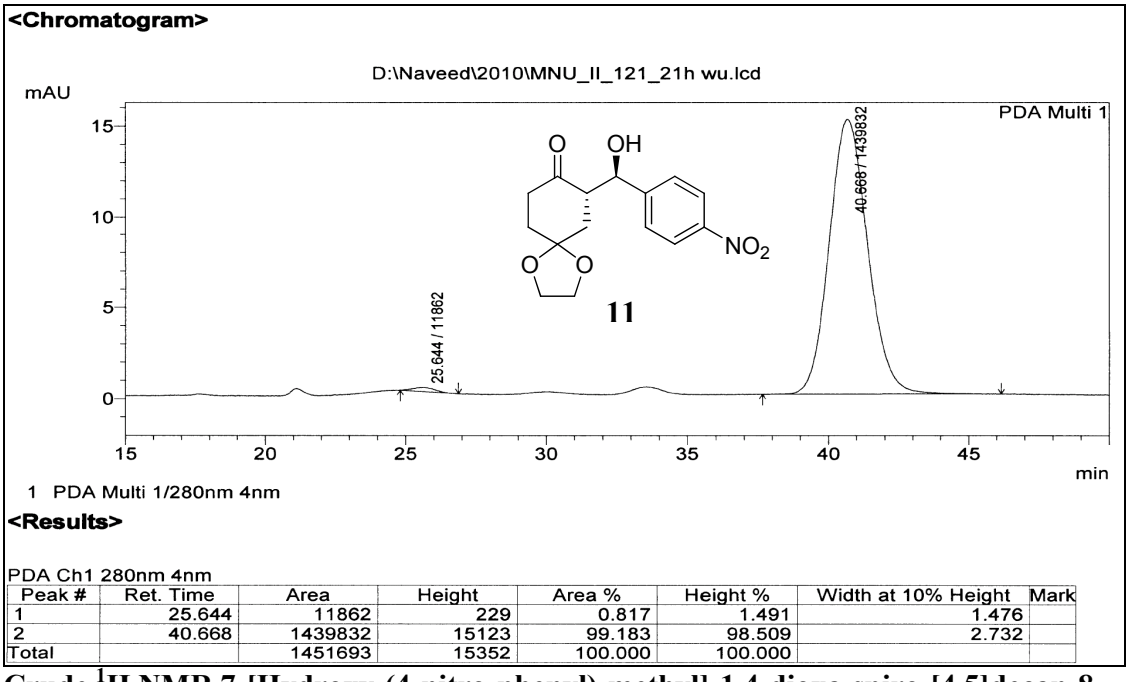


<Results>

PDA Ch1 280nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	24.763	977198	16981	18.350	24.835	1.656	
2	28.980	1618985	18056	30.402	26.407	2.616	
3	33.054	1736108	22930	32.601	33.536	2.166	
4	39.535	992981	10408	18.647	15.221	2.739	
Total		5325272	68376	100.000	100.000		

HPLC of 7-[Hydroxy-(4-nitro-phenyl)-methyl]-1,4-dioxa-spiro-[4.5]decan-8-one (11) (after column chromatography with silica gel)

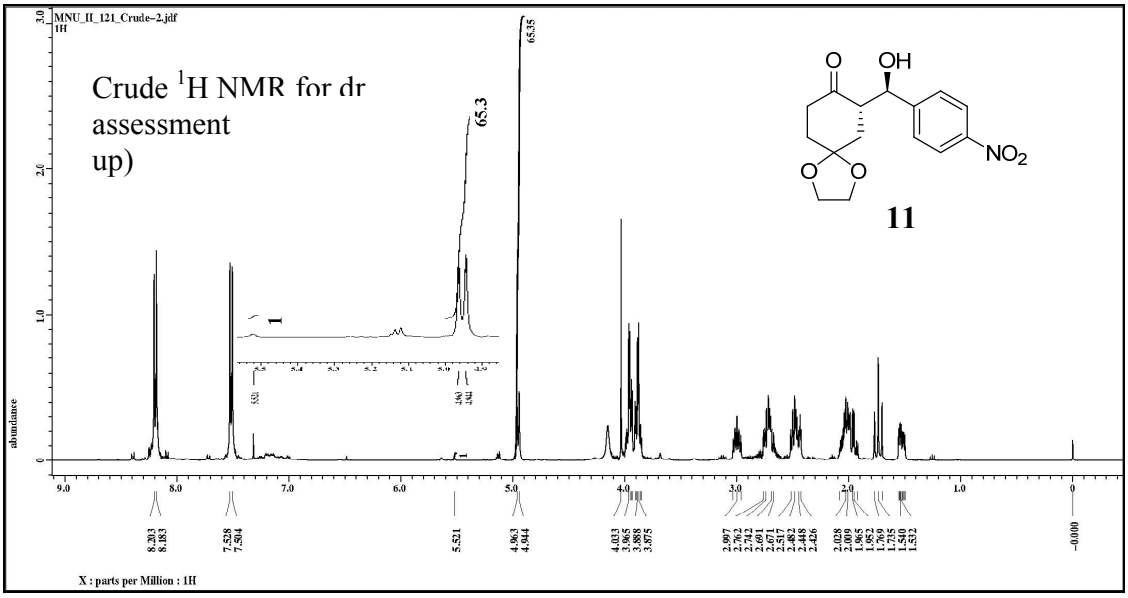


<Results>

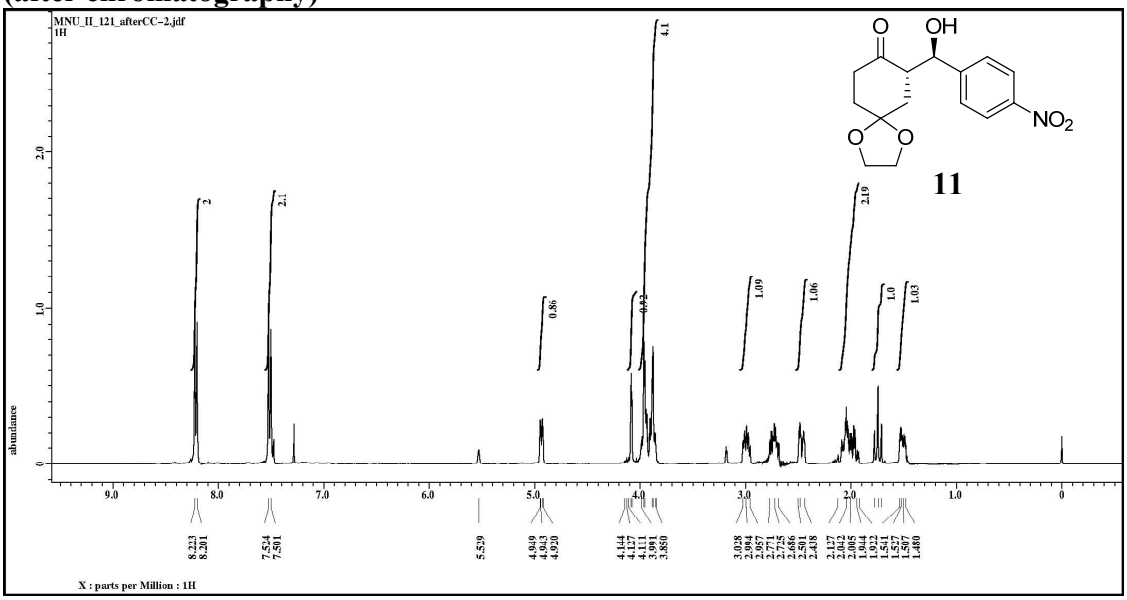
PDA Ch1 280nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	25.644	11862	229	0.817	1.491	1.476	
2	40.668	1439832	15123	99.183	98.509	2.732	
Total		1451693	15352	100.000	100.000		

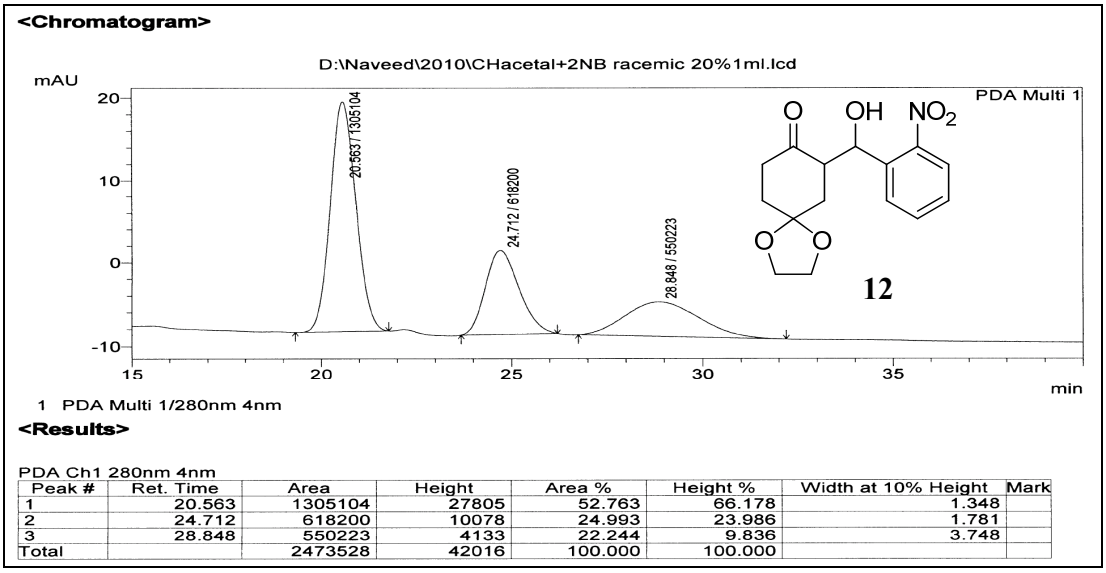
Crude ^{1}H NMR 7-[Hydroxy-(4-nitro-phenyl)-methyl]-1,4-dioxa-spiro-[4.5]decan-8-one (11)



^{1}H NMR 7-[Hydroxy-(4-nitro-phenyl)-methyl]-1,4-dioxa-spiro-[4.5]decan-8-one (11) (after chromatography)



HPLC of Recemic 7-[Hydroxy-(2-nitro-phenyl)-methyl]-1,4-dioxa-spiro-[4.5]decan-8-one (12)

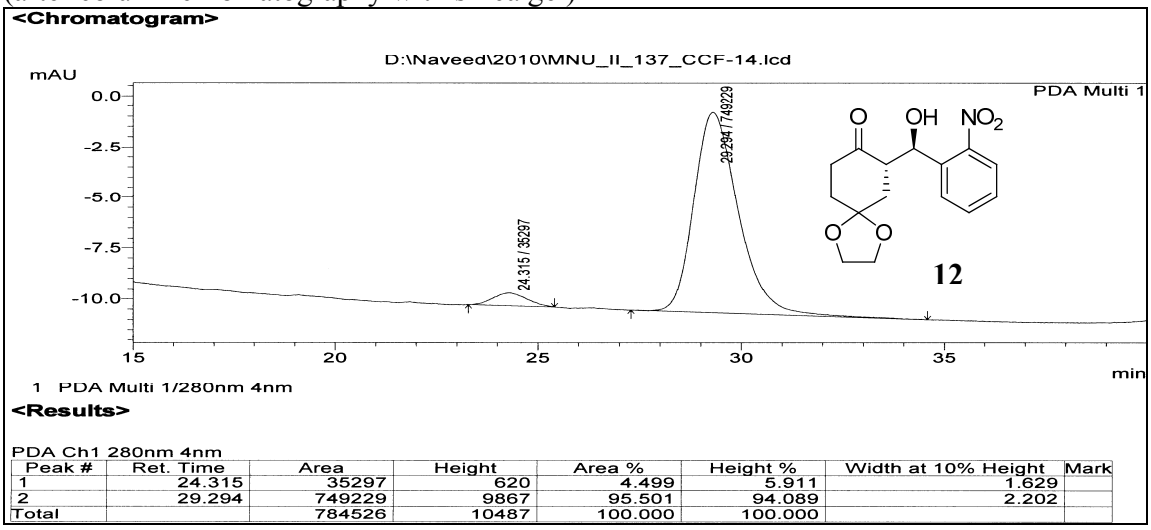


<Results>

PDA Ch1 280nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	20.563	1305104	27805	52.763	66.178	1.348	
2	24.712	618200	10078	24.993	23.986	1.781	
3	28.848	550223	4133	22.244	9.836	3.748	
Total		2473528	42016	100.000	100.000		

HPLC of 7-[Hydroxy-(2-nitro-phenyl)-methyl]-1,4-dioxa-spiro-[4.5]decan-8-one (12)
(after column chromatography with silica gel)

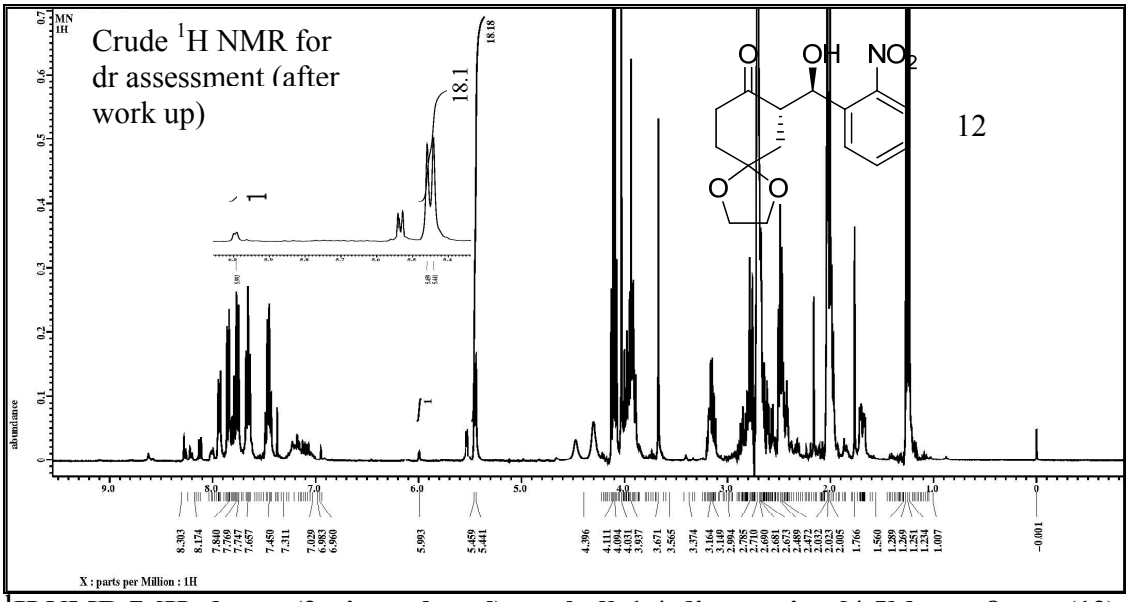


<Results>

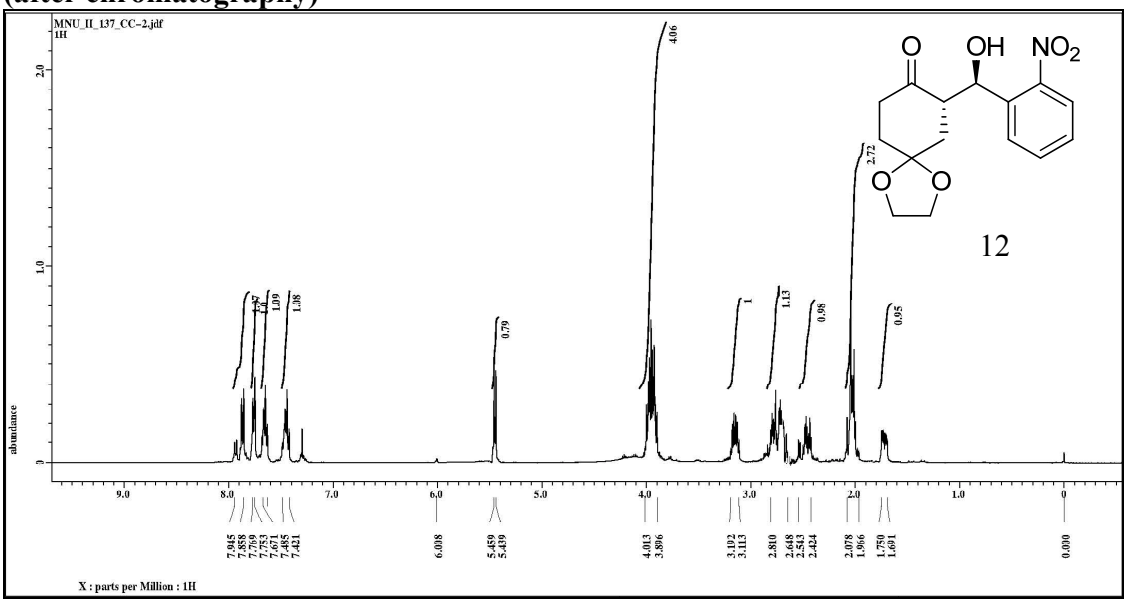
PDA Ch1 280nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	24.315	35297	620	4.499	5.911	1.629	
2	29.294	749229	9867	95.501	94.089	2.202	
Total		784526	10487	100.000	100.000		

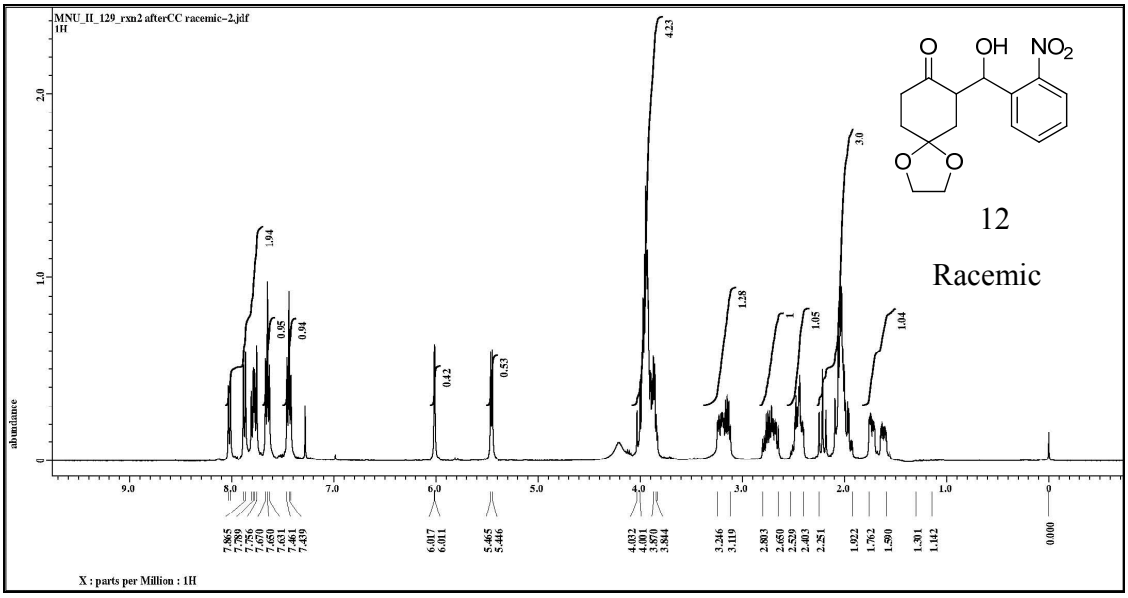
Crude ^{1}H NMR 7-[Hydroxy-(2-nitro-phenyl)-methyl]-1,4-dioxa-spiro-[4.5]decan-8-one (12)



^{1}H NMR 7-[Hydroxy-(2-nitro-phenyl)-methyl]-1,4-dioxa-spiro-[4.5]decan-8-one (12) (after chromatography)



^{1}H NMR of Racemic 7-[Hydroxy-(2-nitro-phenyl)-methyl]-1,4-dioxa-spiro-[4.5]decan-8-one (12) (after chromatography)



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