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Supporting Information

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Highly Enantioselective Synthesis of *cis*-α-Aminocycloalkanols by Ru-Catalyzed Asymmetric Hydrogenation via DKR

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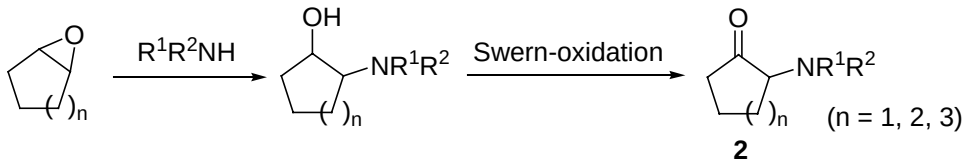
CONTENTS:

General: Anhydrous 2-propanol was freshly distilled from calcium hydride before use. Anhydrous ethanol was treated with magnesium and distilled before use. Chiral spiro diphosphine ligands (*S*)-SDP, (*S*)-Tol-SDP and (*S*)-Xyl-SDP are available from Strem Chemicals Co. Other spiro diphosphine ligands and the catalysts $RuCl_2$(SDPs)(DPEN) were prepared according to previous methods.[1] KO^{t}Bu and 1-benzylpiperidin-4-one were purchased from Acros Chemicals Co. Hydrogen gas (99.999%) was purchased from Boc Gas Inc., Tianjin. ^{1}H and ^{13}C NMR spectra were recorded on Varian Bruker-300 and Varian Bruker-400 spectrometers. Chemical shifts were

reported in ppm downfield from internal $Si(CH_3)_4$ and external 85% H_3PO_4, respectively. Optical rotations were determined using a PerkinElmer 341 polarimeter. HRMS were recorded on an IonSpec FT-ICR mass spectrometer with ESI resource. Melting points were measured on a RY-I apparatus and uncorrected. GC analyses were performed on Hewlett Packard Model HP 6890 Series. HPLC analyses were performed on a Hewlett Packard Model HP 1100 Series or Waters 2996 instruments. SFC analyses were performed on a Berger Analytix SFC instrument.

(A) Preparation and Physical Data of New α-Aminocycloalkanones

The *racemic* α-(dialkylamino)cycloalkanones were prepared by ring-opening of cycloalkene oxides with secondary amines, followed by oxidation of the corresponding α-(dialkylamino)cycloalkanols using Swern-oxidation method.[2]



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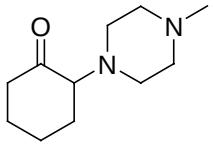
General procedure for ring-opening of cycloalkene oxides: The appropriate dialkylamine (100 mmol) was added to a solution of cycloalkene oxide (100 mmol) in anhydrous ethanol (100 mL), and the resulting mixture was heated under reflux overnight. After cooling to room temperature, the solvent and excessive amine were evaporated under reduced pressure to give crude α-(dialkylamino)cycloalkanol. Further purification by distillation under vacuum afforded pure product.

General procedure for Swern-oxidation of α-(dialkylamino)cycloalkanols: A solution of oxalyl chloride (140 mmol) in 50 mL of freshly distilled CH_2Cl_2 was cooled to −78 °C, and DMSO (280 mmol) was carefully added under nitrogen atmosphere. After stirring for 15 min, a solution of α-(dialkylamino)cycloalkanol (100 mmol) in 10 mL CH_2Cl_2 and 85 mL Et_3N was added successively. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and stirred for 2.5 h. The solvent was removed under reduced pressure, and the residue was extracted with ethyl acetate. The extract was washed with saturated aqueous Na_2CO_3

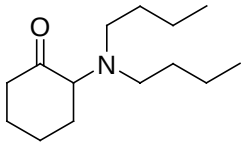
solution, brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was distilled under vacuum to yield the *racemic* α-(dialkylamino)cycloalkanone.

2-(4-Methylpiperazin-1-yl)cyclohexanone (2d)



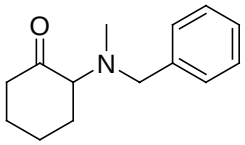
Colorless oil, bp: 102 °C / 0.5 mmHg, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53–1.60 (m, 1H), 1.73–1.99 (m, 5H), 2.18–2.29 (m, 1H), 2.26 (s, 3H), 2.33–2.70 (m, 9H), 2.93 (dd, *J* = 9.4, 3.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 28.0, 29.8, 40.4, 45.8, 49.3, 55.0, 72.1, 210.8. HRMS (ESI) *m*/*z* calcd $C_{11}H_{21}N_2O$ ($[M+H]^+$): 197.1648. Found: 197.1643.

2-[Di(*n*-butyl)amino]cyclohexanone (2g)



Colorless oil, bp: 84 °C / 0.1 mmHg, 87% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, *J* = 7.2 Hz, 6H), 1.19–1.35 (m, 8H), 1.53–1.64 (m, 2H), 1.66–1.78 (m, 1H), 1.85–1.98 (m, 3H), 2.10–2.20 (m, 1H), 2.37–2.47 (m, 3H), 2.52–2.59 (m, 2H), 3.25 (dd, *J* = 10.5, 4.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 19.9, 24.0, 27.1, 30.9, 31.9, 41.1, 51.0, 69.0, 210.2. HRMS (ESI) *m*/*z* calcd $C_{14}H_{28}NO$ ($[M+H]^+$): 226.2165. Found: 226.2168.

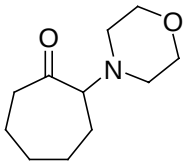
2-(Benzylmethylamino)cyclohexanone (2h)



Colorless oil, bp: 128 °C / 0.1 mmHg, 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60–1.65 (m, 1H), 1.69–1.75 (m, 1H), 1.87–2.00 (m, 3H), 2.07–2.12 (m, 1H), 2.19–2.27 (m, 1H), 2.30 (s, 3H), 2.53–2.57 (m, 1H), 3.17 (dd, *J* = 10.0, 4.4 Hz, 1H), 3.61 (d, *J* = 13.2 Hz, 1H), 3.75 (d, *J* = 13.2 Hz, 1H), 7.22–7.36 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 27.8, 31.0, 38.3, 41.6, 58.4, 71.2,

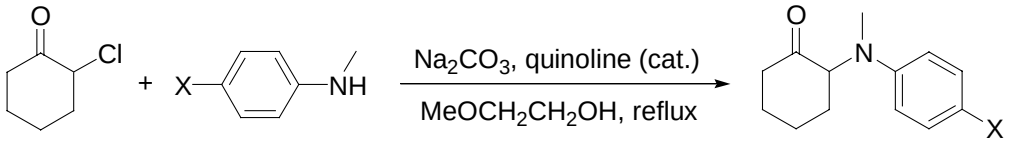
127.0, 128.3, 128.7, 139.9, 211.5. MS (ESI) *m*/*z* 218 ($[M+H]^+$). Anal. calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.15; H, 8.82; N, 6.41.

2-(Morpholin-4-yl)cycloheptanone (2m)



Colorless oil, bp: 110 °C / 0.5 mmHg, 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33–1.48 (m, 2H), 1.53–1.64 (m, 2H), 1.69–1.73 (m, 1H), 1.78–1.94 (m, 3H), 2.32–2.45 (m, 3H), 2.52–2.63 (m, 3H), 3.02 (dd, *J* = 9.2, 4.0 Hz, 1H), 3.69 (t, *J* = 4.8 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 26.1, 27.8, 29.4, 41.6, 50.7, 67.0, 74.4, 213.4. HRMS (ESI) m/z calcd $C_{11}H_{20}NO_2$ ($[M+H]^+$): 198.1489. Found: 198.1495.

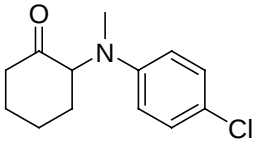
The *racemic* α-(arylmethylamino)cyclohexanones were prepared by substituted 2-chlorocyclohexanone with appropriate arylmethylamines.[3]



(X = H, Me, Cl)

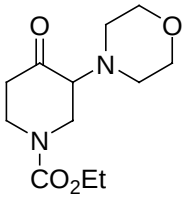
General procedure for preparation of α-(arylmethylamino)cyclohexanone: The appropriate arylmethylamine (0.2 mol), 2-chlorocyclohexanone (0.2 mol), quinoline (0.02 mol), sodium carbonate (0.3 mol) and 150 mL 2-methoxyethanol were added to a dry flask and the resulting reaction mixture was heated to reflux for 2 h. The reaction mixture was cooled to room temperature. The solid was removed by filtration and washed with chloroform. The filtrate was concentrated under reduced pressure to give crude product. Pure *racemic* α-(arylmethylamino)cycloalkanone was obtained by distillation under vacuum.

2-[(4-Chlorophenyl)methylamino]cyclohexanone (2k)



White solid, mp: 110-112 °C, 56% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64–1.74 (m, 1H), 1.76–1.84 (m, 1H), 1.92–1.99 (m, 1H), 2.02–2.70 (m, 1H), 2.10–2.14 (m, 1H), 2.19–2.23 (m, 1H), 2.34–2.43 (m, 1H), 2.52–2.57 (m, 1H), 2.88 (s, 3H), 4.27 (dd, *J* = 12.4, 6.0 Hz, 1H), 6.61 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 27.2, 31.9, 34.6, 42.2, 67.6, 114.7, 122.3, 129.1, 148.8, 208.6. HRMS (ESI) calcd for $C_{13}H_{17}NOCl$ ($[M+H]^+$): 238.0993. Found: 238.0990.

Preparation of ethyl 3-(morpholin-4-yl)-4-oxopiperidine-1-carboxylate (2n)



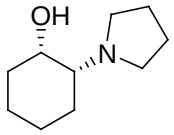
Powdered $CuBr_2$ (4.60 g, 20.6 mmol) was added in portions to a refluxing solution of ethyl 4-oxopiperidine-1-carboxylate (2.02 g, 10.3 mmol) in $CHCl_3$ (20 mL) and EtOAc (20 mL) under nitrogen in 20 min. When the addition was complete, the solution was further refluxed for 1 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with water, 5% $NaHCO_3$, and brine successively. The organic layer was dried over Na_2SO_4 and concentrated to afford a bromide as an oil, which was directly used for the next reaction.[4]

The bromide obtained above was added to a solution of morpholine (1.05 g, 12.0 mmol), triethylamine (1.5 g, 15 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at room temperature overnight. Saturated aqueous Na_2CO_3 solution was then added, and the resulting mixture was extracted with CH_2Cl_2. The extract was dried over $NaSO_4$, and concentrated under reduced pressure. The residue was distillated under vacuum to yield **6n** as colorless liquid, 45% yield. bp: 160 °C / 0.5 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.2 Hz, 3H), 2.30–2.43 (m, 3H), 2.70–2.76 (m, 3H), 2.88 (m, 1H), 3.56–2.73 (m, 6H), 3.86–3.97 (m, 2H), 4.18 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 40.0, 44.3, 45.3, 50.6, 61.8, 66.9, 72.1, 155.4, 207.8. MS (ESI): *m*/*z* 257 ($[M+H]^+$). Anal. calcd for $C_{12}H_{20}N_2O_4$: C, 56.23; H, 7.87; N, 10.93. Found: C, 55.98; H, 8.00; N, 10.85.

(B) General Procedure for Asymmetric Hydrogenation of α-Aminocycloalkanones

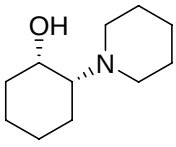
General procedure (S/C = 1000): The catalyst $RuCl_2$[(*S*)-SDP][(*R*,*R*)-DPEN] (**1a**) (2.2 mg, 0.002 mmol) and *i*-PrOH (2.0 mL) were added to a 25 mL hydrogenation vessel. The vessel was placed in an autoclave and purged with hydrogen by pressurizing to 10 atm and releasing the pressure. The procedure was repeated three times and the solution was stirred under 10 atm of H_2 for 5 min. After releasing the pressure, ketone (2 mmol) and a solution of *t*-BuOK in *i*-PrOH (0.2 mmol/mL, 1.0 mL, 0.2 mmol) were added. The autoclave was purged with hydrogen and pressurized to 10 atm. After stirring at room temperature for certain hours, the reaction was stopped. The reaction mixture was filtered through a short silica gel column, and the filtrate was diluted with acetone and analyzed by GC to determine the conversion and the selectivity. The enantioselectivity was determined by chiral GC, HPLC or SFC.

(1*S*,2*R*)-2-(Pyrrolidin-1-yl)cyclohexanol (3a) [5]



White solid, mp: 105–107 °C, 90% yield. $[\alpha]_D^{20}$ –33.4 (*c* 1.00, $CHCl_3$), 99.8% ee [GC conditions: Supelco α-DEX™ 120 column (25 m × 0.25 mm × 0.25 μm); carrier gas, N_2 (2.0 mL/min); injection temp., 230 °C; initial column temp., 100 °C; rate, 0.5 °C/min; final column temp., 200 °C; t_R(1*R*,2*S*) = 31.27 min; t_R(1*S*,2*R*) = 32.46 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17–1.57 (m, 6H), 1.58–1.74 (m, 5H), 1.95–2.03 (m, 2H), 2.47–2.48 (m, 2H), 2.63–2.64 (m, 2H), 3.12 (br, 1H), 3.95 (m, 1H).

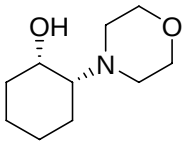
(1*S*,2*R*)-2-(Piperidin-1-yl)cyclohexanol (3b) [5]



White solid, mp: 109–111 °C, 90% yield. $[\alpha]_D^{20}$ –19.0 (*c* 1.00, $CHCl_3$). 99% ee [determined by HPLC analysis of the corresponding 3,5-dinitrobenzoyl derivative using a Chiralcel AD–H column

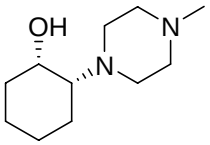
(25 cm); *i*-PrOH /*n*-Hex = 1:99, 1.0 mL/min; t_R(1*S*,2*R*) = 11.17 min; t_R(1*R*,2*S*) = 12.49 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09–1.76 (m, 13H), 1.98–2.08 (m, 2H), 2.46–2.48 (m, 2H), 2.54–2.56 (m, 2H), 3.35 (br, 1H), 4.01 (m, 1H).

(1*S*,2*R*)-2-(Morpholin-4-yl)cyclohexanol (3c) [6]



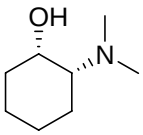
White solid, mp: 96–98 °C, 91% yield. $[\alpha]_D^{20}$ –21.7 (*c* 1.00, $CHCl_3$). 99.9% ee [determined by HPLC analysis of the corresponding 3,5-dinitrobenzoyl derivative using a Chiralcel OD–H column (25 cm); *i*-PrOH /*n*-Hex = 30:70, 1.0 mL/min; t_R(1*S*,2*R*) = 13.85 min; t_R(1*R*,2*S*) = 22.68 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10–1.23 (m, 1H), 1.27–1.41 (m, 3H), 1.47–1.55 (m, 1H), 1.66–1.78 (m, 2H), 1.99–2.10 (m, 2H), 2.48–2.50 (m, 2H), 2.62–2.64 (m, 2H), 3.11 (br, 1H), 3.69–3.72 (m, 4H), 4.01 (m, 1H).

(1*S*,2*R*)-2-(4-Methylpiperazin-1-yl)cyclohexanol (3d) [7]



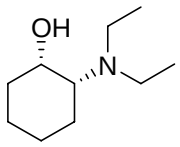
White solid, mp: 78–80 °C, 90% yield. $[\alpha]_D^{20}$ –14.3 (*c* 0.98, $CHCl_3$), 99.6% ee [determined by HPLC analysis of the corresponding benzoyl derivative using a Chiralcel OD–H column (25 cm), *i*-PrOH /*n*-Hex = 10:90, 1.0 mL/min; t_R(1*S*,2*R*) = 4.26 min; t_R(1*R*,2*S*) = 6.93 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14–1.21 (m, 1H), 1.28–1.42 (m, 2H), 1.47–1.57 (m, 1H), 1.67–1.76 (m, 2H), 1.98–2.02 (m, 1H), 2.06–2.10 (m, 1H), 2.27 (s, 3H), 2.20–2.79 (m, 7H), 2.93–3.31 (m, 2H), 3.51 (br, 1H), 4.01 (m, 1H).

(1*S*,2*R*)-2-(Dimethylamino)cyclohexanol (3e) [8]



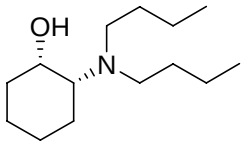
White solid, mp: 45–47 °C, 80% yield. $[\alpha]_D^{20}$ –26.2 (*c* 1.05, $CHCl_3$), 99.9% ee [GC conditions: Suplco α-DEX^{TM} 120 column (25 m × 0.25 mm × 0.25 μm); carrier gas, N_2 (2.0 mL/min); injection temp., 230 °C; initial column temp., 50 °C (30 min); rate, 0.5 °C/min; final column temp., 200 °C; t_R (1*R*,2*S*) = 68.43 min; t_R (1*S*,2*R*) = 70.36 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11–1.23 (m, 1H), 1.28–1.37 (m, 2H), 1.42–1.55 (m, 2H), 1.69–1.76 (m, 2H), 1.94–2.01 (m, 2H), 2.32 (s, 6H), 3.77 (br, 1H), 4.08 (m, 1H).

(1*S*,2*R*)-2-(Diethylamino)cyclohexanol (3f) [6]



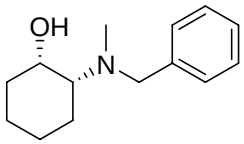
Colorless oil, 89% yield. $[\alpha]_D^{20}$ –13.6 (*c* 1.01, $CHCl_3$), 99% ee [determined by HPLC analysis of the corresponding 3,5-dinitrobenzoyl derivative using a Chiralcel OD–H column (25 cm); *i*-PrOH /*n*-Hex = 10:90, 1.0 mL/min; t_R(1*S*,2*R*) = 12.08 min; t_R(1*R*,2*S*) = 16.77 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.2 Hz, 6H), 1.22–1.27 (m, 1H), 1.34–1.42 (m, 2H), 1.54–1.65 (m, 1H), 1.73–1.84 (m, 3H), 1.97–2.01 (m, 1H), 2.68–2.71 (m, 1H), 2.89–3.06 (m, 4H), 4.28 (m, 1H).

(1*S*,2*R*)-2-(Dibutylamino)cyclohexanol (3g) [9]



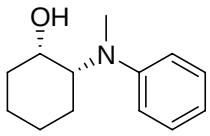
Colorless oil, 91% yield. $[\alpha]_D^{20}$ –8.1 (*c* 1.05, $CHCl_3$), 99.6% ee [determined by HPLC analysis of the corresponding 3,5-dinitrobenzoyl derivative using a Chiralcel OD–H column (25 cm); *i*-PrOH /*n*-Hex = 10:90, 1.0 mL/min; t_R(1*S*,2*R*) = 13.82 min; t_R(1*R*,2*S*) = 19.15 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.2 Hz, 6H), 1.15–1.56 (m, 13H), 1.63–1.67 (m, 1H), 1.74–1.77 (m, 1H), 1.98–2.03 (m, 1H), 2.36–2.39 (m, 1H), 2.55–2.61 (m, 4H), 3.31 (br, 1H), 3.95 (m, 1H).

(1*S*,2*R*)-2-(Benzylmethylamino)cyclohexanol (3h) [7]



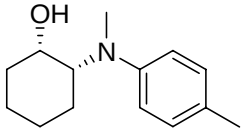
Colorless oil, 93% yield. $[\alpha]_D^{20}$ –6.6 (*c* 1.08, $CHCl_3$), 99% ee [HPLC conditions: Chiralcel AD–H column (25 cm); *i*-PrOH /*n*-Hex = 5:95, 1.0 mL/min; t_R(1*S*,2*R*) = 8.21 min; t_R(1*R*,2*S*) = 9.16 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.23 (m, 1H), 1.35–1.42 (m, 2H), 1.49–1.60 (m, 2H), 1.78–1.81 (m, 2H), 2.05–2.08 (m, 1H), 2.17 (s, 3H), 2.24–2.28 (m, 1H), 3.25 (br, 1H), 3.51 (d, *J* = 13.4 Hz, 1H), 3.71 (d, *J* = 13.4 Hz, 1H), 4.14 (m, 1H), 7.25–7.35 (m, 5H).

(1*S*,2*R*)-2-(Methylphenylamino)cyclohexanol (3i) [10]



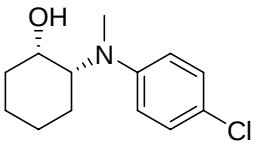
Colorless oil, 94% yield. $[\alpha]_D^{20}$ +117 (*c* 0.99, $CHCl_3$) , 99.3% ee [HPLC conditions: Chiralcel OJ column (25 cm); *i*-PrOH /*n*-Hex = 10:90, 1.0 mL/min; t_R(1*S*,2*R*) = 26.90 min; t_R(1*R*,2*S*) = 41.38 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26–1.38 (m, 1H), 1.46–1.64 (m, 4H), 1.80–2.02 (m, 4H), 2.93 (s, 3H), 3.42–3.47 (m, 1H), 4.19 (m, 1H), 6.77–6.83 (m, 3H), 7.23–7.27 (m, 2H).

(1*S*,2*R*)-2-((4-Methylphenyl)methylamino)cyclohexanol (3j) [11]



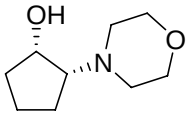
Colorless oil, 92% yield. $[\alpha]_D^{20}$ +66.3 (*c* 1.00, $CHCl_3$), 99.6% ee [SFC conditions: Chiralcel OJ–H column (25 cm); 10% *i*-PrOH, 100 bar CO_2, 2.0 mL/min; t_R(1*S*,2*R*) = 9.40 min; t_R(1*R*,2*S*) = 11.69 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26–1.30 (m, 1H), 1.42–1.61 (m, 4H), 1.75–1.82 (m, 2H), 1.90–1.93 (m, 1H), 2.15 (br, 1H), 2.28 (s, 3H), 2.85 (s, 3H), 3.21–3.26 (m, 1H), 4.13 (m, 1H), 6.81 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H).

(1*S*,2*R*)-2-((4-Chlorophenyl)methylamino)cyclohexanol (3k)



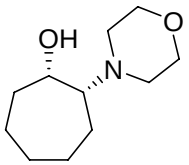
Colorless oil, 93% yield. $[\alpha]_D^{20}$ +131 (*c* 0.98, $CHCl_3$), 99.6% ee [SFC conditions: Chiralcel OJ–H column (25 cm); 10% *i*-PrOH, 100 bar CO_2, 2.0 mL/min; t_R(1*S*,2*R*) = 17.83 min; t_R(1*R*,2*S*) = 19.41 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79–0.87 (m, 1H), 1.25–1.38 (m, 1H), 1.46–1.62 (m, 3H), 1.71 (br, 1H), 1.84–1.90 (m, 2H), 1.96–2.04 (m, 1H), 2.90 (s, 3H), 3.38–3.43 (m, 1H), 4.16 (m, 1H), 6.70 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 25.3, 26.4, 32.8, 34.5, 61.2, 68.5, 115.3, 122.0, 129.1, 148.8. HRMS (ESI) *m*/*z* calcd $C_{14}H_{17}NO$ ([M-H]$^-$): 238.1004. Found: 238.1009.

(1*S*,2*R*)-2-(Morpholin-4-yl)cyclopentanol (3l) [12]



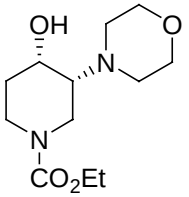
White solid, mp: 80–82 °C, 87% yield. $[\alpha]_D^{20}$ –18.8 (*c* 1.00, $CHCl_3$), 98% ee [determined by HPLC analysis of the corresponding 3,5-dinitrobenzoyl derivative using Chiralcel AD–H column (25 cm), *i*-PrOH /*n*-Hex = 20:80, 1.0 mL/min; t_R(1*R*,2*S*) = 10.35 min; t_R (1*S*,2*R*) = 12.06 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55–1.92 (m, 6H), 2.52–2.55 (m, 2H), 2.66–2.69 (m, 2H), 3.65–3.70 (m, 1H), 3.74 (t, *J* = 4.6 Hz, 4H), 4.11–4.13 (m, 1H), 4.19 (br, 1H).

(1*S*,2*R*)-2-(Morpholin-4-yl)cycloheptanol (3m) [12]



White solid, mp: 84–86 °C, 91% yield. $[\alpha]_D^{20}$ –33.4 (*c* 1.00, $CHCl_3$), 97% ee [determined by HPLC analysis of the corresponding 3,5-dinitrobenzoyl derivative using Chiralcel AD–H column (25 cm); *i*-PrOH /*n*-Hex = 20:80, 1.0 mL/min; t_R(1*S*,2*R*) = 10.19 min; t_R(1*R*,2*S*) = 12.68 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16–1.35 (m, 4H), 1.48–1.90 (m, 6H), 2.56–2.67 (m, 5H), 3.68–3.75 (m, 4H), 3.86–3.90 (m, 1H), 4.40 (br, 1H).

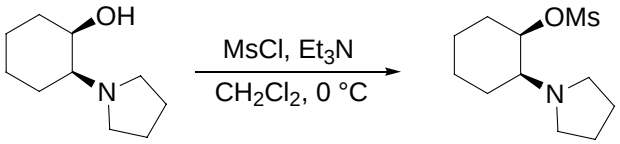
(3*R*,4*S*)-Ethyl 4-hydroxy-3-(morpholin-4-yl)piperidine-1-carboxylate (3n)



White solid, mp: 83–85 °C, 91% yield. $[\alpha]_D^{20}$ +13.5 (*c* 1.00, $CHCl_3$), 99.9% ee [determined by HPLC analysis of the corresponding 3,5-dinitrobenzoyl derivative using Chiralcel OD–H column (25 cm); *i*-PrOH /*n*-Hex = 30:70, 1.0 mL/min; t_R(1*S*,2*R*) = 43.48 min; t_R(1*R*,2*S*) = 65.02 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 9.2 Hz, 3H), 1.53–1.60 (m, 1H), 1.91–1.95 (m, 1H), 2.23–2.25 (m, 1H), 2.46–2.50 (m, 2H), 2.68–2.71 (m, 2H), 2.80–2.86 (m, 1H), 3.03–3.08 (m, 2H), 3.70–3.73 (m, 4H), 3.85–3.88 (m, 1H), 4.09–4.15 (m, 3H), 4.26 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 30.2, 38.1, 41.1, 50.1, 61.5, 62.2, 62.6, 67.2, 155.6. HRMS (ESI) calcd for $C_{12}H_{23}N_2O_4$ ($[M+H]^+$): 259.1652. Found: 259.1654.

(C) Synthesis of U-(–)-50488

(1*R*,2*S*)-2-(Pyrrolidin-1-yl)cyclohexyl methanesulfonate (5)

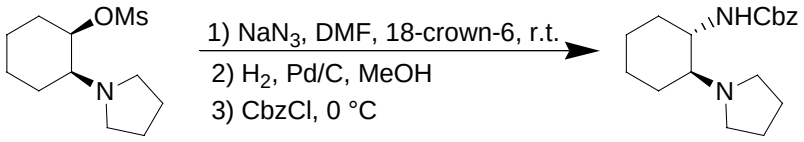


(1*R*,2*S*)-**3a** (1*R*,2*S*)-**5**

A solution of methanesulfonyl chloride (1.3 g, 11 mmol) in 60 mL anhydrous CH_2Cl_2 was added to a mixture of (1*R*,2*S*)-2-(pyrrolidin-1-yl)cyclohexanol (**3a**) (1.7 g, 10 mmol) and triethylamine (1.8 mL, 15 mmol) in 90 mL anhydrous CH_2Cl_2 under nitrogen atmosphere at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for overnight. After quenched with saturated Na_2CO_3 solution, the solvent was removed under reduced pressure and the obtained residue was re-dissolved with EtOAc. The solution was washed with brine, dried over Na_2SO_4 and concentrated to give crude product. Further purification by flash chromatography with ethyl acetate/methanol (10:1) yielded (1*R*,2*S*)-**5** as an oil (2.34 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23–1.33 (m, 1H), 1.47–1.61 (m, 5H), 1.69–1.80 (m, 5 H), 2.10–2.16 (m, 2H), 2.45–2.51 (m, 2H), 2.62–2.66 (m, 2H), 3.10 (s, 3H), 5.07–5.10 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 23.3,

24.4, 26.1, 30.9, 39.2, 51.6, 65.9, 80.7. HRMS (ESI) calcd for $C_{11}H_{22}NO_3S$ ($[M+H]^+$): 248.1315. Found: 248.1319.

Benzyl (1*S*,2*S*)-*N*-[2-(pyrrolidin-1-yl)cyclohexyl]carbamate (6)

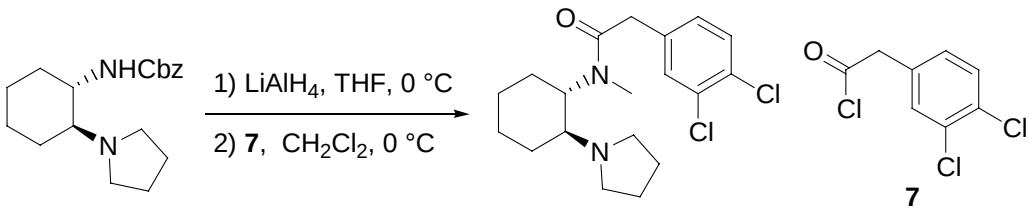


(1*R*,2*S*)-**5** (1*S*,2*S*)-**6**

A mixture of NaN_3 (0.39 g, 6 mmol), 18-crown-6 (1.06 g, 4 mmol) and DMF (3 mL) was stirred at room temperature under nitrogen atmosphere for 3 h. (1*R*,2*S*)-2-(Pyrrolidin-1-yl)cyclohexyl methanesulfonate (**5**) (1.0 g, 4 mmol) was added. After stirred at room temperature for 4 days, the reaction mixture was poured into water, extracted with ether. The extract was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give azide product.

The azide obtained above was dissolved with 10 mL MeOH in a 20 mL hydrogenation vessel. After added 0.1 g Pd/C (10%), the vessel was placed in an autoclave and purged with hydrogen. The hydrogenation was performed under 3 atm of H_2 at room temperature overnight. The reaction mixture was filtered to remove the Pd/C. The filtrate was diluted with EtOAc (15 mL) and cooled to 0 °C and benzyl chloroformate (0.8 mL, 4.8 mmol) in 10 mL EtOAc was added. The reaction mixture was stirred overnight and neutralized with saturated Na_2CO_3 to pH below 10. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product. Purification of the crude product by flash chromatography with ethyl acetate/methanol (10:1) yielded (1*S*,2*S*)-**6** as an oil (0.63 g, 53% yield). $[\alpha]_D^{20}$ +50.2 (*c* 1.05, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.11–1.33 (m, 4H), 1.61–1.79 (m, 7H), 2.43–2.51 (m, 4H), 2.59–2.62 (m, 2H), 3.27–3.34 (m, 1H), 5.05–5.12 (m, 2H), 5.63 (br, 1H), 7.30–7.36 (m, 5H).

U-(–)-50488 (4)



(1*S*,2*S*)-**6** U-(-)-50488 (**4**)

U-(−)-50488 (**4**) was prepared according to the literature methods. [13] The product was obtained as an oil, 90% yield. Hydrochloride salt of U-(−)-50488 (**4**): $[\alpha]_D^{20}$ −36.8 (*c* 0.75, MeOH) [lit. $[\alpha]_D^{20}$ −34.0 (*c* 0.7, MeOH) for 99% ee; [13] $[\alpha]_D^{20}$ −36.05 (*c* 0.73, MeOH) for 99% ee [14]]

Reference:

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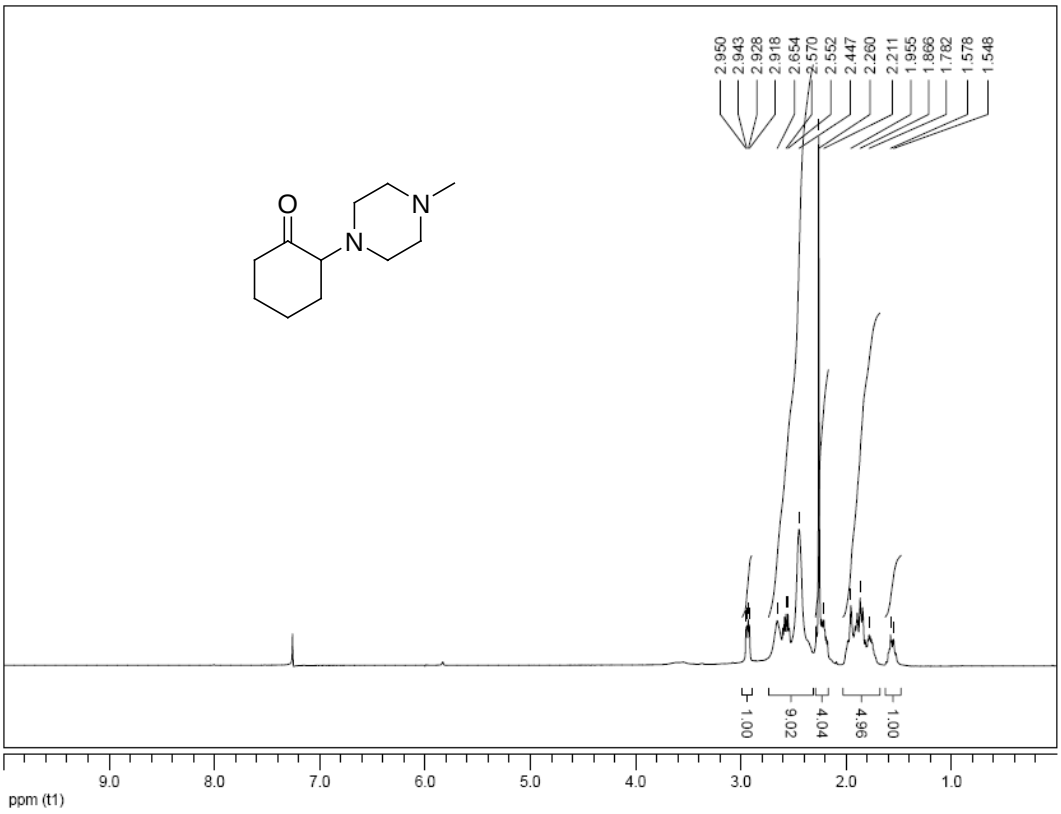
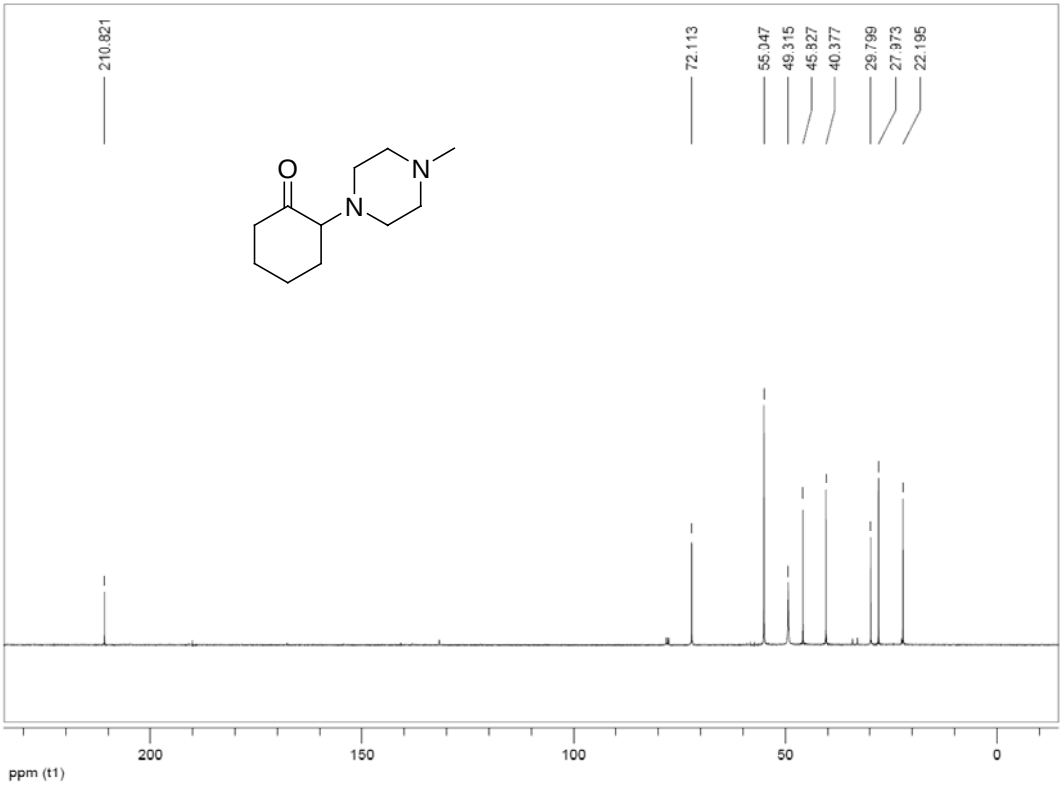
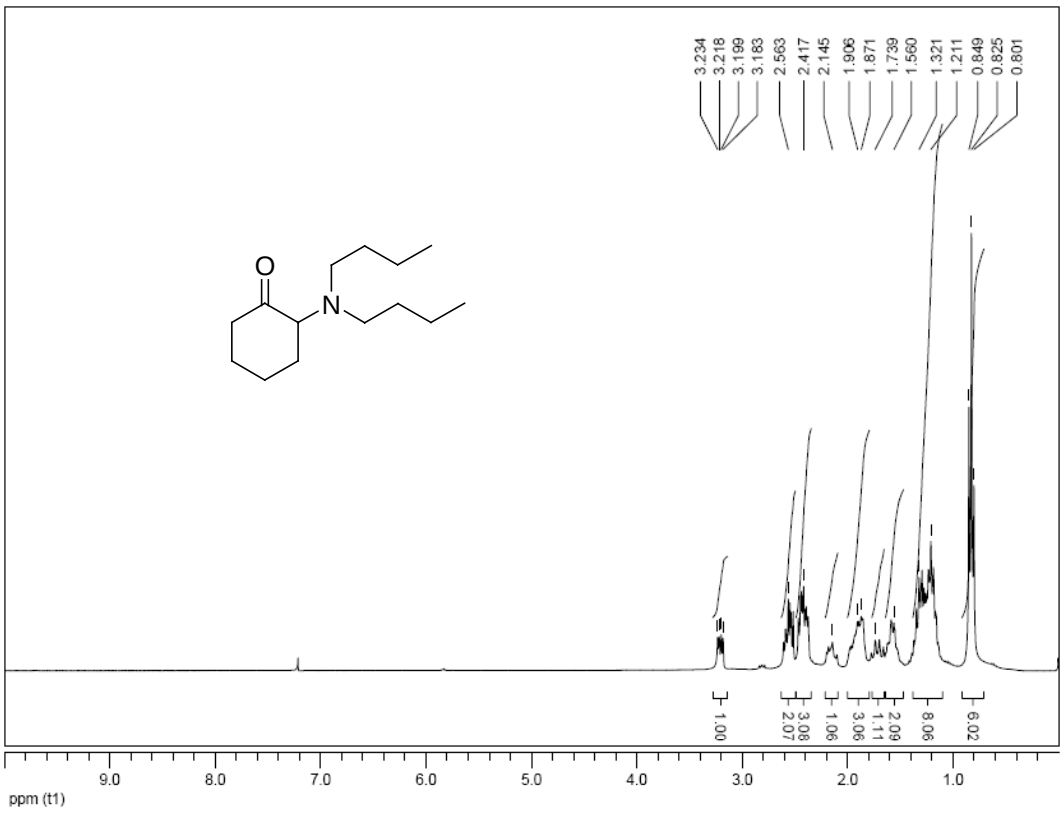
(D) NMR Spectra for New α-Aminocycloalkanones and α-Aminocycloalkanols

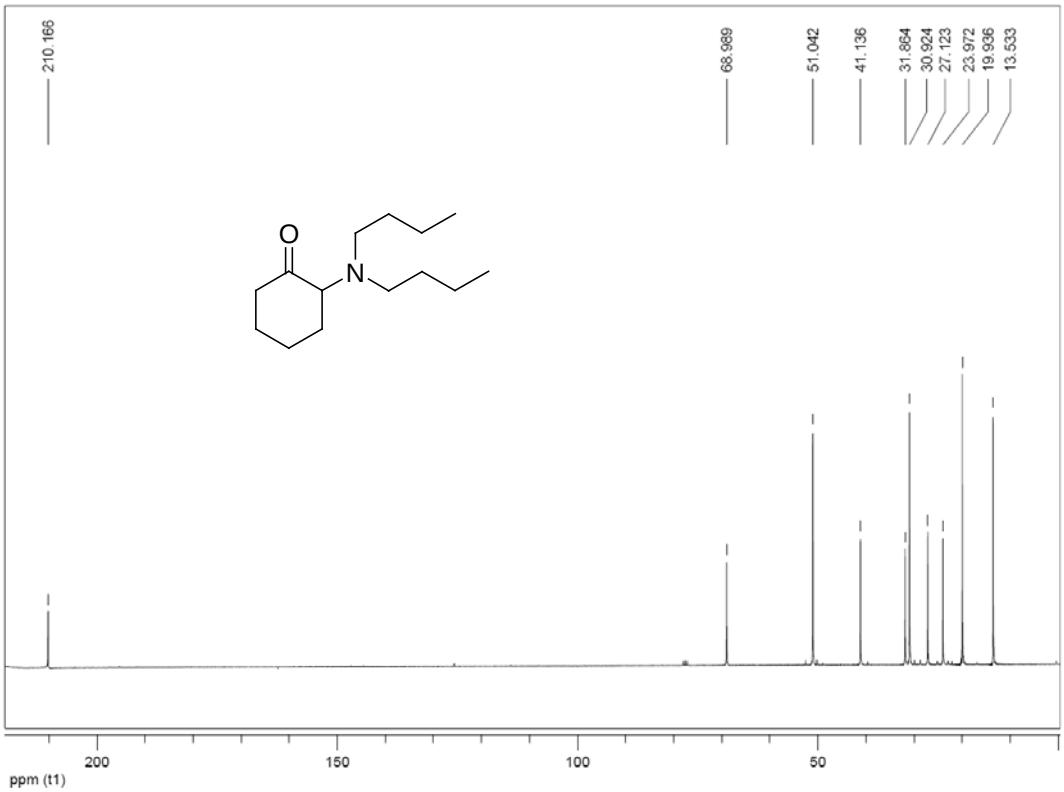
2-(4-Methylpiperazin-1-yl)cyclohexanone (2d)



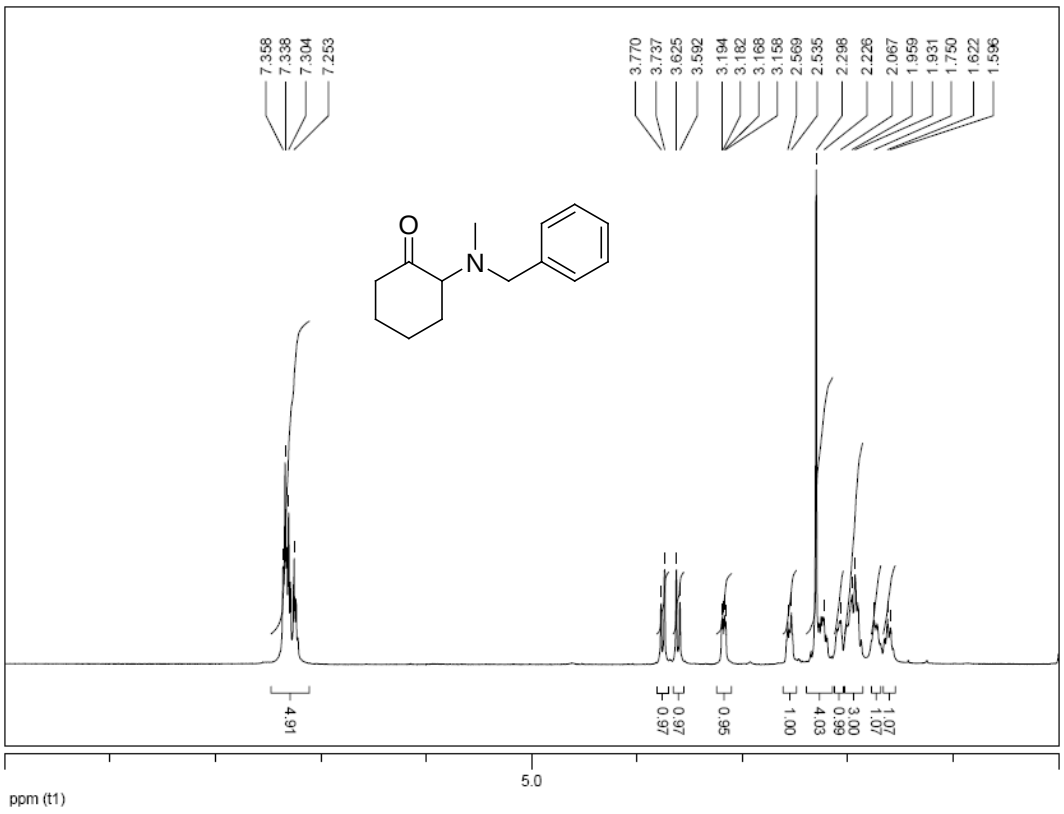


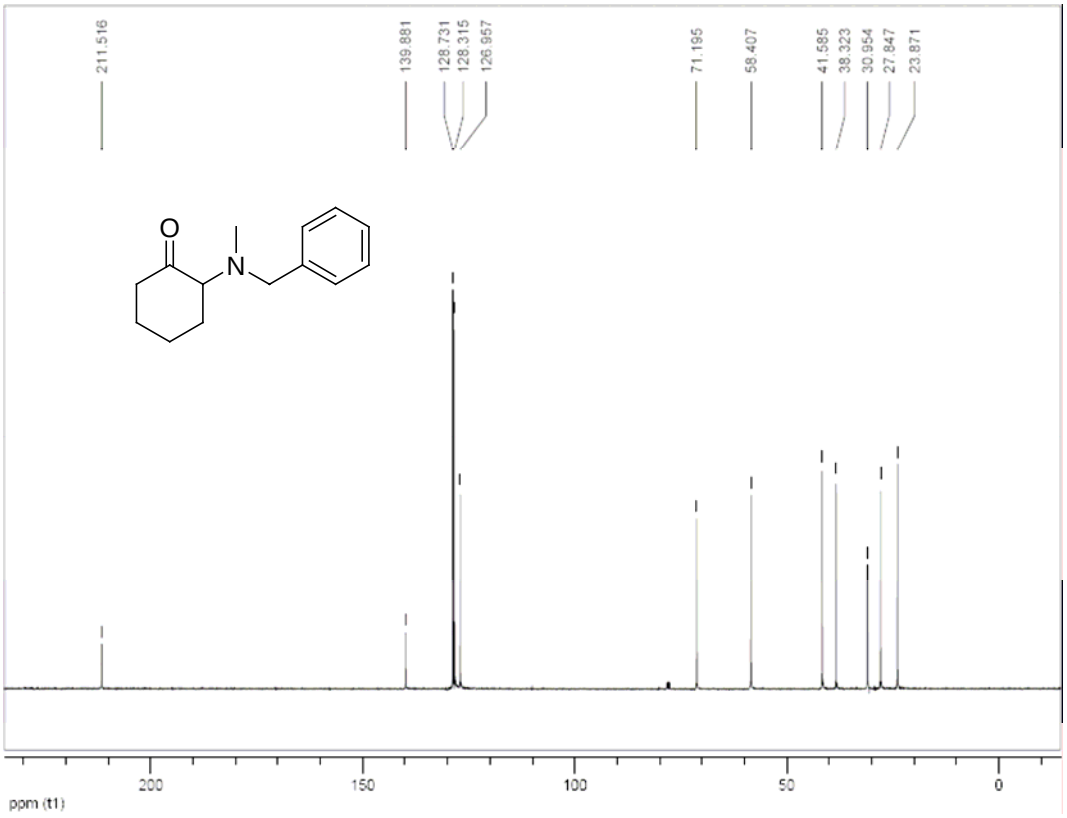
2-(Dibutylamino)cyclohexanone (2g)



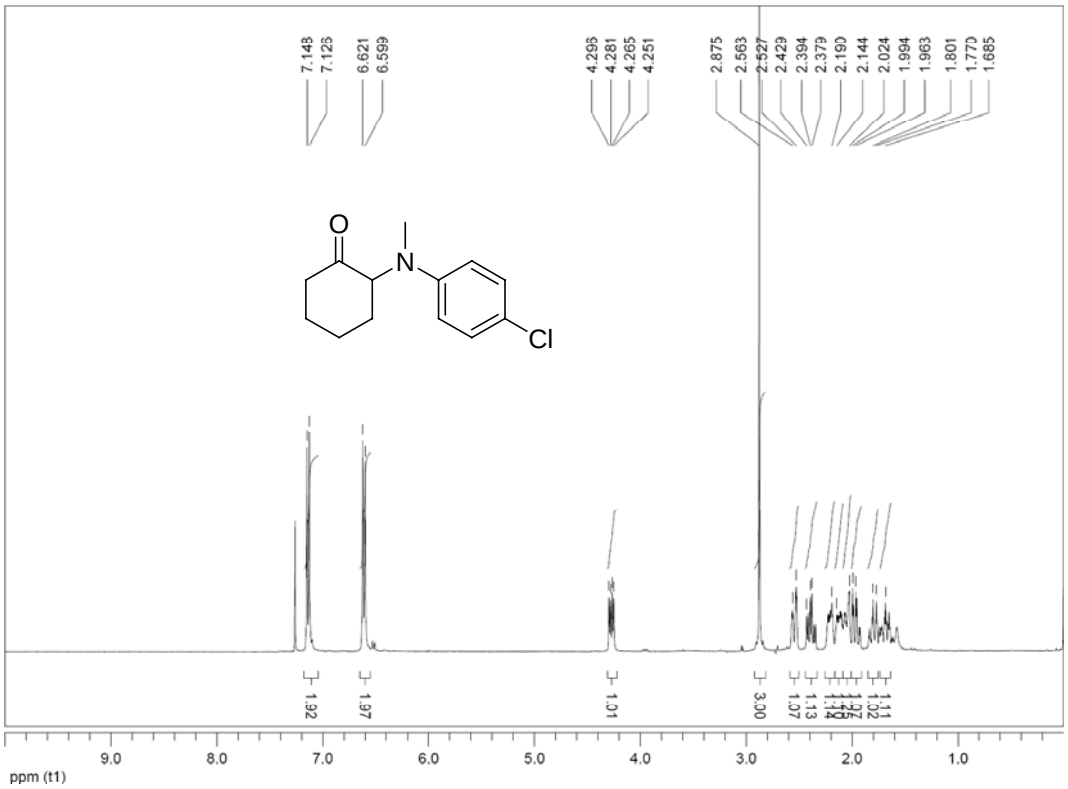


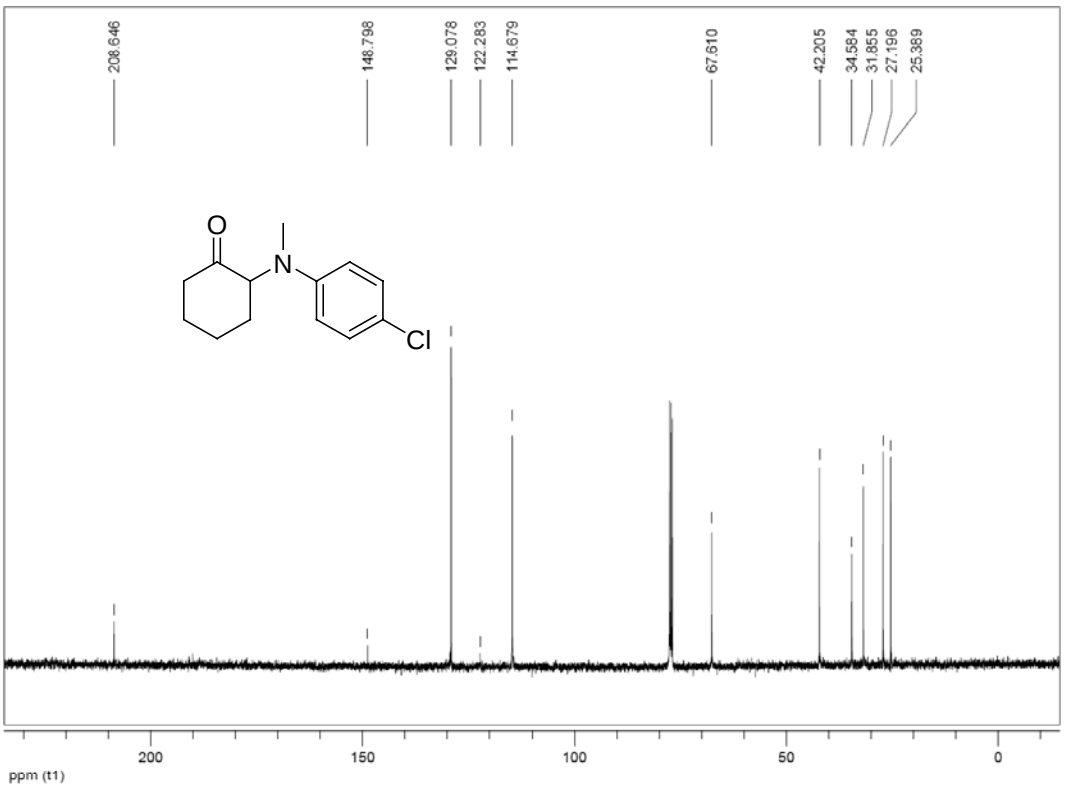
2-(Benzylmethylamino)cyclohexanone (2h)



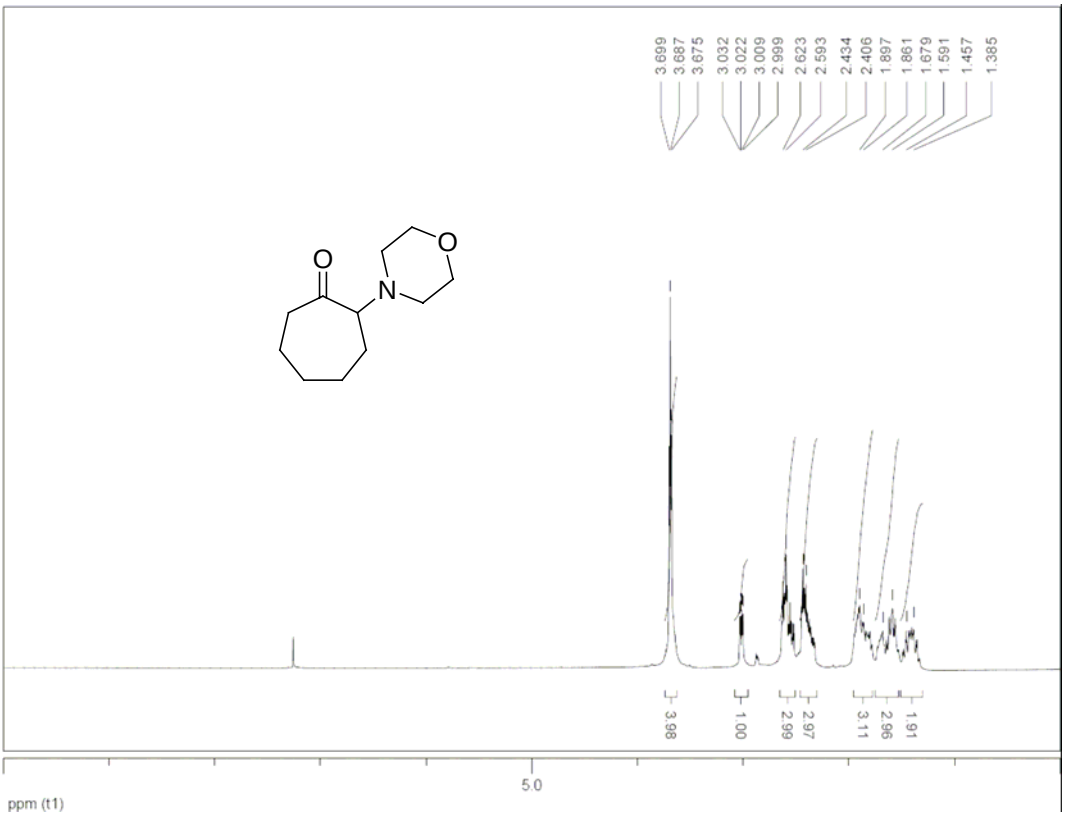


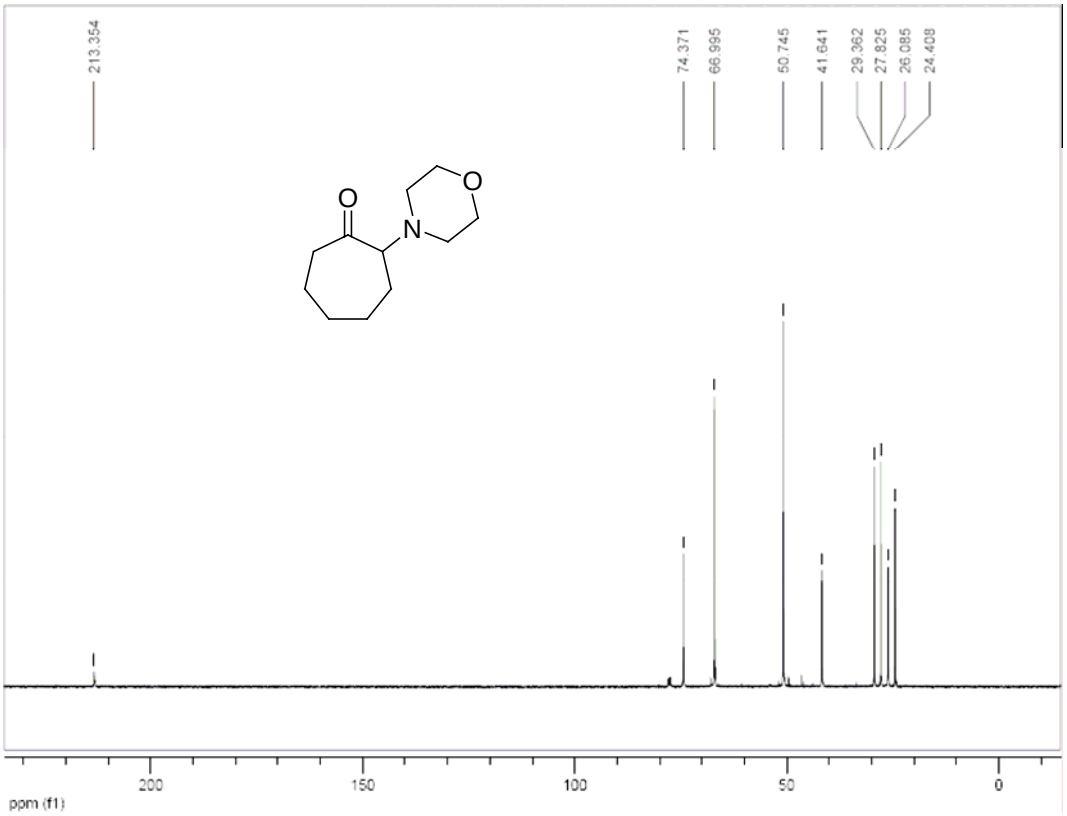
2-((4-Chlorophenyl)methylamino)cyclohexanone (2k)



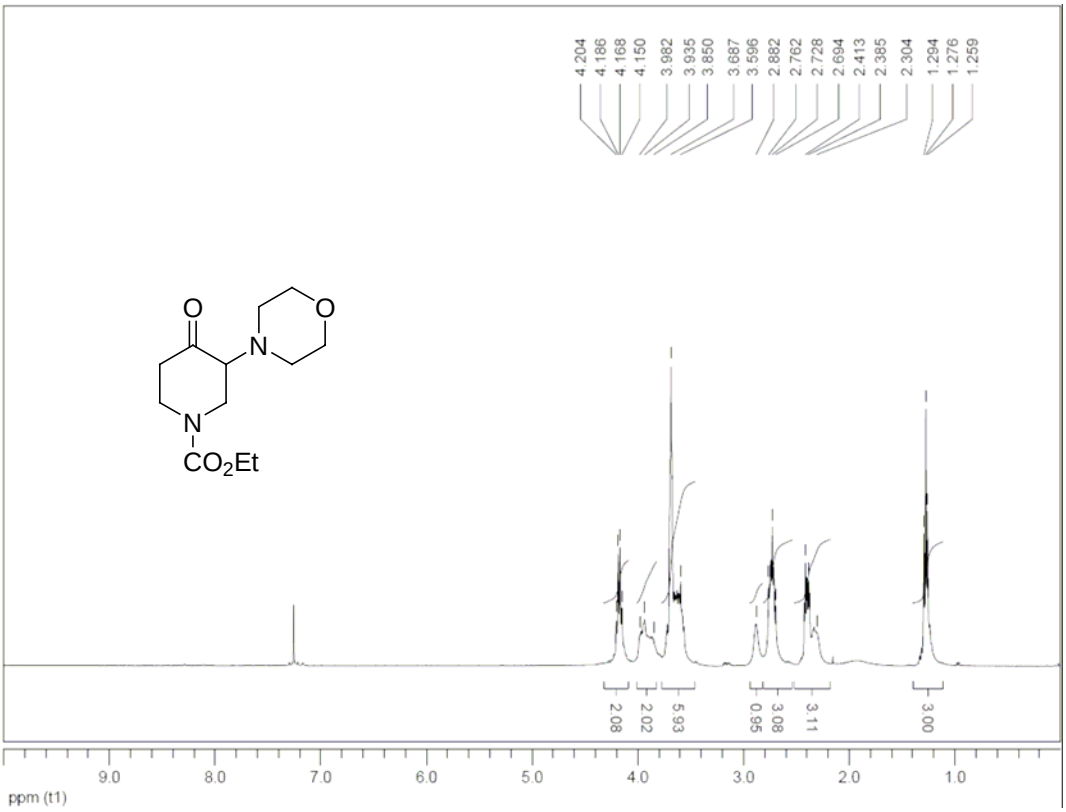


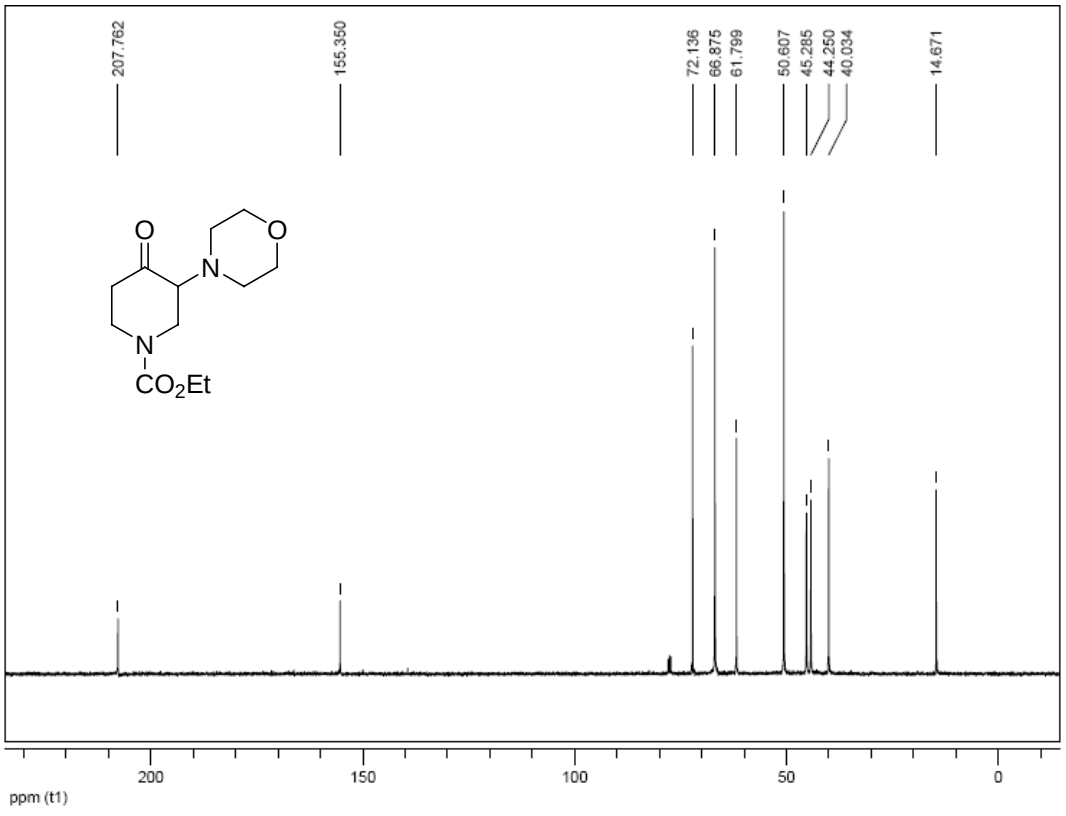
2-(Morpholin-4-yl)-cycloheptanone (2m)



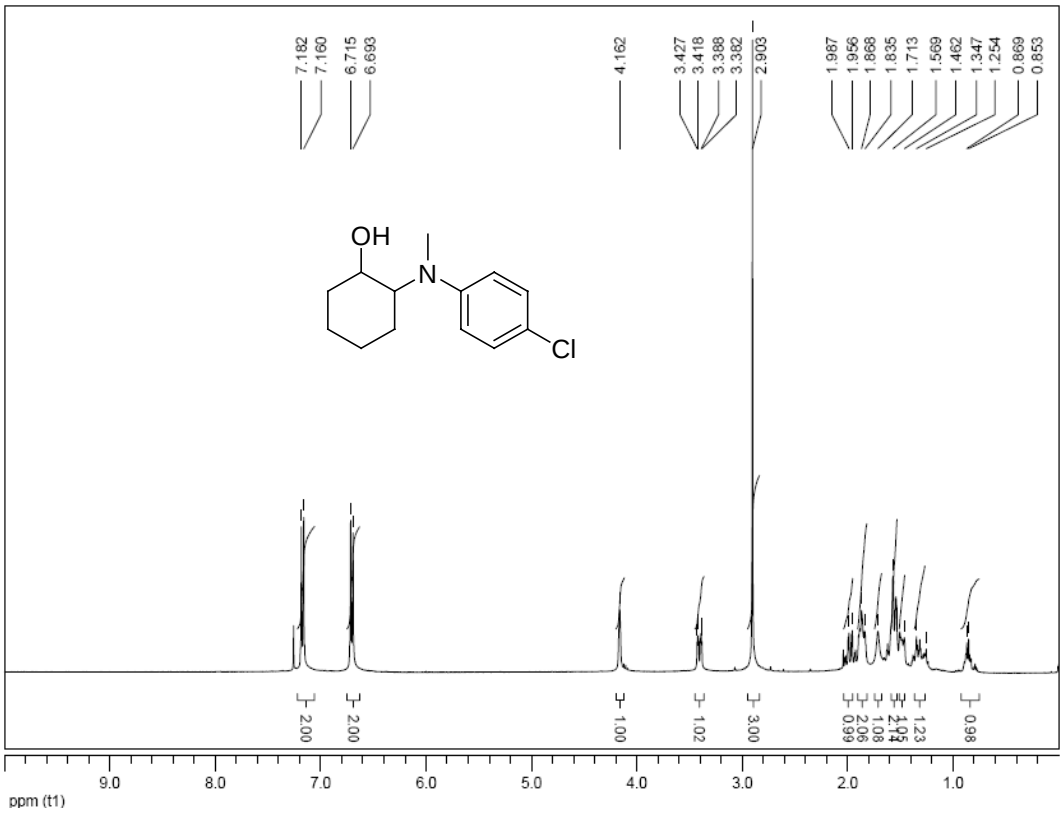


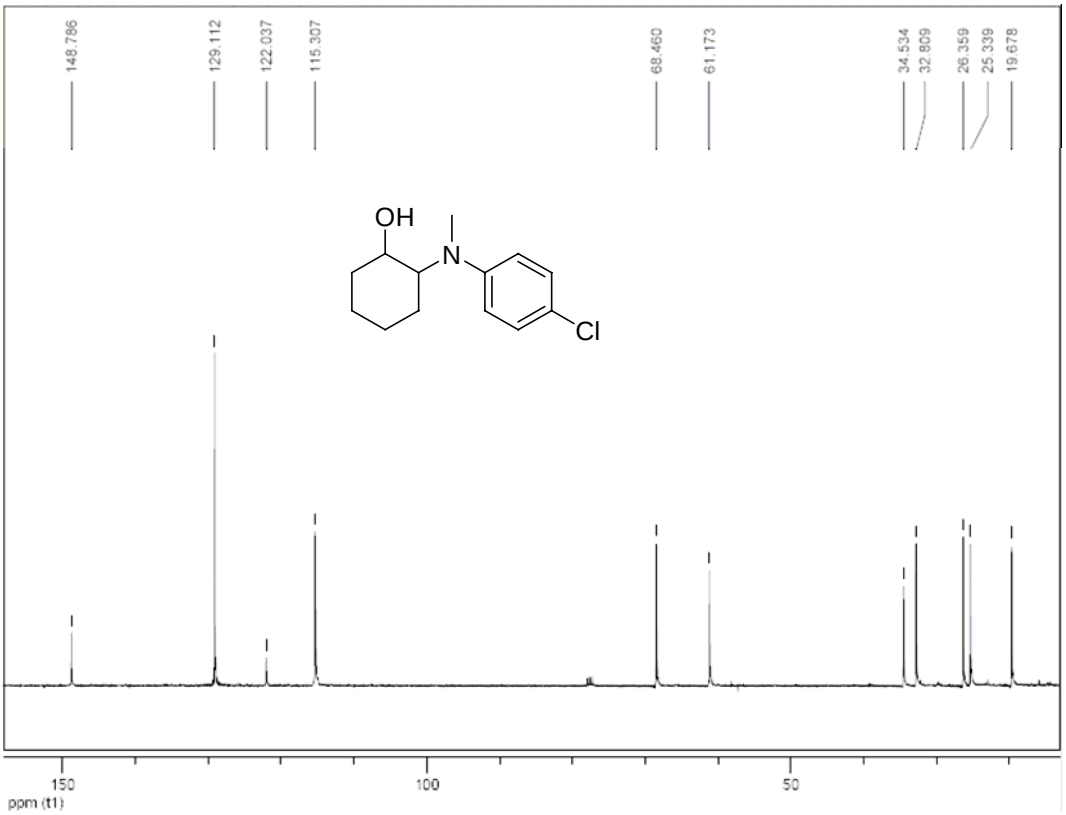
Ethyl 3-(morpholin-4-yl)-4-oxopiperidine-1-carboxylate (2n)



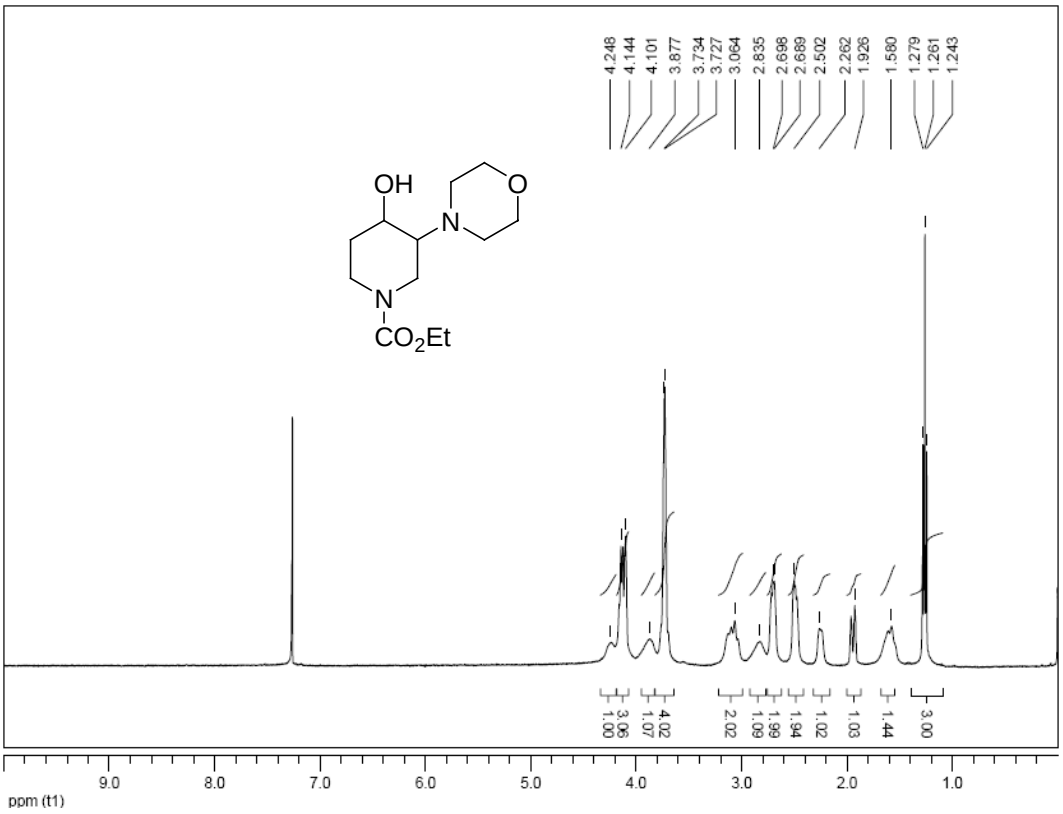


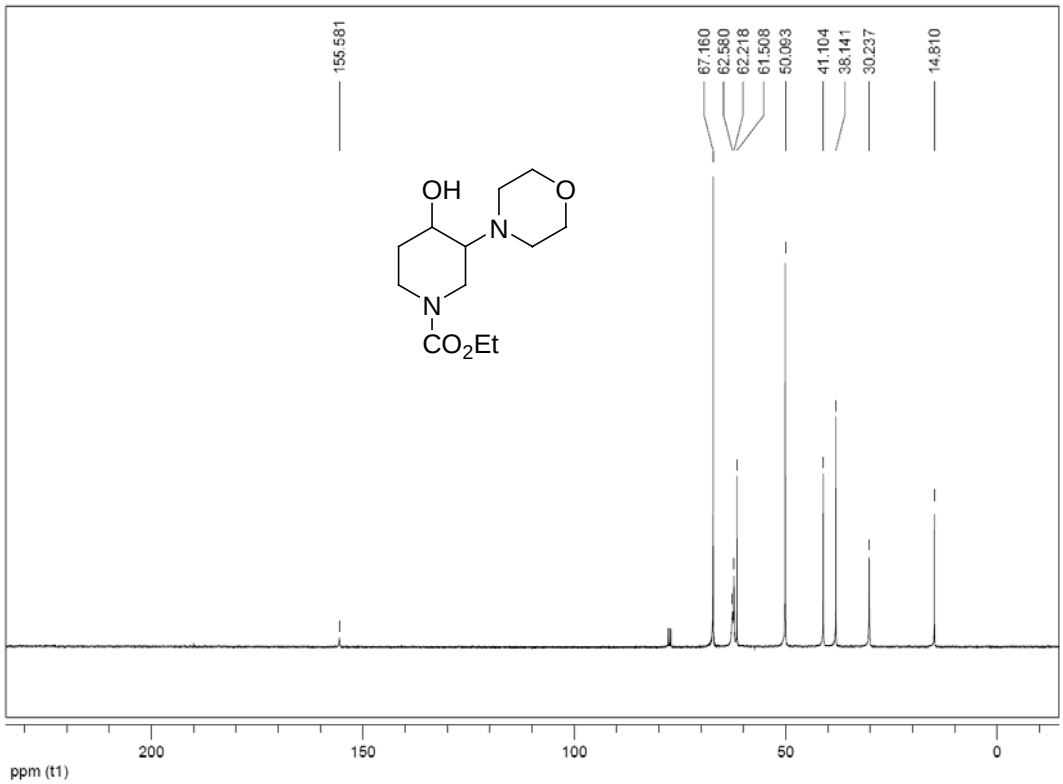
2-((4-Chlorophenyl)methylamino)cyclohexanol (3k)



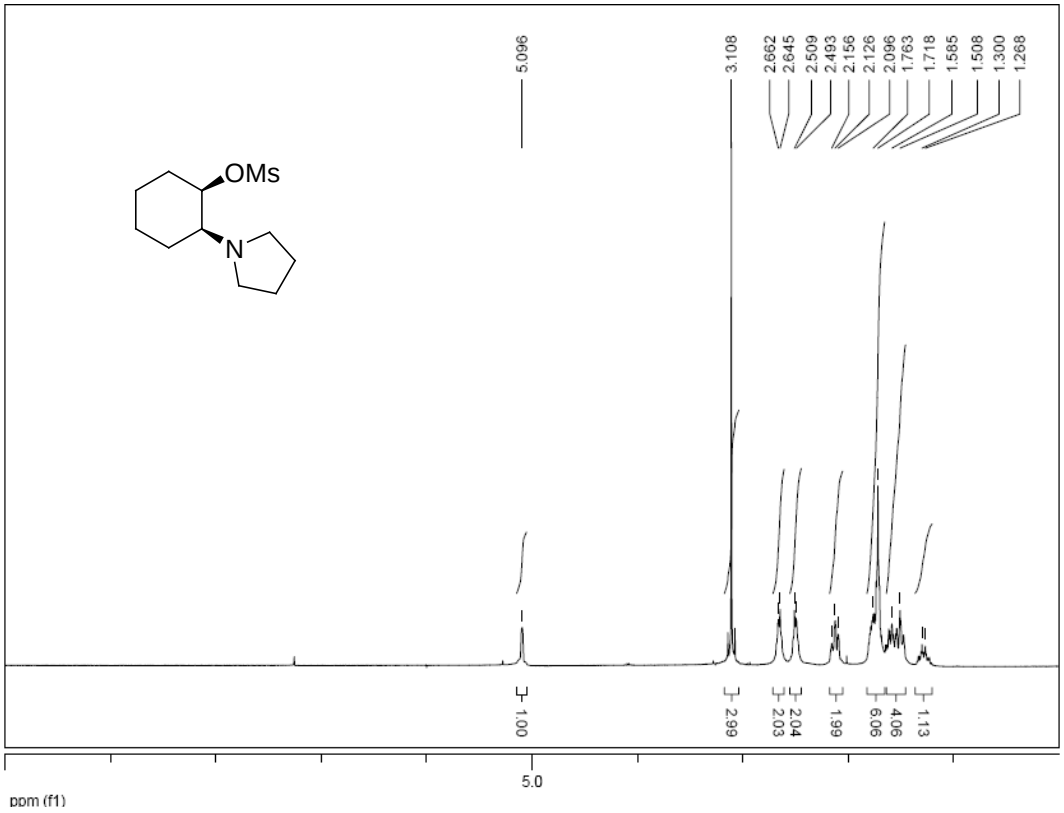


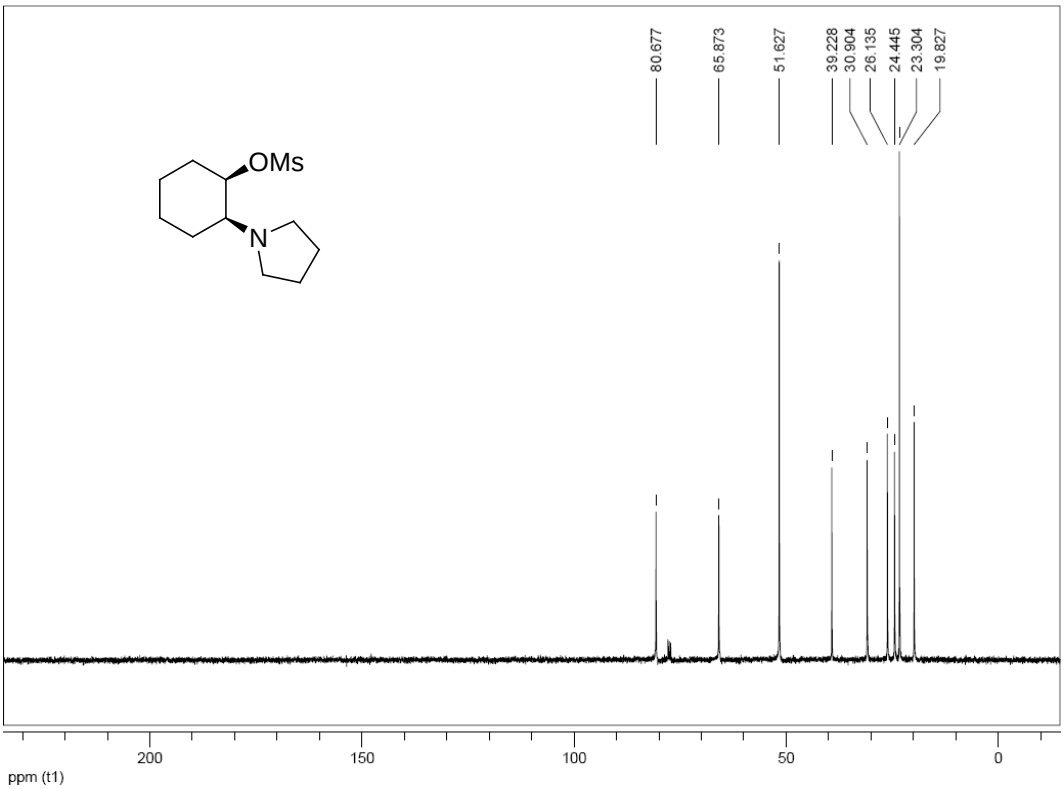
Ethyl 4-hydroxy-3-morpholinopiperidine-1-carboxylate (3n)





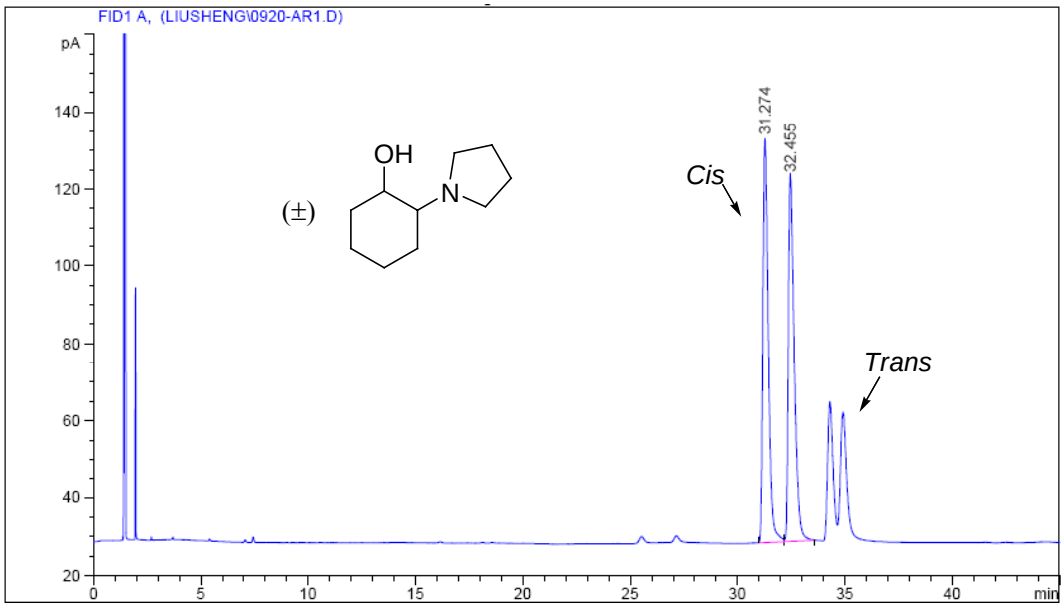
(1*R*,2*S*)-2-(pyrrolidin-1-yl)cyclohexyl methanesulfonate (5)

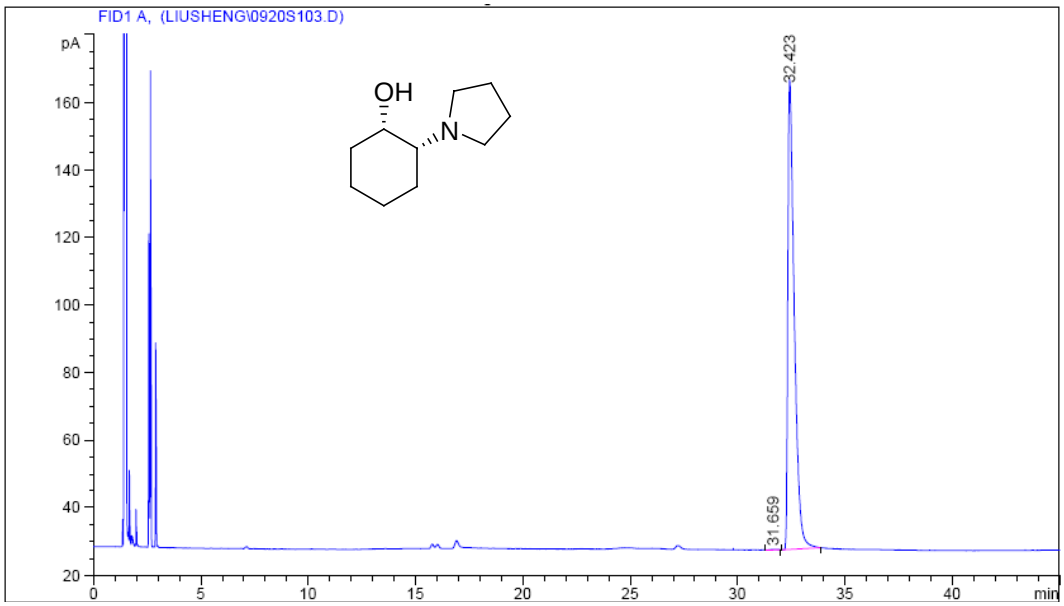




(E) GC, HPLC and SFC Charts for Hydrogenation Products and Derivatives

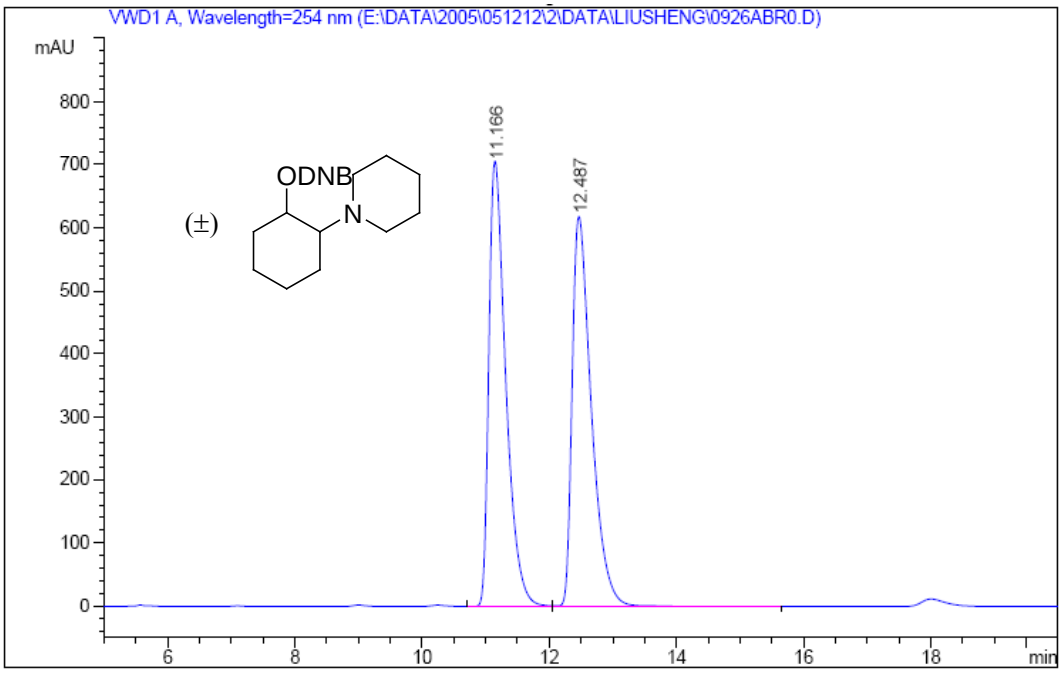
(1*S*,2*R*)-2-(Pyrrolidin-1-yl)cyclohexanol (3a)

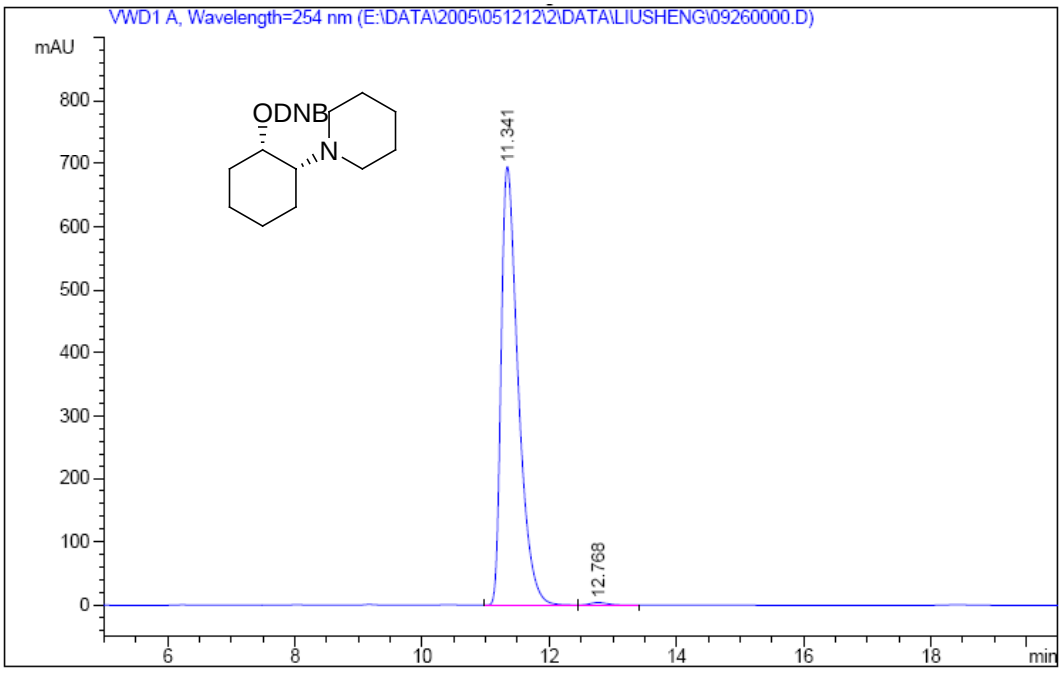




Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	31.659	VV	0.2141	3.04712	1.67190e-1	0.10475
2	32.423	VB	0.2473	2905.84497	139.04449	99.89525
Totals :				2908.89209	139.21168	

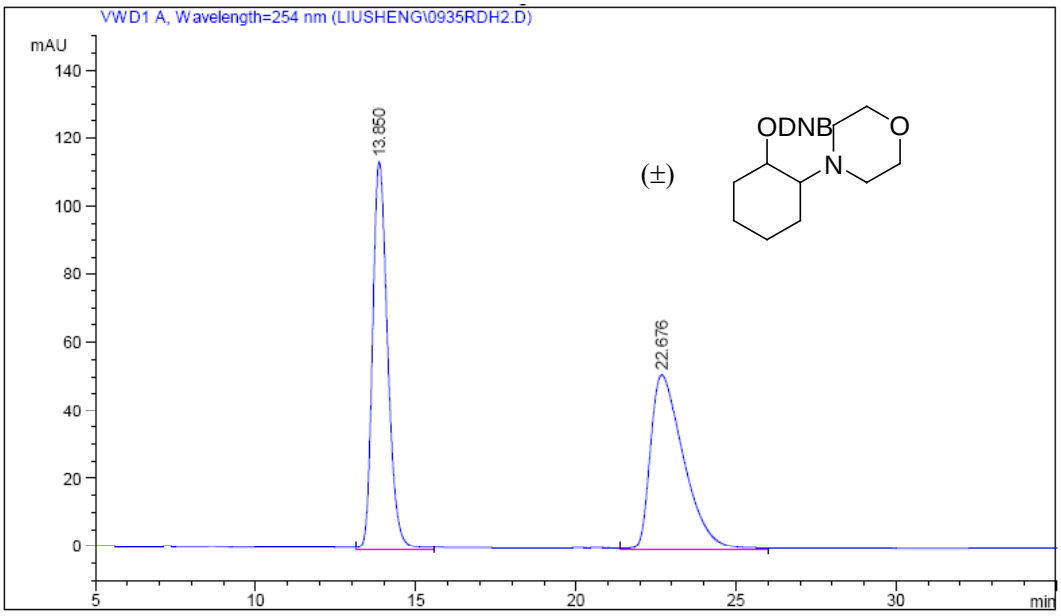
3,5-Dinitrobenzoyl (DNB) derivative of (1*S*,2*R*)-2-(piperidin-1-yl)cyclohexanol (3b)

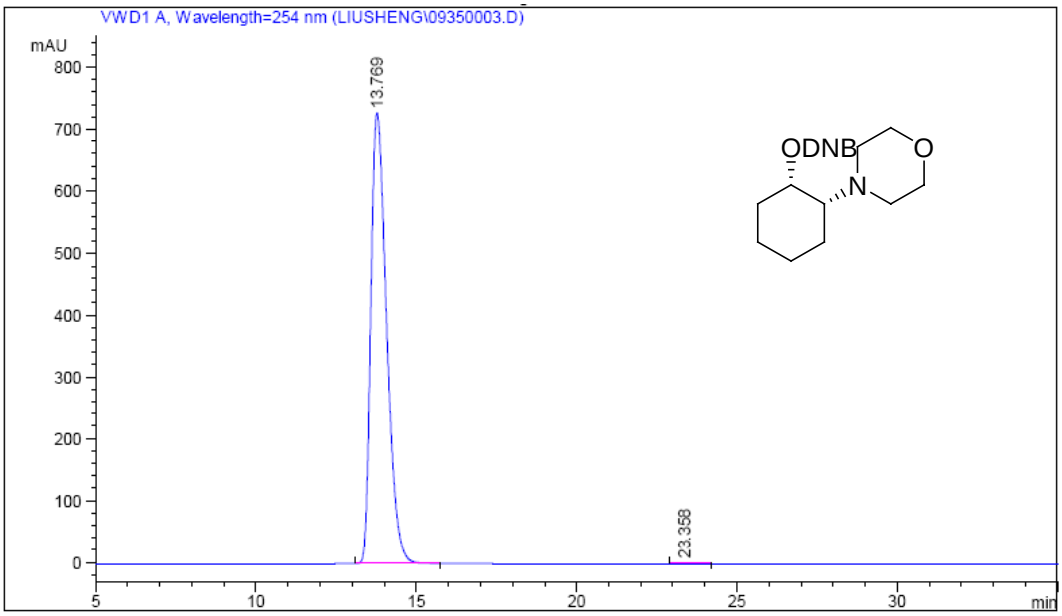




Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.341	VV	0.2814	1.29400e4	694.53522	99.3032
2	12.768	VB	0.3157	90.79616	4.30919	0.6968
Totals :				1.30308e4	698.84441	

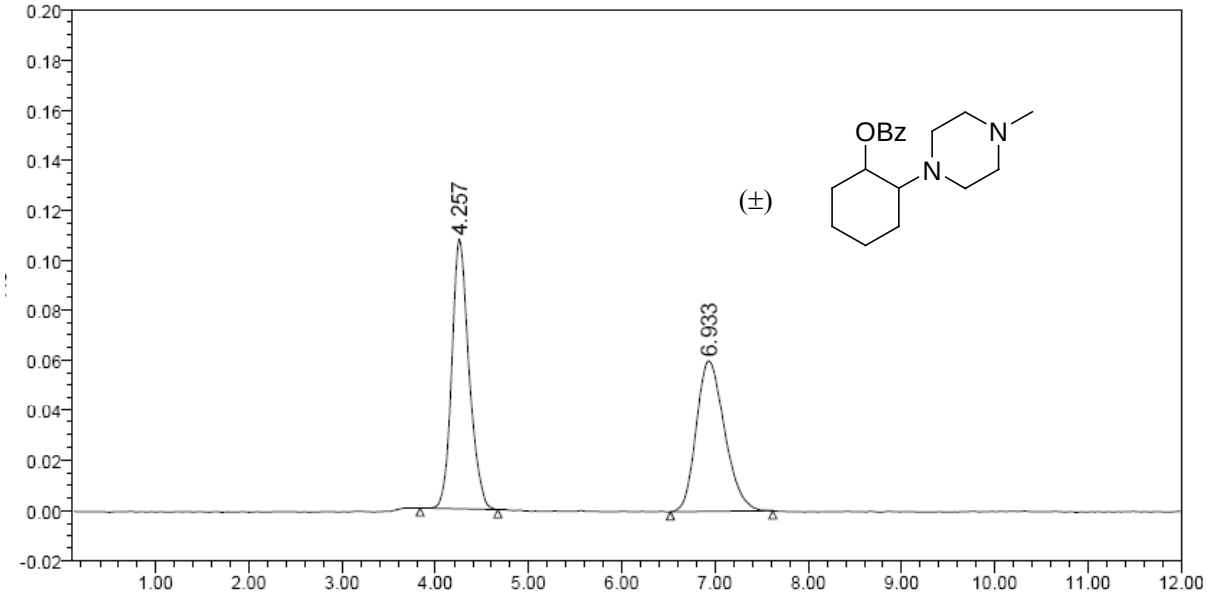
3,5-Dinitrobenzoyl (DNB) derivative of (1*S*,2*R*)-2-(morpholin-4-yl)cyclohexanol (3c)

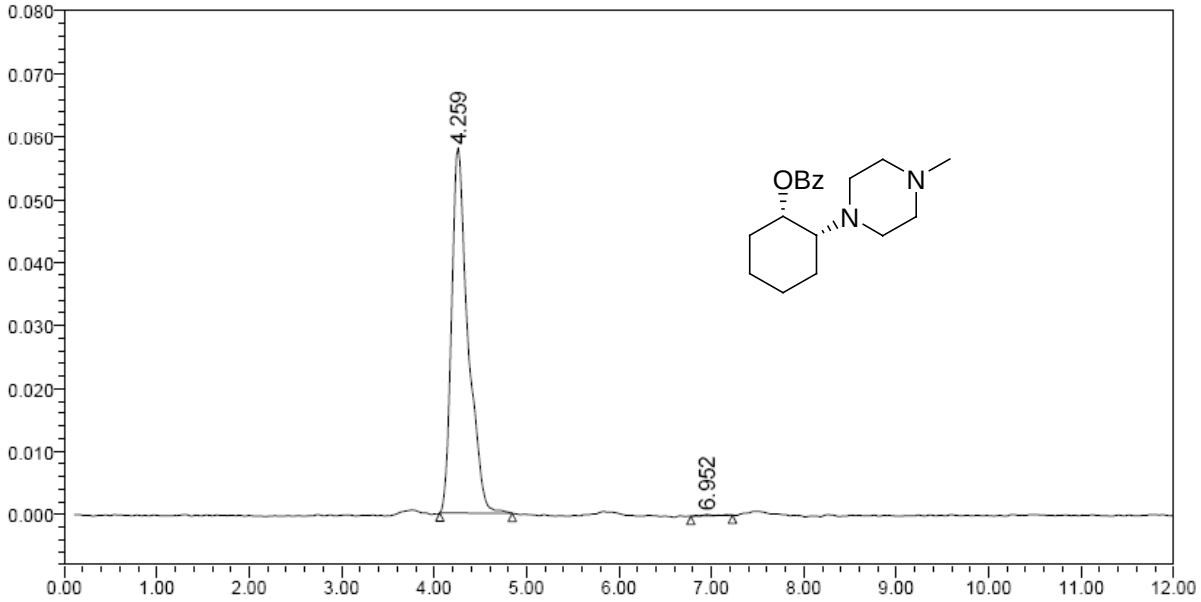




Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.769	BB	0.5261	2.47587e4	728.49951	99.9621
2	23.358	BB	0.6132	9.38574	1.83821e-1	0.0379
Totals :				2.47681e4	728.68333	

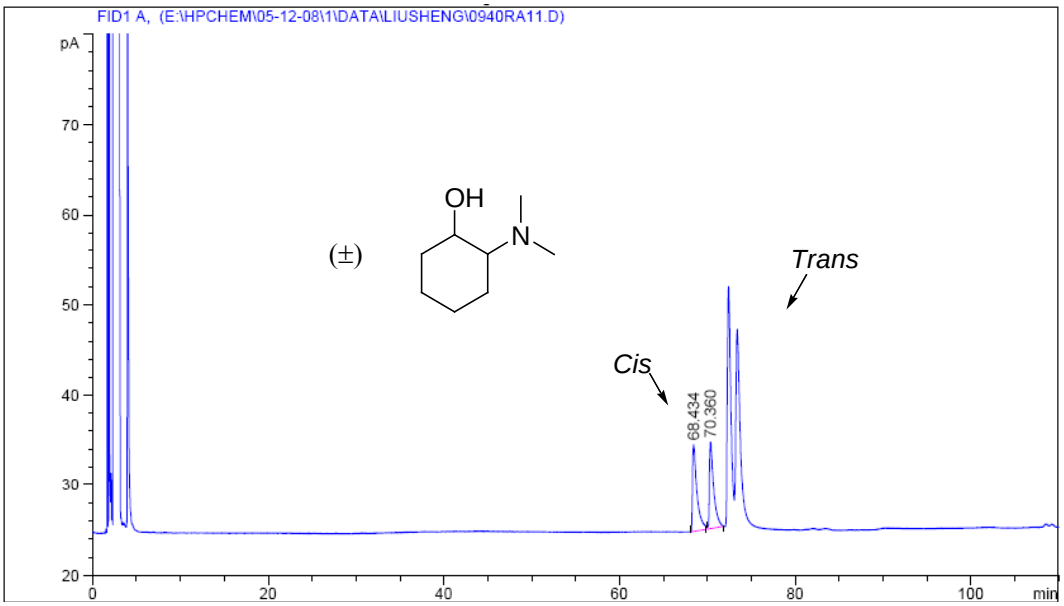
Benzoyl (Bz) derivative of (1*S*,2*R*)-2-(4-methylpiperazin-1-yl)cyclohexanol (3d)

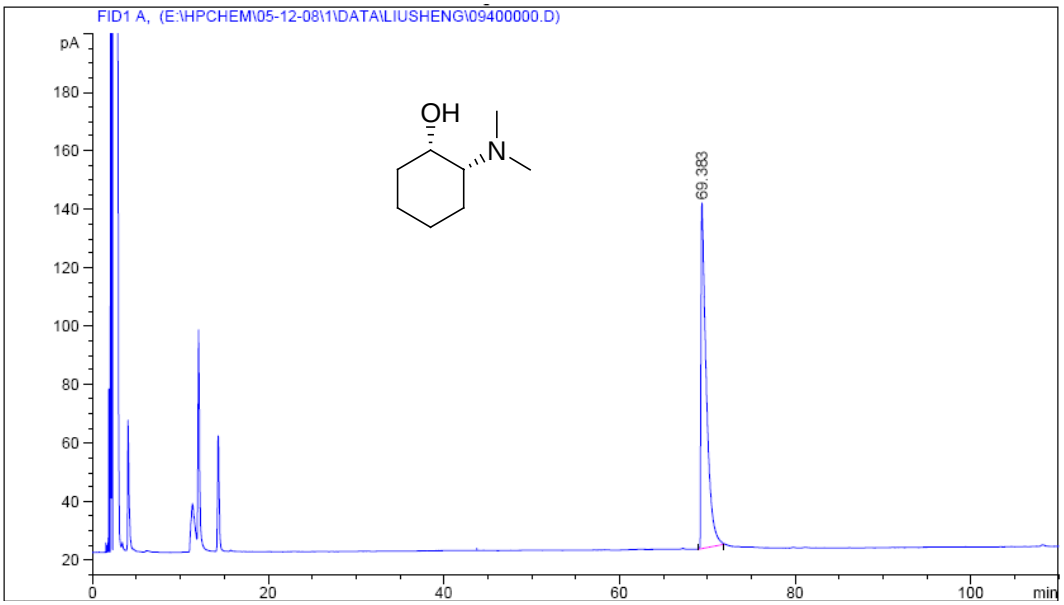




	RT	Area	% Area	Height
1	4.259	717563	99.79	57909
2	6.952	1507	0.21	176

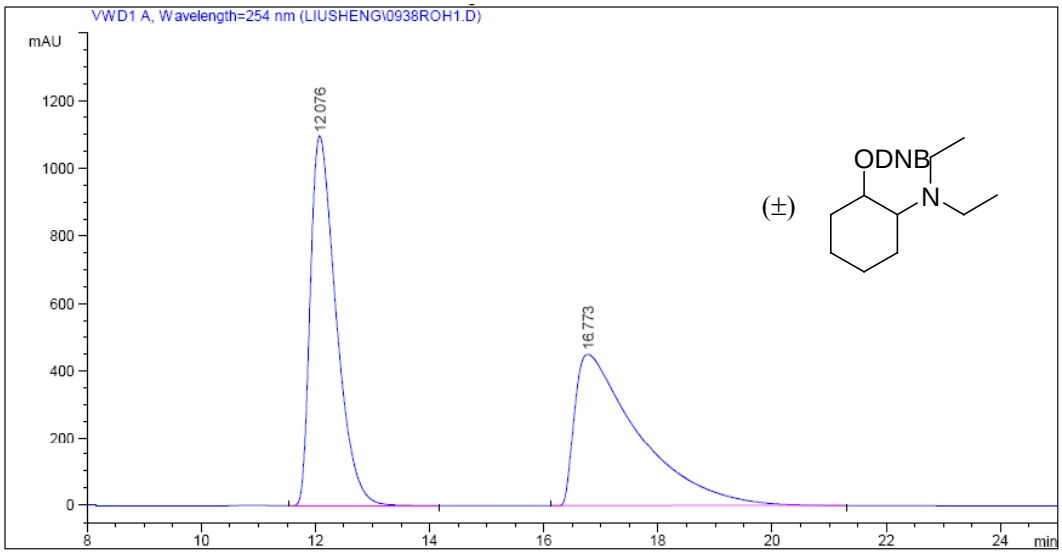
(1*S*,2*R*)-2-(Dimethylamino)cyclohexanol (3e)

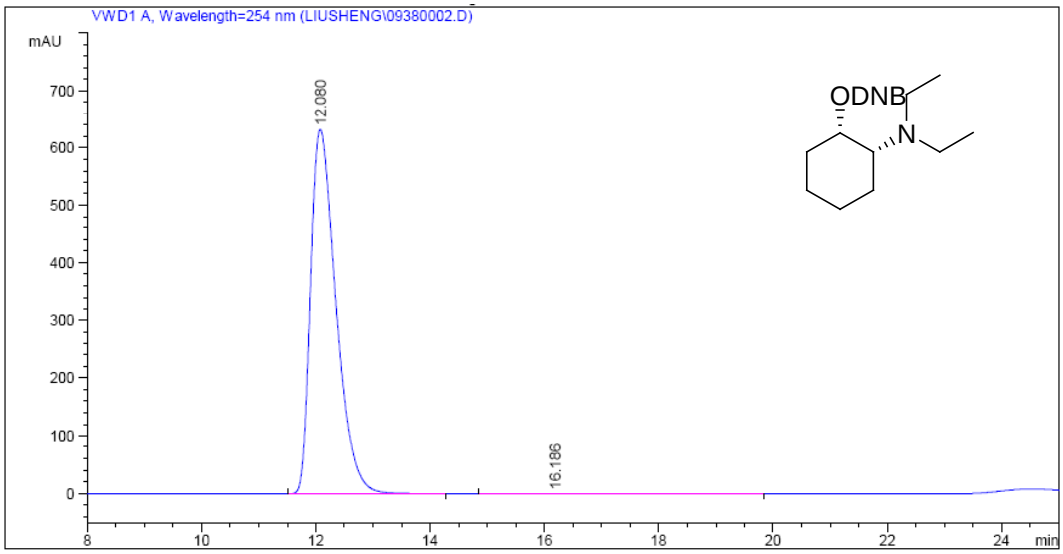




Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	69.383	PV	0.4933	4963.10693	118.10617	1.000e2
Totals :				4963.10693	118.10617	

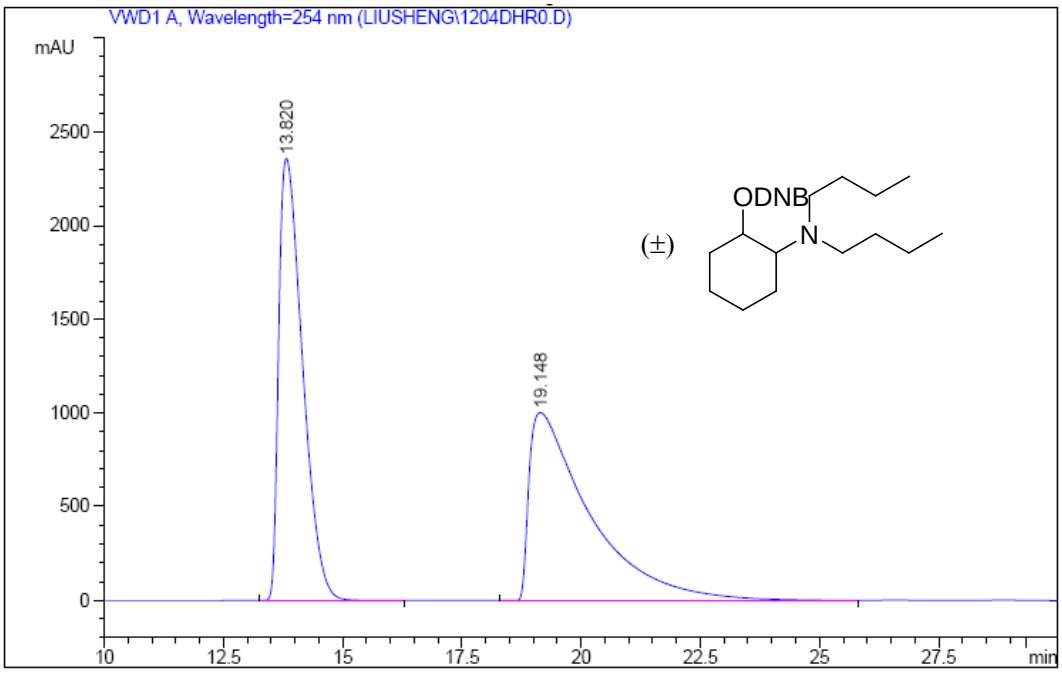
3,5-Dinitrobenzoyl (DNB) derivative of (1*S*,2*R*)-2-(diethylamino)cyclohexanol (3f)

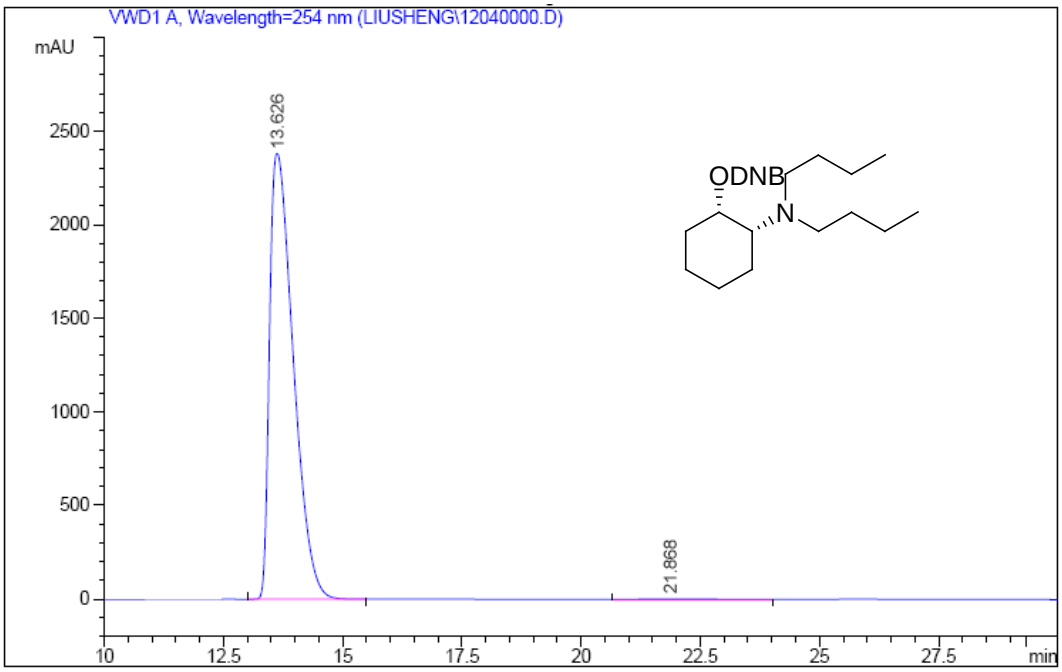




Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	12.080	BB	0.4723	1.94611e4	632.84442	99.3906
2	16.186	BB	1.8833	119.31534	7.43148e-1	0.6094
Totals :				1.95804e4	633.58757	

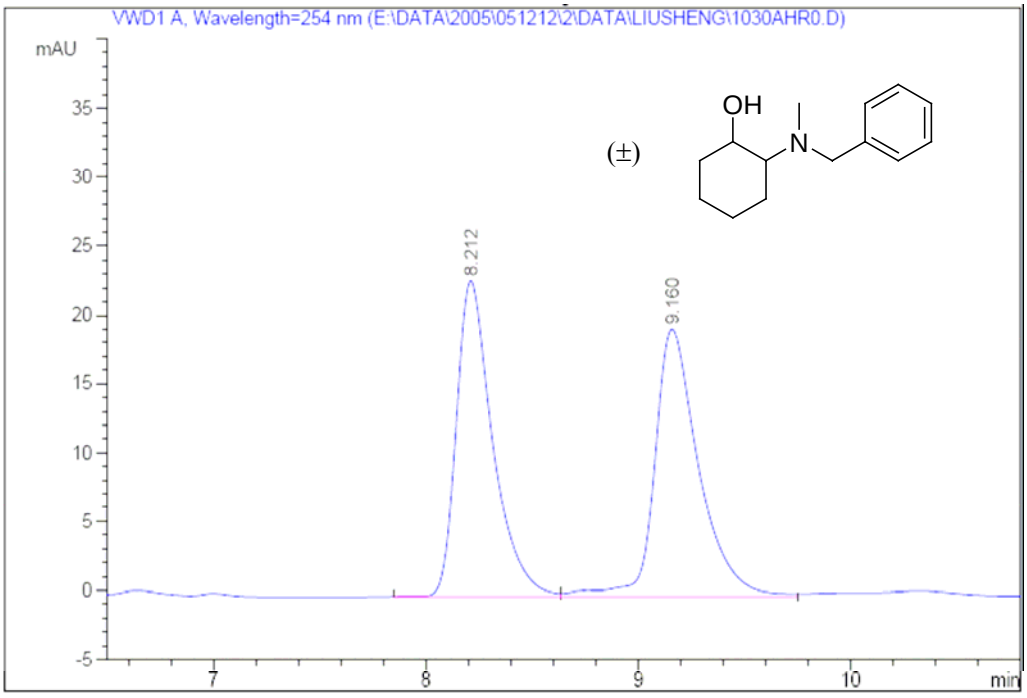
3,5-Dinitrobenzoyl (DNB) derivative of (1*S*,2*R*)-2-(dibutylamino)cyclohexanol (3g)

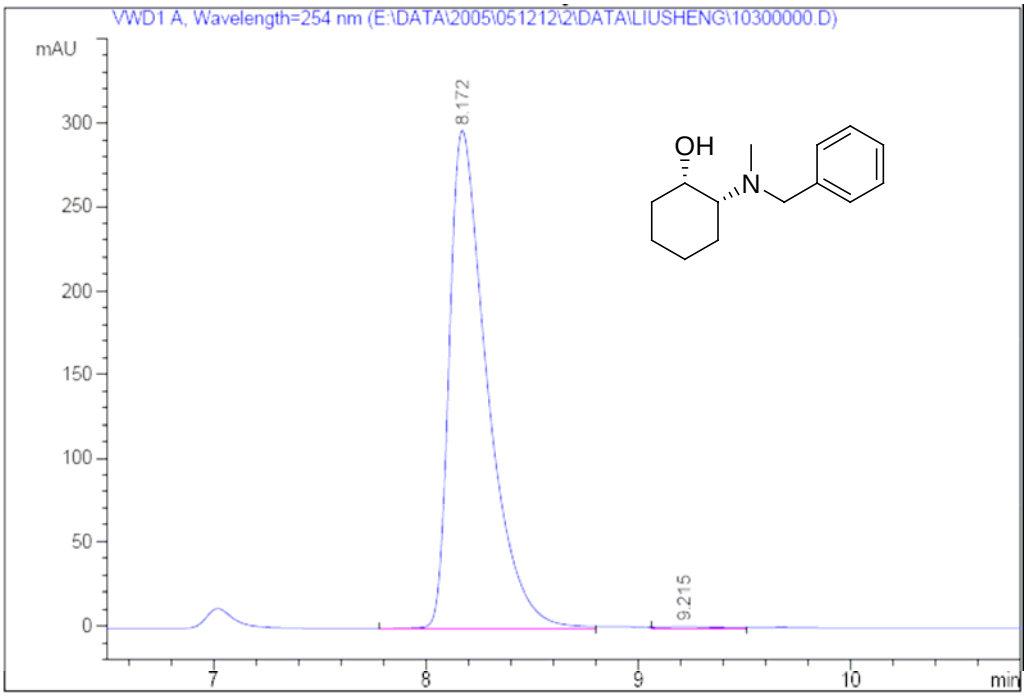




Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.626	VB	0.5360	8.20745e4	2381.69312	99.8056
2	21.868	PB	1.0075	159.83488	1.95247	0.1944
Totals :				8.22343e4	2383.64559	

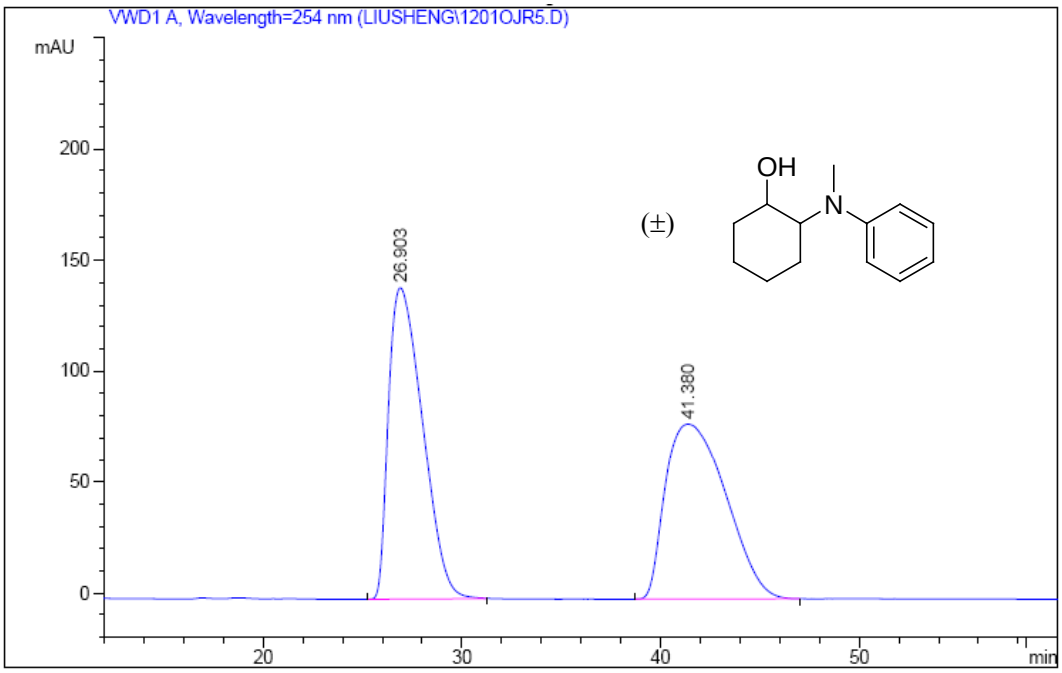
(1*S*,2*R*)-2-(Benzylmethylamino)cyclohexanol (3h)

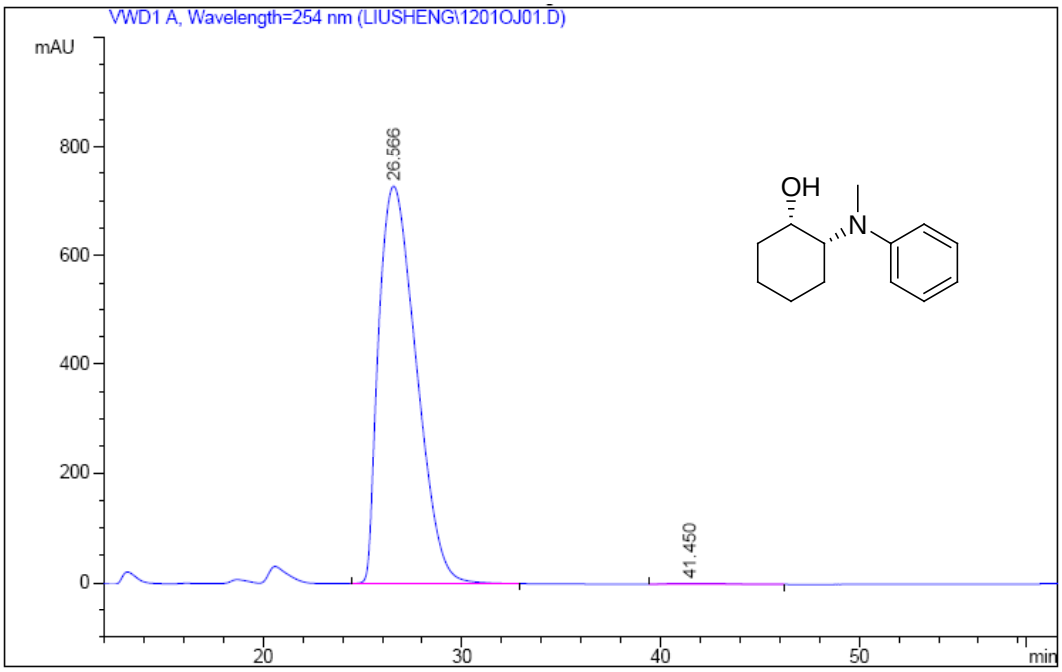




Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	8.172	BV	0.1850	3675.13721	297.20197	99.3786
2	9.215	VV	0.2597	22.97874	1.20862	0.6214
Totals :				3698.11595	298.41059	

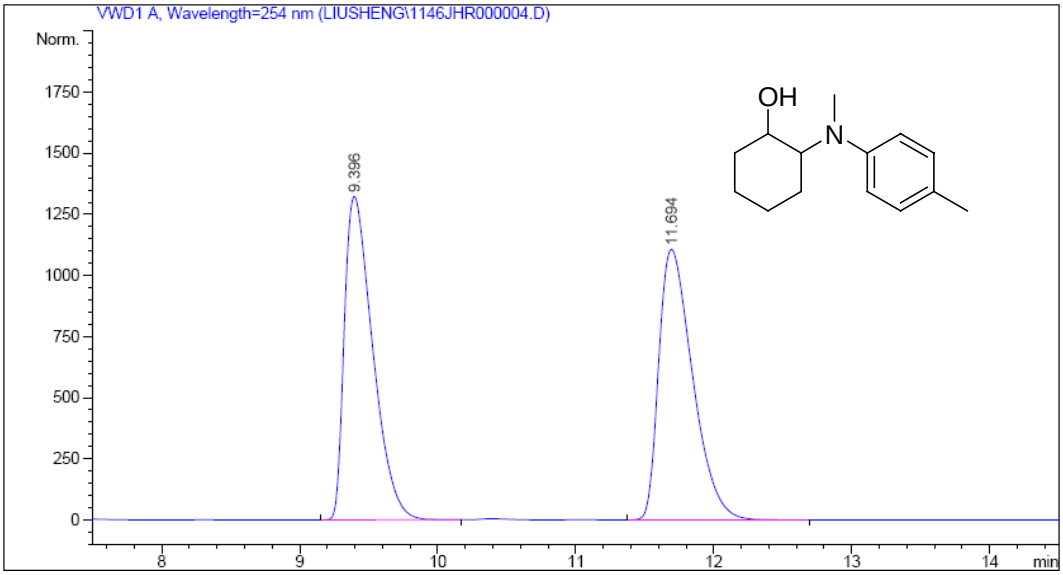
(1*S*,2*R*)-2-(Methylphenylamino)cyclohexanol (3i)

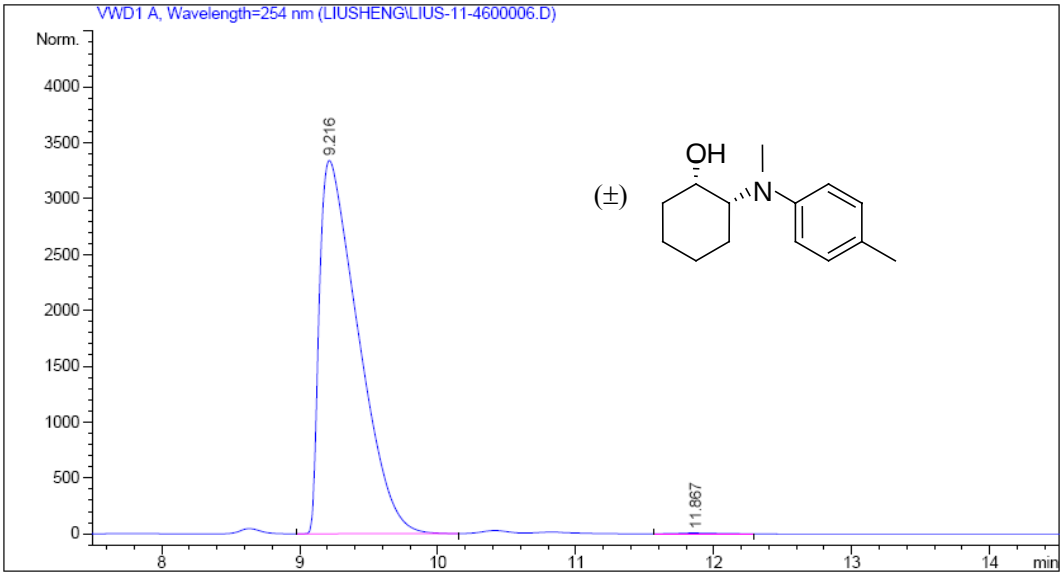




Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	26.566	BB	2.0917	9.51881e4	727.37225	99.6627
2	41.450	BP	2.4637	322.17740	1.54393	0.3373
Totals :				9.55103e4	728.91618	

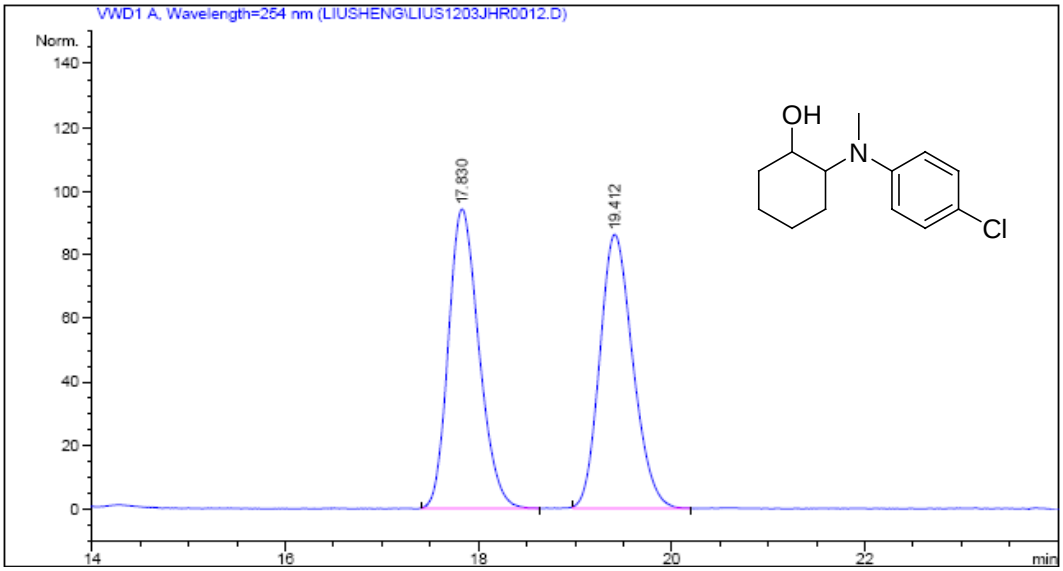
(1*S*,2*R*)-2-((4-Methylphenyl)methylamino)cyclohexanol (3j)

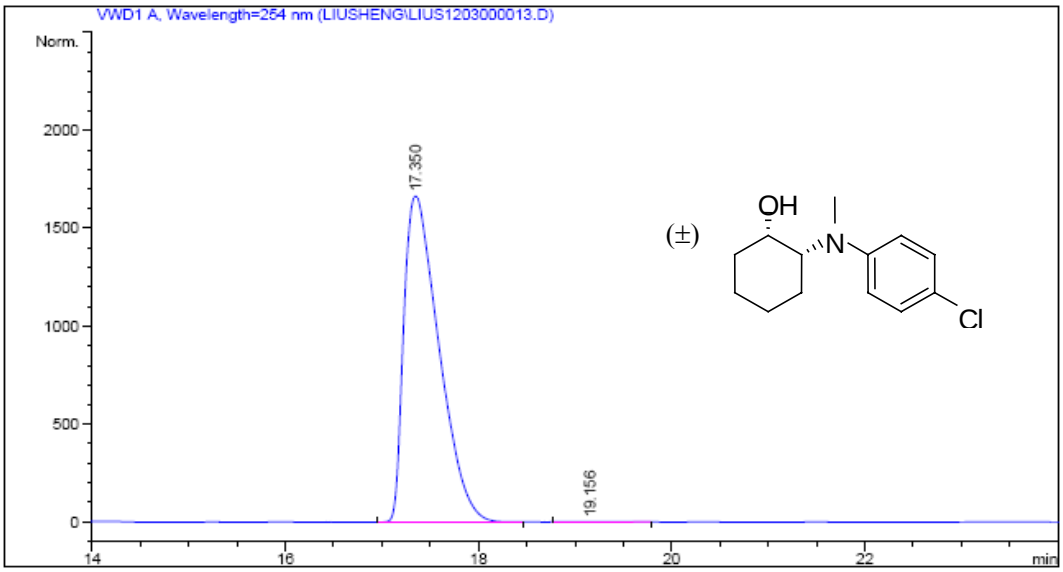




Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Area %
1	9.216	BB	0.3011	6.49445e4	99.8204
2	11.867	BB	0.2514	116.84764	0.1796

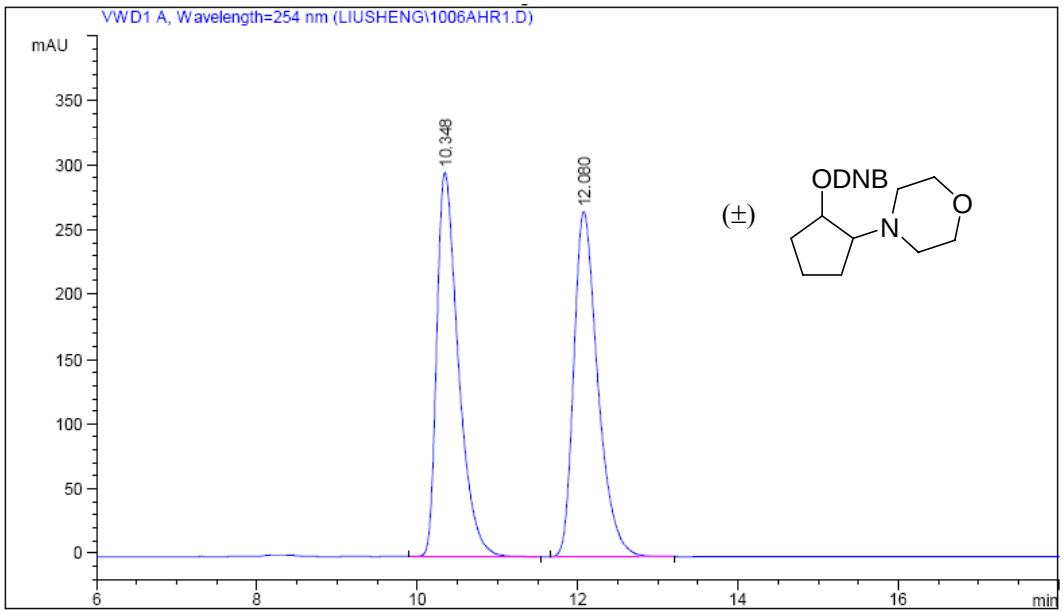
(1*S*,2*R*)-2-((4-Chlorophenyl)methylamino)cyclohexanol (3k)

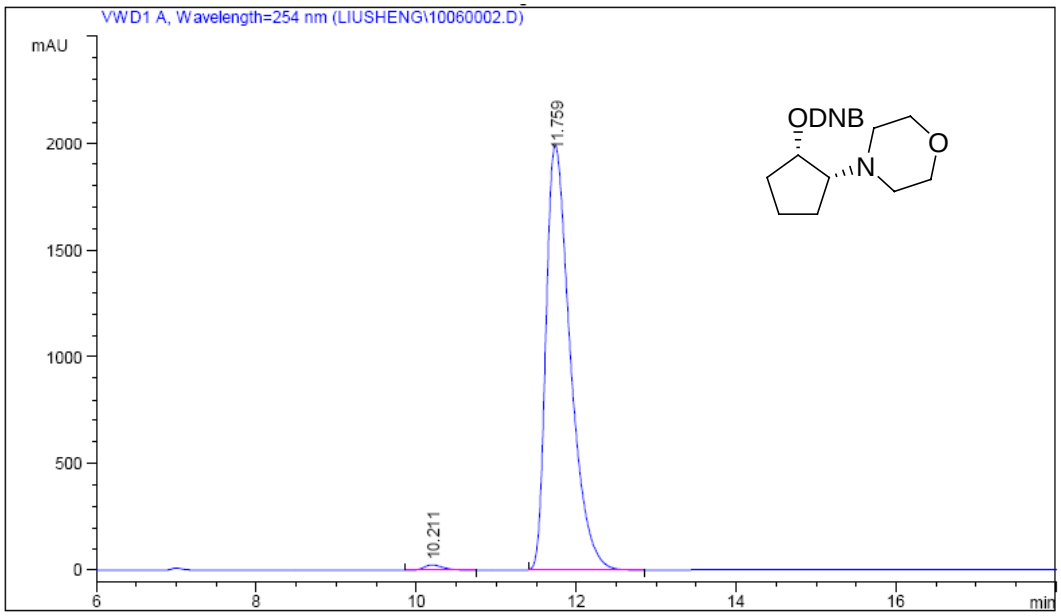




Peak #	RetTime [min]	Type	Width [min]	Area mAU	Area *s	Area %
1	17.350	BB	0.3843	4.19724e4		99.7906
2	19.156	BB	0.4087	88.07236		0.2094
Totals :				4.20605e4		

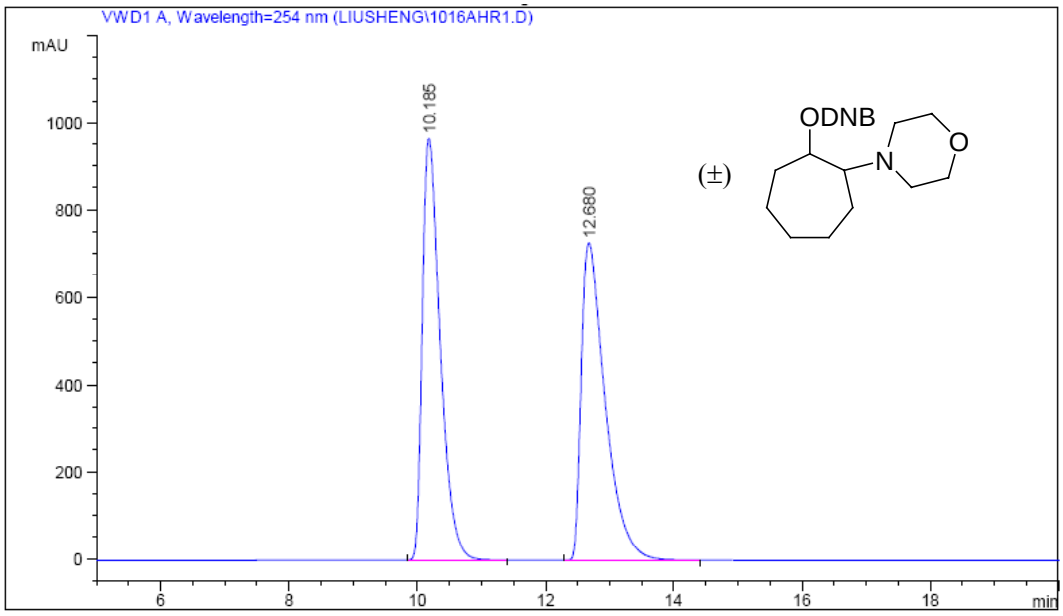
3,5-Dinitrobenzoyl (DNB) derivative of (1*S*,2*R*)-2-(morpholin-4-yl)cyclopentanol (3l)

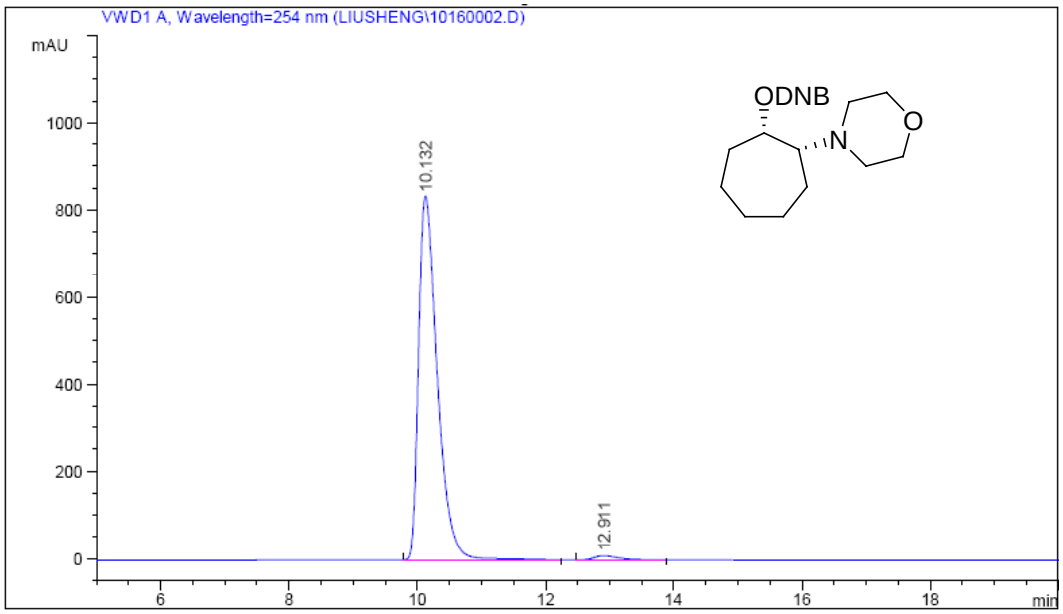




Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.211	BB	0.2763	441.37811	24.94555	1.0408
2	11.759	BB	0.3218	4.19674e4	1943.94592	98.9592
Totals :				4.24087e4	1968.89147	

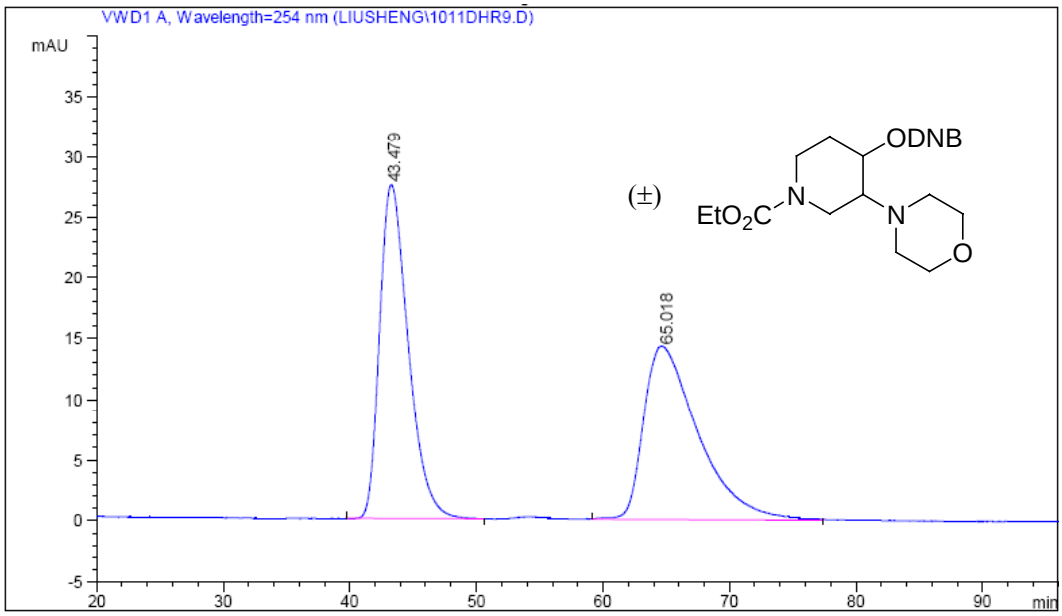
3,5-Dinitrobenzoyl (DNB) derivative of (1*S*,2*R*)-2-(morpholin-4-yl)cycloheptanol (3m)

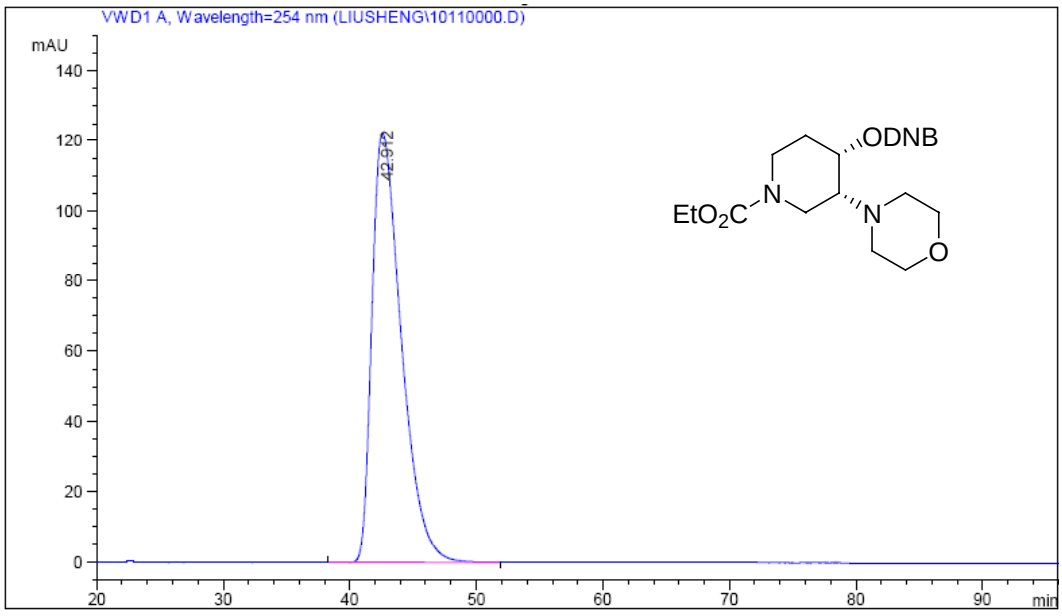




Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.132	BB	0.3096	1.69487e4	834.96985	98.5664
2	12.911	BB	0.3929	246.51622	9.50433	1.4336
Totals :				1.71952e4	844.47417	

3,5-Dinitrobenzoyl (DNB) derivative of (3*R*,4*S*)-ethyl 4-hydroxy-3-(morpholin-4-yl)piperidine-1-carboxylate (3n)





Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	42.912	PB	3.0806	1.97951e4	107.47655	100.0000
Totals :				1.97951e4	107.47655	