

SUPPORTING INFORMATION

Title: Stereodivergent Diversity Oriented Synthesis of Piperidine Alkaloids

Author(s): Louis V. Adriaenssens, Carolyn A. Austin, Mairi Gibson, David Smith, and Richard C. Hartley*

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Experimental

All reactions under an inert atmosphere were carried out using oven dried or flame dried glassware. Solutions were added via syringe. THF was freshly distilled from sodium benzophenone. Dichloromethane, and triethyl phosphite were distilled from CaH_2 prior to use. Petroleum ether refers to the fraction boiling at 40-60 °C. Reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. The solid phase reactions were carried out in normal glassware, but with the resin (particle size = 150-300 μm diameter) contained within porous polypropylene reactors that had an internal volume of 2.4 mL, and a pore size of 74 μm . Purification by column chromatography was carried out using silica gel, mesh size 35-70 μm . as the stationary phase. ^1H and ^{13}C NMR spectra were obtained on a Bruker DPX/400 spectrometer operating at 400 and 100 MHz respectively. All coupling constants are measured in Hz. DEPT was used to assign the signals in the ^{13}C NMR spectra as C, CH, CH_2 or CH_3 . Mass spectra (MS) were recorded on a Jeol JMS700 (MStation) spectrometer. Infra-red (IR) spectra were obtained on a Perkin-Elmer 983 spectrophotometer. A Golden Gate™ attachment that uses a type IIa diamond as a single reflection element was used in some cases so that the IR spectrum of the compound (solid or liquid) could be directly detected (thin layer) without any sample preparation.

6-Propyl-2,3,4,5-tetrahydropyridine (\square -coniceine) **1a**

Following the procedure for imine preparation (except not neutralising with sodium hydroxide due to the volatility of \square -coniceine **1a**), starting with resin-bound butyrate ester **9a** (0.311 milliequiv.) gave a mixture of triphenylmethane and the trifluoroacetate salt of 5-oxooct-1-ylamine. This mixture was dissolved in DCM (1 mL) and ethereal HCl (0.8 mL of a 2 M solution, 1.60 mmol) was added. The cloudy solution was concentrated *in vacuo* and washed with hexane followed by ether to remove triphenylmethane and any other impurities, leaving 5-oxooct-1-ylamine hydrochloride salt as a yellow solid (31.8 mg, 57 %). IR (thin layer): 2964, 1690. δ_{H} (400 MHz, DMSO): 0.94 (3H, t, $J=7.4$), 1.67 (2H, sextet, $J=7.5$), 1.70-1.83 (4H, m), 2.68 (2H, t, $J=7.6$), 2.77 (2H, t, $J=6.0$), 3.57 (2H, m), 3.70 (3H, broad s). δ_{C} (100 MHz, DMSO): 13.31 (CH_3), 16.48 (CH_2), 18.89 (CH_2), 18.95 (CH_2), 28.87 (CH_2), 38.45 (CH_2), 43.57 (CH_2), 190.87 (C). m/z, (CI) 126 $[(\text{M}+\text{H})^+ - \text{H}_2\text{O}, 100\%]$, 97 (12%), 71 (18%). HRMS: 126.1284. $\text{C}_8\text{H}_{16}\text{N}$ requires $[(\text{M}+\text{H})^+ - \text{H}_2\text{O}]$

126.1283. Conversion to \square -coniceine **1a** was carried out by addition of NaOH (4 M), sonication for 1 min, followed by extraction with CDCl_3 . The organic layer was dried with MgSO_4 and used to characterise \square -coniceine **1a** without removing the solvent. IR (thin layer): 2927, 1660, 1459 cm^{-1} . δ_{H} (400 MHz, CDCl_3): 0.91 (3H, t, $J=7.4$), 1.52-1.60 (4H, m), 1.62-1.68 (2H, m), 2.08-2.13 (4H, m), 3.52-3.55 (2H, m). δ_{C} (100 MHz, CDCl_3): 13.90 (CH_3), 19.58 (CH_2), 19.77 (CH_2), 21.91 (CH_2), 28.94 (CH_2), 43.06 (CH_2), 49.11 (CH_2), 171.06 (C). m/z, (CI): 126 $[(\text{M}+\text{H})^+, 100\%]$, 71 (10%). HRMS: 126.1282. $\text{C}_8\text{H}_{16}\text{N}$ requires $(\text{M}+\text{H})^+$, 126.1283. ^1H and ^{13}C NMR data in agreement with the literature.¹

6-Phenethyl-2,3,4,5-tetrahydropyridine **1b**

Following the procedure for imine preparation starting with resin-bound 3-phenylpropionate ester **9b** (0.328 milliequiv.) gave 6-phenethyl-2,3,4,5-tetrahydropyridine **1b** (53.1 mg, 87%) as a yellow oil. IR (thin film): 2929, 1665, 1453 cm^{-1} . δ_{H} (400 MHz, CDCl_3): 1.56-1.58 (2H, m), 1.63-1.69 (2H, m), 2.08-2.12 (2H, m), 2.42-2.46 (2H, m), 2.84-2.88 (2H, m), 3.57-3.60 (2H, m), 7.16-7.21 (3H, m), 7.28-7.29 (2H, m). δ_{C} (100 MHz, CDCl_3): 19.59 (CH_2), 21.93 (CH_2), 29.63 (CH_2), 32.63 (CH_2), 42.45 (CH_2), 49.29 (CH_2), 125.82 (CH), 128.35 (CH), 142.01 (C), 170.12 (C). m/z, (EI): 187 ($\text{M}^{\bullet+}$, 100%), 110 (35), 91 (75). HRMS: 187.1362. $\text{C}_{13}\text{H}_{17}\text{N}$ requires (M^+) , 187.1361.

^1H NMR and ^{13}C NMR agrees with literature.²

6-(Furan-3'-yl)-2,3,4,5-tetrahydropyridine **1c**

Following the procedure for imine preparation starting with resin-bound 3-furoate ester **9c** (0.311 milliequiv.) gave 6-(furan-3'-yl)-2,3,4,5-tetrahydropyridine **1c** (48.9 mg, 70%) as a yellow oil. IR (thin film): 2933, 1636 cm^{-1} . δ_{H} (400 MHz, CDCl_3): 1.63-1.69 (2H, m) 1.76-1.82 (2H, m) 2.45-2.49 (2H, m) 3.74-3.77 (2H, m) 6.76 (1H, dd, J 1.8 Hz, 0.65) 7.39 (1H, t, $J=1.7$) 7.69 (1H, broad s). δ_{C} (100 MHz, CDCl_3): 19.36 (CH_2), 22.10 (CH_2), 27.63 (CH_2), 49.46 (CH_2), 107.92 (CH), 128.64 (C), 141.72 (CH), 143.46 (CH), 160.18 (C). m/z, (EI): 149 ($\text{M}^{\bullet+}$, 45%), 120 (40), 84 (98), 49 (100). HRMS: 149.0840. $\text{C}_9\text{H}_{11}\text{NO}$ requires (M^+) , 149.0841.

6-(Cyclohex-3'-en-1'-yl)-2,3,4,5-tetrahydropyridine **1d**

Following the procedure for imine preparation starting with resin-bound 3-cyclohexene-1-carboxylate ester **9d** (0.310 milliequiv.), gave 6-(cyclohex-3'-en-1'-yl)-2,3,4,5-tetrahydropyridine **1d** (38.8 mg, 77%) as a yellow oil. IR (thin film): 2929, 1662 cm^{-1} . δ_{H} (400 MHz, CDCl_3): 1.47-1.59 (3H, m), 1.64-1.70 (2H, m), 1.85-1.89 (1H, m), 2.07-2.18 (6H, m), 2.25-2.32 (1H, m), 3.56-3.59 (2H, m), 5.66-5.73 (2H, m). δ_{C} (100 MHz, CDCl_3): 19.63 (CH_2), 22.08 (CH_2), 25.55 (CH_2),

26.32 (CH₂), 27.29 (CH₂), 28.87 (CH₂), 44.51 (CH), 49.21 (CH₂), 126.30 (CH), 126.66 (CH), 173.85 (C). m/z, (CI): 164 [(M+H)⁺, 100%], 163 (10%). HRMS: 164.1428. C₁₁H₁₈N requires (M+H)⁺, 164.1439.

N,N-Diethyl-N-[2-(3',4',5',6'-tetrahydropyridin-2'-yl)ethyl]amine 1e

Following the procedure for imine preparation starting with resin-bound 3-(diethylamino)propionate ester **9e** (0.328 milliequiv.) gave *N,N-Diethyl-N-[2-(3',4',5',6'-tetrahydropyridin-2'-yl)ethyl]amine 1e* (43.1 mg, 72%) as a yellow oil. IR (thin film): 2932, 1660, 1444 cm⁻¹. δ_{H} (400 MHz, CDCl₃): 1.03 (6H, t, *J* = 7.2), 1.52-1.58 (2H, m), 1.62-1.70 (2H, m), 2.12-2.18 (2H, m), 2.30 (2H, t, *J* = 7.9), 2.54 (4H, q, *J* = 7.2), 2.69 (2H, t, *J* = 8.0), 3.54-3.56 (2H, m). δ_{C} (100 MHz, CDCl₃): 11.81 (CH₃), 19.57 (CH₂), 21.85 (CH₂), 29.65 (CH₂), 38.14 (CH₂), 46.83 (CH₂), 49.24 (CH₂), 49.66 (CH₂), 169.91 (C). Unstable under all conditions used for mass spectroscopy (CI, EI or FAB).

6-(1'-Phenylethyl)-2,3,4,5-tetrahydropyridine 1f

Following the procedure for imine preparation starting with resin-bound 2-phenylpropionate ester **9f** (0.328 milliequiv.) gave 6-(1'-phenylethyl)-2,3,4,5-tetrahydropyridine (28.2 mg, 46%) as a yellow oil. IR (thin film): 2929, 1662, 1448 cm⁻¹. δ_{H} (400 MHz, CDCl₃): 1.40 (3H, d, *J* = 7.1), 1.51-1.58 (4H, m), 1.87-1.92 (1H, m), 1.93-2.05 (1H, m), 3.51 (1H, q, *J* = 7.1), 3.61-3.70 (2H, m), 7.20-7.32 (5H, m). δ_{C} (100 MHz, CDCl₃): 18.56 (CH₃), 19.58 (CH₂), 22.06 (CH₂), 27.58 (CH₂), 49.39 (CH₂), 49.86 (CH), 126.39 (CH), 127.57 (CH), 128.46 (CH), 143.75 (C), 172.44 (C). m/z, (CI): 188 [(M+H)⁺, 100%], 100 (20%). HRMS: 188.1436. C₁₃H₁₈N requires (M+H)⁺, 188.1439.

2(S)-Propylpiperidine hydrochloride salt [(S)-coniine hydrochloride] (S)-2a

Starting with resin-bound butyrate ester **9a** (0.325 milliequiv.), and using thioacetal (*S*)-**5** gave 2(*S*)-propylpiperidine hydrochloride salt (*S*)-**2a** as a solid (31.4 mg, 60% based on loading of Merrifield resin). $[\alpha]_D^{18} = +8.1$ (*c*=0.52, EtOH), $[\alpha]_D +19.8$ (*c* 0.50, DCM). Lit:³ $[\alpha]_D = +6.5$ (*c*=1.2, EtOH). IR (thin film): 2935, 2725, 1590, 1455 cm⁻¹. δ_{H} (CDCl₃, 400 MHz) 0.94 (3H, t, *J*= 7.6), 1.36-1.53 (3H, m), 1.57-2.10 (7H, m), 2.73-2.85 (1H, m), 2.87-2.98 (1H, m), 3.44 (1H, broad d, *J*=11.1), 9.17 (1H, s), 9.47 (1H, s) δ_{C} (CDCl₃, 100 MHz) 13.69 (CH₃), 18.53 (CH₂), 22.14 (CH₂), 22.57 (CH₂), 28.08 (CH₂), 35.30 (CH₂), 44.71 (CH₂), 57.11 (CH). m/z (CI): 128 (M⁺, 100%), 84 (25). HRMS: 128.1438. C₈H₁₈N requires (M⁺), 128.1439. ¹H NMR and ¹³C NMR data agree with literature.³

Determination of enantiopurity of (*S*)-2a:

Triethylamine in DCM (0.14 mL of a 0.37 M solution, 1.5 equiv.) was added to 2(*S*)-propylpiperidine hydrochloride (**S**)-**2a** (5.3 mg, 32 μ mol, 1 equiv.). The solution was cooled to 0 °C and trifluoroacetic anhydride in DCM (0.14 mL of a 0.30 M solution, 40 μ mol, 1.2 equiv.) was added. The solution was stirred for 18 h at RT, and was washed with saturated NaHCO₃ (2×), 1M HCl (2×), and brine (1×). The organic layer was dried over MgSO₄, and solvent removed *in vacuo* to give the *N*-trifluoroacetyl-2(*S*)-propylpiperidine as an oil (7.0 mg, 97%), existing as a 2:1 mixture of geometrical isomers a, and b. IR (thin film): 2954, 2876, 1686, 1457 cm⁻¹. δ _H (CDCl₃, 400 MHz): 0.93 (3H^a, t *J*= 7.3), 0.94 (3H^b, t *J*= 7.3), 1.17-1.79 (10H^{a&b}, m), 2.84 (1H^b, td *J*=13.7, 1.6), 3.16 (1H^a, td *J*=13.1, 2.8), 3.78 (1H^a, broad d *J*=13.6), 3.97-4.06 (1H^b, m), 4.36-4.43 (1H^b, m), 4.66-4.73 (1H^a, m). m/z (CI): 224 [(M+H)⁺, 100%]. HRMS: 224.1264 C₁₀F₃H₁₇NO requires (M+H⁺), 224.1262. This was then used on a chiral GC (Supelco β -DEX 120 column, 70 °C for 2 min, then the temperature was increased at a rate of 1 °C min⁻¹ to 150 °C) to show a 90 %ee (*t_S*=32.98 min, *t_R*=33.57 min).

2(*R*)-propylpiperidine hydrochloride salt [(*R*)-coniine hydrochloride] (**R**)-**2a**

Starting with resin-bound butyrate ester **9a** (0.311 milliequiv.), and using thioacetal (**R**)-**5** gave 2(*S*)-propylpiperidine hydrochloride salt (**R**)-**2a** as a solid (31.4 mg, 60% based on loading of Merrifield resin). $[\alpha]_D^{18} = -7.3$ (*c*=0.06, EtOH), $[\alpha]_D -20.0$ (*c* 0.20, DCM). Lit:³ $[\alpha]_D -7.3$ (*c*=1.0, EtOH). Other data in agreement with (**S**)-**2a** and literature.³

Determination of enantiopurity of (**R**)-**2a**:

Following the same procedure as for (**S**)-**2a** above, 2(*R*)-propylpiperidine hydrochloride (**R**)-**2a** (10.5 mg) was converted into *N*-trifluoroacetyl-2(*R*)-propylpiperidine (12.1 mg, 84% - data agrees with that of other enantiomer). This was then used on a chiral GC (Supelco β -DEX 120 column, 70 °C for 2 min, then the temperature was increased at a rate of 1 °C /min to 150 °C) to show an 89 %ee (*t_S*=32.97 min, *t_R*=33.55 min).

2(*R*)-Phenylethylpiperidine hydrochloride salt (**R**)-**2b**

Starting with resin-bound 3-phenylpropionate ester **9b** (0.311 milliequiv.), and using thioacetal (**S**)-**5** gave 2(*R*)-phenylethylpiperidine hydrochloride salt (**R**)-**2b** as a solid (30.1 mg, 43% based on loading of Merrifield resin). $[\alpha]_D +13.5$ (*c* 0.38, DCM), +10.1 (*c* 0.139, MeOH). Lit:³ $[\alpha]_D +11.1$ (*c* 0.65, MeOH). IR (thin film): 2944, 2719, 1587, 1493, 1455 cm⁻¹. δ _H (CDCl₃, 400 MHz): 1.29-1.45 (1H, m), 1.63-1.78 (2H, m), 1.79-2.13 (4H, m), 2.27-2.45 (1H, m), 2.61-2.78 (3H, m), 2.80-2.95 (1H, m), 3.31-3.45 (1H, m), 7.13-7.37 (5H, m), 9.30 (1H, s), 9.53 (1H, s) δ _C (CDCl₃, 100 MHz):

22.05 (CH₂), 22.25 (CH₂), 28.12 (CH₂), 31.09 (CH₂), 34.58 (CH₂), 44.68 (CH₂), 56.56 (CH), 126.11(CH), 128.32 (CH), 128.44 (CH), 140.04 (C). m/z (CI): 190 (M⁺, 100%), 84 (25). HRMS: 190.1597 C₁₃H₂₀N requires (M⁺), 190.1596. [α]_D, ¹H NMR, and ¹³C NMR data correspond with the literature.³

Determination of enantiopurity of (*R*)-2b:

Triethylamine (10.0 μL, 0.07 mmol, 3 equiv.) was added to (*R*)-2b (5.2 mg, 0.023 mmol, 1 equiv.) in DCM (0.30 mL). The solution was cooled to 0 °C and benzoyl chloride (5.0 μL, 0.05 mmol, 2 equiv.) was added. The solution stirred 18 h while warming to RT, and was then washed with water (1×). The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo* to yield the crude benzamide as a yellow oil. Column chromatography [SiO₂, Petroleum ether-EtOAc (9:1)] gave *N*-Benzoyl-2(*R*)-phenylethylpiperidine as a colorless oil (3.8 mg, 56 %). R_F [SiO₂, hexane-EtOAc (2:1)]: 0.51. IR (thin film): 2931, 1621, 1495 cm⁻¹. δ_H (CDCl₃, 400 MHz, 50 °C): 1.32-1.69 (6H, m), 1.71-1.83 (1H, m), 1.97-2.08 (1H, m), 2.41-2.61 (2H, m), 2.84-2.98 (1H, m), 3.75-4.16 (1H, m), 4.28-4.64 (1H, m), 7.05-7.11 (2H, m), 7.13-7.18 (3H, m), 7.21-7.30 (5H, m). m/z (EI): 293 (M⁺, 20%), 188 (70), 105 (100), 77 (33). HRMS: 293.1778. C₂₀H₂₃NO requires (M⁺), 293.1780. Chiral HPLC [Chiralcel OD-H, hexane-isopropanol-methanol (98:1:1), 0.5mL min⁻¹] showed 96 %ee (t_R=55.45 min, t_S=62.17 min).

2(*S*)-Phenylethylpiperidine hydrochloride salt (*S*)-2b

Starting with resin-bound 3-phenylpropionate ester 9b (0.311 milliequiv.), and using thioacetal (*S*)-5 gave 2(*S*)-phenylethylpiperidine hydrochloride salt (*S*)-2b as a solid (31.2 mg, 44% based on loading of Merrifield resin). [α]_D -13.9 (c 0.47, DCM), -10.1 (c 0.089, MeOH). Lit:³ [α]_D -11.3 (c 0.95, MeOH). Other data in agreement with (*R*)-2b and literature.³

Determination of enantiopurity of (*S*)-2b:

Following the same procedure as for (*R*)-2b above, 2(*S*)-phenylethylpiperidine hydrochloride salt (*S*) (6.0 mg) was converted into *N*-benzoyl-2(*S*)-phenylethylpiperidine (4.4 mg, 56% - data agrees with that of other enantiomer). Chiral HPLC [Chiralcel OD-H, hexane-isopropanol (98:2), 0.8mL/min] showed 94 %ee (t_R=35.65 min, t_S=41.27 min).

2(*R*)-(3'-Methoxyphenyl)piperidine hydrochloride salt (*R*)-2g

Starting with resin-bound 3-methoxybenzoate ester 9g (0.325 milliequiv.), and using thioacetal (*S*)-5 gave 2(*R*)-(3'-methoxyphenyl)piperidine hydrochloride salt (*R*)-2g as a solid (24.9 mg, 34% based on loading of Merrifield resin). [α]_D +27.8 (c 1.32, DCM) IR (thin film): 2920, 2704, 1602, 1496

cm^{-1} . δ_{H} (CDCl_3 , 400 MHz): 1.45-1.58 (1H, m), 1.68-1.77 (1H, m), 1.90-2.16 (4H, m), 2.68-2.81 (1H, m), 3.14 (1H, broad d, $J=11.7$), 3.75 (3H, s), 3.82-3.91 (1H, m), 6.85 (1H, dd, $J= 8.2, 2.1$), 7.08 (1H, broad d, $J= 7.7$), 7.19-7.24 (2H, m), 9.45-9.61 (2H, m) δ_{C} (CDCl_3 , 100 MHz): 21.60 (CH_2), 23.11 (CH_2), 30.52 (CH_2), 45.63 (CH_2), 55.51 (CH_3), 61.38 (CH), 112.21 (CH), 115.87 (CH), 119.84 (CH), 129.95 (CH), 137.90 (C), 159.91 (C). m/z (CI): 192 (M^+ , 100%). HRMS: 192.1388 $\text{C}_{12}\text{H}_{18}\text{NO}$ requires (M^+), 192.1388. Consistent with, but different from data for the racemic free base.⁴

Determination of enantiopurity of (*R*)-2g:

Triethylamine (18.5 μL , 130 μmol) was added to 2(*R*)-(3'-methoxyphenyl)piperidine hydrochloride salt (**R**)-2g (10.0 mg, 44 μmol) in DCM (0.50 mL). The solution was cooled to 0 °C and benzoyl chloride (10.2 μL , 90 μmol) was added. The solution stirred 18 h while warming to RT, and was then washed with water (1 \times). The organic layer was dried over MgSO_4 , and concentrated *in vacuo* to yield the crude benzamide as a yellow oil. Column chromatography [SiO_2 , petroleum ether-EtOAc (9:1)] gave *N*-benzoyl-2(*R*)-(3'-methoxyphenyl)piperidine as a solid (10.1 mg, 78%). R_F [SiO_2 , hexane-EtOAc (2:1)]: 0.45. IR (thin film): 2947, 1629, 1490 cm^{-1} . δ_{H} (CDCl_3 , 400 MHz, 50 °C): 1.59-1.72 (4H, m), 1.90-2.00 (1H, m), 2.38 (1H, broad d, $J= 14.0$), 2.93-3.00 (1H, m), 3.82 (3H, s), 4.00-4.20 (1H, m), 5.50-5.60 (1H, m), 6.81 (1H, dd, $J= 8.2, 2.5$), 6.88 (1H, broad s), 6.92 (1H, d, $J= 7.7$), 7.30 (1H, t, $J= 8.0$), 7.36-7.39 (3H, m), 7.42-7.47 (2H, m). m/z (EI): 295 (M^{++} , 90%), 190 (95), 105 (100), 77 (50). HRMS: 295.1570. $\text{C}_{19}\text{H}_{21}\text{O}_2\text{N}$ requires (M^+) 295.1572. Chiral HPLC [Chiralcel OD-H, hexane-isopropanol (97:3), 0.8 mL min^{-1}] showed 76 %*ee* ($t_R=32.05$ min, $t_S=42.25$ min).

2(*S*)-(3'-methoxyphenyl)piperidine hydrochloride salt (*S*)-2g

Starting with resin-bound 3-methoxybenzoate ester **9g** (0.325 milliequiv.), and using thioacetal (**R**)-**5** gave 2(*R*)-(meta-methoxyphenyl)piperidine hydrochloride salt (**S**)-2g as a solid (25.0 mg, 34% based on loading of Merrifield resin). $[\alpha]_D -24.6$ (*c* 0.26, DCM). Other data in agreement with (**R**)-2g.

Determination of enantiopurity of (*S*)-2g:

Following the same procedure as for (**R**)-2g above, 2(*S*)-(3'-methoxyphenyl)piperidine hydrochloride salt (**S**)-2g (10.2 mg) was converted into *N*-Benzoyl-2(*R*)-(3'-methoxyphenyl)piperidine (9.9 mg, 75% - data agrees with that of other enantiomer). Chiral HPLC [Chiralcel OD-H, hexane-isopropanol (97:3), 0.8 mL min^{-1}] showed 80 %*ee* ($t_R=32.14$ min, $t_S=41.63$ min).

2(R)-[But-2'(S)-yl]piperidine hydrochloride salt **2h**

Starting with resin-bound 2(S)-methylbutyrate ester **9h** (0.325 milliequiv.), and using thioacetal (**S**)-**5** gave 2(R)-[but-2'(S)-yl]piperidine hydrochloride salt **2h** as a solid (20.2 mg, 35% based on loading of Merrifield resin). $[\alpha]_D +19.1$ (*c* 1.15, DCM) IR (thin film): 2932, 2733, 1590, 1448 cm^{-1} . δ_{H} (CDCl₃, 400 MHz): 0.93 (3H, t, *J*= 7.4), 1.08 (3H, d, *J*= 6.6), 1.21-2.08 (9H, m), 2.75-2.92 (2H, m), 3.52 (1H, broad d, *J*=12.1), 8.88 (1H, s), 9.41 (1H, s) δ_{C} (CDCl₃, 100 MHz): 11.48 (CH₃), 14.10 (CH₃), 22.31 (CH₂), 22.83 (CH₂), 23.78 (CH₂), 26.21 (CH₂), 36.99 (CH), 45.73 (CH₂), 61.74 (CH). m/z (CI): 142 (M⁺, 100%), 84 (25). HRMS: 142.1598. C₉H₂₀N requires (M⁺), 142.1596.

Determination of the diastereomeric purity of **2h**:

Triethylamine (5.9 μL , 42 μmol , 1.5 equiv.) was added to 2(R)-[but-2'(S)-yl]piperidine hydrochloride salt **2h** (5.0 mg, 28 μmol , 1 equiv.) in DCM (0.25 mL). The solution was cooled to 0 °C and trifluoroacetic anhydride (4.7 μL , 34 μmol , 1.2 equiv.) was added. The solution was stirred for 18 h at RT, and was then washed with saturated NaHCO₃ (2×), 1M HCl (2×), and brine (1×). The organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo* to give the *N*-trifluoroacetyl-2(R)-[but-2'(S)-yl]piperidine as an oil (6.3 mg, 94%), existing as a 2.3:1 mixture of geometrical isomers a, and b. IR (thin film): 2962, 1688, 1455 cm^{-1} . δ_{H} (CDCl₃, 400 MHz): 0.87 (3H^{a+b}, t, *J*= 7.3), 0.928 (3H^b, d *J*=6.3), 0.934 (3H^a, d *J*= 6.6), 0.96-1.08 (1H^{a+b}, m), 1.24-1.45 (1H^{a+b}, m), 1.46-1.78 (5H^{a+b}, m), 1.88-1.98 (2H^{a+b}, m), 2.75 (1H^b, broad t *J*=12.8), 3.12 (1H^a, td *J*=13.0, 1.9), 3.52-3.56 (1H^b, m), 3.78 (1H^a, broad d, *J*=13.6), 4.27-4.33 (1H^a, m), 4.36-4.43 (1H^b, m). m/z (CI): 238 [(M+H)⁺, 100%]. HRMS: 238.1421. C₁₁F₃H₁₉NO requires (M+H⁺), 238.1419. This was then used on a chiral GC (Supelco β -DEX 120 column, 70 °C for 2 min, then the temperature was increased at a rate of 1 °C /min to 150 °C) to show a dr (RS:SS) = 87:13 (*t_{RS}*=38.32 min, *t_{SS}*=40.12 min).

2(S)-[But-2'(S)-yl]piperidine hydrochloride salt **2h'**

Starting with resin-bound 2(S)-methylbutyrate ester **9h** (0.325 milliequiv.), and using thioacetal (**R**)-**5** gave 2(S)-[but-2'(S)-yl]piperidine hydrochloride salt **2h'** as a solid (15.0 mg, 26% based on loading of Merrifield resin). $[\alpha]_D -16.7$ (*c* 0.27, DCM) IR (thin film): 2931, 2736, 1590, 1452 cm^{-1} . δ_{H} (CDCl₃, 400 MHz): 0.91 (3H, t, *J*= 7.4), 1.08 (3H, d, *J*= 6.9), 1.19-2.08 (9H, m), 2.73-2.92 (2H, m), 3.53 (1H, broad d, *J*= 12.8), 8.92 (1H, s), 9.18 (1H, s). δ_{C} (CDCl₃, 100 MHz): 11.26 (CH₃), 15.64 (CH₃), 22.24 (CH₂), 22.88 (CH₂), 24.48 (CH₂), 25.46 (CH₂), 37.39 (CH), 45.84 (CH₂), 62.51 (CH). m/z (CI): 142 (M⁺, 100%), 84 (10). HRMS: 142.1594 C₉H₂₀N requires (M⁺) 142.1596.

Determination of the diastereomeric purity of **2h'**:

Triethylamine in DCM (0.12 mL of a 0.37 M solution, 1.5 equiv.) was added to *2(S)*-[but-2'(S)-yl]piperidine hydrochloride salt **2h'** (5.2 mg, 29 μ mol, 1 equiv.). The solution was cooled to 0 °C and trifluoroacetic anhydride in DCM (0.12 mL of a 0.30 M solution, 1.2 equiv.) was added. The solution was stirred 18 h at RT, and was then washed with saturated NaHCO₃ (2 \times), 1M HCl (2 \times), and brine (1 \times). The organic layer was dried over MgSO₄, and solvent removed *in vacuo* to give the *N*-trifluoroacetyl-2(*S*)-(but-2'(*S*)-yl)piperidine as an oil (6.9 mg, 99%), existing as a 2.3:1 mixture of geometrical isomers a, and b. IR (thin film): 2961, 1686, 1459 cm⁻¹. δ _H (CDCl₃, 400 MHz): 0.79 (3H^a, d *J*= 6.7), 0.82 (3H^b, d *J*= 6.8), 0.94 (3H^{a+b}, t *J*= 7.4), 1.08-1.23 (1H^{a+b}, m), 1.24-1.29 (1H^{a+b}, m), 1.46-1.78 (5H^{a+b}, m), 1.88-1.98 (2H^{a+b}, m), 2.75 (1H^b, broad t *J*=13.6), 3.10 (1H^a, td *J*=13.9, 2.9), 3.58-3.65 (1H^b, m), 3.79 (1H^a, broad d, *J*=13.6), 4.32-4.43 (1H^{a+b}, m). m/z (CI): 238 [(M+H)⁺, 100%]. HRMS: 238.1421. C₁₁F₃H₁₉NO requires (M+H⁺), 238.1419. This was then used on a chiral GC (Supelco β -DEX 120 column, 70 °C for 2 min, then the temperature was increased at a rate of 1 °C min⁻¹ to 150 °C) to show a dr (*RS*:*SS*) = 20:80 (*t_{RS}*=38.07 min, *t_{SS}*=**39.82 min**).

2(R)-[2'(*R*)-6'-Dimethylhept-1'-yl]piperidine hydrochloride salt **2i**

Starting with resin-bound (*R*)-citronellate ester **9i** (0.325 milliequiv.), and using thioacetal (*S*)-**5** gave *2(R)*-[2'(*R*)-6'-dimethylhept-1'-yl]piperidine hydrochloride salt **2i** as a solid (23.3 mg, 29% based on loading of Merrifield resin). $[\alpha]_D$ +14.3 (*c* 0.71, DCM) IR (thin film): 2927, 2711, 1607, 1433 cm⁻¹. δ _H (CDCl₃, 400 MHz): 0.85 (3H, d, *J*= 6.6), 0.86 (3H, d, *J*= 6.6), 0.92 (3H, d, *J*= 6.4), 1.08-2.01(16 H, m), 2.73-2.87(1H, m), 2.94-3.04 (1H, m), 3.44 (1H, broad d, *J*=11.0), 9.16 (1H, s), 9.42 (1H, s). δ _C (CDCl₃, 100 MHz) 20.04 (CH₃), 22.21 (CH₂), 22.43 (CH₂), 22.51 (CH₃), 22.71 (CH₃), 24.41(CH₂), 27.90 (CH), 28.63 (CH₂), 28.85 (CH), 36.05 (CH₂), 39.19 (CH₂), 40.91 (CH₂), 44.78 (CH₂), 55.44 (CH). m/z (CI): 212 (M⁺, 100%), 84 (25). HRMS: 212.2379 C₁₄H₃₀N requires (M⁺), 212.2378.

Determination of the diastereomeric purity of **2i**:

Triethylamine (5.7 μ L, 41 μ mol, 3 equiv.) was added to *2(R)*-[2'(*R*)-6'-dimethylhept-1'-yl]piperidine hydrochloride salt **2i** (3.4 mg, 14 μ mol, 1 equiv.) in DCM (0.30 mL). The solution was cooled to 0 °C and benzoyl chloride (3.2 μ L, 28 μ mol, 2 equiv.) was added. The solution stirred for 18 h at RT, and was then washed with water (1 \times). The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo* to yield the crude benzamide as a yellow oil. Column chromatography [SiO₂, Petroleum ether-EtOAc (9:1)] gave *N*-Benzoyl-*2(R)*-[2'(*R*)-6-dimethyl-

heptyl]piperidine as an oil (4.0 mg, 92%). R_f [SiO₂, Petroleum ether-EtOAc (3:1)]: 0.65. IR (thin film): 2927, 2866, 1631 cm⁻¹. δ_H (d6 DMSO, 400 MHz, 80 °C): 0.84 (3H, d, J = 6.2), 0.91 (6H, d, J = 6.6), 1.09-1.90 (16H, m), 2.95-3.08 (1H, m, partly obscured by water peak), 3.72-3.90 (1H, m), 4.38-4.54 (1H, m), 7.31-7.39 (2H, m), 7.42-7.48 (3H, m). m/z (EI): 315 (M^+ , 15%), 188 (95), 105 (100), 77 (20). HRMS: 315.2562 C₂₁H₃₃ON requires (M^+), 315.2560. Chiral HPLC [Chiralcel OD-H, hexane-isopropanol (99:1), 0.8 mL min⁻¹] showed dr ($RR:SR$) = 99.5:0.5 (t_{RR} =**16.28 min**, t_{SR} =19.58 min).

2(S)-[2'(R)-6'-dimethylhept-1'-yl]piperidine hydrochloride salt **2i'**

Starting with resin-bound (*R*)-citronellate ester **9i** (0.325 milliequiv.), and using thioacetal (*R*)-**5** gave 2(S)-[2'(R)-6'-dimethylhept-1'-yl]piperidine hydrochloride salt **2i'** as a solid (21.2 mg, 26% based on loading of Merrifield resin). $[\alpha]_D$ -15.1 (*c* 3.18, DCM) IR (thin film): 2957, 2722, 1455 cm⁻¹. δ_H (CDCl₃, 400 MHz): 0.841 (3H, d, J = 6.6), 0.844 (3H, d, J = 6.6), 0.87 (3H, d, J = 6.5), 1.08-2.00 (16 H, m), 2.82 (1H, broad q, J = 10.9), 2.92-3.06 (1H, m), 3.45 (1H, broad d, J = 11.6), 9.09 (1H, s), 9.37 (1H, s). δ_C (CDCl₃, 100 MHz): 15.24 (CH₃), 22.25 (CH₂), 22.35 (CH₂), 22.56 (CH₃), 22.65 (CH₃), 24.62 (CH₂), 27.87 (CH), 27.93 (CH₂), 28.90 (CH), 37.75 (CH₂), 39.07 (CH₂), 40.39 (CH₂), 44.74 (CH₂), 55.52 (CH). m/z (CI): 212 (M^+ , 100%). HRMS: 212.2376 C₁₄H₃₀N requires (M^+), 212.2378.

Determination of the diastereomeric purity of **2i'**:

Triethylamine in DCM (0.17 mL of a 0.37 M solution, 63 μ mol, 1.5 equiv.) was added to **2i'** (10.3 mg, 42 μ mol, 1 equiv.). The solution was cooled to 0 °C and benzoyl chloride in DCM (0.26 mL of a 0.19 M solution, 49 μ mol, 1.2 equiv.) was added. The solution was stirred for 18 h at RT, and then was washed with brine (1 \times). The organic layer was dried over Na₂SO₄, filtered, and solvent removed *in vacuo* to yield the crude benzamide as a yellow oil. Column chromatography [SiO₂, petroleum ether-EtOAc (9:1)] gave **7i'** as an oil (9.5 mg, 72%). R_F [SiO₂, petroleum ether-EtOAc (3:1)]: 0.63. IR (thin film): 2926, 1625 cm⁻¹. δ_H (d6-DMSO, 400 MHz, 80 °C): 0.84 (3H, d, J = 6.4), 0.90 (6H, d, J = 6.6), 1.05-1.74 (16H, m), 2.96-3.05 (1H, m, partly obscured by water peak), 3.78-3.93 (1H, m), 4.33-4.48 (1H, m), 7.32-7.38 (2H, m), 7.42-7.49 (3H, m). HRMS: 315.2562. C₂₁H₃₃NO requires (M^+), 315.2565. Chiral HPLC [Chiralcel OD-H, hexane-isopropanol (99:1), 0.8 mL min⁻¹] showed dr ($RR:SR$) = 1.5:98.5 (t_{RR} =16.19 min, t_{SR} =**19.04 min**).

N-[4,4-Bis(phenylsulfanyl)but-1-yl]-N-tritylamine 4

Pyridine sulphur trioxide (2.469 g, 15.51 mmol) was added to a solution of 4,4-bis(phenylsulfanyl)butan-1-ol (1.151 g, 3.97 mmol), triethylamine (3.9 mL, 28 mmol), and DMSO (2.8 mL, 39 mmol) in DCM (30 mL) at 0 °C. The solution stirred 16 h at RT. The reaction was cooled to 0 °C and quenched with water followed by saturated aqueous NaHCO₃. The layers were separated and the aqueous layer was extracted with DCM (3×). All organics were combined, washed with water (3×), then brine (1×), dried over MgSO₄, filtered and concentrated under reduced pressure. This gave crude 4,4-bis(phenylsulfanyl)butyraldehyde, as an orange oil which was used without further purification. Tritylamine (2.306 g, 8.90 mmol) was added to a solution of the crude aldehyde and 4 Å molecular sieves (1 g) in DCM (50 mL), and the mixture stirred for 6 h at RT. After this time the reaction mixture was cooled to 0 °C and sodium borohydride (165 mg, 4.37 mmol) was added. After stirring for 16 h at RT, the reaction was cooled to 0 °C, and quenched with water. The layers were separated and the aqueous layer was extracted with DCM (3×). Combined organics were washed with brine and water alternately (2×), then brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Column chromatography [SiO₂, petroleum ether-DCM (2:1)] gave the crude amine as a white solid, which was then recrystallised in methanol to give *N-[4,4-bis(phenylsulfanyl)but-1-yl]-N-tritylamine* as needles (789 mg, 37%). R_F [SiO₂, petroleum ether-DCM (2:1)] 0.54. m.p. 98-100 °C. IR (KBr): 3053, 2934, 2856, 1467 cm⁻¹. δ_H (400 MHz, CDCl₃): 1.42 (1H, s), 1.75-1.82 (2H, m), 1.90-1.95 (2H, m), 2.10 (2H, t, *J* = 6.5), 4.38 (1H, t, *J* = 6.6 Hz], 7.16-7.21 (3H, m), 7.24-7.33 (12H, m), 7.38-7.52 (10H, m). δ_C (100 MHz, CDCl₃): 28.12 (CH₂), 33.44 (CH₂), 42.74 (CH₂), 58.34 (CH), 70.78 (C), 126.17 (CH), 127.71 (CH), 127.75 (CH), 128.56 (CH), 128.87 (CH), 132.86 (CH), 134.06 (C), 146.07 (C). m/z, (FAB+ NOBA): 532 [(M+H)⁺, 8%], 288 (20%), 243 (100%), 166 (15%). HRMS: 532.2139. C₃₅H₃₄NS₂ requires (M + H)⁺, 532.2133. Microanalysis: C, 79.15; H, 6.13; N, 2.69%. C₃₅H₃₃NS₂ requires C, 79.05; H, 6.25; N, 2.63 %.

N-[4,4-Bis(phenylsulfanyl)but-1-yl]-N-[1(R)-phenylethyl]amine (R)-5

4,4-Bis(phenylsulfanyl)butan-1-ol⁵ (11.92 g, 41 mmol) was dissolved in DCM (315 mL). DMSO (29 mL, 41 mmol) and triethylamine (40 mL, 28 mmol) were added. The reaction mixture was cooled to 0 °C. Sulfur trioxide pyridine complex (25.57 g, 160 mmol) was added in 3 g batches. The ice bath was removed and the mixture was stirred at RT for 20 h. The reaction was quenched with aqueous saturated NaHCO₃ (120 mL). The mixture was extracted with DCM (3×) and the organic extracts were combined, washed with water (3×) then brine (1×). The organic layer was dried over MgSO₄ and concentrated *in vacuo* to yield crude 4,4-bis(phenylsulfanyl)butyraldehyde

as a cloudy yellow oil (11.88 g). 4 Å molecular sieves (4.8 g) and half of the crude aldehyde (5.94 g, 21 mmol) were dissolved in DCM (215 mL). Enantiomerically pure 1(*R*)-phenylethylamine (5.7 mL, 41 mmol) was added, and the reaction mixture became cloudy. After 3 h of stirring at RT NaBH₄ (0.87 g, 23 mmol) was added. The mixture was stirred overnight. The reaction was quenched with water (6mL), and the organic layer was washed with water (3×), and brine (1×). The organic layer was dried over MgSO₄, and concentrated *in vacuo*. Column chromatography [SiO₂, petroleum ether-EtOAc (1:1)] followed by column chromatography [SiO₂, eluting first with DCM-petroleum ether (4:1) to remove impurities, and then petroleum ether-EtOAc (1:1)] gave the desired amine (**R**)-5 as a pale yellow oil (4.067 g, 49%). R_F [SiO₂, petroleum ether-EtOAc (1:1)] 0.18. [α]_D +24.6 (c 1.21, DCM) IR (thin film): 3313 (N-H), 3058, 2958, 2925, 1581, 1479, 1450 cm⁻¹. δ_H (CDCl₃, 400 MHz) 1.33 (3H, d, *J* = 6.6), 1.73-1.81 (2H, m), 1.82-1.89 (2H, m), 2.40 (1H, dt, *J* = 11.6, 6.8), 2.47 (1H, ddd, *J* = 11.6, 7.5, 6.2), 3.73 (1H, q, *J* = 6.6), 4.40 (1H, t, *J* = 6.8), 7.19-7.32 (11H, m), 7.38-7.47 (4H, m). δ_C (CDCl₃, 100 MHz): 24.39 (CH₃), 27.55 (CH₂), 33.58 (CH₂), 46.93 (CH₂), 58.17 (CH), 58.19 (CH), 126.51 (CH), 126.60 (CH), 126.82 (CH), 127.60 (CH), 127.63 (CH), 128.39 (CH), 128.85 (CH), 132.65 (CH), 132.70 (CH), 134.24 (C), 134.26 (C), 145.76 (C). m/z (EI): 393 (M⁺, 58%), 284 (100%). HRMS: 393.1586. C₂₄H₂₇NS₂ requires (M⁺) 393.1585. Microanalysis C, 73.25; H, 6.99; N, 3.66; S, 16.09. C₂₄H₂₇NS₂ requires C, 73.28; H, 6.87; N, 3.56; S, 16.28

***N*-[4,4-Bis(phenylsulfanyl)but-1-yl]-*N*-[1(*S*)-phenylethyl]amine (*S*)-5**

In the same way, the other half of the 4,4-bis(phenylsulfanyl)butyraldehyde (5.94 g, 21 mmol) and enantiomerically pure 1(*S*)-phenyl ethylamine (5.7 mL, 41 mmol) gave the desired amine (**S**)-5 as a pale yellow oil (3.8 g 46% yield). [α]_D -24.3 (c 1.08, DCM). All other data in agreement with that for (**R**)-5.

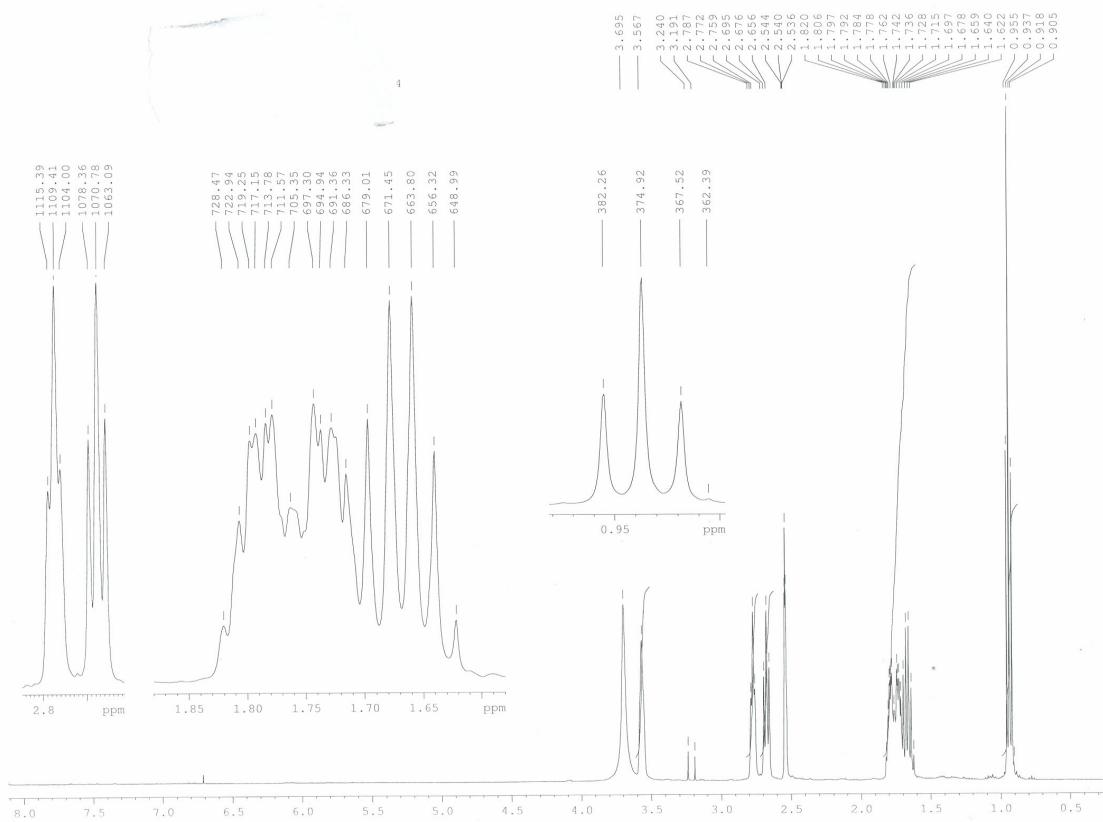
Merrifield resin bound esters 9

Merrifield resin-bound esters were prepared following the published procedure for loading Merrifield resin. Five polypropylene reactors charged with Merrifield resin [0.311 milliequiv. reactor⁻¹, 163 mg of Merrifield resin with a loading of 1.91 milliequiv. (of benzylic chloride) g⁻¹] were stirred in DMF (35 mL) with CsCO₃ (1.517 g, 4.66 mmol), KI (0.130 g, 7.83 mmol), and the carboxylic acid (4.65 mmol) at 80 °C for 20 h. The reactors were washed with DMF-H₂O (9:1, 2×), THF (2×), MeOH (2×), DCM (1×), and MeOH (1×) to give the desired resin-bound esters **9** contained within porous polypropylene reactors, which were then dried under vacuum. The same procedure was used to prepare reactors with a loading of 0.325 milliequiv. reactor⁻¹ [170 mg Merrifield resin with a loading of 1.91 milliequiv. (of benzylic chloride) g⁻¹].

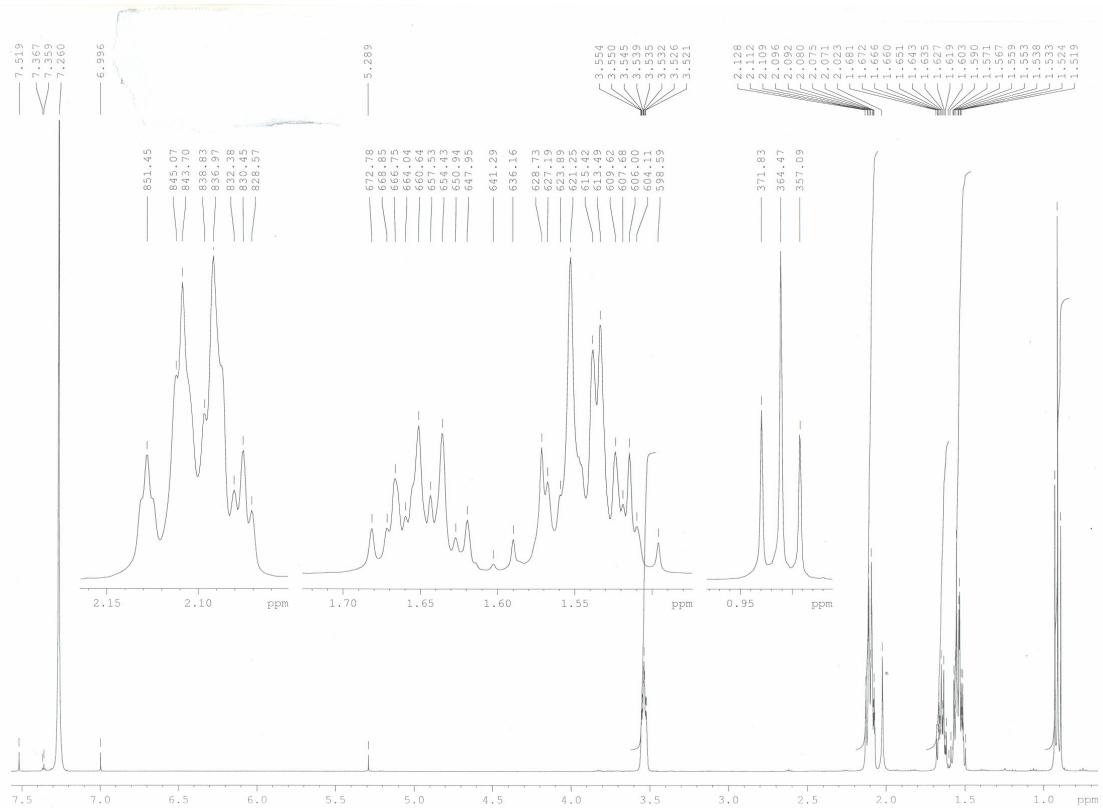
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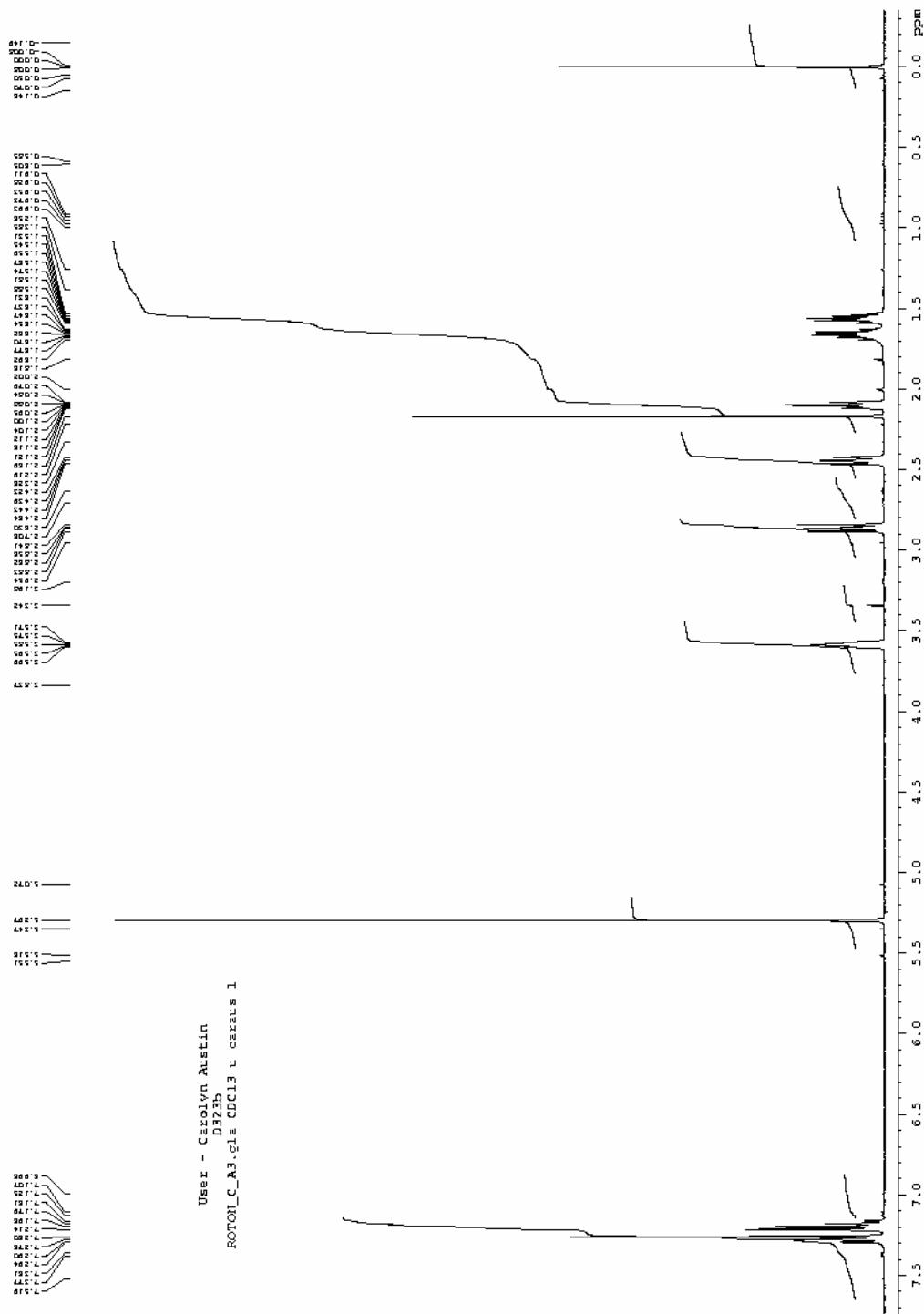
5-oxooct-1-ylamine hydrochloride salt



6-Propyl-2,3,4,5-tetrahydropyridine 1a

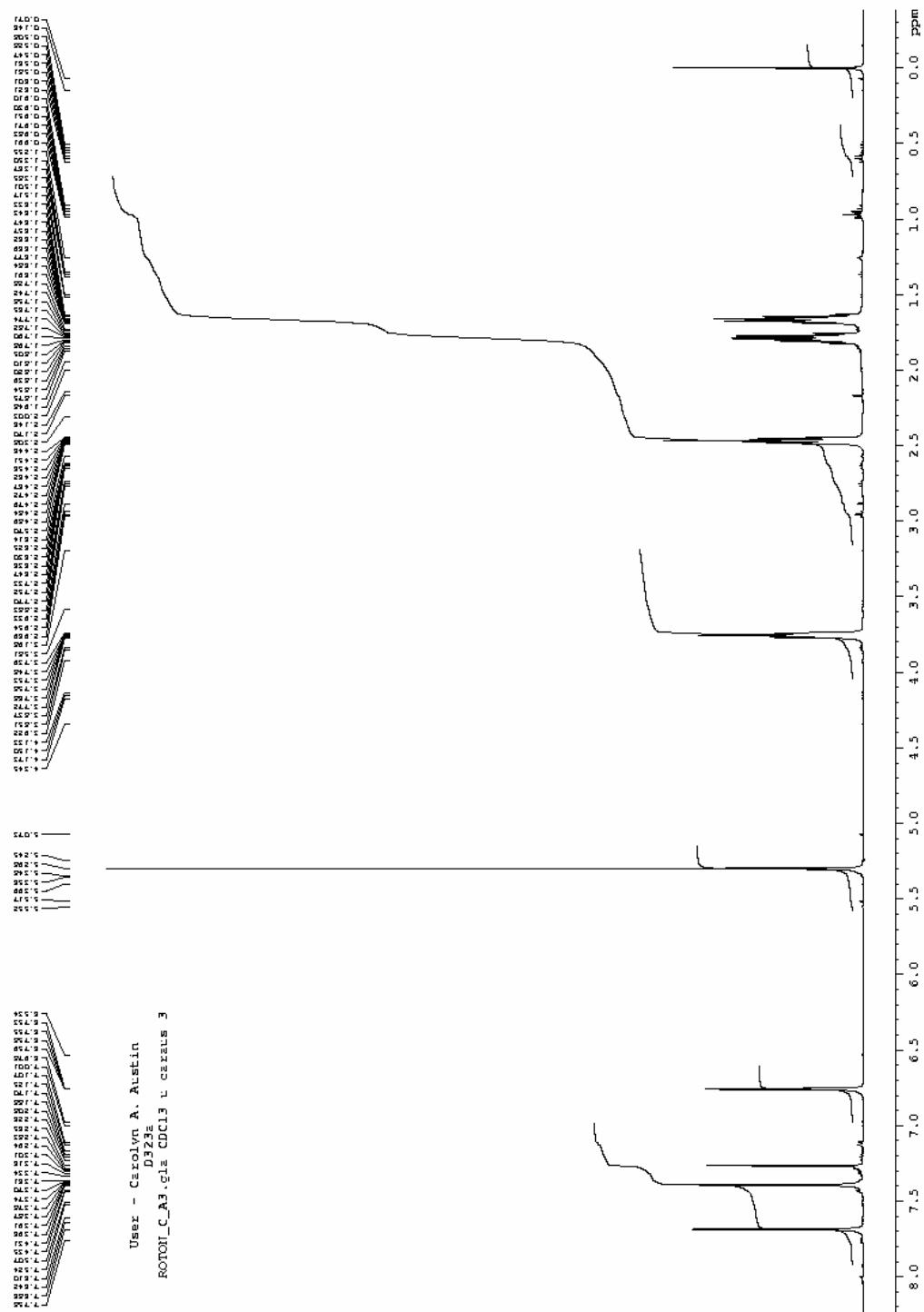


6-Phenethyl-2,3,4,5-tetrahydropyridine 1b



sample contains residual DCM.

6-(Furan-3'-yl)-2,3,4,5-tetrahydropyridine 1c

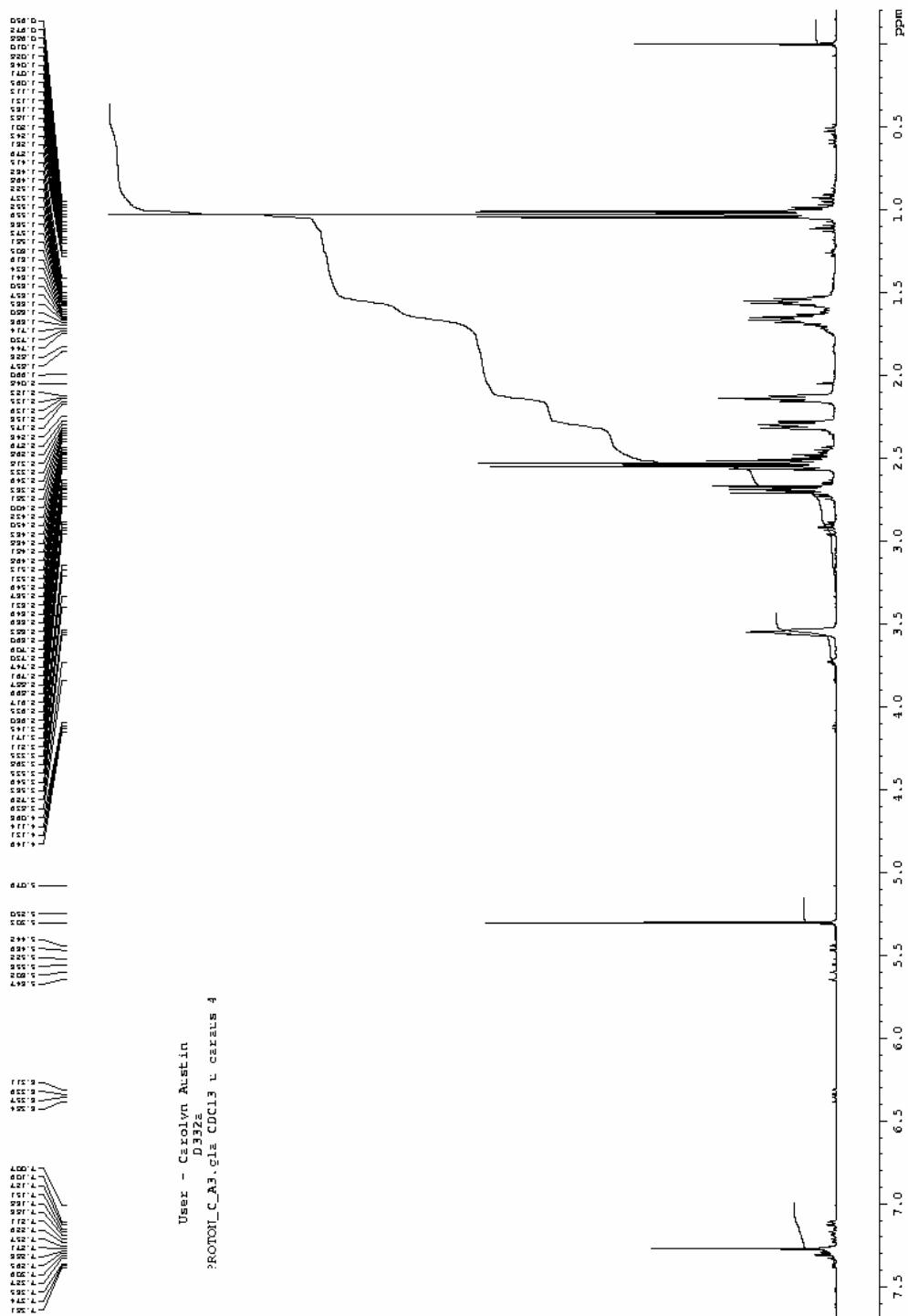


sample contains residual DCM.

6-(Cyclohex-3'-en-1'-yl)-2,3,4,5-tetrahydropyridine 1d

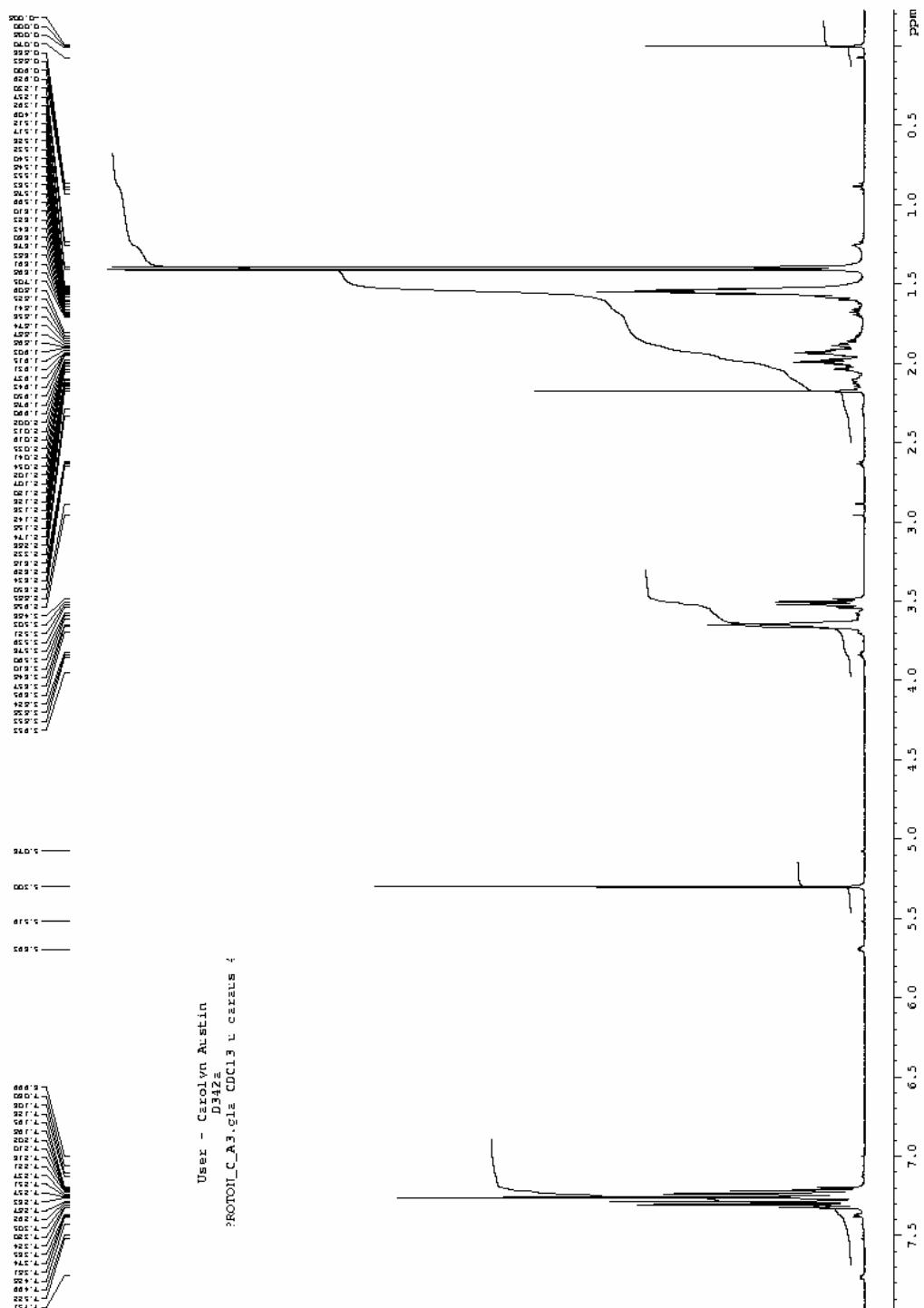


N,N-Diethyl-N-[2-(3',4',5',6'-tetrahydropyridin-2'-yl)ethyl]amine 1e

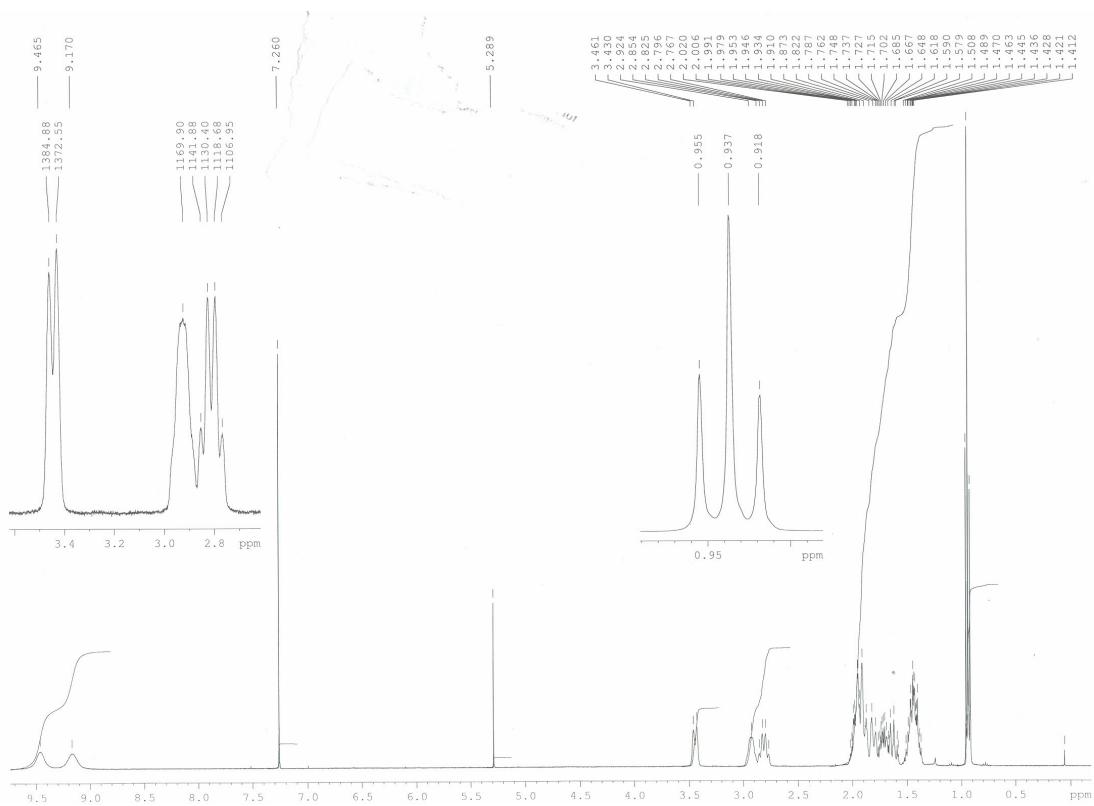


sample contains residual DCM.

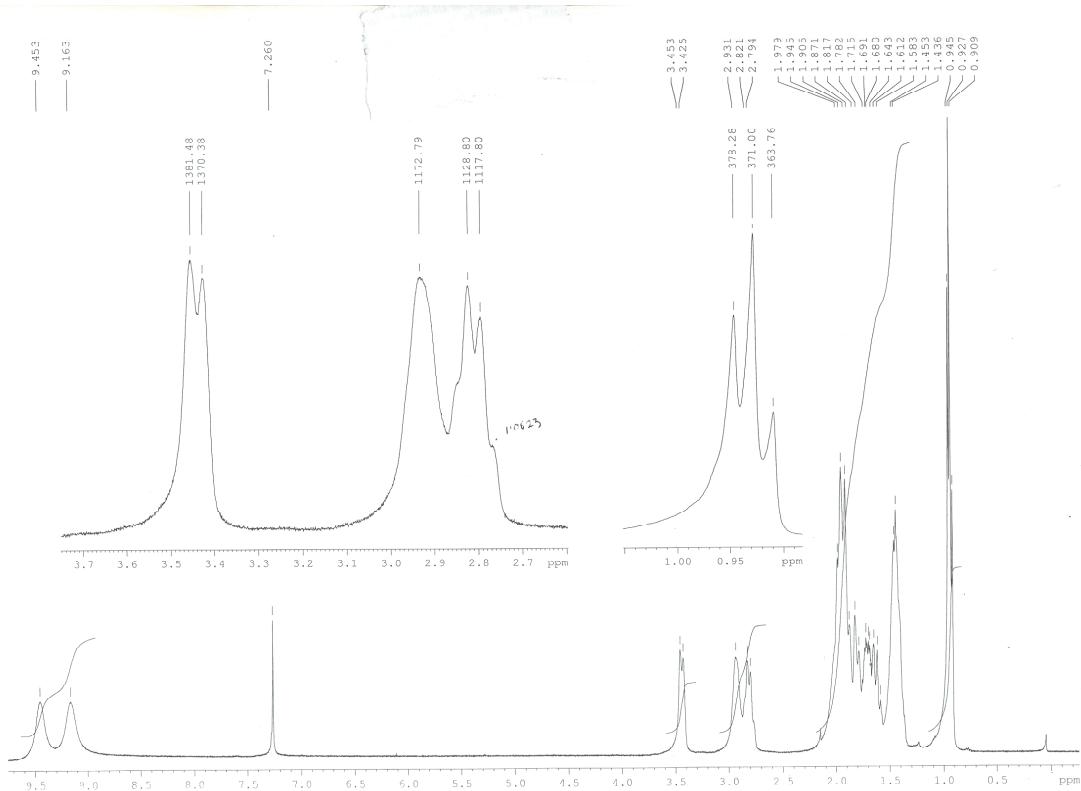
6-(1'-Phenylethyl)-2,3,4,5-tetrahydropyridine 1f



2(S)-Propylpiperidine hydrochloride salt [(S)-coniine hydrochloride] (S)-2a



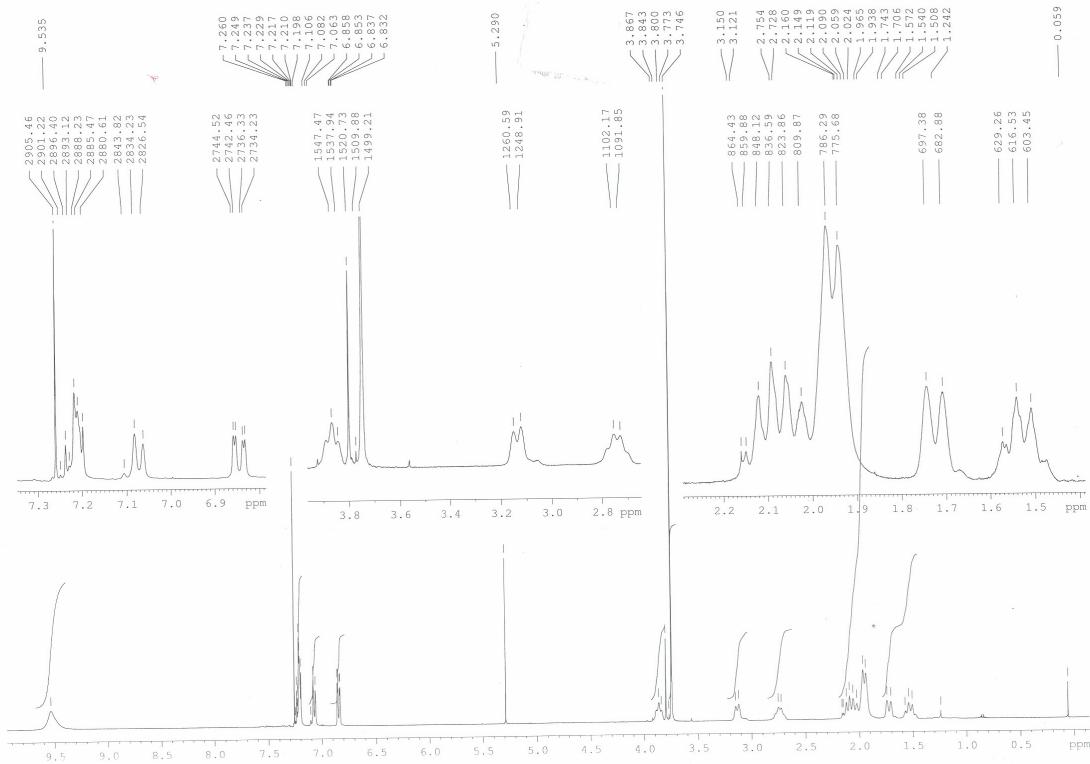
2(R)-propylpiperidine hydrochloride salt [(R)-coniine hydrochloride] (R)-2a



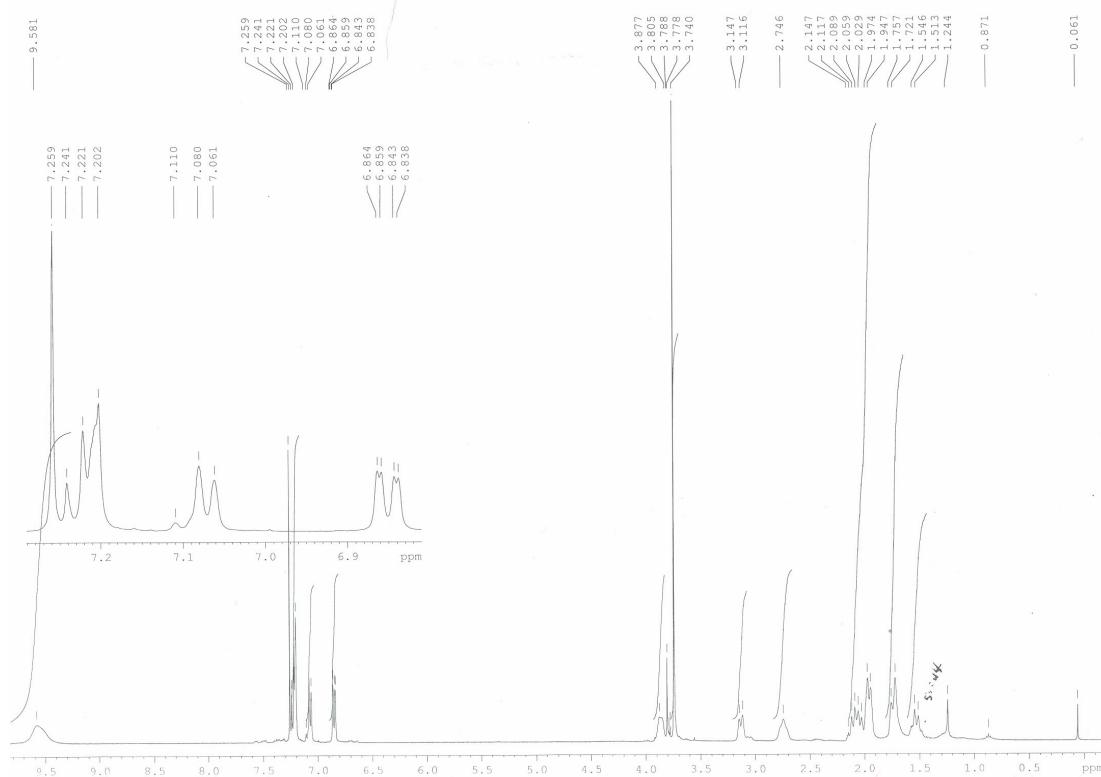
2(R)-Phenylethylpiperidine hydrochloride salt (R)-2b

2(S)-Phenylethylpiperidine hydrochloride salt (S)-2b

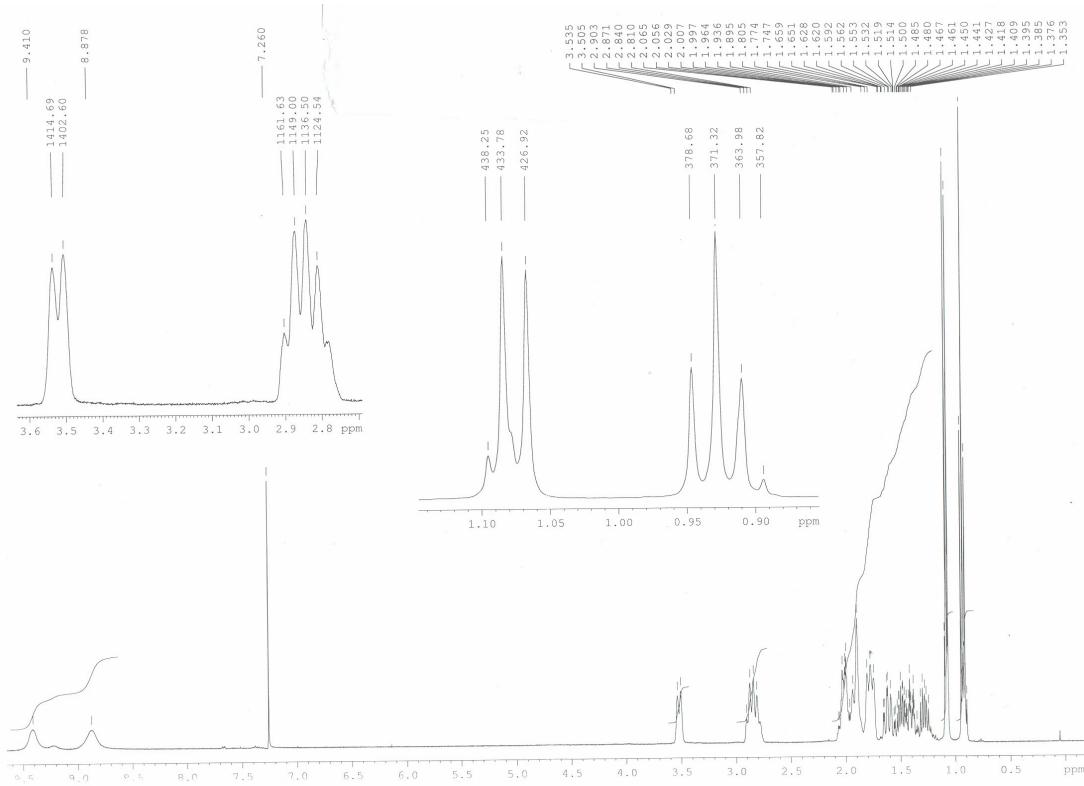
2(R)-(3'-Methoxyphenyl)piperidine hydrochloride salt (R)-2g



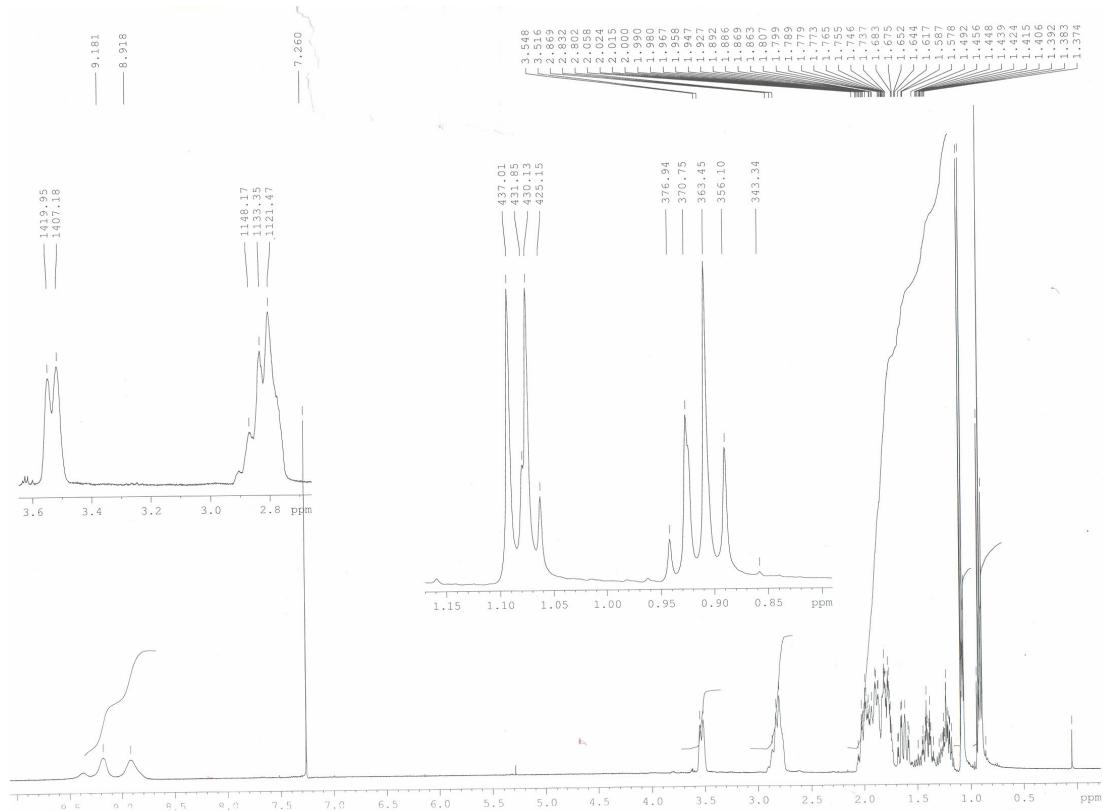
2(S)-(3'-methoxyphenyl)piperidine hydrochloride salt (S)-2g



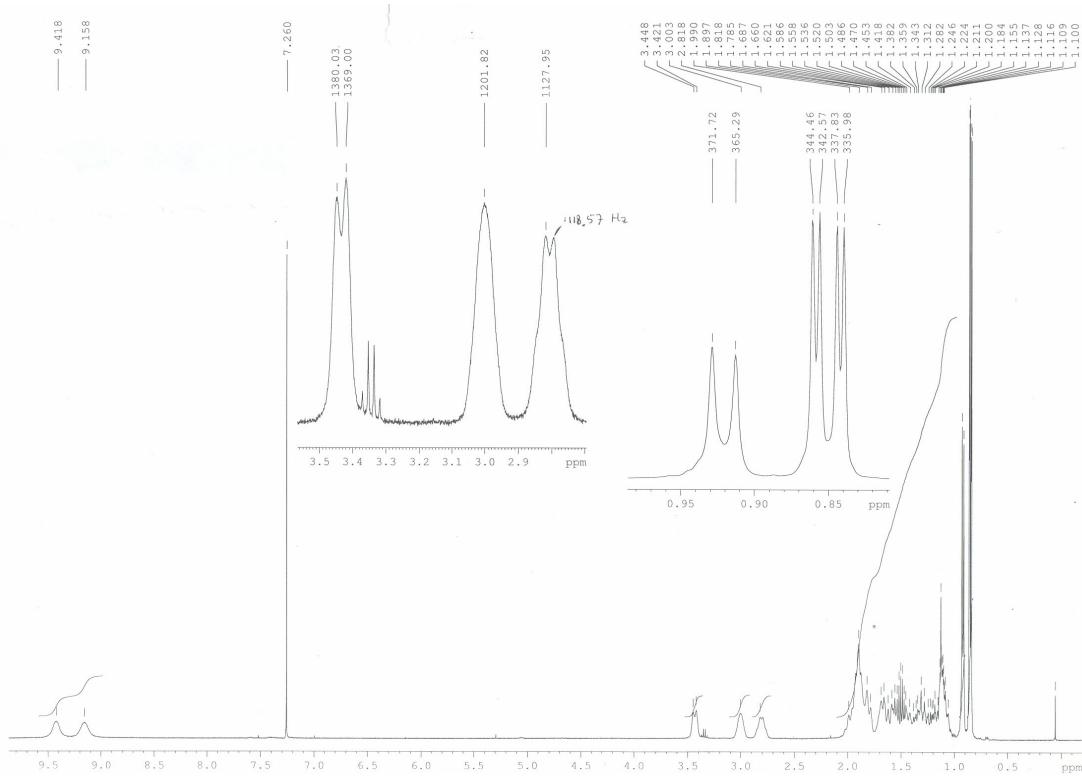
2(R)-[But-2'(S)-yl]piperidine hydrochloride salt 2h



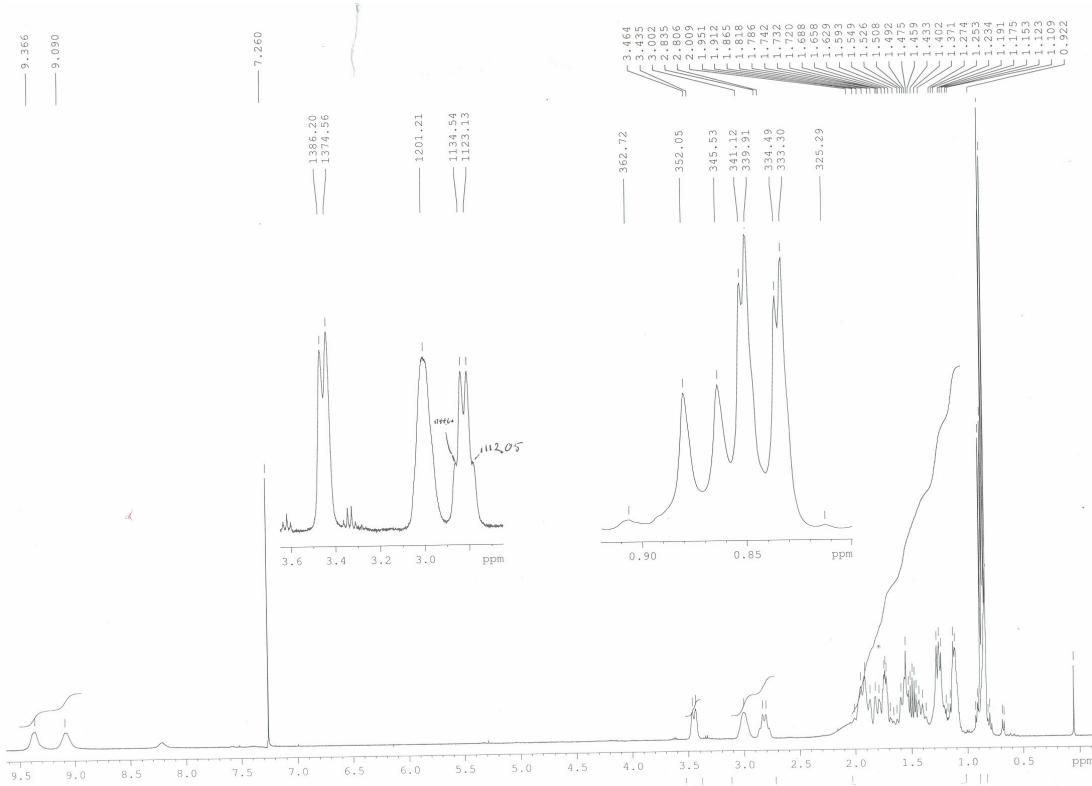
2(S)-(But-2'(S)-yl)piperidine hydrochloride salt 2h'



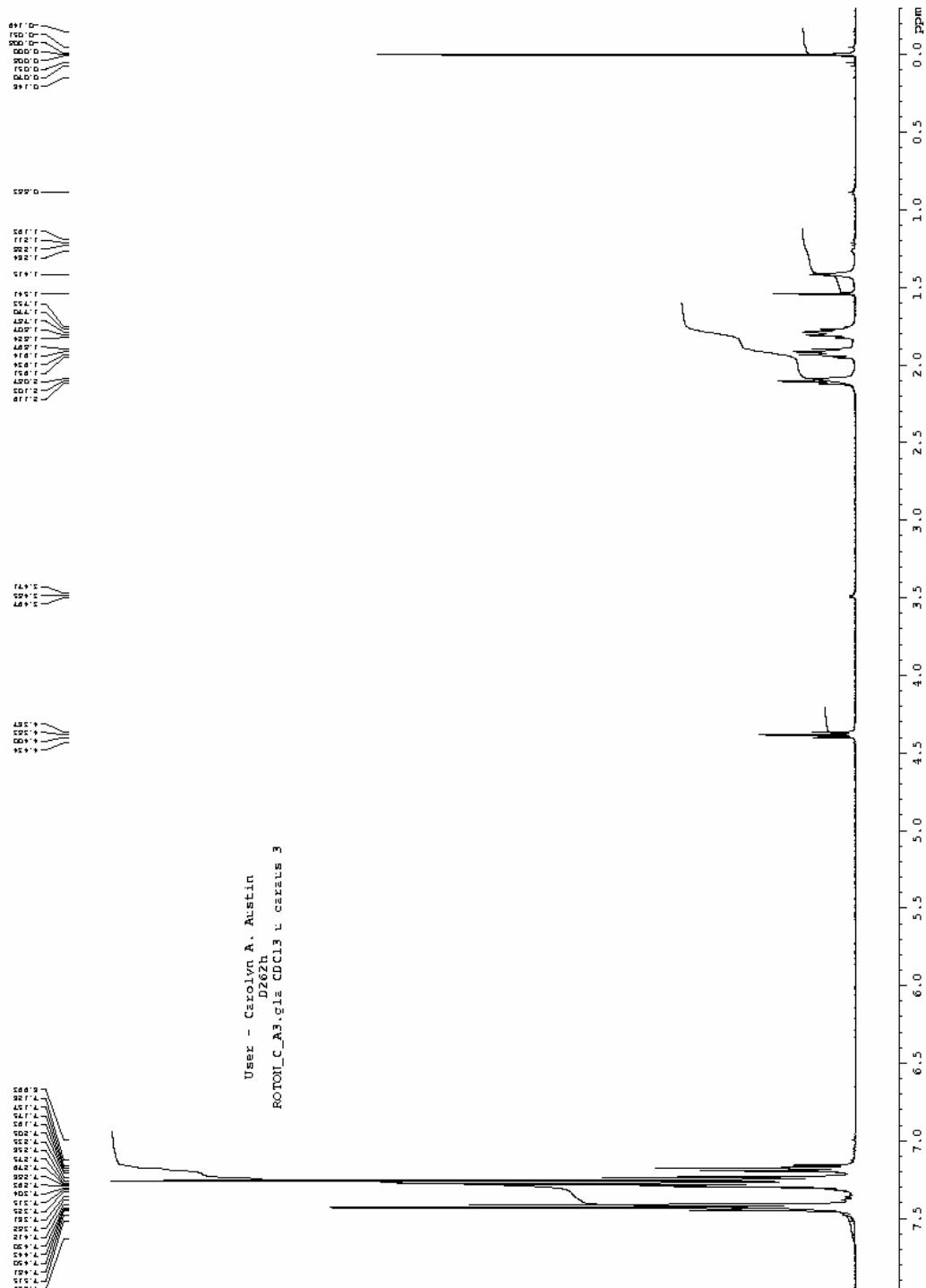
2(R)-[2'(R)-6'-Dimethylhept-1'-yl]piperidine hydrochloride salt 2i



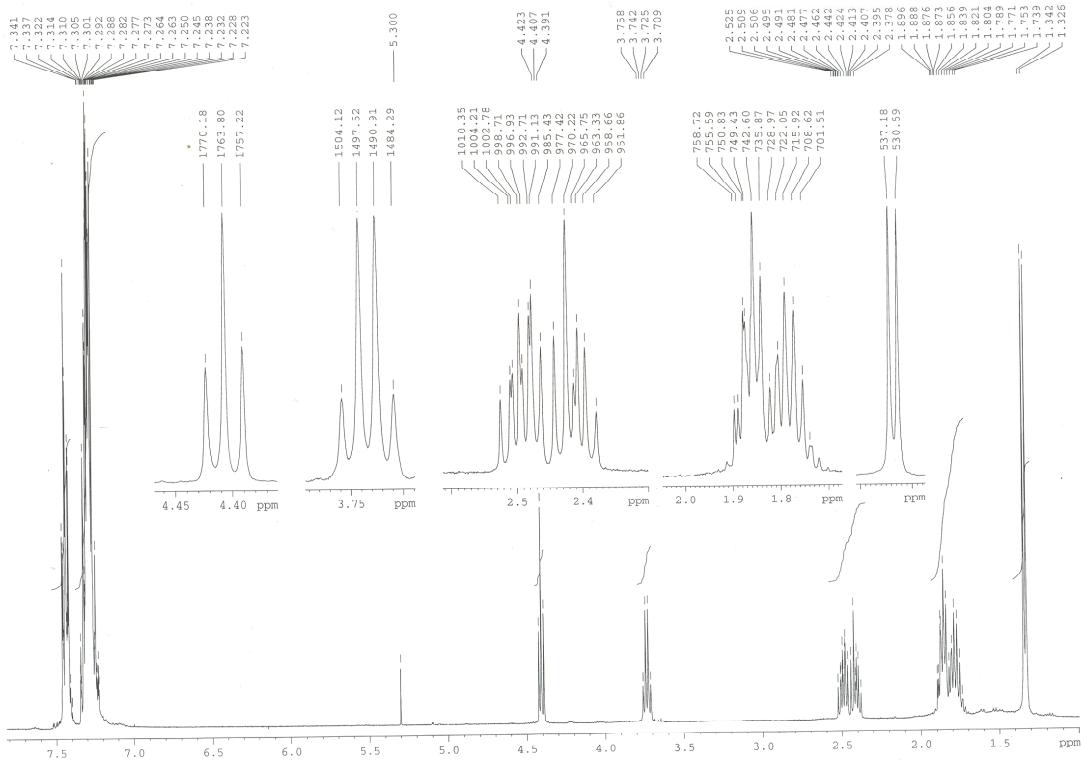
2(S)-[2'(R)-6'-dimethylhept-1'-yl]piperidine hydrochloride salt 2i'



N-[4,4-Bis(phenylsulfanyl)but-1-yl]-*N*-tritylamine 4



***N*-[4,4-Bis(phenylsulfanyl)but-1-yl]-*N*-(1(R)-phenylethyl)amine (*R*)-5**



***N*-[4,4-Bis(phenylsulfanyl)but-1-yl]-*N*-(1(*S*)-phenylethyl)amine (*S*)-5**

