Chemoenzymatic asymmetric total synthesis of (*S*)-Rivastigmine using ω-transaminases.

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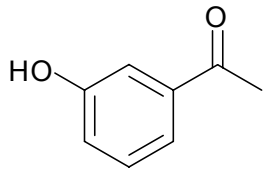
Supplementary Tables:

Table S01. Screening of 3'-hydroxyacetophenone (**2a**).[a]

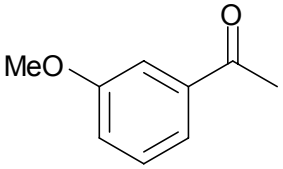


2a

Entry	Enyzme	Conv. [%][c]	E.e. [%][d]
1[b]	CV-ωTA	29	99
2[b]	BM-ωTA	17	99
3[b]	ArS-ωTA	11	80
4	Vf-ωTA	64	98
5	ATA 113	23	99
6	ATA 114	15	99
7[e]	ATA 117	33	98
8[f]	Vf-ωTA	24	98

[a] Reaction conditions: substrate **2a** (50 mM), pyridoxal '5-phosphate (1 mM), L-alanine (250 mM), crude ω-transaminase (10 mg), LDH mix (30 mg) containg LDH, GDH, glucose and NAD^+, shaking at 30 °C for 24 h. [b] Freeze dried whole cells (30 mg) were used after 20 min of resuspension in reaction buffer. [c] Determined via achiral GC-analysis. [d] Determined via chiral GC-analysis. [e] D-Alanine was employed. [f] DMSO (10 v v^{-1} %) was used as cosolvent.

Table S02. Screening of 3'-methoxyacetophenone (**2c**).[a]

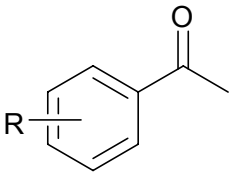


2c

Entry	Enzyme	DMSO [v v^{-1} %]	Conv. [%][c]	E.e. [%][d]
1[b]	CV-ωTA	-	60	99 (*S*)
2[b]	BM-ωTA	-	n.c.	n.d.
3[b]	ArS-ωTA	-	20	99 (*S*)
4	Vf-ωTA	-	86	66 (*S*)
5	ATA 113	-	15	66 (*S*)
6	ATA 114	-	87	99 (*S*)
7[e]	ATA 117	-	58	93 (*R*)
8[b]	CV-ωTA	5	67	99 (*S*)
9[b]	BM-ωTA	5	n.c.	n.d.
10[b]	ArS-ωTA	5	24	70 (*S*)
11	Vf-ωTA	5	89	99 (*S*)
12	ATA 113	5	9	99 (*S*)
13	ATA 114	5	58	99 (*S*)
14[e]	ATA 117	5	45	86 (*R*)

[a] Reaction conditions: substrate **2c** (50 mM), pyridoxal '5-phosphate (1 mM), L-alanine (250 mM), crude ω-transaminase (10 mg), LDH mix (30 mg) containg LDH, GDH, glucose and NAD^+, shaking at 30 °C for 24 h. [b] Freeze dried whole cells (30 mg) were used after 20 min of resuspension in reaction buffer. [c] Determined via achiral GC-analysis; n.c. = no conversion; absolute configuration is given in brackets. [d] Determined via chiral GC-analysis; n.d. = not determined. [e] D-Alanine was employed.

Table S03. Screening of 2'- and 4'-methoxyacetophenone (**2d** and **2e**).[a]

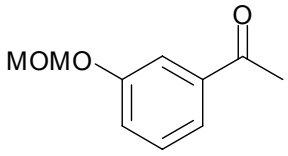


2d, 2e

Entry	Enzyme	Substrate R =	Conv. [%][c]	E.e. [%][d]
1[b]	CV-ωTA	4-MeO (**2d**)	n.c.	n.d.
2[b]	ArS-ωTA	4-MeO (**2d**)	n.c.	n.d.
3	Vf-ωTA	4-MeO (**2d**)	20	99
4	ATA 113	4-MeO (**2d**)	12	99
5	ATA 114	4-MeO (**2d**)	10	99
6[e]	ATA 117	4-MeO (**2d**)	19	77
7	Vf-ωTA	2-MeO (**2e**)	>99	>99
8	ATA 114	2-MeO (**2e**)	13	>99
9[e]	ATA 117	2-MeO (**2e**)	22	>99

[a] Reaction conditions: substrate **2d** or **2e** (50 mM), pyridoxal '5-phosphate (1 mM), L-alanine (250 mM), crude ω-transaminase (10 mg), LDH mix (30 mg) containg LDH, GDH, glucose and NAD^+, shaking at 30 °C for 24 h. [b] Freeze dried whole cells (30 mg) were used after 20 min of resuspension in reaction buffer. [c] Determined via achiral GC-analysis; n.c. = no conversion. [d] Determined via chiral GC-analysis; n.d. = not determined. [e] D-Alanine was employed.

Table S04. Screening of 3'-methoxymethoxyacetophenone (**2f**).[a]



2f

Entry	Enzyme	DMSO [v v^{-1} %]	Conv. [%][c]	E.e. [%][d]
1[b]	CV-ωTA	-	12	n.d.
2[b]	ArS-ωTA	-	9	n.d.
3	Vf-ωTA	-	96	99 (*S*)
4	ATA 113	-	2	n.d.
5	ATA 114	-	81	> 99 (*S*)
6[e]	ATA 117	-	63	94 (*R*)
7	Vf-ωTA	5	91	95 (*S*)
8	ATA 113	5	10	>99 (*S*)
9	ATA 114	5	28	92 (*S*)
10[e]	ATA 117	5	61	98 (*R*)
11[b]	CV-ωTA	10	12	72 (*S*)
12	Vf-ωTA	10	91	99 (*S*)
13	ATA 113	10	8	84 (*S*)
14	ATA 114	10	38	99 (*S*)
15[e]	ATA 117	10	73	84 (*R*)
16[b]	CV-ωTA	15	7	99 (*S*)
17	Vf-ωTA	15	73	97 (*S*)
18	ATA 113	15	7	>99 (*S*)
19	ATA 114	15	24	96 (*S*)
20[e]	ATA 117	15	69	96 (*R*)

[a] Reaction conditions: substrate **2f** (50 mM), pyridoxal '5-phosphate (1 mM), L-alanine (250 mM), crude ω-transaminase (10 mg), LDH mix (30 mg) containg LDH, GDH, glucose and NAD^+, shaking at 30 °C for 24 h. [b] Resting whole cells (30 mg) were used after 20 min of resuspension in reaction buffer. [c] Determined via achiral GC-analysis; n.c. = no conversion. [d] Determined via chiral GC-analysis; n.d. = not determined; absolute configuration is given in brackets. [e] D-Alanine was employed.

Experimental

General. All chemicals were purchased from Sigma Aldrich or Acros Organics and used as received. All solvents were purchased from Roth. Dry THF was freshly distilled from sodium/benzophenone. All moisture sensitive reactions were operated using standard Schlenk techniques in combination with dry argon atmosphere. All biocatalytic reactions and rehydration of enzymes were accomplished in a HT Infors Unitron AJ 260 at 120 rpm and 30 °C (horizontal position). Centrifugation was done at 13000 rpm in a Heraeus Biofuge pico or at 4000 rpm in a Heraeus Biofuge primo. Derivatisation of amines was performed in an Eppendorf thermomixer comfort. NMR spectra were recorded on a Bruker NMR unit at 300 (^{1}H) and 75 (^{13}C) MHz, shifts are given in ppm and coupling constants (*J*) are given in Hz. The conversion towards amines was measured by gas chromatography using a Varian GC3900, equipped with Varian CP8400 Autosampler and an Agilent Technologies DB-1701 column (30 m x 0.25 mm x 0.25 µm). GC program parameters: injector 220 °C; flow 14.5 psi; temperature program 80 °C/hold 6.5 min.; 160 °C/rate 10 °C per min; 170 °C/rate 20 °C per min./hold 2 min. Enantiomeric excess of amines was determined using a Agilent Technologies 7890A GC-system equipped with a Agilent Technologies 7683B Autosampler and a Chirasil Dex CB column (25 m x 0.32 mm x 0.25 µm). Chiral GC-FID Methods: Method A: injector 200 °C; flow 2 mL/min; temperature program 100 °C/hold 2 min.; 130 °C/rate 1 °C per min./hold 5 min; 170 °C/rate 10 °C per min./hold 5 min. Method B: injector 200 °C; flow 2 mL/min; temperature program 100 °C/hold 2 min.; 130 °C/rate 1 °C per min./hold 5 min; 170 °C/rate 2 °C per min/hold 5 min. All GC-MS measurements were carried out with an Agilent 7890A GC system, equipped with an Agilent 5975C mass-selective detector (electron impact, 70 eV) and a HP-5-MS column (30m x 0.25 mm x 0.25 µm) using helium as carrier gas at a flow of 0.55 mL/min. Following temperature program was used in all GC-MS measurements: initial temperature: 100 °C, hold for 0.5 min, 10 °C/min, to 300 °C. Chiral HPLC analysis of (*S*)-Rivastigmine (**1**) was performed on a Shimadzu HPLC system according to a slightly modified method of Srinivasu et al.[1] Optical rotation values were measured on a Perkin Elmer Polarimeter 341.

Compound **2f** was prepared according to literature protocol (86% isolated yield).[2]

The ω-transaminases ATA-113, 114, 117 and Vf-ωTA (amine transaminase Vf-ωTA, 020207KVP, 49 mg mL^{-1}, 7.3 U mg-1; amine transaminase ATA-113, 102907WW, 0.46 U mg^{-1}; ATA-114, Number 1091108MW, 2.7 U mg^{-1}; amine transaminase ATA-117, 102907WW, 1.9 U mg^{-1}), the amine transaminase screening kit, (no. ATA-17000A, 4121207MY) and lactate dehydrogenase mix (LDH mix, PRM-102, 101807KVP, mixture of

lactate dehydrogenase, glucose dehydrogenase, glucose, NAD^+) were obtained from Codexis Inc. One unit of ω-transaminase was defined as the amount of enzyme that catalyzes the formation of 1 μmol acetophenone from 1-phenylethylamine at pH 9.0 and 22 °C within one minute. In case of freeze dried whole cells (BM-ωTA, CV-ωTA and As-ωTA) the coresponding ω-transaminase was overexpressed in *E. coli* as previously reported.[3]

Derivatisation and chiral analysis of compound 3a-e. 4-(Dimethylamino)pyridine (5 mg, 0.04 mmol) and acetic anhydride (200 μL, 216 mg, 2.1 mmol) were combined in a 1.5 mL eppendorf vial and vortexed until the liquid turned yellow. The sample of **3a-e** (3 mg, 0.02 mmol) in 1 mL of EtOAc was added and the mixture was incubated for 4h at 40 °C and 600 rpm. $H_2O_{dest.}$ (300 μL) was added and the suspension was incubated for another 2h under the same conditions. The phases were seperated, the organic layer was dried over Na_2SO_4 and subjected to chiral GC-FID analysis under the following conditions:

1-(3-Hydroxy)phenylethanamine (3a). Chiral GC-FID: Method B, t_{ret}: (*S*)-**3a** 56.20 min, (*R*)-**3a** 57.00 min.

1-(3-Methoxy)phenylethanamine (3c). Chiral GC-FID: Method A, t_{ret}: (*S*)-**3c** 42.26 min., (*R*)-**3c** 42.69 min.;

1-(4-Methoxy)phenylethanamine (3d). Chiral GC-FID: Method B, t_{ret}: (*S*)-**3d** 51.16 min, (*R*)-**3d** 52.14 min.

1-(4-Methoxy)phenylethanamine (3e). Chiral GC-FID: Method B, t_{ret}: (*S*)-**3e** 41.74 min, (*R*)-**3e** 42.30 min.

Derivatisation and chiral analysis of compound 3f. 4-(Dimethylamino)pyridine (5 mg, 0.04 mmol) and triethylamine (200 μL, 146 mg, 1.4 mmol) were combined in a 1.5 mL eppendorf vial and vortexed for 30 s. The sample of **3f** (3 mg, 0.02 mmol) in EtOAc (500 μL) was added followed by acetyl chloride (50 μL, 55 mg, 0.7 mmol) (dropwise addition, virgerous reaction). The mixture was incubated for 2h at 40 °C and 600 rpm. $NaHCO_{3\ aq.,\ sat.}$ (300 μL) was added and the suspension was incubated for another 2h under the same conditions. The phases were seperated, the organic layer was dried over Na_2SO_4 and subjected to chiral GC-FID analysis under the following conditions: GC-FID: Method B, t_{ret}: (*S*)-**3f** 55.77 min, (*R*)-**3f** 56.42 min.

General procedure for the screening of transaminases. Crude preparations of enzymes (10 mg) were suspended for 5 min in phosphate buffer (1 mL, 100 mM, pH 7.0, 1 mM pyridoxal 5-phosphate). In case of whole cell systems the lyophilized cells (30 mg) were rehydrated for 20 min in the same buffer. LDH-mix (30 mg, mixture of lactate dehydrogenase, glucose dehydrogenase, glucose, NAD^+), L-alanine (18 mg, 0.25 mmol) and substrate (0.05 mmol) were added and the suspension was shaken for 24 h. $NaHCO_{3\ aq,sat.}$ was added (200 µL) and the aqueous layer was extracted with EtOAc (2x 500 µL, denaturated enzyme was removed by centrifugation). The combined organic phase was dried over Na_2SO_4 and subjected to GC-FID analysis:

1-(3-Hydroxy)phenylethanamine (3a). Amount of substrate **2a**: 7 mg, 0.05 mmol. GC-FID: t_{ret}: **2a** 18.12 min, **3a** 17.05 min.

1-(3-Methoxy)phenylethanamine (3c). Amount of substrate **2c**: 7 µL, 7.5 mg, 0.05 mmol. GC-FID: t_{ret}: **2c** 15.07 min., **3c** 14.48 min.;

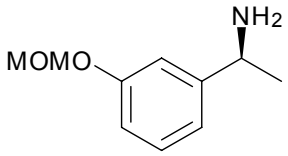
1-(4-Methoxy)phenylethanamine (3d). Amount of substrate **2d**: 7.5 mg, 0.05 mmol. GC-FID: t_{ret}: **2d** 16.52 min, **3d** 15.23 min.

1-(2-Methoxy)phenylethanamine (3e). Amount of substrate **2e**: 7 µL, 7.5 mg, 0.05 mmol. GC-FID: t_{ret}: **2e** 15.65 min, **3e** 14.63 min.

1-(3-Methoxymethoxy)phenylethanamine (3f). Amount of substrate **2f**: 8.3 µL, 9.0 mg, 0.05 mmol. GC-FID: t_{ret}: **2f** 17.57 min, **3f** 16.95 min.

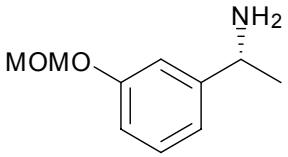
General procedure for the upscaling of transamination. Crude preparation ω-transaminase from *Vibrio fluvialis*, ATA 114 or ATA 117 (60 mg) was rehydrated in phosphate buffer (10 mL, 100 mM, pH 7.0, 1 mM pyridoxal 5'-phosphate) for 10 min in a 15 mL Falcon tube. LDH-mix (300 mg, mixture of lactate dehydrogenase, glucose dehydrogenase, glucose, NAD^+), L-alanine (220 mg, 3.1 mmol) and 1-(3-(methoxymethoxy)phenyl)ethanone (**2f**, 90 mg, 0.5 mmol) was added and the tube was shaken for 24 h. The suspension was transferred to a 50 mL Falcon tube and extracted with EtOAc (2 x 10 mL) to remove any remained ketone (denaturated enzymes were removed by centrifugation). NaOH (30% in water, 5 mL) was added and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give (*S*)- or (*R*)-**3f** with following physical properties: GC-FID: t_{ret}(**3f**) = 16.95 min; δ_H (acetone) 7.23-7.18 (m, 1H), 7.09-7.02 (m, 2H), 6.89-6.86 (m, 1H), 5.18 (s, 2H), 4.61 (q, 1H, J = 6.5 Hz), 3.43 (s, 3H), 1.98-1.94 (m, 1H), 1.86-1.83 (m, 1H), 1.32 (d, 3H, J = 6.5 Hz); δ_C (acetone) 157.5, 148.3, 129.0, 120.1, 114.7, 113.8, 94.2, 58.9, 55.1, 24.4; GC-EI-MS: t_{ret} 8.37 min, m/z (relative intensity [%]): 181 (7), 166 (100), 136 (12), 122 (15), 106 (6), 91 (6), 77 (7), 65 (5), 45 (77).

(*S*)-1-(3-Methoxymethoxy)phenylethanamine [(*S*)-3f]. Compound **2f** (92 mg, 0.51 mmol) was incubated with ω-transaminase of *Vibrio fluvialis* (crude preparation) to give (*S*)-**3f** as yellow oil (74 mg, 41 mmol, 80%). Physical properties were as described above. Chiral GC-FID: t_{ret} = 55.77 min, *ee* > 99 %. $[\alpha]_D^{20}$ -15.8 (c 1.0, CH_2Cl_2).



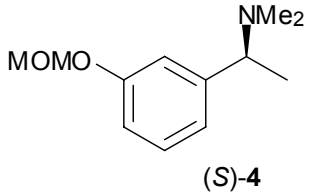
(*S*)-**3f**

(*R*)-1-(3-Methoxymethoxyphenylethanamine [(*R*)-3f]. Compound **2f** (92 mg, 0.51 mmol) was incubated with ω-transaminase ATA 117 to give (*R*)-**3f** as yellow oil (52 mg, 0.29 mmol, 56%). Physical properties were as described above. Chiral GC-FID: t_{ret} = 56.42 min, *ee* = 98 %. $[\alpha]_D^{20}$ +14.3 (c 1.0, CH_2Cl_2).



(*R*)-**3f**

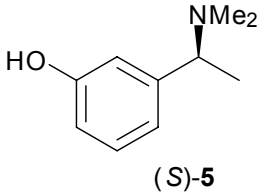
(*S*)-1-(3-(Methoxymethoxy)phenyl-N,N-dimethylethanamine [(*S*)-4]. (*S*)-1-(3-methoxymethoxy)phenyl)ethanamine [(*S*)-**3f**, 30 mg, 0.17 mmol] were dissolved in CH_2Cl_2 (2.4 mL). Formaldehyde (37% in water, 44 µL, 0.54 mmol), Na_2SO_4 (13 mg, 0.09 mmol) and $NaBH(OAc)_3$ (252 mg, 1.19 mmol) were added and the reaction mixture was stirred for 24 h at room temperature. $NaHCO_{3\ aq,sat.}$ was added (5 mL) and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give (*S*)-**4** as pale yellow oil (35 mg, 0.17 mmol, 99%) with following physical properties:



(*S*)-**4**

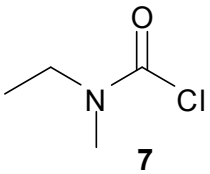
δ_H (acetone) 7.11-7.06 (m, 1H), 6.88-6.75 (m, 3H), 5.05 (s, 2H), 3.29 (s, 3H), 3.05 (q, 1H, J = 6.6 Hz), 2.01 (s, 6H), 1.15 (d, 3H, J = 6.6 Hz); δ_C (acetone) 157.5, 146.7, 129.0, 120.7, 115.2, 114.4, 94.2, 65.7, 55.1, 42.6, 20.0; GC-EI-MS: t_{ret} 8.94, m/z (relative intensity [%]): 209 (11), 194 (100), 165 (5), 150 (53), 134 (4), 121 (4), 103 (4), 91 (6), 72 (52), 45 (20).

(*S*)-3-(1-(Dimethylamino)ethylphenol [(*S*)-5]. (*S*)-1-(3-(methoxymethoxy)phenyl-*N*,*N*-dimethylethanamine [(*S*)-**4**, 32 mg, 0.15 mmol] was dissolved in 2 mL EtOAc and transferred to a seperation funnel. HCl (5 M, 3 mL) was added, the two phases were mixed followed by incubation for 2 min. $K_2CO_{3\ aq,\ sat.}$ (3 mL) was added and the aqueous phase was extracted with EtOAc (3 x 5 mL). Additional K_2CO_3 (1 mL) was added and the reaction mixture was extracted again with EtOAc (2 x 5 mL). This step was repeated once again, the combined organic phase was dried over Na_2SO_4 and the solvent was removed under reduced presure to give compound (*S*)-**5** as white solid (23 mg, 0.14 mmol, 92%) with following physical properties: m.p. 101-102 °C (EtOAc) [lit.: 98-97 °C (CH_2Cl_2/MeOH 8/2)],[4] $[\alpha]_D^{20}$ -40.2 (lit. -36.1, c 1.0, CH_2Cl_2);[5] δ_H ($CDCl_3$) 9.52 (s, 1H), 7.15 (t, 1H, J = 7.8 Hz), 6.79-6.72 (m, 3H), 3.33 (q, 1H, J = 6.7 Hz), 2.24 (s, 6H) 1.41 (d, 3H, J = 6.7 Hz); δ_C ($CDCl_3$) 157.1,143.5, 129.3, 119.6, 115.4, 115.3, 65.8, 42.8, 19.3; GC-EI-MS: t_{ret} 8.11, m/z (relative intensity [%]): 165 (11), 150 (100), 134 (3), 121 (9), 103 (5), 91 (7), 72 (33), 65 (4), 42 (6).



(*S*)-**5**

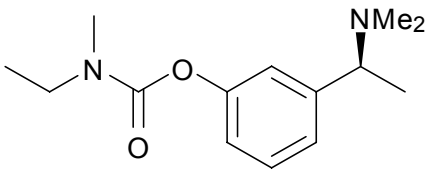
Ethyl(methyl)carbamic chloride (7). Sodium bicarbonate (1.31 g, 15.6 mmol) was dried under vacuum by heat gun. The apparatus was vented with dry Argon, CH_2Cl_2 (6 mL) and triphosgen (1.33 g, 4.5 mmol) were added and the reaction mixture was coold to 5-10 °C via an ice bath. *N*-Ethyl-*N*-methyl-amine (580 µL, 399 mg, 6.8 mmol) was added via syringe and canula to the stirred suspension over a period of 2 h. The reaction mixture was allowed to reach room temperature. After stirring for 3 h, the formed sodium chloride as well as remaining sodium bicarbonate was removed via filtration and the remaining filtrate was concentrated under reduced pressure and dried under high vacuum to give compound **7** as colorless oil (544 mg, > 99%) with following physical properties:



7

δ_H ($CDCl_3$) 3.56-3.35 (m, 2H), 3.12 (s, 1.5H, rotamer 1), 3.03 (s, 1.5H, rotamer 2), 1.25-1.17 (m, 3H); δ_C ($CDCl_3$) 149.2, 149.0, 47.9, 46.3, 37.8, 36.0, 12.9, 12.2 (remark: each carbon gives 2 signals because of the 2-rotamers of the amide).

(*S*)-3-[1-(Dimethylamino)ethyl]phenyl ethyl(methyl)carbamate [(*S*)-Rivastigmine, (*S*)-1].

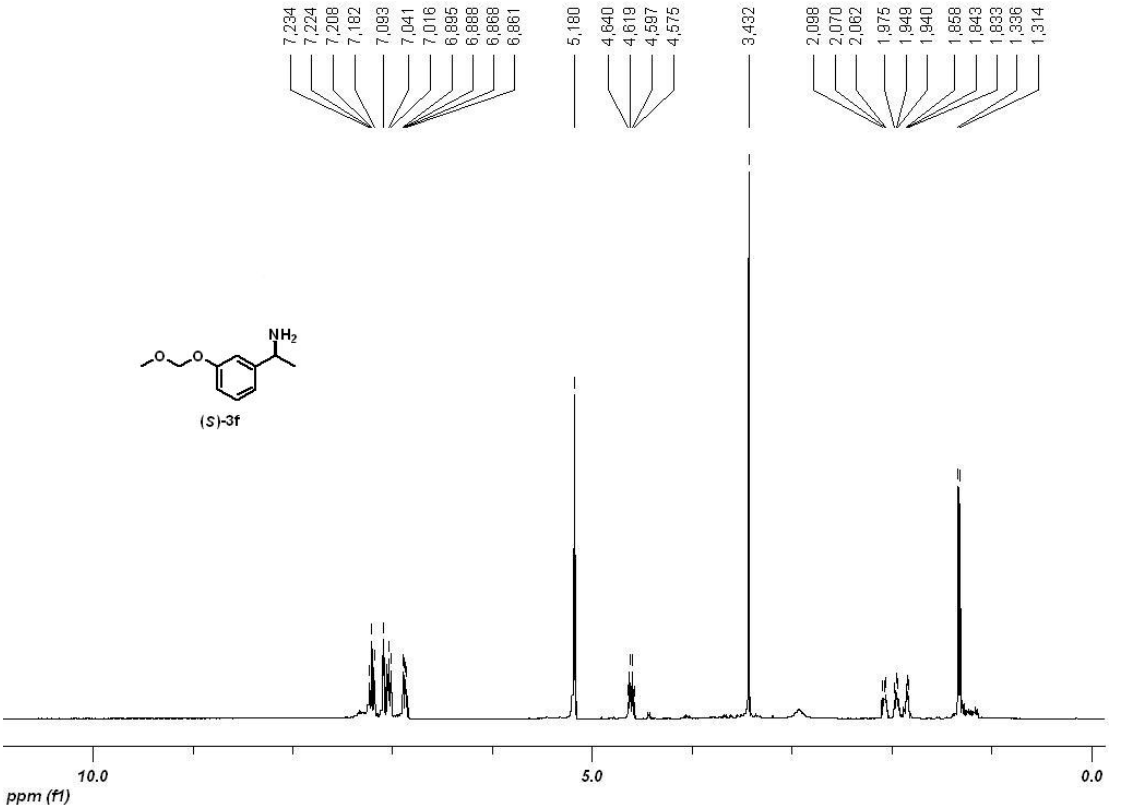


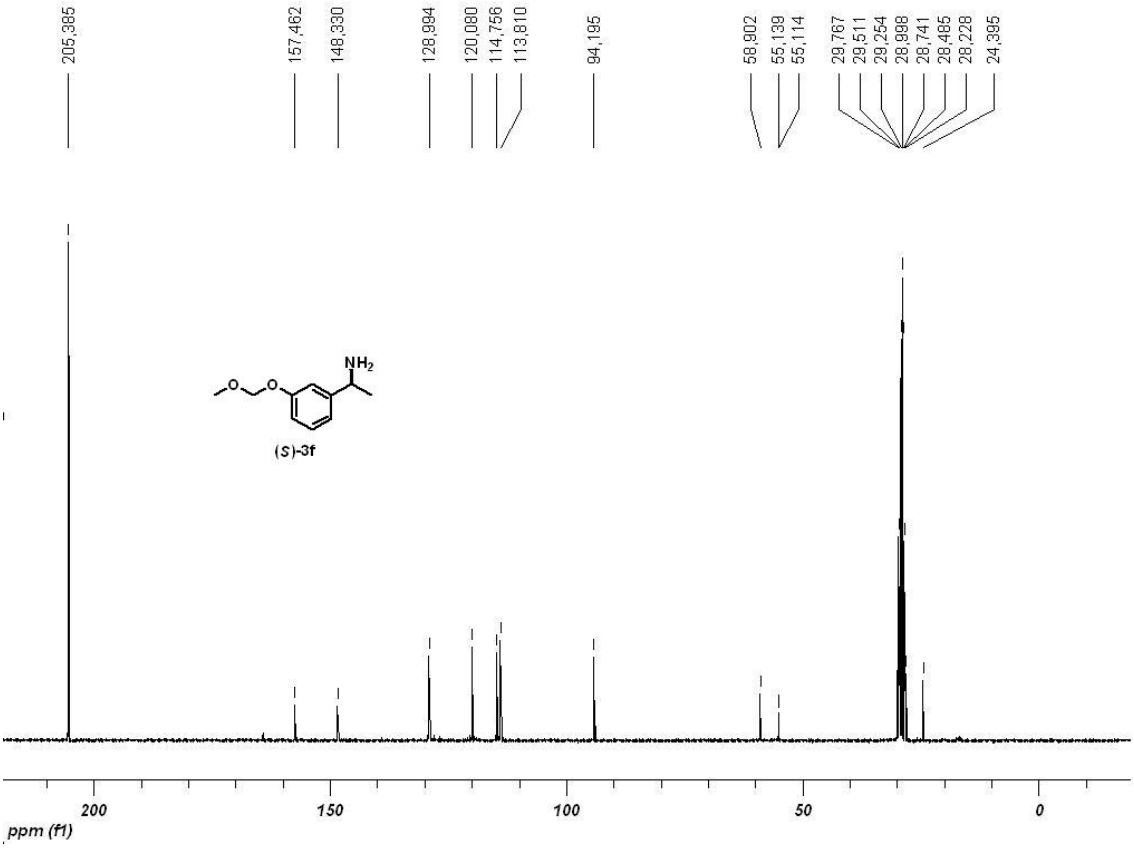
(*S*)-**1**

Sodium hydride (6 mg, 0.25 mmol, prewashed with *n*-pentane to remove mineral oil) was suspended in dry THF (4 mL). (*S*)-3-(1-(dimethylamino)ethyl)phenol (**5**, 19 mg, 0.12 mmol) was added and the supension was stirred for 30 min at room temperature. A solution of ethyl(methyl)carbamic chloride (**7**, 28 µL, 29 mg, 0.24 mmol) in dry THF (2 mL) was added dropwise and the mixture was stirred for 5h. H_2O_{dist} (4 mL) was added followed by 4 mL of saturated K_2CO_3 solution until basic pH (pH = 9-10). The mixture was extracted with EtOAc (3 x 5 mL), aqueous, saturated K_2CO_3 solution (1 mL) was added and the mixture was extracted with EtOAc (2 x 5 mL) again. The combined organic phase washed with NaOH solution (0.11 M, 2 x 5 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure to give (*S*)-Rivastigmine (**1**) as pale yellow oil (28 mg, 0.11 mol, 97 % yield) with following physical properties:

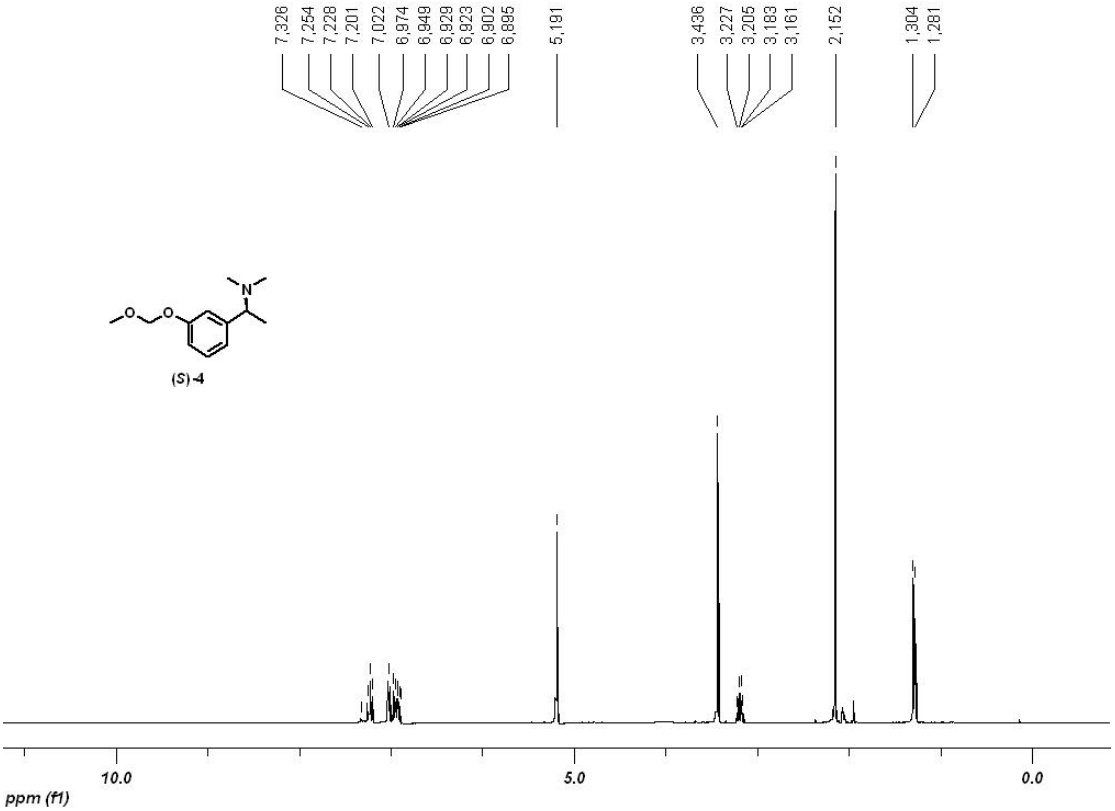
$[\alpha]_D^{20}$ -15.3 (lit. -28.5, c 1.0, CH_2Cl_2);[5] δ_H ($CDCl_3$) 7,33-7,28 (m, 1H), 7.14-7.01 (m, 3H), 3.52-3.39 (m, 2H), 3.26 (q, 1H, J = 6.6), 3.08 (s, 1.5H, rotamer 1), 3.00 (s, 1.5H, rotamer 2), 2.22 (s, 6H), 1.37 (d, 3H, J = 6.6), 1.27-1.18 (m, 3H); d_C ($CDCl_3$) 154.6 (rotamer 1), 154.4 (rotamer 2), 151.5, 145.7, 128.9, 124.3, 120.8, 120.3, 65.7, 44.1 (rotamer 1), 43.2 (rotamer 2), 34.2 (rotamer 1), 33.8 (rotamer 2), 29.7, 20.1, 13.2 (rotamer 1), 12.5 (rotamer 2); GC-EI-MS: t_{ret} 13.02, m/z (relative intensity [%]): 250 (6), 235 (100), 206 (2), 164 (2), 150 (6), 86 (17), 72 (34), 58 (16); chiral HPLC analysis {Diacel Chiracel OD-H, *n*-heptane/2-propanol/TFA 8/2/0.2, 0.8 mL/min, 25 °C, UV 215 nm, t_{ret}[(*R*)-**1**] = 11.3 min, t_{ret}[(*S*)-**1** = 15.4 min]}: t_{ret} = 15.4 min, > 99% *ee*.

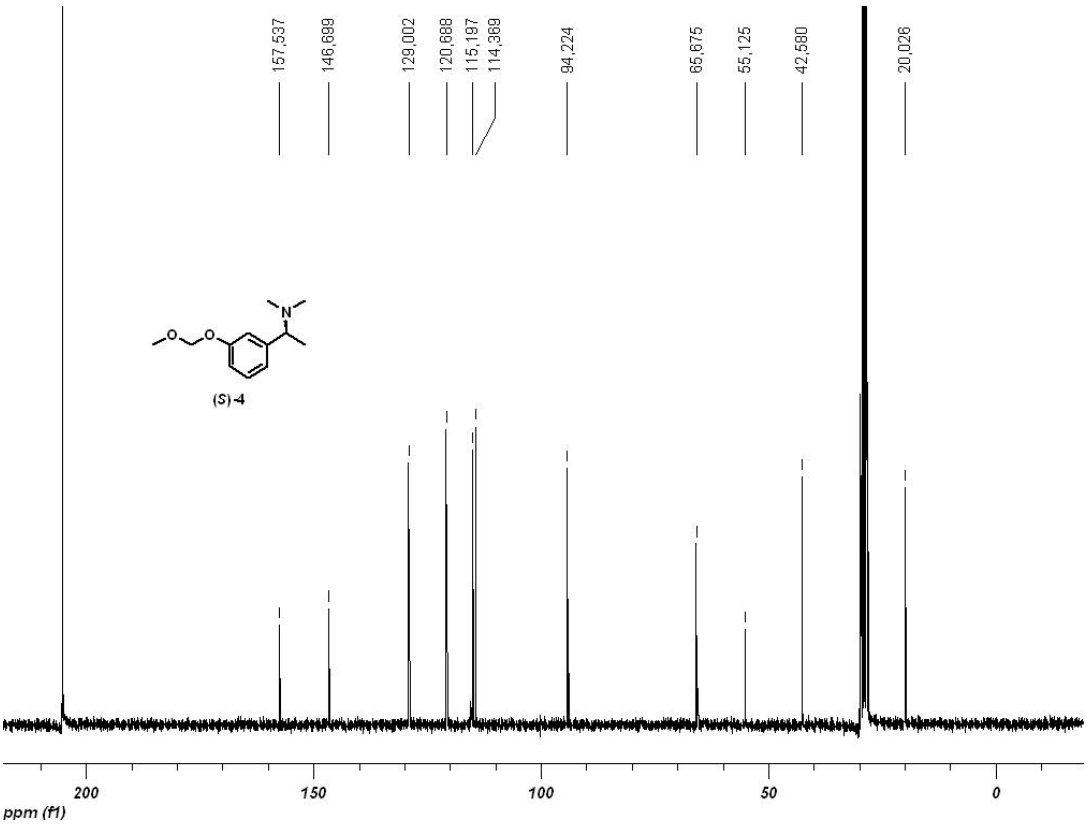
^{1}H- and ^{13}C-NMR spectra
(*S*)-1-(3-Methoxymethoxyphenyl)ethanamine [(*S*)-3f].



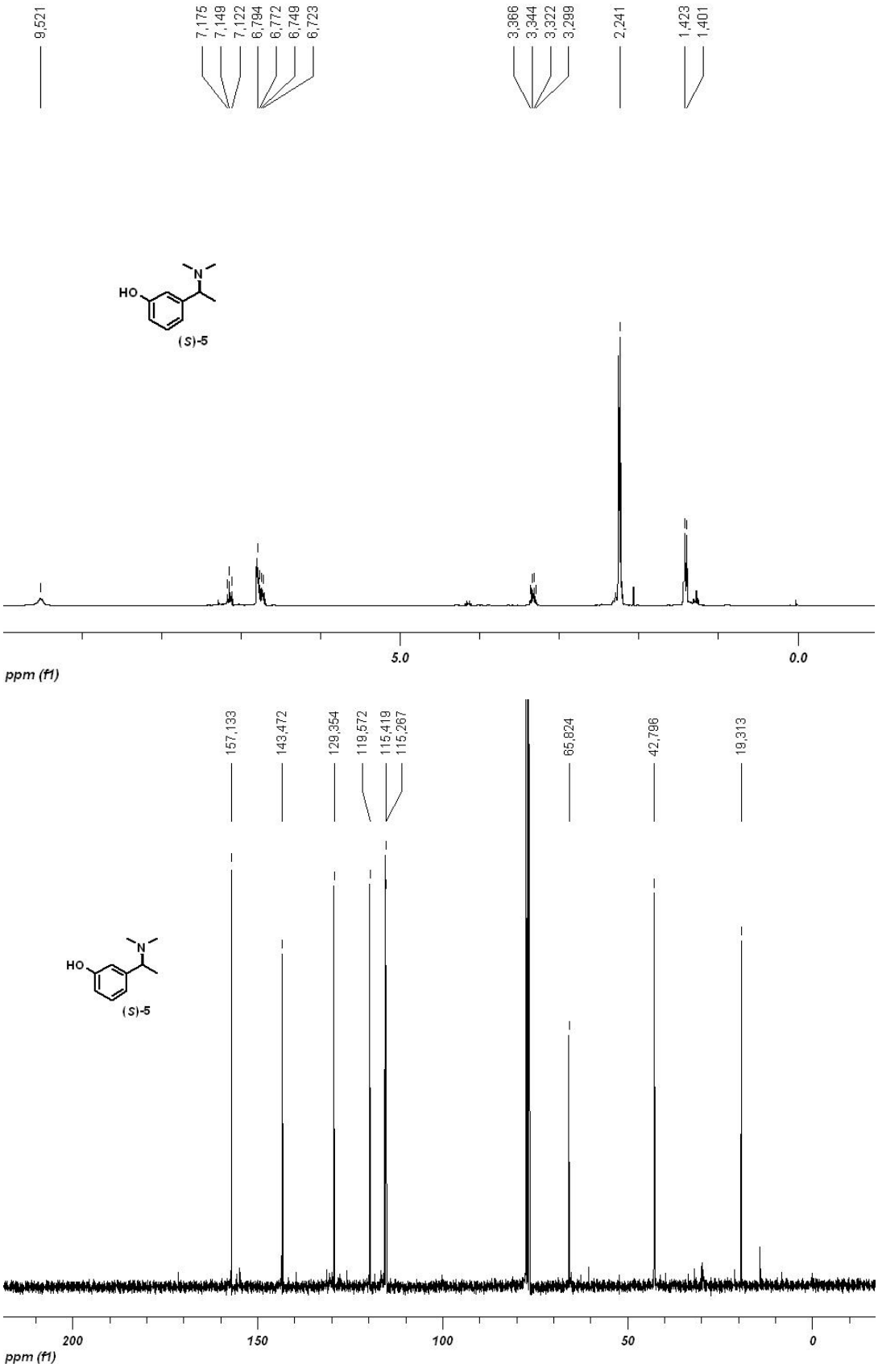


(*S*)-1-(3-(Methoxymethoxy)phenyl-N,N-dimethylethanamine [(*S*)-4].

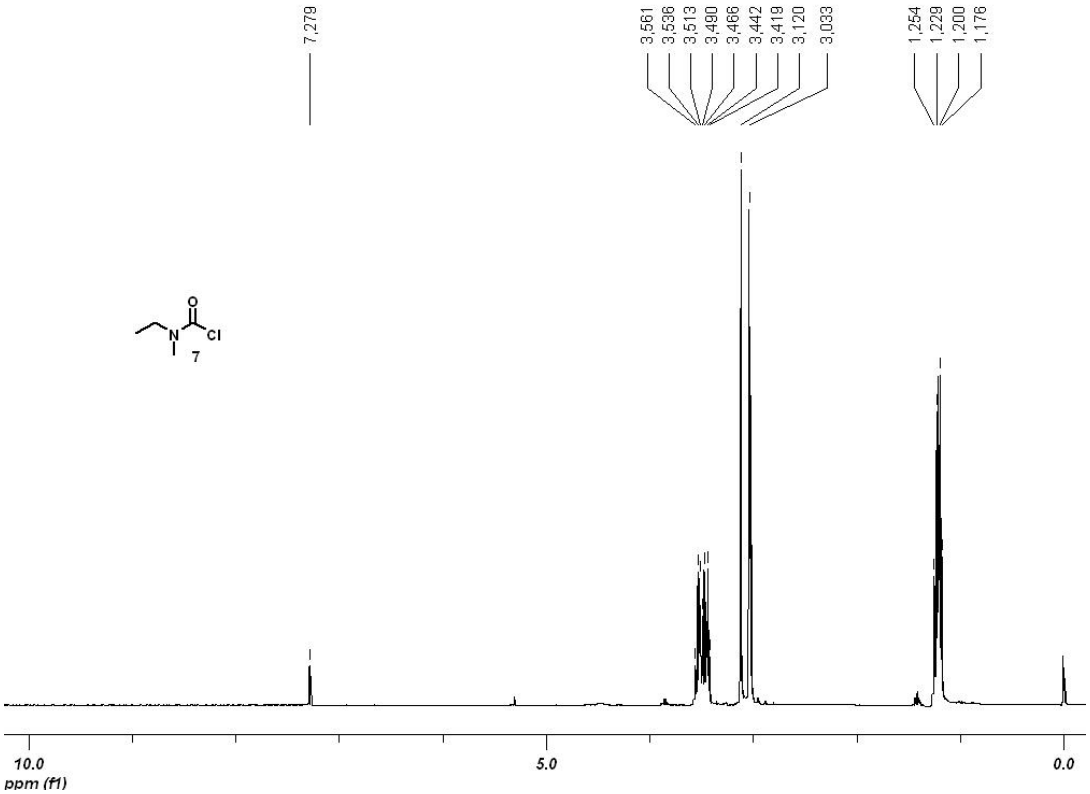


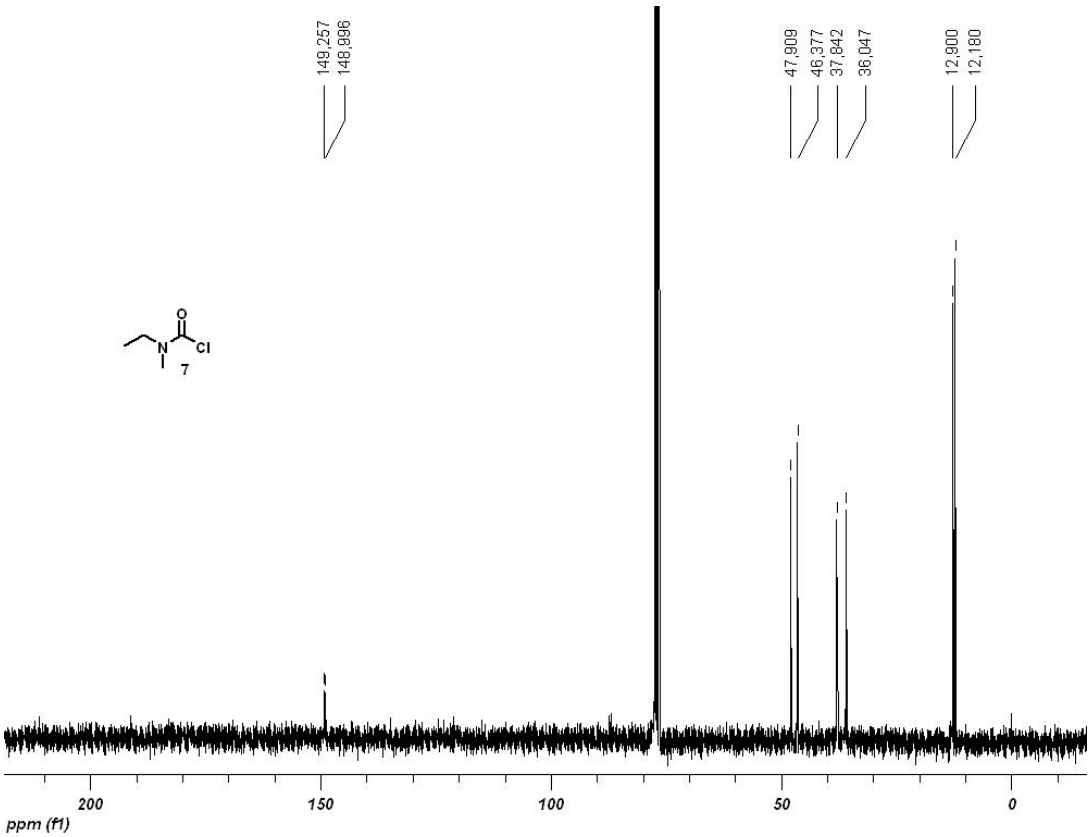


(*S*)-3-(1-Dimethylaminoethyl)phenol [(*S*)-5].

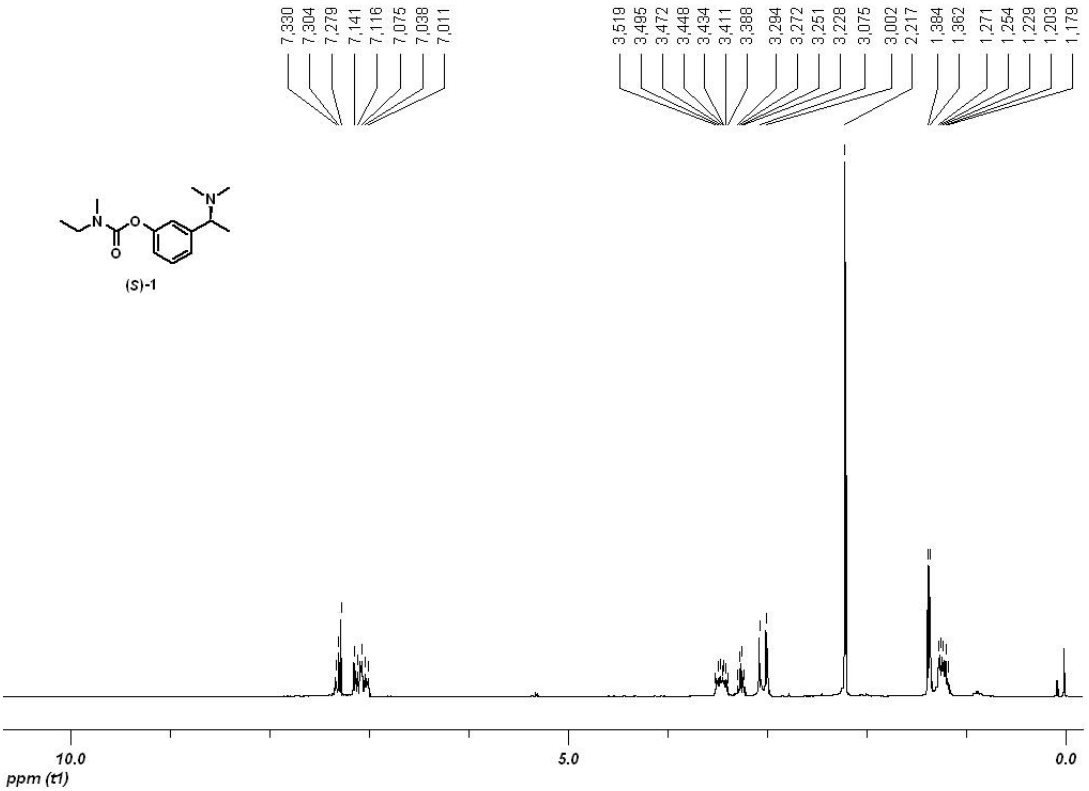


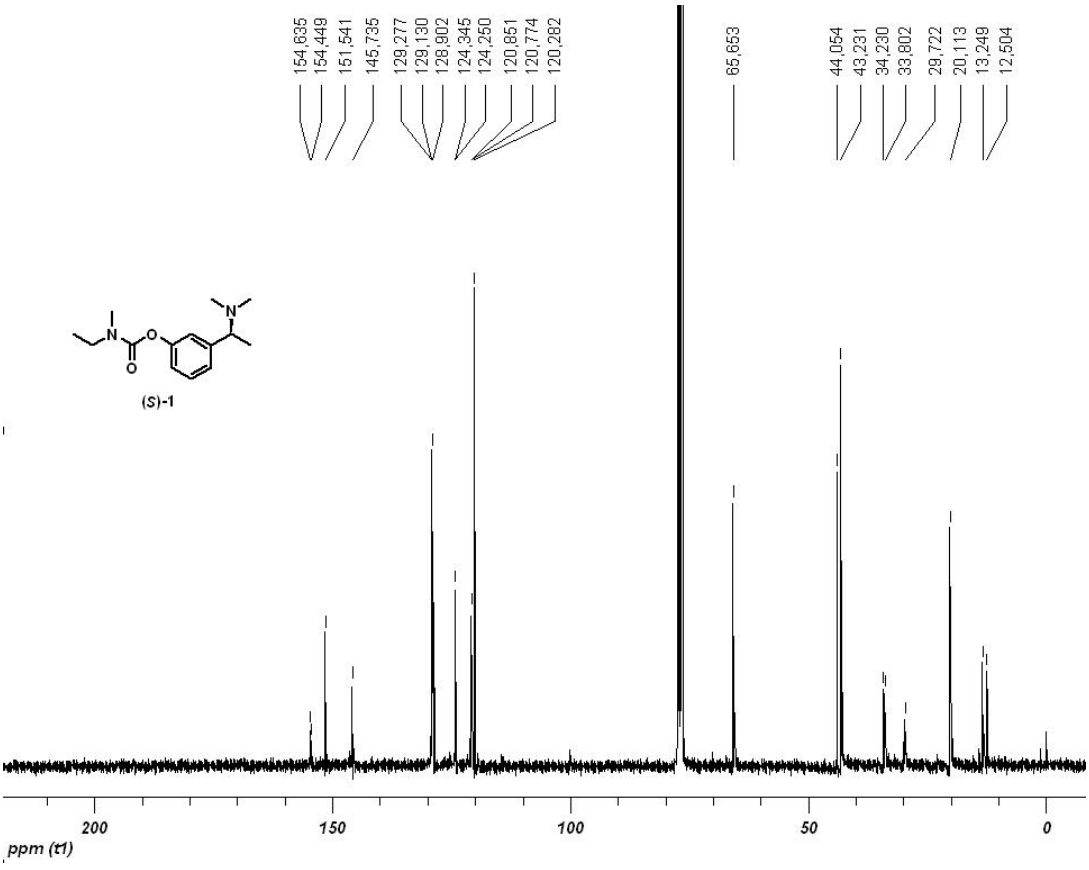
Ethyl(methyl)carbamic chloride (7).





(*S*)-3-[1-(Dimethylamino)ethy]phenyl Ethyl(methyl)carbamate [(*S*)-Rivastigmine, 1].





Chiral GC-FID analysis of (*S*)-1-(3-methoxymethoxy)phenyl)ethanamine [(*S*)-3f].

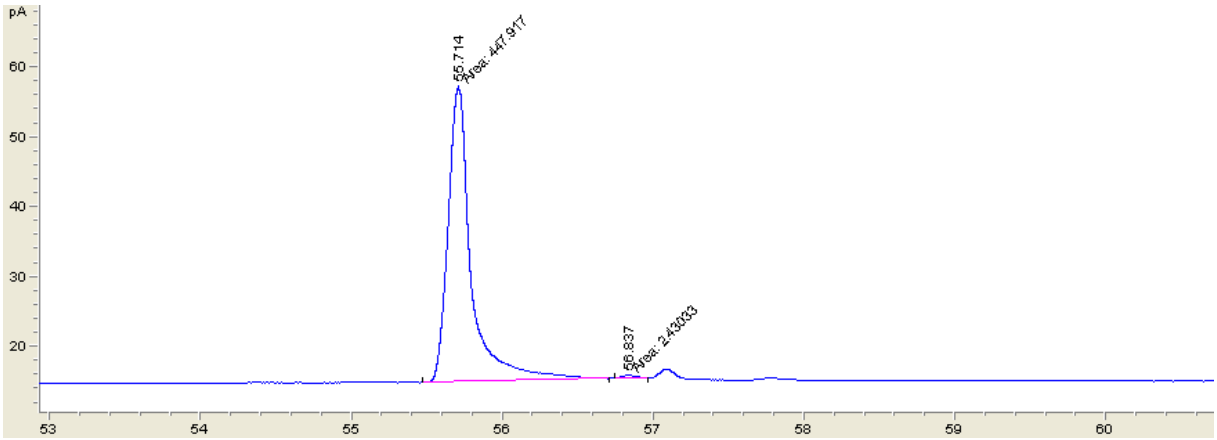


Fig. S01. Chiral GC-FID spectrum of (*S*)-1-(3-methoxymethoxy)phenyl)ethanamine [(*S*)-**3f**].

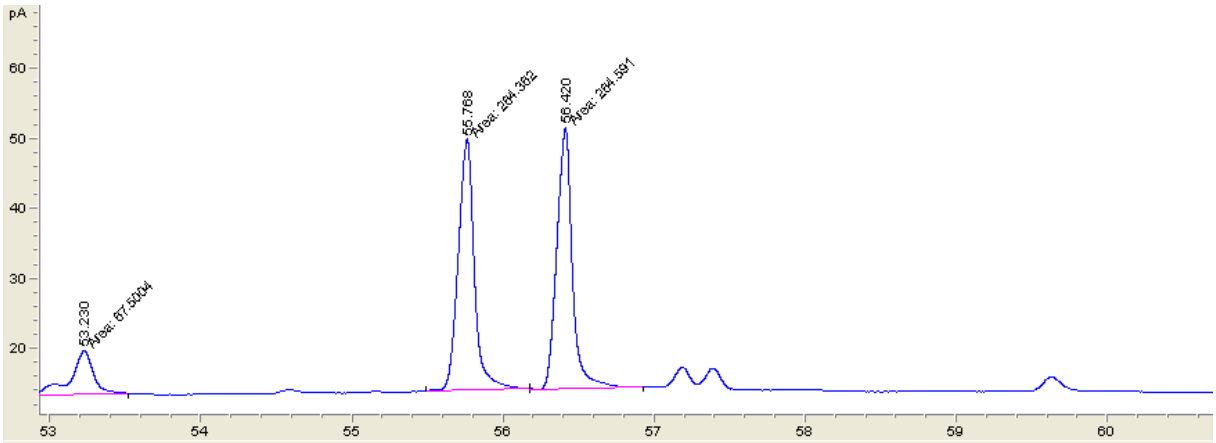
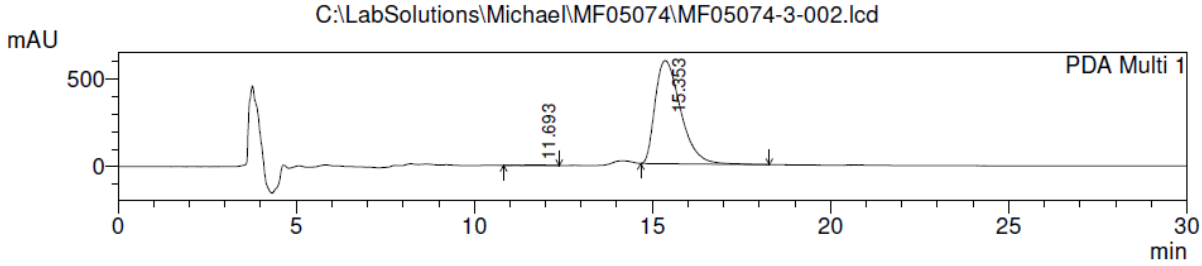


Fig. S02. Chiral GC-FID spectrum of (*rac*)- 1-(3-methoxymethoxy)phenyl)ethanamine [(*rac*)-**3f**].

Chiral HPLC analysis of (S)-3-[1-(Dimethylamino)ethy]phenyl Ethyl(methyl)carbamate [(S)-Rivastigmine, (S)-1].

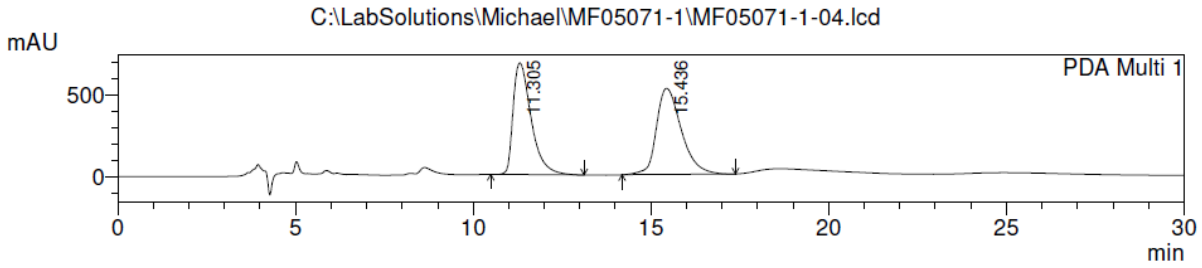


PeakTable

PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.693	126975	3358	0.432	0.567
2	15.353	29234960	588411	99.568	99.433
Total		29361935	591768	100.000	100.000

Fig. S03. Chiral HPLC spectrum (UV, 215 nm) of (*S*)-3-[1-(Dimethylamino)ethy]phenyl Ethyl(methyl)carbamate [(*S*)-Rivastigmine, (*S*)-**1**]



PeakTable

PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.305	24178674	683519	48.477	56.470
2	15.436	25697595	526886	51.523	43.530
Total		49876269	1210405	100.000	100.000

Fig. S04. Chiral HPLC spectrum (UV, 215 nm) of (*rac*)-3-[1-(Dimethylamino)ethy]phenyl Ethyl(methyl)carbamate [(*rac*)-Rivastigmine, (*rac*)-**1**]

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