International Journal of Organic Chemistry, **2011, 1, 26-32**
doi:10.4236/ijoc.2011.12005 Published Online June 2011 (http://www.SciRP.org/journal/ijoc)

A Simple and Highly Efficient Enantioselective Synthesis of (*S*)-Rivastigmine

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Received April 1, 2011; *revised May* 17, 2011; *accepted May* 28, 2011

Abstract

A highly efficient and convenient procedure for the enantioselective synthesis of (*S*)-Rivastigmine, a cholinergic agent for the treatment of mild to moderate dementia of the Alzheimer's type and dementia due to Parkinson's disease, is accomplished by the treatment of versatile, readily accessible (*S*)-(-)-2-methyl-2-propanesulfinamide with 3-hydroxyacetophenone. This protocol provides high yield and excellent enantiomeric excess in short step synthesis.

Keywords: Cholinergic Agent, Enantioselective, Highly Efficient, (*S*)-(-)-2-Methyl-2-Propane Sulfinamide, (*S*)-Rivastigmine

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia, a severe human health threat with more than 30 million sufferers worldwide [1]. Rivastigmine, (*S*)-3-[1-(dimethylamino)ethyl] phenyl ethyl (methyl) carbamate **1**, is the first USFDA approved drug in the form of capsules and patches for the treatment of mild to moderate dementia of the Alzheimer's type [2-5] and for mild to moderate dementia related to Parkinson's disease [6]. In the year 2006, it has been used in more than 6 million patients worldwide. Rivastigmine works by inhibiting both butyrylcholinesterase (BuChE) and acetylcholinesterase (AChE) with the same potency, unlike donepezil **2** (which selectively inhibits acetylcholinesterase), mimantine **3** and galanthamine **4**. Its pharmacological effect is selectively on the central nervous system, preferentially on the monomeric G1 isoform of AChE (selectivity for different isoforms of BuChE have not yet been investigated). The metabolism of rivastigmine is by the enzyme cholinesterase and do not depend on the P450 system in the liver, which reduces the risk of interactions with other medications [7]. The other stigmine products are pyridostigmine **5**, physostigmine **6** and neostigmine **7** (**Figure 1**).

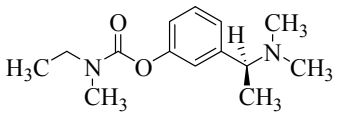
Rivastigmine has one chiral center with amine functionality. Therefore, attention needs to be paid to the synthesis of the correct enantiomer. (*S*)-enantiomer exhibits the desired cholinesterase inhibition, which requires the drug in enantiomerically pure form.

The insertion of chiral amine functionality through *N*-sulfinylimines is a major breakthrough endeavor due to the exceptional behavior of the chiral sulfinyl group in *N*-sulfinylimines, as an activator, chiral controller and useful protective group and finally recyclability [8] makes the sulfinamides extremely versatile chiral reagents (**Figure 2**) [9].

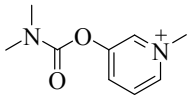
2. Results and Discussion

Our research group has been interested in utilization of these sulfinamides in industrial perspective for the development of facile chemical processes for active pharmaceutical ingredients (API's) [10]. Although several methods for the synthesis of rivastigmine and phenylcarbamate derivatives have been reported (Scheme 1), these methods suffer from limitations. Initial approaches have been developed *via* resolution of recemate using chiral acids [11-14] and transition metal catalysis [15,16]. Recent approaches are based on lipase catalyzed kinetic resolution [17-19], chemoenzymatic asymmetric synthesis [20] and asymmetric transfer hydrogenation [21].

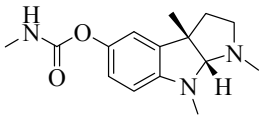
In order to circumvent these difficulties and provide access to feasible industrial process, we have devised a highly efficient enantioselective synthetic route based on the report that enantiopure *tert*-butane-sulfinamides take



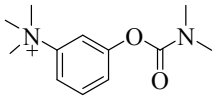
(*S*)-Rivastigmine. 1



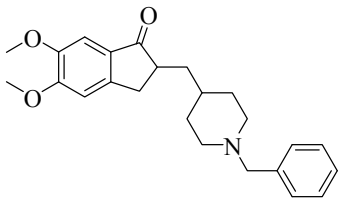
Pyridostigmine. 5



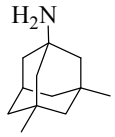
Physostigmine. 6



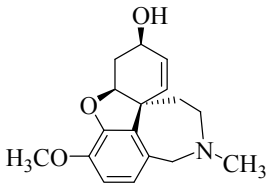
Neostigmine. 7



Donepezil. 2

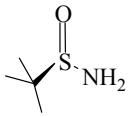


Mimantine. 3

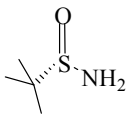


Galanthamine. 4

Figure 1. Acetylcholinesterase inhibitors.

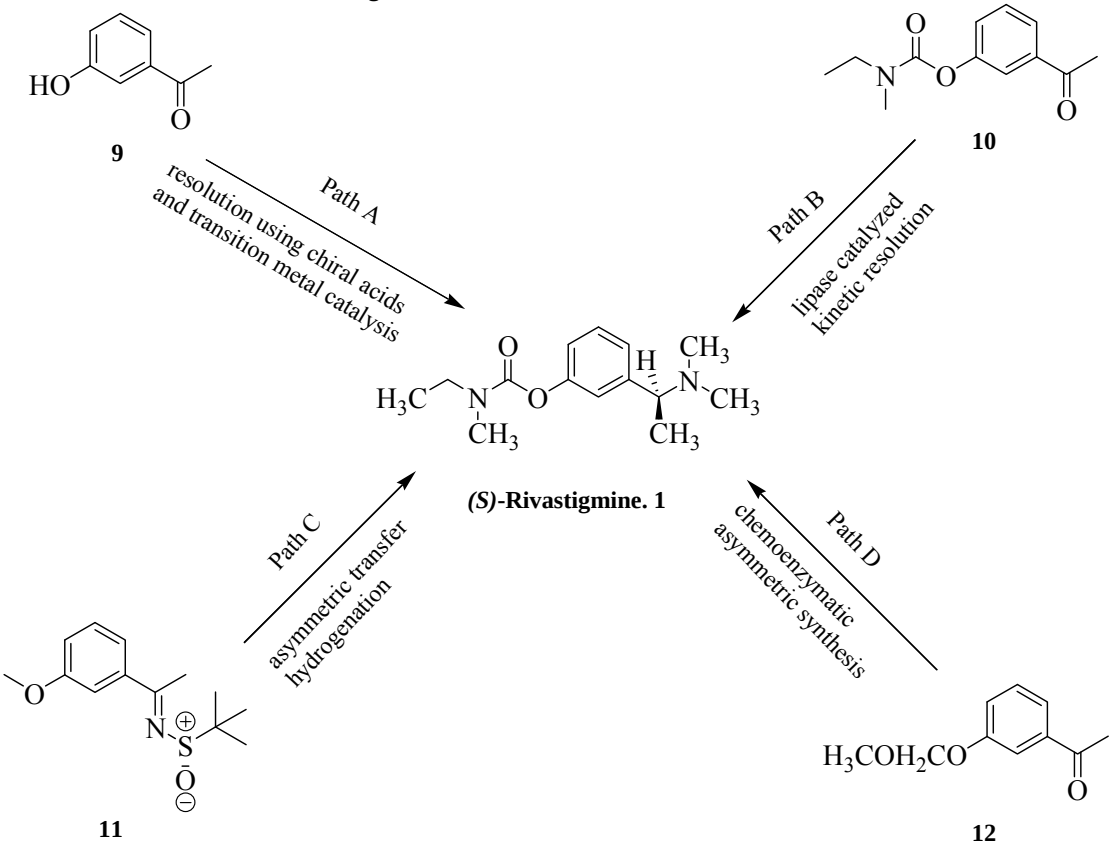


(*R*)-*tert*-butanesulfinamide



(*S*)-*tert*-butanesulfinamide. 8

Figure 2. Chiral *tert*-butanesulfinamides.



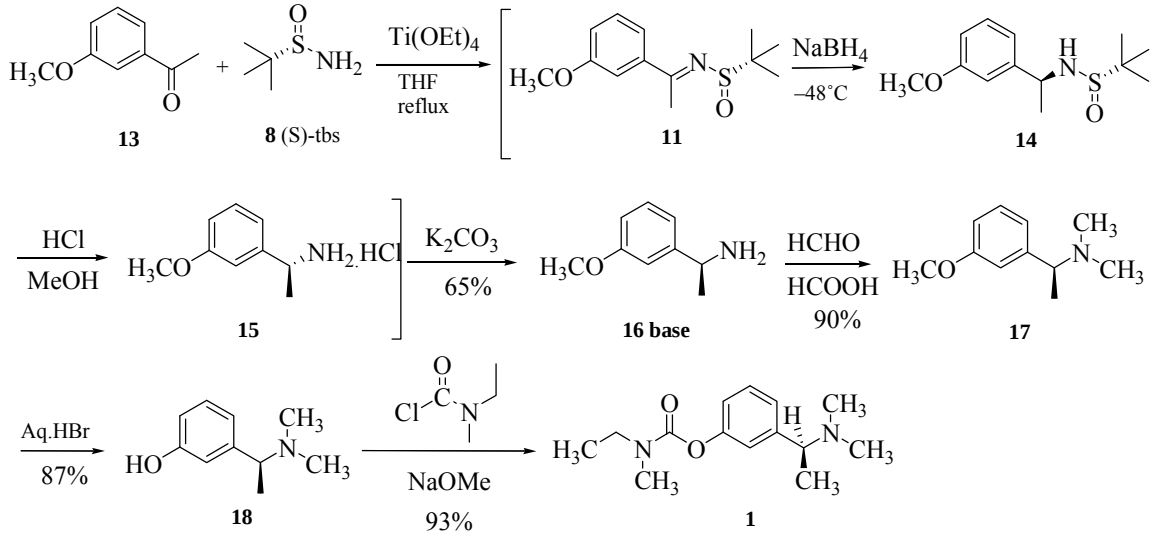
Scheme 1

part in the direct and enantioselective addition to aldehydes and ketones [9].

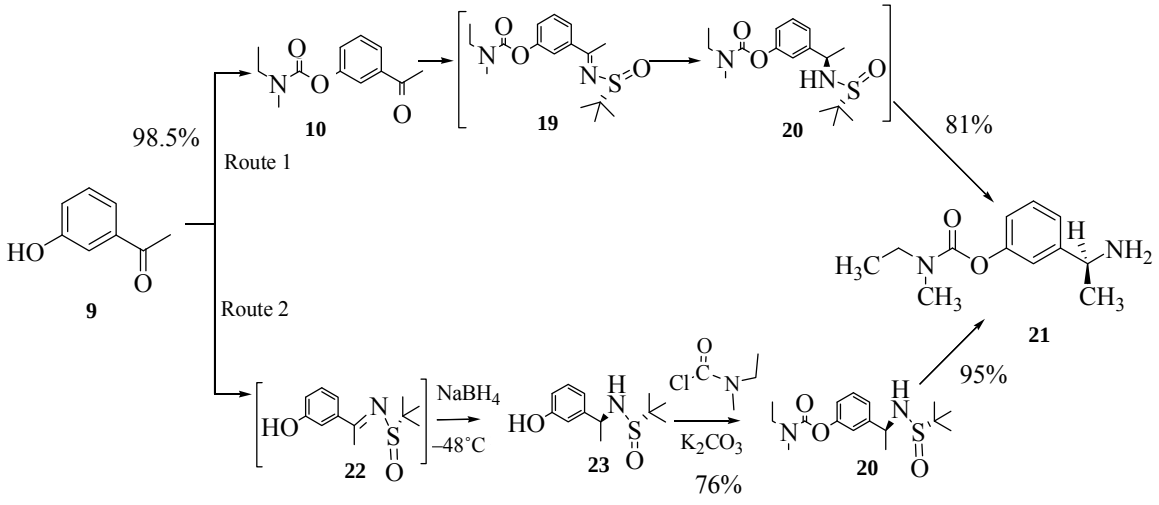
Initially we have synthesized **1** starting from 3-methoxyacetophenone **13** [22] via four step synthesis. The

procedure includes, *insitu* preparation of *N*-sulfinylimine **11** from **13** and (*S*)-**8** using $Ti(OEt)_4$ as Lewis acid and water scavenger in tetrahydrofuran. Imine on reduction with sodium borohydride at –48˚C furnished **14**. Hydrolysis of the sulfinyl group in **14** with dry methanolic hydrogen chloride gives the HCl salt **15** in pure form which on alkali treatment yields the chiral amine intermediate **16** in 65% yield with > 99% ee. **16** was subjected to *N*,*N*-dimethylation using formic acid and formaldehyde results **17** in 90% isolated yield. Demethylation of **17** in 48% aq.HBr proceeded in 87% yield of **18**. Finally treatment of **18** with *N*-ethyl-*N*-methyl carbamoyl chloride in the presence of sodium methoxide furnished the free base of **1** in 93% isolated yield with an enantiomeric excess of >99% (Scheme 2).

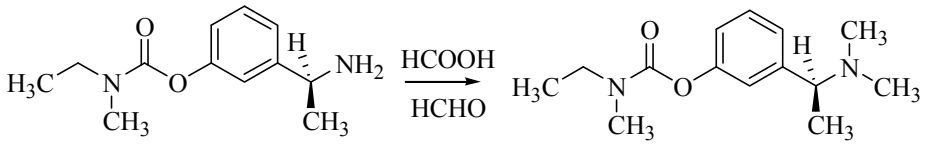
Still not satisfied with this yield and chiral purity, we set out to investigate the alternate possibilities for optimization of the reaction conditions and found great improvement in yield and also achieved the excellent enantiomeric excess of the desired product (100% ee). This time we chose **9** as starting material and synthesized **1** in two different routes. One is by condensing 1.25 equiv of *N*-ethyl-*N*-methylcarbamoyl chloride with **9** in the presence of K_2CO_3 (2.0 equiv) as base and ethyl acetate as solvent medium resulted **10** in 98.5% yield. **10** on condensation with **8** (*S*-isomer) furnished the imine intermediate **19** *insitu*, which was reduced with sodium borohydride at –48˚C to get **20**. Hydrolysis of the sulfinyl group in **20** and alkali treatment at room temperature afforded the desired chiral amine **21** in 81% yield (Scheme 3). *N*,*N*-dimethylation of the amine with 98% formic acid and 35% formaldehyde solution liberates free base of **1** in 95% yield with 100% ee (Scheme 4). And the other route proceeded by the treatment of **9** with



Scheme 2



Scheme 3. Current routes of asymmetric synthesis of 21 from 9.



21 **1**

Scheme 4

8 (*S*-isomer) first, then reduction of the *N*-sulfinylimine **22** followed by amido-ester formation with *N*-ethyl-*N*-methyl carbamoyl chloride to afford **20** in 76% yield. Hydrolysis of sulfinyl group with dry methanolic hydrogen chloride and alkali treatment gives **21** base with chiral purity > 94% in 95% yield (Scheme 3). Finally *N*,*N*-dimethylation of amine **21** with formic acid and 35% formaldehyde solution furnished **1** (free base) with 98% chiral purity in 95% yield (Scheme 4). The chiral purity is then improved to 100% by tartarate salt preparation with *L*-(+)-tartaric acid.

3. Experimental Section

Experiments are conducted under nitrogen atmosphere unless stated otherwise. All solvents and reagents are reagent grade pure and used without further purification. All melting points are determined on Polmon MP_96 melting point apparatus. ^{1}H & ^{13}C NMR spectra are recorded using a Bruker 400 MHz spectrometer (400 & 100 MHz respectively) with TMS as internal standard. Mass spectra are recorded on a Perkin-Elmer mass spectrometer operating at an ionization potential of 70 eV. IR spectra are recorded on Perkin Elmer spectrophotometer as KBr pellets or neat. Analytical TLC is conducted on E-Merck 60F254 aluminum-packed silicagel plates (0.2 mm). Developed plates are visualized under UV light or Iodine chamber. Chiral HPLC spectra are recorded on Waters alliance 2695 with 2487 U. V. detector.

Typical procedure for the preparation of (*S*)-Rivastigmine (1)

Route A.

Synthesis of 3-acetylphenyl ethyl (methyl) carbamate (10): a mixture of **9** (50.0 g, 0.367 mol), K_2CO_3 (101.5 g, 0.734 mol) and *N*-ethyl-*N*-methyl carbamoyl chloride (56.0 g, 0.46 mol) in ethyl acetate (500 ml) is refluxed for 4 hours. (Completion of reaction is monitored by TLC). The reaction mixture is cooled to room temperature and washed with water (3 × 250 mL), then dried over anhydrous Na_2SO_4, filtered and evaporated to get pale yellow oil of **10**. Wt 80.0 g, 98.5% yield; HPLC Purity: 97%; IR (Neat, $\nu_{max,}$ cm^{-1}): 1724 (C = O), 1686 (C = O), 2974 (aliphatic CH); ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.74 (*d*, 1H, *J* = 7.6 Hz, ArH), 7.65 (*s*, 1H, ArH), 7.40 (*t*, 1H, *J* = 7.9 Hz, ArH), 7.30 (*d*, 1H, *J* = 7.5 Hz, ArH), 3.42 (*q*, 1H, *J* = 7.0 Hz, rotamer1 CH_2), 3.37 (*q*, 1H, *J* = 7.0 Hz, rotamer2 CH_2), 3.04 (*s*, 1.5H, rotamer1 CH_3), 2.95 (*s*, 1.5H, rotamer2 CH_3), 2.55 (*s*, 3H, CH_3), 1.21 (*t*, 1.5H, *J* = 7.0 Hz, rotamer1 CH_3), 1.15 (*t*, 1.5H, *J* = 7.0 Hz, rotamer2 CH_3); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 197.08 (1C, C=O), 153.99 (*d*, *J* = 15.0 Hz, 1C, C=O), 151.64 (C_{aryl}), 138.19 (C_{aryl}), 129.26 (C_{aryl}), 126.57 (C_{aryl}), 124.93 (C_{aryl}), 121.47 (C_{aryl}), 43.98 (1C, CH_2 of carbamoyl), 34.14 (rotamer1 $Me_{carbamoyl}$), 33.70 (rotamer2 $Me_{carbamoyl}$), 26.56 (1C, CH_3), 13.10 (rotamer1 $Me_{carbamoyl}$), 12.29 (rotamer2 $Me_{carbamoyl}$); ESI-MS *m/z* (%): 222.0 (M^+, 100), 223.1 (M^+ + H, 20).

Synthesis of (*S*)-Ethyl-methyl-carbamic acid 3-(1-aminoethyl) phenyl ester (21): compound **10** (80.0 g, 0.36 mol) is refluxed with (*S*)-*tert*-butanesulfinamide **8** (48.2 g, 0.39 mol), titanium tetra ethoxide (164.26 g, 0.72 mol) in tetrahydrofuran (800.0 ml) for 30 hours. Cool to ambient temperature and further to –48 to –52˚C. Add $NaBH_4$ (20.5 g, 0.54 mol) in 5 portions. Stir for 3 hours to complete the reduction of imine intermediate **19**. Gradually warm to –5˚C, add methanol (80 ml) drop wise at –5˚C to 0˚C and stir for 30 minutes. Add ethyl acetate (400 ml) and water (500 ml). Stir for 30 minutes to warm to rt and filter off the salts. Separate the organic layer and aqueous layer is washed with ethyl acetate (200 ml). Combined organic layers are washed successively with water (2 × 250 ml) and brine solution (200 ml). The organic layer is dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get yellow oil of crude **20**, which is hydrolyzed with 13% methanolic HCl (126 ml) and then alkali treatment with aq.NaOH at rt, extraction into ethyl acetate and concentration of the solvent afford pale yellow oil. Wt 65.0 g, yield 81%; $[\alpha]_D^{20}$ – 16.5˚ (*c* 1.0, $CHCl_3$); Chiral HPLC Purity: 99.9%, Column: chiral cel OD-H 250 × 4.6 (SRC-583), mobile phase A: *n*-hexane:IPA:DEA (90:10:0.1), Iso: 100%, concentration: 10 mg/10mL, diluent: ethanol, run time: 20 min, temperature: 25˚C, flow rate: 1 mL/min, UV: 225nm, retention time: (*S*)-isomer: 12.8 min and (*R*)-isomer: 11.66 min; HPLC Purity: 98.8%; IR (Neat, $\nu_{max,}$ cm^{-1}): 1716 (C=O), 2974 (aliphatic CH), 3365 (NH_2); ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.31 (*t*, 1H, *J* = 7.8 Hz, ArH), 7.27 (*s*, 1H, ArH), 7.16 (*d*, 1H, *J* = 7.7 Hz, ArH), 6.99 (*d*, 1H, *J* = 7.7 Hz, ArH), 4.12 (*q*, 1H, *J* = 3.4 Hz, CH), 3.46 (*q*, 1H, *J* = 7.2 Hz, rotamer1 CH_2),

3.41 (*q*, 1H, *J* = 7.1 Hz, rotamer2 CH_2), 3.07 (*s*, 1.5H, rotamer1 CH_3), 2.99 (*s*, 1.5H, rotamer2 CH_3), 1.61 (*s*, 2H, NH_2), 1.38 (*d*, 3H, *J* = 6.6 Hz, CH_3), 1.24 (*t*, 1.5H, *J* = 6.1 Hz, rotamer1 CH_3), 1.19 (*t*, 1.5H, *J* = 6.0 Hz, rotamer2 CH_3); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 154.45 (*d*, *J* = 18.0 Hz, 1C, C=O), 151.57 (C_{aryl}), 149.22 (C_{aryl}), 129.10 (C_{aryl}), 122.39 (C_{aryl}), 120.02 (C_{aryl}), 118.95 (C_{aryl}), 50.95 (1C, CH), 43.94 (1C, CH_2 of carbamoyl), 34.11 (rotamer1 $Me_{carbamoyl}$), 33.68 (rotamer2 $Me_{carbamoyl}$), 25.40 (1C, CH_3), 13.10 (rotamer1 $Me_{carbamoyl}$), 12.35 (rotamer2 $Me_{carbamoyl}$); ESI-MS *m/z* (%): 206.0 (M-NH_2, 100), 207.1 ($M^+ - NH_2$, 20), 223.1 (M^+ + H, 15).

The intermediate stages have also isolated for confirmation by analytical and spectral data.

2-Methyl propane-2-sulfinic acid [1-(3-methoxyphenyl)ethylidene]amide (19): yellow oil, yield 87%; $[\alpha]_D^{20}$ – 0.5˚ (*c* 1.0, $CHCl_3$); HPLC Purity: 96.8%; IR (Neat, $\nu_{max,}$ cm^{-1}): 1089 (S-O), 1723 (C=O), 1575 (C=N), 2975 (aliphatic CH); ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.71 (*d*, 1H, *J* = 7.5 Hz, ArH), 7.59 (*s*, 1H, ArH), 7.40 (*t*, 1H, *J* = 7.9 Hz , ArH), 7.25 (*d*, 1H, *J* = 8.0 Hz, ArH), 3.48 (q, 1H, *J* = 7.0 Hz, rotamer1 CH_2), 3.41 (*q*, 1H, *J* = 7.0 Hz, rotamer2 CH_2), 3.08 (*s*, 1.5H, rotamer1 CH_3), 2.99 (*s*, 1.5H, rotamer2 CH_3), 2.74 (*s*, 3H, CH_3), 1.30 (*s*, 9H, $C(CH_3)_3$), 1.24 (*t*, 1.5H, *J* = 7.0 Hz, rotamer1 CH_3), 1.19 (*t*, 1.5H, *J* = 7.0 Hz, rotamer2 CH_3); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 175.27 (1C, C=N), 154.12 (*d*, *J* = 18.0 Hz, 1C, C=O), 151.52 (C_{aryl}), 139.93 (C_{aryl}), 129.11 (C_{aryl}), 125.12 (C_{aryl}), 123.96 (C_{aryl}), 120.53 (C_{aryl}), 57.55 (1C, $C_{t\text{-}butyl}$), 44.02 (1C, CH_2 of carbamoyl), 34.19 (rotamer1 $Me_{carbamoyl}$), 33.76 (rotamer2 $Me_{carbamoyl}$), 22.46 (3C, $C_{t\text{-}butyl}$), 19.77 (1C, Me), 13.14 (rotamer1 $Me_{carbamoyl}$), 12.34 (rotamer2 $Me_{carbamoyl}$); ESI-MS m/z (%): 346.9 (M^+ + Na, 100), 325.0 (M + H, 45), 306.9 (20), 291 (65), 250.9 (47), 243.0 (45).

2-Methyl propane-2-sulfinic acid [1-(3-methoxyphenyl) ethyl]amide (20): yellow oil, yield 98%; $[\alpha]_D^{20}$ + 26.0˚ (*c* 1.0, $CHCl_3$); Chiral HPLC Purity: 99.95%, Column: chiral cel AD-H 250 × 4.6 mm/5 µm (SRC-581), mobile phase A: *n*-hexane:IPA:TFA (90:10:0.1), Iso: 100%, concentration: 10 mg/10 mL, diluent: ethanol, run time: 35 min, temperature: 25˚C, flow rate: 0.8 mL/min, UV: 215 nm, retention time: (*S*)-isomer: 12.78 min and (*R*)-isomer: 7.72 min; HPLC Purity: 92%; IR (Neat, ν_{max}, cm^{-1}): 1055 (S-O), 1718 (C = O), 2978 (aliphatic CH), 3234 (NH); ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.32 (*t*, 1H, *J* = 7.8 Hz, ArH), 7.18 (*d*, 1H, *J* = 7.6 Hz , ArH), 7.08 (*s*, 1H, ArH), 7.04 (*d*, 1H, *J* = 7.0 Hz, ArH), 4.54 (*q*, 1H, *J* = 3.7 Hz, CH), 3.51 (*s*, 1H, NH), 3.47 (*q*, 1H, *J* = 7.0 Hz, rotamer1 CH_2), 3.41 (*q*, 1H, *J* = 7.1 Hz, rotamer2 CH_2), 3.06 (*s*, 1.5H, rotamer1 CH_3), 2.98 (*s*, 1.5H, rotamer2 CH_3), 1.50 (*d*, 3H, *J* = 6.5 Hz, CH_3), 1.25 (*t*, 1.5H, *J* = 7.0 Hz, rotamer1 CH_3), 1.20 (*s*, 9H, $C(CH_3)_3$), 1.19 (*t*, 1.5H, *J* = 7.0 Hz, rotamer2 CH_3); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 154.20 (*d*, *J* = 18.0 Hz, 1C, C=O), 151.59 (C_{aryl}), 145.27 (C_{aryl}), 129.39 (C_{aryl}), 123.28 (C_{aryl}), 121.12 (C_{aryl}), 119.85 (C_{aryl}), 55.33 (1C, $C_{t\text{-}butyl}$), 53.51 (1C, CH), 43.92 (1C, CH_2 of carbamoyl), 34.08 (rotamer1 $Me_{carbamoyl}$), 33.68 (rotamer2 $Me_{carbamoyl}$), 29.14 (1C, Me), 22.48 (3C, $C_{t\text{-}butyl}$), 13.09 (rotamer1 $Me_{carbamoyl}$), 12.32 (rotamer2 $Me_{carbamoyl}$); ESI-MS *m/z* (%): 348.9 (M^+ + Na, 90), 327.0 (M + H, 100), 293.0 (23), 252.9 (54), 245.0 (26), 194.0 (80).

Route B.

Synthesis of 2-Methyl propane-2-sulfinic acid [1-(3-hydroxyphenyl)ethyl]amide (23):

3-Hydroxyacetophenone (10.0 g, 0.066 mol) is refluxed with (*S*)-**8** (8.07 g, 0.066 mol), titanium tetra ethoxide (30.4 g, 0.133 mol) in THF (100 ml) for 30 hr. Cool to ambient temperature and further to –48 to –52˚C and added $NaBH_4$ (3.8 g, 0.099 mol) in 4 portions. Stir for 3 hours to complete the reduction of imine intermediate **22**. Gradually warm to –5˚C and added methanol (10 ml) drop wise at –5˚C to 0˚C. Stir for 30 minutes, added ethyl acetate (50 ml) and water (100 ml). Stir for 30 minutes to warm to rt and filtered off the salts. Separate organic layer and aqueous layer is washed with ethyl acetate (50 ml). Combined organic layers are washed successively with water (2 × 50 mL) and brine solution (30 ml). The organic layer is dried over anhydrous Na_2SO_4 and evaporated to afford pale yellow solid of **23**. Wt 13.7 g; yield 77.6%; mp 140˚C - 144˚C; $[\alpha]_D^{23}$ + 25.5˚ (*c* 1.0, MeOH); Chiral HPLC: 94.76%, Column: chiral pak AD-H 0.46cm × 25cm (SRC-581), mobile phase A: *n*-hexane:IPA:DEA (90:10:0.1), Iso: 100%, concentration: 50 mg/10mL, diluent: ethanol, run time: 45 min, temperature: 25˚C, flow rate: 1 mL/min, UV: 230nm, retention time: (*S*)-isomer: 24.87 min and (*R*)-isomer: 8.13 min; IR (KBr, cm^{-1}): 3277 (NH), 3086 (OH), 2972 (aliphatic CH), 1017 (S-O); ^{1}H NMR (400MHz, CDCl3): δ_H 8.2 (br s, 1H, OH), 7.15 (*t*, 1H, *J* = 8.0 Hz, ArH), 6.81 (*d*, 1H, *J* = 7.7 Hz, ArH), 6.77 (*s*, 1H, ArH), 6.76 (*d*, 1H, *J* = 7.5 Hz, ArH), δ 4.41 (*q*, 1H, *J* = 3.5 Hz, CH), δ 3.64 (*s*, 1H, NH), 1.46 (*d*, 3H, *J* = 6.5 Hz, CH_3), 1.26 (*s*, 9H, $C(CH_3)_3$); ^{13}C NMR (100MHz, DMSO-d_6): δ_C 157.57 (1C, C_{aryl}), 147.13 (1C, C_{aryl}), 129.41 (1C, C_{aryl}), 117.50 (1C, C_{aryl}), 114.07 (1C, C_{aryl}), 113.77 (1C, C_{aryl}), 55.44 (1C, $C_{t\text{-}butyl}$), 54.47 (1C, CH), 24.50 (1C, CH_3), 22.97 (3C, $C_{t\text{-}butyl}$); ESI-MS *m/z* (%): 242.4 (M + H, 100), 168.3 (50), 125.1 (10).

The intermediate stages have also isolated for confirmation by analytical and spectral data.

2-Methyl propane-2-sulfinic acid [1-(3-hydroxyphenyl)ethylidene]amide (22): yellow crystals, yield 77.6%; mp 137˚C - 142˚C; $[\alpha]^{23}_D$ + 3.0˚ (*c* 1.0, MeOH); Chiral HPLC purity: 99.98%, Column: chiral pak AD-H

0.46cm × 25cm (SRC-581), mobile phase A: *n*-hexane: IPA:DEA (90:10:0.1), Iso: 100%, concentration: 5 mg/10mL, diluent: ethanol, run time: 35 min, temperature: 25˚C, flow rate: 1 mL/min, UV: 254nm, retention time: (*S*)-isomer: 16.16 min and (*R*)-isomer: 12.55 min; IR (KBr, cm^{-1}): 3180 (OH), 2987 (aliphatic CH), 1597 (C=N), 1028 (S-O); ^{1}H NMR (400MHz, CDCl3): δ_H 7.72 (br s, 1H, OH), 7.43 (*s*, 1H, ArH), 7.32 (*d*, 1H, *J* = 7.4 Hz, ArH), 7.23 (*t*, 1H, *J* = 7.9 Hz, ArH), 7.01 (*d*, 1H, *J* = 7.9 Hz, ArH), 2.68 (*s*, 3H, CH_3), 1.32 (*s*, 9H, $C(CH_3)_3$); ^{13}C NMR (100MHz, DMSO-d_6): δ_C 176.82 (1C, C=N), 157.78 (1C, C_{aryl}), 140.01 (1C, C_{aryl}), 129.98 (1C, C_{aryl}), 119.34 (1C, C_{aryl}), 118.52 (1C, C_{aryl}), 113.92 (1C, C_{aryl}), 57.08 (1C, $C_{t\text{-}butyl}$), 22.37 (3C, $C_{t\text{-}butyl}$), 20.03 (1C, CH_3); ESI-MS *m/z* (%): 240.3 (M + H, 65), 184.2 (100), 166.1 (82).

Synthesis of (*S*)-Ethyl methyl carbamic acid 3-(1-aminoethyl)phenyl ester (21): a mixture of **23** (13.0 g, 0.053 mol), K_2CO_3 (14.9 g, 0.107 mol) and *N*-ethyl-*N*-methyl carbamoyl chloride (8.18 g, 0.067 mol) in ethyl acetate (130 ml) is refluxed for 4 hours. Cool to room temperature and washed with water (3 × 130 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to get pale yellow oil of **20** (17.37 g, 99% yield), which is hydrolyzed with 13% methanolic HCl (18 ml) and then alkali treatment with aq.NaOH at rt, extraction into ethyl acetate and evaporation of the solvent under reduced pressure afford pale yellow oil of **21**. Wt 11.25 g, yield 95%.

Synthesis of (*S*)-Rivastigmine (1): the pale yellow oil **21** (65.0 g, 0.43 mol) is dissolved in formic acid (198.0 g, 4.3 mol), formaldehyde (44.0 g, 3.4 mol (35% solution in water) and water (650 ml). Heated to reflux temperature (95˚C - 100˚C) and stirred for 5 hr. Cool to ambient temperature; wash with ethyl acetate (2 × 130 ml) to remove the impurities. Aqueous layer is separated, adjusted pH to 10 with 20% aq. NaOH solution (758 ml) and extracted with ethyl acetate (2 × 325 ml). The combined organic layers are washed with brine solution (100 ml), dried over anhydrous sodium sulfate and evaporated under reduced pressure at 45˚C - 50˚C to get pale yellow oil. Wt 78.4 g; yield 95%; $[\alpha]_D^{20}$ – 35.2˚ (*c* 1.0, $CHCl_3$) (lit [6]: $[\alpha]_D^{20}$ – 33.9˚ (*c* 1.0, $CHCl_3$); Chiral HPLC Purity 100%, Column: chiral pak OD-H 250 × 4.6 mm, mobile phase A: *n*-hexane:IPA:TFA (80:20:0.1), Iso: 100%, concentration: 10 mg/25mL, diluent: ethanol, run time: 25 minutes, temperature: 25˚C, flow rate: 0.8 mL/min, UV: 215 nm, retention time: (*S*)-isomer: 14.41 min and (*R*)-isomer: 9.54 min;; IR (Neat, ν_{max}, cm^{-1}): 2975 (aliphatic CH), 1725 (C=O); ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.28 (*t*, 1H, *J* = 7.8 Hz, ArH), 7.10 (*d*, 1H, *J* = 7.8 Hz, ArH), 7.05 (*s*, 1H, ArH), 7.00 (*d*, 1H, *J* = 7.8 Hz, ArH), 3.44 (*q*, 1H, *J* = 7.5 Hz, CH_2 rotamer 1), 3.41 (*q*, 1H, *J* = 7.5 Hz, CH_2 rotamer 2), 3.23 (*q*, 1H, *J* = 6.6 Hz, –CH), 3.05 (*s*, 1.5H, CH_3 rotamer 1), 2.97 (*s*, 1.5H, CH_3 rotamer 2), 2.19 (*s*, 6H, $N(CH_3)2$), 1.34 (*d*, 3H, *J* = 6.7 Hz, CH_3), 1.23 (*t*, 1.5H, *J* = 7.2 Hz, CH_3 rotamer 1), 1.17 (*t*, 1.5H, *J* = 7.2 Hz, CH_3 rotamer 2) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 154.41 (*d*, *J* = 18.0 Hz, 1C, C = O), 151.41 (C_{aryl}), 145.63 (C_{aryl}), 128.77 (C_{aryl}), 124.11 (C_{aryl}), 120.60 (C_{aryl}), 120.14 (C_{aryl}), 65.53 (1C, CH), 43.92 (1C, CH_2 of carbamoyl), 43.11, 34.09 (rotamer1 $Me_{carbamoyl}$), 33.67 (rotamer2 $Me_{carbamoyl}$), 19.98 (1C, Me), 13.12 (rotamer1 $Me_{carbamoyl}$), 12.37 (rotamer2 $Me_{carbamoyl}$); ESI-MS *m/z* (%): 251.2 (M + H, 100), 206.2 (60).

Preparation of (*S*)-(+)-rivastigmine hydrogentartarate (1): (*S*)-(-)-rivastigmine **1** (4.5 g) and *L*-(+)-tartaric acid (2.7 g) are dissolved in anhydrous ethanol (12.5 mL) at 60˚C. Ethyl acetate (63 mL) is added at the same temperature and stirred for 10 minutes. Cool the solution to room temperature and to crystallize at +5˚C for a period of 12 hours. The precipitated solid is collected through filtration and washed the cake with ethyl acetate (10 mL). Dry the solid at 50˚C under vacuum to afford 6.7 g of the desired product. Yield 92%; $[\alpha]_D^{20}$ + 4.6˚ (*c* 5.0, ethanol); mp 117˚C - 120˚C; Chiral HPLC Purity: 100% ee.

4. Conclusions

In summary, a high yielding stereoselective and short synthesis of (*S*)-Rivastigmine is described in two ways with an overall isolated yield of 76% and 70% respectively *via* 3 step procedure starting from 3-hydroxyacetophenone, a commercially available intermediate. [23]

5. Acknowledgements

We greatly acknowledge our thanks to Mr. Venkat Jasti, CEO for his excellent support, Mr. K. R. S. Sharma for Chiral HPLC method development and the analytical group of SUVEN for providing spectral data.

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