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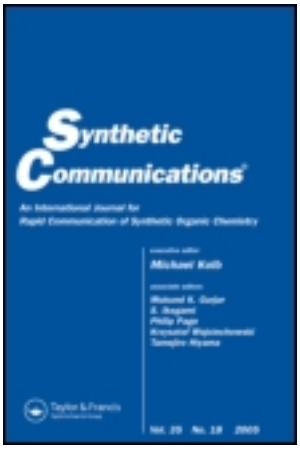

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Novel Convenient Synthesis of Rivastigmine

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Novel Convenient Synthesis of Rivastigmine

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Abstract: A novel and convenient synthesis of rivastigmine has been reported. This procedure provides high yield and excellent enantiomeric excess (100% ee) starting from the diastereromerically pure (*S*)-1-(3-methoxyphenyl)-*N*-[(*S*)-1-phenylethyl] ethanamine.

Keywords: Acetyl cholinesterase inhibitor, rivastigmine, synthesis

Rivastigmine (**1**) [(*S*)-*N*-ethyl-*N*-methyl-3-[1-(dimethylamino)ethyl]-carbamic acid, phenyl ester, (L)-2,3-dihydroxybutanedioic acid salt] is an acetyl cholinesterase inhibitor with brain-region selectivity and a long duration of action.[1] It was approved by the U.S. Food and Drug Administration for the treatment of Alzheimer's disease (AD) on April 21, 2000.

Originally, rivastigmine was synthesized by resolving the racemic rivastigmine with (+)-di-*O,O′*-p-toluoyl tartaric acid monohydrate.[2] However, this method involves three or more recrystallizations to achieve increased enantiomeric excess. Accordingly, the total yield is at a low level and high enantiomeric excess cannot be ensured.

Several other syntheses of rivastigmine have been reported,[3–7] which are either too long or contain unacceptable operations, and thus their are not suitable for plant-scale operations. Most important of all, none of the procedures can obtain high enantiomeric excess of rivastigmine.

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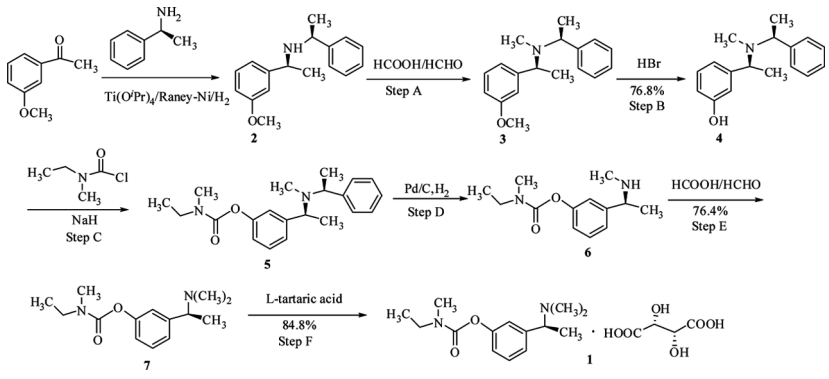
We reported a novel one-pot asymmetric reductive amination of 3-methoxyacetophenone with (*S*)- or (*R*)-α-methylbenzylamine using the combination of $Ti(O^iPr)_4/Raney\text{-}Ni/H_2$ in 2007,[8] and the diastereomerically pure (*S*)-1-(3-methoxyphenyl)-*N*-[(*S*)-1-phenylethyl]ethanamine (**2**) was obtained in 74.2% yield. Here we extend our earlier work and report a novel method to synthesize rivastigmine starting from the diastereomerically pure **2** (Scheme 1).

Compound **2** was subjected to *N*-methylation using formic acid and formaldehyde, and (*S*)-1-(3-methoxyphenyl)-*N*-methyl-*N*-[(*S*)-1-phenylethyl] ethanamine (**3**) was obtained. Demethylation of the methoxy function of **3** in HBr proceeded in 76.8% yield. Processing **4** with *N*-ethyl-*N*-methyl carbomoyl chloride gave the compound **5**. The regioselective hydrogenolysis of **5** is very important. Bringmann et al.[9] described that when the bis(α-methylbenzyl)amine derivatives have an electron-donating group, which increases the electron density of the aromatic ring, a highly regioselective hydrogenolysis may be observed. This observation was consistent with the results described in this communication. The regioselectivity of the cleavage was extremely high for the oxygenated compound **5**, leading to the desired product **6** in excellent yield. After *N*-methylation, the free base of rivastigmine (**7**) was obtained in 76.4% yield, which was finally treated with L-tartaric acid to give rivastigmine (**1**) in 84.8% yield.

The enantiomeric excess of rivastgmine was determined by chiral high-performance liquid chromatography (HPLC), and the enantiomer was not found.



Scheme 1. Synthesis of rivastigmine.

In summary, we present a novel and convenient synthesis of rivastigmine. The total yield is high (49.7%), and the enantiomeric excess of rivastgmine is very high (100% ee).

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian 400-MHz instrument using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard. Mass spectra were determined on a Shimadzu LCMS-2010EV (ESI) instrument. Elemental analyses were performed on a Carlo-Erba 1106 instrument. Melting points were observed in an open capillary tube and were uncorrected. Optical rotations were determined with a Perkin-Elmer 341 automatic polarimeter.

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HPLC Methods

Reaction progress was monitored by HPLC with purities being determined by peak area percent. An Agilent 1100 instrument was used for all analyses. Parameters were TSK C18 column (250 × 4.6 mm); mobile phase, 0.01 M $(NH_4)_2HPO_4$/MeOH = 22:78 (v/v); flow, 1.0 ml/min; detection wavelength, 230 nm; temperature, 40°C, and injection volume, 10 μL.

Enantiomeric excess of rivastigmine was determined under the following chiral HPLC analysis conditions: Chromtech, Chiral-AGP column (100 × 4.6 mm); mobile phase, 0.03 M NaH_2PO_4 (pH adjusted to 7.4 with phosphoric acid)/MeOH = 85:15 (v/v); flow, 0.8 ml/min; detection wavelength, 210 nm; temperature, 25°C, and injection volume, 10 μL. Retention times for rivastigmine (**1**) were 17.1 min and for (*R*)-isomer of **1** were 15.2 min.

Step A: (*S*)-1-(3-Methoxyphenyl)-*N*-methyl-N-[(*S*)-1-phenylethyl] Ethanamine (3)

To **2** (25.5 g, 0.1 mol), 98% aqueous formic acid solution (18.9 g, 0.4 mol) followed by 37% aqueous formaldehyde solution (16.68 g, 0.2 mol) were added. The reaction mixture was heated to reflux for 4 h. After cooling to room temperature, 200 ml water were added. The solution was neutralized with Na_2CO_3 and extracted with ethyl acetate (200 ml × 2). The combined organic layer was washed with 40 ml water and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure

to yield 28.94 g of **7** as oil (99.3% HPLC purity), which was used directly in the next step. $[\alpha]_D^{20} = -75.6^\circ$ (*c* 2.0, EtOH).

^{1}H NMR ($CDCl_3$) δ: 1.31 (d, 3H), 1.33 (d, 3H), 2.01 (s, 3H), 3.82 (s + m, 5H), 6.78 (m, 1H), 6.95 (m, 2H), 7.25 (m, 2H), 7.33 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 159.6, 146.2, 144.1, 128.9, 128.0, 127.8, 126.6, 120.2, 113.6, 111.8, 59.3, 59.2, 55.1, 32.9, 18.6, 18.4; MS (ESI) m/z: 270.2 (M + 1).

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Step B: 3-[(*S*)-1-[Methyl-[(*S*)-1-phenylethyl]amino]ethyl] Phenol (4)

Compound **3** from step A was dissolved in 75 ml 48% solution of HBr, and the resulting solution was refluxed under stirring for 12 h. Excess hydrobromic acid was evaporated under normal pressure. The residue was dissolved in 150 ml water and neutralized with Na_2CO_3. The solution was extracted with ethyl acetate (275 ml × 2). The combined organic layer was washed with 50 ml water and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to yield crude **4**, which was recrystallized from ethyl acetate/petroleum ether to afford **4** as a white crystalline solid (19.58 g, 76.8%, 99.5% HPLC purity), $[\alpha]_D^{20} = -82.5^\circ$ **(*c* 2.0, EtOH), mp 99–100°C.**

^{1}H NMR ($CDCl_3$) δ: 1.30 (d, 3H), 1.33 (d, 3H), 1.99 (s, 3H), 3.78 (q, 1H), 3.85 (q, 1H), 6.70 (m, 1H), 6.91 (m, 2H), 7.20 (m, 2H), 7.33 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 155.6, 146.6, 144.0, 129.2, 128.1, 127.9, 126.6, 120.3, 114.7, 113.8, 59.3, 59.2, 32.9, 18.6, 18.4; MS (ESI) m/z: 256.1 (M + 1). anal. calcd. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.83; H, 8.25; N, 5.47.

Step C: *N*-Ethyl-*N*-methyl-3-[(*S*)-1-methyl-[[(*S*)-1-phenylethyl]amino]ethyl]phenyl Carbamate (5)

Under a nitrogen atmosphere, a 60% oil dispersion of NaH (3.14 g, 78.4 mmol) was added slowly to 80 ml tetrahydrofuran (THF). A solution of **4** (10 g, 39.2 mmol) was added dropwise to the NaH suspension. The mixture was stirred for 30 min, followed by addition of *N*-ethyl-*N*-methyl carbomoyl chloride[10] (9.53 g, 78.4 mmol), which was dissolved in 20 ml THF. After 4 h, the solvent was evaporated under reduced pressure, and the residue was partitioned between 120 ml water and 100 ml ethyl acetate. The organic layer was separated, and the aqueous fraction was extracted with additional ethyl acetate (50 ml × 2). The combined organic layer was washed with

0.1 N NaOH (60 ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to yield 16.03 g of **5** as an oil (93.8% HPLC purity), which was used directly in the next step. $[\alpha]_D^{20} = -65.9°$ (*c* 1.0, EtOH).

^{1}H NMR ($CDCl_3$) δ: 1.31 (d, 3H), 1.33 (d, 3H), 2.0 (s, 3H), 3.0, 3.07 (2 × s, 3H), 3.46 (br, 2H), 3.84 (m, 2H), 7.05 (m, 1H), 7.17 (s, 1H), 7.27 (m, 7H); ^{13}C NMR ($CDCl_3$) δ: 151.6, 146.1, 144.5, 128.7, 128.1, 127.7, 126.5, 124.4, 120.9, 119.9, 59.3, 58.9, 44.0, 32.9, 18.5, 18.2; MS (ESI) m/z: 341.2 (M + 1).

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Step D: (*S*)-*N*-Ethyl-*N*-methyl-3-[1-(methylamino)ethyl]-phenyl Carbamate (6)

Compound **5** from step C was dissolved in 200 ml methanol, and hydrogenolysis was carried out in the presence of 10% Pd/C (0.7 g) under 10 atm at 60°C. After 12 h, the catalyst was filtered out, and the filtrate was evaporated under reduced pressure to yield 10.92 g **6** as oil (92.7% HPLC purity), which was used directly in the next step. $[\alpha]_D^{20} = -32.7°$ (*c* 1.0, EtOH).

^{1}H NMR ($CDCl_3$) δ: 1.21 (br, 3H), 1.40 (d, 3H), 2.32 (s, 3H), 2.99, 3.05 (2 × s, 3H), 3.45 (br, 2H), 3.68 (q, 1H), 7.01 (d, 1H), 7.09 (s, 1H), 7.14 (d, 1H), 7.30 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 151.7, 146.3, 128.9, 123.2, 120.2, 119.8, 59.8, 43.9, 34.1, 23.3; MS (ESI) m/z: 237.1 (M + 1).

Step E: (*S*)-*N*-Ethyl-*N*-methyl-3-[1-(dimethylamino)ethyl]-phenyl Carbamate (7)

To compound **6** from step D, 98% aqueous formic acid solution (7.36 g, 156 mmol) followed by 37% aqueous formaldehyde solution (6.36 g, 78.4 mmol) were added. The reaction mixture was heated to reflux for 4 h. After cooling to room temperature, 70 ml water was added. The solution was neutralized with Na_2CO_3 and extracted with ethyl acetate (80 ml × 3). The combined organic layer was washed with 20 ml water and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure, and the crude product was vacuum distilled. Compound **7** (7.49 g, 76.4%, 99.2% HPLC purity) as a viscous oil was collected at 130–135°C/35 Pa. $[\alpha]_D^{20} = -32.1°$ (*c* 5.0, EtOH) (lit. $[\alpha]_D^{20} = -32.1°$[2]).

^{1}H NMR ($CDCl_3$) δ: 1.22 (m, 3H), 1.34 (d, 3H), 2.19 (s, 6H), 2.99, 3.04 (2 × s, 3H), 3.25 (q, 1H), 3.44 (br, 2H), 6.99–7.12 (m, 3H), 7.27

(m, 1H); ^{13}C NMR ($CDCl_3$) δ: 154.1, 151.3, 145.5, 128.4, 123.7, 120.3, 119.8, 65.2, 43.7, 42.8, 33.7, 19.6, 12.8; MS (ESI) m/z: 251.1 (M + 1), 283.2 (M + 1 + CH_3OH).

Step F: Rivastigmine (1)

L-(+)-Tartaric acid (2.83 g, 18.9 mmol) was added to **7** (4.72 g, 18.9 mmol) in 30 ml acetone. The mixture was heated to reflux for 1 h and left to cool to room temperature. It crystallized at 0°C for 12 h. The precipitated white crystalline product was sucked off, washed with cold acetone, and vacuum dried at 40°C. Finally, 6.4 g (84.8% yield, 99.8% HPLC purity) of the desired product were obtained. Mp 123–124°C (lit. 123–125°C[2]), $[\alpha]_D^{20} = +6.0°$ (*c* 5.0, EtOH) (lit. $[\alpha]_D^{20} = +4.7°$[2]).

IR (KBr), cm^{-1}: 3319.2, 2977.9, 2934.2, 2874.8, 1714.5, 1595.9; ^{1}H NMR ($CDCl_3$) δ: 1.17, 1.23 (2 × t, 3H), 1.68 (d, 3H), 2.65 (s, 6H), 2.96, 3.06 (2 × s, 3H), 3.38, 3.46 (2 × q, 2H), 4.36 (q, 1H), 4.47 (s, 2H), 7.14 (t, 1H),7.21 (s, 1H), 7.28 (t, 1H), 7.39 (t, 1H), 8.42 (br, 4H); ^{13}C NMR ($CDCl_3$) δ 176.2, 154.3, 154.1, 151.8, 135.1, 130.0, 126.1, 123.1, 122.7, 72.5, 65.0, 44.2, 40.3, 34.2, 33.9, 16.5, 13.2, 12.4; MS (ESI) m/z: 251.08 (M + 1). Anal. calcd. for $C_{18}H_{28}N_2O_8$: C, 53.99; H, 7.05; N, 7.0. Found: C, 53.91; H, 7.08; N, 6.93.

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