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Asymmetric synthesis of L-DOPA and (*R*)-selegiline via, OsO_4-catalyzed asymmetric dihydroxylation

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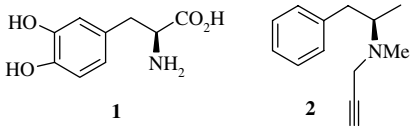
Abstract—A simple and effective procedure for the enantioselective synthesis of two important neurotransmitter drugs, that is, (*S*)-3,4-dihydroxyphenylalanine (L-DOPA) and (*R*)-*N*,α-dimethyl-*N*-2-propynylbenzeneethaneamine [(*R*)-selegiline], is described by employing the Sharpless asymmetric dihydroxylation (AD) as a key step to introduce chirality.

1. Introduction

(*S*)-3,4-Dihydroxyphenylalanine **1** (L-DOPA) is a potent neurotransmitter normally administered to patients suffering from Parkinson's disease.[1] Additionally, (*R*)-*N*,α-dimethyl-*N*-2-propynylbenzeneethaneamine **2** (selegiline), a selective, irreversible inhibitor of monoamineoxidase-B, is widely used, along with L-DOPA, in the treatment of Parkinson's disease as well as Alzheimer's disease[2] (Fig. 1). Subsequent studies have shown that (*R*)-selegiline **2** is quite effective in the treatment of Parkinson's disease as well as Alzheimer's disease when compared to racemic selegiline.[3] While several methods are available for the synthesis of racemic selegiline,[4] scant attention[5] has been given to the enantioselective synthesis of (*R*)-selegiline **2**.



1 **2**

Figure 1.

Most of the literature methods for obtaining **1** and **2** involve either classical resolution of racemic DOPA,[6] oxidation of L-tyrosine[7] or catalytic asymmetric hydrogenation of α-acylamidoacrylic acid.[8] Furthermore, these methods suffer from disadvantages such as low overall yields, the need for separation of diastereomers and the use of expensive chiral catalysts. Herein we report a short and effective procedure for the synthesis of L-DOPA **1** and (*R*)-selegiline **2** in a high enantiomeric excess from easily available starting materials.

2. Results and discussion

Since no practical methods are available for the catalytic asymmetric aziridination of olefins, chiral aziridines have often been made from chiral pool materials involving several steps.[9] Furthermore, the ring opening of chiral aziridines with nucleophiles constitutes a general method for the synthesis of optically active amines.[10] Recently, the catalytic asymmetric dihydroxylation (AD) reaction of olefins using dihydroquinidine or dihydroquinine derivatives as ligands has emerged as a useful and reliable transformation in organic synthesis.[11] We employed the AD reaction in our strategy, coupled with a reductive ring opening of aziridines for the synthesis of L-DOPA **1** and (*R*)-seligiline **2** (Schemes 1 and 2). Accordingly, the key intermediates, 3-phenylaziridine-2-carboxylic ester **7**, and (2*R*,3*R*)-2-methyl-3-phenylaziridine **12** were prepared from the corresponding olefins by employing an AD reaction. Thus, β-methyl styrene and α,β-unsaturated ester **3** were subjected to an AD reaction in the presence of catalytic amount of OsO_4 and hydroquinine-1,4-phthalazinediyl diether [$(DHQ)_2$–PHAL] as the chiral ligand to give chiral diols **4** and **9** in excellent enantiomeric excess. The vicinal diols **4** and **9** on treatment with $SOCl_2$ in presence of Et_3N in CH_2Cl_2 at 0 °C gave the corresponding cyclic sulfites **5** and **10**, respectively, as diastereomeric mixtures in a 1:1 ratio. Several attempts to oxidize

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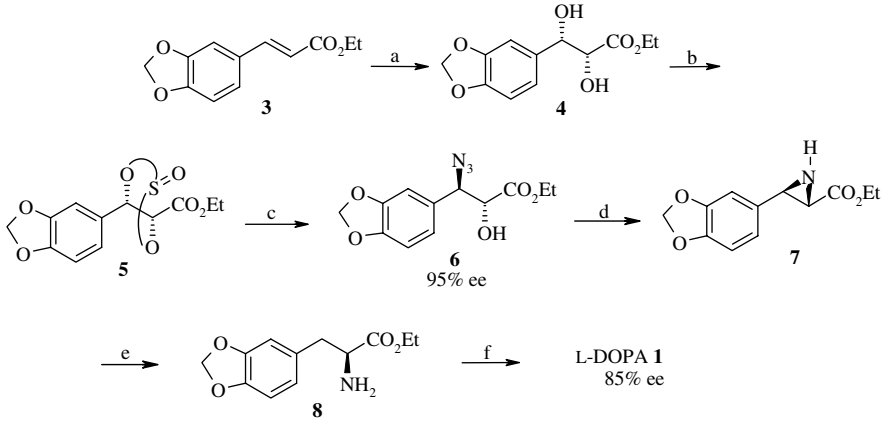
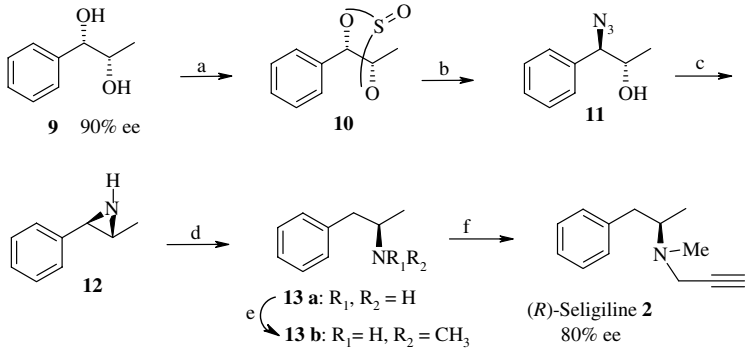


Scheme 1. Reagents and conditions: (a) cat. OsO_4, $(DHQ)_2$–PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH–H_2O, 0 °C, 85%; (b) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 88%; (c) NaN_3, acetone–H_2O, 80 °C, 82% yield, 95% ee; (d) PPh_3, CH_3CN, 90%; (e) 10% Pd/C, HCO_2NH_4, MeOH, reflux, 92%; (f) 6 M HCl, PhOH, AcOH, 130–135 °C, 24 h, 70% yield, 85% ee.



Scheme 2. Reagents and conditions: (a) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 85%; (b) NaN_3, acetone–H_2O, 80 °C, 82%; (c) PPh_3, CH_3CN, 90%; (d) Pd–C (10%), HCO_2NH_4, MeOH, reflux, 88% yield, 83% ee; (e) i. $ClCO_2CH_3$, CH_2Cl_2, aq K_2CO_3, 45 min, 90%, ii. $LiAlH_4$, dry THF, 65 °C, 4 h, 65% yield, 83% ee; (f) propargyl bromide, K_2CO_3, CH_3CN, rt to 80 °C, 72% yield, 80% ee.

cyclic sulfites **5** and **10** to the corresponding cyclic sulfates were unsuccessful, possibly due to the formation of several by-products, which were difficult to isolate. However, when cyclic sulfites **5** and **10** were treated with sodium azide (DMF, 80 °C), the corresponding azido alcohols **6** and **11** were obtained in excellent yields.[12] The enantiomeric excess of azido alcohols **6** and **11** was determined by ^1H and ^{19}F NMR of their corresponding Mosher esters. Azido alcohols **6** and **11** were then treated with triphenylphosphine in acetonitrile to give chiral aziridines **7** and **12** in excellent yields.[13] Aziridines **7** and **12** underwent stereospecific and regioselective ring opening at the benzylic position by subjecting them to Pd-catalyzed reductive ring opening with ammonium formate as the hydrogen source to produce amines **8** and **13a** in excellent yields. Finally, aminoester **8** on treatment with 6 M HCl, PhOH, AcOH, 130–135 °C, directly afforded L-DOPA, **1**, in 70% yield and 85% ee {$[\alpha]_D = -11.0$ (*c* 1.0, 1 M HCl); lit.[8a] $[\alpha]_D = -12.3$ (*c* 1.0, 1 M HCl)}.

Similarly, **13a** was transformed into (*R*)-selegiline **2** in two steps by following the literature method.[14] Yield 72% and ee 80% {$[\alpha]_D$ −9.0 (*c* 6.5, EtOH); lit.[15] $[\alpha]_D$ −10.8 (*c* 6.4, EtOH)}. The spectral data of the synthetic materials **1** and **2** agreed well with the reported values.

3. Conclusion

In conclusion, we have provided an effective procedure for the enantioselective synthesis of two important drugs namely, L-DOPA **1** (29.4% overall yield, 85% ee) and (*R*)-selegiline **2** (17.54% overall yield, 80% ee) from easily available starting materials. In this approach, the key intermediates, chiral aziridines **7** and **12** were prepared from the corresponding olefins by employing the asymmetric dihydroxylation reaction.

4. Experimental

4.1. General information

Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60–80 °C was used. Melting points are uncorrected. Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. Infrared spectra were recorded on an Shimadzu FTIR-8400 spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on Brucker AC-200 and MSL-300 NMR spectrometers, respectively. Mass spectra were obtained with a Finnigan MAT-1020 B-70 eV mass spectrometer. Elemental analyses

were carried on a Carlo Erba CHNS-O analyzer. Enantiomeric excesses were determined by Mosher's agent data by using chiral shift reagents.

4.2. Preparation of ethyl (2*R*,3*S*)-2,3-dihydroxy-3-(3,4-methylenedioxylphenyl)propionate 4

A double-walled 250 mL RB flask was charged with K_3FeCN_6 (8.94 g, 27.2 mmol), K_2CO_3 (3.75 g, 27.2 mmol), $(DHQ)_2$–PHAL (140 mg, 0.18 mmol), $MeSO_2NH_2$ (0.855 g, 9.0 mmol) and *t*-BuOH–H_2O (1:1, v/v, 90 mL) and stirred for 5 min at 25 °C. It was then cooled to 0 °C and a solution of OsO_4 (184 μL, 0.09 mmol, 0.5 M solution in toluene) added followed by cinnamate **3** (2.0 g, 9.0 mmol). The reaction mixture was stirred for 24 h at 25 °C (monitored by TLC). The reaction was then quenched with sodium sulfite (10 g) and extracted with ethyl acetate (3 × 60 mL). The organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using EtOAc–pet. ether (1:1) as eluent to yield 1.95 g of **4**. Yield: 85%; gum; $[\alpha]_D^{25} = +4.0$ (*c* 0.6, $CHCl_3$), IR ($CHCl_3$, cm^{-1}): 3552, 2400, 1731, 1530, 1444, 1215, 1041, 930, 757; ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, $J = 8.0$ Hz, 3H), 2.90 (br s, 1H), 3.75 (br s, 1H), 4.21–4.33 (m, 3H), 4.90 (d, $J = 4.0$ Hz, 1H), 5.96 (s, 2H), 6.75–7.00 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.00, 62.00, 74.35, 74.87, 101.00, 106.99, 107.99, 119.79, 133.94, 147.69, 155.48, 172.53; MS *m/z* (% RI): 254 (M^+, 5), 220 (4), 175 (4), 166 (10), 165 (12), 151 (100), 150 (25), 135 (6), 123 (11), 121 (10), 104 (4), 93 (45), 67 (10), 65 (28), 63 (14). Analysis: $C_{12}H_{14}O_6$ requires C, 56.69; H, 5.54; found C, 56.71; H, 5.50%.

4.3. Preparation of ethyl (4*R*,5*S*)-4-carbethoxy-5-(3,4-methylenedioxylphenyl)-1,3,2-dioxathiolane-2-oxide 5

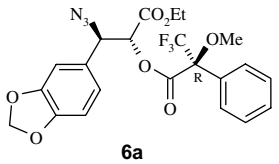
Diol **4** (1.90 g, 7.48 mmol) was dissolved in triethylamine (20 mL) and cooled to 0 °C in an ice bath under an argon atmosphere. Freshly distilled thionyl chloride (1.33 g, 0.81 mL, 11.2 mmol) was added dropwise and the reaction mixture stirred at 0 °C for 45 min (monitored by TLC). After completion of the reaction, ice-cold water (25 mL) was added and extracted with ether (3 × 25 mL). The ethereal layer was washed with 10% HCl, saturated sodium bicarbonate solution and brine, successively. The ether extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography using pet. ether–EtOAc (9:1) as eluent to furnish sulfite **5** as light yellow oil (1.97 g). Yield: 88%; brown liquid; $[\alpha]_D^{25} = -100.0$ (*c* 2.3, EtOH); IR ($CHCl_3$, cm^{-1}): 3448, 3020, 2900, 1735, 1488, 1446, 1251, 1215, 1041, 757; ^1H NMR (200 MHz, $CDCl_3$): δ 1.20–1.45 (m, 3H), 4.20–4.45 (m, 2H), 4.69 and 5.08 (2d, $J = 8.0$ Hz each, 1H), 5.18 and 5.40 (2d, $J = 10.0$ Hz each, 1H), 5.97–6.00 (2s, 2H), 6.38 (d, $J = 10.0$ Hz, 1H), 6.75–7.25 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.85, 62.74, 81.30, 82.44, 83.21, 88.81, 101.26, 102.55, 115.77, 128.09, 128.90, 129.12, 132.43, 132.96, 135.52, 135.70, 166.62; MS *m/z* (% RI): 292 (5), 236 (14), 208 (4), 179 (12), 162 (100), 149 (12), 135 (85), 134 (62), 121 (5), 93 (12), 92 (10), 77 (40), 76 (35), 63 (13). Analysis: $C_{12}H_{12}SO_7$ requires C, 48.00; H, 4.02; found C, 48.05; H, 4.08%.

4.4. Preparation of ethyl (2*R*,3*R*)-3-azido-2-hydroxy-3-(3,4-methylenedioxylphenyl)propionate 6

To a stirred solution of cyclic sulfite **5** (1.85 g, 6.16 mmol) in DMF (5 mL) was added sodium azide (0.16 g, 24.6 mmol). The reaction flask was then heated to 80 °C for 6 h. After completion of the reaction, as monitored by TLC, the reaction mixture was poured into water (25 mL), and then extracted with ether (3 × 25 mL). The combined organic phases were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude azido-alcohol was then purified with silica gel chromatography eluted with pet. ether–EtOAc (9:1) to give azido alcohol **6** (1.63 g). Yield: 95%; gum; $[\alpha]_D^{25} = -65.0$ (*c* 0.8, EtOH); IR ($CHCl_3$, cm^{-1}): 3415, 3020, 2108, 1735, 1504, 1488, 1444, 1225, 1215, 1041, 757; ^1H NMR (200 MHz, $CDCl_3$): δ 1.25 (t, $J = 6.0$ Hz, 3H), 2.45 (br s, 1H), 4.10–4.30 (q, $J = 6.0$ Hz, 2H), 4.48 (d, $J = 6.0$ Hz, 1H), 4.80 (d, $J = 4.0$ Hz, 1H), 5.99 (s, 2H), 6.79 (s, 2H), 6.91 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.00, 62.11, 66.89, 73.62, 101.26, 108.10, 108.28, 121.70, 128.60, 147.91, 148.01, 171.28; MS *m/z* (% RI): 279 (M^+, 4), 176 (15), 164 (6), 149 (20), 148 (100), 135 (13), 121 (60), 105 (3), 92 (7), 90 (12), 76 (14), 65 (43), 63 (24). Analysis: $C_{12}H_{13}N_3O_5$ requires C, 51.61; H, 4.68; N, 15.04; found C, 51.66; H, 4.65; N, 15.10%.

4.5. Preparation of Mosher ester of azido alcohol 6a

A two-neck 25 mL flask with septum was charged with (44 mg, 0.206 mmol) *N*,*N*′-dicyclohexylcarbodiimide (DCC), catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (5 mL) under an argon atmosphere. The flask was allowed to cool at 0 °C for 10 min and a solution of azido alcohol **6** (50 mg, 0.179 mmol) in CH_2Cl_2 (5 mL) then introduced through a syringe. It was allowed to stir for an additional 10 min, followed by the dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (46 mg, 0.196 mmol) in CH_2Cl_2 was done. This reaction mixture was then stirred at 0 °C for an additional hour and then at room temperature overnight. The solvent was evaporated under reduced pressure to give the crude material, which was then purified by column chromatography eluting with 5% ethyl acetate in pet. ether to get Mosher ester of azido alcohol **6a** (85 mg).



6a

Yield: 89%; ^1H NMR (200 MHz, $CDCl_3$): δ 1.23 (t, $J = 8.0$ Hz, 3H), 3.45 (s, 0.15H), 3.61 (s, 2.85H), 4.18

(q, $J = 8.0$ Hz, 2H), 4.93 (s, 1H), 5.42 (s, 1H), 5.96 (s, 2H), 6.55–6.70 (m, 3H), 7.15–7.60 (m, 5H).

4.6. Preparation of ethyl (2*S*,3*R*)-3-(3,4-methylenedioxylphenyl)aziridine-2-carboxylate 7

To a stirred solution of azido alcohol **6** (1.0 g, 3.58 mmol) in acetonitrile (30 mL) was added PPh_3 (0.937 g, 3.58 mmol). The reaction mixture was then stirred at 25 °C for 1 h and then it was refluxed for 6 h. After completion of reaction (monitored by TLC) the solvent was removed under reduced pressure to get crude aziridine. The pure product was isolated by silica gel chromatography eluted with pet. ether–EtOAc (9:1) to give aziridine **7** (0.757 g). Yield: 90%; gum; $[\alpha]_D^{25} = +176.2$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3288, 3020, 2896, 2770, 2401, 1722, 1608, 1504, 1500, 1448, 1365, 1320, 1215, 1120, 1041, 939, 757, 680; ^1H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, $J = 6.0$ Hz, 3H), 2.16 (s, 1H), 2.50 (br s, 1H), 3.18 (br s, 1H), 4.15–4.35 (q, $J = 6.0$ Hz, 2H), 5.93 (s, 2H), 6.65–6.85 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.07, 39.21, 40.17, 61.64, 100.97, 106.08, 108.06, 119.90, 131.81, 147.17, 147.87, 171.58; MS *m*/*z* (% RI): 235 (M^+, 30), 206 (11), 163 (6), 162 (40), 149 (8), 148 (10), 135 (48), 133 (12), 104 (20), 80 (12), 77 (15), 63 (4), 60 (5), 51 (18), 32 (100). Analysis: $C_{12}H_{13}NO_4$ requires C, 61.27; H, 5.56; N, 5.95; found C, 61.22; H, 5.52; N, 5.98%.

4.7. Preparation of ethyl (*S*)-2-amino-3-(3,4-methylenedioxylphenyl)propionate 8

To a stirred solution of aziridine **7** (0.700 g, 2.97 mmol) in methanol (10 mL) was added 10% Pd/C (5 wt%) and ammonium formate (0.281 g, 4.46 mmol). The reaction flask was then heated to reflux for 4 h. After completion of the reaction, the catalyst was filtered off, and the filtrate concentrated under reduced pressure to give a residue. The residue was then purified by silica gel chromatography eluted with EtOAc to give amine **8** (0.634 g). Yield: 90%; gum; $[\alpha]_D^{25} = +7.5$ (*c* 0.6, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3381, 3019, 1735, 1684, 1503, 1489, 1035, 910, 759; ^1H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, $J = 6.0$ Hz, 3H), 2.35–2.70 (br s, 2H), 2.70–2.85 (dd, $J = 14.0$ and 8.0 Hz, 1H), 2.95–3.10 (dd, $J = 16.0$ and 14.0 Hz, 1H), 3.60–3.75 (br s, 1H), 4.10–4.25 (q, $J = 6.0$ Hz, 2H), 5.92 (s, 2H), 6.60–6.80 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.14, 40.50, 55.79, 60.94, 100.86, 108.21, 109.53, 122.36, 130.78, 146.47, 147.72, 174.30; MS *m*/*z* (% RI): 237 (M^+, 17), 220 (12), 206 (5), 165 (40), 164 (30), 149 (12), 136 (38), 135 (100), 121 (5), 106 (15), 102 (14), 91 (4), 77 (24), 69 (12). Analysis: $C_{12}H_{15}NO_4$ requires C, 60.75; H, 6.36; N, 5.90; found C, 60.70; H, 6.36; N, 5.92%.

4.8. Preparation of (*S*)-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid 1

To a 50 mL flask was added amine **8** (0.200 g, 0.84 mmol), phenol (0.236 g, 2.52 mmol), glacial acetic acid (0.151 g, 2.52 mmol) and 6 M HCl (10 mL). The reaction mixture was heated to reflux for 36 h and then concentrated to give a residue. The residue was dissolved in EtOAc and extracted with water. The aqueous layer was adjusted to pH 5 with 28% ammonia water and a trace amount of sodium bisulfate and then cooled in crushed ice to give L-DOPA **1** as white crystals (0.116 g).

Yield: 70%; mp: 298 °C; lit. mp: 295 °C; $[\alpha]_D^{25} = -11.0$ (*c* 1.0, 1 M HCl); {lit.[8a] $[\alpha]_D = -12.3$ (*c* 1.0, 1 M HCl)}; IR (KBr, cm^{-1}): 3500, 3203, 2925, 2854, 2599, 1696, 1654, 1610, 1591, 1514, 1454, 1245, 985, 840; ^1H NMR (200 MHz, D_2O, DCl): δ 3.20 (dd, $J = 6.0$ Hz, 1H), 3.50 (dd, $J = 6.0$ Hz each, 1H), 3.60 (br s, 2H) 4.45 (m, 1H), 6.80–7.05 (m, 3H), 11.8–12.6 (br s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 39.73, 60.20, 119.05, 120.20, 123.87, 128.09, 146.47, 147.43, 164.41. Analysis: $C_9H_{11}NO_4$ requires C, 54.82; H, 5.61; N, 7.10; found C, 54.80; H, 5.66; N, 7.15%.

4.9. Preparation of (4*S*,5*S*)-4-methyl-5-phenyl-1,3,2-dioxathiolane-2-oxide 10

Diol **9** (1.0 g, 6.57 mmol) was dissolved in triethylamine (20 mL) and cooled to 0 °C in an ice bath under an argon atmosphere. Freshly distilled thionyl chloride (0.938 g, 7.88 mmol) was added dropwise and the reaction mixture stirred at 0 °C for 45 min (monitored by TLC). After completion, ice-cold water (50 mL) was added and extracted with ether (3×25 mL). The ethereal layer was washed with 10% HCl, saturated sodium bicarbonate solution and brine, successively. The ether extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography using pet. ether–EtOAc (9:1) as eluent to furnish compound **10** as light yellow oil (1.1 g). Yield: 85%; gum; $[\alpha]_D = -17.1$ (*c* 1.04, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3384, 3024, 2983, 2935, 1612, 1456, 1382, 1215, 1049, 962, 860, 757; ^1H NMR (200 MHz, $CDCl_3$): δ 1.48 and 1.57 (2d, $J = 6.3$ and 5.8 Hz, 3H), 4.30–4.50 (2d, $J = 9.2$ and 6.4 Hz, 1H), 5.44 (d, $J = 9.3$ Hz, 1H), 7.35–7.55 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.88, 17.27, 80.82, 85.34, 85.71, 90.78, 126.99, 127.36, 128.94, 129.27, 129.60, 132.84, 133.64, 159.52; Mass (*m*/*z*, % RI): 198 (M^+, 4), 154 (45), 133 (4), 126 (30), 117 (8), 106 (16), 105 (95), 91 (35), 90 (26), 90 (24), 78 (70), 77 (100), 65 (14), 63 (17), 57 (5). Analysis: $C_9H_{10}SO_3$ requires C, 54.53; H, 5.07; S, 16.18; found C, 54.55; H, 5.11; S, 16.13%.

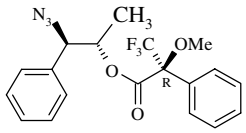
4.10. Preparation of (1*R*,2*S*)-1-azido-1-phenylpropane-2-ol 11

To a stirred solution of cyclic sulfite **10** (0.9 g, 4.54 mmol) in DMF (5 mL) was added sodium azide (1.18 g, 18.18 mmol). The reaction flask was then heated to 80 °C for 6 h. After completion of the reaction, as monitored by TLC, the reaction mixture was poured in 25 mL of water, and then extracted with ether (3×25 mL). The combined organic phases were washed with brine, dried over anhydrous sodium sulfate and concentrated. The crude azidoalcohol was then purified with silica gel chromatography eluted with pet. ether–EtOAc (9:1) to give azido alcohol **11** (0.680 g). Yield: 82%; gum; $[\alpha]_D = -228.16$ (*c* 1.2, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3019, 2855, 2106, 1600, 1525, 1430, 1215, 1120,

1065, 930, 669; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.18 (d, J = 6.4 Hz, 3H), 1.65–1.90 (br s, 1H), 3.90–4.05 (m, 1H), 4.47 (d, J = 5.4 Hz, 1H), 7.30–7.50 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.30, 70.35, 71.27, 127.65, 128.35, 128.57, 136.18; Mass (*m/z*, % RI): 177 (M^+, 4), 159 (15), 131 (13), 115 (10), 105 (56), 104 (58), 103 (24), 91 (14), 77 (100), 63 (17). Analysis: $C_9H_{11}N_3O$ requires C, 61.00; H, 6.83; N, 23.71; found C, 61.05; H, 6.85; N, 23.68%.

4.11. Preparation of Mosher ester of azido alcohol 11a

A two-neck 25 mL flask with septum was charged with (44 mg, 0.206 mmol) *N*,*N*′-dicyclohexylcarbodiimide (DCC), a catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (5 mL) under an argon atmosphere. The flask was allowed to cool at 0 °C for 10 min and a solution of azido alcohol **6** (32 mg, 0.180 mmol) in CH_2Cl_2 (5 mL) introduced through syringe. It was allowed to stir for an additional 10 min, followed by dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (31 mg, 0.196 mmol) in CH_2Cl_2. This reaction mixture was then stirred at 0 °C for an additional hour and then at room temperature overnight. The solvent was evaporated under reduced pressure to give the crude material, which was then purified by column chromatography eluting with 7% ethyl acetate in pet. ether to give the Mosher ester of azido alcohol **6a**.



11a

Yield: 90%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.18 (d, J = 6.4 Hz, 3H), 3.48 (s, 0.15H), 3.65 (s, 2.85H), 3.90–4.05 (m, 1H), 4.47 (d, J = 5.4 Hz, 1H), 7.25–7.55 (m, 10H).

4.12. Preparation of (2*R*,3*R*)-2-methyl-3-phenylaziridine 12

To a stirred solution of azido alcohol **11** (0.650 g, 3.67 mmol) in 25 mL of acetonitrile was added PPh_3 (0.962 g, 3.67mmol). The reaction mixture was then stirred at room temperature for 1 h and then refluxed for 6 h. After completion of the reaction as monitored by TLC, the solvent was removed under reduced pressure to give crude aziridine. The pure product was then isolated by silica gel chromatography eluted with pet. ether–EtOAc (9:1) to give aziridine **12** (0.440 g). Yield: 90%; gum; $[\alpha]_D$ = +58.5 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3285, 2890, 2395, 1608, 1504, 1500, 1470, 1380, 1320, 1215, 1120, 1041, 939, 790, 680; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 (d, J = 5.4 Hz, 3H), 1.90–2.15 (m, 2H), 2.54 (d, J = 2.9 Hz, 1H), 7.00–7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.36, 36.82, 40.28, 125.37, 126.73, 128.24, 140.26. Analysis: $C_9H_{11}N$ requires C, 81.16; H, 8.31; N, 10.51; found C, 81.20; H, 8.35; N, 10.51%.

4.13. Preparation of (*R*)-2-amino-1-phenylpropane 13a

To a stirred solution of aziridine **12**, (0.400 g, 3.0 mmol) in 10 mL of methanol was added Pd–C (10%) and ammonium formate (0.378 g, 6.00 mmol). The reaction flask was then heated to reflux for 4 h. After completion of the reaction, the catalyst was filtered off, and the filtrate concentrated under reduced pressure to give a residue. The residue was then purified by silica gel chromatography eluted with EtOAc to give amine **13a** (0.336 g).

Yield: 88%; mp: gum; $[\alpha]_D$ = −25.6 (*c* 2.0, MeOH); lit.[16] $[\alpha]_D$ = −30.2 (*c* 2.5, MeOH); IR ($CHCl_3$, cm^{-1}): 3415, 3055, 3010, 2995, 1650, 1505, 1435, 1400, 1195, 1100, 1090, 870, 810, 750, 700; ^{1}H NMR (200 MHz, $CDCl_3$ + CD_3OD): δ 1.20 (d, J = 6.40 Hz, 3H), 2.65–2.80 (dd, J = 8.30 and 8.80 Hz, 1H), 2.80–2.90 (br s, 2H), 2.90–3.05 (dd, J = 5.80 Hz each, 1H), 3.40–3.50 (m, 1H), 7.10–7.40 (m, 5H); ^{13}C NMR (50 MHz, CD_3OD): δ 18.28, 41.74, 50.37, 128.34, 129.96, 130.43, 137.20. Analysis: $C_9H_{13}N$ requires C, 79.95; H, 9.68; N, 10.36; found C, 79.91; H, 9.68; N, 10.39%.

4.14. Preparation of (*R*)-2-methylamino-1-phenylpropane 13b

A 25 mL dry flask was charged with amine **13a** (0.300 g, 2.22 mmol) in dry CH_2Cl_2 (8 mL). To this was added methylchloroformate (0.263 g, 0.21 mL, 2.77 mmol) and the reaction flask stirred vigorously. To this vigorously stirred mixture was added K_2CO_3 (1.531 g, 11.10 mmol) in H_2O (8 mL) over a period of 5 min and then stirring continued. After completion of the reaction as indicated by the TLC, the reaction mixture was extracted with CH_2Cl_2, and the solvent evaporated under reduced pressure to give the crude carbamate.

To a solution of lithium aluminum hydride (0.126 g, 3.33 mmol) in dry THF (15 mL) under a nitrogen atmosphere at room temperature was added dropwise a solution of carbamate in dry THF. The reaction flask was then heated under reflux for 2 h. After completion of the reaction the reaction mixture was cooled to room temperature and ethyl acetate slowly added. The reaction mixture was then filtered and the filtrate evaporated under reduced pressure to give a residue, which was purified by column chromatography to yield 0.215 g of amine **13b**. Yield: 65%; mp: 38–40 °C; $[\alpha]_D$ = −8.1 (*c* 0.8, EtOH); lit.[14] $[\alpha]_D$ = −10.9 (*c* 0.8, EtOH); IR ($CHCl_3$, cm^{-1}): ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (d, J = 8.0 Hz, 3H), 1.50 (s, 1H), 2.25 (s, 3H), 2.65–2.95 (m, 3H), 7.20–7.60 (m, 5H); Mass (*m/z*, % RI): 149 (M^+, 4), 134 (10), 119 (5), 117 (5), 91 (45), 65 (16), 58 (100). Analysis: requires $C_{10}H_{15}N$ requires C, 80.49; H, 10.12; N, 9.38; found C, 80.41; H, 10.12; N, 9.45%.

4.15. Preparation of (*R*)-*N*,α-dimethyl-*N*-2-propynylbenzeneethaneamine; (*R*)-selegiline 2

To a stirred solution of (*R*)-2-(methylamino)-1-phenylpropane **13b**, (0.200 g, 1.34 mmol) in acetonitrile (10 mL) was added K_2CO_3 (0.277 g, 2.01 mmol) and

propargyl bromide (0.478 g, 0.36 mL, 4.02 mmol). The reaction mixture was then allowed to stir at room temperature overnight until all the starting material had disappeared. The reaction mixture was then extracted with 5% HCl (5 × 10 mL), made alkaline to give an oil, to give 0.215 g of I-selegiline **1b** in 72% yield. Yield: 72%; gum; $[\alpha]_D = -9.0$ (*c* 6.5, EtOH); lit.[15] $[\alpha]_D = -10.8$ (*c* 6.48, EtOH); IR ($CHCl_3$, cm^{-1}): ^1H NMR (200 MHz, $CDCl_3$): δ 0.95 (d, $J = 6.0$ Hz, 3H), 2.25 (t, $J = 2.0$ Hz, 1H), 2.35 (s, 1H), 2.40–2.55 (m, 3H), 2.80–3.10 (m, 2H), 3.40 (d, $J = 2.0$ Hz, 2H), 7.00–7.50 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.1, 31.4, 46.8, 51.90, 60.8, 68.1, 82.2, 125.6, 128.3, 128.6, 140.2; Mass (*m*/*z*, % RI): analysis: requires $C_{13}H_{17}N$ requires C, 83.37; H, 9.14; N, 7.47; found C, 83.34; H, 9.11; N, 7.53%.

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