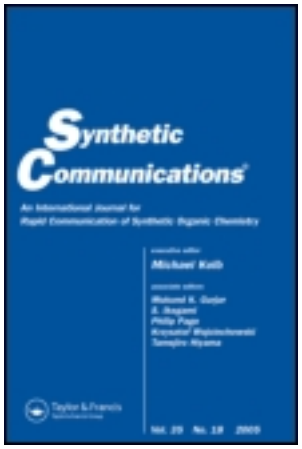

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GENERAL STRATEGY FOR LARGE-SCALE SYNTHESIS OF (+)-RIVASTIGMINE AND (+)-NPS R-568

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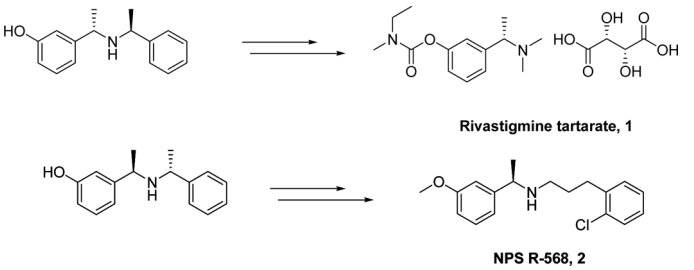
GRAPHICAL ABSTRACT



Abstract *An economically viable strategy for the total synthesis of (+)-rivastigmine and (+)-NPS R-568 has been reported. The strategy involves regioselective hydrogenation of diastereomerically pure bis amine to realize the desired α-methyl chiral substituted benzyl amine. The route is economical, scalable, and versatile enough to be adapted to similar classes of compounds.*

Keywords (*R*)-(+)-1-Phenylethylamine; (*S*)-(−)-1-phenylethylamine; titanium tetra isopropoxide

INTRODUCTION

A specific stereoisomer of a pharmaceutical drug having one or more stereogenic center tends to be responsible for the biological activity. In some cases, the other isomer could cause damaging side effects.[1] The therapeutic inactive isomer is regarded as an impurity that possesses different or undesirable pharmacological

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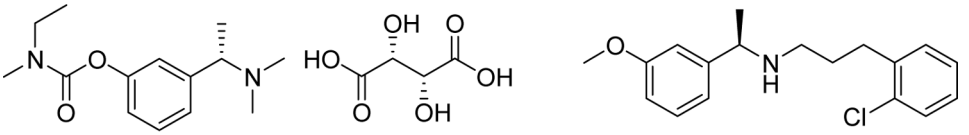


Rivastigmine tartarate, 1 **NPS R-568, 2**

Figure 1. Rivastigmine tartarate and NPS R-568.

activity. This situation may become even more acute if the active enantiomer exhibits a low therapeutic value or there is clinically significant toxicity. A well-known example of a therapeutic specific pair is *R* and *S* enantiomers of thalidomide, wherein the *R* enantiomer is an effective sedative and the *S* enantiomer is teratogenic. Such biological responses and the need to reduce chemical and metabolic waste necessitates better and more efficient synthesis of the single required drug isomers. The drug rivastigmine, which is currently being used for the treatment of dementia, was found to display a 10-fold greater affinity for brain monomeric G protein over the peripheral form of the enzyme.[2] It also shows dual inhibitory action on both AchE and BchE and was found to demonstrate broad benefits across the severity of Alzheimer's disease. We optimized the synthesis of rivastigmine, using an asymmetric induction method, and patented this in 2005.[3] Our continued interest in this chiral induction methodology led us to synthesize (+)-NPS R-568. Calcimimetic (+)-NPS R-568 has been found to activate the calcium-sensing receptors and has a great potential as an innovative medical approach for the treatment of primary and secondary hyperparathyroidism.[4] Both of these molecules have one stereo center having an α-methyl substituted chiral benzyl amine. Several research groups have developed asymmetric syntheses and resolution strategies to prepare these molecules.[5,6] Recently, Khair et al.[7] have shown the importance of *N*-isopropylsulfinylimines as useful intermediates in the synthesis of chiral amines for the synthesis of (+)-NPS R-568. However, the majority of the synthetic routes involve resolution and separation stages or multistep operations. We wanted to explore the scope and plausibility to develop a commercially viable manufacturing process for making these compounds enantiomerically pure while avoiding tedious resolution and recycling of the wrong isomer.

We herein report the synthesis of substituted α-methyl chiral benzyl amine derivatives and extension of this approach for the total synthesis of (+)-rivastigmine and (+)-calcimimetic NPS R-568 (Fig. 1).

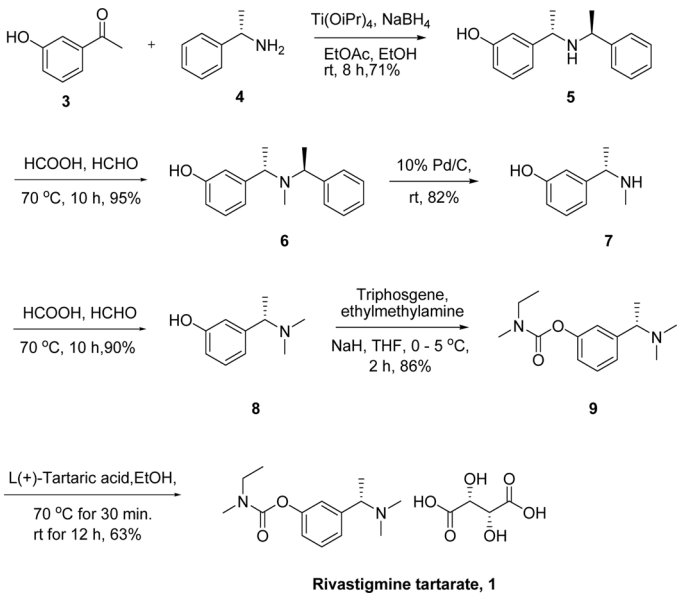
RESULTS AND DISCUSSION

Recently, Ishii et al.[8] have demonstrated the regioselective hydrogenolysis of bis(α-methylbenzyl)amine derivatives and found that the regioselectivity arises because of steric effects and is not governed by electronic effects. We envisaged that a similar approach could be used efficiently to provide the desired α-methyl chiral substituted benzyl amines with high enantioselectivity. Thus, the diastereomerically

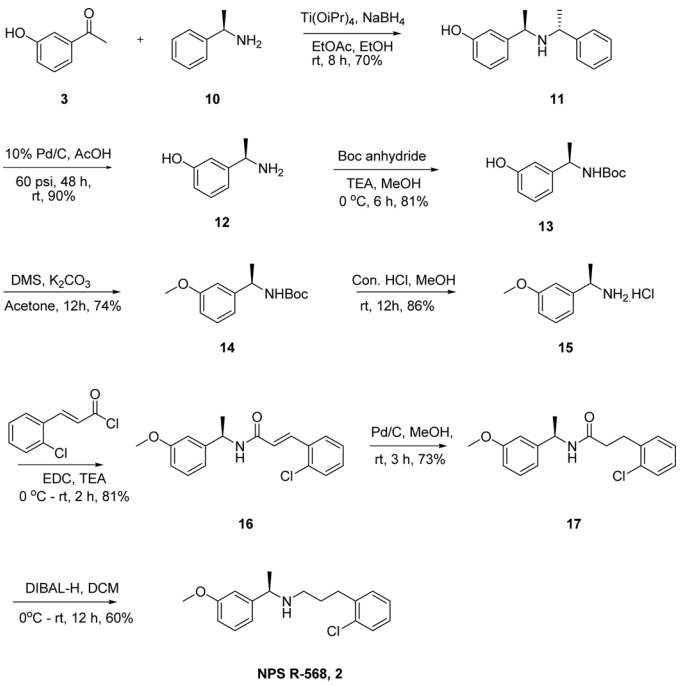
pure bis amine **5** obtained by reductive amination of 3′-hydroxyacetophenone **3** and commercially available (*S*)-(−)-1-phenylethylamine **4** can be regioselectively cleaved to yield the required chiral substituted benzyl amine **6**, which can be utilized as a key intermediate for the synthesis of rivastigmine.

To complete the synthesis of rivastigmine using this strategy, we began with the reductive amination of 3′-hydroxyacetophenone and (*S*)-(−)-1-phenylethylamine in presence of titanium(IV)isopropoxide and $NaBH_4$ to produce amine **5**. The amine **5** was methylated using formaldehyde and formic acid to get the tertiary amine **6**.[9] Regioselective hydrogenation with Pd/C in ethanol yielded the required chiral amine **7** with excellent enantioselectivity (>99%). The secondary amine **7** was again methylated following the earlier procedure to afford **8**. The phenolic functionality was treated with *N*-ethyl-*N*-methyl carbomoyl chloride to yield the carbamate **9**, which was subsequently converted to the required tartarate salt **1** using L(+)-tartaric acid (see Scheme 1).

Similarly, the bis amine **11** obtained by the reductive amination of 3′-hydroxyacetophenone and (*R*)-(+)-1-phenylethylamine was cleaved under hydrogenation conditions to yield **12** exclusively with >99% enantioselectivity. Protection of the compound **12** with di-*tert*-butyl dicarbonate gave carbamate **13** in 81% yield. The phenolic hydroxyl group was converted to the corresponding methyl ether by treatment with dimethyl sulfate and potassium carbonate in refluxing acetone to afford **14** in 74% yield. The product **14** was treated with 10 N HCl to deprotect the Boc group and yield the salt **15**. The salt **15** was treated with 2-chlorocinnamoyl chloride in the presence of dichloroethane to get the carbamate **16**. Hydrogenation of the α,β-unsaturated amide with Pd/C yielded the saturated amide **17**, which on further treatment with diisobutylaluminium hydride(DIBAL)-H) gave the required



Scheme 1. Synthesis of rivastigmine tartarate.



Scheme 2. Synthesis of NPS R-568.

target (+)-NPS R-568 **2**. The product was compared with the earlier reported analytical data and was found to be identical (see Scheme 2).

CONCLUSION

In conclusion, a commercially viable route for the total synthesis of rivastigmine and (+)-NPS R-568 has been developed utilizing a simple reductive amination followed by regioselective hydrogenation of the bis amines. Further extension of this strategy for the synthesis of other biologically active molecules is currently being investigated.

EXPERIMENTAL

The reactions were carried out under an N_2 atmosphere in anhydrous solvents such as CH_2Cl_2, tetrahydrofuran (THF), and EtOAc. THF was freshly distilled over benzophenone prior to use. All reactions were monitored by thin-layer chromatography (TLC; silica-coated plates and visualized under ultraviolet light). Yields refer to isolated yields. Air-sensitive reagents were transferred by a syringe or a double-ended needle. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Brucker Avance 300 spectrometer. Chemical shifts are reported relative to tetramethylsilane (TMS) as an internal standard. Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. TLC

was performed on Merck 60 F-254 silica-gel plates. Optical rotations were recorded on a Jasco P-1020 wavelen($M^+ + H$). HRMS m/z calculated for gth 589 polarimeter.

3-((S)-1-((S)-1-Phenylethylamino)ethyl)phenol (5)

Titanium(IV) isopropoxide (31.20 g, 110.13 mmol, 1.5 equiv) was added to a stirred solution of 3′-hydroxyacetophenone (10 g, 73.44 mmol) and *S*-(α)-methylbenzylamine (8.89 g, 73.44 mmol, 1 equiv) in EtOAc (40 mL), and the mixture stirred for 3 h. It was cooled to 0 °C, and ethanol (100 mL) and sodium borohydride (2.77 g, 73.44 mmol, 1 equiv) were added and stirred for 3 h. The mixture was quenched at 0 °C with acetic acid (3 mL). Solvents were concentrated. Water (100 mL) and saturated Na_2CO_3 (100 mL) were added. The obtained solid was filtered and washed with water (50 mL). The solid was taken into EtOAc (50 mL), refluxed, and filtered hot. The process was repeated twice. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was taken into dichloromethane (DCM; 50 mL), stirred for 1 h, and filtered to give **5** (12.4 g, 71%) as a white solid. Mp 118.5–119 °C. $[\alpha]_D = -158$ (c 1, MeOH). ^{1}H NMR (300 MHz, DMSO): δ 1.13–1.18 (m, 6H) 3.25 (q, $J = 6.5$ Hz, 1H), 3.39 (q, $J = 6.4$, 1H), 6.58–6.45 (m, 3H), 7.03–7.08 (m, 1H), 7.17–7.29 (m, 5H). ^{13}C NMR (75 MHz, DMSO): δ 25.38, 25.47, 55.11, 113.68, 113.87, 117.55, 126.84, 126.91, 128.62, 129.52, 146.73, 148.28, 157.82. MS-ESI: m/z 242.05 ($M^+ + H$). HRMS m/z calculated for $C_{16}H_{20}NO$ 242.1539; found 242.1529. HPLC method: column: Diacel chiralcel OD-H 250 × 4.6 mm, 0.5 u, Mp: 95% n-hexane + 5% IPA + 0.1% TFA, flow rate: 0.8 ml/min, UV detection at 215 nm, sample concentration 1 mg/3 ml diluent, retention time 8.2 min.

(1S)-N-((S)-1-(3-Hydroxyphenyl)ethyl)-N-methyl-1-phenylethanamine (6)[5a]

Formaldehyde (37% in water, 50 mL) was added drop wise to a stirred solution of 3-((S)-1-((S)-1-phenylethylamino)ethyl)phenol **5** (50 g, 0.20 mol) and formic acid (47.68 g). The mixture stirred for 10 h at 70 °C and concentrated. Water (100 mL) and hexane (100 mL) were added, and layers were separated. The aqueous layer was basified with 40% NaOH solution until the pH was 7.5 and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give **6** (50 g, 95%) as a white solid, mp 98.6–99.9 °C. $[\alpha]_D = -51$ (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29–1.35 (dd, $J = 6.84$ Hz, 6H), 2.02 (s, 3H), 3.42–3.50 (bs, 1H), 3.75 (q, $J = 6.7$ Hz, 1H), 3.81–3.88 (q, $J = 6.8$ Hz, 1H), 6.70–6.73 (m, 1H), 6.90–7.16 (m, 2H), 7.19–7.37 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.70, 19.02, 33.25, 59.39, 59.71, 114.46, 115.22, 120.39, 126.89, 128.12, 128.21, 129.43, 143.45, 146.12, 155.94. MS-ESI: m/z 256.10 ($M^+ + H$).

3-[(S)-1-(Methylamino)ethyl]phenol (7)[5g]

To the solution of **6** (20 g, 78.32 mmol) in EtOH (100 mL), 10% Pd/C (2 g) was added, and the mixture was hydrogenated at 75 psi for 16 h. The catalyst was filtered, and the filtrate was concentrated. Toluene (100 mL) was added to the residue, stirred

for 30 min, and filtered to give **7** (9.3 g, 82%) as brown solid. Mp 171–173 °C. $[\alpha]_D = -67.85$ (*c* 5, pyridine). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (d, $J = 6.6$ Hz, 3H), 2.30–2.32 (s, 3H), 3.58–3.64 (q, $J = 6.4$ Hz, 1H), 6.70–6.73 (m, 1H), 6.82–6.84 (m, 2H), 7.15–7.25(m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.67, 32.95, 58.46, 112.06, 112.29, 115.88, 127.62, 145.89, 156.07. MS-ESI: m/z 152, ($M^+ + H$).

3-[(S)-(Dimethyl Amino)ethyl]phenol (8)[5c]

Formaldehyde (37% in water, 16.1 mL) was added dropwise to a stirred solution of **7** (10 g, 66 mmol) in formic acid (12.7 mL). The mixture was stirred for 3 h at 70 °C and concentrated. Water (75 mL) and EtOAc (75 mL) were added, and the layers were separated. The aqueous layer was basified with 40% NaOH solution until the pH was 8 and extracted with EtOAc (3 × 50 ml). The combined organic layers were dried over Na_2SO_4 and concentrated to give **8** (9.7 g, 90%) as a white solid. Mp 102–112 °C. $[\alpha]_D = -49$ (*c* 5, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37–1.39 (d, $J = 6.7$ Hz, 3H), 2.23 (s, 6H), 3.26–3.32 (q, $J = 6.7$ Hz, 1H), 6.69–6.79 (m, 3H), 7.11–7.16 (m, 1H), 7.2–7.4 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.08, 42.49, 65.61, 115.23, 115.82, 119.38, 129.36, 142.93, 157.23. MS-ESI: m/z 166.85 ($M^+ + H$).

3-[(S)-(Dimethyl Amino)ethyl]phenyl N-Ethyl-N-methyl Carbamate (9)[5a]

Pyridine (6.36 g, 80.52 mmol) and *N*-ethylmethyl amine (4.76 g, 80.52 mmol) were added dropwise to a stirred solution of triphosgene (8.98 g, 30.26 mmol) in $CHCl_3$ (50 mL) at 0 °C for 30 min and stirred for 1 h. The reaction mixture was concentrated, and the residue was taken into hexane (50 mL). The salts were filtered off, and the filtrate was added to another reaction mixture containing **8** (5 g, 30.30 mmol) and 60% NaH (0.78 g, 30.31 mmol) in THF (90 mL) at 0 °C for 30 min and stirred for 14 h. The mixture was quenched at 0 °C with ice-cold water (20 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The oily residue was passed through short pad of silica gel, and the pure product was isolated by eluting hexane/EtOAc (3:7) to give **9** (6.6 g, 86%) as colorless oil. $[\alpha]_D = -28.1$ (*c* 5, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16–1.28 (m, 3H), 1.36 (d, $J = 6.7$ Hz, 3H), 2.19–2.23 (s, 6H), 2.98–3.06 (m, 3H), 3.22–3.29 (q, $J = 6.6$ Hz, 1H), 3.39–3.48 (q, $J = 8.3$ Hz, 2H), 6.99–7.12 (m, 3H), 7.26–7.31 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.93, 13.62, 20.34, 34.25, 34.61, 43.41, 44.43, 66.05, 120.87, 121.23, 124.74, 129.32, 145.41, 151.92, 155.01. MS-ESI: m/z 251.73 ($M^+ + H$).

Tartaric Acid Salt of 3-[(S)-(Dimethyl Amino)ethyl]phenyl N-Ethyl-N-methyl Carbamate (1)[5f]

EtOAc (70 mL) was added dropwise to a stirred solution of **9** (5 g, 20 mmol) and L (+) tartaric acid (2.9 g, 19.32 mmol) in EtOH (15 mL) at 60 °C, and the mixture was stirred at 25 °C for 12 h. The solid was filtered to give **1** (5.1 g, 63%) as white crystalline solid. Mp 120–122.8 °C. $[\alpha]_D = +6$ (*c* 5, EtOH). ^{1}H NMR (300 MHz,

$CDCl_3$): δ 1.13–1.24 (m, 3H), 1.67 (d, $J = 6.0$ Hz, 3H), 2.65 (s, 6H), 3.96–3.06 (2S, 3H), 3.35–3.46 (m, 2H), 4.34–4.46 (m, 1H), 4.47 (S, 2H), 7.14–7.41 (m, 4H), 8.45 (s, 2H).^{13}C NMR (75 MHz, $CDCl_3$): δ 12.45, 13.25, 16.42, 33.79, 34.20, 40.28, 44.08, 65.07, 72.62, 122.62, 123.06, 126.07, 130.81, 135.16, 151.68. 154.05, 154.20, 176.32. MS-ESI: m/z 251.05 ($M^+ + H$). Anal. calculated for $C_{18}H_{28}N_2O_8$: C,53.99; H, 7.05; N, 7.0. Found: C, 53.92; H, 7.04; N, 6.95.

3-((R)-1-((R)-1-Phenylethylamino)ethyl)phenol (11)

Titanium(IV) isopropoxide (62.4 g, 220.26 mmol, 1.5 equiv) was added To a stirred solution of 3-hydroxy acetophonone (20 g, 154.8 mmol) and *R*-(α)-methylbenzylamine (18.7 g, 157.8 mmol, 1 equiv) in EtOAc (80 mL), and the mixture was stirred for 3 h. It was cooled to 0 °C, and ethanol (200 mL) and sodium borohydride (5.54 g, 146.88 mmol, 1 equiv) were added and stirred for 3 h. The mixture was quenched at 0 °C with acetic acid (6 mL). Solvents were concentrated. Water (200 mL) and saturated Na_2CO_3 (200 mL) were added. The obtained solid was filtered and washed with water (100 mL). The solid was taken into EtOAc (100 mL), refluxed, and filtered hot. The process was repeated twice. Combined organic layers were dried over Na_2SO_4 and concentrated. The residue was taken into DCM (100 mL), stirred for 1 h, and filtered to give **11** (25 g, 70.5%) as a white solid. Mp 118.5–119 °C. $[\alpha]_D = +158$ (*c* 1, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.13–1.18 (m, 6H), 3.21–3.28 (q, $J = 6.5$ Hz, 1H), 3.39 (q, $J = 6.4$ Hz, 1H), 6.58–6.45 (m, 3H), 7.03–7.08 (m, 1H), 7.17–7.29 (m, 5H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 25.38, 25.47, 55.11, 113.68, 113.87, 117.55, 126.84, 126.91, 128.62, 129.52, 146.8.28, 157.82. MS-ESI: m/z 242.05 ($M^+ + H$). HRMS m/z calculated for $C_{16}H_{20}NO$ 242.1537: found 242.1531. HPLC method column: Diacel chiralcel OD-H 250 × 4.6 mm, 0.5μ, mp: 95% n-hexane + 5% IPA + 0.1% TFA, flow rate : 0.8 ml/min, UV detection at 215 nm, sample concentration 1 mg/3 ml diluent, retention time 9.3 min.

3-((R)-1-Aminoethyl)phenol (12)[6g]

To a solution of **11** (14 g, 65.31 mmol) in AcOH (140 mL), 10% Pd/C (2 g) was added, and the mixture was hydrogenated at 60 psi for 48 h. The catalyst was filtered off, and filtrate was concentrated to give **12** (7 g, 89.7%). The crude product was taken as such for the next reaction. An analytically pure sample was obtained by stirring the crude with IPA and collected by filtration. Mp 155.1–158.6 °C $[\alpha]_D = +20.8$ (*c* 1, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.36 (d, $J = 6.6$ Hz, 3H), 4.03 (q, $J = 6.4$ Hz, 1H), 6.64–6.67 (m, 1H), 6.77–6.82 (m, 2H), 7.06–7.12(m, 1H) ^{13}C NMR (75 MHz, DMSO-d_6): δ 23.30, 50.08, 113.21, 114.41, 116.42, 129.20, 145.42, 157.68. MS-ESI: m/z 138.10 ($M^+ + H$).

tert-Butyl (R)-1-(3-Hydroxyphenyl)ethylcarbamate (13)

Boc anhydride (12.4 g, 56.8 mmol, 1.14 equiv) was added to a stirred solution of **12** (6.8 g, 49.56 mmol) and TEA (7.1 g, 70.29 mmol, 1.4 equiv) in MeOH (68 mL), and the mixture was stirred for 6 h. It was then concentrated and diluted with DCM

(75 mL). The organic layer was washed with water (2 × 30 mL) and brine (30 mL) dried over Na_2SO_4, and concentrated to give **13** (9.4 g, 81.7%) as a thick liquid. $[\alpha]_D = +57.65$ (*c* 0.5, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (s, 12H), 4.60–4.89 (bs, 2H), 6.70–6.84 (m, 3H), 7.14–7.19 (t, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.61, 28.40, 20.21, 79.87, 112.77, 114.42, 117.45, 129.65, 145.45, 155.58, 156.67. MS-ESI: m/z 236 ($M^+ + H$).

tert-Butyl-(R)-1-(3-methoxyphenyl)ethylcarbamate (14)

Dimethylsulfate (4.9 g, 38.84 mmol, 1.01 equiv) was added dropwise to a stirred solution of **13** (9.2 g, 38.77 mmol) and K_2CO_3 (8 g, 57.88 mmol, 1.5 equiv) in acetone (92 mL) at 0 °C and then refluxed for 12 h. The mixture was filtered through celite, and the filtrate was concentrated. The residue was diluted with DCM (100 mL) and washed with water (3 × 50 mL). The organic layer was dried and concentrated to give **14** (7.2 g, 73.9%) as a thick clear liquid. $[\alpha]_D = +62.56$ (*c* 0.5, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (s, 9H), 3.80 (s, 3H), 4.60–4.89 (bs, 2H), 6.76–6.89 (m, 3H), 7.24–7.27 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.69, 28.39, 50.15, 55.17, 79.36, 111.75, 112.32, 118.14, 129.58, 145.83, 155.11, 159.76. MS-ESI: m/z 252.43 ($M^+ + H$).

(R)-1-(3-Methoxyphenyl)ethanamine Hydrochloride (15)[6b]

To a solution of **14** (7 g, 27.85 mmol) in MeOH (70 mL), 10 N HCl (7 mL) was added and stirred overnight. The mixture was concentrated and codistilled using toluene to give **15** (4.5 g, 86%) as HCl salt, which was taken as such for the next reaction. The analytical sample was prepared by taking the salt in 10% NaOH solution and extracted with DCM. Concentration of the solvent offered a thick liquid $[\alpha]_D = +21.2$ (*c* 0.3, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39–1.42 (d, $J = 6.6$ Hz, 3H), 1.58–1.69 (bs, 2H), 3.82 (s, 3H), 3.90–4.25 (q, $J = 6.7$ Hz, 1H), 6.72–6.80 (m, 1H), 6.94–6.90 (m, 2H), 7.24–7.29 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.57, 51.35, 55.25, 111.43, 112.16, 118.17, 129.52, 149.53, 159.82. MS-ESI: m/z 152 ($M^+ + H$).

(*E*)-3-(2-Chlorophenyl)-N-((R)-1-(3-hydroxyphenyl)ethyl)acrylamide (16)[6b]

(E)-3-(2-Chlorophenyl)acryloyl chloride (2.67 g, 13.32 mmol, 1 equiv) in DCM (5 mL) was added dropwise to a stirred solution of **15** (2.5 g, 13.32 mmol), EDC (25 mL), and TEA (3.1 g, 30.6 mmol, 2.6 equiv) and stirred at room temperature for 2 h. The mixture was washed with water (2 × 10 mL), dried over Na_2SO_4, and concentrated. It was purified by filter column using silica gel and 50% EtOAc in hexane as eluent to give **16** (3.2 g, 81%) as a white solid. Mp 141–145 °C. $[\alpha]_D = +31.5$ (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54–1.57 (d, $J = 6.9$ Hz, 3H), 3.81 (s, 3H), 5.22–5.26 (q, $J = 7.2$ Hz, 1H), 5.89 (d, $J = 6.84$ Hz, 1H), 6.36–6.41 (d, $J = 15.6$ Hz, 1H), 6.80–6.83 (m, 1H), 6.90 (s, 1H), 6.96 (d, $J = 7.7$ Hz, 1H), 7.29–7.30 (m, 3H), 7.39–7.41 (m, 1H), 7.52–7.55 (m, 1H), 7.96–8.02 (d, $J = 15.6$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.62, 49.15, 55.37, 112.44, 112.71, 118.53,

123.65, 126.96, 127.68, 129.82, 130.21, 130.40, 133.21, 134.82, 137.22, 144.76, 159.91, 164.42. MS-ESI: m/z 316.05 ($M^+ + H$).

3-(2-Chlorophenyl)-N-((R)-1-(3-methoxyphenyl)ethyl)propanamide (17)[6b]

The solution of **16** (1.5 g, 4.74 mmol) in MeOH (15 mL) was kept for hydrogenation at 50 psi using 10% Pd/C (200 mg) for 3 h. The catalyst was filtered, and the filtrate was concentrated. The product was purified by column chromatography using silica gel and EtOAc–hexane (1:1) as an eluent to give **17** (1 g, 73.31%). Mp 88–92 °C $[\alpha]_D = +46.2$ (c 1, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37–1.40 (d, $J = 6.87$ Hz, 3H), 2.44–2.49 (t, $J = 7.6$ Hz, 2H), 2.93–2.98 (t, $J = 7.6$ Hz, 3H), 3.78 (s, 3H), 5.01–5.11 (m, $J = 7.10$ Hz, 1H), 5.50–5.53 (bs, 1H), 6.77–6.79 (m, 3H), 7.19–7.28 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.65, 31.77, 38.65, 48.71, 55.25, 112.35, 112.57, 118.42, 126.28, 128.43, 128.55, 129.70, 134.50, 136.11, 140.82, 144.75, 159.85, 171.10. MS-ESI: m/z 318.2 ($M^+ + H$).

3-(2-Chlorophenyl)-N-((R)-1-(3-methoxyphenyl)ethyl)propan-1-amine (2)[6b]

DIBAL-H (6 mL, 1 M in hexane, 6 mmol, 3.8 equiv) was added to a stirred solution of **17** (0.5 g, 1.57 mmol) in DCM (2.5 mL) at 0 °C and stirred at room temperature for 16 h. It was quenched with MeOH (2 mL) at 0 °C followed by 10% NH_4Cl (2.5 mL). The reaction mixture was passed through celite, and layers were separated. The organic layer was dried over Na_2SO_4 and concentrated. It was purified by column chromatography using silica gel and EtOAC-hexane (1:1) as an eluent to give **2** (0.32 g, 60%) as oil. $[\alpha]_D = +40.3$ (c 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32–1.34 (d, $J = 6.6$ Hz, 3H), 1.75–1.80 (m, 2H), 2.50–2.62 (m, 4H), 3.68–3.75 (q, $J = 6.7$ Hz, 1H), 3.80 (s, 3H), 6.76–6.79 (m, 1H), 6.86–6.89 (m, 2H), 7.13–7.29 (m, 5H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 24.15, 31.78, 33.62, 47.35, 55.21, 58.48, 112.11, 112.35, 119.10, 125.72, 128.25, 128.36, 129.42, 142.13, 147.0, 159.85. MS-ESI: m/z 304 ($M^+ + H$). HRMS m/z calculated for $C_{18}H_{29}ClNO$ 303.8325; found 303.8318.

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