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A concise enantioselective synthesis of (*R*)-selegiline, (*S*)-benzphetamine and formal synthesis of (*R*)-sitagliptin via electrophilic azidation of chiral imide enolates

Soumen Dey, Arumugam Sudalai *

Chemical Engineering and Process Development Division, CSIR-National Chemical Laboratory, Pashan Road, Pune 411 008, India

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ABSTRACT

A concise and high yielding enantioselective synthesis of (*R*)-selegiline, an anti-Parkinson's drug, (*S*)-benzphetamine, an anti-obesity agent, and (*S*)-sitagliptin, an anti-diabetic drug has been described starting from commercially available starting materials employing Evans' electrophilic azidation of chiral imide enolates as a key chiral inducing step, which proceeds in a highly diastereoselective manner (>99%).

1. Introduction

Chiral homobenzylic amines are subunits widely found in a range of biologically active compounds, for example, **1**–**3**. Furthermore, they serve as extremely useful synthetic intermediates, since they can be transformed into an array of highly functionalized heterocycles. In particular, pharmaceutical substances belonging to this category such as (*R*)-selegiline **1**, (*S*)-benzphetamine **2**, and (*S*)-sitagliptin **3** are currently used in the treatment of a variety of diseases. More importantly, (*R*)-selegiline **1** is a selective irreversible MAO-B inhibitor[1] that works by slowing the breakdown of certain natural substances in the brain (e.g. dopamine, norepinephrine, and serotonin). It is usually used in combination with L-DOPA or carbidopa for the treatment of early-stage Parkinson's disease, depression, and senile dementia, while (*S*)-benzphetamine **2**, an anorectic drug, is an amphetamine derivative that exhibits appetite suppressant activity and is utilized in the long-term management of obesity.[2] In addition, compound **2** has been found to be a superior bronchodilator and a CNS stimulator, which increases heart rate and blood pressure. It has been established that dipeptidyl peptidase IV (DPP-IV) inhibitors are known to stimulate insulin secretion indirectly by enhancing the action of the incretin hormones glucagen-like peptide I (GLP-I) and glucose-dependent insulinotropic polypeptide (GIP).[3] (*R*)-Sitagliptin **3**, a β-amino acid derivative, is a potent DPP-IV inhibitor enzyme, which offers a new mechanism in achieving glycemic control for the treatment of type 2 diabetes (Fig. 1).

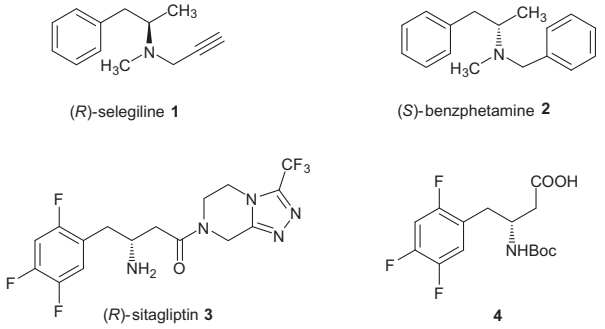

Figure 1. Structures of (*R*)-selegiline **1**, (*S*)-benzphetamine **2**, and (*R*)-sitagliptin **3**.

Due to their highly potent biological activity, considerable efforts have been devoted to their asymmetric synthesis. Although many strategies for the synthesis of (*R*)-selegiline **1** have been reported in recent years, most of them have relied on racemic approaches,[4] chiral pool starting materials,[5] asymmetric hydrogenation, classical/kinetic resolutions,[6] regioselective aziridine ring openings with organocuprates,[7] OsO_4-catalyzed asymmetric dihydroxylations[8a] as well as proline based α-functionalization of aldehydes.[8b] However, for (*S*)-benzphetamine **2**, a recent report[9] used a chiral pool approach for its synthesis. In the case of (*R*)-sitagliptin **3**, the coupling of β-amino acid derivative **4** with a triazolopyrazine unit is generally employed and its asymmetric synthesis mainly focuses on asymmetric reductions: (i) Ru-catalyzed chemo- and stereoselective hydrogenations of a β-ketoester followed by an EDC coupling/Mitsunobu reaction sequence;[10] (ii)

* Corresponding author. Tel.: +91 20 25902565; fax: +91 20 25902676.
E-mail address: a.sudalai@ncl.res.in (A. Sudalai).

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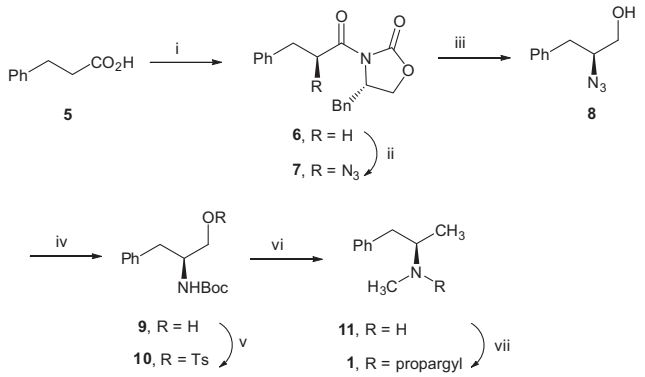
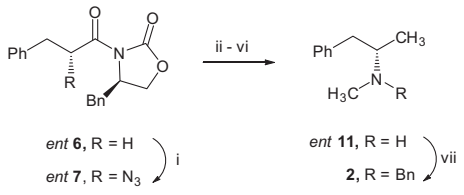
Rh-catalyzed asymmetric hydrogenations of an enamine under high pressure;[11] (iii) biocatalytic or Ru-catalyzed reductive aminations of a β-ketoamide.[12] Quite recently, Davies et al.[13] reported on a highly diastereoselective conjugate addition of enantiopure secondary lithium amides to α,β-unsaturated esters to facilitate an efficient synthesis of (*R*)-sitagliptin **3**. The main challenge in this area is to prepare enantioselectively the stereocenter present in the β-amino acid unit.[14] However, most of the reported methods for the synthesis of these drugs suffer from long reaction sequences, low yields, and diastereoselectivity, and the use of transition metals as catalysts for the introduction of the chiral amine functionality at the homobenzylic position.

The use of Evans' chiral *N*-acyloxazolidinone auxiliaries to control absolute stereoinduction has found wide application in a variety of reactions over the last two decades.[15] The ready availability of the starting materials, the ease of cleavage, and application to a broad range of stereoselective reactions allow oxazolidinone auxiliaries to endure as ideal intermediates for asymmetric synthesis. We envisioned that the chiral amine functionality could be introduced via Evans' electrophilic azidation of chiral imide enolates using a chiral auxiliary, followed by reduction. Herein we report a short, enantioselective synthesis of drug molecules **1**, **2** and the formal synthesis of **3** based on an Evans' chiral azidation approach (Schemes 1–3).



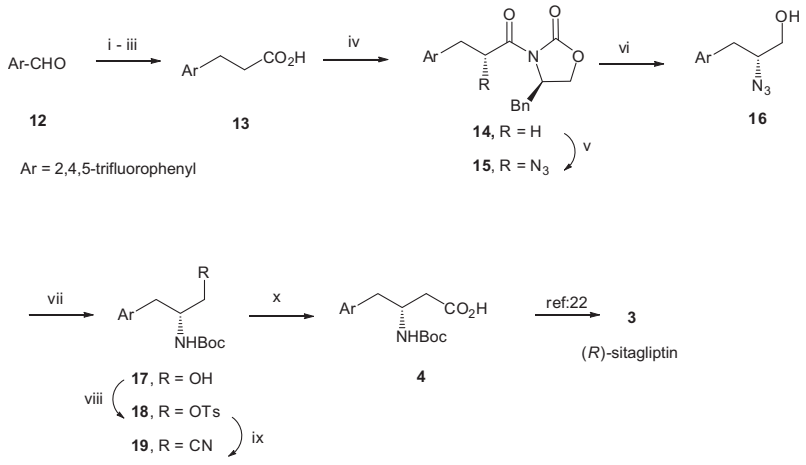
Scheme 1. Reagents and conditions: (i) pivalolyl chloride, Et_3N, dry THF, −20 °C, 3 h then (*S*)-4-benzyloxazolidin-2-one, LiCl, −20 to 25 °C, 8 h, 90%; (ii) KHMDS, −78 °C, dry THF, 45 min, then 2,4,6-triisopropylbenzenesulfonyl azide, 5 min, then AcOH, −78 to 25 °C, 12 h, 85%; (iii) $NaBH_4$, THF/ H_2O (3:1), 0–25 °C, 2 h, 95%; (iv) H_2 (1 atm), 10% Pd/C, Boc_2O, MeOH, 5 h, 90%; (v) TsCl, Et_3N, CH_2Cl_2, 0–25 °C, 3 h; (vi) $LiAlH_4$, THF, reflux, 4 h, 65% (over two steps); (vii) propargyl bromide, K_2CO_3, CH_3CN, 3 h, 25 °C, 71%.



Scheme 2. Reagents and conditions: (i) pivalolyl chloride, Et_3N, dry THF, −20 °C, 3 h then (*S*)-4-benzyloxazolidin-2-one, LiCl, −20 to 25 °C, 8 h, 90%; (ii) KHMDS, −78 °C, dry THF, 45 min, then 2,4,6-triisopropylbenzenesulfonyl azide, 5 min, then AcOH, −78 to 25 °C, 12 h, 85%; (iii) $NaBH_4$, THF/ H_2O (3:1), 0–25 °C, 2 h, 95%; (iv) H_2 (1 atm), 10% Pd/C, Boc_2O, MeOH, 5 h, 90%; (v) TsCl, Et_3N, CH_2Cl_2, 0–25 °C, 3 h; (vi) $LiAlH_4$, THF, reflux, 4 h, 65% (over two steps); (vii) benzyl bromide, K_2CO_3, CH_3CN, 2 h, 25 °C, 73%.

2. Results and discussion

The synthetic sequences of these bioactive molecules are shown in Schemes 1–3, which commenced from commercially available hydrocinnamic acid employing an Evans' chiral auxiliary protocol. Thus the condensation of (*S*)-4-benzyloxazolidin-2-one, the chiral auxiliary, with hydrocinnamic acid **5** via the formation of a pivolyl ester (pivalolyl chloride, Et_3N, −20 °C, THF, 3 h followed by (*S*)-4-benzyloxazolidin-2-one, LiCl, −20 to 25 °C, 8 h) gave oxazolidinone **6** (90%). The electrophilic azidation of chiral imide enolate **6** at the α-position (KHMDS, 2,4,6,-triisopropylbenzenesulfonyl azide, THF, −78 °C; quenching with AcOH) was carried out to produce azido oxazolidinone **7** (85%) {$[\alpha]_D^{25}$ = + 67.6 (*c* 1.0, CH_2Cl_2)} (dr >99%).[15a] The reductive removal of the chiral auxiliary was then achieved using $NaBH_4$ in THF/ H_2O to give the free β-azido alcohol **8** {97% ee as determined by HPLC analysis (Chiracel AD-H column, Hex/*i*-PrOH 95:05, 0.3 mL/min, 220 nm, retention time: t_{major} = 36.12 min and t_{minor} = 38.38 - min.) and 95% yield}. The catalytic hydrogenation [10% Pd/C, H_2 (1 atm), Boc_2O, MeOH] of azide **8** furnished the corresponding amino alcohol (90%) in which the amine function was protected as carbamate **9** followed by formation of tosylate **10**. Reduction of **10** with $LiAlH_4$ gave secondary methyl amine **11**, which was readily *N*-alkylated with propargyl bromide affording (*R*)-selegiline



Scheme 3. Reagents and conditions: (i) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 4 h, 98%; (ii) H_2 (1 atm), 10% Pd/C, MeOH, 1 h, 98%; (iii) LiOH, THF/MeOH/H_2O (3:1:1), 2 h, 96%; (iv) pivolyl chloride, Et_3N, dry THF, −20 °C, 3 h then (*R*)-4-benzyloxazolidin-2-one, LiCl, −20 to 25 °C, 8 h, 94%; (v) KHMDS, −78 °C, dry THF, 45 min, then 2,4,6-triisopropylbenzenesulfonyl azide, 5 min, then AcOH, −78 to 25 °C, 12 h, 88%; (vi) $NaBH_4$, THF/ H_2O (3:1), 0–25 °C, 2 h, 98%; (vii) H_2 (1 atm), 10% Pd/C, Boc_2O, MeOH, 3 h, 98%; (viii) TsCl, Et_3N, CH_2Cl_2, 1 h then (ix) NaCN, DMF, 80 °C, 4 h, 65% (over two steps); (x) 3 M NaOH, H_2O_2, 100 °C, 3 h, 75%.

1 in 30% overall yield. The enantiomeric purity of **1** was determined to be 97% ee based on the comparison of its specific rotation with the reported values $[\alpha]_D^{25} = -10.5$ (*c* 6.3, EtOH) {lit.[16] $[\alpha]_D^{25} = -10.8$ (*c* 6.4, EtOH)}. As the ee values of all these compounds were 97%, it indicates the enantiomeric purity of starting oxazolidinone.

The synthesis of (*S*)-benzphetamine **2** was achieved by following a similar sequence of reactions except that the chiral auxiliary used was (*R*)-4-benzyloxazolidin-2-one (Scheme 2). Excellent yields and ees were obtained in each step. Benzylation of *ent*-**11** was the final step and gave (*S*)-benzphetamine **2** in 31% overall yield. The enantiomeric purity of **2** was determined to be 97% ee based on the comparison of its specific rotation with the reported values $[\alpha]_D^{25} = +52.3$ (*c* 0.28, $CHCl_3$) {lit.[9] $[\alpha]_D^{25} = +53.9$ (*c* 1, $CHCl_3$}. The spectroscopic data of compounds **1** and **2** were found to be in good agreement with the reported values.[16,9]

The synthetic sequence for β-amino acid **4** is shown in Scheme 3 starting from 2,4,5-trifluorobenzaldehyde **12**. Dihydrocinnamic acid **13** was obtained from aldehyde **12** by simple functional group manipulations: (i) two carbon homologation with a stabilized Wittig ylide; (ii) hydrogenation of the benzylic C=C bond by 10% Pd/C over H_2 (1 atm); and (iii) conversion of the ester group into an acid by LiOH-mediated hydrolysis. Azido alcohol **16** {98% ee determined by HPLC (Chiracel AD-H column, Hex/*i*-PrOH 95:05, 0.5 mL/min, 220 nm, retention time: t_{major} = 21.73 min and t_{minor} = 20.03 min.) and 98% yield} was prepared by following a similar reaction sequence using the Evans' chiral auxiliary (*R*)-4-benzyloxazolidin-2-one. Here, compound **15** was obtained with high diastereoselectivity (dr >99%). Consequently, carbamate **17** was obtained from **16** in a single step using catalytic hydrogenation [10% Pd/C, H_2 (1 atm), Boc_2O, MeOH] in 98% yield. The alcohol functionality in **17** was readily transformed into cyanide **19** via S_N2 displacement of its tosylate **18**. Subsequently, the cyanide functionality was converted into the corresponding carboxylic acid (3 M NaOH, H_2O_2, reflux) [17] to give the known intermediate **4** in 75% yield, thereby constituting a formal synthesis of **3**[22]. The enantiomeric purity of **4** was determined to be 98% ee based on the comparison of its specific rotation with the reported values $[\alpha]_D^{25} = +31.8$ (*c* 1, $CHCl_3$) {lit.[21] $[\alpha]_D^{25} = +32.3$ (*c* 1, $CHCl_3$)}.

3. Conclusion

In conclusion, we have specifically provided an efficient procedure for the enantioselective synthesis of two important drugs, (*R*)-selegiline **1** (30% overall yield; 97% ee) and (*S*)-benzphetamine **2** (31% overall yield; 97% ee), and **4** (36% overall yield; 98% ee), an advanced intermediate in the formal synthesis of (*R*)-sitagliptin **3** from commercially available starting materials. In this approach, the key intermediates were readily prepared with high diastereoselectivity from the corresponding carboxylic acids by employing an Evans' asymmetric direct azidation reaction. This methodology should find wide applicability for the synthesis of many drug candidates with homobenzylic amine units with high enantioselectivity and diastereoselectivity.

4. Experimental

4.1. General

Solvents were purified and dried by standard procedures prior to use. Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. IR spectra were recorded on a Thermo Scientific–Nicolet 380 FT-IR and absorption is expressed in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer unless mentioned otherwise. Elemental analysis was carried out on a Carlo Erba CHNS-O analyzer. Purification was carried out using column chromatography (60–120 mesh). Enantiomeric excesses were determined on Agilent HPLC instrument equipped with a suitable chiral column.

4.2. Experimental procedures

4.2.1. (*S*)-4-Benzyl-3-(3-phenylpropanoyl)oxazolidin-2-one 6

To a stirred solution of hydrocinnamic acid **5** (5 g, 33.2 mmol) in dry THF (100 mL) was added pivolyl chloride (4 g, 33.2 mmol) and Et_3N (10 g, 99.6 mmol) at −20 °C and the mixture was stirred at the same temperature for 4 h. To this stirred suspension, (*S*)-4-benzyloxazolidin-2-one (6.5 g, 36.52 mmol) in dry THF (20 mL) was added dropwise followed by the addition of LiCl (1.5 g, 33.2 mmol) after which it was stirred for an additional 15 min at −20 °C and stirring continued at 25 °C for 8 h until the complete consumption of the starting materials (the progress of the reaction was monitored by TLC). The product was then extracted with diethyl ether and the combined organic layer was washed with water, brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product, which upon column chromatographic purification with petroleum ether/ethyl acetate (4:1) gave **6** as a colorless solid. Yield: 9.07 g, 90%; $[\alpha]_D^{25} = +66.6$ (*c* 1.0, $CHCl_3$) {lit.[18] $[\alpha]_D^{25} = +67.4$ (*c* 0.98, $CHCl_3$)}; mp: 101–102 °C; IR ($CHCl_3$, cm^{-1}): υ_{max} 3065, 3030, 1781, 1697, 1387, 1212; ^1H NMR (200 MHz, $CDCl_3$): δ 7.15–7.32 (m, 10 H), 4.63–4.66 (m, 1H), 4.14–4.17 (m, 2H), 3.23–3.29 (m, 3H), 3.02–3.05 (m, 2H), 2.72 (dd, *J* = 9.7, 13.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.2, 153.2, 140.4, 135.2, 129.4, 128.9, 128.6, 127.3, 126.3, 66.0, 55.1, 37.8, 37.1, 30.3; Anal. Calcd for $C_{19}H_{19}NO_3$ requires C, 73.77; H, 6.19; N, 4.53%; found C 73.79; H 6.15; N 4.55%.

4.2.2. (2*R*,4*S*)-3-(2-Azido-3-phenyl-1-oxopropyl)-4-(phenylmethy1)-2-oxazolidinone 7

To a stirred solution of **6** (8.5 g, 28.02 mmol) in dry THF (90 ml), 61.55 ml of 0.5 M in toluene (30.82 mmol) of potassium hexamethyldisilazide (KHMDS) was added under N_2 at −78 °C and the mixture was stirred for 45 min. To this suspension of potassium enolate, stirred at −78 °C, was added 2,4,6-triisopropyl azide (11.2 g, 36.42 mmol) in dry THF (30 mL). After 5 min, the reaction was quenched with 8 ml (140.1 mmol) of glacial acetic acid and stirred at 25 °C for 12 h. The solution was then partitioned between CH_2Cl_2 and brine solution. The organic phase was washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated in vacuo. Column chromatographic purification of the crude product with petroleum ether/ethyl acetate (4:1) gave **7** as a yellow solid. Yield: 8.3 g, 85%; $[\alpha]_D^{25} = +67.6$ (*c* 1.0, CH_2Cl_2); {lit.[15a] $[\alpha]_D^{25} = +68$ (*c* 1.0, CH_2Cl_2)} mp 116–120 °C; IR ($CHCl_3$, cm^{-1}) υ_{max} 3065, 3030, 2987, 2111, 1781, 1701, 1389; ^1H NMR (200 MHz, $CDCl_3$): δ 7.13–7.36 (m, 10 H), 5.18 (q, *J* = 5.0 Hz, 1H), 4.65–4.77 (m, 1H), 4.19–4.29 (m, 2H), 3.34 (dd, *J* = 5.0 Hz and 13.5 Hz, 1H), 3.18 (dd, *J* = 3.1, 13.1 Hz, 1H), 3.03 (dd, *J* = 9.3, 13.6 Hz, 1H), 2.67 (dd, *J* = 9.4, 13.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.3, 152.7, 135.7, 134.6, 129.4, 129.1, 128.7, 127.6, 127.3, 66.6, 61.3, 55.1, 37.7, 37.4; Anal. Calcd for $C_{19}H_{18}N_4O_3$ requires C 65.13; H 5.18; N 15.99%; found C 65.15; H 5.20; N 15.95%.

4.2.3. (*S*)-2-Azido-3-phenylpropan-1-ol 8

To a stirred solution of **7** (5 g, 14.27 mmol) in THF (30 mL) was added a solution of sodium borohydride (1.0 g, 28.54 mmol) in water (10 mL) dropwise at 0 °C. After the addition, it was left to stir at 25 °C for 2 h. Upon completion of the reaction (monitored by checking TLC), 2 M HCl (20 mL) was added slowly so that the temperature was maintained at 25 °C. The reaction mixture was then extracted with ethyl acetate and washed with brine. The organic phase was concentrated and upon column chromatographic

purification with petroleum ether/ethyl acetate (3:7) gave **8** as a colorless liquid. Yield: 2.4 g, 95%; $[\alpha]_D^{25} = -2.3$ (*c* 1, $CHCl_3$) {lit.[19] $[\alpha]_D^{25} = -2.4$ (*c* 1.0, $CHCl_3$)}; IR ($CHCl_3$, cm^{-1}) 3439, 2108, 1092, 1046; ^1H NMR (200 MHz, $CDCl_3$): δ 7.21–7.36 (m, 5H), 3.68 (d, J = 11.1 Hz, 2H), 3.54–3.58 (m, 1H), 2.76–2.87 (m, 2H), 2.30 (br, s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.9, 129.2, 128.6, 126.8, 65.2, 64.2, 36.9; Anal. Calcd for $C_9H_{11}N_3O$ requires C 61.00; H 6.26; N 23.71%; found C 61.03; H 6.24; N 23.73%; Enantiomeric purity: 97% ee determined by HPLC analysis (Chiracel AD-H column, Hex/*i*-PrOH 95:05, 0.3 mL/min, 220 nm). Retention time: t_{major} = 36.12 min and t_{minor} = 38.38 min.

4.2.4. (*S*)-*tert*-Butyl-1-hydroxy-3-phenylpropan-2-yl-carbamate 9

A mixture of azido alcohol **8** (2.5 g, 10.8 mmol), 10% Pd/C, and di-*tert*-butyl dicarbonate (2.35 g, 10.8 mmol) in dry MeOH (20 mL) was stirred under H_2 (1 atm) at 25 °C for 5 h. After completion of reaction (monitored by TLC), it was filtered through Celite (MeOH eluent) and the solvent was evaporated under reduced pressure to afford **9** as a colorless solid. Yield: 2.5 g, 90%; mp: 96–98 °C; $[\alpha]_D^{25} = -26.4$ (*c* 1, MeOH) {lit.[20] $[\alpha]_D^{25} = -27$ (*c* 1, MeOH)}; IR ($CHCl_3$, cm^{-1}) 3353, 2978, 2933, 1685, 1526, 1390, 1268; ^1H NMR (200 MHz, $CDCl_3$): δ 7.19–7.34 (m, 5H), 4.69 (br s, 1H), 3.66–3.83 (m, 1H), 3.51–3.63 (m, 2H), 2.82 (d, J = 7.2 Hz, 2H), 2.32 (br s, 1H), 1.42 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3, 37.4, 53.5, 63.7, 79.5, 126.4, 128.4, 129.3, 137.9, 156.0; Anal. Calcd for $C_{14}H_{21}NO_3$ requires C 66.91; H 8.42; N 5.57%; found C 66.93; H 8.40; N 5.55%.

4.2.5. (*R*)-*N*-Methyl-1-phenylpropan-2-amine 11

To a stirred solution of *N*-Boc protected amino alcohol **9** (0.5 mg, 1.98 mmol) in CH_2Cl_2 (5 mL) were added dry triethylamine (0.3 mL, 2.37 mmol) and *p*-toluenesulfonyl chloride (0.452 g, 2.37 mmol) in the presence of a catalytic amount of 4-dimethylaminopyridine (0.024 g,10 mol%) at 0 °C. The reaction mixture was stirred at 25 °C for 3 h and then quenched by addition of 10% $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, and concentrated to give the crude tosylate, which was then dissolved in dry THF (5 mL), and added dropwise to a suspension of $LiAlH_4$ (0.225 g, 3 mmol) in dry THF (10 mL). The mixture was refluxed for 4 h and then cooled to 0 °C after which the excess $LiAlH_4$ was quenched by the addition of EtOAc. It was then treated with aq. 20% NaOH (0.5 mL). The white precipitate which formed was filtered off, and the residue was washed with EtOAc (3×10 mL). The combined EtOAc layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel using $CHCl_3$ as the eluent to afford the corresponding pure *N*-methyl amine **11**. Yield: 0.192 g, 65%; $[\alpha]_D^{25} = -10.8$ (*c* 4.2, EtOH); {lit.[20] $[\alpha]_D^{25} = -10.9$ (*c* 4.2, EtOH)}; IR ($CHCl_3$, cm^{-1}) 3274, 2917, 2839, 1614,1438; ^1H NMR (200 MHz, $CDCl_3$): δ 7.15–7.28 (m, 5H), 2.63–2.82 (m, 3H), 2.4 (s, 3H), 1.67 (br s, 1H), 1.08 (d, J = 5.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.2, 129.2, 128.4, 126.2, 56.3, 43.3, 33.8, 13.6; Anal. Calcd for $C_{10}H_{15}N$ requires C 80.48; H 10.13; N 9.39%; found C 80.50; H 10.11; N 9.35%.

4.2.6. (*R*)-*N*-Methyl-*N*-(-1-phenylpropan-2-yl)prop-2-yn-1-amine: (*R*)-selegiline 1

To a stirred solution of (*R*)-2-(methylamino)-1-phenylpropane **11** (0.1 g, 0.67 mmol) in CH_3CN (3 mL) were added anhydrous K_2CO_3 (0.185 g, 1.34 mmol) and propargyl bromide (0.1 mL, 0.73 mmol) (80 wt % solution in toluene). The reaction mixture was then stirred for 3 h at 25 °C, after which the solvent evaporated under reduced pressure to provide the crude product, which was purified by column chromatography over silica gel using petroleum ether/ethyl acetate (4:1) to give pure (*R*)-selegiline **1**. Yield: 41 mg, 71%, gum; $[\alpha]_D^{25} = -10.7$ (*c* 6.5, EtOH); {lit.[16] $[\alpha]_D^{25} = -10.8$ (*c* 6.4, EtOH)}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.26–7.23 (m, 2H), 7.19–7.14 (m, 3H), 3.42 (d, J = 2.4 Hz, 2H), 2.92–3.08 (m, 2H), 2.37–2.42 (m, 4H), 2.21 (t, J = 2.4 Hz, 1H), 0.98 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.1, 129.3, 128.3, 125.9, 80.2, 72.6, 59.4, 43.2, 38.8, 37.4, 15.2; Anal. Calcd for $C_{13}H_{17}N$ requires C 83.37; H 9.15; N 7.48%; found C 83.35; H 9.16; N 7.50%.

4.2.7. (*S*)-*N*-Benzyl-*N*-methyl-1-phenylpropan-2-amine: (*S*)-benzphetamine 2

To a stirred solution of (*S*)-2-(methylamino)-1-phenylpropane *ent*-**11** (0.080 g, 0.67 mmol) in CH_3CN (3 mL) were added anhydrous K_2CO_3 (0.146 g, 1.06 mmol) and benzyl bromide (0.1 mL, 0.79 mmol). The reaction mixture was then stirred for 2 h at 25 °C, and then the solvent was evaporated under reduced pressure to provide the crude product, which was purified by column chromatography over silica gel using petroleum ether/ethyl acetate (4:1) to give pure (*S*)-benzphetamine **2**. Yield: 98 mg, 79%; $[\alpha]_D^{25} = +52.3$ (*c* 0.28, $CHCl_3$); {lit.[9] $[\alpha]_D^{25} = +53.9$ (*c* 1, $CHCl_3$)}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.12–7.30 (m, 10H), 3.6 (d, J = 2.4 Hz, 2H), 2.96–3.04 (m, 2 H), 2.42–2.54 (m, 1H), 2.24 (s, 3H), 0.99 (d, J = 6.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.7, 140.0, 129.2, 128.6, 128.1, 126.7, 125.7, 59.7, 57.8, 39.5, 36.8, 14.0; Anal. Calcd for $C_{17}H_{21}N$ requires C 85.30; H 8.84; N 5.85%; found C 85.30; H 8.86; N 5.83%.

4.2.8. 3-(2,4,5-Trifluorophenyl)propanoic acid 13

To a stirred solution of 2,4,5-trifluorobenzalkdehyde **12** (5 g, 31.23 mmol) in benzene (100 mL) stabilized Wittig salt $Ph_3P{=}CHCO_2Et$ (21.7 g, 62.46 mmol) was added and refluxed overnight. After completion of the reaction (checked by TLC), the solvent was evaporated and pure adduct (4.9 g) was obtained by column chromatographic separation using petroleum ether/ethyl acetate (9:1). The product was then hydrogenated using 10% Pd/C, H_2 (1 atm) for 1 h in MeOH. After completion of the reaction (as monitored by TLC), it was filtered through Celite (MeOH eluent) and the solvent was evaporated off under reduced pressure to afford 3-(2,4,5-trifluorophenyl)ethylpropanoate (4.8 g), which was then hydrolyzed using LiOH (1.3 g, 56.1 mmol) in THF/MeOH/H_2O (3:1:1) to give **13** as a colorless gum. Yield: 4.6 g, 96%; IR ($CHCl_3$, cm^{-1}): 3105, 2903, 1772, 1052, 1016; ^1H NMR (200 MHz, $CDCl_3$): δ 6.91–7.02 (m, 1H), 7.04–7.26 (m, 1H), 2.92 (t, J = 7.34 Hz, 2H), 2.67 (t, J = 7.34 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.7, 33.85, 105.4 (dd, J = 20.2, 27.1 Hz), 118.3 (dd, J = 19.5, 6.4 Hz), 123.2 (ddd, J = 4.3, 9.2, 17.7 Hz), 145.5 (ddd, J = 4.2, 5.7, 237.9 Hz), 147.5 (ddd, J = 250.5, 11.6, 3.5 Hz), 157.1 (ddd, J = 239.8, 10.2, 7.6 Hz); Anal. Calcd for $C_9H_7F_3O_2$ requires C 52.95; H 3.46%; found C 52.90; H 3.48%.

4.2.9. (*R*)-4-Benzyl-3-(3-(2,4,5-trifluorophenyl)propanoyl)oxazolidin-2-one 14

To a stirred solution of hydrocinnamic acid **13** (4 g, 19.5 mmol) in dry THF (100 mL) were added pivolyl chloride (2.36 g, 19.5 mmol) and Et_3N (10 mL, 78 mmol) at −20 °C and the mixture was stirred at the same temperature for 4 h. To this stirred suspension, (*R*)-4-benzyloxazolidin-2-one (3.8 g, 21.5 mmol) in dry THF (20 mL) was added dropwise followed by the addition of LiCl (0.9 g, 19.5 mmol) and then stirred for an additional 15 min at −20 °C and stirring continued at 25 °C for 8 h until complete consumption of the starting materials (the progress of the reaction was monitored by TLC). The product was then extracted with diethyl ether and the combined organic layer was washed with water, brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product which upon column chromatographic purification with petroleum ether/ethyl

acetate (4:1) gave **14** as a colorless solid. Yield: 3.7 g, 94%; mp: 128–130 °C; $[\alpha]_D^{25}$ = +62.9 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3065, 3030, 1781, 1700, 1387, 1212; ^1H NMR (200 MHz, $CDCl_3$): δ 7.26–7.33 (m, 4H), 7.12–7.19 (m, 3H), 6.91–6.93 (m, 1H), 4.61–4.67 (m, 1H), 4.17–4.21 (m, 2H), 3.19–3.27 (m, 3H), 3.03 (t, *J* = 7.3 Hz, 2H), 2.80 (dd, *J* = 9.7, 13.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.0, 35.5, 37.8, 55.0, 66.2, 105.4 (dd, *J* = 20.8, 28.1 Hz), 118.5 (dd, *J* = 10.5, 6.4 Hz), 123.7 (ddd, *J* = 4.3, 9.5, 17.5 Hz), 127.4, 128.3, 129.3, 135.0, 146.4 (ddd, *J* = 4.4, 5.1, 227.8 Hz), 148.9 (ddd, *J* = 255.5, 12.5, 2.9 Hz), 158.2 (ddd, *J* = 244.4, 11.2, 9.7 Hz); Anal. Calcd for $C_{19}H_{16}F_3NO_3$ requires C 62.81; H 4.4; N 3.86%; found C 62.80; H 4.42; N 3.82%.

4.2.10. (*R*)-3-((*R*)-2-Azido-3-(2,4,5-trifluorophenyl)propanoyl)-4-benzyloxazolidin-2-one 15

To a stirred solution of **14** (3.8 g, 10.4 mmol) in dry THF (30 mL), 25 mL of 0.5 M in toluene (12.48 mmol) of potassium hexamethyldisilazide (KHMDS) was added under N_2 at −78 °C and the mixture was stirred for 45 min. To this suspension of potassium enolate, stirred at −78 °C, was added 2,4,6-triisopropyl azide (4.27 g, 13.83 mmol) in dry THF (15 mL). After 5 min, the reaction was quenched with 3 mL (52 mmol) of glacial acetic acid and stirred at 25 °C for 12 h. The solution was then partitioned between CH_2Cl_2 and brine solution. The organic phase was washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated in vacuo. Column chromatographic purification of the crude product with petroleum ether/ethyl acetate (4:1) gave **15** as a gum. Yield: 3.3 g, 88%; $[\alpha]_D^{25}$ = +57.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3065, 3030, 2987, 2111, 1781, 1701, 1389; ^1H NMR (200 MHz, $CDCl_3$): δ 7.33–7.20 (m, 4H), 7.02–7.22 (m, 3H), 6.84–6.97 (m, 1H), 5.2 (q, *J* = 4.5 Hz, 1H), 4.61–4.74 (m, 1H), 3.34 (dd, *J* = 5.0, 13.1 Hz, 2H), 3.01 (dd, *J* = 4.1, 13.5 Hz, 2H), 2.8 (dd, *J* = 9.3, 13.3 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 35.4, 37.6, 55.0, 66.2, 71.5, 105.2 (dd, *J* = 20.2, 28.7 Hz), 118.5 (dd, *J* = 10.5, 6.4 Hz), 123.7 (ddd, *J* = 4.7, 9.8, 16.5 Hz), 127.4, 128.3, 129.3, 135.0, 146.4 (ddd, *J* = 4.6, 5.3, 237.8 Hz), 148.9 (ddd, *J* = 253.5, 12.5, 2.7 Hz), 158.2 (ddd, *J* = 244.4, 11.2, 9.7 Hz); Anal. Calcd for $C_{19}H_{16}F_3N_4O_3$ requires C 56.44; H 3.74; N 13.8%; found C 56.42; H 3.76; N 13.8%.

4.2.11. (*R*)-2-Azido-3-(2,4,5-trifluorophenyl)propan-1-ol 16

To a stirred solution of **15** (3 g, 7.42 mmol) in THF (20 mL) was added dropwise a solution of sodium borohydride (0.42 g, 11.13 mmol) in water (2 mL) at 0 °C. After the addition, it was stirred at 25 °C for 2 h. After completion of the reaction (as monitored by TLC), 2 M HCl (15 mL) was added slowly so that the temperature was maintained at 25 °C. The reaction mixture was then extracted with ethyl acetate and washed with brine. The organic phase was concentrated and column chromatographic purification with petroleum ether/ethyl acetate (7:3) gave **16** as a colorless gum. Yield: 2.94 g, 98%; $[\alpha]_D^{25}$ = +4.2 (*c* 1, $CHCl_3$)); IR ($CHCl_3$, cm^{-1}): 3439, 2903, 2100, 1152, 1016; ^1H NMR (200 MHz, $CDCl_3$): δ 7.0–7.16 (m, 1H), 6.87–7.0 (m, 1H), 3.55–3.78 (m, 3H), 2.71–2.84 (m, 2H), 1.82 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.8, 63.5, 64.3, 105.4 (dd, *J* = 20.2, 27.1 Hz), 118.5 (dd, *J* = 10.5, 6.4 Hz), 123.7 (ddd, *J* = 4.3, 9.5, 17.5 Hz), 146.4 (ddd, *J* = 4.4, 5.1, 241.8 Hz), 148.9 (ddd, *J* = 255.5, 11.6, 3.1 Hz), 158.2 (ddd, *J* = 239.4, 10.2, 8.7 Hz); Anal. Calcd for $C_9H_8F_3N_3O$ requires C 46.76; H 3.49; N 18.18%; found C 46.78; H 3.46; N 18.15%; Enantiomeric purity: 98% ee determined by HPLC analysis (Chiracel AD-H column, Hex/*i*-PrOH 95:05, 0.5 mL/min, 220 nm). Retention time: t_{major} = 21.73 min and t_{minor} = 20.03 min.

4.2.12. (*R*)-*tert*-Butyl-1-hydroxy-3-(2,4,5-trifluorophenyl)propan-2-yl)carbamate 17

A mixture of azido alcohol **16** (2 g, 9.28 mmol), 10% Pd/C, and di-*tert*-butyl dicarbonate (1.2 g, 9.28 mmol) in dry MeOH (20 mL) was stirred under H_2 (1 atm) at 25 °C for 3 h. After completion of the reaction (monitored by TLC), it was filtered through Celite (MeOH eluent) and the solvent was evaporated under reduced pressure to afford **17** as a colorless solid. Yield: 1.96 g, 98%; mp: 98–100 °C; $[\alpha]_D^{25}$ = +16.8 (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3401, 2908, 2853, 1682, 1526, 1410, 1128; ^1H NMR (200 MHz, $CDCl_3$): δ 6.88–6.94 (m, 1H), 7.09–7.11 (m, 1H), 4.77–4.84 (m, 1H), 3.78–3.84 (m, 1H), 3.59–3.67 (m, 2H), 2.80–2.86 (t, 2H, *J* = 7.3 Hz), 2.1 (br, s, 1H), 1.40 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3, 30.2, 52.7, 64.2, 105.3 (dd, *J* = 20.2, 27.6 Hz), 119.0 (dd, *J* = 10.2, 6.6 Hz), Anal. Calcd for $C_{14}H_{18}F_3NO_3$ requires C 55.08; H 5.94; N 4.59%; found C 55.06; H 5.96; N 4.54%.

4.2.13. (*R*)-3-(*tert*-Butyl-1-cyano-(2,4,5-trifluorophenyl)propan-2yl)carbamate 19

To a stirred solution of *N*-Boc protected amino alcohol **17** (1.5 g, 4.9 mmol) in CH_2Cl_2 (5 mL) were added dry triethylamine (1.3 mL, 9.8 mmol) and *p*-toluenesulfonyl chloride (1.12 g, 5.88 mmol) in the presence of a catalytic amount of 4-dimethylaminopyridine (0.059 g,10 mol %) at 0 °C. The reaction mixture was stirred at 25 °C for 3 h and then quenched by the addition of 10% $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, concentrated to give the crude tosylate **18**, which was then dissolved in DMF (5 mL), and NaCN (1.4 g, 29.4 mmol) carefully added. The mixture was refluxed for 4 h and then cooled to RT and extracted with EtOAc (3 × 10 mL). The combined EtOAc layers were dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography over silica gel using petroleum ether/ethyl acetate (4:1) to afford the corresponding pure cyano compound **19** as a colorless solid. Yield: 0.97 g, 65% (over two steps); mp: 110–112 °C; $[\alpha]_D^{25}$ = +22.2 (*c* 0.6, $CHCl_3$); mp: 110–112 °C; IR ($CHCl_3$, cm^{-1}): 3101, 2956, 2105, 1685, 1456, 1128; ^1H NMR (200 MHz, $CDCl_3$): δ 6.62–6.98 (m, 1H), 7.05–7.12, 9 m, 1H), 4.87 (m, 1H), 4.05 (m, 1H), 2.90–2.98 (m, 2H), 2.73–2.77 (m, 1H), 2.54–2.58 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.48, 28.57, 32.91, 47.95, 80.73, 105.4 (dd, *J* = 20.8, 28.1 Hz), 117.0, 118.5 (dd, *J* = 10.5, 6.4 Hz), 123.7 (ddd, *J* = 4.3, 9.5, 17.5 Hz), 127.4, 128.3, 129.3, 135.0, 146.4 (ddd, *J* = 4.8, 4.8, 230.8 Hz), 148.7 (ddd, *J* = 239.5, 12.5, 2.6 Hz), 158.2 (ddd, *J* = 255.4, 11.2, 9.3 Hz); Anal. Calcd for $C_{15}H_{17}F_3N_2O_2$ requires C 57.32; H 5.45; N 8.91%; found C 57.33; H 5.46; N 8.94%.

4.2.14. (*R*)-3-((*tert*-Butoxycarbonyl)amino)-4-(2,4,5-trifluorophenyl)butanoic acid 4

To a stirred solution of *N*-Boc protected cyano compound **19** (0.5 g, 1.5 mmol) were added 3 M NaOH (10 mL), H_2O_2 (35%, 6 mL, 22 mmol) and refluxed at 100 °C for 3 h. After the reaction was completed, the reaction mixture was cooled to 0 °C. To remove organic impurities, Et_2O (50 mL) was added and the ether phase was removed. The aqueous phase was acidified with 6 M HCl to neutralize pH and was extracted with Et_2O (50 mL), and dried over Na_2SO_4. Filtration and evaporation of the solvent gave the crude product, which was purified by column chromatography over silica gel using petroleum ether/ethyl acetate (4:1) to afford the corresponding pure compound **4** as a colorless solid. Yield: 0.375 g, 75%; mp: 122–125 °C; {lit.[21] mp: 124–125 °C}; $[\alpha]_D^{25}$ = +31.8 (*c* 1, $CHCl_3$) {lit.[21] $[\alpha]_D^{25}$ = +32.3 (*c* 1, $CHCl_3$)}; IR ($CHCl_3$, cm^{-1}): 3101, 2956, 1770, 1685, 1366, 1095; ^1H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 9H), 2.62–2.56 (m, 2H), 2.88 (d, *J* = 4.9 Hz, 2H), 4.10 (br s, 1H), 5.07 (br s, 1H), 6.94–6.87 (m, 1H), 7.09–7.03 (m, 1H; ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 28.57, 32.71, 47.95, 61.5, 80.73, 105.8 (dd, *J* = 20.6, 28.5 Hz), 118.2(dd, *J* = 10.7, 6.2 Hz), 124.5 (ddd, *J* = 4.5, 9.5, 18.2 Hz), 146.7 (ddd, *J* = 4.1, 5.5, 229.9 Hz), 148.9 (ddd, *J* = 255.5, 12.5, 2.9 Hz), 158.2 (ddd, *J* = 244.4, 11.2, 9.7 Hz),

175.1, 177.3; Anal. Calcd for $C_{17}H_{22}F_3NO_4$ requires C 56.50; H 6.14; N 3.88%; found C 56.53; H 6.16; N 3.89%.

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