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An asymmetric aminohydroxylation route to (+)-L-733,060

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Abstract—An enantioselective synthesis of **(+)-L-733,060** starting from cinnamic acid using Sharpless asymmetric aminohydroxylation and Wittig reactions as the key steps is described.

1. Introduction

Substance P (SP), a peptide neurotransmitter, is a member of the tochynin family of peptides, which includes neurokinins A and B (NKA and NKB).[1] These peptides bind to a series of three neurokinin receptors, NK_1, NK_2 and NK_3, which have a selective affinity for SP, NKA and NKB, respectively.[2] Substance P shows a number of biological activities such as neurogenic inflammation,[3] pain transmission, regulation of the immune response,[4] rheumatoid arthritis,[5] ulcerative colitis,[6] and migraine.[7] The nonpeptidic neurokinin NK_1 receptor antagonists **2** and **3** are good synthetic targets due to a variety of biological activities since a cis-relationship between the two substituents on the piperidine ring is essential for high-affinity binding to the human NK_1 receptor. Various synthetic strategies have been reported for the valuable intermediate **1**[8] and a few asymmetric syntheses for **2**,[9] mainly using chiral pool starting materials. As a part of our research program aimed at developing enantioselective syntheses of naturally occurring lactones[10] and amino alcohols,[11] we became interested in developing a practical and concise route to **(+)-L-733,060**. Herein, we report a new and enantioselective synthesis of **(+)-L-733,060** employing a Sharpless asymmetric aminohydroxylation as the source of chirality (Fig. 1).

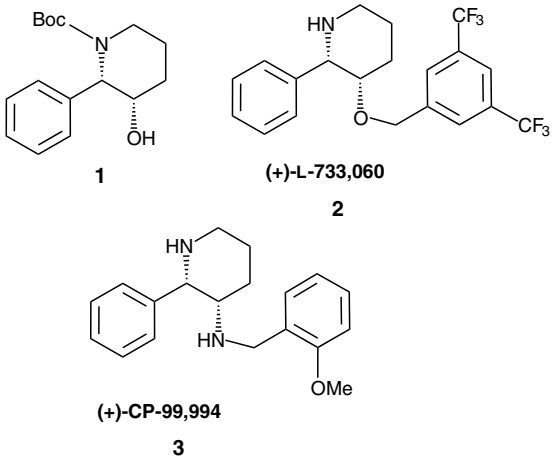

Figure 1.

2. Results and discussion

The synthesis of **(+)-L-733,060** commenced from cinnamic acid **4**, a commercially available starting material, as illustrated in Scheme 1. Cinnamic acid **4** was first converted to isopropyl cinnamate **5** using isopropanol and a catalytic amount of HCl under reflux conditions. Compound **5** was subjected to a Sharpless asymmetric aminohydroxylation[12] using $(DHQ)_2PHAL$ ligand, freshly prepared *N*-bromoacetamide[13] as the nitrogen source and potassium osmate as the oxidant to give the desired amino alcohol **6**[12] as a single isomer in 76% yield and with >99% ee[12c] $[\alpha]_D^{25} = +28.5$ (*c* 1.0, $CHCl_3$) {lit.[12c] $[\alpha]_D^{18} = +28.3$ (*c* 1.0, $CHCl_3$)}. The physical and spectroscopic data of **6** were in full agreement with those reported.[12c] Furthermore, in order to achieve the synthesis of target compound **2** from **6**, we required a suitable amino protecting group for further synthetic manipulations. To this end, amide **6** was subjected to hydrolysis in methanol under reflux to furnish the

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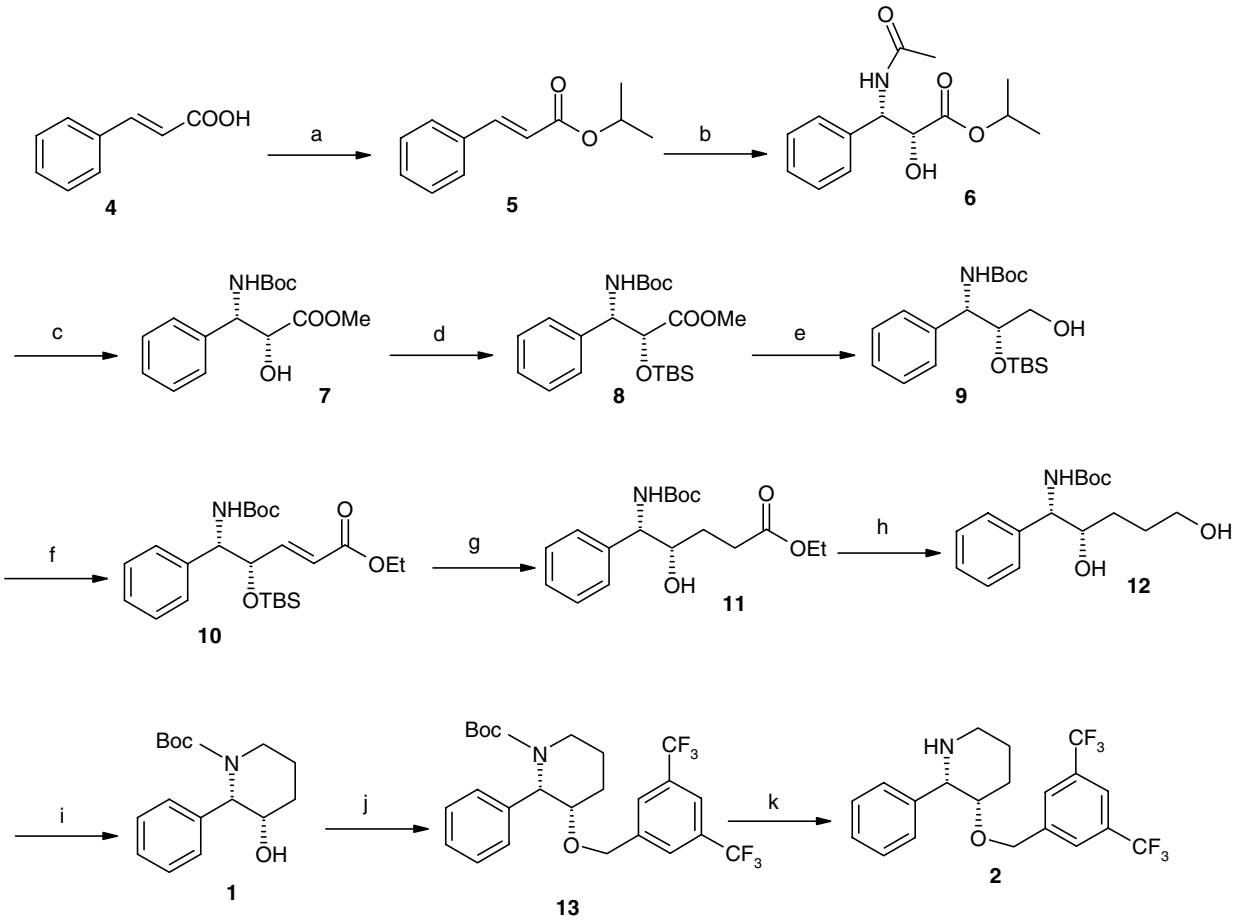

Scheme 1. Reagents and conditions: (a) isopropanol, HCl (cat.), reflux, 12 h, 76%; (b) $(DHQ)_2PHAL$, $K_2[OsO_2(OH)_4]$, $CH_3CONHBr$, LiOH, *t*-BuOH–H_2O (1:1), −5 °C, 4 h, 76%; (c) (i) 0.5 M HCl, MeOH, reflux, 15 h, (ii) Boc_2O, Et_3N, dry CH_2Cl_2, 0–25 °C, 24 h, 94%; (d) TBDMSCl, imidazole, DMAP(cat.), dry CH_2Cl_2, 25 °C, 10 h, 91%; (e) DIBAL-H, dry CH_2Cl_2, 0–25 °C, 3 h, 93%; (f) (i) PCC, anhyd CH_3COONa, Celite, 5 h, 25 °C, (ii) $Ph_3P{=}CHCOOEt$, dry THF, 25 °C, 24 h, 91%; (g) 10% Pd/C, MeOH, 25 °C, 6 h, 93%; (h) DIBAL-H, dry CH_2Cl_2, 0–25 °C, 3 h, 90%; (i) CH_3SO_2Cl, Et_3N, dry CH_2Cl_2, −78 °C, 1 h, 77%; (j) 3,5-bis-(trifluoromethyl)benzyl bromide, NaH, dry DMF, 80 °C, 12 h, 78%; (k) CF_3COOH, methanol, 25 °C, 1 h, 70%.

free amine with concomitant transesterification to the methyl ester.[12c] The successive conversion of the amine into the Boc protected amino alcohol **7** was carried out using Boc_2O in the presence of triethyl amine. It is noteworthy that although compound **7** has been prepared in a straightforward manner by the Sharpless asymmetric aminohydroxylation of methyl cinnamate using *t*-butyl carbamate as a nitrogen source, the enantiomeric purity obtained for **7** was not very high (80% ee).[14] Therefore, in order to prepare the enantiomerically pure aminohydroxy compound **7**, we followed a sequence of reaction from **4** to **7** as depicted in Scheme 1. Having achieved the synthesis of **7** in high enantiomeric purity, we then proceeded with the protection of the hydroxyl group as the TBS–ether to afford **8** in 91% yield. The ester group of **8** was reduced to the corresponding alcohol **9** using DIBAL-H at 0 °C–rt. The oxidation of alcohol **9** was carried out using PCC to give the corresponding aldehyde which on subsequent, Wittig reaction with (ethoxycarbonylmethylene)triphenylphosphorane, afforded olefin **10** in good yield. The olefin reduction by hydrogenation using 10% Pd/C resulted in the concomitant deprotection of the TBS group to furnish compound **11** in excellent yield. The subsequent ester reduction with DIBAL-H in dry CH_2Cl_2 at 0 °C–rt afforded amino diol **12**, which was subjected to cyclization using methanesulfonyl chloride and triethyl amine at −78 °C to furnish the piperidine derivative **1**[9a] in 77% yield. Etherification of the hydroxyl group with 3,5-bis(trifluoromethyl)benzyl bromide using NaH as base gave **13** in 78% yield. Finally, *N*-Boc deprotection of **13**[9a] using TFA afforded the target molecule **(2*S*,3*S*)-(+)-L-733,060** in good yield. The physical and spectroscopic data of **2** were in full agreement with those reported.[9a]

3. Conclusion

In conclusion, a highly enantioselective synthesis of **(+)-L-733,060** has been achieved by employing a Sharpless asymmetric aminohydroxylation and Wittig reaction as key steps. The merits of this synthesis are high yielding steps and high enantioselectivity. To the best of our knowledge, this is the first asymmetric synthesis employing a Sharpless asymmetric aminohydroxylation as the

source of chirality. The synthetic strategy described herein has significant potential for further extension to other NK_1 receptor antagonists.

4. Experimental

4.1. General information

The solvents were purified and dried by the standard procedures prior to use; petroleum ether of boiling range 60–80 °C was used. Optical rotations were measured using a sodium D line on a JASCO-P-1020-polarimeter. Infrared spectra were recorded on Perkin–Elmer FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer. Enantiomeric excesses were measured using either the chiral HPLC or by comparison with optical rotation. Elemental analyses were carried out with a Carlo Erba CHNS–O analyzer.

4.2. Synthesis of *trans*-isopropyl cinnamate 5

To a solution of cinnamic acid **4** (10 g, 67.49 mmol) in isopropanol (60 mL) was added a cat. amount of HCl. The reaction mixture was refluxed for 12 h neutralized with solid $NaHCO_3$ and filtered off. The solvent was evaporated and the residue obtained, purified by silica gel column chromatography using EtOAc–pet. ether (0.5:9.5) as eluent to give **5** (9.76 g) as a colourless oil. Yield: 76%; IR (neat, cm^{-1}): ν_{max} 1713, 1620, 1502, 1486, 1393; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.32 (d, $J = 5$ Hz, 6H), 5.14–5.17 (m, 1H), 6.43 (d, $J = 20$ Hz, 1H), 7.38–7.52 (m, 3H), 7.50 (d, $J = 20$ Hz, 1H), 7.68 (d, $J = 20$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.8, 67.6, 118.7, 127.8, 128.7, 129.9, 134.4, 144.1, 166.3. Anal. Calcd for $C_{12}H_{14}O_2$ (190.24): C, 75.76; H, 7.42. Found: C, 75.72; H, 7.39.

4.3. Synthesis of isopropyl (2*R*,3*S*)-3-(acetylamino)-2-hydroxy-3-phenylpropionate 6

$K_2[OsO_2(OH)_4]$ (90 mg, 1.5 mol %) was dissolved with stirring in 60 mL of aqueous solution of $LiOH{\cdot}H_2O$ (0.69 g, 16.42 mmol). After the addition of *t*-BuOH (90 mL), $(DHQ)_2PHAL$ [123 mg, 1 mol %] was added and the mixture immersed in a cooling bath set at 4 °C. After the addition of isopropyl cinnamate **5** (3 g, 15.77 mmol), *N*-bromo acetamide (2.37 g, 17.77 mmol) was added in one portion, which resulted in an immediate colour change to green and the mixture vigorously stirred at the same temperature. The reaction was monitored by TLC, and pH (full conversion is indicated when the reaction mixture attains pH 7). After 4 h, the reaction mixture was treated with Na_2SO_3 (2.5 g) and stirred at rt for 30 min. The organic layer was separated and the water layer extracted with ethyl acetate (3×60 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The residue was purified by silica gel column chromatography using EtOAc–pet. ether (6:4) to afford **6** (3.2 g) as a white solid. Yield: 76%; $[\alpha]_D^{25} = +28.5$ (*c* 1.0, $CHCl_3$) {lit.[12c] $[\alpha]_D^{18} = +28.3$ (*c* 1.0, $CHCl_3$)}; mp: 112 °C [lit.[12c] mp 111–112 °C]; IR ($CHCl_3$, cm^{-1}): ν_{max} 3492, 3362, 1713, 1620, 1562, 1446, 1343; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.31 (d, $J = 6.4$ Hz, 6H), 2.02 (s, 3H), 3.32 (br s, 1H, OH), 4.49 (dd, $J = 2.2$, 3.6 Hz, 1H), 5.10–5.15 (m, 1H), 5.57 (d, $J = 10$ Hz, 1H), 6.27 (d, $J = 10$ Hz, 1H), 7.31–7.41 (m, 5H).

4.4. Synthesis of methyl (2*R*,3*S*)-3-(*tert*-butoxy carbonylamino)-2-hydroxy-3-phenylpropionate 7

Amino alcohol **6** (0.52 g, 1.95 mmol) was treated with 0.5 M HCl in methanol (50 mL) and heated under reflux for 15 h. After removal of the solvent under reduced pressure, the residue was dissolved in fresh methanol (2×50 mL) and evaporated. Dry CH_2Cl_2 (20 mL) was added to the residue and the solution cooled to 0 °C. To this suspension was added triethyl amine (0.68 mL, 4.08 mmol) in dry CH_2Cl_2 (3 mL) followed by Boc_2O (0.67 mL, 2.9 mmol) in dry CH_2Cl_2 (2 mL). The reaction mixture was stirred for 30 min at 0 °C and then for 24 h at room temperature. After TLC diagnosis, the reaction mixture was evaporated to near dryness and purified by silica gel column chromatography using EtOAc–pet. ether (3:7) to afford **7** (0.54 g) as a white crystalline solid. Yield: 94%; mp: 129 °C; $[\alpha]_D^{25} = -7.1$ (*c* 0.89, $CHCl_3$) {lit.[12c] $[\alpha]_D^{25} = -7.3$ (*c* 1, $CHCl_3$)}; IR ($CHCl_3$, cm^{-1}): ν_{max} 3521, 3362, 1722, 1682, 1517; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.43 (s, 9H), 1.62 (br s, 1H), 3.84 (s, 3H), 4.48–4.49 (m, 1H), 5.22 (d, $J = 8$ Hz, 1H), 5.40 (d, $J = 6$ Hz, 1H), 7.29–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 28.1, 52.8, 56.0, 73.4, 78.9, 126.6, 127.5, 128.4, 139.0, 155.1, 173.2.

4.5. Synthesis of methyl (2*R*,3*S*)-3-(*tert*-butoxycarbonylamino)-2-(*tert*-butyldimethyl-silanyloxy)-3-phenylpropionate 8

To a solution of **7** (0.3 g, 1.02 mmol), in dry CH_2Cl_2 (10 mL) were added imidazole (72 mg, 1.06 mmol), TBDMSCl (0.24 g, 1.59 mmol) and cat. DMAP (6 mg, 0.051 mmol) sequentially. The resulting solution was stirred at rt for 10 h. The solvent was evaporated under reduced pressure and the residue extracted with dichloromethane. The organic layer was separated and dried over Na_2SO_4. The crude product was purified by silica gel column chromatography using EtOAc–pet. ether (1:9) to give **8** (0.38 g) as a colourless liquid. Yield: 91%; $[\alpha]_D^{25} = +11.0$ (*c* 0.92, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3368, 1734, 1634, 1533, 1414; ^1H NMR ($CDCl_3$, 200 MHz): δ −0.17 (s, 3H), −0.08 (s, 3H), 0.75 (s, 9H), 1.43 (s, 9H), 3.78 (s, 3H), 4.44 (d, $J = 10$ Hz, 1H), 5.21 (d, $J = 9.2$ Hz, 1H), 5.53 (d, $J = 8.7$ Hz, 1H), 7.24–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ −6.1, −5.7, 0.9, 18.0, 25.3, 28.1, 52.0, 57.0, 75.7, 126.4, 127.2, 128.1, 139.5, 155.0, 171.6. Anal. Calcd for $C_{21}H_{35}NO_5Si$ (409.57): C, 61.58; H, 8.61; N, 3.42. Found. C, 61.43; H, 8.57; N, 3.39.

4.6. Synthesis of (2*R*,3*S*)-2-[(*tert*-butyldimethyl-silanyloxy)-3-hydroxy-1-phenylpropyl]-carbamic acid *tert*-butyl ester 9

To a solution of **8** (0.225 g, 0.57 mmol) in dry dichloromethane (5 mL) was added a 1 M solution of DIBAL-H (1.42 mL, 1.42 mmol) dropwise at 0 °C and reaction

mixture stirred for 3 h. The solution was cooled to 0 °C and quenched with saturated sodium potassium tartrate (2 mL), filtered through Celite pad and concentrated to near dryness. The crude product was purified by silica gel column chromatography using EtOAc–pet. ether (7:3) as eluent to give **9** (0.195 g) as a colourless oil. Yield: 93%; $[\alpha]_D^{25} = +34.3$ (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3520, 3312, 1562, 1423, 1399; ^1H NMR ($CDCl_3$, 200 MHz): δ −0.17, (s, 3H), −0.08 (s, 3H), 0.75 (s, 9H), 1.43 (s, 9H), 1.62, (br s, 1H, OH), 3.78 (d, $J = 8.7$ Hz, 2H), 4.38–4.41 (m, 1H), 4.71 (d, $J = 9.2$ Hz, 1H), 5.53 (d, $J = 8.7$ Hz, 1H), 7.24–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.7, −5.4, 17.8, 25.5, 28.2, 29.6, 60.1, 64.6, 70.4, 126.5, 126.7, 127.5, 128.4, 137.2, 153.6. Anal. Calcd for $C_{20}H_{35}NO_4Si$ (381.56): C, 62.95; H, 9.25; N, 3.67. Found: C, 62.92; H, 9.21; N, 3.62.

4.7. Synthesis of (4*S*,5*S*)-5-*tert*-butoxycarbonylamino-4-[(*tert*-butyldimethylsilanyloxy)-5-phenylpent-2-enoic acid ethyl ester 10

To a mixture of PCC (0.144 g, 0.67 mmol), Celite powder (200 mg) and anhydrous CH_3COONa (0.54 g, 0.67 mmol) in dry CH_2Cl_2 (5 mL) was added alcohol **9** (0.17 g, 0.45 mmol) at 0 °C. The reaction mixture was stirred for 5 h at rt. The solvent was evaporated and to the residue added ether. The slurry was stirred and filtered through a pad of Celite. The residue was washed 4–5 times with ether. The filtrate was concentrated to give the aldehyde, which was used in the next reaction without any further purification.

To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (0.15 g, 0.43 mmol) in dry THF (5 mL) was added a solution of the above crude aldehyde (0.12 g, 0.32 mmol) in THF (3 mL) at 0 °C. The ice-bath was removed and the reaction mixture stirred at rt for 24 h and concentrated. Silica gel column chromatography of the crude product using EtOAc–pet. ether (0.5:9.5) as eluent gave **10** (0.13 g) as a colourless liquid. Yield: 91%; $[\alpha]_D^{25} = +10.6$ (*c* 0.74, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3342, 1719, 1621, 1522, 1463, 1322; ^1H NMR ($CDCl_3$, 200 MHz): δ −0.23 (s, 3H), 0.04 (s, 3H), 0.77 (s, 9H), 0.86 (t, $J = 6.2$ Hz, 3H), 1.22 (s, 9H), 4.16 (q, $J = 14.2$ Hz, 2H), 4.46–4.53 (m, 1H), 4.84 (d, $J = 7.4$ Hz, 1H), 5.28 (d, $J = 13.3$, 1H), 5.99 (d, $J = 15.1$ Hz, 1H), 6.99 (dd, $J = 15.6$, 4.58 Hz, 1H). 7.20–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ −6.0, −5.0, 0.9, 14.1, 18.0, 25.7, 28.2, 29.6, 60.4, 122.1, 126.4, 127.3, 128.2, 147.6, 155.4, 166.1. Anal. Calcd for $C_{24}H_{39}NO_5Si$ (449.63): C, 64.11; H, 8.74; N, 3.11. Found. C, 63.98; H, 8.71; N, 3.08.

4.8. Synthesis of (4*S*,5*S*)-5-(*tert*-butoxycarbonylamino)-4-hydroxy-5-phenylpentanoic acid ethyl ester 11

To a solution of **10** (0.2 g) in methanol (10 mL) was added 20 mg of 10% Pd/C and mixture stirred under a hydrogen atmosphere for 6 h. After completion of reaction, the solution was filtered and the filtrate was concentrated. The crude product was purified on silica gel column using EtOAc–pet. ether (1:9) as eluent to give **11** (0.14 g) as a viscous liquid. Yield: 93%; $[\alpha]_D^{25} = +10.8$ (*c* 0.68, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 1722, 1533, 1462, 1366, 1252; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.93 (t, $J = 9.2$ Hz, 3H), 1.45 (s, 9H), 1.84–1.94 (m, 2H), 2.02 (br s, 1H), 2.41–2.50 (m, 2H), 3.87–3.90 (m, 1H), 4.12 (q, $J = 8$ Hz, 2H), 4.74–4.81 (m, 1H), 5.44 (d, $J = 4$ Hz, 1H), 7.19–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): 14.0, 25.3, 26.3, 29.2, 64.8, 66.7, 67.8, 71.7, 126.8, 127.8, 127.9, 128.3, 157.2, 170.0. Anal. Calcd for $C_{18}H_{27}NO_5$ (337.40): C, 64.07; H, 8.07; N, 4.15. Found: C, 64.03; H, 8.02; N, 4.13.

4.9. Synthesis of (4*S*,5*S*)-(2,5-dihydroxy-1-phenylpentyl)-carbamic acid *tert*-butyl ester 12

To a stirred solution of **11** (0.19 g, 0.56 mmol) was added DIBAL-H (2.3 M solution in toluene, 0.8 mL, 2.5 mmol) at 0 °C. The reaction mixture was stirred for another 3 h at room temperature and then quenched with saturated sodium potassium tartrate, filtered through Celite powder and concentrated to near dryness. The crude product was purified by silica gel column chromatography using EtOAc–pet. ether (3:7) as eluent to give **12** (0.15 g) as a colourless liquid. Yield: 90%; $[\alpha]_D^{25} = +15.1$ (*c* 0.32, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3541, 3326, 1523, 1463, 1262; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.44–1.48 (m, 4H), 1.46 (s, 9H), 2.12 (br s, 2H), 3.52–3.57 (m, 2H), 4.52–4.63 (m, 1H), 4.73 (d, $J = 12$ Hz, 1H), 5.54 (d, $J = 12.5$ Hz, 1H), 7.19–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): 26.7, 27.0, 29.3, 29.6, 63.3, 70.6, 77.6, 124.2, 126.4, 127.1, 129.3, 156.5. Anal. Calcd for $C_{16}H_{25}NO_4$ (295.36): C, 65.06; H, 8.53; N, 4.74. Found. C, 65.03; H, 8.50; N, 4.72.

4.10. Synthesis of (2*S*,3*S*)-3-hydroxy-2-phenyl-piperidine-1-carboxylic acid *tert*-butyl ester 1

To a stirred solution of **12** (0.1 g, 0.34 mmol) in dry dichloromethane (5 mL) was added methanesulfonyl chloride (0.028 mL, 0.37 mmol) at −78 °C followed by triethyl amine (0.051 mL, 0.37 mmol). After the mixture was stirred at −78 °C for 1 h, aqueous ammonium chloride (3 mL) was added. The mixture was warmed to room temperature and diluted with dichloromethane (10 mL), washed with brine and dried over Na_2SO_4. The solvent was removed and residue was purified by flash chromatography using EtOAc–pet. ether as eluent (8:2) to give **1** (72 mg) as a yellow liquid. Yield: 77%; $[\alpha]_D^{25} = +36.2$ (*c* 0.66, $CHCl_3$) {lit.[9a] +38.3 (*c* 1.92, $CHCl_3$)}; IR ($CHCl_3$, cm^{-1}): ν_{max} 3445, 2933, 1702, 1410, 1352, 1230, 1160; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.40 (s, 9H), 1.52–1.67 (m, 4H), 2.81 (ddd, $J = 6.2$, 10.5, 12.6 Hz, 1H), 3.88–4.05 (m, 1H), 4.12–4.24 (m, 1H), 4.48 (d, $J = 7.5$ Hz, 1H), 5.31 (d, $J = 5.6$ Hz, 1H), 7.17–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 24.1, 27.3, 28.2, 39.0, 62.1, 69.4, 80.0, 127.1, 128.2, 128.3, 138.0, 156.0.

4.11. Synthesis of (2*S*,3*S*)-1-(*tert*-butyoxycarbonyl)-2-phenyl-3-[(3,5)-bis(trifluoromethyl)benzyloxy]piperidine 13

To a stirred solution of sodium hydride (10 mg, 60% dispersion in mineral oil, 0.43 mmol) and dry DMF (1 mL) at 0 °C, was added a solution of **1** (0.1 g, 0.36 mmol) and

3,5-bis(trifluoromethyl)benzyl bromide (110 mg, 0.36 mmol) in dry DMF (1 mL). The reaction mixture was stirred for 12 h at 80 °C. The reaction was quenched with water (3 mL) and extracted with Et_2O (5 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel column using EtOAc–pet. ether (3:7) to provide **13** (0.14 g) as a colourless oil. Yield: 78%; $[\alpha]_D^{25} = +31.4$ (*c* 1.0, $CHCl_3$) {lit.[9a] $[\alpha]_D^{25} = +30.38$ (*c* 1.55, $CHCl_3$)}; IR (neat, cm^{-1}): ν_{max} 2945, 1644, 1381, 1345, 1253, 1172, 875, 665; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.42 (s, 9H), 1.32–1.66 (m, 2H), 1.78–2.12 (m, 2H), 2.76 (ddd, $J = 11.2$, 9.8, 4.6 Hz, 1H), 3.79–3.98 (m, 2H), 4.66 (d, $J = 11.4$ Hz, 1H), 4.74 (d, $J = 12.2$ Hz, 1H), 5.67 (d, $J = 4.6$ Hz, 1H), 7.22–7.38 (m, 3H), 7.42–7.52 (m, 2H), 7.66 (s, 2H), 7.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): 20.2, 25.3, 26.3, 27.2, 44.4, 63.2, 71.2, 77.0, 120.2, 123.1, 126.7, 127.3, 127.8, 132.4, 141.2, 142.4, 159.0.

4.12. Synthesis of (2*S*,3*S*)-2-phenyl-3-[(3,5)-bis(trifluoromethyl)benzyloxy]piperidine [(+)-L-733,060] 2

To an ice-bath solution of **13** (25 mg, 0.05 mmol) in dry CH_2Cl_2 (1 mL) was added trifluoroacetic acid (73 μL, 0.05 mmol). The reaction mixture was stirred at room temperature for 12 h and then quenched with saturated $NaHCO_3$ and extracted with dichloromethane (3×5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using CH_3OH–$CHCl_3$ (1:9) as eluent to give **2** (14 mg), $[\alpha]_D^{25} = +36.2$ (*c* 0.66, $CHCl_3$) {lit.[9a] $[\alpha]_D^{25} = +34.3$ (*c* 1.32, $CHCl_3$)}. Yield: 70%. The physical and spectroscopic data of **2** were in full agreement with those reported.[9a]

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