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Enantioselective synthesis of (+)-L-733,060

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Abstract—An efficient enantioselective synthesis of (+)-L-733,060 from cinnamyl alcohol is described. The key steps include a Sharpless asymmetric epoxidation, a regioselective allyl opening of an epoxide and piperidine ring formation via a one pot Staudinger/aza-Wittig reaction.

1. Introduction

The peptide neurotransmitter, Substance P (SP) involves a variety of biological actions, such as pain transmission, vasodilation, smooth muscle contraction and neurogenic inflammation.[1] This tachykinin family peptide member preferentially binds to the NK1 receptor. The search for non-peptide antagonists of the NK1 receptor led to the discovery of 2,3-disubstituted piperidine derivatives L-733,060 **2**[2] and CP-99,994 **3**[3] (Fig. 1). They have excellent affinity and selectivity with human NK1 receptors and possess potent antiemetic activity.[4] They are expected to act as a remedy for a wide range of diseases, including arthritis, asthma and migrain.[5]

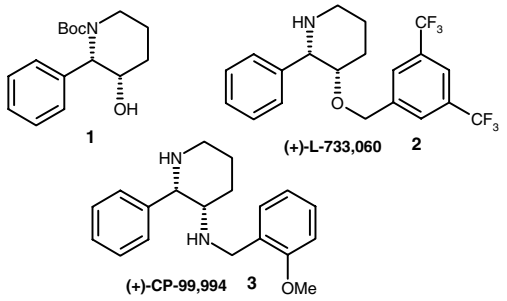

Figure 1.

In recent years, there have been several reports on the synthesis and structural modification studies of the above compounds. Structure–activity relationship studies have shown that the *cis*-relationship between C2 and C3 substituents on the piperidine ring of **2** and **3** is required for optimum binding activity.[6] Routes leading to the valuable intermediate **1** and compounds **2** and **3** mainly rely on racemic synthesis followed by resolution techniques[2b] or lengthy asymmetric synthesis of **1** and **2**, which has been reported in recent literatures.[8] In continuation of our research programme aimed at developing enantioselective synthetic routes to the lactones[9] and amino alcohols,[10] we have developed a new asymmetric synthetic strategy to (+)-L- 733,060 **2**. In this strategy the chirality was introduced by a Sharpless asymmetric epoxidation (AE) while piperidine ring formation was achieved by one pot Staudinger/aza-Wittig reaction.

2. Results and discussion

As shown in Scheme 1, the synthesis of (+)-L-733,060 was initiated by AE of commercially available cinnamyl alcohol **4** to afford *trans*-epoxide **5** in 89% yield with >99% ee. (After recrystallization) $[\alpha]_D^{27} = +48.7$ (*c* 2.4, $CHCl_3$) {lit.[11] $[\alpha]_D^{25} = -49.6$ (*c* 2.4, $CHCl_3$) for (−)-**5**}. The regioselective epoxide opening of **5** with NaN_3 gave a single regioisomer **6** in excellent yield.[12] In order to establish the desired *cis*-configuration, we planned a three-step sequence involving the chemoselective pivalation[13] of diol **6**, mesylation of secondary hydroxyl **7** using MsCl and final treatment of crude mesylate **8** with K_2CO_3 in methanol to furnish the appropriately oriented *cis*-azido-epoxide **9** in 80% overall yield.

With a substantial amount of epoxide **9** in hands, our next aim was to elongate the chain through regioselective ring opening of epoxide **9** by allylation (Scheme 2). The

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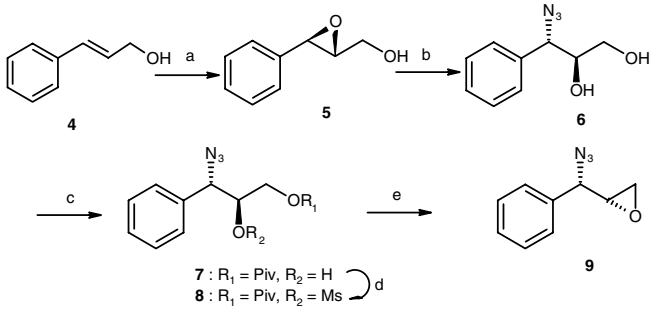
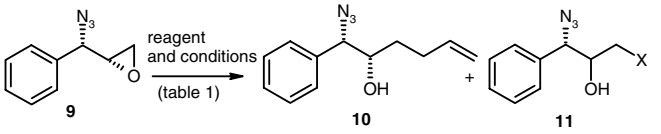


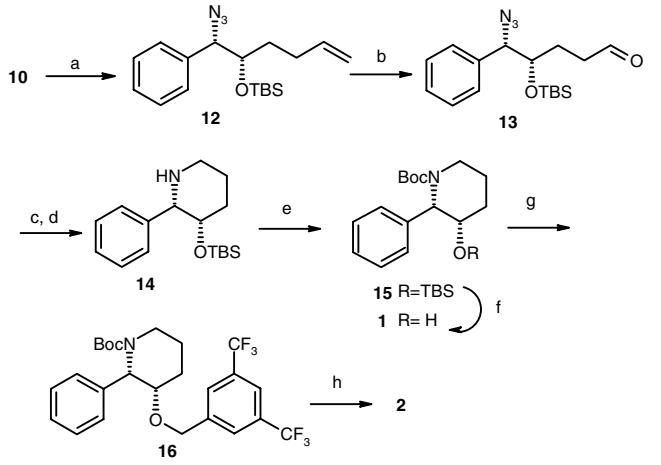
Scheme 1. Reagents and conditions: (a) (*S*,*S*)-(−)-DET, $Ti(OPr\text{-}i)_4$, TBHP, MS 4 Å, CH_2Cl_2, −20 °C, 3 h, 89%; (b) NaN_3, NH_4Cl, MeOH/H_2O (8:1), 65 °C, 5 h, 98%; (c) PivCl, Py/CH_2Cl_2 (1:1), 0 °C–rt, 5 h; (d) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C–rt, 1 h; (e) K_2CO_3, MeOH, rt, overnight, 80% (overall 3 steps).

results are summarized in Table 1. Opening of epoxide **9** with allylmagnesium bromide[14a] (entry 1) gave only halide opened byproducts. Similarly the use of $BF_3{\cdot}OEt_2$ with allylsilane was also disappointing as it resulted in poor yields of the desired product **10** (entries 2 and 3) along with the hydroxyl opened product as major one. The reaction with allylstannane and $TiCl_4$ in CH_2Cl_2 at −78 °C[14b] (entry 4) also failed to give allylated product **10**. The use of 1:1 equiv amounts of allylsilane and $TiCl_4$ in CH_2Cl_2 at −78 °C gave **10** in moderate yield (entry 5). We were finally able to improve the yield of **10** by using 3 equiv of allylsilane with slow addition of freshly distilled $TiCl_4$ (entry 6). The subsequent protection of the secondary hydroxyl group as a TBS ether was successfully carried out using TBS triflate and 2,6-lutidine[15] to afford **12** in 95% yield (Scheme 3).

According to our synthetic strategy, compound **12** had all the ideal functionalities to carry out the required heterocyclic ring formation reaction. The oxidation of olefin[16] **12** gave the crucial azido-aldehyde intermediate **13** required for the one pot Staudinger/aza-Wittig reaction.[17] Without further purification of aldehyde **13**, the Staudinger reduction was performed by the addition of triphenylphosphine to azido-aldehyde **13** in dry THF. The resulting aza-ylide was condensed intramolecularly with aldehyde to provide a six membered imine. The in situ reduction of the imine with $NaBH_4$ and methanol in the same reaction medium provided the free amine **14** in good yield. Subsequently free amine **14** was protected as a Boc derivative and TBS was selectively deprotected using TBAF to obtain compound **1**[18] in 90% yields. Etherification of the hydroxy group of **1** with 3,5-bis(trifluoromethyl)benzyl bromide in the presence of NaH afforded **16**.[7b] Finally *N*-Boc deprotection of **16** using TFA furnished the target molecule **2** in good



Scheme 2.



Scheme 3. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, 0 °C, 1 h, 95%; (b) OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-dioxane/H_2O (3:1), 0 °C, 3 h; (c) PPh_3, THF, rt, 16 h; (d) $NaBH_4$, MeOH, 0 °C, 30 min, (65% yield from **12**); (e) Boc_2O,Et_3N, CH_2Cl_2, 2 h, 95%; (f) TBAF, THF, 0 °C–rt, 10 h, 90%; (g) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, dry DMF, 80 °C, 12 h, 78%; (h) CF_3COOH, MeOH, rt, 12 h, 70%.

yields. The physical and spectroscopic data of **2** were in full agreement with those reported.[7b]

3. Conclusion

In conclusion, a flexible and highly enantioselective synthesis of (+)-L-733,060 has been achieved by employing a Sharpless asymmetric epoxidation and a one pot Staudinger/aza-Wittig reaction as key steps. The synthetic strategy described herein has significant potential for further extension to other NK1 receptor antagonists. Studies are currently in progress in this direction.

4. Experimental

4.1. General experimental

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

Table 1. Allyl opening of epoxide **9** by different nucleophiles under various reaction conditions

Entry	Reaction conditions	Yield % of **10**	Yield % of **11**
1	Allylmagnesium bromide, CuI, THF, 0 °C–rt, over night	—	90% X = Br, I
2	Allyltrimethylsilane, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 2 h	5	75% X = OH
3	Allyltrimethylsilane, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −30 °C to 0 °C, 3 h	8	60% X = OH
4	Allyltributylstannane, $TiCl_4$, CH_2Cl_2, −78 °C, 1 h	—	90% X = Cl
5	Allyltrimethylsilane (1 equiv), $TiCl_4$, CH_2Cl_2, −78 °C, 1 h	55	25% X = Cl
6	Allyltrimethylsilane (3 equiv), $TiCl_4$, CH_2Cl_2, −78 °C, 1 h	65	10% X = Cl

sodium D line on a JASCO-P-1020-polarimeter. Infrared spectra were recorded on Perkin–Elmer FT-IR spectrometer. Enantiomeric excess was measured using either the chiral HPLC or by comparison with specific rotation. Elemental analyses were carried out with a Carlo Erba CHNS-O analyzer.

4.2. Synthesis of (2*R*,3*R*)-(3-phenyl-oxiranyl)-methanol 5

To a stirred solution of (*S*,*S*)-(−)-diisopropyl tartrate (0.83 mL, 0.92 g, 3.91 mmol) in CH_2C1_2 (450 mL) at −20 °C, 2.8 g activated powdered 4 Å molecular sieves, Ti(OPr-*i*)$_4$ (0.78 mL, 0.74 g, 2.61 mmol) and 3 M solution of TBHP in toluene (34.78 mL, 104.34 mmol) were added sequentially. The mixture was allowed to stir at −20 °C for 1 h and then a solution of freshly distilled (*E*)-3-phenyl-2-propenol (cinnamyl alcohol) (7.0 g, 52.17 mmol) in 10 mL of CH_2C1_2 was added dropwise over 30 min. After 3 h at −20 °C, the reaction was quenched at −20 °C with 10% aqueous solution of NaOH saturated with NaCl (4.2 mL). After diethyl ether (60 mL) was added the cold bath was allowed to warm to 10 °C, stirring was maintained at 10 °C while $MgSO_4$ (5 g) and Celite (500 mg) were added. After another 15 min of stirring, the mixture was allowed to settle and clean solution was filtered through a pad of Celite and washed with diethyl ether. Azeotropic removal of TBHP with toluene at a reduced pressure and subjection to high vacuum gave **5** as a yellow oil. Recrystallization from petroleum ether/diethylether gave yellow crystals of **5** (6.97 g, 89%, >99% ee determined by spectroscopic analysis of the ester derived from (+)-MTPA chloride) mp = 53.5–54 °C $[\alpha]_D^{27} = +48.7$ (*c* 2.4, $CHCl_3$) {lit.[11] $[\alpha]_D^{25} = -49.6$ (*c* 2.4, $CHCl_3$) for (−)-**5**}. IR ($CHCl_3$, cm^{-1}): 3428, 3017, 2927, 2871, 1606, 1462, 1392, 1256, 1108, 1068, 1027, 881, 863, 840, 758; ^1H NMR ($CDCl_3$, 200 MHz): 2.25 (br s, 1H), 3.26–3.32 (m, 1H), 3.76–3.84 (d, $J = 4.6$, 12.8 Hz, 1H), 3.93–3.94 (d, $J = 2.5$ Hz, 1H), 4.02–4.10 (dd, $J = 2.57$, 12.76 Hz, 1H), 7.2–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): 55.58, 61.23, 62.44, 127.57, 128.08, 128.28, 136.48. Anal. Calcd for $C_9H_{10}O_2$ (150.18): C, 71.98; H, 6.71. Found. C, 71.94; H, 6.82.

4.3. Synthesis of (2*S*,3*S*)-3-azido-3-phenyl-propane-1,2-diol 6

The epoxy alcohol **5** (6.0 g, 39.95 mmol), NaN_3 (5.19 g, 79.90 mmol) and NH_4Cl (4.27 g, 79.90 mmol) in a solvent mixture of methanol (32 mL) and water (4 mL) were warmed at 65 °C for 5 h. The reaction mixture was cooled and the solid filtered. The filtrate was concentrated to a residue, which was taken into ethyl acetate, washed with brine and water, dried and concentrated to give a syrup, which was purified by column chromatography (eluent: petroleum ether/EtOAc 7:3) to yield a yellow liquid **6**, 7.56 g (98%). $[\alpha]_D^{27} = +166.3$ (*c* 1.2, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3392, 3032, 2932, 2871, 2099, 1602, 1493, 1454, 1384, 1100, 1039, 877, 828, 759; ^1H NMR ($CDCl_3$, 200 MHz): 3.38 (br s, 2H), 3.58–3.75 (m, 2H), 3.78–3.86 (m, 1H), 4.57–4.67 (d, $J = 7$ Hz, 1H), 7.2–7.47 (5H, m); ^{13}C NMR ($CDCl_3$, 50 MHz): 62.83, 66.97, 73.97, 127.76, 128.76, 128.92, 136.02. Anal. Calcd for $C_9H_{11}N_3O_2$ (193.21): C, 55.95; H, 5.74; N, 21.75. Found: C, 55.91; H, 5.73; N, 21.84.

4.4. Synthesis of (2*R*,3*S*)-2-(azido-phenyl-methyl)-oxirane 9

Diol **6** (7.0 g, 36.23 mmol) was dissolved in dry pyridine (40 mL) and dry CH_2Cl_2 (40 mL) at 0 °C under argon and pivaloyl chloride (4.44 mL, 36.23 mmol) was added dropwise over a period of 30 min. The mixture was stirred at room temperature for 5 h. Concentration followed by azeotropic removal of pyridine gave compound **7**, which was used in the next reaction without any further purification.

Compound **7** was then dissolved in dry CH_2Cl_2 (30 mL) under argon and treated with MsCl (2.80 mL, 36.23 mmol), Et_3N (6.0 mL, 43.34 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 1 h, then quenched with water. The water layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give a crude product **8**, which was dissolved in MeOH (20 mL) and treated with K_2CO_3 (5.0 g, 36.23 mmol). This mixture was stirred overnight at room temperature and then filtered through Celite. Removal of the volatiles under reduced pressure, followed by column chromatography on silica gel (eluent: petroleum ether/EtOAc 19:1) produced epoxide **9** (5.08 g, overall yield 80% from **6**) as a yellow liquid. $[\alpha]_D^{27} = +139.0$ (*c* 1.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3019, 2927, 2106, 1601, 1493, 1455, 1251, 1123, 863, 758; ^1H NMR ($CDCl_3$, 500 MHz): 2.77–2.78 (m, 1H), 2.84 (m, 1H), 3.28–3.30 (m, 1H), 4.29 (d, $J = 6$ Hz, 1H), 7.39–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): 44.84, 54.72, 66.89, 127.28, 128.95, 135.73. Anal. Calcd for $C_9H_9N_3O$ (175.19): C, 61.70; H, 5.18; N, 23.99. Found: C, 61.81; H, 5.15; N, 23.91.

4.5. Synthesis of (1*S*,2*S*)-1-azido-1-phenyl-hex-5-en-2-ol 10

To a stirred solution of **9** (3.0 g, 17.12 mmol) and allylTMS (8.16 g, 51.37 mmol) in CH_2Cl_2 (50 mL) at −78 °C, a solution of $TiC1_4$ (1.88 mL, 17.12 mmol) in CH_2Cl_2 (35 mL) was added through the cold inner surface of the flask over a period of 30 min. The mixture was stirred at this temperature for 1 h and then the cold bath removed. Subsequently, 30% aqueous $NaHCO_3$ (5 mL) and ether (50 mL) were added, and the mixture stirred vigorously while being allowed to return to room temperature. The organic phase was separated, washed with brine, dried over Na_2SO_4 and purified by silica gel column chromatography (eluent: petroleum ether/EtOAc 20:1) to give **10** as a yellow liquid, (2.42 g, 65%) $[\alpha]_D^{27} = +178.4$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3430, 3031, 2977, 2921, 2103, 1640, 1603, 1493, 1453, 1080, 995, 913, 874, 757, 701; ^1H NMR ($CDCl_3$, 400 MHz): 1.42–1.52 (m, 1H), 1.62–1.71 (m, 1H), 1.84 (br s, 1H), 2.05–2.18 (m, 1H), 2.23–2.31 (m, 1H), 3.80–3.84 (m, 1H), 4.49–4.50 (d, $J = 5.8$ Hz, 1H), 4.97–5.0 (m, 1H), 5.02–5.07 (m, 1H), 5.75–5.86 (m, 1H), 7.36–7.44 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): 29.78, 31.68, 70.52, 73.50, 115.12, 127.95, 128.78, 136.13, 137.97, 138.58. Anal. Calcd for $C_{12}H_{15}N_3O$ (217.27): C, 66.34; H, 6.96; N, 19.34. Found: C, 66.27; H, 6.91; N, 19.36.

4.6. Synthesis of (1*S*,2*S*)-[1-(azido-phenyl-methyl)-pent-4-enyloxy]-*tert*-butyl-dimethyl-silane 12

2,6-Lutidine (2.45 mL, 21.17 mmol) was added to a stirred solution of **10** (2.30 g, 10.58 mmol) in anhydrous CH_2Cl_2 (20 mL). After the solution was cooled to 0 °C with an ice-bath, TBSOTf (3.65 mL, 15.87 mmol) was added to it. The mixture was stirred for 1 h, then quenched with saturated NH_4Cl (10 mL), extracted with Et_2O (3×15 mL) and dried over anhydrous Na_2SO_4. After concentration, the crude product was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc 30:1) to afford compound **12**, 3.33 g (95%) as a brown liquid, $[\alpha]_D^{27} = +75.26$ (*c* 1.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3018, 2954, 2930, 2896, 2858, 2105, 1640, 1603, 1472, 1453, 1361, 1256, 1104, 1058, 976, 888, 837, 758; ^1H NMR ($CDCl_3$, 200 MHz): −0.06 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.42–1.57 (m, 1H), 1.56–1.81 (m, 1H), 1.94–2.09 (m, 1H), 2.13–2.27 (m, 1H), 3.86–3.96 (m, 1H), 4.56-4.59 (d, $J = 5.05$ Hz, 1H), 4.91–4.94 (m, 1H), 4.96–5.04 (m, 1H), 5.67–5.87 (m, 1H), 7.37–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): −4.72, −4.66, 18.02, 25.79, 28.99, 31.57, 69.72, 75.44, 114.59, 127.83, 128.03, 128.39, 137.13, 138.34. Anal. Calcd for $C_{18}H_{29}N_3OSi$ (331.54): C, 65.21; H, 8.82; N, 12.67; Si, 8.47. Found: C, 65.24, H, 8.83; N, 12.65; Si, 8.45.

4.7. Synthesis of (2*S*,3*S*)-3-(*tert*-butyl-dimethyl-silanyloxy)-2-phenyl-piperidine 14

To a solution of compound **12** (1.50 g, 4.52 mmol) in dioxane–water (3:1, 20 mL) were added 2,6-lutidine (1.05 mL, 9.04 mmol), OsO_4 (0.1 M solution in toluene, 0.78 mL, 0.023 g, 0.09 mmol) and $NaIO_4$ (3.87 g, 18.08 mmol). The reaction was stirred at 25 °C for 3 h. After the reaction was complete, water (10 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was separated, and the water layer extracted with CH_2Cl_2 (3×15 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. After concentration, compound **13** was used in the next reaction without any further purification.

To a solution of compound **13** at room temperature in THF (200 mL) was added solid PPh_3 (4.74 g, 18.08 mmol). The reaction was allowed to stir at room temperature for 16 h until all starting aldehyde was consumed. $NaBH_4$ (0.43 g, 11.30 mmol) and MeOH (0.51 mL, 11.30 mmol) were added at 0 °C. After stirring for 30 min, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuum. Purification by neutralized silica gel column chromatography (eluent: CH_2Cl_2/MeOH 100:1) afforded compound **14** (0.86 g, 65% yield) as a pale yellow oil. $[\alpha]_D^{27} = +51.5$ (*c* 1.1, MeOH); IR ($CHCl_3$, cm^{-1}): 3343, 3019, 2930, 2857, 1603, 1472, 1106, 931, 887, 758. ^1H NMR ($CDCl_3$, 200 MHz): −0.47 (s, 3H), −0.14 (s, 3H), 0.77 (s, 9H), 1.34 (br s, 1H), 1.44–1.73 (m, 2H), 1.71–1.85 (m, 2H), 2.70–2.83 (m, 1H), 3.12–3.18 (br s, 1H), 3.41–3.46 (d, $J = 8.7$ Hz, 1H), 3.52–3.63 (m, 1H), 7.27–7.49 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): −5.78, −4.94, 17.81, 25.31, 25.64, 35.33, 46.75, 69.38, 73.98, 127.33, 127.94, 128.40, 142.61. Calcd for $C_{17}H_{29}NOSi$ (291.51): C, 70.04; H, 10.03; N, 4.80; Si, 9.63. Found: C, 70.05; H, 10.01; N, 4.82; Si, 9.61.

4.8. Synthesis of (2*S*,3*S*)-1-[3-(*tert*-butyl-dimethyl-silanyl-oxy)-2-phenyl-piperidin-1-yl]-2,2-dimethyl-propan-1-one 15

To a suspension of compound **14** (0.6 g, 2.06 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.43 mL, 3.09 mmol). The mixture was cooled to 0 °C and $(Boc)_2O$ (0.71 mL, 3.09 mmol) was added dropwise with stirring. The mixture was then warmed to room temperature and stirred for 2 h. The reaction was quenched with saturated NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3×15 mL), dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the compound was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc 8:1) to give **15** as a pale yellow oil 0.77 g, (95%). $[\alpha]_D^{27} = +18.4$ (*c* 1.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3023, 3018, 2979, 2955, 1696, 1602, 1495, 1418, 1367, 1257, 1168, 1137, 984, 876, 851, 756; ^1H NMR ($CDCl_3$, 400 MHz): 0.05 (s, 3H), 0.14 (s, 3H), 0.92 (s, 9H), 1.50 (s, 9H), 1.66–1.69 (m, 2H), 1.77–1.80 (m, 1H), 1.90–1.96 (m, 1H), 2.71–2.78 (m, 1H), 3.96 (d, $J = 13$ Hz, 1H), 4.06–4.11 (m, 1H), 5.40 (d, $J = 4.5$ Hz, 1H), 7.23–7.35 (m, 3H), 7.58–7.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): −5.09, −4.93, 17.99, 23.98, 25.75, 27.88, 28.30, 38.62, 58.68, 71.87, 79.67, 126.44, 127.89, 126.46, 138.85, 155.25. Calcd for $C_{22}H_{37}NO_3Si$ (391.63): C, 67.47; H, 9.52; N, 3.58; Si, 7.17. Found: C, 67.43; H, 9.51; N, 3.61; Si, 7.15.

4.9. Synthesis of (2*S*,3*S*)-1-(3-Hydroxy-2-phenyl-piperidin-1-yl)-2,2-dimethyl-propan-1-one: 1

To a solution of **15** (0.60 g, 1.53 mmol) in anhydrous THF (20 mL) was added TBAF (2.30 mL, 1 M in THF, 2.30 mmol) successively with stirring. The mixture was stirred for 10 h, then quenched with water (10 mL) at 0 °C and diluted with CH_2Cl_2 (20 mL). After being stirred for about 10 min, the solution was extracted with CH_2Cl_2 (3×15 mL), and dried over anhydrous Na_2SO_4. After concentration, the crude product was purified by silica gel chromatography (eluent: petroleum ether/EtOAc 8:2) to afford product **1**, as a yellow oil 0.38 g (90%). $[\alpha]_D^{27} = +37.5$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3447, 3018, 2979, 2955, 1676, 1602, 1495, 1418, 1367, 1327, 1168, 1137, 984, 876, 851, 756; ^1H NMR ($CDCl_3$, 200 MHz): 1.40 (s, 9H), 1.55–2.01 (m, 5H), 2.74–2.89 (ddd, $J = 3.15$, 9.73, 12.88 Hz, 1H), 4.0–4.09 (m, 1H), 4.45–4.49 (m, 1H), 5.32 (m, 1H), 7.13–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): 23.98, 25.92, 28.36, 39.90, 60.24, 67.48, 80.11, 126.86, 126.89, 138.15, 156.70. Calcd for $C_{16}H_{23}NO_3$ (277.37): C, 69.29, H, 8.36, N, 5.05. Found: C, 69.31; H, 8.32; N, 5.01.

4.10. Synthesis of (2*S*,3*S*)-1-(*tert*-butyoxycarbonyl)-2-phenyl-3-[(3,5)-bis(trifluoromethyl)benzyloxy]piperidine 16

To a stirred solution of sodium hydride (0.020 mg, 60% dispersion in mineral oil, 0.83 mmol) and dry DMF (3 mL) at 0 °C, was added a solution of **1** (0.2 g, 0.72 mmol) and

3,5-bis(trifluoromethyl)benzyl bromide (0.22 g, 0.72 mmol) in dry DMF (2 mL). The reaction mixture was stirred for 12 h at 80 °C. The reaction was quenched with water (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel column (eluent: petroleum ether/EtOAc 7:3) to provide **16** (0.28 g) as a colourless oil. Yield: 78%; $[\alpha]_D^{25} = +31.4$ (*c* 1.0, $CHCl_3$) {lit.[7b] $[\alpha]_D^{25} = +30.4$ (*c* 1.55, $CHCl_3$)}; IR (neat, cm^{-1}): 2945, 1644, 1381, 1345, 1253, 1172, 875, 665; ^1H NMR ($CDCl_3$, 200 MHz): 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.

4.11. 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 **16** (0.10 g, 0.20 mmol) in dry CH_2Cl_2 (5 mL) was added trifluoroacetic acid (15 μL, 0.20 mmol). The reaction mixture was stirred at room temperature for 12 h and then quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 15 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 (eluent: $CH_3OH/CHCl_3$ 1:9) to give **2**, 0.056 g yield (70%). $[\alpha]_D^{25} = +36.2$ (*c* 0.66, $CHCl_3$) {lit.[7b] $[\alpha]_D^{25} = +34.29$ (*c* 1.32, $CHCl_3$)}; IR (neat, cm^{-1}): 3348, 2990, 2945, 1602, 1380, 1349, 1247, 1172, 875, 667; ^1H NMR ($CDCl_3$, 200 MHz): 1.42–2.04 (m, 3H), 2.20 (br d, $J = 13$ Hz, 1H), 2.62 (s, 1H), 2.76–2.81 (m, 1H), 3.23–3.38 (m, 1H), 3.67 (s, 1H), 3.82 (br s, 1H), 4.14 (d, $J = 12$ Hz, 1H), 4.54 (d, $J = 12.2$ Hz, 1H), 7.20–7.43 (m, 7H), 7.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): 20.2, 28.2, 46.8, 64.0, 69.9, 77.4, 121.2, 123.1, 126.7, 127.3, 127.8, 132.4, 142.2, 142.4.

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