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Graphical Abstract

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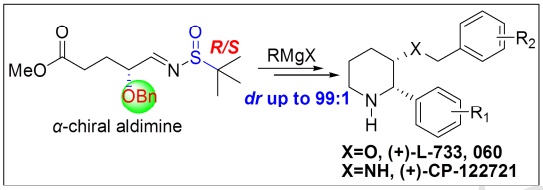

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ABSTRACT

An efficient diastereoselective approach to access *trans*-5-hydroxy-6-substituted 2-piperidinones skeleton has been developed through one-pot intramolecular tandem process of *O*-benzyl protected aldimine **11** with Grignard reagents. The diastereoselectivity of substitution at C-6 position of 2-piperidinone was controlled by α-benzyloxy group. In addition, the utility of this straightforward cascade process is demonstrated by the asymmetric syntheses of (+)-L-733, 060 (**2**) and its 2-substituted analogue **3**, as well as (+)-CP-122721 (**5**).

1. Introduction

The chiral cyclic 1, 2-amino alcohol motif exists in numerous biologically relevant natural products[1] and is a common subunit in medicinal and pharmaceutical candidates or drugs[2]. Moreover, these structures and their ring-opened fragments are widely used as chiral auxiliaries[3] and catalysts for asymmetric synthesis[4]. Among them, chiral functionalized *cis*-3-hydroxy-2-substituted 6-piperidinone **1** (Figure 1) is one of the most representative in synthetic and medicinal chemistry. Typical examples include clinical agents (+)-L-733, 060 (**2**)[5] and (+)-CP-99994 (**4**)[6] as well as (+)-CP-122721 (**5**)[7], which are potent neurokinin substance P receptor antagonists and display a variety of biological activities including inhibition of neurogenic inflammation, blocking of pain transmission and regulation of immune response[5-7]. Other *trans*-3-hydroxy-2-substituted 6-piperidinones examples are antimalarial (+)-febrifugine (**6**)[8], antibiotic and anesthetic *Prosopis* alkaloid (+)-prosophylline (**7**)[9] (Figure 1). Moreover, the *trans*-2-alkyl-3-hydroxypiperidine unit is also embedded in the bicyclic structure of hydroxylated indolizidines, such as the *α*-mannosidase inhibitor (-)-swainsonine (**8**)[10]. Accordingly, tremendous efforts have been devoted to the development of stereospecific methods for the construction of cyclic 1, 2-amino alcohol motif, and a number of powerful approaches have been reported in past years[1-4].

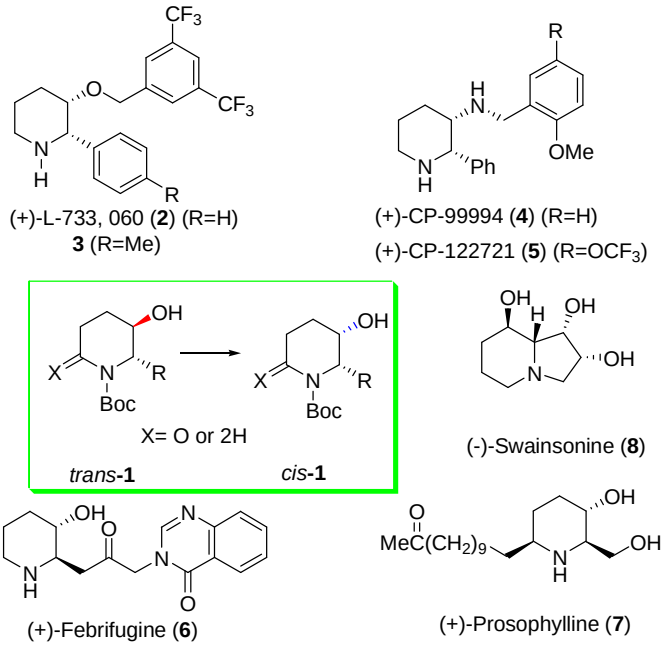

Figure 1. The structure of several bioactive molecules **1**-**8**.

Davis and Ellman's chiral auxiliaries (e.g. *p*-toluenesulfinamide and 2-methylpropane-2- sulfinamide) have been widely used in organic synthesis[11]. In recent years, one of our research interests is to utilize these popular chiral auxiliaries in asymmetric synthesis of natural products[12]. We observed an unusual 1,3-migration for the reaction of *N*-*tert*-butanesulfinyl ester with functionalized organozinc reagents[13], and developed an

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intramolecular tandem process to *trans*-5-hydroxy-6-substituted 2-piperidinones or *trans*-4-hydroxy-5-substituted 2-pyrrolidinones skeleton by switching organozinc species to Grignard reagents (Figure 2. eq.1)[2i,2j,14]. It is noteworthy that different *O*-protective groups of *α*-chiral aldimine substrates could lead to different stereoselectivities, sometimes, generate reversed chirality for the addition products (Figure 2. eq.2)[15]. *Cis*-5-hydroxy-6-substituted 2-piperidinones are also found in numerous biologically relevant natural products and pharmaceutical candidates[5-7]. Although the oxidation and reduction of *trans*-**1** provided an alternative approach to generate *cis*-**1** isomer, only a few direct methods for preparation of *cis*-**1** have been developed, appeared with moderate enantioselectivities[5-7]. Encouraged by Ellman's and our previous results (Figure 2. eq.1 and 2), we decided to investigate on our previous intramolecular tandem protocol through the addition-cylization-deprotection process in one-pot using *O*-benzyl protected aldimine **11** to react with Grignard reagents to afford 5-hydroxy-6-substituted 2-piperidinones skeleton (Figure 2. eq. 3). Herein we report our recent results for this intramolecular tandem process, and the application in divergent syntheses of L-733, 060 (**2**) and CP-122721 (**5**).

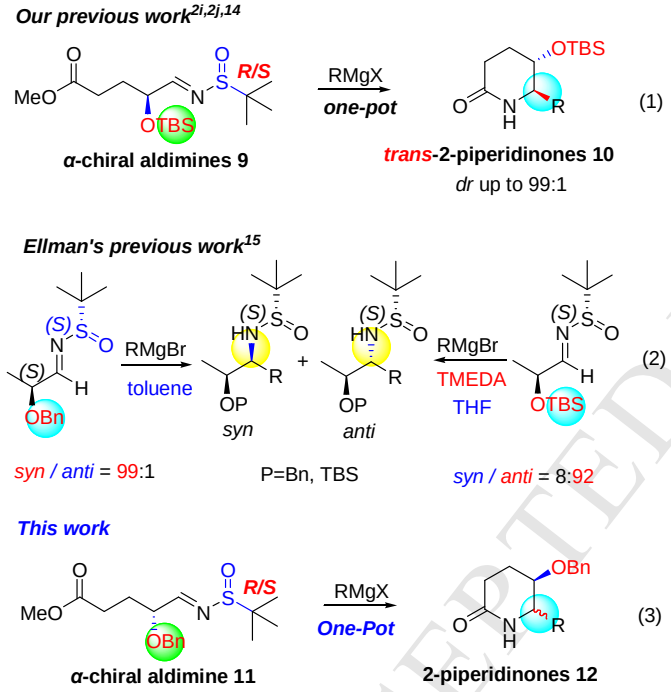
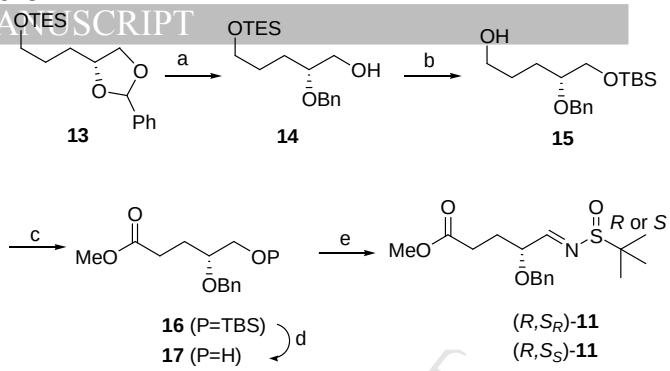


Figure 2. Our strategy to 5-hydroxy-6-substituted 2-piperidinones **12**.

2. Results and Discussion

As shown in **Scheme 1**, *α*-chiral *N*-sulfinyl aldimine **11** was first prepared through the following sequence. A known acetal compound **13**[16] was treated with DIBAL-H[17] in toluene at –78 °C to give desired chiral alcohol **14** in 77% yield with high chemoselectivity. Upon TBS protection of **14**, the TES group was selectively removed in AcOH/DCM/H_2O/MeOH to afford primary alcohol **15** in 83% overall yield. Swern oxidation[19c] **15** and subsequent Pinnick oxidation ($NaH_2PO_4 \cdot 2H_2O$, $NaClO_2$)[18] gave the crude acid, which was converted to its methyl ester **16** in 56% overall yield. Finally, upon CSA-mediated desilyation and DMP oxidation[19a,19b] of **17**, the resulting aldehyde was condensed with sulfinamide in presence of anhydrous cupric sulphate[20] to afford the desired *α*-chiral *N*-sulfinyl aldimine **11** in 85% overall yield.

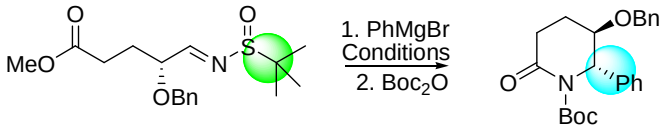
To this end, the intramolecular tandem reaction of *O*-benzyl protected aldimine **11** with Grignard reagents was investigated.



Scheme 1. The preparation of aldimine **11**. *Reagents and conditions*: a. DIBAL-H, toluene, -78 °C, 77%; b. (1) TBSCl, DMAP, TEA, DCM, rt; (2) AcOH/DCM/H_2O/MeOH, 0 °C, 83% over two steps; c. (1) $(COCl)_2$, DMSO, TEA, DCM, -78 °C; (2) $NaH_2PO_4 \cdot 2H_2O$, $NaClO_2$, 2-methyl-2-butene, ^{t}BuOH, rt; (3) $NaHCO_3$, MeI, DMF, 56% over three steps. d. CSA, DCM/MeOH, rt, 100%. e. (1) DMP, DCM; (2) (*S*)-2-methylpropane-2-sulfinamide, $CuSO_4$, DCM, 85% for (*R*, S_R)-**11** and 83% for (*R*, S_S)-**11** over two steps.

Thus, (*R*, S_R)-**11** was treated with phenylmagnesium bromide at –78 °C to room temperature to afford the corresponding lactam, which was in turn treated with Boc anhydride, for the purpose of convenient purification, to afford the *N*-Boc lactam **18a** in 68% yield with high diastereoselectivity (*dr* > 99:1) (Table 1 entry 1). When the addition reaction was conducted at 0 °C to room temperature for 12 h, the subsequent protected **18a** was obtained in 52% yield, and the diastereoselectivity remained essentially unchanged (*dr* > 99:1) (Table 1 entry 2). To examine the effect of auxiliary chirality on the intramolecular tandem reaction, *O*-benzyl aldimine (*R*, S_S)-**11** was used to react with phenylmagnesium bromide. As shown in table 1, both (*R*, S_R)-**11** and (*R*, S_S)-**11** afforded the same product **18a** with high diastereoselectivity (Table 1 entry 3), suggesting that the chiral sulfinamide moiety was not involved in the stereocontrol of this addition process. To further investigate this tandem reaction, different solvents were also screened, and the results indicated that the solvents did not affect the diastereoselectivity of **18a** (Table 1 entries 4-6).

Table 1. The reactions with phenylmagnesium bromide in deferent conditions.



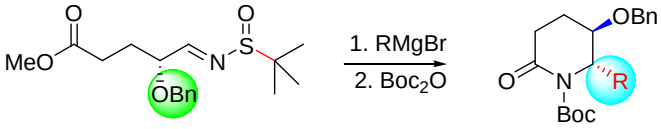
Entry[a]	**11**	Conditions	Y%[b]	*trans/cis*[c]
1	(R,S_R)	THF, -78 °C-rt	68	99:1
2	(R,S_R)	THF, 0 °C-rt	52	99:1
3	(R,S_S)	THF, -78 °C-rt	40	98:2
4	(R,S_R)	THF/TMEDA,-78 °C	65	99:1
5	(R,S_R)	THF/$AlMe_3$, -78 °C	37	65:35
6	(R,S_R)	Toluene, -78 °C	14	99:1
7	(R,S_{RS})	THF, -78 °C-rt	64	99:1

[a] The reaction was performed with aldimine **11** (0.60 mmol), PhMgBr(1.80 mmol) in solvent (2.5 mL) overnight. [b] Isolated yield. [c] *trans/cis* was determined by ^{1}H NMR.

Next, we turned our attention to investigate the scope and limitation of various Grignard reagents for this tandem addition-cyclization of *O*-benzyl protected *α*-chiral aldimine (*R*, S_{RS})-**11**. As shown in Table 2, a variety of substituted aryl Grignard reagents were examined under the above optimal conditions

(Table 1 entry 1). Although the overall yields of **18** were moderate, the diastereoselectivity in all cases were excellent (*dr* > 98:2) (Table 2 entries 1-6). It is noteworthy to mention that *β*-naphthyl Grignard reagent also afforded the desired product in 54% yield and with high diastereoselectivity (*dr* > 99:1) (Table 2 entry 3). When alkyl Grignard reagents were screened, the yields slightly decreased, but the diastereoselectivities still maintained (*dr* > 87:13) (Table 2 entries 7-8). As for substituted benzyl Grignard reagent, the yield of desired product **18j** was reduced to 31% (Table 2 entry 9).

Table 2. Reactions with different Grignard reagents.

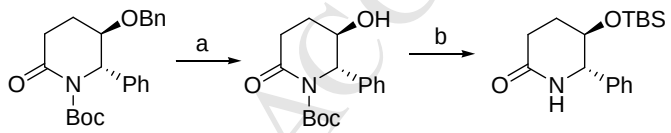


(*R*,*S*$_{RS}$)-**11** **18b-k**

Entry[a]	R	**18b-k**	Y%[b]	*trans/cis*[c]
1	*p*-$CH_3C_6H_4$	**18**b	72	99:1
2	*m*-$CH_3OC_6H_4$	**18**c	50	99:1
3	*β*-naphthyl	**18**d	54	99:1
4	*m*-$CH_3C_6H_4$	**18**e	57	98:2
5	*m*-$CF_3C_6H_4$	**18**f	53	99:1
6	*m*-FC_6H_4	**18**g	54	99:1
7	$CH_3(CH_2)_4$	**18**h	41	90:10
8	$CH_3(CH_2)_8$	**18**i	40	87:13
9	*m*-$CH_3C_6H_4CH_2$	**18**j	31	99:1
10	Ethenyl	**18**k	22	90:10

[a] The reaction was performed with aldimine **11** (0.60 mmol), Grignard reagents (1.80 mmol) in THF (2.5 mL) overnight from -78 °C-rt. [b] Isolated yield. [c] *trans/cis* was determined by ^{1}H NMR.

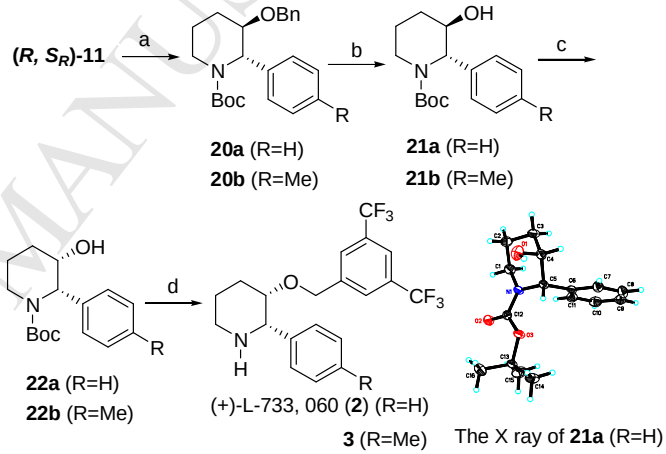
To confirm the relative configuration of the product, **18a** was converted to a known compound **10a**. As shown in Scheme 2, *O*-benzyl protection was switched to *O*-TBS through hydrogenation (Pd/C, HCOOH) of lactam **18a** and subsequent treatment with TBSCl. Removal of the *N*-Boc group with trifluoroacetic acid (TFA) afforded amide **10a** {$[\alpha]_D^{23}$ = -18.9 (*c* 0.63, $CHCl_3$), lit[2h] $[\alpha]_D^{23}$ = -16.9 (0.44, $CHCl_3$) } in 81% overall yield. The spectroscopic and physical data of **10a** were identical to the reported data[2h], which unambiguously confirmed that the one-pot intramolecular tandem process of *O*-benzyl protected aldimine **11** with Grignard reagents generated *trans*-form products **18**.



18a **19** **10a**

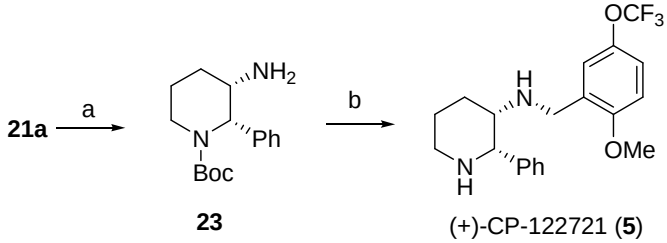
Scheme 2. Synthesis of lactam **10a**. *Reagents and conditions:* a. Pd/C, MeOH, HCOOH; b. (1) TBSCl, imid., DMF, DMAP; (2) TFA, DCM, 81% over three steps.

With chiral lactam **18a** in hand, we focused on the synthesis of (+)-L-733, 060 (**2**) and its 2-substituted analogue **3**. In past decades, tremendous efforts have been devoted to the development of concise method to **2**, and a number of powerful approaches have been reported[21]. However, among these known powerful methods, its 2-substituted analogue was scarcely explored. As a continuation of our program for asymmetric synthesis of nitrogen-containing heterocyclic compounds including L-733, 060(**2**), our synthesis started with the aldimine (*R*, *S*$_R$)-**11**, which was separately treated with phenylmagnesium bromide (PhMgBr) and *m*-methyl phenylmagnesium bromide (*p*-CH_3PhMgBr). The resulting lactams were treated with lithium aluminum hydride (LAH) and subsequent protected with di-*tert*-butyl dicarbonate (Boc_2O) in the presence of triethylamine (TEA) to give *N*-Boc piperidine **20a** in 45% and **20b** in 50% overall yield, respectively. Hydrogenation [Pd/C, $Pd(OH)_2$, H_2] of compounds **20a** and **20b** afforded secondary alcohols **21a** in 90% yield and **21b** in 85% yield. The X-ray crystallography of **21a** further confirmed the formation of trans isomer during the nucleophilic attack and cyclization step (see Supporting Information). The reverse of the secondary hydroxy group was achieved through oxidation and reduction sequence. Oxidation of **21a** and **21b** with Dess-Martin periodinane[19] (DMP) and subsequent reduction with $NaBH_4$ generated the desired *cis*-alcohols **22a** and **22b** in 85% and 71% yield, respectively. Finally, the alcohols **22a** and **22b** were alkylated with substituted benzyl bromide in the presence of sodium hydride (NaH) and then treated with trifluoroacetic acid (TFA) to give desired (+)-L-733, 060 (**2**) { $[\alpha]_D^{23}$ = 46.5 (*c* 1.0, $CHCl_3$), lit.[21e] $[\alpha]_D^{20}$ = 55.0 (*c* 1.0, $CHCl_3$)} in 56% isolated yield, and **3** { mp 181.3-182.3 °C; $[\alpha]_D^{23}$ = 32.8 (*c* 1.0, $CHCl_3$) in 50% isolated yield. The spectroscopic and physical data of the synthetic (+)-L-733, 060 (**2**) were identical to the reported data[21e].



Scheme 3. The preparation of (+)-L-733, 060 (**2**) and its 2-substituted analogue **3**. *Reagents and conditions:* a. (1) Grignard reagents, THF, -78 °C-rt, overnight. (2) LAH, 60°C, 4 h; (3) Boc_2O, DMAP, TEA, DCM, $NaHCO_3$, 12 h, 45% over three steps of **20a** and 50% over three steps of **20b**; b. Pd/C, $Pd(OH)_2$, H_2, MeOH, 2 h, 90% of **21a** and 85% of **21b**; c. (1) DMP, DCM; (2) $NaBH_4$, MeOH, 0 °C, 85% over two steps of **22a** and 71% over two steps of **22b**; d. (1) NaH, DMF, overnight; (2) TFA, DCM, 24h , 56% over two steps of (+)-L-733, 060 (**2**) and 50% over two steps of **3**.

To extend the utility of the 'intramolecular tandem process' to access *trans*-3-hydroxy-2-substituted 6-piperidinones **1**, the synthesis of (+)-CP-122721 (**5**)[22] was also performed. As shown in **Scheme 4**, alcohol **21a** was converted to *cis*-2, 3-disubstituted



23 (+)-CP-122721 (**5**)

Scheme 4. The preparation of (+)-CP-122721 (**5**). *Reagents and conditions:* a. (1) DMP, DCM; (2) $NH_2OMe{\cdot}HCl$, pyridine; (3) $BH_3{\cdot}DMS$, THF, MeOH, reflux, 72% over three steps; b. (1) 2-methoxy-5-(trifluoromethoxy)benzaldehyde, DCM, 4Å MS, $ZnCl_2$; (2) $NaBH_4$, MeOH; (3) HCl/MeOH, 85% over three steps.

amine **23** in three steps: oxidation by DMP, oxime formation with *O*-methyl hydroxyamine hydrochloride ($NH_2OMe{\cdot}HCl$) and subsequent reduction with borane. This synthetic sequence afforded **23** with high diastereoselectivity (*dr* = 95:5) in 72% overall yield[22a,b]. The introduction of substituted benzyl group was accomplished by the reaction of 2-methoxy-5-(trifluoromethoxy)benzaldehyde with Sodium borohydride ($NaBH_4$) in the presence of zinc chloride ($ZnCl_2$). Finally, the *N*-Boc protective group was cleaved with hydrogen chloride in methanol to give (+)-CP-122721 (**5**) {mp 86.5-88.5 °C; $[\alpha]_D^{22}$ = +7.0 (c 0.5, $CHCl_3$); (+)-CP-122721·2HCl, lit.[22b] mp 275-276 °C; $[\alpha]_D^{26}$ +75.6 (c 1.0, CH_3OH) } in 85% yield.

3. Conclusions

In summary, we established a high diastereoselective method to *trans*-5-hydroxy-6-substituted 2-piperidinones skeleton by one-pot intramolecular tandem process of *O*-benzyl protected aldimine **11** with Grignard reagents. The stereogenic center of C-6 was solely controlled by α- benzyloxy substitution. In addition, the utility of chiral δ-lactams **20a/b** in the enantioselective synthesis of specific targets, has been demonstrated by a concise synthetic route to (+)-L-733, 060 (**2**) and its 2-substituted analogue **3**, as well as (+)-CP-122721 (**5**).

4. Experimental Section

4.1. General Methods.

THF was distilled from sodium/benzophenone. Reactions were monitored by thin layer chromatography (TLC) on glass plates coated with silica gel with fluorescent indicator. Flash chromatography was performed on silica gel (300−400) with Petroleum/EtOAc as eluent. Optical rotations were measured on a polarimeter with a sodium lamp. HRMS were measured on LTQ-Orbit. IR spectra were recorded using film on a Fourier Transform Infrared Spectrometer. NMR spectra were recorded at 400 or 600 MHz, and chemical shifts are reported in δ (ppm) referenced to an internal TMS standard for ^{1}H NMR and $CDCl_3$ (77.16 ppm) for ^{13}C NMR.

4.2. Triethyl(3-((4*R*)-2-phenyl-1,3-dioxolan-4-yl)propoxy)silane 13.

Compound **13** was prepared through the known method.[16] Colorless oil. IR (film): ν_{max} 2954, 2876, 2349, 2336, 1582, 1509, 1458, 1409, 1109, 1015, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.44 (m, 2H), 7.40-7.31 (m, 3H), 5.92 (s, 1H), 4.28-4.21 (m, 2H), 3.70-3.64 (m, 2H), 3.63-3.60 (m, 1H), 1.82-1.60 (m, 4H), 0.99-0.91 (m, 9H), 0.64-0.56 (m, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.7, 129.2, 128.5, 126.5, 103.2, 76.5, 70.9, 62.6, 29.9, 29.2, 6.9, 4.6 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{12}H_{16}O_2$: 192.1145, found: 192.1143.

4.3. (*R*)-2-(Benzyloxy)-5-(triethylsilyloxy)pentan-1-ol 14.

Compound **13** (36.0 g，0.19 mol) was dissolved in toluene (500 mL) and cooled to -78 °C, and then a solution of DIBAl-H （380 ml，0.38 mol）was slowly dropped under an argon atmosphere. After being stirred for 1 h at -78 °C, the mixture was warmed to 0 °C. After stirring for another 0.5 h, the resulting mixture was carefully quenched with EtOAc (100 mL) at -78 °C, and then warmed to room temperature. After being stirred for 1h, the resulting mixture was quenched with a saturated aqueous solution of seignette salt. The mixture was diluted with EtOAc (300 mL) and separated. The aqueous layer was extracted with EtOAc (500 mL × 3) and the combined organic layers were washed with brine, dried and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 5/1) to give **14** (28.2 g，77%) as a colorless oil. $[\alpha]_D^{23}$ = -6.4 (*c* 0.50, $CHCl_3$); IR (film): ν_{max} 2941, 2877, 1584, 1508, 1397, 1344, 1316, 1109, 1014, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (m, 5H), 4.64-4.60 (m, 1H), 4.56-4.52 (m, 1H), 3.72-3.65 (m, 1H), 3.63-3.58 (m, 2H), 3.57-3.52 (m, 2H), 2.01 (brs, 1H), 1.73-1.56 (m, 4H), 0.98-0.91 (m, 9H), 0.63-0.54 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 128.5, 128.0, 127.7, 79.8, 72.4, 65.6, 63.1, 28.8, 28.3, 26.0, 18.4, -5.2, -5.3 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{12}H_{18}O_2$: 194.1301, found: 194.1303.

4.4. (*R*)-4-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)pentan-1-ol 15.

Compound **14** (27.0 g，0.14 mol), TBSCl (31.5 g，0.21 mol) and DMAP (855 mg，7 mmol) were stirred in DCM (400 mL) at 0 °C, and then TEA (38.7 ml，0.28 mol) was added in one portion. After stirring for 12 h at room temperature, the mixture was quenched with a saturated aqueous solution of NH_4Cl and separated. The aqueous layer was extracted with DCM (400 mL × 3) and the combined organic layers were washed with brine, dried and concentrated. Without further purification, the above crude compound was dissolved in a mixture of DCM (60 mL)/MeOH (60 mL)/AcOH(180 mL)/H_2O(120 mL) at 0 °C. After being stirred for 0.5h, the mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc (300 mL × 3). The combined organic layers were washed with brine, dried, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 5/1) to give alcohol **15** (37.6 g，83%) as a light yellow oil. $[\alpha]_D^{24}$ = +19.3 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2928, 2858, 1578, 1463, 1406, 1253, 1106, 1063, 831, 778, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (m, 5H), 4.74-4.69 (m, 1H), 4.59-4.54 (m, 1H), 3.75-3.69 (m, 1H), 3.63-3.57 (m, 3H), 3.53-3.47 (m, 1H), 1.91 (brs, 1H), 1.74-1.50 (m, 4H), 0.90 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 128.5, 128.0, 127.7, 79.8, 77.5, 77.2, 76.8, 72.4, 65.6, 63.0, 28.7, 28.3, 26.0, 18.4, -5.2, -5.3 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{18}H_{33}O_3Si$: 325.2194, found: 325.2194.

4.5. (*R*)-Methyl 4-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)pentanoate 16.

$(COCl)_2$ (20.6 mL, 0.24 mol) was stirred in DCM (240 mL) at -78°C, and then a solution of DMSO (34.1 mL, 0.48 mol) in DCM (120 mL) was slowly added dropwise. After the mixture was stirred for 1 h, a solution of **15** (38.9 g, 0.12 mol) in DCM (120 mL) was added dropwise, and the resulting mixture was stirred for 3 h. Once TEA (99.6 mL, 0.72 mol) was added dropwise, the mixture was allowed to warm to room temperature, and the reaction was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with DCM (200 mL × 2). The combined organic layers were washed with brine, dried, filtered, and concentrated to give crude aldehyde without further purification. The above aldehyde was dissolved in anhydrous isopentene (240 mL) / ^{t}BuOH (240 mL) and cooled to 0 °C, and then a solution of an aqueous solution of NaH_2PO_4 (56.4 g) and $NaClO_2$ (32.6 g) was slowly dropped under an argon atmosphere. After being stirred 3h, the mixture was diluted with EtOAc (300 mL) and separated. The aqueous layer was extracted with EtOAc (300 mL × 2) and the combined organic layers were washed with brine, dried and concentrated to give crude acid, which was directly dissolved in dry DMF (240 mL). Then $NaHCO_3$ (20 g, 0.24 mol) was added and MeI (37 mL, 0.60 mol) was dropped at 0 °C and the mixture was stirred for 36 h. The mixture was quenched with water and extracted with EtOAc (200 mL × 4). The combined organic layers were washed with water (20 mL × 2) and brine, dried, filtrated and concentrated. The residue was purified by

flash chromatography on silica gel (PE/EA = 25/1) to give **16** (23.7 g，56%) as a light yellow oil. $[\alpha]_D^{24}$ = +26.6 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2957, 2933, 2855, 1741, 1580, 1253, 1090, 837, 778, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.23 (m, 5H), 4.71-4.66 (m, 1H), 4.55-4.51 (m, 1H), 3.73-3.68 (m, 1H), 3.62 (s, 3H), 3.61-3.57 (m, 1H), 3.52-3.46 (m, 1H), 2.47-2.33 (m, 2H), 1.97-1.87 (m, 1H), 1.83-1.72 (m, 1H), 0.90 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 138.8, 128.4, 127.9, 127.6, 78.8, 72.4, 65.5, 51.6, 30.1, 27.0, 26.0, 18.4, -5.2, -5.3, -5.6 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{19}H_{33}O_4Si$: 353.2143, found: 353.2143.

4.6. (*R*)-Methyl 4-(benzyloxy)-5-hydroxypentanoate 17.

Compound **16** (23.7 g, 67.20 mmol) was dissolved in anhydrous DCM (130 mL) and MeOH (130 mL) and treated with CSA (3.1 g, 13.44 mmol) for 4h at room temperature. The resulting mixture was quenched with TEA (3.7 mL, 26.88 mmol) and concentrated. The residue was dissolved in EtOAc (100 mL) and water (100 mL). The resulting mixture was separated and the aqueous layer was extracted with EtOAc (150 mL × 3). The combined organic layers were washed with brine, dried, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 3/1) to give ester 17 (16.0 g, 100%) as a colorless oil. $[\alpha]_D^{23}$ = +8.5 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2924, 1735, 1454, 1343, 1169, 1101, 1056, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.24 (m, 5H), 4.58-4.54 (m, 2H), 3.73-3.67 (m, 1H), 3.66-3.63 (s, 3H), 3.58-3.52 (m, 2H), 2.44-2.37 (m, 2H), 2.18-2.05 (brs, 1H), 2.00-1.85 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 138.3, 128.6, 127.9, 78.4, 71.8, 63.8, 51.7, 29.7, 26.0 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{13}H_{19}O_4$: 239.1278, found: 239.1281.

4.7. General Procedure for Synthesis of (*R*, S_R)-11 and (*R*, S_S)-11.

A solution of **17** (16.0 g, 67.20 mmol) in dry DCM (250 mL) was treated with DMP (34.2 g, 80.64 mmol) at room temperature for 0.5 h. The reaction mixture was carefully quenched with a saturated aqueous solution of $NaHCO_3$ and solid $Na_2S_2O_3$, then the mixture was separated and then aqueous layer was extracted with DCM (150 mL × 3). The combined organic layers were washed with brine, dried and concentrated to give a crude middle compound without further purification. The above crude product was dissolved in dry DCM (250 mL) and treated with $CuSO_4$ (21.4 g, 134.40 mmol), PPTS (1.7 g, 6.72 mmol) and (*R*)-(+)-2-Methyl-2- propanesulfinamide (8.1 g, 67.20 mmol) or (*S*)-(+)-2-Methyl-2- propanesulfinamide (8.1 g, 67.20 mmol) in one portion. After stirring for 24 h, the mixture was filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 5/1) to give (*R*, S_R)-**11** (19.4 g, 85%) or (*R*, S_S)-**11** (18.9 g, 83%).

4.7.1. (*R, E*)-Methyl 4-(benzyloxy)-5-((R)-2-methylpropan-2-ylsulfinamido)pentanoate (*R, R*)-11.

Light yellow oil. $[\alpha]_D^{24}$ = -80.0 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2951, 2868, 1738, 1620, 1581, 1514, 1169, 1085, 743, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 4.8 Hz, 1H), 7.39-7.27 (m, 5H), 4.71-4.66 (m, 1H), 4.47-4.42 (m, 1H), 4.29-4.22 (m, 1H), 3.65 (s, 3H), 2.53-2.46 (m, 2H), 2.11-2.02 (m, 2H), 1.25 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 169.4, 137.4, 128.5, 128.0, 127.9, 78.8, 72.0, 56.9, 51.7, 29.5, 28.0, 22.5 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{17}H_{26}NO_4S$: 340.1577, found: 340.1575.

4.7.2. (*R, E*)-Methyl 4-(benzyloxy)-5-((*S*)-2-methylpropan-2-ylsulfinamido)pentanoate (*R, S*)-11.

Light yellow oil. $[\alpha]_D^{24}$ = +183.1 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2952, 2871, 1737, 1622, 1455, 1361, 1173, 1085, 1028, 735, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 4.4 Hz, 1H), 7.38-7.27 (m, 5H), 4.72-4.66 (m, 1H), 4.47-4.42 (m, 1H), 4.28-4.23 (m, 1H), 3.64 (s, 3H), 2.52-2.46 (m, 2H), 2.09-1.97 (m, 2H), 1.22 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 169.6, 137.5, 128.6, 128.2, 79.1, 72.2, 57.2, 51.8, 29.7, 28.3, 22.6 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{17}H_{26}NO_4S$: 340.1577, found: 340.1576.

4.8. General Procedure for Synthesis of 18a-k.

To a solution of compound **11** (203 mg, 0.60 mmol) in anhydrous THF (2.5 mL) was treated with a solution of Grignard reagents (1.8 mL, 1 M in THF) at −78 °C to rt overnight. The mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine, dried, filtrated and concentrated. The crude, Boc_2O (196 mg, 0.90 mmol) and DMAP (73 mg, 0.60 mmol) were stirred in DMF (2.5 mL) before TEA (0.3 mL, 1.80 mmol) was added, then the reaction mixture was stirred for 24 h. The mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (20 mL × 4). The combined organic layers were washed with water (10 mL × 2) and brine, dried, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 5/1) to give **18a−k**.

4.8.1. (2*S*,3*R*)-*tert*-Butyl 3-(benzyloxy)-6-oxo-2-phenylpiperidine-1-carboxylate 18a.

Colorless oil, (153 mg, 68%), $[\alpha]_D^{24}$ = -46.0 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2938, 1770, 1719, 1454, 1369, 1251, 1148, 1074, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.23 (m, 8H), 7.18-7.14 (m, 2H), 5.44-5.42 (m, 1H), 4.71-4.63 (m, 2H), 3.82 (dd, *J* = 6.4, 3.2 Hz, 1H), 2.87-2.76 (m, 1H), 2.61-2.53 (m, 1H), 1.87-1.83 (m, 2H), 1.28 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 152.0, 140.2, 137.8, 128.8, 128.6, 128.0, 127.7, 127.6, 125.9, 83.1, 75.8, 70.7, 63.9, 29.8, 27.7, 20.6 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{23}H_{28}NO_4$: 382.2013, found: 382.2013.

4.8.2. (2*S*,3*R*)-*tert*-Butyl 3-(benzyloxy)-6-oxo-2-p-tolylpiperidine-1-carboxylate 18b.

Colorless oil, (171 mg, 72%), $[\alpha]_D^{23}$ = -38.6 (*c* 2.00, $CHCl_3$); IR (film): ν_{max} 2975, 2922, 1770, 1718, 1582, 1512, 1455, 1368, 1250, 1148, 1078, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5H), 7.15-7.10 (m, 2H), 7.05-7.01 (m, 2H), 5.41-5.39 (m, 1H), 4.70-4.61 (m, 2H), 3.78 (dd, *J* = 6.4, 3.2 Hz, 1H), 2.85-2.74 (m, 1H), 2.58-2.50 (m, 1H), 2.31 (s, 3H), 1.86-1.80 (m, 2H), 1.29 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 151.4, 137.2, 136.6, 136.5, 128.8, 127.9, 127.3, 127.0, 125.1, 82.3, 75.1, 70.0, 62.9, 29.1, 27.1, 20.4, 20.0 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{24}H_{30}NO_4$: 396.2169, found: 396.2168.

4.8.3. (2*S*,3*R*)-*tert*-Butyl 3-(benzyloxy)-2-(3-methoxyphenyl)-6-oxopiperidine-1-carboxylate 18c.

Colorless oil, (123 mg, 50%), $[\alpha]_D^{24}$ = -54.4 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2932, 1769, 1720, 1602, 1585, 1454, 1368, 1269, 1250, 1147, 1073, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.20 (m, 6H), 6.82-6.65 (m, 3H), 5.42-5.37 (m, 1H), 4.70-4.64 (m, 2H), 3.85-3.80 (m, 1H), 3.77 (s, 3H), 2.85-2.75 (m, 1H), 2.60-2.51 (m, 1H), 1.87-1.83 (m, 2H), 1.31 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 160.1, 152.2, 142.0, 137.9, 130.0, 128.7, 128.1, 127.8, 118.2, 112.9, 111.9, 83.2, 75.7, 70.8, 63.8, 55.4, 29.9, 27.8, 20.9 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{24}H_{30}NO_5P$: 412.2119, found: 412.2122.

4.8.4. (2*S*,3*R*)-*tert*-Butyl 3-(benzyloxy)-2-(naphthalen-2-yl)-6-oxopiperidine-1-carboxylate 18d.

Colorless oil, (140 mg, 54%), $[\alpha]_D^{25}$ = -44.5 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2359, 2333, 1773, 1716, 1559, 1507, 1147 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85-7.78 (m, 3H), 7.63-7.60 (m, 1H), 7.53-7.45 (m, 2H), 7.40-7.22 (m, 6H), 5.63-5.59 (m, 1H), 4.75-4.65 (m, 2H), 3.94 (dd, *J* = 6.0, 2.8 Hz, 1H), 2.92-2.80 (m, 1H), 2.67-2.57 (m, 1H), 1.91-1.83 (m, 2H), 1.26 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 152.2, 137.8, 137.8, 133.4, 132.8, 128.8, 128.7, 128.0, 127.8, 126.7, 126.3, 124.6, 124.0, 83.2, 75.7, 70.9, 64.0, 30.0, 27.8, 20.8 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{27}H_{30}NO_4$: 432.2169, found 432.2175.

4.8.5. (2*S*,3*R*)-*tert*-Butyl 3-(benzyloxy)-6-oxo-2-m-tolylpiperidine-1-carboxylate 18e.

Colorless oil, (135 mg, 57%), $[\alpha]_D^{25}$ = -55.0 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2928, 1769, 1719, 1608, 1365, 1251, 1147, 1076, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-6.92 (m, 9H), 5.42-5.38 (m, 1H), 4.70-4.61 (m, 2H), 3.85-3.79 (m, 1H), 2.88-2.74 (m, 1H), 2.61-2.51 (m, 1H), 2.32 (s, 3H), 1.88-1.83 (m, 2H), 1.29 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.2, 152.1, 140.2, 138.6, 137.9, 128.7, 128.6, 128.4, 128.0, 127.7, 126.6, 123.0, 83.0, 75.9, 70.7, 63.8, 29.9, 27.8, 21.5, 20.7 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{24}H_{30}NO_4$: 396.2169, found: 396.2170.

4.8.6. (2*S*,3*R*)-*tert*-Butyl 3-(benzyloxy)-6-oxo-2-(3-(trifluoromethyl)phenyl)piperidine-1-carboxylate 18f.

Colorless oil, (143 mg, 53%), $[\alpha]_D^{26}$ = -47.5 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2951, 2868, 1738, 1581, 1512, 1455, 1171, 1085, 1027, 743, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56-7.44 (m, 2H), 7.40-7.29 (m, 7H), 5.41-5.38 (m, 1H), 4.72-4.59 (m, 2H), 3.82-3.77 (m, 1H), 2.89-2.76 (m, 1H), 2.63-2.54 (m, 1H), 1.95-1.77 (m, 2H), 1.28 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 152.0, 141.6, 137.5, 131.4 (q, *J* = 32.2 Hz), 129.5, 129.3, 128.8, 128.2, 127.8, 124.0 (q, *J* = 271.2 Hz), 124.3 (d, *J* = 3.2 Hz), 123.0 (d, *J* = 3.3 Hz), 83.6, 75.7, 71.0, 63.9, 29.9, 29.8, 27.7, 21.0 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{24}H_{27}F_3NO_4$: 450.1887, found: 450.1884.

4.8.7. (2*S*,3*R*)-*tert*-Butyl 3-(benzyloxy)-2-(3-fluorophenyl)-6-oxopiperidine-1-carboxylate 18g.

Colorless oil, (129 mg, 54%), $[\alpha]_D^{25}$ = -57.6 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2937, 1582, 1510, 1376, 1279, 1176, 1131, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.25 (m, 6H), 7.00-6.93 (m, 2H), 6.90-6.85 (m, 1H), 5.41-5.38 (m, 1H), 4.71-4.61 (m, 2H), 3.83-3.77 (m, 1H), 2.88-2.76 (m, 1H), 2.60-2.50 (m, 1H), 1.93-1.76 (m, 2H), 1.32 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 164.0, 162.4, 152.1, 143.1, 143.0, 137.6, 130.6, 130.5, 128.7, 128.2, 127.8, 121.5, 114.7, 114.6, 113.2, 113.1, 83.4, 75.6, 70.9, 63.5, 29.8, 27.8, 20.9 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{23}H_{27}FNO_4$: 400.1919, found 400.1915.

4.8.8. (2*S*,3*R*)-*tert*-Butyl 3-(benzyloxy)-6-oxo-2-pentylpiperidine-1-carboxylate 18h.

Colorless oil, (92 mg, 41%), $[\alpha]_D^{21}$ = +6.2 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2932, 2871, 1769, 1710, 1582, 1509, 1408, 1153, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.23 (m, 5H), 4.62-4.53 (m, 2H), 4.45-4.39 (m, 1H), 3.72-3.69 (m, 1H), 2.75-2.64 (m, 1H), 2.46-2.37 (m, 1H), 2.05-1.95 (m, 2H), 1.53 (s, 9H), 1.35-1.22 (m, 8H), 0.90-0.83 (m, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 153.0, 138.1, 128.7, 128.6, 128.0, 127.9, 127.8, 127.6, 82.8, 72.2, 70.1, 58.5, 34.4, 31.7, 30.0, 28.1, 26.0, 22.6, 22.4, 14.0 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{22}H_{34}NO_4$: 376.2482, found: 376.2488.

4.8.9. (2*S*,3*R*)-*tert*-Butyl 3-(benzyloxy)-2-nonyl-6-oxopiperidine-1-carboxylate 18i.

Colorless oil, (104 mg, 40%), $[\alpha]_D^{22}$ = +7.0 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2929, 2858, 1716, 1583, 1151, 1111, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5H), 4.63-4.52 (m, 2H), 4.45-4.39 (m, 1H), 3.71 (dd, *J* = 6.0, 3.2 Hz, 1H), 2.75-2.65 (m, 1H), 2.46-2.37 (m, 1H), 2.07-1.96 (m, 2H), 1.52 (s, 9H), 1.35-1.20 (m, 16H), 0.91-0.86 (m, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 153.0, 138.1, 128.6, 127.8, 127.6, 82.8, 72.3, 70.1, 58.5, 34.4, 32.0, 30.0, 29.6, 29.4, 28.1, 26.4, 22.8, 22.4, 14.2 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{26}H_{42}NO_4$: 432.3108, found: 432.3112.

4.8.10. (2*S*,3*R*)-*tert*-Butyl 2-(2-methylbenzyl)-3-(benzyloxy)-6-oxopiperidine-1-carboxylate 18j.

Colorless oil, (76 mg, 31%), $[\alpha]_D^{26}$ = -5.0 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2365, 2298, 1767, 1715, 1582, 1510, 1455, 1395, 1368, 1289, 1143, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.09 (m, 9H), 4.79-4.72 (m, 1H), 4.46-4.32 (m, 2H), 3.60 (dd, *J* = 6.0, 3.6 Hz, 1H), 3.03-2.97 (m, 1H), 2.81-2.63 (m, 2H), 2.55-2.46 (m, 1H), 2.32 (s, 3H), 2.22-2.10 (m, 1H), 2.04-1.95 (m, 1H), 1.44 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 152.9, 137.9, 136.5, 135.4, 130.8, 130.0, 128.5, 127.8, 127.7, 127.1, 126.4, 83.0, 71.4, 70.2, 58.7, 37.6, 30.1, 28.0, 22.7, 19.7 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{25}H_{32}NO_4$: 410.2326, found: 410.2325.

4.8.11. (2*S*,3*R*)-*tert*-Butyl 3-(benzyloxy)-6-oxo-2-vinylpiperidine-1-carboxylate 18k.

Colorless oil, (44 mg, 22%), $[\alpha]_D^{23}$ = +75.2 (*c* 0.25, $CHCl_3$); IR (film): ν_{max} 2935, 2360, 2339, 1770, 1723, 1582, 1510, 1409, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5H), 6.13-6.04 (m, 1H), 5.40-5.33 (m, 1H), 5.24-5.15 (m, 1H), 5.03-4.95 (m, 1H), 4.68-4.59 (m, 2H), 3.90-3.83 (m, 1H), 2.75-2.57 (m, 1H), 2.53-2.41 (m, 1H), 2.03-1.84 (m, 2H), 1.50 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 152.2, 137.8, 133.5, 128.7, 128.1, 127.8, 127.7, 117.5, 83.4, 74.4, 71.3, 58.4, 31.8, 28.1, 23.3 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{19}H_{26}NO_4$: 332.1856, found: 332.1856.

4.9. (2*S*,3*R*)-*tert*-Butyl 3-hydroxy-6-oxo-2-phenylpiperidine-1-carboxylate 19.

To a solution of **18a** (158 mg, 0.41mmol) and (10%) Pd/C (150 mg) was stirred in MeOH (10 mL) under hydrogen atmosphere for 10 min. Then HCOOH (0.8 mL) was carefully dropped and the mixture was stirred at room temperature for 2 h. The resulting mixture was filtered and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA =2/1) to give **19** (119 mg, 100%) as a white solid. M.p. 140-142 °C; $[\alpha]_D^{21}$ = +21.2 (*c* 0.25, $CHCl_3$); IR (film): ν_{max} 2931, 1778, 1697, 1583, 1513, 1409, 1367, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 5.45-5.37 (m, 1H), 4.95-4.87 (m, 1H), 4.77-4.72 (m, 1H), 2.32-2.21 (m, 2H), 1.96-1.74 (m, 2H), 1.42 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.9, 155.1, 136.3, 129.0, 128.5, 128.2, 81.6, 80.3, 57.8, 28.4, 27.7, 24.0 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{16}H_{22}NO_4$: 292.1543, found: 292.1545.

4.10. (5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-6-phenylpiperidin-2-one 10a.

To a solution of compound **19** (100 mg, 0.34 mmol) in dry DMF (0.8 mL) was treated with TBSCl (78 mg, 0.51 mmol), imidazole (69 mg, 1.02 mmol) and DMAP (41 mg, 0.34 mmol) at 0 °C. After stirred for 24 h at room temperature, the mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (40 mL × 3). The combined organic layers

were washed with brine, dried and concentrated to give a white solid. Without purification, the solid was dissolved in cooled (0 °C) DCM (1.2 mL) and treated with TFA (0.1 mL) for 1.5 h. The resulting mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA =3/1) to give amide **10a** (84 mg, 81%) as a colorless oil. $[\alpha]_D^{24}$ = -18.9 (*c* 0.63, $CHCl_3$); IR (film): ν_{max} 3211, 3060, 2950, 2925, 2852, 1669, 1467, 1402, 1350, 1253, 1111, 1090, 883, 832, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.26 (m, 5H), 5.94 (brs, 1H), 4.39-4.36 (m, 1H), 3.86-3.81 (m, 1H), 2.67-2.57 (m, 1H), 2.51-2.41 (m, 1H), 1.97-1.91 (m, 1H), 1.87-1.75 (m, 1H), 0.82 (s, 9H), -0.07 (s, 3H), -0.24 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 140.4, 128.8, 128.3, 127.3, 71.5, 64.5, 28.3, 27.3, 25.8, 18.0, -4.9, -5.3 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{17}H_{28}NO_2Si$: 306.1884, found: 306.1883.

4.11. General Procedure for Synthesis of 20a or 20b.

To a solution of aldaldimine **11** (3.0 g, 8.84 mmol) in anhydrous THF (27 mL) was treated with a solution of PhMgBr or *p*-MePhMgBr (26.5 mL, 1 M in THF) at −78 °C to room temperature overnight. The mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine, dried, filtrated and concentrated. After that, LAH (671 mg, 17.68 mmol) was carefully treated with anhydrous THF (35 mL) at 0 °C, then a solution of the above crude imine in THF (35 mL) was carefully dropped. After being stirred at 60 °C for 6 h, the mixture was cooled to 0 °C and diluted with THF (50 mL). The resulting mixture was carefully treated with $Na_2S_2O_3{\cdot}10H_2O$ and filtered, concentrated to give crude intermediate without purification. The above crude product was dissolved in dry DCM (35 mL), then Boc_2O (2.12 g, 9.72 mmol), TEA (1.2 mL, 8.84 mmol) and a 2M aqueous solution of $NaHCO_3$ (1.5 mL) was added in one portion. After stirred for 12 h, the mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine, dried, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 3/1) to give **20a** (1.46 g, 45%) or **20b** (1.69 g, 50%).

4.11.1. (2*S*,3*R*)-*tert*-Butyl 3-(benzyloxy)-2-phenylpiperidine-1-carboxylate 20a.

Colorless oil. $[\alpha]_D^{22}$ = +44.2 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2928, 1690, 1583, 1497, 1417, 1365, 1142, 1127, 1029, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.15 (m, 10H), 5.65-5.58 (m, 1H), 4.77-4.73 (m, 1H), 4.64-4.58 (m, 1H), 4.16-4.07 (m, 2H), 2.92-2.83 (m, 1H), 2.07-1.93 (m, 1H), 1.90-1.81 (m, 1H), 1.60-1.50 (m, 1H), 1.44 (s, 9H), 1.37-1.34 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.3, 139.2, 138.8, 128.7, 128.5, 127.6, 126.8, 126.6, 79.7, 74.2, 70.4, 56.1, 40.1, 28.6, 24.6, 19.5 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{23}H_{30}NO_3$: 368.2220, found: 368.2216.

4.11.2. (2*S*,3*R*)-*tert*-Butyl 3-(benzyloxy)-2-p-tolylpiperidine-1-carboxylate 20b.

Colorless oil. $[\alpha]_D^{22}$ = +60.7 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2930, 2863, 1691, 1514, 1454, 1417, 1365, 1277, 1171, 1128, 739, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.24 (m, 5H), 7.16-7.12 (m, 2H), 7.08-7.04 (m, 2H), 5.63-5.53 (m, 1H), 4.77-4.73 (m, 1H), 4.62-4.57 (m, 1H), 4.15-4.07 (m, 2H), 2.90-2.81 (m, 1H), 2.33 (s, 3H), 2.05-1.91 (m, 1H), 1.87-1.81 (m, 1H), 1.60-1.50 (m, 1H), 1.44 (s, 9H), 1.31-1.25 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 138.8, 136.4, 135.9, 129.4, 128.4, 127.6, 126.4, 79.6, 74.1, 70.4, 55.7, 39.9, 28.5, 24.5, 21.0, 19.6 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{24}H_{32}NO_3$: 382.2377, found: 382.2378.

4.12. General Procedure for Synthesis of 21a or 21b.

Compound **20a** (1.35 g, 3.67 mmol) or **20b** (1.40 g, 3.67 mmol), 10% Pd/C (200 mg) and $Pd(OH)_2$ (200 mg) were stirred in MeOH (50 mL) under hydrogen atmosphere for 2 h. Then the mixture was filtered and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA =15/1) to give **21a** (0.91 g, 90%) or **21b** (0.91 g, 85%).

4.12.1. (2*S*,3*R*)-*tert*-Butyl 3-hydroxy-2-phenylpiperidine-1-carboxylate 21a.

White solid. M.p. 130-132 °C; $[\alpha]_D^{22}$ = +6.2 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2933, 1692, 1666, 1580, 1412, 1365, 1127, 984 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.32 (m, 2H), 7.28-7.17 (m, 3H), 5.40-5.35 (m, 1H), 4.55-4.47 (m, 1H), 4.13-4.05 (m, 1H), 2.91-2.82 (m, 1H), 2.16-2.13 (m, 1H), 1.99-1.85 (m, 1H), 1.79-1.73 (m, 1H), 1.66-1.56 (m, 1H), 1.45 (s, 9H), 1.43-1.35 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 138.3, 128.8, 127.0, 126.4, 80.2, 67.6, 60.4, 40.0, 29.8, 28.5, 26.1, 19.0 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{16}H_{24}NO_3$: 278.1750, found: 278.1749.

4.12.2. (2*S*,3*R*)-*tert*-Butyl 3-hydroxy-2-p-tolylpiperidine-1-carboxylate 21b.

Colorless oil. $[\alpha]_D^{23}$ = +31.1 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3444, 3374, 2977, 2933, 1690, 1514, 1418, 1365, 1276, 1168, 1128, 986 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.49-7.45 (m, 0.5H), 7.31-7.27 (m, 0.5H), 7.18-7.14 (m, 1.5H), 7.10-7.05 (m, 1.5H), 5.36-5.31 (m, 1H), 4.52-4.47 (m, 1H), 4.11-4.07 (m, 1H), 2.90-2.81 (m, 1H), 2.41 (s, 0.7H), 2.33 (s, 2.3H), 2.28-2.25 (m, 1H), 1.99-1.86 (m, 1H), 1.78-1.71 (m, 1H), 1.66-1.56 (m, 1H), 1.46 (s, 7H), 1.42-1.34 (m, 1H), 1.16 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers) δ 156.8, 141.6, 136.7, 136.5, 135.2, 129.4, 129.2, 126.4, 126.3, 80.1, 67.5, 60.1, 55.7, 39.9, 28.5, 26.0, 22.8, 21.5, 21.0, 19.0 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{17}H_{26}NO_3$: 292.1907, found: 292.1908.

4.13. General Procedure for Synthesis of 22a or 22b.

To a solution of **21a** (785 mg, 2.83 mmol) or **21b** (825 mg, 2.83 mmol) in dry DCM (8 mL) was treated with DMP (2.40 g, 5.66 mmol) at room temperature for 0.5 h. The reaction was carefully quenched with a saturated aqueous solution of $NaHCO_3$ and solid $Na_2S_2O_3$, then the mixture was separated and the aqueous layer was extracted with DCM (40 mL × 3). The combined organic layers were washed with brine, dried and concentrated to give crude middle compound without further purification. The above crude was dissolved in cooled (0 °C) MeOH (23 mL) and treated with $NaBH_4$ (118 mg, 3.11 mmol) in one portion. After stirred for 20 min, the mixture was concentrated and the residue was dissolved in EtOAc (30 mL) and water (30 mL). The resulting mixture was separated and the aqueous layer was extracted with EtOAc (40 mL × 3). The combined organic layers were washed with brine, dried and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 5/1) to give **22a** (667 mg, 85%) or **22b** (584 mg, 71%).

4.13.1. (2*R*,3*R*)-*tert*-Butyl 3-hydroxy-2-phenylpiperidine-1-carboxylate 22a.

Colorless oil. $[\alpha]_D^{24}$ = +44.7 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2973, 2870, 1691, 1665, 1582, 1413, 1367, 1169, 1146, 1080, 965, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.42 (m, 2H), 7.38-7.23 (m, 3H), 5.37-5.31 (m, 1H), 4.14-4.04 (m,1H), 4.03-

3.95 (m, 1H), 3.09-2.96 (m, 1 H), 1.88-1.62 (m, 5H), 1.37 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.6, 138.6, 128.6, 128.5, 127.3, 80.0, 70.2, 59.4, 39.6, 28.4, 27.8, 23.2 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{16}H_{24}NO_3$: 278.1751, found: 278.1751.

4.13.2. (2*S*,3*S*)-*tert*-Butyl 3-hydroxy-2-p-tolylpiperidine-1-carboxylate 22b.

Colorless oil. $[\alpha]_D^{22}$ = +52.8 (*c* 0.25, $CHCl_3$); IR (film): ν_{max} 2932, 1607, 1582, 1407, 1366, 1275, 1143, 1111, 763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.31 (m, 2H), 7.15-7.11 (m, 2H), 5.34-5.27 (m, 1H), 4.07-3.93 (m, 2H), 3.05-2.96 (m, 1H), 2.33 (s, 3H), 1.86-1.59 (m, 5H), 1.38 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 136.8, 135.3, 129.1, 128.5, 80.0, 70.2, 58.9, 39.5, 28.4, 27.8, 23.4, 21.1 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{17}H_{26}NO_3$: 292.1907, found: 292.1913.

4.14. General Procedure for Synthesis of (+)-L-733, 060 2 or 3.

To a cooled mixture of sodium hydride (60% dispersion in mineral oil, 51 mg, 2.14 mmol) and dry DMF (2 mL) was added a solution of **22a** (297 mg, 1.07 mmol) or **22b** (311 mg, 1.07 mmol) in dry DMF (2 mL) slowly under nitrogen atmosphere. After being stirred for 0.5 h at room temperature, a solution of 1-(bromomethyl)-3,5-bis(trifluoromethyl)benzene (655 mg, 2.14 mmol) in dry DMF (1 mL) was added and the resulting mixture was stirred for 24 h. The mixture was quenched with water (5 mL) and extracted with Et_2O (10 mL × 3). The combined organic layers were washed with brine, dried, filtered and concentrated. Without purification, the crude product was dissolved in anhydrous DCM (5 mL) and cooled to 0 °C, and then a solution of TFA (0.8 mL, 10.70 mmol) was slowly dropped under an argon atmosphere. After being stirred for 24 h at room temperature, the mixture was concentrated and the residue was dissolved in DCM (10 mL). An aqueous solution of 3 M NaOH (10 mL) was added to pH=9. The resulting mixture was separated and the aqueous layer was extracted with DCM (10 mL × 3). The combined organic layers were washed with brine, dried and concentrated. The residue was purified by flash chromatography on silica gel (DCM/MeOH/NH_4OH = 100/3/1) to give (+)-L-733, 060 **(2)** (242 mg, 56%) or **3** (223 mg, 50%).

4.14.1. (2*R*,3*R*)-3-(3,5-Bis(trifluoromethyl)benzyloxy)-2-phenylpiperidine (+)-L-733, 060 (2).

Colorless oil. $[\alpha]_D^{23}$ = +46.5 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2924, 1769, 1721, 1590, 1455, 1369, 1269, 1250, 1148, 1071 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.50-7.42 (m, 2H), 7.37-7.23 (m, 5H), 4.53-4.47 (m, 1H), 4.15-4.08 (m, 1H), 3.85-3.82 (m, 1H), 3.69-3.65 (m, 1H), 3.31-3.24 (m, 1H), 2.87-2.78 (m, 1H), 2.25-2.16 (m, 1H), 1.94-1.80 (m, 2H), 1.74-1.64 (m, 1H), 1.55-1.48 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.0, 141.4, 131.4 (q, *J* = 33.0 Hz), 128.3, 127.6, 127.3, 126.9, 123.4 (q, *J* = 271.0 Hz), 121.3, 120.7, 77.4, 70.2, 64.4, 47.2, 28.6, 20.7 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{20}H_{20}F_6NO$: 404.1444, found: 404.1436.

4.14.2. (2*S*,3*S*)-3-(3,5-Bis(trifluoromethyl)benzyloxy)-2-p-tolylpiperidine 3.

White solid. M.p. 181-183 °C; $[\alpha]_D^{23}$ = +32.8 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2937, 1588, 1506, 1402, 1278, 1129, 620 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.45-7.42 (m, 2H), 7.27-7.23 (m, 2H), 7.16-7.11 (m, 2H), 4.57-4.53 (m, 1H), 4.18-4.13 (m, 1H), 3.84-3.79 (m, 1H), 3.67-3.63 (m, 1H), 3.32-3.24 (m, 1H), 2.88-2.77 (m, 1H), 2.34 (s, 3H), 2.27-2.16 (m, 2H), 1.95-1.81 (m, 1H), 1.73-1.62 (m, 1H), 1.55-1.48 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 138.7, 136.9, 131.4 (q, *J* = 33.0 Hz), 129.0, 127.6, 126.8, 123.4 (q, *J* = 271.0 Hz), 121.3, 77.4, 70.1, 64.1, 47.2, 28.5, 21.1, 20.5 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{21}H_{22}F_6NO$: 418.1600, found: 418.1601.

4.15. (2*S*,3*S*)-*tert*-Butyl 3-amino-2-phenylpiperidine-1-carboxylate 23.

To a solution of **21a** (580 mg, 2.11 mmol) in dry DCM (8 mL) was treated with DMP (1.34 g, 3.17 mmol) at room temperature for 0.5 h. The reaction was carefully quenched with a solution of $NaHCO_3$ and $Na_2S_2O_3$, then the mixture was separated and the aqueous layer was extracted with DCM (30 mL × 3). The combined organic layers were washed with brine, dried and concentrated to give crude product which was dissolved in pyridine (10 mL), and then $NH_2OMe{\cdot}HCl$ (211 mg, 2.53 mmol) was added. After being stirred for 6 h, the reaction was diluted with THF (8 mL) and treated with $BH_3{\cdot}SMe_2$ (0.6 mL, 1M in THF) at 50 °C for 12 h. The reaction was concentrated and the crude was stirred in anhydrous MeOH (15 mL) for another 2 h at 90 °C. The resulting mixture was concentrated and purified by flash chromatography on silica gel (DCM/MeOH/NH_4OH = 100/4/1) to give **23** (358 mg, 72%) as a light yellow oil. $[\alpha]_D^{25}$ = +17.3 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3369, 2975, 2932, 2866, 1690, 1475, 1454, 1412, 1391, 1365, 1300, 1270, 1252, 1175, 1148, 881, 867, 773, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.24 (m, 5H), 3.87-3.83 (m, 1H), 3.80-3.77 (m, 1H), 3.24-3.16 (m, 1H), 2.84-2.75 (m, 1H), 2.30-2.10 (m, 2H), 2.07-1.98 (m, 1H), 1.95-1.83 (m, 1H), 1.75-1.65 (m, 1H), 1.54-1.46 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.4, 139.2, 129.5, 128.3, 127.3, 79.8, 60.6, 51.2, 39.9, 29.3, 28.4, 24.4 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{16}H_{25}N_2O_2$: 277.1901, found: 277.1912.

4.16. (2*S*,3*S*)-*N*-(2-Methoxy-5-(trifluoromethoxy)benzyl)-2-phenylpiperidin-3-amine (+)-CP-122721 (5)

To a solution of **23** (339 mg, 1.05 mmol), 4Å MS (300 mg) and 2-methoxy-5-(trifluoromethoxy)benzaldehyde (693 mg, 3.15 mmol) in dry DCM (4.2 mL) was added $ZnCl_2$ (6 mL, 0.5 M in THF) and stirred for 24 h. The mixture was concentrated and dissolved in MeOH (4.2 mL), then $NaBH_4$ (238 mg, 6.29 mmol) was added in one portion and the mixture was stirred for 3 h at room temperature. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with DCM (10 mL × 3) and the combined organic layers were washed with brine, dried and concentrated. Without purification, the residue was dissolved in MeOH (2 mL) and 6M HCl (2 mL). After being stirred for 4 h, the mixture was concentrated and the residue was dissolved in DCM (10 mL). An aqueous solution of 3 M NaOH (10 mL) was added to pH=9. The resulting mixture was separated and the aqueous layer was extracted with DCM (10 mL × 4). The combined organic layers were washed with brine, dried and concentrated. The residue was purified by flash chromatography on silica gel (DCM/MeOH/NH_4OH = 100/9/1) to give (+)-CP-122721 **(5)** (280 mg, 85%) as a white solid. M.p. 86-88 °C; $[\alpha]_D^{22}$ = +7.0 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2930, 1582, 1497, 1463, 1423, 1148, 1112, 1032, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.20 (m, 5H), 7.01-6.94 (m, 1H), 6.86-6.82 (m, 1H), 6.63-6.59 (m, 1H), 3.89-3.87 (m, 1H), 3.66-3.61 (m, 1H), 3.49 (s, 3H), 3.40-3.35 (m, 1H), 3.28-3.23 (m, 1H), 2.84-2.75 (m, 2H), 2.13-2.05 (m, 1H), 1.97-1.83 (m, 1H), 1.80-1.65 (brs, 1H), 1.64-1.55 (m, 1H), 1.45-1.38 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.0, 142.6, 142.3, 130.5, 128.3, 126.8, 126.4, 122.5, 120.7 (q, *J* = 254.2 Hz), 120.1, 110.3, 64.3, 55.4, 55.2, 47.9, 46.1, 28.5, 20.4 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]+ Calcd for $C_{20}H_{24}F_3N_2O_2$: 381.1784, found: 381.1785.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.10.047.

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