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Stereoselective Approach to *cis*-2,3-Disubstituted Piperidines via Reduction of *N*-Acyliminium Ion Intermediate: Enantioselective Synthesis of (+)-(2*S*,3*S*)-CP-99,994

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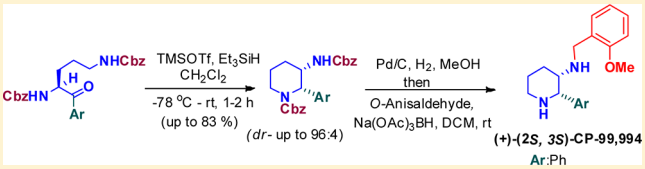
Supporting Information

ABSTRACT: A very simple and efficient stereoselective approach to *cis*-2,3-disubstituted piperidines via the reduction of *N*-acyliminium ion intermediates is described. Application of this methodology is exemplified by the enantioselective total synthesis of (+)-(2*S*,3*S*)-CP-99,994.



Functionalized piperidines are widely distributed in various bioactive alkaloids.[1] Piperidine motifs are also very important pharmacophores for many molecules in clinical and preclinical trials.[2] In particular, 2-aryl-3-amino piperidines are present in many bioactive molecules and drugs. Some of the compounds derived from this general structure are well-known as substance P (SP) receptor antagonists. For example, molecules such as (+)-(2*S*,3*S*)-CP-99,994 (**1**)[3] and (+)-(2*S*,3*S*)-CP-122,721 (**2**)[4] are known to be nonpeptide antagonists of neurokinin-1 (NK-1) substance P receptor (Figure 1). Likewise **3** and **4** have also shown the ability to antagonize the action of substance P.[5]

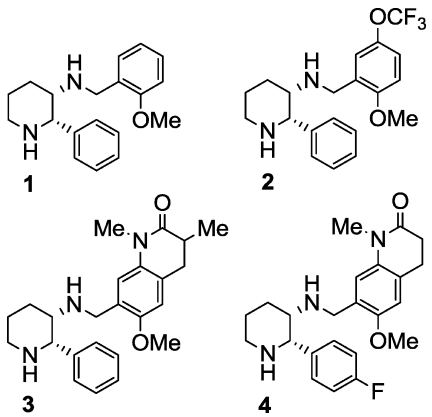
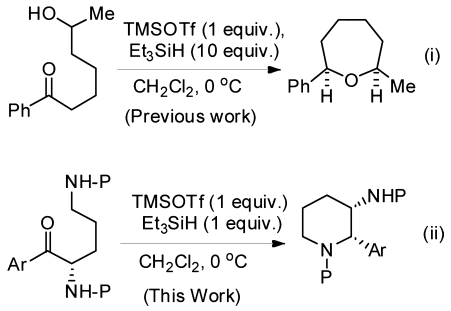


Figure 1. Antagonists of neurokinin-1 (NK-1) substance P receptor.

Interestingly, a *cis* relationship between the two substituents on the piperidine and importantly 2*S*,3*S* configurations are necessary for high affinity binding to human NK-1 receptor.[6] Evidently, significant effort has been made for the asymmetric synthesis of these piperidine derivatives because of their bioactivity.[7−9] However, there are only few approaches[7f,10] for the construction of 2-aryl-3-amino piperidines with diverse aryl groups at C-2, while controlling the stereochemistry of C-2 and C-3 positions. Hence the development of new enantioselective synthetic approaches to functionalized piperidines is still stimulating and useful. With this initiative, and also in connection with our program devoted to the synthesis of functionalized piperidines,[11] herein we describe a highly practical and short approach for the enantioselective synthesis of *cis*-2,3-disubsituted piperidines and concise and efficient asymmetric synthesis of (2*S*,3*S*)-(+)-CP-99,994 (**1**) relying on diastereoselective reduction of diamino ketones.

Earlier, diastereopure oxygenated heterocycles have been prepared by the reductive condensation of hydroxy ketones catalyzed by trimethylsilyl triflate in high yields (Scheme 1, eq i).[12] In spite of the application of this stereoselective and high yielding approach to oxa-heterocycles,[13] to the best of our knowledge this method has not been explored to date for the asymmetric synthesis of substituted piperidines.

Scheme 1. Synthesis of *cis*-2,3-Piperidines via Reductive Cyclization



Hence we planned to synthesize the functionalized piperidines relying on diastereoselective reductive cyclization

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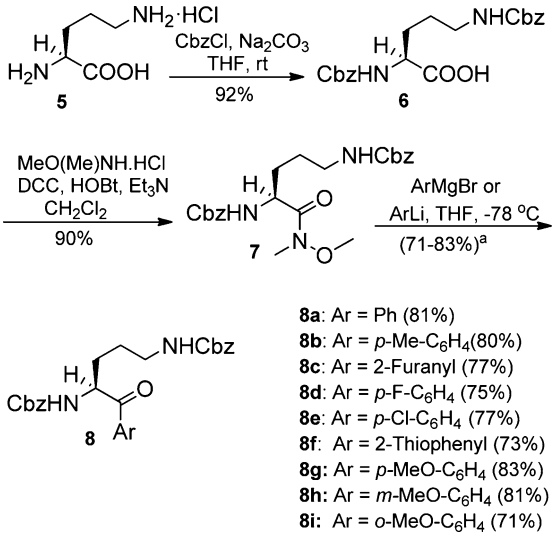
of the corresponding enantiopure diamino ketones (Scheme 1, eq ii).

In order to execute the strategy, it was essential to synthesize suitable enantiopure diamino ketone so as to facilitate the intramolecular cyclization. We envisioned that required diamino ketone can be constructed from easily accessible and less expensive enantiomerically pure L-ornithine **5** (Scheme 2).

Scheme 2. Synthesis of Diamino Ketones 8



[a]Isolated yield of purified compound.

Compound **5** upon treatment with benzyl chloroformate in alkaline condition afforded the corresponding $N(\alpha),N(\delta)$-bis-Cbz-ornithine **6** in excellent yield.[14] This was converted efficiently to *N*-methoxy-*N*-methylamide (Weinreb's amide) **7** in a short time following the common coupling condition.[15] Compound **7** when subjected to treatment with either aryl magnesium bromides (Grignard reagents)[16] or aryl lithium[17] in tetrahydrofuran (THF) at −78 °C afforded the corresponding diaminoarylketones (**8a**−**8i**) in very good yields (up to 83%) (Scheme 2).

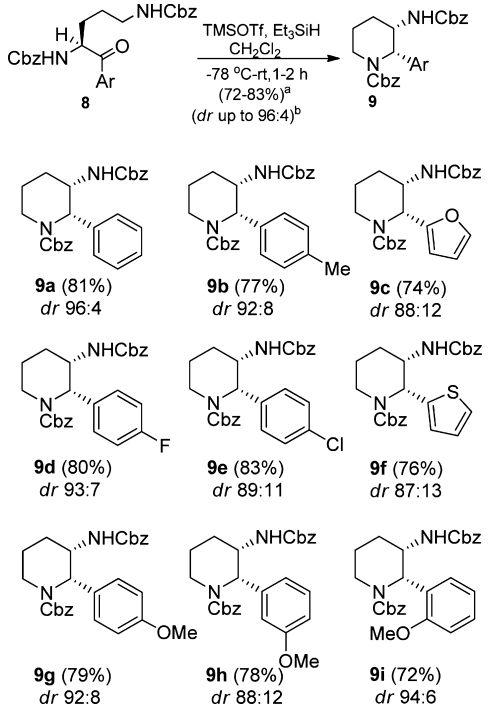
We surmised that 2,3-disubstituted piperidines can be built by intramolecular cyclization of diaminoarylketones via *N*-acyliminium ion intermediate, which could be further reduced by silyl hydrides. In order to explore the new possibility, we subsequently treated the diaminoarylketone **8a** with trimethylsilyl triflate (TMSOTf) (1 equiv) and triethylsilane (Et_3SiH) (1 equiv) in CH_2Cl_2 at −78 °C to afford the piperidine derivative **9a** in very good yield (81%) (Scheme 3).

We observed that optimization of the reaction condition to −78 °C gave the highest yield with excellent diastereoselectivity (96:4). It is gratifying to note that reductive cyclization was highly 2,3-*cis*-diastereoselctive.

Diastereomeric ratio was determined by ^{1}H NMR. The *cis* relationship of the substituents at C-2 and C-3 in compound **9a** was unambiguously deduced from the J_{2-3} coupling constant (J = 6.4 Hz), NOE and NOESY studies (Figure 2).[18] The structure of **9a** was unequivocally established by single-crystal X-ray analysis (Figure 2).[19]

Encouraged by this initial success, we planned to synthesize various 2,3-*cis*-piperidines to demonstrate the synthetic utility of this approach. Strength of the approach lies in the fact that diverse organolithium or Grignard reagents can be effectively

Scheme 3. Stereoselective Synthesis of *cis*-2,3-Disubstituted Piperidines with Diverse Functionality at C-2



[a]Isolated yield of purified compound. [b]dr is determined by ^{1}H NMR.

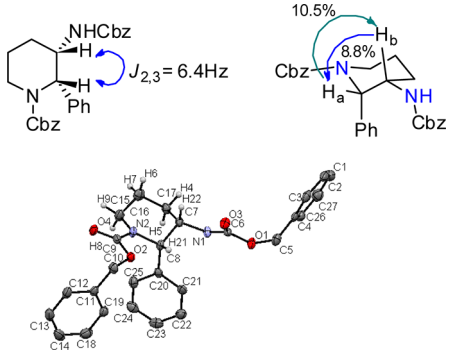


Figure 2. NOE and X-ray single crystal structure of compound **9a** (ORTEP diagram, ellipsoid drawn at 50% probability; aromatic hydrogens and hydrogens at C5, C10, N1, are omitted for clarity).

utilized to prepare various diaminoketone derivatives. Diaminoketones (**8b**−**8i**) upon treatment with trimethylsilyl triflate (TMSOTf) (1 equiv) and triethylsilane (Et_3SiH) (1 equiv) in CH_2Cl_2 at −78 °C afforded the corresponding piperidine derivatives (**9b**−**9i**) in very good yields (up to 83%) and diastereoselectivity (up to 96:4). The stereochemistry of the piperidine derivatives (**9b**−**9i**) was assigned by the analogy.

The high diastereoselectivity observed in the reduction of *N*-acyliminium ion intermediate has been rationalized on the basis of stereoselective addition of hydride ion. High diastereoselectivity leading to *cis*-2,3-disubstituted piperidines could be explained by the plausible mechanistic pathway as shown in Scheme 4. Carbonyl group of the enantiopure diaminoketone gets activated by TMSOTf, which in turn facilitates the intramolecular cyclization by the nucleophilic attack of secondary amine via a planar *N*-acyliminum ion intermediate (I) with a restricted rotation. Subsequently, silane hydride

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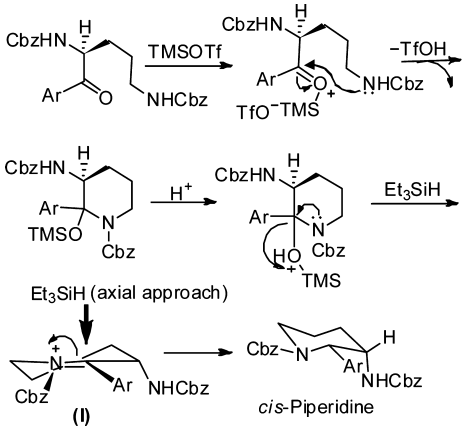
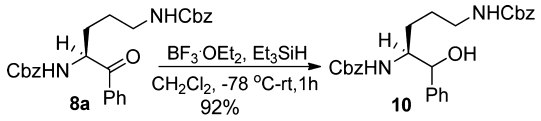
Scheme 4. Plausible Mechanism for the Stereoselective Synthesis of Piperidines via *N*-Acyliminium Ion



(Et_3SiH) approaches from the least sterically hindered face (axial approach) to afford (2*S*,3*S*)-*cis*-piperidines.[20]

It is interesting to note that diaminoarylketone (**8a**), when subjected to reaction with $BF_3{\cdot}Et_2O$ and Et_3SiH,[21] afforded the corresponding amino alcohol **10** even after prolonged reaction condition (Scheme 5). Attempts to synthesize the expected

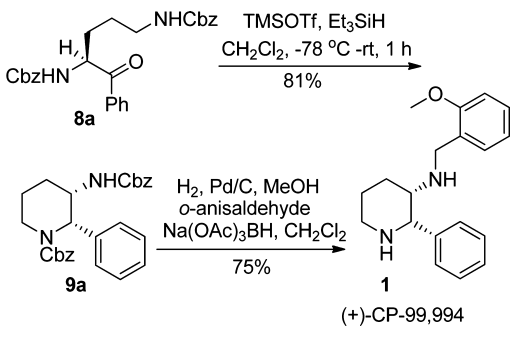
Scheme 5. Reaction of 8a with $BF_3{\cdot}OEt_2$ and Et_3SiH



product **9a** by increasing the amount of $BF_3{\cdot}Et_2O$ along with varying the reaction temperature (−78, 0 °C, and rt) exclusively led to the formation of compound **10**. We also changed the mode of addition by adding Et_3SiH followed by $BF_3{\cdot}Et_2O$, but diaminoarylketone resulted in the formation of amino alcohol **10**.

After successfully synthesizing different 2*S*,3*S*-*cis*-piperidines, we envisioned to apply this methodology for the enantioselective synthesis of (+)-CP-99,994 (**1**). Compound **9a** was treated with Pd/C, H_2 in methanolic solution for 6 h, and the resulting reaction mixture was filtered and treated with *o*-anisaldehyde followed by the addition of $Na(OAc)_3BH$ to furnish the enantiomerically pure (+)-CP-99,994 (**1**) in good yield (75%) (Scheme 6). ^1H, ^{13}C NMR, IR spectroscopic data were in accordance with the reported values.[7e] Final comparison of optical data with reported value[7d] and single X-ray crystal data of **9a** confirmed the configurational

Scheme 6. Enantioselective Synthesis of (+)-CP-99,994



assignment of compound **1**. Enantioselective synthesis of **1** has been achieved in an overall yield of 40% in five steps from L-ornithine **5**.

In conclusion, we have described a highly efficient and useful approach for constructing *cis*-2-aryl 3-amino piperidines with an option of introducing diverse aryl groups at C-2 position. This also gives an easy access to condense different aldehydes at C-3 amine functionality without compromising the stereochemistry. The method described herein opens a wide and easy access to synthesize piperidine derivatives and in particular synthesis of various congeners of (+)-CP-99,994 to test the biological activity against NK1-receptor. The application of this method is further exemplified by the short and concise enantioselective synthesis of (+)-CP-99,994.

EXPERIMENTAL PROCEDURE

General Methods. Unless otherwise noted, all reactions have been carried out with distilled and dried solvents under an atmosphere of dry N_2 and oven-dried glassware. All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin layer chromatography (TLC) was performed using silica gel 60 GF_{254} precoated aluminum backed plates (2.5 mm) with detection by UV light. ^1H NMR and ^{13}C NMR were recorded in $CDCl_3$ and DMSO-d_6. Chemical shifts in ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard, *J* values are given in Hz. ^{13}C NMR are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of chloroform-*d* and DMSO-d_6. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by High resolution mass spectrometry using ESI TOF. FT-IR spectra were obtained using a FT-IR spectrophotometer as thin films on sodium chloride or KBr discs and reported in cm^{-1}. Optical rotations were measured on a polarimeter. Melting points were measured in an open glass capillary, and values are uncorrected.

Weinreb Amide (7). To a cooled and stirred reaction mixture of (*S*)-*N*,*N*-dibenzyloxycarbonylornithine[14] (20 g, 50 mmol), Et_3N(17.4 mL, 125 mmol), HOBt (6.75 g, 50 mmol) followed by DCC (12.37 g, 40.11 mmol) in CH_2Cl_2 (70 mL) were added at 0 °C, and the reaction mixture was stirred for 30 min while maintaining 0 °C and then allowed to stir at room temperature for 6 h. The precipitate that formed was removed by filtration, and the filter cake (residue) was washed with EtOAc. The filtrate was diluted with additional EtOAc and washed with saturated aqueous $NaHCO_3$, water, 5% HCl, and brine solution. The solution was dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated in vacuo to give Weinreb amide, which was purified over silica gel using column chromatography (EtOAc:petroleum ether, 3:7) to furnish pure Weinreb amide **7** as a white solid (20.34 g, 92% yield): R_f = 0.3 petroleum ether:EtOAc (50:50); $[\alpha_D^{25}]$ −4 (*c* 1, $CHCl_3$); mp = 69−71 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.23 (m, 10H), 6.01 (bs, 1H), 5.38 (bs, 1H), 5.21−4.92 (m, 4H), 4.70 (s, 1H), 3.69 (s, 3H), 3.13 (m, 5H), 1.82−1.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 156.3, 156.1, 136.6, 136.2, 128.3, 127.96, 127.92, 127.8, 66.6, 66.3, 61.4, 50.5, 40.4, 31.8, 29.6, 25.6; HRMS (ESI) Calcd. for $C_{23}H_{29}N_3O_6Na$ $(M + Na)^+$ 466.1954 found 466.1954.

General Procedure A for the Preparation of Ketones (8) from Weinreb Amide (7). To a solution of Weinreb amide **7** (0.221 g, 0.5 mmol) in 2 mL of dry THF at −78 °C was added freshly prepared arylmagnesium bromide (2 mmol, 4 equiv), and the solution was allowed to warm to 0 °C. After the completion of the reaction (monitored by TLC), 1 N HCl (5 mL) was added. The resultant mixture was then extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with saturated brine solution (2 × 20 mL), filtered and concentrated to give crude ketone, which was purified over silica gel using column chromatography (EtOAc:petroleum ether, 3:7) to furnish desired ketone (**8a**−**8i**).

(*S*)-*N*,*N*′-Dibenzyl (5-oxo-5-phenylpentane-1,4-diyl)-dicarbamate (8a). The title compound **8a** was synthesized according

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to the general procedure A for ketones from Weinreb amide **7** and phenylmagnesium bromide. Product was isolated as a white solid (0.185 g, 81% yield): R_f = 0.5 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ +24 (*c* 1, $CHCl_3$); mp = 101−103 °C; IR (cm^{-1}) 3320, 1676, 1545; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.40−7.25 (m, 10H), 5.81 (d, *J* = 8.0 Hz, 1H), 5.37 (s, 1H), 5.16−4.99 (m, 4H), 4.77 (s, 1H), 3.24−3.10 (m, 2H), 1.98−1.88 (m, 1H), 1.75−1.40 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6, 156.5, 156.2, 136.6, 136.3, 135.0, 134.1, 129.1, 128.8, 128.7, 128.6, 128.3, 128.2, 127.8, 127.1, 67.2, 66.8, 65.5, 55.2, 40.7, 31.0, 25.6, HRMS (ESI) Calcd. for $C_{27}H_{28}N_2O_5Na$ $(M + Na)^+$ 483.1896, found 483.1896

(*S*)-*N*,*N*′-Dibenzyl 5-oxo-5-(*p*-tolyl)pentane-1,4-diyldicarbamate (8b). The title compound **8b** was synthesized according to the general procedure A for ketone from Weinreb amide **7** and *p*-methylphenylmagnesium bromide. Product was isolated as white solid (0.19 g, 80% yield): R_f = 0.5 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ +49 (*c* 1, $CHCl_3$); mp = 83−85 °C, IR (cm^{-1}) 3326, 1704, 1689, 1531; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.9 Hz, 2H), 7.40−7.18 (m, 12H), 5.83 (d, *J* = 7.6 Hz, 1H), 5.38−5.30 (m, 1H), 5.09 and 5.04 (2s, 4H), 4.79 (s, 1H), 3.17−3.11 (m, 2H), 2.4(s, 3H), 1.96−1.87 (m, 1H), 1.74−1.51 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 156.5, 156.2, 145.2, 136.6, 136.4, 131.7, 129.8, 128.9, 128.7, 128.65, 128.62, 128.3, 128.2, 67.1, 66.8, 55.1, 40.8, 31.2, 25.5, 21.9; HRMS (ESI) Calcd. for $C_{28}H_{31}N_2O_5$ $(M + H)^+$ 475.2233, found 475.2237.

(*S*)-*N*,*N*′-Dibenzyl (5-(furan-2-yl)-5-oxopentane-1,4-diyl)-dicarbamate (8c). To a stirred solution of furan (0.81 g, 12 mmol) in dry THF at −78 °C was added *n*-BuLi (5.3 mL, 8.57 mmol, 1.6 M solution in hexane), and the reaction mixture was stirred for 30 min maintaining the temperature. The resulting reaction mixture was transferred to solution of Weinreb amide (**7**) (0.76 g, 1.71 mmol) in THF at −78 °C via cannula, after which the reaction mixture was allowed to warm to room temperature. After complete consumption of Weinreb amide **7**, the reaction mixture was quenched with 1 N HCl. The resultant mixture was then extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with brine solution (saturated NaCl) (1 × 40 mL), filtered and concentrated to give the corresponding crude ketone, which was purified over silica gel using column chromatography (EtOAc:petroleum ether, 3:7) to furnish desired furanyl ketone **8c** as a dark gray solid (0.17 g, 77% yield): R_f = 0.5 petroleum ether:EtOAc (50:50); mp = 94−96 °C; IR (cm^{-1}) 3330, 1706, 1692, 1546.; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.40−7.20 (m, 11H), 6.50 (s, 1H), 5.89 (d, *J* = 7.8 Hz, 1H), 5.05 (m, 6H), 3.27−2.92 (m, 2H), 1.89 (s, 1H), 1.60 (dq, *J* = 24.0, 7.5, 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.2, 156.5, 156.1, 150.6, 147.4, 136.6, 136.2, 128.5, 128.1, 128.02, 119.3, 112.7, 66.9, 66.5, 55.5, 40.5, 30.3, 25.7; HRMS(ESI) Calcd. for $C_{25}H_{26}N_2O_6Na$ $(M + Na)^+$ 473.1689, found 473.1684.

(*S*)-*N*,*N*′-Dibenzyl 5-(4-fluorophenyl)-5-oxopentane-1,4-diyl-dicarbamate (8d). The title compound **8d** was synthesized according to the general procedure A for ketones from Weinreb amide **7** and *p*-fluorophenylmagnesium bromide. Product was isolated as a white solid (0.178 g, 75%): R_f = 0.5 petroleum ether:EtOAc (50:50); $[\alpha_D^{25}]$.+28.1 (*c* 1, $CHCl_3$); mp = 95−96 °C; IR (cm^{-1}) 3370, 1706, 1677, 1516 ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.32 (m, 10H), 7.14 (t, *J* = 8.5 Hz, 2H), 5.74 (d, *J* = 8.4 Hz, 1H), 5.31 (s, 1H), 5.1 (s, 2H), 5.0 (s, 2H), 4.76 (bs, 1H), 3.17 (bs, 2H), 1.93 (m, 1H), 1.58 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 167.5, 164.9, 156.5, 156.2, 136.5, 136.3, 131.5, 131.4, 130.7, 128.6, 128.5, 128.2, 128.1, 116.3, 116.1, 67.1, 66.7, 55.0, 40.6, 30.7, 25.6; HRMS (ESI) Calcd. for $C_{27}H_{27}N_2O_5FNa$ $(M + Na)^+$ 501.1802, found 501.1797.

(*S*)-*N*,*N*′-Dibenzyl (5-(4-chlorophenyl)-5-oxopentane-1,4-diyl)dicarbamate (8e). The title compound **8e** was synthesized according to the general procedure A for ketones from Weinreb amide **7** and *p*-chlorophenylmagnesium bromide. Product was isolated as a white solid (0.19 g, 77% yield): R_f = 0.5 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ +22.8 (*c* 1, $CHCl_3$); mp = 99−101 °C; IR (cm^{-1}) 3335, 1677, 1656, 1531; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.32 (m, 10H), 5.73 (d, *J* = 8.2 Hz, 1H), 5.31 (s, 1H), 5.10 (s, 2H), 5.05 (s, 2H), 4.76 (bs, 1H), 3.17 (bm, 2H), 1.92 (m, 1H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 156.5, 156.2, 140.7, 136.6, 136.3, 132.6, 130.2, 129.5, 128.70, 128.7, 128.4, 128.2, 67.2, 66.8, 55.1, 40.7, 34.1, 30.9, 25.7; HRMS (ESI) Calcd. for $C_{27}H_{28}N_2ClO_5$ $(M + H)^+$ 495.1686, found 495.1684.

(*S*)-*N*,*N*′-Dibenzyl 5-oxo-5-(thiophene-2-yl)pentane-1,4-diyl-dicarbamate (8f). The title compound **8f** was synthesized according to the general procedure A for ketones from Weinreb amide **7** and 2-thiophenemagnesium bromide. Product was isolated as a white solid (0.17 g, 73% yield): R_f = 0.5 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ +26 (*c* 1, $CHCl_3$); mp = 98−99 °C; IR (cm^{-1}) 1685, 1667, 1515; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.71 (d, *J* = 4.6 Hz, 1H), 7.41−7.28 (m, 10H), 7.20−7.12 (m, 1H), 5.74 (d, *J* = 7.5 Hz, 1H), 5.28−5.13 (m, 1H), 5.10 and 5.07 (2s, 4H), 4.85 (m, 1H), 3.20 (bm, 3H), 2.05−1.92 (m, 1H), 1.65 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 156.5, 156.1, 141.3, 136.6, 136.3, 135.4, 133.4, 128.7, 128.6, 128.3, 128.2, 67.2, 66.8, 56.1, 40.7, 31.6, 25.8; HRMS (ESI) Calcd. for $C_{25}H_{26}N_2O_5SNa$ $(M + Na)^+$ 489.1460, found 489.1463.

(*S*)-*N*,*N*′-Dibenzyl 5-(4-methoxyphenyl)-5-oxopentane-1,4-diyldicarbamate (8g). The title compound **8g** was synthesized according to the general procedure A for ketones from Weinreb amide **7** and *p*-methoxyphenylmagnesium bromide. Product was isolated as a colorless oil (0.2 g, 83%): R_f = 0.5 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ +28.4 (*c* 1, $CHCl_3$); IR (cm^{-1}) 3320, 1706, 1646, 1531; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.6 Hz, 2H), 7.41−7.27 (m, 10H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.83 (d, *J* = 7.8 Hz, 1H), 5.31 (bm, 1H), 5.1 and 5.0 (2s, 4H), 4.79 (bs, 1H), 3.86 (s, 3H), 3.16 (bm, 2H), 2.02−1.84 (m, 1H), 1.69−1.52 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 164.4, 156.5, 156.2, 136.4, 131.1, 128.7, 128.6, 128.3, 128.2, 127.0, 114.3, 67.1, 66.7, 55.7, 54.7, 40.8, 31.4, 22.5; HRMS (ESI) Calcd. for $C_{28}H_{30}N_2O_6Na$ $(M + Na)^+$ 513.2002, found 513.1993.

(*S*)-*N*,*N*′-Dibenzyl 5-(3-methoxyphenyl)-5-oxopentane-1,4-diyldicarbamate (8h). The title compound **8h** was synthesized according to the general procedure A for ketones from Weinreb amide **7** and *meta*-methoxyphenylmagnesium bromide. Product was isolated as colorless oil (0.198 g, 81%): R_f = 0.5 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ +22.8 (*c* 1, $CHCl_3$), IR (cm^{-1}) 3340, 1692, 1666, 1517; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.4 Hz, 1H), 7.45 (s, 1H), 7.41−7.26 (m, 11H), 7.13 (dd, *J* = 8.1, 2.5 Hz, 1H), 5.82 (d, *J* = 7.8 Hz, 1H), 5.41−5.27 (m, 1H), 5.1 and 5.07 (2s, 4H), 4.81 (s, 1H), 3.83 (s, 3H), 3.16 (m, 2H), 1.94 (m, 1H), 1.66−1.41 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 160.1, 156.5, 156.2, 136.6, 136.3, 135.6, 130.1, 128.7, 128.6, 128.3, 128.2, 121.3, 120.7, 112.9, 67.1, 66.8, 55.61, 55.3, 40.7, 31.1, 25.6.HRMS (ESI) Calcd. for $C_{28}H_{3O}N_2O_6Na$ $(M + Na)^+$ 513.2002, found 513.1992.

(*S*)-*N*,*N*′-Dibenzyl 5-(2-methoxyphenyl)-5-oxopentane-1,4-diyldicarbamate (8i). The title compound **8i** was synthesized according to the general procedure for ketones from Weinreb amide **7**and *ortho*-methoxyphenylmagnesium bromide. Product was isolated as white solid (0.173 g, 71%): R_f = 0.5 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ +10 (*c* 1, $CHCl_3$); mp = 97−99 °C; IR (cm^{-1}) 1706, 1680, 1560; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.3 Hz, 1H), 7.54−7.45 (m, 1H), 7.37−7.26 (m, 10H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 5.81 (d, *J* = 8.4 Hz, 1H), 5.44 (m, 1H), 5.07 (2s, 4H), 4.80 (s, 1H), 3.89 (s, 3H), 3.14 (s, 2H), 1.90 (m, 1H), 1.46 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 158.8, 156.4, 134.9, 131.4, 128.7, 128.2, 124.9, 121.2, 111.9, 67.0, 66.7, 59.5, 55.9, 40.9, 30.3, 29.8, 25.8; HRMS (ESI) Calcd. for $C_{28}H_{30}N_2O_6Na$ $(M + Na)^+$ 513.2002, found 513.2003.

General Procedure B for Cyclization. To a stirred solution of ketone (**8a**−**8i**) (0.5 mmol) in CH_2Cl_2 (1 mL) at −78 °C were added successively Et_3SiH (0.6 mmol) and TMSOTf (0.6 mmol), and the reaction mixture was stirred for 30 min maintaining the temperature, after which the reaction mixture was allowed to warm to room temperature. After complete consumption of starting material (monitored by TLC), the reaction mixture was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give cyclized product (2,3-disubstituted piperidine), which was purified over silica gel using

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column chromatography (EtOAc:petroleum ether, 2:8) to furnish 2,3-disubstituted piperidine derivative (**9a**–**9i**).

(2*S*,3*S*)-Benzyl 3-(benzyloxycarbonylamino)-2-phenylpiperidine-1-carboxylate (9a). Synthesized according to the general procedure B. Product was isolated as white solid (0.18 g, 81% yield): R_f = 0.6 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ −2 (*c* 1, $CHCl_3$); mp = 127−129 °C; IR (cm^{-1}) 3390, 1691.1518; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 13H), 7.17 (bm, 2H), 5.44 (d, *J* = 6.4 Hz, 1H), 5.21−4.90 (m, 4H), 4.35 (d, *J* = 9.1 Hz, 1H), 4.21−4.04 (m, 2H), 3.22 (m, 1H), 1.93−1.85 (m, 2H), 1.81−1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 155.5, 138.4, 136.6, 136.4, 129.2, 128.7, 128.1, 128.3, 128.0, 127.8, 67.4, 66.9, 57.4, 50.2, 40.5, 26.1, 24.1; HRMS (ESI) Calcd. for $C_{27}H_{29}N_2O_4$ $(M + H)^+$ 445.2127, found 445.2128.

(2*S*,3*S*)-Benzyl 3-(benzyloxycarbonylamino)-2-(*p*-tolyl)-piperidine-1-carboxylate (9b). Synthesized according to the general procedure B. Product was isolated as colorless oil (0.176 g, 77% yield): R_f = 0.6 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ −4.1 (*c* 1, $CHCl_3$); IR (cm^{-1}) 3329, 1695, 1516; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.25 (m, 8H), 7.19 (m, 4H), 7.08 (d, *J* = 7.9 Hz, 2H), 5.41 (d, *J* = 6.3 Hz, 1H), 5.20−4.93 (m, 4H), 4.38 (d, *J* = 9.1 Hz, 1H), 4.12 (m, 2H), 3.20 (t, *J* = 12.9 Hz, 1H), 2.32 (s, 3H), 1.89 (d, 2H), 1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 155.5, 137.6, 136.7, 136.5, 135.2, 129.4, 129.2, 128.6, 128.5, 128.3, 128.0, 127.9, 77.5, 77.2, 76.8, 67.4, 66.9, 57.2, 50.2, 40.4, 26.2, 24.2, 21.1; HRMS (ESI) Calcd. for $C_{28}H_{31}N_2O_4$ $(M + Na)^+$ 459.2284, found 459.2285.

(2*R*,3*S*)-Benzyl 3-(benzyloxycarbonylamino)-2-(furan-2-yl)-piperidine-1-carboxylate (9c). Synthesized according to the general procedure B. Product was isolated as colorless viscous oil (0.160 g, 74% yield): R_f = 0.6 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ −19.6 (*c* 1, $CHCl_3$); IR (cm^{-1}) 3326, 1694, 1516; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.27 (m, 10H), 6.34 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.16 (bs, 1H), 5.45 (bs, 1H), 5.26 (d, *J* = 7.7 Hz, 1H), 5.21−5.01 (m, 4H), 4.39 (s, 1H), 4.09 (d, *J* = 6.6 Hz, 1H), 2.92 (t, *J* = 12 Hz, 1H), 1.84−1.75 (m, 2H), 1.67−1.59 (m, 2H), 1.56−1.47 (m, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 151.0, 142.2, 136.3, 128.7, 128.6, 128.4, 110.5, 107.7, 67.5, 67.1, 54.6, 47.0, 40.2, 24.6, 19.7; HRMS (ESI) Calcd. For $C_{25}H_{26}N_2O_5Na$ $(M + Na)^+$ 457.1739, found 457.1742.

(2*S*,3*S*)-Benzyl 3-(benzyloxycarbonylamino)-2-(4-fluorophenyl)piperidine-1-carboxylate (9d). Synthesized according to the general procedure B. Product was isolated as a white solid (0.184 g, 80% yield): R_f = 0.6 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ −2.1 (*c* 1, $CHCl_3$); mp = 139−141 °C; IR (cm^{-1}) 3322, 1692, 1656, 1529; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.23 (m, 13H), 6.95 (t, *J* = 8.6 Hz, 2H), 5.46 (d, *J* = 6.4 Hz, 1H), 5.21−4.94 (m, 4H), 4.32 (d, *J* = 8.6 Hz, 1H), 4.13 (d, *J* = 11.9 Hz, 2H), 3.20 (t, *J* = 14.7 Hz, 1H), 1.98−1.87 (m, 2H), 1.86−1.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 155.4, 136.6, 136.4, 130.8, 130.8, 128.7, 128.5, 128.4, 128.1, 127.9, 115.7, 115.4, 67.5, 67.0, 56.8, 50.1, 40.4, 26.0, 24.0; HRMS (ESI) Calcd. for $C_{27}H_{28}FN_2O_4$ $(M + H)^+$ 463.2033, found 463.2037.

(2*S*,3*S*)-Benzyl 3-(benzyloxycarbonylamino)-2-(4-chlorophenyl)piperidine-1-carboxylate (9e). Synthesized according to the general procedure B. Product was isolated as colorless viscous oil (0.198 g, 83% yield): R_f = 0.6 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ −4.6 (*c* 1, $CHCl_3$); IR (cm^{-1}) 3341, 1694, 1646, 1530; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.25 (m, 10H), 7.20 (d, *J* = 2.7 Hz, 3H), 7.17 (s, 2H), 5.43 (d, *J* = 6.5 Hz, 1H), 5.16−4.87 (m, 4H), 4.33 (d, *J* = 8.8 Hz, 1H), 4.15−4.04 (m, 2H), 3.22−3.14 (m, 1H), 1.91−1.83 (m, 2H),1.78−1.68 (m, 1H), 1.67−157 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 155.4, 137.0, 136.5, 136.3, 133.8, 130.4, 128.7, 128.8, 128.5, 128.4, 128.4, 128.1, 127.9, 127.8, 67.5, 67.5, 67.0, 56.8, 50.1, 40.6, 25.9, 23.98; HRMS (ESI) Calcd. for $C_{27}H_{28}ClN_2O_4$ $(M + H)^+$ 479.1738, found 479.1746.

(2*R*,3*S*)-Benzyl 3-(benzyloxycarbonylamino)-2-(thiophen-2-yl)piperidine-1-carboxylate (9f). Synthesized according to the general procedure B. Product was isolated as colorless viscous oil (0.17 g, 76% yield): R_f = 0.6 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ −16.7 (*c* 1, $CHCl_3$); IR (cm^{-1}) 3390, 1694, 1518; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 10H), 6.98−6.92 (m, 1H), 5.63 (s, 1H), 5.26 (d, *J* = 8.4 Hz, 1H), 5.18−5.03 (m, 4H), 4.37 (d, *J* = 8.0 Hz, 1H), 4.18−3.99 (m, 2H), 3.08−2.92 (m, 2H), 1.94−1.77 (m, 2H), 1.68−1.56 (m, 1H), 1.52−1.47(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 155.6, 141.5, 136.5, 136.3, 128.7, 128.6, 128.4, 128.2, 127.9, 127.2, 125.09, 124.9, 67.7, 67.1, 56.2, 48.9, 39.7, 24.0, 19.7.HRMS (ESI) Calcd. for $C_{25}H_{26}N_2O_4SNa(M + Na)^+$ 473.1511, found 473.1511.

(2*S*,3*S*)-Benzyl 3-(benzyloxycarbonylamino)-2-(4-methoxyphenyl)piperidine-1-carboxylate (9g). Synthesized according to the general procedure B. Product was isolated as colorless viscous oil (0.187 g, 79% yield): R_f = 0.6 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ −24.1 (*c* 1, $CHCl_3$); IR (cm^{-1}) 3329, 1695, 1516; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47−7.24 (m, 10H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.44 (s, 1H), 5.30 (m, 1H), 5.20−5.05 (m, 4H), 4.52 (d, *J* = 6.0 Hz, 1H), 4.20−4.09 (m, 1H), 3.80 (s, 3H), 2.89 (t, *J* = 11.3 Hz, 1H), 1.73 −1.58 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 156.9, 155.8, 136.6, 136.4, 129.0, 128.7, 128.3, 128.4, 128.1, 127.8, 127.6, 114.3, 67.0, 58.2, 55.4, 48.0, 39.9, 23.7, 19.8; HRMS (ESI) Calcd. for $C_{28}H_{31}N_2O_5$ $(M + H)^+$ 475.2233, found 475.2237.

(2*S*,3*S*)-Benzyl 3-(benzyloxycarbonylamino)-2-(3-methoxyphenyl)piperidine-1-carboxylate (9h). Synthesized according to the general procedure B. Product was isolated as colorless viscous oil (0.184 g, 78% yield): R_f = 0.6 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ −10 (*c* 1, $CHCl_3$), IR (cm^{-1}) 3331, 1692, 1514; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.24 (m, 9H), 7.20 (s, 2H), 6.86 (m, 3H), 5.42 (d, *J* = 5.8 Hz, 1H), 5.18−4.95 (m, 4H), 4.44 (d, *J* = 8.8 Hz, 1H), 4.18−4.05 (m, 2H), 3.69 (s, 3H), 3.28−3.17 (m, 1H), 1.98−1.83 (m, 2H), 1.83−1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 155.8, 155.5, 139.8, 136.6, 136.4, 129.6, 128.7, 128.6, 128.5, 128.3, 128.2, 128, 127.9, 121.3, 115.4, 113.1, 67.4, 66.9, 57.4, 55.2, 50.1, 40.5, 26.8, 24.1; HRMS (ESI) Calcd. for $C_{28}H_{30}N_2O_5Na$ $(M + Na)^+$ 497.2052, found 497.2051.

(2*S*,3*S*)-Benzyl 3-(benzyloxycarbonylamino)-2-(2-methoxyphenyl)piperidine-1-carboxylate (9i). Synthesized according to the general procedure B. Product was isolated in 72% yield as colorless viscous oil (0.17g, 72% yield): R_f = 0.6 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ + 2.6 (*c* 1, $CHCl_3$), IR (cm^{-1}) 3428, 1695, 1413; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.33 (m, 5H), 7.25−7.21 (m, 4H), 7.16−7.08 (m, 3H), 6.91−6.85 (m, 2H), 5.43 (d, *J* = 2.5 Hz, 1H), 5.29 (d, *J* = 8.2 Hz, 1H), 5.11−5.06 (m, 4H), 4.5 (bs, 1H), 4.28−4.21 (m, 1H), 3.8(s, 3H), 3.35−3.28 (m, 1H), 1.80−1.71 (m, 2H), 1.64−1.58 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 156.7, 145.2, 136.6, 131.1, 130.4, 128.6, 128.4, 128.2, 127.9, 127.5, 126.9, 120.4, 110.9, 67.3, 66.8, 56.6, 55.4, 41.5, 41.3, 24.0, 19.2; HRMS(ESI) Calcd. for $C_{28}H_{30}N_2O_5Na$ $(M + Na)^+$ 497.2052, found 497.2045.

Synthesis of 1,2-Amino Alcohol (10). $BF_3{\cdot}OEt_2$ (0.192 mL, 1.53 mmol) was added to a solution of Et_3SiH (0.6 g, 5.1 mmol) in CH_2Cl_2 (2 mL) at room temperature. The solution was stirred for 5 min and then transferred via cannula to a stirred solution of ketone **8a** (0.2 g, 0.51 mmol) in CH_2Cl_2 (5 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, whereupon the cooling-bath was removed and stirring was continued at room temperature for an additional 1 h. The reaction mixture was recooled to −78 °C and poured into a mixture of saturated aqueous $NaHCO_3$. The organic layers were separated, and the aqueous phase was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford a white solid **10** (0.184 g, 92% yield): R_f = 0.4 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ −27.8 (*c* 1, $CHCl_3$); mp =116−117 °C; IR (cm^{-1}) 3290, 1686, 1545; ^1H NMR (400 MHz, DMSO-d_6) δ 7.43−7.07 (m, 16H), 7.04 (d, *J* = 9.2 Hz, 1H), 5.35 (d, *J* = 4.9 Hz, 1H), 5.06−4.76 (m, 4H), 4.45 (t, *J* = 5.5 Hz, 1H), 3.52 (m, 1H), 2.90 (m, 2H), 1.63−1.11 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.1, 155.8, 143.7, 137.4, 137.3, 128.4, 128.3, 127.75, 127.7, 127.6, 127.3, 126.7, 126.5, 74.7, 65.1, 64.8, 56.8, 40.5, 26.5, 26.3 HRMS (ESI) Calcd. for $C_{27}H_{30}N_2O_5Na$ $(M + Na)^+$ 485.2052, found 485.2055.

Asymmetric Synthesis of (+)-CP-99,994. A mixture of **9a** (0.4 g, 0.87 mmol), and Pd/C (10%, 0.1 g), in MeOH (5 mL) was stirred under an atmosphere of H_2 at rt for 6 h. The crude mixture was filtered through a pad of Celite, and the filtrate was concentrated under vacuum to give crude diamine. To a solution of the crude diamine in CH_2Cl_2 (5 mL) and 2-methoxybenzaldehyde (0.118 g, 0.87 mmol)

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was added $NaBH(OAc)_3$ (0.276 g, 1.30 mmol), and the resulting mixture was stirred under an argon atmosphere for 20 h at room temperature. Saturated aqueous Na_2CO_3 solution (10 mL) was added, and the organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel using a mixture of $CHCl_3$/MeOH (80:20) as eluent to give **1** (0.21 g, 75%) as a pale yellow oil: R_f = 0.6 DCM:MeOH (20:80), $[\alpha_D^{25}]$ +66.7 (*c* 1, $CHCl_3$); IR (cm^{-1}) 3328, 2923, 1465; Lit.[7d] $[\alpha]_D^{25}$ +67.2 (1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.21 (m, 5H), 7.16 (td, *J* = 7.9, 1.7 Hz, 1H), 6.98 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.81 (td, *J* = 7.3, 0.8 Hz, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 3.91 (d, *J* = 2.2 Hz, 1H), 3.71 (d, *J* = 13.8 Hz, 1H), 3.41 (d, *J* = 13.7 Hz, 1H), 3.43(s, 3H), 3.34−3.27 (m, 1H), 2.87−2.82 (m, 2H), 2.6(bs, 2H), 2.14 (d, *J* = 12.5 Hz, 1H), 2.06−1.92 (m, 1H), 1.65−1.57 (m, 1H), 1.43 (d, *J* = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 141.5, 129.9, 128.4, 128.2, 127.5, 127.0, 126.4, 120.2, 109.9, 63.8, 54.9, 54.7, 47.6, 46.8, 27.9, 20.0; HRMS (ESI) Calcd. for $C_{19}H_{25}N_2O$ $(M + H)^+$:297.1967, found 297.1969. HPLC Chiralpak IC, *n*-Hexane/2-propanol 10:90, 290 nm; Retention Time t_{major} = 8.04 min, t_{minor} = 10.11 min; *ee* = 97% (please see the Supporting Information).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H NMR, ^{13}C NMR spectra for the compounds **1**, **7**, **8a**−**8i**, **9a**−**9i**, and **10**. NOE, NOESY, COSY, single crystal X-ray (CIF) and HPLC data of compound **9a**. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

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