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Tetrahedron
Tetrahedron 62 (2006) 7459–7465

Syntheses of enantio-enriched chiral building blocks from L-glutamic acid

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Received 16 March 2006; revised 8 May 2006; accepted 9 May 2006
Available online 5 June 2006

Abstract—Starting from lactone-amide **8**, easily derived from L-glutamic acid, enantioselective syntheses of (*S*)-tetrahydrofuran 2-carboxamide derivative **2** and a protected (*S*)-3-hydroxypiperidin-2-one (**3**) are reported. The building block **3** was converted to (2*S*,3*R*)-3-hydroxypipecolamide (**6**) by a three-step procedure. A solvent altered H-bonding capacity leading to a highly chemoselective tosylation of the primary hydroxyl group in the presence of an α-hydroxy-carboxamide was observed.

1. Introduction

Tetrahydrofuran 2-carboxylic acid derivatives such as **1**[1] (Fig. 1) are key structural units used in designing peptidomimetics. Protected 3-hydroxypiperidin-2-ones such as **3** may serve as useful building blocks,[2] while substituted piperidin-3-ols are key components found in a number of natural products and bioactive compounds.[3] For example, *cis*-3-hydroxypipecolic acid[4] **4** constitutes a part of antitumor antibiotic tetrazomine;[4b] (2*S*,3*R*)-**5**[5] has been served as a key intermediate in the asymmetric synthesis[5c] of (−)-swainsonine. In addition, the N-*tert*-butyl derivative of 3-hydroxypipecolamide (**6**) is an isomer of **7**, the 4-hydroxypipecolamide moiety presented in a class of highly potent HIV proteases inhibitors such as palinavir.[6] Carboxamide **6** may also be useful as an organocatalyst.[7]

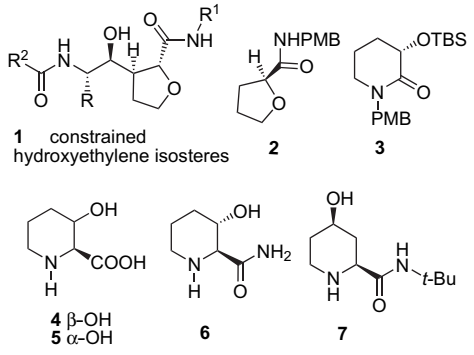

Figure 1.

In continuation of our ongoing program aimed at the development of new multifunctional building blocks starting from L-glutamic acid,[8] we now report the enantioselective syntheses of (*S*)-tetrahydrofuran 2-carboxamide **2**, protected (*S*)-3-hydroxypiperidin-2-one **3** and (2*S*,3*R*)-3-hydroxypipecolamide (**6**).

2. Results and discussion

We first investigated the synthesis of tetrahydrofuran 2-carboxamide (*S*)-**2** by the route depicted in Scheme 1. Lactone-amide[8d] (*S*)-**8**, easily available in multigram quantity from L-glutamic acid in 70% yield, was chemoselectively reduced with sodium borohydride (0 °C–rt) to give diol (*S*)-**9** in 89% yield. For the chemoselective *p*-tosylation of the primary hydroxyl group, (*S*)-**9** was treated with *p*-toluenesulfonyl chloride at low temperature (*p*-TsCl, py, −35 °C, 2 h, then −5 °C, overnight). With pyridine as the base, formation of the expected monotosylate **10** was observed from the TLC analysis. However, this was unstable and cyclized to tetrahydrofuran carboxamide[9] **2** on standing as well as during concentration of the extract. Thus, **2** was obtained in 58% isolated yield along with starting material (30%) and the ditosylate **12** (5%). HPLC analysis of **2** on a chiral column revealed its ee as 92%. On the other hand, with triethylamine as the base,[9g,10] although the yield of **2** was marginally better (62%), its ee was only 8% indicating extensive

Keywords: 3-Hydroxypipecolamide; 3-Hydroxypiperidin-2-one; Building block; Hydrogen bond; Chemoselective reaction.
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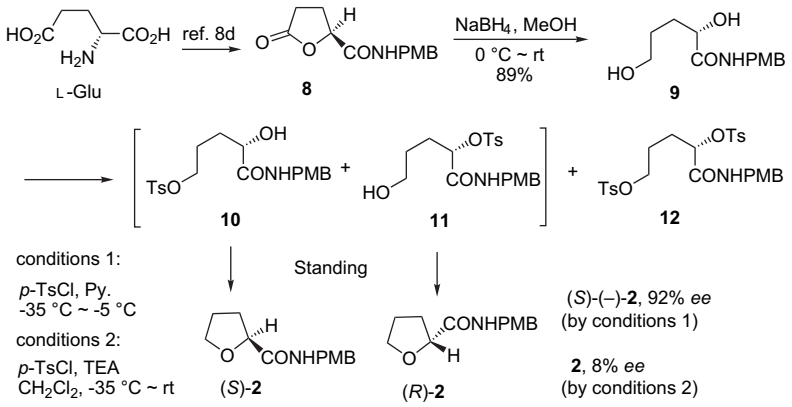
doi:10.1016/j.tet.2006.05.013



Scheme 1.

racemization. In this case, more ditosylate **12** (12%) was also formed, while 20% of the starting material was recovered. These results demonstrated that, attempted selective monotosylation of the primary hydroxyl group in diol **9** was always accompanied by tosylation of the secondary hydroxyl group and both monotosylated isomers **10** and **11** cyclized easily to give the corresponding enantiomer (*S*)-**2** or (*R*)-**2**.

It is worth mentioning that, although partial racemization has been observed in a diethoxytriphenylphosphorane mediated regioselective cyclodehydration of (*R*)-1,4-pentanediol,[11] many *p*-TsCl activated one-pot intramolecular etherification of chiral 1,4-diols have been reported to proceed with complete retention of configuration at the chiral carbinol center.[11] Our observations indicated that caution must be taken when performing a *p*-TsCl activated one-pot intramolecular etherification of chiral 1,4-diols, because tosylation of the secondary hydroxyl group may occur, leading to either racemic ethers or diastereomeric mixtures, in particular when using triethylamine as a base.

The easy tosylation of the secondary hydroxyl group of diol **9** may be explained by H-bonding effects as shown in **13a** and **13b** (Fig. 2).[12] Quantum chemistry calculation showed that **13a** is more stable than **13b** by 2.90 kcal/mol (Fig. 2). The higher stability of **13a** and thus lower reactivity of the primary hydroxyl group toward tosylation can be attributed to the strong hydrogen-bond formation between the primary hydroxyl group and the carbonyl of the amide functional group in **13a**. In more polar and more basic medium, such as when using pyridine as the solvent, formation of the intramolecular hydrogen bonds is efficiently inhibited,[13] thus the primary hydroxyl group shows normally higher reactivity during the tosylation. The phenomena of weakening of hydrogen bonds by polar solvents have been noted previously.[12f,13e]

Next, we turned our attention to the synthesis of protected 3-hydroxypiperidin-2-one **3**. We decided to protect firstly the latent hydroxyl group in **8**. Thus, stirring a methanolic solution of **8** in the presence of a catalytic amount of concentrated H_2SO_4 at rt for 1.5 h led smoothly to the ring-opening product **14**. TLC monitoring of the reaction showed that a small amount of the starting material remained intact even after prolongation of the reaction time. This might reflect that an equilibrium has been established between

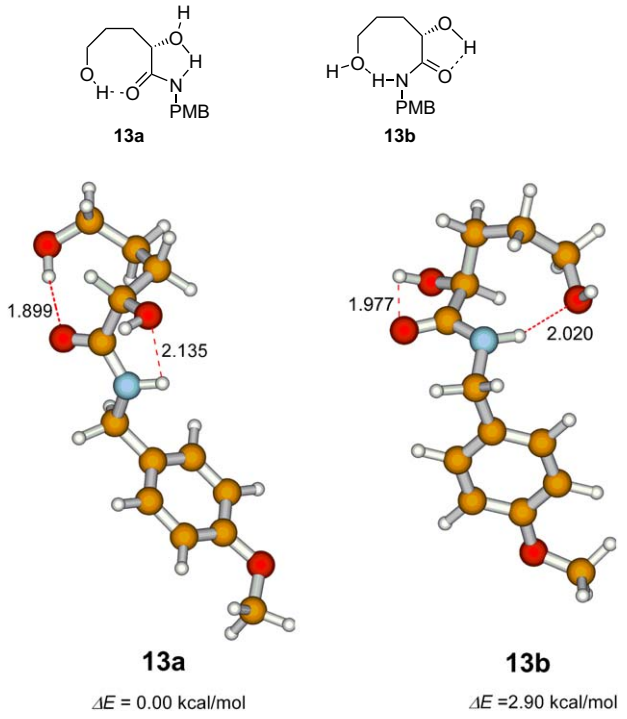
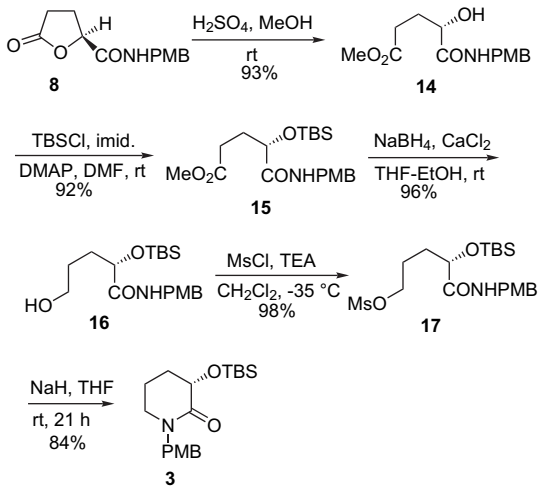


Figure 2. Energy-minimized structures of **13a** and **13b**.

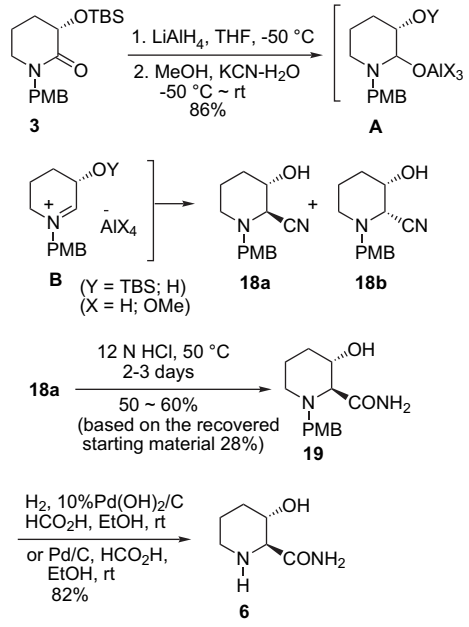
compounds **8** and **14**. Compounds **8** and **14** showed similar R_f and were difficult to separate by column chromatography on silica gel. To our delight, pure **14** could be obtained by recrystallization from EtOAc/Et_2O. The subsequent silylation[14] (TBSCl, imid., DMAP, DMF, rt, 3 h) proceeded smoothly to give compound **15** in 92% yield. Chemoselective ester reduction[15] ($NaBH_4$, $CaCl_2$, THF–EtOH, rt, overnight) followed by mesylation (MsCl, NEt_3) at −35 °C for 15 min furnished **17** in excellent overall yield. Treatment of **17** with NaH at rt for 21 h afforded the desired piperidine-2-one **3** in 84% yield. HPLC analysis on a chiral column showed that the ee of **3** was 94% (Scheme 2).

To demonstrate the utility of **3** as a building block, we sought the synthesis of **6** (Scheme 3). Thus, **3** was subjected to one-pot reductive cyanation,[16,17] which consisted in controlled chemoselective partial reduction of the amide by $LiAlH_4$ (3 molar equiv, THF, −50 °C, 15 min) followed by addition



Scheme 2.

of MeOH, and treating the in situ formed *N*,*O*-semiacetal intermediate with aqueous KCN at rt for 1 h. Under such conditions, concomitant *O*-desilylation[6,18] occurred and a separable diastereomeric mixture of cyanides **18a** and **18b** was obtained in 72:28 ratio with a combined yield of 86%. The α-amino nitriles **18a/18b** were assumed to be formed via the intermediacy of the *N*,*O*-acetal **A** and the *N*-acyliminium ion **B**. The stereochemistry of the major diastereomer was tentatively assigned as *trans* (**18a**) in analogy with its lower homologous.[17]



Scheme 3.

In pursuing the cyano group hydrolysis, both acidic and basic conditions were investigated,[17] and at the best case (12 N HCl, 50 °C, 2–3 days), amide **19** was obtained from **18a** in 50–74% yields based on the recovered starting material (ca. 20%). A single crystal X-ray crystallographic analysis of amide **19**,[19] derived from the major diastereomer **18a**, revealed its *trans*-stereochemistry, which confirmed our previous stereochemical assumption. Cleavage of PMB was performed under catalytic hydrogenolytic conditions (20% $Pd(OH)_2/C$, H_2, HCO_2H (cat.), rt, 5 h, EtOH, yield: 82%), or catalytic transfer hydrogenolytic conditions (10% Pd/C, HCO_2H (cat.), rt, 3 h, EtOH, yield: 79%). The 3-hydroxypipecolamide (**6**) thus obtained may find application in the asymmetric organocatalysis.[7,13a–d,20]

3. Conclusion

In summary, we have shown that by proper selection of synthetic procedures and reaction conditions, one can achieve chemoselective manipulation of multifunctional chiral building block **8**. The compounds thus obtained are also useful motifs. The usefulness of the protected 3-hydroxypiperidin-2-one **3** as a new building block was demonstrated by its conversion into 3-hydroxypipecolamide **6**. Importantly, the observations made during the synthesis of (*S*)-tetrahydrofuran 2-carboxamide derivative **2** from diol **9** indicated that H-bonding may affect the chemoselectivity of the tosylation reaction, which can be tuned by changing the reaction medium.

4. Experimental

4.1. General

Melting points were determined (uncorrected) on a Yanaco MP-500 micro melting point apparatus. Infrared spectra were measured with a Nicolet Avatar 360 FTIR spectrometer. ^{1}H NMR spectra were recorded on a Varian unity +500 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded on a Bruker Dalton Esquire 3000 plus LC–MS apparatus (ESI direct injection). Optical rotations were measured with Perkin–Elmer 341 automatic polarimeter. THF used in the reactions were dried by distillation over metallic sodium and benzophenone; dichloromethane were distilled over P_2O_5. Silica gel (Zhifu, 300–400 mesh) was used for column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60–90 °C) mixtures.

The calculations were performed with the GAUSSIAN 98 package. The hybrid density functional method including Becke's 3-parameter non-local-exchange functional with the correlation functional of Lee–Yang–Parr (B3LYP) was employed. The basis set used is 6-31G* including the polarization d-function on non-hydrogen atoms. Geometry optimizations and vibrational analyses were performed without any constraint. The optimized structures of compounds **13a** and **13b** are characterized by none imaginary frequency. Reported energies are ZPE (zero-point energy)-corrected.

4.1.1. (*S*)-2,5-Dihydroxy-*N*-(4-methoxybenzyl)pentanamide 9. To a methanolic solution (16 mL) of **8**[8] (1.000 g, 4.02 mmol) was added $NaBH_4$ (473 mg, 12.45 mmol) at 0 °C. The mixture was allowed to warm to rt and stirred for 1 h. The reaction mixture was quenched by addition of brine (5 mL) and aqueous $NaHCO_3$ (5 mL) at 0 °C. MeOH was removed under reduced pressure. The mixture was

diluted with water (6 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatographic purification on silica gel (eluent: EtOAc/MeOH) provided **9** (903 mg, yield: 89%) as a colorless solid. Mp 103 °C (EtOAc/PE); $[\alpha]_D^{20}$ −24.3 (*c* 1.1, $CHCl_3$); IR (film) 3394, 3301, 2950, 2932, 2913, 2866, 1617, 1532, 1507, 1430, 1314, 1109, 1085, 1021 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.60–1.80 (m, 3H, $CH_2CH_2CH_2OH$), 1.97–2.05 (m, 1H, $CH_2CH_2CH_2OH$), 3.20 (br s, 1H, OH, D_2O exchangeable), 3.60–3.75 (m, 2H, CH_2OH), 3.78 (s, 3H, OCH_3), 4.17–4.20 (m, 1H, COCH), 4.28–4.40 (m, 2H, $PhCH_2N$), 4.85 (br s, 1H, OH, D_2O exchangeable), 6.86 (d, *J*=8.5 Hz, 2H, Ar–H), 7.20 (d, *J*=8.5 Hz, 2H, Ar–H), 7.18 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.2, 32.4, 42.5, 55.3, 62.5, 72.0, 114.1 (2C), 129.0, 130.1 (2C), 159.0, 174.0; MS (ESI) *m*/*z* 254 ($M+H^+$, 100). Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 62.05; H, 7.44; N, 5.47.

4.1.2. (*S*)-*N*-(4-Methoxybenzyl)-tetrahydrofuran-2-carboxamide 2. Procedure 1: To a solution of **9** (200 mg, 0.79 mmol) in pyridine (1 mL) was rapidly added *p*-TsCl (166 mg, 0.87 mmol) at about −35 °C under nitrogen atmosphere. The mixture was kept at about −20 °C for 2 h, then at −5 °C overnight before quenched by addition of ice-water (1 mL). The mixture was washed with 1 N aqueous HCl (2×1 mL) and extracted with ether (3×1.5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatographic purification of the residue on silica gel (eluent: EtOAc/PE = 1:1) provided, besides the recovered starting material (ca. 30%), ditosylated product **12** (19 mg, yield: 5%) and a mixture of monotosylated product **10** and (*S*)-**2** (132 mg). The latter was formed during the purification and concentration. Upon standing at rt, a complete transformation of **10** to (*S*)-**2** was observed, giving (*S*)-**2** (104 mg) in 58% yield. The enantiomeric excess (ee) of (*S*)-**2** was determined to be 92% by HPLC analysis using a chiral column OD-H (4.6 mm×250 mm, eluting with hexane:2-propanol = 9:1, 1.0 mL/min; detected at 225 nm. $[\alpha]_D^{20}$ −9.6 (*c* 1.3, $CHCl_3$).

Procedure 2: To a solution of **9** (200 mg, 0.79 mmol) in CH_2Cl_2 (1.5 mL) was added Et_3N (0.15 mL, 1.03 mmol). *p*-TsCl (166 mg, 0.87 mmol) in CH_2Cl_2 (0.5 mL) was dropped into the solution at about −35 °C. The reaction temperature was allowed to rise to rt, then stirred at rt for 36 h. The reaction mixture was quenched by addition of 1 mL ice-water and the resulting mixture was extracted with CH_2Cl_2 (3×1.5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatographic purification of the residue on silica gel (eluent: EtOAc/PE = 1:1) provided, besides the recovered starting material (ca. 20%), ditosylated product **12** (53 mg, yield: 12%) and a mixture of two monotosylated products **10/11** and **2** (138 mg). The latter was formed during the purification and concentration. Compound **2** obtained at this stage showed $[\alpha]_D^{20}$ −7.0 (*c* 1.2, $CHCl_3$) and 52% ee. Upon standing at rt, a complete transformation of **10/11** to **2** was observed, giving **2** (115 mg) in 62% yield, which showed $[\alpha]_D^{20}$ 0 (*c* 1.3, $CHCl_3$) and 8% ee.

Compound **2**: colorless oil. IR (film) 3349, 2923, 2853, 1665, 1513, 1247, 1175, 1073, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.82–1.96 (m, 2H, $CH_2CH_2CH_2O$), 2.05–2.14 (m, 1H, $CH_2CH_2CH_2O$), 2.27–2.36 (m, 1H, $CH_2CH_2CH_2O$), 3.80 (s, 3H, OCH_3), 3.82–3.94 (m, 2H, $CH_2CH_2CH_2O$), 4.34–4.44 (m, 3H, COCHO, $NHCH_2$), 6.86 (d, *J*=8.5 Hz, 2H, Ar–H), 7.20 (d, *J*=8.5 Hz, 2H, Ar–H), 6.92 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.5, 30.2, 42.3, 55.3, 69.4, 78.5, 114.1 (2C), 129.0, 130.2 (2C), 159.0, 173.0; MS (ESI) *m*/*z* 236 ($M+H^+$, 100); HR-MALDIMS calcd for $C_{13}H_{17}NO_3Na$ $(M+Na)^+$: 258.1106; found: 258.1110.

4.1.3. Methyl (*S*)-4-hydroxy-5-(4-methoxybenzylamino)-5-oxopentanoate 14. To a solution of **8** (2.045 g, 8.03 mmol) in MeOH (10 mL) was added a catalytic amount of concentrated H_2SO_4. After stirred for 1.5 h at rt, the mixture was neutralized with solid $CaCO_3$ and filtered through Celite. Flash chromatographic purification of the residue on silica gel (eluent: EtOAc/PE = 1.5:1) provided **14** (2.152 g, yield: 93%) as a colorless solid. Mp 97–98 °C (EtOAc/Et_2O); $[\alpha]_D^{20}$ −16.4 (*c* 1.0, $CHCl_3$); IR (film) 3366, 2928, 1735, 1650, 1513, 1438, 1248, 1176, 1103, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.08–2.26 (m, 1H, $COCH_2CH_2CH_2$), 2.19–2.27 (m, 1H, $COCH_2CH_2CH_2$), 2.48–2.63 (m, 2H, $COCH_2CH_2CH_2$), 3.70 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.15 (d, *J*=3.5 Hz, 1H, OH, D_2O exchangeable), 4.19 (ddd, *J*=7.8, 3.5, 3.2 Hz, 1H, CHOH), 4.38 (dd, *J*=15.4, 5.9 Hz, 1H, $PhCH_2N$), 4.41 (dd, *J*=15.4, 5.9 Hz, 1H, $PhCH_2N$), 6.84 (d, *J*=8.5 Hz, 2H, Ar–H), 7.18 (d, *J*=8.5 Hz, 2H, Ar–H), 7.03 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.2, 30.6, 42.7, 52.2, 55.3, 72.0, 114.1 (2C), 129.1 (2C), 130.1, 159.1, 172.9, 175.8; MS (ESI) *m*/*z* 282 ($M+H^+$, 100). Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 60.06; H, 6.84; N, 4.76.

4.1.4. Methyl (*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzylamino)-5-oxopentanoate 15. A mixture of **14** (1.711 g, 6.09 mmol), imidazole (1.029 g, 15.23 mmol), TBSCl (1.120 g, 7.31 mmol), and a catalytic amount of DMAP in dry DMF (12 mL) was stirred at rt for 3 h and then quenched by the addition of water (50 mL). The mixture was extracted with Et_2O (6×10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatographic purification of the residue on silica gel (eluent: EtOAc/PE = 1:5) provided **15** (2.112 g, yield: 92%) as a colorless oil. $[\alpha]_D^{20}$ −22.0 (*c* 1.0, $CHCl_3$); IR (film) 3427, 2953, 2930, 1740, 1678, 1613, 1514, 1464, 1439, 1250, 1174, 1107, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.22 (s, 3H, $Si(CH_3)_2$), 0.23 (s, 3H, $Si(CH_3)_2$), 0.92 (s, 9H, $SiC(CH_3)_3$), 2.02–2.15 (m, 2H, $COCH_2CH_2CH_2$), 2.30–2.44 (m, 2H, $COCH_2CH_2CH_2$), 3.62 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.24 (dd, *J*=5.2, 5.2 Hz, 1H, CHCON), 4.30 (dd, *J*=5.8, 14.5 Hz, 1H, $PhCH_2N$), 4.45 (dd, *J*=5.8, 14.5 Hz, 1H, $PhCH_2N$), 6.79 (br s, 1H, NH), 6.88 (d, *J*=8.5 Hz, 2H, Ar–H), 7.20 (d, *J*=8.5 Hz, 2H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.4, −5.0, 17.9, 25.6 (3C), 28.9, 30.3, 42.5, 51.6, 55.3, 72.4, 114.1 (2C), 129.0 (2C), 130.0, 159.1, 172.6, 173.5; MS (ESI) *m*/*z* 396 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{33}NO_5Si$: C, 60.73; H, 8.41; N, 3.54. Found: C, 60.41; H, 8.08; N, 3.79.

4.1.5. (*S*)-2-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-*N*-(4-methoxybenzyl)pentanamide 16. To a mixture of **15** (1.400 g, 3.54 mmol) and $CaCl_2$ (1.690 g, 14.89 mmol) in EtOH (4.7 mL)/THF (9.4 mL) was added $NaBH_4$ (1.030 g, 27.11 mmol) in one portion at 0 °C. The mixture was allowed to warm to rt and stirred overnight. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and brine (20 mL) at 0 °C. The mixture was extracted with EtOAc (6×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatographic purification of the residue on silica gel (eluent: EtOAc/PE = 1:1) provided **16** (1.303 g, yield: 96%) as a colorless oil. $[\alpha]_D^{20}$ −25.2 (*c* 1.0, $CHCl_3$); IR (film) 3423, 2953, 2930, 2857, 1664, 1613, 1514, 1464, 1250, 1176, 1111, 1037 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.30 (s, 3H, $Si(CH_3)_2$), 0.32 (s, 3H, $Si(CH_3)_2$), 0.85 (s, 9H, $SiC(CH_3)_3$), 1.55–1.70 (m, 2H, $OCH_2CH_2CH_2$), 1.74–1.95 (m, 2H, $OCH_2CH_2CH_2$), 2.10 (br s, 1H, OH, D_2O exchangeable), 3.62 (dd, *J*=6.2, 6.2 Hz, 2H, CH_2OH), 3.80 (s, 3H, OCH_3), 4.25 (dd, *J*=5.1, 5.1 Hz, 1H, CHCON), 4.31 (dd, *J*=5.8, 14.6 Hz, 1H, $PhCH_2N$), 4.45 (dd, *J*=6.2, 14.6 Hz, 1H, $PhCH_2N$), 6.79 (br s, 1H, NH), 6.85 (d, *J*=8.5 Hz, 2H, Ar–H), 7.20 (d, *J*=8.5 Hz, 2H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.4, −4.9, 17.9, 25.6 (3C), 27.5, 31.7, 42.5, 55.3, 62.5, 73.1, 114.1 (2C), 129.0 (2C), 130.0, 159.0, 173.4; MS (ESI) *m*/*z* 368 ($M+H^+$, 100). Anal. Calcd for $C_{19}H_{33}NO_4Si$: C, 62.09; H, 9.05; N, 3.81. Found: C, 61.91; H, 9.35; N, 3.78.

4.1.6. (*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzylamino)-5-oxopentyl methanesulfonate 17. To a solution of **16** (814 mg, 2.22 mmol) and Et_3N (0.46 mL, 3.33 mmol) in CH_2Cl_2 (8.9 mL) was added dropwise MsCl (0.22 mL, 2.88 mmol) at −35 °C. The mixture was stirred at the same temperature for 15 min and then quenched with water (6 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatographic purification on silica gel (eluent: EtOAc/PE = 1:2) provided **17** (970 mg, yield: 98%) as a colorless oil. $[\alpha]_D^{20}$ −6.6 (*c* 1.0, $CHCl_3$); IR (film) 3424, 2955, 2932, 2857, 1673, 1613, 1515, 1467, 1354, 1250, 1174, 1111, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, two rotamers in a ratio of 4.5:1) δ 0.40 (s, 3H, $Si(CH_3)_2$, m+M), 0.45 (s, 3H, $Si(CH_3)_2$, M+m), 0.90 (s, 9H, $SiC(CH_3)_3$, m+M), 1.70–1.95 (m, 4H, $OCH_2CH_2CH_2$, m+M), 3.01, 3.03 (s, 3H, OCH_3, M+m), 3.79, 3.81 (s, 3H, CH_3SO_2, m+M), 4.18–4.24 (m, 3H, $MsOCH_2$, COCH, M+m), 4.32 (dd, *J*=5.4, 14.6 Hz, 1H, $PhCH_2N$, M+m), 4.44 (dd, *J*=6.3, 14.6 Hz, 1H, $PhCH_2N$, M+m), 6.80 (br s, 1H, NH, M+m), 6.86 (d, *J*=8.5 Hz, 2H, Ar–H, M+m), 7.20 (d, *J*=8.5 Hz, 2H, Ar–H, M+m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.4, −4.9, 17.9, 24.1, 25.6 (3C), 31.1, 37.4, 42.5, 55.3, 69.6, 72.6, 114.1 (2C), 129.1 (2C), 129.9, 159.1, 172.7; MS (ESI) *m*/*z* 446 ($M+H^+$, 100). The product is too labile to perform the required elementary analysis or HRMS measurement.

4.1.7. (*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-(4-methoxybenzyl)piperidin-2-one 3. To a cooled (0 °C) solution of **17** (608 mg, 1.37 mmol) in dry THF (3 mL) was added dropwise a suspension of NaH (137 mg, 60% w/w) in anhydrous THF (2.5 mL) over a period of 20 min. The mixture was allowed to warm to rt and stirred overnight. The reaction mixture was quenched with water (30 mL) at 0 °C. The organic layer was separated and the aqueous layer extracted with Et_2O (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatographic purification on silica gel (eluent: EtOAc/PE=1:8) provided **3** (400 mg, yield: 84%) as a colorless oil. $[\alpha]_D^{20}$ −34.0 (*c* 1.1, $CHCl_3$). The enantiomeric excess (ee) of **3** was determined to be 94% by HPLC analysis using a chiral column OD-H (4.6 mm×250 mm, eluting with hexane:2-propanol = 99:1, 0.75 mL/min; detected at 254 nm). IR (film) 2952, 2928, 2854, 1654, 1611, 1512, 1489, 1247, 1172, 1148, 1109, 1039 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.48 (s, 3H, $Si(CH_3)_2$), 0.51 (s, 3H, $Si(CH_3)_2$), 0.92 (s, 9H, $SiC(CH_3)_3$), 1.63–1.71 (m, 1H, H-5), 1.82–1.91 (m, 1H, H-5), 1.90–2.02 (m, 2H, H-4), 3.08–3.21 (m, 2H, H-6), 3.79 (s, 3H, OCH_3), 4.16 (dd, *J*=7.1, 4.6 Hz, 1H, H-3), 4.46 (d, *J*=14.4 Hz, 1H, $PhCH_2N$), 4.53 (d, *J*=14.4 Hz, 1H, $PhCH_2N$), 6.90 (d, *J*=8.5 Hz, 2H, Ar–H), 7.20 (d, *J*=8.5 Hz, 2H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.4, −4.5, 18.3, 19.0, 25.8 (3C), 30.8, 46.7, 49.4, 55.2, 69.6, 113.9 (2C), 129.3, 129.4 (2C), 158.9, 170.0; MS (ESI) *m*/*z* 350 ($M+H^+$, 100); HR-MALDIMS calcd for $C_{19}H_{31}NO_3Si$ $(M+H)^+$: 350.2151; found: 350.2153.

4.1.8. (2*RS*,3*S*)-2-Cyano-3-hydroxy-1-(4-methoxybenzyl) piperidines 18a and 18b. To a cooled (−50 °C) suspension of $LiAlH_4$ (332 mg, 2.81 mmol) in anhydrous THF (18 mL) was added a solution of **3** (980 mg, 2.81 mmol) in anhydrous THF (10 mL) over a period of 20 min. After stirred at the same temperature for 15 min, the mixture was quenched with MeOH (2.2 mL) and a solution of KCN (732 mg, 11.24 mmol) in water (2.2 mL) was added. The mixture was allowed to warm to rt and stirred for another 1 h. After diluted with water (10 mL), the organic layer was separated and the aqueous layer extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatographic purification on silica gel (eluent: EtOAc/PE = 1:2) provided (2*R*,3*S*)-**18a** and (2*S*,3*S*)-**18b** in 72:28 ratio with a combined yield of 86%.

Compound (2*R*,3*S*)-**18a**: colorless crystals, mp 72–73 °C (CH_2Cl_2/PE); $[\alpha]_D^{20}$ −133.4 (*c* 1.0, $CHCl_3$); IR (film) 3493, 2946, 2835, 2219, 1616, 1513, 1465, 1442, 1249, 1178, 1132, 1109, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.56–1.70 (m, 2H, H-5), 1.78–1.90 (m, 2H, H-4), 2.48–2.56 (m, 1H, H-6), 2.76–2.84 (m, 2H, H-6, OH, D_2O exchangeable), 3.49 (d, *J*=12.7 Hz, 1H, $PhCH_2N$), 3.70 (d, *J*=4.0 Hz, 1H, H-2), 3.71 (d, *J*=12.7 Hz, 1H, $PhCH_2N$), 3.80 (s, 3H, OCH_3), 3.97–4.20 (m, 1H, H-3), 6.95 (d, *J*=8.5 Hz, 2H, Ar–H), 7.23 (d, *J*=8.5 Hz, 2H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 27.2, 49.0, 55.3, 56.7, 59.6, 66.1, 114.1 (2C), 115.0, 128.0, 130.3 (2C), 159.4; MS (ESI) *m*/*z* 247 ($M+H^+$, 100). Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.44; H, 7.69; N, 11.15.

Compound (2*S*,3*S*)-**18b**: colorless oil; $[\alpha]_D^{20}$ +97.2 (*c* 1.0, $CHCl_3$); IR (film) 3435, 2934, 2835, 2226, 1612, 1585,

1513, 1465, 1248, 1174, 1128, 1104, 1064, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.48–1.64 (m, 2H, H-5), 1.70–1.76 (m, 1H, H-4), 1.97–2.03 (m, 1H, H-4), 2.35 (dt, J=11.8, 2.9 Hz, 1H, H-6), 2.72–2.77 (m, 1H, H-6), 3.49 (d, J=12.8 Hz, 1H, $PhCH_2N$), 3.69 (d, J=12.8 Hz, 1H, $PhCH_2N$), 3.74 (ddd, J=15.4, 9.3, 4.6 Hz, 1H, H-3), 3.80 (s, 3H, OCH_3), 3.89 (d, J=4.6 Hz, 1H, H-2), 6.95 (d, J=8.5 Hz, 2H, Ar–H), 7.23 (d, J=8.5 Hz, 2H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.0, 30.0, 48.3, 55.3, 59.4 (2C), 67.8, 113.9 (2C), 115.0, 128.5, 130.2 (2C), 159.2; MS (ESI) m/z 247 ($M+H^+$, 100).

4.1.9. (2*S*,3*S*)-2-Aminocarbonyl-3-hydroxy-1-(4-methoxybenzyl)piperidine 19. A solution of **18a** (100 mg, 0.41 mmol) in 12 N aqueous HCl (25 mL) was stirred at 60 °C for 2 days and then neutralized with solid Na_2CO_3. The mixture was extracted with EtOAc (6×25 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatographic purification on silica gel (eluent: EtOAc/MeOH = 30: 1) provided **19** (50 mg, yield: 46%) and the recovered starting material **18a** (28 mg, 28%). Compound **19**: colorless solid, mp 159–160 °C (EtOAc/PE); $[\alpha]_D^{20}$ −77.8 (*c* 0.6, $CHCl_3$); IR (film) 3379, 3200, 2959, 2927, 2855, 2789, 1688, 1662, 1614, 1513, 1444, 1381, 1258, 1113, 1067, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.25–1.55 (m, 2H, H-5), 1.62–1.72 (m, 1H, H-4), 1.95–2.05 (m, 1H, H-4), 2.04–2.14 (m, 1H, H-6), 2.70 (d, J=8.7 Hz, 1H, H-2), 2.83–2.88 (m, 1H, H-6), 3.22 (d, J=13.6 Hz, 1H, $PhCH_2N$), 3.67 (ddd, J=10.8, 8.7, 4.6 Hz, 1H, H-3), 3.79 (s, 3H, OCH_3), 3.85 (d, J=13.6 Hz, 1H, $PhCH_2N$), 6.10 (br s, 1H, OH, D_2O exchangeable), 6.80 (br s, 2H, NH_2, D_2O exchangeable), 6.95 (d, J=8.5 Hz, 2H, Ar–H), 7.23 (d, J=8.5 Hz, 2H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.0, 32.0, 50.6, 55.3, 59.7, 70.5, 73.5, 113.9 (2C), 129.4, 129.8 (2C), 158.9, 176.5; MS (ESI) m/z 265 ($M+H^+$, 100); HR-MALDIMS calcd for $C_{14}H_{20}N_2O_3$ $(M+H)^+$: 265.1552; found: 265.1557.

4.1.10. (2*S*,3*S*)-3-Hydroxy-2-piperidine-carboxamide 6. To a suspension of 20% $Pd(OH)_2/C$ (26 mg) in EtOH (1 mL) were added a solution of **19** (52 mg) in EtOH (1 mL) and a catalytic amount of HCO_2H. The mixture was stirred at rt and under an atmosphere of H_2 for 5 h. After filtration of the catalyst, the filtrate was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent: MeOH/EtOAc/aqueous NH_3 = 1:4:0.1) to provide **6** (23 mg, yield: 82%) as a colorless solid. Mp 149–150 °C (MeOH/Et_2O); $[\alpha]_D^{20}$ +43.8 (*c* 0.4, 10% HCl); IR (KBr) 3376, 3317, 3198, 2947, 2857, 1773, 1677, 1635, 1507, 1077 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 1.42–1.62 (m, 2H, H-4, H-5), 1.76–1.86 (m, 1H, H-5), 2.10–2.18 (m, 1H, H-4), 2.56 (dt, J=12.9, 2.8 Hz, 1H, H-6), 3.04 (dd, J=12.9, 1.7 Hz, 1H, H-6), 3.14 (d, J=9.6 Hz, 1H, H-2), 3.66 (ddd, J=10.7, 9.6, 4.4 Hz, H-3); ^{13}C NMR (125 MHz, D_2O) δ 27.0, 35.0, 46.7, 67.4, 71.4, 178.2; MS (ESI) m/z 145 ($M+H^+$, 100); HR-EIMS calcd for $[C_6H_{12}N_2O_2]^+$: 144.0899; found: 144.0892.

Acknowledgements

The authors are grateful to the NSF of China (20390050, 20572088), the Ministry of Education (Key Project 104201), and the NSF of Fujian Province (China) (C0510001) for financial support.

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