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The efficient synthesis of (3*R*,5*R*)-5-hydroxypiperazic acid and its diastereomer using Lewis acid-promoted diastereoselective Strecker synthesis

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Abstract—The stereoselective synthesis of (3*R*,5*R*)-5-hydroxypiperazic acid, a component of naturally occurring antibiotic cyclodepsipeptides, and its diastereomer was achieved via the use of Lewis acid-promoted diastereoselective Strecker synthesis as a key step, in which an interesting stereochemical reversal of diastereoselectivity by the choice of Lewis acid catalyst was observed.

1. Introduction

Polyoxypeptins A **1** and B **2** are novel 19-membered cyclic hexadepsipeptides isolated from the culture broth of *Streptomyces* species as reported by Umezawa et al. in 1998 (Fig. 1).[1] These cyclodepsipeptides are known to show strong anticancer activity by induction of apoptosis against apoptosis-resistant human pancreatic adenocarcinoma AsPC-1 cells. In addition to their potent biological activities, polyoxypeptins contain unusual amino acids, in particular (3*R*,5*R*)-5-hydroxypiperazic acid (HOPip) and (2*S*,3*R*)-3-hydroxy-3-methylproline (HOMePro), and a unique acyl side chain. HOPips are also found in antibiotic cyclodepsipeptides, monamycins,[2] and himastatin,[3] as (3*S*,5*S*)- and (3*R*,5*R*)-isomers, respectively. HOPip derivatives have already been synthesized by several groups.[4] However, these methods require multi-steps and give low overall yields, meaning that there is still a need for a concise method for large-scale production of this unique component. Herein, we report an efficient synthesis of (3*R*,5*R*)-5-hydroxypiperazic acid and its diastereomer from commercially available (*R*)-4-chloro-3-hydroxybutanoic

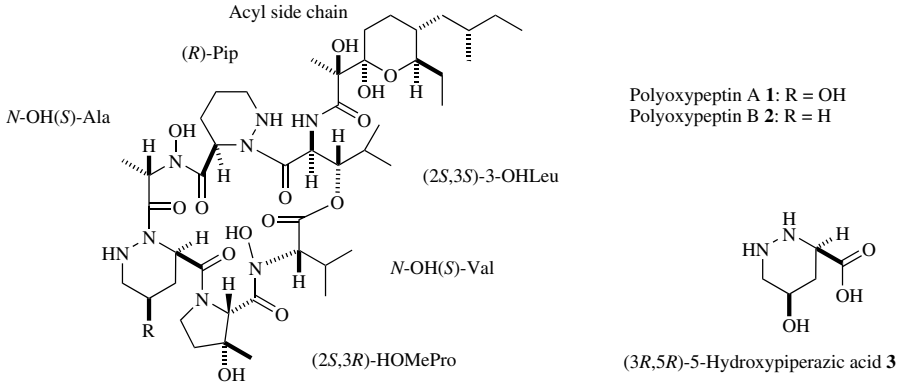

Figure 1. Polyoxypeptins **A** and **B**.

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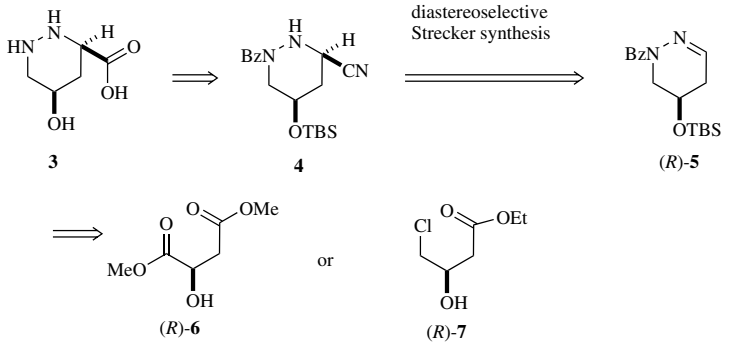
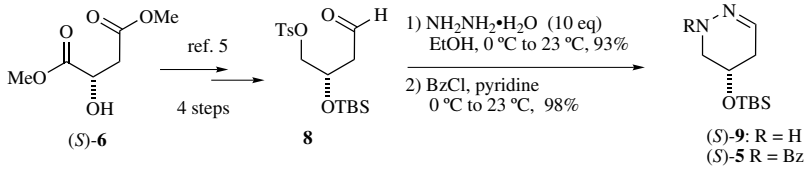


Scheme 1. Retrosynthetic analysis.



Scheme 2.

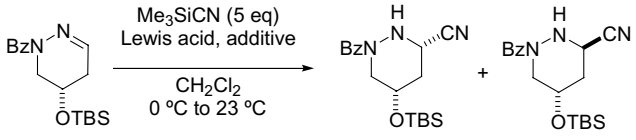
acid ester using Lewis acid-promoted diastereoselective Strecker synthesis and an interesting stereochemical reversal of the diastereoselectivity by the choice of the Lewis acid catalyst.

2. Results and discussion

Our synthetic plan for (3*R*,5*R*)-HOPip is shown in Scheme 1. A key reaction is the Lewis acid-promoted diastereoselective Strecker synthesis using chiral cyclic hydrazone **5**, which could be obtained from (*R*)-malic acid or (*R*)-4-chloro-3-hydroxybutanoic acid ester. First, we employed the (*S*)-malic acid derivative as the starting material for a model reaction (Scheme 2). The (*S*)-cyclic hydrazone **5** was prepared in six steps from commercially available (*S*)-malic acid dimethyl ester **6**. (*S*)-Aldehyde **8**, prepared according to the literature method,[5] was treated with an excess amount of hydrazine monohydrate in ethanol to produce cyclic hydrazone **9**, which was N-protected with benzoyl chloride to give N-protected (*S*)-cyclic hydrazone **5** in excellent yield.

We next investigated the diastereoselective Strecker reaction of chiral cyclic hydrazone **5** (0.2 mmol) using Lewis acids (0.1 equiv) and trimethylsilylcyanide (5 equiv) as a cyanide source. The results are summarized in Table 1. Since the Lewis acid-promoted diastereoselective Strecker synthesis of the chiral cyclic pyrazolines was already reported by two groups,[6] our initial experiments focused on finding an active catalyst for the diastereoselectivity. The stereochemistry of the *syn*- and *anti*-products was determined, after their acid hydrolysis, by analyzing the *N*-(2,4-dinitrophenyl) derivatives of the final HOPips using their ^{1}H NMR spectroscopy.[2b,3a] Surprisingly, neither the hafnium triflate [Hf(OTf)$_4$] catalyst shown by Kobayashi and co-workers[6a] nor titanium tetrachloride ($TiCl_4$) used by Carreira and co-workers[6b] showed any significant diastereoselectivity. After extensive experiments, we were

Table 1. Lewis acid-promoted diastereoselective Strecker synthesis



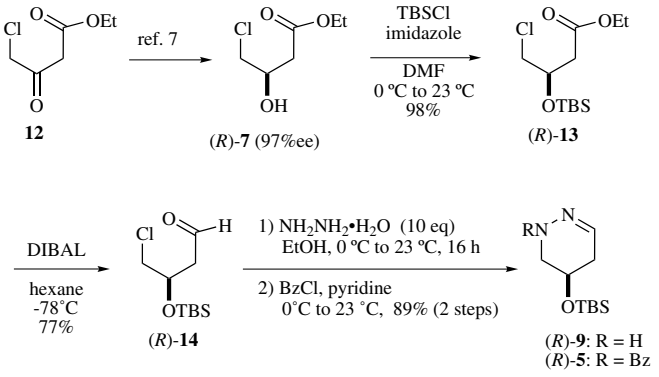
(*S*)-**5** → (3*S*,5*S*)-**10** (*syn*) + (3*R*,5*S*)-**11** (*anti*)

Entry	Lewis acid	Additive	Time (h)	dr[a] *syn*:*anti*	Yield[b]
1	None	—	24	—	0
2	$Zn(OTf)_2$ (1 equiv)	—	24	75:25	52
3	$Zn(OTf)_2$ (1 equiv)	AcOH (1 equiv)	12	—	—[c]
4	$Zn(OTf)_2$ (1 equiv)	AcOH (1 equiv) NaOAc (0.1 equiv)	24	81:19	70
5	$Zn(OTf)_2$ (1 equiv)	NaOAc (0.1 equiv)	24	87:13	42
6	$Hf(OTf)_4$ (0.1 equiv)	—	86	61:39	72
7	$TiCl_4$	—	86	45:55	65
8	$Mg(OAc)_2$ (1 equiv)	—	24	6:94	75
9	$Mg(OAc)_2$ (1 equiv)	AcOH (1 equiv)	1	7:93	96
10	$Mg(OAc)_2$ (0.05 equiv)	AcOH (1 equiv)	17	3:97	99
11	—	AcOH (1 equiv)	24	—	4

[a] Determined by ^{1}H NMR spectra.
[b] Isolated yield.
[c] Decomposition.

pleased to find that zinc triflate [$Zn(OTf)_2$] in combination with acetic acid and sodium acetate is a *syn*-selective catalyst providing *syn* amino nitrile **10** with a diastereoselectivity of ca. 4:1 (entry 4). One equivalent of $Zn(OTf)_2$ and the presence of acetic acid and sodium acetate were essential for a smooth reaction and practical yield (entries 2–5). Fortunately, the diastereomers were separable by column chromatography on silica gel and recrystallized from diisopropyl ether and hexane to afford enantiomericaly pure **10** and **11**. On the other hand, the reaction using magnesium acetate [$Mg(OAc)_2$] in combination with acetic acid proceeded *anti*-selectively to exclusively afford the *anti* product **11** in 93:7 to 97:3 diastereoselectivity (entries 8–10). The addition of acetic acid accelerated the reaction and reduced the amount of $Mg(OAc)_2$ to 0.05 equiv (entry 10). To examine whether both the Strecker reactions described above proceeded under thermodynamic control, diastereomerically pure (3*S*,5*S*)-**10** was subjected to exposure to $Zn(OTf)_2$–AcOH–NaOAc, a *syn*-selective catalyst, at 23 °C for 24 h and $Mg(OAc)_2$–AcOH, *anti*-selective catalyst, at 23 °C for 17 h, respectively. No equilibration in either cases was observed and pure **10** was recovered quantitatively. The result clearly shows that the above Strecker reactions proceed under kinetic control. The reason for the interesting stereochemical reversal of the diastereoselectivity by the choice of Lewis acid is unclear at present.

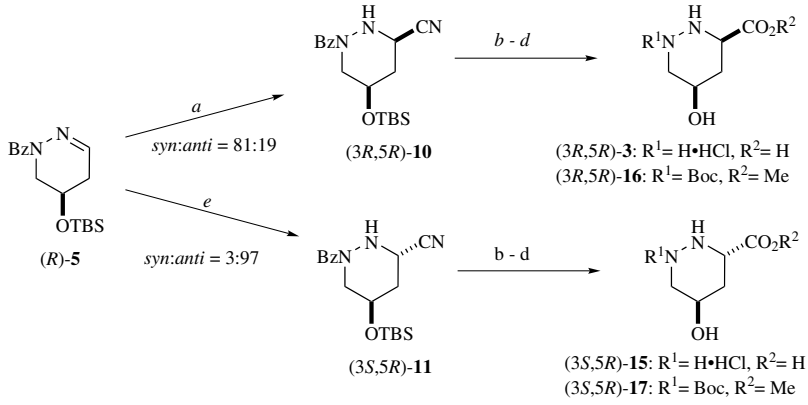
The (*R*)-chiral cyclic hydrazone **5** was also readily prepared by a similar approach from commercially available (*R*)-4-chloro-3-hydroxybutanoic acid ester **7**, which could be alternatively synthesized from ethyl 4-chloroacetoacetate **12**[7] by asymmetric hydrogenation using a Ru-BINAP catalyst (Scheme 3). Protection of **7** with *t*-butylchlorodimethylsilane (TBSCl)[8] and the subsequent reduction of the ethyl ester with DIBAL produced (*R*)-aldehyde **14** in 75% yield (two steps). The hydrazone formation of **14** using hydrazine monohydrate in ethanol proceeded smoothly at room temperature together with the intramolecular N-alkylation followed by the protection of the amino group with benzoyl chloride to give the (*R*)-chiral cyclic hydrazone **5** in 89% yield in two steps. The diastereoselective Strecker reactions using (*R*)-**5** with *syn*- and *anti*-selection were carried out under the same conditions described above in the same diastereoselectivities (Scheme 4). The hydrolysis of the resulting amino nitriles (3*R*,5*R*)-**10** and (3*S*,5*R*)-**11** was accomplished with refluxing 6 M hydrochloric acid for 12 h to afford (3*R*,5*R*)- and (3*S*,5*R*)-5-hydroxypiperazic acid hydrochlorides **3** and **15**, which were unstable but could be isolated as the N-protected esters **16** and **17** in 59% yield (three steps) and 51% yield (three steps), respectively.



Scheme 3.

3. Conclusion

In conclusion, we have developed diastereoselective Strecker reactions of chiral cyclic hydrazones using Lewis acids, $Zn(OTf)_2$–AcOH–NaOAc and $Mg(OAc)_2$–AcOH, and succeeded in obtaining an efficient diastereoselective synthesis of (3*R*,5*R*)- and (3*S*,5*R*)-5-hydroxypiperazic acids. In this reaction, the interesting stereochemical reversal of the diastereoselectivity due to the choice of Lewis acid was observed. The method described is noteworthy because the synthesis is carried out in eight steps and 22–33% overall yields from commercially available starting materials.



Scheme 4. Reagents and conditions: (a) Me_3SiCN (5 equiv), $Zn(OTf)_2$ (1 equiv), AcOH (1 equiv), NaOAc (0.1 equiv), 0–23 °C, 24 h, 70%; (b) 6 M HCl, reflux, 12 h under argon atmosphere; (c) $TsOH{\cdot}H_2O$ (0.05 equiv), MeOH, reflux, 19 h; (d) Boc_2O (3 equiv), Et_3N (3 equiv), 1,4-dioxane–H_2O (1:1), 23 °C, 46 h, 59% yield in three steps for **16**, 51% yield in three steps for **17**; (e) Me_3SiCN (4.83 equiv), $Mg(OAc)_2$ (0.05 equiv), AcOH (1 equiv), 0–23 °C, 17 h, 99% yield.

Further studies directed toward the total synthesis of polyoxypeptins are currently in progress.

4. Experimental

Melting points were measured with a SIBATA NEL-270 melting point apparatus. Infrared spectra were recorded on a JASCO FT/IR-230 Fourier transform infrared spectrophotometer. Optical rotations were measured on a JASCO P-1020 polarimeter with a sodium lamp. NMR spectra were recorded on JEOL JNM-GSX 400A (400 MHz) and JNM ECP400 spectrometers (400 MHz). Mass spectra were obtained on a JEOL HX-110A (LRFAB, LREI) spectrometer. Analytical thin layer chromatography was performed using Merck precoated silica gel (Art. 5715) plates. The chromatogram was visualized by UV light and by exposure to one of the phosphomolybdic acids, cerium-phosphomolybdic acid, ninhydrin, and anisaldehyde solution, followed by heating. Column chromatography was performed with silica gel 60 N (particle size 40–63 μm, 230–400 mesh) and silica gel 60 N (spherical, neutral 63–210 mesh). Unless otherwise noted, reagents and solvents were purified by standard procedures or used as received.

4.1. Ethyl (*R*)-3-*tert*-butyldimethylsilyloxy-4-chlorobutyrate (*R*)-13

To a stirred solution of (*R*)-**7** (19.1 g, 114 mmol) in DMF (115 mL) at 0 °C under an argon atmosphere were added imidazole (11.7 g, 172 mmol) and TBSCl (19.0 g, 126 mmol), and the mixture was gradually warmed to 23 °C. After 20 h, the reaction was quenched with water and the resulting mixture was extracted with ethyl acetate. The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by distillation (104 °C/0.4 mmHg) to give (*R*)-**13** (31.6 g, 112 mmol, 98%) as a colorless oil: $[\alpha]_D^{26} = +22.2$ (*c* 2.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.11 (3H, s), 0.87 (9H, s), 1.27 (3H, t, $J = 7.1$ Hz), 2.52 (1H, dd, $J = 15.2$, 7.3 Hz), 2.68 (1H, dd, $J = 15.2$, 4.8 Hz), 3.50 (1H, dd, $J = 11.0$, 6.0 Hz), 3.53 (1H, dd, $J = 11.2$, 5.1 Hz), 4.08–4.21 (2H, m), 4.27–4.35 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −4.6, 14.2, 17.9, 25.6, 40.4, 48.1, 60.6, 69.5, 171.0; IR (neat, cm^{-1}) 2957, 2931, 2896, 2858, 1738, 1472, 1465, 1377, 1310, 1256, 1200, 1102. HRMS (FAB) calcd for $C_{12}H_{26}ClO_3Si$: 281.1340 (M+H). Found: 281.1338.

4.2. (*R*)-3-*tert*-Butyldimethylsilyloxy-4-chlorobutanal (*R*)-14

To a stirred solution of (*R*)-**13** (14.1 g, 50.1 mmol) in hexane (500 mL) at −78 °C under an argon atmosphere was added dropwise DIBAL (56.5 mL, 52.6 mmol, 0.93 M in hexane). After 2 h, a solution of potassium sodium tartrate (200 g) in water (500 mL) was added at −78 °C, and the resulting mixture was stirred for 1 h at 23 °C. The mixture was extracted with ether and the combined organic extracts were washed with brine (500 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by distillation (90 °C/0.6 mmHg) to give (*R*)-**14** (9.13 g, 38.5 mmol, 77%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.13 (3H, s), 0.88 (9H, s), 2.69 (1H, ddd, $J = 16.7$, 6.8, 2.2 Hz), 2.79 (1H, ddd, $J = 16.7$, 4.8, 1.5 Hz), 3.48 (1H, dd, $J = 11.0$, 6.4 Hz), 3.55 (1H, dd, $J = 11.0$, 4.8 Hz), 4.36–4.43 (1H, m), 9.81 (1H, dd, $J = 2.2$, 1.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.6, 18.0, 25.6, 48.0, 48.8, 67.9, 200.4; IR (neat, cm^{-1}) 2958, 2932, 2898, 2860, 1728, 1435, 1312. HRMS (FAB) calcd for $C_{10}H_{22}ClO_3Si$: 237.1078 (M+H). Found: 237.1076.

4.3. (*R*)-5-(*tert*-Butyldimethylsilanyloxy)-1,4,5,6-tetrahydropyridazine (*R*)-9

To a stirred solution of (*R*)-**14** (9.11 g, 38.5 mmol) in EtOH (190 mL) at 0 °C was added hydrazine monohydrate (18.7 mL, 385 mmol), and the mixture was gradually warmed to 23 °C. After 17 h, the reaction mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and saturated aqueous $NaHCO_3$, and the resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–ethyl acetate = 2:1) to give (*R*)-cyclic hydrazone **9** (7.53 g, 35.1 mmol, 91%) as a pale yellow oil: $[\alpha]_D^{25} = -125$ (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (6H, s, CH_3), 0.89 (9H, s), 2.09 (1H, ddd, $J = 8.0$, 2.4, 0.8 Hz), 2.14 (1H, ddd, $J = 8.0$, 2.0, 0.8 Hz), 2.74 (1H, dd, $J = 10.4$, 9.6 Hz), 3.22 (1H, ddd, $J = 10.8$, 4.4, 2.0 Hz), 4.04–4.12 (1H, m), 5.43 (1H, br s), 6.69 (1H, t, $J = 2.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, 18.0, 25.8, 35.3, 50.1, 63.1, 139.5; IR (neat, cm^{-1}) 3330, 3029, 2955, 2928, 2897, 2857, 1630, 1471, 1463, 1383, 1361, 1288, 1256, 1119. HRMS (EI) calcd for $C_{12}H_{22}N_2OSi$: 214.1501 (M^+). Found: 214.1515.

4.4. (*R*)-1-Benzoyl-5-(*tert*-butyldimethylsilanyloxy)-1,4,5,6-tetrahydropyridazine (*R*)-5

To a stirred solution of (*R*)-cyclic hydrazone **9** (1.18 g, 5.50 mmol) in pyridine (25 mL) at 0 °C was added dropwise benzoyl chloride (0.767 mL, 6.61 mmol), and the mixture was gradually warmed to 23 °C. After 2 h, the reaction mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and saturated aqueous $NaHCO_3$, and the mixture was extracted with ethyl acetate. The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–ethyl acetate = 4:1) to give (*R*)-**5** (1.72 g, 5.39 mmol, 98%) as a pale yellow oil: $[\alpha]_D^{25} = -26.7$ (*c* 1.43, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12 (3H, s), 0.13 (3H, s), 0.90 (9H, s), 2.20 (1H, ddt, $J = 18.4$, 5.6, 2.0 Hz), 2.49 (1H, ddt, $J = 18.4$, 4.8, 2.4 Hz), 3.71 (1H, ddd, $J = 13.2$, 7.2, 1.6 Hz), 4.02 (1H, dt, $J = 13.2$, 2.4 Hz), 4.17–4.24 (1H, m), 6.83 (1H, t, $J = 2.4$ Hz), 7.36–7.46 (3H, m), 7.61–7.66 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.7, 17.9, 25.6, 34.0, 46.3, 60.6, 127.6, 129.4, 130.3, 135.0, 141.5, 170.9; IR (neat, cm^{-1}) 2953, 2929, 2889, 2856, 1659, 1620, 1404, 1254, 1102. HRMS (FAB) calcd for $C_{17}H_{27}N_2O_2Si$: 319.1842 (M+H). Found: 319.1841.

4.5. (3*R*,5*R*)-1-Benzoyl-5-(*tert*-butyldimethylsilanyloxy)-hexahydropyridazine-3-carbonitrile (3*R*,5*R*)-10 and (3*S*,5*R*)-1-benzoyl-5-(*tert*-butyldimethylsilanyloxy)-hexahydropyridazine-3-carbonitrile (3*S*,5*R*)-11

4.5.1. Zinc triflate method. To a stirred mixture of $Zn(OTf)_2$ (2.40 g, 6.60 mmol), NaOAc (54.1 mg, 0.660 mmol), cyclic hydrazone (*R*)-**5** (2.10 g, 6.59 mmol), and Me_3SiCN (4.42 mL, 33.0 mmol) was added dropwise at 0 °C under an argon atmosphere AcOH (0.38 mL, 6.64 mmol), and the mixture was then gradually allowed to warm to 23 °C. After 24 h, the reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C. The resulting mixture was extracted with ethyl acetate. The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–ethyl acetate = 2:1) to give (3*R*,5*R*)-**10** (1.30 g, 3.76 mmol, 57%) and (3*S*,5*R*)-**11** (296 mg, 0.857 mmol, 13%) as pale yellow solids. Compound (3*R*,5*R*)-**10** was purified by recrystallization from diisopropyl ether to yield pure **10** with >99% ee (judged by CHIRALPAK AD, flow rate: 0.5 mL/min, hexane/isopropanol = 85:15, (3*R*,5*R*): 18.1 min, (3*S*,5*S*): 21.3 min).

4.5.2. Magnesium acetate method. To a stirred mixture of $Mg(OAc)_2$ (24.0 mg, 0.169 mmol), cyclic hydrazone (*R*)-**5** (1.08 g, 3.39 mmol), and Me_3SiCN (2.2 mL, 16.4 mmol) at 0 °C under an argon atmosphere was added dropwise AcOH (195 μL, 3.41 mmol), and the mixture was gradually allowed to warm to 23 °C. After 17 h, the reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C. The resulting mixture was extracted with ethyl acetate. The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–ethyl acetate = 2:1) to give (3*R*,5*R*)-**10** (35.0 mg, 0.101 mmol, 3%) and (3*S*,5*R*)-**11** (1.12 g, 3.24 mmol, 96%) as pale yellow solids. Further purification of **11** was carried out by recrystallization from hexane to afford pure **11** with >99% ee (judged by CHIRALPAK AD, flow rate: 0.5 mL/min, hexane/isopropanol = 85:15, (3*R*,5*S*): 17.6 min, (3*S*,5*R*): 21.2 min).

(3*R*,5*R*)-**10**: mp 163–164 °C (diisopropylether); $[\alpha]_D^{25} = +15.8$ (*c* 0.85, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 55 °C) δ −0.01 (3H, s), 0.06 (3H, s), 0.88 (9H, s), 2.01 (1H, dt, $J = 13.2$, 6.4 Hz), 2.22 (1H, dt, $J = 13.2$, 4.0 Hz), 3.52–3.81 (2H, br m), 3.82–3.88 (1H, m), 3.94–4.03 (1H, m), 7.36–7.48 (3H, m), 7.52–7.58 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$, 55 °C) δ −5.0, 18.1, 25.7, 36.0, 44.3, 52.8, 64.1, 117.9, 128.0, 128.3, 130.4, 133.6, 159.4; IR (neat, cm^{-1}) 3257, 2952, 2930, 2894, 2856, 1628, 1469, 1401, 1255, 1108. HRMS (FAB) calcd for $C_{18}H_{28}N_3O_2Si$: 346.1951 (M+H). Found: 346.1955.

(3*S*,5*R*)-**11**: mp 134–135 °C (hexane); $[\alpha]_D^{25} = -26.6$ (*c* 1.19, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 55 °C) δ −0.05 (3H, s), 0.02 (3H, s), 0.83 (9H, s), 1.99 (1H, ddd, $J = 13.2$, 6.8, 4.0 Hz), 2.18 (1H, ddd, $J = 13.2$, 7.6, 3.6 Hz), 3.47 (1H, dd, $J = 13.2$, 6.0 Hz), 3.76 (1H, br d, $J = 11.6$ Hz), 3.98–4.05 (1H, m), 4.21 (1H, dt, $J = 7.2$, 3.2 Hz), 7.37–7.52 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$, 55 °C) δ −5.0, −4.9, 18.0, 25.7, 36.8, 44.3, 52.8, 63.5, 117.8, 127.9, 128.3, 130.5, 133.7, 164.5; IR (neat, cm^{-1}) 3244, 2953, 2931, 2889, 2857, 2249, 1632, 1469, 1393, 1257, 1111. HRMS (FAB) calcd for $C_{18}H_{28}N_3O_2Si$: 319.1951 (M+H). Found: 346.1924.

4.6. (3*R*,5*R*)-1-*tert*-Butoxycarbonyl-5-hydroxypiperazic acid methyl ester (3*R*,5*R*)-16

A stirred mixture of (3*R*,5*R*)-**10** (50 mg, 0.145 mmol) in 6 M HCl (2 mL) was heated at reflux for 12 h under an argon atmosphere. After cooling to 23 °C, the reaction mixture was diluted with water, washed with ether, and concentrated in vacuo to give (3*R*,5*R*)-**3** as a brown solid, which was used for the next reaction without further purification. (3*R*,5*R*)-**3**: ^1H NMR (400 MHz, D_2O) δ 1.96 (1H, dt, $J = 14.3$, 6.1 Hz), 2.20 (1H, dt, $J = 14.1$, 4.2 Hz), 2.97 (1H, dd, $J = 13.2$, 5.9 Hz), 3.23 (1H, dd, $J = 13.2$, 2.4 Hz), 3.83 (1H, dt, $J = 5.9$, 0.9 Hz), 3.98–4.05 (1H, m); ^{13}C NMR (100 MHz, D_2O) δ 31.1, 49.6, 53.1, 60.8, 174.1.

A solution of the above crude hydroxypiperazic acid and *p*-toluenesulfonic acid monohydrate (1.4 mg, 7.36 μmol) in MeOH (2.0 mL) was heated at 80 °C for 19 h. The reaction mixture was concentrated in vacuo to give the methyl ester as a brown solid, which was used for the next reaction without further purification. Triethylamine (62 μL, 0.447 mmol) and Boc_2O (94.9 mg, 0.435 mmol) were added to a stirred solution of the crude methyl ester in 1,4-dioxane (1 mL) and H_2O (1 mL) at 0 °C and the resulting mixture was gradually warmed to 23 °C. After 46 h, the reaction mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography on silica gel (hexane–ethyl acetate = 1:1) to give *N*-Boc piperazic acid methyl ester (3*R*,5*R*)-**16** (22.4 mg, 0.0861 mmol, 59% in three steps) as a pale yellow oil: $[\alpha]_D^{25} = +7.0$ (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (9H, s), 1.74 (1H, dt, $J = 13.2$, 4.4 Hz), 2.34 (1H, dt, $J = 13.2$, 3.6 Hz), 3.11 (1H, t, $J = 9.2$ Hz), 3.58–3.61 (2H, m), 3.76 (3H, s), 3.96 (1H, m), 5.12 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 35.5, 50.9, 52.2, 56.7, 64.4, 81.3, 154.7, 171.2; IR (KBr, cm^{-1}) 3410, 2980, 1738, 1686, 1366, 1236, 1155, 730. HRMS (FAB) calcd for $C_{11}H_{20}N_2O_5Na$: 283.1270 ($M+Na^+$). Found: 283.1265.

4.7. (3*S*,5*R*)-1-*tert*-Butoxycarbonyl-5-hydroxypiperazic acid methyl ester (3*S*,5*R*)-17

A stirred mixture of (3*S*,5*R*)-**11** (1.00 g, 2.91 mmol) in 6 M HCl (29 mL) was heated at reflux for 12 h under an argon atmosphere. After cooling to 23 °C, the reaction mixture was diluted with H_2O, washed with Et_2O, and concentrated in vacuo to give the crude piperazic acid as a brown solid, which was used for the next reaction without further purification. (3*S*,5*R*)-**15**: ^1H NMR (400 MHz, D_2O) δ 1.90 (1H, ddd, $J = 13.9$, 11.5, 2.4 Hz), 2.10 (1H, dt, $J = 14.3$, 4.2 Hz), 3.07–3.17 (2H, m), 4.12 (1H, dd, $J = 11.4$, 3.5 Hz), 4.15–

4.21 (1H, m); ^{13}C NMR (100 MHz, D_2O) δ 31.4, 49.5, 52.3, 60.0, 173.1.

A solution of the above crude hydroxypiperazic acid and *p*-toluenesulfonic acid monohydrate (27.7 mg, 0.146 mmol) in MeOH (20 mL) was heated at 80 °C for 19 h. The reaction mixture was concentrated in vacuo to give the methyl ester as a brown solid, which was used for the next reaction without further purification. Triethylamine (1.2 mL, 8.66 mmol) and Boc_2O (1.91 g, 8.73 mmol) were added to a stirred solution of the crude methyl ester in 1,4-dioxane (7.5 mL) and H_2O (7.5 mL) at 0 °C. The resulting mixture was gradually warmed to 23 °C. After 46 h, the reaction mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–ethyl acetate = 1:1) to give *N*-Boc piperazic acid methyl ester (3*S*,5*R*)-**17** (386.7 mg, 1.49 mmol, 51% in three steps) as a colorless solid: $[\alpha]_D^{26} = +2.0$ (*c* 1.00, $CHCl_3$); mp 91–92 °C (Et_2O–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (9H, s), 1.89 (1H, ddd, $J = 13.6$, 10.8, 2.8 Hz), 2.12 (1H, ddt, $J = 13.6$, 4.0, 2.0 Hz), 3.31 (1H, dd, $J = 13.6$, 1.2 Hz), 3.74 (3H, s), 3.91 (1H, br d, $J = 13.6$ Hz), 3.96 (1H, dd, $J = 10.8$, 2.8 Hz), 4.06 (1H, br s, CH), 5.24 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 34.0, 50.6, 52.1, 53.3, 63.6, 81.3, 156.0, 171.6; IR (KBr, cm^{-1}) 3329, 1734, 1687, 1665, 1237, 1157, 1120. HRMS (FAB) calcd for $C_{11}H_{20}N_2O_5Na$: 283.1270 ($M+Na^+$). Found: 283.1268.

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