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Lipase TL-Mediated Kinetic Resolution of 5-Benzyloxy-1-*tert*-butyldimethylsilyloxy-2-pentanol at Low Temperature: Concise Asymmetric Synthesis of Both Enantiomers of a Piperazic Acid Derivative

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Lipase TL-mediated kinetic resolution of (±)-5-benzyloxy-1-*tert*-butyldimethylsilyloxy-2-pentanol (**5**) at low temperature proceeded to give the corresponding (*S*)-alcohol **5** and (*R*)-acetate **6** in quantitative yields with high enantiomeric purity. The addition of bases such as pyridine, DMAP, 2,4- and 2,6-lutidines, or triethylamine considerably enhanced the rate of kinetic resolution. The alcohol (*S*)-**5** and the acetate (*R*)-**6** were converted to piperazic acid derivatives (*R*)- and (*S*)-**3**, respectively, via the intramolecular Mitsunobu reaction as a key step.

Introduction

Piperazic acids (**2**) are nonproteinogenic amino acids containing a cyclic hydrazine skeleton. Piperazic acid itself inhibits γ-aminobutyric acid (GABA) uptake[1] and substituted piperazic acids are key amino acid components of several biologically active natural peptides, including sanglifehrins,[2,3] novel cyclophilin-binding compounds, polyoxypeptin,[4] a potent inducer of apoptosis in human pancreatic carcinoma cells, and matlystatins.[5] Interestingly, GE3 (**1**)[6,7] (Figure 1) and related compounds such as azinothricin[8] and A83586C,[9] novel depsipeptide antitumor antibiotics produced by *Streptomyces sp*., include both enantiomers of piperazic acid in their structures.

A number of methods have been reported to synthesize the piperazic acid portion of biologically active depsipeptides.[10] During the course of our continuing research on the lipase TL-mediated kinetic resolution of benzoin,[11,12] we have found that lipase TL is an efficient enzyme for the kinetic resolution of several types of alcohols at low temperature. In this paper, we describe the kinetic resolution of (±)-5-benzyloxy-1-*tert*-butyldimethylsilyloxy-2-pentanol (**5**) by lipase TL and the conversion of alcohol (*S*)-**5** and acetate (*R*)-**6** to the corresponding piperazic acids. Lipases, which are employed widely in the synthesis of optically pure compounds, catalyze not only the hydrolysis of natural esters but also hydrolysis and transesterification of a wide range of unnatural substrates. The empirical rule that predicts the enantiomeric preference of lipases has been proposed by

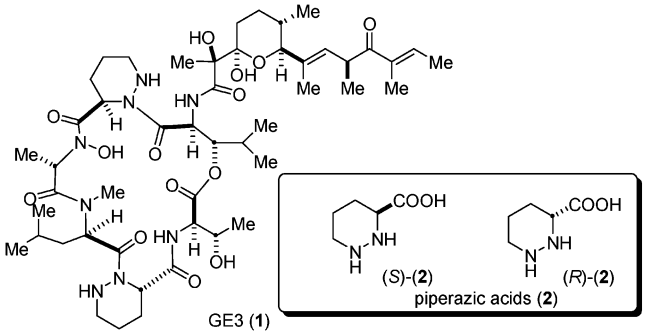

FIGURE 1. Structures of GE3 and piperazic acids.

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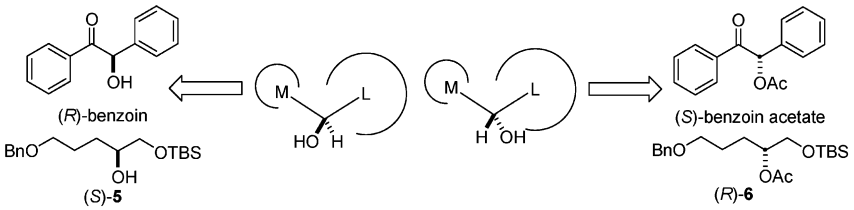
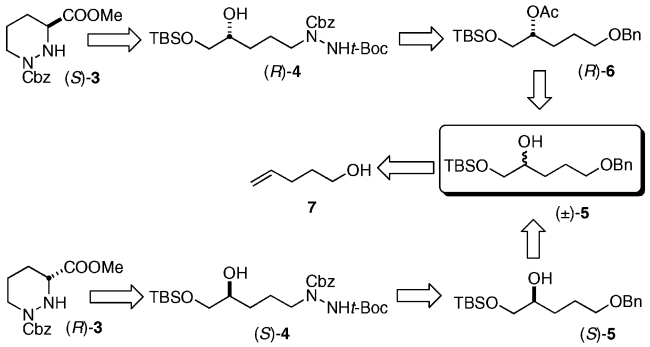


FIGURE 2. Empirical rule that summarizes the enantiopreference of lipases toward chiral secondary alcohols.

Kazlauskas et al.[13,14] The recognition of alcohols by a lipase from *Candida rugosa* (CRL) was discussed on the basis of X-ray crystal structures of covalent complexes of CRL with transition-state analogues for the hydrolysis of menthyl esters.[15] In our previous papers[11,12] on the lipase TL-mediated kinetic resolution of (±)-benzoin, only (*S*)-benzoin was recognized and underwent transesterification to give the (*S*)-benzoin acetate. The stereorecognition of benzoin by lipase TL was identified with the empirical rule already proposed in which the reactive enantiomer is that in which the large and medium groups are disposed as in Figure 2.[13,14]

This indicates the lipase TL-mediated reaction should give (*R*)-acetate **6** when (±)-**5** is employed as a substrate. Retrosynthetic analysis for the preparation of both enantiomers of piperazic acid **3** via kinetic resolution of (±)-**5** is shown in Scheme 1.

SCHEME 1. Synthetic Strategy for the Synthesis of (*R*)- and (*S*)-3

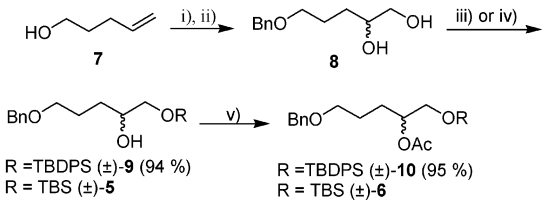


Piperazic acid derivatives (*S*)- and (*R*)-**3** could be synthesized from hydrazino alcohols (*S*)- and (*R*)-**4** via an intramolecular Mitsunobu reaction. Compound **4** might be prepared by introduction of a hydrazino skeleton to compound **6**. Enantiomerically pure alcohol **5** and acetate **6** should be obtained by lipase TL-mediated kinetic resolution of (±)-**5**, which can be prepared from commercially available 4-penten-1-ol (**7**) in three steps: benzylation of a hydroxyl group, dihydroxylation of a double bond, and finally silylation.

Results and Discussion

First, diol **8** was prepared via benzylation and dihydroxylation with catalytic osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO)[16] from commercially available 4-penten-1-ol (**7**). The primary hydroxyl group of **8** was protected by using *tert*-butyldimethylsilyl chloride and imidazole to give the monoprotected alcohol **5**. Acetylation of **5** was carried out to obtain racemic acetate **6** (Scheme 2).

SCHEME 2. Synthesis of *rac*-Alcohols (5 and 9) and Their Acetates (6 and 10)[a]



[a] Reagents and conditions: (i) NaH/BnBr; (ii) OsO_4/NMO; (iii) TBSCl/imidazole/DMF/0 °C then rt; (iv) TBDPSCl/imidazole/DMF/0 °C then rt; (v) Ac_2O/DMAP/CH_2Cl_2/0 °C then rt.

In the same way, alcohol **8** was protected with a *tert*-butyldiphenylsilyl group to give **9**. With racemic secondary alcohols **5** and **9** in hand, the lipase TL-mediated kinetic resolution of **5** was examined under various reaction conditions. Enantiomeric ratios for acetate **6** and recovered alcohol **5** were determined by HPLC analysis, using a chiral column (CHIRALCEL OD-H), and are shown in Table 1. Initially, several kinds of solvents were employed. Among these solvents, hexane gave the best chemical yields and enantiomeric ratios (entries 1−6). It is known that addition of crown ethers[17,18] and amino alcohols[19−21] affects the hydrolysis of esters, and that addition of crown ethers also enhances the rate of transesterification with use of enzymes in apolar organic solvents.[22,23] To identify other nonhazardous and commercially available additives to effect the lipase TL-mediated kinetic resolution, we carried out the resolution using several bases (entries 7−13). Among those examined, DMAP, 2,4-lutidine, 2,6-lutidine, and pyridine were found to be effective. DMAP, in particular, which is the most basic of these additives, considerably enhanced the

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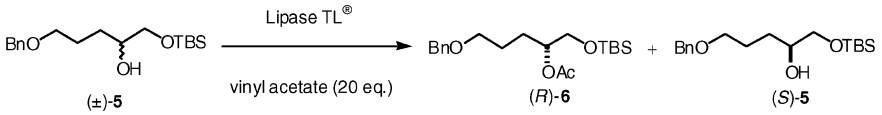
TABLE 1. Lipase TL-Mediated Kinetic Resolution of (±)-5 under Various Conditions[a]



					acetate (*R*)-**6**		recovered (*S*)-**5**			
entry	solvent	reaction time (h)	reaction temp (°C)	additive (equiv)	yield (%)[b]	ee (%)[c]	yield (%)[b]	*ee* (%)[c]	c[d]	E[e]
1	benzene	48	rt	none	11	92	88	12	0.12	27
2	THF	48	rt	none	16	98	78	20	0.17	120
3	hexane	48	rt	none	36	90	64	48	0.35	31
4	AcOEt	48	rt	none	35	96	60	56	0.37	86
5	DMSO	48	rt	none	16	92	77	20	0.18	29
6	DMF	48	rt	none	17	98	82	4	0.04	103
7	hexane	48	rt	*i*-Pr_2NEt (5.0)	44	94	55	68	0.42	66
8	hexane	48	rt	DMAP (5.0)	62	68	40	92	0.58	17
9	hexane	48	rt	$NaHCO_3$ (5.0)	31	96	68	24	0.20	62
10	hexane	48	rt	2,4-lutidine (5.0)	56	90	43	92	0.51	62
11	hexane	48	rt	2,6-lutidine (5.0)	44	98	56	80	0.45	244
12	hexane	48	rt	pyrimidine (5.0)	34	96	62	46	0.32	77
13	hexane	48	rt	pyridine (5.0)	50	94	50	92	0.49	106
14	hexane	48	rt	pyridine (0.5)	33	98	65	46	0.32	156
15	hexane	48	rt	pyridine (1.0)	35	94	61	54	0.36	56
16	hexane	48	rt	pyridine (2.5)	42	94	56	34	0.27	45
17	hexane	48	rt	pyridine (10.0)	47	92	42	92	0.50	79
18	hexane	48	rt	pyridine (20.0)	50	96	50	90	0.48	152
19	hexane	6	rt	pyridine (5.0)	27	96	68	32	0.25	67
20	hexane	12	rt	pyridine (5.0)	32	92	62	62	0.40	45
21	hexane	24	rt	pyridine (5.0)	42	94	56	71	0.43	69
22	hexane	1	rt	DMAP (5.0)	30	98	70	36	0.27	141
23	hexane	3	rt	DMAP (5.0)	41	96	59	48	0.33	79
24	hexane	6	rt	DMAP (5.0)	54	96	45	80	0.45	121
25	hexane	12	rt	DMAP (5.0)	52	92	47	98	0.52	110
26	hexane	24	rt	DMAP (5.0)	56	82	42	98	0.54	46
27[f]	hexane	48	5	pyridine (5.0)	46	96	45	92	0.49	162
28[f]	hexane	48	0	pyridine (5.0)	50	96	49	92	0.49	162
29[f]	hexane	48	−5	pyridine (5.0)	47	98	50	90	0.48	307
30[f]	hexane	48	−10	pyridine (5.0)	48	98	53	82	0.46	254

[a] All reactions were carried out under an Ar atmosphere. Lipase TL (250 mg) and solvent (5 mL) were employed in the reactions. [b] Isolated yields. [c] The enantiomeric excesses (ee) were determined by means of HPLC with a Chiralcel OD-H column. [d] Conversion calculated from $c = ee(\mathbf{5})/(ee(\mathbf{5}) + ee(\mathbf{6}))$ according to ref 24. [e] $E = \ln[1 - c(1 + ee(\mathbf{6}))]/\ln[1 - c(1 - ee(\mathbf{6}))]$. See ref 24. [f] Lipase TL (500 mg) and solvent (10 mL) were employed in the reactions.

reaction rate (entry 8). Weak bases such as sodium bicarbonate and pyrimidine gave essentially the same results as in the absence of base (entries 9 and 12). Next, the number of equivalents of pyridine was examined. When 5 equiv of pyridine were employed in the reaction, satisfactory yields and enantiomeric excess were obtained (entry 13 vs entries 14 to 18). When DMAP (5 equiv) was used, the yield of (*R*)-acetate **6** was increased up to 50% within 6 h (entries 22−26 and 8). On the other hand, in the case of pyridine it took 48 h until all (*R*)-**5** was consumed (entries 19−21 and 13).

However, although DMAP considerably enhanced the kinetic resolution, pyridine, which is cheaper, was selected for use in a practical synthesis. Interestingly, kinetic resolution of alcohol **9** did not proceed under the reaction conditions. This indicates that the identity of the protecting group on the primary hydroxyl group of **8** is important and that the steric bulk of the *tert*-butyldiphenylsilyl group may abrogate binding of the substrate to the enzyme-active site. There are very few reports concerning cold active enzyme-mediated transesterifications. Sakai et al. reported that enhancement of the enantioselectivity in lipase-mediated kinetic resolutions of 3-phenyl-2*H*-azirine-2-methanol by lowering the temperature to −40 °C was observed.[25] Thus, the kinetic resolution of **5** at low temperature was examined (entries 27−30). When the kinetic resolutions were carried out at lower temperatures, the yields of the acetate were the same as that at room temperature after 48 h and the enantiomeric excess of the acetate was extremely high, so lowering the temperature increased the *E* value. This indicates that lipase TL can function as a cold active enzyme.[26] The absolute configuration of acetate **6** was determined as depicted in Scheme 3. Deacetylation of (*R*)-**6** with ethylmagnesium bromide was followed by desilylation with TBAF to give diol **8** in 83% overall yield over two steps. The enantiomeric ratio was determined to be 99:1 and the specific optical rotation was +4.8. As the optical rotation of (*S*)-diol **8** was reported in the literature to be −10.0,[27] the absolute configuration of compound **8** obtained from our synthesis was thus determined to be *R*. As a result, the absolute stereochemistry of the recovered alcohol was deduced to be *S*.

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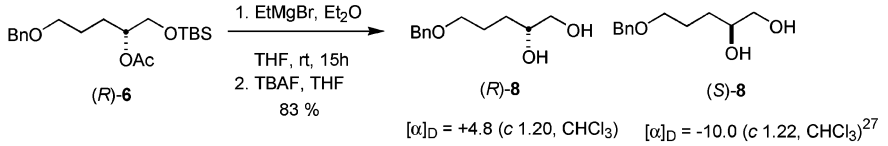
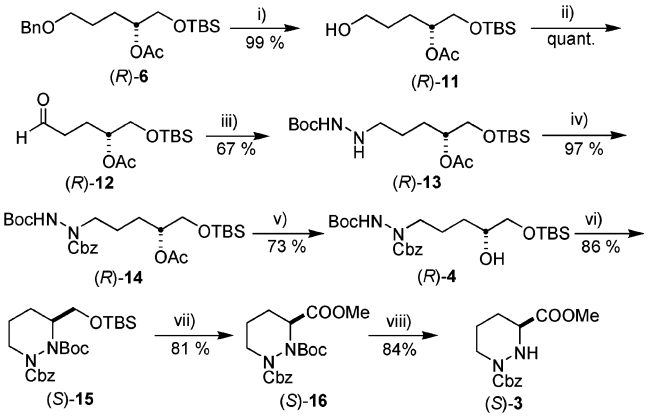
SCHEME 3. Preparation of (*R*)-8



SCHEME 4. Conversion of (*R*)-6 to Piperazic Acid Derivative (*S*)-3[a]



[a] Reagents and conditions: (i) H_2, 10% Pd/C, MeOH, rt; (ii) Dess−Martin periodinane, $CHCl_3$, rt; (iii) $BocNHNH_2$, EtOH, AcOH, rt, then $NaBH_3CN$, rt; (iv) CbzCl, $NaHCO_3$, $CHCl_3$, rt; (v) K_2CO_3, MeOH; (vi) EtOOCN=NCOOEt, PPh_3, THF, reflux; (vii) (a) TBAF, THF, rt, (b) Jones oxidation, acetone, H_2O, rt, (c) $TMSCHN_2$, MeOH, rt; (viii) TFA, CH_2Cl_2 (1:2), 0 °C, rt.

Conversion of the optically active acetate (*R*)-**6** to (*S*)-piperazic acid was carried out as shown in Scheme 4. Acetate (*R*)-**6** was hydrogenated in the presence of 10% palladium on carbon to give an alcohol (*R*)-**11** in 99% yield. Oxidation of (*R*)-**11** with Dess−Martin periodinane[28,29] gave aldehyde (*R*)-**12** in quantitative yield. The reductive amination of aldehyde (*R*)-**12** with *tert*-butyl carbazate and sodium cyanoborohydride in a mixture of acetic acid and methanol was carried out according to the Ernholt method[30] to give the corresponding hydrazine (*R*)-**13** in 67% yield. Protection of (*R*)-**13** with CbzCl and hydrolysis of (*R*)-**14** were carried out successively to give, in 71% overall yield over two steps, a hydrazine-alcohol (*R*)-**4**, which served as a substrate for the intramolecular Mitsunobu reaction. With use of (*R*)-**4**, the intramolecular Mitsunobu reaction was carried out to give the corresponding cyclized product (*S*)-**15** in 86% yield. Finally, (*S*)-**15** was desilylated with TBAF, oxidized with Jones reagent,[31] and methylated with trimethylsilyl diazomethane to afford (*S*)-**16** in 81% yield. This product should prove to be a useful amino acid component for the synthesis of biologically active cyclic depsipeptides such as GE3 as it has three orthogonal protecting groups. To determine the enantiomeric excess of (*S*)-**16**, removal of the Boc group was conducted in the usual manner. The optical rotation of (*S*)-**3** was −34.4, which is consistent with that reported in the literature ($[\alpha]_D$ −30.8).[32] Furthermore, HPLC analysis with a CHIRALCEL OD-H allowed measurement of the enantiomeric purity of (*R*)-**3** as being greater than 98% ee. Next, we prepared the antipode, (*R*)-**3**, from alcohol (*S*)-**5** using almost the same procedure depicted in Scheme 4 except for acetylation of (*S*)-**5**. (*S*)-**6** was converted to (*R*)-**3** in 17% overall yield. The optical rotation and the enantiomeric excess of (*R*)-**3** were +34.3 and >98% ee, respectively.

In summary, lipase TL-mediated kinetic resolution of (±)-**5** at low temperature proceeded smoothly in the presence of bases such as pyridine, 2,4-lutidine, and DMAP to give the corresponding acetate (*R*)-**6** and recovered alcohol (*S*)-**5** in good yields with high enantiomeric purity. (*R*)-**6** and (*S*)-**5** were converted to both enantiomers of a piperazic acid derivative **3** having three different protecting groups. The application of this methodology to the total synthesis of GE3 families is under investigation and will be reported in due course.

Experimental Section

Representative Procedure for Lipase TL-Mediated Kinetic Resolution of (±)-5. To a solution of (±)-**5** (0.5 g, 1.54 mmol), vinyl acetate (2.58 g, 30 mmol), and dry pyridine (0.64 g, 8.0 mmol) in dry hexane (25 mL) was added lipase TL (1.25 g) at −5 °C under an Ar atmosphere. The mixture was stirred at the same temperature for 48 h. The catalyst was separated off by filtration through Celite 545. The filtrate was washed with cooled 1 N HCl (3 × 30 mL), sat. $NaHCO_3$ (3 × 30 mL), and sat. NaCl (3 × 30 mL), dried over $MgSO_4$, and filtered, and the solvents were evaporated in vacuo to give an oily residue, which was purified with MPLC (hexane:AcOEt 5:1) to give (*R*)-**6** as a colorless oil (0.27 g, 47%, 98% ee) and (*S*)-**5** (0.25 g, 50%, 90% ee) as a colorless oil. The physical and spectral data were identical with those of the racemates except for the optical rotation (see Supporting Information).

(*R*)-**6**: $[\alpha]_D$ +14.2 (*c* 0.22, $CHCl_3$). (*S*)-**5**: $[\alpha]_D$ +3.0 (*c* 0.63, $CHCl_3$). The percent ee of the product was determined by means of the HPLC method described below.

Determination of Enantiomeric Excess (ee) of Recovered (*S*)-Alcohol 5 and Its (*R*)-Acetate 6 by Means of HPLC Analysis with a Chiral Column. Column: Daicel CHIRALCEL OD-H column (4.6 × 250 mm). Solvent: hexane: ^{i}PrOH 100:1. UV wavelength: 257 nm. Flow rate: 0.5 mL/min. Pressure: 20 kg/cm^2. (*R*)-acetate **6**; t_R = 12.0 min. (*S*)-acetate **6**; t_R = 10.0 min. (*R*)-alcohol **5**; t_R = 18.0 min. (*S*)-alcohol **5**; t_R = 22.0 min.

Acetylation of (*S*)-5-Benzyloxy-1-*tert*-butyldimethylsilyloxy-2-pentanol (5). To a mixture of (*S*)-**5** (2.1 g, 6.48 mmol, 96% ee), DMAP (0.08 g, 0.65 mmol), and pyridine (0.77 g, 9.72 mmol) in $CHCl_3$ (65 mL) was added dropwise Ac_2O (0.79 g, 7.72 mmol) at 0 °C under an Ar atmosphere. The mixture was stirred at room temperature for 14 h, poured into ice−water (100 mL), diluted with AcOEt (100 mL), and separated. The aqueous phase was extracted with AcOEt (2 × 50 mL). The combined organic phases were washed with sat. NaCl (3 × 100 mL), dried over $MgSO_4$, and filtered, and the solvents were evaporated in vacuo to give an oily residue, which was

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purified with MPLC (hexane:AcOEt 4:1) to give (*S*)-**6** as a colorless oil (2.19 g, 92%, 96% ee). The physical data for (*S*)-**6** were identical with those of (±)-**6** except for the optical rotation (see Supporting Information). (*S*)-**6**: $[\alpha]_D$ −14.4 (*c* 0.23, $CHCl_3$).

Determination of Absolute Configuration of the Acetate (*R*)-6, which Was Obtained in the Kinetic Resolution. To a mixture of (*R*)-acetate **6** (0.22 g, 0.60 mmol) and dry Et_2O (15 mL) was added 1.0 M EtMgBr (15.0 mL, 15.0 mmol) at 0 °C under an Ar atmosphere. After the reaction mixture had been stirred at 0 °C for 1 h, sat. NH_4Cl (10 mL) was added. The aqueous solution was extracted with AcOEt (3 × 15 mL). The combined organic phases were washed with sat. NaCl (3 × 30 mL), dried over $MgSO_4$, and filtered, and the solvents were evaporated in vacuo to give an oily residue, which was purified with MPLC (hexane:AcOEt 5:1) to give a mixture (0.20 g) of **5** and 5-benzyloxy-1-*tert*-butyldimethylsilyloxy-1-pentanol, which was subjected to the next reaction without further separation. To a THF solution (13 mL) of the mixture (0.20 g) thus obtained was added 1.0 M TBAF (1.25 mL, 1.25 mmol) in THF. The reaction mixture was stirred at room temperature for 1 h. AcOEt (30 mL) was then added. The organic phase was washed with sat. NaCl (3 × 20 mL), dried over $MgSO_4$, and filtered, and the solvents were evaporated in vacuo to give an oily residue, which was purified with MPLC ($CHCl_3$:MeOH 10:1) to give (*R*)-**8** as a colorless oil (0.11 g, 83%). The spectral data of **8** were identical with those reported by Matsumoto et al.[27] The ee of the product was 88% on the basis of HPLC analysis. (Column: Daicel CHIRALCEL OB column (4.6 × 250 mm). Solvent: hexane:EtOH 9:1. UV wavelength: 257 nm. Flow rate: 0.5 mL/min. Pressure: 20 kg/cm^2. (*R*)-diol **8**; t_R = 27.0 min. (*S*)-diol **8**; t_R = 42.0 min. (*R*)-**8**: $[\alpha]_D$ +6.6 (*c* 0.79, $CHCl_3$).)

Hydrogenolysis of (*R*)-Acetate 6. In the presence of 10% Pd/C (0.16 g), a MeOH solution (60 mL) of (*R*)-acetate **6** (1.6 g, 4.4 mmol) was stirred at room temperature under a H_2 atmosphere (1 atm) for 0.5 h. After removal of the catalyst by filtration through Celite 545, the filtrate was concentrated in vacuo to give an oily residue, which was purified with MPLC (hexane:AcOEt 1:1) to give (*R*)-alcohol **11** as a colorless oil (1.2 g, 99%). $[\alpha]_D$ +20.6 (*c*= 0.42, $CHCl_3$); ^{1}H NMR (400 MHz, 300 K, $CDCl_3$) δ 4.91 (m, 1H), 3.65 (t, 2H, J = 9.1 Hz), 3.64 (d, 2H, J = 5.2 Hz), 2.05 (s, 3H), 1.66−1.57 (m, 4H), 1.71 (m, 1H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, 300 K, $CDCl_3$) δ 170.8, 74.3, 64.2, 62.6, 28.3, 26.8, 25.8, 21.2, 18.2, −5.4; IR (film) 3437 (OH), 1741 (C=O); HRMS (ESI) calcd for $C_{13}H_{28}O_4$-SiNa 299.1655 (M^+ + Na), found 299.1628.

Hydrogenolysis of (*S*)-Acetate 6. Hydrogenolysis of (*S*)-**6** gave (S)-**11** in 95% yield according to the procedure described above. $[\alpha]_D$ −18.6 (*c* 1.07, $CHCl_3$). The spectral data and HRMS of (S)-**11** were identical with those of (*R*)-**11**.

Oxidation of (*R*)-Alcohol 11. To a solution of (*R*)-**11** (1.58 g, 5.7 mmol) in dry $CHCl_3$ (80 mL) was added Dess−Martin periodinane[28,29] (3.60 g, 8.6 mmol) in portions at 0 °C. After the reaction mixture had been stirred at room temperature for 2 h, sat. $Na_2S_2O_3$ (3 × 40 mL) and sat. $NaHCO_3$ (40 mL) were added. The resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was diluted with AcOEt (80 mL) and separated. The organic layer was washed with sat. NaCl (3 × 40 mL), dried over $MgSO_4$, and filtered, and the solvents were evaporated in vacuo to give an oily residue, which was purified with MPLC (hexane:AcOEt 3:1) to give (*R*)-**12** as a colorless oil (1.56 g, quantitative yield). $[\alpha]_D$ +25.1 (*c* 1.28, $CHCl_3$); ^{1}H NMR (400 MHz, 300 K, $CDCl_3$) δ 9.75 (t, 1H, J = 1.4 Hz), 4.88 (m, 1H), 3.65 (dd, 1H, J = 10.8, 5.1 Hz), 3.61 (dd, 1H, J = 10.8, 5.0 Hz), 2.49 (td, 2H, J = 7.8, 1.4 Hz), 2.03 (s, 3H), 2.01−1.84 (m, 2H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, 300 K, $CDCl_3$) δ 201.3, 170.6, 73.5, 63.9, 39.8, 25.7, 23.1, 21.0, 18.2, −5.5; IR (film) 1739 (C=O); HRMS (ESI) calcd for $C_{13}H_{26}O_4SiNa$ 297.1498 (M^+ + Na), found 297.1477.

Oxidation of (*S*)-Alcohol 11. Oxidation of (*S*)-**11** gave (*S*)-**12** with Dess−Martin periodinane in quantitative yield according to the procedure described above. $[\alpha]_D$ −24.5 (*c* 1.07, $CHCl_3$). The spectral data and HRMS of (*S*)-**12** were identical with those of (*R*)-**12**.

Reductive Amination of (*R*)-12. To a solution of *tert*-butylcarbazate (0.97 g, 7.3 mmol) in dry MeOH (10 mL) was added (*R*)-**12** (1.0 g, 3.7 mmol) in dry MeOH (8 mL) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 1 h and then cooled to 0 °C. AcOH (0.36 mL, 6.3 mmol) was added and the mixture was stirred for 10 min. $NaBH_3CN$ (1.30 g, 21.0 mmol) was then added and the mixture was stirred at room temperature for 1 h. The solvents were evaporated in vacuo and then phosphate buffer solution (pH 7.2, 50 mL) and AcOEt (50 mL) were added. The organic layer was separated and the aqueous layer was extracted with AcOEt (2 × 30 mL). The combined organic layers were washed with sat. NaCl (3 × 30 mL), dried over $MgSO_4$, and filtered, and the solvents were evaporated in vacuo to give an oily residue, which was purified with MPLC (hexane:AcOEt 2:1) to give (*R*)-**13** as a colorless oil (0.96 g, 67%). $[\alpha]_D$ +10.7 (*c* 1.63, $CHCl_3$); ^{1}H NMR (400 MHz, 300 K, $CDCl_3$) δ 6.05 (br s, 1H), 4.89 (m, 1H), 3.62 (d, 2H, J = 5.1 Hz), 2.84 (t, 2H, J = 7.1 Hz), 2.04 (s, 3H), 1.68−1.46 (m, 4H), 1.46 (s, 9H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, 300 K, $CDCl_3$) δ 170.7, 80.4, 64.2, 51.7, 28.4, 28.0, 25.8, 23.5, 21.2, 18.2, −5.4; IR (film) 3583 (NH), 1739, 1716 (C=O); HRMS (ESI) calcd for $C_{18}H_{38}$-N_2O_5SiNa 413.2448 (M^+ + Na), found 413.2447.

Reductive Amination of (*S*)-12. Reductive amination of (*S*)-**12** gave (*S*)-**13** in 58% yield according to the procedure described above. $[\alpha]_D$ −10.3 (*c* 1.10, $CHCl_3$). The spectral data and HRMS of (*S*)-**13** were identical with those of (*R*)-**13**.

Carbobenzoxylation of (*R*)-13. To a mixture of (*R*)-**13** (6.3 g, 16.5 mmol), $CHCl_3$ (25 mL), and 1 N $NaHCO_3$ (25 mL) was added CbzCl (3.57 g, 21.0 mmol) dropwise at 0 °C. After the reaction mixture was stirred vigorously at 0 °C for 1.5 h, the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (2 × 30 mL). The combined organic layers were washed with sat. NaCl (3 × 30 mL), dried over $MgSO_4$, and filtered, and the solvents were evaporated in vacuo to give an oily residue, which was purified with MPLC (hexane:AcOEt 3:1) to give (*R*)-**14** as a colorless oil (8.2 g, 97%). $[\alpha]_D$ +5.5 (*c* 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, 300 K, $CDCl_3$) δ 7.34 (br s, 5H), 6.44 (0.7 H, br s), 6.18 (0.3 H, br s), 5.14 (br s, 2H), 4.89 (br s, 1H), 3.62 (br s, 2H), 3.53 (br s, 2H), 2.04 (s, 3H), 1.62 (br d, 4H), 1.40 (br m, 9H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, 300 K, $CDCl_3$) δ 170.7, 136.0, 128.5, 128.0, 81.4, 74.1, 67.9, 64.1, 49.8, 28.1, 27.5, 25.8, 23.0, 21.1, 18.2, −5.4; IR (film) 3312 (NH), 1739, 1717 (C=O); HRMS (ESI) calcd for $C_{26}H_{44}N_2O_7SiNa$ 547.2816 (M^+ + Na), found 547.2799.

Carbobenzoxylation of (*S*)-13. Carbobenzoxylation of (*S*)-**13** gave (*S*)-**14** in 98% yield according to the procedure described above. $[\alpha]_D$ −5.6 (*c* 1.05, $CHCl_3$). The spectral data and HRMS of (*S*)-**14** were identical with those of (*R*)-**14**.

Deacetylation of (*R*)-14. To a mixture of (*R*)-**14** (1.0 g, 1.9 mmol), MeOH (22 mL), and H_2O (11 mL) was added powdered K_2CO_3 (4.0 g, 28.6 mmol) at room temperature. After the reaction mixture was stirred at room temperature for 6 h, AcOEt (100 mL) was added and the layers separated. The organic layer was washed with sat. NaCl (3 × 50 mL), dried over $MgSO_4$, and filtered, and the solvents were evaporated in vacuo to give an oily residue, which was purified with MPLC (hexane:AcOEt 2:1) to give (*R*)-**4** as a colorless oil (0.67 g, 73%). $[\alpha]_D$ −1.5 (*c* 0.81, $CHCl_3$); ^{1}H NMR (500 MHz, 300 K, $CDCl_3$) δ 7.33 (br m, 5H), 6.49 (br s, 0.7 H), 6.27 (br s, 0.3 H), 5.15 (br s, 2H), 3.56 (br m, 4H), 3.37 (br s, 1H), 2.29 (s, 3H), 1.77 (m, 1H), 1.64 (br s, 1H), 1.41 (br m, 11H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, 300 K, $CDCl_3$) δ 156.1, 136.1, 128.4, 128.1, 81.5, 71.5, 67.9, 67.2, 50.4, 50.0, 29.7, 28.1, 25.9, 23.3, 18.3, −5.36, −5.41; IR (film) 3464 (OH), 3302 (NH), 1712 (C=O); HRMS (ESI) calcd for $C_{24}H_{42}N_2O_6SiNa$ 505.2710 (M^+ + Na), found 505.2678.

Deacetylation of (*S*)-14. Deacetylation of (*S*)-**14** gave (*S*)-**4** in 64% yield according to the procedure described above. $[\alpha]_D$

+1.4 (*c* 0.93, $CHCl_3$). The spectral data and HRMS of (*S*)-**4** were identical with those of (*R*)-**4**.

Intramolecular Mitsunobu Reaction of (*R*)-4. To a THF (330 mL) solution of (*R*)-**4** (0.80 g, 1.66 mmol) and PPh_3 (1.70 g, 6.64 mmol) was added DEAD (0.94 g, 5.0 mmol) at reflux and under an Ar atmosphere. The reaction mixture was refluxed for 0.5 h. After evaporation of the solvents, the oily residue was purified with MPLC (hexane:AcOEt 3:1) to give (*S*)-**15** as a colorless oil (0.67 g, 86%). $[\alpha]_D$ −24.1 (*c* 1.07, $CHCl_3$); ^{1}H NMR (500 MHz, 300 K, $CDCl_3$) δ 7.36−7.28 (m, 5H), 5.15 (d, 1H, J = 12.4 Hz), 5.11 (d, 1H, J = 12.4 Hz), 4.31 (br s, 0.7H), 4.10 (dt, 1H, J = 12.5, 4.6 Hz), 4.00 (m, 0.3H), 3.81 (dd, 0.3H, J = 10.0, 5.0 Hz), 3.70 (br m, 0.7H), 3.59−3.52 (m, 1H), 3.07 (br s, 0.3H), 2.96 (br s, 0.7H), 1.80 (m, 2H), 1.65 (br m, 1H), 1.50−1.32 (m, 10H), 0.88 (s, 2.7H), 0.85 (s, 6.3H), 0.05 (s, 0.9H), 0.04 (s, 0.9H), 0.00 (s, 4.2H); ^{13}C NMR (125 MHz, 300 K, $CDCl_3$) δ 155.5, 136.4, 128.5, 128.1, 127.9, 81.2, 67.4, 61.1, 61.0, 60.3, 53.6, 44.0, 28.10, 25.8, 22.6, 22.2, 21.0, 19.3, 18.9, 18.1, 14.2, −5.4, −5.5; IR (film) 1703 (C=O); HRMS (ESI) calcd for $C_{24}H_{40}N_2O_5SiNa$ 487.2604 (M^+ + Na), found 487.2616.

Intramolecular Mitsunobu Reaction of (*S*)-4. The intramolecular Mitsunobu reaction of (*S*)-**4** gave (*R*)-**15** in 77% yield according to the procedure described above. $[\alpha]_D$ +26.2 (*c* 1.11, $CHCl_3$). The spectral data and HRMS of (*R*)-**15** were identical with those of (*S*)-**15**.

Preparation of (*S*)-Methyl 1-Benzyloxycarbonyl-2-butoxycarbonylpiperazic Acid 16. To a solution of (*S*)-**15** (0.20 g, 0.43 mmol) in dry THF (8.6 mL) was added 1.0 M TBAF in THF (0.9 mL, 0.9 mmol) at room temperature under an Ar atmosphere. The reaction mixture was stirred at the same temperature for 10 min and then diluted with AcOEt (30 mL). The organic solvent was washed with sat. NaCl (3 × 20 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo to give an oily residue, which was purified with MPLC (hexane:AcOEt 1:1) to give the corresponding alcohol as a colorless oil (0.18 g, quantitative yield). To a solution of the alcohol thus obtained (0.18 g, 0.43 mmol) in Me_2CO (9 mL) was added Jones reagent (0.7 mL, 1.8 mmol), prepared from CrO_3 (2.67 g), sulfuric acid (2.3 mL), and H_2O (5.8 mL). The mixture was stirred at room temperature for 1 h then quenched with ^{i}PrOH (3 mL), and the insoluble materials were removed by filtration through Celite 545. The filtrate was diluted with AcOEt (30 mL), washed with sat. NaCl (3 × 20 mL), dried over $MgSO_4$, and filtered, and the solvents were evaporated in vacuo to give the corresponding acid as a crude material (0.20 g), which was employed in the next reaction without further purification. To a solution of the crude acid (0.20 g) in MeOH (4 mL) was added 2.0 M $TMSCHN_2$ in hexane (0.4 mL, 0.8 mmol) at room temperature. After the reaction, the organic solvent was evaporated in vacuo to give an oily residue, which was purified with MPLC (hexane:AcOEt 3:1) to give (*S*)-**16** as a colorless oil (0.13 g, 81%, 3 steps overall yield). $[\alpha]_D$ −33.4 (*c* 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, 300 K, $CDCl_3$) δ (major isomer) 7.40−7.28 (m, 5H), 5.22 (d, 1H, J = 12.0 Hz), 5.12 (d, 1H, J = 12.0 Hz), 5.02 (br s, 1H), 4.19 (br d, 1H, J = 12.6 Hz), 3.55 (br s, 3H), 2.90 (br m, 1H), 2.11 (br d, 1H, J = 13.3 Hz), 1.93−1.83 (m, 1H), 1.76 (br m, 1H), 1.59 (br m, 1H), 1.34 (br s, 9H); ^{1}H NMR (500 MHz, 393 K, DMSO-d_6) δ 7.39−7.25 (m, 5H), 5.14 (d, 1H, J = 12.7 Hz), 5.07 (br d, 1H, J = 12.7 Hz), 4.85 (br m, 1H), 4.00 (br m, 1H), 3.00 (br s, 1H), 2.88 (br s, 3H), 1.92 (br m, 1H), 1.81 (br m, 2H), 1.56 (br m, 1H), 1.39 (s, 1.39); ^{13}C NMR (125 MHz, 300 K, $CDCl_3$) δ 208.9, 170.4, 155.3, 154.4, 136.4, 136.0, 128.6, 128.4, 128.2, 128.0, 127.7, 82.1, 68.3, 68.1, 67.5, 59.6, 57.8, 57.5, 56.5, 54.7, 52.2, 52.0, 49.5, 48.4, 48.0, 45.0, 43.6, 42.3, 42.1, 28.0, 25.7, 25.2, 24.4, 20.3, 20.0, 17.3, 17.1; IR (film) 1728, 1708 (C=O); HRMS (ESI) calcd for $C_{19}H_{26}N_2O_6Na$ 401.1689 (M^+ + Na), found 401.1691.

Preparation of (*R*)-Methyl 1-Benzyloxycarbonyl-2-butoxycarbonylpiperazic Acid 16. Desilylation, oxidation, and methylation of (*R*)-**15** gave (*R*)-**16** in 88% yield according to the procedure described above. $[\alpha]_D$ +36.3 (*c* 1.09, $CHCl_3$). The spectral data and HRMS of (*R*)-**16** were identical with those of (*S*)-**16**.

Deprotection of (*S*)-16. To a solution of (*S*)-**16** (0.13 g, 0.35 mmol) in CH_2Cl_2 (1.2 mL) was added TFA (0.6 mL) at 0 °C. After the reaction mixture had been stirred at the same temperature for 3 h, the solvents was evaporated in vacuo. The residue was diluted with AcOEt (50 mL) and the organic phase was washed with sat. $NaHCO_3$ (3 × 20 mL) and sat. NaCl (3 × 20 mL), dried over $MgSO_4$, and filtered, and the solvents were evaporated in vacuo to give an oily residue, which was purified with MPLC (hexane:AcOEt 2:1) to give (*S*)-**3** as a colorless oil (0.08 g, 84%). $[\alpha]_D$ −34.4 (*c* 1.95, $CHCl_3$) (−30.8°);[32] ^{1}H NMR (500 MHz, 300 K, $CDCl_3$) δ 7.37−7.29 (m, 5H), 5.17 (s, 2H), 4.53 (br s, 1H), 3.99 (br d, 1H, J = 13.0 Hz), 3.71 (s, 3H), 3.55 (dd, 1H, J = 10.1, 3.2 Hz), 3.14 (1H, br dd, J = 11.0, 11.0 Hz), 2.08−2.04 (m, 1H), 1.77−1.67 (m, 2H), 1.59 (br m, 1H); ^{13}C NMR (125 MHz, 300 K, $CDCl_3$) δ 171.3, 155.2, 136.4, 128.5, 128.1, 127.9, 67.5, 58.3, 52.0, 44.7, 27.3, 23.2; IR (film) 3307 (NH), 1739, 1699 (C=O); HRMS (ESI) calcd for $C_{14}H_{19}N_2O_4$ 279.1345 (M^+ + H), found 279.1370.

Deprotection of (*R*)-16. Removal of the Boc group on (*R*)-**16** gave (*R*)-**3** in 80% yield according to the procedure described above. $[\alpha]_D$ +34.4 (*c* 1.95, $CHCl_3$). The spectral data and HRMS of (*R*)-**3** were identical with those of (*S*)-**3**.

Determination of the Enantiomeric Excess (ee) of (*S*)-Piperazic acid 3 and Its Antipode (*R*)-3 by Means of HPLC Analysis with a Chiral Column. Column: Daicel CHIRALCEL OD-H column (4.6 × 250 mm). Solvent: hexane:^{i}PrOH 95:5. UV wavelength: 257 nm. Flow rate: 0.5 mL/min. Pressure: 20 kg/cm^2. (*S*)-**3**; t_R= 40 min. (*R*)-**3**; t_R = 46 min.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **8** to **16**; experimental procedure for the preparation of *rac*-alcohol **5** and its acetate **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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