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Reagent-controlled diastereoselective synthesis of (2*S*,3*R*)- and (2*R*,3*R*)-2,3-diaminobutanoic acid derivatives using proline-catalyzed α-hydrazination reaction

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ABSTRACT

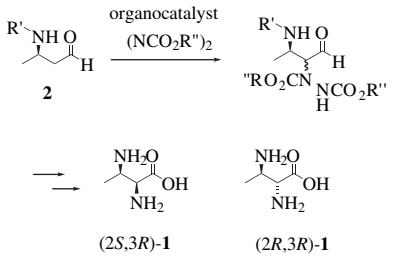
(2*S*,3*R*)- and (2*R*,3*R*)-2,3-Diaminobutanoic acid (Dab) derivatives were efficiently synthesized from Cbz-(*R*)-alanine using the proline-catalyzed diastereoselective α-hydrazination reaction and the SmI_2-promoted reductive cleavage of the N–N bond as the key steps.

1. Introduction

Chiral 2,3-diamino acids and their derivatives are an important class of structurally unusual amino acids broadly found in nature as a component of biologically active natural products and medicinal agents.[1] In connection with our ongoing synthetic studies on papuamides,[2] cyclodepsipeptides with a potent inhibitory activity against the infection of human T-lymphoblastoid cells by HIV-1_{RF}, we needed a practical method for the synthesis of chiral 2,3-diaminobutanoic acids (**1**). Several attractive synthetic approaches to the 2,3-diaminobutanoic acids have been reported in past years.[3] However, there is a need for the simple and secure construction of each 2,3-diaminobutanoic acid diastereomer. Recently, we have been engaged in the organocatalytic synthesis of structurally unusual amino acids and dihydroquinolines.[4] We now describe the reagent-controlled diastereoselective synthesis of (2*S*,3*R*)- and (2*R*,3*R*)-2,3-diaminobutanoic acid derivatives from Cbz-(*R*)-alanine using the proline-catalyzed α-hydrazination reaction as the key step.

2. Results and discussion

Our plan for the synthesis of chiral 2,3-diaminobutanoic acid is shown in Scheme 1. The stereoselective construction of the 2,3-diamino structure is achieved by the organocatalytic asymmetric α-hydrazination reaction[5] of the chiral aldehyde **2** derived from (*R*)-alanine and the subsequent reductive cleavage of the hydrazine N–N bond. This strategy would provide both diastereomeric isomers from a common chiral starting material. Although the asymmetric α-hydrazination of achiral aldehydes catalyzed by proline has been originally reported by List, to the best of our knowledge, the reagent-controlled diastereoselective synthesis of a 2,3-diamino acid from a chiral aldehyde at C3 has never been reported.



Scheme 1.

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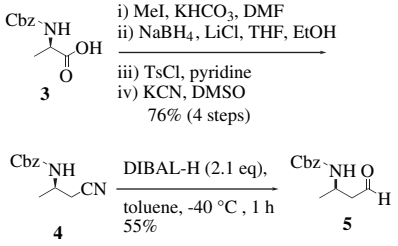
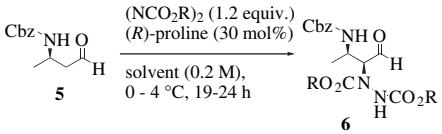
The required (*R*)-3-(benzyloxycarbonylamino)butanal (**5**) was readily prepared from Cbz-(*R*)-alanine (**3**) (Scheme 2). The one-carbon homologation of **3** was carried out by the routine four-step manipulation. The carboxylic acid **3** was esterified with iodomethane and potassium hydrogen carbonate in dimethylformamide, and the resulting ester was reduced with $NaBH_4$/LiCl in ethanol/tetrahydrofuran to give the aminoalcohol, which was tosylated with tosyl chloride and pyridine. The cyanation of the tosylate with potassium cyanide provided the homologated nitrile **4**[6] in 76% yield from **3**. The following reduction of **4** with diisobutylaluminum hydride (DIBAL-H) afforded the aldehyde **5**[7] in 55% yield. The yield was moderate due to the unexpected deprotection of the Cbz group as a side reaction.



Scheme 2. Preparation of β-aminoaldehyde **5** from (*R*)-alanine.

With the starting aldehyde **5** in hand, we initially investigated the optimization of the α-hydrazination reactions. The reaction was carried out using (*R*)-proline (30 mol %) and three dialkyl azodicarboxylates in acetonitrile according to the literature[5] as shown in Table 1. The *syn*/*anti* ratio of the products was determined by the integration of the aldehyde protons (*anti*-isomer: 9.63 ppm, *syn*-isomer: 9.70 ppm, starting material: 9.76 ppm) in the ^{1}H NMR spectra. Although dibenzyl and diethyl azodicarboxylates have a moderate diastereoselectivity, di-*tert*-butyl azodicarboxylate was of excellent diastereoselectivity to give *syn*-**6** as the major isomer (entries 1–3). The choice of the protecting group at the C3-amino group of **5** was critical for the yield. The protection with the Boc group instead of the Cbz one resulted in a complex mixture (entry 4). Since the diastereoselectivity was insufficient, the effect of solvents was examined again. The use of THF or DMF decreased the *syn*/*anti* selectivity. On the other hand, dichloromethane showed a good stereoselectivity (entries 5–7). In terms of the yield and diastereoselectivity, acetonitrile was the most suitable for this α-hydrazination reaction. At this point, the diastereoselectivity was still unsatisfactory. In order to improve the diastereoselectivity, we examined the temperature effect. The reaction at −20 °C enhanced the diastereoselectivity from 87/13 to 95/5 (Table 1, entries 2 and 8). Under the optimized conditions, the reaction using (*S*)-proline instead of (*R*)-proline as the catalyst mainly produced the *anti*-**6** with a *syn*/*anti* ratio of 3/97 (entry 9). These results show that the present diastereoselective reaction proceeds in a reagent-controlled manner to exclusively give the *syn* or *anti* product.

Table 1
The optimization of reaction conditions

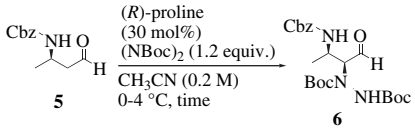


Entry	R	Solvent	Yield[a] (%)	*syn*/*anti*[a]
1	Bn	CH_3CN	100	57/43
2	*t*-Bu	CH_3CN	100	87/13
3[b]	Et	CH_3CN	83	69/31
4[c]	*t*-Bu	CH_3CN	—[d]	—
5	*t*-Bu	CH_2Cl_2	96	83/17
6	*t*-Bu	THF	58	63/37
7	*t*-Bu	DMF	96	44/56
8[b]	*t*-Bu	CH_3CN	69	95/5
9[b,e]	*t*-Bu	CH_3CN	93	3/97

[a] Determined by ^{1}H NMR.
[b] The reaction was carried out at −20 °C.
[c] *N*-*tert*-Butoxycarbonylaminobutanal was used instead of **5**.
[d] Multi-spots reaction.
[e] (*S*)-Proline was used.

In our efforts to improve the diastereoselectivity (Table 1, entry 2), we observed the partial epimerization of the newly formed C2 stereocenter in *syn*-**6** under the conditions of a longer reaction time at 0–4 °C. As shown in Table 2 and Figure 1, the noticeable decrease in the diastereoselectivity from the *syn*/*anti* ratio of 96/4 to 87/13 during 24 h was observed. These results indicate that this α-hydrazination reaction at 0–4 °C competes with the proline-catalyzed epimerization of the product. Although this epimerization was an inherent problem for the proline-catalyzed α-hydrazination, fortunately, lowering the temperature to −20 °C solved this problem and proved to produce the product with no or little epimerization.

Table 2
The epimerization of **6**



Time (h)	Yield[a] (%)	*syn*/*anti*[a]	de (%)
1	39	96/4	92
3	66	96/4	92
6	88	94/6	88
9	93	91/9	82
11	95	90/10	80
15	96	89/11	78
19	98	87/13	74
24	100	87/13	74

[a] Determined by ^{1}H NMR.

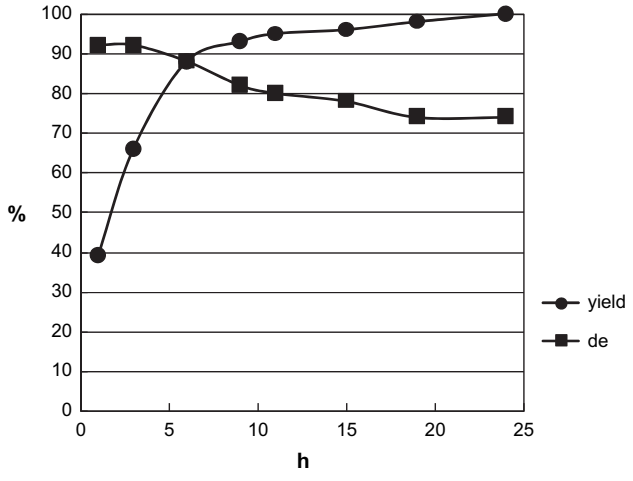
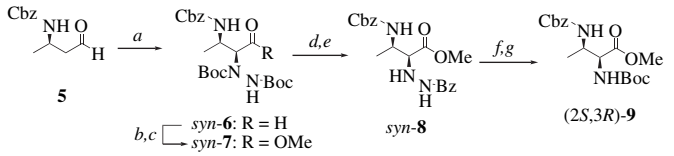


Figure 1.

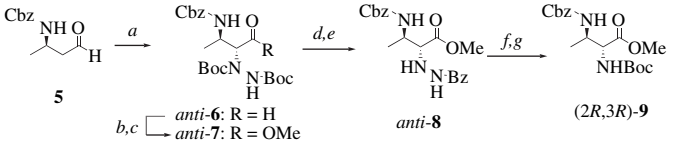
Using the optimized conditions, the synthesis of the Dab derivatives was carried out as shown in Schemes 3 and 4. After the (*R*)-proline-catalyzed α-hydrazination reaction of **5**, the obtained *syn*-**6** with a small amount of *anti*-**6** (*syn*/*anti*=95/5) was oxidized with sodium chlorite, and the resulting carboxylic acid was esterified to afford the ester *syn*-**7** in 75% yield in three steps.

Fortunately, the minor diastereoisomer *anti*-**7** could be separated by silica gel column chromatography. The conversion to the *N*-benzohydrazide *syn*-**8** for the N–N bond cleavage was easily achieved in two steps. The Boc groups of *syn*-**7** were deprotected with trifluoroacetic acid, and the resulting hydrazine was selectively *N*-benzoylated with benzoic anhydride to produce *syn*-**8** in 99% yield (Scheme 3). Although the direct exposure of *syn*-**7** to SmI_2 in MeOH/THF at room temperature only gave the undesired *N*-deprotected product, the cleavage of the N–N bond of the *N*-benzohydrazide *syn*-**8** rapidly occurred under the same conditions to afford the Dab derivative, which was directly protected with di-*tert*-butyl dicarbonate to furnish the *N*,*N*′-diprotected (2*S*,3*R*)-2,3-diaminobutanoic acid derivative **9** (mp 107 °C, $[\alpha]_D^{23}$ +55.0 (*c* 1.49, $CHCl_3$))[3f,8] in 64% yield in two steps. The overall yield of the pure (2*S*,3*R*)-**9** was 47.5% from **5**.



Scheme 3. Diastereoselective synthesis of the (2*S*,3*R*)-Dab derivative from (*R*)-alanine. Reagents and conditions: (a) $(N\text{-Boc})_2$ (1.2 equiv), (*R*)-proline (30 mol %), CH_3CN (0.2 M), −20 °C, 39 h, 100% conversion, *anti*/*syn*=5/95; (b) $NaClO_2$; (c) MeI, $KHCO_3$, 75% yield (three steps); (d) CF_3CO_2H; (e) Bz_2O, 99% (two steps); f) SmI_2, MeOH/THF; g) $(Boc)_2O$, 64% yield (two steps).

On the other hand, pure *anti*-**9** was obtained using (*S*)-proline instead of (*R*)-proline. The α-hydrazination reaction of **5** using (*S*)-proline at −20 °C for 24 h afforded the *anti*-**6** with an *anti*/*syn* ratio of 97/3 in 93% yield. The obtained *anti*-**6** was converted to the (2*R*,3*R*)-2,3-diaminobutanoic acid derivative **9** with a similar efficiency through a similar route (Scheme 4). A chromatographic purification furnished the pure (2*R*,3*R*)-**9** (mp 78–79 °C, $[\alpha]_D^{23}$ +1.1 (*c* 0.50, $CHCl_3$)).[3f,9]



Scheme 4. Diastereoselective synthesis of the (2*R*,3*R*)-Dab derivative from (*R*)-alanine. Reagents and conditions: (a) $(N\text{-Boc})_2$ (1.2 equiv), (*S*)-proline (30 mol %), CH_3CN (0.2 M), −20 °C, 24 h, 93% conversion yield, *anti*/*syn*=97/3; (b) $NaClO_2$; (c) MeI, $KHCO_3$, 79% yield (three steps); (d) CF_3CO_2H; (e) Bz_2O, 95% (two steps); (f) SmI_2; (g) $(Boc)_2O$, MeOH/THF, 82% yield (two steps).

3. Conclusion

In conclusion, we have developed a new and practical route to the (2*S*,3*R*)- and (2*R*,3*R*)-2,3-diaminobutanoic acid derivatives from (*R*)-alanine using the reagent-controlled diastereoselective α-hydrazination reaction as the key step. This method will provide a simple and secure procedure for the construction of 2,3-diaminobutanoic acid derivatives derived from readily available α-amino acids.

4. Experimental

4.1. General

Melting points were measured with a SIBATA NEL-270 melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO P-1020 polarimeter with a sodium lamp (589 nm). Infrared spectra were recorded on SIMADZU FT IR-8100 and JASCO FT/IR-230 spectrometers. NMR spectra were recorded on JEOL JNM-GSX-400A and JNM-ECP-400 spectrometers with tetramethylsilane as an internal standard, unless otherwise indicated. Mass spectra were measured on a JMX-AX-500 spectrometer. Column chromatography was performed with silica gel BW-820MH or BW-200 (Fuji Davison Co.). HPLC analyses were carried out on the chiral column indicated in each experiment. All commercially available reagents were used as received.

4.2. (*R*)-3-(*N*-Benzyloxycarbonylamino)butanenitrile (4)

To a stirred suspension of Cbz-(*R*)-Ala-OH (71.7 g, 0.321 mol) and $KHCO_3$ (64.3 g, 0.642 mol) in DMF (535 mL) at room temperature was added dropwise iodomethane (36.0 mL, 0.578 mol). After 5 h, the reaction mixture was diluted with water, and extracted with ethyl acetate/*n*-hexane (4/1). The organic layer was washed with water and 5% aqueous sodium sulfite. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the ester as white solids. This crude product was used for the next step without further purification.

To a stirred suspension of the crude ester (ca. 0.321 mol), lithium chloride (27.2 g, 0.64 mol), and $NaBH_4$ (24.3 g, 0.64 mol) in THF (350 mL) at room temperature was added dropwise ethanol (800 mL). After 19 h, the reaction mixture was acidified with 10% aqueous citric acid (500 mL) and concentrated in vacuo. The residue was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the alcohol as white solids. This crude product was used for the next step without further purification.

To a stirred solution of the crude alcohol (ca. 0.321 mol) in pyridine (642 mL) at 0 °C was added portionwise tosyl chloride (91.8 g, 0.482 mol). After stirring the mixture for 6.5 h with gradually warming to room temperature, the reaction mixture was diluted with water. The whole was extracted with ethyl acetate. The combined organic layers were washed with aqueous HCl (4 M in H_2O), water, and saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated in vacuo to give the tosylate as a pale yellow oil. This crude product was used for the next step without further purification.

To a stirred solution of the crude tosylate (ca. 0.321 mol) in DMSO (486 mL) at room temperature was added powdered KCN (31.4 g, 0.482 mol). After stirring the mixture at 60 °C for 17 h, the reaction mixture was diluted with water, and the resulting mixture was extracted with ethyl acetate/*n*-hexane (4/1). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=5/2) to give the product (53.2 g, 76% in four steps) as white solids: mp 43–44 °C (diethyl ether/*n*-hexane) (lit.[6] mp 46–47); $[\alpha]_D^{23}$ +68.2 (*c* 1.00, $CHCl_3$) (lit.[6] $[\alpha]_D^{23}$ −76.0 (*c* 0.5, $CHCl_3$) for (*S*)-**4**); IR (ATR) 3328, 2987, 2243, 1685, 1532, 1454, 1335, 1256, 1217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, *J*=6.8 Hz, 3H), 2.56 (dd, *J*=4, 16.8 Hz, 1H), 2.77 (dd, *J*=5.4, 16.6 Hz, 1H), 3.98–4.09 (m, 1H), 4.87 (br s, 1H), 5.06–5.15 (m, 2H), 7.31–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 24.9, 43.6, 66.9, 117.1, 128.0, 128.2, 128.3, 128.5, 136.0, 155.3; HRMS-FAB calcd for $C_{12}H_{15}N_2O_2$ $[M+H]^+$ 219.1134, found 219.1120. Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.93; H, 6.44; N, 12.58.

4.3. (*R*)-3-(*N*-Benzyloxycarbonylamino)butanal (5)

To a stirred solution of the nitrile **4** (7.40 g, 33.9 mmol) in toluene (424 mL) at −40 °C was added dropwise DIBAL-H (0.95 M in hexane, 75.0 mL, 71.2 mmol) under argon atmosphere. After 1 h, the reaction was quenched by a careful addition of diethyl ether

(300 mL) and aqueous tartaric acid (2 M in H_2O, 500 mL) at −40 °C. The resulting mixture was vigorously stirred at room temperature. After 2 h, the mixture was separated and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=2/1) to give the product (3.90 g, 52%) as a colorless oil: $[\alpha]_D^{23}$ +14.6 (*c* 1.00, $CHCl_3$) (lit.[7] $[\alpha]_D^{23}$ +16.9 (*c* 0.7, CH_2Cl_2)); IR (ATR): 3308, 2972, 1685, 1532, 1454, 1337, 1252 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, *J*=6.8 Hz, 3H), 2.66 (dq, *J*=5.6, 17.2 Hz, 2H), 4.15–4.25 (m, 1H), 4.95 (br s, 1H), 5.04–5.15 (m, 2H), 7.30–7.38 (m, 5H), 9.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 42.8, 50.0, 66.6, 128.0, 128.1, 128.5, 136.2, 155.5, 200.8; HRMS-FAB calcd for $C_{12}H_{16}N_1O_3$ $[M+H]^+$ 222.1130, found 222.1112.

4.4. Methyl (2*S*,3*R*)-2-(*N*-*tert*-butyloxycarbonyl-*N*′-*tert*-butyloxycarbonylhydrazino)-3-benzyloxycarbonylamino butyrate (*syn*-7)

To a stirred mixture of di-*tert*-butyl azodicarboxylate (2.82 g, 12.2 mmol) and **5** (2.26 g, 10.2 mmol) in acetonitrile (51 mL) at −20 °C was added (*R*)-proline (353 mg, 3.07 mmol). After stirring the mixture at −20 °C for 39 h under argon atmosphere, the reaction mixture was diluted with ethyl acetate and brine. The mixture was separated, and the organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to give *syn*-**6** (*syn*/*anti*=95/5, >99% conversion) as a yellow oil. This crude product was used for the next step without further purification. The diastereomeric ratio was determined by the aldehyde proton of the ^1H NMR ($CDCl_3$ at 55 °C, *syn*: 9.70 ppm, *anti*: 9.63 ppm, starting material: 9.76 ppm) spectrum.

To a stirred mixture of *syn*-**6** (ca. 10.2 mmol), 2-methyl-2-butene (5.4 mL, 51.0 mmol), NaH_2PO_4 (2.45 g, 20.4 mmol) in *tert*-butyl alcohol (41 mL) and water (14 mL) at 0 °C was added dropwise a solution of $NaClO_2$ (purity 79%, 4.67 g, 40.8 mmol) in water (14 mL). After stirring the mixture at room temperature for 3 h, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with aqueous $Na_2S_2O_3$ (0.5 M in H_2O) and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give the carboxylic acid. This crude product was used for the next step without further purification.

To a stirred mixture of the crude carboxylic acid (ca. 10.2 mmol) and $KHCO_3$ (3.06 g, 30.6 mmol) in DMF (20.4 mL) at room temperature was added dropwise iodomethane (1.3 mL, 20.9 mmol). After 12 h, the reaction mixture was diluted with water and extracted with diethyl ether. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude ester *syn*-**7** as a red oil. This crude product was purified by silica gel column chromatography ($CHCl_3$/diethyl ether=30/1) to give pure *syn*-**7** (3.68 g, 75%, *syn*/*anti* >99/1) as a colorless oil: $[\alpha]_D^{24}$ +4.3 (*c* 0.28, $CHCl_3$); IR (ATR) 3342, 2979, 1697, 1540, 1456, 1393, 1367, 1311, 1234 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ at 55 °C) δ 1.30 (d, *J*=6.8 Hz, 3H), 1.44 (s, 18H), 3.71 (s, 3H), 4.36–4.41 (m, 1H), 4.69 (d, *J*=5.6 Hz, 1H), 5.02–5.11 (m, 2H), 7.25–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$ at 55 °C) δ 18.2, 28.0 28.1, 46.9, 52.1, 62.9, 66.6, 81.2, 82.1, 126.8, 127.8, 127.9, 128.3, 136.5, 155.2, 155.9, 169.2; HRMS-FAB calcd for $C_{23}H_{36}N_3O_8$ $[M+H]^+$ 482.2502, found 482.2471.

4.5. Methyl (1*R*,2*S*)-2-(*N*′-benzoylhydrazino)-3-benzyloxycarbonylaminobutyrate (*syn*-8)

To a stirred solution of *syn*-**7** (1.92 g, 3.99 mmol) in CH_2Cl_2 (15 mL) at room temperature was added trifluoroacetic acid (0.5 mL). After stirring the mixture for 12 h, the reaction mixture was concentrated in vacuo to give the trifluoroacetic acid salt as a yellow oil. This crude product was used for the next step without any further purification.

To a stirred solution of the crude trifluoroacetic acid salt (ca. 3.99 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added benzoic anhydride (904 mg, 4.00 mmol) and diisopropylethylamine (2.8 mL, 16.1 mmol), and the resulting mixture was gradually warmed to room temperature. After stirring the mixture for 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=1/2) to give the product *syn*-**8** (1.52 g, 99%) as a colorless oil: $[\alpha]_D^{22}$ −57.8 (*c* 0.91, $CHCl_3$); IR (ATR): 3313, 1699, 1646, 1523, 1454, 1213, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, *J*=6.8 Hz, 3H), 3.58 (d, *J*=6.1 Hz, 1H), 3.74 (s, 3H,), 4.24–4.30 (m, 1H), 5.09 (d, *J*=12.2 Hz, 1H), 5.13 (d, *J*=12.2 Hz, 1H), 5.14 (d, *J*=8.8 Hz, 1H), 5.44 (br s, 1H), 7.29–7.36 (m, 5H), 7.44 (t, *J*=7.6 Hz, 2H), 7.52 (d, *J*=7.6 Hz, 1H), 7.75 (d, *J*=7.6 Hz, 2H), 8.23 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 47.0, 52.3, 66.6, 66.7, 126.9, 127.9, 128.0, 128.4, 128.5, 131.8, 132.3, 136.2, 156.2, 167.2, 171.2; HRMS-FAB calcd for $C_{20}H_{24}N_3O_5$ $[M+H]^+$ 386.1716, found 386.1689.

4.6. Methyl (2*S*,3*R*)-3-benzyloxycarbonylamino-2-*tert*-butoxycarbonylamino butyrate (*syn*-9)

To a stirred solution of *syn*-**8** (92.5 mg, 0.240 mmol) in MeOH (1.8 mL) at 0 °C was added SmI_2 (0.1 M in THF, 14.4 mL, 1.44 mmol) under argon atmosphere and the resulting mixture was stirred at room temperature. After 20 min, an additional SmI_2 (0.1 M in THF, 5.0 mL, 0.5 mmol) was added at room temperature. After additional 30 min, the reaction was quenched with aqueous $Na_2S_2O_3$ solution (10% in H_2O, 30 mL), and the resulting mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to give the amine as a brown oil. This crude product was used for the next step without further purification.

To a stirred solution of the crude amine (ca. 0.240 mmol) and $NaHCO_3$ (65.1 mg, 0.775 mmol) in 1,4-dioxane (1 mL) and H_2O (1 mL) at 0 °C was added Boc_2O (71.1 mg, 0.326 mmol) and the resulting mixture was gradually warmed to room temperature. After 10 h, the reaction was quenched with 10% aqueous citric acid, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=3/1 to 2/1) to give *syn*-**9** (55.8 mg, 64%) as colorless needles: mp 107 °C (diethyl ether/*n*-hexane); $[\alpha]_D^{23}$ +55.0 (*c* 1.49, $CHCl_3$); IR (ATR): 1719, 1680, 1501, 1253, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, *J*=6.8 Hz, 3H), 1.44 (s, 9H), 3.75 (s, 3H), 4.23–4.27 (m, 1H), 4.33 (dd, *J*=8.4, 3.7 Hz, 1H), 4.92 (d, *J*=8.4 Hz, 1H), 5.05 (d, *J*=14.7 Hz, 1H), 5.08 (d, *J*=12.1 Hz, 1H), 5.36 (d, *J*=7.3 Hz, 1H), 7.30–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 28.2, 49.3, 52.6, 57.6, 66.8, 80.2, 128.0, 128.1, 128.5, 136.3, 155.6, 171.3; HRMS-FAB calcd for $C_{18}H_{27}N_2O_6$ $[M+H]^+$ 367.1869, found 367.1833. Anal. Calcd for $C_{18}H_{26}N_2O_6$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.75; H, 7.37; N, 7.43. The HPLC analysis of the crude *syn*-**9** was carried out using CHIRALCEL OJ-H (*n*-hexane/*i*-PrOH=95/5, 1.0 mL/min, t_R=12.0 min (major) and 16.6 min (minor)). The optical purity of the *syn*-**9** was >99% ee.[8]

4.7. Methyl (2*R*,3*R*)-2-(*N*-*tert*-butyloxycarbonyl-*N*′-*tert*-butyloxycarbonylhydrazino)-3-benzyloxycarbonylamino butyrate (*anti*-7)

To a stirred mixture of di-*tert*-butyl azodicarboxylate (3.92 g, 17.0 mmol) and **5** (3.14 g, 14.2 mmol) in acetonitrile (43 mL) at −20 °C was added (*S*)-proline (490 mg, 4.26 mmol). After stirring the mixture at −20 °C for 24 h under argon atmosphere, the reaction mixture was diluted with ethyl acetate and brine. The mixture was separated, and the organic layer was dried over Na_2SO_4,

filtered, and concentrated in vacuo to give *anti*-**6** (*anti*/*syn*=97/3, 93% conversion yield) as a yellow oil. This crude product was used for the next step without any further purification. The diastereomeric ratio was determined by the aldehyde proton of ^{1}H NMR ($CDCl_3$ at 55 °C, *syn*: 9.70 ppm, *anti*: 9.63 ppm, starting material: 9.76 ppm) spectrum.

To a stirred mixture of *anti*-**6** (ca. 14.2 mmol), 2-methyl-2-butene (7.6 mL, 71.8 mmol), NaH_2PO_4 (3.41 g, 28.4 mmol) in *tert*-butyl alcohol (53 mL) and H_2O (18 mL) at 0 °C was added dropwise a solution of $NaClO_2$ (purity 79%, 6.50 g, 56.9 mmol) in H_2O (18 mL). After stirring the mixture for 3 h at room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with aqueous $Na_2S_2O_3$ (0.5 M in H_2O) and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give the carboxylic acid as a yellow oil. This crude product was used for the next step without further purification.

To a stirred mixture of the crude carboxylic acid (ca. 14.2 mmol) and $KHCO_3$ (4.26 g, 42.6 mmol) in DMF (30 mL) at room temperature was added dropwise iodomethane (1.8 mL, 28.9 mmol). After 12 h, the reaction mixture was diluted with water and extracted with diethyl ether. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude ester as a red oil. This crude product was purified by silica gel column chromatography ($CHCl_3$/diethyl ether=30/1) to give pure *anti*-**7** (5.40 g, 79%, *anti*/*syn* >99/1) as a colorless oil: $[\alpha]_D^{24}$ +26.5 (*c* 0.89, $CHCl_3$); IR (ATR) 3337, 2979, 1712, 1515, 1392, 1367, 1311, 1234, 1148 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ at 55 °C) δ 1.17 (d, *J*=6.8 Hz, 3H), 1.43 (s, 9H), 1.47 (s, 9H), 3.74 (s, 3H), 4.47–4.52 (m, 1H), 5.08–5.15 (m, 3H), 6.20 (br s, 1H), 6.68 (br s, 1H), 7.25–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$ at 55 °C) δ 16.6, 28.0, 28.2, 29.7, 46.8, 52.2, 61.4, 66.6, 77.2, 81.7, 82.7, 127.8, 128.0, 128.4, 137.0, 155.0, 155.9, 169.9; HRMS-FAB calcd for $C_{23}H_{36}N_8O_3$ $[M+H]^+$ 482.2502, found 482.2480.

4.8. Methyl (1*R*,2*R*)-2-(*N*′-benzoylhydrazino)-3-benzyloxycarbonylamino butyrate (*anti*-8)

To a stirred solution of *anti*-**7** (1.22 g, 2.53 mmol) in CH_2Cl_2 (10.5 mL) at room temperature was added trifluoroacetic acid (3.5 mL). After stirring the mixture for 3 h, the reaction mixture was concentrated in vacuo to give the trifluoroacetic acid salt as a yellow oil. This crude product was used for the next step without further purification.

To a stirred solution of the crude product (ca. 2.53 mmol) in CH_2Cl_2 (12.6 mL) at 0 °C was added benzoic anhydride (572 mg, 2.53 mmol) and diisopropylethylamine (1.8 mL, 10.1 mmol) and the resulting mixture was gradually warmed to room temperature. After 4 h, the reaction was quenched with saturated aqueous $NaHCO_3$, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=1/1) to give *anti*-**8** (1.09 g, 95%) as white solids: $[\alpha]_D^{20}$ +37.3 (*c* 1.40, $CHCl_3$); IR (ATR): 3313, 1699, 1646, 1523, 1454, 1213, 1054 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ at 55 °C) δ 1.24 (3H, d, *J*=6.8 Hz), 3.77 (3H, s), 3.82–3.84 (1H, m), 4.23–4.28 (1H, m), 5.09 (1H, d, *J*=12.4 Hz), 5.17 (1H, d, *J*=12.4 Hz), 5.21 (1H, br s), 5.42 (1H, br s), 7.26–7.37 (5H, m), 7.42 (2H, t, *J*=7.4 Hz), 7.50 (1H, m), 7.77 (2H, d, *J*=7.2 Hz), 8.32 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 46.3, 52.2, 65.8, 66.9, 126.9, 127.9, 128.0, 128.4, 128.6, 131.9, 132.3, 136.2, 156.7, 166.9, 170.6; HRMS-FAB calcd for $C_{20}H_{24}N_3O_5$ $[M+H]^+$ 386.1716, found 386.1699.

4.9. Methyl (2*R*,3*R*)-3-benzyloxycarbonylamino-2-*tert*-butoxycarbonylamino butyrate (*anti*-9)

To a stirred solution of *anti*-**8** (512 mg, 1.33 mmol) in CH_3OH (6.7 mL) at 0 °C was added SmI_2 (0.1 M in THF, 40 mL, 4.00 mmol) under argon atmosphere. After 15 min, the reaction was quenched with aqueous $Na_2S_2O_3$ solution (1.0 M in H_2O), and the resulting mixture was filtered through a pad of Celite. The filtrate was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give the amine as a brown oil. This crude product was used for the next step without further purification.

To a stirred solution of the crude amine (ca. 1.33 mmol) and $NaHCO_3$ (358 mg, 4.26 mmol) in 1,4-dioxane (3.0 mL) and H_2O (3.0 mL) at 0 °C was added Boc_2O (350 mg, 1.60 mmol) and the resulting mixture was gradually warmed to room temperature. After 12 h, the reaction was quenched by the addition of 10% aqueous citric acid solution, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=2/1) to give the product *anti*-**9** (401 mg, 82%) as colorless needles: mp 78–79 °C (diethyl ether/hexane); $[\alpha]_D^{23}$ +1.1 (*c* 0.50, $CHCl_3$); IR (ATR) 3348, 1744, 1687, 1528, 1319, 1266, 1228 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, d, *J*=6.8 Hz), 1.44 (9H, s), 3.76 (3H, s), 4.20 (1H, br s), 4.49 (1H, dd, *J*=8.0, 3.2 Hz), 5.07–5.15 (2H, m), 5.36 (1H, br s), 7.27–7.37 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 28.2, 28.3, 49.1, 52.6, 57.4, 66.8, 80.4, 128.1, 128.1, 128.5, 136.3, 155.8, 171.1; HRMS-FAB calcd for $C_{18}H_{27}N_2O_6$ $[M+H]^+$ 367.1869, found 367.1860. Anal. Calcd for $C_{18}H_{26}N_2O_6$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.93; H, 7.03; N, 7.39. The HPLC analysis of the crude product was carried out using CHIRALCEL AS-H (*n*-hexane/*i*-PrOH=95/5, 1.0 mL/min, t_R=13.9 min (minor) and 18.4 min (major)). The optical purity of the *anti*-**9** is >99% ee.[9]

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Supplementary data

The HPLC charts and ^{1}H NMR spectra of (2*R*,3*R*)-**9** and (2*S*,3*R*)-**9**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2009.08.064.

References and notes

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8. The physical data of our synthetic (2*S*,3*R*)-**9** were inconsistent with the reported value (oil, $[\alpha]_D$ −26.3 (*c* 0.56, $CHCl_3$) for (2*R*,3*S*)-isomer).[3f] This discrepancy was solved by HPLC analysis of the synthetic (2*S*,3*R*)-**9**, and its optical purity was unambiguously confirmed by the HPLC analysis of the synthetic (2*R*,3*S*)-**9** and (2*S*,3*R*)-**9**. See Supplementary data.
9. The physical data of our synthetic (2*R*,3*R*)-**9** were inconsistent with the reported value (oil, $[\alpha]_D$=−19.8 (*c* 0.28, $CHCl_3$)).[3f] The optical purity of the synthetic (2*R*,3*R*)-**9** was unambiguously confirmed by HPLC analysis of the synthetic (2*R*,3*R*)-**9** and (2*S*,3*S*)-**9**. See Supplementary data.