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ASYMMETRIC DIECKMANN CONDENSATION VIA MEMORY OF CHIRALITY: SYNTHESIS OF THE KEY INTERMEDIATE FOR AS-3201, AN ALDOSE REDUCTASE INHIBITOR

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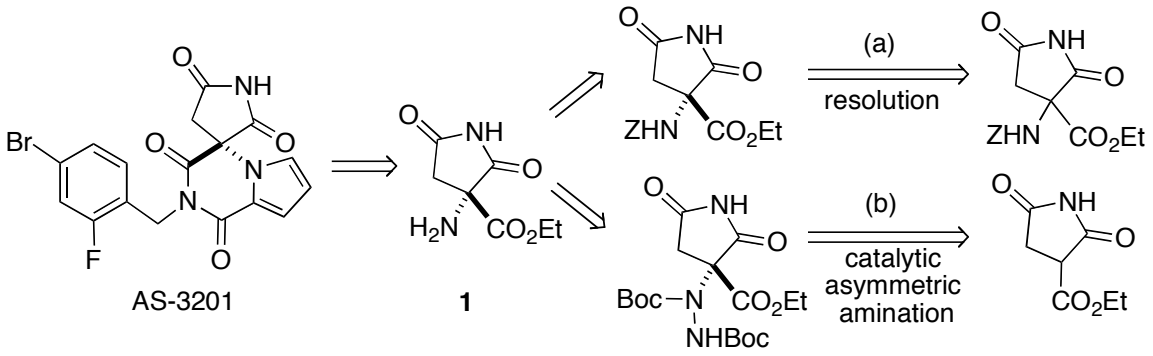
Abstract – Asymmetric Dieckmann condensation via memory of chirality has been developed. A key intermediate for the synthesis of AS-3201, an aldose reductase inhibitor, has been prepared in 94% ee by asymmetric Dieckmann condensation of **8** derived from L-aspartic acid.

INTRODUCTION

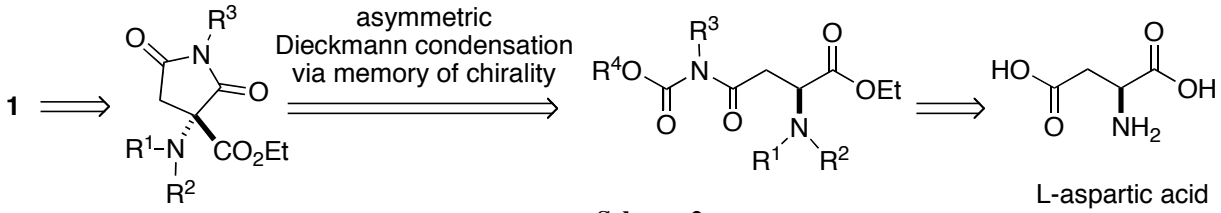
AS-3201 is a structurally novel aldose reductase inhibitor developed by Dainippon Sumitomo Pharma Co., Ltd., and is an orally available candidate for the treatment of diabetic disorders.[1] The key intermediate for the synthesis of AS-3201 is succinimide **1** with a tetrasubstituted carbon center (Scheme 1). Optically pure **1** has been prepared through optical resolution of the racemate with a stoichiometric amount of cinchonidine (Scheme 1, a).[1] Recently, Shibasaki and co-workers has developed an excellent method for the preparation of **1** via catalytic asymmetric amination (Scheme 1, b).[2] Both of the synthetic routes employ racemic precursors of **1**. We report here preparation of **1** by asymmetric Dieckmann condensation of optically active amino acid derivatives derived from L-aspartic acid in the absence of external chiral sources, where L-aspartic acid is employed as a functionalized carbon resource as well as a chiral source for asymmetric induction; *i.e.,* memory of chirality (Scheme 2).

RESULTS AND DISCUSSION

The most straightforward synthesis of **1** might involve Dieckmann condensation of optically active precursors derived from cheap and readily available L-aspartic acid (Scheme 2). However, this has never been achieved due to the expected racemization during enolate formation. We have developed asymmetric intramolecular alkylation of amino acid derivatives via memory of chirality, which proceeds



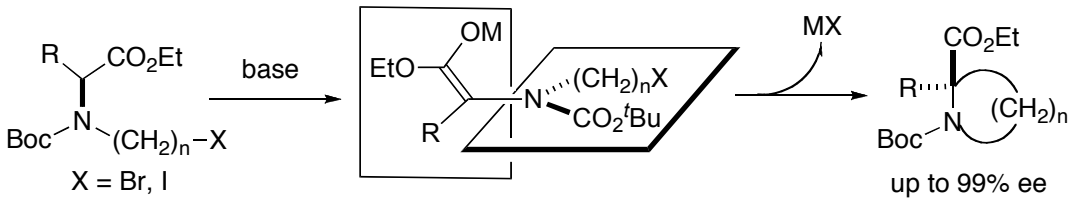
Scheme 1



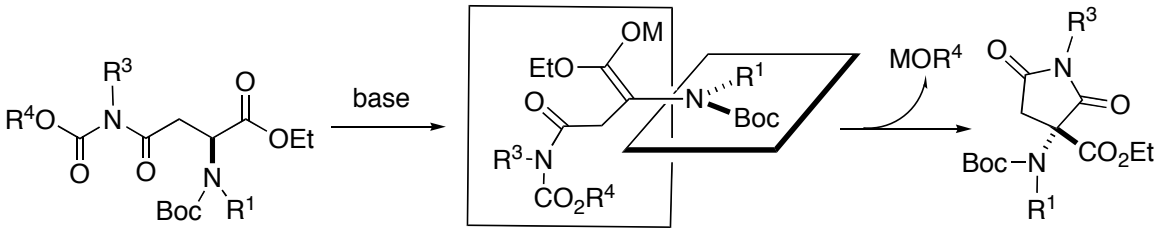
Scheme 2

via axially chiral enolate intermediates to give cyclic amino acids with a tetrasubstituted carbon center (Scheme 3).[3] We had expected that asymmetric Dieckmann condensation could proceed also via axially chiral enolate intermediates to give optically active succinimides with a tetrasubstituted carbon center (Scheme 4).

We chose *N*-*tert*-butoxycarbonyl(Boc)-*N*-methoxymethyl(MOM)-aspartic acid derivative **2** as a precursor of asymmetric Dieckmann condensation (Scheme 5), since Boc- and MOM-substituents on the nitrogen are critical for the generation of axially chiral enolate intermediates.[4] Commercially available L-aspartic

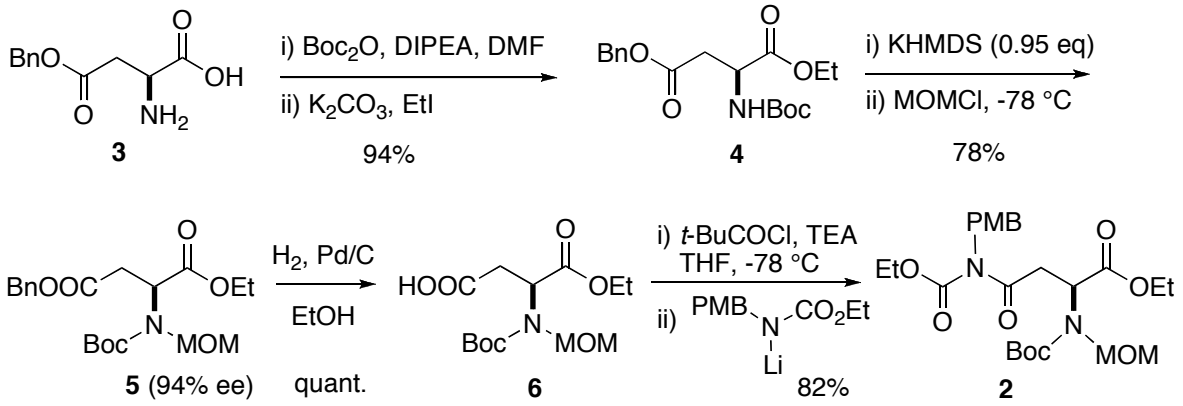


Scheme 3



Scheme 4

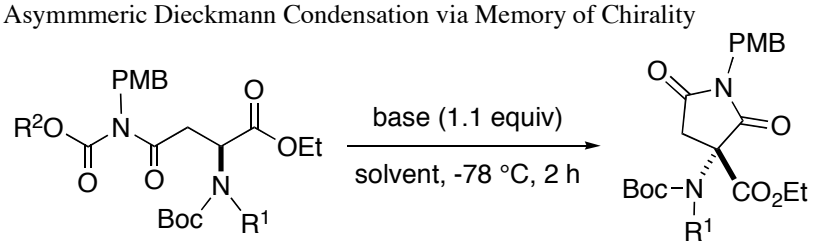
acid β-benzyl ester (**3**) was transformed to *N*-Boc α-ethyl ester **4** in 94% yield. Treatment of **4** with 0.95 equiv. of potassium hexamethyldisilazide (KHMDS) followed by addition of chloromethyl methyl ether at -78 °C gave *N*-Boc-*N*-MOM derivative **5** in 78% yield with partial racemization (94% ee). Carboxylic acid **6** obtained by catalytic hydrogenolysis of **5** was transformed *in situ* to a mixed anhydride with pivaloyl chloride at -78 °C and it was treated with lithium *N*-ethoxycarbonyl-*N*-*p*-methoxybenzylamide to give **2** in 82% yield.



Scheme 5

Asymmetric Dieckmann condensation of **2** was investigated (Table 1). Since KHMDS was a base of choice for asymmetric cyclization via memory of chirality in retention of configuration,[3] Dieckmann condensation of **2** was examined with KHMDS in various solvents. Treatment of **2** with 1.1 equiv. of KHMDS in THF gave **10** in 81% ee but in only 10% yield with 74% recovery of **2** (entry 1). Increasing the amount of KHMDS to 2.2 equiv did not improve the yield (entry 2). Use of DMF as a solvent, which was the best solvent for asymmetric cyclization via memory of chirality,[3] did not give the desired cyclization product (entry 3). Further screening of the solvents (toluene, ether, diisopropyl ether, cyclopropyl methyl ether, *tert*-butyl methyl ether)[5] showed that *tert*-butyl methyl ether gave the best result (78% ee and 24% yield, entry 4). While addition of TMEDA slightly improved the ee of asymmetric Dieckmann condensation (81% ee, entry 5), the reaction did not take place in the presence of 18-crown-6

Table 1. Asymmmeric Dieckmann Condensation via Memory of Chirality

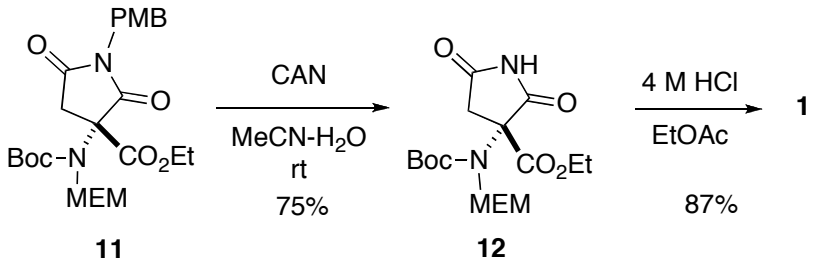


entry	substrate[a]	R^1	R^2	base	solvent	product	yield (%)[b]	ee (%)[c]
1	**2** (94)	MOM	Et	KHMDS	THF	**10**	10 (74)	81
2	**2** (94)	MOM	Et	KHMDS[d]	THF	**10**	10	79
3[e]	**2** (94)	MOM	Et	KHMDS	DMF	**10**	~0	-
4	**2** (94)	MOM	Et	KHMDS	*t*-BuOMe	**10**	24	78
5[f]	**2** (92)	MOM	Et	KHMDS	*t*-BuOMe	**10**	23	81
6[g]	**2** (94)	MOM	Et	KHMDS	*t*-BuOMe	**10**	~0	-
7	**2** (94)	MOM	Et	LDA	*t*-BuOMe	**10**	~0	-
8	**2** (94)	MOM	Et	LiTMP	*t*-BuOMe	**10**	~0	-
9	**7** (90)	MOM	Bn	KHMDS	*t*-BuOMe	**10**	25	82
10	**8** (96)	MEM	Et	KHMDS	*t*-BuOMe	**11**	37	94
11	**9** (92)	MEM	Bn	KHMDS	*t*-BuOMe	**11**	25[h]	90

a) Numbers in the parentheses indicate % ee of the substrate. b) Isolated yield. A number in the parenthesis indicates % recovery of the starting material. c) (*R*)-isomer was obtained in each run. d) 2.2 Equiv. of the base was used. e) The reaction was run at -60 °C. f) TMEDA (5 equiv) was added. g) 18-crown-6 (1.1 equiv) was added. h) The substrate of 50% ee was recovered in 54% yield.

(entry 6). Addition of other additives such as tetrabutylammonium halides, LiOTf, $ZnBr_2$, $MgBr_2$, or DMPU did not improve the yield of the Dieckmann condensation (data not shown). LDA and LiTMP did not promote Dieckmann condensation (entries 7 and 8). Asymmetric Dieckmann condensation of other precursors **7-9** was examined (entries 9-11). Benzyl carbamate **7** gave the desired product **10** in 82% ee in 25% yield (entry 9). Use of an *N*-methoxyethoxymethyl (MEM) group instead of a MOM group improved both yield (37%) and ee (94%) (entry 10). The corresponding benzyl carbamate **9** gave the product **11** in 90% ee and 25% yield (entry 11). The low yield seems not due to incomplete enolate formation because the ee of the recovered substrate was 50%. Thus, asymmetric Dieckmann condensation via memory of chirality has been developed for the first time. The reactions took place highly enantioselectively probably via axially chiral enolates, albeit in low yields.

Succinimide **11** (94% ee) obtained by asymmetric Dieckmann condensation was treated with CAN to give **12** in 75% yield, which was then treated with 4 M HCl to give **1** in 87% yield. Succinimide **10** with a MOM group (81% ee) was also transformed to **1** by the same treatment in 73% yield. Since the absolute



Scheme 6

configuration of **1** is known to be *R*,[1] these transformations indicate that the present asymmetric Dieckmann condensation proceeded in retention of configuration.

In conclusion, we have developed asymmetric Dieckmann condensation via memory of chirality. The product was transformed to the key intermediate for the synthesis of AS-3201.

EXPERIMENTAL

NMR spectra were obtained with a JEOL JMN 400 spectrometer, chemical shifts being given in ppm units (tetramethylsilane or chloroform as internal standards, indicating 0 or 7.24, respectively). IR spectra were recorded with a JACSO FT/IR–300 spectrometer. Specific rotation was measured with a Horiba SEPA–200 automatic digital polarimeter. MS spectra were recorded with a JEOL JMS–DX300 mass spectrometer. TLC analysis and preparative TLC were performed on commercial glass plates bearing a 0.25 mm layer and 0.5 mm layer of Merck Kiesel–gel 60 F_{254}, respectively. Silica gel chromatography was carried out Wakogel C–200, Fuji Silysia BW–1277H, or Nacalai Tesque Silica gel 60 (150–325 mesh). Dry solvents (THF, ether, hexane, dichloromethane, and toluene; <50 ppm water contents) were purchased from Kanto Chemical CO., Inc. and used without further treatment.

(*S*)-4-Benzyl 1-ethyl 2-(*tert*-butoxycarbonylamino)succinate (4)

A suspension of (*S*)-2-amino-4-(benzyloxy)-4-oxobutanoic acid **3** (10.0 g, 45 mmol), diisopropylethylamine (9.40 mL, 54 mmol) and di-*tert*-butyl dicarbonate (11.7 g, 54 mmol) in DMF (300 mL) was stirred for 5 h at rt. Ethyl iodide (7.20 mL, 90 mmol) and K_2CO_3 (12.4 g, 90 mmol) were added to the solution, and the resulting mixture was stirred for 12 h at rt. The reaction mixture was diluted with EtOAc and washed with water twice, brine, dried over Na_2SO_4, filtered and evaporated *in vacuo.* The residue was purified by column chromatography (SiO_2, hexane: EtOAc= 7:1) to give **4** (14.8 g, 94% yield).

Colorless oil. $[\alpha]_D^{20}$ (>99% ee) 22 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (m, 5H), 5.53 (d, *J*=8.2 Hz, 1H), 5.12 (s, 2H), 4.56 (dt, *J*=8.2, 5.0 Hz, 1 H), 4.15 (q, *J*=7.3 Hz, 2H), 3.04 (dd, *J*=16.9, 5.0 Hz, 1 H), 2.87 (dd, *J*=16.9, 5.0 Hz, 1 H), 1.44 (s, 9H), 1.21 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 171.1, 155.8, 135.8, 128.9, 128.74, 128.65, 80.4, 67.1, 62.1, 50.4, 37.2, 28.6, 14.4. IR

(neat, cm^{-1}) 2979, 2933, 1737, 1718, 1499, 1367, 1165, 1028, 698. MS (EI) *m/z* (rel intensity) 351 (M^+, 1), 295 (40), 278 (50), 222 (60), 178 (100). Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99%. Found: C, 61.40; H, 7.07; N, 4.07%.

(*S*)-4-Benzyl 1-ethyl 2-(*tert*-butoxycarbonyl(methoxymethyl)amino)succinate (5)

Lithium hexamethyldisilazide (0.28 mmol) in THF (1.0 mL) was added slowly to a solution of **4** (105 mg, 0.30 mmol) in THF (3.0 mL) and DMPU (0.36 mL, 3.0 mmol) at -78 °C under Ar. After stirring for 30 min at -78 °C, MOMCl (68 μL, 0.90 mmol) was added and the resulting mixture was stirred for additional 15 h. The reaction mixture was poured into saturated aq. NH_4Cl solution and extracted with EtOAc twice. The combined organic phase was washed with saturated aq. $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by preparative TLC (hexane: 1, 4-dioxane= 4: 1) to give **5** (85 mg, 80% yield). The enantiomeric purity was determined to be 94% ee: Daicel Chiralpak AD-H, hexane: EtOH= 98:2, flow 1.0 mL/min., 254 nm, minor peak 18.9 min, major peak 23.7 min.

Colorless oil. $[\alpha]_D^{20}$ (94% ee) -38 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.14 (ABq, $\Delta\nu_{AB}$=12.6 Hz, *J*=12.8 Hz, 2H), 4.85, 4.77 (two d, *J*=11.0 Hz, 11.0 Hz, ratio=4:3, 1H), 4.67 (d, *J*=11.0 Hz, 1H), 4.55 (two t, *J*= 6.9 Hz, 6.9 Hz, ratio=3:4, 1H), 4.25-4.09 (m, 2H), 3.34, 3.31 (two s, ratio=4:3, 3H), 3.26 (dd, *J*=16.9, 6.9 Hz, 1H), 2.90, 2.81 (two dd, *J*=16.9, 6.9 Hz, 16.9, 6.9 Hz, ratio=3:4, 1H), 1.47, 1.43 (two s, ratio=3:4, 9H), 1.27, 1.22 (two t, *J*=7.3Hz, 7.3Hz, ratio=4:3, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5 and 171.3 (rotamer), 170.8 and 170.7 (rotamer), 155.0 and 154.7 (rotamer), 136.2 and 136.0 (rotamer), 129.0, 128.9, 128.8 and 128.6 (rotamer), 82.0 and 81.7 (rotamer), 80.05 and 79.97 (rotamer), 67.1 and 66.9 (rotamer), 62.0 and 61.9 (rotamer), 56.5, 56.1, 36.8 and 35.8 (rotamer), 28.5, 14.5. IR (neat, cm^{-1}) 2979, 2934, 1739, 1712, 1368, 1301, 1159, 1093, 861, 698. MS (EI) *m/z* (rel intensity) 395 (M^+, 1), 294 (50), 264 (20), 222 (70), 160 (30), 91 (100), 57 (30). Anal. Calcd for $C_{20}H_{29}NO_7$: C, 60.74; H, 7.39; N, 3.54%. Found: C, 60.46; H, 7.37; N, 3.57%.

(*S*)-3-(*tert*-Butoxycarbonyl(methoxymethyl)amino)-4-ethoxy-4-oxobutanoic acid (6)

A suspension of **5** (2.40 g, 6.1 mmol) and 10% Pd/C (300 mg) in EtOH (40 mL) was stirred under H_2 at room temperature for 12 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to give **6** (1.85 g, quant).

Colorless oil. $[\alpha]_D^{20}$ (94% ee) -47 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89, 4.82 (two d, *J*=11.0 Hz, 11.0 Hz, ratio=4:3, 1H), 4.73 (d, *J*=11.0 Hz, 1H), 4.50 (two t, *J*= 6.9 Hz, 6.9 Hz, ratio=3:4, 1H), 4.29-4.12 (m, 2H), 3.37, 3.35 (two s, ratio=4:3, 3H), 3.26 (dd, *J*=17.0, 6.9 Hz, 1H), 2.88, 2.79 (two dd, *J*=17.0, 6.9 Hz, 17.0, 6.9 Hz, ratio=3:4, 1H), 1.48, 1.45 (two s, ratio=3:4, 9H), 1.30, 1.26 (two t, *J*=6.8Hz, 6.8Hz, ratio=4:3, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 and 176.5 (rotamer), 170.9 and 170.8 (rotamer), 155.0 and 154.78 (rotamer), 82.3 and 82.0 (rotamer), 80.1 and 80.0 (rotamer), 62.2 and

62.1 (rotamer), 56.5, 56.3 and 56.2 (rotamer), 36.6 and 35.7 (rotamer), 28.6, 14.5. IR (neat, cm^{-1}) 2978, 2924, 1739, 1712, 1369, 1301, 1161, 1094. MS (EI) *m/z* (rel intensity) 305 (M^+, 1), 274 (10), 232 (30), 204 (80), 174 (60), 160 (20), 132 (100), 57 (30). HRMS (EI) calcd for $C_{13}H_{23}NO_7$: 395.1475, found: 395.1485.

(*S*)-Ethyl 9-(4-methoxybenzyl)-5-(methoxymethyl)-2,2-dimethyl-4,8,10-trioxo-3,11-dioxa-5,9-diazatridecane-6-carboxylate (2)

Triethylamine (0.53 mL, 3.8 mmol) and pivaloyl chloride (0.26 mL, 2.1 mmol) were added to a solution of **6** (567 mg, 1.9 mmol) in THF (20 mL) at -78 °C under Ar, and the mixture was stirred at -78 °C for 2 h. A solution of lithium *N*-ethoxycarbonyl-*N*-*p*-methoxybenzylamide, prepared by LDA (2.1 mmol in 5.6 mL of THF) and ethyl 4-methoxybenzylcarbamate (439 mg, 2.1 mmol) in THF (4 mL) at 0 °C, was added to the above reaction mixture and the resulting mixture was stirred at -78 °C for 2 h and then at rt for 1 h. The reaction mixture was poured into saturated aq. NH_4Cl solution and extracted with EtOAc twice. The combined organic phase was washed with saturated aq. $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by column chromatography (hexane: 1,4-dioxane= 11: 1) to give **2** (775 mg, 82% yield). The enantiomeric purity was determined to be 94%: Daicel Chiralpak AD-H, hexane: *i*-PrOH= 90:10, flow 0.7 mL/min., 254 nm, minor peak 20.7 min., major peak 26.1 min.

Colorless oil. $[\alpha]_D^{20}$ (94% ee) -35 (*c* 1.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J*=8.2 Hz, 2H), 6.81 (d, *J*=8.2 Hz, 2H), 4.86 (s, 2H), 4.83-4.75 (m, 2H), 4.71 (d, *J*=10.6 Hz, 1H), 4.26-4.10 (m, 4H), 3.92-3.84 (m, 1H), 3.75 (s, 3H), 3.34-3.27 (m, 1H), 3.32, 3.30 (two s, ratio=9:5, 3H), 1.47, 1.45 (two s, ratio=5:9, 9H), 1.30-1.21 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.43 and 173.35 (rotamer), 171.0 and 170.9 (rotamer), 159.0, 155.0 and 154.6 (rotamer), 154.4, 130.0 and 129.9 (rotamer), 129.6, 113.8, 81.4 and 81.1 (rotamer), 79.5 and 79.4 (rotamer), 63.2, 61.5 and 61.3 (rotamer), 56.1, 55.9 and 55.7 (rotamer), 55.3, 46.9, 40.2 and 39.4 (rotamer), 28.3, 14.2. IR (neat, cm^{-1}) 2979, 2935, 1739, 1707, 1514, 1369, 1301, 1248, 1183, 1035. MS (EI) *m/z* (rel intensity) 496 (M^+, 1), 464 (20), 408 (80), 291 (20), 222 (40), 221 (100), 209 (30), 208 (90), 121 (90), 57 (40). Anal. Calcd for $C_{24}H_{36}N_2O_9$: C, 58.05; H, 7.31; N, 5.64%. Found: C, 57.92; H, 7.36; N, 5.61%.

(*S*)-Ethyl 4-(4-methoxybenzyl)-8-(methoxymethyl)-11,11-dimethyl-3,5,9-trioxo-1-phenyl-2,10-dioxa-4,8-diazadodecane-7-carboxylate (7)

Prepared from **6** (305 mg, 1.00 mmol) and benzyl 4-methoxybenzylcarbamate (298 mg, 1.1 mmol) according to the procedure for **2**. Purification was performed by column chromatography (hexane: dioxane= 4: 1) to give **7** (217 mg, 39% yield). The enantiomeric purity was determined to be 90%: Daicel Chiralpak AD-H, hexane: *i*-PrOH= 90:10, flow 0.8 mL/min., 254 nm, minor peak 19.7 min, major peak 21.8 min.

Colorless oil. $[\alpha]_D^{20}$ (90% ee) -31 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.32 (m, 3H), 7.26 (s, 2H), 7.14 (d, *J*=8.2 Hz, 2H), 6.77 (d, *J*=8.2 Hz, 2H), 5.19 (s, 2H), 4.87 (s, 2H), 4.84-4.69 (m, 3H), 4.24-4.11 (m, 2H), 3.91-3.84 (m, 1H), 3.78 (s, 3H), 3.32-3.26 (m, 1H), 3.31, 3.28 (two s, ratio=3:2, 3H), 1.47, 1.43 (two s, ratio=2:3, 9H), 1.26, 1.22 (two t, *J*=7.3 Hz, 7.3 Hz, ratio=3:2, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8 and 173.7 (rotamer), 171.4 and 171.3 (rotamer), 159.3, 155.3 and 154.9 (rotamer), 154.6, 135.3, 130.2 and 130.1 (rotamer), 129.9, 129.1, 128.9, 114.1, 81.9 and 81.6 (rotamer), 79.8 and 79.6 (rotamer), 69.2, 61.9 and 61.7 (rotamer), 56.5 and 56.4 (rotamer), 56.2 and 56.1 (rotamer), 55.7, 47.3, 40.5 and 39.7 (rotamer), 28.7 and 28.6 (rotamer), 14.6. IR (neat, cm^{-1}) 2977, 1739, 1706, 1514, 1366, 1300, 1248, 1178, 1092, 1035. MS (EI) *m/z* (rel intensity) 558 (M^+, 1), 391 (20), 335 (100), 291 (20), 270 (20), 136 (40), 121 (80), 91 (50). Anal. Calcd for $C_{29}H_{38}N_2O_9$: C, 62.35; H, 6.86; N, 5.01%. Found: C, 62.22; H, 6.90; N, 4.90%.

(*S*)-Ethyl 7-(*tert*-butoxycarbonyl)-11-(4-methoxybenzyl)-10,12-dioxo-2,5,13-trioxa-7,11-diaza-pentadecane-8-carboxylate (8)

Sodium hexamethyldisilazide (1.68 M in THF, 0.16 mL, 0.27 mmol) was added slowly to a solution of **4** (105 mg, 0.30 mmol) in THF (3.0 mL) and DMPU (0.36 mL, 3.0 mmol) at -78 °C under Ar. After stirring the solution for 30 min at -78 °C, MEMCl (103 μL, 0.90 mmol) was added and the resulting mixture was stirred for 19 h at -78 °C. The reaction mixture was poured into saturated aq. NH_4Cl solution and extracted with EtOAc twice. The combined organic phase was washed with saturated aq. $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by preparative TLC (hexane:Et_2O=1:1) to give (*S*)-4-benzyl 1-ethyl 2-(*tert*-butoxycarbonyl-((2-methoxyethoxy)methyl)amino)succinate (112 mg, 85% yield). The enantiomeric purity was determined to be 96% ee: Daicel Chiralcel OD-H, hexane: *i*-PrOH= 95:5, flow 1.0 mL/min., 254 nm, minor peak 12.3 min, major peak 17.8 min.

Colorless oil. $[\alpha]_D^{20}$ (96% ee) -33 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.14 (ABq, $\Delta\nu_{AB}$=14.7 Hz, *J*=12.4 Hz, 2H), 4.97, 4.90, (two d, *J*=11.0 Hz, 11.0 Hz, ratio=5:3, 1H), 4.75 (d, *J*=11.0 Hz, 1H), 4.59, 4.55 (two t, *J*=6.9 Hz, 6.9 Hz, ratio=3:5, 1H), 4.25-4.08 (m, 2H), 3.81-3.74 (m, 1H), 3.66-3.54 (m, 1H), 3.51, (t, *J*=4.6 H, 2H), 3.36 (s, 3H), 3.33-3.22 (m, 1H), 2.92, 2.83 (two dd, *J*=16.5, 6.8 Hz, 16.5, 6.8 Hz, ratio=3:5, 1H), 1.46, 1.42 (two s, ratio=3:5, 9H), 1.25, 1.21 (two t, *J*=7.3 Hz, 7.3 Hz, ratio=5:3, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3 and 171.0 (rotamer), 170.6 and 170.5 (rotamer), 154.8 and 154.4 (rotamer), 136.0 and 135.9 (rotamer), 128.8, 128.7, 128.5 and 128.4 (rotamer), 81.8 and 81.5 (rotamer), 78.7 and 78.6 (rotamer), 71.9, 67.7 and 67.4 (rotamer), 66.8 and 66.6 (rotamer), 61.8 and 61.6 (rotamer), 59.3 and 59.2 (rotamer), 56.2, 36.5 and 35.6 (rotamer), 28.41 and 28.36 (rotamer), 14.3. IR (neat, cm^{-1}) 2979, 1738, 1709, 1429, 1367, 1159, 1091, 860, 699. MS (EI) *m/z* (rel intensity) 439 (M^+, 1), 369 (5), 338 (60), 269 (70), 190 (40), 91(100). Anal. Calcd for $C_{22}H_{33}NO_8$: C, 60.12; H, 7.57; N,

3.19%. Found: C, 59.83; H, 7.57; N, 3.25%.

A suspension of (*S*)-4-benzyl 1-ethyl 2-(*tert*-butoxycarbonyl(methoxymethyl)amino)succinate (1.60 g, 3.6 mmol) and 10% Pd/C (150 mg) in EtOH (30 mL) was stirred under H_2 at rt for 8 h. The mixture was filtered and the filtrate was concentrated in vacuo to give (*S*)-3-(*tert*-butoxycarbonyl((2-methoxyethoxy)methyl)-amino)-4-ethoxy-4-oxobutanoic acid (1.27 g, quant.).

Colorless oil. $[\alpha]_D^{20}$ (96% ee) -52 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.2 (br s, 1H), 4.99, 4.94 (two d, *J*=11.0 Hz, 11.0 Hz, ratio= 5:3, 1H), 4.82 (d, *J*=11.0 Hz, 1H), 4.53, (two t, *J*=6.9 Hz, 6.9 Hz, ratio=3:5, 1H), 4.26-4.12 (m, 2H), 3.82-3.76 (m, 1H), 3.69-3.58 (m, 1H), 3.55 (t, *J*=4.6 Hz, 2H), 3.39 (s, 3H), 3.29, 3.24 (two dd, *J*=16.9, 7.4 Hz, 16.9, 7.4 Hz, ratio=3:5, 1H), 2.91, 2.83 (two dd, *J*=16.9, 7.4 Hz, 16.9, 7.4Hz, ratio=3:5, 1H), 1.47, 1.44 (two s, ratio=3:5, 9H), 1.28, 1.24 (two t, *J*=7.4 Hz, 7.4 Hz, ratio =5:3, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 and 176.4 (rotamer), 170.8 and 170.7 (rotamer), 155.0 and 154.6 (rotamer), 82.2 and 81.9 (rotamer), 78.9 and 78.8 (rotamer), 72.1, 67.8 and 67.5 (rotamer), 62.1 and 61.9 (rotamer), 59.4 and 59.3 (rotamer), 56.3, 36.5 and 35.6 (rotamer), 28.6 and 28.5 (rotamer), 14.4. IR (neat, cm^{-1}) 2979, 1739, 1711, 1432, 1369, 1300, 1160, 1091, 859. MS (EI) *m/z* (rel intensity) 349 (M^+, 1), 248 (50), 174 (100), 100 (90), 57 (80). Anal. Calcd for $C_{15}H_{27}NO_8$: C, 51.57; H, 7.79; N, 4.01%. Found: C, 51.28; H, 7.88; N, 3.91%.

Triethylamine (0.28 mL, 2.0 mmol) and pivaloyl chloride (135 μL, 1.1 mmol) were added to a solution of (*S*)-3-(*tert*-butoxycarbonyl((2-methoxyethoxy)methyl)-amino)-4-ethoxy- 4-oxobutanoic acid (350 mg, 1.0 mmol) in THF (10 mL) and DMPU (0.61 mL, 5.0 mmol) at -78 °C under Ar. After stirring for 2 h at -78 °C, a solution of lithium *N*-ethoxycarbonyl-*N*-*p*-methoxybenzylamide, prepared by *n*-BuLi (1.53M in hexane, 0.72 mL, 1.1 mmol) and ethyl 4-methoxybenzylcarbamate (230 mg, 1.1 mmol) in THF (5 mL) at 0 °C, was added to the reaction mixture and the resulting mixture was stirred at -78 °C and then gradually warmed to room temperature. The reaction mixture was poured into saturated aq. NH_4Cl solution and extracted with EtOAc twice. The combined organic phase was washed with saturated aq. $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by column chromatography (hexane: EtOAc= 7: 3) to give **8** (379 mg, 70% yield). The enantiomeric purity was determined to be 96% ee: Daicel Chiralpak AD-H, hexane: *i*-PrOH= 90:10, flow 0.8 mL/min., 254 nm, minor peak 20.2 min, major peak 23.9 min.

Colorless oil. $[\alpha]_D^{20}$ (96% ee) -31 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J*=8.2 Hz, 2H), 6.81 (d, *J*=8.2 Hz, 2H), 4.97, 4.90 (two d, *J*=11.0 Hz, 11.0 Hz, ratio=5:3, 1H), 4.86 (s, 2H), 4.79, 4.77 (two d, *J*=11.0 Hz, 11.0 Hz, ratio=5:3, 1H), 4.23 (q, *J*=6.9 Hz, 2H), 4.32-4.09 (m, 2H), 3.90, 3.86 (two dd, *J*=17.9, 6.0 Hz, 17.9, 6.0 Hz, ratio=3:5, 1H), 3.79-3.71 (m, 1H), 3.78 (s, 3H), 3.66-3.55 (m, 1H), 3.50 (br t, *J*=4.1 Hz, 2H), 3.36 (s, 3H), 3.28 (dd, *J*=17.9, 6.0 Hz, 1H), 1.46, 1.44 (two s, ratio=3:5, 9H), 1.30 (t,

J=6.9 Hz, 3H), 1.25, 1.21 (two t, *J*=7.9 Hz, 7.9 Hz, ratio=5:3, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8 and 173.6 (rotamer), 171.4 and 171.2 (rotamer), 155.3 and 154.8 (rotamer), 154.7, 130.4 and 130.3 (rotamer), 130.0, 114.1, 81.9 and 81.6 (rotamer), 78.5, 72.1, 67.8 and 67.4 (rotamer), 63.5, 61.8 and 61.7 (rotamer), 59.5 and 59.4 (rotamer), 56.3, 55.7, 47.2, 40.4 and 39.6 (rotamer), 28.7 and 28.6 (rotamer), 14.6, 14.5. IR (neat, cm^{-1}) 2979, 2934, 1739, 1706, 1515, 1369, 1300, 1249, 1182, 1033. MS (EI) *m/z* (rel intensity) 540 (M^+, 1), 464 (10), 408 (50), 291 (20), 221 (60), 208 (90), 121 (100), 57 (20). HRMS (EI) calcd for $C_{26}H_{40}N_2O_{10}$: 540.2683, found: 540.2689.

(*S*)-Ethy l8-(*tert*-butoxycarbonyl)-4-(4-methoxybenzyl)-3,5-dioxo-1-phenyl-2,10,13-trioxa-4,8-diazatetradecane-7-carboxylate (9)

Prepared from (*S*)-3-(*tert*-butoxycarbonyl((2-methoxyethoxy)methyl)-amino)-4-ethoxy-4-oxobutanoic acid **(**105 mg, 0.30 mmol) and benzyl 4-methoxybenzylcarbamate (90 mg, 0.33 mmol) according to the procedure for **8**. Purification was performed by column chromatography (hexane: Et_2O= 2: 3) to give **9** (110 mg, 61% yield). The enantiomeric purity was determined to be 92% ee: Daicel Chiralpak AD-H, hexane: *i*-PrOH= 90:10, flow 0.7 mL/min., 254 nm, minor peak 33.5 min, major peak 40.3 min.

Colorless oil. $[\alpha]_D^{20}$ (92% ee) -31 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.32 (m, 3H), 7.26 (br s, 2H), 7.14 (d, *J*=8.2 Hz, 2H), 6.77 (d, *J*=8.2 Hz, 2H), 5.19 (s, 2H), 4.97, 4.90 (two d, *J*=11.4 Hz, 11.4 Hz, ratio=8:5, 1H), 4.87 (s, 2H), 4.82-4.75 (m, 1H), 4.79 (d, *J*=11.4 Hz, 1H), 4.25-4.06 (m, 2H), 3.90 (dd, *J*=17.9, 6.9 Hz, 1H), 3.79-3.70 (m, 1H), 3.77 (s, 3H), 3.66-3.55 (m, 1H), 3.50 (br t, *J*=4.6 Hz, 2H), 3.34 (s, 3H), 3.30 (dd, *J*=17.9, 6.9 Hz, 1H), 1.47, 1.42 (two s, ratio=5:8, 9H), 1.25, 1.21 (two t, *J*=7.3 Hz, 7.3 Hz, ratio=8:5, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8 and 173.6 (rotamer), 171.3 and 171.1 (rotamer), 159.2, 155.3 and 154.7 (rotamer), 154.5, 135.2, 130.1 and 130.0 (rotamer), 129.9, 129.0, 128.9, 114.1, 81.8 and 81.6 (rotamer), 78.5, 72.1, 69.1, 67.7 and 67.4 (rotamer), 61.8 and 61.7 (rotamer), 59.5 and 59.4 (rotamer), 56.2 and 56.1 (rotamer), 55.6, 47.2, 40.4 and 39.6 (rotamer), 28.7 and 28.6 (rotamer), 14.5. IR (neat, cm^{-1}) 2977, 1739, 1705, 1514, 1366, 1300, 1248, 1177, 1033, 860. MS (EI) *m/z* (rel intensity) 602 (M^+, 1), 526 (5), 427 (5), 335 (90), 291 (20), 270 (20), 136 (40), 121 (100), 91 (50). Anal. Calcd for $C_{31}H_{42}N_2O_{10}$: C, 61.78; H, 7.02; N, 4.65%. Found: C, 61.54; H, 6.94; N, 4.79%.

(*R*)-Ethyl 3-(*tert*-butoxycarbonyl(methoxymethyl)amino)-1-(4-methoxybenzyl)-2,5-dioxopyrrolidine-3-carboxylate (10): General procedure for asymmetric Dieckmann condensation via memory of chirality

A base (1.1-2.2 eq) was added slowly to a solution of **2** (0.25 mmol) in solvent (2.5 mL) at -78 °C under Ar. The reaction mixture was stirred at the temperature indicated in the Table 1 for 2 h. The reaction mixture was poured into saturated aq. NH_4Cl solution and extracted with EtOAc twice. The combined organic phase was washed with saturated aq. $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by preparative TLC (toluene: Et_2O: acetone=7:1:1) to

give **10**.

10 : HPLC conditions: Daicel Chiralpak AD-H, hexane: *i*-PrOH= 90:10, flow 0.8 mL/min., 254 nm, minor peak 17.6 min., major peak 22.5 min. Colorless oil. $[\alpha]_D^{20}$ (>99% ee) -153 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J*=8.2 Hz, 2H), 6.82 (d, *J*=8.2 Hz, 2H), 5.17, 4.99 (two br d, *J*=9.2 Hz, 9.2 Hz, ratio=5:4, 1H), 4.80, 4.75 (two br d, *J*=9.2 Hz, 9.2 Hz, ratio=5:4, 1H), 4.63 (ABq, $\Delta\nu_{AB}$=0.031 Hz, *J*=14.6 Hz, 2H), 4.29-4.10 (m, 2H), 3.85, 3.74 (two d, *J*=18.3 Hz, 18.3 Hz, ratio=4:5, 1H), 3.77 (s, 3H), 2.93, 2.88 (two s, ratio=4:5, 3H), 2.79 (d, *J*=18.3 Hz, 1H), 1.46, 1.43 (two s, ratio=4:5, 9H), 1.27-1.15 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6 and 174.2 (rotamer), 171.0 and 170.4 (rotamer), 168.0 and 167.3 (rotamer), 159.7, 154.7 and 153.8 (rotamer), 130.5, 127.6, 114.3, 83.3 and 82.9 (rotamer), 76.2, 67.8 and 67.5 (rotamer), 63.7 and 63.6 (rotamer), 55.7, 55.4, 44.0 and 43.0 (rotamer), 28.5, 14.3. IR (neat, cm^{-1}) 2979, 1759, 1714, 1514, 1370, 1298, 1250, 1177. MS (EI) *m/z* (rel intensity) 450 (M^+, 40), 361 (40), 317 (80), 289 (80), 245 (50), 162 (40), 121 (100), 57 (50). HRMS (EI) calcd for $C_{22}H_{30}N_2O_8$: 450.2002, found: 450.1996.

(*R*)-Ethyl 3-(*tert*-butoxycarbonyl((2-methoxyethoxy)methyl)amino)-1-(4-methoxybenzyl)-2,5-dioxopyrrolidine-3-carboxylate (11)

Purified by preparative TLC (hexane: EtOAc=2:1). HPLC conditions: Daicel Chiralpak AD-H, hexane: *i*-PrOH= 95:5, flow 1.0 mL/min., 254 nm, minor peak 12.8 min, major peak 15.0 min. Colorless oil. $[\alpha]_D^{20}$ (94% ee) -108 (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J*=8.7 Hz, 2H), 6.82 (d, *J*=8.7 Hz, 2H), 5.32,5.14 (two br d, *J*=10.1 Hz, 10.1 Hz, ratio=5:4, 1H), 5.00, (d, *J*=10.1 Hz, 1H), 4.62 (ABq, $\Delta\nu_{AB}$=0.049 Hz, *J*=14.2 Hz, 2H), 4.30-4.10 (m, 2H), 3.82, 3.68 (two d, *J*=18.8 Hz, 18.8 Hz, ratio=4:5, 1H), 3.77 (s, 3H), 3.41-3.27 (m, 2H), 3.24-3.10 (m, 2H), 3.20, 3.14 (two s, ratio=4:5, 3H), 2.92, 2.87 (two d, *J*=12.4 Hz, 12.4 Hz, ratio=4:5, 1H), 1.46, 1.43 (two s, ratio=4:5, 9H), 1.20, 1.18 (two t, *J*=6.8 Hz, 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6 and 174.3 (rotamer), 171.0 and 170.6 (rotamer), 168.2 and 167.4 (rotamer), 159.7, 154.7 and 154.0 (rotamer), 130.5, 127.7, 114.2, 83.2 and 82.9 (rotamer), 75.9 and 74.7 (rotamer), 71.6, 67.6 and 67.4 (rotamer), 63.6, 59.2, 55.6, 43.9 and 42.8 (rotamer), 42.9, 28.5, 14.3. IR (neat, cm^{-1}) 2979, 1758, 1713, 1515, 1395, 1299, 1250, 1088. MS (EI) *m/z* (rel intensity) 494 (M^+, 10), 361 (10), 317 (80), 289 (60), 245 (40), 162 (40), 148 (30), 121 (100), 57 (40). HRMS (EI) calcd for $C_{24}H_{34}N_2O_9$: 494.2264, found: 494.2266.

(*R*)-Ethyl-3-(*tert*-butoxycarbonyl((2-methoxyethoxy)methyl)amino)-2,5-dioxopyrrolidine-3-carboxylate (12)

CAN (461 mg, 0.84 mmol) was added to a solution of **11** (210 mg, 0.42 mmol) in MeCN (6 mL) and H_2O (2 mL) at 0 °C, and the mixture was stirred at 0 °C for 4 h. Additional CAN (230 mg, 0.42 mmol) was added and stirring was continued for additional 4 h. The reaction mixture was diluted with H_2O and extracted with EtOAc three times. Combined organic phase was washed with saturated aq. $NaHCO_3$

solution and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by preparative TLC (hexane: EtOAc= 1: 1) to give **12** (118 mg, 70% yield).

Colorless oil. $[\alpha]_D^{20}$ (>99% ee) -129 (*c* 1.1, $CHCl_3$,). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (br s, 1H), 5.36, 5.18 (two d, *J*=10.1 Hz, 10.1 Hz, ratio=5:4, 1H), 5.02, 4.99 (two d, *J*=10.1 Hz, 10.1 Hz, ratio=4:5, 1H), 4.38-4.14 (m, 2H), 3.86, 3.74 (two d, *J*= 18.3 Hz, 18.3 Hz, ratio=4:5, 1H), 3.59-3.39 (m, 4H), 3.30 (s, 3H), 2.91 (d, *J*=18.3 Hz, 1H), 1.47, 1.44 (two s, ratio=4:5, 9H), 1.34-1.24 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3 and 174.9 (rotamer), 171.5 and 171.0 (rotamer), 168.1 and 167.2 (rotamer), 154.6 and 153.9 (rotamer), 83.4 and 83.0 (rotamer), 76.1 and 74.9 (rotamer), 71.7, 68.8 and 68.4 (rotamer), 67.6, 63.7 and 63.6 (rotamer), 59.1, 44.7 and 43.5 (rotamer), 28.5, 14.3. IR (neat, cm^{-1}) 3227, 2980, 1731, 1369, 1299, 1257, 1154, 1086, 857. MS (EI) *m/z* (rel intensity) 374 (M^+, 1), 273 (20), 204 (40), 199 (100), 148 (80), 125 (50), 89 (40), 57 (60). HRMS (EI) calcd for $C_{16}H_{26}N_2O_8$: 374.1689, found: 374.1689.

(*R*)-Ethyl 3-amino-2,5-dioxopyrrolidine-3-carboxylate (1)

A solution of **12** (80 mg, 0.21 mmol) in EtOAc (1.0 mL) was added to a 4 M HCl solution in EtOAc (5.0 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. After concentration of the reaction mixture *in vacuo*, the residue was dissolved in distillated water and purified by DOWEX 50W to give **1**[1] (34 mg, 87% yield).

Determination of the absolute configuration of 10 and 11

Determination of the absolute configuration of **10** and **11** was performed by the transformation of (*R*)-**1**[1] into (*R*)-**10** and (*R*)-**11**.

DIPEA (3.0 mL, 18 mmol) and Boc_2O (2.50 g, 12 mmol) were added to a solution of (*R*)-**1** (1.10 g, 5.9 mmol) in DCM (35 mL) at 0 °C, and the mixture was stirred at rt for 14 h. The reaction mixture was evaporated and the residue was diluted with EtOAc and washed with a 10 % aq. citric acid solution, saturated aq. $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude crystals were purified by recrystallization (hexane/Et_2O/acetone) to give (*R*)-ethyl 3-(*tert*-butoxycarbonylamino)-2,5-dioxopyrrolidine-3-carboxylate (1.47 g, 87% yield).

Colorless crystals. $[\alpha]_D^{20}$ (>99% ee) -45 (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (br s, 1H), 6.00 (s, 1H), 4.32 (q, *J*=6.9 Hz, 2H), 3.17 (ABq, $\Delta\nu_{AB}$=34.2 Hz, *J*=18.3 Hz, 2H), 1.45 (s, 9H), 1.30 (t, *J*=6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 173.1, 167.3, 154.8, 82.0, 64.9, 64.4, 41.4, 28.6, 14.3. IR (neat, cm^{-1}) 3240, 2980, 2925, 1730, 1490, 1369, 1293, 1259, 1163, 1028. MS (EI) *m/z* (rel intensity) 286 (M^+, 1), 271 (5), 243 (50), 213 (40), 187 (100), 159 (60), 113 (30). Anal. Calcd for $C_{12}H_{18}N_2O_6$: C, 50.35; H, 6.34; N, 9.79%. Found: C, 50.44; H, 6.25; N, 9.65%.

(*R*)-Ethyl 3-(*tert*-butoxycarbonylamino)-1-(4-methoxybenzyl)-2,5-dioxopyrrolidine-3-carboxylate

To a solution of (*R*)-ethyl 3-(*tert*-butoxycarbonylamino)-2,5-dioxopyrrolidine-3-carboxylate (1.47 g, 5.1 mmol) in DMF (50 mL) were added K_2CO_3 (2.1 g, 15.3 mmol), PMBCl (1.4mL, 10.2 mmol), and NaI

(1.5 g, 10.2 mmol) at 0 °C and the mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with EtOAc and washed with H_2O twice, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by column chromatography (hexane: EtOAc= 6: 1) to give (*R*)-Ethyl 3-(*tert*-butoxycarbonylamino)-1-(4-methoxybenzyl)-2,5-dioxopyrrolidine-3-carboxylate (2.00 g, 97% yield).

Colorless oil. $[\alpha]_D^{20}$ (>99% ee) -68 (*c* 1.0, $CHCl_3$,). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J*=8.7 Hz, 2H), 6.82 (d, *J*=8.7 Hz, 2H), 5.98 (s, 1H), 4.70 (ABq, $\Delta\nu_{AB}$=47.1 Hz, *J*=14.2 Hz, 2H), 4.20-4.05 (m, 2H), 3.77 (s, 3H), 3.12 (ABq, $\Delta\nu_{AB}$=34.6 Hz, *J*=17.9 Hz, 2H) 1.44 (s, 9H), 1.03 (t, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 172.7, 167.4, 159.6, 154.6, 130.3, 127.8, 114.2, 81.6, 64.0, 63.7, 55.6, 42.9, 40.3, 28.5, 13.9. IR (neat, cm^{-1}) 3427, 2979, 1749, 1715, 1514, 1399, 1250, 1173, 1028. MS (EI) *m/z* (rel intensity) 406 (M^+, 25), 351 (20), 350 (90), 349 (20), 289 (10), 162 (20), 121 (100). Anal. Calcd for $C_{20}H_{26}N_2O_7$: C, 59.10; H, 6.45; N, 6.89%. Found: C, 58.82; H, 6.59; N, 6.70%.

Sodium hexamethyldisilazide (1.68M in THF, 0.21 mL, 0.36 mmol) was added slowly to a solution of (*R*)-ethyl-3-(*tert*-butoxycarbonylamino)-1-(4-methoxybenzyl)-2,5-dioxopyrrolidine-3-carboxylate (122 mg, 0.30 mmol) in THF (3.0 mL) and DMPU (0.18 mL, 1.50 mmol) at -78 °C under Ar. After stirring for 30 min, MOMCl (68 μL, 0.90 mmol) was added and the resulting mixture was stirred for 15 h. The reaction mixture was poured into saturated aq. NH_4Cl solution and extracted with EtOAc twice. The combined organic phase was washed with saturated aq. $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by preparative TLC (hexane: dioxane= 3: 1) to give (*R*)-**10** (37 mg, 27% yield).

(*R*)-**11** was prepared from (*R*)-ethyl 3-(*tert*-butoxycarbonylamino)-1-(4-methoxybenzyl)-2,5-dioxopyrrolidine-3-carboxylate (610 mg, 1.50 mmol) and MEMCl (0.51 mL, 4.50 mmol) according to the procedure for (*R*)-**10**. Purification was performed by preparative TLC (hexane: dioxane= 3: 1) to give (*R*)-**11** (336 mg, 45% yield).

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5. The yield and ee of the Dieckmann condensation of **2** in various solvents are as follows: toluene; 12% yield, 61% ee: ether; 22% yield, 75% ee: diisopropyl ether; 18% yield, 72% ee: cyclopropyl methyl ether; 17% yield, 67% ee: *tert*-butyl methyl ether; 24% yield, 78% ee.