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ASYMMETRIC SYNTHESIS OF β-LACTAMS BY INTRAMOLECULAR CONJUGATE ADDITION OF SERINE AND CYSTEINE DERIVATIVES VIA MEMORY OF CHIRALITY

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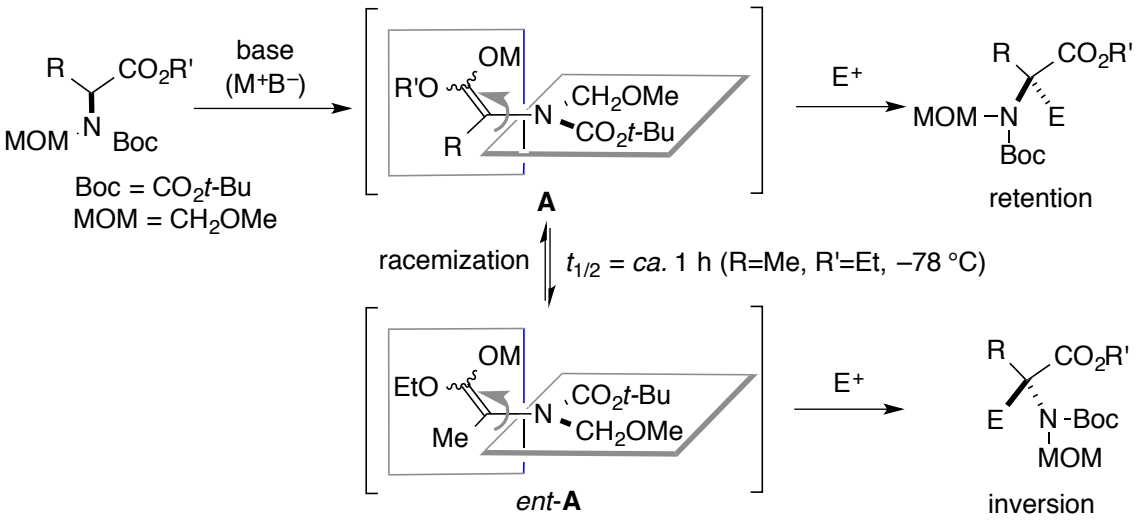
Dedicated to the 70th Birthday of Prof. Kiyoshi Tomioka

Abstract – The *4-exo-trig* cyclization of axially chiral enolates generated from L-serine and L-cysteine dervatives proceeded predominately over β-elimination to give chiral β-lactams with contiguous tri- and tetrasubstituted carbon centers in up to 96% ee. The key to smooth production of β-lactams is the use of Cs_2CO_3 and CF_3CH_2OH as a base and a proton source, respectively. A strongly electron-withdrawing Michael acceptor in the substrates was also critical for high enantioselectivity of the β-lactam formation.

INTRODUCTION

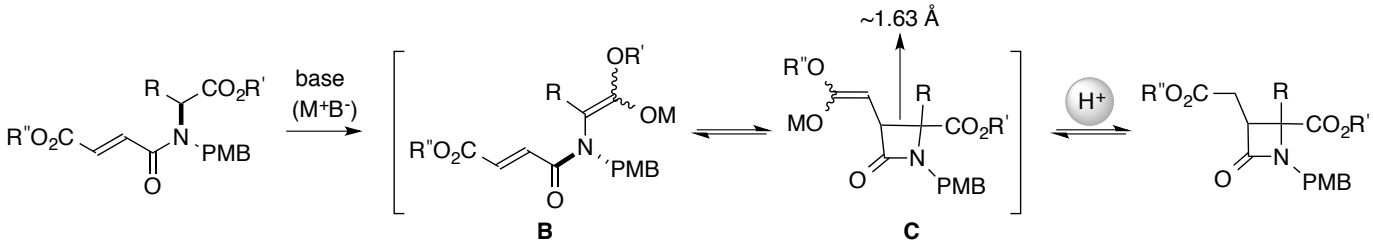
We have studied asymmetric reactions via memory of chirality (MOC).[1] The MOC strategy is characterized by intermediary chiral enolates with the restricted bond rotation around the chiral C-C,[2] C-N,[3-10] and C-O[11,12] axes (for the case of a C-N axis, see Scheme 1). The obvious advantage of the strategy is the use of naturally abundant readily available amino acids as starting materials as well as sole source of chirality. Therefore, the asymmetric synthesis can be performed without any external chiral sources such as chiral catalysts or chiral auxiliaries. On the other hand, the racemization behavior of the chiral enolates is a fatal serious problem, because the desired reaction of the chiral enolates with electrophiles competes always with their own racemization. For instance, axially chiral enolate **A** derived

from alanine has a relatively short half-life of racemization (*ca*. 1 h) even at –78 °C (Scheme 1).[13] While these circumstances sometimes limited the use of axially chiral enolates for asymmetric reactions, chiral enolate **A** derived from alanine effectively underwent asymmetric conjugate addition by employing a highly reactive Michael acceptor.[13]



Scheme 1

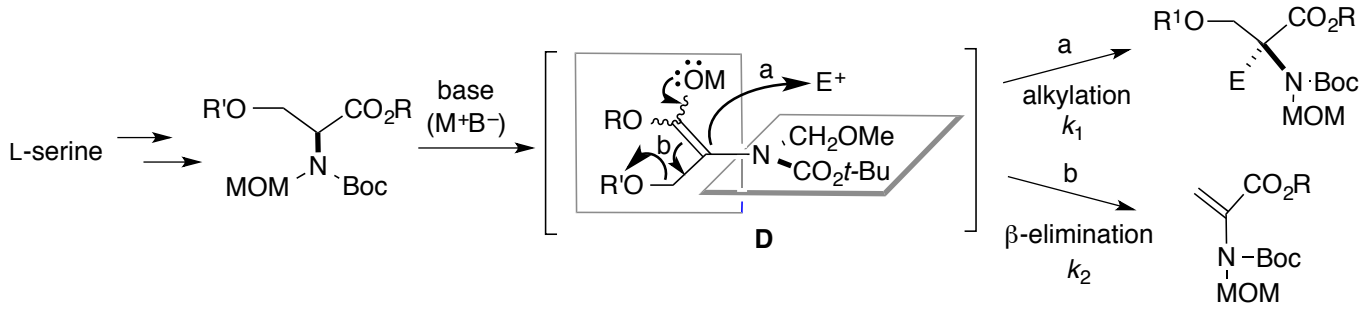
A challenge in the MOC strategy is its application to β-lactam synthesis. β-Lactams are expected to be produced via the 4-*exo-trig* cyclization of axially chiral enolate **B**. However, this process might be unfavorable because the conjugate addition of enolate **B** would produce highly strained β-lactam enolate **C** with a labile C-C bond (1.63 Å by DFT calculations when M=Cs, R=R'=R''=Me).[14] We have solved the expected difficulty by performing the enolate reaction in protic solvents. Prompt protonation of the highly strained β-lactam enolates **C** immediately after its formation successfully gave β-lactams in a highly enantioselective manner.[14]



Scheme 2

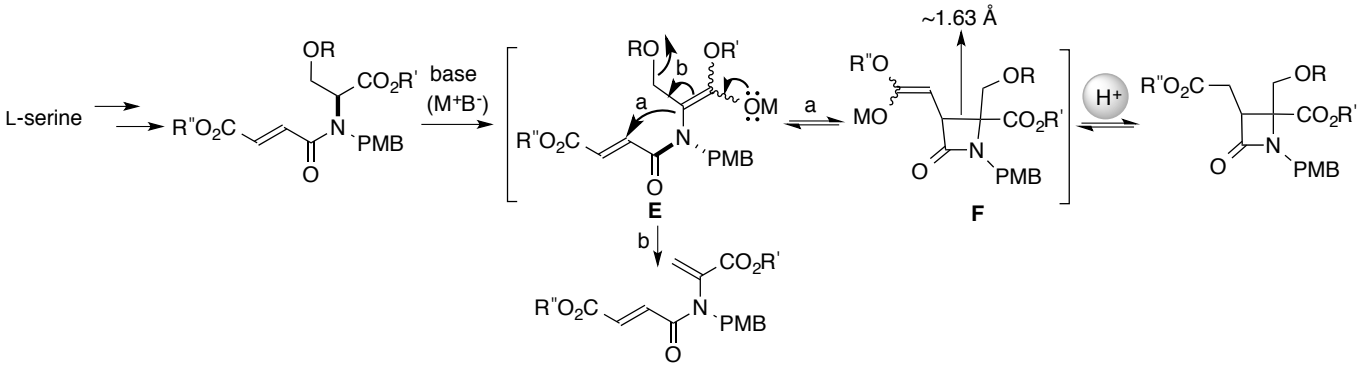
Another challenge in the MOC strategy is the use of serine as a starting amino acid. α-Substituted serine derivatives are important building blocks for the synthesis of biologically active natural products such as sphingofungin-E,[15] lactacystin,[16] salinosporamide A,[17] dysibetaine,[18] kaitocephalin,[19] and

neooxazolomycin.[20] The most straightforward synthesis of optically active α-substituted serines might involve α-alkylation of protected serine derivatives (Scheme 3, path a). However, this strategy has scarcely been achieved due to expected racemization during enolate formation and/or concomitant β-elimination[21-24] (Scheme 3, b). To avoid these problems, chral cyclic *N,O*-acetal analogues generated by self-reproduction of the center of chirality have been used to prepare optically active α-substituted serine derivatives.[25,26] On the other hand, we have achieved the direct asymmetric synthesis of α-substituted serine derivatives according to path a in Scheme 3, overcoming the competing β-elimination process by employing the "amine-free enolate strategy".[7] We assumed that alkylation (path a) of chiral enolate **D** proceeded faster than the β-elimination (path b) ($k_1 > k_2$) due to the high reactivity of the amine-free enolate.



Scheme 3

As further extension of the MOC strategy by combining the β-lactam problem (Scheme 2) and the serine problem (Scheme 3), we describe here asymmetric synthesis of β–lactams of serine and cysteine derivatives (Scheme 4).



Scheme 4

RESULTS AND DISCUSSION

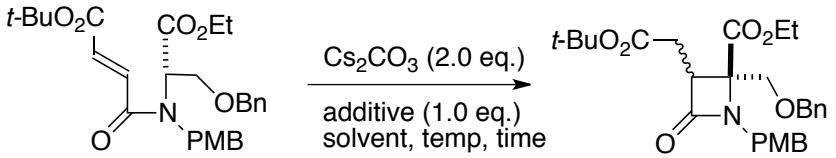
β-Lactams are useful not only as antibiotics[27,28] but also as equivalents of protected β-amino acids[29] and versatile precursors of *N*-heterocyclic compounds for the synthesis of natural products.[30] Enormous

efforts have been devoted to the asymmetric synthesis of β-lactams.[31] We reported a straightforward method for the asymmetric synthesis of β-lactams with contiguous tetra- and trisubstituted carbon centers from readily available α-amino acids such as phenylalanine, valine, and tryptophan via MOC (Scheme 2).[14] If the MOC strategy for the β-lactam synthesis can be applicable to L-serine as a staring α-amino acid, the resulting β–lactams are expected to be useful chiral building blocks of biologically active compounds which possess the α,α-disubstituted serine moiety such as lactasystin,[32] oxazolomycin,[33] ISP-I,[34] and so on. In addition to the potential synthetic utility, a variety of multi-functionalized β-lactams are expected to be obtained by further conversion of the hydroxy group to other functional groups.

Asymmetric intramolecular conjugate addition reaction of 1 derived from l-serine was investigated (Table 1). According to our previous protocol for the β-lactam synthesis via MOC,[14] *tert*-butyl fumarate and p-methoxybenzyl (PMB) group were chosen as a Michael acceptor and a nitrogen protective group, respectively. Use of a strong base (LDA or KOH) in an aprotic solvent (THF or DMSO) gave a complex mixture, as observed in our previous study on β-lactam synthesis via MOC (entries 1 and 2). We then examined the previously reported best conditions for the β-lactam synthesis (Cs_2CO_3, EtOH, 20 °C).[14] Treatment of **1** with two equivalents of Cs_2CO_3 in EtOH at 20 °C for 0.2 h give a 1:1 diastereomeric mixture of the desired β-lactams **2** in a combined yield of 62% (entry 3). The ee's of each of the diasteremers (unknown relative stereochemistry) were determined to be 70% and 68% after HPLC separation. Simply applying the previous conditions for β-lactam synthesis via MOC[14] gave the desired alkoxymethyl-substituted β-lactam **2** as a major product without undesired β-elimination of BnOH. On the other hand, ethyl ether **3** instead of benzyl ether **2** was obtained as a diastreomeric mixture in a combined 34% yield. Because each of the diastereomer of **3** was obtained as a racemate, **3** was expected to be produced via the conjugate addition of EtOH to **1A** generated *in situ* by β-elimination of **1**. In order to facilitate the β-lactam formation by further prompt protonation of the hypothetical β-lactam enolate **F** (Scheme 4), CF_3CH_2OH (pK_a=12.4 *vs*. pK_a of EtOH=15.9) was employed as a proton source (entry 4). While the desired β-lactam **2** was obtained in the increased 78% yield as expected, the ee's of the diastereomers of **2** were decreased to 46% and 44%. Further improved yield of β-lactam **2** overcoming the β-elimination process was achieved by using *tert*-amyl alcohol as a solvent. β-Lactam **2** was obtained in a combined yield of 92% (entry 5). The ee's of each of the diasteremers were found to be 72% and 69%. Thus, predominant β-lactam formation from serine derivative **1** overcoming the competing β-elimination process has been successfully achieved by using Cs_2CO_3 in *tert*-amyl alcohol. The success was ascribed to the amine-free nature of the hypothetical intermediate enolate **E** (Scheme 4) as previously claimed.[7] With the satisfactory yield of the desired β-lactam formation, we then investigated various

conditions to improve the enantioselectivity of the β-lactam formation from **1**. However, further improvement of the eanantioselectivity was not achieved concerning substrate **1**. We anticipated that the higher enantioselectivity could be achieved by further accelerating the conjugate addition process of the enolate intermediate by employing the stronger Michael acceptor as observed in our previous intermolecular conjugate addition reaction via MOC.[13]

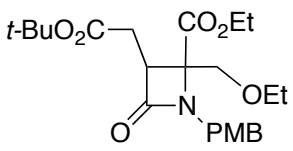
Table 1. Asymmetric Intramolecular Conjugate Addition of Serine Derivative **1**



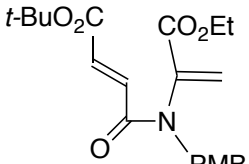
1 **2**

entry	base	solvent	additive	temp (°C)	time (h)	yield (%)	dr (NMR)	ee (%)
1	LDA	THF	-	–78	0.3	~0[a]	-	-
2	KOH	DMSO	-	20	0.3	~0[a]	-	-
3	Cs_2CO_3	EtOH	-	20	0.2	62[b]	50/50	70, 68
4	Cs_2CO_3	MeCN	CF_3CH_2OH	20	0.2	78	44/56	46, 44
5	Cs_2CO_3	*t*-amyl alcohol	-	20	2.6	92	67/33	72, 69

a) Complex mixture. b) Ethyl ether **3** was also obtained as a diastereomeric mixture in a combined yield of 34%. The ee of each of the diastereomers was 0%.



3 (0% ee)

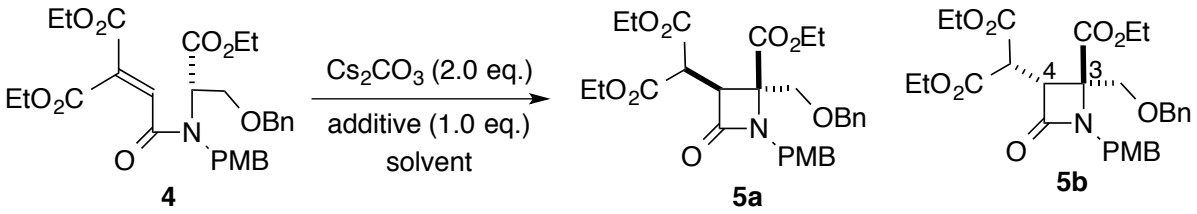


1A

In order to facilitate 4-*exo*-trig cyclization overcoming β-elimination and the partial racemization of the intermediary chiral enolate, the a-amino acid derivative **4** possessing a highly reactive Michael acceptor was prepared as a substrate. Treatment of **4** under the optimized conditions for the reaction of **1** gave β-lactam **5** only in a trace amount (Table 2, entry 1). The observed low yield could be ascribed to poor protonating ability of *tert*-amyl alcohol (pK_a ~ 18) for β-lactam enolate **G** (pK_a of **5** ~ 12). Based on these considerations, phenol (pK_a=10) was added as a proton source in order to facilitate protonation of β-lactam enolate **G**. Treatment of **4** with 2.0 equivalents of Cs_2CO_3 in *tert*-amyl alcohol in the presence of 1.0 equivalent of phenol at 20 °C gave β-lactam **5** as a 57:43 diastereomeric mixture in 69% ee and 62% ee, respectively in a combined yield of 98% without any trace of β-elimination (Table 2, entry 2). The corresponding reaction at 0 °C resulted in the slight increase in the enantioselectivity to give **5a** and **5b** in 79% ee and 65% ee, respectively, in a 56:44 diastereomeric ratio in a combined yield of 86% (entry 3).

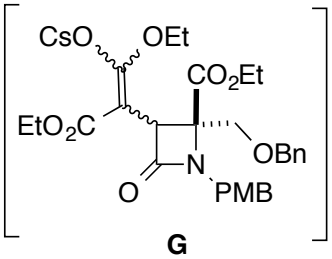
Since further decrease in the temperature of the reaction in *tert*-amyl alcohol was not possible (mp of *tert*-amyl alcohol: –9 °C), the temperature effects were examined in the reactions in MeCN. The corresponding reaction in MeCN at 0 °C gave **5a** (72% ee) and **5b** (73% ee) (entry 4). The reaction at –40 °C gave the β-lactams in much improved ee of 91% and 88% for **5a** and **5b**, albeit the low yield (42%, entry 5). Use of CF_3CH_2OH as a proton source in the reaction in MeCN gave the best result. Treatment of **4** with Cs_2CO_3 in MeCN in the presence of 1.0 equivalent of $(CF_3)_2CHOH$ at –10 °C gave desired β-lactams **5a** and **5b** in a 67:33 diastereomeric ratio in 92% ee and 90% ee, respectively, in a combined yield of 98% without any trace of side products from β-elimination (entry 6).

Table 2. Asymmetric Intramolecular Conjugate Addition of Serine Derivative **4** with a Stronger Michael Acceptor



entry	solvent	additive	temp. (°C)	time (h)	yield (%)	**5a** / **5b**[a,b]	ee (%)
1	*t*-amyl alcohol	-	20	0.3	trace	-	-
2	*t*-amyl alcohol	phenol	20	0.3	98	57 / 43	69, 62
3	*t*-amyl alcohol	phenol	0	1.0	86	56 / 44	79, 65
4	MeCN	phenol	0	0.5	93	49 / 51	72, 73
5	MeCN	phenol	–40	24	42	40 / 60	91, 88
6	MeCN	$(CF_3)_2CHOH$	–10	2.6	98	67 / 33	92, 90

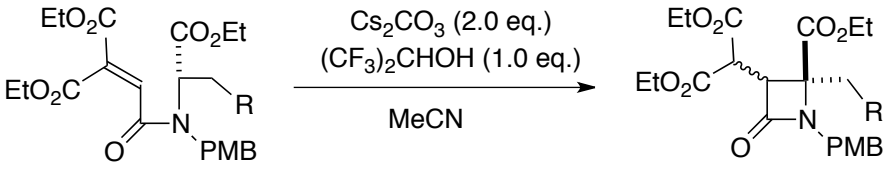
a) The relative stereochemistry was determined by NOESY spectra, see Supporting Information.
b) The absolute configiuration of **5b** was determined to be (3*R*,4*R*) by an X-ray analysis of **10** derived from **5b** (*vide infra*).



The optimized conditions for the β-lactam formation was applied to serine derivative with *tert*-butyldiphenylsilyl ether **6** and l-cysteine derivative **8** (Table 3). Treatment of **6** with Cs_2CO_3 in MeCN in the presence of 1.0 equivalent of $(CF_3)_2CHOH$ at 0 °C gave β-lactam **7** as a 52:48 diastereomeric mixture in 96% ee and 92% ee, respectively in a combined yield of 90% (entry 2).

Similarly, l-cysteine derivative **8** gave b-lactam **9** with a thioether moiety as a 50:50 diastereomeric mixture in 91% ee each in a combined yield of 86% (entry 3).

Table 3. Asymmetric Intramolecular Conjugate Addition of Serine Derivatives **4** and **6** and Cysteine Derivative **8**

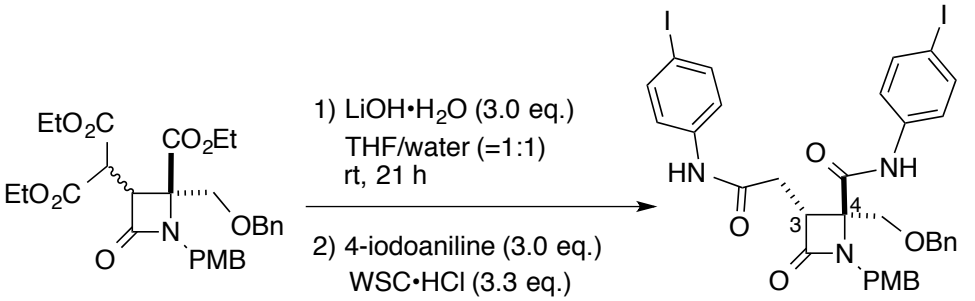


4 (R=OBn)
6 (R=OTBDPS)
8 (R=S*t*-Bu)

5 (R=OBn)
7 (R=OTBDPS)
9 (R=S*t*-Bu)

entry	substrate (parent amino acid)	temp (°C)	time (h)	yield (%)	product	dr	ee (%)
1	**4** (serine)	–10	2.6	98	**5**	67 / 33	92, 90
2	**6** (serine)	0	1	90	**7**	52 / 48	96, 92
3	**8** (cysteine)	0	2	86	**9**	50 / 50	91, 91

The absolute configuration of **5b** was determined to be (3R, 4R) by an X-ray crystallographic analysis of **10** (Figure 1),[35] which was obtained by decarboxylative hydrolysis of the bis-ethyl ester moiety of **5b**, condensation of the resulting carboxylic acid with *p*-iodoaniline, followed by separation of the diastereomeric mixture (Scheme 5). A single crystal for X-ray analysis was obtained by recrystallization of **10** (98% ee). Thus, intramolecular conjugate addition of **4** was found to proceed in inversion of the configuration at the newly formed tetrasubstituted carbon center (It is not possible to determine whether compound **10** is produced from **5b** or **5a**, because epimerization at C(3) may occur under these conditions, see Scheme 6).



5a : **5b** = 65 : 35
93% ee, 89% ee

10

10% yield, 98% ee

Scheme 5

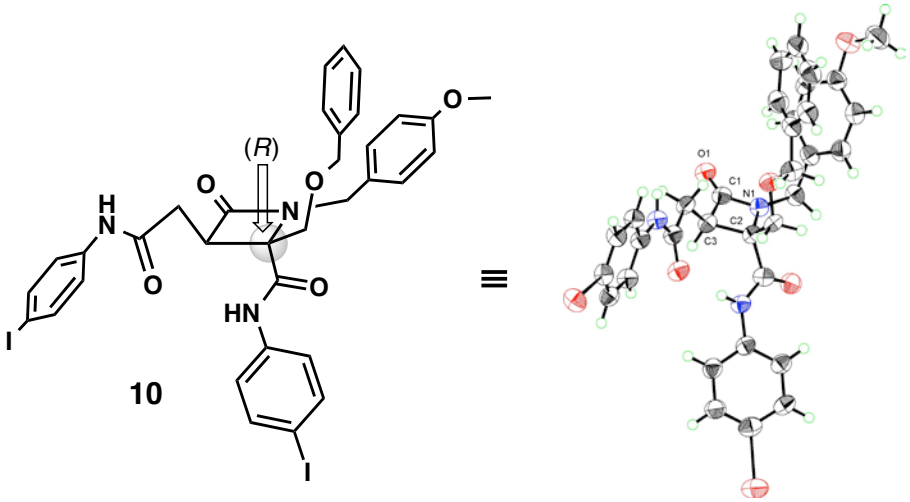
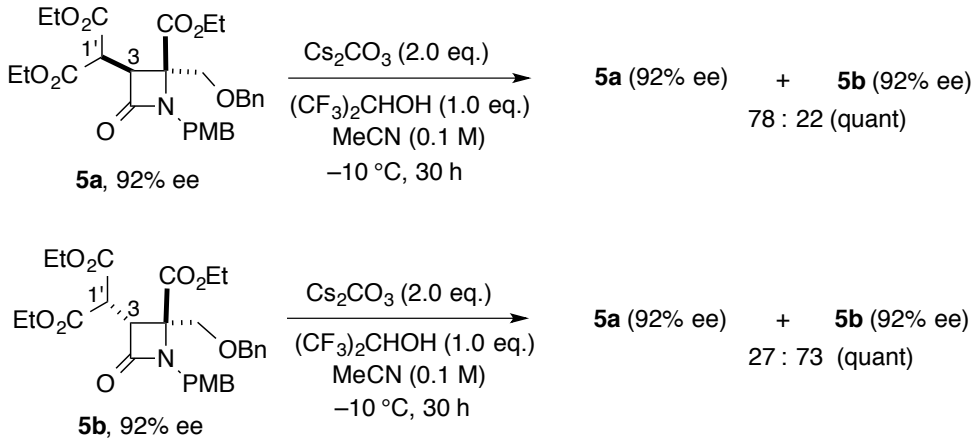


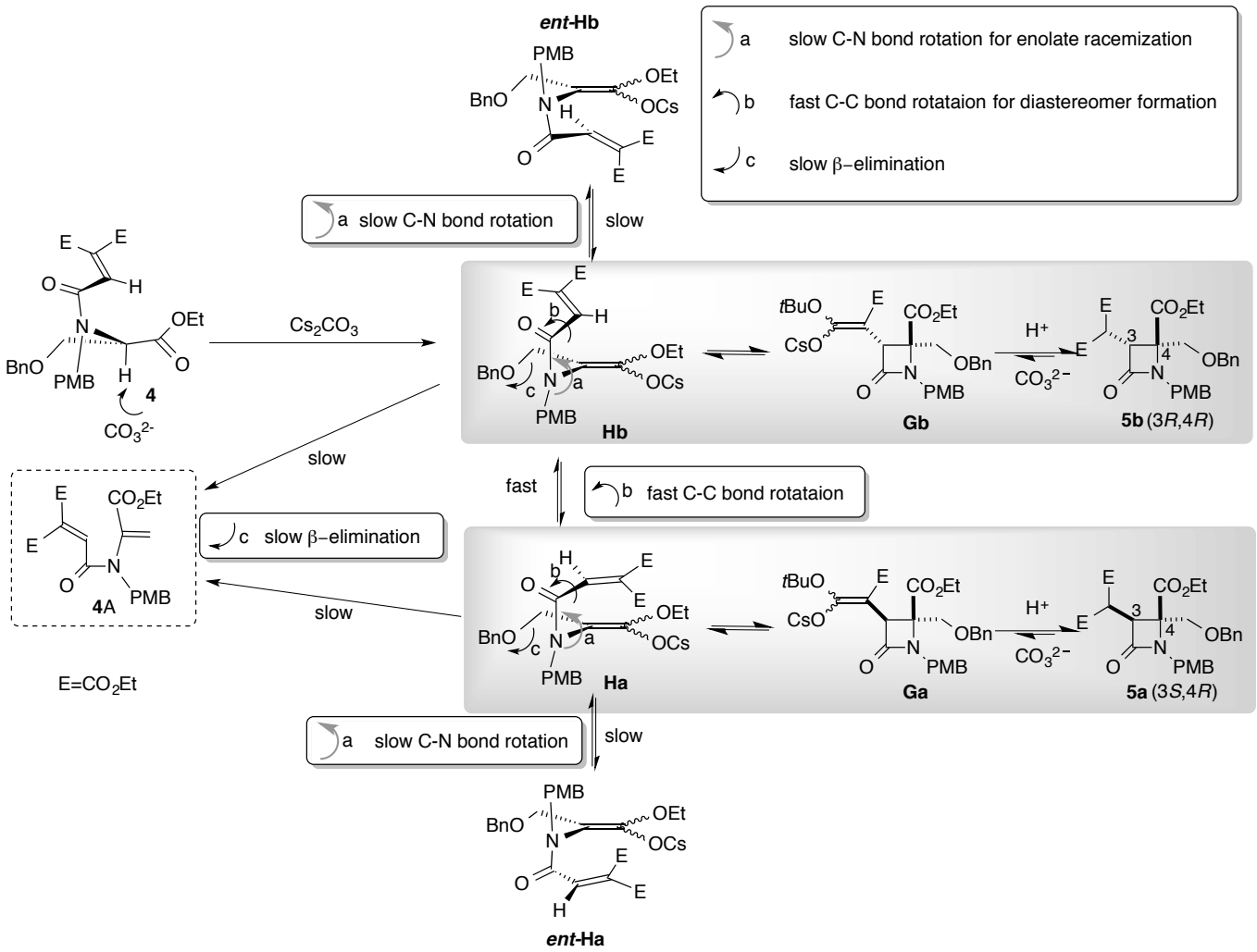
Figure 1

We next examined whether the diastereomeric ratio was determined by kinetic or thermodynamic control. Each of the pure diastereomer, **5a** and **5b**, was treated independently treated under the conditions for the β-lactam formation (Scheme 6). Treatment of **5a** (92% ee) with 2.0 equivalents of Cs_2CO_3 in MeCN at –10 °C for 30 h gave a 78:22 mixture of **5a** and **5b** in 92% ee and 92% ee, respectively, in a quantitative combined yield. On the other hand, a 27:73 mixture of **5a** and **5b** was obtained in 92% ee and 92% ee, respectively, also in a quantitative combined yield on treatment of **5b** (92% ee) with 2.0 equivalents of Cs_2CO_3 in MeCN at –10 °C for 30 h. While these results obviously indicate the existance of the equilibrium process between **5a** and **5b**, the observed different distereomeric ratios suggest that the diastereomeric ratios were partially affected by the thermodynamic equilibrium. The interconversion between **5a** and **5b** was assumed to proceed via retro-Michael addition of β-lactam enolate **G**, formed by deprotonation at C(1') rather than the direct deprotonation-protonation process at C(3) based on the previous studies concerning the deuteration experiment in the related β-lactam formation.[14]



Scheme 6

The stereochemical course of the β-lactam formation via MOC has been extensively studied.[14] Here, we describe a possible rational for the stereichemical course for the formation of β-lactams **5a** and **5b** from **4** according to the previous proposal[14] (Scheme 7). Deprotonation of **4** with Cs_2CO_3 is expected to take place preferentially from the conformer where the C(α)-H bond is antiperiplanar with respect to the neighboring N-C(COCH=C(CO_2Et)$_2$) bond to give chiral enolate **Hb** with a*R* configuration. The stereochemical course of the enantioselective formation of the chiral enolate **Hb** was assumed based on our rationale for previous stereochemical results, in which deprotonation of *N*-Boc-*N*-alkyl-α-amino acid derivatives took place preferentially from the conformer in which C(α)-H bond is antiperiplanar with



Scheme 7

respect to the neighboring N-C(Boc) bond.[3,4,6] The other chiral enolate **Ha** with the same chiral (a*R*)-C-N axis would be formed by the fast rotation (arrow b) of the C-C bond of **Hb**. Enolate **Hb** is expected to undergo intramolecular conjugate addition from its *si*-face to give β-lactam enolate **Gb** in inversion of the

configuration at the newly formed tetrasubstituted carbon. Similarly, enolate **Ha** would give β-lactam enolate **Ga** with the same absolute configuration as that of **Gb** at the tetrasubstituted carbon. Protonation of **Gb** and **Ga** with CF_3CH_2OH would give β-lactams **5b** and **5a**, respectively. Importantly, ee's of **5b** and **5a** were maintained unchanged during the equilibrium process (Scheme 6), even though the equilibrium takes place via chiral enolates **Hb** and **Ha** re-generated from **Gb** and **Ga**, respectively, by the retro-Michael addition process. The racemization-free equilibrium could be ascribed to the slower C-N bond rotation (arrow a) responsible for enolate racemization than the much faster C-C bond rotation (arrow b) responsible for the diastereomer formation. Similarly, β-elimination process (arrow c) seems to be much slower than the C-N bond rotation (arrow a) and the C-C bond rotation (arrow b).

In summary, we have developed a highly enantioselective synthesis of β-lactams with contiguous tetra- and trisubstituted carbon center starting from L-serine and L-cysteine. The salient feature of the present procedure are: (1) Conjugate addition of the chiral enolates was facilitated by a proton source. (2) Undesired competitive β-elimination was totally suppressed during the desired β-lactam formation, probably due to the amine-free nature of the enolate. (3) Diastereomeric ratios of the β-lactam formation were affected by the racemization-free equilibrium process between chiral enolates re-generated by the retro-Michael addition process.

EXPERIMENTAL

General. ^{1}H NMR were measured in $CDCl_3$ or benzene-d_6 and referenced from TMS (0.00 ppm) using JEOL ECX-400 (400 MHz) spectrophotometer, unless otherwise noted. ^{13}C-NMR were measured in $CDCl_3$ or benzene-d_6 and referenced to $\underline{C}DCl_3$ (77.0 ppm) or $\underline{C}_6D_6$ (128.0 ppm) using JEOL ECX-400 (100 MHz) spectrophotometer, unless otherwise noted. Chemical shifts are reported in ppm. When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sept, septet; m, multiplet; br, broadened. IR spectra were recorded on JASCO FT/IR-4200 spectrometer. Mass spectra were obtained on JEOL JMS-700. Elemental analyses were performed with CHN J-science-lab. Microcoder JM10. Optical rotations were determined on HORIBA SEPA-200. Flash column chromatography was performed on Silica Gel (SiliaFlash® F60 or 60N (KANTO)). Thin layer chromatography (TLC) was performed on precoated plates (0.25 mm, silica gel Merck Kieselgel $60F_{245}$), and compounds were visualized with UV light followed by *p*-anisaldehyde stain or phosphomolybdic acid stain. Preparative thin layer chromatography (PTLC) was performed on precoated plates (0.5 mm, silica gel, Merck Kieselgel $60F_{245}$) and visualized with UV light. All anhydrous solvents were purchased from Wako Pure Chemical Corporation or Kanto Chemical Co, Inc. and pre-treated with activated MS3Å for 1 day or longer.

***tert*-Butyl (*S*)-*E*-4-((3-(benzyloxy)-1-ethoxy-1-oxopropan-2-yl)(4-methoxybenzyl)amino)-4-oxobut-2-**

enoate (1). To a solution of *O*-benzyl-L-serine ethyl ester hydrochloride (6.7 g, 25.6 mmol) in DMF (51 mL) were added *i*-Pr_2NEt (12.7 mL, 76.8 mmol) and *p*-methoxybenzyl chloride (3.49 mL, 25.6 mmol) successively at rt. After being stirred for 24 h at 50 ˚C, the resulting mixture was quenched by addition of water and extracted with AcOEt. The extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated. The residual oil was purified through silica gel column chromatography (MeOH/$CHCl_3$ = 1/99) to give *O*-benzyl-*N*-*p*-methoxybenzyl-L-serine ethyl ester (6.5 g, 73%) as a colorless oil. To a solution of fumaric acid mono-*t*-butyl ester (0.78 g, 4.5 mmol) in CH_2Cl_2 (24 mL) were added oxalyl chloride (1.2 mL, 11.3 mmol) and DMF (35 μL, 0.45 mmol) successively at rt. After being stirred for 40 min, the reaction mixture was concentrated to give a crude *t*-butyl (*E*)-4-chloro-4-oxo-2-butenoate, which was dissolved in CH_2Cl_2 (31 mL) and the resulting mixture was added to a solution of *O*-benzyl-*N*-*p*-methoxybenzyl-L-serine ethyl ester (1.3 g, 3.8 mmol) and *i*-Pr_2NEt (1.6 mL, 9.4 mmol) in CH_2Cl_2 (6 mL) at rt. After being stirred for 30 min at the same temperature, the reaction was quenched by addition of sat. aq. $NaHCO_3$ and extracted with $CHCl_3$. The extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residual brown oil was purified through silica gel column chromatography (Et_2O/*n*-hexane = 1/1) to give **1** (0.96 g, 51%) as a pale yellow oil. A 89 : 11 mixture of rotamers of **1**: colorless oil; $[\alpha]_D^{19}$ –74 (*c* 1.07, $CHCl_3$); ^{1}H-NMR (400 MHz, $CHCl_3$): δ 7.37-7.16 (m, 8H), 6.85 (d, *J* = 6.8 Hz, 1.78H), 6.78-6.74 (m, 1.11H), 6.68 (d, *J* = 15.6 Hz, 0.11H) , 4.82 (d, *J* = 17 Hz, 0.89H), 4.76-4.73 (m, 0.22H), 4.69-4.64 (m, 1.78H), 4.48-4.27 (m, 2.33H), 4.20-3.88 (m, 3.77H), 3.83-3.66 (m, 3.22H), 1.49 (s, 0.99H), 1.46 (s, 8.01H), 1.23 (t, *J* = 7.3 Hz, 2.67H), 1.16 (t, *J* = 7.3 Hz, 0.33H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.5, 168.3, 167.0, 165.8, 164.5, 159.0, 158.6, 137.6, 137.2, 134.2, 134.0, 132.7, 132.6, 129.3, 129.0, 128.5, 128.2 (2 peaks), 128.0, 127.7, 127.5, 127.4, 127.37, 113.9, 113.4, 81.4, 73.0, 68.3, 66.9, 61.7, 61.2, 60.2, 59.2, 55.1, 51.6, 27.8, 14.0, 13.8; MS (FAB) *m*/*z* 498 $(M+H)^+$, 520 $(M+Na)^+$, 121 (base peak); HRMS (FAB) *m*/*z* calcd for $C_{28}H_{36}NO_7$ $(M+H)^+$: 498.2492 found 498.2491.

General procedure for the synthesis of β-lactam precursors (4, 6). To a solution of 3,3-di(ethoxycarbonyl)acrylic acid[36] (1.2 eq.) in CH_2Cl_2 (0.2 M) were added oxalyl chloride (3.0 eq.) and DMF (0.1 eq.) successively at rt. After being stirred for 40 min, the reaction mixture was concentrated to give a crude diethyl 2-(2-chloro-2-oxoethylidene)malonate, which was dissolved in CH_2Cl_2 (0.2 M), and the resulting mixture was added to a solution of the corresponding *O*-protected L-serine derivative (1.0 eq.) and *i*-Pr_2NEt (3.0 eq.) in CH_2Cl_2 (0.2 M) at rt. After being stirred for 30 min at same temperature, the reaction was quenched by addition of sat. aq. $NaHCO_3$ and extracted with $CHCl_3$. The extracts were washed with brine, and dried over $MgSO_4$, filtered and concentrated. The residual brown oil was purified through silica gel column chromatography to give the amide.

Diethyl (*S*)-2-(2-((3-(benzyloxy)-1-ethoxy-1-oxopropan-2-yl)(4-methoxybenzyl)amino)-2-oxo-

ethylidene)malonate (4). A 83 : 17 mixture of rotamers of **4**: colorless oil; $[\alpha]_D^{19}$ –52 (*c* 1.09, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 0.17H), 7.35-7.17 (m, 7.83H), 6.85 (d, *J* = 8.7 Hz, 1.66H), 6.78 (d, *J* = 8.7 Hz, 0.34H), 4.77 (d, *J* = 17.0 Hz, 1H), 4.67 (dd, *J* = 6.90, 3.7 Hz, 0.83H), 4.65 (d, *J* = 17.0 Hz, 0.83H), 4.60 (dd, *J* = 7.8, 4.6 Hz, 0.17H), 4.47 (d, *J* = 15.6 Hz, 0.17H), 4.39 (s, 2H), 4.36-4.21 (m, 4H), 4.17-4.07 (m, 2H), 3.97 (dd, *J* = 10.1, 7.4 Hz, 0.83H), 3.92 (dd, *J* = 10.1, 4.1 Hz, 0.83H), 3.80 (s, 1.66H), 3.77 (s, 0.34H), 3.77 (m, 0.17H), 3.66 (dd, *J* = 10.1, 7.8 Hz, 0.17H), 1.33-1.22 (m, 8.49H), 1.18 (t, *J* = 7.3 Hz, 0.51H); ^{13}C-NMR (100 MHz, $CDCl_3$): 168.4, 164.9, 164.4, 162.8, 159.1, 137.7, 135.8, 133.4, 129.2, 128.5, 128.4, 128.3, 128.2, 127.8, 127.6, 127.5, 114.0, 113.5, 73.2, 68.5, 62.1, 61.8, 61.3, 58.6, 55.2, 51.9, 14.0, 13.91, 13.88; IR (neat) cm^{-1}: 2983, 2937, 1741, 1655, 1514, 1449, 1370, 1251, 1207, 1069, 1029; MS (FAB) *m*/*z* 542 $(M+H)^+$, 564 $(M+Na)^+$, 121 (base peak), HRMS (FAB) *m*/*z* calcd for $C_{29}H_{36}NO_9$ $(M+H)^+$: 542.2390 found 542.2394.

Diethyl (*S*)-2-(2-((3-((*tert*-butyldiphenylsilyl)oxy)-1-ethoxy-1-oxopropan-2-yl)(4-methoxybenzyl)-amino)-2-oxoethylidene)malonate (6): A 80 : 20 mixture of rotamers of **6**: colorless oil; $[\alpha]_D^{18}$ –47 (*c* 0.60, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.58-7.11 (m, 12H), 6.84 (d, *J* = 9.2 Hz, 1.6H), 6.74 (d, *J* = 8.7 Hz, 0.4H), 4.82 (d, *J* = 16.9 Hz, 0.8H), 4.76 (d, *J* = 17.0 Hz, 0.8H), 4.70 (dd, *J* = 4.1, 7.3 Hz, 0.8H), 4.58 (d, *J* = 3.2 Hz, 0.2H), 4.54 (dd, *J* = 5.0, 8.2 Hz, 0.2H), 4.32-3.74 (m, 11.2H), 1.31-1.24 (m, 6H), 1.20 (t, *J* = 7.3 Hz, 2.4H), 1.11 (t, *J* = 7.5 Hz, 0.6H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.5, 164.8, 164.5, 162.8, 159.1, 135.9, 135.6, 135.5, 133.0, 132.7, 132.6, 129.8, 129.8, 129.2, 128.3, 127.8, 127.7, 114.1, 113.9, 113.6, 62.6, 62.1, 61.8, 61.3, 60.1, 55.3, 51.6, 26.8, 19.1, 13.9, 13.9; IR (neat) cm^{-1}: 2958, 2933, 2857, 1739, 1656, 1514, 1466, 1426, 1370, 1252, 1205, 1178, 1111, 1069, 1030: MS (FAB) *m*/*z* 690 $(M+H)^+$,712 $(M+Na)^+$, 121 (base peak); HRMS (FAB) *m*/*z* calcd for $C_{38}H_{48}NO_9Si(M+H)^+$: 690.3098 found 690.3095.

Diethyl (*R*)-2-(2-((3-(*tert*-butylthio)-1-ethoxy-1-oxopropan-2-yl)(4-methoxybenzyl)amino)-2-oxo-ethylidene)malonate (8). L-Cysteine (1.0 g, 8.3 mmol) was dissolved in *t*-BuOH (1.0 mL), 3N HCl (4.3 mL). After being stirred at reflux temperature for 11 h, the solvent was evaporated under reduced pressure. The resulting solid was filtered with dry acetone to give crude H-Cys(*t*-Bu)-OH (794 mg). $SOCl_2$ (0.34 mL, 4.7 mmol) was slowly added to EtOH (23.4 mL) at 0 ˚C. After being stirred for 20 min at same temperature, H-Cys(*t*-Bu)-OH (500 mg) was added to the mixture and stirred at rt for 3 days. The reaction mixture was concentrated to give a crude H-Cys(*t*-Bu)-OEt·HCl, which was dissolved in MeOH (10.3 mL) and *p*-anisaldehyde (0.262 mL, 2.5 mmol) was added. After being stirred at same temperature for 2 h, $NaBH_3CN$ (0.26 g, 4.1 mmol) was added and the resulting mixture was stirred for 10 h at rt. The reaction was quenched by addition of sat. aq. $NaHCO_3$ and extracted with AcOEt. The extracts were washed with brine, and dried over $MgSO_4$, filtered and concentrated. The residual brown oil was purified through silica gel column chromatography (AcOEt/*n*-hexane = 3/7) to give *S*-*t*-butyl-*N*-*p*-methoxybenzyl-

L-cysteine ethyl ester (162 mg, 24%) as a colorless oil; $[\alpha]_D^{18}$ –22 (*c* 0.37, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.21 (q, *J* = 6.9 Hz , 2H), 3.80-3.77 (m, 4H), 3.66 (d, *J* = 12.8 Hz, 1H), 3.46 (d, *J* = 6.4 Hz, 1H), 2.84 (m, 2H), 1.31-1.28 (m, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.7, 158.8, 131.7, 129.6, 113.8, 61.0, 60.4, 55.3, 51.4, 42.3, 31.6, 30.9, 14.4: IR (neat) cm^{-1}: 2962, 2902, 2836, 1734, 1612, 1513, 1462, 1367, 1300, 1247, 1178, 1034: MS (FAB) *m*/*z* 326 $(M+H)^+$, 348 $(M+Na)^+$, 121 (base peak); HRMS (FAB) *m*/*z* calcd for $C_{17}H_{28}NO_3S$ $(M+H)^+$: 326.1790 found 326.1786. To a solution of 3,3-di(ethoxycarbonyl)acrylic acid[36] (60 mg, 0.28 mmol) in CH_2Cl_2 (1.4 mL) were added oxalyl chloride (0.076 mL, 2.5 mmol) and DMF (1 drop) successively at rt. After being stirred for 40 min, the reaction mixture was concentrated to give a crude diethyl 2-(2-chloro-2-oxoethylidene)malonate, which was dissolved in CH_2Cl_2 (1.4 mL), and the resulting mixture was added to a solution of *S*-*t*-butyl-*N*-*p*-methoxybenzyl-L-cysteine ethyl ester (60 mg, 0.18 mmol) and *i*-Pr_2NEt (0.096 mL, 0.55 mmol) in CH_2Cl_2 (1.4 mL) at rt. After being stirred for 30 min at same temperature, the reaction was quenched by addition of sat. $NaHCO_3$ and extracted with $CHCl_3$. The extracts were washed with brine, and dried over $MgSO_4$, filtered and concentrated. The residual brown oil was purified through silica gel column chromatography (AcOEt/*n*-hexane = 35/65) to give **8** (57 mg, 59%) as a pale yellow oil. A 80 : 20 mixture of rotamers of **8**: colorless oil; $[\alpha]_D^{18}$ –56 (*c* 1.29, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.54 (s, 0.2H), 7.45-7.27 (m, 2.4H), 7.22 (d, *J* = 8.7 Hz, 0.4H), 6.89 (d, *J* = 8.7 Hz, 1.6H), 6.80 (d, *J* = 8.8 Hz, 0.4H), 4.73 (d, *J* = 16.0 Hz, 0.8H), 4.65 (d, *J* =15.1 Hz, 0.2H), 4.59 (d, *J* = 16.5 Hz, 0.8H), 4.53 (d, *J* = 15.6 Hz, 0.2H), 4.42 (t, *J* = 7.4 Hz, 0.2H), 4.37-3.94 (m, 6.4H), 3.90-3.69 (m, 3.4H), 3.23 (dd, *J* = 8.7, 13.3 Hz , 0.8H), 3.09-2.99 (m, 1 H), 2.78 (dd, *J* = 7.8, 13.8 Hz, 0.2H), 1.36-1.08 (m, 18H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.0, 168.8, 165.7, 165.5, 164.3, 164.3, 162.8, 159.4, 158.9, 136.1, 135.7, 134.3, 133.7, 129.6, 129.3, 128.8, 127.2, 114.0, 113.6, 62.2, 62.0, 61.9, 61.5, 59.9, 55.3, 52.7, 43.0, 42.9, 30.8, 30.7, 28.0, 27.6, 14.0, 13.9, 13.8; IR (neat) cm^{-1}: 2966, 2904, 2839, 1734, 1653, 1514, 1462, 1369, 1303, 1253, 1212, 1069, 1031; MS (FAB) *m*/*z* 524 $(M+H)^+$, 546 $(M+Na)^+$, 121 (base peak), HRMS (FAB) *m*/*z* calcd for $C_{26}H_{38}NO_8S$ $(M+H)^+$: 524.2318 found 524.2313.

General procedure for cyclization of 1 (Table 1). To a solution of **1** (1 eq.) in the exhibited solvent (0.1 M) in Table 1 were added Cs_2CO_3 (2 eq.) and 1 eq. of additive if indicated in Table 1 at 20 ˚C. After being stirred at 20 ˚C for the exhibited time, the reaction was quenched by addition of sat. aq. NH_4Cl and extracted with AcOEt. The extracts were dried over Na_2SO_4, filtered and concentrated. The residual oil was purified through silica gel chromatography (AcOEt/*n*-hexane = 4/6) to give a diastereomeric mixture of **7a** and **7b** and ethyl ether **3**. Mixture of **2a**, **2b**, and **3** were separated by recycle HPLC (AcOEt/*n*-hexane = 1/4, flow = 3.0 mL/min) to obtain **2a**, **2b**, and **3**, respectively. Relative configurations of not only **2a** and **2b** but **3** were not determined.

Ethyl (2*R*)-2-((benzyloxy)methyl)-3-(2-(*tert*-butoxy)-2-oxoethyl)-1-(4-methoxybenzyl)-4-oxoazeti-

dine-2-carboxylate (2a, 2b). 2a: colorless oil; HPLC conditions: Daicel Chiralpak AD-H, hexane/2-propanol = 9/1, flow = 0.9 mL/min, λ = 254 nm, t = 16.9 min, t = 23.2 min; $[\alpha]_D^{18}$ –6.8 (*c* 0.41, $CHCl_3$, 68% ee); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.34-7.16 (m, 7H), 6.78 (d, *J* = 8.7 Hz, 2H), 4.62 (d, *J* = 15.1 Hz, 1H), 4.46 (d, *J* = 11.9 Hz, 1H), 4.28-4.20 (m, 2H), 4.11-4.03 (m, 2H), 3.87 (d, *J* = 9.6 Hz, 1H), 3.77 (s, 3H), 3.64-3.55 (m, 2H), 2.71 (dd, *J* = 4.6, 17.9 Hz, 1H), 2.46 (dd, *J* = 11.0, 17.8 Hz, 1H), 1.40 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.5, 169.5, 167.2, 158.8, 137.5, 129.9, 128.8, 128.3, 127.6, 127.4, 113.6, 81.3, 73.2, 71.0, 67.2, 61.7, 55.2, 51.7, 45.1, 31.3, 27.9, 14.1; IR (neat) cm^{-1}: 2979, 2932, 2867, 1764, 1735, 1612, 1514, 1455, 1392, 1368, 1247, 1154, 1032: MS (FAB) *m/z* 498 $(M+H)^+$, 520 $(M+Na)^+$, 121 (base peak); HRMS (FAB) *m/z* calcd for $C_{28}H_{36}NO_7$ $(M+H)^+$: 498.2492 found 498.2491. **2b**: colorless oil; Daicel Chiralpak AD-H, hexane/2-propanol = 9/1, flow = 0.9 mL/min, λ = 254 nm, t = 16.5 min, t = 19.1 min; $[\alpha]_D^{18}$ –6.5 (*c* 0.77, $CHCl_3$, 70% ee); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36-7.15 (m, 7H), 6.79 (d, *J* = 8.7 Hz, 2H), 4.45 (d, *J* = 15.1 Hz, 1H), 4.34 (d, *J* = 11.9 Hz, 1H), 4.29 (d, *J* = 15.1 Hz, 1H), 4.23 (d, *J* = 11.9 Hz, 1H), 4.16-4.00 (m, 2H), 3.77-3.73 (m, 5H), 4.47 (d, *J* = 10.1 Hz, 1H), 2.71 (d, *J* = 7.8 Hz, 2H), 1.39 (s, 3H), 1.19 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.3, 169.9, 167.7, 158.9, 137.2, 130.0, 128.4, 128.2, 127.8, 127.6, 113.6, 81.3, 73.4, 68.0, 64.5, 61.6, 55.2, 53.5, 44.8, 30.9, 27.9, 13.0; IR (neat) cm^{-1}: 2979, 2931, 2869, 1765, 1732, 1612, 1514, 1456, 1391, 1367, 1248, 1154, 1097, 1063, 1031; MS (FAB) *m/z* 498 $(M+H)^+$, 520 $(M+Na)^+$, 121 (base peak); HRMS (FAB) *m/z* calcd for $C_{28}H_{36}NO_7$ $(M+H)^+$: 498.2492 found 498.2491.

Ethyl (2*R*)-3-(2-(*tert*-butoxy)-2-oxoethyl)-2-(ethoxymethyl)-1-(4-methoxybenzyl)-4-oxoazetidine-2-carboxylate (3). One diastereomer; colorless oil; HPLC conditions: Daicel Chiralcel OD-H, hexane/2-propanol = 90/5, flow = 1.0 mL/min, λ = 230 nm, t = 25.2 min, t = 28.8 min; 1H-NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.2 Hz, 2H), 6.83 (d, *J* = 8.7 H, 2H), 4.64 (d, *J* = 15.1 Hz, 1H), 4.29-4.21 (m, 1H), 4.21 (d, *J* = 15.1 Hz, 1H), 3.28-3.17 (m, 2H), 2.71 (dd, *J* = 17.4, 4.1 Hz, 1H), 2.45 (dd *J* = 17.8, 11.0 H, 1H), 1.43 (s, 9H), 1.24 (t, *J* = 7.6 Hz, 3H), 1.10 (t, *J* = 7.3 Hz, 3H); IR (neat) cm^{-1}: 2983, 2913, 2845, 1767, 1735, 1611, 1588, 1514, 1453, 1388, 1247, 1177, 1105, 1032; MS (FAB) *m/z* 436 $(M+H)^+$, 458 $(M+Na)^+$, 121 (base peak); HRMS (FAB) *m/z* calcd for $C_{23}H_{33}NO_7$ $(M+H)^+$: 436.2335 found 436.2335. The other diastereomer; colorless oil; HPLC conditions: Daicel Chiralpak ID, hexane/2-propanol = 9/1, flow = 1.0 mL/min, λ = 230 nm, t = 37.3 min, t = 43.3 min; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.2 Hz, 2H), 6.82 (d, *J* = 8.2 Hz, 2H), 4.47 (d, *J* = 15.1 Hz, 1H), 4.29 (d, *J* = 15.1 Hz, 1H), 4.19-3.99 (m, 2H), 3.79 (s, 3H), 3.73 (dd, *J* = 9.2, 6.9 Hz, 1H), 3.68 (d, *J* = 10.1 Hz, 1H), 3.54 (d, *J* = 10.1 Hz, 1H), 3.29-3.23 (m, 2H), 2.73-2.71 (m, 2H), 1.43 (s, 9H), 1.20 (t, *J* = 7.3 Hz, 3H), 1.10 (t, *J* = 6.9 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.5, 170.0, 167.9, 159.0, 130.1, 128.3, 113.6, 81.3, 68.0, 66.8, 64.4, 61.6, 55.3, 53.5, 44.8, 30.9, 28.0, 14.9, 14.0: IR (neat) cm^{-1}:2976, 2931, 2873, 1762, 1734, 1613, 1514, 1461, 1390, 1369, 1292, 1244, 1152, 1113, 1064, 1032; MS (FAB) *m/z* 436 $(M+H)^+$, 458 $(M+Na)^+$, 121

(base peak); HRMS (FAB) *m/z* calcd for $C_{23}H_{33}NO_7$ $(M+H)^+$: 436.2335 found 436.2335.

Diethyl 2-((2*R*,3*S*)-2-((benzyloxy)methyl)-2-(ethoxycarbonyl)-1-(4-methoxybenzyl)-4-oxoazetidin-3-yl)malonate (5a) and diethyl 2-((2*R*,3*R*)-2-((benzyloxy)methyl)-2-(ethoxycarbonyl)-1-(4-methoxybenzyl)-4-oxoazetidin-3-yl)malonate (5b). To a solution of **4** (80 mg, 0.15 mmol) in MeCN (0.74 mL) was added a solution of phenol (22 mg, 0.15 mmol) in MeCN (0.74 mL) and the resulting mixture was cooled to –40 ˚C. To this solution was added Cs_2CO_3 (98 mg, 0.30 mmol) at –40 ˚C. After being stirred for 24 h at the same temperature, the reaction was quenched by addition of sat. aq. NH_4Cl, and extracted with AcOEt. The extracts were dried over Na_2SO_4, filtered and concentrated. The residual oil was purified through silica gel column chromatography to give a mixture of **4**, **5a**, and **5b**. The mixture was separated by recycle HPLC (AcOEt/*n*-hexane = 1/4, flow = 3.0 mL/min) to give **5a** (20 mg, 25%) and **5b** (13.2 mg, 17%). The each relative configuration of **5a** and **5b** was determined by NOESY experiment. **5a**: colorless oil; Daicel Chiralcel OD, *n*-hexane/2-propanol = 9/1, flow = 1.0 mL/min, λ = 254 nm, t = 18.4 min (minor), t = 45.3 min (major); $[\alpha]_D^{19}$ –31 (*c* 0.56, $CHCl_3$, 92% ee); ^{1}H-NMR (400 MHz, C_6D_6): δ 7.20-7.03 (m, 7H), 6.67 (d, *J* = 8.7Hz, 2H), 4.61 (d, *J* = 15.1 Hz, 1H), 4.36 (d, *J* = 11.9 Hz, 1H), 4.34 (d, *J* = 15.1 Hz, 1H), 4.21-4.07 (m 2H), 4.11 (d, *J* = 11.9 Hz, 1H), 4.03 (q, *J* = 11.9 Hz, 2H), 3.97 (d, *J* = 10.8 Hz, 1H), 3.94-3.80 (m, 3H), 3.77-3.69 (m, 1H), 3.50 (d, *J* = 10.8 Hz, 1H), 3.27 (s, 3H), 1.04 (t, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 6.9 Hz, 3H), 0.81 (t, *J* = 6.9 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.6, 167.2, 166.8, 164.9, 159.4, 138.1, 130.3, 129.4, 128.5, 128.3, 127.8, 127.7, 113.9, 73.3, 71.1, 66.7, 62.3, 61.9, 61.6, 54.8, 54.7, 50.1, 45.3, 13.9, 13.8, 13.8; IR (neat) cm^{-1}: 2983, 2935, 2869, 1766, 1739, 1612, 1514, 1456, 1392, 1369, 1301, 1249, 1176, 1031; MS (FAB) *m/z* 542 $(M+H)^+$, 564 $(M+Na)^+$, 121 (base peak); HRMS (FAB) *m/z* calcd for $C_{29}H_{36}NO_9$ $(M+H)^+$: 542.2390 found 542.2400. **5b**: colorless oil; Daicel Chiralcel OD, *n*-hexane/2-propanol = 9/1, flow = 1.0 mL/min, λ = 254 nm, t = 20.4 min (minor), t = 94.9 min (major); $[\alpha]_D^{19}$ –19 (*c* 0.92, $CHCl_3$, 92% ee); ^{1}H-NMR (400 MHz, C_6D_6): δ 7.10-7.00 (m, 7H) 6.57 (d, *J* = 8.7 Hz, 2H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.51 (d, *J* = 11.9 Hz, 1H), 4.33 (d, *J* = 14.6 Hz, 1H), 4.16 (d, *J* = 15.1 Hz, 1H), 4.17-4.04 (m, 2H), 3.98 (q, *J* = 12.4 Hz, 2H), 3.86-3.59 (m 6H), 3.20 (s, 3H), 0.99 (t, *J* = 7.3 Hz, 3H), 0.78 (t, *J* = 7.3 Hz, 3H), 0.70 (t, *J* = 6.9 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.9, 167.7, 167.1, 165.7, 159.5, 137.6, 130.5, 128.6, 128.6, 128.3, 128.04, 128.00, 114.0, 73.4, 67.1, 64.2, 62.1, 61.8, 61.5, 56.7, 54.7, 49.4, 44.6, 14.0, 13.8, 13.7; IR (neat) cm^{-1}: 2983, 2935, 2871, 1769, 1735, 1612, 1514, 1458, 1391, 1369, 1301, 1249, 1178, 1098, 1031; MS (FAB) *m/z* 542 $(M+H)^+$, 564 $(M+Na)^+$, 121 (base peak); HRMS (FAB) *m/z* calcd for $C_{29}H_{36}NO_9$ $(M+H)^+$: 542.2390 found 542.2393.

General procedure for cyclization of 4, 6, or 8 with $(CF_3)_2CHOH$. To a solution of **4**, **6**, or **8** (1.0 eq.) and $(CF_3)_2CHOH$ (1.0 eq.) in MeCN (0.1 M solution for substrate) was added Cs_2CO_3 (2.0 eq.) at 0 ˚C. The resulting mixture was stirred for 1 h at 0 ˚C and the reaction was quenched by addition of sat. aq. NH_4Cl. The mixture was extracted with AcOEt. The extracts were washed with brine, and dried over

Na_2SO_4, filtered and concentrated. The residue was purified through silica gel column chromatography.

Diethyl 2-((2*R*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(ethoxycarbonyl)-1-(4-methoxybenzyl)-4-oxoazetidin-3-yl)malonate (7a, 7b). The relative configurations of each diastereomer were not determined. One diastereomer: colorless oil; Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 97/3, flow = 1.0 mL/min, λ = 254 nm, t = 18.0 min (minor), t = 19.6 min (major); $[\alpha]_D^{19}$ –16 (*c* 0.72, $CHCl_3$, 96% ee); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 4.6 Hz, 2H), 7.54 (d, *J* = 6.9 Hz, 2H), 7.48-7.34 (m, 6H) 7.08 (d, *J* = 8.7 Hz, 2H), 6.72 (d, *J* = 8.7 Hz, 2H), 4.50 (d, *J* = 15.1 Hz, 1H), 4.33-4.21 (m, 3H), 4.14-3.79 (m, 8H), 3.75 (s, 3H), 1.29 (t, *J* = 7.3 Hz, 3H), 1.12 (t, *J* = 7.4 Hz, 3H), 1.10 (t, *J* = 7.3 Hz, 3H), 1.06 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.2, 166.7, 166.6, 165.6, 158.9, 135.8, 135.7, 132.4, 130.0, 129.9, 127.8, 127.7, 113.7, 66.8, 63.3, 62.1, 62.0, 61.7, 55.2, 52.9, 49.2, 44.9, 26.8, 19.2, 13.94, 13.80, 13.7; IR (neat) cm^{-1}: 2961, 2934, 2859, 2369, 2315, 1769, 1736, 1650, 1613, 1514, 1468, 1428, 1390, 1370, 1301, 1251, 1177, 1108, 1035; MS (FAB) *m*/*z* 690 $(M+H)^+$, 712 $(M+Na)^+$, 121 (base peak); HRMS (FAB) *m*/*z* calcd for $C_{38}H_{48}NO_9Si$ $(M+H)^+$: 690.3098 found 690.3098. The other diastereomer: olorless oil; Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 9/1, flow = 1.0 mL/min, λ = 254 nm, t = 20.4 min (major), t = 38.3 min (minor); $[\alpha]_D^{19}$ +9 (*c* 0.51, $CHCl_3$, 92% ee); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, *J* = 6.9 Hz, 2H), 7.56-7.34 (m, 8H), 6.78 (d, *J* = 8.2 Hz, 2H), 6.68 (d, *J* = 8.3 Hz, 2H), 4.61 (d, *J* = 15.1 Hz, 1H), 4.44 (d, *J* = 11.9 Hz, 1H), 4.37-4.21 (m, 2H), 4.20-4.04 (m, 5H), 3.87-3.79 (m, 1H), 3.73 (s, 3H), 3.62-3.54 (m, 1H), 3.45 (d, *J* = 14.7 Hz, 1H), 1.32 (t, *J* = 7.3 Hz, 3H), 1.20 (t, *J* = 6.9 Hz, 3H), 1.14 (s, 9H), 0.99 (t, *J* = 6.9 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.5, 167.6, 167.0, 166.0, 158.9, 136.2, 135.7, 132.3, 131.8, 130.3, 130.0, 128.0, 127.8, 126.7, 113.6, 63.9, 62.06, 62.02, 61.4, 59.7, 55.2, 48.3, 44.1, 26.9, 19.0, 13.9, 13.9, 13.6; IR (neat) cm^{-1}: 2961, 2934, 2859, 2369, 2315, 1769, 1736, 1650, 1613, 1514, 1468, 1428, 1390, 1370, 1301, 1251, 1177, 1108, 1035; MS (FAB) *m*/*z* 690 $(M+H)^+$, 712 $(M+Na)^+$, 121 (base peak); HRMS (FAB) *m*/*z* calcd for $C_{38}H_{48}NO_9Si$ $(M+H)^+$: 690.3098 found 690.3098.

Diethyl 2-((2*S*)-2-((*tert*-butylthio)methyl)-2-(ethoxycarbonyl)-1-(4-methoxybenzyl)-4-oxoazetidin-3-yl)malonate (9a, 9b). To a solution of **8** (50 mg, 0.096 mmol) and $(CF_3)_2CHOH$ (16 mg, 0.096 mmol) in MeCN (0.96 ml), which was babbled with Ar for 20 min, was added Cs_2CO_3 (62 mg, 0.19 mmol) at 0 ˚C. After being stirred for 2 h at the same temperature, the reaction was quenched by addition of sat. aq. NH_4Cl and extracted with AcOEt. The extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified through a silica gel column chromatography (AcOEt/*n*-hexane = 35/65) to give **9a** and **9b** as a diastereomeric mixture (43 mg, 86% yield). Diastereomers of **9a** and **9b** were separated by preparative TLC (AcOEt/toluene = 15/85). Relative configurations each diastereomer were not determined. One diastereomer: colorless oil; Daicel Chiralpak IC, *n*-hexane/2-propanol = 1/1, flow = 1.0 mL/min, λ = 230 nm, t = 13.9 min (minor), t = 19.0 min

(major); $[\alpha]_D^{19}$ –31 (*c* 0.45, $CHCl_3$, 91% ee); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 9.6 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.47 (d, *J* = 15.1 Hz, 1H), 4.27 (q, *J* = 7.3 Hz, 2H), 4.22-4.10 (m, 4H), 4.06-3.96 (m, 1H), 3.91-3.83 (m, 1H), 3.81 (d, *J* = 11.4 Hz, 1H), 3.81 (d, *J* = 11.4 Hz, 1H), 3.78 (s, 3H), 3.25 (d, *J* = 12.8 Hz, 1H), 3.05 (d, *J* = 12.8 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.30 (s, 9H), 1.24 (t, *J* = 6.8 Hz, 3H), 1.14 (t, *J* = 6.9 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 169.7, 167.1, 166.6, 159.1, 130.4, 127.4, 113.7, 65.5, 62.2, 62.0, 62.0, 55.5, 55.3, 49.3, 45.3, 42.7, 32.0, 30.7, 13.9, 13.8; IR (neat) cm^{-1}: 2966, 2937, 2868, 1770, 1734, 1613, 1514, 1464, 1389, 1368, 1301, 1248, 1178, 1095, 1033; MS (FAB) *m*/*z* 524 $(M+H)^+$, 546 $(M+Na)^+$, 121 (base peak); HRMS (FAB) *m*/*z* calcd for $C_{26}H_{38}NO_8S$ $(M+H)^+$: 524.2318 found 524.2318. The other diastereomer: colorless oil; Daicel Chiralcel OD-H, *n*-hexane/2-propanol = 8/1, flow = 1.0 mL/min, λ = 230 nm, t = 26.9 min (major), t = 36.9 min (minor); $[\alpha]_D^{19}$ +24 (*c* 0.55, $CHCl_3$, 91% ee); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 9.6 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.50 (d, *J* = 15.1 Hz, 1H), 4.32-4.18 (m, 7H), 4.10-4.02 (m, 1H), 3.96-3.87 (m, 1H), 3.78 (s, 3H), 3.10 (d, *J* = 12.4 Hz, 1H), 2.87 (d, *J* = 12.4 Hz, 1H), 1.32 (t, *J* = 6.8 Hz, 3H), 1.27 (s, 9H), 1.25 (t, *J* = 7.4 Hz, 3H), 1.16 (t, *J* = 6.9 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.9, 167.2, 166.6, 165.4, 159.1, 130.3, 127.6, 113.7, 64.3, 62.19, 62.19, 62.12, 62.0, 56.0, 55.3, 48.5, 45.3, 42.8, 30.3, 29.1, 14.0, 13.8; IR (neat) cm^{-1}:2969, 1769, 1738, 1613, 1514, 1464, 1389, 1369, 1301, 1248, 1178, 1034; MS (FAB) *m*/*z* 690 $(M+H)^+$, 712 $(M+Na)^+$, 121 (base peak); MS (FAB) *m*/*z* 524 $(M+H)^+$, 546 $(M+Na)^+$, 121 (base peak); HRMS (FAB) *m*/*z* calcd for $C_{26}H_{38}NO_8S$ $(M+H)^+$: 524.2318 found 524.2313.

Equilibrium experiment. To a solution of **5b** (47.6 mg, 0.088 mmol, 92% ee) in MeCN (0.88 mL) were added $(CF_3)_2CHOH$ (9.3 μL, 0.088 mmol) and Cs_2CO_3 (57.3 mg, 0.18 mmol) at –10 ˚C. The resulting mixture was stirred for 30 h at the same temperature and quenched by addition of sat. aq. NH_4Cl. The aqueous layer was extracted with AcOEt and the extracts were dried over Na_2SO_4, filtered and concentrated. The residual oil was chromatographed on silica gel (AcOEt/*n*-hexane = 50/50) to give a diastereomeric mixture of **5a** and **5b** (quant, dr = 78/22). The ee of each diastereomer was determined by HPLC after their separation by recycle HPLC. The ee's of **5a** and **5b** were 92% and 92%, respectively.

The equilibrium experiment from **5a** (39.2 mg, 0.072 mmol, 92% ee) was performed as described above. Purification by silica gel column chromatography (AcOEt/*n*-hexane = 50/50) gave a diastereomeric mixture of **5a** and **5b** (quant, dr = 78/22). The ee of each diastereomer was determined by HPLC after their separation by recycle HPLC. The ee's of **5a** and **5b** were 92% and 92%, respectively.

(2*R*,3*R*)-2-((Benzyloxy)methyl)-*N*-(4-iodophenyl)-3-(2-((4-iodophenyl)amino)-2-oxoethyl)-1-(4-methoxybenzyl)-4-oxoazetidine-2-carboxamide (10). To a solution of **5** (40 mg, 0.074 mmol) in THF (0.37 mL) and water (0.37 mL) was added $LiOH·H_2O$ (9.3 mg, 0.22 mmol) at rt. The reaction mixture was stirred at rt for 23 h. The reaction mixture was extracted with sat. aq. $NaHCO_3$. The aqueous layers were acidified to pH 1-2 by dil. HCl and then extracted with AcOEt. The organic layers were dried over

$MgSO_4$, filtered, and evaporated to give a colorless solid (13.2 mg), to which solution in DMF (0.27 mL) were added *p*-iodoaniline (17.7 mg, 0.081 mmol), WSC·HCl (17.1 mg, 0.089 mmol) and HOBt·anhydrous (13.1 mg, 0.097 mmol) and stirred at rt. After for 4 h, *p*-iodoaniline (11.8 mg, 0.054 mmol) was added and stirred for 15 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ and extracted with AcOEt. The organic layers were washed with aq. 10% citric acid, brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by preparative TLC (SiO_2, AcOEt/*n*-hexane = 1/1) to give anilide **10** as colorless solid. Anilide **10** was washed with Et_2O, and recrystallized from CH_2Cl_2/*n*-hexane to give pure crystal **10** (6 mg); ^{1}H-NMR (400MHz, $(CD_3)CO$): δ 10.64 (s, 1H), 9.74 (s, 1H), 7.75-7.70 (m, 4H), 7.57 (d, *J* = 9.2 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.23-7.17 (m, 5H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.66 (d, *J* = 15.1 Hz, 1H), 4.59 (d, *J* = 15.1 Hz, 1H), 4.37-4.30 (m, 2H), 3.99 (dd, *J* = 3.2, 11.9 Hz, 1H), 3.89 (d, *J* = 10.5 Hz, 1H), 3.82 (d, *J* = 10.1 Hz, 1H), 3.80 (s, 3H), 3.25 (dd, *J* = 11.9, 17.8 Hz, 1H), 3.07 (dd, *J* = 3.2, 17.9 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.5, 168.7, 167.7, 159.1, 137.9, 137.7, 137.4, 136.6, 130.3, 128.5, 128.3, 128.1, 127.6, 121.6, 121.4, 113.8, 87.8, 87.5, 73.5, 68.6, 67.0, 55.2, 52.0, 45.8, 31.9; HRMS (FAB) *m*/*z* calcd for $C_{34}H_{31}I_2N_3O_5$ $(M+H)^+$: 816.0432 found 816.0430.

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35. Crystal data of **10**: $C_{34}H_{31}I_2N_3O_5$, M = 815.42, space group $P2_12_12_1$(#19), a = 9.6903 (7) Å, b = 12.0516 (8) Å, c = 27.1658 (19)Å, a = 90°, b = 90°, g = 90°, V = 3172.5 (4)Å^3, Z = 4, r_{calcd} = 1.707 Mg/m^3, Mo_{Ka} radiation, l = 0.71069 Å, m = 2.029 mm^{-1}, T = 173 (2) K. The final *R1* and w*R2* were 0.0528 and 0.1203, respectively. Flack parameter = 0.004 (3). CCDC 1835178 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/
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