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## PROTONATION-ASSISTED CONJUGATE ADDITION OF AXIALLY CHIRAL ENOLATES: ASYMMETRIC SYNTHESIS OF $\beta$ -LACTAMS WITH CONTIGUOUS TETRASUBSTITUTED STEREOCENTERS FROM $\alpha$ -AMINO ACIDS VIA MEMORY OF CHIRALITY

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Dedicated to Professor Emeritus Kaoru Fuji for the celebration of his 80th birthday (Sanju)

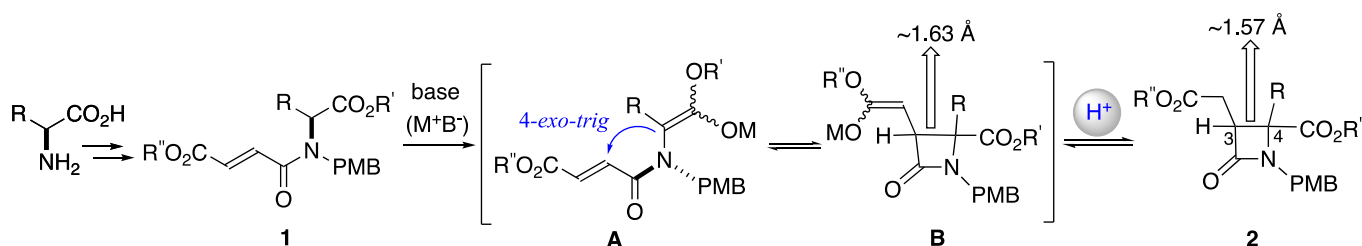
**Abstract** – A method for asymmetric synthesis of highly strained  $\beta$ -lactams with contiguous two tetrasubstituted stereocenters from readily available  $\alpha$ -amino acids has been developed via MOC strategy. *In situ* protonation of the labile  $\beta$ -lactam enolate intermediates formed through 4-*exo-trig* cyclization of the axially chiral enolates generated from  $\alpha$ -amino acid derivatives seems to be the key to successfully produce highly strained  $\beta$ -lactams. A salient feature of this transformation is that a proton source does not quench axially chiral enolate C, but accelerate the overall reaction by protonation of the intermediary  $\beta$ -lactam enolate D.

## INTRODUCTION

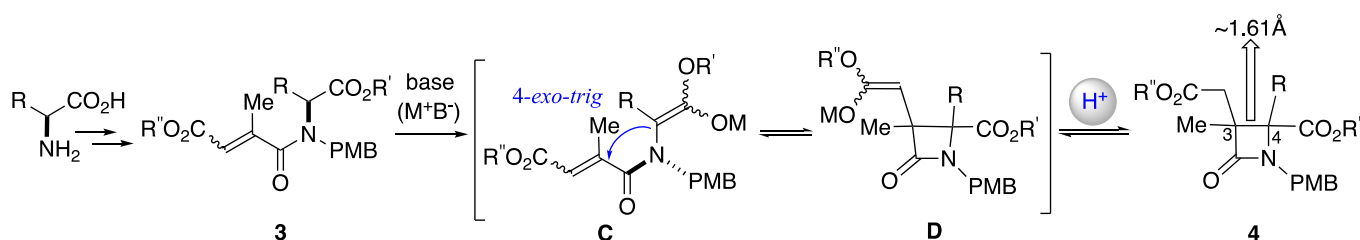
We have studied asymmetric reactions that proceed via enolate intermediates with dynamic chirality (memory of chirality: MOC).<sup>1</sup> Various types of chiral enolates with restricted bond rotation around chiral C-C,<sup>2</sup> C-N,<sup>3-13</sup> and C-O<sup>14,15</sup> axes have been utilized in MOC strategy. The major advantage of the strategy is the use of readily available  $\alpha$ -amino acids as starting materials as well as the sole source of chirality. For example, naturally abundant  $\alpha$ -amino acids can be transformed to optically active  $\beta$ -lactams without

the use of any external chiral sources such as chiral catalysts or chiral auxiliaries.<sup>10,13</sup> Since  $\beta$ -lactams still constitute one of the most important pharmacophores,<sup>16,17</sup> and are useful as  $\beta$ -amino acid equivalents<sup>18</sup> and chiral building blocks,<sup>19</sup> development of synthetic methods for  $\beta$ -lactams is still of importance.<sup>20,21</sup> Our synthetic scheme of  $\beta$ -lactams by MOC strategy is shown in Scheme 1a. Axially chiral enolate **A** generated from  $\alpha$ -amino acid derivative **1** would undergo 4-*exo-trig* cyclization to afford the desired optically active  $\beta$ -lactams by the intervention of  $\beta$ -lactam enolate **B**. We had initially expected that formation of enolate **B** might be unfavorable because the conjugate addition of enolate **A** would produce highly strained  $\beta$ -lactam enolate **B** with a labile C-C bond (1.63 Å by DFT calculations when R=R'=R''=Me and M=Cs).<sup>10</sup> We have solved this problem by performing the enolate reaction in the presence of a proton source. Protonation of the  $\beta$ -lactam enolates **B** immediately after its generation successfully gave  $\beta$ -lactams with contiguous tri- and tetrasubstituted stereocenters in a highly enantioselective manner.<sup>10,13</sup>

a) Previous work: synthesis of  $\beta$ -lactams with contiguous tri- and tetrasubstituted stereocenters via protonation of strained enolate **B**



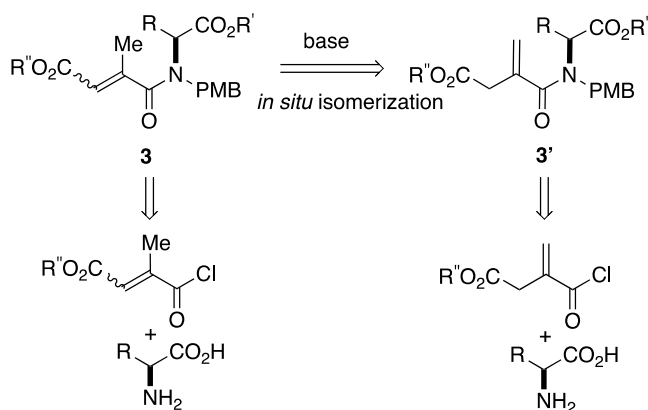
b) This work: synthesis of  $\beta$ -lactams with contiguous two tetrasubstituted stereocenters via protonation of further strained enolate **D**



Scheme 1

The C(3)-C(4) bond length of one of the  $\beta$ -lactams obtained by this method was found to be 1.574 Å by an X-ray single crystal structural analysis.<sup>10</sup> A further challenge in the  $\beta$ -lactam synthesis via the MOC strategy is its application to the synthesis of  $\beta$ -lactams with contiguous tetrasubstituted stereocenters (Scheme 1b),<sup>22</sup> because the intermediary  $\beta$ -lactam enolate **D** is expected to be further strained than **B**. Here, we report our approach toward this goal. A  $\beta$ -lactam with contiguous tetrasubstituted stereocenters obtained by this work was found to have a long C(3)-C(4) bond (up to 1.611 Å).

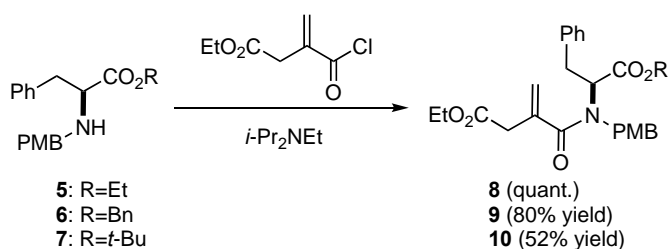
## RESULTS AND DISCUSSION



Scheme 2

The expected precursor for the  $\beta$ -lactams with contiguous tetrasubstituted stereocenters was initially assigned as **3** (Scheme 1b). However, we found that amino acid derivative **3'** (Scheme 2) can be a synthetic equivalent to **3** by *in situ* isomerization of the double bond in the presence of a base employed for the MOC process. Because the corresponding acid chloride for the preparation of **3'** is readily available, we chose **3'**, instead of **3**, as the starting material for the  $\beta$ -lactam synthesis via MOC strategy.

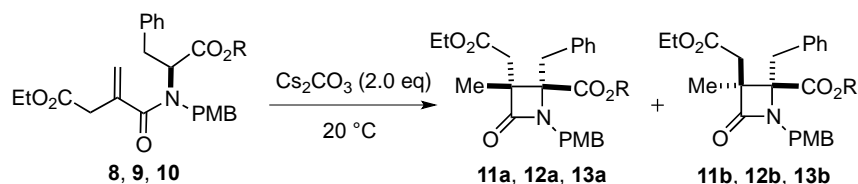
As  $\beta$ -lactam precursor **3'**, amino acid derivatives **8–10** were prepared by acylation of L-phenylalanine ester derivatives **5–7**<sup>10</sup> with ethyl 3-(chlorocarbonyl)but-3-enoate<sup>23</sup> (Scheme 3).



Scheme 3

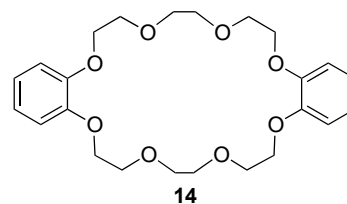
$\beta$ -Lactam formation from **8–10** was examined (Table 1).  $\alpha$ -Amino acid derivative **8** was first treated under the previously optimized conditions for  $\beta$ -lactam formation.<sup>10</sup> Treatment of **8** with 2 equivalents of Cs<sub>2</sub>CO<sub>3</sub> in EtOH at 20 °C for 2 h gave a 5:1 diastereomeric mixture of **11a** (67% ee) and **11b** in 5% combined yield (Table 1, entry 1). Because decomposition of  $\beta$ -lactam **11** was observed under the reaction conditions, the low yield could be attributed to nucleophilic properties of EtOH at least to some extent. Since a proton source is indispensable for the  $\beta$ -lactam formation under the MOC conditions,<sup>10,13</sup> a less nucleophilic and stronger proton source, CF<sub>3</sub>CH<sub>2</sub>OH (pK<sub>a</sub> of CF<sub>3</sub>CH<sub>2</sub>OH=12.4 vs. pK<sub>a</sub> of EtOH=15.9), was next examined. On treatment of **8** with Cs<sub>2</sub>CO<sub>3</sub> in acetonitrile in the presence of 1.5

equivalents of  $\text{CF}_3\text{CH}_2\text{OH}$  for 2 h at 20 °C, a 6:1 diastereomeric mixture of **11a** and **11b** was obtained in an improved combined yield of 35%. The enantioselectivity for the formation of  $\beta$ -lactam **11a** was decreased to 47% ee (entry 2). Since the significant increase in the yield was observed, a  $\text{CF}_3\text{CH}_2\text{OH}/\text{MeCN}$  system was applied to  $\beta$ -lactam formation with benzyl ester **9** and *tert*-butyl ester **10**. Treatment of **9** under the identical conditions in entry 2 gave a 5:1 diastereomeric mixture of **12a** (44% ee) and **12b** in a combined yield of 61% (entry 3). Similarly, a 3:1 diastereomeric mixture of **13a** (29% ee) and **13b** (40% ee) was obtained by the similar treatment of **10** (entry 4). While the best yield (61%) was obtained in the transformation of benzyl ester **9** to  $\beta$ -lactam **12**, we further investigated asymmetric  $\beta$ -lactam formation with ethyl ester **8** because of the better enantioselectivity (entry 1, 47% ee). We then examined the effect of dibenzo-24-crown-8 ether (**14**) in order to facilitate the conjugate addition of the expected cesium enolate such as **C** in Scheme 1b.<sup>24</sup> Treatment of **8** with  $\text{Cs}_2\text{CO}_3$  and  $\text{CF}_3\text{CH}_2\text{OH}$  in acetonitrile in the presence of 2 equivalents of **14** for 2 h gave a 2:1 diastereomeric mixture of **11a** (32% ee) and **11b** (48% ee) in a combined yield of 91% (entry 5). The effect of **14** on significantly increasing the yield of the  $\beta$ -lactam formation could be attributed to improving solubility of  $\text{Cs}_2\text{CO}_3$  and increasing reactivity of the cesium enolate. Although the enantioselectivity is far from satisfaction, it is worthy to note that highly strained  $\beta$ -lactam **11** was successfully obtained in 91% yield via reversible intramolecular conjugate addition of the enolate. While the use of  $\text{CF}_3\text{CH}_2\text{OH}$  is effective for increasing the yield of  $\beta$ -lactam formation, EtOH seems more suitable for better enantioselectivity of the  $\beta$ -lactam formation. We then investigated the effect of EtOH as a proton source in the presence of **14**. Treatment of **8** with  $\text{Cs}_2\text{CO}_3$  in EtOH/MeCN (1:1) for 2 h gave a 3:1 diastereomeric mixture of **11a** (60% ee) and **11b** in a combined yield of 26% (entry 6). While the enantioselectivity was increased as expected, a significant decrease in the yield was observed. We reported that enantioselectivity and diastereomeric ratio of the  $\beta$ -lactam formation by MOC strategy were affected by the reaction time.<sup>10,13</sup> A time-dependent gradual decrease in enantioselectivity of  $\beta$ -lactam formation has been observed, which is attributed to partial racemization of intermediary chiral enolates such as **A** regenerated in an equilibrium process between **B** and **A** (Scheme 1a). Based on these backgrounds, the reaction of **8** was performed for only 0.3 h under the identical conditions in entry 6 except for the reaction time to give a single diastereomer **11a** in 79% ee and 7% yield (entry 7). The use of *t*-amyl alcohol ( $\text{p}K_a \sim 18$ ) as a proton source instead of EtOH (entry 1,  $\text{p}K_a$  15.9) or  $\text{CF}_3\text{CH}_2\text{OH}$  (entry 2,  $\text{p}K_a$  12.4) resulted in recovery of the starting material even after prolonged reaction time (20 h) (entry 8). These results again indicate that a proton source is a key factor for the acceleration of the reaction.

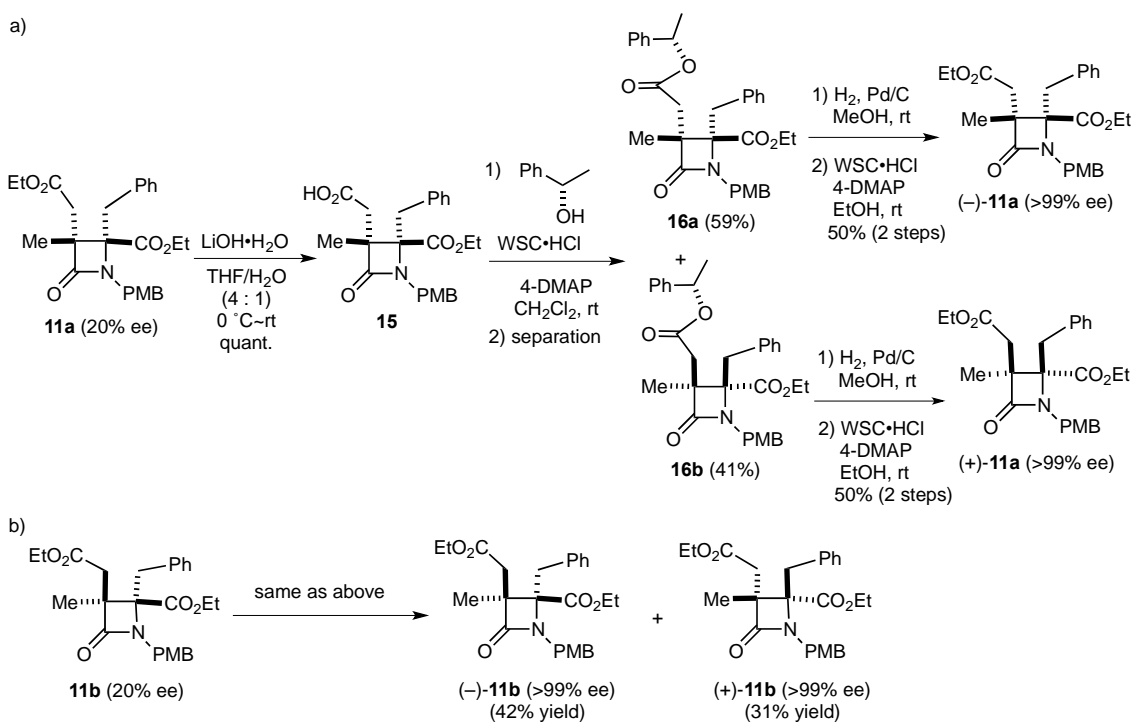
**Table 1.** Asymmetric Intramolecular Conjugate Addition of  $\alpha$ -Amino Acid Derivatives **8**, **9**, and **10**<sup>a</sup>

entry	substrate	R	solvent	additive (eq.)	time (hr)	product	yield (%) <sup>b</sup>	a/b <sup>c,d,e</sup>	ee of a (%) <sup>f</sup>	ee of b (%) <sup>f</sup>
1	<b>8</b>	Et	EtOH	–	2	<b>11a, 11b</b>	5	5 : 1	67	–
2	<b>8</b>	Et	MeCN	CF <sub>3</sub> CH <sub>2</sub> OH (1.5)	2	<b>11a, 11b</b>	35	6 : 1	47	–
3	<b>9</b>	Bn	MeCN	CF <sub>3</sub> CH <sub>2</sub> OH (1.5)	2	<b>12a, 12b</b>	61	5 : 1	44	–
4	<b>10</b>	<i>t</i> -Bu	MeCN	CF <sub>3</sub> CH <sub>2</sub> OH (1.5)	24	<b>13a, 13b</b>	34	3 : 1	29	40
5	<b>8</b>	Et	MeCN	CF <sub>3</sub> CH <sub>2</sub> OH (2.0), <b>14</b> (2.0)	2	<b>11a, 11b</b>	91	2 : 1	32	48
6	<b>8</b>	Et	MeCN/EtOH (1/1)	<b>14</b> (2.0)	2	<b>11a, 11b</b>	26 <sup>i</sup>	3 : 1	60	–
7	<b>8</b>	Et	MeCN/EtOH (1/1)	<b>14</b> (2.0)	0.3	<b>11a</b>	7	a only	79	–
8	<b>8</b>	Et	<i>t</i> -amyl alcohol	<b>14</b> (2.0)	20	– <sup>g</sup>	– <sup>g</sup>	–	–	–

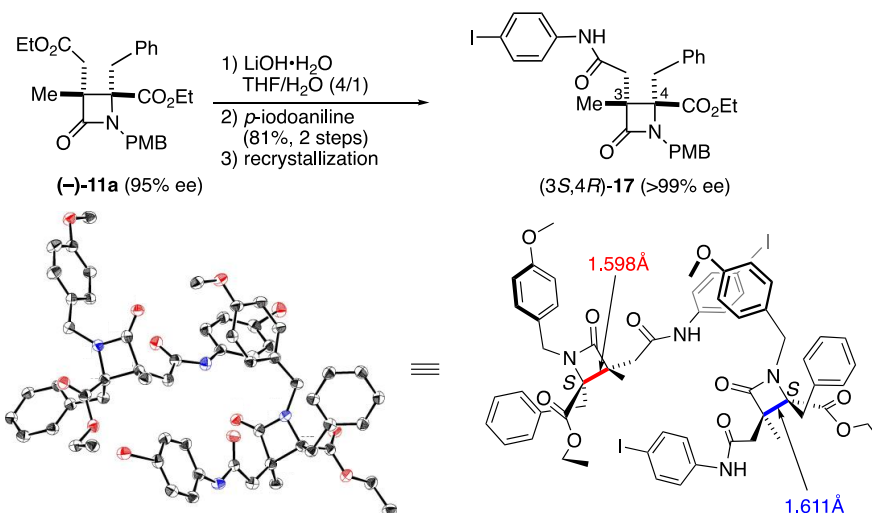
a) Run with a substrate concentration of 0.05 M. b) Yield of a diastereomeric mixture. c) The ratio was determined by <sup>1</sup>H NMR (400 MHz). d) Relative configuration of **11a** was determined by NOESY experiments (See Supplementary Information SI 10). Relative configuration of other products was tentatively assigned by analogy. e) Absolute configuration of **11a** was determined to be (3*R*,4*S*) by an X-ray analysis of **17** derived from **11a** (*vide infra*). Absolute configuration of other products was tentatively assigned by analogy. f) Ee was determined by HPLC analysis with chiral stationary phases. g) No reaction.



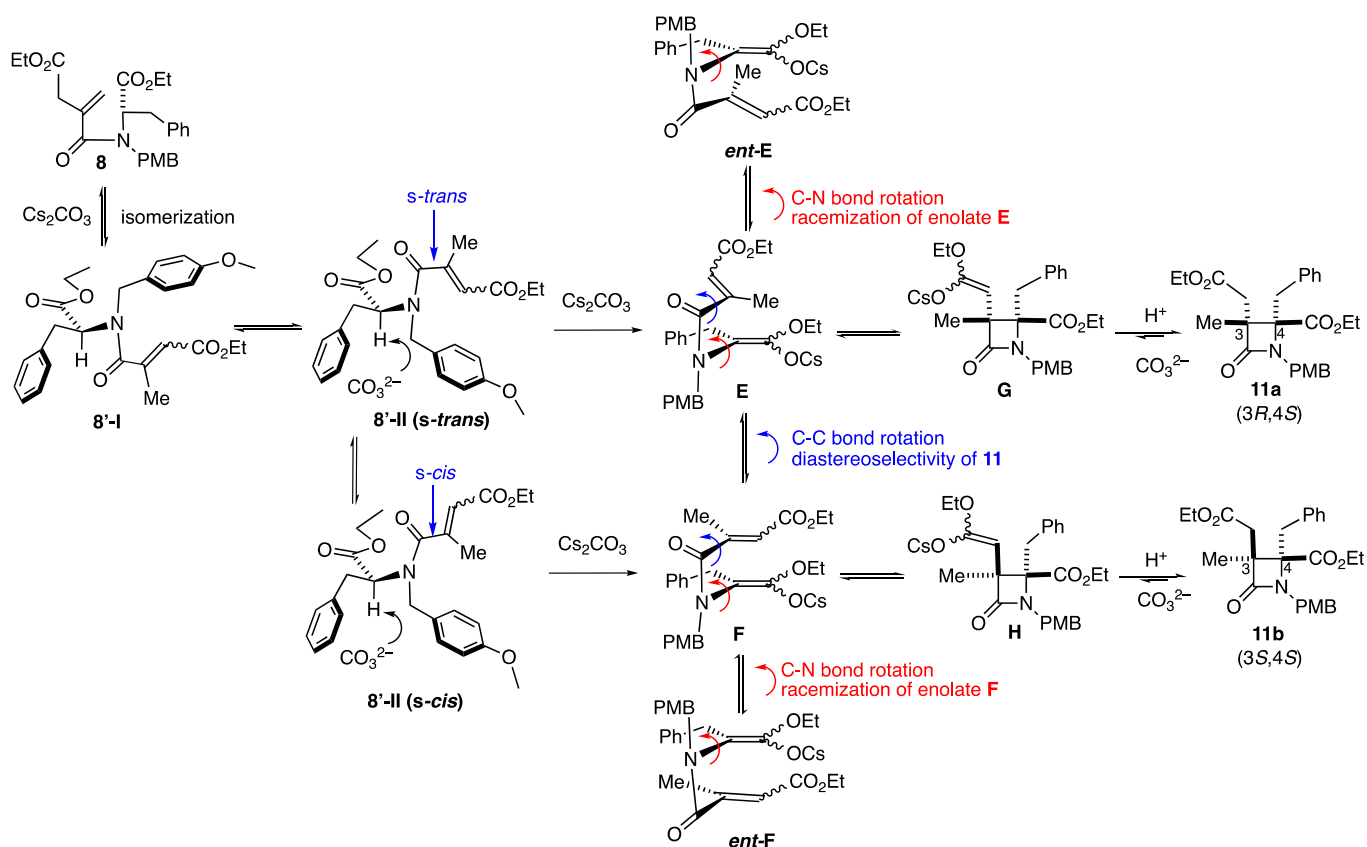
Further improvement in the enantioselectivity for the synthesis of  $\beta$ -lactams with contiguous two tetrasubstituted stereocenters could not be achieved after numerous attempts including performing the reaction at lower temperatures and the use of various proton sources such as *t*-amyl alcohol with higher *pK<sub>a</sub>* (~ 18) and (CF<sub>3</sub>)<sub>2</sub>CHOH (*pK<sub>a</sub>* 9.3). We then performed optical resolution of **11a** and **11b** to provide all four diastereo- and enantiomerically pure **11** (Scheme 4) because chiral multifunctionalized  $\beta$ -lactams with contiguous tetrasubstituted stereocenter such as **11** have been quite rare.<sup>22</sup> Selective ester hydrolysis of **11a** (20% ee) with LiOH•H<sub>2</sub>O in THF/H<sub>2</sub>O gave monoester carboxylic acid **15**. A mixture of chiral esters **16a** and **16b** obtained by condensation of **15** with (*S*)-1-phenylethanol was separated by recyclable HPLC to provide diastereomerically pure **16a** and **16b**. Removal of the (*S*)-1-phenylethyl moiety of diastereomerically pure **16a** and **16b** by hydrogenolysis followed by esterification of the resulting carboxylic acids with EtOH gave optically pure (–)-**11a** and (+)-**11a**, respectively. Similarly, optically pure (–)-**11b** and (+)-**11b** were obtained from **11b** (20% ee) in 42% and 31% overall yield, respectively.



The absolute configuration of (–)-**11a** was determined by an X-ray single crystal analysis (Scheme 5).<sup>25</sup> Hydrolysis of enantiomerically enriched **11a** (95% ee) followed by condensation with *p*-iodoaniline gave amide **17** as a solid. After recrystallization of **17** from EtOH/hexane, single crystals of **11a** (>99% ee) suitable for an X-ray analysis were obtained. The X-ray analysis revealed two conformers of  $\beta$ -lactam **17**. The absolute configuration of each conformer was determined to be (3*R*,4*S*). Thus, the intramolecular conjugate addition of **8** was found to proceed with inversion of configuration. The bond length between C(3) and C(4) of the two conformers was determined to be 1.598 Å and 1.611 Å, which are longer than the usual C(sp<sup>3</sup>)–C(sp<sup>3</sup>) bond length (1.54 Å).



The stereochemical course of the  $\beta$ -lactam formation via MOC has been extensively studied.<sup>10</sup> A possible rationale for the stereochemical course for the formation of  $\beta$ -lactams **11a** and **11b** from **8** is described based on the previous proposal<sup>10</sup> (Scheme 6). Double bond isomerization of **8** would first take place in the presence of  $\text{Cs}_2\text{CO}_3$  to give **8'** consisting of conformers **8'-I** and **8'-II**. The C( $\alpha$ )-H bond in conformer **8'-I** is synperiplanar with respect to the adjacent N-C(=O) bond, whereas that in conformer **8'-II** is antiperiplanar with respect to the adjacent N-C(=O) bond. Deprotonation of **8'** with  $\text{Cs}_2\text{CO}_3$  is expected to take place preferentially from antiperiplanar conformers **8'-II (s-trans)** and **8'-II (s-cis)** to give chiral enolates **E** and **F**, respectively with *aS* configuration. The stereochemical course of the enantioselective formation of the chiral enolate **E** and **F** was assumed based on our rationale for previous stereochemical results, in which deprotonation of *N*-Boc-*N*-alkyl- $\alpha$ -amino acid derivatives took place preferentially from the conformer in which C( $\alpha$ )-H bond is antiperiplanar with respect to the neighboring N-C(Boc) bond.<sup>3,4,6</sup> Chiral enolate **F** may be alternatively formed via *s-trans/s-cis* interconversion between enolate **E** and **F** through fast rotation (blue arrow) of the C-C bond of **E**. Enolate **E** is expected to undergo intramolecular conjugate addition from its *si*-face of the enolate to give  $\beta$ -lactam enolate **G** in inversion of the configuration at C(4). Similarly, enolate **F** would give  $\beta$ -lactam enolate **H** with the same absolute configuration at C(4) as that of **G**. Protonation of **G** and **H** would give  $\beta$ -lactams (3*R*,4*S*)-**11a** and (3*S*,4*S*)-**11b**, respectively.



Scheme 6

In summary, we have developed a method for asymmetric synthesis of highly strained  $\beta$ -lactams with contiguous tetrasubstituted stereocenters from naturally abundant  $\alpha$ -amino acids via MOC strategy. The reaction was assumed to proceed via 4-*exo-trig* cyclization of the axially chiral enolates generated from  $\alpha$ -amino acid derivatives followed by *in situ* protonation of the resulting labile  $\beta$ -lactam enolates. A salient feature of this transformation is that a proton source does not quench the axially chiral enolate, but accelerate the overall reaction by protonation of the intermediary  $\beta$ -lactam enolate.

## EXPERIMENTAL

**General.**  $^1\text{H}$  NMR were measured in  $\text{CDCl}_3$  or  $\text{C}_6\text{D}_6$  solution and referenced from TMS (0.00 ppm), or  $\text{C}_6\text{D}_5\text{H}$  (7.15 ppm) using JEOL ECX-400 (400 MHz) spectrophotometer, unless otherwise noted.  $^{13}\text{C}$  NMR were measured in  $\text{CDCl}_3$  or  $\text{C}_6\text{D}_6$  solution and referenced to  $\text{CDCl}_3$  (77.0 ppm) or  $\text{C}_6\text{D}_6$  (128 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; 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<sup>®</sup> F60). Thin layer chromatography was performed on precoated plates (0.25 mm, silica gel Merck Kieselgel 60F<sub>245</sub>), and compounds were visualized with UV light and phosphomolybdic acid stain or ninhydrin stain. Preparative thin layer chromatography was performed on precoated plates (0.5 mm, silica gel Merck Kieselgel 60F<sub>245</sub>) and visualized with UV light. Anhydrous solvents were purchased from Kanto Chemical or Wako Pure Chemical Industries and pre-treated with activated MS 4Å for 1 day or longer.

**General procedure for synthesis of amides 8, 9, and 10.** To a solution of itaconic acid monoethyl ester (1.2 eq.) in  $\text{Et}_2\text{O}$  (0.1 M) were added  $(\text{COCl})_2$  (1.2 eq.) and a few drops of DMF at rt under Ar. The reaction mixture was refluxed for 4 h with stirring and the solvent was evaporated immediately. The resulting acyl chloride was used for the next step without any purifications. A solution of acyl chloride in  $\text{CH}_2\text{Cl}_2$  was added to a mixture of L-phenylalanine derivative (**5**, **6**, or **7**) (1.0 eq.) and DIPEA (3.0 eq.) in  $\text{CH}_2\text{Cl}_2$  (final concentration of **5**, **6**, or **7** was 0.1 M) at 0 °C under Ar. Then the reaction was allowed to warm up to rt and stirred for 4 h. After quenching with  $\text{H}_2\text{O}$ , the reaction mixture was extracted with AcOEt (3 times). The extracts were washed with brine (1 time) and dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The residue was purified through a silica gel column chromatography (AcOEt:Hexane = 40:60).

**Amide 8.** Following the general procedure, reaction with L-phenylalanine ethyl ester derivative **5** gave amide **8** as a yellow oil quantitatively. A mixture of rotamers;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.25-1.28

(m, 6H), 1.70 (br s, 2H), 3.24 (br s, 1H), 3.44 (br s, 2H), 3.79 (s, 3H), 3.84 (br s, 1H), 4.11-4.19 (m, 4H), 4.80-4.84 (m, 1H), 5.30 (br s, 1H), 5.35 (s, 1H), 6.79 (s, 1H), 6.81 (s, 1H), 7.12-7.27 (m, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.1, 16.5, 34.8, 34.9, 44.9, 55.4, 55.2, 59.5, 60.3, 61.7, 62.7, 113.6, 113.9, 118.9, 119.1, 126.8, 128.6, 129.3, 129.8, 138.0, 150.5, 159.3, 165.6, 169.6, 171.3; IR (neat) 701, 1035, 1134, 1199, 1246, 1367, 1142, 1513, 1637, 1718, 2930; MS (EI)  $m/z$  453 ( $\text{M}^+$ ), HRMS (EI)  $m/z$  calcd for  $\text{C}_{26}\text{H}_{31}\text{NO}_6$  ( $\text{M}^+$ ): 453.2151, found 453.2151; Anal. Calcd for  $\text{C}_{26}\text{H}_{31}\text{NO}_6$ : C, 68.86; H, 6.89; N, 3.09. Found C, 68.38; H, 6.82; N, 3.09.

**Amide 9.** Following the general procedure, reaction with L-phenylalanine benzyl ester derivative **6** gave amide **9** as a yellow oil in 80% yield. A mixture of rotamers;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.25 (t,  $J = 7.3$  Hz, 3H), 3.20-3.50 (m, 4H), 3.74 (br s, 1H), 3.74 (s, 3H), 3.89 (br s, 1H), 4.13 (q,  $J = 7.3$  Hz, 2H), 4.81-4.84 (m, 1H), 5.0-5.33 (m, 3H), 6.66 (br s, 1H), 6.83 (br s, 1H), 6.99 (br, 2H), 7.00-7.40 (m, 14H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.0, 14.2, 16.5, 34.7, 53.5, 55.2, 59.5, 60.3, 67.3, 77.3, 113.7, 113.8, 119.0, 126.5, 126.0, 128.4, 128.5, 128.7, 129.4, 129.8, 150.4, 159.28, 165.6, 169.5, 171.2; MS (FAB)  $m/z$  516 ( $[\text{M}+\text{H}]^+$ ), HRMS (FAB)  $m/z$  calcd for  $\text{C}_{31}\text{H}_{34}\text{NO}_6$  ( $[\text{M}+\text{H}]^+$ ): 516.2386, found 516.2387; Anal. Calcd for  $\text{C}_{31}\text{H}_{33}\text{NO}_6$ : C, 72.21; H, 6.45; N, 2.72. Found C, 72.28; H, 6.48; N, 2.72.

**Amide 10.** Following the general procedure, reaction with L-phenylalanine *t*-butyl ester **7** gave amide **10** as a yellow oil in 52% yield. A mixture of rotamers;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.27 (t,  $J = 5.9$  Hz, 3H), 1.45 (s, 9H), 1.75 (br s, 2H), 2.04 (s, 1.5 H), 2.30 (s, 1.5H), 3.29-3.40 (m, 2H), 3.79 (s, 3H), 3.79-3.83 (m, 1H), 4.10-4.18 (m, 3H), 4.32 (d,  $J = 16.0$  Hz, 0.7H), 4.50-4.54 (m, 0.5H), 4.74 (br d,  $J = 16.0$  Hz, 0.3H), 5.45 (br s, 0.3H), 5.79 (br s, 0.7H), 6.77-6.96 (m, 2H), 7.10-7.41 (m, 9H); IR (neat) 1155, 1256, 1367, 1455, 1513, 1648, 1736, 2854, 2926, 2960  $\text{cm}^{-1}$ ; MS (FAB)  $m/z$  482 ( $[\text{M}+\text{H}]^+$ ), 504 ( $[\text{M}+\text{Na}]^+$ ), HRMS (FAB)  $m/z$  calcd for  $\text{C}_{28}\text{H}_{36}\text{NO}_6$  ( $[\text{M}+\text{H}]^+$ ) 482.2543, found 482.2524.

**Synthesis of  $\beta$ -lactam 11. (Entry 1, Table 1):** Freshly powdered  $\text{Cs}_2\text{CO}_3$  (2.0 eq.) was added to a solution of amide **8** (1.0 eq.) in anhydrous EtOH (concentration was 0.05 M) at 20 °C under Ar. After stirring for 2 h, the reaction was quenched with saturated  $\text{NH}_4\text{Cl}$  aq. The resulting mixture was extracted with AcOEt for 3 times and the extracts were washed with brine. The organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The residue was purified on a preparative thin layer chromatography (AcOEt:Hexane = 30:70). Separation of diastereomers was performed through recyclable HPLC (AcOEt:Hexane = 30:70).

**(Entry 2-4, Table 1):** To a solution of amide (**8**, **9** or **10**) (1.0 eq.) and in anhydrous MeCN (concentration was 0.05 M) were added  $\text{CF}_3\text{CH}_2\text{OH}$  (1.5 eq.) and freshly powdered  $\text{Cs}_2\text{CO}_3$  (2.0 eq.) at 20 °C under Ar. After stirring for 2 h (entry 4: 24 h), the reaction was quenched with saturated  $\text{NH}_4\text{Cl}$  aq. The resulting mixture was extracted with AcOEt for 3 times and the extracts were washed with brine. The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The

residue was purified on a preparative thin layer chromatography (AcOEt:Hexane = 30:70). Separation of diastereomers was performed through recyclable HPLC (AcOEt:Hexane = 30:70).

**(Entry 5, Table 1):** Freshly powdered Cs<sub>2</sub>CO<sub>3</sub> (86 mg, 0.27 mmol) was added to a solution of amide **8** (60 mg, 0.13 mmol), CF<sub>3</sub>CH<sub>2</sub>OH (17 μL, 0.27 mmol), and dibenzo-24-crown-8 ether (118 mg, 0.27 mmol) in MeCN (5.4 mL) at 20 °C under Ar. After stirring for 2 h (or 0.3 h), the reaction was quenched with saturated NH<sub>4</sub>Cl aq. The resulting mixture was extracted with AcOEt for 3 times and the extracts were washed with brine. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified on a preparative thin layer chromatography (AcOEt:Hexane = 30:70) to give a diastereomeric mixture of **11a** and **11b** (54.6 mg, 91%) as a pale yellow oil. Separation of diastereomers **11a** and **11b** was performed through recyclable HPLC (AcOEt:Hexane = 30:70).

**(Entry 6-7, Table 1):** To a solution of amide **8** (1.0 eq.) in MeCN/EtOH (1/1) (concentration was 0.05 M) were added dibenzo-24-crown-8 ether (2.0 eq.) and freshly powdered Cs<sub>2</sub>CO<sub>3</sub> (2.0 eq.), successively at 20 °C under Ar. After stirring for 2 h (or 0.3 h), the reaction was quenched with saturated NH<sub>4</sub>Cl aq. The resulting mixture was extracted with AcOEt for 3 times and the extracts were washed with brine. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified on a preparative thin layer chromatography (AcOEt:Hexane = 30:70). Separation of diastereomers **11a** and **11b** was performed through recyclable HPLC (AcOEt:Hexane = 30:70).

**β-Lactam 11a:** Colorless oil; <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>): δ 0.82 (t, *J* = 7.3 Hz, 3H), 0.96 (t, *J* = 6.9 Hz, 3H), 2.66 (d, *J* = 16.5 Hz, 1H), 2.71 (d, *J* = 16.5 Hz, 1H), 2.88 (d, *J* = 13.8 Hz, 1H), 3.28 (s, 3H), 3.88 (m, 7H), 4.47 (d, *J* = 15.6 Hz, 1H), 6.74 (m, 2H), 7.01 (m, 5H), 7.19 (m, 2H); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.28 (t, *J* = 5.8 Hz, 3H), 1.30 (t, *J* = 5.8 Hz, 3H), 1.40 (s, 3H), 2.82 (d, *J* = 15.4 Hz, 1H), 2.90-2.95 (m, 2H), 3.77-3.81 (m, 2H), 3.78 (s, 3H), 4.19-4.32 (m, 5H), 6.78-6.80 (m, 2H), 6.87-7.03 (m, 4H), 7.14-7.25 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 14.2, 17.6, 36.3, 39.5, 46.3, 55.2, 58.6, 60.9, 61.4, 73.0, 113.5, 127.2, 128.5, 128.8, 129.5, 129.8, 135.2, 158.5, 169.9, 171.0, 171.3; IR (neat) 1032, 1085, 1191, 1247, 1345, 1370, 1393, 1455, 1513, 1731, 1761 cm<sup>-1</sup>; MS (EI) *m/z* 453 (M<sup>+</sup>), HRMS (EI) *m/z* calcd for C<sub>26</sub>H<sub>31</sub>NO<sub>6</sub> (M<sup>+</sup>): 453.2151, found 453.2150; Anal. Calcd for C<sub>26</sub>H<sub>31</sub>NO<sub>6</sub>: C, 68.86; H, 6.89; N, 3.09; O, 21.17. Found C, 68.13; H, 6.78; N, 3.21.

**β-Lactam 11b:** Colorless oil; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 1.17 (t, *J* = 7.3 Hz, 3H), 1.26 (t, *J* = 8.7 Hz, 3H), 2.62 (d, *J* = 17.4 Hz, 1H), 2.73 (d, *J* = 17.4 Hz, 1H), 2.99 (d, *J* = 14.2 Hz, 1H), 3.55 (d, *J* = 14.2 Hz, 1H), 3.79 (s, 3H), 3.86 (d, *J* = 16.0 Hz, 1H), 4.12 (m, 5H), 4.39 (d, *J* = 16.0 Hz, 1H), 6.81 (m, 2H), 7.01 (m, 4H), 7.15 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 13.8, 14.1, 17.5, 37.5, 39.3, 45.7, 55.2, 58.8, 60.6, 61.5, 72.1, 76.7, 113.7, 127.1, 128.3, 128.7, 129.6, 129.9, 135.2, 158.5, 169.9, 171.2, 171.9; IR (neat) 1033, 1084, 1153, 1179, 1207, 1246, 1347, 1372, 1393, 1455, 1513, 1704, 1762 cm<sup>-1</sup> MS (EI) *m/z* 453

(M<sup>+</sup>), HRMS (EI) *m/z* calcd for C<sub>26</sub>H<sub>31</sub>NO<sub>6</sub> (M<sup>+</sup>): 453.2151, found 453.2156; Anal. Calcd for C<sub>26</sub>H<sub>31</sub>NO<sub>6</sub>: C, 68.86; H, 6.89; N, 3.09; O, 21.17. Found C, 68.55; H, 6.89; N, 3.05.

**β-Lactam 12a:** Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.24 (t, *J* = 6.8 Hz, 3H), 2.03 (s, 3H), 2.80 (d, *J* = 16.5 Hz, 1H), 2.92 (d, *J* = 16.5 Hz, 1H), 2.92 (d, *J* = 14.2 Hz, 1H), 3.74-3.82 (m, 2H), 3.78 (s, 3H), 4.08-4.21 (m, 3H), 5.20 (s, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 7.05 (t, *J* = 8.7 Hz, 2H), 7.16 (t, *J* = 8.7 Hz, 1H), 7.34 (s, 5H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 14.1, 17.7, 36.3, 39.6, 46.3, 55.2, 58.9, 60.9, 67.3, 73.1, 113.5, 127.2, 128.5, 128.6, 128.7, 128.8, 129.1, 129.7, 135.1, 136.0, 158.5, 169.9, 170.9, 171.2; IR (neat) 1034, 1189, 1257, 1454, 1513, 1637, 1740, 2919, 3441 cm<sup>-1</sup>; MS (FAB) *m/z* 516 ([M+H]<sup>+</sup>), 538 ([M+Na]<sup>+</sup>), HRMS (FAB) *m/z* calcd for C<sub>31</sub>H<sub>34</sub>NO<sub>6</sub> ([M+H]<sup>+</sup>): 516.2386, found 516.2385. Ee of **12a** was determined by analyzing on CHIRALPAK AD-H<sup>®</sup> (IPA/Hexane 10:90, 1 mL/min), Rt: 22.1 min and 32.0 min.

**β-Lactam 12b:** Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.21 (t, *J* = 7.3 Hz, 3H), 1.65 (s, 3H), 2.53 (d, *J* = 17.0 Hz, 1H), 2.70 (d, *J* = 17.0 Hz, 1H), 2.98 (d, *J* = 14.2 Hz, 1H), 3.56 (d, *J* = 14.2 Hz, 1H), 3.78 (s, 3H), 3.81 (d, *J* = 16.0 Hz, 1H), 4.03 (m, 2H), 4.36 (d, *J* = 16.0 Hz, 1H), 4.99 (d, *J* = 11.9 Hz, 1H), 5.12 (d, *J* = 11.9 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 7.1 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 7.06 (t, *J* = 7.1 Hz, 2H), 7.18 (t, *J* = 7.1 Hz, 1H), 7.20-7.30 (m, 3H), 7.34-7.36 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 14.1, 17.6, 37.5, 39.4, 45.8, 55.2, 59.0, 60.6, 67.4, 72.2, 113.6, 127.1, 128.4, 128.6, 128.75, 128.84, 129.5, 129.9, 158.5, 169.8, 171.1, 171.9; IR (neat) 1028, 1179, 1246, 1513, 1736, 1760, 2850, 2919, 3442 cm<sup>-1</sup>; MS (FAB) *m/z* 516 ([M+H]<sup>+</sup>), 538 ([M+Na]<sup>+</sup>), HRMS (FAB) *m/z* calcd for C<sub>31</sub>H<sub>34</sub>NO<sub>6</sub> ([M+H]<sup>+</sup>): 516.2386, found 516.2387. Ee of **12b** was determined by analyzing on CHIRALPAK AD-H<sup>®</sup> (IPA/Hexane 10:90, 1 mL/min), Rt: 22.1 min and 26.8 min.

**β-Lactam 13a:** Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.28 (t, *J* = 7.3 Hz, 3H), 1.45 (s, 9H), 1.46 (s, 3H), 2.85 (d, *J* = 18.7 Hz, 1H), 2.90 (d, *J* = 13.7 Hz, 1H), 2.91 (d, *J* = 18.7 Hz, 1H), 3.72 (d, *J* = 13.7 Hz, 1H), 3.76 (d, *J* = 13.3 Hz, 1H), 3.77 (d, *J* = 9.8 Hz, 1H), 3.79 (s, 3H), 4.20 (d, *J* = 7.3 Hz, 1H), 4.38 (d, *J* = 16.0 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 7.00-7.20 (m, 7H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 14.2, 17.9, 28.0, 29.7, 36.5, 39.6, 46.3, 55.2, 58.7, 60.9, 73.0, 83.3, 113.6, 127.1, 128.3, 128.50, 129.6, 130.1, 135.4, 158.5, 169.94, 169.98, 171.7; IR (neat) 1031, 1154, 1247, 1458, 1513, 1738, 1761, 2850, 2919 cm<sup>-1</sup>; MS (FAB) *m/z* 482 ([M+H]<sup>+</sup>), 504 ([M+Na]<sup>+</sup>), HRMS (FAB) *m/z* calcd for C<sub>28</sub>H<sub>36</sub>NO<sub>6</sub> ([M+H]<sup>+</sup>): 482.2543, found 482.2537. Ee of **13a** was determined by analyzing on CHIRALPAK OD-H<sup>®</sup> (IPA/Hexane 10:90, 1 mL/min), Rt: 11.5 min and 13.9 min.

**β-Lactam 13b:** Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.28 (t, *J* = 7.3 Hz, 3H), 1.37 (s, 9H), 1.69 (s, 3H), 2.64 (d, *J* = 17.4 Hz, 1H), 2.76 (d, *J* = 17.4 Hz, 1H), 2.95 (d, *J* = 14.2 Hz, 1H), 3.58 (d, *J* = 14.2 Hz, 1H), 3.68 (d, *J* = 16.5 Hz, 1H), 3.80 (s, 3H), 4.14-4.25 (m, 2H), 4.50 (d, *J* = 16.5 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 7.00-7.20 (m, 7H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 14.1, 17.4, 18.9, 27.9, 37.1, 39.2, 45.8,

55.3, 58.7, 60.6, 72.7, 83.5, 113.7, 127.0, 128.2, 128.4, 129.7, 130.3, 135.4, 158.5, 169.9, 170.2, 172.5; IR (neat) 1030, 1153, 1247, 1370, 1393, 1455, 1513, 1743, 1762, 2849, 2917  $\text{cm}^{-1}$ ; MS (FAB)  $m/z$  482 ( $[\text{M}+\text{H}]^+$ ), 504 ( $[\text{M}+\text{Na}]^+$ ), HRMS (FAB)  $m/z$  calcd for  $\text{C}_{28}\text{H}_{36}\text{NO}_6$  ( $[\text{M}+\text{H}]^+$ ): 482.2543, found 482.2542. Ee of **12a** was determined by analyzing on CHIRALPAK AD-H<sup>®</sup> (IPA/Hexane 10:90, 1 mL/min), Rt: 14.3 min and 18.7 min.

**Optical resolution of  $\beta$ -lactam 11a.** To a solution of **11a** (20% ee) (60 mg, 0.13 mmol) in THF (1.06 mL) was added a solution of LiOH $\cdot$ H<sub>2</sub>O in H<sub>2</sub>O (0.26 mL) at 0 °C. After being stirred for 4 h at rt, the mixture was washed with water (3 times). The combined aqueous layers were neutralized by addition of diluted HCl aq. until pH 6 and extracted with Et<sub>2</sub>O (3 times). The extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated to give a crude carboxylic acid, which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL). To this solution were added WSC $\cdot$ HCl (30.7 mg, 0.20 mmol), 4-DMAP (24.2 mg, 0.20 mmol), and (*S*)-1-phenylethanol (24  $\mu\text{L}$ , 0.20 mmol) at rt. After being stirred for 2 h, the mixture was extracted with AcOEt (3 times) and the extracts were washed with brine, and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The diastereomeric mixture of **16a** and **16b** was purified on a preparative thin layer chromatography (AcOEt: Hexane 30:70) and turned out to be 20% de. Separation of **16a** and **16b** was performed through recyclable HPLC (AcOEt:Hexane = 15:85).

**16a:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  1.23 (t,  $J$  = 7.3 Hz, 3H), 1.34 (s, 3H), 1.59 (d,  $J$  = 6.9 Hz, 3H), 2.80-2.95 (m, 3H), 3.77-3.81 (m, 2H), 3.79 (s, 3H), 4.17-4.28 (m, 3H), 5.95 (q,  $J$  = 6.9 Hz, 1H), 6.79 (d,  $J$  = 8.7 Hz, 2H), 6.94 (d,  $J$  = 7.1 Hz, 2H), 7.00 (d,  $J$  = 8.7 Hz, 2H), 7.11-7.35 (m, 6H), 7.39 (d,  $J$  = 7.1 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  14.2, 17.7, 22.1, 36.6, 39.5, 46.3, 55.2, 58.8, 61.4, 73.1, 113.6, 126.3, 127.2, 128.0, 128.4, 128.5, 128.8, 129.5, 129.8, 135.2, 141.1, 158.5, 169.2, 171.0; IR: (neat) 1062, 1086, 1188, 1248, 1514, 1737, 1761, 2853, 2926, 3397  $\text{cm}^{-1}$ ; HRMS (FAB)  $m/z$  calcd for  $\text{C}_{32}\text{H}_{35}\text{NO}_6\text{Na}$  ( $\text{M}+\text{Na}^+$ ): 552.2362 found: 552.2363; Anal. Calcd for  $\text{C}_{32}\text{H}_{35}\text{NO}_6$ : C, 72.57; H, 6.66; N, 2.64. Found C, 70.17; H, 6.68; N, 2.55.

**16b:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  1.23 (t,  $J$  = 7.3 Hz, 3H), 1.40 (s, 3H), 1.60 (d,  $J$  = 6.4 Hz, 3H), 2.84-2.96 (m, 3H), 3.68 (d,  $J$  = 17.8 Hz, 1H), 3.78 (d,  $J$  = 16.0 Hz, 1H), 3.79 (s, 3H), 4.13-4.30 (m, 3H), 5.96 (q,  $J$  = 6.4 Hz, 1H), 6.79 (d,  $J$  = 8.7 Hz, 2H), 6.91 (d,  $J$  = 7.1 Hz, 2H), 7.01 (d,  $J$  = 8.7 Hz, 2H), 7.10-7.22 (m, 3H), 7.26-7.42 (m, 5H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  17.6, 21.1, 22.0, 29.7, 36.7, 39.5, 46.3, 55.3, 58.8, 60.4, 61.4, 73.0, 73.5, 113.8, 126.4, 128.5, 128.8, 129.9, 158.5, 171.0, 171.3; IR: (neat) 1192, 1247, 1390, 1456, 1514, 1737, 1762, 2851, 2923, 3400; HRMS (FAB)  $m/z$  calcd for  $\text{C}_{32}\text{H}_{35}\text{NO}_6\text{Na}$  ( $\text{M}+\text{Na}^+$ ): 552.2362 found: 552.2362; Anal. Calcd for  $\text{C}_{32}\text{H}_{35}\text{NO}_6$ : C, 72.57; H, 6.66; N, 2.64. Found C, 71.34; H, 6.75; N, 2.52.

**Conversion of 16a to (–)-11a.** Pd/C (5 mg) was added to a solution of **16a** (41 mg, 0.077 mmol) in MeOH under Ar. Then Ar was replaced by hydrogen in order to perform reduction of phenylethyl ester.

After stirring for 4 h, the reaction mixture was filtered. The filtrate was concentrated to obtain **15a**. WSC•HCl (24 mg, 0.16 mmol) and DMAP (18.9 mg, 0.16 mmol) were added to a solution of **15a** in EtOH at rt. After stirring for 2 h, the solvent was removed by evaporation and the residue was purified on a preparative thin layer chromatography (AcOEt:Hexane = 30:70). <sup>1</sup>H NMR spectrum of (-)-**11a** was identified with racemate. Ee of (-)-**11a** was determined by analyzing on CHIRALPAK IA<sup>®</sup> (IPA/Hexane = 10:90, 1 mL/min), Rt: 12.70 min.  $[\alpha]_{\text{D}}^{20}$  -38.5 (*c* 0.20, CHCl<sub>3</sub>).

**Conversion of 16b to (+)-11a.** A similar conversion from **16a** to (-)-**11a** was performed using **16b** to obtain (+)-**11a** as an enantiopure product. <sup>1</sup>H NMR spectrum of (+)-**11a** was identified with racemate. Ee of (+)-**11a** was determined by analyzing on CHIRALPAK IA<sup>®</sup> (IPA/Hexane 10:90, 1 mL/min), Rt: 12.70 min.  $[\alpha]_{\text{D}}^{20}$  +38.6 (*c* 0.20, CHCl<sub>3</sub>).

**Optical resolution of β-lactam 11b.** A similar conversion from racemic **11a** to (-)-**11a** and (+)-**11a** was applied on racemic **11b** to obtain (+)-**11b** and (-)-**11b**, respectively. <sup>1</sup>H NMR spectra of (+)- and (-)-**11b** were identified with racemate. Each of ee of (+)- and (-)-**11b** was determined by analyzing on CHIRALPAK IA<sup>®</sup> (IPA/Hexane=10:90, 1 mL/min). Retention times for (+)-**11b** and (-)-**11b** were 12.66 and 15.33 min, respectively. The specific rotations were  $[\alpha]_{\text{D}}^{20}$  +48.8 (*c* 0.13, CHCl<sub>3</sub>) for (+)-**11b** and  $[\alpha]_{\text{D}}^{20}$  -47.9 (*c* 0.23, CHCl<sub>3</sub>) for (-)-**11b**, respectively.

**Conversion of 11a to 17.** A solution of LiOH•H<sub>2</sub>O (2.6 mg, 0.63 mmol) in H<sub>2</sub>O (0.2 mL) was added to a solution of (-)-**11a** (95% ee) (29 mg, 0.064 mmol) in THF (1 mL) at 0 °C. After being stirred for 4 h at rt, the mixture was washed with water (3 times). The combined aqueous layers were neutralized by addition of dil HCl aq. until pH 6. The aqueous layers were extracted with Et<sub>2</sub>O (3 times). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated to give crude carboxylic acid, which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (0.64 mL). To this solution *p*-iodoaniline (42.1 mg, 0.19 mmol), 4-DMAP (2.4 mg, 0.020 mmol), DIPEA (17 μL, 0.096 mmol), and EDCI•HCl (18.4 mg, 0.096 mmol) were added at 0 °C, successively. After being stirred for 1 h at 0 °C, the mixture was warmed to rt and stirred for 5 h. The resulting mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, and the organic layer was washed with 1N HCl, aq. sat. NaHCO<sub>3</sub> aq, and brine. The extract was dried over MgSO<sub>4</sub>, filtered and concentrated. The residual oil was purified through silica gel column chromatography (AcOEt:Hexane = 10:90) to give amide **17** (32.5 mg, 81%, 2 steps). The small amount of amide **17** was recrystallized from EtOH/Hexane to take X-ray crystallographic analysis; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.28 (t, *J* = 7.4 Hz, 3H), 1.40 (s, 3H), 2.68 (d, *J* = 14.7 Hz, 1H), 2.92 (d, *J* = 13.7 Hz, 1H), 3.23 (d, *J* = 15.1 Hz, 1H), 3.60 (d, *J* = 13.7 Hz, 1H), 3.79 (s, 3H), 4.02-4.15 (m, 2H), 4.20-4.35 (m, 2H), 6.81 (d, *J* = 8.7 Hz, 1H), 7.03-7.11 (m, 4H), 7.20-7.30 (m, 3H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 2H), 9.89 (s, 1H).

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25. Crystal structure parameters obtained from **17**: C<sub>30</sub>H<sub>31</sub>N<sub>2</sub>O<sub>5</sub>;  $M = 626.47$ ; space group  $P2_1$  (#4);  $a = 8.8340(5)$  Å,  $b = 28.6016(16)$  Å,  $c = 11.1888(8)$  Å,  $\alpha = 90^\circ$ ,  $\beta = 90.541(4)^\circ$ ,  $\gamma = 90^\circ$ ;  $V = 2826.9(3)$  Å<sup>3</sup>;  $Z = 4$ ;  $\rho_{\text{calcd}} = 1.472$  Mg/m<sup>3</sup>; MoK $\alpha$  radiation;  $\lambda = 0.71705$  Å;  $\mu = 1.174$  mm<sup>-1</sup>;  $T = 173(2)$  K. The final  $R1$  and  $wR2$  were 0.0487 and 0.1071 for the 691 parameters. CCDC-1029430 contains the supplementary crystallographic data reported in this publication. These data may be obtained free of charge from The Cambridge Crystallographic Data Centre at <https://www.ccdc.cam.ac.uk/structures/>.