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DECISIVE EFFECTS OF C-N AXIAL CHIRALITY OF INTERMEDIARY ENOLATES ON THE STEREOCHEMICAL COURSE OF β-LACTAM FORMATION FROM β-BRANCHED α-AMINO ACID DERIVATIVES VIA MEMORY OF CHIRALITY

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Abstract – Stereochemistry of β-lactam formation of β-branched α-amino acid derivatives via a MOC strategy was investigated. The 4-*exo-trig* cyclization of axially chiral enolates generated from L-threonine and L-*allo*-threonine derivatives proceeded predominately with inversion of the configuration at the newly formed tetrasubstituted carbon, irrespective of the chirality at the β-carbon of the β-lactam precursors. These results indicated that C–N axial chirality of the intermediary enolates generated from the α-amino acid derivatives has decisive effects on the stereochemical course of β-lactam formation even in the presence of an sp^3-chiral center at the β-carbon.

INTRODUCTION

We have studied asymmetric transformation via memory of chirality (MOC).[1] The MOC strategy features asymmetric induction via intermediary chiral enolates with the restricted bond rotation around chiral C–C,[2] C–N,[3-14] or C–O[15,16] axes. The obvious advantage of the strategy is the use of naturally abundant readily available amino acids and lactic acids as starting materials as well as a sole source of chirality.[1] For example, treatment of *N*-*tert*-butoxycarbonyl(Boc)-*N*-methoxymethyl(MOM)-α-amino acid

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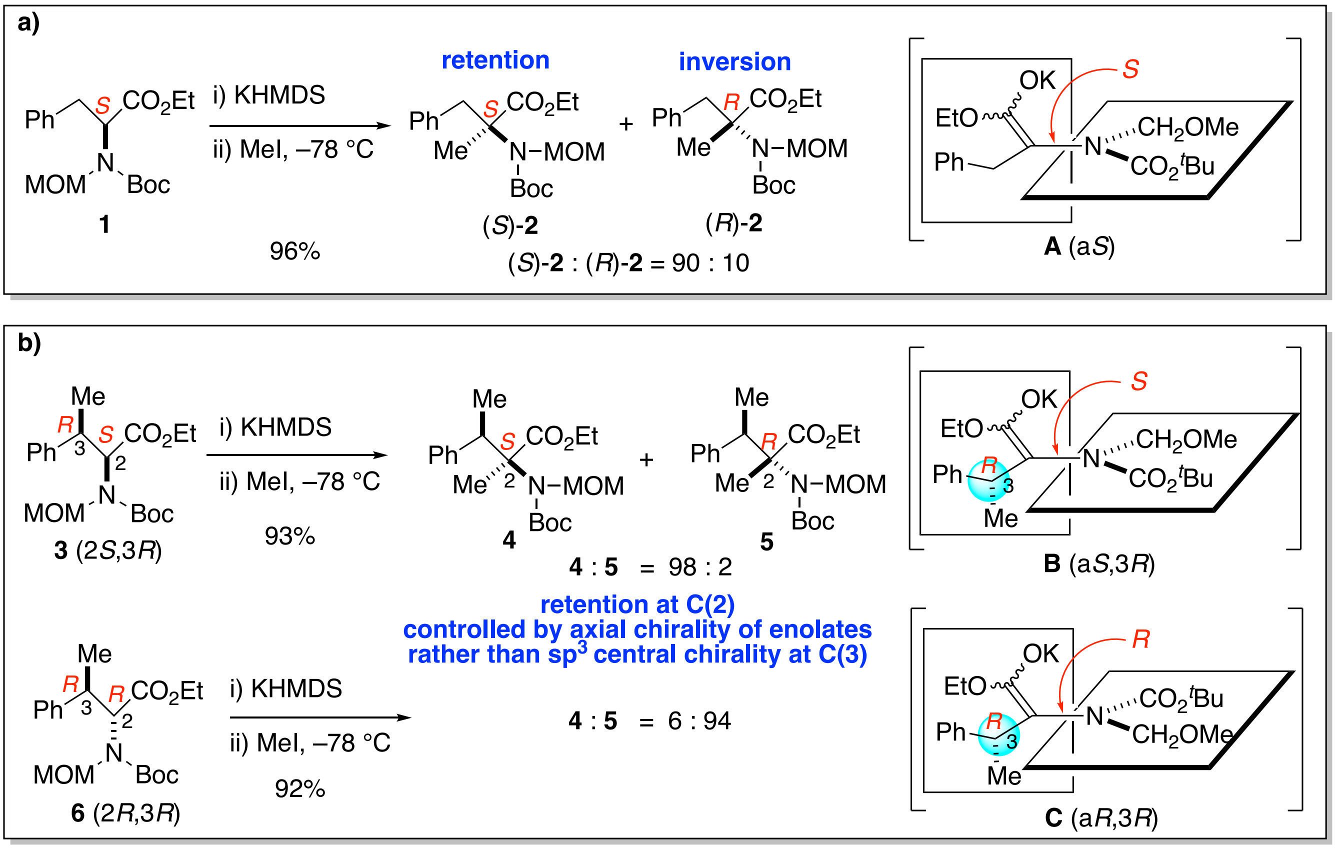
Dedicated to Prof. Yasuyuki Kita on the occasion of his 77th birthday derivative **1** with potassium hexamethyldisilazide (KHMDS) followed by methyl iodide gave (*S*)-**2** in 80% ee in retention of the configuration via proposed axially chiral enolate intermediate **A** with an a*S* axis (Scheme 1a).[3] The asymmetric reaction was applied to β-branched α-amino acid derivatives such as β-methylphenylalanine derivatives **3** and **6** (Scheme 1b).[17,18] α-Methylation of **3** under the similar conditions to those in Scheme 1a gave a 98:2 mixture of **4** and **5** in a combined yield of 93%. On the other hand, the same treatment of **6** gave a mixture of **4** and **5** in a ratio of 6:94 in a combined yield of 92%. Thus, chirality at C(2) has a decisive effect on the stereochemical course of the α-methylation irrespective of the chirality of the adjacent C(3)-chiral center.

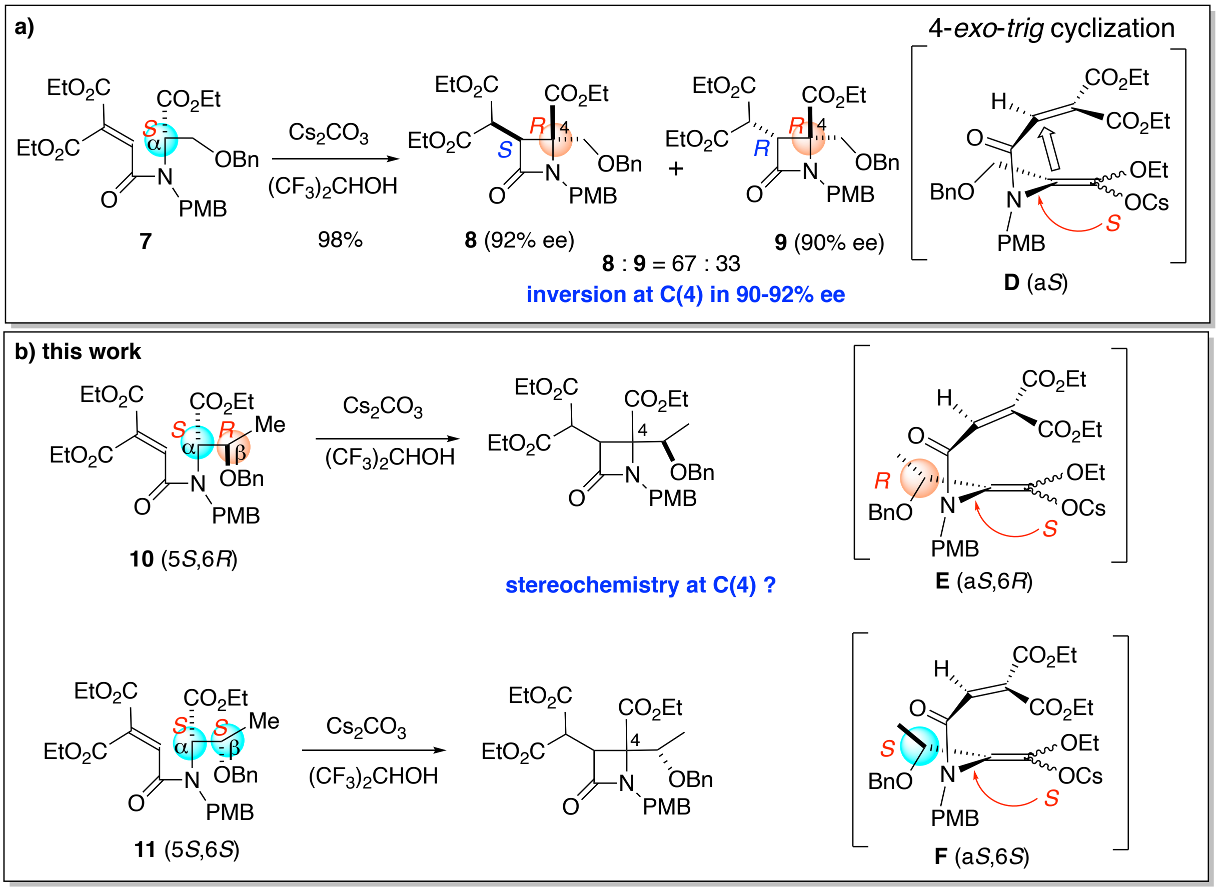


Scheme 1. Stereochemical course of α-alkylation of α-amino acid derivatives via memory of chirality. a) Enantioselective alkylation of **1**. b) Diastereoselective alkylation of **3** and **6**: Decisive effects of axial chirality of the enolate in the presence of an adjacent sp^3-chiral center were observed.

We assumed **B** (a*S*,3*R*) and **C** (a*R*,3*R*) as the possible structures of chiral enolate intermediates generated from **3** and **6**, respectively. Comparing the stereoselectivity of α-methylation of **3** and **6** to that of **1**, which is lacking a chiral center at C(3), it might be expected that one of the diastereomers **3** and **6** should show the higher (matched) stereoselectivity than **1**, and the other would show the lower (mismatched) stereoselectivity than **1**. However, both cases in α-methylation of **3** and **6** showed higher stereoselectivity in their α-methylation than that of **1**. We assumed that the higher stereoselectivity could be the resulting from higher stereochemical purity of the C-N axially chiral enolates **B** and **C** than **A** and/or the higher face selectivity for the reactions of **B** and **C** with methyl iodide than that of **A**. Here, we describe our related stereochemical studies on β-lactam synthesis via a MOC strategy.

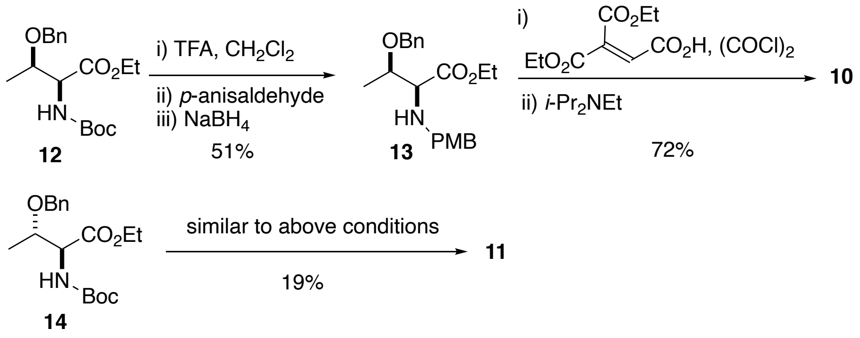
RESULTS AND DISCUSSION

A challenge in MOC strategy involves its application to β-lactam synthesis.[10,13,14] We reported a method for asymmetric synthesis of β-lactams **8** and **9** from α-amino acid derivatives **7** (Scheme 2a).[13] β-Lactam formation was expected to proceed via 4-*exo-trig* cyclization of axially chiral enolate **D**. Although this process has been thought to be unfavorable because the intramolecular conjugate addition of enolate **D** would produce a highly strained β-lactam enolate,[10] this problem was solved by performing the enolate reaction employing β-lactam precursors with a strong Michael acceptor in the presence of a proton source (hexafluoroisopropanol).[13,14] We proposed that the strong Michael acceptor would facilitate the 4-*exo-trig* cyclization of axially chiral enolate **D**, and the resulting highly strained β-lactam enolate could undergo prompt protonation immediately after its formation to successfully give the β-lactams in a highly enantioselective manner.[10,13,14] The addition of the proton source was proposed to be the key for acceleration of the β-lactam formation. Another salient feature of the present procedure was that the undesired β-elimination of the OBn group was totally suppressed during the desired β-lactam formation.[13,19-21] The β-lactams **8** and **9** were obtained in 90~92% ee in inversion of the configuration at C(4). In this report, we further investigated the stereochemical course of the β-lactam synthesis via the MOC strategy with β-lactam precursors **10** and **11** which possess an additional chiral center adjacent to the reacting chiral carbon (Scheme 2b). Since the chirality of the C-N axially chiral enolates generated from **10** and **11** is assumed to be governed by the original chirality (*S*) of the α-carbon, enolates **E** and **F** with a*S* configuration would be formed. The key question is whether the stereochemistry of the 4-*exo-trig* cyclization of axially chiral enolate is to be controlled by the axial chirality of the enolate or the sp^3-chiral center adjacent to the reacting carbon.



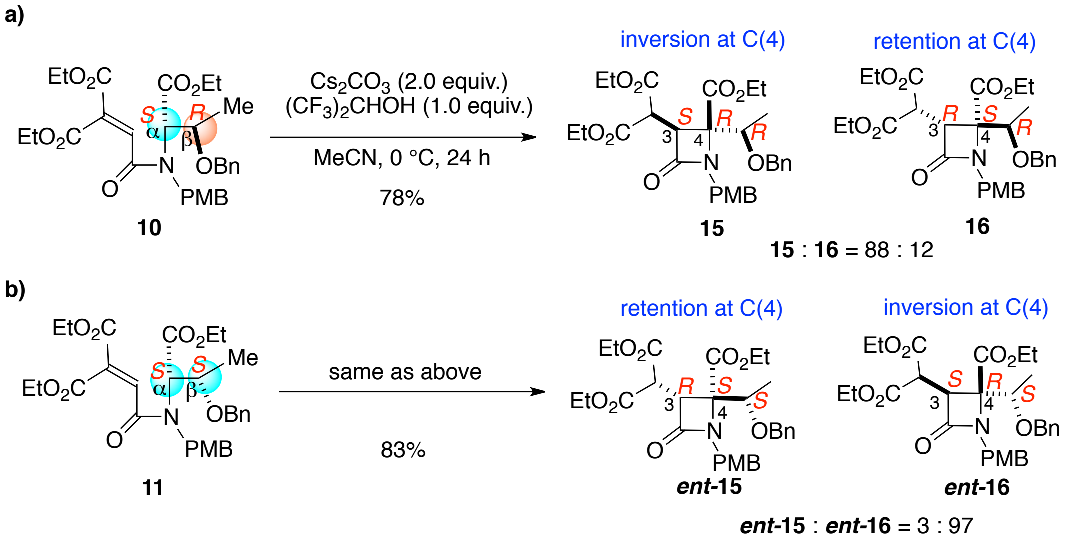
Scheme 2. a) Previous work: β-Lactam formation in inversion of configuration at C(4) via 4-*exo-trig* cyclization. b) This work: Is stereochemistry governed by axial chirality of enolates or sp^3-chirality at the adjacent carbon?

β-Lactam precursor **10** was prepared from commercially available *N*-Boc-L-threonine(OBn)-OEt (**12**) (Scheme 3). Removal of the Boc group of **12** with TFA followed by reductive amination with *p*-anisaldehyde and sodium borohydride gave *N*-*p*-methoxybenzyl(PMB) derivative **13** in 51% yield. *N*-Acylation of **13** with 3,3-di(ethoxycarbonyl)acrylic acid[22] gave **11** in 72% yield.[13] *N*-Boc-L-*allo*-threonine(OBn)-OEt (**14**) was prepared by *O*-benzylation of commercially available *N*-Boc-L-*allo*-threonine followed by esterification with ethanol in 28% yield. Treatment of **14** under the similar conditions to those employed for the preparation of **10** gave **11** in 19% yield.



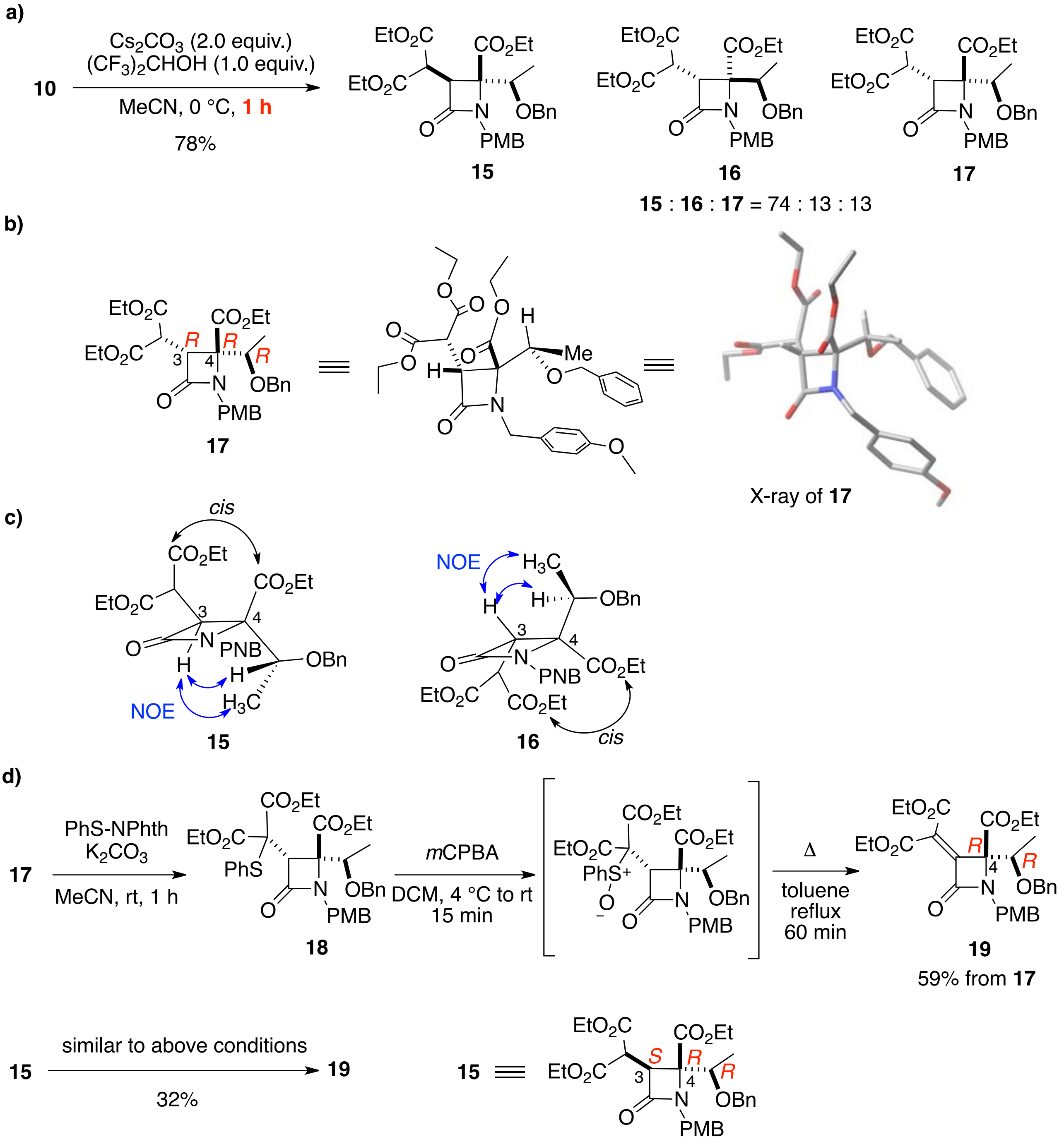
Scheme 3. Preparation of β-lactam precursors **10** and **11**

β-Lactam formation from precursors **10** and **11** was performed under the previously optimized conditions for the synthesis of β-lactams from serine derivatives.[13] Treatment of **10** with 2.0 equivalents of Cs_2CO_3 in the presence of 1.0 equivalent of hexafluoroisopropanol in acetonitrile for 24 h at 0 °C gave an 88:12 diastereomeric mixture of **15** and **16** in 78% combined yield (Scheme 4a). On the other hand, the same treatment of **11** afforded a 3:97 diastereomeric mixture of ***ent*-15** and ***ent*-16** in 83% combined yield (Scheme 4b). The major diastereomers **15** and ***ent*-16** were formed with inversion of the stereochemistry at C(4). The absolute and relative configuration was determined by the methods shown in Scheme 5. These results clearly indicate that stereochemistry of the β-lactams formation was governed predominantly by the chirality of the α-carbon rather than that of the β-carbon. Thus, axial chirality of the expected enolate intermediates **E** and **F** (Scheme 2) has the decisive role in the stereochemical course of the β-lactam formation (see Scheme 6 for the rational).



Scheme 4. Stereochemistry of β-lactam formation from **10** and **11**

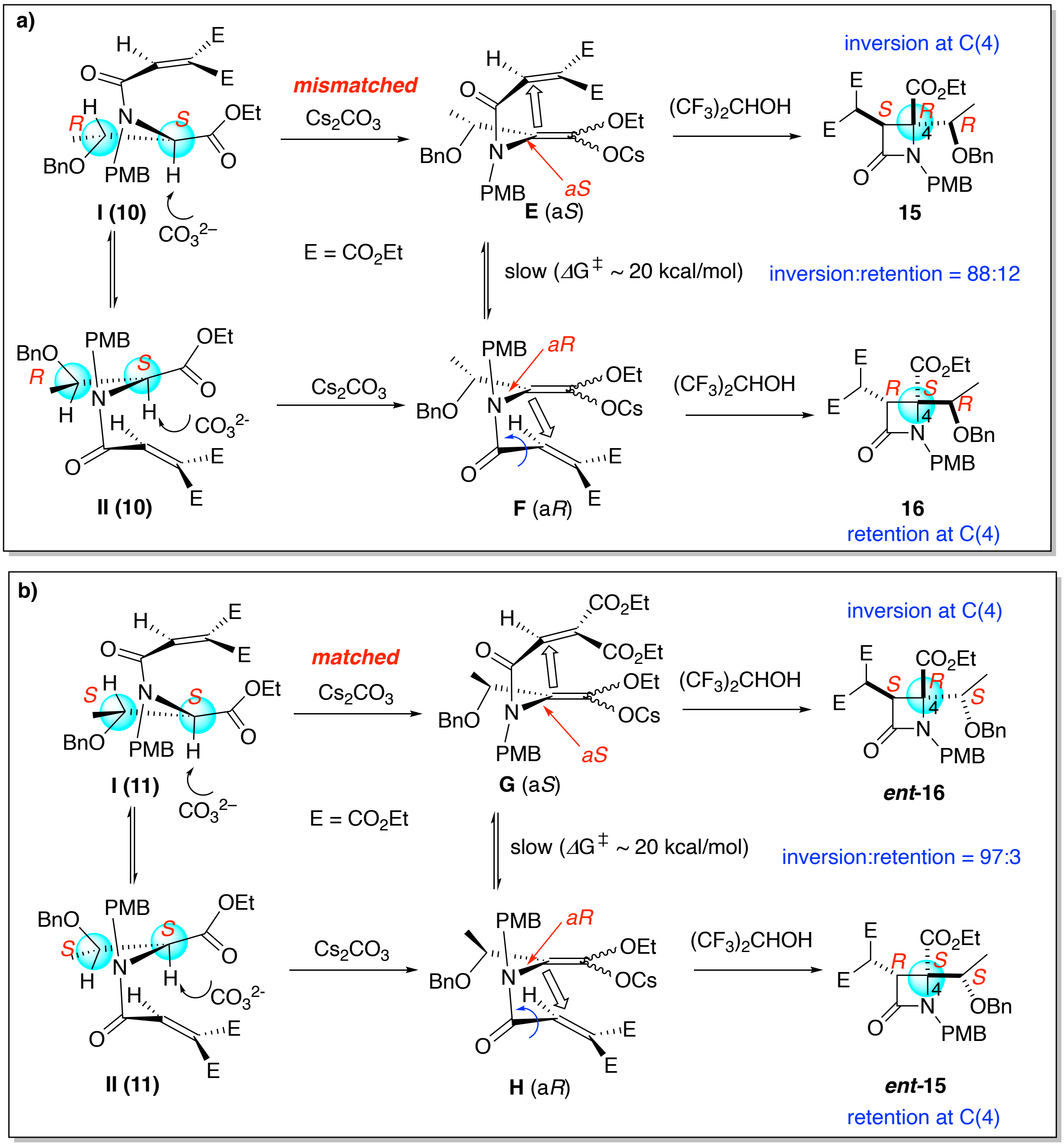
In the course of optimizing the conditions for the asymmetric β-lactam formation, kinetically formed diastereomer **17** was obtained in 10% yield when the reaction was run for 1 h at 0 °C (Scheme 5a, for the discussion about the formation of **17**, see Scheme 7). Separation of **17** from the diastereomeric mixture gave a solid that was recrystallized from CH_2Cl_2/*n*-hexane. An X-ray analysis of a single crystal of **17** revealed its absolute configuration to be 3*R*,4*R* (Scheme 5b).[23] The relative configuration of **15** and **16** was determined to be *cis* between the C(3)-$CH(CO_2Et)_2$ group and the C(4)-CO_2Et group by NOESY spectra (Scheme 5c, see SI). The absolute configuration of **15** was then determined by chemical correlation with **19** (Scheme 5d). Unsaturated β-lactam **19** was obtained in 59% yield by sulfidation of **17** with *N*-(phenylthio)phthalimide(PhS-NPhth) in the presence of K_2CO_3 followed by oxidative elimination with *m*CPBA. Since the absolute configuration of **17** was already revealed to be 4*R*, the absolute configuration of **19** is to be 4*R*. On the other hand, treatment of **15** under the similar conditions to those for the transformation from **17** to **19** also gave **19** in 32% yield. Thus, the absolute configuration of **15** was found to be 3*S*,4*R*. Because both **15** and **16** have the same relative configuration between C(3) and C(4) by NOESY studies (Scheme 5c), the absolute configuration of **16** was clarified to be 3*R*,4*S*. Accordingly, the absolute configuration of **15** and 1**6** were unambiguously determined to be 3*S*,4*R*, and 3*R*,4*S*, respectively.



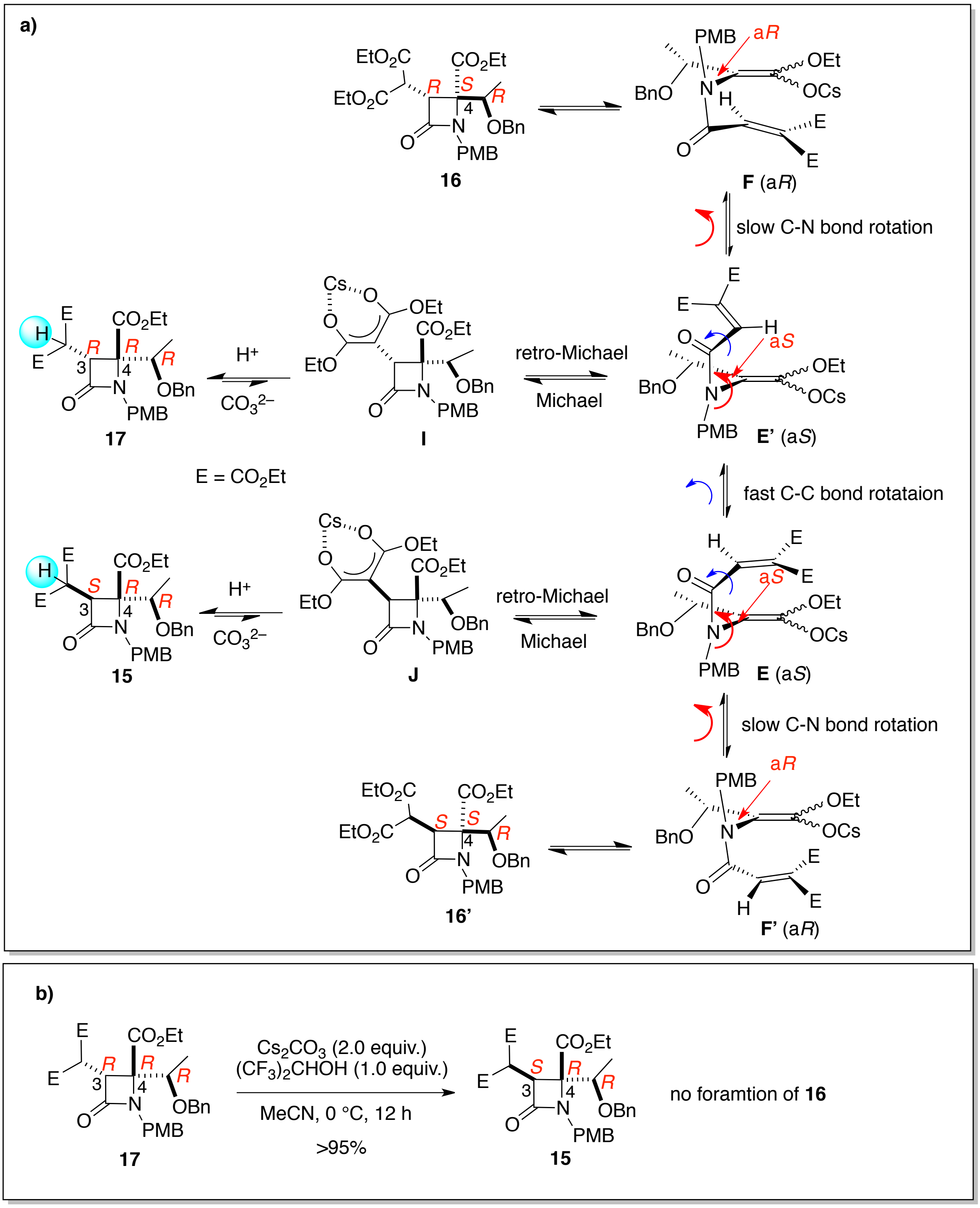
Scheme 5. Determination of absolute configuration **15** - **17**. a) Diastereomeric β-lactams **15-17** obtained by the reaction for a shorter reaction time. b) Determination of the absolute configuration of **17** by an X-ray analysis. c) Determination of the relative configuration of **15** and **16** by NOESY spectra. d) Determination of the absolute configuration of **15** by chemical correlation with **19**.

We describe a possible rationale for the stereochemical course for the β-lactam formation from **10** and **11** according to our previous proposal for the related β-lactam synthesis via a MOC strategy[10] (Scheme 6). Deprotonation of **10** with Cs_2CO_3 is expected to take place preferentially from conformer **I** (**10**) 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 **E** with a*S* configuration, which leads to the formation of β-lactam **15** with inversion of the configuration at C(4) (Scheme 6a). The stereochemical course of the selective formation of chiral enolate **E** was expected based on the proposed rationale, in which deprotonation of *N*-Boc-*N*-alkyl-α-amino acid derivatives would take place preferentially from the conformer in which C(α)-H bond is antiperiplanar with respect to the neighboring *N*-C(Boc) bond.[1,3-7] Another chiral enolate **F** with a*R* configuration would be formed as the minor species by deprotonation from conformer **II** (**10**), which gives β-lactam **16** with retention of the configuration at C(4). Alternatively, **F** could be generated by atropisomerization of **E** followed by C-C bond rotation indicated by a blue round arrow, although the process for the atropisomerization between **E** and **F** seems to be slow at the reaction temperature [half-life of the atropisomerization at 0 °C: ~ 10 min according to the barrier (~20 kcal/mol) estimated for a chiral enolate intermediate of the related β-lactam synthesis.][10] Similarly, deprotonation of **11** with Cs_2CO_3 is assumed to proceed predominantly from conformer **I** (**11**) to give chiral enolate **G** with a*S* configuration that affords β-lactam ***ent*-16** as the major product with inversion of the configuration at C(4) (Scheme 6b). Minor β-lactam ***ent*-15** with retention of the configuration at C(4) is assumed to be produced via chiral enolate **H** obtained by the unfavorable deprotonation process from conformer **II** (**11**) and/or atropisomerization process between **G** and **H**. While the ratio of **15** and **16** was 88:12, that of ***ent*-16** and ***ent*-15** was found to be 97:3. Considering the ratio of inversion/retention (95/5~96/4) in the case of β-lactam formation from **7**, which lacks the chiral center at the β-position (Scheme 2a), precursors **10** and **11** seem to possess mismatched and matched chirality, respectively for the stereoselective β-lactam formation.

We next consider the formation of the kinetically formed diastereomer **17**, and the thermodynamic equilibrium between β-lactams **15** and **17** (Scheme 7a). β-Lactams **17** was expected to be formed as a minor product by the 4-*exo-trig* cyclization of axially chiral enolate **E'** followed by protonation of β-lactam enolate **I**. Axially chiral enolate **E'** with a chiral (a*S*)-C-N axis would be readily formed by the fast rotation (blue round arrow) of the C-C bond of enolate **E**, which would be formed from β-lactam precursor **10** as shown in Scheme 6. β-Lactams **15** and **17** are expected to be interconvertible by an equilibrium process initiated by deprotonation of the acidic C-H (shown in blue circle). The existence of the thermodynamic equilibrium process has been proved for the related β-lactam formation via MOC strategy.[10,13] The preferable formation of β-lactams **15** could be understood by the smaller repulsive steric interaction between the substituents at C(3) and C(4). Formation of **16** and **16'** with retention of the configuration (*S*) at C(4) might be excluded because the atropisomerization between **E'** and **F** and that between **E** and **F'** seems to be slow. Alternatively, β-lactam **16** was expected to be formed directly from enolate **F**, which was assumed to be generated as the minor enolate intermediate from unfavorable conformation **II**(**10**) at the deprotonation process (Scheme 6a). To confirm the proposed mechanism, the equilibrium process was experimentally examined (Scheme 7b). Treatment of **17** under the optimized reaction conditions for the β-lactam formation for 12 h gave **15** as a sole detectable product. These observations are well compatible with the results shown in Scheme 4a and Scheme 5a and the proposed equilibrium process in Scheme 7a.



Scheme 6. Stereochemical course of β-lactam formation from a) **10** and b) **11**



Scheme 7. Thermodynamic equilibrium between β-lactams **15** and **17**. a) A possible mechanism for the interconversion between **17** and **15**. b) An experimental proof of the equilibrium process between β-lactams **15** and **17** and their relative stability.

CONCLUSIONS

The 4-*exo-trig* cyclization of axially chiral enolates generated from L-threonine and L-*allo*-threonine derivatives proceeded predominately with inversion of configuration at the newly formed tetrasubstituted carbon, irrespective of the chirality at the β-carbon of the parent amino derivatives. These results indicated that C–N axial chirality of the intermediary enolates generated from the β-branched α-amino acid derivatives has decisive effects on the stereochemical course of β-lactam formation even in the presence of an sp^3-chiral center in the β-lactam precursors.

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 $CDCl_3$ (77.0 ppm) or 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. 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 or MS4Å for 1 day or longer.

Synthesis of 10. Trifluoroacetic acid (28 mL) was added to a solution of *N*-Boc-*O*-benzyl-L-threonine ethyl ester **12** (1.90 g, 5.6 mmol) in CH_2Cl_2 (28 mL) at rt. After being stirred for 4.5 h at rt, the mixture was concentrated to give the corresponding ammonium salt. The resulted ammonium salt was dissolved in EtOH (8.8 mL). To the solution were added *p*-anisaldehyde (0.64 mL, 5.3 mmol), and 4Å molecular sieves (3.8 g), and the solution was stirred at 50 °C for 22 h. After that time, the reaction mixture was filtered and the filtrated was concentrated under reduced pressure. The resulting residue was dissolved in MeOH (14 mL) and cooled to 0 °C. To the solution was added $NaBH_4$ (0.34 g, 8.93 mmol), and the reaction mixture was allowed to warm to rt. After being stirred for 1 h, the reaction mixture was concentrated under reduced pressure. The residual brown oil was purified through silica gel column chromatography (AcOEt/*n*-hexane = 1/9 to 1/5) to give *N*-*p*-methoxybenzyl-*O*-benzyl-L-threonine ethyl ester (**13**) (1.0 g, 51%) as a colorless oil. $[\alpha]_D^{18}$ –50 (*c* 1.20, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.33-7.23 (m, 7H), 6.84 (d, J = 8.7 Hz, 2H), 4.56 (d, J = 11.9 Hz, 1H), 4.43 (d, J = 11.9 Hz, 1H), 4.20-4.08 (m, 2H), 3.89-3.84 (m, 2H), 3.79 (s, 3H), 3.58 (d, J = 12.8 Hz, 1H), 3.23 (d, J = 4.1 Hz, 1H), 2.19 (s, 1H), 1.26 (d, J = 6.4 Hz, 3H), 1.22 (t, J = 6.9 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.4, 158.6, 138.3, 132.1, 129.5, 128.2, 127.6, 127.5, 113.6, 75.6, 70.8, 64.7, 60.6, 55.2, 51.7, 16.4, 14.2; IR (neat) cm^{-1}: 2979, 2932, 2838, 1734, 1612, 1512, 1459, 1373, 1299, 1247, 1184, 1159, 1094, 1032; MS (FAB) *m/z* 358 (M+H)$^+$, 380 (M+Na)$^+$, 154 (base peak); HRMS (FAB) *m/z* calcd for $C_{21}H_{28}NO_4$ (M+H)$^+$: 358.2018 found 358.2010. To a solution of 3,3-di(ethoxycarbonyl)acrylic acid[13,22] (363 mg, 1.68 mmol) in CH_2Cl_2 (8.4 mL) were added oxalyl chloride (0.46 mL, 4.2 mmol) and DMF (1 drop) at rt. After being stirred for 40 min at rt, the reaction mixture was concentrated to give a crude 3,3-di(ethoxycarbonyl)acryloyl chloride. The crude mixture was dissolved in CH_2Cl_2 (7 mL). The resulting mixture was added to a solution of **13** (500 mg, 1.4 mmol) and *i*-Pr_2NEt (0.73 mL, 4.2 mmol) in CH_2Cl_2 (7 mL) at rt, and the mixture was stirred for 30 min at the same temperature. After that time, the reaction was quenched by the addition of sat. aq. $NaHCO_3$. The resulting mixture was extracted with $CHCl_3$. The combined organic extracts were washed with brine and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The residual brown oil was purified through silica gel column chromatography (AcOEt/*n*-hexane = 35/65) to give **10** (0.56 g, 72%) as a pale yellow oil. A 72 : 28 mixture of rotamers of **10**; $[\alpha]_D^{18}$ –29 (*c* 1.22, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 0.28 H), 7.36-7.23 (m, 6.44H), 7.17 (d, *J* = 8.7 Hz, 0.56H), 7.12 (s, 0.72H), 6.82 (d, *J* = 8.7 Hz, 1.44H), 6.73 (d, *J* = 8.7 Hz, 0.56H), 4.88 (d, *J* = 6.4 Hz, 0.72H), 4.83 (d, *J* = 16.5 Hz, 0.72H), 4.64-4.54 (m, 1.72H), 4.51 (d, *J* = 11.5 Hz, 0.28H), 4.45 (d, *J* = 15.1 Hz, 0.28H), 4.39-3.94 (m, 7.72H), 3.92-3.72 (m, 3.56H), 1.33-1.18 (m, 11.15H), 1.11 (t, *J* = 7.6 Hz, 0.84H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.9, 168.2, 166.4, 165.5, 164.6, 164.1, 163.0, 162.7, 158.9, 158.6, 138.2, 137.7, 136.1, 135.3, 134.0, 133.1, 131.0, 129.6, 129.5, 128.8, 128.32, 128.27, 128.1, 127.7, 127.6, 127.5, 127.3, 126.6, 113.8, 113.3, 74.2, 71.6, 71.4, 70.8, 65.6, 62.2, 62.0, 61.7, 61.2, 55.2, 71.7, 17.3, 16.6, 13.93, 13.85, 13.7; IR (neat) cm^{-1}: 2981, 2936, 2905, 1738, 1652, 1513, 1457, 1372, 1250, 1205, 1177, 1096, 1067, 1030; MS (FAB) *m/z* 556 (M+H)$^+$, 578 (M+Na)$^+$, 121 (base peak); HRMS (FAB) *m/z* calcd for $C_{30}H_{38}NO_9$ (M+H)$^+$: 556.2547 found 556.2547.

Synthesis of 11. To a stirred solution of *N*-Boc-L-*allo*-threonine (800 mg, 3.7 mmol) in DMF (6.1 mL) was slowly added sodium hydride (336 mg, 8.4 mmol, 60% in oil) at –5 °C. After the generation of the H_2 gas was stopped, benzyl bromide (0.52 mL, 4.4 mmol) was slowly added to the solution at the same temperature. After being stirred for 7 h at –5 °C, the reaction mixture was poured into iced-water and washed with Et_2O. The aqueous layer was acidified to pH 1 by addition of 1M HCl aq., and the resulting solution was extracted with AcOEt. The combined organic phase was successively washed with water and brine. The resulted solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The obtained crude mixture was dissolved in CH_2Cl_2 (12.7 mL). To the resulting solution were added EtOH (0.74 mL, 12.7 mmol), WSC•HCl (729 mg, 12.7 mmol), DMAP (30.9 mg, 0.25 mmol), and *i*-Pr_2NEt (0.44 mL, 2.5 mmol) at rt. After being stirred for 2.5 h at the same temperature, the reaction was quenched by addition of sat. aq. $NaHCO_3$. The resulting mixture was extracted with

$CHCl_3$. The combined organic extracts were successively washed with 10% aq. citric acid, water, and brine. The obtained solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residual oil was purified through silica gel column chromatography (AcOEt/*n*-hexane = 1/5) to give *N*-Boc-*O*-benzyl-L-*allo*-threonine ethyl ester **14** (645 mg, 52% in 2 steps). To a solution of *N*-Boc-*O*-benzyl-L-*allo*-threonine ethyl ester **14** in CH_2Cl_2 (9.6 mL) was added trifluoroacetic acid (9.6 mL) at rt. After being stirred for 50 min, the solvent was removed in vacuo to give the crude ammonium salt. The obtained ammonium salt was dissolved in EtOH (5.0 mL). To the solution were added *p*-anisaldehyde (0.12 mL, 1.0 mmol), MS3Å, and *i*-Pr_2NEt (0.17 mL, 1.0 mmol) at rt. The resulting solution was warmed to 50 °C and stirred for 20 h at 50 °C. After the reaction mixture was cooled to 0 °C, $NaBH_4$ (64 mg, 1.7 mmol) was slowly added to the solution. After the solution was stirred for 1.5 h at rt, the solvent was removed in vacuo. The resulting oil was suspended in water and the aqueous layer was extracted with AcOEt. The organic extracts were washed with water and brine and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The residual oil was purified through silica gel column chromatography (AcOEt/*n*-hexane = 1/9 to 1/5) to give *N*-*p*-methoxybenzyl-*O*-benzyl-L-*allo*-threonine ethyl ester (193 mg, 28%) as a colorless oil. $[\alpha]_D^{18}$ –22 (*c* 1.05, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.33-7.22 (m, 7H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.53 (d, *J* = 11.9 Hz, 1H), 4.39 (d, *J* = 11.4 Hz, 1H), 4.19 (q, *J* = 6.9 Hz, 2H), 3.82-3.70 (m, 5H), 3.59 (d, *J* = 12.8 Hz, 1H), 3.34 (d, *J* = 5.9 Hz, 1H), 1.95 (s, 1H), 1.27-1.24 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ173.8, 158.6, 138.3, 131.8, 129.5, 128.2, 127.5, 113.7, 76.3, 70.9, 64.7, 60.7, 55.4, 51.5, 16.6, 14.3; IR (neat) cm^{-1}: 2979, 2933, 2837, 1730, 1611, 1513, 1460, 1372, 1302, 1247, 1185, 1108, 1033; MS (FAB) *m/z* 358 $(M+H)^+$, 380 $(M+Na)^+$, 154 (base peak); HRMS (FAB) *m/z* calcd for $C_{21}H_{28}NO_4$ $(M+H)^+$: 358.2018 found 358.2023. To a solution of 3,3-di(ethoxycarbonyl)acrylic acid (87 mg, 0.40 mmol) in CH_2Cl_2 (2.0 mL) were successively added oxalyl chloride (0.11 mL, 1.0 mmol) and DMF (1 drop) at rt. After being stirred for 40 min, the reaction mixture was concentrated to give a crude 3,3-di(ethoxycarbonyl)acryloyl chloride. The obtained crude mixture was dissolved in CH_2Cl_2 (1.9 mL). The resulting solution was added to a solution of *N*-*p*-methoxybenzyl-*O*-benzyl-L-*allo*-threonine ethyl ester (120 mg, 0.34 mmol) and *i*-Pr_2NEt (0.18 mL, 1.0 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C. After being stirred for 30 min, the reaction was quenched by addition of sat. aq. $NaHCO_3$. The resulting solution was extracted with $CHCl_3$. The organic extracts were washed with brine and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The residual brown oil was purified through silica gel column chromatography (AcOEt/*n*-hexane = 2/8) and PTLC (AcOEt/toluene = 15/85) to give **11** (128 mg, 68%) as a colorless oil. $[\alpha]_D^{18}$ –46 (*c* 1.70, $CHCl_3$); ^{1}H-NMR (400 MHz, $(CD_3)_2SO$, 130 °C): δ 7.37-7.20 (m, 7H), 6.93-6.91 (m, 2H), 4.71-4.44 (m, 5H), 4.27-4.22 (m, 5H), 4.09-4.02 (m, 2H), 3.81-3.77 (m, 3H) 1.31-1.15 (m, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.8, 168.7, 165.9, 164.9, 164.4, 164.0, 162.7, 159.2, 158.9, 138.3, 137.5, 135.8, 135.5, 135.1, 133.6, 129.7, 128.9, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.5, 114.0, 113.6, 74.9, 73.4, 72.2, 71.2, 65.1, 62.2, 62.1, 61.9, 61.5, 61.1, 55.3, 55.2, 51.5, 16.4, 16.2, 14.0; IR (neat) cm^{-1}: 2982, 2937, 2905, 1739, 1656, 1613, 1513, 1450, 1373, 1252, 1203, 1095, 1070, 1030; MS (FAB) *m/z* 556 (M+H)$^+$, 578 (M+Na)$^+$, 121 (base peak); HRMS (FAB) *m/z* calcd for $C_{30}H_{38}NO_9$ (M+H)$^+$: 556.2547 found 556.2549.

β-Lactam formation from 10 (Scheme 4a and Scheme 5a). Cs_2CO_3 (51 mg, 0.16 mmol) was added to a solution of **10** (43 mg, 0.078 mmol) and $(CF_3)_2CHOH$ (13 mg, 0.078 mmol) in MeCN at 0 °C. After being stirred for 24 h at 0 °C, the reaction was quenched by addition of sat. aq. NH_4Cl. The resulting aqueous phase was extracted with AcOEt. The organic extracts were washed with water and brine, and the solution was dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The residue was purified by PTLC (AcOEt/*n*-hexane = 35/65) to give **15** (29.4 mg, 68%) and **16** (4.5 mg, 10%) (Scheme 4a).

The same reaction conditions except for reaction time, which was shortened from 24 h to 1 h, gave **15** (57%), **16** (10%), and **17** (10%), respectively (Scheme 5a).

15: colorless oil; $[\alpha]_D^{19}$ –24 (*c* 0.93, $CHCl_3$); ^{1}H-NMR (400 MHz, C_6D_6): δ 7.26 (d, *J* = 8.7 Hz, 2H), 7.18-7.12 (m, 4H), 7.09-7.05 (m, 1H), 6.69 (d, *J* = 8.7 Hz, 2H), 4.87 (d, *J* = 16.0 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 4.36 (d, *J* = 16.0 Hz, 1H), 4.23 (d, *J* = 11.9 Hz, 1H), 4.24-4.10 (m, 2H), 4.04-3.91 (m, 4H), 3.90-3.81 (m, 2H), 3.78 (q, *J* = 6.9 Hz, 1H), 3.28 (s, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.05 (t, *J* = 7.3 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, C_6D_6): δ 170.2, 167.7, 167.3, 166.3, 159.8, 139.5, 130.8, 130.3, 129.0, 128.9, 128.1, 127.9, 114.5, 78.4, 71.6, 71.3, 62.8, 62.5, 62.1, 55.29, 55.26, 51.3, 46.5, 16.1, 14.54, 14.50, 14.45; IR (neat) cm^{-1}: 2981, 2925, 1766, 1739, 1648, 1612, 1514, 1461, 1390, 1371, 1301, 1249, 1178, 1096, 1031; MS (FAB) *m/z* 556 (M+H)$^+$, 121 (base peak); HRMS (FAB) *m/z* calcd for $C_{30}H_{38}NO_9$ (M+H)$^+$: 556.2547 found 556.2545.

16: colorless oil; $[\alpha]_D^{19}$ +43 (*c* 0.40, $CHCl_3$); ^{1}H-NMR (400 MHz, C_6D_6): δ 7.38 (d, *J* = 8.7 Hz, 2H), 7.24-7.05 (m, 5H), 6.69 (d, *J* = 8.7 Hz, 2H), 4.80 (d, *J* = 14.6 Hz, 1H), 4.36 (q, *J* = 6.4 Hz, 1H), 4.30 (d, *J* = 15.1 Hz, 1H), 4.25 (d, *J* = 11.9 Hz, 1H), 4.25-4.09 (m, 2H), 4.10 (d, *J* = 11.5 Hz, 1H), 4.02 (d, *J* = 11.5 Hz, 1H), 3.97 (q, *J* = 11.9 Hz, 1H), 3.93 (d, *J* = 11.5 Hz, 1H), 3.87-3.79 (m, 2H), 3.24 (s, 3H), 1.06 (t, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H), 0.80 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, C_6D_6): δ 170.7, 167.1, 166.7, 165,1, 159.3, 138.7, 131.2, 130.0, 128.5, 128.3, 127.7, 127.6, 113.8, 76.6, 71.9, 71.6, 62.4, 61.9, 61.6, 54.6, 54.2, 50.5, 46.6, 14.0, 13.9, 12.4; IR (neat) cm^{-1}: 2983, 2938, 1766, 1739, 1613, 1514, 1459, 1373, 1248, 1177, 1148, 1097, 1032; MS (FAB) *m/z* 556 (M+H)$^+$, 121 (base peak); HRMS (FAB) *m/z* calcd for $C_{30}H_{38}NO_9$ (M+H)$^+$: 556.2547 found 556.2549.

17: white crystal; $[\alpha]_D^{19}$ +6.7 (*c* 0.57, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36-7.22 (m, 7H), 6.75 (d, *J* = 8.7 Hz, 2H), 4.63 (d, *J* = 16.0 Hz, 1H), 4.38 (d, *J* = 11.0 Hz, 1H), 4.36 (d, *J* = 11.0 Hz, 1H), 4.29-4.10

(m, 9H), 4.07 (d, *J* = 11.9 Hz, 1H), 3.77 (s, 3H), 1.29-1.25 (m, 6H), 1.23 (t, *J* = 7.3 Hz, 3H), 1.16 (d, *J* = 6.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.5, 167.2, 166.6, 166.3, 158.7, 137.5, 129.6, 128.5, 128.3, 127.7, 127.7, 113.6, 72.2, 70.1, 68.9, 62.0, 61.9, 56.1, 55.2, 48.7, 45.9, 15.5, 14.03, 13.99, 13.96; IR (neat) cm^{-1}: 2983, 2914, 2845, 1767, 1735, 1611, 1588, 1514, 1453, 1388, 1248, 1177, 1105, 1032; MS (FAB) *m/z* 556 $(M+H)^+$, 154 (base peak): HRMS (FAB) *m/z* calcd for $C_{30}H_{38}NO_9$ $(M+H)^+$: 556.2547 found 556.2546.

β-Lactam formation from 11 (Scheme 4b). Cs_2CO_3 (82.1 mg, 0.25 mmol) was added to a solution of **11** (70 mg, 0.13 mmol) and $(CF_3)_2CHOH$ (21.2 mg, 0.13 mmol) in MeCN at 0 °C. After being stirred for 24 h at 0 °C, the reaction was quenched by addition of sat. aq. NH_4Cl. The resulting aqueous phase was extracted with AcOEt. The organic extracts were washed with water and brine, and the solution was dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The residue was purified by PTLC (AcOEt/*n*-hexane = 35/65) to give ***ent*-16** (57.4 mg, 82%) and ***ent*-15** (1.8 mg, 3%), respectively. Each ^{1}H-NMR spectrum was identified with **16** and **15**, respectively and the specific rotation for ***ent*-16** was –44° (*c* 1.0, $CHCl_3$).

Transformation of 17 to 19 (Scheme 5d). To a solution of **17** (13.5 mg, 0.024 mmol) and *N*-(phenylthio)phthalimide (9.2 mg, 0.036 mmol, 1.5 equiv.) in MeCN (240 μL) was added K_2CO_3 (4.7 mg, 0.034 mmol, 1.4 equiv.). After the solution was stirred for 1 h at room temperature, the solution was poured into water. The mixture was extracted with AcOEt and the organic phase was washed with brine, dried over Na_2SO_4, concentrated in vacuo to give a crude mixture. The crude mixture was purified by preparative TLC using hex/AcOEt = 2/1 as an eluent to give **18** as a colorless oil (13.5 mg). **18** was dissolved with 0.5 mL of DCM and cooled to 4 °C. To the solution was added *m*CPBA (with 30% H_2O, 6.0 mg, 0.024 mmol) and the solution was stirred for 15 min at room temperature. After that time, the solution was treated with sat. aq. $NaHCO_3$. The mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a colorless oil (9.8 mg). The resulted oil was dissolved in toluene (1.0 mL) and the solution was refluxed for 1 h. After confirming that the starting material was consumed, toluene was removed under reduced pressure. The resulting oil was purified by preparative TLC using *n*-hexane/AcOEt = 2/1 as an eluent to give **19** as a colorless oil (7.9 mg, 59% yield (3 steps)).

19: colorless oil; $[\alpha]^{20}_{D}$ –22.3 (c 0.47, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.31–7.18 (m 7H), 6.81 (d, *J* = 8.3 Hz, 2H), 4.63–4.47{4.61 (d, *J* = 15.6 Hz, 1H), 4.56 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 15.6 Hz, 1H)}, 4.43–4.35 (m, 4H), 4.07–3.94 (m,3H), 3.85–3.77 (m, 4H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.31 (d, *J* = 6.4 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.6, 162.2, 161.9, 161.0, 159.3, {153.0, 137.9, 130.1, 128.4, 128.1, 127.7, 127.1, 121.3, 114.0}(for 10 carbons), 74.3, 72.6, 71.6, 62.5, 62.2, 62.0, 55.4, 46.3, 16.0, 14.1, 13.9; IR (neat) cm^{-1}: 2983, 1774, 1742, 1612, 1514, 1460, 1371, 1303, 1246, 1179, 1094, 1035, 861, 826, 741, 701; HRMS (ESI) *m/z* calcd for $C_{30}H_{36}NO_9$ (M + H)$^+$:554.2385 found 554.2382.

Transformation of compound **15** (74.7 mg, 0.13 mmol) was performed as same manner as that of **17** to afford 23.7 mg of **19** (32% yield (3 steps)).

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23. Crystal structure parameters obtained from **17**: $C_{30}H_{37}NO_9$; M = 555.61; space group $C2$ (#5); a = 832.3702(12) Å, b = 7.5202(3) Å, c = 23.6650(9) Å, α = 90°, β = 102.5865(14)°, γ = 90°; V = 5622.3(4) Å^3; Z = 8; ρ_{calcd} = 1.313 Mg/m^3; $\mathrm{Mo}_{\mathrm{Ka}}$ radiation; λ = 0.71705 Å; μ = 0.097 mm^{-1}; T = 103(2) K. The final $R1$ and w$R2$ were 0.0641 and 0.1064 for the 721 parameters. CCDC-2003666 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/.