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Protonation-Assisted Conjugate Addition of Axially Chiral Enolates: Asymmetric Synthesis of Multisubstituted β-Lactams from α-Amino Acids

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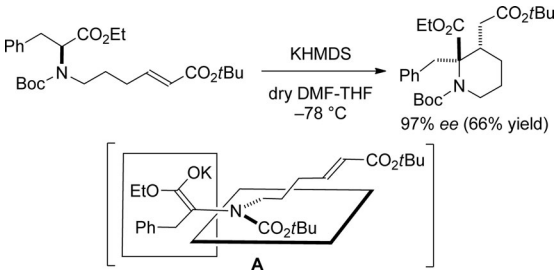
Abstract: β-Lactams with contiguous tetra- and trisubstituted carbon centers were prepared in a highly enantioselective manner through 4-*exo-trig* cyclization of axially chiral enolates generated from readily available α-amino acids. Use of a weak base (metal carbonate) in a protic solvent (EtOH) is the key to the smooth production of β-lactams. Use of the weak base is expected to generate the axially chiral enolates in a very low concentration, which undergo intramolecular conjugate addition without suffering intermolecular side reactions. Highly strained β-lactam enolates thus formed through reversible intramolecular conjugate addition (4-*exo-trig* cyclization) of axially chiral enolates undergo prompt protonation by EtOH in the reaction media (not during the work-up procedure) to give β-lactams in up to 97% *ee*.

Keywords: amino acids · axial chirality · β-lactams · conjugate addition · protonation

Introduction

We previously reported enantioselective intramolecular conjugate addition reactions of enolates derived from α-amino acid derivatives through memory of chirality (Scheme 1).[1–3]



Scheme 1. Asymmetric intramolecular conjugate addition through an axially chiral enolate (KHMDS = potassium hexamethyldisilazide).

A piperidine derivative with contiguous tetra- and trisubstituted stereocenters was prepared from an α-amino acid derivative in 97% *ee* without the use of external chiral sources such as chiral catalysts or chiral auxiliaries. It has been proposed that the reactions proceed through axially chiral enolate intermediate **A**.[1,2] This method could be used for the construction of five- and six-membered nitrogen heterocycles, but not four-membered ones.[4]

We sought to apply this method to the synthesis of β-lactams with contiguous tetra- and trisubstituted stereocenters starting from commercially available α-amino acids (Scheme 2).[5,6] β-Lactams are expected to be produced through 4-*exo-trig* cyclization of axially chiral enolates such as **B**. However, we had expected that this process might be unfavorable because the conjugate addition of enolate **B** should give highly strained β-lactam enolate **C** with a labile C–C bond (1.63 Å by DFT calculations when M = Cs, $R^1 = R^2 = R^3 = R^4$ = Me, see the Supporting Information). Because conjugate addition of the enolates is reversible, enolates **B** and **C** would coexist and both are prone to undergo intermolecular side reactions, which would give a complex mixture. In accordance with this assumption, β-lactam synthesis by reversible intramolecular conjugate addition of enolates has rarely been reported.[7] A hypothetical route to overcome this problem is shown in Scheme 2. The preferential preconditions for β-lactam formation might involve generation of a low concentration of enolate **B** to avoid intermolecular side reactions, and prompt protonation of the β-lactam enolate **C** immediately after its formation to stabilize the labile bond.[8] With this hypothesis in mind, we examined the conditions suitable for β-lactam formation.

Results and Discussion

The precursor for asymmetric β-lactam synthesis through memory of chirality was designed as follows. The choice of the nitrogen substituents is critical for the generation of axially chiral enolates with high enantiomeric purity. Both a

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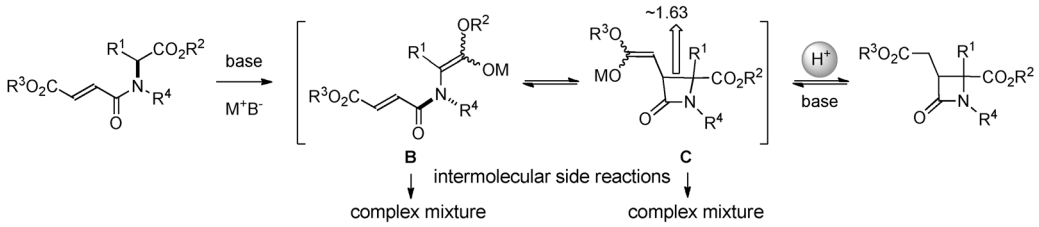
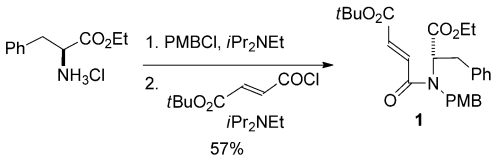


Scheme 2. Strategy for β-lactam synthesis through the reversible intramolecular conjugate addition of enolates followed by protonation.

substituent containing a carbonyl group and an alkyl substituent are necessary for this purpose.[1,2] Because the β-lactam precursor in Scheme 2 already has an amide carbonyl group on the nitrogen, an alkyl substituent is suitable for the second substituent. We chose a *p*-methoxybenzyl (PMB) group as the alkyl substituent of the nitrogen because it is easy to remove (Scheme 3). β-Lactam precursor **1** was readily obtained from L-phenylalanine ethyl ester in two steps in

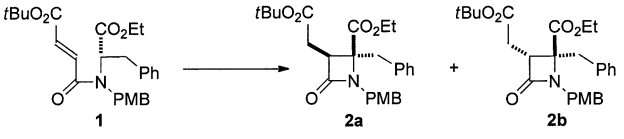


Scheme 3. Preparation of β-lactam precursors from L-phenylalanine ethyl ester.

57% overall yield through *p*-methoxybenzylation followed by acylation with an acid chloride of mono *tert*-butyl ester of fumaric acid.[9]

The conditions for the asymmetric conjugate addition of an enolate derived from **1** were examined (Table 1). The use of KHMDS,[10] lithium tetramethylpiperidide (LTMP),[11] or lithium diisopropylamide (LDA) as a base gave a complex mixture (Table 1, entries 1–3), probably due to the intermolecular side reactions of enolate **B** and/or enolate **C**, as expected (Scheme 2). According to the hypothesis presented in Scheme 2, we next examined bases with lower pK_a values (weaker bases) to decrease the concentrations of enolates **B** and **C**. We examined the use of powdered KOH in dimethyl sulfoxide (DMSO),[12] which was previously found to be an excellent base for asymmetric intramolecular alkylation through axially chiral enolates at ambient temperature.[13] However, a complex mixture was again obtained (Table 1, entry 4). Thus, even weaker bases, such as metal carbonates, were examined. Treatment of **1** with 1.5 equivalents of Cs_2CO_3 in CH_3CN at 20°C for 36 h gave the desired β-lactams **2a** (93% *ee*) and **2b** (91% *ee*) as a 63:37 diastereomeric mixture in 89% combined yield (Table 1, entry 5). Treatment of **1** with Cs_2CO_3 in CH_3CN at 50°C for 23 h gave **2a** and **2b** in a higher diastereomeric ratio (88:12) in 99% combined yield and in 83 and 81% *ee*, respectively (Table 1, entry 6). Rb_2CO_3 and K_2CO_3 were less effective for the reaction. The reaction of **1** with Rb_2CO_3 at 50°C for 90 h gave a mixture of **2a** and **2b** in poor yield (34%; Table 1, entry 7). A higher temperature and longer reaction time were required for the reaction of **1** with K_2CO_3 in CH_3CN, which gave a 62:38 mixture of **2a** and **2b** in 80 and 82% *ee*, respectively (Table 1, entry 8). Use of metal carbonates was found to be effective for the β-lactam formation. The success of intramolecular conjugate addition using metal carbonates was expected to be due to the generation of a very low concentration of enolates (pK_a values of HCO_3^- and the α-proton of α-amino acid derivatives are de-

Table 1. Effects of bases, solvents, and additives on asymmetric intramolecular conjugate addition.[a]



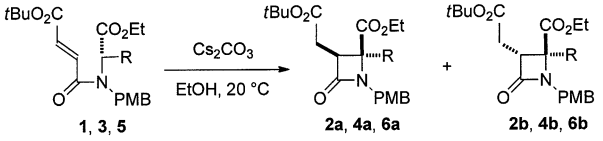
Entry	Base[b]	Solvent	Additive [equiv]	*t* [°C]	*T* [h]	Yield [%][c]	**2a**/**2b**[d,e,f]	*ee* of **2a** [%][g]	*ee* of **2b** [%][g]
1	KHMDS	THF	–	−78	2	–[h]	–	–	–
2	LTMP	THF	–	−78	2	–[h]	–	–	–
3	LDA	THF	–	−78	2	–[h]	–	–	–
4	KOH	DMSO	–	20	2	–[h]	–	–	–
5	Cs_2CO_3	CH_3CN	–	20	36	89	63:37	93	91
6	Cs_2CO_3	CH_3CN	–	50	23	99	88:12	83	81
7	Rb_2CO_3	CH_3CN	–	50	90	34	64:36	84	77
8	K_2CO_3	CH_3CN	–	reflux	111	94	62:38	80	82
9	Cs_2CO_3	CH_3CN	phenol (1.0)	20	0.5	99	41:59	87	90
10	Cs_2CO_3	CH_3CN	CF_3CH_2OH (1.0)	20	0.3	99	87:13	88	86
11	Cs_2CO_3	EtOH	–	20	0.1	82	52:48	93	95
12	Cs_2CO_3	EtOH	–	0	1	94	44:56	95	96
13	Rb_2CO_3	EtOH	–	20	1	98	50:50	94	95
14	K_2CO_3	EtOH	–	20	1.5	99	41:59	93	97

[a] Run with a substrate concentration of 0.1 M. [b] 1.2 or 1.5 Equivalents of the base were used for entries 1–3 or 4–14, respectively. [c] Yield of the diastereomeric mixture. [d] The ratio was determined by ^{1}H NMR spectroscopic analysis (400 MHz) before separation of the diastereomers. [e] Relative stereochemistry was determined by NOESY experiments of each of the pure diastereomers (see the Supporting Information). [f] The absolute configuration was tentatively assigned by analogy to **4a**. [g] The *ee* of the pure diastereomer obtained after HPLC separation. [h] Complex mixture.

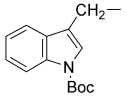
duced to be ca. 10 and ca. 24, respectively, in H_2O)[12,14] as well as protonation of β-lactam enolate **C** by the conjugate acid HCO_3^-. We then investigated the effects of additional proton sources. Because the pK_a value of HCO_3^- is about 10 (in H_2O), we examined additives with pK_a values similar to that of HCO_3^-, such as phenol (pK_a ca. 10) and CF_3CH_2OH (pK_a ca. 12). The addition of only one equivalent of phenol or trifluoroethanol significantly accelerated the reaction (36 h vs. 0.5 h (by phenol) or 0.3 h (by trifluoroethanol), Table 1, entries 5 vs. 9 or 10). Because the addition of proton sources was found to be effective for accelerating the reaction, we then examined the reaction in a pure protic solvent. The reaction in EtOH proceeded more quickly and was completed in 0.1 h to give a 52:48 mixture of **2a** and **2b** in a combined yield of 82% and in 93 and 95% *ee*, respectively (Table 1, entry 11). The yield and enantioselectivity of the reaction were slightly improved by conducting the reaction at 0°C (94% combined yield in 95 and 96% *ee* for **2a** and **2b**, respectively; Table 1, entry 12). The use of Rb_2CO_3 or K_2CO_3 as a base was also effective for the reaction in EtOH. The former gave a 50:50 mixture of **2a** and **2b** in a combined yield of 98% and in 94 and 95% *ee*, respectively, and the latter gave a 41:59 mixture of **2a** and **2b** in a combined yield of 99% and in 93 and 97% *ee*, respectively, although both cases required slightly longer reaction times than that with Cs_2CO_3 (Table 1, entries 11 vs. 13 or 14).

We then investigated the effects of the reaction time for the β-lactam formation from **1** and Cs_2CO_3 in EtOH (Table 2). Whereas a 52:48 mixture of **2a** and **2b** was obtained by the reaction of **1** with Cs_2CO_3 in EtOH at 20°C for 0.1 h, the diastereomeric ratio changed to 91:9 when the reaction was conducted for 10 h, although there was a slight loss of enantioselectivity (91% *ee* for **2a** and 85% *ee* for **2b**; Table 2, entries 1 vs. 2). Diastereomer **2b** was formed as the major product when the reaction of **1** was conducted at a lower temperature (0°C) and for a short reaction time (0.2 h; Table 2, entry 3). This observation indicates that **2b** is the kinetically favored diastereomer and that **2a** is the thermodynamically favored diastereomer. A similar trend was also observed in the intramolecular conjugate addition reactions of L-valine-derived **3** and L-tryptophan-derived **5** (Table 2, entries 7–12). Whereas treatment of **3** with Cs_2CO_3 in EtOH at 20°C for 1 h gave a 76:24 mixture of **4a** and **4b** in a combined yield of 78% and in 91 and 95% *ee*, respectively, that for 5.5 h gave **4a** as the sole detectable diastereomer in 62% yield and 88% *ee* (Table 2, entries 7 and 8).[15] Upon treatment of **5** with Cs_2CO_3 in EtOH at 20°C for 0.5 h, a 43:57 mixture of **6a** and **6b** was obtained in a combined yield of 92% and in 93 and 92% *ee*, respectively (Table 2, entry 10). On the other hand, a 88:12 mixture of **6a** and **6b** was obtained in a combined yield of 75% by the reaction of **5** with Cs_2CO_3 for 5 h (Table 2, entry 11).[15] These results indicate that β-lactams **2a**, **4a**, and **6a** are thermodynamically favored diastereomers. Use of (*Z*)-**1** instead of **1** gave a 50:50 mixture of **2a** and **2b** in a combined yield of 88% and in diminished 73 and 77% *ee*, respectively (Table 2, entry 6). We also found that the use of only catalytic amounts of Cs_2CO_3 was effective for β-lactam formation. Treatment of **1** with 0.1 equivalent of Cs_2CO_3 in EtOH at 20°C for 2 h gave a 38:62 mixture of **2a** and **2b** in a combined yield of 96% and in 95 and 95% *ee*, respectively (Table 2, entry 4). Similarly, use of catalytic amounts of Cs_2CO_3 in EtOH was effective for other enantioselective β-lactam syntheses (Table 2, entries 5, 9, and 12).

Table 2. Effects of the reaction time on the β-lactam syntheses from various α-amino acid derivatives with Cs_2CO_3 in EtOH.[a]



1, 3, 5 **2a, 4a, 6a** **2b, 4b, 6b**

Entry	Substrate	R	Cs_2CO_3 [equiv]	Product	*t* [h]	Yield [%][b]	**a**/**b**[c,d]	*ee* of **a** [%][e]	*ee* of **b** [%][e]
1	**1**	$PhCH_2$	1.5	**2a**, **2b**[f]	0.1	82	52:48	93	95
2	**1**	$PhCH_2$	1.5	**2a**, **2b**[f]	10	80	91:9	91	85
3[g]	**1**	$PhCH_2$	1.5	**2a**, **2b**[f]	0.2	32	42:58	–	–
4	**1**	$PhCH_2$	0.1	**2a**, **2b**[f]	2	96	38:62	95	95
5	**1**	$PhCH_2$	0.3	**2a**, **2b**[f]	0.7	88	40:60	97	95
6	(*Z*)-**1**[i]	$PhCH_2$	1.5	**2a**, **2b**[f]	2.5	88	50:50	73	77
7	**3**	*i*Pr	1.5	**4a**, **4b**[h]	1	78	76:24	91[j]	95[j]
8[k]	**3**	*i*Pr	1.5	**4a**, **4b**[h]	5.5	62	>99:<1	88[j]	–
9	**3**	*i*Pr	0.1	**4a**, **4b**[h]	17	70	87:13	93[j]	94[j]
10	**5**		1.5	**6a**, **6b**[f]	0.5	92	43:57	93	92
11[k]	**5**		1.5	**6a**, **6b**[f]	5	75	88:12	89	85
12	**5**		0.1	**6a**, **6b**[f]	3.5	83	48:52	92	91

[a] Run with a substrate concentration of 0.1 M. [b] Yield of the diastereomeric mixture. [c] The ratio was determined by ^{1}H NMR spectroscopic analysis (400 MHz) before separation of the diastereomers. [d] Relative stereochemistry was determined by NOESY experiments of each of the pure diastereomers (see the Supporting Information). [e] The *ee* of the pure diastereomer obtained after HPLC separation. [f] The absolute configuration was tentatively assigned by analogy with **4a**. [g] Run at 0°C. [h] The absolute configuration was determined by X-ray analysis of **7** derived from **4a** (See text). [i] See ref.[9] [j] The *ee* was determined after conversion into **7** or its C(3)-epimer. [k] Run in *t*BuOH/EtOH (4:1) at 30°C.

The absolute configuration of **4a** was determined to be (3*S*,4*S*) by an X-ray crystallographic analysis of **7** (Figure 1),[16] which was obtained by removal of the *tert*-butyl group of a 76:24 mixture of **4a** (91% *ee*) and **4b** (95% *ee*), condensation of the resulting carboxylic acid with *p*-iodoaniline, and separation of the major diastereomer. A single crystal for X-ray analysis was obtained from **7** (>99% *ee*), which had been prepared by recrystallization of **7** (91% *ee*) obtained by the above procedure. Thus, intramolecular conjugate addition of **3** was found

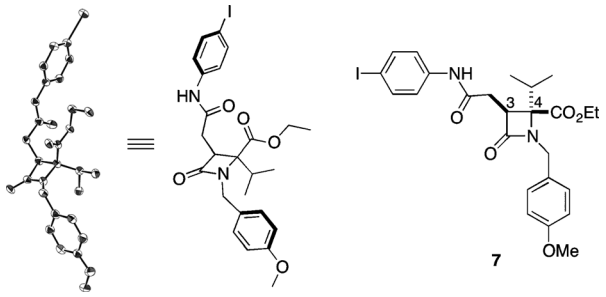


Figure 1. X-ray structure of **7**.

to proceed with an inversion of configuration at the newly formed tetrasubstituted carbon center.

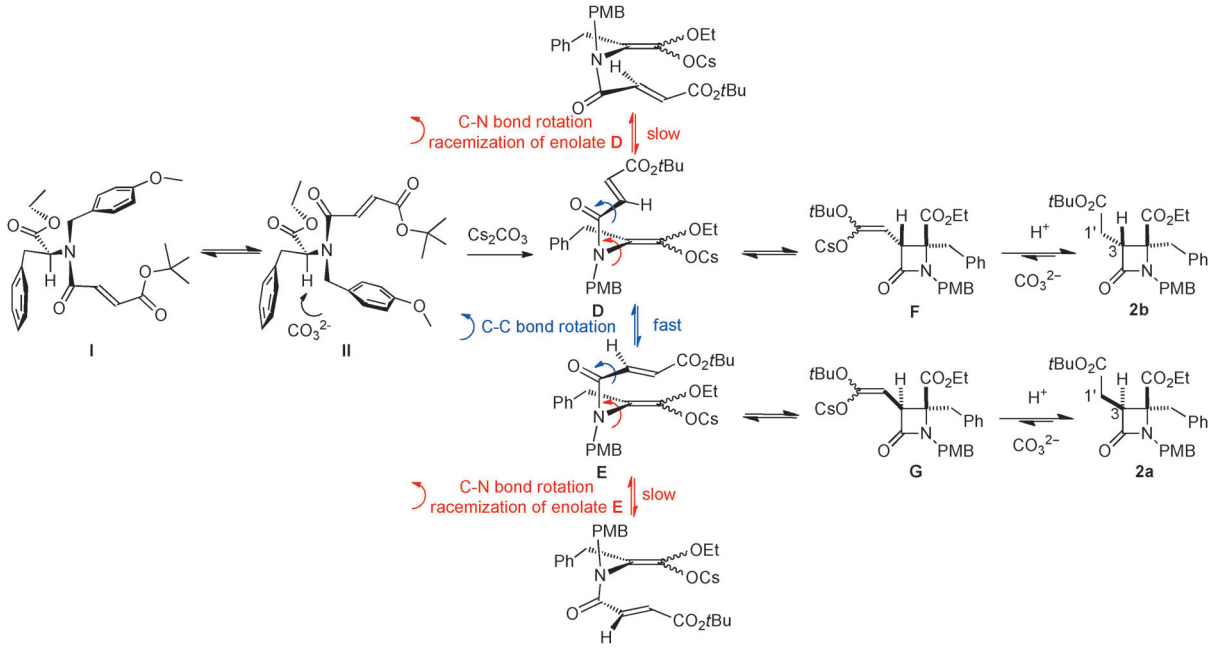
The diastereomeric ratio of **2a** and **2b** obtained by the reactions of **1** depended on the reaction time (Table 2, entries 1 vs. 2), which suggests that there is an equilibrium between **2a** and **2b**, through a retro-conjugate addition process. To examine this issue, diastereomerically pure **2a** and **2b** were obtained by HPLC separation and independently treated under the conditions used for β-lactam formation (Scheme 4). Treatment of **2a** (92% *ee*) with 1.5 equivalents of Cs_2CO_3 in EtOH at 20°C for 10 h gave a 93:7 mixture of **2a** and **2b** in 50% combined yield and 84 and 77% *ee*, respectively.[17] Alternatively, treatment of **2b** (96% *ee*) with 1.5 equivalents of Cs_2CO_3 in EtOH at 20°C for 10 h gave a 92:8 mixture of **2a** and **2b** in 66% combined yield and in 90 and 89% *ee*, respectively. These results clearly indicate the equilibrium between **2a** and **2b** and that the former is the thermodynamically favored diastereomer.

2a (92% *ee*) $\xrightarrow[\text{EtOH, 20 °C, 10 h}]{Cs_2CO_3\ (1.5\ \text{equiv})}$ **2a** (84% *ee*) + **2b** (77% *ee*)
50% 93 : 7

2b (96% *ee*) $\xrightarrow[\text{EtOH, 20 °C, 10 h}]{Cs_2CO_3\ (1.5\ \text{equiv})}$ **2a** (90% *ee*) + **2b** (89% *ee*)
66% 92 : 8

Scheme 4. Thermodynamic equilibrium between **2a** and **2b**.

A rationale for the stereochemical course of β-lactam formation is shown in Scheme 5. A conformational search of **1** gave stable conformers, **I** and **II**.[18] Deprotonation of conformer **II** with Cs_2CO_3, in which the C(α)–H bond is antiperiplanar with respect to the neighboring N–C(COCH=CHCO$_2$*t*Bu) bond, would be preferable to that of conformer **I**, in which the C(α)–H bond is antiperiplanar with respect to the neighboring N–C(PMB) bond. This expectation was based on our rationale for previous stereochemical results, in which deprotonation of *N*-Boc-*N*-alkyl-α-amino acid derivatives preferentially took place from the conformer in which the C(α)–H bond is antiperiplanar with respect to the neighboring N–C(Boc) bond.[10,13,19] Deprotonation of conformer **II** would give enantiomerically enriched enolate **D** with a chiral (a*S*)-C-N axis. The other chiral enolate **E** with a chiral (a*S*)-C-N axis would be formed by fast rotation of the C–C bond (blue curved arrow). Enolate **D** would undergo intramolecular conjugate addition from its *si*-face to give β-lactam enolate **F** with an inversion of configuration at the newly formed tetrasubstituted carbon. Similarly, enolate **E** would give β-lactam enolate **G** with the same absolute configuration as that of **F** at the tetrasubstituted carbon. Protonation of **F** and **G** by the solvent (EtOH) and/or the conjugate acid (HCO_3^-) would give β-lactams **2b** and **2a**, respectively. Equilibrium between **2a** and **2b** affects the ratio between them. Thermodynamically more stable diastereomers **2a**, **4a**, and **6a** were obtained as the major products when



Scheme 5. A possible mechanism for β-lactam formation through the reversible intramolecular conjugate addition of the axially chiral enolates.

the reactions were run for prolonged reaction times (Table 2, entries 2, 8, and 11). The decrease in enantiomeric purity of **2**, **4**, and **6** was less than 12% during the equilibrium process between chiral enolates. This would indicate that the interconversion between **D** and **E** through C–C bond rotation (blue curved arrow) is faster than racemization of the axially chiral enolates **D** and **E** through C–N bond rotation (red curved arrow). For the expected racemization barriers of enolates **D** and **E**, see text below.

It is assumed that the equilibrium between **2a** and **2b** is initiated by the deprotonation of C(1′)–H of **2a** and **2b**. However, it could alternatively result from the deprotonation of C(3)–H of **2a** and **2b**. To investigate this possibility, **2a** was treated under conditions identical to those shown in Scheme 4, except for the use of EtOD instead of EtOH. Thus, 65% deuterium incorporation was observed at C(1′) of **2**-*d*, whereas no deuterium incorporation was detected at C(3) (Figure 2). This indicates that the equilibrium between

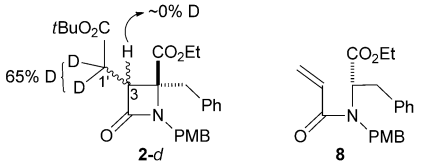
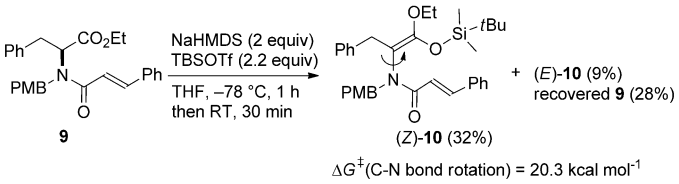


Figure 2. Deuterated product **2**-*d* and compound **8**.

2a and **2b** is initiated by deprotonation of C(1′)–H followed by retro-conjugate addition, C–C bond rotation (blue curved arrow), conjugate addition, and protonation, as shown in Scheme 5. Another interesting phenomenon is that enolates **D** and **E** themselves do not seem to suffer protonation by EtOH, because their protonation should significantly diminish the *ee* values of **2a** and **2b**. In fact, significant racemization was observed in **8** under the standard conditions used for intramolecular conjugate addition (Figure 2). When **8** (>99% *ee*) was treated with 1.5 equivalents of Cs_2CO_3 in EtOH at 20°C for 15 min, **8** with 18% *ee* was recovered in 96% yield. The observed racemization was assumed to come about as a result of protonation of the enolate generated from **8** because the enolate is unlikely to undergo 5-*endo-trig* cyclization to give a γ-lactam enolate. In contrast, intramolecular conjugate addition of enolates **D** and **E** through 4-*exo-trig* cyclization would proceed faster than protonation of themselves by EtOH. This avoids the racemization of **D** and **E**, and, instead, promotes β-lactam formation in a highly enantioselective manner. Overall, the prompt protonation of β-lactam enolates **F** and **G** is essential for β-lactam formation, whereas the protonation of enolates **D** and **E** to give the starting material **1** should be slower than intramolecular conjugate addition of the enolates.[20]

To estimate the rates of racemization of axially chiral enolates **D** and **E**, the rotational barrier of the C–N bond of the related enolate equivalent, silyl ketene acetal (*Z*)-**10**, was determined by variable-temperature NMR measurements (Scheme 6). Compound **9** was employed as a precursor for the silyl ketene acetal because its enolate does not undergo 4-*exo-trig* cyclization, and, instead, could be trapped as the



Scheme 6. Preparation and the rotational barrier of the C–N bond of (*Z*)-**10** (TBSOTf = *tert*-butyldimethylsilyl triflate).

silyl ketene acetal. Two methyl groups of the *tert*-butyldimethylsilyl group of (*Z*)-**10** appeared as two diastereotopic singlets in its ^{1}H NMR spectra measured at 20°C, suggesting restricted rotation along the C–N bond. The rotational barrier was determined to be 20.3 kcal mol^{-1} from $\Delta\nu$ (31.2 Hz) and the coalescence temperature (128°C). The half-life of racemization of axially chiral enolates **D** and **E** are estimated to be about 1 min at 20°C (standard temperature employed for the β-lactam formation in Table 2), based on the assumption that racemization barriers of the axially chiral enolates **D** and **E** are comparable to the rotational barrier of the C–N bond of (*Z*)-**10**, and that $\Delta S^{\neq}$ of the unimolecular process for the bond rotation is nearly zero. Thus, racemization through C–N bond rotation seems slower than the interconversion between **D** and **E** through C–C bond rotation. Another aspect may be worth mentioning; β-Lactams were obtained in 80 to 82% *ee* through the asymmetric conjugate addition of the axially chiral enolate performed even at 81°C (Table 1, entry 8). The half-life of racemization of enolates **D** and **E** might also be estimated to be about 0.2 s at 81°C. Asymmetric conjugate addition was found to be still possible at such a high temperature through axially chiral enolate intermediates.[21]

Conclusion

β-Lactams with contiguous tetra- and trisubstituted carbon centers were prepared in a highly enantioselective manner from readily available α-amino acids. To the best of our knowledge, this is the first example of the asymmetric synthesis of β-lactams through the reversible intramolecular conjugate addition of enolates. Use of a weak base (metal carbonate) in a protic solvent (EtOH) is the key to the smooth production of β-lactams. The present method provides unique access to optically active β-lactams that are still of great importance in the field of medicinal chemistry.[22] β-Lactams are also useful equivalents of protected β-amino acids as well as versatile precursors of N-heterocyclic compounds for the synthesis of natural products.[23]

Experimental Section

Cyclization of 1 with Cs_2CO_3 in EtOH (Table 1, entry 11): A mixture of **1** (3.91 g, 8.40 mmol) and Cs_2CO_3 (4.10 g, 12.6 mmol) in EtOH (90 mL) was stirred for 0.1 h at 20 °C, then the reaction was quenched by addition of sat. NH_4Cl. After removal of volatiles, the aqueous layer was extracted with EtOAc and the extracts were dried over Na_2SO_4, filtered, and concentrated. The residual oil was purified by silica gel column chromatography (EtOAc/hexane = 3:7) to give a 52:48 diastereomeric mixture of **2a** and **2b** (3.20 g, **2a**: 93% *ee*, **2b**: 95% *ee*) as a colorless oil. Compound **2a**: colorless oil; 93% *ee*. For physical data, determination of the enantiomeric excess, ^{1}H NMR, NOESY, ^{13}C NMR spectra of **2a** and **2b**, see the Supporting Information.

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[7] β-Lactam synthesis through irreversible intramolecular conjugate addition of α-lithio amides has been reported, see: J. Clayden, D. W. Watson, M. Helliwell, M. Chambers, *Chem. Commun.* **2003**, 2582–2583.

[8] The length of the labile C–C bond of β-lactam enolate **C** (M = Cs, $R^1 = R^2 = R^3 = R^4$ = Me) was calculated to be 1.63 Å by DFT calculations (see the Supporting Information), whereas the corresponding bond length of C(3)–C(4) of β-lactam **7** was shown to be 1.574 Å by X-ray analysis.

[9] β-Lactam precursor **1** and its *Z* isomer were alternatively obtained by amidation of *N*-PMB-phenylalanine ethyl ester with maleic anhydride followed by esterification of the resulting carboxylic acid with $(Boc)_2O$/DMAP. See the Supporting Information.

[10] KHMDS is a suitable base for the intramolecular alkylation and intramolecular conjugate addition of α-amino acid derivatives with a retention of configuration through memory of chirality. See: a) T. Kawabata, S. Kawakami, D. Majumdar, *J. Am. Chem. Soc.* **2003**, *125*, 13012–13013; b) See also ref. [1].

[11] LTMP is a suitable base for the intramolecular alkylation of α-amino acid derivatives with an inversion of configuration through memory of chirality, see: T. Kawabata, S. Matsuda, S. Kawakami, D. Monguchi, K. Moriyama, *J. Am. Chem. Soc.* **2006**, *128*, 15394–15395.

[12] KOH in DMSO is a strong base that can abstract the α-proton of esters (pK_a values of H_2O and α proton of esters in DMSO are 31 and 18–30, respectively). KOH in DMSO seems to be an even stronger base than KHMDS in DMSO based on their pK_a values: pK_a values of H_2O and HMDS in DMSO are 31 and 30, respectively. See: a) F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456–463; b) N. V. Mashchenko, M. G. Matveeva, I. L. Odinets, E. I. Matrosov, E. S. Petrov, M. I. Terekhova, A. K. Matveev, T. A. Mastryukova, M. I. Kabachnik, *Zh. Obshch. Khim.* **1988**, *58*, 1973–1979; c) R. P. Bell, *The Proton in Chemistry*, Cornell University Press, Ithaca, New York **1959**.

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[14] The reaction of **1** with KHMDS at −10 °C under dilute conditions (0.01 M in EtOH) also gave a mixture of **2a** and **2b** in 79% yield.

[15] The mixed solvent *t*BuOH/EtOH (4:1), was used to avoid ester exchange during the long reaction time in the presence of Cs_2CO_3. For example, treatment of **3** with Cs_2CO_3 in EtOH for 10 h gave **4** in only 31% yield, due to the ester exchange.

[16] Crystal data of **7**: $C_{25}H_{29}IN_2O_5$; $M = 564.40$; space group $P21$(#4); $a = 11.8641$ (4) Å, $b = 6.7776(2)$ Å, $c = 15.5120(5)$ Å, $\alpha = 90°$, $\beta = 90.788(2)°$, $\gamma = 90°$; $V = 1247.20(7)$ Å^3; $Z = 2$; $\rho_{calcd} = 1.503$ mg m^{-3}; $Mo_{K\alpha}$ radiation; $\lambda = 0.71069$ Å; $\mu = 1.321$ mm^{-1}; $T = 103(2)$ K. The final *R1* and w*R2* were 0.0302 and 0.0628 for 332 parameters. CCDC-743570 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] The main reasons for the low recovery of **2** involve ester exchange (ca. 20%) and decomposition.

[18] The stable conformers **I** and **II** were generated by a molecular modeling search (MCMM 50,000 steps) with OPLS 2005 force field with GB/SA solvation model for *n*-butanol using MacroModel (V. 9.0). The difference in potential energies between **I** and **II** was estimated to be 0.22 kcal mol^{-1} (**II** is more stable than **I**). The corresponding *s-trans* conformer of the α,β-unsaturated amide moiety was not found among the low-energy conformers within 10 kcal mol^{-1} (see the Supporting Information).

[19] T. Kawabata, H. Suzuki, Y. Nagae, K. Fuji, *Angew. Chem.* **2000**, *112*, 2239–2241; *Angew. Chem. Int. Ed.* **2000**, *39*, 2155–2157, also see refs. [2a,c,10,11,13].

[20] Protonation of tetrasubstituted enolates **D** and **E** is assumed to be slower than that of trisubstituted enolates **F** and **G**, due to the difference in the steric environments at the sp^2 carbon atoms suffering protonation. Protonation of enolates **D** and **E** is also expected be minimized by the higher rate of the intramolecular conjugate addition than the intermolecular protonation.

[21] Recently, a highly enantioselective cascade rearrangement of enediynes has been reported that proceeds at 80°C through memory of chirality, see: M. Nechab, D. Campolo, J. Maury, P. Perfetti, N. Vanthuyne, D. Siri, M. P. Bertrand, *J. Am. Chem. Soc.* **2010**, *132*, 14742–14744.
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