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Base-Induced Sequential Cyclization–Rearrangement of Enantioenriched 3-Aminoalkanoates to Five- and Seven-Membered Lactams

Takeo Sakai, Ken-ichi Yamada, and Kiyoshi Tomioka*[a]

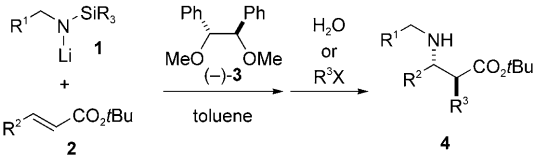
Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract: By treatment with *t*BuLi, linear 3-aminoalkanoates (**4**) were converted stereoselectively into five- and seven-membered lactams (*trans*-**5** and *cis*-**6**). Initial cyclization to azetidin-2-one with subsequent aza-[1,2] and [2,3] rearrangement is the probable mechanistic pathway from **4** to **5** and **6**. Although enantioenriched **4** was converted into nearly racemic **5** and **6**, a linear 3-amino-2-methylalkanoate (**17**) with 90% *ee* bearing chirality at the ester α-position afforded an all-*cis* seven-membered lactam (**18**) bearing three asymmetric centers with 85% *ee*.

Keywords: chirality · cyclization · lactams · lithium · rearrangement

Introduction

The chiral-ligand-controlled asymmetric conjugate addition reaction[1] of lithium arylmethyl(trimethylsilyl)- or allyl(trialkylsilyl)amides **1** (R^1 = Ar,[2a,c–e] CH=CH_2[2b]) with acyclic and cyclic enoates **2** gives the corresponding 3-alkylaminoalkanoates **4** in high enantio- and diastereoselectivity (Scheme 1).[3–5] Chiral 3-aminoalkanoates **4** are known to be the essential and versatile components of biologically potent compounds.[6,7] Herein we describe that 3-benzylamino- or 3-allylaminoalkanoates **4** serve as starting materials for the stereoselective one-pot synthesis of five- and seven-membered lactams *trans*-**5** and *cis*-**6** through a base-induced cyclization–rearrangement sequence.

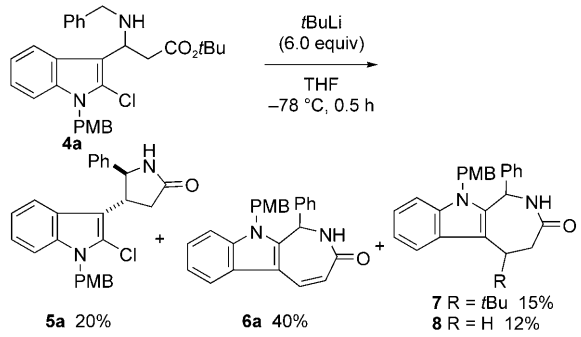


Scheme 1. Chiral ligand **3** controlled asymmetric conjugate addition reaction of lithium amides **1** with enoates **2**.[2]

Results and Discussion

Unexpected Sequential Cyclization–Rearrangement of 3-Aminoalkanoates

We encountered this unexpected behavior of 3-aminoalkanoate **4** during the attempted chlorine–lithium exchange reaction of **4a** (Scheme 2). The reaction of **4a** with 6 equiv of *tert*-butyllithium in THF at −78 °C for 0.5 h gave five-membered lactam *trans*-**5a** in 20% yield and seven-membered lactams **6a**, **7**, and **8** in 40, 15, and 12% yields, respectively.



Scheme 2. *t*BuLi-induced conversion of 3-benzylaminoalkanoate **4a** into five- and seven-membered lactams **5a**, **6a**, **7**, and **8**. PMB = 4-methoxybenzyl.

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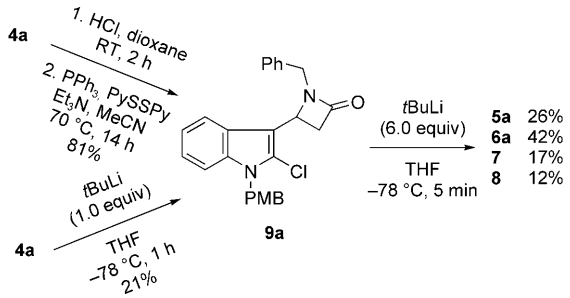
It is also important to note that *trans*-**5a** was obtained as a single diastereomer.[8] Treatment with *n*-butyllithium also gave the similar outcome of *trans*-**5a** in 24% yield and **6a** in 33% yield without formation of **7** and **8**. *N*-benzylazetidin-2-one **9a** (see Scheme 3) would be the initial product expected in the reaction of **4a** with *tert*-butyllithium,[9] and *N*-benzylazetidin-2-ones have been reported to undertake organolithium-induced aza-[1,2] and [2,3] rearrangements giving five- and seven-membered lactams.[10]

In fact, the reaction of **9a**, prepared in 81% yield from **4a** by acidic hydrolysis and β-lactam formation,[11] with *t*BuLi in THF at −78°C for 5 min gave *trans*-**5a**, **6a**, **7**, and **8** in the very similar yields of 26, 42, 17, and 12%, respectively (Scheme 3). It is also important to note that treatment of **4a**



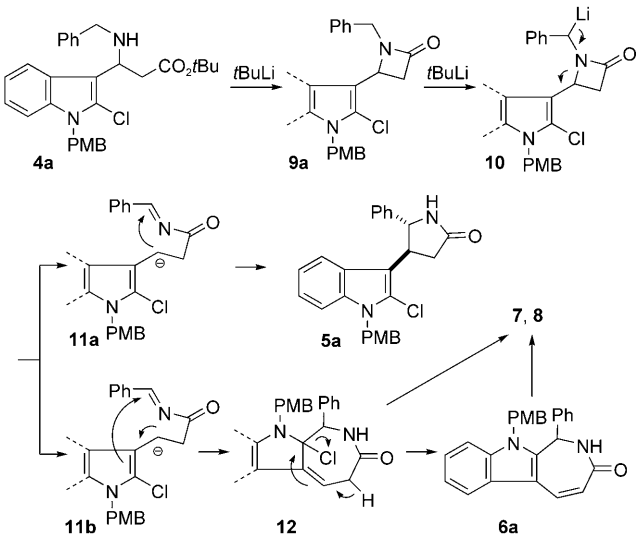
Scheme 3. Formation of azetidin-2-one **9a** from **4a** and its conversion into lactams **5a**, **6a**, **7**, and **8**.

with 1 equiv of *t*BuLi gave **9a** in 21% yield along with rearranged lactams.

The formation of *trans*-**5a**, **6a**, **7**, and **8** can be accounted for by the following mechanism. The *N*-benzylic position of azetidin-2-one **9a** is deprotonated to produce anionic species **10**, in which a N–C bond in the azetidinone[12] is then cleaved, giving an imine **11** bearing an anion moiety. The 5-*endo* cyclization exhibited by **11a** gave **5a**, and the 7-*endo* cyclization exhibited by **11b** gave **12**, which was then dehydrochlorinated to afford **6a** (Scheme 4). Michael reaction of *t*BuLi with **6a** or SN2′ reaction with **12** would give **7**. Reduction of **6a** or lithium–chlorine exchange reaction of **12** with subsequent isomerization of a double bond would be one of the possible pathways to **8**.

Abstract in Japanese:

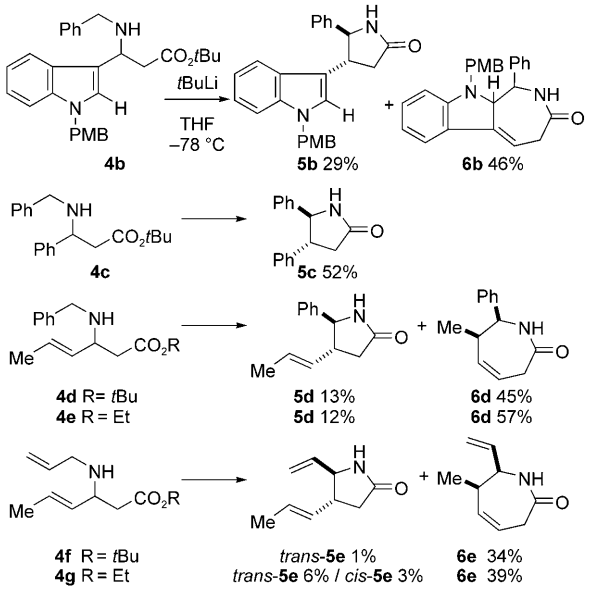
3-アミノカルボン酸エステル **4** を *t*-ブチルリチウムで処理すると *trans* の5員環ラクタム **5** と *cis* の7員環ラクタム **6** が得られた。この反応は、3-アミノカルボン酸エステルのアゼチン-2-オンへの環化、さらに[1,2]-もしくは[2,3]-転位の連続反応であると説明ができる。光学活性な **4** の反応では、ほぼラセミ化した **5** と **6** が得られたのに対し、カルボニルα位にメチル基を導入した3-アミノ-2-メチルカルボン酸エステル **14a** の反応では不斉収率はほぼ維持され、すべて *cis* の7員環ラクタム **18a** を 85% *ee* で得た。



Scheme 4. Plausible pathway to **5a** and **6a**.

Scope of 3-Aminoalkanoates and Determination of Relative Configuration of Product Lactams

The unprecedented one-pot conversion of 3-aminoalkanoate **4** to rearranged lactams and its undeveloped stereochemistry stimulated us to explore the reaction in more detail. As shown in Scheme 5, **4b** bearing a chlorine-free indole



Scheme 5. *t*BuLi-induced sequential cyclization–rearrangement of 3-benzyl- and 3-allylaminoalkanoates **4**.

moiety provided five- and seven-membered lactams *trans*-**5b** and **6b** in 29 and 46% yields as single diastereomers, respectively. The lower stability of **6b** was confirmed by the complete conversion into a 10:1 mixture of **6a** and **8** upon standing for one week at room temperature in $CDCl_3$. Five-mem-

bered lactam *trans*-**5c** (52%) was the sole product in the reaction of **4c**.[10a] 3-Benzylaminoalkenoate **4d** was converted into *trans*-**5d** in 13% yield along with *cis*-**6d** in 45% yield as single diastereomers. 3-Allylaminoalkenoate **4f** was converted into *trans*-**5e** in 1% yield and *cis*-**6e** in 34% yield. The *cis* stereochemistry of **6d** was unambiguously determined by X-ray crystallography, as shown in Figure 1,[13] and

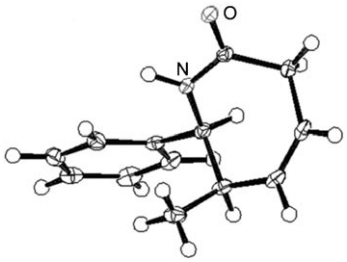


Figure 1. ORTEP plot of **6d**. Thermal ellipsoids are shown at the 50% probability.

the relative configuration of *trans*-**5d**,**e** and *cis*-**6e** was determined by an NOE (nuclear Overhauser effect) experiment, as shown in Figure 2. Corresponding ethyl esters **4e** and **4g**

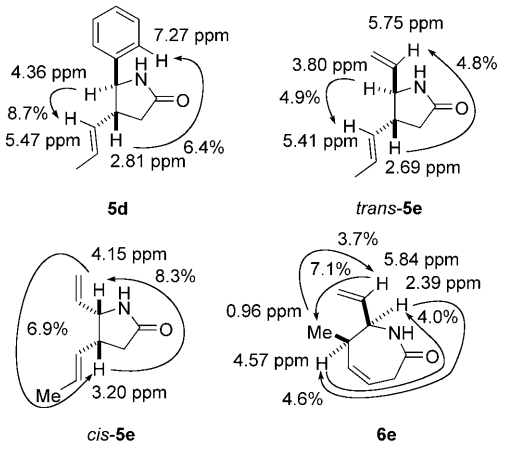
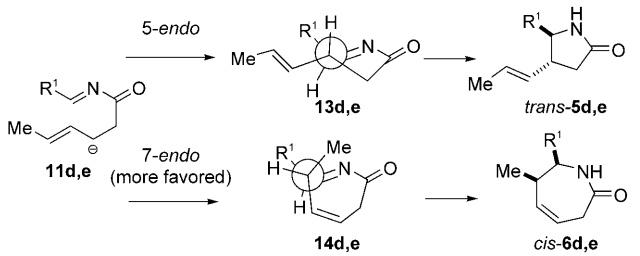


Figure 2. Relative stereochemistry of *trans*-**5d**, *trans*- and *cis*-**5e**, and *cis*-**6e** by NOE.

were relatively better starting esters than sterically demanding *tert*-butyl esters to give **5d,e** and **6d,e** in better yields compared with those obtained by the reaction of *tert*-butyl esters. In the case of **4g**, *cis*-**5e** was also obtained in 3% yield along with *trans*-**5e** in 6% yield and *cis*-**6e** in 39% yield.

Stereoselective production of *trans*-**5** and *cis*-**6** is rationalized by the pathway starting from the anion **11** that is generated from **4** by cyclization to azetidin-2-one with subsequent opening of the four-membered lactam (Scheme 6: represented by the reactions starting from **4d–g**). The anion moiety of **11** attacks an imine carbon atom via the more favorable conformations **13** and **14** to afford *trans*-**5d**,**e** and *cis*-**6d**,**e**,



Scheme 6. Plausible pathway to *trans*-**5d**,**e** and *cis*-**6d**,**e** from **4d-g** via **11**.

respectively. The more favored 7-*endo* cyclization gave **6** as a major product.[14]

Reaction of Enantioenriched 4

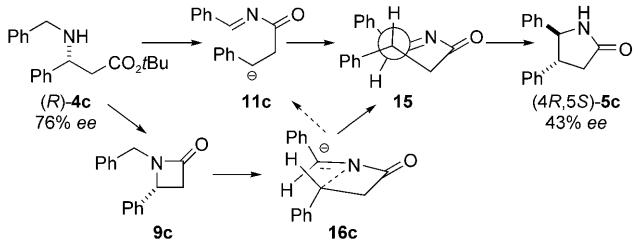
The enantioenriched aminoalkanoates **4** were synthesized by the asymmetric conjugate addition[2] of lithium amide **1** to enoates **2** under the control of **3**. It is quite reasonable to expect that the reaction of *enantioenriched* **4** should give racemic **5** and **6**, because the anion intermediate **11** is not chiral. However, we were very much surprised to find that the enantiomeric purity of (+)-**4a** with 97% *ee* was partially maintained to give **5a** with 2% *ee*, (+)-**6a** with 17% *ee*, (+)-**7** with 17% *ee*, and (−)-**8** with 18% *ee* [Eq. (1)]. Unfortunately (+)-**4d** with 98% *ee* was converted into nearly racemic **5d** and **6d** [Eq. (2)]. Nearly racemic **6e** was also obtained starting from (+)-**4f** with 55% *ee* [Eq. (3)]. These results suggested that the rearrangement step proceeded not by a concerted mechanism but by a stepwise manner.

$$(+)\text{-}\mathbf{4a}\ (97\%\ ee) \rightarrow \mathbf{5a}\ (2\%\ ee),\ (+)\text{-}\mathbf{6a}\ (17\%\ ee),\ (+)\text{-}\mathbf{7}\ (17\%\ ee),\ (-)\text{-}\mathbf{8}\ (18\%\ ee) \quad (1)$$

$$(+)\text{-}\mathbf{4d}\ (98\%\ ee) \rightarrow \mathbf{5d}\ (0\%\ ee),\ \mathbf{6d}\ (3\%\ ee) \quad (2)$$

$$(+)\text{-}\mathbf{4f}\ (55\%\ ee) \rightarrow \mathbf{6e}\ (3\%\ ee) \quad (3)$$

Contrary to the results above, it was our surprise and delight to find that (4*R*,5*S*)-**5c** with 43% *ee* was obtained starting from (*R*)-**4c** with 76% *ee* (Scheme 7). The absolute configuration and *ee* value of **5c** were determined by the specific rotation.[10c]

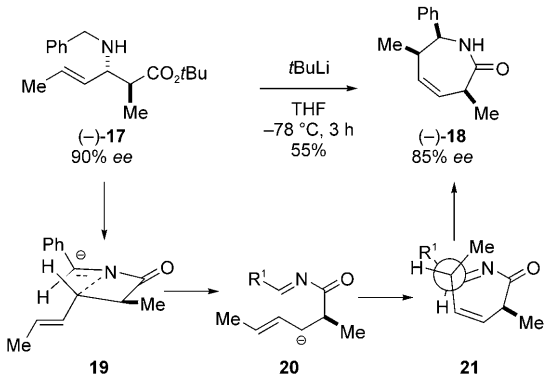


Scheme 7. Conversion of (*R*)-**4c** into (4*R*,5*S*)-**5c** via **16c**, generated from azetidinone **9c**.

The partial but significant retention of enantiomeric purity of **4c** may be rationalized as follows.[15] Azetidinone **9c** could be lithio-deprotonated at the benzylic position to afford an anion in which an N–C bond of the azetidinone ring is then cleaved, leading to an imine bearing another benzylic anion, as shown in **11c** from **16c**. However, it is highly probable that the anionic species **16c** would quickly lead to the reactive conformation **15** rather than to an achiral anion **11c**, thus affording partially racemized (4*R*,5*S*)-**5c** as a major product (Scheme 7).

Anchoring Role of the α-Position Chirality of an Ester Moiety

The mechanistic rationalization above suggests that efficient chirality transfer from **4** to the product **6** would be possible by using the anchoring role of the α-position chirality of an ester moiety in **17**. We expected that the anion moiety **20**, generated via **19**, would still be chiral and the cyclization would proceed through the most favorable reactive conformation (**21**). To our delight, the reaction of *anti*-major α-methyl-substituted ester (−)-**17** with 90% *ee* and 93:7 d.r. gave stereoselectively all-*cis*-(−)-**18** with 85% *ee* bearing three stereogenic centers (Scheme 8).[16] The all-*cis* stereochemistry of (−)-**18** was determined by NOE, as shown in Figure 3. This retention of stereochemical integrity is in sharp contrast to the nearly total loss observed in the conversion of **4d**,**f** into **6d**,**e** and confirms the possible feasibility of the reactive conformations **14** and **21**.



Scheme 8. Expected and confirmed positive role of the chirality at the α-position of an ester moiety of **17**.

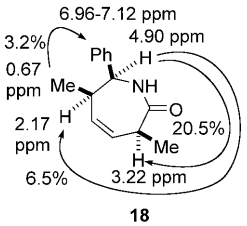


Figure 3. Structure determination of **18** by NOE.

Conclusions

We have demonstrated the usefulness of 3-aminoalkanoates **4** in the one-pot conversion to five- and seven-membered lactams *trans*-**5** and *cis*-**6**. Chirality at the α-position of an ester group is efficiently transferable to the cyclization–rearrangement product bearing three chiral centers. Sequential cyclization to azetidin-2-one and aza-[1,2] and [2,3] rearrangement would be the probable pathway in this transformation.[10,12,17] Preferred production of seven-membered *cis*-lactam **6** is the key to the probable mechanistic consideration. Since seven-membered lactam moieties are included in various types of bioactive compounds[18,19] and constructions of seven-membered heterocycles are attractive topics,[20,21] we believe that our method will contribute to the field of synthetic chemistry.

Experimental Section

General

All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ at 500 and 125 MHz, respectively. ^{13}C peak multiplicity assignments were made based on DEPT data. Chemical shift values are referenced to internal TMS. *J* values are presented in Hz.

Synthetic Procedures

1-(4-Methoxybenzyl)indole-3-carbaldehyde: To a suspension of NaH (60% w/w dispersion in mineral oil, 960 mg, 24 mmol) in DMSO (12 mL) was added a solution of indole-3-carbaldehyde (2.86 g, 20 mmol) in DMSO (12 mL) under Ar at room temperature. After the mixture was stirred for 1 h, *p*-methoxybenzyl chloride (3.27 mL, 24 mmol) was added at 0 °C. After stirring for 3 h at room temperature, the mixture was poured into ice water (100 mL). The whole was extracted with AcOEt and the organic layer was washed with brine and dried over sodium sulfate. Concentration and column chromatography ($CHCl_3$) gave the compound (3.9 g, 74%) as pale yellow needles. M.p. 108.0–109.0 °C; IR (KBr): $\tilde{\nu}$ = 1651, 1512, 1250, 756 cm^{-1}; ^{1}H NMR: δ = 3.80 (3H, s), 5.29 (2H, s), 6.89 and 7.15 (each 2H, d, J = 8.6), 7.30–7.38 (3H, m), 7.68 (1H, s), 8.33 (1H, m), 9.99 ppm (1H, s); ^{13}C NMR: δ = 50.2 (CH_2), 55.1 (CH_3), 110.3 (CH), 114.3 (CH), 118.2 (C), 122.0 (CH), 122.9 (CH), 124.0 (CH), 125.4 (C), 127.0 (C), 128.8 (CH), 137.3 (C), 138.4 (CH), 159.5 (C), 184.6 ppm (CH); MS (EI): 265 $[M]^+$; elemental analysis: calcd (%) for $C_{17}H_{15}NO_2$: C 76.96, H 5.70, N 5.28; found: C 76.70, H 5.74, N 5.20.

tert-Butyl (*E*)-3-[2-chloro-1-(4-methoxybenzyl)indol-3-yl]propenoate: A mixture of 2-chloro-1-(4-methoxybenzyl)indole-3-carbaldehyde[22] (556 mg, 1.86 mmol), $Ph_3P{=}CHCO_2tBu$ (1.40 g, 3.71 mmol), and toluene (10 mL) were stirred under reflux for 48 h. After further addition of $Ph_3P{=}CHCO_2tBu$ (1.40 g, 3.71 mmol), the whole was stirred under reflux for 10 h. After cooling to room temperature, the whole was filtered with suction, and the residue was concentrated. Column chromatography (AcOEt/hexane = 1:10) gave the compound (716 mg, 97%) as a yellow oil. IR (KBr): $\tilde{\nu}$ = 2978, 1697, 1620, 1250, 1150, 741 cm^{-1}; ^{1}H NMR: δ = 1.56 (9H, s), 3.75 (3H, s), 5.36 (2H, s), 6.50 (1H, d, J = 16.1), 6.82 and 7.06 (each 2H, d, J = 8.8), 7.21–7.30 (3H, m), 7.87 (1H, m), 7.89 ppm (1H, d, J = 16.1); ^{13}C NMR: δ = 28.2 (CH_3), 46.8 (CH_2), 55.2 (CH_3), 80.0 (C), 108.8 (C), 110.3 (CH), 114.2 (CH), 116.6 (CH), 119.9 (CH), 121.9 (CH), 123.1 (CH), 125.1 (C), 127.8 (CH), 127.9 (C), 129.9 (C), 134.6 (CH), 136.0 (C), 159.2 (C), 167.5 ppm (C); MS (EI): 399 $[M+2]$, 397 $[M]^+$; elemental analysis: calcd (%) for $C_{23}H_{24}ClNO_3$: C 69.43, H 6.08, N 3.52; found: C 69.68, H 6.10, N 3.57.

tert-Butyl (*E*)-3-[1-(4-methoxybenzyl)indol-3-yl]propenoate: The same procedure for *tert*-butyl 3-(2-chloro-1-(4-methoxybenzyl)indol-3-yl)propenoate with 1-(4-methoxybenzyl)indole-3-carbaldehyde (1.90 g, 7.10 mmol) and column chromatography (AcOEt/hexane = 1:10) gave the compound (2.25 g, 87%) as pale yellow needles. M.p. 89.5–90.5 °C; IR (KBr): $\tilde{\nu}$ = 1697, 1620, 1389, 1142 cm^{-1}; ^{1}H NMR: δ = 1.54 (9H, s), 3.78 (3H, s), 5.24 (2H, s), 6.35 (1H, d, J = 16.2), 6.85 and 7.09 (each 2H, d, J = 8.9), 7.21–7.34 (3H, m), 7.35 (1H, s), 7.79 (1H, d, J = 16.2), 7.92 ppm

(1H, m); ^{13}C NMR: δ=28.3 (CH_3), 49.8 (CH_2), 55.3 (CH_3), 79.7 (C), 110.4 (CH), 112.6 (C), 114.3 (CH), 115.0 (CH), 120.7 (CH), 121.2 (CH), 122.9 (CH), 126.4 (C), 128.2 (C), 128.5 (CH), 131.8 (CH), 136.9 (CH), 137.6 (C), 159.4 (C), 167.7 ppm (C); MS (EI): 363 [M]$^+$, 306 [M−tBu]; elemental analysis: calcd (%) for $C_{23}H_{25}NO_3$: C 76.36, H 7.21, N 3.71, found: C 76.14, H 7.31, N 3.68.

4a: Under Ar atmosphere, a 1.6 M hexane solution of nBuLi (1.8 mL, 3.0 mmol) was added to a solution of an *N*-benzyl-*N*-trimethylsilylamine (0.59 mL, 3.0 mmol) in THF (8 mL) at −78 °C over 5 min. After stirring for 0.5 h, *tert*-butyl (*E*)-3-(2-chloro-1-(4-methoxybenzyl)indol-3-yl)propenoate (398 mg, 1.0 mmol) in THF (2 mL) was added and the mixture was stirred for at −78 °C for 1.0 h and at −40 °C for 2.5 h. The reaction was quenched with saturated NH_4Cl (3.0 mL). After addition of saturated $NaHCO_3$ (10 mL), the mixture was extracted with AcOEt. The organic layer was washed with brine and dried over sodium sulfate. Concentration and silica gel column chromatography (AcOEt/hexane=1:10) gave **4a** (407 mg, 80%) as a yellow oil. IR (KBr): $\tilde{\nu}$=3333, 2978, 1720, 1458, 1250, 1150, 741 cm^{-1}; ^{1}H NMR: δ=1.34 (9H, s), 1.77 (1H, brs), 2.73 (1H, dd, J=5.6, 15.4), 3.00 (1H, dd, J=8.8, 15.4), 3.60 and 3.66 (each 1H, d, J=13.2), 3.75 (3H, s), 4.56 (1H, dd, J=5.6, 8.8), 5.32 (2H, s), 6.81 and 7.04 (each 2H, d, J=8.8), 7.10–7.28 (8H, m), 7.86 ppm (1H, m); ^{13}C NMR: δ=27.9 (CH_3), 42.2 (CH_2), 46.3 (CH_2), 51.6 (overlapped, CH and CH_2), 55.2 (CH_3), 80.5 (C), 109.7 (CH), 111.5 (C), 114.1 (CH), 119.7 (CH), 120.0 (CH), 122.1 (CH), 123.9 (C), 125.7 (C), 126.7 (CH), 127.8 (CH), 128.2 (CH), 128.3 (CH), 129.1 (C), 135.7 (C), 140.6 (C), 159.0 (C), 171.3 ppm (C); MS (EI): 506 [M+2], 504 [M]$^+$; elemental analysis: calcd (%) for $C_{30}H_{33}ClN_2O_3$: C 71.34, H 6.59, N 5.55; found: C 71.52, H 6.58, N 5.49.

4b: The same precedure for **4a** with *tert*-butyl (*E*)-3-(1-(4-methoxybenzyl)-indol-3-yl)propenoate (363 mg, 1.0 mmol) and silica gel column chromatography (AcOEt/hexane=1:3) gave **4b** (360 mg, 77%) as a yellow oil. IR (KBr): $\tilde{\nu}$=3333, 2978, 1720, 1157, 741 cm^{-1}; ^{1}H NMR: δ=1.34 (9H, s), 1.84 (1H, brs), 2.73 (1H, dd, J=5.5, 15.3), 2.85 (1H, dd, J=8.6, 15.3), 3.66 and 3.76 (each 1H, d, J=13.1), 3.77 (3H, s), 4.45 (1H, dd, J=5.5, 8.6), 5.21 (2H, s), 6.82 (2H, d, J=8.9), 7.05–7.30 (11H, m), 7.76 ppm (1H, m); ^{13}C NMR: δ=28.0 (CH_3), 43.2 (CH_2), 49.4 (CH_2), 51.5 (CH_2), 51.8 (CH), 55.2 (CH_3), 80.4 (C), 109.8 (CH), 114.1 (CH), 116.5 (C), 119.1 (CH), 119.9 (CH), 121.8 (CH), 126.1 (CH), 126.7 (overlapped, CH×2), 127.1 (C), 128.3 (overlapped, CH×2), 129.5 (C), 136.9 (C), 140.8 (C), 159.1 (C), 171.7 ppm (C); MS (EI): 470 [M]$^+$, 413 [M−tBu]; elemental analysis: calcd (%) for $C_{30}H_{34}N_2O_3$: C 76.57, H 7.28, N 5.95; found: C 76.79, H 7.36, N 5.89.

4e: The same procedure for **4a** with ethyl sorbate (1.40 g, 10 mmol) and silica column chromatography (acetone/hexane=1:6) gave **4e** (1.04 g, 42%) as a colorless oil. IR (KBr): $\tilde{\nu}$=3333, 2978, 1736, 1173, 732 cm^{-1}; ^{1}H NMR: δ=1.23 (3H, t, J=7.1), 1.705 (3H, dd, J=1.5, 6.4), 1.710 (1H, brs), 2.45 (1H, dd, J=5.8, 15.3), 2.50 (1H, dd, J=7.7, 15.3), 3.46 (1H, ddd, 5.8, 7.7, 8.6), 3.65 and 3.81 (each 1H, d, J=13.1), 4.11 (2H, q, J=7.1), 5.33 (1H, ddq, J=8.6, 15.3, 1.5), 5.61 (1H, dq, J=15.3, 6.4), 7.21–7.33 ppm (5H, m); ^{13}C NMR: δ=14.1 (CH_3), 17.6 (CH_3), 41.1 (CH_2), 51.0 (CH_2), 56.8 (CH), 60.3 (CH_2), 126.8 (CH), 127.9 (CH), 128.2 (CH), 128.4 (CH), 132.3 (CH), 140.5 (C), 172.0 ppm (C); MS (EI): 247 [M]$^+$, 160 [M−CH_2CO_2Et]; elemental analysis: calcd (%) for $C_{15}H_{21}NO_2$: C 72.84, H 8.56, N 5.66; found: C 73.10, H 8.77, N 5.62.

4g: Under Ar atmosphere, a 1.6 M hexane solution of nBuLi (18.8 mL, 30 mmol) was added to a solution of an *N*-allyl-*N*-*tert*-butyldimethylsilylamine (5.14 mg, 30 mmol) in THF (90 mL) at −78 °C over 5 min. After stirring for 0.5 h, ethyl sorbate (1.40 g, 10 mmol) in THF (10 mL) was added and the mixture was stirred for 3 h at −78 °C. The reaction was quenched with saturated NH_4Cl (30 mL). After addition of 40% HF aq. (10 mL), the mixture was stirred for 5 min at room temperature. After acidification with 10% HCl aq. (10 mL) to pH 2, the whole was washed with AcOEt. The aquous layer was treated with sodium bicarbonate to pH 9 and then extracted with AcOEt. The organic layer was washed with brine and dried over sodium sulfate. Concentration and distillation (ca. 150 °C/5 mmHg) gave **4g** (945 mg, 48%) as a colorless oil. IR (KBr): $\tilde{\nu}$=3333, 2978, 1735, 1180 cm^{-1}; ^{1}H NMR: δ=1.25 (3H, t, J=7.0), 1.62 (1H, brs), 1.68 (3H, dd, J=1.6, 6.4), 2.43 (1H, dd, J=6.1, 15.3), 2.49 (1H, dd, J=7.3, 15.3), 3.12 (1H, dddd, J=1.2, 1.2, 6.4, 14.1), 3.26 (1H, dddd, J=1.5, 1.5, 5.5, 14.1), 3.46 (1H, dddd, J=0.6, 6.1, 7.3, 8.3), 4.13 (2H, q, J=7.0), 5.08 (1H, dddd, J=1.2, 1.5, 1.5, 10.4), 5.16 (1H, dddd, J=1.2, 1.5, 1.5, 17.1), 5.28 (1H, ddq, J=8.3, 15.3, 1.6), 5.60 (1H, ddq, J=0.6, 15.3, 6.4), 5.88 ppm (1H, dddd, J=5.5, 6.4, 10.4, 17.1); ^{13}C NMR: δ=14.2 (CH_3), 17.6 (CH_3), 41.0 (CH_2), 49.6 (CH_2), 56.8 (CH), 60.3 (CH_2), 115.8 (CH_2), 127.8 (CH), 132.2 (CH), 136.9 (CH), 172.0 ppm (C); MS (EI): 167 [M−Et−1], 156 [M−CH_2-CH=CH_2], 110 [M−CH_2CO_2Et]; elemental analysis: calcd (%) for $C_{11}H_{19}NO_2$: C 66.97, H 9.71, N 7.10; found: C 66.88, H 9.96, N 7.16.

(+)-**4a**: Under Ar atmosphere, a 1.6 M hexane solution of nBuLi (0.94 mL, 1.5 mmol) was added to a solution of *N*-benzyl-*N*-trimethylsilylamine (0.30 mL, 1.5 mmol) in toluene (4 mL) at −78 °C over 5 min. After stirring for 0.5 h, (1*R*,2*R*)-1,2-dimethoxy-1,2-diphenylethane (−)-**3** (436 mg, 1.8 mmol) in toluene (2 mL) was added and the mixture was stirred for 0.5 h at −78 °C. A toluene solution of *tert*-butyl 3-(2-chloro-1-(4-methoxybenzyl)indol-3-yl)propenoate (398 mg, 1.0 mmol) and TMSCl (0.63 mL, 5.0 mmol) was added over 5 min and the mixture was stirred at −78 °C for 1 h and at −40 °C for 14 h. The reaction was quenched with saturated NH_4Cl (2.0 mL). After addition of saturated $NaHCO_3$ (20 mL), the mixture was extracted with AcOEt. The organic layer was washed with brine and dried over sodium sulfate. Concentration and silica gel column chromatography (AcOEt/hexane=1:10–1:4) gave (+)-**4a** (167 mg, 33%) as a pale yellow oil of $[\alpha]_D^{25}$=+8.8 (c=1.34, $CHCl_3$) with 97% *ee* (Daicel Chiralpak AD-Hx2, hexane/2-PrOH=25:1, 1.0 mL min^{-1}, 254 nm, major 25.2 min and minor 30.6 min). All spectroscopic data were identical to those of (±)-**4a**.

(−)-**17**: Under Ar atmosphere, a 1.6 M hexane solution of nBuLi (7.20 mL, 12 mmol) was added to a solution of *N*-benzyl-*N*-trimethylsilylamine (2.36 mL, 12 mmol) in toluene (32 mL) at −78 °C over 5 min. After stirring for 0.5 h, (1*R*,2*R*)-1,2-dimethoxy-1,2-diphenylethane (−)-**3** (3.48 g, 15 mmol) in toluene (24 mL) was added and the mixture was stirred for 0.5 h at −78 °C. A toluene (8 mL) solution of *tert*-butyl sorbate (672 mg, 4.0 mmol) was added over 5 min and the mixture was stirred at −78 °C for 3.0 h. After successive addition of THF (48 mL) and HMPA (4.16 mL, 40 mmol), the mixture was stirred for 15 min at −78 °C. To the mixture was added methyl iodide (0.93 mL, 15 mmol) and the whole was stirred at −78 °C for 1.5 h. The reaction was quenched with saturated NH_4Cl (12 mL). After addition of saturated $NaHCO_3$ (40 mL), the mixture was extracted with AcOEt. The organic layer was washed with brine and dried over sodium sulfate. Concentration and silica gel column chromatography (AcOEt/hexane=1:10–1:4) gave a 93:7 mixture of *anti*- and *syn*-(−)-**17** (856 mg, 74%) as a colorless oil of $[\alpha]_D^{25}$=−1.2 (c=1.17, $CHCl_3$). The *ee* value of major *anti*-**17** was determined to be 90% *ee* after conversion into the corresonding β-lactam (see below). IR (KBr): $\tilde{\nu}$=3355, 2978, 1728, 1157 cm^{-1}; ^{1}H NMR: δ=1.05 (2.79H, d, J=7.0), 1.12 (0.21H, d, J=7.0), 1.41 (0.63H, s), 1.43 (8.37H, s), 1.55 (1H, brs), 1.72 (0.21H, dd, J=1.5, 6.4), 1.73 (2.79H, dd, J=1.5, 6.4), 2.35 (0.93H, dq, J=8.2, 7.0), 2.48 (0.07H, dq, J=6.1, 7.0), 3.11 (0.07H, dd, J=6.1, 8.9), 3.14 (0.93H, dd, J=8.2, 8.9), 3.608 and 3.80 (each 0.93H, d, J=13.1), 3.612 and 3.82 (each 0.07H, d, J=13.2), 5.17 (0.93H, ddq, J=8.9, 15.3, 1.5), 5.34 (0.07H, ddq, J=8.9, 15.6, 1.5), 5.559 (0.93H, dq, J=15.3, 6.4), 5.560 (0.07H, dq, J=15.6, 6.4), 7.21–7.30 ppm (5H, m); ^{13}C NMR for major *anti*-**17**: δ=14.1 (CH_3), 17.8 (CH_3), 28.0 (CH_3), 45.8 (CH), 51.0 (CH_2), 62.9 (CH), 80.1 (C), 126.7 (CH), 128.20 (CH), 128.24 (CH), 129.0 (CH), 131.1 (CH), 140.7 (C), 175.0 ppm (C); MS (FAB) m/z: 290 [M+H]; HRMS (FAB) m/z: calcd for $C_{18}H_{28}NO_2$: 290.2120; found: 290.2103.

(−)-*trans*-1-benzyl-3-methyl-4-((*E*)-prop-1-enyl)azetidin-2-one: Under Ar atmosphere, a 3.0 M Et_2O solution of EtMgBr (1.0 mL, 3.0 mmol) was added to a solution of (−)-**14a** (289 mg, 1.0 mmol) in THF (20 mL) at 0 °C. After stirring for 15 min at 0 °C, the mixture was quenched with saturated NH_4Cl (5 mL). The whole was extracted with AcOEt and the organic layer was washed with brine and dried over sodium sulfate. Concentration and column chromatography (hexane/AcOEt=4:1) gave the compound (147 mg, 68%) as a colorless oil of $[\alpha]_D^{25}$=−81.0 (c=1.27, $CHCl_3$) with 90% *ee* (Daicel Chiralcel OD-Hx2, hexane/2-PrOH=100:1, 1.0 mL min^{-1}, 254 nm, major 35.5 min and minor 34.3 min). IR (KBr): $\tilde{\nu}$=2923, 1751, 1118; ^{1}H NMR: δ=1.26 (3H, d, J=7.3), 1.69 (3H, dd, J=1.5,

6.7), 2.87 (1H, dq, $J=1.9$, 7.3), 3.44 (1H, dd, $J=1.9$, 8.9), 3.94 and 4.63 (each 1H, d, $J=15.1$), 5.35 (1H, ddq, $J=8.9$, 15.3, 1.5), 5.65 (1H, dq, $J=15.3$, 6.7), 7.21–7.34 ppm (5H, m); ^{13}C NMR: $\delta=12.5$ (CH_3), 17.7 (CH_3), 44.1 (CH_2), 51.2 (CH), 61.2 (CH), 127.5 (CH), 128.4 (CH), 128.7 (CH), 128.8 (CH), 131.1 (CH), 136.3 (C), 170.6 ppm (C); MS (FAB): *m/z* 216 [*M*+H]; HRMS (FAB): *m/z* calcd for $C_{14}H_{18}NO$: 216.1388; found: 216.1409.

Procedure for rearrangement of (+)-**4a** with *t*BuLi to five-membered lactam **5a** and seven-membered lactams (+)-**6a**, (+)-**7**, and (−)-**8**: Under Ar atmosphere, a 1.57 M pentane solution of *t*BuLi (0.79 mL, 1.2 mmol) was added to a solution of (+)-**4a** (100 mg, 0.20 mmol) with 97% *ee* in THF (5 mL) at −78 °C over 5 min. After stirring for 30 min at −78 °C, the mixture was quenched with saturated NH_4Cl (2 mL). After addition of saturated $NaHCO_3$, the whole was extracted with AcOEt. The organic layer was washed with brine and dried over sodium sulfate. Concentration and silica gel column chromatography (hexane/AcOEt=2:1) gave (+)-**6a** (32 mg, 40%) of $[\alpha]_D^{25}=+82.8$ ($c=1.06$, $CHCl_3$) as a yellow amorphous, (+)-**7** (13 mg, 15%) of $[\alpha]_D^{25}=+12.1$ ($c=0.95$, $CHCl_3$) as a yellow amorphous, and a mixture of (−)-**8** and **5a**. Column chromatography (Et_2O/hexane=2:1) of the mixture of (−)-**8** and **5a** gave (−)-**8** (9 mg, 12%) of $[\alpha]_D^{25}=-8.4$ ($c=0.52$, $CHCl_3$) as a yellow amorphous and **5a** (17 mg, 20%) as pale yellow needles of m.p. 189.0–190.0 °C; **5a**: 2% *ee* determined by HPLC (Daicel Chiralcel OD-H, hexane/2-PrOH=1:1, 1.0 mL min^{-1}, 254 nm, major 15.0 min and minor 11.3 min); IR (KBr): $\tilde{\nu}=$ 3209, 2923, 1697, 1458, 1250, 741 cm^{-1}; ^{1}H NMR: $\delta=2.84$ (1H, dd, $J=$ 9.5, 17.4), 3.09 (1H, dd, $J=10.1$, 17.4), 3.76 (3H, s), 3.77 (1H, ddd, $J=$ 8.0, 9.5, 10.1), 5.03 (1H, d, $J=8.0$), 5.26 and 5.30 (each 1H, d, $J=16.5$), 6.07 (1H, brs), 6.81 and 6.99 (each 2H, d, $J=8.6$), 7.13–7.30 (8H, m), 7.59 ppm (1H, m); ^{13}C NMR: $\delta=36.2$ (CH_2), 42.8 (CH), 46.5 (CH_2), 55.2 (CH_3), 63.2 (CH), 109.2 (C), 110.3 (CH), 114.2 (CH), 118.6 (CH), 120.4 (CH), 122.4 (CH), 124.4 (C), 125.2 (C), 125.6 (CH), 127.8 (CH), 128.1 (CH), 128.77 (CH), 128.80 (C), 135.8 (C), 141.1 (C), 159.1 (C), 177.1 ppm (C); MS (EI): 432 [*M*+2], 430 [*M*]$^+$; HRMS (EI) *m/z* calcd for $C_{26}H_{23}ClN_2O_2$: 430.1448; found: 430.1443; (+)-**6a**: 17% *ee* determined by HPLC (Daicel Chiralcel OD-H, hexane/2-PrOH=1:1, 1.0 mL min^{-1}, 254 nm, major 42.3 min and minor 8.4 min); IR (KBr): $\tilde{\nu}=3202$, 2931, 1643, 1458, 1250, 1180, 733 cm^{-1}; ^{1}H NMR: $\delta=3.69$ (3H, s), 5.22 and 5.39 (each 1H, d, $J=16.8$), 5.68 (1H, d, $J=7.7$), 5.90 ppm (1H, d, $J=11.9$), 6.71 and 6.94 (each 2H, d, $J=7.1$), 7.00–7.40 (9H, m), 7.75 (1H, d, $J=$ 7.7), 7.90 ppm (1H, brs); ^{13}C NMR: $\delta=46.6$ (CH_2), 51.0 (CH), 55.2 (CH_3), 110.5 (CH), 112.1 (C), 114.4 (CH), 118.5 (CH), 120.2 (CH), 121.5 (CH), 123.2 (CH), 126.4 (C), 126.5 (CH), 127.3 (CH), 127.8 (CH), 127.9 (C), 128.3 (CH), 130.8 (CH), 136.6 (C), 138.3 (C), 139.9 (C), 159.3 (C), 171.2 ppm (C); MS (EI): 394 [*M*]$^+$, 273 [*M*−*p*-MeOC$_6$H$_4$CH$_2$]; HRMS (EI): *m/z* calcd for $C_{26}H_{22}N_2O_2$: 394.1681; found: 394.1673; (+)-**7**: 17% *ee* determined by HPLC (Daicel Chiralcel OD-H, hexane/2-PrOH=85:15, 1.0 mL min^{-1}, 254 nm, major 28.2 min and minor 10.3 min); IR (KBr): $\tilde{\nu}=$ 3217, 2955, 1666, 1458, 1250, 733 cm^{-1}; ^{1}H NMR: $\delta=0.97$ (9H, s), 2.68 (1H, dd, $J=5.0$, 13.4), 2.90 (1H, dd, $J=9.1$, 13.4), 3.34 (1H, dd, $J=5.0$, 9.1), 3.75 (3H, s), 4.77 and 5.33 (each 1H, d, $J=17.4$), 5.55 (1H, d, $J=$ 4.3), 5.78 (1H, d, $J=4.3$), 6.62 and 6.75 (each 2H, d, $J=8.6$), 7.12–7.38 (8H, m), 7.71 ppm (1H, m); ^{13}C NMR: $\delta=29.5$ (CH_3), 36.7 (C), 38.5 (CH_2), 42.4 (CH), 46.2 (CH_2), 54.2 (CH), 55.2 (CH_3), 109.2 (CH), 114.4 (CH), 116.0 (C), 119.4 (CH), 121.4 (CH), 122.3 (CH), 126.7 (CH), 127.2 (CH), 128.3 (CH), 128.98 (C), 129.01 (C), 129.2 (CH), 135.3 (C), 136.9 (C), 140.3 (C), 159.0 (C), 176.3 ppm (C); MS (EI): 452 [*M*]$^+$, 395 [*M*−*t*Bu]; HRMS (EI) *m/z* calcd for $C_{30}H_{32}N_2O_2$: 452.2464; found: 452.2469; (−)-**8**: 18% *ee* determined by HPLC (Daicel Chiralcel OD-H, hexane/2-PrOH=1:1, 1.0 mL min^{-1}, 254 nm, major 16.3 min and minor 6.4 min); IR (KBr): $\tilde{\nu}=3225$, 2924, 1666, 1458, 1249, 732 cm^{-1}; ^{1}H NMR: $\delta=2.51$ (1H, m), 2.67 (1H, m), 3.13–3.16 (2H, m), 3.75 (3H, s), 4.82 and 5.36 (each 1H, d, $J=17.4$), 5.42 (1H, d, $J=8.2$), 6.76 and 6.80 (each 2H, d, $J=9.2$), 6.89 (1H, brs), 7.10–7.61 ppm (9H, m); ^{13}C NMR: $\delta=20.4$ (CH_2), 34.3 (CH_2), 45.8 (CH_2), 51.6 (CH_3), 55.2 (CH), 109.4 (CH), 112.6 (C), 114.4 (CH), 118.7 (CH), 119.8 (CH), 122.6 (CH), 126.8 (CH), 127.1 (CH), 127.6 (C), 128.0 (CH), 128.8 (CH), 129.3 (C), 133.0 (C), 136.2 (C), 141.0 (C), 159.1 (C), 177.1 ppm (C); MS (EI): 396 [*M*]$^+$; HRMS (EI): *m/z* calcd for $C_{26}H_{24}N_2O_2$: 396.1838; found: 396.1845.

Five-membered lactam **5b** and seven-membered lactam **6b**: The same procedure as (+)-**4a** with **4b** (110 mg, 0.234 mmol) and silica gel column chromatography (hexane/acetone=3:2) gave **5b** (27 mg, 29%) as a yellow amorphous and **6b** (43 mg, 46%) as a yellow amorphous; **5b**: IR (KBr): $\tilde{\nu}=3209$, 1690, 1250, 733 cm^{-1}; ^{1}H NMR: $\delta=2.84$ (1H, dd, $J=9.3$, 16.8), 2.92 (1H, dd, $J=8.9$, 16.8), 3.66 (1H, ddd, $J=7.1$, 8.9, 9.3), 3.78 (3H, s), 4.86 (1H, d, $J=7.1$), 5.19 (2H, s), 5.99 (1H, brs), 6.82–7.37 ppm (14H, m); ^{13}C NMR: $\delta=37.6$ (CH_2), 43.3 (CH), 49.4 (CH_2), 55.2 (CH_3), 64.7 (CH), 110.1 (CH), 114.2 (CH), 114.3 (C), 119.33 (CH), 119.34 (CH), 122.1 (CH), 125.4 (CH), 126.1 (CH), 126.8 (C), 128.1 (CH), 128.2 (CH), 128.8 (CH), 129.2 (C), 137.1 (C), 141.4 (C), 159.2 (C), 177.2 ppm (C); MS (EI): 396 [*M*]$^+$; HRMS (EI) *m/z* calcd for $C_{26}H_{24}N_2O_2$: 396.1838; found: 396.1837; **6b**: IR(KBr): $\tilde{\nu}=3200$, 3017, 1651, 1219, 772 cm^{-1}; ^{1}H NMR: $\delta=3.11$ (1H, m), 3.28 (1H, m), 3.76 (3H, s), 4.42 and 4.55 (each 1H, d, $J=15.6$), 4.65 (1H, m), 4.80 (1H, m), 5.64 (1H, m), 6.62–6.83 (5H, m), 7.07–7.38 ppm (9H, m); ^{13}C NMR: $\delta=38.5$ (CH_2), 51.3 (CH_2), 54.7 (CH), 55.2 (CH_3), 69.0 (CH), 107.9 (CH), 108.9 (CH), 114.2 (CH), 118.7 (CH), 120.1 (CH), 127.2 (C), 127.35 (CH), 127.4 (CH), 127.9 (CH), 129.1 (CH), 129.2 (C), 129.7 (CH), 137.9 (C), 138.9 (C), 152.6 (C), 159.1 (C), 174.0 ppm (C); MS (EI): 396 [*M*]$^+$; HRMS (EI): *m/z* calcd for $C_{26}H_{24}N_2O_2$: 396.1838; found: 396.1843.

Five-membered lactam (4*R*,5*S*)-**5c**: The same procedure as (+)-**4a** with (*R*)-**4c** (156 mg, 0.50 mmol, 76% *ee*) and silica gel column chromatography (hexane/AcOEt=1:1) gave **5c** (62 mg, 52%) of m.p. 103–194 °C (literature: 215–218 °C for racemic **5c**, 104–106 °C for (4*S*,5*R*)-**5c**) and $[\alpha]_D^{25}=+65.5$ ($c=0.86$, MeOH) with 43% *ee* determined by comparison of the specific rotation with that reported ($[\alpha]_D^{25}=-150.1$ ($c=1.1$, MeOH, 4*S*,5*R*)); IR (KBr): $\tilde{\nu}=3186$, 2885, 1697, 1342, 763, 702 cm^{-1}; ^{1}H NMR: $\delta=2.72$ (1H, dd, $J=9.5$, 17.1), 2.89 (1H, dd, $J=8.9$, 17.1), 3.42 (1H, ddd, $J=7.4$, 8.9, 9.5), 4.69 (1H, d, $J=7.4$), 7.80 (1H, brs), 7.15–7.35 ppm (10H, m); ^{13}C NMR: $\delta=38.5$ (CH_2), 51.2 (CH), 66.0 (CH), 125.9 (CH), 127.4 (overlapped, CH×2), 128.2 (CH), 128.9 (overlapped, CH×2), 140.5 (C), 140.7 (C), 176.8 ppm (C); MS (EI): 237 [*M*]$^+$. The melting point, the specific rotation, and all the spectroscopic data were reported in Ref. [10c].

Five-membered lactam **5d** and seven-membered lactam **6d**: The same procedure as (+)-**4a** with **4e** (247 mg, 1.0 mmol) and silica gel column chromatography (hexane/AcOEt=1:1) gave **5d** (23 mg, 12%) as a colorless oil and **6d** (115 mg, 57%) as colorless plates of m.p. 183.0–184.0 °C; **5d**: IR (KBr): $\tilde{\nu}=3217$, 2916, 1697, 748; MS (EI): 201 [*M*]$^+$; ^{1}H NMR: $\delta=1.65$ (3H, d, $J=6.1$), 2.33 (1H, dd, $J=9.8$, 16.8), 2.58 (1H, dd, $J=8.6$, 16.8), 2.81 (1H, dddd, $J=7.6$, 7.9, 8.6, 9.8), 4.36 (1H, d, $J=7.6$), 5.36 (1H, dq, $J=15.3$, 6.1), 5.47 (1H, dd, $J=7.9$, 15.3), 6.18 (1H, brs), 7.26–7.37 ppm (5H, m); ^{13}C NMR: $\delta=17.7$ (CH_3), 37.2 (CH_2), 48.9 (CH), 64.1 (CH), 126.2 (CH), 128.0 (CH), 128.1 (CH), 128.8 (CH), 129.6 (CH), 140.6 (C), 177.1 ppm (C); HRMS (EI): *m/z* calcd for $C_{13}H_{15}NO$: 201.1154; found: 201.1158. The *ee* value of **5d**, synthesized from (+)-**4d** with 98% *ee*, was determined to be 0% *ee* by HPLC (Daicel Chiralpak AD-H, hexane/2-PrOH=1:1, 1.0 mL min^{-1}, 254 nm, 6.7 min and 8.1 min); **6d**: IR (KBr): $\tilde{\nu}=3224$, 1674, 1450, 1412, 756 cm^{-1}; ^{1}H NMR: $\delta=0.94$ (3H, d, $J=7.0$), 2.59 (1H, m), 2.93 (1H, m), 3.63 (1H, m), 5.22 (1H, d, $J=7.1$), 5.61 (1H, m), 5.69 (1H, m), 6.03 (1H, brs), 7.26–7.41 ppm (5H, m); ^{13}C NMR: $\delta=12.6$ (CH_3), 35.2 (CH_2), 39.2 (CH), 57.4 (CH), 118.9 (CH), 126.2 (CH), 127.6 (CH), 128.7 (CH), 135.6 (CH), 138.6 (C), 174.7 ppm (C); MS (EI): 201 [*M*]$^+$; elemental analysis: calcd (%) for $C_{13}H_{15}NO$: C 77.58, H 7.51, N 6.96; found: C 77.70, H 7.51, N 6.91. The *ee* value of **6d**, synthesized from (+)-**4d** with 98% *ee*, was determined to be 17% *ee* by HPLC (Daicel Chiralcel OD-H, hexane/2-PrOH=10:1, 1.0 mL min^{-1}, 254 nm, major 94.7 min and minor 13.9 min). Slow cooling of a hot solution of **6d** in $CHCl_3$ provided plates suitable for X-ray diffraction (Figure 1), and the stereochemistry of **5d** was determined by an NOE experiment (Figure 2).

Five-membered lactams *trans*-**5e** and *cis*-**5e** and seven-membered lactam **6e**: The same procedure as (+)-**4a** with **4g** (197 mg, 1.0 mmol) and silica column chromatography (hexane/AcOEt=2:1–1:1) gave *trans*-**5e** (9 mg, 6%) as a colorless oil, *cis*-**5e** (4 mg, 3%) as a colorless oil, and **6e** (58 mg, 39%) as colorless needles of m.p. 93.0–94.0 °C; *trans*-**5e**: IR (KBr): $\tilde{\nu}=3225$, 2923, 1697, 972 cm^{-1}; ^{1}H NMR: $\delta=1.69$ (3H, d, $J=6.4$),

2.24 (1H, dd, J=9.8, 16.8), 2.49 (1H, dd, J=8.3, 16.8), 2.68 (1H, dddd, J=7.3, 7.7, 8.3, 9.8), 3.80 (1H, dd, J=7.3, 7.3), 5.17 (1H, d, J=10.4), 5.22 (1H, d, J=17.1), 5.41 (1H, dd, J=7.7, 15.3), 5.54 (1H, dq, J=15.3, 6.4), 5.75 (1H, ddd, J=7.3, 10.4, 17.1), 5.77 ppm (1H, brs); ^{13}C NMR: δ=17.8 (CH_3), 36.8 (CH_2), 45.7 (CH), 62.6 (CH), 117.0 (CH_2), 127.8 (CH), 129.7 (CH), 137.0 (CH), 176.9 ppm (C); MS (EI): 151 $[M]^+$; HRMS (EI): m/z calcd for $C_9H_{13}NO$: 151.0997; found: 151.0998; *cis*-**5e**: IR (KBr): $\tilde{\nu}$= 3225, 2916, 1697, 972 cm^{-1}; ^{1}H NMR: δ=1.68 (3H, d, J=6.1), 2.23 (1H, dd, J=9.5, 16.8), 2.37 (1H, dd, J=8.3, 16.8), 3.20 (1H, dddd, J=7.3, 8.3, 8.5, 9.5), 4.15 (1H, dd, J=6.5, 7.3), 5.198 (1H, d, J=11.3), 5.202 (1H, d, J=15.6), 5.35 (1H, dd, J=8.5, 15.3), 5.54 (1H, dq, J=15.3, 6.1), 5.78 (1H, ddd, J=6.5, 11.3, 15.6), 5.80 ppm (1H, brs); ^{13}C NMR: δ=17.8 (CH_3), 35.2 (CH_2), 42.6 (CH), 59.7 (CH), 116.6 (CH_2), 127.9 (CH), 128.8 (CH), 135.8 (CH), 177.4 ppm (C); MS (EI): 151 $[M]^+$; HRMS (EI): m/z calcd for $C_9H_{13}NO$: 151.0997; found: 151.0995; **6e**: IR (KBr): $\tilde{\nu}$=3209, 1674, 1420, 740; ^{1}H NMR: δ=0.96 (3H, d, J=7.1), 2.39 (1H, m), 2.85 (1H, m), 3.50 (1H, m), 4.57 (1H, m), 5.26–5.30 (2H, m), 5.51–5.63 (3H, m), 5.84 ppm (1H, m); ^{13}C NMR: δ=13.0 (CH_3), 35.5 (CH_2), 38.3 (CH), 55.2 (CH), 116.3 (CH_2), 118.8 (CH), 135.4 (CH), 135.9 (CH), 174.6 ppm (C); MS (EI): 151 $[M]^+$; elemental analysis: calcd (%) for $C_9H_{13}NO$: C 71.49, H 8.67, N 9.26; found: C 71.21, H 8.49, N 8.98. The *ee* value of **6e**, synthesized from (+)-**4f** with 55% *ee*, was determined to be 3% *ee* by GC (SUPELCO GAMMA DEX^{TM} 225 with constant 180°C oven temperature, major 4.86 min and minor 5.64 min). The stereochemistry of **6e**, *trans*-**5e** and *cis*-**5e** was determined by an NOE experiment (Figure 2).

(−)-**18**: The same procedure as (+)-**4a** using (−)-**17** (289 mg, 1.0 mmol) with 90% *ee* and silica gel column chromatography (hexane/AcOEt= 4:1–1:1) gave the compound as a white solid of m.p. 70.0–82.0°C (racemic **18**: colorless needles of m.p. 118–119°C) and $[\alpha]_D^{25}=-74.1$ (c=1.22, $CHCl_3$) with 85% *ee* (Daicel Chiralcel OD-H, hexane/2-PrOH=4:1, 1.0 mL min^{-1}, 254 nm, major 17.1 min and minor 6.7 min); IR (KBr): $\tilde{\nu}$= 3233, 1674, 1450, 756 cm^{-1}; ^{1}H NMR: δ=0.88 (3H, d, J=7.0), 1.30 (3H, d, J=7.0), 2.62 (1H, dddq, J=2.2, 2.2, 4.9, 7.0), 3.71 (1H, ddq, J=2.2, 3.1, 7.0), 5.31 (1H, ddd, J=2.2, 2.2, 11.6), 5.33 (1H, dd, J=2.2, 5.8), 5.60 (1H, ddd, J=3.1, 4.9, 11.6), 6.00 (1H, d, J=5.8), 7.25–7.41 ppm (5H, m); ^{13}C NMR: δ=12.7 (CH_3), 16.4 (CH_3), 35.5 (CH), 38.9 (CH), 56.3 (CH), 126.2 (CH), 127.6 (CH), 127.7 (CH), 128.8 (CH), 134.8 (CH), 138.6 (C), 176.3 ppm (C); MS (EI): 215 $[M]^+$; elemental analysis: calcd (%) for $C_{14}H_{17}NO$: C 78.10, H 7.96, N 6.51; found: C 78.21, H 8.01, N, 6.45. The relative configuration of **18** was determined by an NOE experiment (Figure 3).

9a: A mixture of racemic **4a** (100 mg, 0.198 mmol) and 8N HCl in dioxane (1 mL, 8 mmol) was stirred for 2 h at room temperature. After concentration, a mixture of the resulting yellow residue, PPh_3 (208 mg, 0.79 mmol), 2,2′-dipyridinyldisulfide (174 mg, 0.79 mmol), and Et_3N (0.14 mL, 1.9 mmol) in MeCN (20 mL) was stirred at 70°C for 14 h. After concentration, silica gel column chromatography (twice, hexane/AcOEt=5:2 and hexane/acetone=4:1) gave **9a** (69 mg, 81%) as a pale yellow oil. IR (KBr): $\tilde{\nu}$=1744, 1250, 733 cm^{-1}; ^{1}H NMR: δ=3.34 (1H, dd, J=2.6, 14.9), 3.39 (1H, dd, J=5.1, 14.9), 3.71 and 4.74 (each 1H, d, J=14.8), 3.77 (3H, s), 4.81 (1H, dd, J=2.6, 5.1), 5.27 and 5.33 (each 1H, d, J=16.6), 6.83 and 7.05 (each 2H, d, J=8.6), 7.10–7.58 ppm (9H, m); ^{13}C NMR: δ=43.9 (CH_2), 44.8 (CH_2), 46.4 (CH_2), 46.9 (CH), 55.1 (CH_3), 106.7 (C), 110.1 (CH), 114.1 (CH), 118.6 (CH), 120.9 (CH), 122.6 (CH), 124.8 (C), 125.5 (C), 127.5 (CH), 127.8 (CH), 128.50 (C), 128.52 (overlapped, CH×2), 135.4 (C), 135.7 (C), 159.1 (C), 167.1 ppm (C); MS (EI): 432 $[M+2]$, 430 $[M]^+$, 395 $[M-Cl]$; HRMS (EI) m/z calcd for $C_{26}H_{23}ClN_2O_2$: 430.1448; found: 430.1450.

Procedure for rearrangement of **9a** with *t*BuLi: A solution of **9a** (65 mg, 0.16 mmol) in THF (4 mL) was added to a 1.57N pentene solution of *t*BuLi (0.60 mL, 0.94 mmol) at −78°C under Ar. After stirring for 5 min at −78°C, the reaction mixture was quenched with saturated NH_4Cl aq. (2 mL). After addition of saturated $NaHCO_3$ aq. (5 mL), the whole was extracted with AcOEt and the organic layer was washed with brine and dried over sodium sulfate. Silica gel column chromatography (hexane/AcOEt=2:1) gave **6a** (26 mg, 42%), **7** (12 mg, 17%), and a mixture of **8** and **5a**. Further silica gel column chromatography (Et_2O/hexane=2:1) of the mixture gave **8** (8 mg, 12%) and **5a** (17 mg, 26%).

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