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Synthesis of optically active medium-sized α-aminolactams via ring-closing metathesis

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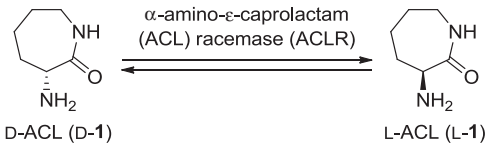
ABSTRACT

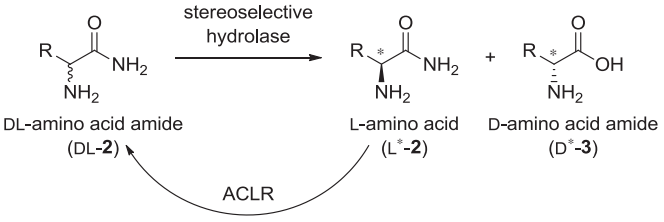
The synthesis of optically active medium-sized α-aminolactams via ring-closing metathesis is described. The amidation of optically active *N*-Boc-allylglycine derivatives with *N*-protected alkenylamine, and ring-closing metathesis resulted in the formation of medium-sized α-aminolactams with good yield.

1. Introduction

The soil bacterium *Achromobacter obae* produces an α-amino-ε-caprolactam (ACL, **1**) racemase (ACLR, EC 5.1.1.15) in the cytoplasm.[1,2] The enzyme was discovered in *A. obae* and used in combination with L-ACL hydrolase from *Cryptococcus laurentii* for industrial L-lysine production from DL-ACL.[3,4] ACLR from *A. obae* is a pyridoxal 5′-phosphate (PLP)-dependent enzyme that catalyzes the racemization of D- and L-ACL (Scheme 1).[1–5] ACLR had been reported to act exclusively on a noncarboxylic compound, an intramolecular cyclic amide with an α-amino group.[1] Recently, Asano et al. discovered amino acid amide racemizing activity in ACLR.[6] Consequently, stereoselective amino acid amidases, such as D-aminopeptidase (DAP),[7] have been used in combination with ACLR for optically active amino acid production with 100% theoretical yield (Scheme 2).[8,9]



Scheme 1. Reaction catalyzed by ACLR.



Scheme 2. Dynamic kinetic resolution of α-amino acid amides to form chiral amino acids.

In continuation of our recent work on ACLR, we have been interested in synthesizing optically active medium-sized (seven- to nine-membered) α-aminolactams. Furthermore, a medium-sized α-aminolactam like **1** is part of a number of biologically active compounds, such as capuramycin[10] and analogs with substituted ACL moiety exhibit significant mycobacterial growth inhibitory activities in vitro and in vivo.[11] Therefore, the development of a method to construct medium-sized α-aminolactams has become an important research topic in synthetic organic chemistry.

2. Results and discussion

In the recent years, the use of ring-closing metathesis for the synthesis of biologically important structures has developed extensively.[12–14] Piscopio et al. reported an efficient approach to the

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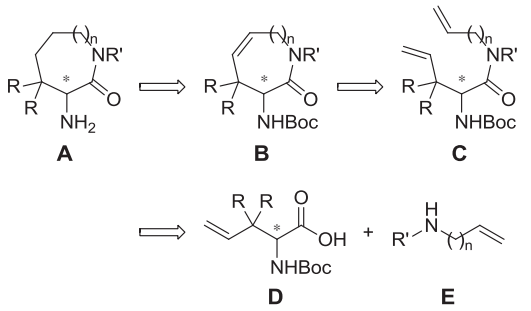
synthesis of seven-membered lactams, such as Freidinger lactams via ring-closing metathesis.[15–17] The seven-membered ring was generated using the peptide mimetic diene as a substrate, which was synthesized from a *N*-Boc-allylglycine derivative by a conventional procedure. Accordingly, a way of producing medium-sized α-aminolactams as shown in Scheme 3 was devised.



Scheme 3. Retrosynthetic analysis of medium-sized α-aminolactams.

The medium-sized α-aminolactams (**A**) were obtained by the cyclization of *N*′-alkenylated amides (**C**) via ring-closing metathesis to generate a new carbon–carbon bond and subsequent deprotection. **C** could be prepared from the known compounds **D** and **E**. Fig. 1 shows the target using the procedure mentioned above. Based on the ACL moiety, the introduction of a methyl group at the *N*′-position (**4**) or carbon–carbon double bond (**5**), the expansion of ring size (**6** and **7**), and the introduction of a dimethyl group into the ring structure (**8**) were investigated.

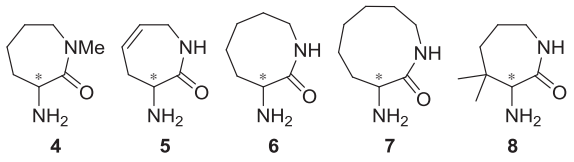
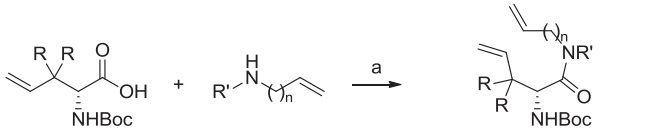


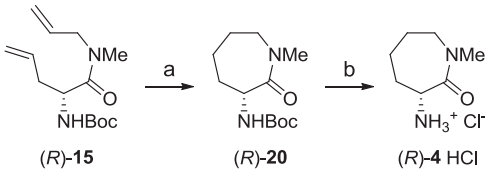
Fig. 1. Synthetic targets using our methodology.

Scheme 4 summarizes the synthesis of the precursors (*R*)-**15**–**19** for the cyclization by ring-closing metathesis. Amidation of the (*R*)-*N*-Boc-allylglycine derivative (*R*)-**9** or **10**[18–20] with the amines **11**–**14** yielded the (*R*)-*N*′-alkenyl-*N*-Boc-allylglycine derivatives (*R*)-**15**–**19** as a mixture of two rotamers, the precursors for cyclization.



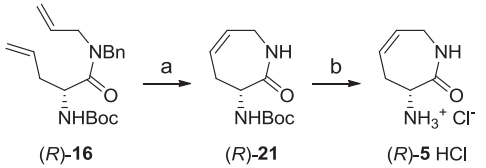
Scheme 4. Synthesis of the precursors of cyclization. Reagents and conditions: (a) EDC·HCl, HOBt·H_2O, *i*Pr_2NEt, CH_2Cl_2 [75% for (*R*)-**15**, 94% for (*R*)-**16**, 95% for (*R*)-**17**, 98% for (*R*)-**18**, 98% for (*R*)-**19**].

The conversion of (*R*)-**15** to (*R*)-**4** is shown in Scheme 5. Treatment of (*R*)-**15** with the first generation Grubbs catalyst in CH_2Cl_2 affected the cyclization, and the resulting double bond was hydrogenated to give (*R*)-**20**. Removal of the Boc group treated with HCl in MeOH yielded (*R*)-**4**.



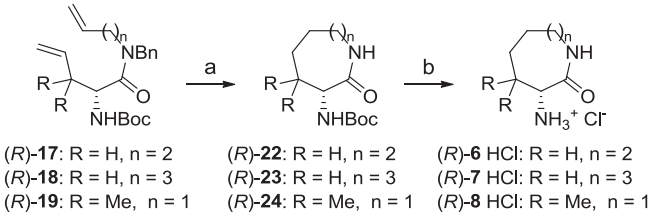
Scheme 5. Synthesis of (*R*)-**4**. Reagents and conditions: (a) (i) first generation Grubbs catalyst, CH_2Cl_2, reflux; (ii) H_2, Pd/C, EtOH (84% for 2 steps); (b) HCl in MeOH (82%).

The conversion of (*R*)-**16** to (*R*)-**5** is shown in Scheme 6. The cyclization of (*R*)-**16** was also done using the first generation Grubbs catalyst in CH_2Cl_2, and then the benzyl group was removed with the Birch reaction to give (*R*)-**21**. The Boc group was removed as described above, yielding (*R*)-**5**.



Scheme 6. Synthesis of (*R*)-**5**. Reagents and conditions: (a) (i) first generation Grubbs catalyst, CH_2Cl_2, reflux; (ii) Li, NH_3, *t*BuOH, −78 °C (32% for 2 steps); (b) HCl in MeOH (74%).

The conversion of (*R*)-**17**–**19** to (*R*)-**6**–**8** is shown in Scheme 7. The ring-closing metathesis of (*R*)-**17**–**19** using the first generation Grubbs catalyst in CH_2Cl_2 proceeded smoothly. Although the attempt to remove the benzyl group by using Pd/C with H_2 was unsuccessful, the reduction of the double bond was achieved. The resulting benzyl group was removed with the Birch reaction to give (*R*)-**22**–**24**. Finally, (*R*)-**22**–**24** was converted to (*R*)-**6**–**8** as described above.



Scheme 7. Synthesis of (*R*)-**6**–**8**. Reagents and conditions: (a) (i) first generation Grubbs catalyst, CH_2Cl_2, reflux; (ii) H_2, Pd/C, EtOH; (iii) Li, NH_3, *t*BuOH, −78 °C [52% for (*R*)-**22**, 49% for (*R*)-**23**, 49% for (*R*)-**24**]; (b) HCl in MeOH [78% for (*R*)-**6**, 72% for (*R*)-**7**, 81% for (*R*)-**8**].

Similarly, (*S*)-**5**–**8**, the enantiomers of the derivatives described above, were synthesized from the (*S*)-*N*–Boc-allylglycine derivative (*S*)-**9** or **10**, and amines **11**–**14**.

3. Conclusion

An efficient synthesis of both enantiomers of α-aminolactams **4**–**8** was accomplished by employing ring-closing metathesis as a key step. *N*-Boc-allylglycine derivatives have proven to be versatile starting materials for the synthesis of α-aminolactams.

4. Experimental

4.1. General

All melting points (mp) have been measured on a Yanaco MP-S3 micro melting point apparatus, and are uncorrected. Optical

rotation values were measured on a Horiba SEPA-300. IR spectra were recorded on a Perkin–Elmer spectrum 100 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Biospin Avance II 400 spectrometer (TMS and/or residual solvents as an internal standard). Mass spectra were recorded on a Bruker Daltonics micrOTOF. All chemicals were purchased from commercial sources and used without further purification.

4.2. General procedure for the synthesis of *N*′-alkenyl-*N*-Boc-allylglycine derivatives (15–19)

To an ice-cooled solution of *N*-Boc-allylglycine derivative (**9** or **10**) (20.0 mmol) and amine (**11**–**14**) (30.0 mmol) in dry CH_2Cl_2 (20.0 mL) were added EDC·HCl (30.0 mmol), HOBt·H_2O (20.0 mmol), and *i*Pr_2NEt (30.0 mmol). The reaction mixture was stirred for 36 h at room temperature and diluted with water. After extraction with EtOAc, the combined organic extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (50 g). Elution with hexane–EtOAc (10:1 to 4:1) afforded the *N*′-alkenyl-*N*-Boc-allylglycine derivative (**15**–**19**) as a mixture of two rotamers.

(*R*)-**15**: 75% from (*R*)-**9** and **11** as a colorless oil, $[\alpha]_D^{21}=-15.6$ (*c* 1.46, $CHCl_3$); IR (ATR) ν_{max} 3303, 2978, 1704, 1636, 1485, 1408, 1165, 915 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (3.78H, s), 1.43 (5.22H, s), 2.30–2.38 (1H, m), 2.43–2.52 (1H, m), 2.93 (1.26H, s), 3.03 (1.74H, s), 3.90–3.98 (1H, m), 4.02–4.10 (1H, m), 4.60–4.65 (0.42H, m), 4.66–4.72 (0.58H, m), 5.08–5.26 (4H, m), 5.34 (0.42H, d, *J*=8.5 Hz), 5.41 (0.58H, d, *J*=8.3 Hz), 5.67–5.85 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 33.6, 34.6, 37.5, 37.9, 49.7, 49.9, 50.3, 52.0, 79.4, 117.46, 117.48, 118.3, 118.5, 132.4, 132.7, 132.9, 155.1, 155.2, 171.3, 171.8; HRMS (ESI): *m*/*z* calculated for $C_{14}H_{24}N_2O_3Na^+$ [M+Na]$^+$: 291.1679, found: 291.1671.

(*S*)-**15**: 75% from (*S*)-**9** and **11** as a colorless oil, $[\alpha]_D^{20}=+15.5$ (*c* 1.48, $CHCl_3$). Its IR and NMR spectra were identical with those of (*R*)-**15**.

(*R*)-**16**: 94% from (*R*)-**9** and **12** as a colorless oil, $[\alpha]_D^{21}=+18.7$ (*c* 1.00, $CHCl_3$); IR (ATR) ν_{max} 3310, 2978, 1703, 1635, 1444, 1165, 917, 732, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (2.79H, s), 1.44 (6.21H, s), 2.29–2.45 (1.33H, m), 2.51 (0.67H, ddd, *J*=6.8, 7.3, 14.1 Hz), 3.87–4.11 (2H, m), 4.48 (0.67H, d, *J*=14.8 Hz), 4.61–4.75 (1.66H, m), 4.72 (0.67H, d, *J*=14.8 Hz), 5.04–5.26 (4H, m), 5.33–5.35 (1H, m), 5.64–5.82 (2H, m), 7.19–7.37 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.27, 28.29, 37.8, 37.9, 47.9, 48.2, 49.1, 49.9, 50.0, 50.1, 79.6, 117.7, 117.8, 118.6, 126.9, 127.4, 127.8, 128.0, 128.6, 128.8, 132.4, 132.5, 132.76, 132.81, 136.2, 136.9, 155.2, 155.3, 172.0, 172.2; HRMS (ESI): *m*/*z* calculated for $C_{20}H_{28}N_2O_3Na^+$ [M+Na]$^+$: 367.1992, found: 367.1996.

(*S*)-**16**: 95% from (*S*)-**9** and **12** as a colorless oil, $[\alpha]_D^{20}=-18.9$ (*c* 1.18, $CHCl_3$). Its IR and NMR spectra were identical with those of (*R*)-**16**.

(*R*)-**17**: 95% from (*R*)-**9** and **13** as a colorless oil, $[\alpha]_D^{20}=+18.9$ (*c* 1.48, $CHCl_3$); IR (ATR) ν_{max} 3307, 2978, 1703, 1636, 1448, 1165, 915, 730, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (3.78H, s), 1.44 (5.22H, s), 2.24–2.43 (3.42H, m), 2.52 (0.58H, ddd, *J*=6.7, 7.3, 14.0 Hz), 3.28–3.38 (1.58H, m), 3.52 (0.42H, ddd, *J*=6.7, 7.3, 14.0 Hz), 4.37 (0.58H, d, *J*=15.0 Hz), 4.57 (0.42H, d, *J*=16.7 Hz), 4.66 (0.42H, d, *J*=16.7 Hz), 4.65–4.73 (1H, m), 4.86 (0.58H, d, *J*=15.0 Hz), 5.00–5.17 (4H, m), 5.31–5.35 (1H, m), 5.64–5.83 (2H, m), 7.18–7.36 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.27, 28.30, 31.8, 33.1, 37.8, 38.1, 45.5, 46.3, 48.6, 49.9, 50.0, 51.2, 79.5, 79.6, 116.9, 117.9, 118.5, 118.6, 126.8, 127.4, 127.8, 127.9, 128.6, 128.8, 132.8, 133.9, 135.1, 136.3, 137.1, 155.1, 155.2, 172.0, 172.1; HRMS (ESI): *m*/*z* calculated for $C_{21}H_{30}N_2O_3Na^+$ [M+Na]$^+$: 381.2149, found: 381.2142.

(*S*)-**17**: 90% from (*S*)-**9** and **13** as a colorless oil, $[\alpha]_D^{20}=-18.9$ (*c* 1.12, $CHCl_3$). Its IR and NMR spectra were identical with those of (*R*)-**17**.

(*R*)-**18**: 98% from (*R*)-**9** and **14** as a colorless oil, $[\alpha]_D^{21}=+11.5$ (*c* 1.37, $CHCl_3$); IR (ATR) ν_{max} 3304, 2977, 1704, 1636, 1445, 1165, 913, 731, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (3.96H, s), 1.44 (5.04H, s), 1.55–1.79 (2H, m), 2.00–2.07 (2H, m), 2.27–2.43 (1.44H, m), 2.51 (0.56H, ddd, *J*=6.8, 7.2, 14.0 Hz), 3.21–3.32 (1.56H, m), 3.37–3.45 (0.44H, m), 4.36 (0.56H, d, *J*=14.9 Hz), 4.57 (0.44H, d, *J*=16.9 Hz), 4.65 (0.44H, d, *J*=16.9 Hz), 4.65–4.70 (1H, m), 4.85 (0.56H, d, *J*=14.9 Hz), 4.94–5.16 (4H, m), 5.31–5.35 (1H, m), 5.63–5.83 (2H, m), 7.18–7.36 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 27.7, 28.28, 28.32, 30.7, 31.0, 37.8, 38.1, 45.8, 46.4, 48.5, 49.9, 50.0, 51.0, 79.6, 115.1, 115.8, 118.5, 118.6, 126.8, 127.4, 127.8, 127.9, 128.6, 128.9, 132.81, 132.83, 136.5, 137.0, 137.2, 137.7, 155.3, 172.0; HRMS (ESI): *m*/*z* calculated for $C_{22}H_{32}N_2O_3Na^+$ [M+Na]$^+$: 395.2305, found: 395.2317.

(*S*)-**18**: 94% from (*S*)-**9** and **14** as a colorless oil, $[\alpha]_D^{21}=-11.7$ (*c* 1.42, $CHCl_3$). Its IR and NMR spectra were identical with those of (*R*)-**18**.

(*R*)-**19**: 98% from (*R*)-**10** and **12** as a colorless oil, $[\alpha]_D^{20}=+61.9$ (*c* 1.02, $CHCl_3$); IR (ATR) ν_{max} 3323, 2974, 1709, 1634, 1442, 1164, 916, 740, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (1.08H, s), 1.08 (1.08H, s), 1.10 (1.92H, s), 1.11 (1.92H, s), 1.42 (3.24H, s), 1.43 (5.76H, s), 3.53 (0.36H, dd, *J*=7.1, 15.1 Hz), 3.91 (0.64H, dd, *J*=6.3, 17.1 Hz), 4.06 (0.64H, dd, *J*=3.6, 17.1 Hz), 4.24 (0.64H, d, *J*=14.7 Hz), 4.38 (0.36H, dd, *J*=6.7, 15.1 Hz), 4.39 (0.36H, d, *J*=16.4 Hz), 4.52 (0.64H, d, *J*=9.9 Hz), 4.68 (0.36H, d, *J*=9.9 Hz), 4.84 (0.36H, d, *J*=16.4 Hz), 4.92 (0.64H, d, *J*=14.7 Hz), 5.03–5.24 (4.36H, m), 5.28 (0.64H, d, *J*=9.9 Hz), 5.32 (0.36H, d, *J*=9.9 Hz), 5.67–5.85 (1H, m), 5.97 (0.36H, dd, *J*=10.6, 17.4 Hz), 5.99 (0.64H, dd, *J*=10.4, 17.8 Hz), 7.20–7.32 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 23.0, 24.3, 24.4, 28.2, 28.3, 41.1, 41.3, 47.5, 47.9, 49.8, 50.9, 55.7, 79.5, 113.48, 113.51, 117.79, 117.84, 127.3, 127.4, 127.7, 128.2, 128.5, 128.7, 132.6, 132.7, 136.2, 137.2, 143.66, 143.69, 155.35, 155.43, 171.5, 171.8; HRMS (ESI): *m*/*z* calculated for $C_{22}H_{32}N_2O_3Na^+$ [M+Na]$^+$: 395.2305, found: 395.2309.

(*S*)-**19**: 99% from (*S*)-**10** and **12** as a colorless oil, $[\alpha]_D^{21}=-61.6$ (*c* 1.14, $CHCl_3$). Its IR and NMR spectra were identical with those of (*R*)-**19**.

4.3. (*R*)- and (*S*)-20

To a solution of (*R*)-**15** (1.35 g, 5.03 mmol) in CH_2Cl_2 (500 mL) was added a first generation Grubbs catalyst (412 mg, 0.501 mmol). The reaction mixture was stirred for 72 h at reflux, then concentrated in vacuo. The residue was filtered through silica gel and washed with hexane–EtOAc, and the combined filtrate was concentrated in vacuo. The residue was dissolved in EtOH (50.0 mL), and a catalytic amount of Pd/C (10% on carbon) was added. The reaction mixture was vigorously stirred for 24 h at room temperature under H_2 and filtered through a Celite pad. The filter cake was washed with EtOAc, and the combined filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (50 g). Elution with hexane–EtOAc (10:1 to 4:1) afforded (*R*)-**20** (1.02 g, 84%). Further purification by recrystallization from hexane–EtOAc afforded an analytical sample of (*R*)-**20** as colorless crystals, mp 110 °C; $[\alpha]_D^{20}=-28.5$ (*c* 1.26, $CHCl_3$); IR (ATR) ν_{max} 3395, 2924, 1703, 1637, 1480, 1437, 1162, 1053, 1015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33–1.54 (2H, m), 1.44 (9H, s), 1.72–1.82 (2H, m), 1.93–2.05 (2H, m), 3.02 (3H, s), 3.18 (1H, dd, *J*=5.4, 15.2 Hz), 3.58 (1H, dd, *J*=11.8, 15.2 Hz), 4.38 (1H, dd, *J*=5.6, 11.0 Hz), 6.00 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 27.8, 28.4, 32.4, 36.0, 50.4, 53.1, 79.2, 155.1, 173.0; HRMS (ESI): *m*/*z* calculated for $C_{12}H_{22}N_2O_3Na^+$ [M+Na]$^+$: 265.1523, found: 265.1512.

In the same manner as described above, (*S*)-**15** was converted to (*S*)-**20**. Further purification by recrystallization from hexane–EtOAc afforded an analytical sample of (*S*)-**20** as colorless crystals, mp

110 °C; $[\alpha]_D^{21}$=+28.7 (*c* 1.08, $CHCl_3$). Its IR and NMR spectra were identical with those of (*R*)-**20**.

4.4. (*R*)- and (*S*)-21

To a solution of (*R*)-**16** (3.45 g, 10.0 mmol) in CH_2Cl_2 (1000 mL) was added a first generation Grubbs catalyst (823 mg, 1.00 mmol). The reaction mixture was stirred for 72 h at reflux, then concentrated in vacuo. The residue was filtered through silica gel and washed with hexane–EtOAc, and the combined filtrate was concentrated in vacuo. To a solution of the residue and *t*BuOH (950 μL, 10.0 mmol) in liq. NH_3 (100 mL) was added lithium (694 mg, 100 mmol) at −78 °C over 10 min. The reaction mixture was stirred for 1 h at the same temperature. The reaction was quenched with MeOH and a saturated aqueous NH_4Cl solution. The pH was adjusted to 2–3 with a 1 M aqueous citric acid solution. After extraction with $CHCl_3$, the combined organic extract was dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (100 g). Elution with $CHCl_3$–MeOH (30:1) afforded (*R*)-**21** (725 mg, 32%). Further purification by recrystallization from $CHCl_3$–MeOH afforded an analytical sample of (*R*)-**21** as white powder, mp 142 °C; $[\alpha]_D^{22}$=−85.8 (*c* 1.10, $CHCl_3$); IR (ATR) ν_{max} 3251, 2980, 1712, 1666, 1539, 1275, 1251, 1165, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (9H, s), 2.21–2.30 (1H m), 2.61–2.69 (1H, m), 3.41–3.49 (1H, m), 4.13–4.18 (1H, m), 4.80–4.85 (1H, m), 5.67–5.78 (3H, m), 6.25 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 32.7, 39.6, 49.8, 79.7, 124.5, 129.1, 155.1, 174.7; HRMS (ESI): *m*/*z* calculated for $C_{11}H_{18}N_2O_3Na^+$ $[M+Na]^+$: 249.1210, found: 249.1205.

In the same manner as described above, (*S*)-**16** was converted to (*S*)-**21**. Further purification by recrystallization from $CHCl_3$–MeOH afforded an analytical sample of (*S*)-**21** as white powder, mp 142 °C; $[\alpha]_D^{21}$=+86.5 (*c* 1.04, $CHCl_3$). Its IR and NMR spectra were identical with those of (*R*)-**21**.

4.5. General procedure for the conversion of *N*′-alkenyl *N*-Boc-allylglycine derivatives (17–19) to *N*-Boc-α-aminolactams (22–24)

To a solution of *N*′-alkenyl-*N*-Boc-allylglycine derivative (**17**–**19**) (10.0 mmol) in CH_2Cl_2 (1000 mL) was added a first generation Grubbs catalyst (823 mg, 1.00 mmol). The reaction mixture was stirred for 72 h at reflux, then concentrated in vacuo. The residue was filtered through silica gel and washed with hexane–EtOAc, and the combined filtrate was concentrated in vacuo. The residue was dissolved in EtOH (100 mL), and a catalytic amount of Pd/C (10% on carbon) was added. The reaction mixture was vigorously stirred for 24 h at room temperature under H_2 and filtered through a Celite pad. The filter cake was washed with $CHCl_3$, and the combined filtrate was concentrated in vacuo. To a solution of the residue and *t*BuOH (950 μL, 10.0 mmol) in liq. NH_3 (100 mL) was added lithium (694 mg, 100 mmol) at −78 °C over 10 min. The reaction mixture was stirred for 1 h at the same temperature. The reaction was quenched with MeOH and a saturated aqueous NH_4Cl solution. The pH was adjusted to 2–3 with a 1 M aqueous citric acid solution. After extraction with $CHCl_3$, the combined organic extract was dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (100 g). Elution with $CHCl_3$–MeOH (30:1) afforded *N*-Boc-α-aminolactam (**22**–**24**). Further purification by recrystallization from $CHCl_3$–MeOH afforded an analytical sample.

(*R*)-**22**: 52% from (*R*)-**17** as white powder, mp 194 °C; $[\alpha]_D^{21}$=−8.24 (*c* 1.05, $CHCl_3$); IR (ATR) ν_{max} 3252, 2929, 1712, 1669, 1532, 1249, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (9H, s), 1.55–1.87 (7H, m), 2.04–2.08 (1H, m), 3.23–3.28 (1H, m), 3.53–3.62 (1H, m), 4.57–4.59 (1H, m), 5.55 (1H, br), 5.91 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 24.6, 28.4, 32.1, 36.3, 41.0, 49.4, 79.5, 155.1, 175.2; HRMS (ESI): *m*/*z* calculated for $C_{12}H_{22}N_2O_3Na^+$ $[M+Na]^+$: 265.1523, found: 265.1509.

(*S*)-**22**: 48% from (*S*)-**17** as white powder, mp 194 °C; $[\alpha]_D^{21}$=+8.47 (*c* 1.06, $CHCl_3$). Its IR and NMR spectra were identical with those of (*R*)-**22**.

(*R*)-**23**: 49% from (*R*)-**18** as white powder, mp 136 °C; $[\alpha]_D^{21}$=−34.6 (*c* 1.10, $CHCl_3$); IR (ATR) ν_{max} 3334, 2931, 1655, 1513, 1234, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27–1.98 (9.33H, m), 1.43 (9H, s), 2.09–2.16 (0.67H, m), 2.90 (0.67H, br), 3.30–3.36 (0.33H, m), 3.4.9–3.58 (0.33H, m), 3.80 (0.33H, br), 4.07 (0.67H, br), 4.69 (0.67H, br), 5.39 (0.33H, br), 5.51 (0.67H, br), 6.20 (0.33H, br), 6.37 (0.67H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 23.4, 25.2, 28.3, 28.6, 28.8, 29.0, 29.7, 33.7, 40.1, 43.7, 50.1, 55.3, 79.5, 155.2, 155.3, 173.7, 175.7; HRMS (ESI): *m*/*z* calculated for $C_{13}H_{24}N_2O_3Na^+$ $[M+Na]^+$: 279.1679, found: 279.1680.

(*S*)-**23**: 47% from (*S*)-**18** as white powder, mp 136 °C; $[\alpha]_D^{21}$=+34.6 (*c* 1.05, $CHCl_3$). Its IR and NMR spectra were identical with those of (*R*)-**23**.

(*R*)-**24**: 49% from (*R*)-**19** as colorless crystals, mp 168 °C; $[\alpha]_D^{21}$=−34.4 (*c* 1.02, $CHCl_3$); IR (ATR) ν_{max} 3398, 3319, 2971, 1697, 1650, 1493, 1479, 1170, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (3H, s), 1.04 (3H, s), 1.44 (9H, s), 1.58–1.73 (4H, m), 3.17–3.23 (1H, m), 3.29–3.37 (1H, m), 4.41 (1H, d, *J*=8.2 Hz), 5.72 (1H, d, *J*=8.2 Hz), 6.02 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 25.6, 28.3, 28.4, 35.5, 42.0, 43.0, 58.7, 79.3, 156.1, 174.4; HRMS (ESI): *m*/*z* calculated for $C_{13}H_{24}N_2O_3Na^+$ $[M+Na]^+$: 279.1679, found: 279.1673.

(*S*)-**24**: 44% from (*S*)-**19** as colorless crystals, mp 168 °C; $[\alpha]_D^{21}$=+34.2 (*c* 1.00, $CHCl_3$). Its IR and NMR spectra were identical with those of (*R*)-**24**.

4.6. General procedure for the conversion of *N*-Boc-α-aminolactams (20–24) to α-aminolactams (4–8)

A mixture of *N*-Boc-α-aminolactam (**20**–**24**) (1.00 mmol) and 4 M HCl in MeOH (5.0 mL) was stirred for 24 h at room temperature, and concentrated in vacuo to afford α-aminolactam hydrochloride (**4**–**8**). Further purification by recrystallization from MeOH–H_2O afforded an analytical sample.

(*R*)-**4**: 82% from (*R*)-**20** as colorless crystals, mp 218 °C; $[\alpha]_D^{24}$=+13.1 (*c* 1.04, H_2O); IR (ATR) ν_{max} 2866, 2610, 1648, 1512, 1068 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 1.44–1.55 (1H, m), 1.66–1.78 (2H, m), 1.81–1.86 (1H, m), 1.93–2.05 (2H, m), 3.02 (3H, s), 3.32–3.38 (1H, m), 3.60 (1H, dd, *J*=11.6, 15.6 Hz), 4.37 (1H, d, *J*=10.9 Hz); ^{13}C NMR (100 MHz, D_2O) δ 25.3, 26.5, 28.2, 35.8, 50.3, 53.0, 171.0; HRMS (ESI): *m*/*z* calculated for $C_7H_{15}N_2O^+$ $[M+H]^+$: 143.1179, found: 143.1183; HPLC [column: Daicel Crownpak CR(+) (5 μm×4 mm×150 mm); solvent: 60 mM $HClO_4$; flow rate: 0.3 mL/min; column temperature: 30 °C; detection: 200 nm]: t_R=7.6 min for (*R*)-**4**.

(*S*)-**4**: 84% from (*S*)-**20** as colorless crystals, mp 218 °C; $[\alpha]_D^{22}$=−12.8 (*c* 1.02, H_2O); HRMS (ESI): *m*/*z* calculated for $C_7H_{15}N_2O^+$ $[M+H]^+$: 143.1179, found: 143.1178; HPLC [column: Daicel Crownpak CR(+) (5 μm×4 mm×150 mm); solvent: 60 mM $HClO_4$; flow rate: 0.3 mL/min; column temperature: 30 °C; detection: 200 nm]: t_R=11.3 min for (*S*)-**4**. Its IR and NMR spectra were identical with those of (*R*)-**4**.

(*R*)-**5**: 74% from (*R*)-**21** as white powder, mp 252 °C; $[\alpha]_D^{23}$=−75.5 (*c* 1.01, H_2O); IR (ATR) ν_{max} 3186, 2967, 1667, 1482, 1304, 1150, 753, 656 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 2.51–2.67 (2H, m), 3.58 (1H, dd, *J*=7.3, 18.2 Hz), 4.13 (1H, dddd, *J*=2.5, 4.0, 6.5, 18.2 Hz), 4.76 (1H, dd, *J*=4.8, 12.2 Hz), 5.76–5.86 (2H, m); ^{13}C NMR (100 MHz, D_2O) δ 28.7, 38.3, 49.7, 125.6, 125.9, 172.6; HRMS (ESI): *m*/*z* calculated for $C_6H_{11}N_2O^+$ $[M+H]^+$: 127.0866, found: 127.0870; HPLC [column: Daicel Crownpak CR(+) (5 μm×4 mm×150 mm); solvent:

60 mM $HClO_4$; flow rate: 0.3 mL/min; column temperature: 30 °C; detection: 200 nm]: t_R=5.7 min for (*R*)-**5**.

(*S*)-**5**: 76% from (*S*)-**21** as white powder, mp 252 °C; $[\alpha]_D^{23}$=+75.5 (*c* 1.23, H_2O); HRMS (ESI): *m*/*z* calculated for $C_6H_{11}N_2O^+$ $[M+H]^+$: 127.0866, found: 127.0863; HPLC [column: Daicel Crownpak CR(+) (5 μm×4 mm×150 mm); solvent: 60 mM $HClO_4$; flow rate: 0.3 mL/min; column temperature: 30 °C; detection: 200 nm]: t_R=8.1 min for (*S*)-**5**. Its IR and NMR spectra were identical with those of (*R*)-**5**.

(*R*)-**6**: 78% from (*R*)-**22** as white powder, mp 256 °C; $[\alpha]_D^{23}$=+30.7 (*c* 1.04, H_2O); IR (ATR) ν_{max} 3333, 2929, 1653, 1583, 1483, 1302, 977, 717 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 1.44–1.56 (1H, m), 1.60–1.81 (6H, m), 2.10–2.17 (1H, m), 3.31 (1H, ddd, *J*=3.1, 3.7, 15.4 Hz), 3.45 (1H, ddd, *J*=7.0, 8.4, 15.4 Hz), 4.45 (1H, dd, *J*=4.3, 11.9 Hz); ^{13}C NMR (100 MHz, D_2O) δ 22.4, 23.5, 30.5, 33.2, 40.2, 49.9, 172.8; HRMS (ESI): *m*/*z* calculated for $C_7H_{15}N_2O^+$ $[M+H]^+$: 143.1179, found: 143.1178; HPLC [column: Daicel Crownpak CR(+) (5 μm×4 mm×150 mm); solvent: 60 mM $HClO_4$; flow rate: 0.3 mL/min; column temperature: 30 °C; detection: 200 nm]: t_R=7.4 min for (*R*)-**6**.

(*S*)-**6**: 74% from (*S*)-**22** as white powder, mp 256 °C; $[\alpha]_D^{23}$=−30.5 (*c* 1.10, H_2O); HRMS (ESI): *m*/*z* calculated for $C_7H_{15}N_2O^+$ $[M+H]^+$: 143.1179, found: 143.1177; HPLC [column: Daicel Crownpak CR(+) (5 μm×4 mm×150 mm); solvent: 60 mM $HClO_4$; flow rate: 0.3 mL/min; column temperature: 30 °C; detection: 200 nm]: t_R=9.1 min for (*S*)-**6**. Its IR and NMR spectra were identical with those of (*R*)-**6**.

(*R*)-**7**: 72% from (*R*)-**23** as white powder, mp 224 °C; $[\alpha]_D^{23}$=−13.1 (*c* 1.07, H_2O); IR (ATR) ν_{max} 2918, 1650, 1615, 1563, 1476, 1319, 1127, 805 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 1.08–1.18 (0.75H, m), 1.29–1.93 (8.25H, m), 1.98–2.05 (0.25H, m), 2.19–2.25 (0.75H, m), 2.99–3.04 (0.75H, m), 3.35–3.46 (0.50H, m), 3.59–3.68 (0.75H, m), 3.86 (0.75H, dd, *J*=6.0, 10.6 Hz), 4.47 (0.25H, dd, *J*=4.3, 10.6 Hz); ^{13}C NMR (100 MHz, D_2O) δ 20.9, 22.3, 22.9, 23.2, 27.3, 27.5, 28.1, 28.2, 30.1, 30.8, 40.2, 42.7, 50.6, 53.4, 171.3, 172.7; HRMS (ESI): *m*/*z* calculated for $C_8H_{17}N_2O^+$ $[M+H]^+$: 157.1335, found: 157.1339; HPLC [column: Daicel Crownpak CR(+) (5 μm×4 mm×150 mm); solvent: 60 mM $HClO_4$; flow rate: 0.3 mL/min; column temperature: 30 °C; detection: 200 nm]: t_R=14.7 min for (*R*)-**7**.

(*S*)-**7**: 68% from (*S*)-**23** as white powder, mp 224 °C; $[\alpha]_D^{24}$=+12.6 (*c* 1.04, H_2O); HRMS (ESI): *m*/*z* calculated for $C_8H_{17}N_2O^+$ $[M+H]^+$: 157.1335, found: 157.1339; HPLC [column: Daicel Crownpak CR(+) (5 μm×4 mm×150 mm); solvent: 60 mM $HClO_4$; flow rate: 0.3 mL/min; column temperature: 30 °C; detection: 200 nm]: t_R=16.9 min for (*S*)-**7**. Its IR and NMR spectra were identical with those of (*R*)-**7**.

(*R*)-**8**: 81% from (*R*)-**24** as colorless crystals, mp 212 °C; $[\alpha]_D^{22}$=+77.8 (*c* 1.01, H_2O); IR (ATR) ν_{max} 2929, 1654, 1594, 1492, 1331, 1115, 1037, 743 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 0.99 (3H, s), 1.13 (3H, s), 1.64–1.84 (4H, m), 3.26–3.29 (2H, m), 4.31 (1H, s); ^{13}C NMR (100 MHz, D_2O) δ 18.5, 24.1, 27.3, 32.5, 41.3, 42.8, 59.8, 172.3; HRMS (ESI): *m*/*z* calculated for $C_8H_{17}N_2O^+$ $[M+H]^+$: 157.1335, found: 157.1333; HPLC [column: Daicel Crownpak CR(+) (5 μm×4 mm×150 mm); solvent: 60 mM $HClO_4$; flow rate: 0.3 mL/min; column temperature: 30 °C; detection: 200 nm]: t_R=9.0 min for (*R*)-**8**.

(*S*)-**8**: 83% from (*S*)-**24** as colorless crystals, mp 212 °C; $[\alpha]_D^{23}$=−77.6 (*c* 0.880, H_2O); HRMS (ESI): *m*/*z* calculated for $C_8H_{17}N_2O^+$ $[M+H]^+$: 157.1335, found: 157.1332; HPLC [column: Daicel Crownpak CR(+) (5 μm×4 mm×150 mm); solvent: 60 mM $HClO_4$; flow rate: 0.3 mL/min; column temperature: 30 °C; detection: 200 nm]: t_R=9.1 min for (*S*)-**8**. Its IR and NMR spectra were identical with those of (*R*)-**8**.

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