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Synthesis of (1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptane derivatives by an epimerization–lactamization cascade reaction

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An epimerization–lactamization cascade of functionalized (2*S*,4*R*)-4-aminoproline methyl esters is developed and applied in synthesizing (1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptane (DBH) derivatives. (2*S*,4*R*)-4-Aminoproline methyl esters are likely to undergo 2-epimerization under basic conditions, followed by an intramolecular aminolysis of the (2*R*)-epimer to form the bridged lactam intermediates. Key factors identified for this cascade reaction include the electron-withdrawal N-protective group in the substrates and a strong base as the promoter.

1. Introduction

The last decade witnessed a fast expansion in the application of cascade reactions. Benefits of cascade reactions include step and atom economy, and time and cost efficiency.[1] Inspiringly, it has been demonstrated that by ingenious design, cascade reactions can be ideal solutions to the selectivity of a unit step, which sometimes is problematic if the reaction is conducted individually.[2] It is widely known that amino acids can undergo epimerization at the α-position under certain conditions. Although this transformation is commonly considered synthetically useless and should be avoided, we hypothesize that it could be of use if included in a suitable reaction cascade.

Derivatives of 2,5-diazabicyclo[2.2.1]heptane (DBH) are important building blocks for the structure–activity relationship study in medicinal chemistry,[3] and useful chiral ligands in asymmetric synthesis as well.[4] Both (1*S*,4*S*)- and (1*R*,4*R*)-DBH can be prepared from natural *trans*-4-hydroxy-L-proline (**1**).[5–7] Currently, synthesis of (1*R*,4*R*)-DBH is based on a ring-closing double *N*-alkylation approach reported by Bouzard and Remuzon (Fig. 1).[6] However, due to the fact that extra steps are necessary for the setup of the proper stereochemistry, the preparation of (1*R*,4*R*)-DBH requires significantly longer route than its (1*S*,4*S*)-isomer, making it much less accessible.[8] Herein, we report an epimerization–lactamization strategy based on the unique reactivity of *N*-protected (2*S*,4*R*)-4-aminoproline esters (Fig. 1). The method provides an alternative access to (1*R*,4*R*)-DBH derivatives.

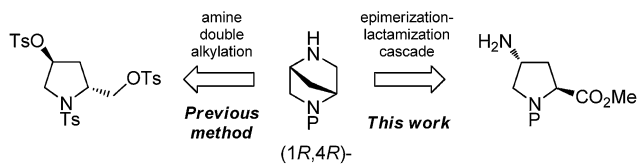

Fig. 1 Key reactions of previous and this synthesis of (1*R*,4*R*)-DBH.

2. Results and discussion

We initiated our study with (2*S*,4*R*)-1-benzoyl-4-aminoproline (**7a**) to test the hypothetical epimerization–lactamization sequence (Scheme 1). A *trans*-4-amino group is expected to initiate an intramolecular aminolysis[9] of the ester group under epimerizing conditions. Thus, benzamide **2a**[10] was obtained from **1** in quantitative yields, and then converted to alcohol **4a** by an intramolecular Mitsunobu reaction[11] and a sodium azide-promoted methanolysis protocol developed by the Silverman group.[12] Following a sequence of mesylation, azidation and hydrogenation,[9,13] a standard protocol in the functional group transformation for the proline scaffold, compound **7a** was obtained in 82% overall yield in 6 steps.

With amine **7a** in hand, the concept of epimerization–lactamization cascade was tested. Several bases were screened (Table 1). To our delight, the reaction using MeONa gave the desired (1*R*,4*R*)-lactam **8a** in a moderate 47% yield (entry 1). This strained bridged lactam was proved stable enough to be purified by silica gel chromatography. *tert*-BuOK, a slightly stronger base than MeONa, afforded better yield (entry 2). KHMDS, the strongest base in the screening, delivered a satisfactory 80% yield (entry 3). Significantly lower yields were obtained when sub-stoichiometric amounts of KHMDS were used (entries 4 and 5), indicating this cascade transformation is non-catalytic. The reaction temperature has little effect on the

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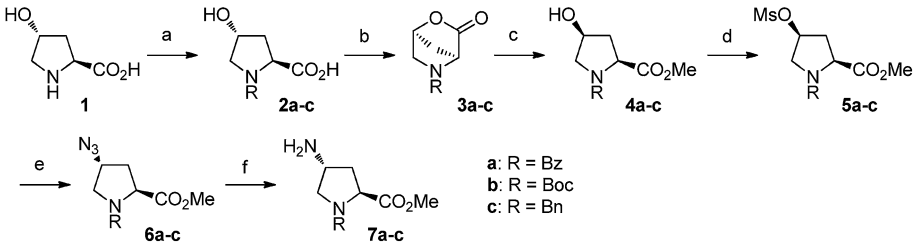
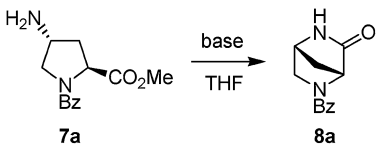


Scheme 1 Synthesis of (2*S*,4*R*)-1-benzoyl-4-aminoproline methyl ester. Conditions: (a) (1) BzCl, NaOH, H_2O, 0 °C (for **2a**, R = Bz), (2) Boc_2O, NaOH, THF–H_2O, rt (for **2b**, R = Boc), (3) (i) MeOH, $SOCl_2$, 0 °C to reflux, (ii) BnBr, Et_3N, $CHCl_3$, reflux, (iii) NaOH, THF–H_2O, 0 °C (for **2c**, R = Bn); (b) DEAD, PPh_3, THF, rt; (c) NaN_3, MeOH, 40 °C; (d) MsCl, Et_3N, DCM, 0 °C; (e) NaN_3, DMF, 70 °C; (f) H_2, 10% Pd/C, MeOH, rt.

Table 1 Optimization of the epimerization–lactamization cascade[a]



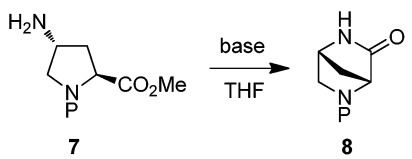
7a **8a**

Entry	Base (equiv.)	Yield[b] (%)
1	MeONa (1.0)	47
2	*t*-BuOK (1.1)	61
3	KHMDS (1.0)	80
4	KHMDS (0.8)	50
5	KHMDS (0.5)	30
6[c]	KHMDS (0.5)	35

[a] Reactions were carried out at 0.5 mmol scales in anhydrous THF at room temperature unless otherwise indicated. [b] Isolated yields. [c] Reaction was carried out at 0 °C.

results (entry 6). Addition of excess amount of KHMDS resulted in extensive decomposition of the product. Reactions in *N*,*N*-dimethylformamide gave similar results. Therefore, the optimized condition was determined as adding 1–1.2 equivalents of KHMDS to a THF solution of the substrate at room temperature.

Table 2 Effects of the N-substituents[a]



7 **8**

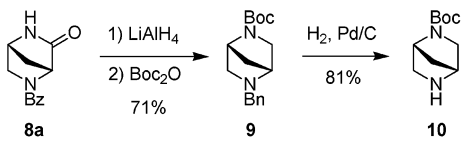
Entry	P	Base (equiv.)	Product	Yield[b] (%)
1	Bz	KHMDS (1.0)	**8a**	80
2	Boc	KHMDS (1.2)	**8b**	70
3	Boc	*t*-BuOK (2.0)	**8b**	61
4	Boc	MeONa (2.5)	**8b**	54
5	Bn	KHMDS (1.2)	**8c**	63
6	Bn	*t*-BuOK (2.0)	**8c**	0
7	Bn	MeONa (2.0)	**8c**	0

[a] Reactions were carried out at 0.5 mmol scales in anhydrous THF at room temperature. [b] Isolated yields.

Next, the effects of 1-protective group were explored (Table 2). Boc and benzyl are chosen to probe the effects of their electron properties, with the expectation that less electron-withdrawal groups need a stronger base to promote the epimerization–lactamization cascade of the substrate. Using similar routes, aminoproline ester **7b** and **7c** were synthesized from *trans*-4-hydroxy-L-proline (Scheme 1). As expected, amine **7b** reacted smoothly upon treated with KHMDS and afforded a 70% yield (entry 2), while the reactions with *tert*-BuOK and MeONa were found less effective, requiring more than 2 equivalents to reach full conversion (entries 3 and 4). For benzyl-protected substrate **7c**, the cascade reaction could not even take place for *tert*-BuOK and MeONa, and a decreased 63% yield was obtained when KHMDS was used (entries 5 to 7). Obviously, an electron-rich protective group like benzyl remarkably reduces the acidity of 2-H, making less strong bases unable to trigger this cascade event.

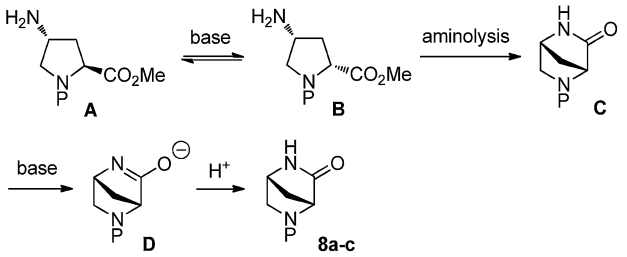
The products of the epimerization–lactamization cascade could be handily converted to various derivatives of (1*R*,4*R*)-DBH. For example, lactam **8a** could be reduced by $LiAlH_4$ and then transformed to Boc-protected **10** in a 58% overall yield (Scheme 2). Thus, an 8-step synthesis of (1*R*,4*R*)-DBH from *trans*-4-hydroxy-L-proline was established. This cascade reaction was also found robust for scale-up synthesis. High yields (70–80%) were obtained consistently for reactions at 5 to 10 gram scales.

The reactions employed in the synthesis of amines **7a–c** are well established, and the epimerization–lactamization cascades took place under a condition which could not result in the epimerization of 4-amino group of **7a–c**, we thus expected that the products **8a–c** should be stereochemically pure. To obtain direct evidences, specific rotations of compounds **7b** and **8b** were measured. The value of amine **7b** (−47.7) is nearly identical to the reported one (−47.4).[14] For lactam **8b**, the specific rotation (−10.4) is consistent with the value of its enantiomer (*ent*-**8b**, +10.2), which was prepared from *trans*-4-hydroxy-L-



8a **9** **10**

Scheme 2 Synthesis of (1*R*,4*R*)-2-Boc-DBH (**10**).



Scheme 3 Proposed mechanism of the epimerization–lactamization cascade.

proline (**1**) according to a known route.[15] These results confirmed that the cascade process is stereo-specific.

Mechanistically, as our results exhibited that the reaction performed better for substrates with an electron-deficient N-protective group, it is likely that substrate **A** converts reversibly to the *cis*-epimer **B** under basic condition first, followed by an intramolecular aminolysis of **B** to form bridged lactam **C** (Scheme 3). This aminolysis is presumably irreversible, and results in the complete conversion of substrate **A** into lactam **C**. Since **C** can be further deprotonated to form stabilized anion **D**, stoichiometric amount of the base is necessary for a complete reaction.

It is worth noting that Dalla Croce and La Rosa[16] pioneered in the epimerization–cyclization chemistry of proline scaffold, and discovered an acetylation–epimerization–lactonization cascade to convert *trans*-4-hydroxy-L-proline to (1*R*,4*R*)-*N*-acetyl-2-oxa-5-azabicyclo[2.2.1]heptan-3-one. Together, these works demonstrated that when combined with an epimer-consuming event, the epimerization of amino acid derivatives is synthetically useful, and showcased the benefits of developing cascade reactions.

3. Conclusion

In summary, we developed an epimerization–lactamization cascade of N-protected (2*S*,4*R*)-4-aminoproline methyl esters, and applied this transformation in a new synthesis of (1*R*,4*R*)-DBH derivatives. An electron-withdrawal *N*-protective group in the substrates and a strong base promoter are found important for an effective epimerization–lactamization reaction.

4. Experimental section

4.1. General methods

^{1}H and ^{13}C NMR spectra were obtained on a Bruker AM-400 MHz spectrometer. Mass spectra were performed by the mass spectrometry facility of Faculty of Life Science and Technology, Kunming University of Science and Technology. Values of optical rotation were recorded on a WZZ-2S spectropolarimeter. Anhydrous solvents were prepared by standard methods. Chemicals were purchased from Adamas, J&K Scientific and Sigma-Aldrich, and were used as received. Silica gel ZCX II (300–400 mesh) was purchased from Qingdao Haiyang Chemicals.

4.2. Synthesis of (2*S*,4*R*)-4-amino-1-benzoylproline methyl ester (7a)

4.2.1. (2*S*,4*S*)-1-benzoyl-4-hydroxyproline methyl ester (4a).[18]

*(2S,4R)-1-Benzoyl-4-hydroxyproline (**2a**).*[17]. To a suspension of *trans*-4-hydroxy-L-proline (26.2 g, 0.2 mol) in water (50 ml) cooled with an ice bath was added NaOH solution (50%, 16.0 g, 0.2 mol) dropwise. Sodium bicarbonate (16.8 g, 0.2 mol) was added to the obtained solution, followed by adding benzoyl chloride (11.6 ml, 0.2 mol) dropwise. After the addition, a 2 N NaOH solution was added to adjust the pH to 10. The mixture was stirred for 30 min, and then acidified by adding concentrated hydrochloric acid. The resulted precipitates were collected by filtration, washed thoroughly with water, and dried to give colorless crystals (46.5 g, 99%, slightly contaminated with benzoic acid). $R_f = 0.67$ (DCM–MeOH–AcOH, 90/10/1).

*(2S,4S)-1-benzoyl-4-hydroxyproline methyl ester (**4a**).*[18]. Compound **2a** (1.0 g, 4.25 mmol) was dissolved in THF (5 ml) under N_2 and cooled with an ice bath. Triphenylphosphine (1.67 g, 6.38 mmol) was added, followed by addition of DEAD (0.87 ml, 5.53 mmol) dropwise. The resulted solution was stirred at room temperature for 20 h, and quenched by adding water. THF was removed under reduced pressure, and the residue was extracted with EtOAc. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was stirred with NaN_3 (0.55 g, 8.50 mmol) in anhydrous MeOH (50 ml) at 40 °C for 5 h. After cooled to room temperature, EtOAc and water were added. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography (petroleum ether–EtOAc, 1/10) to afford compound **4a** (1.02 g, 96% for 2 steps) as a colorless solid. $R_f = 0.64$ (EtOAc–MeOH, 10/1); $[\alpha]_D^{25} = -39.9$ (*c* 1.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.49 (m, 2H), 7.47–7.38 (m, 3H), 4.82 (t, $J = 8.3$ Hz, 1H), 4.45 (bs, 1H), 3.85–3.78 (m, 1H), 3.76 (s, 3H), 3.49 (d, $J = 11.4$ Hz, 1H), 2.38–2.31 (m, 1H), 2.14–2.07 (m, 1H).

4.2.2. (2*S*,4*R*)-4-Azido-1-benzoylproline methyl ester (6a)

*(2S,4S)-1-Benzoyl-4-mesyloxyproline methyl ester (**5a**).*[19]. Compound **4a** (3.0 g, 12.04 mmol) and triethylamine (5.1 ml, 36.12 mmol) were dissolved in CH_2Cl_2 (40 ml) under N_2. Mesyl chloride (1.4 ml, 18.06 mmol) were added at 0 °C slowly. The reaction was stirred at the same temperature for 6 h, and then was quenched by adding water. The aqueous layer was separated and extracted with CH_2Cl_2. The combined extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to afford crude compound **5a** (3.86 g, 98%) as a yellowish solid, which was used in the next step without purification. $R_f = 0.28$ (petroleum ether–EtOAc, 1/1).

*(2S,4R)-4-Azido-1-benzoylproline methyl ester (**6a**).* Crude compound **5a** (3.86 g, 11.79 mmol) was dissolved in anhydrous DMF (40 ml) and NaN_3 (3.9 g, 60.2 mmol) was added under nitrogen. The mixture was stirred at 70 °C for 6 h. After cooled to room temperature, water and petroleum ether–EtOAc (2/1) was added. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. The

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residue was purified by flash column chromatography (petroleum ether–EtOAc, 4/1) to afford compound **6a** (3.0 g, 92%) as colorless oil. R_f = 0.36 (petroleum ether–EtOAc, 1/1); $[\alpha]_D^{25}$ = +96.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.52 (m, 2H), 7.45–7.39 (m, 3H), 4.79 (t, J = 7.9 Hz, 1H), 4.30–4.20 (m, 1H), 3.85 (dd, J = 11.4, 4.9 Hz, 1H), 3.79 (s, 3H), 3.59–3.51 (m, 1H), 2.49–2.38 (m, 1H), 2.28–2.21 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 168.8, 134.3, 129.6, 127.4, 126.3, 58.8, 56.6, 53.6, 51.5, 33.7; HRMS (ESI) calcd for $C_{13}H_{14}N_4NaO_3^+$ $[M + Na]^+$, 297.0964; found 297.0958.

4.2.3. (2*S*,4*R*)-4-Amino-1-benzoylproline methyl ester (7a). A solution of compound **6a** (3.0 g, 10.94 mmol) in MeOH (50 ml) was stirred under H_2 (1 atm) in the presence of 10% Pd/C (0.3 g). After 3 h, the reaction mixture was filtered through celite, and the filtrate was concentrated. The residue was purified by flash column chromatography (EtOAc–MeOH, 10/1) to afford compound **7a** as colorless thick oil (2.6 g, 96%). R_f = 0.47 (EtOAc–MeOH, 1/1); $[\alpha]_D^{25} = -61.6$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.49 (m, 2H), 7.47–7.36 (m, 3H), 4.63 (t, J = 8.0 Hz, 1H), 3.74 (s, 3H), 3.68 (dd, J = 10.2, 6.2 Hz, 1H), 3.53–3.42 (m, 1H), 3.35 (dd, J = 10.2, 7.0 Hz, 1H), 2.55–2.48 (m, 1H), 1.82–1.72 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 169.4, 135.6, 130.3, 128.2, 127.3, 58.2, 57.8, 52.2, 51.4, 37.9; HRMS (ESI) calcd for $C_{13}H_{17}N_2O_3^+$ $[M + H]^+$, 249.1239; found 249.1242.

4.3. Synthesis of (2*S*,4*R*)-4-amino-1-Boc-proline methyl ester (7b)

4.3.1. (1*S*,4*S*)-2-Boc-2-aza-5-oxabicyclo[2.2.1]heptan-6-one (3b).[21]

(2S,4R)-1-Boc-4-hydroxyproline (2b).[20] To a solution of *trans*-4-hydroxy-L-proline (5.0 g, 38.1 mmol) in water (20 ml) was added THF (40 ml) and Boc_2O (9.6 ml, 41.91 mmol). NaOH solution was added to keep the pH greater than 8. After stirred at room temperature overnight, the mixture was concentrated under reduced pressure. The aqueous residue was acidified by adding diluted HCl, and extracted with ethyl acetate. The combined extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to afford crude compound **2b** (8.19 g) as syrup, which was used in the next step without purification. R_f = 0.85 (*n*BuOH–H_2O–AcOH, 40/10/1).

(1S,4S)-2-Boc-2-aza-5-oxabicyclo[2.2.1]heptan-6-one (3b).[21] Crude compound **2b** (0.5 g, 2.16 mmol) was dissolved in THF (5 ml) under N_2 and cooled with an ice bath. Triphenylphosphine (0.85 g, 3.24 mmol) was added, followed by addition of DEAD (0.44 ml, 2.81 mmol) dropwise. The resulted solution was stirred at room temperature for 20 h, and quenched by adding water. THF was removed under reduced pressure, and the residue was extracted with EtOAc. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography (petroleum ether–EtOAc, 2/1) to afford compound **3b** (0.43 g, 87% for two steps) as a colorless solid. R_f = 0.5 (petroleum ether–EtOAc, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (dd, J = 1.6, 0.7 Hz, 1H), 4.65–4.43 (m, 1H), 3.52 (dd, J = 11.0, 1.1 Hz, 1H), 3.44 (d, J = 10.4 Hz, 1H), 2.22–2.16 (m, 1H), 2.00 (d, J = 10.6 Hz, 1H), 1.45 (s, 9H).

4.3.2. (2*S*,4*S*)-1-Boc-4-hydroxyproline methyl ester (4b).[14] A mixture of compound **3b** (0.46 g, 2.16 mmol), NaN_3 (0.28 g, 4.32 mmol) and anhydrous MeOH (25 ml) was stirred at 40 °C for 5 h. After cooled to room temperature, EtOAc and water were added. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by flash column chromatography (petroleum ether–EtOAc, 2/1) to afford compound **4b** (0.48 g, 90%) as a colorless solid. R_f = 0.24 (petroleum ether–EtOAc, 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35–4.23 (m, 2H), 3.75 (s, 1.35H), 3.74 (s, 1.65H), 3.65–3.48 (m, 2H), 3.23 (bs, 1H), 2.35–2.23 (m, 1H), 2.09–2.00 (m, 1H), 1.42 (s, 4H), 1.38 (s, 5H).

4.3.3. (2*S*,4*R*)-4-Azido-1-Boc-proline methyl ester (6b).[14]

(2S,4S)-1-Boc-4-mesyloxyproline methyl ester (5b).[14] Compound **4b** (0.52 g, 2.12 mmol) and triethylamine (0.91 ml, 6.48 mmol) were dissolved in CH_2Cl_2 (10 ml) under N_2. Mesyl chloride (0.25 ml, 3.24 mmol) were added at 0 °C slowly. The reaction was stirred at the same temperature until the full conversion was detected. The reaction was quenched by adding water, and the separated aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to afford crude compound **5b** (0.69 g, 98%) as a yellowish solid, which was used in the next step without purification. R_f = 0.38 (petroleum ether–EtOAc, 2/1).

(2S,4R)-4-Azido-1-Boc-proline methyl ester (6b).[14] The above-obtained crude compound **5b** (0.70 g, 2.16 mmol) was dissolved in anhydrous DMF (15 ml) and NaN_3 (0.71 g, 10.8 mmol) was added. The mixture was stirred at 70 °C for 6 h and then cooled to room temperature. Water and petroleum ether–EtOAc (2/1) were added. The separated organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by flash column chromatography (petroleum ether–EtOAc, 10/3) to afford compound **6b** (0.56 g, 97%) as a yellowish syrup. R_f = 0.25 (petroleum ether–EtOAc, 5/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (t, J = 7.4 Hz, 0.4H), 4.31 (t, J = 7.4 Hz, 0.6H), 4.19 (dd, J = 9.0, 5.0 Hz, 1H), 3.74 (s, 1.2H), 3.73 (s, 1.8H), 3.71–3.66 (m, 1H), 3.58 (dd, J = 11.5, 2.3 Hz, 0.6H), 3.46 (dd, J = 11.5, 2.3 Hz, 0.4H), 2.37–2.25 (m, 1H), 2.20–2.12 (m, 1H), 1.45 (s, 3.6H), 1.40 (s, 5.4H).

4.3.4. (2*S*,4*R*)-4-Amino-1-Boc-proline methyl ester (7b).[14] A solution of compound **6b** (2.81 g, 10.40 mmol) in MeOH (30 ml) was stirred under H_2 (1 atm) in the presence of 10% Pd/C (0.3 g). The reaction mixture was filtered through celite and the filtrate was concentrated. The residue was purified by flash column chromatography (EtOAc–MeOH, 10/1) to afford compound **7b** (2.25 g, 89%) as a colorless solid. R_f = 0.18 (EtOAc–MeOH, 10/1); $[\alpha]_D^{25} = -47.7$ (*c* 0.30, $CHCl_3$) [lit. −47.4 (*c* 0.298, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44–4.31 (m, 1H), 3.75–3.64 (m, 2H), 3.71 (s, 3H), 3.23–3.08 (m, 1H), 2.19–1.94 (m, 2H), 1.88 (bs, 2H), 1.44 (s, 3.6H), 1.39 (s, 5.4H).

4.4. Synthesis of (2*S*,4*R*)-4-amino-1-benzylproline methyl ester (7c)

4.4.1. (2*S*,4*R*)-1-Benzyl-4-hydroxyproline methyl ester.[5b] To a suspension of **1** (3.0 g, 22.9 mmol) in MeOH (30 ml) was added

$SOCl_2$ (2 ml, 27.48 mmol) slowly at 0 °C. The mixture was stirred under reflux overnight, and then cooled to room temperature. The solvent was removed under reduced pressure to give a white solid. To the residue were added $CHCl_3$ (30 ml), Et_3N (15.8 ml, 114.5 mmol), and benzyl bromide (4.1 ml, 34.35 mmol), and the mixture was stirred under reflux for 6 h. After cooled to room temperature, the mixture was diluted with $CHCl_3$, washed with 1 N NaOH, water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography (petroleum ether–EtOAc, 1/2) to afford the titled compound (5.0 g, 93%) as yellowish syrup. $R_f = 0.44$ (petroleum ether–EtOAc, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.22 (m, 4H), 7.21–7.17 (m, 1H), 4.38 (bs, 1H), 3.83 (d, J = 12.8 Hz, 1H), 3.61 (d, J = 12.8 Hz, 1H), 3.59 (s, 3H), 3.55 (t, J = 7.8 Hz, 1H), 3.27 (dd, J = 10.2, 5.6 Hz, 1H), 2.41 (dd, J = 10.2, 3.8 Hz, 1H), 2.23–2.15 (m, 1H), 2.05–1.98 (m, 1H), 1.95–1.85 (m, 1H).

4.4.2. (1*S*,4*S*)-2-Benzyl-2-aza-5-oxabicyclo[2.2.1]heptan-6-one (3c)

*(2S,4R)-1-Benzyl-4-hydroxyproline (**2c**).* To a solution of (2*S*,4*R*)-1-benzyl-4-hydroxyproline methyl ester (7.7 g, 32.73 mmol) in THF (60 ml) was added water (5 ml) and NaOH (2.50 g, 62.5 mmol) at 0 °C. After the full conversion was detected, the mixture was neutralized by adding diluted HCl. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography ($CHCl_3$) to afford compound **2c** (7.1 g, 98%) as a colorless solid.

*(1S,4S)-2-Benzyl-2-aza-5-oxabicyclo[2.2.1]heptan-6-one (**3c**).* Compound **2c** (7.1 g, 32.09 mmol) was dissolved in THF (80 ml) and triphenylphosphine (17.17 g, 65.46 mmol) was added at 0 °C. DEAD (7.7 ml, 42.55 mmol) was added dropwise. The reaction was stirred at room temperature overnight, and quenched by adding water. THF was removed under reduced pressure, and the residue was extracted with EtOAc. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography (petroleum ether–EtOAc, 2/1) to afford compound **3c** (5.3 g, 81%) as a colorless solid. $R_f = 0.48$ (petroleum ether–EtOAc, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.15 (m, 5H), 4.04–3.98 (m, 1H), 3.82 (d, J = 12.9 Hz, 1H), 3.57 (d, J = 12.9 Hz, 1H), 3.50–3.45 (m, 1H), 3.22 (dd, J = 10.1, 6.4 Hz, 1H), 2.45 (dd, J = 10.1, 5.1 Hz, 1H), 2.29–2.21 (m, 1H), 2.12–2.04 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 136.7, 127.9, 127.3, 126.3, 62.6, 58.0, 56.7, 50.8, 34.8.

4.4.3. (2*S*,4*S*)-1-Benzyl-4-hydroxyproline methyl ester (4c).[22]

A mixture of compound **3c** (4.9 g, 24.1 mmol), NaN_3 (3.13 g, 48.2 mmol) and anhydrous MeOH (50 ml) was stirred at 40 °C overnight. After cooled to room temperature, saturated NH_4Cl solution and EtOAc was added. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by flash column chromatography (petroleum ether–EtOAc, 2/1) to afford compound **4c** (4.7 g, 84%) as colorless oil. $R_f = 0.30$ (petroleum ether–EtOAc, 1/1); $[\alpha]_D^{25} = -62.72$ (*c* 1.34, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.15 (m, 5H), 4.18 (m, 1H), 3.81 (d, J = 13.1 Hz, 1H), 3.65 (d, J = 13.1 Hz, 1H), 3.56 (s, 3H), 3.28 (dd, J = 10.0, 3.9 Hz, 1H), 3.16 (bs, 1H), 2.96 (d, J = 9.9 Hz, 1H), 2.57 (dd, J = 9.9, 4.0 Hz, 1H), 2.37–2.28 (m, 1H), 1.92–1.84 (m, 1H).

4.4.4. (2*S*,4*R*)-4-Azido-1-benzylproline methyl ester (6c).

Compound **4c** (3.4 g, 14.45 mmol) and triethylamine (8.2 ml, 57.8 mmol) were dissolved in CH_2Cl_2 (30 ml) at 0 °C. Mesyl chloride (2.3 ml, 28.9 mmol) were added dropwise. The reaction was stirred at 0 °C until the full conversion was detected. The mixture was diluted with CH_2Cl_2, washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue (crude compound **5c**) was dissolved in anhydrous DMF (30 ml), and stirred with NaN_3 (4.7 g, 72.25 mmol) at 70 °C for 6 h. After cooled to room temperature, water and petroleum ether–EtOAc (2/1) were added. The separated organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography (petroleum ether–EtOAc, 8/1) to afford compound **6c** (2.0 g, 56%) as a colorless solid. $R_f = 0.43$ (petroleum ether–EtOAc, 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.27 (m, 5H), 4.11 (m, 1H), 3.91 (d, J = 12.9 Hz, 1H), 3.67 (s, 3H), 3.66 (d, J = 12.9 Hz, 1H), 3.58–3.53 (m, 1H), 3.32 (dd, J = 10.1, 6.4 Hz, 1H), 2.53 (dd, J = 10.1, 5.1 Hz, 1H), 2.38–2.28 (m, 1H), 2.22–2.12 (m, 1H); HRMS (ESI) calcd for $C_{13}H_{17}N_4O_2^+$ $[M + H]^+$, 261.1352; found 261.1356.

4.4.5. (2*S*,4*R*)-4-Amino-1-benzylproline methyl ester (7c).

To a solution of compound **6c** (2.0 g, 7.68 mmol) in THF (30 ml) was added triphenylphosphine (5.04 g, 19.2 mmol) and water (0.4 ml). The mixture was stirred under reflux overnight. The solvent was removed under reduced pressure, and the residue was taken up with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by flash column chromatography (EtOAc–MeOH, 1/1) to afford compound **7c** (1.7 g, 94%) as yellowish oil. $R_f = 0.35$ (EtOAc–MeOH, 1/1). $[\alpha]_D^{25} = -36.9$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.13 (m, 5H), 3.78 (d, J = 12.8 Hz, 1H), 3.55 (s, 3H), 3.55–3.48 (m, 2H), 3.39 (t, J = 7.8 Hz, 1H), 3.17 (dd, J = 8.9, 6.5 Hz, 1H), 2.22–2.14 (m, 1H), 2.10–2.04 (m, 1H), 1.77–1.68 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 136.8, 128.2, 127.2, 126.2, 63.1, 61.0, 57.5, 50.8, 48.7, 38.5; HRMS (ESI) calcd for $C_{13}H_{18}N_2NaO_2^+$ $[M + Na]^+$, 257.1266; found 257.1263.

4.5. General procedure for epimerization–lactamization reactions of N-substituted (2*S*,4*R*)-4-aminoproline methyl ester

N-Substituted (2*S*,4*R*)-4-aminoproline methyl ester (1.0 mmol) was dissolved in anhydrous THF (4.0 ml) under nitrogen at room temperature. KHMDS solution (1.0 M, 1.2 ml, 1.2 mmol) was added dropwise. The resulted solution was stirred at room temperature for 15 min, and then quenched by adding AcOH (1 equiv. to KHMDS). The solvent was removed under reduced pressure. Dichloromethane and water were added, and the separated aqueous layer was extracted again with dichloromethane. The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography to give the titled compounds as colorless to light yellow solids.

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4.5.1. (1*R*,4*R*)-5-Benzoyl-2,5-diazabicyclo[2.2.1]heptan-3-one (8a). 80% yield. $[\alpha]_D^{25}$ = +96.8 (*c* 0.84, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.66 (m, 2H), 7.42–7.38 (m, 3H), 6.50 (bs, 1H), 4.37 (s, 1H), 4.20 (s, 1H), 3.75 (d, J = 11.0 Hz, 1H), 3.47 (d, J = 11.0 Hz, 1H), 2.04–2.00 (m, 1H), 1.88–1.84 (m, 1H); ^{13}C NMR (101 MHz, DMSO) δ 173.6, 167.7, 135.5, 130.4, 128.3, 127.6, 63.3, 52.6, 51.4, 40.9; HRMS (ESI) calcd for $C_{12}H_{13}N_2O_2^+$ $[M + H]^+$, 217.0977; found 217.0985.

4.5.2. (1*R*,4*R*)-5-Boc-2,5-diazabicyclo[2.2.1]heptan-3-one (8b). 70% yield. $[\alpha]_D^{25}$ = −10.4 (*c* 1.40, $CHCl_3$) [*ent*-**8b**, +10.2 (*c* 1.40, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 0.33H), 6.64 (s, 0.67H), 4.47 (s, 0.33H), 4.35 (s, 0.67H), 4.09 (s, 1H), 3.43 (d, J = 9.7 Hz, 1H), 3.24–3.18 (m, 1H), 1.90 (d, J = 9.7 Hz, 1H), 1.83–1.79 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 153.6, 79.6, 60.1, 52.9, 49.6, 40.0, 27.1; HRMS (ESI) calcd for $C_{10}H_{17}N_2O_3^+$ $[M + H]^+$, 213.1239; found 213.1240.

4.5.3. (1*R*,4*R*)-5-Benzyl-2,5-diazabicyclo[2.2.1]heptan-3-one (8c). 63% yield. $[\alpha]_D^{25}$ = −108 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.15 (m, 5H), 3.82 (s, 1H), 3.81 (d, J = 13.0 Hz, 1H), 3.44 (s, 1H), 3.42 (d, J = 13.0 Hz, 1H), 3.20 (dd, J = 9.5, 1.5 Hz, 1H), 2.01 (dd, J = 9.5, 1.5 Hz, 1H), 1.84–1.72 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 137.7, 127.6, 127.3, 126.1, 64.5, 57.4, 56.3, 54.1, 39.6; HRMS (ESI) calcd for $C_{12}H_{15}N_2O^+$ $[M + H]^+$, 203.1184; found 203.1181.

4.6. Synthesis of (1*R*,4*R*)-2-Boc-2,5-diazabicyclo[2.2.1] heptane (10)

4.6.1. (1*R*,4*R*)-2-Boc-5-benzyl-2,5-diazabicyclo[2.2.1] heptane (9).[23]. Compound **8a** (0.32 g, 1.48 mmol) was dissolved in anhydrous THF (3 ml). $LiAlH_4$ (0.28 g, 7.4 mmol) was added at 0 °C slowly. The reaction was stirred under reflux for 1 h. After cooled to room temperature, the excess $LiAlH_4$ was quenched by adding $Na_2SO_4 \cdot 10H_2O$. Boc_2O (0.41 ml, 1.78 mmol) and 2 N NaOH solution was added. THF was removed under reduced pressure. EtOAc and water were added to the residue and the mixture filtered. The separated organic layer was evaporated. The residue was purified by flash column chromatography (petroleum ether–EtOAc, 1/2) to afford the titled compound (0.30 g, 71%) as a colorless solid. R_f = 0.38 (petroleum ether–EtOAc, 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.21 (m, 4H), 7.19–7.15 (m, 1H), 4.31 (s, 0.5H), 4.17 (s, 0.5H), 3.70–3.65 (m, 2H), 3.56 (d, J = 10.3 Hz, 0.5H), 3.44 (d, J = 10.3 Hz, 0.5H), 3.43–3.35 (m, 1H), 3.12–3.07 (m, 1H), 2.85–2.81 (m, 0.5H), 2.80–2.76 (m, 0.5H), 2.67 (d, J = 9.6 Hz, 0.5H), 2.47 (d, J = 9.6 Hz, 0.5H), 1.80 (t, J = 8.8 Hz, 1H), 1.64 (d, J = 9.5 Hz, 0.5H), 1.58 (d, J = 9.5 Hz, 0.5H), 1.41–1.38 (2s, 9H).

4.6.2. (1*R*,4*R*)-2-Boc-2,5-diazabicyclo[2.2.1]heptane (10).[23]. A solution of (1*R*,4*R*)-2-Boc-5-benzyl-2,5-diazabicyclo[2.2.1] heptane (0.23 g, 0.8 mmol) in MeOH (3 ml) was stirred under H_2 (1 atm) in the presence of 10% Pd/C (0.1 g). The reaction mixture was filtered through celite, and the filtrate was concentrated. The residue was purified by flash column chromatography (EtOAc–MeOH, 1/1) to afford compound **10** (0.13 g, 81%) as a colorless solid. R_f = 0.15 (EtOAc–MeOH, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (s, 0.5H), 4.26 (s, 0.5H), 3.66 (bs, 1H), 3.35–3.25 (m, 1H), 3.17–3.09 (m, 1H), 3.05–2.88 (m, 2H), 2.28 (s, 1H), 1.74–1.58 (m, 2H), 1.42–1.36 (2s, 9H).

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