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A facile approach to *trans*-4,5-pyrrolidine lactam and application in the synthesis of nemonapride and streptopyrrolidine

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ABSTRACT

An efficient approach to *trans*-4-hydroxylpyrrolidine lactams **1** starting from amino acid is described. The utility of this method has been demonstrated in the synthesis of antipsychotic nemonapride **3** and antiangiogenic streptopyrrolidine **4**. Compared four synthetic stereoisomers of natural streptopyrrolidine **4** in term of spectroscopic and physical data, the absolute structure of the natural product was proposed as (4*S*,5*S*)-configuration.

1. Introduction

Functionalized 5-substituted pyrrolidine lactams **1** and pyrrolidines **2** (see Fig. 1) are common structural motif found in a wide variety of biologically active natural products and pharmaceuticals. As a prime instance, the racemic form of nemonapride (formerly called emonapride) **3** has been used as a dopamine receptor antagonist since 1991.[1,2] Because of its high efficacy and intriguing structure, the synthesis of nemonapride **3** in optically pure form has attracted lots of attention, and several synthetic approaches have been reported recently.[3] From the practical point of view, the most straightforward way is the asymmetric construction of optically active 2-amino or 2-hydroxyl pyrrolidine unit **2**. The pyrrolidine **2** could be derived from pyrrolidinone **1**, however, the transformation is strongly limited since the control of the desired stereochemistry of the substituents on the heterocycle is a challenge.[4]

In past decades, tremendous efforts have been devoted to the development of stereospecific preparation of *trans* or *cis*-4-hydroxyl-5-substituted pyrrolidine lactams, and a number of powerful approaches have been reported.[3a,e,5,6] A common strategy for the synthesis of optically pure *cis*-**1** was the stereoselective reduction of tetramic acid derivatives,[5a,b,d,7] while *trans*-**1** was obtained from pyrrodinone by reductive alkylation[6] or nucleophilic substitution,[8] which usually required multiple steps, and led to an unsatisfactory overall yield. Only few direct methods for the preparation of *trans*-**1** have appeared, which gave moderate to high enantioselectivities. It is noted that so far either oxidative

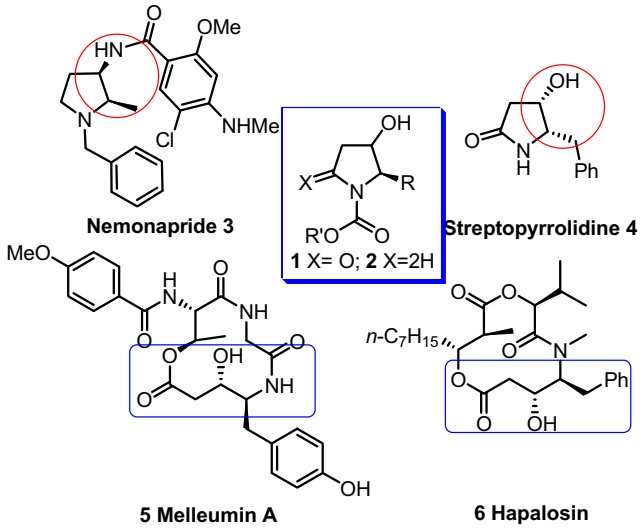

Fig. 1. The structure of several bioactive molecules.

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cyclization[9d] of primary alcohol[9a–c] or the condensation of carboxylic acid with amide in the presence of Bop-Cl[10] appears to be convenient way.

In continuation of our interests in pursuing the building blocks based methods for the synthesis of piperidine alkaloids, depsipeptides, and ceramides,[11] we decided to develop a novel approach for the asymmetric synthesis of 2-substituted 3-hydroxy piperidine alkaloids and their analogues. Herein we report a facile method for the preparation of *trans*-4-hydroxyl-5-substituted pyrrolidine lactam **1** starting from amino acid, and are used in the asymmetric synthesis of nemonapride **3** and all isomers of natural streptopyrrolidine **4**. Moreover, the possible configuration of the natural streptopyrrolidine **4** was proposed by comparing their spectroscopic and physical data with the natural product **4** (Fig. 2). The advantages of this methodology cover: (1) a facile method for preparation of building blocks possessing the skeleton of *trans*-pyrrolidine lactam, (2) high tolerance of functional groups in the substrates, (3) the traditional conversion of terminal olefins to alcohols is replaced by using Ruthenium/$NaIO_4$ oxidative cyclization, (4) all the materials are derived from inexpensive reagents.

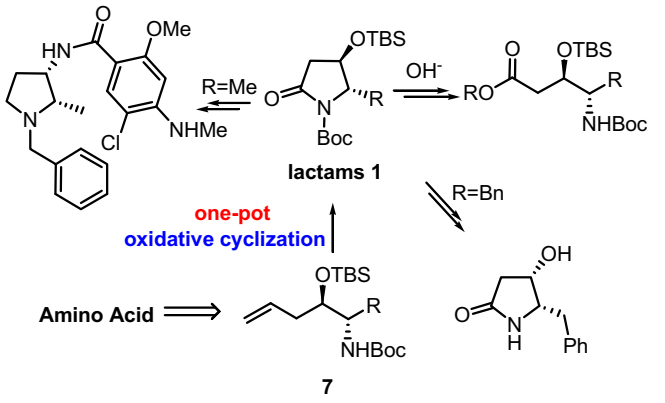
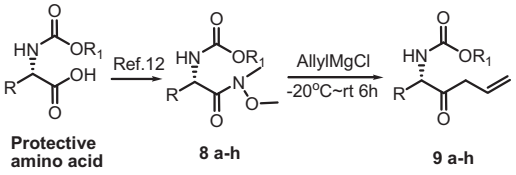


Fig. 2. Multi-purpose building block.

2. Results and discussion

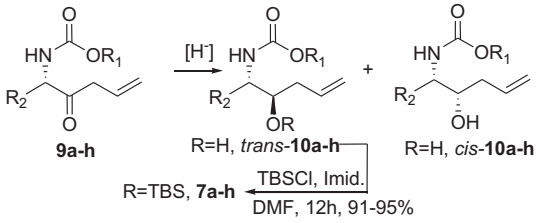
As shown in Fig. 2, lactam **1** is the key intermediate for the synthesis of nemonapride **3** and streptopyrrolidine **4**. Thus, a reliable method for the preparation of protected (*R*,*S*)-amino alcohols **7** is pre-required. To develop a general method to prepare protected alcohols **7**, diastereoselective reduction of α-aminoketones was first examined. A series of commercialized protected amino acids were converted into Weinreb amides **8a**–**h** in excellent yields according to known method.[12] Amides **8a**–**h** could be used in next step without further purification. Then, treated with allylmagnesium bromide, **8a**–**h** was converted to α-aminoketones **9a**–**h** in good yields (Scheme 1).



Scheme 1. Preparation of α-aminoketones **9a**–**h**.

Next, a survey of diastereoselective reduction of ketones was carried out. Treatment of α-aminoketone **9a** with 2.0 equiv of $NaBH_4$ in EtOH at room temperature gave a mixture of *trans*-**10a** and *cis*-**10a** with low diastereoselectivity in 82% combined yield (Table 1, entry 1). When the reaction was performed at −78 °C, the

Table 1
Highly diastereoselective reduction of α-aminoketones[a]



Entry[a]	R_1	R_2	*trans*-**10**	Y[b] %	*anti*/*syn* [c]
1 [d]	*t*-Bu	Me	**10a**	82	53:47
2 [e]	Bn	Me	**10b**	88	99:1
3 [e]	*t*-Bu	Me	**10a**	85	98:2
4 [f]	*t*-Bu	Me	**10a**	93	99:1
5 [g]	*t*-Bu	Me	**10a**	96	99:1
6 [g]	*t*-Bu	$CHMe_2$	**10c**	92	99:1
7 [g]	*t*-Bu	CH_2CHMe_2	**10d**	95	99:1
8 [g]	*t*-Bu	CH_2OTBS	**10e**	91	98:2
9 [g]	*t*-Bu	Cyclohexyl	**10f**	87	97:3
10 [g]	*t*-Bu	Bn	**10g**	94	98:2
11 [d]	*t*-Bu	H	**10h**	95	—

[a] The reaction was performed with 2.0 mmol of reductive reagents and 1 mmol of allyl ketones.
[b] Combined yield of *cis*/*trans* products.
[c] The diastereoselectivity was examined by HPLC or isolated products.
[d] $NaBH_4$, EtOH, rt, 1 h.
[e] $NaBH_4$, EtOH, −78 °C, 1 h.
[f] $LiEt_3BH$, THF, −78 °C, 0.5 h.
[g] Li(*t*-BuO)$_3$AlH, EtOH, −78 °C, 2 h.

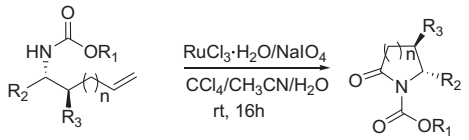
diastereoselectivity of the desired product increased significantly (Table 1, entries 2–3). When $LiEt_3BH$ was used as a reducing agent,[13] *trans*-**10a** was obtained in 99:1 dr (Table 1, entry 4). Li(*t*-BuO)$_3$AlH was also examined and the result showed that *trans*-**10a** was smoothly generated with excellent diastereoselectivity and in 96% yield (Table 1, entry 5). Accordingly, under the similar conditions, compounds **9c**–**g** were smoothly converted to secondary alcohols **10c**–**g** with excellent diastereoselectivities and in good yields (Table 1, entries 6–10). Subsequently, protection (TBSCl, imidazole) of secondary alcohols **10a**–**h** afforded protected compounds **7a**–**h** in high yields.

To explore an efficient method for the synthesis of *trans*-4-hydroxyl-5-substituted pyrrolidine lactam **1**, terminal alkene **7a** was treated with $NaIO_4$ in the presence of a catalytic amount of $RuCl_3 \cdot xH_2O$. Gratifyingly, the main product **1a** was generated in 'one-pot' with an excellent yield (Table 2, entry 1).

It is noteworthy that the uncylized free acid was not observed for the reaction mixture. Encouraged by the 'one-pot' oxidative cyclization, terminal alkenes **7b**, **7g**, and **7i** bearing with phenyl group were subjected to the oxidative cyclization to generate **1b**, **1g**, and **1i** in moderate yields, indicating that the phenyl group was unaffected under this oxidation condition (Table 2, entries 2, 7, 8, and 10). As summarized in Table 2, various substituted terminal alkenes bearing a range of R substituents were examined in the oxidative cyclization. In most cases, the 'one-pot' reaction proceeded smoothly with excellent yields (entries 1–11). Reactions of terminal alkenes **7k** and **7l** under the same conditions were also examined. The results indicated that the 'one-pot' oxidative cyclization could not occur for the formation of four and six-membered lactams (Table 2, entries 12 and 13).

With lactam **1a** in hand, we turned our attention to synthesize nemonapride **3**. Treatment of compound **1a** with TFA in DCM at 0 °C for 6 h and subsequent protection with BnBr gave the amide **11** in 65% overall yield (Scheme 2). Removal of protective group ($SOCl_2$/MeOH) and subsequent reduction of amide **11** with $BH_3 \cdot SMe_2$ gave amine **12** in 84% yield. Treatment of compound **12** with MsCl in the

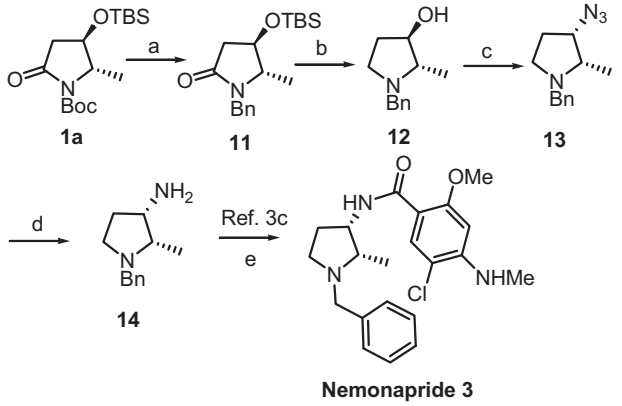
Table 2
Ruthenium-catalyzed 'one-pot' oxidative cyclization of **7a**–**l**



7a-l (**7a**~**j**, n=1; **7k**, n=0; **7l**, n=2) **1a-l**

Entry [a]	R_1	R_2	R_3	**1a**–**l**	Yield [b] %
1	*t*-Bu	Me	OTBS	**1a**	82
2	Bn	Me	OTBS	**1b**	71
3	*t*-Bu	$CHMe_2$	OTBS	**1c**	78
4	*t*-Bu	CH_2CHMe_2	OTBS	**1d**	81
5	*t*-Bu	CH_2OTBS	OTBS	**1e**	76
6	*t*-Bu	Cyclohexyl	OTBS	**1f**	69
7	*t*-Bu	Bn	OTBS	5*S*-**1g**	72
8	*t*-Bu	Bn	OTBS	5*R*-**1g**	68
9	*t*-Bu	H	OTBS	**1h**	75
10	Bn	H	H	**1i**	64
11	*t*-Bu	H	H	**1j**	77
12	*t*-Bu	Me	OTBS	**1k**	0
13	*t*-Bu	Me	OTBS	**1l**	0

[a] Compounds **7a**–**l** (2 mmol) were treated with 8.0 mmol $NaIO_4$ and 5% mmol $RuCl_3 \cdot H_2O$ in $CH_3CN/CCl_4/H_2O$ (v/v/v=2:2:1) at room temperature for 16 h.
[b] Isolated yields.

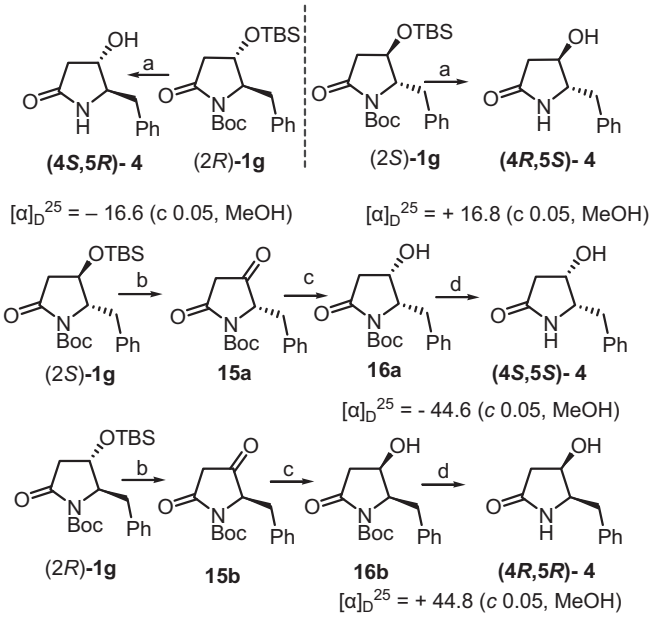


Scheme 2. Synthesis of nemonapride **3**. Reagents and conditions: a. (i) TFA, DCM, 0 °C ~rt, 4 h; (ii) NaH, DMF, BnBr, 0 °C ~rt, 2.5 h, 65%, two steps; b. (i) $SOCl_2$, MeOH, 0 °C ~rt, 2 h; (ii) $BH_3 \cdot SMe_2$, THF, 0 °C ~rt, 20 h, 84%, two steps; c. (i) DMAP, MsCl, TEA, DCM, 0 °C ~rt, 3 h; (ii) NaN_3, DMF, 80 °C, 36 h, 68%, two steps; d. Pd on $PbCO_3$/C, MeOH, H_2, 5 h, quantitative yield; e. TEA, ClCOOEt, 5-chloro-2-methoxy-4-(methylamino)benzoic acid, DCM, 0 °C, 2 h, 72%.

presence of triethylamine and followed by substitution with NaN_3 in DMF smoothly generated azides **13** in 68% yield, which was subjected to hydrogenation (Pd on $PbCO_3$/C, H_2, MeOH) to afford cyclic diamine **14** in quantitative yield. Finally, by the known method[3c] the condensation of amine **14** with 5-chloro-2-methoxy-4-(methylamino)benzoic acid in the presence of $ClCO_2Et$ afforded nemonapride **3** {$[\alpha]_D^{25}$ +2.5 (*c* 0.6, $CHCl_3$); lit.[3c] $[\alpha]_D^{25}$ +2.3 (*c* 0.6, $CHCl_3$); lit.[3b] $[\alpha]_D^{25}$ +4 (*c* 0.6, $CHCl_3$)} in 72% yield. The spectroscopic and physical data of the synthetic nemonapride **3** were identical with the reported data.[3b,c,d]

To extend the utility of the 'one-pot' oxidative cyclization, the synthesis of streptopyrrolidine **4** was also performed. Streptopyrrolidine **4** was isolated from the fermentation broth of a marine *Streptomyces* sp. KORDI-3973 from the deep sea sediment,[14] which could significantly block the capillary tube formation of the cells at the same potency as the known angiogenesis inhibitor SU11248.[14] The absolute configuration of streptopyrrolidine **4** was unsolved due to the significant difference in the specific rotation between natural product and the synthetic samples.[5b,g]

To elucidate the absolute configuration of **4**, it is desirable to synthesize all the possible isomers and compare them with the natural product in term of spectroscopic and physical data. Treatment of lactam (2*S*)-**1g** with $SOCl_2$ in MeOH at 0 °C afforded (4*R*,5*S*)-streptopyrrolidine **4** {$[\alpha]_D^{25}$ +16.8 (*c* 0.05, MeOH)}in 81% yield (Scheme 3). Similarly, (4*S*,5*R*)-streptopyrrolidine **4** {$[\alpha]_D^{25}$ −16.6 (*c* 0.05, MeOH)} was obtained from (2*R*)-**1g**. Deprotection of lactam (2*S*)-**1g** with TBAF and subsequent oxidation with DMSO/$(COCl)_2$ at −78 °C gave compound **15a** in 94% overall yield. Next, compound **15a** was treated with $NaBH_4$ in MeOH to afford **16a** in 96% yield. Finally, treatment of compound **16a** with $SOCl_2$ in MeOH generated the (4*S*,5*S*)-streptopyrrolidine **4** {$[\alpha]_D^{25}$ −44.6 (*c* 0.05, MeOH); lit.[14] $[\alpha]_D^{25}$ −12 (*c* 0.05, MeOH); lit.[5b,g] $[\alpha]_D^{25}$ −44 (*c* 1.0, MeOH)} in 61% yield (three steps). Accordingly, (4*R*,5*R*)-streptopyrrolidine **4** {$[\alpha]_D^{25}$ +44.8 (*c* 0.05, MeOH)} was obtained from (2*R*)-**1g**. The data of the specific rotations show that the two pairs of the synthetic enantiomers are consistent with each other. Then the spectral and specific rotation of the four synthetic isomers were compared with the data of natural product, exhibiting that stereochemistry of streptopyrrolidine was cis. As for the absolute configuration, we think the natural streptopyrrolidine maybe possess (*S*,*S*)-stereochemistry due to having the same negative sign of rotation and the same physical data of NMR as the synthetic (4*S*,5*S*)-**4**, although there is a significant difference in specific rotation value between natural **4** and our synthetic sample. Most possibly, the minute amount of isolated natural streptopyrrolidine **4** prevent a accurate measurement of rotation.



Scheme 3. Synthesis and determination of streptopyrrolidine **4**. Reagents and conditions: a. $SOCl_2$, MeOH, 0 °C ~rt, 2 h, 81%; b. (i) TBAF, THF, rt, 3 h; (ii) DMSO, $(COCl)_2$, TEA, DCM, −78 °C ~rt, 94%; c. MeOH, $NaBH_4$, 0 °C ~rt, 2 h, 96%; d. $SOCl_2$, MeOH, 0 °C ~rt, 2 h, 87%.

3. Conclusions

In summary, an efficient 'one-pot' approach for the preparation of *trans*-4-hydroxylpyrrolidine lactams **1** starting from amino acid has been developed. Using this method, nemonapride **3** and streptopyrrolidine **4** have been synthesized. Comparing four synthetic stereoisomers **4** with natural product for the physical data including specific rotation, the absolute structure of **4** was proposed as (4*S*,5*S*). Further exploration and application in the total synthesis of other bioactive natural products and their analogues are now in progress in our laboratory.

4. Experimental section

4.1. General

THF was distilled from sodium/benzophenone. All reactions were monitored by thin layer chromatography (TLC) on glass plates coated with silica gel with fluorescent indicator (Huanghai HSGF254). Flash chromatography was performed on silica gel (Huanghai 300–400) with petroleum/EtOAc as eluent. Melting points were recorded on a Mel-Temp apparatus and uncorrected. Optical rotations were measured on a JASCO P-1030 polarimeter with a sodium lamp. Mass spectra were recorded on an HP-5989 instrument and HRMS (MALDI/DHB) were measured on an LCMS-IT-TOF (Shimazu Corporation) apparatus. IR spectra were recorded using KBr disks or film, on a Fourier Transform Infrared Spectrometer, Type: Avatar 360 E.S.P, manufactured by Thermo Nicolet Corporation, USA. NMR spectra were recorded on a Varian or a Bruker spectrometer (300 or 400 MHz), and chemical shifts are reported in δ (ppm) referenced to an internal TMS standard for ^{1}H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR.

4.2. General procedure for the preparation of 9a–h

Compound **8a–h** (22.1 mmol) in dry THF (90 mL) was treated with a solution of allylmagnesium chloride (44.2 mmol, 1.7 mol in THF) at −20 °C under argon atmosphere and was stirred for 5 h at −20 to 0 °C. The reaction was quenched with saturated NH_4Cl aqueous solution and diluted with EtOAc (150 mL), and the mixture was separated. The aqueous solution was extracted with EtOAc for two times, and the combined organic layers were washed with brine for three times. Dried over anhydrous Na_2SO_4, filtered, and concentrated, the residue was purified by chromatography on silica gel to give **9a–h**.

*4.2.1. (S)-tert-Butyl 3-oxohex-5-en-2-ylcarbamate (**9a**).* White solid, mp 44–45 °C; (*S*)-**9a**: $[\alpha]_D^{25}$ +54.4 (*c* 1, $CHCl_3$); (*R*)-**9a**: $[\alpha]_D^{25}$ −53.8 (*c* 1, $CHCl_3$); IR (film): ν_{max} 3389, 2975, 1728, 1697, 1520, 1366, 1285, 1177 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.97–5.86 (m, 1H), 5.27–5.20 (m, 1H), 5.19–5.14 (dd, *J*=1.7, 17.2 Hz, 1H), 4.38–4.35 (m, 1H), 3.34–3.32 (dd, *J*=6.80, 17.0 Hz, 1H), 3.24–3.22 (dd, *J*=6.4, 17.0 Hz, 1H), 1.44 (s, 9H), 1.33 (d, *J*=6.80 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=207.3, 155.1, 129.8, 119.3, 79.8, 54.8, 44.0, 28.3, 17.7 ppm; MS (ESI): 236 (M+Na^+); HRMS (ESI) calcd for ($C_{11}H_{19}NO_3$+Na^+): 236.1263, found: 236.1253.

*4.2.2. (S)-Benzyl 3-oxohex-5-en-2-ylcarbamate (**9b**).* Colorless oil; $[\alpha]_D^{25}$ −59.29 (*c* 0.61, $CHCl_3$); IR (film): ν_{max} 3334, 2917, 1714, 1525, 1246, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.26 (m, 5H), 5.95–5.85 (m, 1H), 5.58–5.56 (m, 1H), 5.28–5.06 (m, 2H), 5.10 (s, 2H), 4.47–4.40 (m, 1H), 3.34–3.21 (m, 2H), 1.36 (d, *J*=6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=207.0, 155.8, 136.5, 129.8, 128.5, 128.1, 119.3, 66.8, 55.2, 43.8, 17.4 ppm; MS (ESI): 270 (M+Na^+); HRMS (ESI) calcd for ($C_{14}H_{17}NO_3$+Na^+): 270.1106, found: 270.1097.

*4.2.3. (S)-tert-Butyl 2-methyl-4-oxohept-6-en-3-ylcarbamate (**9c**).* Colorless oil; $[\alpha]_D^{25}$ +84.21 (*c* 1, $CHCl_3$); IR (film): ν_{max} 3346, 2968, 2932, 1712, 1504, 1392, 1367, 1245, 1172, 1012 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.94–5.84 (m, 1H), 5.19–5.10 (m, 3H), 4.30–4.27 (m, 1H), 3.30–3.10 (m, 2H), 2.20–2.10 (m, 1H), 1.40 (s, 9H), 0.98 (d, *J*=6.8 Hz, 3H), 0.76 (d, *J*=6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=207.3, 155.9, 129.9, 119.0, 79.5, 63.7, 45.3, 28.3, 16.7 ppm; MS (ESI): 264 (M+Na^+); HRMS (ESI) calcd for ($C_{13}H_{23}NO_3$+Na^+): 264.1576, found: 264.1570.

*4.2.4. (S)-tert-Butyl 2-methyl-5-oxooct-7-en-4-ylcarbamate (**9d**).* Colorless oil; $[\alpha]_D^{25}$ +27.53 (*c* 1, $CHCl_3$); IR (film): ν_{max} 3301, 2981, 2960, 1723, 1681, 1548, 1367, 1283, 1177, 1041 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90–5.80 (m, 1H), 5.13–5.06 (m, 3H), 4.31–4.26 (m, 1H), 3.21 (d, *J*=6.80 Hz, 2H), 1.68–1.61 (m, 1H), 1.52–1.40 (m, 1H), 1.40 (s, 9H), 1.33–1.25 (m, 1H), 0.89 (d, *J*=6.4 Hz, 3H), 0.86 (d, *J*=6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=208.0, 155.6, 130.1, 119.0, 79.6, 57.5, 44.4, 40.4, 28.3, 24.8, 23.2, 21.6 ppm; MS (ESI): 264 (M+Na^+); HRMS (ESI) calcd for ($C_{14}H_{25}NO_3$+Na^+): 278.1732, found: 278.1720.

*4.2.5. (S)-tert-Butyl 1-(tert-butyldimethylsilyloxy)-3-oxohex-5-en-2-ylcarbamate (**9e**).* Colorless oil; $[\alpha]_D^{25}$ −57.55 (*c* 2.8, $CHCl_3$); IR (film): ν_{max} 3435, 2956, 2930, 1713, 1494, 1473, 1367, 1255, 1172, 1112 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.96–5.85 (m, 1H), 5.45 (d, *J*=6.8 Hz, 1H), 5.18 (dd, *J*=0.8, 10.4 Hz, 1H), 5.12 (dd, *J*=1.2, 18.4 Hz, 1H), 4.32–4.30 (m, 1H), 4.06 (dd, *J*=2.8, 10.4 Hz, 1H), 3.80 (dd, *J*=4.0, 10.4 Hz, 1H), 3.36 (dd, *J*=6.8, 17.6 Hz, 1H), 3.27 (dd, *J*=6.8, 17.2 Hz, 1H), 1.44 (s, 9H), 0.85 (s, 9H), 0.02 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=205.8, 155.3, 129.9, 119.0, 79.8, 63.3, 60.9, 44.9, 28.3, 25.7, 18.1, −5.51, −5.63 ppm; MS (ESI): 264 (M+Na^+); HRMS (ESI) calcd for ($C_{17}H_{33}NO_4Si$+Na^+): 366.2076, found: 366.2061.

*4.2.6. (S)-tert-Butyl 1-cyclohexyl-2-oxopent-4-enylcarbamate (**9f**).* White solid, mp 79–80 °C; $[\alpha]_D^{25}$ +93.63 (*c* 1, $CHCl_3$); IR (film): ν_{max} 3289, 2976, 2929, 1717, 1659, 1452, 1366, 1251, 1164 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.94–5.87 (m, 1H), 5.27–5.25 (m, 1H), 5.21–5.13 (m, 2H), 4.29–4.27 (m, 1H), 3.27–3.24 (m, 2H), 1.82–1.62 (m, 4H), 1.44 (s, 9H) 1.15–0.92 (m, 7H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.5, 199.7, 155.9, 145.4, 129.9, 125.8, 119.0, 64.0, 45.7, 40.7, 40.0, 30.2, 28.3, 27.2, 26.1 ppm; MS (ESI): 304 (M+Na^+); HRMS (ESI) calcd for ($C_{16}H_{27}NO_3$+Na^+): 304.1889, found: 304.1892.

*4.2.7. (S or R)-tert-Butyl 3-oxo-1-phenylhex-5-en-2-ylcarbamate (**9g**).* White solid, mp 89–90 °C; (*S*)-**9g**: $[\alpha]_D^{25}$ +61.2 (*c* 1.1, $CHCl_3$); (*R*)-**9g**: $[\alpha]_D^{25}$ −60.8 (*c* 1.05, $CHCl_3$); IR (film): ν_{max} 3358, 2982, 2935, 1723, 1688, 1520, 1372, 1313, 1170 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.13 (m, 5H), 5.90–5.80 (m, 1H), 5.18–5.03 (m, 3H), 4.58–4.56 (m, 1H), 3.21–3.12 (m, 2H), 3.06–3.03 (m, 1H), 2.98–2.93 (m, 1H), 1.46 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=207.4, 155.1, 136.2, 129.8, 129.3, 128.7, 127.0, 119.2, 79.9, 59.8, 45.5, 37.7, 28.3 ppm; MS (ESI): 236 (M+Na^+); HRMS (ESI) calcd for ($C_{11}H_{19}NO_3$+Na^+): 236.1263, found: 236.1253.

*4.2.8. tert-Butyl 2-oxopent-4-enylcarbamate (**9h**).* Colorless oil; IR (film): ν_{max} 3361, 2979, 2934, 1705, 1506, 1368, 1251, 1161, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.96–5.86 (m, 1H), 5.24–5.17 (m, 3H), 4.07–4.06 (m, 2H), 3.22–2.19 (m, 2H), 1.45 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.6, 155.6, 129.3, 119.8, 79.9, 49.9, 45.0, 28.3 ppm; MS (ESI): 222 (M+Na^+); HRMS (ESI) calcd for ($C_{10}H_{17}NO_3$+Na^+): 222.1106, found: 222.1112.

4.3. General procedure for the preparation of *trans*-10a–h

Compound **9a–h** (1 mmol) in absolute EtOH (30 mL) was treated with Li(*t*-BuO)$_3$AlH (2 mmol) at −78 °C under argon atmosphere for 2 h. The reaction was quenched with 1 M $KHSO_4$ aqueous solution and concentrated to give yellow solid. The crude solid was dissolved in EtOAc (50 mL) and 1 M HCl aqueous solution. The mixture was separated, and the aqueous solution was extracted with EtOAc for two times. The combined organic layers were washed with brine for three times. Dried over anhydrous Na_2SO_4, filtered, and concentrated, the residue was purified by chromatography on silica gel to give **10a–h**.

*4.3.1. tert-Butyl (2S,3R)-3-hydroxyhex-5-en-2-ylcarbamate (**10a**).* White solid, mp 54–55 °C; $[\alpha]_D^{25}$ −22.67 (*c* 1.07, $CHCl_3$); IR

(film): ν_{max} 3359, 2918, 1682, 1532, 1368, 1327, 1290, 1272, 1177, 1040, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.89–5.79 (m, 1H), 5.15 (d, J=10.0 Hz, 1H), 5.12 (s, 1H), 4.78 (br s, 1H), 3.74–3.65 (m, 1H), 2.31–2.12 (m, 3H), 1.45 (s, 9H), 1.11 (d, J=6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=156, 134.7, 118.0, 79.5, 73.3, 50.3, 38.3, 28.4, 14.6 ppm; MS (ESI): 238 ($M+Na^+$); HRMS (ESI) calcd for ($C_{11}H_{21}NO_3+Na^+$): 238.1419, found: 238.1407.

*4.3.2. Benzyl (2S,3R)-3-hydroxyhex-5-en-2-ylcarbamate (**10b**).* White solid, mp 70–71 °C; $[\alpha]_D^{25}$ −17.00 (c 1.1, $CHCl_3$); IR (film): ν_{max} 3316, 2973, 2940, 1686, 1541, 1289, 1267, 1237, 1083, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.25 (m, 5H), 5.85–5.75 (m, 1H), 5.20 (br s, 1H), 5.14–5.08 (m, 4H), 3.75–3.71 (m, 2H), 2.41 (br s, 1H), 2.24–2.11 (m, 2H), 1.11 (d, J=8.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 136.5, 134.5, 128.5, 128.1, 118.1, 73.1, 66.8, 50.7, 38.4, 14.3 ppm; MS (ESI): 272 ($M+Na^+$); HRMS (ESI) calcd for ($C_{14}H_{19}NO_3+Na^+$): 272.1263, found: 272.1269.

*4.3.3. tert-Butyl (3S,4R)-4-hydroxy-2-methylhept-6-en-3-ylcarbamate (**10c**).* White solid, mp 81–82 °C; $[\alpha]_D^{25}$ 0.47 (c 1.0, $CHCl_3$); IR (film): ν_{max} 3376, 2979, 2936, 1686, 1522, 1367, 1310, 1253, 1173, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.92–5.81 (m, 1H), 5.15–5.10 (m, 2H), 4.49–4.47 (m, 1H), 3.60–3.46 (m, 2H), 2.34–2.32 (m, 2H), 2.18–2.10 (m, 1H), 2.03–1.98 (m, 1H), 1.42 (s, 9H), 0.92 (d, J=6.8 Hz, 3H), 0.87 (d, J=6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 135.1, 118.1, 79.4, 71.5, 59.5, 38.1, 28.4, 28.1, 20.3, 17.1 ppm; MS (ESI): 266 ($M+Na^+$); HRMS (ESI) calcd for ($C_{13}H_{25}NO_3+Na^+$): 266.1732, found: 266.1726.

*4.3.4. tert-Butyl (4S,5R)-5-hydroxy-2-methyloct-7-en-4-ylcarbamate (**10d**).* White solid, mp 85–86 °C; $[\alpha]_D^{25}$ −43.32 (c 1.1, $CHCl_3$); IR (film): ν_{max} 3359, 2982, 2953, 1682, 1531, 1367, 1349, 1278, 1174, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.88–5.83 (m, 1H), 5.15–5.10 (m, 2H), 4.68 (br s, 1H), 3.67 (br s, 2H), 2.70 (br s, 1H), 2.22–2.15 (m, 2H), 1.67–1.60 (m, 1H), 1.44 (s, 9H), 1.31–1.22 (m, 2H), 0.95–0.79 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 135.0, 117.7, 79.4, 73.9, 53.1, 38.4, 38.0, 28.4, 24.8, 23.7, 21.6 ppm; MS (ESI): 280 ($M+Na^+$); HRMS (ESI) calcd for ($C_{14}H_{27}NO_3+Na^+$): 280.1889, found: 280.1876.

*4.3.5. tert-Butyl (2S,3R)-1-(tert-butyldimethylsilyloxy)-3-hydroxyhex-5-en-2-ylcarbamate (**10e**).* Colorless oil; $[\alpha]_D^{25}$ −28.14 (c 1.0, $CHCl_3$); IR (film): ν_{max} 3446, 2955, 2929, 2857, 1698, 1504, 1391, 1366, 1254, 1173, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.89–5.78 (m, 1H), 5.20–5.01 (m, 3H), 3.96–3.93 (m, 1H), 3.78–3.66 (m, 2H), 3.53 (br s, 1H), 3.03–3.01 (m, 1H), 2.34–2.30 (m, 2H), 1.42 (s, 9H), 0.88 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 134.6, 117.7, 79.4, 72.7, 63.2, 53.8, 39.3, 28.4, 25.8, 18.1, −5.6 ppm; MS (ESI): 368 ($M+Na^+$); HRMS (ESI) calcd for ($C_{17}H_{35}NO_4Si+Na^+$): 368.2233, found: 368.2226.

*4.3.6. tert-Butyl (1S,2R)-1-cyclohexyl-2-hydroxypent-4-enylcarbamate (**10f**).* Colorless oil; $[\alpha]_D^{25}$ −2.45 (c 1.0, $CHCl_3$); IR (film): ν_{max} 3368, 2981, 2926, 2853, 1685, 1527, 1447, 1367, 1302, 1245, 1173, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.95–5.84 (m, 1H), 5.17–5.13 (m, 2H), 4.53–4.51 (m, 1H), 3.68–3.66 (m, 1H), 3.52–3.47 (m, 1H), 2.44–2.43 (m, 1H), 2.32–2.30 (m, 1H), 2.17–2.11 (m, 1H), 1.80–1.62 (m, 6H), 1.45 (s, 9H), 1.29–0.90 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 135.3, 117.7, 79.3, 71.1, 59.3, 38.3, 37.8, 30.5, 28.4, 27.4, 26.3, 26.2, 26.1 ppm; MS (ESI): 306 ($M+Na^+$); HRMS (ESI) calcd for ($C_{16}H_{29}NO_3+Na^+$): 306.2045, found: 306.2038.

*4.3.7. tert-Butyl (2S,3R) and (2R,3S)-3-hydroxy-1-phenylhex-5-en-2-ylcarbamate (**10g**).* White solid, mp 99–100 °C; (2*S*,3*R*)-**10g** $[\alpha]_D^{25}$ −19.86 (c 1.04, $CHCl_3$); (2*R*,3*S*)-**10g** $[\alpha]_D^{25}$ +22.39 (c 1.02, $CHCl_3$); IR (film): ν_{max} 3361, 2979, 2931, 1684, 1527, 1316, 1171 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.19 (m, 5H), 5.94–5.84 (m, 1H), 5.21 (d, J=8.0 Hz, 1H), 5.18 (s, 1H), 4.65 (br s, 1H), 3.86 (br s, 1H), 3.75 (br s, 1H), 2.98 (dd, J=4.4, 14.0 Hz, 1H), 2.85–2.72 (m, 2H), 2.42–2.25 (m, 2H), 1.34 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.0, 138.2, 134.7, 129.4, 128.4, 126.3, 118.3, 79.6, 72.7, 55.9, 38.4, 28.3 ppm; MS (ESI): 314 ($M+Na^+$); HRMS (ESI) calcd for ($C_{17}H_{25}NO_3+Na^+$): 314.1732, found: 314.1727.

*4.3.8. tert-Butyl 2-hydroxypent-4-enylcarbamate (**10h**).* Colorless oil; IR (film): ν_{max} 3361, 2978, 2931, 1694, 1522, 1367, 1252, 1172 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 5.87–5.77 (m, 1H), 5.16 (d, J=6.0 Hz, 1H), 5.12 (s, 1H), 5.00 (br s, 1H), 3.78–3.72 (m, 1H), 3.36–3.31 (m, 1H), 3.08–3.01 (m, 1H), 2.31–2.17 (m, 2H), 1.45 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.8, 134.1, 118.2, 79.6, 70.5, 46.0, 39.3, 28.4 ppm; MS (ESI): 224 ($M+Na^+$); HRMS (ESI) calcd for ($C_{10}H_{19}NO_3+Na^+$): 224.1263, found: 224.1254.

4.4. General procedure for the preparation of 7a–h

To a mixture of **10a–h** (1 mmol), DMAP (0.1 mmol), and imidazole (2 mmol) in dry DMF (10 mL) was dropped a solution of TBSCl in DMF at 0 °C, then the mixture was allowed to warm to room temperature and stirred for overnight. The reaction was quenched with water and diluted with EtOAc, and the mixture was separated. The aqueous solution was extracted with EtOAc for two times, and the combined organic layers were washed with brine for three times. Dried over anhydrous Na_2SO_4, filtered, and concentrated, the residue was purified by chromatography on silica gel to give **7a–h**.

*4.4.1. tert-Butyl (2S,3R)-3-(tert-butyldimethylsilyloxy)hex-5-en-2-ylcarbamate (**7a**).* Colorless oil; $[\alpha]_D^{25}$ −15.30 (c 0.95, $CHCl_3$); IR (film): ν_{max} 2955, 2930, 2857, 1719, 1496, 1365, 1253, 1173, 1103, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.82–5.71 (m, 1H), 5,09 (d, J=7.6 Hz, 1H), 5.03 (s, 1H), 4.56 (br s, 1H), 3.88–3.79 (m, 1H), 3.75–3.64 (m, 1H), 2.27–2.11 (m, 2H), 1.43 (s, 9H), 1.04 (d, J=6.80 Hz, 3H), 0.9 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.0, 134.4, 117.3, 79.0, 73.8, 49.2, 39.4, 28.5, 28.8, 18.1, 13.3, −4.2, −4.7 ppm; MS (ESI): 352 ($M+Na^+$); HRMS (ESI) calcd for ($C_{17}H_{35}NO_3Si+Na^+$): 352.2284, found: 352.2281.

*4.4.2. Benzyl (2S,3R)-3-(tert-butyldimethylsilyloxy)hex-5-en-2-ylcarbamate (**7b**).* Colorless oil; $[\alpha]_D^{25}$ +6.11 (c 0.89, $CHCl_3$); IR (film): ν_{max} 3345, 2954, 2929, 2857, 1724, 1504, 1471, 1253, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.26 (m, 5H), 5.82–5.71 (m, 1H), 5.11–5.06 (m, 4H), 4.84–4.82 (m, 1H), 3.84–3.56 (m, 2H), 2.31–2.14 (m, 2H), 1.08 (d, J=6.4 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 136.8, 134.2, 128.5, 128.2, 128.1, 117.8, 73.8, 66.6, 49.9, 39.3, 25.9, 18.1, 13.3, −4.2, −4.7 ppm; MS (ESI): 352 ($M+Na^+$); HRMS (ESI) calcd for ($C_{20}H_{33}NO_3Si+Na^+$): 386.2127, found: 386.2130.

*4.4.3. tert-Butyl (3S,4R)-4-(tert-butyldimethylsilyloxy)-2-methylhept-6-en-3-ylcarbamate (**7c**).* Colorless oil; $[\alpha]_D^{25}$ −17.68 (c 1.14, $CHCl_3$); IR (film): ν_{max} 3367, 2959, 2930, 2857, 1703, 1498, 1390, 1365, 1255, 1174, 1079, 1004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.86–5.76 (m, 1H), 5.09–5.03 (m, 2H), 4.56–4.52 (m, 1H), 3.80–3.76 (m, 1H), 3.51–3.47 (m, 1H), 2.28–2.25 (m, 2H), 2.01–1.94 (m, 1H), 1.42 (s, 9H), 0.91–0.87 (m, 6H), 0.89 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8, 134.6, 117.3, 78.7, 73.6, 57.6, 38.8, 28.4, 27.4, 25.8, 20.9, 18.0, 17.4, −4.3, −4.8 ppm; MS (ESI): 352 ($M+Na^+$); HRMS (ESI) calcd for ($C_{19}H_{39}NO_3Si+Na^+$): 380.2597, found: 380.2607.

*4.4.4. tert-Butyl (4S,5R)-5-(tert-butyldimethylsilyloxy)-2-methyloct-7-en-4-ylcarbamate (**7d**).* Colorless oil; $[\alpha]_D^{25}$ −30.36 (c 1.0, $CHCl_3$);

IR (film): ν_{max} 3271, 2956, 2857, 1705, 1498, 1390, 1365, 1254, 1175, 1095, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.83–5.73 (m, 1H), 5.09–5.04 (m, 2H), 4.43–4.41 (m, 1H), 3.82 (br s, 1H), 3.63 (br s, 1H), 2.28–2.15 (m, 2H), 1.67–1.59 (m, 1H), 1.44 (s, 9H), 1.26 (m, 2H), 0.95–0.85 (m, 6H), 0.89 (s, 9H), 0.06–0.0 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4, 134.4, 117.2, 78.8, 74.3, 52.0, 39.1, 36.8, 28.4, 25.9, 24.6, 24.0, 21.6, 18.1, −4.3, −4.7 ppm; MS (ESI): 394 ($M+Na^+$); HRMS (ESI) calcd for ($C_{20}H_{41}NO_3Si+Na^+$): 394.2753, found: 394.2761.

*4.4.5. tert-Butyl (2S,3R)-1,3-bis(tert-butyldimethylsilyloxy)hex-5-en-2-ylcarbamate (**7e**).* Colorless oil; $[\alpha]_D^{25}$ +4.08 (*c* 1.60, $CHCl_3$); IR (film): ν_{max} 3455, 2956, 2929, 2857, 1722, 1496, 1472, 1390, 1365, 1255, 1174, 1097, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.93–5.83 (m, 1H), 5.11–5.07 (m, 2H), 4.67–4.65 (m, 1H), 3.91–3.90 (m, 1H), 3.77–3.67 (m, 3H), 2.38–2.25 (m, 2H), 1.45 (s, 9H), 0.92 (s, 9H), 0.91 (s, 9H), 0.08–0.07 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 134.6, 117.3, 78.9, 71.4, 61.3, 55.3, 38.5, 28.4, 25.9, 18.3, −4.3, −5.3 ppm; MS (ESI): 482 ($M+Na^+$); HRMS (ESI) calcd for ($C_{23}H_{49}NO_4Si_2+Na^+$): 482.3099, found: 482.3104.

*4.4.6. tert-Butyl (1S,2R)-2-(tert-butyldimethylsilyloxy)-1-cyclohexylpent-4-enylcarbamate (**7f**).* Colorless oil; $[\alpha]_D^{25}$ −21.82 (*c* 1.0, $CHCl_3$); IR (film): ν_{max} 3350, 2928, 2854, 1701, 1498, 1450, 1390, 1365, 1251, 1174, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.84–5.79 (m, 1H), 5.10–5.04 (m, 2H), 4.44–4.41 (m, 1H), 4.13–4.08 (m, 1H), 3.80–3.78 (m, 1H), 3.48–3.40 (m, 1H), 2.58–2.36 (m, 1H), 1.86–1.56 (m, 6H), 1.43 (s, 9H), 1.31–1.09 (m, 4H), 0.88 (s, 9H), 0.06–0.06 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 134.8, 131.3, 127.3, 117.3, 78.7, 74.1, 73.1, 59.3, 57.8, 31.0, 28.5, 27.6, 26.5, 26.4, 26.3, 25.8, 18.1, 17.7, −4.79, −5.07 ppm; MS (ESI): 420 ($M+Na^+$); HRMS (ESI) calcd for ($C_{22}H_{43}NO_3Si+Na^+$): 420.2910, found: 420.2922.

*4.4.7. tert-Butyl (2S,3R) or (2R,3S)-3-(tert-butyldimethylsilyloxy)-1-phenylhex-5-en-2-ylcarbamate (**7g**) (2S,3R)-**7g**.* Colorless oil; $[\alpha]_D^{25}$ −19.64 (*c* 0.87, $CHCl_3$); (2*R*,3*S*)-**7g** $[\alpha]_D^{25}$ +22.27 (*c* 1.03, $CHCl_3$); IR (film): ν_{max} 2956, 2928, 2857, 1704, 1496, 1365, 1253, 1172 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28–7.16 (m, 5H), 5.88–5.78 (m, 1H), 5.15 (d, *J*=9.6 Hz, 1H), 5.07 (s, 1H), 4.46 (br s, 1H), 3.93 (br s, 1H), 3.87 (br s, 1H), 2.96 (dd, *J*=4.4, 14.4 Hz, 1H), 2.63–2.57 (m, 1H), 2.37–2.26 (m, 2H), 1.31 (s, 9H), 0.93 (s, 9H), 0.07 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.2, 138.9, 134.3, 130.9, 129.2, 128.9, 128.3, 126.1, 117.5, 78.9, 65.5, 54.9, 39.2, 34.4, 29.7, 28.3, 18.1, −4.6, −4.9 ppm; MS (ESI): 406 ($M+H^+$); HRMS (ESI) calcd for ($C_{23}H_{39}NO_3Si+H^+$): 406.2777, found: 406.2789.

*4.4.8. tert-Butyl 2-(tert-butyldimethylsilyloxy)pent-4-enylcarbamate (**7h**).* Colorless oil; IR (film): ν_{max} 3358, 2979, 2934, 1705, 1506, 1456, 1368, 1250, 1154, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.84–5.74 (m, 1H), 5.08–5.04 (m, 2H), 4.73 (br s, 1H), 3.79–3.78 (m, 1H), 3.26–3.23 (m, 1H), 3.04–2.98 (m, 1H), 2.23–2.20 (m, 2H), 1.43 (s, 9H), 0.90 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 134.2, 117.5, 79.1, 71.0, 45.8, 39.8, 28.4, 25.8, 18.1, −4.5, −4.7 ppm; MS (ESI): 338 ($M+Na^+$); HRMS (ESI) calcd for ($C_{16}H_{33}NO_3Si+Na^+$): 338.2127, found: 338.2126.

4.5. General procedure for the preparation of 1a–l

To a solution of **7a**–**l** (2 mmol) was stirred in $CH_3CN/CCl_4/H_2O$ (v/v=2:2:1) at room temperature, the $NaIO_4$ (8 mmol) was added in one portion and stirred for 10 min. The $RuCl_3\cdot H_2O$ (catalytic amount, 5%) was added in portion. After being stirred for overnight, the reaction was diluted with Et_2O and stirred for 1 h. The mixture was filtered and separated. The aqueous layer was extracted with DCM for three times and the combined organic layers were washed with brine for three tomes. Dried over anhydrous Na_2SO_4, filtered, and concentrated, the residue was purified by chromatography on silica gel to give **1a**–**l**.

*4.5.1. (2S,3R)-tert-Butyl 3-(tert-butyldimethylsilyloxy)-2-methyl-5-oxopyrrolidine-1-carboxylate (**1a**).* Colorless oil; $[\alpha]_D^{25}$ +17.2 (*c* 1.09, $CHCl_3$); IR (film): ν_{max} 3010, 2956, 2937, 1777, 1377, 1359, 1292, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.02 (dd, *J*=6.4, 13.2 Hz, 1H), 3.95 (d, *J*=5.2 Hz, 1H), 2.77 (dd, *J*=5.6, 17.6 Hz, 1H), 2.33 (d, *J*=17.6 Hz, 1H), 1.54 (s, 9H), 1.25 (d, *J*=6.8 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.3, 150.0, 82.8, 70.4, 63.7, 41.3, 28.1, 25.7, 18.0, 17.8, −4.8 ppm; MS (ESI): 352 ($M+Na^+$); HRMS (ESI) calcd for ($C_{16}H_{31}NO_4Si+Na^+$): 352.1920, found: 352.1904.

*4.5.2. (2S,3R)-Benzyl 3-(tert-butyldimethylsilyloxy)-2-methyl-5-oxopyrrolidine-1-carboxylate (**1b**).* Colorless oil; $[\alpha]_D^{25}$ +17.2 (*c* 1, $CHCl_3$); IR (film): ν_{max} 2955, 2928, 1747, 1909, 1379, 1359, 1296, 1205, 1104 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44–7.32 (m, 5H), 5.33 (d, *J*=12.4 Hz, 1H), 5.28 (d, *J*=12.4 Hz, 1H), 4.11 (dd, *J*=6.8, 13.6 Hz, 1H), 3.98 (d, *J*=5.2 Hz, 1H), 2.81 (dd, *J*=5.2, 17.6 Hz, 1H), 2.38 (d, *J*=17.6 Hz, 1H), 1.45 (d, *J*=6.8 Hz, 3H), 0.86 (s, 9H), 0.07 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.1, 151.5, 135.4, 128.6, 128.3, 128.0, 70.5, 67.9, 63.8, 41.2, 30.3, 25.7, 18.0, 17.7, −4.8 ppm; MS (ESI): 386 ($M+Na^+$); HRMS (ESI) calcd for ($C_{19}H_{29}NO_4Si+Na^+$): 386.1764, found: 386.1745.

*4.5.3. (2S,3R)-tert-Butyl 3-(tert-butyldimethylsilyloxy)-2-isopropyl-5-oxopyrrolidine-1-carboxylate (**1c**).* Colorless oil; $[\alpha]_D^{25}$ +45.17 (*c* 1, $CHCl_3$); IR (film): ν_{max} 2958, 2931, 2857, 1786, 1754, 1716, 1471, 1367, 1304, 1156 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.14 (d, *J*=5.6 Hz, 1H), 3.89 (d, *J*=5.6 Hz, 1H), 2.72 (dd, *J*=5.2, 17.6 Hz, 1H), 2.33 (d, *J*=18.0 Hz, 1H), 2.01 (ddd, *J*=6.8, 13.6, 26.8 Hz, 1H), 1.53 (s, 9H), 1.01 (d, *J*=7.2 Hz, 3H), 0.88 (d, *J*=7.2 Hz, 3H), 0.87 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.1, 150.3, 82.8, 72.9, 65.9, 43.0, 29.8, 28.0, 25.6, 19.3, 17.7, 17.6, −4.6, −4.7 ppm; MS (ESI): 380 ($M+Na^+$); HRMS (ESI) calcd for ($C_{18}H_{35}NO_4Si+Na^+$): 380.2233, found: 380.2215.

*4.5.4. (2S,3R)-tert-Butyl 3-(tert-butyldimethylsilyloxy)-2-isobutyl-5-oxopyrrolidine-1-carboxylate (**1d**).* Colorless oil; $[\alpha]_D^{25}$ +36.06 (*c* 1.02, $CHCl_3$); IR (film): ν_{max} 2959, 2934, 2856, 1742, 1717, 1473, 1384, 1368, 1310, 1257, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.29 (d, *J*=4.8 Hz, 1H), 4.01 (dd, *J*=3.2, 10.4 Hz, 1H), 2.77 (dd, *J*=4.8, 17.6 Hz, 1H), 2.33 (d, *J*=17.6 Hz, 1H), 1.72–1.63 (m, 1H), 1.54 (s, 9H), 1.57–1.43 (m, 1H), 1.30–1.23 (m, 1H), 1.06 (d, *J*=6.4 Hz, 3H), 0.97 (d, *J*=6.4 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.7, 149.9, 82.8, 68.6, 66.4, 41.5, 41.2, 28.1, 25.6, 25.3, 23.7, 21.7, 17.9, −4.7 ppm; MS (ESI): 394 ($M+Na^+$); HRMS (ESI) calcd for ($C_{19}H_{37}NO_4Si+Na^+$): 394.2390, found: 394.2371.

*4.5.5. (2S,3R)-tert-Butyl 3-(tert-butyldimethylsilyloxy)-2-((tert-butyldimethylsilyloxy)methyl)-5-oxopyrrolidine-1-carboxylate (**1e**).* Colorless oil; $[\alpha]_D^{25}$ +29.9 (*c* 1.03, $CHCl_3$); IR (film): ν_{max} 2956, 2930, 2858, 1778, 1473, 1366, 1318, 1254, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.29 (d, *J*=6.0 Hz, 1H), 3.96 (dd, *J*=1.6, 4.8 Hz, 1H), 3.80 (dd, *J*=4.4, 11.0 Hz, 1H), 3.78 (dd, *J*=3.2, 11.0 Hz, 1H), 2.85 (dd, *J*=5.6, 17.4 Hz, 1H), 2.31 (d, *J*=17.4 Hz, 1H), 1.54 (s, 9H), 0.87 (s, 18H), 0.08 (m, 6H), 0.04 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.2, 150.1, 82.9, 68.8, 67.7, 62.1, 42.9, 28.1, 25.8, 25.7, 18.2, 18.0, −4.7, −5.6 ppm; MS (ESI): 482 ($M+Na^+$); HRMS (ESI) calcd for ($C_{22}H_{45}NO_5Si_2+Na^+$): 482.2734, found: 482.2726.

*4.5.6. (2S,3R)-tert-Butyl 3-(tert-butyldimethylsilyloxy)-2-cyclohexyl-5-oxopyrrolidine-1-carboxylate (**1f**).* Colorless oil; $[\alpha]_D^{25}$ +40.73 (*c* 0.88, $CHCl_3$); IR (film): ν_{max} 2931, 2856, 1739, 1719, 1367, 1305, 1255,

1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.54 (d, J=4.8 Hz, 1H), 3.91 (d, J=5.6 Hz, 1H), 2.74 (dd, J=5.6, 18.0 Hz, 1H), 2.34 (d, J=18.0 Hz, 1H), 1.92–1.58 (m, 6H), 1.57 (s, 9H), 1.46–1.10 (m, 5H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.1, 150.4, 82.7, 82.3, 72.5, 66.6, 42.9, 40.3, 29.8, 29.0, 28.7, 28.0, 26.3, 26.2, 25.8, 25.7, 25.3, 17.9, −4.6 ppm; MS (ESI): 420 ($M+Na^+$); HRMS (ESI) calcd for ($C_{21}H_{39}NO_4Si+Na^+$): 420.2546, found: 420.2545.

*4.5.7. (2S,3R) or (2R,3S)-tert-Butyl 2-benzyl-3-(tert-butyldimethylsilyloxy)-5-oxopyrrolidine-1-carboxylate (**1g**) (2S,3R)-**1g**.* Colorless-oil; $[\alpha]_D^{25}$ +8.67 (*c* 1.07, $CHCl_3$); (2*R*,3*S*)-**1g** $[\alpha]_D^{25}$ −8.54 (*c* 1.19, $CHCl_3$); IR (film): ν_{max} 2954, 2929, 2957, 1786, 1755, 1713, 1368, 1312, 1257, 1156, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.18 (m, 5H), 4.16 (dd, J=3.6, 10.4 Hz, 1H), 4.06 (d, J=5.2 Hz, 1H), 3.17 (dd, J=3.2, 13.2 Hz, 1H), 2.62 (dd, J=5.2, 17.6 Hz, 1H), 2.51 (dd, J=10.4, 13.2 Hz, 1H), 2.29 (d, J=17.6 Hz, 1H), 1.60 (s, 9H), 0.74 (s, 9H), −0.22 (s, 3H), −0.24 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.7, 150.0, 136.7, 129.3, 128.9, 127.1, 83.0, 69.1, 66.9, 41.3, 38.0, 28.1, 25.6, 17.8, −5.2, −5.3 ppm; MS (ESI): 428 ($M+Na^+$); HRMS (ESI) calcd for ($C_{22}H_{35}NO_4Si+Na^+$): 428.2233, found: 428.2224.

*4.5.8. tert-Butyl 4-(tert-butyldimethylsilyloxy)-2-oxopyrrolidine-1-carboxylate (**1h**).* Colorless oil; IR (film): ν_{max} 2956, 2934, 1766, 1366, 1310, 1254, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.41–4.36 (m, 1H), 3.86 (dd, J=5.20, 11.2 Hz, 1H), 3.62 (dd, J=2.80, 11.6 Hz, 1H), 2.71 (dd, J=6.0, 17.6 Hz, 1H), 2.46 (dd, J=3.2, 17.2 Hz, 1H), 1.53 (s, 9H), 0.88 (s, 9H), 0.08 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.1, 150.1, 83.0, 63.9, 55.4, 43.2, 28.0, 25.7, 25.6, 18.0, −4.8 ppm; MS (ESI): 338 ($M+Na^+$); HRMS (ESI) calcd for ($C_{15}H_{29}NO_3Si+Na^+$): 338.1764, found: 338.1755.

*4.5.9. Benzyl 2-oxopyrrolidine-1-carboxylate (**1i**).* Colorless oil; IR (film): ν_{max} 3033, 2963, 1786, 1751, 1718, 1456, 1383, 1299, 1175 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44–7.26 (m, 5H), 5.28 (s, 2H), 3.81 (t, J=6.8 Hz, 2H), 2.53 (t, J=8.0 Hz, 2H), 2.06–1.99 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.0, 151.5, 135.4, 128.6, 128.4, 128.2, 68.0, 46.4, 32.8, 17.6 ppm; MS (ESI): 242 ($M+Na^+$); HRMS (ESI) calcd for ($C_{12}H_{13}NO_3+Na^+$): 242.0793, found: 242.0788.

*4.5.10. tert-Butyl 2-oxopyrrolidine-1-carboxylate (**1l**).* Colorless oil; IR (film): ν_{max} 2980, 1785, 1712, 1367, 1313, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.75 (t, J=6.7 Hz, 2H), 2.50 (t, J=8.0 Hz, 2H), 2.03–1.95 (m, 2H), 1.53 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.2, 150.3, 82.7, 46.5, 33.0, 28.0, 17.4 ppm; MS (ESI): 208 ($M+Na^+$); HRMS (ESI) calcd for ($C_9H_{15}NO_3+Na^+$): 208.0950, found: 208.0942.

*4.5.11. (4R,5S)-1-Benzyl-4-(tert-butyldimethylsilyloxy)-5-methylpyrrolidin-2-one (**11**).* To a solution of **1a** (2.008g, 6.1 mmol) in CH_2Cl_2 (20 mL) was dropped TFA (3 mL) at 0 °C and stirred for 4 h at 0 °C ~room temperature. The reaction was slowly quenched with saturated $NaHCO_3$ aqueous solution at 0 °C until no bubbles appeared. Then, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 for three times. The combined organic layers were washed with brine, dried over $NaSO_4$, and concentrated in vacuo to give yellow crude product without further purification. The above crude compound was dissolved in cooled (0 °C) DMF (40 mL) and NaH (242 mg, 12 mmol) was carefully added in several portions, and then BnBr (2.03 g, 12 mmol) was dropped. After being stirred for 2.5 h at 0 °C to room temperature, the reaction was cooled to 0 °C and carefully quenched with water. The resulting mixture was extracted with EtOAc for four times and the combined organic layers were washed with brine for three times. Dried over $NaSO_4$ and concentrated in vacuo, the residue was purified by flash chromatography on silica gel to give **11** (1266 mg, 65%) as a colorless foam. $[\alpha]_D^{25}$ −60.6 (*c* 1.09, $CHCl_3$); IR (film): ν_{max} 2953, 2931, 1697, 1463, 1441, 1419, 1413, 1254, 1063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.24 (m, 5H), 5.06 (d, J=15.6 Hz, 1H), 3.97 (dd, J=2.8, 5.6 Hz, 1H), 3.93 (d, J=15.6 Hz, 1H), 3.33 (ddd, J=2.4, 6.4, 13.2 Hz, 1H), 2.72 (dd, J=6.4, 16.8 Hz, 1H), 2.35 (dd, J=3.2, 16.8 Hz, 1H), 1.1 (d, J=6.4 Hz, 3H), 0.85 (s, 9H), 0.04 (s, 3H), −0.01 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.4, 136.4, 128.6, 127.7, 127.3, 72.4, 61.8, 43.5, 40.1, 25.6, 17.9, 16.4, −4.8, −4.9 ppm; MS (ESI): 320 ($M+H^+$); HRMS (ESI) calcd for ($C_{18}H_{29}NO_2Si+H^+$): 320.2046, found: 320.2034.

*4.5.12. (2S,3R)-1-Benzyl-2-methylpyrrolidin-3-ol (**12**).* To a solution of **11** (143 mg, 0.45 mmol) in MeOH (5 mL) was slowly dropped $SOCl_2$ (0.3 mL) at 0 °C. After being stirred for 2 h at room temperature, the mixture was concentrated in vacuo and the residue was stirred in dry THF (5 mL) at 0 °C. A solution of $BH_3 \cdot SMe_2$ was slowly dropped and stirred for 20 h at 0 °C to room temperature. The reaction was carefully quenched with EtOH (4 mL) and refluxed for 6 h. The resulting mixture was concentrated and the residue was purified by flash chromatography on silica gel to give **12** (72 mg, 84%) as colorless oil. $[\alpha]_D^{25}$ +80.31 (*c* 0.67 $CHCl_3$); IR (film): ν_{max} 3315, 2975, 2926, 2783, 2701, 2641, 1452, 1419, 1101, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.23 (m, 5H), 3.95 (d, J=12.8 Hz, 1H), 3.92–3.89 (m, 1H), 3.35 (d, J=12.8 Hz, 1H), 2.83 (ddd, J=2.4, 8.8, 10.4 Hz, 1H), 2.50–2.40 (m, 2H), 2.17–2.07 (m, 2H), 1.64–1.57 (m, 1H), 1.19 (d, J=6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=130.7, 129.5, 129.1, 69.3, 58.1, 52.3, 31.6, 15.4 ppm; MS (ESI): 192 ($M+H^+$); HRMS (ESI) calcd for ($C_{18}H_{29}NO_2Si+H^+$): 192.1383, found: 192.1380.

*4.5.13. (2S,3S)-3-Azido-1-benzyl-2-methylpyrrolidine (**13**).* To a solution of **12** (179 mg, 0.94 mmol) and DMAP (12 mg, 0.095 mmol) in dry CH_2Cl_2 (10 mL) were simultaneously treated with TEA (0.39 mL, 2.82 mmol) and MsCl (214 mg, 1.88 mmol) at 0 °C. After being stirred for 3 h at 0 °C ~room temperature, the reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ for three times. The combined organic layers were washed with brine, dried over $NaSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give yellow oil (239 mg, 95%). The above oil was dissolved in DMF (10 mL) and treated with NaN_3 (183 mg, 2.8 mmol) at room temperature. The reaction was stirred at 80 °C for 36 h and diluted with water. The mixture was extracted with EtOAc for three times and the combined organic layers were washed with brine for three times. Dried and concentrated, the residue was purified by flash chromatography on silica gel to give **13** (137 mg, 68%) as a colorless oil. $[\alpha]_D^{25}$ +158.7 (*c* 1.26, $CHCl_3$); IR (film): ν_{max} 2970, 2932, 2792, 2098, 1453, 1256, 739, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31–7.21 (m, 5H), 4.02 (d, J=13.2 Hz, 1H), 3.67–3.64 (m, 1H), 3.15 (d, J=13.2 Hz, 1H), 3.00–2.96 (m, 1H), 2.54 (ddd, J=5.2, 6.0, 12.6 Hz, 1H), 2.18–2.05 (m, 2H), 1.93–1.85 (m, 1H), 1.24 (d, J=6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.9, 128.7, 128.2, 126.9, 64.3, 63.3, 57.2, 51.6, 28.9, 13.9 ppm; MS (ESI): 217 ($M+H^+$); HRMS (ESI) calcd for ($C_{12}H_{16}N_4+H^+$): 217.1448, found: 217.1442.

*4.5.14. N-((2S,3S)-1-Benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-(methylamino)benzamide (nemonapride) (**3**).* The mixture of **14** (56 mg, 0.26 mmol) and palladium on calcium carbonate (7 mg, 5% Pd, 3.5%Pb) was stirred in MeOH (10 mL) for 5 h under H_2 atmosphere at room temperature. The reaction mixture was filtrated and concentrated in vacuo to give crude (2*S*,3*S*)-1-benzyl-2-methylpyrrolidin-3-amine (49 mg, quantitative yield) as a colorless oil without purification. 5-Chloro-2-methoxy-4-(methylamino) benzoic acid (84 mg, 0.39 mmol) was dissolved in dry DCM (6 mL) and cooled to 0 °C, then TEA (0.15 mL, 1.04 mmol) and $ClCO_2Et$

(0.04 mL, 0.39 mmol) were simultaneously dropped. After being stirred for 45 min at the same conditions, the mixture was treated with a solution of above crude amine in dry DCM (2 mL) and stirred for 2 h at 0 °C. The resulting mixture was quenched with water and extracted with DCM for three times. The combined organic layers were washed with brine, dried over $NaSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give nemonapride **3** (110 mg, 72%) as a colorless solid. $[\alpha]_D^{25}$ +2.50 (*c* 0.76, $CHCl_3$), lit.[3c] $[\alpha]_D^{25}$ +2.3 (*c* 0.6, $CHCl_3$); lit.[3b] $[\alpha]_D^{25}$ +4.0 (*c* 0.6, $CHCl_3$); IR (film): ν_{max} 3387, 2967, 2930, 1635, 1601, 1517, 1455, 1281, 1245, 1213 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 8.01 (d, *J*=8.6 Hz, 1H), 7.36–7.23 (m, 5H), 6.12 (s, 1H), 4.71–4.65 (m, 2H), 4.04 (d, *J*=12.6 Hz, 1H), 3.98 (s, 3H), 3.20 (d, *J*=12.6 Hz, 1H), 3.00 (m, 1H), 2.97–2.93 (m, 3H), 2.65–2.62 (m, 1H), 2.25–2.12 (m, 2H), 1.67–1.63 (m, 1H), 1.13 (d, *J*=6.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 158.1, 148.1, 132.4, 128.7, 128.2, 126.9, 111.5, 93.3, 61.8, 57.6, 56.1, 52.4, 51.7, 31.4, 30.2, 29.7, 14.0 ppm; MS (ESI): 388 ($M+H^+$); HRMS (ESI) calcd for ($C_{21}H_{26}ClN_3O_2+H^+$): 388.1792, found: 388.1806.

*4.5.15. (4R,5S) or (4S,5R)-5-Benzyl-4-hydroxypyrrolidin-2-one (**4**).* To a solution of (2*R*,3*S*) or (2*S*,3*R*)-**1g** (210 mg, 0.518 mmol) in MeOH (5 mL) was slowly dropped $SOCl_2$ (0.3 mL) at 0 °C. The mixture was stirred at room temperature for 2 h and concentrated in vacuo. The dark residue was purified by flash chromatography on silica gel to give **4** as white, slightly red solid (80 mg, 81%). Compound (4*R*,5*S*)-**4** $[\alpha]_D^{25}$ +16.81 (*c* 0.05, MeOH); (4*S*,5*R*)-**4** $[\alpha]_D^{25}$ −16.56 (*c* 0.05, MeOH); IR (film): ν_{max} 3454, 3227, 1694, 1347, 1045 cm^{-1}; ^1H NMR (400 MHz, MD_3OD): δ 7.68 (br s, 1H), 7.32–7.20 (m, 5H), 5.10 (d, *J*=4.0 Hz, 1H), 3.97–3.95 (m, 1H), 3.51 (dd, *J*=6.0, 6.8 Hz, 1H), 2.74–2.64 (m, 2H), 2.28 (dd, *J*=6.4, 16.8 Hz, 1H), 1.83 (dd, *J*=2.8, 16.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, MD_3OD): δ=175.2, 138.2, 129.9, 128.7, 126.7, 69.8, 63.9, 40.6, 39.8 ppm; MS (ESI): 192 ($M+H^+$); HRMS (ESI) calcd for ($C_{11}H_{13}NO_2+H^+$): 192.1025, found: 192.1017.

*4.5.16. (2R,3R) or (2S,3S)-tert-Butyl 2-benzyl-3-hydroxy-5-oxopyrrolidine-1-carboxylate (**16a** and **16b**).* To a solution of **1g** (656 mg, 1.61 mmol) was stirred in dry THF (10 mL) at room temperature, and then a solution of TBAF (3.2 mL, 1.0 mol in THF) was dropped. The reaction was stirred for 3 h and quenched with water. The mixture was extracted with EtOAc for three times and the combined organic layers were washed with brine. Dried over anhydrous Na_2SO_4, filtered, and concentrated, the residue was purified by chromatography on silica gel to give crude intermediate (468 mg), which contain minor impurity of TBAF. To a solution of oxalyl chloride (0.28 mL, 3.26 mmol) in dry CH_2Cl_2 (10 mL) was dropped DMSO (0.47 mL, 6.53 mmol) over 15 min at −78 °C under argon atmosphere. After being stirred for 30 min, a solution of above crude intermediate (468 mg) in dry CH_2Cl_2 (5.0 mL) was dropped and the mixture was stirred for anther 1 h, then Et_3N (1 mL, 6.96 mmol) was dropped and the mixture was allowed to warm to room temperature. The reaction was quenched with aqueous $NaHSO_4$ solution (1 M, 30 mL), then the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 for two times. The combined organic layers were washed with saturated aqueous solution of $NaHSO_4$, saturated aqueous $NaHCO_3$, and brine. Dried, filtered, and concentrated to give crude product **15a** or **15b** (457 mg, 92%) as a colorless oil without further purification. The above crude mixture of **15a** or **15b** was dissolved in MeOH (15 mL) and cooled to 0 °C, then $NaBH_4$ (153 mg, 4.0 mmol) was added in three portions. After being stirred for 2 h at 0 °C to ~room temperature, the reaction was quenched with $NaHCO_3$ aqueous solution and extracted with DCM for three times. The combined organic layers were concentrated and the residue was purified by chromatography on silica gel to give **16a** or **16b** (441 mg, yield 96%) as a white solid. Mp 98–99 °C; (2*S*,3*S*)-**16a** $[\alpha]_D^{25}$ +27.7 (*c* 1.12, $CHCl_3$); (2*R*,3*R*)-**16b** $[\alpha]_D^{25}$ −28.4 (*c* 0.8, $CHCl_3$); IR (film): ν_{max} 3403, 2975, 1770, 1676, 1366, 1287, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.19 (m, 5H), 4.51–4.42 (m, 2H), 3.19–3.09 (m, 2H), 2.60 (dd, *J*=7.2, 17.0 Hz, 1H), 2.40 (dd, *J*=7.6, 17.0 Hz, 1H), 1.48 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.8, 149.8, 137.8, 129.9, 129.7, 128.6, 126.7, 83.3, 65.6, 62.7, 40.1, 33.9, 28.0 ppm; MS (ESI): 314 ($M+Na^+$); HRMS (ESI) calcd for ($C_{16}H_{21}NO_4+Na^+$): 314.1368, found: 314.1372.

*4.5.17. (4S,5S) or (4R,5R)-5-Benzyl-4-hydroxypyrrolidin-2-one (cis-**4**).* To a solution of **16a** or **16b** (298 mg, 1.02 mmol) in MeOH (20 mL) was treated with $SOCl_2$ (1 mL) at 0 °C. After being stirred for 2 h, the reaction was concentrated and the residue was purified by chromatography on silica gel to give *cis*-**4** (170 mg, yield 87%) as a white solid. Mp 132–134 °C, lit.[5g] 133–135; (4*S*,5*S*)-**4** $[\alpha]_D^{25}$ −44.6 (*c* 0.05, MeOH); (4*R*,5*R*)-**4** $[\alpha]_D^{25}$ +43.87 (*c* 1.07, MeOH); IR (film): ν_{max} 3455, 3229, 1693, 1346, 1044 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 7.54 (br s, 1H), 7.31–7.21 (m, 5H), 5.12 (s, 1H), 4.13 (s, 1H), 3.71 (dd, *J*=6.4, 12.8 Hz, 1H), 2.99 (ddd, *J*=3.2, 8.0, 14.0 Hz, 1H), 2.69 (ddd, *J*=3.2, 5.6, 9.2 Hz, 1H), 2.40 (dd, *J*=5.6, 16.4 Hz, 1H), 2.04–1.99 (m, 1H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ=175.4, 139.2, 129.4, 128.7, 126.5, 67.4, 60.6, 43.3, 35.05 ppm; MS (ESI): 192 ($M+H^+$); HRMS (ESI) calcd for ($C_{11}H_{13}NO_2+H^+$): 192.1025, found: 192.1019.

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