ORGANIC CHEMISTRY

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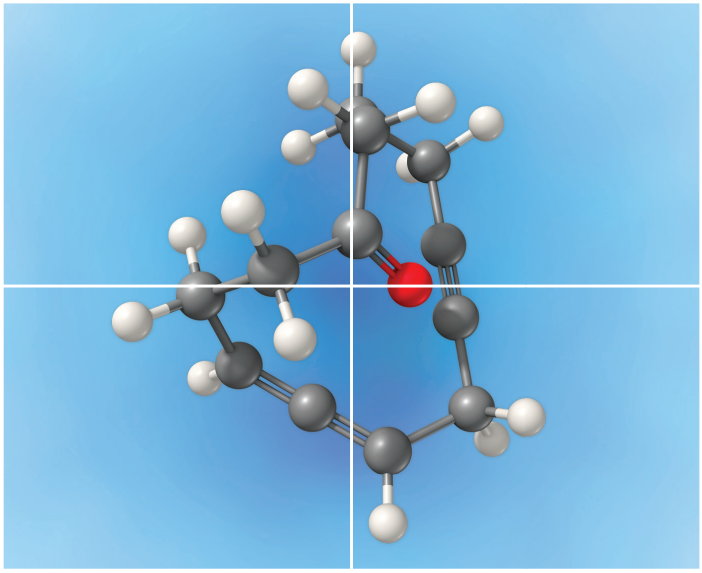

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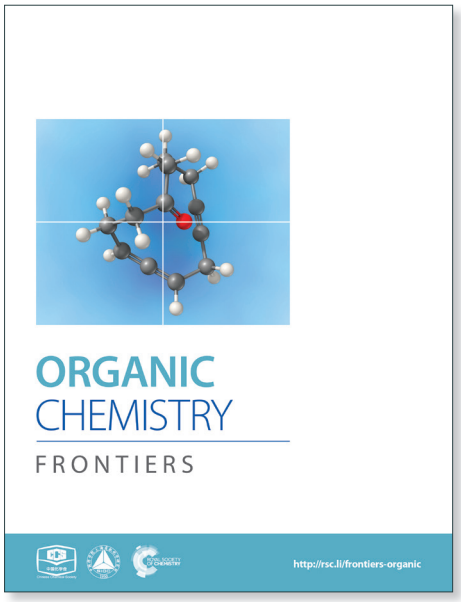

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Organic Chemistry Frontiers

Method

Stereoselective Formation of Chiral *trans*-4-Hydroxy-5-Substituted 2-Pyrrolidinones: Syntheses of Streptopyrrolidine and 3-*epi*-Epohelmin A

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A highly diastereoselective approach for synthesis of *trans*-4-hydroxy-5-substituted 2-pyrrolidinones has been developed through an intramolecular cascade process of α-chiral aldimines using alkyl, aryl, alkynyl, and alkenyl Grignard reagents. Stereochemistry at the C-5 position of 2-pyrrolidinone after reaction with alkyl, aryl, and alkenyl Grignards was solely controlled by α-alkoxy substitution. For alkynyl Grignards, stereochemistry was controlled by coordination of the α-alkoxy substitution and stereochemistry of the sulfinamide. The utility of this one-pot cascade protocol is demonstrated by the asymmetric synthesis of streptopyrrolidine **5** and 3-*epi*-epohelmin A 3-*epi*-**6**.

Introduction

The development of efficient and stereoselective reactions and methodologies for carbon–carbon bond formation is one of the major pursuits in organic synthesis and medicinal chemistry.[1] Ellman and Davis reported, respectively, an effective method to prepare chiral amines through the addition reaction of imines bearing chiral auxiliaries (e.g., *N*-*tert*-butanesulfinamide and *N*-toluenesulfinamide) with nucleophilic reagents.[2,3] Nowadays, the addition of corresponding Grignard reagents to chiral *N*-*tert*-butanesulfinyl imines is widely applied in organic synthesis.[4] Our group has also explored the utility of chiral *N*-*tert*-butanesulfinyl imines, and successfully accomplished the divergent synthesis of several bioactive natural products.[5] In addition, we observed an interesting stereoselective *tert*-butyl migration from sulfur to carbon when *N*-*tert*-butanesulfinyl iminoacetate was treated with various benzylzinc bromides.[6]

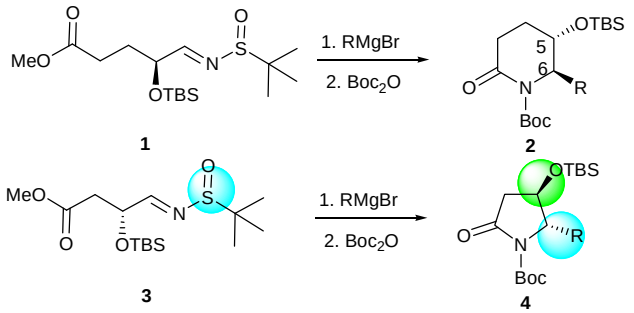

Figure 1. Formation of chiral 2-piperidinones and 2- pyrrolidinones.

More recently, we discovered an intramolecular cascade process for highly diastereoselective synthesis of versatile *trans*-5-hydroxy-6-substituted 2-piperidinones **2**.[7] In this case, the stereoselectivity of C-5 and C-6 strongly favored the *trans* form and the new stereogenic center at the C-6 position was solely controlled by the *tert*-butyldimethylsilyl ether (α-OTBS) group of imine **1**. Encouraged by this highly stereoselective imine addition and the subsequent in situ formation of 2-piperidinones **2**, as a continuous work, we became interested in a similar imine substrate **3** with one less carbon, which would potentially produce *trans*-4-hydroxy-5-substituted 2-pyrrolidinones **4** (Figure 1).

Chiral functionalized *trans*-4-hydroxy-5-substituted 2-pyrrolidinones and the ring-opened form γ-amino-β-hydroxybutyric acids are present as a core structure or subfeature in many biologically relevant alkaloids[8,9] isolated from marine and terrestrial plants and animals, as well as in pharmaceutical agents.[10] For example, streptopyrrolidine **5**, isolated from the fermentation broth of marine *Streptomyces* sp. KORDI-3973,[11] could significantly block the capillary tube formation of cells at the same potency as the known angiogenesis inhibitor SU11248, whereas epohelmin A **6**, isolated from an unidentified fungus (strain FKI-0929), could

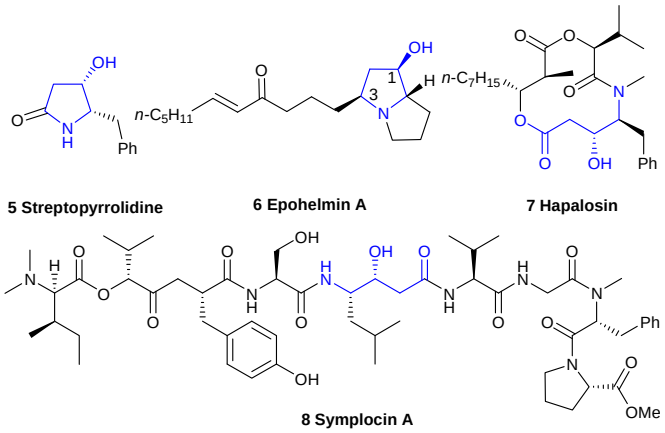

Figure 2. The structure of several bioactive molecules.

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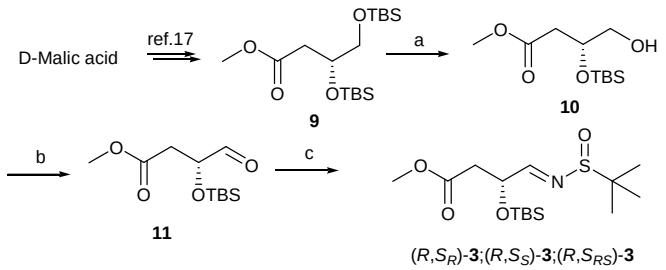
inhibit recombinant lanosterol synthase (IC_{50} = 10 μM).[12] Ring-opened form, (*3R*,*4S*)-*γ*-amino-*β*-hydroxybutyric acid unit,[13] exists in hapalosin **7** and symplocin A **8**. The former showed multi-drug resistance reversing activity in cancer cells,[14] and the latter displayed very potent cathepsin E inhibition (IC_{50} = 300 pM)[15] (Figure 2).

In past decades, a wide range of synthetic methods for the stereoselective construction of *trans*-4-hydroxyl-5-substituted 2-pyrrolidinones **4** and the ring-opened form have been developed.[9] The common approaches among them are based on reductive alkylation[9d-f,9k] and nucleophilic substitution,[9c] which usually require multiple steps and lead to an unsatisfactory overall yield. Therefore, an efficient and stereoselective approach for direct preparation of **4** remains a challenge.[16] Herein we report our results of the one-pot cascade process starting from *α*-chiral aldimine **3** and Grignard reagents to generate chiral 2-pyrrolidinones **4**, as well as the application in asymmetric syntheses of streptopyrrolidine **5** and 3-*epi*-epohelmin A (3-*epi*-**6**).

Results and Discussion

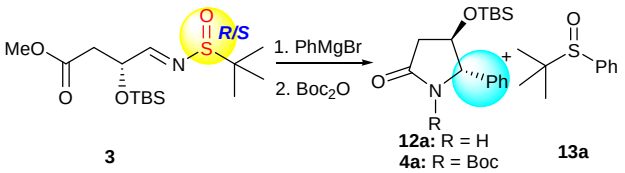
The synthesis of aldimine **3** is demonstrated in Scheme 1. D-Malic acid was conveniently converted to ester **9** according to the known procedure in 74% overall yield.[17] The subsequent regioselective desilylation from the primary hydroxyl group was achieved by controlling the reaction temperature at −40 °C in the presence of camphorsulfonic acid (CSA) to produce alcohol **10** in 65% yield. Oxidation of **10** with Dess–Martin periodinane (DMP)[18] and subsequent condensation with 2-methylpropane-2-sulfinamide in the presence of anhydrous copper sulfate[19] led to *N*-*tert*-butanesulfinyl imines **3** in 84% overall yield (Scheme 1).



Scheme 1. Preparation of *N*-*tert*-butanesulfinyl aldimines **3**. Reagents and conditions: a. CSA, MeOH/DCM, −40 °C, 8 h, 65%; b. DMP, DCM, room temperature (rt), 0.5 h, quantitative yield; c. 2-methylpropane-2-sulfinamide, $CuSO_4$, pyridinium *p*-toluenesulfonate, DCM, 24 h, 84%.

With the desired precusor **3** in hand, we started to investigate the intramolecular tandem sequence by reacting with Grignard reagents. When optically pure (R,S_R)-**3** was treated with phenyl magnesium bromide at −78 °C, the desired product **12a** was obtained. Because of its co-elution with the sulfoxide by-product **13a** in silica gel chromatography, the lactam-NH was protected as the *N*-*tert*-butoxycarbonyl (*N*-Boc) form, and the pure imide **4a** was obtained with high diastereoselectivity (*dr* = 99:1) in spite of low yield (40%, Table 1, entry 1). Like the tandem process involving imine **1**,[7] the yield of **4a** was greatly improved to 74% when the reaction was conducted at −78 °C to room temperature and maintained at room temperature overnight; the diastereoselectivity remained unchanged (*dr* = 99:1, Table 1, entry 2). Regardless of the chirality of sulfur in the imine substrate, both (R,S_S)-**3** and (R,S_R)-**3**, as well as (R,S_{RS})-**3**, led to the same product **4a** with high diastereoselectivities (*dr* = 99:1, Table 1, entries 2–4), indicating that the stereochemistry of the new chiral center at C-5 was solely controlled by the α-OTBS group. Use of different solvents was also investigated for the reaction with (R,S_{RS})-**3**, and the results are summarized in Table 1 (entries 5–7). The reaction in tetrahydrofuran (THF) offered better conversion than in tetrahydrofuran/dichloromethane (Table 1, entries 4 and 5). Different amounts of Grignard reagent were also assessed. The use of less than three equivalents of phenylmagnesium bromide also produced the desired product **4a** with high diastereoselectivity, albeit in much lower yields (Table 1, entries 8 and 9).

Table 1. Optimization of the tandem process.



3 13a

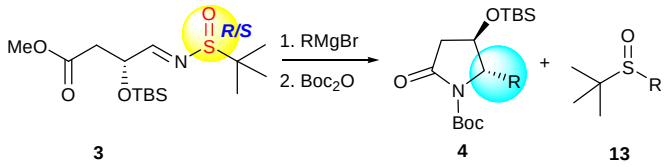
Entry[a]	Imine	T (°C)	Solvent	Yield (%)[b]	*trans*:*cis*[c]
1	(R,S_R)-**3**	−78	THF	40	99:1
2	(R,S_R)-**3**	−78 to rt	THF	74	99:1
3	(R,S_S)-**3**	−78 to rt	THF	69	99:1
4	(R,S_{RS})-**3**	−78 to rt	THF	71	99:1
5	(R,S_{RS})-**3**	−78 to rt	THF/DCM(3/5)	45	99:1
6	(R,S_{RS})-**3**	−78 to rt	THF/Et_2O(3/5)	62	99:1
7	(R,S_{RS})-**3**	−78 to rt	THF/PhMe(3/5)	65	99:1
8[d]	(R,S_{RS})-**3**	−78 to rt	THF	25	99:1
9[e]	(R,S_{RS})-**3**	−78 to rt	THF	47	99:1

a. The reactions were performed with α-chiral substituted aldimines **3** (1.0 mmol), phenyl magnesium bromide (3 mL, 1.0 M in THF) at −78 °C to rt overnight, crude product was treated with Boc_2O (2.0 mmol), DMAP (1.0 mmol), and triethylamine (5.0 mmol) in DMF for 24 h. b. Isolated yield. c. Determined by HPLC or ^{1}H NMR. d. Phenyl magnesium bromide (1 mL, 1.0 M in THF). e. Phenyl magnesium bromide (2 mL, 1.0 M in THF).

Next, we turned our attention to investigate the scope and limitation of this method in the preparation of *trans*-4-hydroxy-5-substituted 2-pyrrolidinones. A survey of different Grignard reagents were conducted by reaction with (R,S_{RS})-**3** under the established optimal conditions, as summarized in Table 2. When substituted phenyl Grignard reagents were used, the intramolecular tandem addition–cyclization proceeded smoothly with high diastereoselectivities and in excellent yields (Table 2, entries 2–9) except that *m*-fluoro-phenylmagnesium reagent led to a slightly lower diastereoselectivity in desired product **4f** (Table 2, entry 6). Bicyclic Grignard reagents, including *α*- and *β*-naphthyl magnesium bromides, also afforded the desired lactams **4j,k**, and the less hindered *β*-naphthyl magnesium bromide provided better diastereoselectivity and higher yield for this tandem process (Table 2, entries 10 and 11). Several alkyl-chain Grignard reagents were also investigated, and the yields of products **4l–p** were slightly lower than those of substituted phenyl Grignard reagents (Table 2, entries 12–16). It is noteworthy that saturated cyclic Grignard reagents also gave the desired lactams **4q,r** in 66–68% yield (Table 2, entries 17 and 18). Although benzylmagnesium bromide could give

the corresponding product **4s** in 70% yield (Table 2, entry 19), the reaction with allylMgBr was very messy (Table 2, entry 20). All the above-mentioned results indicated that the tandem sequence of α-chiral aldimine **3** was quite suitable for different substituted alkyl and aryl Grignard reagents and the stereogenic center at C-5 was solely controlled by the α-OTBS group.

Table 2. Reactions of different Grignard reagents with (R,S_{RS})-**3**.



3 **4** **13**

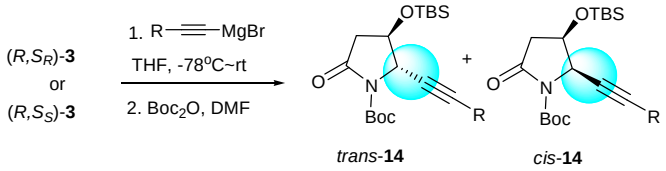
Entry[a]	R	4a–s	Yield %)[b]	*trans*:*cis*[c]
1	C_6H_5	**4a**	71	99:1
2	*o*-$CH_3C_6H_4$	**4b**	62	99:1
3	*m*-$CH_3C_6H_4$	**4c**	73	98:2
4	*p*-$CH_3C_6H_4$	**4d**	68	99:1
5	*p*-$CH_3OC_6H_4$	**4e**	74	99:1
6	*m*-FC_6H_4	**4f**	80	96:4
7	*p*-FC_6H_4	**4g**	81	90:10
8	*m*-$CF_3C_6H_4$	**4h**	59	99:1
9	*p*-PhC_6H_4	**4i**	81	94:6
10	α-Naphthyl	**4j**	59	96:4
11	β-Naphthyl	**4k**	70	99:1
12	Ethyl	**4l**	65	99:1
13	CH_2=$CHCH_2CH_2$	**4m**	69	94:6
14	Isopropyl	**4n**	52	99:1
15	Isobutyl	**4o**	61	99:1
16	$CH_3(CH_2)_4$	**4p**	72	99:1
17	Cyclopropyl	**4q**	68	99:1
18	Cyclohexyl	**4r**	66	99:1
19	Bn	**4s**	70	97:3
20	Allyl	**4t**	--	--

a. Reactions were performed with (R,S_{RS})-**3** (1.0 mmol), Grignard reagents (3 mL, 1.0 M in THF) in dry THF (5 mL) at −78 °C to rt overnight, crude product was treated with Boc_2O (2.0 mmol), DMAP (1.0 mmol), and triethylamine (5.0 mmol) in DMF for 24 h. b. Isolated yield. c. Determined by HPLC or ^{1}H NMR.

The stereochemistry of product **4a** was unambiguously determined as the *trans* form by X-ray crystallography.[26] Other compounds **4b-s** were accordingly assigned as the *trans* forms based on the similar coupling constant (*J*) between protons C4-H (C*H*-OTBS) and C5-H (C*H*-alkyl or aryl).

We previously demonstrated that the reactions of α-chiral aldimines **1** with alkynyl Grignard reagents could lead to 2-piperidinones **2** with different stereoselectivities depending on the chirality of sulfur.[7b] The α-chiral aldimine **3**, with one less carbon in the chain, also performed in a similar way. When (R,S_R)-**3** was treated with (2-phenylethynyl)magnesium bromide and followed by *N*-Boc protection, the desired imide **14a** was produced in 76% yield with high diastereoselectivity (*dr* = 99:1) (Table 3, entry 1). Other aryl- and alkyl-substituted alkynyl Grignard reagents were also investigated for the reaction with (R,S_R)-**3**, and the desired imides **14b–e** were produced with high diastereoselectivities (*dr* = 99:1) (Table 3, entries 2–5). The reactions of α-chiral aldimine (R,S_S)-**3** with alkynyl Grignard reagents also afforded the desired products in comparable combined yields of both *trans* and *cis* isomers, but with significantly lower diastereoselectivities. When (R,S_S)-**3** was treated with (2-phenylethynyl)magnesium bromide, the desired imide **14a** was obtained in 73% combined yield with low diastereoselectivity (*dr* = 38:62), favoring the *cis* form (Table 3 entry 6). Both (2-*m*-tolylethynyl)magnesium bromide and [2-(4-fluorophenyl)ethynyl]magnesium bromide also yielded the imides **14b** and **14c** with low diastereoselectivities, predominantly in the *cis* forms (Table 3, entries 7 and 8). Interestingly, when (3,3-dimethylbut-1-ynyl)magnesium bromide and hept-1-ynylmagnesium bromide were subjected to the reaction sequence, the major isomer of resulting imides **14d** and **14e** were the *trans* forms (Table 3, entries 9 and 10). Our results indicate that the stereochemistry outcome for the reactions with alkynyl Grignard reagents was controlled by both the α-alkoxy substitution and the chiral sulfinamide. When α-chiral aldimine (R,S_R)-**3** was used, imide **14** was obtained with high diastereoselectivity (*dr* = 99:1) for the *trans* form. However, the reactions with α-chiral aldimine (R,S_S)-**3** gave poor diastereoselectivities, with the aryl-substituted alkynyl Grignard reagents producing the major imides **14** in the *cis* forms and alkyl-substituted alkynyl Grignard reagents favoring *trans* products.

Table 3. Reactions of different alkynyl Grignard reagents with **3**.



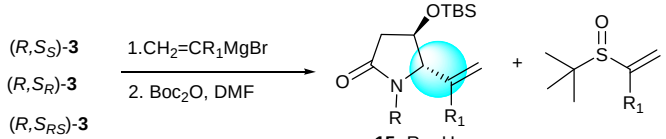
trans-**14** *cis*-**14**

Entry[a]	R	**3**	**14a–e**	Yield(%)[b]	*trans*:*cis*[c]
1	C_6H_5	(R,S_R)	(2*S*,3*R*)-**14a**	76	99:1
2	3-Me-C_6H_4	(R,S_R)	(2*S*,3*R*)-**14b**	80	99:1
3	4-F-C_6H_4	(R,S_R)	(2*S*,3*R*)-**14c**	77	99:1
4	$CH_3(CH_2)_3CH_2$	(R,S_R)	(2*S*,3*R*)-**14d**	79	99:1
5	$C(CH_3)_3$	(R,S_R)	(2*S*,3*R*)-**14e**	70	99:1
6	C_6H_5	(R,S_S)	(2*R*,3*R*)-**14a**	73	38:62
7	3-Me-C_6H_4	(R,S_S)	(2*R*,3*R*)-**14b**	75	35:65
8	4-F-C_6H_4	(R,S_S)	(2*R*,3*R*)-**14c**	72	34:66
9	$CH_3(CH_2)_3CH_2$	(R,S_S)	(2*R*,3*R*)-**14d**	71	61:39
10	$C(CH_3)_3$	(R,S_S)	(2*R*,3*R*)-**14e**	63	68:32

a. Reactions were performed with **3** (1.0 mmol), Grignard reagents (3 mL, 1.0 M in THF) in dry THF (5 mL) at −78 °C to rt overnight, crude product was treated with Boc_2O (2.0 mmol), DMAP (1.0 mmol), and triethylamine (5.0 mmol) in DMF for 24 h. b. Isolated yield. c. Determined by ^{1}H NMR.

The tandem process of reacting α-chiral aldimine **3** with alkenyl Grignard reagents was also investigated. Like the reaction with imine substrate **1**,[7b] the generation of the stereogenic center at C-5 was solely controlled by the α-OTBS group (Table 4, entries 1–5)

Table 4. Reactions of different alkenyl Grignard reagents with 3.



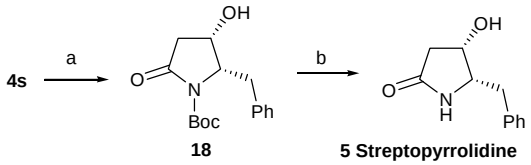
15: R = H
trans-**17:** R = Boc
16

Entry[a]	**3**	R_1	**17**	Yield (%)[b]	*trans*:*cis*[c]
1	(R,S_{RS})	H	**17a**	69	99:1
2	(R,S_R)	H	**17a**	74	99:1
3	(R,S_S)	H	**17a**	65	99:1
4	(R,S_R)	Et-	**17b**	68	98:2
5	(R,S_S)	Et-	**17b**	59	96:4

a. Reactions were performed with α-chiral substituted aldimines **3** (1.0 mmol), alkenyl Grignard reagents (3 mL, 1.0 M in THF) in dry THF (5 mL) at −78 °C to rt

overnight, crude product was treated with Boc_2O (2.0 mmol), DMAP (1.0 mmol), and triethylamine (5.0 mmol) in DMF for 24 h. b. Isolated yield. c. Determined by HPLC or ^1H NMR

With this effective method for the preparation of *trans*-4-hydroxy-5-substituted 2-pyrrolidinones in hand, we decided to use it in the total syntheses of natural products. The synthesis of streptopyrrolidine **5** only requires a chiral inversion at the C-4 positon of **4s**. After the deprotection (*tetra-n*-butylammonium fluoride, TBAF) of **4s**, oxidation (DMP) and subsequent reduction ($NaBH_4$) generated **18** in 89% overall yield, which was treated with trifluoroacetic acid (TFA) to afford streptopyrrolidine **5** in 83% yield (Scheme 2) {$[\alpha]_D^{25}$= −44.5 (*c* 0.15, MeOH); lit.[9j] $[\alpha]_D^{25}$= −44.6 (*c* 0.05, MeOH); lit.[11] $[\alpha]_D^{25}$= −12 (*c* 0.05, MeOH); lit.[20a] $[\alpha]_D^{20}$= −44 (*c* 1.0, MeOH); lit.[20b] $[\alpha]_D^{20}$= −43.5 (*c* 1.0, MeOH)}. The spectroscopic and physical data of the synthetic streptopyrrolidine **5** were identical to the reported data.[9j,11,20]



Scheme 2. Asymmetric synthesis of streptopyrrolidine **5**. Reagents and conditions: a. (1) TBAF, THF, 3 h; (2) DMP, DCM, 30 min; (3) $NaBH_4$, MeOH, 0 °C~rt, 2 h, 89% (3 steps); b. TFA, 0 °C~rt, 4 h, 83%.

Next, we focused on the total synthesis of epohelmin A **6**, a novel lanosterol synthase inhibitor that was isolated from fungal strain FKI-0929.[12a] The chemical structure of **6** was revised from the originally proposed monocyclic core to a bicyclic skeleton by Snider after their asymmetric synthesis in 2005.[12b,c] Our retrosynthetic analysis is shown in Figure 3, hoping to introduce the C-3 chiral center through nucleophilic addition of lactam by allylmagnesium chloride and subsequent stereoselective reduction sequence.

Thus, the intramolecular cascade reaction of *α*-chiral aldimines (*R,S*$_{R,S}$)-**3** with [3-(benzyloxy)propyl]magnesium bromide was initially considered. To our disappointment, the yield of **19a**

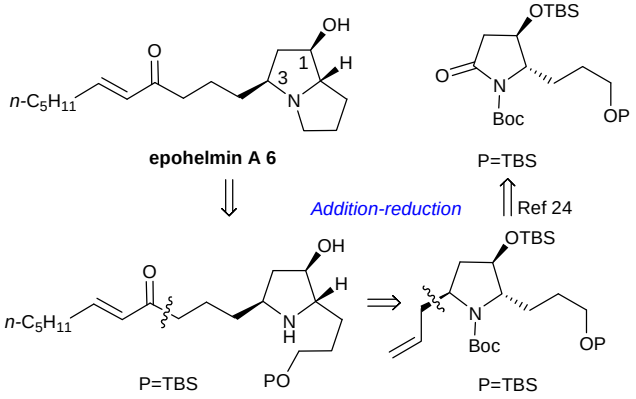
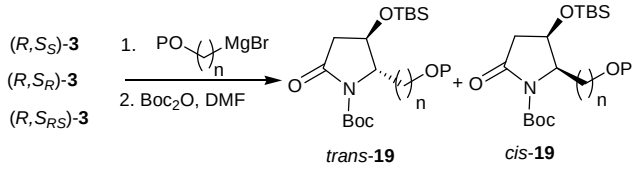


Figure 3. Retrosyntheyic analysis of epohelmin A 6.

was very low and the diastereoselectivity was very low (38:62) (Table 5, entry 1). Moreover, the major imide **19a** was the *cis* form (Table 5, entry 1). Although several conditions including (*R,S*$_R$)-**3** and (*R,S*$_S$)-**3** were investigated, the stereochemistry was still low (Table 5, entries 2 and 3). The use of (3-[(*tert*-butyl)dimethylsilyloxy]propyl)magnesium bromide was also investigated, but the intramolecular tandem process did not proceed (Table 5, entry 4). To further investigate this abnormal result, different [(benzyloxy)alkyl]magnesium bromides were studied. When (*R,S*$_{R,S}$)-**3** was treated with [2-(benzyloxy)ethyl]magnesium bromide, no desired product was produced (Table 5, entry 5). Using [4-(benzyloxy)butyl]magnesium bromide, the yield of desired imide **19d** was improved to 53%, and the ratio of diastereoselectivity for *trans* to *cis* changed to 50:50 (Table 5, entry 6). Interestingly, when (*R,S*$_{R,S}$)-**3** was treated with [6-(benzyloxy)hexyl]magnesium bromide, desired product **19e** was generated in 60% yield and the diastereoselectivity returned to normal, with 90:10 ratio favoring the *trans* (Table 5, entry 7).

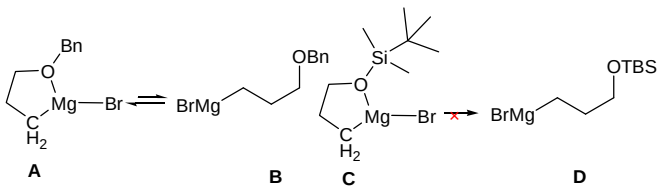
Table 5. Reactions of (benzyloxy) or (silaneoxy) Grignard reagents with **3**



Entry[a]	**3**	*n*	P	**19**	Yield (%)[b]	*trans*:*cis*[c]
1	(*R,S*$_{RS}$)	3	Bn	**19a**	32	38: 62
2	(*R,S*$_R$)	3	Bn	**19a**	35	41:59
3	(*R,S*$_S$)	3	Bn	**19a**	29	35:65
4	(*R,S*$_{RS}$)	3	TBS	**19b**	NR[d]	--
5	(*R,S*$_{RS}$)	2	Bn	**19c**	NR[d]	--
6	(*R,S*$_{RS}$)	4	Bn	**19d**	53	50:50
7	(*R,S*$_{RS}$)	6	Bn	**19e**	60	90:10

a. Reactions were performed with *α*-chiral substituted aldimines **3** (1.0 mmol), Grignard reagents (3 mL, 1.0 M in THF) in dry THF (5 mL) at −78 °C to rt overnight, crude product was treated with Boc_2O (2.0 mmol), DMAP (1.0 mmol), and TEA (5.0 mmol) in DMF for 24 h. b.Isolated yield. c. Determined by HPLC or ^1H NMR. d. No reaction.

In understanding why the intramolecular cascade reaction of (*R,S*$_{RS}$)-**3** with [3-(benzyloxy) propyl]magnesium bromide gave different results, we considered that strong coordination of magnesium with oxygen produced the cyclic form as stable intermediates (Figure 4, structures **A**)[21] that weakly produced **B** to attack the C=N bond. It is likely that steric hindrance caused the abnormal result. For (3-[(*tert*-butyl)dimethylsilyloxy]propyl)magnesium bromide **D**, we think that the steric hindrance of more stable structure **C** is predominant. Thus it could not attach the C=N bond. However, there is balance between the coordination structure **E** and [4-(benzyloxy)butyl]magnesium bromide **F**, and the steric hindrance of **E** caused the *cis*- result. Thus, the ratio of diastereoselectivity for imine **19d** is near 50:50. For [6-(benzyloxy)hexyl]magnesium bromide **H**, the coordination structure **G** is very weak, so the intramolecular cascade reaction of (*R,S*$_{R,S}$)-**3** gave the normal *trans* product.



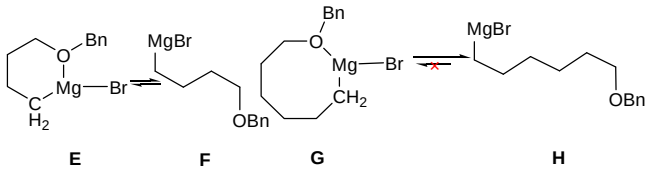
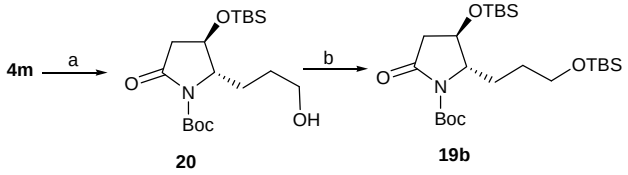


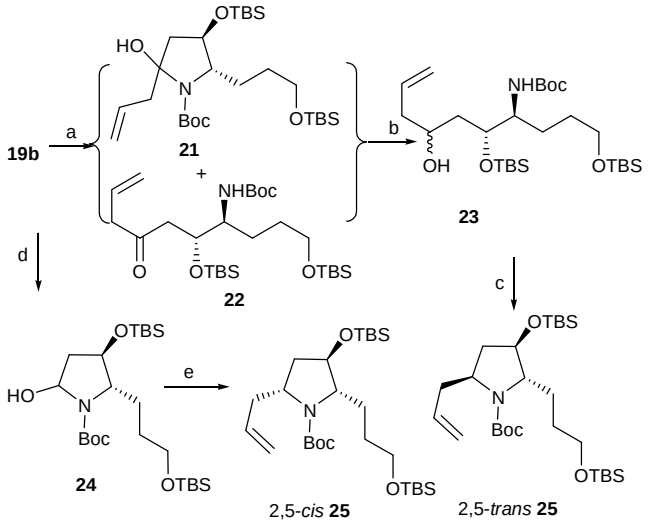
Figure 4. The prososed coordination structures of magnesium with oxygen.

To obtain **19b**, lactam **4m** was selected as a key intermediate for synthesis of epohelmin A **6**. Thus, the dihydroxylation of alkene **4m** with 4-methylmorpholine 4-oxide (NMO) in the presence of 0.1 equivalents of $K_2Os_2O_2(OH)_4$[22] and continuous oxidation with $NaIO_4$[23] as well as subsequent reduction with $NaBH_4$ gave desired alcohol **20** in 87% overall yield (Scheme 3). The hydroxyl group in **20** was then converted to TBS ether in 93% yield.



Scheme 3. Synthesis of **19b**. Reagents and conditions: a. (1) NMO, K_2OsO_4, *t*-BuOH/H_2O, overnight; (2) $NaIO_4$, THF/H_2O, 1.5 h; (3) $NaBH_4$, MeOH, 0 °C, 87% (3 steps); b. TBSCl, DMAP, imidazole, DMF, 24 h, 93%.

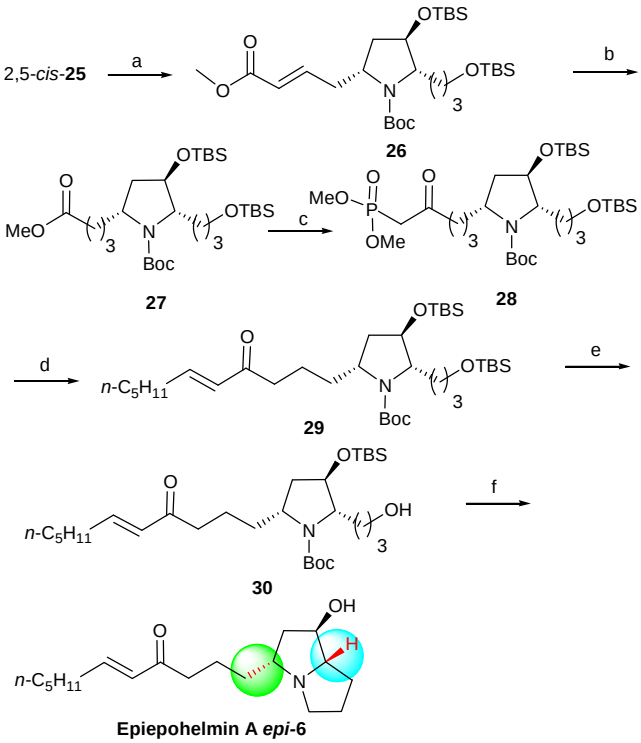
Imine **19b** was treated with a solution of allylmagnesium chloride in dichloromethane at −20 °C; additive product **21** and the tautomeric amidoketone **22** were generated[24](Scheme 4). Without further purification, the crude mixture of compounds **21** and **22** was treated with sodium borohydride (ethanol/$NaBH_4$) in the presence of cerous chloride to afford the crude alcohol **23**, which was directly treated with methanesulfonyl chloride and potassium *tert*-butoxide to give **25** in 70% overall yield with diastereoselectivity (*dr* = 50:50). Methanol was also used as solvent, but the result remained the same (*dr* = 50:50). To obtain diastereoselectivity in **25**, the diastereoselective nucleophilic addition of organic boronic ester to *N*-acyliminium ions[24b] was investigated. Reduction of **19b** with lithium triethylhydridoborate



Scheme 4. Asymmetric allylation of **19b**. Reagents and conditions: a. Allylmagnesium chloride, DCM; b. $NaBH_4$, $CeCl_3$, EtOH; c. (1) MsCl, TEA, DCM; (2) *t*-BuOK, THF, 70% (3 steps); d. $LiBEt_3H$, THF, −78 °C; e. 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, BF_3•Et_2O, −78 °C~−40 °C, DCM, 69% (2 steps from **19b**).

gave *N,O*-acetals **24** in quantitative yield, which was directly treated with 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane to afford desired product 2,5-*cis*-**25** in 69% overall yield with high diastereoselectivity (*dr* > 99:1). The stereochemistry of **25** prepared by the addition–reduction–cyclization process was assigned as the 2,5-*trans* form by comparing data with 2,5-*cis*-**25**.[24b]

With the 2,5-*cis*-**25** in hand, the asymmetric synthesis of 3-*epi*-epohelmin A (3-*epi*-**6**) was considered as shown in Scheme 5. The carbon chain extension of 2,5-*cis*-**25** through Grubbs' second-generation catalyst[25] successfully afforded olefin **26** in 95% yield with excellent selectivity (*E:Z* = 95:5). Reduction (Pd/C, H_2) of **26** gave ester **27** in 92% yield. Compound **27** was treated with a large excess of $LiCH_2PO(OMe)_2$ in THF at −78 °C to −50 °C to obtain keto phosphonate **28** in 97% isolated yield.[12b] Treatment of **28** with NaH in THF, followed by addition of hexanal gave enone **29** in 88% yield with good selectivity (*E:Z* = 98:2).[12b] Selective deprotection of **29** with CSA in a mixture of DCM and methanol at −50 °C for 8 h gave alcohol **30** in 93% yield. Finally, mesylation of compound **30** with methanesulfonyl chloride in the presence of triethylamine and subsequent treatment with triethylsilyl triflate (TESOTf)/2,6-lutidine generated the bicyclic product, which was subjected to desilylation with HCl/methanol in one pot, affording 3-*epi*-epohelmin A (3-*epi*-**6**) in 49% yield {$[\alpha]_D^{25}$ = +7.8 (*c* 0.80, $CHCl_3$)}. The structure of synthetic 3-*epi*-**6** was further confirmed by the spectroscopic and physical data.



Scheme 5. Asymmetric synthesis of 3-*epi*-epohelmin A (3-*epi*-**6**). Reagents and conditions: a. Methyl acrylate, Grubbs[2nd], DCM, reflux, 7 h, 95%; b. Pd/C, H_2, MeOH, 92%; c. dimethyl methylphosphonate, *n*-BuLi, THF, −78 °C, 1 h, then (*5R*)-**27**, −50 °C, 2 h, 97%; d. NaH, (*5R*)-**28**, THF, 1 h, then caproaldehyde, 0 °C, 3 h, 88%; e. CSA, DCM/MeOH, −50 °C, 8 h, 93%; f. (1) MsCl, TEA, DCM, 100%; (2) 2,6-lutidine, TESOTf, DCM, -78 °C~rt, overnight; (3) HCl/MeOH, 24 h, 49% (2 steps).

Conclusions

We established a convenient one-pot method for highly diastereoselective synthesis of *trans*-4-hydroxy-5-substituted 2-pyrrolidinones **4a–s**, **14a–e**, and **17a,b** by an intramolecular cascade process of (R,S_{RS})-**3** with alkyl, aryl, alkynyl, and alkenyl Grignard reagents. For the reaction of (R,S_{RS})-**3** with alkyl, aryl, and alkenyl Grignard reagents, the stereochemistry at the C-5 stereogenic center of the *trans*-4-hydroxy-5-substituted 2-pyrrolidinones was solely controlled by α-alkoxy substitution. In contrast, in reactions of (R,S_{RS})-**3** with alkynyl Grignard reagents, the stereochemistry at the C-5 stereogenic center was controlled by coordination of the α-alkoxy substitution and the stereochemistry of the sulfinamide. The synthetic application of this methodology was demonstrated by the asymmetric syntheses of streptopyrrolidine **5** and 3-*epi*-epohelmin A (3-*epi*-**6**).

Experimental Section

General: THF was distilled from sodium/benzophenone. Reactions were monitored by thin layer chromatography (TLC) on glass plates coated with silica gel with fluorescent indicator. Flash chromatography was performed on silica gel (300–400) with Petroleum / EtOAc as eluent. Optical rotations were measured on a polarimeter with a sodium lamp. HRMS were measured on a LCMS-IT-TOF apparatus. IR spectra were recorded using film on a Fourier Transform Infrared Spectrometer. NMR spectra were recorded at 400 MHz or 500 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.

(*R*)-Methyl 3-(*tert*-butyldimethylsilyloxy)-4-hydroxybutanoate 10 To a solution of **9** (40.0 g, 110.42 mmol) and CSA (20.9 g, 88.34 mmol) was stirred in DCM (200 mL) and MeOH (200 mL) at -40 ^{o}C for 8 h. Then a solution of TEA (15.3 mL, 110.42 mmol) was dropped and the mixture was warmed to room temperature. After being concentrated, the residue was purified by flash chromatography on silica gel (PE/EA=6/1) to give alcohol **10** (17.8 g, 65%) as a colorless oil. $[\alpha]_D^{25}$ = +12.8 (*c* 1.02, $CHCl_3$); IR (film): ν_{max} 3462, 2954, 2930, 2887, 2858, 1740, 1438, 1256, 1169, 1115, 1071, 838, 779 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24-4.16 (m, 1H), 3.67 (s, 3H), 3.63-3.57 (m, 1H), 3.56-3.50 (m, 1H), 2.60-2.50 (m, 2H), 2.03 (dd, *J* = 7.6, 5.2 Hz, 1H), 0.87 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 69.7, 66.2, 51.6, 39.2, 25.7, 18.0, -4.7, -4.9 ppm; HRMS (ESI-TOF) *m/z:* [M + Na]$^+$ Calcd for $C_{11}H_{24}O_4SiNa$: 271.1342, found: 271.1354.

(*E,3R,S*$_{RS}$)-Methyl 3-(*tert*-butyldimethylsilyloxy)-4-(2-methylpropan-2-ylsulfinamido)butanoate 3 Then the above alcohol **10** was dissolved in DCM (200 mL) and treated with new prepared DMP (36.5 g, 86.14 mmol) at room temperature for 30 min. The mixture was quenched carefully with a saturated solution of $NaHCO_3$ and $Na_2S_2O_3$. The resulted mixture was separated and the aqueous was extracted with DCM for three times. The combined organic layers were washed with brine. Dried, filtrated and concentrated to give crude aldehyde **11**, which was dissolved in DCM (200 mL). Then 2-methyl-2-propanesulfinamide (8.7 g, 71.78 mmol), cupric sulphate anhydrous (22.9 g, 143.56 mmol) and PPTS (0.9 g, 3.59 mmol) were added in one portion. After being stirred for 24 h, the reaction was filtrated and concentrated to give the crude product, which was purified by flash chromatography on silica gel (PE/EA=10/1) to give **3** (21.1 g, 2 steps for 84%) as a colorless oil. For the mixture: IR (film): ν_{max} 2955, 2930, 2898, 2858, 1742, 1624, 1473, 1462, 1437, 1364, 1256, 1173, 1090, 1005, 838, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-8.02 (m, 0.33H), δ 7.96-7.94 (m, 0.67H), 4.90-4.84 (m, 0.67H), 4.58-4.54 (m, 0.33H), 3.68-3.67 (m, 1H), 3.65-3.63 (m, 2H), 2.98-2.85 (m, 0.66H), 2.78-2.71 (m, 0.67H), 2.62-2.54 (m, 0.67H), 1.16-1.14 (m, 6H), 1.14-1.12 (m, 3H), 0.86-0.82 (m, 9H), 0.07-0.02 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 170.7, 169.4, 165.7, 71.2, 69.3, 57.0, 56.8, 52.0, 51.8, 40.9, 40.3, 25.6, 22.3, 22.2, 18.2, 18.0,-4.5, -4.9, -5.1, -5.4 ppm; HRMS (ESI-TOF) *m/z:* [M + H]$^+$ Calcd for $C_{15}H_{32}NO_4SSi$: 350.1821, found: 350.1821.

*General procedure for synthesis of **4a-s, 14a-e** and **17a-b***: Compound **3** (350 mg, 1.00 mmol) was dissolved in anhydrous THF (5 mL) and cooled to -78 ^{o}C. Then a solution of Grignard reagent (3 mL, 1 M in THF) was slowly dropped. After being stirred for 3 h, the mixture was warmed to room temperature and stirred for overnight. The reaction was quenched with a saturated NH_4Cl aqueous solution and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine, dried, filtered and concentrated to give crude amide, which was directly dissolved in dry DMF (4 mL), then TEA (0.70 mL, 5.00 mmol), Boc_2O (0.46 mL, 2 mmol) and DMAP (122 mg, 1.00 mmol) was added. After stirring for 24 h, the reaction was diluted with water and extracted with EtOAc for three times. The combined organic layers were washed with water and brine for two times respectively. Dried, filtered and concentrated, the residue was purified by flash chromatography on silica gel (PE/EA = 15/1) to give imide **4a-s, 14a-e** and **17a-b**.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-oxo-2-phenylpyrrolidine-1-carboxylate 4a White solid (277 mg, 71%), m.p 112-113^{o}C. $[\alpha]_D^{25}$ = -5.4 (*c* 1.40, $CHCl_3$); IR (film): ν_{max} 2948, 2931, 2855, 1794, 1458, 1367, 1306, 1255, 1151, 1101, 839, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.30 (m, 3H), 7.22-7.18 (m, 2H), 5.00-4.95 (m, 1H), 4.12 (ddd, *J* = 5.6, 2.4, 1.6 Hz, 1H), 2.87 (dd, *J* = 17.2, 5.6 Hz, 1H), 2.43 (dd, *J* = 17.2, 1.6 Hz, 1H), 1.32 (s, 9H), 0.91 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 149.6, 139.1, 129.0, 128.0, 125.2, 83.0, 72.0, 71.4, 41.0, 27.7, 25.7, 18.0, -4.7, -4.8 ppm; HRMS (ESI-TOF) *m/z:* [M + Na]$^+$ Calcd for $C_{21}H_{33}NO_4SiNa$: 414.2077, found: 414.2066.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-oxo-2-o-tolylpyrrolidine-1-carboxylate 4b Pale yellow oil (251 mg, 62%). $[\alpha]_D^{25}$ = -8.2 (*c* 2.50, $CHCl_3$); IR (film): ν_{max} 2959, 2931, 2849, 1789, 1753, 1721, 1463, 1370, 1307, 1249, 1153, 1079, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.16 (m, 3H), 7.06-7.01 (m, 1H), 5.23-5.21 (m, 1H), 4.07 (ddd, *J* = 5.6, 2.4, 1.6 Hz, 1H), 2.87 (dd, *J* = 17.2, 5.6 Hz, 1H), 2.45-2.39 (m, 4H), 1.28 (s, 9H), 0.90 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 149.4, 137.1, 134.9, 130.8, 127.7, 126.6,

123.2, 82.8, 71.1, 67.9, 41.1, 27.6, 25.6, 19.3, 17.8, -4.6, -4.9 ppm; HRMS (ESI-TOF) *m/z:* $[M + Na]^+$ Calcd for $C_{22}H_{35}NO_4SiNa$: 428.2233, found: 428.2231.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-oxo-2-m-tolylpyrrolidine-1-carboxylate 4c Pale yellow oil (296 mg, 73%). $[\alpha]_D^{25}$ = -2.4 (*c* 2.78, $CHCl_3$); IR (film): ν_{max} 2959, 2931, 2849, 1789, 1753, 1715, 1359, 1307, 1154, 1079, 838, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.17 (m, 1H), 7.08-7.04 (m, 1H), 6.95-6.90 (m, 2H), 4.90-4.87 (m, 1H), 4.05 (ddd, *J* = 5.6, 2.4, 1.6 Hz, 1H), 2.81 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.35 (dd, *J* = 17.6, 1.6 Hz, 1H), 2.29 (s, 3H), 1.26 (s, 9H), 0.84 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 149.6, 138.9, 138.7, 128.9, 128.7, 125.6, 122.3, 82.9, 72.0, 71.4, 41.1, 27.7, 25.7, 21.4, 18.0, -4.7, -4.8 ppm; HRMS (ESI-TOF) *m/z:* $[M + Na]^+$ Calcd for $C_{22}H_{35}NO_4SiNa$: 428.2233, found: 428.2233.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-oxo-2-p-tolylpyrrolidine-1-carboxylate 4d White solid (276 mg, 68%), m.p 98-99°C. $[\alpha]_D^{25}$ = -4.6 (*c* 1.43, $CHCl_3$); IR (film): ν_{max} 2953, 2932, 2855, 1789, 1726, 1370, 1307, 1153, 1068, 921, 838, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19-7.17 (m, 2H), 7.08-7.06 (m, 2H), 4.97-4.93 (m, 1H), 4.09 (ddd, *J* = 5.6, 2.0, 1.2 Hz, 1H), 2.86 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.40 (ddd, *J* = 17.6, 2.0, 0.8 Hz, 1H), 2.36 (s, 3H), 1.33 (s, 9H), 0.90 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 149.7, 137.7, 136.0, 129.6, 125.1, 82.9, 72.1, 71.3, 41.0, 27.7, 25.7, 21.1, 18.0, -4.7, -4.8 ppm; HRMS (ESI-TOF) *m/z:* $[M + Na]^+$ Calcd for $C_{22}H_{35}NO_4SiNa$: 428.2233, found: 428.2222.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(4-methoxyphenyl)-5-oxopyrrolidine-1-carboxylate 4e Pale yellow oil (312 mg, 74%). $[\alpha]_D^{25}$ = -5.7 (*c* 1.66, $CHCl_3$); IR (film): ν_{max} 2953, 2932, 2849, 1787, 1715, 1512, 1364, 1306, 1251, 1153, 1079, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03-7.09 (m, 2H), 6.93-6.89 (m, 2H), 4.94-4.92 (m, 1H), 4.08 (ddd, *J* = 5.6, 2.0, 1.2 Hz, 1H), 3.82 (s, 3H), 2.87 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.41 (dd, *J* = 17.6, 1.6 Hz, 1H), 1.34 (s, 9H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 159.3, 149.6, 131.1, 126.4, 114.3, 82.9, 72.1, 70.1, 55.3, 41.0, 27.8, 25.7, 18.0, -4.7, -4.8 ppm; HRMS (ESI-TOF) *m/z:* $[M + Na]^+$ Calcd for $C_{22}H_{35}NO_5SiNa$: 444.2182, found: 444.2172.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(3-fluorophenyl)-5-oxopyrrolidine-1-carboxylate 4f White solid (327 mg, 80%), m.p 51-53°C. $[\alpha]_D^{25}$ = -6.0 (*c* 1.9, $CHCl_3$); IR (film): ν_{max} 2954, 2931, 2858, 1790, 1758, 1721, 1589, 1453, 1367, 1305, 1258, 1153, 1082, 919, 839, 779 cm^{-1}; ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.82 ppm; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.33 (m, 1H), 7.05-6.98 (m, 2H), 6.93-6.88 (m, 1H), 4.97-4.93 (m, 1H), 4.10 (ddd, *J* = 5.6, 2.8, 2.0 Hz, 1H), 2.86 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.44 (dd, *J* = 17.6, 2.4 Hz, 1H), 1.34 (s, 9H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 163.2 (d, *J* = 246.1 Hz), 149.4, 141.9 (d, *J* = 6.7 Hz), 130.7 (d, *J* = 8.2 Hz), 120.7 (d, *J* = 2.2 Hz), 114.9 (d, *J* = 21.0 Hz), 112.4 (d, *J* = 22.2 Hz), 83.3, 71.9, 70.9, 41.0, 27.7, 25.6, 18.0, -4.5, -4.8, -5.1 ppm; HRMS (ESI-TOF) *m/z:* $[M + Na]^+$ Calcd for $C_{21}H_{32}FNO_4SiNa$:432.1982, found: 432.1985.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(4-fluorophenyl)-5-oxopyrrolidine-1-carboxylate 4g White solid (331 mg, 81%), m.p 111-112°C. $[\alpha]_D^{25}$ = -6.9 (*c* 0.78, $CHCl_3$); IR (film): ν_{max} 2948, 2926, 2849, 1789, 1715, 1518, 1370, 1306, 1249, 1151, 1085, 839 cm^{-1}; ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.11 ppm; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21-7.15 (m, 2H), 7.12-7.06 (m, 2H), 4.95-4.92 (m, 1H), 4.08 (ddd, *J* = 5.6, 2.8, 2.0 Hz, 1H), 2.86 (dd, *J* = 17.6, 6.0 Hz, 1H), 2.45 (dd, *J* = 17.6, 2.4 Hz, 1H), 1.34 (s, 9H), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 162.3 (d, *J* = 245.2 Hz), 149.4, 135.0 (d, *J* = 2.8 Hz), 126.9 (d, *J* = 8.1 Hz), 116.0 (d, *J* = 21.5 Hz), 83.2, 72.0, 70.7, 41.0, 27.7, 25.6, 18.0, -4.5, -4.8, -5.1 ppm; HRMS (ESI-TOF) *m/z:* $[M + Na]^+$ Calcd for $C_{21}H_{32}FNO_4SiNa$:432.1982, found: 432.1977.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-oxo-2-(3-(trifluoromethyl)phenyl)pyrrolidine-1-carboxylate 4h Pale yellow oil (271 mg, 59%). $[\alpha]_D^{25}$ = -4.1 (*c* 0.92, $CHCl_3$); IR (film): ν_{max} 2948, 2931, 2866, 1801, 1452, 1364, 1333, 1255, 1167, 1130, 1096, 893, 839, 780 cm^{-1}; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.78 ppm; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.38 (m, 4H), 4.97 (d, *J* = 2.4 Hz, 1H), 4.11 (ddd, *J* = 6.4, 3.2, 2.8 Hz, 1H), 2.86 (dd, *J* = 17.2, 6.4 Hz, 1H), 2.49 (dd, *J* = 17.6, 3.2 Hz, 1H), 1.31 (s, 9H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 149.3, 140.5, 131.5 (d, *J* = 43.1, 21.6 Hz), 129.6, 128.5, 124.8 (d, *J* = 23.0 Hz),123.8 (d, *J* = 361.0, 180.4 Hz), 122.3 (d, *J* = 22.0 Hz), 83.5, 72.0, 70.8, 41.0, 27.7, 25.6, 17.9, -4.8, -4.9 ppm; HRMS (ESI-TOF) *m/z:* $[M + Na]^+$ Calcd for $C_{22}H_{32}F_3NO_4SiNa$:482.1950, found: 482.1951.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(4-phenyl)-5-oxopyrrolidine-1-carboxylate 4i Colorless oil (378 mg, 81%). $[\alpha]_D^{25}$ = -5.8 (*c* 2.75, $CHCl_3$); IR (film): ν_{max} 2953, 2937, 2849, 1788, 1721, 1359, 1306, 1255, 1152, 1079, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64-7.61 (m, 4H), 7.49-7.45 (m, 2H), 7.40-7.36 (m, 1H), 7.27-7.25 (m, 2H), 5.05-5.03 (m, 1H), 4.17 (ddd, *J* = 5.2, 3.2, 1.2 Hz, 1H), 2.92 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.40 (dd, *J* = 17.6, 1.6, Hz, 1H), 1.36 (s, 9H), 0.93 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 149.7, 140.9, 140.3, 138.0, 128.9, 127.7, 127.6, 127.0, 125.6, 83.1, 72.0, 71.2, 41.1, 27.8, 25.7, 18.0, -4.7, -4.8 ppm; HRMS (ESI-TOF) *m/z:* $[M + Na]^+$ Calcd for $C_{27}H_{37}NO_4SiNa$: 490.2390, found: 490.2381.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(naphthalen-1-yl)-5-oxopyrrolidine-1-carboxylate 4j Colorless oil (260 mg, 59%). $[\alpha]_D^{25}$ = +42.2 (*c* 1.80, $CHCl_3$); IR (film): ν_{max} 2953, 2932, 2860, 1788, 1759, 1726, 1370, 1308, 1153, 1074, 921, 838, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07-8.05 (m, 1H), 7.95-7.92 (m, 1H), 7.84-7.82 (m, 1H), 7.62-7.54 (m, 2H), 7.47-7.43 (m, 1H), 7.28-7.25 (m, 1H), 5.87-5.85 (m, 1H), 4.24 (ddd, *J* = 5.6, 1.6, 1.2 Hz, 1H), 2.85 (dd, *J* = 17.6, 5.2 Hz, 1H), 2.43 (d, *J* = 17.6 Hz, 1H), 1.26 (s, 9H), 0.96(s, 9H), 0.10(s, 3H), 0.04(s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 149.7, 134.3, 134.0, 130.2, 129.1, 128.5, 126.6, 126.1, 125.3, 122.6, 120.8, 83.0, 70.8, 68.2, 41.3, 27.7, 25.7, 17.9, -4.5, -4.7 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{35}NO_4SiNa$: 464.2233, found: 464.2223.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(naphthalen-2-yl)-5-oxopyrrolidine-1-carboxylate 4k White solid (309 mg, 70%), m.p 116-117°C. $[\alpha]_D^{25}$ = -2.6 (*c* 0.44, $CHCl_3$); IR (film): ν_{max} 2953, 2932, 2866, 1789, 1748, 1715, 1468, 1370, 1306, 1255, 1153, 1068, 838, 779 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$) δ 7.91-7.82 (m, 3H), 7.63 (s, 1H), 7.56-7.50 (m, 2H), 7.35-7.33 (m, 1H), 5.17-5.15 (m, 1H), 4.20 (ddd, *J* = 5.2, 2.0, 1.2 Hz, 1H), 2.94 (dd, *J* = 17.4, 5.6 Hz, 1H), 2.47 (dd, *J* = 17.4, 1.6 Hz, 1H), 1.31 (s, 3H), 0.93 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 149.7, 136.3, 133.3, 133.0, 129.1, 127.9, 127.7, 126.7, 126.3, 123.6, 123.3, 83.1, 71.8, 71.5, 41.1, 27.7, 25.7, 18.0, -4.7, -4.7 ppm; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{25}H_{35}NO4SiNa$: 464.2233, found: 464.2231.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-ethyl-5-oxopyrrolidine-1-carboxylate 4l Colorless oil (223 mg, 65%). $[\alpha]_D^{25}$ = +28.6 (*c* 1.28, $CHCl_3$); IR (film): ν_{max} 2948, 2926, 2866, 1797, 1753, 1714, 1463, 1370, 1309, 1249, 1156, 1074, 926, 837, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (d, *J* = 5.2 Hz, 1H), 3.79 (dd, *J* = 9.6, 3.6 Hz, 1H), 2.68 (dd, *J* = 17.6, 5.2 Hz, 1H), 2.27 (d, *J* = 17.6 Hz, 1H), 1.74-1.61 (m, 1H), 1.46 (s, 9H), 1.39-1.28 (m, 1H), 0.94-0.88 (m, 3H), 0.80 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 150.1, 82.7, 69.2, 67.9, 41.8, 28.0, 25.7, 24.9, 17.9, 10.3, -4.6, -4.7 ppm; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{17}H_{33}NO_4SiNa$: 366.2077, found: 366.2067.

(*2S,3R*)-*tert*-Butyl 2-(but-3-enyl)-3-(*tert*-butyldimethylsilyloxy)-5-oxopyrrolidine-1-carboxylate 4m White solid (255 mg, 69%), m.p 51-53^{o}C. $[\alpha]_D^{25}$ = +30.0 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2955, 2930, 2857, 1787, 1754, 1716, 1468, 1369, 1311, 1258, 1155, 1081, 915, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86-5.75 (m, 1H), 5.12-5.00 (m, 2H), 4.10-4.06 (m, 1H), 3.98-3.92 (m, 1H), 2.82-2.74 (m, 1H), 2.38-2.30 (m, 1H), 2.23-2.05 (m, 2H), 1.84-1.75 (m, 1H), 1.55-1.52 (m, 9H), 1.51-1.43 (m, 1H), 0.88-0.85 (m, 9H), 0.09-0.06 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 149.8, 136.7, 115.6, 82.7, 68.0, 67.2, 41.5, 30.9, 29.9, 27.9, 25.5, 17.7, -4.8, -4.9 ppm; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{19}H_{36}NO_4Si$: 370.2414, found: 370.2408.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-isopropyl-5-oxopyrrolidine-1-carboxylate 4n Colorless oil (186 mg, 52%). {$[\alpha]_D^{25}$ = + 31.8 (*c* 1.82, $CHCl_3$), lit^{9j} $[\alpha]_D^{25}$ = +45.17 (c=1 in $CHCl_3$)}; IR (film): ν_{max} 2964, 2926, 2860, 1787, 1752, 1717, 1474, 1370, 1306, 1157, 1068, 915, 837, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (d, *J* = 5.2 Hz, 1H), 3.89 (d, *J* = 5.6 Hz, 1H), 2.72 (dd, *J* = 18.0, 5.6 Hz, 1H), 2.34 (d, *J* = 17.6 Hz, 1H), 2.06-1.95 (m, 1H), 1.53 (s, 9H), 1.01 (d, *J* = 6.8 Hz, 2H), 0.90-0.86 (m, 12H), 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, 29.7, 28.0, 25.6, 19.3, 17.9, 17.6, -4.6, -4.7 ppm; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{18}H_{35}NO_4SiNa$: 380.2233, found: 380.2241.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-isobutyl-5-oxopyrrolidine-1-carboxylate 4o Colorless oil (226 mg, 61%). {$[\alpha]_D^{25}$ = +36.8 (*c* 1.00, $CHCl_3$), lit^{9j} $[\alpha]_D^{25}$ = +36.06 (*c* 1.02, $CHCl_3$); lit^{10c} $[\alpha]_D^{25}$ = -35.9 (*c* 2.3, $CHCl_3$)}; IR (film): ν_{max} 2957, 2931, 2855, 1787, 1754, 1716, 1463, 1368, 1312, 1257, 1157, 1078, 915, 836, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (d, *J* = 4.8 Hz, 1H), 4.01 (dd, *J* = 10.8, 3.2 Hz, 1H), 2.79 (dd, *J* = 17.6, 5.2 Hz, 1H), 2.34 (d, *J* = 17.6 Hz, 1H), 1.71-1.62 (m, 1H), 1.55 (s, 9H), 1.53-1.45 (m, 1H), 1.28 (ddd, *J* = 14.8, 10.8, 4.0 Hz, 1H), 1.04-0.96 (m, 6H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 149.9, 82.8, 68.5, 66.4, 41.5, 41.1, 28.1, 25.6, 25.3, 23.8, 21.7, 17.9, -4.7, -4.8 ppm; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{19}H_{37}NO_4SiNa$: 394.2390, found: 394.2390.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-oxo-2-pentylpyrrolidine-1-carboxylate 4p Colorless oil (277 mg, 72%). $[\alpha]_D^{25}$ = +20.7 (*c* 1.55, $CHCl_3$); IR (film): ν_{max} 2953, 2926, 2855, 1787, 1748, 1704, 1463, 1370, 1310, 1155, 1074, 836, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09-4.05 (m, 1H), 3.95-3.89 (m, 1H), 2.76 (dd, *J* = 17.6, 5.2 Hz, 1H), 2.34 (d, *J* = 17.6 Hz, 1H), 1.71-1.64 (m, 1H), 1.56-1.52 (m, 9H), 1.43-1.26 (m, 7H), 0.95-0.85 (m, 12H), 0.10-0.05 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 150.1, 82.7, 68.3, 68.0, 41.7, 32.0, 31.6, 28.0, 25.7, 25.6, 22.5, 17.9, 13.9, -4.6, -4.7 ppm; HRMS (ESI-TOF) *m/z:* [M + Na]$^+$ Calcd for $C_{20}H_{39}NO_4SiNa$: 408.2546, found: 408.2555.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-cyclopropyl-5-oxopyrrolidine-1-carboxylate 4q Colorless oil (241 mg, 68%). $[\alpha]_D^{25}$ = +22.5 (*c* 1.95, $CHCl_3$); IR (film): ν_{max} 2955, 2930, 2849, 1787, 1754, 1717, 1463, 1368, 1307, 1255, 1156, 1081, 930, 838, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (d, *J* = 4.8 Hz, 1H), 3.40 (d, *J* = 9.2 Hz, 1H), 2.76 (dd, *J* = 17.2, 4.8 Hz, 1H), 2.27 (d, *J* = 17.2 Hz, 1H), 1.46 (s, 9H), 0.79 (s, 9H), 0.72-0.62 (m, 1H), 0.60-0.44 (m, 3H), 0.24-0.14 (m, 1H), 0.00 (s, 3H), -0.01 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 150.3, 82.7, 71.4, 70.3, 41.8, 27.9, 25.6, 17.9, 13.6, 4.5, 1.8, -4.8, -4.9 ppm; HRMS (ESI-TOF) *m/z:* [M + Na]$^+$ Calcd for $C_{18}H_{33}NO_4SiNa$: 378.2077, found: 378.2083.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-cyclohexyl-5-oxopyrrolidine-1-carboxylate 4r Colorless oil (262 mg, 66%) {$[\alpha]_D^{25}$ = +46.2 (*c* 3.33, $CHCl_3$), lit^{9j} $[\alpha]_D^{25}$ = +40.73 (*c* 0.88, $CHCl_3$)}; IR (film): ν_{max} 2930, 2855, 1785, 1748, 1715, 1370, 1305, 1255, 1154, 1068, 932, 833, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (d, *J* = 5.2 Hz, 1H), 3.80 (d, *J* = 5.6 Hz, 1H), 2.65 (dd, *J* = 17.6, 5.2 Hz, 1H), 2.25 (d, *J* = 18.0 Hz, 1H), 1.77-1.68 (m, 2H), 1.66-1.57 (m, 3H), 1.56-1.49 (m, 1H), 1.46 (s, 9H), 1.23-1.01 (m, 4H), 0.87-0.81 (m, 1H), 0.79 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 150.4, 82.7, 72.5, 66.6, 42.9, 40.2, 29.8, 28.0, 26.3, 26.2, 25.6, 17.9, -4.5, -4.6 ppm; HRMS (ESI-TOF) *m/z:* [M + Na]$^+$ Calcd for $C_{21}H_{39}NO_4SiNa$: 420.2546, found: 420.2549.

(*2S,3R*)-*tert*-Butyl 2-benzyl-3-(*tert*-butyldimethylsilyloxy)-5-oxopyrrolidine-1-carboxylate 4s Pale yellow oil (284 mg, 70%). {$[\alpha]_D^{25}$ = +10.4 (*c* 1.00, $CHCl_3$) lit^{9j} $[\alpha]_D^{25}$ = +8.67 (*c* 1.07, $CHCl_3$); lit^{10b} $[\alpha]_D^{23}$ = +37.9 (*c* 1.20, $CHCl_3$)} IR (film): ν_{max} 2959, 2926, 2860, 1787, 1704, 1370, 1312, 1148, 926, 821 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 2H), 7.30-7.24 (m, 1H), 7.23-7.18 (m, 2H), 4.16 (dd, *J* = 10.4, 3.2 Hz, 1H), 4.07 (d, *J* = 5.2 Hz, 1H), 3.17 (dd, *J* = 13.2, 4.0 Hz, 1H), 2.65 (dd, *J* = 17.6, 5.2 Hz, 1H), 2.51 (dd, *J* = 13.2, 10.4 Hz, 1H), 2.31 (d, *J* = 17.6 Hz, 1H), 1.60 (s, 9H), 0.74 (s, 9H), -0.23 (s, 3H), -0.24 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 150.0, 136.6, 129.3, 128.9, 127.1, 83.0, 69.1, 66.9, 41.4, 38.0, 28.1, 25.5, 17.8, -5.2, -5.3 ppm; HRMS (ESI-TOF) *m/z:* [M + Na]$^+$ Calcd for $C_{22}H_{35}NO_4SiNa$: 428.2233, found: 428.2221.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-oxo-2-(2-phenylethynyl)pyrrolidine-1-carboxylate (*2S,3R*)-**14a** Pale yellow oil (316 mg, 76%). $[\alpha]_D^{25}$ = +19.5 (*c* 1.50, $CHCl_3$); IR (film): ν_{max} 2959, 2926, 2860, 2205 (very weak),1790, 1764, 1715, 1468, 1348, 1308, 1255, 1148, 1074, 1019, 915, 838 cm^{-1}; ^{1}H

NMR (400 MHz, $CDCl_3$) δ 7.44-7.38 (m, 2H), 7.37-7.30 (m, 3H), 4.81-4.78 (m, 1H), 4.43 (d, *J* = 5.2 Hz, 1H), 3.01 (dd, *J* = 17.2, 5.2 Hz, 1H), 2.45 (d, *J* = 17.2 Hz, 1H), 1.58 (s, 9H), 0.92 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 149.4, 131.7, 128.8, 128.4, 121.9, 85.5, 84.2, 83.4, 70.5, 59.2, 41.9, 28.1, 25.7, 18.0, -4.8 ppm; HRMS (ESI-TOF) *m/z:* $[M + H]^+$ Calcd for $C_{23}H_{34}NO_4Si$: 416.2257, found: 416.2253.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-oxo-2-(2-m-tolylethynyl)pyrrolidine-1-carboxylate (*2S,3R*)-**14b** Pale yellow oil (343 mg, 80%). $[\alpha]_D^{25}$ = +25.6 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2959, 2920, 2855, 2367 (very weak), 1792, 1766, 1718, 1369, 1348, 1307, 1148, 1079, 1021, 918, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.15 (m, 4H), 4.81-4.78 (m, 1H), 4.42 (d, *J* = 4.8 Hz, 1H), 3.02 (dd, *J* = 17.2, 5.2 Hz, 1H), 2.45 (d, *J* = 17.2 Hz, 1H), 2.35 (s, 3H), 1.58 (s, 9H), 0.92 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 149.4, 138.1, 132.3, 129.7, 128.8, 128.3, 121.7, 85.7, 83.8, 83.4, 70.5, 59.3, 41.9, 28.1, 25.7, 21.2, 18.0, -4.8 ppm; HRMS (ESI-TOF) *m/z:* $[M + H]^+$ Calcd for $C_{24}H_{36}NO_4Si$: 430.2414, found: 430.2408.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(2-(4-fluorophenyl)ethynyl)-5-oxopyrrolidine-1-carboxylate (*2S,3R*)-**14c** Yellow oil (334 mg, 77%). $[\alpha]_D^{25}$ = +18.2 (*c* 2.00, $CHCl_3$); IR (film): ν_{max} 2959, 2937, 2860, 2227 (very weak), 1791, 1760, 1721, 1600, 1508, 1364, 1307, 1257, 1149, 1090, 1014, 921, 837 cm^{-1}; ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.88 ppm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.36 (m, 2H), 7.06-6.99 (m, 2H), 4.79-4.76 (m, 1H), 4.41 (d, *J* = 5.2 Hz, 1H), 2.99 (dd, *J* = 17.2, 5.2 Hz, 1H), 2.44 (d, *J* = 17.2 Hz, 1H), 1.57 (s, 9H), 0.91 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 162.8 (d, *J* = 248.9 Hz), 149.4, 133.7, 133.6, 118.0 (d, *J* = 3.2 Hz), 115.8, 115.6, 84.5, 83.9, 83.5, 70.4, 59.1, 41.9, 28.0, 25.6, 18.0, -4.8 ppm; HRMS (ESI-TOF) *m/z:* $[M + H]^+$ Calcd for $C_{23}H_{33}FNO_4Si$: 434.2163, found: 434.2159.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(hept-1-ynyl)-5-oxopyrrolidine-1-carboxylate (*2S,3R*)-**14d** Pale yellow oil (323 mg, 79%). $[\alpha]_D^{25}$ = +26.4 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2957, 2926, 2855, 2090 (very weak), 1793, 1760, 1720, 1472, 1352, 1306, 1256, 1149, 1085, 927, 828 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56-4.52 (m, 1H), 4.26 (d, *J* = 5.2 Hz, 1H), 2.92 (dd, *J* = 17.2, 5.2 Hz, 1H), 2.36 (d, *J* = 17.2 Hz, 1H), 2.21-2.15 (m, 2H), 1.56 (s, 9H), 1.52-1.45 (m, 2H) , 1.39-1.29 (m, 4H), 0.93-0.87 (m, 12H), 0.11 (s, 3H), 0.10 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 149.5, 86.4, 83.1, 75.4, 70.7, 59.0, 41.8, 30.9, 28.1, 28.0, 25.6, 22.1, 18.6, 18.0, 13.9, -4.9 ppm; HRMS (ESI-TOF) *m/z:* $[M + H]^+$ Calcd for $C_{22}H_{40}NO_4Si$: 410.2727, found: 410.2722.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(3,3-dimethylbut-1-ynyl)-5-oxopyrrolidine-1-carboxylate (*2S,3R*)-**14e** Pale yellow oil (277 mg, 70%). $[\alpha]_D^{25}$ = +22.7 (*c* 1.50, $CHCl_3$); IR (film): ν_{max} 2968, 2931, 2866, 2209 (very weak), 1793, 1764, 1723, 1364, 1348, 1306, 1255, 1149, 1085, 938, 821 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53-4.50 (m, 1H), 4.25-4.22 (m, 1H), 2.90 (dd, *J* = 16.8, 5.2 Hz, 1H), 2.36 (d, *J* = 17.2 Hz, 1H), 1.55 (s, 9H), 1.20 (s, 9H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 149.3, 94.4, 83.0, 73.9, 70.7, 59.0, 41.7, 30.8, 28.0, 27.3, 25.6, 18.0, -4.9 ppm; HRMS (ESI-TOF) *m/z:* $[M + H]^+$ Calcd for $C_{21}H_{38}NO_4Si$: 396.2570, found: 396.2560.

(*2R,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-oxo-2-(2-phenylethynyl)pyrrolidine-1-carboxylate (*2R,3R*)-**14a** Pale yellow solid (303 mg, 73%), m.p 133-134°C. $[\alpha]_D^{25}$ = -37.7 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2953, 2926, 2849, 2370 (very weak), 1781, 1698, 1326, 1288, 1255, 1158, 1093, 937, 840 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.40 (m, 2H), 7.36-7.30 (m, 3H), 5.05 (d, *J* = 6.8 Hz, 1H), 4.49 (ddd, *J* = 14.0, 7.2, 6.4 Hz, 1H), 2.80 (dd, *J* = 16.4, 9.2 Hz, 1H), 2.67 (dd, *J* = 16.4, 7.2 Hz, 1H), 1.58 (s, 9H), 0.94 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 149.0, 131.7, 128.5, 128.3, 122.6, 86.3, 83.6, 83.3, 66.1, 55.6, 40.8, 28.0, 25.6, 18.0, -4.7, -4.8 ppm; HRMS (ESI-TOF) *m/z:* $[M + H]^+$ Calcd for $C_{23}H_{34}NO_4Si$: 416.2257, found: 416.2257.

(*2R,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-oxo-2-(2-m-tolylethynyl)pyrrolidine-1-carboxylate (*2R,3R*)-**14b** Pale yellow oil (322 mg, 75%). $[\alpha]_D^{25}$ = -27.2 (*c* 1.50, $CHCl_3$); IR (film): ν_{max} 2961, 2928, 2855, 2359, 1792, 1721, 1304, 1146, 1107, 932, 827 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10-7.03 (m, 3H), 7.01-6.97 (m, 1H), 4.88 (d, *J* = 4.8 Hz, 1H), 4.33 (ddd, *J* = 9.2, 5.2, 4.4 Hz, 1H), 2.63 (dd, *J* = 11.2, 6.4 Hz, 1H), 2.51 (dd, *J* = 11.2, 4.4 Hz, 1H), 2.18 (s, 3H), 1.41 (s, 9H), 0.78 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 149.0, 137.9, 132.3, 129.3, 128.8, 128.2, 122.4, 86.5, 83.5, 82.9, 66.1, 55.6, 40.8, 28.0, 25.7, 21.2, 18.0, -4.7, -4.8 ppm; HRMS (ESI-TOF) *m/z:* $[M + H]^+$ Calcd for $C_{24}H_{36}NO_4Si$: 430.2414, found: 430.2402.

(*2R,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(2-(4-fluorophenyl)ethynyl)-5-oxopyrrolidine-1-carboxylate (*2R,3R*)-**14c** Pale yellow solid (312 mg, 72%), m.p 105-106°C. $[\alpha]_D^{25}$ = -29.7 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2953, 2930, 2855, 2200 (very weak), 1791, 1721, 1507, 1304, 1255, 1147, 1101, 836 cm^{-1}; ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.55 ppm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.37 (m, 2H), 7.06-6.98 (m, 2H), 5.03 (d, *J* = 7.2 Hz, 1H), 4.49 (ddd, *J* = 14.0, 7.6, 6.8 Hz, 1H), 2.78 (dd, *J* = 16.4, 9.2 Hz, 1H), 2.67 (d, *J* = 16.4, 7.2 Hz, 1H), 1.57 (s, 9H), 0.93 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 162.6 (d, *J* = 248.2 Hz), 149.0, 133.6, 133.5, 118.6 (d, *J* = 3.2 Hz), 115.7, 115.5, 85.2, 83.6, 83.0, 66.0, 55.5, 40.8, 28.0, 25.6, 18.0, -4.7, -4.8 ppm; HRMS (ESI-TOF) *m/z:* $[M + H]^+$ Calcd for $C_{23}H_{33}FNO_4Si$: 434.2163, found: 434.2157.

(*2R,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(hept-1-ynyl)-5-oxopyrrolidine-1-carboxylate (*2R,3R*)-**14d** Pale yellow oil (290 mg, 71%). $[\alpha]_D^{25}$ = -25.2 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2957, 2931, 2858, 2245 (very weak), 1793, 1760, 1725, 1332, 1305, 1256, 1142, 904, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (ddd, *J* = 7.2, 2.4, 1.6 Hz, 1H), 4.36 (ddd, *J* = 14.0, 7.2, 6.4 Hz, 1H), 2.72 (dd, *J* = 16.4, 10.0 Hz, 1H), 2.58 (dd, *J* = 16.4, 7.2 Hz, 1H), 2.24-2.18 (m, 2H), 1.55 (s, 9H), 1.53-1.47 (m, 2H) , 1.40-1.31 (m, 4H), 0.94-0.88 (m, 12H), 0.13 (s, 3H), 0.11 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 149.2, 87.0, 83.3, 73.8, 66.0, 55.1, 40.6, 31.0, 28.2, 28.0, 25.6, 22.2, 18.7, 18.0, 13.9, -4.7, -4.8 ppm; HRMS (ESI-TOF) *m/z:* $[M + H]^+$ Calcd for $C_{22}H_{40}NO_4Si$: 410.2727, found: 410.2721.

(*2R,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(3,3-dimethylbut-1-ynyl)-5-oxopyrrolidine-1-carboxylate (*2R,3R*)-

14e Pale yellow solid (249 mg, 63%), m.p 120-121°C. $[\alpha]_D^{25}$ = -29.4 (*c* 0.50, $CHCl_3$); IR (film): ν_{max} 2967, 2931, 2855, 2044 (very weak), 1780, 1697, 1342, 1297, 1255, 1149, 1023, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.78 (d, *J* = 7.2 Hz, 1H), 4.36 (ddd, *J* = 14.4, 7.6, 6.8 Hz, 1H), 2.71 (dd, *J* = 16.4, 10.4 Hz, 1H), 2.57 (dd, *J* = 16.4, 7.2 Hz, 1H), 1.56 (s, 9H), 1.22 (s, 9H), 0.94 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 149.0, 95.0, 83.2, 72.2, 65.8, 55.1, 40.5, 30.9, 28.0, 27.4, 25.7, 18.0, -4.7, -4.8 ppm; HRMS (ESI-TOF) *m/z:* $[M + H]^+$ Calcd for $C_{21}H_{38}NO_4Si$: 396.2570, found: 396.2565.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-oxo-2-vinylpyrrolidine-1-carboxylate 17a Pale yellow oil (252 mg, 74%). $[\alpha]_D^{25}$ = -0.45 (*c* 2.80, $CHCl_3$); IR (film): ν_{max} 2953, 2926, 2860, 1787, 1715, 1364, 1309, 1255, 1154, 1079, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddd, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.25-5.17 (m, 2H), 4.47-4.43 (m, 1H), 4.07-4.04 (m, 1H), 2.74 (dd, *J* = 17.6, 5.2 Hz, 1H), 2.37-2.30 (m, 1H), 1.50 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 149.8, 133.9, 116.6, 82.9, 69.5, 69.4, 41.1, 27.9, 25.6, 18.0, -4.8 ppm; HRMS (ESI-TOF) *m/z:* $[M + Na]^+$ Calcd for $C_{17}H_{31}NO_4SiNa$: 364.1920, found: 364.1915.

(*2S,3R*)-*tert*-Butyl 2-(but-1-en-2-yl)-3-(*tert*-butyldimethylsilyloxy)-5-oxopyrrolidine-1-carboxylate 17b Pale yellow oil (251 mg, 68%). $[\alpha]_D^{25}$ = +2.6 (*c* 0.50, $CHCl_3$); IR (film): ν_{max} 2957, 2931, 2859, 1790, 1755, 1721, 1474, 1368, 1306, 1257, 1154, 1087, 920, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.90-4.88 (m, 1H), 4.84-4.82 (m, 1H), 4.38-4.34 (m, 1H), 4.04-4.01 (m, 1H), 2.77 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.30 (d, *J* = 17.2 Hz, 1H), 2.20-2.00 (m, 2H), 1.48 (s, 9H), 1.16-1.11 (m, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 149.7, 147.3, 108.1, 82.7, 71.5, 68.6, 41.1, 27.9, 26.5, 25.6, 17.9, 12.1, -4.6, -4.7 ppm; HRMS (ESI-TOF) *m/z:* $[M + Na]^+$ Calcd for $C_{19}H_{35}NO_4SiNa$: 392.2233, found: 392.2232.

(*2S,3S*)-*tert*-Butyl 2-benzyl-3-hydroxy-5-oxopyrrolidine-1-carboxylate 18 To a solution of **4s** (240 mg, 0.59 mmol) was stirred in dry THF (3 mL) at room temperature, and then a solution of TBAF (3 mL, 1.0 mol in THF) was dropped. After being stirring for 3 hours, the mixture was quenched with water and extracted with EtOAc for three times. 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 (172 mg), which was treated with DMP (502 mg, 1.18 mmol) in dry CH_2Cl_2 (5 mL) for 30 min. Then the mixture was quenched carefully with a saturated solution of $NaHCO_3$ and $Na_2S_2O_3$ and separated. The aqueous layer was extracted with DCM for three times and the combined organic layers were washed with brine. Dried, filtrated and concentrated to give crude ketone without further purification. The above crude mixture was dissolved in MeOH (5 mL) and cooled to 0 °C. Then $NaBH_4$ (22 mg, 0.59 mmol) was added in three portions. After being stirred for 2 hours at 0 °C ~ 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 **18** (153 mg, 89 %) as a white solid. m.p. 122-123 °C; lit.[10d] m.p. 122-124 °C. {$[\alpha]_D^{25}$ = +26.9 (*c* 1.00, $CHCl_3$), lit.[10b] $[\alpha]_D^{24}$ = +25.1 (*c* 0.85, $CHCl_3$); lit.[10d] $[\alpha]_D^{25}$ = +25.2 (*c* 0.86, $CHCl_3$); lit.[9j] $[\alpha]_D^{25}$ = +27.7 (*c* 1.12, $CHCl_3$)}; IR (film): ν_{max} 3403, 2975, 1770, 1676, 1366, 1287, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.22 (m, 5H), 4.56-4.44 (m, 2H), 3.24-3.09 (m, 2H), 2.63 (dd, *J* = 17.0, 7.2 Hz, 1H), 2.43 (dd, *J* = 17.0, 8.0 Hz, 1H), 1.51 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ171.8, 149.8, 137.8, 129.9, 128.6, 126.7, 83.3, 65.6, 62.7, 40.1, 40.0, 28.0 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{21}NO_4Na$: 314.1368, found: 314.1372.

Streptopyrrolidine 5 To a solution of **18** (120 mg, 0.41 mmol) in CF_3COOH (1.5 mL) was attired for 4 h at 0 °C to room temperature. Then the mixture was concentrated and the residue was purified by chromatography on silica gel to give **5** (65 mg, 83%) as a white solid. mp 133-134 °C. lit.[9j] mp 132-134 °C; lit.[20a] mp 134-135 °C; lit.[20b] mp 133-135 °C {$[\alpha]_D^{25}$ = -44.5 (*c* 0.15, MeOH); lit.[9j] $[\alpha]_D^{25}$ = -44.6 (*c* 0.05, MeOH); lit.[11] $[\alpha]_D^{25}$ = -12 (*c* 0.05, MeOH)}; lit.[20a] $[\alpha]_D^{20}$ = -44 (*c* 1.0, MeOH)}; lit.[20b] $[\alpha]_D^{20}$ = -43.5 (*c* 1.0, MeOH)}; IR (film): ν_{max} 3455, 3229, 1693, 1346, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.32 (m, 2H), 7.30-7.24 (m, 3H), 5.78 (brs, 1H), 4.51-4.43 (m, 1H), 3.91 (ddd, *J* = 10.4, 5.6, 4.8 Hz, 1H), 3.07 (dd, *J* = 13.6, 5.6 Hz, 1H), 2.98 (d, *J* = 4.8 Hz, 1H), 2.86 (dd, *J* = 13.6, 8.8 Hz, 1H), 2.68 (dd, *J* = 17.2, 6.0 Hz, 1H), 2.42 (dd, *J* = 17.2, 2.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 137.7, 129.0, 128.9, 126.9, 68.7, 60.8, 41.0, 35.4 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{14}NO_2$: 192.1025, found: 192.1010.

(*2S,3R*)-*tert*-Butyl 2-(3-(benzyloxy)propyl)-3-(*tert*-butyldimethylsilyloxy)-5-oxopyrrolidine-1-carboxylate (*2S,3R*)**-19a** Pale yellow oil (56 mg, 12%). $[\alpha]_D^{25}$ = +23.0 (*c* 0.20, $CHCl_3$); IR (film): ν_{max} 2959, 2924, 2854, 1782, 1717, 1457, 1364, 1309, 1260, 1152, 1076, 1019, 921, 828 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.31 (m, 5H), 4.55-4.48 (m, 2H), 4.09 (d, *J* = 5.2 Hz, 1H), 3.96 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.57-3.47 (m, 2H), 2.78 (dd, *J* = 17.6, 5.2 Hz, 1H), 2.36 (d, *J* = 17.6 Hz, 1H), 1.84-1.62 (m, 4H), 1.54 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 150.1, 138.3, 128.4, 127.7, 82.9, 73.1, 69.8, 68.3, 67.9, 28.9, 28.0, 26.4, 25.7, 17.9, -4.6, -4.7 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{41}NO_5SiNa$: 486.2652, found: 486.2653.

(*2R,3R*)-*tert*-Butyl 2-(3-(benzyloxy)propyl)-3-(*tert*-butyldimethylsilyloxy)-5-oxopyrrolidine-1-carboxylate (*2R,3R*)**-19a** White solid (93 mg, 20%), m.p 80-82°C. $[\alpha]_D^{25}$ = -38.9 (*c* 2.42, $CHCl_3$); IR (film): ν_{max} 2959, 2926, 2860, 1787, 1704, 1370, 1312, 1148, 926, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H), 4.55-4.47 (m, 3H), 4.19-4.13 (m, 1H), 3.53-3.46 (m, 2H), 2.65-2.52 (m, 2H), 2.05-1.95 (m, 1H), 1.82-1.64 (m, 3H), 1.53 (s, 9H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 149.8, 138.6, 128.3, 127.5, 127.4, 83.1, 72.8, 70.2, 66.4, 61.4, 40.8, 28.0, 26.7, 25.7, 25.5, 18.0, -4.7, -5.0 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{41}NO_5SiNa$: 486.2652, found: 486.2643.

(*2S,3R*)-*tert*-Butyl 2-(4-(benzyloxy)butyl)-3-(*tert*-butyldimethylsilyloxy)-5-oxopyrrolidine-1-carboxylate (*2S,3R*)**-19d** Yellow oil (129 mg, 27%). $[\alpha]_D^{25}$ = +24.7 (*c* 1.50, $CHCl_3$) ;IR (film): ν_{max} 2959, 2930, 2856, 1786, 1753, 1714, 1368, 1310, 1256, 1152, 1102, 1076, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.19 (m, 5H), 4.44-4.42 (m, 2H), 3.99 (d, *J* = 3.2

Hz, 1H), 3.85 (dd, *J* = 5.6, 2.8 Hz, 1H), 3.43-3.39 (m, 2H), 2.67 (dd, *J* = 12.0, 3.2 Hz, 1H), 2.28 (d, *J* = 12.0 Hz, 1H), 1.65-1.55 (m, 4H), 1.46 (s, 9H), 1.38-1.32 (m, 2H), 0.80 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 150.1, 138.5, 128.4, 127.6, 82.8, 73.0, 69.8, 68.3, 67.9, 41.7, 31.9, 29.7, 28.1, 25.7, 22.8, 17.9, -4.6, -4.7 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{44}NO_5Si$: 478.2989, found: 478.2983.

(*2R,3R*)-*tert*-Butyl 2-(4-(benzyloxy)butyl)-3-(*tert*-butyldimethylsilyloxy)-5-oxopyrrolidine-1-carboxylate (*2R,3R*)-**19d** Pale yellow oil (124 mg, 26%). $[\alpha]_D^{25}$ = +45.0 (*c* 0.40, $CHCl_3$); IR (film): ν_{max} 2953, 2930, 2855, 1789, 1755, 1717, 1368, 1305, 1255, 1162, 839 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.10 (m, 5H), 4.36-4.32 (m, 2H), 4.06 (dd, *J* = 5.2, 4.0 Hz, 1H), 3.79-3.73 (m, 1H), 3.36-3.28 (m, 2H), 2.15 (ddd, *J* = 10.0, 5.6, 4.8 Hz, 1H), 1.89-1.84 (m, 1H), 1.55-1.45 (m, 4H), 1.37 (s, 9H), 1.28-1.19 (m, 2H), 0.74 (s, 9H), 0.00 (s, 3H), -0.03 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 150.3, 138.5, 128.4, 127.6, 127.5, 83.0, 73.0, 71.2, 70.1, 55.3, 34.6, 33.0, 29.6, 28.1, 25.7, 21.8, 18.2, -4.5, -5.3 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{44}NO_5Si$: 478.2989, found: 478.2986.

(*2R,3R*)-*tert*-Butyl 2-(6-(benzyloxy)hexyl)-3-(*tert*-butyldimethylsilyloxy)-5-oxopyrrolidine-1-carboxylate (*2S,3R*)-**19e** Yellow oil (303 mg, 60%). $[\alpha]_D^{25}$ = +22.7 (*c* 2.00, $CHCl_3$); IR (film): ν_{max} 2959, 2930, 2857, 1786, 1748, 1715, 1368, 1310, 1153, 1078, 921, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (m, 5H), 4.53-4.51 (m, 2H), 4.07 (d, *J* = 5.2 Hz, 1H), 3.95-3.90 (m, 1H), 3.51-3.46 (m, 2H), 2.78 (dd, *J* = 17.6, 5.2 Hz, 1H), 2.34 (d, *J* = 17.6 Hz, 1H), 1.73-1.60 (m, 3H), 1.55 (s, 9H), 1.46-1.34 (m, 7H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 150.1, 138.6, 128.4, 127.6, 127.5, 82.8, 72.9, 70.3, 68.3, 67.9, 41.7, 29.7, 29.4, 28.1, 26.1, 26.0, 25.7, 17.9, -4.6, -4.7 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{48}NO_5Si$: 506.3302, found: 506.3296.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(3-hydroxypropyl)-5-oxopyrrolidine-1-carboxylate 20 To a solution of **4m** (4.9 g, 13.26 mmol) in *t*-BuOH/H_2O (60 mL, *V*/*V* = 3/1) was added *N*-methylmorpholine *N*-oxide (5.4 g, 39.79 mmol) and potassium osmate (VI) dihydrateaqueous (245 mg, 0.66 mmol). After being stirred overnight, the reaction mixture was quenched with a saturated aqueous solution of $NaHSO_4$ and stirred for another 1 h. Then the resulted mixture was concentrated and residue was diluted with water. The mixture was extracted with EtOAc (150 mL×3) and the combined organic extracts were washed with brine. The organic layer was dried, filtrated and concentrated to give crude middle compound without further purification, which was dissolved in THF/H_2O (180 mL, *V*/*V* = 1/1) and cooled to 0 °C. Then sodium periodate (5.7 g, 26.52 mmol) was added in one portion. After being stirred for 1.5 h, the reaction was quenched with $Na_2S_2O_3$. The mixture was extracted with EtOAc (150 mL×3) and the combined organic extracts were washed with brine. The organic layer was dried, filtrated and concentrated and the residue was purified by flash chromatography on silica gel (PE/EA=1/1) to give **20** (4.31 g, 87%) as a colorless oil. $[\alpha]_D^{25}$ = +28.2 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2953, 2932, 2849, 1770, 1715, 1364, 1293, 1140, 1074, 833 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11-4.05 (m, 1H), 4.00-3.90 (m, 1H), 3.73-3.62 (m, 2H), 2.83-2.73 (m, 1H), 2.40-2.15 (m, 2H), 1.83-1.57 (m, 3H), 1.56-1.47 (m, 10H), 0.89-0.82 (m, 9H), 0.11-0.03 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 150.2, 83.0, 68.3, 67.7, 61.9, 41.7, 28.8, 28.4, 28.0, 25.6, 17.9, -4.6, -4.7 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{36}NO_5Si$: 374.2363, found: 374.2357.

(*2S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(3-(*tert*-butyldimethylsilyloxy)propyl)-5-oxopyrrolidine-1-carboxylate *trans*-**19b** To a cooled (0 °C) solution of **20** (4.0 g, 10.70 mmol) TBSCl (2.4 g, 16.05 mmol) and DMAP (1.3 g, 10.70 mmol) in DMF (45 mL) was added imidazole (2.2 g, 32.12 mmol) in one portion. After being stirred for 24 h, the mixture was quenched with a saturated aqueous solution of NH_4Cl. The resulted mixture was separated and the aqueous phase was extracted with EA (60 mL × 4). The combined organic layers were washed with water (30 mL × 2) and brine, dried and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 10/1) to give *trans*-**19b** (4.86 g, 93%) as a colorless oil. $[\alpha]_D^{25}$ = +26.1 (*c* 1.50, $CHCl_3$); IR (film): ν_{max} 2956, 2930, 2849, 1788, 1716, 1474, 1310, 1256, 1153, 1074, 836 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (d, *J* = 5.2 Hz, 1H), 3.92 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.68-3.59 (m, 2H), 2.78 (dd, *J* = 17.6, 5.2 Hz, 1H), 2.35 (d, *J* = 17.6 Hz, 1H), 1.81-1.71 (m, 1H), 1.62-1.55 (m, 2H), 1.57 (s, 9H), 1.51-1.42 (m, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.05 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 150.0, 82.8, 68.4, 67.9, 62.5, 41.7, 29.3, 28.5, 28.0, 25.9, 25.7, 18.3, 17.9, -4.6, -4.7, -5.3 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{50}NO_5Si_2$: 488.3228, found: 488.3229.

(*2S,3R,5R*)-*tert*-Butyl 5-allyl-3-(*tert*-butyldimethylsilyloxy)-2-(3-(*tert*-butyldimethylsilyloxy)propyl)pyrrolidine-1-carboxylate 2,5-*cis* **25** To a solution of **19b** (2.2 g, 4.52 mmol) in dry THF (20 mL) was treated with a solution of $LiEt_3BH$ (13.5 mL, 13.56 mmol, 1.0 M in THF) at -78 °C. After being stirred for 30 min, the reaction was carefully quenched with MeOH (5 mL) and stirred for another 5 min. Then a solution of sodium bicarbonate was drooped and warmed to room temperature. The resulting mixture was extracted with EtOAc (50 mL × 3) and the combined organic layers were washed with brine. The dried organic layer was filtered and concentrated to give crude mixture without further purification, which was dissolved in dry CH_2Cl_2 (40 mL) and cooled to -78 °C. Once 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.2 mL, 6.49 mmol) was dropped, a solution of $BF_3{\cdot}OEt_2$ (2.2 mL, 17.31 mmol) was dropped slowly and the reaction mixture was stirred at -78 °C to -40 °C for overnight. The mixture was quenched with a saturated $NaHCO_3$ solution (10 mL) and warmed to room temperature. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 for three times. The combined organic layers were washed with brine, dried and concentrated. The residue was purified by flash chromatography on silica gel（PE/EA = 25/1） to give 2,5-*cis* **25** (1.53 g) in 69% yield as a colorless oil. $[\alpha]_D^{25}$ = +25.2 (*c* 0.50, $CHCl_3$); IR (film): ν_{max} 2956, 2930, 2858, 1472, 1391, 1257, 1175, 1078 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 5.82-5.68 (m, 1H), 5.11-5.00 (m, 2H), 4.10-4.05 (m, 1H), 3.88-3.82 (m, 0.5H), 3.75-3.52 (m, 3.5H), 3.00-2.90 (m, 0.5 H), 2.75-2.65 (m, 1H), 2.56-2,45 (m, 0.5H), 2.44-2.34 (m, 0.5H), 2.06-1.95 (m, 1H),

1.90-1.70 (m, 2H), 1.62-1.44 (m, 11H), 1.28-1.14 (m, 1H), 0.94-0.88 (m, 18H), 0.10-0.07 (m, 6H), 0.06-0.04 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ 154.0 (153.9), 136.4 (136.3), 116.6 (116.5), 79.0, 76.1 (75.2), 67.8, 63.0, 57.6 (57.3), 38.9 (37.6), 35.5 (34.6), 30.2 (30.1), 29.8 (28.0), 28.6, 25.9, 25.8, 18.3 (18.2), 17.9, -4.7, -4.8, -5.3 ppm; ^{1}H NMR (400 MHz, DMSO, 70^{o}C) δ 5.75-5.62 (m, 1H), 5.00-4.90 (m, 2H), 4.07-4.03 (m, 1H), 3.70-3.60 (m, 1H), 3.56-3.48 (m, 2H), 3.47-3.40 (m, 1H), 2.77-2.55 (m, 1H), 2.36-2.22 (m, 1H), 2.07-1.98 (m, 1H), 1.70-1.58 (m, 2H), 1.43-1.31 (m, 11H), 1.20-1.13 (m, 1H), 0.82 (s, 9H), 0.81 (s, 9H), 0.01 (s, 6H), -0.04 (s, 6H) ppm; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{27}H_{56}NO_4Si_2$: 514.3748, found: 514.3742.

(*2S,3R,5R,E*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(3-(*tert*-butyldimethylsilyloxy)propyl)-5-(4-methoxy-4-oxobut-2-enyl)pyrrolidine-1-carboxylate *(5R)*-**26** To solution of **25** (794 mg, 1.55 mmol) and methyl acrylate (2.1 mL, 23.18 mmol) in dry DCM (260 mL) was quickly added Grubbs^{2nd} catalyst (110 mg) and heated to reflux for 7 h, then the mixture was concentrated and the crude was purified by flash chromatography on silica gel to give **26** (884 mg, 95%, *E : Z* = 95 :5) as a colorless oil. $[\alpha]_D^{25}$ = +28.7 (*c* 1.50, $CHCl_3$); IR (film): ν_{max} 2955, 2930, 2860, 1750, 1704, 1391, 1255, 1172, 1097, 1057, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 6.92-6.85 (m, 1H), 5.90-5.81 (m, 1H), 4.11-4.07 (m, 1H), 3.97-3.89 (m, 0.5H), 3.87-3.80 (m, 0.5H), 3.76-3.72 (m, 3H), 3.71-3.52 (m, 3H), 3.17-3.08 (m, 0.5H), 2.91-2.82 (m, 0.5H), 2.75-2.65 (m, 0.5H), 2.64-2.52 (m, 0.5H), 2.11-2.00 (m, 1H), 1.91-1.81 (m, 0.5H), 1.79-1.68 (m, 1.5H), 1.60-1.42 (m, 11H), 1.25-1.12 (m, 1H), 0.93-0.87 (m, 18H), 0.10-0.07 (m, 6H), 0.06-0.03 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ 167.0 (169.9), 154.0 (153.7), 147.0 (146.9), 122.6, 79.5 (79.3), 76.0 (75.1), 67.7, 63.0, 56.7 (56.5), 51.5 (51.4), 37.7 (36.3), 36.1 (35.2), 30.2 (30.1), 29.8 (28.0), 28.5, 25.9, 25.8, 18.3 (18.2), 17.9, -4.7, -4.8, -5.3 ppm; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{29}H_{58}NO_6Si_2$: 572.3803, found: 572.3804.

(*2S,3R,5R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(3-(*tert*-butyldimethylsilyloxy)propyl)-5-(4-methoxy-4-oxobutyl)pyrrolidine-1-carboxylate (*5R*)-**27** Compound **26** (800 mg, 1.40 mmol) and 10% Pd/C (80 mg) was stirred under hydrogen atmosphere for overnight. Then the mixture was filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA=10/1) to give **27** (739 mg, 92%) as a colorless oil. $[\alpha]_D^{25}$ = +23.4 (*c* 2.00, $CHCl_3$); IR (film): ν_{max} 2953, 2929, 2858, 1742, 1693, 1391, 1255, 1178, 1098, 1060, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.10-4.05 (m, 1H), 3.80-3.48 (m, 7H), 2.42-2.22 (m, 2H), 2.12-2.00 (m, 1.5H), 1.89-1.82 (m, 1H), 1.77-1.68 (m, 2H), 1.67-1.43 (m, 13.5H), 1.24-1.10 (m, 1H), 0.92-0.85 (m, 18H), 0.09-0.03 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ 174.1 (174.0), 154.0 (153.9), 79.0, 76.1 (75.2), 67.5, 63.0, 57.6, 51.4, 36.0 (35.2), 34.0 (33.9), 33.8 (32.7), 30.2 (30.1), 29.8 (28.0), 28.6, 25.9, 25.7, 22.2, 18.3 (18.2), 17.9, -4.7, -4.9, -5.3 ppm; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{29}H_{60}NO_6Si_2$: 574.3959, found: 574.3954.

(*2S,3R,5R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(3-(*tert*-butyldimethylsilyloxy)propyl)-5-(5-(dimethoxyphosphoryl)-4-oxopentyl)pyrrolidine-1-carboxylate *(5R)*-**28** To a solution of dimethyl methylphosphonate (0.7 mL, 6.1 mmol) in dry THF (50 mL) was treated with a solution of *n*-BuLi (2.7 mL, 6.1 mmol, 2.4 M in hexane) at -78 ^{o}C for 1 h. Then a solution of compound **27** (500 mg, 0.87 mmol) in THF (10 mL) was slowly dropped, and the reaction was warmed to -50^{o}C and stirred for 2 h. The resulted mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine, dried and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA=30/1) to give **28** (563 mg, 97%) as a colorless oil. $[\alpha]_D^{25}$ = +23.7 (*c* 1.50, $CHCl_3$); IR (film): ν_{max} 2955, 2932, 2855, 1750, 1709, 1463, 1393, 1255, 1179, 1035, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.08-4.03 (m, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.74-3.47 (m, 4H), 3.15-3.08 (m, 1H), 3.07-3.02 (m, 1H), 2.72-2.50 (m, 2H), 2.08-1.98 (m, 1.5H), 1.88-1.66 (m, 3.5H), 1.60-1.44 (m, 13H), 1.22-1.11 (m, 1H), 0.92-0.83 (m, 18H), 0.08-0.02 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ 201.8 (201.4), 154.0 (153.9), 79.0, 76.1 (75.2), 67.5, 63.0, 57.7 (57.6), 53.0, 52.9, 44.1 (44.0), 42.0 (41.8), 40.7 (40.5), 35.2 (35.9), 32.3 (33.5), 30.2 (30.0), 29.8 (28.0), 28.6, 25.9, 25.7, 20.5, 17.9 (18.3), -4.7, -4.9, -5.3 ppm; ^{31}P NMR (125 MHz, $CDCl_3$, rotamers) δ 22.89 (22.73) ppm; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{31}H_{65}NO_8PSi_2$: 666.3986, found: 666.3983.

(*2S,3R,5R,E*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(3-(*tert*-butyldimethylsilyloxy)propyl)-5-(4-oxoundec-5-enyl)pyrrolidine-1-carboxylate 29 To a solution of sodium hydrogen (36 mg, 0.90 mmol) in dry THF (8 mL) was carefully treated with a solution of compound **28** (543 mg, 0.75 mmol) at -0 ^{o}C. After being stirred for 1 h at 0 ^{o}C to room temperature, hexaldehyde (0.11 mL, 0.90 mmol) was dropped and the resulted mixture was stirred for another 3h. Then the reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine, dried and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA=30/1) to give **29** (459 mg, 88%) as a colorless oil. $[\alpha]_D^{25}$ = +30.4 (*c* 0.50, $CHCl_3$); IR (film): ν_{max} 2953, 2928, 2857, 1692, 1458, 1391, 1356, 1175, 1096, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 6.82-6.77 (m, 1H), 6.12-6.03 (m, 1H), 4.10-4.05 (m, 1H), 3.80-3.47 (m, 4H), 2.67-2.45 (m, 2H), 2.25-2.16 (m, 2H), 2.12-1.98 (m, 1.5H), 1.88-1.81 (m, 1H), 1.78-1.68 (m, 2H), 1.63-1.42 (m, 15.5H), 1.37-1.26 (m, 4H), 1.24-1.11 (m, 1H), 0.92-0.86 (m, 21H), 0.08-0.03 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ 200.8 (200.5), 154.1 (153.9), 147.4, 130.4, 79.0, 76.1 (75.2), 67.5, 63.0, 57.7, 39.9, 35.1 (35.9), 32.6 (33.9), 32.4, 31.3, 30.2 (30.1), 29.8 (28.0), 28.6, 27.8, 25.9, 25.7, 22.4, 21.4, 18.3, 17.9, 14.0, -4.7, -4.9, -5.3 ppm; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{35}H_{70}NO_5Si_2$: 640.4793, found: 640.4790.

(*2S,3R,5R,E*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(3-hydroxypropyl)-5-(4-oxoundec-5-enyl)pyrrolidine-1-carboxylate 30 Compound **29** (393 mg, 0.61 mmol) was dissolved in mixture of DCM/MeOH (4 mL, *V* : *V* = 50 : 50) and cooled to -51 ^{o}C. Then camphorsulfonic acid (100 mg, 0.43 mmol) was added in one portion and the reaction was stirred

for overnight. The mixture was quenched with TEA (0.61mmol) was dropped and warmed to room temperature. The resulted mixture was extracted with DCM (20 mL × 3) and the combined organic layers were washed with brine, dried and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 2/1) to give **30** (300 mg, 93%) as a colorless oil. $[\alpha]_D^{25}$ = +23.7 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3449, 2956, 2929, 2858, 1688, 1670, 1631, 1393, 1255, 1173, 1054, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 6.87-6.78 (m, 1H), 6.12-6.04 (m, 1H), 4.10-4.01 (m, 1H), 3.81-3.60 (m, 4H), 3.57-3.53 (m, 0.33H), 2.95-2.88 (m, 0.67H), 2.67-2.44 (m, 2H), 2.25-2.16 (m, 2H), 2.13-2.00 (m, 1.33H), 1.90-1.82 (m, 1H), 1.80-1.70 (m, 2H), 1.67-1.57 (m, 2H), 1.56-1.44 (m, 13.67H), 1.35-1.28 (m, 4H), 1.25-1.15 (m, 1H), 0.93-0.87 (m, 12H), 0.08-0.04 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ 200.4 (200.8), 154.3 (154.0), 147.5, 130.3, 79.4 (79.1), 75.7 (76.0), 66.1 (67.3), 61.4 (62.6), 57.8, 39.8, 35.8 (35.1), 33.8 (32.6), 32.4, 31.3, 29.0 (29.9), 28.5, 28.2 (29.5), , 27.8, 25.7, 22.4, 21.4, 17.9, 13.9, -4.8, -4.9 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{29}H_{56}NO_5Si$: 526.3928, found: 526.3929.

3-*Epi*-epohelmin A 3-*epi*-6 To a solution of alcohol **30** (102 mg, 0.19 mmol) and TEA (0.21 mL, 1.52 mmol) in dry CH_2Cl_2 (5 mL) was cooled to 0 °C. Then MsCl (43 μL, 0.57 mmol) was dropped and the mixture was stirred for 30 min. The reaction was quenched with a saturated NH_4Cl solution (20 mL) and extracted with CH_2Cl_2 (25 mL × 3). The combined organic layers were washed with brine for two times, dried and concentrated to give crude product without further purification. The above crude product and 2,6-lutidine (0.11 mL, 0.91 mmol) were dissolved in CH_2Cl_2 (15 mL) and cooled to -78 °C. The reaction was treated with TESOTf (0.2 mL, 0.87 mmol) and the mixture was allowed to warm to room temperature and stirred for overnight. The mixture was diluted with water and extracted with CH_2Cl_2 (30 mL × 3) and the combined organic layers were washed with brine. The resulted organic layer was dried and concentrated to give crude product without further purification, which was stirred in mixture of MeOH/HCl (3 mL, *V* : *V* = 50 : 50) for overnight. Then the mixture was concentrated to give crude salt, which was dissolved in water (10 mL) and treated with potassium carbonate. The resulted mixture was extracted with $CHCl_3$ (15 mL × 5) and the combined organic layers were dried with $MgSO_4$. After being concentrated, the residue was purified by flash chromatography on silica gel (DCM / CH_3OH = 80/1-10/1) to give 3-*epi*-epohelmin A 3-*epi*-**6** (28 mg, 49%), as a yellow oil, $[\alpha]_D^{25}$ = +7.8 (*c* 0.80, $CHCl_3$); IR (film): ν_{max} 3386, 2959, 2927, 2858, 1668, 1627, 1571, 1458, 1407, 1381, 1261, 1177, 1105, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.84 (ddd, *J* = 10.4, 5.2, 4.4 Hz, 1H), 6.07 (d, *J* = 10.8 Hz, 1H), 4.10-4.05 (m, 1H), 3.85-3.80 (m, 1H), 3.28-3.22 (m, 1H), 2.91-2.82 (m, 2H), 2.65-2.55 (m, 2H), 2.49-2.44 (m, 1H), 2.24-2.19 (m, 2H), 2.17-2.10 (m, 1H), 1.96-1.91 (m, 2H), 1.88-1.80 (m, 2H), 1.77-1.70 (m, 2H), 1.68-1.62 (m, 2H), 1.50-1.43 (m, 2H), 1.34-1.28 (m, 4H), 0.91-0.88 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 148.0, 130.2, 75.3, 73.2, 66.6, 53.5, 40.9, 39.4, 33.5, 32.4, 31.4, 29.1, 27.8, 24.6, 22.4, 21.3, 13.9 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{32}NO_2$: 294.2433, found: 294.2424.

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