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ARTICLE

An efficient approach to *trans*-4-hydroxy-5-substituted 2-pyrrolidinones through stereoselective tandem Barbier process: Divergent Syntheses of (*3R,4S*)- statines, (+)-preussin and (-)-hapalosin

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A diastereoselective approach to *trans*-4-hydroxy-5-substituted 2-pyrrolidinones 1 (P_1=TBS, P_2=H) has been developed through stereoselective tandem Barbier process of (R,S_{RS})-**8** with alkyl and aryl bromide. The stereochemistry at the C-5 stereogenic center of the *trans*-4-hydroxy-5-substituted 2-pyrrolidinones was solely controlled by α-alkoxy substitution. This effective approach was successfully used to prepare a variety of substituted (*3R,4S*)-statines **2**. In addition, two bioactive natural products of (+)-preussin **4** and hapalosin **5** were effectively synthesized through this stereoselective tandem Barbier process.

Introduction

The discovery of a concise and efficient methodology for enantioselective carbon–carbon bond formation is of great interest in synthetic organic chemistry because the resulting chiral centers can be practicably utilized for the syntheses of many natural products and chiral pharmaceutical agents[1]. Nowadays, the diastereoselective addition of Grignard reagents to imines bearing chiral auxiliaries (e.g. *N-tert*-butanesulfinamide[2] and *N*-toluenesulfinamide[3]) is undoubtedly one of the most effective approaches to chiral amines[4]. As a prime instance, the enantioselective method to chiral functionalized *trans*-4-hydroxy-5-substituted-2-pyrrolidinones **1** (Figure 1) and the ring-opened form, substituted statines **2**, is very important in synthetic and medicinal chemistry, because both **1** and **2** serve as a substructure for numerous biologically relevant alkaloids[5,6] isolated from terrestrial plants, animals and marine, as well as for pharmaceutical agents[7]. For example, epohelmin A (**3**), an inhibitor of recombinant lanosterol synthase (IC_{50} = 10 μM)[8], possesses a hydroxy pyrrolidine unit. (+)-Preussin (**4**), a pyrrolidinol alkaloid to induce apoptosis in human tumor cells[9] and hapalosin (**5**) with multidrug-resistance reversing activity in cancer cells[10] bear a (*3R,4S*)-substituted statine unit. Other examples include natural products Lyngbyabellin N (**6**) and Symplocin A (**7**). The former displays anti-cancer acyivity[11], and the latter shows exceptionally potent activity as an inhibitor of cathepsin E (IC_{50} 300 pM)[12].

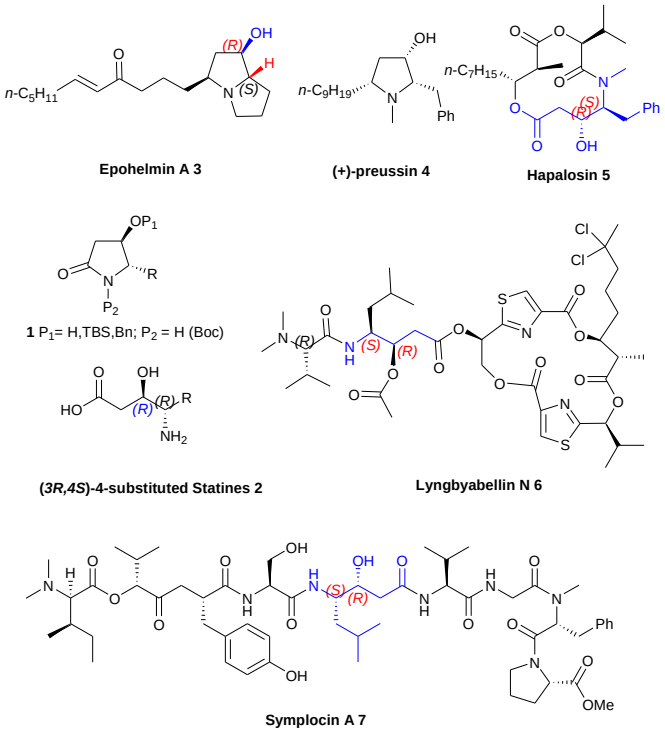

Figure 1. Structures of several bioactive products.

In past decades, tremendous efforts have been devoted to the method development for the stereoselective construction of *trans*-4-hydroxyl-5-substituted 2-pyrrolidinones **1** and its ring-opened form, (*3R,4S*)-substituted statins **2**. Among a number of powerful

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approaches reported so far,[6] the most common approaches include reductive alkylation[6d,f,g,k] or nucleophilic substitution[6c] to construct the chiral center of the amino group, as well as by asymmetric reduction to build the stereochemistry of the hydroxyl group[6e]. Recently, our group discovered a diverse approach for highly diastereoselective synthesis of versatile *trans*-4-hydroxy-5-substituted 2-pyrrolidinones **2** and *trans*-5-hydroxy-6-substituted 2-piperidinones through a one-pot intramolecular tandem protocol[6l,13]. However, such tandem process requires Grignard reagents to react with *α*-chiral aldimine **8**. To avoid the lab operation of Grignard reagents, we envisioned that the Barbier type reaction involving *α*-chiral aldimine **8**, metal and halogenated hydrocarbon could provide similar results in assembling both addition and in situ cyclization through intramolecular aminolysis of esters as well as removal of auxiliaries (Figure 2). In continuation of our efforts to explore utility of *N*-*tert*-butanesulfinyl imines, we have accomplished the synthesis of several bioactive natural products and their analogues[14]. Herein, we describe the first one-pot tandem Barbier process using *α*-chiral aldimine **8**, magnesium and brominated hydrocarbons to provide *trans*-4-hydroxy-5-substituted-2-pyrrolidinones **1** and the ring-opened form substituted statines **2** with high chemo and stereoselectivities, as well as its application in asymmetric syntheses of (+)-preussin **4** and (-)-hapolasin **5**.

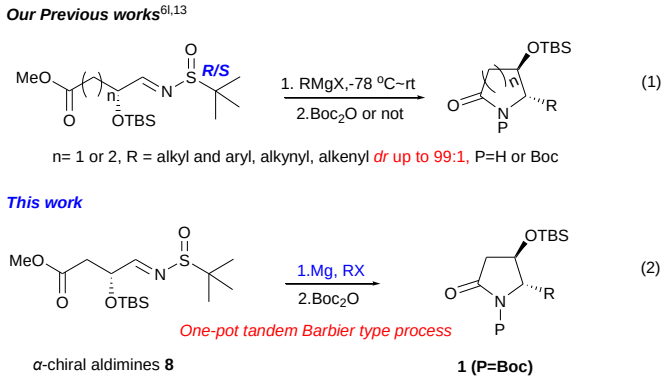
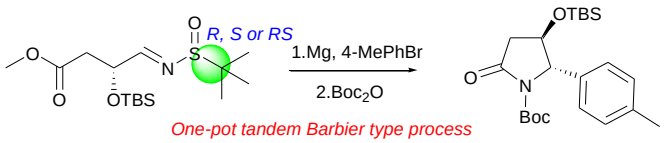


Figure 2. Our strategy to *trans*-4-hydroxy-5-substituted-2-pyrrolidinones **1.**

Results and discussion

As shown in Table 1, α-chiral aldimines **8**[6l,15] was used in our investigation. First, several metals (In, Zn, Ir) were screened and the results turned out to be fruitless (Table 1, entries 1-3). When α-chiral aldimine (*R,S*$_R$)-**8**, magnesium shavings and 4-methyl bromobenzene was stirred for overnight, the desired product was observed, which was not easily purified by silica gel chromatography due to the co-elution with the by-product sulfoxide[6l]. Therefore, the concentrated crude residue was treated with di-*tert*-butyl dicarbonate in the presence of DMAP and TEA for 24 h, affording the N-Boc product **1a** with high diastereoselectivity (*dr* = 99:1) and in 23% yield (Table 1, entry 4). Considering that the particle size of magnesium chips could affect the overall yield of this cascade Barbier process, two types of magnesium powder (50 or 200 mesh) were tried, and the yields were improved to 32% and 59%, respectively (Table 1, entries 5-6). Different reaction solvents were also screened and the results are summarized in Table 1 (entries, 7-9). When diastereomer (*R,S*$_S$)-**8** was used, the stereoselectivity of **1a** was still excellent (*dr* = 99:1), albeit the yield slightly reduced to 44% (Table 1, entry 10). Interestingly, the mixture of (*R,S*$_S$)-**8** and (*R,S*$_R$)-**8**, ie, (*R,S*$_{RS}$)-**8**, gave similar results (Table 1, entry 11), suggesting that the chiral sulfinamide moiety was not involved in the stereocontrol during this tandem Barbier addition process.

Table 1. The reactions mediated by different conditions.



8 **1a**

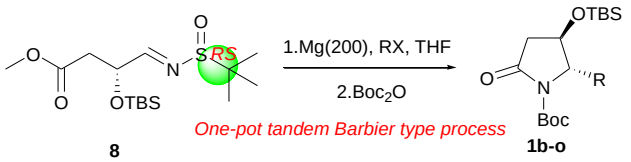
Entry[a]	Metal	Aldimine	Solvent	Y%[b]	*dr*[c]
1	In	(*R,S*$_R$)-**8**	THF	--	--
2	Zn	(*R,S*$_R$)-**8**	THF	--	--
3	Ir	(*R,S*$_R$)-**8**	THF	--	--
4	Mg	(*R,S*$_R$)-**8**	THF	23	99:1
5	Mg(50)	(*R,S*$_R$)-**8**	THF	32	99:1
6	Mg(200)	(*R,S*$_R$)-**8**	THF	59	99:1
7	Mg(200)	(*R,S*$_R$)-**8**	DCM	--	--
8	Mg(200)	(*R,S*$_R$)-**8**	Et_2O	--	--
9	Mg(200)	(*R,S*$_R$)-**8**	DMF	<5	99:1
10	Mg(200)	(*R,S*$_S$)-**8**	THF	44	99:1
11	Mg(200)	(*R,S*$_{RS}$)-**8**	THF	53	99:1

[a] The reaction was performed with α-chiral aldimines **8** (1.0 mmol), Mg (3.2 mmol) and 4-MePhBr (3.0 mmol) in solvent (5 mL) at rt for 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] *dr* was determined by HPLC or ^{1}H NMR.

Next, we turned our attention to investigate the scope and limitation of this intramolecular tandem Barbier type process. With (*R,S*$_{RS}$)-**8** as the starting material, various substituted aryl bromides were screened and the results are summarized in Table 2 (Table 2, entries 1-6 and 8), almost all the substituted aryl bromide could proceed smoothly to give desired products **1b-g** and **1i** with high diastereoselectivities (*dr* = 99:1) in moderate yields. While 1-bromo-3-fluorobenzene was used, the diastereoselectivity of procuct **1h** was slightly reduced (Table 2, entry 7). Notably, when α-naphthyl bromide was used, the desired lactam **1j** was also obtained with excellent diastereoselectivity (*dr* = 95:5), although the yield is reduced to 30% (Table 2, entry 9). Several sp^3 hybridized alkyl bromides were screened, the yields of desired products **1k-m** was slightly decreased, albeit with excellent diastereoselectivities (*dr* = 99:1) (Table 2, entries 10-13). Although BnBr could afford the corresponding product **1n** in 46% yield with excellent diastereoselectivity (*dr* = 97:3) (Table 2, entry 13), to our

disappointment, the reaction with allylBr was very messy (Table 2, entry 14).

Table 2. Reactions with various halogenated hydrocarbon with **8**

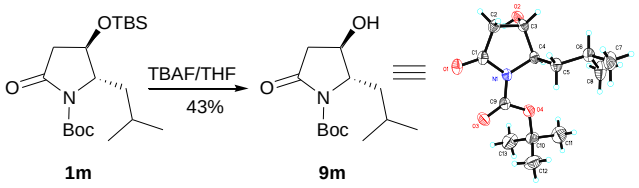


8 **1b-o**

Entry[a]	R	**1b-q**	Yield%[b]	*dr*[c]
1	3-MePh	**1b**	60	98:2
2	2-MePh	**1c**	31	99:1
3	Ph-	**1d**	52	99:1
4	4-MeOPh	**1e**	54	99:1
5	3-MeOPh	**1f**	56	99:1
6	2-MeOPh	**1g**	27	99:1
7	3-FPh	**1h**	55	91:9
8	3-CF_3Ph	**1i**	51	98:2
9	α-Naphthyl	**1j**	30	95:5
10	Ethyl	**1k**	39	99:1
11	Hexyl	**1l**	34	99:1
12	Isobutyl	**1m**	40	99:1
13	Bn	**1n**	46	97:3
14	Allyl	**1o**	--	--

[a] The reaction was performed with α-chiral aldimines (*R,S*$_{RS}$)-**8** (1.0 mmol), Mg(200) (3.2 mmol) and RX (3.0 mmol) in THF (5 mL) at rt for 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] *dr* was determined by HPLC or ^{1}H NMR.

To confirm the relative configurations of the products **1a-n**, compound **1m** was treated with tetrabutylammonium fluoride (TBAF) to give alcohol **9m** in 43% yield (Figure 3), which existed in *trans*-form shown by X-ray crystallographical analysis (see Supporting Information).[26] Thus, the relative configurations of the products **1a-n** were unambiguously assigned as *trans*-form.

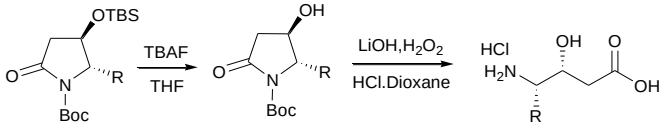


1m **9m**

Figure 3. The X-ray crystallographical analysis of **9m**.

With lactams **1** in hand, we turned our attention to utilize them in organic synthesis. Obviously, substituted (*3R,4S*)-statines **2**[16] could be conveniently prepared. Treatment of compounds **1** with tetrabutylammonium fluoride (TBAF) in THF at 0ºC to room temperature gave alcohols **9**, which could be hydrolyzed with $LiOH/H_2O_2$ and subsequently deprotected with HCl/dioxane to generate substituted (*3R,4S*)-statines **2** as hydrochloride salts (Table 3).

Table 3. Synthesis of several substituted (*3R,4S*)-statines **2a-n**.

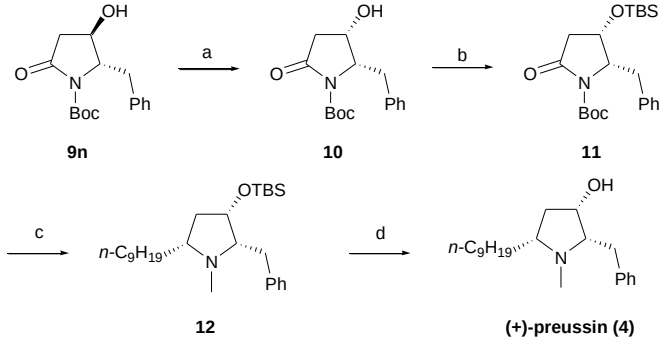


1a-n **9a-n** **2a-n**

Entry	**R**	**9**[a]	Yield%[c]	**2**[b]	Yield%[c]
1	4-MePh	**9a**	69	**2a**	78
2	3-MePh	**9b**	73	**2b**	81
3	4-MeOPh	**9e**	40	**2e**	60
4	3-FPh	**9h**	61	**2h**	72
5	3-CF_3Ph	**9i**	62	**2i**	76
6	α-Naphthyl	**9j**	57	**2j**	67
7	Ethyl	**9k**	55	**2k**	84
8	Isobutyl	**9m**	43	**2m**	81
9	Bn	**9p**	56	**2p**	77

[a]. The reaction was performed with **1** (1.13 mmol) and TBAF (1.50 mmol) in THF (5 mL) at rt for overnight; [b]. The reaction was performed with **9** (0.51 mmol), 30% H_2O_2 (0.5 mL) and $LiOH{\cdot}H_2O$ (1.53 mmol) in THF/H_2O (4/1) (5 mL) at rt for 12h, crude product was treated with HCl/Dioxane and stirred for overnight; [c] Isolated yield.

Another application of **1** is to synthesize (+)-preussin **4**, a pyrrolidinol alkaloid. (+)-Preussin **4** could inhibit the growth of bacteria *Candida* and filamentous fungi,[17a] induce apoptosis in human tumor cells [17b] and inhibit cell growth of the fission yeast *ts* mutants defective on *cdc*2-regulatory genes[17c]. All these reported



9n **10** **11**

12 **(+)-preussin (4)**

Scheme 1. Synthesis of (+)-preussin **4**. *Reagents and conditions:* a. (i) $(COCl)_2$, DMSO, TEA, DCM, -78ºC; (ii) $NaBH_4$, MeOH, for two steps 90%; b. TBSCl, imidazole, DMAP, DMF, 0ºC~rt, 93%; c. (i) *n*-$C_9H_{19}MgBr$, THF, -78ºC--40ºC; (ii) CF_3COOH, rt, 3 h; NaOH, Ph = 10-12; (iii) Pd/C, $Pd(OH)_2$, H_2, $(HCHO)_n$, rt, 20 h, for three steps 51%; d. TBAF, THF, 0ºC~rt, 24 h, 61%.

biological activities made preussin an attractive synthetic target to chemists.[14e,18,19] As shown in Scheme 1, our synthesis started from compound **9n**, chiral inversion was straight-forward through Swern oxidation[20] and the subsequent reduction with sodium borohydride ($NaBH_4$) in methanol, producing the desired (*2S,3S,*)-10 in 90% overall yield. Compound 10 was treated with TBSCl to give 11 in 93% yield. Then the desired 12 was obtained by known addition/ring-opening process and followed by continuous deprotection of the Boc group in 11 as well as methylation in 51% overall yield[21]. Finally, deprotection of compound 12 with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran afforded (+)-preussin 4 {$[\alpha]_D^{25}$ = + 33.6 (*c* 0.4, $CHCl_3$); lit.[18g] $[\alpha]_D^{25}$ = + 32 (*c* 1.1, $CHCl_3$)} in 61% yield. The spectroscopic and physical data of the synthetic 4 were identical to the reported data.[19f]

Hapalosin **5**, a popular marine natural product, has attracted great attention in recent years[22]. Our strategy for asymmetric synthesis of hapalosin **5** is illustrated in Figure 4, with stereoselective synthesis of substituted (*3R,4S*)-statines **2** and straight synthetic route as our main focus in constructing this target molecule.

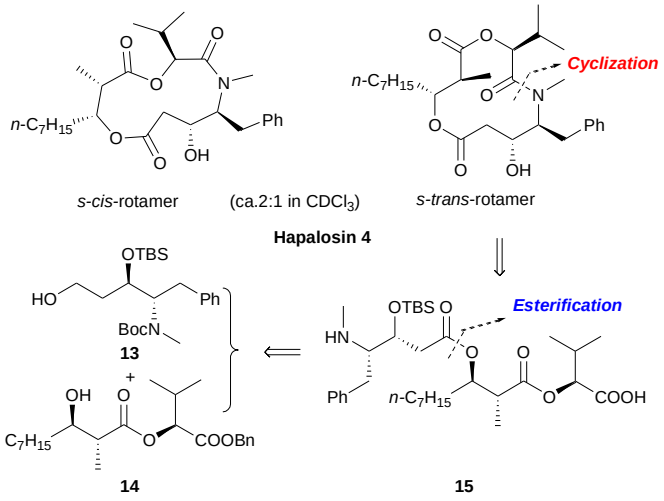
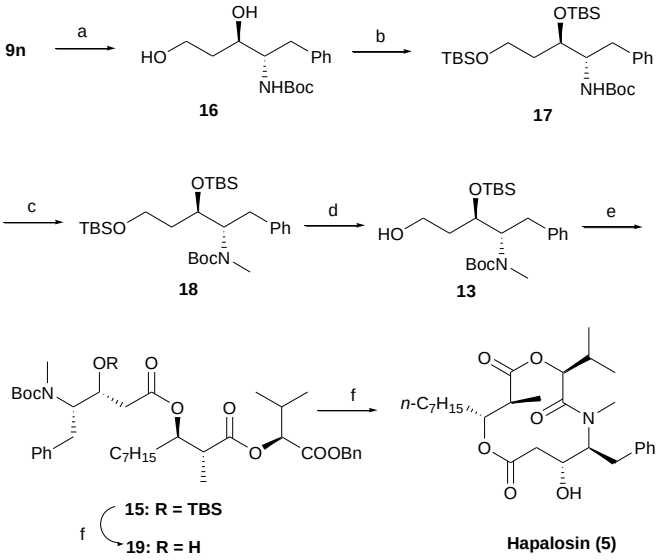


Figure 4. Retrosynthetic analysis of hapalosin **5**.

As shown in Scheme **2**, hydrolysis ($LiOH/H_2O_2$) of lactam **9n** and subsequent reduction ($NMM/ClCO_2Et/NaBH_4$) gave a primary alcohol **16** in 83% overall yield, which was converted to silyl ether **17** by treatment with TBSCl/Imidazole in 70% yield. N-Methylation of **17** was obtained by reacting with MeOTf in the presence of lithium hexamethyldisilazide (LiHMDS) to give compound **18** in 83% yield. Selective desilylation (CSA) of **18** gave **13** in 99% yield. The alcohol **13** was converted to acid in two-step sequence: oxidation to aldehyde with Dess-Martin periodinane[23] and further Pinnick oxidation ($NaH_2PO_4{\cdot}2H_2O$, $NaClO_2$)[24] to give free acid. The coupling of this acid and the alcohol **14**[25] was accomplished under classical yamaguchi[23] condition ($Cl_3C_6H_2COCl$, TEA, DMAP). Desilylation of **15** with TBAF afforded compound **19** in 59% overall yield. Upon the N-Boc deprotection (TFA) and subsequent hydrogenation (Pd/C, EtOH, H_2), the intramolecular cyclization was achieved by the known amidation conditions[22c] to afford desired hapalosin **5** {$[\alpha]_D^{25}$ = -42.1 (*c* 0.15, CH_2Cl_2; lit.[22b] $[\alpha]_D^{18}$ = -41 (*c* 1.0, CH_2Cl_2); lit.[22d] $[\alpha]_D^{25}$ = -41.2 (*c* 1.0, CH_2Cl_2)} in 41% overall yield. The spectroscopic and physical data of the synthetic hapalosin 5 were identical with the reported data.[22d]



Scheme 2. Synthesis of Hapalosin **5**. *Reagents and conditions:* a. (i) LiOH, H_2O_2, THF/H_2O; (ii) NMM, $ClCO_2Et$, THF, 0.5h; $NaBH_4$, 0°C, 1h, for two steps 83%; b. TBSCl, imidazole, DMAP, DMF, 0°C~rt, 70%; c. LiHMDS, HMPA, MeOTf, THF, -78°C~0°C, 83%; d. CSA, DCM/MeOH, -40°C, 8h, 99%; e. (i) DMP, 0.5 h; $NaH_2PO_4{\cdot}2H_2O$, $NaClO_2$, 2-methylbut-2-ene, *t*-BuOH; (ii) $Cl_3C_6H_2COCl$, DMAP, TEA; (iii) TBAF, THF, 0°C~rt, 24 h, for three steps 59%; f. (i) TFA, rt, 4 h; (ii) Pd/C, EtOH, 6 h; (iii) DPPA, DIPEA, DMF, 0°C~rt, 4 d, for three steps 41%.

Conclusions

In summary, we established an asymmetric one-pot method for highly diastereoselective synthesis of *trans*-4-hydroxy-5-substituted 2-pyrrolidinones **1** through an intramolecular stereoselective tandem Barbier process of (R,S_{RS})-**8**, alkyl and aryl bromide. The stereochemistry at the C-5 stereogenic center of the *trans*-4-hydroxy-5-substituted 2-pyrrolidinones was solely controlled by α-alkoxy substitution. This effective approach was successfully used to synthesize the libraries of substituted (*3R,4S*)-statines **2**. In addition, the utility of chiral δ-lactams **1** was demonstrated by asymmetric syntheses of (+)-preussin **4** and hapalosin **5**.

Experimental

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 mesh) with Petroleum ether/EtOAc as eluent. Optical rotations were measured on a polarimeter with a sodium lamp. HRMS were measured on LTQ-Orbitrap-XL or LCMS-IT-TOF apparatus. IR spectra were recorded using film on a Fourier Transform Infrared Spectrometer. NMR spectra were recorded at 400 MHz or 600 MHz, and chemical shifts are reported in δ (ppm) referenced to an internal TMS standard for ^1H NMR and $CDCl_3$ (77.16 ppm) for ^{13}C NMR.

*General procedure for synthesis of **1a-n***: Compound **8** (1.00 g, 2.86 mmol) was dissolved in anhydrous THF (15 mL) at room temperature. Then magnesium powder (200 mesh, 222 mg, 9.15 mmol) was added in one portion. The RBr (8.58 mmol) was slowly dropped. After being stirred for overnight, the reaction 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, filtered and concentrated, the crude amide was directly dissolved in dry DMF (15 mL). Then TEA (2.0 mL, 14.30 mmol), Boc_2O (1.3 mL, 5.72 mmol) and DMAP (349 mg, 2.86 mmol) were added. After being stirred for 24 h, the reaction was diluted with water and extracted with EtOAc (100 mL × 3). 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 **1a-n**.

(2*S*,3*R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-oxo-2-*p*-tolylpyrrolidine-1-carboxylate 1a

White solid (615 mg, 53%), m.p. 98-100°C. $[\alpha]_D^{23}$ = -4.9 (*c* 1.10, $CHCl_3$); IR (film) ν_{max} 2954, 2930, 2857, 1789, 1755, 1721, 1366, 1307, 1153, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18-7.03 (m, 4H), 4.96-4.90 (m, 1H), 4.10-4.04 (m, 1H), 2.84 (dd, *J* = 17.2, 5.6 Hz, 1H), 2.41-2.36 (m, 1H), 2.34 (s, 3H), 1.31 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 173.1, 149.8, 137.8, 136.1, 129.7, 125.2, 83.0, 72.2, 71.4, 41.1, 27.9, 25.8, 21.2, 18.1, -4.6, -4.7 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{35}NO_4SiNa$: 428.2233, found: 428.2222.

(2*S*,3*R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-oxo-2-*m*-tolylpyrrolidine-1-carboxylate 1b

Yellow oil (696 mg, 60%). $[\alpha]_D^{22}$ = -2.0 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2954, 2930, 2857, 1790, 1756, 1721, 1367, 1307, 1154, 1081 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.20 (m, 1H), 7.13-7.07 (m, 1H), 6.98-6.93 (m, 2H), 4.95-4.90 (m, 1H), 4.12-4.04 (m, 1H), 2.85 (dd, *J* = 17.2, 5.6 Hz, 1H), 2.40 (dd, *J* = 17.2, 1.6 Hz, 1H), 2.34 (s, 3H), 1.31 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 173.1, 149.8, 139.1, 138.9, 129.0, 128.8, 125.8, 122.5, 83.1, 72.1, 71.6, 41.2, 27.9, 25.8, 21.6, 18.1, -4.6, -4.7 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{35}NO_4SiNa$: 428.2233, found: 428.2233.

(2*S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-oxo-2-*o*-tolylpyrrolidine-1-carboxylate 1c

Yellow oil (360 mg, 31%). $[\alpha]_D^{22}$ = -8.1 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2958, 2930, 2850, 1790, 1754, 1721, 1367, 1460, 1306, 1154, 1080, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22-7.17 (m, 3H), 7.03-6.98 (m, 1H), 5.20 (d, *J* = 1.2 Hz, 1H), 4.08-4.03 (m, 1H), 2.85 (dd, *J* = 17.2, 5.6 Hz, 1H), 2.43-2.38 (m, 1H), 2.41 (s, 3H), 1.26 (s, 9H), 0.88 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 173.1, 149.6, 137.3, 135.0, 131.0, 127.8, 126.7, 123.4, 83.0, 71.2, 68.0, 41.3, 27.8, 25.7, 19.4, 18.0, -4.4, -4.8 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{35}NO_4SiNa$: 428.2233, found: 428.2231.

(2*S,3R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-oxo-2-phenylpyrrolidine-1-carboxylate 1d

White solid (582 mg, 52%), m.p. 112-114°C. $[\alpha]_D^{22}$ = -5.5 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2950, 2929, 2853, 1790, 1754, 1363, 1306, 1149, 1091, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (m, 3H), 7.20-7.15 (m, 2H), 4.96-4.92 (m, 1H), 4.12-4.03 (m, 1H), 2.84 (dd, *J* = 17.6, 6.0 Hz, 1H), 2.40 (dd, *J* = 17.2, 2.0 Hz, 1H), 1.29 (s, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 173.0, 149.7, 139.2, 129.1, 128.1, 125.3, 83.1, 72.1, 71.6, 41.2, 27.8, 25.8, 18.1, -4.6, -4.7 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{21}H_{33}NO_4SiNa$: 414.2071, found: 414.2066.

(2*S*,3*R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(4-methoxyphenyl)-5-oxopyrrolidine-1-carboxylate 1e

Yellow oil (651 mg, 54%). $[\alpha]_D^{23}$ = -5.8 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2953, 2930, 2857, 1787, 1720, 1515, 1367, 1306, 1251, 1150, 1075, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.12-7.07 (m, 2H), 6.92-6.87 (m, 2H), 4.93-4.89 (m, 1H), 4.09-4.05 (m, 1H), 3.81 (s, 3H), 2.85 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.40 (dd, *J* = 17.6, 1.2 Hz, 1H), 1.32 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 173.0, 159.4, 149.8, 131.2, 126.5, 114.4, 83.0, 72.2, 71.1, 55.5, 41.2, 27.9, 25.8, 18.1, -4.6, -4.7 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{35}NO_5SiNa$: 444.2182, found: 444.2172.

(2*S*,3*R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(4-methoxyphenyl)-5-oxopyrrolidine-1-carboxylate 1f

Yellow oil (675 mg, 56%). $[\alpha]_D^{25}$ = +30.5 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2955, 2930, 2857, 1789, 1755, 1721, 1603, 1473, 1366, 1306, 1153, 1080, 837, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.25 (m, 1H), 6.87-6.82 (m, 1H), 6.79-6.74 (m, 1H), 6.72-6.68 (m, 1H), 4.94-4.91 (m, 1H), 4.12-4.08 (m, 1H), 3.80 (s, 3H), 2.85 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.40 (dd, *J* = 17.6, 1.6 Hz, 1H), 1.33 (s, 9H), 0.89 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.9, 160.3, 149.7, 140.8, 130.2, 117.4, 113.2, 111.1, 83.1, 72.1, 71.5, 55.4, 41.2, 27.8, 25.8, 18.1, -4.6, -4.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{35}NO_5SiNa$: 444.2177, found: 444.2178.

(2*S,3R*)-*tert*-Butyl 3-(tert-butyldimethylsilyloxy)-2-(2-methoxyphenyl)-5-oxopyrrolidine-1-carboxylate 1g

Yellow oil (326 mg, 27%). $[\alpha]_D^{23}$ = +2.3 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2953, 2930, 2858, 1756, 1720, 1588, 1493, 1366, 1246, 1152, 1083, 1022, 836, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (m, 1H), 7.03-6.92 (m, 3H), 5.39-5.31 (m, 1H), 4.18-4.10 (m, 1H), 3.88 (s, 3H), 2.78 (dd, *J* = 17.2, 5.2 Hz, 1H), 2.37-2.27 (m, 1H), 1.35 (s, 9H), 0.92 (s, 9H), 0.14 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 173.8, 156.4, 149.9, 129.1, 126.6, 125.1, 120.8, 110.7, 82.7, 70.3, 66.9, 55.2, 41.5, 27.9, 25.8, 18.1, -4.7, -4.9 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{35}NO_5SiNa$: 444.2177, found: 444.2170.

(2*S*,3*R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(3-fluorophenyl)-5-oxopyrrolidine-1-carboxylate 1h

White solid (644 mg, 55%), m.p. 50-52°C. $[\alpha]_D^{24}$ = -6.2 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2956, 2926, 2852, 1789, 1757, 1721, 1593, 1367, 1304, 1257, 1153, 1078, 921, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 1H), 7.05-6.85 (m, 3H), 4.92 (d, *J* = 1.6 Hz, 1H), 4.12-4.06 (m, 1H), 2.83 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.42 (dd, *J* = 17.6, 2.4 Hz, 1H), 1.32 (s, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.5, 163.3 (d, *J* = 246.1 Hz), 149.6, 142.0 (d, *J* = 6.7 Hz), 130.8 (d, *J* = 8.2 Hz), 120.9 (d, *J* = 2.8 Hz), 115.1 (d, *J* = 21.0 Hz), 112.5 (d, *J* = 22.2 Hz), 83.4, 72.0, 71.0, 71.0, 41.1, 27.9, 25.8, 18.1, -4.7 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{21}H_{32}FNO_4SiNa$: 432.1982, found: 432.1985.

(2*S*,3*R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-oxo-2-(3-(trifluoromethyl) phenyl)pyrrolidine-1-carboxylate 1i

Yellow oil (670 mg, 51%). $[\alpha]_D^{22}$ = -4.2 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2957, 2932, 2859, 1801, 1366, 1333, 1311, 1252, 1167, 1130, 1097, 890, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.37 (m, 4H), 4.96 (d, *J* = 2.4 Hz, 1H), 4.12-4.07 (m, 1H), 2.85 (dd, *J* = 17.2, 6.0 Hz, 1H), 2.48 (dd, *J* = 17.6, 3.2 Hz, 1H), 1.29 (s, 9H), 0.88 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.3, 149.4, 140.7, 131.6 (q, *J* = 32.3 Hz), 129.7, 128.6, 125.0 (q, *J* = 3.7 Hz), 123.9 (q, *J* = 270.8 Hz), 122.5 (q, *J* = 3.6 Hz), 83.6, 72.1, 71.0, 41.2, 27.8, 25.7, 18.1, -4.7, -4.8 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{32}F_3NO_4SiNa$: 482.1950, found: 444.1951.

(2*S*,3*R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(naphthalen-1-yl)-5-oxopyrrolidine-1-carboxylate 1j

Colorless oil (379 mg, 30%). $[\alpha]_D^{23}$ = +42.7 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2955, 2933, 2861, 1790, 1761, 1727, 1375, 1311, 1156, 1078, 923, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.07-8.02 (m, 1H), 7.94-7.90 (m, 1H), 7.84-7.80 (m, 1H), 7.62-7.52 (m, 2H), 7.47-7.41 (m, 1H), 7.26-7.21 (m, 1H), 5.85-5.82 (m, 1H), 4.24-4.20 (m, 1H), 2.84 (dd, *J* = 17.2, 5.2 Hz, 1H), 2.41 (d, *J* = 17.6 Hz, 1H), 1.24 (s, 9H), 0.95 (s, 9H), 0.09 (s, 3H), 0.03 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 173.3, 149.8, 134.4, 134.1, 130.4, 129.3, 128.6, 126.7, 126.2, 125.4, 122.7, 120.9, 83.2, 70.9, 68.4, 41.4, 27.8, 25.8, 18.0, -4.4, -4.6 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{35}NO_4SiNa$: 464.2233, found: 464.2223.

(2*S*,3*R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-ethyl-5-oxopyrrolidine-1-carboxylate 1k

Colorless oil (383 mg, 39%). $[\alpha]_D^{23}$ = +29.0 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2957, 2932, 2858, 1786, 1751, 1714, 1463, 1368, 1309, 1252, 1156, 1072, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.07 (d, *J* = 5.2 Hz, 1H), 3.88-3.82 (m, 1H), 2.75 (dd, *J* = 17.6, 5.2 Hz, 1H), 2.37-2.28 (m, 1H), 1.80-1.68 (m, 1H), 1.53 (s, 9H), 1.45-1.36 (m, 1H), 1.00-0.95 (m, 3H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.8, 150.2, 82.9, 69.4, 68.0, 41.9, 28.2, 25.8, 25.1, 18.1, 10.4, -4.5, -4.6 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{33}NO_4SiNa$: 366.2077, found: 366.2067.

(2*S*,3*R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-hexyl-5-oxopyrrolidine-1-carboxylate 1l

Yellow oil (389 mg, 34%). $[\alpha]_D^{24}$ = +24.7 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2956, 2930, 2857, 1787, 1754, 1716, 1582, 1471, 1368, 1310, 1255, 1155, 1079, 837, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.06 (d, *J* = 5.2 Hz, 1H), 3.94-3.88 (m, 1H), 2.77 (dd, *J* = 17.6, 5.2 Hz, 1H), 2.34 (d, *J* = 17.6 Hz, 1H), 1.54 (s, 9H), 1.39-1.27 (m, 10H), 0.93-0.89 (m, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.8, 150.2, 82.9, 68.4, 68.1, 41.8, 32.1, 31.8, 29.3, 28.2, 26.1, 25.8, 22.7, 18.1, 14.2, -4.5, -4.6 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + Na]^+$ Calcd for $C_{21}H_{41}NO_4SiNa$: 422.2697, found: 422.2692.

(2*S*,3*R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-isobutyl-5-oxopyrrolidine-1-carboxylate 1m

Colorless oil (424 mg, 40%). $[\alpha]_D^{22}$ = +38.7 (*c* 2.00, $CHCl_3$); IR (film) ν_{max} 2958, 2931, 2857, 1788, 1752, 1716, 1471, 1368, 1312, 1157, 1078, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 4.06 (d, *J* = 5.0 Hz, 1H), 4.00 (dd, *J* = 10.8, 2.8 Hz, 1H), 2.78 (dd, *J* = 17.6, 5.0 Hz, 1H), 2.33 (d, *J* = 17.6 Hz, 1H), 1.73-1.62 (m, 1H), 1.54 (s, 9H), 1.50-1.44 (m, 1H), 1.31-1.22 (m, 1H), 1.03-0.99 (m, 3H), 0.99-0.96 (m, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 173.0, 150.0, 82.9, 68.6, 66.5, 41.6, 41.2, 28.2, 25.7, 25.4, 23.9, 21.8, 18.0, -4.5, -4.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{38}NO_4Si$: 372.2565, found: 372.2566.

(2*S*,3*R*)-*tert*-Butyl 2-benzyl-3-(*tert*-butyldimethylsilyloxy)-5-oxopyrrolidine-1-carboxylate 1n

Yellow oil (534 mg, 46%). $[\alpha]_D^{23}$ = +11.0 (*c* 2.00, $CHCl_3$); IR (film) ν_{max} 2956, 2930, 2857, 1787, 1754, 1713, 1368, 1312, 1258, 1148, 1075, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.37-7.24 (m, 3H), 7.21-7.17 (m, 2H), 4.15 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.06 (d, *J* = 5.2 Hz, 1H), 3.18 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.64 (dd, *J* = 17.6, 5.2 Hz, 1H), 2.50 (dd, *J* = 13.6, 10.4 Hz, 1H), 2.30 (d, *J* = 17.6 Hz, 1H), 1.60 (s, 9H), 0.73 (s, 9H), -0.24 (s, 3H), -0.25 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.9, 150.1, 136.8, 129.4, 129.0, 127.2, 83.2, 69.3, 67.0, 41.5, 38.1, 28.3, 25.7, 18.0, -5.1, -5.2 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{35}NO_4SiNa$: 428.2228, found: 428.2221.

*General procedure for synthesis of **9***:

Compound **1** (1.13 mmol) was dissolved in anhydrous THF (5 mL) and treated with TBAF (1.7 mL, 1.70 mmol, 1 M in THF) for overnight at room temperature. 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 = 1/1) to give imide **9**.

(2*S*,3*R*)-*tert*-Butyl 3-hydroxy-5-oxo-2-*p*-tolylpyrrolidine-1-carboxylate 9a

White solid (227 mg, 69%), m.p. 142-143°C. $[\alpha]_D^{23}$ = +28.1 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3459, 2978, 2926, 1775, 1368, 1305, 1152, 1019, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.19-7.14 (m, 2H), 7.13-7.06 (m, 2H), 5.09-5.04 (m, 1H), 4.21-4.16 (m, 1H), 2.91 (dd, *J* = 18.0, 5.6 Hz, 1H), 2.48 (d, *J* = 18.0 Hz, 1H), 2.35 (s, 3H), 1.32 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.8, 149.7, 138.0, 135.7, 129.8, 125.2, 83.3, 71.5, 70.8, 40.6, 27.9, 21.2 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{22}NO_4$: 292.1543, found: 292.1543.

(2*S*,3*R*)-*tert*-Butyl 3-hydroxy-5-oxo-2-*m*-tolylpyrrolidine-1-carboxylate 9b

White solid (240 mg, 73%), m.p. 151-153°C. $[\alpha]_D^{23}$ = +28.2 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3480, 2978, 2926, 1766, 1366, 1329, 1292, 1279, 1152, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.27-7.21 (m, 1H), 7.17-7.08 (m, 1H), 7.05-6.96 (m, 2H), 5.12-5.02 (m, 1H), 4.26-4.16 (m, 1H), 2.92 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.50 (d, *J* = 18.0 Hz, 1H), 2.34 (s, 3H), 1.31 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 173.2, 149.7, 138.9, 138.8, 129.0, 128.9, 125.9, 122.4, 83.3, 71.3, 71.0, 40.6, 27.9, 21.5 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{22}NO_4$: 292.1543, found: 292.1544.

(2*S*,3*R*)-*tert*-Butyl 3-hydroxy-2-(4-methoxyphenyl)-5-oxopyrrolidine-1-carboxylate 9e

White solid (139 mg, 40%), m.p. 127-129°C. $[\alpha]_D^{23}$ = +23.7 (*c* 0.35, $CHCl_3$); IR (film) ν_{max} 2981, 2930, 2838, 1772, 1515, 1368, 1306, 1250, 1151, 1029, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.18-7.10 (m, 2H), 6.93-6.86 (m, 2H), 5.09-5.04 (m, 1H), 4.22-4.14 (m, 1H), 3.81 (s, 3H), 2.91 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.50 (d, *J* = 18.0 Hz, 1H),

1.31 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 159.5, 149.8, 130.9, 126.5, 114.5, 83.2, 71.4, 70.6, 55.5, 40.6, 27.9 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{22}NO_5$: 308.1493, found: 308.1494.

(2*S*,3*R*)-*tert*-Butyl 2-(3-fluorophenyl)-3-hydroxy-5-oxopyrrolidine-1-carboxylate 9h

White solid (204 mg, 61%), m.p. 169-170°C. $[\alpha]_D^{23}$ = +21.6 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2978, 2915, 1771, 1368, 1333, 1291, 1154, 1069, 778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.30 (m, 1H), 7.06-6.98 (m, 2H), 6.98-6.91 (m, 1H), 5.13-5.08 (m, 1H), 4.22 (d, *J* = 5.6 Hz, 1H), 3.03 (brs, 1H), 2.90 (dd, *J* = 18.0, 5.6 Hz, 1H), 2.53 (d, *J* = 18.0 Hz, 1H), 1.32 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 163.4 (d, *J* = 247.5 Hz), 149.6, 141.6 (d, *J* = 6.8 Hz), 130.9 (d, *J* = 8.2 Hz), 120.8 (d, *J* = 3.1 Hz), 115.1 (d, *J* = 21.0 Hz), 112.6 (d, *J* = 22.4 Hz), 83.6, 71.1, 70.5, 40.5, 27.9 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{19}FNO_4$: 296.1293, found: 296.1292.

(2*S*,3*R*)-*tert*-Butyl 3-hydroxy-5-oxo-2-(3-(trifluoromethyl)phenyl)pyrrolidine-1-carboxylate 9i

White solid (242 mg, 62%), m.p. 138-139°C. $[\alpha]_D^{23}$ = +22.9 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2983, 2930, 1776, 1331, 1310, 1152, 1126, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.57 (m, 1H), 7.57-7.49 (m, 2H), 7.46-7.39 (m, 1H), 5.19-5.14 (m, 1H), 4.29-4.21 (m, 1H), 3.10-2.98 (m, 1H), 2.91 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.57 (d, *J* = 18.0 Hz, 1H), 1.30 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 149.5, 140.2, 131.7 (q, *J* = 32.4 Hz), 129.8, 128.5, 125.1 (q, *J* = 3.4 Hz), 124.0 (q, *J* = 272.0 Hz), 122.6 (q, *J* = 3.4 Hz), 83.8, 71.1, 70.6, 40.6, 27.8 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{19}F_3NO_4$: 346.1261, found 346.1260.

(2*S*,3*R*)-*tert*-Butyl 3-hydroxy-2-(naphthalen-1-yl)-5-oxopyrrolidine-1-carboxylate 9j

Colorless oil (211 mg, 57%). $[\alpha]_D^{23}$ = +56.4 (*c* 0.25, $CHCl_3$); IR (film) ν_{max} 2981, 2921, 1776, 1369, 1307, 1150, 1045, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-8.07 (m, 1H), 7.95-7.90 (m, 1H), 7.85-7.80 (m, 1H), 7.65-7.53 (m, 2H), 7.47-7.41 (m, 1H), 7.26-7.22 (m, 1H), 5.97-5.93 (m, 1H), 4.35-4.31 (m, 1H), 2.88 (dd, *J* = 18.0, 5.6 Hz, 1H), 2.75 (brs, 1H), 2.51 (d, *J* = 18.0 Hz, 1H), 1.25 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 149.8, 134.2, 133.8, 130.4, 129.3, 128.8, 127.0, 126.3, 125.4, 122.5, 120.8, 83.4, 70.1, 67.7, 41.1, 27.9 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{22}NO_4$: 328.1543, found: 328.1544.

(2*S*,3*R*)-*tert*-Butyl 2-ethyl-3-hydroxy-5-oxopyrrolidine-1-carboxylate 9k

White solid (142 mg, 55%), m.p. 122-124°C. $[\alpha]_D^{24}$ = +45.5 (*c* 1.36, $CHCl_3$); IR (film) ν_{max} 2973, 2932, 2882, 1773, 1715, 1370, 1300, 1155, 1041, 1019 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21-4.14 (m, 1H), 3.96 (dd, *J* = 9.2, 3.6 Hz, 1H), 2.82 (dd, *J* = 18.0, 5.6 Hz, 1H), 2.77 (d, *J* = 4.0 Hz, 1H), 2.45 (d, *J* = 18.0 Hz, 1H), 1.82-1.72 (m, 1H), 1.53 (s, 9H), 1.50-1.39 (m, 1H), 1.08-0.93 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 150.1, 83.1, 68.8, 67.3, 41.4, 28.1, 25.1, 10.2 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{20}NO_4$: 230.1387, found: 230.1386.

(2*S*,3*R*)-*tert*-Butyl 3-hydroxy-2-isobutyl-5-oxopyrrolidine-1-carboxylate 9m

White solid (125 mg, 43%), m.p. 111-113°C. $[\alpha]_D^{22}$ = +58.0 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3414, 2955, 2933, 2870, 1770, 1717, 1367, 1290, 1152, 1042, 1022 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (d, *J* = 5.2 Hz, 1H), 4.07 (dd, *J* = 10.8, 3.2 Hz, 1H), 2.84 (dd, *J* = 18.0, 5.2 Hz, 1H), 2.77 (brs, 1H), 2.44 (d, *J* = 18.0 Hz, 1H), 1.76-1.65 (m, 1H), 1.53 (s, 9H), 1.49 (dd, *J* = 9.6, 3.2 Hz, 1H), 1.28 (ddd, *J* = 15.2, 11.2, 4.4 Hz, 1H), 1.04-0.93 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 149.9, 83.2, 67.8, 66.1, 41.1, 41.0, 28.2, 25.5, 23.8, 21.9 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{24}NO_4$: 258.1700, found: 258.1695.

(2*S*,3*R*)-*tert*-Butyl 2-benzyl-3-hydroxy-5-oxopyrrolidine-1-carboxylate 9n

Colorless oil (184 mg, 56%). $[\alpha]_D^{25}$ = +30.5 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3452, 2978, 2922, 2847, 1775, 1580, 1369, 1298, 1150, 1044, 1023, 845, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.23 (m, 3H), 7.20-7.16 (m, 2H), 4.28 (dd, *J* = 9.2, 3.6 Hz, 1H), 4.15 (d, *J* = 5.2 Hz, 1H), 3.14 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.66 (dd, *J* = 13.6, 9.2 Hz, 1H), 2.50 (dd, *J* = 18.0, 5.6 Hz, 1H), 2.40-2.29 (m, 2H), 1.57 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 150.0, 136.5, 129.4, 129.0, 127.3, 83.4, 68.3, 66.8, 41.0, 38.0, 28.2 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{22}NO_4$: 292.1543, found: 292.1543.

*General procedure for synthesis of **2***:

To a stirred solution of **9** (0.51 mmol) in THF/H_2O (4/1) (5 mL) at room temperature, $LiOH{\cdot}H_2O$ (64 mg, 1.53 mmol) and an aqueous solution of 30% H_2O_2 (0.5 mL) were added sequentially. The mixture was stirred continued at room temperature for 12 h. Then the reaction mixture was quenched with a solution of 1 M NaOH (30 mL) and extracted with EtOAc (10 mL). The aqueous layer was treated with 1M HCl until pH = 2-3 and resulted mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine. Dried and concentrated, the residue was dissolved in HCl/Dioxane and stirred for overnight. The mixture was directly concentrated to give **2**.

(3*R*,4*S*)-4-Amino-3-hydroxy-4-*p*-tolylbutanoic acid hydrochloride 2a

White solid (98 mg, 78%), m.p. 155-157°C. $[\alpha]_D^{25}$ = +15.0 (*c* 0.5, H_2O); IR (film) ν_{max} 1710, 1622, 1392, 1033 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20-8.10 (m, 2H), 7.38-7.30 (m, 2H), 7.22-7.18 (m, 2H), 4.41-4.33 (m, 1H), 4.25 (d, *J* = 3.2 Hz, 1H), 2.31 (s, 3H), 2.27 (d, *J* = 4.4 Hz, 1H), 1.97 (dd, *J* = 15.6, 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.8, 137.7, 131.0, 128.6, 128.5, 67.2, 57.3, 38.6, 20.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{16}NO_3$: 210.1125, found: 210.1121.

(3*R*,4*S*)-4-Amino-3-hydroxy-4-*m*-tolylbutanoic acid hydrochloride 2b

White solid (101 mg, 81%), m.p. 160-162°C. $[\alpha]_D^{27}$ = +15.4 (*c* 1.00, H_2O); IR (film) ν_{max} 1636, 1518, 1392, 1053 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (brs, 1H), 8.70-8.50 (m, 2H), 7.32-7.23 (m, 3H), 7.23-7.17 (m, 1H), 5.70 (brs, 1H), 4.44-4.34 (m, 1H), 4.28-4.19 (m, 1H), 2.35-2.27 (m, 4H), 1.98 (dd, *J* = 15.6, 8.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.8, 137.2, 134.0, 129.1, 129.0, 128.0, 125.8, 67.2, 57.5, 38.6, 21.0 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{16}NO_3$: 210.1125, found: 210.1122.

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(3*R*,4*S*)-4-Amino-3-hydroxy-4-(4-methoxyphenyl)butanoic acid hydrochloride 9e

Yellow oil (80 mg, 60%). $[\alpha]_D^{24}$ = +17.4 (*c* 1.00, H_2O); IR (film) ν_{max} 1715, 1613, 1518, 1256, 1182, 1032, 837 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.69-8.40 (m, 2H), 7.42-7.37 (m, 2H), 7.00-6.94 (m, 2H), 5.68 (brs, 1H), 4.41-4.33 (m, 1H), 4.23 (d, *J* = 2.4 Hz, 1H), 3.76 (s, 3H), 2.29 (dd, *J* = 15.6, 4.0 Hz, 1H), 1.95 (dd, *J* = 15.6, 8.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.8, 159.3, 130.0, 125.9, 113.5, 67.2, 56.9, 55.1, 38.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{16}NO_4$: 226.1074, found: 226.1072.

(3*R*,4*S*)-4-Amino-4-(3-fluorophenyl)-3-hydroxybutanoic acid hydrochloride 2h

White solid (92 mg, 72%), m.p. 176-178°C. $[\alpha]_D^{24}$ = +15.2 (*c* 1.79, H_2O); IR (film) ν_{max} 3033, 2921, 1713, 1593, 1494, 1454, 1403, 1250, 1181, 1052, 793 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.90-8.60 (m, 2H), 7.51-7.35 (m, 2H), 7.33-7.18 (m, 2H), 5.77 (brs, 1H), 4.47-4.39 (m, 1H), 4.36 (d, *J* = 3.2 Hz, 1H), 2.39 (dd, *J* = 16.0, 4.0 Hz, 1H), 1.95 (dd, *J* = 16.0, 8.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.7, 161.7 (d, *J* = 243.3 Hz), 136.7 (d, *J* = 7.6 Hz), 130.1 (d, *J* = 8.1 Hz), 125.1 (d, *J* = 2.7 Hz), 115.7 (d, *J* = 22.7 Hz), 115.3 (d, *J* = 20.8 Hz), 67.0, 57.0, 38.8 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{13}FNO_3$: 214.0874, found: 214.0873.

(3*R*,4*S*)-4-Amino-3-hydroxy-4-(3-(trifluoromethyl)phenyl)butanoic acid hydrochloride 2i

Yellow oil (116 mg, 76%). $[\alpha]_D^{23}$ = +9.3 (*c* 1.00, H_2O); IR (film) ν_{max} 2921, 1715, 1630, 1328, 1167, 1127, 1075, 1054 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.00-8.50 (m, 2H), 7.95-7.89 (m, 1H), 7.81-7.73 (m, 2H), 7.70-7.62 (m, 1H), 5.84 (brs, 1H), 4.51-4.39 (m, 2H), 2.45-2.35 (m, 1H), 1.88 (dd, *J* = 15.6, 8.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.6, 135.4, 133.1, 129.2, 128.9 (q, *J* = 31.3 Hz), 125.5 (q, *J* = 3.1 Hz), 125.2 (q, *J* = 3.0 Hz), 124.1 (q, *J* = 272.4 Hz), 66.9, 56.8, 38.9 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{13}F_3NO_3$: 264.0842, found: 264.0842.

(3*R*,4*S*)-4-Amino-3-hydroxy-4-(naphthalen-1-yl)butanoic acid hydrochloride 2j

White solid (96 mg, 67%), m.p. 148-150°C. $[\alpha]_D^{25}$ = +47.4 (*c* 0.61, H_2O); IR (film) ν_{max} 1635, 1203, 1142, 1054 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.60-8.52 (m, 2H), 8.25-8.16 (m, 1H), 8.06-7.96 (m, 2H), 7.82-7.74 (m, 1H), 7.68-7.55 (m, 3H), 5.99-5.86 (m, 1H), 5.33-5.20 (m, 1H), 4.59-4.44 (m, 1H), 2.26 (dd, *J* = 16.0, 3.6 Hz, 1H), 2.03 (dd, *J* = 16.0, 9.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.8, 133.1, 130.9, 130.3, 128.9, 128.8, 126.8, 126.0, 125.5, 125.1, 122.8, 67.5, 52.8, 37.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{16}NO_3$: 246.1125, found: 246.1122.

(3*R*,4*S*)-4-Amino-3-hydroxyhexanoic acid hydrochloride 2k

Light yellow oil (79 mg, 84%). $[\alpha]_D^{25}$ = -0.2 (*c* 1.00, H_2O); IR (film) ν_{max} 1671, 1200, 1142, 1047 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.92-7.80 (m, 2H), 5.57 (brs, 1H), 4.17-4.10 (m, 1H), 3.05-2.99 (m, 1H), 2.46 (dd, *J* = 15.6, 4.0 Hz, 1H), 2.29 (dd, *J* = 15.6, 9.2 Hz, 1H), 1.60-1.45 (m, 2H), 0.96-0.90 (m, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.2, 66.6, 56.2, 37.5, 20.3, 10.0 ppm; HRMS (ESI-Orbitrap) *m/z*: $[2M + H]^+$ Calcd for $C_{12}H_{27}N_2O_6$: 295.1864, found: 295.1867.

(3*R*,4*S*)-4-Amino-3-hydroxy-6-methylheptanoic acid hydrochloride 2m

White solid (87 mg, 81%), m.p. 160-162°C. $[\alpha]_D^{24}$ = -8.10 (*c* 1.00, H_2O); IR (film) ν_{max} 2964, 1676, 1202, 1142, 1041 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.92-7.80 (m, 2H), 5.58 (brs, 1H), 4.16-4.10 (m, 1H), 3.19-3.12 (m, 1H), 2.44 (dd, *J* = 15.6, 4.4 Hz, 1H), 2.30 (dd, *J* = 15.6, 9.2 Hz, 1H), 1.72-1.61 (m, 1H), 1.43 (ddd, *J* = 14.8, 9.2, 5.2 Hz, 1H), 1.28 (ddd, *J* = 14.8, 9.2, 4.8 Hz, 1H), 0.92-0.86 (m, 3H), 0.85-0.83 (m, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.1, 67.0, 52.9, 37.3, 36.2, 23.5, 22.9, 21.5 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_8H_{18}NO_3$: 176.1281, found: 176.1282.

(*3R,4S*)-4-Amino-3-hydroxy-5-phenylpentanoic acid hydrochloride 2n

Yellow oil (96 mg, 77%). $[\alpha]_D^{25}$ = -19.9 (*c* 1.00, H_2O); IR (film) ν_{max} 2937, 1672, 1414, 1143, 1055, 1033 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.20-7.90 (m, 2H), 7.38-7.25 (m, 5H), 5.66 (brs, 1H), 4.16-4.08 (m, 1H), 3.44-3.42 (m, 1H), 2.89 (dd, *J* = 14.4, 6.4 Hz, 1H), 2.81 (dd, *J* = 14.4, 7.6 Hz, 1H), 2.55 (dd, *J* = 15.6, 3.6 Hz, 1H), 2.31 (dd, *J* = 15.6, 9.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.2, 136.6, 129.2, 128.6, 126.8, 66.4, 56.3, 37.4, 33.4 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{16}NO_3$: 210.1125, found: 210.1125.

(2*S,3S*)-*tert*-Butyl 2-benzyl-3-hydroxy-5-oxopyrrolidine-1-carboxylate 10

To a solution of $(COCl)_2$ (0.7 mL, 8.10 mmol) in dry DCM (15 mL) was treated with DMSO (1.1 mL, 16.20 mmol) at -78°C. After the mixture was stirred for 1h, a solution of **9n** (1.18 g, 4.05 mmol) in DCM (5 mL) was dropped and stirred for another 3h. Then TEA (3.4 mL, 24.30 mmol) was added and stirred at room temperature for 1h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (50 mL × 3). The combined organic layers were washed with brine. Dried and concentrated, the residue was dissolved in MeOH (20 mL) at 0°C. Then $NaBH_4$ (153 mg, 4.05 mmol) was added in one portion. After being stirred for 30 min, the mixture was concentrated and the residue was dissolved in EtOAc (30 mL) and water (30 mL). The resulted mixture was separated 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 = 1/1) to give **10** (1.06 g, 90%) as a white solid. M.p. 98-100°C. $[\alpha]_D^{23}$ = +26.0 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3400, 2970, 1760, 1650, 1355, 1280, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (m, 4H), 7.26-7.20 (m, 1H), 4.55-4.42 (m, 2H), 3.17-3.13 (m, 2H), 2.63 (dd, *J* = 16.8, 7.2 Hz, 1H), 2.43 (dd, *J* = 17.2, 8.0 Hz, 1H), 2.01-1.94 (m, 1H), 1.50 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 149.9, 137.8, 129.9, 128.8, 126.8, 83.5, 65.8, 62.7, 40.3, 34.1, 28.1 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{21}NO_4Na$: 314.1363, found：314.1372.

(2*S,3S*)-*tert*-Butyl 2-benzyl-3-((*tert*-butyldimethylsilyl)oxy)-5-oxopyrrolidine-1-carboxylate 11

To a solution of **10** (1.00 g, 3.43 mmol), TBSCl (773 mg, 5.15 mmol) and DMAP (419 mg, 3.43 mmol) in DMF (14 mL) was added imidazole (700 mg, 10.29 mmol) in one portion at 0°C. After being stirred for 24 h, the mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (50 mL × 4).

The combined organic layers were washed with water and brine for two times respectively. Dried and concentrated, the residue was purified by flash chromatography on silica gel (PE/EA = 15/1) to give **11** (1.29 g, 93%) as a white solid. M.p. 96-98°C. $[\alpha]_D^{23}$ = +34.9 (*c* 0.49, $CHCl_3$); IR (film) ν_{max} 2958, 2927, 2854, 1797, 1582, 1507, 1360, 1294, 1256, 1167, 1150, 1120, 1019, 850, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.18 (m, 5H), 4.56-4.41 (m, 2H), 3.18 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.94 (dd, *J* = 14.0, 4.8 Hz, 1H), 2.44 (dd, *J* = 16.8, 7.6 Hz, 1H), 2.25 (dd, *J* = 16.8, 10.4 Hz, 1H), 1.43 (s, 9H), 0.91 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 149.7, 137.8, 130.3, 128.5, 126.6, 83.2, 67.0, 62.4, 40.6, 34.2, 28.0, 25.9, 18.2, -4.7, -4.9 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{35}NO_4SiNa$: 428.2228, found: 428.2224.

(*2S,3S,5R*)-2-Benzyl-3-((*tert*-butyldimethylsilyl)oxy)-1-methyl-5-nonylpyrrolidine 12

To a solution of compound **11** (600 mg, 1.48 mmol) in anhydrous Et_2O (6 mL) was slowly added *n*-$C_9H_{19}MgBr$ (4.5 mL, 4.44 mmol, 1M in Et_2O) at -78°C. After being stirred for 3 h at this temperature, the mixture was quenched with a saturated aqueous solution of NH_4Cl and warmed to room temperature. The resulted mixture was extracted with EtOAc (30 mL × 3) and the combined organic layers were washed with brine. Dried, and concentrated, the residue was directly dissolved in CF_3COOH (18 mL) and stirred for 1 h. Then the mixture was alkalized with 30% aqueous solution of NaOH to pH to 10~12. The resulted mixture was extracted with $CHCl_3$ (50 mL × 5) and the combined organic layers were washed with brine. Dried and concentrated to give crude middle product without further purification. The above middle product, 10%Pd/C (100 mg) and 20%$Pd(OH)_2$/C (100 mg) were stirred in MeOH (300 mL) under H_2 atmosphere for 8 h. The reaction mixture was treated with paraformaldehyde (750 mg). After being stirred for 3 h, the mixture was filtered and concentrated. The residue was purified by flash chromatography on silica gel (DCM/MeOH = 40/1, 1% $NH_3 \cdot H_2O$) to give **12** (326 mg, 51%) as a yellow oil. $[\alpha]_D^{23}$ = +46.4 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2956, 2929, 2895, 2857, 1463, 1427, 1116, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.23 (m, 4H), 7.21-7.15 (m, 1H), 4.21-4.14 (m, 1H), 3.08 (dd, *J* = 14.4, 8.0 Hz, 1H), 2.81 (dd, *J* = 14.0, 4.0 Hz, 1H), 2.55-2.45 (m, 1H), 2.24 (s, 3H), 2.14-2.04 (m, 1H), 1.79-1.68 (m, 1H), 1.45 (ddd, *J* = 12.8, 8.4, 3.6 Hz, 1H), 1.34-1.25 (m, 16H), 0.93-0.88 (m, 12H), -0.01 (s, 3H), -0.08 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 129.2, 128.2, 125.8, 73.5, 71.3, 66.1, 40.8, 40.5, 34.7, 34.3, 32.0, 30.1, 29.8, 29.7, 29.7, 29.5, 26.8, 26.2, 22.8, 18.3, 14.3, -4.2, -4.9 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{50}NOSi$: 432.3656, found: 432.3656.

(+)-Preussin 4

Compound **12** (151 mg, 0.35 mmol) was dissolved in anhydrous THF (2 mL) and treated with TBAF (0.53 mL, 0.53 mmol, 1 M in THF) at room temperature for overnight. The resulted mixture 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 (DCM/MeOH = 40/1, 1% $NH_3 \cdot H_2O$) to give **4** (68 mg, 61%) as a yellow oil. $[\alpha]_D^{25}$ = + 33.6 (*c* 0.4, $CHCl_3$) {lit.[18g] $[\alpha]_D^{25}$ = + 32 (*c* 1.1, $CHCl_3$)}; IR (film) ν_{max} 3356, 2950, 2830, 2597, 2512, 2220, 2046, 1650, 1455, 1402, 1111, 1031 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.38-7.18 (m, 5H), 3.84-3.76 (m, 1H), 2.88 (dd, *J* = 13.2, 10.2 Hz, 1H), 2.84 (dd, *J* = 13.2, 4.8 Hz, 1H), 2.33 (s, 3H), 2.26 (ddd, *J* = 9.6, 4.2, 3.0 Hz, 1H), 2.20 (ddd, *J* = 15.6, 9.0, 6.6 Hz, 1H), 2.12-2.09 (m, 1H), 1.76-1.68 (m, 1H), 1.41 (dd, *J* = 14.4, 7.8 Hz, 1H), 1.32-1.25 (m, 16H), 0.90-0.86 (m, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.6, 129.5, 128.5, 126.2, 73.7, 70.5, 66.0, 39.5, 38.8, 35.1, 33.8, 32.0, 30.0, 29.8, 29.8, 29.8, 29.7, 29.4, 26.5, 22.8, 14.2 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{36}NO$: 318.2791, found 318.2790.

***tert*-Butyl ((*2S,3R*)-3,5-dihydroxy-1-phenylpentan-2-yl)carbamate 16**

To a stirred solution of **9n** (630 mg, 2.16 mmol) in THF/H_2O (4/1) (25 mL) at room temperature, $LiOH \cdot H_2O$ (272 mg, 6.48 mmol) and a 30% aqueous solution of H_2O_2 (0.6 mL) were added sequentially. The mixture was stirred at room temperature for 12 h. Then the reaction mixture was added an aqueous solution of 1 M NaOH (50 mL) and extracted with EtOAc (20 mL). The aqueous layer was dropped with 1M HCl until pH = 2-3 and the resulted mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine. Dried and concentrated to give acid without further purification. The crude acid was dissolved in anhydrous THF (8 mL) at 0°C. NMM (0.24 mL, 2.16 mmol) and $ClCO_2Et$ (0.21 mL, 2.16 mmol) were added sequentially. After being stirred for 1 h at this temperature, the mixture was filtered and $NaBH_4$ (245 mg, 6.48 mmol) in H_2O (1 mL) was added in the filtrate. After being stirred for another 1 h, the reaction mixture was added water and extracted with EtOAc (50 mL × 4). The combined organic layers were washed with brine. Dried and concentrated, the residue was purified by flash chromatography on silica gel (PE/EA = 1/1) to give **16** (530 mg, 83%) as a white solid. M.p. 128-130°C. $[\alpha]_D^{25}$ = +23.2 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 3356, 3351, 2978, 2930, 2919, 1683, 1526, 1392, 1367, 1251, 1169, 1055, 1021, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.32-7.20 (m, 5H), 4.70-4.60 (m, 1H), 4.15-3.80 (m, 6H), 2.97-2.87 (m, 1H), 2.82-2.73 (m, 1H), 1.91-1.80 (m, 1H), 1.70-1.50 (m, 1H), 1.40-1.32 (m, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, rotamers) δ 156.0, 154.8, 137.3, 136.9, 128.9, 128.8, 128.7, 128.6, 127.9, 127.8, 125.9, 125.8, 79.3, 78.8, 73.6, 73.4, 61.5, 61.1, 56.2, 54.0, 35.2, 34.8, 34.0, 33.7, 29.1, 27.6 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{25}NO_4Na$: 318.1676, found: 318.1676.

***tert*-Butyl ((*2S,3R*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-1-phenylpentan-2-yl)carbamate 17**

To a solution of **16** (479 mg, 1.62 mmol), TBSCl (729 mg, 4.86 mmol) and DMAP (40 mg, 0.32 mmol) in DMF (6 mL) was added imidazole (551 mg, 8.10 mmol) in one portion at 0°C. After being stirred for 24 h, the mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (40 mL × 4). The combined organic layers were washed with water and brine for two times respectively. Dried and concentrated, the residue was purified by flash chromatography on silica gel (PE/EA = 40/1) to give **17** (594 mg, 70%) as a colorless oil. $[\alpha]_D^{23}$ = +17.0 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 2953, 2927, 2857, 1704, 1581, 1497, 1391, 1254, 1172, 1098, 836, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.24 (m, 2H), 7.22-7.15 (m, 3H), 4.74 (d, *J* = 7.2 Hz, 1H), 3.96-3.82 (m, 2H), 3.78-3.71 (m, 1H), 3.69-3.61 (m, 1H), 2.83 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.77-2.64 (m, 1H),

1.80-1.65 (m, 2H), 1.39-1.29 (m, 9H), 0.90 (s, 18H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 138.9, 129.3, 128.4, 126.2, 78.9, 70.7, 59.6, 56.0, 36.6, 36.1, 28.5, 26.1, 26.0, 18.4, 18.3, -4.4, -4.5, -5.2 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{54}NO_4Si_2$: 524.3586, found: 524.3586.

tert-Butyl ((2S,3R)-3,5-bis((tert-butyldimethylsilyl)oxy)-1-phenylpentan-2-yl)(methyl)carbamate 18

Compound **17** (398 mg, 0.76 mmol) and HMPA (0.2 mL, 1.14 mmol) were dissolved in dry THF (3 mL). LiHMDS (1.1 mL, 1.14 mmol, 1 M in THF) was dropped at -78°C and stirred for 1 h. Then the mixture was allowed to stir at ice-salt baths for 10 min and MeOTf (249 mg, 1.52 mmol) was added dropwise. The resulting mixture was stirred for another 10 min and quenched with a saturated aqueous solution of NH_4Cl. The mixture was extracted with EtOAc (30 mL × 3) and the combined organic layers were washed with brine. Dried, filtered and concentrated, the residue was purified by flash chromatography on silica gel (PE/EA = 40/1) to give **18** (339 mg, 83%) as a colorless oil. $[\alpha]_D^{25}$ = +24.9 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2956, 2929, 2886, 2857, 1697, 1472, 1390, 1365, 1254, 1095, 956, 837, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.25-7.21 (m, 2H), 7.19-7.11 (m, 3H), 4.10-3.99 (m, 1H), 3.98-3.88 (m, 1H), 3.77-3.67 (m, 2H), 3.16-3.09 (m, 1H), 2.76-2.57 (m, 3H), 2.55-2.53 (m, 1H), 1.82-1.76 (m, 1H), 1.74-1.68 (m, 1H), 1.34-1.20 (m, 9H), 0.97-0.93 (m, 9H), 0.88 (s, 9H), 0.15-0.11 (m, 6H), 0.05-0.03 (m, 6H) ppm; ^{1}H NMR (400 MHz, DMSO-d6, 70°C) δ 7.27-7.22 (m, 2H), 7.19-7.12 (m, 3H), 4.05-3.97 (m, 2H), 3.76-3.70 (m, 2H), 2.76-2.66 (m, 1H), 2.61 (s, 3H), 1.83-1.74 (m, 1H), 1.71-1.63 (m, 1H), 1.24 (s, 9H), 0.95 (s, 9H), 0.89 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), 0.06-0.03 (m, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, rotamers) δ 155.8, 139.7, 139.5, 129.2, 128.5, 128.3, 126.2, 126.0, 79.5, 79.1, 71.1, 70.9, 59.4, 59.0, 38.1, 37.7, 34.8, 28.5, 28.3, 26.1, 26.1, 18.4, 18.4, 18.3, 18.2, -3.7, -3.7, -4.3, -5.1 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{29}H_{56}NO_4Si_2$: 538.3742, found: 538.3742.

tert-Butyl ((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-5-hydroxy-1-phenylpentan-2-yl)(methyl)carbamate 13

A solution of **18** (247 mg, 0.46 mmol) and CSA (85 mg, 0.37 mmol) was stirred in DCM (2 mL) and MeOH (2 mL) at -40°C for 8h. Then TEA (64 μL, 0.46 mmol) was added and the mixture was warmed to room temperature. The mixture was concentrated and the residue was purified by flash chromatography on silica gel (PE/EA=5/1) to give **13** (193 mg, 99%) as a colorless oil. $[\alpha]_D^{25}$ = +35.0 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3407, 2955, 2930, 2857, 1692, 1670, 1391, 1366, 1254, 1168, 1063, 955, 836, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.29-7.23 (m, 2H), 7.21-7.12 (m, 3H), 4.32-3.65 (m, 3H), 3.20-3.10 (m, 1H), 2.85-2.20 (m, 5H), 2.00-1.65 (m, 3H), 1.34-1.12 (m, 9H), 0.98-0.93 (m, 9H), 0.21-0.11 (m, 6H) ppm; ^{1}H NMR (400 MHz, DMSO-d6, 70°C) δ 7.27-7.22 (m, 2H), 7.19-7.12 (m, 3H), 4.05-3.97 (m, 2H), 3.76-3.70 (m, 2H), 2.76-2.66 (m, 1H), 2.61 (s, 3H), 1.83-1.74 (m, 1H), 1.71-1.63 (m, 1H), 1.24 (s, 9H), 0.95 (s, 9H), 0.89 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), 0.06-0.03 (m, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, rotamers) δ 156.3, 155.6, 139.3, 139.2, 129.2, 129.1, 128.5, 128.4, 126.4, 126.2, 79.9, 79.7, 72.5, 72.3, 59.2, 58.9, 36.4, 35.5, 35.1, 34.5, 28.4, 28.2, 26.0, 18.1, -3.7, -3.8, -4.5, -4.5 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{42}NO_4Si$: 424.2878, found: 424.2878.

(S)-1-(Benzyloxy)-3-methyl-1-oxobutan-2-yl (2R,3R)-3-(((3R,4S)-4-((tert-butoxycarbonyl)(methyl)amino)-3-hydroxy-5-phenylpentanoyl)oxy)-2-methyldecanoate 19

To a solution of **13** (102 mg, 0.24 mmol) in dry DCM (2 mL) was treated with DMP (204 mg, 0.48 mmol) at room temperature for 0.5 h. The reaction was carefully quenched with a saturated aqueous solution of $NaHCO_3$ and the resulted mixture was extracted with DCM (10 mL × 3). The combined organic layers were washed with brine. Dried and concentrated to give crude middle compound without further purification. The above crude was dissolved in t-BuOH/2-methyl-2-butene (1 mL / 0.5 mL) and treated with a solution of $NaClO_2$ (80%, 217 mg, 1.92 mmol) and NaH_2PO_4 (288 mg, 2.40 mmol) in water (5 mL). After being stirred for 2 h, the mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine. Dried, filtered and concentrated to give the crude acid. A solution of **14** (94 mg, 0.24 mmol) and TEA (0.1 mL, 0.72 mmol) in anhydrous THF (1 mL) was treated with $Cl_3C_6H_2COCl$ (45 μL, 0.29 mmol) for 30 min. Then a mixture of the crude acid and DMAP (59 mg, 0.48 mmol) in toluene (2 mL) was added dropwise. After the mixture was stirred for 18 h, the reaction was quenched with water and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine. Dried, filtered and concentrated, the residue was dissolved in anhydrous THF (2 mL). Then TBAF (0.36 mL, 0.36 mmol, 1 M in THF) was added and stirred for 24h at room temperature. The resulted mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine. Dried, filtered and concentrated, the residue was purified by flash chromatography on silica gel (DCM/MeOH = 10/1) to give **19** (99 mg, 59%) as a colorless oil. $[\alpha]_D^{23}$ = -23.5 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3458, 2964, 2926, 1636, 1450, 1405, 1167, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ7.40-7.29 (m, 5H), 7.28-7.22 (m, 2H), 7.21-7.14 (m, 3H), 5.29-5.23 (m, 1H), 5.22-5.12 (m, 2H), 4.87 (dd, *J* = 4.4 Hz, 1H), 4.29-3.95 (m, 2H), 3.33-3.13 (m, 1H), 2.88-2.80 (m, 1H), 2.76-2.68 (m, 1H), 2.65-2.51 (m, 3H), 2.37 (dd, *J* = 16.4, 10.0 Hz, 1H), 2.28-2.20 (m, 1H), 1.76-1.67 (m, 1H), 1.60-1.54 (m, 1H), 1.35-1.13 (m, 24H), 1.00-0.97 (m, 3H), 0.96-0.93 (m, 3H), 0.90-0.86 (m, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, rotamers) δ173.8, 173.7, 172.1, 172.1, 169.7, 169.5, 156.3, 155.8, 139.1, 135.4, 135.3, 129.2, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 126.3, 126.2, 79.7, 74.5, 74.5, 70.2, 69.1, 67.2, 67.1, 65.7, 58.6, 42.7, 42.3, 39.6, 39.5, 33.4, 31.9, 31.6, 31.2, 30.2, 29.8, 29.4, 29.3, 28.4, 28.2, 25.8, 25.7, 22.7, 18.9, 18.6, 17.3, 14.2, 12.0, 11.6 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{40}H_{60}NO_9$: 698.4263, found 698.4251.

Hapalosin 5

A solution of compound **19** (51 mg, 0.073 mmol) in DCM (1 mL) was treated with TFA (0.5 mL) at 0°C. The mixture was stirred for 2h and then concentrated. The residue and 10% Pd/C (10 mg) were stirred under H_2 atmosphere in EtOH (5 mL) for 6h. Then the mixture was filtrated and concentrated. The residue was dissolved in DMF (100 mL) at 0°C. Then DPPA (47 μL, 0.22 mmol) and DIPEA (73 μL, 0.44 mmol) were added dropwise. After being stirred at 0°C for 5h and then at room temperature for 4d, the mixture was quenched with water and extracted with EtOAc (100 mL × 5). The combined organic layers were washed with brine. Dried and concentrated, the

residue was purified by flash chromatography on silica gel (PE/EA = 2/3) to give **5** (14.6 mg, 41%) as a colorless oil that solidified on standing. $[\alpha]_D^{25}$ = -42.1 (*c* 0.15, CH_2Cl_2) {lit.[22b] $[\alpha]_D^{18}$ = -41 (*c* 1.0, CH_2Cl_2); lit.[22d] $[\alpha]_D^{25}$ = -41.2 (*c* 1.0, CH_2Cl_2)}; ^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 7.37– 7.29 (m, 2H), 7.25– 7.22 (m, 1H), 7.21– 7.17 (m, 2H), 5.13 (d, *J* = 11.4, 1H), 4.31 (d, *J* = 8.4, 1H), 3.90-3.81 (m, 1H), 3.73-3.65 (m, 1H), 3.41 (dd, *J* = 13.8, 2.4 Hz, 1H), 3.25-3.18 (m, 1H), 2.91 (dd, *J* = 18.0, 4.8 Hz, 1H), 2.86 (s, 2H), 2.82 (d, *J* = 11.4, 1H), 2.80 (s, 1H), 2.65-2.62 (m, 1H), 2.36-2.25 (m, 1H), 2.03-1.99 (m, 1H), 1.96-1.88 (m, 1H), 1.28 – 1.24 (m, 10H), 1.17 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 7.2 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 1H), 0.55 (d, *J* = 7.2 Hz, 2H), 0.23 (d, *J* = 6.6 Hz, 2H), 0.19 (d, *J* = 7.2 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, rotamers) δ 172.9, 172.1, 170.4, 170.1, 168.9, 168.7, 137.6, 131.1, 129.9, 129.4, 129.1, 129.0, 128.6, 127.2, 126.6, 83.0, 76.7, 76.0, 74.0, 70.5, 70.4, 61.5, 58.7, 41.2, 40.8, 40.7, 37.2, 36.6, 35.5, 31.9, 31.8, 31.6, 30.7, 30.3, 29.8, 29.5, 29.4, 29.2, 29.1, 29.0, 28.2, 26.2, 25.5, 22.8, 19.8, 18.4, 17.7, 16.9, 14.2, 12.2, 10.9 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{44}NO_6$: 490.3163 found: 490.3166.

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