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Graphical Abstract

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Asymmetric synthesis of epohelmins A, B and 3-epi *ent*-epohelmin A

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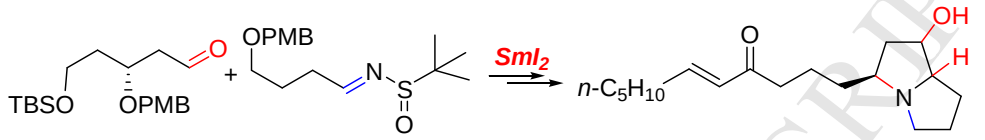

9 (*S or R*)-**10** Cyclization in cascade Epohelmins A **3,** B **4** and their isomer **24**

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Asymmetric synthesis of epohelmins A, B and 3-epi *ent*-epohelmin A

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ABSTRACT

An efficient method for asymmetric synthesis of epohelmins A (**3**), B (**4**) and their isomer **24** is detailed in this report. The key feature in this divergent synthesis includes the SmI_2-induced cross-coupling of *N*-*tert*-butanesulfinyl imine **10** with chiral aldehyde **9** derived from D-malic acid. A cascade cyclization to the pyrrolizidine skeleton is achieved in our synthetic route for epohelmins. In addition, an interesting intramolecular oxa-Michael addition was observed for epohelmin A (**3**).

1. Introduction

Statins, known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are a class of lipid-lowering medications, which play a central role in cardiovascular disease (CVD).[1] Due to their significant clinical effect, a number of statins such as atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin are approved for use to control blood cholesterol level in human.[2] Epohelmins A (**1**) and B (**2**), as novel lanosterol synthase inhibitors, were isolated from a fungal strain FKI-0929.[3] Notably, the chemical structures of **3** and **4** were revised from the originally proposed monocyclic core to a bicyclic skeleton, **3** and **4**, by Snider[4,5] after their asymmetric synthesis in 2005, and were further confirmed by Fürstner[6] in 2008 (**Figure 1**).

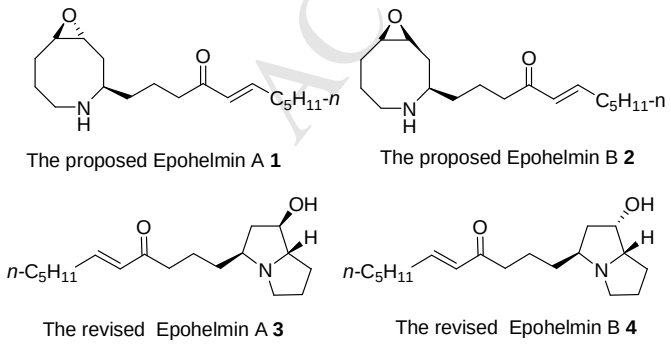

Figure 1. Structures of epohelmins A and B.

Following the pioneering work of Davis and Ellman, chiral auxiliaries (e.g. 2-methylpropane-2-sulfinamide and *N*-toluenesulfinamide) have been widely used in organic synthesis.[7-9] In recent years, one of our research interests is to utilize these popular chiral auxiliaries in asymmetric synthesis of natural products.[10-12] An interesting *tert*-butyl migration-addition from enantioenriched *N*-*tert*-butanesulfinyl iminoacetates[11] and an efficient formation of *trans*-5-hydroxy-6-alkyl/aryl-2-piperidinone skeleton[12] have been discovered in our group. In continuation of our application of chiral 2-methylpropane-2-sulfinamide in the divergent synthesis of alkaloids,[10a,12,13] herein, we present the use of such flexible chiral auxiliaries in the asymmetric synthesis of epohelmins A (**3**), B (**4**) and their isomer **24**.

2. Results and Discussions

Our synthetic strategy for asymmetric synthesis of epohelmins A (**3**) and B (**4**) is illustrated in **Figure 2**, with asymmetric control of stereochemistry and effective formation of the pyrrolizidine skeleton as our main focus in constructing target molecule. A SmI_2-induced cross-coupling for *anti*- vicinal *β*-amino alcohol, which was established in early years[9d] and successfully used in asymmetric synthesis of natural products,[10,14] was proposed for the synthesis of a key fragment **15** from aldehyde 9 and *N*-sulfinyl imine (*S*)-**10**. The enone **16**, derived from 15 using Horner-Wadsworth-Emmons (HWE) reaction, was subjected to cascade cyclization to form the pyrrolizidine

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skeleton.[15] The chiral aldehyde **9** could be prepared from D-malic acid. nickel dichloride monohydrate ($NiCl_2 \cdot H_2O$)[21] to give ester **14** in 86% yield.

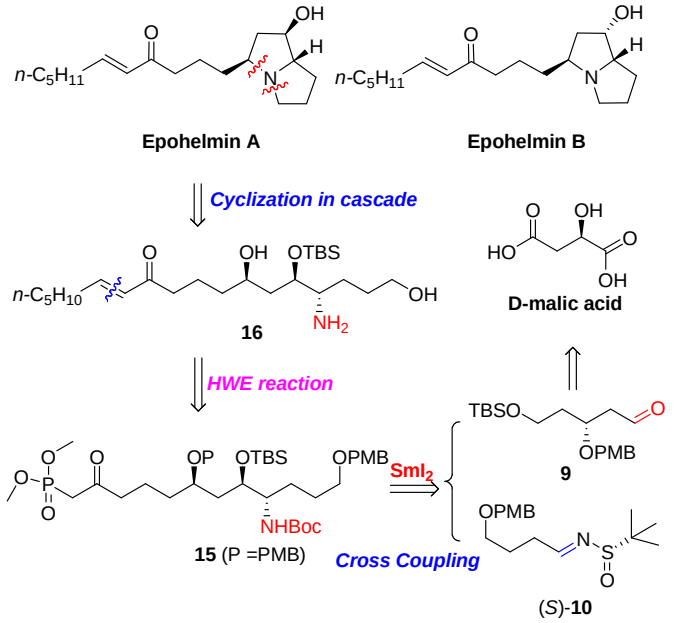
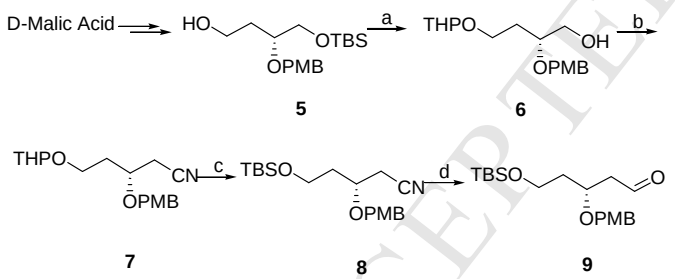


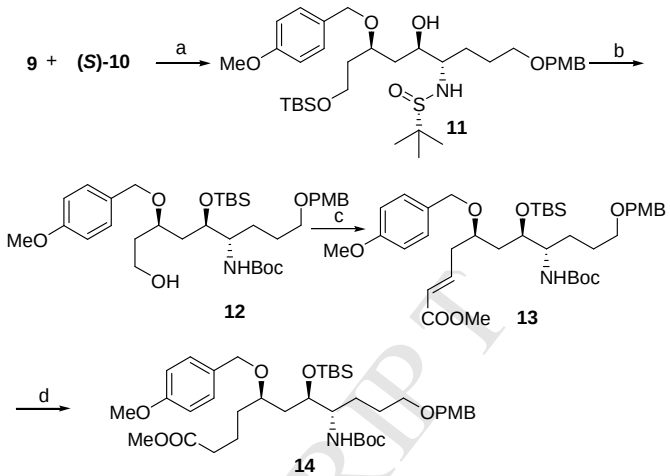
Figure 2. Retrosynthetic analysis of epohelmins A and B.

As shown in **Scheme 1**, aldehyde **9** could be easily prepared by known method,[16] but we could not obtain enough amount for synthesis of epohelmins. Thus chiral alcohol **5** was prepared from D-malic acid according to the known procedure.[17] Protection of **5** with 3,4-dihydro-2H-pyran (DHP) and subsequent removal of silyl group with TBAF gave alcohol **6** in 82% overall yield. The primary alcohol **6** was converted to cyanide **7**, through displacement of the corresponding mesylate with KCN, in 85% overall yield. After the *O*-THP protection was switched to *O*-TBS, the cyano group was reduced by DIBAL-H[18] to afford the desired chiral aldehyde **9** in 70% yield.



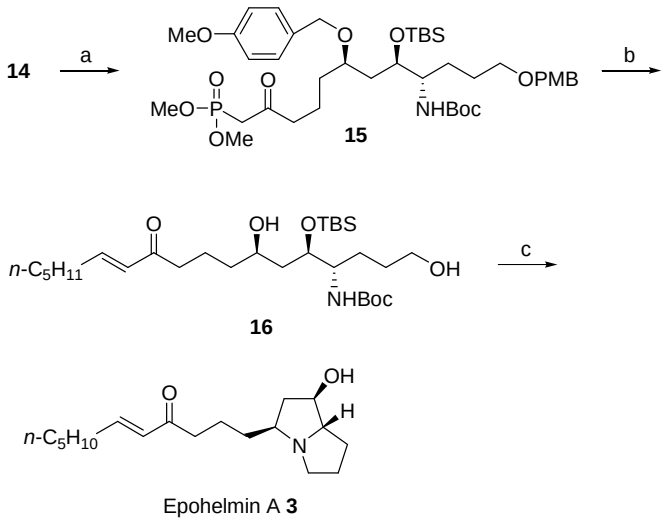
Scheme 1. The preparation of aldehyde **9**. *Reagents and conditions:* a. (1) DHP, PPTS, 100%; (2) TBAF, THF, 82%; b. (1) MsCl, TEA, DCM, 96%; (2) KCN, DMSO, 89%; c. (1) THF: 3M HCl, 90%; (2) TBSCl, Imidazole, DMF, 99%; d. DIBAL-H, THF, -78°C, 70%.

The SmI_2-induced cross-coupling of **9** with (*S*)-*N*-(4-(4-methoxybenzyloxy)butylidene)-2-methylpropane-2-sulfinamide **10**, which was readily prepared from chiral 2-methylpropane-2-sulfinamide, gave desired vicinal *β*-amino alcohol **11** with high diastereoselectivity (*dr* > 99:1) in 76% yield (**Scheme 2**). Upon two following sequential steps, regioselective desilylation from the primary hydroxyl group by *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and removal of the chiral auxiliary using (HCl/dioxane), the resulting amino alcohol was converted to **12** in 52% overall yield.[13a] Then oxidation with Dess-Martin periodinane[19] and subsequent Wittig reaction[20] generated desired olefin **13** in 94% overall yield, which was reduced with sodium borohydride ($NaBH_4$) in the presence of



Scheme 2. The preparation of ester **14**. *Reagents and conditions:* a. SmI_2, *t*-BuOH, THF, -78°C, 76%; b. (1) TBSOTf, 2,6-Lutidine, 0°C; (2) HCl/dioxane, EtOH, 0°C; (3) Boc_2O, TEA, DCM, 3 steps 52%; c. (1) DMP, DCM; (2) $Ph_3PCHCOOCH_3$, DCM, 2 steps 94%; d. $NiCl_2 \cdot H_2O$, $NaBH_4$, CH_3OH, 86%.

With ester **14** in hand, we turned our attention to synthesize epohelmin A (**3**). Reaction of **14** and dimethyl methylphosphonate using *n*-butyllithium as a base produced phosphonate **15** in 86% yield (**Scheme 3**).[4] Upon the removal of both PMB groups by hydrogenolysis (Pd/C, $Pd(OH)_2$, H_2), the crude product was subjected to Horner-Wadsworth-Emmons reaction with hexanal to give *α*,*β*-unsaturated ketone **16** in 54% yield.[22] Finally, mesylation of both hydroxyl groups in **16** with methanesulfonyl chloride (MsCl) and subsequent selectively deprotection of NH-Boc with TESOTf/2,6-lutidine resulted in simultaneous cyclization to pyrrolizidine skeleton, which was subjected to desilylation with MeOH/HCl at room temperature for overnight. The crude epohelmin A (**3**) was purified by flash chromatography on silica gel (DCM/MeOH/AcOH = 100:10:1) to give pure **3**·HOAc {$[\alpha]_D^{23}$ +2.9 (*c* 0.31, CH_3OH)} in 46% yield over three steps. The spectral data of the synthetic **3**·HOAc were identical to the reported data.[4]



Scheme 3. The preparation of Epohelmin A **3**. *Reagents and conditions:* a. *n*-BuLi, dimethyl methylphosphonate, THF, -78°C, 86%; b. (1) Pd/C, $Pd(OH)_2$, H_2, MeOH; (2) LiCl, DBU, hexanal, 2 steps 54%; c. (1) MsCl, TEA, DCM; (2) TESOTf, 2,6-lutidine, DCM, -78°C; (3) HCl/CH_3OH, 3 steps 46%.

However, our synthetic epohelmin A (**3**) was relatively unstable after it was converted to a free base form. As shown in **Figure 3**, both olefin protons gradually decreased and a new signal peak (δ 3.70-3.64) increased in ^{1}H NMR ($CDCl_3$). Significant changes were also observed in ^{13}C NMR ($CDCl_3$). A new signal peak (δ = 209.5) appeared and gradually increased. Although great efforts were devoted to isolate this new structure by preparative HPLC, we failed to obtain the pure compound. In consideration of all these changes, the diminished peaks for the carbon-carbon double bond and carbonyl group, as well as the emergence and enhancement for new carbonyl group, an intramolecular oxa-Michael addition[23,24] was highly possible, leading to the formation of tricyclic compound **17**. We propose that there is an equilibrium between epohelmin A (**3**) and new skeleton **17**, the ipsilateral two corresponding substituents[24a] and the basic nitrogen prompted such an addition process in epohelmin A (**3**). While the structure of epohelmin A (**3**) is very stable in acetic acid condition.[3,4]

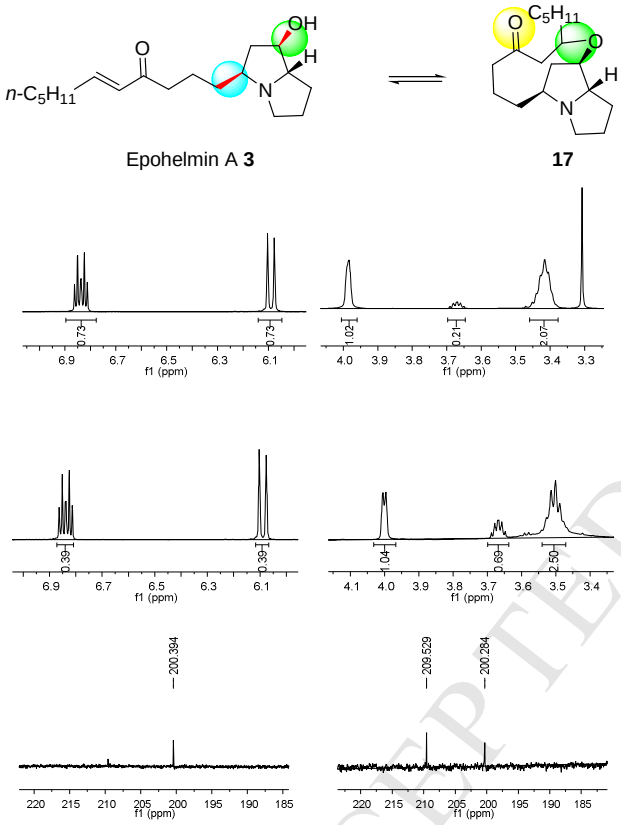
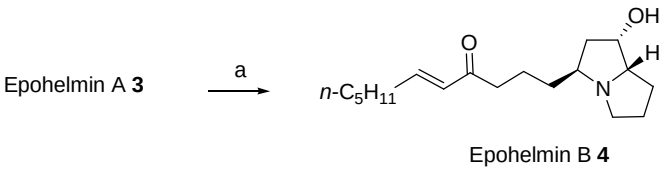


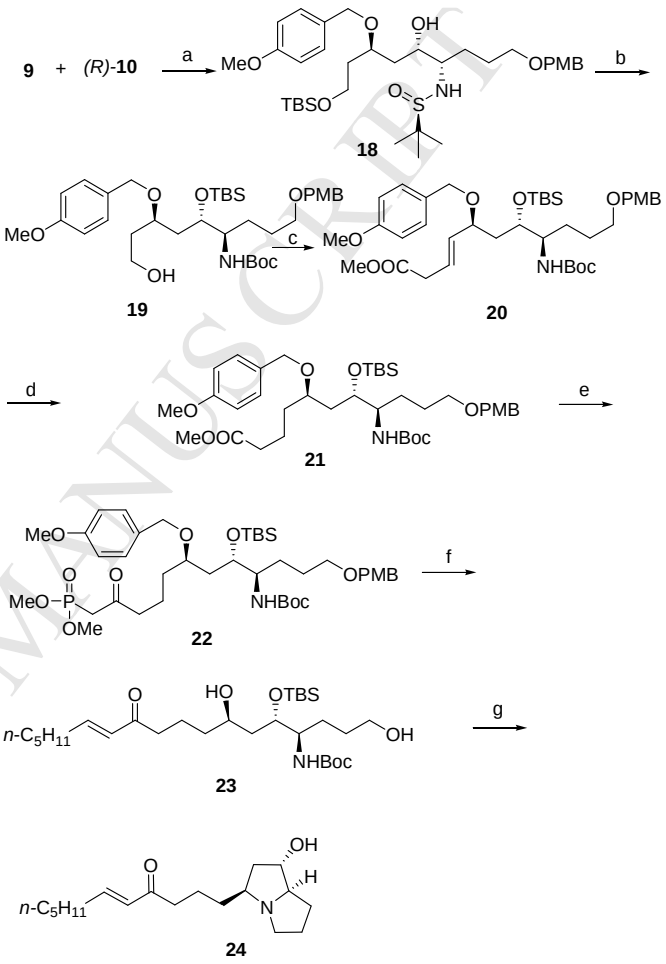
Figure 3. The changes observed in ^{1}H NMR and ^{13}C NMR of **3** and **17**.

To confirm our speculation of this intramolecular oxa-Michael addition reaction, we synthesized epohelmin B (**4**), in which the two corresponding substituents existed at opposite sides. The chemistry was straightforward by following the literature procedure,[4] and epohelmin B (**4**) {$[\alpha]_D^{23}$ +4.3 (*c* 1.00, CH_3OH), $[\alpha]_D^{23}$ +4.9 (*c* 0.40, CH_2Cl_2), lit.[6] $[\alpha]_D^{20}$ +5.3 (*c* 0.67, CH_2Cl_2)} was obtained in 63% yield (**Scheme 4**). The spectral data of the synthetic **4**·HOAc were identical to the reported data.[4,6] Our NMR studies of epohelmin B (**4**) as a free base agreed with our hypothesis, no degradation was observed in $CDCl_3$.



Scheme 4. The preparation of Epohelmin B **4**. *Reagents and conditions:* a. (1) $(COCl)_2$, DMSO, DCM, -78°C; (2) L-Selectride, THF, -78°C~rt; (3) DMP, DCM, 3 steps 63%.

Meantime, another *trans*-epimer **24** of epohelmin A (**3**) was also synthesized. The detailed synthetic sequence was shown in **Scheme 5**, Starting from another enantiomeric imine, (*R*)-*N*-(4-(4-methoxybenzyloxy) butylidene)-2-methylpropane-2-sulfinamide **10**, the isomer **24** {$[\alpha]_D^{23}$ -7.5 (*c* 0.50, $CHCl_3$)} was successfully prepared in 7.7% overall yield in 13 linear steps. The NMR studies also showed that the isomer **24** is more stable than epohelmin A (**3**).



Scheme 5. The synthesis of isomer **24**. *Reagents and conditions:* a. SmI_2, *t*-BuOH, THF, -78°C, 77%; b. (1) TBSOTf, 2,6-lutidine, 0°C; (2) HCl/dioxane, EtOH, 0°C; (3) Boc_2O, TEA, DCM, 3 steps 58%; c. (1) DMP, DCM; (2) $Ph_3PCHCOOCH_3$, DCM, 2 steps 91%; d. $NiCl_2·H_2O$, $NaBH_4$, MeOH, 90%; e. (1) *n*-BuLi, THF, dimethyl methylphosphonate, -78°C, 86%; f. (1) Pd/C, $Pd(OH)_2$, MeOH; (2) LiCl, DBU, hexanal, 2 steps 53%; g. (1) MsCl, TEA; (2) TESOTf, 2,6-lutidine, DCM, -78°C; (3) HCl/MeOH, 3 steps 50%.

3. Conclusions

In summary, we completed the asymmetric synthesis of natural epohelmins A (20 steps from **5**, 3.0% overall yield), B (23 steps from **5**, 1.9% overall yield) and its isomer **24** (20 steps from **5**, 4.1% overall yield) using SmI_2-induced cross-coupling of *N*-*tert*-butanesulfinyl imine **10** with chiral aldehyde **9** to generate the required stereocenters. The cascade cyclization to form the pyrrolizidine skeleton is another feature of our synthetic route for epohelmins. In addition, we observed epohelmin A (**3**) could undergo an intramolecular oxa-Michael process to give a new skeleton **17**. Further efforts on the extension of this strategy are on-going in our laboratory to synthesize other analogs of epohelmin A (**3**). The chemistry and related biological data will be published in due course.

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 ether/ 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}HNMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR if not noted otherwise.

(*2R*)-2-(4-Methoxybenzyloxy)-4-(tetrahydro-2H-pyran-2-yloxy)butan-1-ol 6

Compound **5** (6.50 g, 19.09 mmol), PPTS (0.48 g, 1.91 mmol) and DHP (3.5 mL, 38.18 mmol) were stirred in DCM (80 mL) for overnight. Then the mixture was quenched with a saturated NH_4Cl aqueous solution and extracted with DCM (50 mL × 3). The combined organic layers were washed with brine. Dried, filtered and concentrated, the residue was purified by flash chromatography on silica gel (PE/EA = 10/1) to give alcohol as a colorless oil. The above oil and TBAF (80 mL, 1 M in THF) was stirred in THF (80 mL) for overnight and diluted with water. The resulting mixture was extracted with EtOAc (80 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 = 1/1) to give **6** (4.86 g, 2 steps 82%). IR (film): ν_{max} 3441, 2937, 2882, 2858, 1611, 1507, 1249, 1118, 810 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.23 (m, 2H), 6.90-6.85 (m, 2H), 4.61-4.46 (m, 3H), 3.89-3.81 (m, 2H), 3.80 (s, 3H), 3.76-3.64 (m, 2H), 3.59-3.41 (m, 3H), 2.37-2.25 (m, 1H), 1.97-1.63 (m, 4H), 1.60-1.47 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 129.9, 128.8, 128.7, 113.3, 98.5 (98.4), 76.5 (76.1), 70.6 (70.5), 63.7 (63.6), 63.3, 61.9 (61.8), 54.6, 30.8 (30.7), 30.1 (30.0), 24.8, 19.0 (18.9) ppm; HRMS (ESI) calcd for $[C_{17}H_{26}O_5+H^+]$: 311.1853, found: 311.1854.

(*3S*)-3-(4-Methoxybenzyloxy)-5-(tetrahydro-2H-pyran-2-yloxy)pentanenitrile 7

Compound **6** (4.75 g, 15.30 mmol) and TEA (16.9 mL, 122.40 mmol) were dissolved in dry DCM (60 mL) and cooled to 0^{o}C, then MsCl (3.5 mL, 45.90 mmol) was added dropwise. After being stirred for 1 h at the same temperature, the reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (60 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 = 2/1) to give intermediate as a yellow oil. The above yellow oil and KCN (0.96 g, 14.70 mmol) were stirred in DMSO (60 mL) at 60^{o}C for overnight. Then the mixture was diluted with water and extracted with EtOAc (60 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 = 2/1) to give **7** (4.15 g, 2 steps 85%). IR (film): ν_{max} 2941, 2870, 1613, 1514, 1353, 1249, 1075, 1034, 811 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.24 (m, 2H), 6.91-6.86 (m, 2H), 4.70-4.40 (m, 3H), 3.90-3.81 (m, 3H), 3.80-3.78 (m, 3H), 3.54-3.42 (m, 2H), 2.69-2.34 (m, 2H), 1.99-1.63 (m, 4H), 1.62-1.44 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5 (159.4), 129.6, 129.5, 117.8, 113.9, 99.2 (98.9), 72.1 (71.6), 71.5 (71.4), 63.2 (62.5), 55.3, 34.4 (34.3), 30.7 (30.6), 25.4 (25.3), 23.4 (23.2), 19.7 ppm; HRMS (ESI) calcd for $[C_{18}H_{25}NO_4+H^+]$: 320.1856, found: 320.1856.

(*S*)-3-(4-Methoxybenzyloxy)-5-(*tert*-butyldimethylsilyloxy) pentanenitrile 8

Compound **7** (4.00 g, 12.52 mmol) was stirred in THF/3 M HCl (50 mL, V/V=3/1) at room temperature for overnight. Then the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ 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 intermediate as a colorless oil. To a cooled (0^{o}C) solution of above intermediate (2.60 g, 11.05 mmol), imidazole (1.50 g, 22.10 mmol) and DMAP (0.14 g, 1.11 mmol) in DMF (40 mL) was treated with TBSCl (2.49 g, 16.58 mmol) for 24 h. Then the mixture was quenched with a saturated aqueous solution of NH_4Cl and separated. The aqueous phase was extracted with EtOAc (60 mL × 4) and 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 **8** (3.89 g, 2 steps 89%) as a colorless oil. $[\alpha]_D^{23}$ = +29.0 (*c* 2.50, $CHCl_3$); IR (film): ν_{max} 2954, 2929, 2857, 1616, 1514, 1468, 1304, 1250, 1178, 1095, 1036, 836, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.25 (m, 2H), 6.91-6.86 (m, 2H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.51 (d, *J* = 11.2 Hz, 1H), 3.92-3.84 (m, 1H), 3.80 (s, 3H), 3.74-3.69 (m, 2H), 2.64 (dd, *J* = 16.8, 5.2 Hz, 1H), 2.54 (dd, *J* = 16.8, 5.2 Hz, 1H), 1.91-1.83 (m, 1H), 1.82-1.73 (m, 1H), 0.89 (s, 9H), 0.05 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 129.1, 128.8, 117.1, 113.3, 71.1, 58.2, 54.7, 36.5, 25.3, 22.8, 17.6, -6.0, -6.1 ppm; HRMS (ESI) calcd for $[C_{19}H_{31}NO_3Si+H^+]$: 350.2146, found: 350.2148.

(*R*)-3-(4-Methoxybenzyloxy)-5-(*tert*-butyldimethylsilyloxy) pentanal 9

To a solution of **8** (3.80 g, 10.87 mmol) in THF (50 mL) was treated with a solution of DIBAL-H (21.7 mL, 21.74 mmol, 1 M in hexane) at -78^{o}C for 1 h, and the resulting mixture was warmed to 0^{o}C for another 1 h. Then the mixture was cooled to -78^{o}C and EtOAc (25 mL) was added dropwise and stirred for 1 h -78^{o}C to at room temperature. The mixture was quenched with a saturated seignette salt solution 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 = 5/1) to give **9** (2.68 g, 70%) as a light yellow oil.

***General procedure for synthesis of* (*R/S,E*)-N-(4-(4-Methoxybenzyloxy)butylidene)-2-methylpropane-2-sulfinamide 10**

Butane-1,4-diol (20.00 g, 221.92 mmol) was slowly drooped to a solution of sodium hydride (9.76 g, 244.12 mmol) in dry DMF (180 mL) at 0^{o}C. After being stirred for 10 min, PMBBr (32.4 mL, 221.92 mmol) was added dropwise and the resulting mixture was stirred at room temperature for 24 h. Then the 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 (PE/EA = 1/1) to give alcohol (32.70 g, 70%) as a light yellow oil. $(COCl)_2$ (18.1 mL, 190.24 mmol) was stirred in DCM (350 mL) at -78°C, and then a solution of DMSO (27.0 mL, 380.28 mmol) in DCM (50 mL) was slowly added dropwise. After the mixture was stirred for 1 h, a solution of the above alcohol (20.00 g, 95.12 mmol) in DCM (120 mL) was added dropwise, and the resulting mixture was stirred for 3 h. Once TEA (78.9 mL, 570.70 mmol) was added dropwise, the mixture was allowed to warm to room temperature, and the reaction was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was

separated, and the aqueous layer was extracted with DCM (200 mL × 2). The combined organic layers were dried, filtered, and concentrated to give crude aldehyde without further purification. Then take half of each, dissolved in DCM (200 mL). *R* or *S* 2-Methyl-2-propanesulfinamide (5.76 g, 47.56 mmol), cupric sulphate anhydrous (15.20 g, 95.12 mmol) and PPTS (0.60 g, 2.38 mmol) were added to the solution in one portion and the mixture was stirred for 24 h. The resulting mixture was filtrated and the filtrate was concentrated to give the crude product, which was purified by flash chromatography on silica gel (PE/EA = 3/1) to give (*S*)-**10** (9.70 g, 2 steps 66%) or (*R*)-**10** (8.90 g, 2 steps 60%).

S-**10**: $[\alpha]_D^{23}$ = +134.8 (*c* 2.50, $CHCl_3$); IR (film): ν_{max} 2959, 2921, 2867, 1622, 1513, 1458, 1364, 1247, 1173, 1082, 1035, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09-8.05 (m, 1H), 7.26-7.20 (m, 2H), 6.88-6.83 (m, 2H), 4.43-4.40 (m, 2H), 3.77 (s, 3H), 3.50-3.45 (m, 2H), 2.63-2.56 (m, 2H), 1.96-1.87 (m, 2H), 1.15 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 158.6, 129.8, 128.6, 113.2, 72.0, 68.3, 55.9, 54.6, 32.4, 25.0, 21.7 ppm; HRMS (ESI) calcd for $[C_{16}H_{25}NO_3S+H^+]$: 312.1628, found: 312.1627.

R-**10**: $[\alpha]_D^{23}$ = -119.2 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2956, 2927, 2859, 1622, 1513, 1463, 1363, 1247, 1184, 1082, 1035, 816 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10-8.06 (m, 1H), 7.27-7.21 (m, 2H), 6.89-6.84 (m, 2H), 4.43-4.40 (m, 2H), 3.38 (s, 3H), 3.52-3.46 (m, 2H), 2.64-2.57 (m, 2H), 1.97-1.87 (m, 2H), 1.16 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 158.6, 129.8, 128.6, 113.2, 72.0, 68.3, 55.9, 54.6, 32.4, 25.0, 21.7 ppm; HRMS (ESI) calcd for $[C_{16}H_{25}NO_3S+H^+]$: 312.1628, found: 312.1628.

***General procedure for synthesis of* 11, 18**.

To a mixture of **9** (1.92 g, 5.44 mmol), imine *S*-**10** or *R*-**10** (1.70 g, 5.44 mmol) and *t*-BuOH (2.1 mL, 21.74 mmol) in THF (110 mL) was treated with a solution of freshly prepared SmI_2 (109 mL, 21.74 mmol, 0.2 M in THF) at -78°C under an argon atmosphere. After being vigorously stirred for overnight, the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$. The mixture was separated, and aqueous layer was extracted with EtOAc (100 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 = 1/2) to give title compound.

(*S*)-N-((*4S,5R,7R*)-1,7-bis(4-methoxybenzyloxy)-9-(*tert*-butyldimethylsilyloxy)-5-hydroxynonan-4-yl)-2-methylpropane-2-sulfinamide 11

(2.72 g, 76%) as a yellow oil. $[\alpha]_D^{23}$ = +17.2 (*c* 2.50, $CHCl_3$); IR (film): ν_{max} 3403, 2953, 2929, 2856, 1611, 1514, 1463, 1359, 1299, 1248, 1167, 1091, 1037, 836, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.24 (m, 4H), 6.90-6.85 (m, 4H), 4.57-4.40 (m, 4H), 3.94-3.78 (m, 8H), 3.77-3.66 (m, 2H), 3.53-3.37 (m, 4H), 3.25-3.15 (m, 1H), 1.94-1.53 (m, 8H), 1.23 (s, 9H), 0.91 (s, 9H), 0.08-0.05 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 159.1, 130.6, 129.6, 129.5, 129.3, 113.8, 113.7, 73.9, 72.6, 71.5, 71.3, 69.7, 61.6, 59.6, 55.9, 55.3, 37.3, 36.7, 26.1, 26.0, 22.8, 18.3, -5.3 ppm; HRMS (ESI) calcd for $[C_{35}H_{59}NO_7SSi+H^+]$: 666.3854, found: 666.3856.

(*R*)-N-((*4R,5S,7R*)-1,7-bis(4-Methoxybenzyloxy)-9-(*tert*-butyldimethylsilyloxy)-5-hydroxynonan-4-yl)-2-methylpropane-2-sulfinamide 18

(2.76 g, 77%) as yellow oil. $[\alpha]_D^{23}$ = -27.5 (*c* 2.50, $CHCl_3$); IR (film): ν_{max} 3048, 2953, 2929, 2856, 1611, 1514, 1458, 1353, 1293, 1248, 1173, 1090, 1036, 835, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.24 (m, 4H), 6.90-6.85 (m, 4H), 4.56 (dd, *J* = 10.8 Hz, 1H), 4.45-4.38 (m, 3H), 3.83-3.79 (m, 7H), 3.76-3.66 (m, 4H), 3.52-3.44 (m, 3H), 3.18-3.10 (m, 1H), 1.96-1.82 (m, 2H), 1.81-1.74 (m, 2H), 1.73-1.61 (m, 4H), 1.21 (s, 9H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 159.1, 130.6, 130.1, 129.6, 129.3, 113.9, 113.7, 76.3, 73.8, 72.6, 70.6, 69.7, 61.3, 59.5, 55.9, 55.3, 37.1, 37.0, 26.4, 26.1, 26.0, 22.8, 18.3, -5.3 ppm; HRMS (ESI) calcd for $[C_{35}H_{59}NO_7SSi+H^+]$: 666.3854, found: 666.3855.

***General procedure for synthesis of* 12, 19.**

To a cooled (0°C) solution of **11** or **18** (2.50 g, 3.75 mmol) in DCM (50 mL) was added dropwise 2,6-lutidine (4.3 mL, 18.75 mmol) followed by TBSOTf (4.3 mL, 7.50 mmol) and stirred for 1 h. Then the mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (60 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 intermediate as a light yellow oil. To a solution of the above intermediate in EtOH (20 mL) and added a solution of HCl/1,4-dioxane dropwise at 0°C. After stirring for 10 min, the mixture was removal of hydrochloric acid at 0°C by vacuum distillation. Then the mixture was dissolved in DCM (50 mL). Next, TEA (3.1 mL, 22.50 mmol) and Boc_2O (1.3 mL, 5.63 mmol) were added at room temperature and stirred for overnight. The mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (60 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 = 2/1) to give title compound.

***tert*-Butyl (*4S,5R,7R*)-1,7-bis(4-methoxybenzyloxy)-5-(*tert*-butyldimethylsilyloxy)-9-hydroxynonan-4-ylcarbamate 12**

(1.29 g, 52%) as a colorless oil. $[\alpha]_D^{23}$ = +17.5 (*c* 2.50, $CHCl_3$); IR (film): ν_{max} 3447, 2952, 2931, 2856, 1710, 1605, 1513, 1458, 1364, 1248, 1172, 1096, 1037, 838, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.24 (m, 4H), 6.91-6.84 (m, 4H), 4.62-4.40 (m, 5H), 3.93-3.85 (m, 1H), 3.85-3.67 (m, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.56-3.42 (m, 3H), 2.02-1.88 (m, 2H), 1.80-1.68 (m, 2H), 1.67-1.53 (m, 3H), 1.45 (s, 9H), 1.43-1.37 (m, 1H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ159.2, 159.1, 155.6, 130.6, 130.2, 129.5, 129.2, 113.9, 113.8, 79.1, 74.8, 72.5, 71.9, 70.4, 69.7, 60.2, 55.2, 53.6, 38.6, 36.1, 28.5, 26.3, 25.9, 24.3, 18.1, -4.4, -4.6 ppm; HRMS (ESI) calcd for $[C_{36}H_{59}NO_8Si+H^+]$: 662.4083, found: 662.4092.

***tert*-Butyl (*4R,5S,7R*)-1,7-bis(4-methoxybenzyloxy)-5-(*tert*-butyldimethylsilyloxy)-9-hydroxynonan-4-ylcarbamate 19**

(1.45 g, 58%) as a colorless oil. $[\alpha]_D^{23}$ = -5.7 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3452, 2953, 2931, 2856, 1712, 1611, 1514, 1359, 1249, 1173, 1099, 1038, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.25 (m, 4H), 6.91-6.85 (m, 4H), 4.62-4.51 (m, 2H), 4.49-4.42 (m, 3H), 3.94-3.87 (m, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.80-3.69 (m, 3H), 3.66-3.58 (m, 1H), 3.52-3.45 (m, 2H), 2.52-2.45 (m, 1H), 1.93-1.82 (m, 2H), 1.77-1.70 (m, 2H), 1.68-1.58 (m, 3H), 1.46 (s, 9H), 0.91 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ159.2, 159.1, 155.6, 130.6, 130.4, 129.6, 129.3, 113.8, 113.7, 79.0, 75.5, 72.5, 71.6, 71.1, 69.7, 60.3, 55.3, 54.3, 38.7, 36.1, 28.5, 27.4, 26.4, 25.9, 24.9, 18.1, -4.3, -4.5 ppm; HRMS (ESI) calcd for $[C_{36}H_{59}NO_8Si+H^+]$: 662.4083, found: 662.4086.

***General procedure for synthesis of* 13, 20.**

To a solution of **12** or **19** (1.25 g, 1.89 mmol) in dry DCM (20 mL) was treated with DMP (1.60 g, 3.78 mmol) at room temperature for 0.5 h. The reaction was carefully quenched with a saturated aqueous solution of $NaHCO_3$ and solid $Na_2S_2O_3$, then the resulting mixture was separated and the aqueous layer was

extracted with DCM (30 mL × 3). The combined organic layers were washed with brine, dried and concentrated to give crude product without further purification. The crude product and $Ph_3PCHCOOCH_3$ (758 mg, 2.27 mmol) were stirred in DCM (20 ml) at room temperature for overnight and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 4/1) to give title compound.

(*5R,7R,8S,E*)-Methyl 5,11-bis(4-methoxybenzyloxy)-8-(*tert*-butoxycarbonyl)-7-(*tert*-butyldimethylsilyloxy)undec-2-enoate 13

(1.27 g, 94%) as a colorless oil. $[\alpha]_D^{23}$ = -0.5 (*c* 2.50, $CHCl_3$); IR (film): ν_{max} 2952, 2931, 2856, 1716, 1611, 1514, 1364, 1248, 1172, 1098, 1037, 844, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.23 (m, 4H), 7.02 (ddd, *J* = 15.6, 7.6, 6.8 Hz, 1H), 6.91-6.85 (m, 4H), 5.93 (d, *J* = 15.6 Hz, 1H), 4.58-4.47 (m, 2H), 4.45-4.38 (m, 3H), 3.94-3.88 (m, 1H), 3.82-3.79 (m, 6H), 3.75 (s, 3H), 3.69-3.62 (m, 1H), 3.59-3.49 (m, 1H), 3.47-3.41 (m, 2H), 2.63-2.40 (m, 2H), 1.83-1.64 (m, 2H), 1.63-1.50 (m, 3H), 1.46 (s, 9H), 1.43-1.34 (m, 1H), 0.89 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 159.2, 159.1, 155.6, 145.0, 130.7, 130.4, 129.3, 129.2, 123.5, 113.8, 113.7, 78.9, 74.3, 72.5, 71.8, 70.3, 69.8, 55.2, 54.2, 51.4, 38.8, 36.5, 28.5, 26.4, 25.9, 24.9, 18.1, -4.4, -4.5 ppm; HRMS (ESI) calcd for $[C_{39}H_{61}NO_9Si+H^+]$: 716.4188, found: 716.4189.

(*5R,7S,8R,E*)-Methyl 5,11-bis(4-methoxybenzyloxy)-8-(*tert*-butoxycarbonyl)-7-(*tert*-butyldimethylsilyloxy)undec-2-enoate 20

(1.23 g, 91%) as a colorless oil. $[\alpha]_D^{23}$ = -13.0 (*c* 2.50, $CHCl_3$); IR (film): ν_{max} 2952, 2930, 2856, 1713, 1514, 1365, 1248, 1171, 1099, 1037, 836, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.25 (m, 4H), 6.98 (ddd, *J* = 15.6, 8.0, 7.2 Hz, 1H), 6.91-6.85 (m, 4H), 5.91 (d, *J* = 15.6 Hz, 1H), 4.63 (d, *J* = 9.2 Hz, 1H), 4.52-4.42 (m, 4H), 3.97-3.89 (m, 1H), 3.83-3.80 (m, 6H), 3.75 (s, 3H), 3.69-3.58 (m, 2H), 3.50-3.44 (m, 2H), 2.54-2.36 (m, 2H), 1.82-1.68 (m, 2H), 1.65-1.54 (m, 3H), 1.46 (s, 9H), 1.42-1.34 (m, 1H), 0.90 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 159.2, 159.1, 155.6, 145.3, 130.7, 130.4, 129.6, 129.2, 123.3, 113.8, 78.9, 74.7, 72.5, 71.5, 71.3, 69.8, 55.3, 54.0, 51.5, 39.1, 37.1, 28.5, 26.4, 25.9, 24.8, 18.1, -4.4, -4.6 ppm; HRMS (ESI) calcd for $[C_{39}H_{61}NO_9Si+H^+]$: 716.4188, found: 716.4188.

***General procedure for synthesis of* 14, 21.**

To a solution of **13** or **20** (1.20 g, 1.68 mmol) in CH_3OH (12 mL) was added $NiCl_2$•$6H_2O$ (199 mg, 0.84 mmol) at 0°C. Then $NaBH_4$ (127 mg, 3.36 mmol) was added in batches and stirred for 40 min. The reaction was carefully filtered and concentrated. The residue added water and extracted with EtOAc (30 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 = 4/1) to give title compound.

(*5R,7R,8S*)-Methyl 5,11-bis(4-methoxybenzyloxy)-8-(*tert*-butoxycarbonyl)-7-(*tert*-butyldimethylsilyloxy)undecanoate 14

(1.03 g, 86%) as a light yellow oil. $[\alpha]_D^{23}$ = +1.4 (*c* 2.50, $CHCl_3$); IR (film): ν_{max} 2952, 2931, 2856, 1738, 1712, 1611, 1514, 1365, 1248, 1172, 1097, 1037, 835, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.24 (m, 4H), 6.90-6.85 (m, 4H), 4.58-4.35 (m, 5H), 3.96-3.87 (m, 1H), 3.81-3.79 (m, 6H), 3.69 (s, 3H), 3.61-3.49 (m, 2H), 3.47-3.40 (m, 2H), 2.42-2.31 (m, 2H), 1.82-1.67 (m, 4H)1.65-1.49 (m, 5H), 1.45 (s, 9H), 1.42-1.32 (m, 1H), 0.90 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 159.1, 155.6, 130.8, 130.7, 129.2, 113.7, 78.8, 75.0, 72.5, 72.1, 69.9, 69.8, 55.2, 54.4, 51.5, 38.6, 34.1, 32.9, 28.5, 26.4, 25.9, 25.2, 20.1, 18.1, -4.4, -4.5 ppm; HRMS (ESI) calcd for $[C_{39}H_{63}NO_9Si+H^+]$: 718.4345, found: 718.4345.

(*5R,7S,8R*)-Methyl 5,11-bis(4-methoxybenzyloxy)-8-(*tert*-butoxycarbonyl)-7-(*tert*-butyldimethylsilyloxy)undecanoate 21

(1.08 g, 90%) as a light yellow oil. $[\alpha]_D^{23}$ = -11.6 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2952, 2930, 2855, 1737, 1712, 1605, 1513, 1458, 1365, 1248, 1171, 1100, 1037, 835, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.25 (m, 4H), 6.91-6.85 (m, 4H), 4.63 (d, *J* = 9.2 Hz, 1H), 4.52-4.41 (m, 4H), 3.96-3.90 (m, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.69 (s, 3H), 3.67-3.59 (m, 1H), 3.53-3.44 (m, 3H), 2.39-2.25 (m, 2H), 1.82-1.66 (m, 4H), 1.65-1.53 (m, 5H), 1.46 (s, 9H), 1,43-1.35 (m, 1H), 0.90 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ173.9, 159.1, 155.6, 130.9, 130.7, 129.5, 129.2, 113.8, 113.7, 78.9, 75.6, 72.5, 71.8, 71.0, 69.8, 55.3, 54.0, 51.5, 39.0, 34.1, 33.6, 28.5, 26.4, 25.9, 24.9, 20.6, 18.1, -4.4, -4.6 ppm; HRMS (ESI) calcd for $[C_{39}H_{63}NO_9Si+H^+]$: 718.4345, found: 718.4344.

***General procedure for synthesis of* 15, 22.**

To a solution of dimethyl methylphosphonate (0.94 mL, 8.77 mmol) in dry THF (20 mL) was treated with a solution of *n*-BuLi (3.6 mL, 8.77 mmol, 2.4 M in hexane) at -78°C for 1 h. Then a solution of compound **14** or **21**(900 mg, 1.25 mmol) in THF (5 mL) was added dropwise, and the reaction was warmed to -50°C and stirred for 2 h. The resulting 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 = 1/2) to give title compound.

***tert*-Butyl (*4S,5R,7R*)-1,7-bis(4-methoxybenzyloxy)-5-(*tert*-butyldimethylsilyloxy)-12-(dimethoxyphosphoryl)-11-oxododecan-4-ylcarbamate 15**

(875 mg, 86%) as a colorless oil. $[\alpha]_D^{23}$ = +1.9 (*c* 2.50, $CHCl_3$); IR (film): ν_{max} 2954, 2930, 2855, 1712, 1605, 1514, 1364, 1249, 1173, 1035, 835, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.23 (m, 4H), 6.89-6.84 (m, 4H), 4.59-4.33 (m, 5H), 3.93-3.86 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.60-3.47 (m, 2H), 3.46-3.39 (m, 2H), 3.12 (s, 1H), 3.06 (s, 1H), 2.69-2.60 (m, 2H), 1.80-1.63 (m, 4H), 1.61-1.48 (m, 5H), 1.45 (s, 9H), 1.41-1.33 (m, 1H), 0.89 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H) pm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 201.5, 159.1, 155.6, 130.8, 130.7, 129.3, 129.2, 113.7, 78.8, 75.1, 72.5, 72.0, 69.8, 55.2, 54.3, 53.1, 53.0, 44.1, 41.9, 40.6, 38.6, 32.7, 28.5, 26.4, 25.9, 25.2, 18.6, 18.1, -4.4, -4.5 ppm; HRMS (ESI) calcd for $[C_{41}H_{68}NO_{11}PSi+H^+]$: 810.4372, found: 810.4374.

***tert*-Butyl (*4R,5S,7R*)-1,7-bis(4-methoxybenzyloxy)-5-(*tert*-butyldimethylsilyloxy)-12-(dimethoxyphosphoryl)-11-oxododecan-4-ylcarbamate 22**

(875 mg, 86%) as a colorless oil. $[\alpha]_D^{23}$ = -11.7 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2952, 2928, 2855, 1712, 1605, 1513, 1359, 1248, 1173, 1034, 833, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (m, 4H), 6.91-6.84 (m, 4H), 4.63 (d, *J* = 9.2 Hz, 1H), 4.52-4.39 (m, 4H), 3.95-3.88 (m, 1H), 3.83-3.79 (m, 9H), 3.78 (s, 1H), 3.65-3.57 (m, 1H), 3.53-3.43 (m, 3H), 3.10 (s, 1H), 3.05 (s, 1H), 2.65-2.58 (m, 2H), 1.78-1.66 (m, 3H), 1.66-1.47 (m, 6H), 1.45 (s, 9H), 1.43-1.37 (m, 1H), 0.90 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 201.5, 159.1, 155.6, 130.9, 130.7, 129.5, 129.2, 113.7, 113.6, 78.8, 75.7, 72.5, 71.8, 71.0, 69.8, 55.3, 54.1, 53.1, 53.0, 44.1, 41.9, 40.6, 38.9, 33.3, 28.5, 26.4, 25.9, 24.9, 19.0, 18.1, -4.3, -4.6

ppm; HRMS (ESI) calcd for $[C_{41}H_{68}NO_{11}PSi+H^+]$: 810.4372, found: 810.4373.

***General procedure for synthesis of* 16, 23.**

Compound **15** or **22** (300 mg, 0.37 mmol), 10% Pd/C (300 mg) and 20% $Pd(OH)_2$ (300 mg) were stirred under hydrogen atmosphere for 4 h. Then the mixture was filtrated and concentrated. The residue, LiCl (19 mg, 0.44 mmol), DBU (56 mg, 0.37 mmol) and hexaldehyde (37 mg, 0.37 mmol) were stirred in CH_3CN (5 mL) at 0^oC for 1 h. 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 = 1/2) to give title compound.

***tert*-Butyl (*4S,5R,7R,E*)-5-(*tert*-butyldimethylsilyloxy)-1,7-dihydroxy-11-oxooctadec-12-en-4-ylcarbamate 16**

(109 mg, 54%) as a colorless oil. $[\alpha]_D^{23}$ = +3.2 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3456, 2954, 2928, 2856, 1692, 1496, 1370, 1255, 1172, 1063, 838, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.87 (ddd, *J* = 15.6, 7.2, 6.4 Hz, 1H), 6.11 (ddd, *J* = 15.6, 1.6, 0.8 Hz, 1H), 4.58 (d, *J* = 8.8 Hz, 1H), 4.05-3.90 (m, 1H), 3.80-3.60 (m, 4H), 2.89 (brs, 1H), 2.68-2.50 (m, 2H), 2.30-2.17 (m, 3H), 1.94 (brs, 1H), 1.77-1.66 (m, 4H), 1.62-1.54 (m, 3H), 1.51-1.46 (m, 3H), 1.45 (s, 9H), 1.37-1.28 (m, 5H), 0.94-0.91 (m, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 156.0, 147.9, 130.2, 79.2, 72.6, 67.8, 62.3, 54.2, 40.7, 39.7, 38.0, 32.5, 31.4, 28.8, 28.4, 27.8, 25.9, 25.6, 22.4, 19.6, 18.1, 14.0, -4.5, -4.6 ppm; HRMS (ESI) calcd for $[C_{29}H_{57}NO_6Si+H^+-H_2O]$: 526.3922, found: 526.3908.

***tert*-Butyl (*4R,5S,7R,E*)-5-(*tert*-butyldimethylsilyloxy)-1,7-dihydroxy-11-oxooctadec-12-en-4-ylcarbamate 23**

(107 mg, 53%) as a colorless oil. $[\alpha]_D^{23}$ = -21.3 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3453, 2955, 2928, 2856, 1690, 1501, 1452, 1366, 1252, 1172, 1096, 1058, 837, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (ddd, *J* = 16.0, 7.2, 6.4 Hz, 1H), 6.11 (ddd, *J* = 16.0, 1.6, 0.8 Hz, 1H), 4.72 (dd, *J* = 8.4, 1H), 4.02-3.98 (m, 1H), 3.80-3.73 (m, 1H), 3.72-3.65 (m, 3H), 3.40-3.12 (m, 1H), 2.65-2.55 (m, 2H), 2.26-2.18 (m, 2H), 2.00-1.88 (m, 1H), 1.82-1.68 (m, 4H), 1.67-1.55 (m, 5H), 1.51-1.47 (m, 3H), 1.45 (s, 9H), 1.51-1.47 (m, 3H), 1.45 (s, 9H), 1.35-1.31 (m, 4H), 0.94-0.91 (m, 3H), 0.91 (s, 9H) 0.11 (s, 1H), 0.10 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 156.2, 147.8, 130.2, 79.5, 73.0, 68.5, 62.5, 53.6, 40.3, 39.8, 37.3,32.5, 31.4, 29.1, 28.4, 27.8, 25.9, 25.5, 22.4, 20.1, 18.0, 14.0, -4.5, -4.6 ppm; HRMS (ESI) calcd for $[C_{29}H_{57}NO_6Si+H^+-H_2O]$: 526.3922, found: 526.3910.

***General procedure for synthesis of* Epohelmin A 3 and 3-epi *ent*-Epohelmin A 24.**

To a solution of alcohol **16** or **23** (93 mg, 0.17 mmol) and TEA (0.19 mL, 1.37 mmol) in dry DCM (5 mL) was cooled to 0^oC. Then MsCl (40 μL, 0.51 mmol) was added dropwise and the mixture was stirred for 30 min. The reaction was quenched with a saturated NH_4Cl solution (20 mL) and extracted with DCM (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 (96 μL, 0.82 mmol) were dissolved in DCM (5 mL) and cooled to -78^oC. The reaction was treated with TESOTf (0.18 mL, 0.78 mmol) and the mixture was allowed to warm to room temperature and stirred for overnight. The mixture was diluted with water and extracted with DCM (30 mL × 3) and the combined organic layers were washed with brine. The resulting 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 resulting mixture was extracted with DCM (15 mL × 5). The combined organic layers were dried, concentrated. The residue was purified by flash chromatography on silica gel ($DCM/CH_3OH/HOAc$ = 100/10/1) to give title compound.

Epohelmin A•HOAc (3•HOAc)

(23 mg, 46%) as a yellow oil. $[\alpha]_D^{23}$ = +2.9 (*c* 0.31, CH_3OH); IR (film): ν_{max} 3340, 2950, 2928, 2859, 1674, 1630, 1473, 1390, 1085 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.90-6.83 (m, 1H), 6.08 (d, *J* = 15.6 Hz, 1H), 4.33-4.27 (m, 1H), 4.14-4.02 (m, 2H), 3.61-3.55 (m, 1H), 2.93-2.86 (m, 1H), 2.71-2.63 (m, 2H), 2.51-2.45 (m, 1H), 2.27-2.19 (m, 3H), 2.12-2.07 (m, 1H), 2.03-1.97 (m, 1H), 1.86-1.78 (m, 3H), 1.70-1.62 (m, 2H), 1.53-1.44 (m, 3H), 1.34-1.28 (m, 4H), 0.92-0.88 (m, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.7, 148.5, 130.0, 73.3, 63.1, 48.0, 38.6, 36.7, 32.5, 31.4, 29.3, 28.1, 27.7, 25.7, 22.4, 20.8, 14.0 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{32}NO_2$: 294.2428, found: 294.2430.

3-epi *ent*-Epohelmin A 24

(30 mg, 50%) as a yellow oil. $[\alpha]_D^{23}$ = -7.5 (*c* 0.50, $CHCl_3$); IR (film): ν_{max} 3345, 2955, 2929, 2870, 1670, 1632, 1463, 1389, 1085 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.83 (ddd, *J* = 15.6, 7.2, 6.0 Hz, 1H), 6.08 (ddd, *J* = 15.6, 1.8, 0.6 Hz, 1H), 3.97-3.92 (m, 1H), 3.52-3.46 (m, 1H), 3.06-3.01 (m, 1H), 2.72-2.66 (m, 2H), 2.64-2.52 (m, 2H), 2.38-2.33 (m, 1H), 2.23-2.18 (m, 2H), 2.02-1.96 (m, 1H), 1.83-1.78 (m, 2H), 1.70-1.61 (m, 5H), 1.57-1.52 (m, 1H), 1.49-1.44 (m, 2H), 1.36-1.24 (m, 5H), 0.91-0.88 (m, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.4, 147.7, 130.3, 76.5, 72.5, 65.6, 54.3, 41.6, 39.9, 35.8, 32.4, 31.4, 29.8, 27.8, 25.0, 22.4, 21.6, 13.9 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{32}NO_2$: 294.2428, found: 294.2428.

Epohelmin B 4

To a stirred solution of oxalyl chloride (27 μL, 0.28 mmol) in DCM (5 mL) was added DMSO (40 μL, 0.56 mmol) at -78^oC. The resulting mixture was stirred at -78^oC for 30 min and a solution of **3** (41 mg, 0.14 mmol) in DCM (1 mL) was added followed by TEA (116 μL, 0.84 mmol). The reaction mixture was stirred at -78^oC for 3 h and poured into water. The organic layer was separated and the aqueous layer was extracted with DCM (10 mL× 3). The combined organic layers were washed with brine, dried and concentrated. The residue was dissolved in THF (3 mL) and added L-Selectride (1.0 M in THF, 1.4 mL, 1.4 mmol) dropwise at -78^oC. The reaction was stirred at -78^oC for 1 h, warmed to room temperature and stirred for another 3 h. Then the resulting mixture was quenched with 10% NH_4OH. The organic layer was separated and the aqueous layer was extracted with DCM (10 mL× 3). The combined organic layers were washed with brine, dried and concentrated to give intermediate as a yellow oil. Then to a stirred solution of the yellow oil in $CHCl_3$ (5 mL) was added DMP (72 mg, 0.17 mmol) in one portion. The resulting mixture was stirred at room temperature for 1 h and poured into a mixture of saturated aqueous $Na_2S_2O_3$ solution and saturated aqueous $NaHCO_3$ solution (5 mL/5 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (10 mL× 3). The combined organic layers were dried, concentrated. The residue was purified by flash chromatography on silica gel ($DCM/CH_3OH/HOAc$ = 100/10/1) to give **4•HOAc** (26 mg, 63%) as a yellow oil. $[\alpha]_D^{23}$ +4.3 (*c* 1.00, CH_3OH), $[\alpha]_D^{23}$ +4.9 (*c* 0.40, CH_2Cl_2), lit.[6] $[\alpha]_D^{20}$ +5.3 (*c* 0.67, CH_2Cl_2); IR (film): ν_{max} 3341, 2954, 2928, 2869, 1667, 1627, 1463, 1386, 1085 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (ddd, *J* = 16.0, 7.2, 6.4 Hz, 1H), 6.08 (d, *J* = 16.0 Hz, 1H), 4.56-4.48 (m, 1H), 4.27-4.19 (m, 1H), 3.70-3.60 (m, 1H), 3.48-3.43 (m, 1H), 2.99-2.91 (m, 1H), 2.67-2.61 (m, 2H), 2.55-2.44 (m, 2H), 2.24-2.18 (m, 3H), 2.14-2.04 (m, 4H), 1.85-1.76 (m, 3H), 1.75-1.65 (m, 4H), 1.50-1.43 (m, 2H), 1.35-1.27 (m, 5H), 0.92-0.87 (m, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.1, 147.8, 129.4, 68.3, 58.8, 46.8, 38.1, 36.8, 31.9, 30.7, 29.1, 28.7, 27.1, 25.1, 23.1, 21.8, 20.4, 13.3 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{32}NO_2$: 294.2428, found: 294.2427.

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Supplementary Material

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