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# Formal total synthesis of (−)-spongidepsin

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ABSTRACT

The formal total synthesis of (−)-spongidepsin is described. Three fragments **I**, **II**, and **III** were first prepared from readily available starting materials and then assembled to the target compound. The key steps involved in the synthesis are asymmetric α-hydroxylation, Ender's alkylation, and ring-closing metathesis reactions. An alternative route for the fragment **II** is also achieved involving Sharpless asymmetric epoxidation and Gilman's alkylation as key reactions.



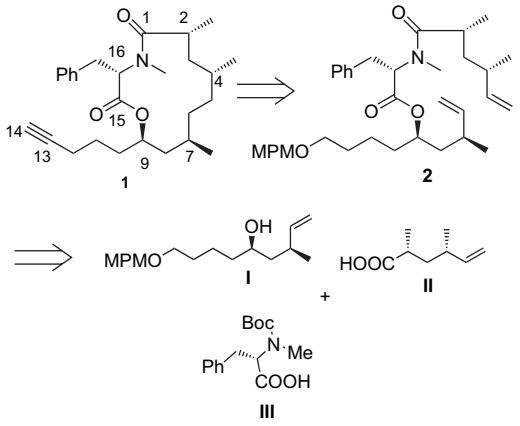
## 1. Introduction

(−)-Spongidepsin (**1**), a novel macrolide, was isolated from the sponge *spongia* sp. collected from the waters of the Vanuata Islands, Australia, by Riccio and associates.[1] Spongidepsin displays cytotoxic and anti-proliferative activities against J774.A1, HEK-293, and WEHI-164 cancer cell lines,[2] This natural product contains a highly functionalized 13-membered macrolactum with 5 stereogenic centers and an amino acid residue of *N*-methylphenylalanine. The complete structure of spongidepsin was initially established by spectral analysis and the amino acid residue with the L-configuration has been identified during the isolation stage.[1] However, the absolute configuration of the other four stereogenic centers was determined by total synthesis of spongidepsin.[3,4] In the year 2004, Forsyth and Chen reported the first total synthesis and structural elucidation of spongidepsin.[3] In the same year, Ghosh and Xu also achieved the total synthesis and assigned the absolute stereochemistry of (−)-spongidepsin,[4] and later two more synthesis have been reported.[5,6] To date, five syntheses of spongidepsin have been reported.[3–7] Recently, we have reported the stereo selective formal total synthesis of the cyclodepsipeptide (−)-spongidepsin.[7]

In this paper, we provide the full details of our efforts toward the total synthesis of (−)-spongidepsin. Along with these details we also describe an alternative route for the synthesis of fragment **II** (Scheme 4).

## 2. Results and discussions

The retrosynthetic strategy for the spongidepsin is summarized in Scheme 1.




**Scheme 1.** Retrosynthesis of (−)-spongidepsin.

Key targeted bonds were C5, C6 (ring-closing metathesis), C9, C15 (Yamaguchi esterification), and C1, *N*-Me (amide bond formation). This divided the molecule into three fragments viz fragment **I** (C5–C13), fragment **II** (C1–C6), and amino acid moiety fragment **III**, which were prepared individually using high yielding reactions. The introduction of chirality was achieved at C4 by Ender's

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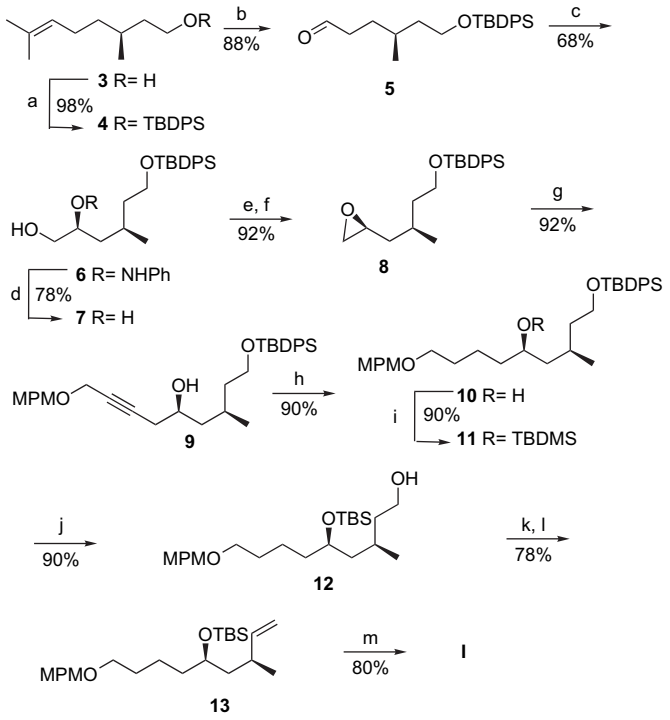
auxiliary mediated enantioselective methylation and McMillan α-hydroxylation of citronellol derivative[8] **5** at C9.

### 2.1. Synthesis of fragment I

The synthesis of fragment **I** is summarized in Scheme 2, for which (−)-citronellol **3** was used as the starting material (chiral synthon). The primary hydroxyl group of (−)-citronellol was protected quantitatively as the *tert*-butyldiphenylsilyl ether **4** using TBDPSCl, imidazole, and DCM at 0 °C to room temperature.

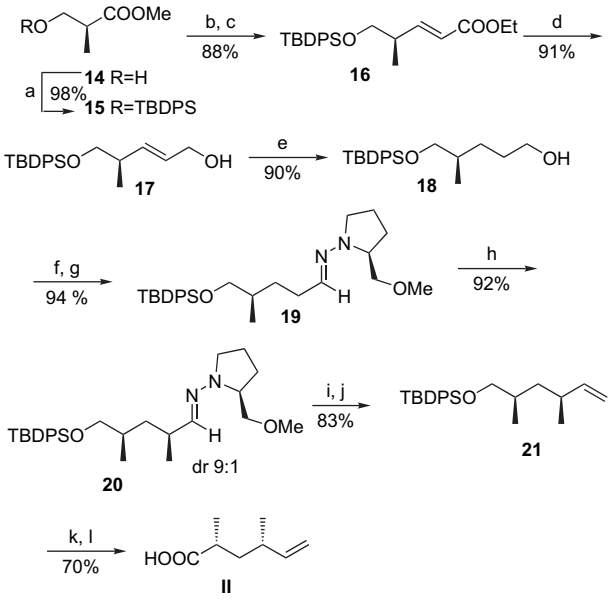



**Scheme 2.** Reagents and conditions: (a) TBDPSCl, imidazole, $CH_2Cl_2$, rt, 1 h. (b) $O_3$, $CH_2Cl_2$, −78 °C, 15 min. (c) PhNO, D-proline (40 mol %), DMSO, rt, 30 min then $NaBH_4$, EtOH. (d) $CuSO_4$, MeOH, 12 h. (e) TsCl, $NEt_3$, $Bu_2SnO$, $CH_2Cl_2$, 3 h. (f) $K_2CO_3$, MeOH, 30 min. (g) [$HCCCH_2OCH_2C_6H_4(OCH_3)$], *n*-BuLi, $BF_3{\cdot}OEt_2$, −78 °C. (h) Pd–$CaCO_3$, $H_2$, 10 h. (i) TBDMSCl, imidazole, $CH_2Cl_2$, rt, 5 h. (j) NaOH (10 mol % in MeOH), reflux, 6 h. (k) TPP, $I_2$, imidazole, $Et_2O$, $CH_3CN$, 30 min. (l) KO$^t$Bu, THF, 0 °C, 1 h. (m) TBAF, THF, rt, 2 h.

The TBDPS protected citronellol subjected to ozonolysis in dichloromethane at −78 °C furnished the aldehyde **5** in 88% yield, which was further exposed to proline-catalyzed α-hydroxylation protocol using nitrosobenzene and D-proline in DMSO at room temperature, followed by the in situ reduction of the resultant anilinoxy aldehyde using sodium borohydride ($NaBH_4$) in ethanol at 0 °C provided the corresponding anilinoxy compound **6** in 68% yield, 98% ee; the chiral purity was determined by chiral HPLC on chiralcel OB-H column, using hexanes and isopropyl alcohol as eluent. Treatment of this anilinoxy compound with 30% copper sulfate ($CuSO_4$) in methanol at room temperature provided the diol[8,9] **7** with high enantio- and diastereoselectivity (78% yield, 98% ee), and no traces of other diastereomer could be detected on chiral OB-H column (hexanes and isopropyl alcohol as eluent). Selective tosylation of the diol **7** using tosyl chloride, triethylamine, and catalytic amount of dibutyltin oxide ($Bu_2SnO$) in dichloromethane at 0 °C furnished the mono tosylated compound, which was further treated with potassium carbonate in dry methanol at 0 °C to give the epoxide[10] **8** (in 92% yield), this allowed the chain extension via epoxide opening under $BF_3{\cdot}OEt_2$ catalysis with propargyl anion[11] of 4-methoxybenzyl protected propargyl alcohol [$HCCCH_2OCH_2C_6H_4(OCH_3)$] gave compound **9** with complete regioselectivity in 92% yield. The exhaustive hydrogenation of the acetylenic functionality to saturation was obtained using Pd–$CaCO_3$ in ethyl acetate for 10 h to give the compound **10**, this on treatment with *tert*-butyldimethylsilylation (TBDMSCl, imidazole, and $CH_2Cl_2$) gave fully and differentially protected triol **11** in 90% yield. The selective deprotection of primary silyl ether (10 mol % NaOH, MeOH, reflux)[12] to **12** was achieved in 90% yield. The fragment **I**, precursor for RCM, was obtained in three steps from **12** [(i) iodination of primary hydroxyl group (TPP, $I_2$, imidazole),[13] (ii) treatment of resultant iodide with KO$^t$Bu[14] followed by (iii) deprotection of silyl ether (TBAF, THF)] in 80% overall yield.

### 2.2. Synthesis of fragment II

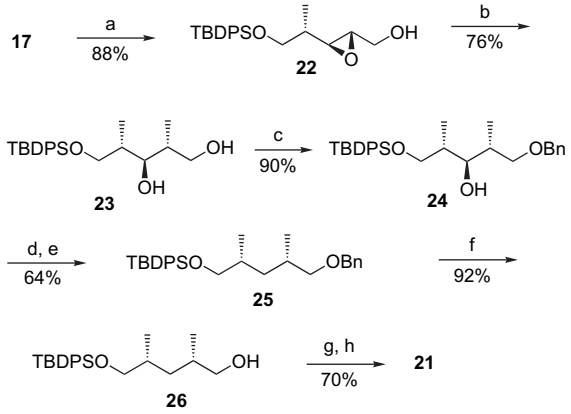
The other partner required for RCM, olefinic acid **II**, was synthesized in a linear fashion (Scheme 3). Commercially available (+)-methyl-L-β-hydroxyisobutyrate (Roche ester)[5] **14** was quantitatively protected as its silyl ether **15** using *tert*-butyldiphenylsilyl chloride (TBDPSCl) and imidazole in dichloromethane at 0 °C, and the protected ester was reduced to alcohol using diisobutylaluminum hydride (DIBAL-H) in dichloromethane at 0 °C. The Swern oxidation[15] of alcohol (DMSO, oxalyl chloride, and triethylamine at −78 °C), followed by homologation with two carbon Wittig ylide gave the *trans*-unsaturated ester **16** in 88% yield (*E*/*Z*=95:5, separable on silica gel column chromatography). DIBAL-H reduction of ester **16** in dichloromethane at 0 °C provided the allylic alcohol **17**, which was hydrogenated to saturated alcohol **18** in 90% yield. The IBX mediated oxidation and hydrazone formation with Enders chiral auxiliary (SAMP) yielded the precursor **19**, which permits installation of chiral methyl group at C4. Thus the exposure of SAMP-hydrazone[16] to LDA at −100 °C followed by quenching with methyl iodide remitted in hydrazone **20** (dr=9:1, separable on silica gel column chromatography using 100–200 mesh, 92%yield).[17] Ozonolysis of **20** followed by one carbon Wittig olefination (KO$^t$Bu, $Ph_3PCH_3I$, THF, 0 °C to −78 °C) to **21** and deprotection of silyl ether using TBAF followed by oxidation (PDC, DMF)[4] of resultant alcohol provided the olefinic acid fragment **II**, the partner for RCM.




**Scheme 3.** (a) TBDPSCl, imidazole, $CH_2Cl_2$, rt, 1 h. (b) DIBAL-H, $CH_2Cl_2$, −10 °C, 1 h. (c) DMSO, $(COCl)_2$, $NEt_3$, $CH_2Cl_2$, −78 °C, 3 h then $Ph_3PCHCOOEt$, $C_6H_6$. (d) DIBAL-H, $CH_2Cl_2$, 0 °C, 1 h. (e) Pd–C, $H_2$, EtOAc. (f) IBX, DMSO, THF, 1 h. (g) SAMP, $CH_2Cl_2$, rt, 24 h. (h) LDA, $CH_3I$, −100 °C, $Et_2O$, 4 h. (i) $O_3$, $CH_2Cl_2$, −78 °C, 30 min. (j) KO$^t$Bu, $Ph_3PCH_3I$, THF, 0 °C to −78 °C. (k) TBAF, THF, rt, 1 h. (l) PDC, DMF, rt, 12 h.

*2.2.1. Alternative route for the synthesis of fragment **II***

The alternative route for the synthesis of fragment **II** is shown in Scheme 4. The allylic alcohol **17** was subjected to Sharpless asymmetric epoxidation (SAE) using (+)-diethyl-L-tartarate, titaniumisopropoxide, and *tert*-butylhydrogen peroxide (TBHP) in dichloromethane at −20 °C to give the epoxide **22** in 88% yield.[18] The Gilman's methylation[19] on epoxide **22** with lithiumdimethyl cuprate in diethyl ether at −40 °C yielded the diol **23** in 76% yield. The primary alcohol was protected as its benzyl ether (NaH, BnBr, THF, 0 °C) **24**, the secondary alcohol was then tosylated at −78 °C using tosyl chloride and *n*-butyllithium in tetrahydrofuran, and the crude tosyl compound was further treated with lithium aluminum hydride (LAH, THF, 60 °C, 90 min) to give the compound[20] **25**. The debenzylation of **25** (Pd–C, EtOAc, 92%) followed by oxidation and Wittig methylenation gave the compound **21** (70%), which was converted into fragment **II** as shown in Scheme 3.




**Scheme 4.** (a) L-(+)-DET, $Ti(O^iPr)_4$, TBHP, $CH_2Cl_2$, −20 °C, 4 Å MS, 5 h. (b) $CH_3Li$, CuI, $Et_2O$, −23 °C, 4 h. (c) NaH, BnBr, THF, 0 °C, 1 h. (d) *n*-BuLi, TsCl, −78 °C, 10 min. (e) $LiAlH_4$, THF, reflux, 1.5 h. (f) Pd–C, $H_2$, EtOAc, 4 h. (g) IBX, DMSO, THF, 1 h. (h) $KO^tBu$, $Ph_3P^+CH_3I^-$, THF, 0 °C to −78 °C, 1 h.

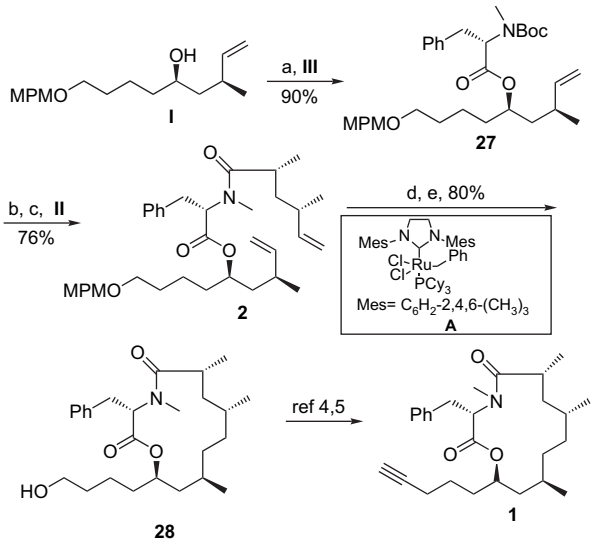
Even though, Scheme 3 is more efficient in overall yield compared to Scheme 4 (~30% overall vs 14%) for the synthesis of fragment **II**, the Ender's alkylation step (from **19** to **20**) was rate determining as the reagents were expensive.

## 2.3. Synthesis of fragment III

The other synthon **III** required for the total synthesis of (−)-spongidepsin was synthesized from natural phenylalanine in a known route.[3] First L-phenylalanine was protected with di-*tert*-butoxy carbonyl $(Boc)_2O$ in 20% aq sodium hydroxide (NaOH) and 1,4-dioxane to yield *N*-Boc-phenylalanine in 90% yield. The Boc-protected amino acid was treated with sodium hydride and methyl iodide in tetrahydrofuran (THF) at 0 °C to give *N*-Boc-*N*-methyl-L-phenylalanine in 90% yield.

## 2.4. Assembling of the fragments I, II, and III

The synthesis of the target compound was successfully completed by combining the synthons **I**, **II**, and **III** in a seven-step sequence as shown in Scheme 5. The synthon **I** was acylated with *N*-Boc-*N*-methyl-phenylalanine **III** under Yamaguchi conditions to obtain ester **27** in 88% yield.[21] This on stepwise deprotection of *N*-Boc group using TBSOTf, 2,6-lutidine, and TBAF[22] gave the amine **28**, which was further treated with fragment **II** under EDCI and HOBt reagent combination for amide bond formation to provide the most desired diene fragment **2** for RCM. The ring-closing metathesis of diene **2** using second generation Grubbs catalyst[23] followed by a palladium-catalyzed hydrogenation (Pd–C, EtOAc, $H_2$, 8 h) provided the macrolactone **28** in 80% yield (two steps).[3] This late stage intermediate has already been converted to the target compound in two steps by the reported procedures.[4–6] Thus this completes the formal total synthesis of bioactive natural product **1**.




**Scheme 5.** (a) $Cl_3C_6H_2COCl$, DIPEA, *N*-Me-*N*-Boc-Phe (**III**), DMAP, toluene, 88%. (b) TBSOTf, 2,6-lutidine, TBAF, THF, rt. (c) EDCI, HOBt, $CH_2Cl_2$, then **II**. (d) Grubbs II catalyst (**A**), $CH_2Cl_2$, reflux, 12 h. (e) Pd–C, $H_2$, EtOAc, 8 h.

## 3. Conclusion

In conclusion, we have completed the total synthesis of (−)-spongidepsin in a fully enantio and stereo controlled manner involving high yielding steps. The convergent of three key building blocks has been achieved using Yamaguchi esterification and Grubbs metathesis reactions. An alternative route for the synthesis of fragment **II** was also demonstrated.

## 4. Experimental

### 4.1. General

All the solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were recorded on Perkin–Elmer 683, Nicolet Nexus 670 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. $^1H$ NMR and $^{13}C$ NMR spectra were recorded in $CDCl_3$ solvent on a Varian Gemini 200, Bruker 300, Varian Unity 400 or Inova 500 NMR spectrometer. Chemical shifts were reported in parts per million with respect to internal TMS. Coupling constants (*J*) are quoted in hertz (Hz). HPLC was recorded on SHIMADZU HPLC using chiralcel OB-H column, and hexanes and isopropyl alcohol as eluent. Mass spectra were obtained on Finnigan MAT1020B, micromass VG 70-70H or agilent technologies LC/MSD trapSL spectrometer operating at 70 eV using direct inlet system.

*4.1.1. (S)-tert-Butyl (3,7-dimethyloct-6-enyloxy)diphenylsilane (**4**)*

To a solution of (*S*)-citronolleol (5.0 g, 32.0 mmol) and imidazole (4.3 g, 64.1 mmol) in dry dichloromethane (50 mL) under nitrogen atmosphere was added dropwise TBDPSCl at 0 °C (8.8 mL, 32.1 mmol) over 10 min and the solution was stirred at room temperature for 2 h. Water (30 mL) was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2×50 mL) and the combined

organic layers were washed with brine (50 mL). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (3% EtOAc in hexanes) to afford **4** as colorless oil (12.5 g, 98%). $R_f$ 0.53 (hexanes–ethyl acetate, 19:1, v/v).

$^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.76–7.56 (m, 4H), 7.46–7.27 (m, 6H), 5.05 (t, $J$=7.2 Hz, 1H), 3.66 (t, $J$=6.5 Hz, 2H), 2.04–1.85 (m, 2H), 1.62 (d, $J$=15.9 Hz, 6H), 1.48–1.09 (m, 5H), 1.04 (s, 9H), 0.83 (d, $J$=6.5 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 135.6, 134.1, 131.0, 129.5, 127.6, 124.9, 62.3, 39.5, 37.2, 29.1, 26.9, 25.7, 25.5, 19.6, 19.1, 17.7; $[\alpha]_D^{23}$ +2.1 ($c$ 1.0, $CHCl_3$); EIMS ($m/z$): 417.2 $(M+Na)^+$; HRMS-ESI calcd for $C_{26}H_{38}OSi$ 395.2763, found 395.2764; IR (neat): $\nu$ 2932, 2858, 1427, 1110, 912, and 794 cm$^{-1}$.

#### 4.1.2. (S)-6-(tert-Butyldiphenylsilyloxy)-4-methylhexanal (**5**)

Ozone gas was bubbled through a solution **4** (12.5 g, 31.7 mmol) in $CH_2Cl_2$ (100 mL) at −78 °C until solution becomes blue color. The reaction mixture was subsequently purged with a flow of $N_2$, treated with dimethyl sulfide (DMS) (3 mL) at −78 °C, slowly warmed to room temperature, and stirred for 1 h. Water (50 mL) was added to the solution, the organic layer was separated, and the aqueous layer was extracted with dichloromethane (3×50 mL). The combined organic extracts were washed with brine (50 mL) and dried over $Na_2SO_4$. Removal of solvent on rotary evaporator under reduced pressure gave aldehyde **5** as colorless oil (10.4 g, 88%). The residue was subjected to the next reaction without purification. $R_f$ 0.42 (hexanes–ethyl acetate, 9:1, v/v).

$^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 9.6 (s, 1H), 7.76–7.56 (m, 4H), 7.46–7.27 (m, 6H), 3.5 (t, $J$=6.5 Hz, 2H), 2.50–2.24 (m, 2H), 1.79–1.68 (m, 1H), 1.53–1.39 (m, 3H), 1.23–1.10 (m, 1H), 1.04 (s, 9H), 0.86 (d, $J$=6.5 Hz, 3H); EIMS ($m/z$): 368 $(M+H)^+$, 391 $(M+Na)^+$, 407 $(M+K)^+$; IR (neat): $\nu$ 2931, 2858, 1710, 1427, 1110, 912, and 794 cm$^{-1}$.

#### 4.1.3. (2S,4R)-6-(tert-Butyldiphenylsilyloxy)-4-methyl-2-(phenylaminooxy)hexan-1-ol (**6**)

To a 2-dram vial equipped with a magnetic stir bar and charged with D-proline (0.73 g, 6.3 mmol) was added DMSO (25 mL) at room temperature under nitrogen atmosphere. After stirring the suspension for 10 min, nitrosobenzene (1.7 g, 15.8 mmol) was added in one portion upon at which time the solution becomes green. Aldehyde **5** (8.77 g, 23.8 mmol) was added in one portion to the above greenish suspension and stirring continued at room temperature until the reaction was determined to be complete (by TLC, the change of green color solution to a yellow homogeneous solution was observed). The reaction mixture was then transferred to a suspension of $NaBH_4$ (0.63 g, 16.3 mmol) in ethanol (20 mL) at 0 °C. After 20 min stirring, the reaction was treated with saturated aq $NaHCO_3$ (30 mL) and extracted with dichloromethane (3×30 mL). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was then purified by silica gel chromatography (15% ethyl acetate and hexanes as eluent) to afford the light yellow anilinoxy diol **6** (6.1 g, 68% yield). $R_f$ 0.35 (hexanes–ethyl acetate, 4:1, v/v).

$^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.71–7.59 (m, 4H), 7.49–7.29 (m, 6H), 7.28–7.17 (m, 3H), 6.98–6.89 (m, 2H), 4.04–3.93 (m, 1H), 3.81–3.64 (m, 4H), 1.99–1.79 (m, 1H), 1.76–1.53 (m, 2H), 1.50–1.33 (m, 2H), 1.04 (s, 9H), 0.93 (s, $J$=6.0 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 149.0, 136.5, 134.2, 130.5, 130.0, 127.8, 123.1, 116.3, 81.6, 64.7, 62.5, 40.2, 38.6, 37.5, 27.6, 26.5, 19.5, 19.0; $[\alpha]_D^{23}$ −10.3 ($c$ 1.0, $CHCl_3$); EIMS ($m/z$): 500.1 $(M+Na)^+$; IR (neat): $\nu$ 3417, 2930, 1617, 1109, and 702 cm$^{-1}$.

#### 4.1.4. (2S,4R)-6-(tert-Butyldiphenylsilyloxy)-4-methylhexane-1,2-diol (**7**)

To a solution of above anilinoxy diol compound **6** (4.0 g, 8.0 mmol) in methanol (40 mL), was added $CuSO_4$ (0.38 g, 2.4 mmol). The reaction mixture was stirred at room temperature overnight, and then quenched with a cold saturated $NH_4Cl$ solution. The mixture was filtered on a Celite pad, washed thoroughly with ethyl acetate, and extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was then purified by silica gel chromatography (40% ethyl acetate and hexanes as eluent) to afford diol **7** as colorless oil (2.10 g, 78% yield, 98% ee). $R_f$ 0.23 (hexanes–ethyl acetate, 7:3, v/v).

$^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.69–7.56 (m, 4H), 7.41–7.30 (m, 6H), 3.79–3.60 (m, 3H), 3.59–3.45 (m, 1H), 3.37–3.24 (m, 1H), 2.61 (br s, 2H), 1.98–1.71 (m, 1H), 1.70–1.20 (m, 3H), 1.18–1.07 (m, 1H), 1.04 (s, 9H), 0.87 (dd, $J$=2.9, 6.5 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 136.1, 134.1, 129.9, 127.8, 70.1, 67.5, 62.3, 40.9, 39.5, 27.7, 26.2, 20.9, 19.14; $[\alpha]_D^{23}$ −5.6 ($c$ 1.0, $CHCl_3$); EIMS ($m/z$): 409 $(M+Na)^+$; HRMS-ESI calcd for $C_{23}H_{34}O_3NaSi$ 409.2174, found 409.2166; IR (neat): $\nu$ 3416, 1617, 1354, and 795 cm$^{-1}$.

#### 4.1.5. tert-Butyl ((R)-3-methyl-4-((S)-oxiran-2-yl)butoxy)-diphenylsilane (**8**)

To a solution of diol **7** (2.0 g, 5.1 mmol) in dry dichloromethane (25 mL) was added $NEt_3$ (1.0 g, 1.5 mL, 10.4 mmol) at 0 °C under nitrogen atmosphere. After 10 min, $p$-toluenesulfonyl chloride (0.98 g, 5.2 mmol) and $n$-butyltin oxide (3 mg, as catalyst) were added to the reaction mixture and stirred at room temperature for 3 h. The reaction mixture was quenched with water (30 mL) and extracted into dichloromethane (3×30 mL). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuo to yield primary tosylated diol as colorless oil (2.62 g, 90%). The residue was then subjected to the epoxidation without further purification. $R_f$ 0.45 (hexanes–ethyl acetate, 4:1, v/v).

$^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.78 (d, $J$=8.3 Hz, 2H), 7.61 (d, $J$=7.5 Hz, 4H), 7.43–7.28 (m, 8H), 4.06–3.76 (m, 3H), 3.75–3.53 (m, 2H), 2.45 (s, 3H), 1.99–1.66 (m, 2H), 1.59–1.30 (m, 3H), 1.03 (s, 9H), 0.84 (d, $J$=6.8 Hz, 3H); EIMS ($m/z$): 563 $(M+23)^+$; IR (neat): $\nu$ 3415, 2931, 1734, 1617, 1356, 1176, and 794 cm$^{-1}$.

To a stirred solution of the above tosylated compound (2.50 g, 4.6 mmol) in dry methanol (25 mL) at 0 °C under nitrogen atmosphere was added $K_2CO_3$ (1.26 g, 9.2 mmol) portionwise. After completion of the reaction (30 min), methanol was removed under reduced pressure, the reaction mass was diluted with water (20 mL), aqueous layer was extracted into diethyl ether (2×30 mL), and then washed with brine (30 mL). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (4% EtOAc in petroleum ether) to afford the epoxide **8** as colorless oil (1.61 g, 92%). $R_f$ 0.66 (hexanes–ethyl acetate, 9:1, v/v).

$^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.73–7.60 (m, 4H), 7.50–7.33 (m, 6H), 3.73 (t, $J$=6.0 Hz, 2H), 2.94–2.83 (m, 1H), 2.77–2.65 (m, 1H), 2.43–2.33 (m, 1H), 1.78–1.26 (m, 3H), 1.08 (s, 9H), 0.98 (dd, $J$=4.1, 6.8 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 135.6, 134.2, 129.5, 127.7, 61.7, 51.2, 46.9, 39.8, 39.3, 28.3, 26.9, 19.9; $[\alpha]_D^{23}$ −4.3 ($c$ 2.9, $CHCl_3$); EIMS ($m/z$): 391 $(M+Na)^+$; HRMS-ESI calcd for $C_{23}H_{32}O_2NaSi$ 391.2069, found 391.2075; IR (neat): $\nu$ 3414, 2929, 1616, 1108, and 703 cm$^{-1}$.

#### 4.1.6. (5S,7R)-9-(tert-Butyldiphenylsilyloxy)-1-(4-methoxybenzyloxy)-7-methylnon-2-yn-5-ol (**9**)

In a 100 mL round bottom flask MPM protected propargyl ether (1.06 g, 6.0 mmol) was weighed and 20 mL of dry THF was added under nitrogen atmosphere. The RB flask was cooled to −78 °C and $n$-BuLi (0.34 g, 1.6 M in hexanes, 3.30 mL, 5.3 mmol) was added slowly, and stirred for 30 min. To the reaction mixture at −78 °C, were added $BF_3\cdot Et_2O$ (0.18 g, 1.2 mmol) and epoxide **8** (1.5 g, 4.0 mmol) diluted in 5 mL of dry THF. After completion of the reaction (monitored by TLC, about 1 h), the reaction was quenched

with slow addition of saturated $NH_4Cl$ (10 mL) at −78 °C, then water (10 mL) was added at room temperature. The aqueous layer was extracted with ethyl acetate (2×30 mL) and the combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (8% EtOAc in petroleum ether) to afford the acetylenic alcohol **9** as colorless oil (2.1 g, 92%). $R_f$ 0.31 (hexanes–ethyl acetate, 4:1, v/v).

$^1$H NMR (200 MHz, $CDCl_3$): δ 7.67–7.60 (m, 4H), 7.40–7.30 (m, 6H), 7.25–7.19 (m, 2H), 6.86–6.78 (m, 2H), 4.48 (s, 2H), 4.14–4.05 (m, 3H), 3.78 (s, 3H), 3.76–3.62 (m, 2H), 2.46–2.23 (m, 2H), 1.92–1.33 (m, 5H), 1.04 (s, 9H), 0.88 (d, *J*=6.4 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 159.1, 135.7, 133.7, 129.6, 127.6, 113.7, 83.4, 78.5, 71.0, 68.0, 62.1, 57.2, 55.1, 43.7, 40.1, 39.0, 28.4, 26.8, 26.4, 26.2, 20.3, 19.4, 19.1. $[\alpha]_D^{23}$ −2.6 (*c* 2.3, $CHCl_3$); EIMS (*m*/*z*): 567 $(M+Na)^+$; HRMS-ESI: calcd for $C_{34}H_{44}O_4NaSi$ 567.2906, found 567.2899; IR (neat): ν 3420, 2924, 2853, 2104, 1615, 1463, 1247, and 704 $cm^{-1}$.

#### 4.1.7. (5R,7R)-5-(4-(4-Methoxybenzyloxy)butyl)-2,2,3,3,7,12,12-heptamethyl-11,11-diphenyl-4,10-dioxa-3,11-disilatridecane (**10**)

To a solution of the hydroxyalkyne **7** (2.0 g, 3.60 mmol) and Pd on $CaCO_3$ (5%) (0.5 g) in EtOAc (30 mL) was bubbled $H_2$ for 12 h. The solution was then filtered over Celite and the filter cake was washed with EtOAc (3×15 mL). Evaporation of the solvent afforded the saturated product as colorless oil **10** (1.8 g, 90%). $R_f$ 0.34 (hexanes–ethyl acetate, 4:1, v/v).

$^1$H NMR (200 MHz, $CDCl_3$): δ 7.66–7.59 (m, 4H), 7.41–7.29 (m, 6H), 7.20 (d, *J*=8.3 Hz, 2H), 6.81 (d, *J*=9.0 Hz, 2H), 4.39 (s, 2H), 3.78 (s, 3H), 3.77–3.56 (m, 4H), 3.40 (t, *J*=6.0 Hz, 2H), 1.93–1.48 (m, 3H), 1.47–1.06 (m, 8H), 1.03 (s, 9H), 0.86 (d, *J*=6.9 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 159.1, 135.5, 134.0, 130.7, 129.5, 129.2, 127.6, 113.7, 72.5, 72.0, 69.8, 61.7, 55.2, 41.6, 40.1, 34.8, 29.6, 26.8, 25.7, 22.0, 21.3, 19.3; $[\alpha]_D^{23}$ +2.5 (*c* 1.2, $CHCl_3$); EIMS (*m*/*z*): 571 $(M+Na)^+$; HRMS-ESI: calcd for $C_{34}H_{48}O_4NaSi$ 571.3219, found 571.3202; IR (neat): ν 3447, 2924, 2853, 1615, 1463, 1247, 1106, and 704 $cm^{-1}$.

#### 4.1.8. (3R,5R)-1-(tert-Butyldiphenylsilyloxy)-9-(4-methoxybenzyloxy)-3-methylnonan-5-ol (**11**)

To a solution of alcohol **10** (1.6 g, 2.9 mmol) and imidazole (0.61 g, 8.8 mmol) in dry dichloromethane (20 mL) under nitrogen atmosphere was added portionwise TBDMSCl at 0 °C (0.45 g, 3.5 mmol) and the solution was stirred at room temperature for 5 h. The reaction was quenched by adding water (20 mL). The aqueous layer was extracted with dichloromethane (2×30 mL) and the combined organic layers were washed with brine (30 mL). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (5% EtOAc in hexanes) to afford the fully and differentially protected triol **11** as colorless oil (1.74 g, 90%). $R_f$ 0.35 (hexanes–ethyl acetate, 9:1, v/v).

$^1$H NMR (200 MHz, $CDCl_3$): δ 7.72–7.62 (m, 4H), 7.46–7.33 (m, 6H), 7.20 (d, *J*=8.3 Hz, 2H), 6.81 (d, *J*=9.0 Hz, 2H), 4.43 (s, 2H), 3.81 (s, 3H), 3.76–3.61 (m, 3H), 3.42 (t, *J*=6.2 Hz, 2H), 1.93–1.50 (m, 4H), 1.47–1.10 (m, 6H), 1.06 (s, 9H), 0.86 (s, 9H), 0.81 (d, *J*=6.9 Hz, 3H), 0.02 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 159.3, 135.8, 134.3, 131.0, 129.7, 129.4, 127.7, 113.9, 72.7, 70.4, 70.3, 62.3, 55.4, 45.1, 40.6, 37.9, 30.2, 27.1, 26.1, 26.1, 22.8, 22.0, 19.8, 19.4, 18.3, −3.9, −4.1; $[\alpha]_D^{23}$ −3.6 (*c* 2.7, $CHCl_3$); EIMS (*m*/*z*): 680 $(M+18)^+$; HRMS-ESI: calcd for $C_{40}H_{62}O_4NaSi_2$ 685.4084, found 685.4092; IR (neat): ν 2920, 2851, 1615, 1463, 1247, 1106, and 702 $cm^{-1}$.

#### 4.1.9. (3R,5R)-5-(tert-Butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)-3-methylnonan-1-ol (**12**)

To a solution of above fully protected triol **11** (1.2 g, 1.8 mmol) was added 10 mol % NaOH in methanol (20 mL) and stirred at reflux conditions for 6 h. After the completion of the reaction (indicated by TLC), methanol was removed on rotary evaporator. Then water (10 mL) was added to the reaction mass. The aqueous layer was extracted with dichloromethane (2×20 mL) and the combined organic layers were washed with brine (20 mL). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10% EtOAc in hexanes) to afford the free alcohol **12** as pale yellow oil (0.69 g, 90%). $R_f$ 0.35 (hexanes–ethyl acetate, 7:3, v/v).

$^1$H NMR (200 MHz, $CDCl_3$): δ 7.14 (d, *J*=8.7 Hz, 2H), 6.76 (d, *J*=8.7 Hz, 2H), 4.34 (s, 2H), 3.74 (s, 3H), 3.70–3.49 (m, 2H), 3.33 (t, *J*=6.5 Hz 3H), 1.69–1.06 (m, 11H), 0.85 (d, *J*=6.5 Hz, 3H), 0.82 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 158.0, 129.7, 128.2, 112.7, 71.4, 69.3, 69.0, 59.8, 54.2, 43.7, 39.1, 35.7, 28.8, 25.2, 24.9, 20.6, 19.2, 17.0, −5.1; $[\alpha]_D^{23}$ −15.9 (*c* 0.75, $CHCl_3$); EIMS (*m*/*z*): 447 $(M+Na)^+$; HRMS-ESI: calcd for $C_{24}H_{44}O_4NaSi$ 447.2906, found 447.2898; IR (neat): ν 3445, 2927, 2855, 1512, 1248, 1040, and 832 $cm^{-1}$.

#### 4.1.10. tert-Butyl ((3S,5R)-9-(4-methoxybenzyloxy)-3-methylnon-1-en-5-yloxy)dimethylsilane (**13**)

To a solution of primary alcohol **12** (1.6 g, 3.7 mmol) in acetonitrile/ether (20 mL, 3:1) were added slowly TPP (1.18 g, 4.5 mmol), iodine (1.15 g, 4.5 mmol), and imidazole (0.31 g, 4.6 mmol) in portionwise at 0 °C under nitrogen atmosphere, and stirred for 20 min. After completion of the reaction (monitored by TLC), solvent was removed on rotary evaporator and the reaction mass was quenched by adding aq saturated hypo solution (20 mL). The aqueous layer was extracted with dichloromethane (2×30 mL) and the combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The product was subjected to the next step without purification. To a stirred solution of the above-obtained iodo compound (1.8 g) in dry THF (20 mL) at 0 °C under nitrogen atmosphere was added KO$^t$Bu (0.75 g, 6.7 mmol) slowly and stirred for 30 min (reaction progress was monitored by TLC). The reaction was quenched with aq saturated $NH_4Cl$ (10 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (5% EtOAc in hexanes) to afford the olefin as colorless oil **12** (1.1 g, 78%). $R_f$ 0.36 (hexanes–ethyl acetate, 9:1, v/v).

$^1$H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, *J*=8.6 Hz, 2H), 6.79 (d, *J*=6.7 Hz, 2H), 5.72–5.56 (m, 1H), 4.96–4.82 (m, 2H), 4.37 (s, 2H), 3.76 (s, 3H), 3.72–3.52 (m, 1H), 3.37 (t, *J*=6.4 Hz, 2H), 2.27–2.10 (m, 1H), 1.60–1.26 (m, 8H), 0.95 (d, *J*=6.7 Hz, 3H), 0.85 (s, 9H), 0.01 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 159.3, 131.0, 129.4, 112.5, 72.6, 70.3, 55.4, 44.4, 37.0, 34.4, 30.1, 26.1, 21.9, 20.5, 18.3, −4.0; EIMS (*m*/*z*): 407 $(M+H)^+$; HRMS-ESI: calcd for $C_{24}H_{42}O_3NaSi$ 429.2800, found 429.2817; IR (neat): ν 3446, 2929, 2856, 1512, 1248, 1098, and 833 $cm^{-1}$.

#### 4.1.11. (3S,5R)-9-(4-Methoxybenzyloxy)-3-methylnon-1-en-5-ol (**I**)

To a solution of olefin silyl ether **13** (1.5 g, 3.6 mmol) in dry THF (30 mL) was added TBAF (1.92 g, 7.4 mmol, 1 M in THF) under nitrogen atmosphere at room temperature. The reaction was stirred for 2 h and quenched by adding aq saturated $NH_4Cl$ (10 mL). The reaction mixture was extracted with diethyl ether (2×25 mL). The combined organic layers were washed with brine (20 mL), dried ($Na_2SO_4$), and evaporated in vacuo, followed by purification on silica gel chromatography (15% ethyl acetate and hexanes) afforded the fragment **I** as pale yellow oil (0.92 g, 80%). $R_f$ 0.24 (hexanes–ethyl acetate, 4:1, v/v).

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J*=9.2 Hz, 2H), 6.87 (d, *J*=9.2 Hz, 2H), 5.90–5.60 (m, 1H), 5.12–5.84 (m, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.75–3.59 (m, 1H), 3.45 (t, *J*=5.8 Hz, 2H), 2.43–2.22 (m, 1H), 1.80–1.2 (m, 8H), 1.00 (d, *J*=6.7 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): 159.3, 145.3, 130.9, 129.4, 114.0, 113.1, 72.8, 70.4, 70.1, 55.4,

44.7, 44.4, 37.7, 35.7, 29.9, 26.2, 22.5, 20.5, 18.4; $[\alpha]_D^{23}$ +4.0 (*c* 1.1, $CHCl_3$); EIMS (*m*/*z*): 293 $(M+H)^+$, 315 $(M+Na)^+$; HRMS-ESI: calcd for $C_{18}H_{28}O_3Na$ 315.1756, found 315.1763; IR (neat): $\nu$ 3425, 2929, 2860, 1612, 1512, 1246, and 1096 $cm^{-1}$.

#### 4.1.12. Methyl (2S)-3-(tert-butyldiphenylsilyloxy)-2-methylpropionate (**15**)[5]

To a solution of (*S*)-(+)-Roche ester (5.44 g, 46.1 mmol) and imidazole (7.83 g, 48.4 mmol) in dry dichloromethane (55 mL) under nitrogen atmosphere was added dropwise TBDPSCl at 0 °C (13.6 mL, 48.4 mmol) in 10 min and the solution was stirred at room temperature for 1 h. The reaction was quenched by adding water (20 mL). The aqueous layer was extracted with dichloromethane (2×75 mL) and the combined organic layers were washed with brine (2×30 mL). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether 100% then 5% EtOAc in hexanes) to afford methyl (2*S*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropionate **15** as a pale yellow oil (16.38 g, 99%). $R_f$ 0.58 (hexanes–ethyl acetate, 9:1, v/v).

$^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.67–7.57 (m, 4H), 7.40–7.30 (m, 6H), 3.80 (dd, *J*=9.6, 6.9 Hz, 1H), 3.68 (dd, *J*=9.6, 5.7 Hz, 1H), 3.67 (s, 3H), 2.74–2.61 (m, 1H), 1.15 (d, *J*=7.0 Hz, 3H), 1.02 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 175.4, 135.6, 133.7, 129.7, 127.8, 66.0, 51.6, 42.4, 26.8, 19.3, 13.5; $[\alpha]_D^{23}$ +16.9 (*c* 1.1, $CHCl_3$); EIMS (*m*/*z*): 379 $(M+Na)^+$; HRMS-ESI: calcd for $C_{21}H_{28}O_3NaSi$ 379.1705, found 379.1699; IR (neat): $\nu$ 3100–2900, 1741, 1472, 1428, 1389, 1362, 1259, 1198, 1176, 1111, 823, 739, and 702 $cm^{-1}$.

#### 4.1.13. (R,E)-Ethyl 5-(tert-butyldiphenylsilyloxy)-4-methylpent-2-enoate (**16**)

To a solution of ester **15** (5.0 g, 14.1 mmol) in 50 mL of dry DCM was added DIBAL-H (20 mL, 28.2 mmol, 20% in hexanes) dropwise at −10 °C under nitrogen atmosphere. The reaction was stirred for 40 min and methanol (1 mL) was added at 0 °C slowly followed by the addition of aq saturated sodium-potassium tartarate solution (30 mL), the resulting reaction mixture was stirred for 2 h, excess of water (50 mL) was added, aqueous layer was extracted with dichloromethane (2×75 mL), and the combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (20% EtOAc in petroleum ether) to afford the alcohol as colorless oil (4.2 g, 88%). $R_f$ 0.25 (hexanes–ethyl acetate, 4:1, v/v).

$^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.71–7.60 (m, 4H), 7.46–7.32 (m, 6H), 3.77–3.50 (m, 4H), 2.39 (br s, 1H), 2.03–1.89 (m, 1H), 1.06 (s, 9H), 0.83 (d, *J*=7.0 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 135.6, 133.2, 129.8, 127.7, 68.6, 67.5, 60.3, 37.3, 26.8, 19.1, 13.1; $[\alpha]_D^{23}$ +6.0 (*c* 1.15, $CHCl_3$); EIMS (*m*/*z*): 351.1 $(M+Na)^+$; HRMS-ESI: calcd for $C_{20}H_{28}O_2NaSi$ 351.1756, found 351.1763; IR (neat): $\nu$ 3406, 3031, 2959, 2873, 2360, 1496, 1454, 1369, 1218, 1095, 1039, 772, and 698 $cm^{-1}$.

To a cold (−78 °C) solution of oxalyl chloride (2.32 g, 18.3 mmol) in dry dichloromethane (40 mL) was added dropwise dimethyl sulfoxide (1.9 g, 24.3 mmol) in dichloromethane (6 mL). The reaction mixture was stirred at −78 °C for 30 min and the above alcohol (4.0 g, 12.2 mmol) in dichloromethane (10 mL) was added dropwise. After 1 h, at −78 °C $Et_3N$ (4.96 g, 48.7 mmol) was added and stirring was continued for 15 min at the same temperature, and then warmed to room temperature. After the disappearance of alcohol (monitored by TLC), $Ph_3P{=}CHCOOEt$ (6.36 g, 18.3 mmol) was added to the reaction mixture, diluted with dichloromethane (15 mL), and then stirred for 1 h. The reaction was diluted with water (20 mL). The organic layer was separated, the aqueous layer was extracted with dichloromethane (2×75 mL), and the combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel chromatography (5% EtOAc in hexanes) to afford the two separable *cis* and *trans* esters in 5:95 ratio. The *trans*-α,β-unsaturated ester **16** was obtained in 89% (4.38 g) yield. $R_f$ 0.81 (hexanes–ethyl acetate, 9:1, v/v).

$^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.66–7.56 (m, 4H), 7.43–7.30 (m, 6H), 6.91 (dd, *J*=15.8, 7.5 Hz, 1H), 5.80 (dd, *J*=15.8, 1.5 Hz, 1H), 4.17 (q, *J*=14.3, 7.1 Hz, 2H), 3.60–3.53 (m, 2H), 2.61–2.42 (m, 1H), 1.29 (t, *J*=7.0 Hz, 3H), 1.12–1.01 (m, 12H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 167.0, 151.4, 135.0, 133.8, 129.2, 127.5, 121.0, 67.2, 60.2, 39.2, 26.4, 19.3, 15.8, 14.2; $[\alpha]_D^{23}$ +14.7 (*c* 1.0, $CHCl_3$); EIMS (*m*/*z*): 419.1 $(M+Na)^+$; HRMS-ESI: calcd for $C_{24}H_{32}O_3NaSi$ 419.2018, found 419.2003; IR (neat): $\nu$ 3416, 2978, 2861, 1717, 1652, 1454, 1366, 1269, 1184, 1098, 1036, 984, and 739 $cm^{-1}$.

#### 4.1.14. (R,E)-5-(tert-Butyldiphenylsilyloxy)-4-methylpent-2-en-1-ol (**17**)

To a solution of *trans*-α,β-unsaturated ester **16** (4.0 g, 9.5 mmol) in 50 mL of dry dichloromethane was added DIBAL-H (2.65 g, 20.2 mmol, 25% in hexanes) dropwise at −10 °C under nitrogen atmosphere. The reaction was stirred for 40 min, 1 mL of methanol was added at 0 °C slowly followed by the addition of 20 mL saturated sodium-potassium tartarate solution, and the resulting reaction mixture was stirred for 2 h and excess of water (50 mL) was added. The aqueous layer was extracted with dichloromethane (2×75 mL) and the combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (20% EtOAc in hexanes) to afford the *trans*-allylic alcohol **17** as colorless oil (3.1 g, 91%). $R_f$ 0.32 (hexanes–ethyl acetate, 7:3, v/v).

$^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.66–7.58 (m, 4H), 7.42–7.28 (m, 6H), 5.64–5.54 (m, 2H), 4.07–3.95 (m, 2H), 3.57–3.43 (m, 2H), 2.50–2.27 (m, 1H), 1.05 (s, 9H), 1.03 (d, *J*=6.9 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 135.6, 135.4, 133.9, 129.6, 128.8, 127.5, 68.4, 63.9, 38.9, 27.0, 19.4, 16.3; $[\alpha]_D^{23}$ +3.1 (*c* 1.0, $CHCl_3$); EIMS (*m*/*z*): 377.1 $(M+Na)^+$; HRMS-ESI: calcd for $C_{22}H_{30}O_2NaSi$ 377.1912, found 377.1918; IR (neat): $\nu$ 3409, 3030, 2961, 2865, 1616, 1496, 1454, 1362, 1218, 1095, 1027, 973, 771, and 698 $cm^{-1}$.

#### 4.1.15. (R)-5-(tert-Butyldiphenylsilyloxy)-4-methylpentan-1-ol (**18**)

To a solution of allyl alcohol **17** (4.1 g, 10.6 mmol) and Pd–C 5% (1.0 g) in EtOAc (40 mL) was bubbled $H_2$ for 4 h. The solution was then filtered over Celite and the filter cake was washed with EtOAc (2×10 mL). Evaporation of the solvent afforded the saturated alcohol **18** as colorless oil (3.9 g, 90%). $R_f$ 0.35 (hexanes–ethyl acetate, 7:3, v/v).

$^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.72–7.58 (m, 4H), 7.43–7.30 (m, 6H), 3.68 (t, *J*=5.8 Hz, 2H), 3.53 (t, *J*=5.4 Hz, 2H), 1.71–1.22 (m, 7H), 1.04 (s, 9H), 0.86 (d, *J*=6.9 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 135.6, 134.0, 129.5, 127.6, 68.7, 63.3, 35.5, 30.1, 29.1, 26.9, 19.3, 16.8; EIMS (*m*/*z*): 407.0 $(M+Na)^+$; HRMS-ESI: calcd for $C_{23}H_{32}O_3NaSi$ 407.2018, found 407.2021; IR (neat): $\nu$ 3409, 3030, 2961, 1454, 1362, 1218, 1027, 973, 771, and 698 $cm^{-1}$.

#### 4.1.16. (S,E)-N-((R)-5-(tert-Butyldiphenylsilyloxy)-4-methylpentylidene)-2-(methoxymethyl)pyrrolidin-1-amine (**19**)

To a solution of iodoxybenzoic acid (3.8 g, 14.1 mmol) in DMSO (6 mL) was added the alcohol **18** (2.3 g, 9.4 mmol) in THF (20 mL) and allowed to stir for 3 h at room temperature. After completion of the reaction, the reaction mixture was filtered through a pad of Celite and washed with ether (200 mL). The filtrate was washed with aq sodium bicarbonate (2×20 mL), water (20 mL), brine (20 mL), dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. The crude product was subjected to hydrazone formation without purification (2.0 g, 92% yield). $R_f$ 0.62 (hexanes–ethyl acetate, 9:1, v/v).

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 9.74 (s, 1H), 7.74–7.53 (m, 4H), 7.47–7.30 (m, 6H), 3.51 (d, $J$=5.5 Hz, 2H), 2.46–2.28 (m, 2H), 1.96–1.31 (m, 3H), 1.10 (s, 9H), 0.96 (d, $J$=6.6 Hz, 3H); EIMS ($m/z$): 377.1 $(M+Na)^+$; HRMS-ESI: calcd for $C_{22}H_{30}O_2NaSi$ 377.1912, found 377.1918.

To a cooled solution (0 °C) of (*S*)-1-amino-2-(methoxymethyl) pyrrolidine (SAMP) (1.0 g, 8.3 mmol) in dry dichloromethane (10 mL), molecular sieves (4 Å, 1.0 g) and the above aldehyde (3.12 g, 8.6 mmol) were added sequentially under nitrogen atmosphere. The mixture was stirred at room temperature for 20 h and diluted with dichloromethane (15 mL), and filtered. The filtrate was dried over $Na_2SO_4$ and concentrated in vacuo to give a pale yellow oil, which was purified by silica gel chromatography (20% EtOAc in petroleum ether) to afford the hydrazone **19** as pale yellow oil (3.72 g, 96%). $R_f$ 0.32 (hexanes–ethyl acetate, 7:3, v/v).

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.66–7.58 (m, 4H), 7.40–7.30 (m, 6H), 6.51 (t, $J$=5.8 Hz, 1H), 3.57–3.40 (m, 3H), 3.37–3.25 (m, 5H), 2.72–2.60 (m, 1H), 2.30–2.01 (m, 2H), 2.01–1.44 (m, 7H), 1.40–1.18 (m, 1H), 1.04 (s, 9H), 0.95 (d, $J$=6.8 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 144.3, 135.4, 134.0, 129.4, 127.6, 74.6, 68.5, 63.7, 59.2, 50.4, 38.3, 34.6, 33.0, 27.2, 26.3, 22.1, 19.6, 16.9; $[\alpha]_D^{23}$ −62.8 (*c* 1.0, $CHCl_3$); EIMS ($m/z$): 466 ($M^+$+1), 489 $(M+Na)^+$; IR (neat): $\nu$ 3359, 3295, 3025, 2949, 2839, 2710, 2607, 1599, 1465, 1388, 1257, 1177, 905, 771, and 688 cm$^{-1}$.

#### 4.1.17. (S,E)-N-((2S,4R)-5-(tert-Butyldiphenylsilyloxy)-2,4-dimethylpentylidene)-2-(methoxymethyl)pyrrolidin-1-amine (**20**)

A flame dried 100 mL two-neck round bottom flask with side arm, rubber septum, and magnetic stirring bar is furnished with nitrogen. The flask was then cooled to 0 °C, and 40 mL of dry ether and dry diisopropyl amine (0.94 g, 9.1 mmol) were added followed by dropwise addition of *n*-butyllithium (0.51 g, 7.7 mmol, 1.6 M solution in hexanes) at 0 °C under nitrogen atmosphere. Stirring is continued for 10 min and a solution of SAMP-hydrazone **19** (3.12 g, 6.4 mmol) in 10 mL of dry ether was added to the stirred mixture over a 5 min period at 0 °C. An additional 5 mL of ether was used to transfer all of the hydrazone into the reaction flask. Stirring is continued for 4 h at 0 °C, while the lithiated hydrazone precipitates. The reaction mixture was cooled to −100 °C (diethyl ether–dry ice bath) and kept for 10 min at this temperature. Then, methyl iodide (2 mL, 19.3 mmol) was added dropwise, and the mixture was allowed to warm to room temperature and stirred for overnight. The contents of the flask were poured into a mixture of ether (100 mL) and water (30 mL) in a separating funnel, the layers were separated, and the aqueous layer was extracted with ether (2×25 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (20% EtOAc in petroleum ether) to afford 2,4-*syn*-dimethyl hydrazone **20** as pale yellow oil (3.18 g, 92%). $R_f$ 0.35 (hexanes–ethyl acetate, 7:3, v/v).

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.68–7.60 (m, 4H), 7.42–7.30 (m, 6H), 6.38 (d, $J$=6.0 Hz, 1H), 3.56–3.42 (m, 3H), 3.38–3.20 (m, 5H), 2.73–2.58 (m, 1H), 2.44–2.29 (m, 1H), 2.00–1.81 (m, 2H), 1.80–1.67 (m, 2H), 1.49–1.37 (m, 2H), 1.32–1.17 (m, 2H), 1.05 (s, 9H), 0.99 (d, $J$=6.8 Hz, 3H), 0.93 (d, $J$=6.8 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): 144.5, 135.5, 134.1, 129.3, 127.6, 74.7, 68.7, 63.5, 59.1, 50.2, 38.8, 34.7, 33.2, 27.0, 26.5, 22.0, 19.3, 18.9, 17.0; $[\alpha]_D^{23}$ −62.9 (*c* 1.0, $CHCl_3$); HRMS-ESI: calcd for $C_{29}H_{45}N_2O_2Si$ 481.3250, found 481.3264; IR (neat): $\nu$ 3425, 2929, 2860, 1612, 1512, 1246, and 1096 cm$^{-1}$.

#### 4.1.18. tert-Butyl ((2R,4S)-2,4-dimethylhex-5-enyloxy)-diphenylsilane (**21**)[3,4]

The methylated SAMP-hydrazone **20** (1.5 g, 3.1 mmol) was dissolved in dichloromethane (20 mL) and cooled to −78 °C (acetone–dry ice bath). Dry ozone gas is passed through the reaction mixture until the solution turns blue. The mixture was then warmed to room temperature and nitrogen was bubbled into the solution to quench excess of ozone. Water (20 mL) was added to the solution and extracted with dichloromethane (3×20 mL). The combined organic layers were washed with 10 mL of brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to give the crude aldehyde (1.1 g, 3.1 mmol) as light yellow color liquid. The crude product was subjected to Wittig methylation. To the suspension of methyltriphenylphosphonium iodide (3.6 g, 8.9 mmol) in dry THF (30 mL) at 0 °C, KO$^t$Bu (1.0 g, 8.8 mmol) was added slowly under nitrogen atmosphere. The reaction mixture became yellowish and it was stirred for 30 min and cooled to −78 °C. The above aldehyde (1.1 g, 2.9 mmol) in THF (5 mL) was added slowly to the yellow phosphorane solution. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was quenched with (10 mL) aq saturated $NH_4Cl$ solution and extracted into ethyl acetate (2×20 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (5% EtOAc in petroleum ether) to afford the olefin compound **21** as colorless oil (0.82 g, 83%). $R_f$ 0.73 (hexanes–ethyl acetate, 9:1, v/v).

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.75–7.72 (m, 4H), 7.49–7.35 (m, 6H), 5.62 (ddd, $J$=17.0, 10.0, and 8.0 Hz, 1H), 4.95–4.91 (m, 2H), 3.56–3.48 (m, 2H), 2.28–2.10 (m, 1H), 1.80–1.65 (m, 1H), 1.52–1.34 (m, 3H), 1.13 (s, 9H), 0.92 (d, $J$=7.0 Hz, 3H), 0.90 (d, $J$=7.0 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 145.4, 135.8, 134.3, 129.7, 127.7, 112.3, 68.8, 40.4, 35.4, 33.4, 27.1, 20.4, 19.5, 17.6; $[\alpha]_D^{23}$ +6.1 (*c* 0.6, $CHCl_3$); EIMS: ($m/z$) 367 $(M+H)^+$; HRMS-ESI calcd for $C_{24}H_{34}ONaSi$ 389.2379, found 389.2370; IR (neat): $\nu$ 3031, 2980, 2928, 1661, 1596, 1485, 1363, 1285, 1175, 912, and 747 cm$^{-1}$.

#### 4.1.19. (2R,4S)-2,4-Dimethylhex-5-enoic acid (**II**)[3–7]

To a solution of silyl ether **21** (1.74 g, 4.7 mmol) in 20 mL dry THF was added TBAF (9.5 mL, 1 M in THF, 9.5 mmol) under nitrogen atmosphere at room temperature. The reaction was stirred for 2 h and quenched by adding aq saturated $NH_4Cl$ (10 mL). The aqueous layer was extracted with diethyl ether (2×30 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$, filtered, and concentrated on rotary evaporator to obtain the crude alcohol, which was oxidized without further purification. The crude alcohol was dissolved in DMF (35 mL) at 0 °C and PDC (17.8 g, 47.5 mmol) was added. The resulting orange solution was stirred for 30 min at 0 °C and allowed to warm to room temperature for 24 h. Water (30 mL) and EtOAc (30 mL) were added to the reaction mixture and the organic layer was separated. The organic layer was washed with water (2×20 mL) and brine (20 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (30% EtOAc in petroleum ether) to afford acid **II** as colorless oil (513 mg, 70%). $R_f$ 0.25 (hexanes–ethyl acetate, 7:3, v/v).

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 10.8 (br s, 1H), 5.62 (ddd, $J$=17.0, 10.0, and 8.0 Hz, 1H), 5.10–4.90 (m, 2H), 2.62–2.42 (m, 1H), 2.10–2.30 (m, 1H), 1.82–1.62 (m, 1H), 1.41–1.21 (m, 1H), 1.18 (d, $J$=7.0 Hz, 3H), 1.02 (d, $J$=7.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 183.7, 143.7, 113.9, 40.5, 37.5, 36.3, 20.7, 16.8; $[\alpha]_D^{23}$ −6.7 (*c* 1.4, $CHCl_3$); EIMS ($m/z$): 142 $(M+H)^+$; HRMS-ESI: calcd for $C_8H_{13}O_2$ 141.0916, found 141.0920; IR (neat): $\nu$ 3450 (br), 3050, 1707, 1460, 1417, 1243, 914, and 684 cm$^{-1}$.

#### 4.1.20. ((2S,3S)-3-((S)-1-(tert-Butyldiphenylsilyloxy)propan-2-yl) oxiran-2-yl)methanol (**22**)

To a cold (−23 °C) solution of 4 Å molecular sieves (5.0 g) and titanium tetraisopropoxide (1.5 g, 1.0 mmol) in dry dichloromethane (30 mL) was added a solution of L-(+)-diethyl tartarate (1.03 g, 1.0 mmol) in 8 mL of dichloromethane. After 30 min at

−23 °C, allylic alcohol **17** (9.28 g, 4.5 mmol) in 20 mL of dichloromethane was added and stirred for 30 min, then 4 M anhydrous TBHP (5 mL, 10.0 mmol) in toluene was added. The resulting mixture was stirred at (−23 °C) for 3 h and warmed to room temperature. The reaction mixture was quenched with 3 mL of water at 0 °C and stirred for 1 h, and then 2 mL of 20% NaOH solution was added and vigorously stirred for 90 min. The reaction mass was filtered through a Celite pad and washed with 3×50 mL of dichloromethane. The organic layer was separated and washed with brine (2×20 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (30% EtOAc in hexanes as eluent.) to afford optically active epoxide **22** as colorless oil (8.8 g, 88%). $R_f$ 0.23 (hexanes–ethyl acetate, 7:3, v/v).

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.67–7.57 (m, 4H), 7.44–7.30 (m, 6H), 3.86 (ddd, $J$=17.8, 12.4, 5.3 Hz, 1H), 3.74–3.51 (m, 3H), 2.98–2.89 (m, 2H), 1.75–1.60 (m, 1H), 1.06 (s, 9H), 0.99 (d, $J$=6.9 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 136.2, 134.2, 130.2, 128.2, 66.5, 62.5, 58.1, 57.5, 38.3, 27.4, 19.9, 14.7; $[\alpha]_D^{23}$ −5.6 ($c$ 1.0, $CHCl_3$); EIMS ($m/z$): 393.1 $(M+Na)^+$; HRMS-ESI: calcd for $C_{22}H_{30}O_3NaSi$ 393.1861, found 393.1856; IR (neat): $\nu$ 3414, 2362, 1618, 1454, 1101, and 614 cm$^{-1}$.

#### 4.1.21. (2R,3R,4S)-5-(tert-Butyldiphenylsilyloxy)-2,4-dimethylpentane-1,3-diol (**23**)

To a cold (−23 °C) suspension of copper iodide (1.52 g, 8 mmol) in dry ether (20 mL), MeLi (0.37 g, 16.0 mmol, 1.6 M in ether) was added dropwise under nitrogen atmosphere until it became a colorless solution. After 30 min at this temperature, the solution was cooled to −40 °C and then epoxide **22** (0.45 g, 1.2 mmol) in 5 mL of dry ether was added dropwise. After being stirred for 5 h at −40 °C and warmed to −23 °C, the reaction mixture was quenched by adding the mixture of saturated $NH_4Cl$ (20 mL) and 28% aq $NH_4OH$ (20 mL) in dropwise passion. The blue aqueous layer was washed with (3×50 mL) of dichloromethane. The organic layer was separated and washed with brine (20 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (30% EtOAc in petroleum ether as eluent) to afford the triol **23** as pale yellow oil (1.12 g, 76%). $R_f$ 0.25 (hexanes–ethyl acetate, 3:2, v/v).

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.72–7.63 (m, 4H), 7.49–7.35 (m, 6H), 4.28 (br s, 1H), 3.91–3.78 (m, 2H), 3.70–3.46 (m, 3H), 2.01–1.78 (m, 2H), 1.09 (s, 9H), 1.00–0.94 (m, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 135.6, 132.4, 128.4, 127.5, 73.2, 68.2, 67.8, 36.5, 36.8, 27.1, 19.0, 14.2, 14.1; $[\alpha]_D^{23}$ +13.4 ($c$ 1.1, $CHCl_3$); EIMS ($m/z$): 409.2 $(M+Na)^+$; HRMS-ESI: calcd for $C_{23}H_{34}O_3NaSi$ 409.2174, found 409.2170; IR (neat): $\nu$ 3425, 2967, 2876, 1454, 1080, 979, and 752 cm$^{-1}$.

#### 4.1.22. (2R,3R,4S)-1-(Benzyloxy)-5-(tert-butyldiphenylsilyloxy)-2,4-dimethylpentan-3-ol (**24**)

The 1,3-diol **23** (0.9 g, 1.0 mmol) in THF (20 mL) was added to a suspension of NaH (0.17 g, 2.0 mmol) in THF (20 mL) at 0 °C. After the mixture was stirred for 30 min, benzyl bromide (0.40 g, 1.0 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with 10 mL of aq saturated $NH_4Cl$ at 0 °C and extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10% EtOAc in petroleum ether as eluent) to afford the mono benzyl ether **24** as colorless oil (1.02 g, 90%). $R_f$ 0.34 (hexanes–ethyl acetate, 4:1, v/v).

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.86–7.63 (m, 4H), 7.41–7.21 (m, 11H), 4.46 (s, 2H), 3.70 (d, $J$=5.7 Hz, 2H), 3.60–3.45 (m, 2H), 3.39 (q, $J$=10.6, 6.1 Hz, 1H), 2.05–1.95 (m, 1H), 1.93–1.82 (m, 1H), 1.06 (s, 9H), 0.94 (dd, $J$=8.6, 6.9 Hz, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 138.5, 135.6, 133.6, 129.6, 128.4, 127.7, 127.6, 127.4, 73.2, 72.1, 72.0, 64.7, 37.8, 35.5, 26.8, 19.2, 14.7, 14.2; $[\alpha]_D^{23}$ +3.1 ($c$ 0.5, $CHCl_3$); EIMS ($m/z$): 499.3 $(M+Na)^+$; HRMS-ESI: calcd for $C_{30}H_{40}O_3NaSi$ 499.2644, found 499.2654; IR (neat): $\nu$ 3417, 1618, 1111, 794, and 613 cm$^{-1}$.

#### 4.1.23. ((2R,4S)-5-(Benzyloxy)-2,4-dimethylpentyloxy)(tert-butyl)diphenylsilane (**25**)

To a solution of protected triol **24** (1.17 g, 3 mmol) in 15 mL of dry THF under nitrogen at −78 °C was added *n*-BuLi (2.29 mL. 3.66 mmol, 1.6 M in hexanes) dropwise. The solution was stirred for 30 min at −78 °C, and then *p*-TsCl (0.69 g, 6.6 mmol) was added in small portions. After 10 min, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. Cold (0 °C) water (20 mL) was then added. After the mixture was stirred for 10 min, the layers were separated and the aqueous layer was extracted with ether (3×20 mL). The combined organic layers were washed successively with 30 mL portions of 0.5 N HCl, aq saturated $NaHCO_3$ (20 mL), and brine (20 mL). The solution was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to give 1.61 g (98% yield) of the crude tosylate as pale yellow liquid. This intermediate was used in the next reaction without further purification. EIMS ($m/z$): 648.2 ($M^+$+18). To a solution of the resulted tosylate compound (0.54 g, 1.0 mmol) in 10 mL of dry THF under nitrogen atmosphere was added $LiAlH_4$ (0.11 g, 3.0 mmol). The resulting mixture was heated to reflux for 1.5 h. After being cooled to 0 °C, the reaction mixture was treated with 10 mL of cold brine (added dropwise). After the mixture was stirred for 15 min, the layers were separated and the aqueous layer was extracted with ether (2×20 mL). The organic layers were washed with brine (20 mL), dried over $Na_2SO_4$, filtered, concentrated under reduced pressure, and purified on silica gel column chromatography (5% ethyl acetate and hexanes) to give 0.23 g (64% yield) of **25** as pale yellow oil. $R_f$ 0.72 (hexanes–ethyl acetate, 9:1, v/v).

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.65–7.59 (m, 4H), 7.44–7.28 (m, 11H), 4.43 (s, 2H), 3.52–3.45 (m, 1H), 3.42–3.33 (m, 1H), 3.31–3.21 (m, 1H), 3.18–3.09 (m, 1H), 1.84–1.64 (m, 2H), 1.55–1.40 (m, 1H), 1.32–1.16 (m, 1H), 1.04 (s, 9H), 0.94 (d, $J$=6.8 Hz, 3H), 0.89 (d, $J$=6.8 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 138.8, 135.6, 134.0, 129.5, 128.3, 127.6, 127.4, 127.4, 76.0, 72.9, 68.8, 37.8, 33.2, 31.0, 26.9, 19.3, 18.1, 17.9; $[\alpha]_D^{23}$ +1.6 ($c$ 2.8, $CHCl_3$); EIMS ($m/z$): 483.2 $(M+Na)^+$; HRMS-ESI: calcd for $C_{30}H_{40}O_2NaSi$ 483.2695, found 483.2711; IR (neat): $\nu$ 2924, 2854, 1463, 1108, 1033, 702, and 504 cm$^{-1}$.

#### 4.1.24. (2S,4R)-5-(tert-Butyldiphenylsilyloxy)-2,4-dimethylpentan-1-ol (**26**)

To a solution of the benzyl ether **25** (230 mg, 0.5 mmol) and 5% Pd–C (6 mg) in EtOAc (3 mL) was bubbled $H_2$ for 4 h. The solution was then filtered over Celite and the filter cake was washed with EtOAc (2×5 mL). Evaporation of the solvent afforded the alcohol **27** as colorless oil (170 mg, 92%). $R_f$ 0.34 (hexanes–ethyl acetate, 7:3, v/v).

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.68–7.59 (m, 4H), 7.44–7.25 (m, 6H), 3.55–3.31 (m, 4H), 1.9–1.5 (m, 4H), 1.3–1.1 (m, 2H), 1.04 (s, 9H), 0.91 (t, $J$=6.8 Hz, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 135.6, 134.8, 129.7, 127.7, 69.5, 68.9, 36.7, 33.0, 26.9, 19.3, 16.6, 16.4; $[\alpha]_D^{23}$ +1.1 ($c$ 0.75, $CHCl_3$); EIMS ($m/z$): 393.2 $(M+Na)^+$; HRMS-ESI calcd for $C_{23}H_{34}O_4NaSi$ 393.2287, found 393.2300; IR (neat): $\nu$ 3415, 2924, 2854, 1707, 1463, 1108, 1033, 702, and 504 cm$^{-1}$.

#### 4.1.25. (S)-2-(tert-Butoxycarbonyl(methyl)amino)-3-phenylpropanoic acid or (S)-N-Boc-N-methylphenylalanine (***III***)[3–6]

To a solution of *N*-Boc-phenylalanine (6.1 g, 22.6 mmol) in dry THF (70 mL) at 0 °C under argon was added NaH (60 wt % in mineral oil, 2.7 g, 68 mmol). After stirring for 30 min at 0 °C, MeI (11 mL, 180 mmol) was added. The reaction was allowed to warm to room temperature and stirring continued for 18 h. The reaction mixture

was quenched with water (2 mL) and then concentrated under reduced pressure. The residue was diluted with water (15 mL), washed twice with $Et_2O$ (15 mL), and the ethereal solution was washed with 15 mL of 10% $NaHCO_3$. The aqueous layer was acidified with HCl (0.1 N) until pH=1–2 and extracted with EtOAc (4×50 mL). The organic layer was then washed with brine (50 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to give (*S*)-*N*-Boc-*N*-methylphenylalanine **III** as a light yellow viscous oil (6.4 g, quantitative). $R_f$ 0.35 (hexanes–ethyl acetate, 4:1, v/v).

$^1$H NMR (400 MHz, $CDCl_3$): (2 rotamers in a 1:1 ratio) $\delta$ 9.95 (br s, 1H), 7.33–7.16 (m, 2H), 7.21–7.00 (m, 3H), 4.85 (dd, *J*=11.0, 5.0 Hz, 0.5H), 4.63 (dd, *J*=11.0, 4.5 Hz, 0.5H), 3.40–3.20 (m, 1H), 3.15–2.98 (m, 1H), 2.76 (s, 1.5H), 2.69 (s, 1.5H), 1.39 (s, 4.5H), 1.33 (s, 4.5H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 76.3, 156.4, 137.5, 129.1, 128.7, 126.8, 80.8, 61.5, 35.3, 32.9, 28.3; $[\alpha]_D^{23}$ −67.5 (*c* 2.1, $CHCl_3$); IR (neat): $\nu$ 2976 (br), 1740, 1695, 1480, 1454, 1392, 1367, 1322, 1253, 1155, 1080, 961, 862, 700, and 666 cm$^{-1}$.

#### 4.1.26. *(S)-((3S,5R)-9-(4-Methoxybenzyloxy)-3-methylnon-1-en-5-yl)-2-(tert-butoxycarbonyl(methyl)amino)-3-phenylpropanoate (**27**)*

To a stirred solution of *N*-Boc-*N*-methyl-phenylalanine **III** (524 mg, 1.88 mmol) in dry toluene (10 mL) were added 2,4,6-trichlorobenzoyl chloride (500 mg, 2.0 mmol) and diisopropylethyl amine (0.7 mL, 5.1 mmol). The mixture was stirred at room temperature for 20 min, diluted with toluene (2 mL), and added dropwise over a period of 3 min to a solution of DMAP (208 mg, 1.7 mmol) in toluene (6 mL) followed by the addition of compound **I** (568 mg, 1.88 mmol) in 5 mL of toluene. After complete addition, the mixture was stirred for an additional 1 h and concentrated in vacuo. Purification of the residue by silica gel flash chromatography (EtOAc–hexanes, 1:10) gave the ester **27** (831 mg, 88%). $R_f$ 0.46 (hexanes–ethyl acetate, 4:1, v/v).

$^1$H NMR (300 MHz, $CDCl_3$): (2 rotamers) $\delta$ 7.38–7.16 (m, 7H), 6.82 (dd, *J*=8.6, 3.0 Hz, 2H), 5.76–5.55 (m, 1H), 5.03–4.65 (m, 3H), 4.39 (s, 2H), 3.77 (s, 3H), 3.45–3.33 (m, 2H), 3.31–3.14 (m, 1H), 3.10–2.82 (m, 1H), 2.80–2.62 (m, 4H), 2.24–1.96 (m, 1H), 1.79–1.45 (m, 4H), 1.42–1.17 (m, 13H), 0.98 (q, *J*=13.2, 6.6 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 171.1, 170.8, 159.2, 155.7, 155.2, 144.0, 143.7, 137.7, 137.6, 130.7, 129.3, 128.2, 126.7, 126.5, 113.1, 112.8, 80.1, 79.8, 73.8, 72.6, 69.8, 60.8, 59.8, 40.6, 35.2, 35.1, 34.7, 34.6, 34.1, 33.9, 32.2, 29.7, 29.6, 21.9, 21.8, 20.3; $[\alpha]_D^{23}$ +4.6 (*c* 2.0, $CHCl_3$); EIMS (*m*/*z*): 576.4 (M+Na)$^+$; HRMS-ESI: calcd for $C_{33}H_{47}O_6Na$ 576.3301, found 576.3320; IR (neat): $\nu$ 2828, 2858, 1735, 1697, 1512, 1455, 1391, 1366, 1324, 1248, 1172, 1142, 1096, 750, and 699 cm$^{-1}$.

#### 4.1.27. *(S)-((3S,5R)-9-(4-Methoxybenzyloxy)-3-methylnon-1-en-5-yl)-3-phenyl-2-((2R,4S)-N-2,4-trimethylhex-5-enamido)propanoate (**2**)*

To a stirred solution of compound **27** (0.54 g, 1.0 mmol) and 2,6-lutidine (0.217 g, 2.0 mmol) in dry dichloromethane (15 mL) at room temperature was added dropwise *tert*-butyldimethylsilyltrifluoromethane sulfonate (*tert*-$BuMe_2SiOTf$; 0.38 g, 1.5 mmol). The reaction mixture was stirred for 15 min, quenched with saturated aq $NH_4Cl$ solution, and extracted with dichloromethane (3×30 mL). The combined organic layers were washed with water (2×20 mL), brine (20 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give OTBS ester, which was further subjected to silyl deprotection without purification. To a stirred solution of OTBS ester obtained by above procedure, in dry THF (10 mL), at room temperature was added TBAF (1 M in THF, 0.52 g, 2.0 mmol). The reaction mixture was stirred for 1 h, quenched with 10 mL of saturated aq $NH_4Cl$ solution, and extracted with ethyl acetate (3×10 mL). The combined organic phase was washed with water (2×20 mL), brine (20 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give the crude amine as colorless oil (0.38 g, 90%), which was subjected to the next reaction without purification. $R_f$ 0.15 (hexanes–ethyl acetate, 2:1, v/v).

$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.40–7.10 (m, 7H), 6.86 (dd, *J*=8.5, 14.3 Hz, 2H), 5.80–5.55 (m, 1H), 5.0–4.88 (m, 3H), 4.42 (s, 2H), 3.80 (s, 3H), 3.50–3.30 (m, 3H), 3.00–2.89 (m, 2H), 2.36 (s, 3H), 2.25–1.96 (m, 1H), 1.70–1.10 (m, 8H), 0.94 (dd, *J*=14.3, 6.2 Hz, 3H); EIMS (*m*/*z*): 454.2 (M+H)$^+$.

To a solution of the above-obtained crude amine, carboxylic acid fragment **II** (110 mg, 0.8 mmol) in $CH_2Cl_2$ (12 mL), was added HOBt (15 mg, 0.1 mmol) followed by EDCI (477 mg, 2.5 mmol). The reaction was stirred for 6 h at room temperature, quenched with HCl (1 N, 15 mL), and diluted with $Et_2O$ (20 mL). The aqueous layer was extracted with $Et_2O$ (20 mL) and the resulting solution washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10% $Et_2O$ in petroleum ether) to afford diene **2** as colorless oil (141 mg, 76%). $R_f$ 0.65 (hexanes–ethyl acetate, 2:1, v/v).

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.32–7.11 (m, 7H), 6.82 (dd, *J*=8.6, 3.0 Hz, 2H), 5.78–5.28 (m, 3H), 5.04–4.76 (m, 4H), 4.42 (s, 2H), 3.80 (s, 3H), 3.49–3.35 (m, 3H), 3.12–2.86 (m, 2H), 2.80 (s, 3H), 2.65–2.44 (m, 1H), 2.25–1.94 (m, 1H), 1.88–1.50 (m, 6H), 1.49–1.18 (m, 5H), 1.10–0.90 (m, 6H), 0.83 (d, *J*=6.8 Hz, 1.5H), 0.65 (d, *J*=6.8 Hz, 1.5H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 177.0, 170.4, 158.7, 144.6, 143.7, 137.0, 130.6, 129.3, 129.2, 128.9, 128.8, 128.3, 113.7, 112.6, 73.7, 72.4, 69.8, 65.2, 55.4, 41.0, 40.7, 36.7, 35.1, 34.2, 33.8, 33.5, 29.8, 21.8, 21.2, 20.1, 17.8; $[\alpha]_D^{23}$ −18.0 (*c* 2.0, $CHCl_3$); EIMS (*m*/*z*): 600.3 (M+Na)$^+$; IR (neat): $\nu$ 2975, 2932, 1736, 1695, 1512, 1245, 1174, and 1036 cm$^{-1}$.

#### 4.1.28. *(3S,6R,8R,11R,13R)-3-Benzyl-13-(4-hydroxy-butyl)-4,6,8,11-tetramethyl-1-oxa-4-azacyclotridecane-2,5-dione (**28**)*

To a solution of diene **2** (14 mg, 0.002 mmol) in dry $CH_2Cl_2$ (80 mL) under nitrogen atmosphere was added Grubbs second generation catalyst **A** (4 mg, 0.02 mmol), and the solution was stirred at reflux for 12 h, a second portion of the catalyst (4 mg, 0.002 mmol) was added, the reflux was continued for another 6 h, then filtered, and the solvent was evaporated to yield the macrolide (*E*/*Z* >10:1). This crude compound was subjected to hydrogenation without further purification. $R_f$ 0.56 (hexanes–ethyl acetate, 2:1, v/v).

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.32–7.28 (m, 5H), 7.22–7.15 (m, 2H), 6.90–6.84 (m, 2H), 5.28–5.04 (m, 2H), 5.01–4.76 (m, 1H), 4.41 (dd, *J*=8.1, 10.1 Hz, 2H), 3.78 (s, 3H), 3.50–3.35 (m, 4H), 3.06–2.95 (m, 1H), 2.93–2.80 (m, 1H), 2.78 (s, 3H), 2.60–2.42 (m, 1H), 2.38–2.30 (m, 1H), 2.05–2.18 (m, 1H), 1.70–1.45 (m, 6H), 1.42–1.31 (m, 1H), 1.31–1.00 (m, 2H), 0.99–0.85 (m, 7H), 0.68 (d, *J*=7.1 Hz, 2H); EIMS (*m*/*z*): 572.3 (M+Na)$^+$; IR (neat): $\nu$ 2960, 1737, 1638, 1513, 1247, 1100, 910, and 726 cm$^{-1}$.

To a solution of the above-obtained MPM protected macrocyclic olefin (10.5 mg, 0.02 mmol) and 5% Pd–C (10 mg) in EtOAc (3 mL) was bubbled $H_2$ for 12 h. The solution was then filtered over Celite and the filter cake was washed with EtOAc (2×5 mL). Evaporation of the solvent afforded the hydrogenated macrolactam **28** as colorless oil (6 mg, 80%). $R_f$ 0.24 (hexanes–ethyl acetate, 2:1, v/v).

The spectral data of this macrolactam matched in all respects with the reported data.[3,4]

$^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.32–7.22 (m, 3H), 7.21–7.15 (m, 2H), 5.28–5.22 (m, 1H), 3.67 (t, *J*=6.4 Hz, 2H), 3.58–3.48 (m, 2H), 3.32–3.25 (m, 1H), 3.00–2.90 (m, 1H), 2.86 (s, 3H), 1.95–1.78 (m, 1H), 1.66–1.18 (m, 13H), 1.16–0.99 (m, 3H), 0.94 (d, *J*=7.1 Hz, 3H), 0.91–0.78 (m, 6H); $^{13}$C NMR (300 MHz, $CDCl_3$): 178.6, 170.2, 138.8, 129.5, 128.4, 126.5, 74.2, 65.2, 62.1, 41.3, 40.8, 37.4, 35.5, 34.3, 33,4, 32.6, 32.2, 32.4, 29.6, 28.3, 23.6, 23,4, 22.5, 21.7, 21.4, 18.8; $[\alpha]_D^{23}$ −186 (*c* 0.4, $CHCl_3$); HRMS-ESI: calcd for $C_{26}H_{41}NO_4Na$ 454.2933, found 454.2941; IR (neat): $\nu$ 3434, 3027, 2925, 2854, 1735, 1632, 1452, 1275, 1213, and 1076 cm$^{-1}$.

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