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Formal synthesis of amphidinin B

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ABSTRACT

An efficient, convergent, and highly stereoselective formal synthesis of amphidinin B (**1**) is reported herein. In Amphidinin B both C10–C21 (**4**) and C1–C9 (**5**) fragments were derived from geraniol **6** and mono-PMB ether of 1,4-butane diol **7** in 19 and 9 steps, respectively. The key steps involved in this synthesis are Sharpless asymmetric epoxidation, Evans aldol, Julia olefination, oxa-Michael, Keck allylation, Mannich reaction, Evans asymmetric alkylation, and Yamaguchi esterification.

1. Introduction

In 2006, Kobayashi et al.[1] reported the isolation and structural determination of amphidinin B (**1**) from the dinoflagellate *Amphidinium* sp. (strain number Y-56). Amphidinin B (**1**) is a linear polyketide and shown potent activity against MCF-7 (breast cancer cell line).[2] Structurally, amphidinin B (**1**) contains a core tri-substituted tetrahydrofuran skeleton with a chiral side-chain at C16. The side chain is endowed with an *exo* methylene, two branched methyl groups, a propyl and two carboxyl groups while another methyl group adorns at C17 on the tetrahydrofuran skeleton. Also, C19 is substituted by an ethanoic acid moiety. Amphidinin B (**1**) displayed activity against MCF (breast cancer cell line) about 100 times better activity[2] than its cyclic analog amphidinolide T_1 (**2**)[3] (Fig. 1).

Amphidinin B (**1**) was recently synthesized by Yadav et al.[2] in 2011 using radical cyclization, diastereoselective reduction of the exocyclic double bond, Evans alkylation, and Yamaguchi esterification. Because of its potent biological activity, interesting structural features and as part of our research program on the total synthesis of natural products, we became interested in designing a flexible synthetic strategy to amphidinin B (**1**).

As outlined in Scheme 1, our retrosynthetic analysis of **1** is convergent and involves the assembly of **4** and **5** by Yamaguchi esterification.[4] Both the fragments **4** and **5** in turn could be accessed from commercially available geraniol **6** and **7**,[5] respectively, by suitable manipulations.

Thus, the synthesis of fragment **4** commenced by the preparation of **8**[6] from geraniol **6** (Scheme 2). Oxidative cleavage of **8** with $NaIO_4$ followed by reduction with $NaBH_4$ furnished alcohol **9** (81% yield over two steps), which on silyl protection (TBDPSCl/imidazole/CH_2Cl_2/0 °C–rt/2 h) afforded **10** (78%). The compound **10** was subjected to ozonolysis followed by Wittig olefination to afford **11** (74%) as *E*-isomer exclusively. Reduction of the olefin with $NiCl_2{\cdot}6H_2O/NaBH_4$ furnished the saturated ester **12**[7] (90%). The ester **12** is partially reduced (DIBAL-H/CH_2Cl_2/−78 °C/2 h) to aldehyde **13** (74%).

Aldehyde **13** was then subjected to non-Evans *syn*-aldol[8] with thiazolidine-2-thione **14**, generating secondary alcohol **15** (75%), whose diastereoselectivity was measured by LCMS (dr, 96.515:3.485) {Column: XDB-C18, acetonitrile/water (70:30), flow rate: 1 mL/min, 210 nm, t_R (major)=1.712 min, t_R (minor)=3.383 min}. The second diastereoisomer was not detected by NMR analysis of the reaction mixture. The resulting secondary alcohol was silylated[9] (TBSOTf/2,6 lutidine/CH_2Cl_2/0 °C) to provide *tert*-butyldimethylsilylether derivative **16** (82%). Reductive cleavage of the auxiliary[10] with $LiBH_4$ afforded alcohol **17** (74%).

Swern oxidation of the resulting alcohol **17** followed by Julia olefination[11] furnished alkene **19** (74%). Hydroboration of **19** ($BH_3{\cdot}SMe_2$/cyclohexene/NaOH/H_2O_2) afforded alcohol **20** (79%). Oxidation of **20** under Swern conditions provided the corresponding aldehyde, which was subjected to Wittig olefination to afford **21** (78% yield over two steps). Selective deprotection of TBS ether[12]

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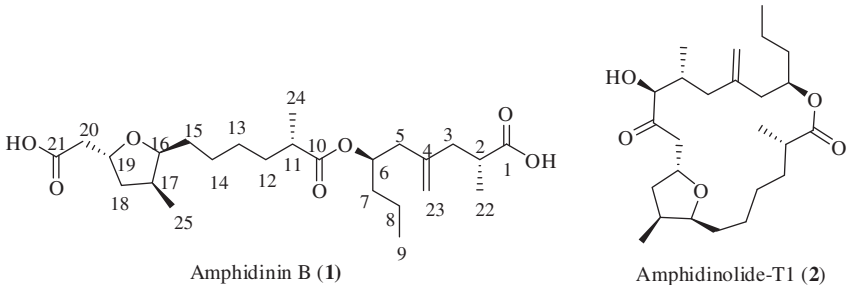
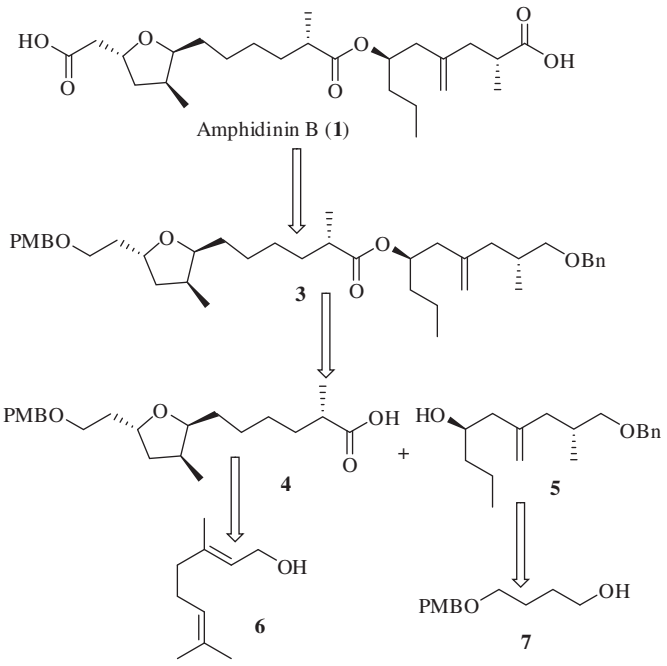


Fig. 1. Structurally similar polyketide metabolites from genus *Amphidinium* sp.



Scheme 1. Retrosynthetic analysis.

with PPTS in MeOH produced alcohol **22** (75%). The alcohol **22** was subjected to oxa-Michael reaction[13] (NaOMe/MeOH/-15 °C/12 h) to afford **23** (81%) in 94:6 selectivity in favor of *trans*-isomer (major). The ratio was measured by HPLC. The two diastereoisomers of the compound **23** were separated by preparative HPLC {Column: XDB-C18, 20% water in acetonitrile, flow rate: 1 mL/min, 210 nm, t_R (major)=1.595 min, t_R (minor)=1.210 min}. The stereochemistry at the newly formed C2 stereocentre in **23** (major) during oxa-Michael addition reaction was relatively assigned as '*anti*' to the existing C5 stereocenter, as evidenced by NOE experiments. Subsequent transformations on **23** led to **4**, which was already reported in the literature;[2] thus, absolute configuration at C2 was assigned as '*R*'. Accordingly, reduction of ester **23** with DIBAL-H at −40 °C furnished alcohol **24** (78%) and the resulting alcohol **24** was protected (NaH/PMBBr/THF/0 °C–rt/6 h) as its PMB ether **25** (80%). Reaction of **25** with TBAF in THF furnished alcohol **26** (74%), which on subsequent oxidation with TEMPO and BAIB[14] furnished acid **4**[2] (84%). The spectroscopic data (^{1}H and ^{13}C NMR) and specific rotation of **4** were in good agreement with the reported data.[2]

The synthesis of fragment **5** commenced with compound **27**, which was synthesized as reported in the literature[15] (Scheme 3). Secondary hydroxyl group in **27** was protected as its *tert*-butyldimethylsilylether **28** (76%). Later, saturation of the terminal double bond in **28** (H_2/Pd/C/EtOAc/rt/12 h) furnished **29** (78%). Compound **29** was oxidized under Swern oxidation conditions to afford aldehyde, which was subjected to Mannich reaction conditions[16] (CH_2Br_2/Et_2NH/55 °C–rt/1.5 h/aldehyde/5 min), followed by DIBAL-H reduction to afford alcohol **30** (66%). Treatment of **30** with triphenylphosphine in presence of iodine and imidazole in THF produced allyl iodide, which on Evans alkylation[17] with *N*-propionyl oxazolidinone afforded **32** (75%) as a single isomer as evidenced from ^{1}H or ^{13}C NMR of crude reaction mixture. Reductive cleavage of the chiral auxiliary using $LiBH_4$ in MeOH furnished alcohol **33** (82%), which was protected (NaH/BnBr/THF/0 °C–rt/2 h) as its benzyl ether **34** (77%). Desilylation of **34** with TBAF in THF produced **5**[2] (71%). The spectroscopic data (^{1}H and ^{13}C NMR) and specific rotation of **5** was in good agreement with the reported data.[2]

With the requisite fragments **4** and **5** in hand, our next task was to couple the two fragments. The coupling of **4** and **5** (Scheme 4) was accomplished using an intermolecular Yamaguchi esterification[2,4] to afford **3** (81%). The spectroscopic data (^{1}H and ^{13}C NMR) and specific rotation of **3** was in good agreement with the reported data.[2] Thus, synthesis of ester **3** concludes the formal synthesis of **1** since transformation of **3** into **1** was already reported.[2]

In summary, we described an efficient and formal synthesis of **1** from commercially available geraniol **6** and mono-PMB ether of 1,4-butane diol **7** using Sharpless asymmetric epoxidation, Evans aldol, Julia olefination, oxa-Michael, Keck allylation, Mannich reaction, Evans asymmetric alkylation, and Yamaguchi esterification.

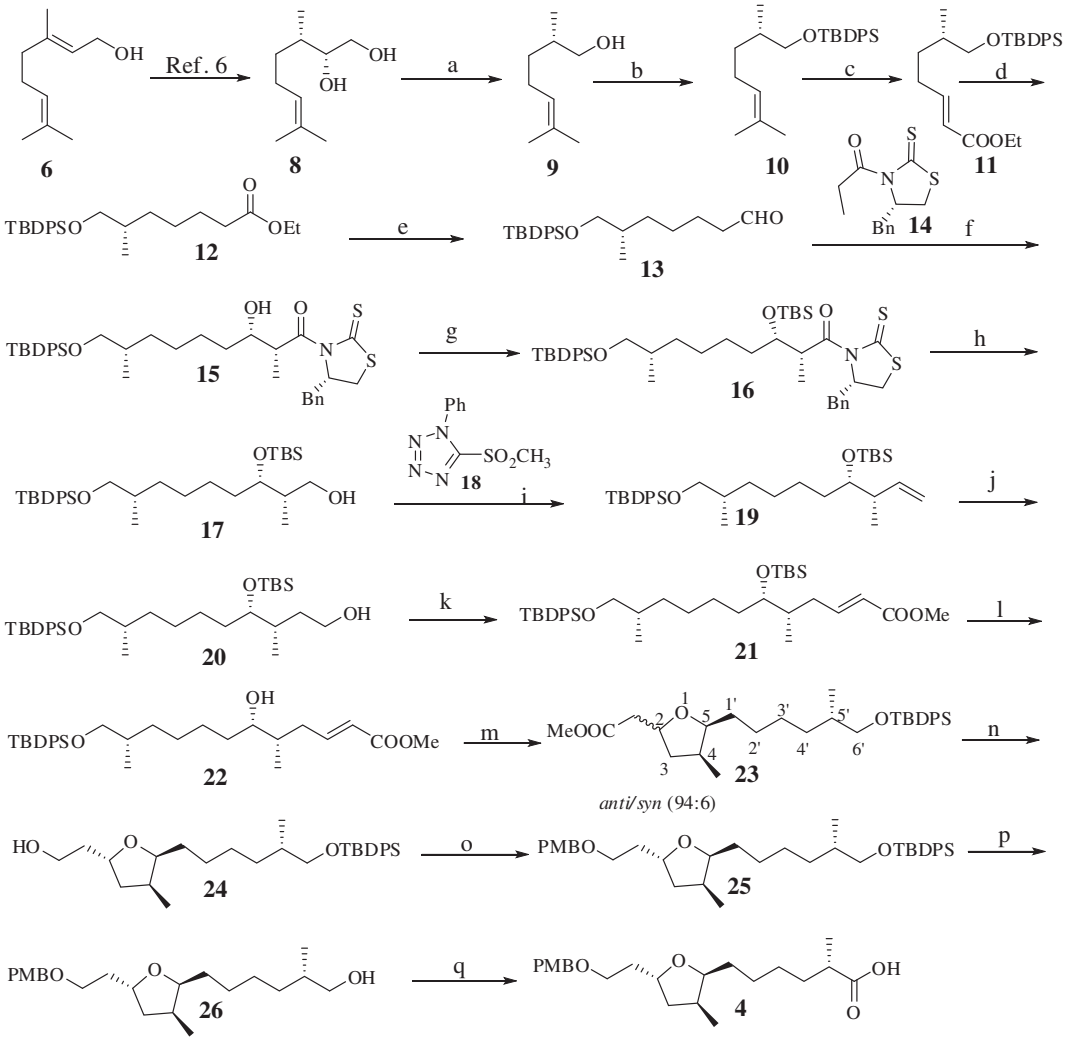
2. Experimental

2.1. General

Solvents were dried over standard drying agents on freshly distilled prior to use. Chemicals were purchased and used without further purification. Column chromatography (CC) was performed on silica gel (*Acme's*, 60–120 mesh) using EtOAc and *n*-hexane as the eluents. TLC was performed on *Merck* 60 F-254 silica gel plates. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous material. Air sensitive reagents were transferred by syringe or double-ended needle. ^{1}H NMR spectra were measured on *Bruker Avance*-300 MHz, and *Inova* 500 MHz and ^{13}C NMR spectra (75 MHz) with a *Bruker Avance* 300 MHz, spectrometers with 7–10 mM solution, in $CDCl_3$ and TMS as internal standard. *J* values are given in Hertz (Hz). IR spectra were recorded on Perkin–Elmer IR-683 spectrophotometer with NaCl optics and elemental analysis was carried on a Vario Micro Cube Elementar at Analytical Chemistry Division, IICT, and Hyderabad. Optical rotations were measured with JASCO DIP 300 digital polarimeter at 25 °C. Mass spectra were recorded on direct inlet system or LC by MSD trap SL (Agilent Technologies). HPLC was recorded using XDB-C18 column.

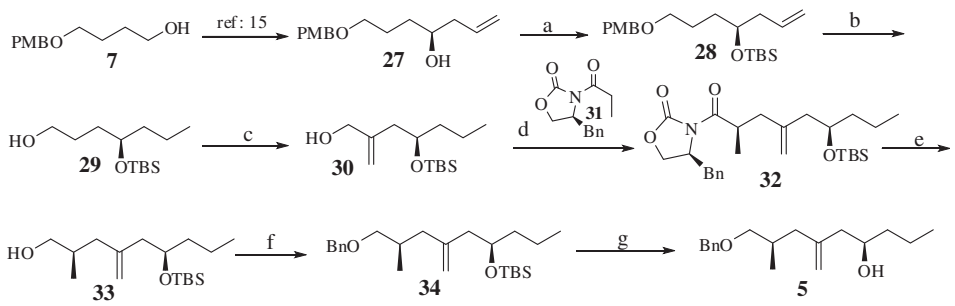
*2.1.1. (S)-2,6-Dimethylhept-5-en-1-ol (**9**).* To a solution of diol **8** (6.7 g, 38.95 mmol) in acetone/H_2O (5:1, 49 mL), $NaIO_4$ (9.99 g, 46.74 mmol) was added at 0 °C and stirred at the same

Synthesis of C_{10}-C_{21} fragment 4



Scheme 2. Reagents and conditions: (a) (i) $NaIO_4$, saturated $NaHCO_3$ solution, acetone/H_2O (5:1), 0 °C, 4 h; (ii) $NaBH_4$, MeOH, 0 °C–rt, 1 h, 81% (over two steps); (b) TBDPSCl, imidazole, CH_2Cl_2, rt, 2 h, 78%; (c) (i) O_3, CH_2Cl_2, dimethylsulphide, −78 °C, 15 min; (ii) Ph_3P=CHCOOEt, benzene, reflux, 10 min, 74% (over two steps); (d) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH, 0 °C–rt, 4 h, 90%; (e) DIBAL-H, CH_2Cl_2, −78 °C, 2 h, 74%; (f) **14**, $TiCl_4$, CH_2Cl_2, 0 °C, 15 min, *i*-Pr_2EtN, 20 min, then cooled to −78 °C, **13**, −78 °C–rt, 2 h, 75%; (g) TBSOTf, 2,6 lutidine, CH_2Cl_2, 0 °C, 10 min, 82%; (h) $LiBH_4$, MeOH, 0 °C–rt, 30 min, 74%; (i) (i) $(COCl)_2$, DMSO, Et_3N, −78 °C, 2 h; 84% (ii) **18**, NaHMDS, THF, −78 °C, 30 min, aldehyde, −78 °C–rt, 4 h, 74%; (j) $BH_3 \cdot SMe_2$, cyclohexene, THF, 0 °C, 2 h, **19**, 0 °C–rt, 3 h, 0 °C, $NaOH/H_2O_2$, 79%; (k) (i) $(COCl)_2$, DMSO, Et_3N, −78 °C, 2 h; (ii) Ph_3P=CHCOOEt, benzene, reflux, 2 h, 78% (over two steps); (l) PPTS, MeOH, 0 °C–rt, 12 h, 75%; (m) NaOMe, MeOH, −15 °C, 12 h, 81%; (n) DIBAL-H, CH_2Cl_2, −40 °C, 1 h, 78%; (o) NaH, PMBBr, THF, 0 °C–rt, 6 h, 80%; (p) TBAF, THF, 3 h, 0 °C–rt, 74%; (q) TEMPO, $PhI(OAc)_2$, CH_2Cl_2/H_2O (1:1), 0 °C–rt, 6 h, 84%.

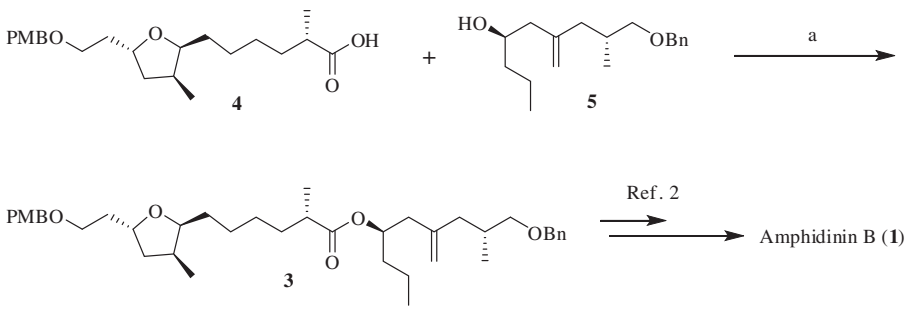
Synthesis of C_1-C_9 fragment 5



Scheme 3. Reagents and conditions: (a) TBSCl, imidazole, CH_2Cl_2, 0 °C–rt, 2 h, 76%; (b) H_2, Pd/C, EtOAc, 12 h, rt, 78%; (c) (i) $(COCl)_2$, DMSO, Et_3N, −78 °C, 2 h, 91%; (ii) Et_2NH, CH_2Br_2, 55 °C–rt, 1.5 h, aldehyde, 5 min, 66%; (iii) DIBAL-H, CH_2Cl_2, −40 °C, 30 min, 80%; (d) (i) TPP, I_2, imidazole, THF, 0 °C, 10 min, 73%; (ii) **31**, LiHMDS, −78 °C, 1 h, allylic iodo compound, −78 to −20 °C, 12 h, 75%; (e) $LiBH_4$, MeOH, 0 °C–rt, 30 min, 82%; (f) NaH, BnBr, THF, 0 °C–rt, 2 h, 77%; (g) TBAF, THF, 3 h, 0 °C–rt, 71%.

temperature for 4 h. Then solvent was evaporated and reaction mixture was extracted with CH_2Cl_2 (3×70 mL). The combined organic layers washed with brine (100 mL), dried over (Na_2SO_4), and evaporated, the residue dissolved in MeOH (60 mL), and treated with $NaBH_4$ (2.14 g, 56.57 mmol) at 0 °C and stirred at the room temperature for 1 h. MeOH was evaporated and residue extracted with EtOAc (3×100 mL). The combined organic layers were dried (Na_2SO_4), evaporated, and purified by column chromatography

Formal synthesis of 1



Scheme 4. Reagents and conditions: 2,4,6-$Cl_3PhCOCl$, $^{i}Pr_2NEt$, 10 h, DMAP, toluene, 24 h, 25 °C, 81%.

(silica gel, 60–120 mesh, R_f 0.60 EtOAc/*n*-hexane 10:90) to afford alcohol **9** (4.51 g, 81%) as a light yellow liquid; [found: C, 75.93; H, 12.78. $C_9H_{18}O$ requires C, 75.90; H, 12.80%]; $[\alpha]_D^{25}$ −18.5 (*c* 4.2, $CHCl_3$); IR (neat): 3016, 2966, 2927, 1452, 1378, 1215, 1037, 745, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.10 (t, *J*=6.7 Hz, 1H, Olefinic–H), 3.50–3.36 (m, 2H, CH_2OH), 2.47–2.37 (br s, 1H, OH), 2.10–1.92 (m, 2H, Allylic–H), 1.67 (s, 3H, Allylic–H), 1.62–1.60 (m, 4H, Allylic–H, CHMe), 1.49–1.36 (m, 1H, CH_aH_bCH), 1.18–1.06 (m, 1H, CH_aH_bCH), 0.93 (d, *J*=6.7 Hz, 3H, CHMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.0, 124.6, 67.7, 35.3, 33.3, 25.6, 17.2, 16.7; MS (ESIMS) *m*/*z* 165 $(M+Na)^+$.

*2.1.2. (S)-tert-Butyl(2,6-dimethylhept-5-enyloxy)diphenylsilane (**10**).* To a stirred solution of **9** (4.42 g, 31.12 mmol) in CH_2Cl_2 (50 mL), imidazole (6.35 g, 93.38 mmol) was added at 0 °C and stirred for 15 min then TBDPSCl (9.38 g, 34.23 mmol) was added and the mixture stirred at room temperature for 2 h. Solvent was evaporated and residue purified by column chromatography (silica gel, 60–120 mesh, R_f 0.90 EtOAc/*n*-hexane 3:97) to give **10** (9.20 g, 78%) as a colorless liquid; [found: C, 78.61; H, 9.62. $C_{25}H_{36}OSi$ requires C, 78.20; H, 9.83%]; $[\alpha]_D^{25}$ −0.92 (*c* 3.5, $CHCl_3$); IR (neat): 3016, 2959, 2930, 2857, 1468, 1427, 1388, 1215, 1108, 822, 740, 701, 667, 612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.68–7.65 (m, 4H, Ar–H), 7.43–7.33 (m, 6H, Ar–H), 5.08 (t, *J*=6.9 Hz, 1H, Olefinic–H), 3.54–3.41 (m, 2H, CH_2OSi), 2.00–1.90 (m, 2H, Allylic–H), 1.73–1.62 (m, 4H, Allylic–H, CHMe), 1.60 (s, 3H, Allylic–H), 1.52–1.42 (m, 1H, CH_aH_bCH), 1.26–1.09 (m, 1H, CH_aH_bCH), 1.05 (s, 9H, *t*-BuSi), 0.91 (d, *J*=6.7 Hz, 3H, CHMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.1, 134.3, 131.17, 129.8, 127.5, 124.9, 68.80, 35.3, 33.2, 26.9, 25.7, 25.5, 19.3, 17.6, 16.9; MS (ESIMS) *m*/*z* 381 $(M+H)^+$.

*2.1.3. (S,E)-Ethyl 7-(tert-butyldiphenylsilyloxy)-6-methylhept-2-enoate (**11**).* A solution of **10** (9.12 g, 24.0 mmol) in CH_2Cl_2 (50 mL) was cooled to −78 °C and subjected to ozonolysis for 15 min and quenched with $(CH_3)_2S$ (4.2 mL). Solvent was evaporated, residue dissolved in benzene (60 mL) and treated with (ethoxycarbonylmethylene)triphenyl phosphorane (9.18 g, 26.40 mmol) at reflux. After 10 min, solvent was evaporated and purified the residue by column chromatography (silica gel, 60–120 mesh, R_f 0.80 EtOAc/*n*-hexane 2:98) to give **11** (7.55 g, 74%) as a colorless liquid. $[\alpha]_D^{25}$ −4.1 (*c* 5.2, $CHCl_3$); IR (neat): 3019, 1709, 1214, 1109, 1046, 743, 667, 615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.67–7.64 (m, 4H, Ar–H), 7.45–7.31 (m, 6H, Ar–H), 6.95 (dt, *J*=13.7, 6.7 Hz, 1H, Olefinic–H), 5.80 (d, *J*=15.6 Hz, 1H, Olefinic–H), 4.19 (q, *J*=7.1 Hz, 2H, OCH_2Me), 3.49 (d, *J*=5.6 Hz, 2H, CH_2OSi), 2.25–2.10 (m, 2H, Allylic–H), 1.73–1.57 (m, 3H, CH_2, CHMe), 1.28 (t, *J*=7.1 Hz, 3H, OCH_2Me), 1.05 (s, 9H, *t*-BuSi), 0.93 (d, *J*=6.6 Hz, 3H, CHMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 149.5, 135.8, 134.1, 129.8, 127.8, 121.4, 68.5, 60.2, 35.2, 31.3, 29.8, 26.8, 19.2, 16.5, 14.2; MS (ESIMS) *m*/*z* 447 $(M+Na)^+$; HRMS (ESI) calcd for $C_{26}H_{36}O_3NaSi$ $(M+Na)^+$ 447.23259, found 447.2368.

*2.1.4. (S)-Ethyl 7-(tert-butyldiphenylsilyloxy)-6-methylheptanoate (**12**).* To a stirred solution of **11** (7.40 g, 17.45 mmol) and $NiCl_2{\cdot}6H_2O$ (0.829 g, 3.49 mmol) in MeOH (50 mL) under an H_2 atmosphere at 0 °C, $NaBH_4$ (0.663 g, 17.45 mmol) was added in small portions (the solution turned black). After complete addition, the reaction mixture was stirred at room temperature for 4 h. The black precipitate formed was filtered through Celite, washed with EtOAc (3×90 mL). Organic layer was evaporated and purified the residue by column chromatography (silica gel, 60–120 mesh, R_f 0.80 EtOAc/*n*-hexane 2:98) to obtain **12** (6.7 g, 90%) as a colorless liquid. $[\alpha]_D^{25}$ −4.2 (*c* 4.9, $CHCl_3$); IR (neat): 3070, 2956, 2930, 2857, 1735, 1467, 1427, 1389, 1371, 1218, 1171, 1109, 938, 823, 771, 703, 613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.67–7.64 (m, 4H, Ar–H), 7.43–7.34 (m, 6H, Ar–H), 4.19 (q, *J*=14.3, 7.1 Hz, 2H, OCH_2Me), 3.52–3.40 (m, 2H, CH_2OSi), 2.26 (t, *J*=7.5 Hz, 2H, CH_2COOEt), 1.69–1.39 (m, 5H, CHMe, CH_2CH_2), 1.37–1.21 (m, 5H, CH_2, OCH_2Me), 1.05 (s, 9H, *t*-BuSi), 0.91 (d, *J*=6.7 Hz, 3H, CHMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 135.5, 133.9, 129.4, 127.5, 68.7, 60.0, 35.4, 34.2, 32.6, 26.8, 26.4, 25.2, 19.2, 16.7, 14.2; MS (ESIMS) *m*/*z* 449 $(M+Na)^+$; HRMS (ESI) calcd for $C_{26}H_{38}O_3NaSi$ $(M+Na)^+$ 449.24824, found 449.24826.

*2.1.5. (2R,3S,8S)-1-((S)-4-Benzyl-2-thioxothiazolidin-3-yl)-9-(tert-butyldiphenylsilyloxy)-3-hydroxy-2,8-dimethylnonan-1-one (**15**).* To a cooled (−78 °C) solution of **12** (6.6 g, 15.49 mmol) in dry CH_2Cl_2 (35 mL), DIBAL-H (12.4 mL, 17.04 mmol, 20% solution in toluene) was added slowly for 15 min. The reaction mixture was stirred at the same temperature for 2 h, cooled to 0 °C, quenched with methanol (10 mL) and sodium potassium tartrate solution (2 mL). The reaction mixture was passed through a short pad of Celite. The filtrate was concentrated and purified the residue by column chromatography (silica gel, 60–120 mesh, R_f 0.90 EtOAc/*n*-hexane 1:99) to furnish **13** (4.4 g, 74%) as a colorless liquid.

To stirred solution of **14** (3.39 g, 12.79 mmol) in dry CH_2Cl_2 (20 mL) under an N_2 atmosphere at 0 °C, $TiCl_4$ (2.82 mL, 25.58 mmol) was added drop wise, and the solution allowed to stir for 5 min. To the yellow slurry was added diisopropylethylamine (1.81 mL, 14.07 mmol). The dark red titanium enolate stirred for 20 min at 0 °C, then was cooled to −78 °C and aldehyde **14** (4.39 g, 11.51 mmol) was added drop wise. The reaction mixture was stirred for 2 h at −78 °C and warmed to 0 °C. The reaction mixture was quenched with saturated ammonium chloride (5 mL) and layer was separated. The aqueous layer further extracted into CH_2Cl_2. The organic extracts were washed with brine (70 mL), dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.6 EtOAc/*n*-hexane 9:91) to

afford alcohol **15** (5.60 g, 75%), as a light yellow viscous liquid. Diastereoselectivity was measured by HPLC (dr, 96.515:3.485). {Column: XDB-C18, acetonitrile/water (70:30), flow rate: 1 mL/min, 210 nm, t_R (major)=1.712 min, t_R (minor)=3.383 min}. $[\alpha]_D^{25}$ +138.7 (*c* 4.0, $CHCl_3$); IR (neat): 3017, 2932, 2858, 1679, 1460, 1427, 1341, 1258, 1214, 1162, 1109, 1039, 743, 666, 614 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.67–7.64 (m, 4H, Ar–H), 7.43–7.25 (m, 11H, Ar–H, CH_2Ph), 5.40–5.33 (m, 1H, CHBn), 4.71–4.64 (m, 1H, CH_aH_bS), 4.15–4.02 (m, 1H, CH_aH_bS), 3.57–3.34 (m, 3H, CHOH, CH_2OSi), 3.26 (dd, *J*=13.0, 3.7 Hz, 1H, CH_2Ph), 3.08 (d, *J*=13.0 Hz, 1H, CH_2Ph), 2.90 (d, *J*=11.5 Hz, 1H, CHMeCO), 2.72 (br s, 1H, OH), 1.70–1.23 (m, 9H, $(CH_2)_4CHMe$), 1.19 (d, *J*=6.9 Hz, 3H, CHMeCO); 1.05 (s, 9H, *t*-BuSi), 0.92 (d, *J*=6.6 Hz, 3H, CHMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.4, 178.3, 136.2, 135.5, 133.9, 129.3, 129.0, 128.9, 127.4, 127.1, 70.8, 68.7, 65.0, 42.5, 40.2, 38.3, 36.8, 35.6, 33.7, 32.9, 31.7, 26.8, 26.1, 19.2, 16.8, 10.3; MS (ESIMS) *m*/*z* 671 $(M+Na)^+$; HRMS (ESI) calcd for $C_{37}H_{49}O_3NNaS_2Si$ $(M+Na)^+$ 670.28153, found 670.28217.

*2.1.6. (2R,3S,8S)-1-((S)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-(tert-butyldimethylsilyloxy)-9-(tert-butyldiphenylsilyloxy)-2,8-dimethylnonan-1-one (**16**).* To a solution of secondary alcohol (5.46 g, 8.43 mmol) in CH_2Cl_2 at 0 °C was added 2,6-lutidine (1.96 mL, 16.87 mmol) followed by TBSOTf (2.03 mL, 8.86 mmol). After 10 min the reaction mixture was quenched with saturated $NaHCO_3$ solution and layers were separated. The aqueous layer further extracted into CH_2Cl_2. The organic extracts were dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.9 EtOAc/*n*-hexane 2:98) to furnish **16** (5.30 g, 82%) as a colorless liquid. $[\alpha]_D^{25}$ +149.7 (*c* 6.8, $CHCl_3$); IR (neat): 3016, 2931, 2857, 1686, 1459, 1427, 1341, 1256, 1215, 1160, 1109, 1029, 834, 744, 700, 666, 614 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.66–7.63 (m, 4H, Ar–H), 7.47–7.25 (m, 11H, Ar–H, CH_2Ph), 5.32 (br t, *J*=10.1 Hz, 1H, CHBn), 4.74–4.68 (m, 1H, CH_aH_bS), 4.19–4.14 (m, 1H, CH_aH_bS), 3.51–3.40 (m, 2H, CH_2OSi), 3.34–3.27 (m, 1H, CHOH), 3.18 (dd, *J*=12.8, 3.0 Hz, 1H, CH_2Ph), 3.01 (d, *J*=10.5 Hz, 1H, CH_2Ph), 2.82 (d, *J*=11.3 Hz, 1H, CHMeCO), 1.64–1.24 (m, 9H, $(CH_2)_4CHMe$), 1.18 (d, *J*=6.7 Hz, 3H, CHMeCO), 1.03 (s, 9H, *t*-BuSi), 0.90–0.88 (m, 12H, *t*-BuSi, CHMe), 0.07 (s, 6H, MeSi (2)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.3, 178.3, 136.4, 135.5, 134.0, 129.3, 128.8, 127.4, 127.1, 72.9, 70.8, 68.8, 43.5, 42.5, 36.9, 35.7, 33.5, 33.0, 31.7, 29.5, 26.8, 26.2, 19.2, 16.8, 14.2, 10.3, −4.3; MS (ESIMS) *m*/*z* 785 $(M+Na)^+$; HRMS (ESI) calcd for $C_{43}H_{63}O_3NNaS_2Si_2$ $(M+Na)^+$ 784.36801, found 784.36837.

*2.1.7. (2S,3S,8S)-3-(tert-Butyldimethylsilyloxy)-9-(tert-butyldiphenylsilyloxy)-2,8-dimethylnonan-1-ol (**17**).* To stirred solution of **16** (5.15 g, 6.76 mmol) in MeOH (30 mL) under an N_2 atmosphere at 0 °C, $LiBH_4$ (0.178 g, 8.12 mmol) was added in small portions. After 30 min the reaction mixture was quenched with saturated $NaHCO_3$ solution. MeOH was evaporated and water was added and extracted with EtOAc (2×70 mL). The organic extracts were washed with brine (90 mL), dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.40 EtOAc/*n*-hexane 11:89) to afford **17** (2.80 g, 74%) as a colorless liquid. $[\alpha]_D^{25}$ −2.7 (*c* 2.3, $CHCl_3$); IR (neat): 3015, 2954, 2930, 2857, 1467, 1427, 1387, 1253, 1215, 1108, 1040, 937, 835, 752, 701, 607, 612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.67–7.64 (m, 4H, Ar–H), 7.44–7.34 (m, 6H, Ar–H), 3.74–3.65 (m, 2H, CH_2OSi), 3.53–3.41 (m, 3H, CH_2OH, CHOSi), 1.95 (br s, 1H, OH), 1.69–1.59 (m, 2H, $CHMeCH_2OSi$, $CHMeCH_2OH$), 1.51–1.39 (m, 2H, CH_2CHOSi), 1.35–1.24 (m, 6H, $(CH_2)_3$), 1.05 (s, 9H, *t*-BuSi), 0.95–0.85 (m, 12H, *t*-BuSi, $CHMeCH_2OSi$), 0.81 (d, *J*=7.1 Hz, 3H, $CHMeCH_2OH$), 0.09 (d, *J*=8.6 Hz, 6H, MeSi (2)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.5, 134.0, 129.4, 127.5, 75.7, 68.8, 65.9, 39.4, 35.6, 33.1, 32.3, 27.1, 26.8, 26.5, 25.8, 19.2, 17.9, 16.8, 11.8, −4.3; MS (ESIMS) *m*/*z* 579 $(M+Na)^+$, 558 $(M+H)^+$; HRMS (ESI) calcd for $C_{33}H_{56}O_3NaSi_2$ $(M+Na)^+$ 579.36602, found 579.36661.

*2.1.8. (5S,10S)-5-((S)-But-3-en-2-yl)-2,2,3,3,10,14,14-heptamethyl-13,13-diphenyl-4,12-dioxa-3,13-disilapentadecane (**19**).* To a solution of oxalyl chloride (0.65 mL, 7.41 mmol) in dry CH_2Cl_2 (7 mL) at −78 °C, dry DMSO (1.05 mL, 14.8 mmol) was added drop wise and stirred for 10 min. A solution of **17** (2.75 g, 4.94 mmol) in dry CH_2Cl_2 (12 mL) was added and stirred for 2 h at −78 °C. It was quenched with Et_3N (8.24 mL, 59.35 mmol) and, extracted with CH_2Cl_2 (2×20 mL). Organic layer was washed with brine (50 mL), dried (Na_2SO_4), evaporated, and purified the residue by column chromatography (silica gel, 60–120 mesh, R_f 0.90 EtOAc/*n*-hexane 2:98) to obtain the aldehyde (2.3 g, 84%) as a colorless liquid.

A solution of sulfone **18** (0.928 g, 4.14 mmol) in THF (12 mL) was cooled to −78 °C. To this NaHMDS (4.14 mL, 4.14 mmol, 1 M in THF) was added drop wise and a yellow color appeared. The reaction mixture was stirred at the same temperature for 30 min then aldehyde (2.29 g, 4.14 mmol) in THF (15 mL) was added and stirring was continued for 2 h at the same temperature. The reaction mixture allowed to warm to room temperature over 4 h, quenched with saturated ammonium chloride and the layer was separated. The aqueous layer further extracted with EtOAc. The organic extracts were washed with brine (50 mL), dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.80 EtOAc/*n*-hexane 4:96) to furnish **19** (1.7 g, 74%) as a colorless liquid. $[\alpha]_D^{25}$ −28.5 (*c* 1.7, $CHCl_3$); IR (neat): 3018, 2932, 2858, 1214, 1109, 835, 743, 667, 615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.75–7.64 (m, 4H, Ar–H), 7.52–7.34 (m, 6H, Ar–H), 5.90–5.79 (m, 1H, Olefinic–H), 5.01–4.95 (m, 2H, Olefinic–H), 3.51–3.39 (m, 3H, CH_2OSi, CHOSi), 2.34–2.25 (m, 1H, $CHMeCH{=}CH_2$), 1.73–1.54 (m, 1H, $CHMeCH_2OSi$), 1.49–1.21 (m, 8H, $(CH_2)_4$), 1.05 (s, 9H, *t*-BuSi), 0.96 (d, *J*=6.7 Hz, 3H, $CHMeCH{=}CH_2$), 0.91–0.88 (m, 12H, *t*-BuSi, $CHMeCH_2OSi$), 0.03 (s, 6H, MeSi (2)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.6, 135.8, 134.2, 129.5, 127.6, 113.6, 75.9, 68.8, 42.7, 35.7, 33.1, 29.6, 27.1, 26.8, 25.9, 25.5, 19.4, 18.1, 16.8, 14.8, −4.3; MS (ESIMS) *m*/*z* 575 $(M+Na)^+$; HRMS (ESI) calcd for $C_{34}H_{56}O_2NaSi_2$ $(M+Na)^+$ 575.37111, found 575.37185.

*2.1.9. (3S,4S,9S)-4-(tert-Butyldimethylsilyloxy)-10-(tert-butyldiphenylsilyloxy)-3,9-dimethyl-decan-1-ol (**20**).* To a stirred solution of cyclohexene (1.2 mL, 11.95 mmol) in anhydrous THF (10 mL) were added $BH_3 \cdot DMS$ (0.52 mL, 5.97 mmol) at 0 °C and stirred for 2 h at 0 °C, after that at same temperature olefin (1.65 g, 2.98 mmol) in THF (15 mL) was added and allowed to stirred for 3 h at room temperature. Sodium hydroxide 3 N (5.6 mL) and hydrogen peroxide 30% (1.6 mL) were added at 0 °C and allowed to stirred for 3 h at room temperature, extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.70 EtOAc/*n*-hexane 15:85) to afford alcohol **20** (1.35 g, 79%) as a colorless liquid. $[\alpha]_D^{25}$ −14.2 (*c* 3.0, $CHCl_3$); IR (neat): 3019, 1214, 1109, 1046, 742, 667, 619 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J*=6.9 Hz, 4H, Ar–H), 7.41–7.34 (m, 6H, Ar–H), 3.72–3.41 (m, 5H, CH_2OSi, CHOSi, CH_2OH), 2.45 (br s, 1H, OH), 1.76–1.60 (m, 3H, $CHMeCH_2$), 1.46–1.14 (m, 9H, $(CH_2)_4CHMe$), 1.04 (s, 9H, *t*-BuSi), 0.91–0.88 (m, 15H, *t*-BuSi, $CHMeCH_2OSi$, $CHMeCH_2$), 0.05 (d, *J*=2.4 Hz, 6H, MeSi (2)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 134.2, 129.6, 127.7, 77.6, 69.1, 62.2, 37.3, 35.9, 35.7, 33.3, 32.3, 29.8, 27.3, 27.06, 26.0, 19.5, 18.2, 17.1, 15.9, −4.3; MS (ESIMS) *m*/*z* 593 $(M+Na)^+$; HRMS (ESI) calcd for $C_{34}H_{58}O_3NaSi_2$ $(M+Na)^+$ 593.38167 found 593.38209.

*2.1.10. (5S,6S,11S,E)-Methyl-6-(tert-butyldimethylsilyloxy)-12-(tert-butyldiphenylsilyloxy)-5,11-dimethyldo-dec-2-enoate (**21**).* To a solution of oxalyl chloride (0.29 mL, 3.36 mmol) in dry CH_2Cl_2 (12 mL) at −78 °C, dry DMSO (0.47 mL, 6.73 mmol) was added drop wise and

stirred for 10 min. A solution of **20** (1.28 g, 2.24 mmol) in dry CH_2Cl_2 (12 mL) was added and stirred for 2 h at −78 °C. It was quenched with Et_3N (3.74 mL, 26.94 mmol) and extracted with CH_2Cl_2 (2×20 mL). Organic layer was washed with brine (50 mL), dried (Na_2SO_4), evaporated and to obtain aldehyde as a colorless liquid.

The above aldehyde was dissolved in benzene (20 mL) and treated with (methoxycarbonylmethylene)triphenyl phosphorane (0.862 g, 2.47 mmol) at reflux. After 2 h, solvent was evaporated and purified the residue by column chromatography (silica gel, 60–120 mesh, R_f 0.80 EtOAc/*n*-hexane 4:96) to afford **21** (1.1 g, 78%) as a colorless liquid. $[\alpha]_D^{25}$ −10.5 (*c* 1.5, $CHCl_3$); IR (neat): 3745, 3610, 3070, 3050, 2929, 2856, 2309, 1726, 1656, 1550, 1515, 1465, 1430, 1378, 1361, 1314, 1254, 1217, 1172, 937, 834, 772, 740, 702, 668, 613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.66–7.64 (m, 4H, Ar–H), 7.41–7.28 (m, 6H, Ar–H), 6.94 (quintet, *J*=15.1, 7.5 Hz, 1H, Olefinic–H), 5.79 (d, *J*=15.9 Hz, 1H, Olefinic–H), 3.71 (s, 3H, OMe), 3.56–3.50 (m, 2H, CH_2OSi), 3.48–3.44 (m, 1H, CHOSi), 2.44–2.37 (m, 1H, CH_aH_bCH), 1.98–1.88 (m, 1H, CH_aH_bCH), 1.75–1.49 (m, 2H, $CHMeCH_2OSi$, $CHMeCH_2$), 1.45–1.13 (m, 8H, $(CH_2)_4$), 1.11–0.95 (m, 12H, *t*-BuSi, $CHMeCH_2OSi$), 0.93–0.81 (m, 12H, *t*-BuSi, $CHMeCH_2$), 0.02 (s, 6H, MeSi (2)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 149.3, 135.5, 134.0, 129.4, 127.5, 121.7, 75.4, 68.8, 51.3, 37.7, 35.6, 35.2, 33.1, 32.9, 27.1, 26.8, 26.2, 25.8, 19.2, 18.0, 16.8, 14.2, −4.3; MS (ESIMS) *m*/*z* 647 $(M+Na)^+$; HRMS (ESI) calcd for $C_{37}H_{60}O_4NaSi_2$ $(M+Na)^+$ 647.39223, found 647.39310.

*2.1.11. (5S,6S,11S,E)-Methyl 12-(tert-butyldiphenylsilyloxy)-6-hydroxy-5,11-dimethyldo-dec-2-enoate (**22**).* To a stirred solution of **21** (1.07 g, 1.71 mmol) in MeOH (10 mL) at 0 °C, catalytic amount of PPTS was added and stirred at room temperature for 12 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution and MeOH was evaporated. Water was added and extracted with EtOAc (2×15 mL). The organic extracts were washed with brine (30 mL), dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.60 EtOAc/*n*-hexane 20:80) to afford **22** (0.66 g, 75%) as a colorless liquid. $[\alpha]_D^{25}$ −14.5 (*c* 1.1, $CHCl_3$); IR (neat): 3744, 3501, 3070, 2929, 2856, 2311, 1724, 1655, 1462, 1430, 1388, 1315, 1314, 1270, 1213, 1172, 1109, 1044, 981, 824, 741, 703, 667, 613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J*=6.4 Hz, 4H, Ar–H), 7.44–7.37 (m, 6H, Ar–H), 6.98 (quintet, *J*=15.4, 7.4 Hz, 1H, Olefinic–H), 5.80 (d, *J*=15.4, 1H, Olefinic–H), 3.74 (s, 3H, OMe), 3.53–3.50 (m, 2H, CH_2OSi), 3.48–3.44 (m, 1H, CHOSi), 2.42–2.36 (m, 1H, CH_aH_bCH), 2.15–2.09 (m, 1H, CH_aH_bCH), 1.74–1.63 (m, 2H, $CHMeCH_2OSi$, $CHMeCH_2$), 1.45–1.41 (m, 2H, CH_2CHOSi), 1.27–1.25 (m, 6H, $(CH_2)_3$), 1.07 (s, 9H, *t*-BuSi), 0.93–0.96 (m, 6H, $CHMeCH_2OSi$, $CHMeCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 148.6, 135.8, 134.2, 129.4, 127.6, 122.1, 74.4, 68.8, 51.3, 37.8, 36.3, 35.7, 34.5, 33.1, 26.9, 26.4, 25.8, 19.3, 16.8, 13.3; MS (ESIMS) *m*/*z* 533 $(M+Na)^+$; HRMS (ESI) calcd for $C_{31}H_{46}O_4NaSi$ $(M+Na)^+$ 533.30576, found 533.30601.

*2.1.12. Methyl 2-((2R,4S,5S)-5-(6-(tert-butyldiphenylsilyloxy)hexyl)-4-methyltetrahydrofuran-2-yl)acetate (anti-**23**).* To a cooled (−20 °C) solution of **22** (0.63 g, 1.23 mmol) in dry MeOH (7 mL), NaOMe (0.073 g, 1.35 mmol) was added in small portions. The reaction mixture was stirred at same temperature for 12 h quenched with saturated ammonium chloride and MeOH was evaporated. Water was added and extracted with EtOAc (2×20 mL). The organic extracts were washed with brine (40 mL), dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.50 EtOAc/*n*-hexane 25:75) to afford **23** (0.50 g, 81%) as a colorless liquid. $[\alpha]_D^{25}$ −15.5 (*c* 1.3, $CHCl_3$); IR (neat): 3857, 3745, 3883, 3610, 3048, 3016, 2928, 2855, 2308, 1740, 1567, 1550, 1532, 1465, 1430, 1387, 1213, 1170, 1109, 1006, 824, 758, 704, 667, 614, 565 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, *J*=6.4 Hz, 4H, Ar–H), 7.45–7.35 (m, 6H, Ar–H), 4.47–4.42 (m, 1H, $OCHCH_2COOMe$), 3.86–3.82 (m, 1H, OCHCHMe), 3.67 (s, 3H, OMe), 3.51–3.48 (m, 1H, CH_aH_bOSi), 3.44–3.41 (m, 1H, CH_aH_bOSi), 2.60 (dd, *J*=14.9, 6.4 Hz, 1H, CH_aH_bCOOMe), 2.42 (dd, *J*=14.9, 6.4 Hz, 1H, CH_aH_bCOOMe), 2.27–2.22 (m, 1H, CHMe), 1.93–1.69 (m, 2H, $CHCH_2CH$), 1.64–1.59 (m, 1H, $CHMeCH_2OSi$), 1.57–1.21 (m, 8H, $(CH_2)_4$), 1.04 (s, 9H, *t*-BuSi), 0.92–0.87 (m, 6H, $CHMeCH_2OSi$, CHMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 135.6, 134.0, 129.4, 127.5, 81.4, 72.9, 68.8, 51.5, 41.4, 39.7, 35.8, 33.2, 31.8, 30.1, 27.0, 26.8, 25.8, 19.2, 16.8, 13.8; MS (ESIMS) *m*/*z* 533 $(M+Na)^+$; HRMS (ESI) calcd for $C_{31}H_{46}O_4NaSi$ $(M+Na)^+$ 533.30576, found 533.30483. HPLC {Column: XDB-C18, 20% water in acetonitrile, flow rate: 1 mL/min, 210 nm, t_R (major)=1.595 min, t_R (minor)=1.210 min}.

*2.1.13. 2-((2R,4S,5S)-5-((S)-6-(tert-Butyldiphenylsilyloxy)-5-methylhexyl)-4-methyltetra-hydro-furan-2-yl)ethanol (**24**).* To a cooled (−40 °C) solution of **23a** (0.48 g, 0.94 mmol) in dry CH_2Cl_2 (5 mL), DIBAL-H (1.50 mL, 2.07 mmol, 20% solution in toluene) was added slowly. The reaction mixture was stirred at the same temperature for 1 h, cooled to 0 °C, quenched with methanol (1 mL) and sodium potassium tartrate solution (1 mL). The reaction mixture was passed through a short pad of Celite. The filtrate was concentrated and purified the residue by column chromatography (silica gel, 60–120 mesh, R_f 0.4 EtOAc/*n*-hexane 30:70) to furnish **24** (0.355 g, 78%) as a colorless liquid. $[\alpha]_D^{25}$ −13.4 (*c* 2.0, $CHCl_3$); IR (neat): 3610, 3049, 3016, 2930, 2855, 2308, 1560, 1550, 1532, 1470, 1430, 1387, 1213, 1178, 1109, 824, 758, 724, 669, 615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (dd, *J*=7.1, 1.5 Hz, 4H, Ar–H), 7.43–7.33 (m, 6H, Ar–H), 4.30–4.21 (m, 1H, $OCHCH_2CH_2OH$), 3.89–3.83 (m, 1H, OCHCHMe), 3.80–3.75 (m, 2H, CH_2OSi), 3.53–3.40 (m, 2H, CH_2OH), 3.20 (br s, 1H, OH), 2.25–2.13 (m, 1H, CHMe), 1.82–1.58 (m, 4H, $CHCH_2CH$, CH_2CH_2OH), 1.47–1.20 (m, 9H, $(CH_2)_4$, $CHMeCH_2OSi$), 1.05 (s, 9H, *t*-BuSi), 0.95–0.85 (m, 6H, $CHMeCH_2OSi$, CHMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.4, 134.0, 129.2, 127.3, 81.2, 76.4, 68.9, 61.8, 40.2, 37.8, 35.4, 32.8, 30.1, 26.9, 26.6, 19.1, 16.6, 14.0; MS (ESIMS) *m*/*z* 505 $(M+Na)^+$; HRMS (ESI) calcd for $C_{30}H_{46}O_3NaSi$ $(M+Na)^+$ 505.31084, found 505.31094.

*2.1.14. tert-Butyl((S)-6-((2S,3S,5R)-5-(2-(4-methoxybenzyloxy)ethyl)-3-methyltetrahydro-furan-2-yl)-2-methylhexyloxy)diphenylsilane (**25**).* To a cooled (0 °C) solution of **24** (0.33 g, 0.684 mmol) in dry THF (4 mL), NaH (0.032 g, 1.36 mmol, 60% w/w dispersion in paraffin oil) was added and stirred for 30 min. A solution of MPM-Br (0.165 g, 0.82 mmol) in dry THF (2 mL) was added and stirred at room temperature for 6 h. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL) and extracted with EtOAc (2×20 mL). The combined organic layers were dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.70 EtOAc/*n*-hexane 4:96) to afford alcohol **25** (0.33 g, 80%) as a light yellow liquid. $[\alpha]_D^{25}$ −13.08 (*c* 0.93, $CHCl_3$); IR (neat): 3745, 3590, 2928, 2855, 2308, 1712, 1678, 1612, 1513, 1464, 1427, 1361, 1301, 1247, 1213, 1173, 1108, 1037, 822, 753, 667, 614 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.67–7.64 (m, 4H, Ar–H), 7.43–7.34 (m, 6H, Ar–H), 7.26 (d, *J*=8.6 Hz, 2H, C_6H_4OMe), 6.87 (d, *J*=8.6 Hz, 2H, C_6H_4OMe), 4.49–4.42 (m, 2H, $OCH_2C_6H_4OMe$), 4.18–4.06 (m, 1H, $OCHCH_2CH_2OPMB$), 3.80–3.78 (m, 4H, OMe, OCHCHMe), 3.57–3.40 (m, 4H, CH_2OPMB, CH_2OSi), 2.24–2.08 (m, 1H, CHMe), 1.91–1.14 (m, 13H, CH_2CH_2OPMB, $CHCH_2CH$, $(CH_2)_4$, $CHMeCH_2OSi$), 1.04 (s, 9H, *t*-BuSi), 0.92–0.82 (m, 6H, $CHMeCH_2OSi$, CHMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 135.5, 134.1, 129.4, 127.5, 113.6, 80.9, 73.8, 72.6, 68.8, 67.6, 55.2, 40.1, 36.8, 35.6, 33.1, 31.9, 30.3, 29.6, 27.2, 26.8, 19.3, 16.8, 13.9; MS (ESIMS) *m*/*z* 625 $(M+Na)^+$; HRMS (ESI) calcd for $C_{38}H_{54}O_4NaSi$ $(M+Na)^+$ 625.36840, found 625.36890.

*2.1.15. (S)-6-((2S,3S,5R)-5-(2-(4-Methoxybenzyloxy)ethyl)-3-methyltetrahydrofuran-2-yl)-2-methylhexan-1-ol (**26**).* To a stirred solution of compound **25** (0.30 g, 0.498 mmol) in anhydrous THF was added TBAF (0.59 mL, 0.597 mmol, 1.0 M solution in THF) at 0 °C and reaction mixture stirred at room temperature for 3 h then reaction mixture adsorbed as such on silica and the crude residue

was purified by column chromatography (silica gel, 60–120 mesh, R_f 0.50 EtOAc/*n*-hexane 11:89) to afford primary alcohol **26** (0.135 g, 74%) as a colorless liquid. $[\alpha]_D^{25}$ −39.06 (*c* 0.45, $CHCl_3$); IR (neat): 3745, 3440, 3395, 2926, 2854, 2308, 1726, 1694, 1611, 1585, 1512, 1460, 1374, 13,000, 1246, 1209, 1173, 1090, 1035, 919, 820, 770, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, *J*=8.6 Hz, 2H, C_6H_4OMe), 6.88 (d, *J*=8.6 Hz, 2H, C_6H_4OMe), 4.47–4.38 (m, 2H, $OCH_2C_6H_4OMe$), 4.20–4.08 (m, 1H, $OCHCH_2CH_2OPMB$), 3.79 (s, 3H, OMe), 3.56–3.37 (m, 5H, OCHCHMe, CH_2OPMB, CH_2OH), 2.23–2.11 (m, 1H, CHMe), 1.91–1.23 (m, 13H, $CHCH_2CH$, CH_2CH_2OPMB, $(CH_2)_4$, $CHMeCH_2OH$), 0.95–0.83 (m, 6H, $CHMeCH_2OH$, CHMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 130.6, 129.2, 113.6, 80.9, 73.8, 72.5, 68.2, 67.5, 55.2, 40.0, 36.8, 35.8, 33.0, 31.8, 30.3, 29.6, 27.1, 16.5, 13.9; MS (ESIMS) *m*/*z* 387 $(M+Na)^+$, 365 $(M+H)^+$; HRMS (ESI) calcd for $C_{22}H_{36}O_4Na$ $(M+Na)^+$ 387.25058, found 387.25120.

*2.1.16. (S)-6-((2S,3S,5R)-5-(2-(4-Methoxybenzyloxy)ethyl)-3-methyltetrahydrofuran-2-yl)-2-methylhexanoic acid (**4**).* To a stirred solution of compound **26** (0.10 g, 0.274 mmol) in CH_2Cl_2/H_2O (1:1, 2 mL) at 0 °C, BAIB (0.273 g, 0.824 mmol) and TEMPO (0.0128 g, 0.082 mmol) were added and stirred at room temperature for 6 h. The reaction mixture was diluted with $CHCl_3$ (10 mL) and washed with saturated $Na_2S_2O_3$ (10 mL), brine (20 mL) and dried (Na_2SO_4), evaporated under reduced pressure, and purified the residue by column chromatography (silica gel, 60–120 mesh, R_f 0.30 EtOAc/*n*-hexane, 15:85) to furnish **4** (0.087 g, 84%) as a colorless liquid. $[\alpha]_D^{25}$ −2.1 (*c* 1.5, $CHCl_3$); IR (neat): 2923, 2853, 1708, 1513, 1462, 1246, 1095, 1036, 820, 761 cm^{--1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J*=8.2 Hz, 2H, C_6H_4OMe), 6.82 (d, *J*=8.2 Hz, 2H, C_6H_4OMe), 4.43 (q, *J*=11.5, 3.3 Hz, 2H, $OCH_2C_6H_4OMe$), 4.18–4.09 (m, 1H, $OCHCH_2$-CH_2OPMB), 3.85–3.79 (m, 4H, OCHCHMe, OMe), 3.53 (t, *J*=6.6 Hz, 2H, CH_2OPMB), 2.49–2.43 (m, 1H, CHCOOH), 2.25–2.12 (m, 1H, CHMe), 1.91–1.67 (m, 3H, $CHCH_aH_bCH$, CH_2CH_2OPMB), 1.51–1.21 (m, 9H, $(CH_2)_4$, $CHCH_aH_bCH$), 1.17 (d, *J*=6.6 Hz, 3H, CHMeCOOH), 0.88 (d, *J*=6.0 Hz, 3H, CHMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.8, 158.8, 130.4, 128.9, 113.4, 80.6, 73.6, 72.4, 67.3, 67.5, 55.0, 39.7, 39.1, 36.5, 35.5, 33.2, 31.6, 27.0, 26.4, 16.5, 13.9; MS (ESIMS) *m*/*z* 401 $(M+Na)^+$; HRMS (ESI) calcd for $C_{22}H_{34}O_5Na$ $(M+Na)^+$ 401.22985, found 401.23044.

*2.1.17. (S)-7-(4-Methoxybenzyloxy)hept-1-en-4-ol (**27**).* To a solution of oxalyl chloride (3.44 mL, 39.28 mmol) in dry CH_2Cl_2 (30 mL) at −78 °C, dry DMSO (5.57 mL, 78.57 mmol) was added drop wise and stirred for 15 min. A solution of **7** (5.5 g, 26.19 mmol) in dry CH_2Cl_2 (25 mL) was added and stirred for 2 h at −78 °C. It was quenched with Et_3N (36.38 mL, 261.9 mmol) and extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), evaporated and to obtain the aldehyde (5.0 g, 91%) as a colorless liquid.

A mixture of (*R*)-BINOL (0.686 g, 2.39 mmol) and $Ti(O^iPr)_4$ (0.71 mL, 2.39 mmol) in CH_2Cl_2 (60 mL) in the presence of 4 Å molecular sieves (3.5 g) was stirred under reflux. After, the reaction mixture was cooled to room temperature, aldehyde (4.99 g, 23.9 mmol) was added and the resulting mixture was stirred for 10 min. The reaction mixture was then cooled to −78 °C and allyl tributylstannane (8.99 mL, 28.78 mmol) was added to it and stirring continued at −20 °C for 12 h. The reaction mixture was quenched with saturated NH_4Cl solution (50 mL) and extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), evaporated under reduced pressure, and purified the residue by column chromatography (silica gel, 60–120 mesh, R_f 0.80 EtOAc/*n*-hexane 8:92) to afford **27** (4.70 g, 78%) as a yellow color liquid. $[\alpha]_D^{25}$ −13.40 (*c* 2.2, $CHCl_3$); IR (neat): 3018, 1513, 1248, 1215, 1081, 1036, 838, 743, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, *J*=8.6 Hz, 2H, C_6H_4OMe), 6.88 (d, *J*=8.l6 Hz, 2H, C_6H_4OMe), 5.89–5.75 (m, 1H, Olefinic–H), 5.12–5.07 (m, 2H, Olefinic–H), 4.43 (s, 2H, $OCH_2C_6H_4OMe$), 3.78 (s, 3H, OMe), 3.67–3.58 (m, 1H, CHOH), 3.47 (t, *J*=6.0 Hz, 2H, CH_2OPMB), 2.29–2.12 (m, 2H, Allylic–H), 1.77–1.42 (m, 4H, $(CH_2)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 135.1, 130.4, 129.4, 117.7, 113.7, 72.6, 70.5, 70.0, 55.1, 42.0, 34.1, 26.3; MS (ESIMS) *m*/*z* 273 $(M+Na)^+$; HRMS (ESI) calcd for $C_{15}H_{22}O_3Na$ $(M+Na)^+$ 273.14612, found 273.14554.

*2.1.18. (S)-tert-Butyl(7-(4-methoxybenzyloxy)hept-1-en-4-yloxy)dimethylsilane (**28**).* To a stirred solution of alcohol **27** (4.65 g, 18.6 mmol) in CH_2Cl_2 (70 mL) at 0 °C, imidazole (3.79 g, 55.8 mmol) and TBSCl (3.06 g, 20.46 mmol) were added and stirred for 2 h. Solvent was evaporated and residue purified by column chromatography (silica gel, 60–120 mesh, R_f 0.90 EtOAc/*n*-hexane 2:98) to furnish silyl ether **28** (5.1 g, 76%) as a colorless liquid. $[\alpha]_D^{25}$ −12.05 (*c* 1.7, $CHCl_3$); IR (neat): 3018, 1513, 1248, 1215, 1081, 1036, 838, 743, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, *J*=8.3 Hz, 2H, C_6H_4OMe), 6.88 (d, *J*=8.3 Hz, 2H, C_6H_4OMe), 5.87–5.73 (m, 1H, Olefinic–H), 5.05–5.00 (m, 2H, Olefinic–H), 4.42 (s, 2H, OCH_2-C_6H_4OMe), 3.79 (s, 3H, OMe), 3.74–3.66 (m, 1H, CHOSi), 3.42 (t, *J*=6.6 Hz, 2H, CH_2OPMB), 2.27–2.14 (m, 2H, Allylic–H), 1.71–1.32 (m, 4H, $(CH_2)_2$), 0.88 (s, 9H, *t*-BuSi), 0.03 (d, *J*=2.0 Hz, 6H, MeSi (2)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 135.1, 129.1, 128.6, 116.6, 113.6, 72.3 71.7, 70.1, 55.1, 41.8, 33.2, 25.8, 25.5, 18.0, −4.4; MS (ESIMS) *m*/*z* 387 $(M+Na)^+$; HRMS (ESI) calcd for $C_{21}H_{36}O_3NaSi$ $(M+Na)^+$ 387.23259, found 387.23256.

*2.1.19. (R)-4-(tert-Butyldimethylsilyloxy)heptan-1-ol (**29**).* To stirred solution of **28** (5.0 g, 0.91 mmol) in EtOAc (10 mL) Pd/C and cat. $NaHCO_3$ was added and stirred under H_2 atmosphere for 12 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure and purified the residue by column chromatography (silica gel, 60–120 mesh, R_f 0.70 EtOAc/*n*-hexane 4:96) to obtain **29** (2.6 g, 78%) as colorless syrup; $[\alpha]_D^{25}$ −1.48 (*c* 2.95, $CHCl_3$); IR (neat): 3349, 2954, 2930, 2857, 1464, 1362, 1375, 1252, 1215, 1127, 1103, 1035, 939, 832, 769, 664 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.92–3.81 (m, 1H, CHOSi), 3.80–3.68 (m, 2H, CH_2OH), 2.51 (br s, 1H, OH), 1.80–1.55 (m, 6H, $(CH_2)_2$, CH_2), 1.49–1.37 (m, 2H, CH_2Me), 1.06–0.98 (m, 12H, *t*-BuSi, Me), 0.19 (s, 6H, MeSi (2)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 71.8, 62.9, 38.7, 33.3, 28.0, 25.7, 18.6, 18.0, 14.19, −4.0; MS (ESIMS) *m*/*z* 247 $(M+H)^+$; HRMS (ESI) calcd for $C_{13}H_{31}O_2Si$ $(M+H)^+$ 247.20878, found 247.20890.

*2.1.20. (R)-4-(tert-Butyldimethylsilyloxy)-2-methyleneheptan-1-ol (**30**).* To a solution of oxalyl chloride (1.36 mL, 15.5 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C, dry DMSO (2.20 mL, 31.0 mmol) was added drop wise and stirred for 15 min. A solution of **29** (2.55 g, 10.3 mmol) in dry CH_2Cl_2 (16 mL) was added and stirred for 2 h at −78 °C. It was quenched with Et_3N (17.28 mL, 124.3 mmol) and extracted with CH_2Cl_2 (2×70 mL). The combined organic layers were washed with brine (150 mL), dried (Na_2SO_4), evaporated under reduced pressure, and purified the residue by column chromatography (silica gel, 60–120 mesh, R_f 0.90 EtOAc/*n*-hexane 1:99) to afford aldehyde (2.3 g, 91%) as a colorless liquid.

A mixture of Et_2NH (2.94 mL, 28.27 mmol) and CH_2Br_2 (9.84 mL, 141.39 mmol) was heated at 55 °C for 1.5 h. The reaction mixture was cooled to room temperature and the aldehyde (2.3 g, 9.42 mmol) was added. The resulting mixture was stirred for 5 min. The solvent was evaporated and residue purified by column chromatography (silica gel, 60–120 mesh, R_f 0.90 EtOAc/hexane 2:98) to obtain aldehyde (1.61 g, 66%) as colorless liquid.

To a cooled (−40 °C) solution of aldehyde (1.61 g, 6.28 mmol) in dry CH_2Cl_2 (15 mL), DIBAL-H (4.98 mL, 6.91 mmol, 20% solution in toluene) was added slowly. The reaction mixture was stirred at the same temperature for 30 min, cooled to 0 °C, quenched with methanol (4 mL) and sodium potassium tartrate solution (2 mL).

The reaction mixture was passed through a short pad of Celite. The filtrate was concentrated and purified the residue by column chromatography (silica gel, 60–120 mesh, R_f 0.80 EtOAc/*n*-hexane 5:95) to furnish **30** (1.3 g, 80%) as a colorless liquid. $[\alpha]_D^{25}$ +34.03 (*c* 2.5, $CHCl_3$); IR (neat): 3745, 3589, 3394, 3353, 2926, 2929, 2856, 2307, 1693, 1646, 1550, 1464, 1363, 1253, 1192, 1038, 938, 899, 773, 664 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.07 (s, 1H, Olefinic–H), 4.85 (s, 1H, Olefinic–H), 4.01 (s, 2H, CH_2OH), 3.83–3.80 (m, 1H, CHOSi), 2.91 (br s, 1H, OH), 2.30–2.23 (m, 2H, Allylic–H), 1.48–1.23 (m, 4H, $(CH_2)_2$), 0.87–0.86 (m, 12H, *t*-BuSi, Me), 0.05 (s, 6H, MeSi (2)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.1, 114.2, 71.9, 66.7, 42.0, 38.7, 26.1, 19.1, 14.3, −4.3; MS (ESIMS) *m*/*z* 259 $(M+H)^+$; HRMS (ESI) calcd for $C_{14}H_{31}O_2Si$ $(M+H)^+$ 259.20878, found 259.20890.

*2.1.21. (S)-4-Benzyl-3-((2R,6R)-6-(tert-butyldimethylsilyloxy)-2-methyl-4-methylenenonan-oyl)oxa-zolidin-2-one (**32**).* To a stirred solution of alcohol **30** (1.25 g, 4.84 mmol) in THF (70 mL) at 0 °C, imidazole (0.659 g, 9.68 mmol), TPP (1.52 g, 5.81 mmol) and iodine (1.26 g, 4.84 mmol) were added and stirred for 10 min. Solvent was evaporated and residue purified by column chromatography (silica gel, 60–120 mesh, R_f 0.90 EtOAc/*n*-hexane 3:97) to furnish allyl iodide (1.25 g, 73%) as a colorless liquid.

To a stirred solution of **31** (0.791 g, 3.39 mmol) in anhydrous THF (70 mL) at −78 °C, LiHMDS was added drop wise under nitrogen atmosphere. After stirring for 1 h at −78 °C, allyl iodide (1.25 g, 3.39 mmol) was added and the reaction mixture was stirred at the same temperature for additional 2 h. The reaction mixture was warmed to −20 °C and stirred for additional 12 h. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL) and extracted with EtOAc (2×20 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), evaporated under reduced pressure, and purified the residue by column chromatography (silica gel, 60–120 mesh, R_f 0.60 EtOAc/*n*-hexane 8:92) to furnish **32** (1.20 g, 75%) as a light yellow solid. $[\alpha]_D^{25}$ +8.2 (*c* 0.71, $CHCl_3$); IR (neat): 3744, 3395, 3070, 3049, 2955, 2929, 2856, 2309, 1710, 1645, 1588, 1567, 1462, 1388, 1363, 1262, 1217, 1188, 1086, 920, 822, 773, 739, 702, 612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.20 (m, 5H, Ar–H), 4.80 (s, 2H, Olefinic–H), 4.74–4.63 (m, 1H, CHBn), 4.21–4.13 (m, 2H, OCH_2CHBn), 3.86–3.78 (m, 1H, CHOSi), 3.26 (dd, *J*=13.9, 3.3 Hz, 1H, CH_2Ph), 2.72–2.53 (m, 2H, CH_2Ph, COCHMe), 2.23–2.08 (m, 4H, Allylic–H), 1.47–1.09 (m, 7H, COCHMe, $(CH_2)_2$), 0.91–0.83 (m, 12H, *t*-BuSi, Me), 0.05 (s, 6H, MeSi (2)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.9, 144.0, 135.0, 129.4, 128.8, 127.2, 114.0, 70.9, 66.0, 55.3, 44.0, 40.3, 39.0, 38.0, 35.7, 26.0, 18.6, 17.2, 14.2, −4.3, 4.5; MS (ESIMS) *m*/*z* 496 $(M+Na)^+$, 259 $(M+H)^+$; HRMS (ESI) calcd for $C_{27}H_{43}O_4NNaSi$ $(M+Na)^+$ 496.28536, found 496.28590.

*2.1.22. (2R,6R)-6-(tert-Butyldimethylsilyloxy)-2-methyl-4-methylenenonan-1-ol (**33**).* To stirred solution of **32** (1.15 g, 2.43 mmol) in MeOH (20 mL) under an N_2 atmosphere at 0 °C, $LiBH_4$ (0.064 g, 2.91 mmol) was added in small portions. After 30 min the reaction mixture was quenched with saturated $NaHCO_3$ solution MeOH was evaporated. Water was added and extracted with EtOAc (2 ×20 mL). The organic extracts were washed with brine (50 mL), dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.50 EtOAc/*n*-hexane 15:85) to afford **33** (0.60 g, 82%) as a colorless liquid. $[\alpha]_D^{25}$ +34.6 (*c* 0.41, $CHCl_3$); IR (neat): 3858, 3833, 3745, 3610, 3394, 3075, 2956, 2929, 2857, 2307, 1693, 1643, 1550, 1515, 1465, 1379, 1253, 1073, 1039, 991, 943, 895, 834, 773, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.80 (s, 2H, Olefinic–H), 3.81–3.77 (m, 1H, CHOSi), 3.49 (dq, *J*=10.2, 5.3 Hz, 2H, CH_2OH), 2.21–2.12 (m, 3H, CHMe, Allylic–H), 1.87–1.82 (m, 2H, Allylic–H), 1.45–1.26 (m, 4H, $(CH_2)_2$), 0.91–0.88 (m, 15H, *t*-BuSi, CHMe, Me), 0.04 (d, *J*=2.9 Hz, 6H, MeSi (2)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.4, 113.6, 70.9, 68.2, 43.7, 40.7, 39.0, 33.7, 29.6, 25.8, 18.6, 16.7, 14.2, −4.3; MS (ESIMS) *m*/*z* 301 $(M+H)^+$, 323 $(M+Na)^+$; HRMS (ESI) calcd for $C_{17}H_{37}O_2Si$ $(M+H)^+$ 301.25573, found 301.25596.

*2.1.23. ((4R,8R)-9-(Benzyloxy)-8-methyl-6-methylenenonan-4-yloxy)(tert-butyl)dimethylsilane (**34**).* To a cooled (0 °C) solution of **33** (0.55 g, 1.83 mmol) in dry THF (30 mL), NaH (0.087 g, 3.66 mmol, 60% w/w dispersion in paraffin oil) was added and stirred for 30 min. Then BnBr (0.344 g, 2.01 mmol) was added drop wise and stirred at room temperature for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL) and extracted with EtOAc (2×15 mL). The organic layers were washed with brine (40 mL), dried (Na_2SO_4), evaporated under reduced pressure, and purified the residue by column chromatography (silica gel, 60–120 mesh, R_f 0.80 EtOAc/*n*-hexane 8:92) to afford **34** (0.55 g, 77%). $[\alpha]_D^{25}$ +14.08 (*c* 1.0, $CHCl_3$); IR (neat): 2955, 2928, 2855, 1727, 1642, 1456, 1362, 1252, 1214, 1092, 1039, 943, 895, 834, 752, 696, 666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.24 (m, 5H, Ar–H), 4.77 (d, *J*=6.0 Hz, 2H, Olefinic–H), 4.49 (s, 2H, OCH_2Ph), 3.79–3.77 (m, 1H, CHOSi), 3.35–3.23 (m, 2H, CH_2OBn), 2.23–2.08 (m, 3H, Allylic–H, CHMe), 2.01–1.90 (m, 1H, Allylic–H), 1.80–1.73 (m, 1H, Allylic–H), 1.47–1.25 (m, 7H, $(CH_2)_2$, CHMe), 0.92–0.87 (m, 12H, *t*-BuSi, Me), 0.03 (s, 6H, MeSi (2)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.9, 138.8, 128.2, 127.4, 113.2, 75.6, 72.8, 70.7, 43.9, 40.7, 38.9, 31.5, 29.6, 25.8, 18.6, 17.0, 14.2, −4.4; MS (ESIMS) *m*/*z* 391 $(M+H)^+$, 413 $(M+Na)^+$; HRMS (ESI) calcd for $C_{24}H_{42}O_2NaSi$ $(M+Na)^+$ 413.28463, found 413.28480.

*2.1.24. (4R,8R)-9-(Benzyloxy)-8-methyl-6-methylenenonan-4-ol (**5**).* To a stirred solution of compound **35** (0.50 g, 1.28 mmol) in anhydrous THF was added TBAF (1.92 mL, 1.92 mmol, 1.0 M solution in THF) at 0 °C and reaction mixture stirred at room temperature for 3 h then reaction mixture adsorbed as such on silica and the crude residue was purified by column chromatography (silica gel, 60–120 mesh, R_f 0.70 EtOAc/*n*-hexane 4:96) to afford alcohol **5** (0.252 g, 71%) as a colorless liquid; $[\alpha]_D^{25}$ +0.6 (*c* 1.2, $CHCl_3$); IR (neat): 2955, 2928, 2855, 1727, 1642, 1456, 1362, 1252, 1214, 1092, 1039, 943, 895, 834, 752, 696, 666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.25 (m, 5H, Ar–H), 4.87 (d, *J*=6.0 Hz, 2H, Olefinic–H), 4.48 (s, 2H, OCH_2Ph), 3.79–3.77 (m, 1H, CHOH), 3.34–3.25 (m, 2H, CH_2OBn), 2.22–2.17 (m, 2H, Allylic–H), 2.08–1.94 (m, 2H, Allylic–H), 1.88–1.84 (m, 1H, CHMe), 1.74 (br s, 1H, OH), 1.51–1.20 (m, 4H, $(CH_2)_2$), 0.95–0.83 (m, 6H, CHMe, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.0, 138.6, 127.4, 127.3, 127.5, 113.6, 75.3, 73.0, 69.0, 44.3, 40.5, 39.2, 31.6, 29.6, 25.8, 18.9, 17.4, 14.0; MS (ESIMS) *m*/*z* 277 $(M+H)^+$, 299 $(M+Na)^+$; HRMS (ESI) calcd for $C_{18}H_{28}O_2Na$ $(M+Na)^+$ 299.19815, found 299.19820.

*2.1.25. (S)-((4R,8R)-9-(Benzyloxy)-8-methyl-6-methylenenonan-4-yl)6-((2S,3S,5R)-5-(2-(4-methoxybenzyloxy)ethyl)-3-methyltetrahydrofuran-2-yl)-2-methylhexanoate (**3**).* To a solution of acid **4** (0.055 g, 0.145 mmol) in dry toluene (1 mL) were added diisopropylethylamine (0.076 mL, 0.436 mmol) and 2,4,6-trichlorobenzoyl chloride (0.034 mL, 0.218 mmol) and the reaction mixture was stirred for 10 h at ambient temperature under argon atmosphere. Then alcohol (0.043 g, 0.145 mmol) in toluene (1 mL) was added slowly to the reaction mixture followed by the addition of DMAP (0.017 g, 0.218 mmol) in toluene (1 mL) at ambient temperature. The mixture was stirred for 24 h and quenched with saturated NH_4Cl, extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), evaporated under reduced pressure, and purified the residue by column chromatography (silica gel, 60–120 mesh, R_f 0.70 EtOAc/*n*-hexane 4:96) to afford **33** (0.075 g, 81%) as a light yellow solid. $[\alpha]_D^{25}$ +1.2 (*c* 1.2, $CHCl_3$); IR (neat): 2923, 2852, 1725, 1612, 1512, 1461, 1378, 1247, 1172, 1093, 1029, 899, 822, 739 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$): δ 7.35–7.20 (m, 7H, Ar–H, C_6H_4OMe), 6.87 (d, J=8.6 Hz, 2H, C_6H_4OMe), 5.06–4.98 (m, 1H, CHOCOR), 4.79 (d, J=4.7 Hz, 2H, Olefinic–H), 4.49 (s, 2H, OCH_2Ph), 4.43 (Abq, J=15.2, 3.7 Hz, 2H, $OCH_2C_6H_4OMe$), 4.19–4.10 (m, 1H, $OCHCH_2CH_2OPMB$), 3.82–3.76 (m, 4H, OCHCHMe, OMe), 3.54 (t, J=7.3 Hz, 2H, CH_2OPMB), 3.37–3.32 (m, 1H, CH_2OBn), 3.26–3.20 (m, 1H, CH_2OBn), 2.40–2.13 (m, 5H, Allylic–H, CHMeCOOR), 2.06–1.93 (m, 2H, OCHCHMe, $CHCH_aH_bCH$), 1.76–1.61 (m, 4H, CH_2CH_2OPMB, $CHCH_aH_bCH$, $CHMeCH_2OBn$), 1.54–1.22 (m, 12H, $(CH_2)_6$), 1.11 (d, J=6.7 Hz, 3H, OCHCHMe), 0.93–0.86 (m, 9H, CHMeCOOR, $CHMeCH_2OBn$, CH_2Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.1, 158.8, 143.5, 138.5, 130.4, 129.0, 128.05, 127.2, 127.1, 113.5, 113.4, 80.6, 75.2, 73.6, 72.6, 72.4, 71.2, 67.3, 54.9, 40.5, 40.1, 39.9, 39.6, 36.6, 35.9, 35.5, 33.5, 31.2, 30.1, 27.3, 26.3, 18.3, 17.0, 13.7; MS (ESIMS) m/z 637 $(M+H)^+$, 659 $(M+Na)^+$; HRMS (ESI) calcd for $C_{40}H_{61}O_6$ $(M+H)^+$ 637.44627, found 637.44776.

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