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Stereoselective synthesis of C1-C11 fragment of antitumor cyclodepsipeptide (–)-doliculide

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A general and stereoselective synthetic route for C1-C11 polyketide fragment of doliculide has been achieved in an efficient manner. The key reactions of our synthetic route are enzymatic desymmetrization of *meso*-diol, application of Evans auxiliary to introduce methyl group, Sharpless asymmetric epoxidation and substrate controlled nucleophilic addition reactions.

Keywords: Depsipeptide, enzymatic resolution, marine natural products, Evan's asymmetric methylation, Sharpless asymmetric epoxidation, deoxypropionates

Marine natural products have attracted the attention of biologists and chemists worldwide over the past few decades[1] and have been the source of many biologically active compounds and life-saving drugs[2]. Doliculide **1**, a marine cytotoxic 16-membered cyclodepsipeptide, has been isolated from the Japanese sea hare *Dolabella auricularia* by Yamada, *et al*.[3] It consists of a polyketide fragment and a substituted D-tyrosine unit. Initially the structure of **1** was elucidated by NMR studies, and latter its absolute configuration was determined by stereoselective total synthesis by Yamada and co-workers[4].

Doliculide possesses structural features similar to the family of cyclodepsipeptides known as geodiamolides and jaspamide[5]. It is particularly unique due to the presence of three alternating *syn/syn* methyl groups, deoxypolypropionate structural unit, in the 11-carbon dihydroxy carboxylic acid subunit. Deoxypropiontes are structurally integral part of many natural products (Figure 1). Such natural products exhibit significant biological activities.

Doliculide is a potent cytotoxic agent against HeLa-S3 cells with an IC_{50} value of 1 ng/mL[6]. The relative importance of specific functional groups in doliculide, evaluated by limited structure–activity relationship (SAR), has shown that the presence of the deoxypolypropionate unit and the iodotyrosine motif is essentially important for its cytotoxic activity[3]. The ''hydrocarbon'' portion is assumed to be crucial in conferring a preorganized bioactive conformation. The cytotoxicity of doliculide is due to its ability to bind with the polymerization of actin in developing cells[7]. Doliculide was shown to be a potent and subtype selective antagonist of prostanoid E receptor 3 (EP3)[8,9].

In the course of our efforts towards the total synthesis of complex natural products[10], the structural complexity coupled with significant biological activity of doliculide tempted us to take up its total synthesis. To date, five total syntheses of doliculide have been reported[3,6,11]. In all these earlier reports, synthesis of peptide fragment is nearly same but that of the crucial polyketide fragment differs significantly.

Results and Discussion

Retrosynthetically, target molecule **1** was envisioned to be synthesized from fragments **5** and **6** through a sequence of esterification followed by cycloamidation reaction (Scheme I). Densely substituted C1-C11 polyketide fragment **5** was synthesised from **9** through enzymatic desymmetrization, Evan's asymmetric alkylation,

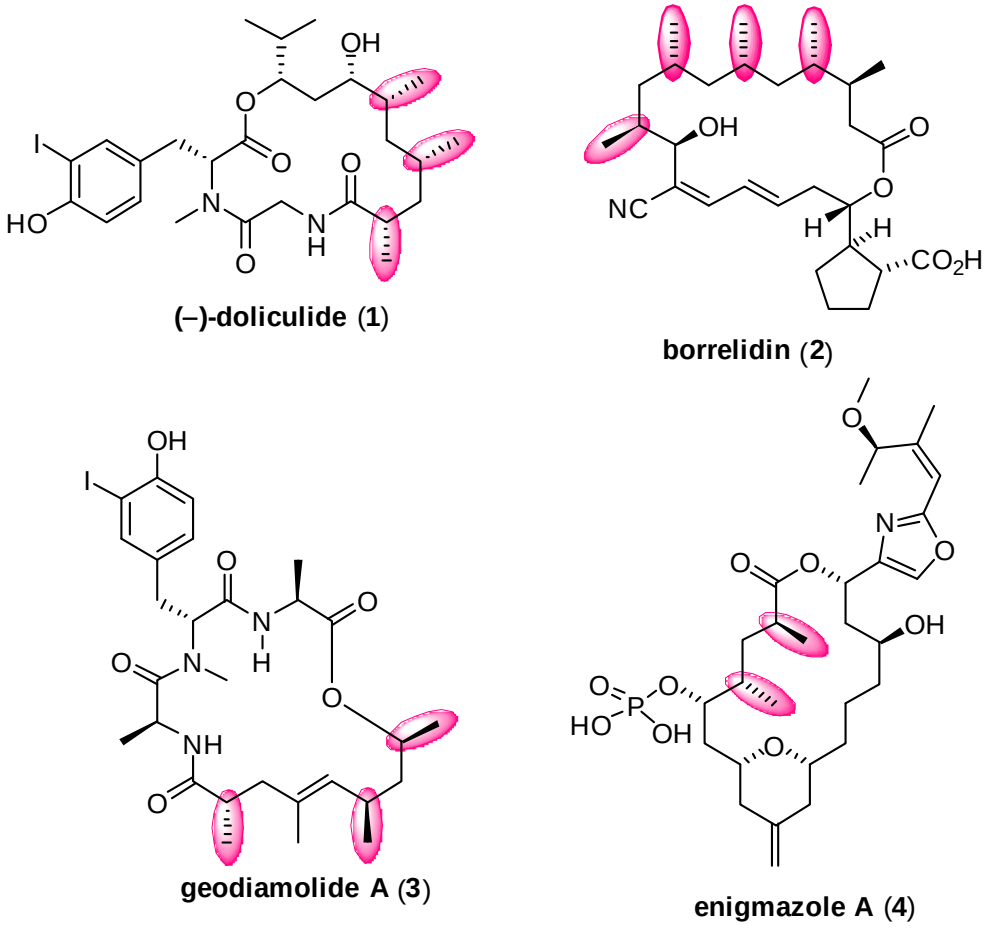
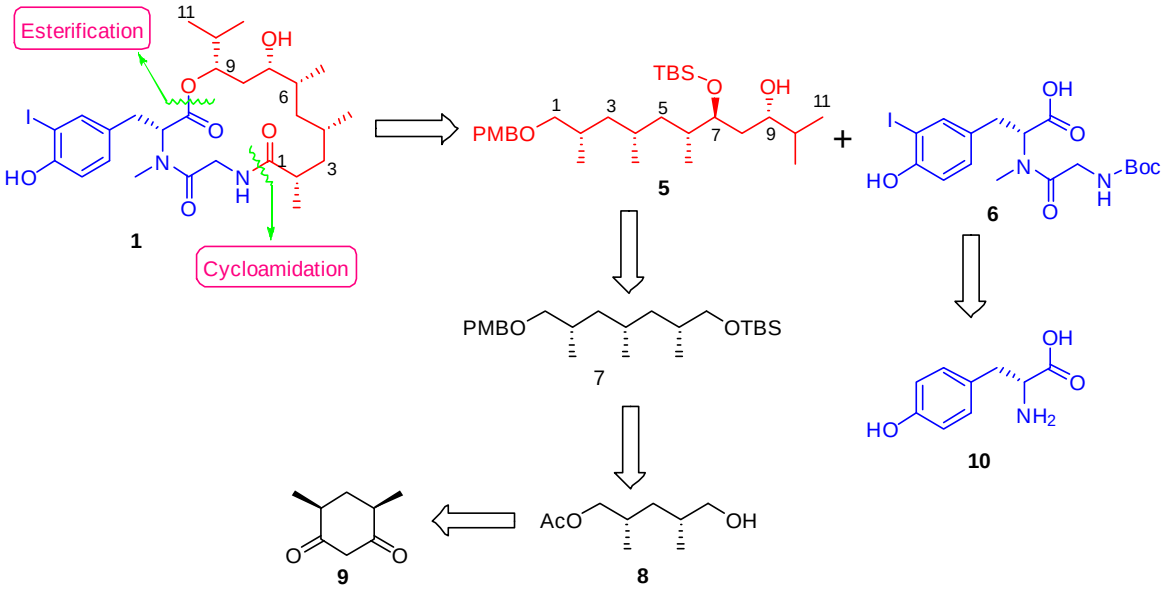


Figure 1 — Some natural products with "deoxypropionate" structural unit



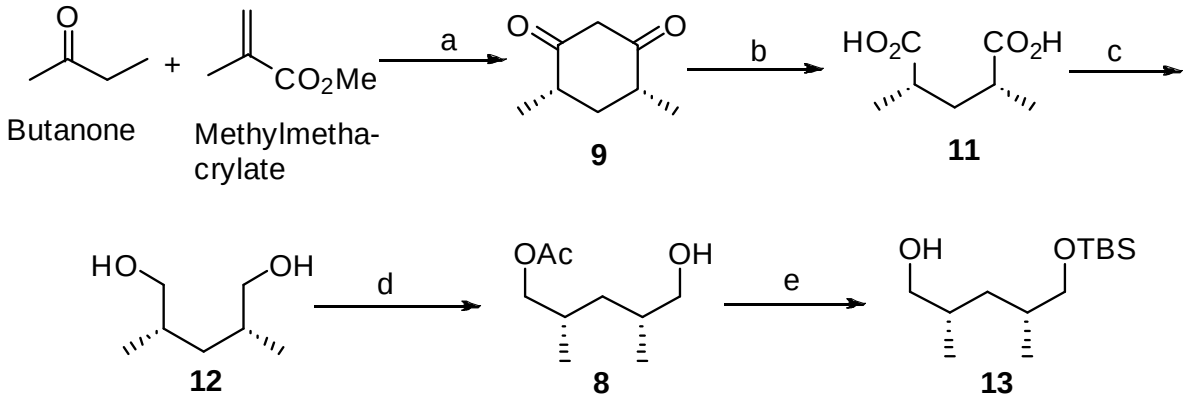
Scheme I — Retro synthetic analysis of (–)-doliculide

Sharpless asymmetric epoxidation, and substrate controlled necleophilic addition reactions. Peptide fragment **6** was assumed to be synthesised from commercially available D-tyrosine **10**.

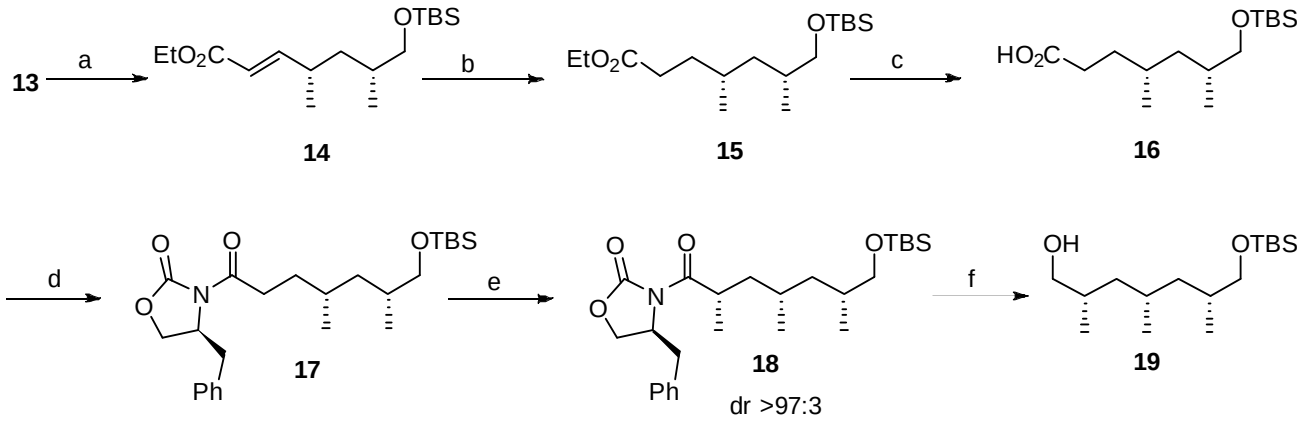
Accordingly, we started the synthesis of **5** from commercially available starting materials butanone and methylmethacrylate (Scheme II). Methylmethacrylate and butanone were condensed to obtain *meso*-dimethyl diketone **9**[12]. Oxidative cleavage of diketone **9** in the presence of $NaIO_4$ furnished *meso*-diacid **11**[13] which in turn was reduced with lithium aluminium hydride to get *meso*-diol **12**. Enzymatic desymmetrization of *meso*-diol **12** with Lipase AK and vinyl acetate in THF resulted in the formation of chiral alcohol **8** in 74% yield and 95% *ee*[14]. Protection of hydroxy group as TBS ether followed by basic hydrolysis of **8** gave alcohol **13**.

Alcohol **13** was oxidized to aldehyde by swern oxidation[15] and resulting aldehyde was treated with Wittig ylide Ph_3PCHCO_2Et to obtain *α, β*-unsaturated ester **14** in 86% yield over two steps (Scheme III). Reduction of double bond in ester **14** with $NiCl_2.6H_2O/NaBH_4$ followed by base catalyzed hydrolysis of ester led to acid **16**. Acid **16** was coupled with (*S*)-oxazolidinone in the presence of pivaloyl chloride, triethyl amine and lithium chloride to obtain compound **17**[16]. Asymmetric methylation[17] of **17** with NaHMDS and CH_3I at −78°C followed by reduction with $NaBH_4$ resulted into *syn*/*syn* deoxypolypropionate intermediate **19** in 88% yield.

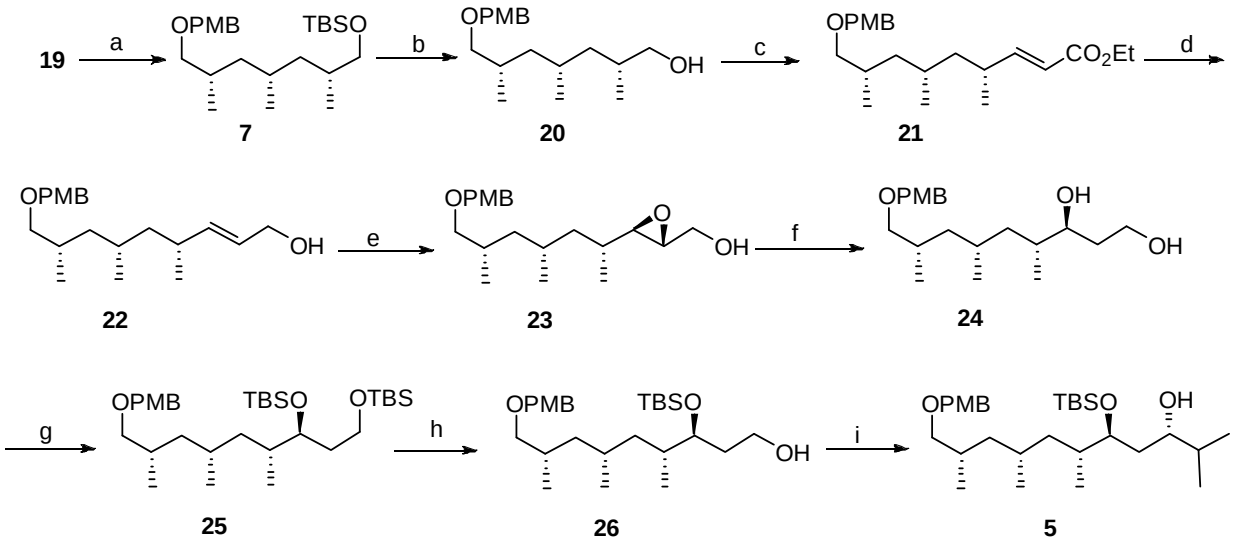
With crucial intermediate **19** in our hand, now stage is set for the introduction of 1,3-anti diol stereocenters at C7 and C9 through Sharpless asymmetric epoxidation and substrate controlled nucleophilic addition. The hydroxyl group in compound **19** (Scheme IV) was protected as its PMB ether using PMB imidate followed by the deprotection of TBS group to end up with alcohol **20** in 97% yield.



Scheme II — (a) NaOMe, Xylene/Benzene, 0°C, 33%; (b) $NaIO_4$, H_2O, 96%; (c) $LiAlH_4$, THF, 97%; (d) Lipase AK, Vinyl acetate, 74%, 95% *ee*; (e) i.TBSCl, imidazole, CH_2Cl_2, 0°C to RT; ii. NaOMe, MeOH, RT, 96% over two steps.



Scheme III — (a) i. $(COCl)_2$, $DMSO,CH_2Cl_2$, −78°C; ii. Ph_3PCHCO_2Et, CH_2Cl_2, RT, 86%; (b) $NiCl_2.6H_2O/NaBH_4$, MeOH 90%; (c) $LiOH{\cdot}H_2O$, MeOH:H_2O (4:1) 93%; (d) (*S*)-oxazolidinone, PivCl, Et_3N, LiCl, THF, −20°C to 0°C, 93%; (e) NaHMDS, CH_3I, THF, −78°C, 91%; (f) $NaBH_4$, MeOH, 0°C to RT, 92%.



Scheme IV — (a) PMBOC(=NH)CCl_3, PPTS, CH_2Cl_2/C_6H_{12}, 76%; (b) TBAF, THF, 97%; (c) i. $(COCl)_2$, DMSO, CH_2Cl_2, −78°C; ii. Ph_3PCHCO_2Et, CH_2Cl_2, RT, 86%; (d) DIBAL-H, CH_2Cl_2,0°C, 2 h, 90%; (e) (–)-DET, CH_2Cl_2, $Ti(O^iPr)_4$, TBHP, −20°C, 12 h, 85%; (f) Red Al, dry THF, 0°C, 3 h, 84%; (g) TBSCl, imidazole, CH_2Cl_2, RT, 24 h, 90%; (h) HF·Pyridine, THF, 4 h, 0°C, 85%; (i) i. $(COCl)_2$, DMSO, CH_2Cl_2, −78°C; ii. Isopropyl bromide, $Mg_{(s)}$, THF, −78°C to 20°C, 55%.

The alcohol **20** was oxidized to aldehyde and the resulting aldehyde was treated with C_2-Wittig ylide to get ester **21** in 86% yield. Ester **21** was reduced to allylic alcohol **22** using DIBAL-*H*.

Allylic alcohol **22** was subjected to Sharpless asymmetric epoxidation conditions[18] to obtain epoxide **23** in 85% yield. Epoxy alcohol **23** was regioselectively opened with Red-Al to obtain 1,3-diol **24**. The 1,3-diol **24** was immediately converted to di-TBS ether **25** using TBSCl in 90% yield, and primary TBS group was selectively deprotected with HF·Pyridine to furnish alcohol **26** in 85% yield. The alcohol **26** was oxidized to aldehyde by Swern oxidation and treated with freshly prepared isopropyl magnesium bromide at −78°C to get desired fragment **5** in 55% yield. The mixture of (*anti/syn*, 80:20) isomers were easily separable in column chromatography. The preference for anti selectivity can be explained through the formation of transition state driven by chelation control[19].

Experimental Section

All reactions were performed under inert atmosphere, if argon mentioned. All glass apparatus used for reactions were perfectly oven/flame dried. Anhydrous solvents were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2, DMSO from CaH_2; MeOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out over silica gel (60–120 mesh) unless otherwise mentioned. Analytical thin layer chromatography (TLC) was run on silica gel 60 F254 pre-coated plates (250 μm thickness). Optical rotations $[\alpha]_D$ were measured on a polarimeter and given in 10^{-1} $degcm^2g^{-1}$. Infrared spectra were recorded in $CHCl_3$/KBr (as mentioned) and reported in wave number (cm^{-1}). Mass spectral data were obtained using MS (EI) ESI, HRMS mass spectrometers. ^{1}H NMR spectra were recorded at 300, 400, 500, 600 and ^{13}C NMR spectra at 75 MHz in $CDCl_3$ solution unless otherwise mentioned. Chemical shifts are in δ (ppm) downfield from tetramethylsilane and coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

(2*S*,4*R*)-5-Hydroxy-2,4-dimethylpentyl acetate, 8: To a stirred solution of meso-diol **12** (4.0 g, 30.30 mmol, 1.0 equiv.) in THF (40 mL) was cooled to 0°C. At this temperature, Amano Lipase AK (220 mg) and vinyl acetate (4.20 mL, 3.90 g, 45.4 mmol, 1.50 equiv) were added. The reaction mixture was stirred for 30 min at 0°C and 7 h at 5°C. The enzyme was removed by suction filtration through Celite. The residue was further washed with diethyl ether (2 × 30 mL) and dried over Na_2SO_4. The homogeneous filtrate was concentrated *in vacuo* and purified by chromatography on silica gel (1:5, EtOAc/hexane) to afford the monoacetate **8** (3.902 g, 74%). $[\alpha]_D^{25}$ + 9.8°

(*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.97 (dd, *J* = 10.5, 5.2 Hz, 1H), 3.85 (dd, *J* = 10.5, 6.7 Hz, 1H), 3.49 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.42 (dd, *J* = 10.5, 6.0 Hz, 1H), 2.05 (s, 3H), 1.96-1.82 (m, 1H), 1.78-1.64 (m, 1H), 1.43 (br, s, 1H), 1.49-1.39 (m, 1H), 1.30-1.15 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.3, 69.1, 67.9, 37.2, 32.9, 29.9, 20.9, 17.8, 17.2.

(2*S*,4*R*)-5-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylpentan-1-ol, 13: To a cold (0°C) solution of alcohol **8** (5.0 g, 28.7 mmol) in anhydrous CH_2Cl_2 (80 mL) was added imidazole (3.9 g, 57.4 mmol) and *tert*-butyldimethylsilylchloride (5.16 g, 34.4 mmol). The resulting mixture was stirred at RT for 3 h. After completion of the reaction as indicated by TLC, the mixture was quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to furnish crude acetate. To the above mixture in MeOH (80 mL) was added sodium methoxide (2.3 g, 43.05 mmol) at RT. Then the mixture was stirred for 1 h at RT and concentrated under reduced pressure. The residue was then quenched by the addition of saturated NH_4Cl and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated in vacuum. The resulting crude product was purified by silica gel column chromatography (1:9 EtOAc/hexane) to give the product as a colorless oil **13** in (6.77 g, 96%) yield. R_f = 0.4 (10% EtOAc/hexane). $[\alpha]_D^{25}$: + 0.9° (*c* 1.2, $CHCl_3$); IR (Neat): 3348, 2954, 2928, 2857, 1466, 1252, 1097, 837, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.50-3.32 (m, 4H), 1.77-1.60 (m, 2H), 1.50-1.36 (m, 2H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 68.2, 67.9, 37.2, 33.1, 25.8, 18.2, 17.7, 17.6, −5.4.

(4*S*,6*R*,*E*)-Ethyl 7-(*tert*-butyldimethylsilyloxy)-4,6-dimethylhept-2-enoate, 14: To a stirred solution of oxalyl chloride (3.43 mL, 40.5 mmol) in dry CH_2Cl_2 (20 mL) at −78°C, was added DMSO (4.32 mL, 60.8 mmol) drop-wise under nitrogen atmosphere. After 15 min stirring, a solution of alcohol **13** (5 g, 20.28 mmol) in 20 mL of dry CH_2Cl_2 was added. After 45 min of stirring at −78°C, Et_3N (17 mL, 122 mmol) was added and the mixture was stirred for 0.5 h at −78°C and then for 0.5 h at 0°C. The mixture was then quenched with sat. NH_4Cl solution (30 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with water (100 mL), followed by brine (100 mL) solution, dried over Na_2SO_4, and concentrated *in vacuo*. To the above crude mixture (4.94 g, 20.1 mmol) in CH_2Cl_2 (150 mL) was added (ethoxycarbonylmethylene) triphenyl phosphorane (17.0 g, 48.9 mmol) and resulting mixture was stirred for 12 h at RT. The reaction mixture was concentrated under reduced pressure and purified on silica gel chromatography (5% EtOAc/hexane) to afford the unsaturated ester **14** (7.3 g, 86% over two steps) as a colourless liquid. R_f = 0.5 (10% EtOAc/hexane). $[\alpha]_D^{25}$: +17.9° (*c* = 1.0 in $CHCl_3$); IR (Neat): 2957, 2859, 1722, 1652, 1465, 1367, 1259, 1180, 1094, 1042, 840, 775 cm^{-1}; HRMS (ESI): Calcd for $C_{17}H_{34}O_3NaSi$: 337.2174. Found: 337.2174; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.76 (dd, *J* = 15.8, 8.3 Hz, 1H), 5.75 (d, *J* = 15.8 Hz, 1H), 4.17 (q, *J* = 14.3, 6.7 Hz, 2H), 3.37 (dd, *J* = 5.2, 1.5 Hz, 2H), 2.51-2.32 (m, 1H), 1.67-1.44 (m, 2H), 1.29 (t, *J* = 6.7 Hz, 3H), 1.15-1.06 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.7, 154.3, 119.7, 68.3, 60.0, 39.8, 34.1, 33.3, 25.8, 20.4, 18.2, 16.5, 14.2, −5.4.

(4*R*,6*R*)-Ethyl 7-(*tert*-butyldimethylsilyloxy)-4,6-dimethylheptanoate, 15: To a cooled (0°C) solution of **14** (7.2 g, 22.9 mmol) and $NiCl_2.6H_2O$ (1.08 g, 4.58 mmol) in MeOH (100 mL), was added $NaBH_4$ (2.0 g, 54.9 mmol) in small portions to the solution. During addition of $NaBH_4$, the reaction temperature was maintained at 0°C. After complete addition of $NaBH_4$, the reaction mixture was stirred for 1 h at RT and the resulting black precipitate was filtered and then washed with MeOH. The solvent was removed under reduced pressure and then diluted with water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure followed by purification on silica gel column chromatography using ethyl acetate/hexane (5% EtOAc/hexane) gave the product **15** (6.9 g, 96% yield) as a colorless oil. R_f = 0.5 (10% EtOAc/hexane). $[\alpha]_D^{25}$: +3.8° (*c* = 1.2 in $CHCl_3$); IR (Neat): 2956, 1738, 1636, 1253, 1094, 772, 570 cm^{-1}; HRMS (ESI): Calcd for $C_{17}H_{36}O_3NaSi$: 339.2331. Found: 339.2321; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.10 (q, *J* = 14.3, 6.7 Hz, 2H), 3.41 (dd, *J* = 9.8, 6.0 Hz, 1H), 3.33 (dd, *J* = 9.8, 6.0 Hz, 1H), 2.34-2.18 (m, 2H), 1.75-1.28 (m, 6H),

1.26 (t, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.87 (d, *J* = 6.0 Hz, 3H)), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.0, 68.2, 60.1, 40.7, 33.0, 31.8, 31.5, 29.6, 25.9, 20.0, 18.2, 17.3, 14.2, −5.4.

(4*R*,6*R*)-7-(*tert*-Butyldimethylsilyloxy)-4,6-dimethylheptanoic acid, 16: $LiOH·H_2O$ (2.7 g, 64.5 mmol) was added portion wise to a cooled solution (0°C) of ester **15** (6.8 g, 21.5 mmol) in 80 mL of CH_3OH:H_2O (4:1) and the stirring was continued for 2 h at RT. The reaction mixture was then concentrated in vacuum and the residue was diluted with EtOAc (80 mL) and washed with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Removal of solvent followed by column chromatography using 20% EtOAc/hexane afforded the acid **16** (5.7 g, 93% yield) as a colorless liquid. R_f = 0.3 (10% EtOAc/hexane). $[\alpha]_D^{25}$: +5.0° (*c* = 0.7 in $CHCl_3$); IR (Neat): 2956, 2930, 2858, 1711, 1464, 1414, 1253, 1094, 938, 839, 775, 667 cm^{-1}; HRMS (ESI): Calcd for $C_{15}H_{32}O_3NaSi$: 311.2018. Found: 311.2028; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.45-3.30 (m, 2H), 2.42-2.24 (m, 2H), 1.78-1.06 (m, 6H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.88 (d, *J* = 6.7 Hz, 3H)), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 180.2, 68.1, 40.6, 33.0, 31.5, 31.2, 29.6, 25.9, 19.9, 18.3, 17.4, −5.3.

(4*R*)-4-Benzyl-3-((4*R*,6*R*)-7-(tert-butyldimethylsilyloxy)-4,6-dimethylheptanoyl) dihydrofuran-2(3H)- one, 17: To a stirred solution of acid **16** (5.6 g, 19.4 mmol) in THF (100 mL) at −20°C was added Et_3N (6.74 mL, 48.5 mmol) followed by PivCl (2.4 mL, 19.4 mmol). After stirring for 1 h at –20°C, LiCl (1.23 g, 29.1 mmol) followed by (*S*)-oxazolidinone (3.77 g, 21.3 mmol) were added to it at the same temperature. The stirring was continued for 1 h at −20°C and then 2 h at 0°C. It was then quenched with saturated NH_4Cl solution (50 mL) and extracted with ethyl acetate (2 × 80 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (1:16) to gave **17** (8.0 g, 93%) as a viscous liquid. R_f = 0.5 (10% EtOAc/hexane). $[\alpha]_D^{25}$: +38.8° (*c* = 1.0 in $CHCl_3$); IR (Neat): 2954, 2928, 2857, 1784, 1700, 1461, 1386, 1353, 1251, 1208, 1093, 839, 772, 701, 591cm^{-1}; HRMS (ESI): Calcd for $C_{25}H_{41}NO_4Si$ Na: 470.2702. Found: 470.2714; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38-7.15 (m, 5H), 4.67-4.54 (m, 1H), 4.23-4.09 (m, 2H), 3.43 (dd, *J* = 9.8, 5.2 Hz, 1H), 3.40-3.25 (m, 2H), 3.03-2.78 (m, 2H), 2.69 (dd, *J* = 13.5, 9.8 Hz, 1H), 1.80-1.08 (m, 6H), 0.95 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.6, 153.3, 135.3, 129.3, 128.8, 127.2, 68.2, 66.0, 55.1, 40.8, 37.8, 33.1, 33.0, 30.8, 29.7, 25.9, 20.0, 18.3, 17.4, −5.3.

(4*R*)-4-Benzyl-3-((2*S*,4*S*,6*R*)-7-(*tert*-butyldimethylsilyloxy)-2,4,6-trimethylheptanoyl) dihydrofuran-2(3*H*)-one, 18: To a stirred solution of **17** (4.0 g, 8.9 mmol) in anhydrous THF (80 mL) at −78°C, NaHMDS (1M solution in THF, 13.35 mL, 13.35 mmol) was added slowly dropwise with stirring under nitrogen atmosphere. After stirring at −78°C for 30 min, MeI (1.56 mL, 26.7 mmol) was added dropwise to the reaction mixture and then stirring was continued for another 2 h at −78°C. Then the mixture was quenched with saturated NH_4Cl (50 mL) and warmed to RT and then extracted with ethyl acetate (2× 100 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (1:19) to afford the product **18** as a colorless liquid (3.73 g, 91%). R_f = 0.6 (10% EtOAc/hexane). $[\alpha]_D^{25}$: +41.6° (*c* = 1.3 in $CHCl_3$); IR (Neat): 2954, 2928, 2857, 1784, 1700, 1461, 1386, 1353, 1251, 1208, 1093, 839, 772, 701, 591cm^{-1}; HRMS (ESI): Calcd for $C_{26}H_{43}O_4$ Si Na: 484.2859. Found: 484.2875; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37-7.17 (m, 5H), 4.68-4.55 (m, 1H), 4.22-4.08 (m, H), 3.93-3.77 (m, 1H), 3.47-3.22 (m, 3H), 2.70 (dd, *J* = 12.8, 9.8 Hz, 1H), 1.98-1.25 (m, 5H), 1.20 (d, *J* = 6.7 Hz, 3H), 1.12-0.96 (m, 1H), 0.89 (s, 9H), 0.88 (d, *J* = 6.7 Hz, 6H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.2, 152.9, 135.2, 129.4, 128.8, 127.2, 68.3, 65.9, 55.2, 41.2, 40.4, 37.8, 35.2, 33.0, 28.1, 25.9, 20.7, 18.5, 18.3, 17.4, −5.3.

(2*S*,4*R*,6*R*)-7-(*tert*-Butyldimethylsilyloxy)-2,4,6-trimethylheptan-1-ol, 19: To a stirred solution of **18** (5.0 g, 10.8 mmol) in MeOH (40 mL) at 0ºC was added $NaBH_4$ portion wise (1.23 g, 32.4 mmol). The reaction mixture was allowed to stir for 1 h at same temperature and then quenched with saturated NH_4Cl solution. The solvent was removed under reduced pressure and the resulting residue was diluted with water and extracted with EtOAc (3 × 100 mL). The combined organic layers

were dried over Na_2SO_4 and concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (10%, EtOAc/hexane) to afford the pure product **19** (2.86 g, 92%) as a viscous liquid. R_f = 0.5 (10% EtOAc/hexane). $[\alpha]_D^{25}$: 5.8° (*c* = 1.0 in $CHCl_3$); IR (Neat): 3351, 2956, 2928, 2858, 1465, 1383, 1253, 1098, 1040, 838, 775, 667 cm^{-1}; HRMS (ESI): Calcd for $C_{16}H_{36}O_2$ Si Na: 311.2382. Found: 311.2398; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.55-3.29 (m, 4H), 2.60 (s, 1H), 1.88-0.96 (m, 7H), 0.93 (d, *J* = 7.5 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 68.1, 67.9, 41.2, 41.0, 33.0, 27.6, 25.9, 21.0, 18.3, 17.9, 17.5, −5.3.

***tert*-Butyl(((2*R*,4*R*,6*S*)-7-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptyl)oxy)dimethylsilane, 7**: *p*-Methoxybenzyl trichloroacetimidate (9.79g, 34.66 mmol) and PPTS (435 mg, 1.73 mmol) were added over 5 min to a solution of compound **19** (2g, 6.93 mmol) in CH_2Cl_2/cyclohexane (1/2, 80 mL) at 0°C. The reaction mixture was stirred at ambient temperature for 48 h before it was filtered through a pad of Celite. The filtrate was evaporated and the residue was purified by flash chromatography (hexanes/ethyl acetate, 40/2) to give the title compound **7** as a colorless oil (2.2g, 78%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39-7.5 (m, 2H), 7.01-7.07 (m, 2H), 4.55-4.84 (m, 2H), 3.97 (s, 3H), 3.62 (dd, *J* = 9.8, 4.5 Hz, 1H), 3.45-3.52 (m, 2H), 3.32 (dd, *J* = 9.1, 7.5 Hz, 1H), 1.96-2.1 (m, 1H), 1.68-1.91 (m, 3H), 1.41-1.56 (m, 2H), 0.94-1.11 (m, 19H), 0.2 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 129.0, 113.6, 75.6, 72.5, 68.0, 55.1, 41.7, 41.0, 33.0, 30.8, 27.6, 25.9, 21.0, 18.2, 17.9, −5.4.

(2*R*,4*S*,6*S*)-7-((4-Methoxybenzyl)oxy)-2,4,6-trimethylheptan-1-ol, 20: A solution of TBAF in THF (1 M, 28.9 mL, 28.9 mmol) was added dropwise to a solution of compound **7** (2.2 g, 5.38 mmol) in THF (60 mL). After stirring for 3 h, the reaction was quenched with sat. aq. NH_4Cl (30 mL) and diluted with tert-butyl methyl ether and water. The aqueous layer was extracted with *tert*-butyl methyl ether and the combined organic phases were dried over Na_2SO_4, filtered and evaporated. Flash chromatography (hexanes/ethyl acetate, 2/1) of the residue provided the title alcohol **20** as a colorless oil (1.53 g, 97%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23-7.28 (m, 2H), 6.85-6.9 (m, 2H), 4.38-4.47 (m, 2H), 3.81 (s, 3H), 3.52 (dd, *J* = 10.5, 5.3 Hz, 1H), 3.25-3.41 (m, 2H), 3.18 (dd, *J* = 9.0, 7.5 Hz, 1H), 1.78-1.90 (m, 1H), 1.49-1.78 (m, 3H), 1.23-1.39 (m, 3H), 0.86-0.97 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 130.7, 129.0, 113.5, 75.4, 72.5, 67.9, 55.1, 41.5, 41.0, 32.9, 30.8, 27.5, 20.9, 18.3, 17.5.

Ethyl (4*R*,6*S*,8*S*,*E*)-9-((4-methoxybenzyl)oxy)-4,6,8-trimethylnon-2-enoate, 21: To a stirred solution of oxalyl chloride (0.6 mL, 6.8 mmol) in dry CH_2Cl_2 (20 mL) at −78°C, was added DMSO (0.73 mL, 10.2 mmol) drop-wise under nitrogen atmosphere. After 15 min stirring, a solution of alcohol **20** (1.0g, 3.4 mmol) in 20 mL of dry CH_2Cl_2 was added. After 45 min of stirring at −78°C, Et_3N (2.8 mL, 20.4 mmol) was added and the mixture was stirred for 0.5 h at −78°C and then for 0.5 h at 0°C. The mixture was then quenched with sat. NH_4Cl solution (30 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with water (100 mL), followed by brine (100 mL) solution, dried over Na_2SO_4, and concentrated *in vacuo*. To a stirred solution of the above crude aldehyde in benzene was added stabilized ylide, Ph_3PCHCO_2Et (2.62g, 6.12 mmol) and the mixture was allowed to reflux for 2 h. It was then concentrated *in vacuo*. Purification of the crude ester by column chromatography on silica gel (1:9 EtOAc/hexane) gave the pure unsaturated ester **21** (1.06g, 86% over two steps) as a colourless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25 (d, *J* = 8.309 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 6.8 (dd, *J* = 15.8, 8.3 Hz, 1H), 5.78 (d, *J* = 15.8 Hz, 1H), 4.37-4.46 (m, 2H), 4.18 (qt, *J* = 7.5 Hz, 2H), 3.8 (s, 3H), 3.28 (dd, *J* = 9.0, 5.2 Hz, 1H), 3.17 (dd, *J* = 9.0, 6.7 Hz, 1H), 2.34-2.49 (m, 1H), 1.75-1.89 (m, 1H), 1.45-1.57 (m, 1H), 1.26-1.43 (m, 3H), 1.28 (t, *J* = 7.5 Hz, 3H), 1.05-1.13 (m, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.6, 158.8, 154.3, 130.6, 128.9, 119.6, 113.5, 75.5, 72.4, 59.9, 55.0, 43.3, 41.7, 34.0, 30.5, 27.6, 20.3, 20.0, 17.7, 14.1.

(4*R*,6*S*,8*S*,*E*)-9-((4-Methoxybenzyl)oxy)-4,6,8-trimethylnon-2-en-1-ol, 22: To a stirred solution of ester **21** (1g, 2.75 mmol) in dry dichloromethane (15 mL) at 0°C was added a solution of DIBAL-H (8.3 mL of 1.0 M solution in toluene, 8.27 mmol) drop-wise. The resulting mixture was stirred for 1 h at RT and then quenched with methanol and sat.sodium potassium tartarate solution (15 mL) at 0°C. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and purified by column

chromatography (3:7, EtOAc/hexane) to give the allyl alcohol **22** (800 mg, 90%) as oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25 (dd, *J* = 8.6, 2.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.6 (dt, *J* = 15.4, 5.4 Hz, 1H), 5.46 (dd, *J* = 15.4, 7.9 Hz, 1H), 4.37-4.47 (m, 2H), 4.06 (d, *J* = 5.4 Hz, 2H), 3.8 (s, 3H), 3.28 (dd, *J* = 9.0, 5.4 Hz, 1H), 3.17 (dd, *J* = 8.8, 6.7 Hz, 1H), 2.16-2.33 (m, 1H), 1.83 (m, 1H), 1.43-1.56 (m, 1H), 1.21-1.35 (m, 3H), 0.9-1.03 (m, 2H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 138.7, 130.7, 129.0, 127.4, 113.5, 75.7, 72.5, 63.6, 55.1, 44.1, 41.8, 33.9, 30.6, 27.6, 21.5, 20.3, 17.8.

((2*R*,3*R*)-3-((2*R*,4*R*,6*S*)-7-((4-Methoxybenzyl)oxy)-4,6-dimethylheptan-2-yl)oxiran-2yl) methanol, 23: To a stirred suspension of powdered 4 Å molecular sieves in CH_2Cl_2 (8 mL) at −20°C were added L-(–)-DET (16 µL, 0.86 mmol) and Ti(O-^{i}Pr)$_4$ (22 µL, 0.69 mmol). After 30 min, a solution of allylic alcohol **22** (200 mg, 0.62 mmol) in CH_2Cl_2 (5 mL) was added to the above suspension, and then 5M TBHP in toluene (0.24 mL, 1.25 mmol) was added. The resulting mixture was stirred at −20°C for 6 h and then quenched with H_2O (6 mL). The above mixture was treated with 3M NaOH and then saturated with solid NaCl and the resulting mixture was stirred vigorously for 30 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–*n*-hexane, 3:7) to afford the epoxy alcohol **23** (175 mg, 85%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26 (d, *J* = 7.5 Hz, 2H), 6.88 (d, *J* = 7.5 Hz, 2H), 4.36-4.47 (m, 2H), 3.82-3.94 (m, 1H), 3.81 (s, 3H), 3.54-3.64 (m, 1H), 3.30 (dt, *J* = 13.5, 3.7 Hz, 1H), 3.19 (dd, *J* = 9.0, 6.7 Hz, 1H), 2.88-2.98 (m, 1H), 2.63-2.75 (m, 1H), 1.70.1.91 (m, 2H), 1.26-1.63 (m, 3H), 0.81-1.10 (m, 11H).

(*S*)-5-((2*R*,4*R*,6*S*)-7-((4-Methoxybenzyl)oxy)-4,6-dimethylheptan-2-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane, 26: To a stirred solution of compound **23** in THF was added Red-Al (1M in THF) at 0°C after completion of starting material **23** the reaction mixture was quenched with aq. solution of NH_4Cl, extracted with EtOAc and organic layer was concentrated under reduced pressure to give crude 1,3-diol **24** which was subjected to further reaction without purification. To a solution of **24** (100 mg, 0.29 mmol) in dry CH_2Cl_2 (8 mL) was added imidazole (60 mg, 0.89 mmol) in one portion and stirred for 30 minutes at 0°C followed by *tert*-butyldimethylsilyl chloride. The reaction mixture was stirred for 6-12 h with the temperature slowly reaching RT. It was quenched with the saturated NH_4Cl solution (8 mL), diluted with EtOAc (10 mL), washed with brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the crude product by column chromatography afforded **25** (134 mg, 80%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 7.6 Hz, 2H), 4.38-4.45 (m, 2H), 3.8 (s, 3H), 3.65-3.74 (m, 2H), 3.57-3.64 (m, 1H), 3.29-3.37 (m, 1H), 3.15 (qt, *J* = 7.6 Hz, 1H), 1.80-1.88 (m, 1H), 1.67-1.75 (m, 1H), 1.56-1.64 (m, 2H), 1.26-1.42 (m, 2H), 1.18-1.24 (m, 1H), 0.77-0.98 (m, 29H), 0.04 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 129.0, 113.6, 75.7, 75.3, 72.6, 71.5, 60.5, 60.3, 55.2, 41.7, 41.4, 40.7, 40.4, 36.4, 36.0, 35.3, 34.2, 30.8, 27.9, 27.6, 25.9, 25.8, 21.2, 21.1, 18.4, 18.3, 15.4, 14.6, −4.3, −4.4, −4.5, −5.3.

(3*S*,4*R*,6*R*,8*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-9-((4-methoxybenzyl)oxy)-4,6,8-trimethylnonan-1-ol, 26: HF/pyridine in pyridine (4.0 mL, prepared by slow addition of 1.2 mL pyridine to 0.3 mL HF/pyridine complex, followed by dilution with 2.5 mL THF), from the liquor solution 0.5mL was added to a solution of TBS ether **25** (50 mg, 0.09 mmol) in THF (3 mL). The mixture was stirred overnight at RT and quenched with saturated $NaHCO_3$ (10 mL). The aqueous layer was separated and extracted with Et_2O (3×10 mL). The combined organic layers were washed with saturated $CuSO_4$ (3 × 10 mL), dried over Na_2SO_4, and concentrated. Flash column chromatography (EtOAc/hexane 1:9) afforded (34 mg, 85%) of alcohol **26** as colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25 (d, *J* = 6.6 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.42 (m, 2H), 3.81 (s, 3H), 3.66-3.78 (m, 3H), 3.28-3.38 (m, 1H), 3.12-3.21 (m, 1H), 1.64-1.87 (m, 3H), 1.15-1.42 (m, 2H), 0.81-0.96 (m, 22H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 130.8, 129.0, 113.6, 75.5, 74.2, 72.6, 61.0, 55.2, 41.6, 41.2, 39.9, 35.9, 35.6, 34.8, 32.9, 30.9, 27.7, 25.8, 21.2, 16.0, 14.2, −4.2, −4.7.

(3*S*,5*S*,6*R*,8*R*,10*S*)-5-((*tert*-Butyldimethylsilyl) oxy)-11-((4-methoxybenzyl)oxy)-2,6,8,10-tetra-methylundecan-3-ol, 5: To a stirred solution of oxalyl chloride (3.7 µL, 0.044 mmol) in dry CH_2Cl_2 (2 mL) at −78°C, was added DMSO (4.5 µL, 0.066 mmol) drop-wise under nitrogen atmosphere.

After 15 min stirring, a solution of alcohol **26** (10 mg, 0.022 mmol) in 2 mL of dry CH_2Cl_2 was added. After 45 min of stirring at −78°C, Et_3N (50 µL, 0.1326 mmol) was added and the mixture was stirred for 0.5 h at −78°C and then for 0.5 h at 0°C. The mixture was then quenched with sat. NH_4Cl solution (3 mL) and extracted with CH_2Cl_2 (2 × 8 mL). The combined organic layers were washed with water (5 mL), followed by brine (3 mL) solution, dried over Na_2SO_4, and concentrated *in vacuo* to get aldehyde. To a suspension of powdered Mg (2.7 mg, 0.113 mmol) in anhydrous THF (2 mL) was added dropwise 2-bromopropane (2.2 µL, 0.111 mmol) under a dry argon atmosphere. After being stirred for 1 h at RT, the mixture was cooled to −78°C, and a solution of aldehyde (10 mg, 0.022 mmol) in anhydrous THF (2 mL) was added drop-wise *via* cannula. The mixture was allowed to warm toRT and was stirred for 12 h. A saturated aqueous solution of NH_4Cl (3 mL) was slowly added and the mixture was extracted with ether (15 mL). The organic phase was washed with brine, dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography (gradient, 4.5% steps, ethyl acetate/hexanes, 1:9 to 3:2) to give alcohol **5** (6 mg, 55%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.42 (m, 2H), 3.8 (s, 3H), 3.77-3.89 (m, 1H), 3.58 (bs, 1H), 3.32 (dd, *J* = 9.0, 5.0 Hz, 1H), 3.16 (dd, *J* = 9.0, 6.9 Hz, 1H), 2.4 (d, *J* = 3.5 Hz, 1H), 1.78-1.9 (m, 2H), 1.51-1.68 (m, 3H), 1.26-1.41 (m, 5H), 0.81-0.95 (m, 24H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 129.0, 113.6, 75.4, 73.6, 73.4, 72.6, 55.2, 41.5, 41.3, 35.6, 34.4, 34.0, 30.9, 27.6, 25.8, 21.3, 18.5, 18.4, 17.7, 14.6, −4.3, −4.5.

Conclusion

In summary, we have achieved the synthesis of C1-C11 fragment of antitumor cyclodepsipeptide doliculide with 6.8% overall yield in 17 longest linear steps starting from **12** following enzymatic desymmetrization, Evan's asymmetric alkylation, Sharpless asymmetric epoxidation, and substrate controlled nucleophilic addition reactions as key steps. Total synthesis of doliculide and the biological activity of its derivatives are under study and will be published in due course.

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