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An iterative, facile stereoselective synthesis of C1-C11 fragment of borrelidin *via* enzymatic desymmetrization strategy†

Jhillu Singh Yadav* and Nagendra Nath Yadav

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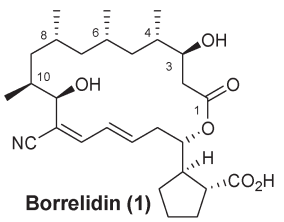
A highly stereoselective and general method for the synthesis of the C1-C11 fragment of borrelidin has been achieved. The main feature of our synthetic route is enzymatic desymmetrization to create two methyl bearing chiral centres, use of Evans auxiliary to introduce two other methyl groups and creation of C3 stereocentre by regioselective opening of an epoxide arising from Sharpless epoxidation protocol. The synthesis of the C1-C11 subunit was achieved in gram scale by a linear synthetic sequence in an overall yield of 18.4%.

Introduction

Natural products derived from polydeoxypropionates are well known to exhibit various biological activities for instance, calcium ionophore ionomycin,[1] which is responsible to chelate various inorganic cations (especially Ca^{++}) and to transport them across lipid membranes, cytotoxic cyclodepsipeptide (–)-doliculide,[2] immune response inducing agent Sulfolipid-I (2,3,6,6′-tetraacyltrehalose 2′-sulfate),[3] the pheromones hexamethyldocosane,[4] vittatalactone,[5] lardolure[6] as well as the cytotoxic metabolite borrelidin. Borrelidin (**1**) a structurally unique 18-membered macrolide antibiotic possessing anti-*Borrelia* activity was first isolated by Berger *et al.*[7] from *Streptomyces rochei* in 1949. The planar structure of borrelidin was assigned by Keller-Schierlein[8] in 1967, and the absolute configuration was determined by Anderson *et al.*[9] by the X-ray crystallography of a chiral solvate. Borrelidin (**1**) exhibits many interesting biological activities such as antiviral,[10] anti-angiogenesis,[11] antibacterial activity which involves selective inhibition of threonyl tRNA synthatase,[7,12] and inhibitory activity towards cyclin-dependent kinase Cdc28/Cln2 of *Saccharomyces cerevisiae*.[13] The structural features of borrelidin (**1**) includes the presence of deoxy propionate moiety with four methyl groups at 4,6,8 and 10 positions in a *syn*/*syn*/*anti* relationship, a *Z*/*E* cyanodiene unit at C12-C15, and a cyclopentane carboxylic acid subunit at C17 (Fig. 1). These complex structural features and interesting biological activity of borrelidin has prompted many synthetic efforts towards the total synthesis as well as formal synthesis.

The first total synthesis was reported Morken and co-workers,[14] followed by efforts from various other groups for the total synthesis[15,16] as well as formal synthesis.[17,18] The reported strategies are essentially based on chiral pool starting materials, iterative catalytic approach, chiral-reagent based strategy, chiral auxiliaries and kinetic resolution. Most recently Minnaard reported the formal synthesis of borrelidin using Cu/Josiphos-catalysed iterative asymmetric conjugate addition of MeMgBr to create the methyl centres.[18f] In the retrosynthetic analysis of Omura and co-workers,[15c,e] **1** was disconnected into two fragments (**2**, **3**), of which the upper part was achieved by kinetic resolution, alkyne addition to aldehyde, chelation-controlled carbotitanation of the homoallylic alcohol under slightly modified Thompson's conditions and hydrogenation using Rh[(nbd)dppb]BF_4 catalyst as key steps.

Our continuing interest in the total synthesis of biologically active natural products by enzymatic desymmetrization strategy[5e,19] and the inherent biological activity of borrelidin (**1**) encouraged us to explore the synthesis of this molecule. We herein, report a facile and general method for the stereoselective synthesis of C1-C11 (**2**) fragment of **1** using Evans alkylation iteratively and regioselective opening of a chiral



Borrelidin (1)

Fig. 1 Chemical structure of Borrelidin (**1**).

Division of Natural Products Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad, 500 607, India. E-mail: yadavpub@iict.res.in; Fax: +91-40-27160512

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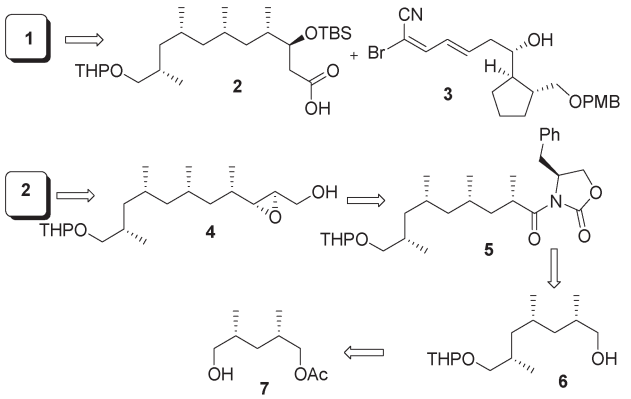


Scheme 1 Retrosynthetic analysis of borrelidin **1**.

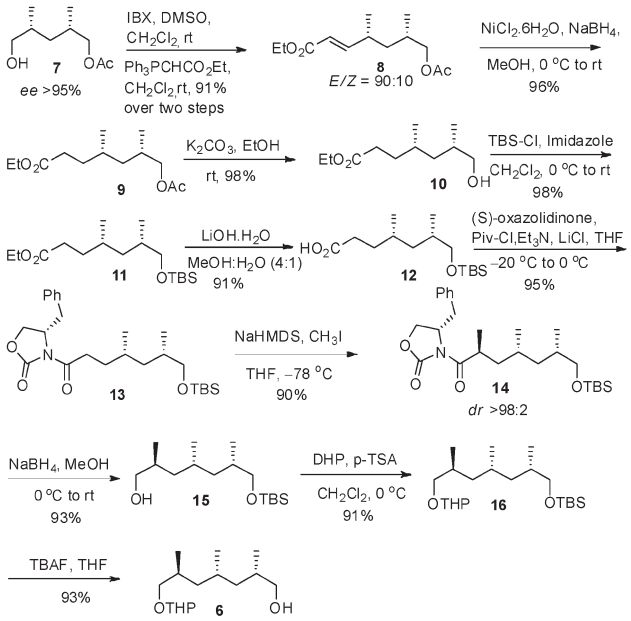
epoxide to generate the three of the five stereogenic centres with good diastereoselectivity.

Results and discussion

The retrosynthetic approach to **1** is depicted in Scheme 1. The target molecule **1** was envisioned to be obtained by coupling of carboxylic acid **2** with the alcohol **3**.[15c,e] Compound **2** can be easily obtained from regioselective opening of epoxide **4**. Further, compound **4** can be obtained from **5** by a sequence of reactions such as reduction with $NaBH_4$, Wittig reaction, DIBAL-H reduction and Sharpless asymmetric epoxidation. Compound **5** can in turn be obtained from a known compound **7** *via* **6** by means of Wittig reaction followed by stereoselective Evans methylation.

Our synthesis began with a known precursor **7**[20,21] possessing two chiral centres which was synthesized by desymmetrization of a *meso*-diol using porcine pancreatic lipase (PPL) and vinyl acetate in THF at ambient temperature in 47% yield (>95% ee) along with the *meso*-diacetate.[22] It is noteworthy to mention that the *meso*-diacetate obtained was again converted back to the *meso*-diol by treatment with CH_3ONa in methanol in quantitative yield for further utilization. Mono acetate **7** was oxidized and subjected to two carbon extension by means of Wittig reaction to afford the *E*/*Z* mixture of α,β-unsaturated ester **8** in 91% yield. The reduction of double bond with $NaBH_4$ in the presence of $NiCl_2{\cdot}6H_2O$ in MeOH afforded the saturated ester **9** in 96% yield.[23] Treatment of acetate **9** with K_2CO_3 in ethanol gave the alcohol **10** which was then protected as its silyl ether using TBSCl and imidazole in dichloromethane to furnish compound **11**.

Hydrolysis of ester **11** under basic conditions furnished the corresponding carboxylic acid **12** in 91% yield. Coupling of acid **12** with Evans chiral oxazolidinone using pivaloyl chloride in presence of triethylamine and LiCl furnished the required compound **13** in 95% yield.[24] Diastereoselective methylation of Na-enolate of compound **13** with MeI furnished the desired compound **14** in 90% yield and in 98 : 2[5d] dr which was confirmed by HPLC analysis. Reduction of compound **14** with

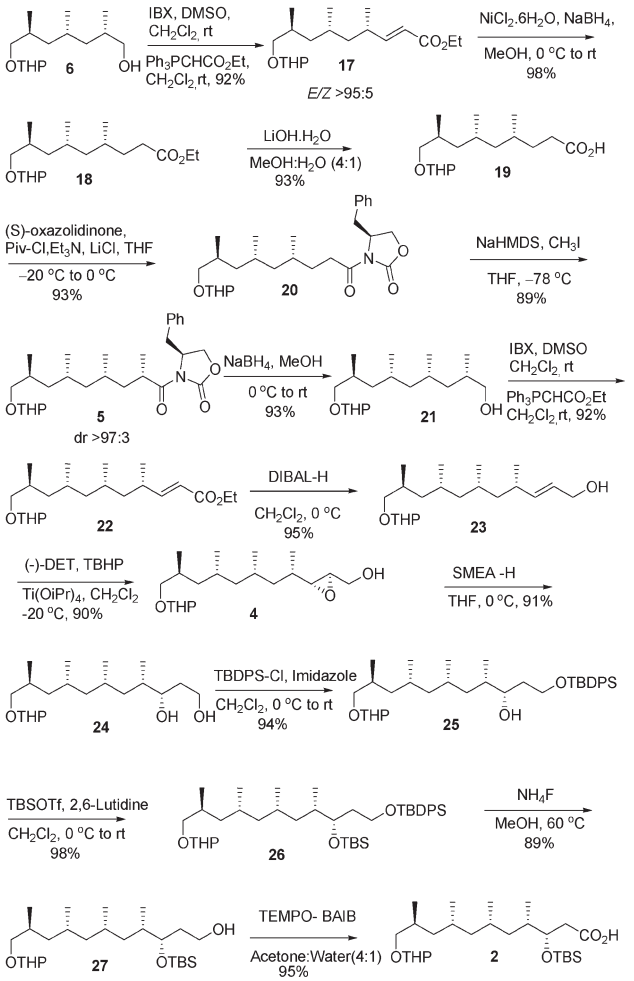


Scheme 2 Synthesis of alcohol **6**.

$NaBH_4$ in MeOH furnished alcohol **15**. Protection of the carbinol as its THP ether **16** followed by deprotection of the silyl ether furnished the desired diastereoisomeric mixture of alcohol **6**, Scheme 2.

Alcohol **6** was subjected to oxidation followed by C_2-Wittig reaction to afford the *E*/*Z* mixture of α,β- unsaturated ester **17** in 92% for two steps. Reduction of the mixture of unsaturated ester **17** followed by hydrolysis furnished acid **19** in 93% yield. Coupling of acid **19** with the Evans chiral oxazolidinone and diastereoselective methylation of **20** furnished the desired compound **5** in 89% yield in good selectivity[5d]. Reduction of compound **5** provided alcohol **21**, which was further converted to *trans*-unsaturated ester **22** (E/Z > 98 : 2 as confirmed by the crude ^{1}HNMR of **23**) by means of oxidation and Wittig olefination.

The ester **22** was then reduced to the corresponding allylic alcohol **23** and subjected to Sharpless asymmetric epoxidation using (−)-DET, $Ti(OiPr)_4$ and TBHP in dichloromethane at −20 °C furnished the corresponding epoxide **4** in 90% yield.[25] Reductive opening of epoxide afforded diol **24**. Selective protection of primary alcohol using TBDPSCl gave the compound **25** in 94% yield. The secondary carbinol was then protected as its TBDMS ether to afford **26** that was subjected to selective deprotection of the TBDPS group using NH_4F in methanol[26] to afford alcohol **27**. Ultimately oxidation of alcohol **27** with TEMPO-BAIB[27] in acetone : water (4 : 1) furnished the target C1-C11 fragment (**2**) of borrelidin in 95% yield (Scheme 3). Analytical data of **2** was compared and found to be identical with the reported compound.[15c,e]



Scheme 3 Synthesis of C1-C11 fragment of borrelidin **2**.

Conclusions

In conclusion, we have accomplished the facile and general stereoselective synthesis of C1-C11 fragment of anti-angiogenic polyketide borrelidin employing enzymatic desymmetrization of a *meso*-diol, Wittig reaction, an iterative Evans methylation, Sharpless asymmetric epoxidation and regioselective opening of a chiral epoxide as key steps. The synthesis follows a linear synthetic sequence with an overall yield of 18.4%.

Experimental section

General

All reactions were carried out under inert atmosphere of argon or nitrogen using standard syringe, septa, and cannula techniques unless otherwise mentioned. Commercial reagents were used without further purification. All solvents were purified by standard techniques. Infrared (IR) spectra were recorded on a Perkin-Elmer 683 spectrometer using NaCl optics. Spectra were calibrated against the polystyrene absorption at 1610 cm^{-1}. Samples were scanned neat, in KBr wafers or in chloroform as a thin film. ^1H NMR spectra were recorded in $CDCl_3$ on Bruker 300, Varian Unity 500 NMR spectrometer. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ using tetramethylsilane as a reference standard. Column chromatography was performed using silica gel (60–120 mesh) and the column was usually eluted with a mixture of ethyl acetate–petroleum ether. Visualization of the spots on TLC plates was achieved either by exposure to iodine vapor or UV light or by dipping the plates to ethanolic anisaldehyde–sulphuric acid–acetic acid or to phosphomolybdic acid–sulphuric acid solution and heating the plates at 120 °C. Mass spectra were obtained on a Finnigan MAT1020B or Micromass VG 70-70H spectrometer operating at 70 eV using a direct inlet system. Optical rotations were recorded on PerkinElmer 241 polarimeter in 1.0 dm, 1.0 mL cells.

(2*S*,4*R*)-5-Hydroxy-2,4-dimethylpentyl acetate (7). To a stirred solution of *meso*-diol (4.0 gm, 22.9 mmol) in THF (130 mL) and water (170 μL) was added PPL (11.6 g) and vinyl acetate at room temperature. The reaction mixture was stirred for 6 h at room temperature. After complete conversion of the starting material (as indicated by TLC), the reaction mixture was filtered off through a pad of celite, washed with ethyl acetate, dried over Na_2SO_4, concentrated *in vacuo* and purified by chromatography on silica gel (1 : 5, EtOAc/hexane) to afford the monoacetate **7** (2.47 g, 47%) as a colorless liquid. $[\alpha]_D$ = +9.8 (c = 0.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): 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), 1.82–1.96 (m, 1H), 1.64–1.78 (m, 1H), 1.43 (br, 1H), 1.39–1.49 (m, 1H), 1.15–1.30 (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 ppm.

Ethyl (*E*,4*R*,6*S*)-7-(acetyloxy)-4,6-dimethyl-2-heptenoate (8). To a stirred solution of IBX (12.25 g, 43.6 mmol) in DMSO (30 mL) at 25 °C, was added drop wise a solution of alcohol **7** (5.0 g, 29.07 mmol) in CH_2Cl_2 (40 mL). The resulting mixture was stirred at 25 °C for 3 h. The solid was filtered and washed with ether. The filtrate was diluted with ether, washed with saturated aqueous $NaHCO_3$ solution, water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to furnish crude aldehyde. To the above crude mixture (4.94 g, 29.07 mmol) in CH_2Cl_2 (150 mL) was added (ethoxycarbonylmethylene) triphenyl phosphorane (25.29 g, 72.68 mmol) and resulting mixture was stirred for 12 h at room temperature and then quenched by the addition of water and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The crude was purified by silica gel column chromatography (1 : 9 EtOAc/hexane) to afford yellow oil **8** in (6.40 g, 91%) yield. $[\alpha]_D^{25}$ −16.4 (c 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.74 (dd, J = 15.6, 8.3 Hz, 1H), 5.76 (d, J = 15.6 Hz, 1H), 4.17 (q, J = 14.1, 7.1 Hz, 2H), 3.78–3.94 (m, 2H), 2.35–2.50 (m, 1H), 2.04 (s, 3H), 1.70–1.87 (m, 1H), 1.41–1.54 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.12–1.24 (m, 1H), 1.09 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 166.4, 153.3, 119.9, 69.0, 59.9, 39.6, 33.8, 30.0, 20.6, 20.2, 16.3, 14.0; IR (Neat): 2966, 1721, 1652, 1461, 1369, 1238, 1182, 1037, 986, 766

cm^{-1}; MS (ESIMS): *m/z* 265 $[M + Na]^+$; HRMS (ESI) calcd for $C_{13}H_{22}O_4Na$ $[M + Na]^+$: 265.1415, Found: 265.1410.

Ethyl (4*S*,6*S*)-7-(acetyloxy)-4,6-dimethylheptanoate (9). To a cooled (0 °C) solution of **8** (6.35 g, 26.23 mmol) and $NiCl_2 \cdot 6H_2O$ (1.25 g, 5.25 mmol) in MeOH (200 mL), $NaBH_4$ (1.95 g, 52.66 mmol) was added in small portions to the solution. The reaction temperature was kept at 0 °C by ice cooling. After complete addition of $NaBH_4$ the reaction mixture was stirred for 1 h at room temperature. The black precipitate formed was filtered and washed with MeOH. The solvent was removed under reduced pressure. Water (100 mL) was added and the solution extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. Concentration under reduced pressure and purification by silica gel column chromatography using ethyl acetate and hexane (1 : 9) afforded the pure compound **9** (6.15 g, 96%) as a colorless liquid. $[\alpha]_D^{25}$ −1.2 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 4.07 (q, *J* = 14.6, 7.3 Hz, 2H), 3.89 (dd, *J* = 10.9, 5.8 Hz, 1H),3.77 (dd, *J* = 10.9, 6.5 Hz, 1H), 2.18–2.37 (m, 2H), 2.04 (s, 3H), 1.83–1.93 (m, 1H), 1.62–1.74 (m, 1H), 1.48–1.60 (m, 1H), 1.28–1.41 (m, 2H), 1.24 (t, *J* = 7.3 Hz, 3H), 0.97–1.05 (m, 1H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 171.0, 69.1, 60.0, 40.7, 31.7, 31.3, 29.7, 29.4, 20.7, 19.6, 17.4, 14.0; IR (Neat): 2961, 1737, 1372, 1239, 1176, 1036, 606 cm^{-1}; MS (ESIMS): *m/z* 267 $[M + Na]^+$; HRMS (ESI) calcd for $C_{13}H_{24}O_4Na$ $[M + Na]^+$: 267.1572, Found: 267.1564.

Ethyl (4*S*,6*S*)-7-hydroxy-4,6-dimethylheptanoate (10). To a solution of **9** (6.1 g, 25 mmol) in ethanol (150 mL) at room temperature was added K_2CO_3 (8.62 g, 62.5 mmol) and the reaction was stirred under nitrogen atmosphere for 12 h. The resulting mixture was vacuum filtered through celite and the filter cake was washed well with CH_2Cl_2 and the filtrate was concentrated under reduced pressure. Purification of the resulting residue by the column chromatography (1.2 : 8.8, EtOAc/hexane) afforded **10** (5.05 g, 98%) as a colorless liquid. $[\alpha]_D^{25}$ −8.6 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.10 (q, *J* = 14.1, 7.1 Hz, 2H), 3.32–3.50 (m, 2H), 2.19–2.37 (m, 2H), 1.61–1.78 (m, 2H), 1.45–1.61 (m, 2H), 1.31–1.45 (m, 2H), 1.26 (t, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 4.5 Hz, 3H), 0.90 (d, *J* = 4.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 67.9, 60.1, 40.4, 32.9, 31.7, 31.3, 29.4, 19.8, 17.1, 14.1; IR (Neat): 3424, 2957, 2923, 1733, 1460, 1375, 1255, 1176, 1109, 1037, 767 cm^{-1}; MS (ESIMS): *m/z* 225 $[M + Na]^+$; HRMS(ESI) calcd for $C_{11}H_{22}O_3Na$ $[M + Na^+]$: 225.1466, Found: 225.1476.

Ethyl (4*S*,6*S*)-7-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-4,6-dimethylheptanoate (11). To a cold (0 °C) solution of alcohol **10** (5.0 g, 24.75 mmol) in dry CH_2Cl_2 (80 mL) was added imidazole (3.36 g, 49.5 mmol) and *tert*-butyldimethylsilylchloride. The resulting reaction mixture was stirred at room temperature for 3 h. After completion of reaction as indicated by TLC, the mixture was quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography using (1 : 30, EtOAc/hexane) afforded **11** (7.66 g, 98%). $[\alpha]_D^{25}$ −2.7 (*c* 1.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 4.07 (q, *J* = 14.3, 7.1 Hz, 2H), 3.40 (dd, *J* = 9.5, 5.5 Hz, 1H), 3.33 (dd, *J* = 9.5, 6.3 Hz, 1H), 2.19–2.33 (m, 2H), 1.28–1.72 (m, 6H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.87 (d, *J* = 6.3 Hz, 3H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 68.1, 60.1, 40.7, 33.0, 31.8, 31.5, 29.6, 25.9, 19.9, 18.3, 17.3, 14.2, −5.4; IR (Neat): 2956, 1738, 1636, 1253, 1094, 772, 570 cm^{-1}; MS (ESIMS): *m/z* 339 $[M + Na]^+$; HRMS (ESI) calcd for $C_{17}H_{36}O_3NaSi$ $[M + Na]^+$: 339.2331, Found: 339.2321.

(4*S*,6*S*)-7-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-4,6-dimethylheptanoic acid (12). $LiOH \cdot H_2O$ (1.97 g, 46.8 mmol) was added portion wise to a cooled solution (0 °C) of ester **11** (7.4 g, 23.4 mmol) in CH_3OH : H_2O (3 : 1) and stirring was continued for 2 h at room temperature. The reaction mixture was concentrated *in vacuo* and residue was diluted with EtOAc (80 mL) and saturated aqueous NH_4Cl, extracted with EtOAc (3 × 50 mL). The combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography using (1 : 9, EtOAc/hexane) afforded the **12** as a viscous liquid (6.14 g, 91%). $[\alpha]_D^{25}$ −2.7 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.29–3.44 (m, 2H), 2.23–2.42 (m, 2H), 1.47–1.75 (m, 4H), 1.28–1.45 (m, 2H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.86 (d, *J* = 6.0 Hz, 3H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.5, 68.1, 40.6, 33.0, 31.6, 31.2, 29.6, 25.9, 19.9, 18.7, 17.4, −5.4; IR (Neat): 2956, 2930, 2858, 1711, 1464, 1414, 1253, 1094, 938, 839, 775, 667 cm^{-1}; MS (ESIMS): *m/z* 311 $[M + Na]^+$; HRMS (ESI) calcd for $C_{15}H_{32}O_3NaSi$ $[M + Na]^+$: 311.2018, Found: 311.2028.

(4*S*)-4-Benzyl-3-((4*S*,6*S*)-7-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-4,6-dimethylheptanoyl)-1,3-oxazolan-2-one (13). To a stirred solution of acid **12** (6.1 g, 21.2 mmol) in THF (90 mL) at −20 °C was added Et_3N (7.43 mL, 53 mmol) followed by PivCl (2.64 mL, 21.2 mmol). After stirring for 1 h at −20 °C, LiCl (1.35 g, 31.8 mmol), (*S*)-oxazolidinone (3.76 g, 21.2 mmol) was added to the above mixture at the same temperature. The stirring was continued for 1 h at −20 °C and then 2 h at 0 °C. The reaction mass 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 **13** (9.0 g, 95%) as a viscous liquid. $[\alpha]_D^{25}$ + 27.1 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.15–7.37 (m, 5H), 4.56–4.69 (m, 1H), 4.08–4.22 (m, 2H), 3.25–3.49 (m, 3H), 2.90 (t, *J* = 7.7 Hz, 2H), 2.71 (dd, *J* = 13.2, 10.0 Hz, 1H), 1.28–1.84 (m, 6H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 153.3, 135.2, 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, 18.2, 17.4, −5.3; IR (Neat): 2954, 2928, 2857, 1784, 1700, 1461, 1386, 1353, 1251, 1208, 1093, 839, 772, 701, 591 cm^{-1}; MS (ESIMS): *m/z* 470 $[M + Na]^+$; HRMS (ESI) calcd for $C_{25}H_{41}NO_4SiNa$ $[M + Na]^+$: 470.2702, Found: 470.2714.

(4*S*)-4-Benzyl-3-((2*S*,4*R*,6*S*)-7-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-2,4,6-trimethylheptanoyl)-1,3-oxazolan-2-one (14). To a solution of **13** (8.7 g, 19.5 mmol) in dry THF (80 mL) at −78 °C, NaHMDS (1 M solution, 29.25 mL, 29.25 mmol) was added slowly with stirring under nitrogen atmosphere. After stirring at −78 °C for 30 min, MeI (3.62 mL, 58.3 mmol) was added drop wise into the reaction mixture and stirred for an

additional 2 h at −78 °C. Then the reaction mixture was quenched with saturated NH_4Cl (50 mL), warmed to room temperature and extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried (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 **14** as a colorless liquid (8.0 g, 90%). $[\alpha]_D^{25}$ + 30.0 (*c* 1.0, $CHCl_3$); HPLC Hibar Lichrospher 5 μm, 4.6 × 250 mm (C_{18}) column, acetonitrile/water 85 : 15, flow rate = 1 mL min^{-1}, 20 °C, detection at 254 nm, PDA detector, t_1 = 10.89 min (minor), t_2 = 11.63 min (major). ^1H NMR (300 MHz, $CDCl_3$): δ 7.15–7.36 (m, 5H), 4.55–4.66 (m, 1H), 4.09–4.19 (m, 2H), 371–3.86 (m, 1H), 3.41 (dd, *J* = 9.0, 5.2 Hz, 1H), 3.23–3.34 (m, 2H), 2.70 (dd, *J* = 13.5, 9.8 Hz, 1H), 1.50–1.5 (m, 2H), 1.38–1.46 (m, 3H), 1.23–1.35 (m, 1H), 1.18 (d, *J* = 6.0 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.6, 152.9, 135.3, 129.4, 128.8, 127.2, 68.3, 65.9, 55.3, 41.6, 40.1, 37.8, 35.4, 32.9, 27.7, 25.9, 19.8, 18.3, 17.3, 16.6, −5.3; IR (Neat): 2956, 2928, 2857, 1783, 1699, 1460, 1385, 1351, 1249, 1208, 1096, 839, 774, 700 cm^{-1}; MS (ESIMS): *m*/*z* 484 $[M + Na]^+$; HRMS (ESI) calcd for $C_{26}H_{43}O_4SiNa$ $[M + Na]^+$: 484.2859, Found: 484.2875.

(2*S*,4*S*,6*S*)-7-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-2,4,6-trimethylheptan-1-ol (15). To a stirred solution of **14** (7.8 g, 17.1 mmol) in MeOH (50 mL) at 0 °C was added $NaBH_4$ (1.95 g, 51.3 mmol) portionwise. The reaction mixture was allowed to stir for 30 min at same temperature. Reaction mixture was then quenched with drop wise addition of saturated aqueous NH_4Cl. MeOH was removed under vacuum and residue was extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Crude was purified by silica gel column chromatography (1 : 19, EtOAc/hexane) to afford the pure product **15** (4.53 g, 93%) as a viscous liquid. $[\alpha]_D^{25}$ −17.7 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.29–3.48 (m, 4H), 1.54–1.78 (m, 3H), 1.22–1.34 (m, 1H), 1.03–1.19 (m, 3H), 0.83–0.91 (m, 18H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 69.1, 68.3, 41.9, 40.2, 33.1, 32.9, 27.1, 25.9, 20.1, 18.3, 17.3, 16.1, −5.3; IR (Neat): 3351, 2956, 2928, 2858, 1465, 1383, 1253, 1098, 1040, 838, 775, 667 cm^{-1}; MS (ESIMS): *m*/*z* 289 $[M + H]^+$; HRMS (ESI) calcd for $C_{16}H_{36}O_2SiNa$ $[M + Na]^+$: 311.2382, Found: 311.2398.

***tert*-Butyl(dimethyl)[(2*S*,4*S*,6*S*)-2,4,6-trimethyl-7-(tetrahydro-2*H*-2-pyranyloxy)heptyl]oxysilane (16).** To the solution of above alcohol **15** (4.5 g, 15.6 mmol) and DHP (2.14 mL, 23.4 mmol) in dry CH_2Cl_2 (60 mL) at 0 °C were added catalytic amount of *p*-toluene sulfonic acid. It was allowed to stir at this temperature for 15 min. The reaction mixture was diluted with DCM, washed with saturated $NaHCO_3$ solution, water, brine successively. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude obtained was purified through column chromatography (1 : 33, EtOAc/hexane) afforded the pure **16** (5.29 g, 91%) as a colorless oil. $[\alpha]_D^{25}$ −10.8 (*c* 1.15, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 4.50–4.56 (m, 1H), 3.77–3.84 (m, 1H), 3.39–3.54 (m, 3H), 3.28–3.36 (m, 1H), 3.05–3.18 (m, 1H), 1.76–1.89 (m, 2H), 1.46–1.71 (m, 8H), 1.24–1.32 (m, 1H), 1.03–1.18 (m, 2H), 0.89 (s, 9H), 0.83–0.92 (m, 9H)), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.9, 98.6, 73.8, 73.6, 68.39, 68.33, 62.1, 61.9, 42.0, 41.9, 40.7, 32.9, 30.8, 30.7, 30.6, 27.1, 25.8, 25.4, 20.0, 19.5, 19.4, 17.3, 16.7, 16.6, −5.4; IR (Neat): 2953, 2857, 1464, 1379, 1253, 1097, 1032, 838, 774, 667 cm^{-1}; MS (ESIMS): *m*/*z* 395 $[M + Na]^+$; HRMS (ESI) calcd for $C_{21}H_{44}O_3NaSi$ $[M + Na]^+$: 395.2957, Found: 395.2960.

(2*S*,4*R*,6*S*)-2,4,6-Trimethyl-7-(tetrahydro-2*H*-2-pyranyloxy)-heptan-1-ol (6). To a stirred solution of silyl ether **16** (5.2 g, 13.9 mmol) in dry THF (30 mL) at 0 °C was added drop wise a solution of TBAF (21 mL, 21 mmol) in THF. The reaction mixture was allowed to warm to 25 °C and stirred for 12 h. Reaction mixture was then quenched with addition of water and extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure and crude was purified by silica gel column chromatography (1 : 9, EtOAc/hexane) to afford the pure product **6** (3.35 g, 93%) as a viscous liquid. $[\alpha]_D^{25}$ −17.4 (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.47–4.58 (m, 1H), 3.66–3.87 (m, 2H), 3.32–3.57 (m, 3H), 3.04–3.21 (m, 1H), 1.40–1.92 (m, 10H), 1.24–1.39 (m, 1H), 1.05–1.18 (m, 2H), 0.84–0.96 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 99.0, 98.6, 73.8, 73.6, 68.9, 68.1, 62.2, 62.1, 62.0, 42.2, 41.5, 41.4, 40.6, 40.5, 32.9, 32.8, 30.7, 30.6, 27.1, 27.0, 25.4, 20.1, 20.0, 19.5, 19.4, 17.1, 16.8, 16.7; IR (Neat): 3448, 2925, 2854, 1632, 1437, 1196, 765, 646 cm^{-1}; MS (ESIMS): *m*/*z* 281 $[M + Na]^+$; HRMS (ESI) calcd for $C_{15}H_{30}O_3Na$ $[M + Na]^+$: 281.2092, Found: 281.2096.

Ethyl (*E*,4*S*,6*R*,8*S*)-4,6,8-trimethyl-9-(tetrahydro-2*H*-2-pyranyloxy)-2-nonenoate (17). To a stirred solution of IBX (5.37 g, 19.2 mmol) in DMSO (15 mL) at 25 °C, was added drop wise a solution of alcohol **6** (3.3 g, 12.8 mmol) in CH_2Cl_2 (30 mL). The resulting mixture was stirred at 25 °C for 3 h. The solid was filtered and washed with ether. The filtrate was diluted with ether, washed with saturated aqueous $NaHCO_3$ solution, water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to furnish crude aldehyde. To the above crude mixture (3.27 g, 12.8 mmol) in CH_2Cl_2 (100 ml) was added (ethoxycarbonylmethylene) triphenyl phosphorane (11.14 g, 32 mmol) and resulting mixture was stirred for 12 h at room temperature and then quenched by the addition of water and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The crude product was purified by silica gel column chromatography (1 : 19 EtOAc/hexane) giving **17** (3.84 g, 92%) as colorless liquid. $[\alpha]_D^{25}$ + 3.8 (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.76 (dd, *J* = 15.8, 8.3 Hz, 1H), 5.74 (d, *J* = 15.8 Hz, 1H), 4.47–4.57 (m, 1H), 4.16 (q, *J* = 14.3, 6.7 Hz, 2H), 3.79 (t, *J* = 9.0 Hz, 1H), 3.38–3.56 (m, 2H), 3.01–3.18 (m, 1H), 2.33–2.51 (m, 1H), 0.75–1.92 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 154.5, 119.5, 98.9, 98.6, 73.6, 73.4, 62.1, 61.9, 60.0, 44.4, 41.2, 34.0, 30.6, 27.4, 25.4, 20.1, 19.5, 19.4, 19.0, 16.9, 16.8, 14.1; IR (Neat): 2956, 2872, 1721, 1651, 1459, 1372, 1269, 1179, 1033, 981, 724 cm^{-1}; MS (ESIMS): *m*/*z* 349 $[M + Na]^+$; HRMS (ESI) calcd for $C_{19}H_{34}O_4Na$ $[M + Na]^+$: 349.2354, Found: 349.2359.

Ethyl (4*R*,6*R*,8*S*)-4,6,8-trimethyl-9-(tetrahydro-2*H*-2-pyranyloxy)nonanoate (18). The procedure was analogous to that used for the preparation of **9**. From the unsaturated ester **17** (3.8 g, 11.66 mmol), $NiCl_2 \cdot 6H_2O$ (0.55 g, 2.33 mmol) and

$NaBH_4$ (0.88 g, 23.32 mmol) was obtained saturated ester **18** (3.75 g, 98%) as colorless liquid. $[\alpha]_D^{25}$ −10.6 (*c* 1.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 4.50–4.57 (m, 1H), 4.10 (q, *J* = 13.6, 6.8 Hz, 2H), 3.80 (t, *J* = 9.7 Hz, 1H), 3.42–3.56 (m, 2H), 3.05–3.17 (m, 1H), 2.18–2.33 (m, 2H), 1.75–1.89 (m, 2H), 1.46–1.73 (m, 8H), 1.31–1.41 (m, 1H), 1.26 (t, *J* = 6.8 Hz, 3H), 1.16–1.24 (m, 1H), 0.95–1.16 (m, 3H), 0.83–0.92 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): 173.9, 98.9, 98.5, 73.7, 73.5, 62.1, 61.9, 60.0, 45.5, 40.7, 31.9, 31.7, 30.77, 30.71, 30.6, 29.4, 27.05, 27.03, 25.4, 19.8, 19.6, 17.0, 14.1; IR (Neat): 2954, 2925, 2872, 1737, 1459, 1375, 1175, 1122, 1031, 976, 905, 770 cm^{-1}; MS (ESIMS): *m*/*z* 351 $[M + Na]^+$; HRMS (ESI) calcd for $C_{19}H_{36}O_4Na$ $[M + Na]^+$: 351.2511, Found: 351.2517.

(4*R*,6*R*,8*S*)-4,6,8-Trimethyl-9-(tetrahydro-2*H*-2-pyranyloxy)-nonanoic acid (19). The procedure was analogous to that used for the preparation of **12**. From the ester **13** (3.7 g, 11.28 mmol) and $LiOH{\cdot}H_2O$ (0.95 g, 22.56 mmol) was obtained carboxylic acid **19** (3.14 g, 93%) as colorless liquid. $[\alpha]_D^{25}$ −11.2 (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.50–4.58 (m, 1H), 3.75–3.87 (m, 1H), 3.40–3.56 (m, 2H), 3.04–3.20 (m, 1H), 2.24–2.42 (m, 2H), 0.92–1.91 (m, 15H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.8, 99.0, 98.6, 73.8, 73.6, 62.2, 62.0, 45.4, 40.7, 31.6, 31.4, 30.7, 30.6, 29.4, 27.0, 25.4, 19.8, 19.6, 19.4, 16.8; IR (Neat): 2954, 2924, 2873, 1710, 1459, 1379, 1177, 1029, 904, 810 cm^{-1}; MS (ESIMS): *m*/*z* 323 $[M + Na]^+$; HRMS (ESI) calcd for $C_{17}H_{32}O_4Na$ $[M + Na]^+$: 323.2198, Found: 323.2206.

(4*S*)-4-Benzyl-3-[(4*R*,6*R*,8*S*)-4,6,8-trimethyl-9-(tetrahydro-2*H*-2-pyranyloxy)nonanoyl]-1,3-oxazolan-2-one (20). The procedure was analogous to that used for the preparation of **13**. From the carboxylic acid **19** (3.0 g, 10.0 mmol), Et_3N (3.50 mL, 25 mmol), PivCl (1.24 mL, 10 mmol), LiCl (0.64 g, 15 mmol) and (*S*)-oxazolidinone (1.77 g, 10.0 mmol) was obtained **20** (4.27 g, 93%) as colorless liquid. $[\alpha]_D^{25}$ + 21.8 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.15–7.37 (m, 5H), 4.57–4.66 (m, 1H), 4.51 (q, *J* = 6.7, 3.7 Hz, 1H), 4.09–4.21 (m, 2H), 3.75–3.86 (m, 1H), 3.41–3.57 (m, 2H), 3.31 (dd, *J* = 13.5, 3.7 Hz,1H), 3.05–3.20 (m, 1H), 2.76–3.03 (m, 2H), 2.70 (dd, *J* = 13.5, 9.8 Hz, 1H), 1.35–1.94 (m, 12H), 1.19–1.33 (m, 1H), 0.99–1.18 (m, 2H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 135.2, 129.3, 128.8, 127.2, 99.0, 98.6, 73.8, 73.6, 66.0, 62.2, 62.0, 55.1, 45.6, 40.7, 37.8, 33.2, 31.1, 30.6, 29.5, 27.0, 25.4, 19.8, 19.7, 19.5, 19.4, 16.8, 16.7; IR (Neat): 2952, 2923, 1783, 1700, 1454, 1384, 1352, 1208, 1029, 702 cm^{-1}; MS (ESIMS): *m*/*z* 482 $[M + Na]^+$; HRMS (ESI) calcd for $C_{27}H_{41}NO_5Na$ $[M + Na]^+$: 482.2882, Found: 482.2871.

(4*S*)-4-Benzyl-3-[(2*S*,4*S*,6*R*,8*S*)-2,4,6,8-tetramethyl-9-(tetrahydro-2*H*-2-pyranyloxy)nonanoyl]-1,3-oxazolan-2-one (5). The procedure was analogous to that used for the preparation of **14**. From the compound **20** (4.2 g, 9.15 mmol), NaHMDS (1 M solution, 13.72 mL, 13.72 mmol) and MeI (1.71 mL, 27.45 mmol) was obtained **5** (3.85 g, 89%) as colorless liquid. $[\alpha]_D^{25}$ + 27.3 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.15–7.37 (m, 5H), 4.59–4.69 (m, 1H), 4.49–4.58 (m, 1H), 4.09–4.23 (m, 2H), 3.73–3.92 (m, 2H), 3.39–3.59 (m, 2H), 3.27 (dd, *J* = 13.0, 3.5 Hz, 1H), 3.04–3.21 (m, 1H), 2.70 (dd, *J* = 13.2, 10.0 Hz, 1H), 1.42–1.97 (m, 9H), 0.94–1.36 (m, 6H), 1.20 (d, *J* = 6.7 Hz, 3H), 0.82–0.94 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): 177.1, 152.8, 135.1, 129.3, 128.7, 127.2, 98.9, 98.5, 73.7, 73.6, 65.8, 62.1, 61.9, 55.1, 45.8, 40.7, 40.5, 37.7, 35.1, 30.6, 27.8, 26.9, 25.4, 20.2, 19.8, 19.4, 18.4, 16.8; IR (Neat): 2962, 2085, 1769, 1643, 1454, 1383, 743, 701 cm^{-1}; MS (ESI): *m*/*z* 496 $[M + Na]^+$; HRMS (ESI) calcd for $C_{28}H_{43}O_5Na$ $[M + Na]^+$: 496.3038, found: 496.3044.

(2*S*,4*S*,6*R*,8*S*)-2,4,6,8-Tetramethyl-9-(tetrahydro-2*H*-2-pyranyloxy)nonan-1-ol (21). The procedure was analogous to that used for the preparation of **15**. From the compound **5** (3.8 g, 8.03 mmol) and $NaBH_4$ (0.92 g, 24.0 mmol) was obtained **21** (2.24 g, 93%) as colorless liquid. $[\alpha]_D^{25}$ −21.2 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.49–4.57 (m, 1H), 3.74–3.87 (m, 1H), 3.29–3.58 (m, 4H), 3.02–3.22 (m, 1H), 0.95–1.93 (m, 16H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.0 Hz, 3H), 0.87 (d, *J* = 6.0 Hz, 3H), 0.85 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.9, 98.5, 73.8, 73.6, 68.0, 62.1, 61.9, 45.7, 41.2, 40.3, 32.9, 30.7, 30.64, 30.6, 27.2, 27.07, 27.02, 25.4, 20.7, 20.2, 19.5, 19.3, 19.2, 17.4, 16.75, 16.7; IR (Neat): 3422, 2953, 2920, 2872, 1459, 1377, 1124, 1031, 977, 550 cm^{-1}; MS (ESIMS): *m*/*z* 323 $[M + Na]^+$; HRMS (ESI) calcd for $C_{18}H_{36}O_3Na$ $[M + Na]^+$: 323.2562, Found: 323.2570.

Ethyl (*E*,4*S*,6*S*,8*R*,10*S*)-4,6,8,10-tetramethyl-11-(tetrahydro-2*H*-2-pyranyloxy)-2-undecenoate (22). The procedure was analogous to that used for the preparation of **17**. From the alcohol **21** (2.2 g, 7.33 mmol), IBX (3.08 g, 11.0 mmol), and (ethoxycarbonylmethylene) triphenyl phosphorane (6.38 g, 18.3 mmol) was obtained **22** (2.48 g, 92%) as colorless liquid. $[\alpha]_D^{25}$ + 2.8 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.76 (d, *J* = 15.6, 8.3 Hz, 1H), 5.74 (d, *J* = 15.6 Hz, 1H), 4.47–4.58 (m, 1H), 4.16 (q, *J* = 14.1, 6.9 Hz, 2H), 3.73–3.86 (m, 1H), 3.37–3.57 (m, 2H), 3.02–3.19 (m, 1H), 2.31–2.49 (m, 1H), 1.24–1.93 (m, 12H), 1.30 (t, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.92–1.24 (m, 3H), 0.76–0.93 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): 166.7, 154.4, 119.6, 98.9, 98.5, 73.7, 73.5, 62.1, 61.9, 60.0, 46.1, 43.6, 40.7, 34.1, 30.7, 30.6, 27.5, 26.9, 25.4, 20.4, 19.8, 19.4, 16.7, 14.1; IR (Neat): 2956, 2922, 2873, 1721, 1651, 1459, 1373, 1269, 1178, 1033, 980, 723 cm^{-1}; MS (ESIMS): *m*/*z* 391 $[M + Na]^+$; HRMS (ESI) calcd for $C_{22}H_{40}O_4Na$ $[M + Na]^+$: 391.2824, Found: 391.2822.

(*E*,4*S*,6*S*,8*R*,10*S*)-4,6,8,10-Tetramethyl-11-(tetrahydro-2*H*-2-pyranyloxy)-2-undecen-1-ol (23). To a cooled (0 °C) solution of **22** (2.4 g, 6.52 mmol) in dry CH_2Cl_2 (20 mL), DIBAL-H (9.78 mL, 9.78 mmol, 1 M solution in toluene) was added slowly for 15 min and stirred for 1 h at 0 °C, before being quenched with methanol (1 mL) and sodium potassium tartarate solution (20 mL). The reaction mixture was passed through a short pad of celite. The filtrate was concentrated and the residue was purified by column chromatography (1 : 9, EtOAc/hexane) to furnish allylic alcohol **23** (2.02 g, 95%) as a colorless liquid. $[\alpha]_D^{25}$ −1.3 (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.39–5.64 (m, 2H), 4.49–4.57 (m, 1H), 3.99–4.09 (m, 2H), 3.75–3.86 (m, 1H), 3.39–3.57 (m, 2H), 3.02–3.19 (m, 1H), 2.13–2.32 (m, 1H), 1.34–1.93 (m, 10H), 0.86–1.32 (m, 8H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.0 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 127.3, 99.0, 98.5, 73.8, 73.6, 63.6, 62.1, 61.9, 46.2, 44.4, 40.8, 33.8, 30.6, 27.4, 26.9, 25.4, 21.4, 20.0, 19.9, 19.5, 19.4, 16.8; IR (Neat): 3409, 2954, 2920, 2871, 1458, 1377, 1123, 1029, 974, 904, 759 cm^{-1}; MS (ESIMS): *m*/*z*

349 $[M + Na]^+$; HRMS (ESI) calcd for $C_{20}H_{38}O_3Na$ $[M + Na]^+$: 349.2718, Found: 349.2728.

(2*R*,3*R*)-3-[(1*S*,3*S*,5*R*,7*S*)-1,3,5,7-Tetramethyl-8-(tetrahydro-2*H*-2-pyranyloxy)octyl]oxiran-2-ylmethanol (4). To a solution of (−)-DET (0.32 mL, 1.84 mmol) in dry CH_2Cl_2 (20 mL) at −30 °C containing MS 4 Å (0.7 (g), was added sequentially, $Ti(O^iPr)_4$ (0.47 mL, 1.6 mmol) and TBHP (6.13 mL, 18.39 mmol, 3 M solution in toluene) and stirred for 30 min. A solution of alcohol **23** (2.0 g, 6.13 mmol) in CH_2Cl_2 (10 mL) was added and stirred for 10 h at −30 °C and then reaction mixture was kept frozen for an additional 12 h. It was then quenched with 45 mL of water, 30% aqueous NaOH solution saturated with NaCl (20 mL) and the resulting mixture stirred vigorously for another 30 min at room temperature. The resulting mixture was vacuum filtered through celite and the filter cake was washed well with CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). Combined organic phases were washed with brine and dried over Na_2SO_4. Removal of solvent under reduced pressure and purification by column chromatography (3 : 7, EtOAc/hexane) afforded 4 (1.88 g, 90%) as a viscous liquid. $[\alpha]_D^{25}$ + 2.6 (*c* 1.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.46–4.58 (m, 1H), 3.73–3.90 (m, 2H), 3.37–3.64 (m, 3H), 3.02–3.22 (m, 1H), 2.87–2.94 (m, 1H), 2.56–2.69 (m, 1H), 1.24–1.92 (m, 12H), 0.94–1.22 (m, 4H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.81–0.93 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.9, 98.6, 73.7, 73.5, 62.1, 61.8, 60.9, 60.6, 58.6, 45.9, 41.4, 40.5, 32.7, 30.6, 30.5, 27.2, 26.9, 25.3, 20.3, 19.9, 19.5, 17.8, 16.7, 16.6; IR (Neat): 3446, 2955, 2922, 2872, 1460, 1378, 1122, 1029, 901, 868, 586 cm^{-1}; MS (ESIMS): *m*/*z* 365 $[M + Na]^+$; HRMS (ESI) calcd for $C_{20}H_{38}O_4Na$ $[M + Na]^+$: 365.2667, Found: 365.2676.

(3*S*,4*S*,6*S*,8*R*,10*S*)-4,6,8,10-Tetramethyl-11-(tetrahydro-2*H*-2-pyranyloxy)undecane-1,3-diol (24). To a stirred solution of epoxy alcohol **4** (1.85 g, 5.4 mmol) in THF was added Red-Al (0.6 g, 1.12 mmol) under nitrogen atmosphere at 0 °C. The reaction mixture was stirred for 3 h at room temperature, then cooled to °C and quenched with drop wise addition of saturated aqueous Na_2SO_4. The precipitate formed was filtered and washed with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure and crude product was purified by silica gel column chromatography (1 : 3, EtOAc/hexane) to afford the pure product **24** (1.69 g, 91%) as a viscous liquid. $[\alpha]_D^{25}$ −26.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.50–4.58 (m, 1H), 3.64–3.87 (m, 4H), 3.41–3.58 (m, 2H), 3.03–3.21 (m, 1H), 2.56–2.78 (br, 2H), 1.76–1.89 (m, 2H), 1.46–1.76 (m, 10H), 1.33–1.42 (m, 1H), 1.17–1.28 (m, 1H), 0.89–1.15 (m, 4H), 0.82–0.93 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 99.0, 98.5, 74.9, 74.8, 73.9, 73.6, 62.2, 61.9, 61.8, 45.3, 40.9, 40.1, 35.9, 35.5, 30.7, 30.6, 27.2, 27.1, 27.0, 25.4, 20.8, 20.4, 19.5, 19.3, 16.7, 14.4; IR (Neat): 3677, 3404, 2954, 2923, 1654, 1459, 1378, 1120, 1029, 975, 759, 668 cm^{-1}; MS (ESIMS): *m*/*z* 367 $[M + Na]^+$; HRMS (ESI) calcd for $C_{20}H_{40}O_4Na$ $[M + Na]^+$: 367.2824, Found: 367.2835.

(3*S*,4*S*,6*S*,8*R*,10*S*)-1-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-4,6,8,10-tetramethyl-11-(tetrahydro-2*H*-2-pyranyloxy)undecan-3-ol (25). To a stirred solution of diol **24** (1.65 g, 4.8 mmol) and imidazole (0.98 g, 14.4 mmol) in CH_2Cl_2 (20 mL) was added drop wise TBDPS-Cl (1.38 mL, 5.2 mmol) at 0 °C over a period of 10 min. The reaction mixture was stirred at room temperature for 2 h and then diluted with CH_2Cl_2 and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash silica gel column chromatography using ethyl acetate and hexane (0.5 : 9.5) to afford TBDPS protected alcohol **25** (2.62 g, 94%) as a colorless oil. $[\alpha]_D^{25}$ −13.1 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56–7.72 (m, 4H), 7.28–7.50 (m, 6H), 4.49–4.58 (m, 1H), 3.64–3.94 (m, 4H), 3.38–3.62 (m, 2H), 3.01–3.22 (m, 1H), 2.64–2.78 (br, 1H), 1.14–1.90 (m, 16H), 1.05 (s, 9H), 0.94–1.15 (m, 2H), 0.78–0.95 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.4, 133.0, 129.7, 127.6, 98.9, 98.5, 74.1, 73.9, 73.7, 63.6, 62.1, 61.9, 45.5, 40.9, 40.2, 35.9, 35.6, 30.8, 30.6, 27.2, 27.0, 26.7, 25.4, 20.8, 20.3, 19.5, 19.4, 18.9, 16.7, 16.6, 14.5; IR (Neat): 3484, 3070, 2954, 1655, 1443, 1380, 1111, 1029, 975, 703, 504 cm^{-1}; MS (ESIMS): *m*/*z* 605 $[M + Na]^+$; HRMS (ESI) calcd for $C_{36}H_{58}O_4Na$ $[M + Na]^+$: 605.4002, Found: 605.4002.

***tert*-Butyl[(3*S*,4*S*,6*S*,8*R*,10*S*)-3-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-4,6,8,10-tetramethyl-11-(tetrahydro-2*H*-2-pyranyloxy)undecyl]oxydiphenylsilane (26).** 2,6-Lutidine (1.25 mL, 10.7 mmol) was added drop wise to a cooled solution (0 °C) of alcohol **25** (2.5 g, 4.29 mmol) in dry CH_2Cl_2 (15 mL). After 10 min *tert*-butyldimethylsilyltrifluoromethane sulfonate (TBSOTf, 1.48 mL, 6.4 mmol) was added drop wise and stirring was continued for 2 h at 0 °C. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with $NaHCO_3$, water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (1 : 40, EtOAc/hexane) to afford TBS ether **26** as a colorless oil (2.92 g, 98%). $[\alpha]_D^{25}$ −24.1 (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56–7.68 (m, 4H), 7.27–7.45 (m, 6H), 4.50–4.57 (m, 1H), 3.74–3.86 (m, 2H), 3.66 (t, *J* = 6.0 Hz, 2H), 3.40–3.57 (m, 2H), 3.03–3.18 (m, 1H), 0.94–1.93 (m, 18H), 1.04 (s, 9H), 0.73–0.92 (m, 12H), 0.84 (s, 9H), 0.02 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.5, 133.9, 129.5, 127.5, 98.9, 98.6, 74.03, 73.8, 72.3, 62.1, 61.9, 61.2, 45.8, 40.7, 40.0, 36.4, 35.03, 30.9, 30.8, 30.7, 27.4, 27.1, 26.8, 25.9, 25.5, 20.77, 20.70, 19.57, 19.50, 19.1, 18.1, 16.6, 15.0, −4.6; IR (Neat): 3070, 2955, 2929, 2858, 1464, 1380, 1253, 1110, 1032, 835, 703, 504 cm^{-1}; MS (ESIMS): *m*/*z* 719 $[M + Na]^+$; HRMS (ESI) calcd for $C_{42}H_{72}O_4NaSi_2$ $[M + Na]^+$: 719.4866, Found: 719.4869.

(3*S*,4*S*,6*S*,8*R*,10*S*)-3-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-4,6,8,10-tetramethyl-11-(tetrahydro-2*H*-2-pyranyloxy)undecan-1-ol (27). To a stirred solution of **26** (2.8 g, 4.02 mmol) in methanol (20 mL) was added ammonium fluoride (1.49 g, 40.2 mmol) at room temperature. The reaction mixture was warmed at 60 °C for 8 h. After completion of reaction as indicated by TLC, reaction mixture was quenched with $NaHCO_3$. The product was extracted with ethyl acetate and purified by flash column chromatography (1 : 19, EtOAc/hexane) to afford alcohol **27** (1.63 g, 89%) as colorless oil. $[\alpha]_D^{20}$ −41.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.49–4.58 (m, 1H), 3.75–3.86 (m, 1H), 3.61–3.74 (m, 3H), 3.39–3.57 (m, 2H), 3.03–3.20 (m, 1H), 0.95–1.91 (m, 18H), 0.90 (s, 9H), 0.78–0.95 (m, 12H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.9, 98.6, 74.7, 74.0, 73.8, 62.1, 61.9, 60.5,

45.5, 40.06, 40.03, 35.5, 34.9, 30.8, 30.6, 27.6, 27.2, 25.9, 25.5, 21.1, 20.7, 19.5, 19.4, 18.0, 16.6, 16.5, 15.9, −4.2, −4.5; IR (Neat): 3444, 2954, 2928, 2856, 1632, 1461, 1378, 1254, 1061, 1031, 835, 773, 665 cm^{-1}; MS (ESIMS): *m/z* 481 $[M + Na]^+$; HRMS (ESI) calcd for $C_{26}H_{54}O_4NaSi$ $[M + Na]^+$: 481.3689, Found: 481.3683.

(3*S*,4*S*,6*S*,8*R*,10*S*)-3-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-4,6,8,10-tetramethyl-11-(tetrahydro-2*H*-2-pyranyloxy)undecanoic acid (2). To a vigorously stirred solution of alcohol **27** (1.63 g, 3.55 mmol) in acetone (16 mL) and water (4 mL) was added TEMPO (0.05 g, 0.35 mmol) and BAIB (2.52 g, 7.8 mmol). Stirring was allowed until TLC indicated complete conversion of the starting material to product. The reaction mixture was quenched by addition of saturated $Na_2S_2O_3$ solution (10 mL). The reaction mixture was then extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The crude acid was purified by silica gel column chromatography using ethyl acetate and hexane (1 : 19) to get pure acid **2** (1.59 g, 95%) as a colorless liquid. $[\alpha]_D^{25}$ −31.5 (*c* 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.52–4.62 (m, 1H), 4.01–4.12 (m, 1H), 3.76–3.89 (m, 1H), 3.41–3.59 (m, 2H), 3.03–3.22 (m, 1H), 2.42 (d, *J* = 6.0 Hz, 2H), 1.33–1.92 (m, 11H), 0.97–1.32 (m, 3H), 0.77–0.96 (m, 23H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.8, 98.9, 98.5, 73.9, 73.7, 72.4, 62.1, 61.9, 45.6, 40.3, 40.0, 39.2, 35.9, 30.8, 30.7, 30.6, 27.4, 27.1, 25.7, 25.4, 20.79, 20.76, 20.6, 19.4, 19.3, 18.0, 16.6, 16.5, 15.18, 15.15, −4.5, −4.6; IR (Neat): 3422, 2953, 1715, 1621, 1462, 1384, 1255, 1118, 1030, 867, 772, 703, 505 cm^{-1}; MS (ESIMS): *m/z* 495 $[M + Na]^+$; HRMS (ESI) calcd for $C_{26}H_{52}O_5NaSi$ $[M + Na]^+$: 495.3481, Found: 495.3492.

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