Tetrahedron 66 (2010) 5000–5007

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Stereoselective synthesis of an advanced *seco* ester intermediate as a precursor toward the synthesis of amphidinolides T1, T3, and T4☆

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ARTICLE INFO

Article history:
Received 20 March 2010
Received in revised form 3 May 2010
Accepted 5 May 2010
Available online 8 May 2010

Keywords:
Amphidinolide T family
Evan's aldol
Evan's alkylation
Oxy-Michael
Cross metathesis
CBS reduction

ABSTRACT

An efficient, convergent, and stereoselective synthesis of a very advanced intermediate toward the total synthesis of amphidinolides T1, T3, and T4 utilising Evan's aldol and alkylation reactions, oxy-Michael, cross metathesis, stereoselective Grignard addition, and Yamaguchi esterification reactions as key steps is described.

1. Introduction

The amphidinolides are a rapidly growing family of macrolides produced by marine dinoflagellates of the genus *Amphidinium*.[1] Though structurally quite diverse all members are distinguished by a pronounced cytotoxicity against various cancer cell lines. In contrast to macrolide antibiotics derived from terrestrial microorganisms, however, the majority of amphidinolides features an *odd*-numbered macrolactone ring, which is biosynthesized by a complex, nonsuccessive mixed polyketide pathway.[2] In particular, the amphidinolide T class (Fig. 1) has garnered significant attention since its discovery in 2000.[3]

Members of this subclass, amphidinolides T1–5 (**1**–**5**), contain a 19-membered macrocycle, a trisubstituted tetrahydrofuran moiety, α-hydroxy ketone, an exocyclic methylene group, and a homoallylic ester linkage. Amphidinolides T3–T5 (**3**–**5**) are the most closely related molecules, all containing a ketone at C13, hydroxyl group at C12, and methyl group at C14, and they differ only in their configuration at C12 and C14. AmphidinolideT2 (**2**) displays the same functionality at C12–C14 as **3**–**5**, but contains 3-hydroxybutyl substituent at C18 where the other four members have an *n*-propyl group. Amphidinolide T1 (**1**) differs from amphidinolides T3–5 (**3**–**5**) in the oxidation states at C12 and C13, possessing the reversed hydroxy ketone moiety.

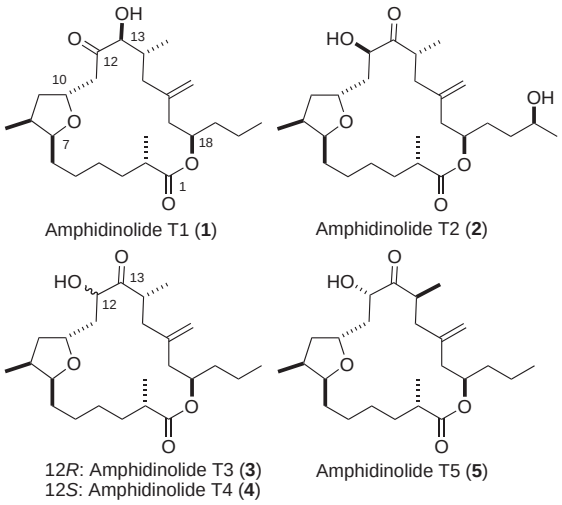

Figure 1. Amphidinolide T family of natural products.

☆ This paper is dedicated to Dr. J. S. Yadav on the occasion of his 60th birthday. DRL Publication No. 718

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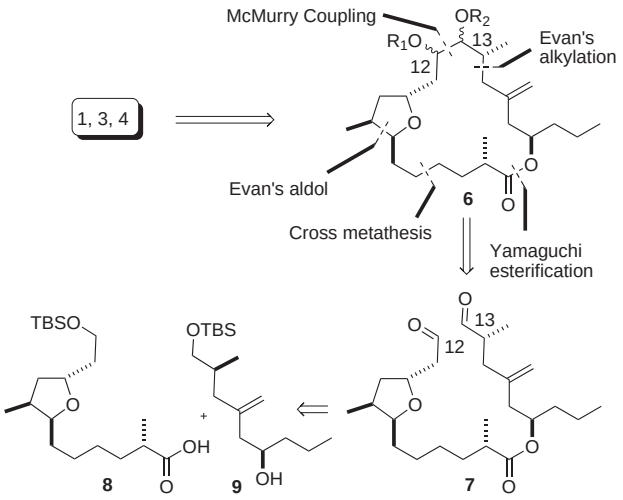
doi:10.1016/j.tet.2010.05.012

Because of the significant cytotoxicity against human epidermoid carcinoma KB and murine lymphoma L1210 cell lines[3] and unusual structural characteristics, these marine natural products constitute highly relevant target structures for total synthesis[4–6] as well as to understand the SAR of this class of molecules.

For the total synthesis of amphidinolides T1, T3, and T4, we envisioned that all these targets might be realized from an intermediate like **6** by suitable protection/deprotection, oxidation and stereochemical adjustments. Retrosynthetically intermediate **6** will be obtained via an intramolecular McMurry coupling on intermediate dialdehyde **7** (Scheme 1) to construct the C12–C13 bond. Compound **7**, in turn, could be obtained by coupling two fragments **8** and **9**. Herein, we describe an efficient and stereoselective synthesis of dialdehyde **7**.



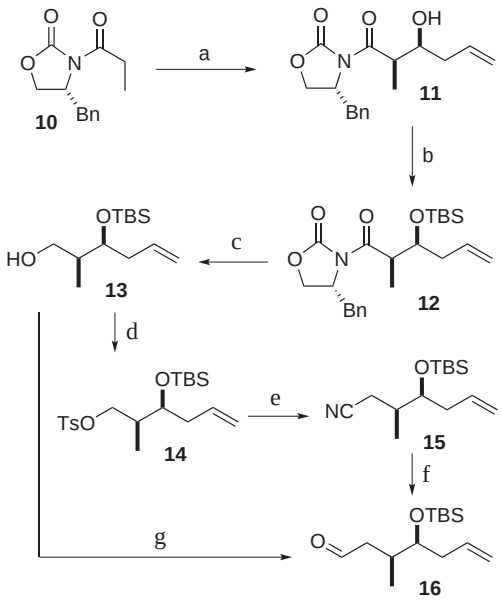
Scheme 1. Retrosynthetic analysis.

2. Results and discussion

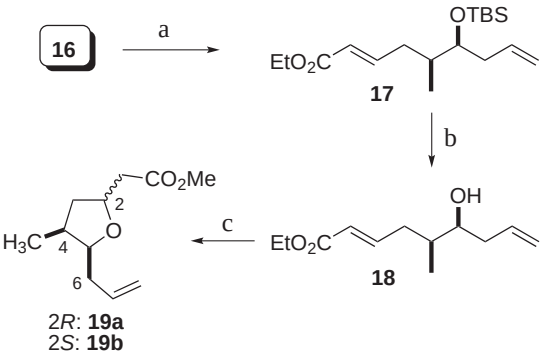
Synthesis of compound **8** commenced with the Crimmins modified Evans' strategy[7] involving condensation of 3-butenal[8] with (*R*)-4-benzyl-*N*-propionyloxazolidinone (**10**), to give the *syn* aldol adduct **11** in 92% yield as a single diastereomer, as confirmed by NMR spectroscopy (Scheme 2). The hydroxyl group was protected as its TBS ether **12**. The chiral auxiliary within **12** was reductively removed[9] with $NaBH_4$ to give the corresponding alcohol **13** in 80% yield. The hydroxyl functionality was converted to its tosyl derivative **14**, which on treatment with NaCN in DMF at room temperature afforded the corresponding cyanide **15**. Reduction of cyanide was achieved by the treatment with DIBAL-H at −78 °C to furnish the aldehyde **16**. Alternatively aldehyde **16** was produced from alcohol **13** utilising Dess/Martin periodinane oxidation of the alcohol followed by Wittig homologation and hydrolysis of the intermediate enol ether in overall 65% yields.

The aldehyde **16** was homologated with carbethoxymethylenetriphenylphosphorane to afford the corresponding α,β-unsaturated ester **17** (*E*/*Z* 19:1) in 90% yield (Scheme 3). Compound **17** was desilylated with 3 N HCl in THF at room temperature to furnish alcohol **18** in 94% yield. At this juncture we explored an intramolecular oxy-Michael reaction[10] to construct the crucial tetrahydrofuran ring with desired 2,5-*trans* selectivity. After detailed investigation[6a] we found that treatment of **18** with NaOMe in MeOH at −15 °C afforded the cyclized product with concomitant transesterification to produce an 82:18 mixture of compounds **19a** and **19b** in 95% yield.[11]

Compound **19a** and **19b** were separated under preparative HPLC conditions[12] and their stereochemistry was confirmed by NOE



Scheme 2. Reagents and conditions: (a) $TiCl_4$, (−)-sparteine, 3-butenal, dry CH_2Cl_2, 0 °C, 30 min, 92%; (b) TBSOTf, DIPEA, dry CH_2Cl_2, 0 °C, 2 h, 90%; (c) $NaBH_4$, THF/H_2O, 0 °C—rt, 40 h, 80%; (d) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C—rt, 16 h, 92%; (e) NaCN, dry DMF, rt, 4 days, 88%; (f) DIBAL-H, dry CH_2Cl_2, −78 °C, 5 h, 90%; (g) (i) DMP, DCM, 0 °C, 2 h; (ii) $CH_3OCH_2PPh_3^+Cl^-$, NaHMDS, THF, −20 °C, 2 h; (iii) PPTS, dioxane/H_2O, 50 °C, 4 h, 65% in three steps.

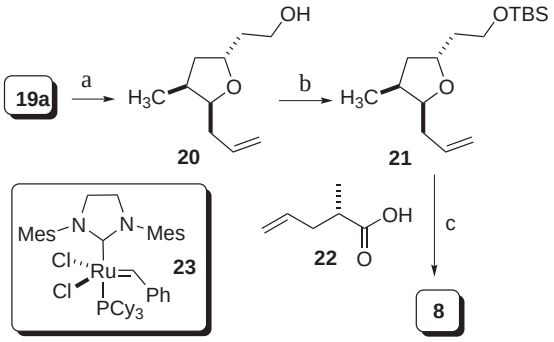


Scheme 3. Reagents and conditions: (a) $Ph_3P{=}CHCO_2Et$, C_6H_6, reflux, 16 h, 90%; (b) 3 N HCl, THF, rt, 16 h, 94%; (c) NaOMe, MeOH, −15 °C, 24 h, 95%.

studies. Upon irradiation of the C2 hydrogen at δ 4.48 significant NOE was observed for C4 methyl protons in case of **19a** whereas such effect was absent in case of **19b**. Similarly, when the C4 methyl at δ 0.95 within **19a** was irradiated, significant NOE was observed for C2 hydrogen along with C6 methylene protons.

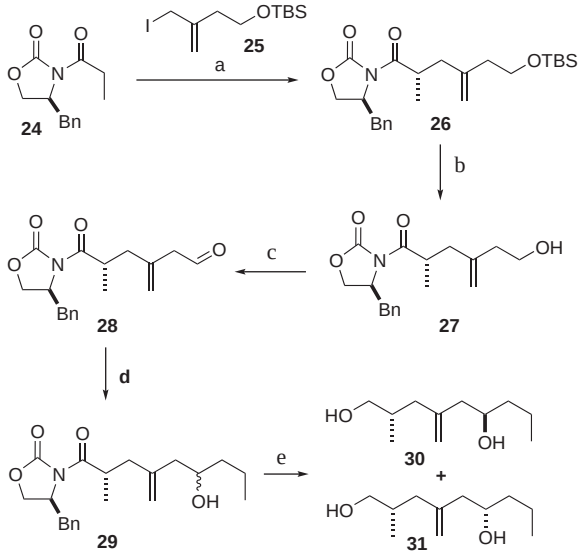
The ester group within **19a** was reduced with $LiAlH_4$ in THF at room temperature to give alcohol **20** in 70% yield (Scheme 4). The hydroxyl group was protected as its TBS ether **21**. The olefinic moiety within **21** was subjected to a cross metathesis[13] reaction with (*S*)-2-methylpent-4-enoic acid (**22**)[14] in dichloromethane under refluxing conditions in the presence of the 'second generation' ruthenium carbene complex **23** as the precatalyst bearing an imidazol-2-ylidene ligand.[15] The crude material of this metathesis reaction was subjected to hydrogenation using 10% Pd/C in ethyl acetate to afford the desired compound **8** as the first fragment in 61% yield over two steps.[16]

Synthesis of compound **9** commenced with the alkylation of (*S*)-4-benzyl-*N*-propionyloxazolidinone (**24**) with *tert*-butyl(3-(iodomethyl) but-3-enyloxy)dimethylsilane (**25**)[17] under Evans conditions[18] to afford compound **26** (Scheme 5). Desilylation of TBS ether within **26** using 3 N HCl in THF furnished the corresponding alcohol **27** in 87%



Scheme 4. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C—rt, 20 min, 70%; (b) TBDMS-Cl, imidazole, DMF, rt, 1 h, 90%; (c) (i) Grubb's second generation catalyst (**23**), DCM, reflux, 5 h; (ii) 10% Pd/C, EtOAc, H_2, rt, 1 h, 61% in two steps.

yield. The hydroxyl group within **27** was oxidized to aldehyde **28** using Dess/Martin periodinane.[19] The aldehyde **28** was then reacted with *n*-propylmagnesium chloride in diethyl ether at −78 °C to afford compound **29** as a mixture of two diastereomeric alcohols.[20] Reductive removal of the chiral auxiliary within **29** by $LiBH_4$[21] resulted alcohols **30** and **31** in 55% and 27% yields, respectively after their separation by flash chromatography.

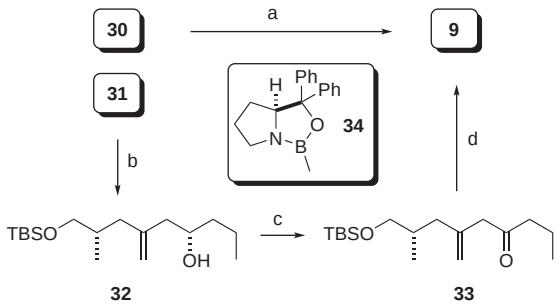


Scheme 5. Reagents and conditions: (a) NaHMDS, **25**, THF, −78 °C, 5 h, 62%; (b) 3 N HCl, THF, 3 h, 87%; (c) DMP, DCM, 0 °C, 4 h, 84%; (d) ^{n}PrMgCl, Et_2O, −78 °C, 5 h, 44%; (e) $LiBH_4$, THF, 0 °C, 1 h, 55% (**30**) and 27% (**31**).

The primary hydroxyl group within **30** was selectively protected as its TBS ether to furnish our desired compound **9** in 80% yield (Scheme 6). The stereochemistry of the chiral center bearing secondary hydroxyl group was confirmed to be in *R*-configuration following the protocol of Riguera.[22]

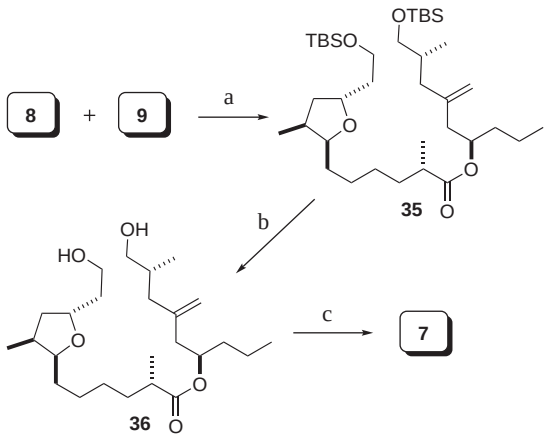
The minor diastereomer **31** was also converted to our desired compound **9** (Scheme 6). For this purpose, the primary hydroxyl group within **31** was selectively protected as its TBS ether **32** in 84% yield. Dess/Martin oxidation of the secondary hydroxyl group afforded the corresponding ketone **33** in 89% yield. Selective reduction of the carbonyl group within **33** employing Corey/Bakshi/Shibata (CBS) conditions[23] using chiral oxazaborolidine (**34**) as ligand also furnished compound **9** in 80% yield with 84% de as measured by ^{1}H NMR. These three steps protocol was really attractive as it not only allowed the recycling of **31** to **9** but also independently proved the stereochemistry in **9**.

Once both the coupling partners **8** and **9** in hand, the stage was set for the crucial esterification reaction. This was carried out



Scheme 6. Reagents and conditions: (a) TBDMS-Cl, imidazole, DCM, 0 °C, 80%; (b) TBDMS-Cl, imidazole, DCM, 0 °C, 84%; (c) DMP, DCM, 0 °C, 2 h, 89%; (d) **34**, BH_3/DMS, THF, −78 °C, 1 h, 80%.

smoothly by employing Yamaguchi conditions[24] to afford compound **35** (Scheme 7). Global deprotection of TBS groups within **35** using TBAF afforded the corresponding diol **36** in 77% yield. Dess/Martin oxidation of diol **36** produced our desired dialdehyde **7** in 88% yield. Few selected reaction conditions were investigated to construct the crucial C12–C13 bond within compound **7**. When Swindell's reaction conditions[25] ($TiCl_4$/Zn/pyridine in THF) were examined, the formation of cyclized product was realized.[26] Additional screening of reagents and optimization of reaction protocols are required for further progress toward our target structures.



Scheme 7. Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, rt—70 °C, 24 h, 44%; (b) TBAF, THF, rt, 3 h, 77%; (c) DMP, DCM, 0 °C, 4 h, 88%.

3. Conclusion

In conclusion, we have achieved an efficient and stereoselective synthesis of a very advanced intermediate toward the total synthesis of amphidinolides T1, T3, and T4 utilising Evan's aldol and alkylation reactions, oxy-Michael, cross metathesis, stereoselective Grignard addition, and Yamaguchi esterification reactions as key steps. The overall assembly is flexible enough to address structure/activity relationship (SAR) around this class of molecules. Further work is ongoing for the total synthesis and SAR studies of these targets results of which will be published in due course.

4. Experimental

4.1. General

All reactions were carried out under inert atmosphere. All solvents were distilled prior to use. Anhydrous solvents were distilled following standard protocols. Low temperature baths were ice/water (0 °C) and CO_2(s)/acetone (−78 °C). Reaction temperatures

refer to that of the bath. IR spectra were recorded either neat or as KBr pallet with a Shimadzu IR-Prestige-21 instrument and only diagnostic and/or intense peaks are reported. Mass spectra were recorded with PE Sciex model API 3000 instrument. HRMS spectra were with Waters LCT Premier XE (Micromass Oa-TOF) instrument. HPLC separation was done using Alliance 2695 HPLC system. Optical rotations were measured by using JASCO DIP-370 polarimeter at 25 °C. ^{1}H NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 with either Varian Gemini 200 MHz or Varian Mercury Plus 400 MHz instruments. ^{13}C NMR spectra were recorded in $CDCl_3$ at 50 MHz with Varian Gemini 200 MHz instrument. Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^{1}H NMR) served as the internal standard. The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of couplings constants (J) corresponds to the order of the multiplicity assignment. Unless otherwise noted, all 'J' refers to $^3J_{HH}$ coupling constant. All reported compounds were homogeneous by thin layer chromatography (TLC) and by NMR.

*4.1.1. (R)-4-Benzyl-3-((2R,3S)-3-hydroxy-2-methylhex-5-enoyl)oxazolidin-2-one (**11**).* A solution of (*R*)-4-benzyl-*N*-propionyloxazolidinone (**10**) (2.66 g, 11.42 mmol) in dichloromethane (6 mL) was cooled to 0 °C. Titanium tetrachloride (1.3 mL, 11.99 mmol) was added drop wise and the solution was allowed to stir for 5 min. To the yellow slurry was added (−)-sparteine (6.6 mL, 28.54 mmol) drop wise. The dark red enolate was stirred for 20 min at 0 °C. To this was added a solution of 3-butenal (0.88 g, 12.56 mmol) in dichloromethane (5 mL) drop wise and the reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution and stirred at room temperature for 10 min. Reaction mixture was diluted with dichloromethane, washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated. The residue was purified on silica gel (100–200 mesh) using 20% ethyl acetate in petroleum ether as eluent to afford compound **11** as colorless oil (3.18 g, 92%). R_f=0.30 (20% ethyl acetate in petroleum ether); $[\alpha]_D$ −62.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.30 (m, 2H), 7.29–7.26 (m, 1H), 7.22–7.19 (m, 2H), 5.89–5.78 (m, 1H), 5.18–5.10 (m, 2H), 4.73–4.67 (m, 1H), 4.25–4.17 (m, 2H), 4.03–4.01 (m, 1H), 3.85–3.79 (m, 1H), 3.26 (dd, J=13.3, 3.4 Hz, 1H), 2.79 (dd, J=13.2,9.7 Hz, 2H), 2.38–2.22 (m, 2H),1.28 (d, J=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 177.0, 152.9, 135.0, 134.5, 129.3, 128.9, 127.4, 117.7, 70.8, 66.1, 55.0, 41.6, 38.4, 37.7, 10.7; IR (Neat): 3509, 2925, 1779, 1694, 1386, 1210 cm^{-1}; MS (ES): *m*/*z* 304.0 (M+1); HRMS: *m*/*z* found 304.1543, calcd for $C_{17}H_{22}NO_4$ 304.1549.

*4.1.2. (R)-4-Benzyl-3-((2R,3S)-3-(tert-butyldimethylsilyloxy)-2-methylhex-5-enoyl) oxazolidin-2-one (**12**).* To an ice cooled solution of compound **11** (1.08 g, 3.56 mmol) in dichloromethane (10 mL) was added *N*-ethyldiisopropylamine (1.5 mL, 8.91 mmol) drop wise followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.2 mL, 5.35 mmol) and stirred at room temperature for 2 h. Reaction mixture was diluted with dichloromethane, washed successively with aqueous $NaHCO_3$ solution, water, and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated. The residue was purified over silica gel (100–200 mesh) using 5% ethyl acetate in petroleum ether as eluent to afford compound **12** as a gummy material (1.34 g, 90%). R_f=0.58 (10% ethyl acetate in petroleum ether); $[\alpha]_D$ −49.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.31 (m, 2H), 7.29–7.27 (m, 1H), 7.25–7.20 (m, 2H), 5.90–5.79 (m, 1H), 5.04–4.99 (m, 2H),4.62–4.57 (m, 1H), 4.18–4.13 (m, 2H), 4.12–4.07 (m, 1H), 3.83 (dt, J=12.8, 6.8 Hz, 1H), 3.27 (dd, J=13.6, 3.2 Hz, 1H), 2.77 (dd, J=13.4,9.8 Hz, 2H), 2.32 (dt, J=6.0, 1.6 Hz, 2H), 1.22 (d, J=10.4 Hz, 3H), 0.89 (s, 9H), 0.06 (s,3H), 0.02 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 175.3, 152.9, 135.3, 134.7, 129.4, 128.9, 127.3, 116.9, 72.3, 65.9, 55.6, 42.9, 40.6, 37.7, 25.8, 17.9, 12.4, −4.2, −4.9; IR (KBr): 2960, 2929, 2858, 1765, 1702, 1391, 1209 cm^{-1}; MS (ES): *m*/*z* 418.2 (M+1); HRMS: *m*/*z* found 418.2419, calcd for $C_{23}H_{36}NO_4Si$ 418.2414.

*4.1.3. (2S,3S)-3-(tert-Butyldimethylsilyloxy)-2-methylhex-5-en-1-ol (**13**).* To an ice cooled solution of compound **12** (9.1 g, 21.82 mmol) in THF (910 mL) was added a solution of sodium borohydride (16.5 g, 436.45 mmol) dissolved in cold water (182 mL) drop wise and stirred at room temperature for 90 h. The reaction was quenched by the addition of saturated ammonium chloride solution. The organic volatiles were removed in vacuo. The residue was diluted with ethyl acetate, washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated. The residue was purified over silica gel (100–200 mesh) using 10% ethyl acetate in petroleum ether as eluent to afford compound **13** as colorless oil (4.26 g, 80%). R_f=0.55 (10% ethyl acetate in petroleum ether); $[\alpha]_D$ +5.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83–5.73 (m, 1H), 5.10–5.02 (m, 2H), 3.87–3.83 (m, 1H), 3.67 (t, J=9.0 Hz, 1H), 3.55–3.50 (m, 1H), 2.38–2.34 (br s, 1H), 2.26 (t, J=1.1 Hz, 2H), 1.97–1.91 (m, 1H), 0.89 (s, 9H), 0.85 (d, J=7.0 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 135.4, 116.9, 74.6, 65.8, 39.5, 38.0, 25.8, 17.9, 11.4, −4.3, −4.7; IR (Neat): 3382, 3078, 2968, 2930, 2858, 1472, 1255, 1046 cm^{-1}; MS (ES): *m*/*z* 245.2 (M+1); HRMS: *m*/*z* found 245.1940, calcd for $C_{13}H_{29}O_2Si$ 245.1937.

*4.1.4. (2S,3S)-3-(tert-Butyldimethylsilyloxy)-2-methylhex-5-enyl 4-methylbenzenesulfonate (**14**).* To an ice cooled solution of compound **13** (9.89 g, 40.53 mmol) in dichloromethane (100 mL) was added triethyl amine (16.9 mL, 121.60 mmol) drop wise followed by *p*-toluenesulfonyl chloride (15.5 g, 81.06 mmol) and DMAP (0.99 g, 8.10 mmol). After stirring for 16 h at room temperature, the reaction mixture was diluted with dichloromethane, washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated. The residue was purified over silica gel (100–200 mesh) using 5% ethyl acetate in petroleum ether as eluent to afford compound **14** as colorless oil (14.8 g, 92%). R_f=0.52 (5% ethyl acetate in petroleum ether); $[\alpha]_D$ +1.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J=8.3 Hz, 2H), 7.33 (d, J=7.8 Hz, 2H), 5.71–5.60 (m, 1H), 5.30–5.01 (m,1H), 4.99–4.98 (m, 1H), 3.98 (dd, J=9.4, 6.6 Hz, 1H), 3.85 (dd, J=9.6, 6.8 Hz, 1H), 3.76–3.72 (m, 1H), 2.45 (s, 3H), 2.21–2.12 (m, 2H), 1.95–1.89 (m, 1H), 0.83 (d, J=6.7 Hz, 3H), 0.81 (s, 9H), 0.02 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.5, 134.5, 133.0, 129.7, 127.8, 117.1, 72.7, 71.0, 38.9, 37.0, 25.7, 21.5, 17.9, 10.0, −4.17, −4.98; IR (Neat): 2956, 2929, 2857, 1366, 1189, 1178 cm^{-1}; MS (ES): *m*/*z* 399.1 (M+1); HRMS: *m*/*z* found 399.2032, calcd for $C_{20}H_{35}O_4SSi$ 399.2025.

*4.1.5. (3S,4S)-4-(tert-Butyldimethylsilyloxy)-3-methylhept-6-enenitrile (**15**).* To a solution of compound **14** (4.54 g, 11.40 mmol) in DMF (45 mL) was added sodium cyanide (1.12 g, 22.80 mmol) and stirred at room temperature for 96 h. The reaction mixture was diluted with ethyl acetate, washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated. The residue was purified over silica gel (100–200 mesh) using 5% ethyl acetate in petroleum ether as an eluent to afford compound **15** as a viscous oil (2.53 g, 88%). R_f=0.60 (2% ethyl acetate in petroleum ether); $[\alpha]_D$ +3.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78–5.68 (m, 1H), 5.11–5.06 (m, 2H),3.75 (dt, J=6.4, 3.2 Hz, 1H), 2.41 (dd, J=16.4, 6.8 Hz, 1H), 2.26–2.17 (m,3H), 2.04–1.97 (m, 1H), 1.02 (d, J=6.8 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 134.1, 119.4, 117.5, 73.2, 38.7, 35.1, 25.8, 25.1, 18.0, 13.3, −4.1, −4.7; IR (KBr): 2930, 2858,

2247, 1465, 1032 cm^{-1}; MS (ES): *m*/*z* 254.3 (M+1); HRMS: *m*/*z* found 254.1941, calcd for $C_{14}H_{28}NOSi$ 254.1940.

*4.1.6. (3S,4S)-4-(tert-Butyldimethylsilyloxy)-3-methylhept-6-enal (**16**). Method A*: To a solution of compound **15** (2.45 g, 9.68 mmol) in dichloromethane (25 mL) at −78 °C was added DIBAL-H (20% solution in toluene) (34.4 mL, 48.41 mmol) drop wise and stirred at the same temperature for 5 h. The reaction mixture was quenched by the addition of saturated aqueous sodium potassium tartrate solution, stirred at room temperature for 1 h and then diluted with dichloromethane. The organic layer was separated and washed successively with water and brine, and dried over anhydrous Na_2SO_4. Concentration and chromatographic purification over silica gel (100–200 mesh) using 1% diethyl ether in petroleum ether as eluent afforded compound **16** as a colorless liquid (2.22 g, 90%).

Method B: To an ice cooled solution of compound **13** (0.35 g, 1.43 mmol) in DCM (10 mL) and H_2O (0.1 mL) was added Dess/Martin periodinane (0.73 g, 1.72 mmol) and stirred at the same temperature for 2 h. Reaction mixture was diluted with additional DCM and quenched with saturated sodium thiosulphate solution. To this was added saturated sodium bicarbonate solution and stirred at room temperature for 30 min. The organic layer was separated and was washed successively with water and brine, and dried over anhydrous Na_2SO_4, and rotary evaporated to afford the corresponding crude aldehyde. A separate round bottomed flask was charged with $MeOCH_2PPh_3^{+}Cl^{-}$ (0.91 g, 2.65 mmol) and dry THF. The solution was cooled to −20 °C and to it was added drop wise NaHMDS (2.4 mL, 1.0 M in THF, 2.40 mmol) and stirred for 30 min. The resulting orange red suspension was cooled to −40 °C and to it was added a solution of above aldehyde in THF (3 mL) drop wise. The reaction mixture was warmed −20 °C over a period of 3 h and then quenched with aqueous saturated NH_4Cl solution (10 mL). The aqueous layer was extracted with ether thrice and the combined organic layers were washed with brine, and dried over Na_2SO_4 and, concentrated in vacuo. The resulting residue (crude enol ether) was dissolved in dioxane/H_2O (10 mL, 9:1) and treated with pyridinium *p*-toluenesulphonate (0.61 g, 2.44 mmol). The reaction mixture was stirred at 50 °C for 16 h, then cooled to room temperature, and quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ether thrice and the combined organic layers were dried over anhydrous Na_2SO_4, and rotary evaporated. The residue was purified over silica gel (100–200 mesh) using 1% diethyl ether in petroleum ether as an eluent to afford compound **16** as a colorless liquid (0.24 g, 65% over three steps). R_f=0.55 (1% diethyl ether in petroleum ether); $[\alpha]_D$ +6.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 9.73 (t, *J*=2.0 Hz, 1H), 5.83–5.73 (m, 1H), 5.09–5.02 (m, 2H),3.65 (dt, *J*=6.4, 3.2 Hz, 1H), 2.61–2.54 (m, 1H), 2.29–2.11 (m, 4H), 0.90 (d, *J*=6.8 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 202.4, 135.2, 116.9, 74.8, 47.2, 38.2, 32.9, 25.8, 18.0, 14.5, −4.3, −4.6; IR (Neat): 3078, 2957, 2930, 2857, 1728, 1254 cm^{-1}; MS (ES): *m*/*z* 257.5 (M+1); HRMS: *m*/*z* found 257.1933, calcd for $C_{14}H_{29}O_2Si$ 257.1937.

*4.1.7. (5S,6S,E)-Ethyl 6-(tert-butyldimethylsilyloxy)-5-methylnona-2,8-dienoate (**17**).* To a solution of compound **16** (8.0 g, 31.25 mmol) in benzene (80 mL) was added carbethoxymethylene-triphenylphosphorane (21.8 g, 62.5 mmol) and stirred at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate, washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated. The residue was purified over silica gel (100–200 mesh) using 1% ethyl acetate in petroleum ether as eluent to afford compound **17** as colorless oil (8.8 g, 90%). R_f=0.67 (1% ethyl acetate in petroleum ether); $[\alpha]_D$ −2.2 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 6.96–6.89 (m, 1H), 5.84–5.73 (m, 1H), 5.81 (d, *J*=15.6 Hz, 1H), 5.09–5.01 (m, 2H),4.18 (q, *J*=6.3 Hz, 2H), 3.65–3.60 (m, 1H), 2.40–2.33 (m, 1H), 2.28–2.18 (m, 2H), 2.04–1.95 (m, 1H), 1.78–1.70 (m, 1H), 1.29 (t, *J*=6.3 Hz, 3H), 0.89 (s, 9H), 0.86 (d, *J*=7.0 Hz, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.5, 148.4, 135.3, 122.3, 116.7, 75.0, 60.1, 38.6, 37.3, 35.7, 25.9, 18.1, 14.3, 13.9, −4.5, −4.1; IR (Neat): 2932, 2858, 1724, 1256, 1046 cm^{-1}; MS (ES): *m*/*z* 327.1 (M+1); HRMS: *m*/*z* found 327.2351, calcd for $C_{18}H_{35}O_3Si$ 327.2355.

*4.1.8. (5S,6S,E)-Ethyl 6-hydroxy-5-methylnona-2,8-dienoate (**18**).* To a solution of compound **17** (2.26 g, 6.93 mmol) in THF (40 mL) was added 3 N HCl (10 mL) and stirred at room temperature for 16 h. Reaction mixture was diluted with ethyl acetate, washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated. The residue was purified over silica gel (100–200 mesh) using 10% ethyl acetate in petroleum ether as eluent to afford compound **18** as colorless oil (1.38 g, 94%). R_f=0.47 (20% ethyl acetate in petroleum ether); $[\alpha]_D$ +6.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 6.95 (dt, *J*=15.6, 7.3 Hz, 1H), 5.85 (d, *J*=15.6 Hz, 1H), 5.87–5.76 (m, 1H), 5.18–5.16 (m, 1H), 5.16–5.13 (m, 1H), 4.19 (q, *J*=7.1 Hz, 2H), 3.60–3.56 (m, 1H), 2.44–2.37 (m, 1H), 2.30–2.23 (m, 1H), 2.21–2.07 (m, 2H), 1.78–1.72 (m, 1H), 1.49 (d, *J*=3.8 Hz, 1H), 1.29 (t, *J*=7.1 Hz, 3H), 0.94 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.5, 147.9, 135.0, 122.5, 118.1, 72.9, 60.1, 38.9, 37.2, 36.1, 14.1, 13.4; IR (Neat): 3485, 2978, 2938, 2905, 1720, 1703, 1651, 1177 cm^{-1}; MS (ES): *m*/*z* 213.2 (M+1); HRMS: *m*/*z* found 235.1319, calcd for $C_{12}H_{20}O_3Na$ 235.1310.

*4.1.9. Methyl 2-((2R,4S,5S)-5-allyl-4-methyltetrahydrofuran-2-yl) acetate (**19a**).* A solution of compound **18** (200 mg, 0.94 mmol) in methanol was cooled to −15 °C and NaOMe (51 mg, 0.94 mmol) was added portion wise and stirred at the same temperature for 16 h. Reaction mixture was diluted with ethyl acetate, washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated. The residue was purified over silica gel (100–200 mesh) using 10% ethyl acetate in petroleum ether as eluent to afford the cyclized product as diastereomeric mixture (177 mg, 95%). Separation of diastereomers using HPLC[12] afforded compound **19a** as a colorless liquid (136 mg, 73% yield, 94% recovery in HPLC). R_f=0.62 (20% ethyl acetate in petroleum ether); ^1H NMR (400 MHz, $CDCl_3$): δ 5.86–5.76 (m, 1H), 5.13–5.03 (m, 2H), 4.52–4.45 (m, 1H), 3.98–3.94 (m, 1H), 3.68 (s, 3H), 2.63 (dd, *J*=15.2, 6.8 Hz, 1H), 2.43 (dd, *J*=15.2, 6.2 Hz, 1H), 2.34–2.26 (m, 2H), 2.20–2.13 (m, 1H), 1.90–1.78 (m, 2H), 0.95 (d, *J*=7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.6, 135.2, 116.5, 80.8, 73.2, 51.6, 41.3, 39.7, 35.7, 34.9, 13.9; IR (Neat): 2963, 2876, 1740, 1437, 1171 cm^{-1}; MS (ES): *m*/*z* 199.2 (M+1); HRMS: *m*/*z* found 221.1161, calcd for $C_{11}H_{18}O_3Na$ 221.1154.

*4.1.10. 2-((2R,4S,5S)-5-Allyl-4-methytetrahydrofuran-2-yl)ethanol (**20**).* To an ice cooled solution of compound **19a** (50 mg, 0.25 mmol) in THF (10 mL) was added lithium aluminum hydride (14 mg, 0.38 mmol) portion wise and stirred at room temperature for 20 min. The reaction mixture was quenched by careful addition of aqueous saturated sodium sulfate solution at 0 °C and stirred at room temperature for 30 min. The separated solid was filtered and washed with excess ethyl acetate. The filtrate was diluted with ethyl acetate, washed successively with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified over silica gel (100–200 mesh) using 30% ethyl acetate in petroleum ether as eluent to afford compound **20** as a colorless liquid (30 mg, 70%). R_f=0.28 (30% ethyl acetate in petroleum ether); $[\alpha]_D$ −22.6 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.86–5.76 (m, 1H), 5.13–5.03 (m, 2H), 4.29 (ddt, *J*=11.2, 7.2, 3.2 Hz, 1H), 3.99–3.95 (m, 1H), 3.84–3.78 (m, 2H), 3.04–2.96 (br s, 1H), 2.31–2.23 (m, 2H), 2.21–2.14 (m, 1H), 1.82–1.79 (m, 2H), 1.77–1.66

(m, 2H), 0.94 (d, J=6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 135.2, 116.5, 80.6, 77.2, 61.9, 40.3, 38.1, 35.5, 34.9, 14.0; IR (Neat): 3435, 2961, 2934, 2876, 1088, 1055 cm^{-1}; MS (ES): m/z 171.5 (M+1); HRMS: m/z found 171.1377, calcd for $C_{10}H_{19}O_2$ 171.1385.

*4.1.11. (2-((2R,4S,5S)-5-Allyl-4-methyltetrahydrofuran-2-yl)ethoxy) (tert-butyl)dimethylsilane (**21**).* To a solution of compound **20** (1.38 g, 8.11 mmol) in DMF (14 mL) was added TBDMS chloride (1.35 g, 8.93 mmol) followed by imidazole (0.829 g, 12.17 mmol) and stirred at room temperature for 1 h. The reaction mixture was diluted with water and extracted with ethyl acetate thrice. The combined organic layers were washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated. The residue was purified on silica gel (100–200 mesh) using 5% ethyl acetate in petroleum ether as eluent to afford compound **21** as colorless oil (2.07 g, 90%). R_f=0.65 (10% ethyl acetate in petroleum ether); $[\alpha]_D$ −27.0 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83–5.73 (m, 1H), 5.08–4.97 (m, 2H), 4.17–4.09 (m, 1H), 3.89–3.84 (m, 1H), 3.68–3.61 (m, 2H), 2.27–2.18 (m, 2H), 2.14–2.11 (m, 1H), 1.79–1.62 (m, 3H), 1.61–1.54 (m, 1H), 0.88 (d, J=7.3 Hz, 3H), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 135.6, 116.2, 80.3, 74.0, 60.3, 40.1, 39.8, 35.8, 35.1, 25.9, 18.3, 14.1, -5.3; IR (Neat): 2957, 2930, 2857, 1256, 1092 cm^{-1}; MS (ES): m/z 285.0 (M+1); HRMS: m/z found 285.2249, calcd for $C_{16}H_{33}O_2Si$ 285.2250.

*4.1.12. (S)-6-((2S,3S,5R)-5-(2-(tert-Butyldimethylsilyloxy)ethyl)-3-methyltetrahydrofuran-2-yl)-2-methylhexanoic acid (**8**).* A mixture of compound **21** (0.2 g, 0.70 mmol) and (*S*)-2-methylpent-4-enoic acid (**22**) (0.32 g, 2.82 mmol), and catalyst (**23**) (60 mg, 0.07 mmol) in dry DCM (5 mL) was refluxed for 5 h. After cooling to room temperature, the reaction mixture was diluted with additional DCM (5 mL). The organic layer was washed successively with water and brine, and dried over anhydrous Na_2SO_4, and passed through a short pad of silica gel. The silica pad was further washed with 2% acetone in DCM. The solvents were evaporated to give the crude metathesis product, which was then dissolved in EtOAc (5 mL). To this solution was added 10% Pd/C (0. 4 g) and the reaction mixture was stirred under hydrogen atmosphere using a hydrogen balloon at room temperature for 1 h. The reaction mixture was filtered through Celite, washed the bed with EtOAc. The filtrate and the washings were concentrated in vacuo and the residue was purified over silica gel (100–200 mesh) using 2% acetone in dichloromethane as eluent to afford compound **8** as an oil (0.16 g, 61% yield over two steps). R_f=0.28 (5% methanol in chloroform); $[\alpha]_D$ −3.4 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.17–4.09 (m, 1H), 3.85–3.78 (m, 1H), 3.74–3.66 (m, 2H), 2.51–2.41 (m, 1H), 2.26–2.14 (m, 1H), 1.87–1.58 (m, 4H), 1.50–1.27 (m, 8H), 1.18 (d, J=7.0 Hz, 3H), 0.89 (s, 9H), 0.89 (d, J=7.0 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 182.2, 80.8, 73.8, 60.7, 40.2, 39.9, 39.3, 35.9, 33.5, 30.3, 27.4, 26.6, 26.0, 18.3, 16.9, 14.1, −5.3; IR (Neat): 2955, 2930, 1738, 1707, 1090 cm^{-1}; MS (ES): m/z 395.0 (M+Na); HRMS: m/z found 395.2594, calcd for $C_{20}H_{40}O_4SiNa$ 395.2589.

*4.1.13. (S)-4-Benzyl-3-((S)-6-(tert-butyldimethylsilyloxy)-2-methyl-4-methylenehexanoyl)oxazolidin-2-one (**26**).* A solution of (*S*)-4-benzyl-*N*-propionyloxazolidinone **24** (5 g, 21.45 mmol) in THF (20 mL) was cooled to −78 °C. To this solution was added NaHMDS (1 M solution in THF) (25.6 mL, 25.6 mmol) drop wise. After stirring for 30 min at the same temperature, a solution of compound **25** (7.7 g, 23.60 mmol) in THF (30 mL) was added drop wise and stirred for 5 h. The reaction mixture was quenched by the addition of saturated ammonium chloride solution and brought it to room temperature while stirring. The reaction mixture was diluted with ethyl acetate, washed successively with water and brine, and dried over anhydrous Na_2SO_4. Concentration and chromatographic purification over silica gel (100–200 mesh) afforded compound **26** as colorless oil (5.7 g, 62%). R_f=0.42 (20% ethyl acetate in petroleum ether); $[\alpha]_D$ +20.1 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.31 (m, 2H), 7.28–7.25 (m, 1H), 7.22–7.20 (m, 2H), 4.85 (s, 2H), 4.71–4.65 (m, 1H), 4.21–4.13 (m, 2H), 4.02 (q, J=7.1 Hz, 1H), 3.73 (t, J=6.8 Hz, 2H), 3.29 (dd, J=13.2, 2.8 Hz, 1H), 2.69 (dd, J=13.4, 9.8 Hz, 1H), 2.58 (dd, J=14.4, 7.2 Hz, 1H), 2.29 (t, J=7.0 Hz, 2H), 2.12 (dd, J=14.0, 7.6 Hz, 1H), 1.17 (d, J=6.8 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 176.9, 153.0, 144.0, 135.3, 129.4, 128.9, 127.3, 112.9, 65.9, 62.1, 55.3, 40.4, 39.0, 37.9, 35.7, 25.9, 18.2, 16.9, −5.3; IR (Neat): 2928, 2856, 1782, 1699, 1385, 1099 cm^{-1}; MS (ES): m/z 432.1 (M+1); HRMS: m/z found 432.2578, calcd for $C_{24}H_{38}NO_4Si$ 432.2570.

*4.1.14. (S)-4-Benzyl-3-((S)-6-hydroxy-2-methyl-4-methylenehexanoyl)oxazolidin-2-one (**27**).* A solution of compound **26** (1.3 g, 3.02 mmol) in THF (13 mL) was added 3 N HCl (6.5 mL) and stirred at room temperature for 3 h. The reaction mixture was diluted with ethyl acetate, washed successively with water and brine, and dried over anhydrous Na_2SO_4. Concentration and purification over silica gel (100–200 mesh) afforded compound **27** as colorless oil (0.83 g, 87%). R_f=0.25 (30% ethyl acetate in petroleum ether); $[\alpha]_D$ +39.7 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.32 (m, 2H), 7.29–7.27 (m, 1H), 7.22–7.20 (m, 2H), 4.93 (s, 2H), 4.71–4.66 (m, 1H), 4.22–4.15 (m, 2H), 4.06 (q, J=7.1 Hz, 1H), 3.76 (t, J=5.1 Hz, 2H), 3.26 (dd, J=13.2, 3.4 Hz, 1H), 2.71 (dd, J=13.2, 9.8 Hz, 1H), 2.62 (dd, J=14.5, 3.8 Hz, 1H), 2.40–2.31 (m, 2H), 2.11 (dd, J=14.5, 6.8 Hz, 1H), 1.69–1.64 (br s, 1H) 1.19 (d, J=6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 176.7, 153.0, 143.5, 135.0, 129.2, 128.7, 127.1, 113.5, 65.9, 60.4, 55.2, 39.4, 38.7, 37.7, 35.5, 16.6; IR (Neat): 3491, 2976, 2933, 2878, 1778, 1697, 1389, 1211 cm^{-1}; MS (ES): m/z 318.1 (M+1); HRMS: m/z found 340.1537, calcd for $C_{18}H_{23}NO_4$ Na 340.1525.

*4.1.15. (S)-6-((S)-4-Benzyl-2-oxooxazolidin-3-yl)-5-methyl-3-methylene-6-oxohexanal (**28**).* To an ice cooled solution of compound **27** (1.77 g, 5.56 mmol) in DCM (20 mL) and H_2O (0.1 mL) was added Dess/Martin periodinane (2.8 g, 6.68 mmol) and stirred at the same temperature for 4 h. The reaction mixture was quenched with saturated sodium thiosulphate solution (5 mL) and saturated sodium bicarbonate solution (5 mL) and stirred at room temperature for 30 min. The DCM layer was separated and the aqueous layer was extracted with additional DCM. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and, rotary evaporated. The residue was purified over silica gel (100–200 mesh) to afford compound **28** as colorless oil (1.48 g, 84%). R_f=0.65 (40% ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (t, J=2.1 Hz, 1H), 7.35–7.31 (m, 2H), 7.29–7.27 (m, 1H), 7.25–7.20 (m, 2H), 5.11 (s, 1H), 4.99 (s, 1H), 4.71–4.65 (m, 1H), 4.22–4.15 (m, 2H), 3.30–3.14 (m, 3H), 2.71 (dd, J=13.2, 9.6 Hz, 1H), 2.62 (dd, J=14.2, 7.0 Hz, 1H), 2.16 (dd, J=14.0, 7.6 Hz, 1H), 1.18 (t, J=6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 199.5, 176.3, 153.2, 138.2, 135.2, 129.4, 128.9, 127.4, 117.2, 66.1, 55.4, 50.2, 40.8, 38.0, 35.6, 16.6; IR (Neat): 2976, 2934, 1778, 1699, 1387 cm^{-1}; MS (ES): m/z 316.0 (M+1); HRMS: m/z found 316.1551, calcd for $C_{18}H_{22}NO_4$ 316.1549.

*4.1.16. (S)-4-Benzyl-3-((2S,6RS)-6-hydroxy-2-methyl-4-methylenenonanoyl)oxazolidin-2-one (**29**).* To a solution of compound **28** (1.66 g, 5.27 mmol) in diethyl ether (17 mL) at −78 °C was added *n*-propylmagnesium chloride (7.9 mL, 2 M solution in diethyl ether, 15.8 mmol) drop wise. After stirring for 5 h at the same temperature, the reaction mixture was quenched by the addition of saturated ammonium chloride solution and stirred at room temperature for 30 min. The aqueous part was extracted with ethyl acetate thrice. The organic layer was washed successively with water and brine, dried over anhydrous Na_2SO_4, and rotary evaporated. The residue was purified over silica gel (100–200 mesh) to

afford 2:1 diastereomeric mixture of compound **29** as colorless oil (0.83 g, 44%; recovered **28**, 21%). Data for the mixture: R_f=0.72 (5% acetone in dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.26 (m, 3H), 7.22–7.19 (m, 2H), 4.95–4.93 (m, 2H), 4.71–4.65 (m, 1H), 4.22–4.07 (m, 2H), 4.07–3.97 (m, 1H), 3.86–3.76 (br s, 1H), 3.29–3.24 (m, 1H), 3.29–3.24 (m, 2H), 2.74–2.60 (m, 2H), 2.36–2.26 (m, 1H), 2.15–2.04 (m, 1H), 1.95–1.87 (m, 1H), 1.54–1.38 (m, 4H), 1.21–1.16 (m, 3H), 0.94 (t, J=7.0 Hz, 3H); IR (Neat): 3514, 2957, 2931, 2872, 1778, 1699, 1387, 1209 cm^{-1}; MS (ES): m/z 360.3 (M+1).

*4.1.17. (2S,6R)-2-Methyl-4-methylenenonane-1,6-diol (**30**) and (2S,6S)-2-methyl-4-methylenenonane-1,6-diol (**31**).* To a solution of compound **29** (0.71 g, 1.97 mmol) in THF (7 mL) was added at 0 °C methanol (0.16 mL, 3.95 mmol) followed by lithium borohydride (86 mg, 3.95 mmol). The reaction mixture was stirred at the same temperature for 1 h and then quenched by the addition of saturated ammonium chloride solution. The aqueous layer was extracted with ethyl acetate thrice. The combined extracts were washed successively with water and brine, dried over anhydrous Na_2SO_4, and rotary evaporated. Purification of the residue over silica gel (230–400 mesh) using a mixture of ethyl acetate/DCM/petroleum ether (1:1:8) as eluent resulted in the separation of two diastereomers affording compound **30** (0.203 g, 55%) and **31** (0.101 g, 27%) as oils. Compound **30**: R_f=0.35 (35% ethyl acetate in petroleum ether); $[\alpha]_D$ −1.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.91 (s, 2H), 3.76–3.70 (m, 1H), 3.52 (d, J=5.6 Hz, 2H), 2.27–2.20 (m, 2H), 2.05 (dd, J=14.0, 9.6 Hz, 1H), 1.86–1.80 (m, 2H), 1.50–1.37 (m, 4H), 0.94 (t, J=7.2 Hz, 3H), 0.90 (d, J=6.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 145.2, 114.0, 68.8, 68.0, 44.1, 40.0, 39.3, 33.8, 18.9, 16.4, 14.0; IR (Neat): 3350, 2957, 2928, 2872, 1643, 1454, 1036 cm^{-1}; MS (ES): m/z 187.2 (M+1); HRMS: m/z found 185.1542, calcd for $C_{11}H_{21}O_2$ 185.1542. Compound **31**: R_f=0.34 (35% ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.91 (d, J=4.4 Hz, 2H), 3.77–3.72 (m, 1H), 3.54–3.46 (m, 2H), 2.26 (dd, J=13.2, 9.6 Hz, 1H) 2.20–2.10 (m, 1H), 2.10–2.06 (m, 1H), 1.95–1.88 (m, 2H), 1.50–1.38 (m, 4H), 0.94 (t, J=7.2 Hz, 3H), 0.94 (d, J=6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 145.4, 113.5, 69.0, 67.7, 44.1, 40.3, 39.3, 33.6, 18.8, 16.6, 14.0; IR (Neat): 3352, 2957, 2926, 2872, 1643, 1452, 1379 cm^{-1}; MS (ES): m/z 187.3 (M+1); HRMS: m/z found 185.1544, calcd for $C_{11}H_{21}O_2$ 185.1542.

*4.1.18. (4S,8S)-9-(tert-Butyldimethylsilyloxy)-8-methyl-6-methylenenonan-4-ol (**32**).* To an ice cooled solution of compound **31** (0.2 g, 1.07 mmol) in DCM (1 mL) were added TBDMS chloride (0.194 mg, 1.29 mmol) and imidazole (0.110 g, 1.61 mmol). After stirring at the same temperature for 2 h, the reaction mixture was diluted with DCM and the organic layer was washed successively with water and brine, and dried over anhydrous Na_2SO_4. Concentration and purification over silica gel (100–200 mesh) afforded compound **15** as colorless oil (0.27 g, 84%). R_f=0.52 (10% ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.88 (s, 2H), 3.73–3.66 (m, 1H), 3.45–3.36 (m, 2H), 2.26–2.17 (m, 2H), 2.06 (dd, J=13.9, 9.6 Hz, 1H), 1.84–1.76 (m, 3H), 1.56–1.33 (m, 4H), 0.94 (t, J=7.1 Hz, 3H), 0.89 (s, 9H), 0.89 (d, J=7.3 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 145.2, 113.5, 68.7, 67.6, 44.5, 40.0, 39.2, 33.8, 25.9, 18.9, 18.3, 16.9, 14.1, −5.4; IR (Neat): 3393, 2957, 2930, 2857, 1470, 1252, 1092 cm^{-1}; MS (ES): m/z 301.3 (M+1); HRMS: m/z found 301.2558, calcd for $C_{17}H_{37}O_2Si$ 301.2563.

*4.1.19. (S)-9-(tert-Butyldimethylsilyloxy)-8-methyl-6-methylenenonan-4-one (**33**).* To a solution of compound **32** (0.17 g, 0.58 mmol) in DCM (10 mL) at 0 °C was added successively water (0.1 mL), solid $NaHCO_3$ (0.099 g, 1.16 mmol) followed by Dess/Martin periodinane (0.49 g, 1.16 mmol). The reaction mixture was stirred at the same temperature for 2 h and quenched with saturated sodium thiosulphate solution followed by saturated sodium bicarbonate solution and stirred at room temperature for 30 min. The aqueous layer was extracted with DCM thrice and the organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. Concentration and purification over silica gel (100–200 mesh) afforded compound **33** as colorless oil (0.15 g, 89%). R_f=0.85 (10% ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.94 (d, J=1.2 Hz, 1H), 4.88 (d, J=1.2 Hz, 1H), 3.44–3.36 (m, 2H), 3.08 (s, 2H), 2.43 (t, J=7.2 Hz, 2H), 2.24–2.17 (m, 1H), 1.77–1.74 (m, 2H), 1.59 (dd, J=14.8, 7.6 Hz, 2H), 0.91 (t, J=7.2 Hz, 3H), 0.89 (s, 9H), 0.85(d, J=6.4 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 208.9, 141.6, 115.2, 67.8, 50.3, 43.9, 40.1, 33.6, 25.9, 18.3, 17.2, 16.4, 13.6, −5.4; IR (Neat): 2957, 2930, 1715, 1462, 1092 cm^{-1}; MS (ES): m/z 299.3 (M+1); HRMS: m/z found 299.2408, calcd for $C_{17}H_{35}O_2Si$ 299.2406.

*4.1.20. (4R,8S)-9-(tert-Butyldimethylsilyloxy)-8-methyl-6-methylenenonan-4-ol (**9**). Method A*: To an ice cooled solution of compound **30** (0.066 g, 0.35 mmol) in DCM (1 mL) was added TBDMS chloride (0.064 mg, 0.43 mmol), imidazole (0.036 g, 0.53 mmol) and stirred at the same temperature for 16 h. The reaction mixture was diluted with DCM, washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated and the residue was purified over silica gel (100–200 mesh) to afford compound **9** as colorless oil (0.085 g, 80%).

Method B: To a solution of compound **33** (0.05 g, 0.168 mmol) in THF (2 mL) at −78 °C was added drop wise chiral oxazaborolidine **34** (0.34 μL, 0.033 mmol) followed by BH_3/DMS (18 μL, 0.252 mmol). The reaction mixture was stirred at the same temperature for 1 h and quenched with methanol (0.5 mL). The reaction was warmed to room temperature, concentrated in vacuo, and the residue was purified over silica gel (100–200 mesh) to afford compound **9** as colorless oil (0.04 g, 80%). R_f=0.52 (10% ethyl acetate in petroleum ether); $[\alpha]_D$ −3.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.89 (s, 2H), 3.74–3.66 (m, 1H), 3.46–3.37 (m, 2H), 2.30 (dd, J=13.4, 4.2 Hz, 1H) 2.24 (dd, J=13.8, 3.0 Hz, 1H), 2.01 (dd, J=13.6, 9.6 Hz, 1H), 1.80–1.71(m, 2H), 1.52–1.33 (m, 4H), 0.94 (t, J=7.0 Hz, 3H), 0.90 (s, 9H), 0.83 (d, J=6.6 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 145.3, 114.1, 68.3, 68.1, 44.0, 39.5, 39.3, 33.9, 25.9, 18.9, 18.3, 16.2, 14.1, −5.4; IR (Neat): 3393, 2957, 2930, 2857, 1464, 1252, 1092 cm^{-1}; MS (ES): m/z 301.3 (M+1); HRMS: m/z found 301.2558, calcd for $C_{17}H_{37}O_2Si$ 301.2563.

*4.1.21. (R)-((4R,8R)-9-(tert-Butyldimethylsilyloxy)-8-methyl-6-methylenenonan-4-yl) 6-((2S,3S,5R)-5-(2-(tert-butyldimethylsilyloxy)ethyl)-3-methyltetrahydrofuran-2-yl)-2-methylhexanoate (**35**).* To a solution of **8** (114 mg, 0.306 mmol) in toluene (4 mL) was added triethyl amine (0.13 mL, 0.92 mmol) followed by 2,4,6-trichlorobenzoyl chloride (0.14 mL, 0.924 mmol). The reaction mixture was stirred at room temperature for 1 h and to this solution was added a solution of **9** (84 mg, 0.28 mmol) and DMAP (34 mg, 0.28 mmol) in toluene (4 mL) drop wise. The mixture was stirred for 16 h at room temperature followed by heating at 70 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and was washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated. The residue was purified over silica gel (100–200 mesh) to afford compound **35** as colorless oil (80 mg, 44%). R_f=0.65 (10% ethyl acetate in petroleum ether); $[\alpha]_D$ −8.54 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.07–5.00 (m, 1H), 4.79 (s, 1H), 4.76 (s, 1H), 4.16–4.09 (m, 1H), 3.82–3.77 (m, 1H), 3.74–3.65 (m, 2H), 3.44 (dd, J=9.8, 5.4 Hz, 1H), 3.37 (dd, J=9.8, 6.2 Hz, 1H), 2.40–2.34 (m, 1H), 2.28–2.14 (m, 4H), 2.40–2.34 (m, 1H), 2.28–2.14 (m, 4H), 1.80–1.61 (m, 6H), 1.54–1.46 (m, 2H), 1.46–1.25 (m, 1H), 1.11 (d, J=6.4 Hz, 3H), 0.94–0.88 (m, 24H), 0.84 (d, J=6.8 Hz, 3H), 0.05 (s, 6H), 0.03(s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 176.3, 144.0, 113.5, 80.8, 73.8, 71.4, 68.1,

60.7, 40.9, 40.3, 40.0, 39.8, 36.5, 35.9, 33.9, 33.8, 30.4, 29.7, 27.5, 26.6, 26.0, 18.6, 18.4, 17.3, 16.6, 14.1, −5.3; IR (Neat): 2957, 2930, 1732, 1462, 1092 cm^{-1}; MS (ES): *m/z* 655.6 (M+1); HRMS: *m/z* found 655.5184, calcd for $C_{37}H_{75}O_5Si_2$ 655.5153.

*4.1.22. (R)-((4R,8R)-9-Hydroxy-8-methyl-6-methylenenonan-4-yl) 6-((2S,3S,5R)-5-(2-hydroxyethyl)-3-methyltetrahydrofuran-2-yl)-2-methylhexanoate (**36**).* To an ice cooled solution of compound **35** (80 mg, 0.12 mmol) in THF (1 mL) was added TBAF (0.6 mL, 1.0 M solution in THF) and stirred at room temperature for 5 h. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated. The residue was purified over silica gel (100–200 mesh) to afford compound **36** as colorless oil (40 mg, 77%). R_f=0.25 (40% ethyl acetate in petroleum ether); $[\alpha]_D$ −8.54 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.08–5.02 (m, 1H), 4.82 (s, 1H), 4.81 (s, 1H), 4.30–4.23 (m, 1H), 3.89–3.85 (m, 1H), 3.83–3.75 (m, 2H), 3.50 (dd, *J*=10.6, 5.4 Hz, 1H), 3.42 (dd, *J*=10.8, 6.0 Hz, 1H), 2.42–2.17 (m, 6H), 1.86–1.77 (m, 4H), 1.74–1.62 (m, 3H), 1.55–1.51 (m, 2H), 1.47–1.26 (m, 8H), 1.12 (d, *J*=7.2 Hz, 3H), 0.92–0.89 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 143.8, 113.8, 81.3, 77.1, 71.5, 68.1, 62.0, 40.8, 40.4, 40.0, 39.7, 38.0, 36.4, 35.6, 33.7, 33.6, 30.2, 27.3, 26.6, 18.6, 17.2, 16.5, 14.0, 13.9; IR (Neat): 3431, 2959, 2934, 2872, 1728, 1192 cm^{-1}; MS (ES): *m/z* 427.4 (M+1); HRMS: *m/z* found 427.3409, calcd for $C_{25}H_{47}O_5$ 427.3424.

*4.1.23. (R)-((4R,8R)-8-Methyl-6-methylene-9-oxononan-4-yl) 2-methyl-6-((2S,3S,5R)-3-methyl-5-(2-oxoethyl)tetrahydrofuran-2-yl) hexanoate (**7**).* To an ice cooled solution of diol **36** (35 mg, 0.082 mmol) in DCM (4 mL) was added solid $NaHCO_3$ (21 mg, 0.25 mmol) followed by Dess/Martin periodinane (104 mg, 0.25 mmol) and stirred at the same temperature for 2 h. The reaction mixture was diluted with additional DCM, quenched with saturated sodium thiosulphate solution and stirred for 30 min. The DCM layer was separated and washed with water and brine, and dried over anhydrous Na_2SO_4. Concentration and chromatographic purification over silica gel (100–200 mesh) furnished compound **7** as colorless oil (30 mg, 88%). R_f=0.35 (30% ethyl acetate in petroleum ether); $[\alpha]_D$ −14.5 (*c* 0.55, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 9.80 (t, *J*=2.1 Hz, 1H), 9.63 (d, *J*=1.8 Hz, 1H), 5.07–5.01 (m, 1H), 4.87 (s, 1H), 4.81 (s, 1H), 4.56–4.50 (m, 1H), 3.88–3.84 (m, 1H), 2.70–2.63 (m, 1H), 2.56–2.47 (m, 3H), 2.40–2.35 (m, 1H), 2.31–2.16 (m, 3H), 2.11–2.03(m, 1H), 1.91–1.84 (m, 1H), 1.81–1.76 (m, 1H), 1.69–1.61 (m, 3H), 1.56–1.50 (m, 3H), 1.48–1.27 (m, 6H), 1.12 (d, *J*=7.0 Hz, 3H), 1.08 (d, *J*=6.7 Hz, 3H), 0.93–0.89 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.5, 201.6, 176.4, 142.1, 114.7, 81.5, 71.6, 71.2, 50.5, 44.2, 41.2, 40.0, 39.8, 36.7, 36.4, 35.8, 33.6, 30.2, 27.4, 26.5, 18.6, 17.2, 13.9, 13.8, 13.4; IR (Neat): 2961, 2934, 2874, 1728, 1462, 1167 cm^{-1}; MS (ES): *m/z* 423.3 (M+1); HRMS: *m/z* found 423.3107, calcd for $C_{25}H_{43}O_5$ 423.3110.

Acknowledgements

We thank Dr. Reddy's Laboratories Ltd. for the support and encouragement. Help from the analytical department in the form of spectral data is also appreciated.

References and notes

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