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# Asymmetric synthesis of a 12-membered macrolactone core and a 6-*epi* analogue of amphidinolide W from 4-pentenoic acid

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ABSTRACT

A flexible and efficient asymmetric route to the synthesis of a 12-membered macrolactone core and a 6-*epi* analogue of amphidinolide W has been accomplished from commercially available 4-pentenoic acid. The successful generation of stereocenters was achieved by utilizing an Evans' chiral auxiliary-based alkylation and aldol reaction. Other key reactions such as a Julia–Kocienski olefination, Kita's macrolactonization, ring closing metathesis (RCM) reaction, and Yamaguchi's esterification were significant for the construction of the macrolactone cores.



## 1. Introduction

Naturally occurring marine microorganisms serve as a limitless source of diverse and highly complex secondary metabolites exhibiting a wide range of biological activities, such as cytotoxicity, antiviral and anti-fungal properties.[1–6] Amphidinolides represent a group of structurally unique naturally occurring marine macrolides that have gained attention from medicinal chemists. Since 1986, Kobayashi et al. have isolated more than 30 novel metabolites belonging to the 'amphidinolide' class from marine dinoflagellates of the genus *Amphidinium* sp.[7] Many of the amphidinolides exhibit potent cytotoxic properties against various cancer cell lines in the standard assays. Despite their common origin and uniform activity profile, the interesting structural architecture, and biological activity (mainly anti-tumor properties) and limited natural abundance of this family of macrolides remain a great challenge to the synthetic organic chemists.[8] Amphidinolide W **1**, a 12-membered macrolide isolated by Kobayashi et al. in 2002, shows potent cytotoxicity against murine lymphoma L1210 cells in vitro with an $IC_{50}$ value of 3.9 μg/mL.[9] It is structurally unique; being the first and only member in the family which lacks an exomethylene unit. Excited by the interesting structural features in combination with its fascinating biological activity, we envisaged developing a potentially useful synthetic method toward the synthesis of amphidinolide W (Fig. 1). In this synthesis, the greatest challenge is to eliminate the risk of epimerization during the esterification and/or macrolactonization step and control the stereochemistries concerning the formation of the double bond in the $\Delta^{9,10}$ position associated with other stereogenic centers, present in the molecules.

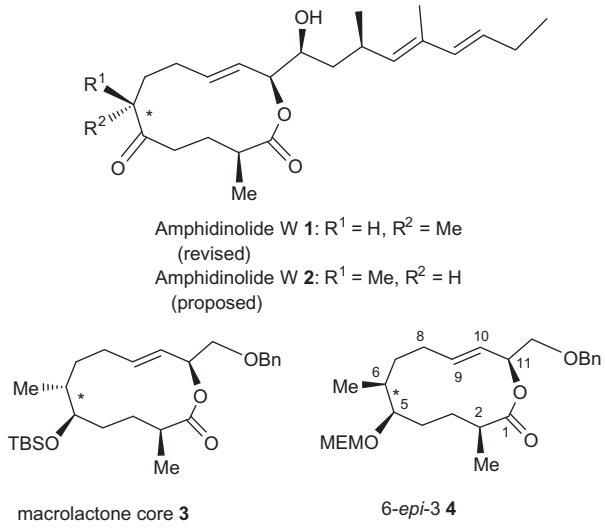


**Figure 1.** Structures of amphidinolide W (**1** and **2**), macrolactone core **3** and 6-*epi* analogue **4**.

The synthesis of the 12-membered macrolactone core **3** of amphidinolide W **1** has recently been reported by us,[10] while the total synthesis of amphidinolide W with its structural revision was deduced earlier[11] when Ghosh et al. reported the stereochemical inversion at the C-6 center of the proposed amphidinolide W **2** that is, the 6-epimer of revised amphidinolide W **1**. In their synthetic efforts, a well established cross metathesis and Yamaguchi's

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lactonisation approach resulted in the synthesis of the proposed amphidinolide W **2** along with its C2-epimer; however major discrepancies in the observed NMR data of proposed amphidinolide W **2** by Kobayashi et al.,[7] compelled them to synthesize the revised amphidinolide W **1**. A comprehensive analysis of the spectroscopic data of the revised amphidinolide W **1** finally revealed it to be a naturally occurring compound.

Herein we report a full account of an efficient and successful synthesis of a 12-membered macrolactone core **3** along with its 6-*epi* analogue **4** of amphidinolide W **1**. Our study could also be useful in investigating the structure-activity relationship of these series of isomeric molecules (Fig. 1).

## 2. Results and discussion

### 2.1. Retrosynthetic analysis and strategy

The central goal was the synthesis of macrolactone cores **3** and **4** containing four stereogenic centers and one $\Delta^{9,10}E$-alkene. Retrosynthetically, the construction of the architectural frame of macrolactone core **3** could be primed via the highly stereoselective Julia–Kocienski olefination of fragments **6**, and subsequently invoking Kita's protocol for the macrolactonization of fragment **5**, whereas for the 6-*epi* analogue **4**, Yamaguchi esterification on fragment **10** and a ring closing metathesis reaction (RCM) of the key fragment **9** were implemented.

The salient feature of this synthesis is the dibutyl boron triflate ($Bu_2BOTf$) mediated highly stereocontrolled Evans' *syn*-aldol reaction using an oxazolidinone based chiral auxiliary which was expected to fix the C5 and C6 centers whereas the C2 center was planned to be generated from the chiral auxiliary assisted Evans' alkylation. The remaining C11 center could be achieved from D-mannitol.[12,13] Our retrosynthesis illustrates that common to both syntheses is fragment **7**, which could be easily prepared from an achiral and commercially abundant material, 4-pentenoic acid **8**. The total synthesis of amphidinolide W could be achieved by assembling the diene fragment with the macrolactone cores **3** and **4** after removal of the *O*-benzyl group. This could be achieved by using Lewis acid conditions[14a,b,c] such as: (1) $TiCl_4$ in $CH_2Cl_2$ or (2) $BCl_3$ or $BBr_3$ in $CH_2Cl_2$ which would sustain the olefin as well as the lactone functionality. Thus, it was envisioned that the side chain could be stitched in both of the macrolactone cores **3** and **4** in a straightforward manner to complete the total synthesis of amphidinolide W[14] (Fig. 2).

In order to validate our strategy, the synthesis of fragment **7** was chosen as the initial target for our investigation. Thus, for the asymmetric Evans' alkylation, the required *N*-pentenoyl oxazolidinone **12** was prepared via N-acylation of the easily available (4*S*)-4-benzyloxazolidin-2-one **11** using a mixed anhydride, obtained from 4-pentenoic acid **8** and pivaloyl chloride in the presence of lithium chloride and $Et_3N$ in THF.[15] The presence of lithium chloride was essential for acylation, possibly due to the chelating ability of the lithium ion, which results in the activation of the acid anhydride. Next, the Evans' alkylation was accomplished with oxazolidinone **12** and $CH_3I$ in the presence of NaHMDS at −78 °C offering **13** with good yield (85%) and high diastereoselectivity (17:1).[10,16] The diastereomeric purity was assessed on the basis of $^1H$ and $^{13}C$ NMR spectroscopy. The stereochemical outcome could be ascertained by hydrolyzing **13** into the corresponding known acid **17**[17] and comparing its analytical

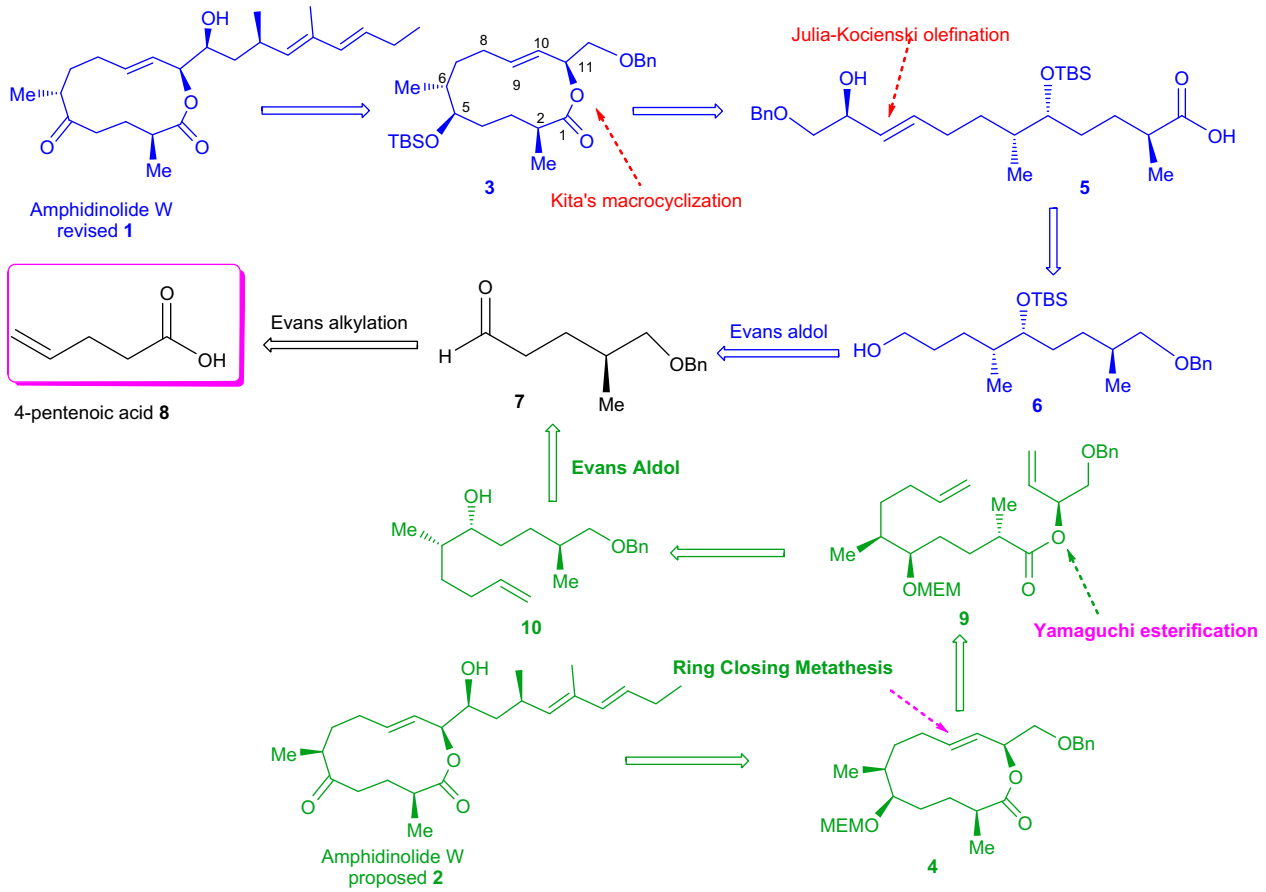
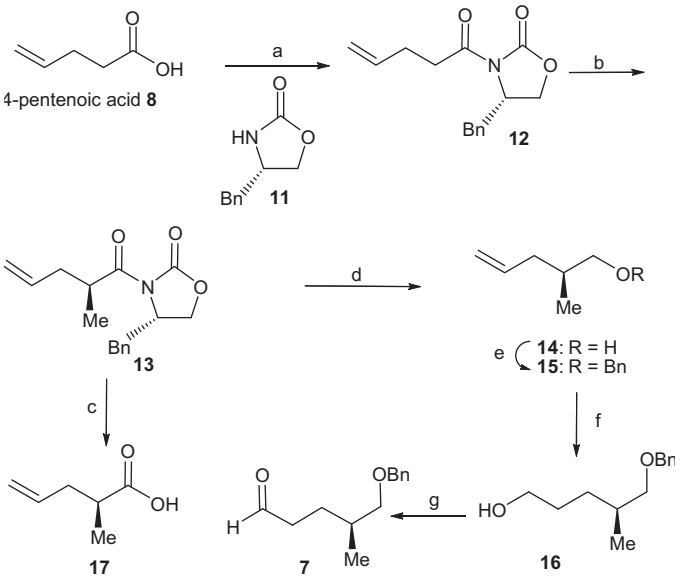



**Figure 2.** Disconnection approach of macrolactone core **3** and its 6-*epi* analogue **4**.

data with reported values [literature $[\alpha]_D^{25} = +10.5$ (*c* 1.0, $CHCl_3$), observed $[\alpha]_D^{25} = +9.9$ (*c* 1.0, $CHCl_3$)]. The oxazolidinone derivative **13** was smoothly cleaved with lithium aluminium hydride[18] in $Et_2O$ to furnish alcohol **14**, which was difficult to purify due to its volatile nature. Therefore, the crude residue was benzylated to afford the benzylated derivative **15** in 86% yield over two steps, after chromatographic purification on silica gel. Next, aldehyde **7** as a common precursor, required for the synthesis of both fragments **3** and **4**, was derived from **15** via hydroboration–oxidation using $BH_3{\cdot}SMe_2$ and $H_2O_2$ in NaOH followed by oxidation with Dess–Martin periodinane[19] in $CH_2Cl_2$ (Scheme 1). When the procedure for the synthesis of **7** was established, we next concentrated on the stereoselective Evans' aldol reaction in both of the strategies for the preparation of macrolactone cores **3** and **4**.

With aldehyde **7** in hand, we next focused our attention on the generation of the C5 and C6 centers of macrolactone **4**. Oxazolidinone **18** was prepared first from (4*S*)-4-benzyloxazolidin-2-one **11**, with a mixed anhydride generated from a mixture of 5-hexenoic acid and pivaloyl chloride using a similar method to that described in Scheme 1. Our next concern was the Evans' aldol reaction[20] between oxazolidinone **18** and aldehyde **7**. Upon subjecting the two components to Evans' *syn* aldol reaction conditions using $Bu_2BOTf$, *i*-$Pr_2EtN$ in $CH_2Cl_2$ at −78 °C, we produced the *syn* aldol product **19** in 72% yield after chromatographic purification. The diastereoselectivity was very high (>97%). The stereoselectivity of **19** was assumed on the basis of literature precedent[21] and the *syn* relationship of the newly-generated homoallyl and hydroxyl stereocenters in **19** was corroborated by the small vicinal coupling constant ($^3J_{H2,H3}$ = 3.90 Hz)[22] while the unambiguous stereochemical assignments were confirmed at a later stage through chemical modification. After installation of the stereogenic centers, the auxiliary was reductively cleaved using sodium borohydride in aqueous THF medium at room temperature to produce the diol **20** in 87% yield.[23] With the aim of obtaining one of the key fragments **10** for the synthesis of macrolactone core **4**, the primary alcohol of **20** was deoxygenated via selective tosylation of the primary alcohol followed by reduction of the resulting tosyl ester using lithium aluminium hydride in 92% yield (Scheme 2).

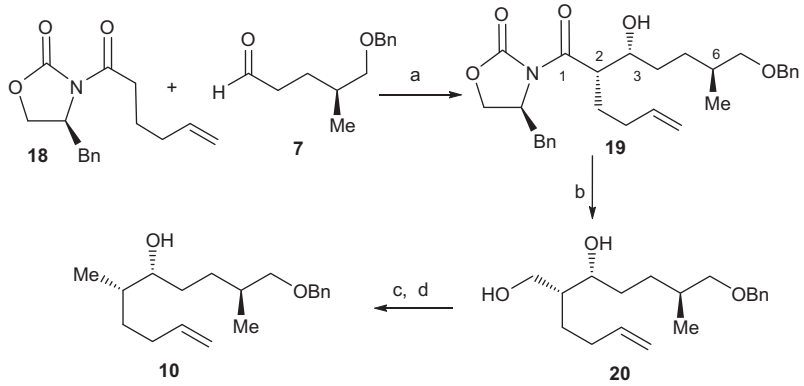
At this stage, it was necessary to confirm the stereochemistry of the newly generated centers at the C2 and C3 positions of adduct **19** which were investigated by transforming compound **10** into compound **23**.[11] For this endeavor, compound **10** was subjected to oxidation with 2-iodoxybenzoic acid (IBX)[24] to give ketone **21** where the carbonyl group was protected as a ketal using ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene to give **22**.[25] As per our requirement, the benzyl ether **22** was transformed into silyl ether in two steps via selective debenzylation under Birch reduction conditions[26] (Li in liquid $NH_3$, −78 °C) followed by silylation to obtain the prerequisite compound **23**. The spectroscopic data and specific rotation values were in complete agreement with the reported ones {lit.[11] $[\alpha]_D^{25} = -10.0$ (*c* 2.5, $CHCl_3$), observed $[\alpha]_D^{25} = -9.8$ (*c* 0.6, $CHCl_3$)} (Scheme 3). This justified the previous statement regarding the *syn* relationship between the homoallyl and hydroxyl groups of adduct **19**.



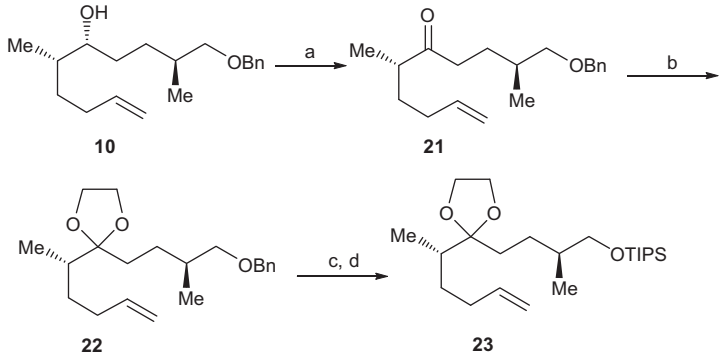

**Scheme 1.** Reagents and conditions: (a) Pivaloyl chloride, LiCl, $Et_3N$, 89%; (b) $CH_3I$, NaHMDS, −78 °C, 85%; (c) LiOOH, THF, $H_2O$, 92%; (d) $LiAlH_4$, ether, 0 °C; (e) NaH, BnBr, THF, 0 °C to rt; 86% over two steps; (f) $BH_3.SMe_2$, THF, 0 °C, NaOH (10%), $H_2O_2$ (30%), 88%; (g) Dess–Martin periodinane, $CH_2Cl_2$, rt, 94%.

After the assignment of the stereocenters present in compound **10**, our next task was to make acid **26** for the pivotal esterification step. The newly-generated secondary hydroxyl group of **10** was protected as its MEM-ether **24**,[27] which on dissolving metal mediated selective debenzylation[26] using Li in liquid $NH_3$ at −78 °C furnished the primary alcohol **25** in good overall yield. Oxidation of the primary hydroxyl group in **25** with pyridinium dichromate (PDC) in DMF afforded acid **26**[28] in moderate yield as shown in Scheme 4.

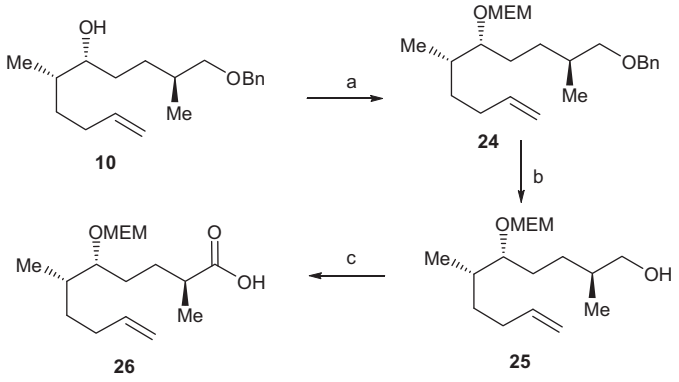
Our next task was the study of the crucial Yamaguchi's esterification followed by the formation of fragment **9** for the ring closing metathesis reaction. For this, we needed to couple **26** with **29**, which was designed in such a manner that it consisted of the olefin




**Scheme 2.** Reagents and conditions: (a) $Bu_2BOTf$, *i*-$Pr_2NEt$, $CH_2Cl_2$, −78 to 0 °C, 72%; (b) $NaBH_4$, THF–$H_2O$, rt, 87%; (c) TsCl, $Et_3N$, DMAP, $CH_2Cl_2$, rt, 89%; (d) $LiAlH_4$, THF, reflux, 92%.

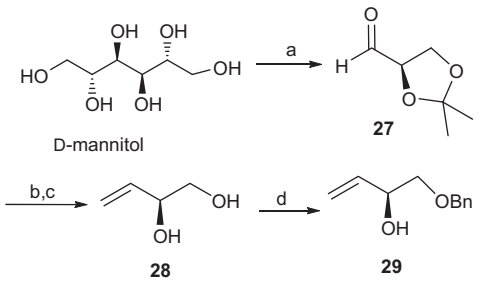



**Scheme 3.** Reagents and conditions: (a) IBX, DMSO, rt, 90%; (b) ethylene glycol, *p*-TSA, benzene, reflux, 74%; (c) Li-metal, liq. $NH_3$, THF, −78 °C, 73%; (d) TIPS-Cl, imidazole, DMAP, $CH_2Cl_2$, rt, 89%.



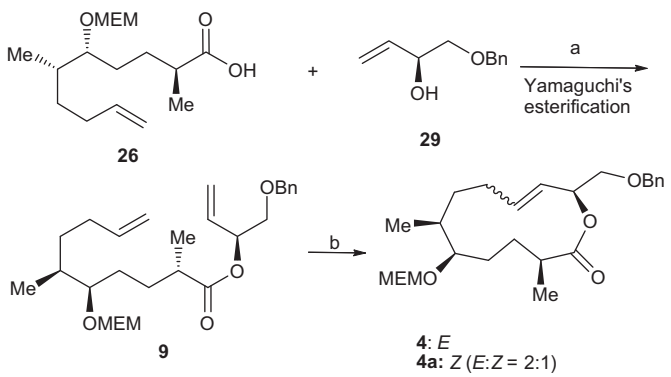

**Scheme 4.** Reagents and conditions: (a) MEMCl, *i*-$Pr_2NEt$, $CH_2Cl_2$, rt, 78%; (b) Li-metal, liq. $NH_3$, THF, 83%; (c) PDC, DMF, rt, 77%.

moiety for the RCM as well as hydroxyl group for Yamaguchi's esterification. At this point, we decided to use the D-mannitol derived allylic alcohol **29**[12,13] (Scheme 5), which would not only help us to study the stereochemical courses of the reactions leading to the macrocycle, but also would act as a surrogate to the side chain implantation for the total synthesis of amphidinolide W. Thus diisopropylidenation of D-mannitol followed by oxidative cleavage with sodium metaperiodate provided aldehyde **27** in good yields. Subsequent one carbon Wittig homologation followed by concomitant acetonide deprotection under mild acidic conditions afforded diol **28**. The latter upon selective benzylation with dibutyltin oxide furnished allylic alcohol **29**. The product was fully characterized from its $^1H$ and $^{13}C$ NMR spectra and comparison of the specific rotation value with the reported ones {lit.[29] $[\alpha]_D^{25} = -5.9$ (*c* 0.5, $CHCl_3$), observed $[\alpha]_D^{25} = -5.4$ (*c* 0.7, $CHCl_3$)} completely justified the structure without any ambiguity (Scheme 5).




**Scheme 5.** Reagents and conditions: (a) (i) $(CH_3)_2C(OMe)_2$, $SnCl_2$, 53%; (ii) $NaIO_4$, $CH_2Cl_2$, 76%; (b) $Ph_3P{=}CH_2$, THF, 0 °C; (c) *p*-TSA, MeOH, rt, 49% over two steps; (d) $Bu_2SnO$, BnBr, TBAI, toluene, reflux, 84%.

The next critical aspect was assembling acid **26** with alcohol **29**, for which various conditions were investigated (i. DCC, DMAP, $CH_2Cl_2$; ii. EDC, DMAP, $CH_2Cl_2$) but none provided the desired results. Instead, some rearranged, uncharacterizable, and intractable mixtures of compounds were obtained. Eventually, the required coupled product **9** was obtained in 75% yield following Yamaguchi's esterification protocol[30] using 2,4,6-trichlorobenzoyl chloride, triethylamine, and DMAP in THF at 0 °C to room temperature. The product was present along with the trace amounts of the other isomer (<5%), which was conveniently separated by flash column chromatography. This diene compound **9** was well placed for the macrocyclization reaction by applying the highly-productive and established RCM reaction.[31,32] With the advent of efficient catalysts, the ring-closing metathesis (RCM) reaction has emerged as a powerful process for the cyclization of dienes. Thus, we applied this method to the diene derivative **9** with the use of 1st generation Grubbs' catalyst[33] to obtain the 12-membered macrocyclic ring but this reaction was unsuccessful. However, a 2nd generation Grubbs catalyst[34] in benzene under refluxing conditions gave the 6-*epi*-12-membered macrolide **4** as a mixture of *E*- and *Z*-isomers (2:1) in a combined 58% yield (Scheme 6). Separation of the two isomers by applying typical chromatographic techniques such as flash silica gel column chromatography and high performance liquid chromatography (HPLC) and enhancement in the selectivity under thorough investigation did not provide much success. With regard to the augmentation of selectivity, we tried manipulations of the hydroxyl protecting groups in the middle of the synthetic strategy. Fragment **26** was used with a TBDMS ether instead of MEM ether and also with an unmasked secondary hydroxyl group to produce several derivatives of **9**. It was found that none of these cases led




**Scheme 6.** Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, $Et_3N$, DMAP, THF, 0 °C to rt, 75%; (b) Grubbs' 2nd generation, benzene, reflux, 58% combined yield.

to an improved selectivity for the RCM reaction. In spite of the successful ring closing metathesis reaction, the diastereoisomeric separation problem inhibited the total synthesis of the macrolide; however, we believe that this synthetic methodology could be used for the total synthesis of this natural product and other macrolides for structure–activity relationship studies (SAR).

Difficulties during the synthesis of macrolide **4** and also the structural revision of the amphidinolide W **2** motivated us to ensure a successful synthesis of macrolide **3**, which in turn would lead to the total synthesis of amphidinolide W **1** through the required modification of our earlier described route. Modifications were made to the above stated synthetic strategy, where at first, the $\Delta^{9,10}E$-alkene was synthesized followed by macrolactonization.

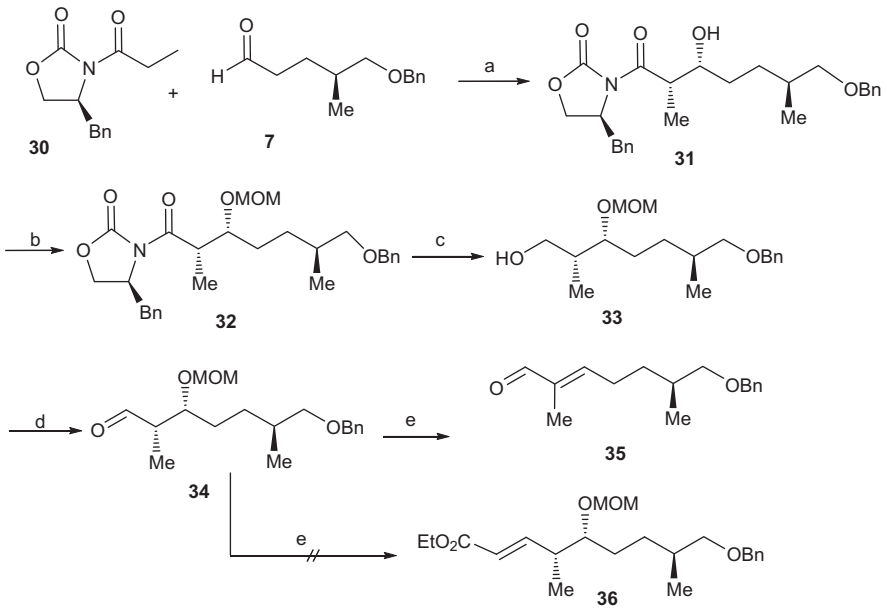
At the onset of our program to synthesize macrolactone **3**, we performed the Evans' *syn* aldol reaction of aldehyde **7**, with oxazolidinone derivative **30**[15a] using $Bu_2B(OTf)$ at −78 °C to afford the desired Evans' *syn* isomer **31** in moderate yield (75%) and with high diastereoselectivity (19:1).[10,20] The compound and its diastereoselectivity were confirmed from the spectroscopic data. The relative stereochemistry of the newly generated stereocenters was initially predicted through the literature precedent[20] and further confirmation of the absolute configuration was achieved in the latter part of the synthesis. To continue our strategy, the secondary hydroxyl group in **31** was protected as its MOM ether **32** with MOM–Cl and Hunig's base in 91% yield. Subsequent removal of the oxazolidinone ring was achieved with lithium borohydride (generated in situ from a mixture of LiCl and $NaBH_4$)[35] in an ethanol and THF mixture to afford alcohol **33**. Elaboration of **33** to the α,β-unsaturated ester **36** was planned in a two-step sequence. Alcohol **33** was first oxidized to aldehyde **34** with IBX and subsequent Wittig olefination resulted in an unexpected α,β-unsaturated aldehyde **35** as an exclusive product instead of the desired Wittig product **36** (Scheme 7). The formation of the α,β-unsaturated aldehyde **35** was confirmed from its spectroscopic data. The $^1$H NMR data of the unexpected compound **35** showed an aldehydic proton at $\delta$ 9.38 ppm as a singlet and an olefinic proton resonating at 6.48 ppm as a triplet and thus proved the formation of the unsaturated aldehyde **35**; the mass spectrum at $m/z$ 269.21 $(M+Na)^+$ also confirmed this. This observed phenomenon could be explained by taking an account of the basicity of the two-carbon Wittig stabilized ylide which abstracts the highly acidic α-proton to the aldehyde due to the electron withdrawing nature of the MOM-ether and/or the aldehyde groups present in **34**.

The hydroxyl protecting group was replaced from MOM to TBS upon treatment with TBSOTf and 2,6-lutidine in $CH_2Cl_2$ to give compound **37**. The oxazolidinone was disconnected from compound **37** using $LiBH_4$ in EtOH and the THF mixture to afford alcohol **38** in 83% yield. The primary hydroxyl group of **38** was oxidized with PDC to an aldehyde with subsequent Wittig homologation thus providing the expected (*E*)-α,β-unsaturated ester **39** as the major product in 78% yield along with a small amount of the (*Z*)-isomer (Scheme 8).

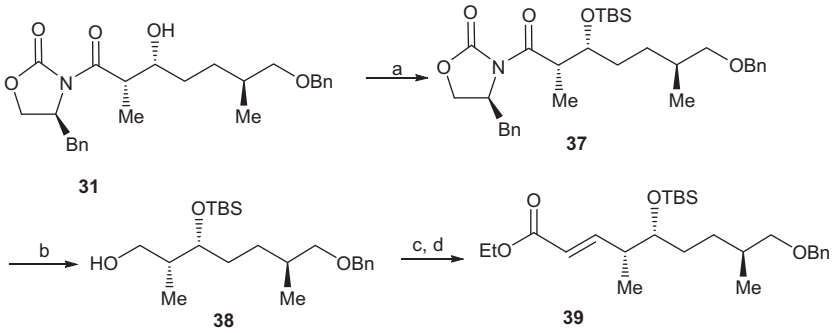
Before moving further ahead, we decided to establish the configurations of the two newly generated stereogenic centers in **31**. For this, **39** was converted into its Mosher ester derivative[36,37] via desilylation with HF-Py in Py/THF at room temperature[38] followed by esterification with (*R*)- and (*S*)-MTPA acid using DCC and DMAP in anhydrous $CH_2Cl_2$ at room temperature to afford the (*R*)-MTPA ester **40** and (*S*)-MTPA ester **41**, respectively (Scheme 9). The $\Delta\delta = (\delta_S - \delta_R) \times 1000$ values were calculated for as many protons as possible from the $^1$H NMR spectrum of **40** and **41** (Table 1). By constructing a molecular model of the compound in question and assigning the $\Delta\delta = (\delta_S - \delta_R) \times 1000$ values uniformly as shown in Figure 3, the absolute stereochemistry of C5-center was determined to be (*R*)-configured.

After determining the stereochemistry of the C5-center, we proceeded to determine the configuration of the adjacent methyl group in **39** by turning **38** into its isopropylidene derivative **42** where NOESY correlations witnessed the *syn*-alignment of the two adjacent chiral centers (Scheme 10). For instance the β-protons $H_1$ and $H_2$ showed significant n*O*e interactions in **42**, thus establishing the stereochemistry of the methyl center also to be (*R*)-configured.

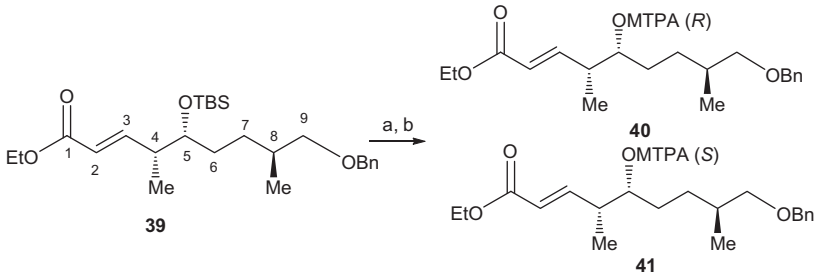
After the successful installation of the C5, C6, and C2 stereocenters of the macrolactone core **3**, our next aim was to incorporate a C11 stereocenter in addition to the $\Delta^{9,10}(E)$-alkene. With the aim of obtaining the $\Delta^{9,10}(E)$-alkene, the Julia–Kocienski reaction was thought to be appropriate. A one step reduction of unsaturated es-




**Scheme 7.** Reagents and conditions: (a) $Bu_2BOTf$, DIPEA, 0 °C, $CH_2Cl_2$, −78 °C, 75%; (b) MOM-Cl, *i*-$Pr_2NEt$,$CH_2Cl_2$, 0 °C to rt, 91%; (c) $LiBH_4$, EtOH, THF, 0 °C to rt, 86%; (d) IBX, DMSO, rt, 93%; (e) $Ph_3P{=}CHCO_2Et$ benzene, rt, 70%.




**Scheme 8.** Reagents and conditions: (a) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C to rt, 95%; (b) $LiBH_4$, EtOH/THF, 0 °C to rt, 83%; (c) PDC, $CH_2Cl_2$, rt, 81%; (d) $Ph_3P{=}CHCO_2Et$, benzene, rt, 78%.




**Scheme 9.** Reagents and conditions: (a) HF–Py, Py, THF, 0 °C to rt, 73%; (b) (*R* or *S*)-MTPA acid, DCC, DMAP, $CH_2Cl_2$, rt, 73% for (*R*)-isomer and 76% for (*S*)-isomer.

ter **39** to alcohol **6** with $LiAlH_4$ produced an inseparable mixture of saturated **6** and allylic alcohol derivatives. In order to circumvent the purification issue, we planned to perform a two-step reaction. Accordingly, the chemoselective reduction of the double bond in **39** with $NiCl_2/NaBH_4$[39] in MeOH at 0 °C was carried out to give saturated ester **43**, which upon reduction with lithium aluminium hydride in THF provided the pure saturated alcohol **6** in 89% yield. The Mitsunobu substitution[40] of the primary alcohol of **6**, by 1-phenyl-1*H*-tetrazole-5-thiol (PTSH) followed by oxidation[41] provided sulfone **44** in good yields. The key $\Delta^{9,10}(E)$-alkene installation with the appropriate stereocenter at C11 was accomplished as shown in Scheme 11. At this point, the D-mannitol derived aldehyde **27** was selected as discussed earlier for further side chain extension of macrolide **3** in support of the total synthesis of amphidinolide W. Although the Julia–Kocienski[42,43] olefination with a variety of conditions was exhaustively investigated, the best results were found using KHMDS in DME at −60 °C with (2*R*)-2,3-isopropylidene glyceraldehyde **27** to produce the desired olefin **45** in 82% yield with exclusive *E*-selectivity (Scheme 11). The confirmation of *E*-selectivity was achieved from the $^1$H NMR spectra wherein the two olefin protons resonated at $\delta$ 5.43 and 5.76 ppm with a coupling constant of $J$ = 15.3 Hz.

For the crucial macrolactonization, the isopropylidine group of **45** was cleaved selectively under mild Lewis acid conditions ($Zn(NO_3)_2{\cdot}6H_2O$, $CH_3CN$),[44] which proved to be the most suitable among the traditional reaction conditions[45] ($FeCl_3{\cdot}SiO_2$, $CHCl_3$; $CeCl_3{\cdot}7H_2O$; oxalic acid, $CH_3CN$, rt; $BiCl_3$, $CH_3CN$, or $CH_2Cl_2$;

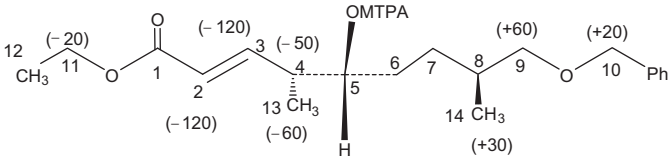
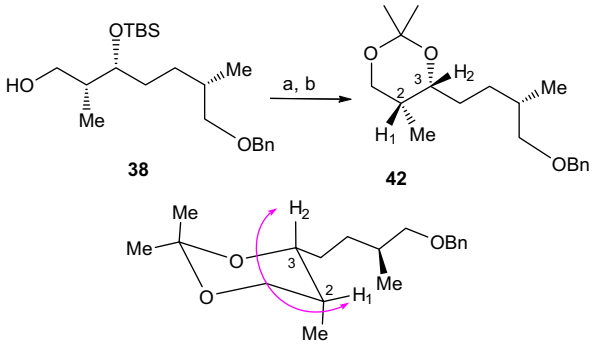


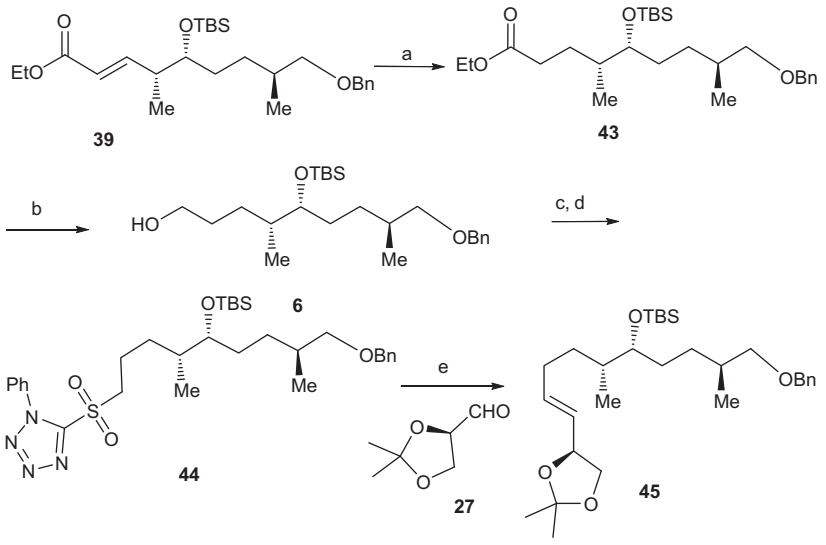

**Figure 3.** Projection of the MTPA ester to determine the stereochemistry of C5-center of **39**.




**Scheme 10.** Reagents and conditions: (a) TBAF, THF, rt, 90%; (b) 2,2-dimethoxy propane, acetone, *p*-TSA, rt,74%.

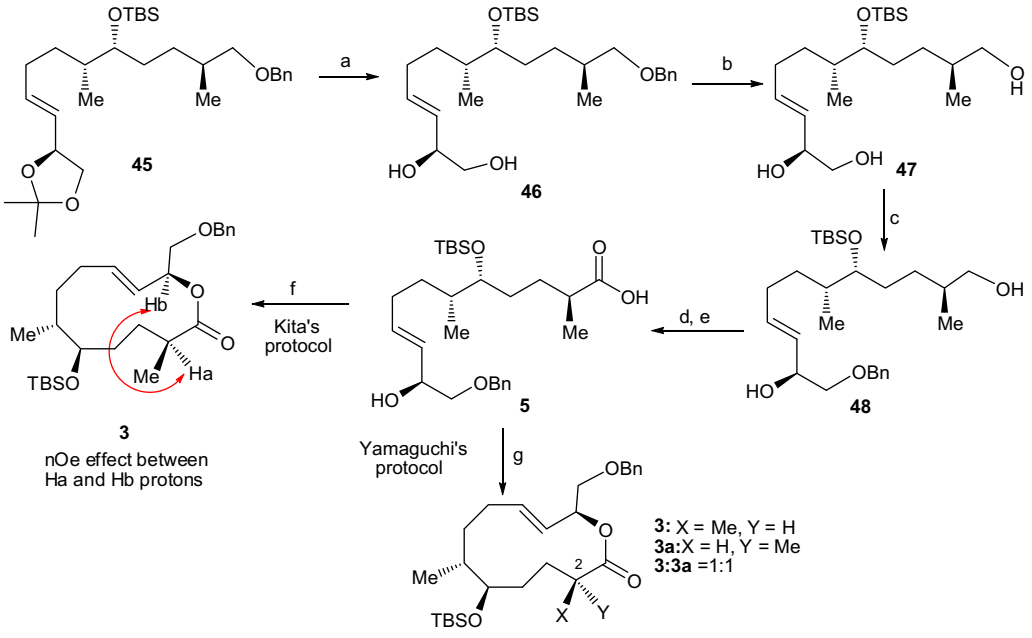
**Table 1**
Calculation of $\Delta\delta$ values for (*S*)- and (*R*)-MTPS ester [$(\delta_S - \delta_R) \times 1000$ values] from $^1$H NMR spectrum

| Protons | H-3 | H-2 | H-10 | H-11 | H-9 | H-4 | H-13 | H-14 |
|---|---|---|---|---|---|---|---|---|
| $\delta_S$ | 6.69 | 5.63 | 4.40 | 4.10 | 3.17 | 2.56 | 0.93 | 0.83 |
| $\delta_R$ | 6.81 | 5.75 | 4.38 | 4.12 | 3.11 | 2.61 | 0.99 | 0.80 |
| $\Delta\delta$ | −120 | −120 | +20 | −20 | +60 | −50 | −60 | +30 |




**Scheme 11.** Reagents and conditions: (a) $NiCl_2$, $NaBH_4$, MeOH, 0 °C, 98%; (b) $LiAlH_4$, THF, 0 °C, 89%; (c) PTSH, DIAD, $Ph_3P$, THF, 0 °C, 89%; (d) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, $H_2O_2$, EtOH, 0 °C to rt, 92%; (e) KHMDS, DME, −60 °C, 82%.

$CuCl_2{\cdot}2H_2O$; pyridinium *p*-toluensulfonate, EtOH) followed by selective Birch reduction of **46** to produce triol **47** in good overall yield. The dibutyl tin oxide ($Bu_2SnO$) mediated selective protection of the homo allylic primary hydroxyl as its benzyl ether **48** followed by selective oxidation of the remaining primary hydroxyl to the seco acid **5** was achieved via a two-step protocol. Oxidation with BAIB in the presence of TEMPO[46] to the aldehyde and further Pinnick oxidation with $NaClO_2$[47] in the presence of an $NaH_2PO_4$ buffer furnished acid **5**. The oxidation process went smoothly without giving any over oxidation products for the secondary allylic hydroxyl group. The spectroscopic and analytical data supported the synthesized compound. Setting the stage for the key lactonization, we decided to work out the Yamaguchi's esterification conditions.[30] Therefore, the seco acid **5** was treated with 2,4,6-trichlorobenzoyl chloride, DIPEA and DMAP and it produced an inseparable mixture of products **3** and **3a** (1:1) in 55% combined yield, possibly due to epimerization at the C-2 center. The rationalization for the stereochemistry was obtained from the corresponding $^1H$ and $^{13}C$ NMR spectra. Both spectra witnessed the formation of a diastereomeric mixture of the compounds **3** and **3a** which could not be separated even by flash column chromatography. This intricate nature of the substrate to the lactonisation due to the intrinsic lability at the C-2 center prompted us to investigate other possible routes to its synthesis. We made an attempt to study Kita's lactonisation




**Scheme 12.** Reagents and conditions: (a) $Zn(NO_3)_2{\cdot}6H_2O$, $CH_3CN$, 50 °C, 74%; (b) Li, liq.$NH_3$, −78 °C, 78%; (c) $Bu_2SnO$, BnBr, TBAI, toluene, reflux, 84%; (d) $PhI(OAc)_2$, TEMPO, $CH_2Cl_2$, rt, 92%; (e) $NaClO_2$, $NaH_2PO_4$, 2-methyl-2-butene, *t*-BuOH/$H_2O$ (3:1), 87%; (f) (i) EtOC≡CH, $[\{Ru(p\text{-cymene})Cl_2\}_2]$, toluene, 0 °C to rt, 30 min; (ii) camphorsulfonic acid (CSA), toluene, rt to 50 °C, 2 h, 42%; (g) 2,4,6-trichlorobenzoyl chloride, DIPEA, THF, rt; DMAP, benzene, 80 °C, 55% combined yield.

protocol. When the lactonization was performed under the conditions described by Kita et al.,[48,49] it produced the single desired macrolactone derivative **3** in 42% yield, thus explaining the absence of epimerization at the C-2 center. The remaining mass was accounted for by an intractable mixture of products and 35% starting material. Its elemental analysis, mass, and NMR studies assigned the structure of the compound while the NOESY experiment showed considerable n*O*e interactions between Ha and Hb protons and supported the stereochemical identifications for the desired isomer. The minimum energy diagram of **3**[10] also unambiguously supported the significant NOE effects between the Ha and Hb protons in **3**. These findings not only resolved the possible drawback of the Yamaguchi's lactonization (Scheme 12) but could also be applied to the highly diastereoselective formation of related bioactive macrolactone compounds.

## 3. Conclusions

In conclusion, a successful synthesis of the 12-membered macrolactone core **3** and its 6-*epi* analogue **4** of amphidinolide W have been described from achiral, inexpensive, and commercially available 4-pentenoic acid **8** while exploring a variety of important reaction conditions. The synthesis features a highly stereo and regioselective incorporation of the stereogenic centers utilizing Evans' asymmetric alkylation and aldol reactions. For the construction of the 12-membered lactone of the 6-*epi* analogue **4** of amphidinolide W, Yamaguchi's esterification gave the suitably-substituted diene precursor for the ring closing metathesis reaction (RCM) in a linear nine-step sequence. In another approach for the 12-membered macrolactone core **3**, a highly stereoselective Julia–Kocienski olefination for the construction of the $\Delta^{9,10}$*E*-alkene was performed. The final lactonization using Kita's protocol, which selectively produced the required isomer thus overcoming the difficulty encountered in the Yamaguchi's lactonization is also a promising approach. These synthetic methods will help synthesize related macrolides. In turn, these products could be useful in the studies of therapeutics based on the structure activity relationship (SAR) of isomeric molecules.

## 4. Experimental

### 4.1. General methods

$^1$H and $^{13}$C NMR chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Column chromatography was carried out using silica gel (60–120 mesh). Specific rotations $[\alpha]_D^{25}$ are given in $10^{-1}$ degcm$^2$ g$^{-1}$. Infrared spectra were recorded in $CHCl_3$/neat (as mentioned) and reported in wave number (cm$^{-1}$). Yields are given after purification, unless stated otherwise. When reactions were performed under anhydrous conditions, the mixtures were maintained under nitrogen. Compounds were named following IUPAC rules as applied by Beilstein-Institute AutoNom software for systematic names in organic chemistry.

#### 4.1.1. (*S*)-4-Benzyl-3-((*S*)-2-methylpent-4-enoyl)oxazolidin-2-one 13

A solution of **12** (5.0 g, 19.3 mmol) in THF (50 mL) was cooled to −78 °C and NaHMDS (29.0 mL, 29.0 mmol, 1 M in THF) was added dropwise and stirred for 1 h, followed by the dropwise addition of methyl iodide (4.8 mL, 77.2 mmol), maintaining the temperature at -78 °C. After stirring for 1 h, the reaction was quenched with saturated $NH_4Cl$ (20 mL) and the two layers were separated. The aqueous layer was extracted twice with EtOAc (2 × 50 mL), and the combined organic layers were dried over $Na_2SO_4$ and concentrated to afford a residue which was purified by flash silica gel chromatography using EtOAc/light petroleum (1:19) yielding **13** (4.5 g, 85%) as a colorless liquid. $[\alpha]_D^{25} = +77.2$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) cm$^{-1}$ 2931, 1781, 1697, 1650, 1496, 1454, 1110, 750; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.23 (d, 3H, *J* = 6.9 Hz), 2.18 (m, 1H), 2.47 (m, 1H), 2.75 (dd, 1H, *J* = 9.6, 13.4 Hz), 3.27 (dd, 1H, *J* = 3.3, 13.4 Hz), 3.82 (m, 1H), 4.15–4.18 (m, 2H), 4.65 (m, 1H), 5.0–5.11 (m, 2H), 5.78 (m, 1H), 7.13–7.37 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 17.0, 37.4, 37.6, 37.9, 55.3, 65.9, 117.0, 127.3, 128.9 (× 2), 129.4 (× 2), 135.3, 135.5, 152.9, 176.3; EIMS: (M+Na)$^+$ calcd for $C_{16}H_{19}NNaO_3^+$ 296.13. Found: 296.19; Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.12; H, 6.86; N, 5.02.

#### 4.1.2. (*S*)-2-Methylpent-4-enoic acid 17

To a solution of imide **13** (0.5 g, 1.8 mmol) in THF/$H_2O$ (1/1, 10 mL) at 0 °C, 30% $H_2O_2$ solution (0.82 mL, 7.2 mmol) was added followed by the addition of LiOH.$H_2O$ (0.15 g, 3.6 mmol) and stirred for 1 h. After completion of the reaction (monitored by TLC), THF was removed in vacuum and the residue was diluted with EtOAc (10 mL) and acidified with 1 M HCl to pH ∼1. The aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic layer was dried over $Na_2SO_4$ and concentrated. Purification by silica gel column chromatography (EtOAc/light petroleum, 3:7) provided acid **17** (0.192 g, 92%) as a clear liquid. $[\alpha]_D^{25} = +9.9$ (*c* 1.0, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.21 (d, 3H, *J* = 6.9 Hz), 2.19 (m, 1H), 2.46 (m, 1H), 2.56 (sextet, 1H, *J* = 6.9 Hz), 5.06–5.11 (m, 2H), 5.78 (m, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$):$\delta$ 16.3, 37.5, 39.2, 117.2, 135.1, 182.8; EIMS: (M+Na)$^+$ calcd for $C_6H_{10}NaO_2^+$ 137.06. Found: 137.11$^+$; Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 62.98; H, 8.96.

#### 4.1.3. (*S*)-(2-Methylpent-4-enyloxy)methylbenzene 15

To a solution of $LiAlH_4$ (2.5 g, 66.0 mmol) in ether (40 mL) at 0 °C, compound **13** (12.0 g, 43.9 mmol) in ether (80 mL) was added dropwise and stirred for 1 h. The reaction mixture was quenched by the addition of a saturated solution of $Na_2SO_4$, filtered and the residue was washed with ether, dried over $Na_2SO_4$, and concentrated to obtain a residue **14**, which was directly benzylated without further purification. The crude residue was dissolved in THF (150 mL) and NaH (2.1 g, 87.9 mmol) was added in small portions at 0 °C and stirred for 30 min. Next, BnBr (7.9 mL, 65.9 mmol) was added followed by the addition of a catalytic amount of TBAI and the reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with ice cold water, diluted with EtOAc, and the layers were separated out and the aqueous layer was extracted twice with EtOAc (2 × 50 mL), washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure to afford a residue which was chromatographed on silica gel eluting with EtOAc/light petroleum (1:19) to provide **15** (7.2 g, 86% over two steps) as a clear liquid. IR ($CHCl_3$) cm$^{-1}$ 2927, 1648, 1385, 1044, 836; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.93 (d, 3H, *J* = 6.5 Hz), 1.83–1.94 (m, 2H), 2.22 (m, 1H), 3.26 (dd, 1H, *J* = 6.3, 8.9 Hz),, 3.31 (dd, 1H, *J* = 6.3, 8.9 Hz), 4.48 (s, 2H), 4.97–5.01 (m, 2H), 5.76 (m, 1H), 7.23–7.31 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 16.9, 33.5, 38.1, 73.0, 75.2, 116.0, 127.4, 127.5 (× 2), 128.3 (× 2), 136.9, 138.8; EIMS: (M+Na)$^+$ calcd for $C_{13}H_{18}NaO^+$ 213.13. Found: 213.17; Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.84; H, 9.29.

#### 4.1.4. (*S*)-5-Benzyloxy-4-methylpentanal 7

To a solution of compound **15** (7.0 g, 36.8 mmol) in THF (40 mL) at 0 °C was added $BH_3$.$SMe_2$ (4.6 mL, 47.9 mmol) dropwise and

stirred for 5 h, then slowly quenched by the simultaneous addition of 10% NaOH solution (20 mL) and 30% $H_2O_2$ solution (7 mL). The mixture was then stirred at rt for 16 h, extracted with EtOAc ($3 \times 30$ mL), dried over $Na_2SO_4$, concentrated under reduced pressure, and purified by silica gel column chromatography eluting with EtOAc/light petroleum (1:4) to give alcohol **16** (6.75 g, 88%) as a clear oil. IR ($CHCl_3$) $cm^{-1}$ 3370, 2928, 1610, 1210, 748; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 0.93 (d, 3H, $J$ = 6.8 Hz), 1.16 (m, 1H), 1.49–1.59 (m, 3H), 1.78 (m, 1H), 2.07 (br s, 1H), 3.27 (dd, 2H, $J$ = 2.4, 6.4 Hz), 3.56 (t, 2H, $J$ = 6.5 Hz), 4.47 (s, 2H), 7.28–7.32 (m, 5H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 17.1, 29.7, 30.0, 33.2, 62.8, 73.0, 75.7, 127.5, 128.3, 138.5; EIMS: $(M+Na)^+$ calcd for $C_{13}H_{20}NaO_2^+$ 231.14. Found: 231.23; Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.89; H, 9.45.

To a solution of alcohol **16** (6.5 g, 31.3 mmol) in $CH_2Cl_2$ (35 mL), was added Dess–Martin periodinane (19.9 g, 46.9 mmol) at room temperature and stirred for 1 h. The reaction mixture was diluted with $H_2O$ (15 mL) and $CH_2Cl_2$ (15 mL) and filtered. The aqueous phase was extracted with $CH_2Cl_2$ ($2 \times 20$ mL) and the combined organic layers were washed with $NaHCO_3$, brine, dried over $Na_2SO_4$, and concentrated. The crude residue was purified by silica gel chromatography (EtOAc/light petroleum, 1:9) to afford aldehyde **7** (6.1 g, 94%) as a colorless liquid. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 0.94 (d, 3H, $J$ = 6.5 Hz), 1.43–1.59 (m, 2H), 1.72–1.90 (m, 2H), 2.44 (m, 1H), 3.29 (d, 2H, $J$ = 6.1 Hz), 4.47 (s, 2H), 7.31 (m, 5H), 9.74 (t, 1H, $J$ = 1.74 Hz).

#### 4.1.5. (*S*)-4-Benzyl-3-((2*S*,3*R*,6*S*)-7-(benzyloxy)-2-(but-3-enyl)-3-hydroxy-6-methylheptanoyl)oxazolidin-2-one 19

To an ice-cooled stirred solution of compound **18** (2.0 g, 7.3 mmol) in $CH_2Cl_2$ (15 mL), dibutylboron triflate (8.1 mL, 1 M in $CH_2Cl_2$, 8.1 mmol) was added dropwise such that the internal temperature was maintained at 0 °C. After 10 min, *i*-$Pr_2NEt$ (1.6 mL, 8.8 mmol) was added and stirring was continued for another 30 min at the same temperature. The reaction mixture was then cooled to −78 °C and aldehyde **7** (1.5 g, 7.3 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise and allowed to stir for another 1 h, then warmed to 0 °C and stirred for another 1 h. At the end, it was quenched slowly with a phosphate buffer (8.1 mL, pH 7.0), MeOH (16.2 mL) and then with a mixture of 30% $H_2O_2$ and MeOH (1:2), (24.3 mL). After stirring at rt for 1 h, the reaction mixture was diluted with $CH_2Cl_2$ (20 mL). The layers were separated out and the aqueous layer was extracted with $CH_2Cl_2$ ($2 \times 20$ mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated. The residue thus obtained was purified by flash silica gel chromatography (EtOAc/light petroleum, 1:6) to furnish aldol product **19** (2.52 g, 72%) as a thick viscous liquid. $[\alpha]_D^{25} = +29.0$(*c* 1.2, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$: 3498, 2930, 1780, 1692, 1645, 1478, 1386, 1028, 699; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 0.95 (d, 3H, $J$ = 6.6 Hz), 1.12–1.2 (m, 1H), 1.44–1.83 (m, 6H), 1.92–2.03 (m, 1H), 2.06–2.16 (m, 2H), 2.66 (dd, 1H, $J$ = 10.2, 13.1 Hz), 3.20–3.40 (m, 3H), 3.72–3.85 (m, 1H), 4.09–4.16 (m, 3H), 4.48 (s, 2H), 4.60–4.75 (m, 1H), 4.95–5.08 (m, 2H), 5.70–5.88 (m, 1H), 7.23–7.33 (m, 10H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 17.3, 26.1, 30.1, 31.2, 31.8, 33.4, 38.0, 47.3, 55.6, 65.9, 73.0, 75.6, 76.4, 115.5, 127.4 ($\times$ 2), 127.5 ($\times$ 2), 128.3 ($\times$ 2), 129.0 ($\times$ 2), 129.3 ($\times$ 2), 135.3, 137.8, 138.7, 153.5, 175.6; EIMS: $(M+Na)^+$ calcd for $C_{29}H_{37}NaO_5^+$ 502.26. Found: 502.37; Anal. Calcd for $C_{29}H_{37}NO_5$: C, 72.62; H, 7.78; N, 2.92. Found: C, 72.77; H, 7.65; N, 2.89.

#### 4.1.6. (2*R*,3*R*,6*S*)-7-(Benzyloxy)-2-(but-3-enyl)-6-methylheptane-1,3-diol 20

To a stirred solution of compound **19** (5.6 g, 11.7 mmol) in a THF/$H_2O$ (3:1, 30 mL) mixture, $NaBH_4$ (1.8 g, 46.8 mmol) was added at room temperature. After stirring overnight, it was quenched with a saturated solution of $NH_4Cl$ (15 mL) and diluted with ethyl acetate; the layers were separated and the aqueous layer was extracted twice with EtOAc ($2 \times 20$ mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated to afford a residue which was chromatographed on a silica gel column using EtOAc/light petroleum (1:3) as eluent to provide diol **20** (3.1 g, 87%) as a colorless viscous liquid. $[\alpha]_D^{25} = +7.5$ (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$: 3368, 2928, 1648, 1452, 1252, 1115, 835, 697; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 0.95 (d, 3H, $J$ = 6.6 Hz), 1.05–1.21 (m, 1H), 1.36–1.55 (m, 4H), 1.58–1.83 (m, 3H), 1.98–2.19 (m, 2H), 2.72 (br s, 2H), 3.29 (dd, 2H, $J$ = 1.5, 6.2 Hz), 3.66–3.83 (m, 3H), 4.48 (s, 2H), 4.93–5.05 (m, 1H), 5.65–5.86 (m, 1H), 7.28–7.34 (m, 5H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 17.3, 24.0, 30.3, 30.7, 31.7, 33.5, 43.2, 64.2, 73.0, 75.3, 75.7, 114.8, 126.8, 127.4, 127.5, 128.2 ($\times$ 2), 138.4 ($\times$ 2); EIMS: $(M+Na)^+$ calcd for $C_{19}H_{30}NaO_3^+$ 329.21. Found: 329.48; Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.25; H, 9.92.

#### 4.1.7. (2*S*,5*R*,6*S*)-1-(Benzyloxy)-2,6-dimethyldec-9-en-5-ol 10

At first, $Et_3N$ (2.5 mL, 17.7 mmol), *p*-toluenesulfonyl chloride (2.52 g, 13.2 mmol), and DMAP (catalytic amount) were sequentially added to a stirred solution of **20** (2.7 g, 8.8 mmol) in $CH_2Cl_2$ (40 mL) at 0 °C. The reaction mixture was stirred at room temperature for 20 h (completion of the reaction was monitored by TLC), then quenched with ice, diluted with $CH_2Cl_2$ (20 mL) and $H_2O$ (20 mL). The aqueous layer was extracted twice with $CH_2Cl_2$ ($2 \times 25$ mL), washed with brine, then dried over anhydrous $Na_2SO_4$, concentrated and purified by silica gel column chromatography (EtOAc/light petroleum, 1:5) to afford a mono tosyl ester (3.6 g, 7.85 mmol, 89%) which was dissolved in THF (30 mL) after which $LiAlH_4$ (0.45 g, 11.8 mmol) was added at room temperature and refluxed for 3 h. The reaction was quenched with a saturated solution of $Na_2SO_4$, then filtered through a pad of Celite, washed with EtOAc. The organic layer was dried over $Na_2SO_4$ and concentrated. The residue was chromatographed on a silica gel column (EtOAc/light petroleum, 1:6), to yield **10** (2.1 g, 92%) as a colorless liquid. $[\alpha]_D^{25} = +5.0$(*c* 1.5, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$: 3374, 2930, 1650, 1461, 1215, 836; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 0.89 (d, 3H, $J$ = 6.8 Hz), 0.95 (d, 3H, $J$ = 6.7 Hz), 1.07–1.40 (m, 8H), 1.69–2.18 (m, 3H), 3.24–3.42 (m, 3H), 4.48 (s, 2H), 4.91–5.05 (m, 2H), 5.67–5.90 (m, 1H), 7.27–7.33 (m, 5H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 15.4, 17.5, 30.3, 31.0, 31.1, 31.5, 33.7, 38.3, 73.1, 75.8, 76.3, 114.5, 127.4, 127.5 ($\times$ 2), 128.3 ($\times$ 2), 138.8, 139.9; EIMS: $(M+Na)^+$ calcd for $C_{19}H_{30}NaO_2^+$ 313.21. Found: 313.28; Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.66; H, 10.52.

#### 4.1.8. (2*S*,6*S*)-1-(Benzyloxy)-2,6-dimethyldec-9-en-5-one 21

To a solution of the deoxy compound **10** (0.15 g, 0.52 mmol) in DMSO (4 mL), IBX (0.29 g, 1.0 mmol) was added at room temperature. After stirring for 2 h, the reaction mixture was diluted with water (15 mL), filtered and the filtrate was extracted with $Et_2O$ ($3 \times 15$ mL). The organic layer was washed with $NaHCO_3$ solution, brine, dried (over $Na_2SO_4$), and concentrated. The crude product was purified on silica gel column eluting with EtOAc and light petroleum (1:19) to provide ketone **21** (0.134 g, 90%) as a colorless oil. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 0.93 (d, 3H, $J$ = 6.6 Hz), 1.06 (d, 3H, $J$ = 7.0 Hz), 1.25–1.46 (m, 3H), 1.70–1.78 (m, 2H), 1.95–2.07 (m, 2H), 2.43–2.58 (m, 3H), 3.29 (d, 2H, $J$ = 6.0 Hz), 4.48 (s, 2H), 4.93–5.04 (m, 2H), 5.62–5.87 (m, 1H), 7.29–7.33 (m, 5H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 16.4, 17.1, 27.7, 31.4, 32.0, 33.1, 38.9, 45.5, 73.1, 75.6, 115.1, 127.5, 127.6 ($\times$ 2), 128.3 ($\times$ 2), 138.1, 138.7, 214.4; EIMS: $(M+Na)^+$ calcd for $C_{19}H_{28}NaO_2^+$ 311.20. Found: 311.54.

#### 4.1.9. 2-((*S*)-4-(Benzyloxy)-3-methylbutyl)-2-((*S*)-hex-5-en-2-yl)-1,3-dioxalane 22

A mixture of ketone **21** (0.1 g, 0.35 mmol), ethylene glycol (0.4 mL, 6.9 mmol) and *p*-TSA (catalytic amount) in dry benzene (20 mL) was heated at reflux for 4 h using a Dean–Stark apparatus. Upon completion of the reaction (monitored by TLC), it was washed with 5% $NaHCO_3$ solution, water, brine and dried (over $Na_2SO_4$). The organic layer was then concentrated to a residue, which upon silica gel column purification (EtOAc/light petroleum, 1:19) afforded **22** (0.085 g, 74%) as a colorless liquid. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.91 (d, 3H, $J$ = 6.9 Hz), 0.94 (d, 3H, $J$ = 6.7 Hz), 1.09–1.18 (m, 1H), 1.34–1.48 (m, 1H), 1.57–1.77 (m, 6H), 1.90–2.04 (m, 1H), 2.08–2.22 (m, 1H), 3.23 (dd, 1H, $J$ = 6.6, 9.1 Hz), 3.32 (dd, 1H, $J$ = 6.0, 9.1 Hz), 3.91 (s, 4H), 4.49 (s, 2H), 4.90–5.05 (m, 2H), 5.70–5.92 (m, 1H), 7.24–7.34 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 14.1, 17.4, 27.0, 30.4, 31.3, 32.0, 33.8, 39.1, 65.1, 65.2, 73.0, 75.9, 114.0, 114.4, 127.4, 127.5 ($\times$ 2), 128.3 ($\times$ 2), 138.9, 139.0; EIMS: $(M+Na)^+$ calcd for $C_{21}H_{32}NaO_3^+$ 355.22. Found: 355.57; Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.69; H, 9.61.

#### 4.1.10. ((*S*)-4-(2-((*S*)-Hex-5-en-2-yl)-1,3-dioxolan-2-yl)-2-methylbutoxy)triisopropylsilane 23

A small piece of lithium was added to a pre-condensed stirred solution of ammonia (10 mL) at -78 °C until a deep blue color persisted. After 30 min, compound **22** (0.060 g, 0.18 mmol) in THF (5 mL) was added dropwise to this solution. The reaction mixture was stirred for 1 h at this temperature, and then quenched with solid $NH_4Cl$, until the blue color disappeared. Ammonia was allowed to evaporate completely and the residue was diluted with $H_2O$ (5 mL) and extracted with EtOAc (3 $\times$ 10 mL). The combined extracts were dried over $Na_2SO_4$, concentrated, and purified on silica gel column using EtOAc/light petroleum (1:6) to produce an alcohol which was used for rgw next sillyl protection. To a solution of this alcohol (0.025 g, 0.1 mmol) in $CH_2Cl_2$ (3 mL), imidazole (0.014 g, 0.2 mmol) was added at 0 °C followed by TIPS-Cl (0.03 mL, 0.15 mmol) and stirred at room temperature for 1 h. It was then diluted with water (5 mL) and extracted with $CH_2Cl_2$ (2 $\times$ 10 mL), washed with brine, dried over $Na_2SO_4$, and concentrated to give a residue, which was purified by flash silica gel column chromatography (EtOAc/light petroleum, 1:19), to furnish the TIPS protected compound **23** (0.036 g, 89%) as a colorless liquid. $[\alpha]_D^{25} = -9.8$ ($c$ 0.6, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 0.90 (d, 3H, $J$ = 6.5 Hz), 0.92 (d, 3H, $J$ = 7.0 Hz), 1.04–1.07 (m, 21H), 1.11–1.19 (m, 2H), 1.45–1.55 (m, 2H), 1.62–1.75 (m, 4H), 1.92–2.00 (m, 1H), 2.12–2.21 (m, 1H), 3.47 (dd, 1H, $J$ = 6.4, 9.6 Hz), 3.52 (dd, 1H, $J$ = 5.8, 9.6 Hz), 3.90–3.93 (m, 4H), 4.94 (d, 1H, $J$ = 10.3 Hz), 5.01 (d, 1H, $J$ = 17.1 Hz), 5.75–5.86 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 11.8 ($\times$ 3), 13.7, 16.6, 17.8 ($\times$ 6), 26.4, 30.1, 31.3, 31.7, 36.1, 38.9, 64.9, 65.0, 68.4, 113.8, 114.1, 138.8; EIMS: $(M+Na)^+$ calcd for $C_{23}H_{46}NaO_3Si^+$ 421.31. Found: 421.44; Anal. Calcd for $C_{23}H_{46}O_3Si$: C, 69.29; H, 11.63. Found: C, 69.07; H, 11.89.

#### 4.1.11. (8*R*,11*S*)-8-((*S*)-Hex-5-en-2-yl)-11-methyl-14-phenyl-2,5,7,13-tetraoxotetradecane 24

To a solution of compound **10** (1.75 g, 6.04 mmol) in $CH_2Cl_2$ (12 mL), *i*-$Pr_2NEt$ (2.1 mL, 12.1 mmol) and MEM-Cl (1.0 mL, 9.1 mmol) were added at 0 °C and stirred overnight at room temperature. After completion (monitored by TLC), it was quenched with ice, diluted with $H_2O$ (10 mL), and extracted with $CH_2Cl_2$ (2 $\times$ 15 mL). The combined organic layer was washed with brine and dried over anhydrous $Na_2SO_4$. The organic layer was concentrated to a give a residue, which upon silica gel column chromatography (EtOAc/light petroleum, 1:9) furnished MEM protected compound **24** (1.78 g, 78%) as a colorless liquid. $[\alpha]_D^{25} = -7.0$ ($c$ 1.0, $CHCl_3$); IR ($CHCl_3$) cm$^{-1}$: 2928, 1647, 1454, 1060, 773, 697; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.88 (d, 3H, $J$ = 6.9 Hz), 0.95 (d, 3H, $J$ = 6.7 Hz), 1.11–1.27 (m, 3H), 1.43–1.48 (m, 2H), 1.52–1.63 (m, 2H), 1.72–1.78 (m, 2H), 1.92–2.04 (m, 1H), 3.25 (dd, 1H, $J$ = 6.6, 8.8 Hz), 3.33 (dd, 1H, $J$ = 5.9, 8.8 Hz), 3.38 (s, 3H), 3.40–3.44 (m, 1H), 3.50–3.53 (m, 2H), 3.68–3.73 (m, 2H), 4.49 (s, 2H), 4.72 (ABq, 2H, $J$ = 7.1 Hz), 4.94 (d, 1H, $J$ = 10.4 Hz), 5.0 (d, 1H, $J$ = 17.0 Hz), 5.70–5.86 (m, 1H), 7.28–7.33 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.7, 17.5, 27.5, 29.9, 31.7, 31.9, 33.8, 35.4, 59.0, 67.2, 71.9, 73.1, 75.8, 82.2, 94.9, 114.5, 127.5 ($\times$ 3), 128.3 ($\times$ 2), 138.9 ($\times$ 2); EIMS: $(M+Na)^+$ calcd for $C_{23}H_{38}NaO_4^+$ 401.27. Found: 401.37; Anal. Calcd for $C_{23}H_{38}O_4$: C, 72.98; H, 10.12. Found: C, 73.11; H, 9.98.

#### 4.1.12. (2*S*,5*R*,6*S*)-5-((2-Methoxyethoxy)methoxy)-2,6-dimethyldec-9-en-1-ol 25

To a vigorously stirred solution of ammonia (15 mL) at −78 °C, lithium (0.19 g, 26.5 mmol) was added. A deep blue color appeared within 5 min and after 30 min the benzylated derivative **24** (1.0 g, 2.6 mmol) in THF (10 mL) was added dropwise. The solution was stirred for 1 h, and then quenched with solid $NH_4Cl$, until the blue color disappeared. Ammonia was allowed to evaporate completely and the residue was diluted with $H_2O$ (15 mL) and extracted with EtOAc (3 $\times$ 20 mL). The combined extracts were dried over $Na_2SO_4$, concentrated, and purified on a silica gel column using EtOAc/light petroleum (2:3) to produce **25** (0.63 g, 83%) as a colorless liquid. $[\alpha]_D^{25} = +15.4$ ($c$ 1.0, $CHCl_3$); IR ($CHCl_3$) cm$^{-1}$: 3375, 2929, 1646, 1459, 1254, 1075, 757, 698; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.88 (d, 3H, $J$ = 7.0 Hz), 0.92 (d, 3H, $J$ = 7.0 Hz) 1.04–1.21 (m, 2H), 1.38–1.61 (m, 5H), 1.68–1.80 (m, 1H), 1.92–2.18 (m, 2H), 2.43 (br s, 1H), 3.39 (s, 3H), 3.43–3.46 (m, 3H), 3.54–3.58 (m, 2H), 3.68–3.85 (m, 2H), 4.74 (ABq, 2H, $J$ = 7.1 Hz), 4.92–5.06 (m, 2H), 5.68–5.92 (m, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 14.3, 16.6, 27.2, 29.2, 31.5, 31.6, 35.2, 35.8, 58.9, 67.0, 67.7, 71.7, 82.4, 94.8, 114.3, 138.7; EIMS: $(M+Na)^+$ calcd for $C_{16}H_{32}NaO_4^+$ 311.22. Found: 311.18; Anal. Calcd for $C_{16}H_{32}O_4$: C, 66.63; H, 11.18. Found: C, 66.82; H, 11.02.

#### 4.1.13. (2*S*,5*R*,6*S*)-5-((2-Methoxyethoxy)methoxy)-2,6-dimethyldec-9-enoic acid 26

To a solution of compound **25** (0.5 g, 1.74 mmol) in DMF (8 mL), PDC (3.3 g, 8.7 mmol) was added and stirred at room temperature overnight. The reaction mixture was diluted with $H_2O$ (25 mL) and extracted with ether (3 $\times$ 25 mL). The combined extracts were dried over $Na_2SO_4$ and concentrated to a residue. Silica gel column purification using EtOAc and light petroleum (1:1) as eluent provided the acid **26** (0.4 g, 77%) as a colorless liquid. $[\alpha]_D^{25} = +23.2$ ($c$ 0.8, $CHCl_3$); IR ($CHCl_3$) cm$^{-1}$: 2928, 1710, 1645, 1462, 1382, 1070, 837; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.87 (d, 3H, $J$ = 6.8 Hz), 1.20 (d, 3H, $J$ = 7.0 Hz), 1.42–1.52 (m, 4H), 1.65–2.21 (m, 5H), 2.37–2.55 (m, 1H), 3.39 (s, 3H), 3.44 (m, 1H), 3.52–3.57 (m, 2H), 3.68–3.78 (m, 2H), 4.73 (ABq, 2H, $J$ = 7.2 Hz), 4.91–5.05 (m, 2H), 5.66–5.90 (m, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 14.4, 17.1, 27.4, 29.6, 31.6, 31.9, 35.2, 39.3, 59.0, 67.2, 71.8, 81.5, 94.8, 114.6, 138.8, 182.5; EIMS: $(M+Na)^+$ calcd for $C_{16}H_{30}NaO_5^+$ 325.20. Found: 325.31; Anal. Calcd for $C_{16}H_{30}O_5$: C, 63.55; H, 10.00. Found: C, 63.34; H, 10.22.

#### 4.1.14. (*S*)-1-(Benzyloxy)but-3-en-2-ol 29

A solution of the (*S*)-but-3-en-1,2-diol **28** (1.0 g, 11.4 mmol), prepared from D-mannitol[13] was treated with dibutyltin oxide (4.2 g, 17.0 mmol) in toluene (35 mL) and refluxed for 4 h using a

Dean–Stark apparatus. After cooling at room temperature, benzyl bromide (2.0 mL, 17.0 mmol) and TBAI (catalytic) were added and refluxed for 2 h. The reaction mixture was diluted with $CH_2Cl_2$ (30 mL), washed with 10% $NaHCO_3$ solution (2 × 20 mL), water, brine, dried (over $Na_2SO_4$) and then concentrated. The residue was purified on silica gel column chromatography using EtOAc and light petroleum (1:6) to provide **29** (1.7 g, 84%) as a light yellow liquid. $[\alpha]_D^{25} = -5.4$ (*c* 0.7, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 2.42 (br s, 1H), 3.36 (dd, 1H, *J* = 7.9, 9.6 Hz), 3.54 (dd, 1H, *J* = 3.5, 9.6 Hz), 4.28–4.40 (m, 1H), 4.57 (s, 2H), 5.19 (d, 1H, *J* = 10.5 Hz), 5.36 (d, 1H, *J* = 17.3 Hz), 5.74–5.94 (m, 1H), 7.30–7.35 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 71.4, 73.3, 74.0, 116.3, 126.8, 127.7 (× 2), 128.4 (× 2), 136.6, 137.7; EIMS: $(M+Na)^+$ calcd for $C_{11}H_{14}NaO_2^+$ 201.09. Found: 201.29; Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.35; H, 7.76.

#### 4.1.15. (2*S*,5*R*,6*S*)-((*S*)-1-(Benzyloxy)but-3-en-2-yl)-5-((2-methoxyethoxy)methoxy)-2,6-dimethyldec-9-enoate 9

At first, 2,4,6-trichlorobenzoyl chloride (0.22 mL, 1.4 mmol) was added to a stirred solution of acid **26** (0.28 g, 0.93 mmol) and *i*-$Pr_2NEt$ (0.33 mL, 1.86 mmol) in THF (10 mL), at 0 °C. After 1 h, alcohol **29** (0.182 g, 1.02 mmol) and DMAP (0.17 g, 1.4 mmol) in THF (5 mL) were added and the reaction mixture was warmed to room temperature and stirred for 6 h. The reaction mixture was quenched with a saturated $NaHCO_3$ solution (10 mL) and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated. Purification by flash silica gel chromatography (EtOAc/light petroleum, 1:9) yielded **9** (0.32 g, 75%). $[\alpha]_D^{25} = +13.2$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$: 2930, 1724, 1650, 1382, 1255, 1026, 773, 621; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.83 (d, 3H, *J* = 6.8 Hz), 1.18 (d, 3H, *J* = 7.0 Hz), 1.38–1.48 (m, 4H), 1.65–1.83 (m, 3H), 1.96–2.14 (m, 2H), 2.43–2.52 (m, 1H), 3.38 (s, 3H), 3.39–3.44 (m, 1H), 3.50–3.57 (m, 4H), 3.67–3.73 (m, 2H), 4.55 (ABq, 2H, *J* = 12.0 Hz), 4.70 (ABq, 2H, *J* = 7.1 Hz), 4.90–5.04 (m, 2H), 5.20–5.37 (m, 2H), 5.48–5.55 (m, 1H), 5.70–5.92 (m, 2H), 7.31–7.33 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 14.3, 17.3, 27.3, 29.7, 31.6, 31.8, 35.1, 39.6, 58.9, 67.1, 71.3, 71.7, 72.6, 73.0, 81.3, 94.6, 114.4, 117.8, 127.5 (× 2), 127.6, 128.3 (× 2), 133.5, 137.9, 138.7, 175.5; EIMS: $(M+Na)^+$ calcd for $C_{27}H_{42}NaO_6^+$ 485.29. Found: 485.38; Anal. Calcd for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found: C, 70.25; H, 9.38.

#### 4.1.16. (3*S*,6*R*,7*S*,12*S*)-12-(Benzyloxymethyl)-6-(2-mehtoxyethoxy)methoxy-3,7-dimethyloxacyclododec-10-en-2-one 4 and 4a

A solution of ester **9** (0.17 g, 0.37 mmol) and Grubbs' second generation catalyst (0.032 g, 0.037 mmol) in dry benzene (70 mL) was degassed under an argon atmosphere and refluxed for 24 h. After completion of the reaction (monitored by TLC), the solvent was evaporated and the residue was chromatographed on flash silica gel column using EtOAc and light petroleum (1:24) to yield **4** and **4a** (0.092 g, combined yield 58%) as an inseparable mixture of *E*- and *Z*- (2:1) isomers as a colorless liquid. IR ($CHCl_3$) $cm^{-1}$: 2927, 1723, 1601, 1370, 1116, 1028; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.90 (d, 1H, *J* = 6.6 Hz), 0.96 (d, 2H, *J* = 6.6 Hz), 1.10 (d, 1H, *J* = 7.1 Hz), 1.16 (d, 2H, *J* = 7.1 Hz), 1.58–1.72 (m, 5H), 2.08–2.14 (m, 3H), 2.26–2.40 (m, 1H), 2.60–2.72 (m, 1H), 3.38 (s, 3H), 3.47–3.61 (m, 5H), 3.65–3.72 (m, 2H), 4.48–4.60 (m, 2H), 4.65–4.75 (m, 2H), 4.98–5.22 (m, 1H), 5.31–5.65 (m, 2H), 7.25–7.35 (m, 5H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 14.0 (× 2), 15.2 (× 2), 18.3/22.8, 26.2/28.7, 30.3/31.9, 34.7/35.1, 36.6/36.9, 39.9 (× 2), 59.1 (× 2), 67.1/67.3, 71.5/71.6, 71.8 (× 2), 72.4 (× 2), 73.1 (× 2), 81.7 (× 2), 94.3 (× 2), 126.1/126.6, 127.6 (× 2), 127.7 (× 2), 128.4 (× 2), 129.6 (× 2), 130.8 (× 2), 132.4 (× 2), 138.1 (× 2), 175.4/175.6; EIMS: $(M+Na)^+$ calcd for $C_{25}H_{38}NaO_6^+$ 457.26. Found: 457.45; Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.10; H, 8.81. Found: C, 69.23; H, 8.97.

#### 4.1.17. (*S*)-4-Benzyl-3-((2*S*,3*R*,6*S*)-7-(benzyloxy)-3-hydroxy-2,6-dimethylheptanoyl)oxazolidin-2-one 31

Using the same procedure as described for the synthesis of **19**, compound **31** was obtained as a thick viscous liquid from oxazolidinone **30** and aldehyde **7**. Purification was performed by flash silica gel chromatography eluting with EtOAC and light petroleum (1:5) to furnish aldol product **31** (4.2 g, 75%). $[\alpha]_D^{25} = +42.0$ (*c* 1.9, $CHCl_3$); IR ($CHCl_3$): 3506, 2931, 2860, 1781, 1697, 1454, 1210, 1015, 749; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.95 (d, 3H, *J* = 6.6 Hz), 1.25 (d, 3H, *J* = 7.1 Hz), 1.48–1.59 (m, 4H), 1.79 (m, 1H), 2.76 (dd, 1H, *J* = 9.5, 13.2 Hz), 2.90 (br s, 1H), 3.21–3.34 (m, 3H), 3.74 (dq, 1H, *J* = 2.5, 7.1 Hz), 3.91 (m, 1H), 4.13–4.21 (m, 2H), 4.48 (s, 2H), 4.67 (m, 1H), 7.22–7.33 (m, 10H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 10.3, 17.1, 29.8, 31.1, 33.3, 37.5, 41.9, 54.9, 65.9, 71.6, 72.7, 75.5, 127.2 (× 2), 127.3, 127.4, 128.1 (× 2), 128.7 (× 2), 129.2 (× 2), 134.9, 138.5, 152.7, 177.1; EIMS: $(M+Na)^+$ calcd for $C_{26}H_{33}NaO_5^+$ 462.23. Found: 462.16; Anal. Calcd for $C_{26}H_{33}NO_5$: C, 71.05; H, 7.57; N, 3.19. Found: C, 70.95; H, 7.39; N, 3.08.

#### 4.1.18. (*S*)-4-Benzyl-3-((2*S*,3*R*,6*S*)-7-(benzyloxy)-3-(methoxymethoxy)-2,6-dimethylheptanoyl)oxazolidin-2-one 32

To a solution of aldol product **31** (1.0 g, 2.3 mL) in $CH_2Cl_2$ (10 mL), *i*-$Pr_2NEt$ (1.6 mL, 9.1 mmol) and MOM-Cl (0.35 mL, 4.5 mmol) were added simultaneously at 0 °C. The reaction mixture was then stirred overnight at room temperature, quenched with ice and water, and extracted with $CH_2Cl_2$ (2 × 10 mL). The combined extracts were dried (over $Na_2SO_4$), concentrated, and purified on a silica gel column using EtOAc and light petroleum (1:9) to give **32** (0.99 g, 91%) as a clear liquid. $[\alpha]_D^{25} = +58.3$ (*c* 1.2, $CHCl_3$); IR ($CHCl_3$): 2928, 1780, 1699, 1454, 1381, 1209, 1098, 1031, 750; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.95 (d, 3H, *J* = 6.6 Hz), 1.23 (d, 3H, *J* = 7.1 Hz), 1.50–1.80 (m, 5H), 2.75 (dd, 1H, *J* = 9.8, 13.3 Hz), 3.26–3.34 (m, 6H), 3.79 (m, 1H), 3.96 (m, 1H), 4.12 (d, 2H, *J* = 4.6 Hz), 4.48 (s, 2H), 4.52–4.63 (m, 3H), 7.21–7.32 (m, 10H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 11.4, 17.2, 29.4, 29.7, 30.1, 33.6, 37.7, 41.4, 55.95, 65.98, 72.9, 75.6, 79.3, 96.4, 127.3 (× 2), 127.4, 127.5, 128.3 (× 2), 128.9 (× 2), 129.4 (× 2), 135.4, 138.7, 153.1, 174.8; EIMS: $(M+Na)^+$ calcd for $C_{28}H_{37}NaO_6^+$ 506.25. Found: 506.42; Anal. Calcd for $C_{28}H_{37}NO_6$: C, 69.54; H, 7.71; N, 2.90. Found: C, 69.42; H, 7.59; N, 2.76.

#### 4.1.19. (2*R*,3*R*,6*S*)-7-(Benzyloxy)-3-(methoxymethoxy)-2,6-dimethylheptan-1-ol 33

At first, LiCl (0.156 g, 6.63 mmol)) and $NaBH_4$ (0.252 g, 6.63 mmol) were taken in a mixture of absolute ethanol (25 mL) and THF (8 mL) and vigorously stirred for 1 h at room temperature. A solution of aldol product **32** (0.8 g, 1.7 mmol) in THF, (8 mL) was then added dropwise and the mixture was then stirred for 6 h at room temperature. The mixture was quenched with a saturated solution of $NH_4Cl$ (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $Na_2SO_4$, concentrated and the residue was purified on silica gel column using EtOAc/light petroleum (1:5) to afford **33** (0.44 g, 86%) as a colorless liquid. $[\alpha]_D^{25} = -28.3$ (*c* 1.2, $CHCl_3$); IR ($CHCl_3$): 3437, 2926, 1736, 1496, 1454, 1208, 1147, 1098, 918, 698; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.75 (d, 3H, *J* = 7.0 Hz), 0.88 (d, 3H, *J* = 6.7 Hz), 1.35–1.56 (m, 4H), 1.69–1.86 (m, 2H), 2.39 (br s, 1H), 3.21 (dd, 2H, *J* = 2.4, 6.3 Hz), 3.33 (s, 3H), 3.41–3.64 (m, 3H), 4.42 (s, 2H), 4.58 (s, 2H), 7.23–7.27 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 10.6, 17.1, 28.8, 29.95, 33.6, 37.8, 55.9, 65.2, 72.99, 75.7, 79.9, 96.7, 127.4 (× 2), 127.5, 128.3 (× 2), 138.7; EIMS: $(M+Na)^+$ calcd for $C_{18}H_{30}NaO_6^+$ 333.20.

Found: 333.11; Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.54; H, 9.63.

#### 4.1.20. (*S*,*E*)-7-(Benzyloxy)-2,6-dimethylhept-2-enal 35

Alcohol **33** (0.35 g, 1.1 mmol) was dissolved in DMSO (4 mL) and then IBX (0.38 g, 1.4 mmol) was added at room temperature and stirred overnight. The reaction mixture was quenched with $H_2O$ and filtered off. The filtrate was extracted with ether ($2 \times 15$ mL), then dried over $Na_2SO_4$, and concentrated. The residue was purified on a silica gel column (EtOAc/light petroleum, 1:9) to produce aldehyde **34** (0.32 g, 93%) as a colorless liquid. To a solution of the aldehyde **34** (0.32 g, 1.04 mmol) in dry benzene (8 mL), (carbethoxymethylene)triphenyl phosphorane (0.72 g, 2.08 mmol) was added at room temperature. It was then stirred overnight, concentrated and the residue was purified by flash silica gel column chromatography (EtOAc/light petroleum, 1:49) to afford the eliminated product **35** (0.18 g, 70%) as a colorless liquid. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.97 (d, 3H, $J$ = 6.7 Hz), 1.36 (m, 1H), 1.65(m, 1H), 1.73 (s, 3H), 1.82 (m, 1H), 2.30–2.42 (m, 2H), 3.32 (d, 2H, $J$ = 6.1 Hz), 4.51 (s, 2H), 6.48 (t, 1H, $J$ = 7.3 Hz), 7.30–7.35 (m, 5H), 9.38 (s, 1H); EIMS: $(M+Na)^+$ calcd for $C_{16}H_{22}NaO_2$ 269.15. Found: 269.21.

#### 4.1.21. (*S*)-4-Benzyl-3-((2*S*,3*R*,6*S*)-7-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-2,6-dimethylheptanoyl)oxazolidin-2-one 37

To a stirred solution of aldol product **31** (5.0 g, 11.4 mmol) in $CH_2Cl_2$ (20 mL), 2,6-lutidine (2.64 mL, 22.7 mmol) was added followed by TBS-OTf (3.9 mL, 17.0 mmol) at 0 °C. The reaction mixture was stirred for 30 min, then quenched with ice, diluted with water (5 mL) and extracted with $CH_2Cl_2$ ($2 \times 20$ mL). The combined organic layer was washed with 1 M HCL ($2 \times 15$ mL), brine, dried over $Na_2SO_4$, and concentrated to a residue which was purified on a silica gel column using EtOAc and light petroleum (1:19) as eluent to provide the TBS protected aldol compound **37** (5.95 g, 95%) as a colorless viscous liquid. $[\alpha]_D^{25} = +28.4$ ($c$ 1.1, $CHCl_3$); IR ($CHCl_3$): 2929, 1783, 1704, 1454, 1382, 1209, 1104, 837; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ −0.02 (s, 3H), 0.02, (s, 3H), 0.87 (s, 9H), 0.93 (d, 3H, $J$ = 6.4 Hz), 1.20 (d, 3H, $J$ = 7.0 Hz), 1.45–1.75 (m, 5H), 2.75 (dd, 1H, $J$ = 9.6, 13.3 Hz), 3.23–3.30 (m, 3H), 3.84 (m, 1H), 4.01–4.14 (m, 3H), 4.47 (s, 2H), 4.55 (m, 1H), 7.22–7.33 (m, 10H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ −4.9, −4.2, 11.5, 17.1, 18.0, 25.6 ($\times$ 2), 25.8 ($\times$ 2), 28.6, 32.7, 33.7, 37.5, 42.6, 55.7, 65.9, 72.9, 75.8, 127.2 ($\times$ 2), 127.3, 127.5, 128.2 ($\times$ 2), 128.9 (x2), 129.4 ($\times$ 2), 135.4, 138.7, 153.0, 175.2; EIMS: $(M+Na)^+$ calcd for $C_{32}H_{47}NNaO_5Si$ 576.31. Found: 576.46; Anal. Calcd for $C_{32}H_{47}NO_5Si$: C, 69.40; H, 8.55; N, 2.53. Found: C, 69.26; H, 8.38; N, 2.42.

#### 4.1.22. (2*R*,3*R*,6*S*)-7-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-2,6-dimethylheptan-1-ol 38

Using the same procedure as described for the synthesis **33**, compound **38** (3.2 g, 83%) was obtained as a colorless liquid from compound **37**. $[\alpha]_D^{25} = -1.95$ ($c$ 0.8, $CHCl_3$); IR ($CHCl_3$): 3430, 2955, 2929, 1471, 1361, 1253, 1096, 836, 774; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.07 (s, 3H), 0.09 (s, 3H), 0.81 (d, 3H, $J$ = 7.0 Hz), 0.89 (s, 9H), 0.95 (d, 3H, $J$ = 6.7 Hz), 1.05 (m, 1H), 1.45–1.55 (m, 3H), 1.75 (m, 1H), 1.92 (m, 1H), 2.38 (br s, 1H) 3.26 (dd, 1H, $J$ = 6.4, 8.9 Hz), 3.32 (dd, 1H, $J$ = 6.3, 8.9 Hz), 3.51 (dd, 1H, $J$ = 5.2, 10.6 Hz), 3.67 (dd, 1H, $J$ = 8.4, 10.6 Hz), 3.75 (m, 1H), 4.50 (s, 2H), 7.29–7.34 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ −4.5, −4.3, 11.6, 17.1, 18.0, 25.8 ($\times$ 3), 29.9, 30.2, 33.6, 39.4, 66.0, 73.0, 75.7, 75.8, 127.4 ($\times$ 2), 127.5, 128.3 ($\times$ 2), 138.7; EIMS: $(M+Na)^+$ calcd for $C_{22}H_{40}NaO_3Si^+$ 403.26. Found: 403.25; Anal. Calcd for $C_{22}H_{40}O_3Si$: C, 69.42; H, 10.59. Found: C, 69.24; H, 10.38.

#### 4.1.23. (4*R*,5*R*,8*S*,*E*)-Ethyl-9-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-4,8-dimethylnon-2-enoate 39

Alcohol **38** (3.0 g, 7.9 mmol) was dissolved in $CH_2Cl_2$ (25 mL) and PDC (5.9 g, 15.7 mmol) was added at room temperature. The mixture was then stirred overnight and filtered off. The filtrate was concentrated to a residue, which was purified on a silica gel column (EtOAc/light petroleum, 1:9) to produce the aldehyde (2.4 g, 81%) as a colorless liquid. A solution of the above aldehyde (2.4 g, 6.3 mmol) and (carbethoxymethylene)triphenyl phosphorane (4.4 g, 12.7 mmol) in dry benzene (20 mL) was stirred at room temperature for 24 h. The reaction was monitored by TLC and after completion, the solvent was removed in vacuum and the residue was purified by flash silica gel column chromatography eluting with EtOAc and light petroleum (1:24) to afford pure Wittig (*E*)-isomer **39** (2.2 g, 78%) as a colorless liquid. $[\alpha]_D^{25} = +20.8$ ($c$ 0.9, $CHCl_3$); IR ($CHCl_3$): 2956, 2930, 2857, 1721, 1652, 1462, 1366, 1257, 1180, 1098, 836, 774; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.03 (s, 6H), 0.88 (s, 9H), 0.92 (d, 3H, $J$ = 6.7 Hz), 1.01 (d, 3H, $J$ = 6.9 Hz), 1.28 (t, 3H, $J$ = 7.1 Hz), 1.39–1.78 (m, 5H), 2.45 (m, 1H), 3.23 (dd, 1H, $J$ = 6.3, 9.0 Hz), 3.30 (dd, 1H, $J$ = 6.3, 9.0 Hz), 3.59 (m, 1H), 4.18 (q, 2H, $J$ = 7.1 Hz), 4.48 (s, 2H), 5.78 (dd, 1H, $J$ = 1.3, 15.8 Hz), 6.99 (dd, 1H, $J$ = 7.3, 15.8 Hz), 7.28–7.33 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ −4.5, −4.2, 13.7, 14.3, 17.2, 18.1, 25.9 ($\times$ 3), 29.2, 31.5, 33.6, 41.3, 60.1, 72.99, 75.3, 75.7, 120.7, 127.4 ($\times$ 2), 127.5, 128.3 ($\times$ 2), 138.7, 152.1, 166.6; EIMS: $(M+Na)^+$ calcd for $C_{26}H_{44}NaO_4Si$ 471.29. Found: 471.20; Anal. Calcd for $C_{26}H_{44}O_4Si$: C, 69.59; H, 9.88. Found: C, 69.44; H, 9.69.

#### 4.1.24. (4*R*,5*R*,8*S*,*E*)-Ethyl-9-(benzyloxy)-4,8-dimethyl-5-((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)non-2-enoate 40 [(*R*)-MTPA ester]

To a solution of Wittig compound **39** (0.050 g, 0.112 mmol) in THF (2 mL) at 0 °C, HF-pyridine in pyridine/THF mixture [prepared from a stock solution containing 42 mL, HF-pyridine (70% HF), 114 mL pyridine and 200 mL THF] (2.0 mL) was added and the resulting solution was warmed to room temperature. After stirring overnight, the reaction was diluted with EtOAc and quenched by the careful addition of a saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with EtOAc ($3 \times 10$ mL). The combined layers were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuum to afford a residue which was purified by flash column chromatography (EtOAc/light petroleum, 1:6) to give the secondary alcohol (0.027 g, 73%) as a colorless liquid. The corresponding (*R*)-MTPA acid (0.011 g, 0.045 mmol), the resulting secondary alcohol (0.010 g, 0.03 mmol), DCC (0.012 g, 0.06 mmol), and DMAP (0.002 g, 0.015 mmol) were taken in $CH_2Cl_2$ (2 mL) and stirred for 12 h at room temperature. The reaction mixture was filtered, concentrated, and purified by flash silica gel column using EtOAc and light petroleum (1:19) to yield **40** (0.012 g, 73%) as a colorless liquid. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.80 (d, 3H, $J$ = 6.7 Hz), 0.99 (d, 3H, $J$ = 6.9 Hz), 1.22 (t, 3H, $J$ = 7.1 Hz), 1.49–1.62 (m, 5H), 2.61 (m, 1H), 3.09 (dd 1H, $J$ = 6.2, 9.3 Hz), 3.13 (dd, 1H, $J$ = 6.3, 9.3 Hz), 3.44 (s, 3H), 4.12 (q, 2H, $J$ = 7.1 Hz), 4.38 (s, 2H), 5.02 (dt, 1H, $J$ = 4.9, 7.7 Hz), 5.75 (dd, 1H, $J$ = 1.3, 15.8 Hz), 6.81 (dd, 1H, $J$ = 7.3, 15.8 Hz), 7.19–7.31 (m, 8H), 7.42–7.46 (m, 2H); EIMS: $(M+Na)^+$ calcd for $C_{30}H_{37}F_3NaO_6^+$ 573.24. Found: 573.55; Anal. Calcd for $C_{30}H_{37}F_3O_6$: C, 65.44; H, 6.77. Found: C, 65.87; H, 6.90.

#### 4.1.25. (4*R*,5*R*,8*S*,*E*)-Ethyl-9-(benzyloxy)-4,8-dimethyl-5-((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)non-2-enoate 41 [(*S*)-MTPA ester]

Using the same procedure as described for the synthesis of MTPA ester **40**, compound **41** (0.013 g, 76%) was obtained as a col-

orless liquid from compound **39**. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.83 (d, 3H, $J$ = 6.7 Hz), 0.93 (d, 3H, $J$ = 6.9 Hz), 1.20 (t, 3H, $J$ = 7.1 Hz), 1.34–1.49 (m, 2H), 1.59–1.73 (m, 3H), 2.56 (m, 1H), 3.17 (d, 2H, $J$ = 6.2 Hz), 3.44 (s, 3H), 4.10 (q, 2H, $J$ = 7.1 Hz), 4.40 (s, 2H), 5.03 (dt, 1H, $J$ = 4.8, 7.8 Hz), 5.63 (dd, 1H, $J$ = 1.3, 15.8 Hz), 6.69 (dd, 1H, $J$ = 7.5, 15.8 Hz), 7.19–7.31 (m, 8H), 7.44–7.48 (m, 2H); EIMS: $(M+Na)^+$ calcd for $C_{30}H_{37}F_3NaO_6^+$ 573.24. Found: 573.55; Anal. Calcd for $C_{30}H_{37}F_3O_6$: C, 65.44; H, 6.77. Found: C, 65.89; H, 6.70.

#### 4.1.26. (4*R*,5*R*)-4-((*S*)-4-(Benzyloxy)-3-methylbutyl)-2,2,5-trimethyl-1,3-dioxane 42

To a solution of **38** (0.2 g, 0.53 mmol), in THF (4 mL) at 0 °C was added TBAF (0.8 mL, 1 M in THF, 0.8 mmol). After stirring for 30 min, the reaction was quenched with a saturated solution of $NH_4Cl$ and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (2 × 15 mL), dried over $Na_2SO_4$, concentrated to a residue and purified on silica gel column (EtOAc/light petroleum, 2:3) to yield a diol compound (0.126 g, 90%) as a colorless liquid. A solution of the above diol (0.1 g, 0.4 mmol) was treated with 2,2-dimethoxy propane (0.07 mL, 0.6 mmol) and *p*-TSA (catalytic) in acetone (5 mL). The solution was stirred overnight at room temperature, then quenched with a saturated solution of $NaHCO_3$, extracted with ethyl acetate (2 × 15 mL), dried over $Na_2SO_4$, and concentrated. The crude residue was purified on a silica gel column (EtOAc/light petroleum, 1:19) to provide the acetonide protected compound **42** (0.085 g, 74%) as a clear liquid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.95 (d, 3H, $J$ = 6.7 Hz), 1.05 (d, 3H, $J$ = 7.0 Hz), 1.13 (m, 1H), 1.29–1.34 (m, 2H), 1.38 (s, 3H), 1.42 (s, 3H), 1.47–1.54 (m, 2H), 1,78 (m, 1H), 3.26 (dd, 1H, $J$ = 6.6, 8.9 Hz), 3.32 (dd, 1H, $J$ = 6.4, 8.9 Hz), 3.58 (d, 1H, $J$ = 11.6 Hz), 3.87 (dt, 1H, $J$ = 2.3, 6.7 Hz), 4.07 (d, 1H, $J$ = 11.6 Hz), 4.49 (s, 2H), 7.28–7.33 (m, 5H).

#### 4.1.27. (4*R*,5*R*,8*S*,)-9-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-4,8-dimethylnonan-1-ol 6

The Wittig *E*-isomer **39** (1.95 g, 4.34 mmol) was dissolved in MeOH (15 mL) and $NiCl_2.6H_2O$ (0.26 g, 1.1 mmol) was added in one portion. The reaction mixture was then cooled to 0 °C and $NaBH_4$ (0.66 g, 17.4 mmol) was added in small portions to avoid a vigorous reaction. Stirring was continued at 0 °C for 30 min, then diluted with $CH_2Cl_2$ (10 mL) and quenched with saturated $NH_4Cl$ (15 mL). The layers were separated out and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, concentrated, and purified on a silica gel column (EtOAc/light petroleum, 1:19) to yield the saturated ester **43** (1.93 g, 98%) as a colorless liquid. $[\alpha]_D^{25} = +4.2$ (*c* 0.9, $CHCl_3$); IR ($CHCl_3$): 3019, 2930, 1726, 1462, 1215, 755, 669; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.02 (s, 6H), 0.82 (d, 3H, $J$ = 6.6 Hz), 0.87 (s, 9H), 0.92 (d, 3H, $J$ = 6.8 Hz), 1.04 (m, 1H), 1.24 (t, 3H, $J$ = 7.1 Hz), 1.32–1.50 (m, 5H), 1.69–1.83 (m, 2H), 2.18–2.38 (m, 2H), 3.18–3.33 (m, 2H), 3.49 (m, 1H), 4.10 (q, 2H, $J$ = 7.1 Hz), 4.48 (s, 2H), 7.28–7.33 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ −4.4, −4.1, 13.8, 14.3, 17.2, 18.2, 26.0 (× 3), 28.2, 29.8, 30.9, 32.7, 33.7, 37.0, 60.1, 73.0, 75.7, 75.8, 127.4 (× 2), 127.5, 128.3 (× 2), 138.7, 173.8; EIMS: $(M+Na)^+$ calcd for $C_{26}H_{46}NaO_4Si^+$ 473.30. Found: 473.43; Anal. Calcd for $C_{26}H_{46}O_4Si$: C, 69.28; H, 10.29. Found: C, 69.13; H, 10.09.

Next, $LiAlH_4$ (0.23 g, 6.0 mmol) was added to a stirred solution of ester **43** (1.8 g, 4.0 mmol) in THF (25 mL) at 0 °C. After 1 h, the reaction was quenched with a saturated solution of $Na_2SO_4$ and filtered. The residue was washed with EtOAc (3 × 25 mL) and the filtrate was dried (over $Na_2SO_4$) and concentrated. The crude residue was purified on a silica gel column using EtOAc/light petroleum (1:4) to provide **6** (1.45 g, 89%) as a colorless oil. $[\alpha]_D^{25} = +4.3$ (*c* 1.3, $CHCl_3$); IR ($CHCl_3$): 3379, 3019, 2930, 1604, 1215, 1075, 757, 668; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.02 (s, 6H), 0.82 (d, 3H, $J$ = 6.7 Hz), 0.87 (s, 9H), 0.92 (d, 3H, $J$ = 6.8 Hz), 1.04–1.44 (m, 8H), 1.58–1.74 (m, 3H), 3.24 (dd, 1H, $J$ = 6.5, 9.0 Hz), 3.30 (dd, 1H, $J$ = 6.2, 9.0 Hz), 3.48 (m, 1H), 3.61 (t, 2H, $J$ = 6.6 Hz), 4.49 (s, 2H), 7.28–7.34 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ −4.5, −4.2, 14.3, 17.2, 18.1, 25.9 (× 3), 28.5, 29.8, 30.7, 30.95, 33.7, 37.4, 63.3, 73.0, 75.9 (× 2), 127.4 (× 2), 127.5, 128.3 (× 2), 138.7; EIMS: $(M+Na)^+$ calcd for $C_{24}H_{44}NaO_3Si^+$ 431.29. Found: 431.36; Anal. Calcd for $C_{24}H_{44}O_3Si$: C, 70.53; H, 10.85. Found: C, 70.37; H, 10.66.

#### 4.1.28. 5-((4*R*,5*R*,8*S*,)-9-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-4,8-dimethylnonylsulfonyl)-1-phenyl-1*H*-tetrazole 44

At first, DIAD (1.0 mL, 5.1 mmol) was added to a solution of **6** (1.3 g, 3.2 mmol), triphenylphosphine (1.5 g, 5.7 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (1.14 g, 6.4 mmol) in THF (20 mL) at 0 °C. After stirring for 1 h, the reaction was quenched with brine and the aqueous layer was extracted with EtOAc (2 × 20 mL), dried (over $Na_2SO_4$), and concentrated. Purification by flash silica gel column chromatography (EtOAc/light petroleum, 1:19) yielded a sulfide (1.6 g, 89%) as a clear oil. The above intermediate sulfide (1.6 g, 2.8 mmol) was dissolved in EtOH (20 mL) and cooled to 0 °C. In a separate flask were mixed 30% $H_2O_2$ (3.2 mL, 28.0 mmol) and ammonium molybdate tetrahydrate (0.348 g, 0.28 mmol), producing a bright yellow solution that was added via syringe to the reaction flask. The reaction was stirred overnight and then quenched by the addition of water (10 mL), and extracted with EtOAc (2 × 20 mL). The organic layers were dried over $Na_2SO_4$ and concentrated to afford a residue which was purified on a flash silica gel column eluting with EtOAc/light petroleum, (1:19) to furnish sulfone **44** (1.55 g, 92%) as a colorless liquid. $[\alpha]_D^{25} = +1.5$ (*c* 1.2, $CHCl_3$); IR ($CHCl_3$): 2929, 1596, 1497, 1344, 1152, 1045, 836, 761; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.02 (s, 6H), 0.82–0.86 (m, 12H), 0.92 (d, 3H, $J$ = 6.9 Hz), 1.03 (m, 1H), 1.25–1.48 (m, 6H), 1.63–1.76 (m, 2H), 1.95 (m, 1H), 3.19–3.32 (m, 2H), 3.49 (m, 1H), 3.68 (t, 2H, $J$ = 7.8 Hz), 4.48 (s, 2H), 7.30 (m, 5H), 7.59–7.71 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ −4.4, −4.1, 13.9, 17.2, 18.1, 20.4, 25.9 (× 3), 29.9, 30.7, 31.3, 33.7, 37.2, 56.2, 72.99, 75.5, 75.8, 125.0 (× 2), 127.4 (× 2), 127.5, 128.3 (× 2), 129.7 (× 2), 131.3, 133.1, 138.7, 153.5; EIMS: $(M+Na)^+$ calcd for $C_{31}H_{48}N_4O_4NaSSi^+$ 623.30. Found: 623.39; Anal. Calcd for $C_{31}H_{48}N_4O_4SSi$: C, 61.96; H, 8.05; N, 9.32. Found: C, 61.82; H, 7.97; N, 9.16.

#### 4.1.29. ((2*S*,5*R*,6*R*,*E*)-1-(Benzyloxy)-10-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,6-dimethyldec-9-en-5-yloxy)(*tert*-butyl)dimethylsilane 45

To a solution of the sulfone **44** (0.5 g, 0.83 mmol) in 1,2-dimethoxy ethane (20 mL) at −60 °C, was added KHMDS (2.5 mL, 0.5 M in toluene, 1.25 mmol). The yellow solution was then stirred for 30 min after which the aldehyde **27** (0.22 g, 1.7 mmol) in DME (6 mL) was introduced slowly via a syringe and stirred at −60 °C for 2 h. The reaction was warmed to 0 °C and then quenched with a saturated solution of $NH_4Cl$ (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated to a residue. Purification on flash silica gel column using EtOAc/light petroleum, (1:49) as eluent, afforded Julia product **45** (0.344 g, 82%) as a colorless liquid. $[\alpha]_D^{25} = +17.9$ (*c* 2.2, $CHCl_3$); IR ($CHCl_3$): 2929, 1591, 1455, 1379,1252, 1061, 836, 773, 697; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.00 (s, 3H), 0.01 (s, 3H), 0.79 (d, 3H, $J$ = 6.7 Hz), 0.86 (s, 9H), 0.92 (d, 3H, $J$ = 6.8 Hz), 1.00

(m, 1H), 1.16 (m, 1H), 1.37 (s, 3H), 1.41 (s, 3H), 1.43–1.52 (m, 4H), 1.71 (m, 1H), 1.93–2.01 (m, 2H), 2.08 (m, 1H), 3.23 (dd, 1H, $J$ = 6.6, 9.0 Hz), 3.30 (dd, 1H, $J$ = 6.2, 9.0 Hz), 3.48 (m, 1H), 3.53 (t, 1H, $J$ = 8.0 Hz), 4.04 (dd, 1H, $J$ = 6.1, 8.0 Hz), 4.45 (m, 1H), 4.49 (s, 2H), 5.41 (dd, 1H, $J$ = 8.0, 15.3 Hz), 5.76 (dt, 1H, $J$ = 6.8, 15.3 Hz), 7.32–7.37 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ −4.5, −4.2, 14.1, 17.2, 18.1, 25.9 (× 3), 26.7, 29.9, 30.3, 30.7, 31.8 (× 2), 33.7, 37.1, 69.5, 72.97, 75.8, 75.9, 77.4, 108.97, 127.0, 127.4, 127.5 (× 2), 128.3 (× 2), 136.3, 138.8; EIMS: $(M+Na)^+$ calcd for $C_{30}H_{52}NaO_4Si^+$ 527.35. Found: 527.47; Anal. Calcd for $C_{30}H_{52}O_4Si$: C, 71.38; H, 10.38. Found: C, 71.14; H, 10.22.

#### 4.1.30. (2*S*,7*R*,8*R*,11*S*,*E*)-12-(Benzyloxy)-8-(*tert*-butyldimethylsilyloxy)-7,11-dimethyldodec-3-ene-1,2-diol 46

A solution of **45** (0.65 g, 1.3 mmol) in acetonitrile (20 mL) was treated with $Zn(NO_3)_2.6H_2O$ (7.6 g, 25.8 mmol) and heated to 50 °C. After 6 h (TLC showed complete disappearance of starting material), the reaction was quenched with a saturated solution of $NaHCO_3$ and extracted with EtOAc (3 × 20 mL). The organic layer was dried (over $Na_2SO_4$), concentrated and purified on a silica gel column (EtOAc/light petroleum, 3:7) giving diol **46** (0.44 g, 74%) as a colorless liquid. $[\alpha]_D^{25} = +11.2$ ($c$ 1.0, $CHCl_3$); IR ($CHCl_3$): 3369, 2928, 1602, 1454, 1384, 1252, 1114, 835, 772; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 0.00 (s, 3H), 0.01 (s, 3H), 0.80 (d, 3H, $J$ = 6.6 Hz), 0.86 (s, 9H), 0.92 (d, 3H, $J$ = 6.8 Hz), 1.01 (m, 1H), 1.15 (m, 1H), 1.21–1.33 (m, 3H), 1.45–1.52 (m, 4H), 1.70 (m, 1H), 1.98 (m, 1H), 2.08 (m, 1H), 3.22–3.31 (m, 2H), 3.44–3.48 (m, 2H), 3.60 (m, 1H), 4.17 (m, 1H), 4.49 (s, 2H), 5.43 (dd, 1H, $J$ = 6.6, 15.5 Hz), 5.74 (dt, 1H, $J$ = 6.7, 15.5 Hz), 7.28–7.33 (m, 5H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ −4.4, −4.1, 14.1, 17.1, 18.2, 25.9 (× 3), 29.8, 30.4, 30.8, 31.99, 33.6, 36.8, 66.6, 73.0, 73.2, 75.7, 76.0, 127.4 (× 2), 127.5, 128.3 (× 2), 128.4, 134.5, 138.8; EIMS: $(M+Na)^+$ calcd for $C_{27}H_{48}NaO_4Si^+$ 487.32. Found: 487.42; Anal. Calcd for $C_{27}H_{48}O_4Si$: C, 69.78; H, 10.41. Found: C, 69.61; H, 10.22.

#### 4.1.31. (2*S*,7*R*,8*R*,11*S*,*E*)-8-(*tert*-Butyldimethylsilyloxy)-7,11-dimethyldodec-3-ene-1,2,12-triol 47

To a vigorously stirred solution of ammonia (10 mL) at −78 °C, small pieces of lithium (0.047 g, 6.7 mmol) were added and stirred for 5 min until the deep blue color appeared. After stirring for 30 min at −78 °C, diol **46** (0.31 g, 0.67 mmol) in THF (10 mL) was added dropwise and stirred for another 1 h, and then quenched with solid $NH_4Cl$ until the blue color disappeared. Ammonia was allowed to evaporate completely and the residue was diluted with $H_2O$ (10 mL) extracted with EtOAc (2 × 20 mL). The combined extracts were dried over $Na_2SO_4$, concentrated and purified on silica gel column using EtOAc/light petroleum (3:1) as eluent to produce triol **47** (0.195 g, 78%) as a colorless liquid. $[\alpha]_D^{25} = +3.8$ ($c$ 1.2, $CHCl_3$); IR ($CHCl_3$): 3370, 2928, 1619, 1461, 1383, 1252, 1039, 835, 772; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.01 (s, 3H), 0.02 (s, 3H), 0.80 (d, 3H, $J$ = 6.7 Hz), 0.87 (s, 9H), 0.89 (d, 3H, $J$ = 6.8 Hz), 0.99 (m, 1H), 1.16 (m, 1H), 1.36 (m, 1H), 1.44–1.55 (m, 5H), 1.98–2.11 (m, 2H), 2.20 (br s, 3H), 3.42–3.50 (m, 4H), 3.62 (m, 1H), 4.18 (m, 1H), 5.44 (dd, 1H, $J$ = 6.7, 15.5 Hz), 5.73 (dt, 1H, $J$ = 6.9, 15.5 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ −4.5, −4.1, 13.9, 16.4, 18.1, 25.9 (× 3), 28.9, 30.1, 30.9, 31.98, 35.8, 35.9, 66.5, 68.4, 73.1, 75.2, 128.6, 134.3; EIMS: $(M+Na)^+$ calcd for $C_{20}H_{42}NaO_4Si^+$ 397.27. Found: 397.35; Anal. Calcd for $C_{20}H_{42}O_4Si$: C, 64.12; H, 11.30. Found: C, 64.34; H, 11.15.

#### 4.1.32. (2*S*,5*R*,6*R*,11*S*,*E*)-12-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2,6-dimethyldodec-9-ene-1,11-diol 48

A solution of triol **47** (0.16 g, 0.43 mmol) and $Bu_2SnO$ (0.16 g, 0.64 mmol) in toluene (20 mL) was refluxed for 4 h using a Dean-Stark apparatus. After cooling it to room temperature, benzyl bromide (0.08 mL, 0.64 mmol) and TBAI (catalytic) were added and refluxed for 2 h. After completion (monitored by TLC), the reaction was diluted with $CH_2Cl_2$ (15 mL) and washed with 10% $NaHCO_3$ solution, water, brine, dried (over $Na_2SO_4$) and then concentrated. Purification of the residue by silica gel column chromatography using EtOAc and light petroleum (3:7) provided **48** (0.166 g, 84%) as a clear liquid. $[\alpha]_D^{25} = +10.8$ ($c$ 1.3, $CHCl_3$); IR ($CHCl_3$): 3392, 2928, 1619, 1384, 1252, 1045, 835, 772; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.01 (s, 3H), 0.02 (s, 3H), 0.80 (d, 3H, $J$ = 6.7 Hz), 0.87 (s, 9H), 0.89 (d, 3H, $J$ = 6.8 Hz), 1.00 (m, 1H), 1.16 (m, 1H), 1.32–1.45 (m, 5H), 1.48–1.55 (m, 3H), 1.98–2.07 (m, 2H), 3.33–3.44 (m, 3H), 3.48–3.50 (m, 2H), 4.29 (m, 1H), 4.56 (s, 2H), 5.42 (dd, 1H, $J$ = 6.6, 15.5 Hz), 5.74 (dt, 1H, $J$ = 6.9, 15.5 Hz), 7.29–7.35 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ −4.5, −4.2, 14.0, 16.5, 18.1, 25.9 (× 3), 29.1, 30.3, 30.8, 31.9, 35.9, 36.5, 68.3, 71.4, 73.3, 74.4, 75.5, 127.8 (× 2), 127.9, 128.1 (× 2), 128.5, 134.1, 137.9; EIMS: $(M+Na)^+$ calcd for $C_{27}H_{48}NaO_4Si^+$ 487.32. Found: 487.43; Anal. Calcd for $C_{27}H_{48}O_4Si$: C, 69.78; H, 10.41. Found: 69.57; H, 10.24.

#### 4.1.33. (2*S*,5*R*,6*R*,11*S*,*E*)-12-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-11-hydroxy-2,6-dimethyldodec-9-enoic acid 5

At first, $PhI(OAc)_2$ (0.115 g, 0.36 mmol) was added to a solution of diol **48** (0.11 g, 0.24 mmol) and TEMPO (0.004 g, 0.024 mmol) in $CH_2Cl_2$ (3 mL). The reaction was stirred for 3 h at room temperature, then quenched with a 10% solution of $Na_2S_2O_3$ (5 mL), and extracted with $CH_2Cl_2$ (3 × 10 mL). The organic layer was washed with aqueous $NaHCO_3$, water and dried over $Na_2SO_4$. Concentration and purification by silica gel column chromatography (EtOAc and light petroleum, 1:4) afforded an aldehyde (0.1 g, 92%) as a clear oil. Next, $NaClO_2$ (0.078 g, 0.87 mmol) was added to a solution of the above intermediate aldehyde (0.1 g, 0.22 mmol), 2-methyl-2-butene (0.023 mL, 0.22 mmol) and $NaH_2PO_4$ (0.1 g, 0.87 mmol) in $t$-butanol and water (3:1), (4 mL) at 0 °C. After stirring for 3 h, the reaction was diluted with water (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried (over $Na_2SO_4$), concentrated and purified by flash silica gel chromatography using EtOAc and light petroleum, (2:3) as eluent, to furnish the seco acid **5** (0.09 g, 87%) as a colorless liquid. $[\alpha]_D^{25} = +20.0$ ($c$ 1.1, $CHCl_3$); IR ($CHCl_3$): 3393, 2928, 1708, 1619, 1462, 1384, 1252, 1070, 835, 773; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.00 (s, 3H), 0.02 (s, 3H), 0.80 (d, 3H, $J$ = 6.7 Hz), 0.86 (s, 9H), 1.17 (d, 3H, $J$ = 7.1 Hz), 1.27–1.46 (m, 6H), 1.49–1.54 (m, 2H), 1.69 (m, 1H), 1.93–2.10 (m, 2H), 2.42 (m, 1H), 3.37 (m, 1H), 3.48–3.51 (m, 2H), 4.29 (m, 1H), 4.56 (s, 2H), 5.42 (dd, 1H, $J$ = 6.7, 15.5 Hz), 5.74 (dt, 1H, $J$ = 6.7, 15.5 Hz), 7.31–7.35 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ −4.4, −4.3, 14.4, 16.9, 18.1, 22.7, 25.9 (× 3), 30.3, 30.8, 31.7, 37.0, 39.3, 71.4, 73.3, 74.3, 75.3, 127.8 (× 2), 127.9, 128.0 (× 2), 128.5, 134.1, 137.9, 181.6; EIMS: $(M+Na)^+$ calcd for $C_{27}H_{46}NaO_5Si^+$ 501.30. Found: 501.342; Anal. Calcd for $C_{27}H_{46}O_5Si$: C, 67.74; H, 9.68. Found: C, 67.56; H, 9.53.

#### 4.1.34. Compounds 3 and 3a

To a solution of the seco acid **5** (0.032 g, 0.07 mmol) in THF (5 mL), $i$-$Pr_2NEt$ (0.5 mL, 2.7 mmol) and 2,4,6-trichlorobenzoyl chloride (0.21 mL, 1.33 mmol) were added and stirred overnight at room temperature. Next, it was diluted with benzene (15 mL) and added slowly to a solution of DMAP (0.4 g, 3.33 mmol) in benzene (70 mL) at 80 °C by syringe pump over a period of 10 h. The mixture was stirred for another 1 h and then quenched by the addition of a saturated $NaHCO_3$ solution, extracted with EtOAc (2 × 20 mL), dried over $Na_2SO_4$ and concentrated. It was purified on a flash silica gel column eluting with EtOAc/light petroleum

(1:49) to yield an inseparable mixture of products **3** and **3a** (1:1) (0.017 g, 55% combined yield) as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.01 (s, 6H), 0.84 (d, 3H, $J$ = 6.7 Hz), 0.87 (s, 9H), 1.18 (d, 1.5H, $J$ = 6.9 Hz), 1.20 (d, 1.5H, $J$ = 6.9 Hz) 1.38–1.53 (m, 7H), 1.77 (m, 1H), 2.14 (m, 1H), 2.28 (m, 1H), 3.28 (m, 1H), 3.53 (m, 1H), 3.59 (m, 1H), 4.58 (ABq, 2H, $J$ = 12.3 Hz), 5.44–5.55 (m, 2H), 5.91 (ddd, 1H, $J$ = 6.2, 9.4, 15.3 Hz), 7.30–7.36 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): −4.9, −4.4, 17.5, 17.9/18.2, 20.1/20.9, 25.9 (× 3), 28.3, 29.7/30.1, 30.3, 33.2, 34.0, 41.6/46.4, 70.6, 72.4, 73.1, 74.0, 127.4, 127.5, 127.6 (× 2), 128.2, 128.4, 138.1, 138.3, 175.5; EIMS: $(M+Na)^+$ calcd for $C_{27}H_{44}NaO_4Si$ 483.29. Found: 483.24; Anal. Calcd for $C_{27}H_{44}O_4Si$: C, 70.39; H, 9.63. Found: C, 70.44; H, 9.56.

### 4.1.35. (3*S*,6*R*,7*R*,12*S*,*E*)-12-(Benzyloxymethyl)-6-(*tert*-butyldimethylsilyloxy)-3,7-dimethyloxacyclododec-10-en-2-one 3

Ethoxyacetylene (0.03 mL, 40% in hexane, 0.14 mmol) was added to a solution of the seco acid **5** (0.045 g, 0.094 mmol) and [{$RuCl_2$(*p*-cymene)}$_2$] (1.2 mg, 0.0018 mmol) in toluene (8 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for another 30 min. The dark red solution was then filtered through a pad of silica gel, and the silica gel was washed with dry $Et_2O$ (60 mL) under a nitrogen atmosphere. The filtrate was then concentrated under reduced pressure. The crude ethoxyvinyl ester was dissolved in toluene (5 mL) and added to a solution of CSA (2.2 mg, 0.0094 mmol) in toluene (20 mL) and heated to 50 °C for 2 h. The mixture was filtered through a pad of silica gel and concentrated to afford a residue which was purified by flash silica gel chromatography eluting with EtOAc and light petroleum, (1:49) to give lactone **3** (0.018 g, 42%) as a colorless liquid. $[\alpha]_D^{25} = +29.0$ (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): 2929, 1722, 1598, 1384, 1255, 1115, 1026, 772, 618; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 0.01 (s, 6H), 0.85 (d, 3H, $J$ = 6.7 Hz), 0.87 (s, 9H), 1.18 (d, 3H, $J$ = 6.9 Hz), 1.36–1.42 (m, 2H), 1.49–1.57 (m, 5H), 1.75 (m, 1H), 2.14 (m, 1H), 2.26 (m, 1H), 3.28 (m, 1H), 3.57 (dd, 1H, $J$ = 4.4, 10.8 Hz), 3.61 (dd, 1H, $J$ = 6.7, 10.8 Hz), 4.58 (ABq, 2H, $J$ = 12.4 Hz), 5.44–5.53 (m, 2H), 5.91 (ddd, 1H, $J$ = 6.2, 9.4, 15.5 Hz), 7.28–7.35 (m, 5H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ −4.9, −4.4, 17.5, 17.8, 18.2, 26.0 (× 3), 28.4, 30.2, 30.4, 33.3, 34.1, 41.7, 70.7, 72.4, 73.2, 74.0, 127.4 (× 2), 127.5, 127.6 (× 2), 128.4, 138.2, 138.3, 175.4; EIMS: $(M+Na)^+$ calcd for $C_{27}H_{44}NaO_4Si^+$ 483.29. Found: 483.24; Anal. Calcd for $C_{27}H_{44}O_4Si$: C, 70.39; H, 9.63. Found: C, 70.34; H, 9.55.

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