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Studies directed towards the total synthesis of koshikalide: stereoselective synthesis of the macrocyclic core

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ABSTRACT

The stereoselective synthesis of the macrolactone core of the natural product koshikalide is described. Starting with readily available 1,4-butanediol and malic acid as synthons, our synthetic strategy involved the reiterative application of Gilman's reaction, Swern oxidation and Sharpless asymmetric epoxidation to establish the required stereocentres. Other key steps in the synthesis include Negishi cross coupling and Horner–Wadsworth–Emmons (HWE) reactions for construction of the main fragments. The 14-membered lactone ring was prepared by a selective Mitsunobu macrolactonization approach.

1. Introduction

Marine cyanobacterium has been recognized as an important source of pharmacologically unique bioactive natural products with novel architectures and functionalities. Recently, Iwasaki et al. reported the isolation of a novel macrolide kloshikalide **1**,[1a] from the marine cyanobacterium *Lyngbya* sp. The gross structure and relative stereochemistry were determined by extensive NMR studies, which clearly indicated that koshikalide **1** is a 14-membered macrolide containing two unusually *Z*-configured disubstituted olefins with methyl groups at the C_3 and C_6 positions. Koshikalide **1** was found to be weakly cytotoxic against $HeLaS_3$ cells, with an IC_{50} value of 42 μg/mL. To date, no total synthesis of this compound has been reported. The presence of two stereogenic centres and a network of diverse and distributed functionalities on its novel framework, together with its potential bioactivity, make koshikalide **1** a challenging and attractive synthetic objective (see Fig. 1).

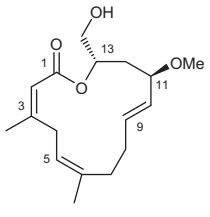

Figure 1. Structure of koshikalide **1**.

Strategically, the most challenging problem is the construction of the lactone ring system as well as the structural moiety possessing the asymmetric centres bearing a methoxy group and *cis*-oriented methyl groups. Our group has recently reported on the facile construction of functionalized lactone rings in the total synthesis of macrolides.[1b–d] In continuation of our focus on the synthesis of bioactive macrolides, we herein report our approach towards the stereoselective construction of the macrolactone core segment of koshikalide **1**.

2. Results and discussion

The retrosynthetic analysis of **1** is outlined in Scheme 1. As indicated, our initial disconnections of the target molecule involved a cleavage of the double bond at C_9–C_{10} as well as the ester linkage to give **3** and **4**. The requisite olefin fragment **3**, could, in turn be accessed from L-malic acid **5** through Wittig and Sharpless asymmetric reactions to install the required stereochemistry and opening of the epoxide with Zn in ethanol under refluxing conditions. On the other hand, the acid fragment **4** could be prepared through Cu mediated cross coupling between **6** and **7**. Fragment **6** could be elaborated by starting from readily available 1,4-butane diol **8** by selective functional group manipulations.

2.1. Synthesis of fragment 3

The preparation of fragment **3** was straightforward and accomplished from readily available L-malic acid **5**. As shown in Scheme 2, the trihydroxy derivative of L-malic acid **9**[2] was converted into the corresponding acetonide **10**,[3] followed by Swern oxidation[4] and then Wittig olefination of the resulting aldehyde with $Ph_3P{=}CHCO_2Et$ to furnish the unsaturated ester **11**[5] in 92% overall

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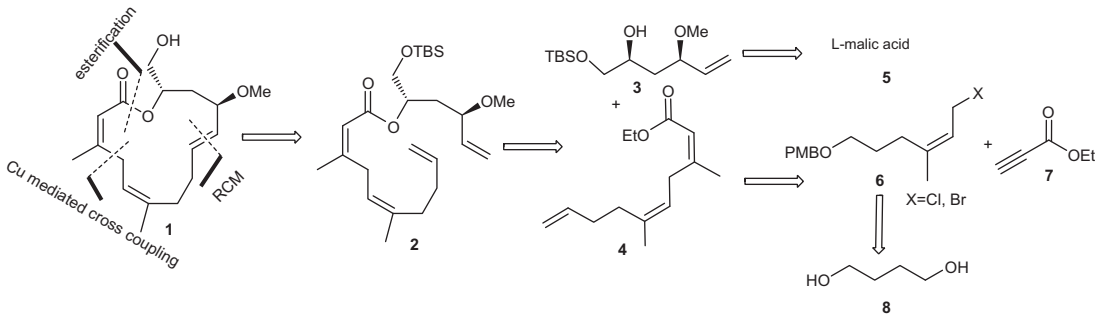
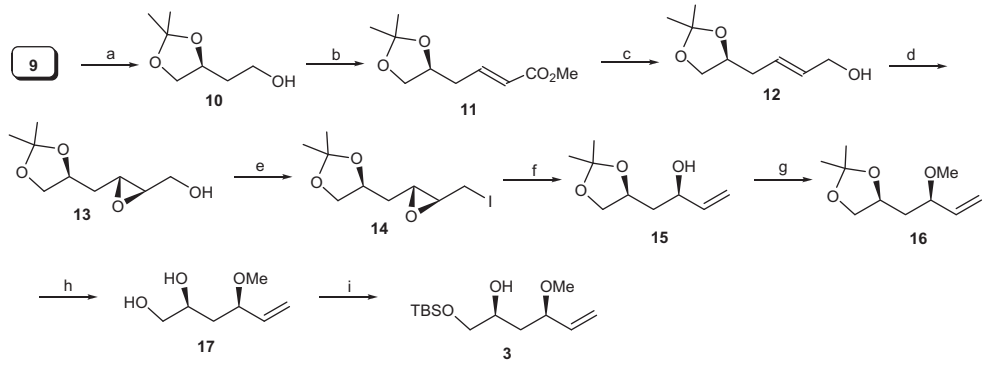


Scheme 1. Retrosynthetic analysis of koshikalide **1**.



Scheme 2. Reagents and conditions: (a) 2,2 DMP, PTSA, dry DCM, 0 °C–rt, 4 h, 98%; (b) (i) $(COCl)_2$, dimethyl sulfoxide (DMSO), Et_3N, CH_2Cl_2, −78 °C, 1 h; (ii) $Ph_3P{=}CHCO_2Et$, C_6H_6, 0 °C–rt, 12 h, 91% for two steps; (c) diisobutylaluminum hydride (DIBAL-H), CH_2Cl_2, −15 °C, 30 min, 95%; (d) $Ti(OiPr)_4$, (−)-DET, 4 Å MS and *t*-BuOOH, dry DCM, −20 °C, 12 h, 96%; (e) TPP, I_2, imidazole, dry DCM, 0 °C–rt, 4 h, 96%; (f) Zn, NaI, MeOH, reflux, 8 h, 96%; (g) NaH, MeI, Dry THF, 0 °C–rt, 2 h, 98%; (h) (−)-camphor-10-sulfonic acid (CSA), MeOH, 0 °C–rt, 4 h, 94%; (i) TBSCl, imidazole, dry DCM, 0 °C–rt, 92%.

yield (three steps). Reduction of ester **11** with DIBAL-H in dichloromethane at −15 °C furnished the allylic alcohol **12**,[6] which was then subjected to a Sharpless asymmetric epoxidation[7] reaction with $Ti(OiPr)_4$, (−)-DET and *t*-BuOOH to obtain the (*R*,*R*)-epoxy alcohol **13** in 96% yield with excellent 97% de (determined by chiral HPLC). The primary hydroxyl group present in **13** was converted into its corresponding iodide with TPP and I_2 to give **14**[8] in 89% yield. The opening of the epoxide ring of **14** with Zn in ethanol under refluxing conditions yielded the secondary allylic alcohol **15**,[9] and subsequent methylation using MeI/NaH[10] afforded **16** in 98% yield. Finally, removal of the acetonide protecting group with (−)-camphor-10-sulfonic acid,[11] and selective protection of the resulting diol furnished the required product **3**[12] in 92% yield.

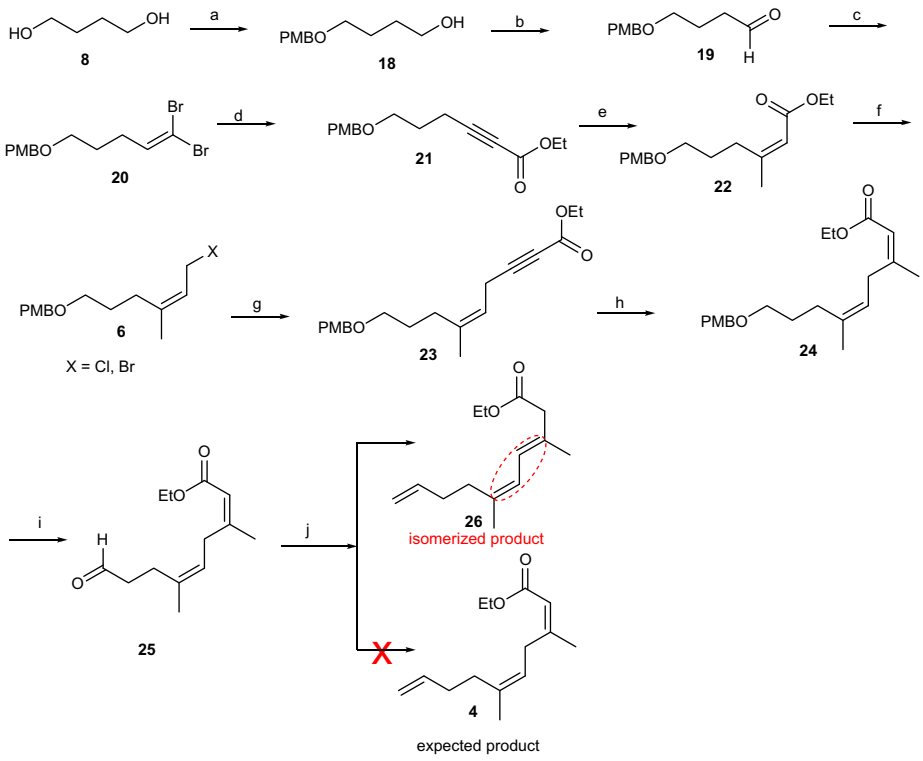
2.2. Synthesis of the C_1–C_{10} fragment 4

The synthesis of **4** started from the readily available 1,4-butanediol **8** (Scheme 3), which was selectively protected as a PMB ether using PMBBr, NaH and a catalytic amount of TBAI in dry DMF to afford **18**[13] in 89% yield. The resultant alcohol **18** was oxidized under Swern conditions to give aldehyde **19**.[4] Next, the Corey–Fuchs reaction of aldehyde **19** yielded the dibromo olefin compound **20**[14] in 82% yield, which was then treated with *n*-BuLi and ethylchloroformate at −78 °C to give ester **21**.[15] The required (*Z*)-geometry of the allylic bromide **6** was achieved by the conjugate addition of Me_2CuLi to hexynoate **21**, which exclusively gave the (*Z*)-hexenoate **22**[16] in 96% yield. Subsequent reduction with DIBAL-H[17] followed by bromination using Corey's procedure afforded the desired bromide **6**[18] in 86% yield (overall yield 92% over two steps). Bromide **6** was treated with ethyl propiolate **7** by using a CuI-mediated cross-coupling reaction to give the coupled product **23**[19] in 89% yield, which was again subjected to Gillman's reaction using Me_2CuLi to afford **24**[16] in 96% yield. Deprotection of the PMB ether[20] with DDQ, followed by Dess–Martin oxidation, gave aldehyde **25**[21] in 98% yield.

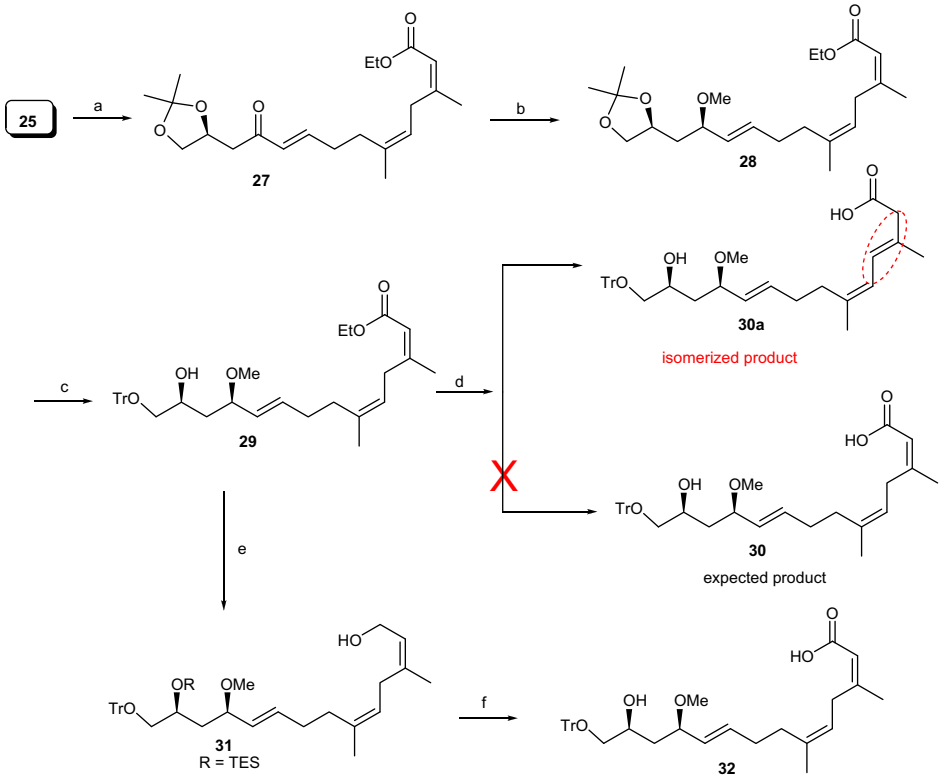
At this stage, we planned for a Wittig olefination reaction[22] with $Ph_3P^+CH_3I^-$ under basic conditions to afford fragment **4**. However, the reaction yielded the rearranged product **26**, in which the double bond was isomerized from C_2–C_3 to C_3–C_4. Several tactical operations on **25** using C_1-Wittig reagents under various basic conditions failed to give the desired product **4** and led to the formation of the isomerized product **26** in 82% yield.

2.3. Synthesis of the seco acid

Originally, we planned to prepare **1** by esterification of **3** and **4**, followed by elaboration of the resulting product according to the established route via RCM (Scheme 1). Despite considerable experimentation, compound **4** was not obtained due to isomerization of the *Z*-double bond. In view of these discouraging results, we decided to revise our synthetic approach to prepare the basic macrocyclic framework by elaborating aldehyde **25** into *seco*-acid **32** and then making the target compound (Scheme 4). To this end, aldehyde **25** was subjected to a Horner–Wadsworth–Emmons (HWE) reaction with a β-ketophosphonate[23] using $Ba(OH)_2{\cdot}8H_2O$, THF/H_2O (40:1) to afford **27**[24] in 86% yield. Subsequent Corey–Bakshi–Shibata (CBS) reduction of **27**[25] gave the secondary alcohol in 85% yield with excellent diastereoselectivity (dr >96:4, determined by chiral HPLC). The resultant alcohol was O-methylated using methyl triflate and a proton sponge to afford **28** in 98% yield.[26] Methylation under basic conditions such as NaH/MeI yielded the double bond isomerization product. Deprotection of the acetonide group[27] in **28** with CSA in methanol, followed by selective protection of the primary alcohol with TrCl gave **29**[28] in 94% yield.



Scheme 3. Reagents and conditions: (a) PMBBr, NaH, TBAI, dry DMF, 0 °C–rt, 12 h, 89%; (b) $(COCl)_2$, dimethyl sulfoxide (DMSO), Et_3N, CH_2Cl_2, −78 °C, 1 h; (c) CBr_4, TPP, CH_2Cl_2, −15 °C–rt, 1 h, 82%; (d) *n*-BuLi, ethyl chloroformate, dry THF, 2 h, −78 °C–rt, 92%; (e) CuI, MeLi, dry THF, pH 7 buffer, −78 °C, 30 min, 96%; (f) (i) diisobutylaluminum hydride (DIBAL-H), CH_2Cl_2, −15 °C, 30 min, 95%; (ii) LiX (X = Cl, Br), *s*-collidine, methanesulfonyl chloride, dry DMF, 0 °C, 2 h, 86%; (g) **7**, CuI, NaI, K_2CO_3, *N*,*N*-dimethylformamide (dry DMF), rt, 4 h, 89%; (h) CuI, MeLi, dry THF, pH 7 buffer, −78 °C, 30 min, 96%; (i) (i) DDQ, pH 7 buffer, DCM, 0 °C–rt, 1 h, 89%; ii. DMP, $NaHCO_3$, 0 °C–rt, 98%; (j) *t*-BuO^-K^+, $Ph_3P^+CH_3I^-$, dry THF, −15 °C–rt, 2 h, 82%.



Scheme 4. Reagents and conditions: (a) $Ba(OH)_2{\cdot}8H_2O$, THF/H_2O (40:1), 89%; (b) (i) (*S*)-CBS, $BH_3{\cdot}DMS$, dry THF, –78 °C–rt, 2 h, 85%; (ii) Me_3OBF_4/proton sponge, dry DCM, 30 min, 98%; (c) (i) (−)-camphor-10-sulfonic acid (CSA), MeOH, 0 °C–rt, 4 h, 92%; (ii) TrCl, pyridine, dry DCM, 0 °C–rt, 4 h, 89%; (d) LiOH, $THF/MeOH/H_2O$ (2:2:1), 2 h, 98%; (e) (i) TESCl, imidazole, dry DCM, 0 °C–rt, 92%; (ii) diisobutylaluminum hydride (DIBAL-H), CH_2Cl_2, −15 °C, 30 min, 93%; (f) (i) DMP, $NaHCO_3$, 0 °C–rt, 1 h, 98%; (ii) 2-methyl-2-butane(M2B), $NaClO_2$, *tert*-butanol/H_2O, 89%; (iii) TBAF, 0 °C–rt, 2 h, 89%.

Saponification[29] of **29** using standard protocols, KOH/THF/MeOH, LiOH, etc., again led to the formation of isomerized product **30a**, instead of the expected compound **30**. Several efforts to saponify **29** were found to be unsuccessful even with mild methods and in all cases, the scrambled double bond product **30a** was observed as a major product (Scheme 4).

In order to overcome this hurdle, a five-step reaction sequence consisting of a protection and reduction/oxidation strategy was employed. Thus, the secondary hydroxyl group in **29** was protected as a TES[30] group and reduction with DIBAL-H yielded **31** in 93% yield. Sequential oxidations[30a] in **31** (Dess–Martin and Pinnick oxidation) followed by the removal of the TES group with TBAF[31] led to the required *seco*-acid **32** in 89% yield.

2.4. Synthesis of the lactone core

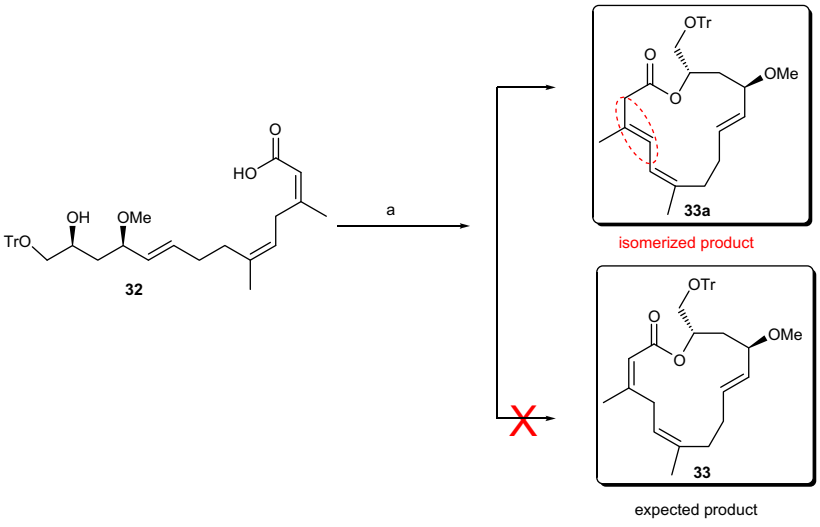
Having successfully accomplished the synthesis of *seco*-acid fragment **32** with the required stereocentres, we next focused our attention on obtaining the lactone core. The *seco*-acid **32** was subjected to Yamaguchi macrolactonization[32] using 2,4,6-trichlorobenzoyl chloride, Et_3N, and DMAP in toluene to afford the desired macrolactone **33**. However, the reaction yielded the double bond scrambled product **33a**, instead of required **33** and again turned out to be another failure due to the isomerization of the *Z*-double bond from C_2–C_3 to (*E*)-C_3–C_4. This isomerization was attributed to the deprotonation of the active methylene between the two unstable, strained Z-double bonds (Scheme 5).

At this point, we decided to investigate nonbasic macrolactonization using Mitsunobu reaction. In order to obtain the correct stereochemistry at C-13 after the Mitsunobu reaction, the corresponding β-ketophosphonate fragment **36**[33] was prepared from commercially available D-malic acid (Scheme 6), which was then converted into the corresponding diester with $BF_3{\cdot}Et_2O$, MeOH with 98% yield. This was then selectively mono reduced with $BH_3{\cdot}$DMS and $NaBH_4$(cat) in dry THF to give **34** in 89% yield, followed by mono protection of **34** with *n*-Bu_2SnO, PMBCl in toluene to afford **35** in 80% yield (Scheme 6).

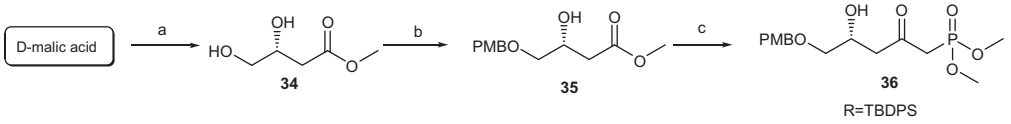
With compound **6** in hand, we designed our synthetic operations in a step wise fashion to implement the Mitsunobu macrolactonization. Thus, fragment **6** was subjected to Negishi cross coupling reaction[34] with (*Z*)-(4-((tetrahydro-2*H*-pyran-2-yl)zinc(II) bromide[34] in the presence of 2.5 mol % of [$Pd_2(dba_3)$] and tri-2-furylphosphine (10 mol %) to give **37** (⩾98% pure) in 82% yield (the *cis*-orientation of the double bond was determined by NOESY experiments). Deprotection of the PMB group in **37** followed by DMP oxidation provided the aldehyde in quantitative yield, which was further elaborated through Horner–Wadsworth–Emmons (HWE)[24] homologation with β-ketophosphonate **36**[33] to give **38** in 92% yield. Removal of the THP[35] deprotection in **38** followed by Dess–Martin oxidation led to an aldehyde, which was then transformed into the carboxylic acid **39** using standard Pinnick oxidation conditions.[30] Deprotection of the TBDPS group in **39** with TBAF furnished the required *seco*-acid **40** in 89% yield.[36] Finally, lactonization of this *seco*-acid **40** under Mitsunobu conditions[37] (DIAD, PPh_3, degassed PhH) yielded the core lactone moiety **41** in 56% yield (Scheme 7). The stereostructure of **41** was determined on the basis of a thorough analysis of its spectroscopic characteristics, particularly the COSY and NOE data (in the NOESY spectra, correlations between Me-3/H-2 and Me-6/H-5 were observed). All of the intermediate products were also well characterized using the NMR and mass spectra techniques.

3. Conclusion

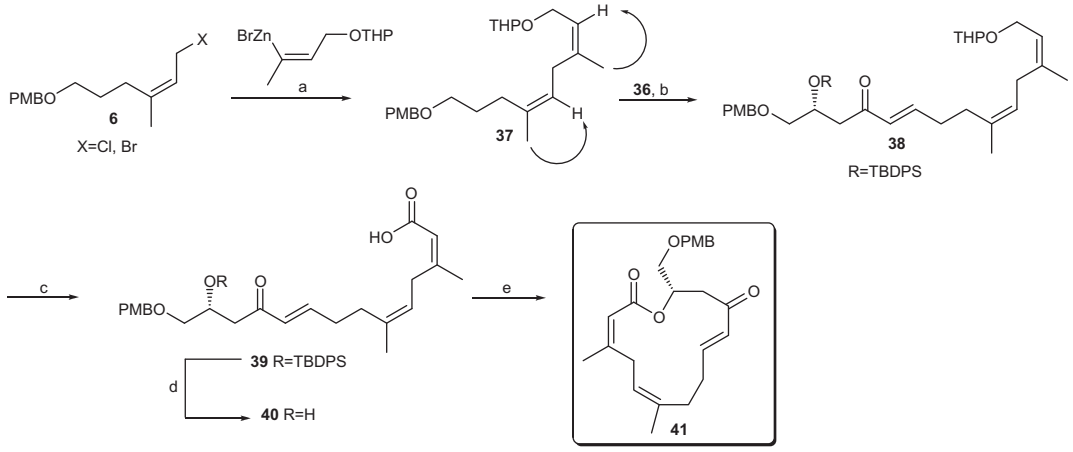
By utilizing high yielding chemical transformations, we have developed a stereoselective and convergent approach towards



Scheme 5. Reagents and conditions: (a) 2,4,6-Trichlorobenzoyl chloride, Et_3N, DMAP, dry toluene, 60 °C, 12 h, 58%.



Scheme 6. Reagents and conditions: (a) (i) $BF_3{\cdot}Et_2O$, MeOH 0 °C–rt, 12 h, 98%; (ii) $BH_3{\cdot}$DMS, $NaBH_4$ (cat) dry THF 89%; (b) *n*-Bu_2SnO, PMBCl, toluene 110 °C, 12 h, 80%; (c) (i) TBDPSCl, imidazole, dry DMF 0 °C–rt, 6 h, 96%; (ii) *n*-BuLi, dimethylphosphonate, dry THF, −78 °C, 1.5 h, 75%.



Scheme 7. Reagents and conditions: (a) [$Pd_2(dba_3)$], tri-2-furylphosphine (TFP), dry DMF, 0 °C–rt, 1 h, 82%; (b) (i) DDQ, pH 7 buffer, DCM, 0 °C–rt, 1 h, 87%; (ii) DMP, $NaHCO_3$, 0 °C–rt, 1 h, 98%; (iii) **36**, $Ba(OH)_2{\cdot}8H_2O$, THF/H_2O (40:1), 4 h, 92%; (c) (i) (−)-camphor-10-sulfonic acid (CSA), MeOH, 0 °C–rt, 4 h, 92%; (ii) DMP, $NaHCO_3$, 0 °C–rt, 1 h, 98%; (iii) 2-methyl-2-butane, $NaClO_2$, *tert*-butanol/H_2O, 89%; (d) TBAF, THF, 0 °C–rt, 6 h, 89%; (e) PPh_3, DIAD, Dry THF, 0 °C–rt, 12 h, 56%.

the synthesis of the macrolactone segment of koshikalide, a cytotoxic macrolide. Initial retrosynthetic analysis on **1** identified two key fragments **3** and **4**; while the former was assembled relatively easily, the latter presented considerable problems due to the migratory aptitude of the double bond, which necessitated a deviation for our model study. The preparation of the koshikalide core serves a dual purpose of providing an advanced intermediate towards the synthesis of koshikalide and an entry into an array of analogues through the attachment of various side chains at C_{14}.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded either in $CDCl_3$ or in MeOH-d_4 solvent on 300, 500 or 75 MHz spectrometer at ambient temperature. Chemical shifts δ is given in ppm, coupling constants J are in Hz. The chemical shifts are reported in ppm on a scale downfield from TMS as the internal standard and signal patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; br s, broad singlet. FTIR spectra were recorded as thin films on KBr or neat. Optical rotations were measured on a digital polarimeter using a 1 mL cell with a 1 dm path length. For low (MS) and high (HRMS) resolution, m/z ratios are reported as values in atomic mass units. All of the reagents and solvents were of reagent grade and used without further purification unless specified otherwise. Technical grade ethyl acetate and hexane used for column chromatography were distilled prior to use. Tetrahydrofuran (THF), when used as a solvent for the reactions was freshly distilled from sodium benzophenone ketyl. Column chromatography was carried out using silica gel (60–120 mesh and 100–200 mesh) packed in glass columns. $Ba(OH)_2{\cdot}8H_2O$ vacuum dried at 110–120 °C. Column chromatography was carried out using silica gel (60–120 mesh and 100–200 mesh) packed in glass columns. All reactions were performed under an atmosphere of nitrogen in flame or oven-dried glassware with magnetic stirring.

4.2. (*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl) ethanol 10

To stirred solution of triol **9** (2.0 g, 18.8 mmol) in dry DCM (30 mL), cooled to 0 °C were added 2,2-DMP (3.93 g, 37.7 mmol) and a catalytic amount of PTSA, then stirred for 4 h at rt. After completion of the reaction, it was quenched with sat. $NaHCO_3$ and the water layer extracted with DCM (2 times). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent gave a crude product, which was purified by column chromatography (2% MeOH in chloroform) to afford **10** (2.699 g, 98%) as a colourless oil. $[\alpha]_D^{25} = -1.6$ (c 1.5, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.32–4.19 (m, 1H), 4.08–4.01 (m, 1H), 3.76 (t, J = 6.9 Hz, 2H), 3.55 (t, J = 7.5 Hz, 1H), 1.82–1.75 (m, 2H), 1.40 (s, 3H), 1.34 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.9, 74.8, 69.3, 60.2, 35.5, 26.7, 25.5 ppm. ESI-MS: m/z = 169 $[M+Na]^+$.

4.3. (*S*,*E*)-Methyl 4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate 11

Under an inert atmosphere at −78 °C, DMSO (4.3 mL, 61.6 mmol) was added dropwise to a solution of oxalyl chloride (2.7 mL, 30.8 mmol) in dichloromethane (35 mL). After stirring for 15 min, a solution of **10** (3.0 g, 20.5 mol) in dichloromethane (20 mL) was added dropwise. After stirring for 25 min, triethylamine (20 mL, 143.6 mmol) was added and the reaction was stirred for an additional 20 min. After completion (monitored by TLC), the reaction mixture was warmed to room temperature, quenched with water (35 mL) and extracted with dichloromethane. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent afforded 2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde, which was used for the next reaction without further purification.

To a stirred solution of the above aldehyde (2.5 g, 17.3 mmol) in benzene (30 mL) was added phosphine ester (6.041 g, 20.8 mmol). The resultant mixture was allowed to stir at room temperature for 12 h (monitored by TLC). The solvent was removed under vacuum to give the crude product which was purified by flash column chromatography (20% ethyl acetate hexane) to afford **11** (3.38 g, 91%) as coloured oil. $[\alpha]_D^{25} = -17.1$ (c 1.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.94–6.81 (m, 1H), 5.86 (dt, J = 15.7 Hz, 1H), 4.17 (q, J = 7.1 Hz, 3H), 4.02 (t, J = 6.3 Hz, 1H), 3.54 (t, J = 6.6 Hz, 1H), 2.56–2.35 (m, 2H), 1.39 (s, 3H), 1.32 (s, 3H), 1.29 (t, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 143.6, 123.8, 109.2, 74.1, 68.7, 60.2, 36.3, 26.9, 25.4, 14.1 ppm. ESI-MS: m/z = 223 $[M+Na]^+$.

4.4. (*S*,*E*)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)but-2-en-1-ol 12

To a stirred solution of compound **11** (1.4 g, 6.54 mmol) in dry DCM (20 mL) at −15 °C was added dropwise DIBAL-H (25% in toluene, 9.28 mL, 16.3 mmol). After stirring for 30 min, the reaction mixture was quenched with sodium potassium tartarate and

diluted with dichloromethane and then stirred until two clear layers appeared, after which the organic layer was separated and washed with brine and dried over sodium sulfate. Removal of the solvent gave a crude product, which was purified by column chromatography (30% ethylacetate hexane) to give alcohol **12** (1.068 g, 95%) as a colourless oil. $[\alpha]_D^{25} = -23.35$ (*c* 1.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.74–558 (m, 2H), 4.16–3.95 (m, 4H), 3.52 (t, *J* = 6.8 Hz, 1H), 2.41–2.21(m, 2H), 1.38 (s, 3H), 1.31 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.2, 126.6, 108.8, 75.1, 68.6, 62.7, 36.4, 26.7, 25.4 ppm. ESI-MS: *m*/*z* = 195 $[M+Na]^+$.

4.5. ((2*R*,3*R*)-3-(((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)methyl) oxiran-2-yl)methanol 13

To a stirred solution of evacuated flame dried powdered 4 Å molecular sieves (2 g) and (−)-DET (0.2 mL, 1.04 mmol) in DCM (20 mL) was slowly added $Ti(OPr^i)_4$ (0.198 g, 0.69 mmol) at −25 °C. The mixture was then allowed to stir for 20 min after which *t*-BuOOH (6 M in dacane, 8.9 mL, 53.9 mmol) was added at the same temperature. After being stirred for 30 min, a solution of compound **12** (1.2 g, 6.97 mmol) in DCM (10 mL) was added dropwise. The reaction mixture was stirred for 5 h at –25 °C and monitored by TLC. After completion, the reaction was quenched by the addition of aqueous NaOH (30% w/v 7.8 mL) and saturated with NaCl at 0 °C and continued to stir for an additional 1 h. By using Celite, the reaction mixture was swirled and the solids were filtered off and dried over anhydrous Na_2SO_4. Evaporation of the filtrate under vacuum yielded the crude product which was purified by flash column chromatography (45% ethyl acetate in hexane) to give **13** (1.259 g, 96%) as a colourless oil. $[\alpha]_D^{25} = +15.9$ (*c* 0.86, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.23–4.12 (m, 1H), 4.07–3.99 (m, 1H), 3.92–3.82 (m, 1H), 3.65–3.56 (m, 2H), 2.99–2.93 (m, 1H), 3.09–3.03 (m, 1H), 1.90–1.82 (m, 2H), 1.39 (s, 3H), 1.33 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 109, 72.8, 68.7, 61.4, 57.7, 52.4, 34.8, 26.7, 25.6 ppm. ESI-MS: *m*/*z* = 211 $[M+Na]^+$.

4.6. (*S*)-4-(((2*R*,3*S*)-3-(Iodomethyl)oxiran-2-yl)methyl)-2,2-dimethyl-1,3-dioxolane 14

To a stirred solution of alcohol **13** (1.8 g, 9.57 mmol) in acetonitrile/ether (1:3, 60 mL) at 0 °C under nitrogen were added imidazole (1.53 g, 23.5 mmol), iodine (4.82 g, 19.05 mmol), and triphenylphosphine (5.01 g, 19.14 mmol) successively. The mixture was stirred for 20–30 min. After completion of the reaction (monitored by TLC), the resulting solution was diluted by cool ether (30 mL) and filtered through Celite. The residue was washed by ether and the combined filtrate was concentrated at low temperatures to afford a pure iodo product as a colourless liquid. This was used for the next step without purification.

4.7. (*R*)-1-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-en-2-ol 15

A mixture of iodo compound **14** (1.25 g, 4.19 mmol), NaI (0.534 g, 8.35 mmol) and freshly activated zinc (1.565 g, 10.43 mmol) in anhydrous MeOH (20 mL) was refluxed for 8 h under a nitrogen atmosphere. After completion of the reaction, the mixture was filtered through Celite and the residue was washed with MeOH. The filtrates were combined and concentrated. The residue was taken in ethyl acetate (20 mL) and washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent and purification by column chromatography (20% ethyl acetate in hexane) afforded pure alcohol **15** (0.692 g, 96% yield) as a colourless oil. $[\alpha]_D^{25} = +7.9$ (*c* 0.96, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.91–5.75 (m, 1H), 5.26 (dt, *J* = 17.3 Hz and 1.51 Hz, 1H), 5.09 (dt, *J* = 17.3 Hz and 1.51 Hz, 1H), 4.34–4.17 (m, 2H), 4.05 (t, *J* = 6.2 Hz, 1H), 3.55 (t, *J* = 6.8 Hz, 1H), 2.79–2.74 (bs, 1H), 1.76–1.71 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.1, 114.7, 109.2, 74.8, 71.6, 69.5, 40.4, 26.8, 25.6 ppm. ESI-MS: *m*/*z* = 195 $[M+Na]^+$.

4.8. (*S*)-4-((*R*)-2-Methoxybut-3-enyl)-2,2-dimethyl-1,3-dioxolane 16

To a suspension of sodium hydride (0.329 g, 13.72 mmol, 60% dispersion in paraffin oil) in dry THF (10 mL) at 0 °C was slowly added a solution of **15** (1.180 g, 6.86 mmol) in dry THF (10 mL) under nitrogen atmosphere and the mixture was allowed to stir for 30 min. The resultant mixture was cooled to 0 °C and then MeI was slowly added dropwise and stirred for an additional 1 h. After completion of the reaction, the mixture was poured into ice-cold water and extracted with ethyl acetate (2 × 20 ml). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated to dryness to afford the crude product, which was purified by column chromatography (5% ethyl acetate hexane) to afford **16** (1.25 g, 98%) as a colourless oil. $[\alpha]_D^{25} = +7.5$ (*c* 0.16, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.69–5.57 (m, 1H), 5.26–5.15 (m, 2H), 4.11–4.04 (m, 1H), 3.97 (t, *J* = 7.8 Hz, 1H), 3.65 (t, *J* = 13.7 Hz, 1H), 3.50 (t, *J* = 6.9 Hz, 1H), 3.23 (s, 3H), 1.98–1.90 (m, 1H), 1.66–1.59 (m, 1H), 1.37 (s, 3H), 1.30 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.8, 117.9, 116.9, 80.1, 72.7, 69.4, 56.0, 38.9, 26.9, 25.7 ppm. ESI-MS: *m*/*z* = 209 $[M+Na]^+$.

4.9. (2*S*,4*R*)-4-Methoxyhex-5-ene-1,2-diol 17

To a solution of compound **16** (0.550 g, 2.95 mmol) in methanol (10 mL) was added a catalytic amount of (−)-camphor-10-sulfonic acid at 0 °C. After the addition, the reaction temperature was brought to room temperature and allowed to stir for 4 h. After 4 h, the solvent was evaporated under reduced pressure and diluted with ethyl acetate (15 mL). The resultant solution was washed with sat. $NaHCO_3$ solution. The organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated to dryness. Purification of the crude residue by silica gel column chromatography (20% ethyl acetate in hexane) yielded **17** (0.401 g, 94%) as a colourless oil. $[\alpha]_D^{25} = +78.6$ (*c* 0.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.73–5.57 (m, 1H), 5.29–5.18 (m, 1H), 3.91–3.75 (m, 2H), 3.59–3.50 (m, 1H), 3.46–3.37 (m, 1H), 3.31 (s, 3H), 2.63–2.24 (bs, 1H), 1.80–1.71 (m, 1H), 1.61–1.51 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.5, 117.8, 82.5, 71.1, 66.5, 55.9, 38.4 ppm. ESI-MS: *m*/*z* = 169 $[M+Na]^+$.

4.10. (2*S*,4*R*)-1-(*tert*-Butyldimethylsilyloxy)-4-methoxyhex-5-en-2-ol 3

To stirred solution of **17** (0.270 g, 1.84 mmol) in dry DCM (10 mL) was added imidazole (0.277 g, 4.08 mmol), after which the reaction mixture was allowed to stir for 10 min. The resulting mixture was then cooled to 0 °C, treated with TBDMSCl (0.331 g, 2.23 mmol) and allowed to stir for an additional 6 h. The mixture was then quenched with a saturated $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL), washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a crude product, which was further purified by flash column chromatography (12% ethyl acetate hexane) to afford **3** (0.442 g, 92%) as a colourless oil. $[\alpha]_D^{25} = +87.5$ (*c* = 0.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.73–5.58 (m, 1H), 5.29–5.19 (m, 1H), 3.88–3.62 (m, 3H), 3.57–3.42 (m, 2H), 3.28 (s, 3H), 2.99–2.93 (bs, 1H), 1.71–1.60 (m, 2H), 1.92 (s, 9H), 0.07 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.8, 117.7, 82.0, 70.4, 67.0, 55.9, 38.6, 25.8 ppm. HRMS (ESI): calcd For $C_{13}H_{28}O_3NaSi$ $[M+Na]^+$ 283.1713; found 283.1687.

4.11. 4-((4-Methoxybenzyl)oxy)butan-1-ol 18

To a suspension of sodium hydride was added to a solution of 1,4-butanediol **8** (3.5 g, 38.8 mmol) in dry DMF (60 mL) at 0 °C and the reaction was allowed to stir for 4 h. Next were added tetrabutylammonium iodide (1.4 g, 3.13 mmol) and 1-(bromomethyl)-4-methoxybenzene (0.042 mol) after which the mixture was stirred for an additional 12 h at rt. The mixture was then poured into ice cold water and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. Removal of the solvent gave a crude product, which was purified by column chromatography (20% ethyl acetate hexane) to afford **18** (7.2 g, 89%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20 (d, J = 8.3 Hz, 2H), 6.82 (d, J = 7.8 Hz, 2H), 3.79 (s, 3H), 3.58 (t, J = 5.29 Hz, 2H), 3.46 (t, J = 5.29 Hz, 2H), 2.41–2.30 (s, br, 1H), 1.71–1.61 (m, 4H) ppm. (NMR 75 MHz, $CDCl_3$): δ = 158.9, 129.1, 113.5, 72.4, 69.8, 62.2, 55.0, 29.8, 26.4, ppm. ESI-MS: m/z = 233 $[M+Na]^+$.

4.12. 4-((4-Methoxybenzyl)oxy)butanal 19

To a solution of oxalyl chloride (1.0 mL, 23.1 mmol) in dichloromethane (25 mL) was added DMSO (3.3 mL, 47.0 mmol) dropwise under an inert atmosphere at –78 °C. After being stirred for 15 min, a solution of compound **18** (2.5 g, 11.9 mmol) in dichloromethane (15 mL) was added dropwise and allowed to stir for 25 min. Next, triethyl amine (13.7 mL, 95.1 mmol) was added and the reaction was stirred for an additional 20 min. After completion (monitored by TLC), the reaction mixture was warmed to room temperature, quenched with water (35 mL), and extracted with dichloromethane. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent afforded **19** and this crude product was used for the next reaction without further purification.

4.13. 1-(5,5-Dibromopent-4-en-1-yl)oxy)methyl)-4-methoxy benzene 20

A solution of TPP (11.9 g, 45.2 mmol) (freshly recrystallized) in dichloromethane was cooled to −15 °C after which was added CBr_4 (7.3 g, 22.2 mmol) under an N_2 atmosphere and then allowed to stir until the reaction mixture turned light yellow. To this mixture was added a solution of aldehyde **19** (2.37 g, 11.3 mmol) in dichloromethane and continued stirring for an additional 10 min. After completion, distilled hexane was added and stirred vigorously for 15 min. The mixture was then filtered through a pad of Celite. Removal of the solvent afforded a crude product. Purification by column chromatography (2% ethyl acetate hexane) gave **20** (3.38 g, 82%) as light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 7.8 Hz, 2H), 6.37 (t, J = 6.8 Hz, 1H), 4.4 (s, 2H), 3.79 (s, 3H), 3.41 (t, J = 5.9 Hz, 3H), 2.19 (q, J = 6.85 Hz, 2H), 1.70 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 138.0, 130.3, 129.1 (2 C), 113.7 (2C), 96.1, 72.6, 68.7, 55.0, 29.9, 27.9 ppm. ESI-MS: m/z = 387 $[M+Na]^+$.

4.14. Ethyl 6-((4-methoxybenzyl)oxy)hex-2-ynoate 21

To a solution of dibromo compound **20** (1 g, 2.77 mmol) in dry THF (15 mL) was added n-BuLi (1.6 M in hexane; 18.5 mL, 6.2 mmol) drop wise at −78 °C. After being stirred for 45 min, the reaction mixture was warmed to room temperature and stirred for an additional 1 h. To this mixture, a solution of ethyl chloroformate (1.3 ml, 13.3 mmol) in dry THF was added at −78 °C, and allowed to stir for 30 min at the same temperature. After completion of reaction, it was quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent led to a crude product, which was purified by column chromatography (4% ethyl acetate hexane) to afford **21** (0.701 g, 92%) as a colourless oil. IR (KBr): ν = 2957, 2934, 2867, 1739, 1248, 1104, 773 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 4.41 (s, 2H), 4.18 (q, J = 7.2 Hz, 2H), 3.7 9 (s, 3H), 3.5 (t, J = 5.8 Hz, 2H), 2.45 (t, J = 7.0 Hz, 2H), 1.89–1.79 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 153.6, 130.1, 129.1 (2C), 113.6 (2C), 88.5, 72.5 (2C), 67.8, 61.6, 55.0, 27.6, 15.4, 13.8 ppm. ESI-MS: m/z = 299 $[M+Na]^+$.

4.15. (*Z*)-Ethyl 6-(4-methoxybenzyloxy)-3-methylhex-2-enoate 22

To a two-neck RB flask containing freshly dried CuI (0.438 g, 2.3 mmol) was added dry THF (15 mL), cooled to −15 °C, and then methyl lithium (1.6 M in ether, 2.8 mL, 4.1 mmol) was slowly added dropwise via a cannula. The solution turned from light yellow to a white precipitate. The mixture was allowed to stir for 30 min at the same temperature. After 30 min, the mixture was cooled to −78 °C after which was added a solution of compound **21** (0.276 g, 1.0 mmol) in dry THF (5 mL). The resultant mixure was allowed to stir for an additional 30 min. After completion of the reaction (monitored by TLC), the reaction was quenched with a buffer solution (pH 7) and sat. NH_4Cl and stirred until the appearance of a blue colour, and then extracted with ethyl acetate. The organic layer was again washed with saturated NH_4Cl and the solvent was evoporated under reduced pressure. The crude product was purified by column chromatography. (3% Ethyl acetate hexane) to give **22** (0.268 g, 96%) as a colourless oil. IR (KBr): ν = 2936, 2857, 1712, 1513, 1247, 1181, 1037, 823 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.62 (s, 1H), 4.4 (s, 2H), 4.1 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 3.45 (t, J = 6.6 Hz, 2H), 2.67 (t, J = 7.0 Hz, 2H), 1.9 (s, 3H), 1.84 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 159.9, 159.0, 130.6, 129.1, 116.3, 113.6, 72.4, 69.9, 59.3, 55.2, 30.1, 28.2, 25.1, 14.2 ppm. ESI-MS: m/z = 315 $[M+Na]^+$.

4.16. (*Z*)-1-((6-Chloro-4-methylhex-4-enyloxy)methyl)-4-metho xybenzene 6

To a stirred solution of **22** (1.8 g, 6.16 mmol) in dry DCM (20 mL) was added DIBAL-H (25% in toluene, 10.9 mL, 15.1 mmol) dropwise at −15 °C under a nitrogen atomsphere and then allowed to stir for 30 min. The reaction mixture was then quenched with sodium potassium tartarate and diluted with DCM and stirred until the appearance of two clear layers. The organic layer was separated, washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a crude product, which was purified by silica gel column chromatography (10% ethylacetate hexane) to give the corresponding allylic alcohol (1.54 g, 95%) as a colourless oil. IR (KBr): ν = 3428, 2938, 2868, 1652, 1438, 1123, 904, 812 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20 (d, J = 9.1 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.47 (t, J = 7.5 Hz, 1H), 4.38 (s, 2H), 4.02 (d, J = 7.5 Hz, 2H), 3.79 (s, 3H), 3.39 (t, J = 6 Hz, 2H), 2.18 (t, J = 7.5 Hz, 2H), 1.71 (s, 3H), 1.70–1.63 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 139.1, 130.2, 129.2, 124.9, 113.6, 72.2, 68.7, 58.5, 55.1, 27.8, 27.4, 23.0 ppm. ESI-MS: m/z = 273 $[M+Na]^+$. This alcohol was used for the next step.

The procedure of Collington and Meyers was followed. To a cooled suspension of anhydrous LiCl (0.500 g, 11.2 mmol), the above alcohol (0.250 g, 1.0 mmol) and *s*-collidine (1.3 mL, 9.1 mmol) in dry DMF (10 mL) was slowly added dropwise methanesulfonyl chloride (0.2 mL, 2.3 mmol). The resulting slurry mixture was then stirred for 2 h at 0 °C under N_2. The reaction mixture

was then poured into ice water (50 mL), and extracted with Et_2O (15 mL × 3). The combined organic extracts were washed with sat. $CuSO_4$, sat. $NaHCO_3$, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford **5** (0.230 g, 86%), which was used for the next reaction immediately without purification.

4.17. (*Z*)-Ethyl 9-((4-methoxybenzyl)oxy)-6-methylnon-5-en-2-ynoate 23

To a stirred solution of previously dried salts of CuI (2.3 g, 12.2 mmol), NaI (1.82 g, 10.1 mmol), and K_2CO_3 (1.2 g, 9.2 mmol) in dry DMF was added a solution of **6** (1.8 g, 6.7 mmol) and ethyl propionate (0.789 g, 8.4 mmol) in DMF (30 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h, and then quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with ether (3 × 50 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4) and filtered. The filtrate was then evaporated under reduced pressure and purified by silica gel column chromatography (3% ethyl acetate in hexanes) to afford **23** (0.199 g, 89%) as a colourless oil. IR (KBr): ν = 2982, 2858, 2938, 2232, 1709, 1614, 1513, 1365, 1249, 1096, 820, 752 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 5.16 (t, J = 7.0 Hz, 1H), 4.38 (s, 2H), 4.18 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 3.37 (t, J = 6.2 Hz, 2H), 3.01 (d, J = 6.6 Hz, 2H), 2.09 (q, 7.5 Hz, 2H), 1.74–1.65 (m, 2H), 1.64 (s, 3H), 1.3 (t, J = 7.2 Hz, 3H) ppm.^{13}C NMR (75 MHz, $CDCl_3$): 150.0, 153.0, 138.6, 130.5, 129.0 (2C), 116.4, 113.6, 96.2, 72.5, 68.9, 61.1, 54.8, 35.9, 27.8, 23.1, 17.7, 14.8 ppm. HRMS (ESI): calcd For $C_{20}H_{26}O_4$ $[M+H]^+$ 331.1904; found 331.1902.

4.18. (2*Z*,5*Z*)-Ethyl 9-((4-methoxybenzyl)oxy)-3,6-dimethylnona-2,5-dienoate 24

To a two-neck RB flask containing freshly dried CuI (1.19 g, 6.2 mmol) was added dry THF (25 mL), cooled to −15 °C. Next methyl lithium (1.6 M in ether, 7.8 mL, 12.5 mmol) was slowly added dropwise via a cannula. The solution turned from light yellow to a white precipitate. The mixture was allowed to stir for 30 min at the same temperature. After 30 min, the mixture was cooled to −78 °C, after which was added a solution of compound **23** (0.9 g, 27.2 mmol) in dry THF (5 mL). The resultant mixure was allowed to stir for an additional 30 min. After completion of the reaction (monitored by TLC), the reaction was quenched with a buffer solution (pH 7) and sat. NH_4Cl and stirred until it turned blue, then extracted with ethyl acetate. The organic layer was again washed with saturated NH_4Cl and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (3% ethyl acetate hexane) to give **24** (0.896 g, 95%) as an oil; IR (KBr): ν = 2972, 2941, 2934, 1719, 1619, 1523, 1465, 1219, 1026, 812, cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.19 (d, J = 9.0 Hz, 2H), 6.81 (d, J = 8.3 Hz, 2H), 5.59 (s, 1H), 5.12 (t, J = 8.5 Hz, 1H), 4.37 (s, 2H), 4.12 (q, J = 7.5 Hz, 2H), 3.78 (s, 3H), 3.42–3.3 (m, 4H), 2.16 (t, J = 6.8 Hz, 1H), 2.06 (t, J = 7.3 Hz, 1H), 1.82 (s, 3H), 1.72–1.62 (m, 5H), 1.27 (t, J = 7.5 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 166.3, 159.1, 141.0, 138.8, 130.6, 129.1 (2C), 120.7, 115.7, 113.6 (2C), 72.4, 69.5, 59.4, 55.1, 36.0, 31.9, 27.9, 24.6, 16.1, 14.2 ppm. HRMS (ESI): calcd For $C_{21}H_{30}O_4Na$ $[M+Na]^+$ 369.2041; found 369.2028.

4.19. (2*Z*,5*Z*)-Ethyl 3,6-dimethyl-9-oxonona-2,5-dienoate 25

To a solution of compound **24** (0.6 g, 1.73 mmol) in dichloromethane (9.5 mL) and buffer solution (0.5 mL, pH 7) was added DDQ (0.393 g, 1.71 mol) at 0 °C. The reaction was then warmed to room temperature and stirred for 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through Celite. The filtrate was washed with saturated sodium hydrogen carbonate solution, dried over anhydrous Na_2SO_4 and concentrated to afford the crude product. Purification by column chromatography (8% ethyl acetate in hexanes) gave (2*Z*,5*Z*)-ethyl 9-hydroxy-3,6-dimethylnona-2,5-dienoate (0.350 g, 89%) as an oil. IR (KBr): ν = 1709, 1643, 1445, 1375, 1257, 1159, 1054, 855 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.61 (s, 1H), 5.16 (t, J = 7.1 Hz, 1H), 4.11 (q, J = 14.1 Hz, 2H), 3.59 (t, J = 6.4 Hz, 2H), 3.44–3.34 (m, 2H), 2.20 (t, J = 7.3 Hz, 1H), 1.84 (s, 3H), 1.70 (s, 3H), 1.69–1.60 (m, 2H), 1.27 (t, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$); δ = 166.3, 158.9, 136.8, 120.9, 115.8, 62.4, 59.5, 35.8, 32.0, 30.6, 24.6, 23.1, 14.1 ppm. HRMS (ESI): calcd For $C_{13}H_{22}O_3Na$ $[M+Na]^+$ 249.1466; found 249.1464.

To a suspension of the above alcohol (0.250 g, 1.1 mmol) and sodium bicarbonate (0.557 g, 6.62 mmol) in dry DCM (10 mL) was added Dess–Martin periodinane (0.703 g, 1.63 mmol) at 0 °C. The reaction mixture was stirred for 1 h at rt. After completion of reaction (monitored by TLC), the reaction was quenched with sat. sodium thiosulfate and allowed to stir until the solution became clear. The organic layer was separated and the aq. layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with satd. $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo to give crude aldehyde **25** (0.242 g, 98%), which was used directly in the next step without further purification.

4.20. (3*E*,5*Z*)-Ethyl 3,6-dimethyldeca-3,5,9-trienoate 26

To a stirred solution of $Ph_3P^+CH_3I^-$, (0.094 g, 0.42 mol) in dry toluene was add *t*-BuO^-K^+ at 0 °C and allowed to stir until the solution turned yellow. To this mixture, a solution of aldehyde **15** (0.094 g, 4.2 mmol) in dry toluene was slowly added dropwise at 0 °C and stirred for an additional 1 h at the same temperature and then warmed to ambient temperature. After completion, the reaction mixture was quenched with water and the aqueous phase was extracted with diethyl ether, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by flash chromatography (3% ethyl acetate hexane) afforded **26** (0.076 g, 82%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.99 (q, J = 11.1 Hz, 2H), 5.85–5.66 (m, 1H), 5.06–4.87 (m, 2H), 4.12 (q, J = 14.1 Hz, 2H), 3.01 (s, 2H), 2.25–2.10 (m, 4H), 1.8 (s, 3H), 1.74 (s, 3H), 1.27 (t, J = 7.17 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4, 138.3, 137.8, 124.8, 121.4, 120.6, 114.5, 60.4, 45.5, 39.5, 32.2, 24.0, 16.4, 14.1 ppm. HRMS (ESI): calcd for $C_{14}H_{22}O_2Na$ $[M+Na]^+$ 245.1517; found 245.1527.

4.21. (2*Z*,5*Z*,9*E*)-Ethyl 12-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,6-dimethyl-11-oxododeca-2,5,9-trienoate 27

To a solution of β-ketophosphonate (2.65 g, 9.9 mmol) in THF (15 mL) was added $Ba(OH)_2{\cdot}8H_2O$ (2.25 g, 7.11 mmol), pre-activated by heating in a 110 °C oven for 2 h and then dried under vacuum. The reaction mixture was then allowed to stir for 30 min at rt. To this reaction mixture, was added a solution of aldehyde **25** (1.6 g, 7.1 mmol) in THF/H_2O (40:1; 10 mL) and allowed to stir for 2 h at rt. Upon completion, the reaction mixture was diluted with a saturated aqueous NH_4Cl solution (50 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography (10% ethyl acetate hexane) to provide the coupled product **27** (2.3 g, 89%) as a colourless oil. $[\alpha]_D^{25} = -6.25$(*c* 0.16, $CHCl_3$) IR (KBr): ν = 2866, 2763, 1719, 1643, 1445, 1375, 1247, 1129, 657 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.83–6.69 (m, 1H), 6.05 (d, J = 15.8 Hz, 1H), 5.60 (s, 1H), 5.16 (t, J = 7.3 Hz, 1H),

4.47–4.37 (m, 1H), 4.21–4.06 (m, 3H), 3.49 (t, J = 6.7 Hz, 1H), 3.37 (d, J = 7.1 Hz, 2H), 3.06–2.97 (m, 1H), 2.66–2.56 (m, 1H), 2.34 (q, J = 14.3 Hz, 2H), 2.17 (t, J = 7.3 Hz, 2H), 1.83 (s, 3H), 1.69 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.8, 165.7, 158.0, 147.1, 135.6, 130.8, 122.6, 116.3, 168.4, 72.0, 59.3, 44.3, 38.1, 32.1, 30.9, 27.0, 25.5, 24.8, 23.3, 16.3, 14.5 ppm. HRMS (ESI): calcd for $C_{21}H_{32}O_5Na$ $[M+Na]^+$ 387.242; found 387.2123.

4.22. (*R*,2*Z*,5*Z*,9*E*)-Ethyl 12-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-11-methoxy-3,6-dimethyldodeca-2,5,9-trienoate 28

A solution of (*S*)-(−)-2-methyl-CBS-oxazaborolidine (0.49 mL of a 1 M solution in toluene, 4.9 mmol) in THF (5 mL) was treated with BH_3·DMS (2.0 M solution in THF) (0.2 mL, 04.1 mmol) at 0 °C for 15 min. A solution of enone **27** (0.150 g, 4.1 mmol) in THF (8 mL) was then added slowly at −78 °C and the reaction mixture was stirred for 1 h at the same temperature. After the addition of saturated NH_4Cl solution, the aqueous layer was extracted with EtOAc; the combined organic phases were dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (10% ethyl acetate hexane) gave (*R*,2*Z*,5*Z*,9*E*)-ethyl 12-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-11-hydroxy-3,6-dimethyldodeca-2,5,9-trienoate (0.128 g, 85%, dr >96:4) as a colourless oil. $[\alpha]_D^{25} = +37.2$ (c 1.2, $CHCl_3$). IR (KBr): ν = 2923, 2836, 1728, 1679, 1562, 1421, 1084, 752 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.66–5.53 (m, 2H), 5.50–5.39 (m, 1H), 5.09 (t, J = 6.6 Hz, 1H), 4.29–4.16 (m, 2H), 4.11 (q, J = 14.1 Hz, 2H), 4.01 (t, J = 7.6 Hz, 1H), 3.50 (t, J = 7.5 Hz, 1H), 3.34 (t, J = 6.0 Hz, 1H), 2.30–2.25 (bs, 1H), 2.18–2.03 (m, 4H), 1.84 (s, 3H), 1.80–1.70 (m, 2H), 1.66 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 158.6, 136.1, 133.3, 130.5, 121.5, 116.1, 108.5, 73.4, 69.7, 69.6, 59.2, 40.6, 39.2, 32.1, 30.5, 27.1, 25.9, 24.9, 16.3, 14.4 ppm. HRMS (ESI): calcd for $C_{18}H_{30}O_5Na$ $[M+Na]^+$ 389.1973; found 389.1942.

To a stirred solution of the above alcohol (0.120 g, 0.32 mmol) in dry CH_2Cl_2 (10 mL) was added proton sponge™ (0.772 g, 3.6 mmol) followed by trimethyloxonium tetrafluoroborate (0.436 g, 2.9 mmol) at 0 °C. The resulting solution was stirred at rt for 1 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, concentrated and purified by flash column chromatography (5% ethyl acetate hexane) to yield **28** (0.122 g, 98%) as a colourless oil. IR (KBr): ν = 3014, 2986, 2936, 2846, 1713, 1462, 1286, 1125, 1095, 742 cm^{-1}. $[\alpha]_D^{25} = +85.7$ (c 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.64 (s, 1H), 5.59 (t, J = 6.4 Hz, 1H), 5.30 (m, 1H), 5.15 (t, J = 6.9 Hz, 1H), 4.25–4.09 (m, 3H), 4.03 (t, J = 5.8 Hz, 1H), 3.65–3.56 (m, 1H), 3.51 (t, J = 7.5 Hz, 1H), 3.38 (d, J = 7.1 Hz, 2H), 3.22 (s, 3H), 2.22–2.04 (m, 4H), 1.84 (s, 3H), 1.80–1.71 (m, 2H), 1.68 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 1.27 (J = 6.9 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 158.9, 136.5, 133.6, 130.0, 121.0, 115.8, 108.2, 79.2, 73.4, 69.8, 59.4, 55.8, 40.3, 39.2, 32.0, 30.5, 26.9, 25.8, 24.7, 16.1, 14.2 ppm. HRMS (ESI): calcd for $C_{22}H_{36}NaO_5$ $[M+Na]^+$ 403.2455; found 403.2451.

4.23. (2*Z*,5*Z*,9*E*,11*R*,13*S*)-Ethyl 13-hydroxy-11-methoxy-3,6-dimethyl-14-(trityloxy) tetradeca-2,5,9-trienoate 29

To a solution of compound **28** (0.115 g, 0.30 mmol) in methanol (5 mL) at 0 °C was added a catalytic amount of (−)-camphor-10-sulfonic acid. The reaction temperature was warmed to room temperature and stirred for 4 h. The reaction mixture was concentrated to remove methanol and diluted with ethyl acetate. The organic layer was washed with sat. Na_2CO_3 solution and the organic layer was concentrated to afford the crude product. Purification by column chromatography (30% ethyl acetate in hexane) led the diol (0.092 g, 92%) as colourless oil. $[\alpha]_D^{25} = +56.8$ (c = 0.64, $CHCl_3$). IR (KBr): ν = 2954, 2866, 2756, 1726, 1495, 1456, 1365, 1243, 1223, 821, 704 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.67–5.56 (m, 2H), 5.39–5.24 (m, 1H), 5.13 (t, J = 6.9 Hz, 1H), 4.14 (q, J = 14.1 Hz, 2H), 3.98–3.86 (bs, 1H), 3.83–3.71 (m, 1H), 3.65–3.55 (m, 1H), 3.52–3.42 (m, 1H), 3.40–3.30 (m, 3H), 3.24 (s, 3H), 2.81–2.62 (bs, 1H), 2.25–2.02 (m, 4H), 1.84 (s, 3H), 1.72–1.60 (m, 5H), 1.27 (t, J = 7.17 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 159.0, 136.3, 133.9, 129.4, 121.1, 115.7, 79.8, 69.2, 66.7, 59.5, 55.8, 39.1, 38.6, 31.9, 30.3, 24.7, 16.1, 14.2 ppm. $C_{19}H_{32}NaO_5$ $[M+Na]^+$ 363.2142; found 363.2152.

To a stirred solution of the above diol (0.046 g, 0.13 mmol) in dry DCM at 0 °C were added TrCl (0.041 g, 0.14 mmol) and pyridine (0.01 mL, 0.14 mmol) and stirring was continued for 4 h at rt. After completion, the reaction was quenched with sat. NH_4Cl and the aqueous phase was extracted with DCM (2 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and the organic layer concentrated to afford the crude product. Purification by column chromatography (10% ethyl acetate hexane) gave **29** (0.070 g, 89%) as a light yellow oil. $[\alpha]_D^{25} = +69.3$ (c 0.5, $CHCl_3$). IR (KBr): ν = 3436, 2983, 2936, 2862, 1734, 1645, 1436, 1309, 1139, 859 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.41 (m, 6H), 7.33–7.17 (m, 9H), 5.63 (s, 1H), 5.61–5.49 (m, 1H), 5.31–5.20 (m, 1H), 5.14 (t, J = 7.3 Hz, 1H), 4.13 (q, J = 14.3 Hz, 2H), 4.06 (t, J = 5.6 Hz, 1H), 3.72–3.62 (m, 1H), 3.36 (d, J = 7.1 Hz, 2H), 3.15 (s, 3H), 3.09 (d, J = 5.6 Hz, 2H), 2.96–2.84 (bs, 1H), 2.20–2.03 (m, 4H), 1.81 (s, 3H), 1.68–1.60 (m, 5H), 1.26 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 158.9, 143.8 (3 C), 136.5, 133.6, 129.8, 128.6 (6 C), 127.7 (6 C), 126.9 (3 C), 121.0, 115.8, 86.4, 79.3, 67.9, 67.3, 59.4, 55.8, 39.2, 32.0, 30.6, 24.7, 16.2, 14.2 ppm. HRMS (ESI): calcd for $C_{38}H_{46}O_5Na$ $[M+Na]^+$ 605.3287; found 605.3236.

4.24. (2*Z*,5*Z*,9*E*,11*R*,13*S*)-13-Hydroxy-11-methoxy-3,6-dimethyl-14-(trityloxy)tetradeca-2,5,9-trienoic acid 32

To stirred solution of **29** (0.065 g, 0.11 mmol) in dry DCM (5 mL) was added imidazole (0.019 g, 0.27 mmol) and stirred for 10 min. The reaction mixture was then cooled to 0 °C, treated with TESCl (0.03 mL, 0.16 mmol) and allowed to stir for an additional 5 h at room temperature. After completion, the reaction was quenched with sat. $NaHCO_3$. The aqueous phase was extracted with Et_2O (2 × 10 mL), washed with brine and dried over Na_2SO_4. Removal of the solvent gave the crude product, which was purified by flash column chromatography (4% ethyl acetate hexane) to afford (2*Z*,5*Z*,9*E*,11*R*,13*S*)-ethyl 11-methoxy-3,6-dimethyl-13-(triethylsilyloxy)-14-(trityloxy)tetradeca-2,5,9-trienoate (0.071 g, 92%) as a colourless oil. This compound was used for the next step.

To a stirred solution of the above TES protected compound (0.068 g, 0.09 mmol) in dry DCM (20 mL) was added DIBAL-H (25% in toluene, 0.14 mL, 0.24 mmol) dropwise at −15 °C. After being stirred for 30 min, the reaction mixture was quenched with sodium potassium tartarate, diluted with DCM and stirred until the appearance of two clear layers. The organic layer was separated, washed with brine and dried over sodium sulfate. Removal of the solvent followed by purification of the crude product by column chromatography (12% ethyl acetate hexane) yielded the corresponding allylic alcohol **31** (0.059 g, 93%) as a colourless oil.

To a suspension of the above primary alcohol (0.055 g, 0.08 mmol) and sodium bicarbonate (0.042 g, 0.54 mmol) in dry DCM (5 mL) was added Dess–Martin periodinane (0.053 g, 0.12 mmol) at 0 °C. After being stirred for 1 h, the reaction mixture was quenched with satd. sodium thiosulfate and stirred until the appearance of a clear solution. The organic layer was separated and the aq layer was extracted with diethyl ether (2 × 5 mL). The combined organic layers were washed with sat. $NaHCO_3$ and brine,

dried over anhydrous Na_2SO_4 and evaporated in vacuo to give the crude aldehyde (0.054 g, 98%), which was used directly in the next step without further purification.

To a solution of the above aldehyde (0.097 g, 0.16 mmol) and 2-methyl-2-butene (2.9 mL, 2 M solution in THF) in *tert*-butanol (5 mL) was added drop wise a solution of $NaH_2PO_4{\cdot}H_2O$ (184 mg) and $NaClO_2$ (184 mg) in H_2O (2 mL) at 0 °C. The temperature was then brought to room temperature. After being stirred for 30 min, the reaction was quenched with water (4 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo. The crude product was purified by flash chromatography (20% ethyl acetate hexane) to give the acid (0.043 g, 89%) as a colourless oil.

To a stirred solution of the acid (0.035 g, 0.06 mmol) in THF (4 mL) was added TBAF (0.02 mL, 1 M solution in THF, 0.07 mmol) at 0 °C. After completion of the reaction (monitored by TLC), the reaction was quenched with a saturated $NaHCO_3$ solution and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography to give *seco*-acid **32** (0.026 g, 90%) as colourless oil. $[\alpha]_D^{25} = +96.8$ (*c* 0.9, $CHCl_3$). IR (KBr): ν = 3445, 3385, 2921, 2863, 2752, 1718, 1624, 1532, 1361, 1264, 1092, 773 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.38 (m, 6H), 7.33–7.17 (m, 9H), 5.63 (s, 1H), 5.55–5.44 (m, 1H), 5.27–5.15 (m, 1H), 5.04 (t, *J* = 6.7 Hz, 1H),4.07–3.97 (m, 1H), 3.70–3.61 (m, 1H), 3.44–3.33 (m, 1H), 3.27–3.18 (m, 1H), 3.14 (s, 3H), 3.05 (d, *J* = 6.7 Hz, 2H), 2.36–2.25 (m, 1H), 2.18–1.95 (m, 4H), 1.86 (s, 3H), 1.64 (s, 3H), 1.60–1.53 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.7, 159.1, 143.4 (3C), 136.2, 133.2, 129.0, 128.1 (6C), 127.2 (6C), 126.4 (3C), 121.1, 114.5, 87.1, 79.4, 68.2, 67.8, 55.9, 39.1, 38.2, 32.1, 30.8, 24.8, 18.7 ppm. HRMS (ESI): calcd for $C_{36}H_{42}O_5Na$ $[M+Na]^+$ 577.2924; found 577.2876.

4.25. (4*E*,6*Z*,10*E*,12*R*,14*S*)-12-Methoxy-4,7-dimethyl-14-(tritylox ymethyl)oxacyclotetradeca-4,6,10-trien-2-one 33a

To a stirred solution of *seco*-acid **32** (0.015 g, 0.027 mmol) and Et_3N (0.004 mL, 0.029 mmol) in THF (2 mL) was added 2,4,6-trichlorobenzoyl chloride (0.004 mL, 0.028 mmol) drop wise at 0 °C. The reaction mixture was stirred at room temperature for 1 h, followed by dilution with dry toluene (10 mL) and added dropwise using a syringe pump over a period of 2 h to a refluxing solution of DMAP (0.102 g, 0.56 mmol) in dry toluene (25 mL). After the addition was complete, the mixture was refluxed for 10 h and then concentrated in vacuum. The residue was dissolved in EtOAc (15 mL) and washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography on silica gel to give macrolactone **33a** (0.008 g, 58%) as a colourless oil. IR (KBr): ν = 2997, 2865, 2792, 1739, 1686, 1523, 1392, 1196, 1036, 675 cm^{-1}. $[\alpha]_D^{25} = +116.3$ (*c* 0.26, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.42 (m, 6H), 7.34–7.18 (m, 9H), 6.17–5.95 (m, 2H), 5.67–5.55 (m, 2H), 5.29–5.15 (m, 1H), 3.99–3.85 (m, 1H), 3.74–3.63 (m, 1H), 3.19 (s, 3H), 3.17–2.99 (m, 3H), 2.39–2.32 (m, 1H), 2.26–2.08 (m, 3H), 1.80 (s, 3H), 1.74 (s, 3H), 1.69–1.58 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3, 145.5 (3C), 135.7, 132.5, 129.3, 128.2 (6C), 127.7 (6C), 126.1 (3C), 125.6, 120.7, 86.7, 78.2, 67.7, 67.3, 56.2, 46.4, 41.3, 37.8, 32.6, 30.6, 24.5, 19.6 ppm. HRMS (ESI): calcd for $C_{36}H_{40}O_4Na$ $[M+Na]^+$ 559.2819; found 559.2782.

4.26. (*R*)-Methyl 3,4-dihydroxybutanoate 34

To a solution of the (*R*)-malic acid (1.5 g, 11.2 mmol) in MeOH (20 mL) at 0 °C was slowly added $BF_3{\cdot}Et_2O$ (0.4 mL) dropwise at 0 °C. After being stirred for 12 h, the solvent was removed under reduced pressure and dissolved in ethyl acetate. The organic layer was then washed with a saturated $NaHCO_3$ solution and dried over Na_2SO_4. Removal of the solvent afforded the crude product, which was purified by silica column chromatography (30% ethyl acetate hexane) to afford (*R*)-dimethyl malate (1.6 g, 98%). $[\alpha]_D^{26} = +11.2$ (*c* 1.12, CH_3OH). ^1H NMR (300 MHz, acetone-d_6): δ = 4.56–4.48 (m, 1H), 3.71 (s, 3H), 3.64 (s, 3H), 2.84–2.62 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6, 170.9, 67.1, 52.7, 51.9, 38.3 ppm.

To a solution of (*R*)-dimethyl malate (6 g, 37.0 mmol) in dry THF (60 mL) was added the $BH_3{\cdot}DMS$ complex (2 M solution in THF 15 mL, 37.0 mmol) at room temperature and the reaction was stirred for 30 min. The reaction mixture was then cooled to 0 °C after which a catalytic amount of $NaBH_4$ (ca. 16 mg) was added under N_2 and allowed to stir for an additional 30 min at 0 °C. After being stirred, the reaction was slowly warmed to rt and stirring continued over night. The reaction mixture was quenched with methanol (15 mL) and then stirred for 0.5 h. The solvent was removed and the crude product was purified by flash column chromatography (25% acetone–hexane) to afford **34** (1.2 g, 89%) as a colourless oil. $[\alpha]_D^{25} = +27.9$ (*c* 1.08, CH_3OH). ^1H NMR (300 MHz, acetone-d_6): δ = 4.09–3.99 (m, 1H), 3.82 (t, *J* = 4.9 Hz, 1H), 3.63 (s, 3H), 3.50 (t, *J* = 5.2 Hz, 1H), 2.62–2.51 (m, 1H), 2.42–2.31 (m, 1H) ppm. ^{13}C NMR (75 MHz, acetone-d_6): δ = 173.7, 70.6, 67.4, 59.7, 40.2 ppm. ESI-MS: *m*/*z* = 257 $[M+Na]^+$.

4.27. (*R*)-Methyl 3-hydroxy-4-(4-methoxybenzyloxy)butanoate 35

A solution of **34** (1.2 g, 8.95 mmol) and dibutyltin oxide (Bu_2SnO) (3.053 g, 12.24 mmol) in toluene (40 mL) was stirred and refluxed under azeotropic conditions, removing H_2O with a Dean–Stark apparatus for 12 h. After cooling to rt, 4-methoxybenzyl chloride (13.4 mmol, 2.09 g) and tetrabutylammonium iodide (4.9 g, 13.2 mmol) were added to the reaction mixture, and the whole reaction mixture was refluxed for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with a brine solution, dried over Na_2SO_4 and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (25% ethyl acetate hexane) to afford **35** (1.8 g, 80%) as a colourless oil. $[\alpha]_D^{25} = +29.6$ (*c* = 1.14, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.23 (d, *J* = 8.9 Hz, 2H), 6.91–6.85 (d, *J* = 9.1 Hz, 2H), 5.01–4.84 (m, 1H), 4.43 (s, 2H), 3.81 (s, 3H), 3.68 (s, 3H), 3.66–3.56 (m, 1H), 3.46–3.35 (m, 1H), 2.14–2.04 (m, 1H), 1.78–1.65 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8, 159.1, 130.0, 129.8, 129.3, 113.8, 113.7, 72.9, 72.7, 67.0, 66.2, 55.1, 38.2 ppm. ESI-MS: *m*/*z* = 277 $[M+Na]^+$.

4.28. (*R*)-Dimethy-4-(*tert*-butyldiphenylsilyloxy)-5-(4-methoxy benzyloxy)-2-oxopentyl phosp-honate 36

To a stirred solution of compound **35** (1.7 g, 6.69 mmol) in dry DMF (25 mL) was added imidazole (1.0 g, 14.2 mmol) and allowed to stir for 10 min. The reaction mixture was cooled to 0 °C, treated with TBDPSCl (2.3 mL, 8.21 mmol) and the whole mixture was stirred at room temperature for 6 h. After being stirred, the reaction was quenched with sat. aq. $NaHCO_3$. The aqueous phase was extracted with Et_2O (3 × 50 mL), washed with brine and dried over Na_2SO_4. Removal of the solvent gave the crude product, which was purified by flash column chromatography (10% ethyl acetate hexane) to afford (*R*)-methyl 3-(*tert*-butyldiphenyl silyl-oxy)-4-(4-methoxybenzyloxy)butanoate (3.1 g, 96%). $[\alpha]_D^{26} = +8.5$ (*c* 0.64, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.60 (m, 4H), 7.45–7.28 (m, 6H), 7.18 (d, *J* = 9.1 Hz, 2H), 7.05 (d, *J* = 9.1 Hz, 2H), 4.36–4.25 (m, 1H), 4.17 (d, *J* = 3.8 Hz, 2H), 3.80 (s, 3H), 3.79 (s,

3H), 3.33 (d, J = 6.0 Hz, 2H), 2.60 (d, J = 6.8 Hz, 2H), 1.0 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 159.4, 135.8 (2 C), 133.8, 133.4, 130.1, 130.0 (2C), 129.6, 129.5, 129.1 (2C), 127.5, 127.4, 133.7, 133.5, 73.1, 72.5, 69.2, 66.0, 55.2, 40.0, 26.8 (3C), 19.2 ppm. HRMS (ESI): calcd for $C_{29}H_{36}O_5NaSi$ $[M+Na]^+$ 515.2184; found 515.2158.

To a stirred solution of dimethyl methylphosphonate (1.172 g, 9.13 mmol) in dry THF (15 mL) was added dropwise *n*-BuLi (5.9 mL, 1.6 M in hexane, 9.2 mmol) at −78 °C and mixture was stirred for 45 min at same temperature. A solution of the above TBDPS protected compound (0.008 g, 3.11 mmol) in dry THF (10 mL) was added to the mixture at the same temperature and stirred for an additional 1.5 h. The reaction was then quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed to give a residue, which was purified by flash column chromatography (40% ethyl acetate hexane) to afford **36** (1.16 g, 75%). $[\alpha]_D^{25} = +15.8$ (c 1.21, $CHCl_3$). IR (KBr): ν = 3070, 3047, 2999, 1716, 1612, 1513, 1253, 1109, 1034, 821, 705, 610 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.64 (m, 4H), 7.44–7.33 (m, 6H), 7.08 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 4.37–4.31 (m, 1H), 4.21 (q, J = 14.5 Hz, 2H), 3.79 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 3.36–3.28 (m, 2H), 3.07–2.77 (m, 4H), 1.02 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.8, 159.0, 135.8 (2C), 135.7 (2C), 133.9, 133.1, 130.0, 129.7, 129.5, 129.2 (2C), 127.6 (2C), 127.4 (2C), 113.5 (2C), 73.0, 72.6, 68.6, 55.2, 52.9, 48.8, 42.7, 41.0, 26.8 (3C), 19.1. HRMS (ESI): calcd For $C_{31}H_{41}O_7NaPSi$ $[M+Na]^+$ 607.2251; found 607.2251.

4.29. 2-(((2*Z*,5*Z*)-9-((4-Methoxybenzyl)oxy)-3,6-dimethylnona-2,5-dien-1-yl)oxy)tetrahydro-2*H*-pyran 37

A solution of Red-Al (3.4 M in toluene, 9.4 ml, 32.1 mmol) in a two-necked dry flask charged with a magnetic stirring bar, a reflux condenser, an addition funnel and an argon in/outlet was diluted with Et_2O (15 ml) and the whole mixture was then cooled to −78 °C. To this mixture, a solution of 2-butyn-1-ol (1.5 g, 21.2 mmol, 1.00 equiv) in Et_2O (10 mL) was added dropwise via the addition funnel. After being stirred at −78 °C for 30 min, the reaction mixture was allowed to warm to rt (CAUTION: exothermic after ca. 1 h). After 12 h, a white suspension had formed which was cooled to 0 °C. A solution of iodine (8.1 g, 32.1 mmol) in THF (15 ml) was slowly added at −78 °C. After warming to rt, the mixture was carefully added to a stirred mixture of saturated aqueous $Na_2S_2O_3$ (20 mL) and saturated aqueous Rochelle salt (20 mL), followed by the addition of ethyl acetate (15 mL). After stirring at rt for 30 min, two clear phases were obtained which were separated. The aqueous phase was extracted with ethyl acetate (3 × 100 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by flash chromatography (25% ethyl acetate hexane) gave (*Z*)-3-iodobut-2-en-1-ol (3.7 g, 98%) as a yellow oil. Note: the product is not stable upon prolonged storage at rt. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.75 (t, J = 7.6 Hz, 1H), 4.11 (d, J = 4.9 Hz, 2H), 2.55 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.0, 102.1, 67.2, 33.5 ppm. ESI-MS: m/z = 207 $[M+Na]^+$.

To a solution of compound (*Z*)-3-iodobut-2-en-1-ol (0.6 g, 3.21 mmol) in dichloromethane (10 mL) was added 3,4-dihydro-2*H*-pyran (2.3 mL, 3.32 mmol) and catalytic amount of (−)-camphor-10-sulfonic acid at 0 °C. The reaction temperature was then increased to room temperature and allowed to stir for 4 h. After completion (monitored by TLC), the reaction was quenched with a saturated sodium hydrogen carbonate solution and the organic layer was dried over sodium sulfate and concentrated to afford the crude product. The product was purified by column chromatography (10% ethyl acetate in hexane) to give (*Z*)-2-((3-iodobut-2-en-1-yl)oxy)tetrahydro-2*H*-pyran (0.8 g, 92%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.73 (t, J = 5.7 Hz, 1H), 4.59 (t, J = 2.9 Hz, 1H), 4.20–4.14 (m, 1H), 3.97–3.92 (m, 1H), 3.84–3.78 (m, 1H), 3.52–3.46 (m, 1H), 2.55 (s, 3H), 1.87–1.78 (m, 1H), 1.70–1.63 (m, 1H), 1.61–1.48 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.2, 102.0, 98.2, 71.6, 62.1, 33.6, 30.4, 25.3, 19.3 ppm. ESI-MS: m/z = 291$[M+Na]^+$.

To a solution of (*Z*)-2-((3-iodobut-2-en-1-yl)oxy)tetrahydro-2*H*-pyran (0.295 g, 1.21 mmol) in dry Et_2O (3 mL) was added *t*-BuLi (1.5 mL, 1.7 M in pentane, 2.1 mmol) slowly (10 min) at −78 °C. The resultant solution was stirred for 30 min at −78 °C. To this mixture was added a solution of dry $ZnBr_2$ (0.235 g, 1.2 mmol) in THF (5 mL) via a cannula. The whole mixture was stirred for 15 min at −78 °C and then warmed slowly to room temperature. In another flask containing $[Pd_2(dba_3)]$ (0.024 g, 0.2 mmol) and tri-2-furylphosphine (0.020 g, 0.1 mmol) was added dry DMF (5 mL) and the resultant dark green solution was stirred at 23 °C for 30 min.

A solution of **6** (0.420 g, 1.6 mmol) in dry DMF (4 mL) and the above generated zinc reagent was then introduced via a cannula at 0 °C. The reaction mixture was stirred for 1 h, and then quenched with water, extracted with ether (2 × 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent gave the crude product, which was purified by column chromatography (5% etyl acetate hexane) to afford **37** (0.387 g, 82%) as an oil. IR (KBr): ν = 2940, 2868, 1607, 1512, 1031,772 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, J = 8.3 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 5.37 (t, J = 6.0H_Z 1H), 5.04 (t, J = 7.5 Hz, 1H), 4.62 (t, J = 3.0 Hz, 1H), 4.43 (s, 2H), 4.28–4.20 (m, 1H), 4.05–3.96 (m, 1H), 3.92–3.83 (m, 1H), 3.81 (s, 3H), 3.54–3.46 (m, 1H), 3.43 (t, J = 6.8 Hz, 2H), 2,78 (d, J = 6.8 Hz, 2H), 2 (t, J = 6.8 Hz, 2H), 1.87–1.78 (m, 1H), 1.73–1.67 (m, 1H), 1.71 (S, 3H), 1.68 (s, 3H), 1.66–1.59 (m, 4H), 1.58–1.50 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 140.3, 135.8, 130.5, 129.1 (2C), 122.8, 120.9, 113.6 (2C), 97.8, 72.5, 69.7, 63.3, 62.1, 52.2, 30.6 (2C), 28.2, 27.9, 25.4, 23.5, 23.2, 19.5 ppm. HRMS (ESI): calcd for $C_{24}H_{36}O_4NH_4$ $[M+NH_4]^+$ 406.2952; found 406.2924.

4.30. (2*R*,5*E*,9*Z*,12*Z*)-2-(*tert*-Butyldiphenylsilyloxy)-1-(4-methoxybenzyloxy)-9,12-dimethyl-14-(tetrahydro-2*H*-pyran-2-yloxy) tetradeca-5,9,12-trien-4-one 38

To a stirred solution of PMB ether **37** (0.650 g, 1.6 mmol) in dichloromethane (10 mL) was added a pH 7 buffer (0.2 mL) and DDQ (0.380 g, 1.6 mmol) in three portions over 30 min. Upon the addition of DDQ, the reaction mixture became orange and as DDQ was consumed the reaction solution became dark green. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with dichloromethane (20 mL) and sat. $NaHCO_3$ (10 mL) and stirred vigorously for 10 min. The phases were separated and the aqueous layer washed with dichloromethane (3 × 15 mL). The organic phases were combined, dried over sodium sulfate and concentrated. The crude oil was purified by silica gel column chromatography (10% ethyl acetate hexane) to afford (4*Z*,7*Z*)-4,7-dimethyl-9-(tetrahydro-2*H*-pyran-2-yloxy)nona-4,7-dien-1-ol (0.399 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.37 (t, J = 7 Hz, 1H), 5.11 (t, J = 7 Hz, 1H), 4.64 (t, J = 3.8 Hz, 1H), 4.31–4.22 (m, 1H), 4.06–3.96 (m, 1H), 3.95–3.84 (m, 1H), 3.64 (t, J = 6.2 Hz, 2H), 3.56–3.48 (m, 1H), 2.81 (t, J = 6.6 Hz, 2H), 2.16 (t, J = 8.1 Hz, 2H), 1.88–1.80 (m, 2H), 1.74 (s, 3H), 1.70 (s, 3H), 1.66–1.50 (m, 6H) ppm. ^{1}H NMR (75 MHz, $CDCl_3$): δ = 140.5, 135.8, 122.6, 120.8, 97.9, 63.4, 62.5, 62.3, 30.8, 30.6 (2 C), 27.9, 25.4, 23.5, 23.2, 19.5 ppm. HRMS (ESI): calcd for $C_{16}H_{28}O_3Na$ $[M+Na]^+$ 291.1823; found 291.1726.

To a suspension of alcohol (4*Z*,7*Z*)-4,7-dimethyl-9-(tetrahydro-2*H*-pyran-2-yloxy)nona-4,7-dien-1-ol (0.399 g, 1.49 mmol) and

sodium bicarbonate (0.750 g, 8.92 mmol) in dry DCM (10 mL) was added Dess–Martin periodinane (0.954 g, 0.22 mmol) at 0 °C. The reaction mixture was stirred for 1 h. After completion, the reaction was quenched with sat. sodium thiosulfate and stirred until the appearance of a clear solution. The organic layer was separated and the aq layer extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with satd. $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo to give the crude aldehyde (0.388 g, 98%), which was used directly in the next step without further purification.

To a solution of β-keto phosphonate **36** (0.388 g, 1.17 mmol) in THF (15 mL) was added $Ba(OH)_2{\cdot}8H_2O$ (0.460 g, 1.42 mmol), preactivated by heating in a 110 °C oven for 2 h and then dried under vacuum and the reaction mixture was allowed to stir for 30 min. To this mixture, was added a solution of the above crude aldehyde (0.388 g, 1.45 mmol) in THF/H_2O (40:1; 10 mL) and stirring continued for 2 h at rt. Upon completion, the reaction mixture was diluted with a saturated aqueous NH_4Cl solution (20 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography (8% ethyl acetate hexane) to give the coupled product **38** (0.844 g, 80%) as a colourless oil. $[\alpha]_D^{26} = +17$ (*c* 0.68, $CHCl_3$). IR (KBr): ν = 3102, 2925, 2855, 1726, 1247, 1118, 704 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.7–6.63 (m, 4H), 7.45–7.31 (m, 6H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.74–6.61 (m, 1H), 6.04–6.93 (m, 1H), 5.38, *J* = 7.7 Hz, 1H), 5.08 (t, *J* = 7.1 Hz, 1H), 4.62 (t, *J* = 3.5 Hz, 1H), 4.44–4.35 (m, 1H), 4.28–4.18 (m, 3H), 4.04–3.96 (m, 1H), 3.91–3.82 (m, 1H), 3.79 (s, 3H), 3.55–3.45 (m, 1H), 3.35 (d, , *J* = 5.1 Hz, 2H), 2.81–2.72 (m, 3H), 2.25–2.14 (m, 4H), 1.86–1.75 (m, 2H), 1.71 (s, 3H), 1.68 (s, 3H), 1.63–1.48 (m, 5H), 1.01 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.3, 158.9, 146.8, 139.8, 135.7, 134.7, 134.2, 133.4, 130.9, 130.3, 129.6 (2 C), 129.4 6 (2 C), 129.1 6 (2 C), 127.5 6 (2 C), 127.3 6 (2 C), 123.5, 121.3, 113.5 6 (2 C), 97.8, 73.4, 72.5, 69.2, 63.2, 62.1, 55.1, 44.7, 30.8, 30.6, 30.2, 29.5, 26.8 (3 C), 25.4, 23.5, 23.2, 19.5, 19.2 ppm. HRMS (ESI): calcd for $C_{45}H_{60}O_6NaSi$ $[M+Na]^+$ 747.40514; found 747.40410.

4.31. (*R*,2*Z*,5*Z*,9*E*)-13-(*tert*-Butyldiphenylsilyloxy)-14-(4-methoxybenzyloxy)-3,6-dimethyl-11-oxotetradeca-2,5,9-trienoic acid 39

To a solution of compound **38** (0.150 g, 0.20 mmol) in methanol (5 mL) was added a catalytic amount of (−)-camphor-10-sulfonic acid at 0 °C. The reaction temperature was then warmed to room temperature and stirring continued for 4 h. After being stirred, the reaction mixture was concentrated to remove methanol and diluted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford the crude product. Purification by column chromatography (15% ethyl acetate in hexane) gave (*R*,5*E*,9*Z*,12*Z*)-2-(*tert*-butyldiphenylsilyloxy)-14-hydroxy-1-(4-methoxybenzyloxy)-9,12-dimethyltetradeca-5,9,12-trien-4-one (0.110 g, 83%) as a colourless oil. $[\alpha]_D^{25}$ = +20.5 (*c* 0.76, $CHCl_3$). IR (KBr): ν = 3216, 3049, 2922, 2933, 2856, 2852, 1729, 1516, 1245, 871, 722 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.67 (t, *J* = 7.7 Hz, 4H), 7.45–7.30 (m, 6H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 6.73–6.61 (m, 1H), 6.0 (d, *J* = 15.8 Hz, 1H), 5.4 (t, *J* = 6.8 Hz, 1H), 5.09 (t, *J* = 6.8 Hz, 1H), 4.44–4.35 (m, 1H), 4.23 (q, *J* = 16.5 Hz, 2H), 4.11 (d, *J* = 6.9 Hz, 2H), 3.79 (s, 3H), 3.35 (d, *J* = 4.7 Hz, 2H), 2.81–2.71 (m, 4H), 2.29–2.06 (m, 4H), 1.70 (s, 3H), 1.69 (s, 3H), 1.01 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.4, 159.0, 146.7, 139.2, 135.9 (2 C), 135.8 (2 C), 134.8, 134.1, 133.4, 131.0, 130.3, 129.6, 129.5, 129.1 (2 C), 127.5 (2 C), 127.4 (2 C), 124.0, 123.5, 113.5 (2 C), 73.4, 72.6, 69.3, 58.9, 55.2, 44.9, 30.7, 30.6, 30.2, 26.9, (3 C), 23.5, 23.1, 19.2 ppm. ESI-MS: *m*/*z* = HRMS (ESI): calcd for $C_{40}H_{52}O_5NaSi$ $[M+Na]^+$ 663.2293; found 663.2282.

To a suspension of the above alcohol (0.100 g, 0.15 mmol) and sodium bicarbonate (0.078 g, 0.92 mmol) in dry DCM (10 mL) was added Dess–Martin periodinane (0.099 g, 0.21 mol) at rt and the reaction mixture was allowed to stir for 1 h. After completion of the reaction (monitored by TLC), it was quenched with sat. sodium thiosulfate and stirred vigorously until the appearance of two layers. The organic layer was separated and the aq layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with satd. $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4 and evaporated in vacuo to give the crude aldehyde (0.097 g, 98%), which was used directly in next step without further purification.

To a solution of the above aldehyde (0.097 g, 0.15 mmol) and 2-methyl-2-butene (4 mL) in *tert*-butanol (10 mL) was added dropwise a solution of $NaH_2PO_4{\cdot}H_2O$ (250 mg) and $NaClO_2$ (250 mg) in H_2O (2.5 mL) at 0 °C. The reaction mixture was then allowed to warm up to rt and stirred for 30 min. After being stirred, the reaction was poured into water (6 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo. The crude product was purified by flash chromatography (25% ethyl acetate hexane) to give **39** (0.088 g, 89%) as a colourless oil. $[\alpha]_D^{25}$= +14.25 (*c* 0.41, $CHCl_3$). IR (KBr): ν = 3741, 2923, 2913, 2858, 2746, 1739, 1563, 1460, 1219, 846 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.63 (m, 4H), 7.44–7.38 (m, 2H), 7.37–7.31 (m, 4H), 7.10 (d, *J* = 8.9 Hz, 2H), 6.81 (d, *J* = 7.9 Hz, 2H), 6.71–6.61 (m, 1H), 5.99 (d, *J* = 15.8 Hz, 1H), 5.67 (s, 1H), 5.17 (t, *J* = 7.9 Hz, 1H), 4.44–4.38 (m, 1H), 4.26 (q, *J* = 16.8 Hz, 2H), 3.79 (s, 3H), 3.49–3.41 (m, 2H), 3.36 (d, *J* = 4.9 Hz, 2H), 2.81–2.74 (m, 1H), 2.47 (t, *J* = 7.9 Hz, 2H), 2.26–2.20 (m, 1H), 1.90–1.83 (m, 5H), 1.69 (s, 3H), 1.0 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.6, 178.2, 161.4, 159.0, 147.1, 136.2, 136.0 (2C), 135.8, 134.1, 133.4, 131.0, 130.1, 129.6, 129.5, 129.3 (2C), 129.2, 127.6, 127.5 (2C), 127.4, 121.9, 115.3, 113.6 (2C), 77.2, 73.3, 69.2, 55.2, 44.8, 31.9, 31.0, 30.8, 30.3, 26.9 (3C), 22.6, 19.7 ppm. HRMS (ESI): calcd for $C_{40}H_{50}O_6NaSi$ $[M+Na]^+$ 677.3269; found 677.3248.

4.32. (*S*,3*Z*,6*Z*,10*E*)-14-((4-Methoxybenzyloxy)methyl)-4,7-dimethyloxacyclotetradeca-3,6,10-triene-2,12-dione 41

To a stirred solution of **39** (0.065 g, 0.099 mmol) in THF (1 mL) was added TBAF (0.15 mL, 1 M solution in THF, 0.149 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 6 h, then diluted with EtOAc (5 mL) and poured into water (2 mL). The aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4. Removal of the solvent gave the crude product, which was purified by flash chromatography (30% ethyl acetate hexane) to afford *seco*-acid **40** (0.034 g, 83%) as a colourless oil. $[\alpha]_D^{25} = +4.9$ (*c* 0.25, $CHCl_3$). IR (KBr): ν = 3304, 2924, 2854, 1730, 1647, 1635, 1462, 1219, 772 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 9.0 Hz, 2H), 6.91–6.81 (m, 3H), 6.12 (d, *J* = 15.8 Hz, 1H), 5.67 (s, 1H), 5.20 (t, *J* = 6.9 Hz, 1H), 4.51 (s, 2H), 4.33–4.26 (m, 1H), 3.92–3.82 (m, 2H), 3.80 (s, 3H), 3.76–3.68 (m, 1H), 3.41–3.32 (m, 2H), 2.78–2.71 (m, 1H), 2.36–2.28 (m, 3H), 1.92–1.85 (m, 4H), 1.70 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.3, 169.1, 161.2, 148.2(2C), 136.0, 130.7, 129.4 (3C), 122.0, 115.2, 113.7 (2C), 77.1, 73.0, 67.0, 55.2, 42.7, 31.7, 30.6, 30.2, 29.6, 22.9 ppm. HRMS (ESI): calcd for $C_{24}H_{32}O_6Na$ $[M+Na]^+$ 439.2186; found 439.2154.

To solution of PPh_3 (0.057 g, 0.218 mmol, azeotropically dried twice with benzene) in dry THF (0.05 M) was added DIAD (0.037 g, 0.187 mmol) at room temperature. The solution was stirred at room temperature for 30 min. To this solution was added a solution of *seco*-acid **40** (0.026 g, 0.063 mmol) in THF (0.003 M) at 0 °C over a

period of 2 h via syringe pump. The resulting mixture was stirred for an additional 4 h at this temperature and quenched with water. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by flash column chromatography (15% ethyl acetate hexane) to afford **41** (0.013 g, 56%) as a colourless oil. $[\alpha]_D^{25} = -4.75$ (*c* 0.08, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 8.3 Hz, 2H), 6.94–6.85 (m, 3H), 6.33 (d, *J* = 14.8 Hz, 1H), 6.05 (s, 1H), 4.71–4.67 (m, 1H), 4.51 (s, 2H), 4.32–4.27 (m, 1H), 4.11–4.01(m, 1H), 3.97–3.89 (m, 2H), 2.78–2.71 (m, 1H), 2.11–1.99 (m, 4H), 1.90 (s, 3H), 1.80 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.7, 165.4, 160.9, 149.2, 148.3, 135.2, 130.5, 129.6 (3C), 127.3, 117.5, 113.6 (2C), 75.2, 72.8, 71.6, 55.4, 43.0, 31.8, 30.8, 30.7, 30.4, 23.2 ppm. HRMS (ESI): calcd for $C_{24}H_{30}O_5Na$ $[M+Na]^+$ 421.1985; found 421.1943.

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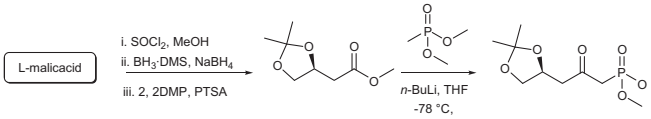

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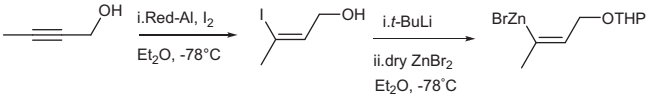

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