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Asymmetric synthesis of naturally occurring (−)-seimatopolides A and B

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ABSTRACT

Asymmetric total synthesis of polyhydroxylated naturally occurring nonenolide seimatopolide A (3*S*,6*S*,7*S*,9*R*) and seimatopolide B (3*S*,6*R*,9*R*) is described in this article. An *E*-selective cross metathesis (CM) reaction between two suitable fragments followed by macrolactonization reaction is the main highlight of our synthesis for the two natural products. The fragment containing 6*S*,7*S*,9*R* stereocenters for seimatopolide A has been synthesized from L-tartaric acid as a chiral pool starting material, by employing (*R*)-CBS-mediated stereoselective keto reduction reaction. Another fragment, which is common for both the molecules, containing the 3*S* stereocenter was prepared by ME-DKR (metal enzyme combined dynamic kinetic resolution) method. The fragment having 6*R*,9*R* stereocenters for seimatopolide B has been prepared from *n*-decanal by adopting (*R*)-CBS-mediated keto reduction and Brown asymmetric allylation reaction.

1. Introduction

Nonanolides (known as decanolides) are biologically active secondary metabolites that contain a 10-membered macrolide core and a C-9 alkyl appendage as its main structural components, which can be broadly classified in two structural families: (i) having a C-9 methyl substitution and (ii) containing higher alkyl substitution at C-9. Cytospolides,[1] Herbarumins,[2] Pinolidoxin,[3] and Achaetolide[4] are few representative examples belonging to the second family of decanolides. Recently two new decanolides seimatopolides A and B were isolated from a fungal culture broth of *Seimatosporium discosioides*, which contain a C-9 nonyl (n-C_9H_{19}) appendage.[5] The structure of both the decanolides was established by extensive NMR analysis of the corresponding Moscher's ester. The absolute configuration of seimatopolide A was proposed to be 3*R*,6*R*,7*R*,9*S* whereas that for seimatopolide B was 3*R*,6*S*,9*S*. Seimatopolides A and B have significant biological activity, as both of them found to activate PPAR-γ receptor (peroxisome proliferator-activated receptor γ) with EC_{50} values of 1.15 and 11.05 μM, respectively. This receptor is known for its regulatory activity of fatty acid storage and glucose metabolism.[6] Hence this receptor has been linked with the pathological function of several diseases such as obesity, diabetes, atherosclerosis, and cancer. Till today, there are six total syntheses reported in the literature[7] for seimatopolide A and two for seimatopolide B.[7g,h] The absolute configuration was reassigned for both the decanolides by Reddy's group[7a] and Schmidt's group[7b] and they proposed that the revised absolute configuration will be 3*S*,6*S*,7*S*,9*R* for seimatopolide A and 3*S*,6*R*,9*R* for seimatopolide B (enantiomeric to the originally proposed structure; Fig. 1). The Schmidt group had also synthesized both the enantiomers of seimatopolide A and reassigned the absolute configuration based on chirooptical methods. In recent times our group is actively engaged in the synthesis of small and medium sized ring macrolides.[8] In continuation to previous effort, herein we intend to report the asymmetric total synthesis of seimatopolides A and B through a reverse sequential strategy. The normal sequential strategy applied for seimatopolide A/B involves esterification followed by ring closing metathesis (RCM) reaction to construct the decanolide core as evident from the earlier reports. The strategy of altered reaction sequences (CM followed by macrolactonization) for asymmetric synthesis of a structurally similar decanolide xyolide was just reported.[8j]

2. Result and discussion

The previously reported synthetic strategies for seimatopolide A/B involve application of a successful late stage *E*-selective RCM (ring closing metathesis) reaction in all the cases. The RCM precursor was constructed through an esterification reaction of properly substituted alcohol and acid. In this setup, it has been decided

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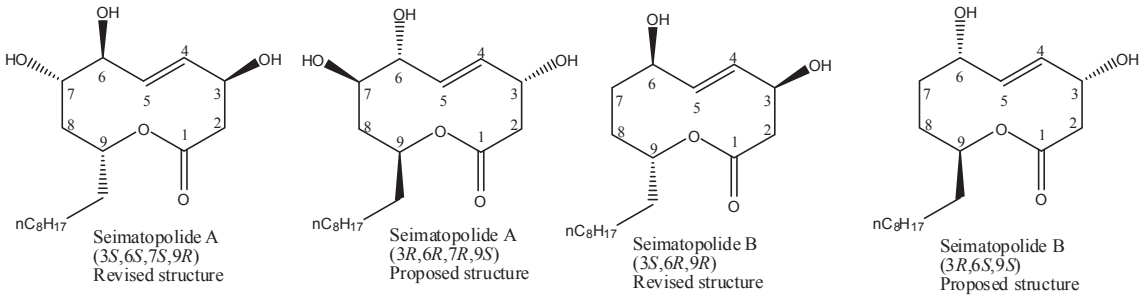
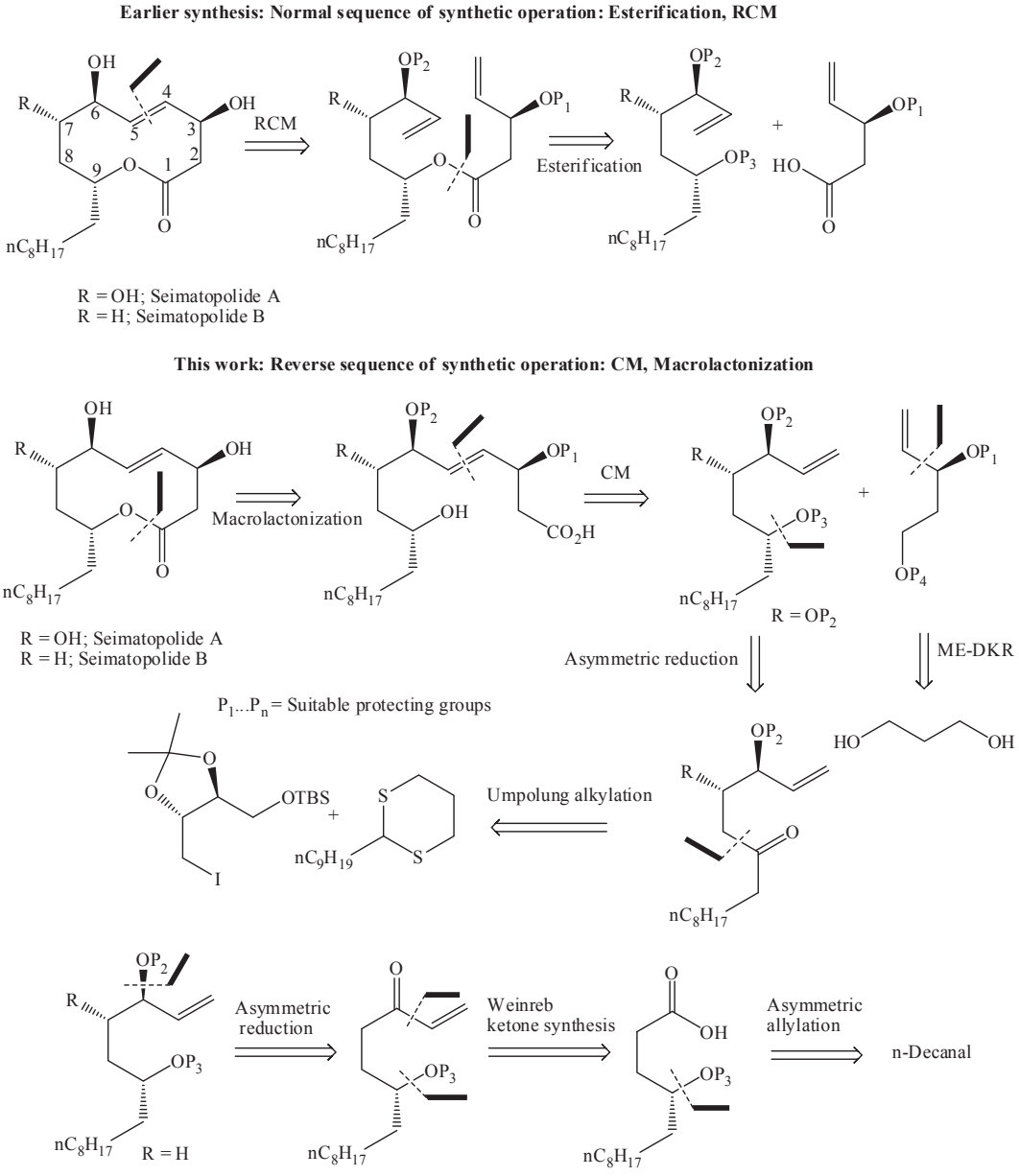


Fig. 1. Structures of seimatopolides A (revised and proposed) and B.

to carry out the synthetic efforts toward seimatopolide A by an altered sequence of chemical reactions. We intend to apply an *E*-selective CM reaction at the beginning followed by a macrolactonization method to construct the core decanolide structure. The proposed retrosynthetic strategy is detailed in Scheme 1. It is envisioned that macrolactonization of the seco-acid could be an alternative option to construct the decanolide core of the target molecule seimatopolide A/B, as it was rarely attempted before.[7f] The seco-acid in turn was planned to be accessed by an *E*-selective (the olefinic unsaturation between C_4 and C_5) CM reaction of the required olefinic fragments in both the cases. For seimatopolide A, the C_9-stereocenter in fragment (C_4–C_9) was created by

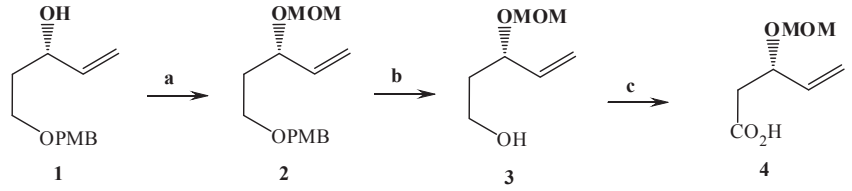


Scheme 1. Retrosynthetic analysis of seimatopolides A and B.

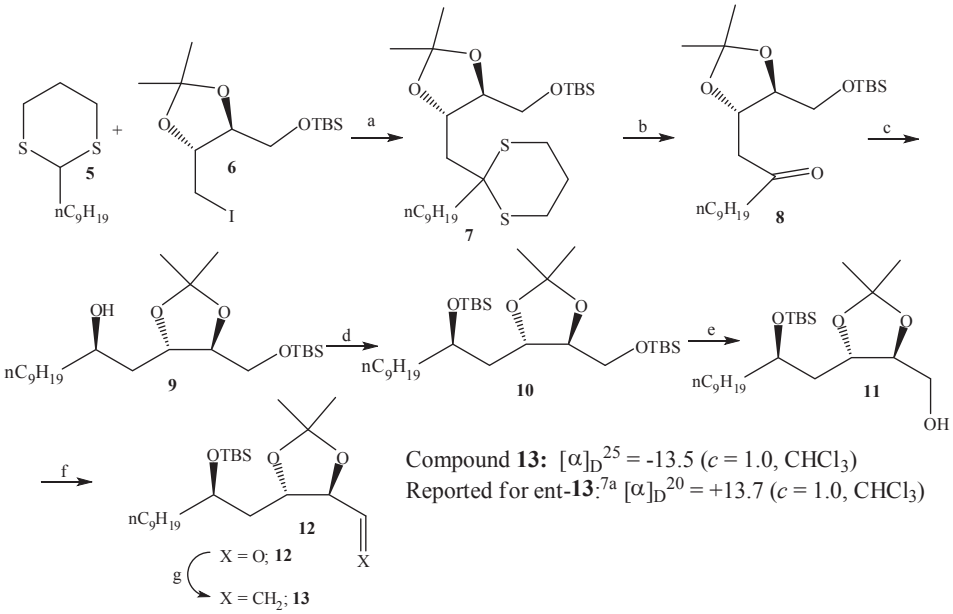
stereoselective CBS reduction of the corresponding ketone. The ketone was synthesized by an umpolung alkylation of substituted 1,3-dithiane (derived from *n*-decanal) with the iodo compound derived from C_2-symmetric L-tartaric acid as a chiral pool. The other fragment (C_1–C_5) was synthesized from a known enantiopure alcohol, which was earlier synthesized in our group by adopting an ME-DKR reaction of the racemic alcohol[8f] and this fragment will be used for both the decanolides. For seimatopolide B, the stereocenter in the C_6 (6*R*) position was created by stereoselective CBS reduction of a vinyl ketone, which in turn was accessed from asymmetric Brown allylation reaction from *n*-decanal (Scheme 1; constitutes the C_9 (9*R*) stereocenter in the target molecule).

2.1. Synthesis of the C_1–C_5 fragment for seimatopolide A/B

The synthesis starts from the known enantiopure alcohol **1**.[8f] The free alcohol group in compound **1** was protected as its MOM-ether by treatment with MOM-Cl and DIPEA to afford compound **2** in 90% yield. The PMB-group in compound **2** was deprotected with DDQ (Na-phosphate buffer; pH=7.0)[9] to afford alcohol **3** in 88% yield. The primary alcohol functionality is then oxidized to carboxylic acid **4** by treatment with BAIB/TEMPO[10] in 88% yield (Scheme 2).



Scheme 2. Reagents and conditions: (a) MOM-Cl, DIPEA, TBAI (cat), DCM, rt, 4 h, 90%; (b) DDQ, DCM/phosphate buffer (9:1, pH=7.0), rt, 1 h, 88%; (c) BAIB, TEMPO (cat), DCM/water (1:1), rt, 4 h, 88%. BAIB: [bis(acetoxy)iodo]benzene.



Scheme 3. Reagents and conditions: (a) *t*-BuLi, −78 °C, THF/HMPA (10:1), 30 min, 80%; (b) I_2, $CaCO_3$, THF:H_2O (4:1), 90%; c) (*R*)-CBS (20 mol %), $BH_3{\cdot}SMe_2$, THF, −78 °C to rt, 6 h, 72%; (d) TBS–OTf, 2,6-lutidine, DCM, 88%; (e) HF/pyridine, THF, rt, 90%; (f) BAIB, TEMPO, $NaHCO_3$, DCM, rt, 2 h, 86%; g) $Ph_3P^+CH_3I^-$; LHMDS, THF, 0 °C to rt, 4 h, 75%.

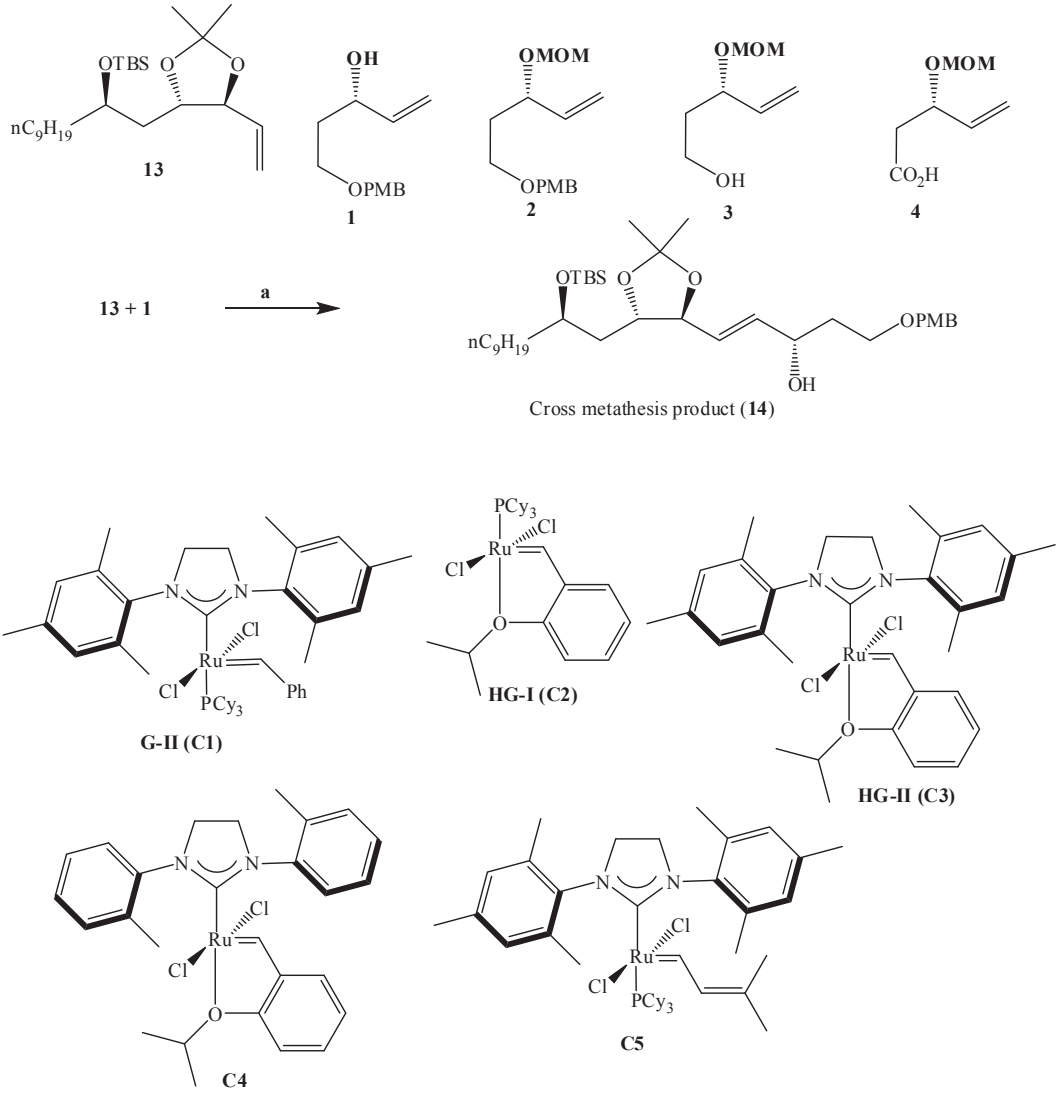
2.2. Synthesis of C_4–C_9 fragment for seimatopolide A

The synthesis was initiated from *n*-decanal, which was protected as its dithiane by treatment with 1,3-propanedithiol to afford compound **5** in 85% yield. Umpolung alkylation of compound **5** with known iodide (**6**) derived from L-tartaric acid in presence of *t*-BuLi afforded compound **7** in 80% yield (brsm). The dithiane group in compound **7** was deprotected by using I_2 and $CaCO_3$ to afford ketone **8** in 90% yield.[11] All the attempts for stereoselective reduction of the carbonyl group in compound **8** (substrate directed approach with hydride sources such as $NaBH_4$, $LiBH_4$, DIBAL-H, L-Selectride) failed, as the desired amount of stereocontrol was not achieved, we have then switched over to reagent control approach. Stereoselective reduction of ketone **8** with (*R*)-CBS[12] afforded the alcohol **9** as a sole product. The secondary hydroxyl group was then protected as its TBS ether by treatment with TBS–OTf and 2,6-lutidine to afford compound **10** in 88% yield. Selective deprotection of 1° TBS group in presence of 2° TBS group was achieved by treating compound **10** with HF/pyridine[13] to afford compound **11** in 90% yield. Oxidation of primary hydroxyl group in compound **11** with BAIB/TEMPO[14] furnished the aldehyde **12** in 86% yield. The aldehyde **12** was then subsequently reacted with $Ph_3P{=}CH_2$ to afford compound **13** in 75% yield (overall yield 26% from *n*-decanal; Scheme 3). The absolute stereochemistry of compound **13** (corresponds to 6*S*,7*S*,9*R* in seimatopolide A) was confirmed by comparing the spectroscopic data ($^1H/^{13}C$ NMR) and optical rotation values with those of a known compound reported from Reddy's group[7a] for their synthesis of (+)-seimatopolide A.

2.3. Fragment coupling and completion of the synthesis for seimatopolide A

After successful construction of both the fragments, our next job is to couple them by cross metathesis reaction. One of the

reacting partners in CM reaction was kept constant, and compound **13** was chosen for that purpose. Whereas for choosing the other partner we have performed a systematic optimization with compounds **1**–**4** with the following Ru-based metathesis catalyst (**C1**–**C5**; Scheme 4). It was observed that olefins **2** and **4** were sluggish in the CM reaction with olefin **13**. In all the cases starting olefin remains unreacted, which implies that both of the olefins (**2** and **4**) are indeed slower in homodimerization process and belongs to type-II olefin as mentioned by Grubbs.[15] In that article by Grubbs it was mentioned clearly that the prerequisite of a successful CM reaction depends on the judicious choice of olefin partners. The best approach toward a successful CM reaction involves reaction of an olefin (type-I; which undergoes fast homodimerization; compound **13** in our case) with a slow reactive olefin (type-II, slow homodimerization, compounds **1**–**4** in our case). But in our initial findings we observed that for olefins **2** and **4**, when reacted with compound **13** (in presence of metathesis catalyst **C1**–**C5**), no CM product was isolated. Compounds **1**–**4**, all having 2° allylic alcohol (free in olefin **1**, in olefins **2** and **4** the alcohol is protected by suitable protecting group and in case of olefin **3**, primary alcohol is free at one terminal) moiety with a terminal olefinic functionality belongs to type-II olefin. When compound **1** was reacted with olefin **13**, we have isolated the CM product in 70% yield (with catalyst **C3**, Scheme 4). The olefin **3** with a free primary –OH group at one end, also reacted with olefin **13** with catalyst **C3**, and the yield of isolated product was lower than in the case of olefin **1** (*E*/*Z*=9:1). It is clear that greater reactivity was observed with free 2° allylic alcohol moiety (in compound **1**) than the protected one (compounds **2** and **4**). The similar observation was also pointed out by Grubbs in his article.[15] Even olefin **3**, with a free 1° alcohol is also reactive under the reaction condition. The reason was not clear, but increasing steric bulk through protecting group might cause inertness of those olefins (**2** and **4**) toward CM reaction. Similar findings were also reported by researchers,[16] in which they have clearly demonstrated that the presence of free 2° allylic alcohol moiety has a rate enhancing effect in RCM reaction. The reason for that high activity is not very clear, but the possibility of rapid and reversible ligand exchange (alkoxy group replaces the Cl) and hydrogen bonding between hydroxyl group and one of the chloride ligands cannot be ruled out. The moderate reactivity (good *E*/*Z* selectivity) of olefin **3**, under the CM condition is beneficial to us in the sense that, this can be used as one of the CM counterpart for the total synthesis of seimatopolide B.



Scheme 4. Reagents and conditions: (a) **C3** (5 mol %), DCM, 24 h reflux, 70%.

The best results in the CM reaction (selectivity and reactivity; *E*/*Z* ~12:1, Table 1) were obtained with catalyst **C3** (Hoveyda–Grubbs second generation catalyst; HG-II).[17] With the catalyst **C1** (G-II),[18] the CM product was isolated in 30% yield with poor selectivity (*E*/*Z* ~1:1). Whereas with catalyst **C2** (HG-I)[19] no product formation was detected, indicating that NHC type metathesis catalyst is the ideal choice for best reactivity and selectivity. The catalyst **C4** (HG-II analogue),[20] reacts extreme slowly and high amount of catalyst (20 mol %) was required to achieve the formation of **14** (Scheme 4, 40% isolated yield, after 80 h, *E*/*Z* ~8:1). The catalyst **C5** (G-II analogue)[21] is similar in reactivity and selectivity when compared with catalyst **C1**. The details for optimization of the CM reaction are presented in Table 1.

Table 1
Optimization of the CM conditions

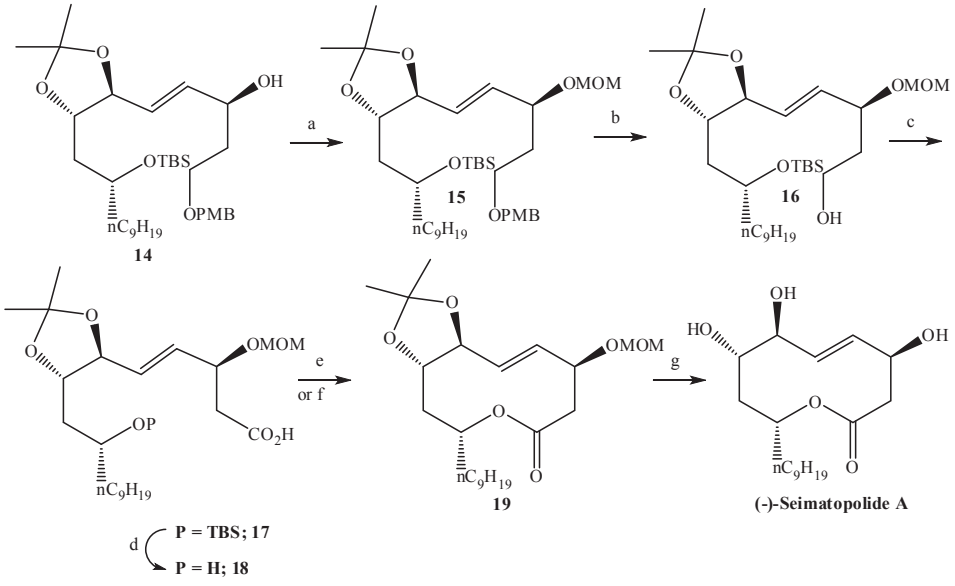
Entry	Type-I olefin[a]	Type-II olefin[a]	Metathesis catalyst	Catalyst loading (mol %)	Yield[b] (%)	Selectivity (*E*/*Z*)
1	**13**	**1**	**C1**	5	30	1:1
2	**13**	**1**	**C2**	5	nr	nr
3	**13**	**1**	**C3**	5	70	12:1
4	**13**	**1**	**C4**	5	10	nr
4	**13**	**1**	**C4**	20	40[c]	8:1
5	**13**	**1**	**C5**	5	25	1:1
6	**13**	**2**	**C1–C5**	5	nr	nr
7	**13**	**3**	**C3**	5	40	9:1
8	**13**	**4**	**C1–C5**	5	nr	nr

nr: No significant reaction was observed.
[a] Type-II olefin of 2 equiv was taken at the beginning, additional 2 equiv was added after 30 min.
[b] Yields refer to isolated yield after refluxing in DCM for 24 h.
[c] After 80 h reflux in DCM.

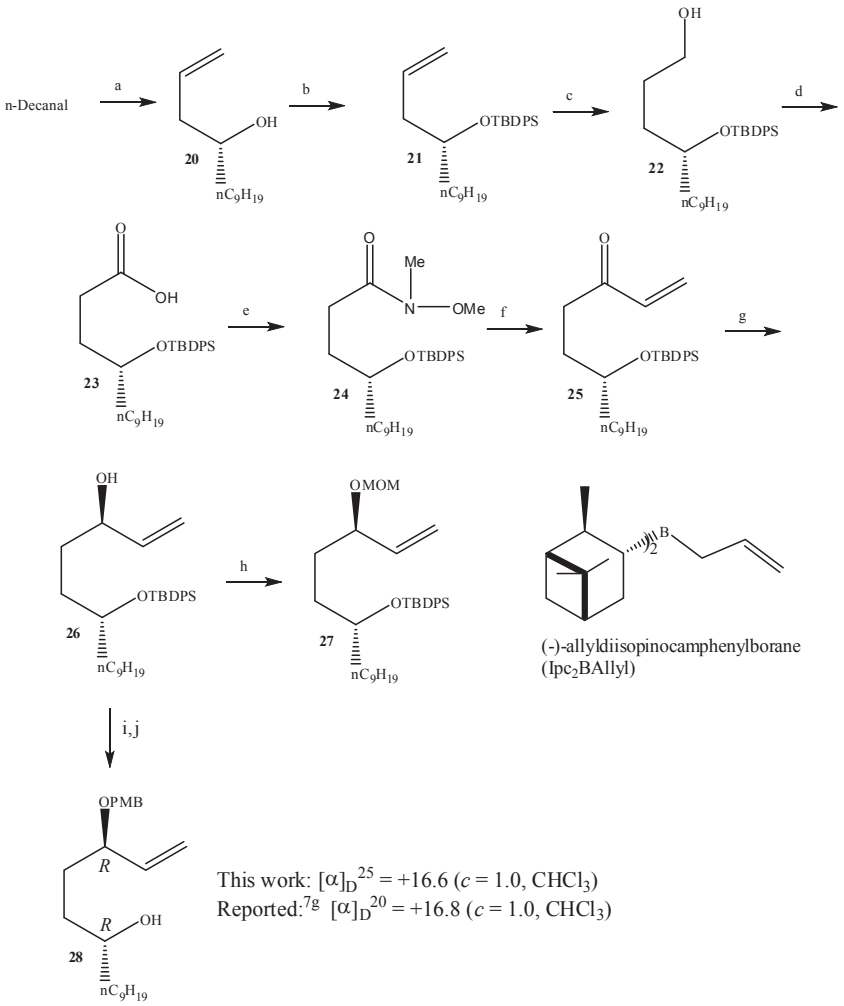
After successful optimization of CM reaction, we have proceeded for the next step. The free hydroxyl group in compound **14** was protected with MOM-Cl to furnish compound **15** in 90% yield. Deprotection of PMB-group was achieved by treating compound **15** with DDQ to afford compound **16** in 82% yield. Oxidation of the primary alcohol group in compound **16** was achieved with DMP to give the corresponding aldehyde, which on subsequent oxidation under Pinnick condition[22] afforded the carboxylic acid **17** in 82% yield (two steps). Deprotection of the TBS group with TBAF/THF afforded the seco-acid **18** in 85% yield. Macrolactonization of the acid **18** under Yamaguchi[23] and Shiina[24] conditions afforded the decanolide core **19** in 62 and 68% yields, respectively. Finally deprotection of acetonide and MOM groups was achieved by treating compound **19** with 2 M HCl in THF to afford the target molecule seimatopolide A (Scheme 5; overall yield=5% from *n*-decanal). The spectral data of our synthesized seimatopolide A ($^1H/^{13}C$ NMR) matches perfectly with those of reported one.[7a,b] Optical rotation value {$[\alpha]_D^{28}$ −27.4 (*c* 0.05, MeOH)} also matches perfectly with those of literature value as reported by Schmidt's group and Reddy's group in their respective synthesis of (−)-seimatopolide A, having absolute configuration 3*S*,6*S*,7*S*,9*R*.

2.4. Synthesis of C_4–C_9 fragment for seimatopolide B

The synthesis was commenced from *n*-decanal, which on asymmetric allylation by Brown method[25] afforded the alcohol **20** in 88% yield with excellent enantioselection (er >99%). Protection of the free alcohol group with TBDPS-Cl afforded compound **21** in 92% yield. Hydroboration of compound **21** with $BH_3 \cdot SMe_2$ followed by oxidation with $NaOH/H_2O_2$ furnished alcohol **22** in 82% yield. Oxidation of alcohol **22** with BAIB/TEMPO afforded corresponding carboxylic acid **23** in 88% yield. Acid **23** is then coupled with *N*,*O*-dimethylhydroxyl amine in presence of EDC·HCl and Et_3N to afford the corresponding Weinreb amide[26] **24** in 90% yield. Vinylmagnesium bromide addition on amide **24** at −78 °C afforded the ketone **25** in 90% yield. Stereoselective ketone reduction with (*R*)-CBS afforded the alcohol **26** (dr ~15:1). Protection of the free hydroxyl group with MOM-Cl in presence of DIPEA afforded the protected MOM-ether **27** in 86% yield (Scheme 6). The absolute stereochemistry of compound **26** (3*R*,6*R*, which corresponds to 6*R*,9*R* stereocenters in the natural product seimatopolide B) was confirmed by converting **26** into a known compound **28** and comparing the spectroscopic data ($^1H/^{13}C$ NMR) and optical rotation values with those of that reported by Reddy et al.[7g] for their synthesis of (+)-seimatopolide B.



Scheme 5. Reagents and conditions: (a) MOM-Cl, DIPEA, DCM, 90%; rt, 8 h; (b) DDQ, DCM/phosphate buffer (9:1, pH=7.0), rt, 2 h, 82%; (c) (i) DMP, $NaHCO_3$, DCM, rt, 2 h, (ii) $NaClO_2$, NaH_2PO_4, *t*-BuOH, 2-methyl-2-butene, H_2O, rt, 4 h, 82% in two steps; (d) TBAF, THF, rt, 6h, 85%; (e) 2,4,6-trichlorobenzoylchloride, DIPEA, DMAP, toluene, 60 °C, 24 h, 62%; (f) MNBA (2-methyl-6-nitro benzoic anhydride), DIPEA (diisopropylethyl amine), DMAP, toluene, 60 °C, 24 h, 68%; (g) 2 M HCl, THF, rt, 12 h, 80%.



Scheme 6. Reagents and conditions: (a) (−)-Ipc_2B-Allyl, 88%; (b) imidazole, TBDPS-Cl, DCM, rt, 4 h, 92%; (c) BH_3/SMe_2, THF, H_2O_2, NaOH, 2 h, 82%; (d) BAIB, TEMPO, DCM/H_2O (1:1), 3 h, rt, 88%; (e) MeNH(OMe)·HCl, Et_3N, DCC, rt, 6 h, 90%; (f) CH_2=CHMgBr, THF, −78 °C to rt, 2 h, 90%; (g) (*R*)-CBS (20 mol %), BH_3·SMe_2, THF, −78 °C to rt, 6 h, 75%; (h) MOM-Cl, DIPEA, DCM, TBAI, rt, 86%; (i) PMB-imidate, $Sc(OTf)_3$, −10 °C, 15 min, 85%; (j) TBAF, THF, rt, 6 h, 95%.

2.5. Fragment coupling and completion of the synthesis for seimatopolide B

With compound **27** in our hand, we next proceeded for the CM reaction with the previously synthesized compound **3**. Cross metathesis reaction of compound **27** with **3** proceeded smoothly as anticipated with catalyst C3 (HG-II) in refluxing DCM solvent afforded compound **29** (75%, *E*/*Z*=15:1). Oxidation of the free alcohol functionality with BAIB/TEMPO afforded corresponding carboxylic acid **30** in 85% yield. Deprotection of the TBDPS group in compound **30** was achieved by treating with TBAF in THF to furnish the seco-acid **31**. Macrolactonization of the crude seco-acid **31** under Shiina condition afforded the decanolide **32** in 72% yield. Finally deprotection of both the MOM groups were achieved by treating compound **32** with 2 M HCl to furnish seimatopolide B as a white solid in 82% yield (Scheme 7; overall yield=10.6% from *n*-decanal). The spectral data of our synthesized seimatopolide B ($^1H/^{13}C$ NMR) match perfectly with those of reported one.[7g] Optical rotation value {$[\alpha]_D^{28}$ −13.4 (*c* 0.02, MeOH)} also matches perfectly with those of the literature value as reported by Reddy's group in the synthesis of (−)-seimatopolide B, having absolute configuration 3*S*,6*R*,9*R*.

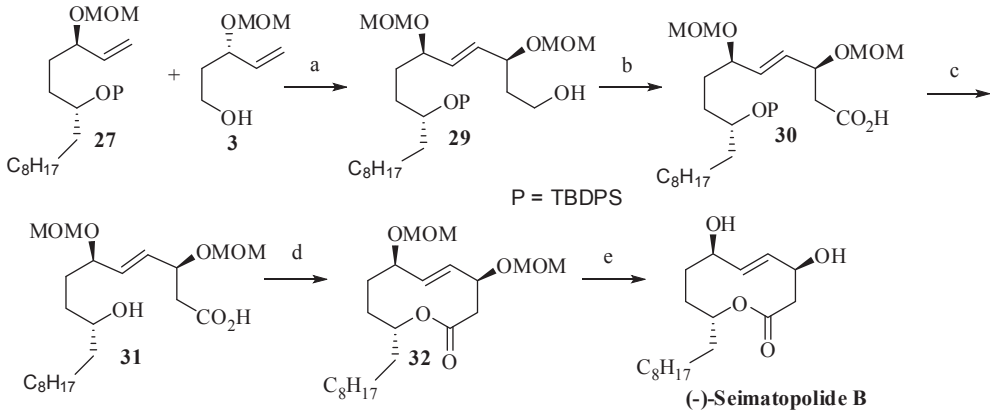
3. Conclusion

In conclusion we have achieved a short and flexible asymmetric synthesis of the naturally occurring decanolides (−)-seimatopolides A and B starting from easily available starting materials. Our reported synthesis of seimatopolides A and B is different and unique from other reported synthesis, as we have exploited a cross metathesis reaction to construct the *E*-olefinic unsaturation in the target molecule. The strategy of altered sequence of chemical reactions (CM followed by macrolactonization) adopted by us had not been explored earlier for the synthesis of such decanolides. In future, we will try to explore the strategy for the total synthesis of such structurally related macrolides.

4. Experimental section

4.1. Materials and methods

All oxygen and/or moisture-sensitive reactions were carried out under N_2 atmosphere in glassware that had been flame-dried under a vacuum (~0.5 mmHg) and purged with N_2 prior to use. Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane (DCM) and HMPA were distilled from calcium hydride. Ru-based metathesis catalysts were purchased commercial suppliers and used as obtained. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, ethanolic anisaldehyde, and phosphomolybdic acid/heat as developing agents. Silicagel 100–200 mesh was used



Scheme 7. Reagents and conditions: (a) **C3** (5 mmol %), DCM, 24 h reflux, 75%; (b) BAIB, TEMPO, DCM/H_2O (1:1), 85%; (c) TBAF, THF, rt, 4 h; (d) MNBA (2-methyl-6-nitro benzoic anhydride), DIPEA (diisopropylethyl amine), DMAP, toluene, 60 °C, 24 h, 72%; (e) 2 M HCl, THF, rt, 12 h, 82%.

for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. ^{1}H NMR spectra were obtained at 200 or 400 MHz in $CDCl_3$ or pyridine-d_5 with $CHCl_3$ (δ=7.26 ppm) or pyridine (δ=7.22 ppm) as internal standards. Coupling constants (J) are reported in hertz (Hz) and the resonance multiplicity abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; dt, doublet of triplets; dd, doublet of doublets; ddd, doublet of doublet of doublets; m, multiplet; ov=overlapped multiplets. ^{13}C NMR spectra were recorded at 50 or 100 MHz in $CDCl_3$ or pyridine-d_5 with $CDCl_3$ (δ=77.23 ppm) and pyridine (δ=135.9 ppm) as internal standards. The chemical shift value is listed as δ_H and δ_C for ^{1}H and ^{13}C, respectively. Mass spectroscopic analysis was performed in the CRF, IIT-Kharagpur (TOF analyzer). Optical rotations were measured on a JASCO digital polarimeter. HPLC analysis was performed with CHIRALPAK AD-H (Daicel) column by using UV–vis detector.

4.2. (*S*)-1-Methoxy-4-((3-(methoxymethoxy)pent-4-enyloxy) methyl)benzene (2)

To a solution of alcohol **1** (2.0 g, 9.01 mmol) in DCM (20 ml), diisopropyl ethyl amine (4.71 mL, 27.03 mmol) was added at 0 °C and stirred for 15 min at the same temperature. MOM-Cl (1.2 mL, 18.02 mmol) and tetra-*n*-butyl ammonium iodide (10 mg) was then added to the reaction mixture and stirred for additional 4 h at room temperature. Water was added to the reaction mixture and extracted with DCM, the organic solution was then washed with water and brine. The organic extracts were dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography (EtOAc/hexane=1:10) to afford the desired product **2** (2.15 g, 8.1 mmol) with 90% yield.

R_f=0.4 (EtOAc/hexane=1:10).

$[\alpha]_D^{28}$ +8.6 (*c* 0.3, $CHCl_3$).

^{1}H NMR of compound **2** (200 MHz, $CDCl_3$) δ: 7.27 (d, J=8.6 Hz, 2H), 6.88 (d, J=8.6 Hz, 2H), 5.70 (ddd, J=16.8, 10.0, 7.4 Hz, 1H), 5.26–5.16 (m, 2H), 4.70 (d, J=6.6 Hz, 1H), 4.54 (d, J=6.6 Hz, 1H), 4.43 (s, 2H), 4.20 (q, J=7.2 Hz, 1H), 3.80 (s, 3H), 3.60–3.41 (m, 2H), 3.35 (s, 3H), 1.90–1.75 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 159.3, 138.3, 130.7, 129.4, 117.3, 113.9, 94.1, 74.7, 72.8, 66.4, 55.6, 55.4, 35.8.

HRMS (ESI) for $C_{15}H_{22}O_4Na$ $[M+Na]^+$, calculated: 289.1416; found: 289.1423.

4.3. (*S*)-3-(Methoxymethoxy)pent-4-en-1-ol (3)

Compound **2** (1.8 g, 6.42 mmol) was taken in 20 mL of DCM/phosphate buffer (9:1). DDQ (1.6 g, 7.07 mmol) was added to it in one portion. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then filtered off, and the filtrate was washed with 5% $NaHCO_3$ solution, water, and brine. The organic layer was dried (over $MgSO_4$) and evaporated. Purification by silica gel column chromatography (EtOAc/hexane=1:3) afforded the desired product **3** (0.82 g, 5.64 mmol) in 88% yield.

R_f=0.4 (EtOAc/hexane=1:3).

$[\alpha]_D^{28}$ −112.6 (*c* 1.6, $CHCl_3$).

^{1}H NMR of compound **3** (200 MHz, $CDCl_3$) δ: 5.72 (ddd, J=17.4, 10.1, 7.2 Hz, 1H), 5.28–5.18 (m, 2H), 4.70 (d, J=6.6 Hz, 1H), 4.55 (d, J=6.6 Hz, 1H), 4.25 (q, J=7.0 Hz, 1H), 3.84–3.79 (m, 2H), 3.35 (s, 3H), 2.66 (br s, 1H), 1.84–1.76 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 137.5, 117.4, 93.9, 76.2, 59.9, 55.6, 37.6.

HRMS (ESI) for $C_7H_{14}O_3Na$ $[M+Na]^+$, calculated: 169.0841; found: 169.0851.

4.4. (*S*)-3-(Methoxymethoxy)pent-4-enoic acid (4)

To a solution of above alcohol **3** (300 mg, 2.05 mmol) in DCM/H_2O (1:1, 8 mL) were added TEMPO (92 mg, 0.61 mmol) and BAIB (1.97 g, 6.15 mmol). After stirring at room temperature for 4 h, the reaction mixture was diluted with DCM (10 mL) and then washed with saturated aqueous $Na_2S_2O_3$ (10 mL). The organic layer was dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure to give the crude carboxylic acid. The crude product was further purified by flash column chromatography (EtOAc/hexane=1:2) to furnish the pure acid **4** (288 mg, 88%) as a colorless oil.

R_f=0.3 (EtOAc/hexane=1:1).

$[\alpha]_D^{28}$ −57.4 (*c* 1.3, $CHCl_3$).

^{1}H NMR of compound **4** (200 MHz, $CDCl_3$) δ: 7.68 (br s, 1H), 5.71 (ddd, J=17.4, 10.0, 7.4 Hz, 1H), 5.32–5.18 (m, 2H), 4.66 (d, J=7.0 Hz, 1H), 4.54–4.45 (m, 2H), 3.32 (s, 3H), 2.69–2.45 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 176.0, 136.5, 118.5, 93.9, 73.8, 55.6, 40.9.

HRMS (ESI) for $C_7H_{12}O_4Na$ $[M+Na]^+$, calculated: 183.0633; found: 183.0634.

4.5. *tert*-Butyl(((4*S*,5*S*)-2,2-dimethyl-5-((2-nonyl-1,3-dithian-2-yl)methyl)-1,3-dioxolan-4-yl)methoxy)dimethylsilane (7)

The dithiane **5** (3 g, 12.20 mmol) was dissolved in a mixture of THF/HMPA (10:1, 30 mL) and cooled to −78 °C. *t*-BuLi (18.7 mL, 1.3 M in pentane, 24.40 mmol) was then added to the solution and 5 min later a precooled solution of the iodide **6** (5.63 g, 14.6 mmol) in THF/HMPA (10:1, 30 mL) was added via double ended needle.

After 20 min, the reaction was quenched with a saturated solution of NH_4Cl and warmed to room temperature. The solution was then diluted with ether (200 mL) and washed successively with water (50 mL) and brine (50 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (EtOAc/hexane=1:20) afforded the product **7** (4.9 g, 9.76 mmol, 80%) as a colorless liquid.

R_f=0.3 (EtOAc/hexane=1:20).

$[\alpha]_D^{28}$ −10.1 (*c* 0.9, $CHCl_3$).

^{1}H NMR of compound **7** (200 MHz, $CDCl_3$) δ: 4.20 (t, *J*=8.0 Hz, 1H), 3.85–3.66 (m, 3H), 2.93–2.66 (m, 4H), 2.13–1.86 (m, 4H), 1.39 (s, 3H), 1.36 (s, 3H), 1.43–1.27 (m, 16H), 0.91–0.85(m, 12H), 0.08 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 108.8, 81.0, 77.2, 63.7, 52.7, 41.0, 39.3, 31.8, 29.7, 29.5, 29.4, 29.3, 27.2, 26.9, 26.0, 25.9, 25.3, 23.8, 22.6, 18.4, 14.0, −5.3.

HRMS (ESI) for $C_{26}H_{52}O_3S_2SiNa$ $[M+Na]^+$, calculated: 527.3025; found: 527.3028.

4.6. 1-((4*S*,5*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)undecan-2-one (8)

Dithiane **7** (1.7 g, 3.37 mmol) was dissolved in THF/H_2O (4:1, 40 mL) and then cooled to 0 °C. Iodine (2.54 g, 10.11 mmol) and $CaCO_3$ (3.37 g, 33.7 mmol) were added successively to the reaction mixture at the same temperature. The reaction mixture was then allowed to stir for 30 min at room temperature, after that it was quenched with saturated $Na_2S_2O_3$ (20 mL) solution. The aqueous phase was separated and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (EtOAc/hexane=1:15) to furnish ketone **8** (1.25 g, 3.03 mmol, 90%) as a colorless oil.

R_f=0.3 (EtOAc/hexane=1:15).

$[\alpha]_D^{28}$ 5.6 (*c* 0.4, $CHCl_3$).

^{1}H NMR of compound **8** (200 MHz, $CDCl_3$) δ: 4.35–4.26 (m, 1H), 3.82–3.63 (m, 3H), 2.69 (d, *J*=6.0 Hz, 2H), 2.45 (t, *J*=7.4 Hz, 2H), 1.37(s, 6H), 1.36–1.25 (m, 14H), 0.90–0.88 (m, 12H), 0.05 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 208.4, 108.9, 80.4, 74.8, 63.5, 46.4, 43.5, 31.8, 29.6, 29.3, 29.2, 29.1, 27.1, 26.8, 25.8, 23.4, 22.6, 18.2, 14.0, −5.4.

HRMS (ESI) for $C_{23}H_{46}O_4SiNa$ $[M+Na]^+$, calculated: 437.3063; found: 473.3025.

4.7. (*R*)-1-((4*S*,5*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)undecan-2-ol (9)

To a stirred solution of (*R*)-2-methyl-CBS-oxazaborolidine (0.3 mL of a 1.0 M solution in toluene, 0.3 mmol) in THF (0.6 mL) at −78 °C under N_2 atmosphere was added BH_3·DMS complex (1 mL of a 2 M solution in THF, 2.0 mmol) followed by the addition of a solution of **8** (660 mg, 1.59 mmol) in THF (3 mL). After 6 h, H_2O (5 mL) was added and the mixture was allowed to warm to room temperature. The aqueous phase was extracted with diethyl ether (2×25 mL), and the combined organic phases were washed with H_2O, then brine and dried over anhydrous $MgSO_4$. The crude residue was purified by column chromatography (EtOAc/hexane=1:10) to give **9** (476 mg, 1.14 mmol, 72%) as a colorless oil.

R_f=0.2 (EtOAc/hexane=1:10).

$[\alpha]_D^{28}$ −18.6 (*c* 1.1, $CHCl_3$).

^{1}H NMR of compound **9** (200 MHz, $CDCl_3$) δ: 4.15–4.09 (m, 1H), 3.83–3.64 (m, 4H), 1.77 (t, *J*=5.8 Hz, 2H), 1.40 (s, 3H), 1.36 (s, 3H), 1.35–1.25 (m, 16H), 0.90–0.80 (m, 12H), 0.05 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 108.5, 80.3, 76.9, 69.0, 63.7, 39.3, 37.4, 31.8, 29.6, 29.5, 29.2, 27.2, 26.7, 25.8, 25.6, 22.6, 18.2, 14.0, −5.5, −5.6.

HRMS (ESI) for $C_{23}H_{48}O_4SiNa$ $[M+Na]^+$, calculated: 439.3219; found: 439.3224.

4.8. *tert*-Butyl((*R*)-1-((4*S*,5*S*)-5-((*tert*-butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)undecan-2-yloxy)dimethylsilane (10)

2,6-Lutidine (492 mg, 4.6 mmol) was added to a solution of compound **9** (1.0 g, 2.3 mmol) in anhydrous DCM (20 mL) at room temperature. After stirring for 15 min TBS-OTf (1.05 mL, 4.6 mmol) was added to the reaction vessel and stirred for 1 h at room temperature. After completion of the reaction, water was added to the reaction mixture and the organic layer was washed with excess water and brine. The organic layer was dried ($MgSO_4$) and evaporated to dryness to afford the crude silylated compound, which was purified by silica gel chromatography (EtOAc/hexane=1:30) to give **10** (1.09 g, 90%) as a colorless oil.

R_f=0.2 (EtOAc/hexane=1:40).

$[\alpha]_D^{28}$ −6.6 (*c* 0.2, $CHCl_3$).

^{1}H NMR of compound **10** (200 MHz, $CDCl_3$) δ: 4.08–3.88 (m, 2H), 3.79–3.57 (m, 3H), 1.75–1.71 (m, 2H), 1.42 (s, 3H), 1.39 (s, 3H), 1.36–1.27 (m, 16H), 0.92–0.89 (m, 21H), 0.05 (s, 12H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 108.6, 82.0, 75.6, 70.1, 63.4, 41.6, 36.6, 32.1, 30.0, 29.8, 29.5, 27.6, 27.1, 26.1, 25.3, 22.9, 18.5, 18.3, 14.3, −4.2, −4.3, −5.1, −5.2.

HRMS (ESI) for $C_{29}H_{62}O_4Si_2Na$ $[M+Na]^+$, calculated: 553.4084; found: 553.4085.

4.9. ((4*S*,5*S*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)undecyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (11)

To the solution of silyl ether **10** (520 mg, 1 mmol) in THF (8 mL) in a plastic vial was added pyridine buffered HF/pyridine solution (8 mL, prepared from 5 mL THF+2 mL pyridine and 1 mL HF/pyridine). The reaction mixture was stirred at room temperature for 12 h before being quenched with saturated aqueous Na_2CO_3 (15 mL). The mixture was extracted with EtOAc (20 mL×3). The combined organic layer was then washed with saturated aqueous NaCl (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (EtOAc/hexane=1:10) afforded alcohol **11** (374 mg, 0.9 mmol) as a colorless oil.

R_f=0.2 (EtOAc/hexane=1:10).

$[\alpha]_D^{28}$ −20.9 (*c* 1.0, $CHCl_3$).

^{1}H NMR of compound **11** (200 MHz, $CDCl_3$) δ: 4.06–3.96 (m, 1H), 3.82–3.63 (m, 4H), 1.80–1.72 (m, 2H), 1.37 (s, 3H), 1.35 (s, 3H), 1.35–1.23 (m, 16H), 0.90–0.80 (m, 12H), 0.04 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 109.2, 81.3, 79.6, 71.3, 63.7, 40.5, 37.5, 32.0, 29.8, 29.7, 29.4, 27.3, 27.0, 26.0, 25.6, 22.8, 18.4, 14.2, −5.3, −5.4.

HRMS (ESI) for $C_{23}H_{48}O_4SiNa$ $[M+Na]^+$, calculated: 439.3219; found: 439.3224.

4.10. (4*R*,5*S*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)undecyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (12)

To a solution of above alcohol **11** (341 mg, 0.82 mmol) in dry DCM (4 mL) were added TEMPO (12 mg, 0.08 mmol), BAIB (263 mg, 0.82 mmol), and $NaHCO_3$ (68 mg, 0.82 mmol). After stirring at room temperature for 2 h, the reaction mixture was diluted with DCM (5 mL) and then washed with saturated aqueous $Na_2S_2O_3$ (5 mL). The organic layer was dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure to give the crude aldehyde **12**, which was used for the next step without further purification.

R_f=0.2 (EtOAc/hexane=1:15).

^{1}H NMR of compound **12** (200 MHz, $CDCl_3$) δ: 9.70–9.63 (m, 1H), 4.24–4.14 (m, 1H), 3.98–3.84 (m, 2H), 1.81–1.75 (m, 2H), 1.45 (s, 3H), 1.40 (s, 3H), 1.38–1.25 (m, 16H), 0.88–0.86 (m, 12H), 0.04 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 200.6, 111.1, 85.1, 73.6, 68.9, 40.4, 38.3, 32.0, 30.0, 29.8, 29.7, 29.5, 27.4, 26.3, 26.0, 24.6, 22.8, 18.2, 14.2, −4.0, −4.6.

4.11. *tert*-Butyl((*R*)-1-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)undecan-2-yloxy)dimethylsilane (13)

To a suspension of methyltriphenylphosphonium iodide (646 mg, 1.6 mmol) in dry THF (5 mL) was added LiHMDS (1.0 M solution in THF, 1.6 mL) at 0 °C. The yellow mixture was stirred at 0 °C for 15 min. A solution of the aldehyde **12** (331 mg, 0.8 mmol) in 2 mL of THF was added to the reaction mixture. The yellow suspension was stirred at room temperature for further 4 h. After that the reaction was quenched with addition of water, and the layers were separated and extracted with 25 mL of ether, washed with brine. It was then dried with $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude residue was purified by flash column chromatography (EtOAc/hexane=1:30) to afford compound **13** (247 mg, 0.6 mmol) in 75% yield.

R_f=0.3 (EtOAc/hexane=1:30).

$[\alpha]_D^{28}$ −13.5 (*c* 1.0, $CHCl_3$).

^{1}H NMR of compound **13** (200 MHz, $CDCl_3$) δ: 5.87–5.70 (m, 1H), 5.29–5.21 (m, 2H), 3.96–3.78 (m, 3H), 1.43–1.27 (m, 8H), 1.25–1.01 (m, 16H), 0.89–0.80 (m, 12H), 0.12–0.06 (m, 6H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 135.3, 119.0, 108.7, 83.1, 77.4, 69.3, 39.2, 38.5, 32.1, 30.1, 29.8, 29.7, 29.5, 27.6, 27.1, 26.1, 24.7, 22.8, 18.2, 14.3, −4.0, −4.5.

HRMS (ESI) for $C_{24}H_{48}O_3SiNa$ $[M+Na]^+$, calculated: 435.327; found: 435.3259.

4.12. General procedure for cross metathesis reaction

Olefin **13** (412 mg, 1 mmol) was taken in a flame-dried round-bottom flask, the 2° allylic alcohol (**1**/**2**/**3**/**4**, 2 mmol) in DCM (10 mL) was added to it, followed by Hoveyda–Grubbs second generation catalyst (HG-II, **C3**, 31 mg, 0.05 mmol). An additional 2 equiv of olefin (**1**–**4**) was added to the reaction mixture after 30 min. The light green solution, which was then refluxed for 24 h under argon atmosphere and then it was concentrated in vacuo to give dark brown oil. Purification of this residue on silica gel by flash chromatography afforded the desired compound as yellow oil.

*4.12.1. (S,E)-1-((4S,5S)-5-((R)-2-(tert-Butyldimethylsilyloxy)undecyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-(4-methoxybenzyloxy) pent-4-en-1-ol (**14**).* R_f=0.3 (EtOAc/hexane=1:2).

$[\alpha]_D^{28}$ −4.2 (*c* 0.9, $CHCl_3$).

^{1}H NMR of compound **14** (400 MHz, $CDCl_3$) δ: 7.24 (d, *J*=8.0 Hz, 2H), 6.87 (d, *J*=8.0 Hz, 2H), 5.83 (dd, *J*=15.2, 5.2 Hz, 1H), 5.64 (dd, *J*=15.2, 7.2 Hz, 1H), 4.44 (s, 2H), 4.41–4.36 (m, 1H), 3.94–3.90 (m, 1H), 3.86–3.81 (m, 2H), 3.80 (s, 3H), 3.70–3.66 (m, 1H), 3.65–3.60 (m, 1H), 1.82–1.77 (m, 2H), 1.59–1.51 (m, 2H), 1.44–1.39 (m, 2H), 1.40 (s, 3H), 1.37 (s, 3H), 1.30–1.23 (m, 14H), 0.90–0.84 (m, 12H), 0.05 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 159.4, 137.6, 130.1, 129.5, 127.0, 114.0, 108.6, 82.2, 77.4, 73.1, 71.1, 69.3, 68.2, 55.4, 39.1, 38.5, 36.5, 32.1, 30.1, 29.8, 29.5, 27.6, 27.1, 26.1, 24.7, 22.8, 18.3, 14.3, −4.0, −4.4.

HRMS (ESI) for $C_{35}H_{62}O_6SiNa$ $[M+Na]^+$, calculated: 629.4213; found: 629.4210.

4.13. *tert*-Butyl((*R*)-1-((4*S*,5*S*)-5-((*S*,*E*)-5-(4-methoxybenzyloxy)-3-(methoxymethoxy)pent-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)undecan-2-yloxy)dimethylsilane (15)

To a solution of alcohol **14** (600 mg, 1 mmol) in anhydrous DCM, diisopropyl ethyl amine (0.24 mL, 1 mmol) was added at 0 °C and stirred for 15 min at the same temperature. MOM-Cl (0.078 mL, 1 mmol) and tetra-*n*-butyl ammonium iodide (TBAI, catalytic) was then added to the reaction mixture and stirred for additional 8 h at room temperature. Water was added to the reaction mixture and extracted with DCM, washed with water and brine. The organic extracts were dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography (EtOAc/hexane=1:10) to afford the desired product **15** (585 mg, 0.9 mmol) with 90% yield.

R_f=0.3 (EtOAc/hexane=1:3).

$[\alpha]_D^{28}$ −17.9 (*c* 0.8, $CHCl_3$).

^{1}H NMR of compound **15** (400 MHz, $CDCl_3$) δ: 7.25 (d, *J*=7.6 Hz, 2H), 6.85 (d, *J*=7.6 Hz, 2H), 5.63 (ov, 2H), 4.63 (d, *J*=6.4 Hz, 1H), 4.50 (d, *J*=6.4 Hz, 1H), 4.41 (s, 2H), 4.23–4.21 (m, 1H), 3.94–3.91 (m, 1H), 3.85–3.83 (m, 3H), 3.79 (s, 3H), 3.58–3.50 (m, 2H), 3.32 (s, 3H), 1.88–1.81 (m, 2H), 1.53–1.50 (m, 2H), 1.45–1.42 (m, 2H), 1.40 (s, 3H), 1.37 (s, 3H), 1.36–1.25 (m, 14H), 0.90–0.80 (m, 12H), 0.04 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 159.1, 134.2, 130.5, 129.8, 129.2, 113.7, 108.6, 94.0, 81.8, 77.3, 73.1, 72.6, 69.0, 66.2, 55.4, 55.2, 39.0, 38.3, 35.7, 31.9, 29.8, 29.6, 29.5, 29.3, 27.4, 26.9, 25.8, 24.4, 22.6, 18.0, 14.1, −4.2, −4.6.

HRMS (ESI) for $C_{37}H_{66}O_7SiNa$ $[M+Na]^+$, calculated: 650.4476; found: 650.4465.

4.14. (*S*,*E*)-5-((4*S*,5*S*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)undecyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(methoxymethoxy) pent-4-en-1-ol (16)

Compound **15** (590 mg, 0.9 mmol) was taken in 5 mL of DCM/phosphate buffer (9:1). DDQ (204 mg, 0.9 mmol) was then added to it in one portion. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then filtered off, and the filtrate was washed with 5% $NaHCO_3$ solution, water, and brine. The organic layer was dried ($MgSO_4$) and evaporated. Purification by silica gel column chromatography (EtOAc/hexane=1:3) afforded the desired product **16** (391 mg, 0.73 mmol) in 82% yield.

R_f=0.2 (EtOAc/hexane=1:3).

$[\alpha]_D^{28}$ −58.6 (*c* 1.3, $CHCl_3$).

^{1}H NMR of compound **16** (400 MHz, $CDCl_3$) δ: 5.68–5.65 (ov, 2H), 4.65 (d, *J*=6.4 Hz, 1H), 4.53 (d, *J*=6.4 Hz, 1H), 4.28 (q, *J*=6.4 Hz, 1H), 3.94 (t, *J*=6.8 Hz, 1H), 3.85–3.70 (m, 4H), 3.37 (s, 3H), 1.83–1.79 (m, 2H), 1.53–1.51 (m, 2H), 1.43–1.41 (m, 2H), 1.39 (s, 3H), 1.37 (s, 3H), 1.35–1.25 (m, 14H), 0.88–0.86 (m, 12H), 0.04 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 133.8, 130.2, 108.9, 94.3, 81.8, 77.6, 75.2, 69.3, 60.1, 55.8, 39.3, 38.5, 37.9, 32.1, 30.1, 29.8, 29.5, 27.6, 27.1, 26.1, 24.7, 22.8, 18.2, 14.3, −3.9, −4.4.

HRMS (ESI) for $C_{29}H_{58}O_6SiNa$ $[M+Na]^+$, calculated: 553.3900; found:553.3900.

4.15. (*S*,*E*)-5-((4*S*,5*S*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)undecyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(methoxymethoxy) pent-4-enoic acid (17)

Alcohol **16** (159 mg, 0.3 mmol) was taken in dry DCM (10 mL) and cooled to 0 °C. Dess–Martin periodinane (DMP, 259 mg, 0.4 mmol) was then added to the reaction mixture. The solution was then warmed to room temperature over 2 h. The reaction mixture was quenched with $Na_2S_2O_3$ and saturated $NaHCO_3$ solution successively and stirred for further 20 min. The organic solution was then dried with $MgSO_4$, filtered, and the solvent was removed in vacuo to furnish the crude aldehyde.

The crude aldehyde was taken in *t*-BuOH (2 mL) and 2-methyl-2-butene (1 mL) was added to it dropwise followed by the addition of a solution of sodium phosphate monobasic (38.4 mg, 0.32 mmol) and sodium chlorite (58 mg, 0.64 mmol) in water (1 mL). The solution was stirred for 4 h at room temperature, then ethyl acetate

and water were added to the reaction mixture. The aqueous layer was extracted twice with EtOAc and the combined organic layers were washed with water and brine, dried ($MgSO_4$). The organic solvent was concentrated and purified by silica gel column chromatography (EtOAc/hexane=1:2) to afford the carboxylic acid **17** in 82% yield.

R_f=0.3 (EtOAc/hexane=1:1).

$[\alpha]_D^{28}$ −27.9 (*c* 1.0, $CHCl_3$).

^{1}H NMR of compound **17** (200 MHz, $CDCl_3$) δ: 5.75–5.72 (ov, 2H), 4.66 (d, *J*=6.8 Hz, 1H), 4.57–4.54 (m, 2H), 3.99–3.77 (m, 3H), 3.35 (s, 3H), 2.65–2.59 (m, 2H), 1.57–1.41 (m, 8H), 1.40–1.30 (m, 16H), 0.91–0.85 (m, 12H), 0.06 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.1, 132.3, 130.9, 108.7, 93.9, 81.4, 77.2, 72.2, 69.0, 55.5, 40.7, 39.0, 38.2, 31.8, 29.8, 29.6, 29.5, 29.4, 27.3, 26.8, 25.8, 24.5, 22.8, 18.0, 14.0, −4.2, −4.6.

HRMS (ESI) for $C_{29}H_{56}O_7SiNa$ $[M+Na]^+$, calculated: 567.3692; found: 567.3682.

4.16. (*S*,*E*)-5-((4*S*,5*S*)-5-((*R*)-2-Hydroxyundecyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(methoxymethoxy)pent-4-enoic acid (18)

To a solution of **17** (144 mg, 0.24 mmol) in dry THF (2 mL) was added TBAF (1.0 M in THF, 0.5 mmol, 0.5 mL) at room temperature and stirring was continued for 6 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$). The organic solvent was concentrated and purified by silica gel column chromatography (EtOAc/hexane=1:2) to afford the carboxylic acid **18** (82 mg, 0.196 mmol) in 85% yield.

R_f=0.2 (EtOAc/hexane=1:1).

$[\alpha]_D^{28}$ −17.9 (*c* 1.0, $CHCl_3$).

^{1}H NMR of compound **18** (400 MHz, $CDCl_3$) δ: 5.73–5.71 (ov, 2H), 4.66 (d, *J*=6.8 Hz, 1H), 4.55 (d, *J*=6.8 Hz, 1H), 4.54–4.50 (m, 1H), 3.96–3.92 (m, 1H), 3.87–3.79 (m, 2H), 3.34 (s, 3H), 2.66 (dd, *J*=15.6, 8.4 Hz, 1H), 2.58 (dd, *J*=15.6, 8.4 Hz, 1H), 1.54–1.50 (m, 2H), 1.40 (s, 3H), 1.37 (s, 3H), 1.30–1.20 (m, 16H), 0.88–0.84 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.6, 133.7, 129.5, 108.9, 94.3, 81.2, 78.1, 73.5, 68.8, 55.4, 37.9, 37.7, 31.8, 29.7, 29.6, 29.3, 26.8, 25.6, 22.6, 14.3.

HRMS (ESI) for $C_{23}H_{42}O_7Na$ $[M+Na]^+$, calculated: 453.2828; found: 453.2810.

4.17. (3a*S*,5*R*,9*S*,11a*S*,*E*)-9-(Methoxymethoxy)-2,2-dimethyl-5-nonyl-4,5,8,9-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*d*]oxecin-7(11a*H*)-one (19)

Yamaguchi procedure:

To a solution of seco-acid **18** (43 mg, 0.1 mmol) in dry toluene (5 mL) were added 2,4,6-trichlorobenzoylchloride (0.18 mL, 1.0 mmol) and diisopropyl ethyl amine (0.4 mL) at 25 °C. The mixture was stirred for 15 h at this temperature. The solution was then diluted by addition of dry toluene (5 mL) and it was added through a syringe pump slowly to the solution of DMAP (122 mg, 1.0 mmol) in toluene (50 mL) at 60 °C over 24 h. The reaction mixture was stirred for an additional 24 h at the same temperature and quenched by adding saturated aqueous NH_4Cl solution. The organic solution was successively washed with water, brine and dried over $MgSO_4$. The organic solvent was evaporated and purified by silica gel column chromatography (EtOAc/hexane=1:20) to afford the lactone **19** (25 mg) in 62% yield.

Shiina procedure:

To a solution of MNBA (46 mg, 0.13 mmol) and DMAP (15 mg, 0.12 mmol) in toluene (35 mL) at room temperature was added a solution of seco-acid **18** (43 mg, 0.1 mmol) in toluene (15 mL). After that the reaction mixture was stirred for 24 h and quenched by adding saturated aqueous $NaHCO_3$ solution. The organic solution was successively washed with water, brine and dried over $MgSO_4$. The organic solvent was evaporated and purified by silica gel column chromatography (EtOAc/hexane=1:20) to afford the lactone **19** (28 mg) in 68% yield.

R_f=0.4 (EtOAc/hexane=1:15).

$[\alpha]_D^{28}$ +17.9 (*c* 1.0, $CHCl_3$).

^{1}H NMR of compound **19** (400 MHz, $CDCl_3$) δ: 5.86 (d, *J*=15.6 Hz, 1H), 5.68 (dd, *J*=15.6, 9.2 Hz, 1H), 5.01–4.98 (m, 1H), 4.69 (s, 2H), 4.63–4.61 (m, 1H), 4.06 (t, *J*=8.8 Hz, 1H), 3.64 (t, *J*=8.8 Hz, 1H), 3.40 (s, 3H), 2.67 (d, *J*=12.0 Hz, 1H), 2.49 (dd, *J*=12.0, 4.0 Hz, 1H), 2.07 (d, *J*=15.6 Hz, 1H), 1.93–1.86 (m, 1H), 1.50–1.47 (m, 2H), 1.39 (s, 6H), 1.30–1.20 (m, 14H), 0.86 (t, *J*=6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6, 136.1, 127.6, 108.2, 94.6, 83.3, 81.5, 74.8, 72.8, 55.6, 43.7, 36.7, 36.0, 31.9, 29.5, 29.4, 27.2, 27.0, 25.3, 22.8, 14.2.

HRMS (ESI) for $C_{23}H_{40}O_6Na$ $[M+Na]^+$, calculated: 435.2723; found: 435.2732.

4.18. Seimatopolide A

To a solution of ring closing compound **19** (20 mg, 0.048 mmol) in THF (2 mL) was added HCl (1 mL, 2M) at room temperature and stirred for 12 h. Water was added to the reaction mixture and it was extracted with ethyl acetate. The organic layer was washed with $NaHCO_3$ and brine. It was then dried over $MgSO_4$, concentrated in a rotary evaporator, and purified by silica gel column chromatography (EtOAc/hexane=2:1) to afford the target molecule seimatopolide A (13 mg, 0.038 mmol) in 80% yield as a white solid.

R_f=0.4 (EtOAc/hexane=2:1).

$[\alpha]_D^{28}$ −27.4 (*c* 0.05, MeOH).

^{1}H NMR (400 MHz, pyridine-d_5) δ 6.46 (dd, *J*=16.0, 9.6 Hz, 1H), 6.14 (dd, *J*=16.0, 3.2 Hz, 1H), 5.14 (dt, *J*=6.8, 6.5 Hz, 1H), 4.98–4.97 (m, 1H), 4.40 (t, *J*=9.2 Hz, 1H), 3.97 (dd, *J*=8.8, 8.4 Hz, 1H), 2.86 (dd, *J*=11.6, 3.2 Hz, 1H), 2.74 (dd, *J*=12.0, 4.0 Hz, 1H), 2.30–2.24 (m, 2H), 1.68–1.66 (m, 1H), 1.57–1.55 (m, 1H), 1.40–1.15 (m, 14H), 0.86 (t, *J*=7.2 Hz, 3H).

^{13}C NMR (100 MHz, pyridine-d_5) δ: 170.7, 136.8, 128.3, 79.9, 77.4, 73.7, 67.5, 44.9, 42.5, 37.7, 32.4, 30.2, 30.2, 30.1, 29.9, 25.8, 23.3, 14.6.

HRMS (ESI) for $C_{18}H_{32}O_5Na$ $[M+Na]^+$, calculated: 351.2142; found: 351.2146.

4.19. (*R*)-Tridec-1-en-4-ol (20)

(−)-Allyldiisopinocamphenylborane (Ipc_2B-Allyl, 25 mmol, 1.0 M solution in pentane, 25 mL) was cooled to −78 °C, and 3.90 g (25 mmol) of decanal in diethyl ether (100 mL) was added to the solution dropwise with stirring. The reaction mixture was then stirred for 1 h at −78 °C and then allowed to warm up to 25 °C. It was then treated with 18.3 mL (55 mmol) of 3 N NaOH and 15 mL of 30% H_2O_2, and the contents were refluxed for 1 h. The organic layer was then separated and washed with water (15 mL) and brine (15 mL) and dried over anhydrous $MgSO_4$. The organic solvent was then concentrated in rotary evaporator to yield the crude product, which was then purified by silica gel column chromatography (EtOAc/hexane=1:10) to furnish compound **20** (4.3 g, 22 mmol) in 88% yield.

R_f=0.3 (EtOAc/hexane=1:20).

$[\alpha]_D^{28}$ +5.9 (*c* 1.8, $CHCl_3$).

^{1}H NMR of compound **20** (200 MHz, $CDCl_3$) δ: 5.84 (ddd, *J*=14.2, 10.4, 7.0 Hz, 1H), 5.15–5.11 (m, 2H), 3.67–3.61 (m, 1H), 2.33–2.27 (m, 1H), 2.17–2.04 (m, 1H), 1.47–1.26 (m, 2H), 1.25–1.03 (m, 14H); 0.89–0.86 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 134.8, 117.7, 70.6, 41.8, 36.7, 31.8, 29.6, 29.5, 29.4, 29.2, 25.5, 22.5, 13.9.

HRMS (ESI) for $C_{13}H_{26}ONa$ $[M+Na]^+$, calculated: 221.1881; found: 221.1875.

4.20. (*R*)-*tert*-Butyldiphenyl(tridec-1-en-4-yloxy)silane (21)

Alcohol **20** (4.3 g, 22 mmol) was taken in anhydrous DCM (60 mL) and cooled to 0 °C. Imidazole (3.03 g, 44 mmol) and DMAP (100 mg) were added to the reaction mixture followed by the addition of TBDPS-Cl (7 mL, 26 mmol). The reaction mixture was then allowed to warm at room temperature for 4 h, after which water was added to it and the organic layer was extracted with DCM, washed with brine, and dried over $MgSO_4$. The organic solvent was concentrated in rotary evaporator and the crude product was purified by silica gel column chromatography (EtOAc/hexane=1:40) to afford the TBDPS-protected compound **21** (8.8 g, 20.24 mmol) in 92% yield.

R_f=0.6 (EtOAc/hexane=1:20).

$[\alpha]_D^{28}$ +8.1 (*c* 1.0, $CHCl_3$).

^{1}H NMR of compound **21** (200 MHz, $CDCl_3$) δ: 7.72–7.67 (m, 4H), 7.47–7.32 (m, 6H), 5.79 (ddd, *J*=14.2, 10.4, 7.0 Hz, 1H), 4.99–4.90 (m, 2H), 3.82–3.71 (m, 1H), 2.24–2.16 (m, 2H), 1.46–1.38 (m, 2H), 1.36–1.11 (m, 14H), 1.07 (s, 9H), 0.92–0.86 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 136.0, 135.1, 134.6, 129.5, 127.5, 116.7, 72.9, 41.1, 36.1, 32.0, 29.6, 27.1, 24.9, 22.8, 19.4, 14.2.

HRMS (ESI) for $C_{29}H_{44}OSiNa$ $[M+Na]^+$, calculated: 459.3058; found: 459.3065.

4.21. (*R*)-4-(*tert*-Butyldiphenylsilyloxy)tridecan-1-ol (22)

$BH_3 \cdot SMe_2$ (5.5 mL, 2.0 M in THF, 11 mmol) was added to a cooled (0 °C) solution of compound **21** (4.36 g, 10 mmol) in THF (20 ml). The mixture was stirred for an additional 2 h and then quenched with EtOH followed by the addition of 3 M aqueous NaOH (4 mL) and 30% H_2O_2 (4 mL). The mixture was stirred vigorously for 3.5 h and 10% aqueous $Na_2S_2O_3$ (3 mL) was added to it. It was then extracted with ether and washed with brine. The organic solvent was dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography (EtOAc/hexane=1:5) to provide the alcohol **22**(3.72 g, 8.2 mmol) with 82% yield.

R_f=0.3 (EtOAc/hexane=1:5).

$[\alpha]_D^{28}$ +7.3 (*c* 0.4, $CHCl_3$).

^{1}H NMR of compound **22** (200 MHz, $CDCl_3$) δ: 7.70–7.66 (m, 4H), 7.47–7.34 (m, 6H), 3.79–3.74 (m, 1H), 3.61–3.52 (m, 2H), 1.61–1.43 (m, 6H), 1.26–1.13 (m, 14H), 1.06 (s, 9H), 0.92–0.85 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 135.9, 134.4, 129.4, 127.4, 72.9, 63.0, 36.0, 32.3, 31.8, 29.5, 29.4, 29.2, 27.8, 27.0, 24.9, 22.6, 19.3, 14.0.

HRMS (ESI) for $C_{29}H_{46}O_2SiNa$ $[M+Na]^+$, calculated: 477.3154; found: 477.3165.

4.22. (*R*)-4-(*tert*-Butyldiphenylsilyloxy)tridecanoic acid (23)

To a solution of above alcohol **22** (3.6 g, 8 mmol) in H_2O/DCM (1:1, 32 mL) were added TEMPO (357 mg, 2.4 mmol) and BAIB (7.69 g, 24 mmol). After stirring at room temperature for 3 h, the reaction mixture was diluted with DCM (100 mL) and then washed with saturated aqueous $Na_2S_2O_3$ (40 mL). The organic layer was dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure to give the crude carboxylic acid, which was further purified by flash column chromatography (silica gel, EtOAc/hexane=1:2) to furnish the acid **23** (3.29 g, 88%) as a colorless oil.

R_f=0.3 (EtOAc/hexane=1:1).

$[\alpha]_D^{28}$ +8.1 (*c* 0.3, $CHCl_3$).

^{1}H NMR of compound **23** (200 MHz, $CDCl_3$) δ: 7.75–7.71 (m, 4H), 7.47–7.30 (m, 6H), 3.82 (t, *J*=5.4 Hz, 1H), 2.45 (t, *J*==7.8 Hz, 2H), 1.88–1.80 (m, 2H), 1.47–1.40 (m, 2H), 1.35–1.15 (m, 14H), 1.11 (s, 9H), 0.97–0.90 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 180.2, 135.8, 134.4, 134.0, 129.5, 129.4, 127.5, 127.4, 72.0, 36.1, 31.8, 30.6, 29.4, 29.2, 27.0, 24.8, 22.6, 19.3, 14.0.

HRMS (ESI) for $C_{29}H_{44}O_3SiNa$ $[M+Na]^+$, calculated: 491.2957; found: 491.2959.

4.23. (*R*)-4-(*tert*-Butyldiphenylsilyloxy)-*N*-methoxy-*N*-methyltridecanamide (24)

Triethylamine (0.36 mL, 2.6 mmol) was added to a solution of acid **23** (936 mg, 2.0 mmol) in DCM (12 mL). To this solution *N*,*O*-dimethylhydroxylamine hydrochloride (0.25 g, 2.6 mmol), 4-dimethylaminopyridine (0.26 g, 2.8 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.47 g, 2.5 mmol) were sequentially added at room temperature. The resulting mixture was stirred at room temperature for 6 h. After the completion of the reaction the organic solution was washed successively with 1 M hydrochloric acid (20 mL), brine (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to afford the crude amide as yellow oil. The crude product was then purified by chromatography (silica gel, hexanes/EtOAc=1:2) to afford the title compound **24** (919 mg, 90%) as a colorless oil.

R_f=0.3 (EtOAc/hexane=1:2).

$[\alpha]_D^{28}$ +3.4 (*c* 0.3, $CHCl_3$).

^{1}H NMR of compound **24** (200 MHz, $CDCl_3$) δ: 7.73–7.68 (m, 4H), 7.43–7.34 (m, 6H), 3.84–3.76 (m, 1H), 3.58 (s, 3H), 3.14 (s, 3H), 2.55–2.33 (m, 2H), 1.88–1.76 (m, 2H), 1.46–1.40 (m, 2H), 1.39–1.16 (m, 14H), 1.08 (s, 9H), 0.93–0.86 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 174.6, 135.8, 134.5, 134.2, 129.4, 127.4, 127.3, 72.9, 60.9, 36.5, 31.8, 30.7, 29.5, 29.4, 29.2, 27.0, 24.8, 22.6, 19.3, 14.0.

HRMS (ESI) for $C_{31}H_{49}NO_3SiNa$ $[M+Na]^+$, calculated: 534.3379; found: 534.3382.

4.24. (*R*)-6-(*tert*-Butyldiphenylsilyloxy)pentadec-1-en-3-one (25)

A 1.0 M solution of vinylmagnesium bromide in THF (8.57 mL, 8.57 mmol) was added to a stirred solution of **24** (1.4 g, 2.85 mmol) in anhydrous THF (10 mL) at −78 °C under N_2. The mixture was stirred at −78 °C for 2 h and then it was quenched with saturated aqueous NH_4Cl (5 mL) solution. The organic solution was extracted with EtOAc (3×20 mL). The combined organic extracts were washed with brine (1×30 mL), and then dried over $MgSO_4$. The organic solution was filtered and concentrated to afford the crude product. The residue was purified by column chromatography (silica gel, EtOAc/hexane=1:6); to furnish the title compound **25** (1.2 g, 90%) as a colorless oil.

R_f=0.4 (EtOAc:hexane=1:6).

$[\alpha]_D^{28}$ +5.3 (*c* 0.3, $CHCl_3$).

^{1}H NMR of compound **25** (200 MHz, $CDCl_3$) δ: 7.71–7.67 (m, 4H), 7.41–7.35 (m, 6H), 6.28 (dd, *J*=17.6, 10.4 Hz, 1H), 6.09 (dd, *J*=17.6, 1.4 Hz, 1H), 5.76 (dd, *J*=10.2, 1.4 Hz, 1H), 3.80 (t, *J*=5.4 Hz, 1H), 2.65–2.54 (m, 2H), 1.85–1.65 (m, 2H), 1.46–1.40 (m, 2H), 1.39–1.05 (m, 14H), 1.08 (s, 9H), 0.93–0.87 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 201.0, 136.7, 136.0, 134.6, 134.5, 129.7, 127.7, 127.6, 72.7, 36.7, 35.3, 32.0, 30.2, 29.6, 27.2, 25.1, 22.8, 19.5, 14.2.

HRMS (ESI) for $C_{31}H_{46}O_2SiNa$ $[M+Na]^+$, calculated: 501.3164; found: 501.3169.

4.25. (3*R*,6*R*)-6-(*tert*-Butyldiphenylsilyloxy)pentadec-1-en-3-ol (26)

To a stirred solution of (*R*)-2-methyl-CBS-oxazaborolidine (0.2 mL of a 1.0 M solution in toluene, 0.2 mmol) in THF (0.6 mL) at

−78 °C and under N_2 atmosphere was added BH_3−SMe_2 complex (1 mL of a 2 M solution in THF, 2.0 mmol) followed by the addition of a solution of **25** (956 mg, 2.0 mmol) in THF (5 mL). After 6 h, H_2O (5 ml) was added and the mixture was allowed to warm to room temperature. Diethyl ether was added and the mixture was washed with 5% aqueous HCl. The aqueous phase was extracted with diethyl ether (2×50 mL), and the combined organic phases were washed with H_2O and brine and then dried over $MgSO_4$. The organic solvent was then evaporated under vacuum to afford the crude alcohol, which was further purified by column chromatography (silica gel, EtOAc/hexane=1:3); to furnish the title compound **26** (720 mg, 1.5 mmol) as a colorless oil.

R_f=0.3 (EtOAc/hexane=1:3).

$[\alpha]_D^{28}$ +6.1 (*c* 0.3, $CHCl_3$).

^{1}H NMR of compound **26** (200 MHz, $CDCl_3$) δ: 7.74−7.70 (m, 4H), 7.42−7.30 (m, 6H), 5.88−5.74 (m, 1H), 5.21−5.05 (m, 2H), 4.00−3.96 (m, 1H), 3.83−3.78 (m, 1H), 1.73−1.46 (m, 6H), 1.36−1.18 (m, 14H), 1.10 (s, 9H), 0.95−0.89 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 141.3, 136.1, 134.7, 129.6, 127.6, 114.6, 73.4, 73.2, 36.3, 32.4, 32.0, 29.7, 29.4, 27.3, 25.1, 22.8, 19.5, 14.3.

HRMS (ESI) for $C_{31}H_{48}O_2SiNa$ $[M+Na]^+$, calculated: 503.3321; found: 503.3317.

4.26. (5*R*,8*R*)-11,11-Dimethyl-8-nonyl-10,10-diphenyl-5-vinyl-2,4,9-trioxa-10-siladodecane (27)

To a solution of alcohol **26** (1.02 g, 2.14 mmol) in DCM, diisopropyl ethyl amine (0.6 mL, 3.21 mmol) was added at 0 °C and stirred for 15 min at the same temperature. MOM-Cl (0.2 mL, 2.56 mmol) and tetra-*n*-butyl ammonium iodide (catalytic) were then added to the reaction mixture and stirred for additional 12 h at room temperature. Water was added to the reaction mixture and extracted with DCM, washed with water and brine. The organic extracts were dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography (EtOAc/hexane=1:10) to furnish the title compound **27** (883 mg, 1.84 mmol) as a colorless oil.

R_f=0.4 (EtOAc/hexane=1:5).

$[\alpha]_D^{28}$ −2.1 (*c* 0.3, $CHCl_3$).

^{1}H NMR of compound **27** (200 MHz, $CDCl_3$) δ: 7.72−7.68 (m, 4H), 7.43−7.35 (m, 6H), 5.70−5.55 (m, 1H), 5.18−5.07 (m, 2H), 4.68 (d, *J*=6.8 Hz, 1H), 4.51 (d, *J*=6.8 Hz, 1H), 3.85−3.72 (m, 2H), 3.34 (s, 3H), 1.60−1.45 (m, 6H), 1.41−1.18 (m, 14H), 1.08 (s, 9H), 0.94−0.87 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 138.5, 136.1, 134.8, 129.6, 127.6, 117.2, 93.8, 77.8, 73.3, 55.4, 36.4, 32.1, 30.5, 29.8, 29.7, 29.5, 27.3, 25.1, 22.8, 19.6, 14.3.

HRMS (ESI) for $C_{33}H_{52}O_3SiNa$ $[M+Na]^+$, calculated: 547.3583; found: 547.3586.

4.27. (3*R*,6*R*)-3-(4-Methoxybenzyloxy)pentadec-1-en-6-ol (28)

To a solution of the *p*-methoxybenzyl tricholoro acetimidate (600 mg) in toluene (5 mL), at −10 °C was added alcohol **26** (480 mg, 1 mmol) in toluene (2.0 mL) followed by scandium triflate (26.6 mg, 0.054 mmol) and the reaction mixture was stirred for 15 min at −10 °C. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (2×20 mL). The combined organic layer was washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo to afford the crude product, which was used directly for the next step.

A solution of crude olefin in THF (4 mL) was cooled to 0 °C, TBAF (2 mL, 2 mmol, 1.0 M solution in THF) was added dropwise and the resulting brown solution was stirred at room temperature for 2 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (2×5 mL). The combined organic layer was washed with brine (15 mL), dried over $MgSO_4$, and evaporated to dryness under reduced pressure to afford the crude product. The crude residue was then purified by flash column chromatography (silica gel, hexanes/EtOAc=80:20) to yield pure **28** (296 mg, 82%) as a colorless oil.

R_f=0.4 (EtOAc/hexane=1:3).

$[\alpha]_D^{28}$ +16.6 (*c* 1.0, $CHCl_3$).

^{1}H NMR of compound **28** (200 MHz, $CDCl_3$) δ: 7.25−7.20 (m, 2H), 6.87 (d, *J*=8.2 Hz, 2H), 5.75 (m, 1H), 5.28−5.19 (m, 2H), 4.53 (d, *J*=11.2 Hz, 1H), 4.29 (d, *J*=11.2 Hz, 1H), 3.80 (s, 3H), 3.70−3.60 (m, 2H), 1.73−1.60 (m, 4H), 1.34−1.20 (m, 16H), 0.90−0.86 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 159.1, 138.8, 130.4, 129.4, 117.1, 113.7, 80.3, 71.5, 69.8, 55.2, 37.4, 33.2, 31.9, 31.6, 29.7, 29.6, 29.5, 29.3, 25.7, 22.6, 14.1.

HRMS (ESI) for $C_{23}H_{38}O_3Na$ $[M+Na]^+$, calculated: 380.2713; found: 380.2720.

4.28. (3*S*,6*R*,9*R*,*E*)-9-(*tert*-Butyldiphenylsilyloxy)-3,6-bis(methoxymethoxy)octadec-4-en-1-ol (29)

Olefin **27** (524 mg, 1 mmol) was taken in a flame-dried round-bottom flask, compound **3** (146 mg, 2 mmol) in DCM (10 ml) was added to it, followed by Hoveyda−Grubbs second generation catalyst (HG-II, **C3**, 31 mg, 0.05 mmol). An additional 2 equiv of olefin (**3**) was added to the reaction mixture after 30 min. The light green solution, which was refluxed for 24 h under argon atmosphere and then it was concentrated in vacuo to give dark brown oil. Purification of this residue on silica gel by flash chromatography afforded the desired compound **29** (481 mg, 75%) as a yellow oil.

R_f 0.3 (EtOAc/exane=1:3).

$[\alpha]_D^{28}$ +5.6 (*c* 0.3, $CHCl_3$).

^{1}H NMR of compound **29** (400 MHz, $CDCl_3$) δ: 7.66−7.62 (m, 4H), 7.40−7.33 (m, 6H), 5.48−5.44 (m, 2H), 4.59 (d, *J*=6.4 Hz, 2H), 4.46 (d, *J*=6.4 Hz, 2H), 4.23−4.21 (m, 1H), 3.76−3.71 (m, 4H), 3.37 (s, 3H), 3.29 (s, 3H), 1.53−1.48 (m, 4H), 1.40−1.33 (m, 4H), 1.24−1.09 (m, 14H), 1.03 (s, 9H), 0.88−0.85 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 135.8, 134.5, 133.6, 131.8, 129.3, 127.3, 93.7, 93.6, 76.7, 75.0, 73.0, 59.9, 55.5, 55.2, 37.8, 36.3, 31.8, 29.6, 29.5, 29.4, 29.1, 26.9, 24.8, 22.5, 19.3, 14.0.

HRMS (ESI) for $C_{38}H_{62}O_6SiNa$ $[M+Na]^+$, calculated: 665.4213; found: 665.4250.

4.29. (3*S*,6*R*,9*R*,*E*)-9-(*tert*-Butyldiphenylsilyloxy)-3,6-bis(methoxymethoxy)octadec-4-enoic acid (30)

To a solution of above alcohol **29** (500 mg, 0.78 mmol) in H_2O/DCM (1/1, 6 mL) were added TEMPO (35 mg, 0.24 mmol) and BAIB (0.75 g, 2.34 mmol). After stirring at room temperature for 2 h, the reaction mixture was diluted with DCM (5 mL) and then washed with saturated aqueous $Na_2S_2O_3$ (10 mL). The organic layer was dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure to give the crude carboxylic acid, which was further purified by flash column chromatography (silica gel, EtOAc/hexane=1:2) to furnish the acid **30** (434 mg, 85%) as a colorless oil.

R_f=0.2 (EtOAc/hexane=1:2).

$[\alpha]_D^{28}$ +1.0 (*c*0.3, $CHCl_3$).

^{1}H NMR of compound **30** (200 MHz, $CDCl_3$) δ: 7.68−7.65 (m, 4H), 7.40−7.33 (m, 6H), 5.50−5.45 (m, 2H), 4.62−4.59 (m, 2H), 4.50−4.45 (m, 2H), 4.11−4.09 (m, 1H), 3.85−3.83 (m, 1H), 3.73−3.70 (m, 1H), 3.36 (s, 3H), 3.27 (s, 3H), 2.63−2.58 (m, 1H), 2.50−2.47 (m, 1H), 1.50−1.40 (m, 6H), 1.30−1.10 (m, 14H), 0.90 (s, 9H), 0.88−0.86 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 175.4, 136.1, 135.0, 134.8, 128.2, 125.7, 94.1, 94.0, 76.1, 73.0, 72.3, 55.8, 55.7, 41.0, 36.6, 31.8, 29.6, 29.4, 29.1, 26.9, 24.8, 22.5, 19.3, 14.0.

HRMS (ESI) for $C_{38}H_{60}O_7SiNa$ $[M+Na]^+$, calculated: 679.4005; found: 679.4008.

4.30. (3*S*,6*R*,9*R*,*E*)-9-Hydroxy-3,6-bis(methoxymethoxy)octadec-4-enoic acid (31)

To a solution of **30** (183 mg, 0.24 mmol) in dry THF (2 mL) was added TBAF (1.0 M in THF, 0.5 mmol, 0.5 ml) at room temperature and stirring was continued for 4 h. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (10 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3×20 ml). The combined organic layers were washed with water and brine, dried over $MgSO_4$. The organic solvent was then concentrated to afford the crude seco-acid **31**, which was subsequently used for the next step without any further purification.

R_f=0.2 (EtOAc/hexane=1:1).

$[\alpha]_D^{28}$ −2.7 (*c* 0.3, $CHCl_3$).

HRMS (ESI) for $C_{22}H_{42}O_7Na$ $[M+Na]^+$, calculated: 441.2828; found: 441.2845.

4.31. (4*S*,7*R*,10*R*,*E*)-4,7-Bis(methoxymethoxy)-10-nonyl-3,4,7,8,9,10-hexahydro-2*H*-oxecin-2-one (32)

To a solution of MNBA (46 mg, 0.13 mmol) and DMAP (15 mg, 0.12 mmol) in toluene (35 mL) at room temperature was added a solution of seco-acid **31** (41 mg, 0.1 mmol) in toluene (15 mL). After that the reaction mixture was stirred for 24 h and then quenched by adding saturated aqueous $NaHCO_3$ solution. The organic solution was successively washed with water, brine and dried over $MgSO_4$. The organic solvent was evaporated and purified by silica gel column chromatography (EtOAc/hexane=1:20) to afford the lactone **32** (29 mg, 0.072 mmol) in 72% yield.

R_f=0.4 (EtOAc/hexane=1:15).

$[\alpha]_D^{28}$ −18.1 (*c* 0.2, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.60 (dd, *J*=16.4, 8.8 Hz, 1H), 5.38 (dd, *J*=16.0, 8.4 Hz, 1H), 4.78–4.71 (m, 1H), 4.70 (d, *J*=3.6 Hz, 1H), 4.64 (d, *J*=3.6 Hz, 1H), 4.61 (d, *J*=3.6 Hz, 1H), 4.59 (d, *J*=3.6 Hz, 1H), 4.44–4.37 (m, 1H), 4.10–4.06 (m, 1H), 3.36 (s, 3H), 3.34 (s, 3H), 2.76 (dd, *J*=10.4, 5.6 Hz, 1H), 2.41 (t, *J*=10.4 Hz, 1H), 2.06–2.00 (m, 1H), 1.83–1.71 (m, 2H), 1.77–1.44 (m, 3H), 1.40–1.15 (m, 14H), 0.86 (t, *J*=7.2 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 170.2, 139.3, 133.5, 94.6, 93.7, 77.4, 77.2, 75.8, 55.6, 55.5, 45.3, 33.8, 31.9, 31.6, 29.8, 29.7, 29.6, 29.2, 28.3, 25.3, 22.7, 14.1.

HRMS (ESI) for $C_{22}H_{40}O_6Na$ $[M+Na]^+$, calculated: 423.2722; found: 423.2775.

4.32. Seimatopolide B

To a solution of ring closing compound **32** (28 mg, 0.070 mmol) in THF (2 mL) was added HCl (1 mL, 2M) at room temperature and stirred for 12 h. Water was added to the reaction mixture and it was extracted with ethyl acetate. The organic layer was then washed successively with $NaHCO_3$ and brine. It was then dried over $MgSO_4$, concentrated in a rotary evaporator and purified by silica gel column chromatography (EtOAc/hexane=2:1) to afford the target molecule seimatopolide B (17 mg, 0.057 mmol) in 80% yield as a white solid.

R_f=0.4 (EtOAc/hexane=2:1).

$[\alpha]_D^{28}$ −13.4 (*c* 0.02, MeOH).

^{1}H NMR (400 MHz, pyridine-d_5) δ: 6.56 (dd, *J*=16.0, 8.6 Hz, 1H), 5.97 (dd, *J*=16.0, 3.0 Hz, 1H), 5.08–5.06 (m, 1H), 4.98–4.95 (m, 1H), 4.63–4.60 (m, 1H), 2.88 (dd, *J*=11.6, 3.2 Hz, 1H), 2.71 (dd, *J*=11.6, 3.8 Hz, 1H), 2.34–2.23 (m, 1H), 2.06–1.90 (m, 2H), 1.77–1.44 (m, 3H), 1.40–1.19 (m, 14H), 0.86 (t, *J*=7.2 Hz, 3H).

^{13}C NMR (50 MHz, pyridine-d_5) δ: 170.5, 133.4, 133.3, 76.4, 74.7, 67.8, 45.7, 38.4, 36.3, 32.3, 31.1, 30.2, 30.1, 30.0, 29.8, 26.0, 23.2, 14.5.

HRMS (ESI) for $C_{18}H_{32}O_4Na$ $[M+Na]^+$, calculated: 335.2198; found: 335.2201.

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Supplementary data

Copies of ^{1}H, ^{13}C NMR spectra for all the compounds and 2D-NMR spectra for compound **19** and seimatopolide A. HPLC chromatogram of benzoate derivative of racemic **20** and enantiopure **20**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.05.021.

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