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Total synthesis and revision of the absolute configuration of seimatopolide B†

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The asymmetric total synthesis of natural seimatopolide B along with its enantiomer is described starting from readily available 5-hexen-1-ol and 3-buten-1-ol. The key steps involved are Jacobson hydrolytic kinetic resolution, proline-catalyzed α-hydroxylation, Yamaguchi esterification and ring-closing metathesis. This asymmetric total synthesis necessitates the revision of the originally assigned (3*R*, 6*S*, 9*S*)-configuration to (3*S*, 6*R*, 9*R*).

Introduction

Nonanolides (decanolides or 10-membered macrolides) constitute an important class of bioactive secondary metabolites due to their notable diverse biological and pharmacological properties such as anti-bacterial, anti-fungal, anti-malarial, cytotoxic, phytotoxic, anti-microfilament, *etc*.[1] Recently, Lee and co-workers isolated two new polyhydroxylated 10-membered macrolides, seimatopolide A (**1**) and B (**2**, Fig. 1), from an ethyl acetate extract of *Seimatosporium discosioides* culture medium.[2] They were found to act as peroxisome proliferator-activated receptor (PPAR)-γ activators. The structures of **1** and **2** were established on the basis of spectroscopic analysis including 1D and 2D NMR and the absolute configurations were determined as 3*R*, 6*R*, 7*R*, 9*S* for **1** and 3*R*, 6*S*, 9*S* for **2** using the Mosher's method. These structural features combined with their interesting biological profile motivated synthetic organic chemists to investigate their total synthesis. In this direction, we have reported the total synthesis of (+)-seimatopolide A (**1**), wherein we found that the absolute configuration of the natural product was misassigned and should be revised as 3*S*, 6*S*, 7*S*, 9*R* (**1a**, Fig. 1).[3] At the same time, two more total syntheses of **1** were published, supporting the originally proposed configuration for seimatopolide A.[4] Very recently, Schmidt and co-workers have described the synthesis of both enantiomers of **1**, studied the CD spectra of their derivatives and concluded that the configuration of the natural product should be revised as 3*S*, 6*S*, 7*S*, 9*R*,[5] which is in agreement with our observation.[3] These results prompted us to analyze the reported Mosher ester data for **2**,[2] which revealed that this might be another case of a misassigned natural product.[6] To further resolve this ambiguity and unequivocally confirm the absolute stereochemistry, we embarked upon the total synthesis of **2** in a stereoflexible manner, wherein both isomers could be synthesized. In continuation of our interest on the synthesis of macrolides,[3,7] we herein report on the asymmetric total synthesis of seimatopolide B (**2**) and its enantiomer **2a** (Fig. 1) along with the revision of the absolute configuration of the natural product.

As shown in Scheme 1, the synthesis of **2** started from the alcohol **3** and the acid **4**, which could be coupled *via* Yamaguchi esterification followed by ring-closing metathesis. Alcohol **3** was to be prepared *via* proline-catalyzed α-hydroxylation of the epoxide **5**, which in turn is accessible from commercially available 5-hexen-1-ol.

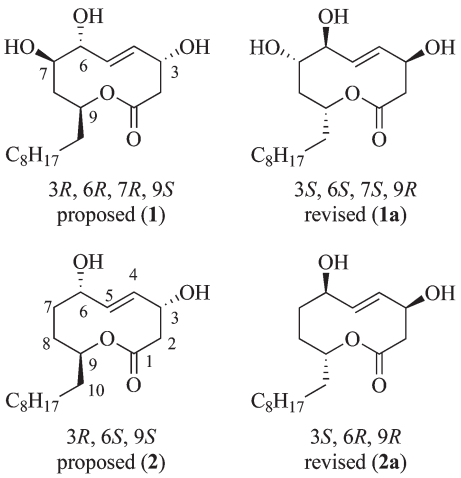

Fig. 1 Structures of seimatopolide A (**1**), B (**2**), and their enantiomers **1a** and **2a**.

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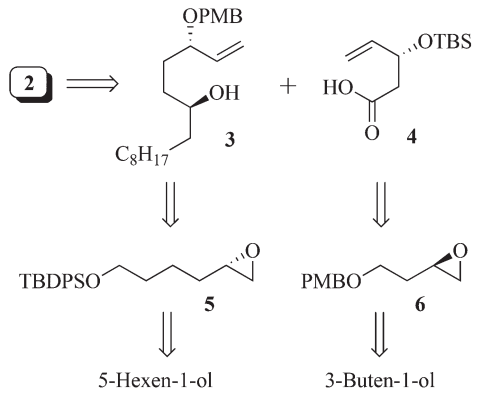
†Electronic supplementary information (ESI) available: Copies of ^{1}H NMR and ^{13}C NMR spectra of all the new compounds. See DOI: 10.1039/c3ob27518c



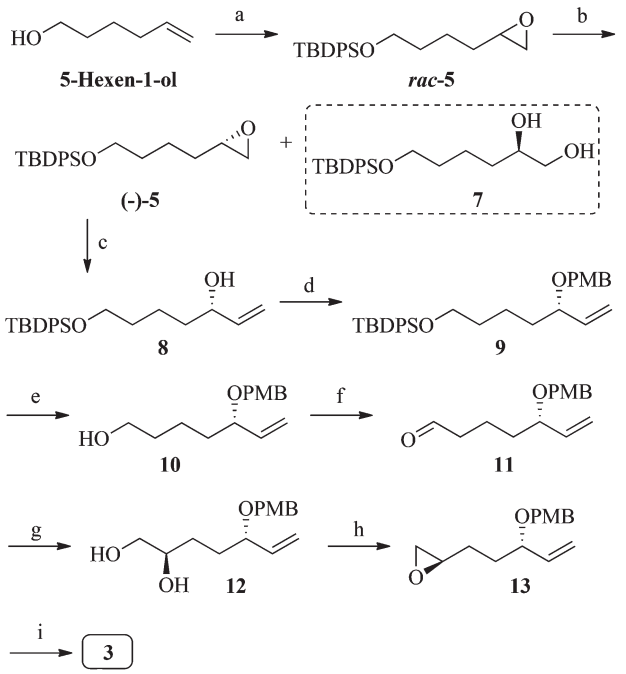
Scheme 1 Retrosynthesis of seimatopolide B (**2**).

The synthesis of the acid fragment **4** was planned starting from 3-buten-1-ol through the epoxide **6** using Jacobson epoxide resolution.

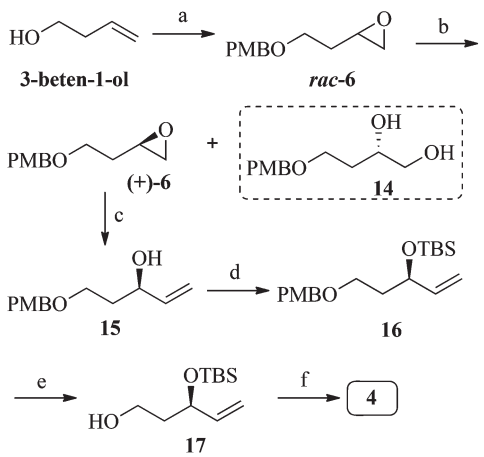
Results and discussion

As presented in Scheme 2, the racemic epoxide **5** was obtained initially in 83% yield from 5-hexen-1-ol using the literature protocol.[8] Resolution of *rac*-**5** with (*S*,*S*)-(salen)Co^{III}·OAc Jacobson catalyst[9] provided the desired epoxide (−)-**5** in 48% yield along with the diol **7** (47%). Enantiomeric purity (>98% ee) of the epoxide (−)-**5** was determined by chiral HPLC.[10] Regioselective ring opening of the epoxide (−)-**5** with trimethylsulfonium iodide in the presence of *n*-BuLi as a base in THF at −20 °C provided the alcohol **8** in 93% yield.[11] Subsequent PMB ether formation using the PMB-trichloroacetimidate (derived from PMB-OH) in the presence of $Sc(OTf)_3$ in toluene at −20 °C provided **9** in 76% yield.[12] Desilylation of compound **9** using TBAF in THF gave the alcohol **10** (92% yield). The PMB protected alcohol **10** was subjected to Dess–Martin periodinane oxidation to furnish the aldehyde **11** in 87% yield. To establish the C9-absolute stereochemistry, aldehyde **11** was subjected to asymmetric α-hydroxylation using L-proline and nitrosobenzene in chloroform at 0 °C followed by the *in situ* reduction of the resulting anilinoxy aldehyde with $NaBH_4$ in ethanol at 0 °C and treatment with Zn to obtain the diol **12** in 70% yield.[13] The diol **12** was achieved with high diastereoselectivity (no traces of the other diastereomer were isolated). Treatment of the diol **12** with tosylimidazole in the presence of NaH in THF at 0 °C to room temperature furnished the epoxide **13** in 89% yield. Then, to install the nine-carbon side chain, the epoxide **13** was treated with *n*-octyl magnesium bromide in the presence of Li_2CuCl_4 at −78 °C to give the desired alcohol fragment **3** in 77% yield.

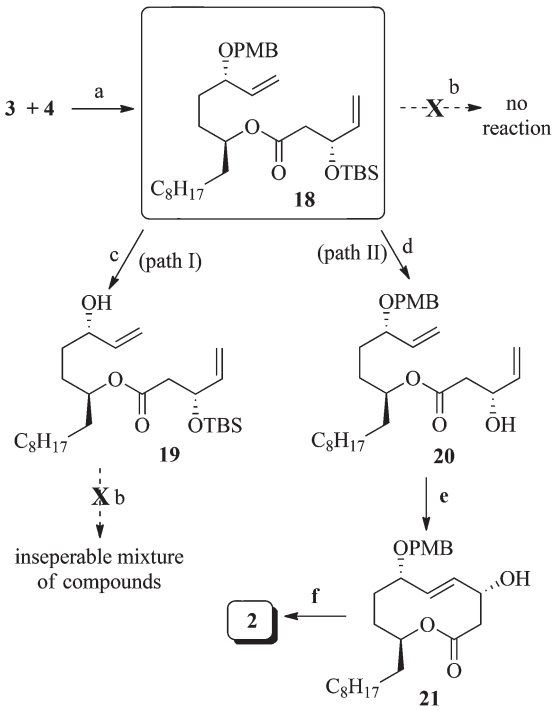
Next, we embarked on the synthesis of acid fragment **4** starting from readily available 3-buten-1-ol (Scheme 3). Consequently, 3-buten-1-ol was converted to (+)-**6** *via* a known three-step sequence.[14] The enantiomeric purity of the epoxide (+)-**6** (>99% ee) was determined by chiral HPLC as well as comparing the specific rotation with the reported data.[15] The conversion of epoxide (+)-**6** to the desired acid **4** was accomplished as described in our earlier communication in four steps[3] involving (i) epoxide opening to **15**, (ii) TBS-protection to obtain **16**,



Scheme 2 Synthesis of fragment **3**; *reagents and conditions*: (a) ref. 8; (b) (*S*,*S*)-(salen)Co^{III}·OAc (0.5 mol%), distd H_2O (0.55 equiv.), 0 °C to r.t., 16 h, 48% for (−)-**5**, 47% for **7**; (c) $Me_3S^+I^-$, *n*-BuLi, THF, −20 °C, 2 h, 93%; (d) $PMBOC(NH)CCl_3$, $Sc(OTf)_3$, −20 °C, toluene, 15 min, 76%; (e) TBAF (1 M in THF), THF, 0 °C to r.t., 2 h, 92%; (f) Dess–Martin periodinane, CH_2Cl_2, r.t., 1 h, 87%; (g) PhNO, L-proline, $CHCl_3$, 0 °C, 2 h then $NaBH_4$, EtOH, 0 °C, 2 h then AcOH, Zn, 12 h, 70%; (h) tosylimidazole, NaH, THF, 0 °C to r.t., 2 h, 89%; (i) 1-bromooctane, Mg, THF, 0 °C to reflux, 2 h, Li_2CuCl_4, −78 °C to −20 °C, 2 h, 77%.



Scheme 3 Synthesis of fragment **4**; *reagents and conditions*: (a) (i) PMBCl, NaH, DMF, 0 °C to r.t., 2 h; (ii) *m*-CPBA, CH_2Cl_2, 0 °C to r.t., 4 h, 87% (2 steps); (b) (*R*,*R*)-(salen)Co^{III}·OAc (0.5 mol%), distd H_2O (0.55 equiv.), 0 °C to r.t., 16 h, 44% for (+)-**6**, 47% for **14**; (c) $Me_3S^+I^-$, *n*-BuLi, THF, −20 °C, 2 h, 90%; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, 88%; (e) DDQ, CH_2Cl_2 : pH 7 buffer (9 : 1), 0 °C, 30 min, 93%; (f) TEMPO, BAIB, CH_2Cl_2 : H_2O (1 : 1), 0 °C to r.t., 2 h, 86%.



Scheme 4 Coupling of **3** and **4** to (3*R*, 6*S*, 9*S*)-seimatopolide B (**2**); *reagents and conditions*: (a) **4**, 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 0 °C to r.t., 2 h, then **3**, DMAP, toluene, 0 °C, 1 h, 82%; (b) Grubbs 2nd generation catalyst (G-II, 10 mol%), CH_2Cl_2, reflux, 12 h; (c) DDQ, $CH_2Cl_2 : H_2O$ (9 : 1), 0 °C, 30 min, 83%; (d) TBAF (1 M in THF), THF, 0 °C to r.t., 2 h, 91%; (e) G-II (10 mol%), CH_2Cl_2, reflux, 8 h, 62%; (f) DDQ, $CH_2Cl_2 : H_2O$ (9 : 1), 0 °C, 30 min, 73%.

Table 1 Comparison of ^1H and ^{13}C NMR (pyridine d_5) data for natural seimatopolide B and synthetic **2** or **2a**

	^1H NMR (δH and J in Hz)		^{13}C NMR (δ_C)	
Position	Natural seimatopolide B	Synthetic **2** or **2a**	Natural	Synthetic **2** or **2a**
1	—	—	170.5	170.5
2	2.89, dd (3.0, 11.5)	2.88, dd (3.2, 11.7)	45.7	45.7
	2.72, dd (3.0, 11.5)	2.74, dd (3.7, 11.5)	—	—
3	4.96, m	4.95–4.98, m	67.8	67.8
4	5.98, dd (3.0, 16.0)	5.97, dd (3.0, 16.0)	133.4	133.4
5	6.56, dd (8.5, 16.0)	6.56, dd (8.5, 16.0)	133.4	133.3
6	4.62, dd (7.5, 7.5)	4.61, dd (7.5, 7.5)	74.9	74.7
7	2.30, m	2.34–2.23, m	38.5	38.4
	2.00, m	2.06–1.90, m		
8	2.00, m	2.06–1.90, m	31.0	31.1
	1.72, m	1.77–1.41, m		
9	5.06, ddd (7.0, 7.0, 13.0)	5.06, ddd (7.0, 7.0, 13.0)	76.5	76.4
10	1.62, m	1.77–1.41, m	36.3	36.3
	1.51, m	1.77–1.41, m		
11	1.22, m	1.38–1.14, m	26.0	26.0
12	1.22, m	1.38–1.14, m	29.9	29.8
13	1.22, m	1.38–1.14, m	30.1	30.1
14	1.22, m	1.38–1.14, m	30.2	30.2
15	1.22, m	1.38–1.14, m	30.1	30.1
16	1.22, m	1.38–1.14, m	32.4	32.3
17	1.22, m	1.38–1.14, m	23.2	23.2
18	0.86, dd (7.0, 7.0)	0.84, dd (7.0, 7.0)	14.6	14.5

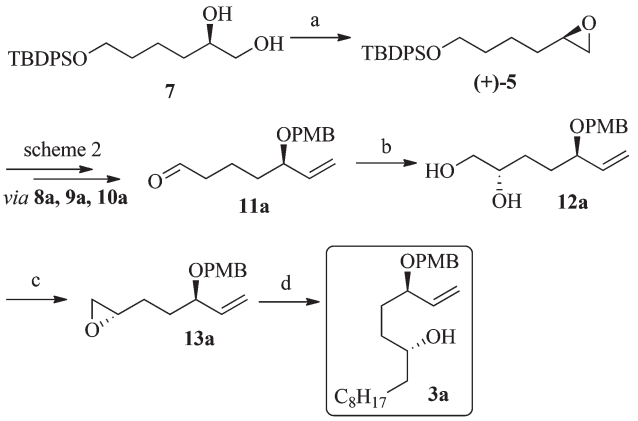
(iii) PMB-deprotection to **17** and (iv) oxidation of the alcohol to the acid **4**.

Having both the alcohol **3** and the acid **4** in hand, construction of the macrocyclic framework was achieved as shown in Scheme 4. The esterification reaction of **3** with acid **4** was carried out under Yamaguchi conditions (2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene)[16] to furnish the RCM precursor **18** in 82% yield. As a first attempt of ring-closing metathesis (RCM),[17] **18** was treated with the Grubbs second generation catalyst (G-II, 10 mol%). However, the reaction did not progress and the starting material was recovered. In a second attempt, the PMB group in compound **18** was deprotected using DDQ in $CH_2Cl_2 : H_2O$ (9 : 1) to obtain **19** (83%), which was then subjected to the RCM reaction using G-II (10 mol%). However, the reaction failed and instead of the desired pure product, the formation of an inseparable mixture of compounds was observed (path I). Subsequently, desilylation of the TBS group in **18** using TBAF in THF provided the alcohol **20** in 91% yield. Treatment of the diene **20** with G-II (10 mol%) lead to the formation of the macrolide **21** in 62% yield and with good *E*-selectivity (>95%). Finally, the deprotection of the PMB group of **21** with DDQ in $CH_2Cl_2 : H_2O$ (9 : 1) completed the synthesis of the target compound, seimatopolide B (**2**), in 73% yield.

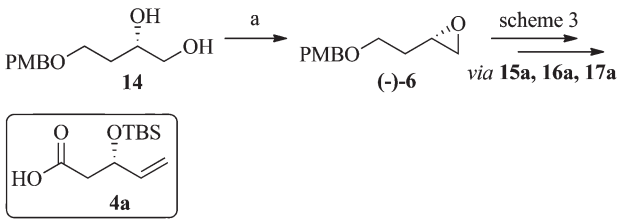
All the spectroscopic data (^1H, ^{13}C NMR, mass and IR), including NOE analysis for synthetic **2**, were in full agreement with those reported for the natural product (Table 1). However, the specific rotation for synthetic **2** was observed as $[\alpha]_D^{20}$ = +16.6 (*c* = 0.03, MeOH), whereas for the isolated compound it is reported as $[\alpha]_D^{26}$ = −125.4 (*c* = 0.03, MeOH).[2] The observation of an opposite sign in optical rotation for synthetic **2** indicates misassignment of the absolute configuration in the isolation paper. To further confirm this, based on the observations for seimatopolide A,[3,5] we decided to synthesize the enantiomer (**2a**) of the proposed structure (**2**).

The synthetic route to the enantiomer of alcohol subunit **3a** is depicted in Scheme 5 from the requisite epoxide (+)-**5**, obtained from the diol **7**. Thus, the treatment of diol **7** with tosylimidazole/NaH in THF at 0 °C provided (+)-**5** in 83% yield with 99% ee.[18] The epoxide (+)-**5** was then converted to **11a** following the sequence of reactions used for the conversion of (−)-**5** to **11**. Next, C9-absolute stereochemistry was introduced to **11a** by asymmetric α-hydroxylation using D-proline to obtain the diol **12a** (70% yield). After this, compound **12a** was transformed to **3a** *via* the epoxide **13a** under the conditions described for the conversion of **12** to **3**.

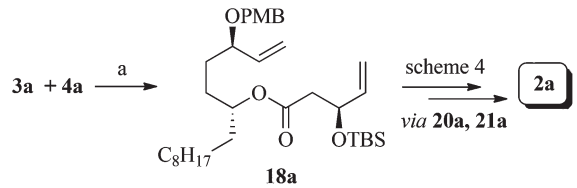
The enantiomer of the acid fragment (**4a**) was synthesized from the diol **14** (Scheme 6). Treatment of diol **14** with tosylimidazole/NaH in THF at 0 °C provided (−)-**6** in 86% yield (98% ee),[19] which was transformed to **4a** following the sequence of reactions used for the conversion of (+)-**6** to **4**.



Scheme 5 Synthesis of the fragment **3a**; *reagents and conditions*: (a) tosylimidazole, NaH, 0 °C to r.t., 2 h, 83%; (b) PhNO, D-proline, $CHCl_3$, 0 °C, 2 h then $NaBH_4$, EtOH, 0 °C, 2 h then AcOH, Zn, 12 h, 70%; (c) tosylimidazole, NaH, THF, 0 °C, 2 h, 89%; (d) 1-bromooctane, Mg, THF, 0 °C to reflux, 2 h, Li_2CuCl_4, −78 °C to −20 °C, 2 h, 77%.



Scheme 6 Synthesis of the fragment **4a**; *reagents and conditions*: (a) tosylimidazole, NaH, 0 °C to r.t., 2 h, 86%.



Scheme 7 Coupling of **3a** and **4a** to (3*S*, 6*R*, 9*R*)-seimatopolide B (**2a**). *Reagents and conditions*: (a) **4a**, 2,4,6-trichlorobenzoylchloride, Et_3N, THF, 0 °C to r.t., 2 h, then **3a**, DMAP, toluene, 0 °C, 1 h, 82%.

The next step was the completion of the synthesis of **2a** from the alcohol **3a** and the acid **4a** (Scheme 7), which was successfully attained by following a sequence similar to the reactions used for the synthesis of **2** (from **3** and **4**).

All the spectral data (^1H, ^{13}C NMR, mass and IR) of **2a** were in full agreement with those reported for the natural product (Table 1). The specific rotation for **2a** was observed {$[\alpha]_D^{20}$ = −13.4 (*c* = 0.03, MeOH)} with an optical rotation with the same sign as the isolated compound {$[\alpha]_D^{26}$ = −125.4 (*c* = 0.03, MeOH)}.[2] The comparison of spectral data (Table 1), specific rotation values for natural and synthetic seimatopolide B as well as the analysis of Mosher ester data reported in the isolation paper, suggests that the absolute configuration of the natural seimatopolide B should be revised as 3*S*, 6*R*, 9*R*

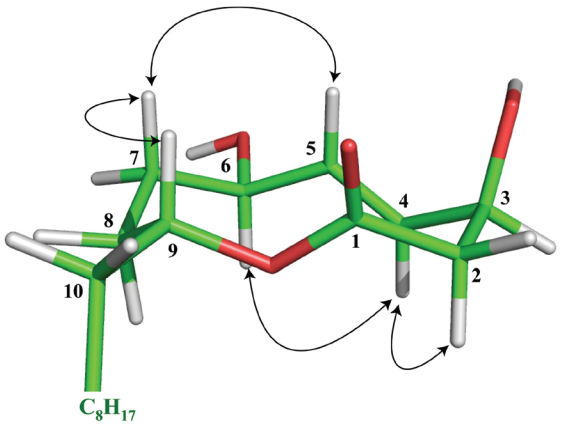


Fig. 2 Energy minimized structure and key NOE correlations for **2a**.

represented by structure **2a** (enantiomer of **2**). Further, NOESY experiments of **2a** show the NOE cross correlations between H2/H4, H4/H6, H5/H7 and H7/H9 (Fig. 2) as well as the large coupling constants among H4–H5 (*J* = 16.0 Hz), H5–H6 (*J* = 8.5 Hz), which are identical to the natural product data.[2] This clearly supports that the relative stereochemistry at C3, C6 and C9 of **2a** is similar to the natural product and the revision of absolute configuration.

During the preparation of the manuscript, Kumar *et al.* reported the total synthesis of seimatopolide B (**2**), and surprisingly, they observed a negative specific rotation {$[\alpha]_D^{25}$ = −212.6 (*c* = 0.035, MeOH)} for the originally proposed structure with (3*R*, 6*S*, 9*S*)-configuration,[20] which is in contrast to our observation. On the other hand, at the same time, Lee and coworkers have revised the initially proposed absolute configurations along with the correction of specific rotations for natural seimatopolide A and B,[21] which are in agreement with our data (Table 2).

Conclusions

In conclusion, we have successfully accomplished the total synthesis of the initially proposed structure of seimatopolide B (**2**) from 5-hexen-1-ol in 14 linear steps with 4.2% overall yield. The specific optical rotations of the synthesized compound and the natural product displayed opposite signs. This observation supports the misassignment of the absolute configuration for the natural product, which was further confirmed through the total synthesis of the enantiomer **2a**. These results suggest that the absolute configuration of the natural product should be 3*S*, 6*R*, 9*R*, which is in accordance with the natural product revised data. Key features of the synthetic approach are: (i) generation of the desired absolute stereochemistry through the Jacobson epoxide resolution and proline-catalyzed asymmetric α-hydroxylation, (ii) construction of the macrocyclic framework using Yamaguchi esterification and ring-closing metathesis reactions, which were readily adapted to obtain the natural enantiomer.

Table 2 Absolute configurations and specific rotations for natural and synthetic seimatopolide A and B

	Seimatopolide A	Seimatopolide B	Reference
Initially proposed for natural product	(3*R*, 6*R*, 7*R*, 9*S*) $[\alpha]_D^{26} = -188.3$ (*c* 0.05, MeOH)	(3*R*, 6*S*, 9*S*) $[\alpha]_D^{26} = -125.4$ (*c* 0.03, MeOH)	2
Through synthesis	(3*R*, 6*R*, 7*R*, 9*S*) **$[\alpha]_D^{25} = +30.00$** **(*c* 0.05, MeOH)**	—	3[a] (our earlier work)
Through synthesis	—	(3*R*, 6*S*, 9*S*) $[\alpha]_D^{20} = +16.6$ (*c* 0.03, MeOH) (3*S*, 6*R*, 9*R*) **$[\alpha]_D^{20} = -13.4$** **(*c* 0.03, MeOH)**	This work
Revised for natural product	(3*S*, 6*S*, 7*S*, 9*R*) **$[\alpha]_D^{29} = -20.8$** **(*c* 0.04, MeOH)**	(3*S*, 6*S*, 9*R*)[b] **$[\alpha]_D^{29} = -12.60$** **(*c* 0.03, MeOH)**	21[b]

[a] The absolute configuration of seimatopolide A has been revised as (3*S*, 6*S*, 7*S*, 9*R*). [b] The structure was revised correctly but the absolute configuration was stated incorrectly.

Experimental

General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on Bruker 300 MHz (Avance), Varian Unity 500 MHz (Innova) spectrometers at ambient temperature. Chemical shifts are reported in ppm relative to TMS as internal standard. FTIR spectra were recorded on a Perkin-Elmer 683 infrared spectrophotometer; neat or as thin films in KBr. Optical rotations were measured on an Anton Paar MLP 200 modular circular digital polarimeter by using a 2 mL cell with a path length of 1 dm. Low-resolution MS were recorded on an Agilent Technologies LC-MSD trap SL spectrometer. All the reagents and solvents were of reagent grade and used without further purification unless otherwise stated. Technical-grade EtOAc and hexanes used for column chromatography were distilled before use. THF, when used as solvent for the reactions, was freshly distilled from sodium benzophenone ketyl. Column chromatography was carried on silica gel (60–120 mesh) packed in glass columns. All the reactions were performed under N_2 in flame or ovendried glassware with magnetic stirring.

(*S*)-*tert*-Butyl(4-(oxiran-2-yl)butoxy)diphenylsilane [(−)-5]. A mixture of (*S*,*S*)-(−)-*N*-*N*′-bis(3,5-di-*tert*-butylsalicylidine)-1,2-cyclohexanediaminocobalt-II (12.7 mg, 0.021 mmol) and acetic acid (0.012 mL, 0.21 mmol) in toluene (1 mL) was stirred while open to air for 1 h at room temperature. The solvent was removed under reduced pressure and the brown residue was dried over high vacuum. The epoxide (1.5 g, 4.2 mmol) was added in one portion and the stirred mixture was cooled in an ice water bath. Water (0.041 mL, 0.23 mmol) was slowly added and the temperature of the reaction mixture was maintained below 20 °C. After the end of the addition, the ice bath was removed and the reaction mixture was stirred for 16 h. The crude reaction mixture was purified by column chromatography to afford the chiral epoxide (−)-**5** (723 mg, 48% yield) and diol **7** (740 mg, 47%) as colourless liquids. $[\alpha]_D^{20} = -2.6$ (*c* = 1.00, $CHCl_3$); IR (KBr): ν_{max} = 3070, 3048, 2934, 2859, 1471, 1428, 1107, 823, 772, 740, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67–7.65 (m, 4H), 7.43–7.36 (m, 6H), 3.67 (t, *J* = 6.2 Hz, 2H), 2.90–2.86 (m, 1H), 2.73 (dd, *J* = 5.1, 3.9 Hz, 1H), 2.44 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.65–1.50 (m, 6H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.7, 134.2, 129.7, 127.7, 63.8, 52.4, 47.2, 32.4, 32.3, 27.0, 22.5, 19.4; MS (ESI): *m*/*z* 377 [M + Na]$^+$; HRMS (ESI): calcd for $C_{22}H_{30}O_2NaSi$ (M + Na)$^+$ 377.1907; found 377.1914.

(*R*)-6-(*tert*-Butyldiphenylsilyloxy)hexane-1,2-diol (7). $[\alpha]_D^{20}$ = −0.4 (*c* = 1.00, $CHCl_3$); IR (KBr): ν_{max} = 3374, 2934, 2860, 1467, 1428, 1389, 1361, 1106, 8232, 739, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69–7.64 (m, 4H), 7.44–7.39 (m, 6H), 3.71–3.61 (3, 4H), 3.41 (dd, *J* = 11.0, 8.0 Hz, 1H), 1.65–1.38 (m, 6H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.5, 133.9, 129.5, 127.6, 72.1, 66.6, 63.6, 32.9, 32.4, 26.8, 21.8, 19.2; MS (ESI): *m*/*z* 395 [M + Na]$^+$; HRMS (ESI): calcd for $C_{22}H_{32}O_3NaSi$ (M + Na)$^+$ 395.2012; found 395.2014.

(*S*)-7-(*tert*-Butyldiphenylsilyloxy)hept-1-en-3-ol (8). A solution of trimethylsulfonium iodide (1.96 g, 9.60 mmol) in THF (30 mL) was cooled to −20 °C, *n*-BuLi (2.5 M solution in hexane, 2.9 mL, 7.20 mmol) was added dropwise and the resulting solution stirred for 1 h at −20 °C. A solution of the epoxide (−)-**5** (850 mg, 2.40 mmol) in THF (10 mL) was added and stirring continued for another 1 h at −20 °C. The reaction mixture was warmed to 0 °C and quenched with saturated aqueous NH_4Cl (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of crude compound by flash chromatography (silica gel, hexanes : EtOAc = 90 : 10) gave alcohol **8** (830 mg, 93%) as a pale yellow oil. $[\alpha]_D^{20} = -3.38$ (*c* = 1.00, $CHCl_3$); IR (KBr): ν_{max} = 3382, 3072, 2933, 2859, 1468, 1428, 1250, 1108, 994, 823, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69–7.64 (m, 4H), 7.44–7.35

(m, 6H), 5.85 (ddd, J = 17.0, 10.0, 7.0 Hz, 1H), 5.21 (d, J = 17.0 Hz, 1H), 5.10 (d, J = 10.0 Hz, 1H), 4.11–4.03 (m, 1H), 3.67 (t, J = 6.9 Hz, 2H), 1.63–1.36 (m, 6H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.1, 135.5, 134.0, 129.5, 127.5, 114.6, 73.1, 63.7, 36.6, 32.3, 26.8, 21.6, 19.2; MS (ESI): m/z 391 $[M + Na]^+$; HRMS (ESI): calcd for $C_{23}H_{32}O_2NaSi$ $(M + Na)^+$ 391.2063; found 391.2076. **8a**: $[\alpha]_D^{20}$ = +3.2 (c = 1.00, $CHCl_3$).

(*S*)-*tert*-Butyl(5-(4-methoxybenzyloxy)hept-6-enyloxy)diphenylsilane (9). To a solution of the *p*-methoxybenzyl trichloroacetimidate (600 mg) in toluene (5 mL), at −20 °C was added alcohol **8** (200 mg, 0.54 mmol) in toluene (2.0 mL) followed by scandium triflate (13.3 mg, 0.027 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 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes : EtOAc = 97 : 03) to give olefin **9** (200 mg, 76%) as a colourless oil. $[\alpha]_D^{20}$ = −11.7 (c = 1.00, $CHCl_3$); IR (KBr): ν_{max} = 3071, 2933, 2859, 1612, 1512, 1427, 1247, 1108, 772, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69–7.63 (m, 4H), 7.45–7.32 (m, 6H), 7.27–7.21 (m, 2H), 6.90–6.80 (m, 2H), 5.71 (ddd, J = 17.0, 10.5, 7.4 Hz, 1H), 5.21 (d, J = 3.8 Hz, 1H), 5.17 (dt, J = 10.9, 1.8 Hz, 1H), 4.51 (d, J = 11.5 Hz, 1H), 4.27 (d, J = 11.5 Hz, 1H), 3.82–3.76 (m, 4H), 3.64 (t, J = 6.4 Hz, 2H), 1.64–1.36 (m, 6H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 139.1, 135.5, 134.0, 130.8, 129.4, 129.2, 127.5, 116.9, 113.6, 80.2, 69.6, 63.8, 55.2, 35.2, 32.4, 26.8, 21.7, 19.2; MS (ESI): m/z 511 $[M + Na]^+$; HRMS (ESI): calcd for $C_{31}H_{40}O_3NaSi$ $(M + Na)^+$ 511.2638; found 511.2641. **9a**: $[\alpha]_D^{20}$ = +10.4 (c = 1.00, $CHCl_3$).

(*S*)-5-(4-Methoxybenzyloxy)hept-6-en-1-ol (10). A solution of **9** (200 mg, 0.41 mmol) in THF (2 mL) was cooled to 0 °C, TBAF (0.82 mL, 0.82 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 layers were washed with brine (15 mL), dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes : EtOAc = 80 : 20) to give pure **10** (95 mg, 92%) as a colorless oil. $[\alpha]_D^{20}$ = −17.2 (c = 0.5, $CHCl_3$); IR (KBr): ν_{max} = 3399, 2994, 2935, 2863, 1612, 1585, 1513, 1300, 1246, 1036, 993, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.25 (d, J = 8.9 Hz, 2H), 6.88 (d, J = 8.9 Hz, 2H), 5.74 (ddd, J = 17.0, 10.0, 8.0 Hz, 1H), 5.25–5.18 (m, 2H), 4.53 (d, J = 12.0 Hz, 1H), 4.28 (d, J = 12.0 Hz, 1H), 3.81 (s, 3H), 3.72 (q, J = 7.0 Hz, 1H), 3.62 (t, J = 6.0 Hz, 2H), 1.71–1.35 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 138.9, 130.7, 129.3, 117.1, 113.7, 80.9, 69.6, 62.6, 55.2, 35.1, 32.5, 21.5; MS (ESI): m/z 273 $[M + Na]^+$; HRMS (ESI): calcd for $C_{15}H_{22}O_3Na$ $(M + Na)^+$ 273.1461; found 273.1468. **10a**: $[\alpha]_D^{20}$ = +19.0 (c = 1.00, $CHCl_3$).

(*S*)-5-(4-Methoxybenzyloxy)hept-6-enal (11). To a stirred solution of alcohol **10** (350 mg, 1.4 mmol) in dry dichloromethane (3 mL) at 0 °C was added Dess–Martin periodinane (890 mg, 2.3 mmol) in one portion. The reaction mixture was stirred for 1 h at 0 °C and quenched with saturated aqueous $Na_2S_2O_3$ (5 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes : EtOAc = 90 : 10) to give aldehyde **11** (301 mg, 87%) as a colourless oil. $[\alpha]_D^{20}$ = −25.2 (c = 1.00, $CHCl_3$); IR (KBr): ν_{max} = 3005, 2934, 2835, 1722, 1611, 1512, 1300, 1220, 1175, 927, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.73 (s, 1H), 7.25 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.73 (ddd, J = 16.8, 10.6, 7.6 Hz, 1H), 5.27–5.18 (m, 2H), 4.53 (d, J = 11.5 Hz, 1H), 4.26 (d, J = 11.5 Hz, 1H), 3.80 (s, 3H), 3.72 (q, J = 6.4 Hz, 1H), 2.41 (dt, J = 6.4, 1.3 Hz, 2H), 1.83–1.45 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 202.5, 159.0, 138.7, 130.6, 129.3, 117.4, 113.7, 79.6, 69.7, 55.2, 43.6, 34.8, 18.0; MS (ESI): m/z = 271 $[M + Na]^+$. **11a**: $[\alpha]_D^{20}$ = +23.5 (c = 1.00, $CHCl_3$).

(2*R*,5*S*)-5-(4-Methoxybenzyloxy)hept-6-ene-1,2-diol (12). Aldehyde **11** (200 mg, 0.80 mmol) was added dropwise to a solution of nitrosobenzene (47.4 mg, 0.443 mmol) and L-proline (4.63 mg, 0.0403 mmol) in chloroform (0.5 mL) at 0 °C, and the solution was vigorously stirred at 0 °C for 2 h. The reaction mixture was transferred dropwise to a solution of sodium borohydride (30 mg, 0.806 mmol) in ethanol (5.0 mL) at 0 °C and the solution stirred at 0 °C for 2 h, then concentrated. Saturated aqueous sodium bicarbonate solution (5 mL) was added and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was dissolved in 3 : 1 ethanol : acetic acid (2 mL) and treated with zinc powder (175 mg, 2.68 mmol) and the reaction mixture was stirred at room temperature for 12 h, then filtered through celite and concentrated. Purification of the residue by flash column chromatography gave the diol **12** (150 mg, 70%) as colourless oil. $[\alpha]_D^{20}$ = −17.9 (c = 0.67, $CHCl_3$); IR (KBr): ν_{max} = 3391, 2933, 2864, 1612, 1513, 1247, 1065, 1035, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.24 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 8.0 Hz, 2H), 5.76 (ddd, J = 17.0, 10.0, 8.0 Hz 1H), 5.27–5.20 (m, 2H), 4.54 (d, J = 11.0 Hz, 1H), 4.28 (d, J = 11.0 Hz, 1H), 1.84–1.74 (m, 1H), 1.76–1.69 (m, 1H), 1.67–1.56 (m, 1H), 1.53–1.43 (m, 1H), 1.43–1.34 (m, 1H), 1.33–1.21 (m, 4H), 0.89 (t, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 138.4, 130.2, 129.5, 117.4, 113.7, 80.1, 71.9, 69.8, 60.6, 55.2, 31.5, 28.9; MS (ESI): m/z 289.2 $[M + Na]^+$; HRMS (ESI): calcd for $C_{15}H_{22}O_4Na$ $(M + Na)^+$ 289.1410; found 289.1413. **12a**: $[\alpha]_D^{20}$ = +15.38 (c = 0.6, $CHCl_3$).

(*R*)-2-((*S*)-3-(4-Methoxybenzyloxy)pent-4-enyl)oxirane (13). A solution of the diol **12** (150 mg, 0.57 mmol) in THF (3 mL) was added to NaH (60 wt% in mineral oil, 55 mg, 2.3 mmol) in THF (2 mL) at 0 °C. The resulting mixture was then warmed to ambient temperature and stirred for 40 min. The mixture was cooled to 0 °C, tosylimidazole (154 mg, 0.67 mmol) was added in one portion, the mixture was allowed to warm up to ambient temperature and stirred for 1 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with

brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes : EtOAc = 90 : 10) to give the oxirane **13** (125 mg, 89%) as a colourless oil. $[\alpha]_D^{20} = -15.6$ (c = 0.9, $CHCl_3$); IR (KBr): ν_{max} = 3453, 2926, 2858, 1612, 1513, 1247, 1071, 1035, 824 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.24 (d, J = 8.3 Hz, 2H), 6.87 (d, J = 8.3 Hz, 2H), 5.74 (ddd, J = 16.6, 10.5, 7.5 Hz, 1H), 5.27–5.18 (m, 2H), 4.53 (d, J = 11.3 Hz, 1H), 4.27 (d, J = 11.3 Hz, 1H), 3.80 (s, 3H), 3.75 (q, J = 12.8, 7.6 Hz, 1H), 2.94–2.87 (m, 1H), 2.73 (t, J = 4.5 Hz, 1H), 2.48–2.42 (m, 1H), 1.81–1.47 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 138.8, 130.7, 129.3, 117.3, 113.7, 79.8, 69.8, 69.7, S52.2, 47.1, 31.8, 28.6; MS (ESI): m/z = 271 $[M + Na]^+$; HRMS (ESI): calcd for $C_{15}H_{20}O_3Na$ $(M + Na)^+$ 271.1304; found 271.1312. **13a:** $[\alpha]_D^{20}$ = +15.0 (c = 1.00, $CHCl_3$).

(3*S*,6*S*)-3-(4-Methoxybenzyloxy)pentadec-1-en-6-ol (3). A solution of *n*-octylmagnesium bromide [prepared from *n*-bromooctane (174 mg, 0.108 mmol) and Mg (30 mg, 0.126 mmol) in dry THF (3 mL) under nitrogen] was added dropwise to a stirred solution of **13** (125 mg, 0.504 mmol) in dry THF (3 mL) at −78 °C. Subsequently, a solution of Li_2CuCl_4 (0.1 M in THF, 0.25 mL, 0.025 mmol) was added dropwise to the stirred mixture, allowed to warm up to room temperature and stirred for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (2 × 10 mL). The organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes : EtOAc = 80 : 20) to give the alcohol **3** (140 mg, 77%) as a colourless oil. $[\alpha]_D^{20}$ = −17.1 (c = 1.00, $CHCl_3$); IR (KBr): ν_{max} = 3413, 2926, 2855, 1514, 1464, 1248, 1038, 821, 722 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.25 (d, J = 7.9 Hz, 2H), 6.87 (d, J = 7.9 Hz, 2H), 6.75 (ddd, J = 17.6, 10.6, 7.9 Hz, 1H), 5.25–5.19 (m, 2H), 4.53 (d, J = 11.5 Hz, 1H), 4.29 (d, J = 11.5 Hz, 1H), 3.80 (s, 3H), 3.75 (q, J = 13.2, 6.2 Hz, 1H), 3.60–3.52 (m, 1H), 1.92 (br s, 1H), 1.73–1.56 (m, 4H), 1.47–1.36 (m, 3H), 1.34–1.20 (m, 13H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 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; MS (ESI): m/z 385 $[M + Na]^+$; HRMS (ESI): calcd for $C_{23}H_{38}O_3Na$ $(M + Na)^+$ 385.2713; found 385.2730. **3a:** $[\alpha]_D^{20}$ = +16.8 (c = 1.00, $CHCl_3$).

(*R*)-2-(2-(4-Methoxybenzyloxy)ethyl)oxirane [(+)-6].[3] A mixture of (*R*,*R*)-(−)-*N*-*N*′-bis(3,5-di-*tert*-butylsalicylidine)-1,2-cyclohexane diaminocobalt-II (46.4 mg, 0.077 mmol) and acetic acid (0.044 mL, 0.77 mmol) in toluene (5 mL) was stirred while open to air for 1 h at room temperature. The solvent was removed under reduced pressure and the brown residue was dried over high vacuum. The epoxide (3.2 g, 15.38 mmol) was added in one portion, cooled in an ice water bath. Water (0.15 mL, 8.46 mmol) was added slowly and the temperature was maintained <20 °C. After the end of the addition, the ice bath was removed and the reaction mixture was stirred for 16 h. The crude reaction mixture was purified by column chromatography to afford the chiral epoxide (+)-**6** (1.45 g, 44% yield) and diol **14** (1.63 g, 47%) as colourless liquids. $[\alpha]_D^{20}$ = +12.5 (c = 1.28, $CHCl_3$); IR (KBr): ν_{max} = 2928, 2860, 1613, 1514, 1461, 1248, 1094, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.27 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 4.46 (s, 2H), 3.81 (s, 3H), 3.64–3.56 (m, 2H), 3.08–3.03 (m, 1H), 2.78 (dd, J = 4.9, 3.9 Hz, 1H), 2.52 (dd, J = 4.9, 2.9 Hz, 1H), 1.94–1.85 (m, 1H), 1.82–1.73 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 130.1, 129.0, 113.6, 72.5, 66.5, 55.0, 49.9, 45.9, 32.8; MS (ESI): m/z 231 $[M + Na]^+$.

(*S*)-4-(4-Methoxybenzyloxy)butane-1,2-diol (14). $[\alpha]_D^{20}$ = +4.0 (c = 1.00, $CHCl_3$); IR (KBr): ν_{max} = 3364, 2947, 2891, 1456, 1427, 1349, 1304, 1106, 823, 772, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.24 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.45 (s, 2H), 3.91 (m, 1H), 3.81 (s, 3H), 3.71–3.59 (m, 3H), 3.56–3.47 (m, 1H), 3.23 (br s, 1H), 2.48 (br s, 1H), 1.89–1.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 129.8, 129.2, 113.6, 72.5, 70.3, 67.2, 66.255.0, 32.7; MS (ESI): m/z 249 $[M + Na]^+$.

(*R*)-5-(4-Methoxybenzyloxy)pent-1-en-3-ol (15).[3] A solution of trimethylsulfonium iodide (1.96 g, 9.61 mmol) in THF (30 mL) was cooled to −20 °C, *n*-BuLi (2.5 M solution in hexane, 2.9 mL, 7.21 mmol) was added dropwise, and the resulting solution was stirred for 1 h at −20 °C. A solution of the epoxide **6** (500 mg, 2.40 mmol) in THF (10 mL) was added and a cloudy suspension was formed. The stirring was continued for another 1 h at −20 °C. The reaction mixture was warmed to 0 °C and quenched with saturated aqueous NH_4Cl (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of crude compound by flash chromatography (silica gel, hexanes : EtOAc = 90 : 10) gave alcohol **15** (480 mg, 90%) as a pale yellow oil. $[\alpha]_D^{20}$ = −10.1 (c = 0.6, $CHCl_3$); IR (KBr): ν_{max} = 3414, 2923, 2858, 1612, 1585, 1513, 1247, 1091, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.25 (d, J = 8.3 Hz, 2H), 6.88 (d, J = 8.3 Hz, 2H), 5.87 (ddd, J = 17.3, 10.5, 6.0 Hz, 1H), 5.27 (dt, J = 17.3, 1.5 Hz, 1H), 5.10 (dt, J = 10.5, 1.5 Hz, 1H), 4.45 (s, 2H), 4.38–4.29 (m, 1H), 3.81 (s, 3H), 3.72–3.57 (m, 2H), 1.92–1.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.3, 140.5, 130.0, 129.3, 114.3, 113.8, 72.9, 71.9, 68.0, 55.2, 36.2; MS (ESI): m/z 245.2 $[M + Na]^+$.

(*R*)-*tert*-Butyl(5-(4-methoxybenzyloxy)pent-1-en-3-yloxy)dimethylsilane (16).[3] To a 0 °C solution of **15** (450 mg, 2.02 mmol) in CH_2Cl_2 (8 mL) was added 2,6-lutidine (0.48 mL, 4.04 mmol) and TBSOTf (0.51 mL, 2.23 mmol). The mixture was stirred at 0 °C for 30 min and diluted with CH_2Cl_2 (15 mL). The organic phase was washed sequentially with a saturated aqueous solution of $NaHCO_3$ (20 mL) and brine (15 mL), dried over Na_2SO_4 and evaporated to dryness. The residue was purified by flash chromatography (silica gel, hexanes : EtOAc = 97 : 03) to give **16** (600 mg, 88% yield) as colorless oil. $[\alpha]_D^{20}$ = −1.9 (c = 1.00, $CHCl_3$); IR (KBr): ν_{max} = 2932, 2857, 1613, 1513, 1249, 1090, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.25 (d, J = 9.1 Hz, 2H), 6.87 (d, J = 9.1 Hz, 2H), 5.80 (ddd, J = 17.1, 10.3, 5.7 Hz, 1H), 5.14 (d, J = 17.1 Hz, 1H), 5.01 (dt, J = 10.3 Hz, 1H), 4.44 (d, J = 11.4 Hz, 1H), 4.38 (d, J = 11.4 Hz, 1H), 4.29 (q, J = 6.8 Hz, 1H), 3.80 (s, 3H), 3.57–3.46 (m, 2H), 1.77 (q, J = 6.8 Hz, 2H), 0.89 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$,

75 MHz): δ 159.0, 141.5, 130.5, 129.2, 113.7, 113.6, 72.5, 70.7, 66.3, 55.1, 38.0, 25.8, 18.1, −4.4, −5.0; MS (ESI): m/z = 359.2 $[M + Na]^+$.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)pent-4-en-1-ol (17).[3] To a solution of **16** (200 mg, 0.60 mmol) in CH_2Cl_2 (5 mL) and a pH 7 buffered solution (1 mL) was added DDQ (162 mg, 0.71 mmol) at 0 °C. The reaction mixture was stirred for 30 min, and then poured into water. The aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with aqueous $NaHCO_3$ (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (silica gel, hexanes : EtOAc = 90 : 10) afforded alcohol **17** (120 mg, 93%) as a colorless oil. $[\alpha]_D^{20}$ = +3.9 (c = 1.00, $CHCl_3$); IR (KBr): ν_{max} = 3367, 2932, 2858, 1613, 1514, 1251, 1089, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.86 (ddd, J = 17.1, 10.3, 5.7 Hz, 1H), 5.22 (d, J = 17.1 Hz, 1H), 5.10 (d, J = 10.3 Hz, 1H), 4.41 (q, J = 5.7 Hz, 1H), 3.86–3.79 (m, 1H), 3.74–3.69 (m, 1H), 2.38 (br s, 1H), 1.90–1.81 (m, 1H), 1.76–1.68 (m, 1H), 0.91 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.5, 114.3, 73.0, 59.9, 39.1, 25.7, 18.0, −4.4, −5.1.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)pent-4-enoic acid (4).[3] To a solution of the above alcohol **17** (250 mg, 1.16 mmol) in H_2O–CH_2Cl_2 (1/1, 4 mL) were added TEMPO (52 mg, 0.35 mmol) and BAIB (1.12 g, 3.48 mmol). After stirring at room temperature for 2 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous $Na_2S_2O_3$ (10 mL). The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give the crude carboxylic acid, which was further purified by flash column chromatography (silica gel, hexanes : EtOAc = 90 : 10) to give the acid **4** (230 mg, 86%) as a colorless oil. $[\alpha]_D^{20}$ = −4.0 (c = 1.0, $CHCl_3$); IR (KBr): ν_{max} = 2930, 2858, 1714, 1466, 1254, 1087, 835, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 10.57 (br s, 1H), 5.85 (ddd, J = 16.8, 10.3, 6.2 Hz, 1H), 5.25 (d, J = 16.8 Hz, 1H), 5.10 (d, J = 10.3 Hz, 1H), 4.58 (q, J = 6.2 Hz, 1H), 2.61–2.47 (m, 2H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.8, 139.6, 115.0, 70.5, 43.3, 25.7, 18.0, −4.4, −5.2; MS (ESI): m/z = 253.1 $[M + Na]^+$.

(*R*)-((3*S*,6*S*)-3-(4-Methoxybenzyloxy)pentadec-1-en-6-yl)3-(*tert*-butyldimethylsilyloxy)pent-4-enoate (18). To a solution of acid **4** (89 mg, 0.386 mmol) in dry THF (7 mL) at 0 °C were added Et_3N (0.16 mL, 1.16 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (0.12 mL, 0.77 mmol), and the resulting mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, and the residue was dissolved in toluene (5 mL). To this mixture at 0 °C was added a solution of DMAP (141 mg, 1.16 mmol) and alcohol **3** (140 mg, 0.386 mmol) in toluene (2 mL), and the resulting mixture was stirred for 15 min. The reaction mixture was diluted with EtOAc (5 mL), washed with saturated aqueous NH_4Cl (5 mL), and then with brine solution (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, hexanes : EtOAc = 97 : 03) gave diene **18** (183 mg, 82%) as a colorless oil. $[\alpha]_D^{20}$ = −13.2 (c = 0.5, $CHCl_3$); IR (KBr): ν_{max} = 3445, 2925, 2855, 1634, 1470, 1249, 844, 766 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.24 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.84 (ddd, J = 16.8, 10.3, 6.2 Hz, 1H), 5.70 (ddd, J = 17.2, 10.3, 7.7 Hz, 1H), 4.90–4.80 (m, 1H), 4.57 (q, J = 6.0 Hz, 1H), 4.51 (d, J = 11.3 Hz, 1H), 4.27 (d, J = 11.3 Hz, 1H), 3.80 (s, 3H), 6.23 (q, J = 6.2 Hz, 1H), 2.48 (ddd, J = 21.0, 14.9, 6.0 Hz, 2H), 1.7–1.4 (m, 6H), 1.36–1.18 (3, 14H), 0.96–0.83 (m, 12H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.7, 159.0, 140.3, 138.8, 130.8, 129.3, 117.4, 114.7, 113.7, 80.2, 74.4, 70.7, 69.7, 55.3, 43.7, 34.0, 31.9, 31.3, 29.9, 29.7, 29.5, 29.3, 25.8, 25.2, 22.7, 14.1, −4.4, −4.9; MS (ESI): m/z = 597 $[M + Na]^+$; HRMS (ESI): calcd for $C_{34}H_{58}O_5NaSi$ $(M + Na)^+$ 597.3945; found 597.3971. **18a**: $[\alpha]_D^{20}$ = +12.3 (c = 1.00, $CHCl_3$).

(*R*)-((3*S*,6*S*)-3-Hydroxypentadec-1-en-6-yl)3-(*tert*-butyl-dimethylsilyloxy)pent-4-enoate (19). To a solution of **18** (70 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) and H_2O (0.2 mL) was added DDQ (33 mg, 0.146 mmol) at 0 °C. The reaction mixture was stirred for 30 min, and then poured into water. The aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with aqueous $NaHCO_3$ (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (silica gel, hexanes : EtOAc = 90 : 10) afforded alcohol **19** (45 mg, 83%) as a colorless oil. $[\alpha]_D^{20}$ = −4.0 (c = 0.5, $CHCl_3$); IR (KBr): ν_{max} = 3454, 2927, 2856, 1733, 1464, 1254, 1181, 1082, 923, 835, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.86 (dd, J = 10.7, 6.2 Hz, 1H), 5.80 (dd, J = 10.1, 6.2 Hz, 1H), 5.20 (d, J = 17.0 Hz, 2H), 5.13–5.03 (m, 2H), 4.91–4.80 (m, 1H), 4.56 (q, J = 6.8 Hz, 1H), 4.13–4.03 (m, 1H), 2.53 (dd, J = 14.9, 7.1 Hz, 1H), 2.49 (dd, J = 14.9, 5.6 Hz, 1H), 1.72–1.43 (m, 6H), 1.36–1.22 (m, 14H), 0.88 (t, J = 6.6 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.7, 141.0, 140.4, 114.9, 114.7, 74.3, 73.0, 70.78, 43.8, 34.2, 32.8, 32.0, 30.0, 29.8, 29.6, 29.4, 25.9, 25.4, 22.8, 18.2, 14.2, −4.3, −4.8; MS (ESI): m/z = 477 $[M + Na]^+$; HRMS (ESI): calcd for $C_{26}H_{50}O_4NaSi$ $(M + Na)^+$ 477.3370; found 477.3375.

(*R*)-((3*S*,6*S*)-3-(4-Methoxybenzyloxy)pentadec-1-en-6-yl)3-hydroxypent-4-enoate (20). A solution of **18** (145 mg, 0.253 mmol) in THF (3 mL) was cooled to 0 °C and TBAF (0.38 mL, 0.38 mmol, 1.0 M solution in THF) was added dropwise. The resulting brown solution was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes : EtOAc = 90 : 10) to give **20** (105 mg, 91%) as a colorless oil. $[\alpha]_D^{20}$ = −14.6 (c = 1.00, $CHCl_3$); IR (KBr): ν_{max} = 3448, 2925, 2855, 1725, 1615, 1513, 1247, 1175, 1038, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.24 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 5.87 (ddd, J = 17.0, 11.0, 6.0 Hz, 1H), 5.71 (ddd, J = 18.0, 10.0, 8.0 Hz, 1H), 5.34–5.12 (m, 4H), 4.94–4.88 (m, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.50 (br s, 1H), 4.27 (d, J = 12.0 Hz, 1H), 3.80 (s, 3H), 3.68 (q, J = 7.0 Hz, 1H), 2.58–2.46 (m, 2H), 1.74–1.46 (m, 6H), 1.33–1.21 (m, 14H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.1, 159.0, 138.8, 138.7, 130.6, 129.4, 117.5, 115.3, 113.7, 79.9, 74.9, 69.7, 68.9, 55.2, 41.3,

34.0, 31.9, 31.0, 29.8, 29.7, 29.5, 29.4, 29.3, 25.2, 22.7, 14.1; MS (ESI): *m*/*z* 483.3 $[M + Na]^+$; HRMS (ESI): calcd for $C_{28}H_{44}O_5Na$ $(M + Na)^+$ 483.3081; found 483.3078. **20a:** $[\alpha]_D^{20}$ = +13.2 (*c* = 1.00, $CHCl_3$).

(4*R*,7*S*,10*S*,*E*)-4-Hydroxy-7-(4-methoxybenzyloxy)-10-nonyl-3,4,7,8,9,10-hexahydro-2*H*-oxecin-2-one (21). Grubbs second generation catalyst (G-II, 8.3 mg, 0.00978 mmol) was dissolved in dry, deoxygenated CH_2Cl_2 (120 mL). After heating the solution to reflux, diene **20** (45 mg, 0.0978 mmol) dissolved in dry, deoxygenated CH_2Cl_2 (30 mL) was added dropwise over 30 min. The mixture was stirred at reflux for 8 h and cooled to room temperature, all volatiles were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes : EtOAc = 85 : 15) to give **21** (26 mg, 62%) as a colourless oil. IR (KBr): ν_{max} = 3431, 2925, 2854, 1737, 1513, 1461, 1245, 1173, 1037, 971, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.22 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 2H), 5.73 (d, *J* = 15.9 Hz, 1H), 5.66 (dd, *J* = 15.9, 6.9 Hz, 1H), 4.82 (q, *J* = 6.0 Hz, 1H), 4.74–4.69 (m, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.27 (d, *J* = 12.0 Hz, 1H), 3.91–3.84 (m, 1H), 3.79 (s, 3H), 2.58 (ddd, *J* = 16.0, 12.0, 4.0 Hz, 2H), 2.06–1.37 (m, 4H), 1.34–1.18 (m, 14H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.0, 159.1, 134.3, 130.1, 130.0, 129.4, 113.8, 77.2, 76.8, 69.5, 67.7, 55.3, 44.2, 33.6, 32.0, 31.9, 29.7, 29.5, 29.4, 29.4, 29.2, 25.3, 22.7, 14.1.

Seimatopolide B (2). To a solution of **21** (18 mg, 0.042 mmol) in CH_2Cl_2 (1 mL) and H_2O (0.1 mL) was added DDQ (11.5 mg, 0.0508 mmol) at 0 °C. The reaction mixture was stirred for 30 min, and then poured into water. The aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with aqueous $NaHCO_3$ (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (silica gel, CH_2Cl_2 : MeOH = 97 : 3) afforded **2** (9.5 mg, 73%) as a colourless solid. $[\alpha]_D^{20}$ = +16.6 (*c* = 0.03, MeOH); IR (KBr): ν_{max} = 3340, 2915, 2849, 1723, 1459, 1257, 1220, 1167, 979, 772 cm^{-1}; ^1H NMR (pyridine d_5, 300 MHz): δ 6.56 (dd, *J* = 16.0, 8.5 Hz, 1H), 5.97 (dd, *J* = 16.0, 3.0 Hz, 1H), 5.06 (ddd, *J* = 13.0, 7.0, 7.0 Hz, 1H), 4.95–4.98 (m, 1H), 4.61 (dd, *J* = 7.5, 7.5 Hz, 1H), 2.88 (dd, *J* = 11.7, 3.2 Hz, 1H), 2.71 (dd, *J* = 11.5, 3.7 Hz, 1H), 2.34–2.23 (m, 1H), 2.06–1.90 (m, 2H), 1.77–1.41 (m, 3H), 1.38–1.14 (m, 14H), 0.84 (dd, *J* = 6.9, 6.9 Hz, 3H); ^{13}C NMR (pyridine d_5, 75 MHz): 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, 30.1, 29.8, 26.0, 23.2, 14.5; MS (ESI): *m*/*z* = 335 $[M + Na]^+$; HRMS (ESI): calcd for $C_{18}H_{32}O_5Na$ $(M + Na)^+$ 335.2192; found 335.2191.

(*R*)-*tert*-Butyl(4-(oxiran-2-yl)butoxy)diphenylsilane [(+)-5]. A solution of diol **7** (200 mg, 0.53 mmol) in THF (5 mL) was added to NaH (60 wt% in mineral oil, 54 mg, 2.1 mmol) in THF (2 mL) at 0 °C. The resulting mixture was then warmed to ambient temperature and stirred for 40 min. The mixture was then cooled to 0 °C and tosylimidazole (146 mg, 0.63 mmol) was added in one portion. The reaction mixture was allowed to warm up to ambient temperature and stirred for 1 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes : EtOAc = 95 : 05) to give oxirane (+)-**5** (157 mg, 83%) as a colourless oil. $[\alpha]_D^{20}$ = +2.8 (*c* = 1.00, $CHCl_3$).

(*S*)-2-(2-(4-Methoxybenzyloxy)ethyl)oxirane [(−)-6]. A solution of diol **14** (230 mg, 1.01 mmol) in THF (10 mL) was added to NaH (60 wt% in mineral oil, 98 mg, 4.07 mmol) in THF (5 mL) at 0 °C. The resulting mixture was then warmed to ambient temperature and stirred for 40 min. The mixture was then cooled to 0 °C and tosylimidazole (279 mg, 1.22 mmol) was added in one portion. The reaction mixture was allowed warm up to ambient temperature and stirred for 1 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes : EtOAc = 90 : 10) to give oxirane (−)-**6** (181 mg, 86%) as a colourless oil; $[\alpha]_D^{20}$ = −11.8 (*c* = 1.00, $CHCl_3$).

Seimatopolide B (2a). $[\alpha]_D^{20}$ = −13.4 (*c* = 0.03, MeOH), All other spectral data are identical to those reported for **2**.

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19 (*a*) Enantiomeric excess (ee) of epoxide (−)-**6** was determined by chiral HPLC [Chiralpack-AD-H, 250 × 4.6 mm, 5 μ, 1.0% iPr-OH in hexanes, flow rate 1.2 mL min^{-1}, retention time 21.41 (0.94%), 22.65 (99.04%)] (*b*) Specific rotation: observed, $[\alpha]_D^{20} = -11.8$ (*c* = 1.00, $CHCl_3$); reported for (−)-**6** formed *via* kinetic resolution, $[\alpha]_D^{26} = -13.9$ (*c* 1.0, $CHCl_3$), see: S. Roy and C. D. Spilling, *Org. Lett.*, 2010, **12**, 5326–5329.; for (−)-**6** prepared from D-aspartic acid, $[\alpha]_D^{24}$ = −14.23 (*c* 0.66, $CHCl_3$); see: F. Glaus and K.-H. Altmann, *Angew. Chem., Int. Ed.*, 2012, **51**, 3405–3409; for (−)-**6** prepared from L-malic acid, $[\alpha]_D^{25} = -13.1$ (*c* 0.58, $CHCl_3$), see: M. J. Gaunt, A. S. Jessiman, P. Orsini, H. R. Tanner, D. F. Hook and S. V. Ley, *Org. Lett.*, 2003, **5**, 4819–4822.

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