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Total Syntheses of Naturally Occurring Seimatopolide A and Its Enantiomer from Chiral Pool Starting Materials Using a Bidirectional Strategy

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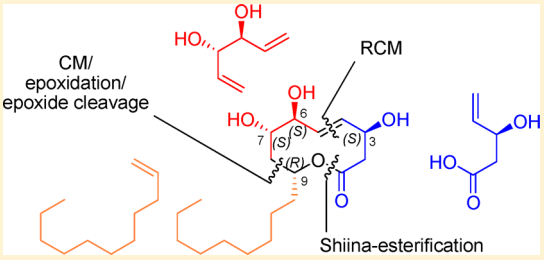
Supporting Information

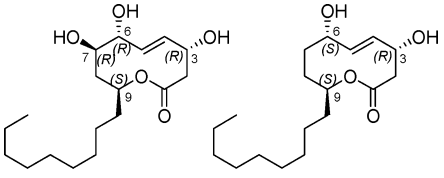
ABSTRACT: Enantioselective total syntheses of both enantiomers of the recently isolated decanolide natural product seimatopolide A are described. The C_2-symmetric building blocks (*R*,*R*)-hexa-1,5-diene-3,4-diol (derived from D-mannitol) and its enantiomer (derived from L-(+)-tartrate) serve as key starting materials, which are elaborated in a bidirectional way using a selective mono-cross-metathesis, regio- and stereoselective epoxidation, and regioselective reductive epoxide opening to furnish the first fragment. Both enantiomers of the second fragment, 3-hydroxypent-4-enoic acid, were conveniently obtained through a lipase-catalyzed kinetic resolution and merged with the first fragment via Shiina esterification. An *E*-selective ring-closing metathesis was used to access the 10-membered lactone. A comparison of the specific optical rotations of synthetic seimatopolides with those reported for the natural product suggests that the originally assigned (3*R*,6*R*,7*R*,9*S*)-configuration should be corrected to (3*S*,6*S*,7*S*,9*R*).



INTRODUCTION

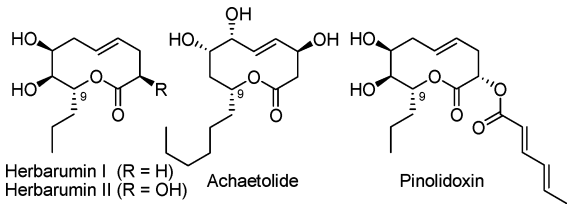
Seimatopolides A and B are recently isolated and structurally characterized metabolites of the fungus *Seimatosporium discosioides*. They were discovered through a bioactivity-guided screening and found to activate the γ-subtype of peroxisome proliferator-activated receptors (PPAR-γ) with EC_{50} values in the micromolar range. As these receptors play an important role in a manifold of metabolic processes, inter alia regulation of the glucose level, the more active seimatopolide A was proposed as a potential candidate for the development of a therapeutic agent against type-2 diabetes.[1,2] On the basis of the NMR spectroscopic analysis of the Mosher esters of seimatopolides A and B, Hiep et al. assigned the structures shown below with a (3*R*,6*R*,7*R*,9*S*)-configuration for seimatopolide A and a (3*R*,6*S*,9*S*)-configuration for seimatopolide B (Chart 1).[1]

Chart 1. Originally Assigned Structures of Seimatopolides A and B



A comparison with other 10-membered lactones reveals that this is insofar remarkable, as the majority of these natural products has the opposite configuration at C9, as illustrated for herbarumins I and II,[3,4] pinolidoxin,[4−6] and achaetolide[7,8] (Chart 2).[9,10]

Chart 2. Structures of Selected Naturally Occurring Decanolides



Intrigued by the discrepancy between the C9 configurations published for seimatopolides A and B and those reported for many other decanolides, we set out to synthesize both enantiomers of seimatopolide A from chiral pool starting materials with reliably assigned absolute configurations. We had just completed the synthesis of seimatopolide A with the absolute configuration depicted in Chart 1 and embarked on the synthesis of its enantiomer, when Reddy et al. published a synthesis of (+)-seimatopolide A, which relies on a Sharpless asymmetric dihydroxylation as the crucial enantiodetermining

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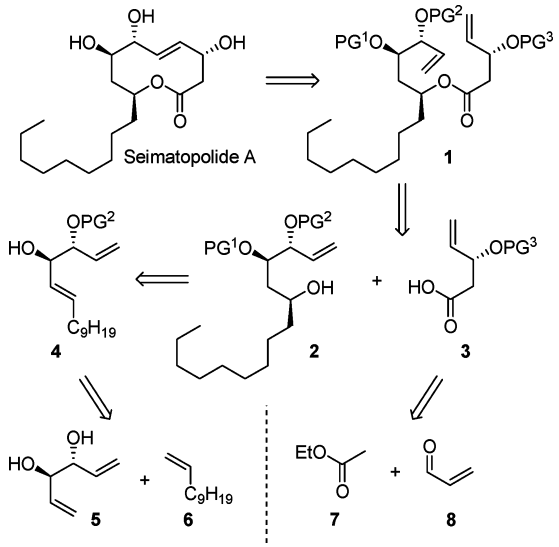
step to establish the absolute configurations at C6 and C7.[11] On the basis of their results, these authors concluded that the structure of seimatopolide A was erroneously assigned and should be corrected for the naturally occurring laevorotatory enantiomer to (3*S*,6*S*,7*S*,9*R*). Herein, we present our syntheses of (+)- and (−)-seimatopolide, starting from a C_2-symmetric building block, which is elaborated in the sense of a bidirectional synthesis.

RESULTS AND DISCUSSION

Retrosynthesis. We envisaged a ring-closing metathesis (RCM) as a macrocyclization step for the synthesis of seimatopolide A. The required RCM precursor **1** should, in turn, be accessible from secondary alcohol **2** and carboxylic acid **3**. For the synthesis of alcohol **2**, the C_2-symmetric (*R*,*R*)-hexa-1,5-diene-3,4-diol (**5**),[12−15] which is available in few steps from D-mannitol, was considered as a suitable starting material. We planned to subject **5** or possibly a monoprotected derivative to mono-cross-metathesis with 1-undecene (**6**). The resulting allylic alcohol **4** should then undergo a highly regio- and diastereoselective epoxidation under Sharpless conditions, and a subsequent regioselective epoxide opening using a hydride reagent as a nucleophile should furnish fragment **2**. For the reasons outlined above, it was important to devise routes to both enantiomers of seimatopolide, and therefore having convenient access to *ent*-**5** was also essential for the entire strategy. An ex-chiral-pool synthesis of *ent*-**5** was previously published by Michaelis and Blechert, starting from L-(+)-tartrate via reduction of the ester with Dibal-H and double Wittig olefination.[16] In order to obtain both enantiomers of the second fragment, β-hydroxy carboxylic acid **3**, a lipase-catalyzed kinetic resolution[17] of the aldol addition product[18] resulting from ethyl acetate (**7**) and acrolein (**8**), was considered as the most convenient solution (Scheme 1).

Scheme 1. Retrosynthetic Analysis of Seimatopolide A



Synthesis of (6*R*,7*R*,9*S*)-C5−C9 Fragment 12 and Its Enantiomer (*ent*-12). To ensure selective mono-cross-metathesis of diene **5** and subsequent OH-directed monoepoxidation, the introduction of a sterically demanding protecting group is required (Scheme 2). Therefore, **5** was first converted into TBS-ether **9a** and trityl ether **9b**. The subsequent cross-metathesis with 1-undecene (**6**) required some optimization, and details are provided in Table 1. In the case of TBS-protected diene **9a**, best results were obtained with 2 mol % of second generation catalyst **A**,[19] 2 equiv of 1-undecene (**6**) present from the outset, and slow addition of further 3 equiv of **6** over 30 min (entry 5). For the sterically more demanding trityl derivative **9b**, a larger excess of cross-metathesis partner was required. Interestingly, significantly improved yields were obtained by using the Ru-indenylidene catalysts **B**[20] and **C**,[21,22] while the catalyst loading could be reduced to 1 mol % at the same time (entries 8−10).

In the next step, the cross-metathesis products **4a**,**b** were subjected to Sharpless epoxidation conditions[23] using L-(+)-diethyl tartrate as chiral ligand. Epoxides **10a** and **10b** were obtained as single diastereomers in good to excellent yields without any complications. The next task was the regioselective reduction of these epoxides with a hydride source to establish the required 1,3-diol pattern (Table 2).

Precedence for this regioselectivity in the reduction of epoxy alcohols exists: Sharpless et al. found that Red-Al often gives better 1,3- to 1,2-diol selectivities than $LiAlH_4$,[24] and Page et al. described that unsatisfactory regioselectivities can be improved by addition of methanol, which presumably reduces the reactivity of the Red-Al.[25] Our first experiments gave rather disappointing results: starting from TBS-protected derivative **10a**, the reduction could be accomplished in excellent yield with 4.0 equiv of Red-Al but with an unsatisfactory 2:1 ratio of regioisomers, with the undesired 1,2-reduction product **11′** being the major isomer (entry 1). Monitoring the reaction by TLC revealed that even prior to hydrolytic workup the TBS group was removed to a significant extent. For these reasons, we chose acidic workup conditions that would ensure a quantitative deprotection and yield only the triols **11** and **11′** as products. Reducing the amount of Red-Al to 2.2 equiv and lowering the temperature to 0 °C (entry 2) as well as addition of 1 equiv of methanol (entry 3) resulted in a virtually unaltered ratio of products. The first experiments with trityl-protected **10b** (entries 4 and 5) were also unsuccessful because no conversion occurred at ambient temperature after 2 days and the starting material was recovered. However, at elevated temperatures, the reduction proceeded slowly to the desired triol **11**, which could be reliably obtained in yields higher than 50% (entry 6). In all experiments using trityl derivative **10b**, the undesired regioisomer **11′** was the minor product. Although the yield of **11** could not be improved by adding methanol, the amount of undesired triol **11′** was reduced, resulting in a slight improvement of the regioselectivity (entries 7−9). Gratifyingly, separation of **11** and **11′** was easily accomplished by chromatography. The synthesis of the C5−C9 fragment **12** was completed by protection of the C6−C7-diol moiety as a propylidene acetal.

The (6*S*,7*S*,9*R*)-C5−C9 fragment (*ent*-**12**) was synthesized from *ent*-**5**[16] via an analogous sequence of steps (Scheme 3). As the optimization experiments described above revealed that significantly better results were obtained for almost all steps with the trityl derivatives, we used only this protecting group for the sequence leading to *ent*-**12**. Obviously, D-(-)- rather than L-(+)-diethyl tartrate was required for the Sharpless epoxidation of *ent*-**4b** to obtain *ent*-**10b**. As expected, all steps proceeded with yields and selectivities comparable to those previously obtained for the synthesis of **12**.

Synthesis of (3*R*)-C1−C4 Fragment 3a and Its Enantiomer (*ent*-3a). Racemic ethyl 3-hydroxy-4-pentenoate

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Scheme 2. Synthesis of (6*R*,7*R*,9*S*) Fragment 12 from Mannitol-Derived Diene 5

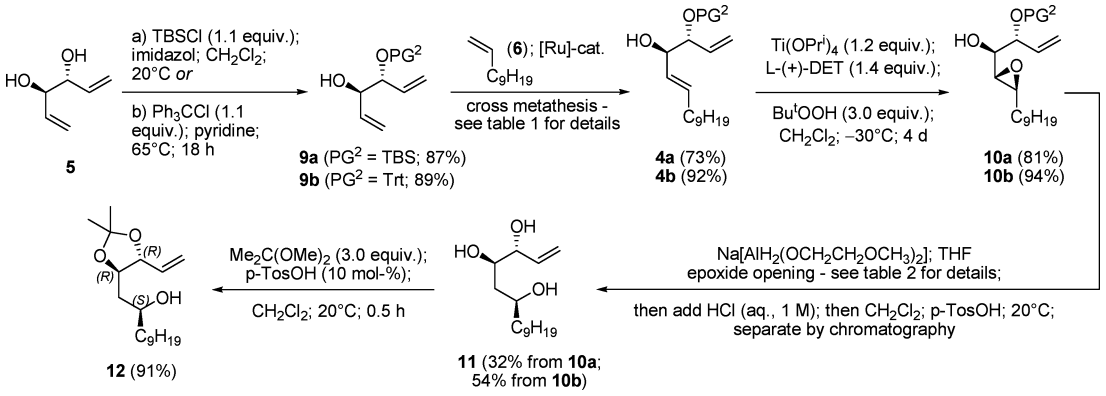
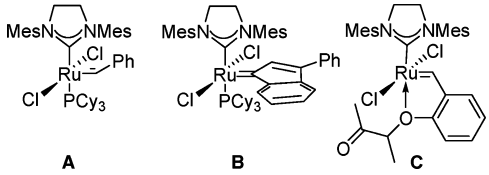


Table 1. Optimization of Cross-Metathesis Conditions



entry	9	catalyst	catalyst loading (mol %)	6 (equiv)	solvent	c (mol·L^{-1})	T (°C)	4	yield (%)
1	**9a**	**A**	2	5	toluene	0.2	80	**4a**	51
2	**9a**	**A**	2	5	CH_2Cl_2	0.5	40	**4a**	53
3	**9a**	**A**	2	5	CH_2Cl_2	0.2	40	**4a**	58
4	**9a**	**A**	2	5	CH_2Cl_2	0.5	20	**4a**	66
5[a]	**9a**	**A**	2	2 + 3	CH_2Cl_2	0.2	20	**4a**	73
6	**9b**	**A**	2	5	toluene	0.2	80	**4b**	53
7	**9b**	**A**	2	5	CH_2Cl_2	0.5	40	**4b**	58
8[b]	**9b**	**B**	2	5 + 5	CH_2Cl_2	0.2	40	**4b**	83
9	**9b**	**C**	1	5	CH_2Cl_2	0.5	20	**4b**	74
10	**9b**	**C**	1	8	CH_2Cl_2	0.5	20	**4b**	92

[a]2 equiv of **6** present from the start, additional 3 equiv added over 30 min. [b]5 equiv of **6** present from the start, additional 5 equiv added after 1 h.

(*rac*-**13**) was synthesized by aldol addition from ethyl acetate and acrolein following a literature procedure (Scheme 4).[18] For this particular derivative, an enzymatic kinetic resolution was unknown; however, the analogous *tert*-butyl ester had been resolved using Amano lipase PS.[17]

We chose isopropenyl acetate as acetylating agent and novozyme 435 as the lipase. Within 48 h, nearly 50% conversion was reached, and the acetate (*S*)-**14** and the resolved *β*-hydroxy ester (*R*)-**13** were isolated in ca. 40% yield. After protection of the hydroxy group in (*R*)-**13** as a TBS ether (*R*)-**15**, the ethyl ester was hydrolyzed in wet methanol under mildly basic conditions, furnishing **3a**. Cleavage of the acetate in (*S*)-**14** requires more carefully controlled conditions because, otherwise, simultaneous hydrolysis of the ethyl ester might occur. With (*S*)-**13** in hand, the opposite enantiomer *ent*-**3a** was synthesized analogously via silylation and saponification. Determination of the enantiomeric ratios was accomplished on the stage of *β*-hydroxy esters **13** using HPLC on a chiral stationary phase, after establishing optimum separation conditions for the racemate *rac*-**13**. For (*R*)-**13**, the enantiomeric ratio was reliably better than 97.5:2.5, whereas for (*S*)-**13** a ratio of enantiomers better than 92.5:7.5 could be obtained.

Completion of the Synthesis. The synthesis of seimatopolide A commenced with the esterification of the C5−C9 fragment **12** and C1−C4 fragment **3a** (Scheme 5). We tested different protocols for this transformation, and the conditions and results are summarized in Table 3. Using Steglich's conditions[26] (entry 1), the desired ester **16** was obtained in 66% yield. With Yamaguchi's method[27] (entry 2), a slight improvement was observed, and **16** could be isolated in 73% yield. It should be noted that Reddy et al.[11] used the same method in their seimatopolide A synthesis and isolated **16** in nearly quantitative yield. In our hands, the best results were obtained with Shiina's protocol[28] (entry 3), using 2-methyl-6-nitrobenzoic anhydride (MNBA) as coupling reagent, which led to a yield of 85% of ester **16**. Ring-closing metathesis of **16** proceeded without complications using 10 mol % of second generation catalyst **A** under high dilution conditions to the fully protected decanolide **17** in high yield and with exclusive formation of the *E*-isomer. From **17**, seimatopolide A could be synthesized either by stepwise deprotection via the intermediate **18** or by global deprotection using a dichloromethane−TFA mixture. Similar to Reddy's results,[11] synthetic seimatopolide A obtained via this route is dextrorotatory, which is in marked contrast to the sign and value of the specific rotation reported for natural seimatopolide A (see Chart1).[1]

We then synthesized (−)-seimatopolide A starting from *ent*-**12** and *ent*-**3a** via the same route (Scheme 6). Comparable yields were obtained for each synthetic step, and eventually laevorotatory (3*S*,6*S*,7*S*,9*R*)-configured seimatopolide A was isolated.

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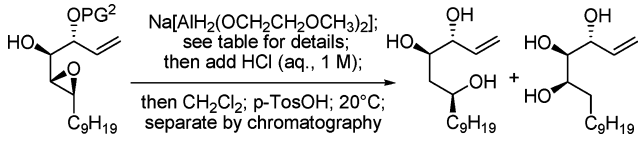
Table 2. Regioselective Reduction of Epoxy Alcohols 10a,b

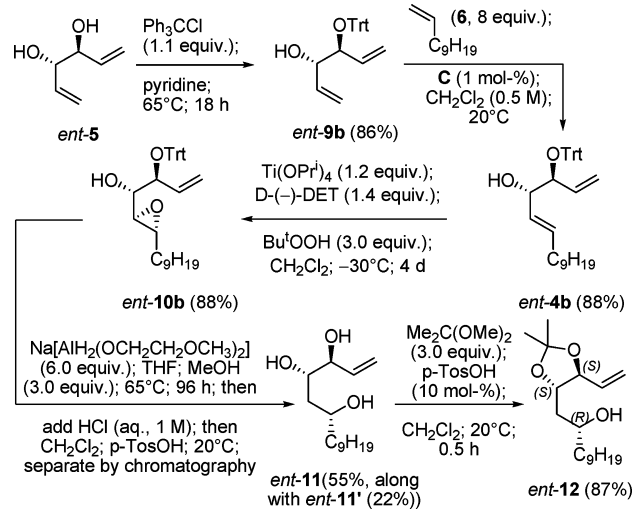


10a (PG^2 = TBS)
10b (PG^2 = trt)

11 **11'**

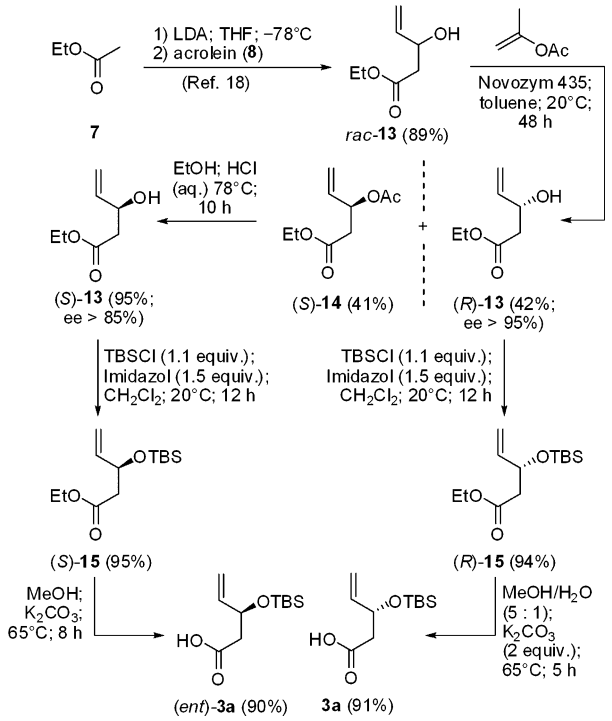
entry	10	Red-Al (equiv)	MeOH (equiv)	conditions	yield (%) of 11	yield (%) of 11′
1	**10a**	4.0	none	THF, 0.5 h, 68 °C	32	67
2	**10a**	2.2	none	THF, 0.5 h, 0 °C	29	64
3	**10a**	3.1	1.0	THF, 0.5 h, 0 °C	30	65
4	**10b**	4.0	none	THF, 48 h, 20 °C		
5	**10b**	2.5	1.0	THF, 48 h, 20 °C		
6	**10b**	4.0	none	THF, 96 h, 50 °C	54	37
7	**10b**	5.5	2.0	THF, 96 h, 50 °C	49	29
8	**10b**	4.5	2.0	THF, 48 h, 65 °C	53	23
9	**10b**	6.0	3.0	THF, 96 h, 65 °C	54	27

Scheme 3. Synthesis of (6*S*,7*S*,9*R*) Fragment *ent*-12 from Tartrate-Derived Diene *ent*-5

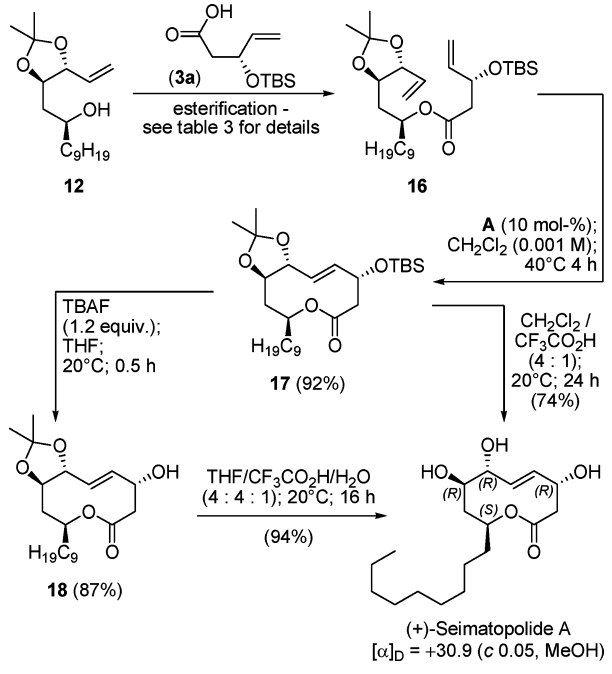


Comparison of Specific Rotations Reported for Seimatopolide and Derivatives. Hiep et al.[1] reported a value for the specific rotation of naturally occurring seimatopolide A with an assigned (3*R*,6*R*,7*R*,9*S*)-configuration that differs significantly from the values obtained by Reddy et al.[11] and by us for the synthetic compound with this configuration. During the preparation of this paper, two further total syntheses of (3*R*,6*R*,7*R*,9*S*)-seimatopolide A were reported.[29,30] In both cases, the authors found a negative specific rotation, as reported for the natural product, which leads them to the conclusion that their total syntheses corroborate the originally assigned absolute configuration.[31] Specific rotations and assigned configurations of seimatopolide A isolated from natural sources or obtained via total synthesis are summarized in Table 4.

Scheme 4. Synthesis of 3a and Its Enantiomer (*ent*-3a)



Scheme 5. Synthesis of (+)-(3*R*,6*R*,7*R*,9*S*)-Seimatopolide A



This confusing situation prompted us to investigate the synthesis and characterization of derivatives of both enantiomers of seimatopolide A. Unfortunately, the complete esterification of seimatopolide A with Mosher's reagent[32] was unsuccessful in our hands and resulted in complex mixtures of partially derivatized products, which could not be reliably compared with the Mosher esters of seimatopolide A derived from the natural product by Hiep et al.[1] We then sought alternative methods to distinguish between the enantiomers of seimatopolide A derivatives and provide enantiomer-specific

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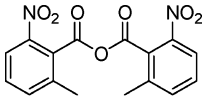
Table 3. Esterification Methods Evaluated for the Synthesis of 16



MNBA

entry	3a (equiv)	method and conditions	yield (%) of 16
1	1.1	Steglich's method: DCC (1.1 equiv), DMAP (20 mol %), CH_2Cl_2, 20 °C, 16 h	66
2	1.2	Yamaguchi's method: 2,4,6-trichlorobenzoyl chloride (1.2 equiv), $NEtPr^i_2$ (2.2 equiv), DMAP (25 mol %), CH_2Cl_2, 20 °C, 16 h	73
3	1.2	Shiina's method: MNBA (1.2 equiv), $NEtPr^i_2$ (2.2 equiv), DMAP (10 mol %), CH_2Cl_2, 20 °C, 16 h	85

Scheme 6. Synthesis of (−)-(3*S*,6*S*,7*S*,9*R*)-Seimatopolide A

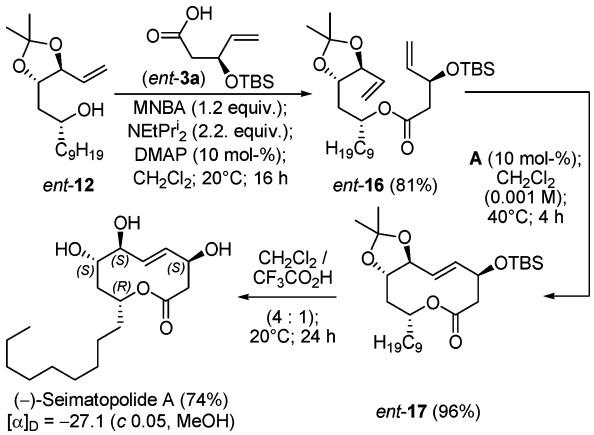
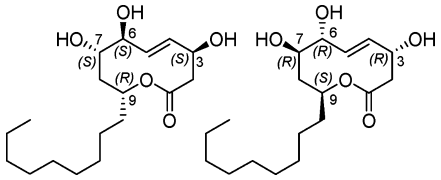


Table 4. Reported Specific Rotations and Assigned Absolute Configurations for Seimatopolides

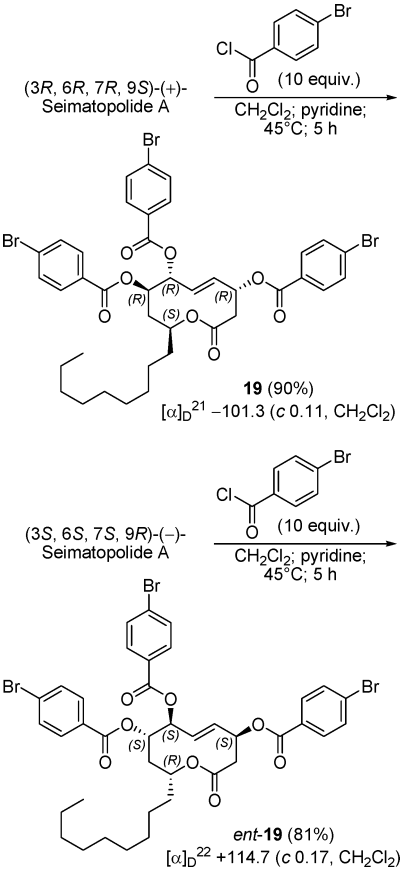


entry	assigned configuration	reported specific rotation	ref
1[a]	(3*R*,6*R*,7*R*,9*S*)	$[\alpha]_D^{26}$ −188.3 (*c* 0.05, MeOH)	1
2[a]	(3*S*,6*S*,7*S*,9*R*)	$[\alpha]_D^{29}$ −20.8 (*c* 0.04, MeOH)	2,31
3[b]	(3*R*,6*R*,7*R*,9*S*)	$[\alpha]_D^{25}$ +30.0 (*c* 0.05, MeOH)	11
4[b]	(3*R*,6*R*,7*R*,9*S*)	$[\alpha]_D^{25}$ −143.5 (*c* 0.05, MeOH)	29
5[b]	(3*R*,6*R*,7*R*,9*S*)	$[\alpha]_D^{20}$ −59.3 (*c* 2.0, MeOH)	30
6[c]	(3*R*,6*R*,7*R*,9*S*)	$[\alpha]_D^{22}$ +30.9 (*c* 0.05, MeOH)	this work
7[c]	(3*S*,6*S*,7*S*,9*R*)	$[\alpha]_D^{22}$ −27.1 (*c* 0.05, MeOH)	this work

[a]Isolated from natural source and absolute configuration based on analysis of the corresponding tris-Mosher ester. [b]Synthetic material, with configurations at C6 and C7 established via stereoselective synthesis. [c]Synthetic material, with configurations at C6 and C7 derived from chiral pool starting materials.

characterization data which might in the future facilitate the comparison with seimatopolide A derived from the natural source. To this end, the *para*-bromobenzoates **19** and *ent*-**19**, respectively, of synthetic (3*R*,6*R*,7*R*,9*S*)-(+)-seimatopolide A and (3*S*,6*S*,7*S*,9*R*)-(−)-seimatopolide A were synthesized to check whether or not crystalline derivatives could be obtained and characterized by single-crystal X-ray structure analysis using anomalous dispersion. Although complete esterification of all hydroxy groups is possible and the resulting *para*-bromobenzoates are solids, we were unable to obtain crystals suitable for crystallographic analysis (Scheme 7).

Scheme 7. Synthesis of Tris-*para*-bromobenzoates 19 and *ent*-19 of Seimatopolides A



Nevertheless, we thought that these derivatives might still be useful because the *para*-bromobenzoate moiety should be a strong chromophore and allow characterization of the enantiomers by chiroptical methods. For this purpose, circular dichroism was recorded for both **19** and *ent*-**19** under otherwise identical conditions. As expected for enantiomers, the CD spectra are nearly perfect mirror images. While **19**, derived from (+)-seimatopolide, shows a strongly negative Cotton effect at 254 nm, its enantiomer *ent*-**19** shows a strongly positive Cotton effect at this wavelength. We predict that a tris-*para*-bromobenzoate derivative of naturally occurring seimatopolide should also have a strongly positive Cotton effect at 254 nm.

■ CONCLUSIONS

In summary, we describe routes to both enantiomers of the recently discovered naturally occurring decanolide seimatopolide A, starting from C_2-symmetric (*R*,*R*)- and (*S*,*S*)-hexa-1,5-diene-3,4-diol. As both starting materials are derived from the well-known chiral pool compounds D-mannitol or L-tartrate, a reliable assignment of the absolute configuration is possible. A comparison with the specific rotation reported for the natural

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product leads us to the conclusion that naturally occurring (−)-seimatopolide has most likely a (3*S*,6*S*,7*S*,9*R*)-configuration, whereas its optical antipode (+)-seimatopolide is (3*R*,6*R*,7*R*,9*S*)-configured. Conversion of both enantiomers into their *para*-bromobenzoates leads to derivatives which could be characterized by circular dichroism.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR spectra were obtained at 300, 500, or 600 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 given in hertz. ^{13}C NMR spectra were recorded at 75, 125, or 150 MHz in $CDCl_3$ or pyridine-d_5 with $CDCl_3$ (δ = 77.0 ppm) and pyridine (δ = 135.9 ppm) as internal standards. The number of coupled protons was analyzed by DEPT or APT experiments and is denoted by a number in parentheses following the chemical shift value. IR spectra were recorded as neat films on NaCl or KBr plates or as KBr discs. Wavenumbers (ν) are given in cm^{-1}. The peak intensities are defined as strong (s), medium (m), or weak (w). Low- and high-resolution mass spectra were obtained by ESI/TOF.

(3*R*,4*R*)-4-(Trityloxy)-hexa-1,5-dien-3-ol (9b). To a solution of diol **5** (800 mg, 7.1 mmol) in pyridine (5 mL) was added chlorotriphenyl methane (2.30 g, 8.2 mmol), and the solution was stirred for 18 h at 65 °C. After cooling to room temperature, water (50 mL) was added and the aqueous layer was extracted three times with MTBE. The organic layers were washed with aqueous $NaHCO_3$ solution, dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica (eluent hexanes/ethyl acetate 12:1) to give **9b** (2.10 g, 89%) as a colorless oil: $[\alpha]_D^{24}$ = 38.4 (*c* 0.35, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.59 (m, 6H), 7.43−7.28 (m, 9H), 6.16 (ddd, *J* = 17.2, 10.7, 4.7, 1H), 5.77 (ddd, *J* = 18.2, 10.5, 8.0, 1H), 5.32 (d, *J* = 17.4, 1H), 5.29 (d, *J* = 10.5, 1H), 5.02 (d, *J* = 10.5, 1H), 4.90 (d, *J* = 17.4, 1H), 4.08 (dd, *J* = 7.6, 5.7, 1H), 3.87 (ddm, *J* = 5.0, 5.0, 1H), 2.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7 (0), 137.0 (1), 135.6 (1), 129.0 (1), 127.6 (1), 127.1 (1), 117.2 (2), 115.7 (2), 87.6 (0), 78.4 (1), 73.0 (1); IR (neat) ν 3445 (m), 3026 (m), 1959 (w), 1447 (m), 1033 (s), 699 (s); MS (ESI) *m*/*z* 105 (13%), 165 (38%), 243 (100%), 357 ([M + H]$^+$, 2%); HRMS (ESI) calcd for $C_{25}H_{25}O_2$ ([M + H]$^+$) 357.1855, found 357.1857. Anal. Calcd for $C_{25}H_{24}O_2$: C, 84.2%; H, 6.8%. Found: C, 84.3%; H, 7.2%.

(3*S*,4*S*)-4-(Trityloxy)hexa-1,5-dien-3-ol (*ent*-9b). Following the procedure for **9b**, *ent*-**9b** was obtained from diol *ent*-**5** (300 mg, 2.6 mmol) as a colorless oil (800 mg, 86%): $[\alpha]_D^{27}$ = −42.7 (*c* 0.30, CH_2Cl_2). All other analytical data are identical to those reported for **9b**.

(3*R*,4*R*,*E*)-3-(*tert*-Butyldimethylsilyloxy)pentadeca-1,5-diene-4-ol (4a). To a solution of **9a**[15] (550 mg, 2.2 mmol) in CH_2Cl_2 (4.4 mL) were added 1-undecene (**6**, 0.66 g, 4.4 mmol) and second generation catalyst **A** (37 mg, 2 mol %) at room temperature. After stirring the solution for 5 min, a solution of 1-undecene (**6**, 1.00 g, 6.6 mmol) in CH_2Cl_2 (4.4 mL) was added dropwise over a period of 30 min. After stirring the reaction mixture for an additional 15 min, the reaction was quenched with ethylvinyl ether (0.2 mL) and the solvent was evaporated. The residue was purified by column chromatography on silica (eluent hexanes/MTBE 20:1) to give **4a** (563 mg, 73%) as a colorless oil: $[\alpha]_D^{24}$ = −4.8 (*c* 0.96, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (ddd, *J* = 17.1, 10.5, 6.5, 1H), 5.70 (ddt, *J* = 15.4, 6.7, 1.0, 1H), 5.41 (ddd, *J* = 15.4, 6.5, 1.4, 1H), 5.22 (dd, *J* = 17.2, 1.2, 1H), 5.16 (dd, *J* = 10.4, 1.1, 1H), 3.94 (ddd, *J* = 6.3, 6.2, 1.1, 1H), 3.86 (dd, *J* = 6.3, 6.2, 1H), 2.55 (br s, 1H), 2.04 (dt, *J* = 6.8, 5.9, 2H), 1.45−1.20 (m, 14H), 0.94−0.86 (m, 12H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0 (1), 133.9 (1), 128.5 (1), 116.6 (2), 77.8 (1), 75.7 (1), 32.4 (2), 31.9 (2), 29.6 (2), 29.5 (2), 29.3 (2), 29.2 (2), 29.1 (2), 25.8 (3), 22.7 (2), 18.2 (0), 14.1 (3), −4.1 (3), −4.9 (3); IR (neat) ν 3567 (m), 3466 (m), 2925 (s), 2856 (s), 1645 (w), 1472 (m), 1361 (m), 1253 (s); MS (ESI) *m*/*z* 337 (100), 355 (2, [M + H]$^+$), 377 (2, [M + Na]$^+$); HRMS (ESI) calcd for $C_{21}H_{43}O_2Si^+$ ([M + H]$^+$) 355.3032, found 355.3009.

(3*R*,4*R*,*E*)-3-(Trityloxy)pentadeca-1,5-dien-4-ol (4b). To a solution of **9b** (500 mg, 1.37 mmol) in CH_2Cl_2 (2.8 mL) were added 1-undecene (**6**, 1.67 g, 10.9 mmol) and Ru catalyst **C** (9.0 mg, 1 mol %) at room temperature. The solution was stirred for 6 h at room temperature, and the solvent was evaporated. The residue was purified by column chromatography on silica (eluent hexanes/MTBE 20:1) to give **4b** (610 mg, 92%) as a colorless oil: $[\alpha]_D^{22}$ = +15.7 (*c* 0.57, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.0, 6H), 7.33−7.23 (m, 9H), 5.64 (ddd, *J* = 17.5, 10.5, 8.0, 1H), 5.58 (m, 1H), 5.47 (dd, *J* = 15.6, 5.8, 1H), 4.87 (dd, *J* = 10.5, 0.7, 1H), 4.72 (d, *J* = 17.4, 1H), 3.87 (dd, *J* = 7.7, 5.8, 1H), 3.77 (dd, *J* = 5.6, 5.4, 1H), 2.05 (dt, *J* = 6.7, 6.7, 2H), 1.87 (d, *J* = 6.1, 1H), 1.45−1.20 (m, 14H), 0.90 (t, *J* = 6.3, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8 (0), 136.1 (1), 133.4 (1), 129.1 (1), 128.5 (1), 127.6 (1), 127.1 (1), 117.0 (2), 87.5 (0), 78.8 (1), 73.5 (1), 32.4 (2), 31.9 (2), 29.6 (2), 29.5 (2), 29.3 (2), 29.2 (2), 29.1 (2), 22.6 (2), 14.1 (3); IR (neat) ν 3455 (w), 3058 (m), 2925 (s), 2854 (s), 1597 (w), 1491 (m), 1449 (s); MS (EI) *m*/*z* 165 (27), 183 (10), 243 (100); HRMS (EI) calcd for $C_{34}H_{42}O_2^+$ ([M]$^+$) 482.3185, found 482.3180. Anal. Calcd for $C_{34}H_{42}O_2$: C, 84.6%; H, 8.8%. Found: C, 84.4%; H, 8.8%.

(3*S*,4*S*,*E*)-3-(Trityloxy)pentadeca-1,5-dien-4-ol (*ent*-4b). Following the procedure for **4b**, *ent*-**4b** was obtained from *ent*-**9b**[16] (750 mg, 2.1 mmol) as a colorless oil (865 mg, 88%): $[\alpha]_D^{24}$ = −12.7 (*c* 0.28, CH_2Cl_2). All other analytical data are identical to those reported for **4b**.

(1*R*,2*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-((2*S*,3*S*)-3-nonyloxiran-2-yl)-but-3-en-1-ol (10a). To a solution of Ti(OPr^i)$_4$ (1.49 mL, 5.0 mmol) in CH_2Cl_2 (42 mL) was added L-(+)-diethyl tartrate (1.06 mL, 5.9 mmol) at −30 °C. The mixture was stirred at this temperature for 15 min, and **4a** (1.50 g, 4.2 mmol) was added. Stirring at −30 °C was continued for another 15 min, and *tert*-butyl hydroperoxide (5.5 M solution in decane, 2.30 mL, 12.6 mmol) was added and the reaction mixture was then stored in a freezer at −30 °C for 4 days. After this time, $FeSO_4$ (3.20 g) was dissolved in an aqueous solution of tartaric acid (15 wt %, 50 mL) and added to the reaction mixture at −30 °C. The mixture was allowed to warm to room temperature and filtered through a pad of Celite, extracted three times with MTBE, and washed with brine. The organic layers were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica (eluent hexanes/MTBE 10:1) to give **10a** (1.26 g, 81%) as a colorless oil and as a single diastereomer, as determined by ^{1}H NMR spectroscopy of the crude reaction mixture: $[\alpha]_D^{24}$ = −2.0 (*c* 0.84, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (ddd, *J* = 17.1, 10.5, 6.2, 1H), 5.29 (dd, *J* = 17.2, 1.4, 1H), 5.19 (dd, *J* = 10.4, 1.2, 1H), 4.27 (ddd, *J* = 6.2, 4.1, 1.3, 1H), 3.32 (ddd, *J* = 5.7, 5.7, 4.2, 1H), 2.93 (dt, *J* = 6.3, 2.2, 1H), 2.77 (dd, *J* = 5.8, 2.2, 1H), 2.40 (d, *J* = 5.7, 1H), 1.70−1.20 (m, 16H), 0.92 (s, 9H), 0.87 (t, *J* = 6.5, 3H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5 (1), 116.5(2), 74.8 (1), 74.2 (1), 57.9 (1), 57.3 (1), 31.9 (2), 31.7 (2), 29.5 (2), 29.5 (2), 29.4 (2), 29.3 (2), 25.9 (2), 25.8 (3), 22.6 (2), 18.2 (0), 14.1 (3), −4.3 (3), −5.0 (3); IR (neat) ν 3448 (m), 2928 (s), 2856 (s), 1644 (w), 1472 (m), 1361 (m), 1253 (s); MS (ESI) *m*/*z* 353 (100), 371 (57, [M + H]$^+$); HRMS (ESI) calcd for $C_{21}H_{43}O_3Si^+$ ([M + H]$^+$) 371.2981, found 371.2950. Anal. Calcd for $C_{21}H_{42}O_3Si$: C, 68.1%; H, 11.4%. Found: C, 67.8%; H, 11.3%.

(1*S*,2*R*)-1-((2*S*,3*S*)-3-Nonyloxiran-2-yl)-2-(trityloxy)-but-3-en-1-ol (10b). To a solution of Ti(OPr^i)$_4$ (1.67 mL, 5.6 mmol) in CH_2Cl_2 (60 mL) was added L-(+)-diethyl tartrate (1.12 mL, 6.7 mmol) at −30 °C. The mixture was stirred at this temperature for 15 min, and **4b** (2.25 g, 4.7 mmol) was added. Stirring at −30 °C was continued for another 15 min, and *tert*-butyl hydroperoxide (5.5 M solution in decane, 2.70 mL, 14.1 mmol) was added and the reaction mixture was then stored in a freezer at −30 °C for 4 days. After this time, $FeSO_4$ (3.60 g) was dissolved in an aqueous solution of tartaric acid (15 wt %, 100 mL) and added to the reaction mixture at −30 °C. The mixture was allowed to warm to room temperature and filtered through a pad of Celite, extracted three times with MTBE, and washed with brine. The organic layers were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica (eluent hexanes/MTBE 10:1) to give **10b** (2.20 g, 94%) as a

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colorless oil and as a single diastereomer, as determined by ^{1}H NMR spectroscopy of the crude reaction mixture: $[\alpha]_D^{22}$ = +24.0 (*c* 0.31, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 6.8, 6H), 7.33−7.23 (m, 9H), 5.77 (ddd, *J* = 16.9, 10.2, 7.3, 1H), 4.97 (d, *J* = 10.2, 1H), 4.95 (d, *J* = 16.9, 1H), 4.12 (dd, *J* = 7.1, 5.2, 1H), 3.33 (ddd, *J* = 7.1, 4.2, 2.6, 1H), 2.95−2.90 (m, 2H), 1.86 (d, *J* = 4.1, 1H), 1.60−1.20 (m, 16H), 0.90 (t, *J* = 6.4, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5 (0), 135.7 (1), 129.0 (1), 127.7 (1), 127.2 (1), 116.7 (2), 87.8 (0), 76.7 (1), 70.4 (1), 58.0 (1), 55.4 (1), 31.9 (2), 31.6 (2), 29.5 (2), 29.5 (2), 29.5 (2), 29.3 (2), 25.9 (2), 22.6 (2), 14.1 (3); IR (neat) ν 3446 (m), 3058 (m), 3023 (m), 2926 (s), 2854 (s), 1597 (w), 1491 (m), 1449 (s), 1220 (m); MS (EI) *m*/*z* 165 (20), 243 (100); HRMS (EI) calcd for $C_{34}H_{42}O_3^+$ ($[M]^+$) 498.3134, found 498.3128. Anal. Calcd for $C_{34}H_{42}O_3$: C, 81.9%; H, 8.5%. Found: C, 81.6%; H, 8.9%.

(1*R*,2*S*)-1-((2*R*,3*R*)-3-Nonyloxiran-2-yl)-2-(trityloxy)-but-3-en-1-ol (*ent*-10b). Following the procedure for **10b** and replacing L-(+)-diethyl tartrate by D-(−)-diethyl tartrate, *ent*-**10b** was obtained from *ent*-**4b** (600 mg, 1.2 mmol) as a colorless oil (543 mg, 88%): $[\alpha]_D^{22}$ = −23.9 (*c* 0.44, CH_2Cl_2). All other analytical data are identical to those reported for **10b**.

(3*R*,4*R*,6*S*)-Pentadec-1-ene-3,4,6-triol (11) and (3*R*,4*R*,5*R*)-Pentadec-1-ene-3,4,5-triol (11′). To a solution of **10b** (500 mg, 1.0 mmol) in THF (10 mL) was added methanol (0.122 mL, 3.0 mmol) at 0 °C. To this mixture was added Red-Al (3.3 M solution in toluene, 1.80 mL, 6.0 mmol), and the reaction mixture was stirred for 4 days at 65 °C. After cooling to ambient temperature, 1 M HCl (aq., 10 mL) was added and the aqueous layer was extracted three times with MTBE. The organic layers were dried with $MgSO_4$, filtered, and evaporated. The crude residue was diluted in DCM (20 mL), *p*-toluenesulfonic acid (17.2 mg, 10 mol %) was added, and the reaction mixture was stirred for 1 h at room temperature. The reaction was quenched by addition of aqueous $NaHCO_3$ solution (20 mL), and the aqueous layer was extracted three times with MTBE (20 mL). The organic layers were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica (eluent hexanes/MTBE 1:1) to give **11** (139 mg, 54%) and **11′** (70 mg, 27%) as white solids. *Analytical data for (3R,4R,6S)-pentadec-1-ene-3,4,6-triol (**11**)*: mp 76 °C; $[\alpha]_D^{23}$ = +13.4 (*c* 0.37, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 17.1, 10.5, 6.6, 1H), 5.32 (d, *J* = 17.2, 1H), 5.23 (d, *J* = 10.5, 1H), 3.98 (dd, *J* = 6.6, 6.6, 1H), 3.90 (m, 1H), 3.78 (m, 1H), 3.20 (br s, 3H), 1.70−1.20 (m, 18H), 0.87 (t, *J* = 6.4, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2 (1), 117.6 (2), 76.3 (1), 71.8 (1), 69.1 (1), 38.6 (2), 37.6 (2), 31.9 (2), 29.6 (2), 29.6 (2), 29.5 (2), 29.3 (2), 25.7 (2), 22.6 (2), 14.1 (3); IR (neat) ν 3321 (m), 2954 (m), 2919 (s), 2850 (m), 1468 (w), 1064 (m); MS (ESI) *m*/*z* 281 ([M + Na]$^+$, 100); HRMS (ESI) calcd for $C_{15}H_{30}O_3Na^+$ ($[M]^+$) 281.2093, found 281.2069. *Analytical data for (3R,4R,5R)-pentadec-1-ene-3,4,5-triol (**11′**)*: mp 89 °C; $[\alpha]_D^{23}$ = +17.1 (*c* 0.44, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (ddd, *J* = 17.2, 10.6, 5.6, 1H), 5.37 (dd, *J* = 17.3, 1.4, 1H), 5.25 (dd, *J* = 10.6, 1.3, 1H), 4.40 (m, 1H), 3.76 (dq, *J* = 4.9, 4.6, 1H), 3.42 (dd, *J* = 3.5, 3.2, 1H), 3.29 (br s, 1H), 2.97 (br s, 2H), 1.57−1.20 (m, 18H), 0.88 (t, *J* = 6.4, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5 (1), 116.8 (2), 75.1 (1), 73.9 (1), 72.3 (1), 32.9 (2), 31.9 (2), 29.6 (2), 29.6 (2), 29.6 (2), 29.3 (2), 25.9 (2), 22.7 (2), 14.1 (3); IR (neat) ν 3330 (m), 2919 (s), 2851 (m), 1463 (w), 1069 (m); MS (ESI) *m*/*z* 281 ([M + Na]$^+$, 100); HRMS (ESI) calcd for $C_{15}H_{30}O_3Na^+$ ($[M]^+$) 281.2093, found 281.2108.

(3*S*,4*S*,6*R*)-Pentadec-1-ene-3,4,6-triol (*ent*-11) and (3*S*,4*S*,5*S*)-pentadec-1-ene-3,4,5-triol (*ent*-11′). Following the procedure for **11**, *ent*-**11** was obtained from *ent*-**10b** (500 mg, 1.0 mmol) as a colorless solid (140 mg, 55%), along with the regioisomer *ent*-**11′** (58 mg, 22%). *(3S,4S,6R)-Pentadec-1-ene-3,4,6-triol (ent-**11**)*: $[\alpha]_D^{22}$ = −12.2 (*c* 0.39, CH_2Cl_2). *(3S,4S,5S)-Pentadec-1-ene-3,4,5-triol (ent-**11′**)*: $[\alpha]_D^{22}$ = −7.5 (*c* 0.41, CH_2Cl_2). All other analytical data are identical to those reported for **11** and **11′**, respectively.

(*S*)-1-((4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-undecan-2-ol (12).[11] To a solution of **11** (460 mg, 1.8 mmol) in CH_2Cl_2 (50 mL) were added 2,2-dimethoxy propane (0.65 mL, 5.34 mmol) and *p*-toluenesulfonic acid (31 mg, 10 mol %) at room temperature. The solution was stirred for 30 min at room temperature. The reaction was quenched by addition of aqueous $NaHCO_3$ solution (20 mL), and the aqueous layer was extracted three times with MTBE (20 mL). The organic layers were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica (eluent hexanes/MTBE 3:1) to give **12** (481 mg, 91%) as a colorless oil: $[\alpha]_D^{27}$ = +6.2 (*c* 0.40, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 17.3, 10.2, 7.2, 1H), 5.35 (dd, *J* = 17.2, 0.9, 1H), 5.25 (dd, *J* = 10.2, 0.7, 1H), 3.04 (dd, *J* = 8.5, 7.3, 1H), 3.96−3.80 (m, 2H), 2.35 (br s, 3H), 1.67 (m, 2H), 1.52−1.20 (m, 22H), 0.87 (t, *J* = 6.5, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.0 (1), 118.9 (2), 108.9 (0), 82.3 (1), 77.9 (1), 68.9 (1), 37.8 (2), 37.6 (2), 31.9 (2), 29.6 (2), 29.6 (2), 29.5 (2), 29.3 (2), 27.3 (3), 26.9 (3), 25.6 (2), 22.6 (2), 14.0 (3); IR (neat) ν 3441 (w), 2924 (s), 2854 (s), 1461 (m), 1374 (s), 1223 (s); MS (ESI) *m*/*z* 223 (100), 241 (40), 299 ([M + H]$^+$, 18); HRMS (ESI) calcd for $C_{18}H_{35}O_3^+$ ($[M + H]^+$) 299.2586, found 299.2577. Anal. Calcd for $C_{18}H_{34}O_3$: C, 72.4%; H, 11.5%. Found: C, 72.2%; H, 11.9%.

(*R*)-1-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-undecan-2-ol (*ent*-12). Following the procedure for **12**, *ent*-**12** was obtained from *ent*-**11** (150 mg, 0.58 mmol) as a colorless oil (151 mg, 87%): $[\alpha]_D^{23}$ = −5.8 (*c* 0.41, CH_2Cl_2). All other analytical data are identical to those reported for **12**.

Ethyl 3-Hydroxypent-4-enoate (*rac*-13).[18] To a solution of diisopropylamine (7.7 mL, 55 mmol) in THF (200 mL) was added *n*-butyllithium (2.5 M in hexane, 22 mL, 55 mmol) at −78 °C. The solution was stirred for 15 min, ethylacetate (4.9 mL, 50 mmol) was added, and the reaction mixture was stirred for 45 min at −78 °C. To the solution was added acrolein (3.4 mL, 50 mmol), and the mixture was stirred for another 15 min at −78 °C. The reaction was quenched by addition of aqueous NH_4Cl solution (50 mL), and the aqueous layer was extracted three times with MTBE. The organic layers were washed with brine, dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica (eluent hexanes/MTBE 8:1) to give *rac*-**13** (6.4 g, 89%) as a colorless oil. All analytical data are identical to those reported below for (*R*)-**13**.

(*R*)-Ethyl 3-Hydroxypent-4-enoate ((*R*)-13) and (*S*)-Ethyl 3-Acetoxy-pent-4-enoate ((*S*)-14). To a solution of *rac*-**13** (1.44 g, 10.0 mmol) in toluene (50 mL) were added novozyme 435 (100 mg) and isopropenyl acetate (1.1 mL, 10.0 mmol), and the reaction mixture was stirred for 48 h at room temperature. After this time, the mixture was filtered through a pad of Celite, washed three times with MTBE, and the solvent was evaporated. The residue was purified by column chromatography on silica (eluent hexanes/hexane 8:1) to give (*R*)-**13** (608 mg, 42%, >95% ee (HPLC)) and acetate (*S*)-**14** (771 mg, 41%) as colorless oils. *(R)-Ethyl 3-hydroxypent-4-enoate ((R)-**13**)*: $[\alpha]_D^{23}$ = +4.6 (*c* 0.31, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (ddd, *J* = 17.1, 10.4, 5.5, 1H), 5.29 (dd, *J* = 17.2, 1.3, 1H), 5.12 (dd, *J* = 10.5, 1.2, 1H), 4.51 (ddm, *J* = 6.2, 5.6, 1H), 4.14 (q, *J* = 7.1, 2H), 3.09 (br s, 1H), 2.56 (dd, *J* = 16.1, 2.5, 1H), 2.47 (dd, *J* = 16.2, 6.9, 1H), 1.25 (t, *J* = 7.1, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (0), 138.9 (1), 115.2 (2), 68.9 (1), 60.7 (2), 41.2 (2), 14.1 (1); IR (neat) ν 3452 (m), 2984 (m), 1721 (s), 1371 (m), 1173 (s); MS (ESI) *m*/*z* 122 (100%), 127 (28%), 167 ([M + Na]$^+$, 32%); HRMS (ESI) calcd for $C_7H_{12}O_3Na$ ($[M + Na]^+$) 167.0694, found 167.0696. Anal. Calcd for $C_7H_{12}O_3$: C, 58.3%; H, 8.4%. Found: C, 57.9%; H, 8.3%. *(S)-Ethyl 3-acetoxy-pent-4-enoate ((S)-**14**)*: $[\alpha]_D^{23}$ = −6.9 (*c* 0.86, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (ddd, *J* = 17.0, 10.4, 6.3, 1H), 5.61 (dt, *J* = 7.0, 6.3, 1H), 5.28 (d, *J* = 17.2, 1H), 5.18 (d, *J* = 10.5, 1H), 4.13 (q, *J* = 7.1, 2H), 2.67 (dd, *J* = 15.6, 7.8, 1H), 2.56 (dd, *J* = 15.6, 5.8, 1H), 2.03 (s, 3H), 1.22 (t, *J* = 7.1, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6 (0), 169.6 (0), 135.1 (1), 117.3 (2), 70.7 (1), 60.6 (2), 39.4 (2), 20.9 (3), 14.1 (1); IR (neat) ν 3087 (m), 2986 (m), 2935 (m), 1739 (s), 1373 (m), 1232 (s); MS (ESI) *m*/*z* 127 (100%), 187 ([M + H]$^+$, 70%); HRMS (ESI) calcd for $C_9H_{15}O_4$ ($[M + H]^+$) 187.0970, found 187.0959.

(*S*)-Ethyl 3-Hydroxypent-4-enoate ((*S*)-13). To a solution of acetate (*S*)-**14** (1.0 g, 5.4 mmol) in ethanol (20 mL) was added concentrated HCl (aq.) (0.1 mL), and the mixture was heated to reflux for 10 h. After this time, saturated $NaHCO_3$ solution (50 mL) was added and the aqueous layer was extracted three times with MTBE. The organic layers were dried with $MgSO_4$, filtered, and evaporated.

The residue was purified by column chromatography on silica (eluent hexanes/hexane 3:1) to give (*S*)-**13** (740 mg, 95%, >85% ee (HPLC)) as colorless oil: $[\alpha]_D^{23} = -4.7$ (*c* 1.09, CH_2Cl_2). All other analytical data are identical to those reported for (*R*)-**13**.

(*R*)-Ethyl 3-(*tert*-Butyldimethylsilyloxy)-pent-4-enoate ((*R*)-15). To a solution of (*R*)-**13** (620 mg, 4.3 mmol) in CH_2Cl_2 (40 mL) were added imidazole (439 mg, 6.5 mmol) and *tert*-butyldimethylsilyl chloride (713 mg, 4.7 mmol) at 0 °C. The solution was stirred for 12 h at room temperature. After this time, water (50 mL) was added and the aqueous layer was extracted three times with MTBE. The organic layers were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica (eluent hexanes/MTBE 10:1) to give (*R*)-**15** (1.04 g, 94%) as a colorless oil: $[\alpha]_D^{22} = +5.7$ (*c* 0.37, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 16.9, 10.3, 6.1, 1H), 5.22 (d, *J* = 17.2, 1H), 5.06 (d, *J* = 10.3, 1H), 4.57 (dt, *J* = 6.7, 6.3, 1H), 4.14 (m, 2H), 2.51 (dd, *J* = 14.5, 7.6, 1H), 2.43 (dd, *J* = 14.5, 5.3, 1H), 1.25 (t, *J* = 7.1, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (0), 140.4 (1), 114.5 (2), 70.9 (1), 60.3 (2), 43.8 (2), 25.7 (3), 18.1 (0), 14.2 (1), −4.4 (3), −5.1 (3); IR (neat) ν 2957 (m), 2930 (m), 2858 (m), 1737 (s), 1252 (m), 1178 (m); MS (ESI) *m*/*z* 196 (100%), 259 ($[M + H]^+$, 5%); HRMS (ESI) calcd for $C_{13}H_{27}O_3Si$ ($[M + H]^+$) 259.1729, found 259.1752.

(*S*)-Ethyl 3-(*tert*-Butyldimethylsilyloxy)-pent-4-enoate ((*S*)-15). Following the procedure for (*R*)-**15**, (*S*)-**15** was obtained from (*S*)-**13** (390 mg, 2.7 mmol) as a colorless oil (663 mg, 95%): $[\alpha]_D^{22} = -5.1$ (c 0.54, CH_2Cl_2). All other analytical data are identical to those reported for (*R*)-**15**.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)-pent-4-enoic acid (3a).[11] To a solution of (*R*)-**15** (500 mg, 1.93 mmol) in methanol (5 mL) and water (1 mL) was added K_2CO_3 (534 mg, 3.86 mmol) at room temperature. The reaction mixture was stirred for 5 h under reflux. After cooling to room temperature, HCl (aq.) (1 M, 10 mL) was added, and the aqueous layer was extracted three times with MTBE. The organic layers were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica (eluent hexanes/hexane 3:1) to give **3a** (405 mg, 91%) as a colorless oil: $[\alpha]_D^{22} = -7.6$ (*c* 0.61, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (ddd, *J* = 16.8, 10.3, 6.1, 1H), 5.25 (dd, *J* = 17.1, 1.3, 1H), 5.11 (dd, *J* = 10.3, 1.2, 1H), 4.57 (dt, *J* = 6.8, 6.1, 1H), 2.57 (dd, *J* = 14.9, 7.2, 1H), 2.51 (dd, *J* = 14.9, 5.5, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6 (0), 139.7 (1), 115.2 (2), 70.6 (1), 43.3 (2), 25.7 (3), 18.1 (0), −4.4 (3), −5.2 (3); IR (neat) ν 2956 (m), 2930 (m), 2858 (m), 1711 (s), 1253 (m), 1085 (m); MS (ESI) *m*/*z* 231 ($[M + H]^+$, 100%); HRMS (ESI) calcd for $C_{11}H_{23}O_3Si$ ($[M + H]^+$) 231.1416, found 231.1418. Anal. Calcd for $C_{11}H_{22}O_3Si$: C, 57.4%; H, 9.6%. Found: C, 57.1%; H, 9.8%.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-pent-4-enoic acid (*ent*-3a). Following the procedure for **3a**, *ent*-**3a** was obtained from (*S*)-**15** (500 mg, 1.93 mmol) as a colorless oil (400 mg, 90%): $[\alpha]_D^{22}$ +7.2 (*c* 0.51, CH_2Cl_2). All other analytical data are identical to those reported for **3a**.

(*R*)-((*S*)-1-((4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-undecan-2-yl)-3-(*tert*-butyl-dimethylsilyloxy)pent-4-enoate (16).[11] *Steglich's Method:* To a solution of **12** (38 mg, 0.13 mmol) in dichloromethane (5 mL) were added **3a** (33 mg, 0.14 mmol), dicyclohexylcarbodiimide (29 mg, 0.14 mmol), and DMAP (3.2 mg, 20 mol %) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 day. The solution was filtered and washed three times with dichloromethane. The combined organic layers were washed with 1 M HCl (aq.) and with aqueous $NaHCO_3$ solution, dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica (eluent hexanes/MTBE 20:1) to give **16** (44 mg, 66%) as a colorless oil.

Yamaguchi's Method: To a solution of **3a** (166 mg, 0.72 mmol), 2,4,6-trichlorobenzoyl chloride (0.113 mL, 0.72 mmol), and **12** (180 mg, 0.60 mmol) in THF (10 mL) were added ethyl diisopropylamine (0.228 mL, 1.32 mmol) and DMAP (18.3 mg, 25 mol %). The solution was stirred for 4 h at room temperature. The reaction was diluted with MTBE (20 mL), quenched by addition of aqueous NH_4Cl solution, and the aqueous layer was extracted three times with MTBE (20 mL). The organic layers were washed with aqueous $NaHCO_3$ solution and aqueous NH_4Cl solution and dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica (eluent hexanes/MTBE 20:1) to give **16** (223 mg, 73%) as a colorless oil.

Shiina's Method: A solution of **3a** (117 mg, 0.50 mmol), MNBA (176 mg, 0.50 mmol), ethyl diisopropylamine (0.181 mL, 1.05 mmol), and DMAP (5.1 mg, 10 mol %) in CH_2Cl_2 (2 mL) was stirred for 20 min at room temperature. To this mixture was added **12** (126 mg, 0.42 mmol) in CH_2Cl_2 (4 mL), and the solution was stirred for 5 h at room temperature. The reaction was diluted with MTBE (20 mL), quenched by addition of water, and the aqueous layer was extracted three times with MTBE (20 mL). The organic layers were washed with aqueous $NaHCO_3$ solution and aqueous NH_4Cl solution and dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica (eluent hexanes/MTBE 20:1) to give **16** (182 mg, 85%) as a colorless oil: $[\alpha]_D^{27} = +0.8$ (*c* 0.33, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 16.9, 10.3, 6.1, 1H), 5.77 (ddd, *J* = 17.3, 10.3, 7.4, 1H), 5.37 (d, *J* = 17.1, 1H), 5.25 (d, *J* = 10.1, 1H), 5.22 (dd, *J* = 17.1, 1.4, 1H), 5.06 (dd, *J* = 10.4, 1.3, 1H), 5.00 (tt, *J* = 7.4, 6.0, 1H), 4.57 (dd, *J* = 8.0, 7.7, 1H), 3.67 (dm, *J* = 8.4, 1H), 2.55 (dd, *J* = 15.0, 6.8, 1H), 2.42 (dd, *J* = 15.0, 6.3, 1H), 1.85−1.50 (m, 4H), 1.40−1.20 (m, 20H), 0.90−0.85 (m, 12H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (0), 140.3 (1), 135.0 (1), 119.0 (2), 114.6 (2), 108.9 (0), 82.8 (1), 77.4 (1), 72.1 (1), 70.6 (1), 43.8 (2), 36.7 (2), 34.5 (2), 31.9 (2), 29.5 (2), 29.5 (2), 29.3 (2), 27.3 (3), 26.9 (3), 25.8 (3), 25.0 (2), 22.6 (2), 18.1 (0), 14.0 (3), −4.5 (3), −4.9 (3); IR (neat) ν 2927 (s), 2856 (m), 1736 (s), 1371 (m), 1250 (s), 1174 (s); MS (ESI) *m*/*z* 453 (100), 511 ($[M + H]^+$, 75); HRMS (ESI) calcd for $C_{29}H_{55}O_5Si^+$ ($[M + H]^+$) 511.3819, found 511.3825. Anal. Calcd for $C_{29}H_{54}O_5Si$: C, 68.2%; H, 10.7%. Found: C, 68.1%; H, 11.0%.

(*S*)-((*R*)-1-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-undecan-2-yl)-3-(*tert*-butyldimethylsilyloxy)pent-4-enoate (*ent*-16). Following the procedure for **16** (Shiina's method), *ent*-**16** was obtained from *ent*-**12** (133 mg, 0.45 mmol) and *ent*-**3a** (123 mg, 0.54 mmol) as a colorless oil (185 mg, 81%): $[\alpha]_D^{23} = -2.1$ (*c* 0.49, CH_2Cl_2). All other analytical data are identical to those reported for **16**.

(3a*R*,5*S*,9*R*,11a*R*,*E*)-9-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-5-nonyl-4,5,8,9-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*d*]-oxecin-7-(11a*H*)-one (17).[11] To a solution of **16** (185 mg, 0.36 mmol) in CH_2Cl_2 (360 mL) was added second generation catalyst **A** (31 mg, 10 mol %), and the solution was stirred at 40 °C for 4 h. The solvent was evaporated, and the residue was purified by column chromatography on silica (eluent hexanes/MTBE 40:1) to give **17** (161 mg, 92%) as a colorless oil: $[\alpha]_D^{27} = +15.2$ (*c* 0.37, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (dd, *J* = 15.4, 2.4, 1H), 5.66 (ddd, *J* = 15.4, 9.3, 1.6, 1H), 4.92 (dt, *J* = 7.6, 6.4, 1H), 4.66 (m, 1H), 4.06 (dd, *J* = 8.9, 8.7, 1H), 3.62 (dd, *J* = 8.6, 8.4, 1H), 2.56 (d, *J* = 3.5, 1H), 2.05 (d, *J* = 5.2, 1H), 1.86 (m, 1H), 1.60−1.20 (m, 22H), 0.92 (s, 9H), 0.87 (t, *J* = 6.5, 1H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 (0), 137.5 (1), 123.3 (1), 107.9 (0), 84.3 (1), 81.8 (1), 72.5 (1), 67.8 (1), 45.3 (2), 36.8 (2), 36.1 (2), 31.9 (2), 29.4 (2), 29.2 (2), 27.0 (3), 27.0 (3), 25.8 (3), 25.2 (2), 22.6 (2), 18.3 (0), 14.0 (3), −4.9 (3), −5.2 (3); IR (neat) ν 2927 (s), 2856 (m), 1738 (s), 1371 (m), 1253 (s), 1157 (s); MS (ESI) *m*/*z* 144 (100), 293 (50), 483 ($[M + H]^+$, 74); HRMS (ESI) calcd for $C_{27}H_{51}O_5Si^+$ ($[M + H]^+$) 483.3506, found 483.3474.

(3a*S*,5*R*,9*S*,11a*S*,*E*)-9-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-5-nonyl-4,5,8,9-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*d*]-oxecin-7(11a*H*)-one (*ent*-17). Following the procedure for **17**, *ent*-**17** was obtained from *ent*-**16** (160 mg, 0.31 mmol) as a colorless oil (145 mg, 96%): $[\alpha]_D^{23} = -15.7$ (*c* 0.28, CH_2Cl_2). All other analytical data are identical to those reported for **17**.

(3a*R*,5*S*,9*R*,11a*R*,*E*)-9-Hydroxy-2,2-dimethyl-5-nonyl-4,5,8,9-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*d*]oxecin-7(11a*H*)-one (18). To a solution of **17** (80 mg, 0.17 mmol) in THF (2 mL) was added TBAF (62 mg, 0.20 mmol), and the solution was stirred for 1 h at room

temperature. The reaction was quenched by addition of water, and the aqueous layer was extracted three times with MTBE. The combined organic layers were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica (eluent hexanes/MTBE 1:1) to give **18** (52 mg, 87%) as a colorless oil: $[\alpha]_D^{28}$ = +22.8 (*c* 0.20, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (dd, *J* = 15.9, 2.3, 1H), 5.63 (dd, *J* = 15.9, 9.2, 1H), 5.05 (dt, *J* = 9.8, 6.4, 1H), 4.71 (m, 1H), 4.06 (dd, *J* = 8.8, 8.6, 1H), 3.64 (dd, *J* = 8.8, 8.6, 1H), 2.63 (dd, *J* = 12.1, 2.3, 1H), 2.52 (dd, *J* = 12.1, 3.7, 1H), 2.07 (d, *J* = 15.3, 1H), 1.89 (m, 1H), 1.60−1.20 (m, 22H), 0.87 (t, *J* = 7.0, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9 (0), 136.8 (1), 123.2 (1), 108.2 (0), 84.0 (1), 81.7 (1), 73.0 (1), 67.3 (1), 44.4 (2), 37.0 (2), 36.0 (2), 31.8 (2), 29.4 (2), 29.4 (2), 29.3, 29.2, 27.0 (3), 26.9 (3), 25.2 (2), 22.6 (2), 14.0 (3); IR (neat) ν 3454 (m), 2924 (s), 2855 (m), 1730 (s), 1371 (m), 1233 (s), 1156 (s); MS (ESI) *m*/*z* 369 ([M + H]$^+$, 100); HRMS (ESI) calcd for $C_{21}H_{37}O_5^+$ ([M + H]$^+$) 369.2641, found 369.2652.

(+)-(3*R*, 6*R*, 7*R*, 9*S*)-Seimatopolide A.[11] *Global deprotection of compound* ***17***: To a solution of **17** (150 mg, 0.31 mmol) in DCM (10 mL) was added TFA (2.5 mL) at 0 °C, and the solution was stirred for 24 h at room temperature. The reaction was quenched by addition of aqueous $NaHCO_3$ solution (30 mL), and the aqueous layer was extracted three times with MTBE. The combined organic layers were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica (eluent hexanes/ethyl acetate 1:4) to give (+)-(3*R*,6*R*,7*R*,9*S*)-seimatopolide A (75 mg, 74%) as a white solid. *Stepwise deprotection of compound* ***18***: To a solution of **18** (85 mg, 0.23 mmol) in THF (2 mL) were added water (0.5 mL) and TFA (2 mL) at 0 °C, and the solution was stirred for 16 h at room temperature. The reaction was quenched by addition of aqueous $NaHCO_3$ solution (30 mL), and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica (eluent hexanes/ethyl acetate 1:2) to give (+)-(3*R*,6*R*,7*R*,9*S*)-seimatopolide A (71 mg, 94%) as a white solid: $[\alpha]_D^{22}$ = +30.9 (*c* 0.05, MeOH); ^{1}H NMR (600 MHz, pyridine-d_5) δ 6.46 (ddd, *J* = 15.7, 9.5, 1.0, 1H), 6.14 (dd, *J* = 15.7, 3.1, 1H), 5.14 (dt, *J* = 6.8, 6.5, 1H), 4.96 (m, 1H), 4.40 (dd, *J* = 9.1, 9.1, 1H), 3.97 (dd, *J* = 8.7, 8.5, 1H), 2.86 (dd, *J* = 11.6, 3.2, 1H), 2.73 (dd, *J* = 11.6, 3.9, 1H), 2.34−2.24 (m, 2H), 1.67 (m, 1H), 1.57 (m, 1H), 1.40−1.15 (m, 14H), 0.86 (t, *J* = 7.1, 1H); ^{13}C NMR (150 MHz, pyridine-d_5) δ 170.8, 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; IR (neat) ν 3344 (m), 2927 (s), 2857 (m), 1667 (s), 1448 (m), 1195 (s), 1138 (s); MS (ESI) *m*/*z* 329 ([M + H]$^+$, 14), 351 ([M + H]$^+$, 21), 359 (100); HRMS (ESI) calcd for $C_{18}H_{32}O_5Na^+$ ([M + Na]$^+$) 351.2147, found 351.2169.

(−)-(3*S*,6*S*,7*S*,9*R*)-Seimatopolide A. Following the procedure for the global deprotection of RCM product **17**, (−)-(3*S*, 6*S*, 7*S*, 9*R*)-seimatopolide A was obtained from *ent*-**17** (145 mg, 0.29 mmol) as a white solid (70 mg, 74%): $[\alpha]_D^{22}$ = −27.1 (*c* 0.05, MeOH). All other analytical data are identical to those reported for (+)-(3*R*,6*R*,7*R*,9*S*)-seimatopolide A.

(2*S*,4*R*,5*R*,8*R*,*E*)-2-Nonyl-10-oxo-3,4,5,8,9,10-hexahydro-2*H*-oxecine-4,5,8-triyl Tris(4-bromobenzoate) (19). To a solution of (3*R*,6*R*,7*R*,9*S*)-(+)-seimatopolide A (11 mg, 0.034 mmol) in pyridine (0.5 mL) and CH_2Cl_2 (0.5 mL) was added 4-bromobenzoyl chloride (75 mg, 0.34 mmol), and the solution was stirred for 5 h under reflux. The reaction mixture was diluted with MTBE (10 mL), and the organic layer was washed with 1 M HCl (aq.) (10 mL), followed by aqueous $NaHCO_3$ solution (10 mL). The organic layers were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica (eluent hexanes/MTBE 5:1) to give **19** (24 mg, 81%) as a white solid: $[\alpha]_D^{21}$ −101.3 (*c* 0.11, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.5, 2H), 7.73 (d, *J* = 8.5, 2H), 7.67 (d, *J* = 8.6, 2H), 7.61 (d, *J* = 8.5, 2H), 7.47 (d, *J* = 8.5, 2H), 7.41 (d, *J* = 8.6, 2H), 6.30 (dd, *J* = 15.3, 3.4, 1H), 5.92 (d, *J* = 3.2, 1H), 5.80−5.70 (m, 2H), 5.35 (dd, *J* = 9.1, 8.8, 1H), 5.05 (dt, *J* = 7.0, 6.5, 1H), 2.84 (dd, *J* = 12.6, 2.1, 1H), 2.72 (dd, *J* = 12.6, 3.9, 1H), 2.25 (m, 1H), 2.00 (d, *J* = 16.1, 1H), 1.70−1.17 (m, 16H), 0.87 (t, *J* = 6.9, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 164.8, 164.8, 164.3, 135.1, 131.9, 131.7, 131.6, 131.4, 131.0, 131.0, 128.6, 128.5, 128.4, 128.3, 122.4, 77.4, 75.3, 72.8, 68.3, 41.1, 39.5, 36.7, 31.8, 29.5, 29.4, 29.4, 29.2, 24.8, 22.6, 14.1; IR (neat) ν 2924 (s), 2854 (m), 1713 (s), 1589 (m), 1398 (m), 1261 (s), 1100 (s); HRMS (ESI) calcd for $C_{39}H_{42}O_8{}^{79}Br_3^+$ ([M + H]$^+$) 875.0430, found 875.0397.

(2*R*,4*S*,5*S*,8*S*,*E*)-2-Nonyl-10-oxo-3,4,5,8,9,10-hexahydro-2*H*-oxecine-4,5,8-triyl Tris(4-bromobenzoate) (*ent*-19). Following the procedure for **19**, *ent*-**19** was obtained from (3*S*, 6*S*, 7*S*, 9*R*)-(-)-seimatopolide A (12 mg, 0.037 mmol) as a white solid (29 mg, 90%): $[\alpha]_D^{22}$ +114.7 (*c* 0.17, CH_2Cl_2). All other analytical data are identical to those reported for **19**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental details, analytical data, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, copies of HPLC chromatograms for compound *rac*-**13** and its separate enantiomers, and copies of the UV spectrum, the individual CD spectra, and superimposed CD spectra for **19** and *ent*-**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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