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The First Total Synthesis of Topsentolide B_3

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The first total synthesis of the cytotoxic oxylipin Topsentolide B_3 has been accomplished in 15 steps with an overall yield of 24 %. Starting with readily available *cis*-butene diol as a synthon, the synthesis involved Marouka allylation and Sharpless hydroxylation for the construction of three asymmetric centers. The nine-membered lactone ring was built through a selective Grubbs ring-closing metathesis reaction. Other key steps in the synthesis are Cu^I-mediated alkynylation and Swern oxidation reactions. This provides a unique approach to the synthesis of oxylipins and offers the advantages of brevity and relatively high overall yield.

Introduction

Marine invertebrates and algae have been recognized as a rich source for a large number of new compounds with unique structural classes. The topsentolides A_1–C_2 comprise a novel group of oxylipins that were isolated from the *Topsia* sp. off the Korean coast in 2006.[1] The structural elucidation of these metabolites was achieved by extensive interpretation of their spectroscopic data. The topsentolides contain cyclopropane and nine-membered lactone rings together with variable degrees of unsaturation at C-5, C-9, and C-17; they are believed to be formed by lipoxygenation followed by cyclization of unsaturated fatty acids. Depending upon the functional groups at C-11 and C-12, they are categorized into three series. Representative members include those originally assigned the structures of topsentolides A, B, and C, respectively.

Because of their important biological properties[1] coupled with the unique stereogenic variations within subfamilies of oxylipins, as well as the limited amounts available from natural sources, topsentolides have attracted the attention of a number of synthetic organic chemists worldwide.

Recently, Kobayashi et al.[2] reported the synthesis of topsentolide A_1 and determined the stereochemistry. However, there are no reports on the synthesis of other topsentolides. These facts coupled with the interesting chiral 1,2-diol group adjacent to the *trans*-double bond of topsentolide B_3 (**1**, Figure 1) prompted us to undertake the synthetic study of topsentolide B_3.

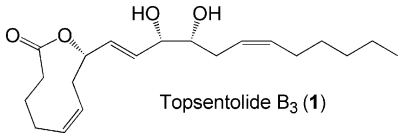

Figure 1. Structure of topsentolide B_3.

In this report, a convergent strategy for the stereoselective synthesis of topsentolide B_3 (Scheme 1) makes use of Marouka asymmetric allylation, Swern oxidation, and Grubbs RCM. In the overall sequence, these are the key reaction steps for the formation of the lactone ring. Installation of the chiral 1,2-diol group was achieved through Sharpless asymmetric dihydroxylation by using AD-mix reagent.[3] To the best of our knowledge this is the first total synthesis of topsentolide B_3.

Results and Discussion

Recognizing the importance of developing an efficient synthesis of **1**, our synthetic approach to a nine-membered unsaturated lactone involved a *Z*-selective ring-closing metathesis (RCM) reaction (Scheme 1). Disconnection of the C-5–C-6 double bond revealed bis-terminal olefin **2** as a potential key intermediate. This compound was synthesized from alcohol **3** by esterification with 5-hexenoic acid. In designing a unified approach to fragment **3**, it was important to consider the genesis of the configuration at C-8. Our goal from the outset was to accomplish this through stereocontrolled allylation of the corresponding aldehyde that would leave us with a handle for installing the stereocenter at C-8. In an earlier study from our laboratory, we demonstrated the versatility of the Marouka allylation and Grubbs cross-metathesis reactions.[4] Thus, we envisioned that key fragment **3** could be obtained through the

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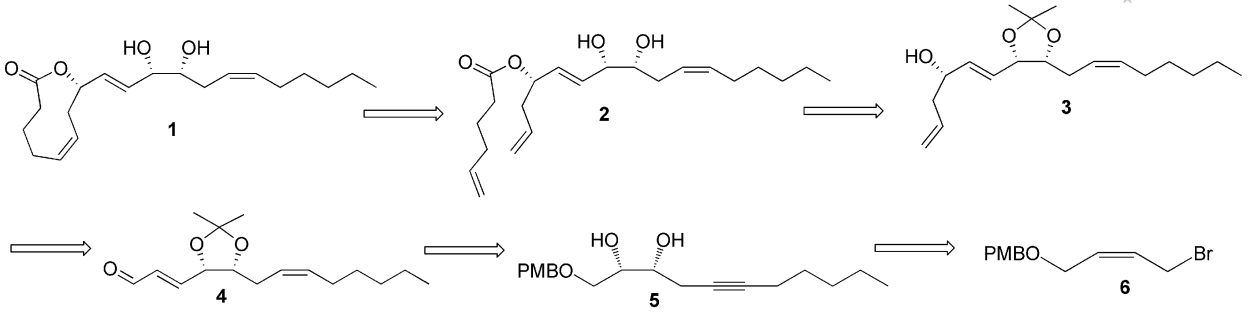
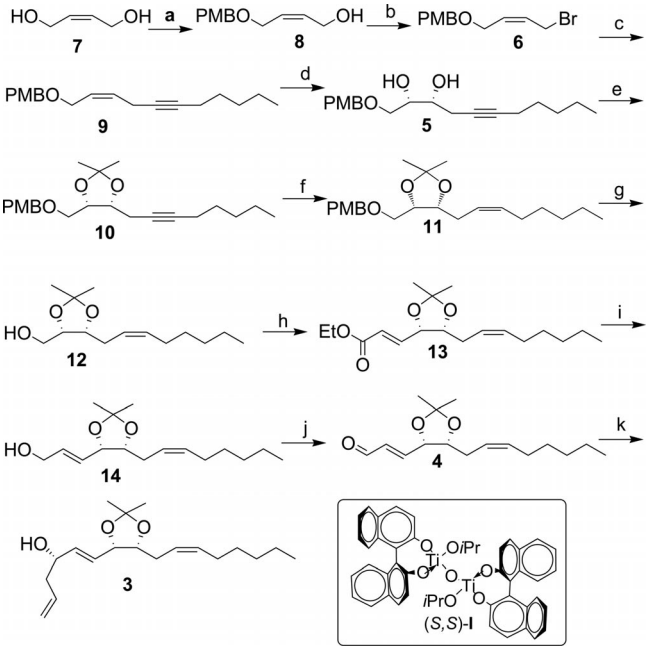


Scheme 1. Retrosynthetic analysis of topsentolide B_3 (**1**).

Marouka asymmetric allylation of aldehyde **4**, which in turn could be realized from compound **5** using Lindlar's catalyst, Swern oxidation, and other steps. Alkyne diol **5** in turn was obtained from compound **6** through sequential condensation with 1-heptyne and Sharpless dihydroxylation reactions. Thus, our present total synthesis is highlighted by utilization of a Marouka asymmetric allylation, which directs construction of the stereocenter at C-8, and Grubbs RCM for the formation of the nine-membered lactone ring. Furthermore, the simplicity of the precursors made this an attractive route for the synthesis of a library of compounds in the oxylipin family, thereby providing ample amounts for more extensive biological screening.

Commercially available *p*-methoxybenzyl (PMB) alcohol was treated with Cl_3CCN in the presence of 1,5,7-triazabicyclo[4.4.0]dec-5-ene to give 4-methoxybenzyl-2,2,2-trichloroacetimidate. The synthesis began with commercially available *cis*-butenediol (**7**), which was selectively protected with freshly prepared 4-methoxybenzyl-2,2,2-trichloroacetimidate and a catalytic amount of (–)-camphor-10-sulfonic acid (CSA) in dichloromethane to give mono-PMB ether **8**[5] (Scheme 2). Resulting allyl alcohol **8** was converted into its allyl bromide by using Appel reaction conditions[6,7] to afford compound **6** in 94% yield, which was further treated with 1-heptyne by using a Cu^I-mediated cross-coupling reaction[7] to give **9** in 96% yield.

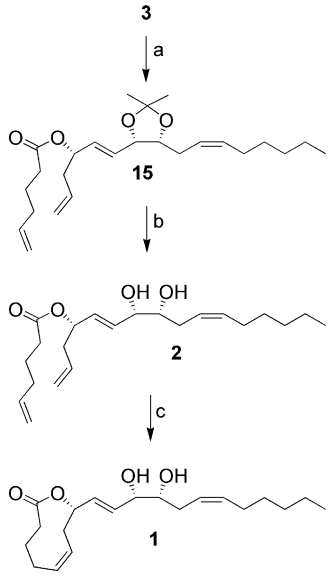
When **9** was treated with AD-mix-α in (1:1) aqueous *t*BuOH at room temperature, a highly stereoselective dihydroxylation[3,8] occurred to give diol **5** in 97% yield, which was then protected as acetonide **10**.[9] Stereospecific hydrogenation[7] of the triple bond in **10** with Lindlar's catalyst and quinoline in benzene resulted in olefin **11**. Removal of the PMB group[10] in compound **11** by using DDQ furnished compound **12**. Swern oxidation[3,11] of alcohol **12** followed by Wittig olefination[12] furnished (*E*)-alkene **13** in 91% overall yield for the two steps. This was converted into corresponding allylic alcohol **14** in 95% yield by reduction with DIBAL-H in dichloromethane under standard conditions.[13] Oxidation of the formed primary alcohol under Swern conditions afforded desired aldehyde **4**. Marouka allylation[4,14] of **4** by using titanium complex (*S*,*S*)-**I** and allyltri-*n*-butyltin yielded key fragment **3** with excellent enantioselectivity of 98%*ee* (determined by chiral HPLC) in 86% yield.



Scheme 2. Reagents and conditions: (a) 4-methoxybenzyl-2,2,2-trichloroacetimidate, CSA, 0 °C to r.t., 1 h, 92%; (b) CBr_4, Ph_3P, CH_2Cl_2, 0 °C to r.t., 2 h, 94%; (c) 1-heptyne, CuI, NaI, K_2CO_3, *N*,*N*-dimethylformamide (DMF), r.t., 8 h, 96%; (d) AD-mix-α, $CH_3SO_2NH_2$, $(CH_3)_3COH/H_2O$ (1:1), 0 °C to r.t., 24 h, 97%; (e) CSA, 2,2-dimethoxypropane, CH_2Cl_2, r.t., 12 h, 89%; (f) H_2/Lindlar's catalyst, quinoline, benzene, 10 °C, 2 h, 91%; (g) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2/H_2O (9:1), 0 °C to r.t., 1 h, 87%; (h) $(COCl)_2$, dimethyl sulfoxide (DMSO), Et_3N, CH_2Cl_2, –78 °C, 1 h; then $Ph_3P{=}CHCO_2Et$, C_6H_6, 92 °C, 2 h, 91% for two steps; (i) diisobutylaluminum hydride (DIBAL-H), CH_2Cl_2, –15 °C, 1 h, 95%; (j) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 1 h, 96%; (k) (*S*,*S*)-**I** (10 mol-%), $Bu_3SnCH_2CH{=}CH_2$, CH_2Cl_2, –15 to 0 °C, 24 h, 86%.

With required fragment **3** in hand, we proceeded with the synthesis of topsentolide B_3 (Scheme 3). Thus, condensation of alcohol **3** with 5-hexenoic acid by using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI)/4-(dimethylamino)pyridine (DMAP) in pyridine[15,3] afforded ester **15**, and subsequent deprotection of the acetonide with (–)-camphor-10-sulfonic acid in methanol afforded desired product **2**. The final step of our synthetic plan involved the generation of the lactone ring by Grubbs RCM. This may

be considered as the most critical step in our synthetic scheme because the preparation of medium-sized rings by RCM may be difficult in some instances, especially in the presence of other reactive sites in the alicyclic chain. Gratifyingly, and in spite of these potential problems, the RCM reaction[16] of compound **2** catalyzed by Grubbs second generation catalyst (10 mol-%) and in dichloromethane heated to reflux proceeded smoothly and afforded topsentolide B_3 (**1**) in 78% yield. Although fragment **2** contained two other double bonds in the alicyclic chain, only terminal double bonds were involved selectively to form the nine-membered lactone ring of **1**. This result implied that the catalyst did not insert into the double bond at the sterically hindered region and the double bond α to the ester hydroxy group. In this case, the reaction was highly *Z*-selective, and there was no spectroscopic or chromatographic evidence for the formation of either the *E*-isomer or other side products. Indeed, to the best of our knowledge, this is the first example of a selective RCM reaction,[17] demonstrating the formation of the lactone ring in the synthesis of the oxylipins class of compounds or any other medium ring lactones. All the intermediate products were well characterized using NMR spectroscopy and mass spectrometry. The data (^{1}H NMR, ^{13}C NMR, and HRMS) of synthetic topsentolide was identical and the optical rotation {$[\alpha]_D^{26}$ = +42 (*c* = 0.1, $CHCl_3$)} was comparable to the reported data for the natural product.



Scheme 3. Reagents and conditions: (a) 5-hexenoic acid, EDCI, DMAP, pyridine, r.t., 16 h, 92%; (b) CSA, CH_3OH, r.t., 6 h, 83%; (c) Grubbs second generation catalyst (10 mol-%), CH_2Cl_2, reflux, 0.5 h, 78%.

Conclusions

In conclusion, we have accomplished the first total synthesis of topsentolide B_3, accomplished in 15 steps in a linear fashion. The key step was a selective RCM reaction. Maruoka asymmetric allylation and Sharpless asymmetric hydroxylation were used for the generation of the chiral centers. Further elaboration by using this sequence of reactions to construct other nine-membered-ring-containing biologically active compounds is underway in our laboratory.

Experimental Section

General: ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature with a 300, 500, or 75 MHz spectrometer by using $CDCl_3$ or CD_3OD as solvents. The chemical shifts are reported using TMS as an internal standard, and signal patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; br. s, broad singlet. FTIR spectra were recorded as thin films on KBr or as neat films. Optical rotations were measured with a digital polarimeter using a 1-mL cell having a 1-dm path length. For low- (MS) and high- (HRMS) resolution mass spectrometry, *m*/*z* ratios are reported as values in atomic mass units. All reagents and solvents were reagent grade and used without further purification unless otherwise specified. Technical-grade ethyl acetate and hexane were used for column chromatography and distilled prior to use. When used as a reaction solvent, tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl. Column chromatography was carried out by using silica gel (60–120 mesh & 100–200 mesh) packed in glass columns. All reactions were performed under an atmosphere of nitrogen by using flame- or oven-dried glassware and magnetic stirring.

(*Z*)-4-(4-Methoxybenzyloxy)but-2-en-1-ol (8): To a stirred solution of 4-methoxybenzyl-2,2,2-trichloroacetimidate (2.82 g, 0.010 mol) and *cis*-butenediol (**7**; 1.0 g, 0.011 mol) in dichloromethane (30 mL) at 0 °C was added (–)-camphor-10-sulfonic acid (0.12 g, 0.0005 mol). The reaction mixture was warmed to room temperature and stirred for 1 h. Upon completion (monitored by TLC), the reaction mixture was quenched with triethylamine (0.5 g, 0.005 mol) and concentrated under reduced pressure to give the crude product. Purification by flash chromatography (23% ethyl acetate in hexanes) yielded pure **8** (2.02 g, 92%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.5 Hz 2 H), 6.84 (d, *J* = 8.5 Hz, 2 H), 5.82–5.63 (m, 2 H), 4.43 (s, 2 H), 4.11 (d, *J* = 6.0 Hz, 2 H), 4.02 (d, *J* = 6.0 Hz, 2 H), 3.79 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 132.3,129.7, 129.2 (2 C), 127.6, 113.6 (2 C), 71.8, 65.0, 58.0, 54.9 ppm. HRMS (ESI): calcd. for $C_{12}H_{16}O_3Na$ $[M + Na]^+$ 231.0992; found 231.0991.

(*Z*)-1-[(4-Bromobut-2-enyloxy)methyl]-4-methoxybenzene (6): A solution of **8** (15.0 g, 0.07 mol) and carbon tetrabromide (26.3 g, 0.08 mol) in dichloromethane (75 mL) was cooled to 0 °C. With vigorous stirring a solution of triphenylphosphane (22.7 g, 0.85 mol) in dichloromethane (50 mL) was slowly added over 30 min using a syringe. The mixture was warmed to room temperature and stirred for another 2 h. The reaction mixture was concentrated to give a brown oil, which was washed with hexane (500 mL). The white precipitate was filtered, and the filtrate was concentrated under reduced pressure to give the crude product. Purification by flash chromatography (3% ethyl acetate in hexanes) yielded pure **6** (18.23 g, 94%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.7 Hz, 2 H), 6.83 (d, *J* = 8.3 Hz, 2 H), 5.91–5.80 (m, 1 H), 5.75–5.65 (m, 1 H), 4.43 (s, 2 H), 4.08 (dd, *J* = 6.0, 1.1 Hz, 2 H), 3.94 (d, *J* = 8.3 Hz, 2 H), 3.80 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.1, 134.4, 133.0, 131.0 (2 C), 129.7, 115.4 (2 C), 73.4, 66.4, 56.4, 28.8 ppm. HRMS (ESI): calcd. for $C_{12}H_{15}BrO_2Na$ $[M + Na]^+$ 294.1375; found 294.1377.

(*Z*)-1-Methoxy-4-[(undec-2-en-5-ynyloxy)methyl]benzene (9): Bromide **6** (13.5 g, 0.05 mol) and 1-heptyne (5.7 g, 0.06 mol) were slowly added to a suspension of the previously dried salts, CuI (18.9 g, 0.10 mol), NaI (14.9 g, 0.10 mol), and K_2CO_3 (10.3 g, 0.07 mol) in DMF (60 mL). The reaction mixture was stirred at room temperature for 8 h, quenched with saturated aqueous ammonium chloride and extracted with diethyl ether. The combined organic layers were washed with brine and dried with sodium sulfate. Removal of the solvent afforded the crude product. Chromatography on silica gel (2% ethyl acetate in hexanes) gave **9** (13.73 g, 96%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.16 (d, J = 8.7 Hz, 2 H), 6.77 (d, J = 8.7 Hz, 2 H), 5.82–5.70 (m, 1 H), 5.66–5.51 (m, 1 H), 4.35 (s, 2 H), 3.90 (dd, J = 5.8, 1.1 Hz, 2 H), 3.73 (s, 3 H), 2.89–2.81 (m, 2 H), 2.14–2.03 (m, 2 H), 1.48–1.21 (m, 6 H), 0.84 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 130.3, 129.1 (2 C), 128.3, 127.7, 113.5 (2 C), 82.5, 76.5, 71.5, 69.7, 54.9, 31.0, 28.6, 22.2, 21.8, 18.7, 14.0 ppm. HRMS (ESI): calcd. for $C_{19}H_{26}O_2Na$ [M + Na]$^+$ 309.1830; found 309.1827.

(2*S*,3*R*)-1-(4-Methoxybenzyloxy)undec-5-yne-2,3-diol (5): To a solution of compound **9** (7.7 g, 0.027 mol) in *tert*-butyl alcohol/water (1:1, 308 mL) at 0 °C was added AD-mix-α (37.9 g). The reaction mixture was stirred for 1 h and $CH_3SO_2NH_2$ (1.9 g, 0.02 mol) was added. After stirring for 1 h, the reaction mixture was warmed to room temperature and allowed to stir for 24 h. The reaction was quenched with sodium sulfite (38 g) and stirred for an additional 30 min. After extracting with ethyl acetate (3 × 80 mL), the combined organic layers were dried with sodium sulfate and concentrated to afford the crude product. Purification by column chromatography (15% ethyl acetate in hexanes gave **5** (8.33 g, 97%) as a colorless oil. $[\alpha]_D^{26}$ = –7 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3290, 3217, 2922, 2859, 1612, 1514, 1463, 1253, 1114, 1081, 1040, 992, 941, 818, 712 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (d, J = 8.5 Hz, 2 H), 6.90 (d, J = 8.7 Hz, 2 H), 4.47 (s, 2 H), 3.90–3.82 (m, 1 H), 3.79 (s, 3 H), 3.76–3.69 (m, 1 H), 3.63–3.48 (m, 2 H), 2.53–2.41 (m, 1 H), 2.37–2.26 (m, 1 H), 2.16–2.09 (m, 1 H), 2.08–2.04 (m, 1 H), 1.50–1.25 (m, 6 H), 0.88 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.1, 132.6, 130.9 (2 C), 115.4 (2 C), 83.1, 78.8, 74.3, 73.5, 72.5, 72.3, 56.5, 32.7, 30.4, 25.4, 23.8, 20.1, 15.2 ppm. HRMS (ESI): calcd. for $C_{19}H_{28}O_4Na$ [M + Na]$^+$ 343.1885; found 343.1894.

(4*S*,5*R*)-4-[(4-Methoxybenzyloxy)methyl]-2,2-dimethyl-5-(oct-2-ynyl)-1,3-dioxolane (10): To a solution of compound **5** (0.8 g, 0.003 mol) in dichloromethane (15 mL) at 0 °C was added 2,2-dimethoxypropane (0.8 g, 0.008 mol) and a catalytic amount of (–)-camphor-10-sulfonic acid. The reaction was warmed to room temperature, and the mixture was stirred for 12 h. After completion (monitored by TLC), the reaction was quenched with a saturated solution of sodium hydrogen carbonate and extracted with chloroform. The organic layer was dried with sodium sulfate and concentrated to afford the crude product. Purification by column chromatography (5% ethyl acetate in hexane) gave **10** (0.8 g, 89%) as a colorless oil. $[\alpha]_D^{26}$ = –4 (c = 2.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23 (d, J = 8.5 Hz, 2 H), 6.84 (d, J = 8.7 Hz, 2 H), 4.57–4.45 (m, 2 H), 4.03–3.95 (m, 1 H), 3.88–3.81 (m, 1 H), 3.79 (s, 3 H), 3.66–3.59 (m, 1 H), 3.57–3.50 (m, 1 H), 2.57–2.39 (m, 2 H), 2.10–2.02 (m, 2 H), 1.47–1.24 (m, 6 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 0.90 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 130.1, 129.1 (2 C), 113.6 (2 C), 108.9, 82.5, 79.6, 76.2, 75.2, 73.0, 70.3, 54.9, 31.1, 28.6, 27.2 (2 C), 23.3, 22.2, 18.7, 14.1 ppm. HRMS (ESI): calcd. for $C_{22}H_{32}O_4Na$ [M + Na]$^+$ 383.2198; found 383.2195.

(4*S*,5*R*,*Z*)-4-[(4-Methoxybenzyloxy)methyl]-2,2-dimethyl-5-(oct-2-enyl)-1,3-dioxolane (11): Dry benzene (30 mL) was added to a 250-mL Erlenmeyer flask with Lindlar's catalyst (1.25 g). At room temperature the mixture was saturated with H_2 and cooled to 10 °C. Under a stream of N_2, a solution of **10** (0.83 g, 0.0023 mol) in benzene (30 mL) and quinoline (1.2 mL) were added. After exchanging the N_2 with H_2, the reaction mixture was stirred for 1 h at 10 °C. The mixture was filtered and washed with 2 M HCl (2 × 30 mL), and the solvent was evaporated to afford the crude residue. Purification by column chromatography (2% ethyl acetate in hexanes) gave **11** (0.76 g, 91%) as a colorless oil. $[\alpha]_D^{26}$ = –10 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, J = 8.5 Hz, 2 H), 6.83 (d, J = 8.5 Hz, 2 H), 5.52–5.30 (m, 2 H), 4.49 (s, 2 H), 3.83–3.72 (m, 2 H), 3.80 (s, 3 H), 3.53–3.46 (m, 2 H), 2.37–2.24 (m, 2 H), 2.04–1.91 (m, 2 H), 1.43–1.20 (m, 12 H), 0.88 (t, J = 6.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 132.2, 130.0, 129.0 (2 C), 124.3, 113.5 (2 C), 108.3, 79.4, 78.0, 73.0, 70.2, 54.8, 31.4, 30.7, 29.2, 27.3, 27.2, 27.0, 22.5, 14.1 ppm. HRMS (ESI): calcd. for $C_{22}H_{34}O_4Na$ [M + Na]$^+$ 385.2354; found 385.2351.

{(4*S*,5*R*)-2,2-Dimethyl-5-[(*Z*)-oct-2-enyl]-1,3-dioxolan-4-yl}-methanol (12): To a solution of compound **11** (0.7 g, 0.002 mol) in dichloromethane/H_2O (9:1, 20 mL) at 0 °C was added DDQ (0.68 g, 0.003 mol). The reaction was warmed to room temperature and stirred for 1 h. After completion (monitored by TLC), the reaction mixture was filtered through Celite. The filtrate was washed with saturated sodium hydrogen carbonate (3 × 20 mL), dried with sodium sulfate, and concentrated to afford the crude product. Purification by column chromatography (5% ethyl acetate in hexanes) gave **12** (0.4 g, 87%) as a colorless oil. $[\alpha]_D^{27}$ = –9 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3470, 2926, 2861, 1613, 1518, 1460, 1378, 1250, 1166, 1062, 841 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.58–5.46 (m, 1 H), 5.45–5.31 (m, 1 H), 3.95–3.55 (m, 4 H), 2.46–2.21 (m, 2 H), 2.09–1.95 (m, 2 H), 1.44–1.22 (m, 12 H), 0.89 (t, J = 6.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.7, 124.1, 108.4, 81.3, 76.3, 61.8, 31.6, 30.7, 29.3, 27.5 (2 C), 27.2, 22.7, 14.2 ppm. HRMS (ESI): calcd. for $C_{14}H_{26}O_3Na$ [M + Na]$^+$ 265.1779; found 265.1785.

(*E*)-Ethyl 3-{(4*S*,5*R*)-2,2-Dimethyl-5-[(*Z*)-oct-2-enyl]-1,3-dioxolan-4-yl}acrylate (13): Under an inert atmosphere at –78 °C, DMSO (0.75 g, 0.01 mol) was added dropwise to a solution of oxalyl chloride (1.7 g, 0.013 mol) in dichloromethane (20 mL). After stirring for 15 min, a solution of **12** (2.0 g, 0.00877 mol) in dichloromethane (10 mL) was added dropwise. After stirring for 25 min, triethylamine (6.2 g, 0.06 mol) was added, followed by stirring for an additional 20 min. Upon completion, the reaction mixture was warmed to room temperature and quenched with water (50 mL). After extracting with dichloromethane, the organic layer was washed with brine and dried with sodium sulfate. Removal of the solvent afforded the crude product (1.92 g), which was immediately utilized for the next step without purification. A solution of Ph_3P=CHCOOEt (3.7 g, 0.01 mol) in benzene (20 mL) was heated to reflux and a solution of the crude aldehyde in benzene (5 mL) was added. After stirring for 2 h, the reaction mixture was warmed to room temperature and concentrated to afford the crude product. Purification by column chromatography (2% ethyl acetate in hexane) gave **13** (2.21 g, 91% for two steps) as a colorless oil. $[\alpha]_D^{27}$ = –8 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.78 (dd, J = 5.1, 15.5 Hz, 1 H), 6.08–5.82 (m, 1 H), 5.56–5.20 (m, 2 H), 4.24–4.04 (m, 3 H), 3.77–3.58 (m, 1 H), 2.42–2.27 (m, 2 H), 2.10–1.92 (m, 2 H), 1.42–1.20 (m, 15 H), 0.90 (t, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 145.3, 132.6, 124.5, 123.1, 109.4, 81.0, 76.0, 60.4, 31.5, 30.1, 29.1, 27.3, 27.0 (2 C), 22.5, 14.2, 14.0 ppm. HRMS (ESI): calcd. for $C_{18}H_{30}O_4Na$ [M + Na]$^+$ 333.2041; found 333.2049.

(*E*)-3-{(4*S*,5*R*)-2,2-Dimethyl-5-[(*Z*)-oct-2-enyl]-1,3-dioxolan-4-yl}-prop-2-en-1-ol (14): Under an inert atmosphere at –15 °C, DIBAL-H (1 M in toluene, 11.0 mL) was added dropwise to a solution of ester **13** (1.32 g, 0.0044 mol) in dichloromethane (27 mL). After stirring for 1 h, the reaction was quenched with a saturated solution of Rochelle salt, warmed to room temperature, and stirred for an additional 3 h. The organic phase was separated and the aqueous phase was extracted with dichloromethane (2×). The combined organic layers were washed with water, brine, dried with anhydrous sodium sulfate, and concentrated to afford the crude product. Purification by column chromatography (11% acetone in hexane) gave **14** (1.13 g, 95%) as a colorless oil. $[\alpha]_D^{28} = -7$ (c = 1.2, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3417, 2926, 2861, 1726, 1459, 1379, 1237, 1164, 1102, 1062, 1005, 970, 855 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.97–5.85 (m, 1 H), 5.71–5.60 (m, 1 H), 5.52–5.33 (m, 2 H), 4.14 (d, J = 4.9 Hz, 2 H), 4.06–3.98 (m, 1 H), 3.72–3.62 (m, 1 H), 2.31 (t, J = 6.0 Hz, 2 H), 2.01 (q, J = 6.8 Hz, 2 H), 1.39 (s, 3 H), 1.38 (s, 3 H), 1.37–1.23 (m, 6 H), 0.90 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.0, 132.6, 127.6, 123.8, 108.5, 81.1, 80.3, 62.5, 31.4, 29.3, 29.1, 27.3, 27.1, 26.9, 22.4, 13.9 ppm. HRMS (ESI): calcd. for $C_{16}H_{28}O_3Na$ $[M + Na]^+$ 291.1936; found 291.1949.

(*E*)-3-{(4*S*,5*R*)-2,2-Dimethyl-5-[(*Z*)-oct-2-enyl]-1,3-dioxolan-4-yl}-acrylaldehyde (4): Under an inert atmosphere at –78 °C, DMSO (0.35 g, 0.0051 mol) was added dropwise to a solution of oxalyl chloride (0.87 g, 0.0066 mol) in dichloromethane (10 mL). After stirring for 15 min, a solution of **4** (1.2 g, 0.0045 mol) in dichloromethane (5 mL) was added dropwise. After stirring for 25 min, triethylamine (3.81 g, 0.031 mol) was added, and the reaction was stirred for an additional 20 min. After completion (monitored by TLC), the reaction mixture was warmed to room temperature, quenched with water (25 mL), and extracted with dichloromethane. The organic layer was washed with brine and dried with sodium sulfate. Removal of the solvent afforded the crude product (1.15 g). Purification by column chromatography (3% ethyl acetate in hexane) gave **4** (1.15 g, 96%) as colorless oil. Compound **4** is unstable.

(*S*,*E*)-1-{(4*S*,5*R*)-2,2-Dimethyl-5-[(*Z*)-oct-2-enyl]-1,3-dioxolan-4-yl}-hexa-1,5-dien-3-ol (3): Dried $Ti(OiPr)_4$ (0.17 mL, 0.0006 mol) was added to a stirred solution of $TiCl_4$ in (1 M in dichloromethane, 0.2 mL, 0.002 mol) in dichloromethane (5 mL) at 0 °C. The solution was warmed room temperature. After 1 h, silver(I) oxide (0.099 g, 0.0004 mol) was added, and the mixture was stirred for 5 h under the exclusion of direct light. The mixture was diluted with dichloromethane (3 mL), and treated with (*S*)-binaphthol (0.235 g, 0.0008 mol) at room temperature for 2 h to furnish chiral bis-Ti^{IV} oxide (*S*,*S*)-**I**. In situ generated (*S*,*S*)-**I** was cooled to –15 °C and treated sequentially with aldehyde **4** (1.06 g, 0.004 mol) and allyltributyltin (1.38 mL, 0.0044 mol). The mixture was warmed to 0 °C and stirred for 4 h. The reaction mixture was quenched with saturated sodium hydrogen carbonate and extracted with dichloromethane. The organic extracts were dried with sodium sulfate and concentrated to afford the crude product. Purification by column chromatography (7% ethyl acetate in hexane) gave **3** (1.05 g, 86%) as a colorless oil. The absolute configuration of the product was determined to be *S* with an enantiomeric purity of 98%*ee* by analytical HPLC analysis. $[\alpha]_D^{29} = -5$ (c = 1.2, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3458, 2926, 2858, 1726, 1641, 1460, 1379, 1220, 1165, 1110, 1057, 970, 913, 859, 773 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.86–5.71 (m, 2 H), 5.70–5.57 (m, 1 H), 5.53–5.33 (m, 2 H), 5.18–5.07 (m, 2 H), 4.23–4.11 (m, 1 H), 4.00 (t, J = 7.5 Hz, 1 H), 3.71–3.60 (m, 1 H), 2.35–2.25 (m, 4 H), 2.01 (q, J = 6.8 Hz, 2 H), 1.39 (s, 3 H), 1.38 (s, 3 H), 1.35–1.23 (m, 6 H), 0.90 (t, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.7, 133.8, 132.6, 127.7, 123.9, 118.5, 108.6, 81.2, 80.3, 70.9, 41.7, 31.5, 29.4, 29.2, 27.4, 27.1, 26.9, 22.5, 14.0 ppm. HRMS (ESI): calcd. for $C_{19}H_{32}O_3Na$ $[M + Na]^+$ 331.2249; found 331.2251.

(*S*,*E*)-1-{(4*S*,5*R*)-2,2-Dimethyl-5-[(*Z*)-oct-2-enyl]-1,3-dioxolan-4-yl}-hexa-1,5-dien-3-yl Hex-5-enoate (15): To a solution of 5-hexenoic acid (0.264 g, 0.0023 mol) in pyridine (10 mL) at 0 °C was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.296 g, 0.0015 mol) and 4-(dimethylamino)pyridine (0.009 g, 0.00008 mol). The resulting white cloudy suspension was warmed to room temperature and stirred until a clear solution formed. A solution of **3** (0.12 g, 0.0004 mol) in pyridine (1 mL) was added dropwise. After stirring for 16 h, the reaction mixture was concentrated to remove pyridine, aqueous 1 N HCl was added, and the mixture was extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with brine, dried, and the solvents were evaporated. Purification by column chromatography (2% ethyl acetate in hexane) gave **15** (0.144 g, 92%) as a colorless oil. $[\alpha]_D^{29} = +3$ (c = 0.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.80–5.58 (m, 4 H), 5.57–5.43 (m, 1 H), 5.42–5.34 (m, 1 H), 5.33–5.27 (m, 1 H), 5.12–5.03 (m, 2 H), 5.03–4.94 (m, 2 H), 4.01–3.95 (m, 1 H), 3.68–3.59 (m, 1 H), 2.42–2.23 (m, 6 H), 2.15–1.97 (m, 4 H), 1.78–1.68 (m, 2 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 1.42–1.24 (m, 6 H), 0.90 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5, 137.5, 132.9, 132.6, 131.9, 129.6, 123.7, 118.0, 115.3, 108.6, 81.0, 80.2, 72.3, 38.8, 33.6, 32.9, 31.4, 29.3, 29.1, 27.3, 27.0, 26.8, 24.0, 22.5, 14.0 ppm. HRMS (ESI): calcd. for $C_{25}H_{40}O_4Na$ $[M + Na]^+$ 427.2824; found 427.2819.

(4*S*,5*E*,7*S*,8*R*,10*Z*)-7,8-Dihydroxyhexadeca-1,5,10-trien-4-yl Hex-5-enoate (2): To a solution of compound **15** (0.12 g, 0.0003 mol) in methanol (6 mL) at 0 °C was added a catalytic amount of (–)-camphor-10-sulfonic acid. The reaction temperature was warmed to room temperature and stirred for 6 h. The reaction mixture was concentrated to remove the methanol and diluted with chloroform. Saturated sodium hydrogen carbonate solution was added, followed by extracting with chloroform, drying the organic layer with sodium sulfate, and concentrating the mixture to afford the crude product. Purification by column chromatography (12% ethyl acetate in hexane) gave **2** (0.09 g, 83%) as a colorless oil. $[\alpha]_D^{29} = -8$ (c = 0.5, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3440, 3077, 2925, 2858, 1734, 1642, 1459, 1379, 1245, 1170, 1072, 971, 916, 733 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.82–5.62 (m, 4 H), 5.59–5.46 (m, 1 H), 5.44–5.32 (m, 1 H), 5.31–5.21 (m, 1 H), 5.12–5.07 (m, 1 H), 5.07–4.93 (m, 3 H), 3.97–3.90 (m, 1 H), 3.49–3.39 (m, 1 H), 2.44–2.34 (m, 2 H), 2.33–2.16 (m, 4 H), 2.16–1.98 (m, 4 H), 1.77–1.65 (m, 2 H), 1.42–1.22 (m, 6 H), 0.90 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8, 137.6, 133.7, 133.0, 132.0, 130.8, 124.2, 118.1, 115.4, 74.3, 73.9, 72.8, 38.8, 33.7, 32.9, 31.4, 30.9, 29.2, 27.3, 24.0, 22.5, 14.0 ppm. HRMS (ESI): calcd. for $C_{22}H_{36}O_4Na$ $[M + Na]^+$ 387.2511; found 387.2509.

Topsentolide B_3 (1): To a solution Grubbs second generation catalyst (0.024 g, 0.000027 mol) in degassed anhydrous dichloromethane (70 mL) heated to reflux was added compound **2** (0.1 g, 0.00027 mol). After stirring for 0.5 h, the reaction was complete (monitored by TLC), quenched with ethyl vinyl ether (5 mL), warmed to room temperature, and concentrated under reduced pressure. Purification by column chromatography (13% ethyl acetate in hexane) gave **1** (0.072 g, 78%) as a colorless oil. $[\alpha]_D^{26} = +42$ (c = 0.1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3283, 1735, 970, 672 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.08–5.21 (m, 7 H), 4.45–4.37 (m, 1 H), 3.74–3.64 (m, 1 H), 2.58–2.29 (m, 4 H), 2.24–1.96 (m, 7 H), 1.80–1.66 (m, 1 H), 1.43–1.23 (m, 6 H), 0.90 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 135.0, 132.1, 132.0, 128.9, 125.0, 124.1, 74.0, 72.1, 66.0, 34.0, 33.5, 32.1, 31.0,

29.1, 27.0, 26.3, 24.9, 22.5, 13.2 ppm. HRMS (ESI): calcd. for $C_{20}H_{32}O_4Na$ $[M + Na]^+$ 359.2356; found 359.2349.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of all products.

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