Unified Total Synthesis, Stereostructural Elucidation, and Biological Evaluation of Sarcophytonolides

Hiroyoshi Takamura,*[,1] Takahiro Kikuchi,[1] Kohei Iwamoto,[1] Eiji Nakao,[1] Naoki Harada,[1] Taichi Otsu,[1] Noriyuki Endo,[2] Yuji Fukuda,[2] Osamu Ohno,[3] Kiyotake Suenaga,[4] Yue-Wei Guo,[5] and Isao Kadota[1]

[1]Department of Chemistry, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushimanaka, Kita-ku, Okayama 700-8530, Japan

[2]Himeji EcoTech Co., Ltd., 841-49 Koh, Shirahama-cho, Himeji 672-8023, Japan

[3]Department of Chemistry and Life Science, School of Advanced Engineering, Kogakuin University, 2665-1 Nakano, Hachioji 192-0015, Japan

[4]Department of Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

[5]Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Zhangjiang Hi-Tech Park, Shanghai 201203, China

takamura@cc.okayama-u.ac.jp

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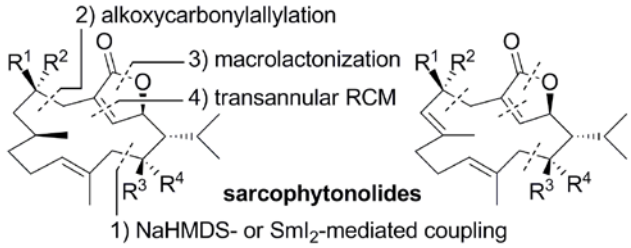


Abstract

Sarcophytonolides are cembranolide diterpenes isolated from the soft corals of genus *Sarcophyton*. Unified total synthesis of sarcophytonolides C, E, F, G, H, and J and isosarcophytonolide D was achieved. The synthetic routes feature NaHMDS- or SmI_2-mediated fragment coupling, alkoxycarbonylallylation, macrolactonization, and transannular ring-closing metathesis. These total syntheses led to the absolute configurational confirmation of sarcophytonolide H, elucidation of sarcophytonolides C, E, F, and G, and revision of sarcophytonolide J and isosarcophytonolide D. We also evaluated the antifouling activity and toxicity of the synthetic sarcophytonolides H and J and their analogues as well as the cytotoxicity of the synthetic sarcophytonolides and the key synthetic intermediates.

Introduction

Corals are an important group of marine invertebrates and have proven to be a rich source of secondary metabolites with a diversity of the chemical structure and biological activity.[1] Among natural products isolated from soft corals, cembranolide diterpenes[2] exhibit a variety of biological activities such as antibacterial,[3] antifouling,[4] antiviral,[5] cytotoxic,[6] ichthyotoxic,[7] and protein tyrosine phosphatase 1B inhibitory activities.[8] In addition, it has been reported that cembranoid diterpens are implicated in defense of soft corals against predators and

competition between soft corals and hard corals.[1a,9]

Guo and co-workers have isolated sarcophytonolides, cembranolide diterpenes, from the soft corals of the genus *Sarcophyton* collected at Hainan Province in China since 2005.[8,10] These natural products have a 14-membered carbon skeleton and butenolide unit as common structures as described in Figure 1. The gross structure of sarcophytonolide C (**1**) was determined by the 2D NMR analysis and comparison of its NMR data with those of brassicolide (**5**), of which the relative configuration was assigned by X-ray crystallographic analysis.[6b,10a] Although the relative stereochemistries at the C1 and C2 positions of **1** were elucidated by NOE observations between H-2 and H-15, the configuration at the C8 position, which is a chiral center remote from the C1 and C2 positions, could not be determined. The relative configurations at the C6 and C8 positions of sarcophytonolide E (**2**) were assigned by NOE correlations of H-6/H_3-19 and analysis of coupling constants and splitting patterns of H_2-5 in the model wherein a hydrogen bond between the hydroxy and the carbonyl groups is formed.[10b] The relative configurations of sarcophytonolides F (**3**) and G (**4**), which have the C7/C8 trisubstituted alkenes and the C6 stereoisomeric relationship, were revealed by NOE experiments and analysis of their coupling constants of H_2-5.[10b] The relative stereochemistry of sarcophytonolide H (**6**) was clarified by the similarity of ^{1}H and ^{13}C NMR data between **6** and **3** and NOE observations such as those of H-2/H-14 and H-2/H-15.[10b] The absolute configuration of **6** was determined by applying the modified Mosher method.[11] The relative stereochemistry of sarcophytonolide D (**7**) possessing the α-oriented acetoxy group at the C14 position was elucidated by NOE experiments.[10a,12] The relative stereochemistries at the C1, C2, and C14 positions of sarcophytonolides I (**8**),[10c] J (**9**),[10c] and isosarcophytonolide D (**10**)[10d] were assigned by the analogy of their ^{1}H and ^{13}C NMR data to those of sarcophytonolide D (**7**), whereas the C8 stereochemistry of **9** has remained to be clarified as in the case of sarcophytonolide C (**1**). Among these sarcophytonolides, sarcophytonolides H (**6**) and J (**9**) display the antifouling activity against the cypris larvae of the barnacle *Balanus* (*Amphibalanus*) *amphitrite* with EC_{50} values of 5.98[13] and 7.50 μg/mL,[14] respectively. Interestingly, there is also a report wherein sarcophytonolide J (**9**) has no inhibitory activity against the larval settlement of the same barnacle.[13] In 2013, as a preliminary communication, we reported the total synthesis of two possible diastereomers of sarcophytonolide C (**1**), which resulted in the absolute configurational determination of this natural product.[15a,16] In 2016, we also reported the total synthesis of sarcophytonolide H (**6**) and isosarcophytonolide D (**10**, proposed structure), which culminated in the absolute stereochemical confirmation of **6** and revision of **10**.[15b] In this full paper, we disclose the unified total synthesis of sarcophytonolides C, E, F, G, H, and J and isosarcophytonolide D by using NaHMDS- or SmI_2-mediated fragment coupling, alkoxycarbonylallylation, macrolactonization, and transannular ring-closing metathesis (RCM) as key steps. These total syntheses culminated in the absolute stereochemical confirmation of sarcophytonolide H, determination of sarcophytonolides C, E, F, and G, and revision of sarcophytonolide J and isosarcophytonolide

D. Furthermore, we report the cytotoxicity of the synthetic sarcophytonolides and the key synthetic intermediates, and the antifouling activity and toxicity of the synthetic sarcophytonolides H and J and their analogues.

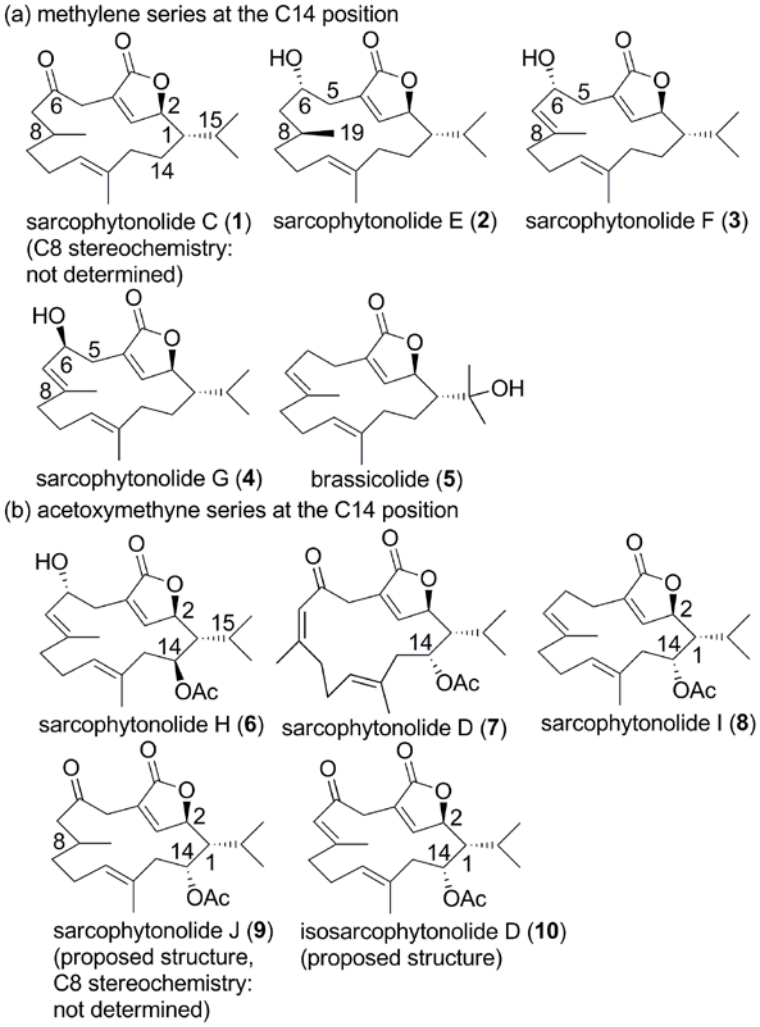


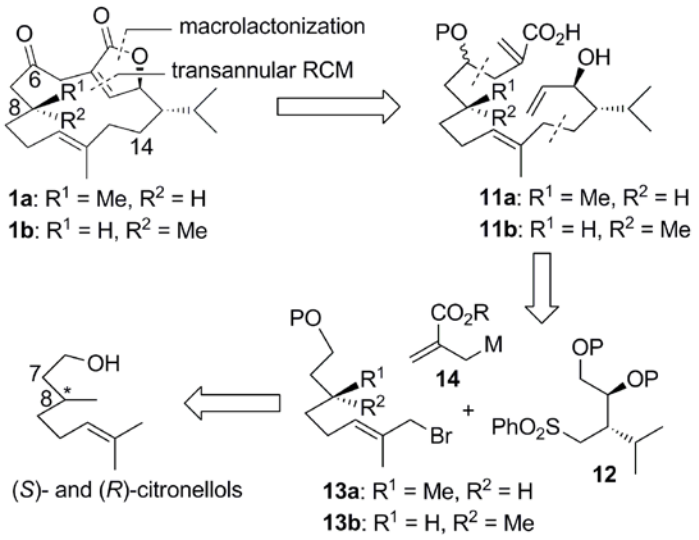
Figure 1. Structures of selected sarcophytonolides and brassicolide.

Results and Discussion

Retrosynthetic Analysis of 1a and 1b. Toward the absolute configurational determination of natural sarcophytonolide C (**1**), we decided to synthesize **1a** and **1b** (Scheme 1), which are two possible diastereomers of this natural product. In the retrosynthetic analysis, we designed hydroxycarboxylic acids **11a** and **11b** as the key synthetic intermediates to construct the cembranolide frameworks of **1a** and its C8 epimer **1b** by macrolactonization[17] and subsequent transannular RCM[18], respectively.[19] We hypothesized that the macrolactonization precursors **11a**,**b** could possibly supplied by the connection of sulfone **12**, allylic bromides **13a** and **13b**, and 2-alkoxycarbonyl allylic metal reagent **14**. The chiral pool synthesis starting from (*S*)- and (*R*)-citronellols could provide the allylic bromides **13a**,**b**, respectively. We envisioned that this retrosynthetic bond-disconnection could be also applied to the synthesis of C6 hydroxylated and/or C14 acetoxylated sarcophytonolides. Moreover, the use of geraniol and nerol instead of citronellol as starting materials would potentially lead to the total synthesis of

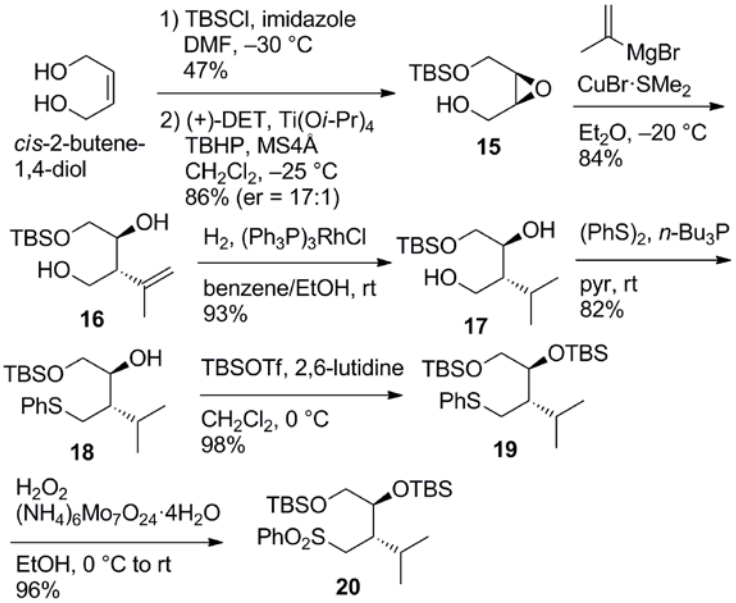
sarcophytonolides bearing the C7/C8 trisubstituted alkene moieties.

Scheme 1. Retrosynthetic Analysis of 1a and 1b



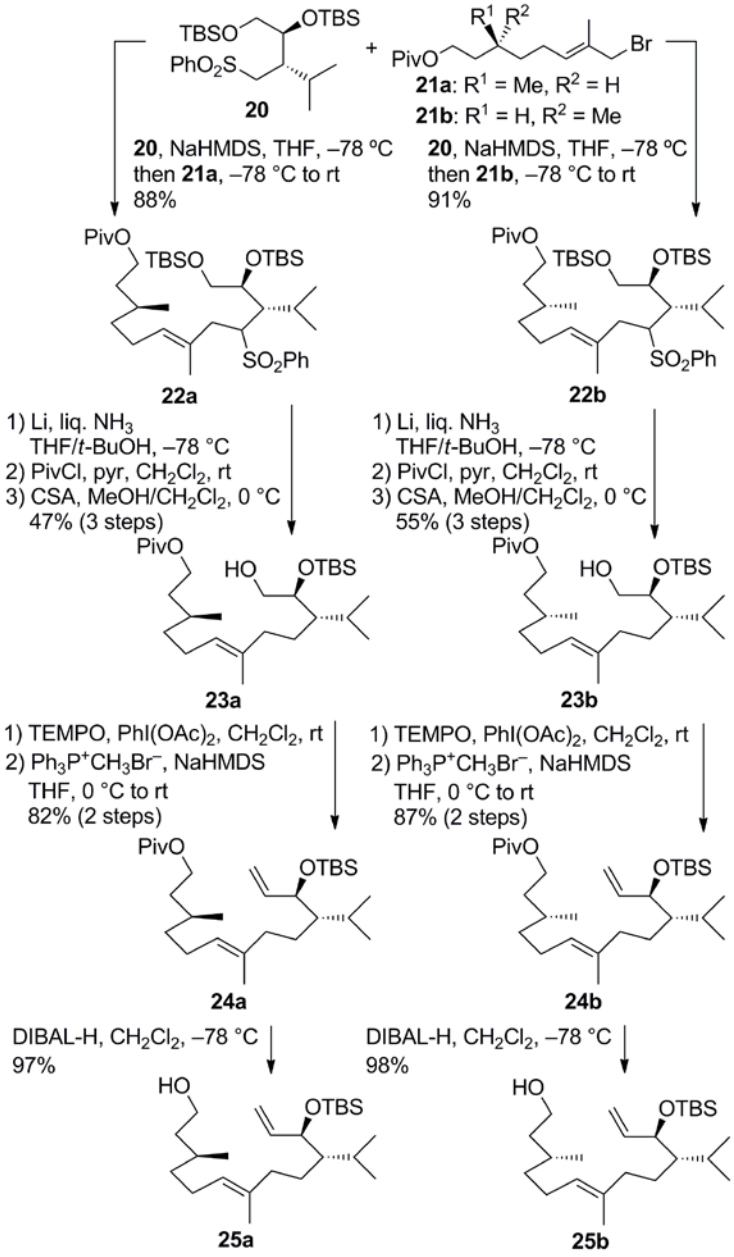
Total Synthesis of Two Possible Diastereomers 1a and 1b of Sarcophytonolide C (1). First, we investigated the enantioselective synthesis of sulfone **20** (Scheme 2). Monosilylation of *cis*-2-butene-1,4-diol with *tert*-butyldimethylsilyl chloride (TBSCl) followed by Sharpless asymmetric epoxidation[20] with (+)-diethyl tartrate (DET) gave epoxy alcohol **15** in 86% yield. The enantiomeric ratio of 17:1 was assigned by the ^{1}H NMR spectra of (*S*)- and (*R*)-α-methoxy-β-(trifluoromethyl)phenylacetyl (MTPA) esters prepared from **15**. The epoxide **15** reacted with isopropenylmagnesium bromide in the presence of $CuBr{\cdot}SMe_2$[21] to provide 1,3-diol **16**, regioselectively.[22] Hydrogenation of the alkene **16** with $(Ph_3P)_3RhCl$ and subsequent selective thioetherification of diol **17**[23] with $(PhS)_2$/*n*-Bu_3P afforded sulfide **18**. After the alcohol **18** was protected as the TBS ether, sulfide **19** was oxidized to furnish the sulfone **20**.[24]

Scheme 2. Synthesis of Sulfone 20



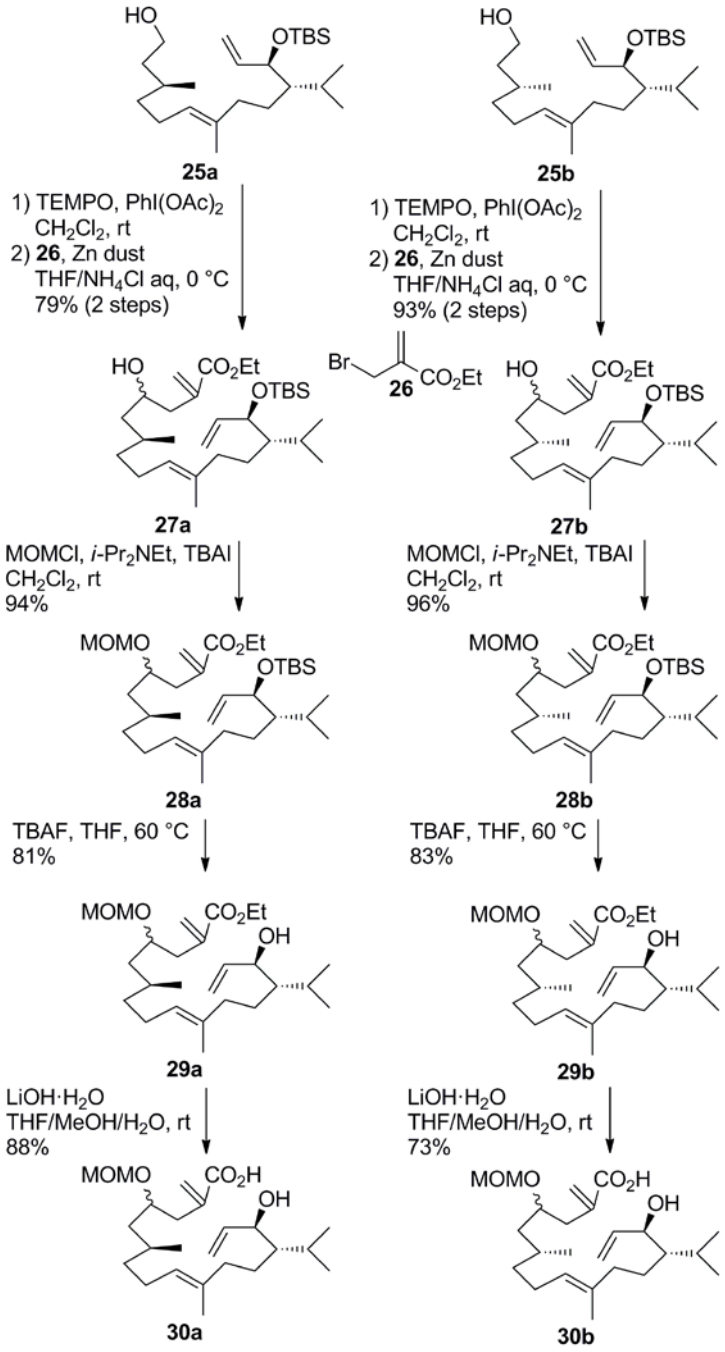
Next, connection of the sulfone **20** and allylic bromides **21a** and **21b**, which were synthesized from (*S*)- and (*R*)-citronellols,[25] was examined (Scheme 3). Thus, the anion derived from **20** with sodium hexamethyldisilazide (NaHMDS) was treated with the optically active **21a** and **21b** to produce the coupling products **22a** and **22b** in 88% and 91% yields, respectively. Reductive removal of the sulfonyl groups of **22a**,**b** under Birch conditions,[26] wherein the pivaloyl (Piv) groups were partially removed,[27] and protection of the resulting alcohols afforded the corresponding pivalates. The primary TBS ethers were selectively deprotected with camphorsulfonic acid (CSA) to give alcohols **23a** and **23b**. Oxidation of **23a**,**b** with 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO)/PhI(OAc)$_2$[28] and subsequent Wittig reaction yielded alkenes **24a** and **24b**. Reductive deprotection of the pivalates **24a**,**b** was carried out with diisobutylaluminum hydride (DIBAL-H) to provide alcohols **25a** and **25b**.

Scheme 3. Synthesis of Alcohols 25a and 25b

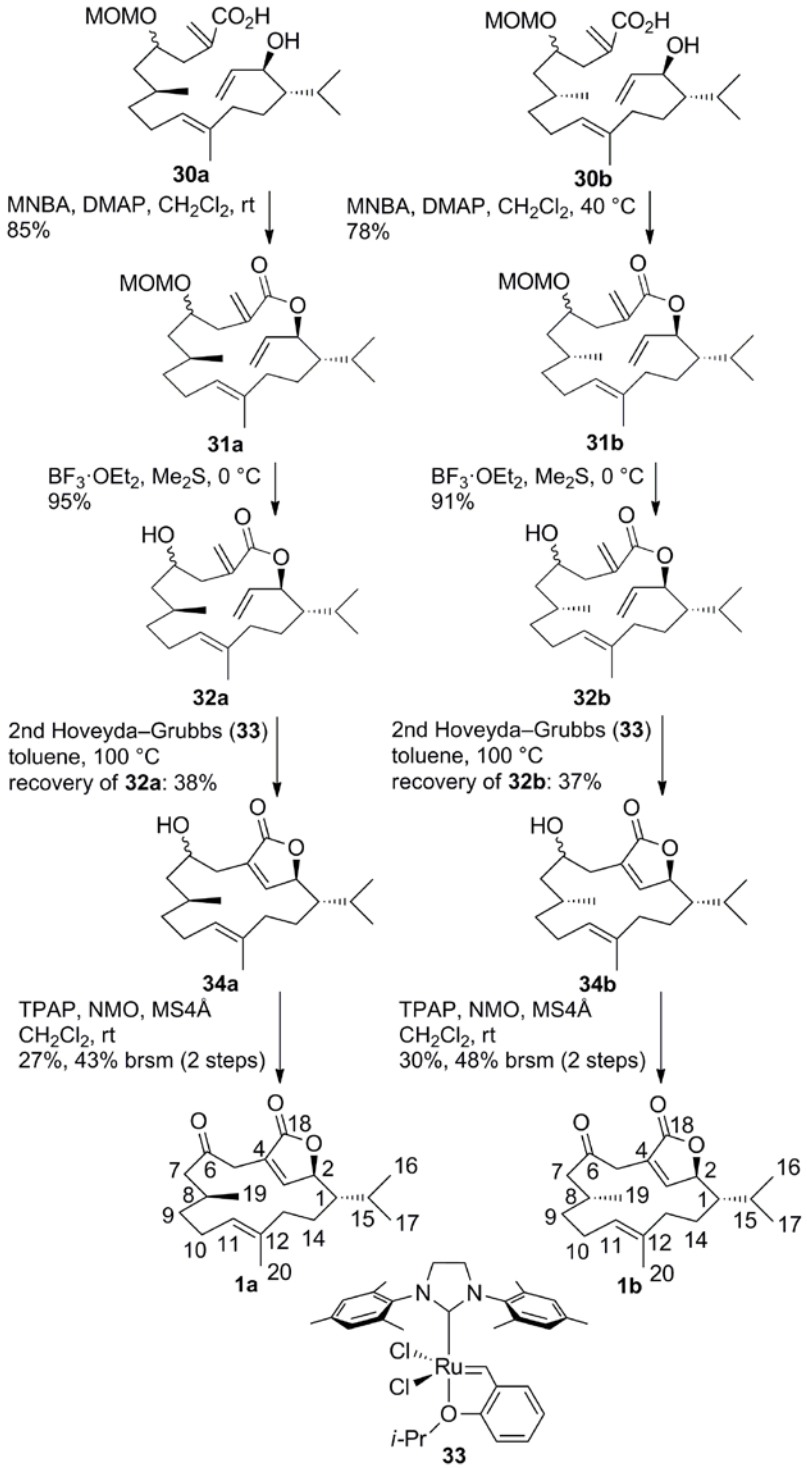


We next tried to synthesize the macrolactonization precursors **30a** and **30b** as shown in Scheme 4. The alcohols **25a**,**b** were oxidized with TEMPO/PhI(OAc)$_2$[28] and the resulting aldehydes were treated with ethyl (2-bromomethyl)acrylate (**26**)/Zn dust in THF/aqueous NH_4Cl[29] to furnish the desired homoallylic alcohols **27a** and **27b** in 79% and 93% yields in two steps as 1:1 diastereomeric mixtures, respectively. After the resulting hydroxy groups of **27a**,**b** were protected as the methoxymethyl (MOM) ethers, the TBS moieties of **28a** and **28b** were removed with tetrabutylammounium fluoride (TBAF) to give alcohols **29a** and **29b**. Alkaline hydrolysis of the ethyl esters **29a**,**b** with LiOH·H_2O afforded hydroxycarboxylic acids **30a** and **30b**.

Scheme 4. Synthesis of Hydroxycarboxylic Acids 30a and 30b



Scheme 5. Completion of the Total Synthesis of 1a and 1b



With the macrolactonization precursors **30a** and **30b** in hand, we next investigated the construction of the cembranolide framework and completion of the total synthesis. Thus, the hydroxycarboxylic acids **30a**,**b** were subjected to the Shiina macrolactonization conditions with 2-methyl-6-nitrobenzoic anhydride (MNBA)[17,30] to give 15-membered macrolactones **31a** and **31b** in 85% and 78% yields, respectively (Scheme 5). After the MOM ethers **31a**,**b** were deprotected with $BF_3{\cdot}OEt_2/Me_2S$,[31] transannular RCM[18] of **32a** and **32b** was conducted by using the second-generation Hoveyda–Grubbs catalyst (**33**)[32] to produce butenolides **34a**

and **34b**.[33,34] In these reactions, the prolonged reaction time caused the formation of byproducts, therefore the starting materials **32a** and **32b** were recovered in 38% and 37% yields, respectively. Finally, TPAP (tetra-*n*-propylammonium perruthenate) oxidation[35] of **34a**,**b** provided the target molecules **1a** and **1b** in 27% (43% based on recovered **32a**) and 30% (48% based on recovered **32b**) in two steps, respectively.[36]

Absolute Configuration of Sarcophytonolide C (1). Having succeeded in the total synthesis of **1a** and **1b**, we analyzed their 2D NMR spectra and assigned the signals in their ^{1}H and ^{13}C NMR spectra. Tables 1 and 2 depict the chemical shifts and their differences of natural sarcophytonolide C (**1**)[10a] and the synthetic products **1a** and **1b** in the ^{1}H and ^{13}C NMR spectra, respectively. The ^{1}H and ^{13}C NMR data of **1a** were in excellent agreement with those of natural sarcophytonolide C (**1**), meanwhile the ^{1}H and ^{13}C NMR data of **1b** were clearly different from those of natural product **1**. It was found that there were critical differences of the chemical shifts between the natural product and the synthetic **1b** at the C7, C8, and C9 positions in the ^{1}H NMR data and at the C9, C10, and C11 positions in the ^{13}C NMR data. The sign of specific rotation of the synthesized **1a**, $[\alpha]_D^{29}$ = +92.2 (*c* = 0.19, $CHCl_3$), was same as that of the data reported for the natural product, $[\alpha]_D^{20}$ = +31.0 (*c* = 0.20, $CHCl_3$).[10a,37] Therefore, the absolute configuration of sarcophytonolide C (**1**) isolated from nature was clarified to be 1*S*, 2*S*, and 8*S* as shown in **1a**.

Table 1. ^{1}H NMR Chemical Shifts and Their Deviations of Natural Sarcophytonolide C (1) and the Synthetic Products 1a and 1b[a]

position	**1**[b]	**1a**	**1b**	$\Delta(\delta_{\mathbf{1}}-\delta_{\mathbf{1a}})$	$\Delta(\delta_{\mathbf{1}}-\delta_{\mathbf{1b}})$
1	1.46	1.47	1.51	–0.01	–0.05
2	4.81	4.81	4.85	0.00	–0.04
3	7.26	7.26	7.28	0.00	–0.02
5	3.50	3.50	3.39	0.00	+0.11
	3.16	3.16	3.20	0.00	–0.04
7	2.37	2.37	2.56	0.00	–0.19
	2.37	2.37	2.09	0.00	+0.28
8	1.74	1.74	1.87	0.00	–0.13
9	1.38	1.37	1.42	+0.01	–0.04
	1.36	1.37	1.20	–0.01	+0.16
10	2.12	2.11	2.05	+0.01	+0.07
	1.95	1.94	2.05	+0.01	–0.10
11	4.97	4.97	5.05	0.00	–0.08
13	2.10	2.10	2.03	0.00	+0.07
	1.93	1.94	2.03	–0.01	–0.10
14	1.58	1.59	1.56	–0.01	+0.02
	1.14	1.14	1.18	0.00	–0.04

15	2.08	2.10	2.05	–0.02	+0.03
16	0.99	1.00	1.03	–0.01	–0.04
17	1.00	1.01	1.04	–0.01	–0.04
19	0.93	0.93	0.92	0.00	+0.01
20	1.60	1.61	1.59	–0.01	+0.01

[a]NMR spectra of the natural product and the synthetic products were recorded at 400 MHz. Chemical shifts are reported in ppm with reference to the internal residual solvent ($CDCl_3$, 7.26 ppm). [b]Data from reference 10a.

Table 2. ^{13}C NMR Chemical Shifts and Their Deviations of Natural Sarcophytonolide C (1) and the Synthetic Products 1a and 1b[a]

position	**1**[b]	**1a**	**1b**	$\Delta(\delta_{\mathbf{1}}-\delta_{\mathbf{1a}})$	$\Delta(\delta_{\mathbf{1}}-\delta_{\mathbf{1b}})$
1	45.8	45.9	45.8	–0.1	0.0
2	83.7	83.6	83.3	+0.1	+0.4
3	151.3	151.1	152.0	+0.2	–0.7
4	127.4	127.4	128.2	0.0	–0.8
5	40.3	40.3	39.9	0.0	+0.4
6	205.9	205.7	205.8	+0.2	+0.1
7	50.0	50.0	50.1	0.0	–0.1
8	28.6	28.6	28.4	0.0	+0.2
9	35.7	35.7	36.8	0.0	–1.1
10	24.3	24.4	25.3	–0.1	–1.0
11	127.1	127.0	128.2	+0.1	–1.1
12	133.9	133.8	133.3	+0.1	+0.6
13	38.7	38.8	38.2	–0.1	+0.5
14	23.2	23.3	23.6	–0.1	–0.4
15	29.5	29.6	29.4	–0.1	+0.1
16	18.4	18.5	19.3	–0.1	–0.9
17	19.9	20.0	19.8	–0.1	+0.1
18	172.8	172.6	172.7	+0.2	+0.1
19	20.7	20.7	19.9	0.0	+0.8
20	16.1	16.1	16.0	0.0	+0.1

[a]NMR spectra of the natural product and the synthetic products were recorded at 100 MHz. Chemical shifts are reported in ppm with reference to the internal residual solvent ($CDCl_3$, 77.0 ppm). [b]Data from reference 10a.

Calculations for **1a** and **1b** were carried out using density functional theory (DFT) calculations at the ωB97X-D/6-31G* level. Conformational analysis and geometry optimization of **1a** and **1b** were performed with the package SPARTAN'16 (Wavefunction Inc., Irvine, CA). As described in Figure 2, in the calculated most stable conformer of **1a**, the

C8 carbon is located more inside the macrocycle structure in comparison with the case of the most stable conformer of **1b**, which seems to make the distances between C1/C2 and C8 in **1a** shorter than those in **1b**. This conformational difference of **1a** and **1b** may have resulted in the deviation in their NMR data in spite of the C8 stereocenter remote from the C1 and C2 positions.

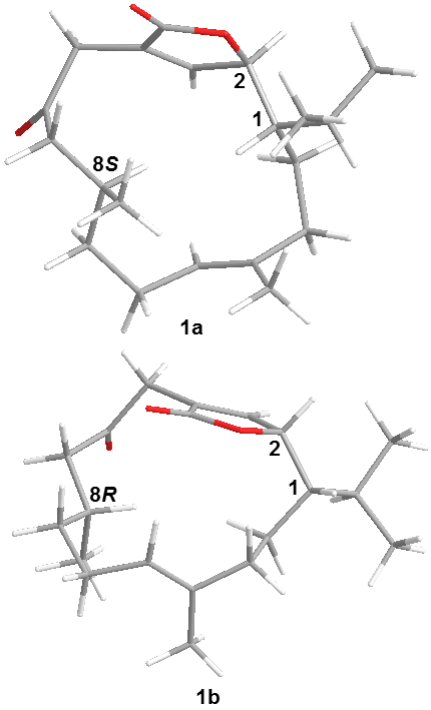
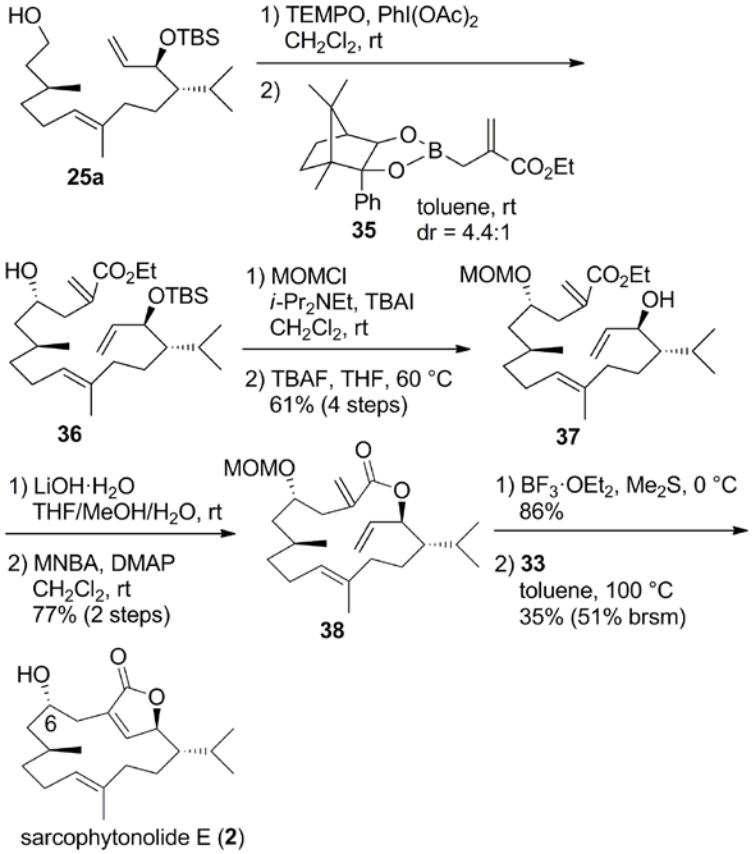


Figure 2. Calculated lowest-energy conformers of **1a** (above) and **1b** (below).

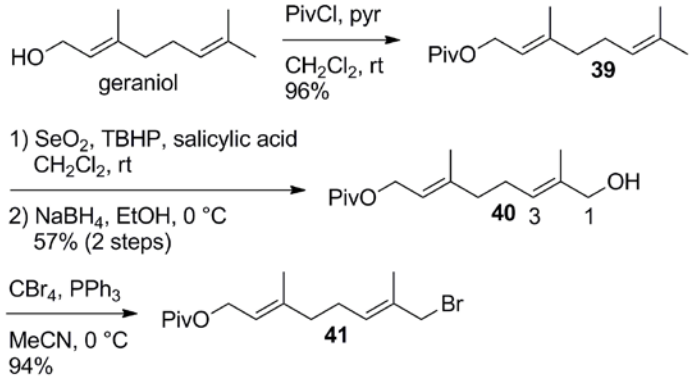
Total Synthesis of Sarcophytonolide E (2). Next, we examined the stereoselective synthesis of sarcophytonolide E (**2**) possessing the chiral alcohol moiety at the C6 position. First, we surveyed the reaction conditions in asymmetric alkoxycarbonylallylation of the aldehyde prepared from the alcohol **25a** and it was proven that treatment of the aldehyde with chiral allylic boronate **35**[38] in toluene at room temperature provided the desired alcohol **36** in a 4.4:1 diastereomeric ratio (Scheme 6).[22] Further transformation from **36** to sarcophytonolide E (**2**) was identical to that used for the total synthesis of **1a** and **1b**. Thus, MOM protection of the resulting hydroxy group of **36** and removal of the TBS moiety afforded alcohol **37**. Alkaline hydrolysis of the ethyl ester **37** followed by Shiina macrolactonization[17,30] yielded 15-membered macrolactone **38**. Deprotection of the MOM ether **38** with $BF_3{\cdot}OEt_2/Me_2S$[31] and subsequent transannular RCM[18] produced sarcophytonolide E (**2**).[39] The ^1H and ^{13}C NMR data and the specific rotation of the synthesized **2** were in good accordance with those of the natural product,[10b,40] which elucidated the absolute stereochemistry of natural sarcophytonolide E to be that described in **2**.

Scheme 6. Total Synthesis of Sarcophytonolide E (2)



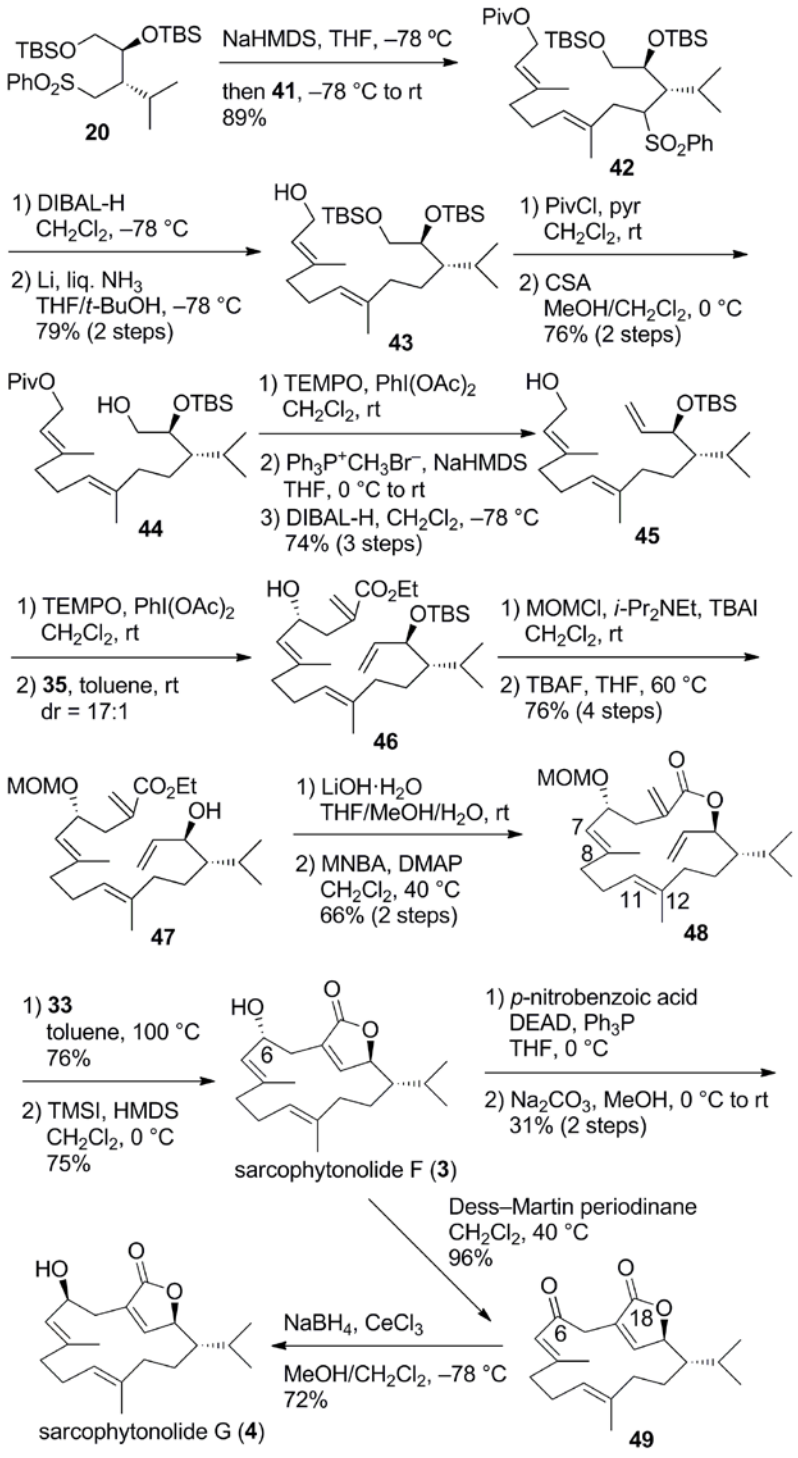
Total Synthesis of Sarcophytonolides F (3) and G (4). Having completed the total synthesis of **1a**, **1b**, and **2** bearing the chiral centers at the C8 positions, we next investigated the stereoselective synthesis of sarcophytonolides F (**3**) and G (**4**) with the C7/C8 (*E*)-trisubstituted alkene portions. First, as shown in Scheme 7, the synthesis of allylic bromide **41**, which is a coupling partner of the sulfone **20**, was carried out. Protection of geraniol with PivCl gave pivalate **39**. Treatment of **39** with SeO_2/TBHP/salicylic acid[41] provided the mixture of allylic alcohol **40** and the corresponding α,β-unsaturated aldehyde. The mixture was treated with $NaBH_4$ to afford the allylic alcohol **40** in 57% yield in two steps. The structure of **40** was confirmed by NOE observations of H_2-1/H-3. The allylic alcohol **40** was converted to the allylic bromide **41** with CBr_4/PPh_3.

Scheme 7. Synthesis of Allylic Bromide 41



We next tried the connection of the sulfone **20** and the allylic bromide **41**, and transformation to sarcophytonolides F (**3**) and G (**4**). Thus, the sulfone **20** was coupled with the allylic bromide **41** in the presence of NaHMDS to afford the desired product **42** (Scheme 8). After deprotection of the pivalate **42** with DIBAL-H, reductive desulfonylation was conducted under Birch conditions[26] to give alcohol **43** in 79% yield in two steps.[42] The alcohol **43** was converted to alkene **45** by the following sequence: 1) protection as the pivalate, 2) selective removal of the primary TBS moiety, 3) TEMPO oxidation[28] of alcohol **44**, 4) Wittig methylenation, and 5) deprotection of the pivalate. The aldehyde, synthesized from the alcohol **45**, was treated with the chiral allylic boronate **35**[38] to result in the diastereoselective formation of alcohol **46** in a 17:1 ratio.[22] After protection of the alcohol **46** and subsequent desilylation, hydrolysis of **47** and Shiina lactonization[17,30] were carried out to afford macrolactone **48**. Transannular RCM[18] of the tetraene **48** proceeded smoothly in the presence of the second-generation Hoveyda–Grubbs catalyst (**33**),[32] wherein two trisubstituted alkene portions of **48** were inert to the reaction conditions, to produce the corresponding butenolide in 76% yield. Finally, the MOM protecting group was cleaved with trimethylsilyl iodide (TMSI)/HMDS[43,44] to furnish sarcophytonolide F (**3**). We next tried to transform sarcophytonolide F (**3**) to sarcophytonolide G (**4**) by stereoinversion at the C6 position. Mitsunobu reaction[45] of **3** with *p*-nitrobenzoic acid/diethyl azodicarboxylate (DEAD)/Ph_3P[46] followed by alkaline hydrolysis with Na_2CO_3 in MeOH provided sarcophytonolides G (**4**) and F (**3**) in 31% and 13% yields in two steps, respectively. The formation of **3** was caused by the esterification with stereoretention in the first step.[47] Changing reaction temperature and carboxylic acid in Mitsunobu reaction[45] could not improve the chemical yield of **4**. Therefore, we next examined the stereoselective reduction of the ketone. Treatment of the allylic alcohol **3** with Dess–Martin periodinane[48] gave α,β-unsaturated ketone **49**. Corey–Bakshi–Shibata (CBS) reduction[49] using (*R*)-Me-CBS/$BH_3{\cdot}SMe_2$ was applied to **49** to result in the formation of **4** and **3** in a 1:1 diastereomeric ratio. After investigation of the reaction conditions, fortunately, Luche reduction conditions[50] in MeOH/CH_2Cl_2 was found to be effective and sarcophytonolide G (**4**) was produced in 72% yield as a sole product. Although the detailed conformational analysis of **49** was not conducted, the stereochemical outcome in this Luche reduction is understandable by the formation of chelation structure as described in Figure 3. In this structure, the proton of methanol could coordinate to two carbonyl oxygens at the C6 and C18 positions and hydride could approach from the outside of the macrocyclic structure. Detailed comparison of the NMR data and specific rotations between the natural products[10b] and the synthetic products in **3** and **4** revealed the absolute configurations of natural sarcophytonolides F and G to be those shown in **3** and **4**, respectively.[40]

Scheme 8. Total Synthesis of Sarcophytonolides F (3) and G (4)



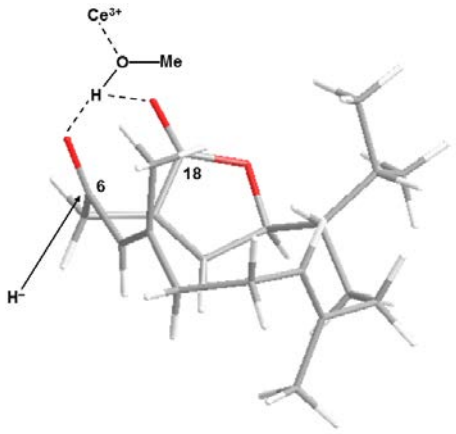
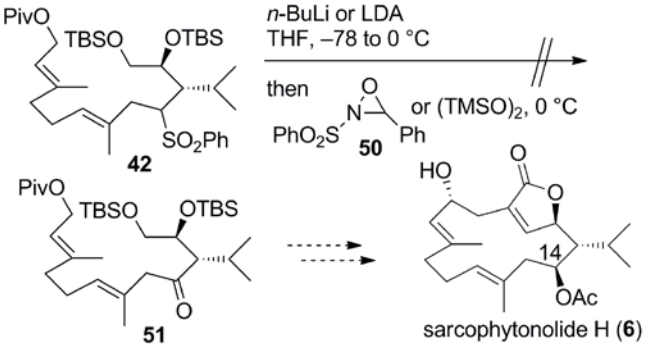


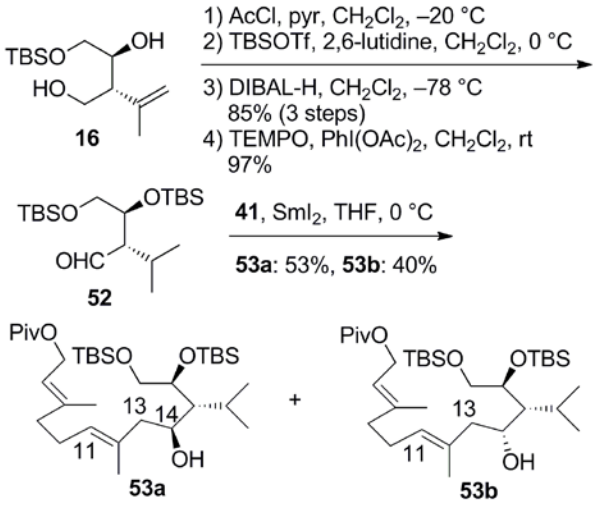
Figure 3. Plausible rationale for the configurational outcome in Luche reduction of ketone **49**.

Total Synthesis of Sarcophytonolide H (6). We next focused on the total synthesis of sarcophytonolides possessing the acetoxy groups at their C14 positions. First, we tried to synthesize sarcophytonolide H (**6**). We initially envisioned that the oxygen-functional group at the C14 position could be introduced by oxidative desulfurization of the sulfone **42**, which is the synthetic intermediate of the total synthesis of sarcophytonolides F (**3**) and G (**4**). Actually, deprotonation of **42** with *n*-BuLi or lithium diisopropylamide (LDA) and subsequent treatment with Davis oxaziridine (**50**)[51] or bis(trimethylsilyl)peroxide[52] did not produce the desired ketone **51** (Scheme 9). Therefore, we planned to introduce the C14 oxymethyne moiety by other fragment couplings. Our synthesis of the C14 stereoisomers **53a** and **53b**, wherein the SmI_2-mediated reaction[53] was used as the fragment coupling, is described in Scheme 10. Selective acetylation of the diol **16** followed by TBS protection of the resulting secondary alcohol gave the corresponding silyl ether. Reductive deprotection of the acetate with DIBAL-H afforded the alcohol, which was oxidized to aldehyde **52** with TEMPO/PhI(OAc)$_2$.[28] The aldehyde **52** was connected with the allylic bromide **41** by using SmI_2[53,54] to furnish the desired α-adducts **53a** and **53b** in 53% and 40% yields, respectively. It is noteworthy that the coupling was successful by using 1.2 equiv of the allylic bromide **41** to the aldehyde **52** and the corresponding γ-allylated product was not formed at all.[55] The observed NOEs of H-11/H$_2$-13 of **53a** and **53b** confirmed the geometries at their C11/C12 alkene portions, respectively. The stereochemistry at the C14 position of **53a** was determined by the modified Mosher method.[11,40]

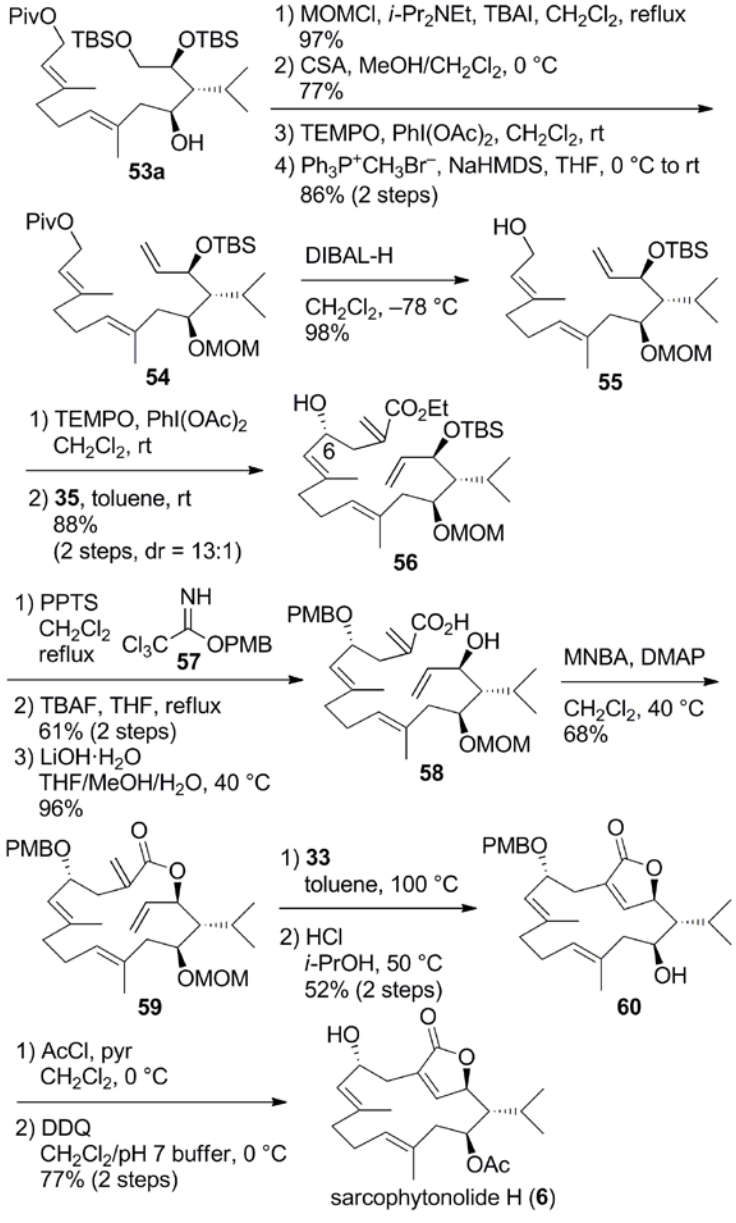
Scheme 9. Unsuccessful Attempt for Oxidative Desulfurization of Sulfone 42



Scheme 10. Synthesis of Alcohols 53a and 53b



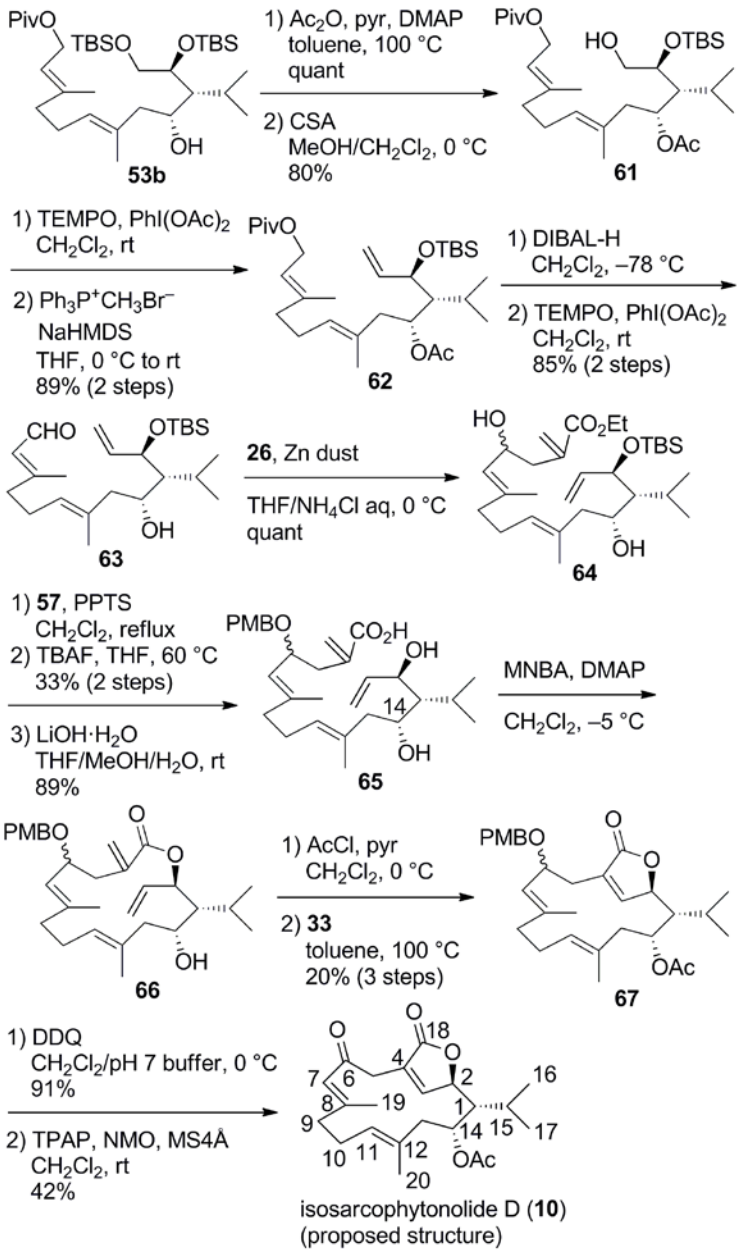
Scheme 11. Total Synthesis of Sarcophytonolide H (6)



Further transformation toward the total synthesis of sarcophytonolide H (**6**) is depicted in Scheme 11. Thus, protection of the hydroxy group of **53a** with MOMCl and subsequent selective removal of the primary TBS moiety gave the corresponding alcohol. Introduction of the terminal alkene portion followed by deprotection of the obtained pivalate **54** afforded alcohol **55**. TEMPO oxidation[28] of **55** and reaction of the aldehyde with the chiral boronate **35**[38] provided the desired allylated product **56** in 88% yield in two steps in a diastereomeric ratio of 13:1. After the C6 hydroxy group of **56** was protected as the *p*-methoxybenzyl (PMB) ether, the TBS ether underwent deprotection and hydrolysis of the ester to yield hydroxycarboxylic acid **58**. Shiina macrolactonization[17,30] and subsequent transannular RCM[18] were successfully performed to produce the corresponding butenolide. The obtained MOM ether was selectively deprotected with HCl in *i*-PrOH[56] to provide alcohol **60**. Finally, acetylation of the alcohol **60** and removal of the PMB moiety with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) took place to furnish sarcophytonolide H (**6**). The synthetic sarcophytonolide H (**6**) was in full agreement with the natural product in the ^{1}H and ^{13}C NMR data and the specific rotation.[10b,40] Therefore, the absolute configuration of natural sarcophytonolide H was confirmed as shown in **6**.

Total Synthesis and Structural Revision of Isosarcophytonolide D. We next investigated synthesis of the proposed structure **10** of isosarcophytonolide D with the 14*R* stereochemistry. Thus, as shown in Scheme 12, the alcohol **53b** was converted to **10** in 15 steps by a synthetic route similar to that used toward the total synthesis of sarcophytonolide H (**6**).[57] Having synthesized the proposed structure **10** of isosarcophytonolide D, we analyzed the 2D NMR data of the synthetic product **10**. As a result, the significant differences in the ^{1}H and ^{13}C NMR data between natural isosarcophytonolide D[10d] and the synthesized **10** were observed.[40] The detailed comparison revealed that the chemical shift deviations were especially critical around the C14 position (Figure 4). We also considered that the stereochemistries at the C1 and C2 positions of isosarcophytonolide D would be same as those of other sarcophytonolides. Therefore, we predicted the correct structure of isosarcophytonolide D isolated from nature to be that drawn in **68**, which is the C14 stereoisomer of **10** (Scheme 13). The predicted structure **68** was synthesized by oxidation of the synthetic sarcophytonolide H (**6**) with Dess–Martin periodinane.[48] As anticipated, the ^{1}H and ^{13}C NMR data and the specific rotation of the synthetic **68** matched those of the natural product.[10d,40] Therefore, the absolute configuration of natural isosarcophytonolide D was reassigned to be that shown in **68**.[58]

Scheme 12. Total Synthesis of the Proposed Structure 10 of Isosarcophytonolide D



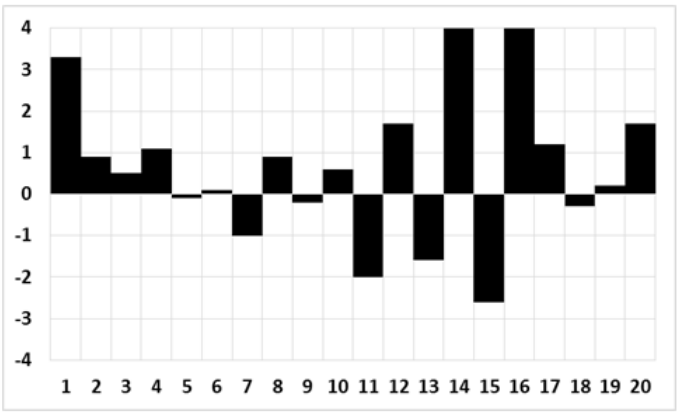
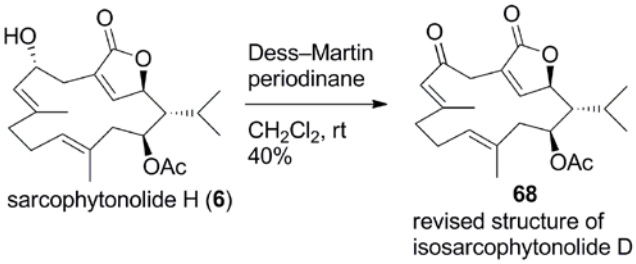


Figure 4. Deviations of the ^{13}C NMR chemical shifts between natural isosarcophytonolide D and the synthetic product **10** ($\Delta\delta = \delta_N - \delta_{10}$ in ppm). N = natural product. The x and y axes represent the carbon number and $\Delta\delta$, respectively.

Scheme 13. Synthesis of the Predicted Structure 68 of Isosarcophytonolide D



Structural Prediction, Total Synthesis, and Structural Determination of Sarcophytonolide J. As noted in Introduction, the relative configurations at the C1, C2, and C14 positions of natural sarcophytonolides I (**8**), J (**9**), and isosarcophytonolide D (**10**) were determined by the similarity of their NMR data to those of sarcophytonolide D (**7**). This way of structural assignment and the stereochemical revision at the C14 position of isosarcophytonolide D indicate that the C14 stereochemistries of sarcophytonolides D (**7**), I (**8**), and J (**9**), which were originally assigned as 14*R*, should be also reexamined. Therefore, we next decided to verify the stereostructure of sarcophytonolide J (**9**, Figure 5a), of which the C8 configuration was not identified. First, in order to predict the C14 stereochemistry of sarcophytonolide J, we compared the ^{1}H and ^{13}C NMR data of natural sarcophytonolide J[10c] with those of the synthetic products **68** (revised structure of isosarcophytonolide D) and **10** (C14 epimer of **68**).[40] Deviations of the ^{13}C NMR chemical shifts at the C1, C2, C13, and C14 positions between natural sarcophytonolide J and the synthetic products **68** and **10** are graphically depicted in Figure 5b. From these comparisons, it was found that the chemical shift differences between natural sarcophytonolide J and **68** were smaller than those between natural sarcophytonolide J and **10**. In addition, for the prediction of the C8 stereochemistry of sarcophytonolide J, the ^{1}H and ^{13}C NMR data between natural sarcophytonolide J[10c] and the synthetic products **1a** (sarcophytonolide C) and **1b** (C8 epimer of **1a**) were compared.[40] As a result, it was elucidated that the chemical shift characteristics at the C7 to C10 positions of **1a** were more similar to those of **1b**. Taken together, we could propose the predicted structure **69** of sarcophytonolide J (Figure 6), which bears the 8*S* and 14*S* absolute configurations same as those of **1a** and **68**.

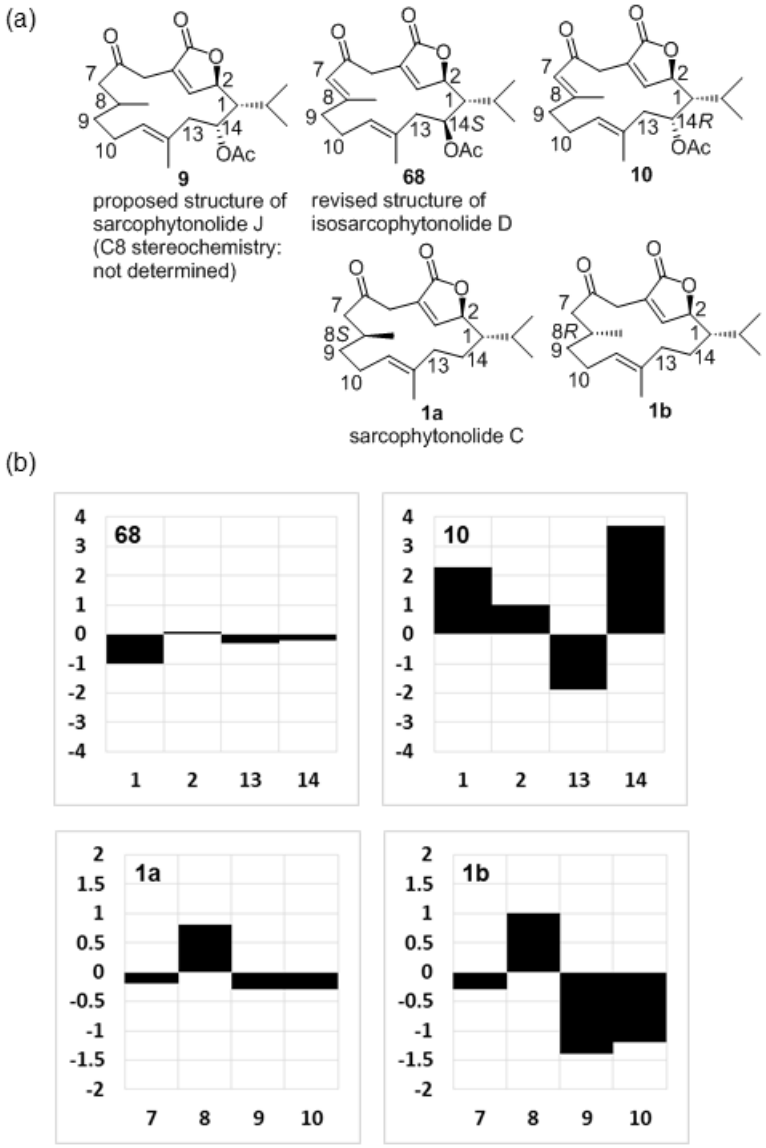


Figure 5. (a) Structures of **9**, **68**, **10**, **1a**, and **1b**. (b) Deviations of the ^{13}C NMR chemical shifts between natural sarcophytonolide J and the synthetic products ($\Delta\delta = \delta_N - \delta_S$ in ppm). N = natural product. S = synthetic product. The x and y axes represent the carbon number and $\Delta\delta$, respectively.

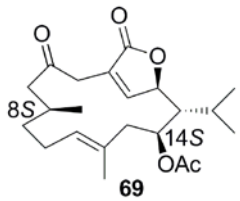
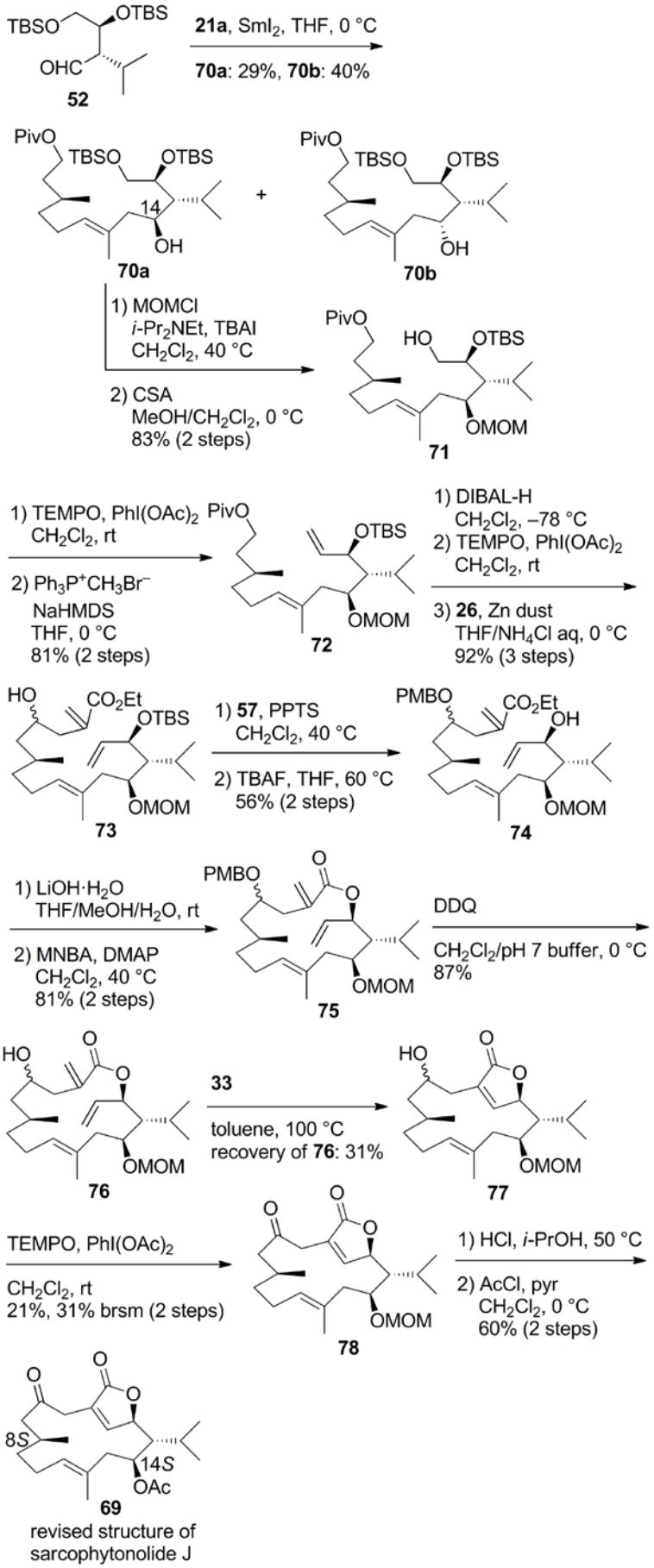


Figure 6. Predicted structure **69** of sarcophytonolide J.

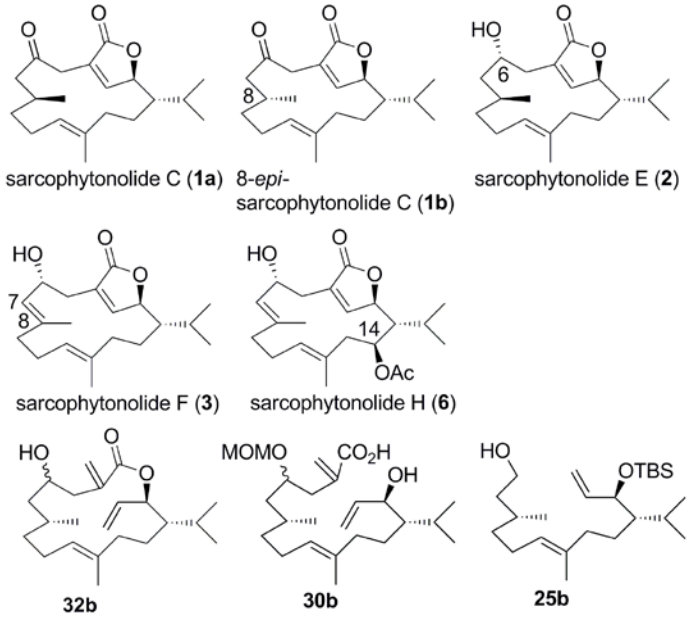
Scheme 14. Total Synthesis of the Predicted Structure 69 of Sarcophytonolide J



In order to confirm our stereostructural prediction of sarcophytonolide J as discussed above, we commenced the total synthesis of the predicted structure **69**. Sequence of the transformation toward **69** was similar to that used toward the total synthesis of sarcophytonolide H (**6**). Thus, SmI_2-mediated reaction of the aldehyde **52** and the allylic bromide **21a** gave the desired product **70a** and its C14 epimer **70b** in 29% and 40% yields, respectively (Scheme 14). The absolute stereochemistry at the C14 position of **70a** was verified by its derivatization and NOE experiments.[40] Subsequently, the alcohol **70a** was transformed to our predicted structure **69** of sarcophytonolide J in overall 16 steps. As expected, the synthetic **69** provided the ^1H and ^{13}C NMR data and the specific rotation which were identical to those reported for natural sarcophytonolide J.[10c,40] These findings clearly revealed that our stereochemical prediction of sarcophytonolide J is correct and this natural product possesses the 8*S* and 14*S* absolute configurations as shown in **69**.

Cytotoxicity of the Synthetic Products. Having successfully completed the total synthesis and established the stereostructures of sarcophytonolides, we next turned our attention to assessment of the biological activity of the synthetic products. First, we evaluated the growth-inhibitory activity by using the MTT assay with HL60 human leukemia cells. The cells were treated in 96-well plates with various concentrations of the synthetic compounds for 72 h. As described in Table 3, interestingly, the synthetic sarcophytonolide C (**1a**) was inactive, whereas 8-*epi*-sarcophytonolide C (**1b**) inhibited the growth of the cells with an IC_{50} value of 18.9 μM, which indicates that the activity is affected by the C8 stereochemistries. Compared to **1a**, **1b** was observed to be more soluble in water, which may also contribute to the growth-inhibitory activity. Sarcophytonolide E (**2**), which possesses the C6 alcohol moiety, exhibited the activity with an IC_{50} value of 33.0 μM. Sarcophytonolide F (**3**) bearing the C7/C8 trisubstituted alkene group showed the activity similar to that of **2** (IC_{50} = 35.9 μM). Introduction of the C14 acetoxy moiety was found to lower the inhibitory activity by comparing IC_{50} values of sarcophytonolides F (**3**, 35.9 μM) and H (**6**, 53.5 μM). Since 8-*epi*-sarcophytonolide C (**1b**) was the most active among five sarcophytonolides, the key synthetic intermediates of **1b** were next biologically evaluated. The cytotoxic activity of the butenolide construction precursor **32b** (IC_{50} = 13.7 μM) was slightly improved in comparison with that of **1b**. The macrolactonization precursor **30b** and the alcohol **25b** retained the activity, while their activities were decreased to IC_{50} values of 55.8 and 24.0 μM, respectively.

Table 3. Growth-Inhibitory Activity against HL60 Human Leukemia Cells[a]



compound	IC_{50}
1a	>100
1b	18.9
2	33.0
3	35.9
6	53.5
32b	13.7
30b	55.8
25b	24.0

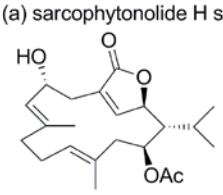
[a] IC_{50} values are given in μM

Antifouling Activity and Toxicity of the Synthetic Products. Since sarcophytonolides H (**6**) and J (**69**) which were isolated from nature are reported to be antifouling active against the cypris larvae of barnacle *Balanus* (*Amphibalanus*) *amphitrite*,[13,14] we next evaluated the antifouling activity[59] and toxicity of the synthetic sarcophytonolides H (**6**) and J (**69**) and their analogues against the cypris larvae of the same barnacle. The larvae were treated in 24-well polystyrene plates with various concentrations of the synthetic compounds in the dark for 96 h and the results are summarized in Table 4. The synthetic sarcophytonolide H (**6**) displayed the antifouling activity with an EC_{50} value of 3.36 μg/mL, which was in good agreement with that of the natural product (5.98 μg/mL).[13] Diol **79**[60] retained the antifoulant activity (EC_{50} = 3.08 μg/mL), which indicates the acetyl group of **6** has little influence on this activity. The antifouling activity of the butenolide construction precursor **80**[60] was marginally increased in comparison with those of **6** and **79** (EC_{50} = 1.61 μg/mL). The hydroxycarboxylic acid **58** turned out to be antifouling active (EC_{50} = 3.27 μg/mL), while the alkoxycarbonylallylation precursor **55** exhibited no antifouling activity. Furthermore, the toxicity was also evaluated

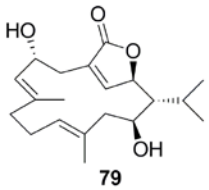
and it was found that **58** was weak toxic (LC_{50} = 19.4 μg/mL) and other compounds **6**, **79**, **80**, and **55** had no toxicity. In addition to the sarcophytonolide H series, we next evaluated the biological activity of the synthetic sarcophytonolide J (**69**) and its synthetic intermediates. The synthetic sarcophytonolide J (**69**), the triene **76**, and the hydroxyester **74** were antifouling active with EC_{50} values of 0.95–2.36 μg/mL without regard to difference of the molecular framework. Interestingly, alcohol **81** also showed the antifoulant activity (EC_{50} = 1.74 μg/mL) in contrast to the allylic alcohol **55** in the sarcophytonolide H series. In the sarcophytonolide J series, only compound **69** displayed the weak toxicity with a LC_{50} value of 34.5 μg/mL and other compounds **76**, **74**, and **81** were non-toxic. These obtained results of the biological activity assessment shown in Table 4 denote that the triene **76**, which exhibited the strongest antifouling activity and no toxicity, is a promising candidate for the creation of environmentally friendly antifouling agents.

Table 4. Antifouling Activity (EC_{50}) and Toxicity (LC_{50}) of the Synthetic Sarcophytonolides H (6) and J (69) and Their Analogues[a]

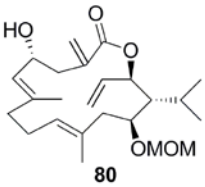
(a) sarcophytonolide H series



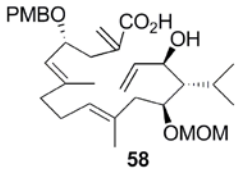
sarcophytonolide H (**6**)



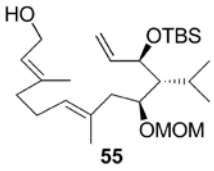
79



80

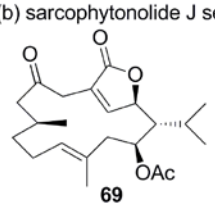


58



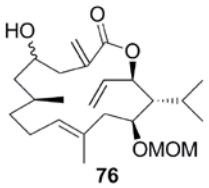
55

(b) sarcophytonolide J series

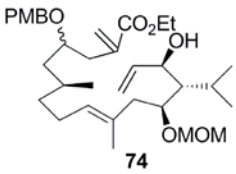


69

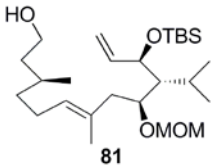
revised structure of sarcophytonolide J



76



74



81

compound	EC_{50}	LC_{50}
6	3.36	>50
79	3.08	>50
80	1.61	>50
58	3.27	19.4
55	>50	>50

69	1.50	34.5
76	0.95	>50
74	2.36	>50
81	1.74	>50

[a]Against the cypris larvae of barnacle *Balanus* (*Amphibalanus*) *amphitrite*. EC_{50} and LC_{50} values are given in μg/mL.

Conclusion

Unified total synthesis of sarcophytonolides, cembranolide diterpenes isolated from the soft corals of genus *Sarcophyton*, was accomplished. In their synthetic routes, NaHMDS-mediated reaction of allylic bromide/sulfone in methylene series at the C14 position and SmI_2-mediated reaction of allylic bromide/aldehyde in acetoxymethyne series at the C14 position were utilized as the fragment couplings, respectively. In addition, the total synthesis features alkoxycarbonylallylation, macrolactonization, and transannular RCM. Because the chirality at the C8 position of sarcophytonolide C (**1**) was not determined, the C8 stereoisomers **1a** and **1b** were stereoselectively synthesized, which elucidated the absolute configuration of natural **1** to be that as drawn in **1a**. Stereoselective total synthesis of sarcophytonolides E (**2**), F (**3**), G (**4**), and H (**6**) culminated in the absolute stereochemical determination of **2**, **3**, and **4** and confirmation of **6**. Furthermore, total synthesis of the proposed structure **10** and the predicted structure **68** of isosarcophytonolide D revealed the correct structure of this natural product to be that in **68**. This stereochemical revision at the C14 position of isosarcophytonolide D and the stereostructural elucidation of sarcophytonolide C led us to the stereochemical prediction of sarcophytonolide J. Total synthesis of the predicted structure **69** of this natural product verified the correct structure of natural sarcophytonolide J. After completing the total synthesis of sarcophytonolides, we assayed the cytotoxicity of selected synthetic products against HL60 cells and found that **1b**, **2**, **3**, **6**, **32b**, **30b**, and **25b** showed the cytotoxicity, while **1a** was inactive. Moreover, we conducted evaluation of the antifouling activity and toxicity of the synthetic sarcophytonolides H (**6**) and J (**69**) and their synthetic analogues against the cypris larvae of barnacle *Balanus* (*Amphibalanus*) *amphitrite*. The obtained findings suggest that **76**, a synthetic intermediate of **69**, is a good candidate for further developing environmentally benign antifouling compounds. Further synthetic study of other classes of cembranolide is currently underway.

Experimental Section

General Methods. Reagents were used as received from commercial suppliers unless otherwise indicated. All reactions were carried out under an atmosphere of argon. Reaction solvents were purchased as dehydrated solvents and stored with active molecular sieves 4Å under argon prior to use for reactions. All solvents for work-up procedure were used as received. Analytical thin-layer chromatography (TLC) was performed with aluminium TLC plates (Merck TLC silica gel $60F_{254}$). Column chromatography was performed with Fuji

Silysia silica gel BW-300 or Kanto Chemical silica gel 60N. Optical rotations were recorded on a JASCO DIP-1000. IR spectra were recorded on a JASCO FT/IR-460 plus. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-AL400 or Varian 400-MR. Chemical shifts in the NMR spectra are reported in ppm with reference to the internal residual solvent (^{1}H NMR, $CDCl_3$ 7.26 ppm, C_6D_6 7.15 ppm; ^{13}C NMR, $CDCl_3$ 77.0 ppm, C_6D_6 128.0 ppm). The following abbreviations are used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (*J*) are in hertz. High resolution mass spectra were recorded on a Micromass LCT (ESI–TOF–MS) spectrometer.

TBS Ether S1. To a solution of *cis*-2-butene-1,4-diol (5.5 mL, 66.9 mmol) in DMF (67 mL) were added imidazole (4.55 g, 66.9 mmol) and TBSCl (10.1 g, 66.9 mmol) at –30 °C. The mixture was stirred at the same temperature for 2 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane, hexane/EtOAc = 6:1) gave mono-TBS ether **S1** (6.31 g, 47%): colorless oil; R_f = 0.36 (hexane/EtOAc = 4:1); IR (neat) 3367, 2953, 2929, 2858 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74–5.64 (m, 2 H), 4.26 (d, *J* = 5.1 Hz, 2 H), 4.20 (d, *J* = 5.9 Hz, 2 H), 2.01 (brs, 1 H), 0.91 (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.3, 130.0, 59.6, 58.9, 26.0, 18.4, –5.2; HRMS (ESI–TOF) calcd for $C_{10}H_{22}O_2SiNa$ $[M + Na]^+$ 225.1287, found 225.1284.

Epoxy Alcohol 15. To a suspension of powdered MS4Å (3.20 g) in CH_2Cl_2 (130 mL) were added (+)-DET (3.3 mL, 19.1 mmol), Ti(O*i*-Pr)$_4$ (5.7 mL, 19.1 mmol), and allylic alcohol **S1** (3.21 g, 15.9 mmol) in CH_2Cl_2 (17 mL + 6.0 mL) at –25 °C. After the resulting mixture was stirred at the same temperature for 20 min, TBHP (ca. 5.0 M solution in 2,2,4-trimethylpentane, 6.4 mL, 32.0 mmol) was added to the mixture at the same temperature. After the resulting mixture was stirred at the same temperature for 63 h, the reaction was quenched with 3 M aqueous NaOH and the mixture was stirred at room temperature for 30 min. The mixture was filtered through a Celite pad and washed with EtOAc. The mixture was washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1) gave epoxy alcohol **15** (2.98 g, 86%, enantiomeric ratio = 17:1): colorless oil; R_f = 0.34 (hexane/EtOAc = 2:1); $[\alpha]_D^{25}$ –12.6 (*c* 1.00, $CHCl_3$); IR (neat) 3399, 2953, 2930, 2858 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (dd, *J* = 11.7, 5.6 Hz, 1 H), 3.79–3.71 (m, 3 H), 3.25–3.17 (m, 2 H), 2.24 (brs, 1 H), 0.90 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.6, 60.9, 56.4, 56.0, 25.9, 18.3, –5.2, –5.3; HRMS (ESI–TOF) calcd for $C_{10}H_{22}O_3SiNa$ $[M + Na]^+$ 241.1236, found 241.1231.

Diol 16. To a suspension of $CuBr{\cdot}SMe_2$ (294 mg, 1.43 mmol) in Et_2O (38 mL) was added isopropenylmagnesium bromide (0.5 M in THF, 31.4 mL, 15.7 mmol) at –50 °C. The mixture was gradually warmed up to –20 °C and stirred at the same temperature for 10 min. To the resulting mixture was added epoxy alcohol **15** (1.04 g, 4.76 mmol) in Et_2O (5.2 mL + 2.0 mL) at –20 °C. The mixture was stirred at the same temperature for 21 h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with

saturated aqueous NH_4Cl, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 3:1) gave diol **16** (1.09 g, 84%): colorless oil; R_f = 0.43 (hexane/EtOAc = 2:1); $[\alpha]_D^{25}$ –4.9 (*c* 1.00, $CHCl_3$); IR (neat) 3399, 2929, 2857 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.00 (t, *J* = 1.6 Hz, 1 H), 4.86 (s, 1 H), 3.81–3.60 (m, 5 H), 2.46–2.37 (m, 3 H), 1.80 (s, 3 H), 0.91 (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 114.5, 71.3, 65.5, 62.2, 52.6, 25.9, 21.3, 18.3, –5.3, –5.3; HRMS (ESI–TOF) calcd for $C_{13}H_{28}O_3SiNa$ $[M + Na]^+$ 283.1705, found 283.1711.

Alkane 17. A mixture of alkene **16** (2.65 g, 10.2 mmol) and $(Ph_3P)_3RhCl$ (236 mg, 0.255 mmol) in benzene (48 mL) and EtOH (16 mL) was stirred for 5 h under H_2 atmosphere at room temperature. Short column chromatography (hexane/EtOAc = 1:1), concentration, and column chromatography (hexane/EtOAc = 7:1) gave alkane **17** (2.48 g, 93%): colorless oil; R_f = 0.50 (hexane/EtOAc = 2:1); $[\alpha]_D^{26}$ +9.9 (*c* 1.00, $CHCl_3$); IR (neat) 3389, 2956, 2930, 2886, 2855 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.92–3.87 (m, 1 H), 3.80–3.63 (m, 4 H), 2.70 (brs, 1 H), 1.86–1.78 (m, 1 H), 1.64–1.58 (m, 1 H), 0.99 (d, *J* = 6.8 Hz, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 0.92 (s, 9 H), 0.11 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.8, 64.6, 60.9, 49.6, 26.2, 25.9, 21.7, 20.0, 18.3, –5.2, –5.3; HRMS (ESI–TOF) calcd for $C_{13}H_{30}O_3SiNa$ $[M + Na]^+$ 285.1862, found 285.1862.

Sulfide 18. To a solution of diol **17** (1.74 g, 6.63 mmol) and $(PhS)_2$ (4.34 g, 19.9 mmol) in pyridine (33 mL) was added *n*-Bu_3P (5.0 mL, 19.9 mmol) at room temperature. The mixture was stirred at the same temperature for 1 h. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 60:1) gave sulfide **18** (1.92 g, 82%): colorless oil; R_f = 0.51 (hexane/EtOAc = 7:1); $[\alpha]_D^{27}$ –16.0 (*c* 1.00, $CHCl_3$); IR (neat) 3490, 2955, 2928, 2855 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.33 (m, 2 H), 7.29–7.26 (m, 2 H), 7.17 (tt, *J* = 7.3, 1.5 Hz, 1 H), 3.89–3.84 (m, 1 H), 3.75 (dd, *J* = 10.0, 3.4 Hz, 1 H), 3.60 (dd, *J* = 10.0, 8.3 Hz, 1 H), 2.99 (dd, *J* = 12.8, 4.5 Hz, 1 H), 2.90 (dd, *J* = 12.8, 7.6 Hz, 1 H), 2.56 (brd, *J* = 2.9 Hz, 1 H), 2.17–2.08 (m, 1 H), 1.67–1.61 (m, 1 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 0.91 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 129.2, 128.8, 125.9, 72.5, 65.9, 45.9, 31.7, 27.5, 26.0, 21.3, 18.7, 18.3, –5.2, –5.2; HRMS (ESI–TOF) calcd for $C_{19}H_{34}O_2SSiNa$ $[M + Na]^+$ 377.1946, found 377.1950.

TBS Ether 19. To a solution of alcohol **18** (1.29 g, 3.64 mmol) in CH_2Cl_2 (36 mL) were added 2,6-lutidine (0.64 mL, 5.46 mmol) and TBSOTf (1.0 mL, 4.37 mmol) at 0 °C. The mixture was stirred at the same temperature for 30 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 1:0, 70:1) gave TBS ether **19** (1.68 g, 98%): colorless oil; R_f = 0.66 (hexane/EtOAc = 20:1); $[\alpha]_D^{28}$ –34.8 (*c* 1.00, $CHCl_3$); IR (neat) 2955, 2929, 2862 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.32 (m, 2 H), 7.27–7.24 (m, 2 H), 7.16–7.12 (m, 1 H), 4.14 (td, *J* = 6.6, 2.9 Hz, 1 H), 3.58 (dd, *J* = 6.6, 2.7 Hz, 2 H), 3.05 (dd, *J* = 12.7, 3.9 Hz, 1 H), 2.95 (dd, *J* = 12.7, 9.6 Hz, 1 H), 2.08–2.00 (m, 1 H), 1.75–1.70 (m, 1 H), 0.96 (d, *J* = 6.8

Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.88 (s, 9 H), 0.85 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H), 0.03 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 129.2, 128.6, 125.5, 73.3, 65.0, 44.8, 31.0, 26.4, 26.0, 26.0, 22.6, 19.1, 18.3, 18.2, –4.1, –4.7, –5.2, –5.4; HRMS (ESI–TOF) calcd for $C_{25}H_{48}O_2SSi_2Na$ $[M + Na]^+$ 491.2811, found 491.2809.

Sulfone 20. To a solution of sulfide **19** (1.68 g, 3.58 mmol) in EtOH (36 mL) were added 30% aqueous H_2O_2 (3.6 mL, 35.8 mmol) and $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (442 mg, 0.358 mmol) at 0 °C. The mixture was stirred at the same temperature for 2 h and at room temperature for 4 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ at 0 °C. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 40:1) gave sulfone **20** (1.72 g, 96%): colorless oil; R_f = 0.34 (hexane/EtOAc = 10:1); $[\alpha]_D^{29}$ –17.8 (*c* 1.00, $CHCl_3$); IR (neat) 2955, 2929, 2855 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92–7.90 (m, 2 H), 7.65–7.61 (m, 1 H), 7.56–7.52 (m, 2 H), 4.16–4.12 (m, 1 H), 3.57 (dd, *J* = 10.0, 5.7 Hz, 1 H), 3.50 (dd, *J* = 10.0, 8.1 Hz, 1 H), 3.36 (dd, *J* = 14.8, 8.6 Hz, 1 H), 2.97 (dd, *J* = 14.8, 2.3 Hz, 1 H), 2.17–2.14 (m, 1 H), 2.09–2.01 (m, 1 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.83 (d, *J* = 6.8 Hz, 3 H), 0.62 (d, *J* = 7.1 Hz, 3 H), 0.14 (s, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 133.3, 129.0, 128.1, 73.4, 64.3, 52.5, 40.1, 25.9, 25.9, 25.6, 21.8, 18.4, 18.2, 18.1, –4.2, –4.7, –5.3, –5.5; HRMS (ESI–TOF) calcd for $C_{25}H_{48}O_4SSi_2Na$ $[M + Na]^+$ 523.2709, found 523.2709.

Sulfone 22a. To a solution of sulfone **20** (1.83 g, 3.65 mmol) in THF (28 mL) was added NaHMDS (1.0 M in THF, 4.4 mL, 4.40 mmol) at –78 °C. The mixture was stirred at the same temperature for 30 min. To the mixture was added allylic bromide **21a** (1.40 g, 4.38 mmol) in THF (4.0 mL + 2.0 mL + 2.0 mL) at –78 °C. The mixture was gradually warmed up to room temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1) gave sulfone **22a** (2.38 g, 88%): colorless oil; R_f = 0.14 (hexane/EtOAc = 20:1); $[\alpha]_D^{26}$ +15.1 (*c* 1.00, $CHCl_3$); IR (neat) 2957, 2929, 2862, 1727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.79 (m, 2 H), 7.58–7.54 (m, 1 H), 7.49–7.45 (m, 2 H), 5.11 (t, *J* = 6.7 Hz, 1 H), 4.33–4.30 (m, 1 H), 4.10–4.06 (m, 2 H), 3.73 (dd, *J* = 10.5, 4.4 Hz, 1 H), 3.67 (dd, *J* = 10.5, 6.8 Hz, 1 H), 3.48 (brd, *J* = 7.8 Hz, 1 H), 2.70–2.58 (m, 2 H), 2.36 (brd, *J* = 7.8 Hz, 1 H), 2.17–2.09 (m, 1 H), 1.82–1.60 (m, 3 H), 1.53–1.35 (m, 2 H), 1.33–1.06 (m, 2 H), 1.20 (s, 9 H), 1.20 (s, 3 H), 0.97–0.89 (m, 9 H), 0.94 (s, 9 H), 0.87 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 140.9, 132.8, 130.3, 128.8, 128.5, 127.9, 73.8, 68.4, 62.9, 61.9, 44.3, 38.8, 36.6, 35.7, 35.6, 35.5, 29.9, 27.3, 26.3, 26.2, 25.5, 23.2, 20.6, 19.6, 18.7, 18.5, 15.3, –3.2, –4.7, –5.1, –5.2; HRMS (ESI–TOF) calcd for $C_{40}H_{74}O_6SSi_2Na$ $[M + Na]^+$ 761.4642, found 761.4632.

Sulfone 22b. To a solution of sulfone **20** (1.52 g, 3.03 mmol) in THF (24 mL) was added NaHMDS (1.0 M in THF, 3.6 mL, 3.60 mmol) at –78 °C. The mixture was stirred at the same temperature for 30 min. To the mixture was added allylic bromide **21b** (1.22 g, 3.82 mmol) in THF (4.0 mL + 1.0 mL + 1.0 mL) at –78 °C. The mixture was gradually warmed up to room

temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1) gave sulfone **22b** (2.03 g, 91%): colorless oil; R_f = 0.14 (hexane/EtOAc = 20:1); $[\alpha]_D^{30}$ +17.7 (*c* 1.00, $CHCl_3$); IR (neat) 2956, 2929, 2858, 1728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82–7.79 (m, 2 H), 7.58–7.54 (m, 1 H), 7.49–7.45 (m, 2 H), 5.10 (t, *J* = 6.7 Hz, 1 H), 4.31–4.30 (m, 1 H), 4.11–4.05 (m, 2 H), 3.73 (dd, *J* = 10.5, 4.6 Hz, 1 H), 3.67 (dd, *J* = 10.5, 6.8 Hz, 1 H), 3.48 (brd, *J* = 8.3 Hz, 1 H), 2.71–2.58 (m, 2 H), 2.36 (brd, *J* = 6.8 Hz, 1 H), 2.17–2.09 (m, 1 H), 1.78–1.60 (m, 3 H), 1.53–1.38 (m, 2 H), 1.31–1.08 (m, 2 H), 1.20 (s, 9 H), 1.20 (s, 3 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.94 (s, 9 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 0.87 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 141.0, 132.8, 130.3, 128.8, 128.5, 127.9, 73.8, 68.4, 62.9, 61.9, 44.3, 38.7, 36.6, 35.7, 35.6, 29.9, 27.3, 26.3, 26.2, 26.2, 25.5, 23.2, 20.6, 19.5, 18.7, 18.5, 15.3, –3.2, –4.7, –5.1, –5.2; HRMS (ESI–TOF) calcd for $C_{40}H_{74}O_6SSi_2Na$ $[M + Na]^+$ 761.4642, found 761.4641.

Alcohol 23a. To a solution of lithium wire (2.23 g, 0.322 mol) in liquid NH_3 (90 mL) was added sulfone **22a** (2.38 g, 3.22 mmol) in THF/*t*-BuOH (44 mL/22 mL) and THF (6.0 mL for rinse) at –78 °C. The mixture was stirred at the same temperature for 5 min. The reaction was quenched with a 1:1 solution of saturated aqueous NH_4Cl and MeOH. The mixture was diluted with EtOAc, warmed up to room temperature, and stirred at the same temperature. The mixture was washed with H_2O and brine, and then dried over Na_2SO_4. Concentration gave the mixture of the corresponding pivalate and alcohol, which was used for the next step without further purification.

To a solution of the mixture obtained above in CH_2Cl_2 (30 mL) were added pyridine (0.39 mL, 4.83 mmol) and PivCl (0.47 mL, 3.86 mmol) at room temperature. The mixture was stirred at the same temperature for 11 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 100:1) gave the corresponding pivalate (1.23 g), which was used for the next step without further purification.

To a solution of the bis-TBS ether obtained above (1.23 g) in MeOH (10 mL) and CH_2Cl_2 (10 mL) was added CSA (142 mg, 0.615 mmol) at 0 °C. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with Et_3N. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 25:1) gave alcohol **23a** (430 mg) and the bis-TBS ether (617 mg).

To a solution of the bis-TBS ether recovered above (617 mg) in MeOH (5.0 mL) and CH_2Cl_2 (5.0 mL) was added CSA (71.8 mg, 0.309 mmol) at 0 °C. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with Et_3N. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 25:1) gave alcohol **23a** (310 mg, totally 741 mg,

47% in three steps): colorless oil; R_f = 0.29 (hexane/EtOAc = 10:1); $[\alpha]_D^{25}$ +3.8 (*c* 1.00, $CHCl_3$); IR (neat) 3520, 2956, 2930, 2862, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.09 (t, *J* = 6.6 Hz, 1 H), 4.14–4.04 (m, 2 H), 3.81–3.77 (m, 1 H), 3.61–3.53 (m, 2 H), 2.06–1.91 (m, 4 H), 1.86–1.78 (m, 1 H), 1.71–1.53 (m, 3 H), 1.60 (s, 3 H), 1.48–1.15 (m, 6 H), 1.19 (s, 9 H), 0.93–0.88 (m, 9 H), 0.91 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 135.4, 124.4, 74.6, 64.3, 62.9, 47.2, 39.7, 38.8, 37.1, 35.6, 29.7, 27.9, 27.3, 26.0, 25.4, 24.7, 21.7, 19.5, 19.4, 18.2, 16.1, –4.2, –4.3; HRMS (ESI–TOF) calcd for $C_{28}H_{56}O_4SiNa$ $[M + Na]^+$ 507.3846, found 507.3836.

Alcohol 23b. To a solution of lithium wire (1.91 g, 0.275 mol) in liquid NH_3 (80 mL) was added sulfone **22b** (2.03 g, 2.75 mmol) in THF/*t*-BuOH (39 mL/19 mL) and THF (4.0 mL for rinse) at –78 °C. The mixture was stirred at the same temperature for 10 min. The reaction was quenched with a 1:1 solution of saturated aqueous NH_4Cl and MeOH. The mixture was diluted with EtOAc, warmed up to room temperature, and stirred at the same temperature. The mixture was washed with H_2O and brine, and then dried over Na_2SO_4. Concentration gave the mixture of the corresponding pivalate and alcohol, which was used for the next step without further purification.

To a solution of the mixture obtained above in CH_2Cl_2 (28 mL) were added pyridine (0.33 mL, 4.13 mmol) and PivCl (0.40 mL, 3.30 mmol) at room temperature. The mixture was stirred at the same temperature for 11 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 100:1) gave the corresponding pivalate (1.37 g), which was used for the next step without further purification.

To a solution of the bis-TBS ether obtained above (1.37 g) in MeOH (12 mL) and CH_2Cl_2 (12 mL) was added CSA (160 mg, 0.687 mmol) at 0 °C. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with Et_3N. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 25:1) gave alcohol **23b** (562 mg) and the bis-TBS ether (366 mg).

To a solution of the bis-TBS ether recovered above (366 mg) in MeOH (3.0 mL) and CH_2Cl_2 (3.0 mL) was added CSA (42.6 mg, 0.183 mmol) at 0 °C. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with Et_3N. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 25:1) gave alcohol **23b** (169 mg, totally 731 mg, 55% in three steps): colorless oil; R_f = 0.29 (hexane/EtOAc = 10:1); $[\alpha]_D^{29}$ +7.6 (*c* 1.20, $CHCl_3$); IR (neat) 3475, 2956, 2929, 2858, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.09 (t, *J* = 7.1 Hz, 1 H), 4.14–4.04 (m, 2 H), 3.81–3.77 (m, 1 H), 3.61–3.53 (m, 2 H), 2.06–1.90 (m, 4 H), 1.86–1.78 (m, 1 H), 1.71–1.51 (m, 2 H), 1.60 (s, 3 H), 1.48–1.26 (m, 6 H), 1.24–1.15 (m, 1 H), 1.19 (s, 9 H), 0.93–0.88 (m, 9 H), 0.91 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 135.4, 124.3, 74.6, 64.4, 62.9, 47.2, 39.7, 38.7, 37.1, 35.6, 29.7,

27.9, 27.3, 26.0, 25.4, 24.7, 21.7, 19.6, 19.4, 18.2, 16.1, –4.2, –4.3; HRMS (ESI–TOF) calcd for $C_{28}H_{56}O_4SiNa$ $[M + Na]^+$ 507.3846, found 507.3843.

Alkene 24a. To a solution of alcohol **23a** (715 mg, 1.47 mmol) in CH_2Cl_2 (15 mL) were added $PhI(OAc)_2$ (712 mg, 2.21 mmol) and TEMPO (45.9 mg, 0.294 mmol) at room temperature. The mixture was stirred at the same temperature for 3 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 70:1) gave the corresponding aldehyde (629 mg), which was used for the next step without further purification.

To a suspension of $Ph_3P^+CH_3Br^-$ (1.31 g, 3.68 mmol) in THF (9.0 mL) was added NaHMDS (1.0 M in THF, 3.5 mL, 3.50 mmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. To the mixture was added the aldehyde obtained above (629 mg) in THF (4.0 mL + 1.0 mL + 1.0 mL) at 0 °C. The mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 70:1) gave alkene **24a** (580 mg, 82% in two steps): colorless oil; R_f = 0.50 (hexane/EtOAc = 20:1); $[\alpha]_D^{26}$ +3.2 (*c* 1.00, $CHCl_3$); IR (neat) 2957, 2930, 2855, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 16.6, 10.4, 5.9 Hz, 1 H), 5.15 (d, *J* = 16.6 Hz, 1 H), 5.09–5.06 (m, 2 H), 4.14 (t, *J* = 5.9 Hz, 1 H), 4.11–4.07 (m, 2 H), 2.08–1.85 (m, 5 H), 1.72–1.63 (m, 1 H), 1.58 (s, 3 H), 1.57–1.52 (m, 1 H), 1.48–1.26 (m, 6 H), 1.20 (s, 9 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.0 Hz, 3 H), 0.90 (s, 9 H), 0.88 (d, *J* = 6.4 Hz, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 140.7, 135.6, 124.2, 114.5, 75.5, 62.9, 50.0, 39.7, 38.8, 37.1, 35.6, 29.7, 27.7, 27.3, 26.0, 25.4, 24.5, 21.9, 19.5, 19.0, 18.3, 16.0, –4.0, –4.8; HRMS (ESI–TOF) calcd for $C_{29}H_{56}O_3SiNa$ $[M + Na]^+$ 503.3896, found 503.3895.

Alkene 24b. To a solution of alcohol **23b** (700 mg, 1.44 mmol) in CH_2Cl_2 (15 mL) were added $PhI(OAc)_2$ (696 mg, 2.16 mmol) and TEMPO (45.0 mg, 0.288 mmol) at room temperature. The mixture was stirred at the same temperature for 4 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 70:1) gave the corresponding aldehyde (626 mg), which was used for the next step without further purification.

To a suspension of $Ph_3P^+CH_3Br^-$ (1.29 g, 3.60 mmol) in THF (9.0 mL) was added NaHMDS (1.0 M in THF, 3.5 mL, 3.50 mmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. To the mixture was added the aldehyde obtained above (626 mg) in THF (4.0 mL + 1.0 mL + 1.0 mL) at 0 °C. The mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 70:1) gave alkene **24b** (605 mg, 87% in two steps): colorless oil; R_f = 0.50

(hexane/EtOAc = 20:1); $[\alpha]_D^{28}$ +6.1 (*c* 1.00, $CHCl_3$); IR (neat) 2957, 2930, 2858, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 17.0, 10.4, 5.7 Hz, 1 H), 5.15 (dt, *J* = 17.0, 1.5 Hz, 1 H), 5.09–5.06 (m, 2 H), 4.14 (t, *J* = 5.7 Hz, 1 H), 4.11–4.07 (m, 2 H), 2.07–1.85 (m, 5 H), 1.72–1.63 (m, 1 H), 1.58 (s, 3 H), 1.57–1.52 (m, 1 H), 1.48–1.14 (m, 6 H), 1.20 (s, 9 H), 0.92 (d, *J* = 6.4 Hz, 3 H), 0.90 (d, *J* = 6.4 Hz, 3 H), 0.90 (s, 9 H), 0.88 (d, *J* = 6.8 Hz, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 140.7, 135.6, 124.2, 114.5, 75.5, 62.9, 50.0, 39.7, 38.8, 37.1, 35.6, 29.7, 27.7, 27.3, 26.0, 25.4, 24.5, 21.9, 19.6, 19.0, 18.3, 16.0, –4.0, –4.8; HRMS (ESI–TOF) calcd for $C_{29}H_{56}O_3SiNa$ $[M + Na]^+$ 503.3896, found 503.3903.

Alcohol 25a. To a solution of pivalate **24a** (554 mg, 1.15 mmol) in CH_2Cl_2 (12 mL) was added DIBAL-H (1.02 M in hexane, 3.4 mL, 3.45 mmol) at –78 °C. The mixture was stirred at the same temperature for 20 min. The reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and column chromatography (hexane/EtOAc = 10:1) gave alcohol **25a** (443 mg, 97%): colorless oil; R_f = 0.11 (hexane/EtOAc = 10:1); $[\alpha]_D^{25}$ +3.0 (*c* 1.00, $CHCl_3$); IR (neat) 3336, 2955, 2928, 2858 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.15 (dt, *J* = 17.2, 1.6 Hz, 1 H), 5.10–5.06 (m, 2 H), 4.14 (t, *J* = 6.0 Hz, 1 H), 3.71–3.66 (m, 2 H), 2.08–1.85 (m, 5 H), 1.66–1.54 (m, 2 H), 1.58 (s, 3 H), 1.45–1.15 (m, 7 H), 0.92–0.87 (m, 9 H), 0.90 (s, 9 H), 0.05 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 135.5, 124.4, 114.5, 75.5, 61.3, 49.9, 40.0, 39.7, 37.3, 29.3, 27.7, 26.0, 25.4, 24.4, 21.9, 19.6, 19.0, 18.3, 16.0, –4.0, –4.8; HRMS (ESI–TOF) calcd for $C_{24}H_{48}O_2SiNa$ $[M + Na]^+$ 419.3321, found 419.3329.

Alcohol 25b. To a solution of pivalate **24b** (585 mg, 1.22 mmol) in CH_2Cl_2 (12 mL) was added DIBAL-H (1.02 M in hexane, 3.6 mL, 3.66 mmol) at –78 °C. The mixture was stirred at the same temperature for 15 min. The reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and column chromatography (hexane/EtOAc = 10:1) gave alcohol **25b** (473 mg, 98%): colorless oil; R_f = 0.11 (hexane/EtOAc = 10:1); $[\alpha]_D^{30}$ +8.2 (*c* 1.00, $CHCl_3$); IR (neat) 3347, 2955, 2929, 2858 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 17.2, 10.4, 6.3 Hz, 1 H), 5.15 (dt, *J* = 17.2, 1.6 Hz, 1 H), 5.10–5.05 (m, 2 H), 4.14 (dd, *J* = 6.3, 5.1 Hz, 1 H), 3.73–3.63 (m, 2 H), 2.08–1.85 (m, 5 H), 1.66–1.53 (m, 2 H), 1.58 (s, 3 H), 1.45–1.14 (m, 7 H), 0.92–0.87 (m, 9 H), 0.90 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 135.5, 124.4, 114.5, 75.5, 61.3, 49.9, 40.0, 39.7, 37.3, 29.3, 27.7, 26.0, 25.4, 24.5, 21.9, 19.7, 19.0, 18.3, 16.0, –4.0, –4.8; HRMS (ESI–TOF) calcd for $C_{24}H_{48}O_2SiNa$ $[M + Na]^+$ 419.3321, found 419.3318.

Alcohol 27a. To a solution of alcohol **25a** (420 mg, 1.05 mmol) in CH_2Cl_2 (10 mL) were added $PhI(OAc)_2$ (509 mg, 1.58 mmol) and TEMPO (32.8 mg, 0.210 mmol) at room temperature. The mixture was stirred at the same temperature for 2 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and

short column chromatography (hexane/EtOAc = 70:1) gave the corresponding aldehyde (386 mg), which was used for the next step without further purification.

To a solution of the aldehyde obtained above (386 mg) in THF (8.0 mL) and saturated aqueous NH_4Cl (1.6 mL) were added ethyl (2-bromomethyl)acrylate (**26**) (0.20 mL, 1.47 mmol) and zinc dust (192 mg, 2.93 mmol) at 0 °C. The mixture was stirred at the same temperature for 15 min. The mixture was filtered through a Celite pad and washed with EtOAc. The mixture was concentrated, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1) gave alcohol **27a** (420 mg, 79% in two steps) as a 1:1 diastereomeric mixture: colorless oil; R_f = 0.20 (hexane/EtOAc = 10:1); IR (neat) 3464, 2956, 2929, 2857, 1716, 1631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.25 (t, J = 1.8 Hz, 1 H), 5.81 (ddd, J = 17.2, 10.5, 5.7 Hz, 1 H), 5.65 (s, 1 H), 5.14 (d, J = 17.2 Hz, 1 H), 5.10–5.05 (m, 2 H), 4.26–4.18 (m, 2 H), 4.14 (t, J = 5.7 Hz, 1 H), 3.85 (brs, 1 H), 2.61 (dd, J = 14.0, 3.2 Hz, 0.5 H), 2.56 (dd, J = 14.0, 3.6 Hz, 0.5 H), 2.34 (dd, J = 14.0, 8.4 Hz, 0.5 H), 2.26 (dd, J = 14.0, 8.4 Hz, 0.5 H), 2.07–1.85 (m, 6 H), 1.74–1.48 (m, 2 H), 1.58 (s, 3 H), 1.44–1.35 (m, 3 H), 1.31 (t, J = 7.2 Hz, 3 H), 1.27–1.10 (m, 3 H), 0.95–0.87 (m, 9 H), 0.89 (s, 9 H), 0.04 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 140.7, 140.7, 137.8, 135.5, 135.4, 127.4, 127.3, 124.4, 124.4, 114.5, 75.5, 68.7, 68.4, 61.0, 49.9, 44.8, 44.7, 41.2, 40.6, 39.7, 37.9, 36.9, 29.5, 29.2, 27.7, 26.0, 25.5, 25.4, 24.5, 21.9, 20.2, 19.3, 19.0, 18.3, 16.0, 14.2, –4.0, –4.8; HRMS (ESI–TOF) calcd for $C_{30}H_{56}O_4SiNa$ $[M + Na]^+$ 531.3846, found 531.3845.

Alcohol 27b. To a solution of alcohol **25b** (453 mg, 1.14 mmol) in CH_2Cl_2 (11 mL) were added $PhI(OAc)_2$ (550 mg, 1.71 mmol) and TEMPO (35.6 mg, 0.228 mmol) at room temperature. The mixture was stirred at the same temperature for 2 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 70:1) gave the corresponding aldehyde (429 mg), which was used for the next step without further purification.

To a solution of the aldehyde obtained above (429 mg) in THF (10 mL) and saturated aqueous NH_4Cl (2.0 mL) were added ethyl (2-bromomethyl)acrylate (**26**) (0.23 mL, 1.71 mmol) and zinc dust (224 mg, 3.42 mmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. The mixture was filtered through a Celite pad and washed with EtOAc. The mixture was concentrated, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1) gave alcohol **27b** (538 mg, 93% in two steps) as a 1:1 diastereomeric mixture: colorless oil; R_f = 0.20 (hexane/EtOAc = 10:1); IR (neat) 3463, 2955, 2929, 2857, 1717, 1635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.25 (t, J = 1.8 Hz, 1 H), 5.81 (ddd, J = 17.2, 10.4, 5.7 Hz, 1 H), 5.64 (s, 1 H), 5.14 (dt, J = 17.2, 1.5 Hz, 1 H), 5.10–5.05 (m, 2 H), 4.26–4.18 (m, 2 H), 4.14 (t, J = 5.7 Hz, 1 H), 3.88–3.82 (m, 1 H), 2.61 (dd, J = 14.0, 3.2 Hz, 0.5 H), 2.56 (dd, J = 14.0, 3.2 Hz, 0.5 H), 2.34 (dd, J = 14.0, 8.4 Hz, 0.5 H), 2.26 (dd, J = 14.0, 8.4 Hz, 0.5 H), 2.07–1.85 (m, 6 H),

1.73–1.61 (m, 2 H), 1.58 (s, 3 H), 1.54–1.35 (m, 3 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 1.27–1.10 (m, 3 H), 0.95–0.87 (m, 9 H), 0.89 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 140.7, 140.7, 137.8, 135.5, 135.4, 127.4, 127.3, 124.4, 124.4, 114.5, 75.5, 68.8, 68.4, 61.0, 50.0, 50.0, 44.8, 44.7, 41.2, 40.7, 39.7, 37.9, 37.0, 29.5, 29.2, 27.7, 26.0, 25.5, 25.4, 24.5, 24.5, 21.9, 20.2, 19.3, 19.0, 18.3, 16.0, 14.2, –4.0, –4.8; HRMS (ESI–TOF) calcd for $C_{30}H_{56}O_4SiNa$ $[M + Na]^+$ 531.3846, found 531.3842.

MOM Ether 28a. To a solution of alcohol **27a** (395 mg, 0.777 mmol) in CH_2Cl_2 (8.0 mL) were added *i*-Pr_2NEt (0.80 mL, 4.66 mmol), MOMCl (0.30 mL, 3.89 mmol), and TBAI (144 mg, 0.389 mmol) at room temperature. The mixture was stirred at the same temperature for 6 h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 40:1) gave MOM ether **28a** (406 mg, 94%): colorless oil; R_f = 0.50 (hexane/EtOAc = 10:1); IR (neat) 2955, 2929, 2862, 1719, 1632 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (s, 1 H), 5.81 (ddd, *J* = 17.3, 10.5, 5.7 Hz, 1 H), 5.61 (s, 0.5 H), 5.60 (s, 0.5 H), 5.14 (d, *J* = 17.3 Hz, 1 H), 5.10–5.06 (m, 2 H), 4.68–4.57 (m, 2 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 4.13 (t, *J* = 5.7 Hz, 1 H), 3.88–3.80 (m, 1 H), 3.34 (s, 1.5 H), 3.33 (s, 1.5 H), 2.58–2.38 (m, 2 H), 2.07–1.84 (m, 5 H), 1.66–1.51 (m, 2 H), 1.58 (s, 3 H), 1.42–1.35 (m, 3 H), 1.31 (t, *J* = 7.2 Hz, 3 H), 1.22–1.12 (m, 3 H), 0.93–0.88 (m, 9 H), 0.89 (s, 9 H), 0.04 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 166.9, 140.7, 137.7, 137.7, 135.5, 135.4, 127.1, 124.4, 124.3, 114.5, 95.6, 95.5, 75.5, 74.4, 74.2, 60.7, 60.7, 55.7, 55.6, 50.0, 42.5, 39.7, 38.4, 38.0, 37.8, 37.1, 29.3, 29.0, 27.7, 26.0, 25.5, 25.3, 24.5, 21.9, 20.0, 19.4, 19.0, 18.3, 16.0, 14.3, –4.0, –4.8; HRMS (ESI–TOF) calcd for $C_{32}H_{60}O_5SiNa$ $[M + Na]^+$ 575.4108, found 575.4110.

MOM Ether 28b. To a solution of alcohol **27b** (518 mg, 1.02 mmol) in CH_2Cl_2 (10 mL) were added *i*-Pr_2NEt (1.1 mL, 6.12 mmol), MOMCl (0.39 mL, 5.10 mmol), and TBAI (188 mg, 0.510 mmol) at room temperature. The mixture was stirred at the same temperature for 11 h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 40:1) gave MOM ether **28b** (544 mg, 96%): colorless oil; R_f = 0.50 (hexane/EtOAc = 10:1); IR (neat) 2955, 2929, 2857, 1718, 1631 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (s, 1 H), 5.81 (ddd, *J* = 17.1, 10.4, 5.6 Hz, 1 H), 5.61 (s, 0.5 H), 5.60 (s, 0.5 H), 5.14 (d, *J* = 17.1 Hz, 1 H), 5.10–5.05 (m, 2 H), 4.67–4.57 (m, 2 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 4.14 (t, *J* = 5.6 Hz, 1 H), 3.88–3.80 (m, 1 H), 3.34 (s, 1.5 H), 3.33 (s, 1.5 H), 2.59–2.38 (m, 2 H), 2.07–1.84 (m, 5 H), 1.65–1.51 (m, 2 H), 1.58 (s, 3 H), 1.44–1.34 (m, 3 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.27–1.09 (m, 3 H), 0.94–0.87 (m, 9 H), 0.90 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 166.9, 140.7, 137.7, 137.7, 135.5, 135.4, 127.1, 124.4, 124.3, 114.5, 95.6, 95.5, 75.5, 74.4, 74.3, 60.7, 55.6, 55.6, 50.0, 42.5, 39.7, 38.4, 38.0, 37.8, 37.1, 29.3, 29.0, 27.7, 26.0, 25.4, 25.3, 24.5, 21.9, 20.0, 19.4, 19.0, 18.3, 16.0, 14.3, –4.0, –4.8; HRMS (ESI–TOF)

calcd for $C_{32}H_{60}O_5SiNa$ $[M + Na]^+$ 575.4108, found 575.4108.

Alcohol 29a. To a solution of TBS ether **28a** (380 mg, 0.687 mmol) in THF (4.8 mL) was added TBAF (1.0 M in THF, 2.1 mL, 2.10 mmol) at room temperature. The mixture was stirred at 60 °C for 5 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1) gave alcohol **29a** (245 mg, 81%): colorless oil; R_f = 0.43 (hexane/EtOAc = 4:1); IR (neat) 3483, 2954, 2929, 1715, 1625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.21 (s, 1 H), 5.90 (ddd, J = 17.3, 10.5, 6.1 Hz, 1 H), 5.61 (s, 0.5 H), 5.60 (s, 0.5 H), 5.24 (d, J = 17.3 Hz, 1 H), 5.15 (d, J = 10.5 Hz, 1 H), 5.10 (t, J = 7.0 Hz, 1 H), 4.67–4.57 (m, 2 H), 4.21 (q, J = 7.1 Hz, 2 H), 4.14–4.10 (m, 1 H), 3.87–3.79 (m, 1 H), 3.34 (s, 1.5 H), 3.33 (s, 1.5 H), 2.58–2.38 (m, 2 H), 2.06–1.89 (m, 5 H), 1.67–1.50 (m, 2 H), 1.58 (s, 3 H), 1.45 (brs, 1 H), 1.42–1.24 (m, 5 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.22–1.13 (m, 1 H), 0.94–0.88 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 166.9, 140.4, 137.7, 137.6, 135.1, 135.1, 127.1, 124.8, 124.7, 115.3, 95.6, 95.5, 74.9, 74.4, 74.2, 60.7, 55.7, 55.6, 48.7, 42.4, 39.4, 38.4, 38.0, 37.7, 37.0, 29.2, 28.9, 27.8, 25.4, 25.3, 24.6, 21.2, 20.0, 19.4, 18.9, 16.0, 14.3; HRMS (ESI–TOF) calcd for $C_{26}H_{46}O_5Na$ $[M + Na]^+$ 461.3243, found 461.3236.

Alcohol 29b. To a solution of TBS ether **28b** (524 mg, 0.948 mmol) in THF (7.0 mL) was added TBAF (1.0 M in THF, 2.8 mL, 2.80 mmol) at room temperature. The mixture was stirred at 60 °C for 6 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1) gave alcohol **29b** (347 mg, 83%): colorless oil; R_f = 0.43 (hexane/EtOAc = 4:1); IR (neat) 3475, 2954, 2929, 1716, 1631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.21 (s, 1 H), 5.90 (ddd, J = 17.1, 10.5, 6.1 Hz, 1 H), 5.61 (s, 0.5 H), 5.60 (s, 0.5 H), 5.24 (d, J = 17.1 Hz, 1 H), 5.15 (d, J = 10.5 Hz, 1 H), 5.10 (t, J = 6.8 Hz, 1 H), 4.67–4.57 (m, 2 H), 4.21 (q, J = 7.1 Hz, 2 H), 4.12 (t, J = 6.1 Hz, 1 H), 3.87–3.79 (m, 1 H), 3.34 (s, 1.5 H), 3.33 (s, 1.5 H), 2.58–2.38 (m, 2 H), 2.06–1.89 (m, 5 H), 1.66–1.50 (m, 2 H), 1.58 (s, 3 H), 1.42–1.25 (m, 6 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.22–1.13 (m, 1 H), 0.94–0.88 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 167.0, 140.4, 137.7, 137.7, 135.1, 135.1, 127.1, 124.8, 124.7, 115.2, 95.6, 95.5, 74.9, 74.4, 74.3, 60.7, 55.6, 55.6, 48.8, 42.5, 39.4, 38.4, 38.0, 37.7, 37.1, 29.2, 29.0, 27.8, 25.4, 25.3, 24.7, 21.2, 20.0, 19.4, 18.9, 16.0, 14.3; HRMS (ESI–TOF) calcd for $C_{26}H_{46}O_5Na$ $[M + Na]^+$ 461.3243, found 461.3247.

Carboxylic Acid 30a. To a solution of ester **29a** (210 mg, 0.479 mmol) in THF (3.0 mL), MeOH (1.0 mL), and H_2O (1.0 mL) was added $LiOH·H_2O$ (30.1 mg, 0.718 mmol) at room temperature. The mixture was stirred at the same temperature for 12 h. The mixture was neutralized with aqueous HCl at 0 °C. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 6:1, 3:1) gave carboxylic acid **30a** (174 mg, 88%): colorless oil; R_f = 0.17 (hexane/EtOAc = 2:1); IR (neat) 3466, 2955, 2930, 1698, 1629 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.34 (t, J = 2.1 Hz, 1 H), 5.90 (ddd, J = 17.3, 10.5, 5.8 Hz, 1 H), 5.74 (s, 0.5 H),

5.72 (s, 0.5 H), 5.25 (d, *J* = 17.3 Hz, 1 H), 5.16 (dd, *J* = 10.5, 1.3 Hz, 1 H), 5.12–5.08 (m, 1 H), 4.67–4.60 (m, 2 H), 4.15 (q, *J* = 5.8 Hz, 1 H), 3.89–3.82 (m, 1 H), 3.35 (s, 1.5 H), 3.34 (s, 1.5 H), 2.58–2.40 (m, 2 H), 2.06–1.89 (m, 5 H), 1.67–1.53 (m, 2 H), 1.58 (s, 3 H), 1.43–1.12 (m, 8 H), 0.93–0.90 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.9, 140.2, 140.1, 137.0, 136.9, 135.1, 135.0, 129.4, 124.9, 124.8, 115.4, 95.6, 95.5, 75.0, 74.6, 74.4, 55.7, 48.5, 42.4, 42.3, 39.3, 39.3, 38.0, 37.6, 37.3, 37.0, 29.1, 28.8, 27.8, 27.8, 25.1, 24.5, 21.1, 20.0, 19.6, 19.0, 18.9, 16.0; HRMS (ESI–TOF) calcd for $C_{24}H_{42}O_5Na$ $[M + Na]^+$ 433.2930, found 433.2934.

Carboxylic Acid 30b. To a solution of ester **29b** (326 mg, 0.743 mmol) in THF (4.5 mL), MeOH (1.5 mL), and H_2O (1.5 mL) was added $LiOH·H_2O$ (46.6 mg, 1.11 mmol) at room temperature. The mixture was stirred at the same temperature for 10 h. The mixture was neutralized with aqueous HCl at 0 °C. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 6:1, 3:1) gave carboxylic acid **30b** (222 mg, 73%): colorless oil; R_f = 0.17 (hexane/EtOAc = 2:1); IR (neat) 3433, 2955, 2930, 1697, 1631 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (d, *J* = 1.5 Hz, 1 H), 5.90 (ddd, *J* = 17.1, 10.5, 6.6 Hz, 1 H), 5.73 (s, 0.5 H), 5.71 (s, 0.5 H), 5.25 (dt, *J* = 17.1, 1.4 Hz, 1 H), 5.16 (dd, *J* = 10.5, 1.4 Hz, 1 H), 5.14–5.10 (m, 1 H), 4.66–4.60 (m, 2 H), 4.19–4.13 (m, 1 H), 3.88–3.82 (m, 1 H), 3.35 (s, 3 H), 2.57–2.42 (m, 2 H), 2.06–1.89 (m, 5 H), 1.67–1.52 (m, 2 H), 1.58 (s, 3 H), 1.43–1.10 (m, 8 H), 0.93–0.90 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 140.1, 140.1, 136.9, 135.0, 134.9, 129.3, 129.2, 125.0, 124.9, 115.5, 115.5, 95.6, 95.5, 75.1, 75.0, 74.7, 74.5, 55.7, 48.4, 48.4, 42.6, 42.4, 39.3, 39.2, 38.0, 37.7, 37.3, 37.1, 29.2, 29.0, 27.8, 25.4, 25.3, 24.5, 24.4, 21.1, 20.0, 19.7, 19.1, 19.0, 16.0; HRMS (ESI–TOF) calcd for $C_{24}H_{42}O_5Na$ $[M + Na]^+$ 433.2930, found 433.2927.

Lactone 31a. To a solution of MNBA (76.1 mg, 0.221 mmol) and DMAP (53.9 mg, 0.441 mmol) in CH_2Cl_2 (64 mL) was slowly added hydroxycarboxylic acid **30a** (60.4 mg, 0.147 mmol) in CH_2Cl_2 (6.0 mL at 0.4 mL/h + 2.0 mL at 4.0 mL/h + 2.0 mL at 4.0 mL/h) at room temperature with a syringe pump for 16 h. The mixture was stirred at the same temperature for further 4 h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was concentrated, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1) gave lactone **31a** (42.6 mg, 85%): colorless oil; R_f = 0.47 (hexane/EtOAc = 7:1); IR (neat) 2954, 2930, 1714, 1631 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (s, 0.5 H), 6.21 (s, 0.5 H), 5.91–5.80 (m, 1 H), 5.74 (s, 0.5 H), 5.66 (s, 0.5 H), 5.62–5.61 (m, 1 H), 5.26–5.18 (m, 2.5 H), 4.98 (t, *J* = 6.8 Hz, 0.5 H), 4.73–4.52 (m, 2 H), 3.87–3.81 (m, 0.5 H), 3.53–3.47 (m, 0.5 H), 3.38 (s, 1.5 H), 3.30 (s, 1.5 H), 2.89 (dd, *J* = 13.7, 4.8 Hz, 0.5 H), 2.77 (dd, *J* = 13.7, 3.7 Hz, 0.5 H), 2.31–2.24 (m, 1 H), 2.11–1.91 (m, 4.5 H), 1.84–1.77 (m, 0.5 H), 1.58 (s, 1.5 H), 1.57 (s, 1.5 H), 1.53–1.43 (m, 4.5 H), 1.37–1.21 (m, 3 H), 1.15–1.05 (m, 0.5 H), 0.97–0.86 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 165.6, 138.0, 137.4, 135.8, 134.7, 134.1, 127.0, 125.9, 125.7, 116.4, 115.9, 95.3, 94.8, 75.9, 75.3, 74.6, 55.6, 55.4, 45.9, 45.7, 43.4, 40.7, 38.3, 37.9,

37.6, 37.1, 37.0, 35.5, 29.7, 28.3, 27.9, 27.1, 24.4, 23.7, 23.5, 23.3, 21.7, 21.0, 20.5, 20.0, 19.6, 18.5, 16.2, 15.7; HRMS (ESI–TOF) calcd for $C_{24}H_{40}O_4Na$ $[M + Na]^+$ 415.2824, found 415.2818.

Lactone 31b. To a solution of MNBA (54.3 mg, 0.158 mmol) and DMAP (38.6 mg, 0.316 mmol) in CH_2Cl_2 (36 mL) was slowly added hydroxycarboxylic acid **30b** (36.0 mg, 87.7 μmol) in CH_2Cl_2 (4.0 mL at 0.4 mL/h + 2.0 mL at 4.0 mL/h + 2.0 mL at 4.0 mL/h) at 40 °C with a syringe pump for 11 h. The mixture was stirred at the same temperature for further 7 h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was concentrated, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1) gave lactone **31b** (26.7 mg, 78%): colorless oil; R_f = 0.47 (hexane/EtOAc = 7:1); IR (neat) 2954, 2929, 1716, 1631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.30 (s, 0.5 H), 6.25 (s, 0.5 H), 5.91–5.76 (m, 1 H), 5.68–5.58 (m, 2 H), 5.26–5.16 (m, 2 H), 5.06 (t, J = 7.2 Hz, 1 H), 4.65–4.62 (m, 2 H), 3.85–3.78 (m, 0.5 H), 3.72–3.66 (m, 0.5 H), 3.35 (s, 1.5 H), 3.34 (s, 1.5 H), 2.68–2.63 (m, 1 H), 2.50–2.43 (m, 1 H), 2.13–1.86 (m, 4.5 H), 1.85–1.77 (m, 0.5 H), 1.60 (s, 1.5 H), 1.58 (s, 1.5 H), 1.54–1.20 (m, 8 H), 0.97–0.92 (m, 6 H), 0.88 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 166.0, 137.8, 137.1, 135.5, 135.4, 134.6, 127.7, 127.6, 126.0, 125.5, 116.9, 115.7, 95.1, 94.9, 76.3, 76.2, 75.3, 73.7, 55.5, 55.5, 47.1, 45.9, 42.9, 38.5, 38.4, 37.4, 37.3, 36.6, 36.5, 28.8, 28.5, 28.2, 28.0, 25.3, 24.6, 24.1, 23.8, 21.3, 21.1, 20.1, 20.0, 19.9, 18.8, 16.3, 15.9; HRMS (ESI–TOF) calcd for $C_{24}H_{40}O_4Na$ $[M + Na]^+$ 415.2824, found 415.2825.

Alcohol 32a. To a solution of MOM ether **31a** (29.5 mg, 75.1 μmol) in Me_2S (1.5 mL) was added $BF_3{\cdot}OEt_2$ (46 μL, 0.376 mmol) at 0 °C. The mixture was stirred at the same temperature for 10 min. The mixture was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 8:1) gave alcohol **32a** (24.8 mg, 95%): colorless oil; R_f = 0.29 (hexane/EtOAc = 4:1); IR (neat) 3417, 2955, 2928, 2873, 1714, 1625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.28 (brs, 0.5 H), 6.20 (brs, 0.5 H), 5.91–5.80 (m, 1 H), 5.67 (s, 0.5 H), 5.65 (s, 0.5 H), 5.62–5.59 (m, 1 H), 5.26–5.18 (m, 2.5 H), 5.02 (t, J = 6.3 Hz, 0.5 H), 3.92–3.86 (m, 0.5 H), 3.68–3.62 (m, 0.5 H), 2.87 (ddd, J = 13.8, 3.4, 1.1 Hz, 0.5 H), 2.69 (ddd, J = 13.4, 5.9, 1.0 Hz, 0.5 H), 2.36 (ddd, J = 13.4, 6.6, 0.7 Hz, 0.5 H), 2.26 (dd, J = 13.8, 7.1 Hz, 0.5 H), 2.12–1.95 (m, 4 H), 1.86–1.78 (m, 1 H), 1.61–1.37 (m, 8 H), 1.59 (s, 1.5 H), 1.58 (s, 1.5 H), 1.25–1.10 (m, 1 H), 0.98–0.90 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 165.8, 137.8, 137.7, 135.5, 134.6, 134.4, 134.0, 127.7, 127.0, 125.8, 125.7, 116.4, 115.9, 76.0, 75.8, 69.5, 69.0, 46.3, 45.9, 45.3, 42.6, 41.7, 40.7, 37.5, 37.2, 37.1, 35.0, 29.3, 28.8, 28.3, 28.1, 25.4, 23.8, 23.4, 23.1, 21.8, 20.8, 20.7, 20.3, 20.0, 18.5, 16.1, 15.9; HRMS (ESI–TOF) calcd for $C_{22}H_{36}O_3Na$ $[M + Na]^+$ 371.2562, found 371.2559.

Alcohol 32b. To a solution of MOM ether **31b** (42.7 mg, 0.109 mmol) in Me_2S (2.2 mL) was added $BF_3{\cdot}OEt_2$ (67 μL, 0.545 mmol) at 0 °C. The mixture was stirred at the same temperature for 10 min. The mixture was quenched with saturated aqueous $NaHCO_3$. The

mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 8:1) gave alcohol **32b** (34.6 mg, 91%): colorless oil; R_f = 0.29 (hexane/EtOAc = 4:1); IR (neat) 3417, 2955, 2927, 2868, 1714, 1627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.29 (t, J = 1.3 Hz, 1 H), 5.91–5.78 (m, 1 H), 5.69–5.62 (m, 2 H), 5.26–5.18 (m, 2 H), 5.14–5.06 (m, 1 H), 3.90–3.83 (m, 0.5 H), 3.81–3.75 (m, 0.5 H), 2.74 (dd, J = 14.3, 3.8 Hz, 0.5 H), 2.55 (d, J = 5.6 Hz, 1 H), 2.30 (dd, J = 14.3, 7.7 Hz, 0.5 H), 2.11–1.95 (m, 4 H), 1.89–1.76 (m, 1 H), 1.65–1.29 (m, 8 H), 1.60 (s, 1.5 H), 1.58 (s, 1.5 H), 1.18–1.07 (m, 1 H), 0.96–0.91 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.9, 138.1, 137.2, 135.5, 135.0, 134.4, 134.4, 127.9, 127.6, 126.2, 125.6, 117.0, 116.2, 76.3, 75.6, 69.9, 68.2, 47.6, 46.0, 44.6, 44.6, 40.7, 40.6, 38.6, 37.4, 36.7, 36.2, 29.1, 28.9, 28.4, 25.4, 25.0, 24.4, 24.2, 21.3, 21.0, 21.0, 20.6, 20.0, 19.4, 16.3, 16.1; HRMS (ESI–TOF) calcd for $C_{22}H_{36}O_3Na$ $[M + Na]^+$ 371.2562, found 371.2567.

Butenolide 1a. To a solution of triene **32a** (10.3 mg, 29.6 μmol) in toluene (6.0 mL) was added the second-generation Hoveyda–Grubbs catalyst (**33**) (1.9 mg, 2.96 μmol) at room temperature. The mixture was stirred at 100 °C for 30 h. The mixture was filtered through short column chromatography (hexane/EtOAc = 1:1). Concentration and column chromatography (hexane/EtOAc = 3:1) gave butenolide **34a** (3.3 mg) and triene **32a** (3.9 mg, 38% recovery). Butenolide **34a** was used for the next step without further purification.

To a solution of alcohol **34a** obtained above (3.3 mg) in CH_2Cl_2 (1.0 mL) were added MS4Å (3.0 mg), NMO (6.0 mg, 51.5 μmol), and a catalytic amount of TPAP at room temperature. The mixture was stirred at the same temperature for 10 min. The mixture was filtered through short column chromatography (hexane/EtOAc = 3:1). Concentration and column chromatography (hexane/EtOAc = 8:1) gave butenolide **1a** (2.5 mg, 27% in two steps, 43% based on recovered **32a** in two steps): colorless amorphous solid; R_f = 0.46 (hexane/EtOAc = 2:1); $[\alpha]_D^{29}$ +92.2 (*c* 0.19, $CHCl_3$); IR (neat) 2955, 2914, 2886, 1746, 1710 cm^{-1}; ^1H and ^{13}C NMR Table S1; HRMS (ESI–TOF) calcd for $C_{20}H_{30}O_3Na$ $[M + Na]^+$ 341.2093, found 341.2092.

Butenolide 1b. To a solution of triene **32b** (13.0 mg, 37.3 μmol) in toluene (7.5 mL) was added the second-generation Hoveyda–Grubbs catalyst (**33**) (1.2 mg, 1.87 μmol) at room temperature. The mixture was stirred at 100 °C for 30 h. The mixture was filtered through short column chromatography (hexane/EtOAc = 1:1). Concentration and column chromatography (hexane/EtOAc = 3:1) gave butenolide **34b** (4.2 mg) and triene **32b** (4.8 mg, 37% recovery). Butenolide **34b** was used for the next step without further purification.

To a solution of alcohol **34b** obtained above (4.2 mg) in CH_2Cl_2 (1.0 mL) were added MS4Å (5.0 mg), NMO (7.7 mg, 65.5 μmol), and a catalytic amount of TPAP at room temperature. The mixture was stirred at the same temperature for 10 min. The mixture was filtered through short column chromatography (hexane/EtOAc = 3:1). Concentration and column chromatography (hexane/EtOAc = 8:1) gave butenolide **1b** (3.6 mg, 30% in two steps, 48% based on recovered **32b** in two steps): colorless amorphous solid; R_f = 0.46

(hexane/EtOAc = 2:1); $[\alpha]_D^{29}$ +97.4 (*c* 0.21, $CHCl_3$); IR (neat) 2956, 2925, 2876, 1751, 1710 cm^{-1}; ^1H and ^{13}C NMR Table S2; HRMS (ESI–TOF) calcd for $C_{20}H_{30}O_3Na$ $[M + Na]^+$ 341.2093, found 341.2098.

Alcohol 37. To a solution of alcohol **25a** (77.3 mg, 0.195 mmol) in CH_2Cl_2 (2.0 mL) were added $PhI(OAc)_2$ (94.2 mg, 0.293 mmol) and TEMPO (6.01 mg, 39.0 μmol) at room temperature. The mixture was stirred at the same temperature for 2 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 80:1) gave the corresponding aldehyde (62.5 mg), which was used for the next step without further purification.

A mixture of the aldehyde obtained above (62.5 mg) and chiral allylic boronate **35** (68.7 mg, 0.187 mmol) in toluene (0.1 mL) was stirred at room temperature for 38 h. After the reaction was quenched with H_2O, the mixture was diluted with EtOAc and dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 10:1) gave a diastereomeric mixture of alcohol **36** and its C6 stereoisomer (100 mg, dr = 4.4:1), which was used for the next step without further purification.

To a solution of a diastereomeric mixture of alcohol **36** and its C6 stereoisomer (100 mg, dr = 4.4:1) in CH_2Cl_2 (1.5 mL) were added *i*-Pr_2NEt (0.48 mL, 2.78 mmol), MOMCl (0.18 mL, 2.34 mmol), and TBAI (28.8 mg, 78.0 μmol) at room temperature. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 30:1) gave a diastereomeric mixture of the corresponding MOM ethers (96.7 mg, dr = 4.4:1), which was used for the next step without further purification.

To a solution of a diastereomeric mixture of the TBS ethers obtained above (96.7 mg, dr = 4.4:1) in THF (1.6 mL) was added TBAF (1.0 M in THF, 0.8 mL, 0.800 mmol) at room temperature. The mixture was stirred at 60 °C for 5 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1) gave a diastereomeric mixture of alcohol **37** and its C6 stereoisomer (52.2 mg, 61% in four steps, dr = 4.4:1): colorless oil; R_f = 0.42 (hexane/EtOAc = 4:1); $[\alpha]_D^{26}$ +7.8 (*c* 0.98, $CHCl_3$); IR (neat) 3476, 2955, 2927, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.21 (brs, 1 H), 5.90 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1 H), 5.62–5.59 (m, 1 H), 5.25 (d, *J* = 17.2 Hz, 1 H), 5.15 (d, *J* = 10.4 Hz, 1 H), 5.10 (t, *J* = 7.2 Hz, 1 H), 4.68–4.57 (m, 2 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 4.14–4.11 (m, 1 H), 3.86–3.80 (m, 1 H), 3.34–3.33 (m, 3 H), 2.58–2.38 (m, 2 H), 2.06–1.91 (m, 5 H), 1.59 (s, 3 H), 1.44–1.26 (m, 7 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.22–1.09 (m, 1 H), 0.94–0.90 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 140.3, 137.7, 135.1, 127.1, 124.8, 124.7, 115.3, 95.6, 95.5, 74.9, 74.4, 60.7, 55.6, 48.8, 42.5, 39.4, 38.4, 38.0, 37.7, 37.0, 29.2, 28.9, 27.8, 25.4, 25.3, 24.6, 21.2, 20.0, 19.4,

18.9, 16.0, 14.2; HRMS (ESI–TOF) calcd for $C_{26}H_{46}O_5Na$ $[M + Na]^+$ 461.3243, found 461.3241.

Lactone 38. To a solution of a diastereomeric mixture of ester **37** and its C6 stereoisomer (148 mg, 0.339 mmol, dr = 4.4:1) in THF (4.1 mL), MeOH (1.4 mL), and H_2O (1.4 mL) was added $LiOH·H_2O$ (42.6 mg, 1.01 mmol) at room temperature. The mixture was stirred at the same temperature for 17 h. The mixture was neutralized with aqueous HCl at 0 °C. The mixture was diluted with EtOAc and washed with H_2O and brine. The aqueous phase was extracted with EtOAc three times and the combined organic phase was dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 3:1) gave a diastereomeric mixture of the corresponding carboxylic acids (130 mg, dr = 4.4:1), which was used for the next step without further purification.

To a solution of MNBA (158 mg, 0.458 mmol) and DMAP (112 mg, 0.918 mmol) in CH_2Cl_2 (138 mL) was slowly added a diastereomeric mixture of the hydroxycarboxylic acids obtained above (130 mg, dr = 4.4:1) in CH_2Cl_2 (9.0 mL at 0.4 mL/h + 3.0 mL at 6.0 mL/h + 3.0 mL at 6.0 mL/h) at room temperature with a syringe pump for 24 h. The mixture was stirred at the same temperature for further 11 h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was concentrated, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1) gave a diastereomeric mixture of lactone **38** and its C6 stereoisomer (102 mg, 77% in two steps, dr = 4.4:1): colorless oil; R_f = 0.58 (hexane/EtOAc = 7:1); $[\alpha]_D^{27}$ –2.8 (*c* 0.99, $CHCl_3$); IR (neat) 2954, 2927, 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.25–6.20 (m, 1 H), 5.92–5.80 (m, 1 H), 5.74 (s, 1 H), 5.69–5.62 (m, 1 H), 5.27–5.18 (m, 2 H), 4.98 (t, *J* = 6.8 Hz, 1 H), 4.73–4.52 (m, 2 H), 3.87–3.81 (m, 1 H), 3.39–3.29 (m, 3 H), 2.91–2.74 (m, 1 H), 2.31–2.24 (m, 1 H), 2.11–1.93 (m, 5 H), 1.85–1.77 (m, 1 H), 1.59–1.21 (m, 10 H), 0.98–0.86 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 137.4, 135.8, 134.7, 134.1, 127.0, 125.7, 116.4, 115.9, 95.3, 94.8, 75.9, 75.3, 74.6, 55.5, 55.4, 45.9, 45.7, 43.4, 40.8, 38.4, 37.9, 37.6, 37.1, 37.0, 35.5, 29.7, 28.3, 27.9, 27.1, 24.4, 23.7, 23.5, 23.3, 21.7, 21.0, 20.5, 20.0, 19.6, 18.5, 16.2, 15.7; HRMS (ESI–TOF) calcd for $C_{24}H_{40}O_4Na$ $[M + Na]^+$ 415.2824, found 415.2825.

Alcohol S8. To a solution of a diastereomeric mixture of MOM ether **38** and its C6 stereoisomer (6.9 mg, 17.6 μmol, dr = 4.4:1) in Me_2S (0.4 mL) was added $BF_3·OEt_2$ (11 μL, 88.0 μmol) at 0 °C. The mixture was stirred at the same temperature for 30 min. The mixture was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1) gave a diastereomeric mixture of alcohol **S8** and its C6 stereoisomer (5.3 mg, 86%, dr = 4.4:1): colorless oil; R_f = 0.38 (hexane/EtOAc = 4:1); $[\alpha]_D^{26}$ –1.5 (*c* 1.02, $CHCl_3$); IR (neat) 3415, 2955, 2927, 2870, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.28 (s, 0.19 H), 6.20 (s, 0.81 H), 6.28–6.20 (m, 1 H), 5.86 (ddd, *J* = 16.8, 10.8, 5.6 Hz, 1 H), 5.67–5.60 (m, 2 H), 5.23 (d, *J* = 16.8 Hz, 1 H), 5.20 (d, *J* = 10.8 Hz, 1 H), 5.03–5.00 (m, 1 H), 3.92–3.86 (m, 1 H), 2.87 (dd, *J* = 13.6, 3.6 Hz, 0.19 H), 2.69 (dd, *J* = 13.6,

6.0 Hz, 0.81 H), 2.38–2.23 (m, 1 H), 2.05–1.96 (m, 4 H), 1.86–1.78 (m, 1 H), 1.68–1.36 (m, 7 H), 1.57 (s, 3 H), 1.17–1.10 (m, 1 H), 0.99–0.89 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 165.8, 137.8, 137.7, 135.5, 135.0, 134.6, 134.4, 134.0, 127.6, 127.0, 125.8, 116.4, 116.0, 76.0, 75.8, 69.5, 69.0, 46.3, 45.9, 45.3, 42.6, 41.7, 40.7, 37.4, 37.2, 37.1, 35.0, 29.3, 28.8, 28.3, 28.1, 25.4, 23.8, 23.4, 23.1, 21.8, 20.8, 20.7, 20.3, 20.0, 18.5, 16.1, 16.0; HRMS (ESI–TOF) calcd for $C_{22}H_{36}O_3Na$ $[M + Na]^+$ 371.2562, found 371.2562.

Sarcophytonolide E (2). To a solution of a diastereomeric mixture of triene **S8** and its C6 stereoisomer (4.0 mg, 11.5 μmol, dr = 4.4:1) in toluene (2.3 mL) was added the second-generation Hoveyda–Grubbs catalyst (**33**) (0.7 mg, 1.15 μmol) at room temperature. The mixture was stirred at 100 °C for 32 h. The mixture was filtered through short column chromatography (hexane/EtOAc = 1:1). Concentration and column chromatography (hexane/EtOAc = 7:1, 2:1) gave sarcophytonolide E (**2**) (1.3 mg, 35%, 51% based on recovered **S8**) and triene **S8** (1.2 mg, 30% recovery): colorless oil; R_f = 0.39 (hexane/EtOAc = 1:1); $[\alpha]_D^{27}$ +48.7 (*c* 0.17, $CHCl_3$); literature[10b] $[\alpha]_D^{20}$ +30 (*c* 0.29, $CHCl_3$); IR (neat) 3424, 2950, 2925, 2870, 2852, 1754 cm^{-1}; ^{1}H and ^{13}C NMR Table S3; HRMS (ESI–TOF) calcd for $C_{20}H_{32}O_3Na$ $[M + Na]^+$ 343.2249, found 343.2250.

Pivalate 39. To a solution of geraniol (1.0 mL, 5.71 mmol) in CH_2Cl_2 (19 mL) were added pyridine (0.69 mL, 8.57 mmol) and PivCl (0.83 mL, 6.85 mmol) at room temperature. After the mixture was stirred at the same temperature for 2 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1) gave pivalate **39** (1.31 g, 96%): colorless oil; R_f = 0.50 (hexane/EtOAc = 10:1); IR (neat) 2970, 2924, 2870, 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (td, *J* = 6.8, 1.2 Hz, 1 H), 5.10–5.06 (m, 1 H), 4.57 (d, *J* = 6.8 Hz, 2 H), 2.13–2.02 (m, 4 H), 1.70 (s, 3 H), 1.68 (s, 3 H), 1.61 (s, 3 H), 1.20 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 141.5, 131.6, 123.7, 118.7, 61.3, 39.5, 38.8, 27.3, 26.4, 25.7, 17.7, 16.5; HRMS (ESI–TOF) calcd for $C_{15}H_{26}O_2Na$ $[M + Na]^+$ 261.1830, found 261.1832.

Allylic Alcohol 40. To a mixture of SeO_2 (8.2 mg, 73.5 μmol) and salicylic acid (20.3 mg, 0.147 mmol) in CH_2Cl_2 (2.0 mL) was added TBHP (ca. 5.0 M solution in 2,2,4-trimethylpentane, 0.59 mL, 2.94 mmol) at room temperature. After the mixture was stirred at the same temperature for 10 min, to the mixture was added alkene **39** (351 mg, 1.47 mmol) in CH_2Cl_2 (0.5 mL + 0.3 mL + 0.2 mL) at room temperature. After the mixture was stirred at the same temperature for 7 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ at 0 °C. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration gave the mixture of allylic alcohol **40** and the corresponding α,β-unsaturated aldehyde (414 mg), which was used for the next step without further purification.

To a solution of the mixture obtained above (414 mg) in EtOH (7.4 mL) was added $NaBH_4$ (27.8 mg, 0.735 mmol) at 0 °C. After the mixture was stirred at the same temperature for 1 h,

the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1) gave allylic alcohol **40** (214 mg, 57% in two steps): colorless oil; R_f = 0.22 (hexane/EtOAc = 4:1); IR (neat) 3437, 2973, 2927, 2868, 1727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.36 (td, J = 6.8, 1.3 Hz, 1 H), 5.31 (td, J = 6.8, 1.2 Hz, 1 H), 4.56 (d, J = 6.8 Hz, 2 H), 3.99 (s, 2 H), 2.20–2.14 (m, 2 H), 2.10–2.07 (m, 2 H), 1.70 (s, 3 H), 1.67 (s, 3 H), 1.19 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 140.9, 135.1, 125.3, 119.1, 68.9, 61.4, 39.1, 38.8, 27.3, 25.8, 16.5, 13.8; HRMS (ESI–TOF) calcd for $C_{15}H_{26}O_3Na$ $[M + Na]^+$ 277.1780, found 277.1783.

Allylic Bromide 41. To a solution of allylic alcohol **40** (524 mg, 2.06 mmol) in CH_3CN (10 mL) were added PPh_3 (808 mg, 3.08 mmol) and CBr_4 (1.01 g, 3.05 mmol) at 0 °C. After the mixture was stirred at the same temperature for 20 min, the mixture was filtered through short column chromatography (hexane/EtOAc = 10:1). Concentration and column chromatography (hexane/EtOAc = 50:1) gave allylic bromide **41** (615 mg, 94%): colorless oil; R_f = 0.36 (hexane/EtOAc = 20:1); IR (neat) 2972, 2932, 2870, 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.57 (t, J = 6.8 Hz, 1 H), 5.34–5.30 (m, 1 H), 4.57 (d, J = 6.8 Hz, 2 H), 3.96 (s, 2 H), 2.19–2.07 (m, 4 H), 1.76 (s, 3 H), 1.70 (s, 3 H), 1.20 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 140.6, 132.3, 130.4, 119.3, 61.2, 41.5, 38.8, 38.6, 27.3, 26.5, 16.5, 14.7; HRMS (ESI–TOF) calcd for $C_{15}H_{25}BrO_2Na$ $[M + Na]^+$ 339.0936, found 339.0946.

Sulfone 42. To a solution of sulfone **20** (142 mg, 0.284 mmol) in THF (2.0 mL) was added NaHMDS (1.0 M in THF, 0.34 mL, 0.340 mmol) at –78 °C. The mixture was stirred at the same temperature for 30 min. To the mixture was added allylic bromide **41** (117 mg, 0.369 mmol) in THF (0.5 mL + 0.3 mL + 0.2 mL) at –78 °C. The mixture was gradually warmed up to room temperature for 3 h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1) gave sulfone **42** (186 mg, 89%): colorless oil; R_f = 0.36 (hexane/EtOAc = 10:1); $[\alpha]_D^{25}$ +18.0 (c 1.05, $CHCl_3$); IR (neat) 2956, 2924, 2852, 1728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82–7.80 (m, 2 H), 7.58–7.55 (m, 1 H), 7.49–7.45 (m, 2 H), 5.29 (t, J = 6.8 Hz, 1 H), 5.11 (t, J = 6.3 Hz, 1 H), 4.55 (d, J = 6.8 Hz, 2 H), 4.33–4.30 (m, 1 H), 3.74–3.64 (m, 2 H), 3.47 (d, J = 8.5 Hz, 1 H), 2.72–2.58 (m, 2 H), 2.36 (d, J = 6.7 Hz, 1 H), 2.17–2.09 (m, 1 H), 1.98–1.96 (m, 2 H), 1.91–1.84 (m, 2 H), 1.67 (s, 3 H), 1.22 (s, 3 H), 1.20 (s, 9 H), 0.95 (d, J = 8.4 Hz, 3 H), 0.94 (s, 9 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.87 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 3 H), 0.13 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 141.3, 140.9, 132.9, 130.8, 128.8, 128.5, 127.0, 118.8, 73.8, 68.3, 61.8, 61.3, 44.2, 39.0, 38.8, 35.6, 27.3, 26.4, 26.3, 26.2, 23.2, 20.6, 18.7, 18.4, 16.5, 15.4, –3.2, –4.7, –5.1, –5.2; HRMS (ESI–TOF) calcd for $C_{40}H_{72}O_6SSi_2Na$ $[M + Na]^+$ 759.4486, found 759.4490.

Alcohol 43. To a solution of pivalate **42** (1.14 g, 1.55 mmol) in CH_2Cl_2 (16 mL) was added DIBAL-H (1.02 M in hexane, 4.6 mL, 4.69 mmol) at –78 °C. The mixture was stirred at the

same temperature for 20 min. The reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and short column chromatography (hexane/EtOAc = 3:1) gave the corresponding alcohol (949 mg), which was used for the next step without further purification.

To a solution of lithium wire (1.01 g, 145 mmol) in liquid NH_3 (60 mL) was added sulfone **42** (949 mg, 1.45 mmol) in THF/*t*-BuOH (20 mL/10 mL) and THF (3.0 mL + 2.0 mL for rinse) at –78 °C. The mixture was stirred at the same temperature for 20 min. The reaction was quenched with a 1:1 solution of saturated aqueous NH_4Cl and MeOH. The mixture was diluted with EtOAc, warmed up to room temperature, and stirred at the same temperature. The mixture was washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1, 3:1) gave alcohol **43** (508 mg) and sulfone **42** (201 mg).

To a solution of lithium wire (214 mg, 30.8 mmol) in liquid NH_3 (30 mL) was added sulfone **42** recovered above (201 mg) in THF/*t*-BuOH (4.2 mL/2.1 mL) and THF (1.0 mL + 1.0 mL for rinse) at –78 °C. The mixture was stirred at the same temperature for 20 min. The reaction was quenched with a 1:1 solution of saturated aqueous NH_4Cl and MeOH. The mixture was diluted with EtOAc, warmed up to room temperature, and stirred at the same temperature. The mixture was washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1) gave alcohol **43** (117 mg, totally 625 mg, 79% in two steps): colorless oil; R_f = 0.41 (hexane/EtOAc = 4:1); $[\alpha]_D^{24}$ –3.9 (*c* 1.07, $CHCl_3$); IR (neat) 3324, 2955, 2727, 2856 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.42 (td, *J* = 6.8, 1.2 Hz, 1 H), 5.11 (t, *J* = 6.2 Hz, 1 H), 4.16 (d, *J* = 6.8 Hz, 2 H), 3.79–3.76 (m, 1 H), 3.60–3.50 (m, 2 H), 2.14–2.02 (m, 5 H), 1.92–1.85 (m, 2 H), 1.69 (s, 3 H), 1.61 (s, 3 H), 1.48–1.29 (m, 4 H), 0.90–0.88 (m, 6 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 135.9, 123.6, 123.3, 74.8, 65.8, 59.4, 46.1, 39.7, 39.1, 27.1, 26.4, 26.1, 26.1, 24.3, 22.6, 19.4, 18.4, 18.3, 16.4, 16.1, –3.9, –4.7, –5.2, –5.3; HRMS (ESI–TOF) calcd for $C_{29}H_{60}O_3Si_2Na$ $[M + Na]^+$ 535.3979, found 535.3976.

Alcohol 44. To a solution of alcohol **43** (701 mg, 1.37 mmol) in CH_2Cl_2 (14 mL) were added pyridine (0.17 mL, 2.06 mmol) and PivCl (0.20 mL, 1.64 mmol) at room temperature. The mixture was stirred at the same temperature for 5 h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O, and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 60:1) gave the corresponding pivalate (770 mg), which was used for the next step without further purification.

To a solution of the bis-TBS ether obtained above (770 mg) in MeOH (6.5 mL) and CH_2Cl_2 (6.5 mL) was added CSA (89.9 mg, 0.387 mmol) at 0 °C. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with Et_3N. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 15:1) gave alcohol **44** (317 mg) and the bis-TBS ether

(309 mg).

To a solution of the bis-TBS ether recovered above (309 mg) in MeOH (2.6 mL) and CH_2Cl_2 (2.6 mL) was added CSA (36.0 mg, 0.155 mmol) at 0 °C. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with Et_3N. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 15:1) gave alcohol **44** (135 mg) and the bis-TBS ether (112 mg).

To a solution of the bis-TBS ether recovered above (112 mg) in MeOH (1.0 mL) and CH_2Cl_2 (1.0 mL) was added CSA (13.1 mg, 56.4 μmol) at 0 °C. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with Et_3N. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 15:1) gave alcohol **44** (50.8 mg, totally 503 mg, 76% in two steps): colorless oil; R_f = 0.39 (hexane/EtOAc = 7:1); $[\alpha]_D^{24}$ +5.9 (*c* 1.05, $CHCl_3$); IR (neat) 3501, 2956, 2927, 2852, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.32 (td, *J* = 6.8, 1.2 Hz, 1 H), 5.11–5.08 (m, 1 H), 4.57 (d, *J* = 6.8 Hz, 2 H), 3.81–3.77 (m, 1 H), 3.58–3.56 (m, 2 H), 2.11–1.94 (m, 6 H), 1.86–1.78 (m, 1 H), 1.70 (s, 3 H), 1.63 (brs, 1 H), 1.60 (s, 3 H), 1.43–1.25 (m, 3 H), 1.20 (s, 9 H), 0.92 (s, 9 H), 0.91 (d, *J* = 6.0 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 0.11 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 141.6, 135.8, 123.6, 118.7, 74.6, 64.3, 61.4, 47.2, 39.7, 39.6, 38.8, 27.9, 27.3, 26.4, 26.0, 24.7, 21.7, 19.4, 18.2, 16.6, 16.1, –4.2, –4.3; HRMS (ESI–TOF) calcd for $C_{28}H_{54}O_4SiNa$ $[M + Na]^+$ 505.3689, found 505.3694.

Alcohol 45. To a solution of alcohol **44** (250 mg, 0.518 mmol) in CH_2Cl_2 (5.2 mL) were added $PhI(OAc)_2$ (250 mg, 0.777 mmol) and TEMPO (16.3 mg, 0.104 mmol) at room temperature. The mixture was stirred at the same temperature for 22 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 30:1) gave the corresponding aldehyde (212 mg), which was used for the next step without further purification.

To a suspension of $Ph_3P^+CH_3Br^-$ (393 mg, 1.10 mmol) in THF (3.0 mL) was added NaHMDS (1.0 M in THF, 1.06 mL, 1.06 mmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. To the mixture was added the aldehyde obtained above (212 mg) in THF (1.0 mL + 0.2 mL + 0.2 mL) at 0 °C. The mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 60:1) gave the corresponding alkene (199 mg), which was used for the next step without further purification.

To a solution of the pivalate obtained above (199 mg) in CH_2Cl_2 (4.1 mL) was added DIBAL-H (1.02 M in hexane, 1.2 mL, 1.24 mmol) at –78 °C. The mixture was stirred at the same temperature for 20 min. The reaction was quenched with MeOH. The mixture was

filtered through a Celite pad and washed with EtOAc. Concentration and column chromatography (hexane/EtOAc = 7:1) gave alcohol **45** (152 mg, 74% in three steps): colorless oil; R_f = 0.36 (hexane/EtOAc = 4:1); $[\alpha]_D^{24}$ +7.0 (*c* 1.08, $CHCl_3$); IR (neat) 3324, 2955, 2927, 2856 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1 H), 5.42 (td, *J* = 6.9, 1.1 Hz, 1 H), 5.15 (dt, *J* = 17.2, 1.4 Hz, 1 H), 5.09–5.06 (m, 2 H), 4.16–4.12 (m, 3 H), 2.14–2.01 (m, 5 H), 1.95–1.85 (m, 2 H), 1.69 (s, 3 H), 1.59 (s, 3 H), 1.43–1.35 (m, 2 H), 1.30–1.17 (m, 2 H), 0.90 (d, *J* = 6.0 Hz, 3 H), 0.90 (s, 9 H), 0.88 (d, *J* = 6.8 Hz, 3 H), 0.05 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 139.8, 136.0, 123.6, 123.3, 114.5, 75.5, 59.4, 49.9, 39.6, 27.7, 26.4, 26.0, 24.5, 21.9, 19.0, 18.3, 16.4, 16.0, –4.0, –4.8; HRMS (ESI–TOF) calcd for $C_{24}H_{46}O_2SiNa$ $[M + Na]^+$ 417.3165, found 417.3166.

Alcohol 47. To a solution of alcohol **45** (127 mg, 0.322 mmol) in CH_2Cl_2 (3.2 mL) were added $PhI(OAc)_2$ (156 mg, 0.483 mmol) and TEMPO (10.1 mg, 64.4 μmol) at room temperature. The mixture was stirred at the same temperature for 5 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 20:1) gave the corresponding aldehyde (121 mg), which was used for the next step without further purification.

A mixture of the aldehyde obtained above (121 mg) and chiral allylic boronate **35** (136 mg, 0.370 mmol) in toluene (0.2 mL) was stirred at room temperature for 2 days. After the reaction was quenched with H_2O, the mixture was diluted with EtOAc and dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 8:1) gave alcohol **46** (231 mg, dr = 17:1), which was used for the next step without further purification.

To a solution of alcohol **46** obtained above (231 mg) in CH_2Cl_2 (3.1 mL) were added *i*-Pr_2NEt (0.95 mL, 5.54 mmol), MOMCl (0.35 mL, 4.62 mmol), and TBAI (56.9 mg, 0.154 mmol) at room temperature. The mixture was stirred at the same temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 15:1) gave the corresponding MOM ether (210 mg), which was used for the next step without further purification.

To a solution of the TBS ether obtained above (210 mg) in THF (3.1 mL) was added TBAF (1.0 M in THF, 1.5 mL, 1.50 mmol) at room temperature. The mixture was stirred at 60 °C for 5 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1) gave alcohol **47** (107 mg, 76% in four steps): colorless oil; R_f = 0.31 (hexane/EtOAc = 4:1); $[\alpha]_D^{21}$ +53.2 (*c* 1.06, $CHCl_3$); IR (neat) 3481, 2954, 2932, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.20 (d, *J* = 1.6 Hz, 1 H), 5.90 (ddd, *J* = 17.1, 10.5, 6.4 Hz, 1 H), 5.60 (s, 1 H), 5.25 (d, *J* = 17.1 Hz, 1 H), 5.16 (d, *J* = 10.5 Hz, 1 H), 5.07 (t, *J* = 6.5 Hz, 1 H), 5.01 (d, *J* = 9.0 Hz, 1 H), 4.64 (d, *J* = 6.4 Hz, 1 H), 4.58–4.53 (m, 1 H), 4.45 (d, *J* = 6.4 Hz, 1 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 4.12 (t,

J = 6.4 Hz, 1 H), 3.31 (s, 3 H), 2.60 (dd, *J* = 13.8, 7.9 Hz, 1 H), 2.47 (dd, *J* = 13.8, 5.7 Hz, 1 H), 2.10–1.91 (m, 7 H), 1.66 (d, *J* = 1.0 Hz, 3 H), 1.59 (s, 3 H), 1.54 (brs, 1 H), 1.37–1.26 (m, 3 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 0.91 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 140.4, 137.2, 135.6, 127.1, 124.5, 123.9, 115.3, 93.2, 74.9, 70.4, 60.6, 55.2, 48.8, 39.6, 39.4, 38.6, 27.8, 26.4, 24.6, 21.2, 18.9, 16.7, 16.1, 14.3; HRMS (ESI–TOF) calcd for $C_{26}H_{44}O_5Na$ $[M + Na]^+$ 459.3087, found 459.3083.

Lactone 48. To a solution of ester **47** (38.8 mg, 88.9 μmol) in THF (0.6 mL), MeOH (0.2 mL), and H_2O (0.2 mL) was added $LiOH·H_2O$ (7.5 mg, 0.178 mmol) at room temperature. The mixture was stirred at the same temperature for 41 h. The mixture was neutralized with aqueous HCl at 0 °C. The mixture was diluted with EtOAc and washed with H_2O and brine. The aqueous phase was extracted with EtOAc three times and the combined organic phase was dried over Na_2SO_4. Concentration and short column chromatography (CH_2Cl_2/MeOH = 20:1) gave the corresponding carboxylic acid (39.9 mg), which was used for the next step without further purification.

To a solution of MNBA (73.3 mg, 0.213 mmol) and DMAP (52.2 mg, 0.427 mmol) in CH_2Cl_2 (34 mL) was slowly added the hydroxycarboxylic acid obtained above (39.9 mg) in CH_2Cl_2 (6.4 mL at 0.4 mL/h + 2.0 mL at 2.0 mL/h + 2.0 mL at 2.0 mL/h) at 40 °C with a syringe pump for 18 h. The mixture was stirred at the same temperature for further 33 h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was concentrated, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1) gave lactone **48** (22.8 mg, 66% in two steps): colorless oil; R_f = 0.44 (hexane/EtOAc = 7:1); $[\alpha]_D^{21}$ +134 (*c* 1.03, $CHCl_3$); IR (neat) 2954, 2929, 1714 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (d, *J* = 1.2 Hz, 1 H), 5.93–5.85 (m, 1 H), 5.73 (s, 1 H), 5.71–5.69 (m, 1 H), 5.27–5.18 (m, 2 H), 4.96–4.91 (m, 2 H), 4.87–4.81 (m, 1 H), 4.68 (d, *J* = 6.4 Hz, 1 H), 4.54 (d, *J* = 6.4 Hz, 1 H), 3.39 (s, 3 H), 3.04 (dd, *J* = 13.2, 5.2 Hz, 1 H), 2.35 (dd, *J* = 13.2, 8.9 Hz, 1 H), 2.19–1.99 (m, 6 H), 1.76–1.68 (m, 1 H), 1.58 (s, 3 H), 1.54 (s, 3 H), 1.51–1.38 (m, 3 H), 0.94 (d, *J* = 7.1 Hz, 3 H), 0.92 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 140.7, 137.4, 134.6, 127.3, 125.1, 124.2, 116.3, 93.3, 76.0, 69.3, 55.3, 45.1, 38.5, 38.4, 36.9, 29.9, 24.3, 23.8, 21.6, 20.0, 15.9, 15.8; HRMS (ESI–TOF) calcd for $C_{24}H_{38}O_4Na$ $[M + Na]^+$ 413.2668, found 413.2673.

Butenolide S11. To a solution of tetraene **48** (4.0 mg, 10.2 μmol) in toluene (2.0 mL) was added the second-generation Hoveyda–Grubbs catalyst (**33**) (0.6 mg, 1.02 μmol) at room temperature. The mixture was stirred at 100 °C for 2 days. The mixture was filtered through short column chromatography (EtOAc). Concentration and column chromatography (hexane/EtOAc = 6:1) gave butenolide **S11** (2.8 mg, 76%): colorless solid; R_f = 0.22 (hexane/EtOAc = 4:1); $[\alpha]_D^{22}$ +212 (*c* 0.49, $CHCl_3$); IR (neat) 2959, 2928, 2845, 1747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1 H), 4.98–4.91 (m, 2 H), 4.69 (d, *J* = 6.4 Hz, 1 H), 4.69–4.64 (m, 2 H), 4.56 (d, *J* = 6.4 Hz, 1 H), 3.40 (s, 3 H), 2.83 (d, *J* = 12.8 Hz, 1 H), 2.40 (dd, *J* = 12.8, 11.1 Hz, 1 H), 2.18–2.10 (m, 6 H), 1.71–1.50 (m, 2 H), 1.54 (s, 3 H), 1.50

(s, 3 H), 1.31–1.21 (m, 2 H), 0.94 (d, J = 5.9 Hz, 3 H), 0.92 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 151.6, 141.1, 133.0, 129.0, 125.6, 124.9, 93.4, 83.6, 69.4, 55.4, 44.9, 38.7, 37.0, 32.5, 28.8, 23.8, 22.8, 20.1, 17.7, 16.1, 16.0; HRMS (ESI–TOF) calcd for $C_{22}H_{34}O_4Na$ $[M + Na]^+$ 385.2355, found 385.2353.

Sarcophytonolide F (3). To a solution of MOM ether **S11** (5.0 mg, 13.8 μmol) in CH_2Cl_2 (1.0 mL) were added HMDS (58 μL, 0.276 mmol) and TMSI (20 μL, 0.138 mmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. The reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 2:1) gave sarcophytonolide F (**3**) (3.3 mg, 75%): colorless solid; R_f = 0.28 (hexane/EtOAc = 1:1); $[\alpha]_D^{23}$ +145 (*c* 0.54, $CHCl_3$); literature[10b] $[\alpha]_D^{20}$ +115 (*c* 0.54, $CHCl_3$); IR (neat) 3438, 2936, 2883, 1727 cm^{-1}; ^{1}H and ^{13}C NMR Table S4; HRMS (ESI–TOF) calcd for $C_{20}H_{30}O_3Na$ $[M + Na]^+$ 341.2093, found 341.2092.

Synthesis of Sarcophytonolide G (4) by Mitsunobu Reaction. To a mixture of sarcophytonolide F (**3**) (1.6 mg, 5.02 μmol), Ph_3P (5.2 mg, 20.1 μmol), and *p*-nitrobenzoic acid (3.4 mg, 20.1 μmol) in THF (1.0 mL) was added DEAD (40% solution in toluene, 9.1 μL, 20.1 μmol) at 0 °C. After the mixture was stirred at the same temperature for 20 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 6:1, 2:1) gave the diastereomeric mixture of the corresponding benzoates (2.0 mg), which was used for the next step without further purification.

To a solution of the mixture of benzoates obtained above (2.0 mg) in MeOH (0.5 mL) was added Na_2CO_3 (0.6 mg, 6.02 μmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. To the mixture was added Na_2CO_3 (0.6 mg, 6.02 μmol) at 0 °C. The mixture was stirred at the same temperature for 10 min. After the mixture was stirred at room temperature for 1 h, the mixture was filtered through short column chromatography (EtOAc). Concentration and column chromatography (hexane/EtOAc = 3:2) gave sarcophytonolide G (**4**) (0.5 mg, 31% in two steps) and sarcophytonolide F (**3**) (0.2 mg, 13% in two steps). Sarcophytonolide G (**4**): colorless solid; R_f = 0.41 (hexane/EtOAc = 1:1); $[\alpha]_D^{21}$ +18.1 (*c* 0.12, $CHCl_3$); literature[10b,61] $[\alpha]_D^{20}$ –1.6 (*c* 0.17, $CHCl_3$); IR (neat) 3420, 2958, 2923, 2851, 1736 cm^{-1}; ^{1}H and ^{13}C NMR Table S5; HRMS (ESI–TOF) calcd for $C_{20}H_{30}O_3Na$ $[M + Na]^+$ 341.2093, found 341.2096.

Ketone 49. To a solution sarcophytonolide F (**3**) (4.3 mg, 13.5 μmol) in CH_2Cl_2 (1.0 mL) was added Dess–Martin periodinane (17.2 mg, 40.5 μmol) at room temperature. After the mixture was stirred at 40 °C for 10 h, to the mixture were added CH_2Cl_2 (0.5 mL) and Dess–Martin periodinane (5.7 mg, 13.5 μmol) at the same temperature. After the mixture was stirred at the same temperature for 13 h, the mixture was filtered through short column chromatography (hexane/EtOAc = 1:1). Concentration and column chromatography

(hexane/EtOAc = 7:2) gave ketone **49** (4.1 mg, 96%): colorless oil; R_f = 0.49 (hexane/EtOAc = 2:1); $[\alpha]_D^{23}$ –8.1 (*c* 0.21, $CHCl_3$); IR (neat) 2958, 2922, 1758, 1686, 1617 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1 H), 6.05 (s, 1 H), 5.04 (dd, *J* = 6.1, 1.2 Hz, 1 H), 4.91–4.88 (m, 1 H), 3.58 (d, *J* = 14.1 Hz, 1 H), 3.13 (d, *J* = 14.1 Hz, 1 H), 2.33–2.26 (m, 2 H), 2.19–2.12 (m, 2 H), 2.09 (s, 3 H), 2.03–1.96 (m, 2 H), 1.84–1.76 (m, 1 H), 1.66–1.61 (m, 2 H), 1.54 (s, 3 H), 1.44–1.35 (m, 1 H), 1.02 (d, *J* = 6.8 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 160.8, 150.3, 135.9, 129.3, 124.9, 123.9, 123.2, 83.8, 47.0, 41.7, 41.1, 39.3, 30.0, 26.9, 24.3, 20.4, 20.2, 18.7, 16.2; HRMS (ESI–TOF) calcd for $C_{20}H_{28}O_3Na$ $[M + Na]^+$ 339.1936, found 339.1935.

Synthesis of Sarcophytonolide G (4) by Stereoselective Reduction. To a solution of ketone **49** (2.9 mg, 9.16 μmol) in MeOH (0.6 mL) and CH_2Cl_2 (0.4 mL) were added $CeCl_3$ (6.8 mg, 27.5 μmol) and $NaBH_4$ (0.5 mg, 13.7 μmol) at –78 °C. After the mixture was stirred at the same temperature for 2 h, the mixture was diluted with Et_2O. The reaction was quenched with 1 M aqueous $NaHSO_4$. The mixture was warmed up to room temperature, and stirred at the same temperature for 20 min. The mixture was washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 3:2) gave sarcophytonolide G (**4**) (2.1 mg, 72%).

Alcohol S12. To a solution of diol **16** (3.95 g, 15.0 mmol) in CH_2Cl_2 (150 mL) were added pyridine (2.4 mL, 29.3 mmol) and AcCl (1.8 mL, 24.8 mmol) at –20 °C. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration gave the corresponding acetate (4.61 g), which was used for the next step without further purification.

To a solution of the alcohol obtained above (4.61 g) in CH_2Cl_2 (150 mL) were added 2,6-lutidine (2.7 mL, 22.8 mmol) and TBSOTf (4.2 mL, 18.2 mmol) at 0 °C. After the mixture was stirred at the same temperature for 30 min, the mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane, hexane/EtOAc = 50:1) gave the corresponding TBS ether (5.44 g), which was used for the next step without further purification.

To a solution of the acetate obtained above (5.44 g) in CH_2Cl_2 (130 mL) was added DIBAL-H (1.02 M in hexane, 31.0 mL, 31.6 mmol) at –78 °C. After the mixture was stirred at the same temperature for 20 min, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and column chromatography (hexane/EtOAc = 20:1) gave alcohol **S12** (4.79 g, 85% in three steps): colorless oil; R_f = 0.33 (hexane/EtOAc = 10:1); $[\alpha]_D^{25}$ +2.0 (*c* 0.96, $CHCl_3$); IR (neat) 3436, 2955, 2858 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.99–3.95 (m, 1 H), 3.83 (brd, *J* = 2.3 Hz, 1 H), 3.73–3.71 (m, 2 H), 3.64–3.59 (m, 2 H), 1.79–1.70 (m, 1 H), 1.52–1.48 (m, 1 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 0.92 (d, *J* = 5.9 Hz, 3 H), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.09 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.0, 64.9, 60.4, 51.6, 26.1,

26.0, 25.9, 21.8, 20.6, 18.4, 18.1, –4.2, –4.9, –5.3; HRMS (ESI–TOF) calcd for $C_{19}H_{44}O_3Si_2Na$ $[M + Na]^+$ 399.2727, found 399.2728.

Aldehyde 52. To a solution of alcohol **S12** (643 mg, 1.71 mmol) in CH_2Cl_2 (17 mL) were added $PhI(OAc)_2$ (1.05 g, 3.26 mmol) and TEMPO (79.7 mg, 0.510 mmol) at room temperature. After the mixture was stirred at the same temperature for 10 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 50:1) gave aldehyde **52** (620 mg, 97%): colorless oil; R_f = 0.48 (hexane/EtOAc = 20:1); $[\alpha]_D^{26}$ +0.4 (*c* 1.34, $CHCl_3$); IR (neat) 2956, 2927, 2856, 1723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.77 (d, *J* = 3.4 Hz, 1 H), 4.17–4.10 (m, 1 H), 3.65 (dd, *J* = 10.2, 4.9 Hz, 1 H), 3.56 (dd, *J* = 10.2, 5.6 Hz, 1 H), 2.30–2.17 (m, 2 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 0.99 (d, *J* = 6.8 Hz, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.09 (s, 3 H), 0.09 (s, 3 H), 0.04 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 71.9, 65.9, 62.2, 26.0, 25.9, 25.7, 21.6, 19.7, 18.4, 18.1, –4.1, –4.9, –5.4; HRMS (ESI–TOF) calcd for $C_{19}H_{42}O_3Si_2Na$ $[M + Na]^+$ 397.2570, found 397.2574.

Alcohols 53a and 53b. To a solution of aldehyde **52** (176 mg, 0.468 mmol) and allylic bromide **41** (178 mg, 0.562 mmol) in THF (4.7 mL) was slowly added SmI_2 (0.1 M in THF, 14.1 mL, 1.41 mmol) at 0 °C for 10 min. After the mixture was stirred at the same temperature for 1 h, to the mixture was added SmI_2 (0.1 M in THF, 7.0 mL, 0.700 mmol) at 0 °C for 5 min. After the mixture was stirred at the same temperature for 20 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with saturated aqueous $Na_2S_2O_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1) gave alcohols **53a** (154 mg, 53%) and **53b** (115 mg, 40%). Alcohol **53a**: colorless oil; R_f = 0.43 (hexane/EtOAc = 10:1); $[\alpha]_D^{21}$ +1.5 (*c* 1.27, $CHCl_3$); IR (neat) 3547, 2956, 2930, 2857, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.35–5.23 (m, 1 H), 5.22–5.16 (m, 1 H), 4.57 (d, *J* = 6.8 Hz, 2 H), 4.10–4.03 (m, 1 H), 3.98–3.92 (m, 1 H), 3.68–3.62 (m, 2 H), 2.48 (brs, 1 H), 2.27–2.03 (m, 6 H), 2.03–1.93 (m, 1 H), 1.70 (s, 3 H), 1.65 (s, 3 H), 1.47–1.41 (m, 1 H), 1.20 (s, 9 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 141.4, 133.4, 126.9, 118.8, 73.5, 67.3, 66.3, 61.3, 53.2, 46.6, 39.5, 38.8, 27.3, 26.4, 26.1, 26.0, 25.9, 22.7, 22.5, 18.5, 18.2, 16.5, 16.1, –3.9, –4.7, –5.3; HRMS (ESI–TOF) calcd for $C_{34}H_{68}O_5Si_2Na$ $[M + Na]^+$ 635.4503, found 635.4504. Alcohol **53b**: colorless oil; R_f = 0.44 (hexane/EtOAc = 10:1); $[\alpha]_D^{24}$ +1.3 (*c* 0.75, $CHCl_3$); IR (neat) 3448, 2954, 2929, 2856, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.36–5.29 (m, 1 H), 5.21–5.14 (m, 1 H), 4.57 (d, *J* = 7.1 Hz, 2 H), 4.16–4.10 (m, 1 H), 3.95–3.88 (m, 1 H), 3.74–3.65 (m, 2 H), 3.07 (d, *J* = 4.6 Hz, 1 H), 2.36–1.94 (m, 7 H), 1.70 (s, 3 H), 1.67 (s, 3 H), 1.49–1.44 (m, 1 H), 1.20 (s, 9 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 0.94 (d, *J* = 7.1 Hz, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.11 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 141.5, 133.2, 126.6, 118.8, 74.3, 68.7, 66.1, 61.3,

51.2, 47.5, 39.5, 38.8, 27.3, 26.5, 26.1, 26.0, 22.1, 20.8, 18.4, 18.1, 16.5, 16.4, –4.0, –4.7, –5.2, –5.3; HRMS (ESI–TOF) calcd for $C_{34}H_{68}O_5Si_2Na$ $[M + Na]^+$ 635.4503, found 635.4501.

MOM Ether S15. To a mixture of alcohol **53a** (104 mg, 0.167 mmol) and TBAI (19.9 mg, 53.9 μmol) in CH_2Cl_2 (0.5 mL) were added *i*-Pr_2NEt (0.17 mL, 1.00 mmol) and MOMCl (60 μL, 0.835 mmol) at room temperature. After the mixture was stirred at reflux for 24 h, to the mixture were added *i*-Pr_2NEt (0.17 mL, 1.00 mmol) and MOMCl (60 μL, 0.835 mmol) at room temperature. After the mixture was stirred at reflux for 4 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1) gave MOM ether **S15** (107 mg, 97%): colorless oil; R_f = 0.46 (hexane/EtOAc = 10:1); $[\alpha]_D^{22}$ –19.0 (*c* 1.44, $CHCl_3$); IR (neat) 2955, 2929, 2857, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.35–5.29 (m, 1 H), 5.22–5.15 (m, 1 H), 4.62 (d, *J* = 6.8 Hz, 1 H), 4.57 (d, *J* = 7.1 Hz, 2 H), 4.46 (d, *J* = 6.8 Hz, 1 H), 4.07–4.01 (m, 1 H), 3.96–3.89 (m, 1 H), 3.63 (dd, *J* = 10.0, 5.0 Hz, 1 H), 3.55 (dd, *J* = 10.0, 6.8 Hz, 1 H), 3.31 (s, 3 H), 2.27–2.01 (m, 6 H), 1.99–1.94 (m, 1 H), 1.70 (s, 3 H), 1.66 (s, 3 H), 1.68–1.51 (m, 1 H), 1.20 (s, 9 H), 1.02 (d, *J* = 6.8 Hz, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.05 (s, 3H), 0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 141.5, 133.1, 126.1, 118.7, 95.1, 74.9, 72.5, 68.0, 61.3, 55.5, 49.3, 42.7, 39.4, 38.8, 27.3, 26.6, 26.2, 26.1, 25.6, 22.9, 22.0, 18.6, 18.3, 16.6, 16.2, –3.4, –4.6, –5.2, –5.2; HRMS (ESI–TOF) calcd for $C_{36}H_{72}O_6Si_2Na$ $[M + Na]^+$ 679.4765, found 679.4769.

Alcohol S16. To a solution of bis-TBS ether **S15** (326 mg, 0.500 mmol) in MeOH (2.5 mL) and CH_2Cl_2 (2.5 mL) was added CSA (34.0 mg, 0.146 mmol) at 0 °C. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with Et_3N. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1, 7:1) gave alcohol **S16** (113 mg) and bis-TBS ether **S15** (176 mg).

To a solution of bis-TBS ether **S15** recovered above (176 mg) in MeOH (1.4 mL) and CH_2Cl_2 (1.4 mL) was added CSA (18.4 mg, 80.7 μmol) at 0 °C. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with Et_3N. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1, 7:1) gave alcohol **S16** (63.3 mg) and bis-TBS ether **S15** (90.1 mg).

To a solution of bis-TBS ether **S15** recovered above (90.1 mg) in MeOH (0.7 mL) and CH_2Cl_2 (0.7 mL) was added CSA (9.2 mg, 39.6 μmol) at 0 °C. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with Et_3N. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1, 7:1) gave alcohol **S16** (31.7 mg, totally 208 mg, 77%) and bis-TBS ether **S15** (46.5 mg). Alcohol **S16**: colorless oil; R_f = 0.33 (hexane/EtOAc = 4:1); $[\alpha]_D^{22}$ –14.1 (*c* 0.53, $CHCl_3$); IR (neat) 3501, 2956, 2930, 2857, 1729

cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.35–5.28 (m, 1 H), 5.21–5.14 (m, 1 H), 4.62 (d, J = 6.8 Hz, 1 H), 4.57 (d, J = 7.1 Hz, 2 H), 4.54 (d, J = 6.8 Hz, 1 H), 4.00–3.91 (m, 2 H), 3.69 (dd, J = 11.5, 5.4 Hz, 1 H), 3.61 (dd, J = 11.5, 4.6 Hz, 1 H), 3.33 (s, 3 H), 2.32–2.17 (m, 2 H), 2.17–2.00 (m, 5 H), 1.70 (s, 3 H), 1.66 (s, 3 H), 1.67–1.61 (m, 1 H), 1.20 (s, 9 H), 1.04 (d, J = 6.8 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.90 (s, 9 H), 0.12 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 141.4, 132.7, 126.6, 118.8, 95.9, 75.1, 71.9, 66.4, 61.3, 55.7, 50.4, 43.3, 39.3, 38.8, 27.3, 26.5, 26.0, 25.6, 22.4, 21.6, 18.3, 16.5, 16.2, –3.9, –4.3; HRMS (ESI–TOF) calcd for $C_{30}H_{58}O_6SiNa$ $[M + Na]^+$ 565.3900, found 565.3901.

Alkene 54. To a solution of alcohol **S16** (97.5 mg, 0.180 mmol) in CH_2Cl_2 (1.8 mL) were added $PhI(OAc)_2$ (86.6 mg, 0.269 mmol) and TEMPO (5.6 mg, 35.8 μmol) at room temperature. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 30:1) gave the corresponding aldehyde (91.0 mg), which was used for the next step without further purification.

To a suspension of $Ph_3P^+CH_3Br^-$ (147 mg, 0.412 mmol) in THF (1.1 mL) was added NaHMDS (1.0 M in THF, 0.40 mL, 0.400 mmol) at 0 °C. After the mixture was stirred at the same temperature for 20 min, to the mixture was added the aldehyde obtained above (91.0 mg) in THF (0.2 mL + 0.2 mL + 0.2 mL) at 0 °C. After the mixture was stirred at room temperature for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1) gave alkene **54** (83.1 mg, 86% in two steps): colorless oil; R_f = 0.31 (hexane/EtOAc = 30:1); $[\alpha]_D^{22}$ –8.0 (c 0.87, $CHCl_3$); IR (neat) 2956, 2930, 2857, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (ddd, J = 17.2, 10.4, 6.8 Hz, 1 H), 5.36–5.29 (m, 1 H), 5.20–5.11 (m, 2 H), 5.04 (d, J = 10.4 Hz, 1 H), 4.58–4.56 (m, 3 H), 4.49 (d, J = 6.6 Hz, 1 H), 4.45–4.42 (m, 1 H), 3.87 (td, J = 6.8, 3.0 Hz, 1 H), 3.32 (s, 3 H), 2.26 (d, J = 6.8 Hz, 2 H), 2.15–1.95 (m, 5 H), 1.70 (s, 3 H), 1.63 (s, 3 H), 1.48–1.43 (m, 1 H), 1.20 (s, 9 H), 1.04 (d, J = 6.7 Hz, 3 H), 1.03 (d, J = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.06 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 141.9, 141.5, 133.0, 126.3, 118.7, 114.1, 96.1, 75.6, 73.0, 61.3, 55.6, 53.7, 44.1, 39.4, 38.8, 27.3, 26.5, 26.1, 25.8, 22.9, 21.8, 18.3, 16.6, 16.2, –3.6, –4.6; HRMS (ESI–TOF) calcd for $C_{31}H_{58}O_5SiNa$ $[M + Na]^+$ 561.3951, found 561.3951.

Alcohol 55. To a solution of pivalate **54** (145 mg, 0.268 mmol) in CH_2Cl_2 (2.7 mL) was added DIBAL-H (1.02 M in hexane, 0.79 mL, 0.806 mmol) at –78 °C. After the mixture was stirred at the same temperature for 20 min, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and column chromatography (hexane/EtOAc = 4:1) gave alcohol **55** (120 mg, 98%): colorless oil; R_f = 0.27 (hexane/EtOAc = 4:1); $[\alpha]_D^{21}$ –8.4 (c 0.97, $CHCl_3$); IR (neat) 3349, 2955, 2929, 2857 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (ddd, J = 17.2, 10.4, 6.8 Hz, 1 H), 5.45–5.38 (m, 1

H), 5.20–5.10 (m, 2 H), 5.04 (d, *J* = 10.4 Hz, 1 H), 4.57 (d, *J* = 6.8 Hz, 1 H), 4.50 (d, *J* = 6.8 Hz, 1 H), 4.46–4.41 (m, 1 H), 4.15 (d, *J* = 6.8 Hz, 2 H), 3.90–3.83 (m, 1 H), 3.32 (s, 3 H), 2.26 (d, *J* = 6.8 Hz, 2 H), 2.17–1.95 (m, 5 H), 1.68 (s, 3 H), 1.63 (s, 3 H), 1.48–1.43 (m, 1 H), 1.04 (d, *J* = 6.8 Hz, 3 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 139.4, 133.0, 126.4, 123.5, 114.2, 96.0, 75.7, 73.0, 59.4, 55.6, 53.8, 44.0, 39.4, 26.4, 26.1, 25.8, 22.8, 21.8, 18.3, 16.3, –3.6, –4.6; HRMS (ESI–TOF) calcd for $C_{26}H_{50}O_4SiNa$ $[M + Na]^+$ 477.3376, found 477.3373.

Alcohol 56. To a solution of alcohol **55** (114 mg, 0.252 mmol) in CH_2Cl_2 (2.5 mL) were added $PhI(OAc)_2$ (121 mg, 0.377 mmol) and TEMPO (11.4 mg, 73.0 μmol) at room temperature. After the mixture was stirred at the same temperature for 4 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 10:1) gave the corresponding aldehyde (106 mg), which was used for the next step without further purification.

A mixture of the aldehyde obtained above (106 mg) and chiral allylic boronate **35** (104 mg, 0.281 mmol) in toluene (0.2 mL) was stirred at room temperature for 2 days. After the reaction was quenched with H_2O, the mixture was diluted with EtOAc and dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1) gave alcohol **56** (127 mg, 88% in two steps, dr = 13:1): colorless oil; R_f = 0.29 (hexane/EtOAc = 4:1); $[\alpha]_D^{21}$ –10.5 (*c* 1.01, $CHCl_3$); IR (neat) 3460, 2955, 2929, 2857, 1716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (d, *J* = 1.4 Hz, 1 H), 5.94 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.64 (brs, 1 H), 5.22–5.10 (m, 3 H), 5.04 (d, *J* = 10.4 Hz, 1 H), 4.60–4.53 (m, 2 H), 4.50 (d, *J* = 6.6 Hz, 1 H), 4.46–4.41 (m, 1 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 3.90–3.83 (m, 1 H), 3.32 (s, 3 H), 2.57–2.44 (m, 2 H), 2.26 (d, *J* = 5.8 Hz, 2 H), 2.15–1.95 (m, 5 H), 1.68 (d, *J* = 1.2 Hz, 3 H), 1.63 (s, 3 H), 1.48–1.42 (m, 1 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 1.04 (d, *J* = 6.6 Hz, 3 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 142.0, 138.4, 137.2, 133.0, 127.5, 127.0, 126.4, 114.1, 96.0, 75.7, 72.9, 67.5, 60.9, 55.6, 53.9, 43.9, 40.7, 39.4, 26.5, 26.1, 25.8, 22.8, 21.8, 18.3, 16.7, 16.3, 14.3, –3.6, –4.5; HRMS (ESI–TOF) calcd for $C_{32}H_{58}O_6SiNa$ $[M + Na]^+$ 589.3900, found 589.3897.

Alcohol S19. To a solution of alcohol **56** (120 mg, 0.211 mmol) in CH_2Cl_2 (2.1 mL) were added *p*-methoxybenzyl 2,2,2-trichloroacetimidate (97 μL, 0.528 mmol) and PPTS (26.4 mg, 0.106 mmol) at room temperature. After the mixture was stirred at reflux for 9 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 10:1, 5:1) gave the corresponding PMB ether (79.9 mg) and alcohol **56** (97.4 mg including impurity).

To a solution of alcohol **56** recovered above (97.4 mg including impurity) in CH_2Cl_2 (1.7 mL) were added *p*-methoxybenzyl 2,2,2-trichloroacetimidate (70 μL, 0.379 mmol) and PPTS (20.8 mg, 82.4 μmol) at room temperature. After the mixture was stirred at reflux for 13 h, the

reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 10:1, 5:1) gave the corresponding PMB ether (42.2 mg) and alcohol **56** (82.7 mg including impurity).

To a solution of alcohol **56** recovered above (82.7 mg including impurity) in CH_2Cl_2 (1.4 mL) were added *p*-methoxybenzyl 2,2,2-trichloroacetimidate (63 μL, 0.365 mmol) and PPTS (18.0 mg, 71.3 μmol) at room temperature. After the mixture was stirred at reflux for 16 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 10:1, 5:1) gave the corresponding PMB ether (27.6 mg) and alcohol **56** (80.2 mg including impurity). The combined PMB ether (150 mg) was used for the next step without further purification.

To a solution of the TBS ether obtained above (150 mg) in THF (1.5 mL) was added TBAF (1.0 M in THF, 0.45 mL, 0.450 mmol) at room temperature. After the mixture was stirred at reflux for 10 h, the mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1, 5:1) gave alcohol **S19** (73.7 mg, 61% in two steps): colorless oil; R_f = 0.22 (hexane/EtOAc = 4:1); $[\alpha]_D^{21}$ +24.7 (*c* 0.87, $CHCl_3$); IR (neat) 3478, 2932, 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 2 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 6.18 (d, *J* = 1.7 Hz, 1 H), 6.01 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.57 (brs, 1 H), 5.29 (d, *J* = 17.2 Hz, 1 H), 5.24–5.18 (m, 1 H), 5.15–5.07 (m, 2 H), 4.61 (d, *J* = 6.8 Hz, 1 H), 4.53 (d, *J* = 6.8 Hz, 1 H), 4.51–4.43 (m, 2 H), 4.31–4.21 (m, 2 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 3.98–3.92 (m, 1 H), 3.79 (s, 3 H), 3.35 (s, 3 H), 2.63 (dd, *J* = 13.9, 7.6 Hz, 1 H), 2.48–2.31 (m, 3 H), 2.25–2.00 (m, 5 H), 1.96–1.86 (m, 1 H), 1.68–1.60 (m, 1 H), 1.64 (s, 3 H), 1.59 (s, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.06 (d, *J* = 6.8 Hz, 3 H), 1.03 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 158.9, 141.4, 139.5, 137.2, 132.4, 131.0, 129.1, 127.0, 125.6, 114.5, 113.6, 96.0, 77.4, 73.3, 72.9, 69.4, 60.5, 55.7, 55.3, 51.7, 42.8, 39.5, 38.6, 26.6, 26.0, 22.8, 21.6, 16.8, 16.1, 14.3; HRMS (ESI–TOF) calcd for $C_{34}H_{52}O_7Na$ $[M + Na]^+$ 595.3611, found 595.3608.

Carboxylic Acid 58. To a solution of ester **S19** (68.2 mg, 0.119 mmol) in THF (0.7 mL), MeOH (0.2 mL), and H_2O (0.2 mL) was added $LiOH·H_2O$ (7.5 mg, 0.179 mmol) at room temperature. After the mixture was stirred at 40 °C for 5 h, to the mixture was added $LiOH·H_2O$ (7.5 mg, 0.179 mmol) at room temperature. After the mixture was stirred at 40 °C for 5 h, the mixture was neutralized with aqueous HCl at 0 °C. The mixture was diluted with EtOAc and washed with H_2O and brine. The aqueous phase was extracted with EtOAc three times and the combined organic phase was dried over Na_2SO_4. Concentration and column chromatography (CH_2Cl_2/MeOH = 30:1) gave carboxylic acid **58** (62.0 mg, 96%): colorless oil; R_f = 0.41 (hexane/EtOAc = 1:1); $[\alpha]_D^{25}$ +18.1 (*c* 0.27, $CHCl_3$); IR (neat) 3459, 2925, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 6.28 (d, *J* = 1.5 Hz, 1 H), 6.01 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.64 (brs, 1 H), 5.28 (dt, *J* =

17.2, 1.5 Hz, 1 H), 5.24–5.19 (m, 1 H), 5.14–5.11 (m, 2 H), 4.62 (d, *J* = 7.2 Hz, 1 H), 4.54–4.50 (m, 3 H), 4.30–4.26 (m, 2 H), 3.99–3.95 (m, 1 H), 3.79 (s, 3 H), 3.34 (s, 3 H), 2.63 (dd, *J* = 13.9, 7.3 Hz, 1 H), 2.51 (dd, *J* = 13.9, 5.8 Hz, 1 H), 2.41 (dd, *J* = 13.9, 9.0 Hz, 1 H), 2.25–2.04 (m, 5 H), 1.98–1.87 (m, 1 H), 1.68–1.63 (m, 1 H), 1.64 (s, 3 H), 1.61 (s, 3 H), 1.06 (d, *J* = 6.8 Hz, 3 H), 1.03 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 159.1, 141.6, 140.0, 136.9, 132.4, 130.3, 129.3, 128.9, 126.9, 125.1, 114.4, 113.7, 95.8, 77.2, 74.4, 72.6, 69.5, 55.7, 55.3, 51.9, 42.5, 39.4, 38.0, 26.2, 25.9, 22.7, 21.8, 16.8, 16.1; HRMS (ESI–TOF) calcd for $C_{32}H_{48}O_7Na$ $[M + Na]^+$ 567.3298, found 567.3311.

Lactone 59. To a solution of MNBA (33.3 mg, 96.7 μmol) and DMAP (23.7 mg, 0.194 mmol) in CH_2Cl_2 (16 mL) was slowly added hydroxycarboxylic acid **58** (22.2 mg, 40.8 μmol) in CH_2Cl_2 (3.2 mL at 0.2 mL/h + 1.0 mL at 1.0 mL/h + 1.0 mL at 1.0 mL/h) at 40 °C with a syringe pump for 18 h. After the mixture was stirred at the same temperature for further 2 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1) gave lactone **59** (14.7 mg, 68%): colorless oil; R_f = 0.30 (hexane/EtOAc = 7:1); $[\alpha]_D^{23}$ +49.5 (*c* 1.00, $CHCl_3$); IR (neat) 2928, 1714, 1613 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.3 Hz, 2 H), 6.86 (d, *J* = 8.3 Hz, 2 H), 6.09 (s, 1 H), 6.00 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.79–5.71 (m, 1 H), 5.58 (s, 1 H), 5.22 (d, *J* = 17.2 Hz, 1 H), 5.13 (d, *J* = 10.4 Hz, 1 H), 5.06–4.92 (m, 2 H), 4.65 (s, 2 H), 4.65–4.58 (m, 1 H), 4.46 (d, *J* = 11.2 Hz, 1 H), 4.31 (d, *J* = 11.2 Hz, 1 H), 3.90–3.83 (m, 1 H), 3.80 (s, 3 H), 3.38 (s, 3 H), 3.05 (dd, *J* = 13.1, 5.1 Hz, 1 H), 2.44–1.98 (m, 8 H), 1.96–1.86 (m, 1 H), 1.62 (s, 3 H), 1.62 (s, 3 H), 1.11 (d, *J* = 6.8 Hz, 3 H), 1.06 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 158.9, 141.3, 137.6, 134.8, 131.8, 131.2, 129.1, 127.0, 126.5, 125.7, 115.5, 113.7, 96.6, 75.2, 73.4, 72.7, 69.5, 55.9, 55.3, 51.1, 44.9, 38.9, 37.7, 26.2, 23.8, 21.9, 19.4, 17.0; HRMS (ESI–TOF) calcd for $C_{32}H_{46}O_6Na$ $[M + Na]^+$ 549.3192, found 549.3190.

Alcohol 60. To a solution of tetraene **59** (34.2 mg, 64.9 μmol) in toluene (13 mL) was added the second-generation Hoveyda–Grubbs catalyst (**33**) (10.0 mg, 16.2 μmol) at room temperature. After the mixture was stirred at 100 °C for 2 days, the mixture was filtered through short column chromatography (hexane/EtOAc = 2:1). Concentration and column chromatography (hexane/EtOAc = 10:1, 7:1, 4:1) gave the corresponding butenolide (25.8 mg) and tetraene **59** (3.8 mg, 11% recovery). The butenolide (25.8 mg) was used for the next step without further purification.

To a solution of the MOM ether obtained above (25.8 mg) in *i*-PrOH (5.2 mL) was added concentrated aqueous HCl (0.1 mL) at room temperature. After the mixture was stirred at 50 °C for 10 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 2:1) gave alcohol **60** (15.3 mg, 52% in two steps): colorless solid; R_f = 0.35 (hexane/EtOAc = 1:1); $[\alpha]_D^{23}$ +88.2 (*c* 0.58, $CHCl_3$); IR

(neat) 3547, 2922, 2842, 1742, 1613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 1 H), 7.26 (d, J = 8.8 Hz, 2 H), 6.87 (d, J = 8.8 Hz, 2 H), 5.17 (d, J = 8.5 Hz, 1 H), 5.04 (d, J = 8.6 Hz, 1 H), 4.89–4.81 (m, 1 H), 4.50–4.38 (m, 3 H), 3.80 (s, 3 H), 3.81–3.77 (m, 1 H), 2.86 (d, J = 13.2 Hz, 1 H), 2.46 (dd, J = 12.9, 9.8 Hz, 1 H), 2.31–1.98 (m, 7 H), 1.62 (s, 3 H), 1.46 (s, 3 H), 1.46–1.41 (m, 1 H), 1.16 (d, J = 6.8 Hz, 3 H), 1.06 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 159.1, 152.0, 141.5, 132.9, 130.4, 129.7, 129.4, 125.3, 124.9, 113.8, 81.5, 72.8, 72.3, 69.9, 55.3, 51.4, 43.7, 39.1, 31.1, 25.3, 24.7, 24.1, 19.7, 19.2, 15.8; HRMS (ESI–TOF) calcd for $C_{28}H_{38}O_5Na$ $[M + Na]^+$ 477.2617, found 477.2616.

Sarcophytonolide H (6). To a solution of alcohol **60** (11.5 mg, 25.3 μmol) in CH_2Cl_2 (0.5 mL) were added pyridine (10 μL, 0.131 mmol) and AcCl (7.9 μL, 0.111 mmol) at 0 °C. After the mixture was stirred at the same temperature for 30 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 4:1) gave the corresponding acetate (11.0 mg), which was used for the next step without further purification.

To a solution of the PMB ether obtained above (11.0 mg) in CH_2Cl_2 (0.5 mL) and phosphate pH standard solution (0.1 mL) was added DDQ (10.8 mg, 44.4 μmol) at 0 °C. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 2:1) gave sarcophytonolide H (**6**) (7.3 mg, 77% in two steps): colorless solid; R_f = 0.27 (hexane/EtOAc = 1:1); $[\alpha]_D^{23}$ +115 (*c* 0.10, $CHCl_3$); literature[10b] $[\alpha]_D^{20}$ +74.7 (*c* 0.20, $CHCl_3$); IR (neat) 3275, 2968, 2948, 2924, 1759, 1732 cm^{-1}; ^1H and ^{13}C NMR Table S6; HRMS (ESI–TOF) calcd for $C_{22}H_{32}O_5Na$ $[M + Na]^+$ 399.2148, found 399.2153.

Acetate S22. To a solution of alcohol **53b** (415 mg, 0.677 mmol) in toluene (6.8 mL) were added pyridine (0.32 mL, 4.06 mmol), Ac_2O (0.32 mL, 3.39 mmol), and DMAP (8.6 mg, 70.4 μmol) at room temperature. After the mixture was stirred at 100 °C for 10 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1) gave acetate **S22** (444 mg, quant): colorless oil; R_f = 0.45 (hexane/EtOAc = 10:1); $[\alpha]_D^{25}$ +5.4 (*c* 0.48, $CHCl_3$); IR (neat) 2954, 2929, 2856, 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.36–5.27 (m, 2 H), 5.14–5.06 (m, 1 H), 4.57 (d, J = 7.1 Hz, 2 H), 4.03–3.97 (m, 1 H), 3.67–3.55 (m, 2 H), 2.33 (dd, J = 13.7, 9.5 Hz, 1 H), 2.17–1.97 (m, 5 H), 1.97–1.87 (m, 1 H), 1.96 (s, 3 H), 1.69 (s, 3 H), 1.65 (s, 3 H), 1.53–1.46 (m, 1 H), 1.19 (s, 9 H), 0.97 (d, J = 5.6 Hz, 3 H), 0.96 (d, J = 5.6 Hz, 3 H), 0.91 (s, 9 H), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 169.8, 141.5, 132.3, 126.7, 118.7, 73.4, 71.1, 66.8, 61.3, 50.4, 45.1, 39.3, 38.8, 27.3, 26.6, 26.3, 26.1, 26.1, 22.7, 21.4, 20.7, 18.5, 18.3, 16.6, 16.1, –3.9, –4.6, –5.1, –5.2; HRMS

(ESI–TOF) calcd for $C_{36}H_{70}O_6Si_2Na$ $[M + Na]^+$ 677.4609, found 677.4609.

Alcohol 61. To a solution of bis-TBS ether **S22** (444 mg, 0.677 mmol) in MeOH (3.4 mL) and CH_2Cl_2 (3.4 mL) was added CSA (47.5 mg, 0.204 mmol) at 0 °C. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with Et_3N. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1, 8:1) gave alcohol **61** (200 mg) and bis-TBS ether **S22** (179 mg).

To a solution of bis-TBS ether **S22** recovered above (179 mg) in MeOH (1.4 mL) and CH_2Cl_2 (1.4 mL) was added CSA (18.8 mg, 80.9 μmol) at 0 °C. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with Et_3N. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1, 8:1) gave alcohol **61** (72.5 mg) and bis-TBS ether **S22** (82.2 mg).

To a solution of bis-TBS ether **S22** recovered above (82.2 mg) in MeOH (0.6 mL) and CH_2Cl_2 (0.6 mL) was added CSA (8.7 mg, 37.5 μmol) at 0 °C. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with Et_3N. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1, 8:1) gave alcohol **61** (21.8 mg, totally 294 mg, 80%) and bis-TBS ether **S22** (51.2 mg). Alcohol **61**: colorless oil; R_f = 0.39 (hexane/EtOAc = 4:1); $[\alpha]_D^{24}$ +6.5 (*c* 0.77, $CHCl_3$); IR (neat) 3437, 2958, 2929, 2856, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.32 (t, *J* = 6.8 Hz, 1 H), 5.26–5.20 (m, 1 H), 5.17 (t, *J* = 6.5 Hz, 1 H), 4.57 (d, *J* = 6.6 Hz, 2 H), 3.99–3.92 (m, 1 H), 3.76 (dd, *J* = 11.5, 4.9 Hz, 1 H), 3.67 (dd, *J* = 11.5, 3.4 Hz, 1 H), 2.34 (dd, *J* = 13.2, 8.2 Hz, 1 H), 2.22 (dd, *J* = 13.2, 5.6 Hz, 1 H), 2.13–1.99 (m, 4 H), 1.97 (s, 3 H), 1.94–1.86 (m, 1 H), 1.69 (s, 3 H), 1.66 (s, 3 H), 1.61 (td, *J* = 5.7, 2.0 Hz, 1 H), 1.20 (s, 9 H), 0.94 (d, *J* = 7.1 Hz, 3 H), 0.92 (s, 9 H), 0.87 (d, *J* = 6.8 Hz, 3 H), 0.13 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 169.7, 141.4, 131.7, 127.4, 118.7, 72.7, 70.2, 65.3, 61.3, 49.2, 45.0, 39.3, 38.8, 27.3, 26.5, 26.4, 26.0, 22.1, 21.4, 19.2, 18.2, 16.5, 16.1, –4.2, –4.4; HRMS (ESI–TOF) calcd for $C_{30}H_{56}O_6SiNa$ $[M + Na]^+$ 563.3744, found 563.3738.

Alkene 62. To a solution of alcohol **61** (294 mg, 0.544 mmol) in CH_2Cl_2 (5.4 mL) were added $PhI(OAc)_2$ (264 mg, 0.819 mmol) and TEMPO (25.4 mg, 0.163 mmol) at room temperature. After the mixture was stirred at the same temperature for 10 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 20:1) gave the corresponding aldehyde (288 mg), which was used for the next step without further purification.

To a suspension of $Ph_3P^+CH_3Br^-$ (478 mg, 1.34 mmol) in THF (3.4 mL) was added NaHMDS (1.0 M in THF, 1.3 mL, 1.30 mmol) at 0 °C. After the mixture was stirred at the same temperature for 20 min, to the mixture was added the aldehyde obtained above (288 mg)

in THF (1.0 mL + 0.5 mL + 0.5 mL) at 0 °C. After the mixture was stirred at room temperature for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1) gave alkene **62** (259 mg, 89% in two steps): colorless oil; R_f = 0.53 (hexane/EtOAc = 7:1); $[\alpha]_D^{24}$ +9.2 (*c* 0.47, $CHCl_3$); IR (neat) 2958, 2927, 2856, 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1 H), 5.35–5.25 (m, 2 H), 5.22 (d, *J* = 17.2 Hz, 1 H), 5.14–5.04 (m, 2 H), 4.57 (d, *J* = 7.1 Hz, 2 H), 4.34 (t, *J* = 6.4 Hz, 1 H), 2.30–2.17 (m, 2 H), 2.11–1.98 (m, 5 H), 1.96 (s, 3 H), 1.69 (s, 3 H), 1.61 (s, 3 H), 1.53 (td, *J* = 5.9, 2.4 Hz, 1 H), 1.20 (s, 9 H), 0.96 (d, *J* = 7.1 Hz, 3 H), 0.94 (d, *J* = 7.1 Hz, 3 H), 0.91 (s, 9 H), 0.06 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 169.7, 141.5, 141.0, 132.2, 126.9, 118.7, 114.7, 73.0, 70.6, 61.3, 53.1, 43.7, 39.3, 38.8, 27.3, 26.4, 26.0, 21.8, 21.4, 20.3, 18.3, 16.5, 16.0, –3.8, –4.7; HRMS (ESI–TOF) calcd for $C_{31}H_{56}O_5SiNa$ $[M + Na]^+$ 559.3795, found 559.3796.

Aldehyde 63. To a solution of pivalate **62** (259 mg, 0.482 mmol) in CH_2Cl_2 (4.8 mL) was added DIBAL-H (1.02 M in hexane, 1.1 mL, 1.12 mmol) at –78 °C. After the mixture was stirred at the same temperature for 30 min, to the mixture was added DIBAL-H (1.02 M in hexane, 0.55 mL, 0.561 mmol) at –78 °C. After the mixture was stirred at the same temperature for 20 min, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and short column chromatography (hexane/EtOAc = 6:1) gave the corresponding alcohol (185 mg), which was used for the next step without further purification.

To a solution of the alcohol obtained above (185 mg) in CH_2Cl_2 (4.5 mL) were added $PhI(OAc)_2$ (215 mg, 0.667 mmol) and TEMPO (21.1 mg, 0.135 mmol) at room temperature. After the mixture was stirred at the same temperature for 3 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1) gave aldehyde **63** (167 mg, 85% in two steps): colorless oil; R_f = 0.37 (hexane/EtOAc = 4:1); $[\alpha]_D^{24}$ +19.2 (*c* 0.30, $CHCl_3$); IR (neat) 3462, 2954, 2928, 2856, 1676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.99 (d, *J* = 8.0 Hz, 1 H), 6.05 (ddd, *J* = 17.2, 10.8, 6.8 Hz, 1 H), 5.88 (d, *J* = 8.0 Hz, 1 H), 5.26–5.12 (m, 3 H), 4.62–4.54 (m, 1 H), 4.03–3.93 (m, 1 H), 3.39–3.28 (m, 1 H), 2.30–2.21 (m, 5 H), 2.17 (s, 3 H), 2.17–2.10 (m, 1 H), 2.05–1.95 (m, 1 H), 1.67 (s, 3 H), 1.49–1.43 (m, 1 H), 1.07 (d, *J* = 6.8 Hz, 3 H), 0.91 (d, *J* = 8.8 Hz, 3 H), 0.90 (s, 9 H), 0.10 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 163.4, 140.0, 134.4, 127.4, 125.2, 115.4, 74.7, 69.1, 54.1, 46.7, 40.6, 26.6, 25.9, 25.8, 21.2, 21.0, 18.1, 17.7, 16.3, –4.0, –4.8; HRMS (ESI–TOF) calcd for $C_{24}H_{44}O_3SiNa$ $[M + Na]^+$ 431.2957, found 431.2961.

Diol 64. To a solution of aldehyde **63** (160 mg, 0.392 mmol) in THF (3.2 mL) and saturated aqueous NH_4Cl (0.6 mL) were added ethyl (2-bromomethyl)acrylate (**26**) (0.14 mL, 1.18 mmol) and zinc dust (154 mg, 2.35 mmol) at 0 °C. After the mixture was stirred at the same

temperature for 10 min, the mixture was filtered through a Celite pad and washed with EtOAc. The mixture was washed with H_2O and brine and dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1) gave diol **64** (205 mg, quant) as a 1:1 diastereomeric mixture: colorless oil; R_f = 0.56 (hexane/EtOAc = 2:1); IR (neat) 3428, 2956, 2927, 2856, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.23 (d, J = 1.6 Hz, 0.5 H), 6.22 (d, J = 1.6 Hz, 0.5 H), 6.08–5.96 (m, 1 H), 5.65–5.59 (m, 1 H), 5.23–5.11 (m, 4 H), 4.61–4.48 (m, 2 H), 4.26–4.16 (m, 2 H), 4.00–3.88 (m, 1 H), 2.53–2.44 (m, 2 H), 2.29–1.95 (m, 7 H), 1.69–1.59 (m, 6 H), 1.47–1.39 (m, 1 H), 1.31 (t, J = 7.2 Hz, 1.5 H), 1.31 (t, J = 7.2 Hz, 1.5 H), 1.06 (d, J = 7.1 Hz, 1.5 H), 1.06 (d, J = 7.1 Hz, 1.5 H), 0.93 (d, J = 7.1 Hz, 3 H), 0.91 (s, 9 H), 0.10 (s, 1.5 H), 0.09 (s, 1.5 H), 0.05 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 140.4, 138.2, 137.8, 137.3, 133.1, 128.2, 127.4, 127.3, 127.3, 127.1, 126.7, 115.2, 115.0, 74.5, 74.4, 68.9, 68.2, 67.5, 67.3, 60.8, 60.8, 54.2, 54.1, 46.8, 46.7, 40.6, 40.5, 39.3, 39.3, 26.5, 26.4, 26.3, 26.1, 26.0, 21.5, 21.3, 21.1, 21.0, 18.2, 18.1, 16.7, 16.4, 16.3, 16.0, 14.3, –4.0, –4.1, –4.8, –4.8; HRMS (ESI–TOF) calcd for $C_{30}H_{54}O_5SiNa$ $[M + Na]^+$ 545.3638, found 545.3641.

Diol S23. To a solution of diol **64** (199 mg, 0.381 mmol) in CH_2Cl_2 (3.8 mL) were added *p*-methoxybenzyl 2,2,2-trichloroacetimidate (0.17 mL, 0.964 mmol) and PPTS (44.0 mg, 0.174 mmol) at room temperature. After the mixture was stirred at reflux for 12 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 10:1, 6:1) gave the corresponding PMB ether (143 mg) and diol **64** (122 mg including impurity). The PMB ether (143 mg) was used for the next step without further purification.

To a solution of the TBS ether obtained above (143 mg) in THF (2.2 mL) was added TBAF (1.0 M in THF, 0.67 mL, 0.670 mmol) at room temperature. After the mixture was stirred at reflux for 2 h, the mixture was diluted with EtOAc and washed with H_2O and brine. The aqueous phase was extracted with EtOAc and the combined organic phase was dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1) gave diol **S23** (82.4 mg, 33% in two steps): yellow oil; R_f = 0.42 (hexane/EtOAc = 2:1); IR (neat) 3386, 2954, 2918, 2874, 1715, 1613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23–7.15 (m, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 6.18 (d, J = 1.5 Hz, 1 H), 5.99 (ddd, J = 16.4, 10.4, 5.2 Hz, 1 H), 5.57 (s, 1 H), 5.33–5.24 (m, 2 H), 5.16 (dt, J = 10.5, 1.5 Hz, 1 H), 5.11 (d, J = 9.0 Hz, 1 H), 4.56 (brs, 1 H), 4.51–4.42 (m, 1 H), 4.32–4.21 (m, 2 H), 4.15 (q, J = 7.1 Hz, 2 H), 4.04–3.96 (m, 1 H), 3.79 (s, 3 H), 3.67 (brs, 1 H), 2.68–2.56 (m, 1 H), 2.47–2.37 (m, 1 H), 2.31 (d, J = 16.6 Hz, 1 H), 2.25–2.12 (m, 3 H), 2.12–1.97 (m, 3 H), 1.67 (s, 3 H), 1.60 (s, 3 H), 1.44–1.38 (m, 1 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.09 (d, J = 7.1 Hz, 3 H), 0.91 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 158.9, 140.3, 139.1, 137.2, 131.9, 130.9, 129.1, 128.8, 128.7, 127.0, 125.9, 114.5, 113.6, 73.3, 72.6, 69.5, 69.4, 68.4, 60.6, 55.3, 52.7, 47.2, 39.4, 38.5, 26.5, 26.4, 21.9, 21.1, 16.8, 16.8, 16.1, 14.3; HRMS (ESI–TOF) calcd for $C_{32}H_{48}O_6Na$ $[M + Na]^+$ 551.3348, found 551.3353.

Carboxylic Acid 65. To a solution of ester **S23** (65.4 mg, 0.124 mmol) in THF (0.7 mL), MeOH (0.3 mL), and H_2O (0.3 mL) was added $LiOH·H_2O$ (7.9 mg, 0.188 mmol) at room temperature. After the mixture was stirred at the same temperature for 2 days, to the mixture was added $LiOH·H_2O$ (7.9 mg, 0.188 mmol) at room temperature. After the mixture was stirred at the same temperature for 10 h, the mixture was neutralized with aqueous HCl at 0 °C. The mixture was diluted with EtOAc and washed with H_2O and brine. The aqueous phase was extracted with EtOAc four times and the combined organic phase was dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 1:1) gave carboxylic acid **65** (54.9 mg, 89%): colorless oil; R_f = 0.56 (EtOAc); IR (neat) 3372, 2954, 2919, 2874, 1696, 1629, 1613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.0 Hz, 2 H), 6.85 (d, J = 8.0 Hz, 2 H), 6.32–6.26 (m, 1 H), 5.98 (ddd, J = 16.0, 10.8, 5.6 Hz, 1 H), 5.66 (s, 1 H), 5.34–5.24 (m, 2 H), 5.20–5.08 (m, 2 H), 4.63–4.60 (m, 1 H), 4.50 (d, J = 11.6 Hz, 1 H), 4.34–4.22 (m, 2 H), 4.07–3.98 (m, 1 H), 3.79 (s, 3 H), 2.63 (dd, J = 13.9, 7.1 Hz, 1 H), 2.49 (dd, J = 13.9, 5.6 Hz, 1 H), 2.30–1.97 (m, 7 H), 1.67 (s, 3 H), 1.62 (s, 1.5 H), 1.62 (s, 1.5 H), 1.44–1.38 (m, 1 H), 1.09 (d, J = 7.1 Hz, 3 H), 0.92 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 159.0, 140.1, 139.5, 136.8, 136.7, 131.9, 130.4, 129.2, 129.2, 129.1, 129.0, 128.7, 128.6, 125.4, 125.4, 114.6, 113.7, 74.1, 74.0, 72.7, 69.6, 68.4, 55.3, 52.6, 52.5, 47.0, 39.4, 39.3, 38.0, 37.9, 26.4, 26.2, 26.2, 21.9, 21.1, 16.8, 16.8, 16.1; HRMS (ESI–TOF) calcd for $C_{30}H_{44}O_6Na$ $[M + Na]^+$ 523.3036, found 523.3036.

Butenolide 67. To a solution of MNBA (45.1 mg, 0.131 mmol) and DMAP (32.8 mg, 0.268 mmol) in CH_2Cl_2 (32 mL) was slowly added dihydroxycarboxylic acid **65** (36.6 mg, 73.1 μmol) in CH_2Cl_2 (3.2 mL at 0.2 mL/h + 1.0 mL at 1.0 mL/h + 1.0 mL at 1.0 mL/h) at –5 °C with a syringe pump for 18 h. After the mixture was stirred at the same temperature for further 5 h, to the mixture was added a solution of MNBA (15.0 mg, 43.6 μmol) and DMAP (11.0 mg, 90.0 μmol) in CH_2Cl_2 (1.0 mL) at –5 °C. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and short chromatography (hexane/EtOAc = 6:1) gave lactone **66** (16.8 mg), which was used for the next step without further purification.

To a solution of alcohol **66** obtained above (16.8 mg) in CH_2Cl_2 (0.4 mL) were added pyridine (7.3 μL, 90.5 μmol) and AcCl (4.9 μL, 69.8 μmol) at 0 °C. After the mixture was stirred at the same temperature for 4 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and short chromatography (hexane/EtOAc = 7:1) gave the corresponding acetate (15.9 mg), which was used for the next step without further purification.

To a solution of the tetraene obtained above (15.9 mg) in toluene (6.0 mL) was added the second-generation Hoveyda–Grubbs catalyst (**33**) (4.6 mg, 7.34 μmol) at room temperature. After the mixture was stirred at 100 °C for 2 days, the mixture was filtered through short

column chromatography (EtOAc). Concentration and column chromatography (hexane/EtOAc = 7:1, 4:1) gave butenolide **67** (7.1 mg, 20% in three steps): colorless oil; R_f = 0.36 (hexane/EtOAc = 2:1); IR (neat) 2958, 2918, 2878, 2852, 1757, 1739, 1613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1 H), 7.28 (d, J = 8.5 Hz, 2 H), 6.87 (d, J = 8.5 Hz, 2 H), 5.28 (dd, J = 11.2, 6.4 Hz, 1 H), 5.11–5.01 (m, 3 H), 4.71–4.64 (m, 1 H), 4.45 (d, J = 10.8 Hz, 1 H), 4.38 (d, J = 10.8 Hz, 1 H), 3.80 (s, 3 H), 2.95–2.85 (m, 1 H), 2.69–2.58 (m, 1 H), 2.48 (dd, J = 12.8, 11.1 Hz, 1 H), 2.39–2.28 (m, 1 H), 2.28–2.06 (m, 5 H), 2.04 (s, 3 H), 1.54 (s, 3 H), 1.46 (dd, J = 10.5, 2.4 Hz, 1 H), 1.41 (s, 3 H), 0.94 (d, J = 7.1 Hz, 3 H), 0.85 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 169.5, 159.0, 151.2, 139.5, 130.7, 130.3, 129.3, 129.2, 127.6, 113.8, 79.9, 72.5, 69.9, 68.8, 55.3, 46.7, 44.0, 38.9, 33.4, 28.3, 22.8, 21.7, 21.4, 16.4, 15.9, 15.5; HRMS (ESI–TOF) calcd for $C_{30}H_{40}O_6Na$ $[M + Na]^+$ 519.2723, found 519.2728.

Alcohol S24. To a solution of PMB ether **67** (7.1 mg, 14.3 μmol) in CH_2Cl_2 (0.2 mL) and phosphate pH standard solution (50 μL) was added DDQ (6.4 mg, 28.2 μmol) at 0 °C. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$, H_2O, and brine. The aqueous phase was extracted with EtOAc twice and the combined organic phase was dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 1:1) gave alcohol **S24** (4.9 mg, 91%): colorless oil; R_f = 0.17 (hexane/EtOAc = 1:1); IR (neat) 3413, 2958, 2919, 2870, 2852, 1731, 1668, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1 H), 5.29 (dd, J = 11.2, 6.4 Hz, 1 H), 5.13 (d, J = 9.5 Hz, 1 H), 5.09–4.95 (m, 3 H), 2.85–2.76 (m, 1 H), 2.64 (dd, J = 12.7, 5.9 Hz, 1 H), 2.47 (dd, J = 12.7, 11.2 Hz, 1 H), 2.38–2.26 (m, 1 H), 2.24–2.17 (m, 1 H), 2.16–1.99 (m, 4 H), 2.04 (s, 3 H), 1.54 (s, 3 H), 1.46 (dd, J = 10.7, 2.4 Hz, 1 H), 1.44 (s, 3 H), 0.94 (d, J = 7.1 Hz, 3 H), 0.86 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 169.5, 151.2, 138.2, 130.3, 129.3, 129.1, 128.8, 79.9, 68.8, 66.1, 46.7, 44.0, 38.8, 35.4, 28.4, 22.7, 21.7, 21.4, 16.4, 15.9, 15.4; HRMS (ESI–TOF) calcd for $C_{22}H_{32}O_5Na$ $[M + Na]^+$ 399.2148, found 399.2151.

Proposed Structure 10 of Isosarcophytonolide D. To a solution of alcohol **S24** (1.2 mg, 3.18 μmol) in CH_2Cl_2 (1.0 mL) were added MS4Å (2.0 mg), NMO (2.0 mg, 17.1 μmol), and a catalytic amount of TPAP at room temperature. After the mixture was stirred at the same temperature for 16 h, to the mixture were added NMO (2.0 mg, 17.1 μmol) and a catalytic amount of TPAP at room temperature. After the mixture was stirred at the same temperature for 1 h, the mixture was filtered through short column chromatography (EtOAc). Concentration and column chromatography (hexane/EtOAc = 2:1) gave the proposed structure **10** of isosarcophytonolide D (0.5 mg, 42%): colorless oil; R_f = 0.47 (hexane/EtOAc = 1:1); $[\alpha]_D^{22}$ +45.0 (*c* 0.10, $CHCl_3$); IR (neat) 2958, 2923, 2878, 2856, 1762, 1739, 1686, 1619 cm^{-1}; ^1H and ^{13}C NMR Table S8; HRMS (ESI–TOF) calcd for $C_{22}H_{30}O_5Na$ $[M + Na]^+$ 397.1991, found 397.1989.

Ketone 68. To a solution of sarcophytonolide H (**6**) (1.0 mg, 2.66 μmol) in CH_2Cl_2 (0.3 mL)

was added Dess–Martin periodinane (3.4 mg, 8.02 μmol) at room temperature. After the mixture was stirred at the same temperature for 16 h, to the mixture was added Dess–Martin periodinane (6.2 mg, 14.6 μmol) at room temperature. After the mixture was stirred at the same temperature for 6 h, the mixture was filtered through short column chromatography (EtOAc). Concentration and column chromatography (hexane/EtOAc = 2:1) gave ketone **68** (0.4 mg, 40%): colorless oil; R_f = 0.55 (hexane/EtOAc = 1:1); $[\alpha]_D^{24}$ –50.9 (*c* 0.07, $CHCl_3$); literature[10d] $[\alpha]_D^{20}$ –66 (*c* 0.67, $CHCl_3$); IR (neat) 2954, 2924, 2874, 2852, 1762, 1734, 1687, 1618 cm^{-1}; ^1H and ^{13}C NMR Table S9; HRMS (ESI–TOF) calcd for $C_{22}H_{30}O_5Na$ $[M + Na]^+$ 397.1991, found 397.1988.

Alcohols 70a and 70b. To a solution of aldehyde **52** (69.8 mg, 0.186 mmol) and allylic bromide **21a** (79.2 mg, 0.248 mmol) in THF (1.9 mL) was added SmI_2 (0.1 M in THF, 5.6 mL, 0.560 mmol) at 0 °C. After the mixture was stirred at the same temperature for 30 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with saturated aqueous $Na_2S_2O_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1) gave alcohols **70a** (33.2 mg, 29%) and **70b** (45.4 mg, 40%). Alcohol **70a**: colorless oil; R_f = 0.48 (hexane/EtOAc = 10:1); $[\alpha]_D^{23}$ –1.0 (*c* 1.28, $CHCl_3$); IR (neat) 3501, 2956, 2929, 2857, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.21 (t, *J* = 6.8 Hz, 1 H), 4.11–4.07 (m, 3 H), 3.98–3.94 (m, 1 H), 3.66 (d, *J* = 5.6 Hz, 2 H), 2.46 (brs, 1 H), 2.25–2.12 (m, 2 H), 2.07–1.93 (m, 3 H), 1.74–1.68 (m, 1 H), 1.65 (s, 3 H), 1.61–1.54 (m, 1 H), 1.47–1.33 (m, 3 H), 1.26–1.21 (m, 1 H), 1.19 (s, 9 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 0.92 (d, *J* = 6.4 Hz, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.07 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 132.9, 127.7, 73.6, 67.4, 66.3, 62.8, 53.2, 46.7, 38.7, 37.0, 35.5, 29.8, 27.3, 26.1, 26.0, 26.0, 25.5, 22.8, 22.5, 19.5, 18.5, 18.2, 16.1, –3.9, –4.7, –5.3; HRMS (ESI–TOF) calcd for $C_{34}H_{70}O_5Si_2Na$ $[M + Na]^+$ 637.4659, found 637.4658. Alcohol **70b**: colorless oil; R_f = 0.34 (hexane/EtOAc = 20:1); $[\alpha]_D^{27}$ +0.15 (*c* 2.28, $CHCl_3$); IR (neat) 3547, 2957, 2928, 2857, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.18 (t, *J* = 8.0 Hz, 1 H), 4.15–4.07 (m, 3 H), 3.95–3.89 (m, 1 H), 3.72–3.67 (m, 2 H), 3.09 (d, *J* = 4.8 Hz, 1 H), 2.23–2.18 (m, 2 H), 2.07–1.97 (m, 3 H), 1.70–1.66 (m, 1 H), 1.66 (s, 3 H), 1.58–1.54 (m, 1 H), 1.48–1.33 (m, 3 H), 1.26–1.22 (m, 1 H), 1.19 (s, 9 H), 1.05 (d, *J* = 7.2 Hz, 3 H), 0.94 (d, *J* = 6.4 Hz, 3 H), 0.92 (d, *J* = 6.4 Hz, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.11 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 132.7, 127.4, 74.4, 68.8, 66.1, 62.9, 51.2, 47.5, 38.7, 37.0, 35.6, 29.8, 27.3, 26.5, 26.1, 26.0, 25.6, 22.0, 20.8, 19.5, 18.4, 18.1, 16.3, –3.9, –4.7, –5.2, –5.3; HRMS (ESI–TOF) calcd for $C_{34}H_{70}O_5Si_2Na$ $[M + Na]^+$ 637.4659, found 637.4659.

Alcohol 71. To a mixture of alcohol **70a** (1.10 g, 1.79 mmol) and TBAI (212 mg, 0.573 mmol) in CH_2Cl_2 (3.6 mL) were added *i*-Pr_2NEt (1.84 mL, 10.7 mmol) and MOMCl (0.68 mL, 8.95 mmol) at room temperature. After the mixture was stirred at 40 °C for 3 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc,

washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 50:1, 30:1) gave the corresponding MOM ether (1.14 g), which was used for the next step without further purification.

To a solution of the bis-TBS ether obtained above (1.14 g) in MeOH (8.7 mL) and CH_2Cl_2 (8.7 mL) was added CSA (121 mg, 0.519 mmol) at 0 °C. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with Et_3N. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 40:1, 15:1, 5:1) gave alcohol **71** (408 mg) and the bis-TBS ether (577 mg).

To a solution of the bis-TBS ether recovered above (577 mg) in MeOH (4.4 mL) and CH_2Cl_2 (4.4 mL) was added CSA (61.1 mg, 0.263 mmol) at 0 °C. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with Et_3N. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1, 15:1, 5:1) gave alcohol **71** (224 mg) and the bis-TBS ether (274 mg).

To a solution of the bis-TBS ether recovered above (274 mg) in MeOH (2.2 mL) and CH_2Cl_2 (2.2 mL) was added CSA (29.0 mg, 0.125 mmol) at 0 °C. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with Et_3N. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1, 10:1, 5:1) gave alcohol **71** (97.3 mg) and the bis-TBS ether (151 mg).

To a solution of the bis-TBS ether recovered above (151 mg) in MeOH (1.0 mL) and CH_2Cl_2 (1.0 mL) was added CSA (14.5 mg, 57.9 μmol) at 0 °C. After the mixture was stirred at the same temperature for 2 h, the reaction was quenched with Et_3N. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1, 10:1, 5:1) gave alcohol **71** (53.9 mg, totally 783 mg, 83% in two steps) and the bis-TBS ether (46.3 mg). Alcohol **71**: colorless oil; R_f = 0.35 (hexane/EtOAc = 4:1); $[\alpha]_D^{26}$ –13.5 (*c* 1.00, $CHCl_3$); IR (neat) 3501, 2957, 2928, 2852, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.18 (t, *J* = 6.8 Hz, 1 H), 4.62 (d, *J* = 6.4 Hz, 1 H), 4.54 (d, *J* = 6.4 Hz, 1 H), 4.11–4.06 (m, 2 H), 3.98–3.95 (m, 2 H), 3.69 (dd, *J* = 11.6, 5.6 Hz, 1 H), 3.61 (dd, *J* = 11.0, 4.4 Hz, 1 H), 3.33 (s, 3 H), 2.31–2.20 (m, 2 H), 2.09–1.96 (m, 2 H), 1.69–1.63 (m, 2 H), 1.65 (s, 3 H), 1.58–1.53 (m, 1 H), 1.47–1.32 (m, 2 H), 1.26–1.17 (m, 2 H), 1.19 (s, 9 H), 1.04 (d, *J* = 6.8 Hz, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 0.90 (s, 9 H), 0.12 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 132.2, 127.4, 95.4, 75.2, 72.0, 66.5, 62.8, 55.7, 50.4, 43.3, 38.7, 36.9, 35.5, 29.8, 27.3, 26.0, 25.6, 25.6, 22.4, 21.6, 19.5, 18.3, 16.2, –3.9, –4.3; HRMS (ESI–TOF) calcd for $C_{30}H_{60}O_6SiNa$ $[M + Na]^+$ 567.4057, found 567.4054.

Alkene 72. To a solution of alcohol **71** (1.01 g, 1.85 mmol) in CH_2Cl_2 (19 mL) were added

$PhI(OAc)_2$ (912 mg, 2.83 mmol) and TEMPO (89.2 mg, 0.570 mmol) at room temperature. After the mixture was stirred at the same temperature for 7 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 40:1, 15:1) gave the corresponding aldehyde (1.01 g), which was used for the next step without further purification.

To a suspension of $Ph_3P^+CH_3Br^-$ (1.68 g, 4.70 mmol) in THF (9.0 mL) was added NaHMDS (1.0 M in THF, 4.5 mL, 4.50 mmol) at 0 °C. After the mixture was stirred at the same temperature for 20 min, to the mixture was added the aldehyde obtained above (1.01 g) in THF (4.0 mL + 3.0 mL + 3.0 mL) at 0 °C. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 70:1, 30:1) gave alkene **72** (816 mg, 81% in two steps): colorless oil; R_f = 0.57 (hexane/ EtOAc = 10:1); $[\alpha]_D^{25}$ –10.6 (*c* 0.98, $CHCl_3$); IR (neat) 2957, 2927, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.18–5.12 (m, 2 H), 5.04 (ddd, *J* = 10.4, 2.0, 1.2 Hz, 1 H), 4.57 (d, *J* = 8.0 Hz, 1 H), 4.46 (d, *J* = 8.0 Hz, 1 H), 4.45–4.43 (m, 1 H), 4.12–4.06 (m, 2 H), 3.87 (td, *J* = 6.8, 2.8 Hz, 1 H), 3.32 (s, 3 H), 2.26 (d, *J* = 4.0 Hz, 2 H), 2.05–1.96 (m, 3 H), 1.71–1.65 (m, 1 H), 1.62 (s, 3 H), 1.48–1.32 (m, 3 H), 1.26–1.15 (m, 2 H), 1.20 (s, 9 H), 1.04 (d, *J* = 6.8 Hz, 3 H), 1,03 (d, *J* = 6.8 Hz, 3 H), 0.92 (d, *J* = 6.4 Hz, 3 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 141.9, 132.6, 127.1, 114.1, 96.1, 75.7, 73.0, 62.9, 55.6, 53.8, 44.1, 38.8, 36.9, 35.6, 29.8, 27.3, 26.1, 25.8, 25.6, 22.9, 21.8, 19.5, 18.3, 16.2, –3.6, –4.5; HRMS (ESI–TOF) calcd for $C_{31}H_{60}O_5SiNa$ $[M + Na]^+$ 563.4108, found 563.4105.

Alcohol 73. To a solution of pivalate **72** (483 mg, 0.893 mmol) in CH_2Cl_2 (8.9 mL) was added DIBAL-H (1.02 M in THF, 2.63 mL, 2.68 mmol) at –78 °C. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and short column chromatography (hexane/EtOAc = 5:1) gave the corresponding alcohol (395 mg), which was used for the next step without further purification.

To a solution of the alcohol obtained above (395 mg) in CH_2Cl_2 (8.7 mL) were added $PhI(OAc)_2$ (416 mg, 1.30 mmol) and TEMPO (42.9 mg, 0.260 mmol) at room temperature. After the mixture was stirred at the same temperature for 2 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 10:1) gave the corresponding aldehyde (386 mg), which was used for the next step without further purification.

To a solution of the aldehyde obtained above (386 mg) in THF (7.1 mL) and saturated aqueous NH_4Cl (1.4 mL) were added ethyl (2-bromomethyl)acrylate (**26**) (0.27 mL, 2.55 mmol) and zinc dust (294 mg, 4.49 mmol) at 0 °C. The mixture was stirred at the same

temperature for 30 min. The mixture was filtered through a Celite pad and washed with EtOAc. The mixture was concentrated, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1, 4:1) gave alcohol **73** (468 mg, 92% in three steps) as a 1:1 diastereomeric mixture: colorless oil; R_f = 0.37 (hexane/EtOAc = 4:1); IR (neat) 3465, 2955, 2928, 2857, 1716, 1630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.26–6.25 (m, 1 H), 5.93 (ddd, J = 17.2, 10.4, 6.8 Hz, 1 H), 5.65 (s, 1 H), 5.19–5.12 (m, 2 H), 5.03 (d, J = 10.4 Hz, 1 H), 4.57 (d, J = 6.8 Hz, 1 H), 4.49 (d, J = 6.8 Hz, 1 H), 4.45–4.42 (m, 1 H), 4.26–4.18 (m, 2 H), 3.86–3.84 (m, 2 H), 3.32 (s, 3 H), 2.63–2.53 (m, 1 H), 2.37–2.24 (m, 3 H), 2.12–1.96 (m, 4 H), 1.71–1.65 (m, 1 H) 1.62 (s, 3 H), 1.47–1.37 (m, 3 H), 1.31 (t, J = 7.2 Hz, 3 H), 1.26–1.15 (m, 2 H), 1.04 (d, J = 6.4 Hz, 3 H), 1.02 (d, J = 6.4 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 1.5 H), 0.90 (d, J = 6.8 Hz, 1.5 H), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 142.0, 137.8, 132.5, 132.4, 127.3, 127.3, 114.1, 96.1, 75.7, 73.0, 68.7, 68.3, 61.0, 55.6, 53.8, 44.8, 44.8, 44.0, 41.3, 40.7, 37.8, 36.8, 29.5, 29.2, 26.1, 25.8, 25.6, 25.5, 22.8, 21.8, 20.2, 19.2, 18.3, 16.2, 14.3, –3.6, –4.5; HRMS (ESI–TOF) calcd for $C_{32}H_{60}O_6SiNa$ $[M + Na]^+$ 591.4057, found 591.4059.

Alcohol 74. To a solution of alcohol **73** (468 mg, 0.823 mmol) in CH_2Cl_2 (1.6 mL) were added *p*-methoxybenzyl 2,2,2-trichloroacetimidate (0.36 mL, 2.06 mmol) and PPTS (104 mg, 0.412 mmol) at room temperature. After the mixture was stirred at 40 °C for 16 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 10:1, 4:1) gave the corresponding PMB ether (217 mg) and alcohol **73** (318 mg including impurity).

To a solution of alcohol **73** recovered above (318 mg including impurity) in CH_2Cl_2 (0.9 mL) were added *p*-methoxybenzyl 2,2,2-trichloroacetimidate (0.20 mL, 1.15 mmol) and PPTS (60.3 mg, 0.239 mmol) at room temperature. After the mixture was stirred at 40 °C for 13 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 10:1, 4:1) gave the corresponding PMB ether (136 mg) and alcohol **73** (224 mg including impurity).

To a solution of alcohol **73** recovered above (224 mg including impurity) in CH_2Cl_2 (0.8 mL) were added *p*-methoxybenzyl 2,2,2-trichloroacetimidate (0.17 mL, 0.985 mmol) and PPTS (49.7 mg, 0.197 mmol) at room temperature. After the mixture was stirred at 40 °C for 14 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 7:1, 4:1) gave the corresponding PMB ether (83.1 mg) and alcohol **73** (159 mg including impurity). The combined PMB ether (436 mg) was used for the next step without further purification.

To a solution of the TBS ether obtained above (436 mg) in THF (6.3 mL) was added TBAF (1.0 M in THF, 1.9 mL, 1.90 mmol) at room temperature. After the mixture was stirred at

60 °C for 12 h, the mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1) gave alcohol **74** (266 mg, 56% in two steps): colorless oil; R_f = 0.58 (hexane/EtOAc = 2:1); IR (neat) 3483, 2955, 2929, 2870, 1714, 1613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.21 (m, 2 H), 6.85 (dd, *J* = 8.0, 2.8 Hz, 2 H), 6.21 (s, 0.5 H), 6.21 (s, 0.5 H), 6.01 (ddd, *J* = 17.2, 10.8, 6.0 Hz, 1 H), 5.62 (s, 0.5 H), 5.61 (s, 0.5 H), 5.30 (dd, *J* = 17.2, 1.6 Hz, 1 H), 5.20–5.12 (m, 2 H), 4.60 (d, *J* = 6.8 Hz, 1 H), 4.53 (d, *J* = 6.8 Hz, 1 H), 4.50–4.38 (m, 3 H), 4.23–4.16 (m, 2 H), 3.96–3.92 (m, 1 H), 3.79 (s, 1.5 H), 3.79 (s, 1.5 H), 3.67–3.59 (m, 1 H), 3.34 (s, 3 H), 2.69 (dd, *J* = 13.6, 6.0 Hz, 0.5 H), 2.56–2.32 (m, 2.5 H), 2.20 (dd, *J* = 13.6, 4.4 Hz, 0.5 H), 2.05–1.89 (m, 2.5 H), 1.67–1.52 (m, 5 H), 1.61 (s, 3 H), 1.48–1.34 (m, 1 H), 1.32–1.27 (m, 3 H), 1.21–1.10 (m, 1 H), 1.07–1.02 (m, 6 H), 0.90 (d, *J* = 6.4 Hz, 1.5 H), 0.80 (d, *J* = 6.4 Hz, 1.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 159.0, 141.4, 141.3, 137.7, 131.9, 131.8, 130.9, 129.3, 128.0, 128.0, 127.1, 114.5, 113.7, 96.0, 77.6, 75.6, 75.3, 73.0, 70.9, 70.8, 60.7, 55.7, 55.3, 51.7, 42.8, 42.0, 41.9, 37.8, 37.6, 36.8, 29.4, 29.0, 26.0, 25.6, 25.5, 22.9, 21.6, 20.1, 29.4, 16.1, 14.3; HRMS (ESI–TOF) calcd for $C_{34}H_{54}O_7Na$ $[M + Na]^+$ 597.3767, found 597.3766.

Lactone 75. To a solution of ester **74** (12.5 mg, 21.7 μmol) in THF (0.6 mL), MeOH (0.2 mL), and H_2O (0.2 mL) was added $LiOH·H_2O$ (1.4 mg, 32.6 μmol) at room temperature. After the mixture was stirred at the same temperature for 16 h, to the mixture was added $LiOH·H_2O$ (2.8 mg, 65.2 μmol) at room temperature. After the mixture was stirred at the same temperature for 7 h, the mixture was neutralized with aqueous HCl at 0 °C. The mixture was diluted with EtOAc and washed with H_2O and brine. The aqueous phase was extracted with EtOAc three times and the combined organic phase was dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 2:1) gave the corresponding carboxylic acid (13.7 mg), which was used for the next step without further purification.

To a solution of MNBA (21.5 mg, 60.2 μmol) and DMAP (14.3 mg, 0.120 mmol) in CH_2Cl_2 (7.4 mL) was slowly added the hydroxycarboxylic acid obtained above (13.7 mg) in CH_2Cl_2 (1.6 mL at 0.1 mL/h + 1.0 mL at 1.0 mL/h + 1.0 mL at 1.0 mL/h) at 40 °C with a syringe pump for 18 h. After the mixture was stirred at the same temperature for further 2 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 12:1) gave lactone **75** (9.3 mg, 81% in two steps): colorless oil; R_f = 0.50, 0.44 (hexane/EtOAc = 4:1); IR (neat) 2952, 2927, 2872, 1714, 1613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.18 (m, 2 H), 6.87–6.82 (m, 2 H), 6.24 (d, *J* = 2.0 Hz, 0.3 H), 6.15 (d, *J* = 1.2 Hz, 0.7 H), 6.06 (ddd, *J* = 15.6, 10.8, 4.9 Hz, 0.7 H), 5.71–5.53 (m, 2.3 H), 5.44 (t, *J* = 6.6 Hz, 0.3 H), 5.29–5.15 (m, 2 H), 4.93–4.91 (m, 0.7 H), 4.67–4.54 (m, 2.7 H), 4.48–4.32 (m, 1.3 H), 3.83–3.77 (m, 2 H), 3.80 (s, 2.1 H), 3.79 (s, 0.9 H), 3.56–3.42 (m, 1 H), 3.38 (s, 2.1 H), 3.36 (s, 0.9 H), 3.02 (dd, *J* = 13.4, 3.7 Hz, 0.7 H), 2.76 (dd, *J* = 14.1, 3.2 Hz, 0.3 H), 2.39–1.91 (m, 5 H), 1.81–1.68 (m, 1 H), 1.65–1.56 (m,

2 H), 1.62 (s, 0.9 H), 1.60 (s, 2.1 H), 1.54–1.26 (m, 4 H), 1.15 (d, *J* = 6.8 Hz, 2.1 H), 1.11 (d, *J* = 6.8 Hz, 2.1 H), 1.06 (d, *J* = 7.2 Hz, 0.9 H), 1.00 (d, *J* = 6.8 Hz, 0.9 H), 0.92 (d, *J* = 6.4 Hz, 0.9 H), 0.85 (d, *J* = 6.4 Hz, 2.1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 165.3, 159.0, 137.9, 137.7, 135.0, 134.5, 132.5, 131.4, 131.0, 130.7, 129.5, 129.2, 128.4, 127.8, 127.6, 126.6, 117.6, 115.4, 113.7, 113.6, 96.9, 95.9, 76.1, 75.8, 75.8, 75.4, 74.0, 70.3, 55.9, 55.7, 55.3, 50.4, 48.1, 45.2, 44.3, 42.5, 38.7, 37.8, 37.6, 36.6, 34.7, 28.4, 26.7, 25.9, 25.6, 24.7, 24.5, 24.0, 22.7, 21.4, 20.5, 20.4, 20.0, 16.7, 16.6; HRMS (ESI–TOF) calcd for $C_{32}H_{48}O_6Na$ $[M + Na]^+$ 551.3348, found 551.3347.

Alcohol 76. To a solution of PMB ether **75** (11.1 mg, 21.0 μmol) in CH_2Cl_2 (0.4 mL) and phosphate pH standard solution (0.1 mL) was added DDQ (9.2 mg, 40.5 μmol) at 0 °C. After the mixture was stirred at the same temperature for 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 3:1) gave alcohol **76** (7.5 mg, 87%): colorless oil; R_f = 0.42, 0.30 (hexane/EtOAc = 2:1); IR (neat) 3460, 2954, 2927, 1714, 1628 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (d, *J* = 1.5 Hz, 0.5 H), 6.16 (d, *J* = 1.4 Hz, 0.5 H), 6.04 (ddd, *J* = 17.2, 10.8, 4.9 Hz, 0.5 H), 5.73 (ddd, *J* = 17.2, 10.8, 6.8 Hz, 0.5 H), 5.67–5.64 (m, 1 H), 5.61 (s, 0.5 H), 5.53 (t, *J* = 6.8 Hz, 0.5 H), 5.31–5.15 (m, 2.5 H), 5.00–4.97 (m, 0.5 H), 4.64 (s, 1 H), 4.63 (d, *J* = 6.6 Hz, 0.5 H), 4.56 (d, *J* = 6.6 Hz, 0.5 H), 3.86–3.75 (m, 2 H), 3.38 (s, 1.5 H), 3.36 (s, 1.5 H), 2.86 (dd, *J* = 13.4, 3.2 Hz, 0.5 H), 2.72 (dd, *J* = 13.4, 5.4 Hz, 0.5 H), 2.41–2.14 (m, 3 H), 2.09–1.96 (m, 2 H), 1.90–1.84 (m, 1 H), 1.64 (s, 1.5 H), 1.63 (s, 1.5 H), 1.61–1.26 (m, 6 H), 1.13–1.05 (m, 6 H), 1.04–0.98 (m, 1 H), 0.95 (d, *J* = 6.4 Hz, 1.5 H), 0.92 (d, *J* = 6.8 Hz, 1.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 165.4, 137.9, 137.7, 135.0, 134.5, 132.4, 131.5, 128.3, 128.0, 126.7, 117.8, 115.3, 97.0, 95.9, 76.3, 76.0, 75.4, 74.3, 69.2, 68.8, 55.9, 55.7, 50.2, 48.4, 45.1, 45.1, 44.3, 42.2, 40.9, 40.5, 36.7, 34.9, 29.1, 27.0, 25.9, 25.6, 24.7, 24.4, 24.0, 23.0, 21.3, 20.6, 20.4, 20.3, 16.6; HRMS (ESI–TOF) calcd for $C_{24}H_{40}O_5Na$ $[M + Na]^+$ 431.2773, found 431.2778.

Ketone 78. To a solution of triene **76** (31.7 mg, 77.6 μmol) in toluene (5.1 mL) was added the second-generation Hoveyda–Grubbs catalyst (**33**) (11.7 mg, 18.7 μmol) at room temperature. After the mixture was stirred at 100 °C for 22 h, the mixture was filtered through short column chromatography (EtOAc). Concentration and column chromatography (hexane/EtOAc = 7:1, 4:1, 1:1) gave butenolide **77** (11.0 mg) and triene **76** (9.9 mg, 31% recovery). Butenolide **77** (11.0 mg) was used for the next step without further purification.

To a solution of alcohol **77** obtained above (11.0 mg) in CH_2Cl_2 (0.5 mL) were added $PhI(OAc)_2$ (14.0 mg, 43.4 μmol) and TEMPO (1.3 mg, 8.67 μmol) at room temperature. The mixture was stirred at the same temperature for 2 h. Column chromatography (hexane/EtOAc = 5:1) gave ketone **78** (6.2 mg, 21% in two steps, 31% based on recovered **76** in two steps): colorless oil; R_f = 0.61 (hexane/EtOAc = 1:1); $[\alpha]_D^{27}$ +97.0 (*c* 0.29, $CHCl_3$); IR (neat) 2955, 2920, 2849, 1759, 1705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1 H), 5.18 (d, *J* = 11.2

Hz, 1 H), 4.94 (d, *J* = 7.2 Hz, 1 H), 4.71 (d, *J* = 7.2 Hz, 1 H), 4.54 (d, *J* = 7.2 Hz, 1 H), 3.73 (dd, *J* = 11.2, 3.2 Hz, 1 H), 3.54 (d, *J* = 14.8 Hz, 1 H), 3.40 (s, 3 H), 3.22 (d, *J* = 14.8 Hz, 1 H), 2.51 (dd, *J* = 12.0, 5.6 Hz, 1 H), 2.31–2.20 (m, 2 H), 2.17–2.05 (m, 4 H), 1.65 (s, 3 H), 1.62–1.44 (m, 4 H), 1.23 (t, *J* = 6.8 Hz, 3 H), 1.13 (d, *J* = 7.2 Hz, 3 H), 0.87 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 172.1, 151.8, 131.9, 127.8, 127.7, 94.9, 81.9, 76.9, 55.9, 50.4, 50.1, 41.4, 40.5, 35.4, 29.7, 29.7, 25.8, 25.3, 24.2, 19.9, 18.8, 18.3; HRMS (ESI–TOF) calcd for $C_{22}H_{34}O_5Na$ $[M + Na]^+$ 401.2304, found 401.2299.

Acetate 69. To a solution of MOM ether **78** (6.2 mg, 16.4 μmol) in *i*-PrOH (0.5 mL) was added concentrated aqueous HCl (10 μL) at room temperature. After the mixture was stirred at 50 °C for 5 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc = 1:1) gave the corresponding alcohol (5.0 mg), which was used for the next step without further purification.

To a solution of the alcohol obtained above (5.0 mg) in CH_2Cl_2 (0.5 mL) were added pyridine (6.3 μL, 77.5 μmol) and AcCl (4.6 μL, 65.6 μmol) at 0 °C. After the mixture was stirred at the same temperature for 20 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1) gave acetate **69** (3.7 mg, 60% in two steps): colorless oil; R_f = 0.58 (hexane/EtOAc = 1:1); $[\alpha]_D^{26}$ +31.7 (*c* 0.08, $CHCl_3$); literature[10c] $[\alpha]_D^{20}$ +32 (*c* 1.08, $CHCl_3$); IR (neat) 3435, 2922, 2851, 1761, 1733, 1646 cm^{-1}; ^{1}H and ^{13}C NMR Table S14, HRMS (ESI–TOF) calcd for $C_{22}H_{32}O_5Na$ $[M + Na]^+$ 399.2148, found 399.2148.

Cell Growth-Inhibitory Activity. HL60 cells were cultured at 37 °C with 5% CO_2 in RPMI (Nissui, Tokyo, Japan) supplemented with 10% heat-inactivated fetal bovine serum (FBS; Sigma-Aldrich Co., St. Louis, MO), 100 units/mL penicillin, 100 μg/mL streptomycin, 0.25 μg/mL amphotericin, 300 μg/mL L-glutamine, and 2.25 mg/mL $NaHCO_3$. HL60 cells were seeded at 1×10^4 cells/well in 96-well plates (Iwaki, Tokyo, Japan). Various concentrations of the synthetic compounds were then added, and cells were incubated for 72 h. Cell proliferation was measured by the MTT assay.

Antifouling Activity and Toxicity. Adult barnacles of *Balanus* (*Amphibalanus*) *amphitrite* were collected at Mega fishing port (Himeji, Hyogo, Japan) and maintained in aquaria at 20 ± 1 °C by feeding with brine shrimp (*Artemia salina*) nauplii for one week. Cypris larvae of barnacle *Balanus* (*Amphibalanus*) *amphitrite* were obtained by larval culture in the laboratory according to the method reported by Nogata and co-workers.[62] Obtained cypris larvae were aged for 2–3 days prior to use at 5 °C in the dark. The effects of the synthetic compounds on the barnacle cyprids settlement were tested using 24-well polystyrene plates (Corning, NY, USA) according to our previous report.[63] Each compound was dissolved in MeOH. If the compound did not dissolve in MeOH, it was dissolved in a small amount of DMSO. Aliquots of the solution were applied to wells of 24-well polystyrene plates (0.1, 0.3, 1.0, 3.0, 10, and

50 μg) and air-dried. DMSO alone showed no effects on larval settlement at the concentration used in this assay (0.2%). Approximately 10 cypris larvae were added to each well filled with filtered natural seawater (28 psu) at final volume of 1.0 mL. After the incubation at 25 °C in the dark for 96 h, the number of larvae, which settled (including metamorphosed larvae), died, or did not settle, was counted under a microscope. Each level of the experiments was carried out with three wells and the assay was repeated three times. The assay was performed with $CuSO_4$ (0.01, 0.03, 0.1, 0.3, 1.0, 3.0, and 10 μg) as a positive control. The assay without compound was performed as a control. The antifouling activity and toxicity were expressed as EC_{50} and LC_{50} values, respectively. The EC_{50} and LC_{50} values were calculated by probit analysis according to Nogata's report.[64] When probit analysis could not be applied to calculate the values, these were estimated by straight-line graphical interpolation.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Stereochemical determination of the synthetic products, NMR data comparison of the natural products and the synthetic products, computed geometries and energies of **1a** and **1b**, and NMR spectra of all compounds (PDF)

Acknowledgments

We are grateful to Ms. Miyuki Uni (Okayama University) for her contribution during the early stage of the study, Professor Ichiro Hayakawa (Okayama University) for valuable discussion on the conformational analysis, and the Division of Instrumental Analysis, Okayama University, for the NMR measurements. We appreciate The Yakumo Foundation for Environmental Science for finalcial support. This research was supported by JSPS KAKENHI Grant Number 17K05862.

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