Total Synthesis and Biological Evaluation of C16 Analogs of (−)-Dictyostatin

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The structure−activity relationship of the crucial C16 region of (−)-dictyostatin was established through total synthesis of analogs followed by detailed biological characterization. A versatile synthetic strategy was used to prepare milligram quantities of 16-normethyldictyostatin, 16-*epi*-dictyostatin, and the C16-normethyl-C15*Z* isomer. Along the way, a number of other *E*/*Z* isomers and epimers were prepared, and a novel lactone ring contraction to make *iso*-dictyostatins with 20-membered macrolactones (instead of 22-membered macrolactones) was discovered. The synthesis of 16-normethyl-15,16-dehydrodictyostatin is the first of any dictyostatin by a maximally convergent route in which three main fragments are assembled, coupled in back-to-back steps, and then processed through refunctionalization and macrolactonization. Cell-based and biochemical evaluations showed 16-normethyl-15,16-dehydrodictyostatin and 16-normethyldictyostatin to be the most potent of the new agents, only 2- and 5-fold less active than (−)-dictyostatin itself. This data and that from previously generated dictyostatin analogs are combined to produce a picture of the structure−activity relationships in this series of anticancer agents.

Introduction

The potent anticancer agent (−)-dictyostatin was discovered over a decade ago,[1] but its initial development was stifled because the full structure was not known and because only small quantities were available from natural sources.[2] A detailed NMR study suggested it to have the structure **1** (Figure 1),[3] sharing identical configurations at all common stereocenters with the potent anticancer agent (+)-discodermolide **2**. This assignment was soon confirmed by back-to-back total syntheses,[4] which also provided larger quantities of the natural product for more detailed characterization. Two additional total syntheses[5] and other studies on fragment synthesis[6] testify to the continued high level of interest in this agent.

Dictyostatin **1** has proven to be somewhat more active than the (already very active) discodermolide, and it potently inhibits the binding of radiolabeled paclitaxel, discodermolide, and epothilone B to microtubules.[7] It is also very active against paclitaxel-resistant cell lines. Accordingly, (−)-dictyostatin is one of the most potent microtubule stabilizing agents discovered to date, and an increased understanding of the structure−activity relationship (SAR) of this class of molecules is an important goal.

Known features of the SAR of discodermolide[8] provide a starting point for addressing the SAR of dictyostatin, and the activities of synthetic analogs and isomers prepared during structure assignment studies provide additional information.[9] With this backdrop, we focused our work on two key portions of the dictyostatin molecule that differ significantly from discodermolide: (1) the bottom chain, C1−C9 region; and (2) the isolated, methyl-bearing stereocenter at C16. The bottom chain is important because there are many active analogs of discodermolide with modifications in this part of the molecule,[10] and indeed preliminary work has shown that both analogs and epimers of dictyostatin in this region of the molecule can be quite active.[11]

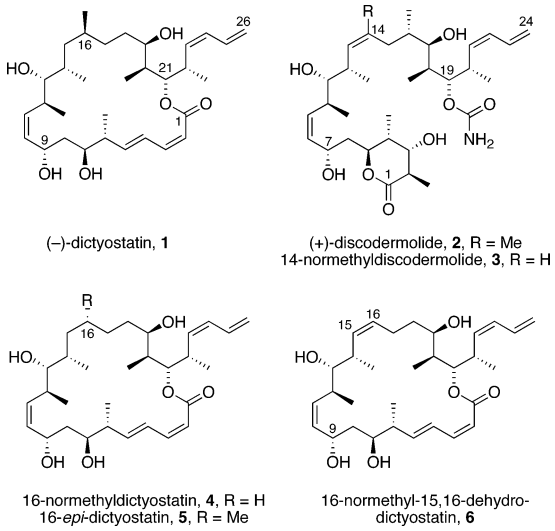

Figure 1. Structures of dictyostatin **1**, discodermolide **2**, and key analogs.

The isolated stereocenter at C16 of dictyostatin **1** is of special interest because discodermolide **2** does not have a corresponding stereocenter; instead, it has a C13−C14 *Z*-alkene. (Note that the carbon backbone of dictyostatin is two atoms longer than that of discodermolide, so C13 and C14 of discodermolide **2** correspond to C15 and C16 of dictyostatin **1**.) The methyl group on C14 of discodermolide **2** is not essential for biological activity; 14-normethyldiscodermolide **3** is a highly potent compound, as are a number of other 14-normethyl analogs.[12]

If the C16 methyl group of dictyostatin is dispensable, then the synthesis of such molecules would be simpler than the parent series because of the effort needed to install this isolated stereocenter. To provide a detailed understanding of SAR in

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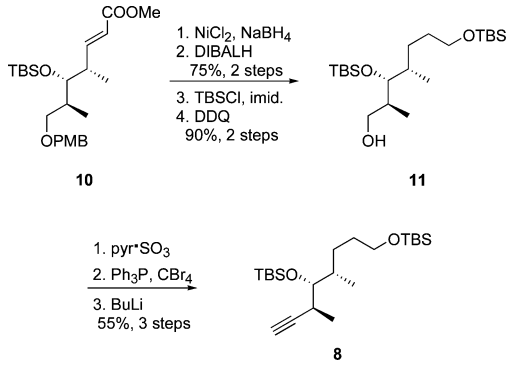
Scheme 1. Synthesis of Middle Fragment **8**



this key region, we undertook the syntheses and biological characterization of 16-normethyldictyostatin **4**, 16-*epi*-dictyostatin **5**, and 16-normethyl-15,16-dehydrodictyostatin **6** and report herein the full details of this work. Along the way, we continued to refine and improve the synthesis of the dictyostatins. We also discovered a ring contraction following the macrolactonization that provides new constitutional isomers called *iso*-dictyostatins. The synthesis and some preliminary biological data on the highly active 16-normethyldictyostatin **4** have been previously communicated.[13] The present results show that *Z*-alkene **6** is also highly active, but that the 16-α-epimer **5** has significantly reduced activity. Taken together with prior results, these data provide an expanded understanding of the SAR of dictyostatin.

Results and Discussion

Synthesis of 16-Normethyldictyostatin 4. The strategy for the synthesis of 16-normethyldictyostatin **4** was patterned after the synthesis of dictyostatin[4b,9] and is summarized in Figure 2. We made the same three primary (in red) and two secondary (in black) disconnections to arrive at top **7**, middle **8**, and bottom **9** fragments. The top **7** and bottom **9** fragments are the same as those used for dictyostatin and their syntheses are detailed elsewhere.[9]

The synthesis of the middle fragment **8** is shown in Scheme 1 and departs from the prior work at the readily available unsaturated ester **10**. Conjugate reduction to the saturated ester and then DIBALH reduction led to a primary alcohol (75%), which was protected as the TBS-ether. Cleavage of the PMB-ether revealed the primary hydroxy group at the other terminus of the molecule, providing **11** in 90% yield for the two steps. Completion of the fragment was effected by the formation of a terminal alkyne by using established conditions. Thus, oxidation

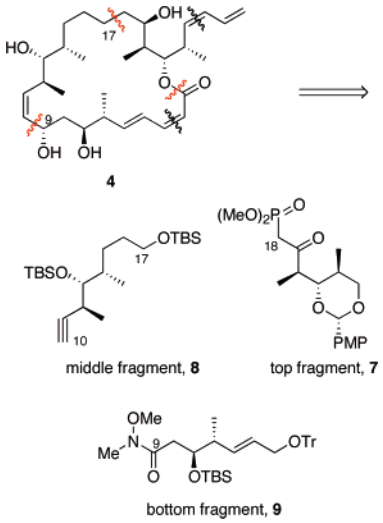


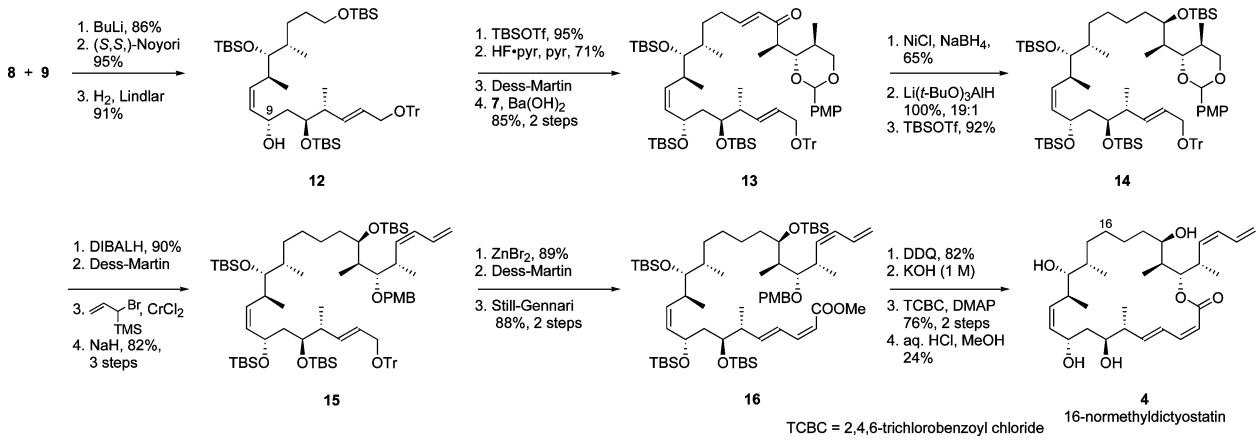
Figure 2. Strategy for the synthesis of 16-normethyldictyostatin **4**.

of alcohol **11** to the aldehyde and Corey−Fuchs dibromoolefination followed by BuLi-promoted conversion of the resulting dibromoolefin into the corresponding alkyne[14] supplied the middle fragment **8** in 55% yield for the three steps.

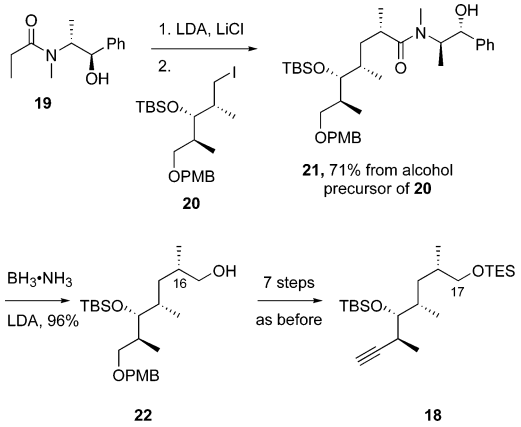
The fragment couplings and completion of the synthesis of **4** are shown in Scheme 2. The bottom and middle fragments were united first. To this end, the lithium acetylide of **8** was combined with Weinreb amide **9** to give the coupled fragment in 86% yield. Stereoselective carbonyl reduction with the (*S*,*S*)-Noyori catalyst[15] followed by Lindlar hydrogenation[16] supplied **12** in 86% yield for the two steps. In preparation for the second coupling step, the newly formed hydroxyl group was protected as the TBS-ether and the primary TBS group was selectively removed by using HF•pyridine. The resulting hydroxy group was oxidized with Dess−Martin periodinane, and the top fragment **7** was connected by using Horner−Wadsworth−Emmons (HWE) conditions, employing $Ba(OH)_2$ as the base. This fragment coupling proceeded efficiently, furnishing **13** in 85% yield over two steps.

Completion of the synthesis followed the established route.[9] Conjugate reduction of **13** using a sodium borohydride/nickel(II) chloride reagent was followed by carbonyl reduction using Li(*t*-BuO)$_3$AlH and TBS-protection of the resulting alcohol to give **14**. A considerably greater stereoselectivity (19:1 in favor of the desired *β*-alcohol) was observed compared to the analogous step in the synthesis of (−)-dictyostatin (2.4:1). As usual, the C19 epimers were readily separable by flash chromatography. The terminal diene was constructed by first opening

Scheme 2. Fragment Coupling and Completion of the Synthesis of 16-Normethyldictyostatin



Scheme 3. Synthesis of Middle Fragment **18**



the PMP-acetal with DIBALH to reveal the primary hydroxyl group, which was oxidized to the corresponding aldehyde by Dess−Martin reagent. Using Paterson's protocol[17] for Nozaki−Hiyama−Kishi reaction, followed by Peterson elimination, the aldehyde was reacted with 1-bromo-1-trimethylsilyl-2-propene to provide a mixture of β-hydroxysilanes, which upon treatment with NaH provided the *Z*-diene **15** in 82% yield for the three-step sequence.

Turning to the bottom part of the molecule and the formation of the dienoate, $ZnBr_2$-promoted cleavage of the trityl ether of **15** was followed by oxidation of the resulting alcohol to an aldehyde. Still−Gennari olefination[18] furnished the dienoate **16** with the desired (2*Z*,4*E*)-geometry in 88% yield over two steps. DDQ-deprotection of **16** followed by ester hydrolysis provided the *seco*-acid for the Yamaguchi macrolactonization.[19] Treatment of this *seco*-acid with trichlorobenzoyl chloride followed by dilute DMAP in toluene resulted in the clean formation of the macrolactone in 76% yield. Finally, global deprotection using 3 M methanolic HCl provided the target 16-normethyldictyostatin **4** in 24% yield after flash chromatographic purification.[20]

Synthesis of 16-*epi*-Dictyostatin 5. The preparation of 16-*epi*-dictyostatin was based on our improved synthesis of dictyostatin as summarized in Figure 3. Here, the C23−C26 diene was already present in the top fragment **17**, and this significantly increased the convergency of the synthesis. Also required were the usual bottom fragment **9** and the new middle fragment **18**.

The middle fragment **18** is a diastereomer of that used to make dictyostatin and was prepared analogously by Myers alkylation[21] as shown in Scheme 3. Deprotonation of the Myers

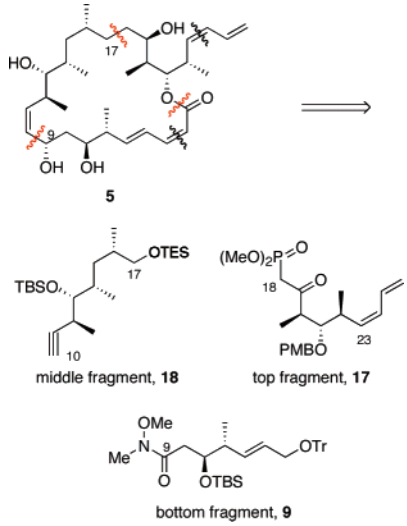


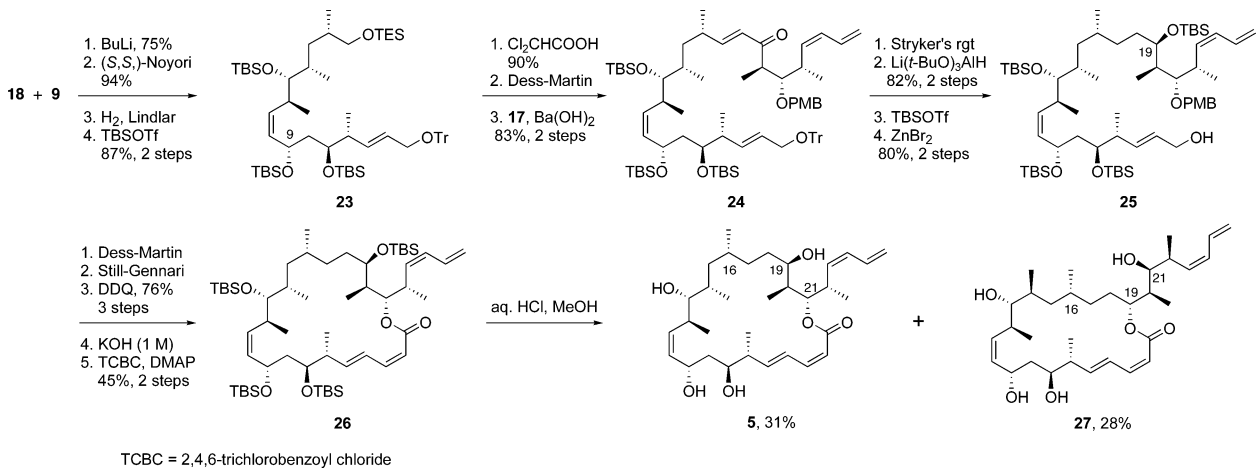
Figure 3. Strategy for 16-*epi*-dictyostatin **5**.

reagent **19** with LDA and alkylation with the iodide **20** provided the adduct **21** in 71% yield (over two steps based on the alcohol precursor of iodide **20**). Reductive cleavage of **21** provided alcohol **22**. Comparison of the ^{1}H NMR spectrum of **22** with spectra of the epimer at C-16[9] revealed that **22** was isomerically pure. A 7-step sequence analogous to that used in the total synthesis of dictyostatin[9] was then employed to elaborate compound **22** into the middle fragment **18**. To simplify the selective desilylation of the C-17 alcohol in preparation for the HWE reaction, we protected this fragment with a TES group rather than a TBS group.

The fragment couplings and completion of the synthesis of **5** are summarized in Scheme 4. First the bottom and middle fragments were combined by addition of the lithium acetylide of **18** to the Weinreb amide **9**. Stereoselective reduction of the carbonyl group with the (*S*,*S*)-Noyori catalyst[15] followed by Lindlar hydrogenation[16] and protection furnished **23** in 82% yield. To prepare for the second coupling reaction, the TES group was removed and the resulting alcohol was oxidized to the corresponding aldehyde. HWE conditions were then employed to join the top fragment **17**, thus providing the fully coupled enone **24**.

Conjugate reduction of **24** was first required to remove the double bond resulting from the HWE reaction, but the previously used conditions (nickel boride) were incompatible with the diene. However, we were able to effect this transformation in

Scheme 4. Fragment Coupling and Completion of the Synthesis of 16-*epi*-Dictyostatin **5**



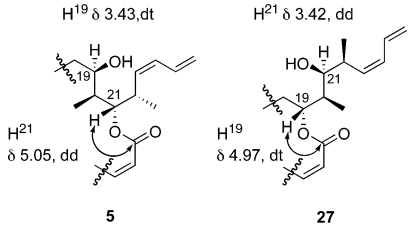


Figure 4. Key chemical shifts and three-bond HMBC correlations (double-headed arrows) in **5** and **27**.

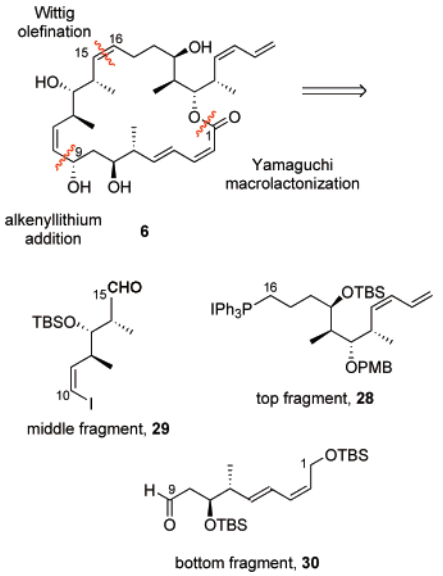


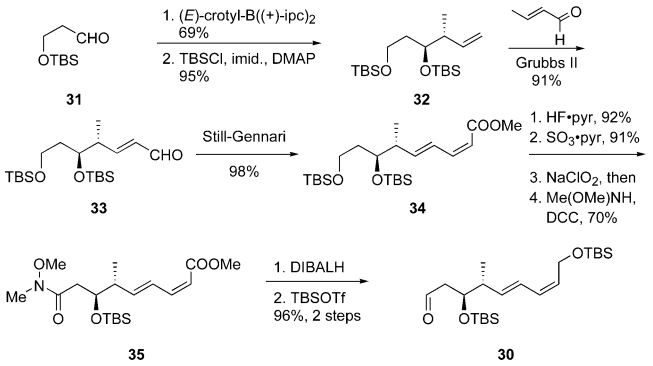
Figure 5. Strategy for the synthesis of 16-normethyl-15,16-dehydrodictyostatin **6**.

high yield by using 0.6 equiv of Stryker's reagent[4a,22] (3.6 equiv of hydride) provided that slow stirring was applied and that the quality of the reagent was high. Stereoselective carbonyl reduction with Li(*t*-BuO)$_3$AlH provided the alcohol as a 5/1 mixture of epimers in 82% yield for the two steps. Separation of the major β-alcohol from its α-isomer by flash chromatography, followed by protection of the hydroxyl group and removal of the trityl group with $ZnBr_2$ supplied compound **25** in 66% overall yield. Slow addition of the $ZnBr_2$ as a solution was crucial to maintaining the integrity of the other protecting groups. Dess−Martin oxidation of **25** followed by a Still−Gennari modification of the HWE olefination efficiently established the (2*Z*,4*E*)-diene methyl ester. Oxidative cleavage of the PMB-ether and hydrolysis of the methyl ester furnished the *seco*-acid. In parallel, a small sample from the PMB deprotection but prior to the hydrolysis was desilylated as usual to provide an open-chain pentahydroxy methyl ester called *seco*-**5a** in Table 1 below (structure not shown, see Supporting Information).

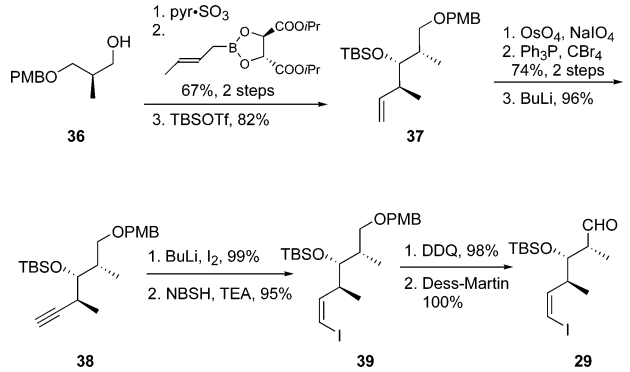
Treatment of the *seco*-acid precursor under Yamaguchi's macrolactonization conditions provided macrolactone **26** in 45% yield for the two steps. Finally, global deprotection yielded an approximately equimolar mixture of two compounds, 16-*epi*-dictyostatin **5** (31%) and a ring-contracted isomer **27** (28%), which were easily separable by column chromatography. Resubmission of each of these two compounds to the deprotection conditions resulted in a similar mixture of the two compounds, so we believe that this may be an equilibrium mixture.

High-field (600 MHz) two-dimensional NMR experiments were employed to discern the identities of the two compounds. Through a series of ^{1}H-COSY, HMBC, HMQC, DEPT-135, and ^{13}C experiments, all protons and carbons in each of the two

Scheme 5. Synthesis of Bottom Fragment **30**



Scheme 6. Synthesis of the Middle Fragment **29**



molecules were assigned, with the exception of a few overlapping resonances in the unsubstituted C17−C19 aliphatic region. The COSY experiments were used to assign the protons from C18 through to the diene terminus for each compound. An HMBC experiment on **5** showed a cross-peak between H21 and C1, thereby confirming the 22-membered lactone structure (Figure 4).

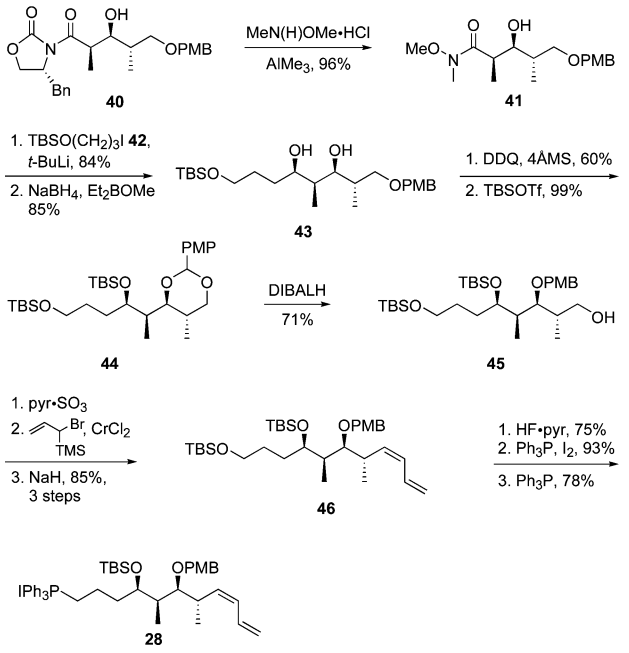
The structure of 16-*epi*-isodictyostatin **27** was determined to be that of a two-atom ring-contracted version of 16-*epi*-dictyostatin, wherein the lactone was formed at C19 rather than at the expected C21 position. The assignment was initially made by a comparison of chemical shift data of H19 and H21 for compounds **5** and **27**; in **5**, H21 is downfield of H19, but in **27**, H19 is downfield of H21. This tentative assignment was later confirmed by observing the three-bond coupling between H19 and C1 in the HMBC spectrum of **27**.

With a sample of pure ring-contracted lactone **27** in hand and well characterized, we revisited ^{1}H NMR spectra of prior crude products from the macrolactonization/deprotection sequence. In the case of dictyostatin and several of its isomers,[9] we were indeed able to identify small peaks in the crude spectra that we can attribute to the analogous ring-contracted isomer;[20] however, in no case was this present in the amount as high as in the 16-*epi* series. Apparently, the configuration at C16 is especially important in determining either the rate or the position of the translactonization equilibrium. Related *trans*-lactonizations have been observed with other macrolactones, including apoptolidin[23] and dolabelide.[24]

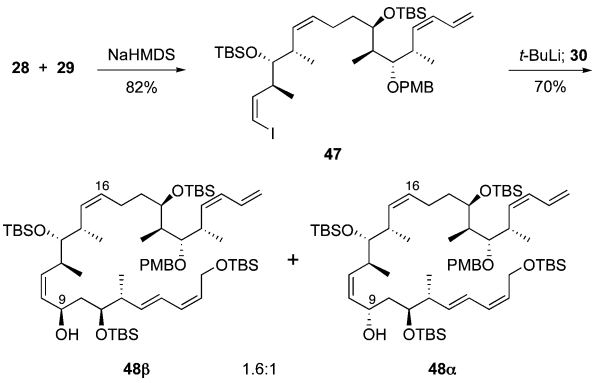
Synthesis of 16-Normethyl-15,16-dehydrodictyostatin, 6. *Z*-Alkene **6** was broken down retrosynthetically by three key disconnections, as shown in Figure 5. As with dictyostatin, the first two were at the lactone and the C9−C10 bonds. The final disconnection, however, now occurred at C15−C16 by a Wittig olefination transformation.

This strategy is highly convergent because there are no secondary disconnections at either diene, and accordingly, no

Scheme 7. Synthesis of Top Fragment **28**



Scheme 8. Fragment Coupling En Route to **6**



C−C bonds need to be formed after the fragment couplings begin. This is the first example of such a "maximally convergent" approach to dictyostatin, where the coupling of the three main fragments is followed only by refunctionalization, macrolactonization, and deprotection.

The three disconnections led to the top **28**, middle **29**, and bottom **30** fragments. We incorporated the entire (23*Z*)-diene into the top fragment **28**. However, due to the possibility of isomerization of the (2*Z*,4*E*)-dienoate ester in the bottom fragment to the more stable (2*E*,4*E*)-dienoate ester, we focused our attention on a protected precursor **30** with C1 in an alcohol oxidation state. The synthesis of this compound is shown in Scheme 5. The two stereocenters in **30** were established by a Brown *anti*-crotylation reaction with aldehyde **31**. Protection of the resulting alcohol with TBSCl provided **32**. This alkene was subjected to Grubbs-II cross-metathesis with crotonaldehyde[25] to cleanly furnish unsaturated aldehyde **33** in 91% yield. Addition of the *Z*-alkene was carried out by the Still−Gennari protocol to yield methyl dienoate **34** as a single isomer. Selective cleavage of the primary TBS-ether, oxidation, and conversion of the resulting carboxylic acid to the corresponding Weinreb amide furnished compound **35** in 58% yield. Single-step reduction of both the ester and the Weinreb amide functionalities of **35** followed by TBS protection of the resulting allylic alcohol provided the bottom fragment **30** in 96% yield.

The synthesis of middle fragment **29** is summarized in Scheme 6. Because of the increased convergence of the plan, the fragment couplings took place back-to-back, the middle fragment **29** containing both coupling functionalities, the *Z*-alkenyliodide and the aldehyde, in unprotected form. Oxidation of known alcohol **36**,[26] (readily available from commercial (*S*)-Roche ester) was followed by a Roush *anti*-crotylation reaction[27] and protection of the resulting secondary alcohol provided TBS-ether **37** in 55% yield. Single-step osmylation and diol-cleavage was followed by a Corey−Fuchs reaction to generate a dibromoalkene, which was converted into a terminal alkyne **38** with BuLi. The acetylene **38** was deprotonated, and the resulting lithium acetylide was iodinated. *cis*-Reduction of the resulting iodoacetylene using NBSH and triethylamine[28] provided *Z*-alkenyl iodide **39** in 94% yield for the two steps. Finally, oxidative cleavage of the PMB-ether (98%) followed by Dess−Martin oxidation (100%) of the resulting alcohol furnished the middle fragment **29**.

The preparation of the top fragment **28** began with Evans aldol adduct **40**,[26] which was converted into Weinreb amide **41** in 96% yield (Scheme 7). Addition of the alkyllithium reagent derived from iodide **42** followed by *syn*-reduction of the carbonyl group furnished diol **43** in 71% yield for the two steps. Oxidation of the PMB-ether to the corresponding PMP-acetal (60%) followed by protection of the remaining hydroxyl-group with TBSOTf (99%) provided PMP-acetal **44**. DIBALH reduction of the PMP-acetal furnished primary alcohol **45** in 71% yield. Oxidation of the alcohol followed by conversion of the resulting aldehyde to the terminal *Z*-diene via a two-step protocol involving a Nozaki−Hiyama−Kishi reaction followed by a Petersen olefination provided diene **46** in 85% yield.[29] Deprotection of the primary hydroxyl group, iodination, and then reaction with triphenylphosphine were employed sequentially to provide phosphonium salt **28**.

The fragment coupling stage of the synthesis required only two steps, as summarized in Scheme 8. Deprotonation of salt **28** with NaHDMS followed by addition of aldehyde **29** provided 15-(*Z*)-alkene **47** in 82% yield. Lithium−iodine exchange with **47** followed by addition of aldehyde **30** then provided a 1.6/l mixture of alcohols **48***β*/α. These C9-epimers were separated by flash chromatography.

Assignment of the configuration of the newly formed stereocenter (C9) was based on experimental and ^{1}H NMR similarities between this series of compounds and analogous intermediates in the dictyostatin synthesis.[30] As a representative example, the signal for H-9 in α-TBS-ether of *seco*-acid **50**α (Scheme 9) is a dd at δ 4.5, with *J*-values of 12.4 and 7.6 Hz. For all analogs of dictyostatin modified at the C-15 and C-16 positions, dd's with similar chemical shifts and *J*-values were observed for H-9. However, the *β*-alcohol of **50***β* (not shown) gave rise to a signal more closely resembling a triplet at δ 4.4, with a *J*-value of 8.1 Hz.

The completion of the synthesis of analog **6** is summarized in Scheme 9. Protection of the secondary alcohol of **48**α with TBSOTf followed by selective desilylation of the primary TBS-ether provided alcohol **49**α in 85% yield. Two-step oxidation of **49**α to the acid followed by removal of the PMB-group with DDQ provided the requisite *seco*-acid **50**α for the macrolactonization. Treatment of **50**α with trichlorobenzoyl chloride followed by addition of dilute (0.01 M) DMAP in toluene (Yamaguchi conditions) supplied the crude macrolactone **51**α in 71% yield. Global deprotection under acidic conditions furnished a 14:1 mixture of dictyostatin analog **6** and its 2-*E*-isomer **53** in 45% yield. These were separated by flash

Scheme 9. Completion of the Syntheses of **6** and Isomers **53**−**55**

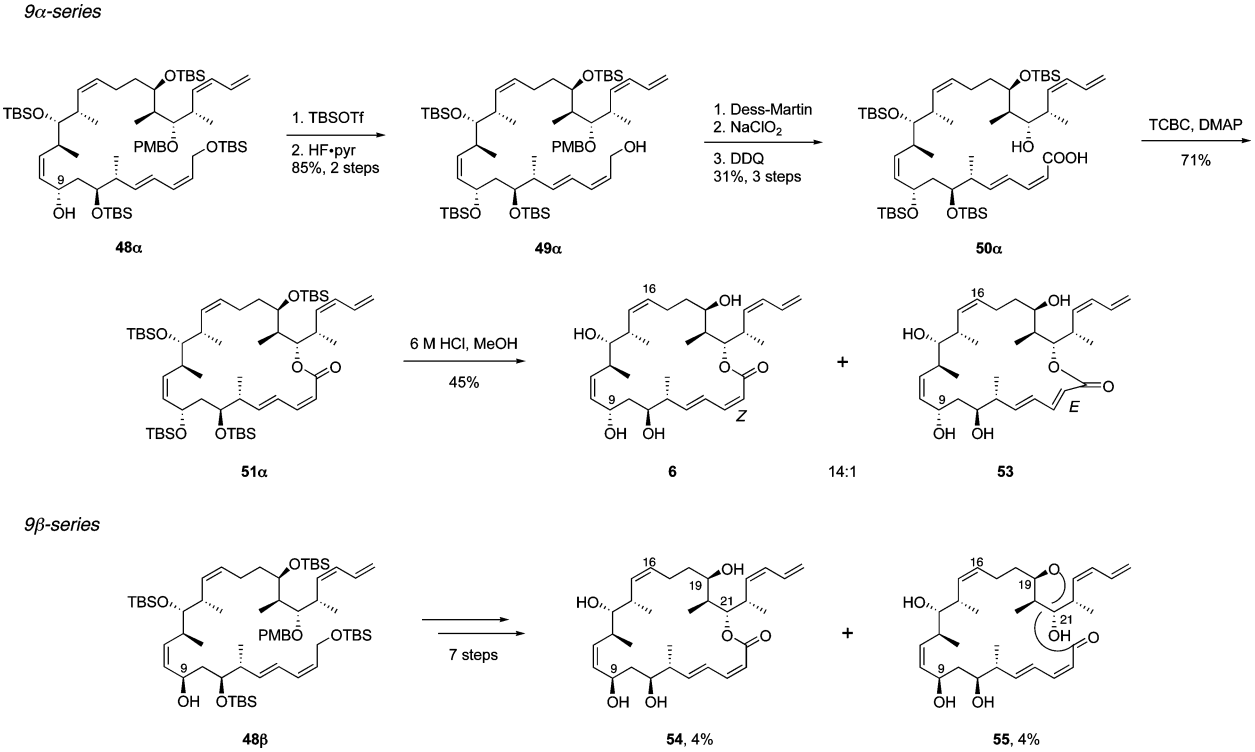


Table 1. Biological Activities of Dictyostatin (**1**) and Analogs as Compared to Discodermolide **2**, 14-Normethyldiscodermolide (**3**), and Paclitaxel

	cellular				in vitro	
test agent	MDEC[a] for tubulin polymer increase, nM ± SD (*N*)	GI_{50},[b] nM (fold-resistance) (*N* = 4) 1A9	1A9/Ptx10	1A9/Ptx22	% tubulin polymerized by 10 μM test agent relative to 10 μM paclitaxel[c]	% inhibition of binding of [^{3}H]paclitaxel to tubulin polymer[d] (*N* ≥ 3)
1	5.4 ± 1.9 (4)	0.69 ± 0.80	3.2 ± 2.4 (5)	1.3 ± 1.0 (2)	157	75 ± 5 (6)
2	65 ± 0 (2)	1.7 ± 1.2	6.2 ± 3.6 (4)	7.0 ± 8.4 (4)	148	76 ± 6 (6)
3	29 ± 21 (2)	3.7 ± 1.5	33 ± 18 (9)	30 ± 0 (8)	nd	75 ± 3 (3)
4	25 ± 9 (3)	0.41 ± 0.52	470 ± 70 (1146)	5.6 ± 4.7 (14)	91	48 ± 3 (3)
5	1278 ± 181 (3)	61 ± 6	862 ± 1680 (14)	543 ± 140 (9)	9	11 ± 3 (3)
seco-**5**[e]	nd	9140 ± 3290	25920 ± 4250	2600 ± 980	7	7 ± 5 (3)
6	11 ± 2 (3)	8.3 ± 0.8	942 ± 250 (113)	62 ± 5 (7)	107	38 ± 9 (3)
27	>5000 (3)	7800 ± 1410	44190 ± 890 (6)	53760 ± 3880 (7)	3	4 ± 0 (3)
53	647 ± 106 (4)	210 ± 110	23680 ± 1090 (113)	847 ± 140 (4)	10	5 ± 2 (3)
54	>5000 (1)	4260 ± 400	19300 ± 530 (5)	4600 ± 500	1	11 ± 1 (3)
55	>5000 (1)	>50000	32700 ± 510	>50000	6	7 ± 2
paclitaxel	5.2 ± 0.4 (4)	0.71 ± 0.11	64 ± 8 (90)	51 ± 9 (72)	100	

[a] Minimum detectable effective concentration of the test agent in HeLa cells after 21 h of continuous exposure. [b] Fifty percent growth inhibitory concentration after 72 h of continuous exposure to the test agent. [c] Bovine brain tubulin (10 μM) in 0.2 M monosodium glutamate was treated at 0 °C with the test agent (predissolved in DMSO). The mixture was transferred to a cuvette in a 6-channel, temperature-controlled spectrophotometer, and the temperature was rapidly raised to 30 °C. Tubulin assembly was monitored by turbidity development at 350 nm, and the percent assembly reported is relative to that caused by 10 μM paclitaxel, analyzed in the same experiment in one of the six cuvettes, after 20 min at 30 °C. [d] Percent competition at 37 °C by 4 μM test agent with 2 μM [^{3}H]paclitaxel for binding to microtubules formed from 2 μM bovine brain tubulin and 20 μM dideoxyGTP. [e] The open chain methyl ester analog of **5**.

chromatography. Carrying out the same seven-step sequence beginning with **48**β provided the C-9 epimer of this analog **54** along with its ring-contracted congener **55**. The structures of these two compounds were assigned analogously to those of **5** and **27**, as described above.

In total, the synthesis of the 15,16-dehydro-16-normethyl analog of dictyostatin was carried out in nine steps, starting from the three fragments and in 1.7% overall yield. The synthesis also provided two new stereoisomers and a constitutional isomer for SAR studies.

Biological Evaluation. Compounds **4**, **5**, **6**, **27**, and **53**−**55**, along with 14-normethyldiscodermolide **3**[12a] (a kind gift from Prof. Amos B. Smith, III) were screened for cellular and biochemical activity in comparison to dictyostatin **1**, discodermolide **2** and paclitaxel. Methods used are described in detail elsewhere.[9] The minimum detectable effective concentrations (MDECs) for increases in cellular tubulin polymer mass in HeLa cells caused by 21 h continuous exposure to the agents are given in Table 1. Both 16-normethyl-15,16-dehydrodictyostatin **6** and 16-normethyldictyostatin **4** were effective in the low nanomolar range, comparable to dictyostatin **1**, 14-normethyldiscodermolide **3**, and paclitaxel. Discodermolide **2** was slightly less active. The fifty percent antiproliferative (growth inhibitory) concentrations (GI_{50}s) of the agents against human ovarian carcinoma 1A9 cells (Table 1) were for the most part well-correlated with the MDECs in HeLa cells: in most instances, the GI_{50} values were about 2- to 7-fold lower than the MDECs. The exceptions were discodermolide **2**, as previously noted (30-fold lower GI_{50}), and 16-

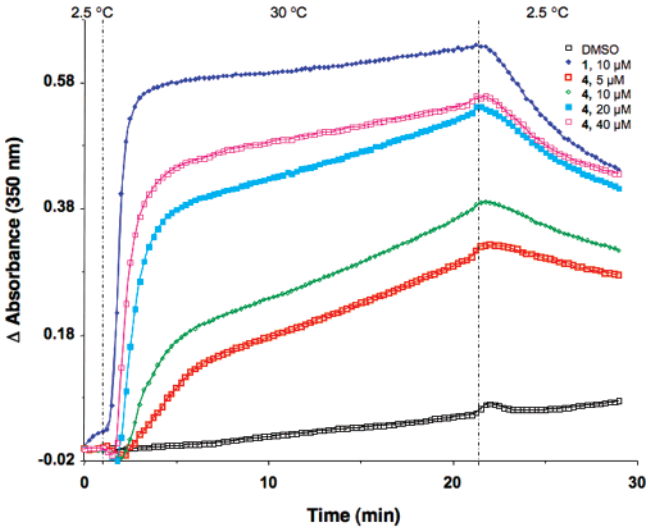


Figure 6. Concentration-dependent tubulin polymerization-inducing actions of 16-normethyldictyostatin **4** in comparison to dictyostatin **1** (see Table 1, footnote c for experimental conditions).

epi-dictyostatin **5** (20-fold lower GI_{50}). The GI_{50} values determined in the mutant β-tubulin-expressing, paclitaxel-resistant clones of the 1A9 cells, 1A9/Ptx10 (βPhe270->Val), and 1A9/Ptx22 (βAla364->Thr) are also given in Table 1. Most of the compounds did not experience appreciable cross-resistance (as compared to the parental, wild type β-tubulin-expressing parental 1A9 cells). However, the very large cross-resistance of the 1A9/Ptx cell lines toward compounds **4**, **6**, and **53** revealed some potentially telling clues about the orientation of the dictyostatin macrocyclic core within the taxoid binding site. Specifically, the C-16 region of these molecules likely interacts with or is situated near the Phe270 region of the binding pocket of β-tubulin. In surprising contrast, 14-normethyldiscodermolide, a direct analog of **4**, experienced no cross-resistance in this cell line, further suggesting the possibility that the dictyostatins and discodermolides may not adopt the same orientations within the taxoid binding site.

With isolated bovine brain tubulin at 30 °C, the test agents were potent inducers of polymer assembly (Table 1). Their potencies in this assay were in general accord with their MDECs for tubulin polymer increase in cells. Dictyostatin **1** and discodermolide **2** were the most potent and nearly equally so, followed by analogs **6** and **4**, both essentially equipotent with paclitaxel. A representative trace showing the concentration-dependent ability of 16-normethyldictyostatin **4** to cause assembly of bovine brain tubulin in comparison to that of 10 μM dictyostatin **1** is shown in Figure 6. Compounds **5** and **53** were less potent than expected based on their cell-based activities.

Finally, in good accord with the other biological and biochemical assays, the agents effectively competed with [^{3}H]-paclitaxel for binding to preformed microtubules. Dictyostatin **1**, discodermolide **2**, and 14-normethyldiscodermolide **3** were the most, and essentially equally, potent in this regard. Compounds **4** and **6** had, respectively, 65 and 50% of the potency of compounds **1**−**3**.

Structure−Activity Relationships. The present data along with earlier data[7,9,10d,11a,11b,13] comprise extensive information on over 20 dictyostatin analogs with a wide range of potencies, and inspection of the data begins to reveal SAR as summarized in Figure 7. The C16 methyl substituent, if present, must be in the *S*-configuration (compare compounds **1** and **5**). This substituent is disposable (compound **4**), however, and a C15:16-(*Z*)-alkene without the C16 methyl group is well-tolerated (compound **6**). Also readily apparent from the present data is the importance for C2:3-(*Z*)-geometry and the 22-membered lactone (C1−C21 ester linkage). A 20-membered lactone (C1−C19 ester linkage) ablates the desired biological actions. A macrolactone is not an absolute necessity, though, as an open-chain methyl ester analog with appropriate, dictyostatin-like substituent configurations and geometries retains good potency. Previously obtained data also clearly show that the C9 hydroxy group must be in the *S*-configuration and that all but a C6,C7,-C9 *anti*−*syn* arrangement of substituents provides extremely good potencies. However, one of our early analogs with a saturated C2−C9 region did retain weak biological activity. Another finding is that the *R*-configuration at C19 (hydroxy group) confers better biological activity. This appears to also be true for the C14 methyl substituent.

Conclusions

In summary, total synthesis of multimilligram quantities of the C16 analogs of (−)-dictyostatin was achieved via a versatile synthetic strategy. Geometric isomerization at C2:3 alkene and C16-epimerization were detrimental to activity, as was formation of a 20-membered macrolactone (*iso*-dictyostatins). 16-Normethyldictyostatin and the C16-normethyl-C15:16-(*Z*)-analog had biological activities near those of the parent compound, and their preparation was achieved in several fewer steps than that required for the natural product. Qualitative structure−activity

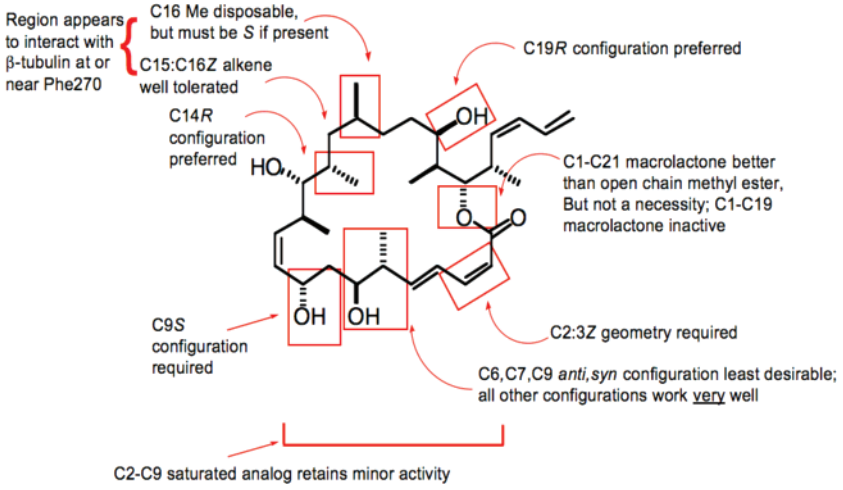


Figure 7. Qualitative structure−activity relationships in dictyostatins.

relationships developed from this data and that from previously generated dictyostatin analogs provide insight into the next generation of targets to prepare. In agreement with recently published modeling studies done taking into account results with a photoaffinity analog of discodermolide,[31] the sum of the biological data place the C16 position of dictyostatin in close proximity to Phe270 of the taxoid binding site on β-tubulin. The fact that 14-normethyldiscodermolide, a direct analog of 16-normethyldictyostatin, does not experience the same cross-resistance in a cell line where this residue is mutated suggests that the dictyostatins and discodermolides may not adopt exactly the same orientations within the taxoid binding site.

Experimental Section

The Experimental Section contains details of the synthesis of the 16-normethyl-15,16-dehydrodictyostatin **6** and related analogs; details for syntheses of **4**, **5**, and their cogeners are found in the Supporting Information.

(2*Z*,4*E*,6*R*,7*S*)-Methyl 7,9-Bis(*tert*-butyldimethylsilyloxy)-6-methylnona-2,4-dienoate (34). A mixture of the shown alkene **32** (0.046 mL, 0.112 mmol) and crotonaldehyde (0.018 mL, 0.224 mmol) in degassed CH_2Cl_2 (1.1 mL, argon sparged) was refluxed for 15 min and then cooled to ambient temperature. Grubbs second generation catalyst (0.007 g, 0.008 mmol) was added and the mixture was refluxed at 50 °C. After 15 h, the mixture was concentrated under vacuum. Purification by column chromatography (4:1 hexanes/diethyl ether) provided the aldehyde **33** (0.039 g, 91%) as a colorless oil, which was used immediately in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (d, J = 7.9 Hz, 1H), 6.93 (dd, J = 7.6, 15.8 Hz, 1H), 6.18 (dd, J = 7.9, 15.8 Hz, 1H), 3.96 (m, 1H), 3.72 (t, J = 5.9 Hz, 1H), 2.72 (m, 1H), 1.82−1.55 (m, 2H), 1.21 (d, J = 6.8 Hz, 3H), 0.98 (s, 9H), 0.96 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), 0.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 160.5, 133.2, 72.4, 59.6, 42.6, 37.7, 26.1, 18.4, 18.3, 15.5, −4.2, −4.3, −5.4.

A mixture of bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)-phosphonate (0.97 mL, 4.56 mmol) and 18-crown-6 (5.02 g, 19.00 mol) in THF (19 mL) at −78 °C was treated with a 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene (11.40 mL, 5.70 mmol) dropwise over 12 min. The mixture was stirred at −45 °C for 1 h, cooled to −78 °C. A solution of the aldehyde **33** (1.47 g, 3.80 mmol) in THF (4 mL) was added. The mixture was stirred to −78 °C for 5.5 h and warmed to ambient temperature over 30 min. After quenching by addition of satd aq NH_4Cl (50 mL), the mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (19:1 hexanes/EtOAc) provided the dienoate **34** (1.68 g, 100%) as a colorless oil: IR (NaCl) 2954, 2857, 1721, 1175, 1097, 835, 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (ddd, J = 0.9, 11.3, 15.4 Hz, 1H), 6.44 (t, J = 11.2 Hz, 1H), 5.93 (dd, J = 7.9, 15.3 Hz, 1H), 5.46 (d, J = 11.3 Hz, 1H), 3.69 (m, 1H), 3.60 (s, 1H), 3.52 (dt, J = 2.0, 6.5 Hz, 1H), 2.37 (m, 1H), 1.56−1.39 (m, 3H), 0.96 (d, J = 6.8 Hz, 3H), 0.80−0.74 (m, 18H), −0.06 (s, 6H), −0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 147.6, 145.8, 127.1, 115.6, 72.6, 60.0, 51.2, 42.9, 37.4, 26.1, 18.5, 18.3, 15.7, −4.1, −5.0; $[\alpha]^{20}_D$ −6.6 (*c* 0.36, $CHCl_3$).

(2*Z*,4*E*,6*R*,7*S*)-Methyl 7-(*tert*-Butyldimethylsilyloxy)-9-hydroxy-6-methylnona-2,4-dienoate. A solution of the TBS ether **34** (0.80 g, 1.75 mmol) in THF (9 mL) at 0 °C was treated with a solution of HF·pyr in pyr/THF (39 mL, prepared by slow dropwise addition of HF·pyr (3 mL) to a solution of pyridine (12 mL) and THF (24 mL)). The reaction mixture was warmed to ambient temperature and stirred for 8 h. After quenching by addition of satd aq $NaHCO_3$, the mixture was extracted with EtOAc (4 × 40 mL). The combined organic layers were washed with satd aq $CuSO_4$ (3 × 30 mL) and brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (2:1 hexanes/EtOAc) provided the target alcohol (0.54 g, 92%) as a colorless oil: IR (NaCl) 3428, 2953, 2857, 1719, 1412, 1196, 1176, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (dd, J = 11.3, 15.4 Hz, 1H), 6.53 (t, J = 11.3 Hz, 1H), 5.97 (dd, J = 7.8, 15.4 Hz, 1H), 5.59 (d, J = 11.3 Hz, 1H), 3.83 (dt, J = 4.5, 7.0 Hz, 1H), 3.73−3.65 (m, 5H), 2.53 (m, 1H), 2.16 (s, 1H), 1.73−1.57 (m, 2H), 1.06 (d, J = 6.8 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 147.2, 145.5, 126.8, 115.5, 73.2, 59.4, 51.0, 42.7, 36.0, 25.8, 18.0, 15.0, −4.4, −4.5; $[\alpha]^{20}_D$ −14.3 (*c* 0.21, $CHCl_3$).

(2*Z*,4*E*,6*R*,7*S*)-Methyl 7-(*tert*-Butyldimethylsilyloxy)-9-(methoxy(methyl)amino)-6-methyl-9-oxonona-2,4-dienoate (35). A solution of the alcohol prepared above (0.52 g, 1.58 mmol) and triethylamine (0.66 mL, 4.74 mmol) in CH_2Cl_2 (4 mL) and DMSO (2 mL) at 0 °C was treated dropwise with a solution of SO_3·pyr (0.63 g, 3.96 mmol) in DMSO (5 mL) over 2 min, and the reaction mixture was stirred for 1 h. After quenching by addition of water (50 mL), the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with satd aq $CuSO_4$ (2 × 30 mL) and brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (9:1 hexanes/EtOAc) provided the desired aldehyde (0.47 g, 91%) as a pale yellow oil, which was used immediately in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (dd, J = 1.7, 2.5 Hz, 1H), 7.39 (ddd, J = 1.1, 11.2, 15.4 Hz, 1H), 6.56 (dt, J = 0.7, 11.3 Hz, 1H), 6.02 (dd, J = 7.6, 15.6 Hz, 1H), 5.65 (d, J = 11.3 Hz, 1H), 4.22 (ddd, J = 4.0, 4.9, 6.8 Hz, 1H), 3.75 (s, 3H), 2.63−2.42 (m, 3H), 1.11 (d, J = 6.8 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H).

A mixture of the aldehyde (0.43 g, 1.32 mmol) and NaH_2PO_4·H_2O (1.09 g, 7.92 mmol) in *t*-BuOH (97 mL) and H_2O (32 mL) at 0 °C was treated with a 2.0 M solution of 2-methyl-2-butene in THF (33.0 mL, 66.00 mmol) and then $NaClO_4$ (0.35 g, 3.96 mmol) was added. The reaction mixture was stirred at 0 °C for 15 min and at ambient temperature for 2 h. After quenching by addition of a mixture of satd aq NH_4Cl (20 mL) and brine (20 mL), the mixture was extracted with diethyl ether (4 × 80 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The carboxylic acid as a pale yellow oil was used immediately in the next step without further purification.

A solution of the carboxylic acid (0.43 g, 1.32 mmol) in CH_2Cl_2 (8.4 mL) at 0 °C was treated with triethylamine (0.35 mL, 2.50 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (0.16 g, 1.67 mmol), and DCC (0.34 g, 1.67 mmol). The reaction mixture was warmed to ambient temperature and stirred for 12 h. After concentration under vacuum, purification by column chromatography (2:1 hexanes/EtOAc) provided the target Weinreb amide **35** (0.36 g, 70% for two steps) as a colorless oil: IR (NaCl) 2955, 2895, 2856, 1721, 1666, 1439, 1196, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (dd, J = 11.2, 15.4 Hz, 1H), 6.57 (t, J = 11.3 Hz, 1H), 6.09 (dd, J = 8.0, 15.4 Hz, 1H), 5.60 (d, J = 11.3 Hz, 1H), 4.29 (ddd, J = 3.2, 5.1, 7.4 Hz, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 3.17 (s, 3H), 2.68−2.48 (m, 2H), 2.33 (dd, J = 5.2, 15.4 Hz, 1H), 1.13 (d, J = 6.8 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 167.1, 146.7, 145.6, 127.6, 115.9, 72.6, 61.5, 51.3, 43.4, 37.1, 26.1, 18.3, 15.8, −4.2, −4.6; LRMS (ESI) 408 $[M + Na]^+$; HRMS (ESI) calcd for $C_{19}H_{35}NO_5SiNa$ $[M + Na]^+$, 408.2182; found, 408.2177; $[\alpha]^{20}_D$ −53.6 (*c* 0.33, $CHCl_3$).

(2*S*,3*S*,4*S*)-1-(4-Methoxybenzyloxy)-2,4-dimethylhex-5-en-3-ol. A solution of the alcohol **36** (4.20 g, 20.0 mmol) and diisopropylethylamine (9.90 mL, 60.0 mmol) in CH_2Cl_2 (200 mL) and DMSO (40 mL) at 0 °C was treated dropwise with a solution of SO_3·pyr (9.74 g, 60.0 mmol) in DMSO (60 mL) over 20 min. The reaction mixture was stirred for 1 h. After quenching by addition of H_2O (200 mL), the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with satd aq $CuSO_4$ (2 × 50 mL) and brine and dried ($MgSO_4$). The concentration under vacuum provided the aldehyde as a colorless oil, which was used immediately in the next step without further purification.

A 1.0 M solution of (*R*,*R*)-diisopropyl tartrate (*E*)-crotylboronate in toluene (28.16 mL, 28.16 mmol) was added to a slurry of powdered 4 Å molecular sieves (0.8 g) in toluene (17 mL) at

ambient temperature. After 20 min, the mixture was cooled to −78 °C, then a solution of the aldehyde (4.20 g, 20.0 mmol) in toluene (17 mL) was added via cannula over 50 min. After 8 h, the reaction mixture was quenched by 1 M NaOH (60 mL), stirred vigorously for 30 min, and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (4:1 hexanes/EtOAc) provided the alcohol (3.54 g, 67% for two steps) as a colorless oil: IR (NaCl) 3479, 2966, 2932, 1613, 1513, 1248, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.80 (ddd, J = 8.4, 10.2, 17.1 Hz, 1H), 5.17−5.06 (m, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.58−3.43 (m, 3H), 2.28 (m, 1H), 1.97 (m, 1H), 0.98 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 142.1, 130.7, 129.4, 115.8, 114.1, 75.9, 74.7, 73.2, 55.5, 42.1, 35.4, 16.9, 10.2; $[\alpha]^{20}_D$ −2.4 (*c* 1.08, $CHCl_3$).

((2*S*,3*S*,4*S*)-1-(4-Methoxybenzyloxy)-2,4-dimethylhex-5-en-3-yloxy)(*tert*-butyl)dimethylsilane (37). A solution of the alcohol prepared above (3.50 g, 13.2 mmol) and 2,6-lutidine (4.0 mL, 17.2 mmol) in CH_2Cl_2 (130 mL) at −78 °C was treated with TBSOTf (4.6 mL, 39.6 mmol). The reaction mixture was stirred for 1 h and warmed to 0 °C over 30 min. After quenching by addition of satd aq $NaHCO_3$ (75 mL), the mixture was extracted with CH_2Cl_2 (3 × 75 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (19:1 hexanes/EtOAc) provided the TBS-ether **37** (4.07 g, 82%) as a colorless oil: IR (NaCl) 2957, 2929, 2856, 1513, 1249, 1039, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 7.6 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 5.86 (ddd, J = 7.7, 10.2, 17.8 Hz, 1H), 5.01−4.94 (m, 2H), 4.43 (d, J = 11.5 Hz, 1H), 4.38 (d, J = 11.5 Hz, 1H), 3.81 (s, 3H), 3.65 (dd, J = 3.4, 4.6 Hz, 1H), 3.37 (dd, J = 6.6, 9.0 Hz, 1H), 3.22 (dd, J = 6.8, 8.8 Hz, 1H), 2.35 (m, 1H), 1.94 (m, 1H), 1.01 (d, J = 6.9 Hz, 3H), 0.91−0.89 (m, 12H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 142.0, 130.9, 129.2, 114.1, 113.8, 76.0, 73.4, 72.5, 55.3, 42.9, 37.2, 26.2, 18.5, 17.4, 12.4, −3.5, −3.9; LRMS (ESI) 401 $[M + Na]^+$; HRMS (ESI) calcd for $C_{22}H_{38}O_3SiNa$, 401.2488 $[M + Na]^+$; found, 401.2481; $[\alpha]^{20}_D$ −5.0 (*c* 0.20, $CHCl_3$).

((2*S*,3*S*,4*S*)-1-(4-Methoxybenzyloxy)-6,6-dibromo-2,4-dimethylhex-5-en-3-yloxy)(*tert*-butyl)dimethylsilane. A solution of the alkene **37** (4.00 g, 10.56 mmol) in dioxane (75 mL) and H_2O (25 mL) at ambient temperature was treated with 2,6-lutidine (2.5 mL, 21.12 mmol), OsO_4 (2.5% in 2-methyl-2-propanol, 2.2 mL, 0.02 mmol), and $NaIO_4$ (9.00 g, 42.24 mmol). After 5 h, additional OsO_4 (2.5% in 2-methyl-2-propanol, 1.1 mL, 0.01 mmol) was added and the mixture was stirred for 1 h. After quenching by the addition of satd aq $Na_2S_2O_3$ (50 mL), the mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The aldehyde as a pale yellow oil was used immediately in the next step without further purification.

A solution of PPh_3 (11.08 g, 42.24 mmol) in CH_2Cl_2 (35 mL) at 0 °C was treated with CBr_4 (7.00 g, 21.12 mmol) portionwise over 7 min. After 10 min, 2,6-lutidine (6.1 mL, 52.80 mmol) was added and the mixture was stirred for 10 min. A solution of the aldehyde in CH_2Cl_2 (20 mL) was added and the mixture was stirred for 1 h. After quenching by the addition of satd aq NH_4Cl (50 mL), the mixture was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (19:1 hexanes/EtOAc) provided the dibromoolefin (4.20 g, 74% for two steps) as a colorless oil: IR (NaCl) 2955, 2930, 2856, 1513, 1249, 1038, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 6.4 (d, J = 9.5 Hz, 1H), 4.44 (d, J = 11.6 Hz, 1H), 4.39 (d, J = 11.6 Hz, 1H), 3.81 (s, 3H), 3.69 (t, J = 3.9 Hz, 1H), 3.38 (dd, J = 6.1, 8.9 Hz, 1H), 3.21 (dd, J = 7.0, 8.9 Hz, 1H), 2.62 (m, 1H), 1.89 (m, 1H), 1.00 (d, J = 7.0 Hz, 3H), 0.93−0.90 (m, 12H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 141.7, 130.7, 129.4, 113.8, 88.0, 75.8, 72.7, 72.4, 55.4, 42.6, 38.5, 26.2, 26.1, 18.4, 17.2, 12.5, −3.7, −3.8; LRMS (ESI) 559 $[M + Na]^+$; HRMS (ESI) calcd for $C_{22}H_{36}O_3SiBr_2Na$ $[M + Na]^+$, 557.0698; found, 557.0715; $[\alpha]^{20}_D$ +3.7 (*c* 0.27, $CHCl_3$).

((2*S*,3*S*,4*S*)-1-(4-Methoxybenzyloxy)-2,4-dimethylhex-5-yn-3-yloxy)(*tert*-butyl)dimethylsilane (38). A solution of the dibromoolefin prepared above (6.43 g, 12.00 mmol) in THF (60 mL) at −78 °C was treated dropwise with a 1.6 M solution of BuLi in hexane (18.75 mL, 30.00 mmol) over 10 min. After 30 min, an additional solution of BuLi (9.3 mL, 14.88 mmol) was added and the mixture was stirred for 2.5 h. After quenching by the addition of satd aq NH_4Cl (50 mL) at −78 °C, the mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (19:1 hexanes/EtOAc) provided the terminal alkyne **38** (4.36 g, 96%) as a colorless oil: IR (NaCl) 3309, 2955, 2930, 2856, 1513, 1249, 1055, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.42 (s, 2H), 3.81 (s, 3H), 3.79 (dd, J = 3.3, 5.1 Hz, 1H), 3.45 (dd, J = 6.8, 9.2 Hz, 1H), 3.29 (dd, J = 6.6, 9.2 Hz, 1H), 2.62 (m, 1H), 2.21 (m, 1H), 2.04 (d, J = 2.5 Hz, 1H), 1.20 (d, J = 7.1 Hz, 3H), 0.98−0.89 (m, 12H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 130.9, 129.3, 113.8, 87.4, 74.5, 73.2, 72.5, 70.1, 55.3, 37.0, 31.7, 26.2, 18.5, 17.5, 12.2, −3.7, −4.0; LRMS (ESI) 399 $[M + Na]^+$; HRMS (ESI) calcd for $C_{22}H_{36}O_3SiNa$ $[M + Na]^+$, 399.2331; found, 399.2336; $[\alpha]^{20}_D$ +2.2 (*c* 0.23, $CHCl_3$).

((2*S*,3*S*,4*S*)-1-(4-Methoxybenzyloxy)-6-iodo-2,4-dimethylhex-5-yn-3-yloxy)(*tert*-butyl)dimethylsilane. A solution of the alkyne **38** (3.50 g, 9.29 mmol) in THF (46 mL) at −50 °C was treated dropwise with a 1.6 M solution of BuLi in hexane (7.00 mL, 11.15 mmol) over 7 min. After 1 h, a solution of I_2 (4.00 g, 15.79 mmol) in THF (4 mL) was added. The mixture was stirred for 20 min and warmed to ambient temperature over 30 min. After quenching by the addition of a mixture of satd aq $Na_2S_2O_3$ (25 mL) and brine (25 mL), the mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (19:1 hexanes/EtOAc) provided the iodoalkyne (4.60 g, 99%) as a colorless oil: IR (NaCl) 2930, 2881, 2855, 1612, 1513, 1462, 1248, 1062, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 4.42 (s, 2H), 3.81 (s, 3H), 3.75 (dd, J = 3.0, 5.5 Hz, 1H), 3.43 (dd, J = 7.0, 9.0 Hz, 1H), 3.26 (dd, J = 6.6, 9.0 Hz, 1H), 2.76 (m, 1H), 2.04 (m, 1H), 1.18 (d, J = 7.1 Hz, 3H), 0.93−0.85 (m, 12H), 0.09 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 130.8, 129.3, 113.8, 97.8, 74.8, 73.0, 72.5, 55.3, 36.9, 34.0, 26.2, 18.5, 17.7, 11.7, −3.7, −4.0, −4.4; LRMS (EI) 445 (M − *tert*-Bu)$^+$; HRMS (EI) calcd for $C_{18}H_{26}O_3SiI$ (M − *tert*-Bu)$^+$, 445.0696; found, 445.0672; $[\alpha]^{20}_D$ −3.3 (*c* 0.42, $CHCl_3$).

((2*S*,3*S*,4*S*,*Z*)-1-(4-Methoxy)benzyloxy)-6-iodo-2,4-dimethylhex-5-en-3-yloxy)(*tert*-butyl)dimethylsilane (39). A solution of the iodoalkyne prepared above (3.50 g, 9.29 mmol) in THF (20 mL) and *i*-PrOH (20 mL) at ambient temperature was treated with triethylamine (1.70 mL, 12.21 mmol) and *o*-nitrobenzenesulfonyl hydrazide (2.30 g, 10.58 mmol). After 12 h, additional triethylamine (0.79 mL, 5.69 mmol) and *o*-nitrobenzenesulfonylhydrazide (1.06 g, 4.88 mmol) were added and the mixture was stirred for 12 h. After quenching by the addition of H_2O (50 mL), the mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (19:1 hexanes/EtOAc) provided the *Z*-iodoalkene **39** (3.90 g, 95%) as a colorless oil: IR (NaCl) 2955, 2929, 2855, 1513, 1249, 1039, 837, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.24 (dd, J = 7.3, 8.8 Hz, 1H), 6.13 (d, J = 7.3 Hz, 1H), 4.61 (s, 2H), 3.81 (s, 3H), 3.74 (t, J = 3.8 Hz, 1H), 3.40 (dd, J = 5.8, 9.0 Hz, 1H), 3.21 (dd, J = 7.1, 9.0 Hz, 1H), 2.69 (m, 1H), 1.90 (m, 1H), 1.00 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 144.0, 130.9, 129.3, 113.8, 81.8, 76.0, 72.7, 55.3, 43.8, 38.9, 26.3, 18.5, 17.7, 13.4, −3.5, −3.7; LRMS (EI) 447 (M − *tert*-

Bu)$^+$; HRMS (EI) calcd, 447.0853 (M − *tert*-Bu)$^+$; found, 447.0851; $[\alpha]^{20}_D$ +32.4 (*c* 0.61, $CHCl_3$).

(2*S*,3*S*,4*S*,*Z*)-3-(*tert*-Butyldimethylsilyloxy)-6-iodo-2,4-dimethylhex-5-en-1-ol. A mixture of the PMB ether **39** (1.5 g, 2.97 mmol) in CH_2Cl_2 (60 mL) and H_2O (4 mL) at 0 °C was treated with DDQ (0.81 g, 3.56 mmol). After 25 min, additional DDQ (0.24 g, 1.48 mmol) was added and the mixture was stirred for 15 min. After quenching by the addition of satd aq $NaHCO_3$ (50 mL), the mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with satd aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was diluted with CH_2Cl_2 (15 mL) and MeOH (1.5 mL). The mixture was cooled to 0 °C and $NaBH_4$ (0.11 g, 2.97 mmol) was added. After 30 min, satd aq NH_4Cl (50 mL) was added, the mixture was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (4:1 hexanes/EtOAc) provided the alcohol (1.13 g, 98%) as a colorless oil: IR (NaCl) 3353, 2956, 2929, 2856, 1471, 1461, 1256, 1024, 837, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.37 (dd, J = 7.4, 9.0 Hz, 1H), 6.18 (d, J = 7.3 Hz, 1H), 3.76 (t, J = 3.4 Hz, 1H), 3.68 (m, 1H), 3.46 (m, 1H), 2.75 (m, 1H), 2.05−1.88 (m, 2H), 1.05 (d, J = 7.0 Hz, 3H), 0.96−0.87 (m, 12H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 81.9, 77.5, 65.4, 42.6, 40.9, 26.1, 18.3, 18.2, 13.1, −3.8, −3.9; LRMS (EI) 327 (M − *tert*-Bu)$^+$; HRMS (EI) calcd for $C_{10}H_{20}IO_2Si$ (M − *tert*-Bu)$^+$, 327.0277; found, 327.0286; $[\alpha]^{20}_D$ +2.3 (*c* 0.57, $CHCl_3$).

(5*R*,6*S*,7*S*)-8-(4-Methoxybenzyloxy)-1-(*tert*-butyldimethylsilyloxy)-6-hydroxy-5,7-dimethyloctan-4-one. A solution of *tert*-butyl(3-iodopropoxy)dimethylsilane **42** (8.53 g, 28.38 mmol) in diethyl ether (240 mL) at −78 °C was treated dropwise with a 1.7 M solution of *tert*-BuLi in pentane (35.6 mL, 60.54 mmol) over 30 min. After 15 min, a solution of the Weinreb amide **41** (3.08 g, 9.46 mmol) in diethyl ether (20 mL) was added dropwise over 15 min. The mixture was stirred at −78 °C for 1 h and at −40 °C for 2.5 h. After quenching at −78 °C by the addition of a satd aq NH_4-Cl (50 mL), the mixture was extracted with diethyl ether (3 × 50 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (2:1 hexanes/diethyl ether) provided the ketone (3.48 g, 84%) as a colorless oil: IR (NaCl) 3480, 2955, 2930, 2856, 1705, 1613, 1249, 1094, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 4.43 (s, 2H), 3.89 (dd, J = 8.4, 3.3 Hz, 1H), 3.79 (s, 3H), 3.60 (t, J = 6.1 Hz, 3H), 3.55 (m, 2H), 2.64 (m, 1H), 2.60 (t, J = 7.2 Hz, 2H), 1.91 (m, 1H), 1.82 (qn, J = 6.8 Hz, 2H), 1.13 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 4.5 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.6, 159.5, 130.3, 129.6, 114.1, 75.3, 74.5, 73.4, 62.4, 55.5, 49.0, 37.5, 36.2, 27.0 26.2, 18.5, 14.2, 9.4, −5.0; LRMS (ESI) 461 [M + Na]$^+$; HRMS (ESI) calcd for $C_{24}H_{42}O_5SiNa$ [M + Na]$^+$, 461.2699; found, 461.2671; $[\alpha]^{20}_D$ +22.5 (*c* 0.08, $CHCl_3$).

(2*S*,3*S*,4*S*,5*R*)-1-(4-Methoxybenzyloxy)-8-(*tert*-butyldimethylsilyloxy)-2,4-dimethyloctane-3,5-diol (43). A solution of the ketone prepared above (3.48 g, 7.93 mmol) in THF (79 mL) and MeOH (20 mL) at −78 °C was treated dropwise with a 1.0 M solution of Et_2BOMe in THF (12.7 mL, 12.69 mmol) over 10 min. After 30 min, $NaBH_4$ (0.36 g, 9.52 mmol) was added in three portions over 10 min. The mixture was stirred at −78 °C for 7 h and quenched by the dropwise addition of acetic acid (7 mL). Water (80 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with NaOH (1.0 M, 100 mL), dried ($MgSO_4$), and concentrated. The residue was taken up in a 1.0 M solution of NaOAc in MeOH (360 mL) and H_2O (40 mL) and then 30% H_2O_2 (30 mL) was added. After stirring at ambient temperature for 1 h, the mixture was concentrated, then diluted with H_2O (50 mL), extracted with CH_2Cl_2 (4 × 50 mL), dried ($MgSO_4$), and concentrated. Purification by column chromatography (1:1 hexanes/diethyl ether) provided the target diol **43** (2.95 g, 85%) as a colorless oil: IR (NaCl) 3440, 2953, 2930, 2856, 1513, 1463, 1249, 1096, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.46 (s, 2H), 4.41 (s, 1H), 4.06 (s, 1H), 3.84 (m, 1H), 3.80 (s, 3H), 3.71−3.64 (m, 3H), 3.57 (dd, J = 4.6, 9.1 Hz, 1H), 3.48 (t, J = 8.6 Hz, 1H), 1.99 (m, 1H), 1.65−1.53 (m, 5H), 0.91 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.77 (d, J = 6.9 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 130.1, 129.5, 114.1, 81.9, 76.8, 76.0, 73.4, 63.6, 55.4, 38.5, 36.3, 32.1, 29.9, 26.2, 18.5, 13.5, 4.6, −5.0; LRMS (ESI) 463 [M + Na]$^+$; HRMS (ESI) calcd for $C_{24}H_{44}O_5SiNa$ [M + Na]$^+$, 463.2856; found, 463.2851; $[\alpha]^{20}_D$ +17.7 (*c* 0.18, $CHCl_3$).

(2*S*,3*R*)-6-(*tert*-Butyldimethylsilyloxy)-2-((2*S*,4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)hexan-3-ol. A solution of the diol **43** (3.48 g, 7.93 mmol) in CH_2Cl_2 (136 mL) was treated with 4 Å molecular sieves (3.00 g). After 20 min, the mixture was cooled to 0 °C and DDQ (3.09 g, 13.62 mmol) was added in three portions over 3 min. The reaction mixture was stirred for 1.5 h, warmed to ambient temperature over 30 min, and then filtered through Celite. Satd aq $NaHCO_3$ (100 mL) was added, the mixture was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic layers were washed with satd aq $NaHCO_3$ (2 × 100 mL), dried ($MgSO_4$), and concentrated. Purification by column chromatography (5:1 hexanes/EtOAc) provided the PMB acetal (3.47 g, 60%) as a colorless oil: IR (NaCl) 3535, 2954, 2929, 2855, 1518, 1251, 1100, 834 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 5.50 (s, 1H), 4.12 (dd, J = 4.7, 11.2 Hz, 1H), 3.87 (m, 1H), 3.79 (s, 3H), 3.69 (dd, J = 2.1, 9.9, 2H), 3.65 (m, 1H), 3.52 (t, J = 11.1 Hz, 1H), 3.24 (s, 1H), 2.12 (m, 1H), 1.80 (tq, J = 1.8, 7.1 Hz, 1H), 1.67−1.49 (m, 4H), 1.04 (d, J = 7.1 Hz, 3H), 0.90 (s, 9H), 0.77 (d, J = 6.7 Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 131.1, 127.5, 113.9, 101.4, 88.7, 76.2, 73.4, 63.5, 55.5, 37.8, 31.6, 30.7, 29.7, 26.2, 18.6, 12.2, 6.3, −4.9; LRMS (ESI) 461 [M + Na]$^+$; HRMS (ESI) calcd for $C_{24}H_{42}O_5SiNa$ [M + Na]$^+$, 461.2699; found, 461.2673; $[\alpha]^{20}_D$ +38.6 (*c* 0.15, $CHCl_3$).

(2*S*,4*S*,5*S*)-4-((2*R*,3*R*)-3,6-Bis(*tert*-butyldimethylsilyloxy)hexan-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxane (44). A solution of the PMB acetal (3.47 g, 7.91 mmol) and 2,6-lutidine (2.80 mL, 23.73 mmol) in CH_2Cl_2 (79 mL) at −78 °C was treated with TBSOTf (2.40 mL, 10.28 mmol). The reaction mixture was stirred for 1 h and warmed to 0 °C over 30 min. After quenching by the addition of satd aq $NaHCO_3$ (50 mL), the mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (9:1 hexanes/EtOAc) provided the target TBS ether **44** (4.32 g, 99%) as a colorless oil: IR (NaCl) 2954, 2929, 2856, 1518, 1462, 1251, 1038, 835, 774 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.43 (s, 1H), 4.11 (dd, J = 4.6, 11.1 Hz, 1H), 3.81 (s, 3H), 3.74 (m, 1H), 3.69 (dd, J = 1.4, 10.1, 2H), 3.60 (m, 1H), 3.51 (t, J = 11.1 Hz, 1H), 3.24 (s, 1H), 2.05 (m, 1H), 1.80 (dqn, J = 1.2, 7.0 Hz, 1H), 1.60 (m, 4H), 1.03 (d, J = 7.0 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.76 (d, J = 6.7 Hz, 3H), 0.06 (d, J = 2.7 Hz, 6H), 0.04 (d, J = 1.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 131.7, 127.3, 113.5, 100.7, 81.9, 74.4, 73.4, 63.6, 55.3, 38.8, 30.8, 29.8, 28.3, 26.1, 18.4, 18.2, 12.4, 10.7, −4.1 −4.2, −5.1 −5.2; LRMS (ESI) 575 [M + Na]$^+$; HRMS (ESI) calcd for $C_{30}H_{56}O_5Si_2Na$ [M + Na]$^+$, 575.3564; found, 575.3616; $[\alpha]^{20}_D$ +26.2 (*c* 0.16, $CHCl_3$).

(2*S*,3*S*,4*R*,5*R*)-3-(4-Methoxybenzyloxy)-5,8-bis(*tert*-butyldimethylsilyloxy)-2,4-dimethyloctan-1-ol (45). A solution of the PMB acetal **44** (3.70 g, 6.69 mmol) in CH_2Cl_2 (33 mL) at −78 °C was treated dropwise with a 1.0 M solution of diisobutylaluminum hydride in hexane (66.9 mL, 66.9 mmol) over 30 min, and the reaction mixture was stirred at −45 °C for 12 h. After quenching by the addition of satd aq potassium sodium tartrate (130 mL), the mixture was stirred at ambient temperature for 1 h and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (4:1 hexanes/EtOAc) provided the alcohol **45** (1.49 g, 41%) as a colorless oil and the corresponding more polar bis-primary diol (1.57 g, 55%) as a colorless oil: IR (NaCl) 3434, 2954, 2929, 2856, 1514, 1250, 1036, 835, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.52 (s, 2H), 3.82 (dd, J = 3.4, 11.0 Hz, 1H),

3.80 (s, 3H), 3.68 (m, 1H), 3.61−3.56 (m, 3H), 3.47 (dd, J = 4.7, 6.3 Hz, 1H), 2.65 (s, 1H), 1.95 (m,1H), 1.88 (m, 1H), 1.59 (m, 2H), 1.48 (m, 2H), 1.11 (d, J = 7.0 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 130.8, 129.5, 114.1, 86.0, 75.4, 73.6, 65.6, 63.4, 55.5, 40.9, 37.4, 31.1, 28.9, 26.2, 18.5, 18.4, 15.9, 10.4, −3.5, −4.1, −5.0; LRMS (ESI) 577 $[M + Na]^+$; HRMS (ESI) calcd for $C_{30}H_{58}O_5Si_2Na$ $[M + Na]^+$, 557.3721; found, 557.3687; $[\alpha]^{20}_D$ +3.5 (*c* 0.17, $CHCl_3$).

Conversion of Diol to 45. A solution of the diol resulting from the reduction of the PMB acetal above (1.57 g, 3.68 mmol) and imidazole (0.38, 5.52 mmol) in CH_2Cl_2 (37 mL) was treated with a solution of TBSCl (0.57 g, 0.57 mmol) in CH_2Cl_2 (18 mL) at −78 °C. The reaction mixture was warmed to 0 °C over 3 h and then additional imidazole (0.38, 5.52 mmol) and TBSCl (0.57 g, 0.57 mmol) were added. The mixture was stirred at −25 °C for 2 h and at ambient temperature for 1.5 h. After concentration in vacuum, purification by column chromatography (4:1 hexanes/EtOAc) provided **45** (1.09 g, 55%), which was identified by TLC and ^{1}H NMR comparison to the above sample.

1-(((5*S*,6*S*,7*R*,8*R*,*Z*)-8,11-Bis(*tert*-butyldimethylsilyloxy)-5,7-dimethylundeca-1,3-dien-6-yloxy)methyl)-4-methoxybenzene (46). A solution of the alcohol **45** (2.10 g, 3.78 mmol) and triethylamine (1.60 mL, 11.34 mmol) in CH_2Cl_2 (8 mL) and DMSO (6 mL) at 0 °C was treated dropwise with a solution of SO_3·pyr (1.50 g, 9.45 mmol) in DMSO (9.5 mL) over 10 min. The reaction mixture was stirred for 1 h. After quenching by the addition of H_2O (80 mL), the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The aldehyde as a colorless oil was used immediately in the next step without further purification.

A suspension of $CrCl_2$ (5.11 g, 41.58 mmol) in THF (42 mL) at ambient temperature was treated with a solution of the aldehyde and 1-bromoallyltrimethylsilane (4.38 g, 22.68 mmol) in THF (19 mL) via cannula, and the mixture was stirred for 17 h. After quenching by the addition of pH 7 phosphate buffer (250 mL), the mixture was extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The alcohol as a pale blue oil was used immediately in the next step without further purification.

A solution of the alcohol in THF (95 mL) at 0 °C was treated with NaH (95 wt %, 1.91 g, 75.60 mmol) in three portions over 3 min. The mixture was stirred at 0 °C for 15 min and at ambient temperature for 1 h. After quenching by the addition of water (100 mL), the mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (19:1 hexanes/EtOAc) provided the terminal diene **46** (1.85 g, 85% for three steps) as a colorless oil: IR (NaCl) 2955, 2929, 2856, 1514, 1249, 1085, 835, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.61 (dt, J = 10.6, 16.6 Hz, 1H), 6.01 (t, J = 11.0 Hz, 1H), 5.58 (t, J = 10.7 Hz, 1H), 5.21 (d, J = 16.9 Hz, 1H), 5.12 (d, J = 10.1 Hz, 1H), 4.57 (d, J = 10.5 Hz, 1H), 4.50(d, J = 10.5 Hz, 1H), 3.80 (s, 3H), 3.65 (m, 1H), 3.53 (dt, J = 1.7, 6.2 Hz, 2H), 3.34 (dd, J = 3.4, 7.6 Hz, 1H), 2.98 (m, 1H), 1.67 (m, 1H), 1.52 (m, 2H), 1.36 (m, 2H), 1.11 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 134.9, 132.6, 131.7, 129.4, 129.2, 117.5, 113.9, 84.5, 75.2, 72.8, 63.4, 55.5, 40.8, 35.6, 31.5, 28.9, 26.3, 26.2, 19.0, 18.5, 18.4, 9.5, −3.4, −4.2, −4.9; LRMS (ESI) 599 $[M + Na]^+$; HRMS (ESI) calcd for $C_{33}H_{60}O_4Si_2Na$ $[M + Na]^+$, 599.3928; found, 599.3958; $[\alpha]^{20}_D$ +2.2 (*c* 0.10, $CHCl_3$).

(4*R*,5*R*,6*S*,7*S*,*Z*)-6-(4-Methoxybenzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5,7-dimethylundeca-8,10-dien-1-ol. A solution of the TBS ether **46** (3.70 g, 6.69 mmol) in THF (34 mL) at 0 °C was treated dropwise with a solution of HF·pyr in pyr/THF (78 mL, prepared by slow addition of HF·pyr (6 mL) to a solution of pyridine (24 mL) and THF (48 mL)), and the reaction mixture was stirred at 0 °C for 1 h and at ambient temperature for 5 h. After quenching by the addition of satd aq $NaHCO_3$ (150 mL), the mixture was extracted with EtOAc (4 × 80 mL). The combined organic layers were washed with satd aq $CuSO_4$ (3 × 50 mL) and brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (4:1 hexanes/EtOAc) provided the target primary alcohol (1.20 g, 75%) as a colorless oil: IR (NaCl) 3366, 2954, 2929, 1514, 1249, 1038, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.60 (dt, J = 10.3, 16.8 Hz, 1H), 6.01 (t, J = 11.0 Hz, 1H), 5.56 (t, J = 10.5 Hz, 1H), 5.21 (d, J = 16.8 Hz, 1H), 5.11 (d, J = 10.1 Hz, 1H), 4.57 (d, J = 10.6 Hz, 1H), 4.46 (d, J = 10.6 Hz, 1H), 3.78 (s, 3H), 3.66 (m, 1H), 3.55 (t, J = 6.4 Hz, 2H), 3.33 (dd, J = 3.9, 7.0 Hz, 1H), 2.99 (m, 1H), 1.71 (m, 1H), 1.50 (m, 2H), 1.41 (m, 2H), 1.09 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 135.1, 132.7, 131.6, 129.4, 129.2, 117.6, 113.9, 84.2, 75.1, 72.7, 63.2, 55.5, 40.7, 35.6, 31.4, 28.8, 26.2, 19.0, 18.4, 9.8, −3.4, −4.1; LRMS (ESI) 485 $[M + Na]^+$; HRMS (ESI) calcd for $C_{27}H_{46}O_4SiNa$ $[M + Na]^+$, 485.3063; found, 485.3071; $[\alpha]^{20}_D$ +38.6 (*c* 0.07, $CHCl_3$).

((4*R*,5*R*,6*S*,7*S*,*Z*)-6-(4-Methoxybenzyloxy)-1-iodo-5,7-dimethylundeca-8,10-dien-4-yloxy)(*tert*-butyl)dimethylsilane. A solution of the alcohol prepared above (1.10 g, 2.38 mmol) in benzene (15 mL) and diethyl ether (30 mL) at ambient temperature was treated with triphenylphosphine (0.93 g, 3.56 mmol) and imidazole (0.24 g, 3.56 mmol). Then iodine (0.90 g, 3.56 mmol) was added to the vigorously stirred mixture portionwise over 10 min. After 30 min, the mixture was diluted with EtOAc (50 mL), quenched with satd aq $Na_2S_2O_3$ (50 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with satd aq $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (19:1 hexanes/EtOAc) provided the desired primary iodide (1.26 g, 93%) as a colorless oil: IR (NaCl) 2955, 2928, 1514, 1249, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 6.60 (dt, J = 10.4, 16.9 Hz, 1H), 6.04 (t, J = 11.0 Hz, 1H), 5.58 (t, J = 10.5 Hz, 1H), 5.25 (d, J = 16.8 Hz, 1H), 5.16 (d, J = 10.0 Hz, 1H), 4.60 (d, J = 10.5 Hz, 1H), 4.51 (d, J = 10.5 Hz, 1H), 3.81 (s, 3H), 3.67 (m, 1H), 3.36 (dd, J = 3.6, 7.2 Hz, 1H), 3.11 (t, J = 6.3 Hz, 2H), 2.99 (m, 1H), 1.66 (m, 3H), 1.58 (m, 2H), 1.12 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 0.94 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 134.9, 132.5, 131.5, 129.4, 129.3, 117.9, 114.0, 84.1, 75.1, 71.9, 55.5, 40.9, 35.8, 35.6, 29.6, 26.2, 19.0, 18.4, 9.8, 7.4, −3.4, −4.1; LRMS (EI) 515 $(M - tert\text{-}Bu)^+$; HRMS (EI) calcd for $C_{23}H_{36}IO_3Si$ $(M - tert\text{-}Bu)^+$, 515.1479; found, 515.1481; $[\alpha]^{20}_D$ +24.6 (*c* 0.15, $CHCl_3$).

((4*R*,5*R*,6*S*,7*S*,*Z*)-6-(4-Methoxybenzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5,7-dimethylundeca-8,10-dienyl)triphenylphosphonium Iodide (28). A solution of the iodide prepared above (1.26 g, 2.20 mmol) in benzene (8 mL) at ambient temperature was treated with triphenylphosphine (2.97 g, 11.0 mmol). The mixture was heated at 80 °C for 16 h in the dark. After concentration under vacuum, purification by column chromatography (19:1 CH_2Cl_2/MeOH) provided the phosphonium salt **28** (1.42 g, 78%) as a white solid: IR (NaCl) 2955, 2928, 2855, 1513, 1438, 1248, 1112 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86−7.73 (m, 15H), 7.29 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.3 Hz, 2H), 6.59 (dt, J = 10.6, 16.8 Hz, 1H), 5.91 (t, J = 10.9 Hz, 1H), 5.60 (t, J = 10.4 Hz, 1H), 5.06 (d, J = 15.8 Hz, 1H), 5.01 (d, J = 9.4 Hz, 1H), 4.64 (d, J = 11.0 Hz, 1H), 4.47 (d, J = 11.0 Hz, 1H), 3.78 (s, 3H), 3.68 (dd, J = 7.2, 12.2 Hz, 1H), 3.59 (q, J = 5.0 Hz, 1H), 3.47 (t, J = 5.0 Hz, 1H), 3.39 (dd, J = 7.2, 12.5 Hz, 1H), 2.95 (m, 1H), 1.96 (m, 1H), 1.77 (m, 1H), 1.58 (m, 3H), 1.03 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.83 (s, 9H), 0.04 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 135.8, 135.5, 135.4, 133.9, 133.8, 132.6, 131.8, 130.9, 130.7, 129.4, 128.9, 128.5, 118.8, 117.7, 117.5, 113.9, 83.4, 74.6, 72.6, 55.6, 40.5, 36.0, 35.6, 35.4, 26.2, 23.9, 23.3, 18.7, 18.5, 18.3, 10.2, −3.5, −4.1; LRMS (ESI) 707 M^+; HRMS (ESI) calcd for $C_{45}H_{60}O_3PSi$ M^+, 707.4049; found, 707.4058; $[\alpha]^{20}_D$ +23.3 (*c* 2.7, $CHCl_3$).

1-(((3*Z*,5*S*,6*S*,7*R*,8*R*,11*Z*,13*S*,14*R*,15*S*,16*Z*)-8,14-Bis(*tert*-butyldimethylsilyloxy)-17-iodo-5,7,13,15-tetramethylheptadeca-1,3,11,16-tetraen-6-yloxy)methyl)-4-methoxybenzene (47). A so-

lution of the alcohol prepared above (0.38 g, 1.00 mmol) in CH_2Cl_2 (10 mL) at 0 °C was treated with Dess−Martin periodinane (0.57 g, 1.30 mmol). The mixture was warmed to ambient temperature and stirred for 1 h. After quenching by the addition of a mixture of satd aq $Na_2S_2O_3$ (10 mL) and satd aq $NaHCO_3$ (10 mL), the mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with satd aq $NaHCO_3$ (2 × 20 mL) and brine and dried ($MgSO_4$). The concentration under vacuum provided the aldehyde **29** as a coloress oil, which used immediately in the next step without further purification.

A solution of the phosphonium salt **28** (0.64 g, 0.77 mmol, dried azeotropically with benzene and at 40 °C for 1 h under vacuum) in THF (2 mL) at 0 °C was treated dropwise with a 1.0 M solution of sodium bis(trimethylsilyl)amide in THF (0.71 mL, 0.71 mmol) over 5 min. The mixture was warmed to ambient temperature and stirred for 45 min. The mixture was cooled to −78 °C, and a solution of the aldehyde **29** (0.38 g, 1.00 mmol) in THF (2 mL) was added via cannula over 5 min. The mixture was warmed to ambient temperature and stirred for 4 h. After quenching by the addition of satd aq NH_4Cl (30 mL), the mixture was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (19:1 hexanes/EtOAc) provided the coupled *Z*-alkene **47** (0.47 g, 82%) as a colorless oil: IR (NaCl) 2956, 2929, 2856, 1514, 1461, 1250, 1078, 1038, 836, 773 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.31 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 6.75 (dt, J = 10.4, 16.7 Hz, 1H), 6.30 (t, J = 7.7 Hz, 1H), 6.08 (t, J = 11.0 Hz, 1H), 6.00 (d, J = 7.3 Hz, 1H), 5.76 (t, J = 10.7 Hz, 1H), 5.41 (dt, J = 7.0, 10.7 Hz, 1H), 5.20 (t, J = 10.3 Hz, 1H), 5.18 (d, J = 18.0 Hz, 1H), 5.11 (d, J = 10.1 Hz, 1H), 4.57 (q, J = 10.6 Hz, 2H), 3.84 (m, 1H), 3.49 (dd, J = 3.6, 7.0 Hz, 1H), 3.38 (dd, J = 2.5, 7.8 Hz, 1H), 3.30 (s, 3H), 3.15 (m, 1H), 2.84 (m, 1H), 2.62 (m, 1H), 2.13 (m, 1H), 2.06 (m, 1H), 1.93 (m, 1H), 1.81 (m, 1H), 1.66 (m, 1H), 1.24−1.17 (m, 7 H), 1.07 (d, J = 6.9 Hz, 3H), 1.05 (s, 9H), 1.03 (d, J = 7.1 Hz, 3H), 0.99 (s, 9H), 0.15 (s, 3H) 0.14 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 143.6, 134.9, 133.3, 132.7, 131.6, 129.5, 129.3, 129.1, 117.6, 114.0, 84.4, 82.2, 79.9, 75.3, 73.0, 55.5, 44.5, 41.0, 37.4, 35.7, 35.6, 26.6, 26.3, 24.1, 19.1, 18.7, 18.6, 18.5, 17.2, 9.8, −3.0, −3.1, −3.3, −3.9; LRMS (ESI) 833 $[M + Na]^+$; HRMS (ESI) calcd for $C_{41}H_{71}IO_4Si_2Na$ $[M + Na]^+$, 833.3833; found, 833.3850; $[\alpha]^{20}_D$ +117.8 (*c* 0.09, $CHCl_3$).

(2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,15*Z*,19*R*,20*R*,21*S*,22*S*,23*Z*)-21-(4-Methoxybenzyloxy)-1,7,13,19-tetrakis(*tert*-butyldimethylsilyloxy)-6,12,14,20,22-pentamethylhexacosa-2,4,10,15,23,25-hexaen-9-ol (48α). A solution of the Weinreb amide **35** (0.37 g, 0.96 mmol) in THF (5 mL) at −78 °C was treated dropwise with a 1.0 M solution of diisobutylaluminum hydride in hexane (3.16 mL, 3.16 mmol) over 3 min, and the reaction mixture was warmed to ambient temperature over 1 h. After quenching by the addition of satd aq potassium sodium tartrate (7 mL), the mixture was stirred for 1 h at ambient temperature and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The alcohol as a pale yellow oil was used immediately in the next step without further purification.

A solution of the alcohol and 2,6-lutidine (0.34 mL, 2.88 mmol) in CH_2Cl_2 (10 mL) at −78 °C was treated with TBSOTf (0.28 mL, 1.25 mmol). The reaction mixture was stirred for 1 h. After quenching by the addition of satd aq $NaHCO_3$ (10 mL) at −78 °C, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (4:1 hexanes/EtOAc) provided the aldehyde **30** (0.38 g, 95%) as a colorless oil, which was used immediately in the next step: ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (dd, J = 1.8, 2.6 Hz, 1H), 6.28 (dd, J = 11.0, 15.1 Hz, 1H), 5.97 (t, J = 11.0 Hz, 1H), 5.59 (dd, J = 7.9, 15.2 Hz, 1H), 5.54 (dt, J = 6.3, 10.9 Hz, 1H), 4.32 (dd, J = 1.5, 6.4 Hz, 1H), 4.17 (ddd, J = 4.3, 5.0, 6.7 Hz, 1H), 2.58−2.38 (m, 3H), 1.05 (d, J = 6.9 Hz, 3H), 0.91−0.86 (m, 18H), 0.09−0.04 (m, 12H).

A solution of the vinyl iodide **47** (0.76 g, 0.94 mmol) in diethyl ether (47 mL) at −78 °C was treated dropwise with a 1.7 M solution of *tert*-BuLi in pentane (1.26 mL, 2.13 mmol) over 5 min. After 15 min, a solution of the aldehyde **30** (0.37 g, 0.88 mmol) in diethyl ether (12 mL) was added via cannula over 10 min. The mixture was warmed to −10 °C over 1 h. After quenching at −10 °C by the addition of a satd aq NH_4Cl (30 mL), the mixture was extracted with diethyl ether (3 × 30 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was diluted with CH_2Cl_2 (10 mL) and MeOH (1 mL). The mixture was cooled to 0 °C and $NaBH_4$ (0.10 g, 2.64 mmol) was added. After 30 min, satd aq NH_4Cl (30 mL) was added, the mixture was extracted with diethyl ether (3 × 30 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (15:1 hexanes/ EtOAc) provided the desired α-alcohol **48**α (0.26 g, 27%) as a colorless oil and the less polar C9 β-epimer **48**β (0.42 g, 43%) as a colorless oil: IR (NaCl) 3493, 2956, 2929, 2856, 1514, 1471, 1462, 1251, 903, 807, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.86 (d, J = 8.5 Hz, 2H), 6.60 (dt, J = 11.1, 16.7 Hz, 1H), 6.27 (dd, J = 11.0, 15.0 Hz, 1H), 6.02 (t, J = 11.2 Hz, 1H), 5.98 (t, J = 11.1 Hz, 1H), 5.64−5.48 (m, 3H), 5.44 (dt, J = 6.4, 10.9 Hz, 1H), 5.34 (dd, J = 8.4, 11.0 Hz, 1H), 5.24−5.15 (m, 3H), 5.10 (d, J = 10.2 Hz, 1H), 4.59 (m, 1H), 4.55 (d, J = 10.5 Hz, 1H), 4.48 (d, J = 10.5 Hz, 1H), 4.34 (d, J = 6.3 Hz, 1H), 3.89−3.75 (m, 4H), 3.65 (m, 1H), 3.37−3.26 (m, 2H), 2.99 (m, 1H), 2.68 (m, 1H), 2.58−2.40 (m, 3H), 1.95−1.62 (m, 4H), 1.53 (m, 1H), 1.45 (m, 1H), 1.11 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 8.0 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.94−0.85 (m, 39H), 0.13−0.03 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 138.6, 134.8, 134.5, 134.1, 132.6, 132.5, 131.6, 129.6, 129.4, 129.3, 128.5, 125.6, 117.6, 113.9, 84.4, 80.5, 75.3, 73.6, 72.8, 65.0, 60.0, 55.5, 42.8, 40.8, 39.8, 37.0, 36.3, 35.6, 35.5, 26.5, 26.3, 26.2, 23.8, 19.8, 19.0, 18.7, 18.4, 18.3, 17.2, 15.1, 9.6, −2.9, −3.2, −3.4, −4.1, −4.2, −4.8; LRMS (ESI) 1119 $[M + Na]^+$; HRMS (ESI) calcd for $C_{63}H_{116}O_7Si_4Na$ $[M + Na]^+$, 1119.7696; found, 1119.7727; $[\alpha]^{20}_D$ +42.0 (*c* 0.94, $CHCl_3$).

48β: IR (NaCl) 3385, 2956, 2929, 2856, 1514, 1462, 1251, 1082, 836, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 2H), 6.87 (d, J = 8.5 Hz, 2H), 6.58 (dt, J = 10.5, 16.8 Hz, 1H), 6.27 (dd, J = 11.2, 14.9 Hz, 1H), 6.01 (t, J = 11.3 Hz, 1H), 5.97 (t, J = 11.1 Hz, 1H), 5.64 (dd, J = 7.8, 15.1 Hz, 1H), 5.57 (t, J = 10.5 Hz, 1H), 5.50−5.32 (m, 3H), 5.28−5.16 (m, 3H), 5.11 (d, J = 10.0 Hz, 1H), 4.55 (d, J = 10.5 Hz, 1H), 4.47 (d, J = 10.5 Hz, 1H), 4.43−4.25 (m, 3H), 3.87−3.72 (m, 4H), 3.66 (m, 1H), 3.37−3.25 (m, 2H), 2.99 (m, 1H), 2.62 (m, 1H), 2.56−2.38 (m, 2H), 2.01 (m, 1H), 1.98−1.73 (m, 2H), 1.72−1.60 (m, 2H), 1.48−1.37 (m, 2H), 1.10 (d, J = 6.7 Hz, 3H), 1.04 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 0.96−0.83 (m, 42H), 0.11−0.00 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 137.9, 134.9, 134.2, 134.1, 133.3, 132.6, 131.6, 129.6, 129.5, 129.4, 129.3, 128.7, 125.8, 117.6, 114.0, 84.4, 80.5, 75.2, 74.5, 72.9, 66.1, 60.0, 55.5, 42.3, 41.3, 40.8, 37.4, 36.6, 35.7, 35.5, 35.0, 34.1, 26.6, 26.3, 26.2, 25.9, 23.9, 19.1, 19.0, 18.7, 18.5, 18.3, 17.8, 15.8, 9.7, −2.7, −3.3, −3.4, −4.0, −4.1, −4.7; LRMS (ESI) 1119 $[M + Na]^+$; HRMS (ESI) calcd for $C_{63}H_{116}O_7Si_4Na$ $[M + Na]^+$, 1119.7696; found, 1119.7708; $[\alpha]^{20}_D$ +38.4 (*c* 0.19, $CHCl_3$).

(2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,15*Z*,19*R*,20*R*,21*S*,22*S*,23*Z*)-21-(4-Methoxybenzyloxy)-7,9,13,19-tetrakis(*tert*-butyldimethylsilyloxy)-6,12,14,20,22-pentamethylhexacosa-2,4,10,15,23,25-hexaen-1-ol (49α). A solution of the alcohol **48**α (0.26 g, 0.24 mmol) and 2,6-lutidine (0.083 mL, 0.71 mmol) in CH_2Cl_2 (4.7 mL) at −78 °C was treated with TBSOTf (0.082 mL, 0.36 mmol). The reaction mixture was stirred for 1 h and warmed to 0 °C over 30 min. After quenching by the addition of satd aq $NaHCO_3$ (5 mL), the mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to provide the desired TBS ether (0.29 g, 100%) as a colorless oil, which was used in the next step without further purification: IR (NaCl) 2956, 2929, 2857, 1471, 1462, 1252, 1171, 836, 774 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.32 (d, J = 8.4 Hz,

2H), 6.96−6.70 (m, 3H), 6.50 (dd, J = 11.0, 15.4 Hz, 1H), 6.12 (t, J = 11.0 Hz, 1H), 6.05 (t, J = 11.2 Hz, 1H), 5.83−5.69 (m, 2H), 5.67−5.42 (m, 6H), 5.23 (d, J = 16.9 Hz, 1H), 5.13 (d, J = 10.4 Hz, 1H), 4.77 (t, J = 7.6 Hz, 1H), 4.59 (d, J = 10.6 Hz, 1H), 4.54 (d, J = 10.6 Hz, 1H), 4.40 (d, J = 6.3 Hz, 1H), 4.16 (m, 1H), 3.87 (m, 1H), 3.54−3.42 (m, 2H), 3.32 (s, 3H), 3.15 (m, 1H), 2.92−2.74 (m, 2H), 2.60 (m, 1H), 2.29−1.87 (m, 3H), 1.86−1.53 (m 4H), 1.27−1.14 (m, 12H), 1.12−0.97 (m, 48H), 0.29−0.06 (m, 30H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 138.5, 134.8, 134.2, 133.9, 132.6, 132.1, 131.6, 129.6, 129.5, 129.3, 129.1, 128.5, 125.4, 117.6, 113.9, 84.5, 80.7, 75.3, 72.7, 72.6, 66.9, 60.0, 55.5, 43.4, 42.2, 40.8, 36.7, 36.1, 35.6, 35.5, 26.6, 26.3, 26.2, 26.0, 23.8, 19.1, 18.9, 18.7, 18.6, 18.5, 18.4, 17.1, 14.4, 9.6, −2.6, −2.7, −2.8, −3.3, −3.4, −3.7, −3.9, −4.0, −4.1, −4.7, −4.9; LRMS (ESI) 1233 [M + Na]$^+$; HRMS (ESI) calcd for $C_{69}H_{130}O_7Si_5Na$ [M + Na]$^+$, 1233.8561; found, 1233.8673; $[\alpha]^{20}_D$ +17.0 (*c* 0.20, $CHCl_3$).

A solution of the TBS ether (0.29 g, 0.24 mmol) in THF (1 mL) at 0 °C was treated dropwise with a solution of HF·pyr in pyr/THF (8 mL, prepared by slow addition of HF·pyr (0.6 mL) to a solution of pyridine (2.4 mL) and THF (4.8 mL)). The reaction mixture was warmed to ambient temperature and stirred for 8 h. After quenching by addition of satd aq $NaHCO_3$, the mixture was extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with satd aq $CuSO_4$ (3 × 6 mL) and brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (19:1 hexanes/EtOAc) provided the target allylic alcohol **49**α (0.22 g, 85%) as a colorless oil: IR (NaCl) 3422, 2955, 1613, 1514, 1462, 1250, 1039, 835, 773, 735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.60 (dt, J = 10.6, 16.8 Hz, 1H), 6.30 (dd, J = 11.1, 14.9 Hz, 1H), 6.06 (t, J = 11.3 Hz, 1H), 6.02 (t, J = 11.2 Hz, 1H), 5.67 (dd, J = 7.0, 15.1 Hz, 1H), 5.58 (t, J = 10.9 Hz, 1H), 5.50 (dt, J = 7.0, 10.7 Hz, 1H), 5.39 (t, J = 11.0 Hz, 1H), 5.34−5.16 (m, 4H), 5.12 (d, J = 10.1 Hz, 1H), 4.58−4.44 (m, 3H), 4.28 (dd, J = 2.4, 6.7 Hz, 2H), 3.91(m, 1H), 3.81 (s, 3H), 3.67 (m, 1H), 3.42−3.26 (m, 2H), 3.01 (m, 1H), 2.68−2.36 (m, 3H), 1.95−1.64 (m, 3H), 1.60−1.31 (m 4H), 1.12 (d, J = 6.7 Hz, 3H), 1.04−0.82 (m, 48H), 0.15−0.02 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 139.1, 134.3, 133.7, 133.5, 132.1, 131.4, 131.2, 131.1, 129.1, 128.9, 128.1, 127.4, 124.5, 117.3, 113.6, 84.1, 80.3, 75.0, 72.2, 72.1, 66.4, 58.7, 55.1, 42.9, 41.8, 40.3, 36.1, 35.8, 35.1, 26.1, 25.8, 23.4, 18.6, 18.4, 18.0, 17.0, 13.4, 9.1, −3.0, −3.2, −3.7, −4.1, −4.3, −4.4, −4.5; LRMS (ESI) 1119 [M + Na]$^+$; HRMS (ESI) calcd for $C_{63}H_{116}O_7Si_4Na$ [M + Na]$^+$, 1119.7696; found, 1119.7795; $[\alpha]^{20}_D$ +16.9 (*c* 0.61, $CHCl_3$).

(2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,15*Z*,19*R*,20*R*,21*S*,22*S*,23*Z*)-21-(4-Methoxybenzyloxy)-7,9,13,19-tetrakis(*tert*-butyldimethylsilyloxy)-6,12,14,20,22-pentamethylhexacosa-2,4,10,15,23,25-hexaenoic Acid. A solution of the alcohol **49**α (0.22 g, 0.20 mmol) in CH_2Cl_2 (20 mL) at 0 °C was treated with Dess−Martin periodinane (0.17 g, 0.40 mmol). The mixture was warmed to ambient temperature and stirred for 2 h. After quenching by the addition of a mixtue of satd aq $Na_2S_2O_3$ (10 mL) and satd aq $NaHCO_3$ (10 mL), the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with satd aq $NaHCO_3$ (20 mL) and brine and dried ($MgSO_4$). The concentration under vacuum provided the aldehyde as a colorless oil, which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.18 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.02 (dd, J = 11.9, 14.3 Hz, 1H), 6.91 (t, J = 10.5 Hz, 1H), 6.86 (d, J = 8.6 Hz, 2H), 6.58 (dt, J = 10.6, 16.8 Hz, 1H), 6.10 (dd, J = 7.2, 14.3 Hz, 1H), 6.01 (t, J = 11.0 Hz, 1H), 5.80 (dd, J = 8.2, 10.3 Hz, 1H), 5.57 (t, J = 10.7 Hz, 1H), 5.37 (t, J = 11.1 Hz, 1H), 5.32−5.14 (m, 4H), 5.10 (d, J = 10.2 Hz, 1H), 4.59−4.43 (m, 3H), 3.93 (m, 1H), 3.80 (s, 3H), 3.66 (m, 1H), 3.38−3.27 (m, 2H), 3.00 (m, 1H), 2.64−2.46 (m, 3H), 1.91−1.62 (m, 3H), 1.54 (m, 1H), 1.49−1.36 (m 3H), 1.11 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H), 1.02−0.81 (m, 45H), 0.16−0.01 (m, 24H).

A mixture of the aldehyde and NaH_2PO_4·H_2O (0.165 g, 1.20 mmol) in *t*-BuOH (15 mL) and H_2O (5 mL) at 0 °C was treated with a 2.0 M solution of 2-methyl-2-butene in THF (5.00 mL, 10.00 mmol) and then $NaClO_4$ (68 mg, 0.60 mmol) was added. The reaction mixture was stirred at 0 °C for 15 min and at ambient temperature for 2 h. After quenching by the addition of a mixture of satd aq NH_4Cl (5 mL) and brine (5 mL), the mixture was extracted with diethyl ether (4 × 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The carboxylic acid as a pale yellow oil was used immediately in the next step without further purification: IR (NaCl) 2956, 2856, 1693, 1471, 1462, 1250, 1039, 835, 773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, J = 11.5, 15.2 Hz, 1H), 7.28 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 6.62 (t, J = 11.4 Hz, 1H), 6.58 (dt, J = 10.6, 16.9 Hz, 1H), 6.03 (dd, J = 7.2, 15.9 Hz, 1H), 5.99 (t, J = 11.0 Hz, 1H), 6.02 (t, J = 11.2 Hz, 1H), 5.58 (d, J = 11.1 Hz, 1H), 5.55 (t, J = 10.6 Hz, 1H), 5.43−5.31 (m, 2H), 5.29−5.15 (m, 3H), 5.10 (d, J = 10.3 Hz, 1H), 4.56 (d, J = 10.6 Hz, 1H), 4.52−4.43 (m, 2H), 3.91(m, 1H), 3.79 (s, 3H), 3.65 (m, 1H), 3.35 (dd, J = 3.2, 7.9 Hz, 1H), 3.28 (t, J = 4.6 Hz, 1H), 2.98 (m, 1H), 2.61−2.42 (m, 3H), 1.85 (m, 1H), 1.79−1.63 (m, 2H), 1.60−1.36 (m 4H), 1.08 (d, J = 6.8 Hz, 3H), 1.02 (t, J = 6.7 Hz, 6H), 0.99−0.77 (m, 42H), 0.12−0.00 (m, 24H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 159.0, 148.1, 147.1, 134.2, 133.7, 133.4, 132.1, 131.5, 130.9, 129.3, 128.9, 128.1, 126.9, 117.3, 115.1, 113.6, 84.2, 80.3, 74.9, 72.2, 71.9, 66.4, 55.1, 43.3, 42.2, 40.2, 36.3, 35.8, 35.1, 29.6, 26.1, 25.8, 23.4, 18.6, 18.3, 18.0, 17.0, 13.4, 9.1, −3.2, −3.7, −4.2, −4.5, −4.6; LRMS (ESI) 1133 [M + Na]$^+$; HRMS (ESI) calcd for $C_{63}H_{114}O_8Si_4Na$ [M + Na]$^+$, 1133.7489; found, 1133.7568; $[\alpha]^{20}_D$ +15.9 (*c* 0.27, $CHCl_3$).

(2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,15*Z*,19*R*,20*R*,21*S*,22*S*,23*Z*)-7,9,13,19-Tetrakis(*tert*-butyldimethylsilyloxy)-21-hydroxy-6,12,-14,20,22-pentamethylhexacosa-2,4,10,15,23,25-hexaenoic Acid (50α). A mixture of the PMB-ether prepared above in CH_2Cl_2 (20 mL) and H_2O (2 mL) at 0 °C was treated with DDQ (0.81 g, 3.56 mmol). After 25 min, additional DDQ (0.136 g, 0.60 mmol) was added and the mixture was stirred for 15 min. After quenching by the addition of satd aq $NaHCO_3$ (20 mL), the mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with satd aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (two columns: 95:1 MeOH/ CH_2Cl_2, then 4:1 hexanes/EtOAc) provided the *seco*-acid **50**α (0.062 g, 31% for three steps) as a colorless oil, which was used immediately in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, J = 11.3, 15.2 Hz, 1H), 6.72−6.53 (m, 2H), 6.10 (t, J = 11.0 Hz, 1H), 6.03 (dd, J = 6.9, 15.5 Hz, 1H), 5.60 (d, J = 11.4 Hz, 1H), 5.47−5.36 (m, 2H), 5.34−5.17 (m, 4H), 5.13 (d, J = 10.1 Hz, 1H), 4.56 (d, J = 10.6 Hz, 1H), 4.48 (m, 1H), 3.93 (m, 1H), 3.77 (m, 1H), 3.49 (dd, J = 3.5, 7.0 Hz, 1H), 3.32 (dd, J = 4.1, 5.5 Hz, 1H), 2.83 (m, 1H), 2.65−2.45 (m, 3H), 2.08−1.80 (m, 2H), 1.78−1.35 (m, 5H), 1.08−0.82 (m, 51H), 0.12−0.02 (m, 24H).

(3*Z*,5*E*,7*R*,8*S*,10*S*,11*Z*,13*S*,14*R*,15*S*,16*Z*,20*R*,21*S*,22*S*)-8,10,14,-20-Tetrakis(*tert*-butyldimethylsilyloxy)-7,13,15,21-tetramethyl-22-((1*S*,2*Z*)-1-methyl-penta-2,4-dienyl)-oxa-cyclodocosa-3,5,11,-16-tetraen-2-one (51α). A solution of the crude *seco*-acid **50**α (0.062 g, 0.063 mmol) in THF (6.3 mL) at 0 °C was treated with triethylamine (0.061 mL, 0.434 mmol) and 2,4,6-trichlorobenzoyl chloride (0.049 mL, 0.313 mmol). The reaction mixture was stirred at 0 °C for 30 min and at ambient temperature for 1 h. A solution of DMAP (0.076 g, 0.625 mmol) in toluene (63 mL) was added at ambient temperature. The reaction mixture was stirred for 17 h. After quenching by the addition of satd aq $NaHCO_3$ (30 mL), the mixture was extracted with diethyl ether (3 × 30 mL) and the combined organic layers were washed with a 0.2 M solution of HCl (3 × 50 mL) and a satd aq $NaHCO_3$ (50 mL), brine, then dried ($MgSO_4$), and concentrated. Purification by column chromatography (98:2 hexanes/EtOAc) provided the macrolactone **51**α (0.043 g, 71%) as a colorless oil: IR (NaCl) 3359, 2956, 2926, 2855, 1713, 1463, 1256, 1086, 835, 773 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.10 (dd, J = 11.5, 14.7 Hz, 1H), 6.61 (dt, J = 10.7, 16.7 Hz, 1H), 6.55 (t, J = 11.2 Hz, 1H), 6.07 (dd, J = 7.6, 15.4 Hz, 1H), 6.00 (t, J = 11.0 Hz, 1H), 5.63 (t, J = 8.2 Hz, 1H), 5.57

(d, J = 11.5 Hz, 1H), 5.40 (t, J = 10.3 Hz, 1H), 5.32 (dd, J = 8.1, 11.1 Hz, 1H), 5.20 (d, J = 16.8 Hz, 1H), 5.17−5.10 (m, 4H), 4.46 (q, J = 7.1 Hz, 1H), 3.88 (m, 1H), 3.54 (m, 1H), 3.37 (d, J = 4.0 Hz, 1H), 3.04 (m, 1H), 2.55−2.29 (m, 3H), 1.96 (m, 1H), 1.85 (m, 1H), 1.77 (m, 1H), 1.65−1.51 (m, 2H), 1.48−1.28 (m, 2H), 1.04 (dd, J = 7.1, 9.7 Hz, 6H), 1.00 (t, J = 6.6 Hz, 6H), 0.97−0.84 (m, 39H), 0.12−0.01 (m, 24H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 144.7, 142.8, 134.0, 133.6, 133.4, 132.1, 131.2, 129.7, 128.1, 127.7, 117.7, 117.5, 79.9, 77.3, 73.4, 71.6, 66.8, 66.1, 43.5, 39.5, 37.6, 37.3, 34.5, 34.4, 29.7, 26.1, 25.9, 25.8, 25.4, 19.6, 18.5, 18.0, 17.9, 17.5, 15.4, 10.5, −2.8, −3.1, −3.6, −4.0, −4.3; LRMS (ESI) 995 $[M + Na]^+$; HRMS (ESI) calcd for $C_{55}H_{104}O_6Si_4Na$ $[M + Na]^+$, 995.6808; found, 995.6902; $[\alpha]^{20}_D$ +5.6 (*c* 0.20, $CHCl_3$).

(3*Z*,5*E*,7*R*,8*S*,10*S*,11*Z*,13*S*,14*R*,15*S*,16*Z*,20*R*,21*S*,22*S*)-8,10,14,-20-Tetrahydroxy-7,13,15,21-tetramethyl-22-((1*S*,2*Z*)-1-methylpenta-2,4-dienyl)-oxacyclodocosa-3,5,11,16-tetraen-2-one (6). A solution of macrolactone **51**α (0.043 g, 0.044 mmol) in THF (2.4 mL) at 0 °C was treated with a 6 M solution of HCl in H_2O/MeOH (2.4 mL, prepared by slow addition of conc. HCl (1.2 mL) to MeOH (1.2 mL)). The reaction mixture was warmed to ambient temperature and stirred. Three portions of a 6 M solution of HCl (2.4 mL) and THF (2.4 mL) were added every 45 min. After 4 h, the solid $NaHCO_3$ was added to the reaction mixture until no gas evolved. The mixture was extracted with diethyl ether (3 × 30 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (3:17 hexanes/EtOAc) provided 16-normethyl-15,16-dehydrodictyostatin **6** (0.0096 mg, 42%) as a colorless powder and the more polar C2−C3 *E*-isomer **53** (0.0007 g, 3%) as a colorless powder.

16-Normethyl-15,16-dehydrodictyostatin 6: IR (NaCl) 3390, 2965, 2927, 1704, 1639, 1455, 1275, 1179, 1002, 959 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (dd, J = 11.2, 15.5 Hz, 1H), 6.60 (dt, J = 11.0, 16.8 Hz, 1H), 6.53 (t, J = 11.3 Hz, 1H), 6.01 (dd, J = 8.5, 15.5 Hz, 1H), 6.00 (t, J = 10.8 Hz, 1H), 5.62 (t, J = 10.8 Hz, 1H), 5.54 (d, J = 11.5 Hz, 1H), 5.52 (dd, J = 8.9, 10.7 Hz, 1H), 5.32 (t, J = 10.5 Hz, 1H), 5.22 (dt, J = 6.9, 10.9 Hz, 1H), 5.19 (t, J = 11.0 Hz, 1H), 5.18 (d, J = 16.7 Hz, 1H), 5.10 (dd, J = 2.9, 8.6 Hz, 1H), 5.08 (d, J = 11.0 Hz, 1H), 4.66 (dt, J = 3.8, 8.4 Hz, 1H), 4.01 (dt, J = 2.6, 10.7 Hz, 1H), 3.38 (ddd, J = 2.8, 6.8, 12.7 Hz, 1H), 3.29 (dd, J = 3.6, 8.0 Hz, 1H), 3.05 (m, 1H), 2.66 (m, 1H), 2.51 (m, 1H), 2.38 (m, 1H), 2.14 (m, 1H), 1.97 (m, 1H), 1.90 (dt, J = 3.0, 6.9 Hz, 1H), 1.66 (m, 1H), 1.59 (ddd, J = 3.9, 10.5, 14.3 Hz, 1H), 1.44 (ddd, J = 2.4, 8.3, 14.2 Hz, 1H), 1.22 (dt, J = 4.1, 9.6 Hz, 1H), 1.17 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.9 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 134.0, 132.5, 132.3, 132.0, 131.8, 129.9, 129.5, 127.9, 79.0, 76.4, 73.0, 71.1, 65.4, 43.3, 40.2, 40.1, 36.9, 35.4, 34.4, 33.9, 24.8, 19.3, 18.0, 17.4, 15.8, 10.1; LRMS (ESI) 539 $[M + Na]^+$; HRMS (ESI) calcd for $C_{31}H_{48}O_6Na$ $[M + Na]^+$, 539.3349; found, 539.3352; $[\alpha]^{20}_D$ −74.0 (*c* 0.17, $CHCl_3$).

The C2−C3 *E*-Isomer 53: IR (NaCl) 3408, 2962, 2926, 1698, 1640, 1455, 1300, 1261, 1003 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 (dd, J = 10.9, 15.3 Hz, 1H), 6.59 (dt, J = 10.3, 17.3 Hz, 1H), 6.16 (dt, J = 10.8, 15.2 Hz, 1H), 6.04 (dd, J = 7.9, 15.3 Hz, 1H), 5.97 (t, J = 10.9 Hz, 1H), 5.73 (d, J = 15.3 Hz, 1H), 5.50 (dd, J = 8.8, 11.0 Hz, 1H), 5.42 (t, J = 10.1 Hz, 1H), 5.38−5.32 (m, 2H), 5.20 (t, J = 10.8 Hz, 1H), 5.17 (d, J = 17.7 Hz, 1H), 5.09 (d, J = 10.1 Hz, 1H), 4.96 (dd, J = 1.7, 8.7 Hz, 1H), 4.79 (dt, J = 2.7, 7.3 Hz, 1H), 4.03 (d, J = 10.5 Hz, 1H), 3.48−3.35 (m, 2H), 3.01 (m, 1H), 2.73 (m, 1H), 2.61 (m, 1H), 2.42 (m, 1H), 2.20 (m, 1H), 2.10 (m, 1H), 1.83 (m, 1H), 1.69 (ddd, J = 2.5, 10.6, 13.9 Hz, 1H), 1.58 (m, 1H), 1.54 (m, 1H), 1.34−1.28 (m, 2H), 1.16 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.7, 145.5, 145.1, 134.3, 133.2, 131.9, 131.5, 131.3, 130.7, 129.7, 129.0, 119.7, 117.8, 78.3, 76.1, 71.7, 71.2, 65.8, 42.4, 40.5, 40.2, 35.9, 34.2, 34.1, 31.8, 23.7, 19.3, 17.3, 15.7, 14.6, 9.8; LRMS (ESI) 539 $[M + Na]^+$; HRMS (ESI) calcd for $C_{31}H_{48}O_6Na$ $[M + Na]^+$, 539.3349; found, 539.3362; $[\alpha]^{20}_D$ +21.9 (*c* 0.16, $CHCl_3$).

(2*Z*,4*E*,6*R*,7*S*,9*R*,10*Z*,12*S*,13*R*,14*S*,15*Z*,19*R*,20*R*,21*S*,22*S*,23*Z*)-21-(4-Methoxybenzyloxy)-7,9,13,19-tetrakis(*tert*-butyldimethylsilyloxy)-6,12,14,20,22-pentamethylhexacosa-2,4,10,15,23,25-hexaen-1-ol (49β). Following the procedure for **48**α, the alcohol **48**β (0.20 g, 0.20 mmol) in CH_2Cl_2 (4.0 mL) was reacted with 2,6-lutidine (0.069 mL, 0.59 mmol) and TBSOTf (0.068 mL, 0.30 mmol) to provide the TBS ether as a colorless oil, which was used in the next step without further purification.

The TBS ether at 0 °C was treated with a solution of HF·pyr in pyr/THF (6.7 mL) for 14 h. Purification by column chromatography (9:1 hexanes/EtOAc) provided the alcohol **49**β (0.12 g, 60%) as a colorless oil: IR (NaCl) 3400, 2956, 2928, 2856, 1250, 1084, 1037, 835, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.61 (dt, J = 10.5, 16.8 Hz, 1H), 6.30 (dd, J = 11.1, 15.2 Hz, 1H), 6.15−5.95 (m, 2H), 5.85 (dd, J = 8.6, 15.2 Hz, 1H), 5.59 (t, J = 10.5 Hz, 1H), 5.50−5.05 (m, 7H), 4.58 (d, J = 10.5 Hz, 1H), 4.51 (d, J = 10.5 Hz, 1H), 4.40 (m, 1H), 4.30 (dd, J = 7.4, 12.8 Hz, 1H), 4.23 (dd, J = 6.9, 12.8 Hz, 1H), 3.87(m, 1H), 3.80 (s, 3H), 3.68 (m, 1H), 3.40 (t, J = 4.2 Hz, 1H), 3.35 (dd, J = 3.2, 7.7 Hz, 1H), 3.00 (m, 1H), 2.67−2.49 (m, 2H), 2.43 (m, 1H), 1.92−1.80 (m, 2H), 1.69 (m, 1H), 1.62−1.40 (m, 4H), 1.12 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H), 1.00−0.84 (m, 45H), 0.12−0.02 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 152.4, 138.8, 134.8, 134.5, 133.6, 132.6, 131.6, 129.4, 129.3, 128.2, 127.5, 125.5, 118.8, 117.5, 114.0, 84.5, 79.8, 75.3, 72.7, 66.7, 59.1, 55.5, 44.8, 41.0, 40.7, 37.7, 35.9, 35.6, 35.4, 29.9, 26.5, 26.2, 26.1, 23.7, 19.0, 18.9, 18.7, 18.4, 18.3, 17.0, 9.68, −3.2, −3.3, −3.7, −4.1, −4.3, −4.4; LRMS (ESI) 1119 $[M + Na]^+$; HRMS (ESI) calcd for $C_{63}H_{116}O_7Si_4Na$ $[M + Na]^+$, 1119.7696; found, 1119.7700; $[\alpha]^{20}_D$ +50.0 (*c* 0.18, $CHCl_3$).

(2*Z*,4*E*,6*R*,7*S*,9*R*,10*Z*,12*S*,13*R*,14*S*,15*Z*,19*R*,20*R*,21*S*,22*S*,23*Z*)-7,9,13,19-Tetrakis(*tert*-butyldimethylsilyloxy)-21-hydroxy-6,12,-14,20,22-pentamethylhexacosa-2,4,10,15,23,25-hexenoic Acid (50β). A solution of the alcohol **49**β (0.11 g, 0.10 mmol) in CH_2Cl_2 (10 mL) at 0 °C was treated with Dess−Martin periodinane (0.085 g, 0.20 mmol). The mixture was warmed to ambient temperature and stirred for 1 h. After quenching by the addition of a mixture of satd aq $Na_2S_2O_3$ (5 mL) and satd aq $NaHCO_3$ (5 mL), the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with satd aq $NaHCO_3$ (10 mL) and brine and dried ($MgSO_4$). The concentration under vacuum provided the aldehyde as a pale yellow oil, which was used in the next step without further purification.

The aldehyde in *t*-BuOH (6 mL) and H_2O (2 mL) was reacted with NaH_2PO_4·H_2O (0.083 g, 0.60 mmol), a 2.0 M solution of 2-methyl-2-butene in THF (2.50 mL, 5.00 mmol), and $NaClO_4$ (0.034 g, 0.30 mmol) to provide the carboxylic acid as a pale yellow oil, which was used in the next step without further purification.

The carboxylic acid in CH_2Cl_2 (10 mL) and H_2O (1 mL) was reacted with DDQ (0.068 g, 0.30 mmol). Purification by chromatography (15:1 hexanes/EtOAc) provided the seco acid **50**β (0.047 g, 47% for three steps) as a colorless oil, which was used immediately in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (dd, J = 11.4, 17.3 Hz, 1H), 6.75−6.52 (m, 2H), 6.24 (dd, J = 8.7, 15.3 Hz, 1H), 6.11 (t, J = 10.9 Hz, 1H), 5.58 (d, J = 11.3 Hz, 1H), 5.52−5.33 (m, 3H), 5.32−5.17 (m, 3H), 5.13 (d, J = 10.2 Hz, 1H), 4.41 (t, J = 8.0 Hz, 1H), 3.92 (d, J = 9.4 Hz, 1H), 3.80 (m, 1H), 3.52 (dd, J = 2.6, 7.5 Hz, 1H), 3.41 (t, J = 3.8 Hz, 1H), 2.81 (m, 1H), 2.64−2.44 (m, 2H), 2.10−1.82 (m, 2H), 1.78 (m, 1H), 1.72−1.31 (m, 5H), 1.11 (d, J = 6.7 Hz, 1H), 1.02−0.80 (m, 48H), 0.18−0.02 (m, 24H).

(3*Z*,5*E*,7*R*,8*S*,10*R*,11*Z*,13*S*,14*R*,15*S*,16*Z*,20*R*,21*S*,22*S*)-8,10,14,-20-Tetrahydroxy-7,13,15,21-tetramethyl-22-((1*S*,2*Z*)-1-methylpenta-2,4-dienyl)-oxacyclodocosa-3,5,11,16-tetraen-2-one (54). A solution of the *seco*-acid **50**β (0.037 g, 0.037 mmol) in THF (3.7 mL) at 0 °C was treated with triethylamine (0.036 mL, 0.259 mmol) and 2,4,6-trichlorobenzoyl chloride (0.029 mL, 0.186 mmol). The reaction mixture was stirred at 0 °C for 30 min and at ambient temperature for 1 h. A solution of DMAP (0.045 g, 0.370 mmol) in toluene (37 mL) was added at ambient temperature. The reaction mixture was stirred for 15 h. After quenching by addition of satd

aq $NaHCO_3$ (15 mL), the mixture was extracted with diethyl ether (3 × 15 mL) and the combined organic layers were washed with a 0.2 M solution of HCl (3 × 25 mL), satd aq $NaHCO_3$ (25 mL), and brine, then dried ($MgSO_4$), and concentrated. Purification by column chromatography (98:2 hexanes/EtOAc) provided the mixture **51**β (0.035 g) of (3*Z*) and (3*E*) as a pale yellow oil. The same reaction with 0.034 g of the *seco*-acid gave the mixture of macrolactone (0.027 g).

A solution of macrolactone **51**β (0.062 g, 0.064 mmol) in THF (3.2 mL) at 0 °C was treated with a 6 M solution of HCl in H_2O/MeOH (3.2 mL, prepared by the slow addition of concd HCl (1.6 mL) to MeOH (1.6 mL)). The reaction mixture was warmed to ambient temperature and stirred. Three portions of a 6 M solution of HCl (1.6 mL) and THF (1.6 mL) were added every 45 min. After 8 h, the solid $NaHCO_3$ was added to the reaction mixture until no gas evolved. The mixture was extracted with diethyl ether (3 × 50 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (3:17 hexanes/EtOAc) provided the title compound **54** (0.004 g, 14%, two steps) as a colorless powder and the more polar C19-lactone **55** (0.005 g, 16%, two steps) as a colorless powder: IR (NaCl) 3384, 2964, 1698, 1635, 1456, 1271, 1001 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.28 (dd, J = 10.9, 15.8 Hz, 1H), 6.61 (dt, J = 10.7, 16.8 Hz, 1H), 6.55 (t, J = 11.4 Hz, 1H), 6.05 (t, J = 11.0 Hz, 1H), 6.02 (dd, J = 5.9, 16.0 Hz, 1H), 5.59 (dd, J = 8.4, 10.9 Hz, 1H), 5.58 (d, J = 11.2 Hz, 1H), 5.38−5.32 (m, 2H), 5.28 (dt, J = 4.9, 10.2 Hz, 1H), 5.22 (d, J = 16.8 Hz, 1H), 5.12 (d, J = 10.0 Hz, 1H), 4.87 (dd, J = 3.3, 6.7 Hz, 1H), 4.67 (dt, J = 3.6, 9.0 Hz, 1H), 4.14 (m, 1H), 3.58 (dt, J = 4.4, 6.4 Hz, 1H), 3.15 (t, J = 7.3 Hz, 1H), 3.00 (m, 1H), 2.74 (m, 2H), 2.61 (m, 1H), 2.40 (m, 1H), 2.05 (m, 1H), 1.80 (m, 1H), 1.66 (m, 1H), 1.55 (m, 1H), 1.31 (m, 1H), 1.10 (d, J = 6.6 Hz, 3H), 1.08 (d, J = 7.1 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.3, 146.3, 144.6, 134.5, 133.9, 133.8, 133.2, 130.0, 128.6, 126.5, 118.0, 116.7, 79.2, 78.7, 73.2, 72.3, 67.8, 41.0, 38.9, 38.3, 38.2, 35.6, 34.1, 29.7, 23.6, 19.1, 18.9, 17.5, 14.7, 8.3; LRMS (ESI) 539 $[M + Na]^+$; HRMS (ESI) calcd for $C_{31}H_{48}O_6Na$ $[M + Na]^+$, 539.3349; found, 539.3339; $[\alpha]^{20}_D$ −58.0 (*c* 0.20, $CHCl_3$).

(3*Z*,5*E*,7*R*,8*S*,10*S*,11*Z*,13*S*,14*R*,15*S*,16*Z*,20*R*)-8,10,14-Trihydroxy-20-((1′*R*,2′*S*,3′*S*,4′*Z*)-2′-hydroxy-1′,3′-dimethylhepta-4′,6′-dienyl)-7,13,15-trimethyloxacycloeicosa-3,5,11,16-tetraen-2-one (55). IR (NaCl) 3390, 2963, 2929, 1698, 1635, 1456, 1267, 1180, 1003 736 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.27 (m, 1H), 6.66 (dt, J = 10.2, 16.8 Hz, 1H), 6.58 (t, J = 11.2 Hz, 1H), 6.17 (t, J = 10.9 Hz, 1H), 6.14 (dd, J = 6.4, 15.7 Hz, 1H), 5.63 (d, J = 11.3 Hz, 1H), 5.50 (dd, J = 8.8, 11.0 Hz, 1H), 5.41−5.29 (m, 3H), 5.27 (d, J = 16.7 Hz, 1H), 5.18 (d, J = 10.1 Hz, 1H), 5.07 (dd, J = 5.0, 6.4 Hz, 1H), 4.57 (m, 1H), 3.40 (dd, J = 3.2, 7.9 Hz, 1H), 3.17 (dd, J = 6.0, 7.7 Hz, 1H), 2.86 (m, 1H), 2.67 (m, 1H), 2.58 (m, 1H), 2.48 (q, J = 7.5 Hz, 1H), 2.13 (m, 1H), 2.00 (dt, J = 3.3, 6.7 Hz, 1H), 1.81 (m, 2H), 1.70 (ddd, J = 7.3, 10.1, 14.1 Hz, 1H), 1.60 (ddd, J = 3.5, 5.2, 14.1 Hz, 1H), 1.14 (d, J = 7.0 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.3, 146.1, 143.8, 134.1, 134.0, 133.8, 133.7, 132.0, 131.4, 128.1, 126.7, 118.7, 117.3, 78.8, 76.2, 75.0, 72.7, 67.3, 41.3, 39.8, 38.4, 38.1, 37.6, 36.1, 31.4, 22.9, 19.5, 18.0, 17.1, 14.1, 8.8; LRMS (ESI) 539 $[M + Na]^+$; HRMS (ESI) calcd for $C_{31}H_{48}O_6Na$ $[M + Na]^+$, 539.3349; found, 539.3356; $[\alpha]^{20}_D$ −10.5 (*c* 0.19, $CHCl_3$).

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Supporting Information Available: Detailed descriptions of the synthesis and characterization of the dictyostatin analogs **5** and **6** along with copies of NMR spectra of all compounds tested (64 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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