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Synthesis and biological evaluation of (−)-dictyostatin and stereoisomers

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Dedicated to Professor Hisashi Yamamoto on his receipt of the Tetrahedron Prize

Abstract—Total syntheses of (−)-dictyostatin, 6,16-bis-*epi*-dictyostatin, 6,14,19-tris-*epi*-dictyostatin, and a number of other isomers and analogs are reported. Three main fragments—top, middle, and bottom—were first assembled and then joined by olefination or anionic addition reactions. After appending the two dienes at either end of the molecule, macrolactonization and deprotection completed the syntheses. The work proves both the relative and absolute configurations of (−)-dictyostatin. The compounds were evaluated by cell-based measurements of increased microtubule mass and antiproliferative activity, and in vitro tubulin polymerization assays as well as competitive assays with paclitaxel for its binding site on microtubules. These assays showed dictyostatin to be the most potent of the agents and further showed that the structural alterations caused from 20- to >1000-fold decreases in activity.

1. Introduction

Microtubule stabilization by small molecule natural products and analogs[1] is a clinically proven chemotherapeutic approach for the treatment of solid tumors, and microtubule stabilizers exhibit a diverse assortment of molecular scaffolds. Dictyostatin and discodermolide (Fig. 1), the taxanes paclitaxel and docetaxel, the epothilones, the sarcodictyins and eleutherobin, and the ketosteroids 2-ethoxy-7-keto-17β-estradiol and the taccalonolides all bind with varying affinities to the paclitaxel binding site on β-tubulin within microtubules.[2–7] The tau neuronal protein binds onto microtubules in the vicinity of the paclitaxel site, and this site is well-described due to high resolution cryoelectron microscopic analyses of zinc-induced sheets of tubulin polymer stabilized by taxanes or epothilones.[8,9] Drugs binding to the site interact with amino acid residues on the M-loop (for example, Phe270, Thr274, and Arg276) and the H7 alpha helix (for example, Ala231 and His227) of β-tubulin.

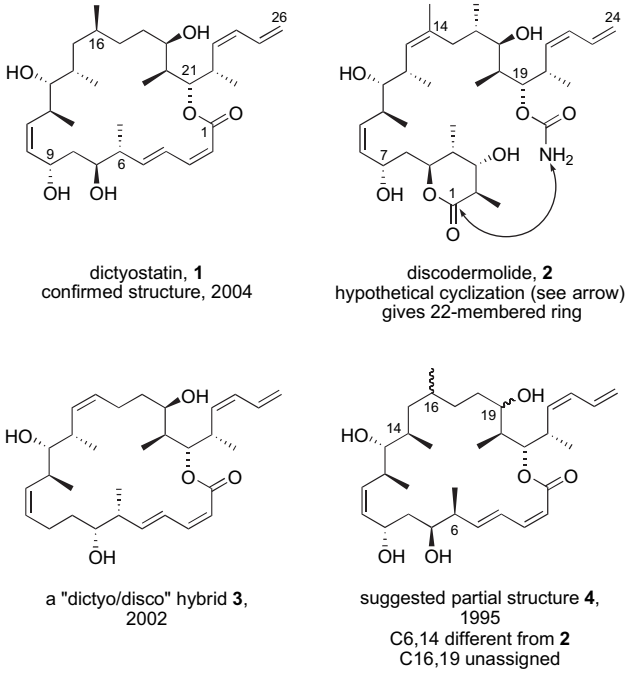

Figure 1. Structures of dictyostatin **1**, discodermolide **2**, and related compounds.

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Interest in the dictyostatin family of microtubule-stabilizing agents has increased significantly over the last several years. Pettit initially isolated dictyostatin **1** from a marine sponge, suggested the correct two-dimensional structure (constitution), and showed that the compound had potent activity against cancer cells.[10] Subsequently, Wright and co-workers isolated **1** from a different sponge species and showed that the compound displays potent microtubule-stabilizing actions.[11]

Dictyostatin is a structural cousin of the important microtubule-stabilizing agent discodermolide **2**.[12] Dictyostatin's 26-carbon backbone is two carbons longer than discodermolide's, and it is joined by a 22-membered macrolactone formed between the carboxyl group on C1 and the alcohol on C21. (The longer chain length means that carbon numbers of dictyostatin are two higher than the comparable carbons of discodermolide.) Dictyostatin also differs from discodermolide by possessing a *Z*/*E* diene (C2–C5) instead of a γ-lactone, and it lacks a double bond at C15,16 and a methyl group at C18. Nonetheless, 10 of dictyostatin's 11 stereocenters are also present in the discodermolide structure.

The three-dimensional structure (configuration) of dictyostatin was uncertain for almost a decade. As an outgrowth of our interest in discodermolide analogs,[13] we made 'dictyostatin/discodermolide' hybrids like **3** in 2002,[14] and these compounds exhibited high biological activities in both tubulin and cell assays. An underlying tenet of this work was that a hypothetical cyclization of the carbamate nitrogen of discodermolide **2** onto its lactone carbonyl (C1) would provide a 22-membered ring, the same size as the macrocycle of dictyostatin **1**. At this juncture, the lack of knowledge of the complete structure of dictyostatin and the tiny quantities available from isolation were serious impediments to further medicinal chemistry research. With a solid foundation in place from the synthesis of compound **3** and related molecules, we decided to address the dictyostatin structure and supply problems by total synthesis.

In a 1995 patent, Pettit and co-workers suggested a partial configuration for dictyostatin,[15] and we selected the absolute configuration depicted for compound **4** because this enantiomer is more closely related to discodermolide. In **4**, seven stereocenters have the same configurations as discodermolide, two are different (C6 and C14), and two are not assigned (C16 and C19). In 2004, Paterson and co-workers suggested structure **1** for dictyostatin based on detailed NMR studies;[16] in addition to assigning the two missing stereocenters, the configurations of two other centers were inverted. Structure **1** was promptly proved by a pair of total syntheses that appeared in simultaneous communications from Paterson's group[17] and ours,[18] and recently Phillips and Ramachandran have also reported the total syntheses of **1**.[19,20]

In this paper, we provide details of our total synthesis of dictyostatin **1**. Along the way, we made several stereoisomers of the natural product as we drew gradually closer to the correct structure. All of these compounds have been characterized by a battery of biological assays. These results, combined with the additional results for new analogs described elsewhere[21–23] and with the known SAR for discodermolide, provide for the first time a good outline of the SAR of dictyostatin. Over 5 mg of synthetic dictyostatin was provided by this work, and this was used for the detailed biological characterization of this molecule. The results of these studies have fully validated the high level of interest in dictyostatin.[2]

2. Results

2.1. Chemistry

2.1.1. Synthesis of 6,16-bis-*epi*-dictyostatin 5. Though differing in relative configuration from Pettit's structure **4** in the middle fragment, we initially decided to make compound **5** because a number of key early intermediates were already in hand. We selected the (*R*) configuration at C16 arbitrarily, and though this proved to be wrong, the molecule—6,16-bis-*epi*-dictyostatin—ultimately turned out to be structurally much closer to dictyostatin than we had initially thought.

The strategy for the synthesis of this molecule is summarized at a high level in Figure 2. Key targeted bonds were C10,11 (Wittig reaction), C17,18 (Horner–Wadsworth–Emmons reaction), and O21–C1 (macrolactonization). This divided the molecule into three approximately equal portions, which we call top, middle, and bottom. The top and bottom fragments were further subjected to secondary disconnections to excise the two dienes. The removal of these two potentially sensitive groups reduced the convergency, but it also expanded

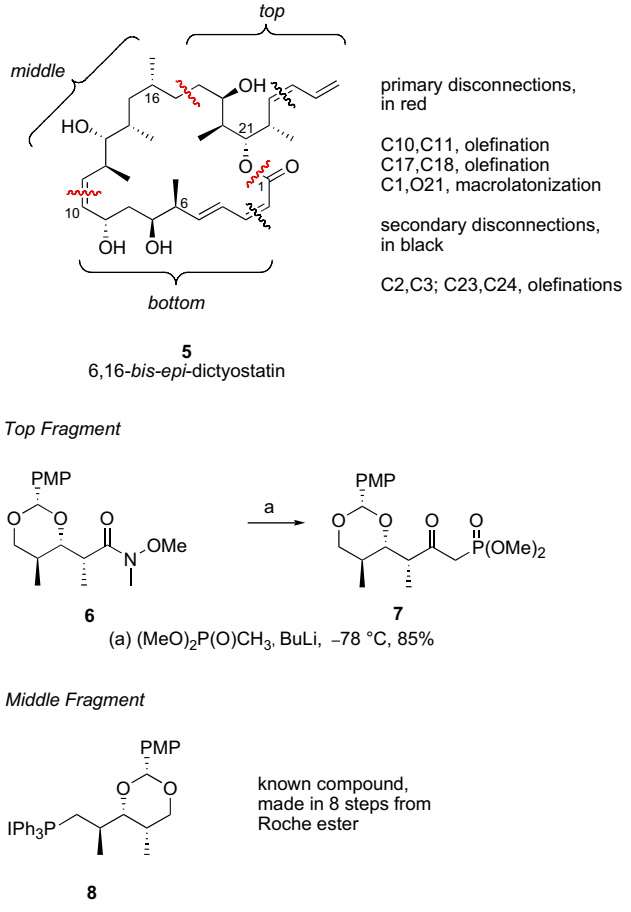
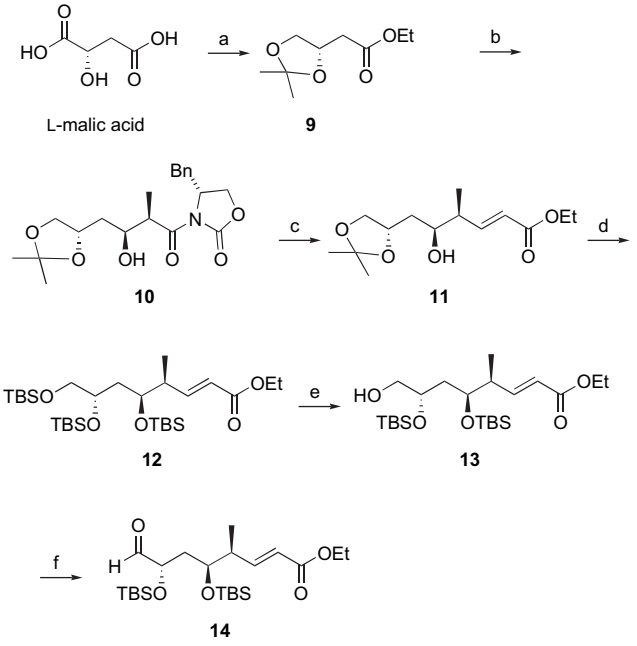


Figure 2. Strategy for the synthesis of **5** with top and middle fragments.

options for fragment coupling based on alkene chemistry. Since speed to the target was more important than efficiency at this stage of the work, we deemed this a worthwhile trade off.

The selected top and middle fragments are also shown in Figure 2. Like all the work described herein, the early stages of the synthesis of the top and middle fragments were borrowed liberally from related work in the discodermolide field. Weinreb amide **6** is readily available in five steps from (2*S*)-3-hydroxy-2-methylpropionic acid methyl ester (Roche ester),[24] and this was parlayed into top fragment **7** in 85% yield by reaction with lithiomethyl trimethylphosphonate. This fragment was used for all of the compounds in this paper. Middle fragment **8** was borrowed from our prior work[13] because it provides reliable results in Wittig olefinations, and it was readily made in eight steps and 33% overall yield from the Roche ester. These reactions were readily conducted on multi-gram scale, and the efficiency of the plan was increased because the first few steps of the syntheses of **7** and **8** were the same.

The synthesis of the bottom aldehyde fragment **14** is summarized in Scheme 1. (L)-Malic acid was esterified and selectively reduced with borane dimethylsulfide and $NaBH_4$ in 97% yield to a diol, which was protected as the acetonide **9** with acetone/*p*-TsOH in 86% yield.[25] The ester in **9** was reduced to an aldehyde with DIBALH in 67% yield, and this was subjected to an Evans *syn*-aldol reaction to give **10** in 98% yield as a single diastereomer.[26] The aldol product **10** was reduced to an aldehyde by using Red-Al, and this was homologated by a Horner–Wadsworth–Emmons (HWE) reaction to the α,β-unsaturated ester **11** in 52% yield. The



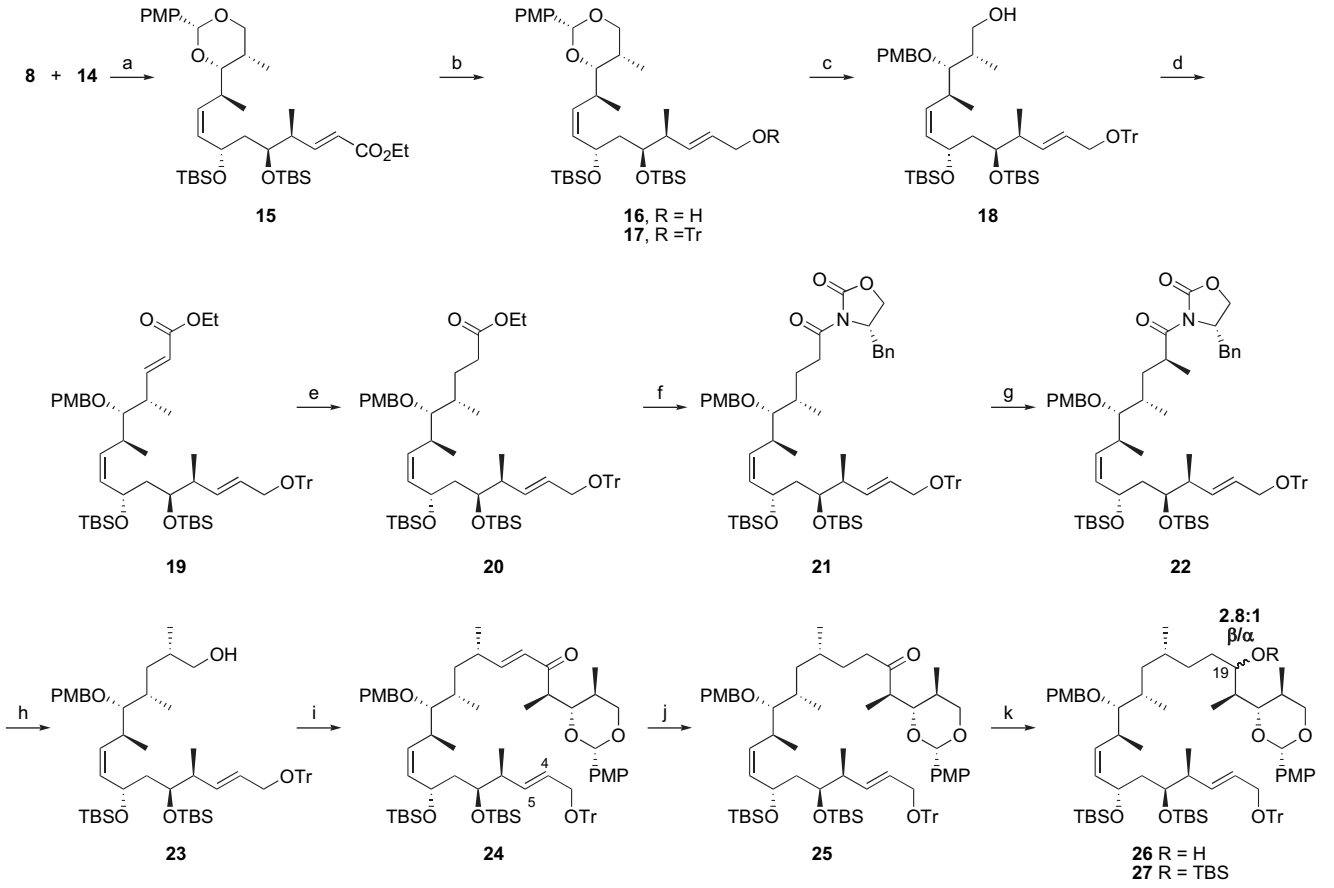
Scheme 1. Synthesis of bottom fragment **14**. (a) (i) EtOH, $SOCl_2$, 99%; (ii) $BH_3 \cdot SMe_2$, $NaBH_4$, THF, 97%; (iii) acetone, *p*-TsOH, 86%. (b) (i) DIBAL, −78 °C, 67%; (ii) *n*-Bu_2BOTf, DIPEA, Evans oxazolidinone, 98%. (c) (i) Red-Al, THF; (ii) triethylphosphonoacetate, KO-*t*-Bu, 52% (two steps). (d) (i) Dowex-H^+; (ii) TBSOTf, 2,6-lutidine, 81% (two steps). (e) HF/pyridine, pyridine, THF, 65%. (f) Dess–Martin, 93%.

acetonide protecting group was removed with Dowex-H^+resin,[27] and the resulting triol was triply protected with TBS groups to give **12** in 81% yield. Selective deprotection of the primary TBS group was achieved in 65% yield with HF/pyridine, and the resulting alcohol **13** was oxidized with the Dess–Martin reagent to give aldehyde **14** in 93% yield.

The fragment couplings and associated steps form the intermediate stage of the synthesis, as summarized in Scheme 2. Wittig coupling of **14** was conducted at high concentration (1 M) of the phosphonium salt **8** to give **15** in 75% yield. The formation of the (*Z*)-alkene at C10–C11 was confirmed by the 10.8 Hz coupling constant between the adjacent vinyl protons. Hydrolysis of the ester functionality in **15** with 1 N KOH, activated ester formation with ethyl chloroformate, and in situ $NaBH_4$ reduction gave the allylic alcohol **16** in 61% yield. Alcohol **16** was protected by a trityl group to give **17** in 99% yield. The PMB acetal in **17** was cleaved with DIBALH to give the primary alcohol **18** in 74% yield, which was oxidized with the Dess–Martin reagent and then subjected to HWE reaction to give ester **19** in 93% yield.[28a,b] The α,β-unsaturated alkene in **19** was reduced selectively with nickel boride to give **20** in 97% yield, and this was subsequently hydrolyzed and coupled with the Evans oxazolidinone by forming the activated ester with pivaloyl chloride to give **21** in 83% yield. Asymmetric methylation gave **22** stereoselectively in 62% yield.[28c] The optimal conditions entailed addition of 3 equiv of methyl iodide dropwise over 30 min, and the temperature was kept at −78 °C for 4 h to minimize the formation of the α-dimethylated byproduct.

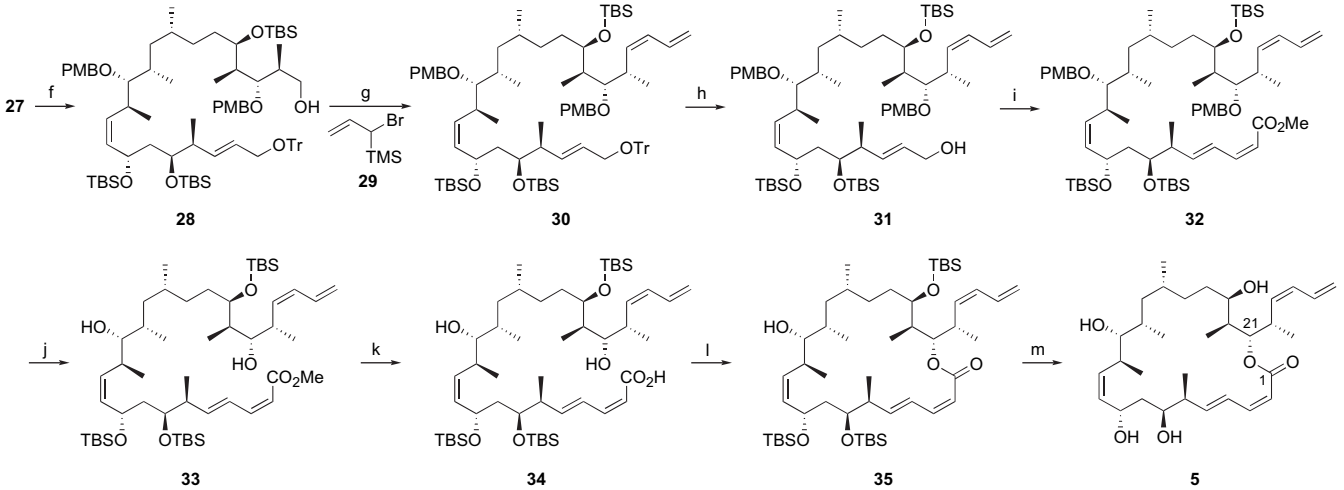
Removal of the Evans auxiliary with $LiBH_4$ produced the primary alcohol **23** in 87% yield (Scheme 2). This was oxidized by the Dess–Martin protocol to the aldehyde, which was subjected to an HWE reaction with top fragment phosphonate **7** to give the coupled product **24** in 90% yield. The α,β-unsaturated alkene was reduced with nickel boride in 89% yield to give **25** (over-reduction of the C4–C5 alkene was also observed as a minor side reaction). Because the configuration of dictyostatin at C19 was unassigned, the ketone in **25** was reduced unselectively with $NaBH_4$ to give a 2.8:1 mixture of diastereomers, which were separated by silica gel column chromatography. The configuration of the major product **26** was assigned as β by conversion of a small sample to a cyclic PMP acetal between O19 and O21, followed by NOE studies.[29] The secondary hydroxy group of the major β diastereomer **26** was then protected with a TBS group to give **27** in 94% yield.

The final stages of the synthesis of **5** included elaboration of the two dienes and macrocyclization, and these are summarized in Scheme 3. The PMB acetal of **27** was opened with DIBALH to give **28** in 97% yield. Primary alcohol **28** was oxidized to an aldehyde and then submitted to a Nozaki–Hiyama reaction[30] with **29** to provide an *anti* β-hydroxy silane. This crude silane was directly subjected to Peterson-type *syn*-elimination with excess NaH (20 equiv) in THF to install the (*Z*)-diene moiety, giving **30** in 72% yield. The trityl group was removed by *B*-chlorocatecholborane[31] to give **31** in 61% yield. This moderate yield was due to the partial PMB deprotection at C21 and due to the difficulty in chromatographic purification because the product **31** had similar retention characteristics to the TrOH byproduct.

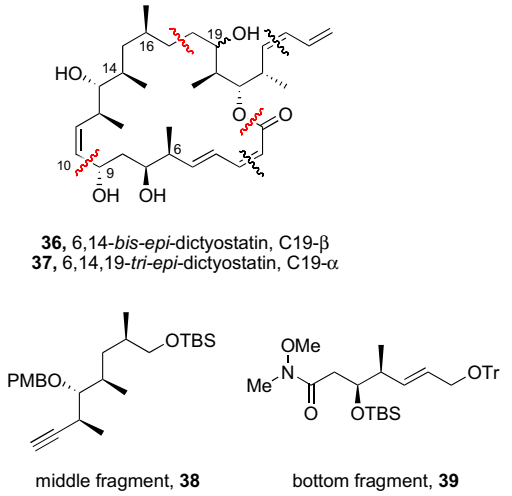


Scheme 2. Intermediate stage of 6,16-bis-*epi*-dictyostatin synthesis. (a) NaHDMS, THF, 75%. (b) (i) KOH, EtOH; (ii) EtOCOCl, Et_3N then $NaBH_4$, 61% (two steps). (c) (i) TrCl, pyridine, DMAP, 99%; (ii) DIBAL–H, 74%. (d) (i) Dess–Martin; (ii) triethylphosphonoacetate, KO-*t*-Bu, 93% (two steps). (e) $NiCl_2 \cdot H_2O$, $NaBH_4$, MeOH, 97%. (f) (i) KOH, EtOH; (ii) PivCl, Et_3N, LiCl, Evans oxazolidinone, 83%. (g) NaHDMS, MeI, 62%. (h) $LiBH_4$, MeOH, THF, 87%. (i) (i) Dess–Martin; (ii) $Ba(OH)_2$, THF/H_2O, **7**, 90% (two steps). (j) $NiCl_2$, $NaBH_4$, MeOH/CH_2Cl_2, 89%. (k) (i) $NaBH_4$, MeOH, 96%. (ii) TBSOTf, 2,6-lutidine, 94%.

The resulting allylic alcohol **31** was oxidized with the Dess–Martin reagent to an aldehyde, which was subjected to a Still–Gennari reaction[32] to give the (*E*,*Z*) doubly unsaturated ester **32** in 82% yield. DDQ deprotection of the two PMB groups at C13 and C21 gave diol **33** in 95% yield. Use of excess DDQ (more than 3 equiv) resulted in the formation of a Diels–Alder adduct with the C2–C5 diene portion, lowering the yield dramatically. Hydrolysis of the methyl ester to acid **34** was achieved by using 1 N KOH in EtOH, setting the stage for the macrocyclization. Finally,



Scheme 3. Final stages of the synthesis of 6,16-bis-*epi*-dictyostatin. (f) DIBAL–H, 97%. (g) (i) Dess–Martin; (ii) $CrCl_2$, THF, **29**; (iii) NaH, THF, 72% (three steps). (h) *B*-Chlorocatecholborane, CH_2Cl_2, −78 °C, 61%. (i) (i) Dess–Martin; (ii) Still–Gennari, 82% (two steps). (j) DDQ, 95%. (k) 1 N KOH, EtOH, 60 °C. (l) Yamaguchi, 49% (two steps). (m) 3 N HCl/MeOH, 73%.



36, 6,14-*bis*-*epi*-dictyostatin, C19-β
37, 6,14,19-*tri*-*epi*-dictyostatin, C19-α

Figure 3. Strategy for the synthesis of 6,14-bis-*epi*-dictyostatin.

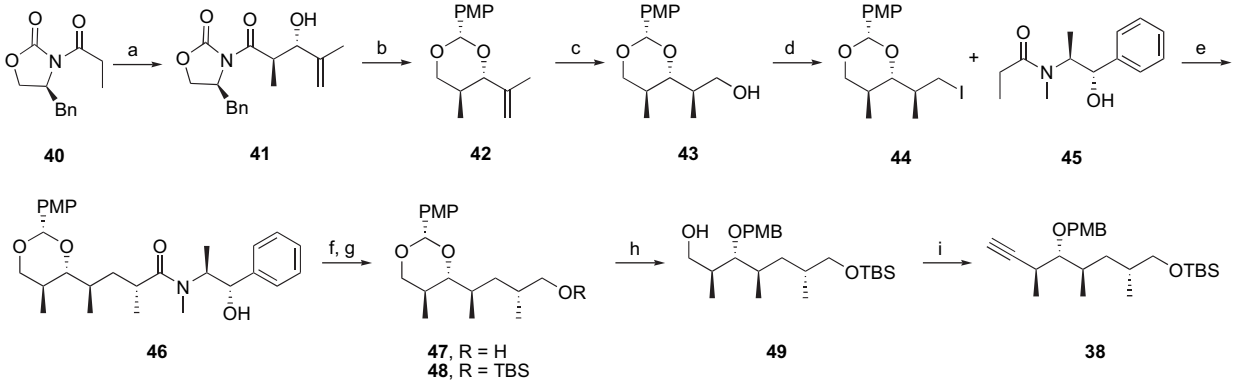
Yamaguchi lactonization[33] gave the macrolactone **35** in 49% yield. TBS deprotection with 3 N HCl in MeOH/THF gave the desired product *C*6,*C*16-bis-*epi*-dictyostatin **5** (73%), whose structure was confirmed by ^{1}H–^{1}H COSY, HMQC, HMBC, and other NMR experiments. In particular, a key crosspeak between H21 and C1 in the HMBC spectrum confirmed the 22-membered lactone.

2.1.2. Synthesis of 6,14-bis-*epi*-dictyostatin. We next decided to make compounds **36** and **37** (Fig. 3), which are two of the four possible diastereomers from the structure proposed by Pettit. These are related to **5**, but have the 14*S* (C13,C14 *anti*) configuration. Based on some simple computational modeling,[34] we also decided to adjust the configuration at C16 from *R* (α) to *S* (β). In the end, the two inversions were a wash, one moving us closer to dictyostatin (C16) and the other further away (C14), providing a target **36** that ultimately proved to be 6,14-bis-*epi*-dictyostatin. Unexpectedly, this target was not accessed in pure form due to the isomerization of the *C*2,*C*3 alkene during the macrolactonization (see below). Also, to get more information about the configuration of the alcohol at C19, we decided to take the α-epimer at this center through the synthesis, and this provided 6,14,19-tris-*epi*-dictyostatin **37**. The macrolactonization reaction again caused some isomerization, but this time both alkene stereoisomers were isolated.

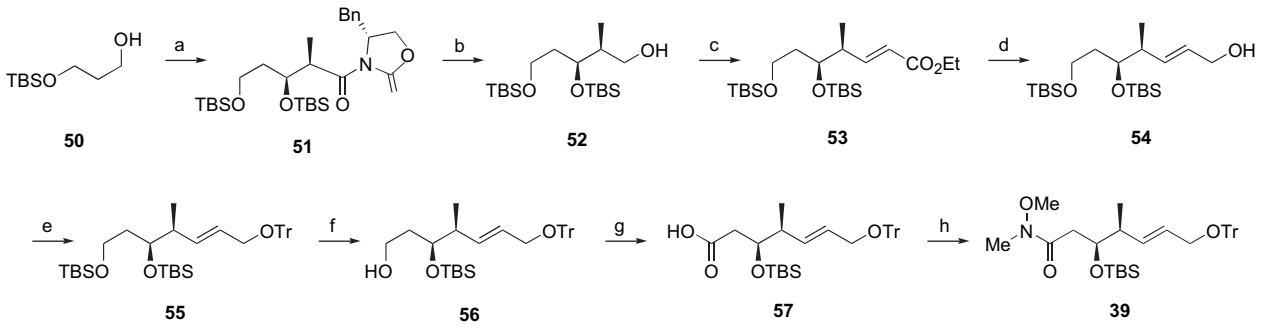
We initially attempted to couple the middle and bottom fragments by the same strategy that was used to make **5**, but the *C*14 epimer of Wittig reagent **8** (not shown) was a white foam that did not well behave in the Wittig reaction. We thus reformulated a strategy, summarized in Figure 3, that used the same top fragment **7** as before, but formed the C9,C10 bond (rather than the C10,C11 bond) in an alkyne addition. Middle fragment **38** and bottom fragment **39** were selected as key intermediates in this route, and their syntheses are shown in Schemes 4 and 5, respectively.

Synthesis of the middle fragment started with preparation of the Evans *anti*-aldol product **41**,[35] which was obtained with 13:1 diastereoselectivity in 71% yield (Scheme 4). The auxiliary was then cleaved with $LiBH_4$, and the resulting diol was protected as the PMB acetal using *p*-anisaldehyde with CSA to give **42** in 65% yield in two steps. Hydroboration of alkene **42** with dicyclohexylborane ($BH_3 \cdot SMe_2$, cyclohexene) afforded the alcohol **43** with the desired *anti*,*anti* configuration in 76% yield. This alcohol was converted to the iodide **44** in 98% yield. An attempt to alkylate **44** with Evans auxiliary was unsuccessful; however, Myers asymmetric alkylation[36] with **45** gave the alkylated product **46** in 88% yield as a single isomer. Removal of the Myers auxiliary with $BH_3 \cdot NH_3$ gave alcohol **47** in 83% yield. TBS protection of the resulting primary alcohol gave **48** in 94% yield. DIBALH cleavage of the PMB acetal gave the product **49** in 84% yield. Oxidation to the aldehyde followed by Corey–Fuchs reaction[37] gave the alkyne **38** in 86% yield in three steps.

To make the bottom fragment **39**, 1,3-propanediol was mono-protected to give **50** (Scheme 5), which was oxidized and subjected to Evans *syn*-aldol reaction to give **51** in 65% yield in two steps. Reduction with $LiBH_4$ gave alcohol **52** (87%), which was oxidized to the aldehyde with the Dess–Martin reagent. Subsequent treatment of the aldehyde with triethyl phosphonoacetate gave the Wadsworth–Horner–Emmons product **53** in 69% in two steps. The ester **53** was reduced with DIBALH to give allylic alcohol **54** in 97% yield, and **54** was protected with a trityl group in 94% yield. The primary TBS group of **55** was deprotected by



Scheme 4. Synthesis of middle fragment **38**. (a) $MgCl_2$, $NaSbF_6$, Et_3N, TMSCl, methacrolein, MeOH, TFA, 71%, dr 13:1. (b) (i) $LiBH_4$, MeOH; (ii) *p*-anisaldehyde, CSA, 65% in two steps. (c) $BH_3 \cdot SMe_2$, cyclohexene then NaOH, H_2O_2, 76%. (d) PPh_3, I_2, imidazole, 98%. (e) LDA, LiCl, 36 h, 88%. (f) $BH_3 \cdot NH_3$, LDA, 83%. (g) TBSCl, imidazole, DMAP, 94%. (h) DIBAL, 84%. (i) (i) $Py \cdot SO_3$, Et_3N, DMSO/CH_2Cl_2; (ii) PPh_3, CBr_4, CH_2Cl_2; (iii) *n*-BuLi, THF, 86% in three steps.

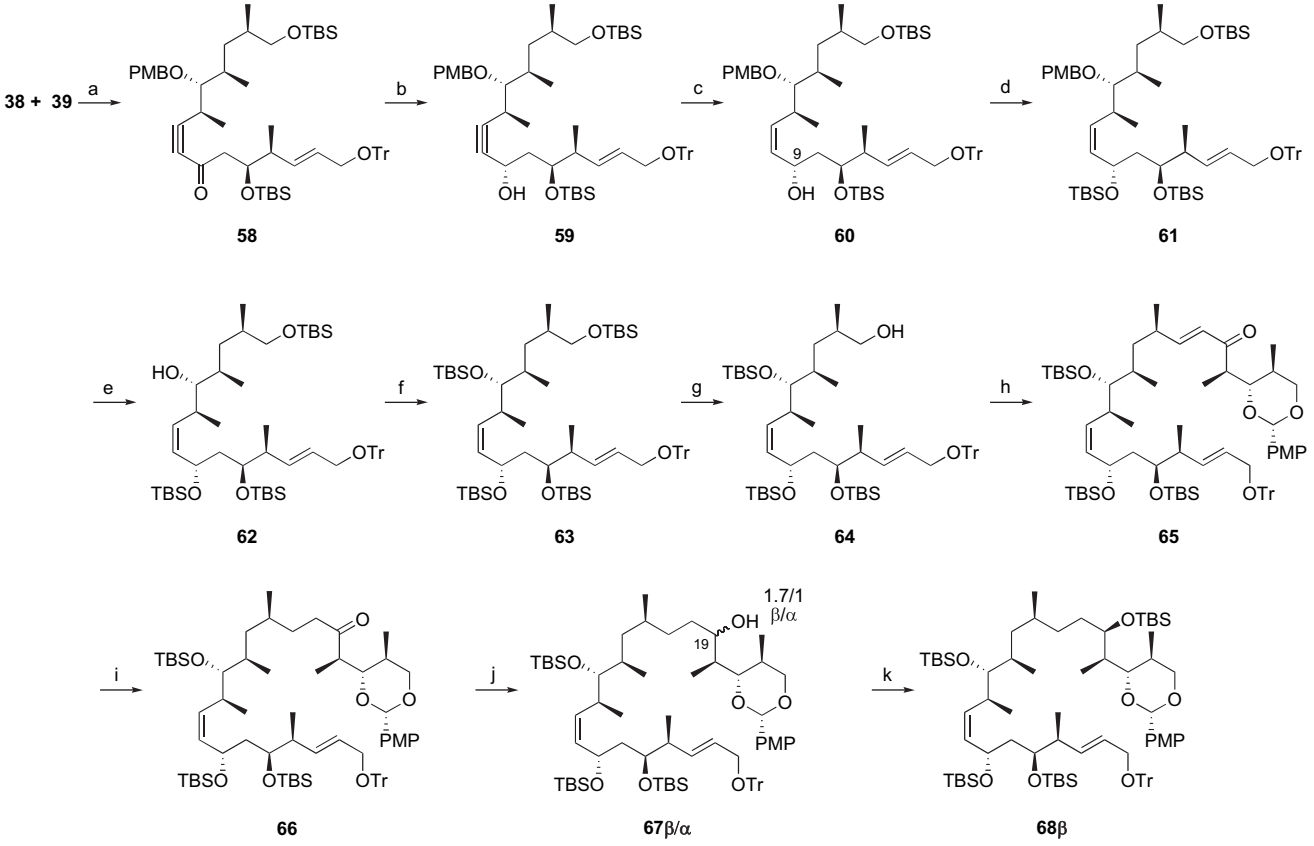


Scheme 5. Synthesis of the bottom fragment **39**. (a) (i) $Py\cdot SO_3$, Et_3N, $DMSO/CH_2Cl_2$; (ii) *n*-Bu_2OTf, DIPEA, 65% in two steps. (b) $LiBH_4$, MeOH, THF, 87%. (c) (i) Dess–Martin; (ii) triethyl phosphonoacetate, NaH, 69% in two steps. (d) DIBAL, 97%. (e) TrCl, DMAP, 94%. (f) HF/Py, 82%. (g) (i) Dess–Martin; (ii) $NaClO_2$, NaH_2PO_4, isobutene, THF/H_2O. (h) $MeNH(OMe)\cdot HCl$, DCC, CH_2Cl_2, 81% in three steps.

HF/pyridine in pyridine to give **56** in 82% yield. This was oxidized to the aldehyde and then to the acid **57**. Finally, coupling with Weinreb's salt by using DCC[38] gave the bottom fragment **39** in 81% in three steps.

The intermediate stage of this synthesis is shown in Scheme 6. Coupling of the middle fragment **38** and bottom fragment **39** parallels related work of Marshall and Jacobsen.[39] The anion of alkyne **38** was added to bottom fragment **39** to give alkynyl ketone **58** in 98% yield. When **58** was subjected to Noyori reduction conditions,[40] a single C9α isomer **59** was formed in 87% yield. About 20 mol % of the (*S*,*S*)-Noyori catalyst was required for rapid, clean reaction. The Noyori product **59** was carefully reduced by using the Lindlar catalyst[41] for 1 h to give the *cis*-alkene **60** in 90% yield. When the reaction time was extended to 1 day, over-reduction of all multiple bonds occurred. The C7,C9 *anti* configuration of **60** was confirmed by ^{13}C NMR analysis of the derived acetonide.[42]

The C9 hydroxy group in **60** was protected with a TBS group to give **61** in quantitative yield. The PMB group was then removed with DDQ to give **62** in 84% yield. The resulting secondary hydroxy group was protected again by a TBS group, giving **63** in 94% yield. Selective deprotection of the primary TBS group was accomplished in 66% yield by treatment



Scheme 6. Intermediate stages of the synthesis of 6,14-bis-*epi*-dictyostatin. (a) *n*-BuLi, THF, 98%. (b) Noyori cat. (20 mol %), *i*-PrOH, 87%. (c) Lindlar cat., H_2, 90%. (d) TBSOTf, 2,6-lutidine, 100%. (e) DDQ, 84%. (f) TBSOTf, 94%. (g) HF/pyridine, 0 °C, 2 days, 66%. (h) (i) Dess–Martin; (ii) **7**, $Ba(OH)_2$, THF/H_2O, 78% (two steps). (i) $NiCl_2$, $NaBH_4$, $MeOH/CH_2Cl_2$, 76%. (j) $NaBH_4$, MeOH, 96%. (k) TBSOTf, 2,6-lutidine, 86%.

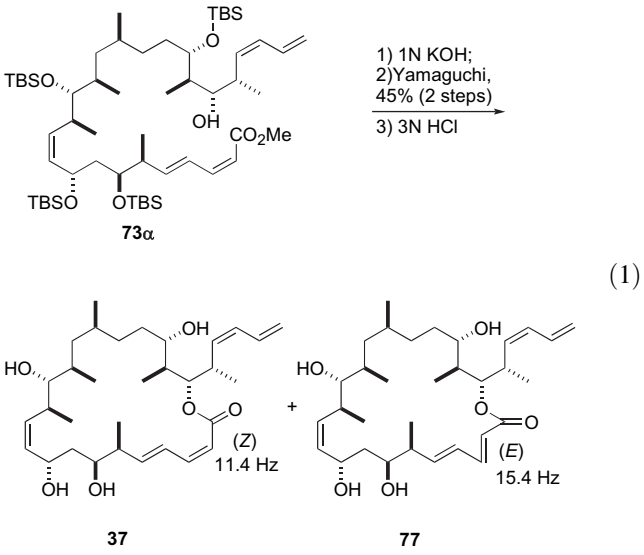
with HF/pyridine complex in buffered pyridine at 0 °C for 2 days to give **64** along with some unselectively deprotected byproducts.

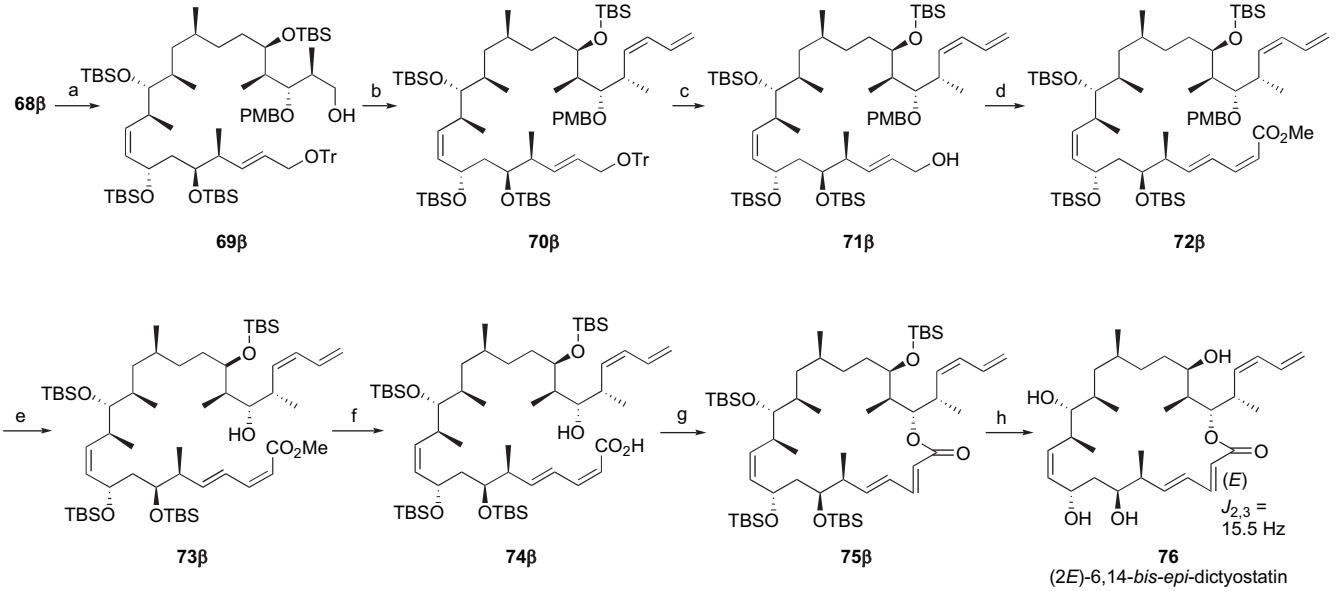
To append the top fragment, **64** was oxidized to the aldehyde, which was then subjected to an HWE reaction with the phosphonate **7**, providing **65** in 78% yield. The alkene in α,β-unsaturated ketone **65** was reduced with nickel boride giving **66** in 76% yield. Some over-reduction of the C4–C5 alkene in the bottom fragment was also observed, but this minor product was separated by chromatography. The C19 ketone was reduced unselectively by $NaBH_4$ yielding a 1.7:1 ratio of diastereomers of **67β/α**, with the β isomer as the major (62%), less polar product and the α isomer as the minor (36%), more polar product. These two diastereomers were separated by silica gel column chromatography and pure **67β** was advanced first. The newly generated C19 hydroxy group in **67** was protected by a TBS group to give **68β** in 86% yield.

The diene elaboration and final stages of the synthesis are shown in Scheme 7. The PMB acetal was cleaved with DIBALH to give the primary alcohol **69β** in 97% yield. Oxidation to the aldehyde and subsequent Nozaki–Hiyama and Peterson *syn*-elimination reactions gave the diene **70β** in 85% yield.

Removal of the trityl group in **70β** with $ZnBr_2$ in CH_2Cl_2/MeOH[43] gave **71β** in 83% yield, which was oxidized to the aldehyde and the (*E*,*Z*)-diene was installed by Still–Gennari reaction in 90% yield. The PMB group in **72β** was removed by DDQ to give **73β** in 90% yield, and the resulting methyl ester was hydrolyzed with 1 N aqueous KOH in EtOH/THF. Although the resulting acid **74β** was exclusively the 2*Z*,4*E*-isomer, macrolactonization by the Yamaguchi method produced mainly the 2*E*,4*E*-lactone **75β**, which was isolated in 68% yield.[44] The isomerization was clearly revealed by a 15.5 Hz coupling constant between H2 and H3 in **75β**, whereas the (2,3*Z*) dictyostatins **1** and **5** have a coupling constant of about 11 Hz. The formation of this geometric isomer might be due to a reversible Michael type addition of 4-DMAP to the activated ester during the lactonization reaction.[45] Final global deprotection of the TBS groups yielded **76** in 25% yield.

The *C*19α-epimer was prepared from **67α** by using the same reaction pathways detailed in Schemes 6 and 7 (not shown, but fully described in Supplementary data). In this case, after hydrolysis of **73α** and Yamaguchi lactonization (Eq. 1), two inseparable spots were observed on TLC. In the final global TBS deprotection step, the (2*Z*,4*E*)-isomer **37** (less polar, 45%) was isolated along with the isomerized (2*E*,4*E*)-isomer **77** (more polar, 15%) in a 3:1 ratio. Coupling constant measurements again secured the alkene geometries.





Scheme 7. Final stages of the synthesis of 6,14-bis-*epi*-dictyostatin. (a) DIBALH, 97%. (b) (i) Dess–Martin; (ii) $CrCl_2$, **29**, NaH, 85% (three steps). (c) $ZnBr_2$, CH_2Cl_2/MeOH, 83%. (d) (i) Dess–Martin; (ii) Still–Gennari, 90% (two steps). (e) DDQ, 90%. (f) 1 N KOH, EtOH/THF. (g) Yamaguchi, 68% (two steps). (h) 3 N HCl, 15%.

2.1.3. Synthesis of (−)-dictyostatin. As this work progressed, we compared spectral data of the intermediates and products with both dictyostatin **1** and discodermolide **2** and began to draw conclusions about the structure of dictyostatin. This exercise was greatly assisted by two-dimensional NMR spectroscopy because it was generally possible to assign all or nearly all ^{1}H and ^{13}C resonances with confidence. First, while all of the isomers made to that date were clearly different from dictyostatin in material respects, their spectra were related enough for us to conclude that the two-dimensional structure proposed by Pettit was correct. Second, the spectra from the series of compounds with the β-hydroxy group at C19 clearly resembled both dictyostatin and discodermolide more than the series with the α-hydroxy group, so we concluded that dictyostatin and discodermolide had the same configuration at the C19–C22 stereotetrad.

The comparisons of resonances in the middle and bottom portions of the molecules were very revealing. First, the resonances of compound **5** with the 'discodermolide-like' middle fragment closely resembled their counterparts of dictyostatin **1** and differed from those of the 6,14-bis-*epi* series, for example, compound **36**. This suggested that dictyostatin has the same configurations as discodermolide for the C12–C14 stereotriad, and not the configuration assigned in compound **4**. Finally, none of the resonances of the spectra in the bottom fragment region closely resembled dictyostatin, and all exhibited significant differences centered in the region of H6/C6 and H7/C7. We thus concluded that this *syn* configuration as assigned in compound **4** was not correct for dictyostatin, and now the clear stereochemical analogy between the top and middle fragments of dictyostatin and discodermolide suggested that the bottom fragment of dictyostatin probably also had the same configurations as discodermolide.

The only remaining configuration to assign was the isolated stereocenter at C16, which has no analogy in discodermolide. The need to select between these two isomers was preempted by the appearance of the paper by Paterson and co-workers suggesting that dictyostatin was **1** (C16-β) based on detailed NMR analysis and modeling.[16] We accordingly decided to focus on making structure **1** as quickly as possible to finally resolve the stereochemical issues.

The strategy for the synthesis of **1** followed closely from the prior work and is summarized in Figure 4. The same disconnections as for the 6,14-bis-*epi* series were used, providing the standard top fragment **7** along with new middle fragment **78** and bottom fragment **79**.

Over the course of the work, we developed two routes to bottom fragment **79**, and both are summarized in Scheme 8. The first route was built on the established route to *syn* alcohol **52** (see Scheme 5). This compound was converted to the *anti*-isomer **82** via tosylation to give **80** and elimination to alkene **81**. Hydroboration with 9-BBN and subsequent oxidation provided a 9:1 mixture **82** and **52**.[46] These were readily separable, and **82** was isolated isomerically pure in 72% yield. The remaining sequence of steps to make **79** followed closely after the analogous sequence described in Scheme 5. The 15 step process starting ultimately from 1,3-propanediol provided key intermediate **79** in 9.5% overall yield.

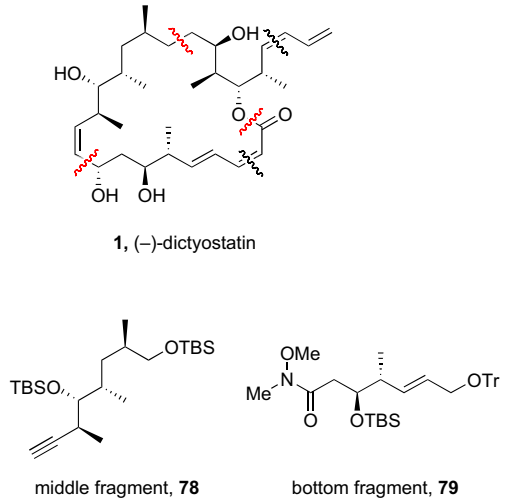
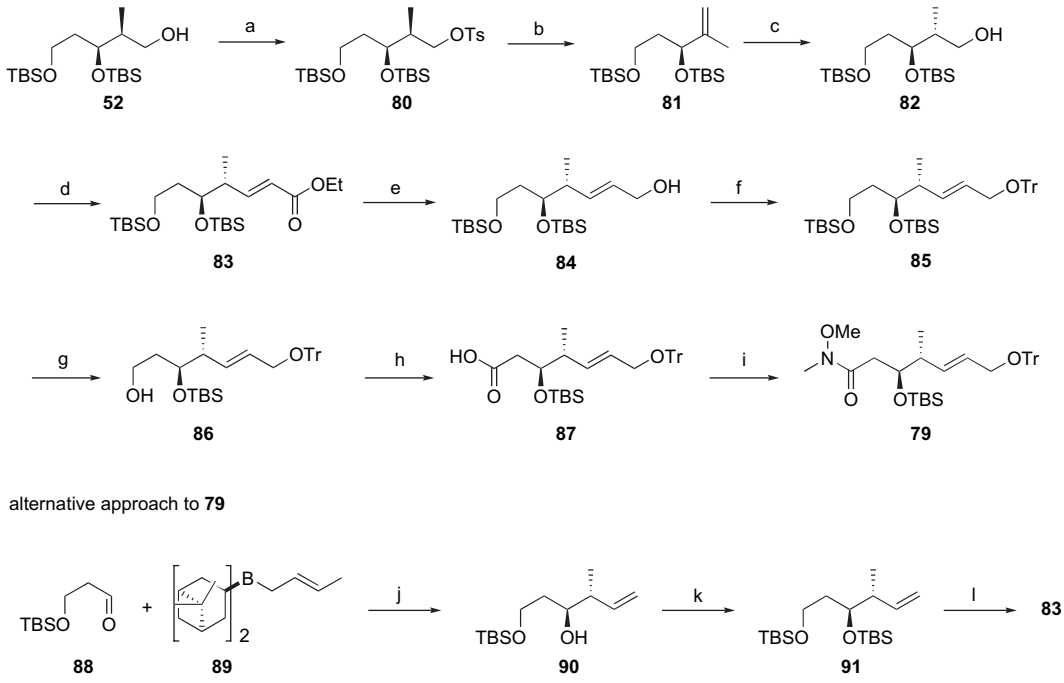


Figure 4. Strategy for the synthesis of (−)-dictyostatin **1**.

We found that the indirect process of converting *syn* **52** to *anti* **82** could be shortened by beginning with Brown crotylation[47] of TBS-protected 3-hydroxypropanal **88** with **89**, which directly provided *anti*-alcohol **90**. Protection of the alcohol with TBSCl, OsO_4-catalyzed dihydroxylation, and diol cleavage with periodate, followed by HWE homologation intersected the prior route at unsaturated ester **83**. This second generation route reduced the number of steps to **79** from 15 to 11 and improved the overall yield (from 1,3-propanediol) to 27%.

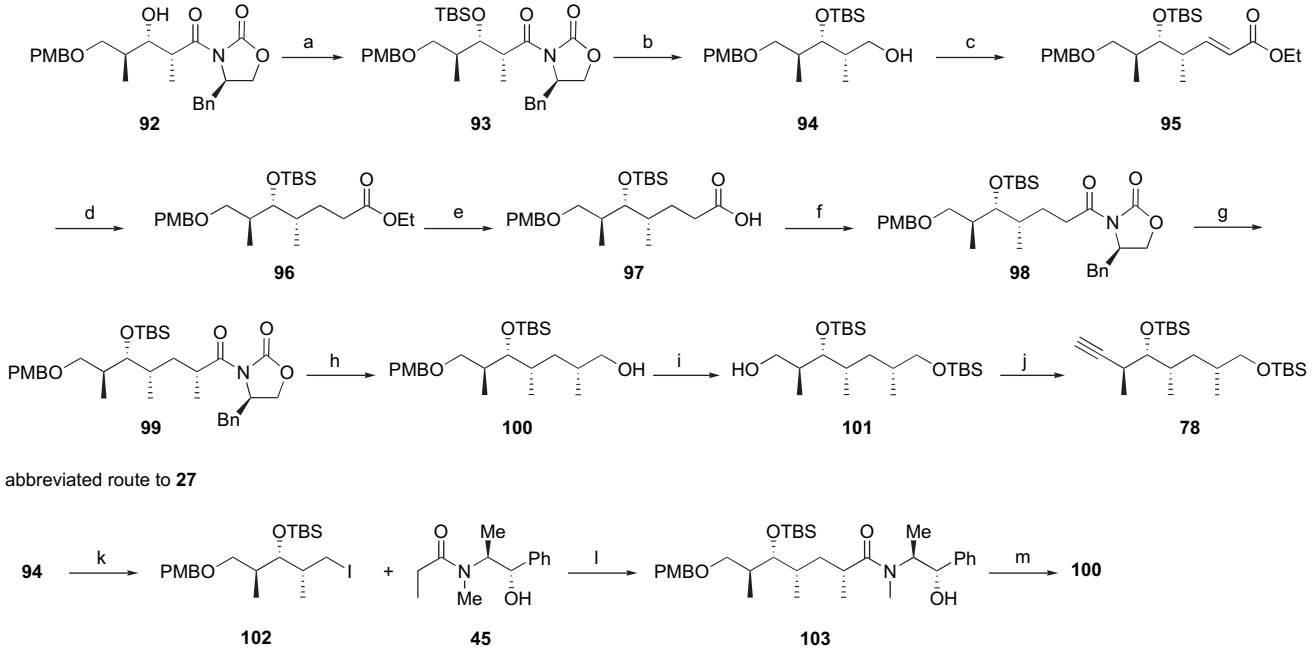
The middle fragment **78** was also prepared in two ways as summarized in Scheme 9. The secondary alcohol of known compound **92**,[48] prepared in four steps from the (*S*)-Roche ester, was TBS-protected and the Evans auxiliary was removed with $LiBH_4$ to give alcohol **93**. Oxidation to the aldehyde and HWE reaction gave the ester **95**. Alkene reduction with nickel boride to **96**, saponification with LiOH to **97**, and coupling with the Evans auxiliary gave amide **98**. Asymmetric methylation provided diastereomer **99** exclusively. Removal of the chiral auxiliary by reduction to give **100**, TBS protection, and PMB deprotection with DDQ gave primary alcohol **101**. Oxidation to the aldehyde and Corey–Fuchs reaction gave the alkyne **78**. This route from **92** to **78** proceeded in 16% overall yield. An improved route to **78** involved conversion of **94** to its iodide and asymmetric alkylation with Myers' auxiliary **45** to give amide **103**. Removal of the auxiliary as usual intersected the prior route at **100**. This second generation approach to **78** from **92** doubled the overall yield to 31%.

The bottom and middle fragments were then coupled and the synthesis of dictyostatin was advanced as summarized in Scheme 10. The Weinreb amide **79** was reacted with 2 equiv of the anion from alkyne **78** to give the coupling product **104** in high yield. Reduction of **104** with the (*S*,*S*)-Noyori catalyst gave one isomer of the alcohol **105**, whose alkyne moiety was reduced by Lindlar hydrogenation to alkene **106**. The newly generated secondary hydroxyl group was protected with TBSOTf to give **107**. Selective deprotection of the primary TBS group with HF/pyridine in buffered pyridine at 0 °C gave **108** in moderate yield. The aldehyde

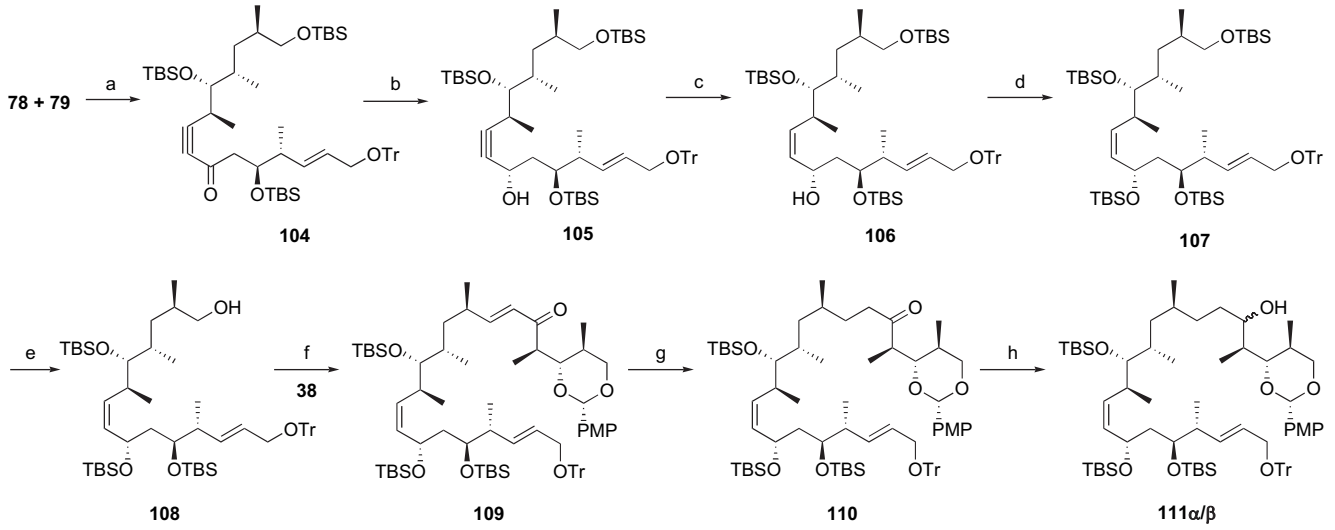


Scheme 8. Two routes to the dictyostatin bottom fragment **79**. (a) TsCl, pyridine, 90%. (b) NaI, DBU, glyme, 70%. (c) 9-BBN, 72%. (d) (i) Dess–Martin; (ii) Horner–Wadsworth–Emmons, 59% (two steps). (e) DIBAL–H, CH_2Cl_2, 97%. (f) TrCl, 4-DMAP, pyridine. (g) HF/pyridine, pyridine, THF, 89% (two steps). (h) (i) Pyridine/SO_3, Et_3N, DMSO–CH_2Cl_2; (ii) $NaClO_2$, $NaHPO_4$, 2-methyl-2-butene, THF/H_2O. (i) NH(Me)(OMe)·HCl, DCC, Et_3N, DMAP, CH_2Cl_2, 73% (three steps). (j) THF, hexane, −90 °C, 55%, 95% ee. (k) TBSCl, imidazole, DMAP, 95%. (l) OsO_4, NMO, THF, H_2O, then NaIO4; (ii) Horner–Wadsworth–Emmons, 83% (two steps).

formed by Dess–Martin oxidation was reacted with the phosphonate **7** (Fig. 2) under HWE conditions to give the conjugated ketone **109** in good yield. Selective reduction with nickel boride gave the ketone **110**, which was again reduced in a purposefully unselective manner with $NaBH_4$ to give a 2.4:1 mixture of the isomers of **111**, with the β isomer, necessary for preparation of (–)-dictyostatin, predominating. The isomers of **111** were readily separated by silica gel chromatography. Later, a 5:1 ratio favoring **111** was obtained by use of the bulkier reducing agent LiAl(O-*t*-Bu)$_3$H, whereas a 1:1 ratio of the α and β isomers was obtained when (L)-Selectride was employed.

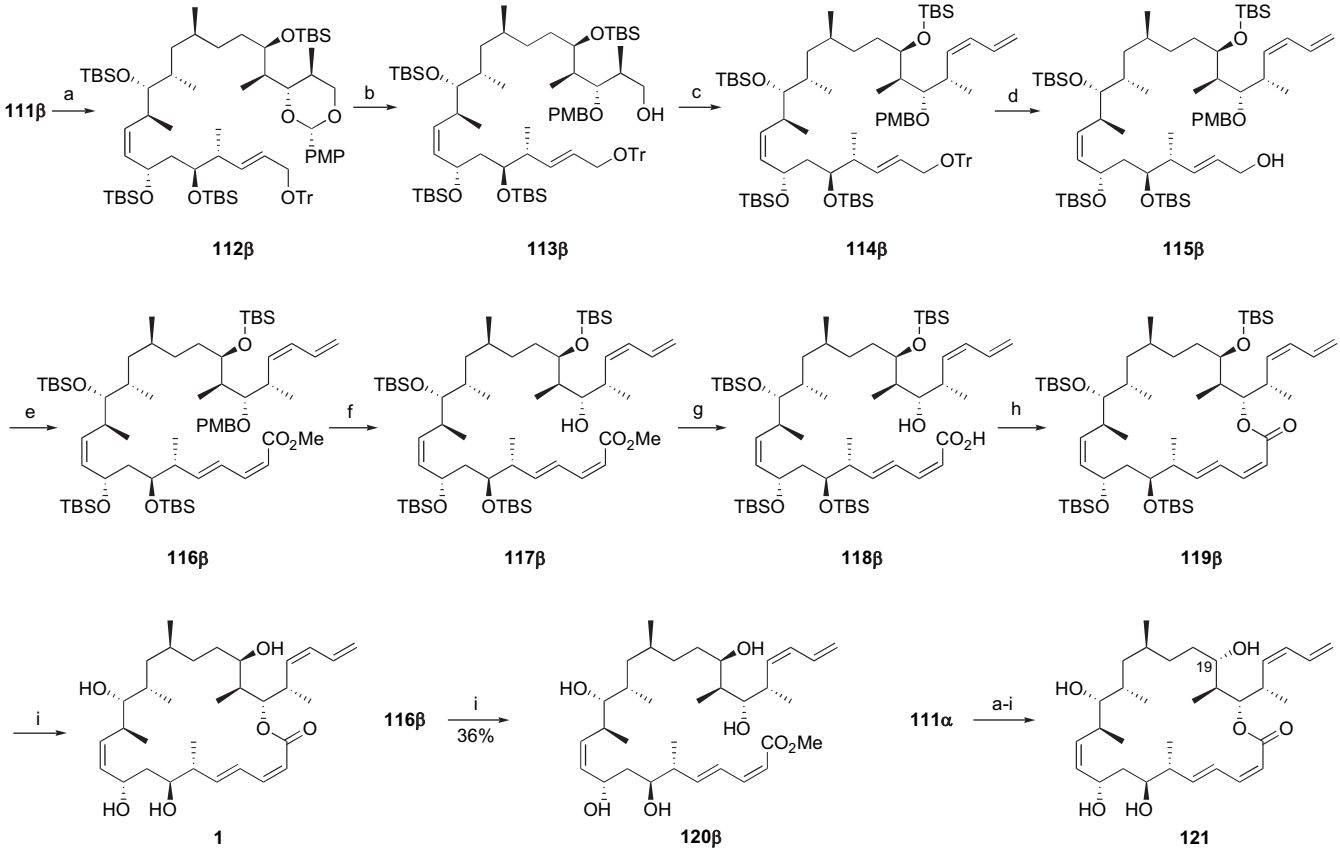


Scheme 9. Two routes to the dictyostatin middle fragment **78**. (a) TBSOTf, 2,6-lutidine. (b) $LiBH_4$, MeOH, THF, 90%. (c) (i) Pyridine/SO_3, Et_3N, DMSO/CH_2Cl_2; (ii) Horner–Wadsworth–Emmons, 70%. (d) $NiCl_2$, $NaBH_4$, 97%. (e) 1 N LiOH, acetone. (f) Evans auxiliary, PivCle, Et_3N, LiCl, 70% (two steps). (g) NaHMDS, MeI, 74%. (h) $LiBH_4$, 83%. (i) (i) TBSCl, imidazole; (ii) DDQ, 81% (two steps). (j) (i) Pyridine/SO_3, DMSO/CH_2Cl_2; (ii) PPh_3, CBr_4; (iii) *n*-BuLi, 73% (three steps). (k) PPh_3, I_2, imidazole, DIPEA; (l) LDA, LiCl, **45**, 87% (two steps). (m) $BH_3 \cdot NH_3$, LDA, 96%.



Scheme 10. Intermediate stages of the synthesis of (−)-dictyostatin **1**. (a) *n*-BuLi, THF, 93%. (b) (*S*,*S*)-Noyori catalyst (20 mol %), *i*-PrOH, 79%. (c) Lindlar catalyst, H_2 (balloon), toluene, 91%. (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 99%. (e) HF/pyridine, pyridine, THF, 0 °C, 1 day, 67%. (f) (i) Dess–Martin oxidation; (ii) $Ba(OH)_2$, **7**, THF/H_2O, 80% (two steps). (g) $NiCl_2$, $NaBH_4$, MeOH/THF, 76%. (h) $NaBH_4$, MeOH/THF, 70% (β), 29% (α).

The final stages of the synthesis paralleled the established steps, as summarized in Scheme 11. Alcohol **111β** was protected with a TBS group to give **112β**, whose PMB acetal was cleaved with DIBALH to give alcohol **113β**. Oxidation to the aldehyde followed by Nozaki–Hiyama addition with **29** and Peterson-type elimination installed the (*E*,*Z*)-diene to give **114β** in high yield. The allylic trityl group was removed with $ZnBr_2$ to give alcohol **115β**. Dess–Martin oxidation to the aldehyde and Still–Gennari reaction gave the (*E*,*Z*)-conjugated ester **116β**. The PMB group was removed with DDQ to give **117β** and saponification with aqueous KOH in EtOH/THF gave acid **118β** in 61% yield after



Scheme 11. Final stages of the synthesis of dictyostatin. (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 99%. (b) DIBAL–H, CH_2Cl_2, 88%. (c) (i) Dess–Martin oxidation; (ii) **29**, $CrCl_2$, THF; (iii) NaH, THF, 89% (three steps). (d) $ZnBr_2$, CH_2Cl_2/MeOH, 77%. (e) (i) Dess–Martin oxidation; (ii) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, 18-crown-6, THF, 78% (two steps). (f) DDQ, CH_2Cl_2/H_2O, 88%. (g) 1 N KOH, EtOH/THF, 61%. (h) 2,4,6-Trichlorobenzoyl chloride, Et_3N, THF then 4-DMAP (10 equiv), toluene, 78%. (i) 3 N HCl/MeOH, THF, 55%.

purification by flash chromatography. Yamaguchi macrolactonization of the purified acid now gave **119β** in 78% yield after flash chromatographic purification. Global deprotection with 3 N HCl in MeOH/THF and careful purification gave ~5 mg of (−)-dictyostatin **1**. There were at least two minor byproducts from the macrolactonization/deprotection sequence whose yields were estimated to be <15%. Neither sample was isolated in highly pure form, but based on comparison of ^{1}H NMR spectra from the chromatographic fractions with spectra of related pure samples, we deduced that one of these side products was the *C*2,*C*3 *E*-isomer (believed to arise during the macrolactonization), while the other was a *trans*-lactonized product with the lactone formed between O19 and C1 with a free O21 hydroxy group (believed to arise during the deprotection).[49]

The Paterson group completed an independent total synthesis of **1** roughly concurrently with us, and the two synthetic samples and one natural sample (from Wright) of (−)-dictyostatin were identical in all respects. The $[\alpha]_D^{25}$ of our sample was −22.6 (*c* 0.27, MeOH), in satisfactory agreement with the values of Pettit (−20, *c*, 0.12, MeOH), Wright (−27.4, *c* 0.16, MeOH), and Paterson (−32.7, *c* 0.22, MeOH), so both the relative and absolute configurations of **1** are confirmed. An open-chain analog of **1** was prepared by global desilylation of **116β** to give tetraol ester **120β**. Finally, the α-epimer at C-19, **111α**, was taken through the same sequence of steps as shown in Scheme 11 to provide 19-*epi*-dictyostatin **121** in comparable overall yield to the β-series (see Supplementary data). Thus, the chapter on the structural assignment of dictyostatin was closed.

2.2. Biology

The target compounds, **1**, **3**, **5**, **37**, **76**, **77**, **120β**, and **121**, were screened for cellular and biochemical activities. The effects of compounds on cellular microtubules were quantified by tubulin immunostaining. In this assay, microtubule-stabilizing agents cause a dramatic increase in tubulin immunoreactivity due to the formation of bright polymer bundles with intense staining.[13c] Human cervical carcinoma HeLa cells were treated for 21 h with 10 two-fold serial dilutions of test compounds in collagen-coated 384 well microplates, fixed and immunostained with an anti-α-tubulin antibody followed by an FITC conjugated secondary antibody as previously described.[2] Paclitaxel and discodermolide **2** were included as known microtubule-stabilizing agent controls. Fluorescence images of 1000 individual cells were acquired on an ArrayScan II (Cellomics, Inc) automated microscope and analyzed for tubulin staining intensity as described.[2,49] Extrapolation of minimum detectable effective concentrations (MDECs)[50] from 10-point concentration-dependence curves revealed that dictyostatin **1** caused microtubule bundling at low nanomolar concentrations, analogs **3**, **120β**, and **121** at submicromolar concentrations (about 20-fold less potent than the parent compound), and compounds **5**, **76**, **37**, and **77** to have little effect on microtubule morphology (Table 1).

These same analogs were examined for their antiproliferative activities against cultures of human ovarian carcinoma 1A9 cells and their paclitaxel-resistant mutants, 1A9/Ptx10 and 1A9/Ptx22.[51] Each of these resistant lines contains single mutations in the major β-tubulin gene that confer to the cells, which do not express drug efflux pumps, appreciable tolerance to paclitaxel.[52] Paclitaxel had subnanomolar potency against the parental 1A9 cells, but the mutant cells showed ca. 90- and 70-fold resistance to the drug (Table 1). The antiproliferative activities, shown as 50% growth inhibitory concentrations (GI_{50}s), of the agents paralleled the activities noted in the cellular microtubule assays, but the GI_{50} values were typically two- to seven-fold lower than the MDECs. Although not a potent agent, compound **3** showed an interesting property in that the 1A9/Ptx10 cells, which express β-tubulin with a Phe270->Val alteration, were 27-fold resistant to it as compared to the parental 1A9 cells. This suggested that the C6 and/or C16 methyl substituents in **1** could be in close proximity to Phe270 in the taxane binding site.

The abilities of the new compounds to cause tubulin polymerization were determined under reaction conditions with purified bovine brain tubulin (1 mg/mL) in the presence or absence of microtubule-associated proteins (MAPs,

Table 1. Biological activities of dictyostatin (**1**) and analogs as compared to discodermolide (**2**) and paclitaxel

	Cellular				In Vitro	
	MDEC[a] for tubulin polymer increase, nM±SD (*N*)	GI_{50},[b] nM (fold resistance) (*N*=4)			Tubulin[c] polymerized by 50 μM test agent, % (*N*≥3)	Inhibition of binding of [^{3}*H*]paclitaxel to tubulin polymer, % (*N*≥3)[d]
Test agent		1A9	1A9/Ptx10	1A9/Ptx22		
1	5.4±1.9 (4)	0.69±0.80	3.2±2.4 (5)	1.3±1.0 (2)	99±4	75±5 (3)
2	65±0 (2)	1.7±1.2	6.2±3.6 (4)	7.0±8.4 (4)	98±5	76±6 (4)
3	328±142 (2)	693±580	18,400±2010 (27)	625±9	52±2	27±8 (6)
5	4375±625 (2)	20,900±400	>50,000 (>2)	11,560±1180	2±2	0±1 (3)
37	>5000 (4)	28,000±1000	26,000±500	30,000±1000	5±1	0±1 (3)
76	>5000 (4)	310±40	780±200 (3)	790±560 (3)	1±1	0±0 (3)
77	>5000 (4)	25,000±2000	25,000±1000	30,000±1000	5±4	0±1 (3)
120β	219±36 (4)	56±16	79±13	85±2	39±7	42±1 (3)
121	284±108 (4)	21±14	120±60 (6)	43±12 (2)	30±2	7±2 (3)
Paclitaxel	5.2±0.4 (4)	0.71±0.11	64±8 (90)	51±9 (72)	89±6	—

[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, 15 min at 20 °C, centrifugation, and Lowry determination of remaining soluble tubulin.
[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.

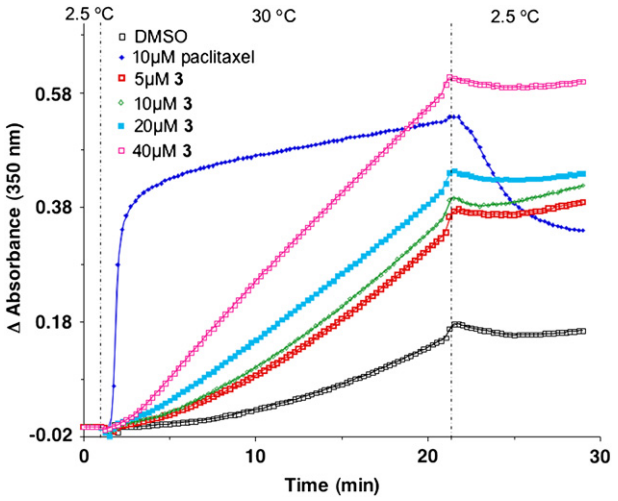


Figure 5. Assembly of bovine brain tubulin induced by compound **3** in comparison to paclitaxel.

0.75 mg/mL) and GTP (100 μM). Test agents were initially screened at 10 and 40 μM. In these experiments, test agent-induced assembly of soluble tubulin into polymer, with respect to the presence and absence of cofactors and at different temperatures, was monitored by turbidimetry in temperature-controlled spectrophotometers. The initial temperature was set at 0 or 2.5 °C (depending upon the instrument used) and then rapidly raised to 10, 20, and 30 °C in succession. This permitted the determination of both the temperature at which a test agent-induced assembly and the extent of agent-induced assembly. The temperature increases were followed by a rapid decrease in temperature back to the initial temperature to determine the cold-stability of the polymer formed.

As we have recently reported, the effects of dictyostatin **1** and discodermolide **2** were similar, and both molecules were far more potent than paclitaxel.[2] Compounds **3**, **120β**, and **121** all showed some activity in this assay, while the remaining agents were inactive. An example of concentration-dependent trace, wherein a single temperature jump from 2.5 to 30 °C was used, for compound **3** is shown in Figure 5. All test agents at 50 μM were then incubated with 10 μM tubulin for 15 min at 20 °C, reaction mixtures were centrifuged, and the percentage of the remaining soluble tubulin was measured. Again, compound **1** was by far the most potent, but compounds **3**, **120β**, and **121** showed moderate activity (Table 1).

Finally, all compounds were tested at 4 μM for their ability to compete with 2 μM [^{3}H]paclitaxel for its binding to 2 μM preassembled bovine brain microtubules. Compounds **120β**, **3**, and **121** showed competitive activity in this assay, although the latter compound did not compete as well as one might expect based on the results from the other assays.

3. Conclusions

In summary, we have provided here the full details of synthesis of dictyostatin **1**, its open-chain methyl ester analog, assorted C6, C16, and *C*19 epimers, and two macrolactone isomers with (*E*,*E*) geometry at C2–C5. The biological evaluation of the compounds revealed a wide range of activities resulting from these very small structural changes. The SAR determined includes the following. The macrolactone is important but not a full requisite for microtubule stabilization and antiproliferative actions. The β configuration of the hydroxyl at C19 is preferred, and the configuration of the C6 and C14 methyl groups is important. The natural *E*/*Z* geometry of the macrocyclic diene also appears to be crucial. Finally, either the C6 or C16 methyl appears to interact with a phenylalanine in the paclitaxel binding site. This SAR provided a starting point for the preparation of more potent dictyostatin analogs, as described elsewhere.[21,23,53]

4. Experimental

4.1. Ethyl (4*R*,5*S*,2*E*)-5,7-bis(*tert*-butyldimethylsilyloxy)-4-methylhept-2-enoate (83)

From **82**: a solution of triethyl phosphonoacetate (3.5 mL, 17.6 mmol) was added to a cooled (0 °C), stirred suspension of NaH (0.43 g, 17.0 mmol, 95% dispersion in mineral oil) in THF (46 mL) dropwise over 10 min. The mixture was brought to room temperature with a water bath (30 min) and then cooled back to −78 °C, and the aldehyde (2.73 g, 7.58 mmol) in THF (5 mL) was added. The resulting mixture was stirred for 1 h at 0 °C, and then pH≈7 phosphate buffer solution (10 mL) and Et_2O (50 mL) were added. The mixture was allowed to warm to room temperature, and the phases were separated. The organic phase was washed with saturated NH_4Cl solution (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated to give oily crude product. Purification by flash chromatography (EtOAc/hexane 1:9) afforded pure ester **83** (2.92 g, 59% in two steps) as a colorless oil: IR ($CHCl_3$) 2956, 2930, 2857, 1724, 1651, 1472, 1463, 1367, 1256, 1180, 1098, 1036, 836, 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (dd, J=15.8, 7.6 Hz, 1H), 5.74 (d, J=15.8 Hz, 1H), 4.19 (q, J=7.1 Hz, 2H), 3.79 (ddd, J=6.7, 4.7, 4.4 Hz, 1H), 3.59 (m, 2H), 2.43 (m, 1H), 1.53 (m, 2H), 1.22 (t, J=7.1 Hz, 3H), 1.01 (d, J=6.8 Hz, 3H), 0.83 (s, 18H), 0.02 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 150.9, 121.3, 71.8, 59.9, 59.5, 42.0, 36.8, 25.82, 25.78, 26.1, 18.1, 18.0, 14.4, 14.2, −4.6, −4.7, −5.4; LRMS (EI) 415 $(M-CH_3)^+$, 373, 303, 147; HRMS (EI) calcd for $C_{21}H_{44}O_4Si_2$ 415.2710 $(M-CH_3)^+$, found 415.2712; $[\alpha]_D^{20}$ +3.8 (*c* 0.21, $CHCl_3$).

4.2. (4*R*,5*S*,2*E*)-5,7-Bis(*tert*-butyldimethylsilyloxy)-4-methylhept-2-en-1-ol (84)

DIBALH (26.5 mL, 26.5 mmol, 1.0 M solution in hexane) was added to the ester **83** (3.14 g, 7.30 μmol) in CH_2Cl_2 (35 mL) at −78 °C dropwise and stirred for 1 h. The reaction mixture was quenched by adding EtOAc (5 mL) and saturated sodium potassium tartrate solution (20 mL), followed by vigorous stirring for 4 h. The aqueous phase was extracted with CH_2Cl_2 (3×30 mL), and the combined organic layers were washed with brine (10 mL). After drying over $MgSO_4$ and evaporation under vacuum, flash column chromatography (hexane/EtOAc 4:1) provided 2.75 g of alcohol **84** (97%) as a colorless oil: IR ($CHCl_3$) 3349, 2956, 2928,

2857, 1471, 1462, 1255, 1099, 836, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.57 (m, 2H), 4.03 (m, 2H), 3.70 (ddd, J=9.7, 6.0, 3.8 Hz, 1H), 3.59 (m, 2H), 2.27 (m, 1H), 2.00 (s, 1H), 1.53 (q, J=6.5 Hz, 2H), 0.96 (d, J=6.9 Hz, 3H), 0.85 (s, 9H), 0.84 (s, 9H), 0.00 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.7, 129.2, 72.4, 63.6, 60.1, 41.8, 36.3, 25.9, 18.2, 18.0, 15.1, 10.7, −4.6, −5.4; LRMS (EI) 370 $(M-H_2O)^+$, 303, 171, 147; HRMS (EI) calcd for $C_{20}H_{42}O_2Si_2$ 370.2723 $(M-H_2O)^+$, found 370.2725; $[\alpha]_D^{20}$ −3.0 (*c* 0.57, $CHCl_3$).

4.3. ((4*R*,5*S*,2*E*)-5,7-Bis(*tert*-butyldimethylsilyloxy)-4-methylhept-2-enyloxy)triphenylmethane (85)

Trityl chloride (4.1 g, 14.7 mmol) and DMAP (1.8 g, 14.7 mmol) were added to a solution of alcohol **84** (2.75 g, 7.1 mmol) in pyridine (71 mL). The mixture was heated to reflux for 18 h, cooled to ambient temperature, and added to a solution of saturated $CuSO_4$ (200 mL). The mixture was extracted with Et_2O (2×20 mL), and the combined organic extracts were washed saturated $CuSO_4$ (2×20 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash column chromatography (EtOAc/hexane 1:19) provided **85** (4.46 g, quantitative) as a pale yellow oil: IR ($CHCl_3$) 2954, 2856, 1471, 1448, 1254, 1095, 835, 773, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 6H), 7.32 (m, 9H), 5.79 (dd, J=15.6, 6.7 Hz, 1H), 5.65 (dd, J=15.7, 5.0 Hz, 1H), 3.85 (m, 1H), 3.74 (m, 1H), 3.66 (d, J=4.9 Hz, 1H), 2.43 (m, 1H), 1.70 (q, J=6.5 Hz, 2H), 1.21 (d, J=6.9 Hz, 3H), 0.99 (s, 9H), 0.97 (s, 9H), 0.154 (s, 3H), 0.150 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 134.2, 128.7, 127.7, 126.9, 126.8, 86.8, 72.6, 65.1, 60.2, 42.1, 36.6, 26.0, 18.3, 18.1, 15.3, −4.4, −5.3; LRMS (ESI) 653.3 $[M+Na]^+$; HRMS (ESI) calcd for $C_{39}H_{58}O_3Si_2Na$ 653.3822 $[M+Na]^+$, found 653.3851; $[\alpha]_D^{20}$ −1.9 (*c* 0.42, $CHCl_3$).

4.4. (3*S*,4*R*,5*E*)-3-(*tert*-Butyldimethylsilyloxy)-4-methyl-7-(trityloxy)hept-5-en-1-ol (86)

HF/pyridine in pyridine (40 mL, prepared by slow addition of 12 mL pyridine to 3 mL HF/pyridine complex, followed by dilution with 25 mL THF) was added to a solution of TBS ether **85** (4.46 g, 7.07 mmol) in THF (10 mL). The mixture was stirred overnight at room temperature and quenched with saturated $NaHCO_3$ (100 mL). The aqueous layer was separated and extracted with Et_2O (3×50 mL). The combined organic layers were washed with saturated $CuSO_4$ (3×50 mL), dried over $MgSO_4$, and concentrated. Flash column chromatography (EtOAc/hexane 1:4) afforded 3.26 g (89%) of alcohol **86** as a colorless oil: IR ($CHCl_3$) 3407, 2955, 2928, 2856, 1490, 1471, 1448, 1254, 1058, 1031, 836, 773, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (m, 6H), 7.37 (m, 9H), 5.78 (dd, J=15.6, 6.5 Hz, 1H), 5.73 (dt, J=15.5, 4.8 Hz, 1H), 3.91 (m, 1H), 3.82 (d, J=5.9 Hz, 2H), 3.69 (d, J=4.4 Hz, 2H), 2.51 (m, 1H), 2.22 (br, 1H), 1.77 (m, 2H), 1.13 (d, J=6.8 Hz, 3H), 1.03 (s, 9H), 0.21 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 134.1, 128.6, 127.7, 127.1, 126.9, 86.8, 74.3, 64.9, 60.4, 42.0, 34.8, 25.9, 18.0, 14.5, −4.4, −4.6; LRMS (ESI) 539.2 $[M+Na]^+$; HRMS (ESI) calcd for $C_{33}H_{44}O_3Si_1Na$ 539.2957 $[M+Na]^+$, found 539.2976; $[\alpha]_D^{20}$ −2.8 (*c* 2.0, $CHCl_3$).

4.5. (3*S*,4*R*,5*E*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*-4-dimethyl-7-(trityloxy)hept-5-enamide (79)

Sulfur trioxide pyridine complex (3.02 g, 19.1 mmol) was added to a stirred solution of alcohol **86** (3.26 g, 6.31 mmol) and triethylamine (2.6 mL, 19.1 mmol) in anhydrous CH_2Cl_2 (6 mL) and DMSO (12 mL) at 0 °C. The reaction mixture was stirred at ambient temperature for 1 h. The mixture was diluted with Et_2O (100 mL) and washed with aqueous 0.5 N HCl (50 mL) and brine (10 mL). The separated organic layer was dried over $MgSO_4$. Filtration and concentration, followed by short flash column chromatography (hexane/EtOAc 4:1), provided the crude aldehyde as a colorless oil, which was used without further purification. A solution of the aldehyde in THF (25 mL) and H_2O (12 mL) was treated with 2-methyl-2-butene in THF (2 M, 18 mL, 9.0 mmol), $NaH_2PO_4 \cdot H_2O$ (2.6 g, 18.8 mmol), and $NaClO_2$ (2.1 g, 18.6 mmol). The reaction mixture was stirred for 2 h, diluted with 1 N HCl (20 mL), and extracted with CH_2Cl_2 (2×40 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and the crude acid **87** was used for the next reaction without further purification. *N*,*O*-Dimethylhydroxylamine hydrochloride (0.62 g, 6.36 mmol), Et_3N (0.88 mL, 6.31 mmol), and DMAP (0.63 mmol) were successively added to a solution of the crude acid in CH_2Cl_2 (10 mL). The reaction mixture was cooled to 0 °C and then DCC (1.30 g, 6.30 mmol) was added. The mixture was stirred at ambient temperature for 15 h and filtered. The filtrate was washed with 0.5 N HCl, saturated aqueous $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, and concentrated. Purification by column chromatography over silica gel (hexane/EtOAc 4:1) gave the Weinreb amide **79** (2.65 g, 73% in three steps) as a colorless oil: IR ($CHCl_3$) 2956, 2929, 2855, 1663, 1448, 1252, 1083, 1032, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (m, 6H), 7.37 (m, 9H), 5.89 (dd, J=15.6, 7.6 Hz, 1H), 5.72 (dt, J=15.6, 5.2 Hz, 1H), 4.38 (ddd, J=8.0, 5.0, 3.0 Hz, 1H), 3.74 (s, 3H), 3.70 (d, J=5.1 Hz, 2H), 3.27 (s, 3H), 2.79 (dd, J=15.1, 7.4 Hz, 1H), 2.52 (m, 2H), 1.20 (d, J=6.9 Hz, 3H), 1.02 (s, 9H), 0.22 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 144.2, 133.3, 128.5, 127.7, 127.5, 126.8, 86.7, 72.4, 64.8, 61.2, 42.4, 36.3, 31.9, 25.8, 18.0, 15.7, −4.6, −5.0; LRMS (ESI) 596.2 $[M+Na]^+$; HRMS (ESI) calcd for $C_{35}H_{47}O_4NSiNa$ 596.3172 $[M+Na]^+$, found 596.3165; $[\alpha]_D^{20}$ −14.7 (*c* 0.65, $CHCl_3$).

4.6. (3*R*,4*S*)-4,6-Bis(*tert*-butyldimethylsilyloxy)-3-methylhex-1-ene (91)

A solution of **90** (9.00 g, 36.8 mmol), imidazole (5.06 g, 73.6 mmol), and DMAP (0.45 g, 3.68 mmol) in DMF (37 mL) was treated with TBDMSCl (7.44 g, 47.9 mmol) at 0 °C. The mixture was stirred at room temperature for 12 h, and then diluted with ethyl ether and water. The aqueous layer was extracted with ethyl ether. The combined organic layers were washed with water and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum to provide the oil. Then flash chromatography (hexane/EtOAc 19:1) afforded the title compound (12.54 g, 95% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (m, 1H), 5.02 (m, 2H), 3.79 (m, 1H), 3.67 (m, 2H), 2.34 (m, 1H), 1.62 (m, 2H), 1.00 (d, J=6.6 Hz, 3H), 0.92 (br s, 18H), 0.06 (m, 12H).

4.7. Ethyl (4*R*,5*S*,2*E*)-5,7-bis(*tert*-butyldimethylsilyloxy)-4-methylhept-2-enoate (83)

From **91**: a mixture of **91** (1.00 g, 2.79 mmol) in acetone (16 mL) and water (2 mL) was treated with OsO_4 (2.5 wt % in *tert*-BuOH, 1.14 mL, 0.11 mmol) at room temperature. After 10 min, NMO (0.43 g, 3.63 mmol) was added. The mixture was stirred at room temperature for 20 h, and then NMO (0.23 g) was added. After 3 h, $NaIO_4$ (0.72 g, 3.35 mmol) and water (5 mL) were added. After 4 h, water was added. The aqueous layer was extracted with ethyl ether. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum to provide the crude aldehyde, which was used for the next reaction without further purification.

A suspension of NaH (0.28 g, 11.16 mmol) in THF (14 mL) was treated with triethyl phosphinoacetate (2.80 mL, 13.95 mmol) at −5 °C. The mixture was stirred at room temperature for 30 min and cooled to −5 °C. Then crude aldehyde in THF (5 mL) was added dropwise. The mixture was stirred at 0 °C for 2 h, and then quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ethyl ether. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum to provide the oil. Then flash chromatography (hexane/EtOAc 19:1) afforded **83** (1.00 g, 83% yield, two steps). See above for spectroscopic data.

4.8. (*R*)-3-((2*R*,3*S*,4*S*)-5-(4-Methoxybenzyloxy)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylpentanoyl)-4-benzyloxazolidin-2-one (93)

2,6-Lutidine (5.14 mL, 44.2 mmol) and TBSOTf (9.36 mL, 40.8 mmol) were added to a solution of **92** (15.0 g, 33.9 mmol) in CH_2Cl_2 (340 mL) that was stirred at 0 °C. The mixture was stirred at 0 °C for 2 h and then quenched by the addition of saturated aqueous $NaHCO_3$. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with 0.5 M aqueous $NaHSO_4$. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc 4:1) to give **93** (17.9 g, 95%) as a colorless oil: IR (film) 1781, 1696, 1513, 1383, 1248, 1209, 1110, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.28 (m, 7H), 6.85 (d, J=8.7 Hz, 2H), 4.49 (m, 1H), 4.38 (d, J=11.7 Hz, 1H), 4.34 (d, J=11.7 Hz, 1H), 4.03 (m, 3H), 3.81 (m, 1H), 3.77 (s, 3H), 3.54 (dd, J=9.2, 5.6 Hz, 1H), 3.22 (dd, J=13.3, 3.1 Hz, 1H), 3.17 (dd, J=9.1, 5.9 Hz, 1H), 2.72 (dd, J=13.3, 9.6 Hz, 1H), 1.97 (m, 1H), 1.25 (d, J=6.5 Hz, 3H), 1.02 (d, J=7.0 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 159.4, 153.1, 135.8, 131.1, 129.8, 129.3, 129.2, 127.6, 75.6, 72.9, 72.0, 66.1, 55.8, 55.6, 41.9, 39.3, 38.0, 26.4, 18.7, 15.3, 15.2, −3.5, −3.6; HRMS (ESI) calcd for $C_{31}H_{45}NO_6SiNa$ 578.2914 $[M+Na]^+$, found 578.2923; $[\alpha]_D^{20}$ −8.1 (*c* 7.6, $CHCl_3$).

4.9. (2*S*,3*R*,4*S*)-5-(4-Methoxybenzyloxy)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylpentan-1-ol (94)

Dry MeOH (1.05 mL, 26.0 mmol) and then $LiBH_4$ (13 mL, 2.0 M solution in THF, 26 mmol) were added to a stirred solution of **93** (4.79 g, 8.62 mmol) in THF (75 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 45 min and at room temperature for 1 h. The solution was cooled to 0 °C and treated carefully with a 1.0 M aqueous NaOH (50 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc 7:3) to give the alcohol **94** (2.98 g, 90%) as a colorless oil: IR (film) 3425, 1613, 1513, 1463, 1249, 1091, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J=8.5 Hz, 2H), 6.88 (d, J=8.5 Hz, 2H), 4.47 (d, J=11.7 Hz, 1H), 4.40 (d, J=11.7 Hz, 1H), 3.84 (s, 3H), 3.75 (dd, J=5.7, 2.9 Hz, 1H), 3.52 (m, 3H), 3.28 (dd, J=9.1, 7.1 Hz, 1H), 2.10 (br, 1H), 2.05 (m, 1H), 1.93–1.81 (m, 1H), 0.97 (d, J=7.0 Hz, 3H), 0.90 (s, 9H), 0.87 (d, J=7.1 Hz, 3H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 130.7, 129.3, 113.8, 74.8, 72.8, 72.7, 66.3, 55.4, 39.0, 37.7, 26.2, 18.4, 15.2, 12.0, −4.1; HRMS (ESI) calcd for $C_{18}H_{31}O_3SiNa$ 323.2042 $[M+Na]^+$, found 323.2035; $[\alpha]_D^{20}$ −0.76 (*c* 2.9, $CHCl_3$).

4.10. (4*S*,5*R*,6*S*,2*E*)-Ethyl-7-(4-methoxybenzyloxy)-5-(*tert*-butyldimethylsilyloxy)-4,6-dimethylhept-2-enoate (95)

The procedure for **84** was used with the aldehyde from **94** (17.5 g, 31.6 mmol), with $Py\cdot SO_3$ (15.2 g, 95.5 mmol) and Et_3N (13.3 mL, 95.5 mmol), followed by NaH (0.90 g, 39.7 mmol) and triethyl phosphonoacetate (7.2 mL, 40.3 mmol) to yield 8.96 g (63% in three steps) of the ester **95** by flash column chromatography (EtOAc/hexane 1:9) as a colorless oil: IR ($CHCl_3$) 2957, 2931, 2856, 1720, 1651, 1613, 1513, 1463, 1366, 1250, 1180, 1093, 1077, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2H), 7.03 (dd, J=15.8, 7.8 Hz, 1H), 6.93–6.91 (m, 2H), 5.83 (dd, J=15.8, 1.3 Hz, 1H), 4.48–4.40 (m, 2H), 4.23 (q, J=7.1 Hz, 2H), 3.84 (s, 3H), 3.67 (m, 1H), 3.52 (m, 1H), 3.30 (dd, J=9.1, 7.2 Hz, 1H), 2.59 (m, 1H), 2.00 (m, 1H), 1.33 (t, J=7.1 Hz, 3H), 1.09 (d, J=6.8 Hz, 3H), 1.01 (d, J=7.0 Hz, 3H), 0.94 (s, 9H), 0.08 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 159.0, 152.7, 130.6, 129.0, 120.4, 113.6, 76.8, 72.5, 71.8, 60.0, 55.1, 40.2, 38.0, 26.0, 18.2, 14.8, 14.3, 14.2, −4.0, −4.2; LRMS (ESI) 473.2 $[M+Na]^+$; HRMS (ESI) calcd for $C_{25}H_{42}O_5SiNa$ 473.2699 $[M+Na]^+$, found 473.2716; $[\alpha]_D^{20}$ −28.3 (*c* 0.41, $CHCl_3$).

4.11. (4*S*,5*R*,6*S*)-Ethyl-7-(4-methoxybenzyloxy)-5-(*tert*-butyldimethylsilyloxy)-4,6-dimethylheptanoate (96)

$NiCl_2\cdot 6H_2O$ (2.4 g, 10.1 mmol) and then portionwise $NaBH_4$ (1.50 g, 39.7 mmol) were added to a stirred solution of unsaturated ketone **95** (8.96 g, 19.9 mmol) in MeOH (66 mL) and THF (20 mL) at 0 °C. After 1 h, the solvent was evaporated and filtered with Celite using Et_2O as an eluant (60 mL). The organic phase was concentrated, and the residue was purified by flash chromatography (EtOAc/hexane 1:9) to yield 8.76 g of **96** (97%) as a colorless oil: IR ($CHCl_3$) 2957, 2856, 1737, 1613, 1513, 1463, 1374, 1249, 1172, 1091, 1038, 836, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.37 (m, 2H), 7.02–6.99 (m, 2H), 4.59–4.50 (m, 2H), 4.25 (q, J=7.1 Hz, 2H), 3.91 (s, 3H), 3.66–3.62 (m, 2H), 3.40 (dd, J=8.8, 7.3 Hz, 1H), 2.52–2.33 (m, 2H),

2.13–2.02 (m, 1H), 1.90–1.82 (m, 1H), 1.78–1.57 (m, 2H), 1.38 (t, J=7.1 Hz, 3H), 1.09 (d, J=6.9 Hz, 3H), 1.03 (s, 9H), 1.00 (d, J=6.5 Hz, 3H), 0.19 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 158.9, 130.7, 129.0, 113.5, 76.8, 72.5, 60.0, 55.0, 38.0, 35.6, 32.5, 29.9, 26.0, 18.3, 14.9, 14.1, 13.7, −3.9, −4.2; LRMS (ESI) 475.3 [M+Na]$^+$; HRMS (ESI) calcd for $C_{25}H_{44}O_5SiNa$ 475.2856 [M+Na]$^+$, found 473.2877; $[\alpha]_D^{20}$ −6.0 (c 1.9, $CHCl_3$).

4.12. (4*S*,5*R*,6*S*)-7-(4-Methoxybenzyloxy)-5-(*tert*-butyldimethylsilyloxy)-4,6-dimethylheptanoic acid (97)

Aqueous LiOH (1 N, 193 mL, 0.19 mol) was added to a THF/H_2O solution of **96** (8.76 g, 19.4 mmol). The resulting solution was warmed to 60 °C and stirred with heating for 6 h. Aqueous 1 N HCl was added to give a neutral pH, and the mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and evaporated to yield 8.22 g of crude acid **97**, which was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.22 (m, 2H), 6.86–6.83 (m, 2H), 4.39 (m, 2H), 3.77 (s, 3H), 3.69 (q, J=7.0 Hz, 1H), 3.52 (m, 1H), 3.47 (q, J=7.0 Hz, 1H), 3.19 (t, J=8.5 Hz, 1H), 2.16 (m, 1H), 1.90 (m, 1H), 1.65–1.51 (m, 2H), 1.21 (t, J=7.0 Hz, 2H), 0.92–0.85 (m, 12H), 0.81 (d, J=6.3 Hz, 3H), 0.00 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.0, 158.9, 130.6, 129.1, 113.6, 72.5, 65.8, 58.0, 55.1, 37.8, 30.6, 26.1, 18.3, 18.1, 15.2, 14.0, −3.5, −4.1.

4.13. (*R*)-3-((4*S*,5*R*,6*S*)-7-(4-Methoxybenzyloxy)-5-(*tert*-butyldimethylsilyloxy)-4,6-dimethylheptanoyl)-4-benzyloxazolidin-2-one (98)

A solution of acid **97** (8.22 g, 19.4 mmol) and Et_3N (5.40 mL, 38.8 mmol) in 100 mL of dry THF was cooled to −78 °C and treated dropwise with pivaloyl chloride (2.86 g, 23.3 mmol), stirred in the cold condition for 2 h and warmed to 0 °C prior to the addition of the oxazolidinone (3.5 g, 19.8 mmol) and LiCl (2.46 g, 58.8 mmol). This mixture was stirred overnight at room temperature and diluted with water (200 mL). The separated aqueous phase was extracted with ether (100 mL), and the combined organic layers were dried and evaporated to give a residue that was chromatographed to yield 7.91 g (70% in two steps) of imide **98** by flash column chromatography (EtOAc/hexane 1:4) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.23 (m, 7H), 6.94–6.91 (m, 2H), 4.71 (m, 1H), 4.51 (d, J=11.6 Hz, 1H), 4.46 (d, J=11.6 Hz, 1H), 4.25–4.16 (m, 2H), 3.84 (s, 3H), 3.63–3.58 (m, 2H), 3.37–3.31 (m, 2H), 3.14–3.04 (m, 1H), 2.94–2.86 (m, 1H), 2.79 (dd, J=13.3, 9.7 Hz, 1H), 2.04 (m, 1H), 1.87–1.60 (m, 3H), 1.03 (d, J=6.9 Hz, 3H), 0.99–0.97 (m, 12H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 158.8, 153.3, 135.2, 130.7, 129.3, 129.0, 128.8, 127.1, 113.5, 77.1, 72.5, 72.4, 65.9, 55.1, 54.9, 37.9, 37.7, 35.6, 33.7, 29.2, 26.0, 18.3, 14.9, 13.9, −3.8, −4.2.

4.14. (*R*)-3-((2*R*,4*S*,5*R*,6*S*)-7-(4-Methoxybenzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2,4,6-trimethylheptanoyl)-4-benzyloxazolidin-2-one (99)

NaHMDS (1 M in THF, 14.9 mL, 14.9 mmol) was added dropwise over a 30 min period to a cooled (−78 °C) suspension of imide **98** (7.91 g, 13.6 mmol) in THF (45 mL). After 15 min of stirring, the resulting cold solution was treated with MeI (2.53 mL, 40.8 mmol) and stirred at −78 °C for 3 h before being warmed to 25 °C overnight (12 h). The reaction was quenched with H_2O (100 mL), and the aqueous layer was extracted with Et_2O (3×150 mL). The combined organic extracts were dried ($MgSO_4$), concentrated in vacuo, and chromatographed (EtOAc/hexane 1:9) to provide 5.97 g (74%) of **99** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.26 (m, 7H), 6.95–6.92 (m, 2H), 4.71 (m, 1H), 4.51 (m, 2H), 4.18 (m, 2H), 3.95 (m, 1H), 3.84 (s, 3H), 3.63 (dd, J=8.9, 3.8 Hz, 1H), 3.57 (dd, J=6.4, 2.7 Hz, 1H), 3.35 (t, J=8.5 Hz, 1H), 3.28 (dd, J=13.3, 3.1 Hz, 1H), 2.83 (dd, J=13.3, 9.4 Hz, 1H), 2.10–1.95 (m, 2H), 1.68 (m, 1H), 1.38 (ddd, J=14.1, 9.8, 4.9 Hz, 1H), 1.31 (d, J=6.8 Hz, 3H), 1.04 (d, J=6.9 Hz, 3H), 0.98 (s, 9H), 0.95 (d, J=6.7 Hz, 3H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 158.8, 152.8, 135.1, 130.8, 129.3, 128.9, 128.7, 127.1, 113.5, 77.6, 72.6, 72.4, 65.7, 55.0, 38.9, 38.0, 37.6, 35.3, 33.8, 26.0, 18.8, 18.3, 14.9, 13.8, −3.8, −4.2.

4.15. (2*R*,4*S*,5*R*,6*S*)-7-(4-Methoxybenzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2,4,6-trimethylheptan-1-ol (100)

From **99**: Dry methanol (1.22 mL, 30 mmol) then $LiBH_4$ (15.0 mL, 2.0 M solution in THF, 30 mmol) were added to a solution of **99** (5.97 g, 9.99 mmol) in THF (75 mL) stirred at 0 °C. The resulting solution was stirred at 0 °C for 45 min and at room temperature for 1 h. The solution was cooled to 0 °C and treated carefully with a 1.0 M aqueous solution of NaOH (50 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc 7:3) to give the alcohol **100** (3.52 g, 83 %) as a colorless oil: IR (film) 3410, 1612, 1513, 1249, 1067, 1038 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J=8.6 Hz, 2H), 6.88 (d, J=8.6 Hz, 2H), 4.44 (d, J=11.7 Hz, 1H), 4.39 (d, J=11.7 Hz, 1H), 3.81 (s, 3H), 3.51 (m, 2H), 3.44 (dd, J=5.6, 3.4 Hz, 1H), 3.37 (dd, J=10.6, 6.5 Hz, 1H), 3.22 (dd, J=9.0, 7.0 Hz, 1H), 2.03–1.95 (m, 1H), 1.78–1.62 (m, 2H), 1.53 (br, 1H), 1.41 (ddd, J=13.5, 7.5, 5.8 Hz, 1H), 0.95 (d, J=6.9 Hz, 3H), 0.94 (d, J=6.7 Hz, 3H), 0.88 (s, 9H), 0.87 (d, J=6.9 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 130.9, 129.4, 113.9, 77.5, 72.8, 67.7, 55.4, 38.3, 38.0, 33.6, 33.2, 26.3, 18.6, 18.0, 15.6, 15.5, −3.5, −3.8; $[\alpha]_D^{20}$ −6.3 (c 1.7, $CHCl_3$).

From **103**: a solution of diisopropylamine (6.65 mL, 47.4 mmol) in THF (48 mL) stirred at −78 °C was treated with *n*-butyllithium in hexane (2.5 M, 17.6 mL, 44 mmol). The solution was stirred at −78 °C for 5 min and warmed to 0 °C for 15 min. Borane/ammonia complex (90%, 1.55 g, 45.2 mmol) was added and the resulting mixture was stirred at 0 °C for 15 min, warmed to room temperature for 15 min, and then cooled to 0 °C. A solution of amide **103** (6.62 g, 11.3 mmol) in THF (35 mL) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. The mixture was then cooled to 0 °C and quenched carefully with saturated aqueous NH_4Cl. The mixture was extracted with diethyl ether and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced

pressure. The residue was purified by flash chromatography (hexane/EtOAc 4:1 to 7:3) to afford the alcohol (4.57 g, 96%) as a colorless oil.

4.16. (2*S*,3*R*,4*S*,6*R*)-3,7-Bis(*tert*-butyldimethylsilyloxy)-2,4,6-trimethylheptan-1-ol (101)

TBSCl (4.16 g, 27.6 mmol) was added to a solution of alcohol **100** (5.86 g, 13.8 mmol), imidazole (2.89 g, 41.4 mmol), and DMAP (169 mg, 1.38 mmol) in CH_2Cl_2 (55 mL). The resulting white suspension was stirred at room temperature for 2 h, and the volatiles were removed under reduced pressure. The residue was dissolved in hexane and brine. The phases were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc 19:1) to afford the TBS-protected alcohol (7.04 g, 95%) as a colorless oil: IR (film) 1513, 1471, 1463, 1249, 1091, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J=8.6 Hz, 2H), 6.91 (d, J=8.6 Hz, 2H), 4.48 (d, J=11.9 Hz, 1H), 4.44 (d, J=11.9 Hz, 1H), 3.82 (s, 3H), 3.60–3.49 (m, 3H), 3.39–3.28 (m, 3H), 2.05–1.95 (m, 1H), 1.80–1.66 (m, 2H), 1.49–1.40 (m, 2H), 1.02 (d, J=6.9 Hz, 3H), 1.0–0.91 (m, 24H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 131.1, 129.3, 127.9, 77.3, 73.1, 72.8, 68.4, 55.3, 38.9, 38.5, 33.5, 26.4, 26.2, 18.7, 18.6, 18.1, 15.3, 15.1, −3.4, −3.8, −5.2; $[\alpha]_D^{20}$ −15.9 (*c* 0.47, $CHCl_3$).

A solution of the above TBS-protected alcohol (5.28 g, 9.8 mmol) in CH_2Cl_2 (332 mL) and pH 7 phosphate buffer solution (33 mL) was treated with DDQ (3.34 g, 14.7 mmol). The reaction mixture was stirred at room temperature for 1 h and was quenched with saturated aqueous $NaHCO_3$ solution. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc 97:3 to 93:7) to afford **101** (4.01 g, 98%) as a colorless oil: IR (film) 3353, 1472, 1463, 1388, 1360, 1255, 1091, 1030, 1005 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.60 (d, J=5.3 Hz, 2H), 3.55–3.45 (m, 2H), 3.32 (dd, J=9.7, 6.7 Hz, 1H), 2.49 (br, 1H), 1.45 (ddd, J=13.5, 7.5, 5.3 Hz, 1H), 0.95 (d, J=7.1 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.93–0.87 (m, 6H), 0.11 (s, 3H), 0.09 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.9, 68.0, 66.2, 38.4, 37.8, 35.4, 33.5, 26.3, 26.1, 18.5, 18.3, 16.2, 15.7, −3.6, −3.9, −5.3; $[\alpha]_D^{20}$ −16.1 (*c* 4.4, $CHCl_3$).

4.17. (3*S*,4*R*,5*S*,7*R*)-4-(*tert*-Butyldimethylsilyloxy)-7-((*tert*-butyldimethylsilyloxy)methyl)-3,5-dimethyloct-1-yne (78)

Sulfur trioxide pyridine complex (5.44 g, 34.2 mmol) was added to a solution of **101** (4.78 g, 11.4 mmol) and triethylamine (4.77 mL, 34.2 mmol) in CH_2Cl_2 (23 mL) and DMSO (46 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and then diluted with Et_2O. The organic phase was washed with cold 0.5 M aqueous $NaHSO_4$ and then with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by short flash chromatography (hexane/EtOAc 9:1) to afford the crude aldehyde as a golden oil, which was used directly in the next reaction without further purification. Carbon tetrabromide (7.56 g, 22.8 mmol) was added to a solution of triphenylphosphine (12.3 g, 45.6 mmol) in CH_2Cl_2 (56 mL) at 0 °C. The resulting dark-red mixture was stirred at 0 °C for 10 min. A solution of the crude aldehyde and 2,6-lutidine (2.66 mL, 22.8 mmol) in CH_2Cl_2 (45 mL) was added dropwise. The dark-brown mixture was stirred at 0 °C for 1 h and then quenched with a saturated aqueous NH_4Cl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by short flash chromatography (hexane 100%) to afford the dibromoolefin (4.76 g, 73% yield from the alcohol) as a colorless oil that was used without further purification. A solution of the dibromoolefin (4.76 g, 8.2 mmol) in THF (40 mL) stirred at −78 °C was treated with *n*-BuLi (1.6 M in hexane, 15.4 mL, 24.6 mmol). The solution was stirred at −78 °C for 2 h and then quenched with saturated aqueous NH_4Cl. The mixture was allowed to reach room temperature and was diluted with Et_2O. The aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc 97:3) to afford the pure alkyne **78** (3.26 g, 95%) as a colorless oil: IR (film) 3313, 2100, 1472, 1463, 1252, 1088, 1005 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.53–3.48 (m, 2H), 3.33 (d, J=9.7, 6.8 Hz, 1H), 2.62 (ddddd, J=7.2, 7.2, 7.2, 5.1, 2.5 Hz, 1H), 2.03 (d, J=2.5 Hz, 1H), 1.97–1.80 (m, 1H), 1.73–1.6 (m, 1H), 1.47 (m, 1H), 1.21 (d, J=7.1 Hz, 3H), 0.99–0.91 (m, 25H), 0.13 (s, 3H), 0.11 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 87.9, 77.8, 70.2, 68.5, 39.2, 33.9, 33.7, 32.3, 26.4, 26.3, 18.6, 17.9, 17.5, 15.7, −3.6, −5.1; LRMS (ESI) 435 $[M+Na]^+$; $[\alpha]_D^{20}$ −8.2 (*c* 3.1, $CHCl_3$).

4.18. (2*R*,4*S*,5*R*,6*S*)-7-(4-Methoxybenzyloxy)-5-(*tert*-butyldimethylsilyloxy)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-2,4,6-tetramethylheptanamide (103)

PPh_3 (7.05 g, 26.2 mmol), imidazole (1.78 g, 26.2 mmol), and diisopropylethylamine (4.6 mL, 26.2 mmol) in benzene (80 mL), diethyl ether (165 mL), and acetonitrile (33 mL) were stirred at room temperature and treated with iodine (6.65 g, 26.2 mmol). The resulting mixture was vigorously stirred until a beige suspension formed. A solution of alcohol **94** (5.0 g, 13.1 mmol) in Et_2O (20 mL) was added dropwise to the suspension, and the resulting mixture was stirred at room temperature for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ and diluted with Et_2O. The aqueous phase was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was triturated with hexane and the triturate was concentrated under reduced pressure. This procedure was repeated two more times to afford iodide **102** as a colorless oil that was used directly in the next reaction. A solution of *n*-BuLi in hexane (2.5 M, 21 mL, 52.4 mmol) was added to a suspension of LiCl (7.05 g, 166.4 mmol) and diisopropylamine (7.85 mL, 56.3 mmol) in THF (40 mL) at −78 °C. The suspension was stirred at −78 °C for 5 min, 0 °C for 15 min, and then cooled to −78 °C. A solution of

(*S*,*S*)-pseudoephedrine propionamide (Myers' auxiliary, **45**) (6.09 g, 27.5 mmol) in THF (70 mL) was added dropwise. The resulting mixture was stirred at −78 °C for 1 h, at 0 °C for 15 min, and at room temperature for 5 min. The suspension was cooled to 0 °C, and the iodide was added as a solution in THF (6 mL followed by a 6 mL rinse). The reaction mixture was stirred at room temperature for 24 h and quenched with half-saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash chromatography (hexane/EtOAc 1:1) to afford the amide **103** (6.69 g, 87%) as a colorless oil: IR (film) 3387, 1616, 1513, 1463, 1248, 1087, 1037 cm^{-1}; HRMS (ESI) calcd for $C_{34}H_{56}NO_5Si$ 586.3928 $[M+H]^+$, found 586.3940; $[\alpha]_D^{20}$ +23.2 (*c* 1.26, $CHCl_3$).

4.19. (4*R*,5*S*,10*S*,11*R*,12*S*,14*R*,2*E*)-5,11,15-Tris(*tert*-butyldimethylsilyloxy)-4,10,12,14-tetramethyl-1-(trityloxy)pentadec-2-en-8-yn-7-one (104)

Alkyne **78** (4.12 g, 10.0 mmol) was dissolved in THF (100 mL), and the mixture was cooled to −78 °C. *n*-BuLi (6.25 mL, 1.6 M hexane solution) was added slowly. After 5 min, the mixture was warmed to 0 °C and stirred for 30 min. The mixture was then cooled to −78 °C and amide **79** (6.47 g, 11.3 mmol) in THF (5 mL) was added slowly. After 5 min, the solution was warmed to 0 °C and stirred for 30 min. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was partitioned in a separatory funnel. The aqueous phase was extracted with Et_2O (3×20 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. Filtration and concentration under reduced pressure, followed by flash chromatography on silica gel (hexane/EtOAc 19:1), afforded the ynone **104** (9.70 g, 93%) as a pale yellow oil: IR ($CHCl_3$) 2955, 2928, 2856, 2209, 1676, 1471, 1462, 1252, 1085, 836, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 6H), 7.36 (m, 9H), 5.80 (dd, *J*=15.6, 7.1 Hz, 1H), 5.69 (dt, *J*=15.7, 4.8 Hz, 1H), 4.37 (m, 1H), 3.69 (d, *J*=4.7 Hz, 2H), 3.61 (m, 1H), 3.58 (dd, *J*=9.7, 5.0 Hz, 1H), 3.43 (dd, *J*=9.7, 6.5 Hz, 1H), 2.87 (m, 1H), 2.73 (m, 1H), 2.46 (m, 1H), 1.88 (m, 1H), 1.76 (m, 1H), 1.59 (m, 1H), 1.31 (d, *J*=7.1 Hz, 3H), 1.15 (d, *J*=6.8 Hz, 3H), 1.05 (m, 1H), 1.00 (m, 34H), 0.194 (s, 3H), 0.190 (s, 3H), 0.17 (s, 3H), 0.15 (s, 3H), 0.14 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.1, 144.2, 132.9, 128.6, 127.7, 126.9, 96.8, 86.8, 83.1, 71.5, 68.0, 64.9, 50.0, 42.3, 38.1, 34.4, 33.2, 32.1, 26.01, 25.96, 25.85, 18.3, 18.0, 17.9, 17.2, 15.5, 15.4, −3.8, −4.1, −4.6, −4.7, −5.4; LRMS (ESI) 947.5 $[M+Na]^+$; HRMS (ESI) calcd for $C_{56}H_{88}O_5Si_3Na$ 947.5837 $[M+Na]^+$, found 947.5875; $[\alpha]_D^{20}$ −12.0 (*c* 0.54, $CHCl_3$).

4.20. (2*E*,4*R*,5*S*,7*S*,10*S*,11*R*,12*S*,14*R*,2*E*)-5,11,15-Tris(*tert*-butyldimethylsilyloxy)-4,10,12,14-tetramethyl-1-(trityloxy)pentadec-2-en-8-yn-7-ol (105)

Ynone **104** (5.28 g, 5.71 mmol) was taken up in *i*-PrOH (58 mL). The (*S*,*S*)-Noyori catalyst (0.77 g, 1.15 mmol, 20 mol %) was added in one portion, and the solution was stirred overnight. The solvent was removed under vacuum, and the crude residue was purified by flash chromatography on silica gel (hexane/EtOAc 97:3), affording propargylic alcohol **105** (4.18 g, 79%) as a pale yellow oil: IR ($CHCl_3$) 3469, 2955, 2856, 1471, 1448, 1252, 1084, 836, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 6H), 7.36 (m, 9H), 5.71 (m, 2H), 4.59 (m, 1H), 4.03 (quint, *J*=3.9 Hz, 1H), 3.65 (d, *J*=3.9 Hz, 2H), 3.58 (dd, *J*=4.6, 3.2 Hz, 1H), 3.55 (dd, *J*=10.1, 5.1 Hz, 1H), 3.38 (dd, *J*=9.7, 6.8 Hz, 1H), 2.71 (m, 1H), 2.50 (m, 1H), 2.32 (d, *J*=5.4 Hz, 1H), 1.88 (m, 1H), 1.80 (m, 2H), 1.55 (m, 1H), 1.23 (d, *J*=7.1 Hz, 3H), 1.11 (d, *J*=6.8 Hz, 3H), 0.98 (m, 34H), 0.20 (s, 3H), 0.17 (s, 3H), 0.16 (s, 3H), 0.14 (s, 3H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 134.0, 128.6, 127.8, 127.1, 126.9, 88.1, 86.8, 83.0, 72.6, 68.3, 65.8, 65.1, 59.5, 41.9, 40.3, 38.7, 33.5, 33.2, 32.1, 26.0, 25.9, 18.4, 18.1, 17.7, 17.4, 15.7, 15.3, 14.2, −3.9, −4.0, −4.4, −4.5, −5.3; LRMS (ESI) 949.7 $[M+Na]^+$; HRMS (ESI) calcd for $C_{56}H_{90}O_5Si_3Na$ 949.5994 $[M+Na]^+$, found 949.6018; $[\alpha]_D^{20}$ −10.0 (*c* 1.2, $CHCl_3$).

4.21. (2*E*,4*R*,5*S*,7*S*,8*Z*,10*S*,11*R*,12*S*,14*R*)-5,11,15-Tris-(*tert*-butyldimethylsilyloxy)-4,10,12,14-tetramethyl-1-(trityloxy)pentadeca-2,8-dien-7-ol (106)

Lindlar catalyst (ca. 200 mg) was added to a solution of alcohol **105** (4.18 g, 4.51 mmol) in toluene (100 mL). The flask was flushed with H_2 via a balloon several times, and then stirred under an atmosphere of H_2 until starting material was consumed (usually 1 h) as indicated by TLC analysis. The mixture was filtered through a pad of Celite and concentrated under reduced pressure to afford the alkene **106** as a colorless oil (3.82 g, 91%): IR ($CHCl_3$) 3436, 2954, 2926, 2855, 1461, 1378, 1252, 1061, 836, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 6H), 7.34 (m, 9H), 5.73 (m, 2H), 5.60 (t, *J*=10.3 Hz, 1H), 5.43 (dd, *J*=10.9, 8.4 Hz, 1H), 4.73 (m, 1H), 3.98 (q, *J*=5.0 Hz, 1H), 3.68 (d, *J*=4.1 Hz, 1H), 3.59 (dd, *J*=9.7, 4.7 Hz, 1H), 3.48 (m, 1H), 3.36 (dd, *J*=9.0, 7.3 Hz, 1H), 2.79 (m, 1H), 2.58 (m, 1H), 2.23 (br, 1H), 1.78 (m, 1H), 1.71 (m, 1H), 1.66 (m, 2H), 1.50 (m, 1H), 1.11 (d, *J*=6.8 Hz, 3H), 1.07 (d, *J*=6.8 Hz, 3H), 1.00 (m, 34H), 0.22 (s, 3H), 0.18 (s, 3H), 0.14 (s, 6H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 135.3, 134.6, 131.5, 128.7, 127.7, 127.0, 126.8, 86.8, 79.6, 73.0, 68.2, 65.0, 64.7, 42.0, 39.6, 38.0, 36.4, 34.9, 33.4, 26.2, 26.0, 25.9, 19.9, 18.4, 18.3, 18.1, 18.0, 15.2, 14.5, −3.4, −3.7, −4.2, −4.4, −4.5, −5.4; LRMS (ESI) 951.7 $[M+Na]^+$; HRMS (ESI) calcd for $C_{56}H_{92}O_5Si_3Na$ 951.6150 $[M+Na]^+$, found 951.6172; $[\alpha]_D^{20}$ 1.0 (*c* 0.62, $CHCl_3$).

4.22. ((2*E*,4*R*,5*S*,7*S*,8*Z*,10*S*,11*R*,12*S*,14*R*)-5,7,11,15-Tetrakis(*tert*-butyldimethylsilyloxy)-4,10,12,14-tetramethylpentadeca-2,8-dienyloxy)triphenylmethane (107)

TBSOTf (2.08 mL, 9.07 mmol) was added to a stirred solution of alcohol **106** (3.82 g, 4.11 mmol) and 2,6-lutidine (1.14 mL, 9.85 mmol) in CH_2Cl_2 (14 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The mixture was quenched by the addition of H_2O (25 mL). The reaction mixture was extracted with CH_2Cl_2, and the organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by short column chromatography (hexane/EtOAc 19:1) to yield **107** (4.27 g, 99%) as a colorless oil: IR ($CHCl_3$) 2956, 2929, 2856, 1471, 1462, 1449, 1255, 1089, 1005, 836, 773, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (m, 6H), 7.39 (m, 9H),

5.77 (m, 2H), 5.56 (t, J=10.8 Hz, 1H), 5.42 (dd, J=11.0, 8.2 Hz, 1H), 4.69 (m, 1H), 4.07 (m, 1H), 3.71 (d, J=3.8 Hz, 2H), 3.64 (dd, J=9.8, 4.8 Hz, 1H), 3.53 (m, 1H), 3.40 (dd, J=9.6, 7.5 Hz, 1H), 2.74 (m, 1H), 2.55 (m, 1H), 1.89 (m, 3H), 1.59 (m, 3H), 1.12 (d, J=6.2 Hz, 6H), 1.04 (m, 42H), 0.26 (s, 3H), 0.24 (s, 3H), 0.19 (s, 6H), 0.18 (s, 3H), 0.17 (s, 6H), 0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 134.5, 132.9, 132.6, 128.7, 127.7, 126.8, 86.8, 79.9, 72.3, 68.3, 66.5, 65.1, 64.1, 42.4, 41.6, 37.9, 36.0, 35.3, 33.6, 26.3, 26.02, 25.97, 25.7, 19.4, 18.5, 18.4, 18.20, 18.15, 18.1, 15.5, 13.3, −2.9, −3.5, −3.7, −4.1, −4.2, −4.3, −5.3; LRMS (ESI) 1065.9 $[M+Na]^+$; HRMS (ESI) calcd for $C_{62}H_{106}O_5Si_4Na$ 1065.7015 $[M+Na]^+$, found 1065.7026; $[\alpha]^{20}$ −10.4 (c 0.53, $CHCl_3$).

4.23. (2*R*,4*S*,5*R*,6*S*,7*Z*,9*S*,11*S*,12*R*,13*E*)-5,9,11-Tris(*tert*-butyldimethylsilyloxy)-2,4,6,12-tetramethyl-15-(trityloxy)pentadeca-7,13-dien-1-ol (108)

HF/pyridine in pyridine (40 mL, prepared by slow addition of 12 mL of pyridine to 3 mL of HF/pyridine complex, followed by dilution with 25 mL of THF) was slowly added to a solution of TBS ether **107** (4.27 g, 4.10 mmol) in THF (5 mL) at 0 °C. The mixture was stirred for 21 h at 0 °C and quenched with saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was separated and extracted with Et_2O (3×50 mL). The combined organic layers were washed with saturated aqueous $CuSO_4$ (3×50 mL), dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (EtOAc/hexane 1:4) afforded 2.55 g (67%) of the alcohol **108** as a colorless oil: IR ($CHCl_3$) 3350, 2956, 2928, 2856, 1471, 1448, 1254, 1086, 836, 773, 705 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (m, 6H), 7.32 (m, 9H), 5.68 (m, 2H), 5.50 (t, J=10.6 Hz, 1H), 5.35 (dd, J=10.9, 8.5 Hz, 1H), 4.61 (t, J=8.5 Hz, 1H), 4.00 (t, J=8.1 Hz, 1H), 3.62 (d, J=3.2 Hz, 2H), 3.58 (dd, J=10.6, 4.3 Hz, 1H), 3.45 (m, 1H), 3.36 (dd, J=9.9, 7.3 Hz, 1H), 2.66 (m, 1H), 2.48 (m, 1H), 1.70 (m, 3H), 1.49 (m, 3H), 1.04 (d, „J=6.6 Hz, 6H), 0.97 (s, 18H), 0.93 (m, 6H), 0.87 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H), 0.11 (s, 6H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 134.4, 133.0, 132.1, 128.7, 127.7, 126.8, 86.7, 79.8, 72.3, 67.7, 66.5, 65.1, 42.4, 41.5, 37.3, 35.7, 35.5, 33.3, 26.2, 26.0, 25.9, 19.6, 18.4, 18.14, 18.06, 17.98, 15.7, 13.2, −2.9, −3.6, −3.7, −4.1, −4.2, −4.3; LRMS (ESI) 951.8 $[M+Na]^+$; HRMS (ESI) calcd for $C_{56}H_{92}O_5Si_3Na$ 951.6150 $[M+Na]^+$, found 951.6162; $[\alpha]_D^{20}$ −12.0 (c 0.71, $CHCl_3$).

4.24. (2*R*,4*E*,6*R*,8*S*,9*R*,10*S*,11*Z*,13*S*,15*S*,16*R*,17*E*)-9,13,15-Tris(*tert*-butyldimethylsilyloxy)-2-((4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-6,8,10,16-tetramethyl-19-(trityloxy)nonadeca-4,11,17-trien-3-one (109)

Alcohol **108** (2.55 g, 2.75 mmol) in CH_2Cl_2 (30 mL) was treated with Dess–Martin periodinane (1.74 g, 4.10 mmol). After 1 h, the mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) and $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with Et_2O (2×30 mL), and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by short flash column chromatography (hexane/EtOAc 4:1) provided the crude aldehyde as a colorless oil, which was used without further purification. A mixture of ketophosphonate **39** (1.06 g, 2.75 mmol) and $Ba(OH)_2$ (0.38 g, activated by heating to 100 °C for 1–2 h before use) in THF (40 mL) was stirred at room temperature for 30 min. A solution of the above aldehyde in wet THF (4×1 mL washings, 40:1 THF/H_2O) was then added. After stirring for 12 h, the reaction mixture was diluted with Et_2O (30 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The organic solution was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed (hexane/EtOAc 9:1) to yield **109** (2.60 g, 80% in two steps) as a colorless oil: IR ($CHCl_3$) 2956, 2928, 2855, 1688, 1618, 1518, 1471, 1461, 1338, 1251, 1080, 1038, 836, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (m, 6H), 7.40 (m, 2H), 7.30 (m, 9H), 6.89 (m, 2H), 6.73 (dd, J=15.6, 8.5 Hz, 1H), 6.29 (d, J=15.6 Hz, 1H), 5.66 (m, 2H), 5.46 (t, J=10.4 Hz, 1H), 5.46 (s, 1H), 5.31 (dd, J=11.0, 8.4 Hz, 1H), 4.58 (t, J=8.1 Hz, 1H), 4.12 (dd, J=11.3, 4.6 Hz, 1H), 3.96 (m, 1H), 3.92 (dd, J=10.0, 4.2 Hz, 1H), 3.80 (s, 3H), 3.60 (d, J=2.8 Hz, 2H), 3.56 (m, 1H), 3.39 (t, J=3.3 Hz, 1H), 2.93 (m, 1H), 2.64 (m, 1H), 2.45 (m, 1H), 2.37 (m, 1H), 2.01 (m, 1H), 1.61 (m, 1H), 1.54 (m, 2H), 1.50 (m, 1H), 1.44 (m, 1H), 1.27 (d, J=7.0 Hz, 3H), 1.06 (d, J=6.6 Hz, 3H), 1.02 (d, J=6.5 Hz, 3H), 0.99 (d, J=6.6 Hz, 3H), 0.95 (s, 9H), 0.94 (s, 9H), 0.88 (d, J=6.6 Hz, 3H), 0.84 (s, 9H), 0.79 (d, J=6.7 Hz, 3H), 0.15 (s, 3H), 0.14 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7, 159.8, 152.3, 144.3, 134.3, 132.8, 132.1, 131.0, 128.6, 127.7, 127.1, 126.8, 126.6, 113.4, 100.8, 86.7, 82.7, 80.0, 72.8, 72.1, 66.4, 65.0, 55.2, 47.1, 42.4, 41.4, 39.3, 35.8, 34.7, 34.6, 32.2, 26.1, 25.92, 25.86, 20.8, 19.7, 18.3, 18.1, 18.0, 15.0, 13.0, 12.4, 10.8, −2.9, −3.7, −3.8, −4.18, −4.25, −4.35; LRMS (ESI) 1209.6 $[M+Na]^+$; HRMS (ESI) calcd for $C_{72}H_{110}O_8Si_3Na$ 1209.7406 $[M+Na]^+$, found 1209.7474; $[\alpha]_D^{20}$ −6.7 (c 0.11, $CHCl_3$).

4.25. (2*R*,6*S*,8*S*,9*R*,10*S*,11*Z*,13*S*,15*S*,16*R*,17*E*)-9,13,15-Tris(*tert*-butyldimethylsilyloxy)-2-((4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-6,8,10,16-tetramethyl-19-(trityloxy)nonadeca-11,17-dien-3-one (110)

$NiCl_2 \cdot 6H_2O$ (0.26 g, 1.09 mmol) and $NaBH_4$ (0.17 g, 4.49 mmol) in portions were added to a stirred solution of unsaturated ketone **109** (2.60 g, 2.19 mmol) in 80 mL of 3:2 MeOH/THF at 0 °C. After 1 h, the reaction mixture was evaporated and filtered through Celite eluting with Et_2O (30 mL). The organic phase was concentrated, and the residue was purified by flash chromatography (EtOAc/hexane 1:9) to yield 1.98 g of **110** (76%) as a colorless oil: IR ($CHCl_3$) 2955, 2927, 2855, 1711, 1614, 1518, 1461, 1251, 1076, 835, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (m, 6H), 7.27 (m, 11H), 6.85 (m, 2H), 5.60 (m, 2H), 5.43 (s, 1H), 5.40 (m, 1H), 5.27 (m, 1H), 4.52 (m, 1H), 4.11 (dd, J=11.1, 4.7 Hz, 1H), 3.91 (m, 2H), 3.78 (s, 3H), 3.55 (m 2H), 3.50 (m, 1H), 3.35 (m, 1H), 2.67 (m, 1H), 2.58 (m, 1H), 2.51 (m, 1H), 2.41 (m, 1H), 2.01 (m, 1H), 1.68 (m, 3H), 1.41 (m, 5H), 1.23 (d, J=7.1 Hz, 3H), 0.96 (d, J=6.7 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.88 (m, 1H), 0.87 (m, 3H), 0.80 (s, 9H), 0.78 (m, 6H), 0.10 (s, 3H), 0.08 (s, 3H), 0.04 (s, 3H), 0.03 (s, 6H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.9, 159.8, 144.5, 144.3, 134.4, 132.9, 132.4, 130.9, 128.6, 127.9, 127.8, 127.7, 127.1, 126.8, 113.4, 100.8, 86.7, 83.1, 79.9, 72.8, 72.2,

66.4, 65.1, 55.1, 48.3, 42.3, 41.5, 41.2, 38.1, 35.7, 35.0, 31.2, 29.8, 29.7, 26.2, 25.92, 25.87, 20.2, 19.4, 18.4, 18.1, 18.0, 15.2, 13.2, 12.1, 9.6, −3.0, −3.5, −3.7, −4.2, −4.28, −4.34; LRMS (ESI) 1211.9 $[M+Na]^+$; HRMS (ESI) calcd for $C_{72}H_{112}O_8Si_3Na$ 1211.7563 $[M+Na]^+$ found 1211.7616; $[\alpha]_D^{20}$ +1.6 (*c* 0.50, $CHCl_3$).

4.26. (2*S*,3*R*,6*S*,8*S*,9*R*,10*S*,11*Z*,13*S*,15*S*,16*R*,17*E*)-9,13,15-Tris(*tert*-butyldimethylsilyloxy)-2-((4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-6,8,10,16-tetramethyl-19-(trityloxy)nonadeca-11,17-dien-3-ol (111β)

$NaBH_4$ (0.095 g, 2.51 mmol) was added to a solution of ketone **110** (1.98 g, 1.67 mmol) in MeOH (28 mL) at 0 °C. After stirring for 2 h at 0 °C, the reaction mixture was evaporated and water (30 mL) was added. The reaction mixture was extracted with ether (2×40 mL), and the organic phase was washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexane 1:9) to yield as major product the title compound **111β** (1.39 g, 70%, less polar) and as minor product **111α** (0.58 g, 28%, more polar) as colorless oils. Compound **111β**: IR ($CHCl_3$) 3398, 2954, 2926, 2854, 1517, 1460, 1251, 1072, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (m, 6H), 7.39 (m, 2H), 7.33 (m, 9H), 6.89 (m, 2H), 5.66 (m, 2H), 5.54 (s, 1H), 5.46 (m, 1H), 5.32 (m, 1H), 4.58 (m, 1H), 4.14 (dd, *J*=11.3, 4.6 Hz, 1H), 3.95 (m, 1H), 3.87 (m, 1H), 3.80 (s, 3H), 3.72 (d, *J*=9.8 Hz, 1H), 3.61 (m, 2H), 3.55 (m, 1H), 3.41 (m, 1H), 3.24 (br, 1H), 2.64 (m, 1H), 2.46 (m, 1H), 2.16 (m, 1H), 1.82 (m, 1H), 1.71 (m, 2H), 1.53 (m, 5H), 1.35 (m, 2H), 1.06 (d, *J*=7.2 Hz, 3H), 1.01 (d, *J*=6.6 Hz, 3H), 0.95 (s, 9H), 0.93 (s, 9H), 0.90 (m, 9H), 0.85 (s, 9H), 0.78 (d, *J*=6.6 Hz, 3H), 0.14 (m, 6H), 0.09 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 144.5, 144.3, 134.4, 132.9, 132.4, 130.7, 128.7, 127.9, 127.8, 127.7, 127.6, 127.2, 127.1, 126.8, 113.6, 101.2, 89.1, 86.7, 80.0, 76.9, 73.1, 72.2, 66.5, 65.1, 42.3, 41.5, 41.4, 37.0, 36.7, 35.1, 32.5, 32.1, 30.4, 30.3, 26.2, 25.93, 25.87, 20.4, 19.4, 18.4, 18.1, 18.0, 15.4, 13.2, 11.8, 5.4, −3.0, −3.5, −3.7, −4.2, −4.27, −4.33; LRMS (ESI) 1213.7 $[M+Na]^+$; HRMS (ESI) calcd for $C_{72}H_{114}O_8Si_3Na$ 1213.7719 $[M+Na]^+$, found 1213.7861; $[\alpha]_D^{20}$ +6.5 (*c* 0.31, $CHCl_3$). Compound **111α**: IR ($CHCl_3$) 3540, 2956, 2929, 2855, 1615, 1518, 1461, 1383, 1251, 1074, 835, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (m, 6H), 7.51 (m, 2H), 7.44–7.32 (m, 9H), 7.00 (m, 2H), 5.77 (m, 2H), 5.61 (s, 1H), 5.55 (m, 1H), 5.45 (m, 1H), 4.71 (m, 1H), 4.24 (dd, *J*=11.1, 4.5 Hz, 1H), 4.07 (m, 1H), 4.01 (m, 1H), 3.88 (s, 3H), 3.73–3.60 (m, 4H), 3.54 (m, 1H), 2.76 (m, 1H), 2.56 (m, 1H), 2.49 (m, 1H), 2.24 (m, 1H), 1.94–1.78 (m, 4H), 1.72–1.46 (m, 6H), 1.42–1.31 (m, 2H), 1.22 (d, *J*=7.0 Hz, 3H), 1.13 (d, *J*=5.9 Hz, 3H), 1.06 (s, 18H), 1.03 (m, 6H), 0.96 (s, 9H), 0.86 (d, *J*=6.6 Hz, 3H), 0.27–0.18 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 144.4, 144.3, 134.3, 132.9, 132.4, 131.0, 128.6, 127.6, 127.2, 126.8, 113.5, 101.0, 86.7, 82.8, 79.8, 74.8, 73.2, 72.2, 66.4, 65.0, 55.1, 42.3, 41.5, 37.8, 35.9, 34.9, 33.2, 32.4, 30.3, 30.2, 26.2, 25.92, 25.87, 20.4, 19.3, 18.4, 18.1, 18.0, 15.3, 13.2, 11.8, 11.0, −3.0, −3.4, −3.7, −3.9, −4.2, −4.28, −4.34; LRMS (ESI) 1213.9 $[M+Na]^+$; HRMS (ESI) calcd for $C_{72}H_{114}O_8Si_3Na$ 1213.7719 $[M+Na]^+$, found 1213.7760; $[\alpha]_D^{20}$ +2.3 (*c* 0.75, $CHCl_3$).

4.27. (4*S*,5*S*)-4-((2*R*,3*R*,6*S*,8*S*,9*R*,10*S*,11*Z*,13*S*,15*S*,16*R*,17*E*)-3,9,13,15-Tetrakis(*tert*-butyldimethylsilyloxy)-6,8,10,16-tetramethyl-19-(trityloxy)nonadeca-11,17-dien-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxane (112β)

TBSOTf (0.40 mL, 1.74 mmol) was added to a stirred solution of alcohol **111β** (1.39 g, 1.17 mmol) and 2,6-lutidine (0.27 mL, 2.33 mmol) in CH_2Cl_2 (23 mL) at 0 °C. After stirring for 1 h at ambient temperature, the reaction mixture was quenched by the addition of water (50 mL) and extracted with CH_2Cl_2. After drying the organic phases over $MgSO_4$ and concentrated under reduced pressure, the residue was purified by short column chromatography (hexane/EtOAc 9:1) to yield **112β** (1.51 g, 99%) as a colorless oil: IR ($CHCl_3$) 2955, 2928, 2855, 1615, 1517, 1461, 1250, 1074, 1039, 835, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (m, 6H), 7.52 (m, 2H), 7.41 (m, 9H), 7.01 (m, 2H), 5.74 (m, 2H), 5.57 (s, 1H), 5.50 (m, 1H), 5.43 (m, 1H), 4.67 (m, 1H), 4.25 (dd, *J*=11.3, 4.6 Hz, 1H), 4.04 (m, 1H), 3.94 (s, 3H), 3.78 (m, 1H), 3.70 (m, 3H), 3.49 (m, 1H), 3.16 (m, 1H), 2.72 (m 1H), 2.54 (m, 1H), 2.18 (m, 1H), 2.01 (m, 1H), 1.82 (m, 3H), 1.54 (m, 6H), 1.14 (d, *J*=6.9 Hz, 3H), 1.11 (d, *J*=6.8 Hz, 3H), 1.10 (d, *J*=6.5 Hz, 3H), 1.05 (s, 9H), 1.03 (s, 9H), 1.02 (s, 12H), 0.98 (d, *J*=6.3 Hz, 3H), 0.94 (s, 9H), 0.87 (d, *J*=6.7 Hz, 3H), 0.24 (s, 3H), 0.22 (s, 3H), 0.17 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 144.5, 144.3, 134.4, 133.1, 132.6, 131.5, 128.6, 127.7, 127.6, 127.1, 126.8, 126.7, 113.3, 100.4, 86.7, 81.9, 79.8, 74.9, 73.3, 72.2, 66.4, 65.1, 55.1, 42.3, 41.5, 38.8, 35.9, 34.5, 31.3, 31.2, 30.8, 30.7, 26.3, 25.99, 25.97, 25.91, 22.6, 20.3, 19.2, 18.5, 18.10, 18.05, 15.1, 14.1, 13.1, 12.4, 10.6, −3.0, −3.2, −3.6, −4.2, −4.25, −4.30; LRMS (ESI) 1327.8 $[M+Na]^+$; HRMS (ESI) calcd for $C_{78}H_{128}O_8Si_4Na$ 1327.8584 $[M+Na]^+$, found 1327.8693; $[\alpha]_D^{20}$ +7.6 (*c* 0.17, $CHCl_3$).

4.28. (2*S*,3*S*,4*R*,5*R*,8*S*,10*S*,11*R*,12*S*,13*Z*,15*S*,17*S*,18*R*,19*E*)-3-(4-Methoxybenzyloxy)-5,11,15,17-tetrakis(*tert*-butyldimethylsilyloxy)-2,4,8,10,12,18-hexamethyl-21-(trityloxy)henicosa-13,19-dien-1-ol (113β)

DIBALH (1.0 M in hexane, 11.7 mL, 11.7 mmol) was added dropwise to a stirred solution of acetal **112β** (1.53 g, 1.17 mmol) in anhydrous CH_2Cl_2 (2.3 mL) under an atmosphere of N_2 at 0 °C. After stirring for additional 30 min at 0 °C, the reaction was quenched by careful addition of saturated aqueous potassium sodium tartrate (30 mL). The resulting mixture was stirred for 3 h at room temperature. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were washed with brine and dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane 1:9) to yield pure **113β** (1.35 g, 88%) as a colorless oil: IR ($CHCl_3$) 3464, 2956, 2929, 2856, 1613, 1514, 1471, 1252, 1087, 836, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (m, 6H), 7.28 (m, 11H), 6.88 (m, 2H), 5.61 (m, 2H), 5.39 (m, 1H), 5.28 (m, 1H), 4.57 (m, 1H), 4.53 (s, 2H), 3.92 (m, 2H), 3.83 (m, 1H), 3.80 (s, 3H), 3.60 (m, 2H), 3.56 (m, 2H), 3.46 (dd, *J*=6.2, 4.5 Hz, 1H), 3.37 (m, 1H), 3.03 (m, 1H), 2.86 (m 1H), 2.59 (m, 1H), 2.41 (m, 1H), 1.93 (m, 1H), 1.88 (m, 1H), 1.66 (m, 2H), 1.35 (m, 4H), 1.11 (d, *J*=7.0 Hz, 3H), 1.01 (d, *J*=6.8 Hz, 3H), 0.97 (d, *J*=6.8 Hz,

3H), 0.92 (m, 27H), 0.85 (m, 10H), 0.81 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 6H), 0.05 (s, 6H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 144.4, 144.3, 134.3, 133.0, 132.4, 130.5, 129.1, 128.6, 127.6, 126.7, 113.8, 86.7, 85.4, 79.8, 75.1, 73.8, 72.2, 66.4, 65.0, 55.0, 42.3, 41.6, 41.5, 40.5, 37.1, 35.8, 34.8, 32.0, 31.9, 30.7, 26.2, 25.94, 25.86, 20.3, 19.2, 18.4, 18.1, 18.0, 15.6, 15.2, 13.2, 10.0, −3.0, −3.4, −3.8, −3.9, −4.2, −4.28, −4.34, −4.4; LRMS (ESI) 1329.8 $[M+Na]^+$; HRMS (ESI) calcd for $C_{78}H_{130}O_8Si_4Na$ 1329.8741 $[M+Na]^+$, found 1329.8779; $[\alpha]_D^{20}$ −8.9 (*c* 0.46, $CHCl_3$).

4.29. ((2*E*,4*R*,5*S*,7*S*,8*Z*,10*S*,11*R*,12*S*,14*S*,17*R*,18*R*,19*S*,20*S*,21*Z*)-19-(4-Methoxybenzyloxy)-5,7,11,17-tetrakis-(*tert*-butyldimethylsilyloxy)-4,10,12,14,18,20-hexamethyltetracosa-2,8,21,23-tetraenyloxy)triphenylmethane (114β)

Alcohol **113β** (1.35 g, 1.03 mmol) in CH_2Cl_2 (20 mL) was treated with Dess–Martin periodinane (0.66 g, 1.56 mmol). After 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) and $Na_2S_2O_3$ (20 mL). The aqueous layer was extracted with Et_2O (2×20 mL), and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by short flash column chromatography (hexane/EtOAc 9:1) provided the crude aldehyde as a colorless oil, which was used without further purification. $CrCl_2$ (1.06 g, 8.62 mmol) was added to a stirred solution of the crude aldehyde and 1-bromoallyl trimethylsilane (1.28 g, 5.20 mmol) in anhydrous THF (26 mL) under an atmosphere of N_2 at room temperature. After 14 h at ambient temperature, the reaction mixture was diluted with hexane followed by filtration through Celite. The solvent was evaporated under reduced pressure, and the residue was purified by short silica gel column chromatography using EtOAc/hexane (1:9) as eluant. This product in THF (40 mL) was cooled to 0 °C, and NaH (95% w/w, 0.52 g, 20.6 mmol) was added in one portion. The ice bath was removed after 15 min, and the mixture was stirred for 2 h at ambient temperature and then cooled to 0 °C. The reaction was quenched with H_2O (5 mL) and the mixture extracted with Et_2O (2×20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc 49:1) to obtain **114β** (1.17 g, 85% in three steps) as a colorless oil: IR ($CHCl_3$) 2956, 2928, 2856, 1614, 1514, 1471, 1462, 1249, 1088, 836, 772 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (m, 6H), 7.27 (m, 11H), 6.86 (m, 2H), 6.58 (ddd, *J*=17.0, 10.6, 10.5 Hz, 1H), 6.00 (t, *J*=11.0 Hz, 1H), 5.60 (m, 3H), 5.31 (m, 2H), 5.17 (d, *J*=16.9 Hz, 1H), 5.09 (d, *J*=10.4 Hz, 1H), 4.51 (m, 3H), 3.90 (m, 1H), 3.80 (s, 3H), 3.61 (m, 1H), 3.56 (d, *J*=3.7 Hz, 1H), 3.33 (m, 2H), 3.00 (m, 1H), 2.56 (m, 1H), 2.40 (m, 1H), 2.21 (m, 1H), 1.63 (m, 3H), 1.38–1.21 (5H), 1.10 (d, *J*=6.7 Hz, 3H), 0.96 (m, 3H), 0.93 (s, 9H), 0.91 (s, 9H), 0.89 (s, 9H), 0.86 (m, 6H), 0.82 (m, 6H), 0.80 (s, 9H), 0.79 (m, 3H), 0.08 (m, 6H), 0.05 (m, 6H), 0.04 (m, 6H), 0.01 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 146.2, 144.5, 144.4, 134.6, 134.5, 133.1, 132.7, 132.3, 131.4, 129.0, 128.9, 128.7, 127.7, 126.8, 117.1, 113.7, 86.8, 84.4, 79.9, 75.0, 72.9, 72.3, 66.5, 65.1, 55.2, 42.4, 41.9, 41.6, 40.6, 36.0, 35.6, 35.3, 34.5, 32.5, 31.7, 30.5, 26.3, 26.0, 25.9, 20.2, 19.2, 18.8, 18.5, 18.2, 18.1, 15.1, 13.3, 9.3, −2.9, −3.0, −3.3, −3.6, −3.7, −4.2, −4.3, −4.4; LRMS (ESI) 1351.8 $[M+Na]^+$; HRMS (ESI) calcd for $C_{81}H_{132}O_7Si_4Na$ 1351.8948 $[M+Na]^+$, found 1351.9012; $[\alpha]_D^{20}$ +1.1 (*c* 1.7, $CHCl_3$).

4.30. (2*E*,4*R*,5*S*,7*S*,8*Z*,10*S*,11*R*,12*S*,14*S*,17*R*,18*R*,19*S*,20*S*,21*Z*)-19-(4-Methoxybenzyloxy)-5,7,11,17-tetrakis-(*tert*-butyldimethylsilyloxy)-4,10,12,14,18,20-hexamethyltetracosa-2,8,21,23-tetraen-1-ol (115β)

$ZnBr_2$ (0.41 g) in 1.2 mL of 5:1 CH_2Cl_2/MeOH was added dropwise over 30 min to a stirred solution of **114β** (0.24 g, 0.18 mmol) in 1.4 mL of 6:1 CH_2Cl_2/MeOH at 0 °C. After 4 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) and the mixture was extracted with Et_2O (2×10 mL). The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (EtOAc/hexane 1:9) to yield **115β** (0.15 g, 77%) as a colorless oil: IR ($CHCl_3$) 3432, 2956, 2856, 1613, 1514, 1471, 1462, 1360, 1250, 1082, 835, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 2H), 6.88 (m, 2H), 6.58 (ddd, *J*=16.9, 10.6, 10.6 Hz, 1H), 6.00 (t, *J*=11.0 Hz, 1H), 5.63 (m, 3H), 5.38 (t, *J*=11.0 Hz, 1H), 5.27 (dd, *J*=11.2, 8.3 Hz, 1H), 5.17 (d, *J*=16.8 Hz, 1H), 5.10 (d, *J*=10.3 Hz, 1H), 4.53 (m, 3H), 4.08 (d, *J*=4.4 Hz, 2H), 3.90 (m, 1H), 3.81 (s, 3H), 3.62 (m, 1H), 3.33 (m, 2H), 2.99 (ddd, *J*=10.0, 6.8, 3.2 Hz, 1H), 2.57 (m, 1H), 2.39 (m, 1H), 1.63 (m, 3H), 1.42 (m, 3H), 1.28 (m, 5H), 1.11 (d, *J*=6.8 Hz, 3H), 0.97 (d, *J*=6.8 Hz, 3H), 0.96 (d, *J*=6.9 Hz, 3H), 0.93 (s, 9H), 0.91 (s, 18H), 0.89 (m, 3H), 0.88 (s, 9H), 0.81 (d, *J*=6.7 Hz, 3H), 0.80 (d, *J*=6.2 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 6H), 0.06 (s, 3H), 0.05 (s, 6H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 146.9, 135.2, 134.6, 133.0, 132.7, 132.3, 131.4, 129.2, 129.1, 128.9, 127.93, 127.90, 127.2, 84.4, 80.0, 75.0, 72.8, 72.2, 66.6, 63.9, 55.2, 42.4, 41.8, 41.7, 40.5, 35.9, 35.2, 34.6, 32.6, 31.6, 30.5, 26.3, 25.99, 25.96, 25.93, 20.2, 19.2, 18.8, 18.5, 18.2, 18.1, 15.1, 13.2, 9.2, −3.0, −3.3, −3.6, −3.7, −4.2, −4.4, −4.5; LRMS (ESI) 1109.8 $[M+Na]^+$; HRMS (ESI) calcd for $C_{62}H_{118}O_7Si_4Na$ 1109.7852 $[M+Na]^+$, found 1109.7897; $[\alpha]_D^{20}$ +1.6 (*c* 0.94, $CHCl_3$).

4.31. (2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,23*Z*)-Methyl-21-(4-methoxybenzyloxy)-7,9,13,19-tetrakis(*tert*-butyldimethylsilyloxy)-6,12,14,16,20,22-hexamethylhexacosa-2,4,10,23,25-pentaenoate (116β)

Alcohol **115β** (127 mg, 0.117 mmol) in CH_2Cl_2 (4 mL) was treated with Dess–Martin periodinane (75 mg, 0.18 mmol). After 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (5 mL). The aqueous layer was extracted with Et_2O (2×10 mL), and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by short flash column chromatography (hexane/EtOAc 9:1) provided the crude aldehyde as a colorless oil, which was used for the next reaction without further purification. KHMDS (0.28 mL, 0.14 mmol, 0.5 M solution in toluene) was added dropwise to a stirred solution of bis(2,2,2-trifluoroethyl)-(methoxycarbonylmethyl) phosphate (0.030 mL, 0.14 mmol) and 18-crown-6 (0.15 g, 0.57 mmol) in THF (2.3 mL) at −78 °C. The aldehyde in

THF (0.5 mL) was added and the solution was stirred for 4 h at −78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL) and the mixture was diluted with Et_2O (20 mL). The organic phase was washed with brine (30 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (EtOAc/hexane 1:19) yielding ester **116β** (0.104 g, 86% in two steps) as a colorless oil: IR ($CHCl_3$) 2955, 2929, 2856, 1722, 1514, 1471, 1462, 1250, 1174, 1085, 1041, 836, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (dd, J=15.4, 11.3 Hz, 1H), 7.29 (m, 2H), 6.88 (m, 2H), 6.59 (ddd, J=16.9, 10.8, 10.6 Hz, 1H), 6.55 (t, J=11.3 Hz, 1H), 6.01 (t, J=11.0 Hz, 1H), 6.00 (dd, J=15.7, 7.0 Hz, 1H), 5.60 (d, J=11.3 Hz, 1H), 5.59 (t, J=10.4 Hz, 1H), 5.39 (t, J=10.4 Hz, 1H), 5.27 (dd, J=11.0, 8.3 Hz, 1H), 5.18 (d, J=16.8 Hz, 1H), 5.11 (d, J=10.3 Hz, 1H), 4.54 (m, 3H), 3.96 (m, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 3.63 (m, 1H), 3.34 (m, 2H), 3.00 (m, 1H), 2.57 (m, 2H), 1.64 (m, 3H), 1.55 (m, 1H), 1.46 (t, J=5.9 Hz, 2H), 1.26 (m, 5H), 1.11 (d, J=6.8 Hz, 3H), 1.05 (d, J=6.7 Hz, 3H), 0.97 (d, J=6.9 Hz, 3H), 0.96 (d, J=7.1 Hz, 3H), 0.94 (s, 9H), 0.92 (s, 9H), 0.91 (s, 9H), 0.87 (s, 9H), 0.83 (d, J=6.4 Hz, 3H), 0.82 (d, J=6.0 Hz, 3H), 0.13 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.05 (s, 6H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 159.0, 147.3, 145.5, 134.6, 132.9, 132.8, 132.4, 131.4, 129.0, 128.9, 126.9, 117.1, 115.5, 113.7, 84.4, 80.0, 75.0, 72.9, 72.1, 66.5, 55.2, 50.9, 43.5, 42.5, 41.8, 40.5, 36.0, 35.3, 34.5, 32.5, 31.6, 30.5, 26.3, 25.99, 25.96, 25.91, 20.2, 19.2, 18.8, 18.5, 18.2, 18.1, 15.0, 13.4, 9.2, −3.0, −3.2, −3.3, −3.6, −3.7, −4.1, −4.4, −4.5; LRMS (ESI) 1163.9 $[M+Na]^+$; HRMS (ESI) calcd for $C_{65}H_{120}O_8Si_4Na$ 1163.7958 $[M+Na]^+$, found 1163.7985; $[\alpha]_D^{20}$ −9.3 (*c* 1.2, $CHCl_3$).

4.32. (2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,23*Z*)-Methyl-7,9,13,19-tetrakis(*tert*-butyldimethylsilyloxy)-21-hydroxy-6,12,14,16,20,22-hexamethylhexacosa-2,4,10,23,25-pentaenoate (117β)

Ester **116β** (81 mg, 71 μmol) was added to a mixture of CH_2Cl_2 (2 mL) and H_2O (0.1 mL), and DDQ (20 mg, 88 μmol) was added at 0 °C. After 1 h at 0 °C, the reaction was quenched by adding saturated aqueous $NaHCO_3$ (5 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (3×10 mL) and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (EtOAc/hexane 1:9) furnished **117β** (64 mg, 88%) as a colorless oil: IR ($CHCl_3$) 3541, 2956, 2929, 2856, 1722, 1639, 1471, 1462, 1377, 1360, 1254, 1175, 1086, 836, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (dd, J=15.4, 11.2 Hz, 1H), 6.61 (ddd, J=16.8, 10.7, 10.6 Hz, 1H), 6.51 (t, J=11.3 Hz, 1H), 6.06 (t, J=11.0 Hz, 1H), 5.96 (dd, J=15.4, 7.1 Hz, 1H), 5.56 (d, J=11.3 Hz, 1H), 5.39 (t, J=10.1 Hz, 1H), 5.38 (t, J=10.3 Hz, 1H), 5.22 (dd, J=11.0, 8.5 Hz, 1H), 5.17 (d, J=18.7 Hz, 1H), 5.09 (d, J=10.1 Hz, 1H), 4.50 (m, 1H), 3.92 (m, 1H), 3.71 (m, 1H), 3.70 (s, 3H), 3.44 (m, 1H), 3.32 (m, 1H), 2.74 (m, 1H), 2.52 (m, 2H), 2.31 (br, 1H), 1.61 (m, 4H), 1.39 (m, 2H), 1.31 (m, 2H), 1.26 (m, 3H), 1.00 (d, J=6.7 Hz, 3H), 0.93 (d, J=6.9 Hz, 3H), 0.92 (d, J=6.7 Hz, 3H), 0.86 (m, 27H), 0.84 (m, 6H), 0.82 (m, 12H), 0.05 (s, 9H), 0.02 (s, 3H), 0.01 (s, 6H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 147.3, 145.5, 135.3, 132.7, 132.6, 132.3, 129.9, 126.8, 117.7, 115.5, 79.9, 77.6, 76.6, 72.1, 66.5, 51.0, 43.5, 42.4, 41.5, 37.7, 36.1, 35.7, 35.0, 32.1, 31.5, 30.6, 26.3, 25.9, 25.9, 20.4, 19.4, 18.5, 18.1, 17.9, 17.7, 15.3, 13.3, 6.9, −3.0, −3.4, −3.7, −4.1, −4.2, −4.4; LRMS (ESI) 1043.6 $[M+Na]^+$; HRMS (ESI) calcd for $C_{57}H_{112}O_7Si_4Na$ 1043.7383 $[M+Na]^+$, found 1043.7417; $[\alpha]_D^{20}$ −25.3 (*c* 0.61, $CHCl_3$).

4.33. (2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,23*Z*)-7,9,13,19-Tetrakis(*tert*-butyldimethylsilyloxy)-21-hydroxy-6,12,14,16,20,22-hexamethylhexacosa-2,4,10,23,25-pentaenoic acid (118β)

A stirred solution of alcohol **117β** (26 mg, 24 μmol) in 2.4 mL of 12:5 EtOH/THF was treated with 1 N aqueous KOH (0.24 mL), and the mixture was refluxed gently for 3 h. The ethanolic solution was concentrated and then diluted with Et_2O (4 mL). After the solution was acidified to pH 3 with 1 N aqueous HCl, the organic phase was separated and the aqueous phase was extracted with Et_2O (2×5 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography (15% EtOAc/hexane) to give 15.7 mg (61%) alcohol: IR ($CHCl_3$) 2956, 2929, 2857, 1693, 1635, 1600, 1471, 1462, 1254, 1088, 836, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (dd, J=15.2, 11.3 Hz, 1H), 6.61 (t, J=11.4 Hz, 1H), 6.61 (m, 1H), 6.07 (t, J=11.0 Hz, 1H), 6.02 (dd, J=15.8, 7.2 Hz, 1H), 5.58 (d, J=11.3 Hz, 1H), 5.39 (m, 2H), 5.23 (dd, J=11.0, 8.2 Hz, 1H), 5.18 (d, J=16.8 Hz, 1H), 5.09 (d, J=10.2 Hz, 1H), 4.50 (m, 1H), 3.92 (m, 1H), 3.73 (m, 1H), 3.46 (dd, J=7.3, 2.6 Hz, 1H), 3.34 (m, 1H), 2.78 (m, 1H), 2.54 (m, 2H), 1.66 (m, 4H), 1.42 (m, 4H), 1.24 (m, 3H), 1.01 (d, J=6.8 Hz, 3H), 0.95 (d, J=6.7 Hz, 3H), 0.94 (d, J=6.7 Hz, 3H), 0.88 (m, 30H), 0.84 (m, 15H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 6H), 0.02 (s, 6H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 148.2, 147.3, 135.2, 133.2, 132.7, 132.3, 123.0, 127.0, 117.7, 115.2, 79.9, 77.6, 76.5, 72.1, 66.4, 43.5, 42.6, 41.6, 37.8, 36.0, 35.8, 34.9, 32.1, 31.5, 30.6, 26.2, 25.93, 25.87, 20.3, 19.4, 18.4, 18.10, 18.05, 17.7, 15.3, 13.6, 6.9, −3.0, −3.4, −3.7, −4.1, −4.19, −4.24, −4.4; LRMS (ESI) 1029.7 $[M+Na]^+$; HRMS (ESI) calcd for $C_{56}H_{110}O_7Si_4Na$ 1029.7226 $[M+Na]^+$, found 1029.7274; $[\alpha]_D^{20}$ −25.7 (*c* 0.54, $CHCl_3$).

4.34. (8*S*,10*S*,14*R*,20*R*)-Tetrakis(*tert*-butyldimethylsilyloxy)-(7*R*,13*S*,15*S*,17*S*,21*S*)-pentamethyl-(22*S*)-((1*S*)-methylpenta-2,4-dienyl)oxacyclodocosa-3,5,11-trien-2-one (119β)

A solution of **118β** (15.7 mg, 15.6 μmol) in THF (2 mL) was treated at 0 °C with Et_3N (0.013 mL, 93 μmol) and 2,4,6-trichlorobenzoyl chloride (0.012 mL, 77 μmol). The reaction mixture was stirred at 0 °C for 30 min and then added to 4-DMAP (7.8 mL, 0.02 M solution in toluene) at 25 °C. After stirring for 12 h, the reaction mixture was concentrated, Et_2O (10 mL) was added, and the mixture was washed with 1 N HCl (2×5 mL) and dried over $MgSO_4$. Purification by flash column chromatography (EtOAc/hexane 1:49) furnished the macrolactone (12 mg, 78%) as a colorless oil: IR ($CHCl_3$) 2955, 2929, 2857, 1716, 1642, 1474, 1225, 1043, 836, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.98 (dd, J=14.8, 11.3 Hz, 1H), 6.55 (m, 1H), 6.52 (t, J=11.2 Hz, 1H), 6.04 (t, J=10.5 Hz, 1H), 6.01 (dd, J=15.4,

6.4 Hz, 1H), 5.59 (d, *J*=11.2 Hz, 1H), 5.58 (m, 1H), 5.38 (t, *J*=10.6 Hz, 1H), 5.33 (dd, *J*=11.3, 8.1 Hz, 1H), 5.19 (d, *J*=16.6 Hz, 1H), 5.11 (d, *J*=10.5 Hz, 1H), 5.06 (dd, *J*= 7.6, 3.7 Hz, 1H), 4.52 (m, 1H), 4.01 (m, 1H), 3.63 (m, 1H), 3.19 (d, *J*=6.2 Hz, 1H), 3.03 (m, 1H), 2.58 (m, 1H), 2.52 (m, 2H), 1.81 (m, 4H), 1.45 (m, 3H), 1.25 (m, 3H), 1.09 (m, 3H), 1.02 (d, *J*=6.8 Hz, 3H), 1.01 (d, *J*=7.0 Hz, 3H), 0.97 (d, *J*=6.6 Hz, 3H), 0.95 (d, *J*=6.4 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.77 (d, *J*=6.4 Hz, 3H), 0.75 (d, *J*=6.5 Hz, 3H), 0.10 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.033 (s, 6H), 0.026 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 143.1, 141.8, 133.9, 132.7, 131.8, 130.2, 129.8, 128.0, 118.4, 118.1, 81.0, 78.0, 70.4, 66.5, 62.5, 43.1, 42.3, 41.4, 39.1, 35.2, 34.8, 34.5, 31.6, 30.3, 29.7, 29.3, 26.2, 26.0, 25.94, 25.85, 20.2, 19.7, 18.5, 18.24, 18.16, 18.08, 16.2, 14.0, 9.9, −2.7, −3.4, −3.5, −3.8, −3.9, −4.2, −4.3; $[\alpha]_D^{20}$ −18.1 (*c* 0.24, $CHCl_3$). A small amount of the impure 2*E*,4*E*-isomer was also isolated: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, *J*=11.2, 15.5 Hz, 1H), 6.63 (dt, *J*=10.5, 16.8 Hz, 1H), 6.44 (t, *J*=11.3 Hz, 1H), 6.01–5.80 (m, 2H), 5.57 (t, *J*=10.6 Hz, 1H), 5.50 (d, *J*=11.4 Hz, 1H), 5.38 (t, *J*=10.3 Hz, 1H), 5.30 (dd, *J*=8.5, 11.0 Hz, 1H), 5.22–5.01 (m, 3H), 4.47 (m, 1H), 3.77 (m, 1H), 3.48 (m, 1H), 3.30 (m, 1H), 2.97 (m, 1H), 2.56 (m, 1H), 2.44 (m, 1H), 1.91 (m, 1H), 1.65 (m, 1H), 1.52–0.71 (m, 63H), 0.12–0.04 (m, 24H).

4.35. (8*S*,10*S*,14*R*,20*R*)-Tetrahydroxy-(7*R*,13*S*,15*S*, 17*S*,21*S*)-pentamethyl-(22*S*)-((1*S*)-methylpenta-2,4-dienyl)oxacyclodocosa-3,5,11-trien-2-one (1)

A stirred solution of macrolactone **119β** (18 mg, 18 μmol) in THF (3 mL) at 0 °C was treated with 3 N HCl (10 mL, prepared by adding 2.5 mL of concd HCl to 7.5 mL MeOH). After 24 h at room temperature, the reaction mixture was diluted with EtOAc (4 mL) and H_2O (4 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (2×4 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (EtOAc/hexane 3:2) to yield **1** as a white solid (5.3 mg, 55%): IR ($CHCl_3$) 3406, 2960, 2924, 2872, 1693, 1637, 1461, 1378, 1274, 1181, 1069, 998, 738 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) δ 7.21 (dd, *J*=15.6, 11.1 Hz, 1H), 6.71 (ddd, *J*=16.9, 11.0, 10.6 Hz, 1H), 6.65 (dd, *J*=11.3, 11.3 Hz, 1H), 6.17 (dd, *J*=15.6, 6.7 Hz, 1H), 6.06 (dd, *J*=11.1, 11.1 Hz, 1H), 5.56 (d, *J*=11.3 Hz, 1H), 5.55 (dd, *J*=11.0, 11.0 Hz, 1H), 5.41 (dd, *J*=11.1, 8.8 Hz, 1H), 5.34 (dd, *J*=10.7, 10.6 Hz, 1H), 5.25 (dd, *J*=16.8, 1.8 Hz, 1H), 5.15 (d, *J*=10.1 Hz, 1H), 5.14 (dd, *J*=7.0, 5.0 Hz, 1H), 4.65 (ddd, *J*=9.5, 9.5, 3.3 Hz, 1H), 4.05 (ddd, *J*=10.6, 3.7, 2.8 Hz, 1H), 3.37 (m, 1H), 3.17 (ddq, *J*=10.1, 6.8, 6.6 Hz, 1H), 3.10 (dd, *J*=8.1, 2.9 Hz, 1H), 2.76 (m, 1H), 2.60 (m, 1H), 1.89 (m, 1H), 1.84 (dddd, *J*=12.9, 11.2, 6.4, 5.4 Hz, 1H), 1.60 (m, 1H), 1.58 (m, 1H), 1.54 (m, 1H), 1.50 (ddd, *J*=14.1, 10.7, 3.5 Hz, 1H), 1.42 (ddd, *J*=14.0, 10.0, 2.7 Hz, 1H), 1.25 (ddd, *J*=13.7, 10.6, 3.6 Hz, 1H), 1.15 (d, *J*=6.9 Hz, 3H), 1.12 (d, *J*=7.0 Hz, 3H), 1.10 (m, 1H), 1.07 (d, *J*=6.9 Hz, 3H), 1.01 (d, *J*=6.8 Hz, 3H), 0.95 (d, *J*=6.5 Hz, 3H), 0.93 (d, *J*=6.5 Hz, 3H), 0.90 (m, 1H), 0.71 (dddd, *J*=12.9, 12.8, 8.7, 4.9 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 168.10, 146.42, 144.90, 134.87, 134.54, 133.43, 131.32, 131.27, 128.60, 118.58, 118.04, 80.37, 78.64, 73.73, 70.41, 65.53, 44.07, 42.28, 40.84, 40.65, 35.84, 35.78, 35.33, 32.75, 32.51, 31.23, 21.81, 19.36, 18.08, 15.98, 13.80, 10.41; LRMS (ESI) 555.3 [M+Na]$^+$; HRMS (ESI) calcd for $C_{32}H_{52}O_6Na$ 555.3662 [M+Na]$^+$, found 555.3665; $[\alpha]_D^{20}$ −22.6 (*c* 0.27, MeOH).

4.36. (2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,16*S*, 19*R*,20*S*,21*S*,22*S*,23*Z*)-Methyl-7,9,13,19,21-pentahydroxy-6,12,14,16,20,22-hexamethylhexacosa-2,4,10,23,25-pentaenoate (120β)

HCl (3 N, 10 mL, prepared by adding 2.5 mL of concd HCl to 7.5 mL MeOH) was added to a stirred solution of **116β** (23 mg, 23 μmol) in THF (3 mL) at 0 °C. After 24 h at room temperature, the reaction mixture was diluted with EtOAc (4 mL) and H_2O (4 mL). The organic phase was retained, and the aqueous phase was extracted with EtOAc (2×4 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (EtOAc/hexane 3:2) to yield the product **120β** (4.5 mg, 36%) as a colorless oil: IR ($CHCl_3$) 3399, 2917, 2849, 1713, 1635, 1600, 1461, 1439, 1197, 1178, 970, 757 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) δ 7.36 (dd, *J*=15.3, 11.2 Hz, 1H), 6.67 (ddd, *J*=16.9, 11.1, 10.6 Hz, 1H), 6.63 (dd, *J*=11.3, 11.3 Hz, 1H), 6.14 (dd, *J*=15.4, 8.3 Hz, 1H), 6.03 (dd, *J*=11.0, 11.0 Hz, 1H), 5.59 (d, *J*= 11.4 Hz, 1H), 5.43 (dd, *J*=10.7, 10.7 Hz, 1H), 5.42 (dd, *J*= 10.8, 9.2 Hz, 1H), 5.32 (dd, *J*=10.4, 10.4 Hz, 1H), 5.17 (dd, *J*=16.8, 2.0 Hz, 1H), 5.08 (d, *J*=10.2 Hz, 1H), 4.61 (ddd, *J*=12.9, 8.5, 4.6 Hz, 1H), 3.80 (ddd, *J*=8.9, 4.4, 4.4 Hz, 1H), 3.69 (s, 3H), 3.63 (m, 1H), 3.46 (t, *J*=5.8 Hz, 1H), 3.13 (dd, *J*=8.0, 3.2 Hz, 1H), 2.93 (m, 1H), 2.71 (m, 1H), 2.38 (m, 1H), 1.73 (m, 1H), 1.56–1.53 (m, 3H), 1.52–1.46 (m, 2H), 1.44–1.36 (m, 3H), 1.09 (d, *J*=6.9 Hz, 3H), 0.98 (d, *J*=6.8 Hz, 3H), 0.96 (d, *J*=6.6 Hz, 3H), 0.95 (m, 2H), 0.94 (d, *J*=6.9 Hz, 3H), 0.87 (d, *J*=6.6 Hz, 3H), 0.86 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 168.4, 148.5, 146.9, 135.7, 135.4, 133.85, 133.82, 130.6, 128.2, 117.7, 116.2, 79.2, 78.5, 74.8, 72.4, 65.8, 51.5, 45.1, 43.2, 43.0, 41.0, 37.2, 36.5, 34.0, 33.3, 33.1, 31.0, 20.7, 18.6, 18.4, 16.7, 13.8, 7.8; LRMS (ESI) 587.5 [M+Na]$^+$; HRMS (ESI) calcd for $C_{33}H_{56}O_7Na$ 587.3924 [M+Na]$^+$, found 587.3953; $[\alpha]_D^{20}$ +8.7 (*c* 0.30, $CDCl_3$).

4.37. (4*S*,5*S*)-4-((2*R*,3*S*,6*S*,8*S*,9*R*,10*S*,11*Z*,13*S*,15*S*,16*R*, 17*E*)-3,9,13,15-Tetrakis(*tert*-butyldimethylsilyloxy)-6,8,10,16-tetramethyl-19-trityloxynonadeca-11,17-dien-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxane (112α)

The procedure for **112β** was used with **112α** (0.58 g, 0.49 mmol), TBSOTf (0.17 mL, 0.74 mmol), and 2,6-lutidine (0.11 mL, 0.97 mmol) to yield 0.62 g (97%) of the product by flash column chromatography (EtOAc/hexane 1:9) as a colorless oil: IR ($CHCl_3$) 2955, 2856, 1615, 1518, 1462, 1385, 1251, 1082, 835, 773, 705 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 6H), 7.49 (m, 2H), 7.40–7.27 (m, 9H), 6.96 (m, 2H), 5.72 (m, 2H), 5.53 (m, 1H), 5.52 (s, 1H), 5.38 (m, 1H), 4.65 (m, 1H), 4.19 (dd,

J=11.0, 4.4 Hz, 1H), 4.03 (m, 1H), 3.95 (d, J=8.7 Hz, 1H), 3.86 (m, 1H), 3.84 (s, 3H), 3.66 (d, J=3.7 Hz, 2H), 3.56 (t, J=11.1 Hz, 1H), 3.50 (m, 1H), 2.71 (m, 1H), 2.52 (m, 1H), 2.12 (m, 1H), 1.90–1.79 (m, 2H), 1.75–1.68 (m, 3H), 1.61–1.37 (m, 6H), 1.08 (d, J=6.6 Hz, 6H), 1.02–0.91 (m, 45H), 0.81 (d, J=6.5 Hz, 3H), 0.22–0.13 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 144.5, 134.4, 132.8, 132.6, 131.7, 128.7, 127.7, 127.3, 126.8, 113.4, 100.9, 86.7, 81.4, 80.1, 73.4, 72.3, 71.5, 66.5, 65.1, 55.1, 42.4, 41.5, 37.9, 35.5, 35.1, 31.3, 30.8, 30.2, 27.9, 26.3, 26.01, 25.99, 25.93, 25.7, 20.6, 19.5, 18.4, 18.11, 18.07, 15.4, 13.4, 13.3, 12.2, 9.2, −2.9, −3.5, −3.7, −3.9, −4.1, −4.2, −4.3, −4.9; LRMS (ESI) 1328.0 [M+Na]$^+$; HRMS (ESI) calcd for $C_{78}H_{128}O_8Si_4Na$ 1327.8584 [M+Na]$^+$, found 1327.8624; $[\alpha]_D^{20}$ +6.1 (c 0.93, $CHCl_3$).

4.38. (2*S*,3*S*,4*R*,5*S*,8*S*,10*S*,11*R*,12*S*,13*Z*,15*S*,17*S*,18*R*,19*E*)-3-(4-Methoxybenzyloxy)-5,11,15,17-tetrakis(*tert*-butyldimethylsilyloxy)-2,4,8,10,12,18-hexamethyl-21-trityloxyhenicosa-13,19-dien-1-ol (113α)

The procedure for **113β** was used with **112α** (0.62 g, 0.47 mmol) and DIBALH (1.0 M in hexane, 4.7 mL, 4.7 mmol) to yield 0.54 g (87%) of the product after flash column chromatography (EtOAc/hexane 1:9) as a colorless oil: IR ($CHCl_3$) 3479, 2955, 2928, 2856, 1613, 1514, 1471, 1251, 1084, 835, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.52 (m, 6H), 7.38–7.33 (m, 9H), 7.30 (m, 2H), 6.94 (m, 2H), 5.72 (m, 2H), 5.52 (m, 1H), 5.38 (m, 1H), 4.67 (d, J=10.3 Hz, 1H), 4.65 (m, 1H), 4.60 (d, J=10.4 Hz, 1H), 4.03 (m, 1H), 3.83 (s, 3H), 3.70 (m, 3H), 3.65 (d, J=3.7 Hz, 2H), 3.49 (m, 1H), 3.02 (m, 1H), 2.71 (m 1H), 2.52 (m, 1H), 1.91 (m, 2H), 1.80–1.64 (m, 3H), 1.60–1.34 (m, 8H), 1.09–0.90 (m, 54H), 0.21–0.12 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 144.5, 144.3, 134.4, 132.8, 132.4, 130.6, 129.0, 128.6, 127.7, 126.8, 113.8, 86.7, 84.7, 80.0, 74.8, 74.5, 72.2, 66.5, 66.2, 65.1, 55.1, 42.3, 41.4, 38.7, 35.5, 35.2, 35.0, 31.5, 30.9, 30.7, 29.8, 26.2, 26.00, 25.95, 25.89, 20.5, 19.4, 18.4, 18.13, 18.08, 18.02, 15.4, 15.2, 13.2, 10.4, −3.0, −3.6, −3.7, −3.8, −4.18, −4.24, −4.3, −4.4; LRMS (ESI) 1329.8 [M+Na]$^+$; HRMS (ESI) calcd for $C_{78}H_{130}O_8Si_4Na$ 1329.8741 [M+Na]$^+$, found 1329.8782; $[\alpha]_D^{20}$ −6.8 (c 0.66, $CHCl_3$).

4.39. ((2*E*,4*R*,5*S*,7*S*,8*Z*,10*S*,11*R*,12*S*,14*S*,17*S*,18*R*,19*S*,20*S*,21*Z*)-19-(4-Methoxybenzyloxy)-5,7,11,17-tetrakis-(*tert*-butyldimethylsilyloxy)-4,10,12,14,18,20-hexamethyltetracosa-2,8,21,23-tetraenyloxy)triphenylmethane (114α)

The procedure for **114β** was used with **113α** (0.54 g, 0.41 mmol) and Dess–Martin periodinane (0.26 g, 0.61 mmol), 1-bromoallyl trimethylsilane (0.50 g, 2.60 mmol) and $CrCl_2$ (0.42 g, 3.42 mmol), and NaH (95% w/w, 0.21 g, 8.31 mmol) to yield 0.46 g (83% in three steps) of the product by flash column chromatography (EtOAc/hexane 1:9) as a colorless oil: IR ($CHCl_3$) 2955, 2928, 2856, 1613, 1514, 1462, 1250, 1069, 835, 773, 705 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.54 (m, 6H), 7.40–7.35 (m, 9H), 7.33–7.30 (m, 2H), 6.96–6.93 (m, 2H), 6.69 (ddd, J=16.8, 10.6, 10.5 Hz, 1H), 6.12 (t, J=11.0 Hz, 1H), 5.80–5.67 (m, 3H), 5.52 (t, J=10.4 Hz, 1H), 5.40 (m, 1H), 5.28 (d, J=16.8 Hz, 1H), 5.19 (d, J=10.2 Hz, 1H), 4.63 (m, 3H), 4.03 (m, 1H), 3.85 (s, 3H), 3.67 (m, 2H), 3.51 (m, 1H), 3.38 (m, 1H), 2.96 (m, 1H), 2.72 (m, 1H), 2.53 (m, 1H), 1.93–1.74 (m, 2H), 1.66–1.37 (m, 7H), 1.31–1.23 (m, 3H), 1.18 (d, J=6.8 Hz, 3H), 1.09 (m, 6H), 1.03–0.92 (m, 45H), 0.23–0.10 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 144.5, 144.4, 134.7, 134.5, 133.0, 132.6, 132.2, 131.4, 129.1, 129.0, 128.7, 127.7, 126.8, 117.5, 113.7, 86.8, 84.6, 79.9, 74.7, 73.6, 72.3, 66.5, 65.1, 55.2, 42.5, 42.4, 41.6, 36.1, 35.9, 34.8, 32.0, 30.8, 29.8, 26.3, 26.02, 25.96, 20.5, 19.3, 18.6, 18.5, 18.2, 18.1, 15.4, 13.3, 10.5, −2.9, −3.4, −3.7, −4.1, −4.2, −4.3; LRMS (ESI) 1352.0 [M+Na]$^+$; HRMS (ESI) calcd for $C_{81}H_{132}O_7Si_4Na$ 1351.8948 [M+Na]$^+$, found 1351.8987; $[\alpha]_D^{20}$ −8.6 (c 1.6, $CHCl_3$).

4.40. (2*E*,4*R*,5*S*,7*S*,8*Z*,10*S*,11*R*,12*S*,14*S*,17*S*,18*R*,19*S*,20*S*,21*Z*)-19-(4-Methoxybenzyloxy)-5,7,11,17-tetrakis(*tert*-butyldimethylsilyloxy)-4,10,12,14,18,20-hexamethyltetracosa-2,8,21,23-tetraen-1-ol (115α)

The procedure for **115β** was used with **114α** (0.46 g, 0.35 mmol) and $ZnBr_2$ (0.41 g in 5.8 mL of 24:5 CH_2Cl_2/MeOH) to yield 0.21 g (55%) of the product after flash column chromatography (EtOAc/hexane 1:9) as a colorless oil: IR ($CHCl_3$) 3410, 2956, 2929, 2856, 1614, 1514, 1471, 1462, 1251, 1075, 836, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.87 (m, 2H), 6.60 (ddd, J=16.8, 10.7, 10.6 Hz, 1H), 6.03 (t, J=11.0 Hz, 1H), 5.67–5.57 (m, 3H), 5.41 (m, 1H), 5.29 (m, 1H), 5.20 (d, J=18.2 Hz, 1H), 5.11 (d, J=10.2 Hz, 1H), 4.56 (m, 3H), 4.10 (d, J=4.4 Hz, 1H), 3.93 (m, 1H), 3.81 (s, 3H), 3.66–3.57 (m, 2H), 3.40 (dd, J=4.6, 2.6 Hz, 1H), 3.28 (dd, J=6.2, 4.2 Hz, 1H), 2.85 (m, 1H), 2.60 (m, 1H), 2.39 (m, 1H), 1.79 (m, 1H), 1.70 (m, 1H), 1.66–1.56 (m, 2H), 1.51–1.19 (m, 8H), 1.09 (d, J=6.8 Hz, 3H), 0.98 (d, J=6.8 Hz, 3H), 0.97 (d, J=6.9 Hz, 3H), 0.92–0.86 (m, 45H), 0.11–0.00 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 135.2, 134.7, 132.8, 132.7, 132.3, 131.4, 129.2, 129.1, 129.0, 117.4, 113.7, 84.6, 80.0, 74.7, 73.6, 72.2, 66.6, 63.9, 63.3, 55.3, 42.4, 41.7, 36.1, 35.8, 34.8, 31.9, 30.8, 29.8, 26.3, 26.0, 25.9, 20.5, 19.4, 19.3, 18.6, 18.5, 18.1, 15.3, 13.3, 10.5, −3.0, −3.4, −3.7, −4.2, −4.3, −4.5; LRMS (ESI) 1109.9 [M+Na]$^+$; HRMS (ESI) calcd for $C_{62}H_{118}O_7Si_4Na$ 1109.7856 [M+Na]$^+$, found 1109.7902; $[\alpha]_D^{20}$ −12.0 (c 1.7, $CHCl_3$).

4.41. (2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*S*,20*R*,21*S*,22*S*,23*Z*)-Methyl-21-(4-methoxybenzyloxy)-7,9,13,19-tetrakis(*tert*-butyldimethylsilyloxy)-6,12,14,16,20,22-hexamethylhexacosa-2,4,10,23,25-pentaenoate (116α)

The procedure for **116β** was used with **115α** (117 mg, 0.108 mmol) and Dess–Martin periodinane (69 mg, 0.16 mmol), bis(2,2,2-trifluoroethyl)-(methoxycarbonylmethyl) phosphate (0.027 mL, 0.13 mmol), 18-crown-6 (0.14 g, 0.53 mmol), and KHMDS (0.26 mL, 0.13 mmol, 0.5 M solution in toluene) to yield 69 mg (56% in two steps) of the product after flash column chromatography (EtOAc/hexane 1:19) as a colorless oil: IR ($CHCl_3$) 2956, 2929, 2856, 1722, 1640, 1514, 1471, 1462, 1250, 1174, 1080, 836, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, J=15.2, 11.3 Hz, 1H), 7.28 (m, 2H), 6.88 (m, 2H), 6.60 (ddd, J=16.7, 10.6, 10.5 Hz, 1H), 6.56 (t, J=11.3 Hz, 1H),

6.04 (dd, J=15.5, 7.1 Hz, 1H), 6.00 (t, J=11.0 Hz, 1H), 5.62 (m, 2H), 5.42 (m, 1H), 5.27 (m, 1H), 5.21 (d, J=16.8 Hz, 1H), 5.11 (d, J=10.3 Hz, 1H), 4.54 (m, 3H), 3.97 (m, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 3.60 (m, 1H), 3.40 (m, 1H), 3.29 (m, 1H), 2.86 (m, 1H), 2.57 (m, 2H), 1.80–1.67 (m, 3H), 1.55–1.41 (m, 4H), 1.40–1.20 (m, 4H), 1.09 (d, J=6.8 Hz, 3H), 1.06 (d, J=6.8 Hz, 3H), 0.99 (d, J=6.6 Hz, 3H), 0.98 (d, J=6.7 Hz, 3H), 0.95–0.85 (m, 42H), 0.13–0.00 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 159.0, 147.3, 145.5, 134.7, 132.9, 132.7, 132.3, 131.4, 129.1, 129.0, 126.9, 117.4, 115.5, 113.7, 84.6, 80.0, 74.7, 73.6, 72.1, 66.5, 55.3, 51.0, 43.5, 42.4, 41.6, 36.1, 35.8, 34.8, 31.9, 30.7, 29.8, 26.3, 26.0, 25.9, 20.5, 19.3, 18.6, 18.5, 18.1, 15.3, 13.4, 10.5, −3.0, −3.3, −3.7, −4.10, −4.15, −4.19, −4.3, −4.4; LRMS (ESI) 1163.8 $[M+Na]^+$; HRMS (ESI) calcd for $C_{65}H_{120}O_8Si_4Na$ 1163.7958 $[M+Na]^+$, found 1163.8000; $[\alpha]_D^{20}$ −16.7 (c 0.33, $CHCl_3$).

4.42. (2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*S*,20*R*,21*S*,22*S*,23*Z*)-Methyl-7,9,13,19-tetrakis(*tert*-butyldimethylsilyloxy)-21-hydroxy-6,12,14,16,20,22-hexamethylhexacosa-2,4,10,23,25-pentaenoate (117α)

The procedure for **117β** was used with **116α** (68 mg, 60 μmol) and DDQ (15 mg, 66 μmol) to yield 56 mg (92%) of the product after flash column chromatography (EtOAc/hexane 1:9) as a colorless oil: IR ($CHCl_3$) 3499, 2956, 2929, 2856, 1723, 1641, 1471, 1462, 1255, 1175, 1081, 836, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, J=15.2, 11.3 Hz, 1H), 6.64 (ddd, J=16.9, 10.6, 10.5 Hz, 1H), 6.52 (t, J=11.3 Hz, 1H), 6.07 (t, J=11.0 Hz, 1H), 5.96 (dd, J=15.5, 7.1 Hz, 1H), 5.56 (d, J=11.3 Hz, 1H), 5.44–5.33 (m, 2H), 5.26–5.21 (m, 1H), 5.17 (d, J=16.7 Hz, 1H), 5.07 (d, J=10.1 Hz, 1H), 4.49 (m, 1H), 3.92 (m, 1H), 3.73–3.67 (m, 5H), 3.34 (m, 1H), 3.25 (br, 1H), 2.73 (m, 1H), 2.52 (m, 2H), 1.82–1.50 (m, 4H), 1.44–1.16 (m, 7H), 1.01 (d, J=6.8 Hz, 3H), 0.97 (d, J=7.1 Hz, 3H), 0.93 (d, J=6.9 Hz, 3H), 0.90 (d, J=6.9 Hz, 3H), 0.88–0.81 (m, 42H), 0.08–0.00 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 147.3, 145.5, 136.5, 132.8, 132.7, 132.6, 129.6, 126.8, 117.3, 115.5, 79.8, 78.4, 74.2, 72.1, 66.5, 51.0, 43.5, 42.5, 41.4, 36.0, 35.9, 35.8, 35.0, 32.4, 31.9, 30.7, 26.3, 26.0, 25.9, 20.4, 19.4, 18.5, 18.12, 18.08, 17.98, 17.4, 15.3, 13.4, 10.8, −3.0, −3.4, −3.7, −4.1, −4.2, −4.3, −4.4, −4.8; LRMS (ESI) 1043.7 $[M+Na]^+$; HRMS (ESI) calcd for $C_{57}H_{112}O_7Si_4Na$ 1043.7383 $[M+Na]^+$, found 1043.7435; $[\alpha]_D^{20}$ −9.4 (c 0.62, $CHCl_3$).

4.43. (2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*S*,20*R*,21*S*,22*S*,23*Z*)-7,9,13,19-Tetrakis(*tert*-butyldimethylsilyloxy)-21-hydroxy-6,12,14,16,20,22-hexamethylhexacosa-2,4,10,23,25-pentaenoic acid (118α)

The procedure for **118β** was used with **117α** (56 mg, 55 μmol) and 1 N aqueous KOH (0.54 mL) to yield **118α**, which was used without further purification: IR ($CHCl_3$) 2956, 2929, 2857, 1693, 1634, 1471, 1462, 1254, 1082, 836, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (dd, J=15.1, 11.4 Hz, 1H), 6.64 (ddd, J=16.5, 10.6, 10.5 Hz, 1H), 6.61 (t, J=11.2 Hz, 1H), 6.07 (t, J=11.0 Hz, 1H), 6.01 (dd, J=15.5, 7.2 Hz, 1H), 5.58 (d, J=11.3 Hz, 1H), 5.44–5.34 (m, 2H), 5.23 (dd, J=11.0, 8.2 Hz, 1H), 5.17 (d, J=18.0 Hz, 1H), 5.08 (d, J=10.1 Hz, 1H), 4.50 (m, 1H), 3.92 (m, 1H), 3.69 (m, 1H), 3.35 (m, 1H), 2.75 (m, 1H), 2.54 (m, 2H), 1.74–1.56 (m, 4H), 1.49–1.20 (m, 8H), 1.02 (d, J=6.8 Hz, 3H), 0.98 (d, J=7.2 Hz, 3H), 0.94 (d, J=7.0 Hz, 3H), 0.90–0.82 (m, 45H), 0.09–0.01 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 148.2, 147.4, 136.4, 132.7, 132.6, 129.6, 127.0, 117.4, 115.1, 79.8, 78.4, 74.2, 72.1, 66.5, 43.5, 42.6, 41.5, 36.0, 35.9, 35.8, 35.0, 31.9, 30.8, 29.7, 26.3, 26.0, 25.9, 20.4, 19.3, 18.5, 18.13, 18.08, 17.97, 17.4, 15.4, 13.7, 10.8, −3.0, −3.4, −3.7, −4.1, −4.2, −4.3, −4.4, −4.8; LRMS (ESI) 1029.8 $[M+Na]^+$; HRMS (ESI) calcd for $C_{56}H_{110}O_7Si_4Na$ 1029.7226 $[M+Na]^+$, found 1029.7255; $[\alpha]_D^{20}$ −6.5 (c 0.17, $CHCl_3$).

4.44. (8*S*,10*S*,14*R*,20*S*)-Tetrakis(*tert*-butyldimethylsilyloxy)-(7*R*,13*S*,15*S*,17*S*,21*S*)-pentamethyl-(22*S*)-((1*S*)-methylpenta-2,4-dienyl)-oxacyclodocosa-3,5,11-trien-2-one (119α)

The procedure for **119β** was used with **118α**, Et_3N (0.046 mL, 33 μmol), 2,4,6-trichlorobenzoyl chloride (0.043 mL, 28 μmol), and 4-DMAP (27 mL, 0.02 M solution in toluene) to yield 42 mg (78% in two steps) of **119α** after flash column chromatography (EtOAc/hexane 1:49) as a colorless oil: IR ($CHCl_3$) 2956, 2929, 2856, 1704, 1638, 1471, 1462, 1378, 1361, 1255, 1086, 1044, 1004, 835, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (dd, J=15.3, 11.3 Hz, 1H), 6.58 (ddd, J=16.9, 10.6, 10.5 Hz, 1H), 6.42 (t, J=11.4 Hz, 1H), 5.94 (t, J=9.2 Hz, 1H), 5.92 (dd, J=9.5, 5.2 Hz, 1H), 5.55 (m, 1H), 5.42 (d, J=11.6 Hz, 1H), 5.33–5.21 (m, 3H), 5.12 (d, J=15.1 Hz, 1H), 4.99 (d, J=9.7 Hz, 1H), 4.54 (m, 1H), 3.99 (m, 1H), 3.44 (m, 1H), 3.17 (m, 1H), 2.99 (m, 1H), 2.54 (m, 1H), 2.19 (m, 1H), 1.99 (m, 1H), 1.61–1.42 (m, 7H), 1.37–1.18 (m, 3H), 1.10 (d, J=6.9 Hz, 3H), 1.05 (d, J=7.1 Hz, 3H), 1.00 (d, J=6.3 Hz, 3H), 0.98 (d, J=6.4 Hz, 3H), 0.98–0.82 (m, 36H), 0.79 (d, J=6.6 Hz, 3H), 0.66 (d, J=6.7 Hz, 3H), 0.11–0.01 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 146.5, 143.9, 134.3, 132.7, 132.2, 130.8, 129.8, 127.9, 117.4, 117.1, 81.6, 78.0, 77.1, 73.0, 66.7, 46.9, 45.7, 41.2, 37.5, 35.8, 35.1, 34.5, 31.1, 29.7, 26.2, 26.1, 26.0, 25.9, 20.5, 19.5, 19.1, 18.5, 18.4, 18.2, 17.9, 17.3, 16.9, 7.9, −2.6, −3.4, −3.5, −4.3, −4.4, −4.6; LRMS (ESI) 1011.7 $[M+Na]^+$; HRMS (ESI) calcd for $C_{56}H_{108}O_6Si_4Na$ 1011.7121 $[M+Na]^+$, found 1011.7164; $[\alpha]_D^{20}$ −61.6 (c 2.8, $CHCl_3$).

4.45. (8*S*,10*S*,14*R*,20*S*)-Tetrahydroxy-(7*R*,13*S*,15*S*,17*S*,21*S*)-pentamethyl-(22*S*)-((1*S*)-methylpenta-2,4-dienyl)-oxacyclodocosa-3,5,11-trien-2-one (121)

HCl (3 N, 10 mL, prepared by adding 2.5 mL of concd HCl to 7.5 mL MeOH) was added to a stirred solution of macrolactone **119α** (42 mg, 42 μmol) in THF (3 mL) at 0 °C. After 24 h at room temperature, the reaction mixture was diluted with EtOAc (4 mL) and H_2O (4 mL). The organic phase was retained, and the aqueous phase was extracted with EtOAc (2×4 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (EtOAc/hexane 3:2) to yield **121** (7.9 mg, 35%) as a colorless oil: IR ($CHCl_3$) 3415, 2961, 2917, 2849, 1681, 1637, 1461, 1279, 1067, 965, 758 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) δ 7.05 (dd, J=15.3, 11.3 Hz,

1H), 6.65 (ddd, J=16.9, 10.2, 10.1 Hz, 1H), 6.53 (dd, J=11.5, 11.5 Hz, 1H), 5.97 (dd, J=15.3, 9.5 Hz, 1H), 5.94 (dd, J=11.0, 11.0 Hz, 1H), 5.60 (dd, J=10.8, 9.6 Hz, 1H), 5.41 (d, J=11.5 Hz, 1H), 5.20 (dd, J=10.5, 10.3 Hz, 1H), 5.11 (dd, J=16.9, 2.0 Hz, 1H), 5.10 (dd, J=9.7, 2.1 Hz, 1H), 5.01 (d, J=10.1 Hz, 1H), 4.60 (ddd, J=10.1, 9.7, 2.7 Hz, 1H), 3.94 (ddd, J=11.0, 2.1, 2.0 Hz, 1H), 3.38 (ddd, J=9.8, 3.0, 2.0 Hz, 1H), 3.09 (ddq, J=13.0, 7.0, 4.9 Hz, 1H), 3.01 (dd, J=8.3, 2.7 Hz, 1H), 2.70 (m, 1H), 2.23 (ddd, J=9.3, 7.0, 2.4 Hz, 1H), 2.07 (ddd, J=7.0, 2.6, 2.5 Hz, 1H), 1.67 (m, 2H), 1.56 (ddd, J=14.0, 10.9, 2.9 Hz, 1H), 1.51 (m, 1H), 1.47 (ddd, J=14.1, 10.5, 1.9 Hz, 1H), 1.17 (d, J=6.9 Hz, 3H), 1.13 (m, 1H), 1.11 (d, J=7.1 Hz, 3H), 1.09 (d, J=7.0 Hz, 3H), 1.02 (d, J=6.7 Hz, 3H), 1.00 (m, 1H), 0.93 (d, J=6.4 Hz, 3H), 0.92 (m, 1H), 0.78 (m, 1H), 0.76 (d, J=6.7 Hz, 3H), 0.74 (m, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 168.3, 147.6, 145.3, 135.4, 134.3, 133.5, 131.3, 131.0, 130.1, 118.1, 81.2, 79.9, 77.6, 72.0, 65.1, 45.9, 44.8, 42.4, 38.7, 36.0, 35.6, 31.8, 29.8, 27.8, 22.2, 19.8, 18.4, 17.6, 16.4, 9.1; LRMS (ESI) 555.3 $[M+Na]^+$; HRMS (ESI) calcd for $C_{32}H_{52}O_6$ 555.3662 $[M+Na]^+$, found 555.3655; $[\alpha]_D^{20}$ −76.2 (c 0.45, MeOH).

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Supplementary data

Contains detailed descriptions of the synthesis of the dictyostatin epimers and copies of NMR spectra of all compounds submitted for biological testing (59 pages). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.05.033.

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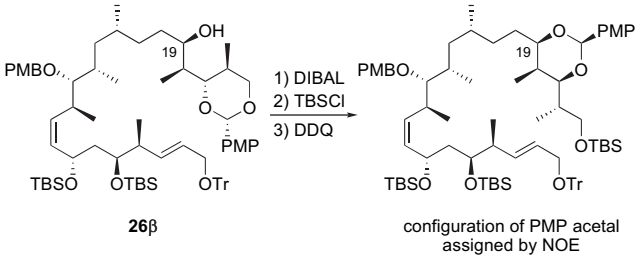
29. To determine the configuration at C19, the major product from $NaBH_4$ reduction was treated with excess (10.0 equiv) DIBALH to open the PMB acetal, and the resulting primary alcohol was selectively protected with a TBS group. DDQ oxidation to remove the PMB group was attempted; however, mixtures of the PMB acetal (less polar) and the overoxidation product (more polar) were obtained. These were separated by silica gel column chromatography. The H19, H21, and Ha (the PMB acetal) protons of the PMB acetal were assigned by a ^1H–^1H COSY NMR (500 MHz) study. A NOESY NMR (500 MHz) experiment was carried out, and the major isomer was assigned as β from the crosspeak between Ha–H19 and Ha–H21.



26β configuration of PMP acetal assigned by NOE

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