Simplified Discodermolide Analogues: Synthesis and Biological Evaluation of 4-*epi*-7-Dehydroxy-14,16-didemethyl-(+)-discodermolides as Microtubule-Stabilizing Agents

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Several novel analogues of (+)-discodermolide were synthesized via a convergent strategy that used Wittig reactions to append left and right side chains to a central scaffold and then tested for biological activity. Three of the analogues in the 4-*epi*-7-dehydroxy-14,16-didemethyl series, **6a**−**c**, had interesting actions. The C3-methoxymethyl ether analogue **6b** was more active in antiproliferative cell-based assays as well as in hypernucleation and paclitaxel site competition assays with isolated tubulin than the other analogues, including **6a**, which contained a free hydroxyl group at the C3 position. The biological results validated the initial hypothesis that the C7 hydroxy group and the C14 and C16 methyl groups of (+)-discodermolide could be deleted without undermining activity. Although less potent than (+)-discodermolide and paclitaxel, compounds **6b** and **6c** both showed properties unique to (+)-discodermolide. These properties, particularly the capacity to cause hypernucleation of isolated tubulin at lower temperature than paclitaxel, as well as stabilizing preformed microtubules to cold disassembly, are considered mechanistically superior to those of paclitaxel. Other variations in the right and left sides of the discodermolide scaffold revealed additional structure/activity information.

Introduction

The microtubule-stabilizing agent (+)-discodermolide (**1**, Figure 1)[1] has potential as a cancer chemotherapeutic agent. Compound **1** has significantly higher affinity for the paclitaxel binding site on tubulin than does paclitaxel itself[2,3] and is a promising candidate for clinical development in cancer chemotherapy either alone[4] or in combination with paclitaxel.[5] The scarcity of this marine sponge-derived product has spurred the development of both total[4−9] and partial syntheses.[10]

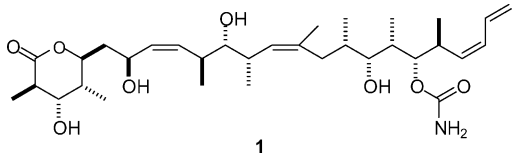

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Figure 1. (+)-Discodermolide (**1**).

Four groups have reported the synthesis of analogues for structure−activity relationship (SAR) studies.[3,4,6,11] Key features of this work are summarized in Table 1. Schreiber's group reported that C16-demethyldiscodermolide (**2**) is no less antiproliferative than natural **1**, suggesting that no significant loss of microtubule binding is associated with the absence of the C16-methyl group.[4] Longley and co-workers reported SAR studies with discodermolide analogues **3a**−**e** prepared by acetylation of the hydroxyl groups at C3, C7, C11, and/or C17 of **1**. Interestingly, C3- and/or C7-acetylated versions **3a**−**c** of **1** retain cytotoxicities equivalent to that of **1** against carcinoma cells, while acetylation at the C11 and C17 hydroxyl groups (**3d**,**e**) decreases biological potency.[12] Smith and co-workers constructed C14-*cis*/*trans*-demethyl analogues **4a**,**b** and C3-dehydro and C3-dehydro/C7-deoxy analogues **4c**,**d**. Interestingly, the C14-*cis*-demethyl analogue **4a** is just 2-fold less cytotoxic than **1**. A large decrease in activity is associated with the trans geometry at C14 **4b**. In addition, the C3-dehydro and C3-dehydro/C7-deoxy analogues, **4c** and **4d**, are approximately 2-fold more and 3-fold less cytotoxic, respectively, than **1**. The Smith group reported studies that suggest that one of the hydroxyl groups at either C3 or C7 must be present in order for an analogue to have activity similar to that of **1**.[3] The Paterson group recently reported the synthesis of several epimers of discodermolide,[6] but did not give results of biological analyses.

Even with all of this information, the SAR analysis of discodermolide is far from well understood. We sought to develop a synthetic route that could easily access simplified and more diverse analogues, an important step for the further understanding of the SAR surrounding **1**. Herein we report the synthesis and comparison of biological activities of several new simplified discodermolide analogues. The results present important new structural information for the further development of analogues of this potent microtubule-stabilizing agent.

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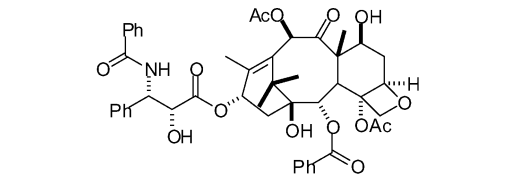
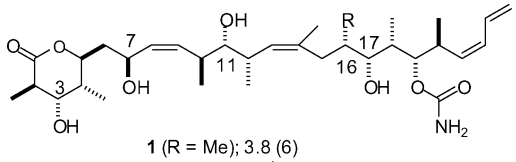
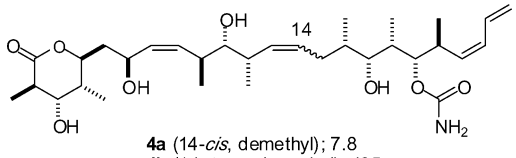
Table 1. Antiproliferative Potencies (IC_{50}, nM) Against A549 or MG63[a] Cells of Paclitaxel, Discodermolide (**1**), and Literature Compounds **2**−**4d**



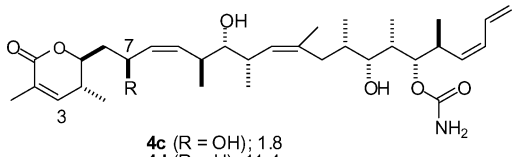
paclitaxel; 1.4



1 (R = Me); 3.8 (6)
2 (R = H); n.d.[b] (10)
3a (R = Me, 3-OAc); 3.8
3b (R = Me, 7-OAc); 0.8
3c (R = Me, 3,7-OAc); 0.8
3d (R = Me, 3,11-OAc); 164
3e (R = Me, 3, 17-OAc); 524



4a (14-*cis*, demethyl); 7.8
4b (14-*trans*, demethyl); 485

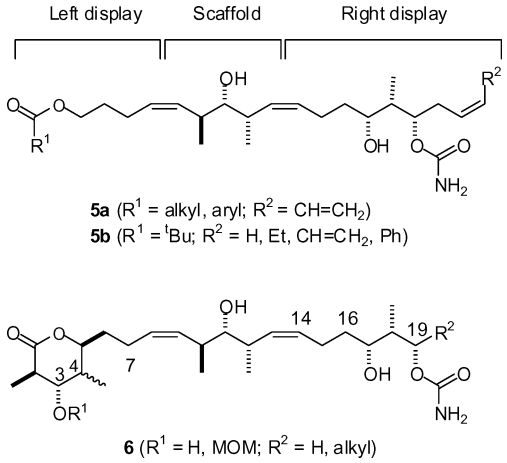


4c (R = OH); 1.8
4d (R = H); 11.4

[a] IC_{50} values against MG63 cells are shown in parentheses. [b] Not determined.

Results and Discussion

Structure Design. The structure of **1** as determined by X-ray crystallographic analysis[1] shows that the molecule adopts a curved conformation. The U-turn shape at the center of **1** arises from avoidance of *syn*-pentane interactions by the methyl groups in the main chain and avoidance of A-1,3 strain by the vinyl groups projecting from the methyl-bearing stereocenters.[13] In addition, avoidance of A-1,2 strain by the C14 methyl group may also play a role. We have recently explored SARs of the discodermolide backbone by using a fixed center piece, or scaffold, including two cis-double bonds, as shown in compound **5**, while removing the lactone, the hydroxy groups at C7 and the methyl groups at C14 and C16.[14] Because of the additive negative effect of removing those groups, however, we considered another possibility: that hydrogen bonding between the C3 hydroxy group of the lactone and the C19 carbamate might help to stabilize the U-turn shaped conformation. NMR solution structures of **1** recently reported by Smith[15] and Snyder[16] suggest possible hydrogen bonding between those groups. Accordingly, as part of our continuing efforts toward analogue syntheses using both classical (**5a**)[14] and fluorous mixture (**5b**)[17] methods, we decided to introduce lactone moieties **6** so as to compare the original configuration of the left side of the natural product with its C4-*epi*-lactone along with various degrees of truncation of the right side from C19 (Figure 2). Protection of the C3 hydroxy group with methoxymethyl (MOM, CH_2OCH_3) was chosen to satisfy both the synthetic approach and to provide an extended H-bond acceptor compared to the free hydroxy group found on the natural product.



5a (R^1 = alkyl, aryl; R^2 = CH=CH_2)
5b (R^1 = ^{t}Bu; R^2 = H, Et, CH=CH_2, Ph)

6 (R^1 = H, MOM; R^2 = H, alkyl)

Figure 2. Design of simplified analogues.

Retrosynthetic Analysis. The retrosynthetic analysis shown in Figure 3 includes two Wittig reactions to generate the (*Z*)-alkenes between C8−C9 and C13−C14. In addition, the aldehyde **10** was envisioned as a penultimate form of the left-side lactone display[18] and three phosphonium salts **8**, **9**, **11** were selected for Wittig reactions in the center and right displays. The preparation of these fragments **8**−**11** of the molecule begins with commercially available methacrolein (**13**), 1,4-butanediol (**14**), and (*S*)-3-hydroxy-2-methylpropionic acid methyl ester (**15**) and features aldol condensations along with protecting group manipulations.

Synthesis of Left Display with Natural Configuration. The synthesis of the left display **10a** bearing the configuration of (+)-discodermolide started with commercially available methacrolein (**13**) (Scheme 1). Reaction of **13** with the boron enolate of Evans oxazolidinone **16**[19] gave the corresponding alcohol, which was silylated to give compound **17** in 90% yield. Lactonization followed by the introduction of an allyl group was performed by our previously reported method to give **19** in good yield.[7,10] Conversion to the methyl acetal was easily accomplished by diisobutylaluminum hydride (DIBAL) reduction to the corresponding lactol followed by treatment with camphorsulfonic acid (CSA) in methanol to give a desilylated intermediate, which was protected with MOM chloride to give a mixture of anomers **20** (β:α = 1:1). These were separable by silica gel flash chromatography. The final left display **10a** was obtained by hydroboration of the α-anomer **α-20** with BH_3−DMS (borane−dimethyl sulfide) followed by oxidation with SO_3−pyridine.

Synthesis of Left Display with C4-epi Configuration. The synthesis of the C4-*epi*-lactone left display **10b** started from 1,4-butanediol (**14**) (Scheme 2). Monoprotection with *p*-methoxybenzyl (PMB) bromide was performed with NaH in DMF.[21] After oxidation, reaction of the crude aldehyde **21** with the boron enolate of Evans oxazolidinone **16** gave the corresponding *syn*-alcohol, which was silylated to give compound **22** in 90% yield. Lithium borohydride reduction followed by oxidation gave the aldehyde **23**. A second *syn*-aldol addition was

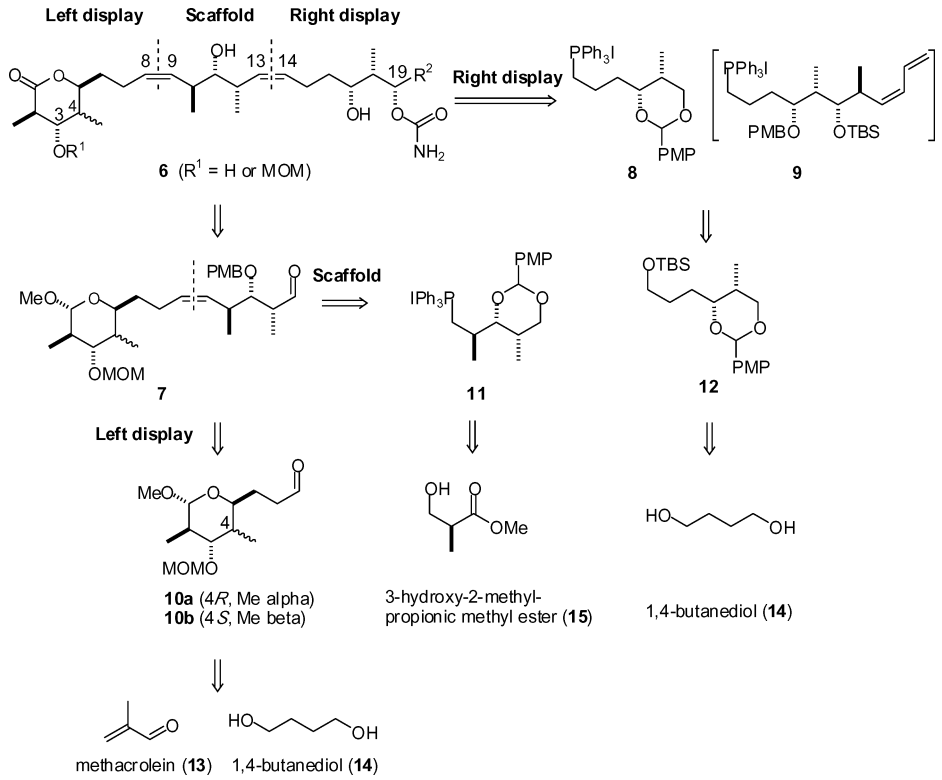
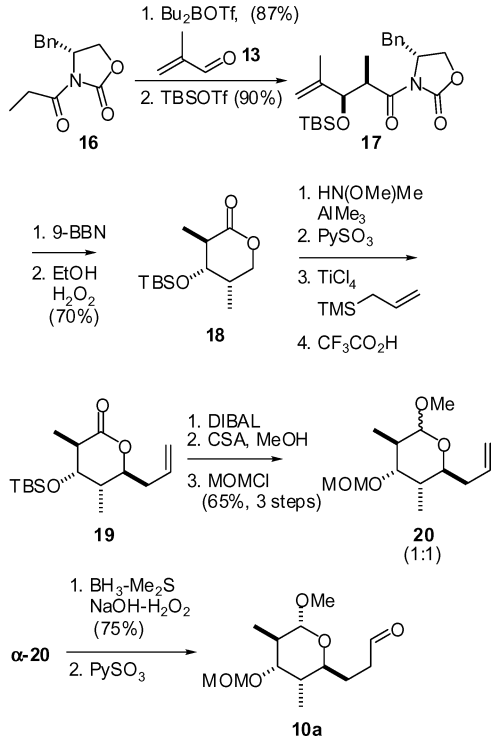


Figure 3. Retrosynthetic analysis of discodermolide analogues.

Scheme 1

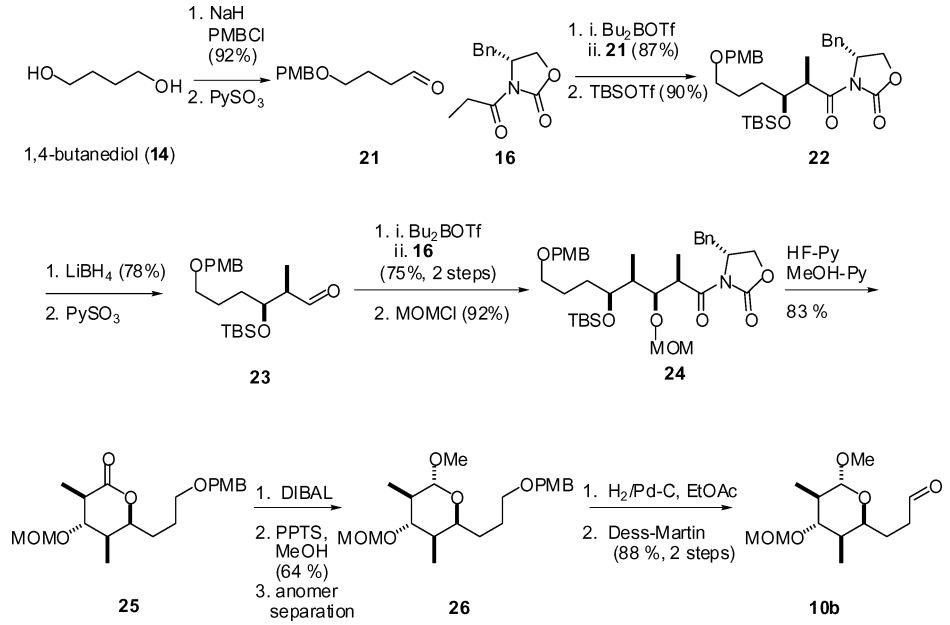


performed with same Evans oxazolidinone **16** to give the corresponding alcohol, which was protected with MOM chloride to give compound **24**. Desilylation of **24** with HF gave the cyclized product **25** in high yield. Conversion to the methyl acetal was easily accomplished by DIBAL reduction to the corresponding lactol followed by treatment with pyridinium *p*-toluenesulfonate (PPTS) in methanol to give **26** as a 2.5:1 (α:*β*) mixture of anomers from which the major α-anomer was separable by silica gel flash chromatography. The final left display **10b** was obtained by hydrogenolysis of the PMB protecting group followed by Dess−Martin oxidation.

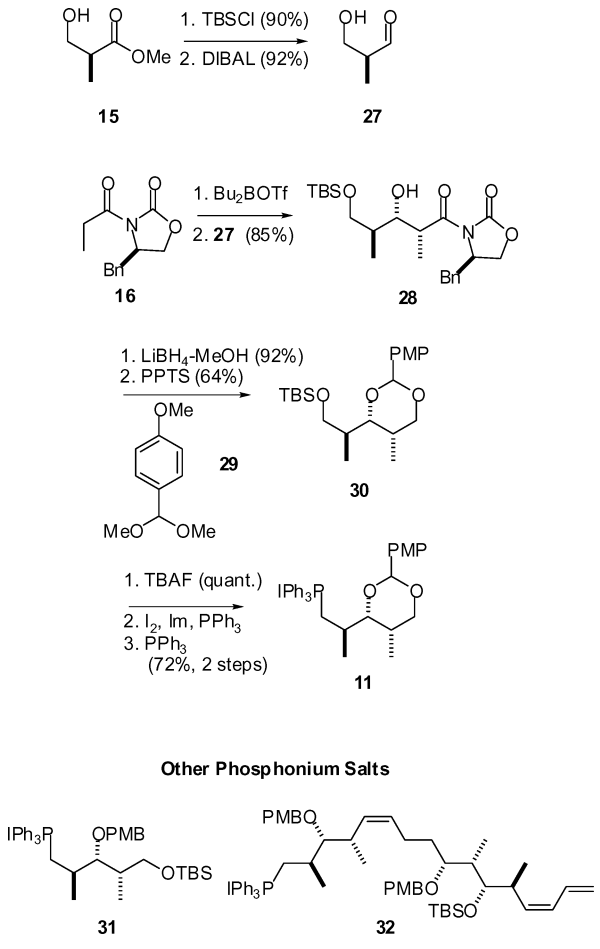
Scaffold. Compound **28** was prepared from (*S*)-3-hydroxy-2-methylpropionic acid methyl ester (**15**) by the known procedure for the preparation of *ent*-**28**.[21] Reduction of **28** with lithium borohydride gave the diol, which was protected by anisaldehyde dimethyl acetal **29** to give the acetal **30** (Scheme 3). Deprotection of the primary TBS group with tetrabutylammonium fluoride (TBAF), iodination, and treatment with triphenylphosphine afforded the phosphonium salt **11**[22] in 72% yield. We had originally prepared the phosphonium salts **31** and **32**[14] for Wittig olefination, but reactions were unsuccessful due to the hygroscopic properties of these reagents. On the other hand, reactions with compound **11** were reliable even though no special care was taken with its storage (for example, salt **11** was useful for reactions even after it was stored at room temperature for several months).

Backbone Assembly and Testing of C19-Truncated Analogues. Our attention turned to both simplification at the C19 position and comparison of the configuration at C4 along with a C3 MOM-protected and/or free hydroxyl group (Scheme 4). The aldehydes **10a** and **10b** were separately reacted under Wittig conditions with phosphonium salt **11** to give alkenes **33** and **34** in 60% and 67% yields, respectively. Selective acetal opening was performed with DIBAL to give the corresponding primary alcohols, which were oxidized with the Dess−Martin periodinane to give aldehydes **35** and **36**. Mono-TBS-protected 1,4-butanediol **14** was oxidized to its aldehyde, which was used without purification in an Evans *syn*-aldol condensation with **37** to give known compound **38**.[23] Reduction of **38** with lithium borohydride gave a diol, which was treated with

Scheme 2



Scheme 3



p-anisaldehyde dimethyl acetal **29** to give *p*-methoxyphenyl (PMP) acetal **39**. The second of the Wittig reactions was performed with phosphonium salt **8**, which was prepared from compound **39**, to give olefins **40** and **41** in good yield.

To introduce an isopropyl group at C19 for truncated analogues where $R^1 = i$-Pr, the primary alcohols from DIBAL opening of acetals **40** and **41** were oxidized with Dess−Martin periodinane to give aldehydes **42** and **43**. Treatment with isopropylmagnesium chloride[24] and carbamoylation afforded carbamates **44** and **45a** in good yields. For a truncated analogue where $R^1 = H$, the primary alcohol derived from **41** was elaborated to the carbamate to yield the PMB-protected methyl lactol **45b**. The lactone was built from the methyl acetal in **44** and **45a**,**b** by using aqueous 60% acetic acid in THF followed by Dess−Martin oxidation. The final target compounds, **46** and **48a**,**b**, were prepared from their respective intermediates by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation. An additional analogue **47** containing a free C3 hydroxyl on the lactone ring was obtained by the removal of MOM group with 4 N HCl followed by removal of the PMB protecting group by DDQ oxidation.

The biological activities of analogues **46**, **47**, and **48a**,**b** were measured in comparison to paclitaxel and **1** in several assays. Compound-induced hypernucleation of isolated bovine brain tubulin was determined in a standard assay (tubulin held at 2.5 °C, test agent or DMSO added, temperature held at 2.5 °C for 1 min, temperature raised to 30 °C in 0.5 min and held there for 20 min, temperature lowered back to 2.5 °C within 2.5 min). Paclitaxel and **1**, in the absence of GTP, cause temperature-dependent assembly of the tubulin into microtubules and ordered sheets of the protein. The extent of this assembly is monitored by spectrophotometric measurement of increases in absorbance (turbidity). As shown in Table 2, compounds **46**, **47**, and **48a**,**b** were inactive in this assay. Furthermore, these four analogues showed neither appreciable antiproliferative activity against human carcinoma cell lines, nor the ability to compete with [^{3}H]paclitaxel for binding to preformed (with a nonhydrolyzable GTP analogue, dideoxyGTP) microtubules.

Alteration of the Right Display. On the basis of the lack of biological activity exhibited by this first set of analogues, our attention turned to analogues containing the original diene moiety in the right display along

Scheme 4

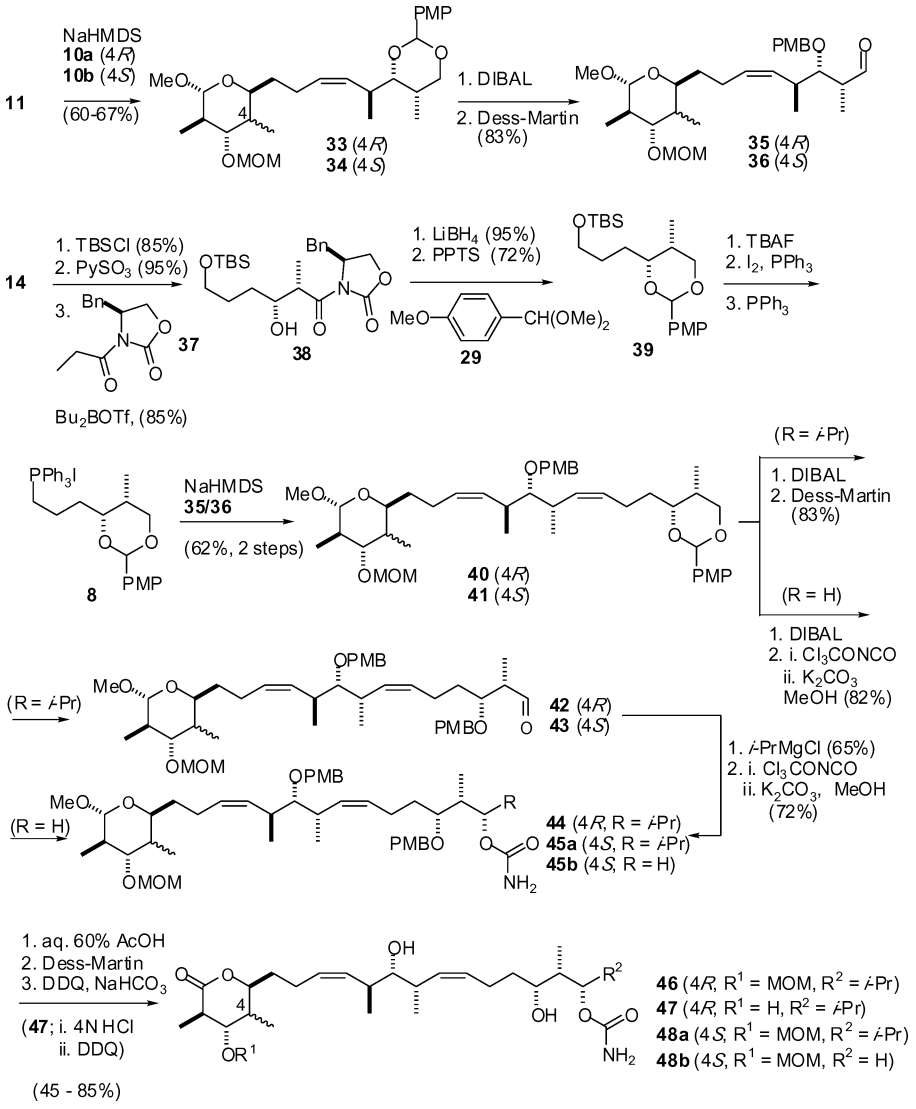


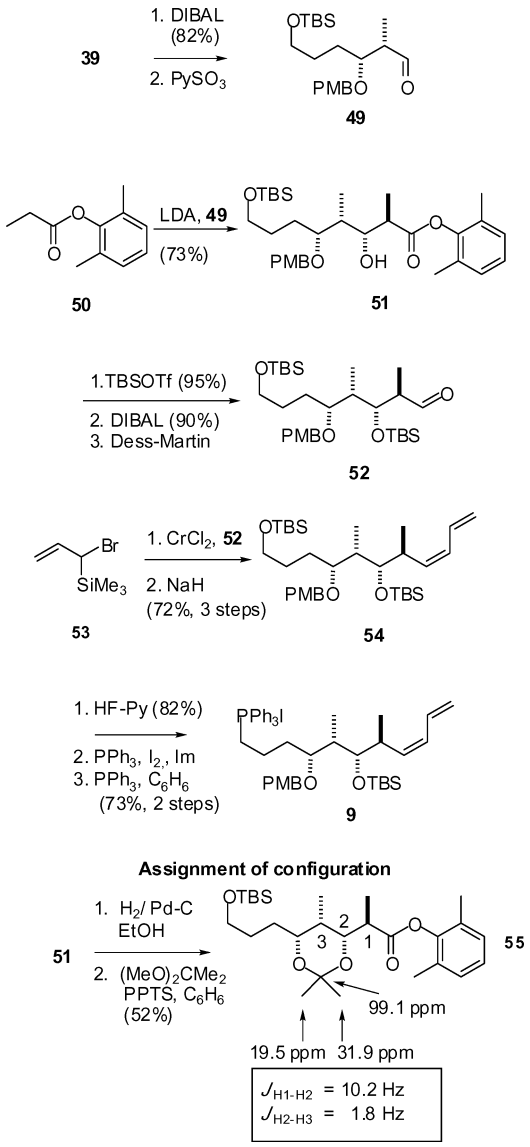
Table 2. Microtubule-Stabilizing, Antiproliferative, and Paclitaxel Site-Competitive Properties of Compounds **46**, **47**, and **48a**,**b** in Comparison to (+)-Discodermolide (**1**) and Paclitaxel

compound	MT-stabilizing activity (%)[a]	GI 50 (μM)[b]			competition with [^{3}H]paclitaxel (%)[c]
		MDA-MB231 (breast)	PC3 (prostate)	2008 (ovarian)	
46	7	>50	>50	>50	10 ± 1
47	13	>50	>50	>50	10 ± 3
48a	<5	46 ± 1	>50	>50	3 ± 10
48b	<5	30 ± 8	>50	>50	13 ± 1
1	>100	0.016 ± 0.003	0.067 ± 0.004	0.072 ± 0.005	64 ± 2
paclitaxel	100	0.0024 ± 0.0016	0.015 ± 0.002	0.0092 ± 0.0016	37 ± 1

[a] Percent assembly of bovine brain tubulin induced by test agent at 10 μM vs that caused by 10 μM paclitaxel; single determinations at 30 °C. [b] Concentration at which test agent caused 50% inhibition of cell growth; means (N = 4 over 10 concentrations) ± SD after 72 h of continuous exposure to the agent. [c] Percent competition by 4 μM test agent with 2 μM [^{3}H]paclitaxel incubated with microtubules formed from 2 μM bovine brain tubulin and 20 μM dideoxyGTP.

with a C4-*epi*-lactone in the left display. As shown in Scheme 5, the construction of the right display featured *anti*-aldol reactions. Selective opening of the benzylidine ring of **39** with DIBAL gave a primary alcohol, which was oxidized to aldehyde **49**.[25] The subsequent *anti*-aldol condensation using Heathcock's aldol reaction[26] with dimethylphenyl propionate furnished compound **51** as the major product in 73% yield. The relative configuration of intermediate **51** was confirmed by ^{13}C and ^{1}H NMR analyses[27] of the corresponding acetonide **55**. Silylation of the newly formed hydroxyl group of **51**, reduction of the aryl ester with DIBAL and Dess−Martin oxidation of the resultant primary alcohol afforded aldehyde **52**. The (*Z*)-diene moiety was introduced by a two-step procedure developed by Paterson and co-workers using a Nozaki−Hiyama reaction.[28] Addition of the aldehyde **52** and allyl bromide **5**[29] to a suspension of $CrCl_2$ in THF produced an intermediate β-hydroxy silane (not shown), which upon treatment with NaH underwent syn elimination to generate the required (*Z*)-diene **54**.[6] Selective deprotection of the primary TBS group, iodination, and then treatment

Scheme 5



with triphenylphosphine gave the phosphonium salt **9**[14] in good yield.

Backbone Assembly and Testing of Diene-Containing Analogues with the C4-*epi*-Lactone. The second Wittig olefination was accomplished with phosphonium salt **9** (Scheme 6). Silyl ether deprotection with TBAF followed by carbamoylation using Koçovsky's method[9,30] afforded the C19 carbamate-containing compound **56**. The lactone was built from the methyl acetal in the left display using aqueous 60% acetic acid in THF followed by Dess−Martin oxidation. The final target compound **6a** containing a free C3 hydroxy group on the lactone was obtained by the removal of MOM group with 4N HCl followed by removal of the PMB protecting group via DDQ oxidation. Two additional compounds, **6b** and **6c**, were prepared from the intermediate **56** by using similar conditions. The three compounds were then examined in the biological assays described above.

All three of these analogues exhibited significant biological activity. Surprisingly, the C3-MOM-protected analogues **6b** and **6c** showed better microtubule hypernucleation activities than the analogue with a free C3-hydroxy group **6a**. As can be seen in Figure 4A, **1** is superior to paclitaxel in that it causes equivalent microtubule assembly at both lower concentrations and temperatures (the increase in absorbance caused by **1** occurs at a time point earlier than that caused by paclitaxel). Additionally, the polymer induced to form by **1** is more resistant to cold-induced disassembly than is the paclitaxel-induced polymer. Both analogues **6b** (Figure 4C) and **6c** (Figure 4D) showed these more rapid polymer-inducing and cold-resistant properties, albeit at lower potencies (for example, higher concentrations of the analogues were necessary for these effects to be detected) than **1**. MOM ether lactone **6b** was the most potent among the new analogues.

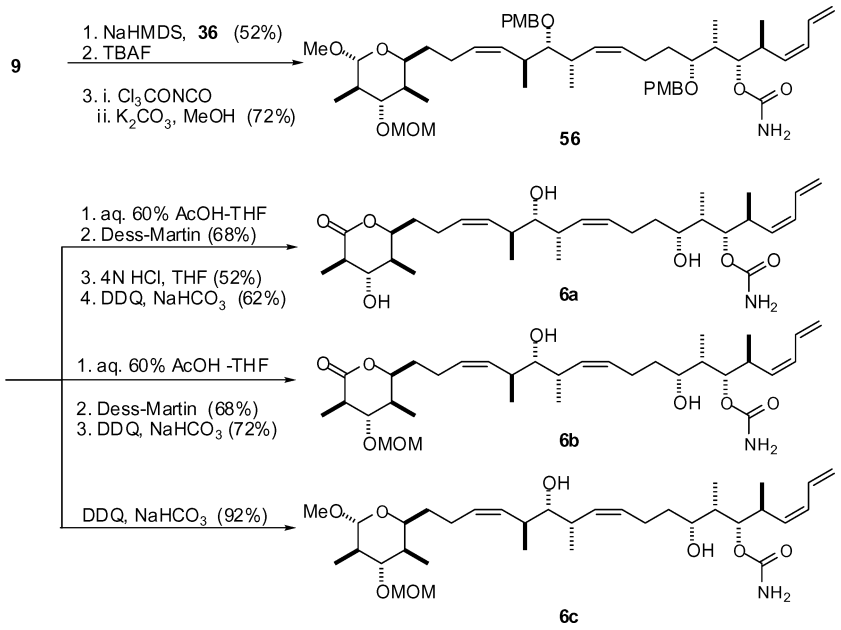
Table 3 shows microtubule-stabilizing, antiproliferative, and paclitaxel site-competing properties of **6a**−**c**. Again, the lactone MOM ether **6b** was more potent than the lactol **6c** or free hydroxy **6a** relatives. The cellular activity of **6b** was encouraging, showing a submicromolar 50% growth inhibitory (GI_{50}) concentration. This compound also showed considerable affinity for the paclitaxel binding site on tubulin. Compound **6b** competed with [^{3}H]paclitaxel for microtubules better than paclitaxel and at almost the same potency as **1**. Compound **5a** contains the pivaloyl group instead of a lactone system in the left side region, and it is the most potent of our previously reported discodermolide analogues.[14] Although 2- to 3-fold less potent than **6b** as an antiproliferative agent, it competed well for the paclitaxel site on microtubules. But and in contrast to **6b**, compound **5a** catalyzed assembly of tubulin into polymer only weakly and did not induce assembly at low temperature (data not shown).

Wholesale Replacement of the Diene. Finally, with highly active analogues in hand, we briefly investigated the wholesale replacement of the right-hand diene fragment. Analogues **57** and **58** were targeted and their preparations are summarized in Scheme 7. Both analogues have the diene saturated and the C19 stereocenter is erased. In compound **57**, this was accomplished by deleting a methyl group and in compound **58** by adding one. Addition of hexylmagnesium bromide to aldehyde **43** followed by carbamate formation and deprotection gave **57**. The requisite tertiary anion needed for analogue **58** was prepared by reductive metalation of 2-phenylthio-2-methylheptane with LDBB (lithium di-*tert*-butylbiphenyl). Addition, carbamate formation and deprotection as above provided analogue **58**. The data in Table 3 show that both analogues **57** and **58** were considerably less active than the benchmark compound **6c**, with antiproliferative potencies in the 20−50 μM range and only modest ability to stabilize microtubules or compete for the paclitaxel site on microtubules.

Conclusions

This work shows analogues of discodermolide that are simpler and considerably more synthetically accessible and which retain many of the interesting features of the natural product. The biological results validated our initial hypothesis that the C7 hydroxy group and the C14 and C16 methyl groups can be deleted without completely undermining activity. Moreover, our hypothesis that extension of the H-bond acceptor at the C3 position, in the case of compounds **6b** and **6c** a MOM

Scheme 6



ether in place of the hydroxyl moiety in the natural product, to assist in keeping the lactone and carbamate moieties in close spatial proximity seems to be supported, as compound **6a** with the C-3 hydroxyl was less active than its MOM-bearing counterparts. Although less potent than discodermolide and paclitaxel, compounds **6b** and **6c** both showed properties unique to discodermolide. These properties, particularly the capacity to cause hypernucleation of isolated tubulin at lower temperature than paclitaxel as well as to stabilize preformed MTs to cold disassembly (Figure 4), are considered mechanistically superior to those of paclitaxel.

In the broader picture, our studies and those of others suggest that the right display of discodermolide is much more sensitive to change than is the left display. The entire left side of discodermolide can be simplified to an alkanoyl ester, and the resulting molecule still retains the ability to compete for the paclitaxel site on microtubules. This simplification causes, however, a decrease in antiproliferative activity and has a negative effect on its ability to cause hypernucleation of tubulin to form microtubules at low temperatures. The terminal alkene of the right side diene, which at present seems to be the optimum substituent for activity, can be replaced with a number of lipophilic groups while retaining activity;[14] however, the contraction of this substituent to an isopropyl group or the wholesale replacement of the diene with concomitant erasure of the C19 stereocenter causes a significant drop in activity.

Experimental Section

Chemistry. General. All reactions were run under a dry argon atmosphere unless otherwise noted. THF and benzene were used freshly distilled from sodium benzophenone. Other reagents were used as received from Aldrich Chemical Co. NMR spectra were obtained on Bruker DPX-300 or DPX-500 spectrometers at ambient temperature in the solvent specified. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane and proton−proton coupling constants (J) in Hz. Infrared (IR) spectra were recorded on an ATI Mattson Genesis Series Fourier transform spectrometer. Low resolution electron ionization (EI) mass spectra were obtained on a Hewlett-Packard 5971A MSD equipped with a 5890 Series II GC, and both low and high-resolution spectra were obtained on a VG 70-G or Micromass Autospec double focusing instrument using EI or electrospray ionization (ESI). Flash chromatography was performed with ICN silica gel 60, 230−400 mesh, with the designated solvents. Reactions were monitored by thin-layer chromatography on Kieselgel 60 F_{254} silica gel plates. Optical rotations were recorded on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as $[\alpha]^{°C}_{\lambda}$ (c = g/100 mL). The purity of compounds tested in biological assays was >95% as determined by HPLC analysis in two solvent systems as well as high-resolution mass spectrometric and ^{13}C NMR spectroscopic analyses.

(4*R*)-4-Benzyl-3-[(2*R*,3*R*)-3-(*tert*-butyldimethylsilanyloxy)-2,4-dimethylpent-4-enoyl]oxazolidin-2-one (17). *tert*-Butyldimethylsilyl triflate (TBSOTf, 3.44 mL, 15 mmol) was added to a stirred solution of 2,6-lutidine (2.32 mL, 20 mmol) and the Evans methacrolein aldol product (3.03 g, 10 mmol) obtained from compound **16** in CH_2Cl_2 (20 mL) at −78 °C. The mixture was stirred for 2 h at ambient temperature. The reaction was quenched by the addition of aqueous HCl (0.5 N, 50 mL). The resulting mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$ followed by the evaporation of solvent under reduced pressure. The product was purified by short column chromatography (hexane/EtOAc 9:1) and used without further purification.

(2*S*,3*R*,4*S*,5*R*)-2-Allyl-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran (20). DIBAL (1 M in THF, 3.3 mL, 3.3 mmol) was added dropwise to a stirred solution of **19** (894 mg, 3 mmol) in anhydrous CH_2Cl_2 (30 mL) under an atmosphere of N_2 at −78 °C, and the resulting mixture was stirred for an additional 1 h at −78 °C. The reaction was quenched by the careful addition of saturated aqueous potassium sodium tartrate (50 mL) and stirred for 3 h at room temperature. Once the organic and aqueous layers had separated, the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over $MgSO_4$ followed by the evaporation of the solvent under reduced pressure. The crude lactol was used for the next reaction without further purification.

A solution of the lactol and CSA (0.3 mmol) in MeOH was stirred for 24 h at room temperature. The reaction mixture was diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ (50 mL). The aqueous layer was extracted with

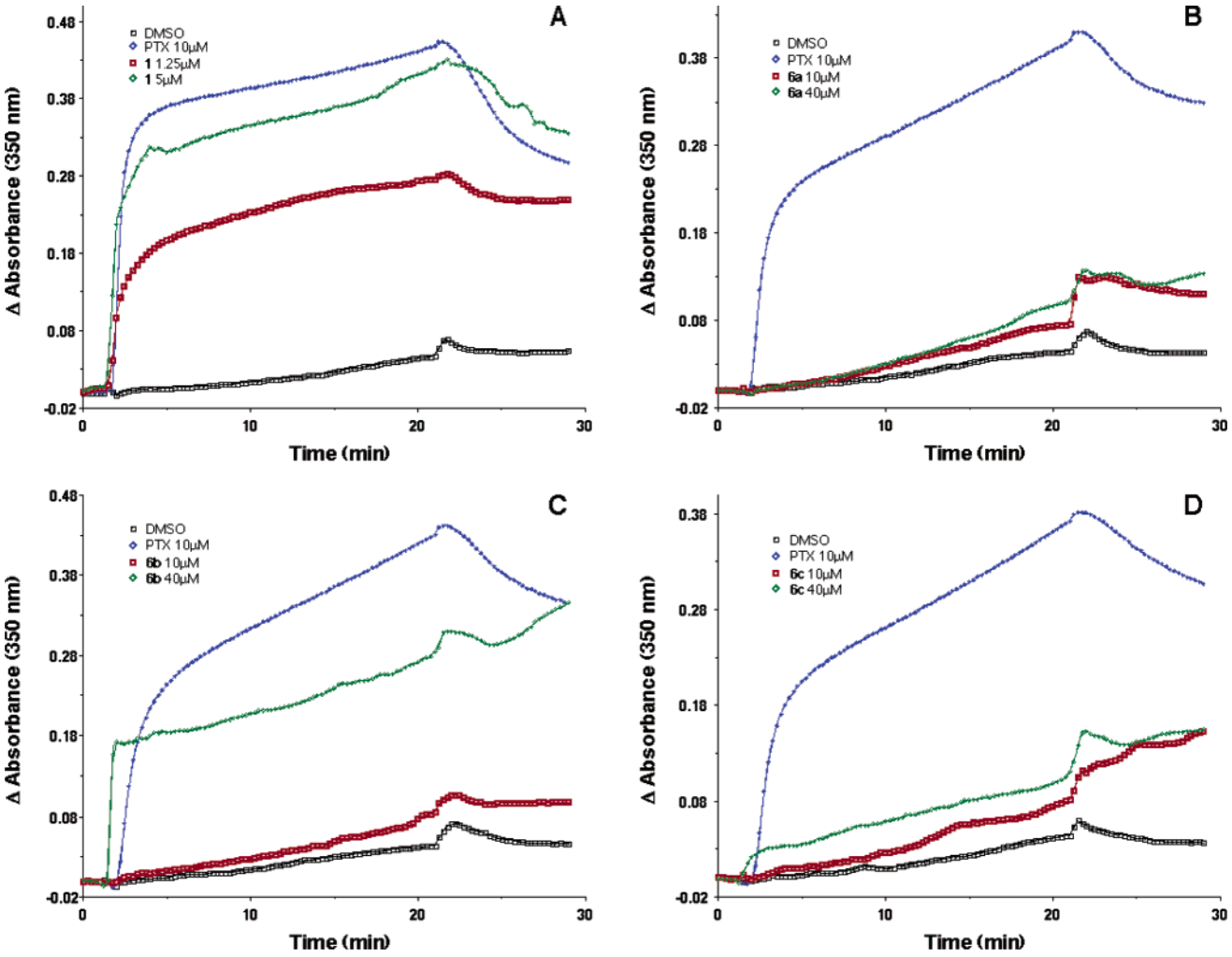


Figure 4. Tubulin assembly inducing properties of **1** (A), **6a** (B), **6b** (C), and **6c** (D) in comparison to 10 μM paclitaxel (PTX). Reaction mixtures containing 10 μM purified bovine brain tubulin in 0.8 M monosodium glutamate without test agent were cooled to 0 °C and added to cuvettes held at 0.25−0.5 °C in a temperature-controlled spectrophotometer. Test agent in DMSO (final concentration 4% v/v) was then rapidly mixed in the reaction mixture to give the concentrations listed. Baselines were established at 0.25−2.5 °C, and temperature was rapidly raised to 30 °C (in approximately 1 min) and held there for 20 min. The temperature was then rapidly lowered back to 0.25−2.5 °C. Each run contained 10 μM paclitaxel (blue diamonds) and a DMSO only negative control (black squares).

Table 3. Microtubule-Stabilizing, Antiproliferative, and Paclitaxel Site-Competitive Properties of Compounds **5a**, **6a**−**c**, **57**, and **58** in Comparison to (+)-Discodermolide (**1**) and Paclitaxel

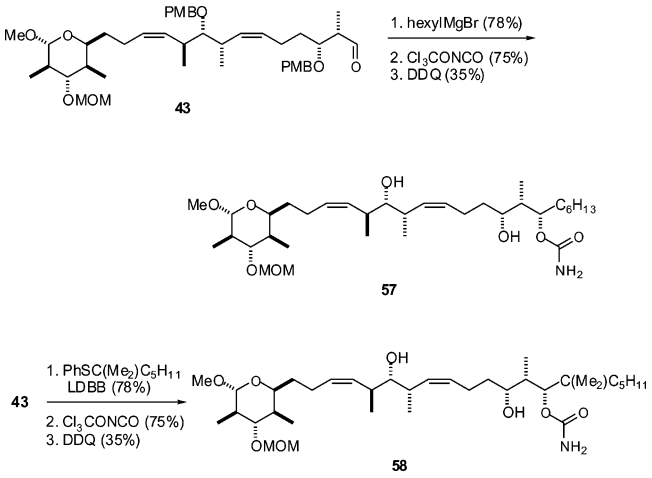
compound	MT-stabilizing activity (%)[a]	GI_{50} (μM)[b]			competition with [^{3}H]paclitaxel (%)[c]
		MDA-MB231 (breast)	PC3 (prostate)	2008 (ovarian)	
1	>100	0.016 ± 0.003	0.067 ± 0.004	0.072 ± 0.005	64 ± 2
paclitaxel	100	0.0024 ± 0.0016	0.015 ± 0.002	0.0092 ± 0.0016	37 ± 1
5a (R_1 = *t*-Bu)[14]	14	2.6 ± 0.9	3.0 ± 0.8	1.5 ± 1.0	32 ± 6
6a	11	2.1 ± 1.8	7.5 ± 2.0	5.2 ± 1.0	21 ± 1
6b	27	0.87 ± 0.21	1.8 ± 0.9	0.65 ± 0.25	57 ± 2
6c	11	3.4 ± 0.8	15 ± 3	4.7 ± 0.6	19 ± 2
57	6	24 ± 1	>50	29 ± 4	9 ± 0
58	9	23 ± 0	38 ± 1	42 ± 5	15 ± 5

[a] Percent assembly of bovine brain tubulin induced by 10 μM test agent vs that caused by 10 μM paclitaxel; single determinations at 30 °C. [b] Concentration at which test agent caused 50% inhibition of cell growth; means (N = 4 over 10 concentrations) ± SD after 72 h of continuous exposure to the agent. [c] Percent competition by 4 μM test agent with 2 μM [^{3}H]paclitaxel incubated with microtubules formed from 2 μM bovine brain tubulin and 20 μM dideoxyGTP.

EtOAc (50 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was used for the next reaction.

N,*N*-Diisopropylethylamine (7.5 mL) and chloromethyl methyl ether (1.13 mL, 15 mmol) were added to a solution of the alcohol in CH_2Cl_2 (15 mL). The reaction mixture was heated to reflux and stirred overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL) followed by washing with brine. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (hexane/EtOAc 7:3) to provide the pure anomers of **20** (β, 33%; α, 32%). **β-20**: IR ($CHCl_3$) 3053, 2985, 2305, 1422, 1264 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04 (m, 1H), 5.20−5.10 (m, 2H), 4.81 (d, 1H, J = 6.9 Hz), 4.73 (d, 1H, J = 2.37 Hz), 4.67 (d, 1H, J = 6.8 Hz), 3.62 (m, 2H), 3.55 (s, 3H), 2.47 (m, 1H), 2.30 (m, 1H), 2.16 (m, 1H), 1.85 (m, 1H), 1.03 (d, 3H, J = 7.1 Hz),

Scheme 7



0.97 (d, 3H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 135.1, 116.4, 101.3, 95.9, 81.9, 75.8, 56.4, 55.7, 37.5, 37.3, 33.6, 13.2, 9.9; HRMS (EI) calcd for $C_{13}H_{24}O_4$ 244.1596, found 244.1592. α-**20**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 (m, 1H), 5.22−5.12 (m, 2H), 4.83 (d, 1H, J = 6.9 Hz), 4.69 (d, 1H, J = 7.2 Hz), 4.49 (d, 1H, J = 1.8 Hz), 3.88 (dt, 1H, J = 3.6, 8.8 Hz), 3.53 (t, 2H, J = 3.6 Hz), 3.48 (s, 3H), 2.45 (m, 1H), 2.28−2.11 (m, 3H), 1.94 (m, 1H), 1.12 (d, 3H, J = 7.3 Hz), 1.00 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 135.2, 116.7, 103.4, 95.6, 78.7, 69.6, 55.7, 37.2, 35.8, 33.6, 15.9, 13.5.

(2*S*,3*R*,4*S*,5*R*,6*R*)-3-(6-Methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl)propionaldehyde (10a). BH_3-Me_2S (1 M in THF, 3 mL, 3 mmol) was added to a solution of **20** (488 mg, 2 mmol) in THF (10 mL) at 0 °C with stirring. The mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched with 2 N aqueous NaOH (10 mL) followed by H_2O_2 (30%, 3 mL). After 1 h, the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, evaporated, and chromatographed (hexane/EtOAc 7:3) to yield 392 mg (75%) of alcohol as a colorless oil: IR ($CHCl_3$) 3103, 2982, 1375, 1240 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83 (d, 1H, J = 6.9 Hz), 4.76 (d, 1H, J = 2.4 Hz), 4.69 (d, 1H, J = 6.9 Hz), 3.75 (t, 2H, J = 5.4 Hz), 3.61 (t, 1H, J = 2.7 Hz), 3.57 (s, 3H), 2.58 (br s, 1H), 2.17 (m, 1H), 1.90−1.80 (m, 4H), 1.04 (d, 3H, J = 7.1 Hz), 0.97 (d, 3H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 101.5, 96.0, 82.0, 75.9, 62.8, 56.6, 55.8, 37.6, 34.0, 29.4, 28.6, 13.4, 9.8; HRMS (EI) calcd for $C_{13}H_{26}O_5$ 262.1780, found 262.1792.

Pyridinium sulfur trioxide (477 mg, 3 mmol) was added to a stirred solution of alcohol (262 mg, 1 mmol) and *N*,*N*-diisopropylethylamine (0.52 mL, 3 mmol) in anhydrous CH_2Cl_2 (6 mL) and DMSO (12 mL) at 0 °C. The reaction mixture was stirred at the ambient temperature for 1 h. The mixture was diluted with ethyl ether (50 mL) and washed with aqueous HCl (0.5 N, 50 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. Flash silica gel column chromatography filtration (hexane/EtOAc 4:1) to remove SO_3−pyridine residue provided the crude aldehyde **10a** as a colorless oil, which was used without further purification.

(4*R*)-4-Benzyl-3-[(2*R*,3*S*)-3-hydroxy-6-(4-methoxybenzyloxy)-2-methylhexanoyl]oxazolidin-2-one. Pyridinium sulfur trioxide (7.15 g, 45 mmol) was added to a stirred solution of the mono-PMB-protected alcohol derived from **14** (3.15 g, 15 mmol) and *N*,*N*-diisopropylethylamine (8.0 mL, 45 mmol) in anhydrous CH_2Cl_2 (15 mL) and DMSO (30 mL) at 0 °C. The mixture was stirred at ambient temperature for 1 h, diluted with ethyl ether (300 mL), and washed with aqueous HCl (0.5 N, 200 mL) and then with brine. The separated organic layer was dried over $MgSO_4$. Filtration and concentration provided the crude aldehyde **21**[31] as a colorless oil, which was used for the next reaction without further purification.

N,*N*-Diisopropylethylamine (1.9 mL, 11 mmol) was added to a solution of propionyloxazolidinone (2.33 g, 10 mmol) in anhydrous CH_2Cl_2 (110 mL) at 0 °C, followed by dropwise addition of Bu_2BOTf (1 M in CH_2Cl_2, 11 mL, 11 mmol). The solution was stirred for 0.5 h at 0 °C. Crude **21** in anhydrous CH_2Cl_2 (30 mL) was added at −78 °C. The mixture was stirred for 10 min at −78 °C followed by an additional 2 h at 0 °C. The reaction was quenched by addition of phosphate buffer, pH 7.0 (50 mL). A solution of hydrogen peroxide (30%, 10 mL) in methanol (20 mL) was added, and the mixture was allowed to stir for 1 h at 0 °C. After separation of organic and aqueous layers, the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, evaporated, and chromatographed (hexane/EtOAc 4:1) to yield the aldol adduct (3.83 g, 87%) as a colorless oil: IR ($CHCl_3$) 3472, 2954, 2860, 2252, 1778, 1691, 1383 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.36 (m, 7H), 7.01 (d, 2H, J = 8.7 Hz), 4.58 (m, 1H), 4.33 (s, 2H), 4.18 (br s, 1H), 3.94 (s, 3H), 3.91 (m, 1H), 3.63 (t, 2 H, J = 6.0 Hz), 3.40 (dd, 1H, J = 3.2, 13.3 Hz), 3,37 (br s, 1H), 2.90 (dd, 1H, J = 3.8, 13.3 Hz), 1.97−1.59 (m, 5H), 1.40 (d, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 177.3, 159.2, 153.1, 135.3, 130.6, 129.5, 129.3, 129.0, 127.4, 113.8, 72.5, 71.5, 69.9, 66.2, 55.2, 42.7, 37.7, 31.3, 26.4, 14.3, 11.1; HRMS (EI) calcd for $C_{25}H_{31}NO_6$ 441.2151, found 441.2162.

(4*R*)-4-Benzyl-3-[(2*R*,3*S*)-3-(*tert*-butyldimethylsilanyloxy)-6-(4-methoxybenzyloxy)-2-methylhexanoyl]oxazolidin-2-one (22). TBSOTf (1.7 mL, 7.5 mmol) was added to a stirred solution of the above alcohol (2.20 g, 5 mmol) and 2,6-lutidine (1.2 mL, 10 mmol) in CH_2Cl_2 (50 mL) at −78 °C, and the mixture was stirred for 2 h at ambient temperature. The reaction was quenched by addition of aqueous HCl (0.5 N, 100 mL). The reaction mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$ followed by the evaporation of the solvent under reduced pressure. The product was purified by column chromatography (hexane/EtOAc 9:1) to yield **22**: IR ($CHCl_3$) 3020, 2955, 2858, 1779, 1362, 1211 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.36 (m, 7H), 7.00 (d, 2H, J = 8.7 Hz), 4.70 (m, 1H), 4.56 (s, 2H), 4.27−4.15 (m, 3H), 4.04 (dd, 1H, J = 5.4, 6.8), 3.91 (s, 3H), 3.60 (m, 3 H), 3.40 (dd, 1H, J = 3.0, 13.2 Hz), 2.90 (dd, 1H, J = 9.5, 13.2 Hz), 1.80 (br m, 4H), 1.38 (d, 3H, J = 6.8 Hz), 1.05 (s, 9H), 0.21 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 175.4, 159.2, 153.2, 135.5, 130.9, 129.6, 129.3, 129.0, 127.4, 113.8, 72.9, 72.5, 70.2, 66.1, 55.9, 55.3, 42.8, 37.7, 32.1, 26.0, 25.2, 18.2, 12.2, −3.92, −4.65; LRMS (ESI) 578.3 (M + Na)$^+$.

(2*S*,3*S*)-3-(*tert*-Butyldimethylsilanyloxy)-6-(4-methoxybenzyloxy)-2-methylhexan-1-ol. Lithium borohydride (2 M in THF, 5 mL, 10 mmol) was added dropwise to a stirred solution of **22** (2.77 g, 5 mmol) and methanol (0.4 mL, 10 mmol) in anhydrous THF (20 mL) under an atmosphere of N_2 at 0 °C. The mixture was stirred for 20 min at 0 °C and then warmed to ambient temperature. After 3 h at room temperature, the reaction was quenched with aqueous NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, evaporated, and chromatographed (hexane/EtOAc 7:3) to yield the alcohol (1.48 g, 78%) as a colorless oil: IR ($CHCl_3$) 2948, 2856, 2302, 1612, 1265 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, 2H, J = 8.5 Hz), 7.00 (d, 2H, J = 8.5 Hz), 4.43 (s, 2H), 3.78 (s, 3H), 3.67 (dd, 1 H, J = 8.6, 10.5 Hz), 3.51−3.41 (m, 3H), 2.78 (br s, 1H), 1.94 (m, 1H), 1.72−1.49 (m, 4H), 0.90 (s, 9H), 0.81 (d, 3H, J = 7.0 Hz), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.2, 130.6, 129.3, 113.8, 75.4, 72.6, 70.1, 65.8, 55.9, 55.3, 39.7, 29.1, 26.6, 25.9, 18.0, 12.1, −4.28, −4.38; LRMS (ESI) 405.2 (M + Na)$^+$.

(4*R*)-4-Benzyl-3-[(2*R*,3*S*,4*R*,5*S*)-5-(*tert*-butyldimethylsilanyloxy)-3-hydroxy-8-(4-methoxybenzyloxy)-2,4-dimethyloctanoyl]oxazolidin-2-one. Pyridinium sulfur trioxide (2.38 g, 15 mmol) was added to a stirred solution of the above TBS-protected alcohol (1.91 g, 5 mmol) and *N*,*N*-diisopropylethylamine (2.65 mL, 15 mmol) in anhydrous CH_2Cl_2 (5 mL) and DMSO (10 mL) at 0 °C. The mixture was stirred at the ambient temperature for 1 h, diluted with ethyl ether (100 mL), washed with aqueous HCl (0.5 N, 100 mL) and brine, then dried over $MgSO_4$. Filtration and concentration provided the crude aldehyde as a colorless oil, which was used without further purification.

N,N-Diisopropylethylamine (0.97 mL, 5.5 mmol) was added to a solution of propionyloxazolidinone (1.16 g, 5 mmol) in anhydrous CH_2Cl_2 (11 mL) at 0 °C, followed by dropwise addition of Bu_2BOTf (1 M in CH_2Cl_2, 5.5 mL, 5.5 mmol). The solution was stirred for 0.5 h at 0 °C. A solution of crude aldehyde from above in anhydrous CH_2Cl_2 (10 mL) was added at −78 °C. The reaction mixture was stirred for 10 min at −78 °C then for 2 h at 0 °C. The reaction mixture was quenched with phosphate buffer, pH 7.0 (50 mL). A solution of hydrogen peroxide (30%, 10 mL) in methanol (20 mL) was slowly added, and the mixture was stirred for 1 h. After the separation of organic and aqueous layers, the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, evaporated, and chromatographed (hexane/EtOAc 4:1) to yield desired compound (2.29 g, 75%) as a colorless oil: IR ($CHCl_3$) 2949, 2855, 2253, 1779, 1692, 1463 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.19 (m, 7H), 7.01 (d, 2H, J = 8.1 Hz), 4.42 (m, 1H), 4.44 (s, 2H), 4.16 (d, 1H, J = 5.1 Hz), 4.01 (m, 1H), 3.95 (t, 1H, J = 6.3 Hz), 3.85 (m, 1H), 3.79 (s, 3 H), 3.43 (br s, 2H), 3,24 (br s, 1H), 3.20 (dd, 1H, J = 2.4, 13.5 Hz), 2.77 (dd, 1H, J = 9.6, 13.2 Hz), 1.56−1.31 (m, 5H), 1.32 (d, 3H, J = 6.9 Hz), 0.95 (d, 3H, J = 6.9 Hz), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 177.2, 159.2, 152.7, 135.1, 130.6, 129.5, 129.3, 129.0, 127.5, 113.8, 76.8, 74.2, 72.6, 70.0, 66.1, 55.3, 55.0, 40.6, 38.1, 37.8, 31.3, 25.9, 18.1, 13.2, 7.4, −3.5, −4.6; HRMS (EI) calcd for $C_{34}H_{51}NO_7Si$ 613.3435, found 613.3427.

(4*R*)-4-Benzyl-3-[(2*R*,3*S*,4*R*,5*S*)-5-(*tert*-butyldimethylsilanyloxy)-8-(4-methoxybenzyloxy)-3-methoxymethoxy-2,4-dimethyloctanoyl]oxazolidin-2-one (24). *N,N*-Diisopropylethylamine (7.5 mL) and chloromethyl methyl ether (1.13 mL, 9 mmol) were added to a solution of the alcohol from above (1.83 g, 3 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred at reflux overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL) and washed with brine. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (hexane/EtOAc 4:1) to provide the pure product in 92% yield: IR ($CHCl_3$) 3020, 2862, 1781, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.27 (m, 7H), 6.94 (d, 2H, J = 8.7 Hz), 4.75 (s, 2H), 4.69 (m, 1H), 4.53 (s, 2H), 4.19 (dd, 1H, J = 10.2, 15.0 Hz), 3.97 (dd, 1H, J = 3.0, 6.6 Hz), 3.84 (br s, 4H), 3.43 (br t, 2H), 3,45 (s, 3H), 3.30 (dd, 1H, J = 3.0, 13.2 Hz), 2.77 (dd, 1H, J = 9.3, 13.5 Hz), 1.81−1.75 (m, 5H), 1.36 (d, 3H, J = 6.9 Hz), 1.02 (d, 3H, J = 6.9 Hz), 0.98 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 175.5, 159.1, 153.0, 135.4, 131.0, 129.5, 129.2, 129.0, 127.4, 113.7, 98.3, 80.3, 76.9, 73.2, 72.3, 70.5, 66.0, 56.3, 55.6, 55.2, 41.7, 40.8, 37.6, 30.6, 26.1, 24.2, 18.3, 14.0, 10.5, −3.9, −4.3; HRMS (EI) calcd for $C_{34}H_{50}NO_7Si$ (M − CH_2OCH_3) 612.3356, found 612.3367 (M − CH_2OCH_3).

6-[(3*R*,4*S*,5*S*,6*S*)-3-(4-Methoxybenzyloxy)propyl]-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-one (25). HF-pyridine (6 mL) was added to a solution of **24** (1.31 g, 2 mmol) in MeOH (20 mL) and pyridine (10 mL) at 0 °C. The mixture was stirred at room temperature for 48 h, diluted with EtOAc (100 mL), and washed with aqueous HCl (0.5 N, 2 × 50 mL) and with brine. The aqueous layer was extracted with EtOAc (50 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (hexane/EtOAc 4:1) to provide the pure product in 83% yield: IR ($CHCl_3$) 3020, 2952, 1730, 1513, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, 2H, J = 8.7 Hz), 6.87 (d, 2H, J = 8.7 Hz), 4.72 (d, 1H, J = 7.2 Hz), 4.60 (d, 1H, J = 7.2 Hz), 4.48 (m, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.50−3.39 (m, 2H), 3.39 (s, 3H), 3.26 (dd, 1H, J = 1.1, 7.0 Hz), 2.58 (t, 1H, J = 6.9 Hz), 2.03 (d, 1H, J = 7.5 Hz), 1.81−1.63 (m, 4H), 1.31 (d, 3H, J = 6.7 Hz), 0.91 (d, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 174.1, 159.2, 130.5, 129.3, 113.8, 95.5, 82.6, 76.7, 72.6, 69.4, 55.9, 55.3, 40.5, 38.4, 28.6, 26.0, 14.4, 11.9, −3.9; HRMS (EI) calcd for $C_{20}H_{30}O_6$ 366.2042, found 366.2050.

2-Methoxy-6-[(3*R*,4*S*,5*S*,6*S*)-3-(4-methoxybenzyloxy)-propyl]-4-methoxymethoxy-3,5-dimethyltetrahydropyran (26). Diisobutylaluminum hydride (1 M in THF, 2.2 mL, 2.2 mmol) was added dropwise to a stirred solution of **25** (732 mg, 2 mmol) in anhydrous CH_2Cl_2 (20 mL) under an atmosphere of N_2 at −78 °C, and the mixture was stirred for 1 h at −78 °C. The reaction was quenched by the careful addition of saturated aqueous potassium sodium tartrate (50 mL) and stirring for 3 h at room temperature. Once the organic and aqueous layers separated, the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over $MgSO_4$ followed by the evaporation of solvent under reduced pressure. The crude lactol obtained was used without further purification.

A solution of the lactol and PPTS (0.2 mmol) in MeOH was stirred for 15 h at room temperature. The reaction mixture was diluted with EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with EtOAc (50 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (hexane/EtOAc 7:3) to provide the pure product each anomer **26** (β, 64%; α, 26%). **β-26**: IR ($CHCl_3$) 3020, 2858, 2299, 1514, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, 2H, J = 8.7 Hz), 6.95 (d, 2H, J = 8.7 Hz), 4.76 (d, 2H, J = 3.0 Hz), 4.52 (s, 2H), 4.37 (d, 1H, J = 4.6 Hz), 4.09 (m, 1H), 3.89 (s, 2H), 3.57 (m, 2H), 3.47 (s, 3H), 3.32 (t, 1H, J = 5.7 Hz), 1.89−1.71 (m, 6H), 1.16 (d, 3H, J = 7.2 Hz), 1.07 (d, 3H, J = 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 159.2, 130.7, 129.3, 113.8, 103.2, 96.3, 82.0, 72.6, 69.9, 69.3, 55.7, 55.3, 39.1, 38.0, 27.1, 26.5, 16.0, 13.1; HRMS (EI) calcd for $C_{21}H_{34}O_6$ 382.2353, found 382.2355. **α-26**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, 2H, J = 8.7 Hz), 6.95 (d, 2H, J = 8.7 Hz), 4.72 (s, 2H), 4.70 (d, 1H, J = 2.8 Hz), 4.52 (s, 2H), 4.09 (br m, 4H), 3.67 (br s, 1H), 3.56 (m, 5H), 3.44 (s, 3H), 2.08−1.54 (m, 6H), 1.11 (d, 3H, J = 3.0 Hz), 1.08 (d, 3H, J = 2.9 Hz)

(2*S*,3*S*,4*S*,5*R*,6*R*)-3-(6-Methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl)propionaldehyde (10b). A mixture of PMB ether **26** (458 mg, 1.2 mmol) and palladium (10% Pd/C, 5 mg) was stirred in EtOAc (12 mL) for 3 h at room temperature under an H_2 atmosphere (balloon), filtered, and concentrated to yield the debenzylated alcohol, which was used without further purification.

The crude alcohol in CH_2Cl_2 (12 mL) was treated with Dess−Martin periodinane (636 mg, 1.5 mmol) at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 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 274 mg (88%) of the crude aldehyde as a colorless oil which was used without further purification: ^1H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 4.67 (dd, 2H, J = 7.0, 12.5 Hz), 4.27 (d, 1H, J = 4.5 Hz), 3.99 (dd, 1H, J = 3.5, 4.0 Hz), 3.36 (s, 6H), 3.24 (t, 1H, J = 6.0 Hz), 2.61 (m, 1H), 2.52 (m, 1H), 1.83 (m, 3H), 1.68 (m, 1H), 1.05 (d, 3H, J = 7.0 Hz), 1.01 (d, 3H, J = 7.5 Hz).

(2*S*,3*R*,4*S*)-5-(*tert*-Butyldimethylsilanyloxy)-2,4-dimethylpentane-1,3-diol. Methanol (0.51 mL) and $LiBH_4$ (2 M in THF, 6.2 mL, 12.4 mmol) were added dropwise to a stirred solution of aldol product **28**[22] (5.38 g, 12.3 mmol) in THF (50 mL) at 0 °C. After the mixture was stirred for 1 h at 0 °C, saturated aqueous sodium potassium tartrate (70 mL) was added. The mixture was allowed to warm to room temperature and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was washed with brine (40 mL), dried over anhydrous $MgSO_4$, concentrated, and flash column chromatographed (hexane/EtOAc 4:1) to yield 2.99 g (92%) of the desired product as a colorless oil: IR ($CHCl_3$) 3409, 2958, 2927, 2853, 2878, 1469, 1385, 1361, 1252, 1082, 838, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.45 (br s, 1H), 3.54 (br s, 1H), 1.92 (m, 1H), 1.83 (m, 1H), 1.06 (d, 3H, J = 6.98 Hz), 1.00 (s, 9H), 0.84 (d, 3H, J = 6.88 Hz), 0.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 79.3, 69.7, 67.5, 37.4, 36.6, 25.9, 18.1, 12.8, 8.9, −5.5, −5.6; LRMS (EI) 263 (M + H); HRMS (EI) calcd for $C_{13}H_{30}O_3Si$ 263.2042, found 263.2042; $[\alpha]^{20}_D$ +35.5 (*c* 0.85, $CHCl_3$).

(2*S*)-*tert*-Butyl-{(4*R*,5*S*)-2-[2-(4-methoxyphenyl)-5-methyl[1,3]dioxan-4-yl]propoxy}dimethylsilane (30). A

solution of the above diol (2.8 g, 10.7 mmol), *p*-anisaldehyde dimethylacetal (2.0 mL, 11.7 mmol), and PPTS (0.27 g, 1.1 mmol) in benzene was heated to reflux for 3 h. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (hexane/EtOAc 9:1) to give **30** (2.6 g, 6.8 mmol) in 64% yield: IR ($CHCl_3$) 2955, 2927, 2853, 1617, 1518, 1459, 1382, 1157, 1101, 1033, 826 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (m, 2H), 6.98 (m, 2H), 5.50 (m, 2H), 3.89 (s, 3H), 3.82 (dd, 1H, J = 10.9, 4.9 Hz), 3.76 (dd, 2H, J = 8.1, 2.8 Hz), 1.87 (m, 1H), 1.71 (m, 1H), 1.23 (d, 3H, J = 7.6 Hz), 1.00 (d, 3H, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 160.1, 132.1, 127.6, 113.8, 113.7, 101.9, 80.1, 74.3, 65.2, 64.3, 55.5, 37.4, 30.0, 26.3, 26.2, 18.7, 12.4, 11.3, −5.0, −5.1; LRMS (EI) 323, 207, 187, 157, 145, 121, 75; HRMS (EI) calcd for $C_{21}H_{36}O_4Si_1$ 323.1678 (M − C_4H_9), found 323.1694 (M − C_4H_9); $[\alpha]^{20}_D$ −33.6 (*c* 1.24, $CHCl_3$).

(2*S*)-2-[(4*R*,5*S*)-2-(4-Methoxyphenyl)-5-methyl[1,3]-dioxan-4-yl]propan-1-ol. TBAF (1 M in THF, 22 mL, 22 mmol) was added to a solution of **30** (2.8 g, 7.3 mmol) in THF (70 mL) at room temperature, and the mixture was stirred for 2 h. The mixture was diluted with ethyl ether (100 mL) and brine. The organic layer was dried over $MgSO_4$. Filtration and concentration followed by flash column chromatography (hexane/EtOAc 7:3) provided alcohol (1.95 g, 7.2 mmol) in 99% yield as a yellow oil: IR ($CHCl_3$) 3428, 2964, 2930, 2835, 1614, 1512, 1463, 1391, 1249, 1098, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (m 2H), 6.87 (m, 2H), 5.48 (s, 1H), 4.11 (dd, 2H, J = 4.6, 4.5 Hz), 3.75 (s, 3H), 3.73 (m, 2H), 3.52 (apparent t, 1H, J = 11.1 Hz), 2.08 (m, 1H), 2.00 (m, 1H), 1.04 (d, 3H, J = 7.1 Hz), 0.77 (d, 3H, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 160.0, 131.5, 127.4, 113.6, 101.6, 83.4, 73.9, 66.3, 55.2, 36.8, 30.4, 11.9, 9.9; LRMS (EI) 266, 207, 177, 153, 135, 77; HRMS (EI) calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1517; $[\alpha]^{20}_D$ −4.8 (*c* 0.67, $CHCl_3$).

(2S)-{2-[(4*R*,5*S*)-2-(4-Methoxyphenyl)-5-methyl[1,3]-dioxan-4-yl]propyl}triphenylphosphane Iodide (11). I_2 (4.48 g, 17.6 mmol) was added at 0 °C to a solution of the alcohol from above (2.35 g, 8.82 mmol) in CH_2Cl_2 (110 mL) containing imidazole (1.32 g, 19.4 mmol) and triphenylphosphine (4.63 g, 17.6 mmol). The resulting slurry was stirred for 1 h and quenched with saturated aqueous $Na_2S_2O_3$(10 mL). The organic layer was separated, washed with water (20 mL) and brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (hexane/EtOAc 9:1) to give the pure iodide.

The iodide was quickly dissolved in benzene (44 mL), PPh_3 was added (11.5 g, 44.1 mmol), and the mixture was heated to reflux for 36 h. The reaction mixture was cooled to room temperature, and anhydrous ethyl ether (50 mL) was added, whereupon a white solid precipitated. Filtration followed by washing of the solid with ethyl ether (10 mL) provided the phosphonium salt (4.5 g) as a white foam: IR ($CHCl_3$) 3054, 2961, 2909, 1611, 1515, 1435, 1246, 1107, 993, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 9H), 7.37 (m, 6H), 7.21 (m, 2H), 6.65 (m, 1H), 5.41 (s, 1H), 3.95 (d, 1H, J = 10.2 Hz), 3.68 (d, 2H, J = 12.3 Hz), 3.54 (s, 3H), 3.26 (m, 1H), 1.85 (m, 1H), 1.46 (apparent d, 1H, J = 6.5 Hz), 0.78 (d, 3H, J = 6.8 Hz), 0.44 (d, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 160.0, 135.2, 135.1, 133.7, 133.5, 131.1, 130.5, 130.4, 127.9, 119.0, 117.9, 113.5, 101.9, 82.3, 82.1, 73.2, 55.5, 30.7, 29.2, 25.3, 15.7, 10.4 HRMS (EI) calcd for $C_{33}H_{36}O_3P$ 511.2402, found 511.2428; $[\alpha]^{20}_D$ +31.9 (*c* 0.78, $CHCl_3$).

(4*R*,5*S*)-4-{(1*S*,2*Z*)-5-[(2*S*,3*R*,4*S*,5*R*,6*R*)-6-Methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-1-methylpent-2-enyl}-2-(4-methoxyphenyl)-5-methyl[1,3]-dioxane (33). NaHMDS (1 M in THF, 1.1 mL, 1.1 mmol) was slowly added to a solution of the salt **11** (701 mg, 1.1 mmol) in dry THF (2.2 mL) at 0 °C. The resulting red solution was stirred at room temperature for 20 min. The mixture was cooled to −78 °C, and a solution of the aldehyde **10a** (260 mg, 1 mmol) in THF (2 × 1 mL) was added dropwise. The mixture was stirred for 20 min at −78 °C and then warmed to room temperature. After 4 h at room temperature, the mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, evaporated, and chromatographed (hexane/ether 9:1) to yield 329 mg (67%) of **33** as a colorless oil: IR ($CHCl_3$) 2922, 2866, 2628, 2350, 1740, 1516 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, 2H, J = 8.4 Hz), 6.88 (d, 2H, J = 8.4 Hz), 5.46 (m, 2H), 5.30 (t, 1H, J = 9.9 Hz), 4.77 (d, 1H, J = 6.9 Hz), 4.70 (d, 1H, J = 1.8 Hz), 4.63 (d, 1H, J = 6.9 Hz), 4.06 (br d, 1H, J = 2.1 Hz), 3.80 (s, 3H), 3.54 (m, 3H), 3.43 (s, 3H), 3.32 (s, 3H), 2.77 (m, 1H), 2.31 (dd, 2H, J = 7.5, 14.7 Hz), 1.79−1.55 (m, 4H), 1.22 (d, 3H, J = 6.6 Hz), 1.02 (d, 3H, J = 7.2 Hz), 0.96 (d, 3H, J = 6.9 Hz), 0.86 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 133.4, 131.8, 130.1, 127.3, 113.3, 101.5, 101.3, 95.9, 83.5, 82.0, 75.2, 73.9, 56.4, 55.7, 55.2, 37.6, 34.2, 33.6, 33.0, 30.0, 23.4, 16.1, 13.3, 11.2, 9.9; HRMS (EI) calcd for $C_{27}H_{40}O_6$ 460.2824, found 460.2846.

(4*R*,5*S*)-4-{(1*S*,2*Z*)-5-[(2*S*,3*S*,4*S*,5*R*,6*R*)-6-Methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-1-methylpent-2-enyl}-2-(4-methoxyphenyl)-5-methyl[1,3]-dioxane (34). NaHMDS (1 M in THF, 1.1 mL, 1.1 mmol) was slowly added to a solution of the salt **9** (0.70 g, 1.1 mmol) in dry THF (2 mL) at 0 °C. The resulting red solution was stirred at room temperature for 20 min. The mixture was cooled to −78 °C, and a solution of the aldehyde **10b** (260 mg, 1 mmol) in THF (1 mL) was added dropwise. The mixture was stirred for 20 min at −78 °C and then warmed to room temperature. After 4 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, evaporated, and chromatographed (hexane/ether 9:1) to yield 329 mg (67%) of **34** as a colorless oil: IR ($CHCl_3$) 2922, 2866, 2628, 2350, 1740, 1516 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, 2H, J = 9.0 Hz), 6.91 (d, 2H, J = 9.0 Hz), 5.46 (m, 2H), 5.32 (t, 1H, J = 9.6 Hz), 4.73 (s, 2H), 4.31 (d, 1H, J = 5.4 Hz), 4.07 (br s, 2H), 3.81 (s, 1H), 3.57 (dd, 1H, J = 1.8, 9.6 Hz), 3.45 (s, 3H), 3.43 (s, 3H), 3.20 (t, 1H, J = 6.6 Hz), 2.77 (m, 1H), 2.31−2.17 (m, 2H), 1.90−1.62 (m, 4H), 1.24−0.98 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 133.7, 131.7, 129.4, 127.2, 113.4, 102.8, 101.5, 96.6, 83.5, 82.2, 73.9, 70.0, 55.7, 55.2, 39.8, 38.4, 33.6, 30.0, 29.9, 24.3, 15.9, 15.5, 13.2, 11.1; HRMS (EI) calcd for $C_{27}H_{40}O_6$ (M-$HOCH_3$) 460.2824, found 460.2846.

(2*R*,3*S*,4*S*,5*Z*)-3-(4-Methoxybenzyloxy)-8-[(2*S*,3*R*,-4*S*,5*R*,6*R*)-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-2,4-dimethyloct-5-enal (35). DIBAL (1 M in hexane, 2.1 mL, 2.1 mmol) was added dropwise to a solution of the acetal **33** (329 mg, 0.67 mmol) in dry CH_2Cl_2 (6.7 mL) at 0 °C. After being stirred for 2 h, the reaction was quenched with saturated aqueous sodium tartrate (20 mL) then vigorously stirred for several hours. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with brine (10 mL). The residue obtained after drying over $MgSO_4$ and evaporation under vacuum was dissolved in anhydrous CH_2Cl_2 (6 mL) and DMSO (12 mL), treated with *N*,*N*-diisopropylethylamine (0.52 mL, 3 mmol), cooled to 0 °C, and treated with pyridinium sulfur trioxide (477 mg, 3 mmol). The reaction mixture was stirred at ambient temperature for 1 h, diluted with ethyl ether (50 mL), and washed with aqueous HCl (0.5 N, 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 **35** (270 mg, 0.55 mmol) as a colorless oil, which was used without further purification.

(2*R*,3*S*,4*S*,5*Z*)-3-(4-Methoxybenzyloxy)-8-[(2*S*,3*S*,-4*S*,5*R*,6*R*)-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-2,4-dimethyloct-5-enal (36). DIBAL (1 M in hexane, 2.1 mL, 2.1 mmol) was added dropwise to a solution of the acetal **34** (329 mg, 0.67 mmol) in dry CH_2Cl_2 (6.7 mL) at 0 °C. After the mixture was stirred for 2 h, the reaction was quenched with saturated aqueous sodium tartrate (20 mL) followed by vigorous stirring for several hours. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with brine (10 mL). After being dried over $MgSO_4$ and evaporation under vacuum,

the residue was used for the next reaction without further purification. The crude alcohol in CH_2Cl_2 (13 mL) was treated with Dess−Martin periodinane (341 mg, 0.80 mmol). After the reaction was complete, the mixture was quenched with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by short flash column chromatography filtration (hexane/EtOAc 9:1) provided crude aldehyde **36** (267 mg, 81%) as a colorless oil, which was used without further purification.

(4*R*,5*R*)-*tert*-Butyl-{3-[2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]propoxy}dimethylsilane (39). Lithium borohydride (2 M in THF, 25 mL, 50 mmol) was added dropwise to a stirred solution of **38** (8.70 g, 20 mmol) and MeOH (1.61 mL, 40 mmol) in anhydrous THF (100 mL) under an atmosphere of N_2 at 0 °C. The mixture was stirred for 20 min at 0 °C and then warmed to ambient temperature. After 2 h at room temperature, the reaction was quenched with aqueous NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, evaporated, and chromatographed (hexane/EtOAc 7:3) to yield 4.97 g (95%) of the diol as a colorless oil.

A solution of the diol (2.62 g, 10 mmol), anisaldehyde dimethyl acetal (2.00 g, 11.0 mmol), and PPTS (0.1 equiv) in benzene was stirred for 15 h at reflux. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL) followed by washing with water. The aqueous layer was extracted with ethyl ether (2 × 50 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (hexane/EtOAc 7:3) to provide the pure **38** in 72% yield: IR ($CHCl_3$) 2992, 1742, 1373, 1240 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, 2H, J = 8.4 Hz), 6.88 (d, 2H, J = 8.4 Hz), 5.45 (s, 1H), 4.08 (dd, 2H, J = 10.5, 29.9 Hz), 3.90 (br s, 1H), 3.80 (s, 3H), 3.67 (m, 2H), 1.67−1.50 (m, 5H), 1.17 (d, 3H, J = 7.0 Hz), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.9, 131.6, 127.4, 113.6, 101.7, 79.7, 73.9, 63.1, 55.3, 31.8, 29.3, 28.7, 26.0, 18.4, 11.1, −5.1; LRMS (ESI) 402.68 (M + Na).

(4*S*,5*R*)-{3-[2-(4-Methoxyphenyl)-5-methyl[1,3]dioxan-4-yl]propyl}triphenyl-l5-phosphane Iodide (8). TBAF (1 M in THF, 20 mL, 20 mmol) was added at room temperature to a solution of **39** (3.80 g, 10 mmol) in THF (30 mL). After 2 h, the mixture was diluted with ethyl ether (100 mL) and brine followed by drying over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (hexane/EtOAc 9:1) to give the pure alcohol in 97% yield: IR ($CHCl_3$) 2949, 2854, 2253, 1616, 1465, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, 2H, J = 8.6 Hz), 6.96 (d, 2H, J = 8.7 Hz), 5.55 (s, 1H), 4.21−4.00 (m, 4H), 3.87 (s, 3H), 3.54 (s, 3H), 3.72 (t, 2H, J = 5.7 Hz), 1.99 (br s, 1H), 1.78−162 (m, 5H), 1.27 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 160.0, 131.3, 127.4, 113.7, 101.8, 80.1, 73.9, 62.8, 55.0, 32.2, 29.8, 29.3, 11.2; HRMS (EI) calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1513.

I_2 (4.48 g, 17.6 mmol) was added to a solution of the alcohol from above (2.35 g, 8.82 mmol) containing imidazole (1.32 g, 19.4 mmol) and triphenylphosphine (4.63 g, 7.6 mmol) in CH_2Cl_2 (88 mL) at 0 °C. The resulting slurry was stirred for 1 h and quenched with saturated aqueous $Na_2S_2O_3$ (10 mL). The organic layer was separated and washed with water (20 mL) and brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was used for the next reaction without further purification.

The iodide was quickly dissolved in benzene (88 mL), PPh_3 was added (11.5 g, 44.1 mmol), and the mixture was heated to reflux for 36 h. The reaction mixture was cooled to room temperature and anhydrous ethyl ether (50 mL) was added, whereupon a white solid precipitated. Filtration and washing with diethyl ether (10 mL) provided the phosphonium salt (4.5 g) as a white foam: ^1H NMR (300 MHz, $CDCl_3$) δ 8.27−7.40 (m, 17H), 6.96 (d, 2H, J = 7.8 Hz), 5.71 (s, 1H), 4.42 (d, 1H, J = 9.5 Hz), 4.32 (d, 1H, J = 10.7 Hz), 4.20 (m, 1H), 4.06 (d, 1H, J = 11.3 Hz), 3.95 (s, 3H), 3.65 (m, 1H), 2.07−1.74 (m, 5H), 0.98 (d, 3H, J = 6.8 Hz).

(4*S*,5*R*)-4-{(3*Z*,5*S*,6*S*,7*S*,8*Z*)-6-(4-Methoxybenzyloxy)-11-[(2*S*,3*R*,4*S*,5*R*,6*R*)-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-5,7-dimethylundeca-3,8-dienyl}-2-(4-methoxyphenyl)-5-methyl[1,3]dioxane (40). NaHMDS (1 M in THF, 1.1 mL, 1.1 mmol) was slowly added to a solution of the salt **8** (350 mg, 0.55 mmol) in dry THF (1.1 mL) at 0 °C. The resulting red solution was stirred at room temperature for 20 min. The mixture was cooled to −78 °C, and a solution of the aldehyde **35** (246 mg, 0.5 mmol) in THF (2 × 0.5 mL) was added dropwise. The mixture was stirred for 20 min at −78 °C and then warmed to room temperature. After 4 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, evaporated, and flash column chromatographed (hexane/diethyl ether 9:1) to yield 329 mg (67%) of **40** as a colorless oil: IR ($CHCl_3$) 3020, 2752, 2332, 1516, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.50 (d, 2H, J = 8.7 Hz), 7.37 (d, 2H, J = 8.4 Hz), 6.95 (m, 4H), 5.58−5.32 (m, 5H), 4.81 (d, 1H, J = 6.9 Hz), 4.74 (d, 1H, J = 2.1 Hz), 4.64 (m, 3H), 4.10 (dd, 2H, J = 9.6, 18.3 Hz), 3.95 (t, 1H, J = 6.0 Hz), 3.85 (s, 6H), 3.59 (m, 2H), 3.56 (s, 3H), 3.46 (s, 3H), 3.14 (dd, 1H, J = 3.3, 7.5 Hz), 2.89 (m, 1H), 2.76 (m, 1H), 2.33−2.11 (m, 5H), 1.82−1.51 (m, 6H), 1.24 (d, 3H, J = 6.9 Hz), 1.12 (m, 6H), 1.02 (d, 3H, J = 7.0 Hz), 0.94 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 159.9, 159.1, 134.0, 132.5, 131.6, 131.3, 129.5, 129.2, 128.4, 127.4, 113.7, 113.6, 101.7, 101.3, 96.0, 88.0, 82.0, 79.2, 75.2, 74.9, 73.8, 56.4, 55.8, 55.3, 37.6, 35.9, 35.3, 34.2, 33.2, 32.9, 31.7, 23.4, 19.0, 17.6, 13.5, 11.2, 9.9; LRMS (ESI) 747.4 $(M + Na)^+$.

(4*S*,5*R*)-4-{(3*Z*,5*S*,6*S*,7*S*,8*Z*)-6-(4-Methoxybenzyloxy)-11-[(2*S*,3*S*,4*S*,5*R*,6*R*)-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-5,7-dimethylundeca-3,8-dienyl}-2-(4-methoxyphenyl)-5-methyl[1,3]dioxane (41). This was prepared by the same procedure as compound **40**. IR ($CHCl_3$) 3020, 2752, 2332, 1516, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.42 (d, 2H, J = 7.8 Hz), 7.27 (d, 2H, J = 7.8 Hz), 6.87 (m, 4H), 5.53−5.30 (m, 5H), 4.67 (br t, 2H, J = 7.5 Hz), 4.54 (dd, 1H, J = 10.5, 21.3 Hz), 4.26 (d, 1H, J = 4 86 Hz), 4.07−3.98 (m, 3H), 3.87 (t, 1H, J = 6.0 Hz), 3.79 (s, 6H), 3.39 (s, 6H), 3.19 (t, 1H, J = 6.3 Hz), 3.07 (dd, 1H, J = 3.9, 6.9 Hz), 2.75−2.62 (m, 2H), 2.16 (m, 5H), 1.87 (m, 3H), 1.63 (m, 3H), 1.16 (d, 3H, J = 6.6 Hz), 1.08−0.96 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.9, 159.1, 134.1, 132.7, 131.6, 131.3, 129.2, 128.9, 128.3, 127.4, 113.7, 103.0, 101.7, 96.5, 88.0, 82.1, 79.3, 75.0, 73.8, 69.7, 55.8, 55.7, 55.3, 39.4, 38.3, 35.8, 35.4, 32.8, 31.6, 30.3, 29.8, 24.2, 23.3, 18.9, 17.4, 15.7, 13.2, 11.2; LRMS (ESI) 747.4 $(M + Na)^+$.

(2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-3,9-Bis(4-methoxybenzyloxy)-14-[(2*S*,3*R*,4*S*,5*R*,6*R*)-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl)-2,8,10-trimethyltetradeca-6,11-dienal (42). DIBAL (1 M in hexane, 0.3 mL, 0.3 mmol) was added dropwise to a solution of **40** (72.4 mg, 0.1 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. After the mixture was stirred for 2 h, the reaction was quenched with saturated aqueous sodium tartrate (10 mL) followed by vigorous stirring for several hours. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with brine (10 mL). After drying over $MgSO_4$ and evaporation under vacuum, the residue was used for the next reaction without further purification. The crude alcohol in CH_2Cl_2 (10 mL) was treated with Dess−Martin periodinane (63.6 mg, 0.15 mmol). After the reaction was complete, it was quenched with saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by short flash column chromatography filtration (hexane/EtOAc 9:1) provided 60 mg (83%) of the crude aldehyde **42** as a colorless oil which was used without further purification.

(2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-3,9-Bis(4-methoxybenzyloxy)-14-[(2*S*,3*S*,4*S*,5*R*,6*R*)-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-2,8,10-trimethyltetradeca-6,11-dienal (43). DIBAL (1 M in hexane, 0.3 mL, 0.3 mmol) was added dropwise to a solution of **41** (72.4 mg, 0.1 mmol) in

dry CH_2Cl_2 (10 mL) at 0 °C. After stirring for 2 h, the reaction was quenched with saturated aqueous sodium tartrate (10 mL) followed by vigorous stirring for several hours. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with brine (10 mL). After drying over $MgSO_4$ and evaporation under vacuum, the residue was purified by column chromatography (hexane/EtOAc 7:3) to give the alcohol: IR ($CHCl_3$) 3019, 2897, 2286, 1778, 1515, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.43 (m, 2H), 6.99 (m, 4H), 5.64 (t, 1H, J = 10.8 Hz), 5.54−5.37 (m, 3H), 4.81 (dd, 2H, J = 6.9, 9.6 Hz), 4.72−4.57 (m, 4H), 4.39 (d, 1H, J = 5.1 Hz), 4.12 (m, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.81 (m, 1H), 3.63 (m, 2H), 3.52 (s, 6H), 3.33 (t, 1H, J = 6.3 Hz), 3.19 (dd, 1H, J = 3.9, 7.5 Hz), 2.91 (m, 1H), 2.75 (m, 1H), 2.31−1.38 (m, 11H), 1.21−0.99 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.3, 159.1, 134.0, 132.8, 131.3, 130.5, 129.6, 129.2, 128.9, 128.4, 113.9, 113.7, 103.9, 96.6, 88.0, 82.2, 81.6, 75.0, 71.5, 69.8, 66.1, 55.8, 55.7, 55.3, 39.5, 38.3, 37.0, 35.9, 35.4, 30.3, 29.8, 24.5, 24.3, 19.0, 17.5, 15.7, 13.2, 11.8; LRMS (ESI) 749.5; HRMS (ESI) calcd for $C_{43}H_{66}O_9Na$ 749.4605, found 749.4601 $(M + Na)^+$.

The alcohol in CH_2Cl_2 (10 mL) was treated with Dess−Martin periodinane (63.6 mg, 0.15 mmol). After the reaction was complete, it was quenched with saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried over anhydrous $MgSO_4$. Filtration and concentration followed by short flash column chromatography filtration (hexane/EtOAc 9:1) to remove the residue from Dess−Martin reagent provided 60 mg (83%) of the crude aldehyde **43** as a colorless oil, which was used without further purification.

Carbamic Acid, (1*S*,2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-1-Isopropyl-3,9-bis(4-methoxybenzyloxy)-14-[(2*R*,3*R*,4*S*,5*R*,6*R*)-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-2,8,10-trimethyltetradeca-6,11-dienyl Ester (44). Isopropylmagnesium chloride (1 M in THF, 0.8 mL, 0.8 mmol) was added to a solution of **42** (60 mg, 0.083 mmol) in dry THF at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, evaporated, and chromatographed (hexane/ether 9:1) to yield the alcohol (41.4 mg, 65%) as a colorless oil: IR ($CHCl_3$) 3019, 2897, 2286, 1778, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.35 (m, 4H), 6.95 (m, 4H), 5.57 (t, 1H, J = 10.5 Hz), 5.44−5.35 (m, 3H), 4.81 (d, 1H, J = 7.2 Hz), 4.72 (d, 1H, J = 2.4 Hz), 4.67 (m, 4H), 4.43 (d, 1H, J = 10.8 Hz), 3.58 (t, 1H, J = 2.4 Hz), 3.55 (s, 3H), 3.46 (s, 3H), 3.36 (m, 1H), 3.14 (dd, 1H, J = 3.6, 7.5 Hz), 2.86 (m, 1H), 2.69 (m, 1H), 2.36−1.53 (m, 6H), 1.24−0.98 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.7, 159.1, 134.1, 132.4, 131.3, 129.5, 129.4, 129.2, 128.1, 113.9, 113.7, 101.3, 95.9, 88.0, 84.1, 82.0, 81.5, 75.1, 74.9, 70.7, 56.4, 55.8, 55.3, 37.6, 36.0, 35.3, 34.2, 33.1, 31.7, 31.4, 30.4, 23.9, 23.3, 19.6, 19.2, 17.7, 14.2, 13.4, 9.9, 5.8; LRMS (ESI) 791.5 $(M + Na)^+$.

A solution of the alcohol in CH_2Cl_2 (8 mL) at 0 °C was treated with trichloroacetyl isocyanate (0.025 mL, 0.21 mmol) and stirred at room temperature. After 30 min, the solution was concentrated under reduced pressure, and the residue was taken up in MeOH (4 mL). Solid K_2CO_3 (50 mg) was added to this solution, and the mixture was stirred at room temperature for 3 h. The mixture was diluted with EtOAc (30 mL), and the organic layer was washed with brine. The aqueous layer was extracted with EtOAc, and the combined extracts were dried over anhydrous Na_2SO_4. Filtration and concentration followed by flash column chromatography (hexane/EtOAc 3:2) provided carbamate **44** (84.9 mg, 72%) as a yellow oil: IR ($CHCl_3$) 3103, 3020, 2866, 2399, 1730, 1248, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.33 (m, 4H), 6.91 (m, 4H), 5.54 (t, 1H, J = 10.5 Hz), 5.35 (m, 3H), 5.14 (br s, 1H), 4.93 (s, 1H), 4.81−4.29 (m, 7H), 3.86 (s, 3H), 3.84 (s, 3H), 3.72 (s, 2H), 3.60−3.34 (m, 8H), 3.32 (m, 1H), 3.13 (dd, 1H, J = 3.0, 7.5 Hz), 2.85 (m, 1H), 2.71 (q, 1H, J = 7.5 Hz), 2.35 (m 12H), 1.10−0.92 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.1, 159.0, 157.5, 133.7, 132.6, 131.4, 131.0, 129.4, 129.3, 129.2, 128.6, 113.7, 101.2, 95.9, 88.0, 82.0, 80.1, 79.7, 75.2, 74.8, 71.2, 60.4, 56.4, 55.8, 55.3, 37.6, 37.2, 35.8, 35.3, 34.2, 33.1, 30.8, 30.0, 23.6, 23.3, 19.6, 18.9, 17.5, 14.2, 13.4, 10.1, 9.9; LRMS (ESI) 834.7 $(M + Na)^+$.

(1*S*,2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-5,11-Bis(4-methoxybenzyloxy)-16-[(2*R*,3*S*,4*S*,5*R*,6*R*)-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-2,4,10,12-tetramethylhexadeca-8,13-dien-3-ol. This was prepared by the procedure described for compound **44**. IR ($CHCl_3$) 3019, 2897, 2286, 1778, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 4H), 6.99 (m, 4H), 5.64 (t, 1H, J = 10.8 Hz), 5.55−5.43 (m, 3H), 4.81 (dd, 1H, J = 6.9, 9.6 Hz), 4.73−4.62 (m, 3H), 4.48 (d, 1H, J = 10.8 Hz), 4.39 (d, 1H, J = 5.1 Hz), 4.19 (m, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.67 (m, 1H), 3.53 (s, 6H), 3.42 (m, 2H), 3.33 (t, 1H, J = 6.9 Hz), 3.20 (dd, 1H, J = 3.9, 7.5 Hz), 2.90 (m, 1H), 2.75 (dd, 1H, J = 7.8, 15.0 Hz), 2.27−1.67 (m, 6H), 1.22−1.10 (m, 15H), 1.05 (d, 3H, J = 7.2 Hz), 0.95 (d, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 159.1, 134.2, 132.7, 131.3, 130.2, 129.4, 129.2, 129.0, 128.2, 114.0, 113.8, 103.1, 96.6, 88.0, 84.1, 82.2, 81.4, 76.7, 75.0, 70.8, 69.8, 55.8, 55.7, 55.3, 39.5, 38.4, 36.2, 35.4, 31.4, 30.5, 30.4, 24.3, 23.9, 19.6, 19.2, 18.9, 17.5, 15.7, 13.2, 5.9; LRMS (ESI) 791.5 $(M + Na)^+$.

Carbamic Acid, (1*S*,2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-1-Isopropyl-3,9-bis(4-methoxybenzyloxy)-14-[(2*R*,3*S*,4*S*,5*R*,6*R*)-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-2,8,10-trimethyltetradeca-6,11-dienyl Ester (45a). This was prepared by the procedure described for compound **44**. IR ($CHCl_3$) 3103, 3020, 2866, 2399, 1730, 1248, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 4H), 6.95 (m, 4H), 5.57 (t, 1H, J = 10.5 Hz), 5.41 (m, 3H), 4.78−4.72 (m, 5H), 4.66−4.52 (m, 2H), 4.43 (d, 1H, J = 11.1 Hz), 4.33 (d, 1H, J = 5.1 Hz), 4.06 (m, 1H), 3.86 (s, 6H), 3.32 (d, 1H, J = 5.4 Hz), 3.27 (t, 1H, J = 6.6 Hz), 3.15 9dd, 1H, J = 3.9, 7.2 Hz), 2.84−2.71 (m, 2H), 2.25−1.57 (m, 11H), 1.38 (m, 1H), 1.04−0.93 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 159.0, 157.3, 133.8, 132.8, 131.4, 131.0, 129.3, 129.2, 128.8, 128.6, 113.7, 102.9, 96.5, 88.0, 82.1, 80.1, 79.8, 75.0, 71.2, 69.8, 55.7, 55.3, 52.3, 39.5, 38.2, 37.3, 35.8, 35.4, 30.8, 30.2, 30.0, 24.2, 23.6, 18.9, 17.6, 15.7, 13.2, 11.4; LRMS (ESI) 834.7 $(M + Na)^+$.

Carbamic Acid, (2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-3,9-Bis(4-methoxybenzyloxy)-14-[(2*R*,3*S*,4*S*,5*R*,6*R*)-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-2,8,-10-trimethyl-1-(1-methylpenta-2,4-dienyl)tetradeca-6,11-dienyl Ester (45b). DIBAL (1 M in hexane, 0.3 mL, 0.3 mmol) was added dropwise to a solution of **41** (72.4 mg, 0.1 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. After the mixture was stirred for 2 h, the reaction was quenched with saturated aqueous sodium tartrate (10 mL) followed by vigorous stirring for several hours. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with brine (10 mL). After the organic fraction was dried over $MgSO_4$ and evaporated under vacuum, the residue was purified by column chromatography (hexane/EtOAc 7:3) to give the alcohol. IR ($CHCl_3$) 3019, 2897, 2286, 1778, 1515, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (m, 2H), 6.99 (m, 4H), 5.64 (t, 1H, J = 10.8 Hz), 5.54−5.37 (m, 3H), 4.81 (dd, 2H, J = 6.9, 9.6 Hz), 4.72−4.57 (m, 4H), 4.39 (d, 1H, J = 5.1 Hz), 4.12 (m, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.81 (m, 1H), 3.63 (m, 2H), 3.52 (s, 6H), 3.33 (t, 1H, J = 6.3 Hz), 3.19 (dd, 1H, J = 3.9, 7.5 Hz), 2.91 (m, 1H), 2.75 (m, 1H), 2.31−1.38 (m, 11H), 1.21−0.99 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 159.1, 134.0, 132.8, 131.3, 130.5, 129.6, 129.2, 128.9, 128.4, 113.9, 113.7, 103.9, 96.6, 88.0, 82.2, 81.6, 75.0, 71.5, 69.8, 66.1, 55.8, 55.7, 55.3, 39.5, 38.3, 37.0, 35.9, 35.4, 30.3, 29.8, 24.5, 24.3, 19.0, 17.5, 15.7, 13.2, 11.8; LRMS (ESI) 749.5; HRMS (ESI) calcd for $C_{43}H_{66}O_9Na$ 749.4605, found 749.4601 $(M + Na)^+$.

A solution of the alcohol in CH_2Cl_2 (8 mL) at 0 °C was treated with trichloroacetyl isocyanate (0.05 mL, 0.42 mmol) and stirred at room temperature. After 30 min, the solution was concentrated under reduced pressure, and the residue was taken up in MeOH (4 mL). Solid K_2CO_3 (50 mg) was added to this solution, and the mixture was stirred at room temperature for 3 h. The mixture was diluted with EtOAc (30 mL), and the organic layer was washed with brine. The aqueous layer was extracted with EtOAc, and the combined extracts were

dried over anhydrous Na_2SO_4. Filtration and concentration followed by flash column chromatography (hexane/EtOAc 3:2) provided carbamate **45b** (63.0 mg, 82%) as a yellow oil: IR ($CHCl_3$) 3103, 3020, 2866, 2399, 1730, 1514 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (m, 4H), 7.00 (m, 4H), 5.64 (t, 1H, J = 10.8 Hz), 5.55−5.40 (m, 3H), 4.91 (br s, 2H), 4.79 (dd, 2H, J = 7.2, 13.2 Hz), 4.69 (d, 1H, J = 10.5 Hz), 4.57 (d, 1H, J = 10 5 Hz), 4.51 (d, 1H, J = 5.1 Hz), 4.24−4.06 (m, 3 H), 3.93 (s, 3H), 3.91 (s, 3H), 3.52 (s, 6H), 3.33 (t, 1H, J = 6.6 Hz), 3.20 (dd, 1H, J = 3.6, 7.5 Hz), 2.88 (m, 1H), 2.76 (m, 1H), 2.30−1.64 (m, 11H), 1.21−1.05 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.19, 159.12, 157.1, 133.9, 132.7, 131.3, 130.9, 129.3, 129.2, 128.9, 128.4, 113.8, 113.7, 103.0, 96.5, 88.0, 82.1, 78.8, 75.0, 71.7, 69.4, 67.4, 55.8, 55.7, 55.3, 39.4, 38.3, 35.9, 35.8, 35.4, 31.2, 30.3, 29.8, 24.2, 18.9, 17.6, 15.7, 13.2, 11.4; LRMS (ESI) 792.5 $(M + Na)^+$.

Carbamic Acid, (1*S*,2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-3,9-Dihydroxy-14-[(2*S*,3*R*,4*S*,5*R*)-4-methoxymethoxy-3,5-dimethyl-6-oxotetrahydropyran-2-yl]-2,8,10-trimethyl-1-(1-methylpenta-2,4-dienyl)tetradeca-6,11-dienyl Ester (46). A solution of **44** (40.5 mg, 0.05 mmol) in THF (0.5 mL) and 60% aqueous acetic acid (2.5 mL) was stirred at 70 °C for 4 h. After the reaction was complete by TLC, the reaction mixture was neutralized slowly with saturated aqueous K_2CO_3 and diluted with EtOAc (20 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude lactol was used without further purification.

Dess−Martin periodinane reagent (31.8 mg, 0.075 mmol) was added to a solution of the lactol in CH_2Cl_2 (5 mL). The resulting solution was stirred for 1 h and quenched by the simultaneous addition of saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by flash column chromatography (hexane/EtOAc 4:1) provided 27.0 mg (68%) of the lactone PMB ether as a color oil: IR ($CHCl_3$) 2992, 2361, 2332, 1742, 1374, 1242, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 4H), 6.94 (m, 4H), 5.60 (t, 1H, J = 7.8 Hz), 5.37 (m, 3H), 5.44−5.32 (m, 10H), 3.87 (s, 3H), 3.85 (s, 3H), 3.64 (t, 1H, J = 3.0 Hz), 3.45 (s, 3H), 3.49 (dd, 1H, J = 5.4, 11.1 Hz), 3.15 (dd, 1H, J = 3.9, 7.4 Hz), 2.88 (m, 2H), 2.72 (m, 1H), 2.25 (m, 4H), 2.00 (m, 4H), 1.68 (m, 6H), 1.34 (m, 6H), 1.10−0.95 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 159.1, 159.0, 157.3, 133.7, 133.5, 131.4, 131.0, 129.3, 129.2, 128.6, 128.1, 113.79, 113.71, 96.0, 88.0, 80.4, 80.2, 79.7, 79.2, 74.9, 71.3, 55.9, 55.3, 40.7, 37.3, 35.9, 35.3, 33.5, 33.1, 30.8, 30.0, 29.8, 23.6, 22.7, 19.6, 18.9, 17.5, 17.4, 16.4, 13.4, 10.9; LRMS (ESI) 818.7 $(M + Na)^+$.

A solution of the PMB ether (16 mg, 0.02 mmol) from above in CH_2Cl_2 (2 mL) at 0 °C was treated with $NaHCO_3$ (4.2 mg, 0.5 mmol) and DDQ (0.2 M in CH_2Cl_2, 0.75 mL, 0.15 mmol). After 1 h, the mixture was diluted with CH_2Cl_2 and washed with water. The aqueous layer was extracted with CH_2Cl_2, and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by flash column chromatography (EtOAc/hexane 3:2) provided carbamate **46** (8.6 mg, 78%) as a colorless oil: IR ($CHCl_3$) 3402, 2363, 1751, 1373, 1240, 1052 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 5.53−5.44 (m, 4H), 4.80 (d, 1H, J = 7.2 Hz), 4.74 (br s, 2H), 4.69 (d, 1H, J = 7.2 Hz), 4.40 (dt, 1H, J = 2.4, 9.0 Hz), 3.68 (m, 2H), 3.47 (s, 3H), 3.32 (t, 1H, J = 5.7 Hz), 2.91 (ddd, 1H, J = 3.6, 7.5, 18.3 Hz), 2.74 (m, 2H), 2.37−1.57 (m, 11H), 1.38 (d, 3H, J = 7.5 Hz), 1.27−0.92 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) 173.9, 157.7, 133.5, 132.7, 130.0, 95.9, 81.5, 80.4, 79.2, 79.1, 73.3, 55.9, 40.7, 39.7, 35.4, 34.7, 34.6, 33.6, 33.2, 30.7, 24.2, 22.8, 19.3, 18.1, 18.0, 16.4, 15.5, 13.4, 7.9; LRMS (ESI) 578.6 $(M + Na)^+$; HRMS (ESI) calcd for $C_{30}H_{53}NO_8Na$ 578.3669, found 578.3680 $(M + Na)^+$; $[\alpha]^{20}_D$ +32.0 (*c* 0.25, $CHCl_3$).

Carbamic Acid, (1*S*,2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-3,9-Dihydroxy-14-[(2*S*,3*R*,4*S*,5*R*)-4-hydroxy-3,5-dimethyl-6-oxotetrahydropyran-2-yl]-1-isopropyl-2,8,10-trimethyltetradeca-6,11-dienyl Ester (47). Compound **44** (8.49 mg, 0.01 mmol) was subjected to the lactonization procedure described above. Aqueous 4 N HCl (2.5 mL) was added to a solution of the lactone (40.0 mg, 0.05 mmol) in THF (5 mL). The flask was fitted with a glass stopper, and the resulting solution was stirred at room temperature for 72 h. Saturated aqueous K_2CO_3 was added dropwise followed by EtOAc. The organic layer was extracted with EtOAc, and the combined extracts were dried over $MgSO_4$. Filtration and concentration followed by flash column chromatography (EtOAc/hexane 3:2) provided the crude MOM-deprotected compound. The PMB was removed by treatment with $NaHCO_3$ and DDQ. Flash chromatography (EtOAc/hexane 3:2) of the crude product provided **47** (2.9 mg, 49%, three steps) as a colorless oil: IR ($CHCl_3$) 3114, 2745, 2323, 1706, 1487, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.58−5.43 (m, 4H), 4.85 (br s, 2H), 4.67 (dd, 1H, J = 3.6, 7.3 Hz), 4.41 (dt, 3.1, J = 3.1, 9.0 Hz), 3.81 (br t, 1H), 3.69 (dd, 1H, J = 2.1, 6.0 Hz), 3.32 (t, 1H, J = 5.7 Hz), 3.68 (m, 2H), 2.74 (m, 3H), 2.36−1.72 (m, 10H), 1.61 (t, 1H, J = 7.5 Hz), 1.40 (d, 3H, J = 7.2 Hz), 1.14 (d, 3H, J = 7.2 Hz), 1.08−0.94 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 157.8, 133.5, 132.6, 130.0, 128.9, 81.6, 79.5, 79.3, 73.4, 43.3, 39.8, 35.5, 35.3, 35.1, 34.7, 33.1, 30.8, 29.8, 24.3, 23.0, 19.3, 18.3, 18.1, 15.9, 15.8, 12.7, 7.9; LRMS (ESI) 534.8 $(M + Na)^+$; HRMS (ESI) calcd for $C_{28}H_{49}NO_7Na$ 534.3407, found 534.3383 $(M + Na)^+$; $[\alpha]^{20}_D$ +6.9 (*c* 0.35, $CHCl_3$).

Carbamic Acid, (1*S*,2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-3,9-Dihydroxy-14-[(2*S*,3*R*,4*R*,5*R*)-4-methoxymethoxy-3,5-dimethyl-6-oxotetrahydropyran-2-yl]-2,8,10-trimethyl-1-(1-methylpenta-2,4-dienyl)tetradeca-6,11-dienyl Ester (48a). Prepared by the procedure described for compound **47**. IR ($CHCl_3$) 3020, 2400, 1730, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 5.46 (m, 4H), 4.81 (d, 1H, J = 7.2 Hz), 4.74 (br s, 2H), 4.70 (d, 1H, J = 7.2 Hz), 4.58 (d, 1H, J = 7.5 Hz), 3.87 (m, 2H), 3.71 (m, 1H), 3.49 (s, 3H), 3.36 (d, 1H, J = 7.2 Hz), 3.25 (t, 1H, J = 5.7 Hz), 2.71 (m, 2H), 2.71 (m, 2H), 2.37−1.57 (m, 11H), 1.40 (d, 3H, J = 7.5 Hz), 1.07−0.84 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.3, 157.6, 133.3, 132.8, 129.6, 113.7 95.4, 82.6, 81.5, 79.1, 73.3, 55.8, 40.4, 39.7, 35.3, 34.8, 34.6, 33.6, 31.9, 29.6, 24.2, 22.6, 19.2, 18.1, 17.9, 15.6, 14.3, 11.9, 7.9; LRMS (ESI) 578.3 $(M + Na)^+$; HRMS (ESI) calcd for $C_{30}H_{54}NO_8$ 556.3849, found 556.3800 $(M + H)^+$; $[\alpha]^{20}_D$ +8.6 (*c* 0.15, $CHCl_3$).

Carbamic Acid, (2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-3,9-Dihydroxy-14-[(2*S*,3*R*,4*R*,5*R*)-4-methoxymethoxy-3,5-dimethyl-6-oxotetrahydropyran-2-yl]-2,8,10-trimethyltetradeca-6,11-dienyl Ester (48b). A solution of 26b (38.4 mg, 0.05 mmol) in THF (0.5 mL) and 60% aqueous acetic acid (2.5 mL) was stirred at 70 °C for 4 h. After the reaction was complete by TLC, it was neutralized slowly with saturated aqueous K_2CO_3 and diluted with EtOAc (20 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude lactol was used without further purification.

Dess−Martin periodinane reagent (31.8 mg, 0.075 mmol) was added to a solution of the lactol in CH_2Cl_2 (5 mL). The resulting solution was stirred for 1 h and quenched by the simultaneous addition of saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by flash column chromatography (hexane/EtOAc 4:1) provided 18.8 mg (50%) of the lactone PMB ether as a colorless oil: IR ($CHCl_3$) 3024, 2954, 2873, 1730, 1374, 1241 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 4H), 6.99 (m, 4H), 5.68 (t, 1H, J = 9.9 Hz), 5.45−5.35 (m, 3H), 4.87−4.51 (m, 7H), 4.13 (m, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 3.53 (s, 6H), 3.40 (d, 1H, J = 7.2 Hz), 3.20 (dd, 1H, J = 3.6, 7.8 Hz), 2.76 (m, 1H), 2.71 (m, 2H), 2.31−1.68 (m, 14H), 1.45 (d, 3H, J = 6.6 Hz), 1.17−1.02 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 159.2, 157.1, 133.6, 131.2, 131.0, 129.4, 129.3, 128.6, 127.9, 113.8, 95.5, 88.0, 82.7, 78.8, 75.1, 71.7, 67.4, 55.9, 55.4, 40.6, 38.7, 36.1, 35.8, 35.4, 31.8, 31.2, 29.8, 24.2, 23.7, 19.1, 17.7, 14.5, 12.1, 11.5; LRMS (ESI) 776.4 $(M + Na)^+$.

A solution of the PMB ether (15.0 mg, 0.02 mmol) from above in CH_2Cl_2 (2 mL) at 0 °C was treated with $NaHCO_3$ (4.2 mg, 0.5 mmol) and DDQ (0.2 M in CH_2Cl_2, 0.5 mL, 0.10 mmol). After 1 h, the mixture was diluted with CH_2Cl_2 and washed

with water. The aqueous layer was extracted with CH_2Cl_2, and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by flash column chromatography (hexane/EtOAc 2:3) provided carbamate **48b** (3.8 mg, 38%) as a colorless oil: IR ($CHCl_3$) 3020, 2400, 1730, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.46−5.35 (m, 4H), 4.79 (br s, 2H), 4.75 (d, 1H, J = 7.2 Hz), 4.62 (d, 1H, J = 7.2 Hz), 4.48 (br d, 1H, J = 8.1 Hz), 4.20 (dd, 1H, J = 9.3, 10.7 Hz), 3.86 (dd, 1H, J = 5.4, 11.1 Hz), 3.64 (br s, 1H), 3.40 (s, 3H), 3.27 (m, 2H), 2.62 (m, 3H), 2.46 (br s, 1H), 2.26−2.01 (m, 5H), 1.89−1.57 (m, 5H), 1.33 (d, 3H, J = 6.6 Hz), 1.04−0.86 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 157.6, 133.6, 132.9, 129.7, 128.9, 95.5, 82.7, 79.3, 69.8, 67.3, 55.9, 40.6, 38.7, 38.3, 35.5, 35.0, 34.1, 31.7, 24.4, 23.9, 18.3, 15.9, 14.5, 12.1, 9.8; LRMS (ESI) 536.3 $(M + Na)^+$; HRMS (ESI) calcd for $C_{27}H_{47}NO_8Na$ 536.3199, found 536.3197 $(M + Na)^+$; $[\alpha]^{20}_D$ +27.4 (*c* 0.58, $CHCl_3$).

(2*S*,3*R*)-6-(*tert*-Butyldimethylsilanyloxy)-3-(4-methoxybenzyloxy)-2-methylhexanal (49). DIBAL (1 M in THF, 15 mL, 15 mmol) was added dropwise to a stirred solution of **39** (1.90 g, 5 mmol) in anhydrous CH_2Cl_2 (50 mL) under an atmosphere of N_2 at 0 °C, and the mixture was stirred for 1 h at 0 °C. The reaction was quenched by the careful addition of saturated aqueous potassium sodium tartrate (100 mL) and stirring for 3 h at room temperature. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over $MgSO_4$ followed by the evaporation of the solvent under reduced pressure. The crude alcohol (1.56 g, 4.1 mmol) was used without further purification.

Pyridinium sulfur trioxide (2.38 g, 15 mmol) was added to a stirred solution of the crude alcohol from above and diisopropylethylamine (2.6 mL, 15 mmol) in anhydrous CH_2Cl_2 (10 mL) and DMSO (20 mL) at 0 °C. The mixture was stirred at ambient temperature for 1 h. After the reaction was complete, the mixture was diluted with diethyl ether (100 mL) and washed with 0.5 N HCl (100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$. Filtration and concentration followed by short flash column chromatography filtration (hexane/EtOAc 4:1) to remove SO_3−pyridine provided the crude aldehyde **49** as a colorless oil, which was used without further purification.

(2*R*,3*R*,4*R*,5*R*)-8-(*tert*-Butyldimethylsilanyloxy)-3-hydroxy-5-(4-methoxybenzyloxy)-2,4-dimethyloctanoic acid, 2,6-dimethylphenyl Ester (51). LDA (2 M in THF, 3.1 mL, 6.2 mmol) was added to a solution of 2,6-dimethylphenyl propionate (1.10 g, 6.2 mmol) in anhydrous THF (12.4 mL) at −78 °C, followed by stirring for 1 h at −78 °C. The crude aldehyde (4.1 mmol) from above was dissolved in anhydrous THF (10 mL) and added slowly at −78 °C. After 2 h at room temperature, the mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$, evaporated, and chromatographed (hexane/EtOAc 4:1) to yield **51** (1.67 g, 2.99 mmol) as a colorless oil: IR ($CHCl_3$) 3120, 2857, 1744, 1514, 1216, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, 2H, J = 8.4 Hz), 6.87 (d, 2H, J = 8.4 Hz), 4.62 (d, 1H, J = 11.1 Hz), 4.40 (d, 1H, J = 11.1 Hz), 4.06 (d, 1H, J = 6.8 Hz), 3.79 (s, 3H), 3.66−3.61 (m, 3H), 2.89 (m, 1H), 2.19 (s, 6H), 1.86 (m, 2H), 1.55 (m, 3H), 1.27 (d, 3H, J = 6.8 Hz), 1.01 (d, 3H, J = 6.9 Hz), 0.93 (s, 9 H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 159.2, 148.0, 130.0, 129.9, 129.4, 128.4, 125.6, 113.8, 83.5, 70.7, 62.9, 55.1, 44.0, 35.6, 28.7, 26.6, 25.8, 18.2, 16.3, 14.2, 5.7, −5.3; HRMS (EI) calcd for $C_{32}H_{50}O_6Si$ 558.3377, found 558.3392.

(2*S*,3*S*,4*R*,5*R*)-3,8-Bis(*tert*-butyldimethylsilanyloxy)-5-(4-methoxybenzyloxy)-2,4-dimethyloctan-1-ol. TBSOTf (0.68 mL, 3 mmol) was added to a stirred solution of **51** (1.11 g, 2 mmol) and 2,6-lutidine (0.69 mL, 6 mmol) in CH_2Cl_2 (20 mL) at −78 °C. The mixture was stirred for 2 h at ambient temperature. The reaction was quenched by the addition of 0.5 N HCl (50 mL). The reaction mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Short column chromatography (hexane/EtOAc 4:1) provided the crude product.

DIBAL (1 M in THF, 6 mL, 6 mmol) was added dropwise to a stirred solution of the TBS-protected aryl ester (1.90 g, 2 mmol) from above in anhydrous CH_2Cl_2 (20 mL) under an atmosphere of N_2 at 0 °C, and the mixture was stirred for additional 1 h at 0 °C. The reaction was quenched by the careful addition of saturated aqueous potassium sodium tartrate (50 mL). The mixture was stirred for 3 h at room temperature. Once the aqueous and organic layers had separated, the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layer was washed with brine and dried over $MgSO_4$ followed by the evaporation of the solvent under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane 7:3) to give the title compound in pure form (997 mg, 1.8 mmol): IR ($CHCl_3$) 3125, 1544, 1289, 1065 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, 2H, J = 8.7 Hz), 6.89 (d, 2H, J = 8.7 Hz), 4.51 (d, 1H, J = 11.1), 4. 41 (d, 1H, J = 10.8 Hz), 3.83 (d, 3H), 3.79 (m, 1H), 3.64 (m, 4H), 3.36 (m, 1H), 2.45 (br s, 1H), 1.93 (m, 2H), 1.63 (m, 4H), 1.00 (d, 2H, J = 7.0 Hz), 0.92 (s, 24H), 0.14 (s, 6H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 130.6, 129.4, 113.6, 80.3, 76.0, 71.2, 65.2, 63.0, 55.1, 39.1, 39.0, 29.0, 27.1, 26.1, 25.9, 18.2, 14.5, 11.6, −3.6, −3.9, −5.3; LRMS (ESI) 576.8 $(M + Na)^+$.

(2*R*,3*S*,4*R*,5*R*)-3,8-Bis(*tert*-butyldimethylsilanyloxy)-5-(4-methoxybenzyloxy)-2,4-dimethyloctanal (52). Pyridinium sulfur trioxide (858 mg, 5.4 mmol) was added to a stirred solution of the alcohol (997 mg, 1.8 mmol) from above, diisopropylethylamine (0.94 mL, 5.4 mmol) in anhydrous CH_2Cl_2 (3.6 mL), and DMSO (7.2 mL) at 0 °C. The mixture was stirred at ambient temperature for 1 h. After the reaction was complete, the mixture was diluted with ethyl ether (50 mL) and washed with aqueous HCl (0.5N, 50 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$. Filtration and concentration followed by short flash column chromatography filtration (hexane/EtOAc 4:1) to remove SO_3−pyridine provided the crude aldehyde **52** as a colorless oil which was used without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.22 (d, 2H, J = 8.6 Hz), 6.85 (d, 2H, J = 8.6 Hz), 4.45 (d, 1H, J = 11.1 Hz), 4.28 (d, 1H, J = 11.1 Hz), 3.94 (dd, 1H, J = 5.5, 4.0 Hz), 3.79 (s, 3H), 3.60 (t, 2H, J = 6.0 Hz), 3.40−3.34 (m, 1H), 2.66−2.58 (m, 1H), 1.92−1.84 (m, 1H), 1.67−1.59 (m, 2H), 1.55−1.45 (m, 2H), 1.02 (d, 3H, J = 7.0 Hz), 0.98 (d, 3H, J = 7.0 Hz), 0.89 (s, 9H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 9H).

(1*R*,2*R*,3*S*,4*S*,5*Z*)-1-{3-(*tert*-Butyldimethylsilanyloxy)-1-[3-(*tert*-butyldimethylsilanyloxy)propyl]-2,4-dimethylocta-5,7-dienyloxymethyl}-4-methoxybenzene (54). $CrCl_2$ (1.09 g, 9.0 mmol) was added to a stirred solution of the crude aldehyde (1.8 mmol) from above and 1-bromoallyltrimethylsilane **53** (578 mg, 5.4 mmol) in anhydrous THF (18 mL) under an atmosphere of N_2 at room temperature. The mixture was stirred for 14 h at ambient temperature, then diluted with ethyl ether followed by filtration through Celite. After the evaporation of the solvent under reduced pressure, the residue was purified by short column silica gel column chromatography (CH_2Cl_2).

The above product in THF (50 mL) was cooled to 0 °C, and NaH (95% w/w in mineral oil, 207 mg, 9.0 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. The reaction mixture was cooled to 0 °C, quenched with H_2O (10 mL), and extracted with diethyl ether (2 × 50 mL). The combined organic layer was washed with brine and dried over $MgSO_4$ followed by the evaporation of the solvent under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc 4:1) to give pure **54** (622 mg, 1.2 mmol): IR ($CHCl_3$) 2954, 2931, 2857, 1608, 1513, 1463, 1251, 1098, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, 2H, J = 8.6 Hz), 6.96 (d, 2H, J = 8.6 Hz), 6.41 (ddd, 1H, J = 16.7, 11.0, 10.1 Hz), 6.04 (dd, 1H, J = 11.1, 11.0 Hz), 5.57 (dd, 1H, J = 10.1, 16,8 Hz), 5.20 (d, 1H, J = 16.7 Hz), 5.06 (d, 1H, J = 10.1 Hz), 4.51 (d, 1H, J = 11.3 Hz), 4.35 (d, 1H, J = 11.3 Hz), 3.81 (s, 3H), 3.63−3.57 (m, 3H), 3.28 (dt, 1H, J = 5.5, 5.5 Hz), 2.70 (ddq, 1H, J = 10.3, 6.9, 3.2 Hz), 1.73−1.58 (m, 3H), 1.50−1.44 (m, 2H), 0.94 (d, 3H, J = 6.9 Hz), 0.93−0.91 (m, 21H), 0.06 (s, 6H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.1,

134.8, 132.5, 131.0, 129.5, 128.9, 117.1, 113.7, 78.9, 76.6, 70.7, 63.2, 55.2, 40.0, 36.4, 31.6, 28.7, 26.2, 26.0, 18.9, 18.5, 18.3, 10.9, −3.3, −3.4, −5.3; LRMS (EI) 576, 519, 467, 387, 357, 293, 225, 121; HRMS (EI) calcd for $C_{29}H_{51}O_4Si_2$ 519.3326, found 519.3332; $[\alpha]^{20}_D$ −18.8° (*c* 0.75, $CHCl_3$).

(2*R*)-2-{(4*R*,5*S*,6*R*)-6-[3-(*tert*-Butyldimethylsilanyloxy)-propyl]-2,2,5-trimethyl[1,3]dioxan-4-yl}propanoic Acid, 2,6-Dimethylphenyl Ester (55). A mixture of PMB ether **51** (55.8 mg, 0.1 mmol) and palladium (10% Pd/C, 5 mg) in EtOAc (10 mL) was stirred at room temperature under an H_2 atmosphere (balloon) for 3 h. The mixture was filtered and concentrated to yield the diol, which was used without further purification. A solution of the crude diol, 2,2-dimethoxypropane (12.4 mg, 0.12 mmol) and PPTS (0.1 equiv) in benzene was stirred for 5 h at 65 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL) followed by washing with water. The aqueous layer was extracted with ethyl ether (2 × 50 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (hexane/EtOAc 9:1) to provide the pure **55** in 52% yield: IR ($CHCl_3$) 2855, 1742, 1510, 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.03 (br s, 3H), 4.20 (dd, 1H, J = 1.7, 10.2 Hz), 3.91 (m, 1H), 3.64 (m, 2H), 2.91 (dq, 1H, J = 10.2, 6.9 Hz), 2.16 (s, 6H), 1.59−1.32 (m, 6H), 1.41 (s, 3H), 1.39 (s, 3H), 1.24 (d, 3H, J = 4.2 Hz), 0.92 (br s, 12H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 173.7, 148.2, 130.3, 128.5, 125.8, 99.1, 75.2, 73.0, 63.1, 42.3, 31.8, 29.9, 29.3, 28.8, 26.0, 19.5, 18.4, 16.4, 12.9, 4.54, −5.19; HRMS (EI) calcd for $C_{27}H_{46}O_5Si$ 478.3115, found 463.2889 (M − CH_3)$^+$.

(1*S*,2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-[3,9-Bis(4-methoxybenzyloxy)-14-[(2*S*,3*S*,4*S*,5*R*,6*R*)-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-2,8,10-trimethyl-1-[(1*S*,2*Z*)-1-methylpenta-2,4-dienyl)tetradeca-6,11-dienyloxy]-*tert*-butyldimethylsilane. NaHMDS (1 M in THF, 0.54 mL, 0.54 mmol) was added slowly to a solution of the salt **9** (475.9 mg, 0.54 mmol) in dry THF (1.08 mL) at 0 °C. The mixture was cooled to −78 °C, and a solution of the aldehyde **36** (267 mg, 0.54 mmol) in THF (1.08 mL) was added dropwise. The mixture was stirred for 20 min at −78 °C and then warmed to room temperature. After 4 h at room temperature, the mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$, evaporated, and chromatographed (hexane/EtOAc 9:1) to yield the desired compound (257 mg, 0.28 mmol) as a colorless oil: IR ($CHCl_3$) 2920, 2861, 2620, 1740, 1520 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) 7.38 (m, 4H), 6.96 (m, 4H), 6.47 (ddd, 1H, J = 16.8, 11.0, 10.1 Hz), 6.04 (t, 1H, J = 11.1 Hz), 5.57 (t, 1H, J = 10.5 Hz), 5.49−5.12 (m, 6H), 4.75 (d, 2H, J = 2.1 Hz), 4.67−4.33 (m, 5H), 4.07 (m, 1H), 3.65 (dd, 1H, J = 3.3, 6.0 Hz), 3.47 (br s, 7H), 3.35 (dd, 1H, J = 4.5, 4.7 Hz), 3.27 (t, 1H, J = 6.6 Hz), 3.15 (dd, 1H, J = 4.5, 6.9 Hz), 2.77 (m, 3H), 2.18 (m, 2H), 1.91 (m, 2H), 1.74−1.62 (m, 4H), 1.11−0.99 (m, 18H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.2, 159.0, 134.7, 133.7, 132.9, 132.5, 131.4, 131.0, 129.6, 129.1, 128.9, 128.6, 117.3, 113.8, 113.7, 103.0, 96.5, 88.0, 82.1, 78.8, 74.9, 70.8, 69.7, 55.8, 55.3, 40.0, 39.5, 38.3, 35.6, 35.4, 31.3, 30.3, 26.4, 24.2, 23.7, 19.0, 18.8, 18.6, 17.3, 15.7, 13.2, 11.0, −3.1, −3.2; LRMS (ESI) 942.5 (M + Na)$^+$.

Carbamic Acid, (1*S*,2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-3,9-Bis(4-methoxybenzyloxy)-14-[(2*S*,3*S*,4*S*,5*R*,6*R*)-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-2,8,10-trimethyl-1-[(1*S*,2*Z*)-1-methylpenta-2,4-dienyl]tetradeca-6,11-dienyl Ester (56). The above compound (128.5 mg, 0.14 mmol) in THF (4 mL) was treated with TBAF (1 M in THF, 0.40 mL, 0.40 mmol), and the mixture was stirred at room temperature for 48 h. The mixture was diluted with ethyl ether (30 mL) and washed with water (10 mL). After drying over $MgSO_4$ and evaporation under vacuum, the resulting alcohol was used without further purification.

A solution of the alcohol in CH_2Cl_2 (8 mL) at 0 °C was treated with trichloroacetyl isocyanate (0.05 mL, 0.42 mmol) and stirred at room temperature. After 30 min, the solution was concentrated under reduced pressure, and the residue was taken up in MeOH (4 mL). Solid K_2CO_3 (50 mg) was added to this solution and the mixture was stirred at room temperature for 3 h at room temperature. The mixture was diluted with EtOAc (30 mL). The organic layer was washed with brine. The aqueous layer was extracted with EtOAc, and the combined extracts were dried over anhydrous Na_2SO_4. Filtration and concentration followed by flash column chromatography (hexane/EtOAc 3:2) provided carbamate **56** (84.9 mg, 72%) as a yellow oil: IR ($CHCl_3$) 3100, 3019, 2430, 2286, 1720, 1524 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.41 (m, 4H), 7.01 (m, 4H), 6.46 (ddd, 1H, J = 16.8, 11.0, 10.1 Hz), 6.11 (t, 1H, J = 10.8 Hz), 5.62 (t, 1H, J = 10.5 Hz), 5.53−5.18 (m, 6H), 4.94 (t, 1H, J = 6.0 Hz), 4.84 (br s, 2H), 4.81 (d, 2H, J = 2.1 Hz), 4.71−4.45 (m, 4H), 4.39 (d, 1H, J = 5.1 Hz), 4.12 (m, 1H), 3.37 (m, 2H), 3.19 (dd, 1H, J = 4.5, 6.9 Hz), 2.90 (m, 3H), 2.27 (m, 2H), 1.91 (m, 2H), 1.74−1.61 (m, 4H), 1.11−0.99 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.2, 159.0, 157.1, 133.7, 133.3, 132.8, 132.2, 131.4, 130.9, 129.8, 129.6, 129.1, 128.5, 117.8, 113.8, 113.7, 102.9, 96.5, 88.0, 82.1, 78.4, 78.1, 74.9, 70.5, 69.8, 55.8, 55.7, 55.3, 39.5, 38.2, 37.7, 35.8, 35.4, 34.3, 30.6, 30.3, 24.2, 23.6, 18.9, 17.8, 17.4, 15.7, 13.2, 9.8; LRMS (ESI) 888.4 (M + K)$^+$.

Carbamic Acid, (1*S*,2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-3,9-Bis(4-methoxybenzyloxy)-14-[(2*S*,3*S*,4*S*,5*R*)-4-methoxymethoxy-3,5-dimethyl-6-oxotetrahydropyran-2-yl]-2,8,10-trimethyl-1-[(1*S*,2*Z*)-1-methylpenta-2,4-dienyl]tetradeca-6,11-dienyl Ester. A solution of **56** (42.4 mg, 0.05 mmol) in THF (0.5 mL) and 60% aqueous acetic acid (2.5 mL) was stirred at 70 °C for 4 h. After the reaction was complete by TLC, the mixture was neutralized slowly with saturated aqueous K_2CO_3 and diluted with EtOAc (20 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude lactol was used for the next reaction without further purification.

Dess−Martin periodinane reagent (31.8 mg, 0.075 mmol) was added to a solution of the lactol in CH_2Cl_2 (5 mL). The resultant solution was stirred for 1 h and quenched by the simultaneous addition of saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by flash column chromatography (hexane/EtOAc 8:2) provided 28.3 mg (68%) of the lactone as a colorless oil: IR ($CHCl_3$) 2992, 2361, 2332, 1742, 1374, 1242, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.40 (m, 4H), 7.03 (m, 4H), 6.51 (ddd, 1H, J = 16.8, 11.1, 10.0 Hz), 6.11 (t, 1H, J = 11.1 Hz), 5.67 (t, 1H, J = 10.8 Hz), 5.52−5.18 (m, 7H), 4.94 (t, 1H, J = 6.0 Hz), 4.87−4.47 (m, 9H), 3.94 (br s, 4H), 3.93 (s, 3H), 3.54 (s, 3H), 3.40 (m, 2H), 3.19 (dd, 1H, J = 4.5, 6.9 Hz), 2.87 (m, 2H), 2.72 (m, 2H), 2.32−1.89 (m, 7H), 1.45 (d, 3H, J = 6.6 Hz), 1.15−01.02 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) 174.2, 159.2, 159.0, 156.9, 133.6, 133.5, 133.4, 132.2, 131.3, 130.9, 129.8, 129.6, 129.5, 129.2, 128.7, 127.8, 113.8, 113.7, 95.4, 88.0, 82.7, 79.9, 78.4, 76.5, 75.0, 55.9, 55.7, 55.3, 40.5, 38.6, 37.7, 36.0, 35.4, 34.3, 31.3, 30.6, 23.9, 23.6, 23.5, 19.0, 17.8, 14.4, 12.1, 9.8; LRMS (ESI) 872.4 (M + K)$^+$.

Carbamic Acid, (1*S*,2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-3,9-Dihydroxy-14-[(2*S*,3*S*,4*S*,5*R*)-4-hydroxy-3,5-dimethyl-6-oxotetrahydropyran-2-yl]-2,8,10-trimethyl-1-[(1*S*,2*Z*)-1-methylpenta-2,4-dienyl]tetradeca-6,11-dienyl Ester (6a). A solution of the above lactone (2.83 mg, 0.005 mmol) in THF (2 mL) was treated with 4 N HCl (1 mL). The flask was fitted with a glass stopper, and the resulting solution was stirred at room temperature for 48 h. Saturated aqueous K_2CO_3 was added dropwise followed by EtOAc. The aqueous layer was extracted with EtOAc, and the combined extracts were dried over $MgSO_4$. Filtration and concentration followed by simple short flash column chromatography (EtOAc/hexane/diethyl ether 3:2:1) provided the crude MOM-deprotected compound. A solution of PMB ether in CH_2Cl_2 (2 mL) at 0 °C was treated with $NaHCO_3$ (4.2 mg, 0.5 mmol). After 1 h, the mixture was diluted with CH_2Cl_2 and washed with water. The aqueous layer was extracted with CH_2Cl_2, and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by flash column chromatography (EtOAc/hexane 3:2) provided carbamate **6a** (1.1 mg, 0.002 mmol) as a colorless

oil: IR ($CHCl_3$) 2995, 2937, 2323, 1755, 1449, 1374, 1242, 1049 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 6.63 (ddd, 1H, J = 16.8, 11.0, 10.1 Hz), 6.06 (t, 1H, J = 11.0 Hz), 5.46−5.32 (m, 5H), 5.25 (d, 1H, J = 17 Hz), 5.14 (d, 1H, J = 10.0 Hz), 4.94 (t, 1H, J = 6.0 Hz), 4.74 (m, 1H), 4.60 (br s, 1H), 4.54 (m, 1H), 3.65 (m, 1H), 3.38 (d, 1H, J = 5.0 Hz), 3.27 (t, 1H, J = 6.0 Hz), 3.00 (m, 1H), 2.78 (m, 1H), 2.63 (m, 2H), 2.18 (m, 1H), 2.01 (m, 1H), 1.83 (m, 1H), 1.77 (m, 1H), 1. 35 (d, 3H, J = 7.0), 1.01−0.93 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) 174.2, 157.3, 133.6, 132.9, 129.6, 128.9, 125.0, 121.4, 118.0, 95.5, 82.6, 79.7, 79.2, 72.8, 55.9, 40.5, 39.9, 38.6, 35.4, 34.7, 31.6, 23.8, 19.2, 18.2, 17.7, 15.7, 14.8, 12.0; LRMS (ESI) 572.4 $(M + Na)^+$; HRMS (ESI) calcd for $C_{31}H_{51}NO_7K$ 588.3303, found 588.3336 $(M + K)^+$; $[\alpha]^{20}_D$ +34.0 (*c* 0.05, $CHCl_3$).

Carbamic Acid, (1*S*,2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-3,9-Dihydroxy-14-[(2*S*,3*S*,4*S*,5*R*)-4-methoxymethoxy-3,5-dimethyl-6-oxotetrahydropyran-2-yl]-2,8,10-trimethyl-1-[(1*S*,2*Z*)-1-methylpenta-2,4-dienyl]tetradeca-6,11-dienyl Ester (6b). Carbamate **56** (8.49 mg, 0.01 mmol) was subjected to the lactonization procedure described above. Removal of the PMB protecting group was accomplished by treating with $NaHCO_3$ and DDQ. Flash chromatography (EtOAc/hexane 3:2) provided **6b** (2.9 mg, 49%, 3 steps) as a colorless oil: IR ($CHCl_3$) 3404, 2362, 1749, 1373, 1241, 1049 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 6.62 (ddd, 1H, J = 16.8, 11.0, 10.1 Hz), 6.04 (t, 1H, J = 11.0 Hz), 5.48−5.33 (m, 5H), 5.24 (d, 1H, J = 17 Hz), 5.13 (d, 1H, J = 10.0 Hz), 4.77−4.60 (br m, 5H), 4.48 (m, 1H), 3.65 (m, 1H), 3.41 (s, 3H), 3.28 (d, 1H, J = 7.0 Hz), 3.23 (t, 1H, J = 5.5 Hz), 3.02 (m, 1H), 2.62 (m, 2H), 2.25−2.18 (m, 3H), 2.04 (m, 2H), 1.90 (m, 1H), 1.88 (m, 1H), 1.83 (m, 1H), 1.77−1.67 (m, 2H), 1.51 (m, 2H), 1.34 (d, 3H, J = 7.0), 1.02−0.92 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) 174.1, 157.3, 133.6, 132.9, 132.2, 129.6, 128.9, 125.0, 121.4, 118.0, 95.5, 82.6, 79.7, 79.2, 72.8, 55.9, 40.5, 39.8, 38.6, 35.4, 34.9, 34.7, 31.6, 23.8, 19.2, 18.2, 17.2, 15.7, 14.8, 12.0; LRMS (ESI) 616.3 $(M + Na)^+$; HRMS (ESI) calcd for $C_{33}H_{55}NO_8Na$ 616.3825, found 616.3829 $(M + Na)^+$; $[\alpha]^{20}_D$ +59.0 (*c* 0.1, $CHCl_3$).

Carbamic Acid, (1*S*,2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-3,9-Dihydroxy-14-[(2*S*,3*S*,4*S*,5*R*,6*R*)-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-2,8,10-trimethyl-1-[(1*S*,2*Z*)-1-methylpenta-2,4-dienyl]tetradeca-6,11-dienyl Ester (6c). Carbamate **56** (4.25 mg, 0.005 mmol) was subjected to the deprotection procedure of PMB described in the preparation of **6a**. Flash chromatography (EtOAc/hexane 3:2) of the crude product provided **6c** (2.8 mg, 92%) as a colorless oil: IR ($CHCl_3$) 3115, 2749, 2328, 1676, 1508, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 6.76 (ddd, 1H, J = 16.8, 11.0, 10.1 Hz), 6.18 (t, 1H, J = 10.8 Hz), 5.70−5.46 (m, 5H), 5.35 (d, 1H, J = 16.8 Hz), 4.49 (dd, J = 4.5, 6.6 Hz), 4.82 (d, 2H, J = 2.4 Hz), 4. 73 (br s, 2H), 4. 43 (d, 1H, J = 5.1 Hz), 4.15, (m, 1H), 3.78 (m, 1H), 3.56 (s, 3H), 3.54 (s, 3H), 3.36 (t, 2H, J = 6.9 Hz), 3.14 (m, 1H), 2.76 (m, 2H), 2.35−2.18 (m, 6H), 2.00−1.60 (m, 7H), 1.22 (d, 3H, J = 7.2 Hz), 1.16−1.12 (m, 12H), 1.07 (d, 3H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 157.3, 133.7, 133.5, 132.2, 132.0, 130.0, 128.7, 118.0, 109.6, 103.0, 96.5, 82.1, 79.7, 79.1, 72.7, 55.8, 39.9, 39.5, 38.3, 35.5, 35.0, 34.8, 34.6, 30.2, 29.8, 24.3, 18.1, 17.7, 15.7, 15.4, 14.2, 13.2, 8.1; LRMS (ESI) 632.4 $(M + Na)^+$; HRMS (ESI) calcd for $C_{33}H_{55}NO_8Na$ 632.4138, found 632.4139 $(M + Na)^+$; $[\alpha]^{20}_D$ +21.6 (*c* 0.25, $CHCl_3$).

Carbamic Acid 1-Hexyl-3,9-dihydroxy-14-(6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl)-2,8,10-trimethyltetradeca-6,11-dienyl Ester (57). Dess−Martin periodinane (26.1 mg, 0.062 mmol) was added to a solution of **41** (30 mg, 0.041 mmol) in CH_2Cl_2. After 2 h at room temperature, saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL) were added. After being stirred for 30 min at room temperature, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ to provide the crude aldehyde **43** as a colorless oil, which was used without further purification.

Hexylmagnesium bromide (2 M in THF, 0.2 mL, 0.04 mmol) was added to a solution of **43** in THF (0.2 mL) at 0 °C. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, and the crude product was purified by column chromatography (pentane/diethyl ether 2:1) to provide the pure product (25 mg, 0.031 mmol, 78%) as a colorless oil: IR ($CHCl_3$) 3462, 2923, 1612, 1513, 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.00 (d, J = 7.1 Hz, 2H), 7.00 (d, J = 7.1 Hz, 2H), 5.65 (dd, J = 10.3, 10.3 Hz, 1H), 5.53 (m, 3H), 4.83 (d, J = 7.1 Hz, 1H), 4.80 (d, J = 7.1 Hz, 1H), 4.67 (m, 3H), 4.48 (d, J = 10.9 Hz, 1H), 4.41 (d, J = 5.0 Hz, 1H), 4.13 (m, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.86 (m, 1H), 3.68 (m, 1H), 3.53 (s, 6H), 3.35 (dd, J = 11.5, 5.0 Hz, 1H), 3.21 (dd, J = 7.1, 3.5 Hz, 1H), 2.89 (m, 1H), 2.76 (m, 1H) 2.24 (m, 2H), 2.11 (m, 2H), 1.95 (m, 3H), 1.76 (m, 6H), 1.42 (m, 10H), 1.13 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 159.1, 134.2, 132.7, 132.3, 130.3, 129.4, 129.1, 128.9, 128.1, 114.0, 113.7, 103.1, 96.5 88.0, 83.9, 82.3, 75.6, 74.9, 70.8, 69.8, 55.7, 55.6, 55.3, 39.4, 39.0, 38.4, 35.9, 35.4, 35.3, 31.9, 30.4, 30.3, 29.4, 26.2, 24.2, 23.9, 22.6, 18.8, 17.4, 15.7, 14.1, 13.2, 5.8.

The above alcohol (23 mg, 0.028 mmol) in CH_2Cl_2 (2.5 mL) was treated at 0 °C with trichloroacetyl isocyanate (0.014 mL, 0.118 mmol). After 40 min., the solvent was removed under reduced pressure, and the residue was taken up in MeOH (1 mL). Solid K_2CO_3 (15 mg) was added. The mixture was stirred for 3 h at room temperature, diluted with EtOAc (8 mL), and washed with brine, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (pentane/EtOAc 3:1) to provide the pure carbamate (18 mg, 0.021 mmol, 75%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.01 (d, J = 2.6 Hz, 2H), 6.99 (d, J = 2.6 Hz, 2H), 5.52 (m, 4H), 4.97 (m, 1H), 4.83 (d, J = 7.0 Hz, 1H), 4.80 (d, J = 7.0 Hz, 1H), 4.72 (br s, 2H), 4.58 (m, 4H), 4.40 (d, J = 5.1 Hz, 1H), 4.13 (m, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.53 (s, 6H), 3.44 (m, 1H), 3.33 (m, 1H), 3.21 (dd, J = 7.2, 3.8 Hz, 1H), 2.85 (m, 2H), 2.24 (m, 3H), 2.09 (m, 1H), 1.96 (m, 3H), 1.74 (m, 3H), 1.65 (m, 3H), 1.39 (m, 10H), 1.15 (m, 18H), 1.03 (t, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 158.9, 156.8, 133.7, 132.7, 131.2, 130.9, 129.2, 128.8, 128.5, 113.6, 113.6, 102.9, 96.4, 87.9, 82.1, 79.6, 78.5, 76.2, 74.9, 70.9, 69.7, 55.7, 55.6, 55.2, 39.4, 39.2, 38.2, 35.8, 32.4, 31.7, 30.9, 30.2, 29.7, 29.3, 25.5, 24.1, 23.7, 22.6, 18.8, 17.4, 15.6, 14.1, 13.1 10.0; LRMS (ESI) 876.6 $(M + Na)^+$.

The carbamate obtained above (15 mg, 0.018 mmol) in CH_2Cl_2 (2 mL) was treated with $NaHCO_3$ (4.3 mg, 0.5 mmol) and DDQ (34 mg, 0.15 mmol). After being stirred for 1 h at room temperature, the mixture was diluted with CH_2Cl_2 (5 mL) and washed with H_2O (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (pentane/EtOAc 1:1) to provide pure **57** (4.0 mg, 0.0031 mmol, 35%) as a colorless oil: IR ($CHCl_3$): 3684, 3620, 3020, 2976, 2400, 1521, 1423, 1208 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.52 (m, 1H), 5.38 (m, 3H), 4.85 (m, 1H), 4.71 (d, J = 7.0 Hz, 1H), 4.68 (d, J = 7.0 Hz, 1H), 4.65 (br s, 2H), 4.30 (d, J = 5.2 Hz, 1H), 4.02 (m, 1H), 3.68 (m, 1H), 3.43 (s, 3H), 3.40 (s, 3H), 3.23 (m, 2H), 2.66 (m, 2H), 2.16 (m, 4H), 1.84 (m, 2H), 1.64 (m, 3H), 1.51 (m, 3H), 1.28 (m, 10H), 1.09 (d, J = 7.1 Hz, 3H), 1.00 (m, 9H), 0.93 (d, J = 7.0 Hz, 3H), 0.89 (t, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.2, 133.7, 132.1, 131.0, 128.8, 103.1, 96.6, 82.2, 79.1, 72.94, 69.8, 55.8, 41.9, 39.5, 38.4, 35.5, 34.9, 34.7, 33.0, 31.8, 30.2, 29.8, 19.3, 25.7, 24.3, 24.2, 22.6, 18.1, 15.7, 15.4, 14.1, 13.2, 8.0; HRMS (ESI) calcd for $C_{34}H_{63}NO_8Na$ 636.4451, found 636.4460 $(M + Na)^+$; $[\alpha]^{25}_D$ −3.8 (*c* 0.26, $CHCl_3$).

Carbamic Acid 1-(1,1-Dimethylhexyl)-3,9-dihydroxy-14-(6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl)-2,8,10-trimethyltetradeca-6,11-dienyl Ester (58). A solution of LDBB (2 mmol, prepared from 532 mg DBB and 14 mg of Li in 5 mL THF at 0 °C) was cooled to −78 °C and treated with 2-phenylthio-2-methylhexane (222 mg, 1 mmol). The dark blue solution turned to red. After 15 min,

half of the solution was transferred via cannula to a solution of the crude aldehyde obtained above. The mixture was stirred 4 h at −78 °C and 4 h at room temperature, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (pentane/diethyl ether 2:1) to provide the pure product (20.9 mg, 0.025 mmol) as a colorless oil: IR ($CHCl_3$) 3684, 3020, 2400, 1522, 1424, 1221 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 9.3 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 7.00 (d, J = 8.6 Hz, 2H), 5.64 (m, 1H), 5.47 (m, 3H), 4.83 (d, J = 7.0 Hz, 1H), 4.80 (d, 7.0 J = Hz, 1H), 4.72 (d, J = 10.5 Hz, 1H), 4.65 (d, J = 10.9 Hz, 1H), 4.64 (d, J = 10.5 Hz, 1H), 4.52 (d, J = 10.9 Hz, 1H), 4.41 (d, J = 5.1 Hz, 1H), 4.13 (m, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.53 (s, 6H), 3.34 (m, 1H), 3.22 (dd, J = 7.3, 3.9 Hz, 1H), 2.89 (m, 1H), 2.77 (m, 1H), 2.31−2.02 (m, 5H), 1.95 (m, 3H), 1.83−1.64 (m, 5H), 1.50−1.29 (m, 8 H), 1.22−0.99 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 159.1, 139.9, 132.6, 131.2, 130.3, 129.4, 129.1, 128.9, 128.2, 113.8, 113.6, 103.0, 96.4, 87.9, 85.4, 82.0, 80.3, 74.9, 70.9, 69.6, 55.7, 55.6, 55.2, 39.9, 39.4, 38.2, 37.9, 35.8,35.3, 34.4, 33.0, 30.3, 29.7, 24.2, 23.7, 23.5, 22.7, 18.8, 17.4, 15.7, 14.2, 13.1, 8.2; LRMS (ESI) 861.5 $(M + Na)^+$.

The above alcohol (19 mg, 0.023 mmol) in CH_2Cl_2 (2 mL) was treated at 0 °C with trichloroacetyl isocyanate (0.014 mL, 0.118 mmol). After 40 min, the solvent was removed under reduced pressure, the residue was taken up in MeOH (1 mL), and solid K_2CO_3 (15 mg) was added. The mixture was stirred for 3 h at room temperature, diluted with EtOAc (8 mL), and washed with brine, the aqueous layer was extracted with EtOAc, the combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (pentane/EtOAc 3:1) to provide the pure carbamate (15.7 mg, 0.018 mmol, 78%) as a colorless oil: IR ($CHCl_3$) 3155, 2979, 2874, 2254, 1794, 1711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 4H), 6.82 (m, 4H), 5.34, (m, 4H), 4.70 (m, 1H), 4.66 (d, J = 7.0 Hz, 1H), 4.63 (d, J = 7.0 Hz, 1H), 4.54 (br s, 2H), 4.45 (m, 3H), 4.34 (d, J = 10.9 Hz, 1H), 4.23 (d, J = 5.2 Hz, 1H), 3.95 (m, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.36 (s, 6H), 3.16 (m, 2H), 3.03 (dd, J = 7.2, 4.2 Hz, 1H), 2.72 (m, 1H), 2.61 (m, 1H), 2.11 (m, 3H), 1.80 (m, 3H), 1.56 (m, 5H), 1.24 (m, 8H), 1.04 (d, J = 7.1 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 3.9 Hz, 3H), 0.92 (d, 3.6, 3H), 0.84 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 156.7, 133.7, 133.0, 131.4, 131.1, 129.3, 129.1, 128.7, 113.6, 103.0, 96.5, 88.0, 82.9, 82.2, 79.5, 74.8, 71.5, 69.8, 55.7, 55.6, 55.2, 39.5, 39.0, 38.9, 38.3, 35.6, 35.5, 35.4, 32.9, 30.9, 30.2, 29.7, 24.3, 24.1, 23.7, 23.5, 22.6, 18.7, 17.1, 15.6, 15.3 14.1, 13.1, 11.5; LRMS (ESI) 904.5 $(M + Na)^+$.

The carbamate obtained above (3.5 mg, 3.97 μmol) in CH_2Cl_2 (1 mL) was treated with $NaHCO_3$ (1.2 mg, 14.3 μmol) and DDQ (3.9 mg, 17.3 μmol). After being stirred for 1 h at room temperature, the solvent was removed with a stream of Ar. The crude product was purified by column chromatography (pentane/EtOAc 1:1) to provide pure **58** (2.1 mg, 3.28 μmol, 83%) as a colorless oil: IR ($CHCl_3$) 3154, 2253, 1816, 1794, 1470, 1382 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.53 (m, 1H), 5.36 (m, 3H), 5.13 (m, 1H), 4.71 (d, J = 7.0 Hz, 1H), 4.68 (d, J = 7.0 Hz, 1H), 4.70 (br s, 2H), 4.30 (d, J = 5.1 Hz, 1H), 4.02 (m, 1H), 3.62 (m, 1H), 3.43 (s, 3H), 3.40 (s, 3H), 3.23 (m, 2H), 2.67 (m, 2H), 2.17 (m, 4H), 1.83 (m, 2H), 1.58 (m, 5H), 1.31 (m, 8H), 1.09 (d, J = 7.1, 3H), 0.99 (m, 9H), 0.89 (m, 9H), 0.83 (d, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 135.3, 133.7, 132.3, 131.1, 103.1, 96.2, 83.7, 82.1, 79.1, 75.4, 55.8, 39.5, 38.8, 38.4, 38.3, 35.6, 34.4, 34.2, 32.9, 32.3, 30.2, 29.8, 29.4, 26.5, 24.6, 24.3, 23.5, 23.4, 23.1, 22.7, 17.9, 15.8, 14.9, 14.2, 13.2, 7.7; LRMS (ESI) 664.5 $(M + Na)^+$; HRMS (ESI) calcd for $C_{36}H_{67}NO_8Na$ 664.4764, found 664.4757 $(M + Na)^+$; $[\alpha]^D_{25}$ −6.9 (*c* 0.11, $CHCl_3$).

Biology. General. Tubulin without microtubule-associated proteins was prepared from fresh bovine brains.[32] Paclitaxel was provided by the Drug Synthesis and Chemistry Branch, National Cancer Institute. (+)-Discodermolide was received from Dr. Kenneth Bair at Novartis Pharmaceutical Corporation. Ca^{2+}- and Mg^{2+}-free RPMI-1640 culture medium were from GIBCO/BRL-Life Technologies. Fetal bovine serum (FBS) was from Hyclone. Cell lines were obtained from American Type Culture Collection (Manassas, VA).

Tubulin Assembly.[33] Tubulin assembly was followed in a Beckman-Coulter 7400 spectrophotometer, equipped with an electronic Peltier temperature controller, reading absorbance (turbidity) at 350 nm. Reaction mixtures (0.25 mL final volume) contained tubulin (final concentration 10 μM; 1 mg/mL), monosodium glutamate (0.8 M from a stock solution adjusted to pH 6.6 with HCl), DMSO (final concentration 4% v/v), and differing concentrations of test agent where indicated. Reaction mixtures without test agent were cooled to 0 °C and added to cuvettes held at 0.25−0.5 °C in the spectrophotometer. Test agent in DMSO was then rapidly mixed in the reaction mixture. Each run contained one positive control (paclitaxel, 10 μM final concentration) and one negative control (DMSO only). Baselines were established at 0.25−2.5 °C and temperature was rapidly raised to 30 °C (in approximately 1 min) and held there for 20 min. The temperature was then rapidly lowered back to 0.25−2.5 °C.

Cell Growth Inhibition.[34] Cells were plated (500−2000 cells/well depending on the cell line) in 96-well microplates, allowed to attach and grow for 48 h, then treated with vehicle (4% DMSO, a concentration that allowed doubling times of 24 h or less) or test agent (50, 10, 2, 0.4, and 0.08 μM for the new agents; 0.100, 0.020, 0.004, 0.0008, and 0.00016 μM for paclitaxel and discodermolide) for the given times. One plate consisted of cells from each line used for a time zero cell number determination. The other plates in a given determination contained eight wells of control cells, eight wells of medium and each agent concentration tested in quadruplicate. Cell numbers were obtained spectrophotometrically (absorbance at 490 nm minus that at 630 nm) in a Dynamax plate reader after treatment with 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium (MTS) using phenazine methanesulfonate as the electron acceptor. After initial screening with the above 5-fold dilutions, 50% growth inhibitory concentration (GI_{50}) values were determined for each agent by repeating the screen using 2-fold dilutions (five concentrations) centered on the initial estimated GI_{50} concentration, again in quadruplicate.

Paclitaxel Binding Site Competition Assay.[35] A stock solution of [^{3}H]paclitaxel (26.8 μM, 16.2 Ci/mmol), obtained from the NCI, was prepared in 37% (v/v) DMSO. The test agents were prepared in 25% (v/v) DMSO−0.75 M monosodium glutamate (prepared from a 2 M stock solution adjusted to pH 6.6 with HCl). The radiolabeled paclitaxel and test agents, as indicated in terms of final concentrations, were mixed in equal volumes and warmed to 37 °C. A reaction mixture (50 μL) containing 0.75 M monosodium glutamate, 4.0 μM tubulin, and 40 μM ddGTP (a nonhydrolyzable analogue of GTP) was prepared and incubated at 37 °C for 30 min to preform microtubules. An equivalent volume of drug mixture with [^{3}H]-paclitaxel was added to preformed polymer and incubated for 30 min at 37 °C. Bound [^{3}H]paclitaxel was separated from free drug by centrifugation of the reaction mixtures at 14000 rpm for 20 min at room temperature. Radioactive counts from the supernatant (50 μL) were determined by scintillation spectrometry. Bound [^{3}H]paclitaxel was calculated from the following: total paclitaxel added to each reaction mixture minus the paclitaxel present in the supernatant (free drug). The % bound values were normalized to the control values with no inhibitor added.

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Supporting Information Available: Representative HPLC chromatograms for key analogues subjected to biological testing. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Posting

The Supporting Information paragraph omitted in the manuscript posted May 29, 2003, was added and the manuscript reposted June 16, 2003.

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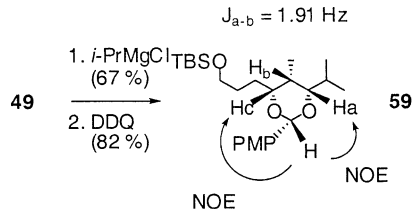

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