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Synthesis and Biological Assessment of Simplified Analogues of the Potent Microtubule Stabilizer (+)-Discodermolide☆

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Abstract—An efficient, convergent and stereocontrolled synthesis of simplified analogues of the potent antimitotic agent (+)-discodermolide has been achieved and several small libraries have been prepared. In all the libraries, the discodermolide methyl groups at C14 and C16 and the C7 hydroxy group were removed and the lactone was replaced by simple esters. Other modifications introduced in each series of analogues were related to C11, C17 and C19 of the natural product. Key elements of the synthetic strategy included (a) elaboration of the main subunits from a common intermediate and (b) fragment couplings using Wittig reactions to install the (*Z*)-olefins. Library components were analyzed for microtubule-stabilizing actions in vitro, for displacement of [^{3}H]paclitaxel from its binding site on tubulin, for antiproliferative activity against human carcinoma cells, and for cell signaling and mitotic spindle alterations by a multiparameter fluorescence cell-based screening technique. The results show that even significant structural simplification can lead to analogues with actions related to microtubule targeting.

Introduction

(+)-Discodermolide (**1**) is a polyketide natural product isolated from the marine sponge *Discodermia dissoluta* by Gunasekera and co-workers in 1990.[1] Its structure, shown in Figure 1, comprises a linear polypropionate backbone with 13 stereogenic centers, three (*Z*) double bonds at C8–C9, C13–C14 and C21–C22, a tetrasubstituted lactone (C1–C5), a carbamate (C19) and a terminal *cis*-diene (C21–C24). Discodermolide adopts a U-shape conformation in the solid state and also in solution to minimize the A(1,3) strain and *syn*-pentane interactions.[2]

Discodermolide was initially found to be a potent immunosuppressive agent and also displayed antifungal activity.[3] Subsequently, its potent activity as an antimitotic agent was discovered.[4] Discodermolide arrests the cell cycle in the G2/M phase by stabilizing microtubules and promoting the polymerization of tubulin. This mechanism of action similar to that of paclitaxel (Taxol), but discodermolide is the superior microtubule stabilizer. Beyond its potent antiproliferative, microtubule-stabilizing and apoptosis-inducing actions, discodermolide has some advantages over other classes of microtubule stabilizing agents (taxanes, epothilones, eleutherobin), particularly in its effects on isolated tubulin. Importantly, (+)-discodermolide is active against cancer cell lines expressing altered β-tubulins that make the cells resistant to taxanes, and has the unique property of being synergistic with paclitaxel.[5,6]

The remarkable biological profile and novel structure of discodermolide make it a promising candidate for clinical development as a chemotherapeutic agent. These properties, along with the scarcity of the natural material, have stimulated intensive synthetic effort. To date, several total syntheses of (+)-discodermolide and its enantiomer have been developed.[6] These elegant syntheses have not proven simple—all requiring 30 or more steps from commercially available starting materials to

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☆Information on synthesis and characterization of intermediates can be seen in the supplementary data associated with this article, which be found at doi:10.1016/S0968-0896(03)00186-X and at http://preprint.chemweb.com

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doi:10.1016/S0968-0896(03)00186-X

arrive at the final product. Consequently, few analogues have been reported and structure–activity relationship data are sparse.[6a,7]

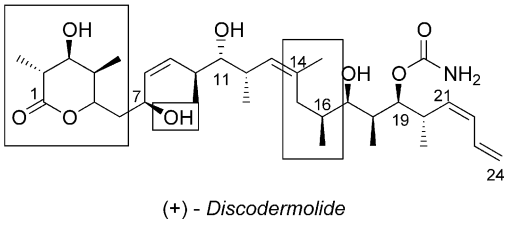
Our goal in this study was to prepare simpler analogues of discodermolide in fewer synthetic steps than necessary for the natural product and the full length congeners reported to date. Herein, we describe libraries of simplified discodermolide analogues that differ from the natural product in that the methyl groups at C14 and C16 as well as C7 hydroxyl group are omitted and the left side lactone moiety is replaced by simple esters (see boxes in Fig. 1).

The biological activities of all the library members were examined in order to expand structure–activity relationships. These and previously reported results[8] show that even drastic structural simplifications and variations can lead to analogues with microtubule targeting actions.

Results and Discussion

Design of structural and variations in the analogues: Our first objective was to synthesize simplified analogues of discodermolide bearing structural modifications with respect to the natural product. The goal was to study the influence that variations in some areas of the molecule would provoke on microtubule assembly-inducing properties, on the ability to displace paclitaxel from its binding site on tubulin and on antiproliferative actions.

All the derivatives prepared retained key structural properties of discodermolide including the two (*Z*)-alkenes of the central core (C8 and C13 discodermolide numbering) that give the molecule its characteristic shape, and Z-diene 'display' (C21–24) (Fig. 2).



(+) - *Discodermolide*

Figure 1. Discodermolide with areas targeted for simplification in boxes.

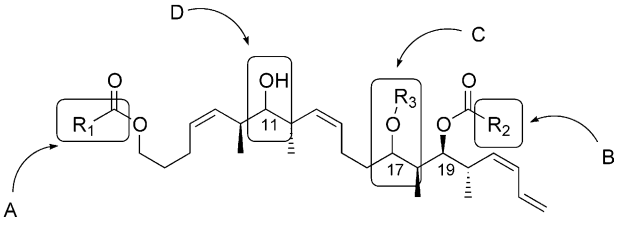


Figure 2. Simplified analogues of discodermolide: domains of variation.

The methodology that we established for the synthesis influenced our choice of target analogues. The modifications introduced in the design of the series of analogues were:

- Replacement of the lactone with simple esters (domain A).
- Replacements of the carbamate on C19 with an acetoxy group (domain B).
- Inversion of the configuration of the C17 stereocenter and derivatization of its hydroxy group, keeping the hydroxy group at C19 free (domain C).
- Inversion of the C11 stereocenter (domain D).

Synthetic plan

The synthetic design of the simplified analogues was based on a highly convergent approach (Scheme 1). Retrosynthetically, the polypropionate backbone was divided into three fragments disconnecting at the C8–C9 and C13–C14 double bonds: a THP-protected phosphonium salt as the 'left display'; a diene phosphonium salt as the 'right display'; and an aldehyde as the central fragment or 'scaffold'.

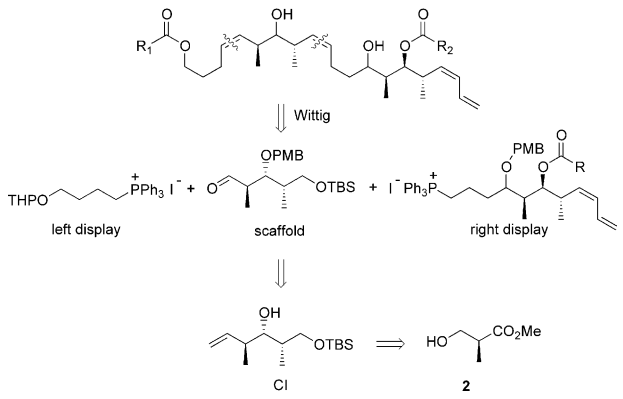
A common stereochemical triad appears in the central and right fragments that can be retrosynthetically reduced to a common intermediate (CI). This homoallylic alcohol is readily prepared in high diastereomeric excess from the commercially available methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (+)-**2** via protection and addition of a Roush chiral crotylboronates.[9] An interesting feature of the synthesis arises from the pseudo C2-symmetry of the targets. By switching the order of the Wittig couplings, it is possible to synthesize analogues with inversion of the configuration of the C11 hydroxy group.

Synthesis of 11*S*, 17*R*, 19*S*-carbamoyloxy analogues

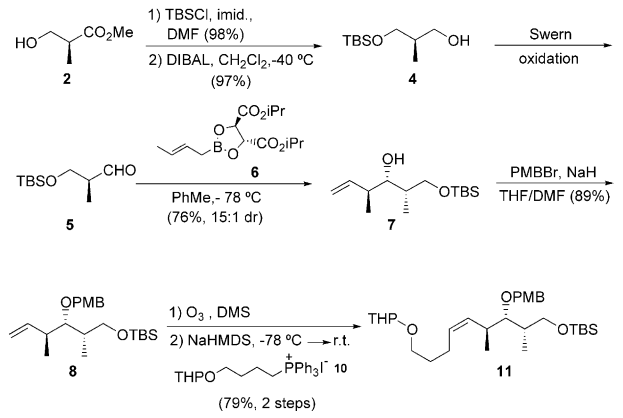
The synthetic methodology for all the analogue libraries—with appropriate modifications in each series—began with commercially available hydroxy ester (+)-**2**. Protection as the TBS ether **3** (not shown) and reduction with DIBAL provided alcohol **4**[10] (Scheme 2). Swern oxidation[11] then furnished aldehyde **5**,[10] which was used without purification in an asymmetric crotylation reaction with Roush chiral (*R*,*R*)-diisopropyl tartrate *E*-crotylboronate **6**[12] to give the common intermediate, homoallylic alcohol **7**[9] (76% yield, 15:1 d.r.).

Protection of **7** as its *p*-methoxybenzyl (PMB) ether under basic conditions provided olefin **8**, which was oxidatively cleaved to yield the aldehyde **9** (not shown). Wittig olefination reaction of **9** with the ylide derived from phosphonium salt **10**[13] (NaHMDS, THF, −78 °C→rt) afforded olefin 11 in 79% yield with excellent *Z*-selectivity (>20:1).

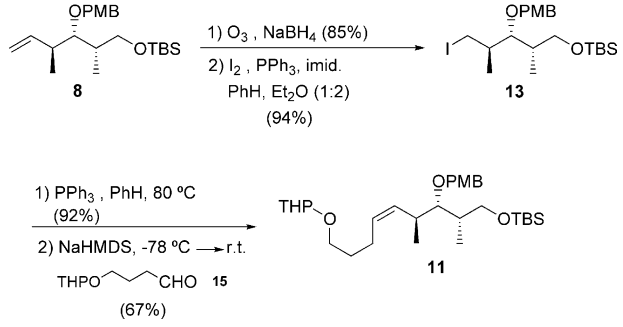
We also explored the alternative Wittig reaction for the synthesis of olefin **11** (Scheme 3). Starting from **8**, ozo-



Scheme 1.

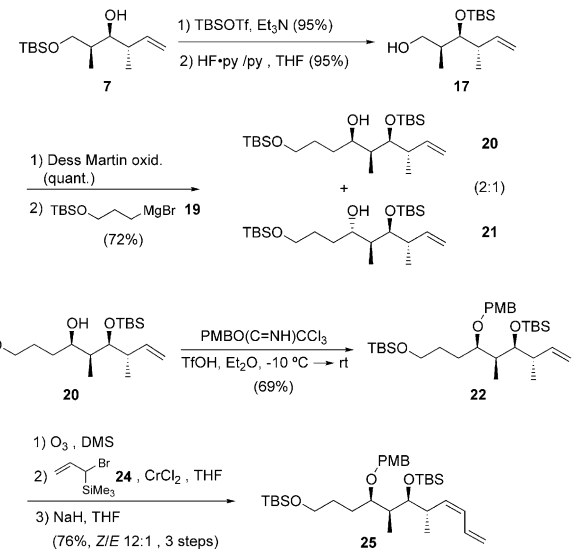


Scheme 2.

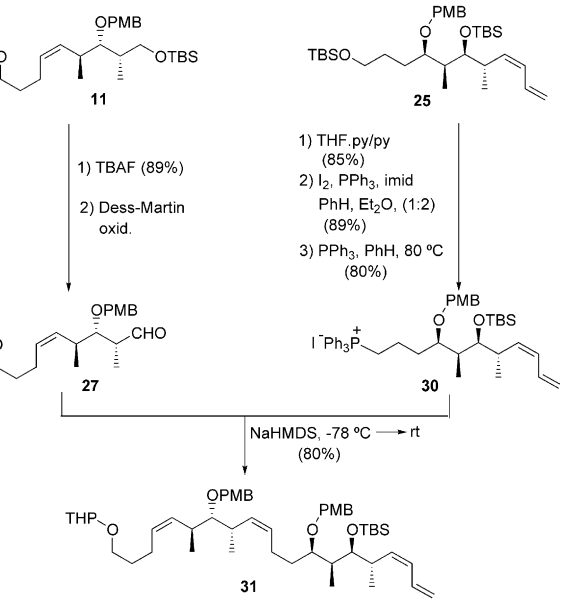


Scheme 3.

nolysis and subsequent reduction with $NaBH_4$ provided alcohol **12**, which was converted to the iodide **13** by using modified Garegg conditions[14] (I_2, PPh_3, imidazole, Et_2O/PhH 2:1). Treatment of the iodide with excess triphenylphosphine (5 equiv) in dry benzene at 80 °C generated the phosphonium salt **14** (92% yield, not shown). Unfortunately, this salt was more hygroscopic than the analogous salt **10**, and its Wittig coupling with the aldehyde **15**[15] always gave olefin **11** in lower yield, especially when reactions were performed at the multigram scale.

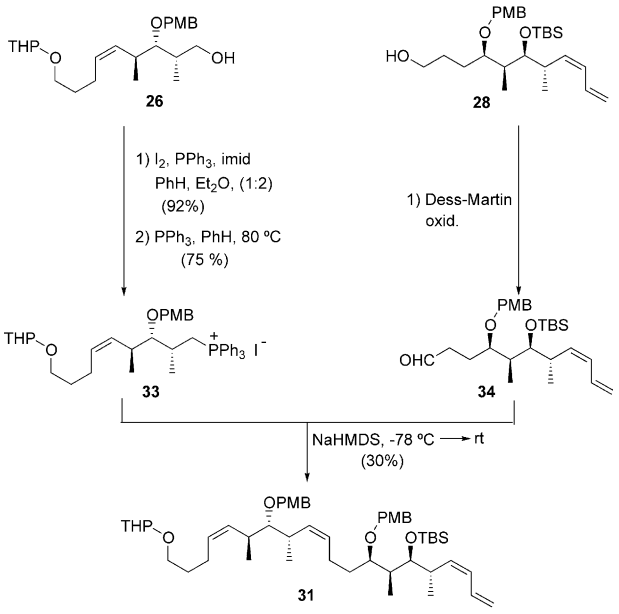


Scheme 4.



Scheme 5.

The synthesis of the C14–C24 *cis* diene fragment started from the common intermediate **7**. TBS protection of the secondary alcohol (TBSOTf, Et_3N) and selective deprotection of the primary silyl ether with HF-pyridine furnished alcohol **17** (90%, two steps). Dess–Martin oxidation[16] provided aldehyde **18**, which was treated with 3-(*t*-butyldimethylsilyloxy)propyl magnesium bromide **19** to give a 2:1 mixture of the epimeric alcohols **20** and **21** in 72% yield. The major compound **20** had the desired *R* configuration at the position equivalent to discodermolide C17.[8] Protection of the hydroxy group in **20** was achieved by using high-purity *p*-methoxybenzyl trichloroacetimidate and triflic acid (0.3 mol%)[17] to provide olefin **22** (Scheme 4). Introduction of the terminal C21–C24 (*Z*)-diene unit was achieved by using a three-step protocol. First, ozonolysis of **22** afforded aldehyde **23** (not shown). Nozaki–Hiyama reaction



Scheme 6.

between this aldehyde and the allyl chromium reagent generated in situ from 1-bromoallyl-trimethylsilane **24** and chromium chloride in THF[18] provided the intermediate hydroxy silanes. These crude products were then directly subjected to Peterson-type *syn* elimination[19] with NaH in THF to give the desired (*Z*)-diene **25** exclusively (76%, three steps from **22**).

The second Wittig coupling scheme began with the fragments **11** and **25**. Deprotection of the TBS ether **11** (TBAF, THF) and Dess–Martin oxidation of the intermediate alcohol **26** (not shown) furnished aldehyde **27** in high yield (89%, two steps). From the fragment **25**, selective primary silyl ether deprotection (HF-pyridine) afforded an alcohol **28** (not shown). Iodination (iodine, PPh_3, imidazole, 89%) gave an iodide **29**, which upon treatment with excess of triphenylphosphine at 80 °C furnished the phosphonium salt **30** (Scheme 5). Deprotonation of **30** with sodium bis(trimethylsilyl)amide in THF gave the ylide, which underwent (*Z*)-selective Wittig coupling [(*Z*)/(*E*) > 20:1] with aldehyde **27** to afford **31** in 80% yield.

We also explored the alternative Wittig reaction, switching the aldehyde and the phosphonium salt fragment. Thus, alcohol **26** was iodinated to furnish iodide **32** (not shown), which upon treatment with PPh_3 at 80 °C in dry benzene provided the phosphonium salt **33** (Scheme 6). To build the right side in this coupling scheme, the alcohol **28** was oxidized with Dess–Martin reagent to aldehyde **34**. The branched phosphonium salt **33** was extremely hygroscopic and very difficult to handle; its reaction with **34** afforded **31** in low yields (7–30%), especially on large scale. The main product of the reaction was the corresponding diphenyl phosphine oxide derived from **33**.

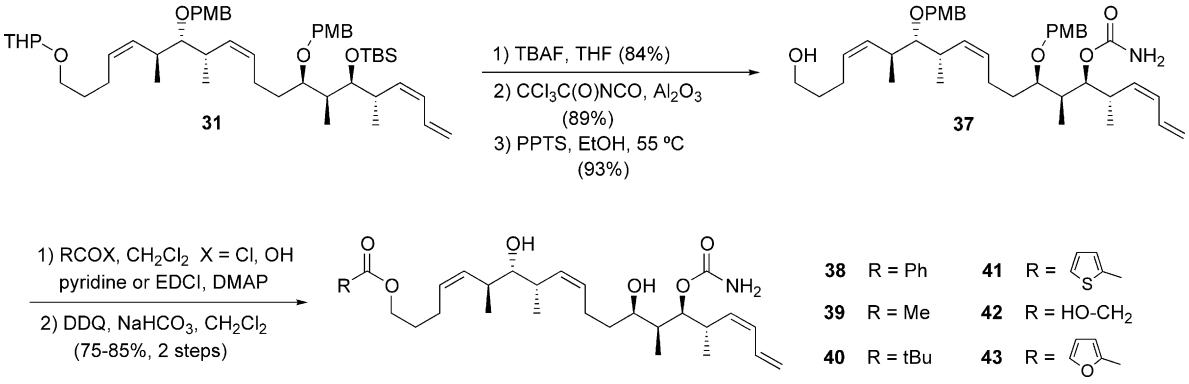
The synthesis of the first library of analogues was completed in a further five steps (Scheme 7). Deprotection of the TBS ether of **31** with TBAF provided **35** (not shown) with the free alcohol at position C19. The C19 carbamate moiety was installed following the Koçovsky protocol.[20] Reaction of **35** with trichloroacetyl isocyanate and in situ hydrolysis of the trichloroacetyl derivative with Al_2O_3 provided the carbamate ester **36** (89% yield, not shown). Deprotection of the THP ether with catalytic pPTS in EtOH gave the alcohol **37**. Esterification reactions of **37** with different acyl chlorides (alkanoyl, benzoyl, heteroaroyl) followed by the oxidative removal of both PMB groups (DDQ, $NaHCO_3$, CH_2Cl_2) provided the library of 11*S*, 17*R*, 19*S*-carbamoyloxy analogues **38**–**43** (75–85% yield, two steps). This first library of discodermolide analogues was obtained in about 5% overall yield (21 steps in the longest linear sequence).

With the exception of compound **42**, these analogues showed a weak but consistent ability to cause assembly of isolated bovine brain tubulin (Table 1).[8] Moreover, when present in a 2-fold molar excess over that of [^{3}H]paclitaxel stoichiometrically bound to preformed microtubules induced to assemble with dideoxyGTP, compounds **38**–**41** displaced appreciable amounts of the radiolabel from the protein, suggesting they bound at a site coincident with or overlapping that of paclitaxel. The analogues were not as potent as discodermolide in

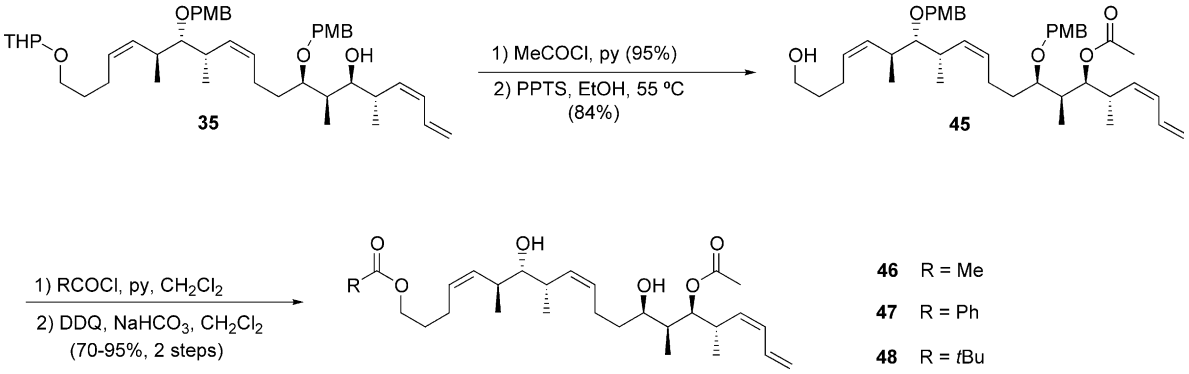
Table 1. Biological activities of discodermolide analogues **38**–**43**

Compd	MT assembly (%)[a]	GI_{50} (μM)[b]			Displacement of [^{3}H]paclitaxel (%)[c]
		MDA-MB231 (breast)	PC-3 (prostate)	2008 (ovarian)	
38	13	7.2±0.4	11±1	7.7±0.5	19±3
39	5	12±1	6.6±0.3	5.8±0.7	19±4
40	14	2.6±0.9	3.0±0.8	1.5±1.0	32±6
41	10	8.0±0.3	15±2	7.1±0.6	23±9
42	<5	41±2	>50	24±2	23±1
43	21	7.5±0.1	14±1	6.4±0.6	18±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 into microtubules induced by test agent at 10 μM versus that caused by 10 μM paclitaxel (100%) and by DMSO (vehicle, 0%); single determinations at 30 °C.
[b]Concentration at which test agent caused 50% inhibition of cell growth; means (N = 4 over 5–10 concentrations) + S.D. after 72 h of continuous exposure to the agent.
[c]Percent displacement by 4 μM test agent of 2 μM [^{3}H]paclitaxel bound to microtubules formed from 2 μM tubulin and 20 μM dideoxyGTP.



Scheme 7.



Scheme 8.

Table 2. Biological activities of discodermolide analogues **46–48**

Compd	MT assembly (%)[a]	GI_{50} (μM)[b]			Displacement of [^{3}H]paclitaxel (%)[c]
		MDA-MB231 (breast)	PC-3 (prostate)	2008 (ovarian)	
46	18	22±2	25±4	15±1	19±2
47	9	20±2	21±2	20±2	17±1
48	8	6.8±1.9	14±1	14±2	24±2

[a,b,c]See legend of Table 1.

these two assays. Analogues **38–41** and **43** had 50% growth inhibitory concentrations against human breast (MDA-MB231), prostate (PC-3) and ovarian (2008) carcinoma cells in the low micromolar range, whereas compound **42** was much less active. These antiproliferative activities were considerably less than that of (+)-discodermolide, whose potency against the breast carcinoma cells is in the low nanomolar range.[4a]

The methodology established in the preparation of **38–43** served as the basis for making several other series of analogues.

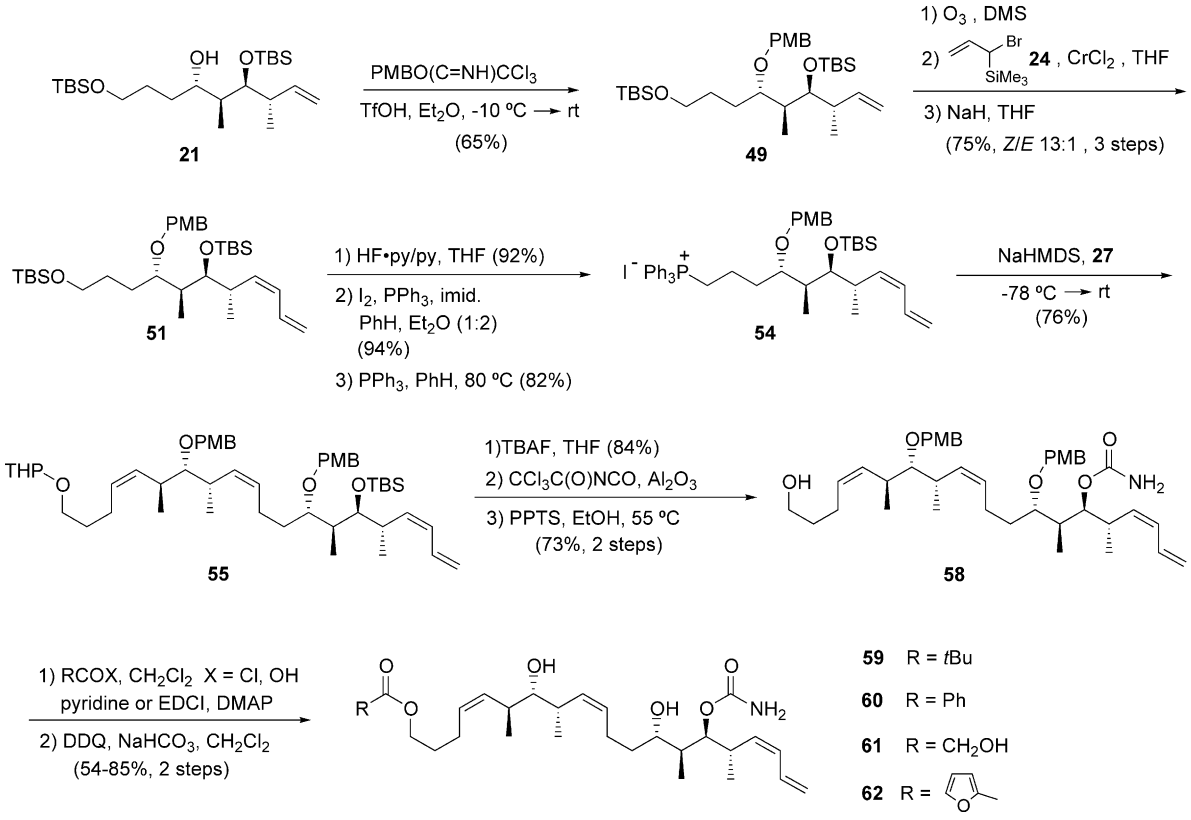
Synthesis of 11*S*,17*R*,19*S*-acetoxy analogues

The next modification explored was the introduction of an ester (acetoxy) group at C19 in place of the carbamate to check if the latter moiety was essential for activity (Scheme 8). Thus, the intermediate alcohol **35** was acetylated (acetyl chloride, pyridine, 95% yield) to provide **44** (not shown), which was subjected to deprotection of the THP group to give primary alcohol **45**. Reaction with different acyl chlorides and finally deprotection of the *p*-methoxybenzyl groups afforded C19 acetoxy derivatives **46–48** (70–95%, two steps).

The introduction of the acetoxy group at C19 in place of the carbamate proved somewhat detremental to biological activity (Table 2). Microtubule assembly-inducing actions were decreased only slightly, but antiproliferative potencies decreased by a factor of 2–10.

Synthesis of 11*S*,17*S*,19*S*-carbamoyloxy analogues

The 17*S*-analogues, with opposite configuration of discodermolide, were prepared from intermediate alcohol **21** (produced as minor product in the Grignard reaction that formed **20**). Alcohol **21** was protected as its PMB ether with PMB-trichloroimidate to afford **49**. By following the same sequence used for the 17*R* series, the *cis*-diene **51** was installed (75% yield, three steps).



Scheme 9.

Selective deprotection of the primary alcohol, iodination and subsequent formation of the corresponding phosphonium salt provided **54** (Scheme 9). The Wittig olefination reaction of the ylide derived from **54** and the aldehyde **27** using NaHMDS as base afforded the olefin **55** in respectable yield (76%) and with good *Z*-selectivity. The carbamate was introduced as above to give **57** (not shown). Deprotection of the THP ether, esterification of the alcohol **58** with several acyl chlorides, and oxidative removal of the PMB protective groups with DDQ (54–85%, two steps) furnished the 17*S*,19*S*-carbamoyloxy analogues **59–62**.

Although some microtubule formation-inducing and paclitaxel-displacing activity was retained by these analogues, a decrease in antiproliferative potency occurred on inversion of the configuration at C17 (Table 3).

Synthesis of 11*S*,17*R*-carbamoyloxy or 11*S*,17*R*-acetoxy analogues

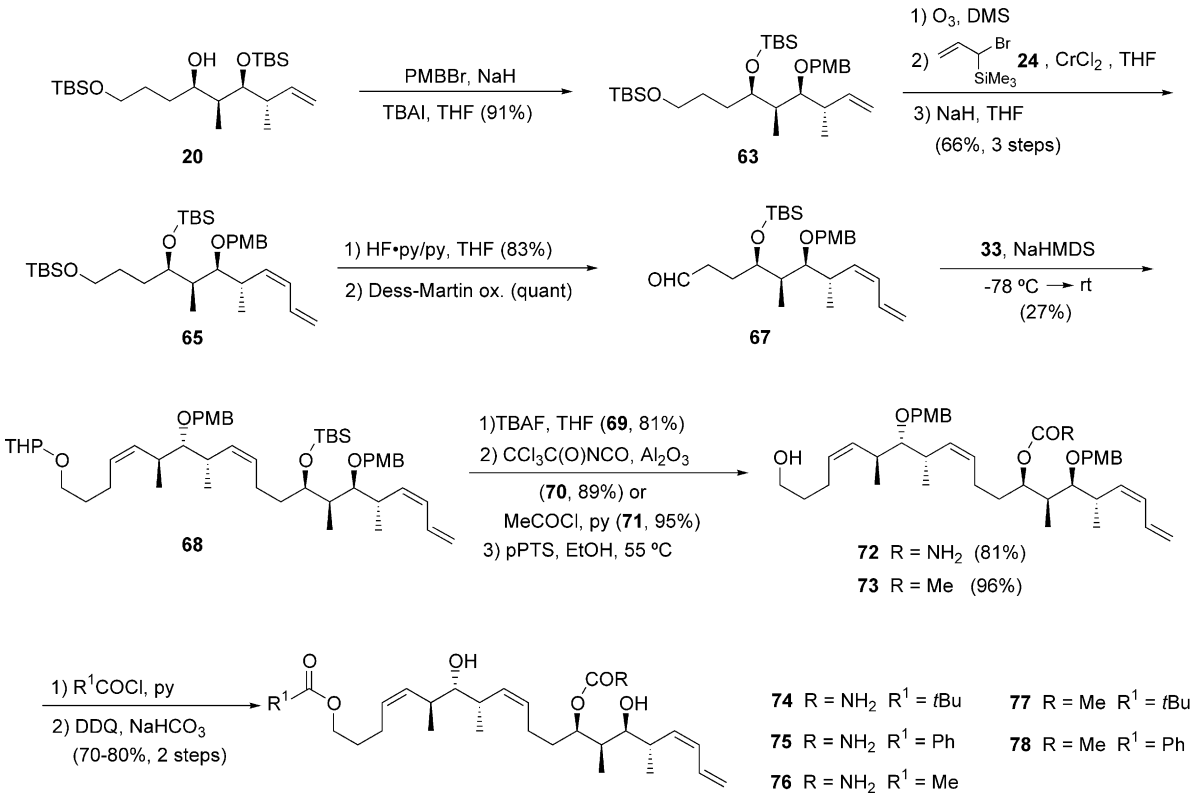
While attempting PMB protection of alcohol **20**, under basic conditions we observed that the product **63** was obtained in 91% yield (Scheme 10). The formation of **63** is due to a migration of the *t*-butyldimethyl silyl group[21] from C19 alcohol to the less hindered C17[8] alcohol under the basic conditions of the reaction. After migration, subsequent protection of the free C19 alcohol with the PMB group occurred.

Following the same overall synthetic strategy, we were therefore able to obtain analogues with a carbamate or acetoxy groups at C17 from **63** (Scheme 10). Thus, the introduction of the terminal diene from **63** provided **65** (66%, three steps). Selective deprotection of the primary

Table 3. Biological activities of discodermolide analogues **59–62**

Compd	MT assembly (%)[a]	GI_{50} (μM)[b]			Displacement of [^{3}H]paclitaxel (%)[c]
		MDA-MB231 (breast)	PC-3 (prostate)	2008 (ovarian)	
59	7	24±1	23±2	27±1	17±1
60	17	20±2	23±2	21±3	11±2
61	15	>50	>50	>50	18±0
62	20	19±0	23±1	20±7	20±4

[a,b,c]See legend of Table 1.



Scheme 10.

silyl ether followed by Dess–Martin oxidation afforded aldehyde **67**. Olefination of **67** with the hygroscopic phosphonium salt **33** furnished exclusively the (*Z*)-olefin **68**, although in a low yield (27%). The carbamate or the acetoxy group at C17, and the different esters in the left display, were introduced as described above. After final PMB deprotection, the derivatives **74–78** were formed.

Analogues **74–77** caused some microtubule formation from isolated tubulin, while compound **78** was inactive in this assay (Table 4). Analogues **75** and **76** also displaced a small amount of radiolabeled paclitaxel from polymer. The presence of the carbamate moiety at C17 was not as detrimental to antiproliferative activity in general as was inversion of stereochemistry at this position, especially with the ovarian carcinoma cells.

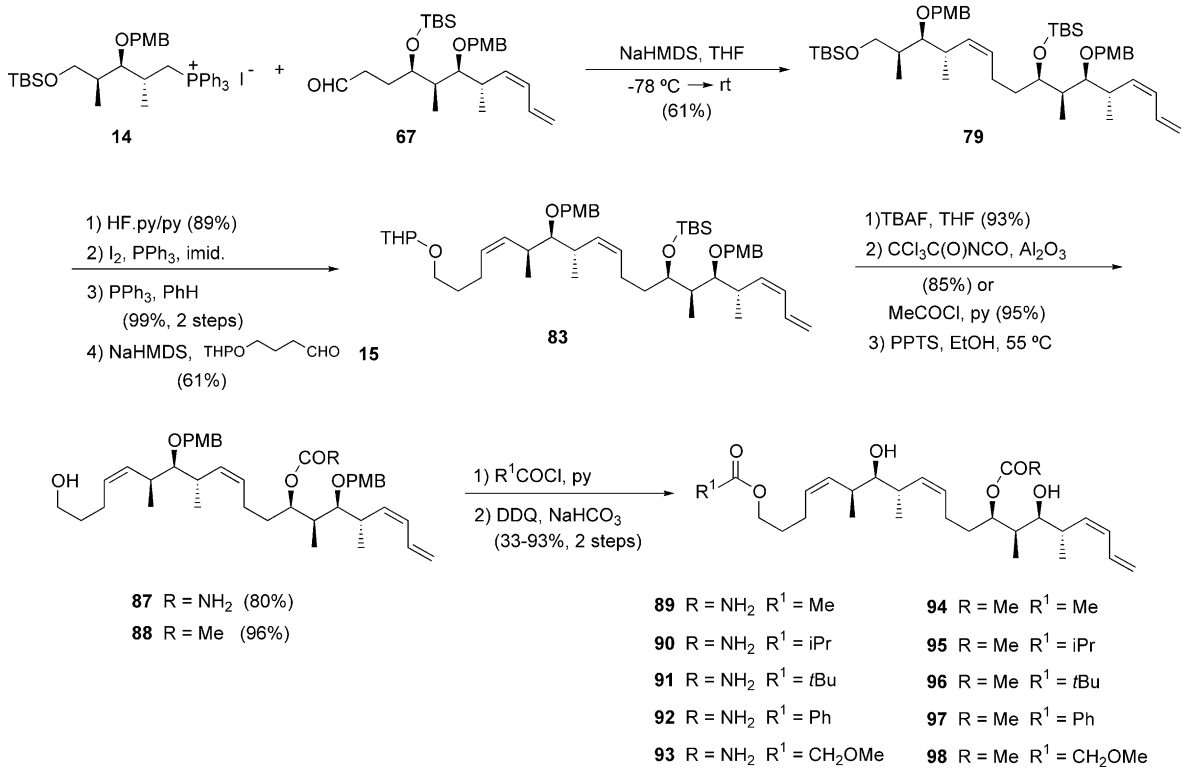
Synthesis of 11*R*,17*R*-carbamoyloxy and 11*R*,17*R*-acetoxy analogues

Finally, by switching the order of the two Wittig couplings, we could obtain inverted 11*R* analogues of discodermolide. For the synthesis of these products, the first Wittig reaction coupled the central part and the right fragment. Thus, the reaction of phosphonium salt **14** and aldehyde **67** with NaHMDS provided olefin **79** in 61% yield with good *cis*-selectivity (Scheme 11). Selective deprotection of the primary TBS ether (HF-pyridine, 89%), iodination and treatment of the iodide with excess of triphenylphosphine afforded the salt **82** (not shown, 99%, two steps). Subsequent Wittig reaction of **82** with aldehyde **15** furnished **83** (61% yield). Following a similar route to that for the other series, the carbamate or acetoxy groups were introduced at C17,

Table 4. Biological activities of discodermolide analogues **74–78**

Compd	MT assembly (%)[a]	GI_{50} (μM)[b]			Displacement of [^{3}H]paclitaxel (%)[c]
		MDA-MB231 (breast)	PC-3 (prostate)	2008 (ovarian)	
74	12	11±2	20±3	2.7±3.5	15±3
75	13	15±0	15±1	21±2	12±5
76	18	>50	>50	>50	10±4
77	10	20±4	20±3	5.8±2.2	21±3
78	<5	25±6	>50	3.0±0.9	16±2

[a,b,c]See legend of Table 1.



Scheme 11.

Table 5. Biological activities of discodermolide analogues **89–98**

Compd	MT assembly (%)[a]	GI_{50} (μM)[b]			Displacement of [^{3}H]paclitaxel (%)[c]
		MDA-MB231 (breast)	PC-3 (prostate)	2008 (ovarian)	
89	<5	>50	>50	>50	21±2
90	<5	>50	>50	31±4	19±2
91	<5	22±2	33±1	33±1	17±1
92	<5	25±6	20±1	26±4	18±1
93	<5	>50	>50	>50	18±1
94	<5	>50	>50	>50	15±1
95	<5	12±5	>50	>50	17±2
96	<5	23±1	43±11	41±5	17±2
97	<5	7.0±3.0	26±6	29±2	20±5
98	<5	>50	>50	>50	16±2

[a,b,c]See legend of Table 1.

and different alkanoyl and benzoyl esters were installed in the left display. After the PMB deprotections, 10 11*R* derivatives **89–98** were obtained in moderate to good yields (33–95%, two steps).

Inversion of stereochemistry at C11 proved highly detrimental to biological activity (Table 5). None of the compounds caused microtubule assembly in vitro. Analogues **91**, **92**, **96** and **97** were weakly antiproliferative, but the remainder of the compounds in this series were essentially inactive in all biological assays.

Conclusion

In conclusion, we have prepared a series of 28 simplified analogues of the antimitotic marine natural product (+)-discodermolide. Despite drastic modifications, including the wholesale removal of the lactone and the deletion of three other substituents, many of the compounds retain biological activity and exhibit discodermolide-like behavior in tubulin assays. Because of this, important structure–activity information can be gleaned from the substituent alterations within and especially across libraries. In particular, analogues lacking the carbamate moiety at C-19 are devoid of significant microtubule assembly-enhancing or cell growth inhibitory effects. Some detriment in biological activity results when the carbamoyl moiety is moved from C-19 to C-17. Furthermore, an acetyl group is not bioisosteric with the carbamate. It appears that configurations of the C-11 and C-17 hydroxyls are important factors in both the interactions with tubulin as well as cell growth inhibition. Most importantly, when the C-19 carbamate

is intact and stereochemistries of C-11 and C-17 match that of the natural product, the left-side lactone moiety of discodermolide can be replaced with some success by simple alkanoyl esters. This raises the possibility that drastically simplified yet still highly active analogues of discodermolide can be identified.

Experimental

Chemistry

General experimental methods. Unless otherwise noted, all the reactions were performed under argon atmosphere. All reagents used in chemical syntheses were purchased from Aldrich Chemical Co. and used without further purification. Nuclear magnetic resonance (^{1}H NMR and ^{13}C 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*) are 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-9000 GC–MS, and high resolution spectra were obtained on a VG 70-G or Micromass Autospec double focusing instrument under EI or fast atom bombardment (FAB)—with NaI or *m*-nitrobenzyl alcohol (MNBA) as a matrix—modes. Optical rotations were recorded on a Perkin–Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as $[\alpha]^{^\circ C}\lambda$ (cg/100 mL). Flash chromatography purifications were done on silica gel (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.

(2*S*,3*S*,4*S*)-(1-*tert*-Butyldimethylsilanyloxy)-2,4-dimethylhex-5-en-3-ol (7). A solution of oxalyl chloride (9.3 mL, 106.4 mmol) in 440 mL of dry dichloromethane was cooled to −78 °C and DMSO (17.74 mL, 248.3 mmol) was added dropwise. After 5 min, a solution of the alcohol **4** (18.1 g, 88.7 mmol) in 90 mL of dichloromethane was slowly added to the solution at −78 °C. The resulting white slurry was stirred for 1 h and then triethylamine (61.83 mL, 443.6 mmol) was slowly added. After 5 min, the white foam was warmed to room temperature, and stirred at that temperature for 1 more hour. Then, the mixture was diluted with dichloromethane (400 mL), washed with ice-cold 0.5 N HCl (800 mL) and with water (600 mL). The aqueous phases were extracted with dichloromethane (3×100 mL), and the combined organic layer was dried over $MgSO_4$ and concentrated to give 15.5 g of (*S*)-3-(*tert*-butyldimethylsilanyloxy)-2-methylpropionaldehyde **5**,[10] as a yellowish oil. The crude aldehyde was used for the next step without further purification.

To a slurry of powdered 4-Å molecular sieves (1.18 g) in 56 mL of dry toluene was added (*R,R*)-diisopropyl tartrate (*E*)-crotylboronate **6**[12] (1.0 M in toluene, 100.2 mL, 100.2 mmol) under argon. After 20 min of stirring at room temperature, the mixture was cooled to −78 °C and then the aldehyde **5** (13.5 g, 66.83 mmol) in toluene (56 mL) was slowly added by syringe. After 3 h at −78 °C, the reaction was quenched with $NaBH_4$ (423 mg) in 6 mL of EtOH and warmed to 0 °C. At this point, 1 N NaOH (180 mL) was added. After stirring vigorously for 30 min, the layers were separated, and the aqueous phase was extracted with ether (5×200 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by chromatography (hexane/ether 19:1) to yield 13.1 g (76%) of the alcohol **7** as a yellowish oil.[9] ^{1}H NMR (300 MHz, $CDCl_3$) 5.84 (ddd, 1H, *J* = 17.3, 10.3, 8.3 Hz), 5.12 (d, 1H, *J* = 17.3 Hz), 5.09 (d, 1H, *J* = 10.3 Hz), 3.77–3.68 (m, 2H), 3.55 (dd, 1H, *J* = 8.7, 2.2 Hz), 2.30–2.23 (m, 1H), 1.84–1.78 (m, 1H), 0.96 (d, 3H, *J* = 7.0 Hz), 0.95 (d, 3H, *J* = 7.0 Hz), 0.90 (s, 9H), 0.07 (s, 6H).

(2*S*,3*S*,4*S*)-1-(*tert*-Butyldimethylsilanyloxy)-3-(4-methoxybenzyloxy)-2,4-dimethylhex-5-ene (8). To an ice-cold suspension of sodium hydride (2.67 g, 95% purity, 106.45 mmol) in 10 mL of THF and 10 mL of DMF was slowly added a solution of the alcohol **7** (8.66 g, 34.34 mmol) in 18 mL of THF. The mixture was stirred for 10 min and then PMBBr (16.31 mL, 89.28 mmol) was added. After being stirred at ambient temperature for 48 h, the reaction mixture was poured into 200 mL of 10× PBS buffer and diluted with 300 mL of diethyl ether. The organic layer was washed with 3×50 mL of 10×PBS buffer, dried over K_2CO_3, concentrated and chromatographed using hexane/ether 19:1 as eluent, to provide 11.5 g (89%) of the PMB ether **8** as a colorless oil.[6a] ^{1}H NMR (300 MHz, $CDCl_3$) 7.27 (d, 2H, *J* = 8.6 Hz), 6.86 (d, 2H, *J* = 8.6 Hz), 5.94 (ddd, 1H, *J* = 17.8, 10.3, 6.9 Hz), 5.07 (d, 1H, *J* = 17.8 Hz), 5.02 (d, 1H, *J* = 10.3 Hz), 4.54 (d, 1H, *J* = 10.7 Hz), 4.47 (d, 1H, *J* = 10.7 Hz), 3.81 (s, 3H), 3.58–3.45 (m, 2H), 3.37 (dd, 1H, *J* = 6.9, 3.9 Hz), 2.47 (ddq, 1H, *J* = 6.9, 6.9, 6.9 Hz), 1.90–1.83 (m, 1H), 1.02 (d, 3H, *J* = 6.9 Hz), 0.92–0.89 (m, 12H), 0.04 (s, 6H).

(2*R*,3*R*,4*S*)-5-(*tert*-Butyldimethylsilanyloxy)-3-(4-methoxybenzyloxy)-2,4-dimethylpentanal (9). To a cooled (−78 °C) solution of 0.5 g (1.32 mmol) of the olefin **8** in 12 mL of MeOH and 4 mL of CH_2Cl_2 containing 0.1 mL of pyridine was bubbled a stream of ozone until the color of the solution became blue. The solution was treated with 3.3 mL of dimethyl sulfide, stirred 30 min at −78 °C and then stirred at room temperature for 3 h. The solution was concentrated under vacuum, diluted with EtOAc (30 mL) and washed with NH_4Cl (20 mL), H_2O (20 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$, and concentrated under vacuum, to yield the aldehyde **9**[6a] (0.5 g) that was used crude in the following reaction. ^{1}H NMR (300 MHz, $CDCl_3$) 9.75 (s, 1H), 7.24 (d, 2H, *J* = 8.6 Hz), 6.87 (d, 2H, *J* = 8.6 Hz), 4.55 (d, 1H, *J* = 10.8 Hz), 4.48 (d, 1H, *J* = 10.8 Hz), 3.86 (dd, 1H, *J* = 7.5, 3.4 Hz), 3.79 (s, 3H), 3.59–3.54 (m, 2H), 2.78–2.70 (m, 1H), 1.91–1.82 (m, 1H), 0.99 (d, 3H, *J* = 6.7 Hz), 0.92 (d, 3H, *J* = 6.9 Hz), 0.91 (s, 9H), 0.06 (s, 6H).

4-(Tetrahydropyran-2-yloxy)-butyl triphenylphosphonium iodide (10). 4-Iodobutan-1-ol, tetrahydropyran-2-yl ether[13] (2.7 g, 9.5 mmol) was dissolved in 5 mL of dry benzene with PPh_3 (7.47 g, 28.50 mmol) and the mixture was heated at 80 °C for 36 h in the dark. The solvent was evaporated, and the residue was chromatographed ($CHCl_3$ to $CHCl_3$/MeOH 19:1) to provide 2.6 g (51%) of the phosphonium salt **10**[13] as a white solid that was azeotropically dried with benzene, and dried under vacuum before using. ^{1}H NMR (300 MHz, $CDCl_3$) 7.87–7.80 (m, 9H), 7.74–7.70 (m, 6H), 4.49 (dd, 1H, J = 6.0, 2.4 Hz), 3.85–3.70 (m, 4H), 3.58–3.42 (m, 2H), 2.04–1.96 (m, 2H), 1.88–1.63 (m, 4H), 1.58–1.36 (m, 4H).

(*Z*)-(2*S*,3*S*,4*S*)-3-(4-Methoxybenzyloxy)-2,4-dimethyl-9-(tetrahydropyran-2-yloxy)non-5-en-1-ol, *tert*-butyldimethylsilyl ether (11). At 0 °C, to a solution of phosphonium salt **10** (1 g, 1.83 mmol) dried with benzene and under vacuum, in THF (1.5 mL) was slowly added NaHMDS (1.0 M in THF, 2 mL, 2 mmol), and the resulting red solution was stirred for 50 min at room temperature. The solution was then cooled to −78 °C, and a solution of the aldehyde **9** (0.5 g, 1.28 mmol) in 1.5 mL of THF was added dropwise. The reaction was stirred for 20 min at −78 °C and warmed to room temperature. After 5 h of stirring at room temperature, the reaction was quenched with saturated NH_4Cl (25 mL) and extracted with ether (3×25 mL). The combined organic layer was washed with saturated NaCl (2×25 mL), dried over $MgSO_4$, and concentrated under vacuum. Flash chromatography of the resulting residue gave 0.55 g (81%) of the Wittig product **11** as a colorless oil. IR (thin film/NaCl) 2928, 1612, 1514, 1249, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.26 (d, 2H, J = 8.5 Hz), 6.86 (d, 2H, J = 8.5 Hz), 5.48–5.34 (m, 2H), 4.57–4.54 (m, 1H), 4.56 (d, 1H, J = 10.6 Hz), 4.45 (d, 1H, J = 10.6 Hz), 3.89–3.81 (m, 1H), 3.80 (s, 3H), 3.75–3.69 (m, 1H), 3.55–3.34 (m, 5H), 2.78 (ddq, 1H, J = 6.8, 6.8, 6.8 Hz), 2.26–2.05 (m, 2H), 1.88–1.82 (m, 2H), 1.76–1.51 (m, 7H), 0.96 (d, 3H, J = 6.8 Hz), 0.92 (d, 3H, J = 6.8 Hz), 0.91 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 158.8, 133.7, 131.7, 129.1, 128.7, 113.5, 98.8, 82.9, 74.1, 67.0, 65.7, 62.2, 55.2, 38.5, 34.9, 30.7, 29.8, 25.9, 25.5, 24.2, 19.6, 18.4, 18.2, 11.4, −5.4; MS (EI, m/z) 520 (M)$^+$, 435, 379, 205, 121; HRMS (EI) calcd for $C_{25}H_{43}O_4Si$ (M−THP)$^+$ 435.2930, found 435.2929.

(2*S*,3*S*,4*S*)-1-(*tert*-Butyldimethylsilanyloxy)-2,4-dimethyl-5-en-3-ol, *tert*-butyldimethyl silyl ether (16). To a cooled (0 °C) solution of 3.50 g (13.56 mmol) of the alcohol **7** in 40 mL of dichloromethane was added 3.77 mL (27.13 mmol) of triethylamine followed by the addition dropwise of TBSOTf (5.38 g, 20.35 mmol). The solution was stirred at 0 °C for 30 min when 40 mL of saturated NaCl was added. The mixture was warmed to ambient temperature, the aqueous phase was separated, and extracted with 3×50 mL of dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by column chromatography (hexane to hexane/ether 19:1) to give 4.9 g (95%) of the silyl ether **16** as a colorless oil. IR (thin film/NaCl) 2927, 2851, 1473, 1251, 1093, 1045, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 5.86 (ddd, 1H, J = 17.1, 10.5, 7.6 Hz), 5.02 (d, 1H, J = 17.1 Hz), 4.99 (d, 1H, J = 10.5 Hz), 3.72 (dd, 1H, J = 5.1, 3.2 Hz), 3.48–3.38 (m, 2H), 2.38 (ddq, 1H, J = 7.6, 6.9, 3.2 Hz), 1.84–1.75 (m, 1H), 1.02 (d, 3H, J = 6.9 Hz), 0.93 (s, 9H), 0.92 (s, 9H), 0.88 (d, 3H, J = 6.9 Hz), 0.08 (s, 6H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 141.7, 113.9, 75.2, 66.0, 43.2, 39.2, 25.8, 17.7, 17.0, 11.7, −4.2, −5.3; MS (EI, m/z) 372 (M)$^+$, 371, 357, 329, 317, 315, 143, 73; HRMS (EI) calcd for $C_{16}H_{37}O_2Si_2$ (M−C_4H_7)$^+$ 317.2332, found 317.2326; $[\alpha]_D^{20}$ +2.0 (*c* 0.75, $CHCl_3$).

(2*S*,3*S*,4*S*)-3-(*tert*-Butyldimethylsilanyloxy)-2,4-dimethyl-hex-5-en-1-ol (17). To a solution of TBS ether **16** (5.0 g, 13.7 mmol) in 60 mL of THF was slowly added HF-pyr/pyr (250 mL, prepared by slow addition of 130 mL of pyridine to 34 mL of THF-pyr at 0 °C followed by dilution with 320 mL of THF) via cannula. The mixture was stirred 12 h at room temperature and then, it was slowly quenched with saturated $NaHCO_3$ (600 mL). The aqueous layer was separated and extracted with dichloromethane (3×300 mL). The combined organic extracts were washed with saturated $CuSO_4$ (3×200 mL), dried over anhydrous $MgSO_4$, and concentrated. Flash chromatography of the crude residue using hexane/ether 3:2 as eluent afforded 3.38 g (95%) of the alcohol **17** as a colorless oil. IR (thin film, NaCl) 3386, 2958, 2885, 1637, 1472, 1359, 1253, 1043 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 5.93 (ddd, 1H, J = 17.1, 10.3, 7.9 Hz), 5.05 (d, 1H, J = 17.1 Hz), 5.01 (d, 1H, J = 10.3 Hz), 3.70–3.63 (m, 2H), 3.48 (dd, 1H, J = 10.5, 5.7 Hz), 2.47–2.37 (m, 1H), 1.96–1.86 (m, 1H), 1.04 (d, 3H, J = 6.9 Hz), 0.92 (s, 9H), 0.89 (d, 3H, J = 6.9 Hz), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 141.5, 114.2, 76.8, 65.5, 42.0, 39.5, 25.9, 18.1, 17.9, 12.2, −4.0, −4.2; MS (EI m/z) 258 (M)$^+$, 257, 243, 227, 203, 159, 145, 119; HRMS (EI) calcd for $C_{14}H_{30}O_2Si$ (M)$^+$ 258.2015, found 258.2021; $[\alpha]_D^{20}$ −0.6 (*c* 0.65, $CHCl_3$).

(2*R*,3*S*,4*S*)-3-(*tert*-Butyldimethylsilanyloxy)-2,4-dimethyl-hex-5-enal (18). To a solution of the alcohol **17** (3.38 g, 13.10 mmol) in 35 mL of dichloromethane at 0 °C was added 7.2 g (17.0 mmol) of Dess–Martin periodinane. The resulting slurry was stirred at room temperature for 1 h, diluted with ether (200 mL), and poured into 100 mL of saturated $NaHCO_3$ and 100 mL of saturated $Na_2S_2O_3$. The layers were separated and the organic layer was washed with saturated $NaHCO_3$ (3×100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated, to yield the aldehyde **18** (3.3 g) that was used crude in the following reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) 9.18 (s, 1H), 5.87–5.75 (m, 1H), 5.04 (d, 1H, J = 10.6 Hz), 5.03 (d, 1H, J = 17.4 Hz), 4.00 (dd, 1H, J = 4.4, 4.4 Hz), 2.63–2.55 (m, 1H), 2.47–2.40 (m, 1H), 1.10 (d, 3H, J = 7.0 Hz), 1.05 (d, 3H, J = 6.9 Hz), 0.90 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H).

(4*R*,5*S*,6*S*,7*S*)-1,6-Bis(*tert*-butyldimethylsilanyloxy)-5,7-dimethylnon-8-en-4-ol (20). A flame-dried 3-neck flask equipped with a reflux condenser was charged with Mg (330 mg, 13.4 mmol), 1,2-dibromoethane (0.1 mL), and

THF (2.0 mL). The mixture was briefly heated at 50 °C and cooled to room temperature. At this point, a solution of (3-bromopropoxy)-*tert*-butyldimethylsilane[22] (2.71 g, 10.8 mmol) in 50 mL of THF was slowly added, and the resulting gray mixture was stirred for 1 h at ambient temperature. A solution of the crude aldehyde **18** (8.98 mmol) in 20 mL of THF was then slowly added to the mixture. After 10 h of stirring, the reaction was diluted with ether (30 mL) and quenched with saturated NH_4Cl (100 mL). The separated aqueous layer was extracted with ether (3×100 mL), and the combined organics were washed with saturated NaCl (2×100 mL) and dried over $MgSO_4$. Chromatography of the residue (hexane/ether 19:1) afforded 950 mg (24%) of the less polar alcohol **21** and 1.83 g (48%) of the more polar alcohol **20**. IR (thin film, NaCl) 2978, 2935, 1613, 1383, 1123, 845 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 5.93 (ddd, 1H, $J=17.2$, 11.6, 7.7 Hz), 5.04 (d, 1H, $J=17.2$ Hz), 5.02 (d, 1H, $J=11.6$ Hz), 3.73–3.65 (m, 4H), 2.47 (ddq, 1H, $J=7.7$, 6.9, 3.7 Hz), 2.36 (bs, 1H), 1.68–1.51 (m, 5H), 1.05 (d, 3H, $J=6.9$ Hz), 0.93 (s, 9H), 0.92 (d, 3H, $J=7.0$ Hz), 0.91 (s, 9H), 0.08 (s, 6H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 141.7, 114.8, 78.5, 72.4, 63.6, 42.6, 41.7, 32.5, 29.9, 26.3, 26.2, 18.5, 17.5, 9.6, −3.4, −3.8, −5.1; MS (EI, *m*/*z*) 430 $(M)^+$, 261, 203, 185, 145, 107, 75; HRMS (FAB) calcd for $C_{23}H_{51}O_3Si_2$ $(M+H)^+$ 431.3376, found 431.3378; $[\alpha]_D^{20}+0.7$ (*c* 1.09, $CHCl_3$).

(4*S*,5*S*,6*S*,7*S*)-1,6-Bis(tert-butyldimethylsilanyloxy)-5,7-dimethylnon-8-en-4-ol (21). IR (thin film, NaCl) 2980, 1614, 1444, 1382, 1126, 845 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 5.98 (ddd, 1H, $J=17.3$, 10.3, 7.9 Hz), 5.04 (d, 1H, $J=17.3$ Hz), 5.00 (d, 1H, $J=10.3$ Hz), 3.84 (dd, 1H, $J=4.2$, 2.5 Hz), 3.72–3.66 (m, 3H), 3.46 (bs, 1H), 2.52–2.42 (m, 1H), 1.74–1.62 (m, 4H), 1.37–1.30 (m, 1H), 1.04 (d, 3H, $J=7.0$ Hz), 0.92 (s, 9H), 0.90 (s, 9H), 0.84 (d, 3H, $J=7.0$ Hz), 0.11 (s, 3H), 0.08 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 141.8, 114.5, 78.5, 72.8, 63.7, 42.8, 41.9, 31.9, 28.5, 26.3, 26.2, 18.9, 18.5, 12.8, −3.8, −4.0, −5.1; MS (EI, *m*/*z*) 430 $(M)^+$, 241, 185, 149, 107, 75; $[\alpha]_D^{20}$ −14.6 (*c* 0.675, $CHCl_3$).

(4*R*,5*S*,6*S*,7*S*)-1,6-Bis(*tert*-butyldimethylsilanyloxy)-5,7-dimethylnon-8-en-4-ol, 4-methoxybenzyl ether (22). To a solution of the alcohol **20** (1.01 g, 2.35 mmol) and *p*-methoxybenzyltrichloroacetimidate (1.31 g, 4.65 mmol) in 15 mL of ether at −10 °C was added dropwise triflic acid (0.3 mol%, 0.25 mL of a 0.028 N solution in Et_2O). After 24 h at room temperature, a second allotment of acetimidate was added (1.31 g) and after 48 h, the reaction was quenched with saturated $NaHCO_3$ (30 mL). The aqueous phase was extracted with ether (3×25 mL) and the combined organic layers were washed with brine (2×25 mL). After drying over $MgSO_4$ and concentration, the residue was purified by chromatography (hexane/ether 9:1) to give 0.90 g (69%) of the PMB ether **22**. IR (thin film, NaCl) 2942, 2857, 1613, 1514, 1463, 1250, 1098, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.26 (d, 2H, $J=8.8$ Hz), 6.89 (d, 2H, $J=8.8$ Hz), 5.83 (ddd, 1H, $J=17.7$, 10.3, 7.6 Hz), 4.98 (d, 1H, $J=10.3$ Hz), 4.96 (d, 1H, $J=17.7$ Hz), 4.45 (d, 1H, $J=11.1$ Hz), 4.37 (d, 1H, $J=11.1$ Hz), 3.82 (s, 3H), 3.64–3.57 (m, 3H), 3.30 (dt, 1H, $J=5.3$, 5.3 Hz), 2.34–2.26 (m, 1H), 1.84–1.74 (m, 1H), 1.65–1.44 (m, 4H), 0.93 (d, 3H, $J=7.2$ Hz), 0.91–0.90 (m, 21H), 0.05 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.2, 141.3, 131.1, 129.4, 114.3, 113.7, 79.9, 75.7, 70.9, 63.2, 55.2, 43.0, 38.8, 30.3, 29.7, 28.9, 27.1, 26.2, 26.0, 16.9, 11.0, −3.4, −3.7, −5.3; MS (EI, *m*/*z*) 550 (M^+), 535, 493, 373, 225, 199, 122; HRMS (EI) calcd for $C_{27}H_{49}O_4Si_2$ $(M-{}^tBu)^+$ 493.3169, found 493.3168; $[\alpha]_D^{20}$ −9.4 (*c* 0.875, $CHCl_3$).

(2*R*,3*R*,4*S*,5*R*)-3,8-Bis(*tert*-butyldimethylsilanyloxy)-5-(4-methoxybenzyloxy)-2,4-dimethyloctanal (23). To a cooled (−78 °C) solution of the alkene **22** (895 mg, 1.63 mmol) in 24 mL of MeOH and 8 mL of dichloromethane containing 0.2 mL of pyridine was bubbled a stream of ozone until the color of the solution became blue. The solution was treated with 6 mL of dimethyl sulfide, stirred for 30 min at −78 °C and then 3 h at room temperature. The solution was concentrated under vacuum, diluted with EtOAc (75 mL) and washed with saturated NH_4Cl (50 mL), H_2O (50 mL) and brine (50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum, to give the aldehyde **23**, which was used immediately without further purification. ^1H NMR (300 MHz, $CDCl_3$) 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).

(*Z*)-(4*R*,5*S*,6*S*,7*S*)-1,6-Bis(*tert*-butyldimethylsilanyloxy)-5,7-dimethylundeca-8,10-dien-4-ol, 4-methoxybenzyl ether (25). To a solution of aldehyde **23** (1.63 mmol) in THF (25 mL) was added (1-bromoallyl)-trimethylsilane **24**[18a] (1.57 g, 8.13 mmol). The mixture was added to a suspension of $CrCl_2$ (1.66 g, 13.50 mmol) in 16 mL of THF via cannula and stirred at room temperature for 16 h. The solvent was removed in vacuo, and the brownish residue was taken up in a minimal amount of ether. The chromium salts were precipitated with hexane and the mixture was filtered through a short pad of Celite washing with hexane (300 mL). The filtrate was concentrated, and the oily brown residue was used immediately for the next reaction. This product (1.63 mmol) in THF (40 mL) was cooled to 0 °C, and NaH (411 mg, 95% purity, 16.3 mmol) was added in one portion. The ice bath was removed after 15 min, and the mixture was stirred for 1 h at room temperature, at which time another portion of NaH (411 mg) was added. The resulting suspension was stirred for an additional 2 h, cooled to 0 °C, quenched carefully with H_2O (50 mL), and extracted with ether (3×50 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (hexane/ether 9:1) to afford the *cis*-diene **25** as a colorless oil (0.71 g, 76% overall yield for three steps from olefin **22**). IR (thin film, NaCl) 2954, 2931, 2857, 1608, 1513, 1463, 1251, 1098, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.26 (d, 2H, $J=8.6$ Hz), 6.89 (d, 2H, $J=8.6$ Hz), 6.41 (ddd, 1H, $J=16.7$, 11.0, 10.1 Hz), 5.97 (dd, 1H, $J=11.0$, 11.0 Hz), 5.50 (dd, 1H,

$J=10.3$, 10.3 Hz), 5.15 (dd, 1H, $J=16.7$, 1.8 Hz), 5.06 (d, 1H, $J=10.1$ Hz), 4.51 (d, 1H, $J=11.4$ Hz), 4.35 (d, 1H, $J=11.4$ 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; MS (EI, *m/z*) 576 (M^+), 519, 467, 387, 357, 293, 225, 121; HRMS (EI) calcd for $C_{29}H_{51}O_4Si_2$ $(M-{}^tBu)^+$ 519.3326, found 519.3332; $[\alpha]_D^{20}$ −18.8 (*c* 0.75, $CHCl_3$).

(*Z*)-(2*S*,3*S*,4*S*)-3-(4-Methoxybenzyloxy)-2,4-dimethyl-9-(tetrahydropyran-2-yl-oxy)-non-5-en-1-ol (26). To a solution of 0.69 g (1.32 mmol) of **11** in 88 mL of dry THF, was added slowly TBAF (1.0 M in THF, 13.2 mL, 13.2 mmol). The mixture was stirred at room temperature for 1 h, quenched with saturated NaCl (100 mL) and extracted with EtOAc (3×100 mL). The combined organic layer was washed with water (100 mL), brine (100 mL), dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by chromatography (hexane/EtOAc 4:1 to hexane/EtOAc 1:1) to yield the alcohol **26** as a colorless oil (0.48 g, 89%). IR (thin film/NaCl) 3436, 2939, 1613, 1514, 1248, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.26 (d, 2H, $J=8.6$ Hz), 6.86 (d, 2H, $J=8.6$ Hz), 5.52–5.35 (m, 2H), 4.58 (d, 1H, $J=10.8$ Hz), 4.56–4.53 (m, 1H), 4.46 (d, 1H, $J=10.8$ Hz), 3.89–3.81 (m, 1H), 3.79 (s, 3H), 3.78–3.69 (m, 1H), 3.60 (dd, 1H, $J=10.6$, 6.9 Hz), 3.52–3.47 (m, 2H), 3.43–3.33 (m, 2H), 2.82 (ddq, 1H, $J=6.9$, 4.2, 2.3 Hz), 2.16–2.04 (m, 3H), 1.97–1.91 (m, 1H), 1.86–1.80 (m, 1H), 1.70–1.63 (m, 3H), 1.58–1.49 (m, 3H), 0.97 (d, 3H, $J=6.9$ Hz), 0.95 (d, 3H, $J=6.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 159.0, 133.3, 130.9, 129.3, 128.9, 113.6, 98.7, 84.1, 73.7, 66.9, 66.0, 62.3, 55.1, 37.6, 34.4, 30.7, 29.6, 25.4, 24.2, 19.6, 18.5, 11.5; MS (EI, *m/z*) 406 $(M)^+$, 321, 205, 121; HRMS (EI) calcd for $C_{24}H_{38}O_5$ $(M)^+$ 406.2719, found 406.2718.

(*Z*)-(2*R*,3*S*,4*S*)-3-(4-Methoxybenzyloxy)-2,4-dimethyl-9-(tetrahydropyran-2-yl-oxy)-non-5-enal (27). To a solution of 0.15 g (0.36 mmol) of the alcohol **26** in 5 mL of CH_2Cl_2 at 0 °C was added Dess–Martin periodinane (0.2 g, 0.47 mmol). The mixture was stirred at room temperature for 1 h, then poured into 10 mL of saturated $NaHCO_3$ and 10 mL of saturated $Na_2S_2O_3$, and diluted with 20 mL of ether. The organic layer was washed with saturated $NaHCO_3$ (2×10 mL), dried over $MgSO_4$ and concentrated under vacuum, to provide 0.13 g of the aldehyde, that was used crude in the following reaction. ^{1}H NMR (300 MHz, $CDCl_3$) 9.72 (s, 1H), 7.24 (d, 2H, $J=8.5$ Hz), 6.88 (d, 2H, $J=8.6$ Hz), 5.44–5.39 (m, 2H), 4.57–4.54 (m, 1H), 4.53 (d, 1H, $J=10.9$ Hz), 4.47 (d, 1H, $J=10.9$ Hz), 3.88–3.84 (m, 1H), 3.81 (s, 3H), 3.77–3.72 (m, 1H), 3.69 (dd, 1H, $J=5.0$, 5.0 Hz), 3.52–3.35 (m, 2H), 2.88–2.73 (m, 1H), 2.64–2.55 (m, 1H), 2.22–1.97 (m, 2H), 1.89–1.52 (m, 8H), 1.17 (d, 3H, $J=7.0$ Hz), 1.04 (d, 3H, $J=6.9$ Hz).

(*Z*)-(4*R*,5*S*,6*S*,7*S*)-6-(*tert*-Butyldimethylsilanyloxy)-4-(4-methoxybenzyloxy)-5,7-dimethylundeca-8,10-dien-1-ol (28). To a solution of TBS ether **25** (0.68 g, 1.18 mmol) in THF (2.5 mL) was slowly added HF-pyr/pyr (21.7 mL, prepared by slow addition of 6.5 mL of pyridine to 1.66 mL of THF-pyr at 0 °C followed by dilution with 16.0 mL of THF) via cannula. The mixture was stirred for 12 h at room temperature and then it was slowly quenched with saturated $NaHCO_3$ (50 mL). The aqueous layer was separated and extracted with dichloromethane (3×50 mL). The combined organic extracts were washed with saturated $CuSO_4$ (3×50 mL), dried over anhydrous $MgSO_4$, and concentrated. Flash chromatography of the crude residue using hexane/ether 3:7 as eluent afforded 0.46 g (85%) of the alcohol **28** as a colorless oil. IR (thin film, NaCl) 3385, 2929, 2859, 1612, 1513, 1462, 1248, 1042 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.26 (d, 2H, $J=8.6$ Hz), 6.89 (d, 2H, $J=8.6$ Hz), 6.43 (ddd, 1H, $J=16.6$, 11.0, 10.2 Hz), 5.98 (dd, 1H, $J=11.0$, 11.0 Hz), 5.50 (dd, 1H, $J=10.4$, 10.4 Hz), 5.17 (d, 1H, $J=16.6$ Hz), 5.07 (d, 1H, $J=10.2$ Hz), 4.49 (d, 1H, $J=11.3$ Hz), 4.38 (d, 1H, $J=11.3$ Hz), 3.82 (s, 3H), 3.63–3.58 (m, 3H), 3.30 (dt, 1H, $J=5.3$, 5.3 Hz), 2.73 (ddq, 1H, $J=10.4$, 6.9, 3.3 Hz), 1.79–1.71 (m, 1H), 1.66–1.47 (m, 4H), 0.95 (d, 3H, $J=6.9$ Hz), 0.94 (d, 3H, $J=6.9$ Hz), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.1, 134.9, 132.4, 130.7, 129.6, 128.9, 117.2, 113.7, 79.0, 76.3, 70.9, 62.9, 55.2, 39.7, 36.5, 28.6, 27.2, 26.2, 18.7, 18.4, 11.0, −3.3, −3.5; MS (EI, *m/z*) 462 (M^+), 405, 345, 225, 173, 137, 122, 73; HRMS (EI) calcd for $C_{23}H_{37}O_4Si$ $(M-{}^tBu)^+$ 405.2461, found 405.2456; $[\alpha]_D^{20}$ −18.7 (*c* 0.9, $CHCl_3$).

(*Z*)-(5*S*,6*S*,7*S*,8*R*)-11-Iodo-8-(4-methoxybenzyloxy)-5,7-dimethylundeca-1,3-dien-6-ol, *tert*-butyldimethylsilyl ether (29). To a solution of the alcohol **28** (0.33 g, 0.71 mmol) in 5 mL of benzene and 10 mL of diethyl ether, was added PPh_3 (0.28 g, 1.07 mmol) and imidazole (73 mg, 1.07 mmol) until complete dissolution. Then iodine (0.27 g, 1.07 mmol) was added at room temperature, and the resulting mixture was stirred in the dark at room temperature for 1 h. The reaction was diluted with ether (25 mL) and washed with saturated $Na_2S_2O_3$ (3×20 mL), H_2O (25 mL) and saturated NaCl (25 mL). The organic layer was dried over anhydrous $MgSO_4$, concentrated and purified by column chromatography (hexane/EtOAc 19:1) to provide 360 mg (89%) of the iodide **29** as a colorless oil. IR (thin film, NaCl) 2940, 2923, 2851, 1612, 1509, 1465, 1299, 1247, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.27 (d, 2H, $J=8.6$ Hz), 6.90 (d, 2H, $J=8.6$ Hz), 6.39 (ddd, 1H, $J=16.9$, 11.0, 10.1 Hz), 5.98 (dd, 1H, $J=11.0$, 11.0 Hz), 5.50 (dd, 1H, $J=10.4$, 10.4 Hz), 5.18 (dd, 1H, $J=16.9$, 1.5 Hz), 5.09 (d, 1H, $J=10.1$ Hz), 4.49 (d, 1H, $J=11.4$ Hz), 4.37 (d, 1H, $J=11.4$ Hz), 3.81 (s, 3H), 3.60 (dd, 1H, $J=5.8$, 3.4 Hz), 3.28 (dt, 1H, $J=5.4$, 5.4 Hz), 3.14 (t, 2H, $J=6.2$ Hz), 2.69 (ddq, 1H, $J=10.4$, 6.8, 3.2 Hz), 1.81–1.64 (m, 5H), 0.96 (d, 3H, $J=6.8$ Hz), 0.94 (d, 3H, $J=6.8$ Hz), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.1, 134.6, 132.3, 130.6, 129.6, 128.9, 117.4, 113.7, 77.8, 76.3, 70.7, 55.2, 39.8, 36.3, 31.6, 29.2, 26.2, 22.6, 18.8, 18.4, 11.1, 7.4, −3.3, −3.4; MS (EI, *m/z*) 572 (M^+), 515, 491, 440, 355, 293, 225, 172, 137, 122; HRMS (EI) calcd for $C_{23}H_{36}IO_3Si$ $(M-{}^tBu)^+$ 515.1478, found 515.1471; $[\alpha]_D^{20}$ −22.0 (*c* 0.7, $CHCl_3$).

(*Z*)-(4*R*,5*S*,6*S*,7*S*)-[6-(*tert*-Butyldimethylsilanyloxy)-4-(4-methoxybenzyloxy)-5,7-dimethylundeca-8,10-dienyl]-triphenylphosphonium iodide (30). A mixture of the iodide **29** (0.34 g, 0.59 mmol) and triphenylphosphine (0.78 g, 2.90 mmol) in 2 mL of benzene was heated at 80 °C for 40 h in the dark. The solvent was evaporated under vacuum, and the residue was chromatographed ($CHCl_3$ to $CHCl_3$/MeOH 19:1) to give 0.39 g (80%) of the phosphonium salt **30** as a white solid which was dried azeotropically with benzene, and dried under vacuum before its use. Mp 121–123 °C; IR (thin film, NaCl) 2928, 2856, 1611, 1512, 1462, 1438, 1249, 1132, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.84–7.65 (m, 15H), 7.25 (d, 2H, $J=8.6$ Hz), 6.80 (d, 2H, $J=8.6$ Hz), 6.29 (ddd, 1H, $J=16.8$, 11.0, 10.1 Hz), 5.76 (dd, 1H, $J=11.0$, 11.0 Hz), 5.40 (dd, 1H, $J=10.3$, 10.3 Hz), 4.93 (d, 1H, $J=16.8$ Hz), 4.89 (d, 1H, $J=10.1$ Hz), 4.48–4.40 (m, 2H), 3.77 (s, 3H), 3.65–3.48 (m, 3H), 3.31 (dt, 1H, $J=5.5$, 5.5 Hz), 2.68–2.58 (m, 1H), 2.06–1.88 (m, 2H), 1.63–1.48 (m, 3H), 0.88 (d, 3H, $J=6.9$ Hz), 0.87 (s, 9H), 0.84 (d, 3H, $J=7.0$ Hz), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 158.6, 134.7, 134.6, 133.2, 133.1, 131.8, 131.6, 131.4, 130.1, 130.0, 129.5, 129.2, 128.3, 128.1, 128.0, 118.0, 116.9, 116.8, 113.1, 77.2, 75.5, 69.9, 54.9, 38.9, 35.9, 30.3, 25.7, 22.7, 22.0, 18.3, 17.9, 10.6, −3.6, −3.8; MS (EI, *m*/*z*) 707 $(M-I)^+$, 659, 608, 515, 440; $[\alpha]_D^{20}$ −20.0 (*c* 0.695, $CHCl_3$).

(*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*R*,14*S*,15*S*,16*S*)-15-(*tert*-Butyldimethylsilanyloxy)-7,13-bis(4-methoxybenzyloxy)-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraen-1-ol, tetrahydropyran-2-yl ether (31). To an ice-cold solution of the phosphonium salt **30** (0.38 g, 0.46 mmol) in 0.5 mL of dry THF was slowly added NaHMDS (1.0 M in THF, 0.41 mL, 0.41 mmol) and the resulting red solution was stirred at room temperature for 45 min. The mixture was then cooled to −78 °C and a solution of the aldehyde **27** (0.13 g, 0.32 mmol) in 1 mL of THF was added dropwise. The reaction was stirred for 20 min at −78 °C and warmed to room temperature. After 12 h at ambient temperature, the reaction was quenched with saturated NH_4Cl (10 mL) and extracted with ether (3×10 mL). The combined organics were washed with saturated NaCl (2×10 mL), dried over anhydrous $MgSO_4$, concentrated and chromatographed (hexane/ether 9:1) to give 0.214 g (80%) of the Wittig product **31** as a colorless oil. IR (thin film, NaCl) 2954, 2857, 1613, 1514, 1463, 1248, 1119, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.31–7.25 (m, 4H), 6.90 (d, 2H, $J=8.7$ Hz), 6.88 (d, 2H, $J=8.7$ Hz), 6.42 (ddd, 1H, $J=16.8$, 11.0, 10.1 Hz), 5.97 (dd, 1H, $J=11.0$, 11.0 Hz), 5.54–5.45 (m, 2H), 5.40–5.27 (m, 3H), 5.16 (d, 1H, $J=16.8$ Hz), 5.07 (d, 1H, $J=10.1$ Hz), 4.60–4.49 (m, 4H), 4.35 (d, 1H, $J=11.4$ Hz), 3.89–3.84 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.78–3.70 (m, 1H), 3.59 (dd, 1H, $J=6.1$, 3.2 Hz), 3.53–3.46 (m, 1H), 3.41–3.32 (m, 1H), 3.28 (dt, 1H, $J=5.8$, 5.8 Hz), 3.07 (dd, 1H, $J=7.3$, 3.9 Hz), 2.80–2.60 (m, 3H), 2.18–1.80 (m, 4H), 1.74–1.52 (m, 11H), 1.03 (d, 6H, $J=6.7$ Hz), 0.95–0.92 (m, 15H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.1, 159.0, 134.6, 133.6, 132.6, 132.3, 131.3, 130.9, 129.5, 129.0, 128.9, 128.8, 128.4, 117.1, 113.6, 113.5, 98.7, 87.9, 78.7, 76.5, 74.6, 70.7, 67.0, 66.9, 62.2, 55.2, 39.8, 36.4, 35.5, 35.1, 31.2, 30.7, 29.8, 29.6, 26.2, 25.4, 24.1, 23.6, 19.6, 18.8, 18.5, 17.3, 10.9, −3.3, −3.4; MS (EI, *m*/*z*) 832 (M^+), 751, 635, 549, 495, 457, 373, 345, 121. HRMS (EI) calcd for $C_{47}H_{71}O_7Si$ $(M-C_4H_9)^+$ 775.4969, found 775.4980.

(*Z*,*Z*,*Z*)-(5*S*,6*S*,7*S*,8*R*,13*S*,14*S*,15*S*)-8,14-Bis(4-methoxybenzyloxy)-5,7,13,15-tetramethyl-20-(tetrahydropyran-2-yloxy)eicosa-1,3,11,16-tetraen-6-ol (35). To a solution of 49 mg (0.06 mmol) of **31** in THF (7 mL) was added TBAF (1.0 M in THF, 0.6 mL, 0.6 mmol) and the resulting yellowish solution was stirred 24 h at room temperature. The reaction was quenched with saturated NaCl (25 mL) and the aqueous layer was extracted with EtOAc (3×25 mL). The combined organic layer was dried over $MgSO_4$, and concentrated under vacuum. Flash chromatography of the residue using hexane/ether 1:1 as eluent gave 36 mg (84%) of the alcohol **35**. IR (thin film, NaCl) 3437, 2948, 2865, 1611, 1514, 1453, 1363, 1247, 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.26 (d, 2H, $J=8.5$ Hz), 7.23 (d, 2H, $J=8.5$ Hz), 6.87 (d, 2H, $J=8.5$ Hz), 6.84 (d, 2H, $J=8.6$ Hz), 6.60 (ddd, 1H, $J=16.9$, 11.0, 10.3 Hz), 6.09 (dd, 1H, $J=11.0$, 11.0 Hz), 5.48 (dd, 1H, $J=10.3$, 10.3 Hz), 5.42–5.26 (m, 4H), 5.20 (d, 1H, $J=16.9$ Hz), 5.10 (d, 1H, $J=10.3$ Hz), 4.59–4.48 (m, 4H), 4.35 (d, 1H, $J=10.9$ Hz), 3.87–3.78 (m, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.74–3.66 (m, 1H), 3.51–3.43 (m, 3H), 3.40–3.31 (m, 1H), 3.06 (dd, 1H, $J=7.6$, 3.7 Hz), 2.84 (s, 1H), 2.81–2.70 (m, 2H), 2.68–2.60 (m, 1H), 2.20–1.93 (m, 4H), 1.82–1.77 (m, 2H), 1.68–1.50 (m, 9H), 1.02 (d, 6H, $J=6.7$ Hz), 0.97 (d, 3H, $J=7.0$ Hz), 0.91 (d, 3H, $J=6.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 159.2, 159.1, 135.7, 134.0, 132.6, 132.4, 131.3, 130.3, 130.1, 129.5, 129.2, 129.0, 128.3, 117.9, 113.9, 113.7, 98.8, 88.0, 83.0, 78.1, 74.8, 70.9, 67.2, 67.1, 62.4, 55.3, 36.6, 36.2, 35.9, 35.3, 30.8, 30.5, 29.9, 25.5, 24.2, 23.7, 19.7, 18.8, 17.6, 17.4, 6.8. MS (EI) 718 $(M)^+$, 633, 492, 474; HRMS (EI) calcd for $C_{45}H_{66}O_7$ $(M)^+$ 718.4809, found 718.4815.

Carbamic acid, (*Z*,*Z*)-(1*S*,2*S*,3*R*,8*S*,9*S*,10*S*)-3,9-bis(4-methoxybenzyloxy)-2,8,10-trimethyl-1-[(*Z*)-(*S*)-1-methylpenta-2,4-dienyl]-15-(tetrahydropyran-2-yloxy)pentadeca-6,11-dienyl ester (36). To a solution of 36 mg (50 μmol) of the alcohol **35** in 3 mL of dichloromethane was added trichloroacetylisocyanate (8 μL, 65 μmol) and the mixture was stirred for 30 min at room temperature. Alumina (neutral, Brockmann I, activated, 390 mg) was then added to the reaction mixture, and the resulting suspension was stirred at room temperature for 6 h. The mixture was filtered through a short pad of silica gel washing with EtOAc, and the filtrate was concentrated under vacuum and chromatographed (CH_2Cl_2/EtOAc 9:1) to afford 34 mg (89%) of the carbamate **36** as a colorless oil. IR (thin film, NaCl) 3356, 3318, 2933, 2870, 1728, 1162, 1513, 1248, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.31–7.27 (m, 4H), 6.91 (d, 2H, $J=8.9$ Hz), 6.89 (d, 2H, $J=8.9$ Hz), 6.38 (ddd, 1H, $J=16.9$, 11.0, 10.1 Hz), 6.00 (dd, 1H, $J=11.0$, 11.0 Hz), 5.48 (dd, 1H, $J=11.0$, 10.0 Hz), 5.40–5.25 (m, 4H), 5.19 (dd, 1H, $J=16.9$, 1.8 Hz), 5.08 (d, 1H, $J=10.1$ Hz), 4.83 (dd, 1H, $J=5.9$, 5.9 Hz), 4.60–4.47 (m, 6H), 4.36 (d, 1H, $J=11.4$ Hz), 3.90–3.83 (m, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.79–3.69 (m, 1H), 3.54–3.47 (m, 1H), 3.43–3.35

(m, 1H), 3.25 (dt, 1H, $J=5.5$, 5.5 Hz), 3.07 (dd, 1H, $J=7.6$, 3.8 Hz), 2.82–2.72 (m, 2H), 2.67–2.58 (m, 1H), 2.13–1.81 (m, 5H), 1.72–1.50 (m, 10H), 1.04 (d, 3H, $J=6.7$ Hz), 1.03 (d, 3H, $J=6.9$ Hz), 0.98 (d, 3H, $J=6.9$ Hz), 0.94 (d, 3H, $J=6.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 159.1, 159.0, 157.1, 133.6, 133.2, 132.5, 132.1, 131.3, 130.8, 129.7, 129.5, 129.1, 128.8, 128.4, 117.6, 113.7, 113.6, 99.8, 87.9, 78.2, 74.7, 70.5, 67.1, 67.0, 62.2, 55.2, 37.5, 35.7, 35.1, 34.2, 30.7, 30.5, 29.8, 25.4, 24.1, 23.5, 19.6, 18.6, 17.7, 17.4, 9.6; MS (EI, *m/z*) 761 (M^+), 676, 540, 504; HRMS (EI) calcd for $C_{46}H_{67}NO_8$ $(M)^+$ 761.4867, found 761.4870.

Carbamic acid, (*Z*,*Z*)-(1*S*,2*S*,3*R*,8*S*,9*S*,10*S*)-15-hydroxy-3,9-bis(4-methoxybenzyloxy)-2,8,10-trimethyl-1-[(*Z*)-(*S*)-1-methylpenta-2,4-dienyl]pentadeca-6,11-dienyl ester (37). To a solution of the THP ether **36** (30 mg, 39 μmol) in 3 mL of EtOH was added PPTS (0.039 M solution in EtOH, 0.150 mL, 5.9 μmol). The mixture was heated at 55 °C. After 8 h, the solution was concentrated under vacuum, and the residue was purified by chromatography using CH_2Cl_2/EtOAc 3:2 as eluent, to provide 25 mg (93%) of the alcohol **37**. IR (thin film, NaCl) 3357, 2960, 2870, 1720, 1612, 1514, 1323, 1248, 1038 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.29 (d, 2H, $J=8.6$ Hz), 7.28 (d, 2H, $J=8.6$ Hz), 6.88 (d, 2H, $J=8.7$ Hz), 6.87 (d, 2H, $J=8.7$ Hz), 6.41 (ddd, 1H, $J=16.8$, 11.0, 10.1 Hz), 5.99 (dd, 1H, $J=11.0$, 11.0 Hz), 5.48 (dd, 1H, $J=11.0$, 9.7 Hz), 5.38–5.27 (m, 4H), 5.18 (dd, 1H, $J=16.8$, 1.9 Hz), 5.07 (d, 1H, $J=10.1$ Hz), 4.80 (dd, 1H, $J=5.9$, 5.9 Hz), 4.56–4.47 (m, 5H), 4.37 (d, 1H, $J=11.3$ Hz), 3.81 (s, 3H), 3.79 (s, 3H), 3.54 (t, 2H, $J=6.2$ Hz), 3.23 (dt, 1H, $J=5.7$, 5.7 Hz), 3.07 (dd, 1H, $J=7.0$, 4.5 Hz), 2.84–2.71 (m, 2H), 2.66–2.58 (m, 1H), 2.13–1.83 (m, 5H), 1.70–1.51 (m, 4H), 1.03 (d, 3H, $J=6.5$ Hz), 1.01 (d, 3H, $J=6.7$ Hz), 0.98 (d, 3H, $J=6.9$ Hz), 0.93 (d, 3H, $J=6.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 159.1, 159.0, 156.9, 133.6, 133.4, 132.8, 132.2, 131.1, 130.8, 129.8, 129.5, 129.2, 128.7, 128.6, 117.7, 113.7, 113.6, 87.9, 78.7, 78.2, 77.1, 75.0, 70.8, 62.0, 55.3, 37.7, 35.6, 35.3, 34.4, 32.4, 30.7, 23.6, 23.5, 18.9, 17.7, 16.9, 9.8; MS (FAB in MNBA/NaCl, *m/z*) 700 $(M+Na)^+$, 678 $(M+H)^+$, 645; HRMS (FAB) calcd for $C_{41}H_{60}NO_7$ $(M+H)^+$ 678.4370, found 678.4368; $[\alpha]_D^{20}$ +45.4 (*c* 0.65, $CHCl_3$).

General procedure for the synthesis of (17*R*,19*S*)-carbamoyloxy analogues of discodermolide

To a solution of the alcohol **37** (10 μmol) in 1 mL of dichloromethane was added pyridine (50 μmol) followed by the corresponding acyl chloride (30 μmol). The mixture was stirred at room temperature for the required time, concentrated under vacuum and purified by column chromatography (CH_2Cl_2 to CH_2Cl_2/EtOAc 9:1) to afford the corresponding esters.

To the esters obtained (10 μmol) in 1 mL of dichloromethane, was added $NaHCO_3$ (40 mg) and DDQ (30 μmol). The mixture was stirred at room temperature for 1 h, concentrated and the crude residue was purified by chromatography to provide the *(17R,19S)-carbamoyloxy* analogues of discodermolide.

Benzoic acid, (*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*R*,14*S*,15*S*,16*S*)-15-carbamoyloxy-7,13-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (38). Following the general procedure, a mixture of 3.5 mg (5.1 μmol) of the alcohol **37**, pyridine and benzoyl chloride was stirred for 16 h. After concentration and purification, the corresponding *benzoic acid, (Z,Z,Z)-(6S,7S,8S,13R,14S,15S,16S)-15-carbamoyloxy-7,13-bis(4-methoxybenzyloxy)-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester* was obtained.

^{1}H NMR (300 MHz, $CDCl_3$) 8.04 (d, 2H, $J=8.5$ Hz), 7.53–7.41 (m, 3H), 7.29–7.26 (m, 4H), 6.88 (d, 2H, $J=8.6$ Hz), 6.86 (d, 2H, $J=8.6$ Hz), 6.36 (ddd, 1H, $J=16.8$, 11.0, 10.1 Hz), 5.98 (dd, 1H, $J=11.0$, 11.0 Hz), 5.52 (dd, 1H, $J=11.0$, 9.8 Hz), 5.40–5.24 (m, 4H), 5.17 (d, 1H, $J=16.8$ Hz), 5.06 (d, 1H, $J=10.1$ Hz), 4.81 (dd, 1H, $J=5.9$, 5.9 Hz), 4.59 (bs, 2H), 4.57–4.48 (m, 3H), 4.34 (d, 1H, $J=11.5$ Hz), 4.29 (t, 2H, $J=6.6$ Hz), 3.80 (s, 3H), 3.79 (s, 3H), 3.23 (dt, 1H, $J=5.7$, 5.7 Hz), 3.05 (dd, 1H, $J=7.4$, 4.0 Hz), 2.81–2.69 (m, 2H), 2.64–2.57 (m, 1H), 2.29–2.16 (m, 2H), 2.12–1.74 (m, 5H), 1.69–1.52 (m, 2H), 1.02 (d, 3H, $J=6.7$ Hz), 1.01 (d, 3H, $J=6.9$ Hz), 0.96 (d, 3H, $J=6.9$ Hz), 0.92 (d, 3H, $J=6.8$ Hz).

To the ester above obtained (3.0 mg, 3.8 μmol) was added $NaHCO_3$ and DDQ, Chromatography of the crude residue using CH_2Cl_2 to CH_2Cl_2/EtOAc 1:1 as eluent, gave 1.9 mg (95%) of the analogue **38** as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) 8.06 (d, 2H, $J=7.4$ Hz), 7.61–7.55 (m, 1H), 7.48–7.43 (m, 2H), 6.61 (ddd, 1H, $J=16.7$, 11.0, 10.1 Hz), 6.05 (dd, 1H, $J=11.0$, 11.0 Hz), 5.57–5.49 (m, 1H), 5.42–5.31 (m, 4H), 5.23 (d, 1H, $J=16.7$ Hz), 5.13 (d, 1H, $J=10.1$ Hz), 4.76 (dd, 1H, $J=6.5$, 4.6 Hz), 4.60 (bs, 2H), 4.37–4.29 (m, 2H), 3.67–3.62 (m, 1H), 3.23 (dd, 1H, $J=5.7$, 5.7 Hz), 3.00 (ddq, 1H, $J=10.3$, 6.9, 3.3 Hz), 2.68–2.60 (m, 2H), 2.32–2.05 (m, 4H), 1.92–1.71 (m, 3H), 1.53–1.46 (m, 2H), 1.01 (d, 3H, $J=6.9$ Hz), 0.98 (d, 3H, $J=6.9$ Hz), 0.97 (d, 3H, $J=6.9$ Hz), 0.93 (d, 3H, $J=6.9$ Hz); MS (FAB in glycerol/ *m/z*) 542 $(M+H)^+$, 524, 463, 393, 301, 225, 185; HRMS (FAB in glycerol) calcd for $C_{32}H_{48}NO_6$ $(M+H)^+$ 542.3484, found 542.3481; $[\alpha]_D^{20}$ +64.4 (*c* 0.09, $CHCl_3$).

Acetic acid, (*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*R*,14*S*,15*S*,16*S*)-15-carbamoyloxy-7,13-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (39). Following the general procedure, a mixture of **37** (4.0 mg, 5.9 μmol), pyridine and acetyl chloride was stirred for 16 h. After chromatography of the residue, *acetic acid, (Z,Z,Z)-(6S,7S,8S,13R,14S,15S,16S) - 15 - carbamoyloxy - 7,13 - bis(4 - methoxybenzyloxy) - 6,8,14,16 - tetramethyleicosa-4,9,17,19-tetraenyl ester* was obtained.

^{1}H NMR (300 MHz, $CDCl_3$) 7.29–7.26 (m, 4H), 6.89 (d, 2H, $J=8.6$ Hz), 6.85 (d, 2H, $J=8.5$ Hz), 6.37 (ddd, 1H, $J=16.9$, 11.0, 10.2 Hz), 5.98 (dd, 1H, $J=11.0$, 11.0 Hz), 5.50 (dd, 1H, $J=10.2$, 10.2 Hz), 5.38–5.24 (m, 4H), 5.17 (d, 1H, $J=16.9$ Hz), 5.07 (d, 1H, $J=10.2$ Hz), 4.81 (dd, 1H, $J=5.9$, 5.9 Hz), 4.57–4.45 (m, 5H), 4.35 (d, 1H,

J = 11.4 Hz), 4.03 (t, 2H, J = 6.5 Hz), 3.81 (s, 3H), 3.79 (s, 3H), 3.23 (dt, 1H, J = 5.6, 5.6 Hz), 3.05 (dd, 1H, J = 7.5, 3.8 Hz), 2.79–2.67 (m, 2H), 2.65–2.55 (m, 1H), 2.15–2.01 (m, 1H), 2.03 (s, 3H), 1.99–1.79 (m, 3H), 1.73–1.56 (m, 5H), 1.02 (d, 3H, J = 6.8 Hz), 1.00 (d, 3H, J = 6.7 Hz), 0.96 (d, 3H, J = 6.9 Hz), 0.92 (d, 3H, J = 6.8 Hz).

The ester above obtained (3.0 mg, 4.1 μmol) was treated with $NaHCO_3$ and DDQ, according to the general method. Flash chromatography of the crude residue (CH_2Cl_2 to CH_2Cl_2/EtOAc 1:1) yielded 1.6 mg (82%) of the acetyl analogue **39** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) 6.63 (ddd, 1H, J = 16.8, 11.0, 10.1 Hz), 6.06 (dd, 1H, J = 11.0, 11.0 Hz), 5.52–5.33 (m, 5H), 5.23 (d, 1H, J = 16.8 Hz), 5.14 (d, 1H, J = 10.1 Hz), 4.76 (dd, 1H, J = 6.7, 4.5 Hz), 4.58 (bs, 2H), 4.10–4.05 (m, 2H), 3.69–3.62 (m, 1H), 3.24 (dd, 1H, J = 5.8, 5.8 Hz), 3.06–2.97 (m, 1H), 2.70–2.58 (m, 2H), 2.20–2.03 (m, 4H), 2.06 (s, 3H), 1.78–1.64 (m, 3H), 1.57–1.48 (m, 2H), 1.01 (d, 3H, J = 6.9 Hz), 1.00 (d, 3H, J = 6.8 Hz), 0.99 (d, 3H, J = 6.9 Hz), 0.94 (d, 3H, J = 6.9 Hz); MS (FAB in glycerol/NaCl, m/z) 502 $(M+Na)^+$, 469, 301, 207; $[\alpha]_D^{20}$ +73.7 (c 0.08, $CHCl_3$).

2,2-Dimethylpropionic acid, (*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*R*,14*S*,15*S*,16*S*)-15-carbamoyloxy-7,13-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (40). A mixture of **37** (4.0 mg, 5.9 μmol), pyridine and pivaloyl chloride was stirred for 17 h following the general procedure, *to obtain the compound 2,2-dimethylpropionic acid, (Z,Z,Z)-(6S,7S,8S,13R,14S,15S,16S)-15-carbamoyloxy-7,13-bis(4-methoxybenzyloxy)-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester*.

^{1}H NMR (300 MHz, $CDCl_3$) 7.30–7.27 (m, 4H), 6.89 (d, 2H, J = 8.6 Hz), 6.87 (d, 2H, J = 8.6 Hz), 6.36 (ddd, 1H, J = 17.1, 11.0, 10.2 Hz), 5.98 (dd, 1H, J = 11.0, 11.0 Hz), 5.50 (dd, 1H, J = 11.0, 9.8 Hz), 5.39–5.24 (m, 4H), 5.17 (dd, 1H, J = 17.1, 1.4 Hz), 5.07 (d, 1H, J = 10.2 Hz), 4.81 (dd, 1H, J = 5.9, 5.9 Hz), 4.56 (bs, 2H), 4.57–4.48 (m, 3H), 4.35 (d, 1H, J = 11.4 Hz), 4.02 (t, 2H, J = 6.5 Hz), 3.81 (s, 3H), 3.80 (s, 3H), 3.23 (dt, 1H, J = 5.6, 5.6 Hz), 3.06 (dd, 1H, J = 7.5, 3.8 Hz), 2.82–2.67 (m, 2H), 2.65–2.54 (m, 1H), 2.20–2.04 (m, 1H), 2.02–1.77 (m, 4H), 1.72–1.54 (m, 4H), 1.20 (s, 9H), 1.02 (d, 3H, J = 6.7 Hz), 1.01 (d, 3H, J = 6.8 Hz), 0.96 (d, 3H, J = 6.8 Hz), 0.92 (d, 3H, J = 6.8 Hz).

To 3.0 mg (3.9 μmol) of the ester above obtained were added $NaHCO_3$ and DDQ. Chromatography of the crude residue using CH_2Cl_2 to CH_2Cl_2/EtOAc 1:1 provided 1.9 mg (95%) of the analogue **40** as a yellow oil.

IR (thin film, NaCl) 3437, 2916, 2846, 1713, 1653, 1457, 1162, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 6.62 (ddd, 1H, J = 16.8, 11.0, 10.1 Hz), 6.07 (dd, 1H, J = 11.0, 11.0 Hz), 5.58–5.46 (m, 1H), 5.42–5.32 (m, 4H), 5.25 (d, 1H, J = 16.8 Hz), 5.16 (d, 1H, J = 10.1 Hz), 4.78 (dd, 1H, J = 6.7, 4.6 Hz), 4.60 (bs, 2H), 4.15–4.05 (m, 2H), 3.69–3.64 (m, 1H), 3.25 (dd, 1H, J = 5.7, 5.7 Hz), 3.02 (ddq, 1H, J = 10.0, 6.8, 3.3 Hz), 2.71–2.58 (m, 2H), 2.23–2.04 (m, 4H), 1.81–1.66 (m, 3H), 1.59–1.51 (m, 2H), 1.23 (s, 9H), 1.03 (d, 3H, J = 6.8 Hz), 1.01 (d, 3H, J = 6.8 Hz), 1.00 (d, 3H, J = 6.9 Hz), 0.96 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 178.3, 157.3, 133.5, 133.4, 132.4, 132.1, 130.2, 130.0, 128.7, 118.0, 79.7, 79.0, 72.8, 63.8, 39.9, 38.7, 35.3, 34.9, 34.7, 34.5, 28.7, 27.2, 24.2, 24.1, 18.0, 17.6, 15.3, 7.9; MS (FAB in glycerol/NaCl, m/z) 544 $(M+Na)^+$, 443, 301, 245, 191; HRMS (FAB in glycerol) calcd for $C_{30}H_{52}NO_6$ $(M+H)^+$ 522.3795, found 522.3798; $[\alpha]_D^{20}$ +67.0 (c 0.27, $CHCl_3$).

Thiophene 2-carboxylic acid, (*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*R*,14*S*,15*S*,16*S*)-15-carbamoyloxy-7,13-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (41). A mixture of 7.0 mg (10 μmol) of the alcohol **37**, pyridine and 2-thiophene carbonyl chloride was stirred for 18 h. Following the general procedure *thiophene 2-carboxylic acid, (Z,Z,Z)-(6S,7S,8S,13R,14S,15S,16S)-15-carbamoyloxy-7,13-bis(4-methoxybenzyloxy)-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester* was obtained.

^{1}H NMR (300 MHz, $CDCl_3$) 7.80 (d, 1H, J = 3.9 Hz), 7.54 (dd, 1H, J = 4.9, 0.8 Hz), 7.30–7.26 (m, 4H), 7.10 (dd, 1H, J = 4.8, 3.9 Hz), 6.89 (d, 2H, J = 8.5 Hz), 6.87 (d, 2H, J = 8.5 Hz), 6.37 (ddd, 1H, J = 18.0, 11.0, 10.1 Hz), 5.98 (dd, 1H, J = 11.0, 11.0 Hz), 5.52 (dd, 1H, J = 11.0, 9.8 Hz), 5.41–5.24 (m, 4H), 5.18 (d, 1H, J = 18.0 Hz), 5.07 (d, 1H, J = 10.1 Hz), 4.82 (dd, 1H, J = 5.9, 5.9 Hz), 4.58–4.49 (m, 5H), 4.35 (d, 1H, J = 11.4 Hz), 4.27 (t, 2H, J = 6.3 Hz), 3.81 (s, 3H), 3.80 (s, 3H), 3.24 (dt, 1H, J = 5.5, 5.5 Hz), 3.06 (dd, 1H, J = 7.5, 3.8 Hz), 2.82–2.70 (m, 2H), 2.64–2.55 (m, 1H), 2.25–2.15 (m, 1H), 2.08–1.90 (m, 2H), 1.89–1.57 (m, 6H), 1.02 (d, 3H, J = 6.8 Hz), 1.01 (d, 3H, J = 6.8 Hz), 0.96 (d, 3H, J = 6.9 Hz), 0.93 (d, 3H, J = 6.9 Hz).

The ester above obtained (8.0 mg, 10.1 μmol) was treated with $NaHCO_3$ and DDQ following the general protocol. Chromatography of the crude residue (CH_2Cl_2/EtOAc 1:1) yielded **41** as a colorless oil (3.9 mg, 72%). IR (thin film, NaCl) 3418, 2962, 2925, 1712, 1695, 1600, 1418, 1265, 1101 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.81 (dd, 1H, J = 3.7, 1.2 Hz), 7.56 (dd, 1H, J = 5.0, 1.2 Hz), 7.11 (dd, 1H, J = 5.0, 3.7 Hz), 6.62 (ddd, 1H, J = 16.9, 11.0, 10.1 Hz), 6.05 (dd, 1H, J = 11.0, 11.0 Hz), 5.55–5.47 (m, 1H), 5.42–5.31 (m, 4H), 5.22 (d, 1H, J = 16.9 Hz), 5.13 (d, 1H, J = 10.1 Hz), 4.76 (dd, 1H, J = 6.7, 4.6 Hz), 4.58 (bs, 2H), 4.37–4.25 (m, 2H), 3.67–3.62 (m, 1H), 3.23 (dd, 1H, J = 5.7, 5.7 Hz), 3.05–2.95 (m, 1H), 2.69–2.61 (m, 2H), 2.30–2.05 (m, 3H), 1.88–1.72 (m, 4H), 1.53–1.45 (m, 2H), 1.00 (d, 3H, J = 7.0 Hz), 0.98 (d, 3H, J = 7.0 Hz), 0.97 (d, 3H, J = 6.8 Hz), 0.93 (d, 3H, J = 7.0 Hz); MS (FAB in MNBA, m/z) 548 $(M+H)^+$, 487, 391, 257, 227, 154, 136; HRMS (FAB in MNBA) calcd for $C_{30}H_{46}NO_6S$ $(M+H)^+$ 548.3046, found 548.3039; $[\alpha]_D^{20}$ +60.5 (c 0.185, $CHCl_3$).

Hydroxyacetic acid, (*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*R*,14*S*,15*S*,16*S*)-15-carbamoyloxy-7,13-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (42). A mixture of **37** (7.0 mg, 10 μmol), (4-methoxybenzyloxy) acetic acid (20 μmol), EDCI (20 μmol) and DMAP (0.5 μmol) was stirred at room temperature for 40 h. After chromato-

graphy of the residue using CH_2Cl_2/EtOAc 9:1, *(4-methoxybenzyloxy) acetic acid, (Z,Z,Z)-(6S,7S,8S,13R,14S,15S,16S)-15-carbamoyloxy-7,13-bis(4-methoxybenzyloxy)-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester* was obtained.

^{1}H NMR (300 MHz, $CDCl_3$) 7.31–7.26 (m, 6H), 6.90–6.86 (m, 6H), 6.35 (ddd, 1H, J = 16.6, 11.0, 10.1 Hz), 5.98 (dd, 1H, J = 11.0, 11.0 Hz), 5.50 (dd, 1H, J = 11.0, 10.0 Hz), 5.38–5.23 (m, 4H), 5.17 (d, 1H, J = 16.6 Hz), 5.07 (d, 1H, J = 10.1 Hz), 4.81 (dd, 1H, J = 5.8, 5.8 Hz), 4.55–4.48 (m, 7H), 4.35 (d, 1H, J = 11.4 Hz), 4.13 (t, 2H, J = 6.3 Hz), 4.05 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.23 (dt, 1H, J = 5.7, 5.7 Hz), 3.04 (dd, 1H, J = 7.5, 3.8 Hz), 2.79–2.55 (m, 3H), 2.15–1.78 (m, 5H), 1.71–1.60 (m, 4H), 1.02 (d, 3H, J = 6.8 Hz), 1.00 (d, 3H, J = 6.8 Hz), 0.96 (d, 3H, J = 6.9 Hz), 0.92 (d, 3H, J = 6.8 Hz).

The ester above obtained (3.8 mg, 4.4 μmol) was treated with $NaHCO_3$ and DDQ (22 μmol). After 6 h of stirring, the residue was purified by chromatography (EtOAc) to provide 1.5 mg (71%) of the corresponding analogue **42**.

^{1}H NMR (300 MHz, $CDCl_3$) 6.62 (ddd, 1H, J = 17.0, 11.0, 10.2 Hz), 6.04 (dd, 1H, J = 11.0, 11.0 Hz), 5.50–5.30 (m, 5H), 5.23 (dd, 1H, J = 17.0, 1.3 Hz), 5.14 (d, 1H, J = 10.2 Hz), 4.77–4.72 (m, 1H), 4.61 (bs, 2H), 4.21 (t, 2H, J = 6.4 Hz), 4.17 (s, 2H), 3.67–3.62 (m, 1H), 3.24 (dd, 1H, J = 5.7, 5.7 Hz), 3.03–2.95 (m, 1H), 2.68–2.54 (m, 2H), 2.18–2.05 (m, 2H), 1.78–1.47 (m, 7H), 1.01 (d, 3H, J = 6.8 Hz), 1.00 (d, 3H, J = 6.8 Hz), 0.99 (d, 3H, J = 6.8 Hz), 0.94 (d, 3H, J = 7.0 Hz); $[\alpha]_D^{20}$ +76.0 (*c* 0.025, $CHCl_3$).

Furan-2-carboxylic acid, (*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*R*,14*S*,15*S*,16*S*)-15-carbamoyloxy-7,13-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (43). Following the general procedure, a mixture of 7.0 mg (10.0 μmol) of **37**, pyridine and 2-furoyl chloride was stirred for 14 h. After concentration and chromatography, the corresponding *furan 2-carboxylic acid, (Z,Z,Z)-(6S,7S,8S,13R,14S,15S,16S)-15-carbamoyloxy-7,13-bis(4-methoxybenzyloxy)-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester* was obtained.

IR (thin film, NaCl) 3360, 2960, 1721, 1609, 1513, 1298, 1248, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.57 (d, 1H, J = 1.7 Hz), 7.30–7.26 (m, 4H), 7.17 (d, 1H, J = 3.3 Hz), 6.90 (d, 2H, J = 8.5 Hz), 6.88 (d, 2H, J = 8.6 Hz), 6.51 (dd, 1H, J = 3.3, 1.7 Hz), 6.37 (ddd, 1H, J = 18.0, 11.0, 10.1 Hz), 5.99 (dd, 1H, J = 11.0, 11.0 Hz), 5.52 (dd, 1H, J = 11.0, 9.8 Hz), 5.40–5.25 (m, 4H), 5.18 (d, 1H, J = 18.0 Hz), 5.08 (d, 1H, J = 10.1 Hz), 4.82 (dd, 1H, J = 5.9, 5.9 Hz), 4.58–4.46 (m, 5H), 4.36 (d, 1H, J = 11.4 Hz), 4.28 (t, 2H, J = 6.4 Hz), 3.81 (s, 3H), 3.80 (s, 3H), 3.24 (dt, 1H, J = 5.8, 5.8 Hz), 3.07 (dd, 1H, J = 7.4, 3.9 Hz), 2.82–2.70 (m, 2H), 2.70–2.60 (m, 1H), 2.27–2.16 (m, 1H), 2.06–1.95 (m, 2H), 1.91–1.58 (m, 6H), 1.03 (d, 3H, J = 6.8 Hz), 1.02 (d, 3H, J = 6.9 Hz), 0.97 (d, 3H, J = 6.9 Hz), 0.93 (d, 3H, J = 6.8 Hz).

To the ester above obtained (7.8 mg, 10.1 μmol) was added $NaHCO_3$ and DDQ. Purification of the crude residue by chromatography (CH_2Cl_2/EtOAc 1:1) afforded 4.0 mg (80%) of the corresponding analogue **43**.

IR (thin film, NaCl) 3405, 2964, 2919, 1713, 1580, 1397, 1299, 1122, 1046 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.58 (dd, 1H, J = 1.7, 0.8 Hz), 7.18 (dd, 1H, J = 3.5, 0.8 Hz), 6.62 (ddd, 1H, J = 16.8, 10.9, 10.1 Hz), 6.52 (dd, 1H, J = 3.5, 1.7 Hz), 6.05 (dd, 1H, J = 10.9, 10.9 Hz), 5.55–5.32 (m, 5H), 5.23 (dd, 1H, J = 16.8, 1.8 Hz), 5.13 (d, 1H, J = 10.1 Hz), 4.76 (dd, 1H, J = 6.6, 4.6 Hz), 4.59 (bs, 2H), 4.37–4.25 (m, 2H), 3.68–3.62 (m, 1H), 3.23 (dd, 1H, J = 5.7, 5.7 Hz), 3.04–2.94 (m, 1H), 2.69–2.60 (m, 2H), 2.30–2.09 (m, 3H), 1.92–1.71 (m, 4H), 1.56–1.46 (m, 2H), 1.01 (d, 3H, J = 7.0 Hz), 0.98 (d, 6H, J = 6.8 Hz), 0.93 (d, 3H, J = 7.0 Hz); MS (FAB in MNBA, *m*/*z*) 532 $(M+H)^+$, 507, 391, 307, 257, 154, 136; HRMS (FAB in MNBA) calcd for $C_{30}H_{46}NO_7$ $(M+H)^+$ 532.3274, found 532.3279; $[\alpha]_D^{20}$ +71.6 (*c* 0.19, $CHCl_3$).

General procedure for the synthesis of (17*R*,19*S*)-acetoxy analogues of discodermolide

To a solution of the alcohol **45** (10 μmol) in 1 mL of dichloromethane was added pyridine (50 μmol) followed by the corresponding acyl chloride (30 μmol). The mixture was stirred at room temperature for the required time, concentrated under vacuum and purified by column chromatography (CH_2Cl_2 to CH_2Cl_2/EtOAc 19:1) to afford the corresponding esters.

To the esters above obtained (10 μmol) in 1 mL of dichloromethane, was added $NaHCO_3$ (30 mg) and DDQ (30 μmol). The mixture was stirred at room temperature for 1 h, concentrated and the crude product was purified by chromatography to afford the (17*R*,19*S*)-acetoxy analogues of discodermolide.

Acetic acid, (*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*R*,14*S*,15*S*,16*S*)-15-acetoxy-7,13-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (46). Following the general procedure, a mixture of 7.5 mg (11.0 μmol) of **45**, pyridine and acetyl chloride was stirred for 20 h. After concentration and chromatography, the corresponding *acetic acid, (Z,Z,Z)-(6S,7S,8S,13R,14S,15S,16S)-15-acetoxy-7,13-bis(4-methoxybenzyloxy)-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester* was obtained.

^{1}H NMR (300 MHz, $CDCl_3$) 7.30–7.26 (m, 4H), 6.89 (d, 2H, J = 8.7 Hz), 6.88 (d, 2H, J = 8.6 Hz), 6.38 (ddd, 1H, J = 16.8, 11.0, 10.1 Hz), 5.97 (dd, 1H, J = 11.0, 11.0 Hz), 5.49 (dd, 1H, J = 11.0, 9.7 Hz), 5.34–5.26 (m, 4H), 5.17 (dd, 1H, J = 16.8, 1.9 Hz), 5.08 (d, 1H, J = 10.1 Hz), 4.97 (dd, 1H, J = 5.9, 5.9 Hz), 4.58–4.45 (m, 3H), 4.34 (d, 1H, J = 11.4 Hz), 4.09–3.98 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.21 (dt, 1H, J = 5.7, 5.7 Hz), 3.06 (dd, 1H J = 7.5, 4.0 Hz), 2.82–2.67 (m, 2H), 2.65–2.57 (m, 1H), 2.24–2.05 (m, 1H), 2.03 (s, 3H), 1.99 (s, 3H), 1.98–1.82 (m, 3H), 1.70–1.53 (m, 5H), 1.03 (d, 3H, J = 6.7 Hz), 1.01 (d, 3H, J = 6.7 Hz), 0.95 (d, 3H, J = 6.9 Hz), 0.89 (d, 3H, J = 6.8 Hz).

To the ester above obtained (4.8 mg, 6.6 μmol) was added $NaHCO_3$ and DDQ. Chromatography of the

crude product using CH_2Cl_2 to CH_2Cl_2/EtOAc 7:3 gave 3.1 mg (95%) of the analogue **46** as a yellowish oil.

IR (thin film, NaCl) 3469, 2966, 2931, 2867, 1739, 1735, 1453, 1370, 1239, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 6.62 (ddd, 1H, $J=16.8$, 11.0, 10.1 Hz), 6.04 (dd, 1H, $J=11.0$, 11.0 Hz), 5.52–5.28 (m, 5H), 5.23 (dd, 1H, $J=16.8$, 1.9 Hz), 5.14 (d, 1H, $J=10.1$ Hz), 4.94 (dd, 1H, $J=6.4$, 5.1 Hz), 4.13–4.01 (m, 2H), 3.63–3.58 (m, 1H), 3.23 (dd, 1H, $J=5.7$, 5.7 Hz), 3.01 (ddq, 1H, $J=10.1$, 6.8, 3.2 Hz), 2.71–2.56 (m, 2H), 2.21–2.04 (m, 2H), 2.06 (s, 3H), 2.02 (s, 3H), 1.79–1.53 (m, 5H), 1.53–1.46 (m, 2H), 1.00 (d, 3H, $J=6.8$ Hz), 0.99 (d, 6H, $J=6.8$ Hz), 0.93 (d, 3H, $J=6.9$ Hz); MS (FAB in MNBA/Na, *m/z*) 501 $(M+Na)^+$, 462, 401, 383, 257, 176, 154, 136; HRMS (FAB in MNBA) calcd for $C_{28}H_{47}O_6$ $(M+H)^+$ 479.3373, found 479.3379; $[\alpha]_D^{20}$ +74.2 (*c* 0.155, $CHCl_3$).

Benzoic acid, (*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*R*,14*S*,15*S*,16*S*)-15-acetoxy-7,13-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (47). A mixture of **45** (7.5 mg, 11.0 μmol), pyridine and benzoyl chloride was stirred for 17 h following the general method. After purification of the residue, *benzoic acid, (Z,Z,Z)-(6S,7S,8S,13R,14S, 15S,16S)-15-acetoxy-7,13-bis(4-methoxybenzyloxy)-6,8, 14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester* was obtained.

^1H NMR (300 MHz, $CDCl_3$) 8.04 (d, 2H, $J=7.6$ Hz), 7.58–7.53 (m, 1H), 7.43 (t, 2H, $J=7.6$ Hz), 7.28 (d, 2H, $J=8.6$ Hz), 7.27 (d, 2H, $J=8.6$ Hz), 6.88 (d, 2H, $J=8.6$ Hz), 6.86 (d, 2H, $J=8.6$ Hz), 6.37 (ddd, 1H, $J=16.8$, 11.0, 10.1 Hz), 5.97 (dd, 1H, $J=11.0$, 11.0 Hz), 5.51 (dd, 1H, $J=11.0$, 9.7 Hz), 5.40–5.25 (m, 4H), 5.17 (dd, 1H, $J=16.8$, 1.8 Hz), 5.07 (d, 1H, $J=10.1$ Hz), 4.96 (dd, 1H, $J=5.9$, 5.9 Hz), 4.56–4.48 (m, 3H), 4.32 (d, 1H, $J=11.4$ Hz), 4.31–4.22 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.21 (dt, 1H, $J=5.6$, 5.6 Hz), 3.05 (dd, 1H, $J=7.4$, 4.0 Hz), 2.81–2.70 (m, 2H), 2.67–2.57 (m, 1H), 2.34–2.17 (m, 1H), 2.10–1.96 (m, 2H), 1.98 (s, 3H), 1.95–1.74 (m, 4H), 1.61–1.55 (m, 2H), 1.02 (d, 3H, $J=6.7$ Hz), 1.01 (d, 3H, $J=6.9$ Hz), 0.94 (d, 3H, $J=6.9$ Hz), 0.88 (d, 3H, $J=6.8$ Hz).

The ester above obtained (7.4 mg, 9.4 μmol) was treated with $NaHCO_3$ and DDQ, according to the general procedure. Flash chromatography of the crude product using CH_2Cl_2/EtOAc 7:3 yielded 3.5 mg (70%) of the corresponding benzoyl analogue **47**.

IR (thin film, NaCl) 3453, 2962, 2923, 1730, 1719, 1453, 1370, 1271, 1113, 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 8.05 (d, 2H, $J=7.7$ Hz), 7.60–7.54 (m, 1H), 7.45 (t, 2H, $J=7.7$ Hz), 6.61 (ddd, 1H, $J=16.9$, 11.0, 10.1 Hz), 6.03 (dd, 1H, $J=11.0$, 11.0 Hz), 5.55–5.32 (m, 5H), 5.22 (d, 1H, $J=16.9$ Hz), 5.13 (d, 1H, $J=10.1$ Hz), 4.94 (dd, 1H, $J=6.3$, 5.2 Hz), 4.38–4.29 (m, 2H), 3.63–3.57 (m, 1H), 3.22 (dd, 1H, $J=5.7$, 5.7 Hz), 3.00 (ddq, 1H, $J=10.1$, 6.7, 3.4 Hz), 2.69–2.60 (m, 2H), 2.29–2.00 (m, 3H), 2.01 (s, 3H), 1.88–1.70 (m, 4H), 1.50–1.45 (m, 2H), 1.06–0.96 (m, 9H), 0.92 (d, 3H, $J=6.9$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 171.3, 166.7, 133.7, 133.5, 133.0, 132.7, 132.1, 130.4, 130.2, 130.0, 129.6, 128.7, 128.4, 118.1, 79.1, 78.4, 72.6, 64.4, 39.7, 35.4, 34.9, 34.6, 33.7, 28.8, 28.0, 24.2, 21.1, 18.0, 17.6, 15.4, 8.3; MS (FAB in MNBA/Na, *m/z*) 563 $(M+Na)^+$, 520, 461, 391, 336, 227, 176, 154; $[\alpha]_D^{20}$ +71.4 (*c* 0.175, $CHCl_3$).

2,2-Dimethylpropionic acid, (*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*R*,14*S*,15*S*,16*S*)-15-acetoxy-7,13-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (48). Following the general procedure a mixture of **45** (7.5 mg, 11.0 μmol), pyridine and pivaloyl chloride was stirred for 18 h. After usual purification, *2,2-dimethylpropionic acid, (Z,Z,Z)-(6S,7S,8S,13R,14S, 15S,16S)-15-acetoxy-7,13-bis(4-methoxybenzyloxy)-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester* was obtained.

^1H NMR (300 MHz, $CDCl_3$) 7.30–7.26 (m, 4H), 6.89 (d, 2H, $J=8.6$ Hz), 6.87 (d, 2H, $J=8.7$ Hz), 6.36 (ddd, 1H, $J=16.8$, 11.0, 10.1 Hz), 5.97 (dd, 1H, $J=11.0$, 11.0 Hz), 5.49 (dd, 1H, $J=11.0$, 9.7 Hz), 5.35–5.25 (m, 4H), 5.17 (dd, 1H, $J=16.8$, 1.9 Hz), 5.07 (d, 1H, $J=10.1$ Hz), 4.97 (dd, 1H, $J=5.9$, 5.9 Hz), 4.56 (d, 1H, $J=11.4$ Hz), 4.54–4.48 (m, 2H), 4.33 (d, 1H, $J=11.4$ Hz), 4.06–3.98 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.21 (dt, 1H, $J=5.6$, 5.6 Hz), 3.06 (dd, 1H, $J=7.4$, 4.0 Hz), 2.80–2.67 (m, 2H), 2.64–2.55 (m, 1H), 2.17–2.03 (m, 2H), 1.99 (s, 3H), 1.96–1.82 (m, 3H), 1.69–1.53 (m, 4H), 1.20 (s, 9H), 1.03 (d, 3H, $J=6.7$ Hz), 1.01 (d, 3H, $J=6.9$ Hz), 0.94 (d, 3H, $J=6.9$ Hz), 0.89 (d, 3H, $J=6.8$ Hz).

To the ester above obtained (6.0 mg, 7.9 μmol) was added $NaHCO_3$ and DDQ. Purification of the crude product by column chromatography (CH_2Cl_2 to CH_2Cl_2/EtOAc 7:3) provided 2.8 mg (70%) of the analogue **48** as a colorless oil.

IR (thin film, NaCl) 3434, 2965, 2922, 2871, 1724, 1715, 1455, 1364, 1237, 1161, 1019 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 6.62 (ddd, 1H, $J=16.8$, 11.0, 10.1 Hz), 6.04 (dd, 1H, $J=11.0$, 11.0 Hz), 5.53–5.30 (m, 5H), 5.23 (dd, 1H, $J=16.8$, 1.9 Hz), 5.14 (d, 1H, $J=10.1$ Hz), 4.94 (dd, 1H, $J=6.4$, 5.1 Hz), 4.13–4.00 (m, 2H), 3.63–3.58 (m, 1H), 3.23 (dd, 1H, $J=5.7$, 5.7 Hz), 3.00 (ddq, 1H, $J=10.1$, 6.7, 3.3 Hz), 2.71–2.56 (m, 2H), 2.22–2.00 (m, 3H), 2.02 (s, 3H), 1.78–1.62 (m, 4H), 1.53–1.45 (m, 2H), 1.21 (s, 9H), 0.99 (d, 3H, $J=6.8$ Hz), 0.98 (d, 6H, $J=6.8$ Hz), 0.93 (d, 3H, $J=6.9$ Hz); MS (FAB in MNBA/Na, *m/z*) 543 $(M+Na)^+$, 503, 426, 340, 154, 121; HRMS (FAB in MNBA) calcd for $C_{31}H_{53}O_6$ $(M+H)^+$ 521.3842, found 521.3835; $[\alpha]_D^{20}$ +79.3 (*c* 0.14, $CHCl_3$).

General procedure for the synthesis of 17*S*-dis-codermolide analogues

To a solution of the alcohol **58** (10 μmol) in 1 mL of dichloromethane was added pyridine (50 μmol) followed by the corresponding acyl chloride (30 μmol). The mixture was stirred at room temperature for the required time, concentrated under vacuum and purified by chromatography (CH_2Cl_2 to CH_2Cl_2/EtOAc 9:1) to provide the corresponding esters.

The esters obtained (10 μmol) were dissolved in dichloromethane (1 mL) and $NaHCO_3$ (30 mg) was added

to the solution, followed by the addition of DDQ (30 μmol). The mixture was stirred for 1 h at room temperature, concentrated and the crude residue purified by chromatography to afford the corresponding (17*S*)-analogues of discodermolide.

2,2-Dimethylpropionic acid, (*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*S*,14*S*,15*S*,16*S*)-15-carbamoyloxy-7,13-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (59). Following the general procedure, a mixture of 6.5 mg (9.6 μmol) of **58**, pyridine and pivaloyl chloride was stirred for 16 h. After concentration and chromatography, the product *2,2-dimethylpropionic acid, (Z,Z,Z)-(6S,7S,8S,13S,14S,15S,16S)-15-carbamoyloxy-7,13-bis(4-methoxybenzyloxy)-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester* was obtained.

^{1}H NMR (300 MHz, $CDCl_3$) 7.29 (d, 4H, J = 8.6 Hz), 6.89 (d, 2H, J = 8.6 Hz), 6.87 (d, 2H, J = 8.5 Hz), 6.64 (ddd, 1H, J = 16.7, 11.0, 10.1 Hz), 6.08 (dd, 1H, J = 11.0, 11.0 Hz), 5.56–5.29 (m, 5H), 5.24 (d, 1H, J = 16.7 Hz), 5.15 (d, 1H, J = 10.1 Hz), 4.91 (dd, 1H, J = 6.5, 5.2 Hz), 4.62–4.50 (m, 4H), 4.42 (d, 1H, J = 10.6 Hz), 4.29 (d, 1H, J = 10.6 Hz), 4.09–4.00 (m, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.34–3.28 (m, 1H), 3.09 (dd, 1H, J = 7.2, 4.1 Hz), 2.92 (ddq, 1H, J = 10.0, 6.8, 3.3 Hz), 2.79–2.62 (m, 2H), 2.20–1.99 (m, 5H), 1.71–1.51 (m, 4H), 1.21 (s, 9H), 1.05 (d, 3H, J = 6.8 Hz), 1.03 (d, 3H, J = 6.9 Hz), 1.01 (d, 3H, J = 6.9 Hz), 0.92 (d, 3H, J = 6.9 Hz).

The ester (6.0 mg, 7.8 μmol) was treated with $NaHCO_3$ and DDQ following the general method. Chromatography of the residue in CH_2Cl_2/EtOAc 1:1 afforded 3.4 mg (84%) of the analogue **59** as a colorless oil.

IR (thin film, NaCl) 3431, 2966, 2930, 1715, 1703, 1456, 1398, 1325, 1161, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 6.65 (ddd, 1H, J = 17.0, 11.0, 10.1 Hz), 6.04 (dd, 1H, J = 11.0, 11.0 Hz), 5.53–5.28 (m, 5H), 5.23 (dd, 1H, J = 17.0, 1.7 Hz), 5.13 (d, 1H, J = 10.1 Hz), 4.83 (dd, 1H, J = 9.7, 1.6 Hz), 4.57 (bs, 2H), 4.11–4.00 (m, 2H), 3.24–3.17 (m, 2H), 2.95 (ddq, 1H, J = 9.6, 7.0, 2.6 Hz), 2.70–2.56 (m, 2H), 2.24–2.03 (m, 4H), 1.75–1.58 (m, 4H), 1.49–1.40 (m, 1H), 1.21 (s, 9H), 0.99 (d, 3H, J = 7.0 Hz), 0.98 (d, 3H, J = 6.9 Hz), 0.96 (d, 3H, J = 6.8 Hz), 0.87 (d, 3H, J = 7.0 Hz); MS (FAB in MNBA/Na, m/z) 544 $(M+Na)^+$, 522 $(M+H)^+$, 413, 340, 176, 154; HRMS (FAB) calcd for $C_{30}H_{52}NO_6$ $(M+H)^+$ 522.3795, found 522.3790; $[\alpha]_D^{20}$ +92.2 (c 0.155, $CHCl_3$).

Benzoic acid, (*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*S*,14*S*,15*S*,16*S*)-15-carbamoyloxy-7,13-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (60). Following the general procedure, a mixture of 6.5 mg (9.6 μmol) of **58**, pyridine and benzoyl chloride was stirred for 20 h. After purification, *benzoic acid, (Z,Z,Z)-(6S,7S,8S,13S,14S,15S,16S)-15-carbamoyloxy-7,13-bis(4-methoxybenzyloxy)-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester* was obtained.

^{1}H NMR (300 MHz, $CDCl_3$) 8.12 (d, 2H, J = 7.1 Hz), 7.65–7.58 (m, 1H), 7.55–7.49 (m, 2H), 7.28 (d, 2H, J = 8.6 Hz), 7.27 (d, 2H, J = 8.6 Hz), 6.86 (d, 2H, J = 8.6 Hz), 6.84 (d, 2H, J = 8.6 Hz), 6.62 (ddd, 1H, J = 16.9, 11.0, 10.1 Hz), 6.06 (dd, 1H, J = 11.0, 11.0 Hz), 5.56–5.26 (m, 5H), 5.22 (d, 1H, J = 16.9 Hz), 5.13 (d, 1H, J = 10.1 Hz), 4.91 (dd, 1H, J = 6.5, 5.1 Hz), 4.85 (bs, 2H), 4.55 (d, 1H, J = 10.6 Hz), 4.49 (d, 1H, J = 10.6 Hz), 4.40 (d, 1H, J = 10.5 Hz), 4.32–4.25 (m, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.32–3.25 (m, 1H), 3.06 (dd, 1H, J = 7.2, 4.1 Hz), 2.90 (ddq, 1H, J = 10.0, 6.7, 3.3 Hz), 2.80–2.62 (m, 2H), 2.25–1.97 (m, 5H), 1.85–1.71 (m, 2H), 1.56–1.48 (m, 2H), 1.02 (d, 3H, J = 6.7 Hz), 1.00 (d, 3H, J = 7.0 Hz), 0.98 (d, 3H, J = 7.0 Hz), 0.89 (d, 3H, J = 6.9 Hz).

To the ester obtained above (7.2 mg, 9.2 μmol) was added $NaHCO_3$ and DDQ. Chromatography of the crude product using CH_2Cl_2/EtOAc 1:1 gave 3.6 mg (72%) of the benzoyl analogue **60**.

IR (thin film, NaCl) 3345, 2964, 2927, 1712, 1696, 1602, 1400, 1321, 1276, 1119, 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 8.08 (d, 1H, J = 7.0 Hz), 8.05 (d, 1H, J = 7.0 Hz), 7.55–7.40 (m, 3H), 6.65 (ddd, 1H, J = 16.7, 10.9, 10.2 Hz), 6.05 (dd, 1H, J = 10.9, 10.9 Hz), 5.55–5.28 (m, 5H), 5.23 (d, 1H, J = 16.7 Hz), 5.13 (d, 1H, J = 10.2 Hz), 4.84 (dd, 1H, J = 9.7, 1.5 Hz), 4.72 (bs, 2H), 4.40–4.26 (m, 2H), 3.22 (dd, 1H, J = 5.9, 5.9 Hz), 3.19 (td, 1H, J = 9.3, 2.2 Hz), 2.96 (ddq, 1H, J = 9.6, 7.0, 2.8 Hz), 2.70–2.57 (m, 2H), 2.30–2.15 (m, 4H), 1.90–1.80 (m, 2H), 1.72–1.60 (m, 2H), 1.46–1.40 (m, 1H), 0.98 (d, 3H, J = 6.9 Hz), 0.96 (d, 6H, J = 7.0 Hz), 0.87 (d, 3H, J = 6.9 Hz); MS (FAB in MNBA/Na, m/z) 564 $(M+Na)^+$, 543, 521, 487, 437, 313, 241, 154; HRMS (FAB in MNBA) calcd for $C_{32}H_{48}NO_6$ $(M+H)^+$ 542.33482, found 542.3487; $[\alpha]_D^{20}$ +86.7 (c 0.18, $CHCl_3$).

Hydroxyacetic acid, (*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*S*,14*S*,15*S*,16*S*)-15-carbamoyloxy-7,13-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (61). A mixture of **58** (6.5 mg, 9.6 μmol), (4-methoxybenzyloxy) acetic acid (19.2 μmol), EDCI (19.2 μmol) and DMAP (0.48 μmol) was stirred at room temperature for 48 h. After purification of the residue by chromatography using CH_2Cl_2/EtOAc 1:1, *(4-methoxybenzyloxy)acetic acid, (Z,Z,Z)-(6S,7S,8S,13S,14S,15S,16S)-15-carbamoyloxy-7,13-bis(4-methoxybenzyloxy)-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester* was obtained.

^{1}H NMR (300 MHz, $CDCl_3$) 7.31–7.26 (m, 6H), 6.92–6.83 (m, 6H), 6.62 (ddd, 1H, J = 17.4, 11.0, 10.1 Hz), 6.06 (dd, 1H, J = 11.0, 11.0 Hz), 5.54–5.27 (m, 5H), 5.21 (d, 1H, J = 17.4 Hz), 5.13 (d, 1H, J = 10.1 Hz), 4.88 (dd, 1H, J = 6.4, 5.3 Hz), 4.63–4.51 (m, 6H), 4.40 (d, 1H, J = 10.6 Hz), 4.26 (d, 1H, J = 10.6 Hz), 4.12 (t, 2H, J = 6.7 Hz), 4.05 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.29 (td, 1H, J = 6.2, 4.1 Hz), 3.06 (dd, 1H, J = 7.2, 4.1 Hz), 2.90 (ddq, 1H, J = 10.1, 7.0, 3.2 Hz), 2.74–2.61 (m, 2H), 2.15–1.95 (m, 4H), 1.70–1.59 (m, 2H), 1.58–1.46 (m, 3H), 1.02 (d, 3H, J = 7.0 Hz), 1.00 (d, 3H, J = 7.0 Hz), 0.98 (d, 3H, J = 6.8 Hz), 0.90 (d, 3H, J = 7.0 Hz).

The ester obtained above (4.4 mg, 5.1 μmol) was treated with $NaHCO_3$ and DDQ (25 μmol). After 5 h of stirring, the residue was chromatographed using EtOAc as eluent to provide 1.1 mg (54%) of the analogue **61**.

^{1}H NMR (300 MHz, $CDCl_3$) 6.65 (ddd, 1H, J = 16.7, 11.0, 10.1 Hz), 6.05 (dd, 1H, J = 11.0, 11.0 Hz), 5.51–5.28 (m, 5H), 5.23 (dd, 1H, J = 16.7, 1.9 Hz), 5.13 (d, 1H, J = 10.1 Hz), 4.83 (dd, 1H, J = 9.8, 1.6 Hz), 4.63 (bs, 2H), 4.29–4.17 (m, 2H), 4.17 (s, 2H), 3.22 (dd, 1H, J = 5.8, 5.8 Hz), 3.17 (td, 1H, J = 9.5, 2.0 Hz), 3.02–2.92 (m, 1H), 2.71–2.56 (m, 2H), 2.26–2.10 (m, 4H), 1.78–1.38 (m, 5H), 0.99 (d, 3H, J = 6.9 Hz), 0.98 (d, 3H, J = 6.8 Hz), 0.96 (d, 3H, J = 6.8 Hz), 0.87 (d, 3H, J = 6.9 Hz); MS (FAB in MNBA, m/z) 496 $(M+H)^+$, 391, 368, 307, 289, 154, 136; $[\alpha]_D^{20}$ +72.0 (c 0.05, $CHCl_3$).

Furan-2-carboxylic acid, (*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*S*,14*S*,15*S*,16*S*)-15-carbamoyloxy-7,13-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (62). Following the general procedure, a mixture of the alcohol **58** (6.5 mg, 9.6 μmol), pyridine and 2-furoyl chloride (20 μmol) was stirred for 20 h to obtain *furan-2-carboxylic acid, (Z,Z,Z)-(6S,7S,8S,13S,14S,15S,16S)-15-carbamoyloxy-7,13-bis(4-methoxybenzyloxy)-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester*.

^{1}H NMR (300 MHz, $CDCl_3$) 7.63–7.60 (m, 1H), 7.28 (d, 4H, J = 8.5 Hz), 7.15 (d, 1H, J = 3.2 Hz), 6.87 (d, 2H, J = 8.5 Hz), 6.84 (d, 2H, J = 8.5 Hz), 6.62 (ddd, 1H, J = 16.8, 11.0, 10.2 Hz), 6.49 (dd, 1H, J = 3.3, 1.7 Hz), 6.06 (dd, 1H, J = 11.0, 11.0 Hz), 5.51 (dd, 1H, J = 10.6, 10.6 Hz), 5.48–5.27 (m, 4H), 5.22 (d, 1H, J = 16.8 Hz), 5.13 (d, 1H, J = 10.2 Hz), 4.89 (dd, 1H, J = 5.8, 5.8 Hz), 4.57–4.47 (m, 4H), 4.40 (d, 1H, J = 10.6 Hz), 4.30–4.24 (m, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.28 (td, 1H, J = 6.2, 4.1 Hz), 3.06 (dd, 1H, J = 7.2, 4.1 Hz), 2.90 (ddq, 1H, J = 10.0, 6.8, 3.4 Hz), 2.80–2.62 (m, 2H), 2.20–1.97 (m, 4H), 1.80–1.69 (m, 2H), 1.58–1.47 (m, 3H), 1.02 (d, 3H, J = 6.7 Hz), 1.00 (d, 3H, J = 6.8 Hz), 0.98 (d, 3H, J = 7.0 Hz), 0.89 (d, 3H, J = 6.9 Hz).

The ester above obtained (6.0 mg, 7.7 μmol) was treated with $NaHCO_3$ and DDQ, according to the general procedure. Chromatography of the crude product using CH_2Cl_2/EtOAc 19:1 to 1:1 yielded 3.1 mg (78%) of the corresponding analogue **62** as a colorless oil.

IR (thin film, NaCl) 3420, 2864, 2927, 1713, 1584, 1399, 1299, 1181, 1122 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.60–7.58 (m, 1H), 7.18 (d, 1H, J = 3.6 Hz), 6.65 (ddd, 1H, J = 16.5, 10.9, 10.2 Hz), 6.52 (dd, 1H, J = 3.6, 1.7 Hz), 6.04 (dd, 1H, J = 10.9, 10.9 Hz), 5.56–5.30 (m, 5H), 5.23 (d, 1H, J = 16.5 Hz), 5.13 (d, 1H, J = 10.2 Hz), 4.83 (dd, 1H, J = 9.7, 1.5 Hz), 4.59 (bs, 2H), 4.39–4.24 (m, 2H), 3.22 (dd, 1H, J = 5.8, 5.8 Hz), 3.18 (td, 1H, J = 9.1, 2.0 Hz), 2.96 (ddq, 1H, J = 9.6, 7.0, 2.8 Hz), 2.73–2.55 (m, 2H), 2.27–2.12 (m, 4H), 1.87–1.58 (m, 4H), 1.48–1.39 (m, 1H), 0.98 (d, 3H, J = 6.7 Hz), 0.97 (d, 3H, J = 6.7 Hz), 0.96 (d, 3H, J = 6.8 Hz), 0.87 (d, 3H, J = 6.9 Hz); MS (FAB in MNBA/Na, m/z) 554 $(M+Na)^+$, 532 $(M+H)^+$, 413, 329, 307, 176, 154; HRMS (FAB in MNBA) calcd for $C_{30}H_{46}NO_7$ $(M+H)^+$ 532.3274, found 532.3277; $[\alpha]_D^{20}$ +85.8 (c 0.155, $CHCl_3$).

General procedure for the 17*R*-carbamoyloxy or 17*R*-acetoxy analogues of discodermolide

To a solution of the alcohols **72** or **73** (10 μmol) in 1 mL of dichloromethane was added pyridine (50 μmol) followed by the corresponding acyl chloride (30 μmol). The mixture was stirred at room temperature for the required time, concentrated under vacuum and purified by chromatography (CH_2Cl_2 to CH_2Cl_2/EtOAc 95/5) to provide the corresponding esters.

The esters above obtained (10 μmol) were dissolved in 1 mL of dichloromethane and $NaHCO_3$ (40 mg) was added to the solution, followed by the addition of DDQ (30 μmol). The mixture was stirred at room temperature for 1 h, concentrated and the crude residue was purified by chromatography to afford the corresponding 17-carbamoyloxy or 17-acetoxy analogues of discodermolide.

2,2-Dimethylpropionic acid, (*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*R*,14*S*,15*S*,16*S*)-13-carbamoyloxy-7,15-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (74). Following the general procedure, a mixture of 2.0 mg (2.9 μmol) of **72**, pyridine and pivaloyl chloride was stirred for 24 h. After concentration and chromatography, the product *2,2-dimethylpropionic acid, (Z,Z,Z)-(6S,7S,8S,13R,14S,15S,16S)-13-carbamoyloxy-7,15-bis(4-methoxybenzyloxy)-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester* was obtained.

^{1}H NMR (300 MHz, $CDCl_3$) 7.28 (d, 4H, J = 8.4 Hz), 6.87 (d, 4H, J = 8.4 Hz), 6.72 (ddd, 1H, J = 17.2, 11.0, 10.1 Hz), 6.04 (dd, 1H, J = 11.0, 11.0 Hz), 5.55–5.42 (m, 2H), 5.40–5.25 (m, 3H), 5.19 (d, 1H, J = 17.2 Hz), 5.12 (d, 1H, J = 10.2 Hz), 4.88–4.79 (m, 1H), 4.60–4.44 (m, 6H), 4.03 (t, 2H, J = 6.4 Hz), 3.81 (s, 6H), 3.22–3.07 (m, 3H), 2.77–2.58 (m, 2H), 2.15–1.90 (m, 4H), 1.87–1.50 (m, 5H), 1.19 (s, 9H), 1.09 (d, 3H, J = 6.7 Hz), 1.01 (d, 9H, J = 6.7 Hz).

The ester above obtained (1.3 mg, 1.7 μmol) was treated with $NaHCO_3$ and DDQ, following the general method. Flash chromatography of the residue using CH_2Cl_2 to CH_2Cl_2/EtOAc 1:1 gave 0.6 mg (70%) of the analogue **74**.

^{1}H NMR (300 MHz, $CDCl_3$) 6.67 (ddd, 1H, J = 16.5, 10.7, 10.1 Hz), 6.15 (dd, 1H, J = 10.7, 10.7 Hz), 5.51–5.46 (m, 1H), 5.39–5.28 (m, 4H), 5.25 (d, 1H, J = 16.5 Hz), 5.17 (d, 1H, J = 10.1 Hz), 4.87 (dt, 1H, J = 12.4, 5.1 Hz), 4.58 (bs, 2H), 4.09–4.02 (m, 2H), 3.40 (dd, 1H, J = 7.6, 3.3 Hz), 3.21 (dd, 1H, J = 5.8, 5.8 Hz), 2.89–2.83 (m, 1H), 2.65–2.57 (m, 2H), 2.18–1.97 (m, 4H), 1.90–1.81 (m, 2H), 1.75–1.58 (m, 3H), 1.21 (s, 9H), 0.99–0.96 (m, 12H); MS (EI, m/z) 503 $(M-18)^+$, 429, 355, 281, 221, 207; HRMS (EI) calcd for $C_{30}H_{49}NO_5$ $(M-H_2O)^+$ 503.3610, found 503.3594; $[\alpha]_D^{20}$ +28.0 (c 0.025, $CHCl_3$).

Benzoic acid, (*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*R*,14*S*,15*S*,16*S*)-13-carbamoyloxy-7,15-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (75). A mixture of **72** (4.5 mg, 6.6 μmol), pyridine and benzoyl chloride was stirred for 20 h. Following the general procedure, *benzoic acid, (Z,Z,Z)-(6S,7S,8S,13R,14S,15S,16S)-13-carbamoyloxy-*

7,15 - bis(4 - methoxybenzyloxy) - 6,8,14,16 - tetramethyleicosa-4,9,17,19-tetraenyl ester was obtained.

^{1}H NMR (300 MHz, $CDCl_3$) 8.04 (dd, 2H, J = 8.3, 1.3 Hz), 7.55–7.48 (m, 1H), 7.46–7.42 (m, 2H), 7.28 (d, 4H, J = 8.7 Hz), 6.86 (d, 4H, J = 8.7 Hz), 6.70 (ddd, 1H, J = 16.7, 11.0, 10.0 Hz), 6.02 (dd, 1H, J = 11.0, 11.0 Hz), 5.51 (dd, 1H, J = 10.5, 10.5 Hz), 5.53–5.48 (m, 1H), 5.41–5.21 (m, 3H), 5.18 (d, 1H, J = 16.7 Hz), 5.11 (d, 1H, J = 10.0 Hz), 4.84–4.79 (m, 1H), 4.58–4.44 (m, 6H), 4.29 (t, 2H, J = 6.5 Hz), 3.81 (s, 3H), 3.80 (s, 3H), 3.21–3.11 (m, 2H), 3.04 (dd, 1H, J = 7.5, 4.0 Hz), 2.75–2.66 (m, 1H), 2.63–2.56 (m, 1H), 2.12–2.07 (m, 1H), 2.03–1.96 (m, 1H), 1.88–1.76 (m, 4H), 1.62–1.50 (m, 3H), 1.09 (d, 3H, J = 6.7 Hz), 1.02-0.98 (m, 9H).

The ester above obtained (4.0 mg, 5.1 μmol) was treated with $NaHCO_3$ and DDQ according to the general protocol. Chromatography of the crude product using CH_2Cl_2 to CH_2Cl_2/EtOAc 7:3 yielded 2.0 mg (77%) of the corresponding analogue **75**.

^{1}H NMR (300 MHz, $CDCl_3$) 8.05 (dd, 2H, J = 8.5, 1.4 Hz), 7.57–7.54 (m, 1H), 7.47–7.43 (m, 2H), 6.65 (ddd, 1H, J = 17.6, 10.9, 10.1 Hz), 6.15 (dd, 1H, J = 10.9, 10.9 Hz), 5.52 (dd, 1H, J = 10.5, 10.5 Hz), 5.41–5.31 (m, 4H), 5.24 (d, 1H, J = 17.6 Hz), 5.16 (d, 1H, J = 10.1 Hz), 4.86 (dt, 1H, J = 5.2, 5.2 Hz), 4.58 (bs, 2H), 4.35–4.30 (m, 2H), 3.39 (dd, 1H, J = 7.5, 3.7 Hz), 3.21 (dd, 1H, J = 5.9, 5.9 Hz), 2.90–2.84 (m, 1H), 2.66–2.57 (m, 2H), 2.33–2.05 (m, 4H), 1.92–1.77 (m, 3H), 1.69–1.62 (m, 2H), 0.96 (d, 12H, J = 6.7 Hz); MS (EI, m/z) 460 $(M-C_6H_9)^+$, 433, 417, 399, 247, 105; HRMS (EI) calcd for $C_{26}H_{38}NO_6$ $(M-C_6H_9)^+$ 460.2699, found 460.2704; $[\alpha]_D^{20}$ +44.7 (c 0.085, $CHCl_3$).

Acetic acid, (*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*R*,14*S*,15*S*,16*S*)-13-carbamoyloxy-7,15-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (76). Following the general procedure, a mixture of 4.5 mg (6.6 μmol) of the alcohol **72**, pyridine and acetyl chloride was stirred for 40 h. After purification of the crude product, *acetic acid, (Z,Z,Z)-(6S,7S,8S,13R,14S,15S,16S)-13-carbamoyloxy-7,15 - bis(4 - methoxybenzyloxy) - 6,8,14,16 - tetramethyleicosa-4,9,17,19-tetraenyl ester* was obtained.

^{1}H NMR (300 MHz, $CDCl_3$) 7.28 (d, 4H, J = 8.6 Hz), 6.87 (d, 4H, J = 8.6 Hz), 6.70 (ddd, 1H, J = 16.8, 11.0, 10.0 Hz), 6.02 (dd, 1H, J = 11.0, 11.0 Hz), 5.52 (dd, 1H, J = 10.5, 10.5 Hz), 5.50 (dd, 1H, J = 11.0, 11.0 Hz), 5.36–5.21 (m, 3H), 5.18 (d, 1H, J = 16.8 Hz), 5.12 (d, 1H, J = 10.0 Hz), 4.82 (dt, 1H, J = 8.4, 5.2 Hz), 4.57 (bs, 2H), 4.56–4.51 (m, 3H), 4.47 (d, 1H, J = 10.3 Hz), 4.03 (t, 2H, J = 6.6 Hz), 3.81 (s, 6H), 3.21 (dd, 1H, J = 7.1, 3.7 Hz), 3.19–3.12 (m, 1H), 3.05 (dd, 1H, J = 7.5, 4.0 Hz), 2.71–2.64 (m, 1H), 2.64–2.58 (m, 1H), 2.06–2.01 (m, 2H), 2.05 (s, 3H), 1.90–1.79 (m, 2H), 1.67–1.55 (m, 5H), 1.09 (d, 3H, J = 6.7 Hz), 1.01 (d, 9H, J = 6.9 Hz).

To the ester above obtained (2.0 mg, 2.7 μmol) was added $NaHCO_3$ and DDQ. Chromatography of the crude product using CH_2Cl_2 to CH_2Cl_2/EtOAc 1:1 gave 1 mg (77%) of the analogue **76** as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) 6.68 (ddd, 1H, J = 17.3, 10.9, 10.1 Hz), 6.16 (dd, 1H, J = 10.9, 10.9 Hz), 5.50–5.29 (m, 5H), 5.26 (d, 1H, J = 17.3 Hz), 5.17 (d, 1H, J = 10.1 Hz), 4.91–4.85 (m, 1H), 4.60 (bs, 2H), 4.09–4.01 (m, 2H), 3.43–3.39 (m, 1H), 3.22 (dd, 1H, J = 8.8, 5.8 Hz), 2.92–2.84 (m, 1H), 2.65–2.54 (m, 2H), 2.18–2.02 (m, 2H), 2.06 (s, 3H), 1.86–1.84 (m, 1H), 1.75–1.59 (m, 6H), 1.01–0.97 (m, 12H); MS (EI, m/z) 480 $(M+H)^+$, 467, 398, 337, 324, 319, 301; HRMS (EI) calcd for $C_{21}H_{36}NO_6$ $(M-C_6H_9)^+$ 398.2543, found 398.2544; $[\alpha]_D^{20}$ +53.3 (c 0.045, $CHCl_3$).

2,2-Dimethylpropionic acid, (*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*R*,14*S*,15*S*,16*S*)-13-acetoxy-7,15-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (77). Following the general procedure, a mixture of the alcohol **73** (1.9 mg, 2.8 μmol), pyridine and pivaloyl chloride was stirred for 40 h. After purification of the crude product, *2,2-dimethylpropionic acid, (Z,Z,Z)-(6S,7S,8S,13R,14S,15S,16S)-13-acetoxy-7,15-bis(4-methoxybenzyloxy)-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester* was obtained.

^{1}H NMR (300 MHz, $CDCl_3$) 7.27 (d, 4H, J = 8.1 Hz), 6.89 (d, 4H, J = 8.1 Hz), 6.70 (ddd, 1H, J = 16.3, 10.9, 10.0 Hz), 6.03 (dd, 1H, J = 10.9, 10.9 Hz), 5.51 (dd, 1H, J = 10.1, 10.1 Hz), 5.53–5.48 (m, 1H), 5.33–5.25 (m, 3H), 5.23 (d, 1H, J = 16.3 Hz), 5.14 (d, 1H, J = 10.0 Hz), 4.99–4.93 (m, 1H), 4.58–4.52 (m, 3H), 4.47 (d, 1H, J = 10.5 Hz), 4.06–4.02 (m, 2H), 3.82 (s, 6H), 3.16–3.05 (m, 3H), 2.74–2.67 (m, 1H), 2.63–2.55 (m, 1H), 2.12–1.92 (m, 4H), 2.06 (s, 3H), 1.84–1.80 (m, 2H), 1.70–1.55 (m, 3H), 1.21 (s, 9H), 1.09 (d, 3H, J = 6.7 Hz), 1.02–0.98 (m, 9H).

To the ester above obtained (1.6 mg, 2.1 μmol) was added $NaHCO_3$ and DDQ. Flash chromatography of the residue (CH_2Cl_2 to CH_2Cl_2/EtOAc 7:3) afforded 0.7 mg (70%) of the corresponding analogue **77**.

^{1}H NMR (300 MHz, $CDCl_3$) 6.66 (ddd, 1H, J = 16.3, 10.8, 10.2 Hz), 6.16 (dd, 1H, J = 10.8, 10.8 Hz), 5.50–5.45 (m, 1H), 5.38–5.23 (m, 5H), 5.17 (d, 1H, J = 10.2 Hz), 5.05–5.00 (m, 1H), 4.11–4.03 (m, 2H), 3.36 (dd, 1H, J = 7.6, 3.5 Hz), 3.20 (dd, 1H, J = 5.8, 5.8 Hz), 2.85–2.78 (m, 1H), 2.63–2.57 (m, 2H), 2.16–2.00 (m, 2H), 2.06 (s, 3H), 1.92–1.85 (m, 1H), 1.76–1.58 (m, 6H), 1.21 (s, 9H), 1.00–0.97 (m, 12H); MS (FAB in MNBA/NaCl, m/z) 543 $(M+Na)^+$, 521 $(M+H)^+$, 483, 462, 448, 413; $[\alpha]_D^{20}$ +56.6 (c 0.03, $CHCl_3$).

Benzoic acid, (*Z*,*Z*,*Z*)-(6*S*,7*S*,8*S*,13*R*,14*S*,15*S*,16*S*)-13-acetoxy - 7,15 - dihydroxy - 6,8,14,16 - tetramethyleicosa - 4,9,17,19-tetraenyl ester (78). A mixture of the alcohol **73** (1.9 mg, 2.8 μmol), pyridine and benzoyl chloride was stirred for 24 h. Following the general procedure, *benzoic acid, (Z,Z,Z)-(6S,7S,8S,13R,14S,15S,16S)-13-acetoxy-7,15-bis(4-methoxybenzyloxy)-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester* was obtained.

^{1}H NMR (300 MHz, $CDCl_3$) 8.04 (dd, 2H, J = 8.6, 1.5 Hz), 7.57–7.53 (m, 1H), 7.48–7.40 (m, 2H), 7.28–7.25 (m, 4H), 6.87 (d, 2H, J = 8.5 Hz), 6.85 (d, 2H, J = 8.5 Hz), 6.68 (ddd, 1H, J = 18.5, 11.0, 10.0 Hz), 6.01 (dd, 1H, J = 11.0, 11.0 Hz), 5.54–5.45 (m, 2H), 5.40–5.20 (m,

3H), 5.19 (d, 1H, $J=18.5$ Hz), 5.12 (d, 1H, $J=10.0$ Hz), 4.94 (dt, 1H, $J=8.3$, 5.2 Hz), 4.58–4.50 (m, 3H), 4.48 (d, 1H, $J=9.2$ Hz), 4.25–4.19 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.16–3.07 (m, 2H), 3.03 (dd, 1H, $J=7.4$, 4.2 Hz), 2.75–2.68 (m, 1H), 2.59–2.49 (m, 1H), 2.36–2.18 (m, 2H), 2.04 (s, 3H), 2.05–1.96 (m, 1H), 1.84–1.74 (m, 4H), 1.64–1.55 (m, 2H), 1.07 (d, 3H, $J=6.7$ Hz), 1.01–0.97 (m, 9H).

The ester above obtained (1.6 mg, 2.0 μmol) was treated with $NaHCO_3$ and DDQ according to the general method. Chromatography of the crude product using CH_2Cl_2 to CH_2Cl_2/EtOAc 17:3 provided 0.7 mg (70%) of the corresponding analogue **78**.

^{1}H NMR (300 MHz, $CDCl_3$) 8.05 (d, 2H, $J=7.5$ Hz), 7.58–7.54 (m, 1H), 7.47–7.43 (m, 2H), 6.65 (ddd, 1H, $J=16.5$, 11.0, 10.6 Hz), 6.16 (dd, 1H, $J=11.0$, 11.0 Hz), 5.57–5.49 (m, 1H), 5.41–5.23 (m, 5H), 5.18 (d, 1H, $J=10.6$ Hz), 5.04–5.00 (m, 1H), 4.34–4.30 (m, 2H), 3.37–3.33 (m, 1H), 3.20 (dd, 1H, $J=5.5$, 5.5 Hz), 2.87–2.79 (m, 1H), 2.67–2.59 (m, 2H), 2.21–2.11 (m, 2H), 2.06 (s, 3H), 1.90–1.79 (m, 4H), 1.66–1.58 (m, 3H), 0.98–0.95 (m, 12H); MS (FAB in glycerol, *m*/*z*) 541 $(M+H)^+$, 492, 477, 409, 371, 208, 105; HRMS (FAB in glycerol) calcd for $C_{33}H_{49}O_6$ $(M+H)^+$ 541.3529, found 541.3531; $[\alpha]_D^{20}$ +36.6 (*c* 0.03, $CHCl_3$).

General procedure for the (11*R*,17*R*)-carbamoyloxy or (11*R*,17*R*)-acetoxy analogues of discodermolide

Acetic acid, (*Z*,*Z*,*Z*)-(6*S*,7*R*,8*S*,13*R*,14*S*,15*S*,16*S*)-13-carbamoyloxy-7,15-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (89). To a solution of **87** (3.2 mg, 4.7 μmol) in 500 μL of dichloromethane was added pyridine (2.0 μL, 24 μmol) followed by acetyl chloride (1.0 μL, 13 μmol). After 3 h, the solution was concentrated and chromatographed (hexane/ether 2:3) to afford 3.3 mg (98%) of the acetate. The acetate obtained above was dissolved in dichloromethane (1.0 mL) and $NaHCO_3$ (120 mg) was added to the solution followed by DDQ (4.0 mg, 18 μmol). After 1 h of stirring at ambient temperature, the mixture was concentrated under a stream of nitrogen and chromatographed (hexane/EtOAc 1:2) to give 2.2 mg (99%) of the analogue **89**.

IR (thin film, NaCl) 3445, 2961, 1718, 1602, 1251 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 6.79–6.66 (td, 1H, $J=16.6$, 10.4 Hz), 6.03 (dd, 1H, $J=11.1$, 11.1 Hz), 5.56–5.46 (m, 2H), 5.38–5.12 (m, 5H), 4.87–4.83 (m, 1H), 4.71 (bs, 2H), 3.61 (t, 2H, $J=6.5$ Hz), 3.22–3.11 (m, 2H), 3.06 (dd, 1H, $J=7.7$, 3.2 Hz), 2.71–2.60 (m, 2H), 2.11–1.76 (m, 6H), 2.03 (s, 3H), 1.65–1.50 (m, 3H), 1.10 (d, 3H, $J=6.6$ Hz), 1.04–1.00 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 159.2, 159.2, 157.2, 140.8, 134.4, 134.1, 132.7, 132.4, 131.4, 131.2, 129.6, 129.3, 128.6, 125.7, 117.7, 113.9, 88.2, 84.3, 75.6, 75.1, 75.0, 62.7, 55.5, 40.3, 36.3, 35.6, 35.5, 32.9, 30.5, 29.9, 24.1, 23.8, 19.3, 18.9, 17.8, 10.3; MS (APCI, *m*/*z*) 478 $(M-H)^+$, 462, 401, 383, 323, 282. HRMS (EI) calcd for $C_{21}H_{36}NO_6$ $(M-C_6H_9)^+$ 398.2543, found 398.2544.

Isobutyric acid, (*Z*,*Z*,*Z*)-(6*S*,7*R*,8*S*,13*R*,14*S*,15*S*,16*S*)-13-carbamoyloxy-7,15-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (90). The above procedure was repeated starting from **87** (3.0 mg, 4.4 μmol) to give **90** (2.0 mg, 4.1 μmol, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) 6.66 (td, 1H, $J=16.5$, 10.6 Hz), 6.15 (t, 1H, $J=10.9$ Hz), 5.49–5.15 (m, 7H), 4.91–4.85 (m, 1H), 4.62 (bs, 2H), 3.72 (t, 2H, $J=6.4$ Hz), 3.40 (dd, 1H, $J=7.4$, 3.6 Hz), 3.19 (t, 1H, $J=5.8$ Hz), 2.91–2.83 (m, 1H), 2.64–2.50 (m, 3H), 2.17–1.99 (m, 4H), 1.86–1.61 (m, 7H), 1.18 (d, 6H, $J=6.7$ Hz), 0.98 (d, 6H, $J=6.7$ Hz), 0.97 (d, 6H, $J=6.5$ Hz); MS (EI, *m*/*z*) 476, 410, 386, 368, 121.

2,2-Dimethylpropionic acid, (*Z*,*Z*,*Z*)-(6*S*,7*R*,8*S*,13*R*,14*S*,15*S*,16*S*)-13-carbamoyloxy-7,15-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (91). Following the general procedure, starting from 3.0 mg (4.4 μmol) of **87** was obtained 1.6 mg (3.1 μmol, 70%) of **91**. ^{1}H NMR (300 MHz, $CDCl_3$) 6.66 (td, 1H, $J=16.9$, 10.6 Hz), 6.15 (t, 1H, $J=11.0$ Hz), 5.49–5.15 (m, 7H), 4.91–4.85 (m, 1H), 4.61 (bs, 2H), 4.06 (t, 2H, $J=6.3$ Hz), 3.40 (dd, 1H, $J=7.3$, 3.6 Hz), 3.19 (t, 1H, $J=5.7$ Hz), 2.93–2.82 (m, 1H), 2.65–2.55 (m, 2H), 2.19–2.01 (m, 4H), 1.84–1.59 (m, 7H), 1.20 (s, 9H), 0.98 (d, 6H, $J=6.8$ Hz), 0.97 (d, 6H, $J=7.0$ Hz); MS (APCI, *m*/*z*) 521 $(M)^+$, 520, 504, 443, 425, 341.

Benzoic acid, (*Z*,*Z*,*Z*)-(6*S*,7*R*,8*S*,13*R*,14*S*,15*S*,16*S*)-13-carbamoyloxy-7,15-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (92). The above procedure was repeated starting from 3.0 mg (4.4 μmol) of **87** to yield **92** (1.7 g, 3.2 μmol, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) 8.05 (d, 2H, $J=7.4$ Hz), 7.56 (d, 1H, $J=7.4$ Hz), 7.45 (t, 2H, $J=7.4$ Hz), 6.67 (td, 1H, $J=16.9$, 10.8 Hz), 6.14 (t, 1H, $J=11.0$ Hz), 5.48–5.15 (m, 7H), 4.90–4.84 (m, 1H), 4.60 (bs, 2H), 4.33 (t, 2H, $J=6.3$ Hz), 3.39 (dd, 1H, $J=7.0$, 3.3 Hz), 3.19 (t, 1H, $J=5.2$ Hz), 2.90–2.82 (m, 1H), 2.66–2.54 (m, 2H), 2.29–1.98 (m, 4H), 1.93–1.58 (m, 7H), 0.98–0.92 (m, 12H); MS (APCI, *m*/*z*) 540 $(M-H)^+$, 524, 463, 445, 323; HRMS (EI) calcd for $C_{26}H_{38}NO_6$ $(M-C_6H_9)^+$ 460.2699, found 460.2696.

Methoxyacetic acid, (*Z*,*Z*,*Z*)-(6*S*,7*R*,8*S*,13*R*,14*S*,15*S*,16*S*)-13-carbamoyloxy-7,15-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (93). The general procedure was repeated starting from 3.0 mg (4.4 μmol) of **87** to afford 2.0 mg (4.1 μmol, 93%) of **93**. ^{1}H NMR (300 MHz, $CDCl_3$) 6.67 (td, 1H, $J=16.9$, 10.6 Hz), 6.15 (t, 1H, $J=10.9$ Hz), 5.49–5.15 (m, 7H), 4.88 (td, 1H, $J=7.9$, 4.6 Hz), 4.62 (bs, 2H), 4.18 (t, 2H, $J=6.6$ Hz), 4.04 (s, 2H), 3.46 (s, 3H), 3.40 (dd, 1H, $J=7.5$, 3.4 Hz), 3.19 (t, 1H, $J=5.7$ Hz), 2.91–2.83 (m, 1H), 2.63–2.54 (m, 2H), 2.16–2.01 (m, 4H), 1.85–1.63 (m, 7H), 0.98 (d, 6H, $J=6.7$ Hz), 0.97 (d, 6H, $J=6.4$ Hz); MS (APCI, *m*/*z*) 508 $(M-H)^+$, 492, 431, 413, 341.

Acetic acid, (*Z*,*Z*,*Z*)-(6*S*,7*R*,8*S*,13*R*,14*S*,15*S*,16*S*)-13-acetoxy-7,15-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (94). Following the general method starting from **88** (3.0 mg, 4.5 μmol) was obtained **94** (1.5 mg, 3.1 μmol, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) 6.65 (td, 1H, $J=16.9$, 10.8 Hz), 6.16 (t, 1H, $J=10.9$ Hz), 5.50–5.16 (m, 7H), 5.10–5.00 (m, 1H), 4.06 (t, 2H, $J=6.5$ Hz), 3.36 (dd, 1H, $J=7.6$, 3.5

Hz), 3.19 (t, 1H, $J=5.4$ Hz), 2.88–2.80 (m, 1H), 2.71–2.53 (m, 2H), 2.06 (s, 3H), 2.05 (s, 3H), 2.18–2.00 (m, 4H), 1.88–1.80 (m, 1H), 1.75–1.60 (m, 6H), 1.10–0.95 (m, 12H); MS (EI, *m*/*z*) 478 $(M)^+$, 418, 346, 185, 121, 95; HRMS (EI) calcd for $C_{22}H_{37}O_6$ $(M-C_6H_9)^+$ 397.2590, found 397.2591.

Isobutyric acid, (*Z*,*Z*,*Z*)-(6*S*,7*R*,8*S*,13*R*,14*S*,15*S*,16*S*)-13-acetoxy-7,15-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (95). The above reaction was repeated from 5.0 mg (7.5 μmol) of **88** to give 2.6 mg (5.3 μmol, 71%) of the analogue **95**. ^{1}H NMR (300 MHz, $CDCl_3$) 6.66 (td, 1H, $J=16.8$, 10.5 Hz), 6.16 (t, 1H, $J=11.0$ Hz), 5.49–5.16 (m, 7H), 5.03 (q, 1H, $J=5.7$ Hz), 4.07 (t, 2H, $J=6.5$ Hz), 3.35 (dd, 1H, $J=7.5$, 3.2 Hz), 3.19 (t, 1H, $J=5.5$ Hz), 2.88–2.80 (m, 1H), 2.65–2.50 (m, 3H), 2.06 (s, 3H), 2.20–1.98 (m, 4H), 1.87–1.60 (m, 7H), 1.18 (d, 6H, $J=6.7$ Hz), 0.99–0.96 (m, 12H); MS (EI, *m*/*z*) 440, 368, 284, 95.

2,2-Dimethylpropionic acid, (*Z*,*Z*,*Z*)-(6*S*,7*R*,8*S*,13*R*,14*S*,15*S*,16*S*)-13-acetoxy-7,15-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (96). The above procedure was repeated with **88** (3.0 mg, 4.5 μmol) to give **96** (0.8 mg, 1.5 μmol, 33%). ^{1}H NMR (300 MHz, $CDCl_3$) 6.66 (td, 1H, $J=16.6$, 10.5 Hz), 6.16 (t, 1H, $J=11.0$ Hz); 5.49–5.16 (m, 7H), 5.04 (q, 1H, $J=5.9$ Hz), 4.07 (t, 2H, $J=6.4$ Hz), 3.36 (dd, 1H, $J=7.6$, 3.5 Hz), 3.19 (t, 1H, $J=5.8$ Hz), 2.88–2.80 (m, 1H), 2.68–2.53 (m, 2H), 2.06 (s, 3H), 2.18–1.99 (m, 4H), 1.89–1.80 (m, 1H), 1.75–1.55 (m, 6H), 1.21 (s, 9H), 0.99 (d, 3H, $J=6.5$ Hz), 0.97 (d, 6H, $J=6.8$ Hz), 0.96 (d, 3H, $J=6.5$ Hz); MS (APCI, *m*/*z*) 519 $(M-H)^+$, 503, 443, 425, 251; HRMS (EI) calcd for $C_{25}H_{43}O_6$ $(M-C_6H_9)^+$ 439.3060, found 439.3063.

Benzoic acid, (*Z*,*Z*,*Z*)-(6*S*,7*R*,8*S*,13*R*,14*S*,15*S*,16*S*)-13-acetoxy - 7,15 - dihydroxy - 6,8,14,16 - tetramethyleicosa - 4,9,17,19-tetraenyl ester (97). Following the general protocol starting from **88** (5.0 mg, 7.5 μmol) 2.7 mg (5.0 μmol, 67%) of **97** was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) 8.05 (d, 2H, $J=7.3$ Hz), 7.58 (d, 1H, $J=7.3$ Hz), 7.45 (t, 2H, $J=7.3$ Hz), 6.65 (td, 1H, $J=16.9$, 10.7 Hz), 6.15 (t, 1H, $J=10.9$ Hz), 5.50–5.12 (m, 7H), 5.03 (q, 1H, $J=5.8$ Hz), 4.34–4.30 (m, 2H), 3.35 (dd, 1H, $J=7.6$, 3.4 Hz), 3.18 (t, 1H, $J=5.3$ Hz), 2.89–2.78 (m, 1H), 2.66–2.53 (m, 2H), 2.30–2.02 (m, 4H), 2.05 (s, 3H), 1.89–1.81 (m, 3H), 1.70–1.60 (m, 4H), 0.98 (d, 3H, $J=6.5$ Hz), 0.95 (d, 6H, $J=6.5$ Hz), 0.93 (d, 3H, $J=6.9$ Hz); MS (APCI, *m*/*z*) 523 $(M-OH)^+$, 463, 445, 341, 323.

Methoxyacetic acid, (*Z*,*Z*,*Z*)-(6*S*,7*R*,8*S*,13*R*,14*S*,15*S*,16*S*)-13-acetoxy-7,15-dihydroxy-6,8,14,16-tetramethyleicosa-4,9,17,19-tetraenyl ester (98). The above reaction was repeated with 3.0 mg (4.5 μmol) of **88** to afford 2.0 mg (3.9 μmol, 87%) of the analogue **98**. ^{1}H NMR (300 MHz, $CDCl_3$) 6.65 (td, 1H, $J=16.9$, 10.6 Hz), 6.16 (t, 1H, $J=10.9$ Hz), 5.50–5.18 (m, 7H), 5.03 (q, 1H, $J=5.8$ Hz), 4.18 (t, 2H, $J=6.6$ Hz), 4.04 (s, 2H), 3.46 (s, 3H), 3.36 (dd, 1H, $J=7.6$, 3.5 Hz), 3.19 (t, 1H, $J=5.9$ Hz), 2.90–2.81 (m, 1H), 2.66–2.54 (m, 2H), 2.06 (s, 3H), 2.18–1.95 (m, 4H), 1.85–1.62 (m, 7H), 0.98 (d, 3H, $J=6.3$ Hz), 0.97 (d, 6H, $J=6.5$ Hz), 0.96 (d, 3H, $J=6.2$ Hz); MS (APCI, *m*/*z*) 509 $(M-H)^+$, 491, 431, 413, 341, 323.

Biological evaluation

Electrophoretically homogenous tubulin free from microtubule associated proteins was isolated as described.[23]

Microtubule assembly assay.[4a,8] Assembly of tubulin into polymer was followed by turbidity measurement at 350 nm with a temperature-controlled, six-cuvette Beckman-Coulter 7400 spectrophotometer. 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 volume 4% v/v), and test agent (10 μM). 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. The change in absorbance 20 min after samples reached 30 °C was used to calculate the extent of polymerization. The change in absorbance at this time point for the addition of vehicle plus paclitaxel was considered 100% assembly (positive control), while the change in absorbance for addition of vehicle alone (negative control) was taken as 0% assembly.

Paclitaxel binding site inhibition assay.[24] 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 non-hydrolyzable 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 14,000 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.

Antiproliferative activity.[8,25,26] 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; 0.01, 0.05, 0.010, 0.020 and 0.100 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)-2H-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.

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