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Conception, Synthesis, and Biological Evaluation of Original Discodermolide Analogues

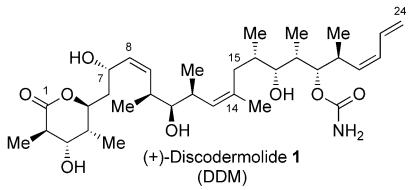
Elsa de Lemos,[a] Evangelos Agouridas,[a] Geoffroy Sorin,[a] Antonio Guerreiro,[b] Alain Commerçon,[b] Ange Pancrazi,[a] Jean-François Betzer,*[a] Marie-Isabelle Lannou,*[a] and Janick Ardisson*[a]

Abstract: Due to its intriguing biological activity profile and potential chemotherapeutic application discodermolide (DDM) proved to be an attractive target. Therefore, notable efforts have been carried out directed toward its total synthesis and toward the production and evaluation of synthetic analogues. Recently, we achieved the total synthesis of DDM. At the present, guided by the knowledge gained during our DDM total synthesis and by the requirement of keeping the bioactive "U" shape conformation, we report the convergent preparation of five original analogues. Three types of changes were realized through modification of the terminal (*Z*)-diene moiety, of the methyl group at the C14-position, and the lactone region. All analogues were active in the nanomolar range and two of them turned out to be equipotent to DDM.

Keywords: anticancer agents · cross-coupling · discodermolide · nickel · polyketides

Introduction

(+)-Discodermolide (DDM **1**) is a polypropionate natural product originally isolated from the marine sponge *Discodermia dissoluta*.[1] It was found to be a potent microtubule stabilizer that binds with remarkable affinity to the taxoid site on β-tubulin in microtubules.[2] Further studies, however, revealed clear differences between the two drugs. In vitro, DDM exhibits greater tubulin polymerization potency than Taxol, and formed microtubules are much shorter. Additionally, DDM is a poor substrate of the P-glycoprotein pump and retains antiproliferative potency against β-tubulin mutant cell lines that are resistant to taxanes and epothilones.[2j] Interestingly, discodermolide can induce accelerated cell senescence, which is not a typical characteristic of Taxol.[3] Of particular relevance are the findings that DDM and Taxol act synergistically, both in in vitro and in vivo tumor models, something that is not observed with taxanes and epothilones.[4]



(+)-Discodermolide **1** (DDM)

These exciting activities resulted in a Phase I clinical trial initiated by Novartis, which was suspended due to pulmonary toxiticy, despite encouraging results.[5] Work towards nontoxic and active DDM analogues is, however, still ongoing.[6]

(+)-DDM (**1**) comprises a linear polypropionate backbone, punctuated by 13 stereogenic centers, (*Z*)-olefinic linkages at C8–C9 and C13–C14, a terminal (*Z*)-diene substituent at C21–C24, and a δ-lactone. Reported solid-state, solution, and protein-bound DDM conformations reveal the unusual result that a common hairpin conformational motif exists in all three microenvironments.[2a,7] No other flexible microtubule binding agents exhibit such constancy of conformation. The stability of this strongly preferred form with respect to the central sector of the molecule, is due to steric factors (i.e. $A^{1,3}$ and $A^{1,2}$ strains and *syn*-pentane interactions) arising from repeated modular segments, composed of the C(Me)–CHX–C(Me) fragment and the C8–C9 and C13–C14 *Z* double bonds.

The natural product was only isolated in low yields, and no biosynthesis method has been found to produce DDM; therefore, the material necessary for biological studies must be generated synthetically. The unique profile of this medicinally relevant product has incited a number of efforts direct-

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ed toward the total synthesis of (+)-DDM[8,9,10] and toward the production of synthetic analogues.[10,11] These studies have helped to define critical requirements for activity. Changes in the C15–C24 fragment of DDM were some of the first modifications investigated. The configuration of the C16 and C17 stereocentres and the geometry of the C21–C22 double bond seem crucial for activity. In the C8–C14 region of the molecule, only scarce variations have been reported. This can be attributed to the crucial importance of the middle part on the spatial orientation of the molecule. On the contrary, modifying the δ-lactone fragment has yielded most of the analogues that have been generated to date. Thus, while the carbon backbone is required to set the overall conformation of the molecule, the diene and lactone regions provide opportunities to develop analogues with improved potency, pharmacokinetic properties, or simplified structure.

Recently, we achieved the total synthesis of DDM (**1**) by using a straightforward and highly convergent route.[8m,n] As a result of the modulable character of our approach allowing specific structural modifications, we report here the elaboration of five original DDM analogues and their biological evaluation.

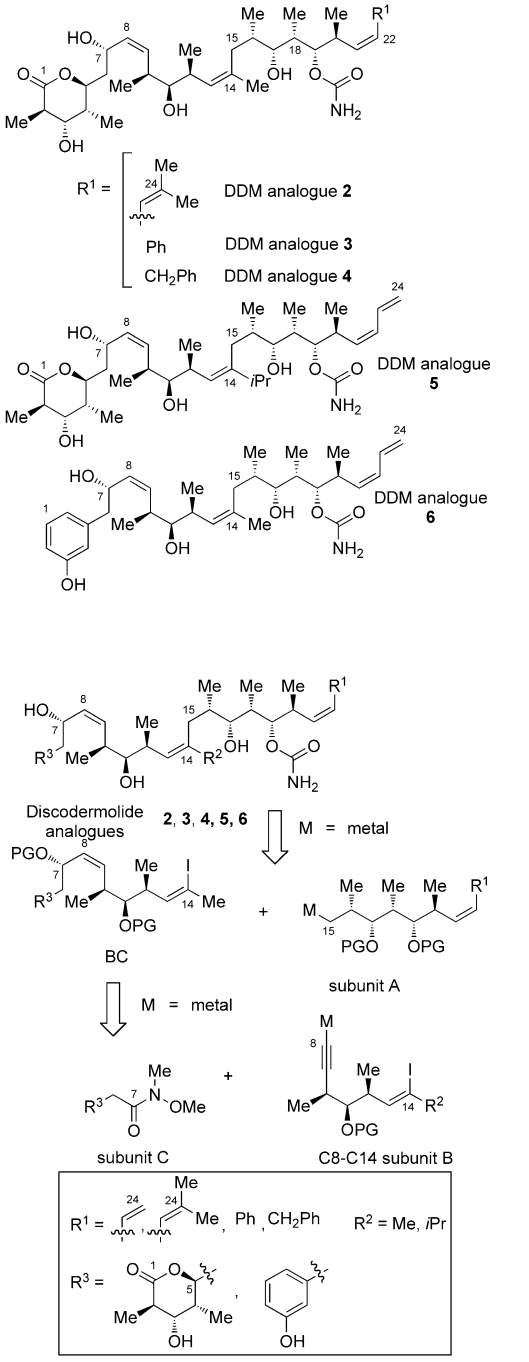
Results and Discussion

The design of the analogues was guided by the chemical knowledge gained during the total synthesis and by the strong constraint of keeping the essential "U"-shaped conformation of DDM. Therefore, computational conformational analysis was performed on the focused analogues to check if the hairpin conformation is still favored.[12]

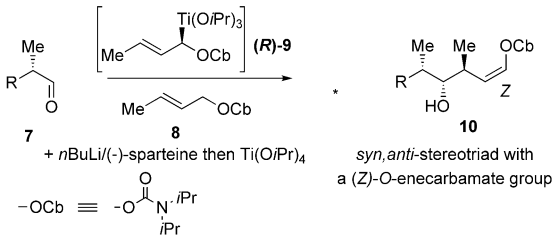
We envisioned modifying or replacing the terminal C21–C24 diene, the lactone region, and the methyl group at the C14-position of DDM. Therefore, we focused on the synthesis of five analogues, **2** (including a C24 *gem*-di-Me group), **3** and **4** (encompassing a phenyl or a benzyl group at the C22-position), **5** (substituted by an isopropyl group at C14), and **6** (in which an aromatic group replaced the δ-lactone).

The strategy for the preparation of the five analogues **2**–**6** patterned after the synthesis of **1** is summarized in Scheme 1. The same disconnections were made to provide **A**, **B**, and **C** fragments. The linkage of these subunits will rely on acetylide addition to Weinreb amide (**B**–**C**) and a Suzuki Pd-catalyzed sp^2–sp^3 coupling reaction (**A**–**BC**).

A central feature of our DDM (**1**) total synthesis was the repeated addition of the chiral (*R*)-crotyltitanium reagent **9** to a (*S*)-methyl aldehyde **7** to yield homoallylic adducts **10** encompassing a *syn–anti* methyl–hydroxy–methyl triad linked to a (*Z*)-*O*-enecarbamate group, with excellent diastereoselectivity (Scheme 2). The enantioenriched (*R*)-α-(*N*,*N*-diisopropylcarbamoyloxy) crotyltitanium (**9**) was readily prepared in situ from crotyl diisopropylcarbamate **8**, an equimolar mixture of *n*BuLi/(−)-sparteine, and tetra(isopropoxy)titanium.[13,14]

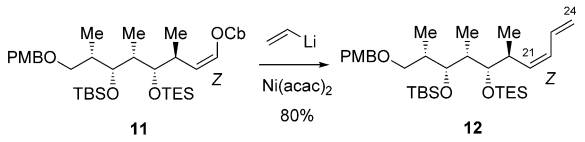


Scheme 1. DDM analogues: Retrosynthetic analysis.



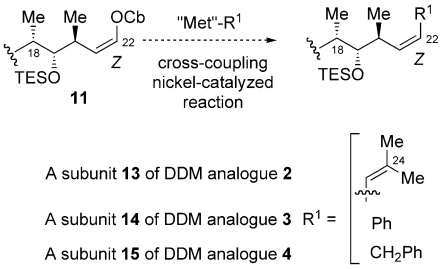
Scheme 2. DDM total synthesis: Crotyltitanation of aldehyde **7**.

Furthermore, reactivity of the (*Z*)-*O*-enecarbamate moiety was critical in the preparation of the C21–C24 terminal (*Z*)-diene **12** of DDM. The direct vinylation of vinylcarbamate **11** was performed through a nickel-catalyzed cross-coupling reaction in the presence of [Ni(acac)$_2$] with vinyllithium (Scheme 3).[8m–n,15,16]



Scheme 3. DDM total synthesis: Formation of the terminal (*Z*)-diene **12**. PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

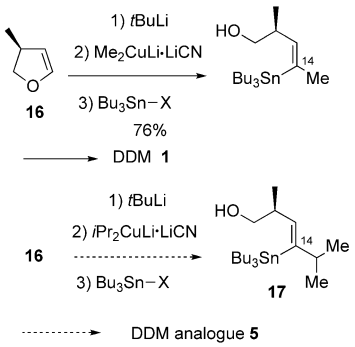
This approach could allow us to modify the (*Z*)-C21–C24 diene core through an extension of the nickel-catalyzed cross-coupling reaction from the terminal (*Z*)-*O*-enecarbamate compound **11**. Hence, the elaboration of three original and more lipophilic DDM analogues was considered, one including a (*Z*)-diene unit with a C24 *gem*-di-Me group (**13**) and two nondiene derivatives with a phenyl or a benzyl core (**14** and **15**) (Scheme 4).



Scheme 4. Synthetic analysis of DDM analogues: Setup of the analogous terminal (*Z*)-dienes through a nickel-catalyzed cross-coupling reaction.

The replacement of the methyl group at the C14-position by a more sterically demanding isopropyl group was very original and innovative. Although such a variation has never been reported so far, we were convinced it could enhance the specific active conformation of DDM (**1**). For the building of the corresponding analogue **5**, we studied an improvement of the dyotropic rearrangement developed for our DDM total synthesis,[8m–n,17] involving an isopropyl cuprate instead of a methylcuprate, from dihydrofuran **16**, to lead to olefin **17** (Scheme 5).

Replacing the δ-lactone fragment by a phenol group suggested great promise even if such already reported analogues were characterized by a slightly lower activity.[11k,18] However, this loss of activity was not clearly linked to δ-lactone modification, since literature compounds were, at the same time, desoxygenated at the C7-position; structure–activity investigations addressing this point showed that the hydroxyl function at C7 could play a significant role in the biological activity (possibility of hydrogen bonding in the



Scheme 5. Synthetic analysis of DDM analogues: Installation of an isopropyl group at the C14-position through dyotropic rearrangement.

binding site). Therefore, we investigated the simplification of the DDM backbone with a phenol core to afford analogue **6** while keeping the DDM C7-hydroxyl function.

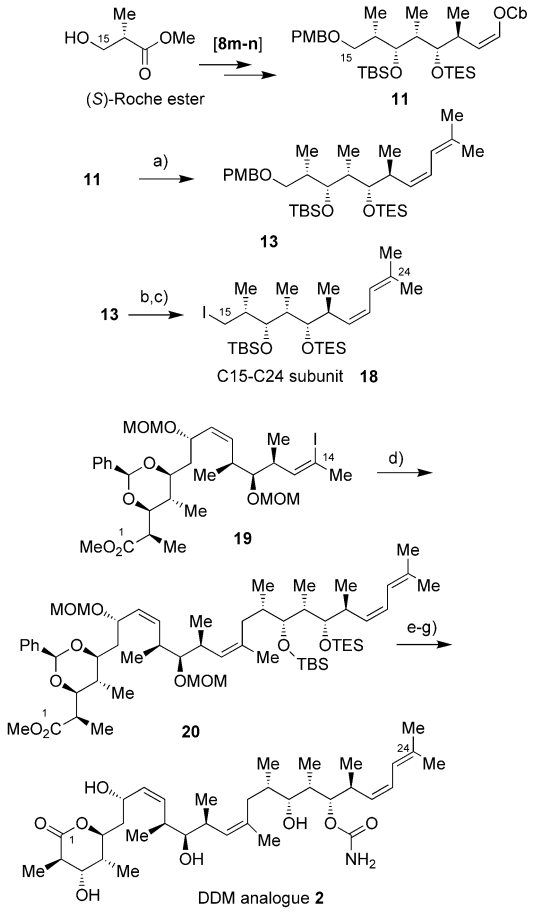
The synthesis of the DDM analogue **2** bearing a C24 *gem*-di-Me group started with the construction of the (*Z*)-C21–C24 diene unit (Scheme 6). It was planned by a Ni-mediated Grignard coupling reaction between the C15–C22 vinylcarbamate **11** previously prepared by us during the total synthesis of DDM[8m–n] and 2-methylpropenylmagnesium bromide. The required diene **13** was delivered in very high yield (94%) and the geometric control was total. This compound was then smoothly transformed into the corresponding C15–C24 subunit **18** in two steps. The second key step involved an sp^2–sp^3 Suzuki coupling reaction[19] by using B-alkyl organoborane species prepared from alkyl iodide **18** and C1–C14 vinyl iodide **19** already described in our DDM synthesis,[8m–n] to afford adduct **20** in a nonoptimized 51% yield.

Selective cleavage of the C19-TES ether followed by carbamate moiety installation and final total deprotection with concomitant lactonization provided DDM analogue **2**.

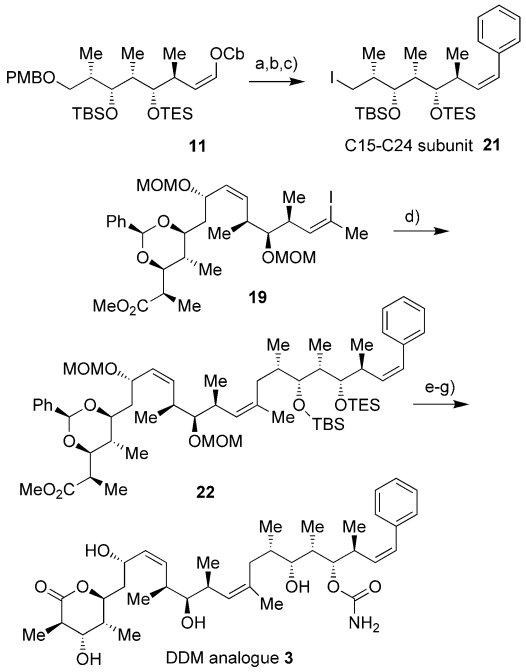
The elaboration of the nondiene analogue **3** possessing a phenyl group followed a similar sequence from vinylcarbamate **11** (Scheme 7). Thus, the nickel-catalyzed cross-coupling reaction involving phenylmagnesium bromide ensured the construction of the C15–C24 subunit **21** with high selectivity. Then, sp^2–sp^3 Suzuki coupling reaction (formation of **22**), carbamate function setup, and deprotection delivered the desired DDM analogue **3**.

For the synthesis of the second nondiene analogue **4** bearing a benzyl group, DDQ cleavage of the PMB ether at the C15-position did not proceed in the presence of the benzyl function. Therefore, we inverted the order of the first two steps, DDQ deprotection and Ni-mediated coupling reaction (Scheme 8). Except for this minor modification, completion of the synthesis following the established route (Suzuki reaction between alkyl iodide **23** and vinyl iodide **19** to yield **24**, selective carbamate installation, and final deprotection) allowed the preparation of DDM analogue **4**.

The synthesis of the fourth analogue **5**, substituted at the C14-position by an isopropyl group, was then investigated. DHF (+/−)-**16**[8m–n] was subjected to metallate rearrangement under the previously developed optimized laboratory



Scheme 6. Synthesis of DDM analogue **2**: a) $[Ni(acac)_2]$, Et_2O, 0°C, 2-methylpropenylmagnesium bromide, 16 h, 94%; b) DDQ, CH_2Cl_2/H_2O 95:5, 0°C→RT, 3.5 h, 83%; c) I_2, PPh_3, imid, C_6H_6/Et_2O, 0°C→RT, 2 h, 61%; d) **18**, *t*BuLi, Et_2O, −78°C, 5 min, *B*-methoxy-9-BBN, THF, −78°C→RT, then **19**, Cs_2CO_3, $[PdCl_2(dppf)]$, $AsPh_3$, DMF, H_2O, 16 h, 51%; e) PTSA, MeOH, 0°C, 1 h, 70%; f) $Cl_3CC(O)NCO$, CH_2Cl_2, RT, 15 min, then K_2CO_3, MeOH, RT, 1.15 h, 78%; g) HCl 4 N, THF, RT, 72 h, 47%. acac = acetylacetonate, BBN = borabicyclo[3,3,1]nonane, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, dppf = (diphenylphosphino)-ferrocene, imid = imidazole, PTSA = *p*-toluenesulfonic acid.



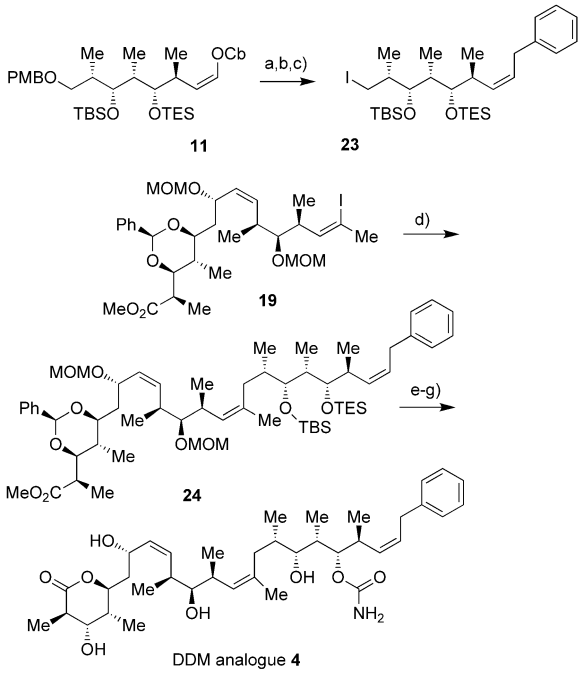
Scheme 7. Synthesis of DDM analogue **3**: a) **14**: $[Ni(acac)_2]$, Et_2O, 0°C, phenylmagnesium bromide, 16 h; b) DDQ, CH_2Cl_2/H_2O 95:5, 0°C→RT, 3.5 h, 59% over 2 steps; c) I_2, PPh_3, imid, C_6H_6/Et_2O, 0°C→RT, 3 h, 86%; d) **21**, *t*BuLi, Et_2O, −78°C, 5 min, *B*-methoxy-9-BBN, THF, −78°C→RT, then **19**, Cs_2CO_3, $[PdCl_2(dppf)]$, $AsPh_3$, DMF, H_2O, 16 h, 10%; e) PTSA, MeOH, 0°C, 1 h, 69%; f) $Cl_3CC(O)NCO$, CH_2Cl_2, RT, 15 min, then K_2CO_3, MeOH, RT, 1.15 h, 58%; g) HCl 4 N, THF, RT, 72 h, 91%.

conditions with a cyano-Gilman isopropylcuprate to lead to the expected (*Z*)-alkene (+/−)-**17** in a satisfactory 72% yield and total diastereoselectivity (Scheme 9). A two-step sequence, oxidation, and crotyltitanation with the inherently chiral secondary organometallic reagent (*R*)-**9**, delivered the required homoallylic alcohol **25** as the main product in 41% yield along with its diastereomer **26** in 25% yield. To confirm the configuration of the (*S*)-C11 secondary hydroxy center, secondary alcohol **25** was derivatized to give the (*R*)- and (*S*)-α-methoxy-phenylacetic acid (MPA) esters.[20,21] From vinylcarbamate **25**, α-elimination reaction upon a *t*BuLi treatment and subsequent C11 alcohol protection furnished alkyne **27**.

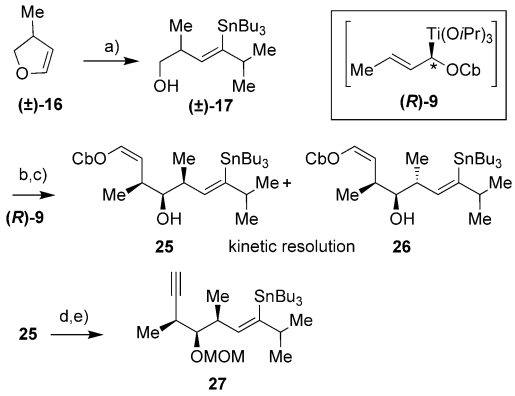
Coupling of the compound **27** with the amide **28**[8m–n] delivered the ketone **29** (Scheme 10). Diastereoselective reduction of this intermediate under CBS conditions[22] led, after protection of the alcohol at C11, to alkyne **30**. Oxidation followed by partial hydrogenation with PtO_2 (catalyst of choice for this congested alkyne) and iodine–tin exchange then completed the formation of vinyliodide **31**. The convergent coupling of **31** with alkyliodide **32**[8m–n] was carried out under Suzuki conditions.[23] Deprotection of the C1–C24 fragment **33** and carbamate formation at C19 then furnished DDM analogue **5**.

The synthesis of the simplified DDM analogue **6** bearing a phenolic group instead of the δ-lactone was much faster. It started with the preparation of amide **35** from commercial 3-hydroxyphenylacetic acid **34** in two steps and 66% yield (Scheme 11). Subsequent coupling of the C8–C14 alkyne **36** previously prepared in the laboratory,[8m–n] with amide **35** delivered adduct **37** after reduction by the (*S*)-CBS reagent[24] and protection of the newly generated hydroxy function at C7. Hydrogenation and iodine–tin exchange then led to vinyliodide **38**. Whereas the formation of this vinyliodide **38** proceeded smoothly, significant problems were encountered during the Suzuki cross-coupling reaction between vinyliodide **38** and alkyliodide **32**. The required adduct **39** was obtained in a rather low 17% yield, the main isolated product being the cyclohexene derivative **40**, which certainly arose from an intramolecular Heck coupling reaction.[25]

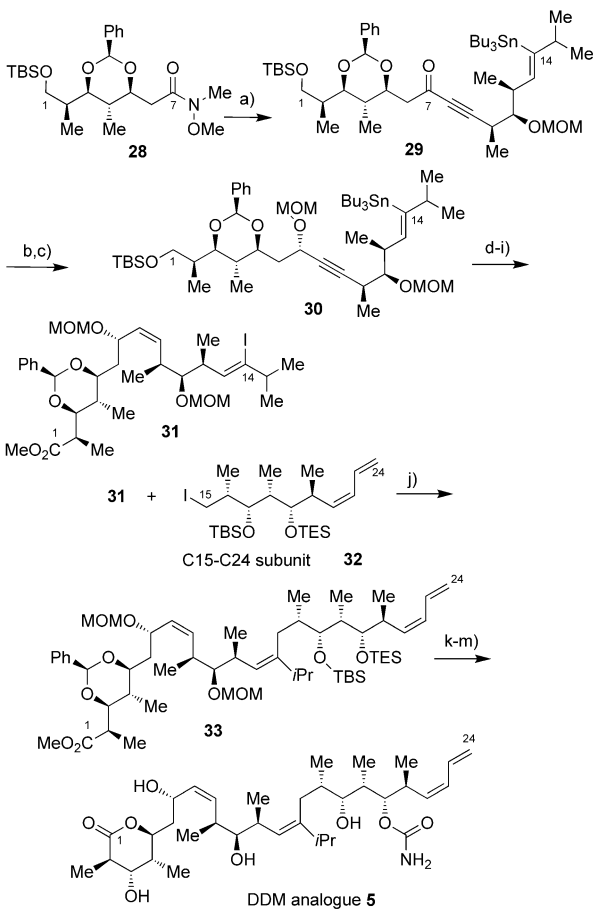
The same final three-step sequence (deprotection of the C1–C24 fragment and carbamate formation at C19) delivered analogue **6**.



Scheme 8. Synthesis of DDM analogue **4**: a) DDQ, CH_2Cl_2/H_2O 95:5, 0 °C→RT, 30 min, 60 % b) **15**: $[Ni(acac)_2]$, Et_2O, RT, benzylmagnesium chloride, 3 h; 73 %; c) I_2, PPh_3, imid, C_6H_6/Et_2O, 0 °C→RT, 2 h, 77 %; d) **23**, *t*BuLi, Et_2O, −78 °C, 2 min, *B*-methoxy-9-BBN, THF, −78 °C→RT, then **19**, Cs_2CO_3, $[PdCl_2(dppf)]$ $AsPh_3$, DMF, H_2O, 16 h, 30 %; e) PTSA, MeOH, 0 °C, 1 h, 80 %; f) $Cl_3CC(O)NCO$, CH_2Cl_2, RT, 15 min, then K_2CO_3, MeOH, RT, 1.15 h, 27 %; g) HCl 4 N, THF, RT, 72 h, 56 %.



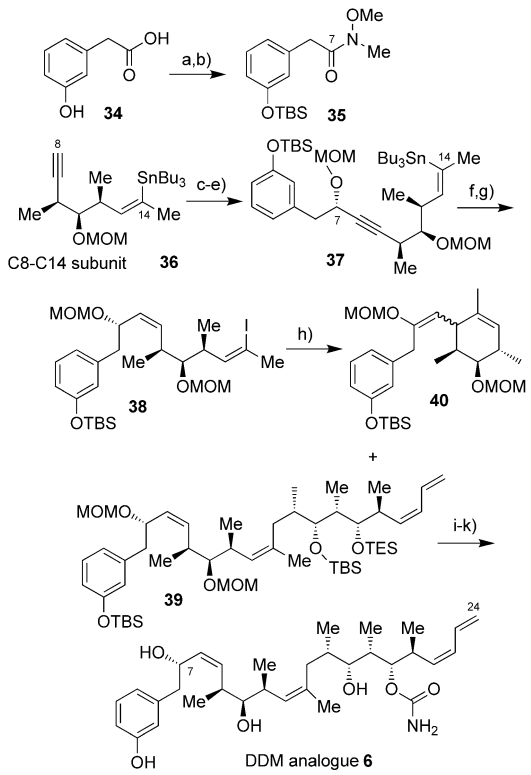
Scheme 9. Synthesis of alkyne **27**: a) *t*BuLi, $iPr_2CuLi.LiCN$, Et_2O/DMS 4:1, 0 °C→RT, 12 h, then nBu_3SnCl, −30 °C→RT, 5 h, 72 %; b) TEMPO (10 mol %), BAIB, CH_2Cl_2, RT, 2 h; c) (*R*)-**9**, cyclohexane/pentane 1:7, −78 °C, 3 h, compound **25** 41 % over 2 steps and compound **26** 25 % over 2 steps; d) *t*BuLi, THF, −40 °C→−20 °C, 20 min, 62 %; e) MOMCl, TBAI, Hunig's base, CH_2Cl_2, RT, 24 h, 88 %. BAIB = [bis-(acetoxy)iodo]benzene, MOM = methoxymethyl, TBAI = tetra-*n*-butylammonium iodide, Hunig's base = diisopropylethylamine, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy free radical.



Scheme 10. Synthesis of analogue **5**: a) **27**, *n*BuLi/Et_2O, THF, −40 °C, 50 min, then **28**, −40→0 °C, 1 h, 86 %; b) (*S*)-(−)-2-methyl-CBS-oxazaborolidine, $BH_3.Me_2S$, THF, −30 °C, 2 h, 89 %, d.r. 98:2; c) MOMCl, TBAI, Hunig's base, CH_2Cl_2, RT, 12 h, 97 %; d) HF/Py, Py/THF, RT, 4 h, 87 %; e) TEMPO (10 mol %), BAIB, CH_2Cl_2, RT, 3 h; f) $NaClO_2$, NaH_2PO_4, 2-methyl-but-2-ene, *t*BuOH/H_2O, RT, 1 h; g) $TMSCHN_2$, C_6H_6/MeOH, RT, 15 min, 65 % over 3 steps; h) H_2, PtO_2 (30 mol %), AcOEt, RT, 12 h; i) I_2, CH_2Cl_2, 0 °C, 10 min, 76 % over 2 steps; j) **32**, *t*BuLi, Et_2O, −78 °C, 5 min, *B*-methoxy-9-BBN, THF, −78 °C→RT, then **31**, Cs_2CO_3, $[PdCl_2(dppf)]$, $AsPh_3$, DMF, H_2O, 16 h, 10 %; k) PTSA, MeOH, 0 °C, 1 h, 72 %; l) $Cl_3CC(O)NCO$, CH_2Cl_2, RT, 15 min, then K_2CO_3, MeOH, RT, 1.15 h, 40 %; m) HCl 4 N, THF, RT, 72 h, 50 %. CBS = Corey-Bakshi-Shibata, Py = pyridine.

Biological evaluation: The five DDM analogues **2**, **3**, **4**, **5**, and **6** were finally screened for cellular activity in comparison to DDM (previously synthesized in the laboratory). Cytotoxicity asssays were performed on three different cell lines. All analogues were effective in the nanomolar range comparable to DDM (IC_{50} (nM) HCT116 and MDA-MB-231). C24 *gem*-di-Me analogue **2** and C14-isopropyl analogue **5** were the most potent and both essentially equipotent to DDM (Table 1, entries 1, 2, and 3). They were followed in this order by phenolic **6** and C22-Ph **3** analogues (entries 5 and 6). The C22-benzyl analogue **4** was the least potent (entry 4).

The present data reveal that a lipophilic C24 *gem*-di-Me group or a sterically demanding C14-isopropyl substituent is very well-tolerated and confers extremely good biological activity. This last result suggests the possibility that the C14-isopropyl substituent may increase the "U" shape bioactive conformation. The phenolic analogue **6** retains good potency considering the structure simplification and may be of utility in the design of straightforward analogues.



Scheme 11. Synthesis of analogue **6**: a) TBSCl, imid, DMF, RT, 4 days; b) $HN(CH_3)OCH_3$·HCl, Hunig's base, EDCI·HCl, HOBt, CH_2Cl_2, RT, 24 h, 66% over 2 steps; c) **36**, *n*BuLi/Et_2O, THF, −40°C, 50 min, then **35**, −40°C- > 0°C, 1 h, 63%; d) (*S*)-(−)-2-Methyl-CBS-oxazaborolidine, BH_3·Me_2S, THF, −30°C, 2 h, 81%, d.r. 98:2; e) MOMCl, TBAI, DMAP, Hunig's base, CH_2Cl_2, RT, 12 h, 90%; f) H_2, PtO_2 (30 mol%), AcOEt, RT, 12 h; g) I_2, CH_2Cl_2, 0°C, 10 min, 76% over 2 steps; h) **32**, *t*BuLi, Et_2O, −78°C, 5 min, *B*-methoxy-9-BBN, THF, −78°C→RT, then **38**, Cs_2CO_3, [$PdCl_2$(dppf)], $AsPh_3$, DMF, H_2O, 16 h, **39** 17% and **40** 20%; i) **39**, PTSA, MeOH, 0°C, 1 h, 58%; j) $Cl_3CC(O)NCO$, CH_2Cl_2, RT, 15 min, then K_2CO_3, MeOH, RT, 1.15 h, 58%; k) HCl 4 N, THF, RT, 24 h, 88%. DMAP = dimethylaminopyridine, EDCI = 1-ethyl-3-[3-dimethylamino)propyl]carbodiimide, HOBt = 1-hydroxybenzotriazole.

Table 1. Biological evaluation of synthesized analogues **2**–**6**.[a,b]

Entry	Compound	IC_{50} [nM] HCT116[b]	IC_{50} [nM] MDA- MB231[b]	IC_{50} [nM] MDA-A1[b]
1	DDM (**1**)	5.0	15.6	105.8
2	C-24-*gem*-dimethyl **2**	1.3	3.7	155
3	C-22-phenyl **3**	19	110	4494
4	C-22-benzyl **4**	321	1009	8709
5	C-14-isopropyl **5**	2.3	17.5	2200
6	phenol **6**	16	66	4836

[a] Cytotoxicity asssays were based on the determination of the inhibition of cell growth by measuring the inhibition of the incorporation of ^{14}C-thymidine. [b] Cells lines used: human colon cancer epithelial cell line HCT116, human breast cancer cell lines MDA-MB-231 (wild type) and MDA-A1 (anthracycline resistant).

Conclusion

The underlying synthesis blueprint of DDM (**1**) allowed for the convergent preparation of five original analogues **2**, **3**, **4**, **5**, and **6** of DDM, each of them exhibiting potent cytotoxicity.

The first requirement was to keep the bioactive U-shaped conformation of DDM, therefore modeling studies were achieved before starting the synthesis. Three types of variation were envisioned depending on our synthetic possibilities: 1) Modifying the diene, which is a lipophilic part of the compound, with a *gem*-di-Me group at the C24-position, phenyl, or benzyl group at C22. 2) Replacing the C14 methyl group by a more sterically demanding alkyl group to reinforce the U-shaped bioative conformation. 3) Replacing the δ-lactone by a phenol moiety. If the third variation did efficiently shorten the synthesis of the C1–C7 fragment, the first two modifications were readily accessible through two key reactions of our synthesis of DDM. The first one is a robust and original nickel-catalyzed cross-coupling reaction between an enecarbamate and the corresponding magnesium derivative and the second is a dyotropic rearrangement performed on a methyldihydrofuran with the corresponding isopropylcuprate. Noteworthy, in both cases, the selectivities were excellent.

Cytotoxicity assays were performed for these five analogues on three different cell lines. All analogues were active in the nanomolar range, especially the C24-*gem*-di-Me and the C14-*i*Pr analogues **2** and **5** both equipotent to DDM. The phenolic analogue **6** retained a very significant and encouraging in vitro activity considering the structure simplification.

Investigation work towards novel simplified DDM analogues is ongoing in the laboratory.

Experimental Section

General: All reactions were carried out in oven or flame-dried glassware under an argon atmosphere employing standard techniques in handling air-sensitive materials. All solvents employed were reagent grade. THF and diethyl ether (Et_2O) were freshly distilled from sodium/benzophenone under argon immediately prior to use. Dichloromethane, cyclohexane, and pentane were freshly distilled over calcium hydride. All other reagents were used as supplied. Reactions were magnetically stirred and monitored by TLC analysis with 0.20 mm SDS 60F254 pre-coated silica gel plates. Visualization was accomplished with UV light then treatment with a 10% ethanolic phosphomolybdic acid solution followed with heating. Flash chromatography was performed with silica gel 60 (particle size 0.040–0.063 mm) supplied by SDS. Yield refers to chromatography and spectroscopically pure compounds, unless otherwise noted. ^{1}H NMR spectra were recorded by using an internal deuterium lock at ambient temperature on a JEOL JNM-ECX 270 or 400 MHz spectrometer. Internals references of $\delta_H = 7.26$ and 1.96 ppm were used for $CDCl_3$ and CD_3CN, respectively. Data are represented as follows: chemical shift (in ppm), multiplicity (s = single, d = doublet, t = triplet, q = quartet), integration, coupling constant (*J*). ^{13}C NMR spectra were recorded on a Jeol 67.5 or 100.5 MHz spectrometer. Internal references of $\delta_C = 77.16$ and 118.26 ppm were used for $CDCl_3$ and CD_3CN, respectively. IR spectra were recorded on a Nicolet Impact-400 and wavelength (ν) is given in cm^{-1}. Mass spectra were recorded on a GCMS coupling unit with a MSD 5973 spectrometer and a Hewlett–Packard HP-GC 6890 chromatograph. Ionization was obtained either by electronic impact (EI) or chemical ionization with methane (CI, CH_4). Mass spectral data are reported as *m*/*z*. Optical rotations were recorded on a Jasco P-1010 digital polarimeter at 589 nm and reported as follows: $[\alpha]_D^{20}$, concentration (*c* in g/100 mL), and solvent. Elemental analyses were performed on a CHN 240 Perkin–Elmer instrument by the Service de Microanalyses, Centre d'Etudes

Pharmaceutiques, Chatenay-Malabry, F-92296. HRMS were obtained on a Thermo-Electron MAT-95 spectrometer in the ICMMO, Mass Spectrometry Laboratory, Orsay University, F-91 405 Orsay. IUPAC nomenclature was used for all compounds.

24-Dimethyl discodermolide 2: *p*-Toluenesulfonic acid (7 mg, 0.035 mmol, 0.28 equiv) was added to a solution of compound **20** (130 mg, 0.13 mmol, 1.0 equiv) in MeOH (15 mL) at 0 °C. After stirring for 1 h at 0 °C, triethylamine was added to the reaction mixture (0.3 equiv) and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt, 95:5 to 70:30) to give the expected alcohol [2*S*,4*R*(1*R*),5*S*,6*S*(2*S*,3*Z*,5*S*,6*R*,7*S*,8*Z*,11*S*,12*R*,13*S*,14*S*,15*S*,16*Z*)]-4-(2-methoxy-carbonyl-1-methyl ethyl-1-yl)-6-{12-(*tert*-butyldimethylsilyloxy)-5,7,9,11,13,15,19-heptamethyl-14-hydroxy-2,6-bis[(methoxymethyl)oxy]-icosa-3,8,16,18-tetraen-1-yl}-5-methyl-2-phenyl-1,3-dioxinan (73 mg, 70% yield). $[\alpha]_D^{20} = +13.9$ ($c = 1.48$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.48$–7.42 (m, 2H), 7.35–7.28 (m, 3H), 6.34 (dd, $J = 11.5$, 11.0 Hz, 1H), 6.07 (d, $J = 11.5$ Hz, 1H), 5.58 (s, 1H), 5.55 (dd, $J = 11.0$, 10.1 Hz, 1H), 5.20 (dd, $J = 11.0$, 10.1 Hz, 1H), 5.18 (dd, $J = 11.0$, 9.6 Hz, 1H), 4.99 (d, $J = 10.1$ Hz, 1H), 4.84 (dd, $J = 9.6$, 9.2 Hz, 1H), 4.71 (d, $J = 6.9$ Hz, 1H), 4.54 (s, 2H), 4.50 (d, $J = 6.9$ Hz, 1H), 4.05 (dd, $J = 10.1$, 3.2 Hz, 1H), 3.82 (dd, $J = 10.1$, 9.6 Hz, 1H), 3.73 (s, 3H; CH_3), 3.63 (dd, $J = 6.4$, 2.7 Hz, 1H), 3.33 (s, 6H; $2CH_3$), 3.35–3.30 (m, 2H), 3.07 (dd, $J = 5.9$, 5.5 Hz, 1H), 2.85–2.75 (m, 3H), 2.55 (dqd, $J = 10.1$, 6.9, 5.9 Hz, 1H), 2.21 (t, $J = 12.4$ Hz, 1H), 2.00–1.94 (m, 1H), 1.94–1.86 (m, 1H), 1.81 (s, 3H; CH_3), 1.76 (s, 3H; CH_3), 1.68–1.61 (m, 5H), 1.61 (s, 3H; CH_3), 1.22 (d , $J = 7.3$ Hz, 3H; CH_3), 1.01 (d, $J = 6.9$ Hz, 3H; CH_3), 0.98 (d, $J = 6.9$ Hz, 3H; CH_3), 0.97 (d, $J = 6.9$ Hz, 3H; CH_3), 0.96 (s, 9H; $3CH_3$) , 0.94 (d , $J = 6.9$ Hz, 3H; CH_3), 0.92 (d, $J = 6.9$ Hz, 3H; CH_3), 0.85 (d, $J = 6.9$ Hz, 3H; CH_3), 0.08 (s, 3H; CH_3). 0.07 ppm (s, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 174.8$ (C), 138.8 (C), 136.9 (CH), 136.8 (C), 132.7 (C), 131.2 (CH), 130.2 (CH), 129.0 (CH), 128.2 (CH), 127.9 (2CH), 126.8 (CH), 125.8 (2CH), 120.0 (CH), 99.6 (CH), 97.8 (CH_2), 93.2 (CH_2), 86.8 (CH), 82.3 (CH), 79.0 (CH), 77.7 (CH), 75.6 (CH), 66.3 (CH), 56.0 (CH_3), 55.2 (CH_3), 51.9 (CH_3), 41.0 (CH), 39.1 (CH_2), 37.9 (CH), 36.8 (CH_2), 36.0 (CH), 35.8 (CH), 35.3 (CH), 34.5 (CH), 34.4 (CH_3), 27.1 (CH_3), 26.3 (CH_3), 26.2 ($3CH_3$), 23.3 (CH_3), 18.7 (C), 17.5 (CH_3), 17.1 (CH_3), 16.4 (CH_3), 13.1 (CH_3), 11.7 (CH_3), 9.5 (CH_3), 9.3 (CH_3), −3.2 (CH_3), −3.6 ppm (CH_3); IR (film): $\tilde{\nu} = 3382$, 2969, 2930, 2839, 2857, 1743, 1460, 1453, 1152, 1110, 1092, 1045, 772 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{52}H_{88}O_{10}NaSi$: 923.6044 $[M+Na]^+$; found: 923.6045.

Trichloroacetylisocyanate (10 μL, 0.085 mmol, 1.05 equiv) was added to a solution of the above alcohol (73 mg, 0.08 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL). After stirring for 15 min at 20 °C, the resulting mixture was concentrated in vacuo and the residue taken up in MeOH (8 mL). K_2CO_3 (61 mg, 0.44 mmol, 5.5 equiv) was added and the resulting solution was stirred for 1 h 15 min and then concentrated in vacuo and extracted with AcOEt. The organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 90:10 to 50:50) to give the title carbamate [2*S*,4*R*(1*R*),5*S*,6*S*(2*S*,3*Z*,5*S*,6*R*,7*S*,8*Z*,11*S*,12*R*,13*S*,14*S*,15*S*,16*Z*)]-4-(2-methoxycarbonyl-1-methyl ethyl-1-yl)-6-{12-(*tert*-butyldimethylsilyloxy)-14-(carbamoyloxy)-5,7,9,11,13,15,19-heptamethyl-14-(carbamoyloxy)-2,6-bis[(methoxymethyl)oxy]- icosa-3,8,16,18-tetraen-1-yl}-5-methyl-2-phenyl-1,3-dioxinan (59 mg, 78% yield) as a pale oil. $[\alpha]_D^{20} = +30.3$ ($c = 1.18$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$) > $\delta = 7.49$–7.43 (m, 2H; H-Ar), 7.36–7.28 (m, 3H), 6.20 (dd, $J = 11.4$, 11.0 Hz, 1H), 6.04 (d, $J = 11.4$ Hz, 1H), 5.58 (s, 1H), 5.53 (dd, $J = 11.0$, 10.1 Hz, 1H), 5.25 (dd, $J = 10.5$, 10.1 Hz, 1H), 5.22 (dd, $J = 11.0$, 10.1 Hz, 1H), 4.97 (d, $J = 10.1$ Hz, 1H), 4.79–4.70 (m, 1H), 4.83 (dd, $J = 10.5$, 9.6 Hz, 1H), 4.71 (d, $J = 6.9$ Hz, 1H), 4.73–4.70 (m, 1H), 4.54 (s, 2H), 4.50 (d, $J = 6.9$ Hz, 1H), 4.52–4.49 (m, 1H), 4.05 (dd, $J = 10.1$, 3.2 Hz, 1H), 3.82 (dd, $J = 10.1$, 9.2 Hz, 1H), 3.73 (s, 3H; CH_3), 3.45 (dd, $J = 4.6$, 4.2 Hz, 1H), 3.33 (s, 6H; $2CH_3$), 3.06 (dd, $J = 5.9$, 5.5 Hz, 1H), 2.98 (dqm, $J = 10.1$, 6.4 Hz, 1H), 2.85–2.76 (dq, $J = 6.9$, 3.2 Hz, 1H), 2.85–2.76 (m, 1H), 2.55–2.45 (m, 1H), 2.10–1.82 (m, 6H), 1.82 (s, 3H; CH_3), 1.76 (s, 3H; CH_3), 1.66 (tq, $J = 10.1$, 6.9 Hz, 1H), 1.57 (s, 3H; CH_3), 1.23 (d , $J = 6.9$ Hz, 3H; CH_3), 0.99 (d, $J = 6.9$ Hz, 3H; CH_3), 0.98 (d, $J = 6.9$ Hz, 3H; CH_3), 0.96 (s, 9H; $3CH_3$), 0.93 (d, $J = 6.9$ Hz, 3H; CH_3), 0.89 (d, $J = 6.9$ Hz, 3H; CH_3), 0.87 (d, $J = 6.9$ Hz, 3H; CH_3), 0.71 (d, $J = 6.9$ Hz, 3H; CH_3), 0.10 (s, 3H; CH_3). 0.09 ppm (s, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 174.8$ (C), 157.0 (C), 138.7 (C), 136.8 (CH), 136.0 (C), 132.4 (C), 130.6 (CH), 130.1 (2CH), 128.9 (CH), 128.2 (CH), 127.8 (2CH), 125.8 (2CH), 125.1 (CH), 99.5 (CH), 97.7 (CH_2), 93.1 (CH_2), 86.9 (CH), 82.1 (CH), 79.1 (CH), 77.6 (CH), 77.0 (CH), 66.3 (CH), 56.0 (CH_3), 55.2 (CH_3), 51.9 (CH_3), 41.1 (CH), 39.0, 37.9, 36.1, 35.8, 35.2, 35.1, 34.4, 34.0 (6CH, $2CH_2$), 26.8 ($3CH_3$), 26.3 (CH_3), 23.0 (CH_3), 18.4 (CH_3), 18.0 (C), 17.6 (CH_3), 17.3 (CH_3), 16.5 (CH_3), 13.8 (CH_3), 11.6 (CH_3), 10.1 (CH_3), 9.3 (CH_3), −3.4 (CH_3), −3.6 ppm (CH_3); IR (film): $\tilde{\nu} = 3382$, 3315, 3304, 3215, 2983, 2956, 2930, 2901, 2880, 1726, 1090, 1045 cm^{-1}.

HCl (4 N, 6 mL) was added to a solution of the above carbamate (58 mg, 0.06 mmol, 1.0 equiv) in THF (6 mL). The resulting mixture was stirred 72 h at 20 °C and then solid $NaHCO_3$ was added and the reaction mixture extracted three times with AcOEt. The organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH 95:5 to 90:10) to give the title compound, DDM analogue **2** (18 mg, 47% yield) as an oil. $[\alpha]_D^{20} = +22.0$ ($c = 1.8$ in MeOH); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 6.19$ (dd, $J = 11.2$, 11.0 Hz, 1H), 6.03 (d, $J = 11.2$ Hz, 1H), 5.50 (dd, $J = 11.4$, 7.8 Hz, 1H), 5.43 (dd, $J = 11.4$, 9.6 Hz, 1H), 5.23 (dd, $J = 11.0$, 10.5 Hz, 1H), 5.13 (d, $J = 10.1$ Hz, 1H), 4.78–4.65 (m, 4H), 4.62 (t, $J = 10.1$ Hz, 1H), 3.71 (dd, $J = 4.1$, 3.2 Hz, 1H), 3.29 (dd, $J = 5.0$, 4.6 Hz, 1H), 3.19 (dd , $J = 5.9$, 5.5 Hz, 1H), 2.98 (dqm, $J = 10.5$, 6.9 Hz, 1H), 2.81–2.73 (m, 2H), 2.70 (qd, $J = 7.3$, 4.1 Hz, 1H), 2.72–2.68 (m, 1H), 2.55–2.45 (m, 3H, H-12), 1.99–1.64 (m, 7H), 1.81 (s, 3H; CH_3), 1.75 (s, 3H; CH_3), 1.64 (s, 3H; CH_3), 1.29 (d, $J = 7.3$ Hz, 3H; CH_3), 1.06 (d, $J = 6.9$ Hz, 3H; CH_3), 1.01 (d, $J = 6.9$ Hz, 3H; CH_3), 1.00 (d, $J = 6.9$ Hz, 3H; CH_3), 096 (2d, $J = 7.3$ Hz, 6H), 0.94 ppm (d, $J = 6.4$ Hz, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 174.8$ (C), 158.5 (C), 136.8 (C), 133.9 (CH), 133.7 (CH), 130.9 (CH), 130.4 (CH), 125.9 (C), 121.1 (CH), 118.3 (CH), 79.7 (2CH), 77.3 (CH), 75.8 (CH), 73.1 (CH), 63.2 (CH), 43.9 (CH), 42.0, 38.4, 37.3, 36.7, 36.3, 36.1, 34.3, 34.1 (6CH, $2CH_2$), 26.3 ($2CH_3$), 23.3 (CH_3), 19.8, 18.4, 18.0, 16.0, 15.7, 13.0, 9.2 ppm ($7CH_3$); IR (film): $\tilde{\nu} = 3382$, 2962, 2929, 2870, 2856, 2360, 2340, 1726, 1682, 1454, 1395, 1032, 668 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{35}H_{59}NO_8NaSi$: 644.4138 $[M+Na]^+$; found: 644.4142.

22-Phenyl discodermolide 3: *p*-Toluenesulfonic acid (1.7 mg, 0.009 mmol, 0.28 equiv) was added to a solution of compound **22** (40 mg, 0.032 mmol, 1.0 equiv) in MeOH (4 mL) at 0 °C. After stirring for 1 h at 0 °C, triethylamine was added to the reaction mixture (0.3 equiv) and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt, 95:5 to 60:40) to give the expected alcohol (20 mg, 69% yield). $[\alpha]_D^{20} = +19.1$ ($c = 0.4$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.48$–7.44 (m, 2H), 7.39–7.23 (m, 8H), 6.59 (d, $J = 11.4$ Hz, 1H), 5.61–5.54 (m, 2H), 5.59 (s, 1H), 5.23 (t, $J = 10.1$ Hz, 1H), 4.99 (d, $J = 10.1$ Hz, 1H), 4.84 (dd, $J = 10.1$, 9.2 Hz, 1H), 4.72 (d, $J = 6.9$ Hz, 1H), 4.56 (s, 2H), 4.50 (d, $J = 6.9$ Hz, 1H), 4.06 (dd, $J = 10.1$, 3.2 Hz, 1H), 3.82 (dd, $J = 9.6$, 9.2 Hz, 1H), 3.74 (s, 3H; CH_3), 3.49 (dd, $J = 5.0$, 3.7 Hz, 1H), 3.35–3.31 (ddd, $J = 7.8$, 3.7, 3.2 Hz, 1H), 3.34 (s, 6H; $2CH_3$), 3,11 (t , $J = 5.5$ Hz, 1H), 3.02 (dqd, $J = 7.3$, 6.4, 3.7 Hz, 1H), 2.88–2.76 (m, 2H), 2.56 (dqd, $J = 10.1$, 6.9, 5.5 Hz, 1H), 2.13 (t , $J = 12.4$ Hz, 1H), 1.98 (m, 1H), 1.88–1.57 (m, 6H), 1.56 (s, 3H; CH_3), 1.22 (d, $J = 7.3$ Hz, 3H; CH_3), 1.03 (d, $J = 6.4$ Hz, 3H; CH_3), 1.01 (d, $J = 6.4$ Hz, 3H; CH_3), 0.93 (d, $J = 6.9$ Hz, 3H; CH_3), 0.90 (d, $J = 6.9$ Hz, 3H; CH_3), 0.90 (s, 9H; $3CH_3$), 0.87 (d, $J = 6.9$ Hz, 3H; CH_3), 0.69 (d, $J = 6.9$ Hz, 3H; CH_3), 0.00 (s, 3H; CH_3), −0.05 ppm (s, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 174.8$ (C), 138.8 (C), 137.1 (C), 136.8 (CH), 134.7 (CH), 132.7 (C), 130.8 (CH), 130.2 (CH), 129.0 (CH), 128.6 (2CH), 128.3 (2CH), 128.2 (CH), 127.9 (2CH), 126.9 (CH), 125.8 (2CH), 99.6 (CH), 97.8 (CH_2), 93.1 (CH_2), 86.8 (CH), 82.2 (CH), 78.7 (CH), 77.7 (CH), 76.7 (CH), 66.3 (CH), 56.0 (CH_3), 55.2 (CH_3), 51.9 (CH_3), 41.0 (CH), 39.1 (CH_2), 38.1 (CH), 36.4 (CH_2), 35.9 (CH), 35.8 (CH), 35.3 (CH), 34.6 (CH), 34.5 (CH), 26.2 ($3CH_3$), 23.3 (CH_3), 18.4 (C), 17.5 ($2CH_3$), 16.4 (CH_3), 13.7 (CH_3), 11.6 (CH_3), 9.4 (CH_3), 9.3 (CH_3), −3.3 (CH_3), −3.6 ppm (CH_3); IR (film): $\tilde{\nu} = 3440$, 3377, 2960, 2929, 1461, 1453, 1435, 1151, 1092, 1036 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{54}H_{86}O_{10}NaSi$: 945.5888 $[M+Na]^+$; found: 945.5876.

Trichloroacetylisocyanate (2.7 μL, 0.023 mmol, 1.05 equiv) was added to a solution of the preceding alcohol (20 mg, 0.022 mmol, 1.0 equiv) in CH_2Cl_2 (1.7 mL). After stirring for 15 min at 20 °C, the resulting mixture was concentrated in vacuo and the residue taken up in MeOH (2.2 mL). K_2CO_3 (17 mg, 0.12 mmol, 5.5 equiv) was added and the resulting solution was stirred for 1 h 15 min and then concentrated in vacuo and extracted with AcOEt. The organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 90:10 to 50:50) to give the title carbamate (12 mg, 58% yield) as a pale oil. $[\alpha]_D^{20} = +33.0$ ($c = 1.2$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.49$–7.44 (m, 2H), 7.37–7.22 (m, 8H), 6.48 (d, $J = 11.9$ Hz, 1H), 5.62 (dd, $J = 11.9$, 11.0 Hz, 1H), 5.60 (t, $J = 10.1$ Hz,1H), 5.58 (s, 1H), 5.24 (t, $J = 10.1$ Hz, 1H), 4.96 (d, $J = 10.1$ Hz, 1H), 4.84 (dd, $J = 10.1$, 9.6 Hz, 1H), 4.76 (dd, $J = 6.4$, 5.9 Hz, 1H), 4.72 (d, $J = 6.9$ Hz, 1H), 4.62–4.57 (m, 2H; NH_2), 4.56 (s, 2H; CH_2), 4.51 (d, $J = 6.9$ Hz, 1H), 4.05 (dd, $J = 11.7$, 3.2 Hz, 1H), 3.83 (t, $J = 9.2$ Hz, 1H), 3.73 (s, 3H; CH_3), 3.33 (s, 6H; $2CH_3$), 3.21–3.13 (m, 2H), 3.08 (dd, $J = 5.9$, 5.5 Hz, 1H), 2.85–2.78 (m, 2H), 2.54 (dqd, $J = 10.1$, 6.4, 5.5 Hz, 1H), 1.98–1.87 (m, 2H), 1.85 (m, 1H), 1.78–1.60 (m, 4H), 1.54 (s, 3H; CH_3), 1.22 (d, $J = 7.3$ Hz, 3H; CH_3), 1.11 (d, $J = 6.9$ Hz, 3H; CH_3), 1.02 (d, $J = 6.9$ Hz, 3H; CH_3), 0.92 (d, $J = 6.4$ Hz, 3H; CH_3), 0.90 (d, $J = 7.3$ Hz, 3H; CH_3), 0.88 (d, $J = 6.4$ Hz, 3H; CH_3), 0.88 (s, 9H; $3CH_3$), 0.56 (d, $J = 6.9$ Hz, 3H; CH_3), 0.01 (s, 3H; CH_3), −0.12 ppm (s, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 174.8$ (C), 156.9 (C), 138.7 (C), 137.3 (C), 136.6 (CH), 133.5 (CH), 132.5 (C), 130.1 (CH), 129.5 (CH), 129.1 (CH), 128.4 (2CH), 128.3 (2CH), 128.2 (CH), 127.9 (2CH), 126.8 (CH), 125.8 (2CH), 99.6 (CH), 97.9 (CH_2), 93.2 (CH_2), 87.0 (CH), 82.2 (CH), 79.1 (CH), 77.7 (CH), 77.0 (CH), 66.3 (CH), 56.0 (CH_3), 55.2 (CH_3), 51.9 (CH_3), 41.1 (CH), 39.0 (CH_2), 37.9 (CH), 36.0 (CH_2), 35.9 (CH), 35.3 (CH), 34.8 (CH), 34.7 (CH), 34.2 (CH), 26.1 ($3CH_3$), 23.0 (CH_3), 18.5 (C), 17.7 (CH_3), 17.4 (CH_3), 16.7 (CH_3), 14.1 (CH_3), 11.6 (CH_3), 9.9 (CH_3), 9.4 (CH_3), −3.5 ppm ($2CH_3$); IR (film): $\tilde{\nu} = 3376$, 2961, 2930, 1728, 1460, 1147, 1094, 1035, 757 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{55}H_{87}NO_{11}NaSi$: 988.5946 $[M+Na]^+$; found: 988.5957.

HCl (4 N, 1.2 mL) was added to a solution of the preceding carbamate (12 mg, 0.012 mmol, 1.0 equiv) in THF (1.2 mL). The resulting mixture was stirred 72 h at 20 °C and then solid $NaHCO_3$ was added and extracted three times with AcOEt. The organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH 100:0 to 70:30) to give the title compound **3** (7 mg, 91% yield). $[\alpha]_D^{20} = +3.2$ ($c = 0.7$ in MeOH); ^{1}H NMR (400.0 MHz, CD_3CN): $\delta = 7.34$–7.25 (m, 4H), 7.25–7.18 (m, 1H), 6.50 (d, $J = 11.9$ Hz, 1H), 5.74 (dd, $J = 10.5$, 10.1 Hz, 1H), 5.64 (dd, $J = 11.9$, 11.4 Hz, 1H), 5.49 (t, $J = 10.1$ Hz, 1H), 5.15–5.05 (m, 1H), 4.90 (d, $J = 10.1$ Hz, 1H), 4.64 (dd, $J = 9.2$, 3.2 Hz, 1H), 4.46–4.38 (m, 4H), 3.59 (t, $J = 4.6$ Hz, 1H), 3.56–3.50 (m, 1H), 3.19–3.12 (m, 1H), 3.10–3.08 (m, 1H), 2.71–2.61 (m, 1H), 2.50 (m, 1H), 2.31–2.20 (m, 1H), 1.81–1.40 (m, 10H; 6CH, $2CH_2$), 1.53 (s, 3H; CH_3), 1.14 (d, $J = 7.3$ Hz, 3H; CH_3), 1.08 (d, $J = 6.9$ Hz, 3H; CH_3), 1.02 (d, $J = 7.3$ Hz, 3H; CH_3), 0.98 (d, $J = 6.9$ Hz, 3H; CH_3), 0.90 (d, $J = 6.4$ Hz, 3H; CH_3), 0.66 (d, $J = 6.9$ Hz, 3H; CH_3), 0.34 ppm (d, $J = 6.4$ Hz, 3H; CH_3); ^{13}C NMR (100.5 MHz, CD_3CN): $\delta = 174.7$ (C), 158.4 (C), 138.3 (C), 134.2 (CH), 133.9 (CH), 133.8 (C), 130.9 (CH), 130.3 (CH), 129.4 (CH), 129.3 (5CH), 79.8 (CH), 79.7 (CH), 77.2 (CH), 75.4 (CH), 73.1 (CH), 63.1 (CH), 43.9 (CH), 42.1 (CH_2), 38.5 (CH), 37.7 (CH), 36.8 (CH, CH_2), 35.8 (CH), 34.2 (CH), 34.1 (CH), 23.6 (CH_3), 20.0 (CH_3), 18.2 ($2CH_3$), 15.8 (CH_3), 15.7 (CH_3), 13.0 (CH_3), 9.1 ppm (CH_3); IR (film): $\tilde{\nu} = 3364$, 2961, 2930, 2868, 1706, 1456, 1396, 1387, 1034, 737, 702 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{37}H_{57}NO_8Na$: 666.3982 $[M+Na]^+$; found: 666.3990.

22-Benzyl discodermolide 4: *p*-Toluenesulfonic acid (7 mg, 0.037 mmol, 0.28 equiv) was added to a solution of compound **24** (140 mg, 0.13 mmol, 1.0 equiv) in MeOH (15 mL) at 0 °C. After stirring for 1 h at 0 °C, triethylamine was added to the reaction mixture (0.3 equiv) and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt, 95:5 to 60:40) to give the expected alcohol (99 mg, 80% yield). ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta =$ 7.50–7.43 (m, 2H), 7.35–7.29 (m, 6H), 7.23–7.17 (m, 2H), 5.59 (s, 1H), 5.59–5.50 (m, 3H), 5.22 (dd, $J = 10.1$, 9.2 Hz, 1H), 5.04 (d, $J = 9.2$ Hz, 1H), 4.84 (dd, $J = 11.9$, 9.2 Hz, 1H), 4.71 (d, $J = 6.4$ Hz, 1H), 4.55 (s, 2H), 4.51 (d, $J = 6.4$ Hz, 1H), 4.40–4.35 (m, 1H), 4.16 (dd, $J = 5.9$, 5.5 Hz, 1H), 4.06 (dd, $J = 10.1$, 3.2 Hz, 1H), 3.83 (m, 1H), 3.74 (s, 3H, CH_3), 3.53–3.43 (m, 3H; CH, CH_2), 3.33 (s, 6H; $2CH_3$), 3.09 (dd , $J = 5.9$, 5.5 Hz, 1H), 2.99–2.79 (m, 3H), 2.64–2.54 (m, 1H), 2.18 (dd, $J = 12.3$, 11.9 Hz, 1H), 1.99 (m, 1H), 1.90–1.78 (m, 3H), 1.70–1.60 (m, 2H), 1.60 (s, 3H; CH_3), 1.25 (d, $J = 6.9$ Hz, 3H; CH_3), 0.97 (d, $J = 6.4$ Hz, 3H; CH_3), 0.94 (s; $3CH_3$), 0.97–0.90 (m, 9H; $3CH_3$), 0.88 (d , $J = 6.9$ Hz, 3H; CH_3), 0.74 (d, $J = 6.9$ Hz, 3H; CH_3), 0.10 (s, 3H; CH_3), 0.06 ppm (s, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$) $\delta = 174.6$ (C), 140.9 (C), 138.6 (C), 136.9 (CH), 133.4 (CH), 132.2 (C), 130.2 (CH), 128.7 (CH), 128.2 (2CH), 128.1 (2CH), 128.0 (CH), 127.8 (2CH), 127.7 (2CH), 125.5 (2CH), 99.4 (CH), 97.5 (CH_2), 93.0 (CH_2), 86.5 (CH), 82.0 (CH), 77.6 (CH), 77.0 (CH), 74.7 (CH), 66.2 (CH), 55.8 (CH_3), 55.0 (CH_3), 51.7 (CH_3), 40.9 (CH), 38.9 (CH_2), 38.1 (CH_2), 36.8 (CH), 35.7 (CH), 35.2 (CH), 34.3 (CH), 34.0 (CH), 33.8 (CH_2), 31.4 (CH), 26.0 ($3CH_3$), 21.7 (CH_3), 18.3 (C), 17.8 (CH_3), 17.1 (CH_3), 16.0 (CH_3), 13.2 (CH_3), 11.5 (CH_3), 9.9 (CH_3), 9.1 (CH_3), −3.3 (CH_3), −3.6 ppm (CH_3); IR (film): $\tilde{\nu} = 3889$, 2928, 2897, 2956, 1746, 1690, 1452, 1410, 1154, 1090, 1000, 735, 699 cm^{-1}.

Trichloroacetylisocyanate (12.5 μL, 0.106 mmol, 1.05 equiv) was added to a solution of the preceding alcohol (99 mg, 0.10 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL). After stirring for 15 min at 20 °C, the resulting mixture was concentrated in vacuo and the residue taken up in MeOH (10 mL). K_2CO_3 (81 mg, 0.58 mmol, 5.5 equiv) was added and the resulting solution was stirred for 1 h 15 min and then concentrated in vacuo and extracted with AcOEt. The organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 90:10 to 50:50) to give the corresponding carbamate (27 mg, 27% yield) as a pale oil. $[\alpha]_D^{20} = +11.3$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.52$–7.45 (m, 2H), 7.35–7.25 (m, 6H), 7.25–7.15 (m, 2H), 6.64 (m, 1H), 6.32 (m, 1H), 5.62 (ddd, $J = 10.5$, 7.8, 7.3 Hz, 1H,), 5.58 (s, 1H), 5.53 (t, $J = 10.5$ Hz, 1H), 5.42 (dd, $J = 10.5$, 10.1 Hz, 1H), 5.21 (dd, $J = 10.5$, 10.1 Hz, 1H), 5.00 (d, $J = 9.6$ Hz, 1H), 4.82 (t, $J = 10.1$ Hz, 1H), 4.75–4.70 (m, 1H), 4.70 (d, $J = 6.4$ Hz, 1H), 4.53 (s, 2H), 4.49 (d, $J = 6.4$ Hz, 1H), 4.05 (dd, $J = 10.1$, 3.2 Hz, 1H), 3.82 (t, $J = 9.6$ Hz, 1H), 3.73 (s, 3H; CH_3), 3.48–3.43 (m, 1H), 3.38–3.30 (m, 2H), 3.32 (s, 6H; $2CH_3$), 3.07 (t, $J = 5.5$ Hz, 1H), 2.96 (dqd, $J = 10.1$, 6.9, 2.7 Hz, 1H), 2.87–2.75 (qd, $J = 6.9$, 3.2 Hz, 1H), 2.87–2.75 (dqd, $J = 10.5$, 6.9, 5.5 Hz, 1H), 2.54 (dqd, $J = 9.6$, 7.3, 5.5 Hz, 1H), 2.16 (dd, $J = 12.5$, 12.4 Hz, 1H), 2.00–1.80 (m, 4H), 1.79–1.60 (m, 2H), 1.59 (s, 3H; CH_3), 1.23 (d, $J = 6.9$ Hz, 3H; CH_3), 1.00 (d, $J = 6.9$ Hz, 3H; CH_3), 0.99 (d, $J = 6.9$ Hz, 3H; CH_3), 0.96 (d, $J = 6.9$ Hz, 3H; CH_3), 0.92 (s, 9H; $3CH_3$), 0.91 (d, $J = 7.3$ Hz, 3H; CH_3), 0.87 (d, $J = 6.4$ Hz, 3H; CH_3), 0.73 (d, $J = 6.4$ Hz, 3H; CH_3), 0.11 (s, 3H; CH_3), 0.05 ppm (s, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$) $\delta = 174.8$ (C), 163.5 (C), 157.0 (C), 138.7 (C), 136.8 (CH), 132.3 (CH), 132.1 (C), 130.3 (CH), 128.9 (CH), 128.6 (CH), 128.4 (2CH), 128.3 (2CH), 128.2 (CH), 127.8 (2CH), 125.9 (CH), 125.7 (2CH), 99.6 (CH), 97.7 (CH_2), 93.2 (CH_2), 86.8 (CH), 82.2 (CH), 78.7 (CH5), 77.7 (CH), 77.3 (CH), 66.3 (CH), 55.9 (CH_3), 55.2 (CH_3), 51.8 (CH_3), 41.1 (CH), 39.0 (CH_2), 37.6 (CH), 35.9 (CH), 36.4 (CH), 35.8 (CH), 35.3 (CH_2), 34.3 (CH), 34.1 (CH), 33.7 (CH_2), 26.1 ($3CH_3$), 23.0 (CH_3), 18.4 (C), 17.6 (CH_3), 17.3 (CH_3), 16.4 (CH_3), 13.2 (CH_3), 11.6 (CH_3), 10.2 (CH_3), 9.3 (CH_3), −3.7 (CH_3), −3.3 ppm (CH_3); IR (film): $\tilde{\nu} = 3354$, 2957, 2930, 2889, 2856, 1726, 1600, 1459, 1439, 1375, 1146, 1110, 1093, 1032 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{56}H_{89}NO_{11}NaSi$: 1002.6103 $[M+Na]^+$; found: 1002.6097.

HCl (4 N, 2.7 mL) was added to a solution of preceding carbamate (27 mg, 0.027 mmol, 1.0 equiv) in THF (2.7 mL). The resulting mixture was stirred for 72 h at 20 °C and then solid $NaHCO_3$ was added and extracted three times with AcOEt. The organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH 95:5 to 60:40) to give the title 22-benzyl discodermolide **4** (10 mg, 56% yield). $[\alpha]_D^{20} = +4.6$ ($c = 1.0$ in MeOH); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.33$–7.14 (m, 5H), 5.66–5.58 (m, 1H), 5.51 (dd, $J = 11.0$, 7.8 Hz, 1H), 5.45–5.34 (m, 2H), 5.16 (d, $J = 9.6$ Hz, 1H), 4.78–4.67 (m, 3H), 4.64–59 (m, 2H), 3.75–3.67 (m, 2H), 3.44 (dd,

J=15.5, 7.8 Hz, 1H), 3.38 (dd, J=15.5, 8.7 Hz, 1H), 3.28 (dd, J=5.9, 3.7 Hz, 1H), 3.19 (dd, J=6.4, 4.6 Hz, 1H), 3.00–2.91 (m, 1H), 2.83–2.75 (m, 1H), 2.74–2.68 (m, 1H), 2.66–2.58 (m, 1H), 2.58–2.45 (m, 1H), 2.03–1.80 (m, 9H; 5CH, 2CH_2), 1.65 (s, 3H; CH_3), 1.30 (d, J=7.3 Hz, 3H; CH_3), 1.08 (d, J=6.9 Hz, 3H; CH_3), 1.04–0.95 (m, 12H; 4CH_3), 0.83 ppm (d, J=5.5 Hz, 3H; CH_3); ^{13}C NMR (100.5 MHz, CD_3CN): δ=174.7 (C), 157.2 (C), 141.1 (C), 133.0 (CH), 132.9 (CH), 131.5 (C), 130.3 (CH), 128.9 (CH), 128.6 (2CH), 128.4 (2CH), 126.0 (CH), 117.0 (CH), 78.8 (CH), 78.4 (CH), 76.8 (CH), 75.4 (CH), 72.3 (CH), 62.7 (CH), 43.1 (CH), 41.4 (CH_2), 37.6 (CH), 36.1 (CH), 35.6 (CH), 35.5 (CH, CH_2), 33.6, (CH_2), 33.4 (CH), 32.7 (CH), 22.5 (CH_3), 18.6 (CH_3), 17.4 (CH_3), 16.4 (CH_3), 14.8 (CH_3), 14.3 (CH_3), 12.1 (CH_3), 8.4 ppm (CH_3); IR (film): $\tilde{\nu}$= 3384, 2984, 2932, 2877, 2859, 1712, 1698, 1454, 1390, 1387, 1285, 1100, 1031, 739, 700 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{38}H_{59}O_8NaN$: 680.4138 [M+Na]$^+$; found: 680.4133.

14-Isopropyl discodermolide 5: *p*-Toluenesulfonic acid (2 mg, 0.008 mmol, 0.28 equiv) was added to a solution of compound **33** (30 mg, 0.029 mmol, 1.0 equiv) in MeOH (4 mL) at 0°C. After stirring for 1 h at 0°C, triethylamine was added to the reaction mixture (0.3 equiv) and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 95:5 to 70:30) to give expected alcohol (19 mg, 72% yield). $[\alpha]_D^{20}$=+8.4 (c=0.38 in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): δ=7.50–7.42 (m, 2H), 7.38–7.27 (m, 3H), 6.63 (ddd, J=16.9, 11.0, 10.5 Hz, 1H), 6.16 (dd, J=11.0, 10.5 Hz, 1H), 5.59 (s, 1H), 5.53 (dd, J=10.5, 10.1 Hz, 1H), 5.33 (t, J=10.5 Hz, 1H), 5.27–5.23 (m, 1H), 5.20 (d, J=16.9 Hz, 1H), 5.16 (d, J=10.5 Hz, 1H), 5.05 (d, J=9.6 Hz, 1H), 4.85 (dd, J=10.1, 9.6 Hz, 1H), 4.72 (d, J= 6.9 Hz, 1H), 4.50 (s, 2H; CH_2), 4.49 (d, J=6.9 Hz, 1H), 4.06 (dd, J=10.1, 2.7 Hz, 1H), 3.84 (dd, J=10.1, 9.2 Hz, 1H), 3.73 (s, 3H; CH_3), 3.62 (dd, J=5.9, 3.2 Hz, 1H), 3.35–3.32 (m, 1H), 3.34 (s, 3H; CH_3), 3.31 (s, 3H; CH_3), 3.08 (t , J=5.5 Hz, 1H), 2.87–2.78 (m, 3H), 2.65–2.53 (m, 1H), 2.19–2.06 (m, 2H), 1.95 (dd, J=14.2, 12.4 Hz, 1H), 1.90–1.79 (m, 2H), 1.72–1.60 (m, 3H), 1.44 (s, 1H), 1.23 (d, J=6.9 Hz, 3H; CH_3), 1.02–0.87 (m, 12H; 6CH_3), 0.93 (s, 9H; 3CH_3), 0.88 (d, J=6.9 Hz, 3H; CH_3), 0.75 (d, J=6.9 Hz, 3H; CH_3), 0.10 ppm (s, 6H; 2CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=175.1 (C), 142.5 (C), 139.0 (C), 138.0 (CH), 134.9 (CH), 132.3 (CH), 131.4 (CH), 129.0 (CH), 128.5 (CH), 128.2 (2CH), 126.1 (2CH), 127.2 (CH), 118.8 (CH_2), 99.9 (CH), 98.0 (CH_2), 93.4 (CH_2), 87.0 (CH), 82.5 (CH), 79.2 (CH), 77.6 (CH), 76.3 (CH), 66.5 (CH), 56.3 (CH_3), 55.5 (CH_3), 52.2 (CH_3), 41.1 (CH), 39.3 (CH_2), 38.3 (CH), 36.5 (CH), 35.6 (CH_2), 35.5 (CH), 35.1 (CH), 34.4 (CH), 33.9 (CH), 32.3 (CH), 26.5 (3CH_3), 18.5 (C), 22.9 (CH_3), 22.4 (CH_3), 18.7 (CH_3), 17.5 (CH_3), 16.1 (CH_3), 13.9 (CH_3), 11.9 (CH_3), 9.7 (CH_3), 9.5 (CH_3), −2.9 (CH_3), −3.4 ppm (CH_3); IR (film): $\tilde{\nu}$=3055, 2956, 2931, 2909, 1742, 1736, 1460, 1453, 1433, 1377, 1146, 1093, 1013, 836, 772 cm^{-1}.

Trichloroacetylisocyanate (2.6 μL, 0.022 mmol, 1.05 equiv) was added to a solution of preceding alcohol (19 mg, 0.021 mmol, 1.0 equiv) in CH_2Cl_2 (1.7 mL). After stirring for 15 min at 20°C, the resulting mixture was concentrated in vacuo and the residue taken up in MeOH (2.1 mL). K_2CO_3 (16 mg, 0.45 mmol, 5.5 equiv) was added and the resulting solution was stirred for 1 h 15 min and then concentrated in vacuo and extracted with AcOEt. The organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 90:10 to 50:50) to give the title carbamate (8 mg, 40% yield) as a pale oil. $[\alpha]_D^{20}$=+20.7 (c=0.80 in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): δ=7.50–7.42 (m, 2H), 7.37–7.27 (m, 3H), 6.60 (ddd, J=16.5, 11.0, 10.5 Hz, 1H), 6.04 (t, J=11.0 Hz, 1H), 5.58 (s, 1H), 5.53 (t, J=10.5 Hz, 1H, H-9, m, 1H), 5.39 (dd, J=11.0, 10.5 Hz, 1H), 5.25–5.11 (m, 4H), 5.03 (d, J=10.1 Hz, 1H), 4.85 (dd, J=10.1, 8.7 Hz, 1H), 4.71 (d, J= 6.4 Hz, 1H), 4.71–4.67 (m, 1H), 4.51 (s, 2H; CH_2), 4.50 (d, J=6.4 Hz, 1H), 4.05 (dd, J=11.0, 2.7 Hz, 1H), 3.84 (dd, J=10.1, 9.6 Hz, 1H), 3.73 (s, 3H; CH_3), 3.43 (dd, J=4.6, 4.1 Hz, 1H), 3.32 (s, 3H; CH_3), 3.30 (s, 3H; CH_3), 3.05 (t, J=5.5 Hz, 1H), 3.03–2.96 (m, 1H), 2.87–2.78 (m, 2H), 2.58 (dqd, J=10.1, 6.9, 5.5 Hz, 1H), 2.12 (hept, J=6.4 Hz), 2.03–1.67 (m, 7H; 2CH_2, 3CH), 1.23 (d, J=7.3 Hz, 3H; CH_3), 1.00 (d, J=6.9 Hz, 3H; CH_3), 0.99 (d, J=6.9 Hz, 3H; CH_3), 0.96–0.90 (m, 9H; 3CH_3), 0.93 (s, 9H; 3CH_3), 0.89 (d, J=6.9 Hz, 3H; CH_3), 0.88 (d, J=6.9 Hz, 3H; CH_3), 0.73 (d, J=6.9 Hz, 3H; CH_3), 0.11 (s, 3H; CH_3), 0.08 ppm (s, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=174.8 (C), 157.1 (C), 141.7 (C), 138.7 (CH), 137.7 (C), 133.5 (CH), 132.0 (CH), 129.8 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 127.9 (2CH), 125.8 (2CH), 117.9 (CH_2), 99.7 (CH), 97.7 (CH_2), 93.1 (CH_2), 86.8 (CH), 82.2 (CH), 78.8 (CH), 77.7 (CH), 77.0 (CH), 66.3 (CH), 56.0 (CH_3), 55.2 (CH_3), 51.9 (CH_3), 41.2, 39.0, 37.9, 35.9, 35.8, 35.4, 34.4, 33.6, 31.6 (9CH, 2CH_2, C-2, C-4, C-6, C-10, C-12, C-15, C-16, C-18, C-20, $CH(CH_3)_2$), 26.2 (3CH_3), 18.5 (C), 22.6 (CH_3), 21.9 (CH_3), 17.5 (CH_3), 17.1 (CH_3), 15.9 (CH_3), 13.7 (CH_3), 11.7 (CH_3), 9.4 (CH_3), 9.3 (7CH_3), −3.3 (CH_3), −3.8 ppm (CH_3); IR (film): $\tilde{\nu}$=3440, 3355, 2998, 2933, 1730, 1721, 1460, 1450, 1409, 1395, 1094, 1034 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{54}H_{93}O_{11}NNaSi$: 982.6415 [M+Na]$^+$; found: 982.6437.

HCl (4 N, 0.9 mL) was added to a solution of preceding carbamate (8 mg, 0.008 mmol, 1.0 equiv) in THF (0.9 mL). The resulting mixture was stirred for 72 h at 20°C and then solid $NaHCO_3$ was added and the mixture extracted three times with AcOEt. The organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH 95:5 to 70:30) to give 14-isopropyl discodermolide **5** (2 mg, 50% yield). ^{1}H NMR (400.0 MHz, $CDCl_3$): δ= 6.64 (ddd, J=17.4, 10.5, 10.1 Hz, 1H), 6.05 (dd, J=11.0, 10.5 Hz, 1H), 5.55 (dd, J=11.0, 7.8 Hz, 1H), 5.45 (dd, J=12.4, 11.0 Hz, 1H), 5.37 (dd, J=11.0, 10.1 Hz, 1H), 5.25 (d, J=17.4 Hz, 1H), 5.20 (d, J=10.1 Hz, 1H), 5.14 (d, J=10.5 Hz, 1H), 4.80–4.76 (m, 1H), 4.72 (dd, J=6.9, 4.1 Hz, 1H), 4.70–4.59 (m, 4H), 3.80–3.72 (m, 2H), 3.30 (t, J=5.0 Hz, 1H), 3.21 (dd, J=7.3, 4.6 Hz, 1H), 3.06–2.98 (m, 1H), 2.88–2.80 (m, 1H), 2.75–2.62 (m, 2H), 2.16 (hept, J=7.8 Hz, 1H), 2.00–1.85 (m, 9H; 5CH, 2CH_2), 1.33 (d, J=7.3 Hz, 3H; CH_3), 1.09 (d, J=6.9 Hz, 3H; CH_3), 1.06 (d, J= 7.3 Hz, 3H; CH_3), 1.05 (d, J=6.0 Hz, 3H; CH_3), 1.03 (d, J=6.9 Hz, 3H; CH_3), 1.01 (d, J=6.9 Hz, 6H; 2CH_3), 0.96 (d, J=6.4 Hz, 3H; CH_3), 0.85 ppm (d, J=6.0 Hz, 3H; CH_3); HRMS (ESI): m/z: calcd for $C_{35}H_{59}O_8NNa$: 644.4138 [M+Na]$^+$; found: 644.4133.

Phenol discodermolide 6: Compound **39** (16 mg, 0.017 mmol, 1.0 equiv) was diluted in MeOH (2 mL) at 0°C and *p*-toluenesulfonic acid (0.9 mg, 0.0047 mmol, 0.28 equiv) was added. After stirring for 1 h at 0°C, triethylamine was added to the reaction mixture (0.3 equiv) and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et_2O 95:5 to 60:40) to give the expected alcohol (8 mg, 58% yield). $[\alpha]_D^{20}$=+20.8 (c=0.8 in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): δ=7.13 (t, J=7.8 Hz, 1H), 6.84 (d, J= 7.8 Hz, 1H), 6.76 (s, 1H), 6.68 (d, J=7.8 Hz, 1H), 6.66 (ddd, J=16.5, 11.0, 10.5 Hz, 1H), 6.13 (t, J=11.0 Hz, 1H), 5.49 (dd, J=10.5, 10.1 Hz, 1H), 5.33 (dd, J=11.0, 10.1 Hz, 1H), 5.25 (d, J=16.5 Hz, 1H), 5.24 (t, J=10.5 Hz, 1H), 5.16 (d, J=10.5 Hz, 1H), 4.89 (d, J=10.1 Hz, 1H), 4.61 (s, 2H), 4.59 (d, J=6.4 Hz, 1H), 4.61–4.55 (m, 1H), 4.36 (d, J=6.4 Hz, 1H), 3.62 (dd, J=5.5, 3.2 Hz, 1H), 3.40 (s, 3H; CH_3), 3.33 (ddd, J=8.7, 3.2, 2.7 Hz, 1H), 3.16 (d, J=8.7 Hz, 1H), 3.02 (s, 3H; CH_3), 2.93 (dd, J= 6.4, 5.0 Hz, 1H), 2.85–2.76 (m, 3H), 2.75 (dd, J=7.8, 5.0 Hz, 1H), 2.58–2.52 (m, 1H), 2.21 (dd, J=12.4, 11.9 Hz, 1H), 1.95–1.85 (m, 1H), 1.82–1.75 (m, 2H), 1.60 (s, 3H; CH_3), 0.98 (s, 18H; 6CH_3), 0.99–0.92 (m; 4CH_3), 0.74 (d, J=6.9 Hz; CH_3), 0.18 (s, 6H; 2CH_3), 0.09 ppm (s, 6H; 2CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=155.3 (C), 140.2 (C), 137.0 (CH), 134,7 (CH), 132.4 (CH), 132.0 (CH), 131.0 (C), 130.4 (CH), 128.9 (CH), 128.7 (CH), 122.7 (CH), 121.7 (CH), 118.5 (CH_2), 117.7 (CH), 97.7 (CH_2), 93.0 (CH_2), 87.0 (CH), 78.9 (CH), 76.2 (CH), 71.9 (CH), 55.9 (CH_3), 54.9 (CH_3), 42.0 (CH_2), 37.9 (CH), 36.5 (CH_2), 36.3 (CH), 35.6 (CH), 34.6 (CH), 34.4 (CH), 26.6 (3CH_3), 26.2 (3CH_3), 23.3 (CH_3), 18.4 (2C), 18.1 (CH_3), 17.1 (CH_3), 16.9 (CH_3), 13.4 (CH_3), 9.4 (CH_3), −3.2 (2CH_3), −3.7 (CH_3), −4.4 ppm (CH_3); IR (film): $\tilde{\nu}$=3373, 2957, 2929, 2857, 1148, 1096, 1031, 1004, 838 cm^{-1}.

Trichloroacetylisocyanate (2.3 μL, 0.019 mmol, 1.05 equiv) was added to a solution of preceding alcohol (15 mg, 0.018 mmol, 1.0 equiv) in CH_2Cl_2 (1.4 mL). After stirring for 15 min at 20°C, the resulting mixture was concentrated in vacuo and the residue was taken up in MeOH (1.8 mL). K_2CO_3 (14 mg, 0.10 mmol, 5.5 equiv) was added and the resulting solution was stirred for 1 h 15 min and then concentrated in vacuo and extracted with AcOEt. The organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the solvents were removed under

reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 90:10 to 50:50) to give the title carbamate (9 mg, 58% yield). $[\alpha]_D^{20} = +31.7$ ($c = 0.9$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.15$ (t, $J = 7.8$ Hz, 1H), 6.84 (d, $J = 7.8$ Hz, 1H), 6.73 (s, 1H), 6.72 (d, $J = 7.8$ Hz, 1H), 6.60 (ddd, $J = 16.5$, 11.0, 10.1 Hz, 1H), 6.03 (dd, $J = 11.0$, 10.5 Hz, 1H), 5.48 (dd, $J = 10.5$, 10.1 Hz, 1H), 5.34 (dd, $J = 10.5$, 10.1 Hz, 1H), 5.25–5.22 (m, 1H), 5.22 (d, $J = 16.5$ Hz, 1H), 5.19 (dd, $J = 10.5$, 10.1 Hz, 1H), 5.13 (d, $J = 10.1$ Hz, 1H), 4.73 (d, $J = 6.9$ Hz, 1H), 4.73–4.64 (m, 1H), 4.64 (d, $J = 6.9$ Hz, 1H), 4.62 (d, $J = 6.9$ Hz, 1H), 4.62–4.53 (m, 3H; 1CH, $1CH_2$), 4.45 (d, $J = 6.9$ Hz, 1H), 3.46 (s, 3H; CH_3), 3.48 (dd, $J = 6.4$, 3.2 Hz, 1H), 3.18 (s, 3H; CH_3), 2.92–2.87 (m, 2H), 2.81–2.73 (m, 2H), 2.69 (dd, $J = 13.7$, 5.9 Hz, 1H), 2.54 (dqm, $J = 10.1$, 6.9 Hz, 1H), 2.18 (t, $J = 12.4$ Hz, 1H), 2.01–1.87 (m, 2H), 1.70–1.66 (m, 1H), 1.58 (s, 3H; CH_3), 0.99 (d, $J = 6.9$ Hz; CH_3), 0.98 (d, $J = 6.9$ Hz; CH_3), 0.93 (d, $J = 6.9$ Hz; CH_3), 0.92 (s, 18H; $6CH_3$), 0.89 (d, $J = 6.9$ Hz; CH_3), 0.71 (d, $J = 6.9$ Hz; CH_3), 0.08 (s, 6H; $2CH_3$), 0.07 ppm (s, 6H; $2CH_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$) $\delta = 157.3$ (C), 156.0 (C), 139.9 (C), 137.0 (CH), 134.0 (CH), 132.5 (CH), 132.1 (C), 130.5 (CH), 130.1 (CH), 129.6 (CH), 128.7 (CH), 122.1 (CH), 117.9 (CH_2), 116.2 (CH), 113.7 (CH), 97.3 (CH_2), 93.0 (CH_2), 87.2 (CH), 78.9 (CH), 77.3 (CH), 71.3 (CH), 56.0 (CH_3), 55.2 (CH_3), 41.7 (CH_2), 37.8 (CH), 37.3 (CH_2), 35.5 (CH), 34.9 (CH), 34.4 (CH), 34.3 (CH), 26.2 ($6CH_3$), 22.7 (CH_3), 18.5 (2C), 17.8 (CH_3), 17.3 (CH_3), 17.1 (CH_3), 12.7 (CH_3), 10.1 (CH_3), −3.2 ($2CH_3$), −3.3 (CH_3), −3.4 ppm (CH_3); IR (film): $\tilde{\nu} = 3353$, 2960, 2930, 2885, 1720, 1711, 1455, 1096, 1031 cm^{-1}. HRMS (ESI): m/z: calcd for $C_{48}H_{85}O_8NNaSi_2$: 882.5711 $[M+Na]^+$; found: 566.3447.

Preceding carbamate (9 mg, 0.010 mmol, 1.0 equiv) was dissolved in MeOH (1 mL). HCl (4 N, 1 mL) was added and the resulting mixture was stirred for 24 h at 20 °C and then solid $NaHCO_3$ was added. The reaction mixture was extracted three times with AcOEt. The organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH 95:5 to 80:20) to give phenol discodermolide **6** (5 mg, 88% yield). $[\alpha]_D^{20} = +7.54$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.16$ (t, $J = 8.2$ Hz, 1H), 6.77–6.70 (m, 3H), 6.61 (ddd, $J = 16.9$, 10.5, 10.1 Hz, 1H), 6.04 (dd, $J = 11.0$, 10.5 Hz, 1H), 5.52 (d, $J = 8.2$ Hz, 1H), 5.33 (dd, $J = 11.0$, 9.6 Hz, 1H), 5.23 (d, $J = 16.9$ Hz, 1H), 5.21 (d, $J = 8.2$ Hz, 1H), 5.13 (d, $J = 10.1$ Hz, 1H), 5.08 (d, $J = 10.1$ Hz, 1H), 4.72 (dd, $J = 9.2$, 3.2 Hz, 1H), 4.70–4.62 (m, 3H; 1CH, $1CH_2$), 3.40 (dd, $J = 9.2$, 2.7 Hz, 1H), 3.36 (dd, $J = 5.5$, 2.7 Hz, 1H), 3.14 (t, $J = 5.9$ Hz, 1H), 3.01–2.97 (m, 1H), 2.82–2.63 (m, 2H), 2.56–2.48 (m, 1H), 2.20–2.10 (m, 2H), 2.00–1.90 (m, 2H), 1.66 (s, 3H; CH_3), 1.07–0.88 (m; $4CH_3$), 0.71 ppm (d, $J = 5.5$ Hz; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 157.4$ (C), 139.4 (C), 135.3 (C), 133.8 (CH), 133.4 (C), 132.2 (CH), 131.8 (CH), 130.1 (CH), 129.7 (CH), 129.4 (CH), 129.3 (CH), 121.3 (CH), 118.0 (CH_2), 115.8 (CH), 114.1 (CH), 79.5 (CH), 77.6 (CH), 76.2 (CH), 68.6 (CH), 44.0 (CH_2),, 42.9 (CH), 37.1 (CH_2), 36.5 (CH), 36.2 (CH), 34.7 (CH), 32.0 (CH), 23.0 (CH_3), 18.9 (CH_3), 17.4 (CH_3), 17.1 (CH_3), 12.1 (CH_3), 9.3 ppm (CH_3); IR (film): $\tilde{\nu} = 3360$, 2350, 2341, 1620, 1434, 1396, 668 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{35}H_{59}O_8NNa$: 566.3457 $[M+Na]^+$; found: 566.3447.

Antiproliferative activity of discodermolide analogues 2–6: The antiproliferative activity of discodermolide analogues **2–6** was determined by measuring the inhibition of cell proliferation of HCT116, MDA-A1, and MDA-MB-231 cells.

The cells were seeded in cell culture medium at a concentration of 10,000 cells per well in 0.17 mL of medium, and 20 μL of test product at various concentrations and 10 μL of thymidine [methyl-^{14}C] (100 μCi mL^{-1}—specific activity 47.90 mCi mmol^{-1}, NEN Technologies, Reference batch technologies NEC568 3550–001) were added; then the cells were incubated at 37 °C and 5% CO_2. Medium used for growing HCT116 cells: DMEM 2 mM L-glutamine, 200 IU mL^{-1} penicillin, 200 μg mL^{-1} streptomycin, and 10% (V V^{-1}) fetal calf serum (Life Technologies).

After 96 h, the incorporation of ^{14}C-thymidine was counted in a liquid scintillation counter 1450 Microbeta Wallac Trilux. R results are expressed in cpm (counts per minute) and converted to percentage of growth inhibition GI% by first subtracting the average number of cpm of wells without B cells and then dividing by the number of cpm of wells of untreated cells comprising C 20 μL of dilution medium containing 1% of the product of ethanol. (GI% = (R−B) × 100/C%). The IC_{50} values are calculated by using the equation 205, XLFit software (IDBS company, UK) by nonlinear regression analysis with the Marquardt algorithm.[26]

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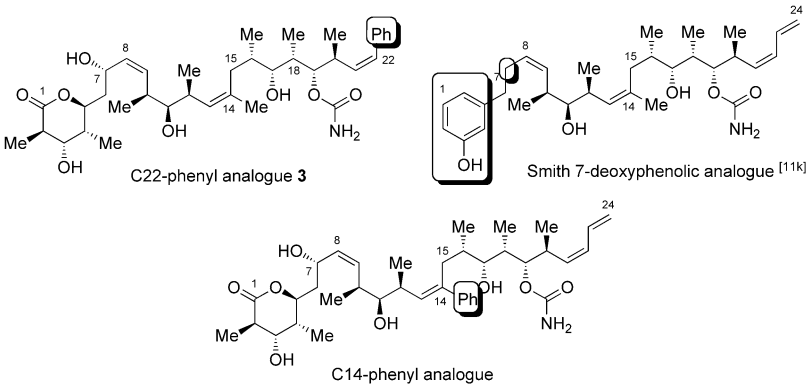

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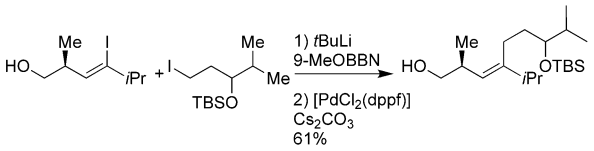
[24] The C7 centre of configuration of the alcohol precursor of **37** was confirmed through derivatization to the corresponding (*R*)- and (*S*)-



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