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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] 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 as well as 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 in 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 • polyketides • discodermolide analogues • cross-coupling • nickel

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.^[2] 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]

These exciting activities resulted in a Phase I clinical trial initiated by Novartis which was suspended due to pulmonary

toxicity, despite encouraging results.^[5] However, investigation work towards non toxic and active DDM analogues is 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 (Figure 1). Reported solid-state, solution and protein-bound DDM conformations reveal the unusual result that a common hairpin conformational motif exists in all three microenvironments.^[7] No other flexible microtubule binding agents exhibits 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 as well as the C8-C9 and C13-C14 (Z) double bonds.

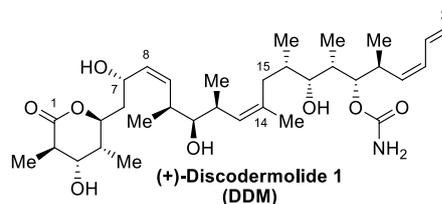


Figure 1. Discodermolide structure.

The natural product was only isolated in low yields, and no biosynthesis allowed to produce DDM to date; 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 directed toward the total synthesis of (+)-DDM [8,9,10] as well as 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

[a] Dr. E. de Lemos, Dr. E. Agouridas, Dr. G. Sorin, Dr. A. Pancrazi, Dr. J.-F. Betzer, Dr. M.-I. Lannou, Prof. J. Ardisson
Université Paris Descartes
Faculté de Pharmacie, CNRS UMR 8638
4 avenue de l'Observatoire
75270 Paris Cedex (France)
Fax: (+33)143291403
E-mail: jean-francois.betzer@icsn-gif.fr
marie-isabelle.lannou@parisdescartes.fr
janick.ardisson@parisdescartes.fr

[b] Dr. A. Guerreiro, Dr. A. Commerçon
Chemical & Analytical Sciences
Natural Product Chemistry, Sanofi-Aventis
Centre de Recherche de Vitry-Alfortville
13 Quai Jules Guesde
94403 Vitry-sur-Seine Cedex (France)

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, this is by modifying the δ -lactone fragment that most of the analogues have been generated. 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** using a straightforward and highly convergent route.^[8m-n] The modifiable 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 in order 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) (Figure 2).

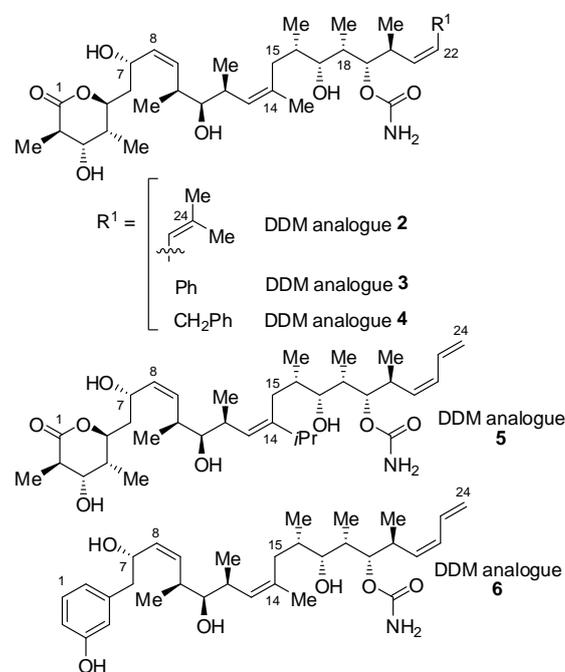
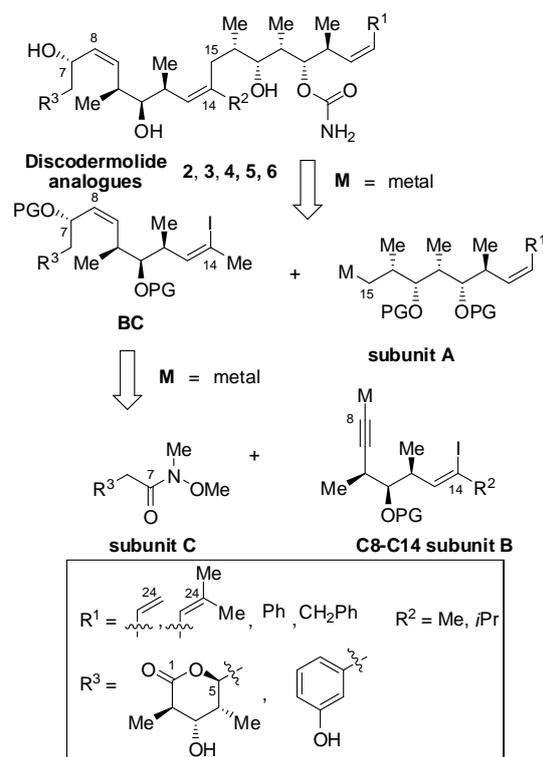


Figure 2. Focused DDM analogues.

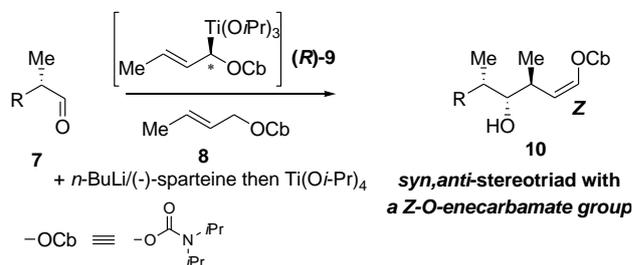
The strategy for the preparation of the five analogues **2-6** patterned after the synthesis of DDM **1**, is summarized in Scheme 1. The same disconnections were made to provide **A**, **B** and **C**

fragments. The linkage of these subunits will rely on acetylide addition to Weinreb amide [**B-C**] and Suzuki Pd-catalyzed sp^2 - sp^3 coupling reaction [**A-BC**].



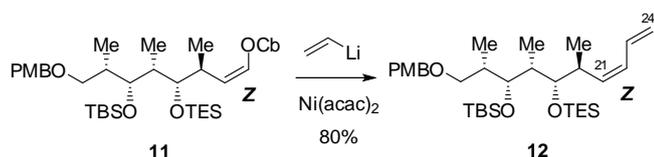
Scheme 1. DDM analogues: retrosynthetic analysis.

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]



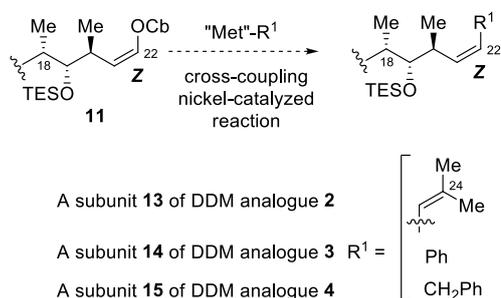
Scheme 2. DDM total synthesis: crotyltitanation of aldehyde **7**.

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 nickel-catalyzed cross-coupling reaction in the presence of Ni(acac)₂ with vinylolithium (Scheme 3).^[8m-n,15,16]



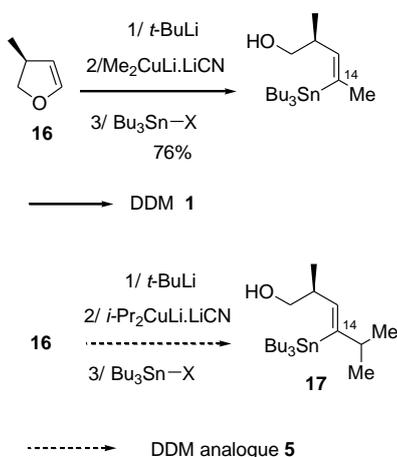
Scheme 3. DDM total synthesis: formation of the terminal (Z)-diene **12**.

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-encarbamate 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 non-diene derivatives with a phenyl or a benzyl core (**14** and **15**) (Scheme 4).



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

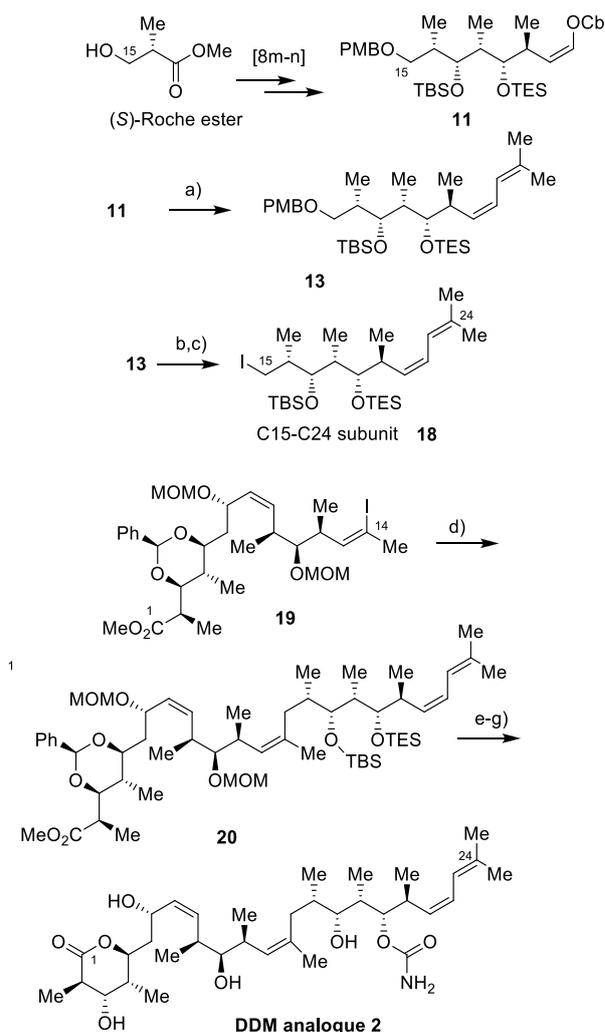
The replacement of the methyl group at the C14 position by a more sterically demanding isopropyl group was very original and innovative. Although such a variation has never been reported so far, we were convinced it could enhance the specific active conformation of DDM **1**. For the building of the 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).



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

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 investigation 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 binding site). Therefore, we investigated the simplification of DDM backbone with a phenol core to afford analogue **6** while keeping 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 sub-unit **18** in two steps. The second key step involved an sp²-sp³ 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 non optimized 51% yield.

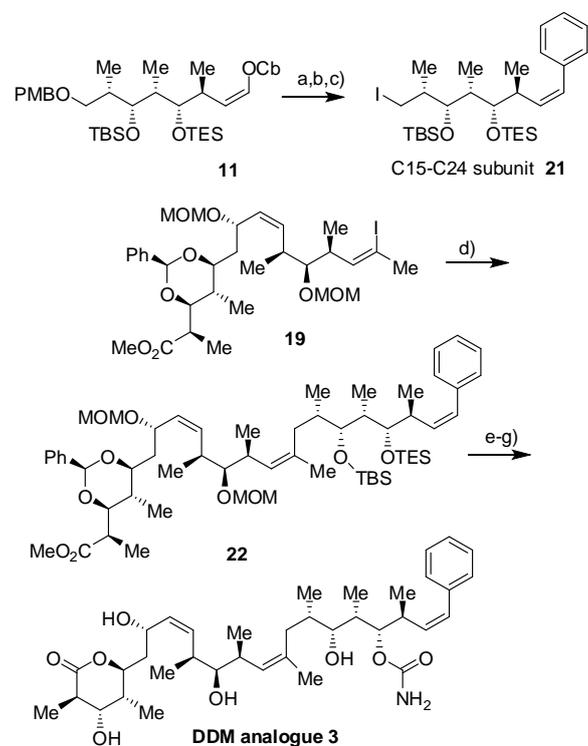


Scheme 6. Synthesis of DDM analogue **2**. a) Ni(acac)₂, Et₂O, 0 °C, 2-methylpropenylmagnesium bromide, 16h, 94%; b) DDQ, CH₂Cl₂/H₂O 95:5, 0 °C → RT,

3h30, 83%; c) I₂, PPh₃, imid, C₆H₆/Et₂O, 0 °C → RT, 2 h, 61%; d) **18**, *t*BuLi, Et₂O, -78 °C, 5 min, *B*-methoxy-9-BBN, THF, -78 °C → RT, then **19**, Cs₂CO₃, PdCl₂dppf, AsPh₃, DMF, H₂O, 16 h, 51%; e) PTSA, MeOH, 0 °C, 1 h, 70%; f) Cl₃CC(O)NCO, CH₂Cl₂, RT, 15 min, then K₂CO₃, MeOH, RT, 1.15 h, 78%; g) HCl 4N, THF, RT, 72 h, 47%. acac=acetylacetonate, DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone, imid=imidazole, BBN=borabicyclo[3,3,1]nonane, dppf=(diphenylphosphino)ferrocene.

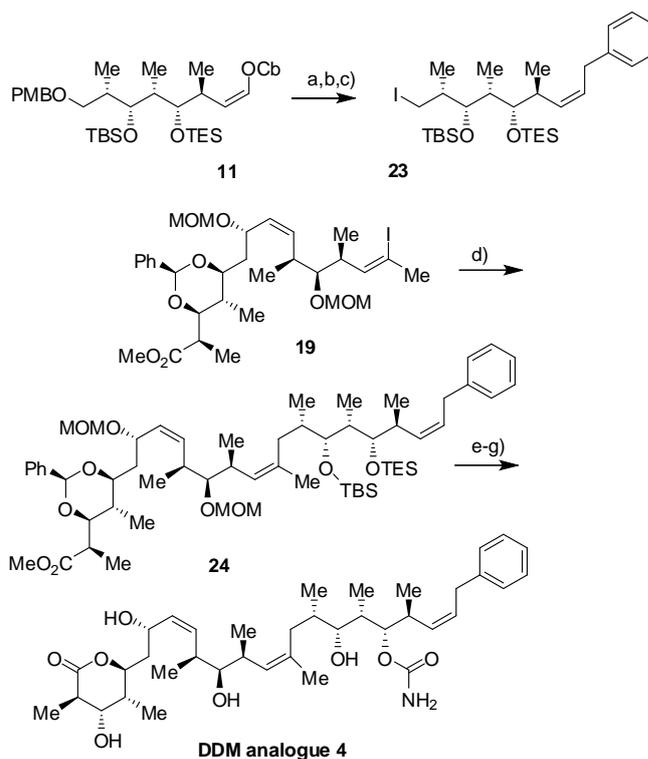
Selective cleavage of the C19-TES ether followed by carbamate moiety installation and final total deprotection with concomitant lactonisation provided DDM analogue **2**.

The elaboration of the non-diene analogue **3** possessing a phenyl group followed a similar sequence from vinylcarbamate **11** (Scheme 7). Thus, nickel-catalyzed cross-coupling reaction involving phenylmagnesium bromide ensured the construction of the C15-C24 sub-unit **21** with high selectivity. Then, sp²-sp³ Suzuki coupling reaction (formation of **22**), carbamate function set-up and deprotection delivered desired DDM analogue **3**.



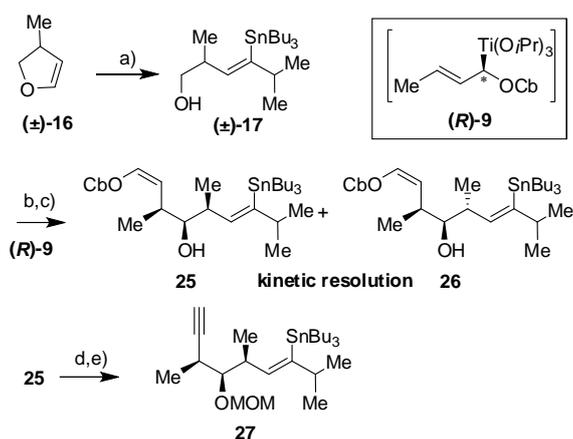
Scheme 7. Synthesis of DDM analogue **3**. a) **14**: Ni(acac)₂, Et₂O, 0 °C, phenylmagnesium bromide, 16h; b) DDQ, CH₂Cl₂/H₂O 95:5, 0 °C → RT, 3h30, 59% over 2 steps; c) I₂, PPh₃, imid, C₆H₆/Et₂O, 0 °C → RT, 3 h, 86%; d) **21**, *t*BuLi, Et₂O, -78 °C, 5 min, *B*-methoxy-9-BBN, THF, -78 °C → RT, then **19**, Cs₂CO₃, PdCl₂dppf, AsPh₃, DMF, H₂O, 16 h, 10%; e) PTSA, MeOH, 0 °C, 1 h, 69%; f) Cl₃CC(O)NCO, CH₂Cl₂, RT, 15 min, then K₂CO₃, MeOH, RT, 1.15 h, 58%; g) HCl 4N, THF, RT, 72 h, 91%. acac=acetylacetonate, DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone, imid=imidazole, BBN=borabicyclo[3,3,1]nonane, dppf=(diphenylphosphino)ferrocene.

For the synthesis of the second non-diene 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 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**.



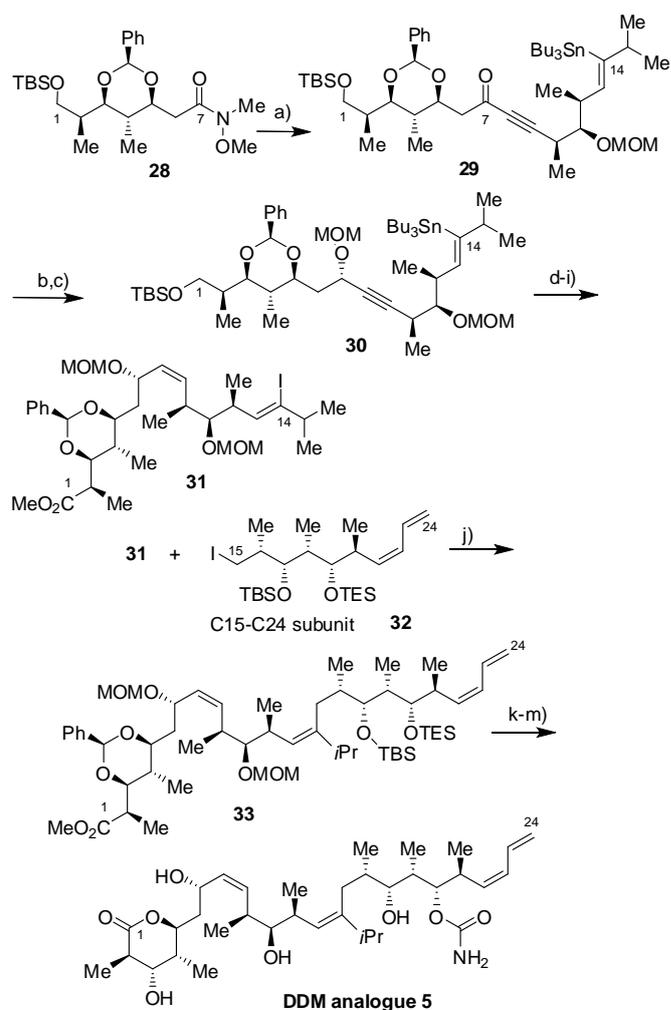
Scheme 8. Synthesis of DDM analogue **4**. a) DDQ, CH₂Cl₂/H₂O 95:5, 0 °C → RT, 30 min, 60% b) **15**: Ni(acac)₂, Et₂O, rt, benzylmagnesium chloride, 3h; 73%; c) I₂, PPh₃, imid, C₆H₆/Et₂O, 0 °C → RT, 2 h, 77%; d) **23**, *t*BuLi, Et₂O, -78 °C, 2 min, *B*-methoxy-9-BBN, THF, -78 °C → RT, then **19**, Cs₂CO₃, PdCl₂dppf, AsPh₃, DMF, H₂O, 16 h, 30%; e) PTSA, MeOH, 0 °C, 1 h, 80%; f) Cl₃CC(O)NCO, CH₂Cl₂, RT, 15 min, then K₂CO₃, MeOH, RT, 1.15 h, 27%; g) HCl 4N, THF, RT, 72 h, 56%. acac=acetylacetonate, DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone, imid=imidazole, BBN=borabicyclo[3,3,1]nonane, dppf=(diphenylphosphino)ferrocene.

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 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 main product in 41% yield along with its diastereomer **26** in 25% yield. To confirm the configuration of the (*S*)-C11 secondary hydroxy centre, 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**.



Scheme 9. Synthesis of alkyne **27**. a) *t*BuLi, *i*Pr₂CuLi·LiCN, Et₂O/DMS 4:1, 0 °C → RT, 12 h, then *n*-Bu₃SnCl, -30 °C → RT, 5 h, 72%; b) TEMPO (10 mol%), BAIB, CH₂Cl₂, 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, TBAl, Hunig's base, CH₂Cl₂, RT, 24 h, 88%. TEMPO=2,2,6,6-tetramethyl-1-piperidinyloxy free radical, BAIB=[bis(acetoxy)iodo]benzene, MOM=methoxymethyl, TBAl=tetra-*n*-butylammonium iodide, Hunig's base=diisopropylethylamine.

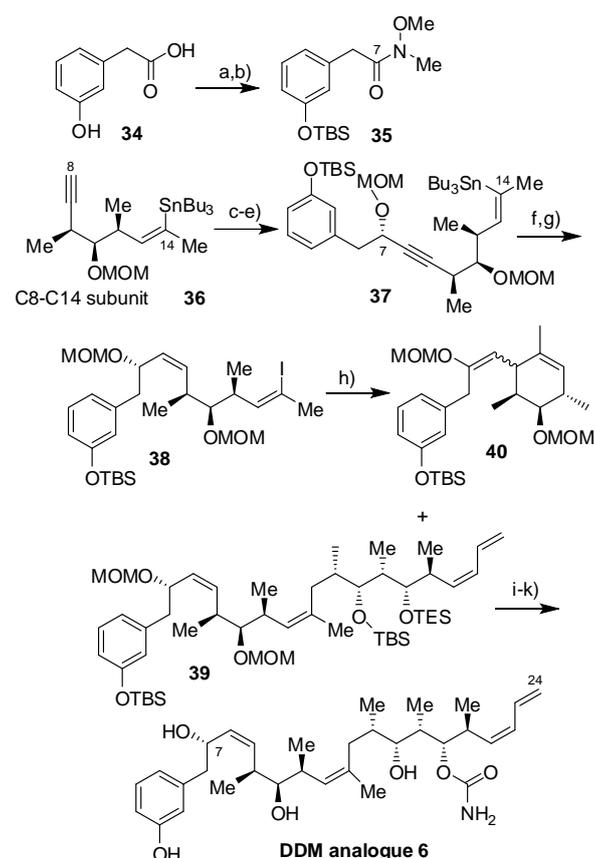
Coupling of the compound **27** with the amide **28** [^{8m-n}] delivered the ketone **29** (Scheme 10). Diastereoselective reduction of this intermediate under CBS conditions [²²] led, after protection of the alcohol at C11, to alkyne **30**. Oxidation followed by partial hydrogenation with PtO₂ (catalyst of choice for this congested alkyne) and iodine-tin exchange then completed the formation of vinyl iodide **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**.



Scheme 10. Synthesis of analogue **5**. a) **27**, *n*BuLi/Et₂O, THF, -40 °C, 50 min, then **28**, -40 °C → 0 °C, 1 h, 86%; b) (*S*)-(-)-2-Methyl-CBS-oxazaborolidine, BH₃·Me₂S, THF, -30 °C, 2 h, 89%, dr 98:2. c) MOMCl, TBAl, Hunig's base, CH₂Cl₂, RT, 12 h, 97%; d) HF/Py, Py/THF, RT, 4 h, 87%; e) TEMPO (10 mol%), BAIB, CH₂Cl₂, RT, 3 h; f) NaClO₂, NaH₂PO₄, 2-methyl-but-2-ene, *t*-BuOH/H₂O, RT, 1 h; g) TMSCHN₂, C₆H₆/MeOH, RT, 15 min, 65% over 3 steps; h) H₂, PtO₂ (30 mol%), AcOEt, RT, 12 h; i) I₂, CH₂Cl₂, 0 °C, 10 min, 76% over 2 steps; j) **32**, *t*BuLi, Et₂O, -78 °C, 5 min, *B*-methoxy-9-BBN, THF, -78 °C → RT, then **31**, Cs₂CO₃, PdCl₂dppf, AsPh₃, DMF, H₂O, 16 h, 10%; k) PTSA, MeOH, 0 °C, 1 h, 72%; l) Cl₃CC(O)NCO, CH₂Cl₂, RT, 15 min, then K₂CO₃, MeOH, RT, 1.15 h, 40%; m) HCl 4N, THF, RT, 72 h, 50%. CBS= Corey-Bakshi-Shibata, MOM=methoxymethyl, TBAl=tetra-*n*-butylammonium iodide, Py=pyridine, TEMPO=2,2,6,6-tetramethyl-1-piperidinyloxy free radical, TMS=trimethylsilyl, BBN=borabicyclo[3.3.1]nonane, dppf=(diphenylphosphino)ferrocene, BAIB=[bis(acetoxy)iodo]benzene.

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 (*S*)-CBS reagent [²⁴] and protection of the newly generated hydroxy function at C7. Hydrogenation and iodine-tin exchange then led to vinyl iodide **38**. While the formation of this vinyl iodide **38** proceeded smoothly, significant problems were encountered during Suzuki cross-coupling reaction between vinyl iodide **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 3-step sequence (deprotection of the C1-C24 fragment and carbamate formation at C19) delivered analogue **6**.



Scheme 11. Synthesis of analogue **6**. a) TBSCl, imid, DMF, RT, 4 days; b) $\text{HN}(\text{CH}_3)\text{OCH}_3\cdot\text{HCl}$, Hunig's base, $\text{EDCl}\cdot\text{HCl}$, HOBt , CH_2Cl_2 , RT, 24 h, 66% over 2 steps; c) **36**, $n\text{BuLi}/\text{Et}_2\text{O}$, THF, $-40\text{ }^\circ\text{C}$, 50 min, then **35**, $-40\text{ }^\circ\text{C}$ \rightarrow $0\text{ }^\circ\text{C}$, 1 h, 63%; d) (*S*)-(-)-2-Methyl-CBS-oxazaborolidine, $\text{BH}_3\cdot\text{Me}_2\text{S}$, THF, $-30\text{ }^\circ\text{C}$, 2 h, 81%, dr 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 , $0\text{ }^\circ\text{C}$, 10 min, 76% over 2 steps; h) **32**, $n\text{BuLi}$, Et_2O , $-78\text{ }^\circ\text{C}$, 5 min, *B*-methoxy-9-BBN, THF, $-78\text{ }^\circ\text{C}$ \rightarrow RT, then **38**, Cs_2CO_3 , PdCl_2dppf , AsPh_3 , DMF , H_2O , 16 h, **39** 17% and **40** 20%; i) **39**, PTSA , MeOH , $0\text{ }^\circ\text{C}$, 1 h, 58%; j) $\text{Cl}_3\text{CC}(\text{O})\text{NCO}$, CH_2Cl_2 , RT, 15 min, then K_2CO_3 , MeOH , RT, 1.15 h, 58%; k) HCl 4N, THF, RT, 24 h, 88%. Imid=imidazole, Hunig's base=diisopropylethylamine, EDCl =1-ethyl-3-(3-dimethylamino)propyl carbodiimide, HOBt =1-hydroxybenzotriazole, CBS=Corey-Bakshi-Shibata, MOM=methoxymethyl, DMAP =dimethylaminopyridine, TBAI =tetra-*n*-butylammonium iodide, BBN=borabicyclo[3,3,1]nonane, dppf=(diphenylphosphino)ferrocene.

Biological evaluation: The five DDM analogues **2**, **3**, **4**, **5** and **6** were finally screened for cellular activity in comparison to DDM **1** (previously synthesized in the laboratory). Cytotoxicity assays were performed on three different cell lines. All analogues were effective in the nanomolar range comparable to DDM **1** [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 (entries 1, 2 and 3, Table 1). They were followed in this order by phenolic **6** and C22-Ph **3** analogues (entries 5 and 6, Table 1). The C22-benzyl analogue **4** was the less potent (entry 4, Table 1).

Table 1. Biological evaluation of synthesized analogues **2-6**.^{[a],[b]}

Entry	Compound	IC_{50} (nM)	IC_{50} (nM)	IC_{50} (nM)
		HCT116 ^[a]	MDA-MB231 ^[b]	MDA-A1 ^[c]
1	DDM 1	5.0 ^l	15.6	105.8
2	C-24- <i>gem</i> -dimethyle 2	1.3	3.7	155
3	C-22-phenyle 3	19	110	4494
4	C-22-benzyle 4	321	1009	8709
5	C-14-isopropyle 5	2.3	17.5	2200
6	Phenol 6	16 ^l	66	4836

[a] *In vitro* cytotoxic activities were determined on triplicate samples in WST-8 cell proliferation assays after 4 days of incubation. [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).

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.

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 **1**, each of them exhibiting potent cytotoxicity.

The first requirement was to keep the bioactive U shaped conformation of DDM, therefore modelling 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 in order to reinforce the U shaped bioactive conformation and 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 one is a dyotropic rearrangement performed on a methyl-dihydrofuran 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

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 were employing reagent grade. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were freshly distilled from sodium/benzophenone under argon immediately prior to use. Dichloromethane (DCM), cyclohexane and pentane were freshly distilled over calcium hydride. All other reagents were used as supplied. Reactions were magnetically stirred and monitored by thin layer chromatography 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. ¹H NMR spectra were recorded using an internal deuterium lock at ambient temperature on a JEOL JNM-ECX 270 or 400 MHz spectrometer. Internals references of δ_H 7.26 and 1.96 were used respectively for CDCl₃ and CD₃CN. Data are represented as follows: chemical shift (in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet), integration, coupling constant (J/Hz). ¹³C-NMR spectra were recorded on a Jeol 67.5 or 100.5 MHz spectrometer. Internals references of δ_C 77.16 and 118.26 were used respectively for CDCl₃ and CD₃CN. Infrared spectra were recorded on a Nicolet Impact-400 and wavelength (ν) is given in cm⁻¹. Mass spectra were recorded on a GC/MS 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, CH₄). 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 analysis were performed on a CHN 240 Perkin-Elmer instrument by the Service de Microanalyses, Centre d'Etudes Pharmaceutiques, Chatenay-Malabry, F-92296. High-resolution mass-spectra 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.

(2Z,4Z,6S,7S,8R,9S,10S)-9-(tert-Butyldimethylsilyloxy)-11-(4-methoxybenzyloxy)-7-(triethylsilyloxy)-1,5,7,9-tetramethyl undeca-2,4-diene (13): A solution of 2-methylpropenylmagnesium bromide (0.5 M in THF, 43 mL, 21.6 mmol, 10 equiv) was added to a solution of carbamate **11** (1.5 g, 2.16 mmol, 1.0 equiv) and Ni(acac)₂ (55 mg, 0.22 mmol, 0.1 equiv) in Et₂O (43 mL) at -5°C/0°C. The resulting mixture was stirred for 16h at 0°C. An aqueous saturated NH₄Cl solution was then added, and the solution was extracted with Et₂O. The organic layers were washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et₂O 100:0 to 80:20) to give 1.22 g (94% yield) of compound **13**. $[\alpha]_D^{20} = +5.91$ (c = 1.72, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃) δ = 7.24 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 6.13 (dd, J = 11.5, 11.0 Hz, 1H), 6.03 (d, J = 11.5 Hz, 1H), 5.33 (dd, J = 11.0, 10.1 Hz, 1H), 4.41 (d, J = 11.5 Hz, 1H), 4.35 (d, J = 11.5 Hz, 1H), 3.80 (s, 3H, CH₃), 3.78 (dd, J = 5.5, 3.7 Hz, 1H), 3.51 (dd, J = 5.0, 4.6 Hz, 1H), 3.36 (dd, J = 8.7, 5.9 Hz, 1H), 3.12 (dd, J = 8.7, 8.2 Hz, 1H), 2.80 (m, 1H), 1.94 (m, 1H), 1.78 (s, 3H, CH₃), 1.74 (s, 3H, CH₃), 1.68-1.62 (m, 1H), 0.97 (d, J = 6.9 Hz, 3H, CH₃), 0.94 (t, J = 7.8 Hz, 9H, 3CH₃), 0.89 (s, 9H, 3CH₃), 0.87 (d, J = 6.9 Hz, 3H, CH₃), 0.84 (d, J = 6.9 Hz, 3H, CH₃), 0.60 (q, J = 7.8 Hz, 6H), 0.05 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃) δ = 158.9 (C), 135.1 (C), 132.5 (C), 130.8 (CH), 129.2 (2CH), 124.4 (CH), 120.6 (CH), 113.6 (2CH), 77.0 (CH), 73.4 (CH₂, CH), 72.5 (CH₂), 55.2 (CH₃), 40.1 (CH), 38.0 (CH), 36.2 (CH), 26.9 (CH₃), 26.2 (3CH₃), 18.5 (C, CH₃), 18.0 (CH₃), 12.1 (CH₃), 11.6 (CH₃), 7.2 (3CH₃), 5.6 (3CH₂), -3.3 (CH₃), -3.9 (CH₃); IR (Film) ν = 2957, 2931, 2877, 2856, 1574, 1462, 1249, 1092, 1040, 1006 cm⁻¹; elemental analysis calcd (%) for C₃₃H₆₄O₄Si₂: C 69.48, H 10.66; found: C 69.27, H 10.59.

(2Z,4Z,6S,7S,8R,9S,10S)-9-(tert-Butyldimethylsilyloxy)-11-iodo-7-(triethylsilyloxy)-1,5,7,9-tetramethyl undeca-2,4-diene 18: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 648 mg, 2.85 mmol, 1.1 equiv) was added to a solution of compound **13** (1.57 g, 2.6 mmol, 1.0 equiv) in CH₂Cl₂ (52 mL)/H₂O (2.6 mL) at 0°C. The mixture was stirred for 10 min at 0°C, warmed to 20°C and stirred for 3h30. The mixture was quenched with a saturated aqueous NaHCO₃ solution, diluted with Et₂O, washed with water and brine. The combined organic layers were dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/AcOEt 98:2 to 80:20) to give the expected alcohol **(2Z,4Z,6S,7S,8R,9S,10S)-9-(tert-Butyldimethylsilyloxy)-11-hydroxy-7-(triethyl-**

silyloxy)-1,5,7,9-tetramethyl undeca-2,4-diene (1.04 g, 83% yield). $[\alpha]_D^{20} = +4.6$ (c = 2.24, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃) δ = 6.16 (dd, J = 11.4, 10.5 Hz, 1H), 6.02 (d, J = 11.4 Hz, 1H), 5.45 (dd, J = 11.0, 10.5 Hz, 1H), 3.67 (t, J = 4.1 Hz, 1H), 3.59-3.47 (m, 2H), 3.45-3.38 (m, 1H), 2.85 (m, 1H), 1.82 (s, 3H, CH₃), 1.74 (s, 3H, CH₃), 1.70-1.60 (m, 3H), 1.03 (d, J = 7.3 Hz, 3H, CH₃), 0.99 (t, J = 7.8 Hz, 9H, 3CH₃), 0.94 (d, J = 6.9 Hz, 3H, CH₃), 0.92 (s, 9H, 3CH₃), 0.82 (d, J = 6.9 Hz, 3H, CH₃), 0.65 (q, J = 7.8 Hz, 6H, 3CH₂), 0.11 (s, 3H, CH₃), 0.10 (s, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃) δ = 135.9 (C), 131.0 (CH), 124.4 (CH), 120.2 (CH), 78.1 (CH), 73.5 (CH), 66.0 (CH₂), 40.7 (CH), 40.4 (CH), 35.4 (CH), 26.9 (CH₃), 26.3 (3CH₃), 19.0 (CH₃), 18.4 (C), 18.1 (CH₃), 12.5 (CH₃), 11.8 (CH₃), 7.2 (3CH₃), 5.6 (3CH₂), -3.5 (CH₃), -3.7 (CH₃); IR (Film) ν = 3410, 2957, 2929, 2878, 2857, 1461, 1251, 1098, 1076, 1006, 833, 772, 736 cm⁻¹.

A solution of iodine (1.07 g, 4.21 mmol, 1.5 equiv) in Et₂O (10 mL) was slowly added to a solution of the above alcohol (1.36 g, 2.81 mmol, 1.0 equiv), triphenylphosphine (PPh₃, 1.4 g, 5.34 mmol, 1.9 equiv) and imidazole (363 mg, 5.34 mmol, 1.9 equiv) in a benzene (10 mL)/Et₂O mixture (20 mL) at 0°C. After stirring for 2h at 20°C, a 1 M Na₂S₂O₃ solution was added and the reaction mixture was extracted with Et₂O. The organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et₂O 100:0 to 80:20) to give 738 mg (61% yield) of the title compound **18**. $[\alpha]_D^{20} = +10.7$ (c = 1.03, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃) δ = 6.17 (dd, J = 11.4, 11.0 Hz, 1H), 6.01 (d, J = 11.4 Hz, 1H), 5.38 (dd, J = 11.0, 10.5 Hz, 1H), 3.58 (dd, J = 4.6, 4.1 Hz, 1H), 3.50 (dd, J = 6.4, 3.2 Hz, 1H), 3.30 (dd, J = 9.6, 4.6 Hz, 1H), 2.94 (dd, J = 9.6, 9.2 Hz, 1H), 2.81 (m, 1H), 1.97 (dqdd, J = 9.2, 6.4, 4.6, 3.2 Hz, 1H), 1.81 (s, 3H, CH₃), 1.75 (s, 3H, CH₃), 1.64 (m, 1H), 1.00 (d, J = 6.4 Hz, 3H, CH₃), 0.98 (t, J = 7.8 Hz, 9H, 3CH₃), 0.96 (d, J = 6.4 Hz, 3H, CH₃), 0.91 (s, 9H, 3CH₃), 0.89 (d, J = 6.9 Hz, 3H, CH₃), 0.64 (q, J = 7.8 Hz, 6H, 3CH₂), 0.08 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃) δ = 135.7 (C), 130.9 (CH), 124.6 (CH), 120.5 (CH), 77.8 (CH), 75.0 (CH), 42.1 (CH), 40.7 (CH), 35.6 (CH), 26.9 (CH₃), 26.4 (3CH₃), 18.8 (CH), 18.4 (CH₃), 18.1 (C), 15.2 (CH₃), 13.7 (CH₂), 12.2 (CH₃), 7.2 (3CH₃), 5.6 (3CH₂), -3.6 (2CH₃); IR (Film) ν = 3015, 2958, 2930, 2878, 2857, 1462, 1215, 1097, 1030, 1007, 836, 669 cm⁻¹; elemental analysis calcd (%) for C₂₇H₅₅O₂Si₂: C 54.52, H 9.32; found: C 55.09, H 9.66.

[2S,4R(1R),5S,6S(2S,3Z,5S,6R,7S,8Z,11S,12R,13S,14S,15S,16Z)]-4-(2-Methoxycarbonyl-1-methyl ethyl-1-yl)-6-[12-(tert-butylidimethylsilyloxy)-5,7,9,11,13,15,19-heptamethyl-2,6-bis(methoxymethyl)oxy]-14-(triethylsilyloxy)-icosa-3,8,16,18-tetraen-1-yl]-5-methyl-2-phenyl-1,3-dioxinan 20: tBuLi (1.5 M in pentane, 395 μ L, 0.59 mmol, 3.8 equiv) was rapidly added to a solution of the alkyl iodide **18** (166 mg, 0.28 mmol, 1.8 equiv) in Et₂O (4 mL) at -80°C; 2 min later were added 9-MeOBBN (1 M in hexane, 670 μ L, 0.67 mmol, 4.3 equiv) then THF (4 mL). The resulting mixture was stirred 10 min at -78°C and allowed to warm to 20°C during 1h15; an aqueous 3.5 M Cs₂CO₃ solution was then added (243 μ L, 0.85 mmol, 5.5 equiv), followed by the addition of the vinyl iodide **19**^[8m-n] (105 mg, 0.15 mmol, 1.0 equiv) in DMF (4 mL). Finally PdCl₂dppf (13 mg, 0.015 mmol, 0.10 equiv) and triphenylarsine (6 mg, 0.019 mmol, 0.12 equiv) were added, and the resulting dark solution was stirred at 20°C for 16h. After extraction with Et₂O, the organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et₂O 85:15 to 50:50) to give the title compound **20** (71 mg, 51% yield). **20:** $[\alpha]_D^{20} = +16.1$ (c = 0.60, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃) δ = 7.47-7.43 (m, 2H, H-Ar), 7.35-7.31 (m, 3H), 6.16 (dd, J = 11.4, 10.5 Hz, 1H), 6.03 (d, J = 11.4 Hz, 1H), 5.58 (s, 1H), 5.54 (t, J = 10.5 Hz, 1H), 5.38 (dd, J = 10.5, 10.1 Hz, 1H), 5.22 (dd, J = 10.5, 9.6 Hz, 1H), 4.98 (d, J = 10.1 Hz, 1H), 4.84 (dd, J = 10.5, 9.6 Hz, 1H), 4.71 (d, J = 6.9 Hz, 1H), 4.53 (s, 2H), 4.51 (d, J = 6.9 Hz, 1H), 4.05 (dd, J = 10.1, 3.2 Hz, 1H), 3.82 (dd, J = 10.1, 8.7 Hz, 1H), 3.74 (s, 3H, CH₃), 3.54 (dd, J = 6.4, 3.7 Hz, 1H), 3.47 (dd, J = 4.6, 4.1 Hz, 1H), 3.33 (s, 3H, CH₃), 3.32 (s, 3H, CH₃), 3.09 (dd, J = 5.9, 5.5 Hz, 1H), 2.90-2.80 (m, 3H), 2.53-2.49 (m, 1H), 1.80 (s, 3H, CH₃), 1.75 (s, 3H, CH₃), 1.67 (tq, J = 10.1, 6.4 Hz, 1H), 2.51-2.41 (m, 6H), 1.54 (s, 3H, CH₃), 1.24 (d, J = 6.9 Hz, 3H, CH₃), 0.99 (t, J = 7.8 Hz, 3CH₃), 1.05-0.87 (m, 6CH₃), 0.93 (s, 3CH₃), 0.65 (q, J = 7.8 Hz, 3CH₂), 0.08 (s, 3H, CH₃), 0.07 (s, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃) δ = 174.8 (C), 138.8 (C), 136.9 (C), 135.3 (C), 132.4 (CH), 131.2 (CH), 130.3 (CH), 128.9 (CH), 128.2 (CH), 127.9 (2CH), 125.8 (2CH), 124.4 (CH), 120.5 (CH), 99.6 (CH), 97.8 (CH₂), 93.2 (CH₂), 86.9 (CH), 82.2 (CH), 77.9 (CH), 77.7 (CH), 77.0 (CH), 66.4 (CH), 56.0 (CH₃), 55.2 (CH₃), 51.9 (CH₃), 41.1, 40.2, 39.0, 36.5, 35.8, 35.7, 35.3, 35.0, 34.8 (7CH), 27.1 (CH₃), 26.9 (3CH₃), 18.7 (C), 18.6, 18.1, 17.3, 16.6, 13.9, 11.7, 11.5, 9.3 (9CH₃), 7.2 (3CH₃), 5.7 (3CH₂), -3.1 (CH₃), -3.3 (CH₃); IR (Film) ν = 3383, 2957, 2932, 2879, 2857, 1461, 1453, 1396, 1152, 1093, 1045 cm⁻¹; HRMS (ESI): m/z: calcd for C₅₈H₁₀₂O₁₀NaSi₂: 1037.6909 [M+Na]; found: 1037.6913.

24-Dimethyl discodermolide 2: p-toluene sulfonic 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 1h 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 **[2S,4R(1R),5S,6S(2S,3Z,5S,6R,7S,8Z,11S,12R,13S,14S,15S,16Z)]-4-(2-methoxycarbonyl-1-methyl ethyl-1-yl)-6-[12-(tert-butylidimethylsilyloxy)-5,7,9,11,13,15,19-**

heptamethyl-14-hydroxy-2,6-bis[(methoxymethyl)oxy]- icoso-3,8,16,18-tetraen-1-yl]-5-methyl-2-phenyl-1,3-dioxinan (73 mg, 70% yield). $[\alpha]_D^{20} = +13.9$ ($c = 1.48$, CHCl_3); $^1\text{H NMR}$ (400.0 MHz, CDCl_3) δ 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, 2 CH_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 (dq, $J = 10.1, 6.9, 5.9$ 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, 3 CH_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 (s, 3H, CH_3); $^{13}\text{C NMR}$ (100.5 MHz, CDCl_3) δ 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 (CH₂), 93.2 (CH₂), 86.8 (CH), 82.3 (CH), 79.0 (CH), 77.7 (CH), 75.6 (CH), 66.3 (CH), 56.0 (CH₃), 55.2 (CH₃), 51.9 (CH₃), 41.0 (CH), 39.1 (CH), 36.8 (CH₂), 36.0 (CH), 35.8 (CH), 35.3 (CH), 34.5 (CH), 34.4 (CH₃), 27.1 (CH₃), 26.3 (CH₃), 26.2 (3CH₃), 23.3 (CH₃), 18.7 (C), 17.5 (CH₃), 17.1 (CH₃), 16.4 (CH₃), 13.1 (CH₃), 11.7 (CH₃), 9.5 (CH₃), 9.3 (CH₃), -3.2 (CH₃), -3.6 (CH₃). IR (Film) $\nu = 3382, 2969, 2930, 2839, 2857, 1743, 1461, 1092, 1152, 1110, 1092, 1045, 727$ cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{32}\text{H}_{58}\text{O}_{10}\text{NaSi}$ [$M+\text{Na}$]: 923.6044; 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 1h15, then concentrated *in vacuo* and extracted with AcOEt. The organic layers were washed with water, 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]- icoso-3,8,16,18-tetraen-1-yl]-5-methyl-2-phenyl-1,3-dioxinan (59 mg, 78% yield) as a pale oil. $[\alpha]_D^{20} = +30.3$ ($c = 1.18$, CHCl_3); $^1\text{H NMR}$ (400.0 MHz, CDCl_3) δ 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, 2 CH_3), 3.06 (dd, $J = 5.9, 5.5$ Hz, 1H), 2.98 (dq, $J = 10.1, 6.4$ 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, 3 CH_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 (s, 3H, CH_3); $^{13}\text{C NMR}$ (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 (CH₂), 93.1 (CH₂), 86.9 (CH), 82.1 (CH), 79.1 (CH), 77.6 (CH), 77.0 (CH), 66.3 (CH), 56.0 (CH₃), 55.2 (CH₃), 51.9 (CH₃), 41.1 (CH), 39.0, 37.9, 36.1, 35.8, 35.2, 35.1, 34.4, 34.0 (6CH, 2CH₂), 26.8 (3CH₃), 26.3 (CH₃), 23.0 (CH₃), 18.4 (CH₃), 18.0 (C), 17.6 (CH₃), 17.3 (CH₃), 16.5 (CH₃), 13.8 (CH₃), 11.6 (CH₃), 10.1 (CH₃), 9.3 (CH₃), -3.4 (CH₃), -3.6 (CH₃). IR (Film) $\nu = 33282, 3315, 3304, 3215, 2983, 2956, 2930, 2901, 2880, 1726, 1090, 1045$ 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 then added with solid NaHCO_3 and extracted 3 times with AcOEt. The organic layers were washed with water, brine, dried over MgSO_4 , filtered and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95:5 to 90:10) to give the title compound, DDM analogue 2 (18 mg, 47% yield) as an oil. 2: $[\alpha]_D^{20} = +22.0$ ($c = 1.8$, MeOH); $^1\text{H NMR}$ (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 (dq, $J = 10.5, 6.9$ 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), 0.96 (2d, $J = 7.3$ Hz, 6H), 0.94 (d, $J = 6.4$ Hz, 3H, CH_3); $^{13}\text{C NMR}$ (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, 2CH₂), 26.3 (2CH₃), 23.3 (CH₃), 19.8, 18.4, 18.0, 16.0, 15.7, 13.0, 9.2 (7CH₃); IR (Film) $\nu = 3382, 2962, 2929, 2870, 2856, 2360, 2340, 1726$,

1682, 1454, 1395, 1032, 668 cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{35}\text{H}_{59}\text{NO}_8\text{NaSi}$: 644.4138 [$M+\text{Na}$]; found: 644.4142.

22-Phenyl discodermolide 3: *p*-toluene sulfonic 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 1h 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). $[\alpha]_D^{20} = +19.1$ ($c = 0.4$, CHCl_3); $^1\text{H NMR}$ (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, 2 CH_3), 3.11 (t, $J = 5.5$ Hz, 1H), 3.02 (dq, $J = 7.3, 6.4, 3.7$ Hz, 1H), 2.88-2.76 (m, 2H), 2.56 (dq, $J = 10.1, 6.9, 5.5$ 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, 3 CH_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 (s, 3H, CH_3); $^{13}\text{C NMR}$ (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 (CH₂), 93.1 (CH₂), 86.8 (CH), 82.2 (CH), 78.7 (CH), 77.7 (CH), 76.7 (CH), 66.3 (CH), 56.0 (CH₃), 55.2 (CH₃), 51.9 (CH₃), 41.0 (CH), 39.1 (CH₂), 38.1 (CH), 36.4 (CH₂), 35.9 (CH), 35.8 (CH), 35.3 (CH), 34.6 (CH), 34.5 (CH), 26.2 (3CH₃), 23.3 (CH₃), 18.4 (C), 17.5 (2CH₃), 16.4 (CH₃), 13.7 (CH₃), 11.6 (CH₃), 9.4 (CH₃), 9.3 (CH₃), -3.3 (CH₃), -3.6 (CH₃); IR (Film) $\nu_{\text{max}} = 3440, 3377, 2960, 2929, 1461, 1453, 1435, 1151, 1092, 1036$ cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{55}\text{H}_{90}\text{O}_{10}\text{NaSi}$: 961.6201 [$M+\text{Na}$]; found: 961.6208.

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 1h15 then concentrated *in vacuo* and extracted with AcOEt. The organic layers were washed with water, 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. $[\alpha]_D^{20} = +33.0$ ($c = 1.2$, CHCl_3); $^1\text{H NMR}$ (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, NH₂), 4.56 (s, 2H, CH₂), 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, 2 CH_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 (dq, $J = 10.1, 6.4, 5.5$ 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, 3 CH_3), 0.56 (d, $J = 6.9$ Hz, 3H, CH_3), 0.01 (s, 3H, CH_3), -0.12 (s, 3H, CH_3); $^{13}\text{C NMR}$ (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 (CH₂), 93.2 (CH₂), 87.0 (CH), 82.2 (CH), 79.1 (CH), 77.7 (CH), 77.0 (CH), 66.3 (CH), 56.0 (CH₃), 55.2 (CH₃), 51.9 (CH₃), 41.1 (CH), 39.0 (CH₂), 37.9 (CH), 36.0 (CH₂), 35.9 (CH), 35.3 (CH), 34.8 (CH), 34.7 (CH), 34.2 (CH), 26.1 (3CH₃), 23.0 (CH₃), 18.5 (C), 17.7 (CH₃), 17.4 (CH₃), 16.7 (CH₃), 14.1 (CH₃), 11.6 (CH₃), 9.9 (CH₃), 9.4 (CH₃), -3.5 (2CH₃); IR (Film) $\nu_{\text{max}} = 3376, 2961, 2930, 1728, 1460, 1147, 1094, 1035, 757$ cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{56}\text{H}_{91}\text{NO}_{11}\text{NaSi}$: 1004.6259 [$M+\text{Na}$]; found: 1004.6250.

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 72h at 20°C then added with solid NaHCO_3 and extracted 3 times with AcOEt. The organic layers were washed with water, brine, dried over MgSO_4 , filtered and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 100:0 to 70:30) to give the title compound 3 (7 mg, 91% yield). $[\alpha]_D^{20} = +3.2$ ($c = 0.7$, MeOH); $^1\text{H NMR}$ (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 (qd, $J = 7.3, 4.6$ Hz, 1H), 2.31-2.20 (dq, $J = 10.1, 6.4$ Hz, 1H), 1.81-1.40 (m, 10H, 6CH, 2CH₂), 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 (d, $J = 6.4$ Hz, 3H, CH_3); $^{13}\text{C NMR}$ (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 (3CH), 122.7 (2CH), 79.8 (CH), 79.7 (CH), 77.2 (CH), 75.4 (CH), 73.1 (CH), 63.1 (CH), 43.9 (CH), 42.1 (CH₂), 38.5 (CH), 37.7 (CH), 36.8 (CH, CH₂), 35.8 (CH), 34.2 (CH), 34.1 (CH), 23.6 (CH₃), 20.0 (CH₃), 18.2

(2CH₃), 15.8 (CH₃), 15.7 (CH₃), 13.0 (CH₃), 9.1 (CH₃); IR (Film) ν_{\max} = 3364, 2961, 2930, 2868, 1706, 1456, 1396, 1387, 1034, 737, 702 cm⁻¹; HRMS (ESI): m/z calcd for C₃₇H₅₇NO₈Na: 666.3982 [M+Na]; found: 666.3990.

22-Benzyl discodermolide 4: *p*-toluene sulfonic 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). ¹H NMR (400.0 MHz, CDCl₃) δ = 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, CH₃), 3.53-3.43 (m, 3H, CH, CH₂), 3.33 (s, 6H, 2CH₃), 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, CH₃), 1.25 (d, J = 6.9 Hz, 3H, CH₃), 0.97 (d, J = 6.4 Hz, 3H, CH₃), 0.94 (s, 3CH₃), 0.97-0.90 (m, 9H, 3CH₃), 0.88 (d, J = 6.9 Hz, 3H, CH₃), 0.74 (d, J = 6.9 Hz, 3H, CH₃), 0.10 (s, 3H, CH₃), 0.06 (s, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃) δ = 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 (CH₂), 93.0 (CH₂), 86.5 (CH), 82.0 (CH), 77.6 (CH), 77.0 (CH), 74.7 (CH), 66.2 (CH), 55.8 (CH₃), 55.0 (CH₃), 51.7 (CH₃), 40.9 (CH), 38.9 (CH₂), 38.1 (CH₂), 36.8 (CH), 35.7 (CH), 35.2 (CH), 34.3 (CH), 34.0 (CH), 33.8 (CH₂), 31.4 (CH), 26.0 (3CH₃), 21.7 (CH₃), 18.3 (C), 17.8 (CH₃), 17.1 (CH₃), 16.0 (CH₃), 13.2 (CH₃), 11.5 (CH₃), 9.9 (CH₃), 9.1 (CH₃), -3.3 (CH₃), -3.6 (CH₃); IR (Film) ν_{\max} = 3889, 2928, 2897, 2956, 1746, 1690, 1452, 1410, 1154, 1090, 1000, 735, 699 cm⁻¹.

Trichloroacetylisocyanate (12.5 μ l, 0.106 mmol, 1.05 equiv) was added to a solution of preceding alcohol (99 mg, 0.10 mmol, 1.0 equiv) in CH₂Cl₂ (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). K₂CO₃ (81 mg, 0.58 mmol, 5.5 equiv) was added and the resulting solution was stirred 1h15 then concentrated *in vacuo* and extracted with AcOEt. The organic layers were washed with water, brine, dried over MgSO₄, 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, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃) δ = 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, CH₃), 3.48-3.43 (m, 1H), 3.38-3.30 (m, 2H), 3.32 (s, 6H, 2CH₃), 3.07 (t, J = 5.5 Hz, 1H), 2.96 (dq, 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 (dq, J = 10.5, 6.9, 5.5 Hz, 1H), 2.54 (dq, 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, CH₃), 1.32 (d, J = 6.9 Hz, 3H, CH₃), 1.00 (d, J = 6.9 Hz, 3H, CH₃), 0.99 (d, J = 6.9 Hz, 3H, CH₃), 0.96 (d, J = 6.9 Hz, 3H, CH₃), 0.92 (s, 9H, 3CH₃), 0.91 (d, J = 7.3 Hz, 3H, CH₃), 0.87 (d, J = 6.4 Hz, 3H, CH₃), 0.73 (d, J = 6.4 Hz, 3H, CH₃), 0.11 (s, 3H, CH₃), 0.05 (s, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃) δ = 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 (CH₂), 93.2 (CH₂), 86.8 (CH), 82.2 (CH), 78.7 (CH₅), 77.7 (CH), 77.3 (CH), 66.3 (CH), 55.9 (CH₃), 55.2 (CH₃), 51.8 (CH₃), 41.1 (CH), 39.0 (CH₂), 37.6 (CH), 35.9 (CH), 36.4 (CH), 35.8 (CH), 35.3 (CH₃), 34.3 (CH), 34.1 (CH), 33.7 (CH₂), 26.1 (3CH₃), 23.0 (CH₃), 18.4 (C), 17.6 (CH₃), 17.3 (CH₃), 16.4 (CH₃), 13.2 (CH₃), 11.6 (CH₃), 10.2 (CH₃), 9.3 (CH₃), -3.7 (CH₃), -3.3 (CH₃); IR (Film) ν_{\max} = 3354, 2957, 2930, 2889, 2856, 1726, 1600, 1459, 1439, 1375, 1146, 1110, 1093, 1032 cm⁻¹; HRMS (ESI): m/z calcd for C₅₆H₈₉NO₁₁NaSi: 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 72h at 20°C then added with solid NaHCO₃ and extracted 3 times with AcOEt. The organic layers were washed with water, brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (CH₂Cl₂/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, MeOH); ¹H NMR (400.0 MHz, CDCl₃) δ = 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), 4.64-5.9 (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, 2CH₃), 1.65 (s, 3H, CH₃), 1.30 (d, J = 7.3 Hz, 3H, CH₃), 1.08 (d, J = 6.9 Hz, 3H, CH₃), 1.04-0.95 (m, 12H, 4CH₃), 0.83 (d, J = 5.5 Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CD₃CN) δ = 173.7 (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 (CH₂), 37.6 (CH), 36.1 (CH), 35.6 (CH), 35.5 (CH, CH₂), 33.6 (CH₂), 33.4 (CH), 32.7 (CH), 22.5 (CH₃), 18.6 (CH₃), 17.4

(CH₃), 16.4 (CH₃), 14.8 (CH₃), 14.3 (CH₃), 12.1 (CH₃), 8.4 (CH₃); IR (Film) ν_{\max} = 3384, 2984, 2932, 2877, 2859, 1712, 1698, 1454, 1390, 1387, 1285, 1100, 1031, 739, 700 cm⁻¹; HRMS (ESI): m/z calcd for C₃₈H₅₉O₈NaN: 680.4138 [M+Na]; found: 680.4133.

14-Isopropyl discodermolide 5: *p*-toluene sulfonic 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 1h 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, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃) 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, CH₂), 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, CH₃), 3.62 (dd, J = 5.9, 3.2 Hz, 1H), 3.35-3.32 (m, 1H), 3.34 (s, 3H, CH₃), 3.31 (s, 3H, CH₃), 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, CH₃), 1.02-0.87 (m, 12H, 6CH₃), 0.93 (s, 9H, 3CH₃), 0.88 (d, J = 6.9 Hz, 3H, CH₃), 0.75 (d, J = 6.9 Hz, 3H, CH₃), 0.10 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃) 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 (CH₂), 99.9 (CH), 98.0 (CH₂), 93.4 (CH₂), 87.0 (CH), 82.5 (CH), 79.2 (CH), 77.6 (CH), 76.3 (CH), 66.5 (CH), 56.3 (CH₃), 55.5 (CH₃), 52.2 (CH₃), 41.1 (CH), 39.3 (CH₂), 38.3 (CH), 36.5 (CH), 35.6 (CH₂), 35.5 (CH), 35.1 (CH), 34.4 (CH), 33.9 (CH), 32.3 (CH), 26.5 (3CH₃), 18.5 (C), 22.9 (CH₃), 22.4 (CH₃), 18.7 (CH₃), 17.5 (CH₃), 16.1 (CH₃), 13.9 (CH₃), 11.9 (CH₃), 9.7 (CH₃), 9.5 (CH₃), -2.9 (CH₃), -3.4 (CH₃); IR (Film) ν_{\max} = 3055, 2956, 2931, 2909, 1742, 1736, 1460, 1453, 1433, 1377, 1146, 1093, 1013, 836, 772 cm⁻¹.

Trichloroacetylisocyanate (2.6 μ l, 0.022 mmol, 1.05 equiv) was added to a solution of preceding alcohol (19 mg, 0.021 mmol, 1.0 equiv) in CH₂Cl₂ (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), K₂CO₃ (16 mg, 0.45 mmol, 5.5 equiv) was added and the resulting solution was stirred 1h15 then concentrated *in vacuo* and extracted with AcOEt. The organic layers were washed with water, brine, dried over MgSO₄, 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, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃) 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), 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 (d, J = 6.4 Hz, 1H), 4.51 (s, 2H, CH₂), 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, CH₃), 3.43 (dd, J = 4.6, 4.1 Hz, 1H), 3.32 (s, 3H, CH₃), 3.30 (s, 3H, CH₃), 3.05 (t, J = 5.5 Hz, 1H), 3.03-2.96 (m, 1H), 2.87-2.78 (m, 2H), 2.58 (dq, J = 10.1, 6.9, 5.5 Hz, 1H), 2.12 (hept, J = 6.4 Hz), 2.03-1.67 (m, 7H, 2CH₂, 2CH₃), 1.23 (d, J = 7.3 Hz, 3H, CH₃), 1.00 (d, J = 6.9 Hz, 3H, CH₃), 0.99 (d, J = 6.9 Hz, 3H, CH₃), 0.96-0.90 (m, 9H, 3CH₃), 0.93 (s, 9H, 3CH₃), 0.89 (d, J = 6.9 Hz, 3H, CH₃), 0.88 (d, J = 6.9 Hz, 3H, CH₃), 0.73 (d, J = 6.9 Hz, 3H, CH₃), 0.11 (s, 3H, CH₃), 0.08 (s, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃) 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 (CH₂), 99.7 (CH), 97.7 (CH₂), 93.1 (CH₂), 86.8 (CH), 82.2 (CH), 78.8 (CH), 77.7 (CH), 77.0 (CH), 66.3 (CH), 56.0 (CH₃), 55.2 (CH₃), 51.9 (CH₃), 41.2, 39.0, 37.9, 35.9, 35.8, 35.4, 34.4, 33.6, 31.6 (9CH, 2CH₂, C-2, C-4, C-6, C-10, C-12, C-15, C-16, C-18, C-20, CH(CH₃)₂), 26.2 (3CH₃), 18.5 (C), 22.6 (CH₃), 21.9 (CH₃), 17.5 (CH₃), 17.1 (CH₃), 15.9 (CH₃), 13.7 (CH₃), 11.7 (CH₃), 9.4 (CH₃), 9.3 (7CH₃), -3.3 (CH₃), -3.8 (CH₃); IR (Film) ν_{\max} = 3440, 3355, 2998, 2933, 1730, 1721, 1460, 1450, 1409, 1395, 1094, 1034 cm⁻¹; HRMS (ESI): m/z calcd for C₅₃H₈₉O₁₁NNaSi: 966.6103 [M+Na]; found: 966.6097.

To a solution of preceding carbamate (8 mg, 0.008 mmol, 1.0 equiv) in THF (0.9 mL) was added HCl (4 N, 0.9 mL). The resulting mixture was stirred 72 h at 20°C then added with solid NaHCO₃ and extracted 3 times with AcOEt. The organic layers were washed with water, brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (CH₂Cl₂/MeOH 95:5 to 70:30) to give 14-Isopropyl discodermolide **5** (2 mg, 50% yield). ¹H NMR (400.0 MHz, CDCl₃) 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, 2CH₂), 1.33 (d, J = 7.3 Hz, 3H, CH₃), 1.09 (d, J = 6.9 Hz, 3H, CH₃), 1.06 (d, J = 7.3 Hz, 3H, CH₃), 1.05 (d, J = 6.0 Hz, 3H, CH₃), 1.03 (d, J = 6.9 Hz, 3H, CH₃), 1.01 (d, J = 6.9 Hz, 6H, 2CH₃), 0.96 (d, J = 6.4 Hz, 3H, CH₃), 0.85 (d, J = 6.0 Hz, 3H, CH₃); HRMS (ESI): m/z calcd for C₃₅H₅₉O₈NNa: 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*-toluene sulfonic acid (0.9 mg, 0.0047 mmol, 0.28 equiv) was added. After stirring for 1h 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/Et₂O 95:5 to 60:40) to give the expected alcohol (8 mg, 58% yield). $[\alpha]_D^{20} = +20.8$ ($c = 0.8$, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃) $\delta = 7.13$ (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, CH₃), 3.33 (ddd, $J = 8.7, 3.2, 2.7$ Hz, 1H), 3.16 (d, $J = 8.7$ Hz, 1H), 3.02 (s, 3H, CH₃), 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, CH₃), 0.98 (s, 18H, 6CH₃), 0.99-0.92 (m, 4CH₃), 0.74 (d, $J = 6.9$ Hz, CH₃), 0.18 (s, 6H, 2CH₃), 0.09 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃) $\delta = 155.3$ (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 (CH₂), 117.7 (CH), 97.7 (CH₂), 93.0 (CH₂), 87.0 (CH), 78.9 (CH), 76.2 (CH), 71.9 (CH), 55.9 (CH₃), 54.9 (CH₃), 42.0 (CH₂), 37.9 (CH), 36.5 (CH₂), 36.3 (CH), 35.6 (CH), 34.6 (CH), 34.4 (CH), 26.6 (3CH₃), 26.2 (3CH₃), 23.3 (CH₃), 18.4 (2C), 18.1 (CH₃), 17.1 (CH₃), 16.9 (CH₃), 13.4 (CH₃), 9.4 (CH₃), -3.2 (2CH₃), -3.7 (CH₃), -4.4 (CH₃); IR (Film) $\nu_{\max} = 3373, 2957, 2929, 2857, 1148, 1096, 1031, 1004, 838$ cm⁻¹.

Trichloroacetylisocyanate (2.3 μ l, 0.019 mmol, 1.05 equiv) was added to a solution of preceding alcohol (15 mg, 0.018 mmol, 1.0 equiv) in CH₂Cl₂ (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). K₂CO₃ (14 mg, 0.10 mmol, 5.5 equiv) was added and the resulting solution was stirred for 1h15 then concentrated *in vacuo* and extracted with AcOEt. The organic layers were washed with water, brine, dried over MgSO₄, 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). $[\alpha]_D^{20} = +31.7$ ($c = 0.9$, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃) $\delta = 7.15$ (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, 1CH₂), 4.45 (d, $J = 6.9$ Hz, 1H), 3.46 (s, 3H, CH₃), 3.48 (dd, $J = 6.4, 3.2$ Hz, 1H), 3.18 (s, 3H, CH₃), 2.92-2.87 (m, 2H), 2.81-2.73 (m, 2H), 2.69 (dd, $J = 13.7, 5.9$ Hz, 1H), 2.54 (dq, $J = 10.1, 6.9$ 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, CH₃), 0.99 (d, $J = 6.9$ Hz, CH₃), 0.98 (d, $J = 6.9$ Hz, CH₃), 0.93 (d, $J = 6.9$ Hz, CH₃), 0.92 (s, 18H, 6CH₃), 0.89 (d, $J = 6.9$ Hz, CH₃), 0.71 (d, $J = 6.9$ Hz, CH₃), 0.08 (s, 6H, 2CH₃), 0.07 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃) $\delta = 157.3$ (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 (CH₂), 116.2 (CH), 113.7 (CH), 97.3 (CH₂), 93.0 (CH₂), 87.2 (CH), 78.9 (CH), 77.3 (CH), 71.3 (CH), 56.0 (CH₃), 55.2 (CH₃), 41.7 (CH₂), 37.8 (CH), 37.3 (CH₂), 35.5 (CH), 34.9 (CH), 34.4 (CH), 34.3 (CH), 26.2 (6CH₃), 22.7 (CH₃), 18.5 (2C), 17.8 (CH₃), 17.3 (CH₃), 17.1 (CH₃), 12.7 (CH₃), 10.1 (CH₃), -3.2 (2CH₃), -3.3 (CH₃), -3.4 (CH₃); IR (Film) $\nu_{\max} = 3353, 2960, 2930, 2885, 1720, 1711, 1455, 1096, 1031$ cm⁻¹. HRMS (ESI): m/z calcd for C₄₈H₈₈O₈NNaSi₂: 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 24h at 20°C then solid NaHCO₃ was added. The reaction mixture was extracted 3 times with AcOEt. The organic layers were washed with water, brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (CH₂Cl₂/MeOH 95:5 to 80:20) to give phenol discodermolide **6** (5 mg, 88% yield). $[\alpha]_D^{20} = +7.54$ ($c = 0.5$, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃) $\delta = 7.16$ (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, 1CH₂), 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, CH₃), 1.07-0.88 (m, 4CH₃), 0.71 (d, $J = 5.5$ Hz, CH₃); ¹³C NMR (100.5 MHz, CDCl₃) $\delta = 157.4$ (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 (CH₂), 115.8 (CH), 114.1 (CH), 79.5 (CH), 77.6 (CH), 76.2 (CH), 68.6 (CH), 44.0 (CH₂), 42.9 (CH), 37.1 (CH₂), 36.5 (CH), 36.2 (CH), 34.7 (CH), 32.0 (CH), 23.0 (CH₃), 18.9 (CH₃), 17.4 (CH₃), 17.1 (CH₃), 12.1 (CH₃), 9.3 (CH₃); IR (Film) $\nu_{\max} = 3360, 2350, 2341, 1620, 1434, 1396, 668$ cm⁻¹; HRMS (ESI): m/z calcd for C₃₅H₅₉O₈NNa: 566.3457 [M+Na]; found: 566.3447.

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Smith 7-deoxyphenolic analogue [11k]

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- [25] The formation of the cyclohexene **40** through an intramolecular coupling reaction proves the fold of the C8-C14 core.

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