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Discodermolide : Total Synthesis of Natural Product and Analogues

Janick Ardisson^{*1} and Jean-François Betzer^{†1}

^{*}Faculté de Pharmacie, CNRS UMR 8638, Université Paris Descartes, 4 avenue de l'Observatoire, 75270 Paris Cedex, France;

[†]Institut de Chimie des Substances Naturelles, CNRS UPR 2301, 91198 Gif-sur-Yvette, France;

¹Corresponding author : janick.ardisson@parisdescartes.fr, jean-francois.betzer@cnrs.fr

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Abstract:

This account describes an efficient and modifiable total synthesis of (+)-discodermolide and analogues. Particularly notable is the repeated application of a crotylation reaction of aldehydes, with α -oxygenated crotyltitanium reagent to ensure the stereocontrolled elaboration of *syn-anti* methyl-hydroxy-methyl triads connected to a *Z-O*-enecarbamate. This particular group allowed direct and easy access to either a triple bond or terminal *Z*-diene function. The stereocontrolled generation of the trisubstituted *Z*-double bond, representing a significant synthetic challenge, is ensured by a 1,2-dyotropic rearrangements on dihydrofuran with organocopper reagents. The synthesis of natural product was achieved in 21 steps with 1.6% overall yield. The same methodologies and synthetic strategy were applied for the preparation of five original analogues. The biological activities of natural product and synthetic analogues have also been studied.

Key-Words:

discodermolide, polyketides, natural products, anticancer agents, total synthesis, synthetic analogues, allylation, cross-coupling reactions, Grignard reagents, dyotropic rearrangement, organocopper reagents

1. INTRODUCTION

Natural products play an important role in cancer therapy since they have led to the development of several clinically useful anti-cancer agents. As cancer is a major public health problem and will become the leading cause of death worldwide in the 21st century, the search for novel drugs represents an important challenge for the improvement of cancer therapy.^[1]

Marine metabolites are of great interest for their high pharmacological potential^[2] Notably, polyketides (produced by various organisms such as marine bacteria and invertebrates) exhibit a wide range of biological activities (particularly as antibiotic, antitumor or immunomodulatory agents) along with great molecular diversity and complexity. However, the development of such compounds as research tools or commercial drugs is hampered by the available supply; natural source populations usually cannot sustain direct harvesting because the concentrations of the target compounds are usually low. The finding of the microorganism species producing the compound of interest may give the hope to a secured access to the molecule by a fermentation process.^[3] However, total synthesis often remained the best way to deliver significant quantities of pure and well-characterized material for extensive preclinical testing.

In 1990, Gunasekera and co-workers reported the isolation of discodermolide (DDM) **1**, a unique polyketide marine metabolite obtained in low yields (0.002 % of wet weight) from the Caribbean deep-water sponge *Discodermia dissoluta*.^[4] This sponge usually lives at depths greater than 30 m; however, very recently, a shallower population was found in Colombia. Currently, the mariculture of fragments of this sponge for DDM production is achievable but needs to be improved.^[5] On the other hand, research on biosynthesis methods for DDM production was being attempted, but the results are not known.^[6]

The cytotoxicity values reported for DDM against breast, prostate, colon, lung, and ovarian cancer cell lines are generally in the low nM range. Biological studies revealed DDM to be a potent microtubule stabilizer that binds with remarkable affinity to the taxoid site on β -tubulin in microtubules.^[7] Further studies showed clear differences between DDM and Taxol[®]. *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.^[7b] Interestingly, discodermolide can induce accelerated cell senescence, which is not a typical characteristic of Taxol[®].^[8] 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.^[9]

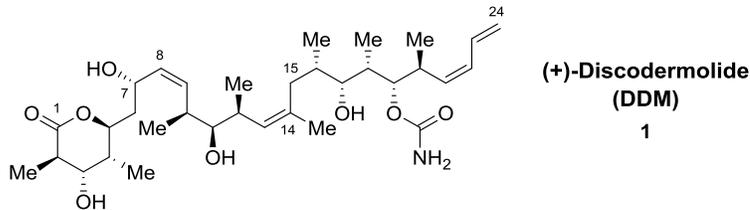


FIGURE 1 Chemical structure of (+)-discodermolide **1**.

Structurally, (+)-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, a carbamate function and a δ -lactone (Figure 1).

Due to the potential therapeutic applications and the extreme scarcity of this compound, considerable synthetic efforts directed towards DDM have been made, culminating in several total syntheses,^[10] including the development of a preparative-scale approach. Thus, taking inspiration from previous work by the Smith and Paterson groups, Novartis Pharma AG reported

a 39-step synthesis (26 steps in the longest linear sequence) of 60 g of (+)-DDM for early phase clinical oncology trials (Figure 2).^[11]

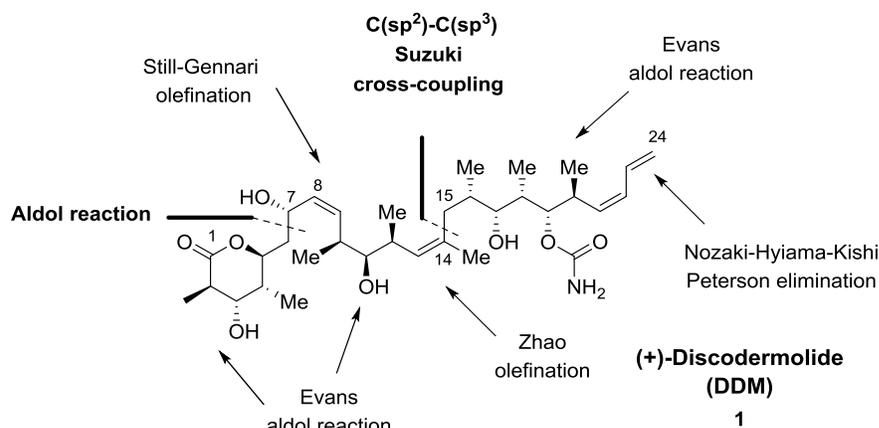


FIGURE 2 (+)-Discodermolide **1**: Novartis synthetic strategy.

However, despite encouraging results, Phase I clinical trials were suspended due to pneumotoxicity at high doses.^[12] It is not yet known whether toxicity arose from DDM itself or from metabolic products.^[7m] Work towards non-toxic and active DDM analogues is, nevertheless, still ongoing.^[10o,13] However, the ability to make a natural product at this level of complexity indicates that the total synthesis of complex, challenging natural product targets can be achieved to deliver sufficient material for clinical studies with the aid of modern synthetic chemistry.

The successful effort to produce DDM was broadened to the production of structurally related analogues.^[10p-s,14] A thorough structure-activity relationship (SAR) has been developed based on these analogues.

2. SYNTHETIC APPROACH AND SYNTHETIC METHODS DEVELOPMENT

In previous total synthesis of other natural compounds, we have been interested in the stereoselective construction of conjugated polyenic systems.^[15] These olefinic sequences can be obtained by palladium-catalyzed cross-coupling reactions from vinyl- or dienyl functionalized

subunits. To realize this disconnection, the selective preparation of vinyl- or dienylmetal species were crucial. In achieving this goal, we have developed efficient hydrometallation reactions, *via* regio- and stereoselective stannylation reactions of substituted alkynes or enynes.^[16] During the stannylation reaction, the tin and copper were delivered on the same face of the triple bond (*cis* addition process) and led to the formation of a trisubstituted *E*-double bond. Therefore, these methodologies of stannylation, or more generally hydrometallation, may not be used for the control of stereochemistry of the di- and trisubstituted *Z*-alkenes or terminal *Z*-diene of DDM. With respect to our synthetic approach of DDM, we have planned to control the *Z*-stereochemistry of double bonds by the use of acyclic or cyclic *Z*-enol ethers representing efficient alternatives to organohalides in cross-coupling reactions. The di- and trisubstituted *Z*-double bonds can be obtained respectively by transition-metal-catalyzed cross-coupling reactions and metallate rearrangements (Figure 3).

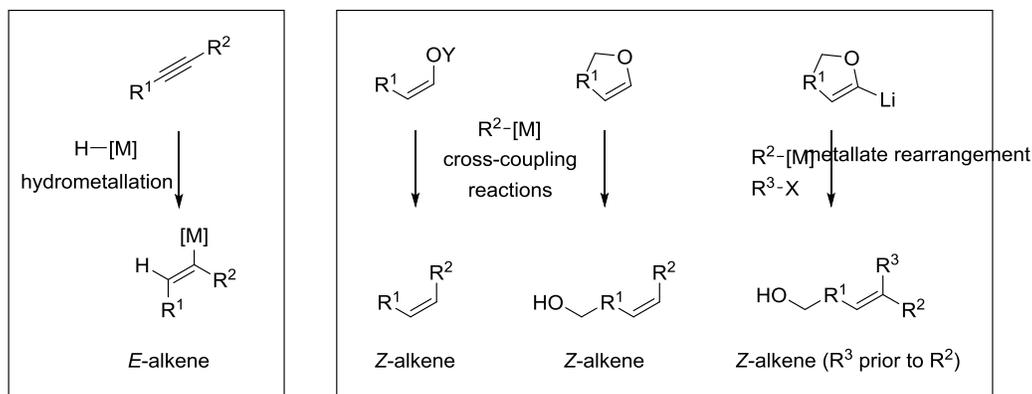


FIGURE 3 Stereoselective preparations of *E*- and *Z*-alkenes.

2.1 Reactivity of an α -Oxygenated Crotyltitanium

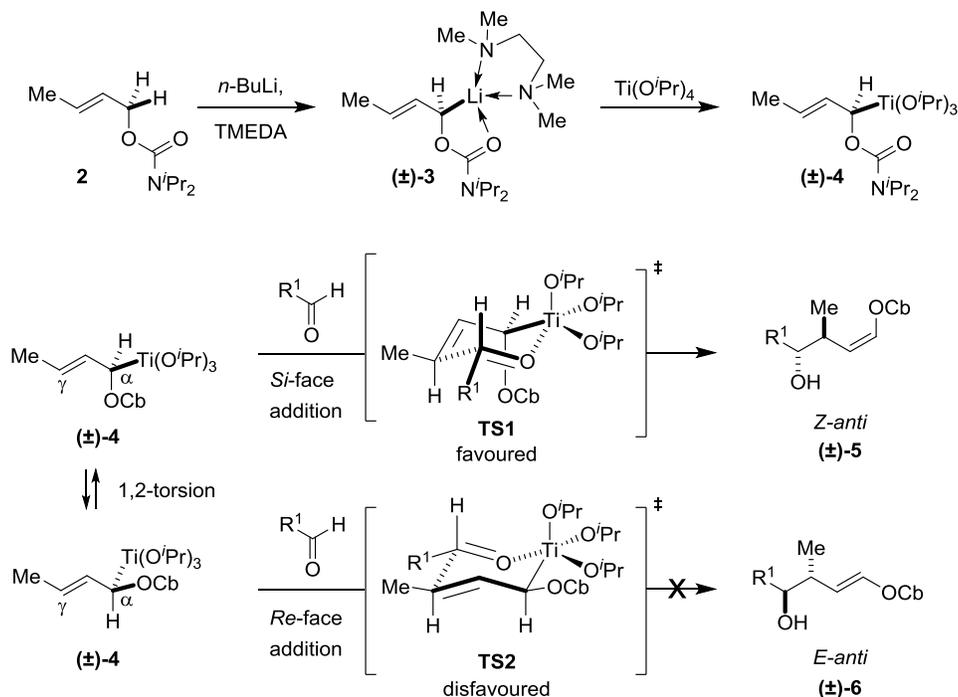
As will be discussed in detail in the retrosynthetic analysis (Section 3.1), our synthetic strategy relied upon the disassembly of DDM into three fragments of similar size and stereochemical complexity. Each of these subunits, or its precursors, possesses a *syn-anti* methyl-hydroxy-

methyl triad linked to a *Z*-double bond. In order to provide an efficient synthetic path, we planned to set up the desired stereotriad and the *Z*-double bond in a single operation by the same reaction for these three fragments. To carry this out, addition reactions of metallated 2-alkenyl *N,N*-dialkylcarbamates to aldehydes were considered. More specifically, α -oxygenated crotyltitanium reagents developed by Dieter Hoppe were selected.^[17] The metallated 2-alkenyl *N,N*-dialkylcarbamates were recognized to be valuable homoenolate equivalents and react with aldehydic compounds, in a stereoselective manner, providing a robust, reproducible, and scalable methodology to prepare the desired stereotriads connected to the *Z*-double bonds.^[18] Moreover, we have worked successfully on this methodology of crotyltitanation of aldehydes during previous synthetic studies on tylosin,^[19] spiramycin,^[20] herbimycin A,^[21] and salinosporamide A.^[22]

As reported previously for different crotylmetallation reactions^[23] the *anti* relationship between the two new formed chiral centers is directly related to the configuration of the double bond, where a *E*-crotylmetal produces the *anti* diastereomer *via* a cyclic six-membered Zimmerman-Traxler-type transition state.^[24] In the case of α -substituted crotylmetal reagent, when the crotylmetal reacts with an electrophile regioselectively to deliver the γ -adduct *via* an allylic S_E2' process ("allyl inversion"), the generated double bond can have an *E* or *Z*-stereochemistry. For α -heterosubstituted crotylmetal compounds, with polar substituents (heteroatoms), the *Z*-isomers are preferred. Whereas the *anti* relationship is easily understood by a chair-type transition state, the strong preference for the *Z*-isomer is more subtle.^[25] The α -oxygenated crotyltitanium (\pm)-**4** is generated in situ from 2-butenyl-*N,N*-diisopropylcarbamate **2** by treatment with *n*-BuLi and TMEDA (Scheme 1). This *N,N*-dialkylcarbamate group (OCb) facilitates the deprotonation as it stabilizes the η^1 -crotyllithium intermediate (\pm)-**3**. The desired

titanium reagent(\pm)-**4** is obtained by transmetallation of (\pm)-**3** with titanium isopropoxide. If we consider the chair-type transition state where the substituent of aldehyde occupies a pseudoequatorial position, there are two possibilities for facial diastereoselectivity (*Si* or *Re* facial attack on the aldehyde moiety) in both **TS1** and **TS2**, respectively. The only difference between these two transition states is the position of the carbamoyl moiety: in **TS1** the *N,N*-diisopropylcarbamoyl group adopt a pseudoaxial position whereas in **TS2** this same group adopts a pseudoequatorial position. In the case of an α -oxygenated crotyltitanium bearing a carbamate moiety, only the *anti* compound (\pm)-**5** with a *Z-O*-enecarbamate group is obtained, from the transition state **TS1** in which carbamoyl moiety is in a pseudoaxial position. This preference with respect to *E-anti*-(\pm)-**6** can be explained by the sum of several factors.^[25] First, for steric reasons, the sterically demanding *N,N*-diisopropylcarbamate substituent prefers adopt the more favorable pseudoaxial position. In this case, the destabilizing *gauche* interactions, between the *N,N*-diisopropylcarbamate group (OCb) and the isopropoxide ligands of titanium are minimized. A second component can be rationalized by polar effects. When the OCb group adopts a pseudoaxial position, the vectorial sum of dipole moments is minimized and also **TS1** takes advantage of stabilization by anomeric effect. Finally, considering stereoelectronic effects, a polar substituent OCb in the α -heterosubstituted crotylmetal possesses a low lying C-O σ^* orbital. In this case, the electron density of the π orbital of C=C double bond of crotylmetal can be transferred into C-O σ^* orbital, thus reducing its reactivity. This electron density transfer is possible for **TS2**, in which the π orbital of C=C and C-O σ^* orbital are parallels and allow this overlap. In contrast, for **TS1** where π orbital of C=C and C-O σ^* orbital are orthogonal, this overlap is prohibited, precluding any delocalization. Therefore, this *N,N*-diisopropylcarbamate

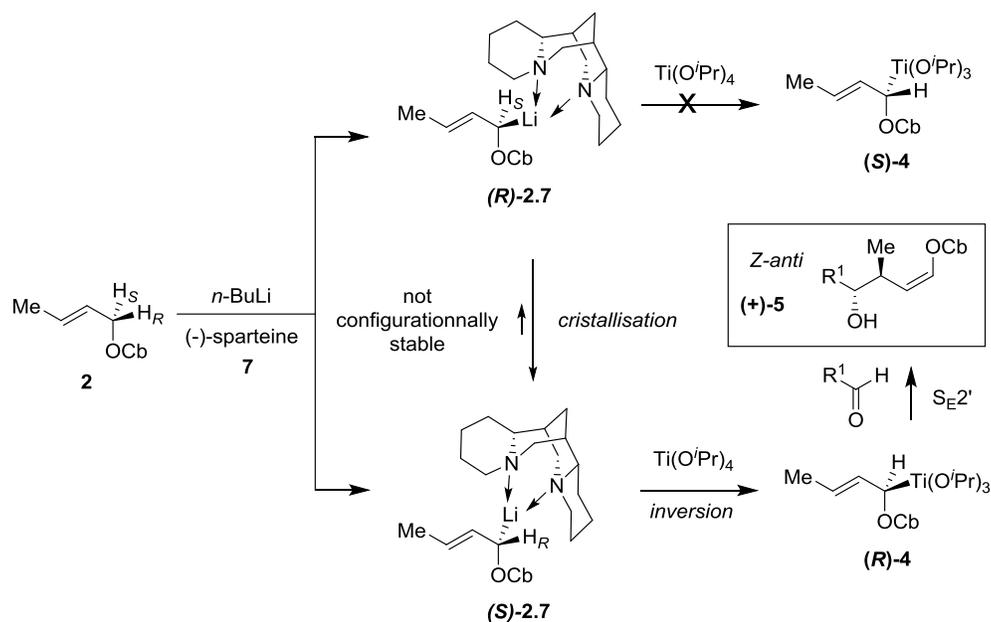
function effectively ensures the diastereoselectivity of addition of α -oxygenated crotyltitanium (\pm)-**4** to an aldehyde to produce the desired *Z-anti* compound (\pm)-**5**.



SCHEME 1 Diastereoselectivity for addition of an α -oxygenated crotyltitanium to aldehydes.

As we have seen above, the α -oxygenated crotyltitanium reacts with an aldehyde in a stereoselective manner. If chiral non-racemic crotyltitanium **4** is employed in reactions with aldehydes, the enantioenriched *Z-anti* **5** can be obtained, depending on optical purity of crotyltitanium **4**. With the use of (-)-sparteine **7**, a chiral diamine belonging to the family of lupine alkaloids, the two (-)-sparteine-lithium complexes (**R**)-**2.7** and (**S**)-**2.7** are formed (Scheme 2). At this stage, an equilibrium between these two species is driven to one side by preferential crystallization of the (-)-sparteine-lithium complex (**S**)-**2.7**. Since these two lithio species are not configurationally stable, this crystallization resulted in the specific formation of (**S**)-**2.7** via a *dynamic-thermodynamic resolution* (DTR), also called *second-order asymmetric induction*.^[26] Transmetalation of the solid (**S**)-**2.7** with titanium isopropoxide, proceeds with

complete inversion of configuration and leads to a selective formation of a configurationally stable α -oxygenated crotyltitanium (**R**)-**4**.^[27] This enantioenriched crotyltitanium reacts with achiral aldehydes to give the *Z-anti* homoallylic alcohol (+)-**5** in an enantioselective manner.



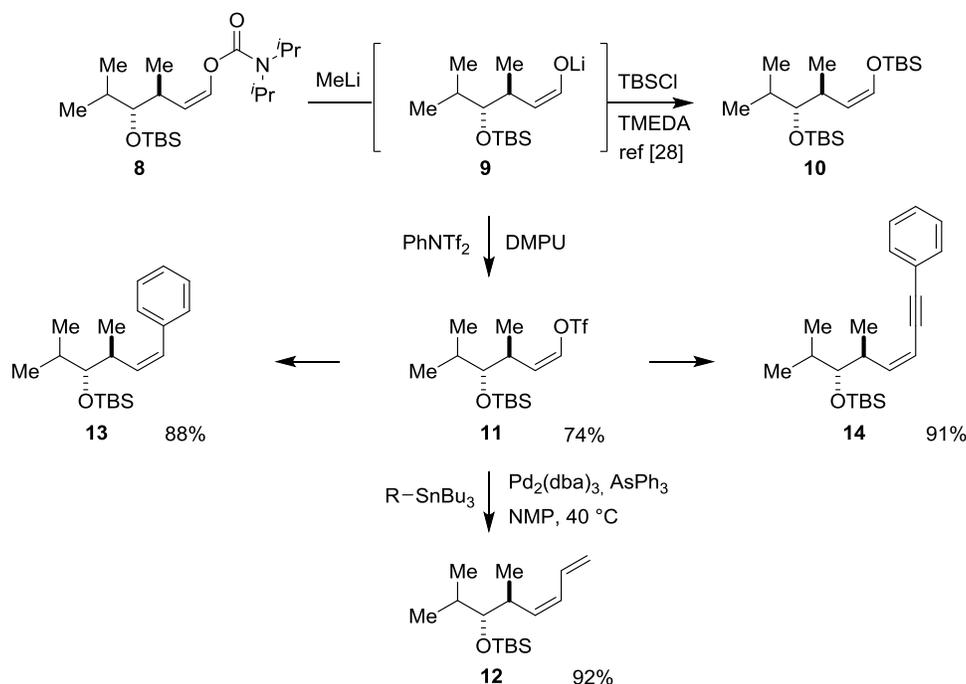
SCHEME 2 Enantioselective preparation of α -oxygenated crotyltitaniums.

2.2 Reactivity of a *Z-O*-Enecarbamate Group

As part of this project directed toward total synthesis of DDM and analogues, we wanted to take advantage of the *Z*-double bond of compound **5** to realize homologation reactions and provide access directly to the desired building blocks.

At first, we considered the transformation of the carbamate moiety into more reactive functions. It was shown that *Z-O*-enecarbamate can be transformed into *Z*-silyl enol ether **10** by treatment of **8** with methyllithium and quenching of this intermediate lithium enolate **9** by electrophilic silicon reagents.^[28] Assuming this lithium enolate intermediate **9** would be able to react with other electrophile reagents, the preparation of more reactive functions including *Z*-

vinyl phosphate and *Z*-vinyl triflate was considered. The remaining and important question was whether the *Z*-stereochemistry of this double bond would be preserved.

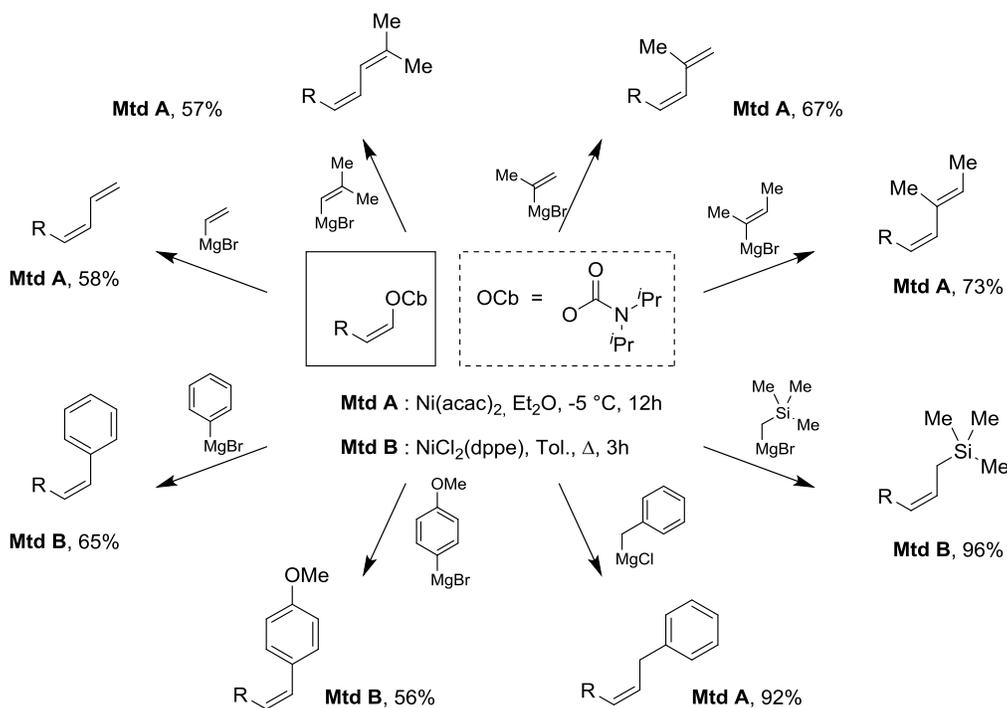


SCHEME 3 *Z*-*O*-Enecarbamate group as an efficient precursor of *Z*-vinyl triflate and its further palladium-catalyzed cross-coupling reactions.

When the lithium enolate intermediate **9** was trapped by addition of a solution of *N*-phenyltriflimide in HMPA or DMPU, the reaction smoothly delivered the *Z*-vinyl triflate **11** in 74% yield (Scheme 3).^[29] With the pure *Z*-vinyl triflate in hand, we turned our attention to its palladium-catalyzed cross-coupling with tin species. Under optimized conditions, Pd₂(dba)₃ and triphenylarsine in NMP at 40 °C, the cross-coupled products were obtained in good yields with retention of the *Z*-stereochemistry of the starting *Z*-vinyl triflate. These optimized conditions applied to tributyl(vinyl)stannane and the *Z*-vinyl triflate from **11** delivered the *Z*-diene compound **12**, corresponding to substitution pattern of DDM C21-C24 terminal diene. Reaction with tributyl(phenyl)stannane and tributyl(phenylethynyl)stannane, respectively, led to the

corresponding *Z*-coupled products **13** and **14** in good yields. This conclusively demonstrated that a *Z*-*O*-enecarbamate group could be transformed in one step to the desired *Z*-vinyl triflate, which underwent palladium-catalyzed cross-coupling reactions with tin derivatives, without loss of the *Z*-geometry of the double bond.

In a second part of this study, we also thought of the carbamate moiety as a leaving group *via* a metal insertion into the C-O bond of the carbamate moiety, based on one-step transformations of enol ethers into olefins mediated by low-valent nickel species developed by Wenkert.^[30] These reactions were described with alkyl^[31] and alkynyl^[32] Grignard reagents, but there were no examples with sp^2 -hybridized carbon nucleophiles. After optimization, it was established that vinylic Grignard reagents can be used with success under nickel(II) acetylacetonate catalysis in diethyl ether at low temperature (Method A) whereas aryllic Grignard reagents react with *Z*-*O*-enecarbamate group using a $NiCl_2(dppp)$ catalyst at higher temperature (Method B) (Scheme 4).^[33]



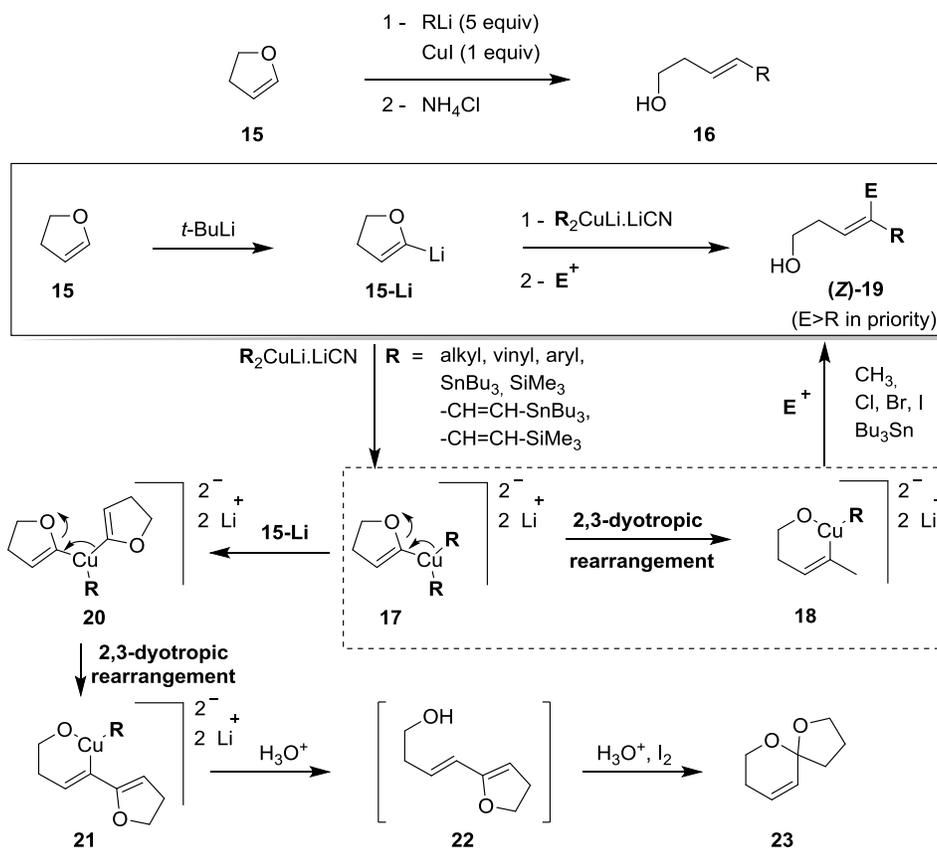
SCHEME 4 Preparation of *Z*-alkenyl derivatives from *Z*-vinyl (*N,N*-diisopropyl)carbamate via Ni-catalyzed cross-coupling reactions.

These methodological studies served to demonstrate that reactions of an α -oxygenated crotyltitanium reagent and aldehyde lead to *anti*-homoallylic alcohol with a *Z*-*O*-enecarbamate group in a one-step sequence. We can take advantage of this functionality to give access either to the natural product or to synthetic analogues.

2.3 1,2-Dyotropic Rearrangement of Dihydrofuran

The stereoselective construction of the trisubstituted *Z*-double bond at the C13-C14 position has proven to be one of the most synthetically challenging tasks for the synthesis of DDM. For the stereocontrolled formation of this functionalized trisubstituted *Z*-double bond, we focused on a dyotropic rearrangement of 5-lithio-2,3-dihydrofuran species with organocopper reagents. In 1982, Fujizawa reported the regio- and stereospecific reaction of organocuprates, prepared from an excess of alkyllithium and copper iodide, with 2,3-dihydrofuran **15**, leading to pure *E*-alken-1-ols **16**.^[34] A few years later, Kociński described a more convenient procedure and has extended this methodology for the stereocontrolled preparation of trisubstituted alkenes. Reaction with “higher order” cyano Gilman cuprate reagents ($R_2CuLi\cdot LiCN$) and 5-lithio-2,3-dihydrofuran **15Li**, prepared by metalation of 2,3-dihydrofuran **15** with *tert*-butyllithium, and quenching (trap) by a suitable electrophile afforded a pure (*Z*)-**19** compound type (assuming $E > R$ in priority) The reaction between **15Li** and the “higher order” cuprate $R_2CuLi\cdot LiCN$ provides an α -alkoxyalkenylcuprate **17** that undergoes a 1,2-dyotropic rearrangement^[35] in which the alkoxy part serve as the nucleofuge. After rearrangement, the new vinyl copper species **18** is sufficiently nucleophilic to react with suitable electrophilic reagents. This methodology, allowing the stereoselective formation of compounds like **19**, displays remarkably

broad scope since not only alkyl-, vinyl-, and arylorganocuprates can be used, but also functionalized groups as SnBu_3 or SiMe_3 (and also their vinylogous counterparts) (Scheme 5).



SCHEME 5 Stereoselective synthesis of functionalized trisubstituted Z-double bond.

This metallate rearrangement is very attractive from the synthetic point of view, because it can be applied for the introduction of a methyl substituent for the synthesis of the natural product, as well as for the introduction of different substituents to give access to analogues. Moreover we have previously worked with this powerful tool during synthetic studies on rosaramycin,^[36] and tylosin^[37] and in preparing 1,1-dimetalated-1-alkenes^[38] and homo- or hetero-1,1-dihalo-1-alkenes.^[39]

With respect to our disconnection of DDM and for the synthesis of the functionalized trisubstituted Z-double bond, we studied this metallate rearrangement with a “higher order”

dimethylcuprate in order to introduce the desired methyl group for the natural product. Under standard conditions for this dyotropic process (3 hours at room temperature), commercial 2,3-dihydrofuran (DHF) **15** afforded the corresponding ring-opened product (**Z**)-**16** in a modest 61% yield (Table 1, entry 1). The same reaction, performed on methyl-substituted DHF **24**, (methyl in C12 position, DDM numbering), led to the expected trisubstituted *Z*-double bond, compound (**Z**)-**25**, in a disappointing 27% yield (Table 1, entry 2). Utilization of magnesio-cuprates, prepared from MeMgBr and CuBr·Me₂S gave also poor results.^[40]

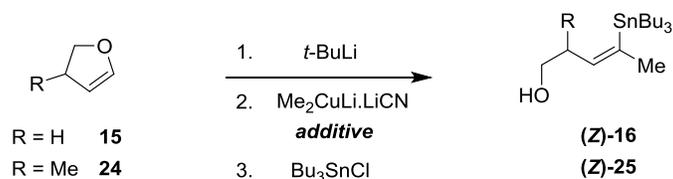
A similar loss of reactivity for the methyl transfer was observed by Kocięński on the homologous 6-lithio-3,4-dihydro-2H-pyran.^[41] This low migratory aptitude of a methyl group for this dyotropic rearrangement can be compared to the decrease in reactivity for the 1,4-addition of methyl group *versus* more longer alkyl group^[42] due to the difficulties in stabilizing organometallic methyl species with small degrees of aggregation.^[43] In the case of a group with low migratory aptitude, the α -alkoxyalkenylcuprate intermediate **17** can evolve to form **20** by ligand exchange with another **15**·Li. This new intermediate **20** can lead to the self-coupling compound **21**, which after aqueous work-up affords to the spiroacetal **23**.^[44]

To further improve the effectiveness of the methyl transfer by this methodology, we decided to investigate the influence of different reaction parameters. The reaction was run in pure THF (in THF, the main species of Me₂CuLi·LiCN is a monomeric solvent-separated ion pair) or diethyl ether (whereas in Et₂O the main species of Me₂CuLi·LiCN is a contact ion pair) but no improvement was noted (Table 1, entries 3-4).^[45]

In order to activate the C-O bond of the dihydrofuran ring, we performed the reaction in the presence of a Lewis acid, without any improvement (Table 1, entries 5-6). Due to the oligomeric structures of organolithium and organocuprate species, we also added some dipolar

aprotic solvents like DMF, DMPU and HMPA, but in these cases we obtained lower yields of compound (**Z**)-**25** (Table 1, entries 7-9). Utilization of nitrogen Lewis bases, like pyridine or TMEDA, did not make significant improvement (Table 1, entries 10-11). Gratifyingly, the use of sulfur additives like dimethyl sulfide (DMS)^[46] resulted in much better yields (Table 1, entries 12-14), due to the stabilizing effect of DMS on the organocopper reagent.^[47]

TABLE 1 Optimization of Dyotropic Rearrangement on Dihydrofurans for Methyl Transfer



Entry	Starting material	Additive	Conditions	Yield of (Z)- 16 or (Z)- 25 (%)
1	15	none ^a	rt, 3 h	61
2	24	none ^a	rt, 3 h	27
3	15	none, solvent pure THF	rt, 3 h	18
4	15	none, solvent pure Et ₂ O	rt, 3 h	47
5	15	BF ₃ ·OEt ₂ (2.5 equiv) ^a	rt, 3 h	13
6	15	TMSCl (4 equiv) ^a	rt, 3 h	46
7	15	DMF (5 equiv) ^a	rt, 3 h	0
8	15	DMPU (5 equiv) ^a	rt, 3 h	0
9	15	HMPA (5 equiv) ^a	rt, 3 h	29
10	15	Pyridine (10 equiv) ^a	rt, 3 h	16
11	15	TMEDA (10 equiv) ^a	rt, 3 h	45
12	15	Thiophene (20 equiv) ^b	rt, 12 h	55
13	15	Tetrahydrothiophene (20 equiv) ^b	rt, 12 h	67
14	15	DMS (20 equiv) ^b	rt, 12 h	76
15	24	DMS (20 equiv) ^b	rt, 12 h	68

^aEt₂O/THF 2:1.

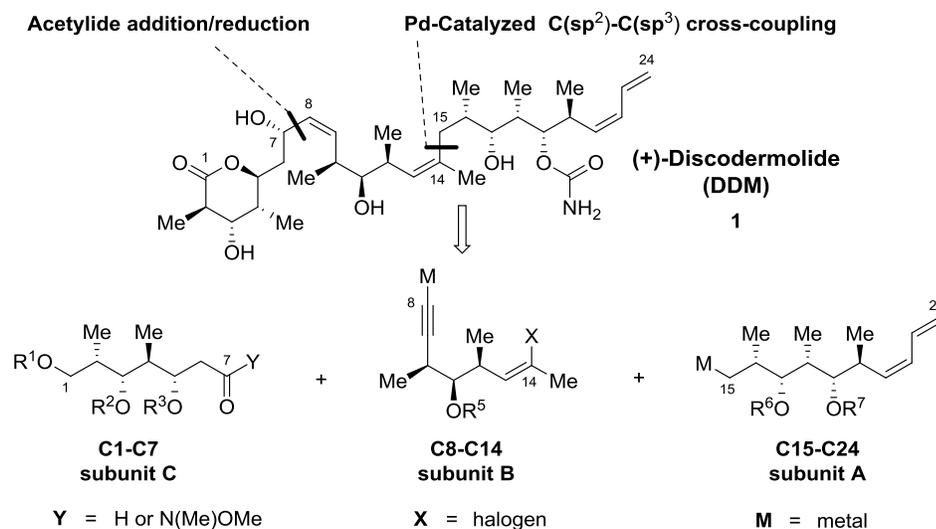
^bEt₂O/Sulfide 4:1.

Application of these optimized conditions to DHF **24** led to the desired compound (**Z**)-**25** in a satisfactory 68% yield (Table 1, entry 15).

3. TOTAL SYNTHESIS OF (+)-DISCODERMOLIDE (DDM)

3.1 Strategic Considerations

With the goal of devising a convergent approach toward DDM (**1**), two key disconnection points at C7-C8 and C14-C15 were identified, the two internal *Z*-alkenes C8-C9 and C13-C14 being pivotal in the choice of the strategy. Formation of the C7-C8 bond was envisaged through an acetylide addition/reduction sequence, whereas formation of the C14-C15 linkage would be accomplished by a Pd-catalyzed C(sp²)-C(sp³) cross-coupling reaction. Therefore, the synthesis of DDM was planned from three key subunits of similar size and stereochemical complexity (**A** C15-C24, **B** C8-C14, **C** C1-C7) (Scheme 6).

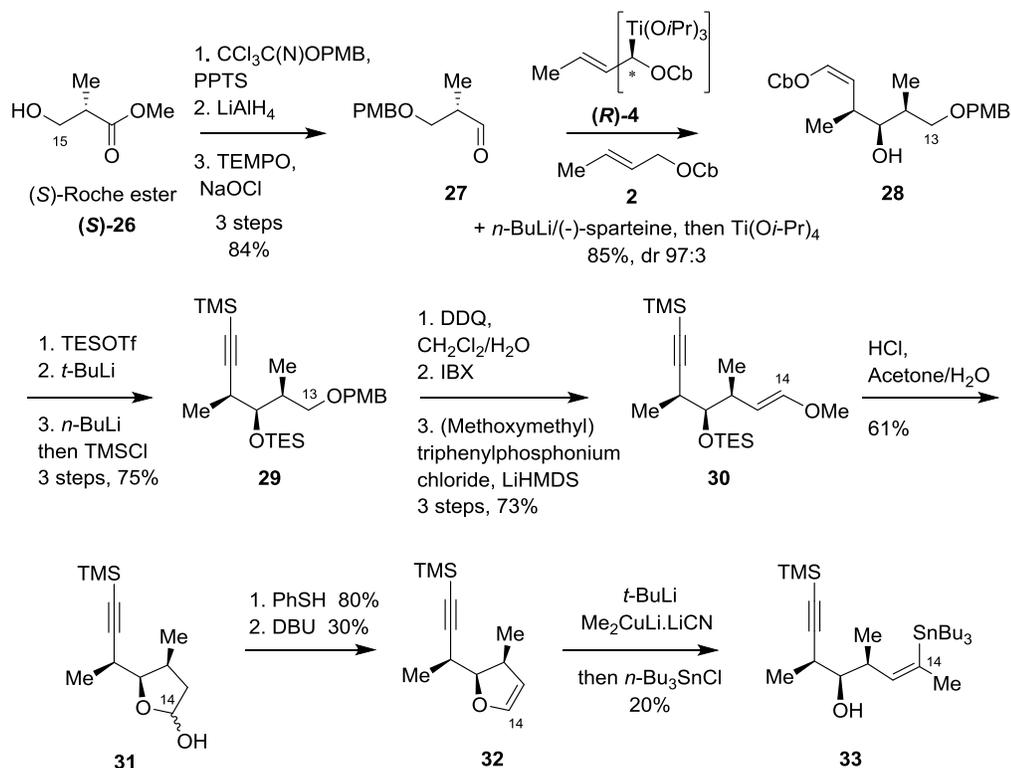


SCHEME 6 Retrosynthetic analysis of discodermolide (DDM).

3.2 Preparation of C8-C14 Subunit B

Synthesis of the central C8-C14 fragment **B**, including the C10-C12 *anti-syn* stereotriad, the C13-C14 trisubstituted *Z*-double bond, and a terminal alkyne group, was a real challenge. The strategy involved two main stages, a crotyltitanation reaction for the installation of the stereotriad and a dyotropic rearrangement in order to build the *Z*-double bond. Two alternative routes were examined, differing in the ordering of the two key steps.

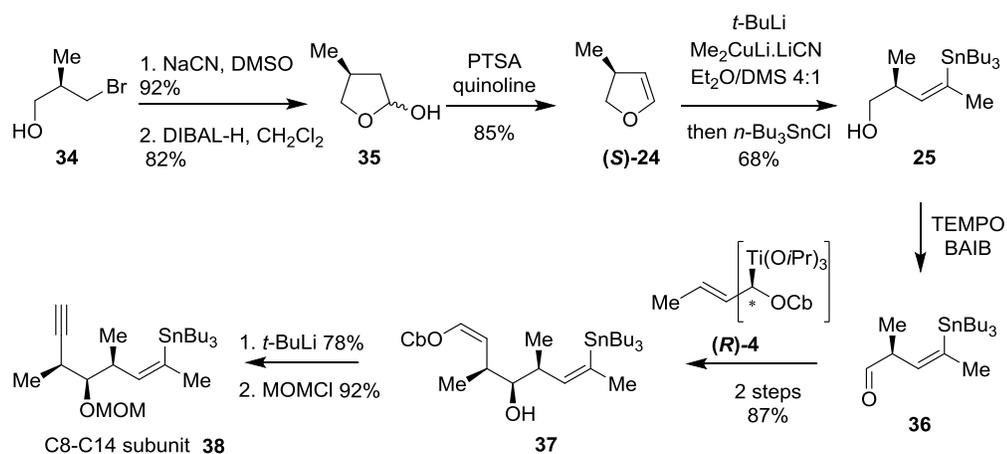
The first route started with the crotyltitanation of aldehyde **27**, readily available from (*S*)-(+)-Roche ester **26**,^[48] with enantioenriched reagent (*R*)-**4**, to afford the required homoallylic alcohol **28** in good yield and excellent diastereomeric ratio (dr 97:3).^[17] After conversion of the *O*-enecarbamate **28** into alkyne **29** by *t*-BuLi treatment (Fritsch-Buttenberg-Wiechell rearrangement)^[49] followed by homologation into enol ether **30** and aqueous acidic hydrolysis, lactol **31** was obtained in 33% overall yield over seven steps (Scheme 7). The installation of the C13-C14 trisubstituted functionalized *Z*-double bond *via* a dyotropic rearrangement was then undertaken.^[34,36-39,41,50] However, the transformation of lactol **31** or derivatives into the dihydrofuran (DHF) **32** turned out to be more difficult than expected. After considerable optimization, it was found that the most effective method relied on pyrolysis of corresponding phenyl sulfide to deliver DHF **32** in only 24% yield.^[51] This procedure did not allow for sufficient quantities for the synthesis. Furthermore, subsequent dyotropic rearrangement (1,2-cuprate transfer from “higher order” dimethylcuprate followed by tin chloride trapping) led to the required C8-C14 segment **33**, but in a low 20% yield. This result was another matter of concern for this 14 step synthesis of the C8-C14 fragment.



SCHEME 7 First generation route to C8-C14 fragment.

Due to the difficulties encountered, an alternative tactic was devised wherein the order of the crotyltitanation-dyotropic rearrangement sequence was inverted. The earlier formation of the DHF ring and installation of the C13-C14 double bond would allow for an optimization of these two steps on a multigram scale. However, we were uncertain about the stability of the C13-C14 double bond bearing a metal or halide function in a very early stage of synthesis. Metal/halogen exchange or vinyl iodide hydrogenolysis could occur during subsequent $t\text{-BuLi}$ α -elimination or Lindlar reduction step,^[10],52] and therefore we chose to introduce a vinyl tin function as precursor of the vinyl halide core at the C14 position. After some experimentation, preparation of enantiopure DHF (**S**)-**24** was achieved through a straightforward dehydration of lactol **35** (readily prepared from commercially available optically pure (*R*)-(-)-3-bromo-2-methyl-1-propanol **34**) with PTSA in quinoline in 85% yield (Scheme 8).^[53] DHF (**S**)-**24** was then

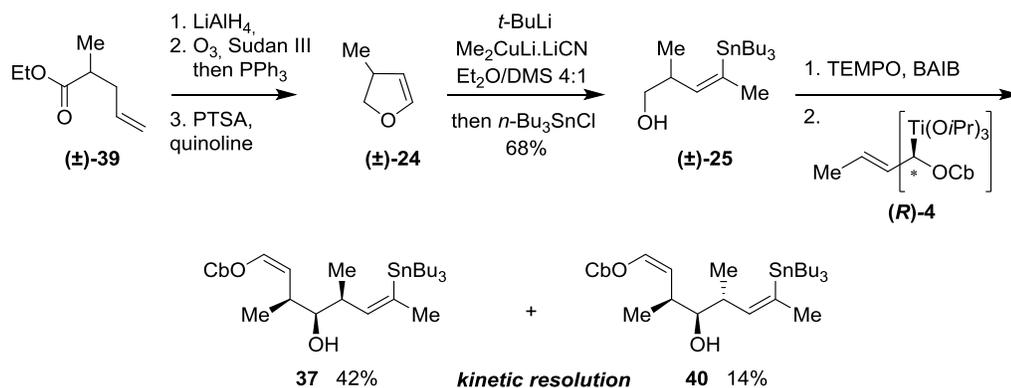
subjected to the metallate rearrangement. The optimized conditions (see Section 2.3) allowed for the formation of the expected *Z*-vinyl stannane **25** in a satisfactory 68% yield. Significant problems were encountered during oxidation of alcohol **25** into aldehyde **36**. Extensive screening was performed. Finally, we were pleased to find that the use of 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) and [bis(acetoxy)iodo]benzene (BAIB) as the co-oxidant led to a major improvement.^[54] Subsequent crotyltitanation reaction of this very unstable aldehyde with (*R*)-**4**, delivered homoallylic alcohol **37** as a single diastereomer in 87% yield. As a final point, a Fritsch-Buttenberg-Wiechell α -elimination reaction (*t*-BuLi treatment) and protection as methoxymethyl ether provided alkyne **38**. The order of these two steps was crucial to avoid β -elimination on *t*-BuLi treatment. Finally, it was very satisfying to find that the *Z*-vinyl stannane function was sufficiently stable during C8-C14 subunit elaboration. Thus, central C8-C14 fragment **38**, armed for further functionalization at both termini, was obtained in eight steps in 26.3% yield from enantiopure bromopropanol **34**.



SCHEME 8 Second generation route to C8-C14 fragment from enantiopure DHF (*S*)-**24**.

Interestingly, an approach involving racemic DHF (\pm)-**24** was also examined. Preparation of this racemic DHF was smoothly achieved from commercially available

pentenoate (\pm)-**39** (Scheme 9). Then, a three step-sequence involving formation of the 1,2-cuprate transfer product (\pm)-**25** followed by oxidation and crotyltitanation, delivered the required Felkin-Anh homoallylic alcohol **37** in 42% yield along with the corresponding minor C12-epimer **40** in 14% yield. Subsequently, from pentenoate (\pm)-**39**, C8-C14 fragment **38** was obtained in eight steps in 13.9% yield (through a kinetic resolution step). However, taking into account the low cost of the starting material (\pm)-**39** and the convenient separation of the C12-epimeric compounds **37** and **40**, we preferred using the racemic DHF (\pm)-**24** to produce C8-C14 subunit **38** on a multigram scale.

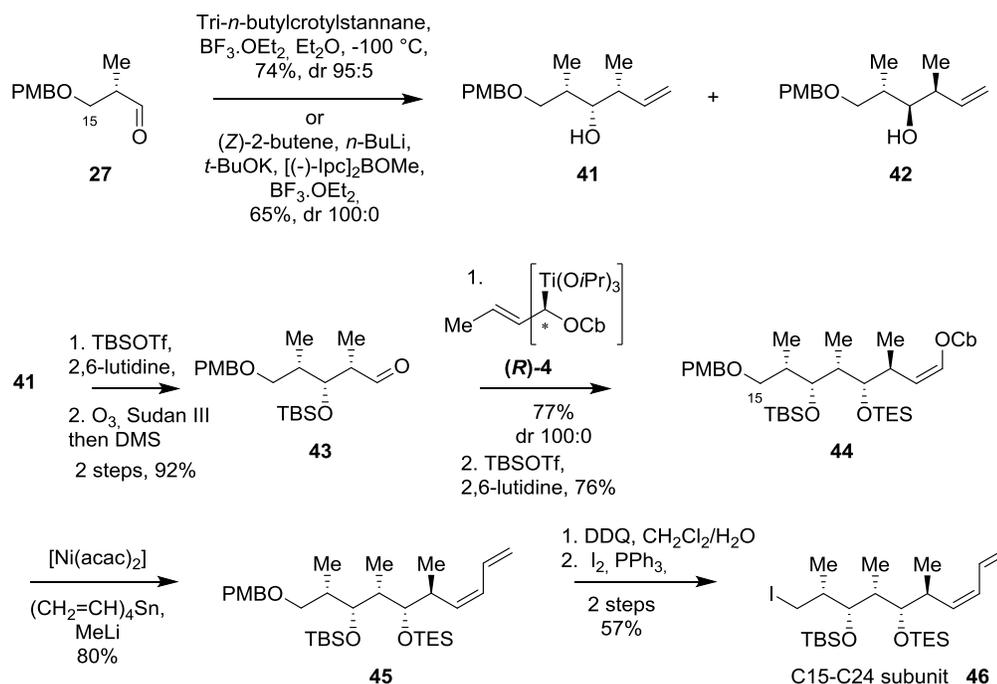


SCHEME 9 Multigram scale second generation route to C8-C14 fragment from racemic DHF (\pm)-**24**.

3.3 Preparation of C15-C24 Subunit A

The C15-C24 subunit A comprises five contiguous stereocenters and a terminal Z-diene. Its synthesis started with the preparation of the C16-C18 *syn-syn* stereotriad, planned by means of a substrate-based crotylation reaction under Keck's conditions.^[55] After optimization, the addition of achiral tri-*n*-butylcrotylstannane to chiral aldehyde **27** led to a 95:5 mixture of diastereomers **41** and **42** (Scheme 10). However, large scale production of **41** was impeded by difficulties associated with diastereomer separation. This difficulty was readily overcome using the chiral

crotylborane procedure developed by Brown.^[56] The desired homoallylic alcohol **41** was cleanly formed in a stereospecific manner from the *Z*-crotyldiisopinocampheylborane reagent derived from (-)-Ipc₂B(OMe). For the construction of the second C18-C20 *syn-anti* stereotriad, we selected a crotyltitanation reaction of aldehyde **43** with (*R*)-**4**. Classical conditions delivered the desired isomer **44** in 77% yield with total stereocontrol, after protection of the secondary alcohol by a TES group.



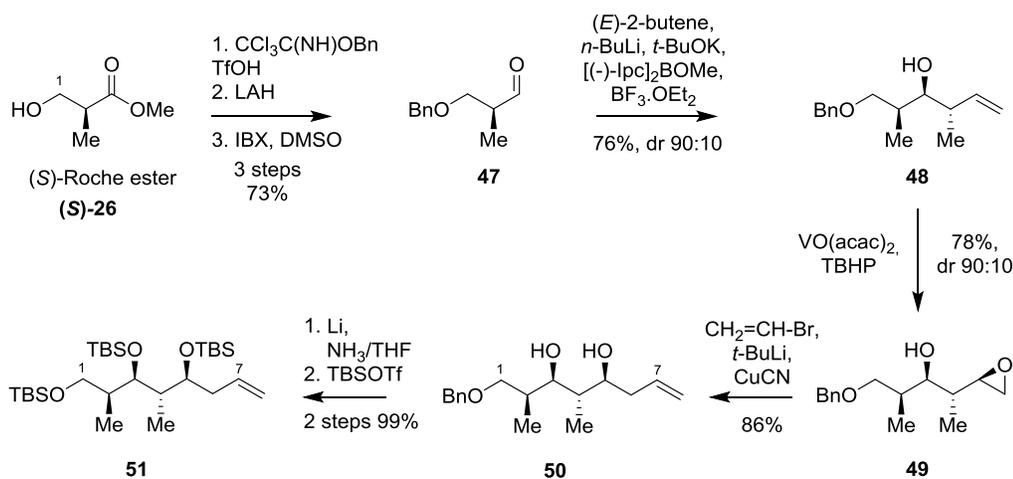
SCHEME 10 Preparation of C15-C24 subunit **46**.

Application of this crotyltitanation reaction was essential in the preparation of the required terminal *Z*-diene. As previously described by our group, the direct vinylation of a *Z*-*O*-enecarbamate moiety was performed in the presence of Ni(acac)₂ with commercially available or laboratory-prepared vinylmagnesium bromide.^[33] To our dismay, from carbamate **44** this reaction gave highly variable but mostly disappointingly low yields. Substantial optimization studies demonstrated that the reaction with vinylolithium species (without magnesium salts),

produced from tetravinyltin and MeLi,^[57] led to the selective formation of the cross-coupled product **45** in a reproducible 80% yield and allowed scaling up the reaction to 2.5 grams. Thus, the C15-C24 subunit **46** was obtained in 13.7% overall yield for 11 steps.

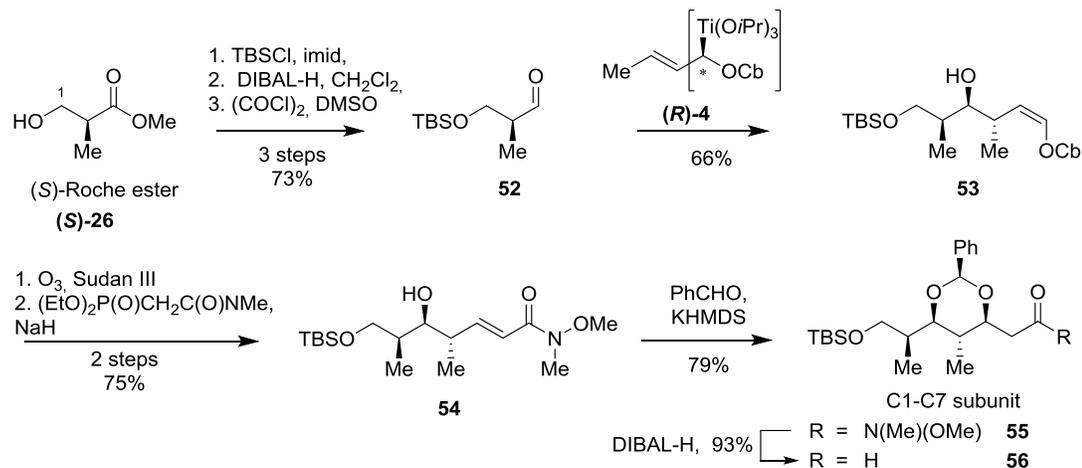
3.4 Preparation of C1-C7 Subunit C

The third building block C1-C7 subunit C incorporates four stereocenters. Our first approach started with standard Brown crotylation of aldehyde **47** (derived from (*S*)-Roche ester (**S**)-**26**), to afford the desired *syn-anti* homoallylic alcohol **48** in 76% yield (Scheme 11). We envisaged a substrate-controlled epoxidation/oxirane regioselective ring-opening sequence for the installation of the missing C5 chiral center. The epoxidation of homoallylic alcohol **48** turned out to be more difficult than expected. Recourse to VO(acac)₂/TBHP^[58] led to oxirane **49** in 78% yield and a 90:10 dr. However, upon attempted optimization and scale-up, this reaction was not reproducible. Finally, the C1-C7 subunit **51** was obtained after regioselective ring-opening by the divinyl cuprate (CH₂=CH)₂CuLi•LiCN^[59] (formation of **50**) and deprotection/protection sequence.



SCHEME 11 Preparation of C1-C7 subunit **51**.

An alternative route allowed the generation of the C5 chiral center by hetero-Michael addition on α,β -unsaturated Weinreb amide **54**, which in turn could be derived from aldehyde **52** through crotyltitanation and homologation (Scheme 12). Thus, crotyltitanation reaction of aldehyde **52** with (*R*)-**4** cleanly led to the *syn-anti* homoallylic alcohol **53**. α,β -Unsaturated Weinreb amide **54** was obtained through a classical two-step sequence involving a Horner-Wadsworth-Emmons olefination. Then, reaction of **54** with benzaldehyde mediated by KHMDS afforded benzylidene **55** in 79% yield with an excellent diastereoselectivity (dr > 95:5).^[60] After reduction to aldehyde **56**, the last C1-C7 subunit was obtained in 32.7% overall yield for 8 steps.

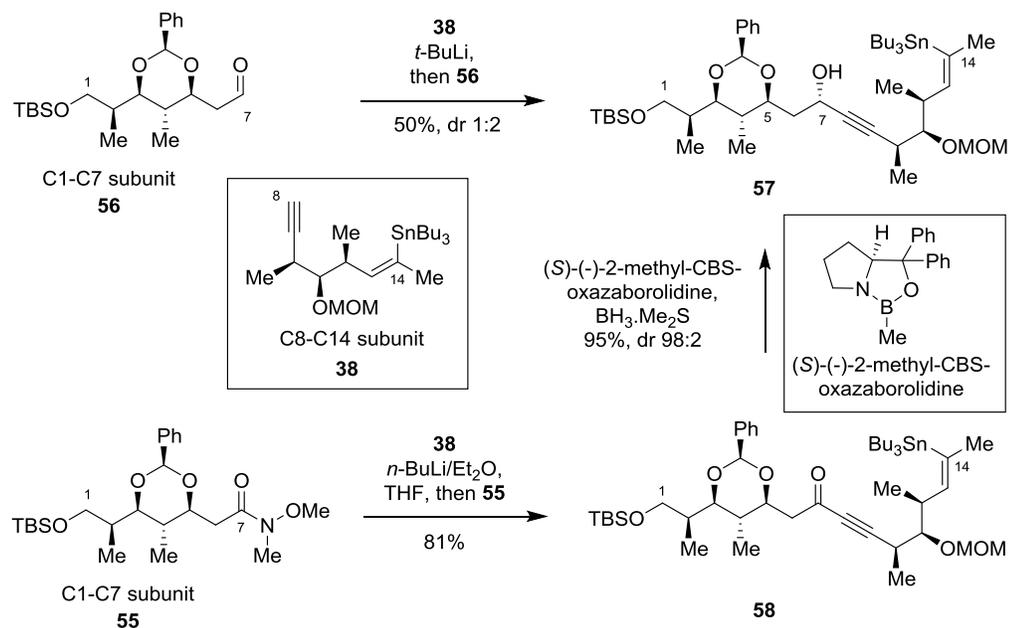


SCHEME 12 Preparation of C1-C7 subunits **55** and **56**.

3.5 Completion of Total Synthesis of DDM

With the required fragments finally in hand, our focus turned toward their assembly. The first coupling reaction involved an addition of the C8-C14 acetylenic compound **38** to C1-C7 aldehyde **56** (Scheme 13). The lithiated acetylide of **38** was chemoselectively produced by action of *t*-BuLi at low temperature; however, to our surprise and dismay,^[61] its reaction with aldehyde **56** afforded the required 5,7-*anti* alcohol **57** as the minor C-7 diastereomer (dr 1:2). A more appropriate solution was found with the addition of acetylenic derivative **38** on Weinreb

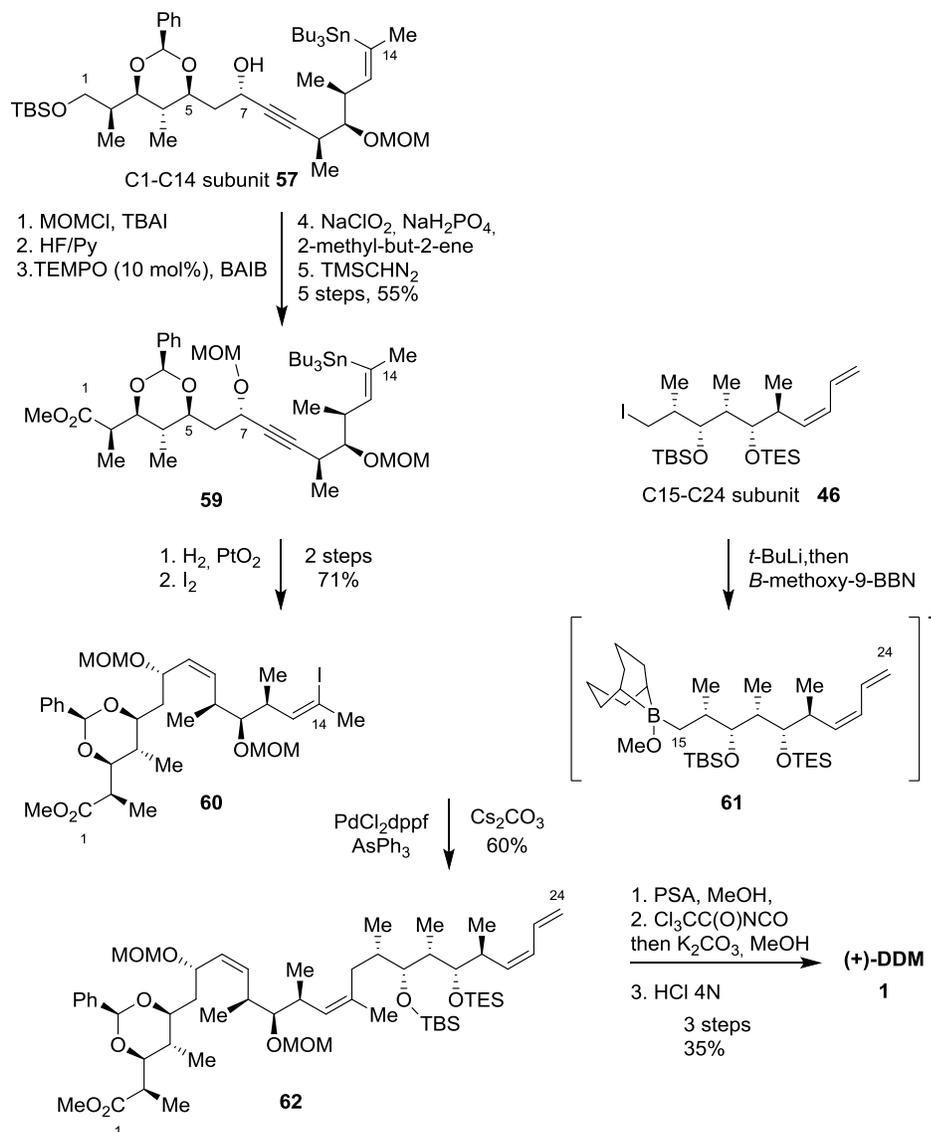
amide **55** followed by stereoselective reduction of ynone **58** (Scheme 13). After careful optimization, it was found that this addition reaction proceeded best using a solution of *n*-BuLi generated by treatment of butyl bromide by lithium metal in Et₂O,^[62] to lead to the desired ynone **58** in a reliable 81% yield. Subsequent reduction of **58** with the (*S*)-CBS reagent^[63] provided alcohol **57** in high yield (95%) and diastereoselectivity (dr > 98:2).



SCHEME 13 Addition of the C8-C14 fragment **38** to C1-C7 subunit **55** or **56**.

Anticipating a *B*-alkyl Suzuki-Miyaura cross-coupling reaction^[64] between the C1-C14 and C15-C24 subunits, alcohol **57** was smoothly converted to vinyl iodide **60** in seven steps, including a PtO₂ reduction of the crowded triple bond of intermediate **59**, without overreduction. The coupling of the vinyl iodide **60** and C15-C24 subunit was performed by using trialkyl boronate species **61**, prepared from alkyl iodide **46**, under [Pd(dppf)Cl₂] and AsPh₃ conditions^[65] to afford the discodermolide backbone **62** in 60% yield (Scheme 14). Finally, after carbamate formation^[66] and total deprotection, discodermolide **1** was obtained in 70% yield. The

spectroscopic and analytical data of the synthetic samples of as well as their *in vitro* cytotoxicity levels were in full accord with those of the natural product reported in the literature.



SCHEME 14 *B*-Alkyl Suzuki-Miyaura cross-coupling reaction between the C1-C14 and C15-C24 subunits **60** and **61**.

The investigation outlined above resulted in a total synthesis of the anticancer marine metabolite discodermolide **1** in 1.6% overall yield for 21 linear steps.^{[67],[10n]}

4. CONCEPTION, SYNTHESIS AND BIOLOGICAL EVALUATION OF DDM-ANALOGUES

4.1 Conformation of DDM and Conception of Analogues

Reported solid-state, solution and protein-bound DDM conformations have revealed the unusual result that a common hairpin conformational motif exists in all three microenvironments (Figure 4).^[71,9c,14q,68] No other flexible microtubule binding agents exhibit such constancy of conformation. The lactone ring and the diene side chain moieties were found to display more flexibility compared to the rest of the molecule.

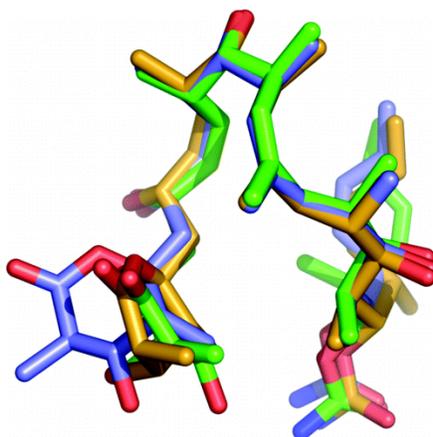


FIGURE 4 Overlap of DDM tubulin-bound (golden), X-ray (green) and NAMFIS-10 (blue) conformations.^[68c]

The stability of this strongly preferred form with respect to the central sector of the molecule is due to steric factors (i. e. $A^{1,3}$, $A^{1,2}$ strain^[69] and *syn*-pentane interactions^[70]) 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 5).^[68a]

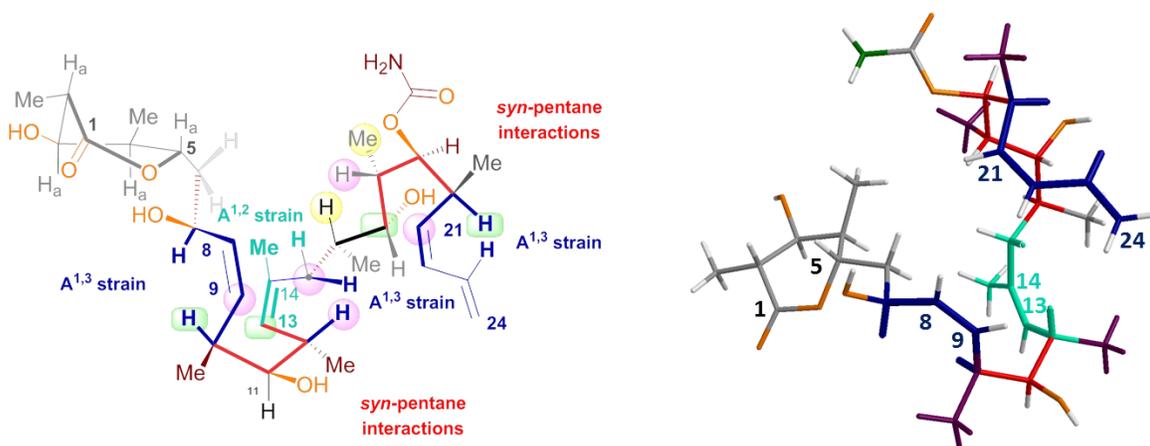


FIGURE 5 Conformation of DDM: A^{1,3} and A^{1,2} strain and *syn*-pentane interactions.

However, since the discodermolide/tubulin complex has not been crystallized, the binding mode of DDM on tubulin remains unclear. Even if extensive docking and NMR experiments have demonstrated that the turn structure of DDM fits tightly in a region quite close to the paclitaxel site with important hydrogens bonds and hydrophobic interactions, the binding site is not clearly defined (Figure 6).

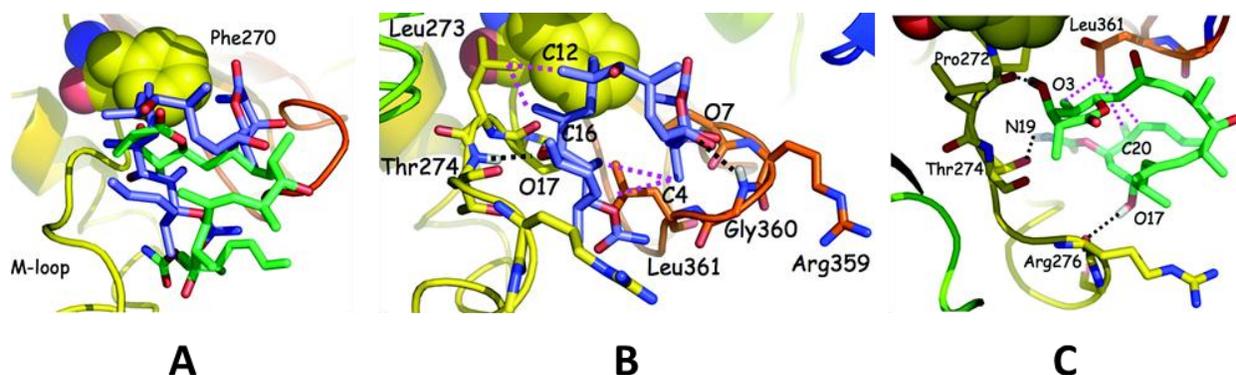


FIGURE 6 A) Two distinct orientations of discodermolide in the taxane β -tubulin site. B and C) Illustration of the major polar (black dotted lines) and nonpolar (magenta dotted lines) contacts with the M-loop (yellow) and the adjacent loop (orange) linking β -strands B9 and B10 for both poses.^[71,68c]

The unique profile of DDM has inspired a number of efforts directed toward the production of synthetic analogues.^[10p-s,14a-p] Importantly, 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 stereocenters 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 was required to set the overall conformation of the molecule, the diene and lactone regions provided opportunities to develop analogues with improved potency, pharmacokinetic properties or a simplified structure.

On the basis of these observations, we designed five original analogues. Their conception was guided by the chemical knowledge gained during the total synthesis of DDM and by the strong constraint of keeping the essential “U”-shaped conformation of DDM. Therefore, at first computational conformational analysis was performed on the focused analogues in order to check if the hairpin conformation was still favored. By stochastic conformational analysis (Monte Carlo method, Spartan’04 Win. Software, MMF94aq force field) from RX diffraction DDM structure, we showed that the “U”-shaped conformers of the considered analogues were the lowest in energy.

Hence, the elaboration of three original and more lipophilic DDM analogues was undertaken, one including a *Z*-diene unit with a C24 *gem*-di-Me group (**63**) and two non-diene derivatives with a phenyl or a benzyl core (**64** and **65**) (Figure 7). The replacement of the methyl group at the C14 position by a more sterically demanding isopropyl group was very provocative

(analogue **66**). Although such a variation had never been reported so far, we were convinced it could enhance the specific active conformation of DDM (**1**). Finally, replacing the δ -lactone fragment by a phenol group suggested great promise even though similar reported analogues were characterized by a slightly lower activity.^[14k,71] 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 binding site). Therefore, we investigated the simplification of DDM backbone with a phenol core to afford analogue **67** while keeping the DDM C7-hydroxyl function.

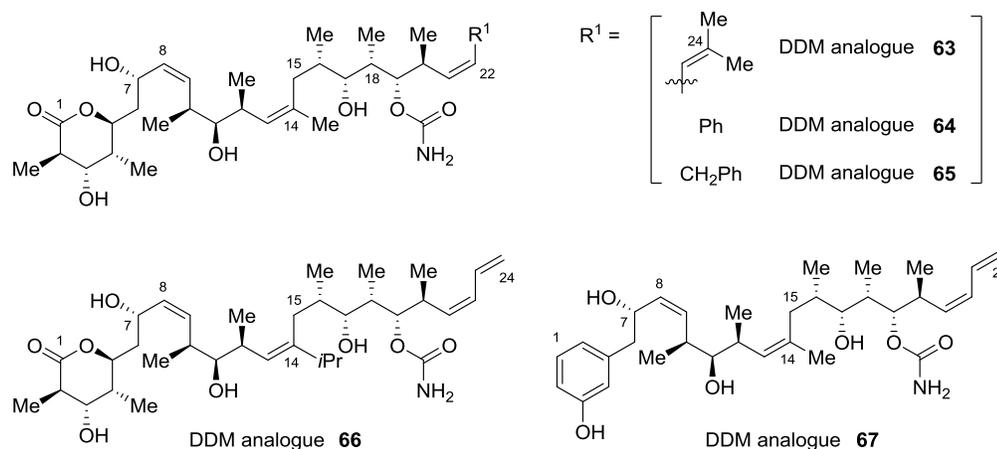
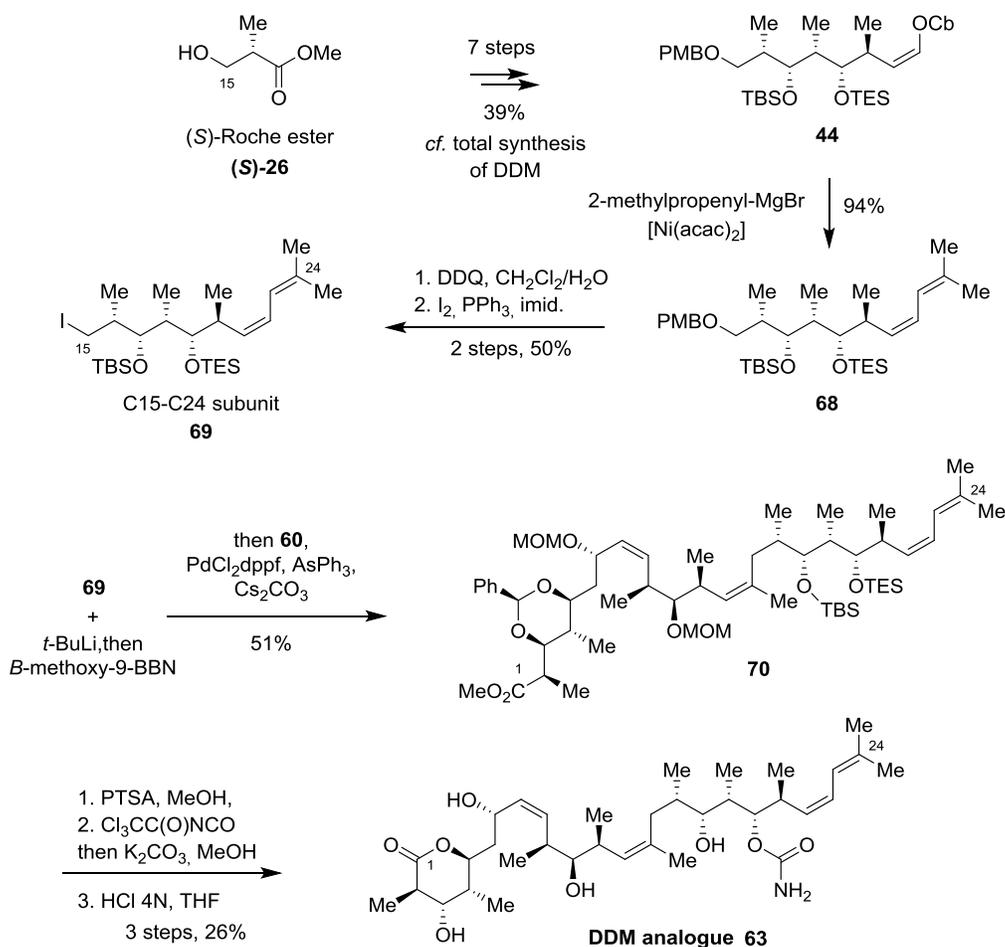


FIGURE 7 Focused DDM analogues.

4.2 Modification of Terminal Diene C15-C24 Part

The synthesis of the DDM analogue **63**, which bears a C24 *gem*-di-Me group, started with the construction of the *Z*-C21-C24 diene unit (Scheme 15). It was initiated as a Ni-mediated Grignard coupling reaction between the C15-C22 vinylcarbamate **44**, previously prepared by us during the total synthesis of DDM, and 2-methylpropenylmagnesium bromide. The required

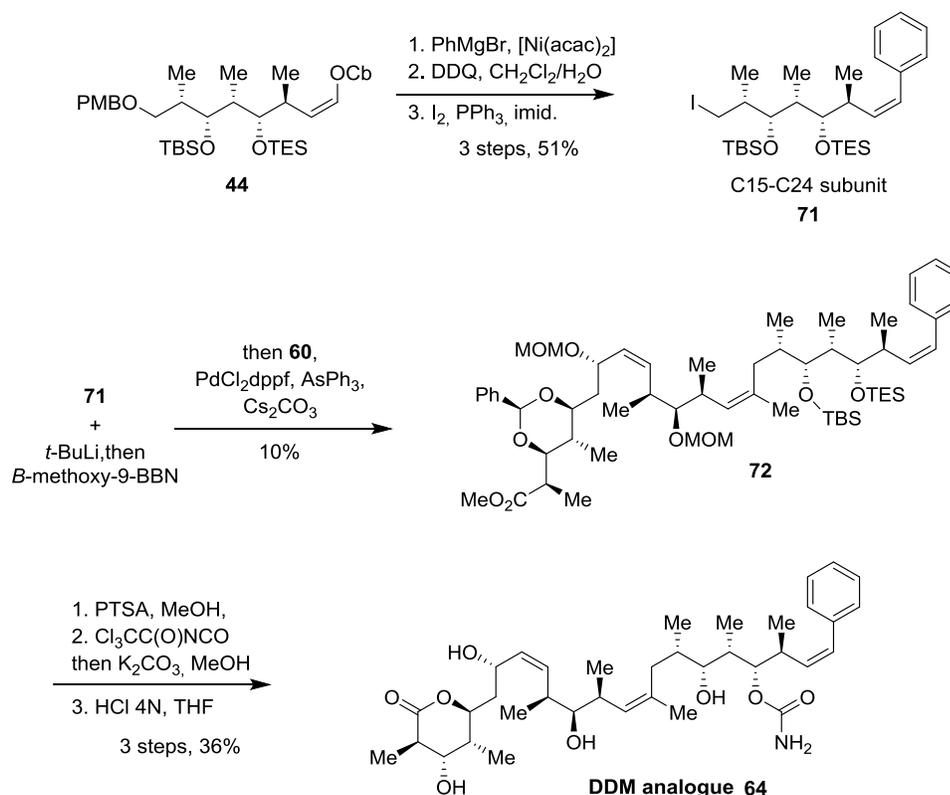
diene **68** was obtained in very high yield (94%), and the stereochemical control was total. This compound was then smoothly transformed into the corresponding C15-C24 subunit **69** after deprotection and iodination. The second key step involved a C(sp²)-C(sp³) *B*-alkyl Suzuki-Miyaura cross-coupling between a trialkyl boronate species prepared from alkyl iodide **69** and C1-C14 vinyl iodide **60** already described in our DDM synthesis, affording adduct **70** in a non-optimized 51% yield. Final carbamate moiety installation and total deprotection provided DDM analogue **63**.



SCHEME 15 Synthesis of DDM analogue **63**.

The elaboration of analogue **64**, which possesses a phenyl group, followed a similar sequence from vinylcarbamate **44** (Scheme 16). Thus, a nickel-catalyzed cross-coupling reaction

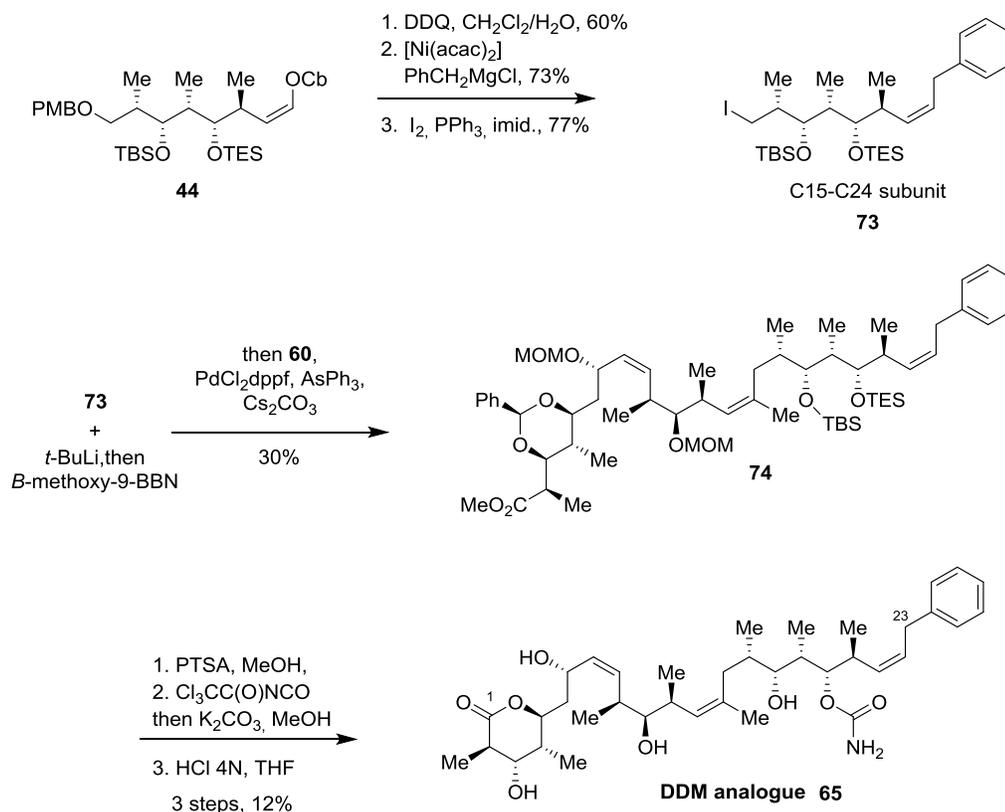
involving phenylmagnesium bromide ensured the construction of the C15-C24 subunit **71** with high selectivity. Then, a C(sp²)-C(sp³) *B*-alkyl Suzuki-Miyaura cross-coupling reaction between **71** and **60** (formation of **72**), carbamate formation, and deprotection delivered desired DDM analogue **64**.



SCHEME 16 Synthesis of DDM analogue **64**.

For the synthesis of the nondiene analogue **65**, which bears a benzyl group in the terminal position (Scheme 17), DDQ cleavage of the PMB ether at the C15-position did not proceed in the presence of the benzyl moiety (oxidation of the methylene in allylic-benzylic-position in C23-position). Therefore, we inverted the order of the first two steps: 1) DDQ deprotection on **44** and 2) nickel-catalyzed cross-coupling reaction performed on a free primary alcohol in C15 position. After this minor modification, completion of the synthesis followed the established route: Suzuki-Miyaura cross-coupling reaction between alkyl iodide **73** (*via* its

trialkylboronate species) and vinyl iodide **60** to yield **74**; selective carbamate installation; and final deprotection to afford DDM analogue **65**.

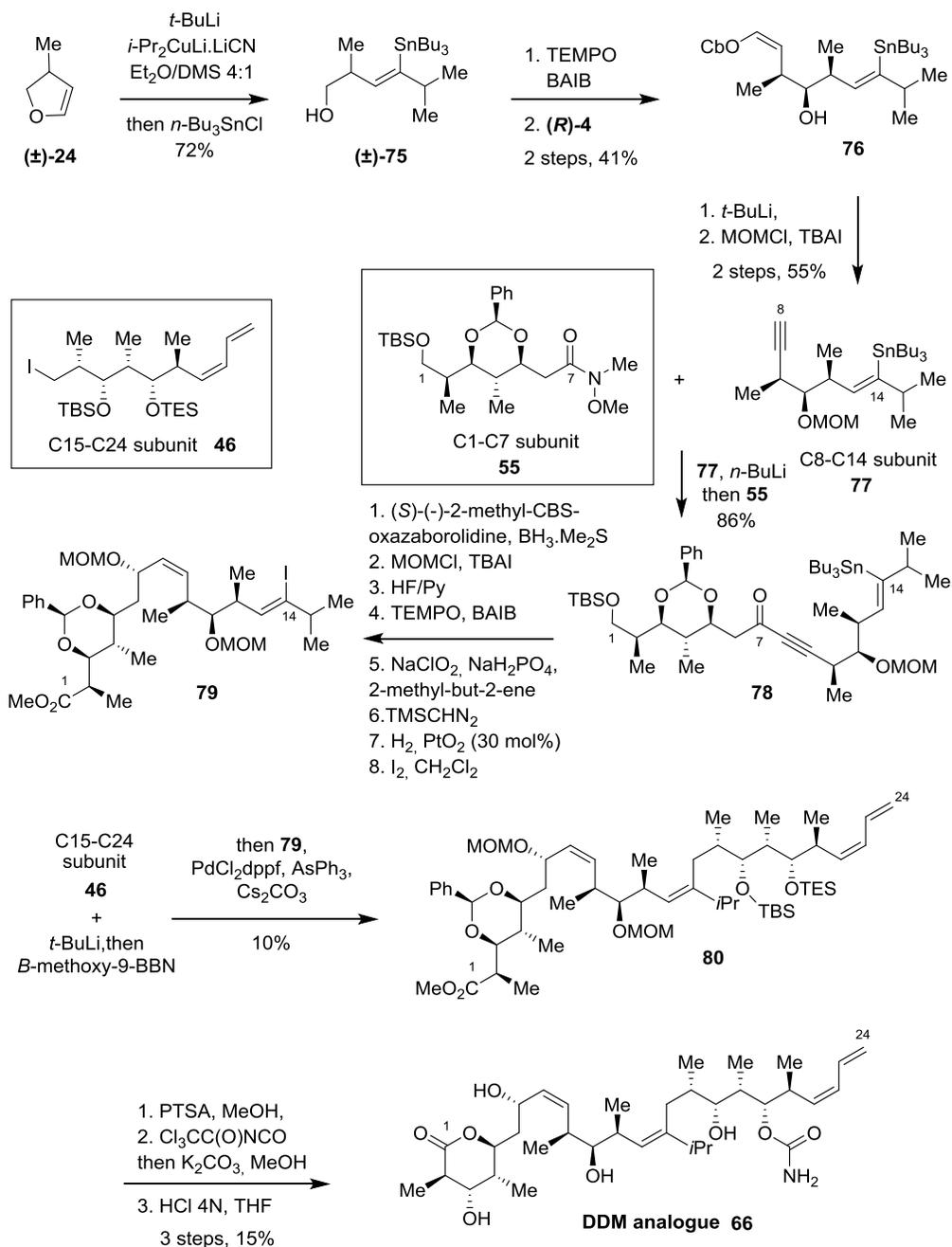


SCHEME 17 Synthesis of DDM analogue **65**.

4.3 Modification of the Trisubstituted C13-C14 Double Bond

The synthesis of the fourth analogue **66**, substituted at the C14 position by an isopropyl group, was then investigated. DHF (\pm)-**24** was subjected to metallate rearrangement under the previously developed optimized laboratory conditions with a “higher order” lithium cyano(diisopropyl)cuprate, giving the expected *Z*-alkene (\pm)-**75** in a satisfactory 72% yield with complete diastereoselectivity (Scheme 18). Oxidation and crotyltitanation of (\pm)-**75** with (*R*)-**4** delivered the required homoallylic alcohol **76** as main product in 41% yield along with its C12-epimer in 25% yield. Vinylcarbamate **76** was then transformed into alkyne **77**. Coupling of **77** with the amide **55** afforded the ynone **78**. A subsequent eight-step sequence completed the

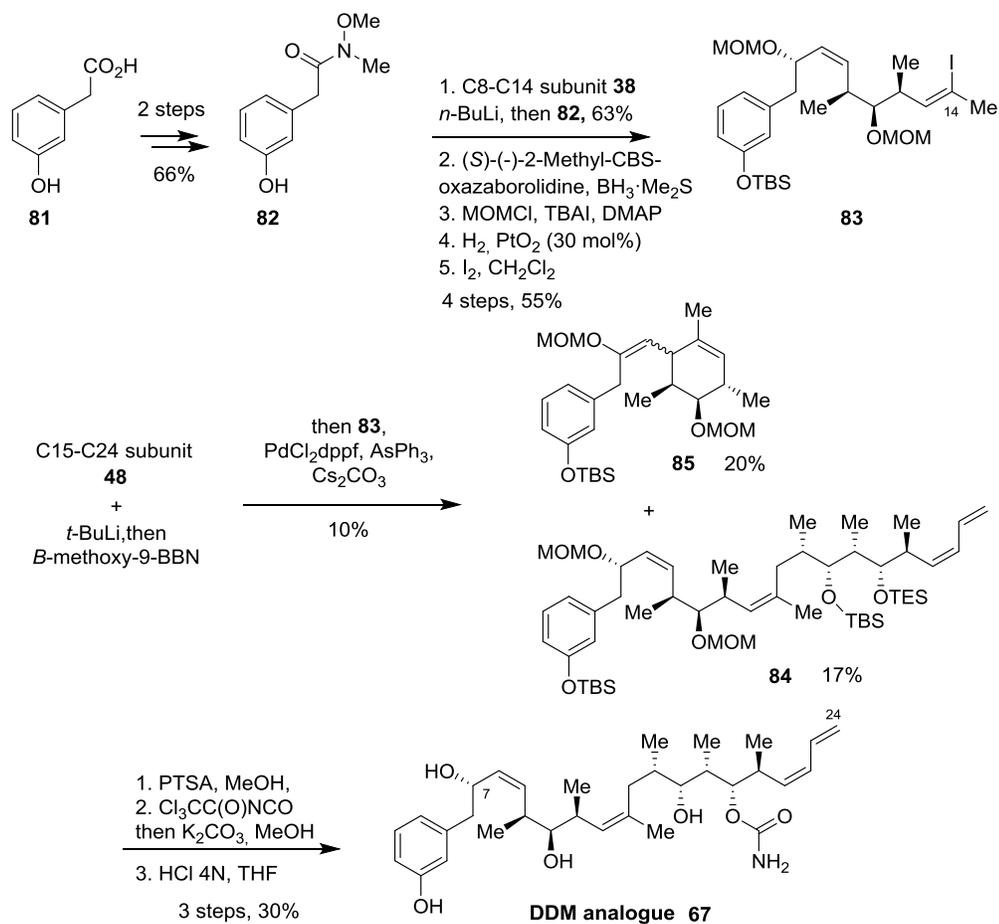
formation of vinyl iodide **79**. The convergent coupling of **79** with alkyl iodide **46** was carried out under Suzuki conditions. The yield was disappointingly low (10%). We suspected that the isopropyl group could have deleterious effects for steric reasons. Final deprotection of the C1-C24 fragment **80** and carbamate formation at C19 then furnished DDM analogue **66**.



SCHEME 18 Synthesis of DDM analogue **66**.

4.4 Modification of C1-C5 Lactone Part

The synthesis of the simplified DDM analogue **67**, which possesses a phenolic group instead of the δ -lactone, was much faster. It started with the preparation of amide **82**, obtained from commercial 3-hydroxyphenylacetic acid **81** in two steps (Scheme 19). Subsequent coupling of the C8-C14 subunit alkyne **38** with amide **82** proceeded smoothly to deliver vinyl iodide **83** in a five-step sequence. However, significant problems were encountered during the Suzuki cross-coupling reaction between vinyl iodide **83** and alkyl iodide **46** (*via* its trialkyl boronate species). The required adduct **84** was obtained in a rather low 17% yield, the main isolated product being the cyclohexene derivative **85**, which certainly arose from an intramolecular Heck coupling reaction. This last result proved the fold of the C8-C14 core. The same final 3-step sequence (carbamate installation and deprotection) delivered analogue **67**.



SCHEME 19 Synthesis of DDM analogue **67**.

4.5 Biological Evaluation of Synthetic Analogues

The five DDM analogues **63**, **64**, **65**, **66** and **67** were finally tested for cellular activity, in comparison to DDM **1**. 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 **63** and C14-isopropyl analogue **66** were the most potent and both were essentially equipotent to DDM (entries 1, 2 and 3, Table 2). They were followed in this order by phenolic **67** and C22-Ph **64** analogues (entries 5 and 6, Table 2). The C22-benzyl analogue **65** was the least potent (entry 4, Table 2).

TABLE 2 Biological Evaluation of Synthesized Analogues 63, 64, 65, 66 and 67.^{a,b}

Entry	Compound	IC ₅₀ (nM)	IC ₅₀ (nM)	IC ₅₀ (nM)
		HCT116 ^b	MDA-MB231 ^b	MDA-A1 ^b
1	DDM 1	5.0 ^l	15.6	105.8
2	C24- <i>gem</i> -dimethyl 63	1.3	3.7	155
3	C22-phenyl 64	19	110	4494
4	C22-benzyl 65	321	1009	8709
5	C14- <i>iso</i> -propyl 66	2.3	17.5	2200
6	Phenol 67	16	66	4836

^aCytotoxicity assays were based on the determination of the inhibition of cell growth by measuring the inhibition of the incorporation of ¹⁴C-thymidine.

^bCells 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 of **66**. The phenolic analogue **67** retains good potency considering the structural simplification and may be of utility in the design of straightforward analogues.

In summary, the design and preparation of five original analogues (**63**, **64**, **65**, **66** and **67**) of DDM (**1**) have been achieved. Aiming to retain the bioactive U-shaped conformation of DDM, three types of variation were defined: 1. modifying the diene with a *gem*-di-Me group at the C24 position and phenyl or benzyl group at C22; 2. replacing the C14 methyl group by an isopropyl group; and 3. replacing the δ -lactone by a phenol moiety. The first two modifications were readily accessible through two key reactions of our synthesis of DDM, a nickel-catalyzed cross-coupling reaction between a *Z*-*O*-enecarbamate and the corresponding magnesium derivative and a dyotropic rearrangement performed on a 3-methyl-2,3-dihydrofuran with the

corresponding diisopropylcuprate. Noteworthy, in both cases, the selectivities were excellent. The third variation did efficiently shorten the synthesis of the C1-C7 fragment. Cytotoxicity assays were performed for these five analogues on three different cell lines. In accord with our design strategy, all analogues revealed activity in the nanomolar range, especially the C24-*gem*-di-Me and the C14-*i*-Pr analogues **63** and **66**, both of which were equipotent to DDM. The phenolic analogue **67** retained a very significant and encouraging *in vitro* activity considering the structure simplification.^[72]

5. CONCLUSION

The synthesis of the anticancer marine metabolite discodermolide (+)-DDM has been accomplished in 1.6% overall yield in 21 linear steps. In these studies, we have shown that crotylation reactions onto aldehydes with enantioenriched secondary α -oxygenated crotyltitanium reagent simultaneously ensured the stereocontrolled elaboration of *syn-anti* methyl-hydroxy-methyl triads and set up a *Z*-O-enecarbamate. This functional group allowed direct access to either a triple bond or could be used directly to introduce the terminal *Z*-diene. The second highlight of our strategy was the 1,2-dyotropic rearrangements on dihydrofuran with organocopper reagents for the stereocontrolled formation of a functionalized trisubstituted *Z*-double bond. This convergent and flexible approach allowed us to prepare five novel discodermolide analogues.

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