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# Total synthesis of novel dictyostatin analogs and hybrids as microtubule-stabilizing anticancer agents*

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*Abstract*: Structural modification of the dictyostatin macrolide template through adaptation of our total synthesis has led to the identification of a number of potent analogs of this novel microtubule-stabilizing agent. A common synthetic strategy was exploited, employing a (*Z*)-selective Still–Gennari olefination between various advanced C11–C26 aldehyde and C4–C10 (or C1–C10) β-ketophosphonate intermediates. In vitro evaluation of the growth inhibitory activity of these analogs against both Taxol-sensitive and -resistant human cancer cell lines has provided a foundation for structure–activity relationship (SAR) studies to help define the pharmacophore region.

*Keywords*: natural products; anticancer; macrolides; tubulin; stereocontrolled synthesis.

## INTRODUCTION

The Earth's oceans support a unique ecological environment, harboring a diverse collection of sessile marine invertebrates and symbionts from which have been isolated a significant number of novel bioactive secondary metabolites with therapeutic potential in human medicine, particularly in the cancer area [1]. However, both from an economic and ecological perspective, significant challenges are faced in solving the supply problem that would enable these lead structures to be developed as drug candidates. Total synthesis provides a powerful solution, where a reliable and sustainable means of accessing useful quantities of these rare natural products and designed analogs can be developed [2]. Hence, studies that were previously hampered by supply issues, such as achieving a complete stereochemical assignment or detailed biological evaluation of the lead compound are facilitated. From a pragmatic standpoint, the identification of simplified analogs with reduced molecular complexity, yet retaining the biological function and potency of the parent natural product, should further impact the supply problem through total synthesis, in addition to offering a more realistic starting point for drug development by the pharmaceutical industry.

The tubulin/microtubule system is an important target in the development of anticancer drugs, with Taxol® (**1**, Fig. 1) and Taxotere® (**2**) being widely used in the treatment of breast, lung, and ovarian cancers [3]. Whilst these antimitotic drugs are highly effective, both acquired and intrinsic resistance are a major problem in the clinic. This has led to the search for novel microtubule-stabilizing agents that have similar antimitotic activity to the taxanes, but lack the interaction with P-glycoprotein or bind to unique sites on tubulin [4]. Discodermolide (**3**), a marine sponge-derived polyketide, and Ixempra® (**4**), a semi-synthetic lactam analog of epothilone B (**5**), which is now approved by the Food and Drug Administration (FDA) for the treatment of advanced breast cancer, are representative mem-

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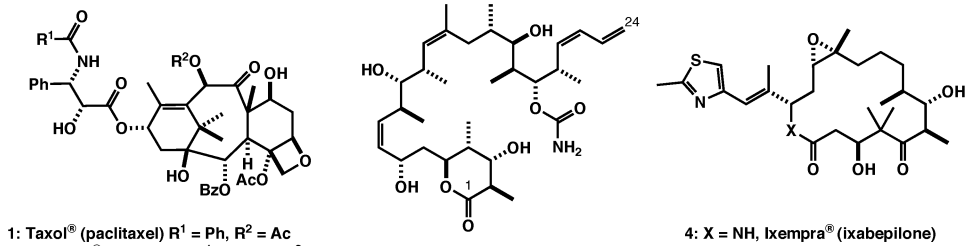



**Fig. 1**

bers of the resulting expanded class of microtubule-stabilizing anticancer agents [5]. In the case of discodermolide, extensive efforts to develop a practical total synthesis have provided sufficient drug substance to enable clinical trials, and have facilitated access to a range of novel analogs for structure–activity relationship (SAR) studies [6,7].

Herein, we provide an overview of our recent work directed toward the design, synthesis, and biological evaluation of novel analogs of the microtubule-stabilizing anticancer agent dictyostatin and hybrid molecules of dictyostatin and discodermolide. The results from the cytotoxicity assays are discussed in regard to elucidating the pharmacophore region of dictyostatin associated with its interactions with the taxoid binding site on β-tubulin.

## DICTYOSTATIN

First isolated in 1994 off the coast of the Maldives by Pettit and coworkers from a marine sponge of the genus *Spongia* (family Spongiidae), dictyostatin was identified as a potent cytotoxic agent [8a]. An incomplete stereochemical assignment, as in **6** (Fig. 2), attributable to its low isolation yield hampered early synthetic efforts. However, upon re-isolation from a *Corallistidae* deep-sea sponge source in the Caribbean by Wright and coworkers, detailed NMR analysis combined with molecular modeling led us in 2004 to assign the full stereochemistry of dictyostatin as in **7** [8b,c]. Concurrent total syntheses ensued from the groups of Paterson and Curran, confirming this stereostructure and facilitating a more extensive investigation of the biological profile of this potent antimitotic agent [9,10].

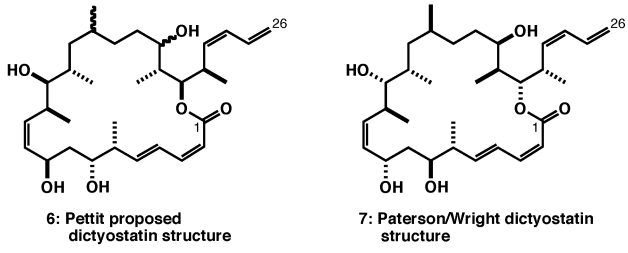



**Fig. 2**

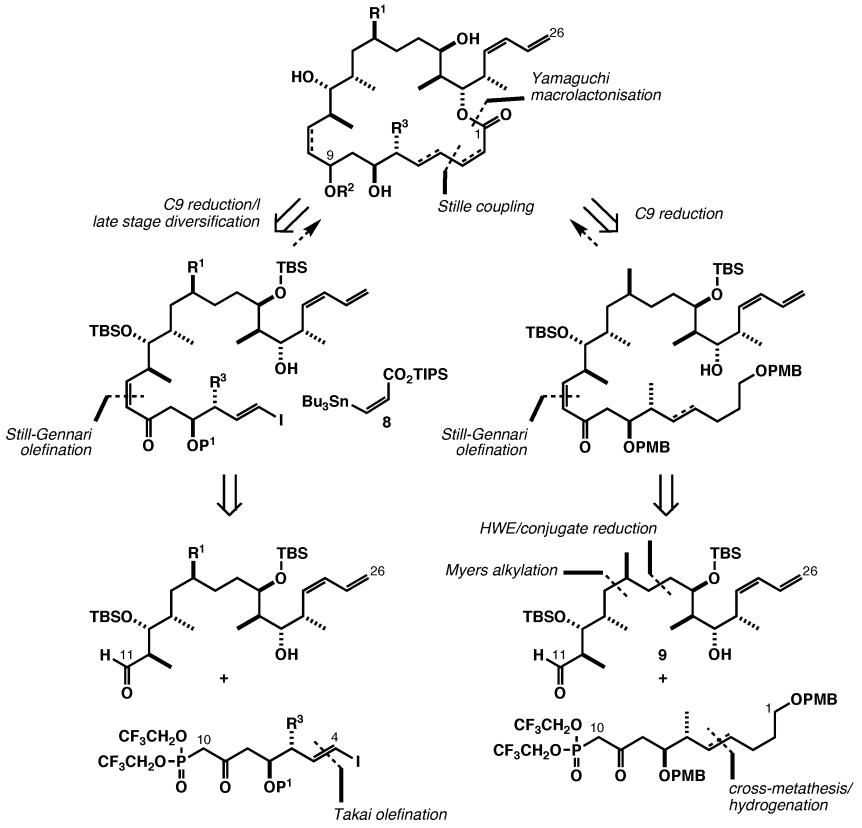
Binding to the taxoid binding site on β-tubulin, dictyostatin displays enhanced microtubule-stabilizing properties and antiproliferative activity relative to Taxol in a wide range of human cancer cell lines, including multi-drug-resistant cells. Recent NMR studies by Díaz, Jiménez-Barbero, and coworkers, in combination with molecular modeling, have revealed the bioactive conformation of dictyostatin bound to microtubules [11]. The resulting 3D structure shows a strong correlation with the bioactive conformation of the structurally related polyketide discodermolide, sharing common contacts

with the tubulin protein [12]. Hence, the large library of SAR information available for discodermolide offers a useful starting point for the design of active dictyostatin analogs. Furthermore, the concept of combining chosen structural features of these two cytotoxic natural products into a single hybrid molecule might prove similarly successful.

## DICTYOSTATIN ANALOGS

### Synthesis of analogs 10–17

Our 2004 total synthesis of dictyostatin [9a], which relied on the sequential coupling of three key fragments, C1–C3 vinyl stannane **8**, C11–C26 aldehyde **9**, and a C4–C10 β-ketophosphonate component, was envisioned as providing the framework on which the syntheses of the targeted dictyostatin analogs **10–17** would be based (Scheme 1) [13,14]. Strategically, the desired structural permutations were translated onto the dictyostatin system through either (i) modification of the aldehyde partner, (ii) modification of the β-ketophosphonate partner, prior to Still–Gennari olefination [15], or (iii) late-stage diversification of available dictyostatin intermediates.

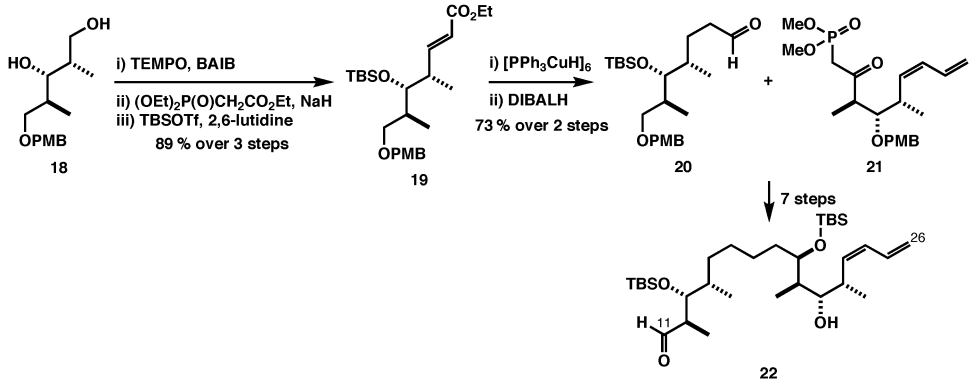



| | $R^1$ | C9 | $R^2$ | $R^3$ | $P^1$ | –Δ |
|---|---|---|---|---|---|---|
| 10: 16-desmethyl- | H | *S* | H | Me | PMB | - |
| 11: 9-*epi*-16-desmethyl- | H | *R* | H | Me | PMB | - |
| 12: 9-methoxy- | Me | *S* | Me | Me | TBS | - |
| 13: 9-*epi*- | Me | *R* | H | Me | TBS | - |
| 14: 10,11-dihydro- | Me | *S* | H | Me | PMB | 10,11 |
| 15: 6-desmethyl- | Me | *S* | H | H | PMB | - |
| 16: 2,3-dihydro- | Me | *S* | H | Me | PMB | 2,3 |
| 17: 2,3,4,5-tetrahydro- | Me | *S* | H | Me | PMB | 2,3,4,5 |

**Scheme 1**

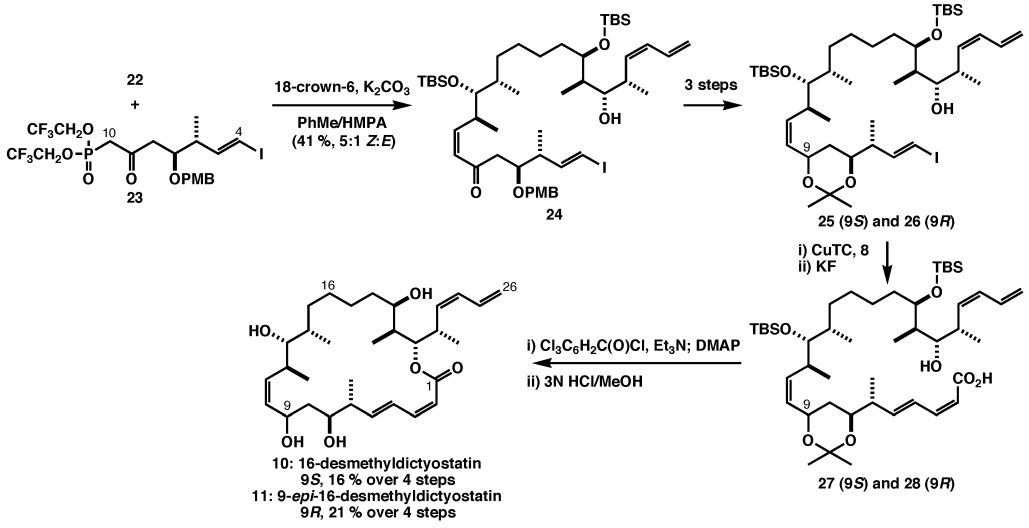
*16-Desmethyldictyostatin (**10**) and 9-epi-16-desmethyldictyostatin (**11**)*

Initially, efforts were directed toward applying this general strategy to the synthesis of 16-desmethyldictyostatin (**10**). Previously, Smith had shown that removal of the corresponding C14-methyl group in discodermolide provided an analog with similar cytotoxicity in non-resistant cell lines to the parent natural product [6a,16]. Therefore, the 16-desmethyl analog **10** was expected to display a similar biological profile relative to dictyostatin. Deletion of the C16-methyl group in dictyostatin permitted a simplification to the original synthetic route toward the C11–C26 aldehyde: where the Myers alkylation step was replaced by a Horner–Wadsworth–Emmons (HWE)/conjugate reduction sequence (Scheme 2). The common stereotriad **18** was readily prepared using our boron aldol methodology and chain extended to give **19** [13a,17]. Following reduction to aldehyde **20**, a HWE olefination with phosphonate **21** enabled assembly of the C11–C26 aldehyde **22**.




**Scheme 2**

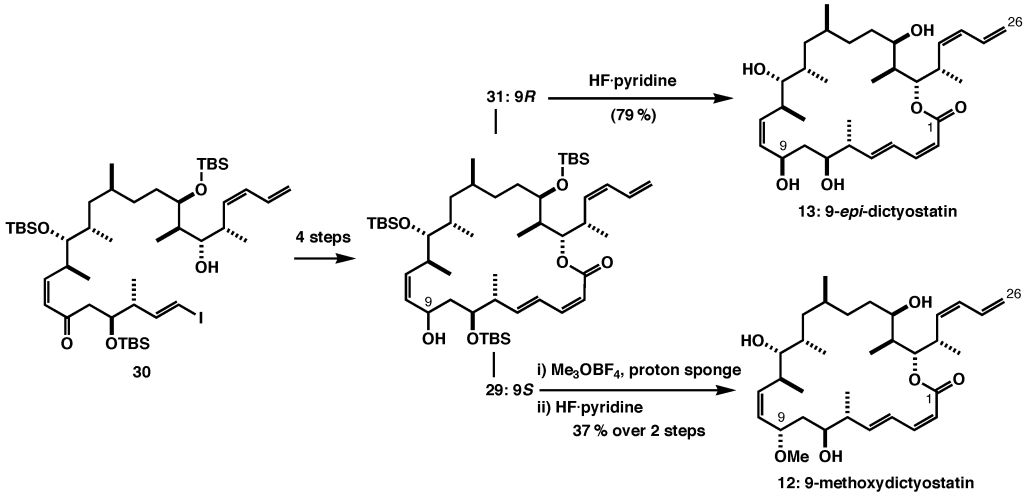
A subsequent Still–Gennari olefination of **22** with the C4–C10 β-ketophosphonate **23** {*p*-methoxybenzyl (PMB) ether at C7 replacing the previously used *tert*-butyldimethylsilyl (TBS) ether [9a]} provided (*Z*)-enone **24** (Scheme 3). The ensuing C9 reduction proceeded with moderate selectivity (83:17 dr), providing sufficient stocks of the (9*S*)- and (9*R*)-acetonides **25** and **26** to be progressed through the Stille coupling with the vinyl stannane **8** to afford **27** and **28**, respectively. The Yamaguchi macrolactonization then provided 16-desmethyldictyostatin (**10**) and 9-*epi*-16-desmethyldictyostatin (**11**) for biological evaluation [13a].




**Scheme 3**

### *9-Methoxydictyostatin (**12**)*

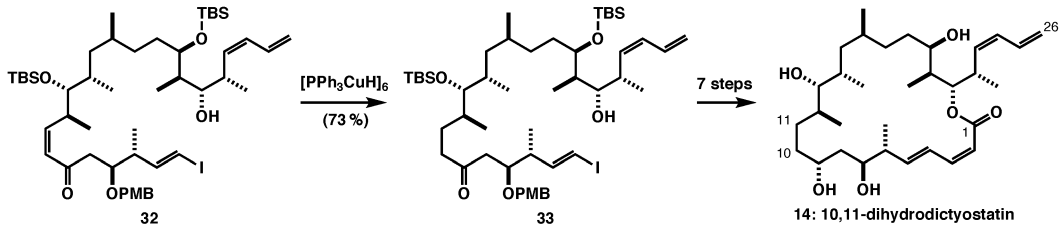
Discodermolide analogs with C7 modifications (removal/acylation/methylation) had been observed to show comparable and sometimes increased cytotoxicity relative to the natural product [6a,18]. Thus, our next targeted dictyostatin analog was selected as the C9 methyl ether **12** (Scheme 4). Late-stage diversification of the advanced dictyostatin intermediate **29**, as derived from **30**, through O-methylation with Meerwein salt, afforded ready access to this analog [13a]. Furthermore, the moderate selectivity (68:32 dr) of the C9 enone reduction meant that 9-*epi*-dictyostatin (**13**) could be obtained from **31** after deprotection, providing further SAR information relating to the importance of the C9 configuration.




**Scheme 4**

### *10,11-Dihydrodictyostatin (**14**)*

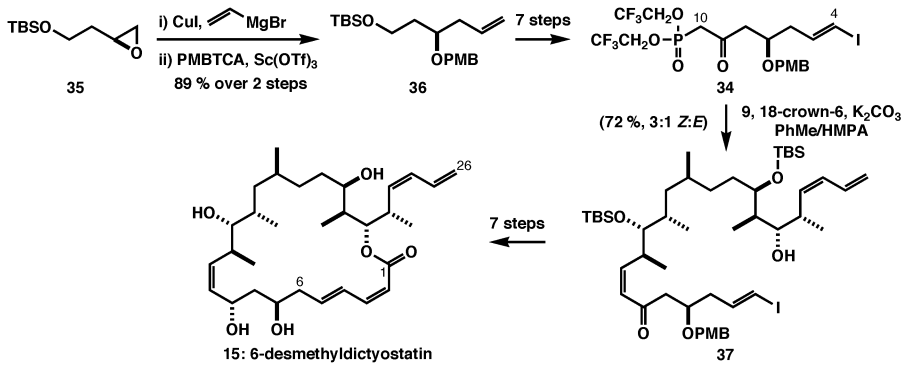
Turning our attention to the olefins present in dictyostatin, examination of the SAR data available for a series of reduced discodermolide derivatives led us to target 10,11-dihydrodictyostatin (**14**) [18]. Although not reported directly in these prior results, retention of biological activity in the corresponding 8,9-dihydro analog of discodermolide was implied by consideration of the $IC_{50}$ data (P-388 cell line) of various saturated derivatives. Notably, the presence of the $\Delta^{13,14}$ alkene appeared to be critical in maintaining biological potency (as opposed to the other olefins). Hence, we postulated that saturation solely of the (10*Z*)-alkene in dictyostatin might lead to a useful structural simplification without adversely affecting the cytotoxicity [13b]. Employing a late-stage diversification strategy was similarly attractive (Scheme 5), in that manipulation of the dictyostatin (*Z*)-enone **32** would rapidly provide the desired analog. Conjugate reduction using Stryker's reagent [19] provided ketone **33**, which was subject to the dictyostatin endgame sequence, providing 10,11-dihydrodictyostatin (**14**) in readiness for biological evaluation.




**Scheme 5**

### *6-Desmethyldictyostatin (**15**)*

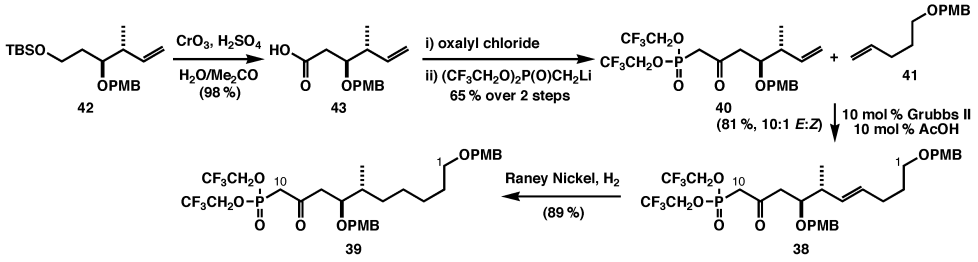
Further identification of likely active analogs of dictyostatin from early 2008 was aided by the results of docking studies reported by Díaz, Jiménez-Barbero, and coworkers [11]. These indicated that the C6-methyl group appeared to be in a relatively "open" region of the taxoid binding pocket. Therefore, its removal might provide a further structural simplification without impacting adversely on the binding affinity and hence cytotoxicity. Access to 6-desmethyldictyostatin (**15**) required synthesis of a novel C4–C10 phosphonate **34**, lacking the C6-methyl group [13c,d]. The original Brown crotylation reaction used to install the 6,7-*anti* relationship was replaced by a vinyl Grignard opening of epoxide **35** to give **36** which was then progressed through a similar reaction sequence to afford β-ketophosphonate **34** (Scheme 6). Still–Gennari olefination of **34** with the C11–C26 aldehyde **9** provided (*Z*)-enone **37**, which was elaborated into 6-desmethyldictyostatin (**15**) for biological evaluation.




**Scheme 6**

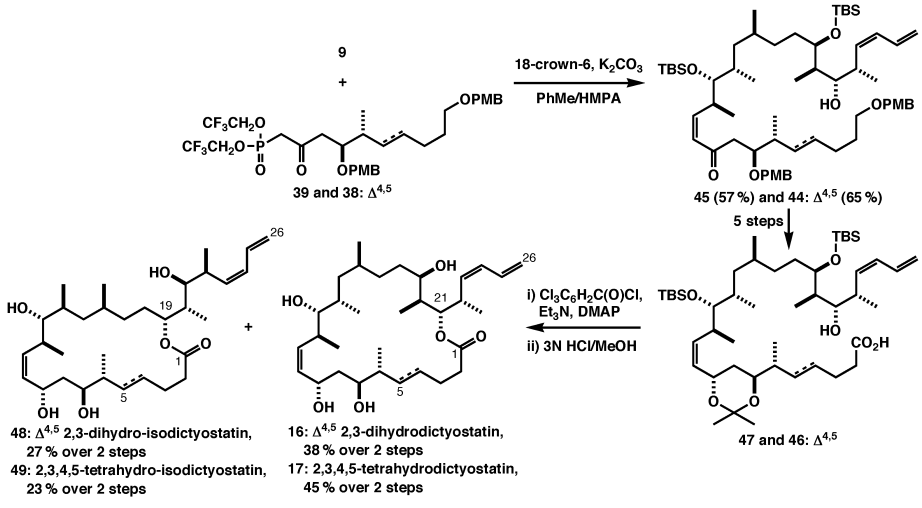
### *2,3-Dihydrodictyostatin (**16**) and 2,3,4,5-tetrahydrodictyostatin (**17**)*

The next series of dictyostatin analogs explored modifications to the C1–C5 olefinic region [13c,d]. A low structural homology between dictyostatin and discodermolide exists in this region, as dictyostatin features a (2*Z*,4*E*)-dienoate and discodermolide a δ-lactone moiety [11]. Therefore, we looked to probe the SAR associated with this unique region of dictyostatin through the total synthesis of two novel reduced analogs, 2,3-dihydro- (**16**) and 2,3,4,5-tetrahydrodictyostatin (**17**). Their synthesis was anticipated to employ the key Still–Gennari coupling of the β-ketophosphonates **38** and **39**, differing only in the presence or absence of a $\Delta^{4,5}$ olefin. These fully elaborated phosphonates were accessed using a novel strategy, employing a cross-metathesis reaction between phosphonate **40** and the simple PMB ether containing olefin **41** to give **38** (Scheme 7) [20]. Hydrogenation of **38** using Raney nickel provided the fully saturated C1–C10 phosphonate **39**.




**Scheme 7**

In a parallel sequence, Still–Gennari olefination of phosphonates **38** and **39** with the C11–C26 aldehyde **9** provided the respective (*Z*)-enones **44** and **45** (Scheme 8). After C9 reduction, manipulation of the C1 terminus provided acids **46** and **47**, which were subjected to Yamaguchi macrolactonization and deprotection to afford 2,3-dihydro- (**16**) and 2,3,4,5-tetrahydrodictyostatin (**17**). Also isolated from the global deprotection step were the corresponding C21 to C19 translactonized *iso*dictyostatin derivatives **48** and **49**, presumably formed due to the increased reactivity of the C1 ester relative to the corresponding dienoate of dictyostatin. All four partly hydrogenated analogs **16**, **17**, **48**, and **49** were subject to biological evaluation [13c].




**Scheme 8**

## Biological evaluation

In a series of cytotoxicity assays performed by Wright and coworkers [13] at the Harbor Branch Oceanographic Institution (HBOI), the cell growth inhibitory activities of all the fully synthetic dictyostatin analogs **10** to **17** (including **48** and **49**) were evaluated in vitro against four cancer cell lines—AsPC-1 (pancreatic), DLD-1 (colon), PANC-1 (pancreatic), and NCI/ADR-RES (Taxol-resistant ovarian) relative to dictyostatin (**6**), discodermolide (**3**), and Taxol (**1**) (Table 1).

**Table 1** Cell growth inhibitory activities of dictyostatin analogs and hybrids with discodermolide.

| Compound | $IC_{50}$/nM[a] | | | |
|---|---|---|---|---|
| | AsPC-1 (pancreatic) | DLD-1 (colon) | PANC-1 (pancreatic) | NCI/ADR-RES (Taxol-resistant) |
| Dictyostatin (**6**) | 6.2 | 2.2 | 4.2 | 6.6 |
| Discodermolide (**3**) | 98 | 29 | 59 | 160 |
| Taxol (**1**) | 89 | 22 | 9.9 | 1300 |
| 16-Desmethyldictyostatin (**10**) | 170 | 85 | 130 | 1500 |
| 9-*epi*-16-Desmethyldictyostatin (**11**) | 2100 | 790 | 1500 | 2100 |
| 9-Methoxydictostatin (**12**) | 31 | 2.4 | 9.7 | 8.2 |
| 9-*epi*-Dictyostatin (**13**) | 410 | 150 | 240 | 1100 |
| 10,11-Dihydrodictyostatin (**14**) | 43 | 10 | 18 | 300 |
| 6-Desmethyldictyostatin (**15**) | 56 | 8.1 | 17 | 43 |
| 2,3-Dihydrodictyostatin (**16**) | 94 | 22 | 42 | 66 |
| 2,3-Dihydro-*iso*dictyostatin (**48**) | 3100 | 930 | 1900 | 1600 |
| 2,3,4,5-Tetrahydrodictyostatin (**16**) | 118 | 55 | 64 | 132 |
| 2,3,4,5-Tetrahydro-*iso*dictyostatin (**17**) | 4900 | 1900 | 3200 | 3100 |
| Macrocyclic discodermolide **50** | 2800 | 2100 | 1800 | 8200 |
| Macrocyclic hybrid **51** | 34 | 5.9 | 13 | 66 |

[a]Values from a minimum of three experiments.

Notably, the most potent analogs were 9-methoxy- (**12**), 6-desmethyl- (**15**), and 2,3-dihydrodictyostatin (**16**), displaying low nanomolar cytotoxicities in both Taxol-sensitive and -resistant cell lines, which were comparable to dictyostatin (**6**) itself. Furthermore, 10,11-dihydro- (**14**) and 2,3,4,5-tetrahydrodictyostatin (**17**) were also highly active and directly comparable to discodermolide (**3**). From these cytotoxicity assay results, we were able to formulate SAR conclusions regarding the importance of the modified regions of the dictyostatin structure and hence speculate on ligand interactions with the β-tubulin binding site.

The desmethyl dictyostatin analogs **10** and **15** showed significant antiproliferative activities across the four cell lines. For 16-desmethyldictyostatin (**10**), the reduction in activity relative to dictyostatin, particularly in regard to the Taxol-resistant NCI/ADR-RES cell line, led us to conclude that the C16-methyl group is both important in maximizing the binding of dictyostatin to tubulin, and in helping the natural product circumvent the P-glycoprotein efflux pump. Interestingly, these conclusions contrasted with the initial findings of Curran, Day, and coworkers, who had independently synthesized **10** and reported it to have a cytotoxicity profile comparable to dictyostatin in both resistant and non-resistant cell lines [14a]. These differences in cytotoxicity assay results were attributed by us to the cell lines selected and experimental parameters employed. Pleasingly, 6-desmethyldictyostatin (**15**) showed an activity intermediate between that of dictyostatin and discodermolide, affirming our predictions that the C6-methyl group was unlikely to contribute to a strong interaction with the tubulin binding site and occupies a relatively "open" region. This conclusion is further supported by the results of Curran, Day, and coworkers for a series of C6,C7-isomers of dictyostatin, where the 6-*epi*-analog was determined to be essentially equipotent to dictyostatin [14b,d].

The comparable cytotoxicity of 9-methoxydictyostatin (**12**) to dictyostatin implied that the C9 hydroxyl was unlikely to be acting as a hydrogen bond donor to proximal residues in tubulin or to other intramolecular hydrogen-bond acceptors. However, what did appear to be important with regard to the C9 position was retaining the natural (9*S*)-configuration. Both 9-*epi*- analogs **11** and **13** showed a large reduction in activity relative to both dictyostatin and discodermolide, indicating that the configuration of this stereocenter is important in maintaining the bioactive conformation of the natural product and hence maximizing its binding interactions with the tubulin binding site.

Of the reduced dictyostatin derivatives **14**, **16**, and **17**, saturation of the (10*Z*)- or (2*Z*)-alkene appeared to affect the antiproliferative activity of dictyostatin the least, with a low nanomolar cytotoxicity for **14** and **16** comparable to discodermolide being observed across the non-resistant cell lines. Interestingly, the cytotoxicities of the 2,3-dihydro- (**16**) and 2,3,4,5-tetrahydro- (**17**) analogs were better in the resistant NCI/ADR-RES cell line than the 10,11-dihydro compound **14**, indicating their relative abilities to circumvent the P-glycoprotein pump. Predictably, both *iso*dictyostatin derivatives **48** and **49** were much less active (low micromolar) in all four cell lines, presumably due to large alterations to the bioactive conformation of dictyostatin as a result of the 22- to 20-membered ring contraction.

In addition to these cytotoxicity assays, experiments were carried out to determine if these synthetic analogs shared the microtubule-stabilizing mechanism of action of dictyostatin [13]. All of the analogs upon analysis of the cell cycle showed a $G_2$/M phase block, and in confocal microscopy imaging showed the patterns of microtubular bundling characteristic of microtubule-stabilizing agents such as Taxol and dictyostatin. Similarly, the more potent cytotoxic analogs were able to induce both apoptosis and microtubule stabilization in the PANC-1 cell line at lower concentrations than the less potent analogs.

## HYBRIDS OF DICTYOSTATIN AND DISCODERMOLIDE

### Synthesis of hybrids 50 and 51

Considering the structural and stereochemical homology between dictyostatin and discodermolide, it was proposed that constraining the conformationally more flexible discodermolide into the 22-membered macrocycle of dictyostatin might provide an active hybrid of these two natural products [21,22]. Initial molecular modeling studies, whereby the lowest energy conformation of "macrocyclic discodermolide" **50** was overlaid with the X-ray-derived 3D structure of discodermolide, indicated pronounced conformational similarities (Fig. 3).

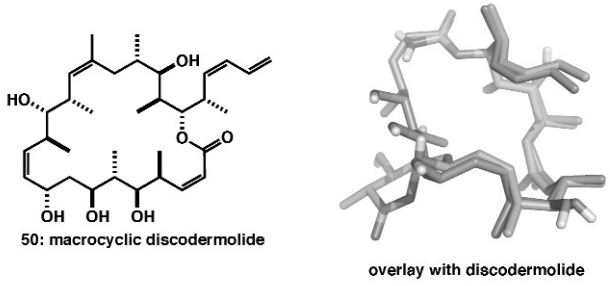
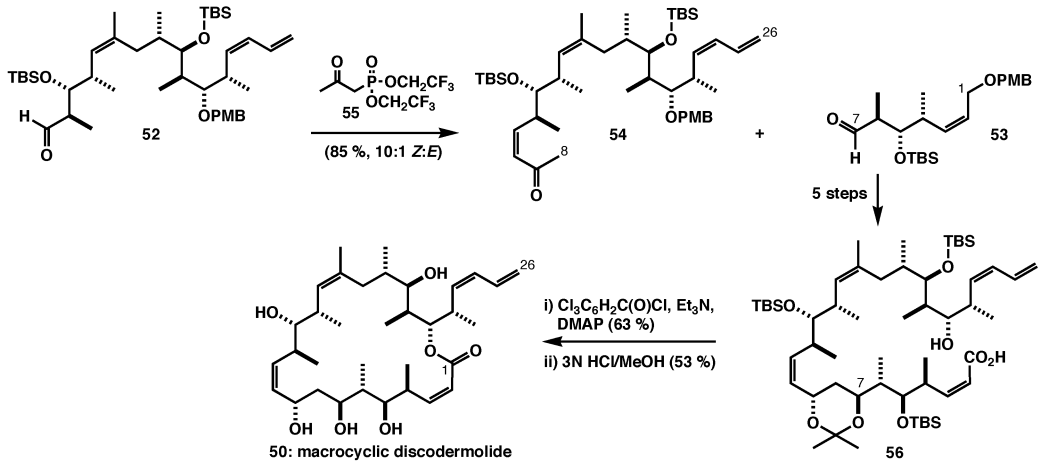



**Fig. 3**

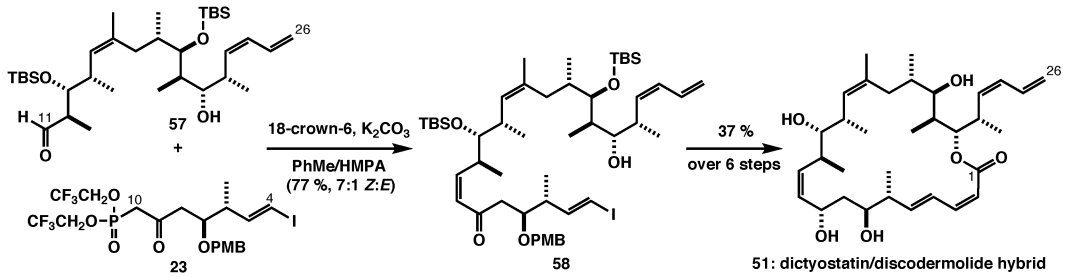
Hence, a synthesis of **50** was embarked upon employing intermediates available from the group's earlier synthetic work on discodermolide (Scheme 9) [17,21a]. A key 1,6-*anti* boron aldol reaction [17c,d] was employed to couple the C1–C7 aldehyde **53** with the C8–C26 methyl ketone **54** (obtained by a Still–Gennari olefination of aldehyde **52** with phosphonate **55**) with excellent levels of stereo-




**Scheme 9**

induction at C7 (>95:5 dr). Subsequent manipulation of the aldol adduct provided the acid **56** for Yamaguchi macrolactonization, yielding after global deprotection macrocyclic discodermolide **50** in readiness for biological evaluation.

Next, a more dictyostatin-like hybrid **51** (Scheme 10) was designed after examination of a superimposition of the NMR-determined bioactive conformations of discodermolide and dictyostatin docked into the taxoid binding site on β-tubulin [11]. The superior binding affinity of dictyostatin was postulated to be at least partly attributable to the C1–C5 dienoate region. Hence, macrocyclic hybrid **51** was proposed, featuring identical substitution and stereochemistry to discodermolide from C8 through to C26, and dictyostatin from C1 through to C7. In this case, suitable intermediates from both our discodermolide and dictyostatin synthetic campaigns could be utilized [21b]. A Still–Gennari olefination of the C11–C26 aldehyde **57** (from discodermolide) with the C4–C10 phosphonate **23** (from dictyostatin) gave the (*Z*)-enone **58**, and this was elaborated into the designed hybrid **51** in readiness for biological evaluation.




**Scheme 10**

## Biological evaluation

Employing the same cytotoxicity assay described before, macrocyclic discodermolide **50** and hybrid **51** were evaluated in vitro against a panel of human cancer cell lines (Table 1). The moderate cytotoxicity (single digit micromolar) determined for **50** indicated that this macrocyclic discodermolide had inferior biological activity, and hence reduced binding affinity, relative to the natural product. Gratifyingly, a much better result was obtained with the more dictyostatin-like hybrid **51**, where low nanomolar cyto-

toxicity was obtained across all four cell lines, intermediate between that of discodermolide and dictyostatin. Furthermore, cell cycle analysis and confocal immunofluorescence microscopy imaging revealed both agents induced $G_2$/M block and significant intracellular microtubular bundling, characteristic of typical microtubule-stabilizing agents, although as expected at significantly different concentrations. Hybrid **51** represents a promising new potent dictyostatin analog for further biological studies and is available by an efficient total synthesis using our lactate aldol chemistry [21b,23].

## CONCLUSIONS

A diverse set of dictyostatin analogs (**10–17**) and hybrids with discodermolide (**50** and **51**) have been prepared by total synthesis, exploiting a common strategy. Significant progress has been made in defining the pharmacophore region of this potent antimitotic macrolide and understanding the structural requirements for maximizing its interactions with the taxoid binding site on β-tubulin. SAR conclusions made in respect to the cytotoxicity data appear to correlate well with preliminary docking studies, facilitating the design and synthesis of potent dictyostatin analogs and hybrid molecules with a greater accuracy. In the longer term, this approach may lead to anticancer drug candidates with significantly increased cytotoxicity and reduced resistance relative to their parent natural products.

## ACKNOWLEDGMENTS

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