The Structure Activity Relationship of Discodermolide Analogues

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Abstract: The marine polyketide discodermolide is a member of a class of natural products that stabilize microtubules. Many analogues have been synthesized suggesting that few changes can be made to the internal carbon backbone. Both ends of the molecule, however, can be modified. The majority of analogues have been generated *via* modification of the lactone region. This suggests that significant simplifications can be made in this region provided that the lactone moiety is maintained.

INTRODUCTION

(+)-Discodermolide **1** was first isolated from the Caribbean sponge *Discodermia dissoluta* in 1990 [1]. The molecule, a polyketide (Fig. **1**), is characterized by 13 stereocentres, two cis double bonds and a terminal diene. It was first thought to be an immunosuppressant [2], but was later shown to target the microtubule system, through the binding to tubulin [3, 4]. This binding results in stabilization of microtubules leading to cell cycle arrest in the G2 and M-phase and ultimately apoptosis, placing it in a class of molecules including the taxanes and epothilones. Indeed, discodermolide binds microtubules more strongly than paclitaxel, and displaces it from microtubules [5]. However, cells with tubulin mutations that show resistance to paclitaxel are not resistant to discodermolide, suggesting that the two molecules have overlapping but not identical binding sites [6]. It is interesting to note that discodermolide also shows synergy with paclitaxel both *in vitro* and in *in vivo* tumor models [6, 7, 8], something that is not observed with paclitaxel and epothilones. It is thought that the *in vivo* synergy may be a result of the superior suppression of angiogenesis compared with the two agents individually.

Discodermolide shows low nanomolar antiproliferative activity across a range of human cancer cell lines. Importantly, it is active against multi-drug resistant (MDR) cell lines which are resistant to paclitaxel through over-expression of the P-glycoprotein efflux pump (eg NCI/ADR) and certain tubulin mutants (eg A549/t12) (Table 1). Further, discodermolide has greater water solubility than paclitaxel [3]. It was this exciting activity that resulted in a Phase I clinical trial being initiated by Novartis in 2001 [9]. While there were encouraging results from this trial it was suspended due to adverse toxicity at higher doses.

The natural product is only isolated in low yield from the sponge (0.002% w/w from frozen sponge). To date it has not been possible to obtain the genes responsible for its biosynthesis or to culture the producing organism, postulated to be a symbiont of the sponge. Due to the scarcity of discodermolide from natural sources, the material necessary for the clinical trial (over 60 g) was generated synthetically [11] - a notable effort given the complexity of the molecule.

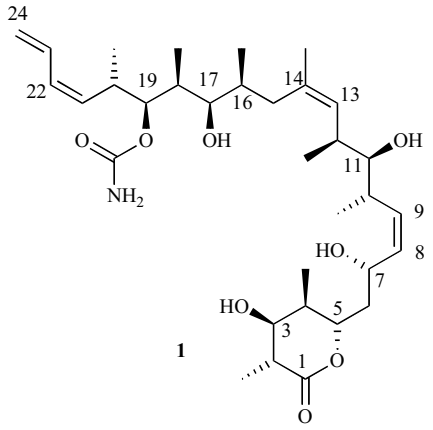

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Fig. (1).

TOTAL SYNTHESES

Discodermolide proved to be an attractive target for synthetic organic chemists with Schreiber reporting the first total synthesis, initially of the enantiomer, in 1993 [12]. Several syntheses have followed from a number of research groups [13]. Of these, both the Paterson and Smith groups have refined their synthetic approaches to make them shorter and easier to achieve [14, 15]. In general all the syntheses to date take a similar approach - the molecule is cut into three fragments (A-C) of approximately equal complexity, which are then coupled together. The Smith group went further and identified a stereo triad which appears in all three fragments. In this way it was possible to begin with a common precursor to generate these three fragments (Fig. **2**) [16].

All the current syntheses begin by coupling the A and B fragments before attaching the final C fragment, which accounts for the greater number of analogues in the lactone portion of the molecule. The Novartis group used the Smith approach to generate the AB **2** from the A and B fragments (**3** and **4** respectively) combined with the Paterson approach to coupling the C fragment **5** in their synthesis of the phase I material (Scheme **1**) [11].

Recently there have been approaches to generate discodermolide through the assembly of small polyketide units

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Table 1. Cytotoxicity of Discodermolide in Cell Lines Sensitive and Resistant to Paclitaxel [10]

	Antiproliferative Activity (nM)			
	A549	**MCF-7**	**NCI/ADR**	**A549/t12**
Discodermolide	22	28	240	30
Paclitaxel	8	4	2000	44

obtained from fermentation – the fragment assembly approach [17, 18]. This may ultimately provide a useful technology not only to produce discodermolide but also to produce other polyketides which cannot be obtained efficiently from nature.

THE STRUCTURE OF DISCODERMOLIDE

In the original work describing the isolation and characterization of discodermolide an X-ray crystal structure was reported [1]. In addition, there have been two solution structures reported in acetonitrile [19] and DMSO [20]. There is considerable agreement between the solid state and the solution structure reported by Smith, in which the molecule adopts a sickle motif resulting from the *syn*-pentane interactions along the carbon backbone as well as the geometric constraints of 8,9- and 13,14-cis double bonds. In the second NMR structure, discodermolide is reported to adopt primarily three different conformations. The most populated of these is a corkscrew, while the second most populated is the sickle structure observed in the solid state. The final conformation is an extended or awl form. However, which conformation, if any, the molecule adopts to bind to tubulin is unknown. It is interesting to note that all three structures support the substituents about the lactone ring adopting equatorial positions. This requires the ring to be in a flattened twist-boat conformation.

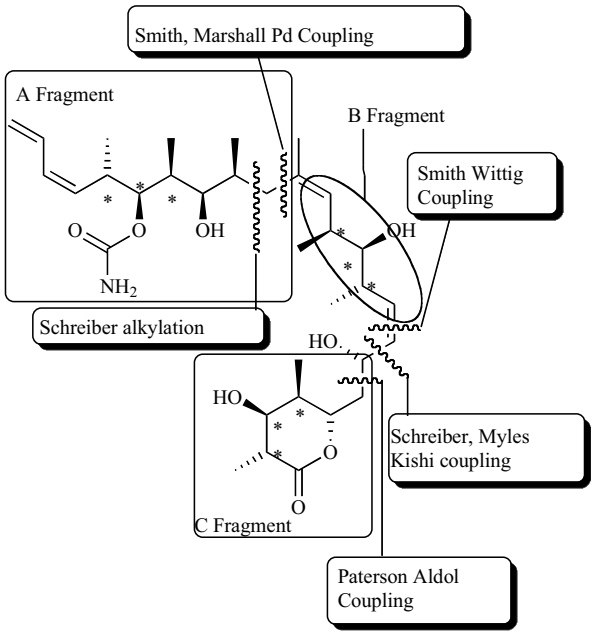


Fig. (2).

STRUCTURE ACTIVITY RELATIONSHIPS

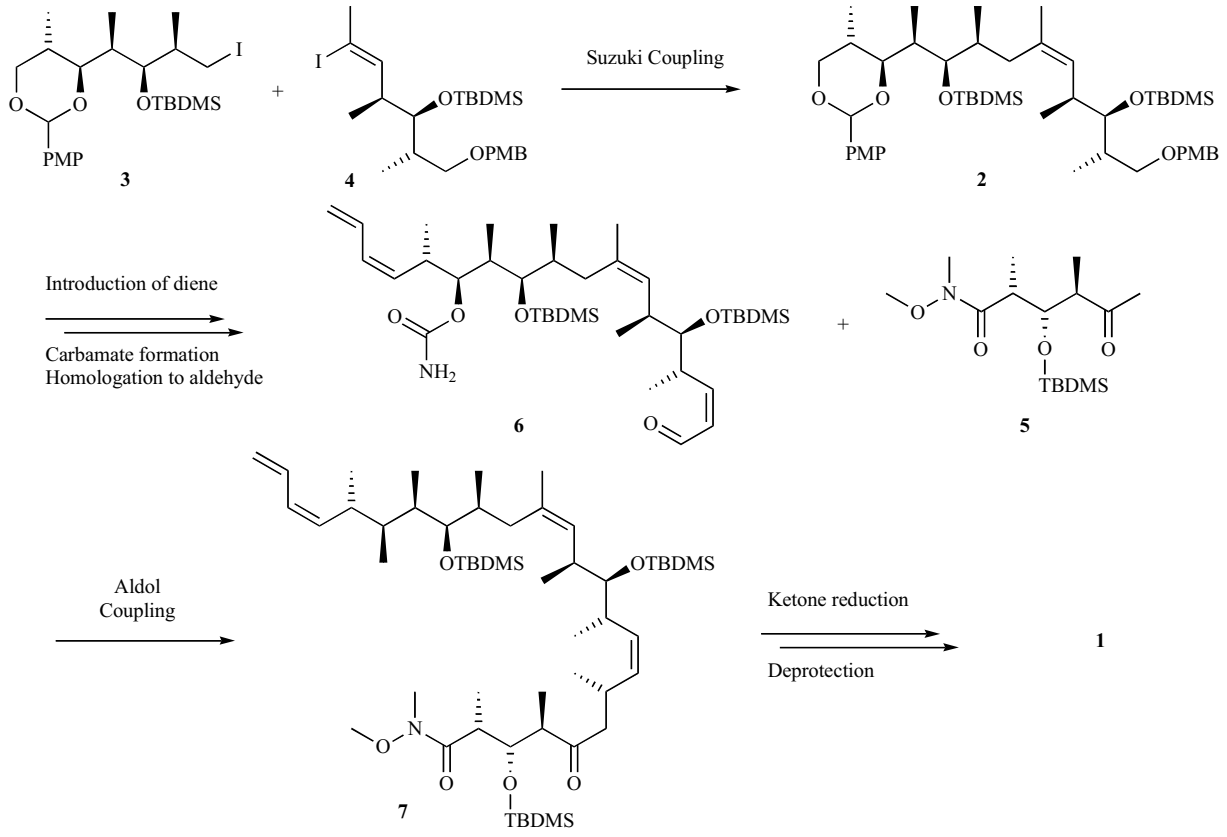
There have been many analogues of discodermolide synthesized either through semi-synthesis, as by-products in total syntheses, or as tagged derivatives for the further understanding of the biology behind the activity, which have helped to determine the requirements necessary for potent antiproliferative activity. In conjunction, there have been a number of studies both in academia and industry directed towards generating analogues. Together these studies have defined the necessary requirements for activity and therefore a structure activity relationship for discodermolide.

A FRAGMENT ANALOGUES

Modifications in the A fragment of discodermolide were some of the first modifications investigated. While attempting to attach linkers to investigate affinity binding, the Schreiber group appended a linker to the terminal diene [21]. The linker unit led to a compound that maintained nanomolar antiproliferative activity, suggesting that there is space to accommodate larger groups in this position. A similar result was obtained when both a photoaffinity tag **8** and a fluorescent probe were attached at this position [22]. Despite the significant increase in size of the molecules, they showed potencies similar to discodermolide. The Novartis group went on to systematically study the diene region by synthesizing a series of analogues in which the diene was successively reduced to the 23,24-dihydro **9** and 21,22,23,24-tetrahydro **10** compounds (Fig. **3**) [23].

The results of this study suggest that the reduction of the terminal olefin does not impact the antiproliferative activity and may perhaps lead to a more active compound. However, there is a reduction in potency, especially in resistant cell lines when both double bonds of the diene are reduced. This suggests that the internal cis double bond may be required for optimal activity. The Novartis group went further in replacing the diene with either a phenyl or benzyl ether that were both reduced in potency by 10 to 100-fold. Both of these compounds lack the cis alkene, confirming this as a necessary requirement for high potency. Removing the diene is desirable since it simplifies the synthesis and may remove a potential site of metabolism. Indeed a series of analogues have been made in the 23,24-dihydro series (*vide infra*). It may be possible that the diene region could be used as a means of introducing groups to tune to pharmacokinetic (PK) parameters of the molecule.

A second site for tuning PK properties has been the carbamate region. The de-carbamoyl compound has been iso-



Scheme 1.

lated from the sponge and shows a 5-10 fold drop in potency compared with discodermolide [24]. A series of analogues have been synthesized in which alkyl or aryl groups were attached to the nitrogen of the carbamate [25]. In this series both non-polar and polar groups showed potencies similar to discodermolide in sensitive cell lines, however, in the cell line expressing the P-glycoprotein efflux pump, almost all the analogues were inactive.

There have been few A fragment analogues in the remainder of this region. Those synthesized suggest that the configuration of the stereocentres is crucial to activity. Both the 17-epimer and 16, 17-epimer were completely inactive [26, 21]. However, the 16-de-methyl compound **11** showed low nanomolar antiproliferative activity similar to the natural product (Fig. **4**). By contrast, adding a linker for affinity binding at the 16-position resulted in an inactive molecule. Esterification of the 17-hydroxyl has also been investigated. Schreiber suggests that the 17-acetyl compound **12** is within 10-fold of discodermolide and a second 17-ester with a linker to investigate affinity binding is similarly active [21]. By contrast, the semi-synthetic 3-,17-diacetyl compound **13**

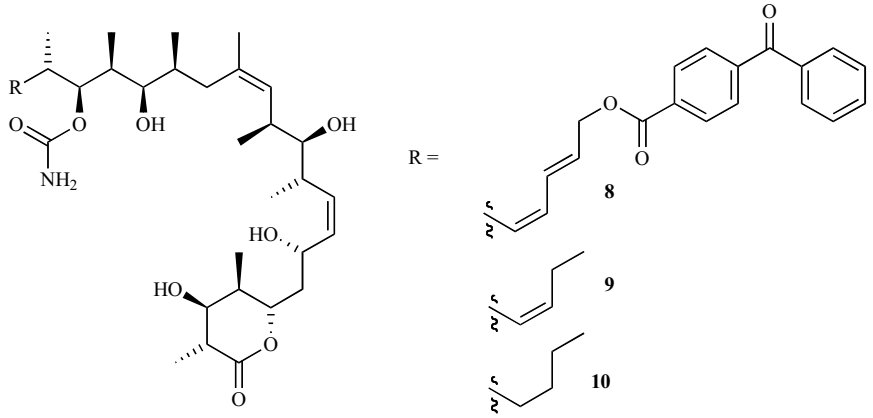


Fig. (3).

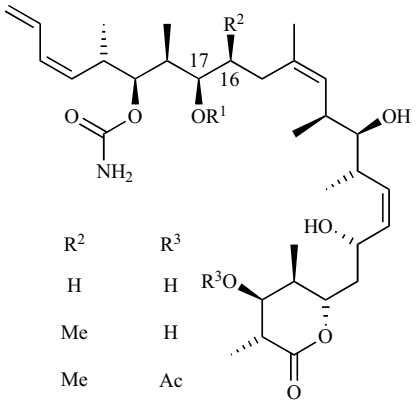


Fig. (4).

is reported to be inactive, which is thought to be due to the 17-acetyl group since the 3-acetyl compound is similar in activity to discodermolide [27]. In addition the 2,3-anhydro-17-acetyl-discodermolide is inactive [28]. Again this is considered to be a consequence of the 17-acetyl group since the 2,3-anhydro-discodermolide is a potent compound (vide infra).

Based on the structure of the molecule both in the solid state and in solution it is not surprising that epimerization of stereocentres in this region has a big impact on the ability of the molecule to bind tubulin and as such exert its activity. The relevance of the 17-hydroxyl is unclear at this time and further analogues will be required to resolve the confusion. The 16-de-methyl compound **11** activity may be of utility in the design of simplified analogues.

THE AB LINKAGE

Based on the exciting activity of the 16-de-methyl compound, Smith investigated the 14-de-methyl compound **14** (Fig. **5**) [29]. This molecule was particularly attractive from the synthetic point of view since it simplified the formation

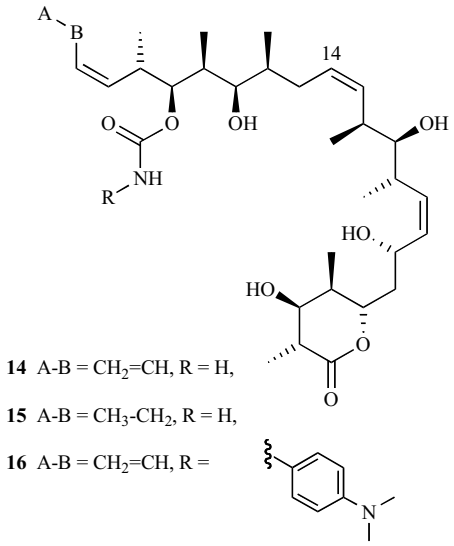


Fig. (5).

of the B fragment and eased the formation of the phosphonium salt required to couple the C fragment. The potency of this molecule is within a factor of two of discodermolide itself, however, there is a considerable drop in potency in the MDR cell line. The synthetic simplification in conjunction with the retention of activity led to a number of analogues being generated based on this scaffold [30, 25]. The SAR of the 14-de-methyl-discodermolide scaffold is similar to that discussed above in the diene and carbamate region of the molecule, with the 23,24-dihydro-14-de-methyl molecule **15** being similar in potency to both **14** and **1** while the *N*,*N*-dimethylanaline substituted carbamate **16** was more potent. Again these molecules are not active in the MDR cell line suggesting that removal of the 14-methyl group makes the molecules better substrate for the MDR efflux pump.

Making changes in the lactone C fragment of the molecule in conjunction with the 14-de-methyl does not correlate well with the trends in the discodermolide series; however, more analogues would be needed to investigate this trend more fully.

To further investigate the effect of the methyl group at the 14-position, Smith developed a route to two cyclopropane analogues (the 13*R*, 14*R* **17** and the 13*S*,14*S*), reasoning that the cyclopropane function would effectively re-introduce the 14-methyl group while maintaining a similar conformation about this region of the molecule (Fig. **6**) [31].

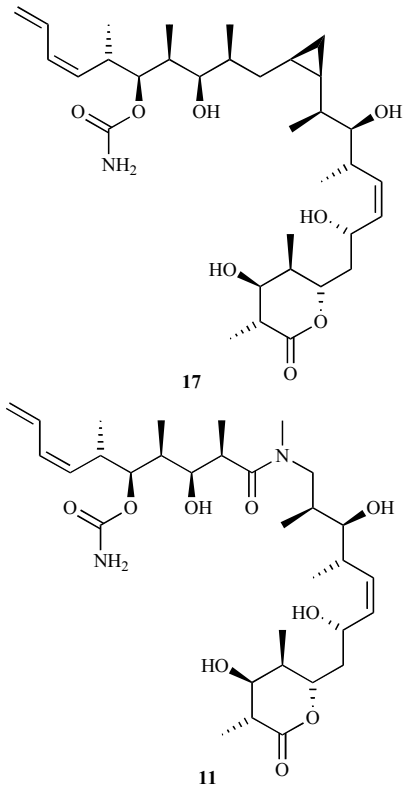


Fig. (6).

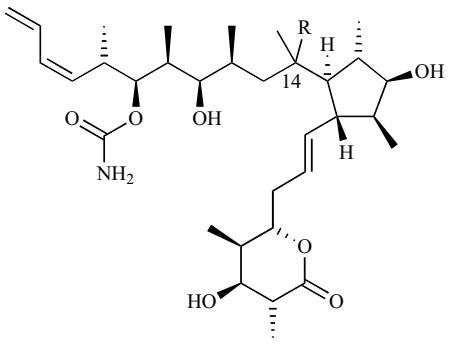
While both molecules show antiproliferative activity, there is a drop in potency relative to both discodermolide **1** and 14-de-methyl-discodermolide **14**. Interestingly, these

molecules are only micromolar cytotoxins in the resistant cell line. These results suggest that the cyclopropane cannot substitute for the methyl group at the 14-position. It seems likely that neither diastereomer of the cyclopropane is able to mimic the double bond perfectly.

A second strategy for simplifying the coupling of the A and B fragments was developed by the group at Novartis, who replaced the double bond by with a *N*-methylamide isostere [32]. While this modification makes the linking of the A and B fragments tri*via*l it resulted in a compound that was 50-1000 fold weaker. In this molecule the isosteric replacement is effectively at the 14,15-position compared with the 13,14-position of the double bond, which may have an impact on the activity.

THE B FRAGMENT AND BC LINKAGE

In the B fragment region of the molecule there have been few analogues synthesized. This is probably due to the importance that this region of the molecule is thought to have on correctly orienting the molecule. Those compounds that have been reported confirm the crucial nature of this part of the molecule; the 3,11-diacetyldiscodermolide is 10-fold lower in potency compared to the 3-acetyldiscodermolide [27], while acylation of the 11-hydroxyl of 2,3-anhydrodiscodermolide reduces the potency by 10 to 100 times [28]. In producing sufficient quantities of discodermolide for the clinical study a number of very minor impurities were isolated from the final acidic deprotection step. These included a number of 9,13-cyclopentane analogues either with or without a hydroxyl at the 14-position (**18** and **19** respectively) (Fig. **7**) [33]. Not surprisingly, none of these molecules is particularly potent with most having IC_{50} values in the micromolar range, although given the structural change it is difficult to read a great deal into these analogues.



18 R = H

19 R = OH

Fig. (7).

The 8,9-cis double bond linkage appears to assist in positioning the lactone. Not surprisingly, the 8,9-trans analogue, obtained as a minor product in the Smith discodermolide synthesis, shows a 100-fold drop in potency relative to discodermolide [29]. However, the saturated version generated by semisynthesis, in which the diene was also saturated, has a less dramatic effect on potency compared to the tetrahydrodiscodermolide **10** [28]. It is noteworthy that inserting a methyl group at the 8-position to form a tri-substituted double bond is well tolerated [34]. This suggests that there may be space to explore analogues in this region of the molecule, potentially improving binding or introducing groups to tailor PK properties.

C FRAGMENT

It is in the C fragment that the most analogues have been generated. These analogues have led to a good understanding of the SAR in this region of the molecule and to several compounds that have been considerably simplified but still maintain low nanomolar antiproliferative activity even in resistant cell lines.

In the course of several total syntheses, the 7-epi compound has been generated [35, 36]. While it not surprising that inversion of this stereocenter has a deleterious effect on potency, simply removing the hydroxyl has little effect, while acetylation of this position results in a compound **20** (Fig. **8**) that is almost 10-fold more potent than discodermolide. These results suggest that the hydroxyl is not involved in a hydrogen bonding interaction with tubulin [27]. Indeed a similar observation is made when the 7-hydroxyl is alkylated to form either a methoxymethyl **21** or methyl ether **22** [34]. The excellent potency of the 7-alkyl ethers is retained in lactone analogues that do not have the 3-hydroxyl group, suggesting that this is a consistent SAR point across scaffolds [31].

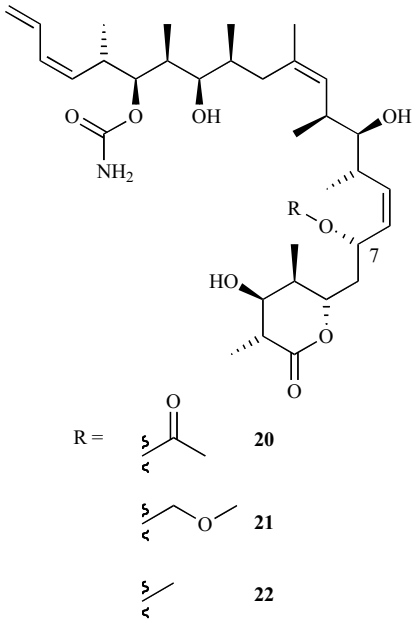


Fig. (8).

In the lactone ring itself, the 2,3-anhydrodiscodermolide **23** was isolated through semisynthesis and as a by-product of total synthesis (Fig. **9**) [28, 29]. It is more potent than the natural product. Further the 3-acetyl-discodermolide has improved potency over discodermolide [27]. It is interesting to note that the carbamate SAR developed in the discodermolide series does not translate to the 2,3-anhydro scaffold, where the substituted carbamates are all significantly less potent than **23** itself [25].

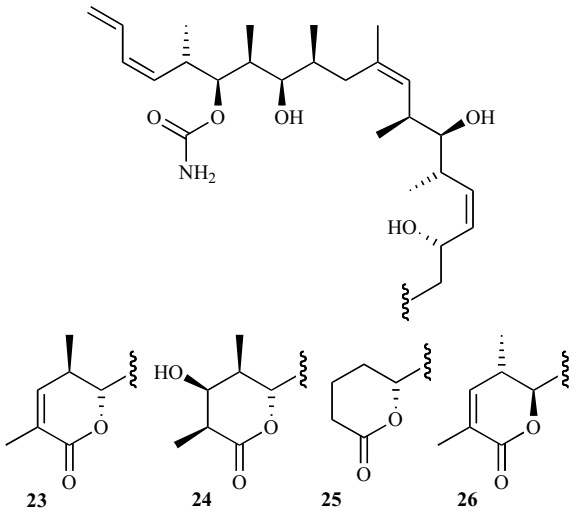


Fig. (9).

The 3-position has been probed further in the 23,24-dihydro series in which both the 3-methoxy- and 3-deoxy-discodermolides were synthesized [37]. Both compounds have potencies in the single digit nanomolar range. These data taken together suggest that the 3-hydroxyl is not required for activity. This appears to be the case with all the substituents around the lactone ring. Removing the 2-methyl group from 2,3-anhydro compound **23** has no effect on potency [38], however, inversion of the stereocenter is deleterious to activity as is exemplified by 2-*epi*-discodermolide **24** isolated from a *Discodermia* species of sponge [24]. This molecule is 5 to 10-fold less potent than discodermolide. The same is observed in **25** where three substituents from the 2-, 3-, and 4- positions have been removed. This molecule maintains single digit nanomolar activity against sensitive cell lines, although there is a lowering in potency against the resistant cell line [38]. Perhaps even more surprising is the observation that compound **26** with inversion of both the 4- and 5-stereocentres of 2,3-anhydrodiscodermolide **23** has similar antiproliferative activity (Fig. **9**). These results can be rationalized by considering the solution and solid-state structures discussed above. In these, it appears that the ring adopts a twist-boat conformation with all the substituents equatorial, resulting in a planar ring. The SAR discussed above is in line with these structures, for inverting a single stereocenter lowers potency, presumably due to a resultant change in the conformation of the ring. However, if a substituent is removed, the ring can still maintain the same conformation. In the case of the 2,3-anhydro-4,5-epi compound **26**, the ring can maintain a planar conformation as both substituents have been inverted.

Several groups have tried to make simplified analogues in the lactone ring by replacing it with an aromatic group. Given the planar nature of the ring this is a reasonable isosteric replacement. The first two compounds of this type were reported in 2002 [39], and suggested great promise. The phenol analogue **27** has antiproliferative activity within 3-fold of discodermolide. Interestingly it was subsequently reported that the 7-deoxyphenol analogue **28** (Fig. **10**) shows only a slight lowering in potency over **27** [40]. The resulting

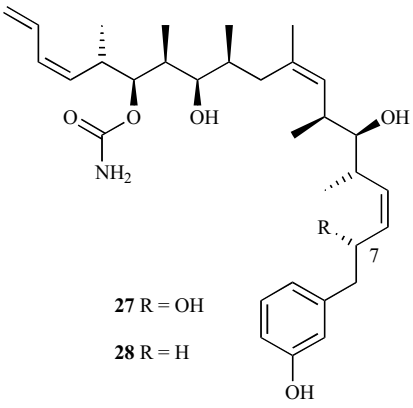


Fig. (10).

compound is significantly simplified over the natural product and provided an ideal starting point to optimize potency.

Investigation into this class of compounds with a range of electron-rich and electron-deficient substituted aromatics was not able to improve upon this lead. Indeed while the compounds have sub-micromolar potencies, there was no clear SAR, save for the phenol compounds being significantly more potent.

It is interesting to note that many of the aromatic derivatives are similar in potency to that of the truncated C-24 to C-7 portion of discodermolide. Since the substituents about the lactone ring do not appear to be critical, these results suggest that the 100-fold difference in potency can be at least partially explained by the lactone moiety itself. There are very few compounds to probe the lactone more fully; however, a ring-opened 3-deoxy methyl ester has been reported as well as a molecule in which the lactone has been replaced by a carbamate [37]. Both compounds (reported in the 23,24-dihydro series) have micromolar potencies similar to many of the aromatic compounds. By contrast, provided the lactone moiety is retained the C fragment can be simplified. The most striking example of this is the butyrolactone **29** (Fig. **11**) [38]. The molecule not only lacks the three substituent found in the natural product, but is also ring-contracted. Nevertheless, it shows equivalent or improved potency over discodermolide in both sensitive and resistant cell lines. These data suggest that the lactone ring functions as a template for positioning the lactone moiety to make a critical interaction with the tubulin. The molecule provides significant advantages in terms of synthesis for, using the Paterson aldol approach, the lactone C fragment is synthesized in one-step from leuvilinic acid. Going a step further the coumarin derivative **30** removes the five stereocentres found in the C fragment and has similar potency **1** emphasizing the role of the ring in positioning the lactone for optimal potency [41].

FURTHER SIMPLIFIED MOLECULES

A number of simplified analogues have been synthesized in which a range of A and C fragments with reduced complexity were investigated while retaining the intact B fragment. In particular, the 14- and 16-methyl groups were removed along with the 7-hydroxyl. The diene was varied and

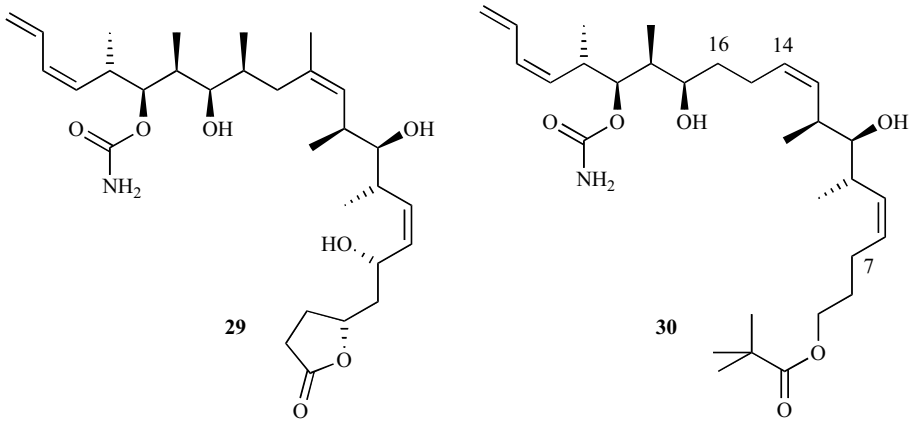


Fig. (11).

the lactone moiety either varied or replaced with a range of simple esters, eg **31** (Fig. **12**) [42, 43].

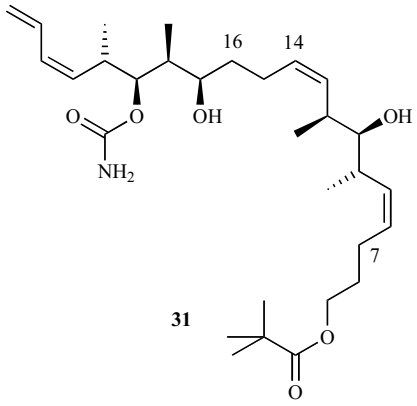


Fig. (12).

Although the molecules had antiproliferative activities in the micromolar range, they do still interact with tubulin [44].

IMPLICATIONS FOR DICTYOSTATIN

The marine polyketide dicytostatin **32** was first reported by Petit in 2004 [45]. The stereochemistry was determined in 2005 through both NMR analysis and total synthesis [46, 47, 48]. Dictyostatin, which can be considered to be a cyclic version of discodermolide (Fig. **13**), shares a similar mechanism of action and shows sub-nanomolar potencies across a range of cell lines.

Analogues of dictyostatin are currently being investigated and the SAR developed for discodermolide may well prove to be useful in this respect. Already the 16-de-methyl dictyostatin, which can be considered to be analogous to the 14-de-methyl discodermolide, has been synthesized and shown to be a very potent compound [49].

CONCLUSIONS

Despite the complexity of discodermolide a significant number of analogues have been synthesized, which have helped to define the critical requirements for high activity. The key components are shown in Fig. (**14**). In particular, while the carbon backbone is required to set the overall conformation of the molecule the diene, carbamate, and lactone regions provide opportunities to develop analogues with improved potency or pharmacokinetic properties. Within the SAR there is the opportunity to simplify the molecule, which is important given that total synthesis is the only route to discodermolide at this point. The SAR developed for discodermolide may be a useful starting point from which to investigate dictyostatin analogues.

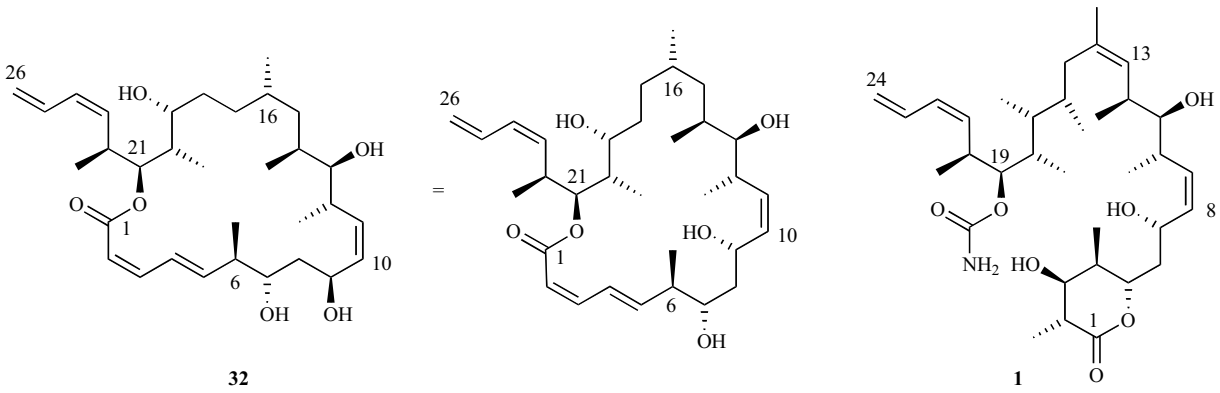


Fig. (13).

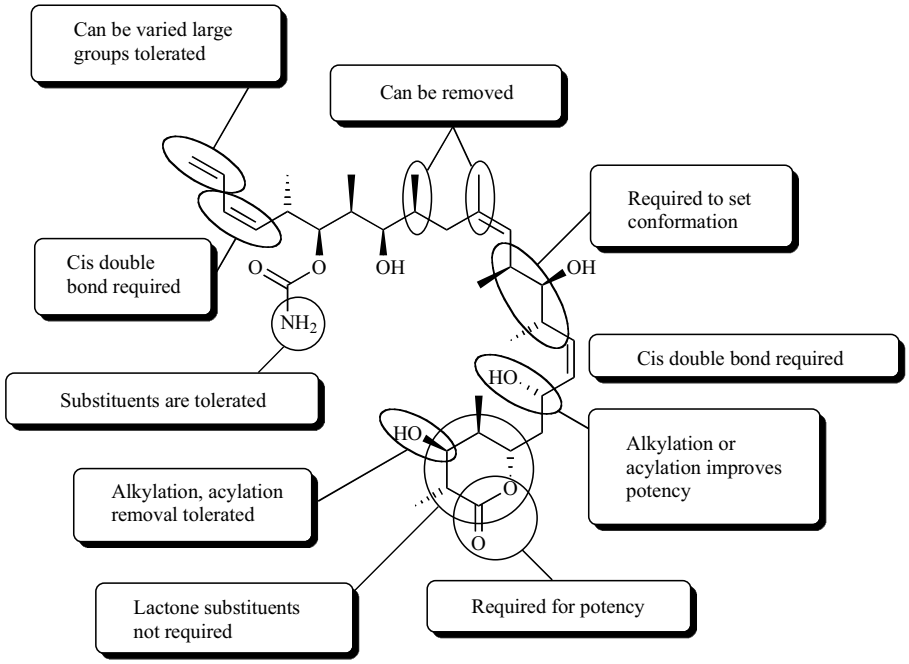


Fig. (14).

ACKNOWLEDGEMENTS

I would like to thank Drs John R. Carney and Gary W. Ashley (Kosan Biosciences, Inc) for helpful comments concerning this manuscript.

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Received: 07 October, 2006 Revised: 28 August, 2007 Accepted: 29 August, 2007

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