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Discodermolide/Dictyostatin Hybrids: Synthesis and Biological Evaluation[†]

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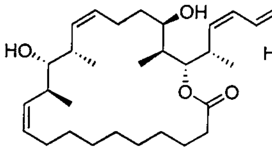
ABSTRACT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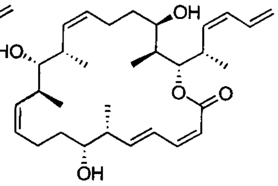
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Two hybrid analogues of discodermolide and dictyostatin (3, 26) have been designed and synthesized. These are the first macrocyclic analogues of discodermolide and biological activities were evaluated and compared with linear discodermolide analogues.

Discodermolide **1** is a polyketide natural product isolated from the deep-water Caribbean sponge *Discodermia dissoluta* that possesses potent antimitotic and substantial immunosuppressive activity (Figure 1).[1] It has a mode of action similar to that of paclitaxel (Taxol), arresting the cell cycle at the M phase, but it remains potent against multidrug resistant (MDR) carcinoma cell lines.[2] Several groups have reported total syntheses of discodermolide,[3] and we have developed a flexible synthetic route to make discodermolide analogues that lack the natural product's C7-OH, C14-Me, and C16-Me groups. These omissions were based on conformational and SAR (Structure Activity Relationship) analyses.[4]

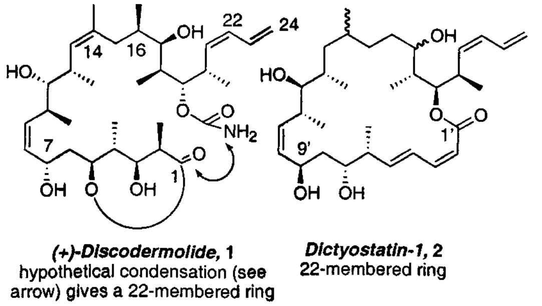

Figure 1. Structures of discodermolide and dictyostatin-1.

The discodermolide-like macrocyclic natural product dictyostatin-1 has been isolated by Pettit and assigned the structure **2**.[5] It exhibits antiproliferative activity superior to **1** (ED$_{50}$ 0.38 nM, P388 leukemia cells), and the configurations of two stereocenters at C16′ and C19′ and the absolute configuration are as yet unassigned.[5]

Structures of **1** and **2** have notable similarities, although the carbon backbone of dictyostatin **2** is two atoms longer

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[†] Dedicated to Professor Andrew S. Kende.

(1) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem*. **1990**, *55*, 4912; (correction) **1991**, *56*, 1346.

(2) (a) Ter Haar, E.; Kowalski, R. J.; Hamel, E.; Lin, C. M.; Longley, R. E.; Gunasekera, S. P.; Rosenkranz, H. S.; Day, B. W. *Biochemistry* **1996**, *35*, 243. (b) Kowalski, R. J.; Giannakakou, P.; Gunasekera, S. P.; Longley, R. E.; Day, B. W.; Hamel, E. *Mol. Pharmacol.* **1997**, *52*, 613.

(3) Paterson, I.; Florence, G. I.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc*. **2001**, *123*, 9535 and references therein.

(4) (a) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc*. **1996**, *118*, 11054. (b) Martello, L. A.; LaMarche, M. J.; He, L.; Beauchamp, T. J.; Smith, A. B., III; Horwitz, S. B. *Chem. Biol.* **2001**, *8*, 843. (c) Isbrucker, R. A.; Gunasekera, S. P.; Longley, R. E. *Cancer Chemother. Pharmacol*. **2001**, *48*, 29.

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and there are stereochemical and other differences. A hypothetical condensation of the carbamate NH_2 group of discodermolide **1** with the proximate[6] lactone carbonyl group (C1) gives a 22-membered ring (not shown), which is the same size as the ring in dictyostatin. This suggests that macrocyclic analogues of discodermolide will be of interest, and we report herein the synthesis of the first such analogues, which are in effect hybrids of discodermolide and dictyostatin-1.

Macrocyclic hybrid **3** with an alkyl chain bridging the lactone carbonyl group and the alkene was the initial target. This can be synthesized convergently from three components (**4**, **5**, and **6**) via sequential Wittig couplings[7] and a macrocyclization (Figure 2).

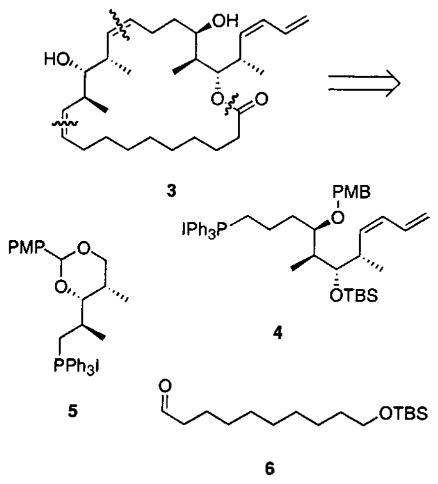
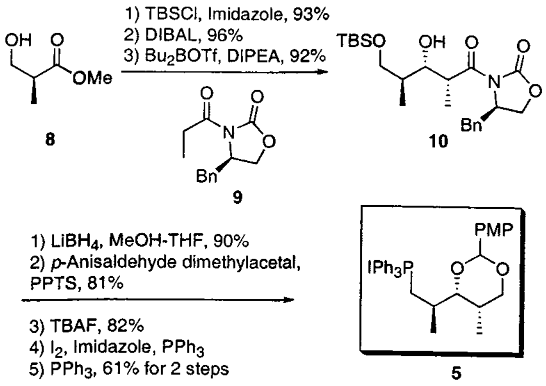


Figure 2. Retrosynthetic analysis of hybrid **3**.

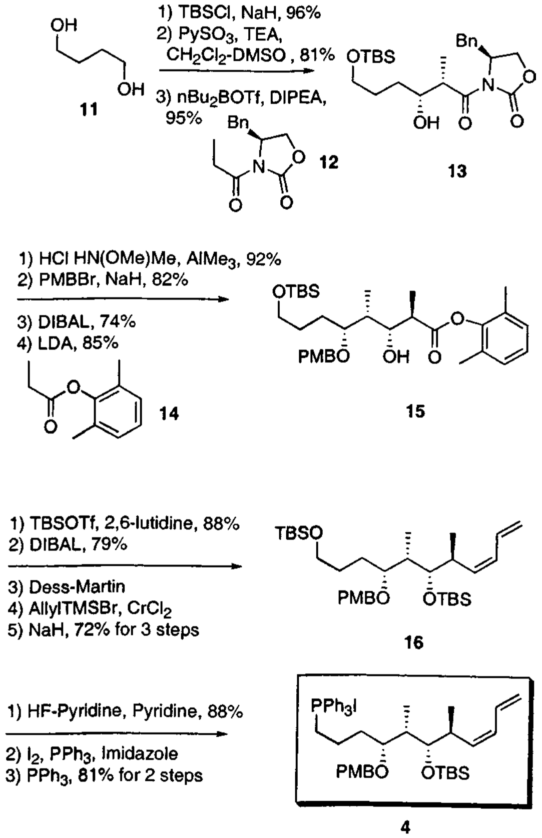
Fragment **6** was synthesized from 1,10-decanediol (**7**, not shown) by mono-TBS protection (NaH/TBSCl, 42%) followed by Dess−Martin oxidation (80%). Fragment **5** was prepared from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate **8** (Scheme 1). The aldehyde derived from TBS protection and DIBAL reduction of **8** was submitted to an Evans aldol reaction with **9** to produce **10** in excellent overall yield. Subsequently, **10** was reduced with $LiBH_4$ and protected with *p*-anisaldehyde dimethylacetal (PMP is *p*-methoxyphenyl). TBAF deprotection followed by conversion of the hydroxy group to an iodide and exposure of this to excess PPh_3 in refluxing benzene gave the phosphonium salt **5**.

Scheme 1



Fragment **4** was prepared starting from 1,4-butanediol (**11**, Scheme 2). Protection with TBSCl followed by oxidation yielded an aldehyde that was subjected to Evans *syn*-aldol conditions to give **13**. This product was converted to the Weinreb amide, and the secondary hydroxyl group was protected with *p*-methoxybenzyl bromide (PMBBr). DIBAL reduction yielded an aldehyde, which was reacted with **14** in an *anti*-aldol fashion to yield ester **15**.[8] The anti relationship was confirmed by comparing ^{13}C NMR chemical shift data with that of a reference compound.[9]

Scheme 2



The secondary hydroxyl group of **15** was then protected as a TBS ether. DIBAL reduction and subsequent oxidation

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(5) (a) Pettit, G. R.; Linchacz, Z. A.; Gao, F.; Boyd, M. R.; Schmidt, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1111. (b) The stereostructure is taken from the following patent: Pettit, G. R.; Cichacz, Z. A. US5430053, 1995. Given its similarity to discodermolide, dictyostatin-1 may be the enantiomer of **2**.

(6) For conformational studies of discodermolide, see: (a) Smith, A. B., III; LaMarche, M. J.; Falcone-Hindley, M. *Org. Lett.* **2001**, *3*, 695. (b) Monteagodo, E.; Cicero, D. O.; Cornett, B.; Myles, D. C.; Snyder, J. P. *J. Am. Chem. Soc.* **2001**, *123*, 6929.

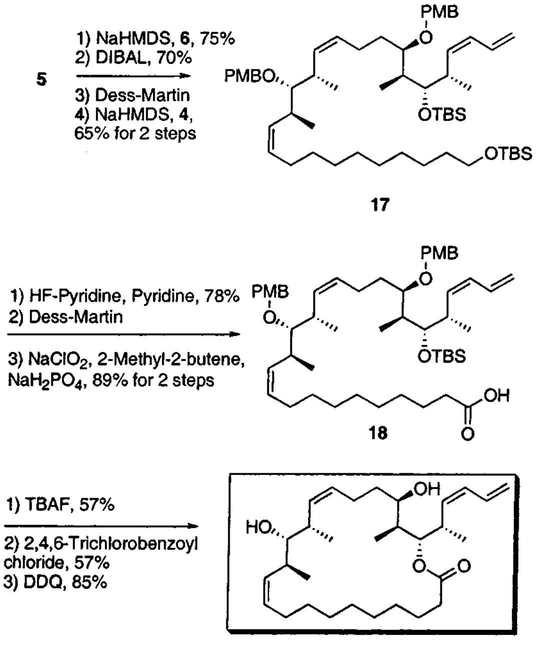
(7) Furukawa, T.; Curran, D. P. *Org. Lett.* **2002**, *13*, 2233.

(8) Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. *Tetrahedron* **1981**, *37*, 4087.

of the primary alcohol produced an aldehyde that was subjected to Peterson olefination[10] to install the required diene **16**. Selective deprotection of the primary TBS group of **16** worked well in a HF-pyridine solution with excess pyridine. The resulting alcohol was converted to an iodide, which in turn was treated with PPh_3 to give the foamy white phosphonium salt **4**.

The coupling of the three fragments is summarized in Scheme 3. Generation of the ylide from phosphonium salt **5** and NaHDMS followed by addition of aldehyde **6** gave the Wittig product in good yield (75%) provided that the reaction was conducted at high concentration (1 M in **5**). The formation of the *Z*-alkene was confirmed by the 10-Hz coupling constant between the vinyl protons.

Scheme 3



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Selective opening of the PMB acetal was accomplished by addition of 3 equiv of DIBAL to give a primary alcohol. This was oxidized to an aldehyde under Dess–Martin conditions. Wittig conditions similar to those above were then deployed to prepare **17** from this aldehyde and phosphonium salt **4**.

Selective deprotection of **17** was achieved using HF-pyridine and the resulting primary alcohol was oxidized to acid **18**. The other TBS group was then removed with TBAF. Using the Yamaguchi protocol,[11] the macrolactone ring was then constructed. PMB deprotection using DDQ provided target product **3**, whose protons and carbons were assigned by COSY and HMQC NMR experiments. The location of the macrolactone ring was confirmed by HMBC NMR experiments.

To gauge the effect of the macrocyclic system on biological activity, we also synthesized several acyclic reference molecules. Compounds **19**, **20**, and **21** were readily made from appropriate synthetic intermediates (**17** or **18**) in reasonable yields (Figure 3).

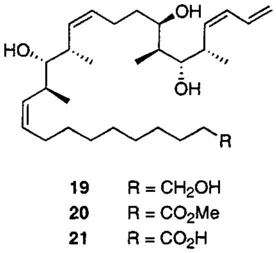

Figure 3. Acyclic compounds for biological testina.

These analogues were tested for antiproliferative activity in vitro against two human cancer cell lines (Table 1).[12]

Table 1. Human Cancer Cell Growth Inhibitory and Paclitaxel Displacing Properties of Macrolactone Discodermolide Analogues

	GI_{50} (μM)		
	MDA-MB-231 (breast)	2008 (ovary)	displacement of [^{3}H]paclitaxel (%)[c]
3	27 ± 1[a]	16 ± 1[a]	18 ± 5
19	18 ± 1[a]	22 ± 5[a]	21 ± 2
20	26 ± 3[a]	19 ± 2[a]	17 ± 1
21	>50[a]	>50[a]	16 ± 3
26	1.4 ± 0.1[b]	1.0 ± 0.1[b]	27 ± 8
1	0.016 ± 0.003[b]	0.072 ± 0.005[b]	64 ± 2

[a] 50% growth inhibitory concentration after 48 h of continuous exposure (mean ± standard deviation; $N = 4$). [b] 50% growth inhibitory concentration after 72 h of continuous exposure (mean ± standard deviation; $N = 4$). [c] Percent displacement by 4 μM test agent of 2 μM [^{3}H]paclitaxel bound to microtubules formed from 2 μM tubulin and 20 μM dideoxyGTP ($N = 6$, mean ± SD).

Macrolactone **3** and noncyclized alcohol **19** and ester **20** exhibited similar 50% growth inhibitory concentrations, in the 15–30 μM range. Carboxylic acid **21** was inactive (>50 μM) possibly due to poor cell membrane penetration. The modest activity of these compounds is encouraging given the simplicity and flexibility of their lower chain. We therefore decided to introduce the more complex bottom part of dictyostatin-1 **2** lacking only the C9′-OH group.

Synthesis of the needed aldehyde **23** (Scheme 4) started from the intermediate **13**, which was reduced to an alcohol

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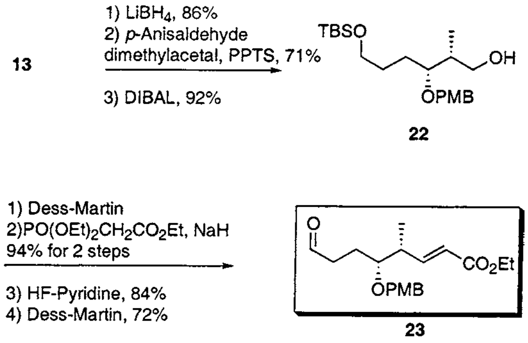
(9) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.

(10) (a) Andringa, H.; Heus Kloos, Y. A.; Brandsma, L. *J. Organomet. Chem.* **1987**, *336*, C41. (b) Paterson, I.; Schlapbach, A. *Synlett.* **1995**, 498.

(11) Inanaga, J.; Kuniko, H.; Hiroko, S.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(12) Wipf, P.; Reeves, J. T.; Balachandran, R.; Giuliano, K. A.; Hamel, E.; Day, B. W. *J. Am. Chem. Soc.* **2000**, *122*, 9391.

Scheme 4

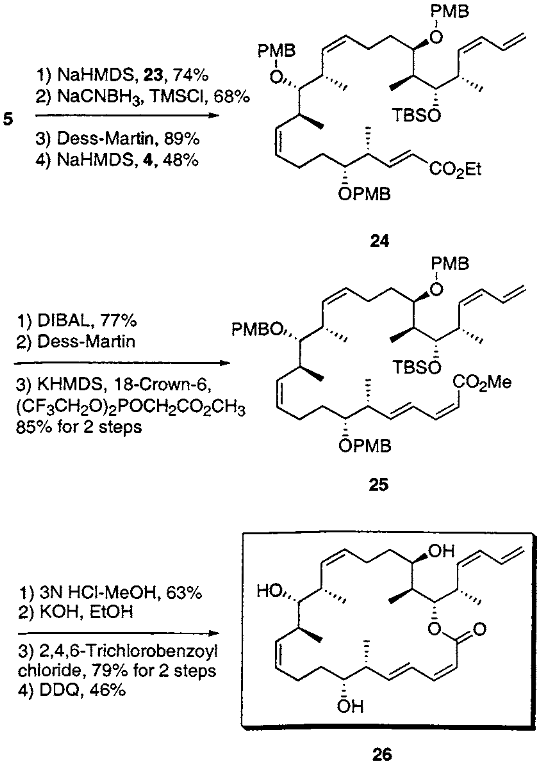


with $LiBH_4$, followed by PMB acetal protection. Selective acetal opening produced alcohol **22**, which was subjected to Dess–Martin oxidation to give an aldehyde. Wittig–Horner reaction and removal of the TBS group with HF-pyridine gave a primary alcohol, which was oxidized to aldehyde **23**.

Center part Wittig salt **5** was reacted with aldehyde **23** to give the (*Z*)-olefin (Scheme 5). This was followed by selective PMP acetal opening with $NaCNBH_3$-TMSCl[13] to yield a primary alcohol. The aldehyde obtained after Dess–Martin oxidation was again subjected to Wittig reaction with **4** to generate **24**. Ester **24** was reduced to the alcohol with DIBAL, followed by Dess–Martin oxidation and application of the Still (*Z*)-variant[14] of the Wittig reaction to afford (*E*,*Z*) doubly unsaturated ester **25**. Selective removal of the TBS groups was problematic; however, we learned from extensive experimentation that exposure to 3 N HCl-MeOH in THF (1:1) worked well. The resulting ester was hydrolyzed by using 1 N KOH in refluxing in EtOH. Finally, the Yamaguchi lactonization protocol followed by DDQ deprotection gave macrolactone **26**, whose structure was confirmed by HMBC and other NMR experiments. No isomerization of either of the dienes was detected.

Compound **26**, the most functionalized of the analogues, proved to be the most potent in terms of antiproliferative activity against human carcinoma cells (Table 1) showing a 50% growth inhibitory concentration against breast and ovarian cancer cells of about 1 μM. Furthermore and unlike the other new analogues, compound **26** displaced [^{3}H]-paclitaxel stoichiometrically bound to microtubules[15] at about one-third the potency of **1**.

Scheme 5



In summary, we have designed and synthesized hybrids of discodermolide and dictyostatin-1. The hybrids exhibit moderate biological activities with the most “dictyostatin-like” compound **26** being the most promising. These are the first macrocyclic analogues of discodermolide, and the synthetic route paves the way for the synthesis of other hybrids as well as for dictyostatin-1.

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Supporting Information Available: Spectroscopic and analytical data for compounds **3**, **19–21**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371.

[14] Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

[15] Hamel, E.; Sackett, D. L.; Vourloumis, D.; Nicolaou, K. C. *Biochemistry* **1999**, *38*, 5490.