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# A series of 23,24-dihydrodiscodermolide analogues with simplified lactone regions

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**Abstract**—A collection of seven new 23,24-dihydrodiscodermolide analogues have been synthesized with modifications to the lactone ring, some of which show antiproliferative activities similar to discodermolide.


The marine natural product (+)-discodermolide **1** (Fig. 1), isolated from the sponge *Discodermia dissoluta*, is potently cytotoxic to human cancer cell lines.[1] It has been well established that it has a similar mechanism of action to paclitaxel, namely the binding and stabilisation of microtubules, which leads to mitotic arrest and ultimately apoptosis.[2] Discodermolide also shows some activity against cell lines that express the P-glycoprotein efflux pump and are thus resistant to paclitaxel.

The organism responsible for the biosynthesis of **1**, presumably a bacterial symbiont, has not been identified. Thus, total chemical synthesis has been the only viable option for obtaining useful quantities of this material.[3] Indeed, a combination of two of these syntheses has been used to generate the material required to support a phase I clinical trial.[4] However, the 13 stereocentres and three cis double bonds make the manufacture of this material a daunting proposition.

There have been a number of efforts to generate simplified analogues that maintain the biological activity of discodermolide itself.[5] Of these the most promising have been modifications to the lactone region, in which a number of stereocentres can be removed without impacting the cytotoxicity.[6] In this communication, we report a group of new lactone analogues that have been further simplified by replacing the diene with a system in which the terminal double bond has been reduced to yield a monoene.

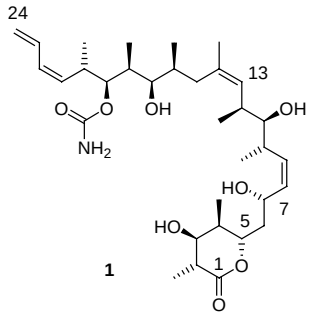


**Figure 1.** (+)-Discodermolide **1**.

Modification of the diene has a number of attractions; it has been reported by the Novartis group on the parent discodermolide where it was shown to result in similar potency[7] and it allows for a more facile construction of the C-24 to C-19 section of the molecule through a straightforward Wittig reaction resulting in improved material throughput.

When considering a synthetic strategy, we choose to use a similar approach to the Novartis group in which the molecule was divided into three sections, all available from the Smith common precursor **2** (Fig. 2).[4] This essentially combines the Smith coupling of the A and B sections with the Paterson approach to the AB and C coupling.[8] However, because we were intending to

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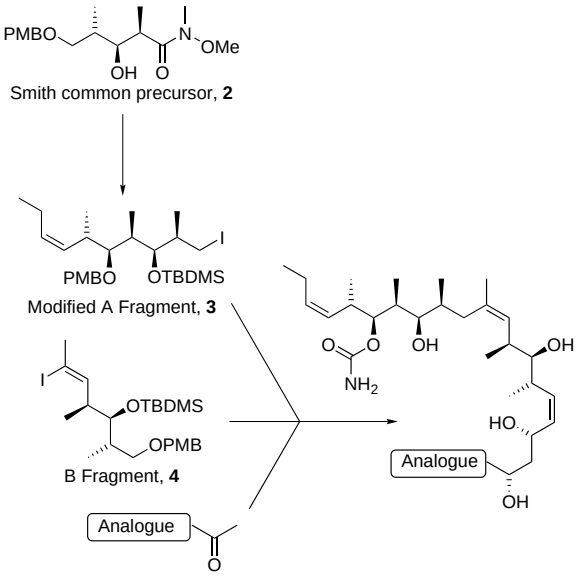



**Figure 2.** Approach to discodermolide analogues.

use a monoene instead of the diene it was considered that this could be introduced prior to the coupling reaction with the Smith B piece. In this way, late stage modifications were avoided making the route more convergent.

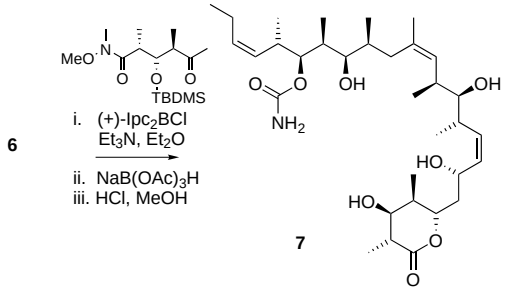
To obtain the modified A fragment **3**, we used chemistry similar to that recently reported by the Smith group.[6b] This route could be easily carried out on a multigram scale in good yield.

As expected, coupling to the B piece **4** was not affected by the monoene and yielded the complete C-24 to C-12 carbon backbone **5**. Using the standard conditions reported by the Paterson group this material was converted to the enal **6** in six steps (Scheme 1, see Supporting information for further details).[8c]

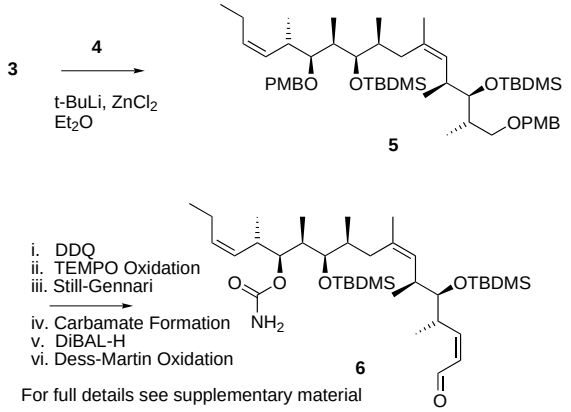
We were now in a position to begin generating lactone analogues, however, we first generated the previously described 23,24-dihydrodiscodermolide **7** to validate this compound in our own assays. Thus, aldol reaction with the methyl ketone derived from the common precursor[4] using (+)-diisopinocampheylboron chloride generated the complete carbon skeleton. Subsequent directed anti-reduction of the resulting ketone and acidic deprotection yielded **7** (Scheme 2).

With the monoene version of discodermolide **7** in hand we began to look at modifications of the lactone region. The Smith group has reported the 2,3-anhydro compound to be particularly potent.[9] Subsequently in collaboration with the Smith group we demonstrated that the methyl substituents could be removed from the ring while still maintaining strong potency.[6a] However, there has been only one report in which the 3-hydroxyl group was investigated in isolation. In this report, the 3-*O*-acetyl compound showed activity superior to that of discodermolide itself.[10] The excellent activity of the 3-acetate justified the further investigation of this position and the 3-methoxy- and 3-deoxy-23,24-dihydrodiscodermolide derivatives, **8** and **9**, were targeted. Both of these compounds are accessed through the common precursor **2** by O-methylation using the Meerwein reagent and Barton–McCombie deoxygenation via the pentafluorophenylthiocarbonate,[11] respectively, followed by conversion to the corresponding methyl ketones **10** and **11** (Scheme 3) using standard procedures.[4]

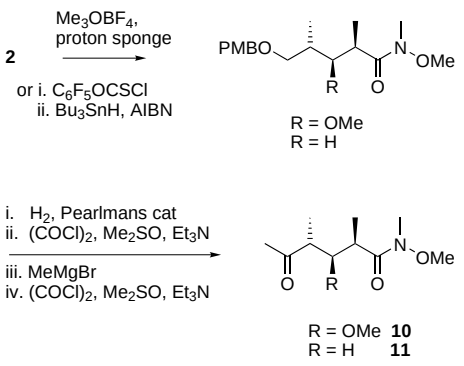
Both of these substrates underwent aldol reaction in good yield with excellent selectivity and were taken through to obtain the desired discodermolide analogues. In the case of the 3-deoxy compound, it was found that in addition to the expected 3-deoxy-23,24-dihydro-




**Scheme 2.** Completing the synthesis of 23,24-dihydrodiscodermolide **7**.




**Scheme 1.** Coupling of the modified A fragment and conversion to the enal.




**Scheme 3.** Generation of the 3-methoxy and 3-deoxy methyl ketones, **10** and **11**, respectively.

discodermolide **9**, the open chain methyl ester **12** was also obtained (Fig. 3). Presumably the lack of a substituent at the 3-position makes the acid catalysed cyclization less favourable.

Next, we examined the nature of the lactone itself by first converting it to a carbamate **13**. In this case, the necessary azido methyl ketone **14** could be easily obtained from Roche ester **15** (Scheme 4). The carbamate was installed prior to removal of the silyl groups by Staudinger reduction and treatment with carbonyldiimidazole. When the same approach was attempted to form the corresponding carbonate from methyl ketone **16**, the final deprotection removed the carbonate resulting in the triol **17**. Attempted reinstallation of the carbonate at this stage was not successful.

To complete the series, the simple butyrolactone **18** similar to that reported in the diene series was also synthesized along with its 7,5-epimer **19**.[6a]

The compounds were tested for their antiproliferative activity in the standard cell lines, including the MDR cell line NCI/ADR, which expresses the P-glycoprotein efflux pump and the A549/t12 cell line which has a tubulin mutation making it resistant to paclitaxel. It was encouraging to see that the 23,24-dihydrodiscodermolide **7** is slightly more potent than the parent discodermolide **1** in line with what has been reported (Table 1).[7]

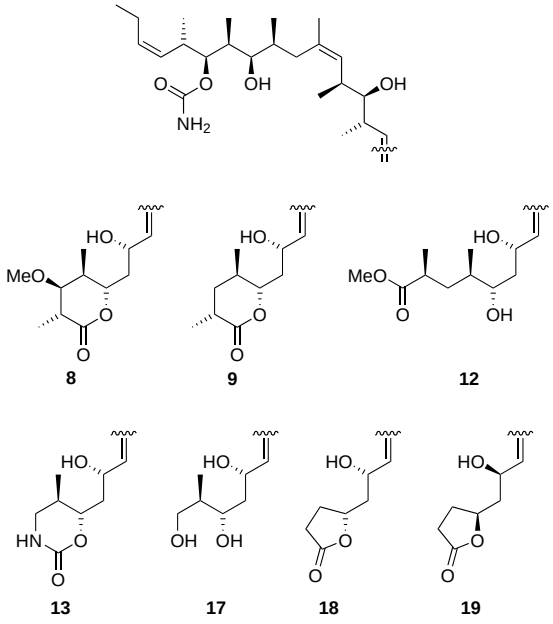
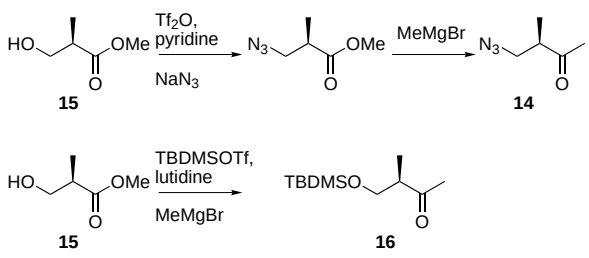



**Figure 3.** Compounds in the study.




**Scheme 4.** Generation of the methyl ketones **14** and **16**, for forming the carbamate **13** and triol **17**, respectively.

The two 3-position analogues show excellent activity. However, the open chain form of the 3-deoxy compound **12** is not active. This contrasts with the methyl ester of discodermolide, which was reported to have nanomolar activity.[12,13] The activity of 3-methoxy compound **8** is consistent both with the reports from the Curran and Day groups in which a simplified discodermolide analogue with a methoxymethyl ether at the 3-position showed a slightly improved activity over the parent molecule[5c] and the 3-*O*-acetyldiscodermolide reported by Harbor Branch.[10]

Both the carbamate and the triol compounds **13** and **17**, respectively, do not show significant cytotoxicity. This lack of activity suggests that the nature of the carbonyl of the lactone ring is important. As expected the butyrolactone **18** with the stereochemistry found in discodermolide is an active compound.

The three most active compounds were further investigated in a range of resistant leukaemia cell lines. All cell lines express the P-glycoprotein efflux pump but to varying degrees. All compounds are active with each compound showing improved activity over discodermolide in at least one cell line (Table 2).

In conclusion, we have generated a series of new analogues of discodermolide in the 23,24-dihydro series, of which three are as good or better than discodermolide. This scaffold does not appear to affect the activity of the compounds and allows for material to be moved

**Table 1.** Antiproliferative activity for compounds **9**–**16** and discodermolide **1**

| Compound | Antiproliferative activity, $GI_{50}$ (nM) | | | |
|---|---|---|---|---|
| | MCF-7 | NCI/ADR | A549 | A549t12 |
| **1** | 28 | 240 | 22 | 30 |
| **7** | 6.2 | 190 | 7 | nd |
| **8** | 3.8 | 250 | 6.5 | 12 |
| **9** | 5.8 | 140 | 11 | 50 |
| **12** | 1000 | 10,000 | 4000 | 4000 |
| **13** | 110 | 10,000 | 520 | 1000 |
| **17** | 1000 | 10,000 | 3000 | 5000 |
| **18** | 6.4 | 730 | 46 | 63 |
| **19** | 2000 | 10,000 | 4000 | 10,000 |

**Table 2.** Antiproliferative activity for compounds **10**, **11**, **15** and discodermolide **1** in a range of resistant cell lines

| Compound | Antiproliferative activity, $GI_{50}$ (nM) | | | |
|---|---|---|---|---|
| | CCRF-CEM | CCRF-CEM/PTX | CCRF-CEM/VBL | CCRF-CEM/VP16 |
| **1** | 16 | 92 | 158 | 52 |
| **8** | 4.4 | 79 | 416 | 8.4 |
| **9** | 8.6 | 65 | 209 | 12 |
| **18** | 6.5 | 285 | 3807 | 7.1 |

through the synthetic sequence more effectively. From these compounds, it appears the lactone ring is important for activity. Changing to a carbamate or opening the ring lowers the activity. The 3-methoxy and 3-deoxy compounds are both more potent than discodermolide and have a better profile in the resistant cell lines. It is noteworthy that the most simplified analogue in this series, the butyrolactone **18**, is also one of the most active compounds.

## Acknowledgments

We thank Fenghua Liu and Wei Ma for antiproliferative assays.

## Supporting information

A full scheme outlining the synthesis of **8** from the coupling of **3** with **4** and full experimental details are available in the supporting information. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2005.12.066.

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13. We speculate that the discodermolide methyl ester cyclises to discodermolide in the assay but the 3-deoxy compound does not.