Coumarin-derived discodermolide analogues possessing equivalent antiproliferative activity to the natural product—a further simplification of the lactone region†

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Analogues of discodermolide in which the complete C-1 to C-7 fragment is replaced with a coumarin moiety display equivalent potency to that of the natural product.

The goal in medicinal chemistry is to understand and improve the structural elements of the molecules required to deliver a desired therapeutic effect. This goal is usually achieved by exploiting the interaction of a prospective drug with a macromolecule. In small molecule drug discovery, the approach has been highly successful in achieving selective, potent drugs for a large range of biological targets. In the natural products arena, in which the biological activity is often built in, the compounds can in some cases be used directly or more often tuned for the desired pharmacokinetic properties. It is, however, challenging to commercialize natural products that cannot be readily obtained either from natural sources or *via* fermentation.

A case in point is the polyketide (+)-discodermolide **1** (Fig. 1).[1] This marine natural product, a potent stabilizer of microtubules, leads to cell cycle arrest, and ultimately apoptosis—a mechanism similar to the anticancer agents paclitaxel and the epothilones.[2] Indeed, discodermolide entered phase I clinical trials due to this activity. Discodermolide **1**, however, is only available in small quantities from the sponge *Discodermia dissoluta*, and neither the producing organism (thought to be a symbiont) has been cultured, nor have the genes responsible for biosynthesis been obtained. Thus, the large quantities required for the Phase I trial could only be obtained through total synthesis, a formidable task.[3–5]

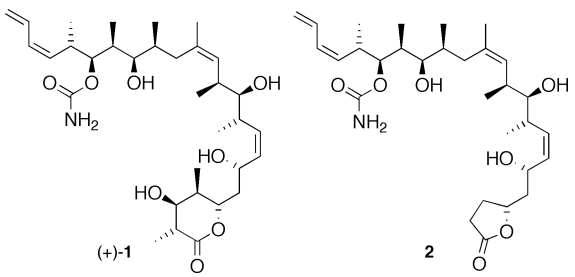
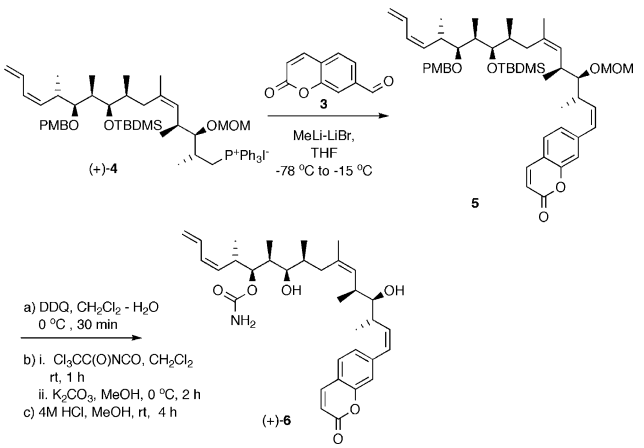


Fig. 1 (+)-Discodermolide **1** and the butyrolactone **2**.

To reduce the complexity of discodermolide while maintaining potency, we and others have explored simplification of the structure.[6,7] A significant step in this direction was our discovery that butyrolactone **2**, which lacks three stereocentres, is a potent antiproliferative agent.[8] With this observation in hand, we reasoned that further reduction in the complexity might be possible in the lactone region by replacement of the complete C-1 to C-7 unit. Consistent with this conjecture, we already had discovered that the 7-hydroxyl group is not required for activity, since both alkylation and acylation result in compounds with similar nanomolar activity.[9,10] We also reasoned that an aromatic unit that would maintain the appropriate lactone orientation as found in both the solution and solid-state structures[1,11] might serve to mimic this region. Ideal in this regard appeared to be an appropriately substituted coumarin, since replacement would position the lactone moiety in a similar position to that found in discodermolide. Importantly, coumarins are found in a number of natural products including the antibiotic novobicin, which inhibits DNA gyrase and more recently has been shown to have antitumour activity.[12]

We postulated that 7-coumarincarboxaldehyde **3**, available in one step from commercially available 7-methylcoumarin *via* selenium dioxide oxidation, could be employed directly with Wittig salt (+)-**4** using the coupling tactic developed and refined in our laboratory (Scheme 1).[3a,13] This indeed proved to be the case; coumarin **5** was obtained in 35%. Following union, standard conditions were then employed to generate coumarin (+)-**6**. Specifically, removal of the PMB ether permitted installation of the carbamate before global deprotection.



Scheme 1 Synthesis of the coumarin compound (+)-**6**.

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† Electronic supplementary information (ESI) available: Full reaction schemes for the synthesis of analogues **9–12**, and analytical data for all final compounds. See DOI: 10.1039/b708884c

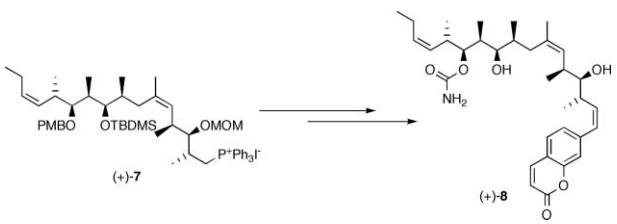
Table 1 Antiproliferative activities of the compounds in the study

Compound	Antiproliferative activity/nM		
	SKOV3	MCF-7	NCI/ADR
(+)-Discodermolide **1**	25	26	260
Butyrolactone **2**	nd[a]	3	350
(+)-**6**	44	12	190
(+)-**8**	35	15	230
(+)-**9**	1800	1600	3300
(−)-**10**	790	430	840
(+)-**11**	2400	1600	3200
(+)-**12**	2900	3000	4000

[a] Not determined.

Coumarin (+)-**6** displayed nanomolar activity similar to (+)-discodermolide **1** against a wide range of cell lines, including breast (MCF-7) and ovarian (SKOV3), as well as the multi-drug resistant (MDR) cell line (NCI/ADR), which over-expresses the MDR efflux pump, P-glycoprotein (Table 1). These results are particularly striking given that the entire C-1 to C-7 section has been replaced, including five of the 13 stereocentres.

Having demonstrated that the coumarin replacement maintained excellent antiproliferative activity, we moved to the 23,24-dihydro discodermolide scaffold, to generate a series of analogues to probe further the viability of the coumarin replacement. The ability to use the 23,24-dihydro series would greatly improve material throughput, given the synthetic simplification resulting from removal of the 23,24-alkene. This modification has been shown not to affect potency.[14] Towards this end, union of the corresponding 23,24-dihydro Wittig salt (+)-**7** (Scheme 2) with coumarin aldehyde **3** proceeded smoothly.[9] Further elaboration led to the 23,24-dihydro analogue (+)-**8**, a compound that proved equivalent to (+)-**1** and (+)-**6** in the antiproliferative assays.



Scheme 2 Synthesis of the dihydrocoumarin compound (+)-**8**.

To provide additional information on the requirements of the lactone region, we constructed four related analogues: the 6-coumarin (+)-**9** to explore the positioning of the lactone ring and three lactam analogues, (−)-**10**, (+)-**11**, (+)-**12**, varying the lactam nitrogen substitution (H, Me and MOM; Fig. 2). These analogues were constructed using a route similar to that described above (see ESI for complete synthetic schemes†). The requisite unprotected lactam aldehyde proved readily accessible.[15]

The antiproliferative activities for the six analogues are listed in Table 1.[16] Positioning the lactone ring proved crucial for high potency, with the 6-coumarin (+)-**9** displaying a 50–100-fold lower activity compared to (+)-discodermolide **1** and the two 7-coumarins (+)-**6** and (+)-**8**. Although the three lactam analogues displayed less activity than the corresponding coumarins, lactam (−)-**10** (R = H) does appear to be somewhat more active than the two *N*-substituted congeners (+)-**11** and (+)-**12**. The drop in activity in moving from the lactone to the lactam is either the result of a difference in the electrostatics or due to the change in the ring, which has been altered by insertion of an oxygen atom. Further analogues will be required to provide a definitive answer.

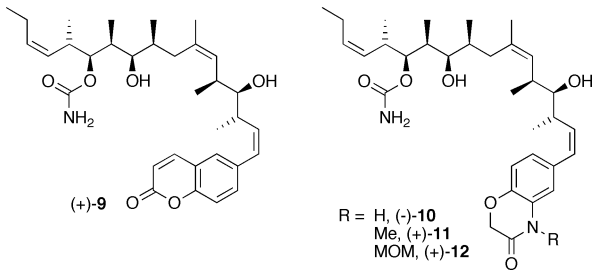


Fig. 2 6-Coumarin analogue (+)-**9** and lactams (−)-**10**, (+)-**11**, and (+)-**12**.

In summary, we have designed and constructed a series of discodermolide lactone analogues wherein the entire C-1 to C-7 unit, possessing five stereogenic centers, has been replaced with either a coumarin or cyclic lactam. In spite of the significant change, the 7-coumarins (+)-**6** and (+)-**8** display equivalent antiproliferative activity to (+)-discodermolide **1** over a series of cell lines. Importantly, these congeners represent the structurally simplest discodermolide analogues reported to date with nanomolar antiproliferative activity in cell culture. Compared to (+)-discodermolide, these molecules are considerably easier to synthesise, which would reduce the time and cost of a large scale synthesis. Equally important, the 7-coumarins (+)-**6** and (+)-**8**, in association with the 6-coumarin (+)-**9**, add weight to the hypothesis that positioning the lactone moiety is crucial for strong activity.[17]

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