

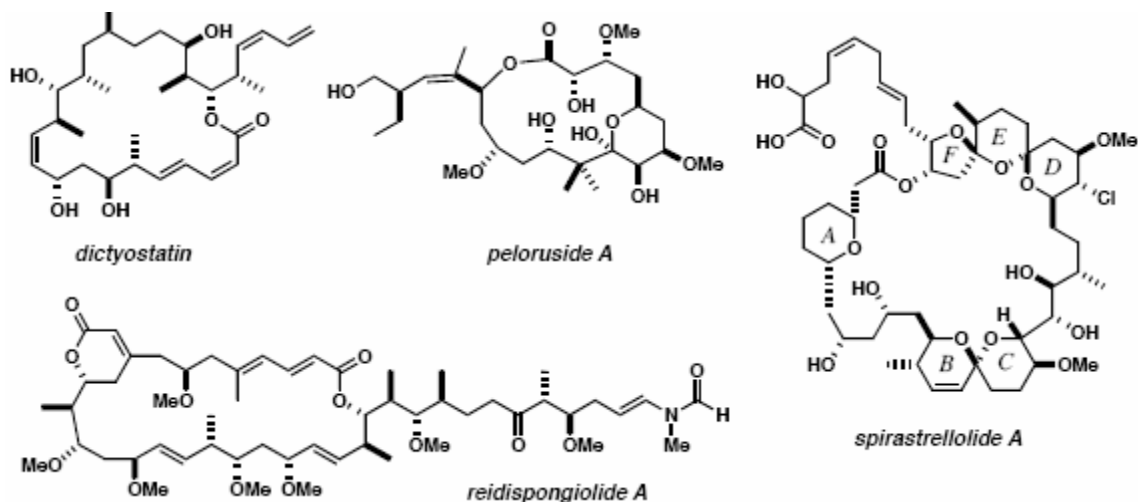
Total Synthesis of Bioactive Marine Polyketides
Professor Ian Paterson, University Chemical Laboratory, University of Cambridge

Marine organisms, particularly sponge invertebrates are a prolific source of novel biologically active compounds with unusual, and often complex, structures. The harsh environment in which marine sponges inhabit, together with their lack of physical defenses, requires that these organisms develop chemical deterrents for defense and survival. As a result, many of their associated organic compounds exhibit exceptional levels of biological activity, often combined with unique modes of action.

However, the pre-clinical and development of marine-derived natural products is often hampered by the unsustainable and limited supply – making total synthesis of vital importance. Not only does total synthesis enable the unambiguous structural determination of newly isolated natural products but it also allows for the production of novel analogues, which may have more desirable therapeutic properties and greater accessibility.

We are currently working on the synthesis of several rare marine natural products – dictyostatin, peloruside, spirastrellolide, reidispongiolide – that represent promising anticancer agents based on their preliminary biological evaluation in potently inhibiting the growth of cancer cell lines, including multidrug-resistant cells. In several cases, the full stereostructure of the bioactive component is not fully known, making chemical synthesis an even more adventurous undertaking.

In all our projects, the full structural characterization of synthetic intermediates and final target molecules is dependent on data provided by the EPSRC National MS Service.



Publications:

- Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; O'Brien, M.; Scott, J. P.; Sereinig, N. A second-generation total synthesis of (+)-discodermolide. The development of a practical route using solely substrate-based stereocontrol. *J. Org. Chem.* **2005**, *70*, 150.
- Paterson, I.; Chen, D.Y.-K.; Coster, M. J.; Acena, J. L.; Bach, J.; Wallace, D. J. The stereocontrolled total synthesis of althoyrtin A/spongistatin 1. Fragment couplings, completion of the synthesis, analogue generation and biological evaluation. *Org. Biomol. Chem.* **2005**, *3*, 2431.
- Paterson, I.; Anderson, E. A.; Dalby, S. M.; Loiseleur, O. Toward the synthesis of spirastrellolide A: Construction of a tetracyclic C26–C40 subunit containing the DEF-bis-spiroacetal. *Org. Lett.* **2005**, *7*, 4121.
- Paterson, I.; Anderson, E. A.; Dalby, S. M.; Loiseleur, O. Toward the synthesis of spirastrellolide A: Construction of two C1–C25 diastereomers containing the BC-spiroacetal. *Org. Lett.* **2005**, *7*, 4125.
- Paterson, I.; Britton, R.; Ashton, K.; Knust, K.; Stafford, J. Synthetic studies towards the sphinxolide/reidispongiolide group of antimicrofilament macrolides: stereocontrolled synthesis and configurational reassignment of a C5–C16 degradation fragment of reidispongiolide A. *Proc. Natl. Acad. Sci. USA*, **2004**, *101*, 11986.