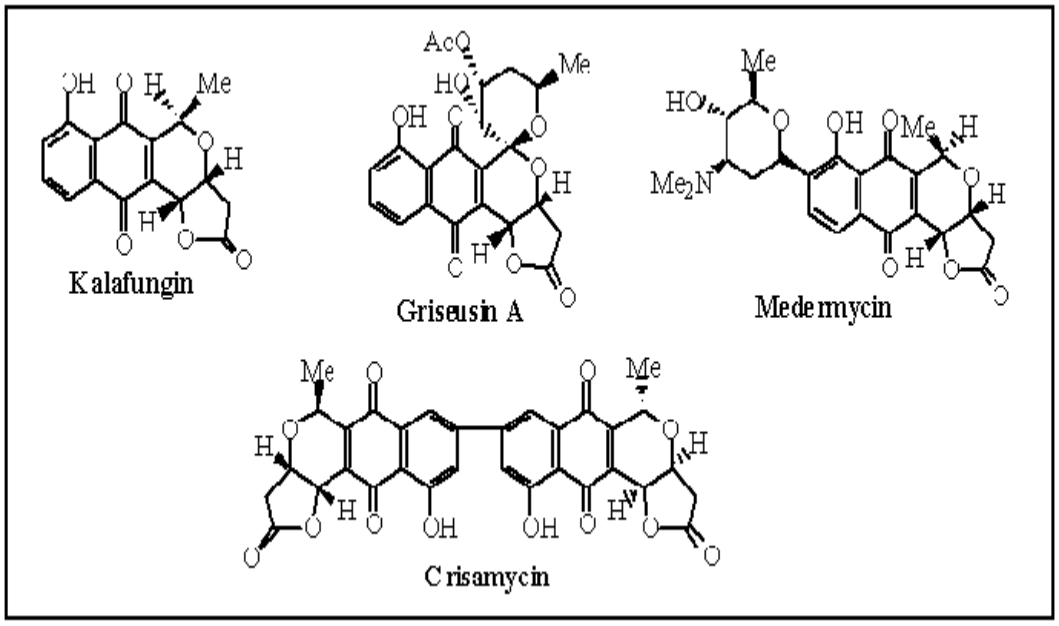
The Synthesis of Potential Chemotherapeutic

Margaret A. BrimbleNatural products have long been regarded as "Nature's medicine chest" providing a rich source of lead compounds to synthesize for pharmaceutical development. Natural product synthesis has also been described as an '**enabling science**' because it provides unlimited opportunity for discovery at the interface with biology and medicine. Our research in synthetic organic chemistry and medicinal chemistry focuses on making and modifying naturally occurring bioactive compounds that have been isolated from plants, animal tissue, microbes or marine and soil organisms, which are rare or hard to isolate in abundance. These compounds provide rich and diverse chemical structures that challenge the synthetic chemist to develop new synthetic methodology for the construction of the novel and diverse heterocyclic arrays which they contain. Over the last decade our research group in Australasia has focused on the development of flexible synthetic approaches to several natural products which have important biological activity. The synthesis of the molecules described in detail below has also allowed the preparation of synthetic analogues of the natural compound which may lead to improvements in biological activity and an understanding of the way the naturally occurring compounds act.

- **SYNTHESIS OF PYRANONAPHTHOQUINONE ANTIBIOTICS**

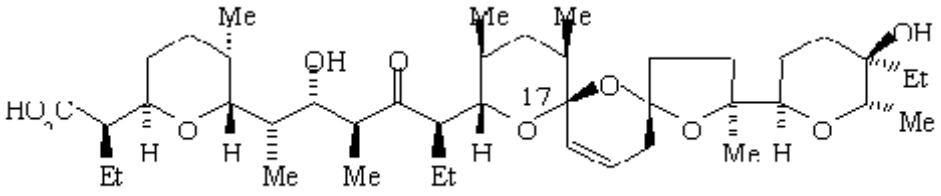
The pyranonaphthoquinone family of antibiotics, of which one of the simplest members is kalafungin, exhibits inhibitory activity against a variety of pathogenic fungi, yeast and gram-positive bacteria. Another property of these compounds is their ability to act as bioreductive DNA alkylating agents via quinone methide intermediates thereby resulting in cross-linking of DNA strands. These alkylated DNA adducts then interfere with the cell replication process. This concept of bioreductive alkylation offers an exciting mechanism of drug action for the development of new antineoplastic agents based on the pyranonaphthoquinone skeleton. Our research group has developed an efficient synthesis of several simpler members of pyranonaphthoquinone antibiotics as well as the spiroacetal-containing pyranonaphthoquinone, griseusin A, and the C-glycosidic pyranonaphthoquinone, medermycin, which exhibits antileukaemia activity. The first efficient synthesis of a dimeric pyranonaphthoquinone similar to the antiviral agent, crisamycin, has also been successfully executed using our synthetic strategy.



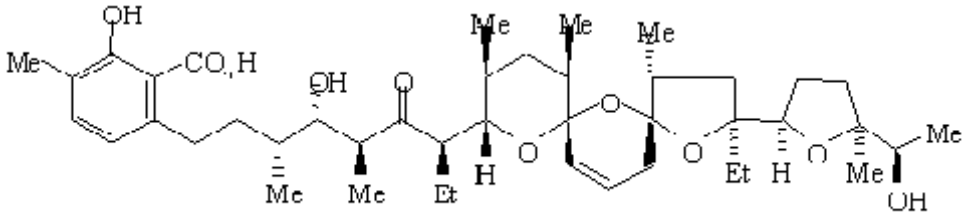
- **SYNTHESIS OF NATURAL PRODUCTS CONTAINING BIS-SPIROACETAL**

RING SYSTEMS

The polyether antibiotics salinomycin and CP44,161 exhibit antimicrobial l activity against gram-positive bacteria, mycobacteria and fungi. They also play an important role in veterinary medicine as growth promotants in ruminants. The characteristic property of these polyether antibiotics is their ability to act as ionophores and conduct ions across membranes.

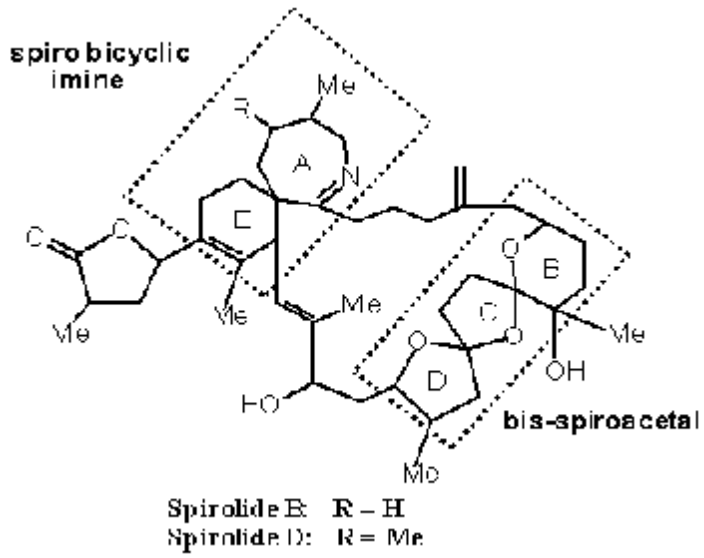


epi-17-deoxy-(O-8)-salinomycin



Antibiotic CP44,161

The main structural feature of these polyether antibiotics is the presence of the bis-spiroacetal ring system. Our synthetic approach2 to the bis-spiroacetal ring systems of epi-17-deoxy-(O-8)-salinomycin and antibiotic CP44,161 hinged on the use of a key oxidative cyclization of a hydroxyspiroacetal to a bis-spiroacetal. Our work in this area has culminated in the synthesis of an isomer of the tetracyclic BCDE moiety of the polyether antibiotic, CP44,161.

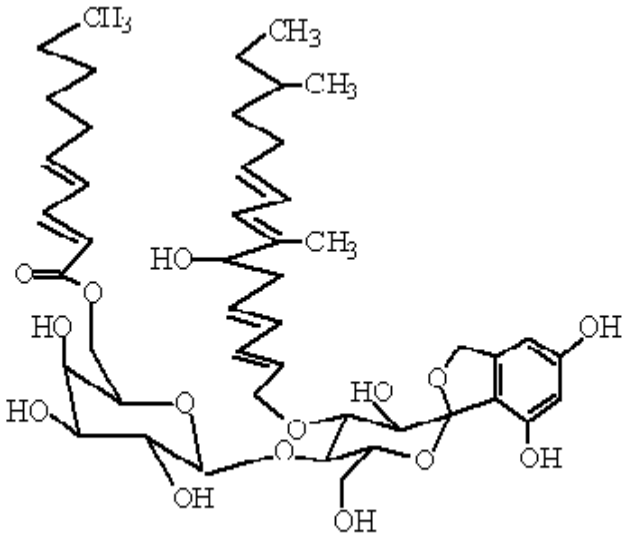


During chemical investigations of polar bioactive molecules from microalgae and shellfish, two lipid-soluble macrocycles, spirolides B and D, were isolated from the digestive glands of both mussels (Mytilus edulis) and scallops (Placopecten magellanicus). These macrocycles contain a novel bis-spiroacetal ring system and an unusual seven-membered spiro-linked cyclic iminium moiety. They cause potent and characteristic symptoms in the mouse bioassay and were found to be weak activators of type L calcium channels. The spirolides are therefore useful lead compounds for the development of new therapeutic agents to treat cardiovascular disorders such as hypertension. We have recently completed the synthesis of the bis-spiraocetal moiety of the spirolides using an iterative oxidative cyclization to construct this key ring system.

- **SYNTHESIS OF THE ANTIFUNGAL AGENTS THE PAPULACANDINS**

The papulacandins are a group of aryl-C-glycosyl spiroacetal antifungal agents isolated from Papularia spherosperma which exhibit potent in vitro activity against

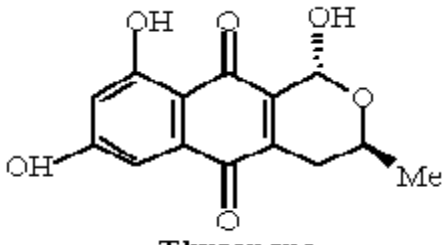
Candida albicans and Pneumoocystis carinii pneumonia, the common opportunistic infection in AIDS patients. We have therefore been involved with the synthesis of analogues of the papulacandins in order to provide a better understanding of the structural elements responsible for the potent antifungal activity exhibited by this family of antibiotics.



Papulacandin C

- **SYNTHESIS OF THE HUMAN RHINOVIRUS 3C PROTEASE INHIBITOR**

THYSANONE

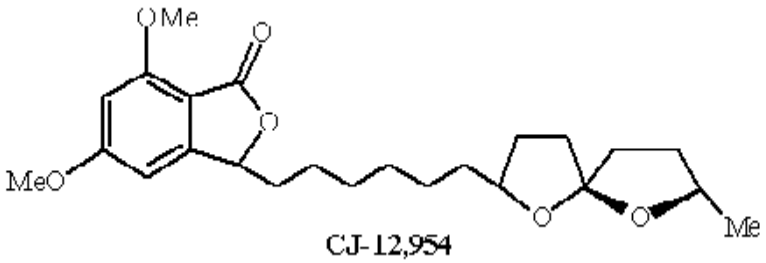


Thysanone

The replication of many animal and plant viruses relies on proteolytic processing and is dependent upon two virally encoded enzymes, 3C-protease and 2A-protease. Human rhinoviruses are responsible for causing common colds in humans, therefore, 3C-protease and 2A-protease are attractive targets for the development of antiviral chemotherapeutic agents for eventual control / cure of the common cold. Thysanone, isolated from Thysanophora penicilloides, is one of few effective inhibitors of human

rhinovirus 3C-protease. We have therefore engaged in the synthesis of thysanone in order to provide lead compounds for understanding the mechanism of 3C-protease inhibition.

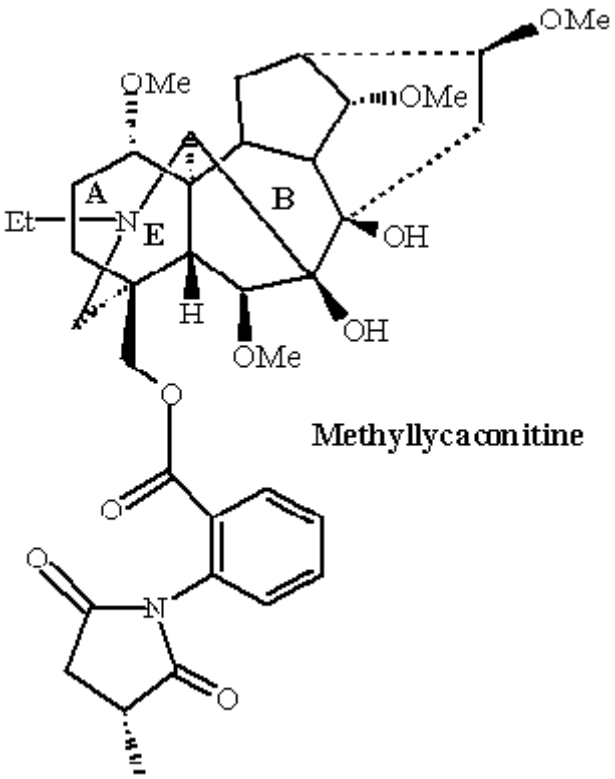
- **SYNTHESIS OF ANTI-HELICOBACTER PYLORI AGENT CJ-12,954**



CJ-12,954

Recent studies have shown a relationship between gastric and duodenal ulcers and the presence of the microaerophilic spiral-shaped Gram negative bacterium Helicobacter pylori which is present in the mucus layer of the stomach. The natural product CJ-12,954 produced by Phanerochaete velutina, exhibits potent activity against Helicobacter pylori and is therefore a lead compound for the treatment of ulcers in humans. Recent research has been directed towards the first synthesis of CJ-12,954 and analogues thereof, in order to provide novel antiulcer agents.

- **SYNTHESIS OF LIGANDS FOR NICOTINIC ACETYLCHOLINE RECEPTORS BASED ON METHYLLYCACONITINE**



Methyllycaconitine

Methyllycaconitine (MLA) is the principal insecticidal toxin isolated from the cattle-stock poison Delphinium brownii. MLA is a potent inhibitor of ?-bungarotoxin nicotinic acetylcholine receptor (nAChR) binding in mammalian and insect neural membranes. At this subset of nAChR, methyllycaconitine is the most potent small molecule antagonist yet reported. Methyllycaconitine is therefore a valuable neurobiological tool for the study of the comparative pharmacology of nicotinic acetylcholine receptors and is a lead compound for the treatment of Alzheimer's disease. The synthesis of simpler tricyclic ABE analogues of methyllycaconitine has been undertaken such that the pharmacological properties of these simpler analogues can be evaluated. This area of research is a collaborative project with Dr Malcolm McLeod at the University of Sydney and Dr Paul Savage at CSIRO, Division of Molecular Science, Melbourne.

References

1. M. A. Brimble,"Synthetic Strategies Towards Pyranonaphthoquinone Antibiotics,"Pure and Applied Chem.,2000, **72,** 1635-1639.

2. M. A. Brimble, "Synthetic Studies Towards Natural Products Containing Bis-spiroacetals."J. Heterocyclic Chem., 1999,**36**,1373-1389.