Professor Martin Banwell

A major focus of activities is the development of new methods and strategies for the synthesis of biologically active natural products and their analogues. The use of *cis*- and *trans*-1,2-dihydrocatechols, (–)-3-dehydroshikimic acid [(–)-3-DHS], *gem*-dibromocyclopropanes, and pyrroles as readily available building blocks for that end represents a continuing theme. Aspects of this work are funded by Australian companies. For example, two APA(I)-funded PhD scholars have been working on research relevant to the activities of Melbourne-based Mimotopes Pty Ltd and Biota Holdings Ltd. Furthermore, Brisbane-based Progen Industries Ltd is funding two postdoctoral fellows who have been working on a collaborative project focused on novel carbohydrate chemistries. Two patent filings resulted from this last project in 2002.

Research highlights include the completion, in collaboration with colleagues at the University of Munich, of a total synthesis of the pharmacologically significant and structurally novel marine alkaloid halitulin. Poly-functionlised bis-piperidines related to the ecologically important haliclonacyclamine-class of marine alkaloid have also recently been obtained through a novel cross-coupling procedure whilst the stereo-controlled synthesis of enantiomerically pure sialic acids [from abundant (–)-3-DHS] has been achieved, as has a total synthesis of the cytotoxic styryllactone (+)-goniodiol. Various important methodological developments have occurred. These include the establishment of methods for converting (–)-3-DHS into derivatives of the (+)-enantiomer and the development of two distinct strategies for introducing the side-chains of the phomoidrides A and B onto a bicyclo[2.2.2]octanyl precursor to the carbobicyclic core of these biologically important and structurally complex natural products.

## Exploitation of *cis*- and *trans*-1,2-Dihydrocatechols as Starting Materials for Chemical Synthesis

Certain of the title compounds, which can be obtained by enantioselective microbial oxidation of the corresponding arene or manipulation of the shikimic acid biosynthetic pathway, continue to serve as important starting materials for the preparation of a structurally diverse array of poly-oxygenated natural products and their analogues. In particular, a *trans*-1,2-dihydrocatechol provided by colleagues in Germany is being used in developing a concise total synthesis of macrocarpalide, a potent microfilament disrupting agent from an endophytic fungus. As noted in last year's report, the bicyclic cores associated with phomoidrides A and B (two nonadrides that are potent inhibitors of Ras farensyl transferase) have now been assembled from the so-called bromobenzene diol. In a significant recent advance, two distinct strategies for the attachment of the *trans*-related side-chains associated with these targets have been developed, thus setting the stage for the completion of the total synthesis. Other target natural products within this category include the alkaloids galanthamine, brunsvigine and vindoline as well as the macrolide tricholomenyn B and the fungal metabolite diversonol. The synthesis of certain rare sugars together with various sugar mimetics has been another activity in this area and one that has been carried out in collaboration with commercial partners. *(with C. Chun, M. Essers, P. Guan, G.J. Harfoot, N.L. Hungerford, J.Jury, O.P. Karunaratne, D.T.J. Loong, D.W. Lupton, X.H. Ma, J. Renner, M.M. Vögtle, and R.H. Don. V. Ferro [Progen*

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## New Synthetic Strategies and Methodologies

The reaction of pyrroles with certain C-centred electrophiles continues to provide the means by which various useful scaffolds, including C-gylcosides, can be constructed. The pyrrole-containing marine natural product halitulin, a potent cytotoxic agent isolated from the sponge *Haliclona tulearensis*, has been synthesised using a combination of cross-coupling and ring-closing metathesis (RCM) reactions to assemble the macrocyclic amine portion of the molecule. The latter process is also being exploited in efforts to prepare the related natural product haliclonacyclamine A, as well as the anti-malarial agent quinine. A very simple, effective and versatile new method for preparing indoles has been uncovered and this has important implications in the rapid construction of libraries of compounds that will allow identification of the pharmacophore associated with the structurally complex and clinically important agent vinblastine.

The electrocyclic ring-opening of ring-fused *gem*-dibromocyclopropanes continues to be exploited within the group as a key step in the construction of various natural products. A very concise method for construction of the polycyclic framework of the hapalindole class of alkaloids has recently been accomplished by such means.

Other work has focused on continuing the development of chemoenzymatic routes to the spinosyn class of insecticides. Indeed, a route to the carbotricyclic core of this compound has now been established but this will require improvement before it can be exploited in a total synthesis of the target insecticides. Utilising modifications of established cycloaddition methodologies, a concise route to the stilbenolignan aiphanol has been completed. Biological evaluation of this compound and various congeners has revealed that the compounds possess very potent and unusual biological properties. *(with D.A.S. Beck, S. Chand, M.J. Coster, M.J. Harvey, B.D. Kelly, O.J. Kokas, P. Stanislawski, M.O. Sydnes, R. Taylor, D.J. Wong, and A.M. Bray [Mimotopes Pty Ltd, Melbourne], R.H. Don, V. Ferro [Progen Industries Ltd, Brisbane], C.C. Freeman, K.A. Jolliffe [U. Sydney], C.R. Parish [JCSMR, ANU], G.P. Savage [CSIRO Molecular Science, Melbourne], J.A. Smith [U. Tasmania])*

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