ORGANIC CHEMISTRY

Synthesis and Mechanism — Professor Martin Banwell

The group's activities remain focused on the development of new synthetic strategies and methodologies as well as the application of these in the total synthesis of biologically active natural products and certain analogues. The whole-cell biotransformation, in collaboration with Dr Gregg Whited of Genencor International (Palo Alto, CA), of various poly-substituted aromatics into metabolites suitable for construction of key parts of various structurally complex and clinically significant compounds is another important area of activity. The metabolites resulting from such processes are not only enantiomerically pure but also sufficiently rich in functionality that they can serve as important new starting materials in our synthesis program. Two key targets of particular interest at the present time are vinblastine (a binary indole-indoline alkaloid used in the treatment of early childhood leukaemia and bladder cancer, see figure 1) and galanthamine (a plant-derived alkaloid used in the treatment of Alzheimer's disease). Australian companies have funded a significant portion of our work. For example, Progen Industries, a Brisbane-based biotech company, is continuing to support two postdoctorals who have been working on a very enjoyable collaborative project focused on novel carbohydrate and related chemistries. An APA(I)-funded PhD scholar has recently started work on a collaborative project with Biota Holdings and another similarly funded scholar is working with Starpharma Pty Ltd on the development of new drug delivery systems. Collaborations with the Melbourne-based company Cytopia and our colleague Professor Chris Parish (JCSMR) continue and have resulted in the identification of novel analogues of certain alkaloids that display potent anti-angiogenic activity but show none of the toxic effects of the natural products themselves. The Alexander von Humboldt Foundation is providing Feodor Lynen Fellowships to two German postdoctorals working in the group, one of whom is focusing on developing, in collaboration with A/Professor Mary Garson of the University of Queensland, a total synthesis of the marine alkaloid haliclonacyclamine A. The bis-piperidinyl core of this target molecule has recently been obtained and efforts are now underway to construct, using ring-closing alkyne metathesis techniques, the two remaining ring systems associated with this ecologically important compound. In a joint venture involving Dr Paul Savage of CSIRO Molecular Science we have recently completed total syntheses of both enantiomeric forms of the stilbenolignan aiphanol and thereby determined the absolute stereochemistry of this natural product.

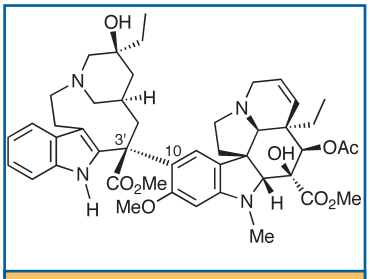


Figure 1: Vinblastine, a binary indole-indoline alkaloid used for the clinical treatment of certain types of cancer.

Other research highlights include:

(i) the completion of a total synthesis of aspidospermidine, an alkaloid embodying certain key structural components associated with the clinically significant natural product vinblastine;

(ii) the identification of techniques for constructing the pivotal C10-C3' linkage between the northern and southern hemispheres of vinblastine;

(iii) the enantiodivergent construction of the pivotal quaternary carbon centre associated with both the natural and non-natural enantiomeric forms of the alkaloid galanthamine;

(iv) the development of the first enantioselective total synthesis of the macrolide (–)-cladospolide B (Figure 2) and the subsequent revision of the absolute stereochemistry of the natural product;

(v) the exploitation of novel cyclopropane ring-cleavage reactions in the construction of certain unusual terpenoid and alkaloid frameworks.

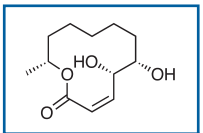
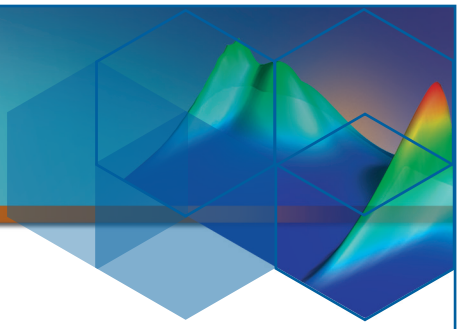


Figure 2: Cladospolide B, a fungal metabolite possessing novel plant growth regulating properties.



In the methodological area, extensions of our studies on palladium[0]-catalysed Ullmann cross-coupling chemistry have continued and a range of new heterocyclic systems are now available as a result. Several patents relating to this work have been filed.

Exploitation of cis*-1,2-Dihydrocatechols and Quinic Acid Derivatives as Starting Materials for Chemical Synthesis*

The title compounds, which can be obtained by enantioselective microbial oxidation of the corresponding arene or through 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 related structures. Methods for the enantiodivergent elaboration of *cis*-1,2-dihydrocatechols through the application of Diels–Alder chemistry continues to be a major area of activity and the adducts derived from such processes have been converted, using photochemical processes, into the polycyclic skeleta associated with a diverse range of terpenoid natural products. Other natural products being targeted include the alkaloids galanthamine (a clinically useful agent for the treatment of Alzheimer's disease), brunsvigine and vindoline (a clinically important anti-cancer agent) as well as the macrolide tricholomenyn B (a potent anti-mitotic agent), the fungal metabolite diversonol and the plant-growth regulating substance cladospolide C. The preparation of various sugar mimetics has been another activity in this area and one that has been carried out with commercial partners. *(With K Austin, M Bonnet, L Fearnside, M Friend, G J Harfoot, J Jury, O P Karunaratne, D T J Loong, D W Lupton, X H Ma, J Renner, and R H Don, V Ferro [Progen Industries Ltd, Brisbane], J N Lambert [Biota Pty Ltd, Melbourne], G Krippner, T McCarthy [Starpharma Pty Ltd, Melbourne], G M Whited (Genencor International Inc, Palo Alto])*

New Synthetic Strategies and Methodologies

The electrocyclic ring-opening of ring-fused *gem*-dibromo- and *gem*-dichloro-cyclopropanes continues to be employed in various contexts, with one especially notable activity being focused on the construction of the spirocyclic framework associated with the erythrina alkaloids. The exploitation of pyrroles as nucleophilic scaffolds for the construction of various heterocyclic compounds also continues to be a major activity within the group. Novel modes of reactivity involving this ring system have been developed recently and these have been or are currently being exploited in the construction of various biologically active systems including showdomycin analogues. Other work has focused on the development of chemoenzymatic routes to the spinosyin class of insecticides and the carbotricyclic core of these natural products has now been obtained but more efficient routes to this important substructure will need to be developed before total syntheses can be completed. *endo*-Selective Diels–Alder cycloaddition reactions are being developed with this objective in mind. Novel aldol chemistries have been exploited as a means for construction of the bis-piperidinyl core associated with the Australian marine natural product haliclonacyclamine A. Significantly, ecological and other evaluations of this core molecule, as carried out by our collaborators including A/Professor Mary Garson, reveal that the compound retains much of the potency of the structurally much more complex parent (natural) compound. *(With D A S Beck, S Chand, J Crossman, S Gross, M J Harvey, O J Kokas, S Lampe, D Pinkerton, J Renner, P Stanislawski, M O Sydnes, R Taylor, and C Burns [Cytopia, Melbourne], R H Don, V Ferro [Progen Industries Ltd, Brisbane], M J Garson [U Qld], C R Parish [JCSMR, ANU], G P Savage (CSIRO Molecular Science, Melbourne])*

http://rsc.anu.edu.au/research/banwell.php