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. Vinblastine (a binary indole-indoline alkaloid used in the treatment of early childhood leukaemia and bladder cancer) and galanthamine (a plant-derived alkaloid used in the treatment of Alzheimer's disease) remain key targets and have inspired a considerable number of methodological studies. Australian companies have funded a significant portion of our work. For example, Cryptopharma Pty Ltd, a Melbourne-based biotech company, is supporting two PhD candidates who have been working on a very enjoyable collaborative project focused on the identification of non-steroidal compounds capable of treating acute forms of asthma. Another PhD scholar is working on a collaborative project with Biota Holdings that is directed towards the preparation of potent anti-infective agents while a fourth such person is working with Starpharma Pty Ltd on the development of new drug delivery systems. A very productive and longstanding collaboration with the Brisbane-based company Progen has continued throughout the year and involved two postdoctoral co-workers. They have been focused on the preparation of novel classes of anti-angiogenic agents as second-generation analogues of the highly promising drug candidate PI-88 originally developed in Professor Chris Parish's laboratories at the John Curtin School of Medical Research.

Other research highlights include:

(i) the completion of a chemoenzymatic total synthesis of the triquinane-type natural product (–)-complicatic acid (Figure 1), a fungal metabolite possessing powerful anti-bacterial properties;

(ii) the completion of a total synthesis of the non-natural enantiomeric form of the alkaloid erythramine (Figure 2);

(iii) the identification of a new methods for constructing annulated furans;

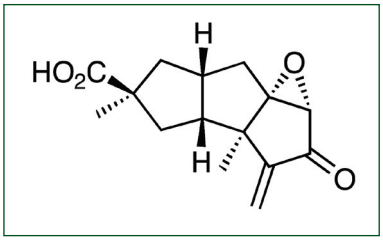

Figure 1: (–)-Complicatic acid, a fungal metabolite possessing anti-bacterial properties.

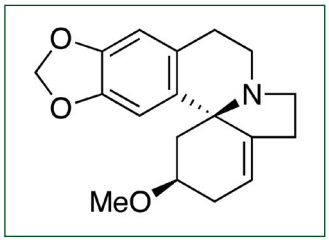

Figure 2: *ent*-Erythramine, the non-natural enantiomeric form of the alkaloid erythramine.

(iv) the rapid assembly of tetracyclic frameworks related to gibberellins;

(v) the identification of enzymatic methods for the efficient preparation of enantiomerically pure *gem*-dibromocyclopropanes;

(vi) the exploitation of the palladium[0]-catalysed Ullmann cross-coupling reaction in the generation of annulated isoquinolines.

During the course of the year, a number of group members reached significant milestones and/or received important recognition for their research efforts. For example, Drs David Lupton and Rebecca Taylor each received their PhD degrees. David was subsequently awarded a Sir Keith Murdoch Fellowship from the American Australian Association and he is now undertaking postdoctoral studies at Stanford University with Professor B Trost in the Department of Chemistry. Former PhD candidate Dr David Loong has been awarded a Ramsay Memorial Fellowship and is now undertaking postdoctoral studies in the Department of Chemistry at Imperial College,

London, with Professor A Barrett. Dr Gwion Harfoot has been awarded a Fellowship from the von Humboldt Foundation and is now undertaking postdoctoral studies in the Department of Chemistry, RWTH-Aachen, Germany and working with Professor C Bolm. Ms Jasmine Jury was the co-recipient of the prize for the best oral presentation by a PhD student within the RACI's Organic Chemistry Division program associated the CONNECT 2005 Conference held in Sydney in July. Ms Kerrie Austin received the prize for the best poster presentation by a PhD student at the RACI's NSW Organic Chemistry Group's 26th Annual One-day Synthesis Symposium held at the University of Wollongong in November.

Exploitation of *cis*-1,2-Dihydrocatechol 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 various pericyclic processes, continue to be a major area of activity and some of the products derived from such reactions have been converted, using photochemically-promoted transformations, into the polycyclic skeleta associated with a diverse range of terpenoid natural products. Other natural products being targeted include the alkaloid brunsvigine and the macrolide tricholomenyn B (a potent anti-mitotic agent). The preparation of various sugar mimetics continues to be another activity in this area and one that has been carried out with commercial partners. The search for synthetic equivalents for the title compounds has started and some promising results have been obtained. *(With K A B Austin, M Backes, T Bilski, M Bonnet, L Fearnside, J S Foot, M P Friend, G J Harfoot, J Jury, J Kitching, M Knoke, D T J Loong, D W Lupton, X Ma, J Renner, T Reekie, P Sharpe and R H Don, V Ferro [Progen Industries Ltd, Brisbane], J Lambert [Biota Pty Ltd, Melbourne], G Krippner, T McCarthy [Starpharma Pty Ltd, Melbourne], G Whited [Genencor International Inc, Palo Alto], A Stewart [Cryptopharma Pty Ltd])*

New Synthetic Strategies and Methodologies

The electrocyclic ring-opening of ring-fused *gem*-dibromo- and *gem*-dichloro-cyclopropanes continues to be employed in a wide variety of contexts, with one especially notable activity being focused on the construction of the polycyclic frameworks associated with a range of alkaloids. The exploitation of pyrroles and indoles as nucleophilic scaffolds for the construction of various alkaloids also remains a major activity within the group. Knoevenagel chemistries have been exploited in the construction of the bis-piperidinyl core associated with the Australian marine natural product haliclonacyclamine A and work is now focused on constructing, using the Ramberg–Bäcklund reaction, the two remaining ring systems associated with this ecologically important compound. *(With D A S Beck, A Bissember, D Dauge, S Gross, M J Harvey, K Holden, M Jones, O J Kokas, D A Offermann, D Pinkerton, J Renner, P C Stanislawski, M O Sydnes, R Taylor, and C Burns [Cytopia, Melbourne], R H Don, V Ferro [Progen Industries Ltd, Brisbane], M Garson [U Queensland], C R Parish [JCSMR, ANU])*

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