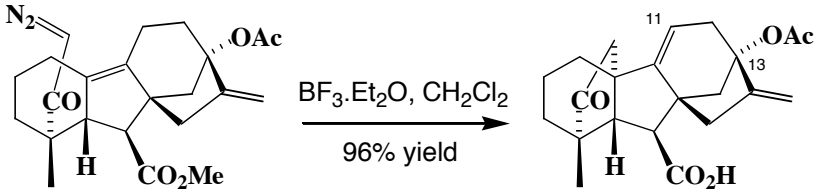
Professor Lew Mander

Our research interests are concerned primarily with methods and strategies for the synthesis of complex natural products that have interesting biological properties. Within this context, members of the group have successfully completed syntheses of numerous complex natural products and developed a number of useful synthetic procedures. We are also interested in the molecular basis of plant growth regulation, using organic synthesis as an enabling technology, with special reference to the gibberellins (GAs). GAs affect numerous aspects of plant growth and development, for example, germination, induction of stem growth and flowering, and there are several commercially valuable applications. Studies pursued in collaboration with groups in the CSIRO and the University of Calgary have led to the discovery of semi-synthetic derivatives that interfere with the plant's natural production of phytohormones, thereby inhibiting growth.

Structural and Synthetic Studies on New Gibberellins

There are now approximately one hundred and forty confirmed naturally occurring gibberellins. Most of the recently isolated compounds have been obtained in trace amounts and so the usual tools for structure elucidation cannot be deployed. Fortunately, it is possible to make educated guesses regarding the new structures from mass spectra and then to confirm the assignments by synthesis from one of the more readily available fungal GAs. Over the past two years, methodology has been developed for the preparation of several 11,13-dihydroxy-GAs and has allowed the identification of four new GAs from loquat fruit. The pivotal steps in these syntheses involve an acid catalysed cyclisation of diazoketone **1** to the 9(11),16-diene **2** which, after protection of the bridged ketone functionality, was subjected to a double hydroboration to introduce the desired 11β-hydroxy group. *(with T.P. Le, B. Twitchin)*

See also: http://www.plant-hormones.info/gibberellins.htm

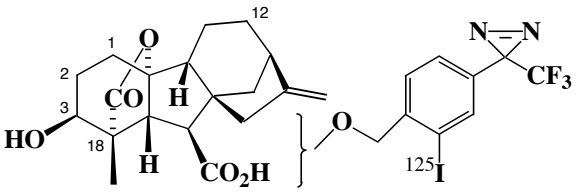


1 **2**

Preparation of Photo-affinity Probes for Labelling of Gibberellin Receptors

In order to understand more fully the molecular basis of gibberellin bioactivity, we are presently undertaking the synthesis of gibberellins with attached groups designed to crosslink to binding sites in receptors and other gibberellin ("GA")-binding proteins. Trifluoromethyl aryl diazirines have been shown to be some of the most effective auxiliaries for photo-affinity labelling, but their steric bulk may interfere with binding. Before attempting to prepare a fully elaborated probe, *e.g.* **3**, we have made and tested a

series of benzyloxy substituted GAs and evaluated their bioactivity. Substituents at C-1, C-2 and C-18 have been shown to substantially reduce bioactivity, but the 12-substituted GA **4** retains the biological potency of the parent GA, encouraging us to construct probes based on GA derivatives of this type. *(with J.R. Crow, M.J. McDonough)*



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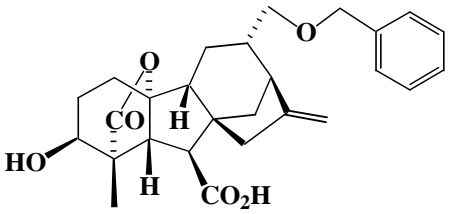

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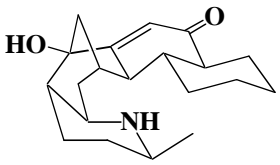
Total Synthesis of Natural Products

Synthetic studies are being directed towards the assembly of several highly caged natural products. They include members of an unusual group of alkaloids isolated from the Northern Australian rain forest species, *Galbulimima belgraveana*. One compound, himbacine, is a potent muscarinic antagonist and is a lead compound in the search for drugs to treat Alzheimer's disease. Our own efforts have been focused on the more complex members of the family, for example, himaline (GB 13) **5** and himandridine **6**. The synthesis of **5** has been achieved and the full hexacyclic skeleton of **6** assembled.



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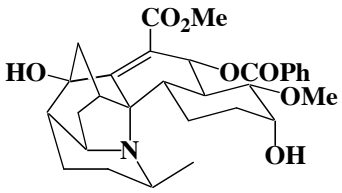

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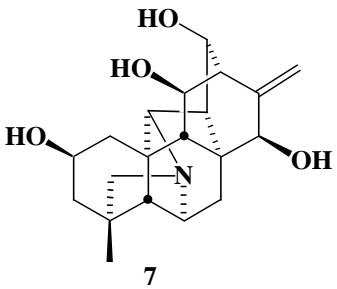
Preliminary studies on the construction of the heptacyclic family of diterpenoid alkaloids typified by hetisine **7** have been undertaken. A number of promising leads have been developed, but have failed because of the intervention of unusual and unprecedented rearrangements. An enantio-convergent synthesis of the anti-fungal agent sordaricin **8** has been completed, while a promising beginning has been made towards the total synthesis of the anti-malarial diterpenoid, diisocyanoadociane **9**. *(with O.E. Hutt, K.A. Fairweather, M.M.W. McLachlan, P.D. O'Connor, R.J. Thomson)*



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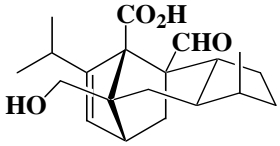

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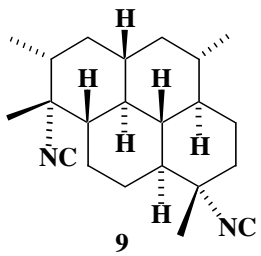

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http://rsc.anu.edu.au/research/mander.php