



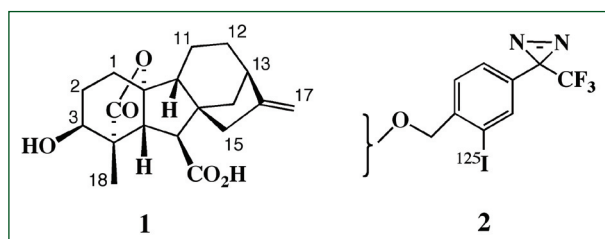
ORGANIC SYNTHESIS

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, including 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.

Preparation of Photo-affinity Probes for Labelling of Gibberellin Receptors

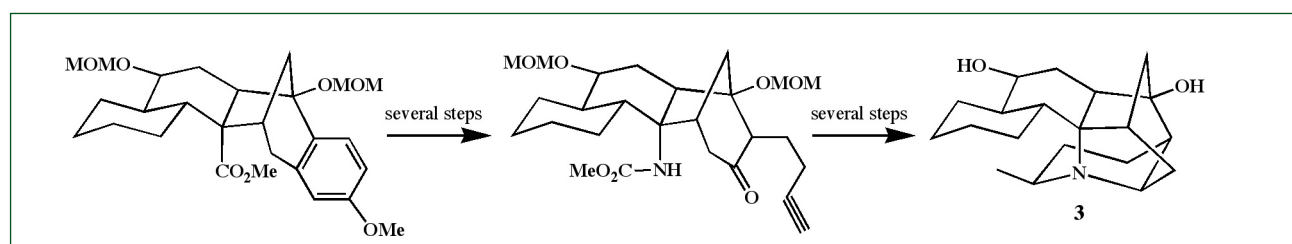
In order to understand more fully the molecular basis of gibberellin bioactivity, we are presently undertaking the synthesis of gibberellins with attached groups designed to crosslink to binding sites in receptors and other gibberellin ("GA")-binding proteins. Trifluoromethyl aryl diazirines have been 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, we have made and tested a series of benzyloxy substituted GAs and evaluated their bioactivity. Substituents at C-1, C-2, C-11, C-12, C-13, C-15, C-17 and C-18 (see structure 1 for numbering) have been screened in leaf-growth and barley endosperm bioassays with those substituted at C-2 α , C-11 and C-12 shown to retain acceptable levels of bioactivity. However, when the benzyl group was substituted with iodine and the diazirine photophore (as in part structure 2), biological activity dropped to <1% of the corresponding parent gibberellin. We have therefore directed recent endeavours to gibberellin derivatives

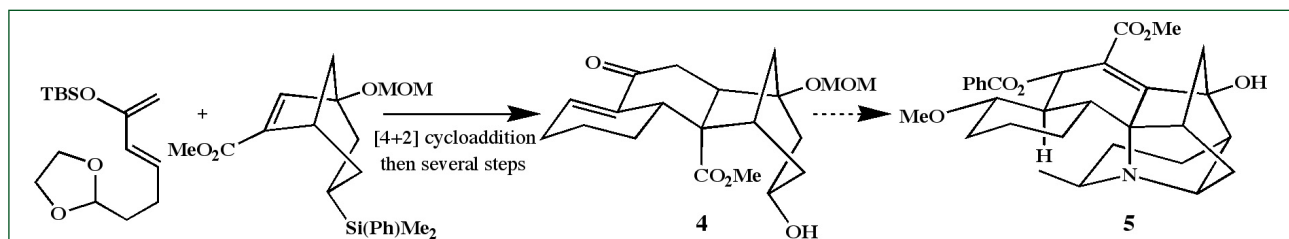


that have the substituted benzyl group attached *via* an extended linker based on tetraethylene glycol. (With J R Crow, M J McDonough, S M McAteer, L C Axford)

Total Synthesis of Natural Products

Synthetic studies are being directed towards the assembly of several highly caged natural products. They include members of a group of 28 novel alkaloids isolated from the Northern Australian rain forest species, *Galbulimima belgraveana*. Recent studies have culminated in the assembly of the hexacyclic skeleton 3, which was envisaged as an advanced intermediate





for the preparation of the alkaloid himandrine 5. However, difficulties with the logistics of continuing with this plan have prompted us to take a more direct approach, proceeding *via* 4, the preparation of which is outlined in the following scheme.

Preliminary studies on the construction of the heptacyclic family of diterpenoid alkaloids typified by nominine 6 have been undertaken. A number of promising leads have been developed, culminating in the assembly of the tetracyclic intermediate 7, while the diester 8 has been prepared with complete stereocontrol of all ten stereocentres *en route* to the total synthesis of the potent anti-malarial diterpenoid, diisocyanoadociane 9. All that remains to be done in this last sequence is the conversion of the ester functionality to isonitrile through means of a Curtius rearrangement. (With G Del Signore, O E Hutt, K A Fairweather, A C Willis)

