ORGANIC CHEMISTRY

New routes to natural products

John Mann

At one time, the synthesis of complex molecules was the noblest pursuit for an organic chemist. During the past ten years, however, many organic chemists have been lured by the fat research grants and contemporary glamour of bio-organic chemistry. So it is good to see two excellent examples of natural-product synthesis reported by Ley *et al.*[1-7]. The biological interest of one of the compounds (*myo*-inositol 1,4,5-triphosphate (IP_3)) is well known, but that of the other (the anti-parasitic agent avermectin B1a), is also considerable.

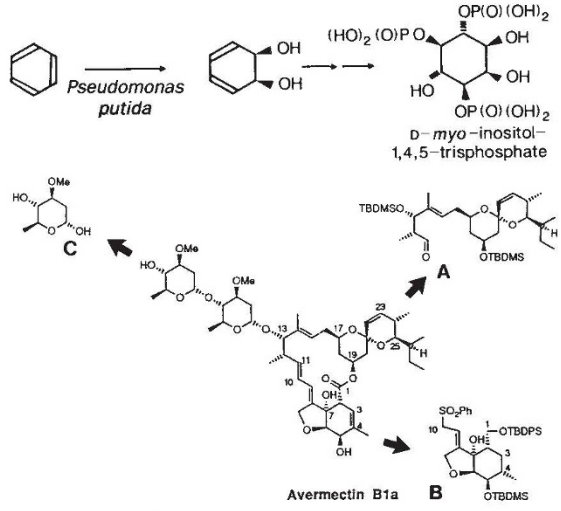
There has been enormous interest in the inositol phosphates, in particular the role of IP_3 as a second messenger, ever since their involvement in intracellular signalling was first proposed by Mitchell[8] in 1975. A number of syntheses of both the natural compounds and certain analogues have been described, but almost all of these commence with *myo*-inositol and proceed via a tortuous sequence of hydroxyl-group protections and deprotections in order to establish the desired phosphorylation pattern. Ley's approach[1-3] is conceptually different in that *cis*-3,5-cyclohexadiene-1,2-diol is used as the starting material (top in figure). This is produced from microbial oxidation of benzene by *Pseudomonas putida* and is thus cheap and readily available.

The remaining hydroxyl groups are introduced in a regio- and stereocontrolled manner to produce IP_3 and a large number of analogues. This new route is concise, does not use expensive or esoteric reagents, and provides access to the racemic forms of the compounds, or the pure enantiomers (both natural and unnatural) with only minor modifications. The approach makes a novel range of IP_3-related compounds readily accessible for biological investigation.

The avermectins are mould metabolites first isolated in 1976 from a strain of *Steptomyces avermitilis*[9]. They were shown to have high potency and broad spectrum of activity against animal parasites. The compounds seem to act at GABA receptors and to maintain the chloride channels in the open form, thus potentiating the inhibitory activity of GABA at neuronal junctions. Several avermectins are now produced routinely using fermentation technology, and ivermectin (the dihydro-analogue of avermectin B1a) is at present sold in more than 60 countries worldwide for the control of both internal and external parasites of livestock.

Notwithstanding this availability, the compounds are challenging targets for synthesis. Avermectin B1a, for example, has 20 stereocentres and a host of delicate functional groups; and to probe the biological activity of these interesting molecules, selected analogues must be prepared. Several research groups have accepted the challenge, but only one complete synthesis[10] of an avermectin has been reported previously.

Ley's new route[4-7] (bottom in figure) has the advantages of both conciseness and convergence of the various synthetic routes. The innovative chemistry devised to solve particular synthetic problems is the most interesting aspect of the work. Highlights include the use of organo-iron chemistry to produce not only the key spiroacetal (**A** in figure) but also the oleandrose subunits (**C**); and the coupling of the fragments **A** and **B** to form the aglycone. The final steps of the synthesis were achieved with the minimum of protection/deprotection of hydroxyl groups by an elegant exploitation of the selective reactivities of these groups. The overall route is flexible enough to allow for the synthesis of analogues, and should be of great value for further biological investigation of the way that these compounds work. □



Synthetic schemes to two natural products (see text).

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OCEAN DRILLING PROGRAM

Evolution of the Japan Sea

Leg 127 and Leg 128 shipboard scientific parties

Legs 127 and 128 of the Ocean Drilling Program spent the summer and early autumn of 1989 drilling at six sites in the Japan Sea (see figure). The goals of these two expeditions aboard the RV *JOIDES Resolution* were to assess the timing, style and dynamics of the opening of this sea and to decipher its subsequent palaeoceanographic evolution.

The western Pacific region is characterized by a series of marginal basins bordered by many island arcs. The formation of these marginal seas is intimately linked to the subduction of oceanic crust at adjacent deep-sea trenches. This process fuels the volcanic arcs and creates new oceanic crust and marginal seas through sea-floor spreading and faulting in the back-arc areas between the subduction zone and the continent. The Japan Sea is a large back-arc basin with water depths greater than 3,500 m, separated from the adjacent Pacific Ocean by shallow bathymetric sills of less than 150 m depth. The geology and geophysical structure of the Japanese Islands point to the presence of continental crust beneath the Japan arc, which in turn calls for a history involving continental rifting and separation of the arc from mainland Asia through back-arc formation of the Japan Sea — a tectonic scenario thought to be responsible for the evolution of many ancient continental margins.

Sixteen years ago, Leg 31 of the Deep Sea Drilling Project (DSDP) attempted to study the history of the Japan Sea but failed to penetrate the sedimentary cover and sample basement rocks, thus leaving many fundamental questions unanswered. So the highest priority of Legs 127 and 128 was recovery of basement rocks, which should record the earliest phases in the evolution of the sea. Leg 127 drilled four locations in the Yamato and Japan basins (sites 794, 795, 796 and 797), where rocks that represent acoustic basement on seismic reflection profiles were