the preparation of intermediate **3**, was chiral. They introduced the desired stereochemistry in the other intermediates by asymmetric catalysis.

The key step in the synthesis of intermediates **1** and **2** is the initial introduction of chirality. For intermediate **1**, this was achieved by introducing the two hydroxyl groups at carbons C-5 and C-6 by means of the Sharpless asymmetric dihydroxylation protocol[9]. The equally effective Sharpless asymmetric epoxidation methodology[10] introduced the stereocentres at C-4′ and C-5′ of intermediate **2**.

The construction of S1 from these three fragments was also a notable accomplishment, especially when one considers the vast array of functionality contained within them. There are several steps which required careful choice of reagents and conditions to effect the desired transformation selectively, so it is not surprising that six of the twelve steps required to complete the synthesis produce the desired compounds in yields of 50 per cent or less. Overall, the route used by Nicolaou *et al.* has more than 30 sequential steps, with an overall yield of less than 0.01 per cent.

Zaragozic acid C, as with all the isolated compounds in this family, differs only in the substitution pattern of the two side chains (the structure is shown in part *b* of the figure). It is therefore not surprising that Carreira and Du Bois adopt a similar approach to that of Nicolaou and coworkers in their synthesis of this compound. But their preparation of the 'core' began with D-erythronic γ-lactone (**4**), a commercially available compound containing two chiral centres. Carreira and Du Bois also adopt the Sharpless asymmetric dihydroxylation reaction to introduce the hydroxyl groups stereoselectively at C-6 and C-7. Although zaragozic acid C has a slightly less complicated structure than S1, this synthesis is ostensibly far more efficient. It embraces a similar number of linear steps, but here the overall yield is 2.5–3.9 per cent.

Much remains to be done. 'Lead' compounds — those initially identified as having a desired biological activity — rarely become drugs as they may have either low activity *in vivo* or a poor therapeutic selectivity. They may have detrimental side effects that potentially preclude them from medical use. Many derivatives must be synthesized and their biological activity evaluated to identify the one with the greatest potency and selectivity, and the least toxicity. In this context, these syntheses are considerable achievements. Both represent flexible approaches to this family of compounds and will allow the preparation of many derivatives that may be inaccessible by the known fermentation process. □

Mike J. Kelly and Stanley M. Roberts are in the Department of Chemistry, University of Exeter, Stocker Road, Exeter EX4 4QD, UK.

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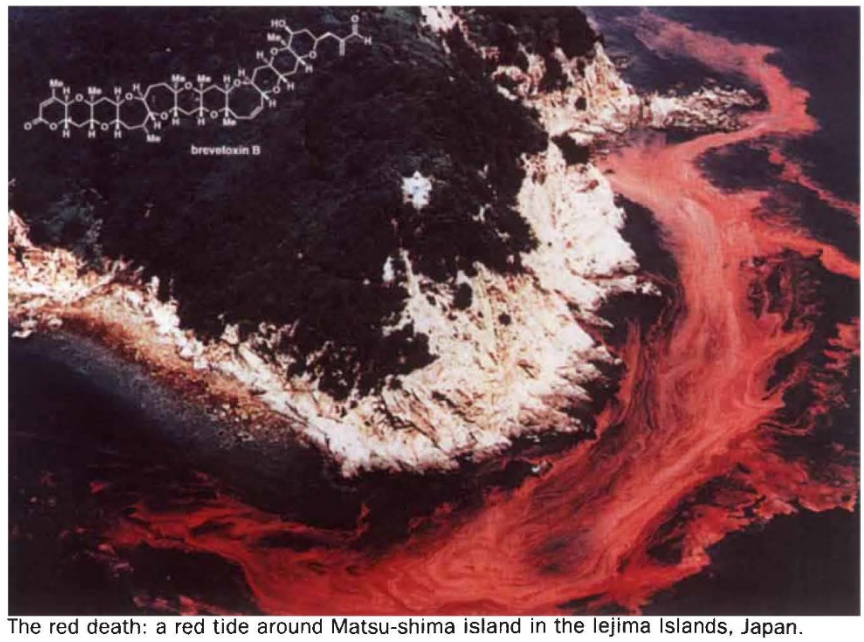
Manufacture of a marine menace



K C Nicolaou

The red death: a red tide around Matsu-shima island in the Iejima Islands, Japan.

SCALING the pinnacles of synthetic chemistry can be a risky business. The synthesis, in 1989, of palytoxin by Yoshito Kishi and colleagues at Harvard, showed the world how to make the most toxic non-protein compound known. Now K. C. Nicolaou's team at Scripps have constructed another potent marine biotoxin, brevetoxin B (*J. Am. chem. Soc.* 117, 1171–1172 and 1173–1174; 1995).

The interest in both of these toxins is stimulated by their lethal effects in the marine environment. Brevetoxin B is produced by the algae *Gymnodinium breve*, one of the common components of the notorious 'red tides' that have plagued coastlines throughout the world. Neurotoxins of the brevetoxin family are thought to have killed hundreds of bottlenose dolphins from New Jersey to Florida in 1987–88, and episodically to devastate fish in the Gulf of Mexico.

Red tides are the result of vast algal blooms, which often occur in nearshore environments near populated areas (particularly around Japan and North America) as a result of coastal pollution. The red colour derives from the common presence of red-pigmented phytoplankton — although some so-called 'red tides' are brown, green or do not involve discolouration at all.

Brevetoxin B, first characterized in 1981, contains a snake-like assembly of eight six-membered, two seven-membered and one eight-membered rings, and no fewer than 23 chiral carbon centres (by comparison, taxol has a mere 11). Nicolaou and colleagues have applied a convergent synthetic strategy that first involves building the central unit of two six-rings and two seven-rings. To either end of this structure they add a string of three six-rings. The second of these steps begins with a Wittig coupling of an aldehyde to an ylid pendant to the central polycyclic unit — this creates the carbon–carbon double bond of the eight-ring, which is then cyclized by a straightforward condensation reaction.

What might one want to do with a synthetic neurotoxin that kills fish and marine mammals and is highly harmful to humans? Of course, a synthetic feat of this sort is inevitably a trail-breaking exercise that involves the development of new general strategies. But the immediate value of the work may be to facilitate exploration of the biochemical mechanism of brevetoxin's neurotoxicity, perhaps through the creation of new derivatives. Philip Ball