Structural chemistry

Complete structure of palytoxin elucidated

from Yuzuru Shimizu

ABOUT two years ago, two groups — one at Hawaii led by R. Moore and the other at Nagoya, Japan, led by Y. Hirata — independently reported the elucidation of the gross structure of palytoxin, a potent neurotoxin of marine origin^{1,2}. The news created a considerable sensation among chemists and toxicologists. The toxin, with a molecular formula $C_{129}H_{223}N_3O_{54}$ (molecular weight 2,678.5), has no repeating unit and is frilled with many functional groups, including hydroxyl groups, and is considered to be the most complicated molecule ever elucidated by the conventional method without the use of X-ray crystallography. At the time, however, few people imagined that the stereochemistry of the whole molecule, which includes 64 chiral centres and seven double bonds allowing geometrical isomerism, could ever be solved in the near future. In the 15 December issue of *Journal of the American Chemical Society*, four consecutive communications appeared as joint contributions from a group at Harvard headed by Y. Kishi and the aforementioned Japanese group³⁻⁶. In the last of the four communications, the authors present the structure of palytoxin with complete stereochemistry including absolute configurations.

The publication had, in fact, been preceded by another report on the stereochemical structure of palytoxin from the Hawaii group⁷. The two structures differed in the assignment of 11 chiral centres in the molecule. The structure presented by Professor Kishi's group does appear to be unequivocal, however, as it is supported by synthetic evidence.

Palytoxin was first isolated by J. Scheuer's group at the University of Hawaii from a marine zoanthid, *Palythoa toxica*⁸, and later from other *Palythoa* species — there are minor structural variations depending on the sources and locations. For their research the Hawaii group used mostly the toxin from one location at Maui Island, Hawaii, and the Japanese group, material collected from Okinawa. The toxin is the most deadly nonproteinous one ever isolated and its reported LD₅₀ of 0.15 µg per kg (intravenous injection in mice) makes it 50 times more toxic than tetrodotoxin and saxitoxin. Its mechanism of action, which seems rather complex, has raised tremendous interest among pharmacologists and it is also known to exhibit strong cytotoxicity against malignant cells.

The toxin consists of a 115-carbon straight-chain backbone with several cyclic

ethers, methyl groups and numerous hydroxyl groups. The ends of the chain are linked with a primary amino group and a small amide-containing moiety. The gross structure was elucidated by both the Hawaii and Japanese groups by first establishing the structures of various fragments and later their connectivity.

Kishi tackled the stereochemistry by synthesizing all the essential fragments derived from the oxidative cleavage of palytoxin in strictly stereochemically controlled conditions, and matching them with samples obtained from the natural compound. This approach, which obviously aims at the total synthesis of the toxin and requires knowledge of the stereochemistry of the molecule, was very clever in running the synthetic work and the stereochemical determination together. The astonishing thing is that despite the complex stereochemistry the Harvard group synthesized all the fragments in a very short time — less than two years.

Behind this breakthrough are the recent rapid developments in the stereospecific synthesis of polyhydroxylated natural products. Beginning with the synthesis of macrocyclic antibiotics, and then of polyalkylether-type antibiotics, in which Kishi's group was notably successful, synthetic chemists are now finding ways to synthesize stereospecifically various pentoses, hexoses and amino sugars, which no synthetic chemist dared to undertake decades ago. With the methodology at hand, it is natural for synthetic chemists to look at palytoxin with its numerous chiral centres and drastic biological activity as a challenging molecule. At least one more group is known to be competing with the

Harvard group to totally synthesize palytoxin⁹.

The Hawaii group's approach relied heavily upon high-resolution NMR spectroscopy. They carried out literally thousands of laborious proton-proton spin-decoupling studies and, although the results may have led to some erroneous conclusions, the effort was well worthwhile as a test case to determine the limitations of the approach in structural determination. The failure to assign several chiral centres derives partly from the dilemma intrinsic to the approach — to predict the stereochemistry of certain chiral centres from the spin-spin coupling data in NMR, one has to assume a certain conformation or shape of the molecule at the measurement. It is not an easy task to predict conformation, especially with such a large flexible molecule as palytoxin. Normally the conformation of a molecule is deduced from the NMR data of nuclei with known stereochemistry.

At all events, this seems to be a triumphant moment for synthetic chemists. The Harvard group concluded their report by saying "(the misassignment by NMR methods) points out the limitation of these types of experiments and the continuing importance of organic synthesis in structure elucidation". □

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The structure of palytoxin (from ref. 6).

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