Figure 1. Professor D. John Faulkner (copyright Scripps Institution of Oceanography).

D. John Faulkner (1942–2002): Marine Natural Products Chemistry and Marine Chemical Ecology

John Faulkner (Figure 1) made fundamental and highly insightful contributions to the study of marine natural products chemistry and chemical ecology for more than 30 years. His sense of rigor, coupled with a strong interest in education, made him an outstanding leader in these fields.

Faulkner's fascination with the chemistry of marine life began with his appointment as Assistant Professor of Marine Chemistry at the Scripps Institution of Oceanography (SIO), University of California, San Diego in 1968. Prior to taking up this appointment, Faulkner had received his PhD in 1965 in organic chemistry under the guidance of Sir Derek Barton at Imperial College, London. After graduation, Faulkner moved to Harvard University for postdoctoral studies with Robert B. Woodward, and later took up another postdoctoral position with William S. Johnson at Stanford University. With these extraordinary credentials in organic chemistry, Faulkner's decision to move to a career position at an oceanographic institution seemed strange to many people. But John Faulkner had the ocean in his heart, the rigors of chemistry in his mind. Born on June 10, 1942 in Bournemouth, England, Faulkner grew up next to the sea. When he joined the faculty at the SIO, he quickly began to recognize the paucity of information on the natural products in the sea. In comparison with the well-studied natural chemical diversity on land, the oceans and their inhabitants had received virtually no attention. In the early 1970s, Faulkner and his students made important chemical discoveries that provided the foundation of our understanding today. His chemical studies of marine plants showed for the first time that halogenation was a prominent natural process in marine environments. During the formative period of the 1970s, when science-policy makers worried about the use of commercial halogenated pesticides, it was shocking to realize that halogenation with chlorine and bromine (from seawater) could be involved in such robust natural processes. Faulkner and his students went on to demonstrate the widespread nature of halogenation in invertebrates as well, and to illustrate the structural diversity of over 100 halogenated terpenes and polyketides from marine sources.

During these early years, Faulkner began his selfinitiated education in ecology, a pursuit he continued until his death on November 23, 2002. Although not formally trained in this area, Faulkner collaborated with biologists to recognize that secondary metabolites in the ocean were the foundation of a complex chemical adaptation for defense. His studies of the herbivorous sea hares, for example, showed the complexity of an evolutionary adaptation in which sea hares selectively feed on "toxic" marine plants and concentrate the secondary metabolites for their own defense.

As part of Faulkner's great interest in marine chemistry, he developed a lifelong fascination with the secondary metabolites produced by marine sponges. He was convinced that the incredible diversity of novel structures, coupled with their rich bioactivities, provided the foundation for defense in soft-bodied invertebrates. Faulkner was clearly a leader in this field and identified more than 300 invertebrate-derived molecules in his career. As with the sea hares, the related shell-less molluscs, known as the nudibranchs, were found to feed on sponges and other chemically rich animals and to concentrate toxic metabolites for their own defense. Faulkner recognized that this group of shell-less molluscs had evolved to use diet-derived chemical defenses. This led to one of Faulkner's most significant contributions in ecology, published with Michael Ghiselin, which provided a justified hypothesis that opisthobranchs had coevolved with toxic foods, thus facilitating the loss of their shells over evolutionary time.

Despite his interest in ecology, Faulkner was the chemist's chemist. He and his students studied hundreds of sponges and isolated and defined the structures of complex secondary metabolites with unprecedented carbon skeletons and new functional groups. For example, he discovered the naturally occurring carbonimidic dichloride functional group ($C=NCl_2$) in sponges of the genus *Pseudaxinyssa*. The discovery of this functional group, which was previously only known in synthesis, exemplified his curiosity and the rigor and precision that he applied to his daily chemical research.

In the early 1980s, Faulkner made a significant career shift when he realized the enormous biomedical potential of marine metabolites. From his previous work, he knew that sponges, in particular, were a rich storehouse of bioactive molecules of largely unprecedented structural types. Working with his colleague Robert Jacobs (University of California, Santa Barbara), Faulkner made many chemical discoveries, which were found to be important in the development of antiinflammatory drugs. None were of greater importance than the discovery of manoalide, a terpenoid sponge metabolite which selectively inhibits the important inflammation enzyme Phospholipase A2. Subsequent to this discovery, Faulkner and his colleagues completely deciphered the chemical mechanism of action of manoalide, which stirred significant industrial interest in this new class of antiinflammatory agents. Manoalide is still used today as a molecular probe to investigate the specific functions of PLA2.

Faulkner's interests in marine biomedical research grew to include projects involving the isolation and structural determination of more than 25 new antibiotics and numerous new anticancer agents. During the period 1985–2000, Faulkner took part in major collaborations with biomedical researchers to explore the application of marine-invertebrate metabolites in various medical applications. Faulkner's work resulted in the discovery of a unique

inhibitor of protein transport that induces Golgi-membrane vesiculation, a potent inhibitor of kinesin motor proteins, three new inhibitors of HIV Integrase, a new marine bacterial siderophore, and several new antifungal agents.

Faulkner's fascination with sponges was partly derived from the fact that many sponges harbor symbiotic bacteria in very high densities. These bacteria often comprise up to 50 % of the sponge mass. He routinely professed that it was impossible to know if the unique secondary metabolites from sponges were products of sponge cells or of the bacterial symbionts. Chemical evidence, namely the structural similarity of many sponge metabolites to those produced by terrestrial bacteria, strongly suggested a symbiont source, but scientific evidence was lacking. In a series of clever experiments, Faulkner and his students methodically separated sponge cells from bacterial cells by density centrifugation. Analysis of the isolated cells showed that in Lithistid sponges, metabolites are stored in, and presumably produced by, bacterial cells. These experiments provided the first strong evidence for a major chemically based symbiotic association in marine invertebrates. Faulkner and his students went on to explore these symbionts by molecular-genetic methods. Although the symbionts could not be cultured under the conditions examined, genetic-sequence analysis of their cloned 16S rRNA genes showed these bacteria to be of an entirely new class.

Faulkner was a prolific writer and published more than 350 peer-reviewed papers, among which was an excellent Review in this journal.[1] His most often cited papers were his scholarly reviews published for 17 consecutive years in *Natural Products Reports*. These reviews, now considered the most authoritative works in this field, are comprehensive analyses containing both critical and laudatory remarks on findings within this discipline.[2] In recognition of his extraordinary contributions to this field, Faulkner was the recipient in 2000 of the Paul J. Scheuer Award in Marine Natural Products Chemistry.

William Fenical
La Jolla, CA (USA)

[1] C. A. Bewley, D. J. Faulkner, *Angew. Chem.* **1998**, *110*, 2280; *Angew. Chem. Int. Ed.* **1998**, *37*, 2162.
[2] D. J. Faulkner, *Nat. Prod. Rep.* **2000**, *17*, 1 – 57.

