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# *Editorial*

## Special Issue in Honor of Professor Kenneth L. Rinehart

Ken Rinehart. Photograph by John Katzenellenbogen © 1985

The Guest Editors for this special issue of the *Journal of Natural Products* consider it an honor to bring to our readers a collection of papers, reviews, and notes on contemporary natural products research dedicated to the late Professor Kenneth L. Rinehart. We would like to express our gratitude and appreciation to Ken's former students, postdoctoral fellows, visiting scientists, and other colleagues for generously contributing their time and effort to produce such a diverse, high-quality set of manuscripts for this issue.

Kenneth L. Rinehart Jr. was born on March 17, 1929, in Chillicothe, Missouri, and died on June 13, 2005, at his home in Urbana, Illinois. During the intervening period, he established himself as an exceptional scientist with prodigious talent. Professor Rinehart received a B.S. with High Honors from Yale University in 1950 and earned his Ph.D. in chemistry from the University of California (Berkeley) in 1954. Soon thereafter, he joined the faculty at the University of Illinois at Urbana−Champaign and spent his entire career there. Starting with his appointment as an Instructor in Organic Chemistry in 1954, he rose through the ranks to become Professor of Chemistry in 1964 and, eventually, a University Scholar in the School of Chemical Sciences. During his distinguished and productive career of nearly 50 years, he authored or coauthored approximately 390 scientific papers and book chapters, 35 patents, and seven books. Ken's research focused on all aspects of natural products chemistry, including isolation, structure elucidation, biological evaluation, biosynthesis, and chemical synthesis. He was a true pioneer who made important, fundamental contributions in a remarkably wide range of areas, including mass spectrometry, biosynthesis, structure determination, mutasynthesis, and marine natural products chemistry. The myriad results arising from his work were influential in demonstrating the value of bioassay-guided fractionation and interdisciplinary collaboration, and continue to have a major impact in the field of drug development from natural sources.

Professor Rinehart's earliest independent investigations involved studies of ferrocenes and related organometallic compounds, but he quickly developed a keen interest in the chemistry and biological activity of natural products that remained with him for the balance of his career. His initial efforts in the natural products arena focused on structure elucidation and biosynthetic studies of antibiotics produced by actinomycetes. He was particularly interested in the neomycins, a new class of aminoglycoside antibiotics produced by *Streptomyces fradiae*. The structures of these and other antibiotics, representing a wide variety of structural types, including streptolydigin, streptovaricins, and antiamoebins, were determined largely

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through spectroscopic methods developed during these studies. Many of the results from this work were incorporated into his book *The Neomycins and Related Antibiotics*, published in 1964.[1] This early interest in structure and biosynthesis led Ken to develop a novel method for the preparation of new metabolites, called mutasynthesis.[2] This approach to biotransformation of substrates into new compounds without interference from the naturally produced metabolite was embraced by research groups around the world, and many new antibiotics were discovered by application of this technique. In one particularly successful application, the avermectin derivative doramectin was prepared by Pfizer scientists using mutasynthesis, and this compound was eventually developed and commercialized as an antiparasitic agent.[3]

Professor Rinehart explored the biosynthetic pathways leading to formation of many important antibiotics employing radioisotopes, stable isotopes, and microbiological techniques. He was a pioneer in the use of carbon-13 labeling to investigate biosynthesis, as applied in his investigation of the neomycins. He also explored the biosynthesis of polyketides, the $C_7N$ unit found in pactamycin, and the peptide antibiotic berninamycin, where he was one of the first to prove that dehydro amino acids can be produced via dehydration of the corresponding hydroxyl precursor.

In 1960, Professor Rinehart played a leading role in obtaining the initial funding for state-of-the-art mass spectrometry instrumentation at the University of Illinois. The mass spectral behavior of natural products and the development of mass spectral methods for studying nonvolatile and labeled compounds were of major interest. Beginning with the use of GC/MS to characterize extracts, mainly in search of halogenated compounds, and extending through the mystery of FDMS into the FABMS/LCMS era and beyond, Ken was always at the forefront of research into the applications of mass spectrometry to the structure determination of natural products.

In the 1970s, Professor Rinehart became interested in the fledgling field of marine natural products chemistry. His work in this area led to the discovery of many new and interesting bioactive natural products, but two classes (didemnins and ecteinascidins) stand out as exceptional contributions. Didemnins constitute a unique class of cyclic depsipeptides discovered by the Rinehart group in the early 1980s from the Caribbean tunicate *Tridemnum solidum*.[4] These compounds have generated great interest due to their unique chemical properties and biological effects. Didemnin B, a major component, was the first marine-derived compound to undergo phase I clinical trials as an anticancer agent and was also the first to reach phase II testing for efficacy. The second-generation agent dehydrodidemnin B (also known as Aplidin), also arising from Professor Rinehart's work, is 6−10 times more active, but lacks the cardiotoxicity of didemnin B. It is currently in phase II clinical trials against both solid tumors and hematological malignancies. The didemnins display other remarkable bioactivities as inhibitors of both DNA and RNA viruses and as immunosuppressive agents. Natural didemnins and synthetic or semisynthetic analogues have been isolated, prepared, and/or investigated in many other laboratories, and their bioactivities and modes of action have been extensively explored.

Several years after the discovery of the didemnins, a second group of antitumor compounds, the ecteinascidins (Et's) were isolated by Professor Rinehart's group from another tunicate, *Ecteinascidia turbinata*.[5] The antitumor activity of the tunicate extract had been demonstrated earlier by the National Cancer Institute, but 15 years of efforts by chemists elsewhere to isolate the compound(s) responsible were unsuccessful. Et 743, the most abundant component, is present at only trace (ca. 1 ppm) levels in the tunicate. These compounds have fascinating structures containing bis- and tris(tetrahydroisoquinoline) units, and Et 743 shows in vivo activity in mice against ovarian, mammary, and lung tumors, as well as leukemia and melanoma. Numerous complete remissions of established tumors in human xenografts have been documented. Although Et 743 started clinical development later than didemnin B, it is regarded as a considerably more potent and probably more widely useful anticancer candidate. Et 743 (also known as trabectedin or Yondelis) has repeatedly worked safely and effectively in animal studies and through three stages of human clinical trials against soft-tissue sarcomas, as well as lung, breast, and ovarian cancers. The University of Illinois has licensed the rights to the compound to PharmaMar SA of Spain, and the compound is being developed jointly by PharmaMar and Johnson & Johnson.

Didemnins and ecteinascidins are the most conspicuous successes of the Rinehart group's marine natural products program, but numerous other bioactive compounds of differing structural types from a variety of phyla were also discovered through his work. Many of these discoveries came with the aid of innovative on-site bioassays. Considering the geographical disadvantage of performing marine research in Illinois, Professor Rinehart's group and collaborating scientists developed protocols in which small samples of accessible marine organisms were collected at a site, then extracted and assayed shipboard or on shore for the desired bioactivity: cytotoxicity, antiviral or antimicrobial activity, immunomodulation, even cardiostimulation. These on-site assays enabled testing of fresh organisms, presumably at their peak of activity, immediate recollection of active species, and selection of only active species for re-collection, sparing large-scale collection of other species.

Professor Rinehart's research was consistently supported over the years by major government granting agencies, particularly the National Institute of Allergy and Infectious Diseases, the National Cancer Institute, and the National Institute of General Medical Sciences, but he was also exceptionally successful in establishing productive collaborations with industrial groups and obtaining support from industrial sources. Indeed, Professor Rinehart displayed considerable entrepreneurial skills in his efforts to foster the development of marine natural products. Notably, he was involved with companies that targeted the discovery and development of marine-derived drugs, including SeaPharm, Inc. and PharmaMar SA, serving on the boards of both.

Ken's contributions were recognized through numerous honors and invited and plenary lectures in the U.S. and at international conferences. He was awarded an Honorary Doctor of Science degree from the University of Missouri in 1998, the Ernest Guenther Award in the Chemistry of Natural Products from the American Chemical Society in 1997, the Research Achievement Award from the American Society of Pharmacognosy (ASP) in 1989, and a 25th Anniversary Medal by the Kitasato Institute, Tokyo, in 1988, as well as Erskine and Sloan Fellowships. In 1995−1996, he served as President of the ASP. Ken also served on the editorial boards of several journals, including the *Journal of Natural Products*, *Journal of Organic Chemistry*, *Journal of Antibiotics*, *Journal of Medicinal Chemistry*, and *Biomedical Mass Spectrometry*, as well as a variety of advisory committees and review panels. During Ken's tenure at the University of Illinois, he trained 139 graduate students and 67 undergraduate research students, as well as 124 postdoctoral research associates and visiting senior scientists, many of whom were from abroad and a number of whom were repeat visitors. His academic progeny have filled a number of high-ranking industrial and academic positions and have been able to continue the Rinehart natural products research legacy into a new generation.

No such commentary would be complete without acknowledgment of Ken's wife and close companion, Marlyn—affectionately known to Ken (and his group) as Corky. Mrs. Rinehart has ensured that Ken's legacy will be remembered in the Chemistry Department at the University of Illinois for generations to come through her generous contribution that has enabled establishment of a chaired professorship in Ken's name.

All of the Guest Editors for this issue of the *Journal* were associated with Professor Rinehart at early stages in their careers

and learned much under his guidance. Intense esprit de corps, whether in the laboratory, in the field during collecting trips, or at the local pub, was a common feature of our experiences. Science with Ken Rinehart was always an interesting adventure, and a difficult act to follow.

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