Preface to *Heterocycles* Issue

Honoring the 70th Birthday of Professor Yoshito Kishi

It is both a considerable pleasure and great honor to acknowledge the many achievements of Professor **Yoshito Kishi** of Harvard University's Department of Chemistry and Chemical Biology. Yoshito Kishi was born on April 13, 1937 in Nagoya, Japan. He received both the B.S. (1961) and Ph.D.(1966) degrees from Nagoya University under the supervision of Professors Yoshimasa Hirata and Toshio Goto. During the period from 1966 through 1969 when he was instructor in the Department of Chemistry at Nagoya University, he took a leave of absence to conduct research at Harvard University as a post-doctoral fellow with the late Professor Robert Burns Woodward (1966-68). Upon returning to Nagoya, he was promoted to the position of Associate Professor in the Department of Agricultural Chemistry, which he held from 1969 through 1974. He was invited as a visiting Professor of Chemistry at Harvard for the academic year 1972-73, and was appointed as Professor of Chemistry at Harvard in July of 1974. He currently holds the title of Morris Loeb Professor of Chemistry at Harvard University where he served as Chairman of the Department from 1989-1992. In 1963, Yoshito Kishi married his wife Tokiko and has two daughters, Hiromi and Satoko. Professor Kishi is also responsible for the creation of the Eisai Research Institute in Andover, Massachusetts. He founded the Eisai Research Institute in 1997 and served as its Chairman for almost two decades. Professor Kishi has also previously served on the Board of Directors, and is currently Chief Scientific Advisor to the CEO for Eisai Co., Ltd.

Professor Kishi's record of achievement in the area of natural products total synthesis and synthetic methodology are unparalleled by any researcher of our time and it is not unreasonable to say that Kishi has become "a legend in his own time". His syntheses have uniformly been characterized by breath-taking daring in design, astonishing structural complexity and ingenious analysis coupled with swift, "first strike" execution. What is remarkable of his published total synthesis efforts are that, for virtually every molecule he has tackled, he has been the very first to achieve a synthesis of the target. In many cases, the Kishi synthesis remains the only synthesis (gliotoxin, sporidesmins, palytoxin, halichondrin B and many others).

After being attracted to Harvard, largely the efforts of the late Professor R.B. Woodward with whom Kishi spent a post-doctoral stint on the vitamin B_{12} synthesis from 1966-68, the publications that emerged from his lab at Harvard have set the cutting edge in complex molecule synthesis. More than any researcher of our time, Kishi has ventured to the very outer reaches of organic synthesis and has defined the present limits, strengths and weaknesses of the craft. He has been very selective in problem choice; each project that he has published on were ground-breaking and startling achievements. A few examples illustrate this point.

Kishi’s landmark total synthesis of tetrodotoxin, completed at Nagoya University in 1972, set the tone for what was to follow when he continued his brilliant academic career at Harvard University. His landmark achievement of the epidithiapiperazinedione syntheses including, sporidesmins A and B in 1973 and 1974, dehydrogliotoxin in 1973 and finally, gliotoxin in 1976 illustrate the amazing daring and brilliance of design in his synthetic conquests. These substances are notoriously unstable to base, oxidation and reduction. Kishi devised a brilliant dithioacetal blocking group for the disulfide that also allowed bridgehead carbanion functionalization of the piperazinedione ring to introduce the amino acid substituents into the glycine framework and also controlled stereochemistry. In many ways, this was a reinvention of the idea "protecting group" where, the protecting group was an integral functional group for the build-up of molecular complexity and "reserved" the unstable, strained bicyclic disulfide system in a stable form for final unmasking in the very final stages. None of these substances have ever been made by another lab despite many efforts.

This type of brilliant daring-do was also evident in the mitomycin syntheses reported in the late 1970's. These unstable alkaloids were constructed by synthesizing an eight-membered ring precursor, (a daring and important achievement at the time in it's own right) and performing a very delicate transannular cyclization to close the labile bicyclo[3.3.0] carbinolamine functional group.

In the late 1970's Kishi stunned the chemical world with the successive announcements of the total syntheses of the polyether antibiotics lasalocid, monensin, narasin and salinomycin. These substances were of unprecedented complexity at this time and through these works, Kishi pioneered the strategy of acyclic stereocontrol. These syntheses identified for the first time, the potential difficulties and tremendous potential of accessing a stereochemically complex acyclic array and ran counter to the proven strategy of building conformationally defined cyclic systems to control stereochemistry. These syntheses initiated the study of remote stereochemical control and the detailed conformational analysis of acyclic systems. Through these studies, Kishi has advanced the rules to predict the stereochemical course of reactions on an acyclic system, particularly those containing allylic groups. While others have subsequently synthesized lasalocid and monensin, Kishi took the most bold and daring approach. This is analogous to a mountaineering team ascending a peak that has never been climbed before by selecting the most difficult and daring route *first*. A stark contrast of these approaches could be seen ironically, at Harvard in the late 1970's: Prof. R.B. Woodward (Kishi's mentor) was in the final stages of completing erythromycin using classical, rigid, cyclic dithiadecalin rings; concomitantly, Kishi was in the final stages of the monensin synthesis (a substance more complex than the erythromycin aglycone with 2^{17} stereoisomers) using completely, acyclic stereocontrol elements.

Kishi followed this with the first synthesis of an ansa-macrolide, rifamycin S. The rifamycin synthesis coupled the use of acyclic stereocontrol with a brilliant and daring macrocyclic ring closure to form an unusual ketal enolether.

These studies into ever more complicated systems led Kishi to contemplate the total synthesis of the enormous marine toxin palytoxin. The Kishi work on the structure elucidation and total synthesis of this huge molecule containing 64 stereogenic centers and over 10^{21} possible stereoisomers, consumed most of a decade between 1980 and 1989 when Kishi again stunned the world with the announcement of the total synthesis of the largest and most complicated organic molecule ever assembled. Kishi applied a brilliant and logical method to break the palytoxin structure into smaller fragments for structural elucidation first and finally synthesis. Due to the size and functional group complexity of the palytoxin molecule, it was not possible to obtain crystals for X-ray analysis and nmr studies were unable to unambiguously assign every stereogenic center. Kishi used the unique vantage point of synthesis coupled with brilliant analysis to unravel the complete correct stereostructure for this molecule in 1982. This work culminated with the breath-taking announcement of the total synthesis in 1989. What is also surprising is the relatively small number of co-authors on the palytoxin synthesis paper (21 co-authors); given the size and complexity of the molecule, this provides striking evidence for Kishi's efficiency and mastery of strategic planning and problem execution. Kishi also studied the solution conformational properties of palytoxin and, through this work, has advanced the rules to predict the preferred solution conformation of oligosaccharides. To define the global conformational characteristics of palytoxin, Kishi developed a molecular ruler for the 15-50Å range and has applied this to oligosaccharides and fatty acids. The synthesis of the palytoxin molecule is without question a landmark achievement in organic synthesis; it has not only awed and inspired many of us, but has also served a very important philosophical and pedagogical role. This achievement and many of his other recent works have, in many respects, defined the outer limits of our current technology and understanding of molecular shape and reactivity. Another pioneering development from the Kishi laboratory which resulted from painstaking and brilliant analysis of acyclic stereochemically complex arrays, is the creation of an nmr data base which is just beginning to be recognized as a highly useful method for assigning relative stereochemistry in conformationally flexible, acyclic arrays found in many polyketide-derived natural products.

In 1992, the Kishi laboratory disclosed the total synthesis of halichondrin, an unusually potent cytotoxic marine natural product. This synthesis served to define, refine and test the utility of the Nozaki-Hiyama-Kishi Ni-Cr coupling reaction (NHK reaction). The halichondrin molecule has served as a template from which the Eisai company, has carved a smaller, yet still dauntingly complex clinical drug candidate (E7389) for the treatment of cancer. The industrial synthesis of this extremely potent antitumor agent, which possesses nineteen stereogenic centers, is at the very cutting edge of industrial process research and is also unmatched in terms of the sheer magnitude of the complexity of the molecule and the technical challenges posed to the manufacture of a drug substance of such complexity. The Kishi-Eisai collaboration on this project has redefined and might potentially revolutionize what might be possible in the future of pharmaceutical drug discovery and process manufacturing.

The Kishi work has paved the way for important future advancements in reaction technology, new methods, blocking groups, conformational analysis and strategic thinking. These pioneering contributions and aspects of Kishi's work must not be lost upon our community, nor the next generation of organic chemists and richly merits recognition. There are many who are currently preaching the "end of organic synthesis" and extolling the virtues of combinatorial chemistry and other biologically-based ways to obtain complex molecules and perform organic synthesis. Kishi's work in complex molecule synthesis will continue to hold numerous important lessons for the vital importance of organic synthesis in many problems, including traditional areas like structure elucidation and new trendy areas such as combinatorial chemistry. His brilliant strategic approach to many synthesis problems can not be rivaled or matched on a computer. It is very important for many of us, particularly the next generation of young chemists, to aspire to stand on the unclaimed summits that only Yoshito Kishi has stood upon and share the unique vantage point that his work has provided. Kishi has shown the scientific world what it is possible to do with our current and imperfect set of synthetic and analytical tools and where we must endeavor to go from here.

Professor Kishi has been recognized by many awards which includes: The Japan Chemistry Society Prize (Sinppo Sho, 1967); The Chunichi Press Award (Japan, 1973); ACS Award for Creative Work in Synthetic Organic Chemistry (1980); Guggenheim Fellowship (1980); Harrison Howe Award (1981); Member, American Academy of Arts and Sciences (elected in 1985); Arthur C. Cope Scholar Award (1988); Javits Neuroscience Investigator Award (1988); Naito Prize (1993); Nagoya Medal of Organic Chemistry (Japan, 1995); Prelog Medal (1995); Havinga Medal (1996); Imperial Prize (Japan, 1999); Japan Academy Prize (1999); Fellow, American Association for the Advancement of Science (elected in 1999); Honorary Member, The Chemical Society of Japan (elected in 2000); ACS Ernest Guenther Award in the Chemistry of Natural Products (2001); Tetrahedron Prize (2001); and the Person of Cultural Merits (Japan, elected in 2001).

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