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PREFACE TO SPECIAL ISSUE OF *HETEROCYCLES* HONORING THE 85TH BIRTHDAY OF PROF. DR. ALBERT ESCHENMOSER

> "….In my opinion, there **is** a problem that is central to organic chemistry alone and in which biologists cannot help us. We all agree…that the emphasis in synthetic research is the synthesis of **properties**," and not just compounds. Now, the most important property that we can attack by synthesis is the property of living. The problem, rigorously a problem of synthesis, is to study the laws, the rules, and the principles of self-organization of organic matter…."[1]

If ever there were a statement that epitomizes *the* grand challenge to the science of organic chemistry, it would be the one above from Albert Eschenmoser who, for more than six decades, has epitomized the vanguard of vision and practice in the field he has cherished and shaped.

The honor and pleasure of preparing a Foreword for this Special Issue of *Heterocycles* dedicated to the celebration of the 85th birthday of Professor Albert Eschenmoser also presents a formidable challenge in light of the breadth and impact of his contributions to organic chemistry. It is with greatest appreciation and respect for his inspiring mentorship and towering achievements that this necessarily brief and incomplete description of his scientific and personal legacy is composed.

Albert Eschenmoser was born on August 5, 1925 in Erstfeld, Switzerland. He received his Diploma in Natural Science in 1949 at the Swiss Federal Institute of Technology (ETH-Zürich). His doctoral studies continued at the ETH under the guidance of Prof. L. Ruzicka and Prof. H. Schinz and he was awarded the Dr. Sc. Nat. in Organic Chemistry in 1951.

Professor Eschenmoser has been at the ETH-Zürich throughout his career, first as Privatdozent in 1956, then as Associate Professor in 1960 and since 1965, Professor of Organic Chemistry. He has been Professor Emeritus since 1992, and became Member of the Skaggs Institute for Chemical Biology, California in 1996. In addition, Professor Eschenmoser has held the Arthur D. Little (MIT 1961), Morris S. Kharasch (U. of Chicago, 1970), Alexander Todd (Cambridge, 1981) and Robert B. Woodward (Harvard, 1984) Visiting Professorships in Chemistry.

In recognition of a lifetime of outstanding contributions to chemistry Professor Eschenmoser has received many awards from different countries. His native Switzerland has awarded him the Werner Prize (1956), Ruzicka Prize (1958) and Marcel Benoist Prize (its highest scientific award, 1973). From Germany, the A. W. von Hofmman Medal (1976), the Cothenius Medal, Halle (1991), and the H.H. Inhoffen Medal, Braunschweig (1995) have been awarded. From England, he has received the Davy Medal (1978) and the Derek Barton Gold Medal (2004) from the Royal Society of London. In the United States, Professor Eschenmoser has received the Ernst Guenther Award (1966), Robert A. Welch Award (1974), the Arthur

C. Cope Award (1984) and the Roger Adams Award (2003). He has received the prestigious Wolf Prize from Israel (1986) and the M.-M. Janot Medal from France (1988). He has received honorary degrees from Universities of Fribourg; Chicago; Edinburgh; Bologna; J. W. Goethe University, F
rankfurt; Université Louis Pasteur, Strasbourg; Harvard University. He is Honorary Member of the American Academy of Arts and Science (1966); the National Academy of Sciences, USA (1973); the German Academy, Leopoldina (1976); the Royal Society, UK (1986); the Göttingen Science Academy (1986); the Orden pour le mérite, Bonn (1992); the Osterr. Ehrenzeichen für Wissenschaften und Künste, Wien (1993); and the Croatian Academy of Sciences, Zagreb (1994).

> "….In the history of natural science, natural products synthesis has played a very special role, the demystification of nature. It started with the synthesis of urea by Wöhler in 1828….."[2]

The echo of Wöhler's landmark discovery can be felt resoundingly as the foundation of Eschenmoser's manifold contributions to natural products chemistry. During the golden age of natural products synthesis (the "Woodwardian era") the gradient of molecular complexity provided the direction chemists followed and was sufficient justification for their synthetic endeavors. Although he was a major contributor to these activities, Eschenmoser has throughout his career sought a deeper purpose for the synthesis and study of natural products, namely, the chemical etiology of their existence. Whereas Wöhler's synthesis of urea ushered in the end of "vitalism", namely the belief that organic compounds can only arise from living matter; Eschenmoser's studies of natural products from the terpenes, to vitamin B_{12} to the nucleic acids, represent the conviction that living matter (i.e. life itself) must ultimately arise from organic compounds.

> "The supreme property of chemical matter is its potency to have given rise to the emergence of life. Yet life's origin continues to be one of the big unanswered questions of natural science. Life as we know it is a chemical life, thus chemistry is supposed to play a central role in the interdisciplinary effort to pursue the question of life's origin as a scientific problem, implying that it may be amenable to a solution."[3]

Professor Eschenmoser's early contributions on acid-catalyzed cyclizations of aliphatic polyenes served as guidelines for critical reexamination of old structural assignments of many terpenes. Through his detailed mechanistic analysis of acid-catalyzed cyclizations of aliphatic polyenes, Eschenmoser recognized that cation-initiated π-cyclizations and Wagner-Meerwein rearrangements could be the central reaction processes in the biogenesis of the structures of the cyclic terpenes. This revelation created the mechanistic foundation for the evolution of the *empirical* isoprene rule to the *biogenetic* isoprene rule first articulated by his mentor Professor Leopold Ruzicka in 1953. These insights allowed the brilliant

deduction of both the structure and configuration of the thirteen, known, basic representatives of the cyclic triterpenes and also rectified a number of flawed structural proposals. The ideas lead to the publication of a landmark paper in 1955 that articulated the final formulation of the biogenetic isoprene rule.

In the area of organic synthesis, Professor Eschenmoser's achievements are characterized by remarkable originality, incisive intellectual vigor and unusual ingenuity. His investigations in the synthesis of corrins which culminated in the total synthesis of the biochemically crucial cofactor vitamin B_{12} (the result of a legendary twelve-year collaboration with R. B. Woodward) has been cited as the most spectacular achievement in organic synthesis in the twentieth century. The conquest of vitamin B_{12} redefined the frontier of organic natural product synthesis and profoundly influenced the science of organic chemistry. At the outset, the unique connection between the A and D rings was recognized as the most daunting synthetic challenge and early approaches created this union in an indirect and classical fashion. Nevertheless, Eschenmoser seized upon this challenge as an opportunity to vanquish the opponent at its seemingly most impenetrable flank. Among the most brilliant of the many successful methods he developed for the construction of this crucial union stands the photochemically initiated *antarafacial* 1,16-hydrogen shift inspired by the Woodward-Hoffman rules of Conservation of Orbital Symmetry. Inevitably, the gleanings of an enterprise of this magnitude are admirable achievements in their own right and have proven of general value, including the sulfide ring contraction and the "diabolically clever" invention of α-chloro nitrones to solve the vexing problem of selective cleavage of the *f*-amide residue in the presence of six other ester moieties. Remarkably, it was Eschenmoser's fixation with the uniqueness of this critical side-chain for the successful synthesis of the vitamin that inspired his discovery that the nucleotide moiety "finds" its natural attachment site without any external guidance. Here again, Eschenmoser demystifies the outward complexity of the vitamin B_{12} structure in terms of "the biomolecule's intrinsic potential for self assembly."[4]

In recent years Professor Eschenmoser has focused his efforts in the area of nucleic acids in search of a chemical etiology of the natural nucleic acids structure. In asking the intriguing question "why pentose- and not hexose-nucleic acids?" Professor Eschenmoser has formulated one of the most fundamental questions that can be addressed by chemical synthesis, namely "why do the natural nucleic acids have the structures that they do?" In addressing this fundamental question, Albert Eschenmoser and his students have created a number of structural alternatives to the natural nucleic acids and compared their chemical and structural properties with those of the natural nucleic acids to establish the criteria by which Nature selected ribo- and deoxyribonucleic acids as the genetic system. Eschenmoser's research has revealed that maximization of base pairing strengths is not the decisive selection criterion in the domain of pentose-derived oligonucleotide systems; that the helicality of double stranded DNA is a direct consequence of the five-memberedness of the sugar ring; that by being helical, DNA achieves optimal base-pair stacking distances and selects purine-pyrimidine parings over purine-purine pairings; and that Watson-Crick pairing rules arise not only from the constitutions of the nucleic acid bases but also from the structure of

the sugar backbone. To show that potential nucleic acid alternatives are inferior to the natural nucleic acids with respect to those chemical properties that are fundamental to biological function would provide support for the hypothesis that Natures' evolutionary choice of RNA and DNA was made from a diversity of constitutionally related alternatives on the basis of functional criteria.

The search for an understanding of the chemistry of life's origin is inexorably connected to an understanding of the origin of biomolecular homochirality in Earth. Eschenmoser has contributed to this long-standing puzzle with a fundamental insight about the statistical inevitability of homochirality. Libraries of oligonucleotide sequences that arise by stochastic oligomerization of racemic pairs of short nucleotide sequences must break mirror symmetry when the products exceed the critical level of constitutional complexity.

> "The breaking of molecular mirror symmetry by de-racemization is an intrinsic property of such a system and does not require the stereo-directing influence of any external chiral catalyst or physical quantity."[5]

Although the chemistry of natural products has always been the primary focus of research efforts in the Eschenmoser laboratories, his creative contributions to innovative methods of outstanding utility for organic synthesis and his penetrating mechanistic insights into chemical reactivity are no less inspiring. For example, the α-chloro nitrones developed in the vitamin B_{12} enterprise engendered a new class of reactive heterodienes, vinyl nitrosonium cations that engaged in [4+2] cycloadditions for the synthesis of various heterocycles. In addition, the sulfide ring contraction has been adopted by many researchers for the construction of vinylogous amidines in alkaloid synthesis. Eschenmoser has indulged in a life-long "love affair with fragmentation reactions" that began with early observations on the cleavage of β-tosyloxy ketones with Grignard reagents through the base-mediated deconstructions of α,β-epoxy sulfonylhydrazones that lead to alkynyl ketones and culminating in the spectacular 8-bond decarboxylative double fragmentation of acetals for the construction of macrolactones. These developments also reveal a deep understanding of stereoelectronic effects as was beautifully illustrated in his refinement of the colinearity mandate for bimolecular nucleophilic substitution at saturated carbon.

Anyone privileged enough to have trained in his laboratories or fortunate enough to have engaged in scientific discussions with Albert Eschenmoser would marvel at his uncanny ability to formulate, ad hoc, compelling and lucid explanations for impenetrable problems. The lessons learned either in group seminars or during the coveted tea time discussions in the laboratories were but a glimpse into the workings of an extraordinary intellect. Professor Eschenmoser set for those of us who aspired to academic careers, a difficult-to-emulate example of scientific standards and of addressing the most important questions in chemistry.

As a personal note, Albert Eschenmoser is known to all who passed through his laboratories as an extraordinarily compassionate man. Deeper than his legendary capacity for critical thought is his

abiding respect for each individual co-worker. The students, postdocs and visiting professors in his laboratory were treated as if they were his personal guests; a particularly friendly and supportive environment for the many foreigners.

Many years ago, one of us (SED) had an astrological chart prepared for Professor Eschenmoser with the help of his wife Elizabeth who kindly provided the key details of exact time and place of birth. The astrologer described his attributes in both professional and personal domains.

Professional:

Two potentials that elude so many people are immediately apparent in your chart; career success and financial success.

- your career and recognition can reach any goals that you set for yourself
- you have a talent for research, your work will be scientific, pragmatic and a great involvement with and attention to detail
- you have a great intellect and a need for creative self expression
- you can put in practical and rational terms what you discover intuitively and irrationally
- there can be much travel in your live, especially connected to your work

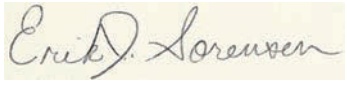
Personal:

- you have a natural charm and refined affability which is attractive to others
- a talent for communication, oratory, sharp tongue
- innate aesthetic sense, a refined discriminating taste

Overall:

- you are a fortunate man, great intellect, financial comfort, long life, discriminating taste, world travel and popularity among those who know you. Very few ever achieve so much!

Dear Albert, we wish you continued good health, great happiness with Elizabeth and your family and heartfelt affection on the festive occasion of your 85th birthday.



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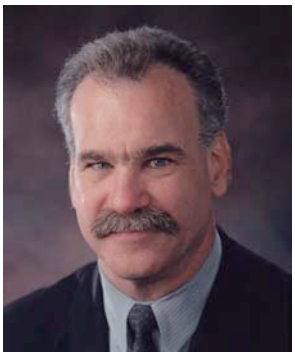

Scott E. Denmark was born in Lynbrook, New York on 17 June 1953. He obtained an S.B. degree from MIT in 1975 (working with Richard H. Holm and Daniel S. Kemp) and his D.Sc.Tech. (under the direction of Albert Eschenmoser) from the ETH Zürich in 1980. That same year he began his career at the University of Illinois. He was promoted to associate professor in 1986, to full professor in 1987 and since 1991 he has been the Reynold C. Fuson Professor of Chemistry. His research interests include the invention of new synthetic reactions, exploratory organoelement chemistry and the origin of stereocontrol in fundamental carbon-carbon bond forming processes. Prof. Denmark is pleased to have been selected as an ACS Fellow in the inaugural year.

Erik J. Sorensen was born in 1966 and raised in Tully, New York. He graduated from Syracuse University in 1989 and received his Ph. D. degree in Chemistry in 1995 from the University of California, San Diego under the direction of K. C. Nicolaou. From 1995–1997, he was an NSF postdoctoral fellow in the laboratory of Samuel Danishefsky at The Memorial Sloan-Kettering Cancer Center. In 1997, he joined the faculty in the Department of Chemistry at The Scripps Research Institute and the Skaggs Institute for Chemical Biology and achieved the rank of Associate Professor in 2001. In 2003, he moved to Princeton University, where he is the Arthur Allan Patchett Professor in Organic Chemistry. His laboratory develops concepts to rapidly form molecular complexity in the course of syntheses of biologically active natural products. For his achievements in chemical research and education, he received a Beckman Young Investigator Award, a Camille Dreyfus Teacher-Scholar Award, and the Arthur C. Cope Scholar Award in 2009. In 2001, he was a Woodward Scholar at Harvard University. In 2007, he was the Givaudan/Karrer Distinguished Visiting Professor at the University of Zürich.