Albert Eschenmoser

On 19 May 2000, The Scripps Research Institute bestowed an Honorary Doctoral Degree to Professor Albert Eschenmoser *on the occasion of the Doctoral Program Graduation Ceremony at Scripps. This is a slightly modified and expanded transcript of the introduction given for* Albert Eschenmoser

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Today, I am so pleased and honored to discuss, on this special occasion, some of the magnificent scientific accomplishments of one of the greatest organic chemists in this century and the last – *Albert Eschenmoser*. When I was invited to introduce *Albert Eschenmoser* by Drs. *Gilula* and *Lerner*, I accepted with high enthusiasm, but also with some measure of trepidation, because *Albert*'s contributions to the science of Chemistry are so important and impressive in scope. Of course, I am honored to introduce my mentor and friend *Albert Eschenmoser*, and I would like to express my gratitude to Drs. *Gilula* and *Lerner* for allowing me to actively participate in this event, where The Scripps Research Institute will bestow an Honorary Doctoral Degree to *Albert Eschenmoser*. I would also like to thank Ms. *Lucy Stark* and Mr. *Warren Lewis*, two students in our graduate program in Chemistry, for translating some of *Albert*'s important manuscripts that were published in German. I am particularly pleased that we are honoring *Albert* in the same year that he will celebrate his 75th birthday, and that his lovely wife *Elisabeth* is here with us today.

Organic chemistry, the field to which *Albert Eschenmoser* has devoted his career, is chiefly concerned with the reactions and properties of carbon-containing compounds. Within this broad discipline, the activity of synthesis, the process of creating carbon-containing compounds by way of chemical reactions, is central. While the incentives for performing a laboratory synthesis of an organic compound vary, I believe that the late physicist *Richard Feynman*'s dictum '*What I cannot create, I do not understand*' captures, quite clearly, the essence of much of what drives research in organic chemistry, organic synthesis in particular.

Synthetic organic chemistry is far from a juvenile science, and its glorious history can be traced to *Wöhler*'s influential synthesis of the organic compound urea from materials from the mineral world in 1828. Without the involvement of a living organism, *Wöhler* created urea, a product of human metabolism, by heating ammonium cyanate. That early achievement had an immense psychological impact, because it debunked the prevailing vitalistic theory that only living organisms could produce organic matter. It may be said that *Wöhler*'s chemical synthesis of urea commenced a systematic demystification of Nature by chemists and biologists [1].

Today, *Wöhler*'s legacy is found in the achievements of organic natural-product synthesis and is expressed most clearly in the research accomplishments of *Albert Eschenmoser*. On the subject of organic natural-product synthesis, *Albert* once wrote:

'*Natural product synthesis poses the challenge to consider and develop new pathways of structural transformation. Natural products as targets for synthetic research possess a special fertility in this regard, because the structural channels of biosynthesis are not necessarily the conduits of organic synthesis*' [2]. This statement was and continues to be cherished by the pioneers and disciples of the modern era of organic synthesis. But as I studied *Albert*'s vast and varied contributions to Chemistry, I began to realize that he always had a strong affinity for questions pertaining to the structural origins of molecules of great biochemical significance, and that he thought deeply about intrinsically favorable reaction channels of potential relevance in the biosynthesis of such compounds. His commitment to the types of reaction processes that Nature uses to create molecular structure calls to mind the visionary designs of the famous American architect *Frank Lloyd Wright*, which were deeply rooted in his *principle of organic architecture*; *Wright* and *Eschenmoser* derived much inspiration from the architectural feats of Nature.

As a young graduate student with the late Professor *Leopold Ruzicka*, who also made major contributions to chemistry and received the *Nobel* Prize in 1939 for his work, *Albert* was granted complete freedom in his doctoral research [3]. In early work, *Albert* conceived of mechanistic schemes for acid-catalyzed cyclizations of aliphatic polyenes and recognized that cation-initiated π-cyclizations and *Wagner-Meerwein* rearrangements could be the central reaction processes in the biogeneses of the structures of the cyclic terpenes. *Albert Eschenmoser* was thus the architect of a mechanistic framework that provided the impetus and basis for the transition from the era of the empirical *isoprene rule* to the era of the mechanistically-rooted *biogenetic isoprene rule* propounded in 1953 by *Ruzicka*. These concepts allowed a number of flawed structural proposals in the sesquiterpene field to be rectified and facilitated the structural elucidation of many new terpenes.

In the wake of the constitutional version of the biogenetic isoprene rule, Professors *Eschenmoser*, *Ruzicka*, *Jeger*, and *Arigoni* published a landmark paper in *Helvetica Chimica Acta* in 1955 [4] that was aptly characterized by *J. W. Cornforth* as the apotheosis of the isoprene rule [5]. In essence, the beautifully stereospecific cyclizations of squalene, which turned out to be central steps in the biosyntheses of polycyclic triterpenes and cholesterol, were viewed as *trans-antiperiplanar* additions of electron-deficient carbon centers to alkenes *via* well-defined conformations. This paper clearly explained how the conformational diversity of the transition states of squalene polycyclizations can translate into the constitutional and configurational diversity of the cyclic triterpenes. In a nearly simultaneous publication, *Gilbert Stork* and *Albert Burgstahler* of Columbia University described their independent studies of the stereochemical aspects of polyene cyclizations and also recognized the potential of stereospecific polyolefinic cyclizations for the biosynthesis of cyclic triterpenes. The pioneering contributions of the groups from ETH and Columbia to the stereochemistry of polyene cyclizations were later referred to as the '*Stork-Eschenmoser Hypothesis*' by *William S. Johnson*, and they paved the way for the subsequent, spectacular synthetic achievements of *Johnson*, *van Tamelen*, and many others.

Beginning in the 1960's and extending through the 1980's, *Albert* and his students at the ETH in Zürich made manifold contributions to Chemistry through their outstanding synthetic studies of the corrins, a major family of compounds that includes the

biochemically crucial cofactor vitamin B_{12}. The elucidation of the formidable structure of vitamin B_{12} in 1956 by *Dorothy Crowfoot-Hodgkin* of Oxford University was appropriately characterized by *Albert* as one of the '*finest contributions of British science to the chemistry of low-molecular-weight natural products*' [6]. Well, it could be said that the chemical synthesis of vitamin B_{12}, the culmination of a unique twelve-year collaboration between the research groups of *Albert Eschenmoser* and the late *Robert Burns Woodward* of Harvard, is one of the finest contributions to organic chemistry. This Herculean accomplishment defined the frontier of organic natural-product synthesis and profoundly influenced the science of organic chemistry. Those familiar with this great achievement will recall how work on the problem of forging the carbon-carbon bond joining rings A and D of the vitamin B_{12} structure engendered the *Woodward-Hoffmann* rules concerning the role of orbital symmetry in chemical reactions, and how this pervasive theoretical advance provided a basis for Professor *Eschenmoser*'s new and visionary strategy for creating the corrin nucleus. Although the bond connecting rings A and D was long regarded as the main obstacle on the path to a synthetic vitamin B_{12}, *Albert* and his talented students in Zürich discovered a whole spectrum of reaction conditions under which this diabolical bond and the corrin nucleus forms efficiently and with a high degree of stereoselectivity. In fact, one of their transformations may be regarded as a chemical model for the reaction path taken by Nature in the biosynthesis of vitamin B_{12}. In the course of this great work, the *Eschenmoser* group also discovered that the salient nucleotide chain of the vitamin 'finds' its natural attachment site without any external instruction! In the spirit of *Wöhler*'s urea synthesis, the research of *Eschenmoser* has certainly demystified the outwardly complex structure of vitamin B_{12}. *Albert* himself captured the essence of this beautiful work when he stated that '*the goal is to arrive experimentally at a perception of the biomolecule's intrinsic potential for structural self-assembly*' [7].

This articulate statement also expresses a main theme of his current research focus that seeks a chemical etiology of the structures of natural ribo- and deoxyribonucleic acids. When my esteemed colleague Professor *Paul Schimmel* commented on the scientific achievements of last year's Honorary Doctoral degree recipient, Professor *Norman Davidson*, he indicated that *Norman Davidson* addressed the question of '*What does the structure of DNA mean?*' Well, this year's Honorary Doctoral degree recipient has turned his considerable intuition and experimental sense to the question of '*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. *Albert*'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 pairings over purine-purine pairings; and that the *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 Nature's evolutionary choice of RNA and DNA was made from a diversity of constitutionally related alternatives on the basis of functional criteria.

When *Albert Eschenmoser* was not showing to us the beautiful reaction pathways leading to compounds of great biochemical significance, he was contributing innovative methods of outstanding utility for organic synthesis, and he was shaping our understanding of fundamental chemical reactions. His pioneering synthesis of the alkaloid colchicine provided an instructive, early application of an electrocyclic reaction of a norcaradiene derivative [8]. His early investigations of alkoxide fragmentations [9] and base-induced fragmentations of α,β-epoxy sulfonylhydrazones were forerunners of an important and large class of reactions. His extraordinarily insightful approach to the construction of unsaturated macrolides employed a structural type that is predisposed for a facile and concerted decarboxylative fragmentation. His studies of the unique reactivity of unsaturated oximes were among the earliest examples of the important concept of *umpolung*. His imino ester/enamine condensation, and alkylative and oxidative variants of the *Eschenmoser* sulfide contraction are outstanding methods for the construction of vinylogous amidines. His demonstration of the importance of colinearity between an incoming nucleophile and a departing leaving group in bimolecular nucleophilic substitution reactions [10] is the heart of our view of this fundamental reaction type and is part of the empirical and theoretical foundation of *Baldwin*'s *rules*. His uncanny sense in matters having to do with reaction mechanism and stereoelectronic control elements allowed him to contribute a key insight that explains the marvelous ability of the enzyme triose-phosphate isomerase to avoid a self-destruction of its substrate [11]. *Albert* has also taught us that oligonucleotide sequence libraries that arise by stochastic oligomerizations of racemic pairs of short nucleotide sequences inevitably break molecular mirror symmetry when the products exceed a critical level of constitutional complexity [12]. *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!* This is a profound contribution to theories about the origin of biomolecular homochirality on Earth.

Few have influenced the science of organic chemistry so fundamentally as *Albert Eschenmoser* has. His explorations of the dimly illuminated domains of organic chemistry, and the maturity and depth of the questions that he has addressed have educated us all and have forever changed our science. It is with deep respect and affection that I make these remarks about your outstanding career. We at The Scripps Research Institute congratulate you, and we wish you much continued professional success and happiness.

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