The Biology–Chemistry Interface
A Tribute to Koji Nakanishi

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Preface

Natural products science, a fascinating cornerstone of modern research, has long bridged the traditional frontier between chemistry and biology. Humankind has always been intrigued by the power and potential of plants and nature. Many old texts reveal how the ancient cultures drew on the beneficial properties of plants. They learned the wisdom of extracting the ingredients and using such potions as foods, medicines, and mood enhancers long before anyone understood how these worked. Slowly we have found the tools to explore the chemistry of these ingredients, and thus the systematic study of natural products began. Morphine was isolated in 1805 and strychnine in 1819, although their structures remained mysteries for more than 100 years, and pure camphor has been an article of commerce for centuries. Today the biosynthetic machinery of plants and other organisms is purposefully manipulated to produce new "natural products" of biological significance in medicine and agriculture.

In the nineteenth century, early progress in natural products research centered on the study of pigments from flowers as colored dyes. Originally, extraction of drug compounds, particularly alkaloids, from plants was achieved by using simple isolation methods: a water steep or a solvent (generally alcohol) extraction. The impetus was set to explore this research area further and, not surprisingly, more and more intellectual pursuit of natural sciences and our environment encouraged universities and scientific centers throughout the world to study natural products, which then formed the nucleus of chemistry programs.

As source material to begin any research investigation, plants were abundant and easily obtained. The first natural products to be studied in detail were generally the major constituents of plants, since these often precipitated from solution and could be purified through recrystallization. How well do we recall

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today that the purity of chemicals up to the latter half of the twentieth century was determined solely by melting point? As increasing numbers of chemical constituents with more complexity were found, structural analysis relied on chemical transformations and degradation studies. Total synthesis was confirmatory. The discovery of one or two compounds based on these research studies was usually acceptable to earn a doctorate.

The second half of the twentieth century has witnessed incredible advances in natural products research. These have been achieved through the discovery of new chromatographic separation methods and remarkable advances in spectroscopy. As new technologies for isolation and structure identification have evolved, the isolation and detection of ever-diminishing amounts of natural products, coupled with the determination of structures on a microscale, have become almost routine.

In addition to identifying important targets for total synthesis, and thereby spurring innumerable advances in fundamental organic chemistry, studies of natural products have led to significant research efforts in the related fields of bioorganic chemistry and biosynthesis, as chemists, biologists, and biochemists have striven to understand how these molecules are produced in nature and to establish the molecular basis of the biological activity of these compounds. The structural determination of natural products has impacted our basic understanding of nature. One very important aspect of structure determination is the use of spectroscopy, particularly nuclear magnetic resonance, mass spectrometry, circular dichroism, and x-ray diffraction methods. Circular dichroism is particularly important in establishing absolute stereochemistry, as chirality is correlated directly to biological activity of the biomolecule. Thus, as we approach the end of this century, we see the challenging questions in biology requiring answers at the molecular level being met by increasingly sophisticated techniques and comprehension of the chemistry of nature.

Professor Koji Nakanishi has been a pioneer and a towering figure in natural products research. He has been a major contributor at the crossroads of bioorganic chemistry over the past 40 years. His extraordinary and broad vision of natural products chemistry and its close relationship to bioorganic studies is now universally accepted and was the inspiration for this book. He has constantly looked at challenges in bioorganic chemistry and pushed ever closer the boundaries at the interface between chemistry and biology. He has achieved this through his lifelong studies in natural products, his investigations into the chemistry of vision, his pursuit of new and ever more powerful analytical and spectroscopic microtechniques for solving complex structural problems, and his study of infrared and circular dichroism and their applications to bioorganic science. Koji's curiosity and insights in applying the right solution to challenging problems are among his legacies, to which we as students of his are deeply grateful.

Koji Nakanishi was born in 1925 in Hong Kong to parents of Japanese descent. As a result of his father's business postings abroad, Koji's early childhood was spent in various European capitals as well as in Alexandria, Egypt, thereby giving birth to and nurturing his unique world vision. He returned to Japan for his formal university training and received his B.Sc. degree at Nagoya University in 1947. He first came to the United States in 1950–52 to study with the legendary Professor Louis Fieser at Harvard University, and he returned to Japan as an assistant professor to embark on his remarkable career in natural products and bioorganic chemistry. He completed his Ph.D. in 1954 under the mentorship of Professors Egami and Hirata, then took positions at Nagoya University (1955–58), Tokyo Kyoika University (1958–63), and Tohoku University (1963–69). In 1969 he was invited to join the faculty at Columbia University, New York, where he currently holds the chair of "Centennial Professor of Chemistry."

Indeed, it was at Columbia University that former and current students, postdoctoral fellows, and esteemed colleagues of Professor Nakanishi gathered to celebrate his 70th birthday and to honor him for his years of mentorship and friendship, as well as for his considerable contributions to bioorganic science. Two days of stimulating presentations on various topics in bioorganic chemistry gave birth to the idea behind this book: to produce a volume with contributed chapters from his former students in his honor.

This text reflects Koji's own research interests in its scope and attempts to bridge the gap between biology and chemistry: a gap that is rapidly diminishing as investigators use the tools and vision that Koji has provided. Koji humbly reminds us that he is "only a technician"; we respectfully differ. He is a visionary, and in essence the investigatory seeds planted by Koji are now in full bloom in research gardens headed by those he taught.

We choose to highlight current research activities from former members of his research groups from Asia, the United States, Europe, and Australia, thereby illustrating Koji's global scientific influence. As with Koji's own research, one goal of this text is to further dissolve the boundary that has kept chemistry and biology apart; the contributions in this volume are by investigators for whom this boundary has long since disappeared. It is hoped that readers will come to understand the highly interactive nature of research in biological chemistry and chemical biology, and find the transition between chemistry and biology far less intimidating. Thus, this book reflects the ideals of Professor Nakanishi and his impact.

Although the chapter titles may at first glance seem to suggest a relatively large breadth of subjects, in fact they all fit snugly within the focus of the chemical basis of biological activity. Subjects range from hydrolytic enzymes to combinatorial chemistry, yet all the chapters strive to elucidate biological responses at the molecular level. The contributing authors provide detailed accounts of their current research rather than presenting formal reviews of disparate subjects. The rationale for this approach is to emphasize the interactive nature of the research in bioorganic chemistry. The unifying theme throughout is the original skills that developed in natural products research and chemistry of vision. The microanalytical techiques, the spectroscopic challenges, have now evolved into the application of chemical minds to biological problems. Thus, the selection of authors reflects a blend of investigations in academic and industrial research.

Koji's pioneering contributions and world vision of science have inspired several generations of chemists from around the globe, and demonstrations of his mastery of the magical arts have left numerous audiences of the brightest minds completely and delightfully mystified. We can identify the defining moment of our education and scientific growth as the time we spent with Koji, and we offer our profoundest gratitude to him for his tireless leadership and support.

Raymond Cooper
John K. Snyder

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Tribute Letters

March 16, 1998

Dear Koji,

On the occasion of your 70th birthday, many of your old friends and colleagues came to Columbia for a wonderful celebration in 1995. Now we are assembling a permanent record of our appreciation for your friendship and as a tribute to your many elegant and important contributions to the chemistry and biology of natural products.

I can remember our first meeting, 34 years ago, in Tokyo, at the Presymposium to the IUPAC meeting in Kyoto. In the next two weeks you were our host almost every evening and introduced us to Japanese food and customs. It was a great awakening to the realization that Japanese chemistry was rapidly gaining tremendous momentum and a turning point in my career. Since that meeting I have had the pleasure and privilege of working with 26 Japanese colleagues (several of whom came from your lab).

It was a pleasure to repay a little of your hospitality when you visited our homes in Sussex, New Haven and College Station, and you know that you and your wife are always welcome in Texas.

You are a true pioneer in solving different problems at the chemistry–biology interface using every possible technique on vanishingly small amounts of material and your work continues to be an inspiration to all of us. Most importantly your personal qualities have ensured a permanent legacy in your many students who have done so well in our profession. It must make you feel very proud to have had so many loyal and dedicated coworkers. Above all (and almost uniquely in our field) you have remained a gentleman, with the highest ethical standards in dealing with your colleagues. I don't know how you manage to work so hard yet still find time for your magic and your friends.

I can guess the secret of your success in chemistry and life—that you are fortunate like myself, to have such a long and happy marriage.

Betty joins with me in wishing you and your wife continued health, happiness and success for many more birthdays to come.

As always!
Yours very sincerely,

Ian

A. I. Scott, F.R.S.
Davidson Professor of Science
Director of Center for Biological NMR
Texas A&M University, College Station, Texas

March 8, 1998

Dear Koji,

"They" never stop celebrating you! "They," of course, are those who have had the privilege to obtain from you, as post-docs or as Ph.D. students, part of their life baggage. They have been also kind enough to associate to them some of your long time friends, and it was indeed a great pleasure to have the opportunity to pay tribute to you in Columbia nearly half a century after we had first met in the basement of Converse Laboratory, at Harvard, in Louis Fieser's group.

When I was invited to contribute to this volume with a letter, I tried to call back the oldest memories of our meetings I could muster. For some odd reason, even though I am neither a gourmet nor a gourmand, they were nearly all memories of food. The experience of learning from you (and from Huang Wey Yuan) to use chopsticks (a very useful lesson), the dinners of frog[1] or lamb[2] legs in

[1] My wife was working at Harvard Medical School in Pharmacology with Fieser's friend Prof. O. Krayer, on the action of the *Veratrum* alkaloids on frog heart. A frog: one heart, two legs. We always had a few dozen frozen legs aside for our friends. These legs, and frozen guinea pigs (one heart, one guinea pig), helped us survive on our starvation scholarships.

[2] On affluent months, for a change from frogs and guinea pigs, I was buying lamb by the half at the

the stable-boy's rooms of the mock-French castle I was living in with Paula in Brookline.[3]

Food apart, another very old memory I can retrieve is that of the innumerable small sealed tubes in which you were desperately heating pristimerin with something (was it zinc or selenium?), to find its structure.

Food and pristimerin apart, I also revive with a little nostalgy our outing to White Mountains, to a mountain the name of which escapes me, when we had to climb very large oblique stone slabs and you lost grip at the top, to slide down slowly at first, then quickly, on your fingers and stomach, to arrive at the bottom half skinned.

But, food and pristimerin and outing apart, it is also then that I first became one of your favorite stooges, always ready to serve on any available stage, many, many times later, as a *faire-valoir* to your other profession. A simpleton glad to oblige.

Koji, I have only one regret: that I could never find a pretext to share some (serious) work with you, in Japan, in Nairobi or in New York, even though we have both always held the same conviction that chemistry and biology share more than one border and that to follow fashion is silly when there is so much else to explore.

Merci, Koji, pour ton amitié

Professor Guy Ourisson
Vice President de l'Académie des Sciences
Strasbourg, France

Italian market. The subway passengers had to sit next to a very un-American young man carrying half a lamb protruding from his rucksack.

[3] We were living in the small rooms above the stables built by a former U.S. Ambassador to Italy and to Japan, in the middle of the huge estate he had bequeathed to the township of Brookline, Lars Andersen Park. The stables were in the form of the Château de Chambord, or nearly so, and were the seat of the Veteran Motor Cars Association of America, the "vie de château," which we shared with some 100 old cars.

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1

Insect Antifeeding Limonoids from the Chinaberry Tree *Melia azedarach* Linn. and Related Compounds

Munehiro Nakatani
Kagoshima University, Kagoshima, Japan

I. INTRODUCTION

Limonoids are tetranortriterpenoids derived from euphane (H-20β) or tirucallane (H-20α) triterpenoids with a 4,4,8-trimethyl-17-furanylsteroidal skeleton [1]. Over 300 limonoids have been isolated to date, and they are the most distinctive secondary metabolites of the plants in the order Rutales. Particularly, they characterize members of the family Meliaceae, where they are abundant and varied [2–4]. Almost every part of the trees of this family has been used in folkloric and traditional systems of medicine [5,6]. Recent work has established a wide range of biological activities for these compounds, including insect antifeedant and growth-regulating properties, a variety of medicinal effects in animals and humans, and antifungal, bacteriocidal, and antiviral activities. The biological activities of limonoids from Rutales have been reviewed [7].

In particular, the limonoids from the neem tree *Melia azadirachta indica* Juss and the Chinaberry tree *Melia azedarach* Linn. have attracted considerable interest because of their marked insect antifeedant properties and intriguing structural variety. The most potent insect antifeedants are azadirachtin and related highly oxidized C-seco limonoids from *M. azadirachta*. Their antifeedant activities and structure–activity relationships have been reviewed [8–10].

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