PERKIN 1 COVER FEATURE

Professor K. C. Nicolaou *

RSC Centenary Lecturer

Career

K. C. Nicolaou was born on July 5, 1946 in Cyprus, where he grew up and went to school until the age of 18. In 1964, he emigrated to England where he spent two years learning English and preparing to enter university. His advanced studies in chemistry were carried out at the University of London (B.Sc., 1969, Bedford College, First Class Honors; Ph.D. 1972, University College, with Professors F. Sondheimer and P. J. Garratt). In 1972, he crossed the Atlantic to the United States and completed postdoctoral appointments at Columbia University (1972–1973, Professor T. J. Katz) and Harvard University (1973–1976, Professor E. J. Corey) after which he joined the faculty at the University of Pennsylvania, where he rose through the ranks to become the Rhodes-Thompson Professor of Chemistry. In 1989, he accepted joint appointments at the University of California, San Diego, where he is Professor of Chemistry, and The Scripps Research Institute, where he is the Chairman of the Department of Chemistry and holds the Darlene Shiley Professor Chair in Chemistry and is also the Aline. W. and L. Skaggs Professor of Chemical Biology.

For his scientific work, Professor Nicolaou has received numerous awards and honors, including the Humboldt Foundation US Senior Scientist Prize (Germany, 1987), the A.C. Cope Scholar Award, American Chemical Society (1987), the Award for Creative Work in Synthetic Organic Chemistry, American Chemical Society (1993), the Dr Paul Janssen Prize for Creativity in Organic Synthesis, Janssen Research Foundation (1994), the Rhone-Poulenc Medal, Royal Society of Chemistry (U.K., 1995), the William H. Nichols Medal, New York Section-American Chemical Society (1996), the Inhoffen Medal, Gesellschaft fur Biotechnologische Forschung mbH (GBF) (Germany, 1996), the Ernest Guenther Award in the Chemistry of Natural Products, American Chemical Society (1996), the Chemical Pioneer Award, American Institute of Chemists (1996), the Linus Pauling Award, Oregon, Portland, Puget Sound Sections-American Chemical Society (1996), the Decoration of the Order of the Commander of Honor Medal (bestowed by the President of Greece, 1998), the Esselen Award for Chemistry in the Public Interest, North-Eastern Section American Chemical Society (1998), the Yamada Prize (Japan, 1999), the first Aspirin Prize for Solidarity through Chemistry (Spain, 1999), the Max Tishler Lecture Prize, Harvard University (2000), the Paul Karrer Gold Medal, Universitat Zurich (Switzerland, 2000), the Centenary Medal, Royal Society of Chemistry (U.K., 2000–2001), the Ernst Schering Prize, Ernst Schering Research Foundation (Germany, 2001), and the Nagoya Gold Medal of Organic Chemistry, Nagoya University (Japan, 2001). Additionally, Nicolaou is a Member of the New York Academy of Sciences (1987), a Fellow of the American Academy of Arts and Sciences (1993), a Member of the National Academy of Sciences (USA, 1996), a Fellow of the American Association for the Advancement of Science (1999), a Foreign Member, Academy of Athens (Greece, 2001), and holds eight honorary degrees. To date, he has published over 500 papers and book chapters, 70 patents (52 issued, 18 pending), and two books, the most recent entitled "Classics in Total Synthesis" co-authored with Erik Sorensen.

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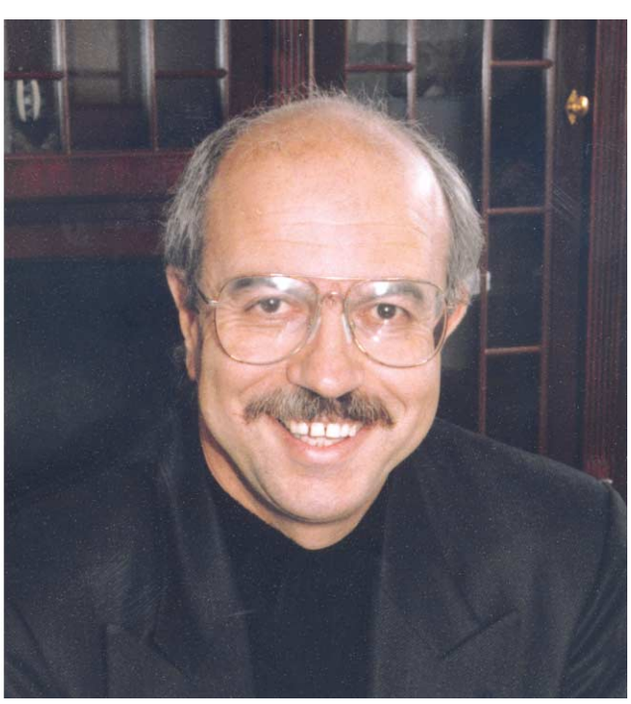

K. C. Nicolaou

Research

Over the past twenty-five years, Professor Nicolaou's campaigns to synthesize some of nature's most intriguing molecular architectures have led to new fields of investigation and expanded our knowledge in the disciplines of chemistry, biology, and medicine. While elegance was a key factor in all total syntheses, other aspects of research were also actively pursued, namely, the discovery of novel chemistry, the development of new synthetic technologies, and studies in chemical biology. In many projects, he successfully interweaved these themes creating a cohesive wholeness to the endeavors.

A recurring theme throughout Nicolaou's career has been the development and execution of "biomimetic" approaches in natural product synthesis, often *via* cascade sequences, in the hope of mirroring at some level nature's synthetic ability and conceptual brilliance which far exceeds the current skills of organic chemists. Seminal examples of such research include the synthesis of the endiandric acids (1982), in which a remarkable series of electrocyclizations simultaneously furnished the two distinct but related molecular architectures of the target molecules, in a stereospecific fashion from prochiral polyunsaturated precursors. More recently, Nicolaou accomplished the synthesis of three members of the bisorbicillinoids (trichodimerol, bisorbibutenolide, and bisorbicillinol, 1999) using two different reaction cascades, one proceeding through a series of Michael reactions and internal ketalizations, and the other

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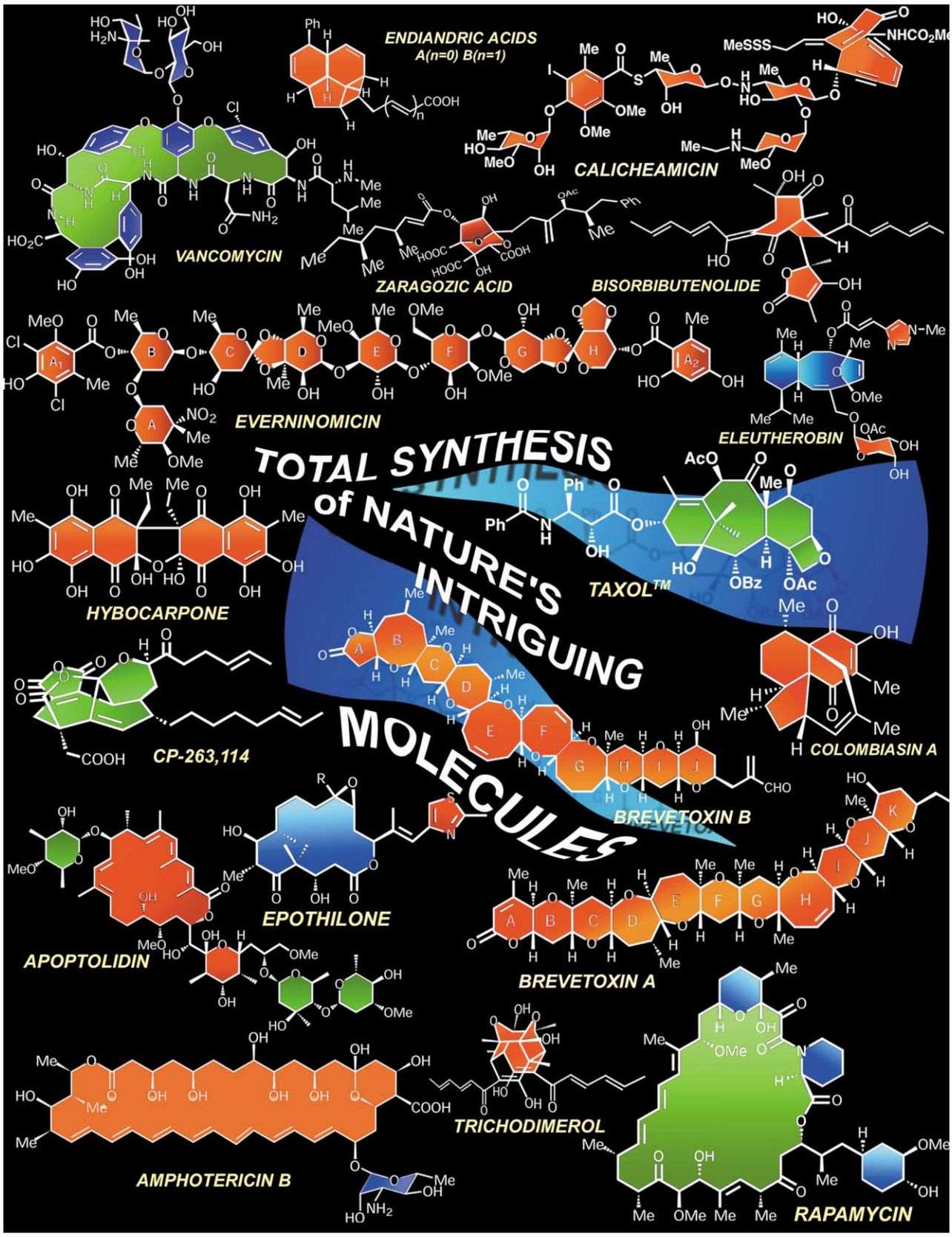

through a Diels–Alder cycloaddition; both were initiated by the oxidation of sorbicillin. During this past year, the Nicolaou group has completed the total synthesis of the terpenoid colombiasin A *via* an iterative Diels–Alder strategy appending three rings onto a quinone core which allows efficient construction of the complete framework of the target molecule, including its two adjacent and seemingly formidable quaternary centers. Additionally, the group prepared the quinone-derived natural product hybocarpone through a single-electron transfer dimerization of a naphtharazin precursor followed by a hydration event. This cascade strategy concomitantly formed a highly hindered carbon–carbon bond and selectively installed four stereogenic centers.

Although biosynthetic approaches are typically elegant in their execution, similar levels of beauty and ingenuity can often be achieved in multi-step total synthesis through the application of a particularly bold or daring synthetic plan, wherein success hinges upon enlisting the aid of one or more key reactions. An

early illustration of this concept includes Nicolaou's preparation of the polyene macrolide antibiotic amphotericin B (1987), in which a remarkable macrocyclization process involving a ketophosphonate-aldehyde condensation efficiently and stereoselectively formed the molecule's 38-membered ring. Similarly, in 1993, the Nicolaou group was the first to complete the synthesis of the potent immunosuppressant agent rapamycin *via* an unprecedented maneuver in the final step of the synthesis which forged the molecule's macrocycle by using a tandem double Stille-stitching cyclization from a precursor which was free from costly protecting groups.

As part of these endeavors to create complex molecular architectures, the Nicolaou group has also pursued and developed numerous new synthetic methods and technologies as a requisite part of the drive to complete the synthesis of the target structure. For example, during the early 1980s, the Nicolaou group recognized the importance of carbohydrates in natural products chemistry and the synthetic deficiencies in methods for their installation onto complex molecular frameworks. As such, new and creative methods for the attachment of sugars onto certain aglycons were sought and found through the use of phenylthioglycosides as glycosyl donors under the activating influence of electrophilic reagents such as *N*-bromosuccinimide. Additionally, the group developed the so-called two-stage activation procedure for oligosaccharide synthesis using stable thioglycosides and highly reactive glycosyl fluorides. These methodological advances were first featured in the total synthesis of efrotomycin (1984) and have proven invaluable for the synthesis of even more complex oligosaccharides. Along these lines, in 1999, the Nicolaou group synthesized perhaps the most complex oligosaccharide-based molecule to date in the form of the antibiotic everninomicin. Among the new synthetic technologies required for this successful campaign were a tin acetal-based approach to stereoselectively construct 1,1′-disaccharide linkages and a 1,2-phenylseleno migration reaction utilized for the stereocontrolled synthesis of sensitive orthoesters.

Outside the realm of carbohydrates, in 1982 Nicolaou began what turned out to be a sixteen-year odyssey to synthesize the potent neurotoxins brevetoxins A and B, compounds associated with the red tide phenomena. The numerous medium-sized rings contained within each of these imposing structures necessitated the invention of new synthetic technologies; among the most powerful and applicable methods developed to answer this challenge were the hydroxydithioketal cyclization to form oxocenes, the palladium-catalyzed coupling of vinylketene-acetal phosphates with vinylstannanes, and the bridging of macrodithionolactones to form bicycles. In 1999, Nicolaou also completed the first total synthesis of the CP-molecules, whose uniquely challenging molecular features were tackled by numerous designed cascade strategies and novel methodologies until the target molecule succumbed. Perhaps even more significant were several discoveries made during this campaign which have since led to a renaissance in the synthetic chemistry of hypervalent iodine-based reagents. Accessible transformations with these reagents were expanded for the synthesis of α,β-unsaturated compounds, diverse heterocycles, *cis*-aminosugars, and aromatic aldehydes and ketones.

For the Nicolaou group, target selection has also been predicated, towards compounds possessing intriguing modes of biological activity as a means to pursue chemical biology studies. An early example of such an endeavor is the synthesis of the enediyne antitumor antibiotic calicheamicin (1987–1992), a project which resulted not only in the completion of the total synthesis of the target molecule using several bold synthetic maneuvers, but also in many designed enediyne analogs ranging from simple hydrocarbons to sophisticated molecular systems equipped with triggering devices. Activated by light, pH change, or other chemical means, these devices could initiate the Bergman cycloaromatization reaction leading to DNA-damaging benzenoid diradicals. Taken as a whole, these extensive studies clearly defined parameters for the stability, activation, and biological mode of action of such systems and helped shape the current face of enediyne research pursuing potential chemotherapeutic agents.

Along related lines, in 1994 Nicolaou completed the total synthesis of the anticancer agent Taxol™, now in clinical use, *via* a strategy featuring Diels–Alder cycloadditions to construct two of the four major ring systems, and a challenging, McMurry-type process to form the molecule's 8-membered core. This achievement was further elaborated when the Nicolaou group designed, synthesized, and evaluated several water-soluble taxoids and pro-drugs, a self-assembling taxol derivative which formed helices in solution, and a number of fluorescent probes which enabled detailed biological studies of tubulin-binding agents. More recently, as part of a program directed towards vancomycin, the antibiotic of last resort, Nicolaou developed a novel triazene-driven cyclization to form the imposing macrocyclic bisaryl ether, a critical step in the total synthesis, and simultaneously explored the chemical biology of this natural product by employing a target-accelerated combinatorial synthesis strategy utilizing either olefin metathesis or disulfide bond formation to prepare dimeric derivatives (2000). These latter studies led to the discovery of a series of analogs with high levels of potency against vancomycin-resistant bacteria. During this past year (2001), using the symmetrically arranged disulfide structure of the marine natural product psammaplin A for a source of inspiration, Nicolaou developed a rapid combinatorial strategy to synthesize heterodimeric disulfide-type compounds with several possessing levels of antibacterial activity higher than that of the natural product, some rivaling vancomycin *in vitro*.

The Nicolaou group has also sought to use natural product total syntheses as a vehicle to advance solid phase chemistry enabling specific and combinatorial synthesis, techniques which over the course of the past decade have become powerful and invaluable tools in studies pertaining to chemical biology and drug discovery. Thus, through the incorporation of novel resins and linking strategies in the context of complex natural product total synthesis, as well as the extension of new reactions to the solid phase, Nicolaou and his co-workers have advanced considerably the frontiers of this important technology. In 1997, Nicolaou employed an olefin metathesis-based cyclo-release strategy in combination with a novel radiofrequency encoded deconvolution blueprint (developed in collaboration with IRORI) to generate libraries of epothilones, a family of potent anticancer agents currently in clinical trials. These studies led to a comprehensive picture of the structure–activity relationships in the epothilone field with the corollary that several analogs possessing potencies greater than those of the naturally occurring substances were produced. A similar approach was applied in the synthesis of libraries of the marine-derived antitumor agents eleutherobin and sarcodictyin (1997), where three sites of diversification were identified, enabling facile analog construction. In 1998, Nicolaou developed a novel, doubly cleavable linker along with a set of orthogonally protected monosaccharides to prepare complex oligosaccharides through a block-type, reiterative strategy. Amenable to automation, this highly efficient strategy has already been used to synthesize a naturally occurring heptasaccharide and a designed dodecasaccharide. More recently, the Nicolaou group prepared a library of over 10 000 discrete compounds inspired by the benzopyran class of natural products by employing a chemically robust, yet easily cleavable, selenium-based resin in conjunction with a robotically-controlled optical encoding strategy (in collaboration with IRORI). Preliminary biological screening of this library has already revealed a number of promising leads in antibiotic, antitumor, and antiviral assays, demonstrating the power of these enabling technologies in chemistry, biology and medicine.

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