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Tribute

Arkivoc **2019**, part iii, 1-8

Professor George A. Kraus

A Tribute

Dedicated to Prof. George A. Kraus on the occasion of his outstanding contribution to organic synthetic chemistry

Published on line 11-26-2018

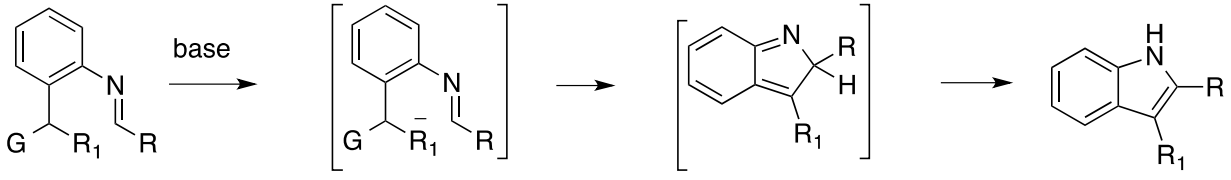
George Kraus was born in Buffalo, New York in 1950. He received a B.S. degree in chemistry from the University of Rochester in 1972 and his Ph.D. degree in chemistry from Columbia University in 1976, working with Professor Gilbert Stork on the use of kinetic anions in organic synthesis. Following Graduate School, Dr. Kraus went directly to Iowa State University (ISU) as an Assistant Professor in the Department of Chemistry. He was promoted to Associate Professor in 1981, full Professor in 1986, and was named University Professor of Chemistry in 2004. Dr. Kraus has held numerous administrative positions at ISU during his career including Chair of the Department of Chemistry (1993 – 1999), Director of the Bio-renewable Resources Consortium (2000-2007), Director of the Center for Catalysis (2002-2007), and Director of the Institute for Physical Research and Technology (2007-2012). In addition, he currently serves as the Assistant Director for Bio-related Initiatives at the U.S. Department of Energy's Ames Laboratory. His scientific awards include an Alfred P. Sloan Fellowship, DuPont Young Faculty Award, 3M Young Faculty Award, Frasch Award, American Soybean Association Production Research Award, Iowa State Institutional Service Award, College of Liberal Arts and Sciences Award for Excellence in Research/Artistic Creativity, and the Federated Laboratories Consortium Distinguished Service Award, along with numerous invited lectureships around the globe. He is a member of the American Chemical Society (ACS), ACS Division of Organic Chemistry, ACS Division of Medicinal Chemistry, Center for Crops Utilization Research, and the International Society for Antiviral Research. Dr. Kraus holds Fellowships in both the American Association for the Advancement of Science and the Royal Society of Chemistry.

Dr. Kraus has published over 320 papers and book chapters in a variety of areas including synthetic methodology, total synthesis of natural products, stereo- and enantiomeric synthesis, synthesis of heterocyclic molecules, use of bridgehead carbocations in synthesis, photoactivation of biomolecules, and biological activity of xenobiotics. He holds 20 patents in diverse areas including chemical transformations, antibiotics, antifungals, photoactivation of biomolecules, and HIV inhibition.

Current Research Interests

Indole synthesis via electrocyclic reactions[1,2]

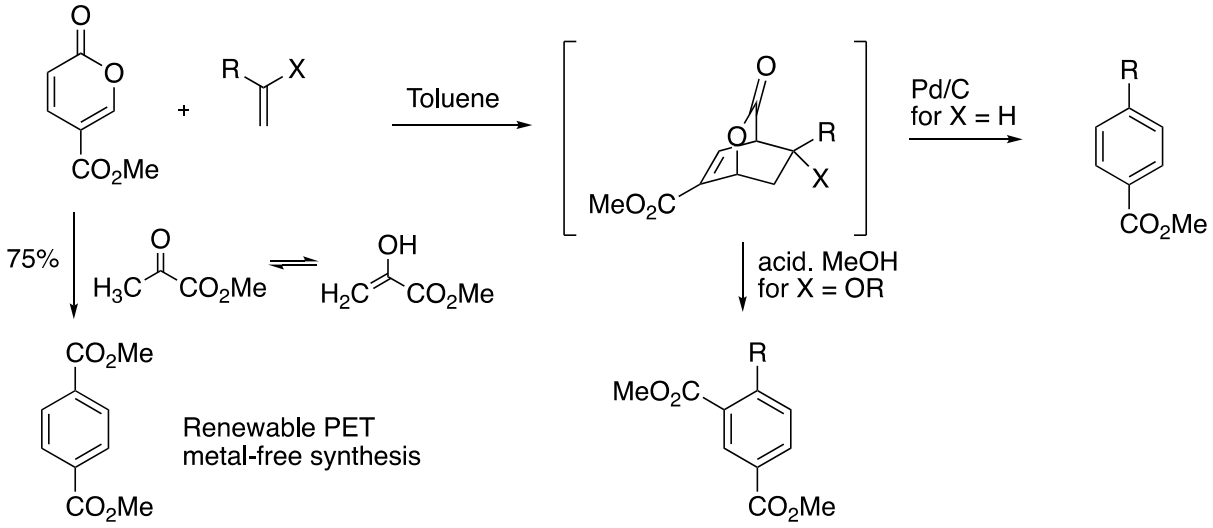
The synthesis of five-membered heterocyclic rings via anion-mediated electrocyclic reactions was, until recently, an unexplored area. Dr. Kraus discovered that when 2-aminobenzyl triphenylphosphonium bromide was allowed to react with benzaldehyde to form an imine and then reacted with base, 2-phenylindole was formed in 95% yield. Subsequently, over fifty aromatic and unsaturated aldehydes were studied. A wide range of functionalized aldehydes, with both electron-donating and electron-withdrawing substituents, react effectively. Use of this novel indole-forming reaction led to the synthesis of the natural product arcyriacyanin A in only two steps from commercially available starting materials.



G = $P(Ph)_3^+$, CN, SO_2Ph

Biobased chemistry from coumalic acid[3-7]

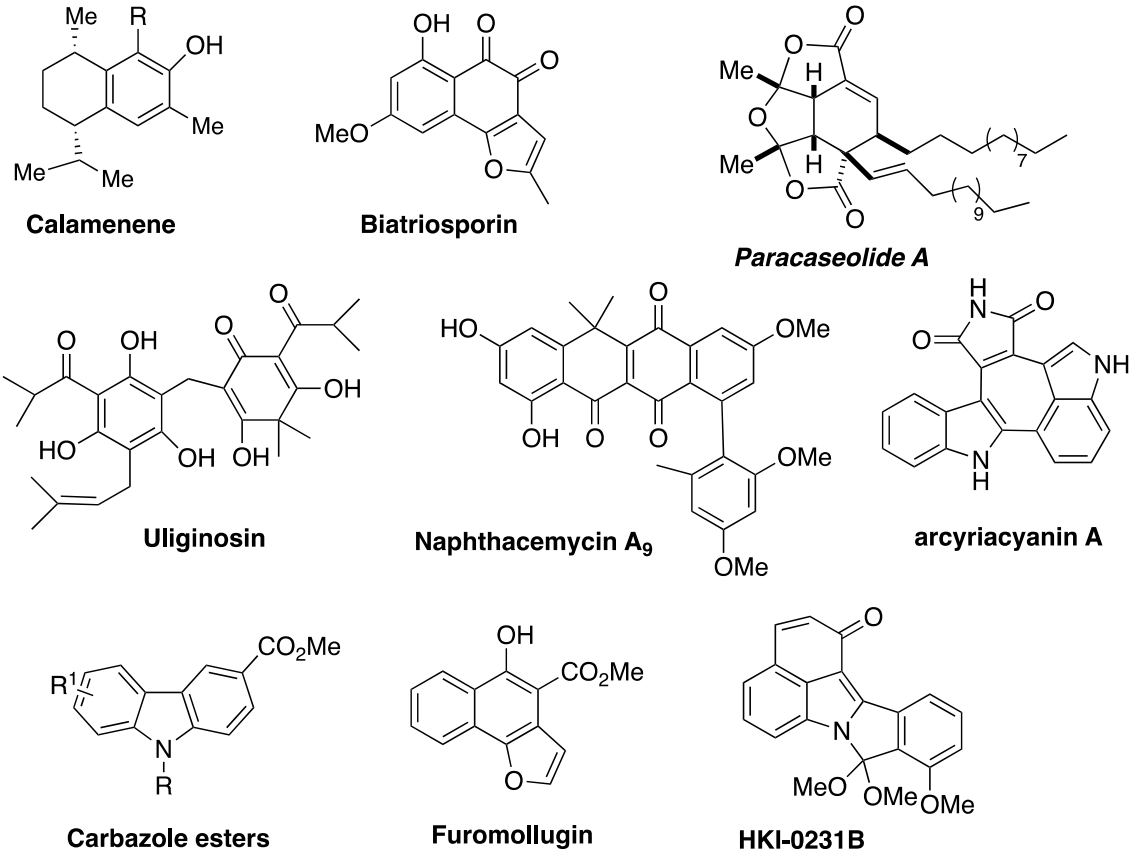
Dr. Kraus and co-workers reported a scalable and inexpensive route to coumalic acid and its esters from malic acid. They used methyl coumalate (shown below) as a platform to generate commodity and specialty chemicals that were 100% bio-based.



They were the first to report that alkenes such as 1-hexene undergo the cycloaddition/dehydrogenation/ aromatization pathway to para-substituted benzoates in high yields. When enol ethers were used, the bicyclic adducts could be isolated at temperatures below 80 °C and converted into isophthalates by treatment with acid in methanol. They also discovered that methyl pyruvate reacted *directly* (via its enol tautomer) with methyl coumalate to afford dimethyl terephthalate, a key intermediate in a renewable, metal-free synthesis of PET.

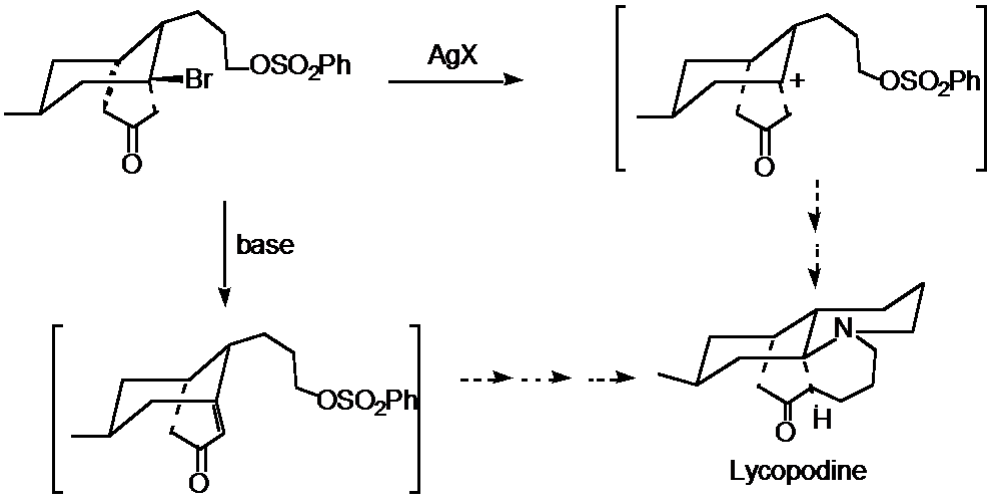
Synthesis of Natural Products

The structures of several natural products recently synthesized in the Kraus group are shown below. They achieved the first synthesis of biatriosporin, a quinone that exhibits potent antivirulent activity. Dr. Kraus and coworkers also completed a direct synthesis of naphthacemycin A_9, a novel circumventor of beta-lactam resistance in MRSA, using their cyanophthalide chemistry as the key step. An efficient total synthesis of paracaseolide A[8], a tetracyclic cell cycle progression regulator, was featured in a special guest editorial in *Organic Letters*. Other recent synthetic targets include uliginosins A and B[9], a two-step synthesis of arcyiacyanin A[1], an efficient total synthesis of calamenenes *via* a strategy that employed allylic strain to enforce stereochemistry[10], the novel indole HKI0231B[11], the synthesis of carbazole esters from methyl coumalate and 3-chloroindoles[1], and the synthesis of furomollugin[7], a natural antibacterial.



Bridgehead Intermediates in Organic Synthesis[12-18]

Dr. Kraus has been a leader in the use of bridgehead intermediates in organic synthesis. He accomplished novel syntheses of lycopodine using both bridgehead carbocation and bridgehead enone pathways. Using bridgehead radical chemistry, Dr. Kraus synthesized key intermediates in the synthesis of diterpene alkaloids and giberellins.



Studies of bridgehead reactions led to the discovery of a novel nucleophilic addition/ring contraction reaction. He employed this reaction in an innovative total synthesis of modhephene.

A Molecular Flashlight[19-24]

Hypericin is a naturally occurring polycyclic quinone which has been shown to exhibit potent activity against enveloped viruses and certain cancers, reducing the infectivity of cell-free stocks of virus by 99.99%. Dr. Kraus, in collaboration with Dr. Carpenter, a microbiologist, was the first to report that light was required for the antiviral activity of hypericin. Light activation permits the development of a drug that will target only virus-infected cells. An expedient choice for the light source is luciferin whose reaction with luciferase and molecular oxygen produces light in the 520-680 nm region with a quantum efficiency close to unity. Hypericin absorbs light strongly in this range and *in vitro* experiments showed that energy transfer between the product of the chemiluminescent reaction and hypericin results in significant antiviral activity.

Their finding that hypericin can be activated by chemiluminescent reactions has important implications for the development of novel methods for the treatment of disease. *In vivo* generation of luciferase could be accomplished using gene therapy approaches that employ luciferase as a susceptibility gene. Expression of the luciferase gene could be regulated if placed under the control of a tumor-specific promoter, limiting photoactivation of hypericin to cancer cells (or virus-infected cells). This would result in a "molecular flashlight" in which light is turned on or off, depending on the presence of the transacting viral protein. In order to avoid the problems inherent in requiring three separate units to come together in the virus-infected cell, Dr. Kraus connected hypericin and luciferin covalently. This tethered molecule, when added to intact virus-infected cells that contain the luciferase gene, has recently been shown to be highly effective in reducing viral infectivity (99.99% viral inactivation).

Teaching

Throughout his career, Dr. Kraus has been an effective and dedicated teacher. To date, his infectious enthusiasm for science and learning has been shared with 61 Ph.D. students and 21 M.S. students, along with numerous undergraduate and postdoctoral research associates. I remember him loading three graduate students into his tiny Datsun for a road trip to Kansas City so we could attend the 1982 American Chemical Society national meeting. Dr. Kraus is generous with his finances as well as his time; upon winning an award early in his career, he gifted each of his graduate students and postdocs the reference book of their choice. The training in critical thinking and problem solving provided by Dr. Kraus resulted in his students being prepared for success in areas far outside the “box” of synthetic organic chemistry. Kraus alumni have gone on to successful careers in academia throughout the world, governmental service, industrial research, scientific and business management, medical research, and patent law. Recognition of the quality of Dr. Kraus’ teaching ability includes the John Wilkenson Award for Outstanding Teaching, the ISU College of Liberal Arts and Sciences Teaching Excellence Award, the ISU Regents Faculty Excellence Award, and the ISU Liberal Arts and Sciences Outstanding Achievement in Graduate Teaching Award.

Outside Interests

When he isn’t in the office or the laboratory, Dr. Kraus enjoys jogging in the summer months and cross-country skiing or snow shoeing in the winter months. Although he doesn’t train for marathons anymore, he completed two marathons in the early 1980s. These days, he participates in 5K and 10K runs.

Now that they are empty nesters, George enjoys travelling with his wife Nancy. They travel throughout the US visiting relatives and one of their long-term goals is to visit each of the national parks. They recently visited Rome and spent two days exploring the museums in Vatican City. They are planning a trip to England in 2019.

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Selected Publications

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