Professor Madeleine M. Joullié

A Tribute

It is a distinct honor and great personal pleasure to serve as facilitator of this special issue of the ARKIVOC, dedicated to the venerable Professor Madeleine M. Joullié, Class of 1970 Professor of Chemistry at the University of Pennsylvania, on the occasion of her 80th birthday. Prof. Joullié was born in Paris, France, but grew up in Rio de Janeiro, Brazil. She moved to the United States for her undergraduate studies, obtaining a B.S. degree in chemistry from Simmons College in Boston, and then attended the University of Pennsylvania, earning an M.S. in 1950 and a Ph.D. in 1953 under the direction of Prof. Allan R. Day, whose interests in mechanistic organic and heterocyclic chemistry played a significant role in influencing her early academic interests. Prof. Joullié became the first woman to join the Penn chemistry faculty and of note was also the first female organic chemist to be appointed to a tenure track position in a major American university. She rose through the ranks to become full professor in 1974, during which period she was appointed as one of the first affirmative action officers at Penn and played a seminal role in the recruiting of women and minority faculty at Penn. During the course of her career, she has remained a proactive advocate of equal opportunity at Penn and has served as District Councilor on several American Chemical Society Professional Relations committees.

Prof. Joullié has a distinguished record as a scientist, teacher, and mentor of many students, and she currently remains a highly creative, prolific, and well-funded organic chemist. During her prodigious career at Penn, she has co-authored three textbooks of organic chemistry, authored over 18 review articles, and published over 300 scientific papers. Having taught undergraduate and graduate-level organic chemistry since joining the Penn faculty in 1953, she is truly a pedagogical institution in her own right. Over the years her unique, colorful persona has achieved legendary status on the Penn campus, where she has mentored over 150 graduate students and post-doctoral fellows and instructed literally thousands of undergraduate and graduate students during the course of her 50+ year tenure.
Prof. Joullié was a Fulbright lecturer at the University of Brazil (1965) and has been a visiting Professor at Columbia University, CRNS (Grenoble, France) and the University of California at Santa Barbara. In 1972, she received the ACS Philadelphia Section Award for investigations of the photochemistry of heterocyclic ketones. In recognition of her many contributions to synthetic organic chemistry and to teaching, Prof. Joullié received the 1978 Garvan Medal. She has been an active participant in the American Chemical Society since her graduate days. She is a member of many honorary and professional societies. Her awards include: American Cyanamid Faculty Award (1984); American Institute of Chemists 34th Annual Scroll Award (1988); Lindback Award for Distinguished Teaching (1991); Second Annual Association of American Women in Science, Philadelphia Chapter Award (1991); Philadelphia Organic Chemist’s Club Award (1994); Henry Hill Award (1994); H. Martin Friedmann Lectureship, Rutgers University (1995); ACS Award for Encouraging Women into Careers in the Chemical Sciences (1998); Distinguished Achievement Award University of Pennsylvania Graduate Student Associate and Phi Lambda Upsilon (1999); and the A.C.S. Cope Senior Scholar Award (2002).

Heterocyclic chemistry, medicinal chemistry, new synthetic technologies, and natural product total synthesis are hallmarks of Prof. Joullié’s research. Early in her career Prof. Joullié developed an active interest in structure-reactivity relationships in aromatic and heterocyclic scaffolds and conducted pioneering work on fluorinated heterocycles. During the 1970’s her research shifted to novel [3+2] and [2+2] cycloadditions of ketene and ketene sulfur dioxide adducts, heterocyclic scaffolds with antimalarial activity, and tilorone, an orally bioavailable interferon inducer. Photochemical studies on heterocyclic ketones, in collaboration with Peter Yates of the University of Toronto, utilized deuterium labeling probes for mechanistic studies and led to the 1972 ACS Philadelphia Section Award.

In 1980, Prof. Joullié entered the natural products arena and reported the first asymmetric total synthesis of the antibiotic (+)-furanomycin. This work is noteworthy since it marked the first example of the use of the Ugi 4CC in the synthesis of a non-proteinogenic amino acid. Methodologies were also developed for construction of hexasubstituted aromatic systems, functionalized 3(2H)-dihydrofuranones, and selective modification of carbohydrate templates derived from glucose, D-riboono-1,4-lactone, and 2-deoxy-D-riboono-1,4-lactone for “chirality transfer,” (a term first dubbed by Prof. Joullié and now widely used in the synthetic literature), resulting in the total synthesis of several natural products, including muscarine diastereomers and analogs, bullatenone, geiparvarin, ascofuranone, colletochlorin D, (-)-litsenolides C1 and C2, furanomycin diastereomers, ascochlorin, and cristic acid. With K.C. Nicolaou, she co-developed the phenylselenoetherification reaction, a highly efficient cyclization process for the synthesis of oxygen- and sulfur-heterocycles.

Prof. Joullié then focused on increasingly complex peptide and depsipeptide natural products. In 1984 she reported the total synthesis of dihydromauritine A, a highly strained 14-membered cyclopeptide alkaloid prototype. This work set the stage for more complex congeners (-)-
nummularine F (1992), sanjoine G1, and its C-11 epimer (1998). Concurrent investigations on
detoxin depsipeptide metabolites, produced by Streptomyces caespitosus, resulted in a concise
synthesis of (-)-detoxinine (1986). Total syntheses of detoxins B1, B3 (1986), D1 (1992), and
(+)-valyldetoxinine (1993) followed. More recently her group reported the total synthesis of astin
G (1999), a prototype from the astin family of anti-tumor cyclopentapeptides, which features
several noncoded amino acids.

The asymmetric total synthesis of didemnin B in 1990 and subsequent investigations over
nearly two decades mark a milestone in Prof. Joullié’s prolific career that has resulted in
fundamental contributions to both the chemistry and biology of this intriguing class of natural
products. The didemnin class of macrocyclic depsipeptide, isolated from a marine tunicate of the
family Didemnidae, exhibit antitumor, antiviral and immunosuppressive activities. Didemnin B,
featuring a 23-membered macrocycle, is one of the most potent and thoroughly investigated
congeners to date and notably was the first marine natural product to enter clinical trials against
cancer. Revision of the stereochemistry of the hydroxyisovalerylpropionyl (HIP) subunit,
synthetic studies on statine moieties, and development of new depsipeptide methodologies
served as forays to the stereocontrolled construction of didemnin B. This was followed by
efficient total synthesis of didemmins A and C. X-ray crystallographic studies were conducted on
rigidified analogs in addition to design and synthesis of several novel, conformationally modified
analogs and fluorescent biological probes thereof. Cell biology and mode of action studies on in
vitro protein biosynthesis inhibition and antitumor activity were evaluated on didemnin
analogue in collaboration with Peter Toogood at the University of Michigan. The first total
synthesis of (-)-Tamandarins A and B, natural products similar in structure, but more active in
vitro than didemnin B against pancreatic carcinoma, were reported in 1999 and 2001.

In collaboration with Judah Folkman of Harvard University and Paul B. Weisz from Penn,
Prof. Joullié designed and synthesized a novel series of β-cyclodextrin sulfates featuring
lipophilic moieties that act as cyclic oligosaccharide heparin mimetics. These polyanionic
compounds expressed potent cellular growth modulating activity and can capture other
molecules including cortisone. The combination of cortisone with these agents potently inhibits
aberrant angiogenesis, as found in tumor metastasis and macular degeneration.

Research in the Joullié laboratories on ninhydrin analogs over the past decade has resulted in
a series of benzo[f]ninhydrins, 5-arylninhydrins, and 1,2-indandiones with enhanced
chromogenic and fluorogenic properties. The improved sensitivity and potential application of
these compounds in forensic science not only prompted a visit to Penn by Secret Service agents
but has also led to fluorescent products now in use in some countries for fingerprinting.

Current targets in the Joullié group include the ustiloxin family of 13-membered macrocyclic
heterodetic cyclopeptides, highly potent inhibitors of microtubule assembly. In 2005 the total
synthesis of Ustiloxin D was achieved and her group is currently pursuing more complex
congeners and analogs of this series. Studies are also underway on Callipeltin A, a macrocyclic
22-membered depsipeptide isolated from a shallow water sponge of the genus Callipelta that
expresses antiviral, antitumor and antifungal properties. It is a selective, potent inhibitor of the cardiac sodium/calcium exchanger and is of interest as a regulator of myocardial contractility.

In addition to being an outstanding scientist and mentor, Prof. Joullié has many unique personal qualities that make her unforgettable, the distinct voice, the lively conversation, the ever-inquisitive mind and the amazing dedication to her chemistry and teaching. Prof. Joullié is greatly admired by her diverse, but tight-knit group of graduate students and post-docs who now span the decades. These former MMJ students remember well the weekly seminar sessions for review of research progress and current topics, the high expectations and constant encouragement during those graduate years, and the lifelong camaraderie that follows. They are all proud to have been students of the intense, original, yet warm and caring Madeleine M. Joullié.

J. Edward Semple, Ph.D., San Diego, CA

Selected publications of Madeleine M. Joullié (30 publications)


