University Distinguished Professor James M. Cook

A Tribute

James M. Cook was born in Bluefield, West Virginia on August 6, 1945. He obtained his BS in Chemistry with Honors from West Virginia University in 1967. During his undergraduate years Jim spent his summers working at Fikes Chemicals in Nitro, West Virginia. Initially working as a laboratory technician, later as a supervisor of the research laboratory and ultimately as a plant foreman, it was while he was at Fikes Chemicals that Jim gained an interest in synthetic chemistry and an appreciation for high-yielding large-scale reactions. This appreciation would later become an underlying theme in much of the research of his professional academic career. Jim then went on to graduate school at the University of Michigan in 1967 where he studied alkaloid chemistry under Professor Philip LeQuesne. He received his Ph.D. degree in organic chemistry in 1971. He then was awarded an NIH Postdoctoral Fellowship and went to the University of British Columbia where he continued his studies in the field of alkaloid chemistry with Professor James P. Kutney from 1972-1973. In the fall of 1973, Jim was appointed Assistant Professor of Chemistry at the University of Wisconsin-Milwaukee. He was later promoted to Associate Professor in 1979 and Professor of Chemistry in 1986. He served as Chairman of the Department of Chemistry at UWM from 1996-1999. Finally in 2002, he was recognized for his scholarly achievement and academic contributions by promotion to the rank of University Distinguished Professor of Chemistry.

Jim has received several awards during his tenure at UWM. These include the UW-Milwaukee Foundation Award for Research (1981), the Milwaukee Section ACS Award in Chemistry (1989), Japanese Society for the Promotion of Science Fellowship (2001), WiSys (Wisconsin System) 2006 Innovation Scholar Award and the UW – Milwaukee 2007 Innovator Award. In addition, he has also served on the editorial advisory boards of a variety of leading research journals. These include *The Journal of Medicinal Chemistry* (1996-2001), *Medicinal Chemistry Research* (1996-2006), *Expert Opinion on Therapeutic Patents* (1999-2004), *Current Topics in Medicinal Chemistry* (2001-2004), *Current Organic Synthesis* (2002-2007) and *Drug Design, Development and Therapy* (2007-2009). He is a widely used referee for international journals. In addition to all of this, he is the author of 14 patents and more than 350 original research articles in international journals that include several review articles and book chapters. He has also given numerous lectures at colleges and universities all over the United States and has participated in professional conferences all over the world.

Research Interests

At the start of his academic career in the late 70s Jim's research interest continued to be focused on the chemistry of indole alkaloids. Early studies in this area examined the scope and limitations of the Pictet-Spengler reaction for the construction of β-carboline ring systems. This work provided some of the fundamental mechanistic understanding of the Pictet-Spengler reaction. Continued studies on this reaction have led to the development of stereospecific and enantiospecific Pictet-Spengler reactions. It was these studies that provided the foundation for his work directed toward the total synthesis of indole alkaloids from the *Alstonia* and *Sarpagine* families of alkaloids. In a series of papers published in the *Journal of the American Chemical Society* and the *Journal of Organic Chemistry* from 1991 to date his research group has synthesized well over 40 indole alkaloids using the Pictet-Spengler reaction for the construction of the core alkaloid skeletons. The recent adaptation of the enolate-driven palladium cross-coupling reaction has added a new dimension to the field of alkaloid chemistry. Clearly this body of work has established Jim as one of the premier indole alkaloid chemists of our time. Highlights in this area of research include the stereospecific synthesis of (+)-vellosimine, the enantiospecific total syntheses of (-)-suavoline, (+)-ajmaline (+)-corynantheidine and mitragynine as well as the enantiospecific total synthesis of many bis-indole alkaloids including macralstonine, macralstonidine and accedinisine. In order to prepare macralstonine, the Cook group designed a new synthesis of enones, which has now been termed the Wacker-Cook reaction by Maldonado and coworkers. This one-pot reaction has been employed to prepare novel isoflavones and flavones that bind to benzodiazepine receptors.

A second area of research has been aimed at the construction of novel polyquinene and polyquinane ring systems via the condensation of 1,2- and 1,3-dicarbonyl compounds. This research led to the development of the Weiss-Cook reaction and elucidation of the scope and limitations of this highly efficient process. True to his roots in industry, this facile process for the construction polycyclopentane ring systems can be performed on kilogram-scales and has greatly

advanced synthetic organic chemistry in this area. This work was published in a series of papers from 1976-1997 and has been employed in the total synthesis of the natural product (±)-modephene, the non-natural compounds, staurene and ellacene, as well as a host of other structurally unique molecules of theoretical interest that include propellanes and fenestranes. To date, the Weiss-Cook reaction continues to be an important focus of the Cook Group's research effort directed toward the synthesis of novel carbocyclic systems. However, this area of study has recently been expanded to include the elucidation of the synthetic scope and utility of the transition metal mediated tandem Pauson-Khand reaction for the construction of novel cyclopentapentalenes. These investigations of the tandem Pauson-Khand reaction have added a new dimension to this area of synthetic organic chemistry and have made it possible to prepare novel annulenes in a highly convergent manner. As documented in the *Journal of the American Chemical Society* the tandem allenic Pauson-Khand reaction was used to prepare the first 14π cyclopentapentalene derivative to study homoconjugation, stability, electron delocalization and aromaticity. Current efforts in this area are directed toward the preparation of novel 10π and 14π cyclopentapentalenes as well as unique molecular scaffolds that are capable of housing a planar tetra-coordinate carbon atom.

Intimately related to his alkaloid research, Jim has always maintained a strong medicinal chemistry research program. The benzodiazepine receptor/GABA receptor/chloride ion channel system has been the primary pharmacological target of this research with an emphasis on the elucidation of the binding motifs of benzodiazepine receptor agonists and antagonists as well as medication development for anxiety, epilepsy pain and alcohol addiction. In a series of papers from 1982-1998 published in the *Journal of Medicinal Chemistry* Jim established himself as one of the pioneering researchers in this field. Initially, he explored the structure-activity relationships of a plethora of β-carboline derivatives to provide a unique insight to the function of benzodiazepine receptors. In the late 90s and to date, this research has expanded to explore the structure-activity relationships of novel benzodiazepines at benzodiazepine receptors. This coupled with his prior work led to the development of some of the first benzodiazepine receptor subtype selective ligands. With over 70 publications to date in the field of benzodiazepine receptor medicinal chemistry and pharmacology, Jim is one of the most often cited researchers and is widely recognized as one of the world's leading authorities in this field. Many pharmaceutical companies have employed Jim's pharmacophore/receptor model to develop variations of their own. These companies include, Johnson & Johnson, Merck & Co., Inc. and Neurogen. One of his non-sedating anxiolytics was chosen for Phase I clinical trials in humans.

In addition to his love for medicinal and synthetic chemistry Jim enjoys spending time with his family, his loving wife Gloria of 43 years, his two daughters, Christine and Catherine and three grandchildren, Caroline, Benjamin and Oliver. He also enjoys spending time with his professional family and can often be seen at professional meetings surrounded by current and past students and postdocs reminiscing about past achievements or discussing future directions of research. More details of his scientific and other endeavors can be found on Jim's website: http://www.uwm.edu/~capncook/.

Finally, on behalf of the contributors to this commemorative issue as well as all other students, postdoc and colleagues that are working with Jim or have worked with him in the past, we wish him a Happy 65th Birthday and many years of continued success.

Mark L. Trudell
University of New Orleans

Selected Publications of Professor James M. Cook

Pictet-Spengler Reaction and Indole Alkaloid Total Synthesis

1. Study of the Pictet-Spengler Reaction in Aprotic Media: Synthesis of the β-Galactosidase Inhibitor, Pyridindolol. Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44,* 535.
2. General Method for the Assignment of Stereochemistry of 1,3-Disubstituted-1,2,3,4-Tetrahydro-β-Carbolines by Carbon-13 Spectroscopy. Ungemach, F.; Soerens, D.; Weber, R.; DiPierro, M.; Campos, O.; Mokry, P.; Silverton, J. V.; Cook, J. M. *J. Am. Chem. Soc.* **1980**, *102,* 6976.
3. Stereospecific Synthesis of 1,3-Disubstituted-1,2,3,4-Tetrahydro β-Carbolines. Ungemach, F.; DiPierro, M.; Weber, R.; Cook, J. M. *J. Org. Chem.* **1981**, *46,* 164.
4. The Pictet-Spengler Condensation: New Directions for an Old Reaction. Cox, E.; Cook, J. M. *Chem. Rev.* **1995**, *95,* 1797.
5. General Approach for the Synthesis of Ajmaline/ Sarpagine Indole Alkaloids. Enantiospecific Total Synthesis of (+) Ajmaline, Alkaloid G, and Novsuaveoline *via* the Asymmetric Pictet-Spengler Reaction. Li, J.; Wang, T.; Yu, P.; Peterson, A.; Soerens, D.; Weber, R.; Grubisha, D.; Bennett, D.; Cook, J. M. *J Am. Chem. Soc.* **1999**, *121*, 6998.
6. General Approach for the Synthesis of Indole Alkaloids *via* the Asymmetric Pictet- Spengler Reaction. First Enantiospectific Total Synthesis of (-)-Corynantheidine as well as the Enantiospecific Total Synthesis of (-)-Corynantheidol (-)-Geissoschizol, and (+)-Geissoschizine. Yu, S.; Berner, M.; Cook, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 7827.
7. Efficient Asymmetric Synthesis of Biologically Important Tryptophan Analogues *via* a Palladium Heteroannulation Reaction. Ma C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.* **2001**, *66*, 4525.
8. Stereocontrolled Total Synthesis of (-)-Vincamajinine and (-)-11-Methoxy-17-epivincamajine. Yu, J.; Wearing, A.; Cook, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 1358.
9. The Syntheisis of the Macroline Alkaloids: A Recent Review. Edwanker, C. S.; Edwanker, R.; Rallapalli, S.; Cook, J. M. *Nat. Prod. Commun.* **2008**, *3*, 1839.
10. General Approach to the Total Synthesis of 9-Methoxy-Substituted Indole Alkaloids: Synthesis of Mitragynine, as well as 9-Methoxygeissoschizol and 9-Methoxy-N_b-Methylgeissoschizol. Ma, J.; Yin, W.; Zhou, H.; Liao, X.; Cook, J. M. *J. Org. Chem.* **2009**, *74,* 264.

The Weiss-Cook Reaction, Polyquinanes, Polyquinenes and Polycyclopentapenta-lenes

11. Stereocontrolled Synthesis of (±)-Modhephene *via* the Weiss Reaction. Wrobel, J.; Takahashi, K.; Honkan, V.; Bertz, S.; Lannoye, G.; Cook, J. M. *J. Org. Chem.* **1983**, *48*, 139.
12. General Approach for the Synthesis of Polyquinenes. II. Synthesis of Tetracyclo-[5.5.1.$0^{4,13}$.$0^{10,13}$]tridecane-2,5,8,11-tetraene. Deshpande, M. N.; Jawdosiuk, M.; Kubiak, G.; Venkatachalam, M.; Weiss, W.; Cook, J. M. *J. Am. Chem. Soc.* **1985**, *107,* 4786.
13. General Approach for the Synthesis of Polyquinenes *via* the Weiss Reaction. Gupta, A. K.; Fu, X.; Snyder, J. P.; Cook, J. M. Tetrahedron Report Number 291, *Tetrahedron* **1991**, *47*, 3665.
14. General Approach for the Synthesis of Polyquinenes *via* the Weiss Reaction. XIV. Synthesis of Ellacene (1,10-Decanotriquinacene) and Studies of the Proposed Dimerization to a Substituted Dodecahedrane. Fu, X.; Cook, J. M. *J. Org. Chem.* **1992**, *57,* 5121.
15. The Synthesis of a Dicyclopenta[a,e]pentalene *via* a Molybdenum Hexacarbonyl-Mediated Tandem Allenic Pauson-Khand Reaction. Cao, H.; Flippen-Anderson, J.; Cook, J. M. *J. Am. Chem. Soc.* **2003**, *125,* 3230.

Benzodiazepine Receptor Structure Activity Studies

16. β-Carbolines: Synthesis, Neurochemical and Pharmacological Actions on Brain Benzodiazepine Receptors. Cain, M.; Weber, R.; Guzman, F.; Cook, J. M.; Barker, S. A.; Rice, K. C.; Skolnick, P. *J. Med. Chem.* **1982**, *25,* 1081.
17. Synthetic and Computer-Assisted Analyses of the Pharmacophore of the Benzodiazepine Receptor Inverse Agonist Site. Allen, M. S.; Tan, Y.-C.; Trudell, M. L.; Narayanan, K.; Schindler, L. R.; Martin, M.; Schultz, C., Hagen, T. J.; Koehler, K. F.; Codding, P. W.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1990**, *33,* 2343.
18. Pharmacophore/Receptor Models for GABAA/BzR Subtypes (α1β3γ2, α5β3γ2, and α6β3γ2) via a Comprehensive Ligand-Mapping Approach. Huang, Qi.; He, X.; Ma, C.; Liu, R.; Yu, S.; McKernan, R.; Wenger, G.; Dayer, C., Cook, J. M. *J. Med. Chem.* **2000**, *43*, 71.
19. An Updated Unified Pharmacophore Model of the Benzodiazepine Binding Site on γ-Aminobutyric Acid(A) Receptors: Correlation with Comparative Models. Clayton, T.; Chen, J.; Ernst, M.; Richter, L.; Cromer, B. A.; Morton, C. J.; Ng, H.; Cook – Kaczorowski, C.; Helmstetter, F. J.; Furtmüeller, R.; Ecker, G.; Parker, M. W.; Sieghart, W.; Cook, J. M. *Curr. Med. Chem.* **2007,** *14,* 2755.
20. A Study of the Structure-activity Relationship of GABA(A)-benzodiazepine Receptor Bivalent Ligands by Conformational Analysis with low Temperature NMR and X-ray Analysis. Han, D.; Forsterling, F. H.; Li, X.; Deschamps, J. R.; Parrish, D.; Cao, H.; Rallapalli, S.; Clayton, T.; Teng, Y.; Majumder, S.; Sankar, S.; Roth, B. L.; Sieghart, W.; Furtmuller, R.; Rowlett, J. K.; Weed, M. R.; Cook, J. M.; *Bioorg. Med. Chem.* **2008**, *16*, 8853.