

## Professor Alfred Hassner

### A Tribute



Alfred Hassner was born in Czernowitz, Romania (now part of the Ukraine) in 1930 where he was only able to complete the third grade before WWII changed the life of Fred and the other 60,000 Jewish residents of the city. Surviving the holocaust, Fred enrolled directly (skipping grades 4 - 12) into the Technische Hochschule in Vienna (1949-1951) moving to the University of Nebraska where he completed his B. Sc. in 1952. Continuing his graduate studies at Nebraska under the direction of Norman Cromwell, he finished his Ph. D. studies in 1952. He continued his post-doctoral training under Louis Fieser at Harvard during 1956-7, joining the faculty at the University of Colorado as an Assistant Professor in 1957. Rising through the ranks, he became Full Professor in 1966, a position he held until 1975 when he moved to the State University of New York at Binghamton being awarded the prestigious rank of Leading Professor. In 1983, he moved to Bar-Ilan University in Ramat-Gan, Israel where he is now Professor Emeritus.

Fred and his wife Cyd are the proud parents of a daughter, Lily and a son, Lawrence. They now also have five grandchildren who are the joy of their lives. Times have not always smiled upon the Hassners who have also suffered the tragic loss of three children. Added to this, Cyd has been very recently diagnosed with Creutzfeldt-Jakobs, a prion disease, found in one in a million, for which neither the cause nor treatment are known. Fred has been looking into several experimental drug treatments for her, but to date there has been little progress. A year ago, a special symposium was held in Bar-Ilan University in Fred's honor entitled "Recent Advances in Organic-Bioorganic Chemistry" which featured many of his former students, colleagues and friends. It was a wonderful gathering which gave us the opportunity to catch up on the lives of the Hassners, including Lily, who holds a Ph. D. in genetics and Lawrence, who holds M.S. degrees in chemistry and business management. Cyd was in good health then and it was a personal joy for me to be a part of this celebration.

As a scholar, Fred has held visiting professorships and appointments in many universities throughout the years. These include Harvard (1966), ETH (NIH Special Fellow, 1967), Wurzburg (1971), Weizmann Institute of Science (NIH Special Fellow, 1972-73, 1981-2), Hebrew University (1969), Universite Claude Bernard, Lyon, (1980), Kyushu Institute of Technology (1985), Stanford (1987), University of California, Berkeley (1989), University of Nijmegen (1995), University of California, San Diego (1998). He has also served as a consultant with S.P. Corp., Lincoln, NE Research Chemistry (1952-54), E. I. du Pont de Nemours Co. (1954), Univ. of Colorado Medical School (1958-62), Physics-Engineering-Chemistry Corp. (1962-64), Food and Drug Administration (1967), Boulder Research Instruments (1969-73), 3M Company (1975-77), TAMI, Haifa (1988- 1999), SKB, King of Prussia (1990).

Professor Hassner has also been the recipient of numerous distinctions and awards for his outstanding contributions to chemistry. He was a Monsanto Fellow (1954-56), on the Council on Research Fellowship, Harvard University (1966), a National Cancer Institute Special Fellow, ETH, Zurich (Prof. Prelog) (1967), recipient of a von Humboldt Award (1971), a Weizmann Senior Fellow - NIH Special Fellow (1972-77), ACS National Awards Committee, Lady Davis Foundation Award (1979), NSF US-India Exchange Lecturer (1979), France-US Lecturer, Univ. of Lyon (1980), Nominee SUNY Chancellor's Award for Excellence in Teaching (1979), Meyerhoff Fellow (1981-82), Fulbright Senior Award (1983), Member NIH Medicinal Chemistry Study Session (1981-84), Japan Society for Promotion of Science Award (1985), U.S. National Research Council Award (1993), A.W. Killam Award, Canada (1998), President, Israel Chemical Society (1991 – 1994). In addition, Fred has served on the Editorial Boards of the *Journal of Organic Chemistry*, *Organic Preparations and Procedures International* and *Heterocyclic Communications*.

Throughout the chemical community, Fred has played an important role in both the organization and content of many National and International Meetings including contributing over 150 scientific papers. He has chaired symposia including the Gordon Research Conference on Heterocycles (1977), ACS Symposium on Electrophilic Additions (1964), Centennial Symposium (1976), International Symposium on Chemistry of Strained Rings (1977), 12th International Congress of Heterocyclic Chemistry (1989), Co-Chairman of the International Symposium on "Selectivity on Basic and Applied Organic Chemistry (1995). He has given over 250 invited seminars at universities and industrial laboratories. In addition, he has presented 37 plenary or invited symposia lectures over his career. He has authored or been the Editor on numerous books and monographs: A. Hassner and C. Stumer, "Organic Syntheses Based on Name Reactions and Unnamed Reactions". Pergamon Elsevier Science, (1994), 452 pp.; A. Hassner, Editor, "Small Ring Heterocycles, Part 1. Aziridines, Azirines, Thiiranes, Thiirenes", J. Wiley & Sons, New York (1983) 696 pp.; "Small Ring Heterocycles, Part 2. Azetidines,  $\beta$ -Lactams, Diazetidines, Diaziridines", J. Wiley & Sons, New York (1983) 656 pp.; "Small Ring Heterocycles, Part 3, Oxiranes, Arene Oxides, Oxaziridines, Dioxetanes, Thietanes, Thietes, Thiazetes", John Wiley and Sons, New York, (1985) 874 pp.; "Advances in Asymmetric Synthesis", vol. 1, JAI Press, (1995), 320 pp.; vol. 2, JAI Press (1997), 310 pp.; "Advances in

Asymmetric Synthesis", vol. 3, JAI Press (1998), 365 pp.

With more than 300 research articles in print, Professor Hassner has had a major impact on chemical science, particularly on reagent and small ring heterocyclic chemistry. Some of his major contributions include the stereoselective introduction of nitrogen functionality including nitro, azido, isocyanate, nitrile oxide into organic molecules. In the steroid field, he developed the synthesis of steroidoheterocycles and was one of the first to recognize the application of NMR half-widths to stereochemical structure assignments before high resolution NMR became available. He discovered stereo- and regio-selective halogen azide additions to multiple bonds through elucidating condition dependent free radical or ionic mechanisms. He further developed these and other pseudohalogen additions, including chlorosulfonyl isocyanate, into new syntheses of small ring heterocycles such as aziridines, azirines, azetines, and also of azepines and other heterocycles. He first proposed the concept of regiochemistry and regioselectivity, now universally used terminology in organic chemistry. In parallel with Steglich, he developed the use of 4-dialkylamino pyridines (e.g. dimethylaminopyridine DMAP) as super-acylation catalysts in enhancing direct esterification of hindered alcohols. He also developed stereo- and regioselective [2+2] ketene – olefin cycloadditions and the preference for axial approach for the synthesis of cyclobutanones. He developed the synthetic utility of stereoselective intramolecular [3+2] dipolar cycloadditions of silyl nitronates, nitrile oxides, oximes to unsaturated substrates. His pioneering work in Michael Induced Ring Closures (MIRC) led to stereoselectively functionalized and enantiomerically pure cyclopentanes.

Current research interests of Professor Hassner have centered on the development of new synthetic methods and stereochemical aspects of organic and bioorganic chemistry. In his medicinal chemistry program, his interests include the synthesis of potential anticancer and antiviral agents. This involves finding new methods of introducing functional groups to modify the structure of biologically active compounds including nucleosides. The use of reactive intermediates is being explored in the synthesis of small ring heterocycles and their subsequent ring expansions to larger rings. Highly stereoselective dipolar cycloadditions have been discovered that can be used in the construction of functionalized homocyclic and heterocyclic ring systems. These result from the discovery of a new method for the stereoselective and enantioselective synthesis of highly functionalized cyclopentane derivatives via a trimethylenemethane synthon. This method can also be used to prepare optically active pyrrolidines. These have been applied to the synthesis of naturally occurring compounds. The scope of the intramolecular [3+2]-cycloaddition is being examined in nitrile oxide-olefin cycloadditions and new intramolecular oxime-olefin cycloadditions leading to interesting new heterocyclic systems, glycosidase inhibitors and to natural products.

Having been the research director of over fifty (50) M.S. and Ph.D. students and of more than sixty (60) post-doctoral research associates, Dr. Hassner has provided invaluable mentoring and guidance to many scientists throughout the world. Fred knows how to bring out the best in people. I often cite my own Ph.D. work in his group at Colorado as perhaps the most productive and enjoyable part of my life. We all worked hours that would simply be incredible to many of

today's graduate students. But it was truly wonderful to be a part of this intellectually vital research group. During this period, Fred had graduate students like Susan Burke-Hurt, Richard Fibiger, Joseph Keogh, Larry Krepksi, and Jerald Rasmussen in addition to Benjamin Belinka Jr.(SUNY Binghamton) in his group. Both in Colorado and in SUNY Binghamton during my tenure in the group, Hassner also had a treasure trove of post-doctoral associates including Vazken Alexanian, Boaz Amit, David J. Anderson, Charles Bunnell, Gerald C. Jan, William F. Masler, David Middlemiss, Thomas K. Morgan Jr., Harold W. Pinnick, Robert Reuss, David Y. Tang and Darrel Watson. I have also had the pleasure of meeting a number of Hassner's former students and post-doctorals over the years including John L. Dillon, Bilha Fischer, Frank W. Fowler, James E. Galle, Clayton H. Heathcock and Alan B. Levy.

Among my fondest memories of my graduate student days, I will never forget Fred and Cyd white-water rafting the Cache le Poudre River near Fort Collins, CO during the 1974 Organic Chemistry Symposium hosted by Al Meyers. It was quite a site. I also have fond memories of Fred's group meetings which were superb, normally producing many scholarly synthetic and mechanistic discussions regarding both group research and literature articles. However, no meeting was more memorable than one held on a Colorado evening when ~500 streakers ran through the campus in full view of Fred and the group from the second floor chemistry seminar room. After watching this Boulder bizarre spectacle, we went back to discussing a plausible carbene mechanism for an interesting rearrangement. The graduate students and post-docs always looked forward to an annual get-together at the Hassner home and Cyd's great dinners. In addition, the Colorado group often went on week-end hikes and cross-country ski trips. Although we could never talk Fred into taking up golf, this was also a week-end group activity for some of us during the summer months. Fred has always been interested in everything and he always made time for his students. His enthusiasm for chemistry is infectious. He is a gracious gentleman who I am proud to call my teacher and my friend. It is a pleasure for me to be a part of this tribute to a man who has done so much for chemistry.

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