

Professor James R. Bull

A Tribute



James Bull was born in East London, South Africa in 1937, and grew up in KwaZulu-Natal, where he attended school and commenced his University studies. He completed an MSc degree at the University of Natal, Durban, on flavonoid plant extractives, then proceeded to Oxford University as a Commonwealth Scholar in 1961, to further his studies at the Dyson Perrins Laboratory. Here, he made a first acquaintance with steroid chemistry under the tutelage of Sir Ewart Jones and Dennis Meakins, and completed his DPhil degree on this topic in 1964. Following a post-doctoral period year under William S Johnson at Stanford University, during the early unfolding of the strategy directed toward total synthesis of steroids based upon biomimetic cyclization of polyenes, he returned to South Africa in 1965, taking up a position as researcher at the National Chemical Research Laboratory (NCRL) in Pretoria. His initial research assignment entailed beneficiation of local plant products through selective structural modification, aimed at seeking out potential precursors of novel steroidal hormone analogs. This project evolved into a more broadly based program of predictive design and synthesis, in which steroids and related bioactive substances constituted a strong connective theme that has been sustained throughout his career.

During his NCRL career, James progressed through the ranks and, after serving as Head of the Organic Division for 10 years, was appointed as Chief Director, in succession to Piet Enslin, in 1984. At that stage the Laboratory enjoyed international recognition for research excellence and the provision of high quality research services to the South African academic community.

Programs of perceived national and regional significance were complemented by an environment in which nascent talent was nurtured in preparation for career outlets in academic and industrial life. This congenial and creative institutional culture was the brainchild of visionary founders of the parent Council for Scientific and Industrial Research (CSIR) in 1947, and was responsible for nurturing an entire generation of outstanding chemists and the attendant growth in strength and stature of the academic sector in South Africa during the intervening years. Sadly, this irreplaceable resource was to be dismantled within 3 years, following an ill-considered policy shift by the CSIR executive hierarchy in 1987, which resulted in disestablishment of this and other discipline-defined Laboratories, in order to pursue more overtly business-oriented programs based on technology transfer at the expense of innovation. James's fierce opposition to the detrimental impact of this policy change on the national infrastructure of chemistry was unavailing, and precipitated his departure from the CSIR and subsequent appointment to the Mally Chair of Organic Chemistry at the University of Cape Town in 1988, a position which he retains until statutory retirement at the end of 2002. I might add, that many of the top Universities in South Africa were vying for James at that time.

The record of James's research career and outputs was shaped to a large extent by the influences of his early training. The Oxford experience proved to be decisive, and kindled a lifelong fascination in the interplay between organic synthesis and conformational analysis, a theme which recurs frequently in his subsequent research career and outputs. His DPhil investigation entailed development of a general stereoselective method for converting steroidal ketones into nitro compounds via nitration – oxidation of oximes, followed by reductive monodenitration, and application of spectroscopic and chiroptical methodology in structural and stereochemical analysis, the latter through collaboration with two of the pioneers in these techniques, William Klyne and Günther Snatzke. During the initial stage of his NCRL career, he enjoyed a fruitful period of collaboration with Piet Enslin, in a study stimulated by the configurational analogy of the cucurbitacin family of tetracyclic triterpenoids with a class of progesterone analogs derived from lumisterol. This entailed extensive skeletal and functional group modification of selected cucurbitacins, in attempts to mimic the functional group patterns of steroidal hormones in templates of unnatural backbone configuration. Although this phase of the project was eventually terminated in favor of synthetic approaches to lead compounds, it contributed new insights into remote functionalization methodology, molecular rearrangements, ring aromatization, and chiroptical analysis, and set the scene for delineating the most promising structural features of the natural product family for incorporation into synthetic targets.

Early successes included the first total syntheses of 9-methyl-9 β ,10 α -analogs of 19-nortestosterone and 19-norprogesterone. The absence of bioactivity in these analogs proved to be significant, since it hinted at a new interpretation of structure-activity in 9 β ,10 α -steroids. Based upon conformational adaptability, a hypothesis was formulated that led to a total synthesis of a series of 14 α -methyl-9 β ,10 α -19-norsteroids, in which bioactivity could be correlated with susceptibility to conformational deformation of the *cis*-fused central rings. A tangential finding, that certain 14-methyl estradiols of natural configuration display favorable affinity toward the

estrogen receptor, broadened the scope of the project to embrace the more general question of the role of steric congestion in modulating substrate-receptor interactions. A cycloaddition-fragmentation strategy for elaborating 14-alkyl and 14-functionalised-alkyl steroidal hormones was turned to further advantage with the discovery that 14,17-bridged analogs of estradiol are not only high-affinity receptor probes, but display oral bioavailability. This finding resulted in a period of intensive collaboration with Schering AG, Berlin, during which a large number of novel hormone analogs were synthesized and subjected to biological evaluation. This program has made a significant contribution to delineating biocompatible substructural features around the steroid ring D, and in defining synthetic targets in search of new expressions of agonist and antagonist function.

Complementary and parallel studies have been pursued on a variety of methodological topics, dealing with epoxide rearrangement, organocuprate chemistry, homologation studies and steroid conformational analysis, as well as new methods and applications of intermolecular and intramolecular cycloaddition. During the relatively brief academic phase of his career, at which time he handled the change from an almost purely research oriented vocation to that of an academic at the University of Cape Town with dignified ease, James was immediately popular among the student body who greatly respected his interactive manner and enthusiasm for the research ventures he put forward to encourage their participation. As a consequence has supervised 26 graduate student studies at MSc and PhD level, and has contributed enthusiastically to promoting a strong research culture at UCT, through supervision of numerous Honors student research projects and post-doctoral programs, whilst at the same time cultivating international interaction and links through scholarship exchange programs that have materially contributed toward the personal growth of many graduate students. Several former students have made their way into academic and research careers both in South Africa and abroad. He has delivered numerous invited lectures on the national and international stage, and served on numerous national evaluation and strategic planning panels.

James joined the South African Chemical Institute as a student member in 1958 and, upon commencing his career in Pretoria, became involved in professional activities, serving in various capacities at regional and national level. In addition to his service as member of the Council of the Chemical Institute for 20 years and as President in 1986–1988, he took a particular interest in scientific programs and communications. He undertook the Editorship of the *Journal of the South African Chemical Institute* in 1972, and played a central role in negotiations that culminated in the formation of a statutory body responsible for supporting publication of national scientific journals. The Institute *Journal* thus assumed a new identity as the *South African Journal of Chemistry* in 1976, whereupon he continued as Scientific Editor until 1992, and Chairman of the Editorial Board until 1996, whilst also serving on the National Council for Scientific Publications.

James has been an enthusiastic participant in conference planning of several national and international events in South Africa, and played a leading role in organizing the 13th IUPAC Symposium on the Chemistry of Natural Products in Pretoria in 1982, an event that attracted

widespread international interest and participation, and showcased the healthy regional state of organic chemistry at that time. More recently, he was instrumental in facilitating an initiative between the Royal Society of Chemistry and the SA Chemical Institute, culminating in a highly acclaimed 1st Binational Conference on Organic Chemistry in Cape Town in 2001. Other international activities include periods of service as member of the IUPAC Commission on Nomenclature of Organic Chemistry and the IUPAC-IUB Joint Commission on Biochemical Nomenclature over several years. More recently, he has undertaken the task as Special Topics Editor of *Pure and Applied Chemistry*, an initiative targeted at broadening the scope and coverage of the publication as the flagship publication of IUPAC. He has served as Chairman of the SA National Committee for IUPAC, the SA National Board for International Council of Scientific Unions (ICSU), the Chemistry Committee of Foundation for Research Development, and as a member of the Council of the Royal Society of South Africa

The scientific and professional contributions of James have been recognized by numerous awards and duties. In 1984, he was awarded the Gold Medal of the SA Chemical Institute for scientific contributions, and was inducted as Honorary Member of the Institute in 1993 in recognition of professional and community service. In 1992, he received the AECI Medal for published works, and was elected to Fellowship of the Royal Society of South Africa in 1993 and Founder Membership of the Academy of Science of SA, a multidisciplinary umbrella body launched in 1994 to promote the sciences in service of the new democracy.

On a more personal note, in my experience James has always displayed a wonderful preparedness to make time available for both his students and colleagues and has a disposition which makes one both welcome and at ease. With a superb command of the English language and a well endowed and acute wit he is able to have colleagues and students in fits of laughter at times whilst more often than not, at the edge of their seats listening in fascination to the latest escapades from his students in the development of new synthetic methodologies to address very specific problems in the protocols put forward for target molecules. In this way he is able to convince students to appreciate their potential contributions to his strong and respected group at UCT.

It has been my privilege to be a colleague, albeit at a sister University, of James over the past many years and is indeed an honour to pay tribute to him as one of the most respected and outstanding Organic Chemists South Africa has produced.

Professor Ivan R Green
University of the Western Cape

Selected Publications

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