Professor Rodney W. Rickards

A Tribute

This special issue of the *ARKIVOC* is dedicated to Professor Emeritus Rodney W. Rickards to mark and celebrate the occasion of his 70th birthday. Upon Rod's formal retirement at age 65 he shared in the dedication of an issue of *The Australian Journal of Chemistry* (1999, **52**, 99) that acknowledged his contribution to Australian science through his outstanding achievements in the organic and biological chemistry of compounds of medical, biological, agricultural and veterinary importance. Rod's close and long-time friend and colleague Professor (now Emeritus) Donald W. Cameron wrote a fitting tribute in that issue and parts of that are reproduced and further embellished in the paragraphs that follow.
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Rod Rickards was born in the Sydney northern beach suburb of Manly, NSW, on June 30 1934 and the majority of his early years were spent there. He was educated at North Sydney Boys High School and thence, from 1952, at the University of Sydney. His undergraduate years at Sydney overlapped with the arrival (and departure) of a new Professor of Organic Chemistry, Arthur J. Birch, who introduced him to research at the highest international level. Rod graduated from Sydney in 1955 with 1st class Honours and the University Medal in Organic Chemistry. In 1956 Rod joined Birch's research group at the Victoria University of Manchester.

The major cities in the North of England during that time were a far cry from Manly. The region as a whole, which included Manchester and its environs, still carried the stains and scars of the Industrial Revolution and the bombs of the Second World War. But scientifically both place and time were exciting. During his brief spell at Sydney, Birch had postulated the polyketide biosynthetic pathway that involves biological acetate as the common building block for many phenolic natural products. Originally, the polyketide theory was based on structural analysis of an encyclopedic catalogue of phenolic natural products but Rod was among the first to experimentally validate the concept by exploiting the use of isotopic labeled putative

precursors, their feeding to microorganisms and the detection and location of the label in the resulting natural product.

This work, initiated in Sydney, was pursued comprehensively at Manchester, where greater resources were then available. This work not only confirmed the acetate-pathway but was also extended into biosynthetic *C*-alkylation and terpenoid biosynthesis, which was very much a 'hot' topic at that time.

In 1958, Rod was appointed Assistant Lecturer at Manchester and in 1961 was promoted to a Lectureship. He continued working on microbial metabolites and developed what was to become his signature strategy of involving a synergy of organic synthesis, biomimetic synthesis and biosynthesis with ingenious structural and stereochemical deduction. The first, and possibly the most spectacular, example of this integrated approach is the determination of the structure of the polyene macrolide antibiotic nystatin, a 38-membered cyclic lactone bearing numerous appended substituents and complex stereochemical features. Nystatin was the first polyene macrolide antibiotic to be discovered and the first to be introduced into human chemotherapy. Younger readers should note that Rod's group solved this extremely complex structure without the availability of ^{13}C and high field ^{1}H NMR spectroscopy. During the nystatin project, the use of poly-trimethylsilylation as a vehicle for increasing the volatility, stability and solubility (in organic solvents) of such polyhydroxy compounds was developed and applied. Rod began work on nystatin in Manchester in collaboration with Arthur Birch and Carl Djerassi but finished it with his own group shortly after moving, as a Fellow, in 1966 to the Research School of Chemistry (RSC) at the Australian National University (ANU) in Canberra. Remarkably, nystatin had been in clinical use for 20 years before Rod and his colleagues defined the structure.

During the 10 years that Rod spent in Manchester there were colossal developments in chromatography, structural elucidation, spectroscopy and crystallography. In Canberra, the Federal Government astutely recognized (with some help from Arthur J. Birch *inter alia*) the need for a national, world-class chemical research institute equipped at the highest levels and manned by Australia's foremost chemists. As a consequence, the RSC was created. Rod returned to Australia along with Birch as one of the foundation appointees and played a major consultative role in the design of, what is still, one of the most attractive and functional chemical research buildings in Australia. Over the years since then, Rod has shouldered numerous responsibilities within the School and the University. He was appointed Professorial Fellow in 1968 and Professor in 1992. In 1981 he was elected a Fellow of the Australian Academy of Science.

Rod's 37 years in Canberra have led to numerous papers and patents on the chemistry of organic compounds of medicinal, biological, agricultural and veterinary significance. His work has encompassed a remarkable breadth of chemistry and structural types including, for example, more than 20 different families of antibiotics.

Rod's earliest major contribution to the total synthesis of biologically active molecules was his development of an efficient and flexible synthetic route from phenol to mammalian hormones of the prostaglandin group in stereochemically pure form. There was intense international

competition at that time aimed towards the development of commercially viable synthetic routes to these bioactive lipids due to their influence at very low concentration on a host of essential mammalian physiological processes such as reproduction, cardiovascular activity and the workings of the central nervous system.

2-Alkyl-4-hydroxycyclopent-2-enones carrying the prostaglandin α-side chain were recognized as important intermediates in prostaglandin synthesis, conjugate addition of the ω-side chain then leading to the natural products and their analogues. What made Rod's strategy spectacularly different from others was his knowledge of some very old work of Hantsch who discovered that the extended chlorination of phenol affords a highly functionalized cyclopentene carboxylic acid. Members of Rod's group were able to resolve this acid into its individual enantiomers, and all intermediates thereafter were stereochemically homogeneous. Three further steps gave the key chiral intermediate, 3-chloro-4-t-butyldimethylsilyloxycyclopent-2-enone, which served first as the substrate for conjugate addition of the elements of the α-chain and secondly, after some refunctionalization, yielded the target 2-alkyl-4-hydroxycyclopent-2-enones. International patents were granted, and this route from phenol to prostaglandins was described by Dr J. H. Edwards of Syntex Research as being "superior to all other chemical methods published to date" (1979).

Another important achievement took place in an entirely different area and represents one of Rod's most incisive contributions to biosynthesis. It began with the structural elucidation of a new member of the clinically important ansamycin group, actamycin ($C_{39}H_{45}NO_{10}$), which was dramatically simplified by the novel use of heavy isotopes; utilization of deuterated reagents in degradation reactions permitted the location of carbonyl, hydroxyl and olefinic functionality, while biosynthetic ^{13}C-labelling, a development of biosynthetic ^{14}C-labelling first used structurally during the nystatin project, gave crucial information about the carbon skeleton. The structure was confirmed and the relative stereochemistry of actamycin was established by X-ray crystallography.

As a member of the important ansamycin group, actamycin naturally prompted Rod to contemplate its biosynthesis, particularly the origin of the C_7N aromatic core. The source of the aromatic core of the ansamycins, and of the related antibiotics of the mitomycin and maytansin groups, was a long-standing problem that had been addressed by many others, but which, despite much speculation and experimentation, had defied identification. Rod's analysis of the structures of all of these natural products led him to the prediction of the existence of a new natural amino acid, 3-amino-5-hydroxybenzoic acid (AHB), as the common biogenetic progenitor of the aromatic core of the families that we eluded to earlier, and thereby uniting them. Isotopic labeling experiments proved the hypothesis to be correct. The existence of AHB as a new free, naturally occurring amino acid in the antibiotic cultures was established by shrewd isotope dilution techniques. On the pharmaceutical front, supplementation of fermentation broths of the bacteria concerned with exogenous AHB led to a substantial increase in production of antibiotics of the ansamycin and mitomycin groups.

Rod has made many more rapier-like incisions into bio-organic chemistry than can be adequately dealt with in a relatively brief biography such as this. Nevertheless, some brilliant pieces of work must be mentioned. There was early work that corrected structures of the antibiotics picromycin and methymycin, leading to revision of the accepted configuration throughout the non-polyene macrolide antibiotic group known at that time. He determined the absolute configuration of the dienenitrile-containing macrolide antibiotic, borrelidin, using a conceptually simple method involving crystallization of a chiral molecule from a chiral solvent and X-ray crystallographic analysis of the solvate. Working with minute quantities of natural material Rod was able to determine the absolute configuration of juvenile hormone III bisepoxide (JHB_3), the predominant and characteristic juvenile hormone of higher dipteran insects, the flies. The conclusions reached by ^3H-labelling and exquisite chromatography were confirmed by synthesis using Sharpless chemistry as the source of chirality. Synthetic JBH_3 was obtained efficiently and in at least 99.5% enantiomeric excess. Other work has established a commercial biomimetic synthesis of tetrahydrocannabinol (THC), the principal psychoactive component of *Cannabis* resin. Many other impressive biomimetic routes have been developed, for example, to the bacterial autoregulator A-factor and related butanolides, and to the bacterial elicitor syringolide 2, and several structural elucidation problems of long standing, including the axially chiral steptonigrin, were also solved.

Rod's professional interests extend well beyond his research and his service to the RSC and the ANU. Elected Fellow of the Australian Academy of Science in 1981 he served that body *inter alia* as chairman of its National Committee for Chemistry during 1986-1989. A Fellow of the Royal Australian Chemical Institute (RACI) since 1968, he chaired the Institute's Division of Organic Chemistry between 1980 and 1982 and in 1982 was chair of the Division's 7th National Convention and was a member of the RACI Executive Council at that time. His work has been widely recognized both inside and outside Australia. He was awarded the H. G. Smith Memorial Medal and Award of the RACI in 1982, the Adrien Albert Award of the Medicinal and Agricultural Chemistry Division of the RACI in 1992 and an Australian Centenary Medal in 2003. He has given plenary lectures in Japan, Indonesia, Malaysia, Pakistan, Thailand, South Korea, Israel the UK, and the USA, as well as being a Plenary Lecturer at no fewer than three RACI Organic Divisional International Conferences and giving the ANZAAS Liversidge Memorial Lecture in 1975, the Abbott Lecture in 1967, and the inaugural Sir Robert Price Lecture (CSIRO) in 1990, the Royal Society of Chemistry Lectures in 1994-1995, the G. I. Feutrill Memorial Lecture in 1998, and the inaugural Australian Journal of Chemistry Lecture in 2000.

Since his 'retirement' Rod has continued to maintain an office at the RSC where he is a Visiting Fellow, and has also been appointed as a Visiting Scientist at CSIRO Entomology.

Like others, I have enjoyed and valued Rod's friendship for many years. We have all been impressed by the incisive and highly original nature of his research and have listened, fascinated and ultimately enlightened, by his many lucid lectures. We have respect and admiration for his strong sense of values, his integrity and his wisdom. Those of us who continue to enjoy the

pleasure of his informal company admire his sharp wit, keen sense of humour and his skills as a raconteur. His many friends, not only those represented in this issue, collectively congratulate Rod in the celebration of his 70th birthday.

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Selected Publications of R. W. Rickards

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2. Calothrixins A and B, Novel Pentacyclic Metabolites from *Calothrix* Cyanobacteria with Potent Activity against Malaria Parasites and Human Cancer Cells. Rickards, R.W.; Rothschild, J.M.; Willis, A.C.; de Chazal, N.M.; Kirk, J.; Kirk, K.; Saliba, K.J.; Smith, G.D. *Tetrahedron* **1999**, *55*, 13513.
3. Biomimetic Synthesis of the Microbial Elicitor Syringolide 2. Henschke, J.P.; Rickards, R.W. *Tetrahedron Lett*. **1996**, *37,* 3557.
4. The Absolute Configuration of Juvenile Hormone III Bisepoxide. Herlt, A.J.; Rickards, R.W.; Thomas, R.D.; East, P.D. *J. Chem. Soc., Chem. Comm.* **1993**, 1497.
5. Bio-organic Chemistry of Ansamycin and Mitomycin Antibiotics. Rickards, R.W. In *Studies in Natural Products Chemistry. Structure and Chemistry (Part B),* Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1991; Vol. 9, p 431.
6. Crystal and Molecular Structures of Two Isomorphous Solvates of the Macrolide Antibiotic Borrelidin: Absolute Configuration Determination by Incorporation of a Chiral Solvent in the Crystal Lattice. Anderson, B.F.; Herlt, A.J.; Rickards, R.W.; Robertson, G.B. *Aust. J. Chem.* **1989**, *42*, 717.
7. The Ansamycin Antibiotic Actamycin. II. Determination of the Structure using Carbon-13 Biosynthetic Labelling. McDonald, I.A.; Rickards, R.W. *Tetrahedron Lett*. **1981**, 1149.
8. Biosynthesis of the Mitomycin Antibiotics from 3-Amino-5-hydroxybenzoic Acid. Anderson, M.G.; Kibby, J.J.; Rickards, R.W.; Rothschild, J.M. *J. Chem. Soc., Chem. Comm.* **1980**, 1277.
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10. Synthesis of Chiral Prostanoid Intermediates from Phenol. Gill, M.; Rickards, R.W. *J. Chem. Soc., Chem. Comm.* **1979**, 121.
11. Macrolide Antibiotic Studies. XVI. The Structure of Nystatin. Chong, C.N.; Rickards, R.W. *Tetrahedron Lett*. **1970**, 5145.
12. Nystatin. Part V. Biosynthetic Definition of Some Structural Features. Birch, A.J.; Holzapfel, C.W.; Rickards, R.W.; Djerassi, C.; Suzuki, M.; Westley, J.; Dutcher, J.D.; Thomas, R. *Tetrahedron Lett*. **1964**, 1485.

