Rodney Warren Rickards 1934–2007

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Rod Rickards graduated with first class honours from the University of Sydney in 1955 and began his academic career at the University of Manchester in close association with Arthur Birch. In 1966 he returned to Australia to a foundation appointment in the Research School of Chemistry at the Australian National University, where he spent the remainder of his career. His research was primarily concerned with the organic and biological chemistry of compounds of medical, biological, agricultural and veterinary importance, and was characterized by an integration of organic synthesis, biomimetic synthesis, structural and stereochemical studies, and biosynthetic studies using isotopically labelled precursors *in vivo*. His interests ranged widely and included antibiotics, regulatory factors that initiate antibiotic production and control cell differentiation and sexuality in microorganisms, elicitors that communicate between bacteria and plants, mammalian hormones of the prostaglandin group that control many aspects of human physiology, juvenile hormones, which mediate the development and reproductive physiology of higher dipteran insects and the therapeutically active components *of Cannabis* resin.

Rodney Warren ('Rod') Rickards made outstanding contributions to the organic and biological chemistry of compounds of medical, biological, agricultural and veterinary importance. His interests ranged widely and included antibiotics produced by microorganisms, regulatory factors that initiate antibiotic production or control cell differentiation and sexuality in microorganisms, elicitors that communicate between bacteria and plants, mammalian hormones of the prostaglandin group that control many aspects of human physiology, juvenile hormones that mediate the development and reproductive physiology of higher dipteran insects and the therapeutically active components of *Cannabis* resin. His group's research dealt with more than twenty different types of antibiotics, and was distinguished by a combination of ingenious organic synthesis, biomimetic synthesis, structural and stereochemical studies, and biosynthetic studies using isotopically labelled precursors *in vivo*. This integrated approach, in part inherited from his mentor, Arthur Birch, came to be recognized as Rickards' trademark strategy. It is illustrated in much of his published research, most notably in that dealing with the chemistry and biochemistry of the clinically important antibiotics of the ansamycin and mitomycin groups, described in more detail below.
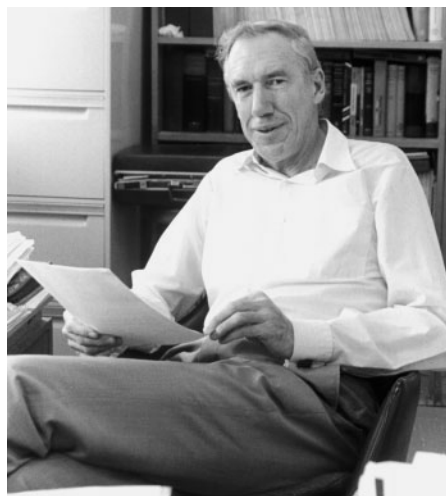
Family Background and Education

Rod was born in Manly on 30 June 1934 and lived there with his parents and elder brother Alan for most of his early life. His father, Redvers Ernest Rickards, was New South Wales Crown Solicitor while his mother, Marjorie Edna Marjason, was a Commonwealth Bank officer who gave up employment when she married. Mother and children moved to Inverell in northern New South Wales for a year in 1942 to avoid a feared

Japanese attack on Sydney. Rod attended Manly Primary School and North Sydney Boys' High School, where he studied chemistry, physics, mathematics, English, French, Latin and German, and acquired a lifelong love of cricket. In later life, he would fondly recall watching Lindwall and Miller bowling to Hutton and Washbrook in a Test Match against 'the Old Enemy' at the Sydney Cricket Ground and, ever the traditionalist in such matters, regarded this Clash of the Titans as infinitely superior to the modern limited-overs game. At school he excelled in chemistry and physics, receiving Honours in these subjects on his Leaving Certificate, but was surprised that he had done better in physics, into which he had put less effort. Only when he entered the University of Sydney as an undergraduate in 1952 did he realize that his ageing school chemistry teacher had been using out-of-date material. After a brief flirtation with chemical engineering, Rod settled on chemistry. Because of his interest in the chemistry of living systems, he elected to study for an Honours degree with Professor Arthur Birch, one of the great masters of the subject, who had returned to Australia in 1952, after a prolonged period in the UK, as Professor of Organic Chemistry and Head of Department. Together with another student, Rod first met Birch by chance on a crowded Sydney tram. During their irreverent conversation, the students mentioned that the newly arrived Professor of Organic Chemistry was believed to work on sex hormones, a subject that naturally engaged their interest. They were interrupted by Birch's voice from the next seat: 'You want to be careful about what you say on these trams, you never know who you are sitting next to.'

In 1955, Rod graduated with First Class Honours as well as the University Medal and, despite his inauspicious introduction, began a long-lasting research collaboration with Birch in biosynthesis, the study of how, by the use of enzymes, living organisms make natural products from the simple precursors available to them. During his time at the University of Sydney, Rod was also a member of the 13th National Service Training Battalion, in the Number 9 Platoon, C Company, which consisted mainly of students; he served in the fifth intake from January to April 1953. As part of these duties, he was called on to assist in the

Figure 1. Arthur Birch's biosynthesis group at the University of Manchester during the late 1950s. Rod Rickards is second from right.

severe floods that afflicted the Singleton and Maitland areas in 1955.

Early Career

In late 1955, frustrated at the restrictive research environment in which he found himself, Birch left the University of Sydney to take up the prestigious Chair of Organic Chemistry at the University of Manchester. Rod joined him there in 1956 to continue biosynthetic work on mould metabolites that had been started in Sydney. Until 1958 Rod was supported by a CSIRO Overseas Student Scholarship; in that year he was appointed Assistant Lecturer and in 1961 promoted to Lecturer. Although he had accumulated extensive amounts of research by then, he never submitted this material in the form of a PhD thesis, perhaps because of his involvement in the day-to-day supervision of the biosynthesis group in a highly competitive field. Nevertheless, Rod evidently enjoyed life to the full (Figure 1).

As a city still bearing the scars of the Industrial Revolution and the heavy bombing of the Second World War, Manchester was very different in character and appearance from Manly. Nevertheless, Rod came to appreciate the dry sense of humour of the people and to admire their stoic ability to watch cricket on a gloomy day at Old Trafford with the street-lights on. Stanley Holloway's rendering of 'Albert and the Lion' remained a perennial favourite with Rod throughout his life. Rod also undertook several holiday car trips on the cheap in Continental Europe. In one case, he and a fellow student, Jim Moye, slept every night in the back of a Ford Thames van, to the great discomfort of the

long-legged Rod. In a later year, the chosen vehicle was an Austin 7, which expired somewhere in northern Germany with a broken camshaft. His attempts to explain the problem to a mechanic in broken German provided the material for one of Rod's many amusing reminiscences.

Early Scientific Work

In 1953 Birch and Donovan had published a suggestion that many naturally occurring phenolic compounds are formed partially or wholly by the head-to-tail linkage of acetate units, and had used this so-called polyketide hypothesis to deduce the correct formulae for a number of these compounds. The first direct evidence for the correctness of the proposal was obtained in 1955 (in Sydney) by Birch, Massy-Westropp and Moye. They fed the mould *Penicillium griseofulvium* Dierckx with acetate labelled with ^{14}C at the carbonyl carbon atom and showed that the distribution of the label in the resulting 2-hydroxy-6-methylbenzoic acid corresponded with that predicted. In his early work at Manchester, Rickards was involved in a similar experiment in which the ^{14}C-labelled griseofulvin was isolated from a different strain of the same mould and the distribution of the label was determined. The results were so conclusive as to eliminate any remaining doubt about the validity of the acetate hypothesis (4, 7). A combination of ^{14}C-labelling and degradation applied, for example, to methymycin biosynthesis in *Streptomyces venezuelae* demonstrated that four molecules of propionic acid and one molecule of acetic acid participate in the construction of the carbon skeleton of this molecule (13, 32). Similar techniques were applied by Rickards and colleagues to biosynthetic C-alkylation and to the biosynthesis of terpenoids and microbial metabolites; examples include the antimycin-A antibiotics (16, 20), rosenonolactone (6, 8), gibberellic acid (8, 12), pleuromutilin (22, 38), curvularin (9, 19), citromycetin (31) and cycloheximide (23, 43).

The establishment of the structure and even the correct elemental composition of many macrolides is a challenging problem because these compounds have high molecular weight, are often poorly soluble, do not readily crystallize, and tenaciously retain solvent or impurities. An important contribution made by Rickards and his collaborators was to adapt a technique previously used in carbohydrate chemistry, namely, to convert the polar hydroxy groups in the macrolide into relatively non-polar trimethylsilyloxy [$(CH_3)_3SiO$] groups. The volatility and thermal stability of the resulting derivatives proved to be sufficient to allow, for the first time, measurement of mass spectra and determination of accurate masses. In this way, the correct elemental compositions and structures of smaller polyene antibiotics, including the non-carbohydrate-containing substances filipin and lagosin (30), and the carbohydrate-containing materials pimaricin (39) and lucensomycin (40, 41), were determined. Undoubtedly this work was facilitated by the proximity of the University of Manchester to Associated Electrical Industries (AEI), the manufacturers of the first high-resolution mass spectrometers.

Probably the most spectacular example of the integrated approach developed in Manchester combining synthetic, structural and biomimetic techniques was the determination of the structure of nystatin, which was the first polyene macrolide antibiotic produced by *Streptomycete* bacteria to be discovered (in 1949) and the first to be introduced into human chemotherapy (in 1953). Nystatin continues to be widely used in the treatment of human fungal and yeast infections. It was in extensive clinical use for nearly twenty years before the correct molecular formula, $C_{47}H_{75}NO_{17}$, and structure (Figure 2) were established. Nystatin consists of a 38-membered lactone ring carrying diene, tetraene, amino-sugar, carboxyl and eight hydroxy functions.

The structural work was begun by Birch and Rickards in Manchester in collaboration with Professor Carl Djerassi at Stanford University (26, 27), and was concluded by Rickards independently after his move to Canberra (see below) (58); the final stages required revision of a structure that had been published separately by Djerassi. The structure was deduced by a clever combination of extensive degradative chemistry, biosynthetic ^{14}C-labelling and mass spectrometry, and the deduction represents a true *tour de force,* since, in those days, ^{13}C NMR spectroscopy and 2D-NMR techniques were yet to be established. Moreover, the poor solubility and structural complexity of the compound rendered ^{1}H NMR spectra at 60 MHz of little use. Nystatin remains probably the most complex
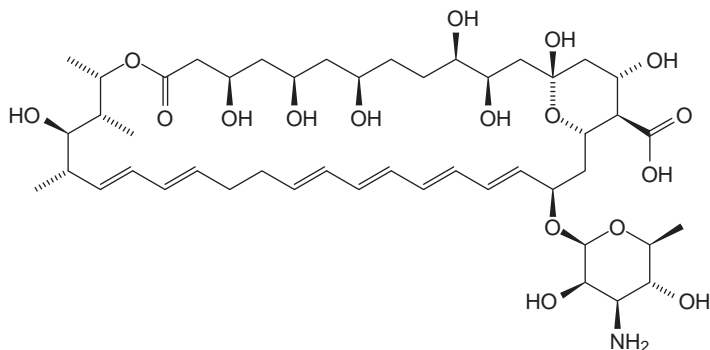
Figure 2. The structure of nystatin.

natural product whose structure has been defined (finally) in Australia.

The Move to Canberra

In 1963 the Australian National University decided to establish a world-class Research School of Chemistry (RSC) as part of the Institute of Advanced Studies in Canberra. Together with Professors Arthur Birch at Manchester and David Craig at University College London, Rickards was deeply involved as a consultant in the planning and design of the new chemistry building and its laboratories. Later he, along with Richard Bramley (a physical chemist) and John Harper (the RSC laboratory manager), played a critical supervisory role in its construction, working closely with the architects, Eggleston, Secomb and McDonald. During the ten-year period that Rickards spent in Manchester, there had been striking developments in the routine physical techniques that increased the power of separation and structure elucidation available to organic chemists, particularly in chromatography, ^{1}H NMR spectroscopy, mass spectrometry and X-ray crystallography, and the new Research School was equipped to the highest levels then available. In 1966 Rickards joined the Foundation Professors, Birch and Craig, as a foundation appointment in the School, a move that also enabled him and his colleague, the crystallographer Glen Robertson, to indulge an interest in trout fishing in the nearby Snowy Mountains. Rickards declined an offer to return to Manchester as Professor of Organic Chemistry and was promoted to Professorial Fellow in 1968 and to Professor in 1992. It is a tribute to the skilful and

devoted efforts of Rickards, together with Birch, Craig and others that, even though a new Chemistry building is currently under construction, their Research School of Chemistry building has stood the test of 45 years while remaining one of the most attractive and functional chemistry buildings in Australia.

Research in Canberra 1966–2007

The move to Canberra enabled Rickards to develop further his programme for the determination of the structure and stereochemistry of antibiotics and other biologically active microbial products. In this account a brief indication is given of the range of other problems that Rickards tackled, followed by a more detailed description of some selected results of his main programme (italicized headings).

- In addition to completing the work on nystatin, discussed above, the structure of the non-polyene macrolide antibiotic picromycin was shown by Rickards to contain an additional, previously overlooked, propionate-derived biosynthetic unit (COCHCH$_3$) (45), and the partial absolute configurations of methymycin, neomethymycin, narbomycin and picromycin were determined (55). This necessitated revision of the accepted configurational correlations throughout the non-polyene macrolide group and laid the foundations for subsequent total syntheses in other laboratories.
- Homothallins I and II, unstable, volatile factors from the fungus *Trichoderma koningii*, were isolated in trace amounts and their structures identified. These compounds induce

homothallic sexuality in one mating type of the fungus *Phytophthora cinnamoni*, which is recognized as the most destructive plant pathogen in native Australian vegetation. Remarkably, the *Trichoderma* fungus is not related to the pathogen. The instability and limited availability necessitated verification of their novel cyclopentenoid isonitrile structures by synthesis of homothallin II and its deoxy analogue (79).

- The structure of streptonigrin, which, since its isolation in 1959, has been used extensively in anti-tumour chemotherapy and has potent cytotoxic and anti-viral properties, was determined (101). Exciton-coupled circular dichroism spectroscopy was employed to establish the absolute configuration of the axially chiral phenylpyridyl segment as *R* (127).

- The oligosporons and related flagranones, which are prenylated cyclohexenoxides, were characterized (118, 134). These were the first antibiotics to be isolated from nematode-trapping fungi.

- Actinotetraose hexatiglate, a unique glucotetraose from an *Actinomycete* bacterium (133), and the calothrixins, metabolites from cyanobacteria of the genus *Calothrix* containing novel indolo[3,2-*j*]phenanthridine ring systems (135, 136), were structurally defined. The biomedical potential of the calothrixins, which show potent activity against malaria parasites and human cancer cells, was being explored in collaboration with pharmaceutical companies at the time of Rickards' death. The actinotetraose hexatiglate and flagranone work was carried out in collaboration with Dr Ernest Lacey, Microbial Screening Technologies Pty. Ltd., and the calothrixin work with Dr Geoffrey Smith, Division of Biochemistry and Molecular Biology, and Professor Kiaran Kirk, Research School of Biology, Australian National University.

- As part of a programme to survey Australian terrestrial invertebrates as possible sources of biologically active compounds, in collaboration with Dr Stephen Trowell, CSIRO Division of Entomology, the extract of the Australian termite *Nasutitermes triodiae* was shown to exhibit anti-bacterial activity arising from the presence of novel hydroxylated 1(15),8(19)-trinervitadienes and the known 1(15),8(9)-trinervitadiene-2β-3α-diol (140).
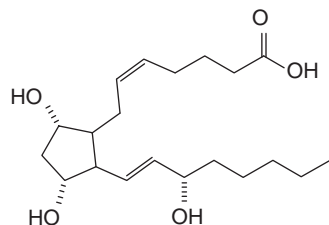

Figure 3. Structure of a typical prostaglandin.

An efficient and flexible synthetic route from phenol to the natural prostaglandins and their analogues in stereochemically pure form (72, 74, 80–83, 88, 89)

Prostaglandins (e.g. Figure 3) are natural lipids that play crucial roles in a wide variety of human physiological processes, from reproduction to cardiovascular and central nervous system activity. Their pharmaceutical potential gave rise to intense international competition in the 1970s directed towards the development of commercially viable synthetic routes.

Rickards' ingenious approach to synthesizing these molecules was based on a neglected observation of Hantzsch, dating from 1887, that the cheap starting material, phenol, underwent ring contraction on treatment with alkaline hypochlorite to give, after just two steps, a cyclopentene carboxylic acid that Rickards and Gill could readily resolve into its enantiomers. All subsequent intermediates were, therefore, stereochemically homogeneous. Rickards' route was described by Dr J. H. Edwards of Syntex Research in 1979 as 'superior to all other chemical methods published to date'.

Prediction of the existence of the novel natural aromatic amino acid, 3-amino-5-hydroxybenzoic acid, and its establishment as the key biogenetic precursor of the ansamycin and mitomycin antibiotics (77, 78, 99, 102, 104, 110)

Antibiotics of the ansamycin and mitomycin groups from *Actinomycete* bacteria, in particular rifampicin and mitomycin C, are of major clinical importance in the chemotherapy of tuberculosis and cancer, respectively. Their
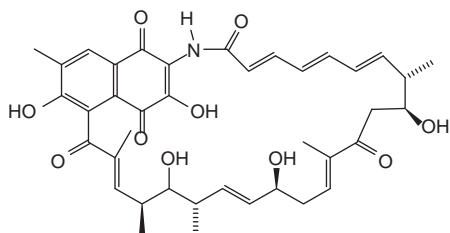
Figure 4. Structure of actamycin.

biochemical origins had remained unknown since their initial discovery in the mid-1950s, despite much speculation and experimentation. Rickards' research in this area emphasizes the synergy resulting from the integration of structural, biosynthetic, synthetic and biomimetic approaches.

Rickards' research began with the definition of the structure of actamycin, a new member of the ansamycin group, named as such to mark its discovery in the Australian Capital Territory. The structure elucidation of this complex macrocyclic $C_{39}H_{45}NO_{10}$ lactam was dramatically simplified by the novel use of heavy isotopes; use of deuterated reagents in degradation reactions permitted definition and location of carbonyl, hydroxyl and olefinic functionality, while biosynthetic ^{13}C-labelling, a development of the biosynthetic ^{14}C-radiolabelling used, for example, in the case of nystatin, gave crucial information about the carbon skeleton (86, 87). The derived structure (Figure 4) was later confirmed by three-dimensional X-ray crystallography of the underivatized antibiotic (with Dr Glen Robertson) (111). The unstable crystals contained two dissimilar conformations of the antibiotic per unit cell, and the solution of the structure, which also provided full relative stereochemistry, represented the limit of direct methods technology available at the time.

With the structure of actamycin defined, Rickards analyzed the structures of the known ansamycin antibiotics and related maytansinoids

from higher plants in order to define the key biogenetic precursor of the characteristic C_7N segment present in the nuclei of these natural products. This analysis led to the prediction of the existence of a new natural amino acid, 3-amino-5-hydroxybenzoic acid (AHB) that was expected to be the long-sought precursor. Biosynthetic studies with ^{14}C- and ^{13}C-labelled AHB verified its predicted role, not only in the biosynthesis of ansamycins and maytansinoids, but also in the biosynthesis of the highly functionalized tetracyclic antibiotics of the mitomycin group (Figure 5) (77, 78, 84, 85).

The existence of AHB as a free amino acid occurring naturally in the antibiotic fermentations was confirmed by isotope dilution techniques. Supplementation of the bacterial fermentation media with exogenous AHB led to substantially increased production of antibiotics of both the ansamycin and mitomycin groups. The ansamycin and mitomycin synthase enzyme systems were shown to utilize AHB specifically, rejecting all analogues including the minimally modified 4-fluoro derivative during attempts to direct the biosynthetic process towards novel antibiotics (94, 97).

Biomimetic synthesis provided convincing evidence for the stages in the biochemical conversion of AHB into the nuclei of the naphthoquinonoid ansamycins (94, 107, 132). 3-Acetylaminophenols with 5-(3^1,5^1-dioxoheptyl) substituents, models for the hypothetical enzyme-bound polyketide, could be oxidized in high yield to naphthoquinones carrying the typical ansamycin substitution pattern. The crucial intermediates were the corresponding benzoquinones, which cyclized spontaneously in water to naphthohydroquinones. Related biomimetic studies successfully mimicked the proposed conversion of AHB and D-glucosamine via alkylaminocresols, which undergo sequential oxidative and reductive ring closures to form the indoloquinonoid nuclei of the mitomycins.
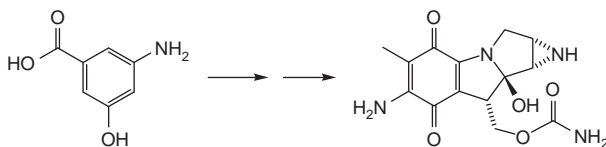
Figure 5. Biosynthesis of mitomycin C from 3-amino-5-hydroxybenzoic acid.
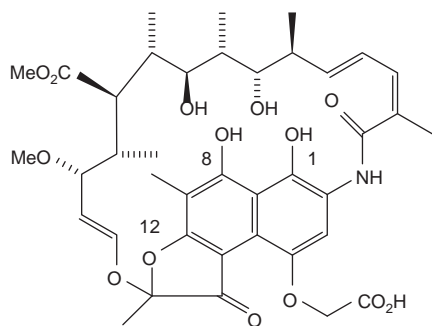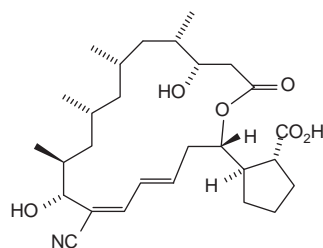
Figure 6. Structure of rifamycin B.

Figure 7. Structure and absolute configuration of borrelidin.

Rifamycin B (Figure 6) and its relatives O, S and SV are the most important natural antibiotics of the ansamycin group, since from these fermentation products the valuable semi-synthetic anti-tubercular agent rifampicin is prepared. The phenolic C8-hydroxyl function at the *peri* position of their naphthalenoid nuclei is crucial for their biological potency. It had been suggested elsewhere that this feature was introduced in a hydroxylation step late in their biosynthesis, implying that utilization of AHB proceeded with complete loss of its carboxyl oxygen functionality. However, this conclusion was disproved by Rickards' results, which showed that of the oxygen atoms of rifamycin B only two, the phenolic C l-hydroxyl and the C12-aryl ether, arose from enzymic processes involving atmospheric oxygen. The specific incorporation of [carboxy-^{13}C,^{14}C,^{18}O$_2$]-labelled AHB confirmed that the carboxyl carbon of the amino acid was converted with retention of an attached oxygen atom into the phenolic C8-hydroxyl functionality of rifamycin B. Analysis of the incorporation of [carboxy-^{13}C,^{14}C,^{18}O$_2$]-labelled propionate defined the origins of the remaining oxygen atoms of rifamycin B, and established that the macrocyclic lactam bond was formed by direct ring closure of an acyl-enzyme intermediate, without release of the corresponding free amino acid from the enzyme (107). This conclusion can be expected to apply to the biosynthesis of all ansamycin antibiotics.

*Crystallographic determination
of absolute configuration by incorporation
of a chiral solvent in the crystal lattice*

Two approaches are commonly used for the determination of the absolute configuration of

organic CHNO compounds by X-ray crystallography. The Bijvoet method requires preparation of a heavy atom derivative to produce anomalous scattering; alternatively, a derivative is made containing a centre of known chirality that acts as a reference. Rickards, Robertson and co-workers (105) showed that there is no need for the chiral reference site to be covalently or even ionically bonded to the organic framework; inclusion in the crystal lattice suffices. This point was established by X-ray diffraction study of the *S*-2-methylbutan-1-ol solvate of the unique dienenitrile-containing macrolide borrelidin (Figure 7) from *Streptomyces rochei,* which is active against spirochetes and micrococci. Some of its structural features had been established by earlier degradative and spectroscopic work in Manchester (34), but the X-ray study revealed the total structure and absolute configuration. The method avoids the unknown and sometimes undesirable distortion of molecular conformation that can result from derivatization.

*Definition of the absolute stereochemistry
of juvenile hormone III bisepoxide
and its first enantioselective synthesis
(114–117, 123)*

Juvenile hormone III bisepoxide (JHB$_3$) is the predominant and characteristic juvenile hormone of higher dipteran insects, that is, flies. Its discovery in 1989 by Gilbert's group in North Carolina introduced a new dimension to our extensive knowledge of the hormones of the farnesate group that mediate the neurohormonal control of development and reproduction of many insect species. Although flies are vectors of some of the most severe and debilitating diseases of man and livestock, their juvenile hormone system had been less well understood than
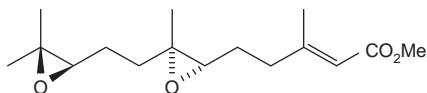
Figure 8. Structure of juvenile hormone JHB$_3$.

that of other insect groups like the Lepidoptera, (that is, the moths and butterflies).

The first challenge in defining the absolute stereochemistry of JHB$_3$ (Figure 8) lay in the minute levels of natural hormone produced by flies. Corpora allata from the insect used in this work, the economically important Australian sheep blowfly *Lucilia cuprina,* produce <1 nanogram per gland per hour. This necessitated enzymatic labelling of the methyl ester group of the natural hormone by incubation of excised glands in the presence of L-[methyl-^{3}H]methionine (with Dr P. D. East, CSIRO Division of Entomology). The radiolabelled natural hormone was then tracked against synthetic reference stereoisomers added as carriers at levels detectable by their ultraviolet absorption. The diastereoisomers were separated by high-performance liquid chromatography, while the enantiomers were separated by a novel radio-chromatographic adaptation of the technique of micellar electrokinetic capillary chromatography in the presence of β-cyclodextrin as a chiral host solute.

The second challenge in the stereochemical definition of JHB$_3$ was the synthesis of the required reference stereoisomers of known absolute configuration. Biosynthetic considerations predicted that the olefinic configurations of farnesoic acid, the probable natural precursor of JHB$_3$, should be conserved in the two epoxidation processes, thus limiting to four the number of stereoisomers to be considered. These were prepared from geraniol, Sharpless asymmetric epoxidation of the 2,3-olefinic bond being used to introduce the ultimate 6,7-epoxide function of the JHB$_3$ stereoisomers. Stereo-random epoxidation of the remaining olefinic bond then afforded diastereomeric bis-epoxy-alcohols that, after separation, were subjected to stereospecific rearrangement to substituted tetrahydrofurans in order to establish their relative and absolute configurations. The four possible bis-epoxy-alcohols were then converted into the required stereoisomers of JHB$_3$. E. D. Morgan of the University of Keele said of this work: 'They

have used ingenious chemistry on very small samples to get the exact structure [of JHB$_3$]. This may lead to new directions in using juvenile hormones for insect control' *(New Scientist*, 23 October 1993, p. 15).

With the stereochemistry of JHB$_3$ established, the publication by Sharpless of an effective procedure for asymmetric dihydroxylation enabled the first completely enantioselective synthesis of the hormone. The intermediate 2,3-epoxygeraniol was now elaborated directly to the corresponding methyl 4,5-dehydro-6,7-epoxyfarnesate. This substrate underwent asymmetric dihydroxylation regiospecifically at the isolated 10,11-olefinic bond. Closure of the 10,11-epoxide followed by selective reduction of the 4,5-olefin afforded JHB$_3$. The route provided the synthetic hormone efficiently and in the high stereochemical purity (>99.5%) necessary for biological studies. Further research (with Drs P. D. East and S. C. Trowell, CSIRO Division of Entomology) examined the synthesis and transport of juvenile hormones by the Australian sheep blowfly. The production of JHB$_3$ by the corpora allata is regulated both by the developmental stage of the insect and by neural control from the brain. The larval haemolymph contains a high-affinity juvenile hormone-carrying protein, the structure and binding cleft of which have been partially characterized.

Commercial biomimetic synthesis of the therapeutic agent 6aR,10aR-◆^{9}-tetrahydro-cannabinol (THC) (70, 75, 76, 95, 98)

6a*R*,10a*R*-◆^{9}-Tetrahydrocannabinol (THC, Figure 9), the principal psychoactive component of *Cannabis* resin, is of increasing importance as a therapeutic agent due to its analgesic, anti-emetic, anti-convulsant and anti-glaucoma properties, and more significantly as a palliative in cancer chemotherapy and an appetite stimulant for AIDS patients. Its synthesis has been extensively studied and traditionally involves the C-alkylation of the phenol olivetol with various monoterpenes, followed by closure of the pyran ring. The use of conventional Lewis acid catalysis for both stages results in the formation of polyalkylation products together with numerous regio- and stereo-isomers, from which the desired THC is separable only in low yield after
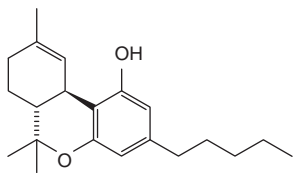
Figure 9. Structure of 6a*R*,10a*R*-◆⁹-Tetra-hydrocannabinol (THC).

Figure 10. Structure of A-factor.

laborious purification. This is true even of the current American commercial synthesis.

Rickards' early work in the cannabinoid area demonstrated that the metabolism of THC in man could be more conveniently modelled in fungi than in the animals that were then being used (70). Certain fungi that had been isolated from *Cannabis sativa* plant material, and were thus expected and shown to be immune to the anti-fungal effects of the phenol, readily afforded known physiologically active hydroxylation products of THC, including the pharmacologically important 11-hydroxy derivative. Synthesis of 11-methylthio-◆⁹-tetrahydrocannabinol provided an entry to this 11-hydroxy and other 11-substituted cannabinoids in racemic form, while l*S*,4*R* − *p*-mentha-2,8-dien-l-ol, an important chiral intermediate in the synthesis of THC itself, was synthesized from readily available limonene (75, 76).

Rickards' first synthesis of THC used a carbanionoid rather than the conventional carbocationoid approach (95). The diarylcuprate from olivetol dimethyl ether coupled regio- and stereo-selectively under mild boron trifluoride catalysis with l*S*,4*R*-*p*-mentha-2,8-dien-l-yl acetate. The synthesis of THC was completed by boron tribromide-promoted cyclization and demethylation, the thermodynamically unstable ◆⁹-olefin being automatically protected during this procedure as its hydrobromide, from which it was finally regenerated with base. Although a high overall yield was obtained, the required use of sensitive cuprate reagents rendered the route unsuitable for commercial application.

Rickards then achieved a second, remarkably efficient synthesis of high purity THC (98), for which an international patent was granted. Significantly, the route is biomimetically based and parallels the probable biosynthesis of THC in coupling l*S*,4*R*-*p*-mentha-2,8-dien-l-ol with methyl olivetolate to afford
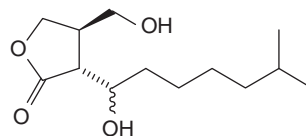
methyl cannabidiolate. The desired mono-alkylation is controlled and directed by the ester substituent. Regiospecific cyclization is then effected, without isomerization of the ◆⁹-olefin, by the unusual catalyst zinc triflate. Demethoxy-carbonylation, under alkaline conditions in order to again avoid olefin isomerization, affords the target THC. The product contains less than 0.5% of the corresponding ◆⁸-isomer, a purity that readily meets the stringent requirements of the United States Federal Drug Administration.

Biomimetic syntheses of the bacterial autoregulator A-factor and related butanolides, and the revision of their structures

A-factor (Figure 10) is the first member to be discovered of an expanding series of structurally related butanolides that function as potent autoregulators in bacterial fermentations. Produced at minute levels by various *Actinomycete* bacteria, it is responsible for initiating antibiotic production and cell differentiation. Its biological significance has led to several published syntheses, all of which follow essentially the same conventional retrosynthetic strategy, namely, the construction of a derivative of 3-hydroxymethyl butanolide which is then acylated in the 2-position.

Rickards and his PhD student, Roger Waring, developed a biomimetic synthesis of A-factor, based upon the quite different approach of 'retrobiosynthetic' analysis of its structure (see R. B. Waring, PhD thesis, Australian National University, 1994). The putative key biosynthetic precursor, a β-ketoester of 1,3-dihydroxyacetone, undergoes facile Knoevenagel ring closure followed by 1,4-reduction of the resulting butenolide to yield A-factor. This synthesis is convenient and efficient, while also providing circumstantial evidence for the validity of the proposed biosynthetic pathway. Surprisingly, in view of the extensive previous
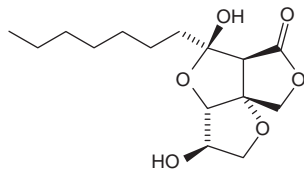
Figure 11. Structure of syringolide 2.

synthetic work, it also led to revision of the structure of A-factor, which was shown to be not a single compound but rather a mixture of four compounds in equilibrium. The previously accepted structure constitutes only 63% of this mixture. The equilibrium can be shifted to yield almost entirely crystals of another of the four components. This work raises the question as to the exact nature of the biologically active form of A-factor. Extension of this biomimetic synthesis to related butanolide autoregulators also necessitated revision of their stereochemistry.

Biomimetic synthesis of the bacterial elicitor syringolide 2 (121, 128, 138)

Syringolides 1 and 2 (Figure 11) are microbial elicitors, specific signal molecules produced by the bacterial plant pathogen *Pseudomonas syringae* pv. *tomato*, which are recognized by and trigger a hypersensitive defence response in resistant soybean cultivars. Reported initially in 1993, they are the first specific nonproteinaceous elicitors. They have occasioned considerable international interest and seven total syntheses have been reported to date, usually requiring multiple protecting groups and some twenty reaction steps.

In 1996 Rickards and Henschke (121) described the biomimetic synthesis of syringolide 2 in just four steps from D-xylulose, with the use of a single protecting group. Acylation of the anisylidene acetal of xylulose with 3-oxodecanoic acid afforded a β-ketoester, hydrogenolysis of which released the β-ketoester of free xylulose. This presumed acyclic biosynthetic intermediate then underwent a totally stereospecific triple cyclization to form syringolide 2. This route not only constitutes a convenient total synthesis, but also provides compelling evidence for the proposed biosynthetic pathway to the syringolides. The methodology was further adapted to the preparation of the isotopically labelled syringolide 2 required for studying the

binding of these elicitors to their receptors in resistant plants (128).

Professional Achievements and Community Activities

On the basis of his outstanding research, Rod was elected a Fellow of the Royal Australian Chemical Institute (RACI) in 1968 and a Fellow of the Australian Academy of Science in 1981. In the following year he received the H. G. Smith Memorial Medal, the premier research award of the RACI, and, ten years later, the Adrien Albert award of the Medical and Agricultural Division of the RACI. He also received an Australian Centenary Medal in 2003. He gave many plenary lectures at national and international conferences, especially in the Pacific region, and presented the Liversidge Memorial Lecture of ANZAAS in 1975, the inaugural Sir Robert Price Lecture (CSIRO) in 1990, the Royal Society of Chemistry Lectures in 1994–5, and the inaugural Australian Journal of Chemistry Lecture in 2000.

Rod held visiting academic appointments at the Universities of Wisconsin (USA), Auckland (New Zealand), Cape Town (South Africa) and Canterbury (Christchurch, New Zealand) and for several years was an external examiner and advisor for the BSc Honours degree at the University of Mauritius. His broad knowledge of the chemistry of antibiotics and his excellent command of the English language allowed him to provide significant assistance to many researchers during his almost forty years as a member of the editorial board of the *Journal of Antibiotics*.

Rod was Chairman of the RACI's Division of Organic Chemistry between 1980 and 1982, and was a member of the RACI Executive Council during 1982. He also chaired the National Committee for Chemistry of the Australian Academy of Science in the period 1986–9 and served as a member of several of the Academy's overseas exchange committees for over fifteen years, chairing the Europe Exchange Committee from 2003 to 2006. He served on the Occupational Health and Safety Committee of the Australian National University for many years, including a period as its chair.

Rod also used his expertise to serve the wider community. From 1993 to 2007 he represented the Australian Academy of Science on the

Council of the National Science Summer School (the National Youth Science Forum). As a member of the Science Forum's Executive he helped to develop the programme that enables promising Year 12 students who are interested in pursuing a career in science to participate in research projects in various institutions in Canberra over a two-week period in January. Furthermore, he greatly assisted the ACT Department of Health in the careful wording of the Australian Capital Territory's Act governing prohibited substances and drugs of dependence so as to remove possible loopholes.

After his retirement in 1999, Rod was appointed Emeritus Professor at the Australian National University and a Visiting Scientist at the CSIRO Division of Entomology, thus enabling him to continue several productive research collaborations.

Rod had an uncanny eye for the smallest yet often significant detail, and brought an impressive and wide-ranging knowledge of chemistry to problems. He was always generous with his time, ready to discuss and modestly to offer advice based on his extensive knowledge and experience. He gave members of his research group considerable independence in setting up and solving their particular problem and impressed on them the necessary rigorous, critical attitude in interpreting results. Invariably, his good humour, good sense and approachability were recognized and appreciated by colleagues at all levels.

Rod's lectures were masterpieces of lucidity and logical presentation. He was also a superb raconteur with an excellent memory and a fund of amusing anecdotes. He could recite, from memory, extracts from works as diverse as Caesar's *Gallic Wars* (in Latin, with English translation), *The Rime of the Ancient Mariner*, and *Clancy of the Overflow*. He had the gift of making people laugh, though never at others' expense, and was respected and admired for his strong sense of values, his integrity and his wisdom. He was a very private person, devoted to his family.

Rod died suddenly and unexpectedly at home on 17 December 2007, his last completed task having been, ironically enough, a detailed biographical memoir of his mentor, Arthur Birch, written with Sir John Cornforth (Nobel Prize, 1975) (142, 143). He is survived by his wife of 22 years, Anna who, as Anna Becker, had been one of his PhD students, and by his daughter, Helen, of whose promise and achievements he was intensely, though never openly, proud.

Acknowledgements

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