

Sir Jack Baldwin, FRS: Biomimetic studies at Oxford†

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Professor Sir Jack Baldwin, FRS, has recently stepped down as the Waynefleete Professor of Organic Chemistry at the University of Oxford. This article is intended to overview some aspects of Professor Baldwin's spectacular career, with an emphasis on his contributions towards the field of biomimetic synthesis.

Introduction

October 2005 has brought about the end of an era in organic chemistry at the University of Oxford. Almost two years since the doors of the Dyson Perrins (DP) Laboratory were closed to organic chemistry, the last Head of this renowned department has retired his chair. Professor Sir Jack Baldwin, FRS (Fig. 1), Waynefleete Professor of Organic Chemistry, joined Oxford in 1978, succeeding Sir Ewart Jones, FRS.

Continuing a tradition of great scientific achievement, and building upon standards set by his predecessors, Sir Jack, or "The Prof", as known by many past and present students, has been at the forefront of scientific achievement throughout his tenure at Oxford.

Born in London in 1938, Jack Baldwin studied chemistry at Imperial College,

London, where he gained a PhD in organic chemistry working for the Nobel laureate, Professor Sir Derek Barton, FRS. He remained at Imperial for a short period where he was appointed lecturer, before moving overseas to pursue a career in the USA. The move proved very successful, and it wasn't too long before Professor Baldwin had built an international reputation for pioneering work in organic chemistry. Beginning his career at Pennsylvania State University, and then later moving to MIT, Sir Jack quickly moved up the ranks, gaining ever-increasing attention from the chemistry community. As a result of his success, he was elected as Fellow of the Royal Society (FRS) in 1978, and made a Foreign Honorary member of the American Academy of Arts and Science. His varied scientific achievements at that time include the landmark



Fig. 1 Professor Sir Jack Baldwin, FRS.

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† Dedicated to Professor Sir Jack Baldwin, FRS on the occasion of his 67th birthday.



John Moses graduated from the University of Bath in 2001 with a 1st class M.Chem. degree, having spent a year in Purdue University, USA, undertaking research with Professor Ian P. Rothwell. He then moved on to the University of Oxford to pursue a D.Phil. in synthetic organic chemistry, working under the supervision of Professor Sir Jack Baldwin, FRS. John then spent a short spell at The Scripps Research Institute,

La Jolla, working with Professor K. B. Sharpless, before returning to the UK to take up an EPSRC academic fellowship at The School of Pharmacy. His research interests include natural product synthesis, biomimetic synthesis and chemical biology.



Robert Adlington graduated from Imperial College, London in 1980 with a PhD in organic chemistry, supervised by Professor A. G. M. Barrett, FRS. Robert then joined the Dyson Perrins Laboratory, University of Oxford to work as a postdoctoral research associate of Professor Sir Jack Baldwin, FRS. In 1990 he became a full University Lecturer and Collegiate

Fellow of Lady Margaret Hall. Over the years Robert has formed a productive partnership with Sir Jack (over 200 co-authored publications), especially in the areas of synthesis and mechanistic evaluation.

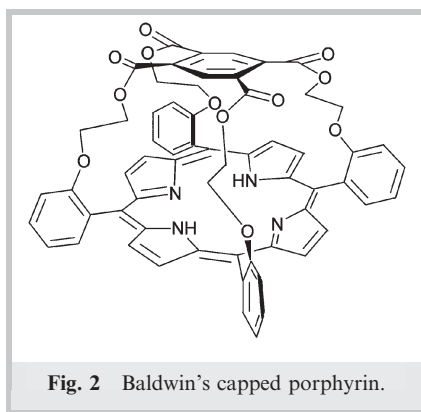


Fig. 2 Baldwin's capped porphyrin.

synthesis of an artificial capped porphyrin, capable of reversibly binding oxygen when complexed with ferrous iron,¹ thus laying the foundations for a potential source of synthetic blood (Fig. 2).

Sir Jack can also lay claim to the recognition of the general class of [2,3]-sigmatropic rearrangements,² further emphasising his many and diverse research interests. However, it was his "Rules for Ring Closures" published in 1976³ that cast Sir Jack into the chemistry limelight and made him a textbook name in organic chemistry. The rules, which distinguish between two types of ring closure, *Exo* and *Endo*, have proved to be an extremely valuable tool for organic chemists ever since. The scientific importance of Sir Jack's 1976 paper is reflected in the fact that it has recently been identified as the most cited article in the history of *Chemical Communications*, with more than 1500 citations.³

Upon appointment at Oxford, Professor Baldwin's research interests became increasingly focused towards the interface of organic chemistry and biology, with a particular emphasis upon achieving an understanding of, and

elucidating the mechanistic details on, the biosynthesis of the β -lactam antibiotics. This pioneering study, which was initially undertaken in collaboration with Sir Edward Abraham, FRS, led to the isolation, cloning and ultimately the structure of the enzyme isopenicillin N synthase which catalyzes the formation of the penam nucleus from its tripeptide precursor δ -(L- α -aminoadipoyl)-L-cysteinyl-D-valine (Scheme 1) and molecular oxygen.⁴ The elegant and insightful work carried out by the Baldwin group placed Oxford at the centre of biosynthetic β -lactam antibiotic research, building upon the legacy established by Chain, Florey and Abraham.⁵

In recognition of Professor Baldwin's pioneering work in the sciences, he was knighted in 1997 for his contributions to organic chemistry.

Trained as a synthetic organic chemist, Sir Jack never lost his appetite for the challenge of natural product synthesis. However, unlike conventional approaches towards total synthesis, the Prof's keen interest in biological processes influenced his style, and led him to establish an ongoing programme dedicated to the biomimetic synthesis of complex natural products.

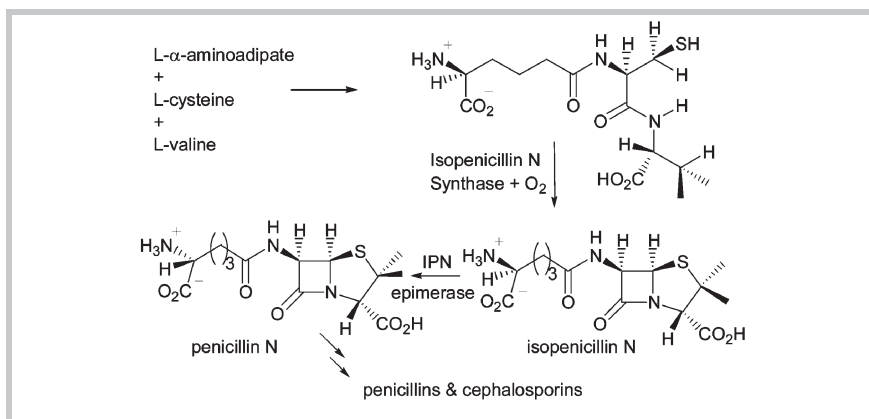
It would be impossible to comprehensively review the lifetime work of Sir Jack in an article of this size, a career that has borne over 600 scientific publications, and trained scores of doctoral students. However, it is highlights of his contribution to the field of biomimetic synthesis that will be briefly discussed, since this body of work presents significant progress in the field of organic synthesis and has not been previously reviewed.

The biomimetic approach

Biomimetic synthesis—from the Greek word "bios", meaning life, and mimetic—the adjective for "mimesis"—imitation or mimicry—is the application of methods and systems found in Nature to the study and design of synthetic systems. This technology transfer is desirable because evolutionary pressure typically forces natural systems to become highly optimised and efficient. When applied to natural product syntheses, biomimetic approaches can often facilitate rapid access to complex structures that may otherwise require inconceivable conventional synthetic pathways. In general, biomimetic approaches mimic a key step in the proposed (or known) biosynthetic pathway, and are mostly applicable to those systems that are not under strict enzymatic control. Instead the structure itself is predisposed to the biomimetic chemical change. Heathcock has written of the biomimetic strategy that "The basic assumption of this approach is that Nature is the quintessential process development chemist. We think that the molecular frameworks of most natural products arise by intrinsically favourable chemical pathways—favourable enough that the skeleton could have arisen by a non-enzymatic reaction in the primitive organism. If a molecule produced in this purely chemical manner was beneficial to the organism, enzymes would have evolved to facilitate the production of this useful material".⁶

Biomimetic syntheses, by their nature, are often elegant and efficient processes, providing novel pathways to some of Nature's most complex structures. The origin of the field of biomimetic synthesis can be traced back to 1917, when Sir Robert Robinson, FRS, reported a one pot synthesis of the bicyclic alkaloid, tropinone.⁷ Since those pioneering early days there have been significant advances in the field, with ever increasingly complex molecular structures being synthesised using biomimetic approaches.⁸

In more recent times the powerful "retro-synthetic analysis" approach developed by Corey has dictated the thinking and learning processes of the new generation of synthetic organic chemists.⁹ In this approach the sub-skeletal functionalisation generally occurs early on in the synthetic plan,



Scheme 1 Biosynthesis of the β -lactam antibiotics.

and problems sometimes arise in assembling together such highly functionalised sub-units into structures resembling the targeted natural products. In contrast, Nature generally assembles the molecular scaffolding firstly with relatively few, but key, functional groups in place, and then such structures are functionalised in a highly specific manner, by the process of secondary metabolism *etc.* Biomimetic chemistry in the Baldwin group is directed towards developing a deeper understanding of the processes that actually make natural products which themselves, due to evolutionary factors, have been pre-selected due to their beneficial properties and also an elegance of synthetic approach. A criticism of a biomimetic chemical approach is that at times yields may be low, and the final target may not be the completed natural product due to lack of further skeletal functionalisation. However, solutions to such problems can be the target of future generations of synthetic chemists. Indeed, some progress has already been made in these areas, such as remote functionalisation, as exemplified by the work of Barton¹⁰ and Breslow.¹¹ Although both approaches towards natural product synthesis differ in principle, each has the potential to offer elegant solutions to challenging problems, often complementary to each other in practice.

Molecules from Mars

Natural products have been the focal point of organic synthesis for decades. Often the more complex the molecular framework, and the more unusual the functionality possessed by the compound, the more enticing targets they become to the synthetic chemist.¹²

The same criteria towards target selection, coupled with a desire to understand how such strange entities are created in Nature are the driving force behind much of Jack Baldwin's biomimetic work. In particular, if no obvious biosynthetic pathways can explain the formation of certain compounds, this makes them all the more attractive targets, and this has led Baldwin to describe such metabolites as "Molecules from Mars".¹³

The manzamines

No discussion on biomimetic synthesis would be complete without mentioning Baldwin's studies on the manzamines. Perhaps the group's most pioneering and elegant example of a biomimetic approach towards natural product synthesis, the story behind the manzamines is intriguing at every stage. The manzamines represent a fascinating group of complex polycyclic β -carboline alkaloids which have been isolated from several different families of marine sponge. The first member of this class, manzamine A (1) was isolated in 1986 by Higa *et al.*¹⁴ Manzamine B (2) and C (3) were subsequently isolated from the same sponge (Fig. 3).¹⁵ The unprecedented structures have provoked the statement "its [manzamine A's] provenance is problematic as there appears to be no obvious biogenetic path",¹⁴ thus the manzamines fit perfectly into the category of a "Molecule from Mars".

Consequently in 1992, after much discussion with the editors, Baldwin and Whitehead put forward, without experimental evidence, an intriguing biogenetic hypothesis for the formation of the manzamines, proposing that each structure

could be reduced into four building blocks: ammonia, a C₁₀ dialdehyde, tryptophan, and a C₃ acrolein equivalent, shown in Scheme 2 for manzamine B (2).¹⁶ The key step in the proposal is an intramolecular *endo*-Diels–Alder cycloaddition of the enamine form and iminium form of the macrocyclic bis-dihydropyridine (4). Of his manzamine proposal Baldwin later said, "If I was God, I would have made it [manzamines] this way". Interestingly, since the publication of the biosynthetic hypothesis, a large number of manzamine and related alkaloids have been isolated from various species of sponge, and despite the lack of experimental evidence, the proposal has been applied to explain their biosynthetic origin. One such compound is Kerampidin B (6),¹⁷ which happens to correspond to the reduced form of the proposed biosynthetic intermediate (5).

In order to demonstrate the chemical feasibility of the proposed biosynthesis of the manzamine alkaloids, the Baldwin group undertook a series of successful model studies that proved, in concept, the viability of the key *endo*-Diels–Alder cycloaddition.¹⁸ With the success of the model system in hand, efforts were turned towards the biomimetic synthesis of Kerampidin B (6). To this end, the desired macrocyclic precursor (10) was prepared using the well-established pyridinium salt reduction protocol. In a subsequent Potier–Polonovsky sequence they arrived at a product mixture containing (3) and (4), which when left at room temperature, followed by another borohydride reduction gave rise to a very complex mixture which, however, after careful chromatographic separation yielded 0.3% of the desired Kerampidin B (6) (Scheme 3).¹⁹ The low yield undoubtedly results from a highly competitive redox process, and may reflect the possible involvement of a Diels–Alderase in the biosynthesis. Nevertheless, this pioneering study proved to be a landmark achievement in biomimetic synthesis.

The *Galbulimina* type I alkaloids

In 1995 the Baldwin group published a general biosynthetic proposal (supported by some experimental verification) to explain the formation of the type I

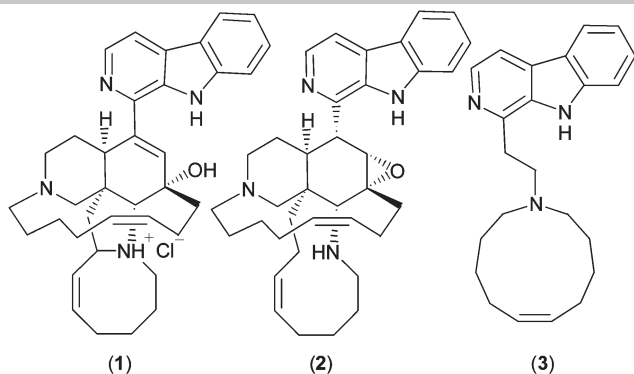
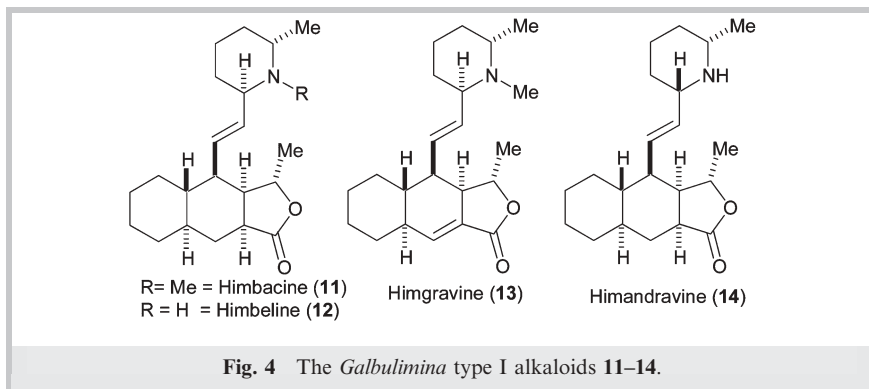
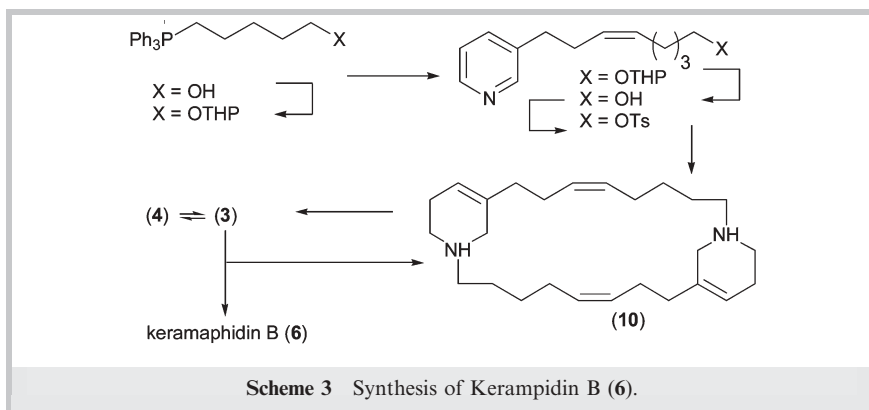
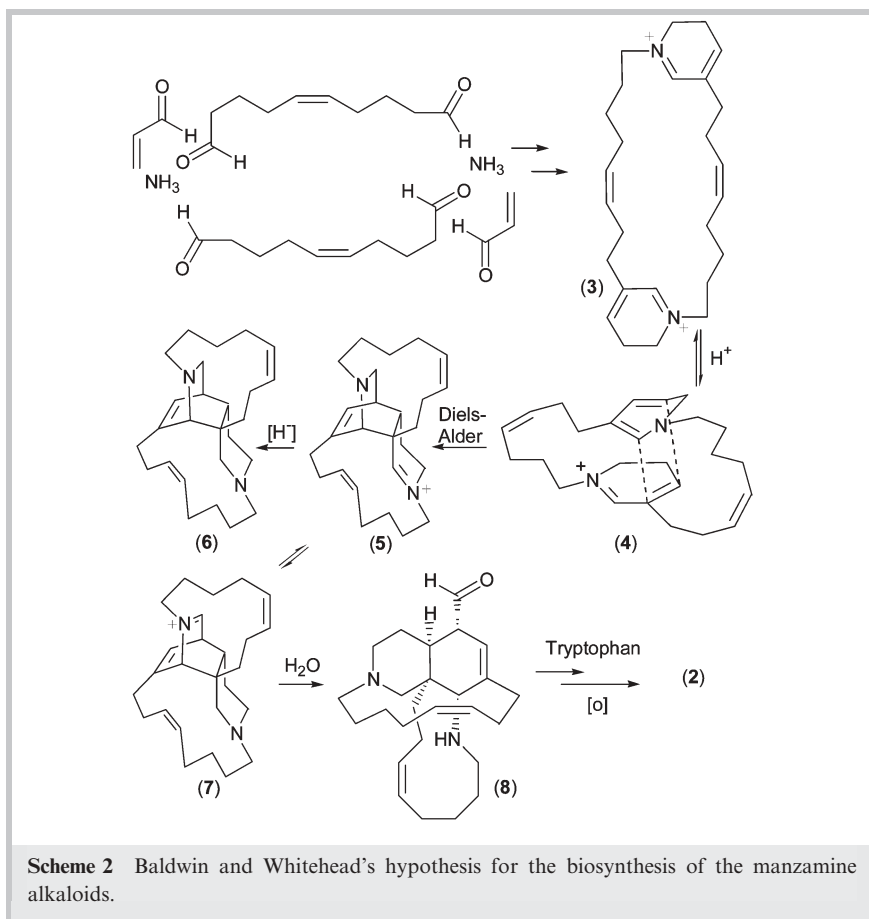
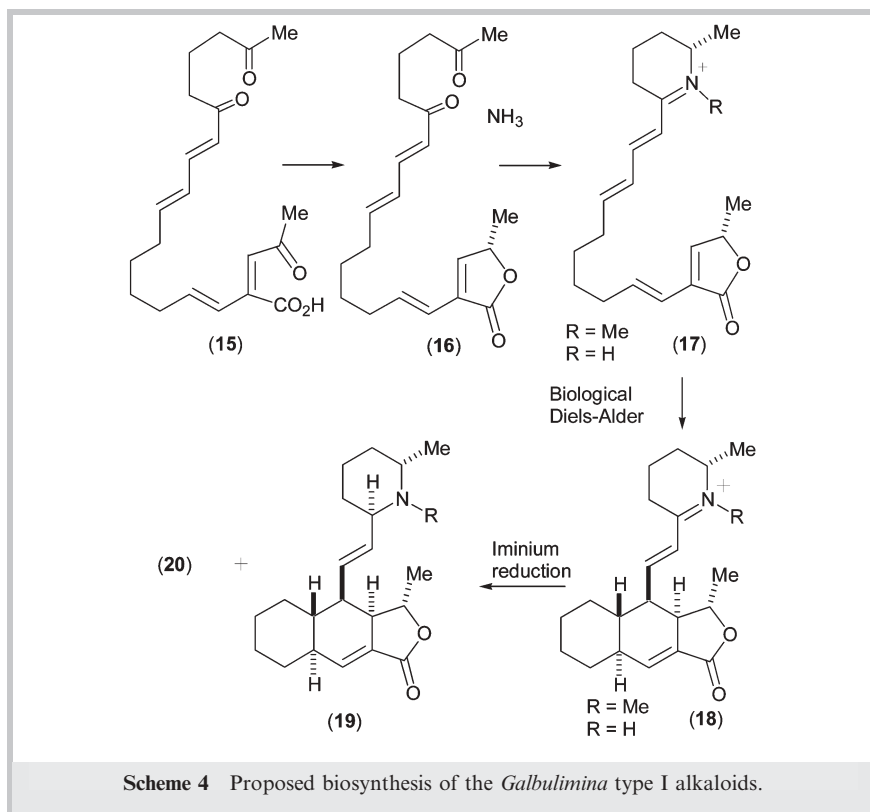


Fig. 3 Manzamine A (1), B (2), and C (3).



Galbulimina alkaloids.²⁰ So far 28 *Galbulimina* alkaloids have been isolated and they appear to fall into four classes based upon their structures. Class I consists of four tetracyclic lactones as shown in Fig. 4.

The proposed biosynthetic pathway for the *Galbulimina* Class I alkaloids postulates ketide (**15**) formation from nine acetates and a pyruvate *via* standard polyketide biosynthesis.²¹ Reductive lactonisation would result in butenolide (**16**), which on reductive amination followed by iminium ion formation *via* *N*-methylation or *N*-protonation would provide the Diels–Alder precursor (**17**). Intramolecular Diels–Alder cycloaddition *via* an *endo* transition state with facial selection controlled by the butenolide methyl group, would afford tetracycle (**18**). Finally, hydride reduction of the iminium from either the α or β face would furnish either the himbacine (*trans*-piperidine ring) precursor (**19**) or the himandravine (*cis*-piperidine ring) precursor (**20**) (Scheme 4). Having completed a successful model study which demonstrated the feasibility of the key Diels–Alder cycloaddition, the Baldwin group next focused their attention towards a total synthesis of the *Galbulimina* Class I alkaloids.²¹ Unlike the model system, which utilised Gassman's Diels–Alder chemistry, Tchabanenko *et al.* employed an alternative iminium ion activated biomimetic Diels–Alder process. Thus, the key intermediate (**21**) was successfully prepared by an olefination of known aldehyde (**22**) and Horner–Emmons reagent (**23**). Treatment of tetraene (**21**) with trifluoroacetic acid at 0 °C effected Boc-cleavage and condensation to the desired iminium species (**17**) R = H, that after quenching at room temperature with sodium cyanoborohydride successfully revealed the desired type I core of the *Galbulimina* alkaloids, as a mixture of diastereoisomers. Further straightforward chemical steps successfully yielded enantiomerically pure synthetic himbeline (**12**), himbacine (**11**) and himandravine (**14**), all of which had spectroscopic data matching that of the naturally occurring substances (Scheme 5).²² This powerful and elegant entry towards a class of complex natural products, further demonstrates the brilliant and insightful approach that Baldwin applies towards biomimetic chemistry.



The epoxyquinol dimer: panepophenanthrin

It is more than coincidental that in the biomimetic syntheses described above, the key step responsible for rapid

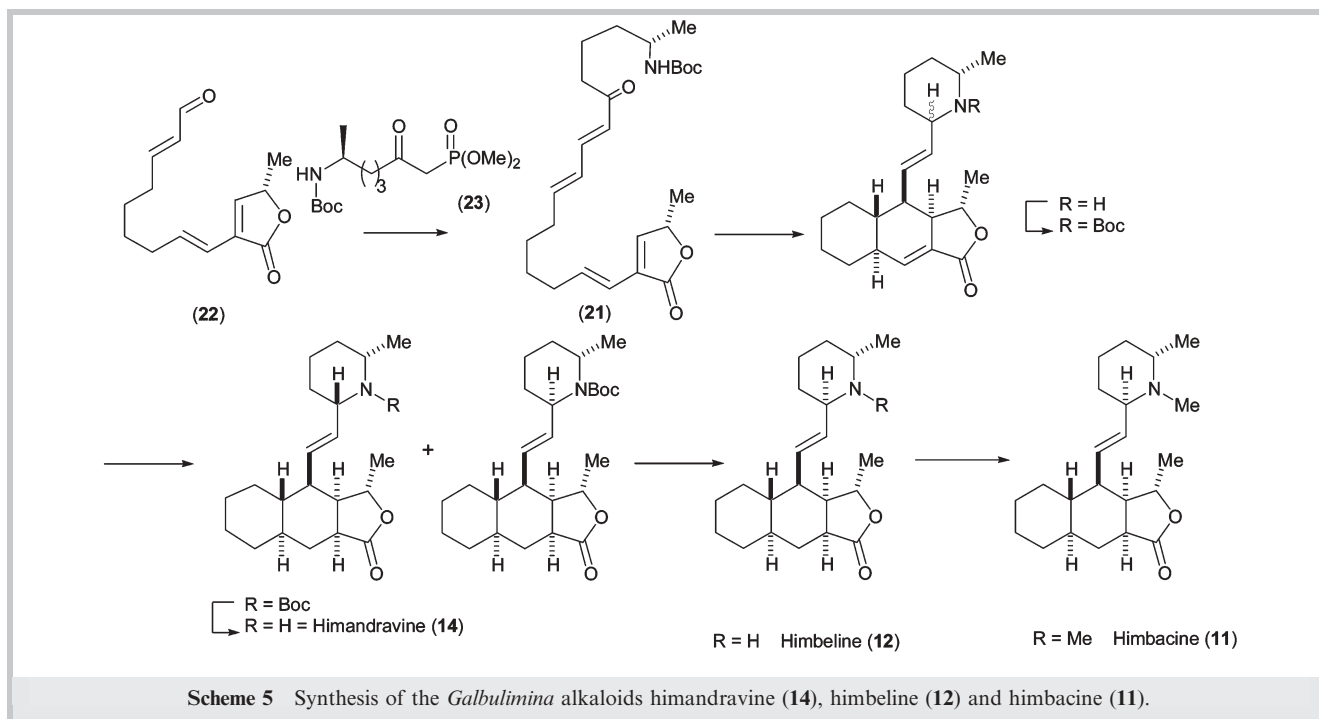
assembly of the complex frameworks involves an intramolecular Diels–Alder cycloaddition. Possibly one of the most powerful of all known chemical processes, it is to the chemist’s good fortune that such a biomimetic reaction

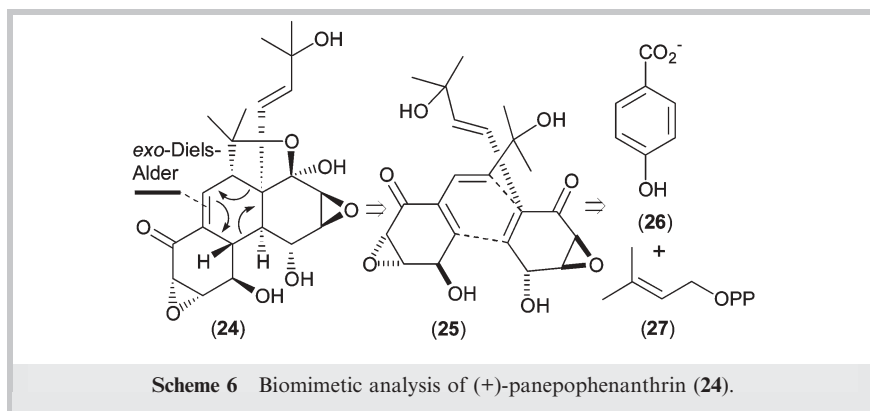
is amenable to the application of organic synthesis. Although the intramolecular Diels–Alder reaction appears to play an important role in biosynthesis, the intermolecular variant also provides exciting biomimetic opportunities which the Baldwin group have embraced.

An interesting example of a structurally unique and complex natural product that recently attracted the attention of the Baldwin group, was the ubiquitin activating enzyme E1 inhibitor, (+)-panepophenanthrin (**24**), isolated from the mushroom strain *Panus rudis* IF08994.²³

A member of the epoxyquinoid family, the fascinating molecular architecture assigned to (+)-panepophenanthrin (**24**) revealed a complex, densely functionalised structure, consisting of a highly oxygenated tricyclic ABC core ring system, containing eleven contiguous stereocentres. Intrigued by this unusual secondary metabolite, Moses and Baldwin proposed a biosynthesis of **24** starting from 4-hydroxybenzoate (**26**) and dimethylallyl pyrophosphate (DMAPP) (**27**) as depicted in Scheme 6.

Central to the proposal is an *exo*-Diels–Alder dimerisation of the epoxyquinol monomer (**25**), itself a known compound.





analysis revealed that (**25**) could be accessed through a Stille cross coupling reaction of the known building blocks bromoxone (**28**) and vinyl stannane (**29**). This pathway was particularly attractive since it is closely parallel to the proposed prenylation process in the biosynthesis. The vinyl stannane was prepared following a literature procedure, and (\pm)-bromoxone (**28**) was initially prepared in racemic form following the procedure of Altenbach,²⁴ although both enantiomers were available *via* this methodology. Gratifyingly, Stille cross-coupling of the TES-protected (\pm)-bromoxone (**30**) and vinyl stannane (**29**) gave the desired monomer, which was not stable and underwent the proposed tandem dimerisation/hemi-ketal reaction sequence to yield the TES-protected panepophenanthrin (**31**) in 75% yield, and as a single diastereoisomer. Deprotection of **31** smoothly gave rise to the desired (\pm)-panepophenanthrin (**24**) in excellent yield, thus providing convincing evidence to support the intriguing biosynthetic proposal (Scheme 7).²⁵ This powerful combination of biomimetic and retro-synthetic planning uncovered a route to this biologically

important compound in multi-gram quantities. It is difficult to imagine how else one could synthesise this complex structure in so few steps, without embracing the biomimetic cascade.

The nitrophenyl pyrones: spectinabilin, SNF4435 C & D

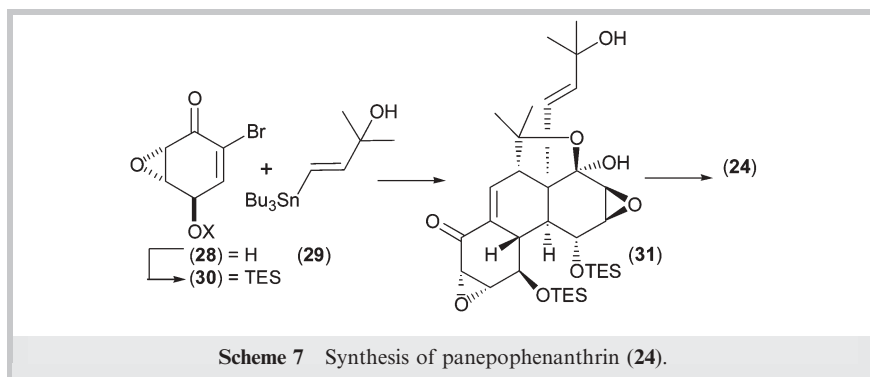
Another group of structurally unusual compounds that recently puzzled Sir Jack are the nitrophenyl pyrones. Although members of this family of compounds have been known for several years, it was the isolation of two new additions that intrigued the Baldwin group. In 2001, Kurosawa *et al.* reported the discovery of the immunosuppressive diastereoisomers SNF4435 C (**32**) & D (**33**).²⁶ Structurally, compounds **32** and **33** are pentacyclic structures exhibiting a hexa-substituted bicyclo[4.2.0] core comprising a cyclohexadiene unit in the major ring. This bicyclo[4.2.0]octadiene is connected to a spiro furan unit, which in turn is connected to a γ -pyrone fragment. Interestingly, examination of the structure of spectinabilin (**34**),²⁷ a constitutional isomer of compounds **32** and **33**, led to the suggestion that

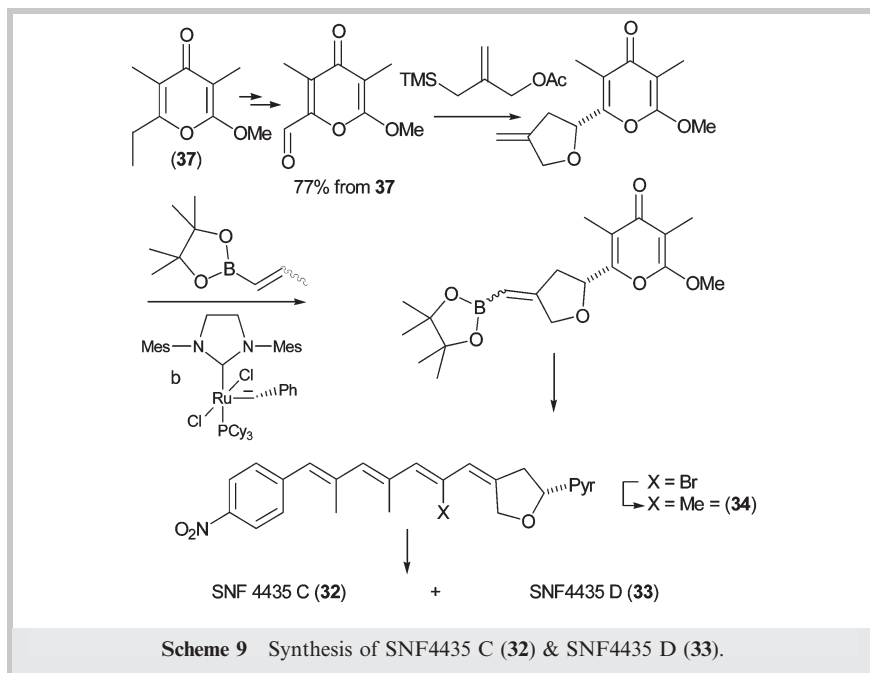
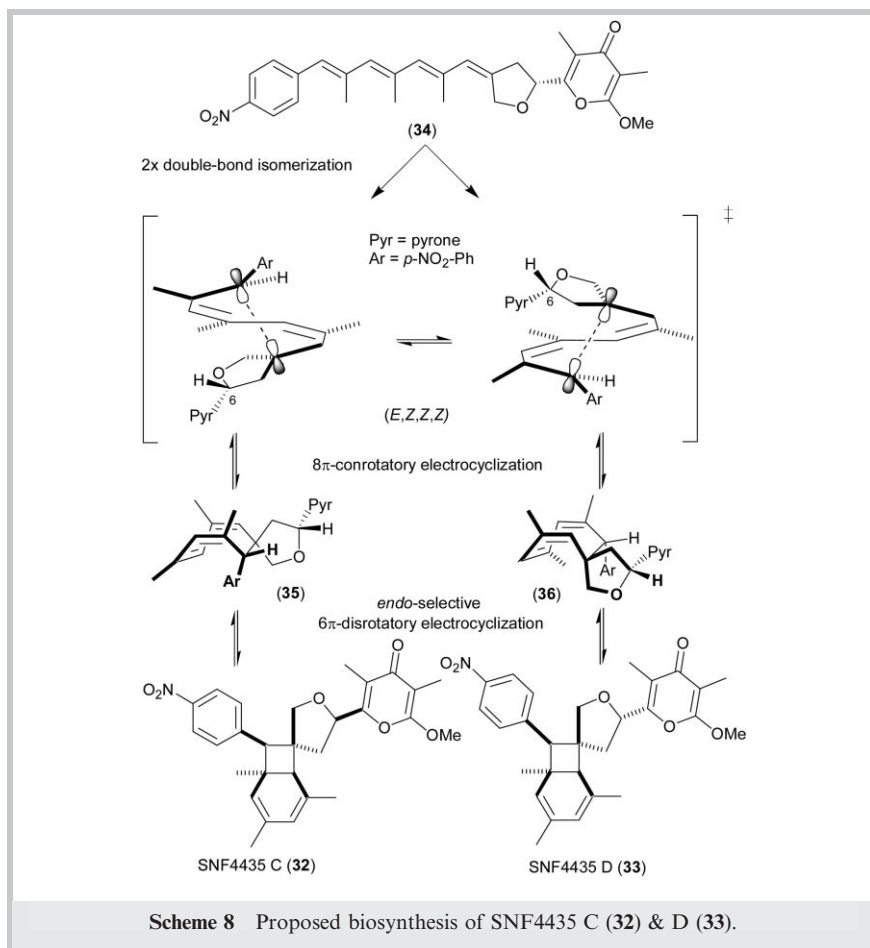
spectinabilin could be a biosynthetic precursor to the SNF compounds. The basis for this proposal is related to the biosynthesis of the endiandric acids as proposed by Black, and experimentally verified by K. C. Nicolaou's group.²⁸ Thus, in the proposed biosynthesis, **32** and **33** were envisaged as having originated from the *E,Z,Z,Z*-tetraene, an isomer of spectinabilin (**34**) which is able to undergo a diastereoselective thermal 8π conrotatory electrocycloisolation giving rise to the major octatriene **35**, along with the minor diastereoisomer **36**. An *endo*-selective 6π disrotatory electrocycloisolation of octatrienes **35** and **36** gave rise to SNF4435 C (**32**) and SNF4435 D (**33**) respectively (Scheme 8).

The key to validating the biosynthetic proposal was the selective isomerisation of the tetraene backbone of **34**, since it was envisaged that the cascade of electrocycloisolation would occur spontaneously, given the correct geometry. Gratifyingly, model studies with a related tetraene ester revealed that the addition of a palladium catalyst could facilitate this complex transformation,²⁹ and as a result a more complete study was undertaken. Thus, spectinabilin (**34**) became the primary target, which itself presented several synthetic challenges. Nevertheless, after much effort, compound **34** was successfully prepared by Jacobsen *et al.*, employing a range of novel chemical transformations (Scheme 9). Upon treatment of synthetic **34** under optimised reaction conditions, a complex mixture of products was obtained, that upon chromatographic purification gave rise to the target compounds **32** and **33** in a diastereomeric ratio of 2.5:1, similar to the ratio found in Nature.³⁰ This spectacular reaction sequence represents another great achievement for biomimetic synthetic approaches towards natural products.

Conclusions

Biomimetic synthesis has come a long way since the days of Sir Robert Robinson, with many pioneering chemists making significant contributions to the field. As the chemistry described in this article illustrates, clearly Sir Jack continues to be a major exponent of biomimetic synthesis as an intellectual and worthwhile approach to structural





assembly. Although some may have their misgivings about the biomimetic approach, Sir Jack's opinion on the

matter is clear. On one occasion, when asked his thoughts on a non-biomimetic chemical approach to asymmetric

synthesis, Sir Jack commented "of course Nature considered this approach, then rejected it".

Acknowledgements

Throughout his career, Sir Jack has been supported by an army of capable and dynamic students who are too many to name, and the authors apologise for omitting their valuable contributions to Professor Baldwin's success.

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