THE INSIDE STORY

A Discussion with Professor Sir Jack E. Baldwin, FRS

SYNSTORIES

- Total Synthesis of (+)-Neopeltolide by a Prins Macrocyclization
- Biomimetic Enantioselective Approach to Decahydroquinoline Dendrobatid Alkaloids

CONTACT

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Dear readers,

This issue of SYNFORM is somewhat special for at least two reasons: (1) for the first time there is an article authored by somebody else than me, specifically by the SYNLETT Regional Editor Professor Laurence M. Harwood; (2) we have the privilege to publish an INSIDE STORY based on an exclusive interview with Professor Jack E. Baldwin, one of the scientists who most deeply influenced modern organic chemistry and who discloses herein unknown aspects of his life, of his career, and much more.

The issue is completed by two SYNSTORY articles, both related to the total synthesis of natural compounds: the first accomplished by Professor Eun Lee (South Korea), and the second by Professor Mercedes Amat (Spain).

Enjoy your reading!

Matteo Zanda
Editor of SYNFORM

IN THIS ISSUE

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COMING SOON
INTERVIEW

(Questions by L. M. Harwood (University of Reading, UK), answers by Sir J. E. Baldwin, FRS (University of Oxford, UK)

Question 1 | Could you give a personalised summary of your life and career?

Answer 1 | I was born on the 8th of August 1938 – 8/8/38; three eights are a symbol of good luck for the Chinese – within the sound of Bow bells which means I can lay claim to being a genuine Cockney.

My father moved to Sussex during 1941 in order to escape the bombing of London and I grew up in Haywards Heath. One of my earliest memories was of arriving there in a taxi in deep snow. My childhood was spent in a very rural environment. After primary school I first went to Brighton Grammar School and, after the family moved to Maresfield, I attended Lewes Grammar School for Boys.

In 1957 I obtained a state scholarship to study chemistry at Imperial College, having first applied to Oxford and having been rejected by Exeter College. After finishing my undergraduate degree in 1960 I carried out my PhD studies with Derek Barton, obtaining my doctorate in 1964.

I remained at Imperial as an Assistant Lecturer until 1967 when I moved across the Atlantic to a Professorship at Penn State in the January. There I launched my independent research career discovering the 2,3-sigmatropic rearrangement of sulfonium ylids, far extending the usefulness of the Sommelet–Hauser reaction. In the harsh Boston Winter of late 1969 I moved to MIT, returning to the UK fleetingly to be the Daniell Professor of Organic Chemistry at Kings College London before returning to MIT where I stayed until 1978. I once again returned to the UK and arrived at Oxford University, where I had known rejection some 20 years earlier, to take up the Wayneflete Professorship, associated with Magdalen College at the Dyson Perrins Laboratory. I headed the department until my retirement in 2005 (when I was appointed the retirement age was 67) and remain an Emeritus Professor there.

Of course, I still maintain an active interest in chemistry but now I have more time to enjoy walking with my wife Christine and our two Labradors, Lucy and Niblet, in the woods at the back of my house and enjoy the views over the spires of Oxford.

Question 2 | What was it that led you to follow a career in organic chemistry?

Answer 2 | Even as a small child I devoured books – at my infants school my schoolteacher used to call me the “walking encyclopaedia”. At the age of 9 I discovered a book on chemistry and was immediately struck by how it revealed a world totally distinct from that in which I had lived so far. Elements such as bromine, chlorine, hydrogen, sodium and potassium were totally beyond my experience to that point but I wanted to meet them.

At about that time a person in the village, who had employed my friend’s mother as a cleaner, passed away leaving an extensive chemistry kit that was obtained for the sum of £10.00. It was a real chemistry kit with retorts, funnels and flasks as well as lots of chemicals including 98% sulfuric acid, a substance I would have found very difficult to source at my age. I rapidly found out that this syrupy, corrosive liquid was essential for so many inorganic chemical reactions, allowing me to prepare the hydrogen, chlorine, bromine and iodine that I longed to meet. When I ran out of my initial supply of concentrated sulfuric acid I found I could generate fairly concentrated solutions – about 70% – by heating hydrated zinc sulfate, “white vitriol”.

After that my father let me have a battery and I constructed a cell to electrolyse molten sodium hydroxide to prepare metallic sodium. I couldn’t make very much but I was fascinated by the glistening globules of molten sodium appearing and reacting at the cathode.

Then I graduated to organic chemistry of a sort, filling oil drums with acetylene generated from calcium carbide and igniting them with a fuse made from a long piece of string soaked in paraffin. This resulted in huge explosions; although sometimes the fuse would go out and this would lead to hot
debates about who among my friends would “volunteer” to relight the shortened fuse!

I loved the acrid smell of the chlorine, the rich red colour of the bromine and the yellow flames as the sodium reacted with water. Sulfuric acid, the “goddess of chemistry” and inorganic chemistry had opened a door into a whole new and wonderful world that I had never guessed could exist. I have maintained the wonder for chemistry throughout my life. The love of the colours and smells and the whole visual – and of course three-dimensional – aspects of chemistry has stayed with me and has been central to my career.

Naturally, during the course of such experimentation my mother’s kitchen did suffer a certain degree of attrition; but what can you expect when a 10 year old is working with such things as concentrated sulfuric acid? The trouble nowadays is that health and safety issues dominate the teaching of chemistry. Young people would turn more readily to the sciences if they could benefit from a little less restriction and more imagination in the provision of practical work at school.

Question 3 | What have been the high points and what have been the low points of your career?

Answer 3 | I have been fortunate to experience many high points. If I were to list some off the top of my head I would list the 2,3-sigmatropic rearrangement of sulfonium ylids, the first stereospecific synthesis of a penicillin, the rules for ring closure, the first synthesis of a reversible oxygen carrier based on iron, the elucidation of the biosynthesis of penicillin and the whole area of biomimetic synthesis.

As for low points, they have all come from people, not chemistry – chemicals you can rely on. I don’t want to name individuals – they know who they are – but I would state very strongly that my greatest moments of frustration have been with institutions that stifle creativity of British science by their desire to control. This is all quite wrong. There are some really good people in our universities but the research councils are presiding over the guaranteed decline of academia in this country. Furthermore, it is my opinion that the close association of the British chemical industry with academic research, which has developed as academics have had to seek alternative sources of funding, is highly damaging to the scientific integrity of our academic institutions. The chemical industry is not interested in basic research; its sole objective is to make commodities that they can sell. It is in our universities that basic discoveries, on which industry can ultimately feed, are made and the university research departments are being killed off.

Question 4 | What is the next big question that holds your fascination?

Answer 4 | For some time now I have been wrestling with trying to rationalise the reasons and driving forces behind the origin of life. I have decided that this isn’t just a case of having the right size planet, containing the right cocktail of elements or molecules at the right distance from a star so that liquid water can exist. Organic chemistry has to take place before life can begin and it is how that happened that has attracted my interest.

Put simply, the formation of a planet involves an aggregation of small particles until gravity moulds them together. As a consequence of such gravitationally directed aggregation, the cores of planets contain the heaviest elements. In the case of Earth, the core is iron and it has a lighter silicaceous mantle; this is important. In the early development of the planet there was an atmosphere composed largely of carbon dioxide. The carbon was there but in too highly oxidised a state for organic chemistry to take place – the pre-requisite for life to have a chance to develop. Until the carbon dioxide could be reduced at least to formaldehyde, if not hydrocarbons, no organic chemistry is possible. What is special about the Earth is that, not long after its formation in astronomical terms (some 50–100 million years after its formation, bearing in mind that the Earth is around 4.5 billion years old), it received an impact from a large body which resulted in the ejection of a substantial proportion of its matter – both mantle and core – which went into orbit around the Earth and became the Moon as we know it today.

This impact, disrupting and ejecting contents from the iron core, was so violent and energetic that the core was probably released as a gaseous plasma at a temperature in the
region of 16,000 K. This iron plasma was able to reduce the primordial atmosphere of carbon dioxide down to carbon monoxide or even formaldehyde. These simple compounds could act as the precursors of simple organic molecules such as the sugars by the formose reaction.

So organic chemistry has been established on Earth – but does this lead inexorably to life? No! There has to be more, as the mere presence of organic molecules is insufficient to give rise to life. There has to be a driving force – a certain level of organisation is necessary before molecules can start to arrange themselves to lead ultimately to a living cell, an incredibly organised situation.

Another directing influence is necessary – that of a “cycle” or feedback loop. Something that reinforces development when it leads in the direction of more organisation. To use a chemical example, a series of interchanging species in dynamic equilibrium will be driven by the thermodynamics of the overall system. If an intermediate is depleted then the system grinds to a halt if it cannot be replenished by its neighbouring species in the equilibrium sequence – either before or after. However in a cyclic reaction system any depletion of an intermediate can be compensated by the cycle itself, leading to a survival of the cycle in spite of environmental changes. This survivability is enhanced by two cycles sharing a common intermediate and eventually a network of cycles becomes able to sustain itself against major perturbations. This the basis of the biosphere.

Of course, although I have used a chemical example, this is a general principle applicable to all systems and I believe that this is what lies at the basis of the carbon cycle, first expounded by Hans Bethe in the late ’30s, and for which he was awarded the Nobel Prize in 1967. There is some sort of feedback loop in the sequence of transmutation of the elements, within the sun and other stars, from hydrogen through deuterium to helium and then on to carbon, oxygen and nitrogen.

Any cycle which retains a memory of its past will ultimately concentrate certain aspects of the cycle. As I have said, this is a general principle and so applies as much to physical cycles as atmospheric and ocean convection as chemical cycles. Whether the cycle be physical or chemical, if it has a feedback loop within it, favouring one aspect of the cycle – a memory if you like – then that entity is favoured and will accumulate. If two cycles overlap to favour the same entity, then its existence is particularly favoured. I believe that this situation has to exist, within a context in which organic chemistry can take place, in order for life to develop.

This is, of course, all fantastic speculation and my thoughts are still at a very preliminary stage, but can we find any experimental evidence for naturally occurring “feedback loops”? The Earth’s climate is surely one example of such a feedback system? Despite our recent concerns about “global warming” the Earth’s surface temperature has remained more or less static for the greater part of its existence – at least during the presence of life which relies on the existence of liquid water. I believe that this points to a series of feedback mechanisms, both physical and chemical, that work in parallel to maintain the status quo.

A big problem that remains is to identify the process for the origin of all of the water on Earth. Current theories point to “dirty snowballs”; ice comets impacting on Earth and – somehow – this has to tie in with the whole carbon monoxide, formaldehyde balance. We are only scraping the surface, but I believe that one thing is important. It is necessary for a catastrophic event such as the breaking away of our Moon, to take place, in order to put into being the train of events that could set up a series of systems capable of coming together, by chance, to favour a situation that would ultimately lead to the development of organic chemistry as we know it and eventually to life. Such a viewpoint excludes the possibility of life originating on Mars.

Laurence M. Harwood

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Total Synthesis of (+)-Neopeltolide by a Prins Macrocyclization


Sang Kook and Min Sang, who started as MS students in Professor Eun Lee’s group from the Department of Chemistry, Seoul National University (South Korea) some time ago, were ready for the kick-off of their PhD research projects, Professor Lee suggested they could collaborate. Indeed, in Professor Eun Lee’s group, students frequently collaborate on projects. “I have this vague realization from the experience that ‘two projects for two students’ is somehow more productive than ‘one student, one project’ provided they do not quarrel with each other,” said Professor Lee. Their first project was the total synthesis of exiguolide, which was successfully concluded in a relatively short time (Angew. Chem. Int. Ed. 2008, 47, 1733). When Min Sang was busy wrapping up the project (July 2007), Sang Kook was free, and Professor Lee suggested he could look into neopeltolide. “The assessment,” said Professor Lee, “was that he would be able to synthesize the macrolactone core of the molecule without too much pain if he used the homoallylic alcohol–aldehyde Prins cyclization reaction and then macro lactonization, and maybe Min Sang would join the project later and provide the known carboxylic acid fraction needed for Mitsunobu coupling.”

Sang Kook was able to complete the macrolactone core in two months. The idea of an intramolecular version popped up rather casually in one group meeting and was quite appealing. According to this synthetic strategy, a bicyclic structure would form in one shot from an acyclic ester intermediate. “It was not difficult to adapt the scheme for an intramolecular version,” said Professor Lee, “and we were all happy to know that the intramolecular Prins macrolactonization reaction was feasible with the substrate possessing both the TBS-protected homoallylic alcohol fragment and the 3,3-diethoxypropionate fragment.” TBS deprotection was tricky in the presence of the sensitive acetal group, and the Prins reaction proceeded without deprotection (40%) when Sang Kook used the reaction conditions previously established in Professor Lee’s laboratory in the synthesis of blepharocalyxin D (Org. Lett. 2007, 9, 141).

“The only problem was that the reaction was a little bit dirty (5.5:1) due to ‘racemization’, which is frequently the problem when you perform Prins cyclizations,” said Professor Lee. Sang Kook then started synthesizing the alternative intermediate in which the location of the aldehyde and homoallylic alcohol fractions were swapped; he intended to find out which route was better. “We were happy that the second scheme provided a cleaner product (10:1 ‘racemization’) in higher yield (59%),” said Professor Lee. Sang Kook was waiting for the supply of the carboxylic acid when Panek’s paper (Angew. Chem. Int. Ed. 2007, 46, 9211) was published. “Since Panek corrected the configuration at two stereogenic centers in the neopeltolide structure,” said Professor Lee, “Sang Kook immediately started synthesizing epimeric intermediates following the second intramolecular strategy. We were happy that the second scheme provided a cleaner product (no ‘racemization!’) in higher yield (68%) with complete control of the configuration of the newly generated stereogenic centers.” Sang Kook then found out that the original intramolecular Prins macrolactonization scheme worked in this case too (47%), yielding the correct macrolactone core with proper stereochemistry (9:1 ‘racemization’). In the meantime, Min Sang succeeded in preparing the carboxylic acid following the known Panek scheme. When Sang Kook started the final Mitsunobu reaction, which yielded neopeltolide efficiently, the Scheidt paper (J. Am. Chem. Soc. 2008, 130, 804) came out. “We recognized that the Scheidt scheme followed a similar general strategy: intra-
molecular Prins cyclization. Thank goodness they had used a different starting material (a dioxinone derivative) for the Prins cyclization and the Scheidt scheme produced a ketone product in a relatively low yield (21%),” concluded Professor Lee. If one judges from the results obtained by Professor Lee, close collaboration among graduate students definitely adds value to the productivity of a research group!

**About the authors**

**Professor Eun Lee** graduated from Seoul National University in 1969 and studied organic chemistry at Yale University (USA), where he received his PhD on biosynthetic studies of fungal tropolones and vitamin B_{12} under the supervision of Professor A. I. Scott. After postdoctoral research with Professor K. Nakani- shi at Columbia University (USA) on the synthesis of α-ecdysone, he spent a year and a half at Zoecon Corporation working on the biosynthesis of insect juvenile hormones. He was appointed as an Assistant Professor at the Department of Chemistry, College of Natural Sciences, Seoul National University (South Korea) in 1977, and since then has been promoted to Associate Professor (in 1981) and Professor (in 1987). He served as the Chairman of the Department of Chemistry from 1986–1988. He spent one year (1985–1986) at Dyson Perrins Laboratory, University of Oxford (UK), as a Visiting Professor in the laboratory of Professor Sir J. E. Baldwin. His main research interests are centered on the selectivity of organic reactions involving radical and carbenoid intermediates in conjunction with the total synthesis of natural products. He received the Korean Chemical Society Award in 1995 and the Korea Science Award in 1997, and has served as both the secretary general (1996) and the president (2006) of the Korean Chemical Society.

**Sang Kook Woo** received his BSc in Chemistry in 2006 from the Yeungnam University (South Korea), and subsequently started his PhD at the Department of Chemistry, Seoul National University (South Korea).

**Min Sang Kwon** received his BSc in Material Science in 2006 from the Seoul National University (South Korea), and subsequently started his PhD at the Department of Chemistry of the same university.
Biomimetic Enantioselective Approach to Decahydroquinoline Dendrobatid Alkaloids


According to Professor Mercedes Amat from the Faculty of Pharmacy, University of Barcelona (Spain), “ants, frogs of the Dendrobatidae family, the polyketide route, and decahydroquinoline alkaloids are four elements of an incompletely solved ecological and biosynthetic puzzle.”

In fact, the source of decahydroquinoline amphibian alkaloids remains an intriguing question, in particular after the discovery that some of these alkaloids also occur in ants, thus strengthening a dietary hypothesis for their origin in frogs. Although there are no conclusive studies concerning the biosynthesis of these biologically active alkaloids, it is thought that they might derive from the polyketide route by aminocyclization of 1,5-polycarbonyl intermediates, leading to decahydroquinolines with a side chain substituent at both the C2 and C5 positions.

Mimicking these key steps believed to occur in nature, the group of Professor Amat and Professor Bosch recently developed the enantioselective synthesis of (−)-pumiliotoxin C (cis-195A) from a 1,5-polycarbonyl derivative and (R)-phenylglycinol, which acts as a chiral latent form of ammonia, providing experimental support for the presumed biosynthetic route to the decahydroquinoline class of dendrobatid alkaloids.

By choosing the appropriate 1,5-polycarbonyl derivative, the above biomimetic double cyclocondensation could be extended to the enantioselective synthesis of a variety of 2,5-disubstituted decahydroquinoline alkaloids.

According to one of the referees of the manuscript, this work “is a nice example of a biomimetic synthesis that has been developed before the biosynthesis has been proven,” and “with this synthesis the authors have proven that a hypothetical biosynthetic pathway via a polyketide is feasible, although clear-cut investigations dealing with this topic are still missing.”

“In fact,” agreed Professor Amat, “the methodology used in the key step, i.e., a cyclocondensation reaction of a chiral aminoalcohol with a δ-oxoacid derivative, has been used extensively in our laboratory to generate oxazolopiperidine lactams, which are extremely useful chiral building blocks for the enantioselective synthesis of piperidine derivatives, including simple piperidine alkaloids, more complex piperidine-containing benzo[α]quinolizidine and indole alkaloids, as well as synthetic products of biological interest (for a review, see: Chem. Eur. J. 2006, 12, 8198).” Interestingly, the biomimetic strategy developed by the authors was inspired by a serendipitous observation. “When we attempted a double phenyl-
glycinol-induced cyclocondensation in the context of model studies on the synthesis of (+)-anaferine,” explained Professor Amat, “we unexpectedly obtained a tricyclic lactam in a single synthetic step instead.”

“We would like to remember Dr. John W. Daly (National Institutes of Health scientist emeritus),” concluded Professor Amat, “a world authority on amphibian alkaloids, who passed away in March 2008. Dr. Daly forged new paths in natural products research, particularly in the isolation, structure elucidation, and pharmacology of alkaloids discovered in frog skin, and found to be derived from dietary arthropods.”

**About the research group and the corresponding authors**

The research interests of the Amat and Bosch group are focused on the field of organic synthesis, with the ultimate goal of developing general synthetic methods and strategies and applying them to the synthesis of natural products, particularly indole and piperidine alkaloids, and other bioactive nitrogen compounds, both in the racemic series and enantiopure form. The group’s experience in this area has allowed them to tackle interdisciplinary research projects in the field of biomedicine, in collaboration with research groups involved in other areas. Similarly, they are participating in joint projects with chemical and pharmaceutical companies aimed at the synthesis of compounds with therapeutic interest. Mercedes Amat studied Pharmacy at the University of Barcelona (Spain) and completed her PhD under the supervision of Professor Bosch in 1984. She then moved to the University of Virginia (USA) as a Fulbright Scholar, where she carried out postdoctoral studies in the laboratory of Professor Richard J. Sundberg working in the total synthesis of natural products. In 1987 she returned to the University of Barcelona, where she is currently Professor of Organic Chemistry at the Faculty of Pharmacy. She is co-author of about 80 scientific papers and has been the advisor of nine PhD theses. Since January 2005 she has been Head of the Department of Pharmacology and Therapeutic Chemistry.

Joan Bosch completed his PhD in 1973 at the University of Barcelona, where he has been Professor of Organic Chemistry at the Faculty of Pharmacy since 1982. From 1983 through 1986 he was Vice-Dean of this Faculty, and then Dean for the years 1986 through 1992. He was also Head of the Department of Pharmacology and Therapeutic Chemistry from 1992 to 1998. He has published 260 scientific papers and is also one of the inventors of 80 patents resulting from collaborative research with pharmaceutical companies. He has supervised 36 PhD theses and in 2002 was awarded the ‘Distinction for the Promotion of University Research’ by the Autonomous Government of Catalunya.
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