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The Marvels of Biosynthesis: Tracking Nature's Pathways

Alan R. Battersby
University of Cambridge, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

Introduction

How ever did it come about that a substantial part of my research has been aimed at understanding the marvellous chemistry used by living systems to construct the substances they produce? I must admit that I had not in the past thought much about that particular 'pathway' but was encouraged to do so by Derek Barton, Chairman of the Executive Board of Editors for Tetrahedron Publications. He suggested that this article, invited by Professor Chi-Huey Wong, should be a personal one giving some background on how my interests evolved. I shall try to do that but this approach raises a substantial problem. Our group has worked on biosynthetic problems for over 40 years so it is impractical to cover everything. Therefore it seems best to indicate briefly the range of our interests and to expand on the major topics by giving some examples. In this way, I want the reader to see how the field of bioorganic chemistry has undergone a marvellous evolution, blossoming especially during the past 15 years or so. By combining the approaches of chemistry, spectroscopy and biology, the possibilities are now almost limitless. I hope many young scientists will be stimulated by my article to enter this field of research; there has never been a better time to do so.

The Outset

My love of chemistry started early. As a boy in the early 1930's, I scanned through the many books that my father had collected. He was a builder by trade, clearly without any direct connection with science. Yet among these books, covering all sorts of topics, were a few about chemistry. They contained drawings of crystals and many types of apparatus with descriptions of a wide variety of experiments, such as the generation of hydrogen from zinc and acid. I returned with great interest to these books time and again and soon my rather meagre pocket money was being spent on test tubes, flasks, a Bunsen burner, an evaporating dish and other such treasures. At that time, it was possible for a boy to buy, at the local pharmacy, hydrochloric and nitric acids, zinc, sulphur, copper sulphate and many more materials. Those days are gone and there are pluses and minuses to the change. At any rate, I was able to assemble a good set of equipment to run lots of simple experiments which I enjoyed enormously.

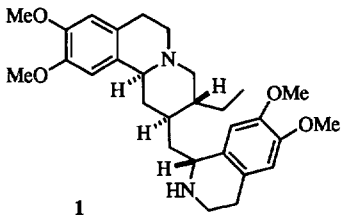
I believe the next important influence on me came at school where I had the great good fortune to be taught more about chemistry by a superb teacher, Mr Evans. The seed of my love for chemistry which had been planted earlier by my father's books was strongly fed by his teaching. Then I read my first books about organic chemistry. They were at about the level of sixth form teaching at that time, rather simple in fact, but I was excited about the huge variety of substances based on carbon–carbon bonds.

With hindsight, it is clear that chance and serendipity played a crucial role in the further development of my interests in chemistry. I won a scholarship which allowed me to study at a university and mainly practical factors caused me to enter the University of Manchester. What an excellent choice that turned out to be because the Professor of Organic Chemistry was the inspirational Alexander Todd. At that time, he was already deeply involved in his pioneering work on the building blocks for nucleic acids and his syntheses of the nicotinamide and related cofactors for which he was awarded the Nobel Prize. His example and his teaching had a profound influence on me and my debt to him is enormous. I had not finished my undergraduate course when Alex Todd was invited to the Chair in Cambridge and I remained in Manchester to graduate as Bachelor of Science. However, I was very happy, and I felt privileged, to be given the chance to join him again as his Professorial colleague at Cambridge in 1969.

During the undergraduate course at Manchester, we had been introduced to almost all the major groups of natural products. From this array, I had become especially attracted by the plant alkaloids and I was very excited when Hal Openshaw told me about the work he had started on the structure of emetine, the alkaloid used for the treatment of amoebic infections. Happily he let me take on this work in 1946 and he guided my research efforts during the next three years; I am extremely grateful to him.

The challenge was to solve the structure of emetine by the only approach then possible, that of chemical

Key words: alkaloids, biosynthesis, carbon-13, enzymes, vitamin B_{12}.
Four close friends influenced me greatly at many points during my 50 years of research; they are Alex Todd, Hal Openshaw, Duilio Arigoni and Albert Eschenmoser. They taught, helped and guided me and their example was an inspiration throughout. This article is dedicated to them all with respect and affection.



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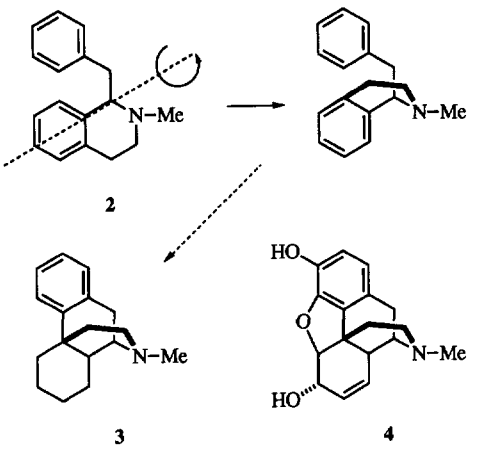
degradation; essentially none of the modern spectroscopic methods, involving IR, NMR and mass spectroscopy, were available at that time. We did have a manual UV instrument but not thin-layer chromatography. The highly satisfying outcome was that the structure of emetine (**1**) was solved[1] by these slow, laborious methods, but they *were* fun. There will be a connection to this work in the section on indole alkaloids. Some years later (1950–1952), I had the marvellous opportunity to work in the United States as a Commonwealth Fund Fellow. For the first year, I worked with Lyman C. Craig at what was then the Rockefeller Institute in New York City. Then I moved to Biochemistry at the University of Illinois for the second period to join Herbert E. Carter. The experiences at both centres were highly rewarding and they turned my interests strongly in a biological direction. This influence blended with some earlier thinking, covered below, to set up the first phase of our researches.

The Alkaloids and Terpenes

It was my involvement with the plant alkaloids in the mid-forties that prompted the first stirrings of my interest in what we now know as biosynthesis. How do plants construct the vast array of structures such as morphine, strychnine, colchicine, yohimbine and chelidonine, to mention just a few. I was intensely curious about this question of natural synthesis but frustratingly, this curiosity could not be satisfied until some time later. Only when a range of substances labelled with carbon-14 became available in the late 1940s and early 1950s could experimental work be started. First, there was labelled carbonate, cyanide and acetate but soon one could buy ^{14}C-labelled phenylalanine and tyrosine. At last there was the chance to start direct experiments on plants.

Our early work was strongly influenced by the remarkable speculations of Sir Robert Robinson, based on his recognition of structural relations among natural products. These ideas were collected together in his Weizmann Memorial Lectures[2] and among them was the proposal that morphine (**4**) is related to the 1-benzylisoquinoline system **2** by rotation and oxidative ring-closure to the morphine skeleton **3** as in Scheme 1. Such insight comes only to few.

Our hope was to use ^{14}C-labelled precursors to work out the biosynthetic pathway by which the opium



2 3 4

Scheme 1.

poppy constructs morphine and its relatives.* We wanted to pin-point not only the simple building blocks for these alkaloids by incorporation experiments with labelled tyrosine[3] but crucially, to test whether the plant enzymes could convert a 1-benzylisoquinoline into morphine. The plan was to synthesize a ^{14}C-labelled form (singly labelled) of a 1-benzylisoquinoline carrying what on mechanistic grounds should be the appropriate phenolic hydroxyl groups. Then we had to introduce it into the biosynthetic system of the living plant. In retrospect, it is fortunate that at the outset, we were not over-aware of the difficulties of working with living plants; our biological colleagues were not too optimistic about our plans! However, 'faint heart ne'er won fair lady', so we simply injected our ^{14}C-labelled 1-benzylisoquinoline into the poppy seed capsule. Later the morphine was isolated and to our delight it was strongly labelled. Moreover, the ^{14}C-label was shown by systematic degradation of the morphine to lie at the one carbon matching the corresponding site in the precursor.[4] This study established the conversion of a 1-benzylisoquinoline into morphine and also into the other opium alkaloids.† It was a crucial first step which eventually led forward to reticuline (**5**) being pin-pointed[4] as the actual 1-benzylisoquinoline system which undergoes the oxidative coupling step; initially labelled reticuline was fed to the poppies in racemic form (Scheme 2). The coupling step was shown to generate the dienone, salutaridine (**6**) which is then reduced to the dienol **7** ready for the illustrated ring closure to yield thebaine (**8**). Several further modifications were proved to occur by way of codeinone (**9**) and codeine (**10**) before morphine (**4**) is reached.[5–7]

*I must stress here the request to me that this article should follow personal threads so it cannot be a full review. I hope my many friends who also worked in several of the fields I discuss will understand the approach.

†Much more recently, sets of enzymes have been isolated from plants and their use has allowed further important advances. Particularly the excellent work of Professor M. H. Zenk (Bochum) has given further details of a number of biosynthetic sequences to a variety of alkaloids.

This success in revealing how the opium alkaloids are built had a dramatic effect on my whole thinking about the future. Beforehand, we dreamed that such a discovery might be possible and finally, we knew it could be done. The main thrust of our research from that time forward was aimed at tracking Nature's pathways and also at understanding the chemistry and biochemistry involved.

All the steps shown in Scheme 2 were supported by careful labelling experiments. I should also say that this Scheme 2 and the text touch only part of our work on the morphine group of alkaloids; e.g. the necessary synthetic work, preparation of labelled precursors, stereochemical studies and experiments on redox relationships are all left aside. Nevertheless, enough has been given for the reader to appreciate how the researches evolved from incorporation of labelled tyrosine at the outset to partial synthesis, labelling and incorporation of salutaridine (**6**) during the later stages. Several other groups contributed independently to knowledge of the opium alkaloids. The papers under refs 5–7 refer to that work and the field was reviewed[8] in 1965. In addition, the oxidative coupling that occurs at a late stage in the biosynthesis of the morphine group was recognized by Barton and Cohen[9] as involving phenol oxidation and a reaction of importance for the biosynthesis of a variety of natural products.

The next example is chosen because it illustrates well how a biosynthetic problem was solved by systematic and logical experiments based on incorporation of labelled precursors, combined in this case with some good fortune. The pathway is the one by which the tropolone alkaloid colchicine (**15**) is built in the autumn crocus and other species of *Colchicum* plants and it is a gem. This structure was an obscure puzzle which mystified everyone and simple inspection of the molecule gave few clues concerning its biosynthesis. The problem was eventually solved by the same approach used for the opium alkaloids involving the following steps:

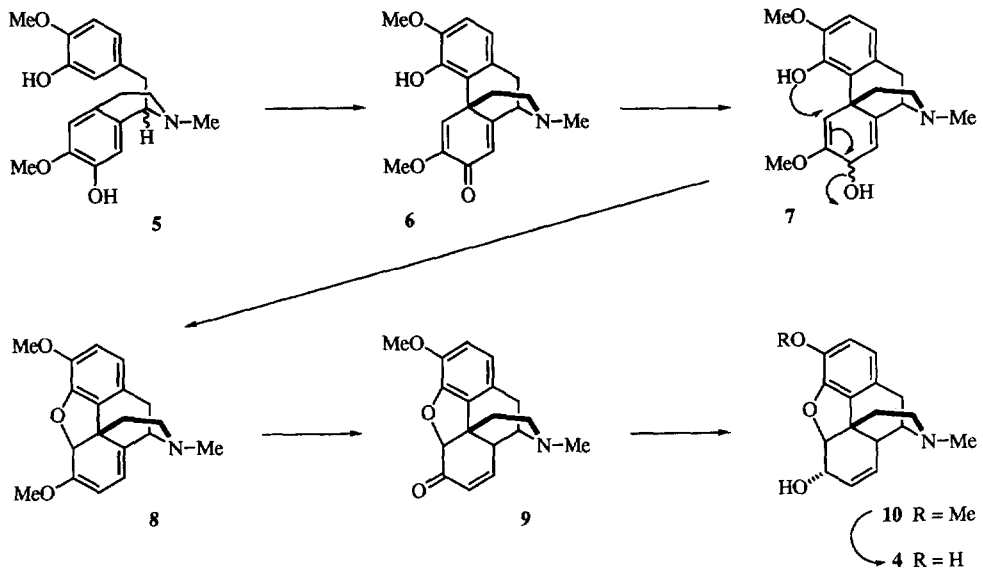
(i) Find out what simple building blocks are used and where they fit into the final structure.

(ii) From the clues gained in this way, postulate likely intermediates.

(iii) Label the putative intermediate(s) with carbon-14 (or tritium in some later experiments) for studies of incorporation into colchicine in the living plants.

(iv) Degrade the labelled products throughout these steps in a controlled way to establish the labelling patterns.

Chance played a role at a late stage in this detective story. We worked hard for years to pin-point the building blocks for colchicine and around 1964, I was describing at a Symposium all the many results[10] from stages (i) and (ii) above of the labelling experiments. Our conclusion was presented that the labelling patterns could be explained if colchicine arose from a $C_6—C_3—C_6—C_1$ dienone such as **14** with subsequent ring-expansion as indicated. It happened that Professor F. Šantavý) from Czechoslovakia was in the audience; he was an expert on natural products from *Colchicum* and related species. Imagine the excitement when he told me he had found a substance in a plant related to *Colchicum* which was a dienone, but of unknown structure. A joint effort[11] led to the structure **13** for this dienone and from this structure it was clear that our postulated dienone **14** lacked one carbon i.e. the true precursor should be dienone **12**. All the necessary labelling experiments confirmed this postulate and established that colchicine (**15**) is in fact a heavily modified isoquinoline alkaloid based on a 1-phenethylisoquinoline precursor[12] **11** with oxidative coupling to give dienone **12**. Some of the key stages on the



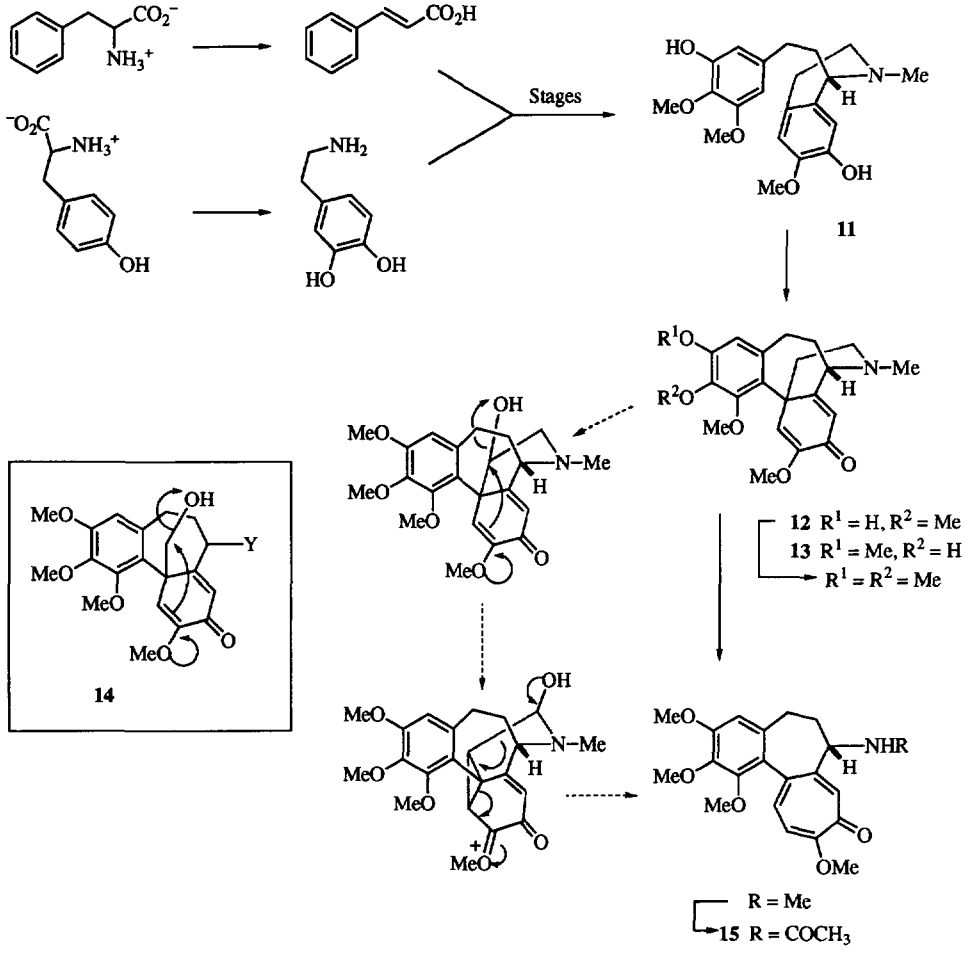
Scheme 2.

pathway are shown in Scheme 3. This new class of 1-phenethylisoquinoline alkaloids later grew appreciably in size; our contributions to the family have been described.[13]

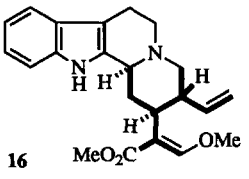
We should not leave the alkaloids without touching on those based on indole, which make up one of the largest families of plant bases. Examples are corynantheine (**16**), vindoline (**17**) and catharanthine (**18**). The intriguing part of these structures is the C_{10}-unit picked out with thick bonds. This often appears as seen in **16** and a backward glance at emetine (**1**) at the start of this article reveals that nine carbons of the same C_{10}-unit are present there. However, rearrangement of the C_{10} piece has taken place for **17** and **18**. How does the C_{10}-unit arise and from what? We will focus here just on those questions.

When our work started on these problems, four possible sources for the C_{10}-unit had been suggested from (a) an aromatic ring by cleavage; (b) shikimic acid; (c) acetate and malonate units; (d) a monoterpene. Proposals (a)–(c) also required one or two C_1-units to be added. Proposal (d) was extended[14] by suggesting that the C_{10}-unit might arise from some unknown cyclopentane monoterpene by cleavage as in Scheme 4.

It would be out of place to attempt here a detailed account of the major effort needed to establish the full



Scheme 3.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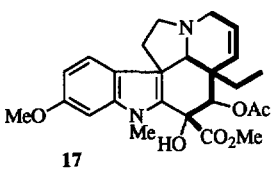
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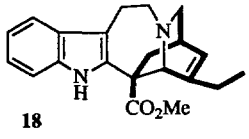
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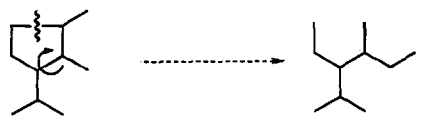


Scheme 4.

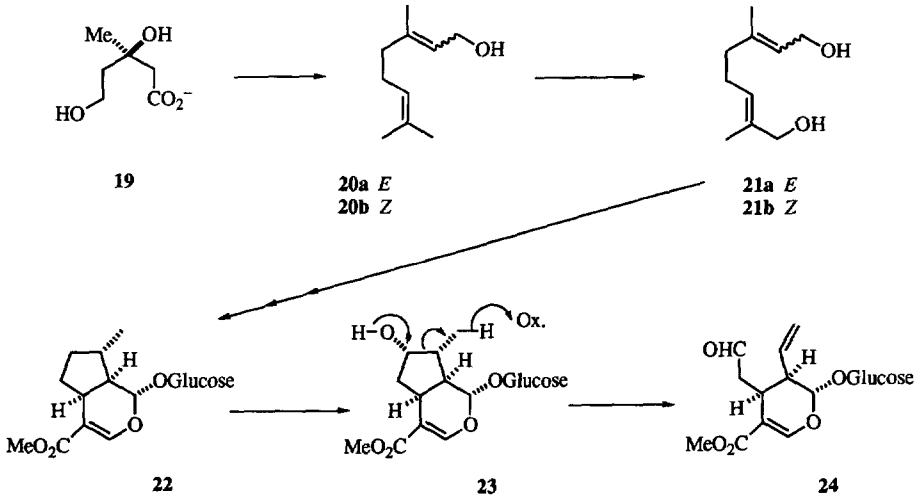
pathway. My aim is to give a snapshot of a research area as it developed some 25 years ago. The experiments were carried out mainly by three groups, those of my team, Duilio Arigoni's and Ian Scott's. The reader should consult reviews[15] written at the time for the references to the papers from all three groups.

The satisfying outcome was that the C_{10}-unit was indeed shown to be monoterpenoid in origin and Scheme 5 shows the main steps that were demonstrated. The door was opened when labelled mevalonate (**19**) and geraniol and nerol (**20a,b**) (which undergo interconversion in the plants) were shown to be incorporated specifically into a variety of indole alkaloids. We were greatly helped in the next step forward by work we were doing in collaboration with Professors Janot and Levisalles on ipecoside. This occurs in the same plants that produce emetine (**1**) and the structure[16] of ipecoside (**25**) was highly informative. Comparison of emetine (**1**) with desacetylipecoside (**26**) suggested a likely biosynthetic relationship and the precursors of **26** could be dopamine and an aldehyde such as **24** or a close relative. By using tryptamine in place of dopamine for condensation with the same aldehyde, the start of an attractive route to the indole alkaloids opened up.

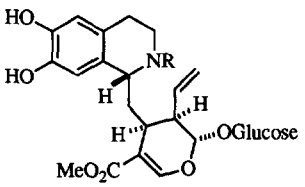
Clearly the putative aldehyde **24** could well be derived from a cyclopentane monoterpene and we tested several, in labelled form, which might have fragmented to give **24**. Only one, loganin (**23**), was incorporated into the indole alkaloids[17] and Duilio Arigoni's group also set loganin securely on the pathway.[18] The required fragmentation of loganin (**23**) could be oxidative as indicated in Scheme 5. Then some of the intermediate steps were filled in including the diol(s) **21a** and **b** and deoxyloganin (**22**) which was shown[19] to precede loganin. However, the putative aldehyde **24** was still missing and as so often happens, we gained it from an unexpected source. Duilio's group[20] and ours[21] were working on terpenoid substances from *Menyanthes trifoliata* which both groups showed had structure **27** where R is a variable monoterpene unit. These substances contain the aldehyde **24** in masked form and, under rather delicate conditions, it was possible to convert one of these lactols into **24**, which we called secologanin.[22] At last, we had the unadorned C_{10}-unit in hand and it was shown to be well incorporated by the appropriate plants into the indole alkaloids and emetine and its relatives.[22] Naturally, we also put a major effort into exploring the pathway going forward from secologanin (**24**) to the indole alkaloids together with several other research groups but here we must move soon to other topics.

However, before doing that, I want to say that these researches on alkaloids spanned roughly two decades and during that period, I was immensely fortunate to work in turn with a succession of outstanding senior colleagues, Bob Binks, Jim Staunton and Bob Ramage. They all made invaluable contributions to what we achieved together during a long period of exciting research. I and the other members of the constantly evolving research teams are greatly indebted to this very special trio.

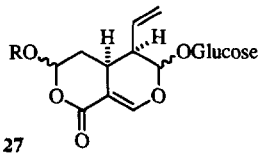
One could add to the foregoing researches on the opium and indole alkaloids and colchicine, dozens more examples from our group and from the other teams working in this area during the late 1950s to early 1970s. It is fair to say that knowledge of how alkaloids are biosynthesized was transformed by these efforts. The approach in which labelled precursors were introduced into living plants turned out to be an extremely powerful one. Nevertheless, one had to be aware of some possible difficulties. The selection of the appropriate advanced precursors was not always easy



Scheme 5.



25 R = $COCH_3$
26 R = H



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as the work on colchicine showed. Also, two plant species producing the same alkaloid could give vastly different incorporations of the correct labelled precursors so plants had to be screened as well. Finally, the plant's enzyme systems sometimes caused some confusion by generating sufficient of a true intermediate (so giving an incorporation) from a close relative that had been chosen as the test precursor. Nevertheless, by carrying out sets of interlocking experiments, it was possible to trace the biosynthetic pathway to the alkaloid or terpene, at very least in broad form and usually in satisfying detail.

This was the position in the late 1960s and I felt the time was ripe to move into new fields, possibly away from the higher plants. Such a move offered hope of our being able to produce cell-free enzyme systems from bacteria or algae. If we were successful in that endeavour, many doors would be open. An equally important reason for seeking a fresh area was because developments in nuclear magnetic resonance spectroscopy (NMR) were offering many new opportunities for biosynthetic research on very complex molecules without the need for specific degradation to locate labelled sites. The ^{13}C NMR approach also allowed study of the making and breaking of carbon–carbon bonds and the importance of this will be clear from the examples in the sections that follow. Finally, I wanted the selected new field to involve natural products of fundamental biochemical importance.

The Pigments of Life

Where would the new pastures lie? Reading what was known about the tetrapyrroles, I felt rather confident that this family would be the right choice.The tetrapyrrolic family includes heme (**33**) and chlorophyll *a* (**34**) together with vitamin B_{12} which will be covered later. Such is their importance for living systems that they have been called the Pigments of Life.

I was filled with admiration for what had been discovered about the biosynthesis of heme (**33**), for example, by the tetrapyrrolic pioneers during the 1940s and 1950s.[23] The main pioneers were Bogorad, Granick, Neuberger, Rimington and Shemin. Scheme 6 summarizes the lovely biosynthetic pathway they uncovered. Briefly, two molecules of 5-aminolaevulinic acid (ALA) (**28**) are enzymically condensed to form porphobilinogen (**29**) (PBG). Then two enzymes, hydroxymethylbilane synthase (often called *deaminase*) and uroporphyrinogen III synthase (shortened to *cosynthetase*) cooperate in some way, then unknown, to convert four molecules of PBG into uroporphyrinogen III (**30**) (uro'gen III). This is carried through many steps, including protoporphyrin IX (**32**), finally to produce heme (**33**) and also chlorophyll *a* (**34**). Clearly, much was known about this crucially important family of substances but far more remained to be discovered.

Biosynthesis of uroporphyrinogen III†

Our initial focus was on the problem of how uro'gen III (**30**) is built from PBG (**29**). This was a fascinating problem because this structure **30** is unexpected. The acetate and propionate groups on ring D are reversed relative to these substituents on the other rings. The expected product from straightforward tetramerization of PBG is uro'gen I (**31**); indeed, the pioneers showed that this is formed when deaminase acts alone on PBG. However, uro'gen I (**31**) was not converted into uro'gen III (**30**) by cosynthetase. We recognized, some two decades after the work outlined above, that the door to further progress could be opened by ^{13}C NMR.

There were more than 25 theories in the literature suggesting how the unexpected structure of uro'gen III (**30**) might arise. Many of them differed as to which of the four bridging methylene groups of uro'gen III at C-5, C-10, C-15 and C-20 had remained attached to its original pyrrole ring. Accordingly, doubly labelled [2,11-$^{13}C_2$]PBG (**29a**) was prepared with a high ^{13}C level at the two sites and was then heavily diluted with unlabelled PBG. Incubation of this sample with deaminase and cosynthetase first gave uro'gen III (**30a**) (Scheme 7), but this was enzymically modified in situ to yield protoporphyrin IX as **32** for NMR analysis. The spectra allowed three important conclusions[24] to be drawn:

(a) Only ring D undergoes rearrangement; rings A–C arise from intact PBG units.

(b) The rearrangement involves at some stage, detachment of the methylene group which had been attached to the PBG unit for ring D: that pyrrole is turned over for reattachment to the same methylene.

(c) The rearrangement is **intramolecular**.

This single rearrangement could in principle occur at any step of the conversion of the monopyrrole into the

† Since the request to the two Prize winners was for a personal account of sometimes overlapping research, it was decided by friendly agreement with Ian that each of us will simply outline his own studies without constant cross-reference to the other.

macrocyclic tetrapyrrole. However, the trapping experiments by Albert Neuberger's group [25] which yielded the aminomethylbilane **35** when deaminase acted on PBG in the presence of ammonia, indicated that an unrearranged bilane may be an intermediate on the pathway. Our group and that of Gerhard Müller synthesized this bilane (**35**) and both showed that it cyclized non-enzymically to form uro'gen I (**31**) whereas treatment with a mixture of deaminase and cosynthetase yielded[26] uro'gen III (**30**). The Cambridge group then synthesized the two doubly ^{13}C-labelled forms of this bilane shown as **35a** in Scheme 8 and, after dilution of each with unlabelled material, they were reacted separately with deaminase–cosynthetase. The labelling patterns[27] of the uro'gen III (**30b**) formed proved:

(i) Rearrangement occurs after assembly of an open-chain unrearranged tetrapyrrole (a bilane);

(ii) Ring-D of uro'gen III is derived from ring D of the bilane;

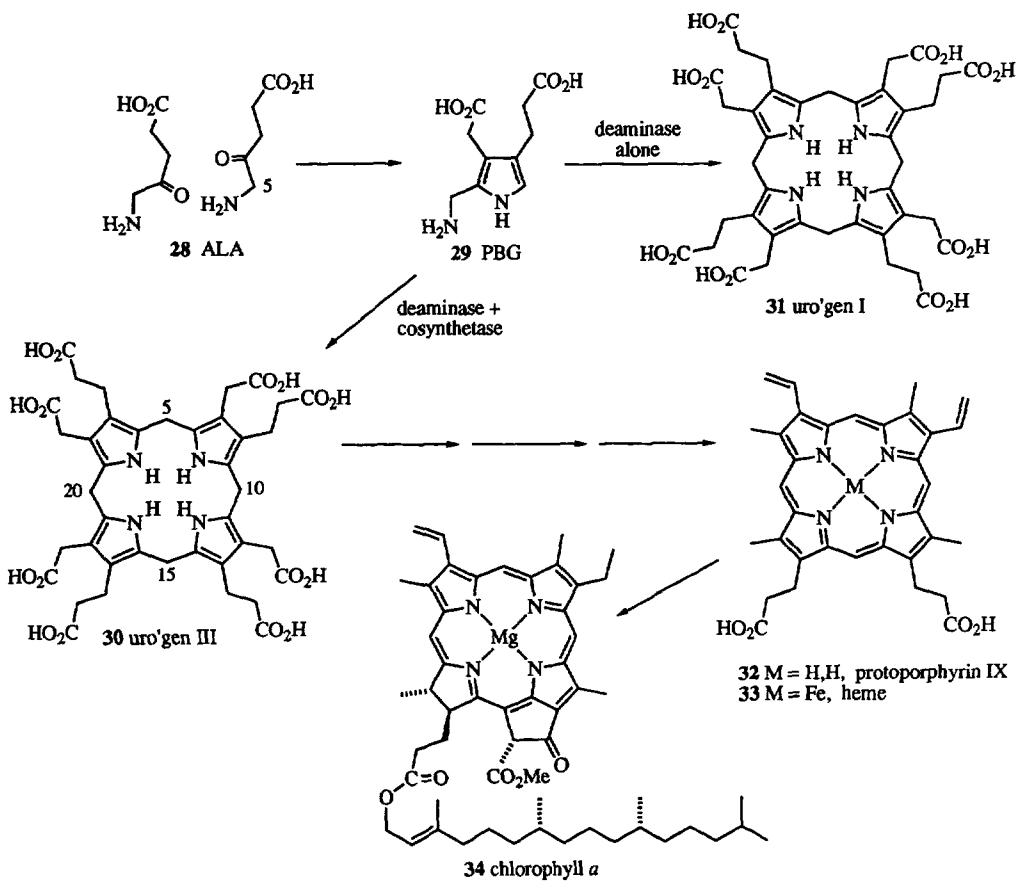
(iii) The rearrangement is **intramolecular**.

These conclusions were rigorous but it became clear[28,29] from kinetic measurements, that though the bilane **35** could act as a substrate for deaminase–cosynthetase, it is not a true intermediate. There was a marked time-lag in the production by deaminase of uro'gen I (**31**) from the bilane **35**. The bilane **35** was evidently being converted by deaminase into a different product and it was this that was acted upon by cosynthetase. Importantly, by incubating PBG with a large amount of deaminase, the time lag was even more pronounced and the true intermediate could be generated more rapidly than it ring-closed non-enzymically to give uro'gen I (Scheme 9); its structure could therefore be studied by appropriate ^{13}C-labelling experiments.[28,29] The final solution was that the true intermediate is the hydroxymethylbilane **36** and we confirmed this structure by unambiguous synthesis.[30]

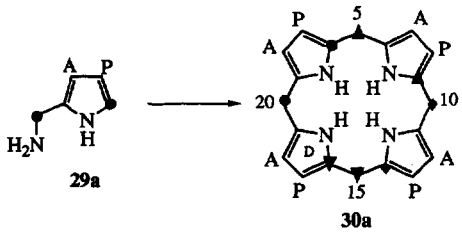
These results, and many more, revealed what the two enzymes do. Deaminase assembles the hydroxymethylbilane **36** from four molecules of PBG (**29**): it does not catalyze any ring-closure. It is cosynthetase which catalyzes the cyclization with concomitant rearrangement of ring D to give uro'gen III (**30**).

Rearrangement by the spiro mechanism?

An attractive mechanism for the rearrangement of the bilane **36** as it is ring-closed to uro'gen III (**30**) is shown in Scheme 10 which involves the spiro-pyrrolenine **37** as a key intermediate. This could undergo fragmentation and recombination as illustrated to generate the rearranged product **30**. Scheme 10 is based on the original idea of Mathewson and Corwin[31] but shows it in a form slightly modified from the original one.



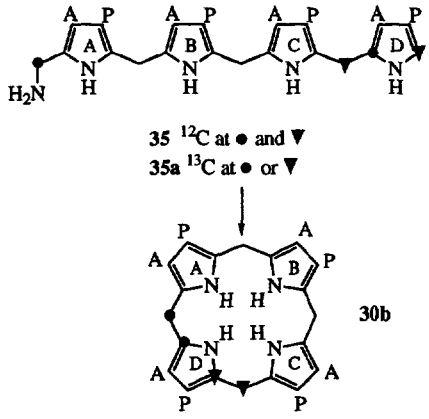
Scheme 6.



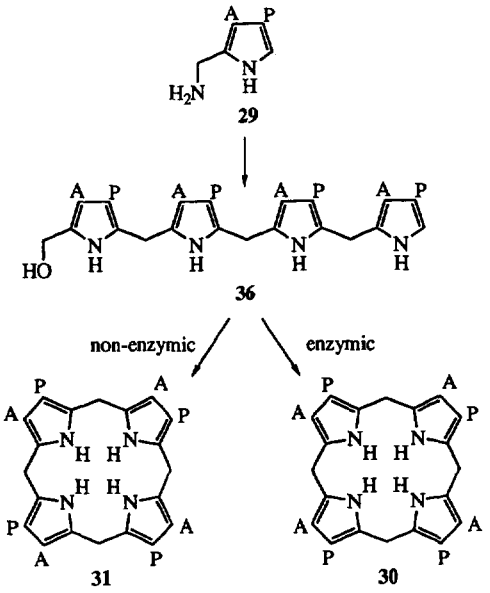
Scheme 7.

We decided to test the spiro mechanism by a synthetic approach and our target was the spiro lactam **38** initially in racemic form. The successful synthesis[32] depended on a novel reaction of an acetoxymethylpyrrole with an iodopyrrole and the final macrocyclization is illustrated. We were then happy to find that the derived octa-acid **39** was a strong competitive inhibitor of cosynthetase with a K_i value roughly one order of magnitude lower than the K_m for the substrate.[32] Strong support was thus given to the spiro mechanism and further strength was added when, after much sweat and tears, the two enantiomers of the spiro lactam **38** were prepared;[33] just one is shown in Scheme 10. Again the derived octa-acids **39** were tested as inhibitors of cosynthetase and one enantiomer was ca. 20 times more potent than the other.[33] The final piece of the puzzle has recently been set in place by developing a novel approach for the determination of the absolute configuration of the strongly inhibiting enantiomer[34] and it is the one shown in Scheme 10. The sum of all this evidence strongly supported the intermediacy of the spiro-pyrrolenine **37** for the biosynthesis of uro'gen III (**30**) and pointed to its absolute configuration being as shown in Scheme 10.

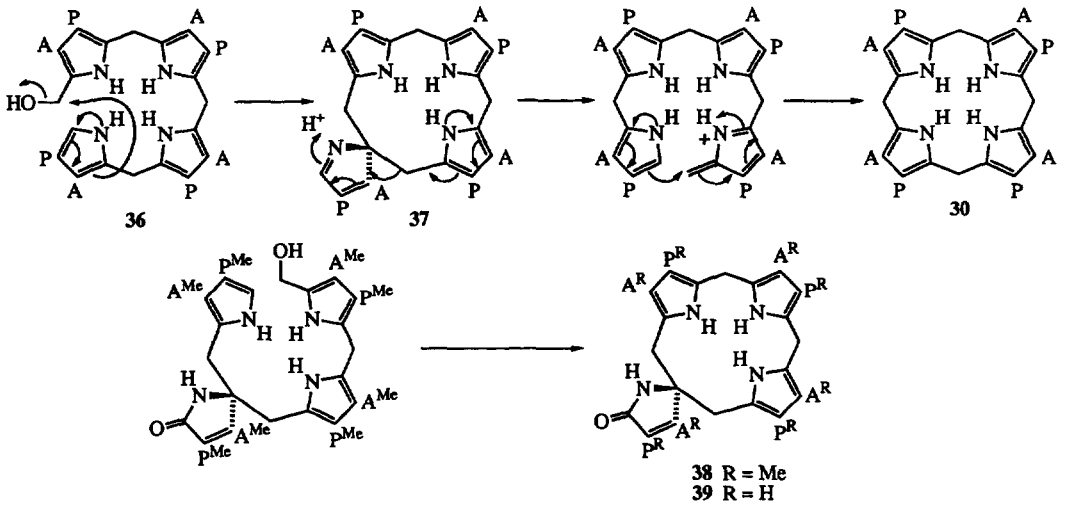
Again we must be content with the few foregoing examples from our work on the porphyrins. However, I must at least mention the surprising finding we made, and Peter Jordan too, that deaminase uses a dipyrrolic cofactor **40** in the assembly of the bilane **36**. So it starts



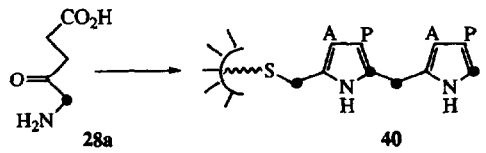
Scheme 8.



Scheme 9.



Scheme 10.



28a 40

Scheme 11.

from a dipyrrole **40**, builds a hexapyrrole and releases the tetrapyrrole **36**, to return to the original dipyrrole **40**. The dipyrrole is attached covalently to the protein through the sulphur of a cysteine residue as shown by the ^{13}C-labelling illustrated on **40** (Scheme 11). This fascinating story is given more fully in a recent review[23] which also outlines much of the rest of the biosynthetic work in Cambridge on deaminase, cosynthetase and their products.

It is important to emphasize that many of the experiments on deaminase and cosynthetase, especially during the later phases of that research, would not have been possible without the key decision to add molecular biology to our armoury of methods. What an enormous difference this made to our work on these two enzymes and also later for the enzymes of the B_{12} pathway. For example, we laboured long and hard in the early days to produce a few milligrams of deaminase. In contrast, by developing a strain of *E. coli* which over produced this enzyme, one fermenter growth yielded around 100 mg of pure deaminase after a few days work.

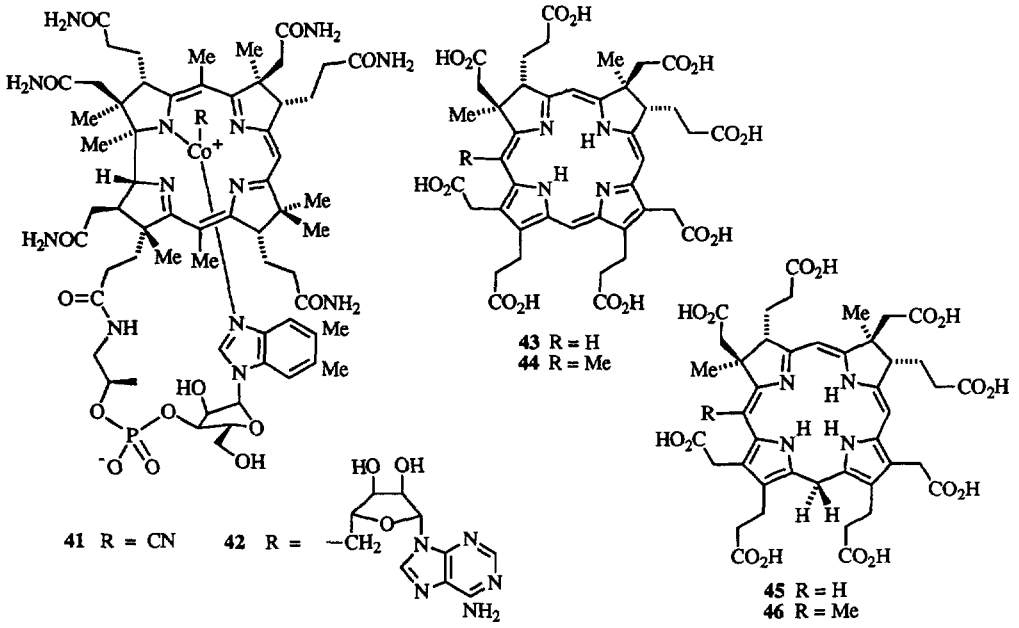
In parallel with these researches, we decided early in the 1970s to tackle vitamin B_{12} and the next section will illustrate with a few examples, the remarkable developments on that problem. However, before starting that new topic, this is the right point to emphasize that during the research on uro'gen III, on the other topics mentioned very briefly above and on vitamin B_{12}, our group had the great good fortune to be helped by a succession of three senior colleagues. They were, in chronological order, Ted McDonald, Chris Fookes and my present colleague, Finian Leeper. I am happy to have this opportunity to acknowledge publicly their great contributions to the tetrapyrrole team; they were invaluable. In addition, Chris Abell was the driving force bringing molecular biology into our group and I thank him very warmly for that important initiative.

Biosynthesis of Vitamin B_{12}

When one looks at the structure **41** of vitamin B_{12} (Scheme 12) it is clear that the discovery of how it is constructed in the living system represents a major challenge, probably one of the greatest; the corresponding coenzyme involved in the various enzymic reactions has the structure **42**. I have often compared this biosynthetic adventure to that of climbing Mount Everest. The full story of how the problem was solved is a huge one, far too large for the present article. My plan, therefore, is to leap over all the early experiments in which the framework of B_{12} was shown to be derived from ALA (**28**) and the added *C*-methyl groups from Nature's methylating agent, *S*-adenosylmethionine (SAM). All this work has been reviewed in, e.g., ref 35. The start here will be at the stage after vitamin B_{12} (**41**) and its late precursor in *Propionibacterium shermanii*, cobyrinic acid (**55**) (Scheme 13) had been shown to be derived from uro'gen III (**30**), as were heme and chlorophyll. Then we will follow how my group came to be involved with the first few *C*-methylated intermediates on the pathway to B_{12} and what we found out about them. Finally, we will focus on our contribution to the researches which solved the B_{12} biosynthetic problem carried out in a marvellous collaboration with a group of French biological scientists. The outcome was that the complete pathway to vitamin B_{12} was revealed and it will be illustrated at the end of this section. A full review of this very recent collaborative effort has been published.[36]

Comparison of uro'gen III (**30**) with cobyrinic acid (**55**) shows that at least the following steps will be needed for conversion of the former into the latter: (a) a series of *C*-methylations, (b) ring-contraction, (c) decarboxylation of the C-12 acetate residue, (d) cobalt insertion, (e) possible redox changes. These steps could be carried out in huge number of possible sequences so the problem facing us differed in kind from most of those in our work on alkaloids. There, knowledge of the simple building blocks often allowed reasonable proposals to be made as to the nature of later biosynthetic precursors. Clearly, this was not possible for vitamin B_{12} and therefore our effort aimed at detection of partly-built intermediates in the living system. In particular, we were seeking molecules carrying fewer *C*-methyl groups than does cobyrinic acid (**55**). So our antennae locked onto the reports from Vladimir Bykhovsky in Moscow that by growing *P. shermanii* in the absence of cobalt, mixtures of pigments were excreted which might be partly methylated substances;[35] he called them corriphyrins. Contact between Moscow and Cambridge then led to a powerful collaboration between the two groups. As a result, two pure pigments were isolated[35] from the mixture of corriphyrins and both turned out to be bis-lactones. It seemed probable that lactonization had resulted from aerial oxidation during handling of the materials. Indeed, by excluding oxygen from our incubations in Cambridge, the non-lactonized parents **43** and **44** were isolated and their structures determined[35] (Scheme 12). Satisfyingly, both were specifically incorporated in labelled form into cobyrinic acid (**55**) [35] by an appropriate soluble enzyme preparation from *P. shermanii*.

One might deduce from these results that two intermediates beyond uro'gen III (**30**) en route to cobyrinic acid (**55**) had been set in place. However, there was a further twist. *C*-Methylation of uro'gen III (**30**) should not lead to a change in the oxidation level of the product, yet **43** and **44** carry two hydrogens less than uro'gen III (**30**). The first evidence, and more has been added subsequently, that the true intermediates are the dihydro-forms of **43** and **44** came from direct isolation



Scheme 12.

from *P. shermanii* of **45**, the dihydro-form of **43**, followed by proof of its structure.[37] This and the corresponding reduced trimethyl system **46** were shown[37] to act as biosynthetic precursors of cobyrinic acid (**55**). Now indeed, two early precursors of vitamin B_{12} lying just beyond uro'gen III (**30**) were well established; they are now known as precorrin-2 (**45**) and precorrin-3A (**46**) (Scheme 12). The incorporation of the aromatized macrocycles **43** and **44** into cobyrinic acid (**55**) reported above is because they undergo reduction to the two dihydro-forms **45** and **46** in the incubation mixture.

For perspective, it is vital to emphasize that the work just outlined is like the tip of an iceberg; a huge amount of research in Cambridge from that period lies hidden. All the following topics are in that bulk below the surface: proof that **43** is identical to sirohydrochlorin, the prosthetic group of siroheme isolated by Kamin and Siegel; proof that acetic acid is eliminated during the ring-contraction process (also demonstrated by Duilio Arigoni); studies of decarboxylation of the 12-acetate residue and stereochemical work at that centre; origin of the hydrogens at C-18 and C-19; development of pulse labelling to reveal the order in which the eight *C*-methylation steps are carried out. These hidden studies have been fully covered in a review.[38]

Why from all this mass of work did I choose the topic outlined above? Firstly, because two important early intermediates were set on the B_{12}-pathway and secondly, to emphasize that, despite enormous efforts, no further new intermediates beyond precorrin-3A (**46**) could be detected in *P. shermanii*. Something new was needed to renew forward progress and the remarkable developments in genetics and molecular biology provided that fresh impetus.

The involvement of my group in this new phase started with an invitation around 1983–1984 from Dr Alain Rambach to act as consultant to his small company near Paris called Genetica. He had assembled a group of scientists skilled in genetics, molecular biology and enzymology and one of their projects was to work out the genetics of the B_{12}-pathway. I felt strongly that this approach offered real hope of moving forward again on the biosynthesis of vitamin B_{12} and, further, that chemical expertise would be an essential complementary component for the biological research if it was to have a successful outcome. So I jumped at the chance to make this scientific connection. One of the ways we helped Genetica in those early days was to invite one of their senior scientists to Cambridge to gain experience of the techniques we used in the B_{12} field, especially the handling of the known biosynthetic intermediates, making enzyme preparations from *P. shermanii* and carrying out incorporation experiments. This scientist was Francis Blanche; much will be seen of Francis and his colleagues in the papers referenced in the sequel. Some time later, Genetica was combined with Rhône-Poulenc Rorer and my connection with the B_{12} teams continued there, powerfully supported and encouraged by Jean Lunel. They were working on one of the organisms used for the commercial production of B_{12}, the aerobic *Pseudomonas denitrificans*. The biochemistry group was led by Francis Blanche, key members being Laurent Debussche and Denis Thibaut whilst that responsible for genetics was headed by Joel Crouzet, with Beatrice Cameron as his senior colleague.

There is a danger in my following, as requested, a personal thread through these collaborative researches that the reader could get a distorted impression of who did what. So I say clearly that the French effort was the

larger one during the recent period spanning the Paris–Cambridge collaboration. It is fair to say though that the chemical effort in Cambridge was also essential to allow the problem of B_{12}-biosynthesis to be solved by setting full structures on the biosynthetic pathway and by providing mechanistic understanding of key enzymic transformations. Each group needed the other and this outstanding collaboration led to dramatic advances.

Because of the very recent detailed review[36] of this joint work already mentioned, it is sufficient to outline here the studies on a short section of the pathway to show the approaches we used. Their work on genetics and molecular biology had provided the French group with relatively large quantities of a mixture of the enzymes necessary for the conversion of precorrin-3A (**46**) into hydrogenobyrinic acid (**53**) (Scheme 13) which in *P. denitrificans*, is the first corrin to be formed en route to vitamin B_{12}. They further showed that this conversion was dependent on having the reducing cofactor NADPH in the incubation mixture. The critical experiment was then carried out in which this same incubation of precorrin-3A (**46**) was run without NADPH; the reward was huge. A new yellow pigment was formed in place of the corrin (**53**) and when this new product was incubated in labelled form with the above assembly of enzymes now *with* NADPH, it was converted into hydrogenobyrinic acid (**53**). So after a long wait, a new biosynthetic intermediate was in hand.[39] They further showed that this intermediate carried three more methyl groups than precorrin-3A (**46**) (hence it is called precorrin-6A) and that these three methyls appeared at positions 1, 12 and 17 of hydrogenobyrinic acid (**53**) biosynthesized from it. Finally, precorrin-6A still carried an intact 12-acetate group and, remarkably, its oxidation level was two hydrogens fewer than that of the final corrin (**53**), so later reduction must occur.[39]

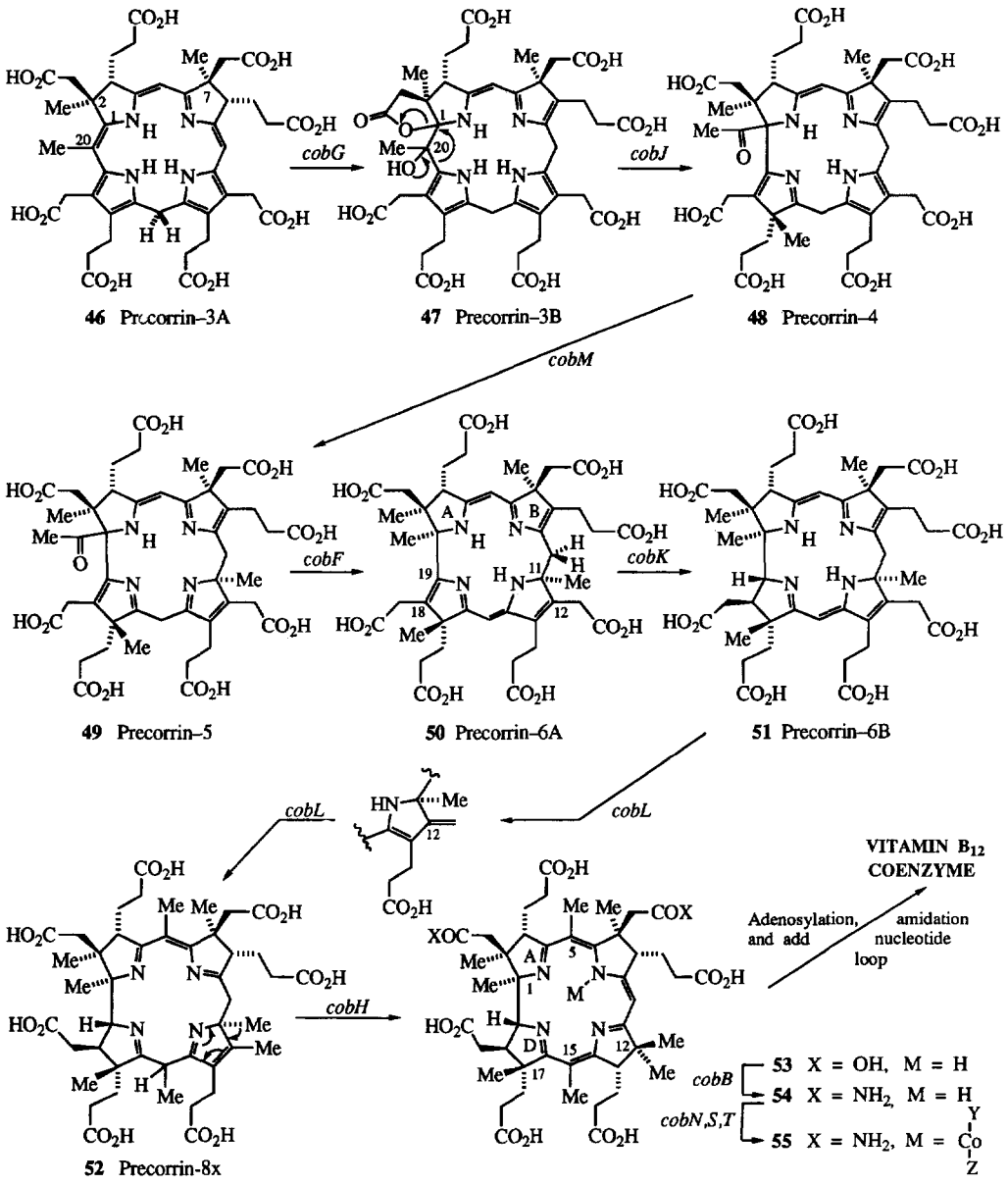
The full might of the French and Cambridge teams was then applied collaboratively to solving the structure of precorrin-6A which was available only in small amounts (ca. 500 μg). The plan was to biosynthesize three samples of precorrin-3A from three ^{13}C-labelled forms of ALA, one with ^{13}C at position 5 and the other two at C-4 and C-3, respectively; just the C-4 labelling is illustrated in Scheme 14 as **28b** for the [4-^{13}C]ALA, **46a** for precorrin-3A and **50a** for the precorrin-6A formed from it. These three labelled samples of precorrin-3A were then enzymically converted into precorrin-6A and for the latter two experiments, [*methyl*-^{13}C]SAM was used as cofactor for the stage forward from precorrin-3A. The resultant three samples of precorrin-6A, taken together, provided a ^{13}C-label at every carbon of the macrocycle. They were studied by ^{13}C NMR and by ^{1}H–^{13}C correlations to pick out ^{1}H–^{13}C couplings through up to three bonds.

The structure **50** (Scheme 13) so revealed[40] for precorrin-6A was a very surprising one and it changed our entire thinking about the way B_{12} is biosynthesized; indeed, this striking structure acted as the guiding light for everyone interested in this problem. Precorrin-6A told us that the ring contraction step is not a late one as had been thought and also, because of the oxidation level of **50**, an oxidation step must precede precorrin-6A and a reduction step must occur later on the pathway. Finally, the very surprising *C*-methyl group at C-11 of **50** is that which appears at C-12 in the corrin (**53**) and hence rearrangement must occur. The C-11 methylation also fits in with retention in precorrin-6A (**50**) of the C-12 acetate group. Notice that the C-11 methyl group prevents formation of a fully conjugated system which results in the pale yellow colour of precorrin-6A (**50**).

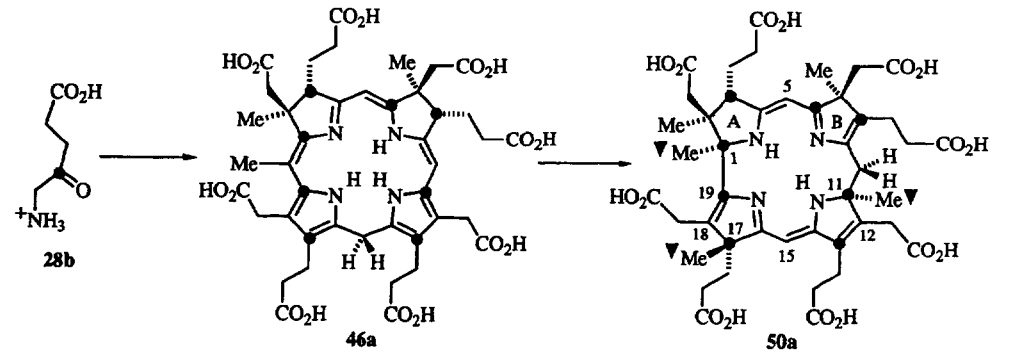
It is difficult in cold print to convey the intense excitement of this period of research. Labelled precursors, labelled products and spectra were shuttling between Paris and Cambridge. To find precorrin-6A (**50**) so startlingly informative was immensely satisfying to us all.

The breakthrough on precorrin-6A (**50**) was the start of remarkably rapid progress which revealed the complete pathway to vitamin B_{12}; this is shown in Scheme 13. I cannot give for all this research even a thumbnail sketch but the thread of our Cambridge contributions can be briefly followed. A fuller account and all the relevant references to the Paris–Cambridge work can be found in the detailed review.[36]

Following precorrin-6A (**50**), two more intermediates were isolated in Paris, precorrin-6B (**51**), the next B_{12}-precursor on the pathway, and precorrin-8x (**52**). Both these structures were solved[41,42] by our joint effort using exactly the same methods developed for the work on precorrin-6A. We also established[43] the regiochemistry and stereochemistry of the reduction step which generates precorrin-6B (**51**) from precorrin-6A (**50**). As with a jigsaw puzzle, things simplify as the whole picture starts to fill in and now new intermediates were being detected more rapidly in Paris; they were precorrin-3B (**47**), precorrin-4 (**48**) and precorrin-5 (**49**). Structural work on these three materials was carried out in Paris using the same approach based on ^{13}C-labelling and NMR we had jointly developed above. Our contribution from Cambridge to this stage of the research was confirmation of the C-1 location of the acetyl residue in precorrin-4 (**48**) by a combination of rigorous synthesis, ^{13}C-labelling and NMR.[44] Also, we carried out a mechanistic study[46] of the lactone-forming step, based on ^{18}O-labelling, by which precorrin-3B (**47**) is formed from precorrin-3A (**46**) (see below). By this stage, the relevant enzyme and the corresponding gene for every step of the biosynthesis of vitamin B_{12} shown in Scheme 13 had been established by the Paris–Cambridge researches. In addition, the structures of all the illustrated intermediates had been rigorously determined save one, precorrin-5. Partial structural information was available for it and this final structure was contributed by Ian Scott's group together with their study of precorrin-3B which interlocked with that published from Europe.



Scheme 13.



Scheme 14.

As adumbrated above, this intense interdisciplinary effort[36] allowed the full biosynthetic pathway to hydrogenobyrinic acid (**53**), and on via **54** and **55** to vitamin B_{12} and its coenzyme to be drawn (Scheme 13). The pathway could hardly have turned out in a more interesting way. Any organic chemist cannot fail to be impressed by the route Nature uses to fashion the complex B_{12} molecule drawing on relatively simple chemistry for each step.

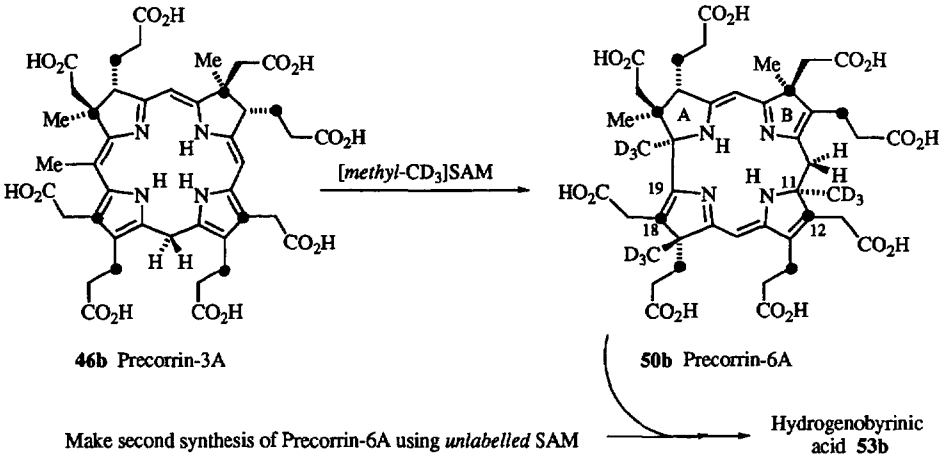
At this stage, our interests in Cambridge turned to several outstanding mechanistic questions and a number of the required enzymes were routinely overproduced in our group to afford large amounts of protein. The first question asked what is the nature of the rearrangement as the C-11 methyl group migrates to C-12 when **52** is enzymically isomerized to **53**. The way we solved this problem illustrates an application of ^{13}C-labelling differing from that used earlier. Previously, ^{13}C NMR was the analytical tool whereas now we planned to use mass spectrometry and the ^{13}C atoms were to cause a crucially important shift of mass. We aimed to test whether the methyl migration was an intramolecular rearrangement or not by a crossover experiment. In its simplest form, this work involved mixing roughly equal quantities of unlabelled precorrin-6A (**50**) with a sample of enzymically prepared precorrin-6A having deuteriomethyl groups (CD_3-) at C-1, C-11 and C-17. The hydrogenobyrinic acid (as **53**) formed from this mixture by the CobH enzyme would then be analyzed by mass spectrometry. If this product contained just two species, unlabelled **53** and its isotopomer carrying three CD_3-groups, then the rearrangement must be intramolecular. Any mixing of the unlabelled and labelled species in the hydrogenobyrinic acid produced would point to an intermolecular process being involved.

This simplest form of the crossover experiment could not, however, be used because the available enzyme preparation of CobH contained a large amount of endogenous hydrogenobyrinic acid (**53**) which would upset the mass spectrometric analysis. Therefore, $^{13}C_8$-precorrin-3A (**46b**) was prepared (Scheme 15) and from it two samples of precorrin-6A were enzymically synthesized, one carrying three CD_3-groups (**50b**) and the other with CH_3-groups. These samples were mixed in equal amounts and the mixture was enzymically converted into hydrogenobyrinic acid (**53b**) (Scheme 15). In this way, the mass spectrometric peaks from the materials of interest were moved eight units away from the huge peak corresponding to the endogenous hydrogenobyrinic acid, so giving us an unambiguous result. This was that the methyl migration is intramolecular[45] and is best viewed as a suprafacial 1,5-sigmatropic rearrangement. Remember that this migrating methyl group was derived from SAM and our very early work on vitamin B_{12} had proved[35] that of the two methyl groups at C-12 of the corrin ring system, it is the α-methyl which is derived from SAM. So it follows from the foregoing mechanistic study that the C-11 methyl group of precorrin-6A (**50**) is correctly assigned with the α-orientation.

The solutions to the other two mechanistic problems should also just be mentioned without details. For one, ^{18}O-labelling established[46] that as precorrin-3A (**46**) is oxidatively lactonized to form precorrin-3B (**47**), just one atom of ^{18}O is incorporated from $^{18}O_2$; the necessity for O_2 in this step had been demonstrated by the Texas group. Finally, we firmly established that the ring contraction process in *P. denitrificans* results in extrusion of acetic acid,[47] as had earlier been shown for *P. shermanii*.

I do not believe the problem of B_{12} biosynthesis could have been solved in any other way than by an interdisciplinary team highly skilled in genetics, molecular biology, enzymology, synthetic and structural chemistry, isotopic labelling and NMR spectroscopy. The members of the Cambridge group were happy to be involved in this deeply satisfying research.

Looking back over the personal thread running through this article, one can see how new approaches were invented for solving biosynthetic problems and also, at each stage, that techniques from the forefront of knowledge at the time in chemistry, spectroscopy



Scheme 15.

and biology were drawn into action. I hope the reader will recognize that this account gives a bird's eye view of the whole development of research on biosynthesis from a rather uncomplicated start of injecting simple ^{14}C-labelled precursors into plants through to the full sophistication of the experiments on vitamin B_{12} where chemistry, spectroscopy, enzymology and molecular biology were pulled together synergistically. Let me reinforce the message given at the beginning of my article. The interdiscipinary approach I have illustrated for exploring and using the chemistry of living systems has enormous potential. Many red-blooded young organic chemists will surely leap at the chance to be a part of this exciting field. I certainly hope so and no one knows what further remarkable advances lie ahead. Remember that it was curiosity about how plants build alkaloids that led me to study biosynthesis and I never dreamed at the outset that this adventure would eventually lead to research on uro'gen III, heme and vitamin B_{12} by the full panoply of chemical and biological approaches. All I can say is that it was and is a good time to be around.

It is not enough, however, just to be in the right place at the right time. As well as swimming in a nutritious scientific 'soup', one's personal environment needs to be right and in my case this could not have been bettered. The person responsible for it being so is my wife Margaret and I devote this final paragraph to her. She has been throughout the most important person in my life. Her warmth, energy, organizational skills and solid common sense have carried our family safely through every step we have taken together. In addition, she acts as secretary, horticultural adviser, crew for sailing and enthusiastic partner, not only for camping and hiking but for a vast array of joint activities including our love of classical music. A true friend and a wonderful wife, Margaret's contribution to what has been achieved scientifically is huge and certainly no less than mine.

Acknowledgements

I am glad to have this opportunity to record my warmest thanks and gratitude to all the postgraduate students and postdoctoral chemists who made up our group over the years. They had the courage and skills to join me in tackling the sometimes daunting problems posed by Nature's biosynthetic pathways. We enjoyed all the successes together and we climbed out of the hard times together; it was a joy to work with them and I am greatly indebted to all for what each one contributed to the group as a whole. Indeed, the award of the Tetrahedron Prize honours all the members of our team; their names are recorded in the full list of references. My senior colleagues must be included again here but the reader is referred to the main text where, at the appropriate places, their names are given with special thanks for their marvellous support. The biological aspects of our work in Cambridge depended on the senior biochemists and molecular biologists who joined our group. In chronological order they were Bruce Middleton, Clive Williams, George Matcham, Graham Hart, Peter Alefounder and Pat Stamford. I wish to thank them for their many contributions; their skills were of crucial importance for our researches. I also want to thank Katherine and Chris Abell, Finian Leeper and Pat Ingrey for their help with this manuscript.

For 1995, two Tetrahedron Prizes were awarded the one to me and the other to Ian Scott. It is very satisfying to us both, and fitting also, that these Tetrahedron Prizes have been made for the first time in the field of bioorganic chemistry. I also want to thank Ian for the friendly way in which we have cooperated in the preparation of our two articles.

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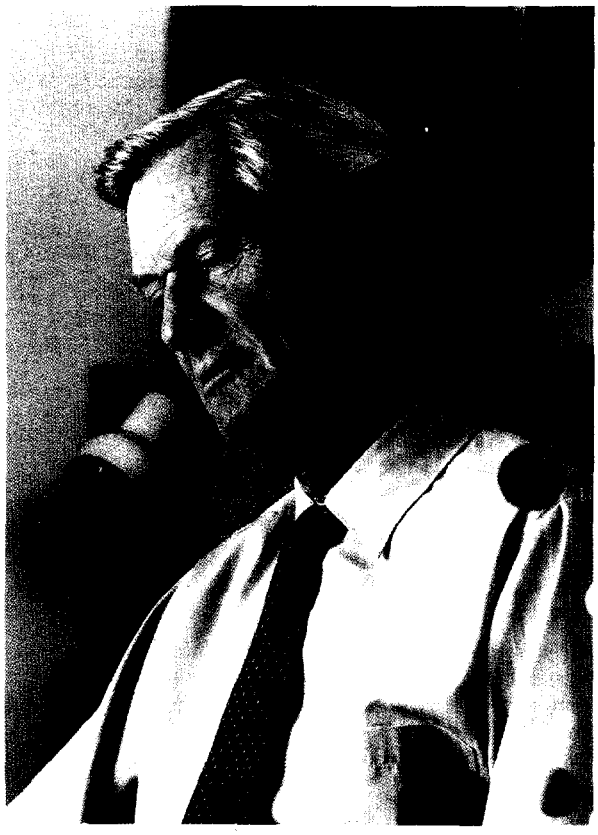
Biographical Summary



Alan Battersby was born in 1925. He studied at the University of Manchester, graduating B.Sc. in 1946. Then he moved to the University of St. Andrews and was awarded the Ph.D. degree in 1949 and was appointed to the faculty there (1948–1954). During that period, he gained a Commonwealth Fund Fellowship (1950–1952) for study in the United States with L. C. Craig at the Rockefeller Institute, then with H. E. Carter at the University of Illinois. He was appointed in 1954 at the University of Bristol and there his research on biosynthesis was initiated. In 1962, Battersby accepted a Chair at the University of Liverpool to be followed by the invitation in 1969 to a Chair at Cambridge, a position he held until 1988 when he was elected to the Cambridge 1702 Chair. He became Emeritus Professor in 1992 and continued both experimental research and his writing.

Battersby's research interests have been broadly concerned with the chemistry of living systems. Isolation work, structure determination, synthesis, isotopic labelling and spectroscopy, especially NMR, have been combined in these studies synergistically with enzymology and molecular biology. Four main themes can be picked out: (a) biosynthesis of the alkaloids and some terpenes; (b) stereochemical studies of enzyme catalysed reactions; (c) biosynthesis of porphyrins; (d) biosynthesis of vitamin B_{12}.

Awards and honours

Battersby has been awarded various honours including the Corday–Morgan Medal (1959), and the Tilden (1963), Hugo Müller (1972), Flintoff (1975), Pedler (1980), Longstaff (1984) Medals of the Royal Society of Chemistry and the Award for the Chemistry of Natural Products from the Society (1979). He was awarded the Davy Medal (1977) and the Royal Medal (1984) of the Royal Society and the Paul Karrer Medal (1977) and in 1978 and 1979, respectively, the Max Tischler Award (Harvard) and August Wilhelm von Hofmann Award (Germany). The Roger Adams Medal from the American Chemical Society came in 1983, the Havinga Medal from Holland and the Bakerian Lectureship of The Royal Society in 1984, the Antonio Feltrinelli International Prize (Rome), and the Robert Robinson Medal and Lectureship in 1986, the Adolf Windaus Medal and the Varro Tyler Award, Purdue, U.S.A. in 1987, the Wolf Prize (Israel) in 1989 and the August Wilhelm von Hofmann Memorial Medal (Germany) in 1992. One of the two Tetrahedron Prizes for Creativity in Organic Chemistry for 1995 represents the latest award.

He has been elected to the following Societies and Academies: Fellow of the Royal Society, London, 1966; Foreign Member of the Deutsche Akademie der Naturforscher Leopoldina, 1967; Honorary Member, Société Royal de Chimie, Belgium, 1987 and of the American Academy of Arts and Sciences, 1988; Foreign Fellow National Academy of Sciences, India, 1990 and of the Indian National Science Academy, 1993.

Invitations from abroad have come to him to deliver the following Named Lectures: Treat B. Johnson Lecturer, Yale, 1969; Pacific Coast Lecturer, U.S.A, 1971; Karl Folkers Lecturer, University of Wisconsin, 1972; First North-East Coast Lecturer, U.S.A., 1974; Andrews Lecturer, Sydney, Australia, 1975; President, Burgenstock Conference, 1976; First Middle Rhine Lecturer, France, Germany and Switzerland, 1976; Paul Karrer Lecturer, University of Zurich, 1977; Rennebohm Lecturer, University of Wisconsin, 1981; Morris S. Kharasch Lecturer, University of Chicago, 1982; Baker Lecturer, Cornell, 1984; Lady Masson Memorial Lecture, Melbourne, 1987; Atlantic Coast Lectureship, U.S.A., 1988; Elected to Federation of European Chemical Societies, Lectureship, Bologna, Italy, 1988; Nehru Centenary Lecturer, Central Drug Research Institute, Lucknow, India, 1989; Zaheer Memorial Lecturer, India, 1989; Seshadri Memorial Lecturer, Delhi, India, 1989; University of Auckland Foundation Lecturer, New Zealand, 1989; Marvel Lecturer, University of Illinois, U.S.A., 1989; Gilman Lecturer, Iowa State University, U.S.A., 1989; Kurt Alder Lecture, University of Cologne, Germany, 1991; University Lectureship, University of Ottawa, 1993; Dauben Lecturer, University of California, 1994; First Alexander Cruickshank Lecture, Gordon Conferences, U.S.A., 1994; Linus Pauling Distinguished Lectures, Oregon State University, U.S.A., 1996.

He has received Honorary Doctorates from Rockefeller University, New York (1977), and from the Universities of St. Andrews (1977), Sheffield (1986), Heriot-Watt (1987) and Bristol (1994). He was Knighted in 1992.