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Travels of an Organic Chemist Along Nature's Pathways†

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Prologue

In preparing this autobiographical account at the invitation of Professor Chi-Huey Wong, I decided that, rather than produce a chronological catalogue, I should try to convey the excitement of working with the biochemical machinery responsible for the synthesis of natural products. The result is a description of my encounters with the beautiful structures of nature,‡ first from the viewpoint of a synthetic organic chemist, next as an investigator of biosynthesis and finally, coming full circle, as a synthetic chemist interested in harnessing the power of molecular biology to the field of multi-enzyme synthesis. I also wish to impart a second message to my readers. This is a wonderful time in the history of chemistry to be able to explore the pathways of nature using recombinant DNA and NMR spectroscopy, together with the modern tools of analysis and synthesis, for the barrier between chemistry and biology is rapidly disappearing. It is my hope that these personal reminiscences will carry the clear signal that bioorganic chemistry has undergone a profound change in the last decade and that my chosen area, genetically engineered synthesis of natural products, has come of age.

Early Days

My first encounter with the world of chemistry was in my grandfather's pharmacy in Callander, Perthshire, in the 1930s where I watched him weighing out the ingredients for prescriptions from 19th century apothecary's jars, many of which were labeled in Latin. I was intrigued by the chemicals in the jars and the meaning of their inscriptions but had to wait until I had studied Latin and chemistry at school before their significance was revealed.§ On leaving school in 1945, my father, who was the dentist in our Ayrshire village of Beith, suggested that I might study pharmacy and arranged an interview at the Royal Technical College (now the University of Strathclyde) but some innate desire to learn more about the fundamentals of pure chemistry led me to enroll in the honours chemistry class at Glasgow University which turned out to be, for me, a much better choice. There I was fascinated by the first-year chemistry lectures, which were given by the senior professors and were accompanied by practical demonstrations in which organic and inorganic compounds were prepared by the professor's technician. In the freshman laboratory my demonstrators were Jack Dunitz and Sid Abraham, both of whom would go on to distinguished careers in X-ray crystallography.

In the second year, we studied organic chemistry and spent 15 hours a week preparing organic compounds from Gattermann's textbook, which was an excellent way of learning organic synthesis and, simultaneously, translation from the original German text. I also took the physiology class in the medical school, the only course which included biochemistry, and at once became intrigued by the connections between molecular structure and biological activity, tenuous and primitive as they were in 1946.

The courses at Glasgow contained material which I later found not only useful but unique for an undergraduate education, including lectures on the theory and practice of circular dichroism and X-ray diffraction, as well as practical micro analysis and the history of chemistry. In the third and fourth years, we spent 30 hours a week in the chemistry laboratory and there I had my first opportunity to carry out some original research on hydrocarbons with Geoffrey Badger, an

Key words: biosynthesis, alkaloids, vitamin B_{12}, genetic engineering, NMR.

†Dedicated to my mentors, Ralph Raphael, whose infectious enthusiasm for organic chemistry launched my career; Sir Derek Barton, my colleague, who taught me (and continues to teach me) so much about the scientific method and how to choose problems in research; and finally Albert Eschenmoser, whose work on B_{12} has been my inspiration and guide for 30 years.

‡Following the injunction of Sir Derek Barton that the article should not contain too many formulae, only a few structures representative of the natural products which I have studied for the last forty years are included, in chronological order, in schemes 1–4.

§I attended a rugby playing school whose first headmaster (1886) was the classicist R. Bruce Lockhart and, counting my school years, played for more than 20 seasons (1939–1962). I believe the game instilled in me a perseverance to try to succeed in spite of seemingly impossible odds, especially when playing against old rivals in Ayrshire Club Rugby including A. (Sandy) McKillop (a member of the Tetrahedron Executive Board) with whom I had little physical contact, since he was a wing three quarter and I was in the second row of the scrum.

Australian associate of the Professor, J. W. Cook. On graduation, I applied for a research grant and began my Ph.D. work with Cook, a formidable figure whose school of chemistry was already internationally recognized, and included J. D. Loudon, E. C. Clar, Geoff Badger, Bill Carruthers and Regina Schoental. I began with the synthesis of 4,5-dimethyl phenanthrene and was in the final stages when I received my first salutary lesson in research. We were scooped by the publication of Melvin Newman (*J. Am. Chem. Soc.*, 1949) but since our route was different, the paper was accepted by *J. Chem. Soc.*[1+] At that juncture, the department had just hired Ralph Raphael as lecturer, fresh from his synthetic successes (with Franz Sondheimer) in acetylene chemistry at Imperial College and fortunately, since Cook had by now assumed heavy administrative duties, Ralph took on several of his students to explore the possibility of synthesizing the natural tropolones whose structures had been postulated by Michael Dewar.

Soon, I became aware that our small but productive research team at Glasgow was involved in an international competition to synthesize naturally occurring tropolones as well as the hitherto unknown parent structure, tropolone itself. We had a formidable list of friendly competitors—Doering and Rapoport in the U.S., Erdtman in Sweden, the Cambridge group led by A. W. Johnson and from Japan, a veritable explosion of publications from Nozoe, whose fine work appeared in batches of 10–20 papers at a time. By the end of 1950, the group had prepared not only tropolone (Cook, et al. *J. Chem. Soc.*, 1950) but also the three isomeric thujaplicins[2] (α,β,γ-isopropyl tropolones) first isolated and structurally characterized by Erdtman from the heartwood of *Thuja plicata*.[‖] It was exciting for the entire Glasgow group to participate in the first tropolone symposium held in London in 1951, and I was particularly pleased that the pioneering work of Jim Loudon on colchicine was so well recognized at the meeting.

Postdoctoral Experiences

On graduation in 1952, J. W. Cook asked me if I would like to spend a postdoctoral year in the U.S.A. with Melvin Newman, who had just published his seminal work on the Newman Projection. I accepted, and Elizabeth and I sailed for New York on the Queen Mary. Since butter and tea were still rationed in Britain in 1952, the luxury of unlimited supplies of food (even below the waterline in tourist class) was memorable. We travelled to Columbus by train from New York and were met at the station by Newman himself, who was so relaxed and friendly that we immediately felt at home, especially since we shared a common interest in the music of Louis Armstrong.[¶]

The Newman Lab was at its scientific peak, and we enjoyed the freedom of life in the States and the friendship of the other postdoctorals including Geoff Eglinton, Derek Davenport, and John Tedder. I worked on the synthesis of equilenin analogues and completed the project begun by Geoff Eglinton in 1953.[5,6] I then had to make another decision, when I was offered a position as Research Officer in I.C.I. Nobel Division, as part of the military service still required of all post-war graduates in the U.K. Therefore we returned to Scotland and I spent a year in the explosives division working on rocket fuels which were tested in Woomera, Australia. This turned out to be a useful but dangerous experience, since several workers were killed by accidental detonations of nitroglycerine during my stay. I was, however, given permission to work on my own research in the evenings, and kept abreast of the literature in the library.

Having completed my national service obligations I had to choose between continuing in industry or returning to academia. As a graduate student I had learned the principles of conformational analysis and realized that D. H. R. Barton's (Birkbeck College) laboratory in London was fast becoming the most exciting place in Britain for natural product chemistry. I applied and was accepted as a Glaxo Fellow.

The Birkbeck laboratory was different from anything I had previously encountered. An international group of postdoctorals and graduate students working on a wide variety of structural and synthetic problems with Derek's office between the two main labs instantly changed my approach to organic chemistry. There was constant discussion of organic mechanisms fueled by lectures given by many international visitors. In addition to Derek's visits three times a day to ask what was new, I was challenged to solve many chemical puzzles offered by Karl Overton, Paul deMayo, J. B. Hendrickson and O. E. (Ted) Edwards.

[+]Superscripts refer to the publications list.

[‖]Many years later when I first met Shô Ito (a student of T. Nozoe), we discovered that our Ph.D. dissertations on thujaplicin synthesis were virtually identical, including the melting points of our crystalline derivatives.

[¶]Music, both classical and jazz, has always played a prominent role in our family life. I became fairly proficient on the tenor saxophone and by age 16 was playing in a small group at regular Friday and Saturday dances for troops stationed at local barracks during World War II. This experience turned out to be not only enjoyable but helped financially during graduate school. My love for the music of the jazz and swing era (1928–1958) had another bonus. During long evenings in 1961–1962, I was writing a book on the UV spectroscopy of natural products and listening to the 'Voice of America' jazz program hosted by Willis Conover. The book (Interpretation of the UV Spectra of Natural Products, Pergamon, London, 1964) was finally dedicated to W. Conover and L. Armstrong. Many chemists, not knowing of my love for Louis Armstrong's trumpet playing, thought that the dedication was to the chemist Armstrong (of the Armstrong– Bayer Theory). When I finally reached the New World, I was introduced to my musical hero by Melvin Newman. Later, I sent Louis a copy of the UV book and, in return, received an autographed photograph, one of my most cherished possessions. My participation in occasional faculty jazz ensembles also continued to provide relaxation with fellow scientists who were also amateur musicians, including John Postgate at Sussex and Harry Wasserman at Yale.

My lab partner (we each had 4 × 2 feet of bench space) was Dov Elad and we competed in tests of stamina. Dov arrived every day at 7:00 a.m. and I made it by 7:30. We seldom left before 8 p.m. I worked on the first Barton version of the aldosterone synthesis using retro-Michael chemistry to open ring D of a steroidal 11,20-diketone, followed by functionalization of the 18 methyl (→CHO) then reclosure. This system worked well but to our chagrin, after a long hot summer, we found that the stereochemistry had been inverted at C-14 on reclosure. Nevertheless, with André Campos-Neves we completed the synthesis of the unnatural analogue.[7]

On his retirement, J. W. Cook's chair at Glasgow became vacant and Derek accepted the call to move into a much larger department with room for 40 or more co-workers, so we packed everything into a large van and moved north.

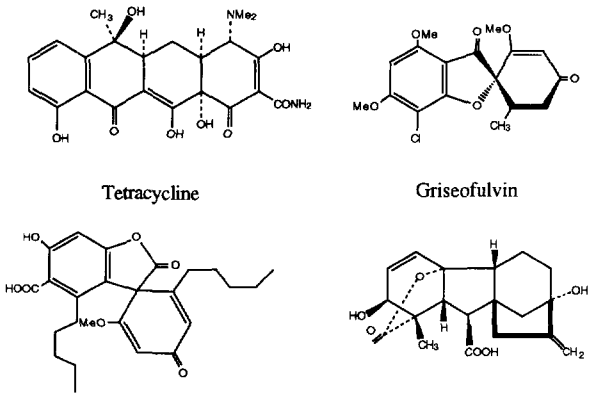
Back in Glasgow we had a fresh influx of postdoctorals including W. C. Taylor (Sydney), Andrew Kende (Harvard), Ted Cohen (USC), and Jacques Levisalles (Paris). It was an exhilarating experience to see the rejuvenation of natural product chemistry at Glasgow. The crystallographic group (J. M. Robertson and his students, Struther Arnott and George Sim) was also drawn into the excitement of the structural determination of natural products. At the same time, Ted Cohen collaborated with Derek on a critical survey of phenol oxidative coupling which was to become the touchstone for my first independent research. It was also at this point that I decided to begin experiments as soon as possible on biogenetic-type synthesis via oxidative coupling. This transition was further reinforced by the opportunity to work on the two of H. Raistrick's mould metabolites from *Aspergillus*, geodin and erdin, whose structures revealed a biogenetic origin of phenol coupling.[8] In 1957, Derek was recalled to the Hoffman Chair of Organic Chemistry at Imperial College and I had to decide whether to accept the offer of a lectureship in London or take my chances in Glasgow.

Glasgow (1957–1962)

After much heart searching, including a month at Imperial College, helping to set up the Barton group in the Whiffen Laboratory, I eventually decided to go back to Glasgow where Ralph Raphael had just been appointed Regius Professor on his return from Queens University. Ralph's firm but kindly control of the Chemistry Department made it possible for his younger faculty members to pursue their own research and also to collaborate with him on his many synthetic projects. So I was fortunate in being able to direct a small but enthusiastic group of graduate students including Tom Money and Douglas Young, and with funding from Glaxo, a number of postdoctoral fellows (A. C. Day from Oxford and M. B. Meyers from the U.S.) and with the return of Frank McCapra from Johns Hopkins, the compact team began to explore biomimetic synthesis of natural products.[9] We began with phenol oxidation to synthesize griseofulvin[12] and picrolichenic acid[13] and then moved on to the tetracycline antibiotics with Colin Bedford, who discovered a high yielding insertion of oxygen to convert anhydrotetracyclines into the full tetracycline structure,[20] following the presumed biosynthesis. In collaboration with George Sim we solved the structure and stereochemistry of gibberellic acid[18] (Scheme 1). My long-standing interest in circular dichroism also led to the construction of a manual CD instrument based on the original model of Stotherd Mitchell, which had been in the department since 1930, but had never been used to explore the chirality of natural products. We chose cafestol as the first project, and were able to assign the absolute configuration,[19] thereby leading to revision of stereochemistry for several deterpenoid families.[26] During our many blackboard discussions on terpenoid chemistry, we were often joined by Bob Ramage, then a graduate student, who, twenty five years later, was to succeed me as Forbes Professor at Edinburgh. These were halcyon days, for the rigorous experimental training at Glasgow ensured a supply of excellent co-workers.

Vancouver (1962–1965)

Work was progressing well and by 1962 we had completed the tetracycline project and had started a biogenetic-type synthesis of colchicine. I had begun to think about a return to North America, when an advertisement in *Nature* caught my attention and I applied for a position at the University of British Columbia in Vancouver. The interview for the professorship took place in London, and consisted of a one-to-one encounter with Charles McDowell, Head of the Chemistry Department at UBC. I accepted his offer without ever seeing Vancouver and in August 1962 the entire family once again embarked on a voyage, this time lasting three weeks, from Southampton to Vancouver on the S.S. Orsova. This was not so tedious as it sounds for we called at Lisbon, Bermuda, Jamaica, Panama City, Los Angeles, and San Francisco on the way to Vancouver. On our brief stop in Jamaica, I met my old friend Willie Chan (a previous Barton postdoc)



Glasgow 1957–1962

Scheme 1.

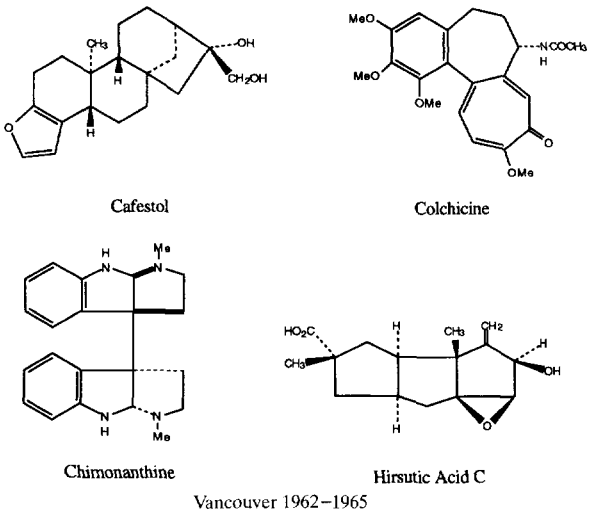
at the Mona Campus and, within a few hours, had decided that we should launch a series of natural product symposia in Jamaica beginning in January 1966. These were very successful and continue to this day to attract an international audience.

The challenge of setting up a new laboratory 6000 miles from Glasgow and at the same time teaching both undergraduate and graduate courses was met by the rapid establishment of an active research team consisting of Frank McCapra, Douglas Young, and, the following year, Tom Money. The setting of UBC was idyllic, with fine views of the mountains and the Pacific. The chemistry department was expanding rapidly and although the University had lost Gobind Khorana and Jack Halpern just before we arrived, my young colleague Neil Bartlett discovered the new chemistry of xenon and there was excitement and enthusiasm in the air, combined with excellent facilities for research and several first-rate Canadian graduate students. The time seemed propitious to begin our first experimental work on biosynthesis, since we were nearing the completion of the synthesis of colchicine based on an oxidative coupling hypothesis[11,21,35] and it became important to test our biogenetic theories with real experiments.

One of the most exciting topics in the early 1960s was the origin of the so-called 'C-10' unit of the indole alkaloids for which three plausible, but mutually exclusive theories had been proposed. The first was the 'Woodward fission' concept in which the ring of an aromatic amino acid is cleaved to form the ubiquitous 'C-10' pattern found in the corynanthé-strychnos alkaloids. A second idea, which had already received some indirect experimental support, was a modified polyketide pathway. The third theory had been developed independently by Ernest Wenkert and Bob Thomas and involved the C—C cleavage of a monoterpenoid of the iridoid family to provide the C-10 segment of the alkaloids directly. The fragment could then combine with tryptophan and by subsequent rearrangement afford the more complex *Aspidosperma* and *Iboga* patterns, but in spite of several attempts, the monoterpenoid theory had not received experimental support. In 1964, I attended the IUPAC Natural Product Symposium in Kyoto, where Sir Robert Robinson expressed keen interest in this problem and characteristically threw down the gauntlet in favor of the polyketide pathway. Challenged by the conflicting theories we decided to enter the arena and, since this was to be our first experience of the intricacies of plant feeding, looked outside the Chemistry Department for a source of biological material. We chose to work on *Catharanthus roseus*, the tropical periwinkle, from which the anti-tumor dimeric indole alkaloid vinblastine had been isolated by W. Noble and C. T. Beer in Toronto. Fortunately, Noble and Beer had recently moved to the Cancer Institute at UBC and were extremely helpful in providing us with plants, which Ian Wright fed hydroponically with 2-^{14}C-mevalonate. After recrystallization of the isolated vindoline to constant radioactivity, we found that the incorporation was positive and immediately realized that the entire family of indole alkaloids (today numbering nearly 2000) were monoterpenoids.[32] At this juncture we were joined by Alan Battersby and Duilio Arigoni and when intact incorporation had been established by degradation,[36] we exchanged manuscripts and published independently and simultaneously. So began a fine working relationship, and throughout the work on the alkaloids we exchanged data prior to publication. Looking back, this single, successful experiment changed forever my philosophy about the future direction of research, and strengthened my determination to find out in detail how natural product structures were assembled, using every possible physical technique which might cast light on the metabolic machinery which lay at the heart of nature's design.

Sussex (1965–1968)

In order to prepare for this new endeavour, Tom Money began the synthetic assembly (via condensed polypyrones) of linear polyketide structures which by cyclization could not only serve as models for aromatic biosynthesis but, if properly constructed, could correspond with the natural events leading to the actual intermediates of acetate–malonate polymerization.[31,37,43] In the alkaloid field, the oxidative dimerization of *N*-methyl tryptamine provided the biomimetic one-step synthesis of the hexacyclic calycanthine–chimonanthine manifold[24] (Scheme 2). Now came the offer of a Chair in the U.K. at the new University of Sussex, and we returned to England to set up a laboratory which combined organic chemistry with facilities for plant and bacterial cultures, together with excellent spectroscopic equipment. Life in Sussex was pleasant and many graduate students and postdoctorals (including K. Fukumoto, A. Terahara, and M. D. Bachi) came to work on diverse problems, including alkaloid,[39,47,61–63,68] polyketide,[51,58] and terpenoid biosynthesis. We also continued CD studies on natural product sterochemistry, including the taxane family[67] (before the discovery of taxol itself) as well as deriving rules (with Tony Wrixon) for determining the absolute



Vancouver 1962–1965

Scheme 2.

configuration of olefins.[52,64–66] However, in my administrative role as Chairman of the School of Molecular Sciences I felt that I was losing some of the day-to-day, hands-on contact with the laboratory which, from the beginning of my independent career, had always been my *modus operandi*. I also began to miss some of the excitement of North America where the peer-review system for funding had always seemed to me a fair, if challenging, yardstick for self-evaluation. I also welcomed the opportunity to work long hours without interruption by meetings and the accompanying bureaucratic tasks. So after much thought and discussion, I decided to accept an offer from Yale and in 1968 our family embarked again for New York, this time on the S.S. United States.

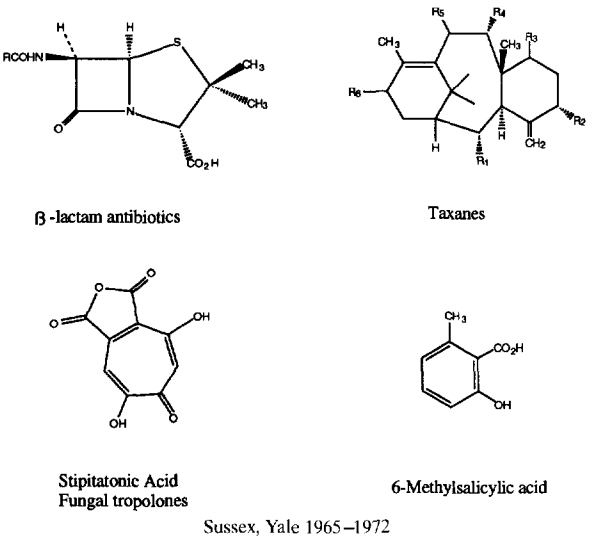
Yale (1968–1977)

At Yale we set up fermentation laboratories in the Sterling Laboratory and quickly established a good working relationship with Bob Cushley in the Medical School, who had just constructed an instrument for FT NMR spectroscopy, one of the earliest facilities available for what is now a standard technique.

While at Sussex we had laid the theoretical and experimental basis for the three main themes which were to continue for the next thirty years. These were the biosynthesis of porphyrins and corrinoids, indole alkaloids, and antibiotics (polyketides and β-lactams).

The conscious decision was made to move away from feeding experiments to cell free systems (and eventually the purified biosynthetic enzymes) so that we could study selected reactions of the biosynthetic pathways by NMR. That was the grand plan, but as we shall see, it was by no means easy to translate into practice. First we had to establish the overall pathway by classical incorporation, then search for intermediates and the enzymes which connected them to the target. As always in research, everything depended on the skill, enthusiasm and perseverance of my young colleagues. Perhaps the enormous challenge of vitamin B_{12} biosynthesis raised the level of our performance. In the event, with Masa Kajiwara, Kuni Okada and Craig Townsend we were able to succeed, using ^{13}C NMR enrichment as our structural guide, in finding the porphyrin–corrin connection by showing that uro'gen III is the ubiquitous precursor, not only of heme and chlorophyll but also of the corrin nucleus[89] and we could count the number of C-methyl groups (seven) inserted by $^{13}CH_3$-methionine into B_{12}.[90] Now it seemed that everything would fall quickly into place, for Boris Yagen had found the way to make a cell free system from *Propionibacterium shermanii*,[97] which produced cobyrinic acid, and with this advance we felt that most of the intermediates would emerge by classical isolation studies.

While the B_{12} group was making rapid advances, our other projects were also moving along (Scheme 3), and Eun Lee found the aromatic precursor of the fungal tropolones,[73,84] stipitatic and puberulic acids. Gareth



Sussex, Yale 1965–1972

Scheme 3.

Phillips and Les Beadling purified 6-methylsalicylic acid (MSA) synthase[81] and used *N*-acetyl cysteamine derivatives for substrate incorporation and inhibition studies of polyketide synthesis,[103] while Charles Wiesner developed models for the polyketide synthases,[126] and L. Zamir showed that patulin was derived from an aromatic precursor.[92] C.C. (Jim) Wei discovered a working mimic of the putative hetero Diels–Alder reactions of indole alkaloid biosynthesis[85–88] and it was gratifying to see that these early models, featuring the production and rearrangement of the acrylic ester–dihydropyridine system, were later brought to synthetic reality by F. Ziegler and M. Kuehne. Paul Reichardt, Jim Sweeny, and Mike Slaytor defined the early stages of indole alkaloid biosynthesis by pulse-labelling of young seedlings.[78] We also labored long and hard in the field of β-lactam biosynthesis[113,133] (with S. K. Chung and Eric Gordon), searching for reagents which could transform tripeptides into penicillin-like structures. Although S.-Y. Yoo discovered a high-yielding ring closure to β-lactam structures, based on the unusual chemistry of peptide hydroxamates,[133] the development of an efficient chemical process for the cyclization of δ-aminoadipoyl-cysteinyl-valine to iso Penicillin N continues to elude us to this day. Nature's secret for this process is of course locked in the structure of isoPen N synthase (IPNS) and still remains cryptic.

By 1975, the main thrust of the laboratory had undoubtedly become the enzymology of natural product biosynthesis, but in spite of a great deal of isolation and synthetic work, the B_{12} intermediates had not revealed themselves. Quite unexpectedly a break in the clouds appeared in the form of a tentative structure for sirohydrochlorin published by Lewis Siegel and Howard Kamin (Duke University). This was a bis-methylated isobacteriochlorin, which if written in slightly different form from that proposed, would correspond exactly to the insertion of two new methyl groups on the uro'gen III template. Although it

seemed at first inconceivable that sirohydrochlorin, part of the machinery for the 6-electron sulfite and nitrite reductases, could also be a B_{12} intermediate, we collaborated with Siegel and Tony Irwin isolated 200 μg of pure sirohydrochlorin from 5 grams of *Escherichia coli* sulfite reductase. This was sent to Jim Shoolery at Varian who kindly dedicated 11 days of his Christmas vacation to the acquisition of 10^6 transients on his FT-80 instrument. The structure,[148] which was finally solved by incorporating ^{13}C biosynthetically, corresponded exactly to that of Factor II just isolated by Gerhard Müller from cobalt-free extracts of *P. shermanii*. Most importantly, factor II was an excellent precursor of cobyrinic acid in the cell free system, so at last we had a new intermediate. Using the same approach of ^{13}C enrichment from the building block 5-aminolevulinic acid (ALA) with Gerhard Müller we were able to solve the structure of the next intermediate, Factor III,[106] which remarkably bears its third SAM derived methyl group on the western carbon (C-20). This discovery altered our cherished, earlier views on the ring contraction mechanism,[149] since the structure of factor III dictated that a 2-carbon unit had to be lost on the way to B_{12}. Concurrently, Alan Battersby had solved the structures of Vladimir Bykhovsky's corriphyrins which were identical to Factors II and III.

Preliminary studies with Tony Irwin[182] had suggested that acetic acid was the two-carbon unit excised during or after ring contraction, but there were considerable difficulties in reproducing the result, for although there was no doubt that acetic acid could be isolated (Arigoni; Battersby), we constantly wondered if the 'biochemical' C-2 species was, in fact, acetaldehyde, which could be transformed to acetic acid by oxidative enzymes present in the cell-free extract, a point which, in my opinion, remains to be resolved, especially in view of G. Müller's experiment in which acetaldehyde was trapped in situ. Thus, while there is ample and clear cut evidence that acetic acid is extruded during aerobic biosynthesis of B_{12} in *Pseudomonas denitrificans*, the pathway in anaerobic bacteria is different in several important aspects, including early insertion of cobalt, and may indeed involve a completely unexpected mechanism of ring contraction.

We had now reached 1977, another year of decision about future directions. Although the isolation of the two new B_{12} intermediates was satisfying, there seemed no logical way to solve the key problems of ring contraction and the isolation of the later intermediates. We had by now built up a strong enzymology group in order to study the entire B_{12} pathway from the beginning, one enzyme at a time, starting with PBG deaminase and uro'gen III synthase (cosynthetase), since these were readily available from the heme pathway in *E. coli*. and from photosynthetic bacteria.

Concurrently, S.-L. Lee had established the first cell free synthesis of the indole alkaloids,[127] and we isolated the enzymes leading to strictosidine, ajmalicine and geissochizine.[143,147,164,167] The quest for a probe to study the mechanisms of our newly discovered enzymes at the structural level required the synthesis of ^{13}C-labelled substrates, and we realized from the outset that the key to the successful observation of fleeting intermediates (sometimes on the surface of the enzyme) was a dedicated high field NMR instrument, rather than the necessarily restricted use of the departmental machine.

Texas A&M (1977–)

At this juncture, a solution to our instrumental requirements as well as the opportunity to build a truly interdisciplinary laboratory presented itself in the form of an offer to join the Texas A&M faculty with a serious commitment to establishing state-of-the-art biological and NMR facilities which, in combination with a suite of organic laboratories, would make it possible to combine all three of our major interests in one center.

So far, this was the hardest decision of my career, because I enjoyed the stimulation of a first rate department as well as the cultural activities at Yale. As a fellow of Davenport College, I found the far ranging discussions on medicine, philosophy, drama, and music with my colleagues a most rewarding experience.*

Yet the opportunity and freedom to explore the interface of chemistry and biology through the eyes of NMR spectroscopy was hard to refuse. The transition turned out to be remarkably smooth, however, and once installed in our new laboratories, we began to examine covalent complexes of the biosynthetic enzymes with Peter Jordan and Gerardo Burton. We also introduced living cells into the NMR tube to study aerobic and anaerobic porphyrin biosynthesis in *Rhodobacter spheroides* and, in order to prepare for the work with the biosynthetic enzymes, we chose to work[163,178] with the serine and thiol proteases. In this way, we became proficient at detecting new species at millimolar concentration of enzyme and substrate and found the first intermediate in the process catalyzed by PBG deaminase,[161,162] which turned out to be a linear tetrapyrrole which cyclized chemically to uro'gen I and was also the substrate for the next enzyme on the heme–corrin pathway, uro'gen III synthase (cosynthetase) which brings about the remarkable intramolecular rearrangement leading to the unsymmetrical type III urogen, the precursor of all natural porphyrinoids and B_{12} (see Figure 1).

Here again, we found ourselves in friendly rivalry with Alan Battersby's group, yet the approaches were different, and in view of the complexity of the problem, it was valuable and important to have reached the identical conclusions independently.

*Where else would I have informally met visitors such as Dorothy Hodgkin, Anna Freud, Thornton Wilder, and Dizzy Gillespie or experts on Boswell and Johnson (Fred Pottle), rare books (Fritz Liebert), economics (Jim Tobin), protein structure and biochemical mechanisms (Fred Richards and Joe Fruton) and drug addiction (David Musto; who also provided much new insight into the Sherlock Holmes genre).

Edinburgh (1980–1982) and the return to Texas

In 1980, after twelve happy years in the U.S., the Forbes Chair of Organic Chemistry at Edinburgh became vacant when John Cadogan joined B.P. I had not previously considered returning to the U.K. but the opportunity to give back something to Scotland in return for the excellent education traditionally provided to Scottish children, tinged with nostalgia for the Scottish way of life and the memory of the generations of excellent students I had encountered at Glasgow swung the balance in favor of making the return. A suite of laboratories in the Kings Buildings was refurbished with first rate NMR and biological facilities so that, with little down-time, we resumed operations. With Paul Malthouse we began a series of cryoenzymological NMR experiments which allowed detection of covalent intermediates of the serine and

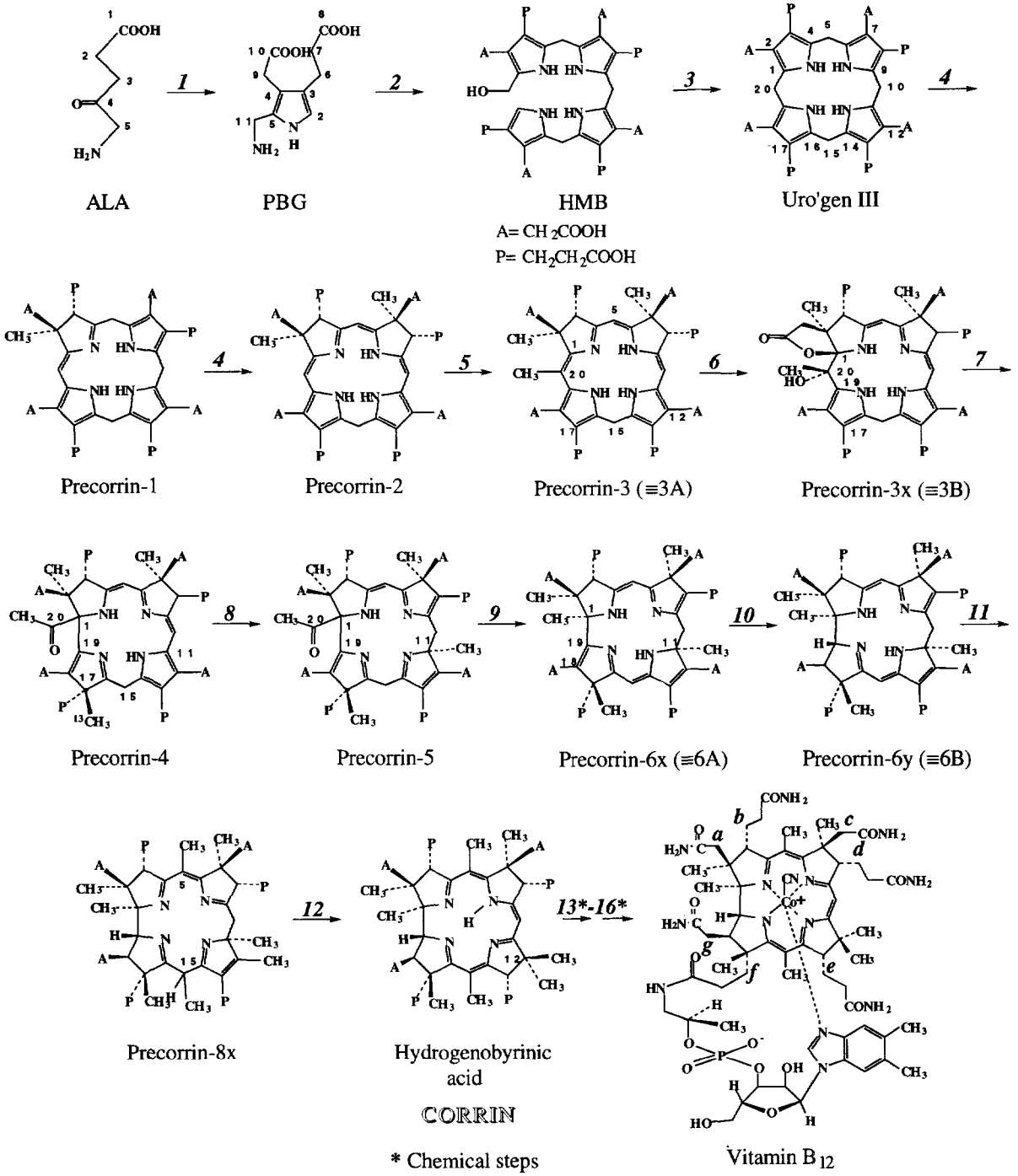
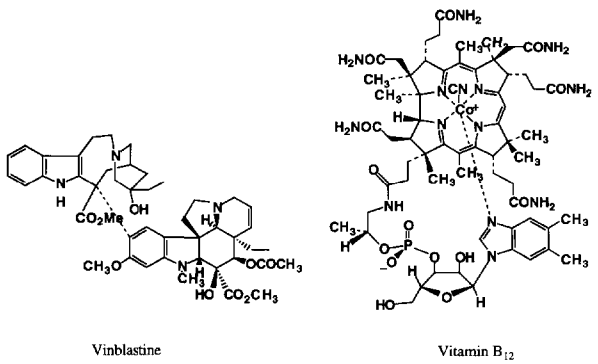


Figure 1. 1. ALA dehydratase (*hemB*); 2. PBG deaminase (*hemC*); 3. Uro'gen III synthase [cosynthase] (*hemD*); 4. Uro'gen III methylase [M-1] (*cysG*/*cobA*); 5. M-2 (*cobI, cbiL*); 6. Precorrin-3x synthase (*cobG*); 7. Ring contractase/17 methyl transferase [M-3] (*cobJ*); 8. M-4 (*cobM*); 9. M-5 (*cobF*); 10. Reductase (*cobK*); 11. Precorrin-8x synthase (M-6/decarboxylase) (*cobL*); 12. [1,5]-Sigmatropic shiftase [hydrogenobyrinic acid synthase] (*cobH*); 13. Insert Co; 14. Esterify; 15. Add nucleotide; 16. Ammonolysis.

thiol proteases at sub-zero temperature in 40% DMSO. Our NMR acquisition times became 24 hours instead of 30 minutes and we could observe and characterize several transient species corresponding to acyl[201,204] and thioacyl[192,200] enzyme substrate complexes as well as the structures of ^{13}C-enriched inhibitors bound to enzyme.[194,219,228,229] This valuable experience was to stand us in good stead when we began work with the B_{12} enzymes. Although the facilities were superb and my colleagues enthusiastic, the professional satisfaction was offset by the feeling that although little had changed since we left Scotland for Vancouver in 1962, we had become accustomed to the North American way of life and our children were now grown, with independent careers in the U.S. Contrary to our initial expectations, we soon realized that our stay was going to be temporary. On a brief visit to Texas A&M, I was invited to come back to my original laboratory, which had remained unoccupied and, although I had resigned my position with every intention of staying in Edinburgh, the Texas A&M administration made it clear that they would welcome my return. Since I had been able to transfer my NIH funding to Scotland the reverse transition was remarkably smooth and our laboratory reopened as a Center for Biological NMR, with greatly improved NMR facilities. With the recruitment of young faculty and an influx of new graduate students, bioorganic chemistry flourished at A&M. The search for B_{12} intermediates and the biosynthetic enzymes continued as did the work on enzyme mechanism, [214,215,219,228,229,235] and indole alkaloids[199] (begun with S. L. Lee, T. Hirata, M. Hasan and R. L. Baxter) (Scheme 4). This was again a period of consolidation and preparation for what was to come later.

Now came the most important decision of my professional career, beside which all of our moving between countries pales into insignificance. In 1987, I decided to introduce molecular biology into the laboratory so that we could hunt for the genes encoding the elusive enzymes of the entire B_{12} pathway.

In my experience, just as they must learn spectroscopy and molecular modeling, organic chemists quickly adapt to the cloning and overexpression techniques of molecular biology, regarding them as a set of powerful tools necessary for the acquisition of enzymes for synthetic and mechanistic studies. Thus, in the early days, we depended on 15–20 liter fermentations followed by tedious, multi-step purification to obtain a few milligrams of precious enzyme. Now a rapid clean up of protein from one liter of engineered *E. coli* cells provided multi-milligram quantities of almost pure enzyme.



Vinblastine Vitamin B_{12}

Yale, Texas A&M 1968–1996

Scheme 4.

By early 1988, we had assembled the multi-disciplinary team for the final assault on the B_{12} problem. The molecular biology section was in the capable hands of Charles Roessner, experienced in gene technology, while Howard Williams supervised the smooth running of the NMR instruments with Yanding Gao, and Neal Stolowich brought valuable experience in enzymology and the NMR analysis of complex molecular structures. The synthetic tetrapyrrole team of Patricio Santander, Clotilde Pichon, and Mario Gonzales was joined by another generation of postdocs, including Peter Karuso from Sydney, and Martin Warren and Joe Spencer from Peter Jordan's group in the UK. The full account of how the genes for porphyrin and corrin biosynthesis, from both anaerobic and aerobic organisms were identified, cloned and expressed has been given elsewhere.[306,334,340] Suffice it to say that the rate of progress accelerated exponentially** so that by early 1994 we had assembled all of the necessary biosynthetic enzymes to make B_{12}; uncovered the structure of the unique dipyrromethane cofactor attached to a cysteine residue in the polymerizing enzyme, porphobilinogen deaminase [250,256,295] (independently revealed by the works of Alan Battersby and Peter Jordan), discovered the unique role of molecular oxygen in the aerobic pathway to corrins,[313,319,325] and, step by step, had literally watched each new precorrin intermediate being formed by on-line ^{13}C NMR spectroscopy. Now we were ready to attempt the ex vivo reconstitution of

**At this juncture (1988–1994) we were joined by another major laboratory in the search for the missing B_{12} intermediates, when Rhone-Poulenc (Paris) described a genetically-engineered strain of the aerobe, *Pseudomonas denitrificans* and isolated the eight gene cluster necessary for the conversion of precorrin-2 to the cobalt-free corrin, hydrogenobyrinic acid (HBA; Fig. 1). Using cell-free extracts from engineered strains of *P. denitrificans*, the French group demonstrated the conversion of ALA to hydrogenobyrinic acid (HBA). In our approach, which we have termed genetically engineered synthesis, all of the 12 enzymes necessary for synthesis are separately overexpressed by heterologous gene transfer and then combined to give the product. In this way all extraneous metabolic trafficking and 'background' from the host strain are eliminated. By removing NADPH from their system, a new intermediate, precorrin 6x (≅6A), was discovered and its structure elucidated by Alan Battersby's group as described in the accompanying article. This opened up the way to find the remaining intermediates, 6y (≅6B) and 8x on the way to HBA. Our laboratory concentrated on the gap between precorrin-2 and 6x, and we were able to delineate the details of the ring contraction mechanism (precorrin-3→3x (≅3B)→4) as well as the final intermediate precorrin-5 which is converted to 6x by loss of acetic acid and C-methylation (see Fig. 1). Thus, the problem of corrin synthesis was solved by the joint efforts in Texas, Cambridge, and France, thanks to the use of biosynthetic labelling and structural analysis using ^{13}C-enriched substrates, combined with molecular biology, as described in further detail in Alan's article.

the entire pathway from ALA to corrin, shown in Figure 1.

The *dénoument* came in the Summer of 1994 with the 17-step synthesis of cobalt-free corrin (HBA) using 12 enzymes in a single reactor, which represented >90% yield for each of the steps, starting with the 5-carbon building block, ALA, and completed in 16 hours.[333]

We had indeed come full circle from synthetic chemistry through natural product biosynthesis, and then, via molecular biology back to total synthesis, only now using the biosynthetic enzymes as catalysts to prepare complex structures overnight in single-flask, multi-enzyme reaction sequences.[337]

The implications of this result for the total synthesis of many classes of natural product has now become apparent and our current research is directed towards the heterologous transfer of biosynthetic genes from plants to bacteria,[292] to expedite the genetically engineered synthesis of rare natural products which until now have only been accessible from plants, frequently in low yield. Although time-consuming, this approach must lead logically to the discovery of the complete set of genes, perhaps fifteen to twenty, required for the synthesis of a complex alkaloid or terpenoid structure, and will allow the in vitro synthesis of the target molecule with perfect stereochemical fidelity. This new discipline is, of course, complementary to synthetic organic chemistry since at present only the natural products and their biosynthetic intermediates are the targets of choice. However, it is clear from recent work in the polyketide field that the mixing and matching of genes from several different sources can be harnessed to synthesize 'unnatural' natural products, thereby adding a new approach for increasing molecular diversity.

Epilogue

From my personal viewpoint of natural product chemistry,[††] this is the most exciting time to be working at the chemistry–biology interface and the award of the Tetrahedron Prize is not only a signal honor, but most importantly, is testimony to the perseverance and hard work of my younger colleagues, who made the dream come true. It also seems entirely appropriate that two Tetrahedron Prizes were awarded this year for work on biosynthesis, especially that of vitamin B_{12}, for although this account is based on my own research we have not been alone in the long and arduous search for the elusive intermediates of the B_{12} pathway and it gives me great satisfaction that both Sir Alan Battersby and myself were selected on this occasion, since our contributions, frequently employing different approaches, have been complementary, yet inseparable and I would like to take this opportunity to thank Alan for his friendly exchange of views during the preparation of our articles. In fact, I do not believe the B_{12} problem could have been solved independently within a single scientific lifespan, especially since we are now confronted with the mystery of a different, anaerobic pathway to the vitamin, a problem which is turning out to be just as fascinating as the route which employs molecular oxygen.[341] In the above memoir, I have mentioned several of my co-workers whose contributions came at decisive junctures in the voyage of exploration, but I have been blessed with many enthusiastic students and postdoctorals and since it was not possible to name them all in the text, they will find their names in the full bibliography which follows.

In retrospect, I have no doubt that those early impressions gained during summer vacations in the Trossachs left an indelible imprint which was later to form the basis of my decision to become a chemist rather than a classicist, in spite of the emphasis on translations from Virgil which occupied much of my time in my formative years at high school.

From the above narrative it is abundantly clear that I have travelled extensively during my scientific career and have taken my family several times across the Atlantic and Pacific oceans. Throughout all of these adventures, my wife Elizabeth has not only set up each new home, arranged for our children's education and made it possible for me to work the long hours necessary for a research scientist, but has done it all without complaint. She has been my literary critic, tennis coach, travel organizer and above all my marvellous wife for 46 years, and surely deserves equal recognition for any scientific success which I may have achieved.

Acknowledgments

I thank all my present and previous students, postdoctoral fellows and research technicians for their perseverance and hard work which brought to fruition many of the projects described above, whose conception took place over 30 years ago. I realize that while the strategical and tactical planning took place at my desk, the successful execution was not only demanding, but called for many hours of synthetic, biochemical and spectroscopic experimental work on their part. Throughout the B_{12} work we have enjoyed a most stimulating collaboration with Gerhard Müller (Stuttgart), who has devoted most of his scientific lifetime to the study of B_{12} biosynthesis. Generous financial support from the National Institutes of Health, the National Science Foundation, S.E.R.C., NATO, the Robert A. Welch Foundation, and the Texas Advanced Technology Research Program is also gratefully acknowledged.

[††]If there has been one overriding theme throughout all of this research, it has been my curiosity about the innate beauty of natural processes and the development of the physical techniques necessary to unravel their secrets, so it is not surprising that from boyhood, one of my literary heroes was the first consulting detective, Sherlock Holmes.[306]

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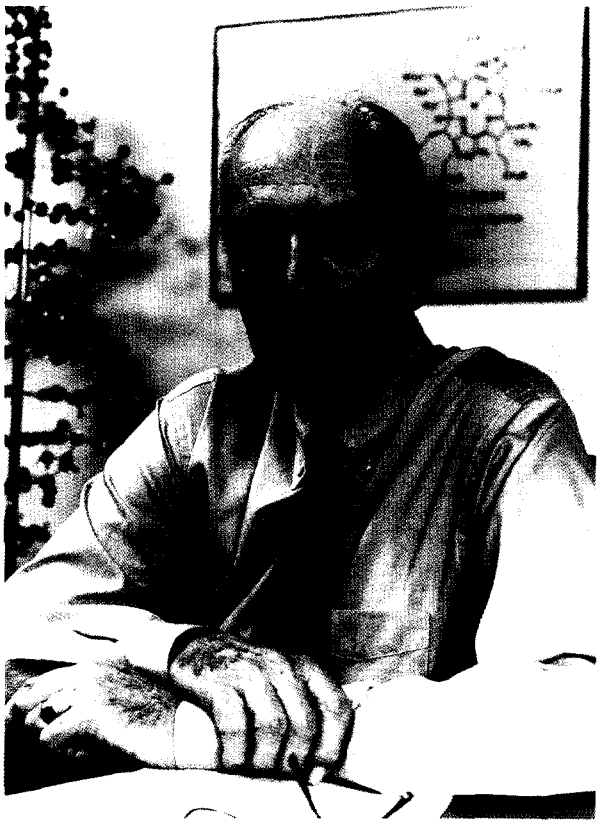
Biography



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