The Spirit of Adventure and the Art of Creation

Camphor to Vitamin B_{12}

Setty Mallikarjuna Babu and Subramania Ranganathan

What is described in the pages that follow, is the recounting of an exciting epoch in creative chemistry, namely, the synthesis of the complex molecule cyanocobalamin or vitamin B_{12}. It is the saga of the total laboratory synthesis of a molecule that we humans cannot do without and yet do not have the built-in biochemical machinery within ourselves to make it. We depend on the micro-organisms that have colonized our intestines to biosynthesize it for us, in a symbiotic manner.

With Woodward too, the challenges that he met increased in grandeur, from the total synthesis of quinine in 1944, to strychnine in 1954, to cephalosporin C and chlorophyll in the 1960s and finally win over vitamin B_{12} in 1976.

With Woodward too, the efforts and the strengths (technical and theoretical) that he had to commandeer varied from challenge to challenge, and climaxed with vitamin B_{12}, when he and his associates had to put together 181 atoms in space in over a dozen circles with nine centers of chiral asymmetry.

In any endeavor of this dimension, and the challenges and efforts of this scale, strategy, techniques and the creativity of approach are noteworthy. lt is this aspect of creativity that is addressed in large measure in the following pages. Any act of creativity is a fusion of matrices of thought. These matrices run independent of one another, with no connectivity or commonality. lt is when the twain meet that creativity is manifested. Arthur Koestler, in his book *The Act of Creation*, has discussed several instances where such impacting of two different matrices of thought has led to novelty and creativity. One can describe Woodward's art in organic synthesis in the same words – his naming the challenge, his courage and efforts to meet it and his creative ways of winning it.

(left) Setty Mallikarjuna Babu received his PhD degree from Osmania University, Hyderabad in 2009 under the guidance of S Ranganathan. His dissertation comprised of novel strategies for solubilization of silica where he developed methodologies for the formation of silicic acid embedded in hydrogen-bonded networks at the water-silica interface. These benchmark efforts led to methodologies for significant improvement in the health of rice plants. At present he is a Senior Research Associate attached to the Centre for Semeo Chemicals at IICT, Hyderabad.

(right) Subramania Ranganathan received his PhD degree from the Ohio State University, Columbus, USA in 1962. During 1962–1964 he worked in the research group of Woodward on the synthesis of Vitamin B_{12}; from 1964–1966 he was a member of the Woodward Research Institute and worked on the total

continued next page

synthesis of Cephalosporin C, which constituted Professor Woodward's Nobel Lecture. From 1966–1994 he was a Professor at Indian Institute of Technology, Kanpur. From 1994–1999 he was senior scientist of Indian National Science Academy at RRL, Trivandrum and IICT, Hyderabad. Since 1998 he is a distinguished scientist at IICT, Hyderabad and is an honorary professor at Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore. He has worked on XV different areas, ranging from organic to bio-organic to inorganic and bio-inorganic chemistry resulting in about 250 publications and 10 books.

We are most grateful to Prof D Balasubramanian, Director of Research, L. V. Prasad Eye Institute, Hyderabad for carefully examining the total synthesis of Vitamin B_{12} and using his fertile mind to highlight the creativity associated with this adventure.

Keywords
Camphor, vitamin B_{12}, art of creation.

The synthesis of vitamin B_{12} will remain as the parting masterpiece offering by Robert Burns Woodward to the world that he left in 1979.

From his early days, two aspects of carbon science, namely, the principle of aromaticity and the logical construction of molecules captivated Woodward. These two fortuitously found convergence in the synthesis of vitamin B_{12}, and this alone should make the adventure unique.

More explanation is needed to understand how Woodward, in his own lifetime, became a cult personality. He deliberately created an aura around him, setting himself as an example of a highly motivated and dedicated person who considered his time most precious and was loath to part with it. His liking for blue, manifested in his tie and suit, his meticulous attention to appearance, his prodigious smoking with matches that were custom made, his proclivity to imbibe vast quantities of spirit, his addiction to give lengthy lectures which were so meticulously prepared and so beautifully delivered and his famous Woodward Seminars that gave him a splendid opportunity to cut people to their dimensions, all contributed to this. He built for himself a reputation of total knowledge of what was happening and happened in the domains of organic chemistry and even distantly related subjects. His voracious reading habits became a legend. The stories got passed on and with each transfer more color was added! He enjoyed these immensely. Who can forget the scene, where Woodward was carried by four of his group in a sedan chair, on the occasion of his birthday, a year before he passed away . Sitting pretty in full regalia and puffing away, he remarked, "This harkens back to days of yore – days of monarchy – in my opinion better days!"

During the synthesis of strychnine, at one very difficult stage, he made the comment to his group, "Either we make strychnine or we take strychnine!" Indeed it is such conviction that made his colleagues do reactions under esoteric, exotic, unusual, wild and dangerous conditions, to accomplish the desired targets. The

extent of such involvement can be assessed from the fact that during the later stages of vitamin B_{12} synthesis, apart from the rigors that had to be imposed in terms of exclusion of air and moisture, the analysis had to be performed in tanks that had admixed in it hydrogen cyanide! In most cases his convictions actually paid off. This could be illustrated with his obsession to transform chlorin to chlorophyll as happens in Nature and his obstinacy in crafting cephalosporin-C from the simple amino acid cysteine and his design for the prostanoid nucleus from glucose. This is best reflected in his plan for vitamin B_{12}, where he was able to craft all the four rings of the vitamin from camphor! He created the two left-hand rings of the vitamin from the left-handed camphor and the two right-hand rings from the right-handed camphor!

Infrequently, his analysis of the situation became awry but even here he emerged as a notable winner gaining great advantages. His pondering on how strychnine was made in Nature laid out a plan for the chemical synthesis, which is one of the most amazing feats in synthetic organic chemistry. Years later, it was shown that his biosynthetic plan was not correct, but by that time he had accomplished the feat of strychnine synthesis based on such erroneous principles! In the case of vitamin B_{12} the isoxazole route had as the linchpin the cyclisation of a triene system generating two chiral centers whose disposition was absolutely critical for the total synthetic plan. In the event, the reaction preferred an exactly opposite path. Still Woodward took great advantage of this failure to generate the now famous Woodward–Hoffmann rules, which arguably enjoys a greater impact.

The great irony in the vitamin B_{12} synthesis is that Nature had the last laugh and showed that there is much to be learned about its very subtle nuances. The point I am trying to make is that the entire synthetic plan to vitamin B_{12} rested on the differentiation of one of the carboxyl groups of the corrin system from the remaining six, which was thought to be essential for the attachment of the complete nucleotide. Years later, it was found that in even the undifferentiated hepta acid system, the preference was for the

Woodward pondering on how strychnine was made in Nature laid out a plan for the chemical synthesis, which is one of the most amazing feats in synthetic organic chemistry.

Woodward took great advantage of the failure to generate the now famous Woodward–Hoffmann rules, which arguably enjoys a greater impact.

correct carboxyl group to interact with the nucleotide over six others, and therefore there was no need for a strategy based on such differentiation! In retrospect, one could argue that because in Nature a particular carboxyl group is differentiated, it must enjoy a preference. A sample set of experiments would have shown this and saved a lot of efforts, but then such hindsight is quite prevalent in our efforts at simulation of Nature. As mentioned earlier RBW's biosynthetic route to strychnine was wrong, so also his triene cyclisation that lead to Woodward–Hoffmann Rules!

From 1962 when synthesis of vitamin B_{12} was initiated, to 1976 when the totally synthetic vitamin B_{12} was made, an odyssey spanning 15 long years and involving more than 100 collaborators and amounting to over 200 post-doctoral years at Cambridge and a similar contingent across the seas at Zurich under the banner of Eschenmoser, encompasses a mural that seems to bring out all the subtle, elegant and ingenious nuances in the art of building molecular structures. One can asseverate that never in the history of human endeavours was there such a prodigious amount of energy injected to achieve a single objective, namely, the aggrandizement of vitamin B_{12}, a formidably complex natural product, which perhaps could be ranked amongst the very first in terms of evolution protocols. ln the annals of carbon science, the synthesis of vitamin B_{12} would always stand as a unique monument to the glory of the organic chemist, as a genius in understanding the myriads of ways by which carbon seeks and discards partners and use this to specific advantage in the construction of molecular edifices of extreme complexity.

Work on synthesis of vitamin B_{12} gave rise to new principles such as the Woodward–Hoffmann rules, which perhaps constitute the most significant theoretical advance pertaining to formation of covalent bonds and their disruption.

The subset of elements that followed the train of the synthetic flow and over such a long period, provided knowledge of immense value, in the realm of synthesis, reaction mechanisms, strategies, pitfalls, pointers and a complete and fascinating story of lasting value! Indeed, in the realm of the synthesis of vitamin B_{12}, one could see synthesis, reaction mechanisms, reagents, discovery and new principles, the latter exemplified with the enunciation of the Woodward–Hoffmann rules, which perhaps

constitute the most significant theoretical advance pertaining to formation of covalent bonds and their disruption. This directly arose from work on vitamin B_{12}.

1. Prolog

Unlike other epics in this turf, the full story of the vitamin B_{12} synthesis has neither been told nor the details published. It is this aspect I wanted to rectify above all, to put on record, even after 40 years, the complete story of the vitamin B_{12} synthesis.

I strongly feel, and was encouraged by many, that this should be done to preserve in our annals such a precious achievement. During my examination of many articles related to this topic, in spite of the fact that four decades have elapsed and in spite of the fact that science tends to become old fashioned as a function of time, I found that here was an example of accomplishment that would always stand the test of time and would serve as a beacon that illustrates the art of organic synthesis.

From the synthesis of quinine in the forties to the culmination of the construction of vitamin B_{12} in the late seventies, run a stream of unparalleled accomplishments by Woodward. In this journey, one could also perceive that the challenges that were taken and met were of increasing complexity. This upward gradient, in a sense, towards the end, made Woodward a prisoner of circumstances. Thus, after the completion of chlorophyll synthesis he had little choice but to embark on an attack on vitamin B_{12}.

From the synthesis of quinine in the forties to the culmination of the construction of vitamin B_{12} in the late seventies, run a stream of unparalleled accomplishments by Woodward. After the completion of chlorophyll synthesis he had little choice but to embark on an attack on vitamin B_{12}.

2. The Plan

Described simply, vitamin B_{12} is an assembly of four rings, which though look similar to the porphyrins, are far more complex, in the sense that the rings are saturated and harbor a string of chiral centers. In the plan that won the quest, each of the four rings either arises from camphor or is correlated to camphor. Thus camphor, whose absolute configuration has been rigorously established, not only provided all the four rings but also supplied chemical proof for the absolute configuration of vitamin B_{12}, whose three-

In the plan that won the quest, each of the four rings either arises from camphor or is correlated to camphor. Thus camphor, whose absolute configuration has been rigorously established, not only provided all the four rings but also supplied chemical proof for the absolute configuration of vitamin B_{12}.

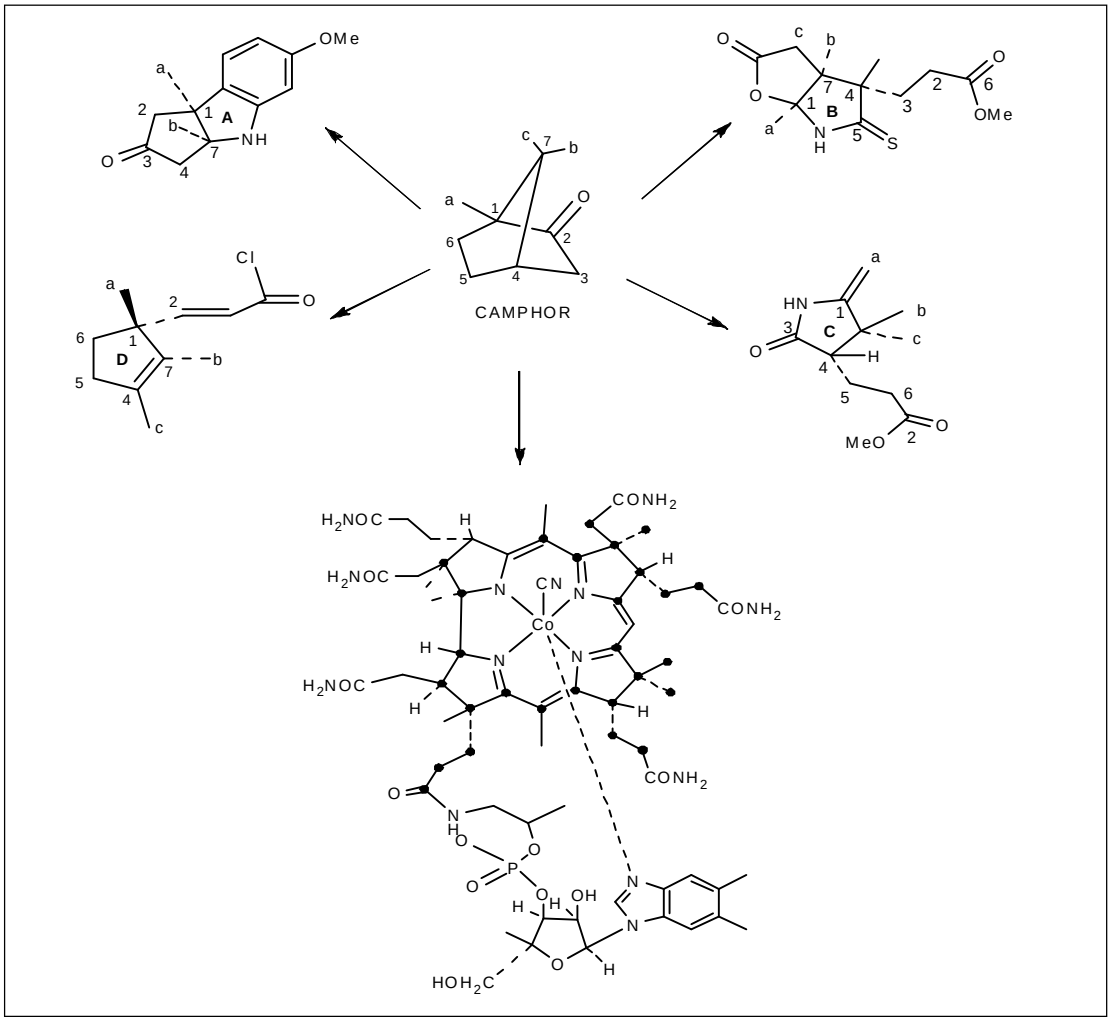


Figure 1.

dimensional disposition was accepted, as revealed by X-ray crystallography.

The plan presented in *Figure* 1 shows the quintessence of the adventure. The left rotating camphor was correlated to ring A and restructured to ring D and from the right rotating camphor were created rings B and C of vitamin B_{12}. The top half of the figure shows where the atoms of camphor end up in the rings of *Figure* 1, in which all the highlighted carbon centers arise from camphor.

The union of the left-hand side (LHS/western-half) and the right-hand side (RHS/ eastern-half) (*Figure* 2) encapsulates the core of

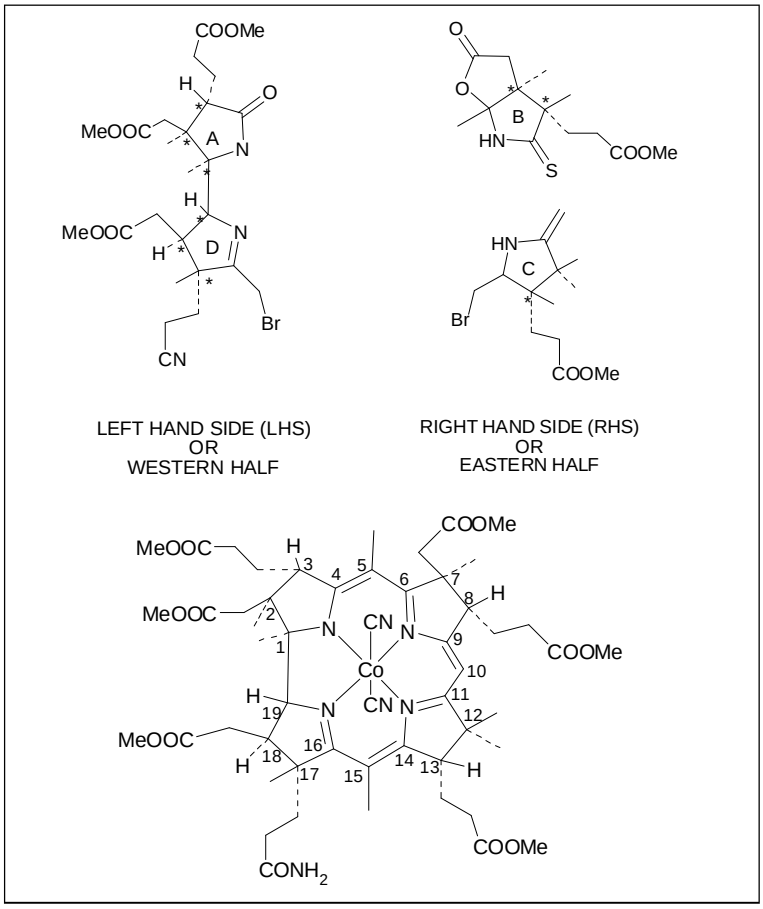


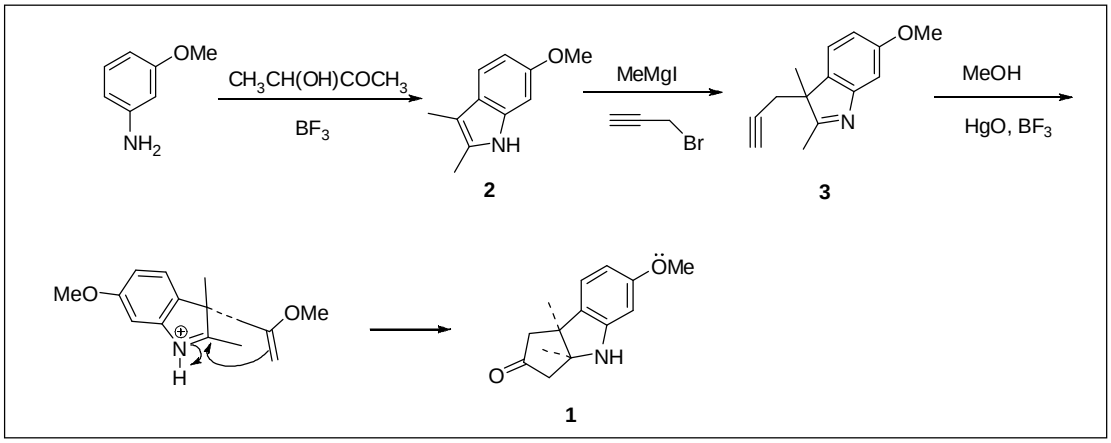
Figure 2.

the plan. To make reading and correlation easier the corrin numbering system is provided. LHS having six contiguous asymmetric centers reflects a brilliant effort by Nature, and Woodward deemed it as a most covetable object to create, a notion from which he never wavered, in spite of incredible obstacles.

3. TCK, the Mascot for the Team!

Tricyclic ketone (TCK) (**1**) enjoys a pre-eminent position in this story by virtue of its presence from the debut to curtains. TCK possesses all the elements needed to mold the ring A of vitamin B_{12} and has the information to direct the correct union to ring D as well as the generation of, in a specific manner, all the carbon asymmetric centers.

Tricyclic ketone (TCK) (**1**) enjoys a pre-eminent position in this story by virtue of its presence from the debut to curtains.



Scheme 1.

The boron trifluoride mediated condensation of m-anisidine with acetoin afforded 2,3-dimethyl-6-methoxy indole (**2**) (*Scheme* 1), which was transformed to the indoline 3 by reaction with propargyl magnesium bromide. The reaction of **3** with mercuric oxide–boron trifluoride–methanoI smoothly afforded TCK (**1**).

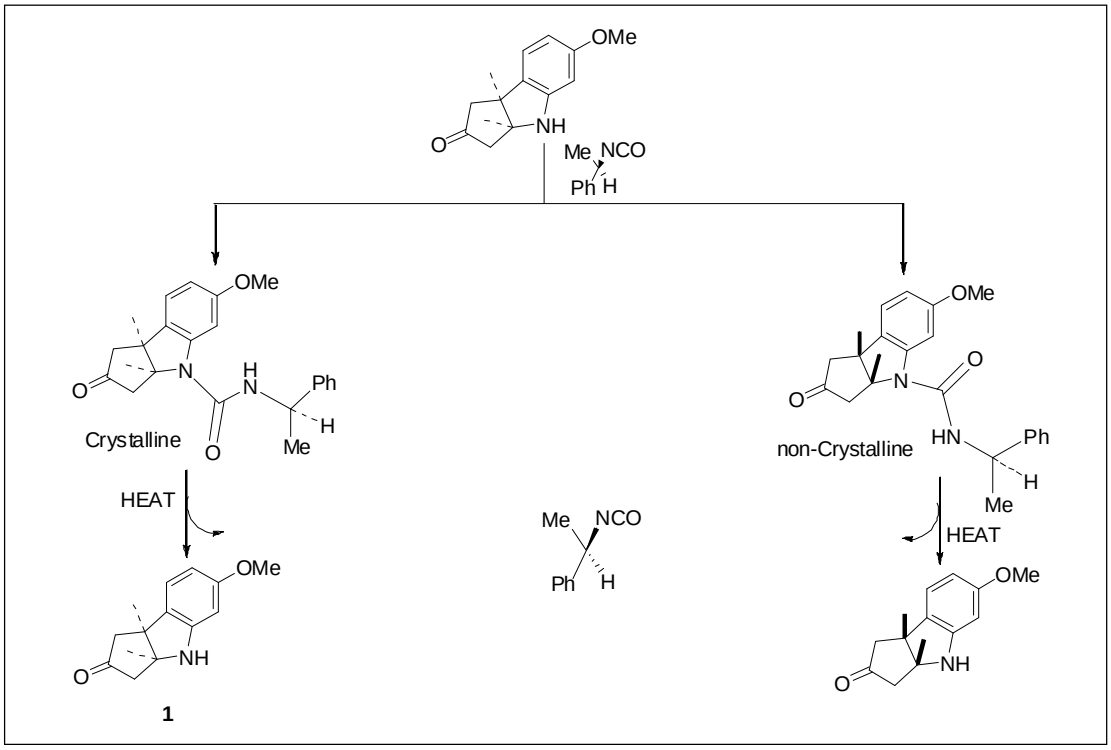
Two inputs are needed to take TCK to the mainstream, namely, resolution and determination of the absolute configuration. Woodward took advantage of the amphoteric NH unit in TCK, to bring about an exceptionally easy resolution, as shown in *Scheme* 2 . The reaction of **1** with (–)α-phenethyl isocyanate afforded the diasteromeric mixtures from which one crystallized and the other not at all! Therefore their separation was exceptionally facile. On thermolysis these reverted to chiral TCK. lt turned out that TCK obtained from the crystalline diastereomer had the required absolute configuration presented as **1**.

Woodward took great delight in stating that starting with a racemic material has great advantages since the undesired mirror image is a perfect system to carry out model experiments.

The delightful correlation of **1** with left rotating camphor is shown in *Schemes* 3 and 4.

4. Correlation of 1 with (–) Camphor to 6

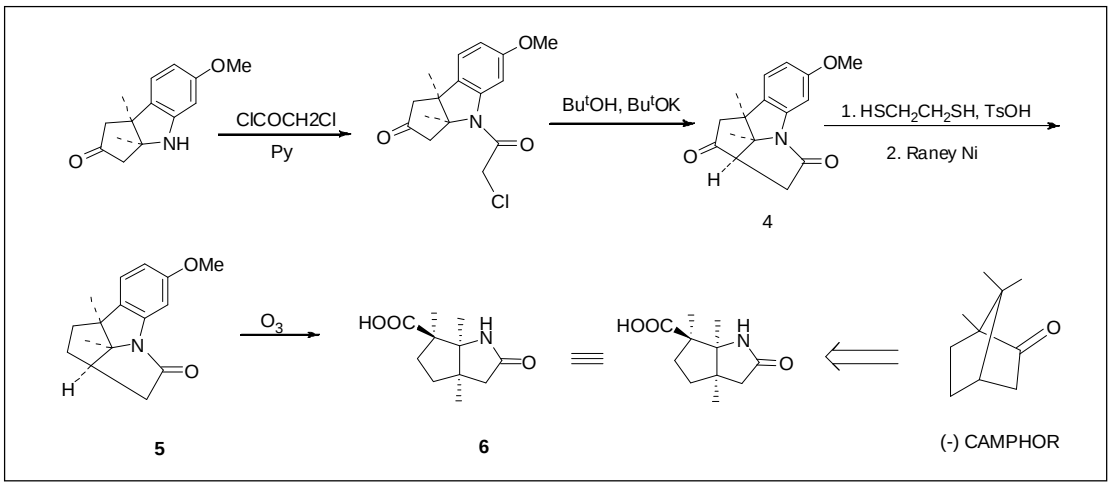
(–) Camphor was subjected to fuming sulfuric acid to afford

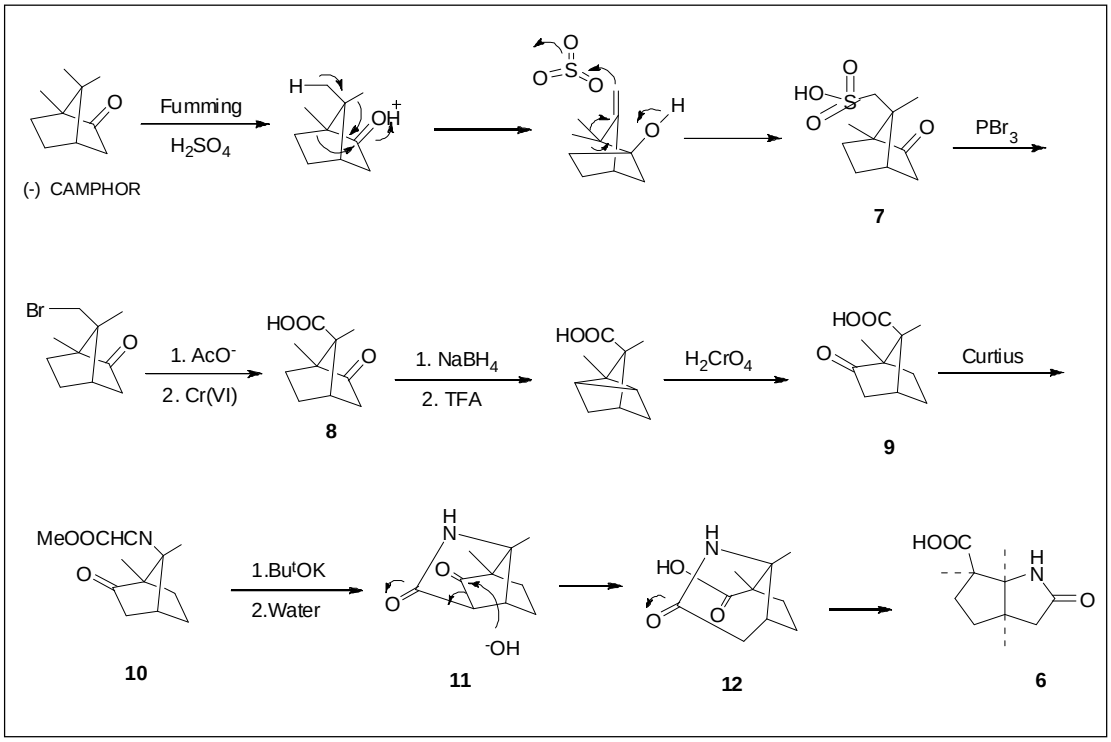


Scheme 2.

camphor-10-sulfonic acid **7**, by a series of rearrangements as shown in *Scheme* 4. Treatment with PBr_3 and NaOAc followed by oxidation leads to the carboxylic acid **8**. The (–) camphor → **8** → **9** change represents an elegent carbonyl switch and mirror image formation mediated by the carboxyl group (*Scheme* 4).

Scheme 3.





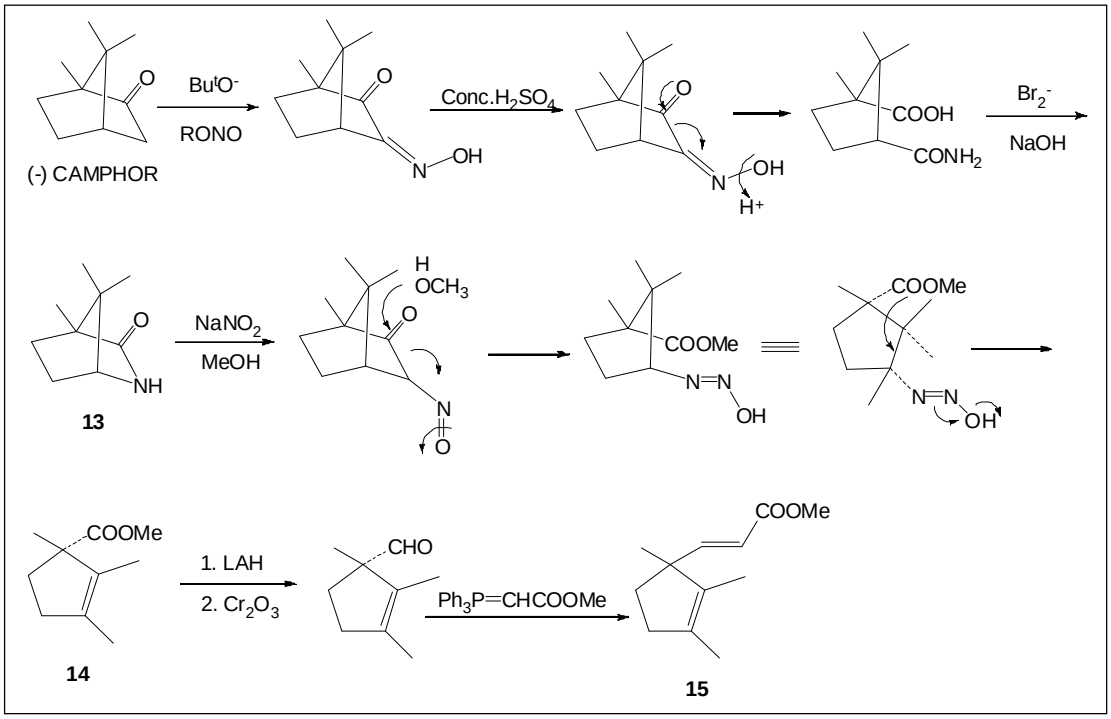
Scheme 4.

Compound **9** was subjected to Curtius rearrangement and the resulting isocyanate on addition of methanol gave urethane **10**. Treatment with potassium tertiary butoxide followed by quenching with water gave **6,** identical in all respects to that derived from **1** (*Scheme* 3). The **10**→**6** change presents a unique sequence. The strong base brings about a cyclization to a fragile 1,3-diketo system that readily relaxes with hydroxide to give **6.**

The **10**→**6** change presents a unique sequence. The strong base brings about a cyclization to a fragile 1,3-diketo system that readily relaxes with hydroxide to give **6.**

5. The Making of the D-ring from Camphor

The reaction of (–) camphor with amyl nitrite-potassium-*t*-butoxide afforded the isonitroso compound, which in the presence of sulfuric acid underwent the Beckman rearrangement (fragmentation mode) to give the carboxy amide. This, on Hoffmann degradation readily afforded the amusing lactam **13**, the overall change amounting to the replacement of a methylene of camphor with the NH equivalent! The nitroso derivative of **13**, under carefully defined conditions underwent a clean N-nitroso rearrangement leading to the desired chiral **14**, the overall process involving



Scheme 5.

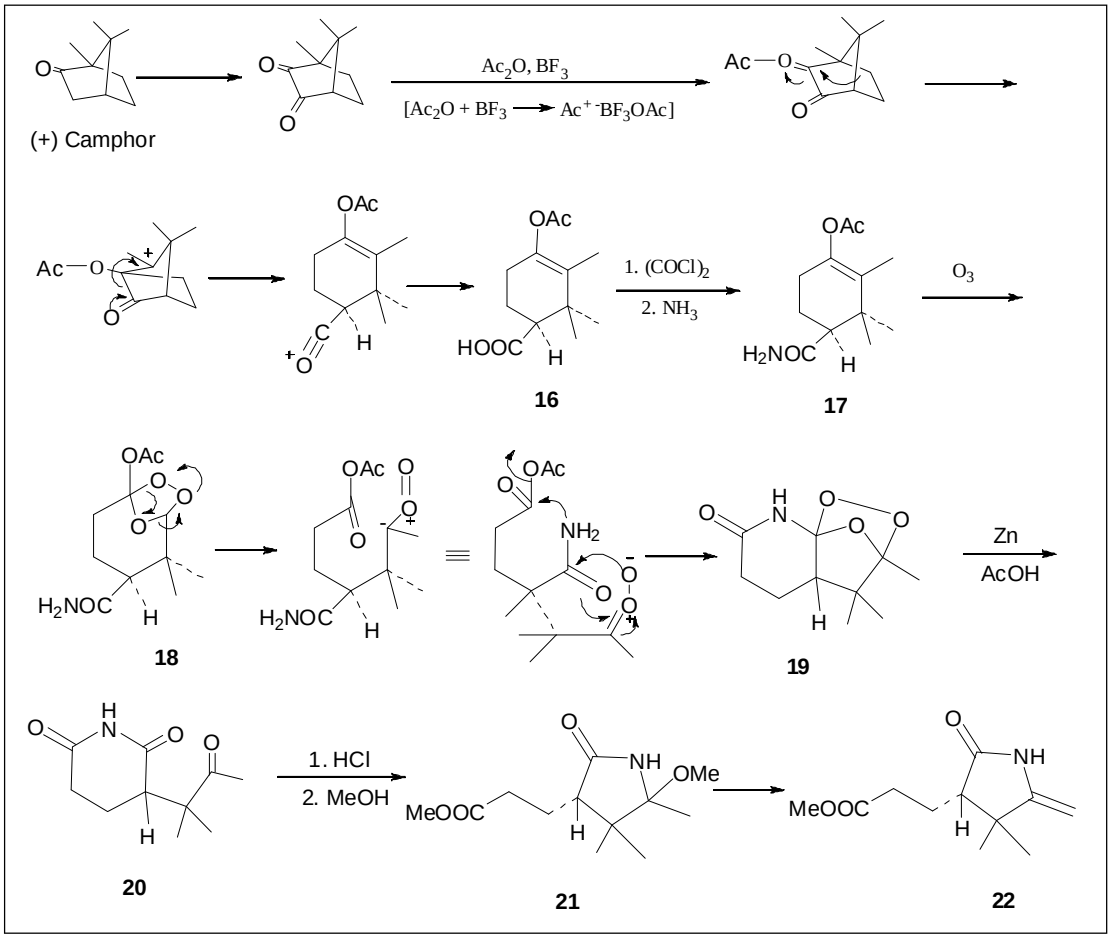
fragmentation, specific methyl group migration and loss of nitrogen (*Scheme* 5).

Being now familiar with the vitamin B_{12} structure (*Figure* 1), it can be concluded that the single chiral center in **14**, that carries the methyl group, is destined to be the C-17 of the vitamin B_{12}. This center is unique; it is a spatially unalterable center where the downward disposition of the propionic acid side chain is to serve as the link to the cobalt center through a nucleotide. In terms of the plan, this would be the sixth center of LHS . TCK harbors centers 2 and 3 and the aromatic ring is programmed to generate the first one by a Birch reduction sequence. Therefore the union of TCK with **15** should lead to **35** (*Scheme* 9) that can generate centers 4 and 5 in a specific manner to give a single product. A sequence as shown in *Scheme* 5 readily took **14** to the acrylate **15** having the required qualities.

The single chiral center in **14**, that carries the methyl group, is destined to be the C-17 of the vitamin B_{12}. This center is unique.

6. Camphor → False Ozonide → Ring C

Camphorquinone arising from the selenium dioxide oxidation of



Scheme 6.

(+) camphor when subjected to careful treatment with boron trifluoride in dry acetic anhydride afforded **16** (*Scheme* 6). Although the acyl cation that initiates the rearrangement can complex with either of the two carbonyl units, the course of the reaction seems to be dictated by the stability of cation that can arise by this complexing, as shown in *Scheme* 6. Compound **16** was readily transformed to the key amide **17** via the acid chloride.

The relation between **17** and ring C of vitamin B_{12} is clear, viewed from vantage of the gem dimethyl marker. Thus, the bonding of the amide nitrogen with a carbonyl generated proximal to the gem dimethyl unit could lead to ring C. Although this was achieved eventually, the path involved the condensation with the opposite carbonyl to form the glutarimide **20** (*Scheme* 6).

Treatment of **17** with ozone results in ozonide **19**, which is stable enough to be chromatographically purified! In truth, this ozonide bears no resemblance to that expected from **17,** namely, **18** (*Scheme* 6) and therefore it is appropriately labelled a false ozonide, an imposter! Compound **17**, endowed with proximal and distal combatants, is the one really programmed to perform unusual acrobatics. The real fellow fragments to an anhydride and a keto-oxide (*Scheme* 6). The distal amide nitrogen steps in to remove the acetate to form a glutarimide whose neucleophilic carbonyl readily accepts the waiting keto-oxide to form the false ozonide **19**. Zinc reduction to **20** followed by treatment with methanolic hydrochloric acid leads to the α-methoxy pyrrolidone **21**, which thermally eliminates methanol to give unit **22** to be incorporated as the ring C of vitamin B_{12}.

Compound **17**, endowed with proximal and distal combatants, is the one really programmed to perform unusual acrobatics.

7. Two Approaches to Ring B of Vitamin B_{12}

Although quantities of ring B precursor, **27** were made by a short sequence initiated with a cyclo-addition, along the path shown in *Scheme* 7, the one from (+) camphor not only fulfilled aesthetic expectations but also was pivotal in determining the correct absolute configuration to be used.

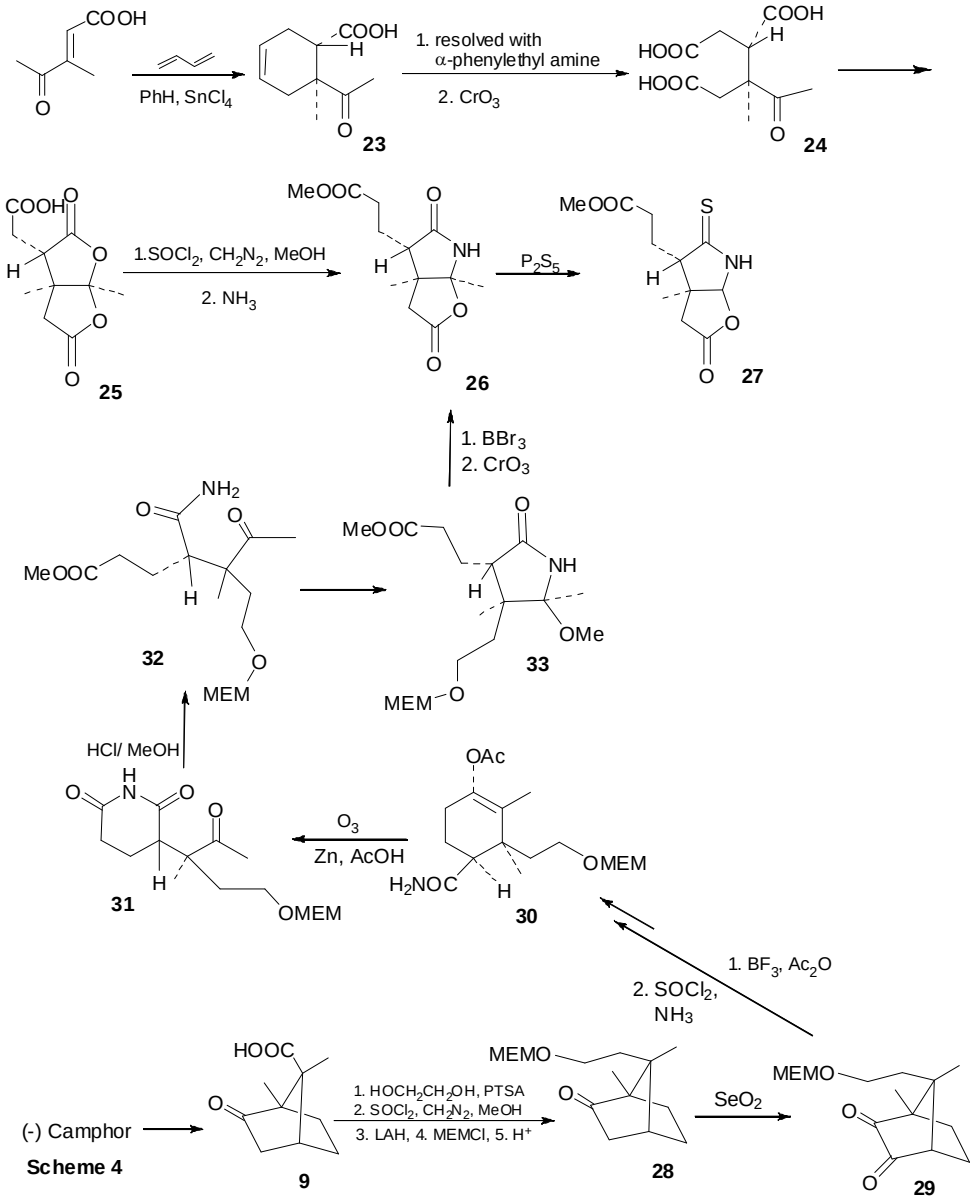
The cyclo-addition of butadiene with E-3-methyl-4-oxo pent-2-enoic acid in presence of stannic chloride gave the cyclo adduct **23**, which was resolved with (–) α-phenethyl amine. The absolute configuration needed, namely **23**, was determined by correlation with that of (+) camphor (vide infra) as well as with fragment derived from ozonolysis of heptamethyl cobyrinate, the methanolysis product of vitamin B_{12}. In this reaction ring C fragment is also obtained. The π bond of **23** was cleaved to **24** with chromium trioxide. Under the acidic conditions of the reaction, compound **24** underwent cyclization to the bicyclic system **25**, whose acetic acid side chain was transformed to that of propionic acid by Arndt–Eistert homologation protocol. Ammonolysis afforded lactam **26**. At first sight it may look strange that, in the bicyclic system **25** the more-hindered carbonyl is preferentially lactamized, a process that involves attack from the α-side. The reality is that both the lactams are formed. The

At first sight it may look strange that, in the bicyclic system **25** the more-hindered carbonyl is preferentially lactamized, a process that involves attack from the α-side. The reality is that both the lactams are formed.

resulting compound having two nitrogen functions attached to the same carbon is unstable and equilibrates with open conformers that could recyclize either through the oxygen or the nitrogen. In this dynamic flux, the imino lactone corresponding to the less

Schemes 7 and 8.

Scheme 7



Scheme 8

hindered site prevails, which on hydrolysis gives **26**. We know all this because Woodward took great pains, typical of him, to understand this apparent aberration. Treatment with phosphorous pentasulfide specifically yielded the thiolactam **27**. the construct that would be ring B of vitamin B_{12} (*Scheme* 7).

To reach the same objective (+) camphor was transferred to **9** by procedures outlined in *Scheme* 4 and the carboxyl function was re-structured to **28,** as shown in *Scheme* 8. The transformation of **28** to the camphor quinone **29** followed by sequence, metamorphosis to cyclohexene **30** by real ozonide and false ozonide protocol (*Scheme* 6) afforded **31**, which in methanolic HCI was transformed to **32** and then **33**. Deprotection followed by Cr(Vl) oxidation under carefully controlled conditions afforded **26**, identical in all respects to that secured from the Diels–Alder approach.

The transformation of **28** to the camphor quinone **29** followed by sequence, metamorphosis to cyclohexene **30** by real ozonide and false ozonide protocol afforded **31.**

8. The Crafting of LHS, a Unique Molecular Constellation (*Figure* 2)

In the general plan for vitamin B_{12}, outlined in Section 2, the coveted synthetic objective was the left-hand side of vitamin B_{12}, LHS, possessing six contiguous asymmetric centers, where all the carbons, excepting those involved in the bridging to the right side carry chiral centers.

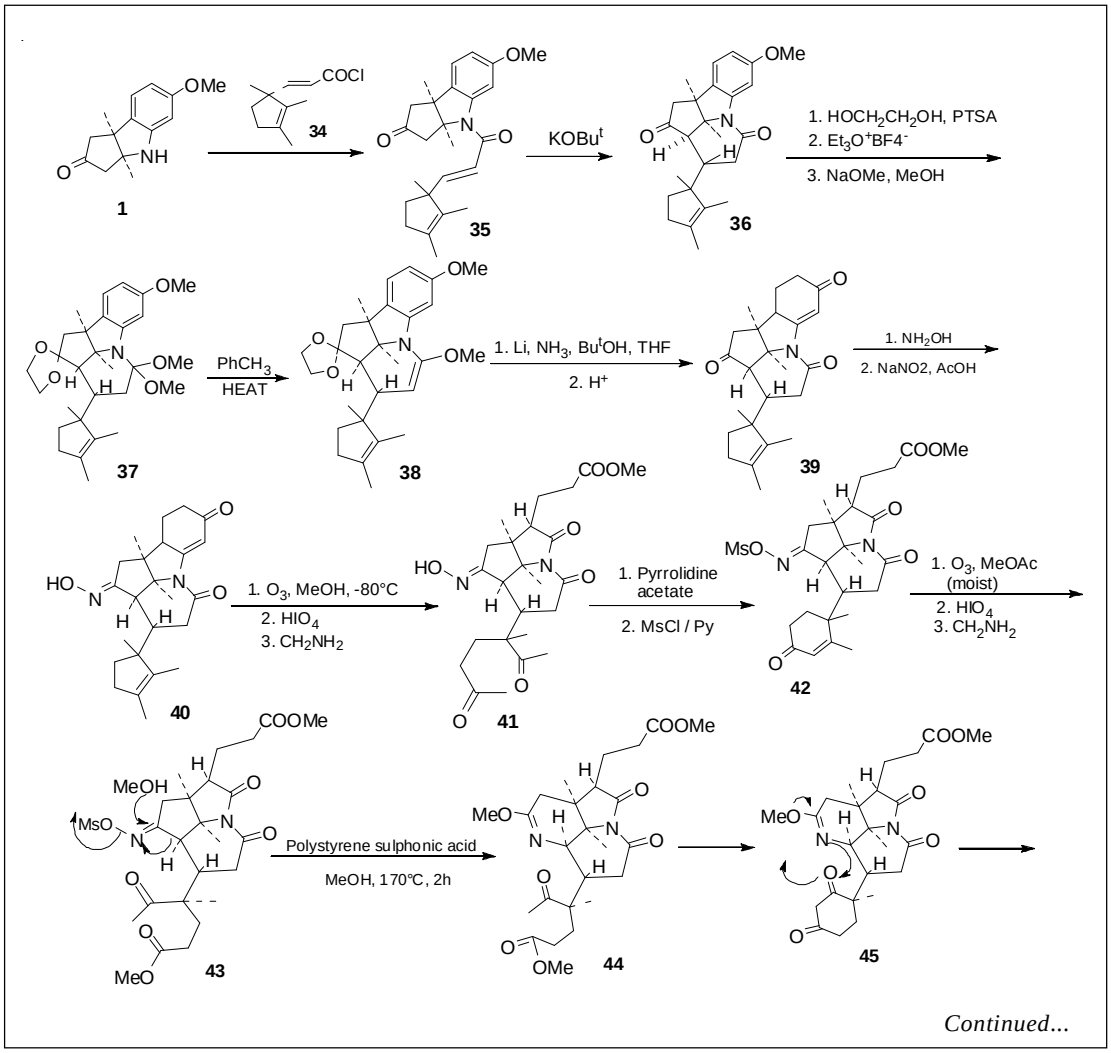
The cyclopentene acrylic ester **15** derived from (–) camphor (*Scheme* 5) was saponified and converted to the acid chloride **34** with oxalyl chloride. The reaction of TCK (**1**) and **34** afforded the composite **35** (*Scheme* 9). Compound **35** has the required 2,3 and 6 chiral centers, with the first masked as the aromatic ring. The intervening chiral centers 4 and 5 were created in one move in a specific manner by Michael addition of the conjugate base of the TCK segment to the π - bond of the acrylic system to afford, in excellent yields **36**, which now harbors five of the required six centers in their proper absolute configuration. The convex nature of the TCK, coupled with the presence of *endo*-oriented methyl groups, which augment the convex profile, further ensure the addition from the top side to the *trans*-oriented receiving unit.

The cyclopentene acrylic ester **15** derived from (–) camphor was saponified and converted to the acid chloride **34** with oxalyl chloride.

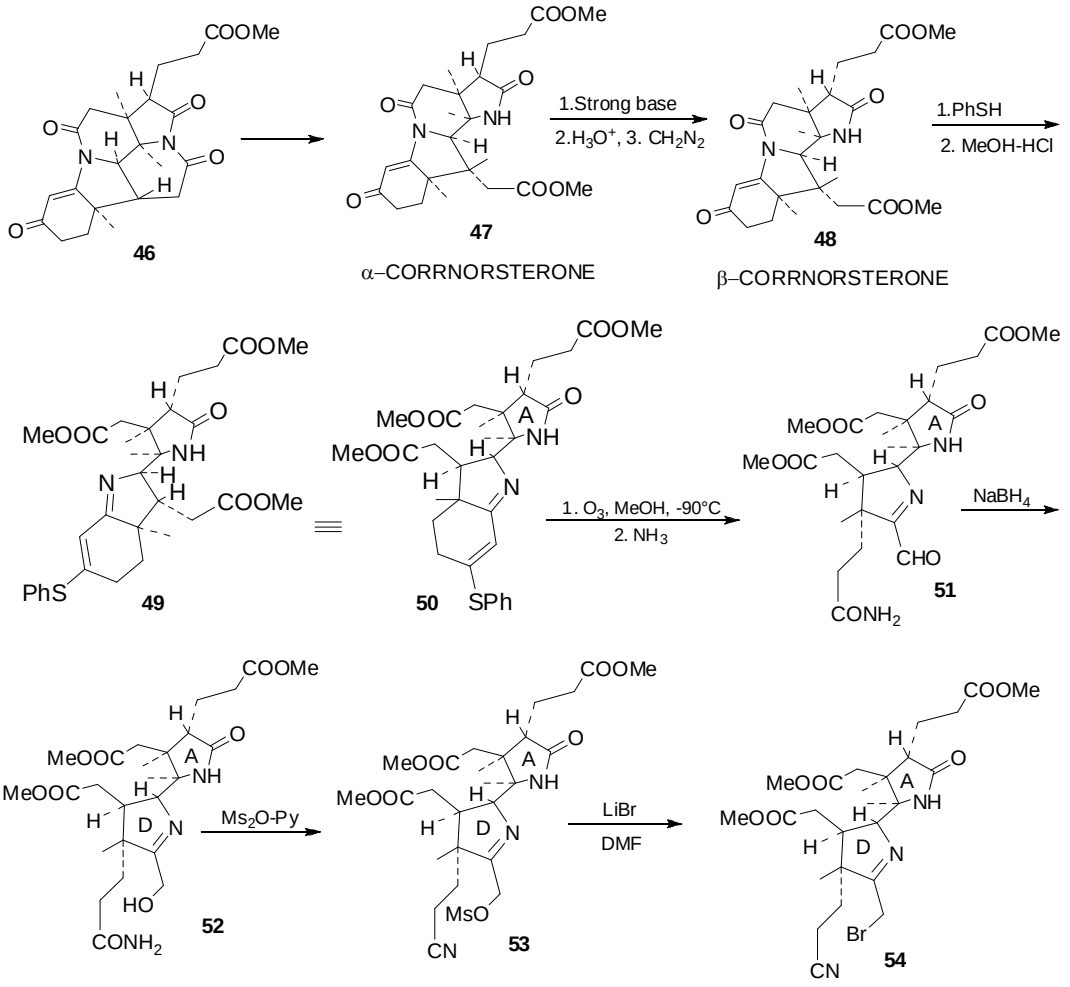
These ensure the stereochemical disposition as shown in **36**.

The stage is now set to unmask the chiral center at the first position. The obvious choice is the Birch reduction, which should be preceded by proper protection of the susceptible functions like the carbonyl group and the lactam unit. Whilst the former could be accomplished by ketalization, the latter took considerable efforts and the solution found was unique. The reaction of the ketal with triethyloxonium fluoroborate afforded the lactam ether, which on treatment with methoxide gave the unusual ortho system **37** (*Scheme* 9) This being possessed of three lone pair

Scheme 9.



Scheme 9 continued.



harboring ligands converging on a single carbon center, readily ejected methanol on heating to give the imino ether **38**. The bond in **38** harboring two electron donating groups at single termini, is highly electron rich and is totally impervious to the conditions of the Birch reduction. In the event, treatment of **38** with lithium in ammonia in presence of butyl alcohol with dry THF as the solvent followed by treatment with acid gave enone **39**. Obviously, the initial Birch reduction product underwent a series of prototropic rearrangements leading to the more stable **39**. This molecule harbors

The cleavage of the cyclohexenone system generated the five-membered lactam, destined to be the A ring of the B_{12} on the one hand and α-diketo system on the other.

all the six chiral centers of LHS. Whilst the position of the prevailing five are certain, that for the nascent one is uncertain. lt turned out from subsequent experimentation that at this point the configuration is the undesired one, having α-orientation for the hydrogen (*Scheme* 9).

The stage is now set to bring in the second nitrogen needed for the corrin structure. As could be seen from *Figure* 1, the two nitrogens on the LHS of vitamin B_{12} are 1,4 positioned, linked by two chiral centers. Such a positioning could be realized from a Beckman rearrangement of the cyclopentanone oxime. provided the oxime hydroxyl is placed anti to the remaining part of the molecule. Considering the steric constraints this is to be expected. In the event, the reaction of **39** with hydroxylamine hydrochloride–sodium acetate afforded the dioxime, which could be readily transformed to the desired mono-oxime **40**, by the removal of the more exposed oxime with sodium nitrite acetic acid.

The treatment of **40** with ozone in methanol at –80°C followed with periodic acid and esterification with diazomethane afforded in good yields compound **41**. ln this series of reactions, both the double bonds present in **40** were cleaved without affecting the obviously very sterically hindered oxime function. The cleavage of the cyclohexenone system generated the five-membered lactam, destined to be the A ring of the B_{12} on the one hand and α- diketo system on the other. The latter suffered loss of carbon atom on periodic acid treatment to the required propionic acid chain, which was protected by esterification.

The enamine of the less-hindered carbonyl smoothly underwent addition to the desired enone which by the reaction of methane sulfonyl chloride-pyridine to afford **42**. The reaction of **42**, under conditions described earlier, namely, treatment with ozone followed by periodic acid and esterification with diazomethane afforded compound **43** where the methyl group carrying the chiral center originally designed from (–) camphor harbors the ligands for further transformation. Having the required chiral centers and ligands at hand in structure **43**, endeavors were taken up to place the oximino nitrogen at the correct position enabling the

formation of ring D. This turned out to be an extremely difficult process, since under most conditions, the mesylate was unaffected. The fact that the ultimate conditions that won the rearrangement involved heating of **43** in methanol at 170°C for 2 hours in presence of the strong acid, polystyrene sulfonic acid, highlights the recalcitrant profile of this compound. Under such drastic conditions little control could be expected on the events that follow. However, in one of the few fortunate occurrences in this story, it led to the delightful **47**, (*Scheme* 9) which has the elements of the A–D composite with all chiral centres in the correct disposition excepting at the carbon 3, whose configuration needed to be established. Compound **47** was fondly called as α-corrnorsterone, which name harbors diverse nuances, the most significant being that it is the cornerstone for further progress to produce the corrin system from something that looks like a steroid. The one-step transformation of **43**$\rightarrow$ **47** highlights a cascade of events that has taken place dictated by, naturally, the strong conditions of the reaction. The analysis presented in *Scheme* 9 provides a rational explanation for the change, although permutation of the sequence is perfectly plausible. In its simplest form this change could be understood as initiated by the Beckman rearrangement wherein methanol plays a key role to produce the enol lactam ether **44**. Compound **44** then undergoes an acid induced Claisen condensation to afford the 1,3 diketone system **45** which is exceptionally well aligned for the formation of the critical bond uniting the nitrogen and the carbonyl function generating, at last, the D ring of the vitamin B_{12}. This process is made very facile by the highly nucleophilic imino ether function and by events shown in *Scheme* 9 leading to the enone **46**. These highly interesting series of dramatic events are provided with a fitting finale in the liberation of the acetic acid side chain, the ligand at the 18 position of corrin, by methanolysis. Whilst liberating the acetic acid side chain from the grip of lactam relating to ring D was facile, that pertaining to similar ligand in ring A proved to be an extraordinary adventure which is undoubtedly one of the points that finds illustration as to how seemingly impossible objectives could be obtained, by carrying out several

The one-step transformation of **43**$\rightarrow$ **47** highlights a cascade of events that has taken place dictated by, naturally, the strong conditions of the reaction.

These highly interesting series of dramatic events are provided with a fitting finale in the liberation of the acetic acid side chain, the ligand at the 18 position of corrin, by methanolysis.

parallel reactions coupled with an analysis of each of such events in detail. The success here not only led to the desired construct but also enabled the identification of the stereochemical disposition at chiral center 1, apart from magnificent insights into physical organic chemistry.

The methanolysis of the six-membered lactam in **47** proved extremely difficult under acidic and basic conditions. Several pathways were explored with uniform failures. At this point Woodward remembered that along with **47** there was obtained, as he puts it, a minute quantity of another crystalline compound, whose chemical and spectroscopic properties left no doubt that it was **48** isomeric to **47** (*Scheme* 9). In sharp contrast to **47** this isomeric compound very readily underwent methanolysis of the lactam giving rise to the desired product. Analysis of this event clearly pointed out that whereas the lactam grouping in **47** is hindered, that in the isomeric **48** was easily accessible to the rupture of the lactam carbonyl. A comparison of **47** with isomeric **48** would easily show that the β-oriented propionic ester grouping at C-3 in the former offers significant steric hindrance to the methanolysis of the lactam which has to also take place from β–side. In view of the enormous overcrowding at the α-location, the shifting of the propionic acid side chain from [$\beta \rightarrow \alpha$] (*Scheme* 9) removes a major obstacle and makes the opening of the lactam ring easy. Having determined that the isomer which is now called β-corrnorsterone (**48**) as the appropriate intermediate for further progress, the problem was to have this compound in 'substantial amounts', on the face of the finding that in the Beckman rearrangement cascade, the near exclusive product was the α-corrnorsterone **47**! Studies showed that, under equilibrium conditions, the concentrations of **47** and **48** were nearly equal. ln sharp contrast, in the case of the corresponding acid salts, arising from treatment with strong base, the equilibrium was heavily shifted in favour of the desired **48**. Thus, treatment of α-isomer **47** with strong base, equilibration, acidification and esterification led to production of the desired corrnorsterone, **48,** in over 90% yields.

Studies showed that, under equilibrium conditions, the concentrations of **47** and **48** were nearly equal. ln sharp contrast, in the case of the corresponding acid salts, arising from treatment with strong base, the equilibrium was heavily shifted in favour of the desired **48**.

This marvellous illustration provides a rationale for the great success of Woodward, always arising from a conviction, detailed experimentation and an incise analysis.

The reaction of **48** in methanol containing hydrogen chloride with phenyl mercaptan afforded smoothly in excellent yields the thiophenyl compound **49** (*Scheme* 9). Compound **49** is written in a corrin profile as **50**.

Treatment of **49≡50** with ozone followed by liquid ammonia readily afforded **51** which has all the six stereo centres in the right configuration and where the crucial propionic acid side chain is differentiated from the others in the form of an amide. A noteworthy point is that the ene-aldehyde survived the ozone treatment. The aldehyde grouping was re-structured for union with the BC fragment by transformation to the corresponding bromomethyl compound **54**, by reduction to the alcohol **52,** transformation to the mesylate **53** and neucleophilic displacement with lithum bromide.

The aldehyde grouping was re-structured for union with the BC fragment by transformation to the corresponding bromomethyl compound **54.**

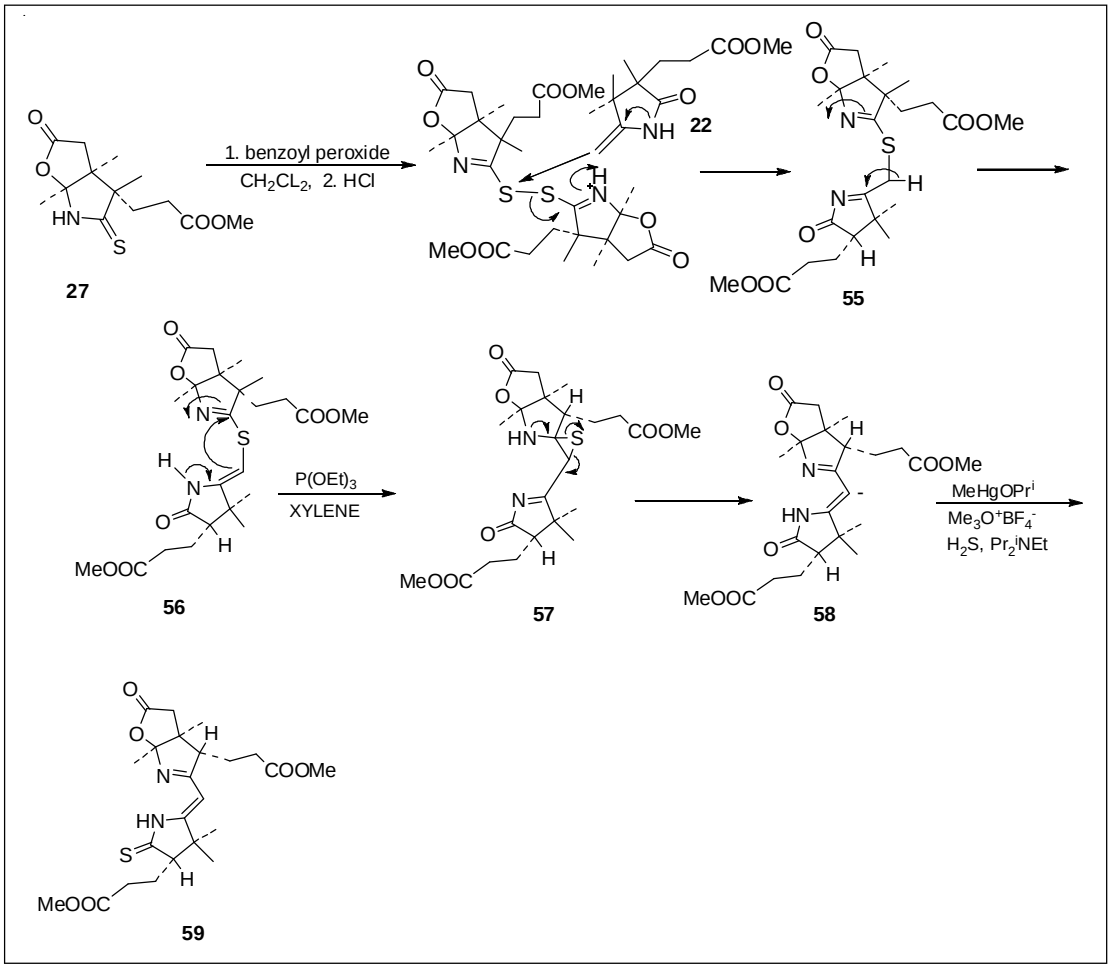
In this process the amide function was transformed into the nitrile, so that in the completion of the synthesis it had to be converted to a carboxylic acid, differentiated from the others.

What we have seen here in the transformation of TCK (**1**) to LHS (**54**) is a story of significance in the art of organic synthesis and those who traverse it would derive great satisfaction and encouragement arising from the feeling that those edifices crafted by Nature can be constructed provided basic facets underlying them are understood. lt would not be out of place to mention here that extremely complex natural products that abound must have evolved over a large time span. When viewed from this vantage the synthesis of the LHS of vitamin B_{12} in a matter of a decade deserves great appreciation.

What we have seen here in the transformation of TCK (**1**) to LHS (**54**) is a story of significance in the art of organic synthesis and those who traverse it would derive great satisfaction and encouragement.

9. The Union of Rings B and C

This was achieved by a novel and general strategy with sulfur as the initial linker followed by its extrusion uniting the two



Scheme 10.

The role of sulfur here has been colorfully described by Woodward as the agent which brings in enforced propinquity of the partners, leading to greater intimacy.

fragments. The role of sulfur here has been colorfully described by Woodward as the agent which brings in enforced propinquity of the partners, a sure medicine for leading to greater intimacy. The strategy here is best illustrated with the union of the B and C rings, which proceeded without major complications. The reaction of **27** with **22** with benzoyl peroxide in methylenechloride containing catalytic amounts of hydrogen chloride led to the sulfur bridged system **56** (*Scheme* 10). The overall process taking place here can be envisaged as oxidation of the thiolactam grouping in **27** to an electrophilic disulfide, which, in presence of acid, readily accepts the nucleophilic termini of **22** giving rise to the intermediate **55** which by an expected prototropic shift leads to **56.**

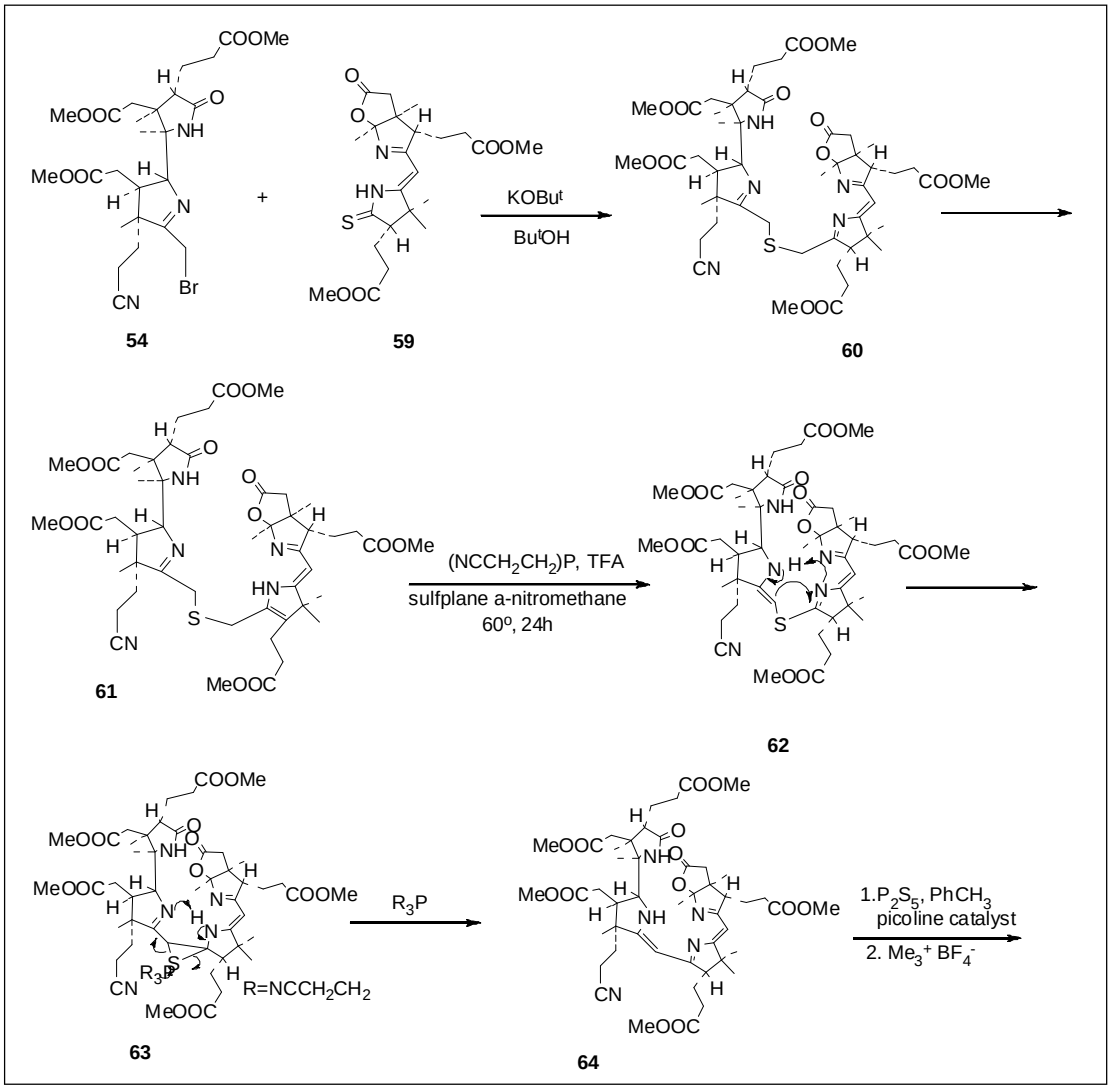
On treatment of **56** with triethyl phosphite in xylene, the sulfur is extruded to give the desired bridged system **58**. This change can be understood as shown in *Scheme* 10, as taking place via an episulfide intermediate **57**. The B-C composite was then prepared to accept the A-D segment by transformation to the thiolactam **59**, which could be best achieved by initial transformation to a lactam ether with trimethyl oxonium fluorborate in presence of isopropyl methyl mercury followed by treatment with hydrogen sulfide. The facility with which the B-C ring construct was achieved was not an unqualified success. It was found that the propionic acid side chain at the 8 position readily underwent epimerizatin to give mixtures. In these complicated structures the mixture behaved as a single entity, crystallized beautifully and required careful spectroscopic analysis for their differentiation and HPLC for separation. From this point on, the constructs were generally a mixture of epimers, which at an appropriate stage could be easily separated to pure components. Whilst such easy epimerization arising from proximity to a carbon nitrogen double bond was an unwelcome intrusion, it also provided a solution to a most vexing problem relating to the union of the left-hand side with the right-hand side bridging rings D and C.

Whilst such easy epimerization arising from proximity to a carbon nitrogen double bond was an unwelcome intrusion, it also provided a solution to a most vexing problem relating to the union of the left-hand side with the right-hand side bridging rings D and C.

10. The Construction of the Southern Bridge

The union of LHS (**54**) and RHS (**59**) was the next logical step to establish the southern bridge.

The reaction of **54** and **59**, representing the left/west and the right/east segments, with potassium tertiary butoxide in tertiary butyl alcohol afforded the sulfur-linked composite **60** (*Scheme* 11). Under stringent conditions compound **60** (thioether I) can be prepared in quantitative yields. However the reaction of this with trialkyl phosphite, which under mild conditions led to successful B-C bridging (*Scheme* 10) failed. Most such efforts led to the isomer **61** (thioether ll), arising from a prototropic shift from the chiral 13 position to the nitrogen. This compound was quite stable and could be prepared easily by treatment of **60** with traces of trifluoroacetic acid. The failure of bridging arises from the fact



Scheme 11.

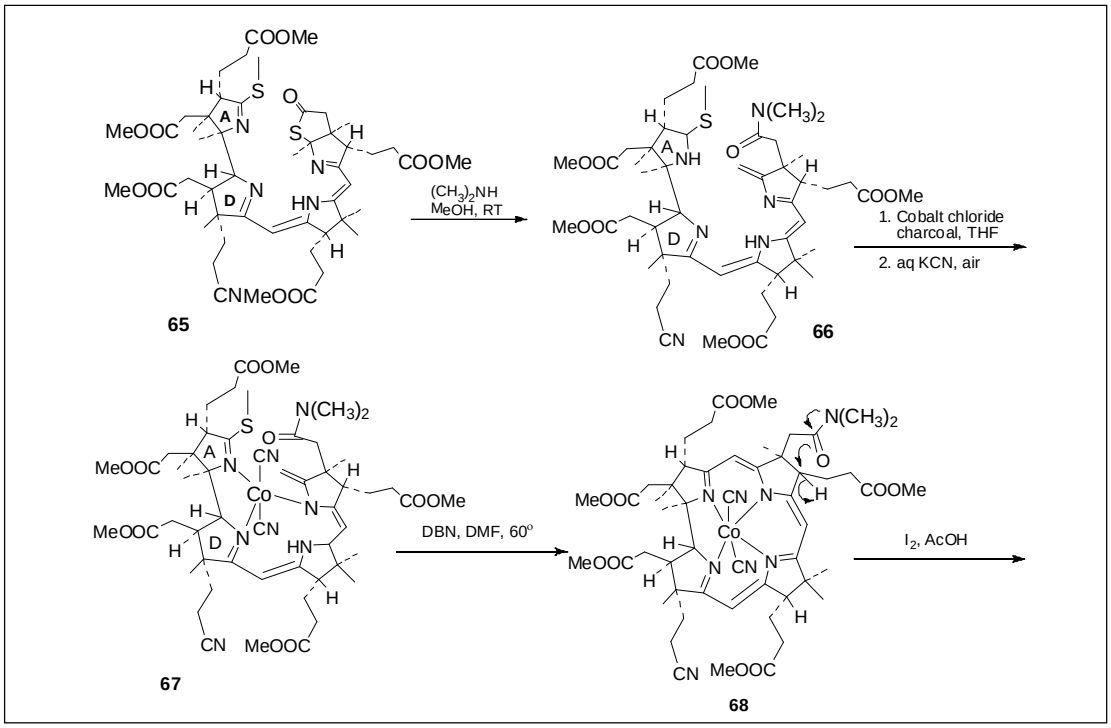
The light at the end of the tunnel came from the observation that during purification of thioether I, in addition to thioether II another isomer, thioether III was obtained.

that under these conditions, **60** isomerizes to **61**, which cannot participate in the sulfur extrusion protocol. In addition to all this confusion, the isomerization epimerized the chiral center 8, a most unkindest shift! Woodward vents his exasperation thus: "The situation at this point may be summarized by depicting thioether l as a substance precariously balanced on a precipice, of which all of our efforts pushed it into the valley represented by the dormant thioether II ..." The light at the end of the tunnel came from the observation that during purification of thioether I, in

addition to thioether II another isomer, thioether III was obtained. The latter had the southern part intact and arose from an equally dirty trick now performed in ring B, which destroyed the chirality in position 8.

When the recalcitrant **61** was treated with 4.5 equivalents of tris 5-cyanoethyl phosphine and 5.3 equivalents of trifluoroacetic acid in sulfolane nitromethane at 60°C for 24 hr, the bridged system **64** was obtained in 85% yields. The overall change could be understood in terms of shift of hydrogen from ring C to the chiral center at 13 to give **62** and the extrusion of sulfur from the resulting episulfide **63** (*Scheme* 11). The lactam unit present in **64** is the magnet to bring about the last bond on the northern side that will create the corrin system. Towards this objective, compound **64** was treated with phosphorous pentasulfide in presence of catalytic amounts of picoline. The thiolactam (A) thiolactone (B) intermediates so produced was specifically converted into the ene-thioether **65** by treatment with trimethyl oxonium fluoborate (*Scheme* 12).

Scheme 12.



12. Enter Cobalt, Creation of the Northern Bridge and the Corrin Framework

Dimethyl amine smoothly opens the thiolactone **65** giving rise to a stable dimethyl amide **66** with its all-important exo-cyclic methylene group (*Scheme* 12). The reaction of **66** with cobalt chloride in tetrahydrofuran followed by aerated aqueous potassium cyanide afforded the cobalt system **67**.

The reaction of **67** (*Scheme* 12) with diazabicyclononane in dimethyl acetamide at 60 °C for a few hours affected a smooth cyclization leading to the establishment of the cobalt corrin complex **68**.

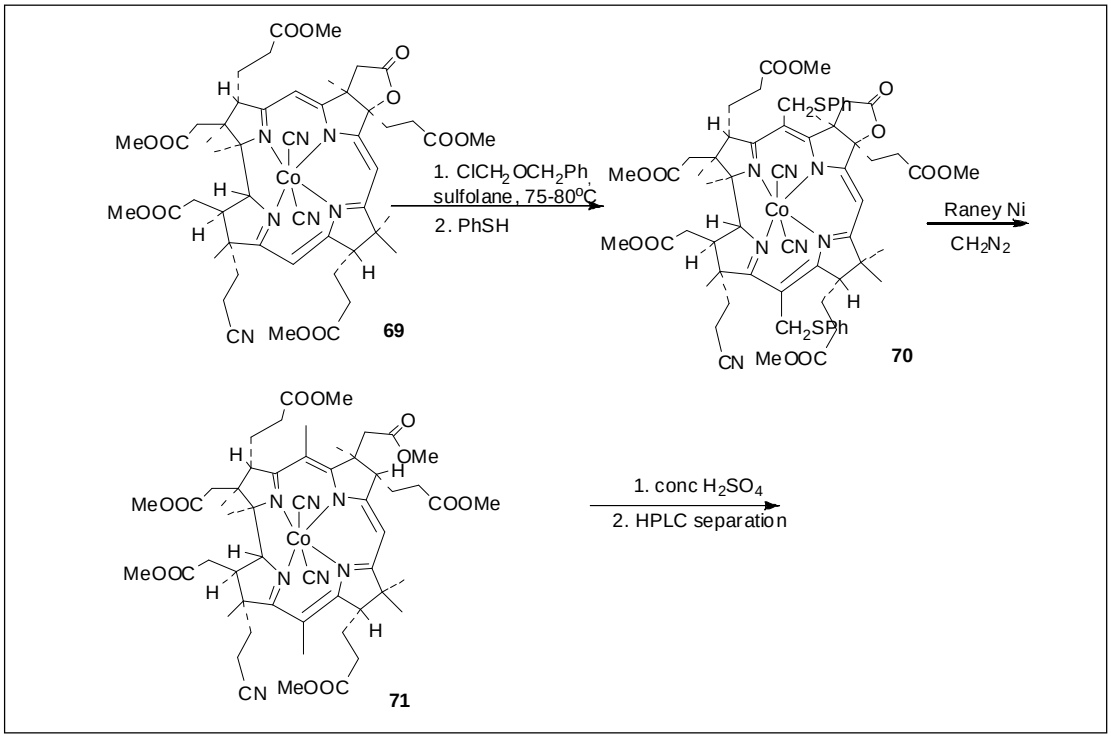
13. Selective Methylation of Corrin 68

A problem that was well foreseen was the need to introduce methyl groups at two of the three bridges present in the corrin system **68**. An obvious plan to achieve this selectivity would be to take advantage of the fact that in compound **68** (*Scheme* 12), whilst the 10 position is flanked in the south by a gem dimethyl grouping and in the north by the propionic acid chain, the others, namely the 5 and 15 locations, are relatively more accessible. The northern bastion was further secured by transforming position 8, to that one fully substituted by crafting a ring in a simple and ingenious manner. Thus, the reaction of **68** with iodine in acetic acid afforded lactone **69** (*Scheme* 13) where the 10 location is completely boxed in from both sides.

A problem that was well foreseen was the need to introduce methyl groups at two of the three bridges present in the corrin system **68**.

The reaction of **69** with chloromethylbenzyl ether in sulfolane at 75–80°C for few hours followed by treatment with thiophenol afforded the bis thiophenyl methyl compound **70** (*Scheme* 13). The reaction takes place via initial substitution at both the locations by the benzyloxy methyl group, which undergoes acid-induced fragmentation to the corresponding halide and benzyl alcohol. Introduction of thiophenol at the appropriate stage gives rise to compound **70**.

Treatment of **70** with Raney nickel and esterification with



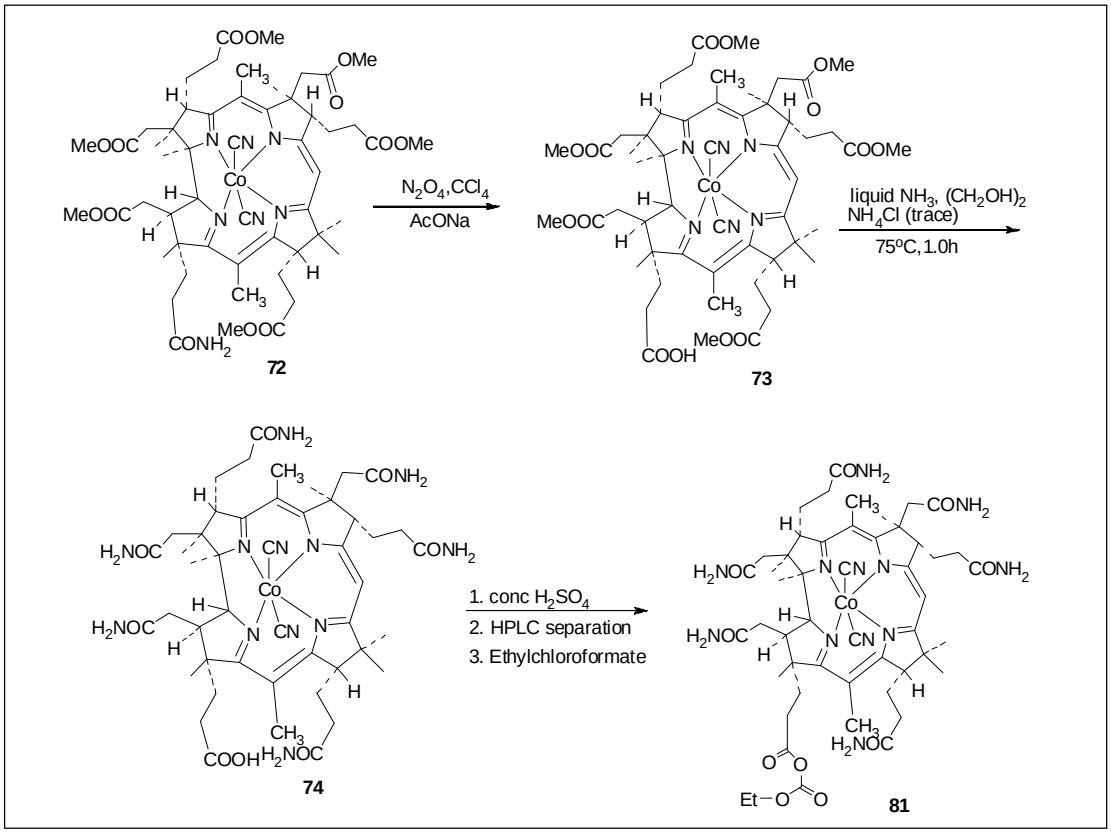
Scheme 13.

diazomethane afforded cobyrinic acid abcdeg hexa methyl ester *f*-nitrile **71** (*Scheme* 13) as a mixture of epimers.

14. Total Synthesis of Cobyrinic Acid abcdeg Hexamethyl Amide *f*-Acid: The Formal Synthetic Goal

As stated previously, compound **71** is a mixture of epimers related to position 13. Treatment of this with concentrated sulfuric acid for one hour brings about a smooth transformation to the *f*-nitrile to the *f*-amide without affecting any other functionalities. At this point the *f*-amide **72** (*Scheme* 14) and the isomer called the neo-amide could be separated cleanly by preparative HPLC. Ironically, it turns out that at equilibrium the desired *f*-amide **72** was present only at 25% levels. (The *f*-amide **72** so obtained was identical to that secured from vitamin B_{12} via vigorous methanolysis to give the heptamethyl ester followed by ammonolysis under mild conditions). Separation of these by HPLC gave a compound, which was identical in all respects to **72** obtained by total synthesis. The problem now was to transform the *f*-amide **72** to the *f*-acid

Ironically, it turns out that at equilibrium the desired *f*-amide **72** was present only at 25% levels.



Scheme 14.

by hydrolysis without affecting the susceptible six ester units present. ln the arsenal available to the organic chemist, there appears to be only one method to achieve preferential amide hydrolysis, which is the treatment with nitrous compounds. Unfortunately, in many variations of this approach, rather than the desired transformation of the *f*-amide to the acid, the 10 position of the corrin system was nitrosated.

Around the same time in Cambridge, which was not used to taking, as Woodward puts it, any nonsense about a reaction being not possible, it was eventually found that the treatment of **72** with nitrogentetroxide in carbon tetrachloride in presence of sodium acetate for one hour at 0°C, afforded the desired acid **73** in very good yields.

The glorious culmination of all the efforts over a period of 15

years was reached by the transformation of **73** with liquid ammonia–ethylene glycol–NH_4 (trace) to cobyric acid (**74,** *Scheme* 14).

The compound so obtained was found to be identical in all respects most particularly in HPLC with the cobyric acid derived from natural sources. With the footnote that cobyric acid was transformed to vitamin B_{12}, the synthesis is now complete.

The glorious culmination of all the efforts over a period of 15 years was reached by the transformation of **73** with liquid ammonia–ethylene glycol–NH_4 (trace) to cobyric acid.

15. Totally Synthetic Vitamin B_{12}

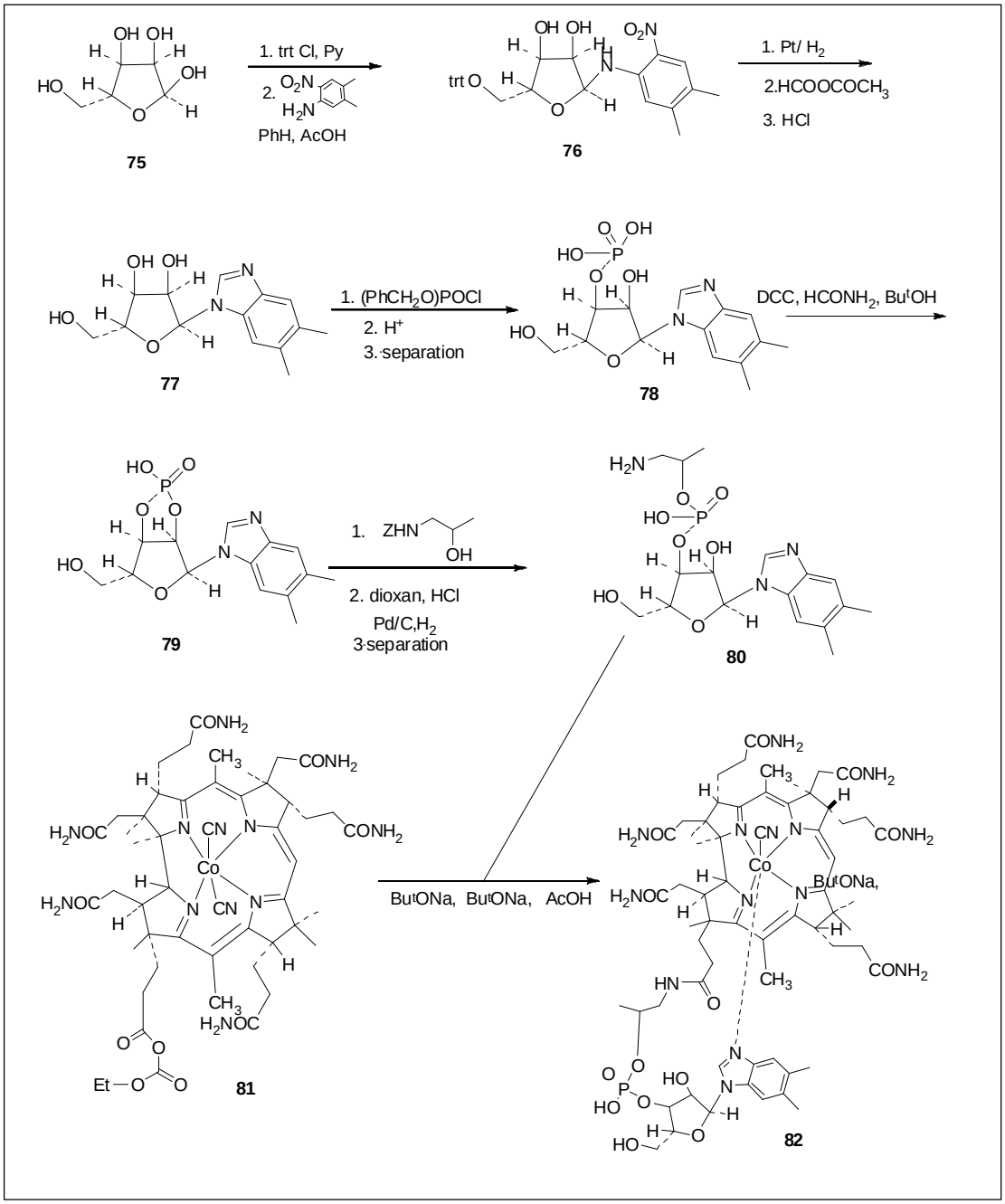
Woodward's determination to create crystals of totally synthetic vitamin B_{12}, where each one of the 181 atoms was placed at its precise location, a feat accomplished at the expense of colossal human efforts, is indeed very laudable.

The connection starts with ribazole (5,6-dimethyl-1-α-D-ribofuranosyl-1H- benzimidazole (**77**) (*Scheme* 15), whose synthesis from α-D-Ribose (**75**), accomplished in the fifties of the last century, is very much worth recounting to show that organic synthesis was well progressed even those days!

The primary hydroxyl in α-D-ribose **75** was specifically protected as the trityl derivative, the nitrogen function introduced at the mesomeric position by reaction with 2-nitro 4,5-dimethyl aniline in refluxing dry benzene containing acetic acid, to afford the composite **76**, which on catalytic hydrogenation, formylation, acid-promoted cyclization and deprotection afforded ribazole **77** (*Scheme* 15).

Treatment of **77** with dibenzylchlorophosphate followed by treatment with acid and separation afforded the 3' ribazole phosphate **78**. Compound **78** was transformed to the cyclic phosphate **79** by treatment with DCC in formamide-tertiary butyl alcohol. Opening of **79** with N-benzyloxy carbonyl amino 2-R-hydroxy propane in dioxan containing hydrogen chloride afforded mixtures, which were de-protected by hydrogenation and separated to afford the desired composite **80**. Cobyric acid **74** was activated by treatment with ethylchloroformate to the anhydride **81** which on condensation with **80** with potassium *t*-butoxide in *t*-butanol-acetic acid, followed by chromatographic separation afforded

Woodward's determination to create crystals of totally synthetic vitamin B_{12}, where each one of the 181 atoms was placed at its precise location, a feat accomplished at the expense of colossal human efforts is indeed very laudable.



Scheme 15.

vitamin B_{12} (**82**) identical in all respects to the natural compound. The souvenir that was gifted to all associated with this adventure consisted of pictures taken from a polarizing microscope of

crystals of both the natural and synthetic vitamin B_{12}, placed side by side. They were identical!

Suggested Reading

[1] ***Robert Burns Woodward: Architect and Artist in the World of Molecules*, Ed. O T Benfey and P J T Morris, Chemical Heritage Foundation, Philadelphia, 2001.**

[2] **N Anand, J S Bindra and S Ranganathan, *Art in organic synthesis* (second edition), Wiley Interscience, 1988.**

[3] **R B Woodward, The total synthesis of vitamin B_{12}, *Pure.Appl.Chem*., Vol.33, p.145, 1973.**

[4] **R B Woodward, Recent advances in the chemistry of natural products, *Pure. Appl. Chem*., Vol.25, p.283, 1971.**

[5] **R B Woodward, Recent advances in the chemistry of natural products, *Pure. Appl Chem*., Vol.17, p.519, 1968.**

[6] **R B Woodward, *Aromaticity*, Special Publication No.21 of the Chemical Soceity Burlington House, London, 1967; *Chem.Eng.News*, Vol.43, p.38, Dec.6, 1965.**

Address for Correspondence
S Ranganathan
212, Discovery Laboratory
IICT
Hyderabad 500 607, India.
Email: srgiict@gmail.com