Eschenmoser Approach to Vitamin B_{12} by A/D Strategy

An Unexpected Journey

G Wayne Craig

G Wayne Craig, a native of Hawaii has an impressive academic record: PhD (Organic Synthesis, 1982), Post Doctoral (Organic synthesis, 1983–1985). Following a stint at Genentech Ltd and Zoecon Research Institute, he took up a permanent position as head of chemistry lab for fungicide research at Sandoz AG (1981). In 2008 he founded a company for lead finding. He is passionately interested in the history of chemistry and has written several articles on this domain.

This article is dedicated to Professor Kevin M Smith, recipient of the Robert Burns Woodward Award, 2006 on the occasion of his 72nd birthday.

Keywords
History of chemistry, total synthesis, vitamin B_{12}, cobyric acid, Woodward–Hoffmann rules.

East is East, West is West, The twain shall never meet.

– Rudyard Kipling

They can indeed meet if there is a will!

The Woodward–Eschenmoser collaboration across the seas broadened the mural of organic synthesis as never before! The left-hand side of B_{12} harboring six contiguous centres (AB) was crafted by RB as a single piece whereas Eschenmoser generated all the rings A, B, C, D from a single dilactone! The great irony is that the Woodward–Hoffmann rules, whose origins came directly during the vitamin B_{12} synthesis by RB was brilliantly used by Eschenmoser for a correct photo-induced union of A and D rings.

In the following pages Dr. G W Craig provides a gripping account of the endeavours from Zurich, which has not received as much attention as it deserves. We are immensely grateful to him for this comprehensive and painstaking effort.

S Ranganathan

Human subtlety will never devise an invention more beautiful, more simple or more direct than does Nature because in her inventions nothing is lacking, and nothing is superfluous.

– Leonardo Da Vinci

Introduction

The American chemist, Robert Burns Woodward (1917–1979) intellectualized the synthesis of complex molecules based on a paramount mechanistic rationale and a sense of Nature culminating in an impressive list of chemical achievements. Although Woodward received the Nobel Prize in Chemistry in 1965, his more prestigious accomplishments were forthcoming. Joining forces with the Swiss chemist and corrin expert, Albert

Eschenmoser (b. 1925), they orchestrated and conquered the highest synthetic pinnacle imaginable at that time, the total synthesis of vitamin B_{12}.

Their collaborative Harvard–ETH approach, termed the A/B strategy, was based on Eschenmoser's east-west synthesis of an early corrin model. However, during the synthesis of the east-fragment, Eschenmoser recognized that an A/D strategy to synthesize vitamin B_{12} was theoretically attainable, in accord with the principles of orbital symmetry conservation elucidated by Woodward and Roald Hoffmann (b.1937). These post-Nobel Prize accomplishments, the Woodward–Hoffmann (W–H) rules (1965–1969) and the synthesis of vitamin B_{12} (1972–1976) respectively, were to become the major hallmark of Woodward's crowning legacy in his '*meritorious achievements to the art of organic chemistry*'

R B Woodward
(1917–1979)

A Eschenmoser
(b.1925)

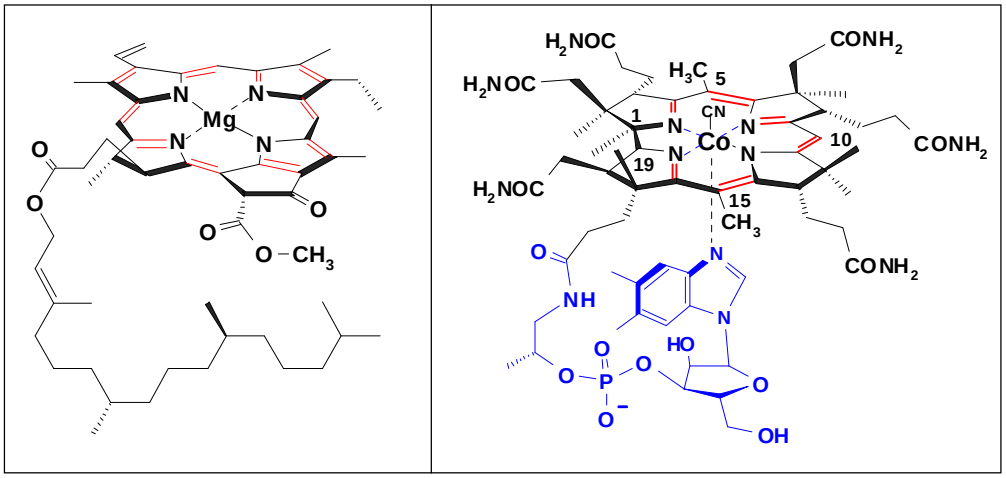
Courtesy: Novartis Archive.

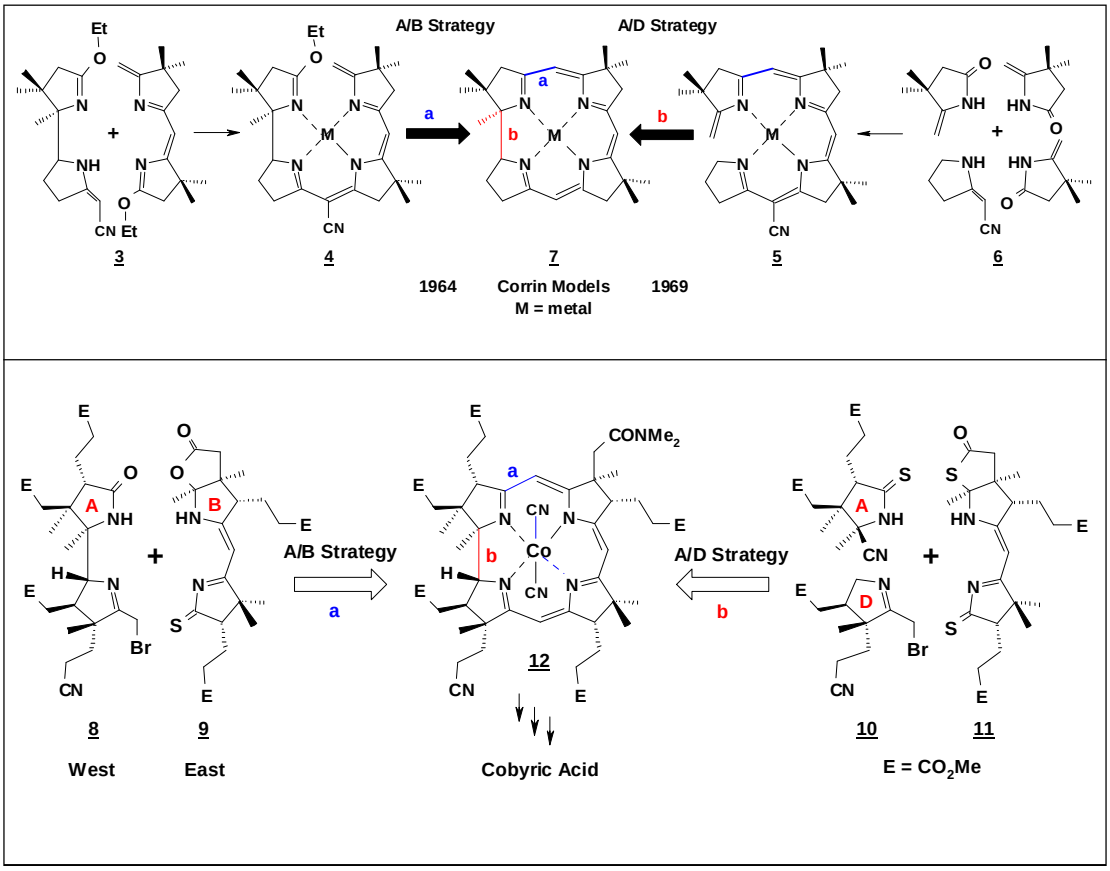
A Competitive Challenge

Before Woodward had completed the total synthesis of chlorophyll-a (**1**) (*Figure* 1) in 1960, he had already set his sights on an exceedingly more complex tetrapyrrole, vitamin B_{12} (**2**) (*Figure* 2). Between 1960 and 1961, Woodward began synthetic investigations into the west wing (**8**) of vitamin B_{12}. However, Eschenmoser at the ETH, had already initiated corrin model studies in 1959 which

Figure 1 (left). Chlorophyll-a, (**1**) red, aromatic chlorin chromophore.

Figure 2 (right). Vitamin B_{12}, (**2**) red, nonaromatic corrin chromophore.





Scheme 1 (top). Eschenmoser corrin model studies.

Scheme 2 (bottom). Two strategies to norcobyrinate *f*-nitrile (**12**).

successfully utilized iminoester-enamine chemistry to build the vinylogous amidine corrin chromophore in 1963 (highlighted red bonds, *Scheme* 1) [1, 2]. In October of 1960, Eschenmoser began synthesis of the east wing (**9**) of the natural product. These early milestones formed the chemical foundation for their eminent collaborative but competitive total synthesis of vitamin B_{12} in 1965 (*Scheme* 2) [1, 3].

Total Synthesis of Cobyric Acid, Precursor to Vitamin B_{12}

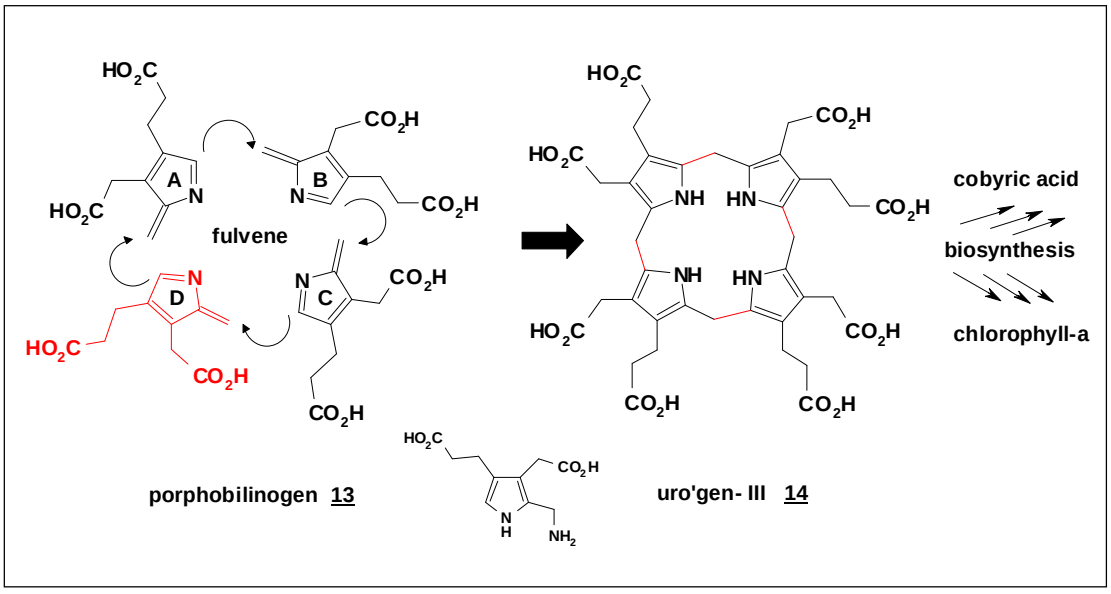
The heroic 37-step synthesis of the west-fragment (**8**) of vitamin B_{12} by Woodward's group at Harvard has been described in several excellent reviews [4–6]. The focus of this article highlights Eschenmoser's 'new road' A/D strategy toward the total synthesis of vitamin B_{12} whose crucial step relied on the

stereospecific bond formation between the pyrrolidine A- and D-rings (*Scheme* 2).

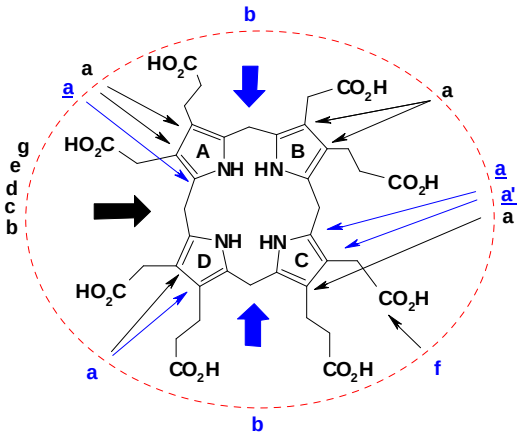
Cobyric acid (**2a**, CO_2H-group in place of the CONH-phosphate-ribose-adenosyl-chain, blue highlighted, *Figure* 2) was the obvious target since it had been transformed to vitamin B_{12} by Bernauer *et al* in 1960 [7]. However, its complex structure still encompassed a number of arduous synthetic tasks to solve, namely: (i) formation of a nonaromatic corrin ring containing (ii) nine stereogenic centers (iii) six pyrrolic CH_3-groups (iv) one CH_3-group each at the north/south corrin bridges (v) six $CONH_2$-groups and (vi) one propionate CO_2H-group located in the D-ring.

Biogenetic Symmetry

The structural complexity of cobyric acid (**2a**) can be *formally* simplified from its biosynthesis from uro'gen-III (**14**, *Scheme* 3), the first closed tetrapyrrole precursor to chlorophyll-a and vitamin B_{12}. Four head-to-tail polymerizations of porphobilinogen (**13**), assumed to occur via a short-lived fulvene intermediate after deamination, are followed by a reversal of the fourth D-ring before ring-closure to a porphyrinogen (*Scheme* 3)[8].

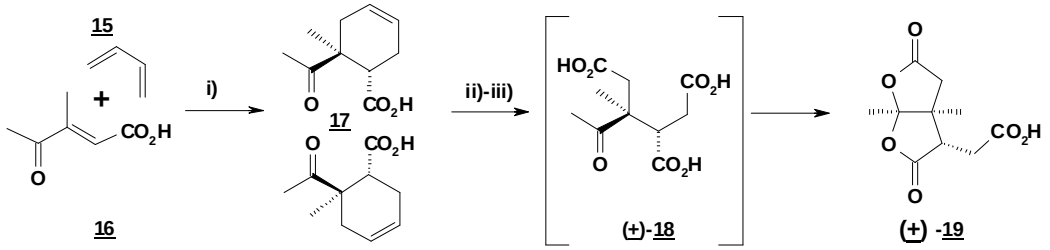


Scheme 3. Uro'gen-III (**14**) biosynthesis from porphobilinogen (**13**).



a- back-side ring methylation at first beta-pyrrole position and front-side H-reduction at *next beta-pyrrole position
a- back-side ring methylation at alpha-pyrrole position
a'- migration to *next beta-pyrrole position
b- bridge methylation
c- bridge hydroxylation
d- acetyl rearrangement and bond A-ring direct to D-ring
e- deacylation
f- decarboxylation
g- C1 assisted oxidation by acetate carboxyl group

* clockwise direction
** black / blue indicate early / late biosynthesis of cobyric acid



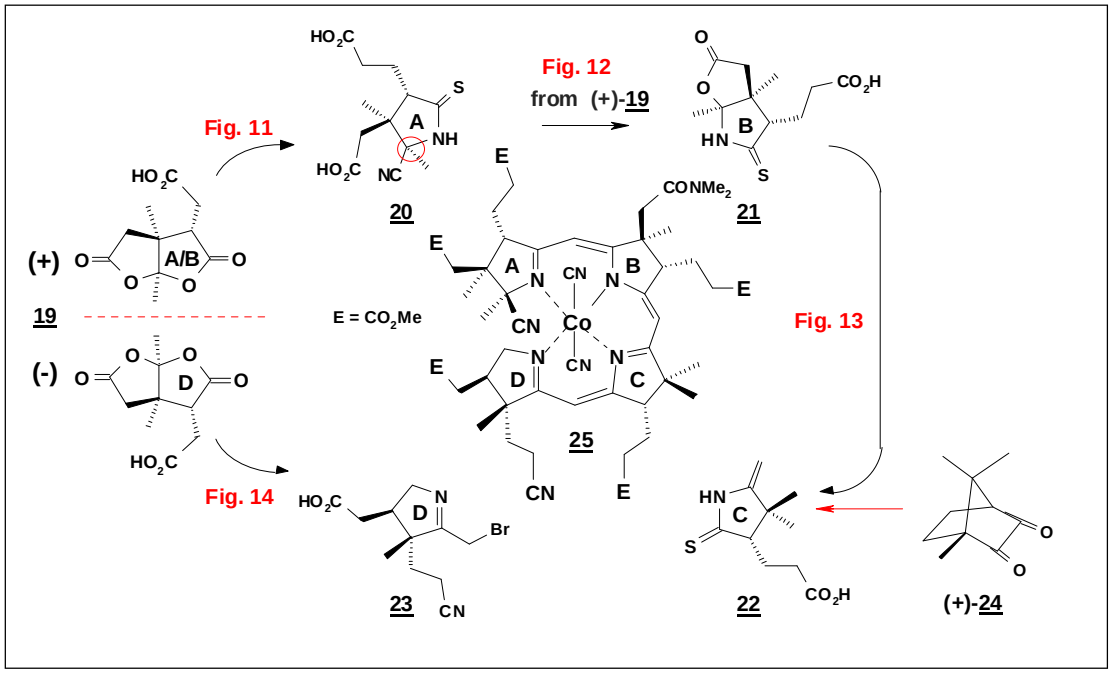
i) $SnCl_4$, C_6H_6, RT, 73% ii) resolution with chiral phenylethylamine
iii) Jones oxidation of (+) enantiomer with CrO_3-H_2SO_4-acetone in 75%

Scheme 4 (top). Biochemical transformations of uro'gen-III core[1].

Scheme 5 (bottom). Diels–Alder synthesis of racemic dilactone [12].

[1]The specific order of many structural changes in the biosynthesis of vitamin B_{12} was not known during the early total synthesis work.

Transformation of uro'gen-III (**14**) to cobyric acid (**2a**) can be briefly summarized into a condensed list of biosynthetic events (**a**–**f**, *Scheme* 4) in which some repeat in a regular fashion [8–9], particularly, stereospecific methylation (**a**, **a**′, and **b**, *Scheme* 4) transform the uro'gen-III macrocycle into a *regularly* substituted corrin nucleus whose periphery is exemplified on each pyrrole by a CH_3- and H- group lying on opposite faces of the corrin ring (*Figure* 2). This biosynthetic symmetry[1] was the underlying inspiration for Eschenmoser's convergent synthesis of each of the pyrrolidine A-, B-, C-, D-rings from a single dilactone racemate (**19**), obtained by Diels–Alder reaction described in *Scheme* 5 [10–11].



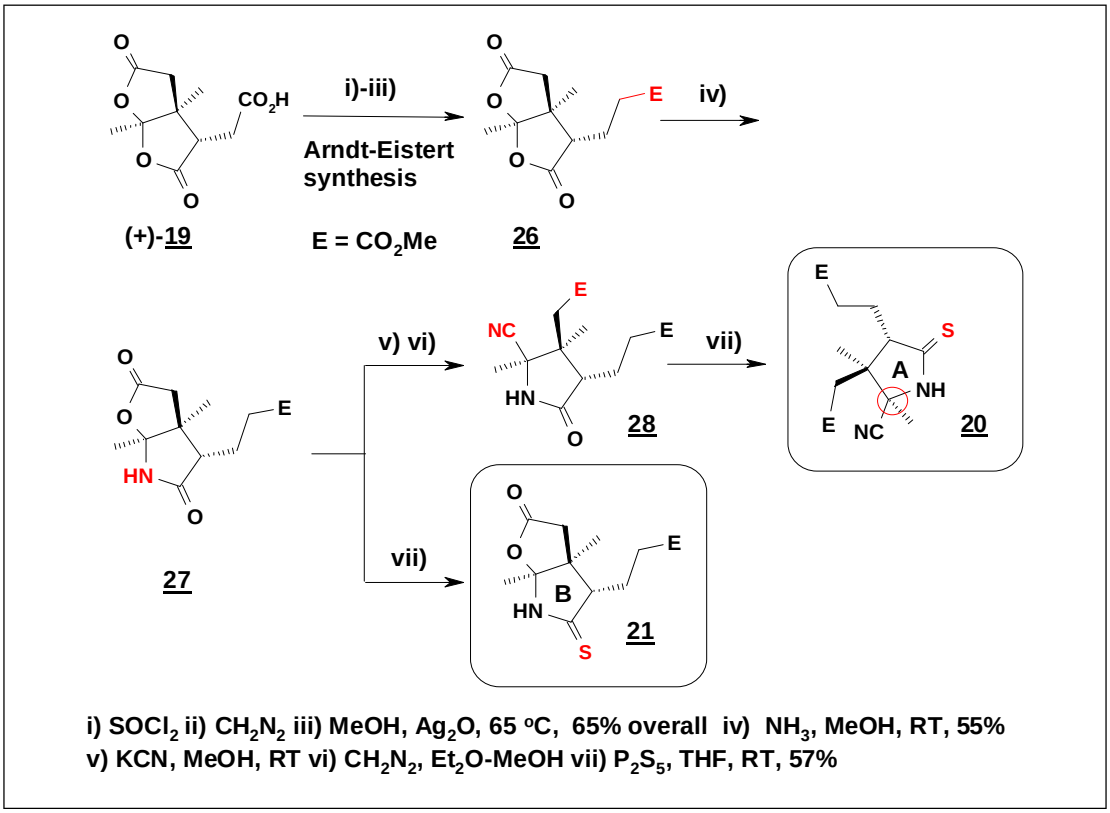
Scheme 6. Diels–Alder strategy to pyrrolidine A-, B-, C- and D-rings [12].

Synthetic Symmetry

The $SnCl_4$ catalyzed Diels–Alder reaction of 1,3-butadiene (**15**) with β-acetyl-β-methyl acrylic acid (**16**) produced the cyclohexene (**17**) as a racemic mixture which was cleaved by Jones oxidation and (**18**) cyclized to produce the key dilactone ketal (**19**, *Scheme* 5). The (±)-enantiomers were resolved with chiral phenylethylamine and each antipode transformed to the appropriate pyrrolidine A-, B-, C- or D-rings, as indicated in *Scheme* 6.

Syntheses of Pyrrolidine A- and B-Rings

The acetic acid residue on (–)-dilactone (**19**) was elongated by an Arndt–Eistert homologation sequence (i-iii, *Scheme* 7) in 65% overall yield. Equilibration of the dilactone homologue (**26**) in the presence of NH_3 in CH_3OH gave regioselectively the aminal (**27**) in 55% yield. Treatment of (**27**) with KCN displaced the more reactive lactone carbonyl which was esterified with diazomethane to produce the cyanolactam diester (**28**). Afterwards, (**28**) was thiolated to the desired thiolactam diester (**20**)

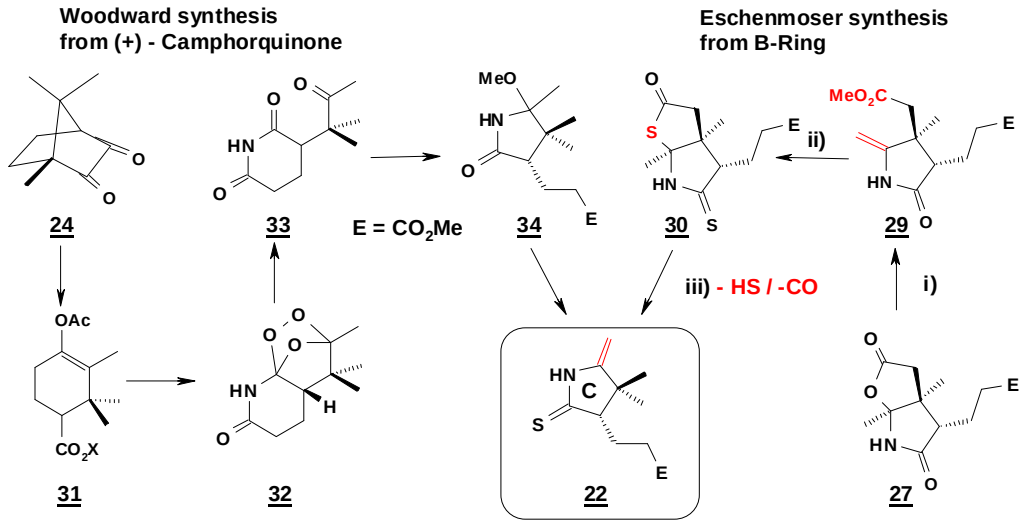


Scheme 7. Syntheses of the pyrrolidine A- and B-rings [12].

A-ring. The CN-group essentially protected the exo-double bond, unveiled later at the ring closure stage. In parallel, aminal (**27**) was transformed with P_2S_6 to produce lactone thiolactam (**21**) B-ring, in 57% overall yield.

Synthesis of Pyrrolidine C-Ring

Eschenmoser's approach to ring C (*Scheme* 8) was essentially the same as that of Woodward's scheme (see *Scheme* 6 on p.593 of this issue) [13–15]. However, Eschenmoser was able to convert the pivotal aminal (**27**) by base elimination, ring opening of the lactone carbonyl, and esterification with diazomethane to the ene-lactam (**29**, *Scheme* 8). Mild thiolation with H_2S provided the thiolactone-thiolactam (**30**) in 78% yield, followed by decarbonylation with Wilkinson catalyst gave efficiently the C-ring (**22**, *Scheme* 8).



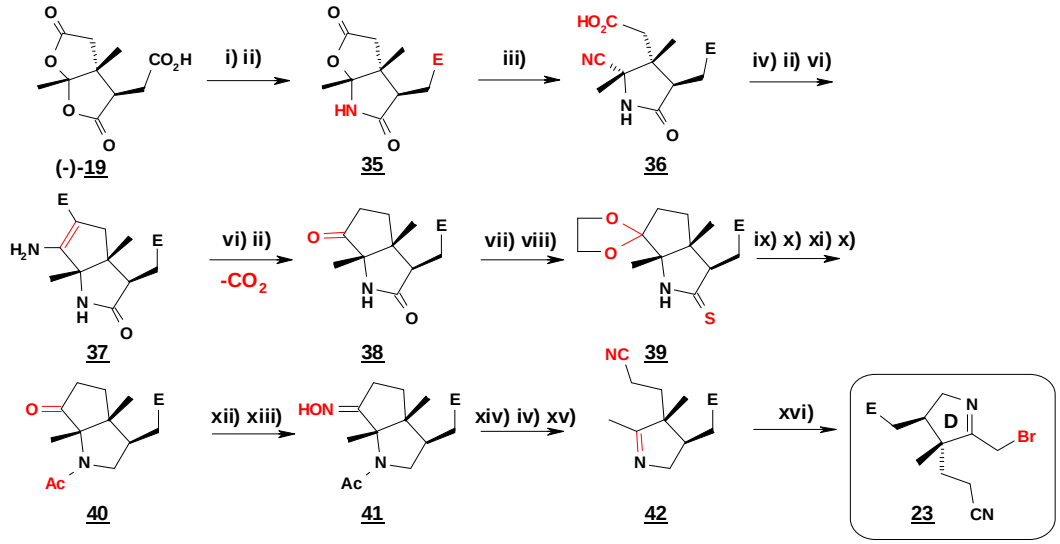
Scheme 8. Eschenmoser's synthesis of the pyrrolidine C-ring [12].

Although Eschenmoser's sequence to the pyrrolidine C-ring (**22**) required fewer steps, it drained the pool of costly material away from the synthesis of the other pyrrolidine A- (**20**), and B-rings (**21**). In practice, the camphorquinone transformation proved more amenable for preparative production of C-ring (**22**, *Scheme* 8)[6].

Synthesis of Pyrrolidine D-Ring

Reversal of the D-ring in the biosynthesis of uro'gen-III (red highlighted, *Scheme* 3) required the opposite dilactone antipode (-)-(**19**) as the optimal starting pyrrolidine for the desired D-ring (**23**, *Scheme* 9).

Treatment of (-)-lactone lactam (**35**) with KCN–MeOH opened the lactone to the cyano lactam acetic acid (**36**), elongated by the Arndt-Eistert sequence to the propionate group, and Thorpe condensation onto the CN-group produced the enamine lactam (**37**, *Scheme* 9). The enamine was hydrolyzed to the ketone and re-protected as a dioxolane ketal before thiolation with P_2S_5 to the thiolactam (**39**). Reduction of sulfur with Raney-Ni gave a pyrrolidine which was N-acylated before hydrolysis to the ketone



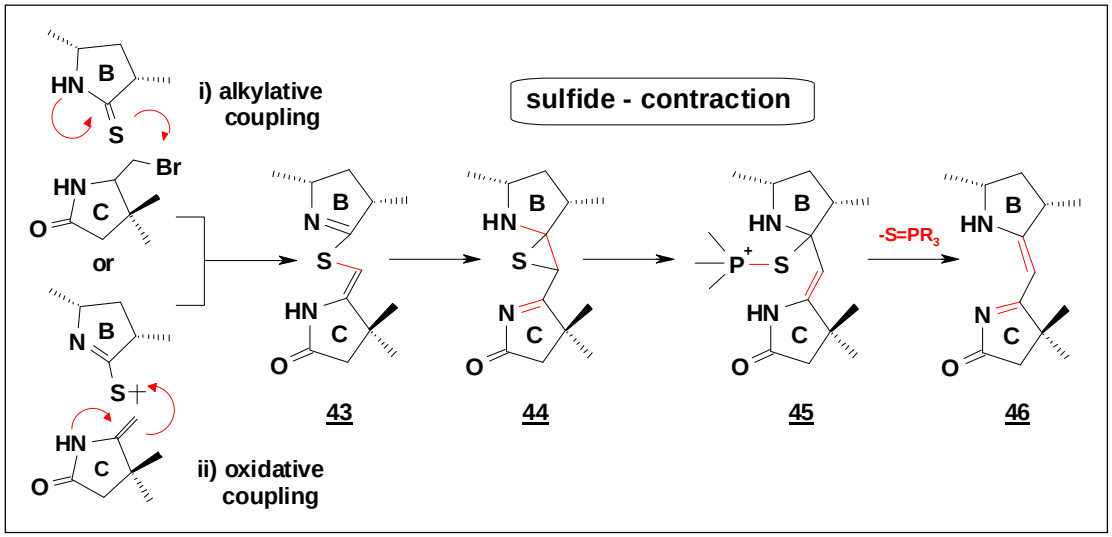
Scheme 9. Synthesis of the pyrrolidine D-ring [12].

(**40**). Transformation of (**40**) to the oxime (**41**) occurred in 95% yield and Beckmann fragmentation of the oxime produced the pyrrolidine propionitrile (**42**). Acidic deprotection of the N-acetyl group followed by allylic bromination gave the cyanobromide D-ring (**23**).

Sulfide-Contraction Linkage of Pyrrolidine Rings

Eschenmoser's early A/B strategy, which utilized iminoester-enamine condensation to link vinylogous amidine west- and east-fragments in the model corrin system (*Scheme* 1) proved unsuccessful to link B- and C-rings containing the steric-demanding acetate/propionate substitutents required for cobyric acid [1, 11].

However, an improved variation exploited the greater nucleophilicity of sulfur to bring the two pyrrolidine rings together, tethered through a C–S bond in (**43**), which lowered the entropy for C–C bond formation and ring contraction to episulfide (**44**). The elimination step was made irreversible by trapping the lost sulfur



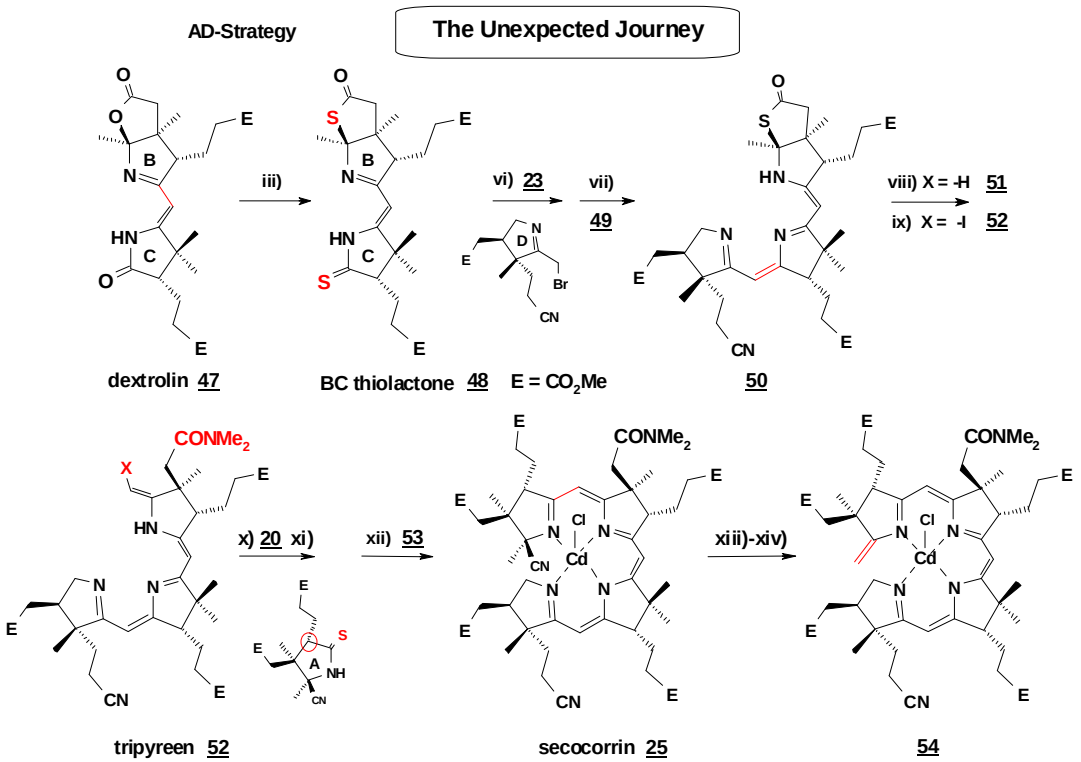
Scheme 10. Sulfide contraction to link pyrrolidine rings.

atom with triethylphosphine (**46**, *Scheme* 10) [11]. Generally, the sulfide contraction method permitted stepwise connection of pyrrolidine rings but proved difficult with prior terminal double-bond substitution to produce an alkylated methine-bridge [16]. Only recently, novel chemical developments by Mulzer [17] and Jacobi [18] have overcome some of these initial difficulties to introduce a bridge substituent before corrin ring synthesis by a north/south strategy.

The New Road, an Unexpected Journey

In 1965, during the synthetic investigations of the west-fragment, the important role of orbital symmetry in concerted reactions was first elucidated by Woodward and Hoffmann [19]. Eschenmoser realized then that an A/D strategy (*Scheme* 2) was conceivable using photochemical conditions. In 1969 he demonstrated that a metal-templated ring closure was feasible in a corrin model system (*Scheme* 1) [20]. He relaunched his efforts into a synthesis of the secocorrin (**25**, *Scheme* 11) by stepwise usage of sulfide contraction. In retrospect, his journey was to continue long after the total synthesis of vitamin B_{12} was completed [21].

The pivotal east-fragment required for the A/B strategy, dextrolin (**47**, *Scheme* 11) was thiolated with P_2S_5 to give the thiolactam

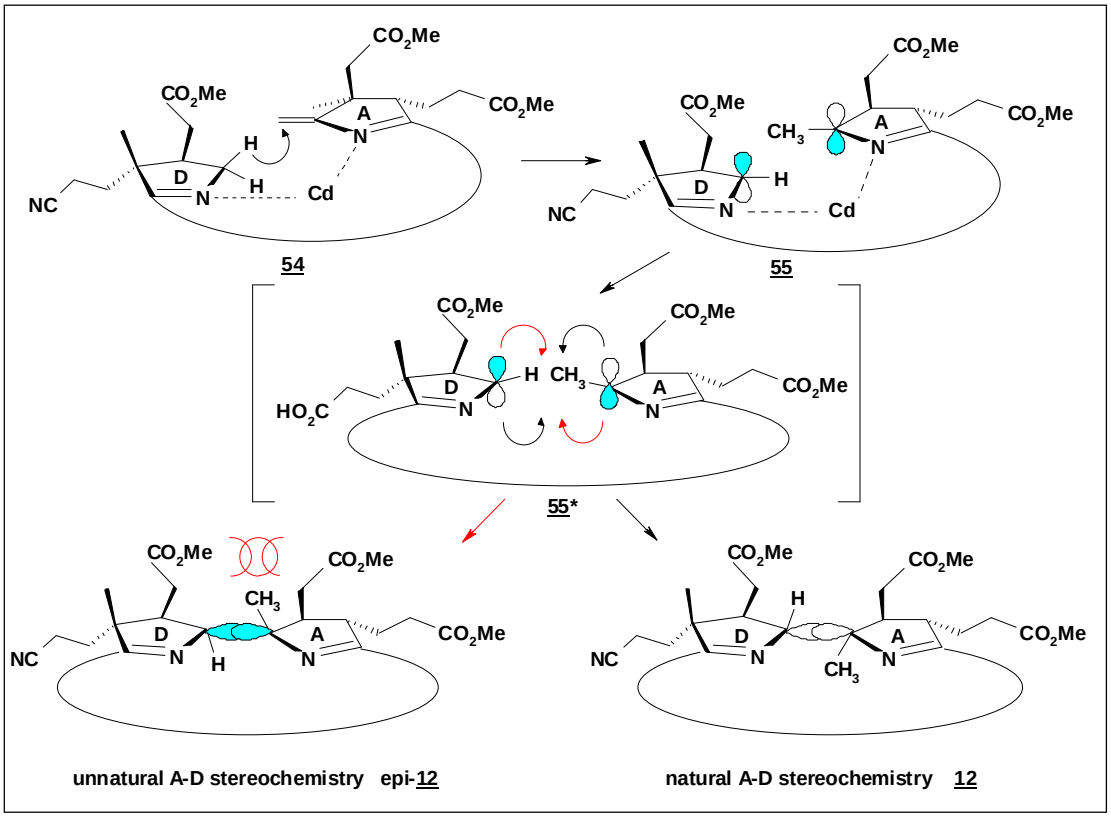


Scheme 11. Pyrrolidine ring condensation to secocorrin (**25**)[12].

(**48**) in 84% yield. Thioalkylation of the thiolactam (**48**) with D-ring (**23**) gave after sulfide contraction, the thiolactam tripyreen (**50**) in 64% overall yield [1]. Repeating this two-step process with tripyreen (**50**) and A-ring (**20**) gave the desired secocorrin (**25**) after sulfur elimination in 46% overall yield.

A-D Ring Closure

In a sense, the advancement to the ring closure stage for the Zurich A-D step, (achieved in January, 1971) and the Harvard A-B step (achieved in May, 1971) was an open race [1]. In the photochemical induced A-D step, the highest occupied molecular orbital (HOMO) of the 18-electron secocorrin ring exhibited



Scheme 12. A/D ring closure to norcobyrinate *f*-nitrile (**12**).

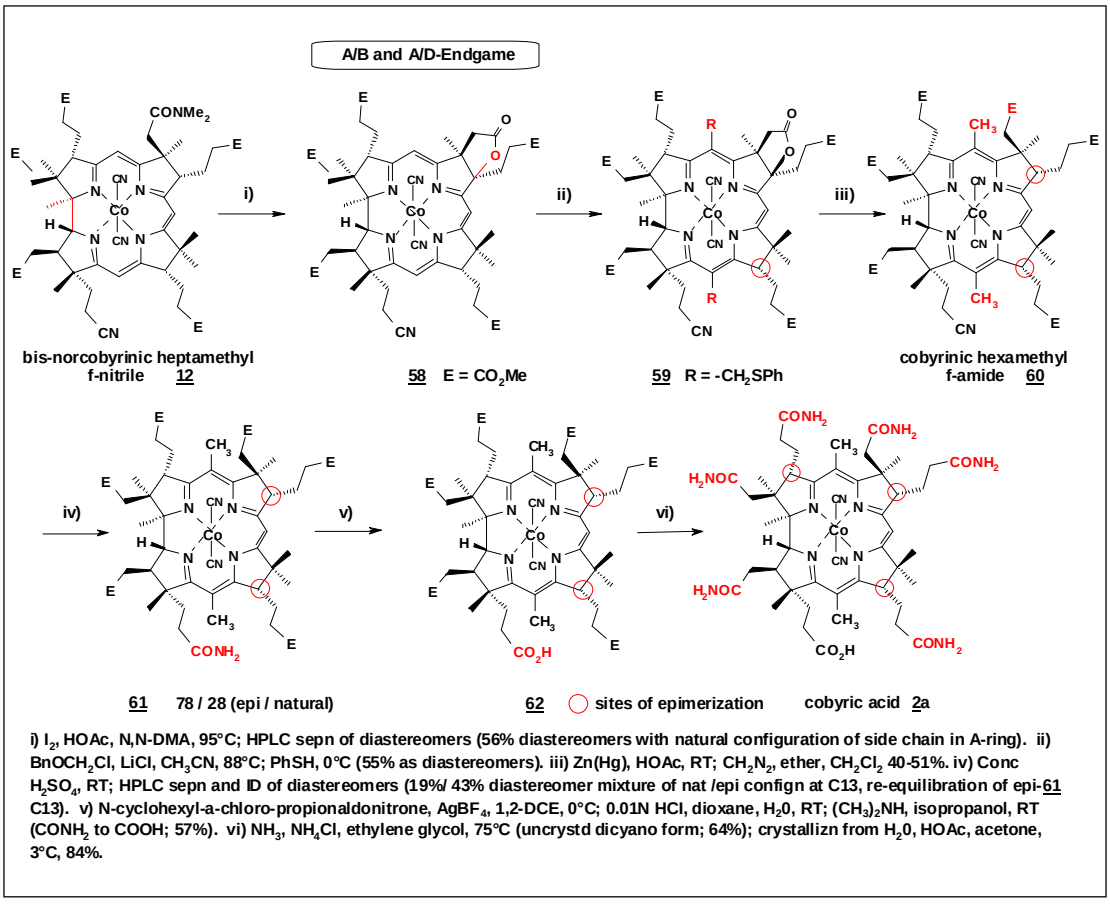
antisymmetric character (**55***, *Scheme* 12). In W–H theory, a concerted antarafacial 1-17 sigmatropic-H migration from (**54**) was allowed to produce the 1,15-diradical (**55**), held together by metal coordination. This 16-electron mesoionic intermediate (**55**) ring closed by a thermal allowed conrotatory interaction to the norcobyrinate *f*-nitrile (**12**, *Scheme* 12) [22].

Eschenmoser's A/D route was a magnificent 'synthetic' gambit which gave exclusively the W–H predicted *and* 'natural' B_{12} trans-configuration at the A-D bridge! The alternative 'unnatural' B_{12} conrotatory product epi-(**12**) (red highlighted arrows, *Scheme* 12) was not observed, attributed to a strained juxtaposition of the CH_3-group to the two *cis*-acetate substitutents on the pyrrolidine A- and D-rings! The convincing rationale obtained by the principle of orbital symmetry was fully consistent with the results of Eschenmoser's A/D synthesis. On one hand, the W–H

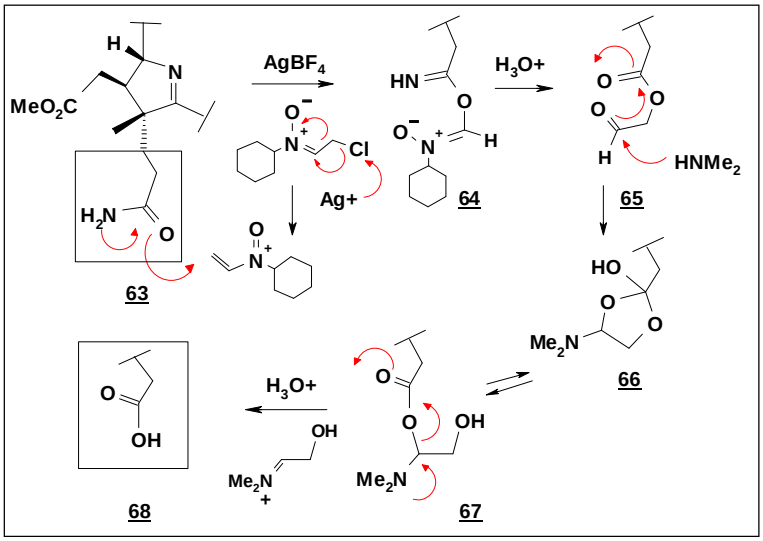
rules offered the rite-of-passage but on the other hand, Eschenmoser's brave new synthetic strategy was a brilliant 'all or nothing' gamble that paid rich dividends!

Final Steps to Cobyric Acid

Sulfide contraction to form the north/south bridges with CH_3-groups on the terminal positions prior to ring closure proved difficult [16]. However, Woodward and Eschenmoser were able to exploit peripheral ring substitution after ring closure to the desired reaction at the C10-bridge (*Scheme* 13) [1, 22]. Because the bridge positions of porphrinoid systems were highly prone to electrophilic reaction [22], the C8-position was protected as the lactone (**58**) followed by Zn(Hg)-metal/acetic acid reduction



Scheme 13. Final steps to cobyric acid (**2a**)[12].



Scheme 14. Amide hydrolysis to cobyric acid (**2a**).

produced simultaneous removal of the north/south PhS groups and ring opening of the allylic lactone to the cobyrinate *f*-nitrile (**60**) in 40–61% yields after diazomethane treatment [12].

The inevitable task to transform the cobyrinate *f*-nitrile (**60**) to the *f*-amide (**61**) was not trivial and the harsh H_2SO_4 treatment gave an equilibrium mixture (28:72) of desired (**61**) and C13 epi-(**61**) amide. The allylic sites C3, C8 and C13 were highly epimerizable and diastereomers produced at a late stage required rigourous HPLC separation (circled positions highlighted in red, *Scheme* 13). However, more crucial was the chemoselective hydrolysis of the weak electrophilic $CONH_2$ group of (**61**) to cobyrinic acid (**62**) without hydrolysis of the CO_2Me-groups.

This synthetic problem at Harvard was neatly solved by optimized N_2O_4-CCl_4 treatment which gave readily the hexamethyl ester *f*-acid (**62**) [23]. In Zurich, Eschenmoser devised a selective fragmentation of the $CONH_2$-group which was in Woodword's words, a *diabolical* usage of cyclohexylnitrone which avoided hydrolytic conditions (*Scheme* 14) [12, 23]. Finally, conversion of the six CO_2CH_3 to their $CONH_2$-groups required careful optimization of the ammonia-ammonium chloride conditions which gave cobyric acid (**2a**, *Scheme* 13) in 64% yield.

Conclusions

Completion in 1973 of the vitamin B_{12} formal total synthesis was a monumental effort of the Woodward era. It reaffirmed the usage of mechanistic logic based on physical properties and chemical reactivity to verify chemical structure, rather than by tedious degradation and identification of fragments of the complete molecule, a common approach during the golden age of Sir Robert Robinson [24].

Moreover, Eschenmoser's contributions in the total synthesis of vitamin B_{12} and his immense pioneering influence on the landscape of corrin chemistry stand above his many achievements. Improving on Nature, he elegantly forged a second total synthesis into a convergent strategy where each chiral pyrrolidine ring came from a common Diels–Alder racemate. Except for the A-D junction, he had shown that his sulfide-contraction to link the four pyrrolidine rings was an efficient strategy, amenable to oxidative or alkylative variations.

Eschenmoser's ingenuity was reflected in the nontrivial final step to cobyric acid that employed a nitrone alkylation of the nucleophilic amide-nitrogen, and transformed the amide into its carboxylic acid by fragmentation rather than by hydrolysis.

However, the unexpected discovery of the W–H principles of orbital symmetry [1] was the catalytic stimulus for Eschenmoser's embarkment on the new-road A/D synthesis of cobyric acid, in parallel with the A/B route already in progress. Success in his initial A/D corrin model studies and the photochemical ring closure of the secocorrin provoked the question whether Nature might follow such a biosynthetic path, in which the crucial A-D bond was formed by sunlight or by a dark non-photochemical alternative, a clue[2] in the evolution of the B_{12} molecule [3].

Eschenmoser's synthetic journey did not abruptly end with the photochemical solution of the problem. He proposed intriguing questions based on the discovered metal coordination reference of the corrin chromophore over its unconjugated porphrinogen

[2] During the total synthesis, biosynthetic studies with ^{14}C-labeling verified that the excised A/D CH-bridge was not the origin of the C1-CH_3-group [8].

precursor and their biological significance in Nature [25]. In retrospect, his research revealed later that the amino-phosphate-ribose-adenosyl residue selectively reacted at the D-ring propionate of an undifferentiated hepta-CO_2CH_2CN cobyrinate of (**62**) [25]. The evolutionary role of B_{12} and its ribose arm led to the study of *Nature's* preference of pentose (ribose) over hexose (pyranose) and its connection to ribo- and deoxyribonucleic acids (RNA, DNA) [26]. Today, Eschenmoser's research provides fundamental ideas in an exciting journey to understand chemical evolution and biogenesis, the origin of life. What began as a theoritical proof to verify a W–H prediction of orbital symmetry became an unexpected journey to understand primordial RNA and DNA, long after the formal total synthesis was completed [27].

Acknowledgments

It is my pleasure to acknowledge Professor Subramania Ranganathan, who invited me to highlight Professor Albert Eschenmoser's major contributions to the Herculean total synthesis of vitamin B_{12} by the A/D strategy with the late Professor Robert B Woodward. More importantly, I am grateful for Professor Ranganathan's personal *Woodward* reminiscences while he undertook research at Harvard and in Basel. I am also indebted to my colleagues, Dr Andrew J F Edmunds and Dr Andre Jeanguenat who kindly proofread early versions of the manuscript and provided many helpful comments. It was indeed a pleasure to discuss with all of them the many facets of Woodward's impact on chemical synthesis today. Finally, I thank Dr Walter Dettwiler for permission to reproduce photographs from the Novartis Archive.

Suggested Reading

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