Total Synthesis of Cobyric Acid: Historical Development and Recent Synthetic Innovations

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Dedicated, with admiration, to Albert Eschenmoser

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The total synthesis of vitamin B_{12} and its precursor, cobyric acid, has been one of the most demanding and elusive goals in synthetic organic chemistry for over thirty years. This review outlines the historical development leading to the first and so far only total synthesis, by Woodward and Eschenmoser, and gives an account of later contributions from the groups of R. V. Stevens, P. A. Jacobi, and J. Mulzer.

The total synthesis of cobyric acid (**1**) and thus vitamin B_{12} (**2**) (Scheme 1) has been a challenging target for organic chemists for four decades. The outstanding achievements of the close collaboration between R. B. Woodward and A. Eschenmoser,[1] the first two total syntheses of vitamin B_{12} (**2**) had an enormous impact on the science of organic synthesis. Novel bond-forming strategies, an ingenious solution to formidable synthetic problems, elegant applications of synthetic methodology, intriguing hypotheses about the biogenesis[2] and the principles of orbital symmetry conservation[3] all issued from this landmark achievement. Since then, cobyric acid has remained an elusive goal for several groups. This article highlights the contributions from the groups of Stevens, Jacobi and Mulzer.

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Historical Background

The vitamin B_{12} story started with the discovery of the liver-based therapy against pernicious anaemia in 1926, but it was not until 1948 that Folkers et al. first isolated this antipernicious factor.

In 1956, D. Crowfoot-Hodgkins' single-crystal X-ray diffraction studies resulted in the elucidation of the complete structure of vitamin B_{12},[4] at that time a great achievement in crystallography. Vitamin B_{12} belongs to the family of uroporphyrinoid cofactors, the so-called "pigments of

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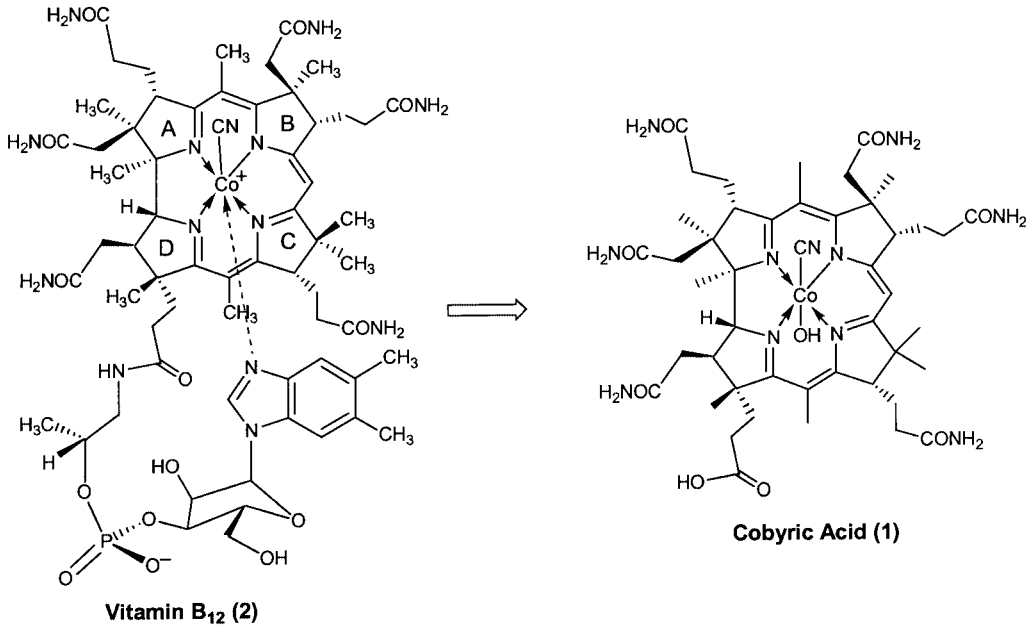
Johann Mulzer was born in 1944 at Prien in Upper Bavaria. In 1974 he received his Ph.D. under the supervision of Rolf Huisgen at the Ludwig-Maximilian-Universität in Munich, and subsequently joined E. J. Corey's group at Harvard as a postdoctoral fellow. From 1982 to 1996 he held professorships at the University of Düsseldorf, the Free University of Berlin, and the Johann-Wolfgang-Goethe-University in Frankfurt. Since 1996 he has been a full professor at the Institute of Organic Chemistry of the University of Vienna. His main research interests are focussed on the total synthesis of structurally and physiologically interesting natural products: among others morphine, tartrolone B, epothilones, cobyric acid and laulimalide.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.



Scheme 1

life'',[5] which include such vital substances as chlorophyll A, used by plants in photosynthesis, and heme, the red blood pigment essential for oxygen transport. Other members of this family include siroheme, which has been discovered in sulfite and nitrite reductases of bacteria and plants, and the nickel-containing factor F430, the prosthetic group of the coenzyme M reductase of primitive methanogenic bacteria. Cobalamines, vitamin B_{12}, methylcobalamin, and coenzyme B_{12} each contain a reduced tetrapyrrole, a corrin macrocycle, that is less symmetric than porphyrin and is characterized by a direct junction between rings A and D. The macrocyclic nucleus, comprising four five-membered heterocyclic rings A, B, C, and D, is organized around a central cobalt atom and the periphery is decorated with methyl, acetamide and propionamide substituents, so that nine out of the ten sp^3 ring carbon atoms are stereogenic centres, three of them quaternary.

In the 1960s it was shown by Bernhauer et al.[6] that cobyric acid (**1**) can be transformed into vitamin B_{12} (**2**) simply by treating it with the free nucleotide moiety. Additionally, access to the nucleotide was afforded either by the total synthesis developed by Todd and Folkers, or directly from the vitamin **2**.[7] This made cobyric acid (**1**) the primary synthetic goal.

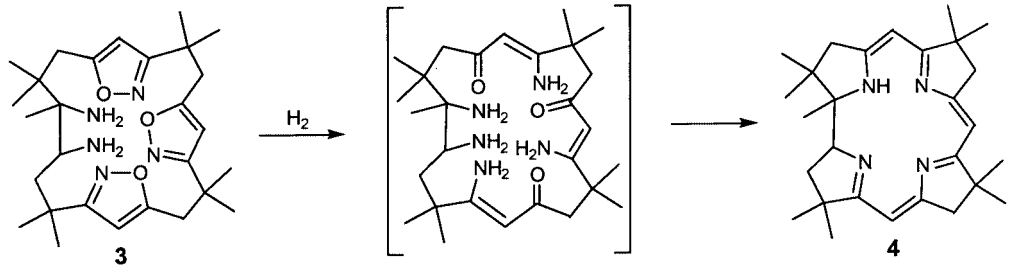
Cobyric acid (**1**) offers two major challenges for organic synthesis. The first is the requirement for highly efficient, stereoselective syntheses of the four highly substituted five-membered rings. Although the C and D units are different from A and B, it should be noted that there are some singularly striking structural and stereochemical similarities between all four subunits. Furthermore, it should be pointed out that the two carboxyl group bearing side chains of ring D have to be differentiable so that the nucleotide moiety can be attached at the proper position of **1** to form **2**. The second challenge lies in the construction of the macrocyclic ring from the four components A−D, which must be compatible with the various functional groups adorning the periphery of the ligand and, finally, must also allow the introduction of the two *meso*-methyl groups into the sterically encumbered bridging positions between rings A/B and C/D, respectively.

Initial Synthetic Studies by J. W. Cornforth

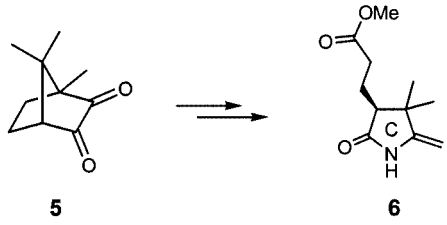
Although Cornforth discussed his work in many lectures, very little of that was published.[8] Cornforth's work started in the M. R. C. Laboratories in London in the late 1950s and continued in the Shell Laboratories (Milstead) and at Warwick University. The basic strategy of the Cornforth approach was aimed at the synthesis of a macrocyclic intermediate **3** containing three isoxazole units, which it was hoped would undergo reductive fission followed by cyclocondensation to give the corrin chromophore **4** (Scheme 2).

The initial objectives were therefore to synthesize fragments of compound **3** with the correct absolute stereochemistry. Potential A and B ring intermediates were thus prepared, whereas two syntheses of C ring fragment **6** were achieved (Scheme 3). One of these started from optically active camphorquinone (**5**), which already contains both the stereocenter and the geminal dimethyl group, and this strategy was later adapted in the Woodward−Eschenmoser synthesis (some work on the D ring fragment was also done, and seems to have influenced parts of the Woodward−Eschenmoser synthesis).

Although Cornforth's experiments were more of a tentative nature, and a considerable amount of additional work would have been required until a promising strategy could



Scheme 2



Scheme 3

have emerged, the impact on the later work of Woodward, Eschenmoser and, in particular, Stevens is undeniable and cannot be underestimated.

First Total Synthesis: the Woodward–Eschenmoser Approach

A transatlantic, though close, collaboration between Eschenmoser's group in Zürich and Woodward's group in Harvard culminated in the first total synthesis of cobyric acid. The strategy of the approach involves the retrosynthesis of the target cobyric acid (**1**) to two molecules: the "western" A–D fragment **7** and the "eastern" B–C fragment **8** (Scheme 4).[1]

The A–D fragment **7**, which was allocated to the Harvard group, is the synthetically more demanding of the halves, with its "*crowded concatenation of six contiguous asymmetric centers*". Any Swiss effort spared by this division of labour was to be made up in full by the experience in the corrin field available to the Zürich workers, in particular the sulfide contraction method. While Woodward prepared the A–D fragment **7** in a linear sequence of 37 steps, of which several were crucial key steps,[1g] Eschenmoser achieved a convergent synthesis of **8** in 17 steps by connecting fragments B (**9**) and C (**10**) (Scheme 5). The synthesis of the B ring fragment **9** was based on a Diels–Alder reaction and optical resolution, while the C ring synthesis was derived from camphorquinone (**5**) in an adaptation of Cornforth's synthesis.

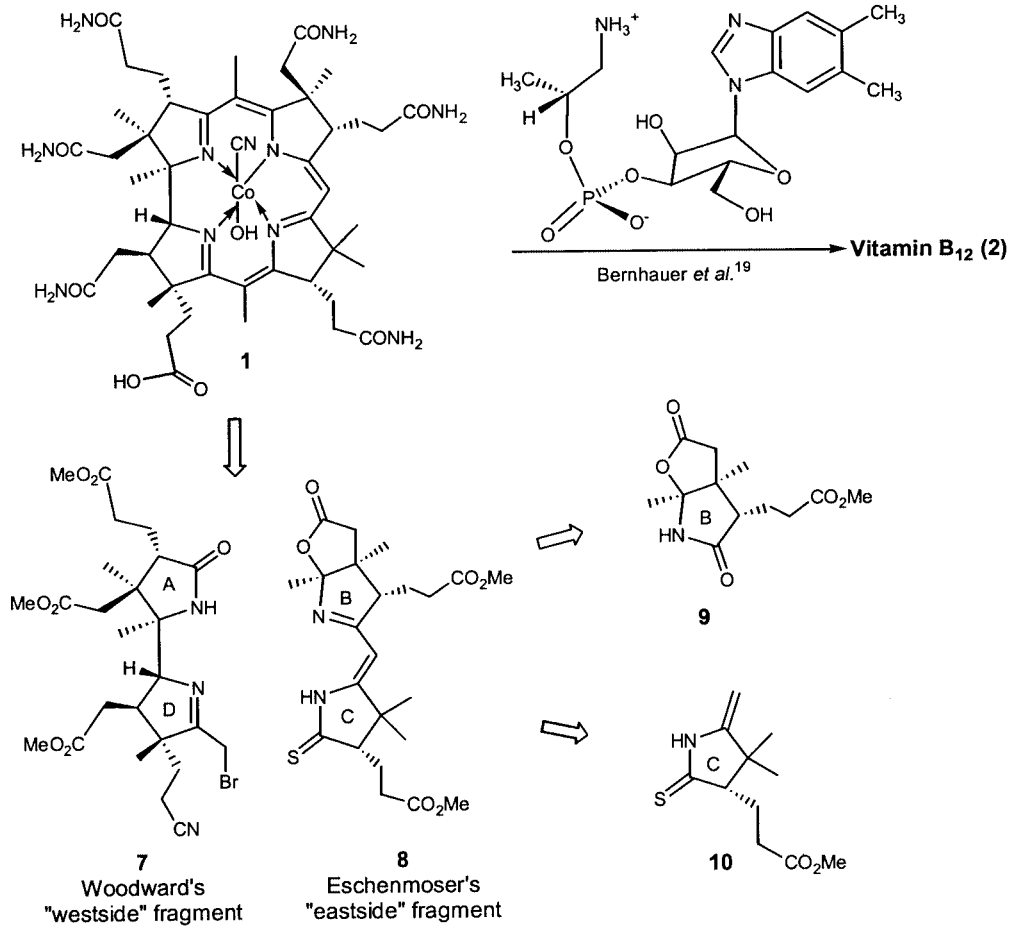
The Zürich group made a great contribution to corrin chemistry by their development of the sulfide contraction for the joining of the sterically demanding ring fragments of cobyric acid (**1**):[9] "*Whenever in the synthesis of complex organic molecules one is confronted with a situation where the success of an intermolecular synthetic process is thwarted by any type of kinetically controlled lack of reactivity, one should look for opportunities of altering the structural stage in such a way that the critical synthetic step can proceed intramolecularly rather than intermolecularly.*"[10] In this method the sulfur atom of a thiolactam **11**, which is sterically unhindered thanks to the length of the carbon–sulfur bond, is linked to the methylidene carbon atom of the enamide **12** to give a sulfur-bridged intermediate **13**. Thermal rearrangement provides the tautomeric episulfide **14**, which in the presence of a suitable sulfur acceptor undergoes sulfur extrusion to give the required vinylogous amidine system **15**.[11]

By application of this method, the A–D and B–C halves **7** and **8** were joined together, via the thioether **16**, to provide an A–B–C–D semicorrin **17**. Thioactivation of A and B afforded **18**, and after incorporation of cobalt, the macrocycle was closed between rings A and B to form **19** (Scheme 7).

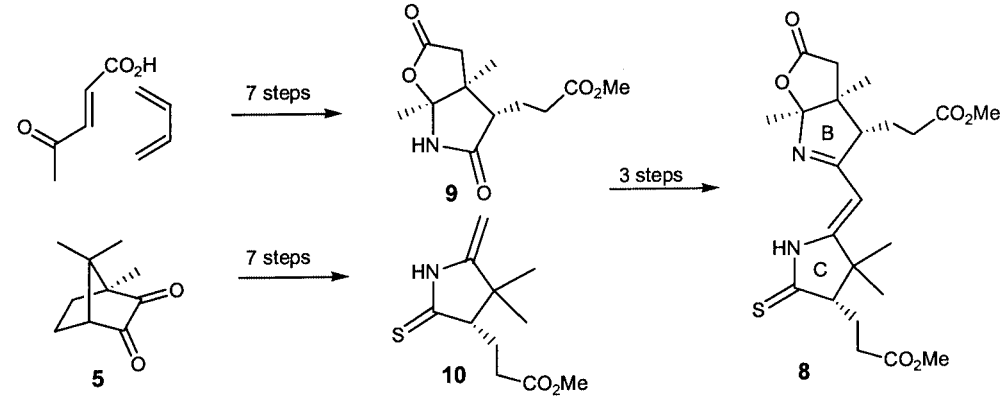
The template effect in the cobalt complex of the secocorrin was thus crucial to the success of the macrocyclization reaction. The *meso* substituents, methyl groups at position C-5 and C-15, were introduced at this point in the synthesis (since the sulfide contraction cannot be performed with these substituents already present). The synthesis was completed by the introduction of the appropriate functionalities at the side chains and HPLC separation of the diastereomers (propionic ester side chains of rings A, B, and C) formed by epimerization during the course of the ring connection. After that, the procedure of Bernhauer et al.[6] for the attachment of the nucleotide moiety was executed, and rumour has it that it was Woodward himself who eventually isolated the "beautiful red" crystals of vitamin B_{12} (**2**).

Eschenmoser's A–D-Route

Independently of the cooperative Harvard/Zürich approach, the Eschenmoser group[12] also developed an alternative route on their own. In contrast to the A–B/C–D strategy applied previously, the key step of Eschenmoser's corrin synthesis is a mechanistically very different A–D cyclization. The stereochemical challenge of the A–D connection was solved by means of a light-induced, antarafacial [1,16]-hydrogen shift followed by a thermally allowed, antarafacial electrocyclic ring-closure of a secocorrinoid



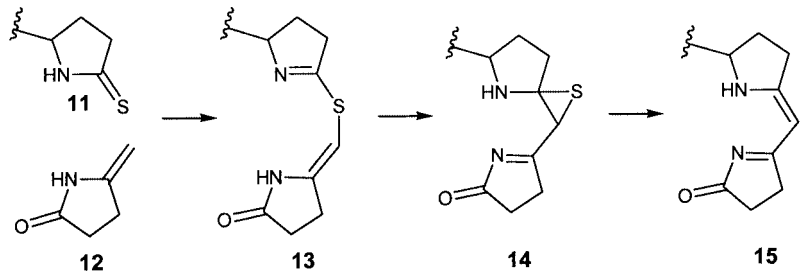
Scheme 4



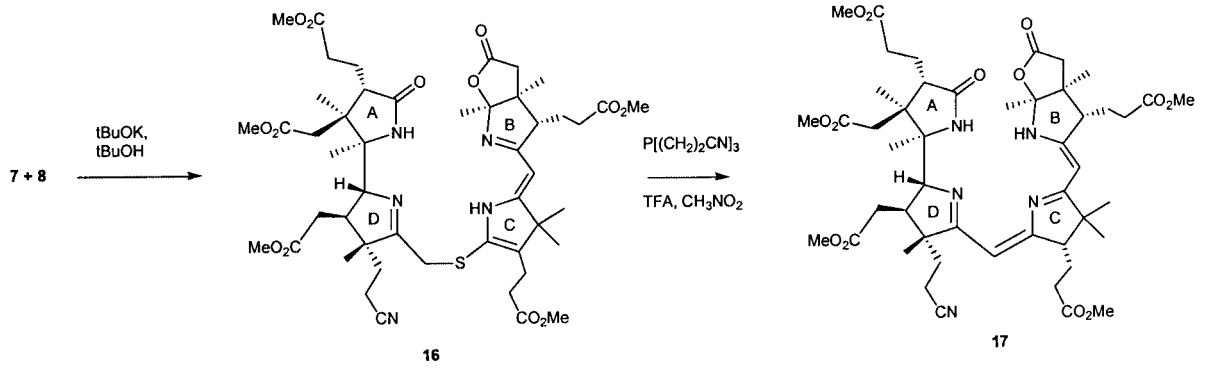
Scheme 5

metal complex (Scheme 8). Remarkably, this step has some remote precedence in earlier work by W. A. Johnson (Scheme 9).[13] The metal complex assisted cycloisomerization is a highly specific reaction in terms of constitution and configuration, dictated to a greater or a lesser extent by the helical arrangement of the polyene ligand around the metal center. Cyclization precursor **20**, with its exocyclic methylene group, was not isolated, but smoothly underwent an antarafacial sigmatropic [1,16]-hydrogen shift from the methylene group in ring D to the exocyclic methylidene group in ring A upon irradiation with visible light. This step was followed by an electrocyclic [1,15] $\pi \rightarrow \sigma$ isomerization to provide corrin **21**.

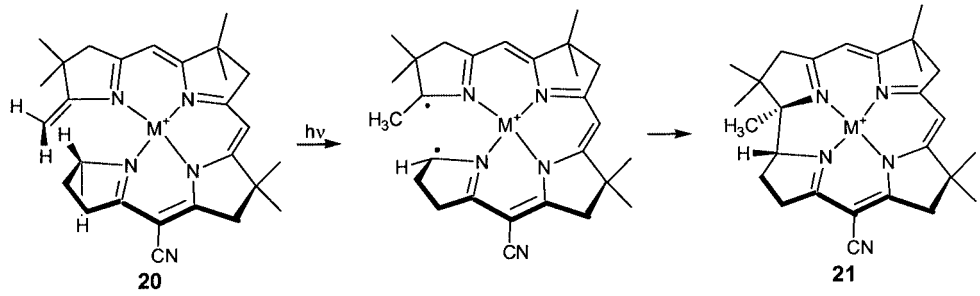
The use of this "all or nothing" process at such a late stage of a complex natural product synthesis illustrated the impact of Woodward's and Hoffmann's concept of sigmatropic rearrangements on organic synthesis in a highly impressive fashion.[14]



Scheme 6



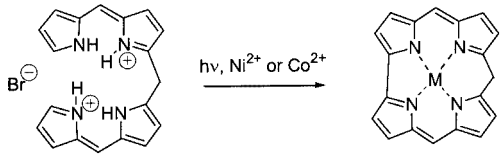
Scheme 7



Scheme 8

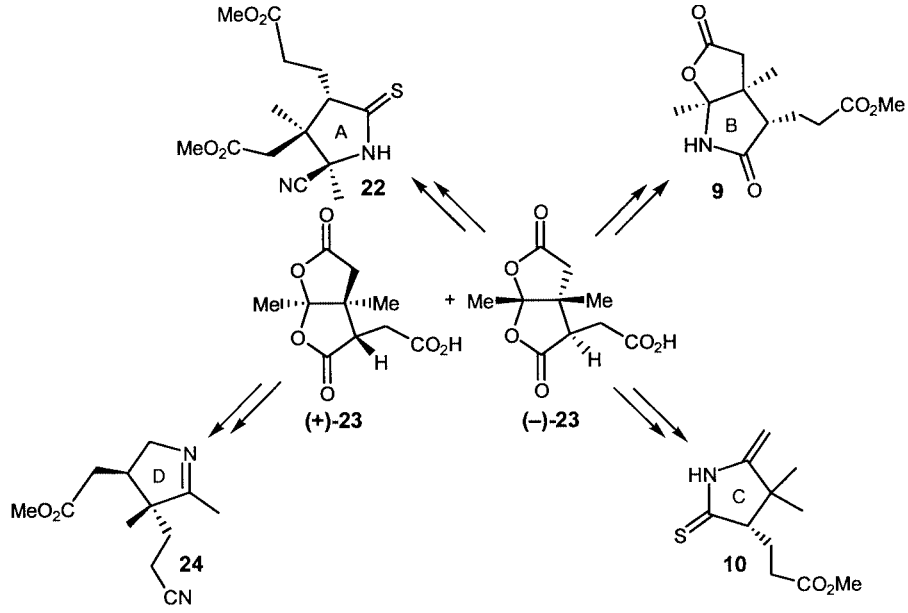
The synthetic problem was now reduced to the synthesis of four heterocyclic rings A (**22**), B (**9**), C (**10**), and D (**24**), each in enantiomerically pure form, and the development of efficient coupling strategies. An elegant feature of the A−D variant is the finding that all four rings could be elaborated from a single racemic precursor, namely the bis(lactone) **23** (Scheme 10)!

While ring fragments A (**22**), B (**9**), and C (**10**) were synthesized from the enantiomer (+)-**23**, ring D (**24**) was obtained from (−)-**23**. Thus, the racemic precursor (±)-**26** was



Scheme 9

sideration of the effects of orbital symmetry on the course first of electrocyclic and sigmatropic reactions, and later on pericyclic processes in general. These have become enshrined in the "Woodward–Hoffmann rules" and indeed without their aid Eschenmoser might not have ventured onto his "new road" to corrins and ultimately to vitamin B_{12} (**2**) itself.



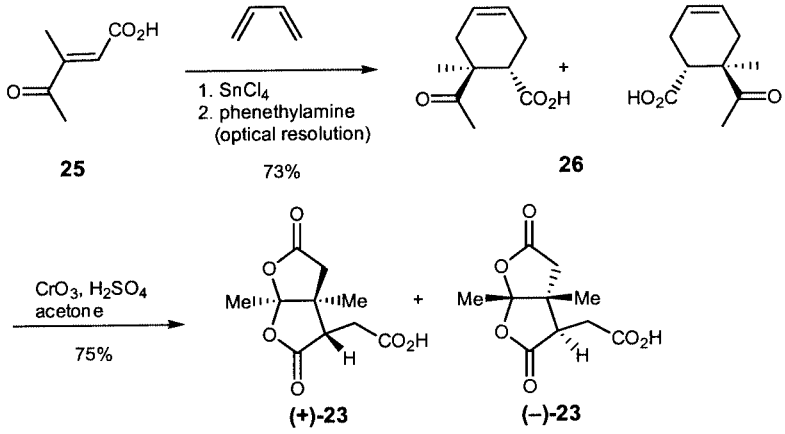
Scheme 10

prepared by means of a Diels–Alder reaction between β-acetyl-β-methylacrylic acid (**25**) and butadiene. By classical resolution, the two enantiomers of (±)-**26** were obtained in pure form. Treatment of **26** with chromic acid furnished both enantiomers of dilactone **23** (Scheme 11).

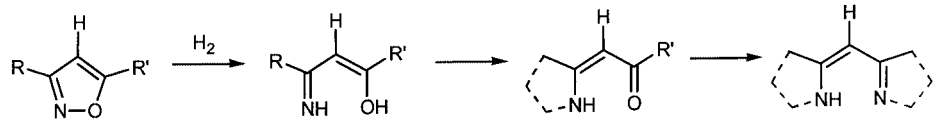
The completion of this gigantic task by the groups of Woodward and Eschenmoser, employing, all told, some 100 PhD students and postdocs over 12 years, still represents one of the foremost accomplishments of organic synthesis. The truly epochal spin-off of the work, however, arose from a redundant route followed at Harvard,[15] which led to con-

Stevens' Isoxazole Approach

Inspired by the achievements of Woodward and Eschenmoser, R. V. Stevens at Rice University and later at the University of California at Los Angeles, returned to Cornforth's idea of synthesizing the vitamin B_{12} chromophore from isoxazoles.[16] The vinylogous amidine systems are regarded as aza analogues of vinylogous amides. Catalytic hydrogenation of isoxazoles provides a suitable method for this transformation (Scheme 12).[17]

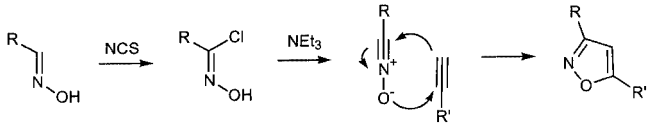


Scheme 11



Scheme 12

Among the different available methods for the synthesis of isoxazoles, the fairly well-defined 1,3-dipolar cycloaddition of nitrile oxides to terminal acetylenes was considered suitable for this purpose (Scheme 13).



Scheme 13

Aiming at the synthesis of cobyric acid, Stevens showed in model studies that, by application of this method, all the structural features of octamethylcorrin (**29**) can be incorporated into appropriately substituted tris(isoxazole) systems, which are in turn elaborated from carefully selected nitrile oxides and terminal acetylenes in either of two modes: a "clockwise" or a "counterclockwise" fashion. In the "counterclockwise" approach, fragments B and A were successively connected into a CD subunit to give **28**, while in the "clockwise" approach the tris(isoxazole) scaffold **27** was made by coupling a "northern" AB subunit and a "southern" CD subunit. In the case of the counterclockwise approach, it was shown that the resulting tris(isoxazole) **27** could then be reductively opened and subsequently condensed with an amine to give the vinylogous amidine system. Macrocyclization to octamethylcorrin **29** was achieved by applying Eschenmoser's photochemically induced cycloisomerization (Scheme 14).[9] In the case of the synthesis of cobyric acid itself, Stevens' primary targets were the tris(isoxazoles) **30** and **31** (Scheme 15).

Following the clockwise approach and recognizing the similarities of the secocorrin precursors **32A**−**D**, Stevens decided to use a common method for their syntheses: the Eschenmoser fragmentation of appropriately substituted cyclopentenones **33A**−**D** (Scheme 16).

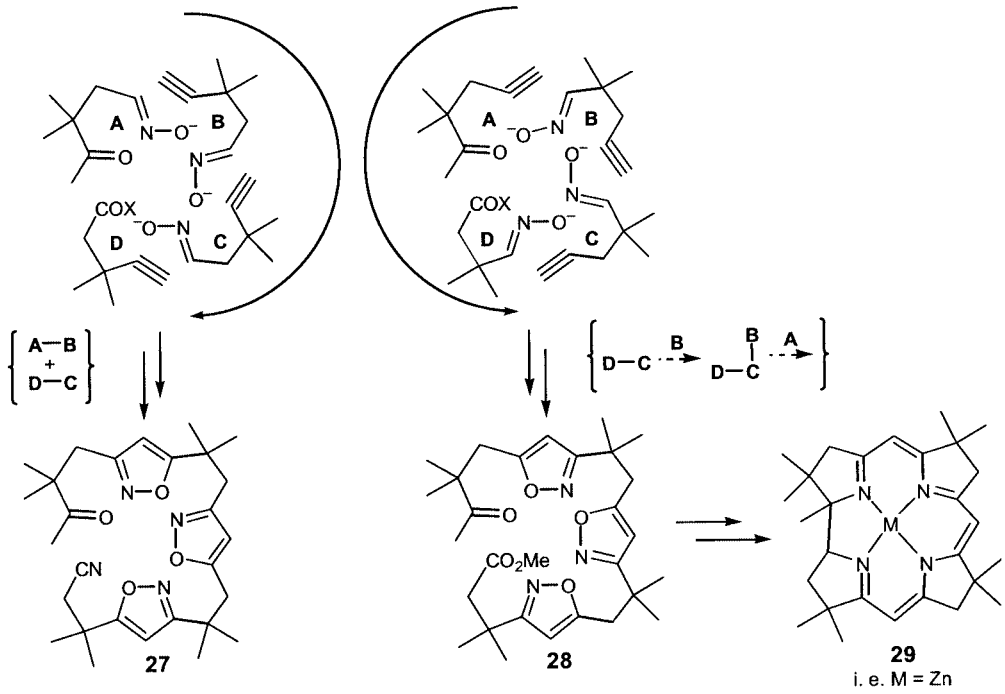
It having been shown that simple cyclopentenones **34a** and **34b** readily undergo the fragmentation sequence to acetylenes **37a** and **37b** via the epoxides **35a** and **35b** and the hydrazones **36a** and **36b** (Scheme 17), it was also demonstrated in the synthesis of racemic C ring that the Eschenmoser sequence would also work for more complex substrates.[18] Nevertheless, Stevens claimed at that time that, because of its "anomalous" nature, the D-ring precursor **32D** requires an entirely different method, and he thus accomplished the synthesis of the racemic compound through a Diels−Alder reaction.

Seven years later, the partially successful efforts towards the stereoselective synthesis of the fragments of type **32A**−**D** were published, with the fragmentation applied as a key step.[19] All four syntheses started from camphor as a chiral starting material and were designed in such a way that substituted cyclopentenone oxides with the correct absolute stereochemistry were the primary targets. It was hoped that Eschenmoser fragmentation of these precursors would then give the desired fragments. The enantioselective synthesis of the C-ring fragment **43** was successfully accomplished according to this strategy: homologation of known aldehyde **38** to ester **39**, prepared from (−)-borneol or (−)-α-pinene, was achieved via a ketene thioacetal. Subsequent allylic oxidation, reduction and treatment with *m*CPBA provided epoxide **40**. Regio- and stereoselective opening of **40** to **41** with selenophenol was followed by oxidative elimination to give a cyclopentenone, which was subsequently epoxidized. Periodate cleavage then gave ketone **42**. Disappointingly, Eschenmoser fragmentation to **43** turned out to be much more difficult than anticipated and gave only a 39% yield after extensive optimization (Scheme 18).

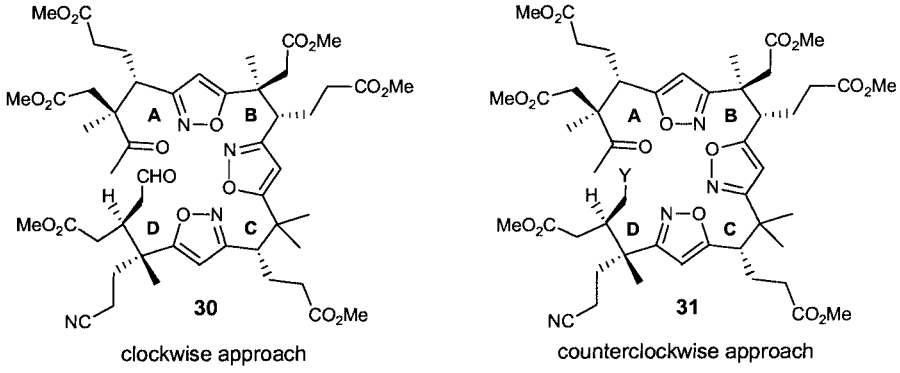
In the synthesis of the A-ring fragment **48** (Scheme 19), the first stereocenter was derived from (−)-camphor, while the second one was created by a remarkably selective functionalization of the C-9 methyl group to give bromide **44** − a sequence of reactions first reported in 1893.[20] After displacement of this neopentyl-type bromide with cyanide and reduction of the ketone to a mixture of epimeric alcohols, the aldehyde **45** underwent fragmentation and homologation of the side chain to provide ester **46**. A four-step sequence − allylic oxidation, reduction to the alcohol, epoxidation and oxidation to the ketone − was used to generate **47**. The direct route (without reduction and oxidation) gave competing reactions. In contrast to the difficulties encountered in the fragmentation of **42**, Eschenmoser fragmentation of **47** was performed without incident. Protection of the ketone and oxidative cleavage of the double bond furnished **48** in 13 steps and 1.3% overall yield [starting from (−)-9-bromocamphor].

The same Eschenmoser fragmentation methodology was also expected to afford B- and D-ring fragments of type **32B** and **32D**. However, these efforts failed, the fragmentation reaction of **49** and **50** affording only complex mixtures (Scheme 20). Having therefore to abandon his first generation strategy, Stevens wrote in an NSF proposal: "*Nevertheless, the synthesis of the vitamin remained a dream unfulfilled, and as experiment after experiment failed, we thought seriously of abandoning our dream. However, rather than giving up we decided to undertake an entirely different approach.*"[21]

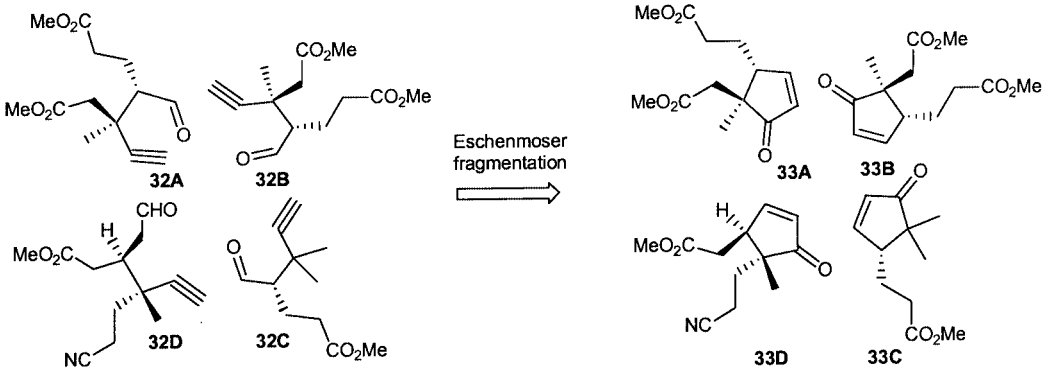
In 1986, more than ten years after the first Stevens publication on B_{12} had appeared, the efforts of twenty people



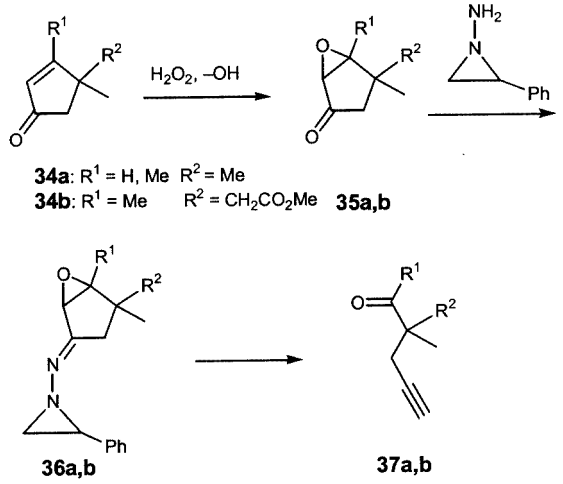
Scheme 14



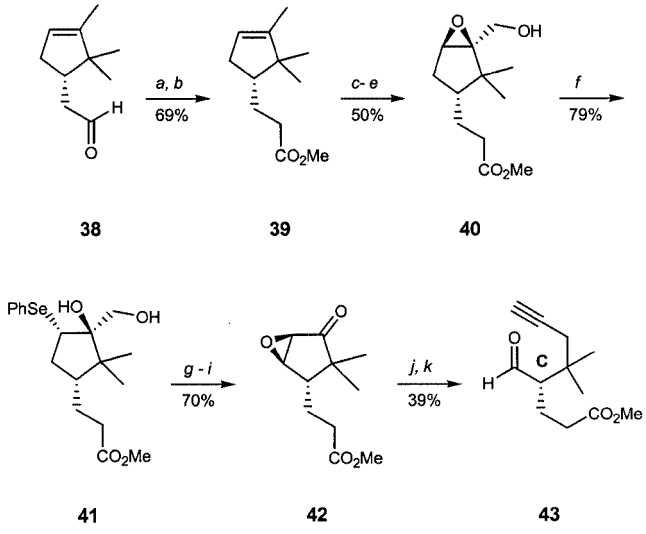
Scheme 15



Scheme 16



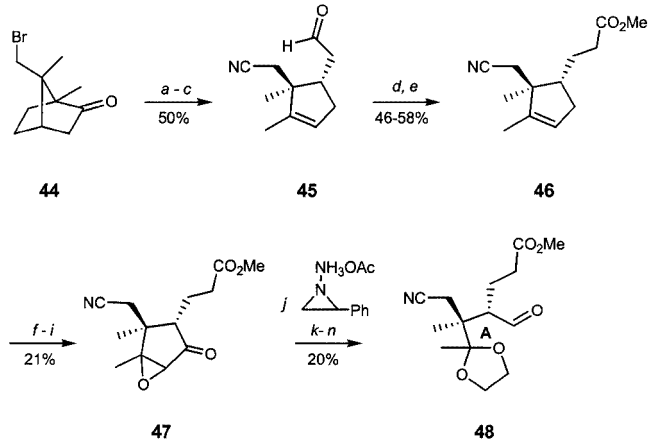
Scheme 17



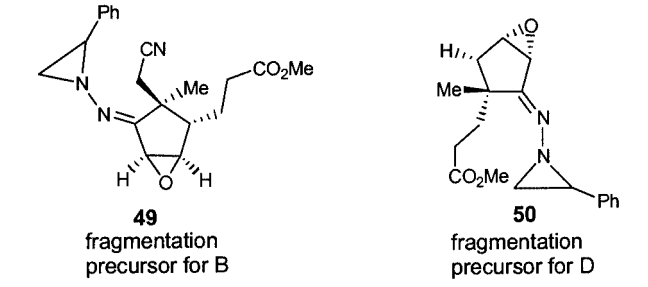
Scheme 18. Reagents and conditions: a) $LiCTMS(SMe)_2$; b) $HgCl_2$; c) SeO_2; d) $NaBH_4$; e) *m*CPBA; f) PhSeH, *i*PrNEt$_2$; g) *t*BuOOH, Al_2O_3; h) *t*BuOOH, $VO(acac)_2$; i) $NaIO_4$; j) $TsNHNH_2$, H^+; k) BF_3

finally culminated in the stereoselective syntheses of all ring fragments, each of them by an individual approach.[22] The successful synthesis of the A-ring fragment **48**, published in 1983, had been modified, although leaving the first six steps unchanged. Homologation of the side chain of **45** was accomplished by reduction of the aldehyde, tosylation, and displacement with sodium cyanide to provide nitrile **51**. Oxidative ring cleavage furnished oxo aldehyde **52**, which was transformed into oxo olefin **53** by reductive amination, oxidation to the *N*-oxide and Cope elimination. The last steps of the synthesis included protection of the ketone, transformation of the nitriles into methyl esters, ozonolysis of the double bond and oxime formation, yielding the desired fragment **54** in 17 overall steps and 7% yield (Scheme 21).

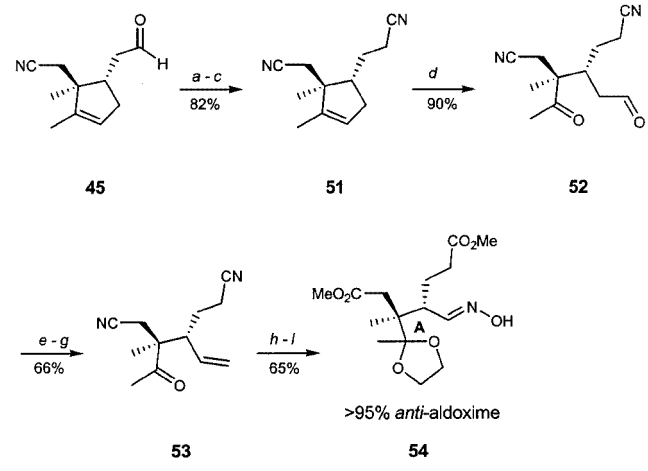
The B- and D-ring fragments **59** and **63** have quaternary centres with similar substituents of opposite configuration,



Scheme 19. Reagents and conditions: a) KCN, 76%; b) $NaBH_4$; c) CAN; d) 1,3-dithiacyclohexane-2-thione, PPh_3; e) $HgCl_2$, MeOH; f) CrO_3, 3,5-dimethylimidazole; g) $NaBH_4$; h) *m*CPBA; i) CrO_3·2Py; k) 200−250 °C; l) H_2/Pd (Lindlar); m) $(MeO)_3CH$, TsOH; n) O_3

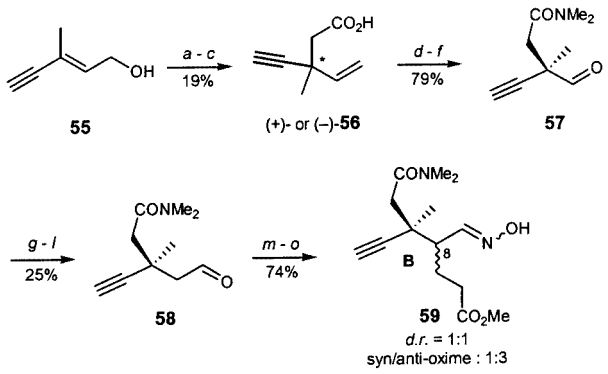


Scheme 20



Scheme 21. Reagents and conditions: a) $NaBH_4$; b) TsCl, pyridine; c) NaCN, DMF; d) *i.* O_3, *ii.* $P(OMe)_3$; e) $HNMe_2$, $NaCNBH_3$; f) *m*CPBA; g) DMSO, Δ; h) $(CH_2OH)_2$, TsOH; i) NaOH; j) MeI; k) *i.* O_3, *ii.* $P(OMe)_3$; l) $HONH_2$·HCl, pyridine

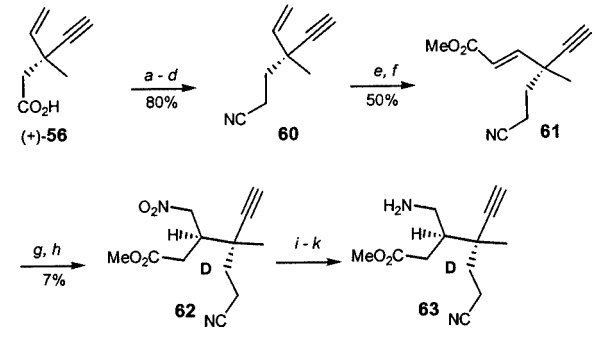
and the same starting material can thus be used for both building blocks. Claisen rearrangement of alcohol **55** gave both enantiomers of **56**, which were resolved to provide (−)-**56** as starting material for the B ring and (+)-**56** for the D ring (Scheme 22).



Scheme 22. Reagents and conditions: a) $CH_3C(OEt)_3$; b) NaOH; c) (+)- or (−)-phenyl-ethylamine; d) $SOCl_2$; e) $HNMe_2$; f) *i.* O_3, *ii.* DMS; g) CH_3NO_2, KF; h) MsCl, NEt_3; i) $NaBH_4$; j) NaOMe, MeOH; *k*) H_2SO_4; l) HCl; m) pyrrolidine; n) methyl acrylate; o) $HONH_2$·HCl, pyridine

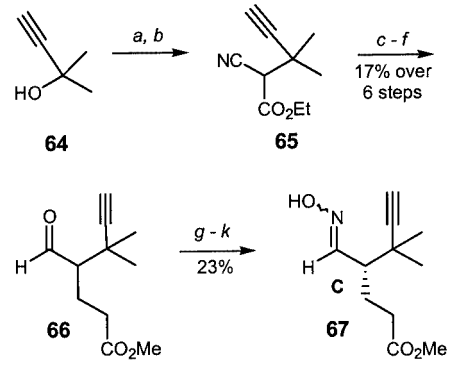
The B-ring synthesis involves the transformation of acid **56** into the *N*,*N*-dimethylamide, followed by ozonolysis of the double bond. The resulting aldehyde **57** was homologated to **58**. Michael addition of **58** (via the enamine) to methyl acrylate (*d.r.* = 1:1) and oxime formation gave a 1:3 mixture of *syn*- and *anti*-oximes **59**. The crystalline, diastereomeric (1:1) *anti*-oximes **59** were suitable for the synthesis, since it was known from the Woodward-Eschenmoser synthesis that the stereochemistry at C-8 could be adjusted later.[1a,1b,23]

The synthesis of the D-ring fragment **63** is summarized in Scheme 23: after reduction of the ester of (+)-**56** to the alcohol, the nitrile **60** was generated. The double bond was then oxidatively cleaved and the acetate side chain was introduced by Horner−Wadsworth−Emmons reaction to furnish ester **61**. Introduction of the second chiral centre was accomplished by means of a Michael addition of nitromethane (*d.r.* = 2:1), giving **62**. Finally, the nitro group was reduced and cyclized to give a mixture of the γ-lactams. The desired lactam diastereomer was enriched by crystallization and then opened hydrolytically to give **63** in 14 steps and 0.5% yield.



Scheme 23. Reagents and conditions: a) MeOH, AcCl; b) LAH; c) TsCl, pyridine; d) NaCN, DMSO; e) *i.* O_3, *ii.* DMS; f) $(MeO)_2P(O)CH_2CO_2Me$; g) CH_3NO_2, base; h) crystallization; i) HCl, Zn; j) NaOH; k) HCl, MeOH, Δ

For the synthesis of C fragment **67**, an alternative to the low-yielding and long fragmentation pathway was developed. The chloro derivative of alcohol **64** was alkylated with cyano acetate to afford **65**, and subsequent deethoxycarbonyllation and reduction was followed by enamine Michael addition to afford acetylenic aldehyde **66**. Transformation into the oxime and resolution of the racemic product gave **67** in 11 overall steps and 4% yield (Scheme 24).



Scheme 24. Reagents and conditions: a) HCl, CaCl, Cu, CuCl; b) $NCCH_2CO_2Et$, LiOEt, Cu, CuCl; c) KOH, Δ; d) DIBAL-H; e) pyrrolidine, methyl acrylate; f) $HONH_2$·HCl; g) NaOH; h) crystallization with (−)-phenyl-ethylamine; i) HCl; j) CH_2N_2; k) $HONH_2$·HCl pyridine

On the basis of model studies for the 1,3-dipolar cycloaddition to construct the tris(isoxazole) skeleton, fragments **54**, **59**, **62**, and **67** were connected by the "A−B plus C−D" strategy. Thus, "northern" fragment **68** was joined to "southern" fragment **69** to yield tris(isoxazole) **70**. Since the cycloaddition turned out to be troublesome with the amino acid D fragment **63**, intermediate **62** was used, postponing the reduction of the nitro group (Scheme 25).

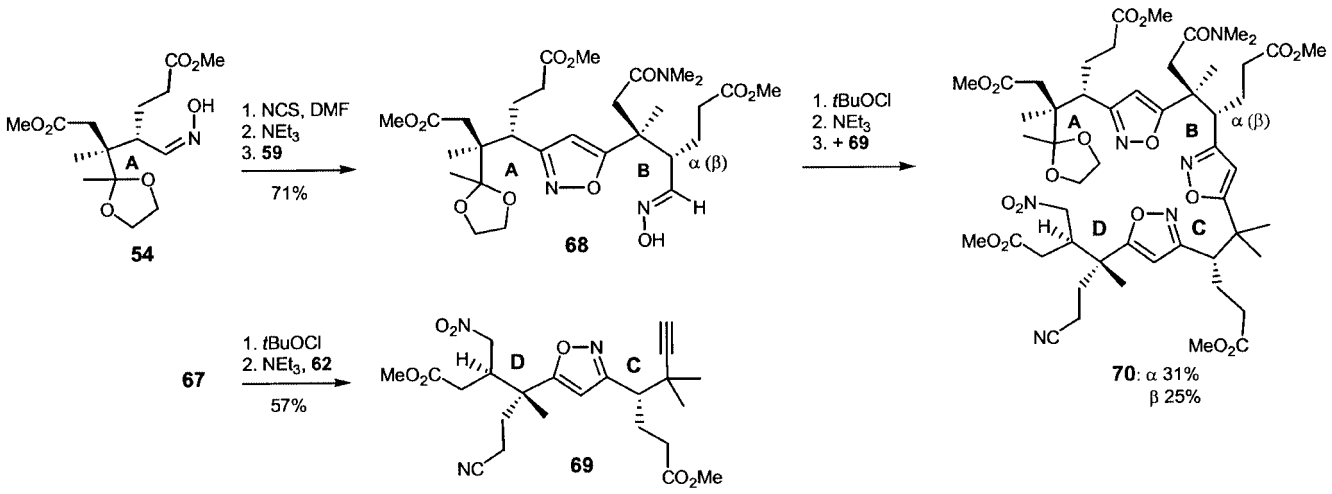
This remarkable achievement was reported in Stevens' last publication on the synthesis of vitamin B_{12}. However, the stereoselective synthesis of the key intermediate **70** was to be the last step in this B_{12} project, which has indeed remained a "dream unfulfilled" in a very tragic turn of events. Shortly after this publication, R. V. Stevens succumbed to an early death.

P. A. Jacobi's Ring-Connection Strategy

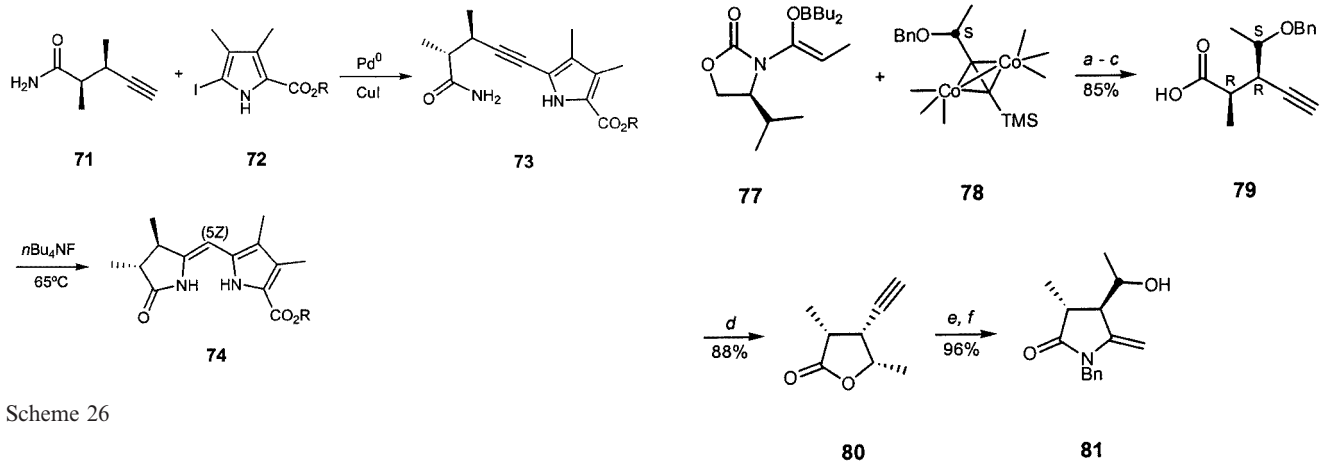
Since the early 1990s, the Jacobi group at Wesleyan and later at Dartmouth have been involved in the synthesis of cobyric acid (**1**). In 1995, they reported the Pd^0-mediated coupling of acetylenic amide **71** with iodopyrrole **72** to form **73**, which upon fluoride ion catalysed 5-*exo*-*dig* cyclization gave dihydropyrromethenone **74** with (5*Z*) stereochemistry (Scheme 26).[23]

It was further shown that acetylenic ester **75** affords enamide **76** upon treatment with $LiAl(NHBn)_4$ at 65 °C (Scheme 27). Both the Sonogashira-type coupling and the cyclization methodology were to be utilized in the synthesis of cobyric acid (**1**).

The cyclization methodology was first employed in a highly efficient synthesis of enantiomerically pure enamides



Scheme 25



Scheme 26

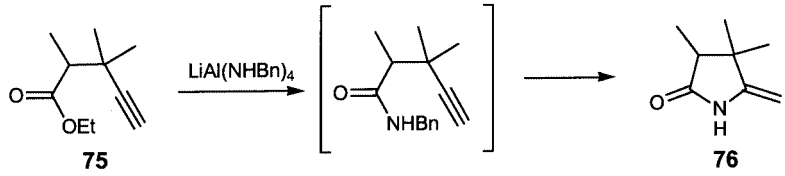
81. By use of the Nicholas−Schreiber reaction, adduct **79** from Evans enolate **77** and cobalt complex **78** was formed as a single enantiomer with a *syn* selectivity of > 98%. Deprotection and lactonization of **79** gave **80**, which was treated with $LiAl(NHBn)_4$ to afford **81** (Scheme 28).[24]

Scheme 28. Reagents and conditions: a) Bu_2BOTf; b) CAN; c) LiOOH; d) P_4S_{10}; e) $LiAl(NHBn)_4$; f) 25 °C, THF

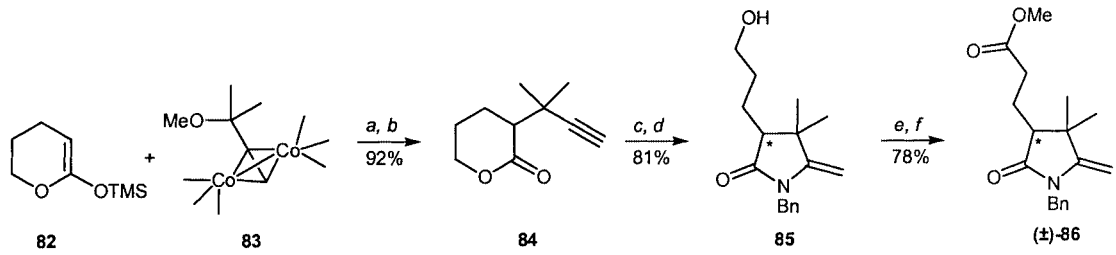
This methodology was used in very efficient syntheses of two potential C-ring precursors **86** and **90**. In the first approach, silyl enol ether **82** and cobalt complex **83** gave Nicholas adduct **84**, which was subsequently converted into an amide. Subsequent 5-*exo*-*dig* cyclization at 65 °C gave **85**, which was transformed into the methyl ester to give fragment **(±)-86**[25a] (Scheme 29).

The second synthesis is even more direct and was achieved by the formation of the Nicholas monoadduct from bis(silylenol ether) **87** and the propargylic cation equivalent **88**. The acetylenic ester **89** formed was treated with lithium aluminium amide, and the enamide benzyl protecting group was selectively cleaved to give **90** in excellent overall yield (Scheme 30). However, these two syntheses are racemic and the promised stereoselective synthesis, in which it was planned that Evans-type imides would undergo the Nicholas−Schreiber reaction, has not yet been published.

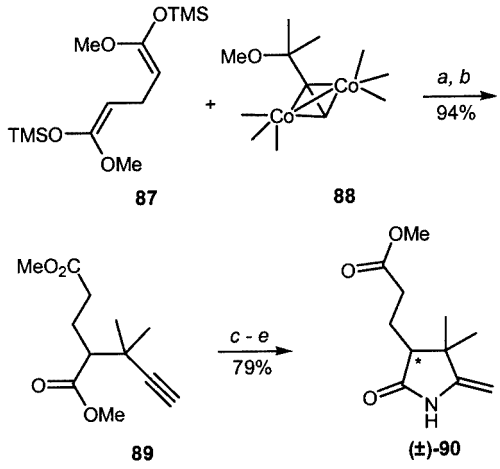
Since these synthetic efforts to synthesize the C-ring fragment, Jacobi's work has mainly focused on methodologies for new connection strategies of the ring fragments. The goal was to generate the corrin framework in such a way as



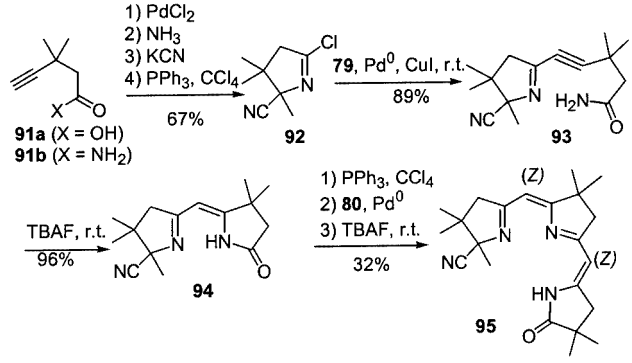
Scheme 27



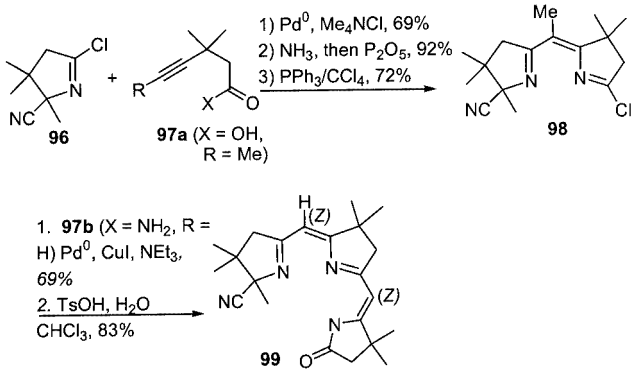
Scheme 29. Reagents and conditions: a) $BF_3{\cdot}Et_2O$; b) CAN; c) $LiAl(NHBn)_4$; d) 65 °C, THF; e) CrO_3, pyridine; f) I_2, KOH, MeOH



Scheme 30. Reagents and conditions: a) $BF_3{\cdot}Et_2O$; b) CAN; c) $LiAl(NHBn)_4$; d) 65 °C, THF; e) Na, NH_3



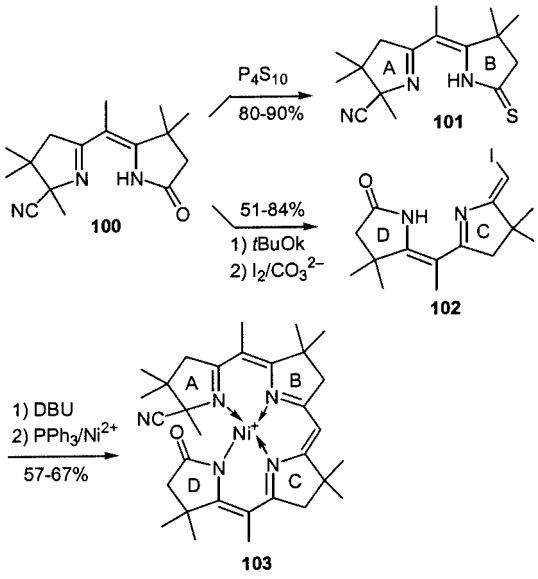
Scheme 31



Scheme 32

to solve not only the racemization problem of the sulfide contraction, but also the introduction of the *meso* substituents (the methyl groups at C-5 and C-15). The sulfide contraction is a method that can be highly efficient, but it is very sensitive towards steric demands. For this reason, the ring contraction fails when the *meso*-methyl groups are introduced earlier in the synthesis. These peripheral substituents were therefore added after the formation of the macrocyle in Woodward and Eschenmoser's work, by an unselective and low-yielding reaction. The connection strategy − a Pd^0-catalysed Sonogashira coupling of an iminoyl chloride with an alkyne amide followed by 5-*exo*-*dig* ring closure − was tested with enamide derivative **92**, derived from a 5-*exo*-*dig* cyclization of the alkyne acid **91a**, followed by aminolysis. The enamide was then converted into iminoyl chloride **92** by initial protection with KCN and chlorination. Sonogashira coupling of **92** with the alkyne amide **91b** was accomplished by use of the reagent system Pd^0/CuI. Upon treatment with TBAF the resultant pyrrolinoalkyne **93** was cleanly converted into the (*Z*)-semicorrin **94**. Repetition of this sequence (coupling without CuI) further led to the (*Z*,*Z*)-tripyrroline **95** (Scheme 31).[25b]

The effect of adjacent substituents on both the coupling and the cyclization steps was explored and it was demonstrated that steric crowding is not a problem. In the same year, another paper was published, in which the Pd methodology was readily extended to the synthesis of *meso*-substituted semicorrins.[26] Iminoyl chloride **96** with alkyne acid **97a** afforded an enol lactone [(*E*)/(*Z*) mixture] which upon aminolysis and dehydration gave iminoyl chloride **98** as the (*Z*) isomer. By further coupling of **98** with **97b**, the (*Z*,*Z*)-tripyrroline **99** could be prepared (Scheme 32). Moving ahead to produce tetrahydropyrroles in the form of secocorphin **103**, however, the Jacobi group returned to a convergent "A−B plus C−D" approach by Eschenmoser's sulfide contraction procedure (Scheme 33).[26]



Scheme 33

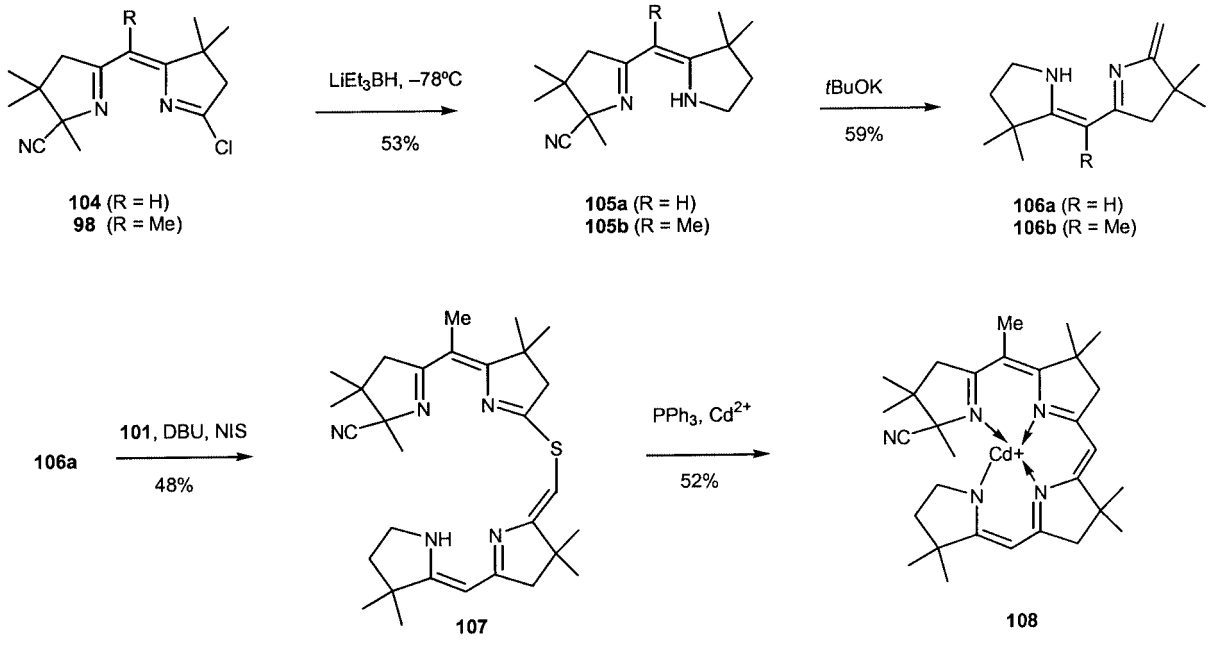
In principle, the reduction of ring D in **103** could provide secocorrin **108** in the correct oxidation state. However, it had already been shown by Eschenmoser that this transformation was difficult to achieve.[27] In an alternative route to **108**,[29] Jacobi solved this problem by preparing dipyrrins **106a** and **106b** from **104** and **98**. By Eschenmoser's methodology, thiolactam **101** and dipyrrin **106a** were oxidatively coupled to secocorrin **107**. Treatment with PPh_3 and $CdCl_2$ then provided **108**, in the correct oxidation state for the photochemical cycloisomerization and including the methyl group at the *meso* position C-5 (Scheme 34).[28]

J. Mulzer's Approach

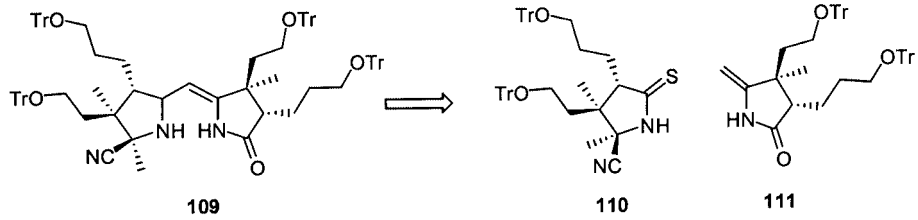
Since the mid-1990s, the Mulzer group has also pursued synthetic efforts towards cobyric acid (**1**). So far, their work has mainly focused on new strategies for the syntheses of the ring fragments.

B. List developed a flexible and convergent "A−B plus C−D" strategy: an A−B fragment **109** was made by simple dimerization of two virtually identical fragments **110** and **111** (Scheme 35). This approach should also be applicable to the synthesis of porphyrinoid structures such as siroheme (**112**) factor F430 (**113**), and sirohydrochlorin, which only differ in their C−D fragment (Scheme 36).[29]

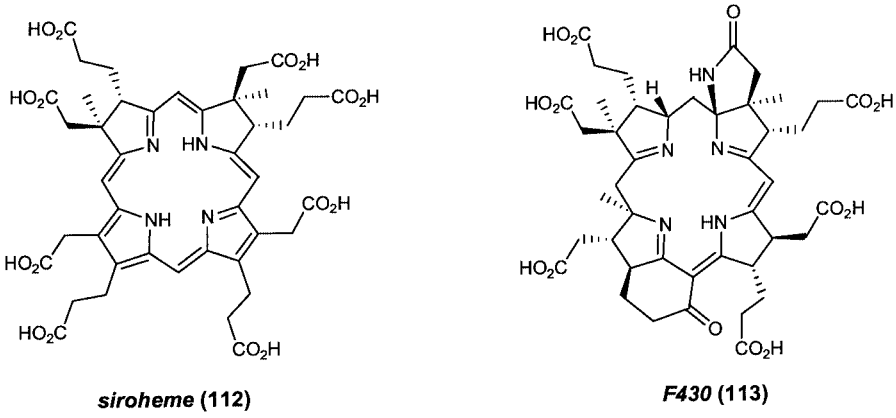
The flexible "northern" A−B fragment **109** was synthesized in such a way that both fragments A (**110**) and B (**111**) were prepared from the same precursor. Thus, the easily available chiral PMB-protected isobutyl D-lactate (**114**) was



Scheme 34



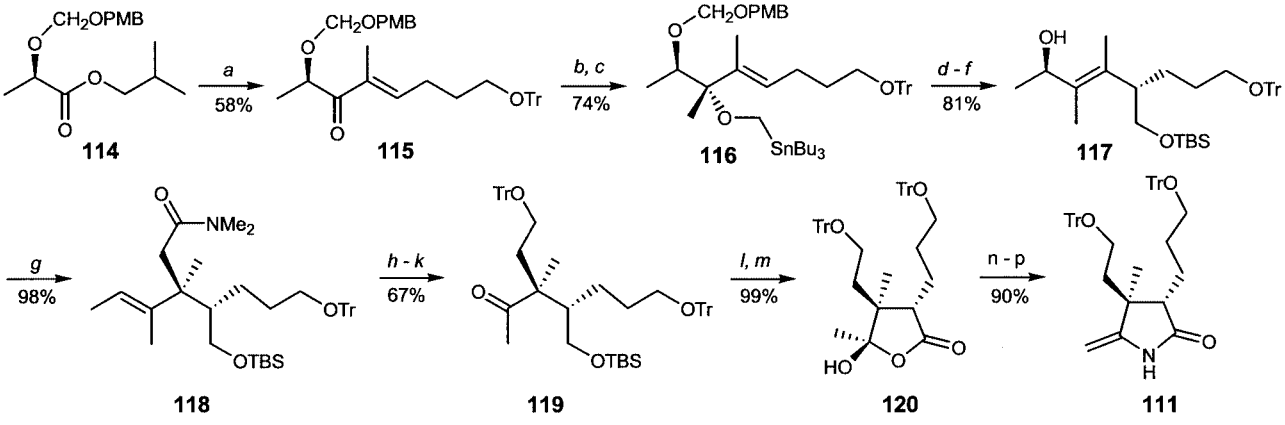
Scheme 35



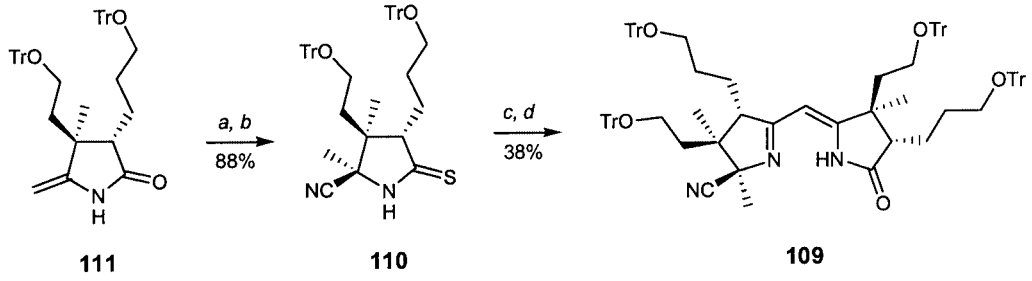
Scheme 36

treated with 1-(lithioethyl)phosphonate followed by water and 4-(trityloxy)butyraldehyde in a Corey−Kwiatkowski/Horner−Wadsworth−Emmons tandem reaction.[30] This three-component one-pot synthesis readily gave enone **115**, which stereoselectively reacted with MeMgBr, following the Cram−Felkin−Anh model. The allylic alcohol was transformed into stannane **116**, which upon treatment with *n*BuLi underwent a [2,3]-Wittig−Still rearrangement to give the homoallylic alcohol **117**, from which an Eschenmoser−Claisen rearrangement provided dimethylamide **118**. The problem that the oxidative cleavage of the trisubstituted double bond could not be effected by standard methods was solved in an elegant biomimetic fashion: a reaction sequence derived from the biosynthesis of vitamin B_{12} (**2**), an *intramolecularizaton*,[31] managed to cleave the inert, highly substituted double bond. Thus, oxylactonization, reduction, tritylation of the primary alcohol of the resulting triol,[32] and in situ cleavage gave ketone **119**. Removal of the TBS group and oxidation gave **120**. Oxo amide **111** was prepared with ammonia as a nitrogen source (Scheme 37). Oxo amide **111** was converted into thiolactam **110**, which was connected with **111** by sulfide contraction to yield the "northern" A−B semicorrin **109** in 16 steps (isolated intermediates) and a total yield of 7% (Scheme 38).

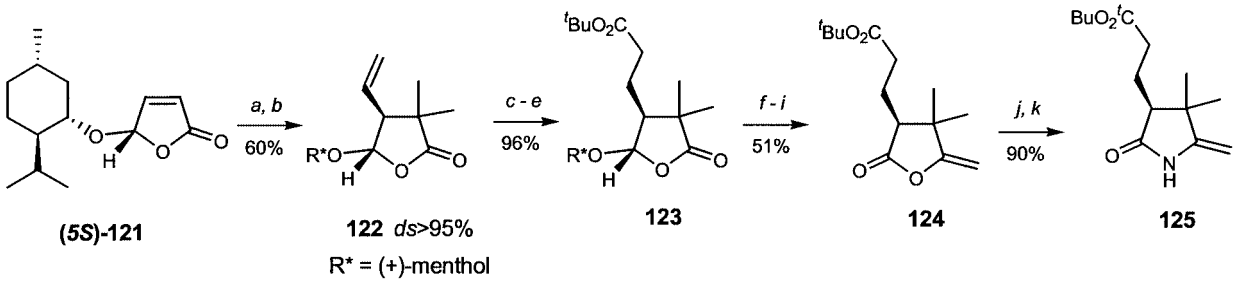
D. Riether developed highly efficient and stereoselective syntheses of the C and D ring fragments **125** and **133**. These fragments differ from the Woodward−Eschenmoser inter-



Scheme 37. Reagents and conditions: a) DEEP, *n*BuLi, then H_2O, 4-(trityloxy)butyraldehyde; b) MeMgCl; c) KH, Bu_3SnCH_2I, DMPU, THF; d) *n*BuLi; e) TBSCl; f) DDQ; g) *N*,*N*-dimethylamino dimethylacetal, toluene; h) *m*-chloroperbenzoic acid; i) LAH; j) TrCl; k) $Pb(OAc)_4$; l) TBAF; m) PDC; n) MsCl, Hünig's base; o) NH_3; p) 110 °C



Scheme 38. Reagents and conditions: a) KCN; b) Lawesson reagent; c) $(PhCOO)_2$, **111**; d) $P(OEt)_3$, HPLC



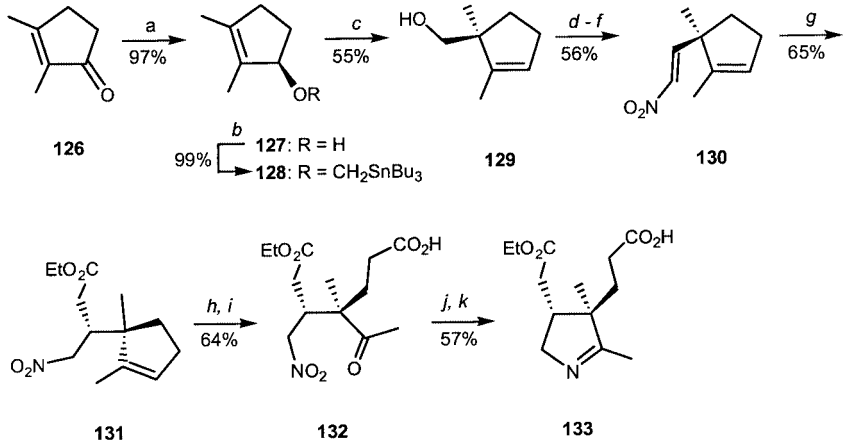
Scheme 39. Reagents and conditions: a) vinylMgCl, CuI, TMSCl, then TBAF; b) LiHMDS, MeI; c) *i*. O_3, *ii*. PPh_3; d) $Ph_3PCHC(O)OtBu$; e) H_2, $Pd/CaCO_3$; f) MeLi; g) *p*TsOH cat.; h) PDC, DMF; i) MsCl, $EtiPr_2N$; j) NH_3; k) 110 °C, 1 mbar

mediate **20** only with respect to the functionalization of the side chains. However, the synthetic strategies are totally different from that applied by Woodward and Eschenmoser and by B. List for the AB fragment **109**.

The preparation of the C-ring fragment **125** started from (5*S*)-menthyloxy-2(5*H*)-furanone (**121**), readily available from furan. By use of methodology developed by B. Feringa,[33] **121** was used in a 1,4-addition of vinyl cuprate, which proceeded with > 95% *ds*. The geminal dimethyl group in **122** was introduced by double alkylation of the enolate with methyl iodide. Ozonolytic oxidation of the vinyl substituent followed by a Wittig reaction with [(*tert*-butoxycarbonyl)methylene]triphenylphosphorane and subsequent hydrogenation of the newly formed double bond provided the desired propionate **123**. Addition of methyllithium, furnishing a hemiketal, was followed by acid-catalysed cleavage of the menthyloxy acetal. Subsequent oxidation with PDC and dehydration delivered enol lactone **124**. Treatment of **124** with ammonia in ethanol gave lactam **125** in 10 isolated steps and 27% overall yield (Scheme 39).[34] This building block could now be used for condensation by sulfide contraction with an A−B thioamide derivative of A−B semicorrin **109**.

The challenge of the synthesis of the D ring fragment **133**, which differs from the other fragments not only in its substitution pattern but also by its lower oxidation state, was met with a totally different strategy. Corey−Bakshi−Shibata (CBS) reduction of commercially available 2,3-dimethyl-2-cyclopentenone (**123**) gave the corresponding allylic alcohol **127** (96% *ee*), which was converted into the stannylmethyl ether **128**. Tin/lithium exchange and a [2,3]-sigmatropic Wittig−Still rearrangement furnished the homoallylic alcohol **129** along with 10% of the [1,2]-Wittig rearrangement product. Parikh−Doering (SO_3·Py) oxidation of **129** provided the corresponding aldehyde. Henry reaction with nitromethane under phase-transfer conditions, followed by dehydration, gave nitro olefin **130**. Michael addition of the lithium enolate of ethyl acetate to **130** at −100 °C furnished **131** in good yield and a diastereomeric ratio of 86:14. The endocyclic olefinic linkage of **131** was oxidized to the acid **132** by ozonolysis and subsequent Pinnick oxidation ($NaClO_4$). The completion of the synthesis of **133** required the reduction of the nitro group in two steps: treatment of **132** with ammonium formate and Pd/C gave a nitrone, by condensation of the hydroxylamine intermediate with the methyl ketone part of the molecule; further reduction was achieved with $TiCl_3$ to furnish the desired cyclic imine **133**. The two diastereomers of **133** (86:14) could be separated by chiral HPLC, this building block thus being synthesized in 11 isolated steps and 7% overall yield (Scheme 40).[35]

The fact that rings A−D have now been synthesized by two PhD students in altogether no more than six man/woman years underscores the advance in organic synthesis, es-



Scheme 40. Reagents and conditions: a) BH_3·THF, 0.1 equiv. α,α-diphenylprolinol, $nBuBH_2$; b) KH, ICH_2SnBu_3; c) *n*BuLi; d) SO_3·Py, NEt_3; e) CH_3NO_2, CTACl; f) NEt_3, MsCl; g) ethyl acetate, LiHMDS, HMPA; h) O_3, PPh_3; i) $NaClO_2$, 2,3-dimethylbutene, *t*BuOH, KH_2PO_4; j) $HCO_2^-NH_4^+$, Pd/C; k) $TiCl_3$, water, NaOAc

pecially when compared to the considerable sizes of the Eschenmoser or the Stevens groups decades ago.

Epilogue

In conclusion, on reviewing more than thirty years of cobyric acid total synthesis, it has to be noted with astonishment and admiration that the venerable Woodward−Eschenmoser syntheses have maintained their monumental and individual character. None of the following research groups has succeeded in completing a synthesis of their own: Stevens, who might have been close, died prematurely, and the Jacobi and the Mulzer group have so far only concentrated on partial aspects of the overall project: either testing new means of ring connection other than sulfide contraction or improving the synthesis of the individual ring fragments by introducing the elements of modern enantiocontrolled methodology. Either way, the scientific community will have to wait for a while until the second total synthesis of cobyric acid is completed!

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