

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Synthetic Studies of Vitamin B12

David Joshua Ferguson

Abstract

Overall these are selections from the total synthesis of vitamin B12. Through the use of selected reactions in the reaction schema, hypothetical mechanisms have been provided. It is the hope of the author, that it will provide insight for students in organic chemistry. Additionally the focus was on the Eschenmoser's Variant of the total synthesis of vitamin B12. This required the reviewing of the lectures of Dr. A. Eschenmoser as well as reviews of the different mechanistic process involved. Due to constraints all of the mechanisms have not been developed, but selected ones have been provided and shown for understanding.

Keywords: mechanisms, vitamin B12

1. Section 1

1.1 Introduction

Vitamin B12 otherwise known as cyanocobalamin is a compound with synthetic elegance. Since it is composed of an aromatic macrocyclic corrin there are key features of this molecule that are observed either in its synthesis or in the biochemical reactions it plays a role in whether they be isomerization reactions or transfer reactions. In this paper the focus for the discussion will be on the history, chemical significance, and total synthesis of vitamin B12. Even more so the paper will concentrate on one of the two variants of the vitamin B12 synthesis, namely, the ETH Zurich variant spearheaded by Albert Eschenmoser. Examining the structure as a whole, it is observed that a large portion of the vitamin B12 is a corrin structure with a cobalt ion in the center of the macrocyclic part and that same cobalt ion has cyanide ligands. The general macrocyclic portion of the structure is rimmed with either methyl or amide group attachments. One of the amide groups is N-alkylated by a large isopropanol group, then a phosphate, followed by a ribose which is attached to the dimethylbenzimidazole. However, in terms of history, there were some key steps in the process of determining and synthesizing the overall structure of vitamin B12.

"We made up in our minds that we're going to specialize in research in the field of vitamins. We're going to isolate every vitamin. We're going to determine their structures if it hasn't already been done and synthesize them and make them available," Randolph Major, as told by Mac Tishler, said in 1983. Our understanding of disease in the modern world was aided by the work of Louis Pasteur and the germ theory. The issue came into being with diseases such as pellagra, anemia, and beriberi in which the origin is not pathogenic typically but based in nutrient deficiency and in this case vitamin B. This new category came into being in the 1900s.

In 1889 **Dutch physician Christiaan Eijkman** investigated beriberi. He and **Gerrit Grijns** studied the effects of dietary variations on the occurrence of beriberi. After, in 1906 English biochemist **Frederick Gowland Hopkins** suggested a connection between nutrition and diseases such as beriberi and scurvy. Following that in 1911 Casimir Funk, a Polish biochemist working in London, further advanced this idea. University of Wisconsin biochemist Elmer McCollum was able to distinguish two different species of vitamins “fat-soluble factor A” and “water-soluble factor B.” Moreover, in 1926 Dutch chemists Barend Jansen and Willem Donath isolated crystal of anti-beriberi factor from extracts of rice polishings. Chemists were arduously working with natural product chemistry, with Merck in 1930 already working on this task.

Williams of Bell Laboratories approached Merck to help isolate and make thiamine.

Randolph Major was chosen to head the new research and development laboratory Merck built as a part of its efforts to grow basic research. Eventually, Williams and Cline synthesized thiamine. As was seen in 1922, riboflavin, vitamin B2, had been discovered in 1922 by Richard Kuhn in Germany and Theodor Wagner-Jauregg in Austria. Moreover in 1933 riboflavin was isolated by Kuhn and Gyorgy in Germany. As time progressed in 1934, vitamin B6, pyridoxine, was discovered by Gyorgy and colleagues. After this in 1938, the active compound of pyridoxine was isolated by Samuel Lepovsky of U.C. Berkley, after which in 1939, Folkers and Harris along with Kuhn in Germany determined the structure of pyridoxine. Eventually in 1940, the synthesis of vitamin B5, pantothenic acid, was reported by Merck.

1.1.1 Discovery of cobalamin

Cobalamin was discovered through an interesting process. First in 1926 at Harvard University, a team of physicians found out that ingesting a half a pound of liver would prevent pernicious anemia. As time progressed liver extracts were fed to willingly participating patients. Folkers ultimately learned that Mary Shorb a microbiologist found a bacterium that reacted to liver extracts. Also it was determined that the most promising extracts were those with the “pinkish color,” which implied that the vitamin being sought was a red compound. In 1947, Folkers and his team isolated vitamin B12 (cobalamin) which resulted in tiny, bright, red crystals of the vitamin [1].

1.1.2 Nominal definitions

1. Homologation
2. Corrin
3. Ammonolysis
4. Thionation
5. Methanolysis
6. Woodward-Hoffman rules
7. Protection/deprotection

1.1.2.1 Homologation

Essentially homologation is a reaction that converts the reactant into the next member of the homologous series [2]. In many cases a homologous series is a group of compounds that differ by a constant unit. Homologation occurs simply when the repeated structural unit is increased, and in the reaction above, it is a methylene ($-\text{CH}_2-$).

1.1.2.2 Corrin

A corrin is a macrocycle. Specifically a corrin is a species consisting of four reduced pyrrole rings joined by three $-\text{CH}=\text{}$ and one double bond [3].

A common prefix associated with corrin is “seco-” which refers to a macrocycle in which cleavage of a ring has occurred with the addition of one or more hydrogen atoms at each terminal group as indicated.

One distinction is made between the porphyrin, seen below, and the corrin, seen above, based on size in that the porphyrin is larger.

1.1.2.3 Ammonolysis

Ammonolysis is a reaction similar to hydrolysis in which ammonia reacts with another compound as a nucleophile and oftentimes the solvent usually to result in the formation of an amine functional group of the molecule [4]. An example seen above is the ammonolysis of esters which results in amides.

1.1.2.4 Thionation

Thionation is a chemical reaction in which the oxygen in a moiety (e.g., carbonyl, hydroxyl) is converted to a sulfur. In this step in the Eschenmoser variant for the total synthesis of vitamin B₁₂, a cyclic carbonyl-containing molecule is thionated which results in the precursor to ring A for cobyrinic acid and vitamin B₁₂.

1.1.2.5 Methanolysis

Methanolysis is similar to hydrolysis, but instead of water functioning as the nucleophile and solvent, methanol is functioning in that way. Overall in the reaction as seen above, the methanolysis process results in the elimination of the hydroxyl from the ester. This can also be considered a type of transesterification.

1.1.2.6 Woodward-Hoffman rules

The Woodward Hoffman rules were sorted out by Robert B. Woodward and Roald Hoffman, although further work was done by Fukui [5]. These rules involve the use of a simple procedure for determining whether a pericyclic reaction is thermally allowed. Primarily the focus is on the aromaticity of the transition state, which is understood based on orbital topology and electron count. The reaction above shows an example where these rules can be applied in this unique cycloaddition in the form of a Diels-Alder reaction. In short, these rules state that whenever possible, reactions go through aromatic transition states.

As Eschenmoser [6] wrote in his lecture, “but I should perhaps propose that we enjoy the figure just from an aesthetic point of view, by watching the corrinoid chromophore system evolve, like a bud blooming into a flower.”

For the total synthesis of vitamin B12, there are two variants, both of which were accomplished in 1972. In 1960, the ETH Zurich variant was started by Albert Eschenmoser and his team. Following that in 1961, the Harvard variant was started, and after 1965 the work was collaboratively pursued. In terms of the amount of collaboration, it required the work of 91 post-doctoral fellows and 12 Ph.D. students from several different nations [7].

2. Section 2

2.1 Synthesis of the rings

Within the descriptions, both general and or mechanistic, the numbering of the compounds was based on Albert Eschenmoser's overall schema [8].

For the schema with identical steps, the mechanism and explanations are explained once. Also selected mechanisms are listed below from the overall schema.

Ring A:

1. Claisen-Schmidt condensation [9]
2. and 3. Diels-Alder
4. Oxidation
5. Arndt-Eistert
6. Ammonolysis
7. Ring opening
8. Thionation [10]

Ring B:

1. Claisen-Schmidt condensation
2. and 3. Diels-Alder [9]
4. Oxidation
5. Arndt-Eistert [11]
6. Ammonolysis
7. Thionation

Ring C:

1. Claisen-Schmidt condensation
2. Diels-Alder
3. Oxidation
4. Arndt-Eistert

5. Ammonolysis
6. Esterification and methanolysis
7. Thioesterification [12]
8. Reductive decarbonylation

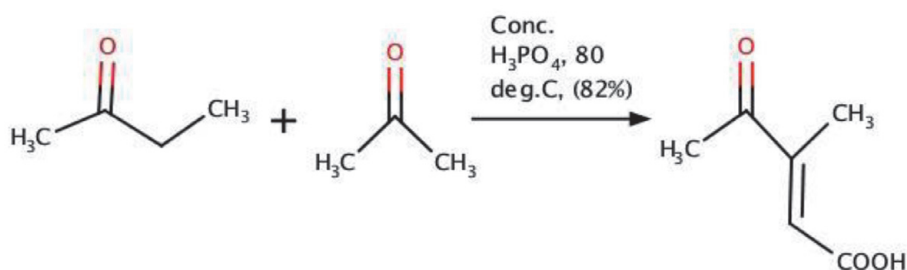
Ring D:

1. Claisen-Schmidt condensation
2. Diels-Alder reaction
3. Oxidation reaction
4. Ammonolysis reaction
5. Ring opening reaction
6. Arndt-Eistert reaction
7. Hydrolysis, decarboxylation, and esterification
8. Protection/sulfonation
9. Reduction/deprotection
10. Protonation
11. Beckmann fragmentation
12. Bromination of the ketimine.

3. Section 3

Ring A:

1. Claisen-Schmidt condensation

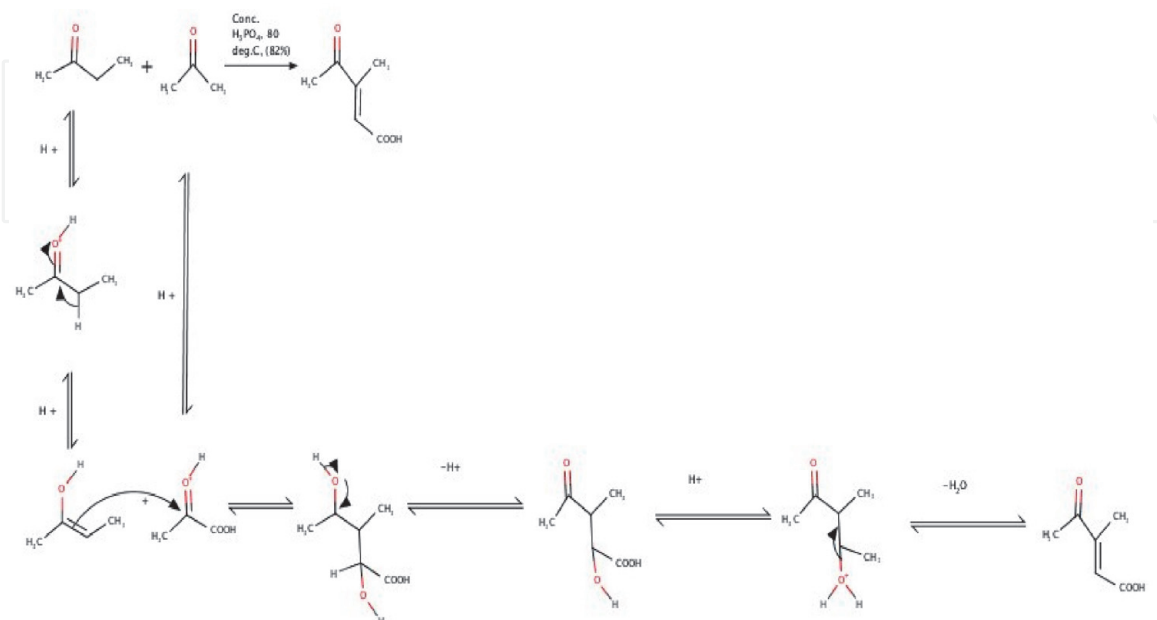


This first reaction of the B12 reaction scheme involves an ethyl methyl ketone (Compound 1A) reacting with acetaldehyde (Compound 1B) using reagents which are concentrated phosphoric acid (H₃PO₄) at 80°C, and the yield is 82%. The type

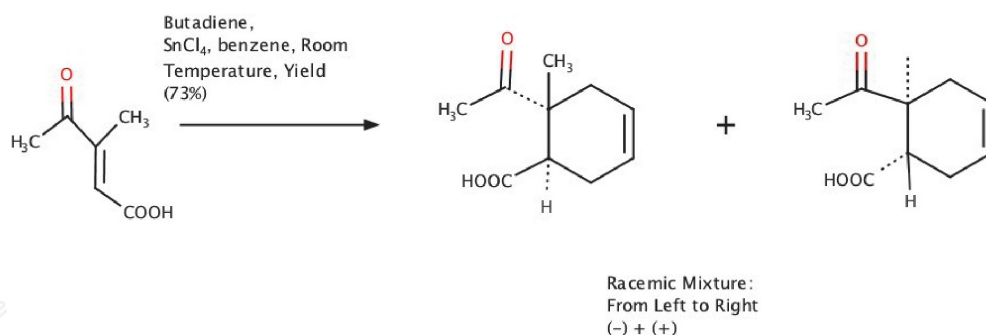
of reaction that is occurring the Claisen-Schmidt condensation in which you have the formation of (2E)-3-methyl-4-oxopent-2-enoic acid. This reaction plays the role in producing the dienophile that will be used in the following reaction.

Overall if simplified this reaction is a type of condensation that results in the formation of an electron-poor molecule.

Mechanism:



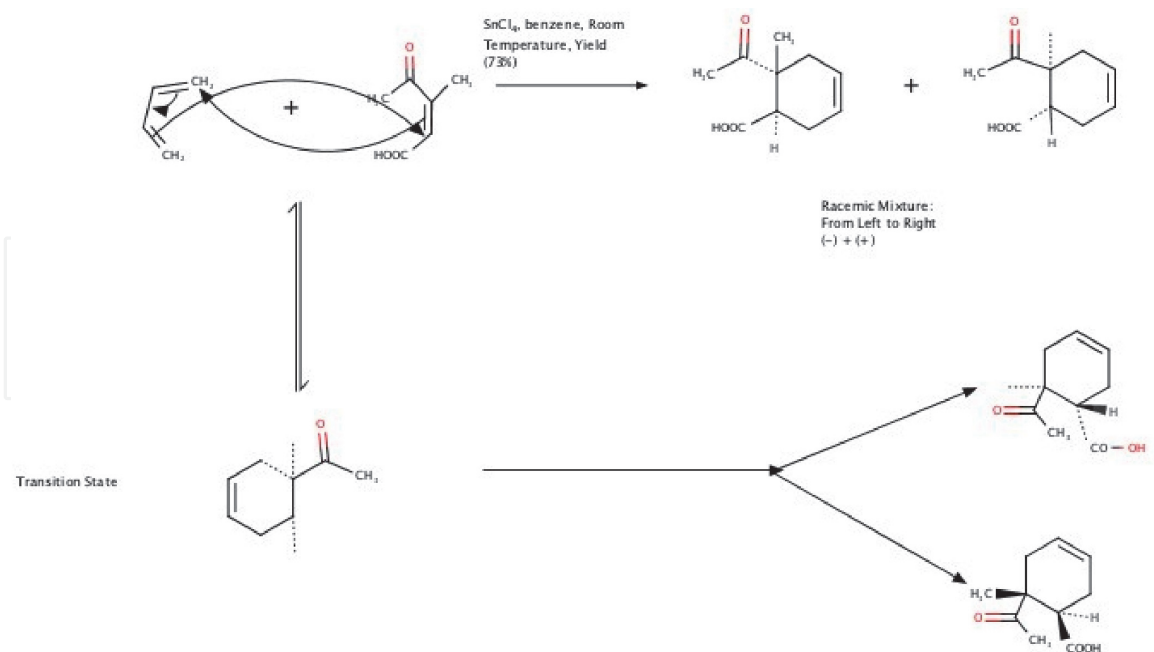
2. and 3. Diels-Alder



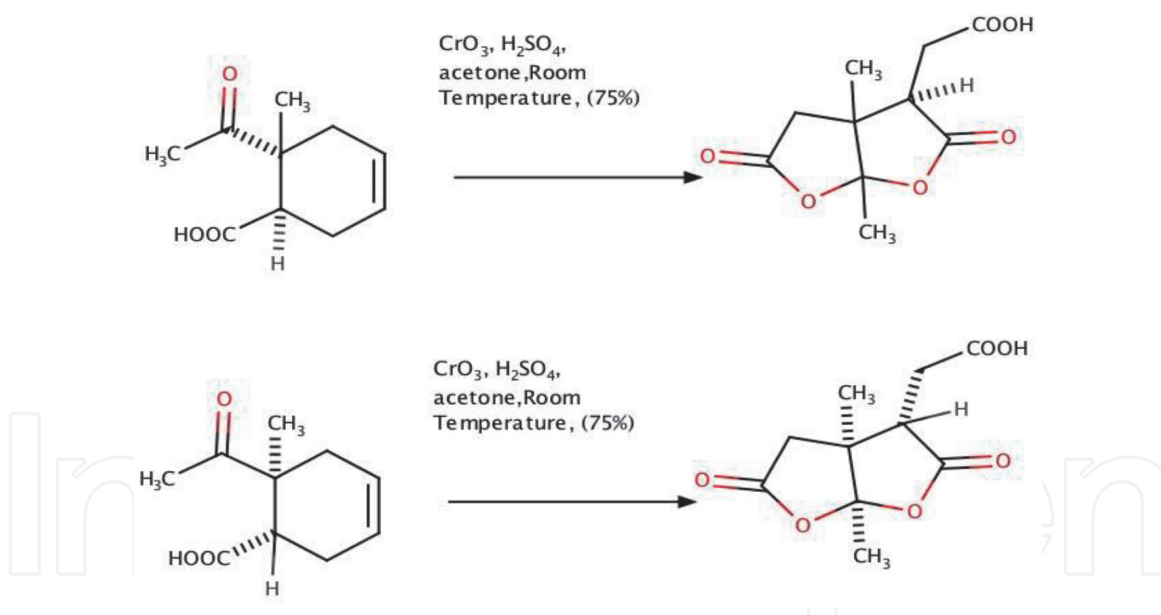
The second reaction of the B12 schema involves (2E)-3-methyl-4-oxopent-2-enoic acid (Compound 2) reacting with butadiene in tin (IV) chloride (SnCl_4) and benzene at conditions of room temperature. This results in a yield of 73%. The type of reaction that is occurring is the Diels-Alder reaction which involves the formation of a racemic mixture of two carboxylic acid-like molecules with ketone-like moieties attached to it. For the purposes of this discussion, the products will be labeled compounds 3A(-) and 3B(+).

Overall if simplified the type of reaction, Diels-Alder, is stereospecific and a type of concerted reaction in that all the bond breaking and bond forming occur at the same time. Moreover addition is syn. Also if this reaction follows the typical Diels-Alder format, it is a one-step cyclo-addition or conjugate addition. This reaction, which resulted in enantiomers which were resolved using phenylethylamine in chloroform and hexane, followed by the use of diluted HCl.

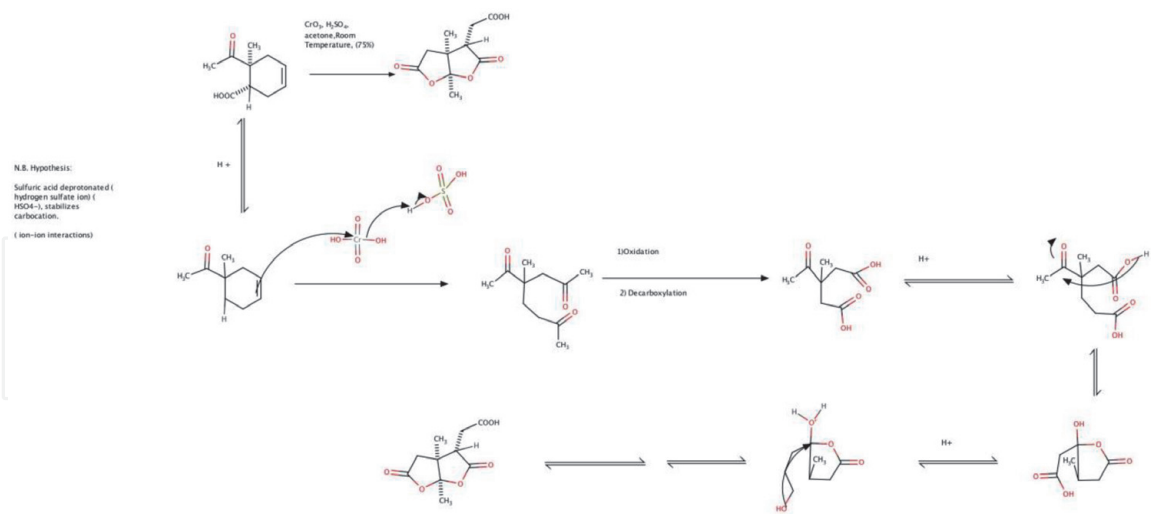
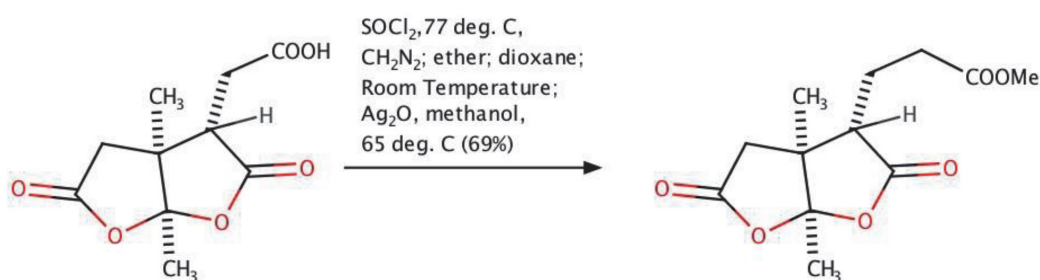
Mechanism:



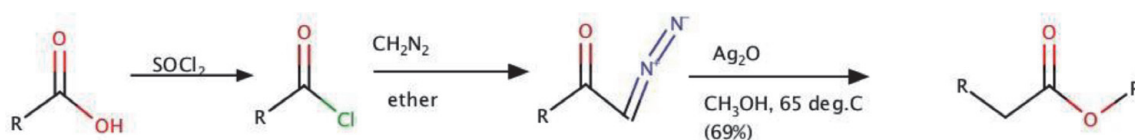
4. Oxidation



The fourth reaction in the B12 reaction schema involves compounds 3A(−) and 3B(+) reacting with chromate and sulfuric acid in acetone at room temperature to form dilactone carboxylic acids which will be labeled compounds 4B(−) and 4A(+) (from top to bottom), both of which are starting products for B12 ring reactors. This fourth reaction has a predicted yield of 75%. From the reagents and the reactants, this appears to be an organic redox reaction, possibly a Jones oxidation, in which we have a molecule being oxidized and or gaining hydrogen deficiency in the form of another ring. Stated simply, these reactions involve the oxidation of compounds 3A(−) and 3B(+) into ten carbon dilactone-carboxylic acids using reagents that normally are used in a type of organic redox reaction.

Mechanism:**5. Arndt-Eistert**

The fifth reaction in the B12 reaction schema involves compound 4A(+) reacting with thionyl chloride at 77°C. This was followed by reacting the acid chloride with diazomethane in ether at room temperature. After which it was reacted with silver dioxide in methanol at 65°C. This fifth reaction had a predicted yield of 69%. However the overall name of the reaction that is occurring is an Arndt-Eistert synthesis. Additionally an important step in the Arndt-Eistert reaction is the Wolff rearrangement of diazoketones to ketenes. The overall Arndt-Eistert reaction, excluding the Wolff rearrangement, can be seen from the reaction drawn below; this sequence involves several steps that result in a higher-order or homologated carboxylic acid.

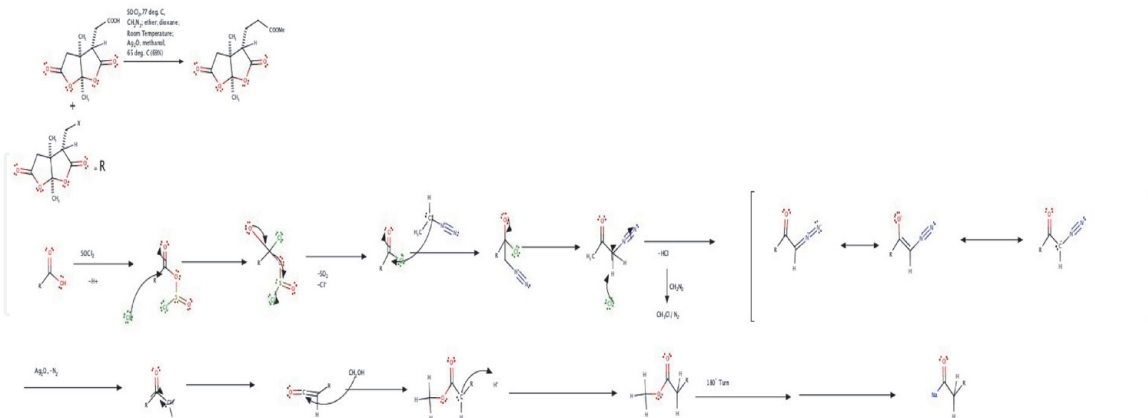


Stated simply this is a multistep reaction that involves the conversion of a carboxylic acid to an acid chloride, then to a diazo-ketone type molecule, and then the ester.

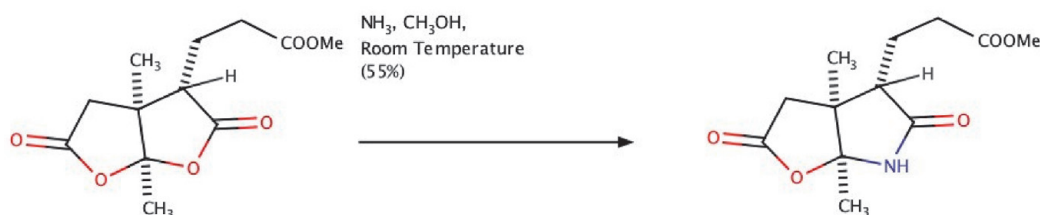
Some key points to note on the reaction, from Eschenmoser's notes for his 1973 German lecture at ETH Zurich, are as follows: "the treatment of the acid chloride with methanol/ pyridine at room temperature gives the same methyl ester as

obtained by esterification with diazomethane; in the preparation of the acid chloride, there is no other structural change.”

Mechanism:

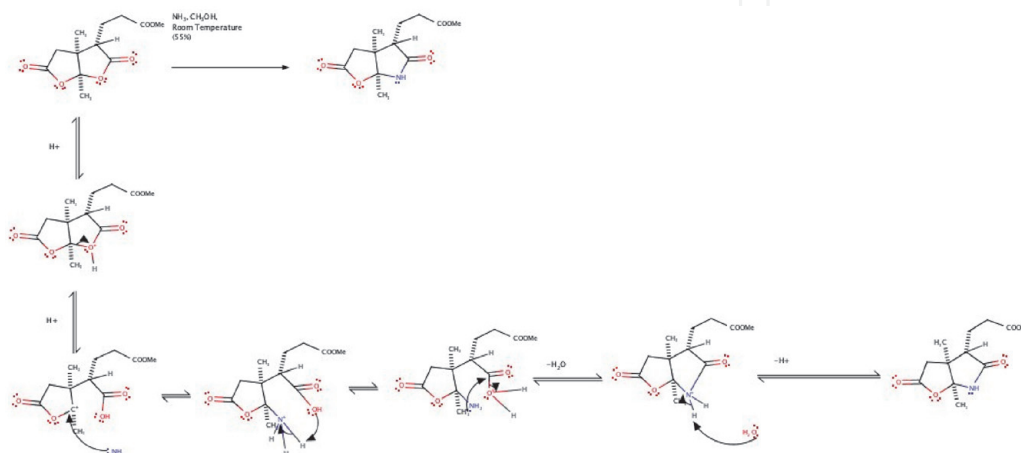


6. Ammonolysis

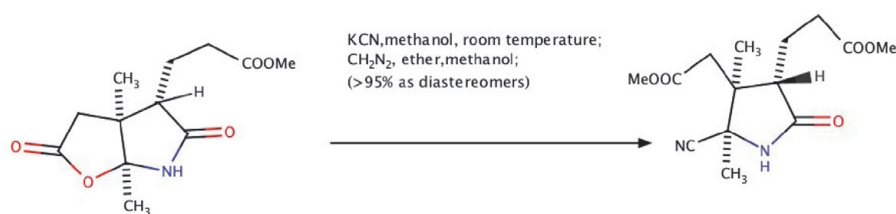


The sixth reaction in the B12 reaction schema involves compound 5A reacting with ammonia in methanol at room temperature. The sixth reaction had a yield of 55%. From this reaction it appears to be an ammonolysis reaction in the presence of a methanolic solvent. Also “the carbonyl groups of the dilactone moiety are much more nucleophilic towards ammonia than normal lactone or ester groups. ‘Ammonolysis’ of this type are much faster in methanol than in non-hydroxyl containing solvents. The constitution assignment for the isomeric lactone-lactams resulted from the identity of compound 6A with the main product of intramolecular NH transfer.” Stated simply this reaction involved an intramolecular NH transfer using ammonia in methanol at room temperature [6].

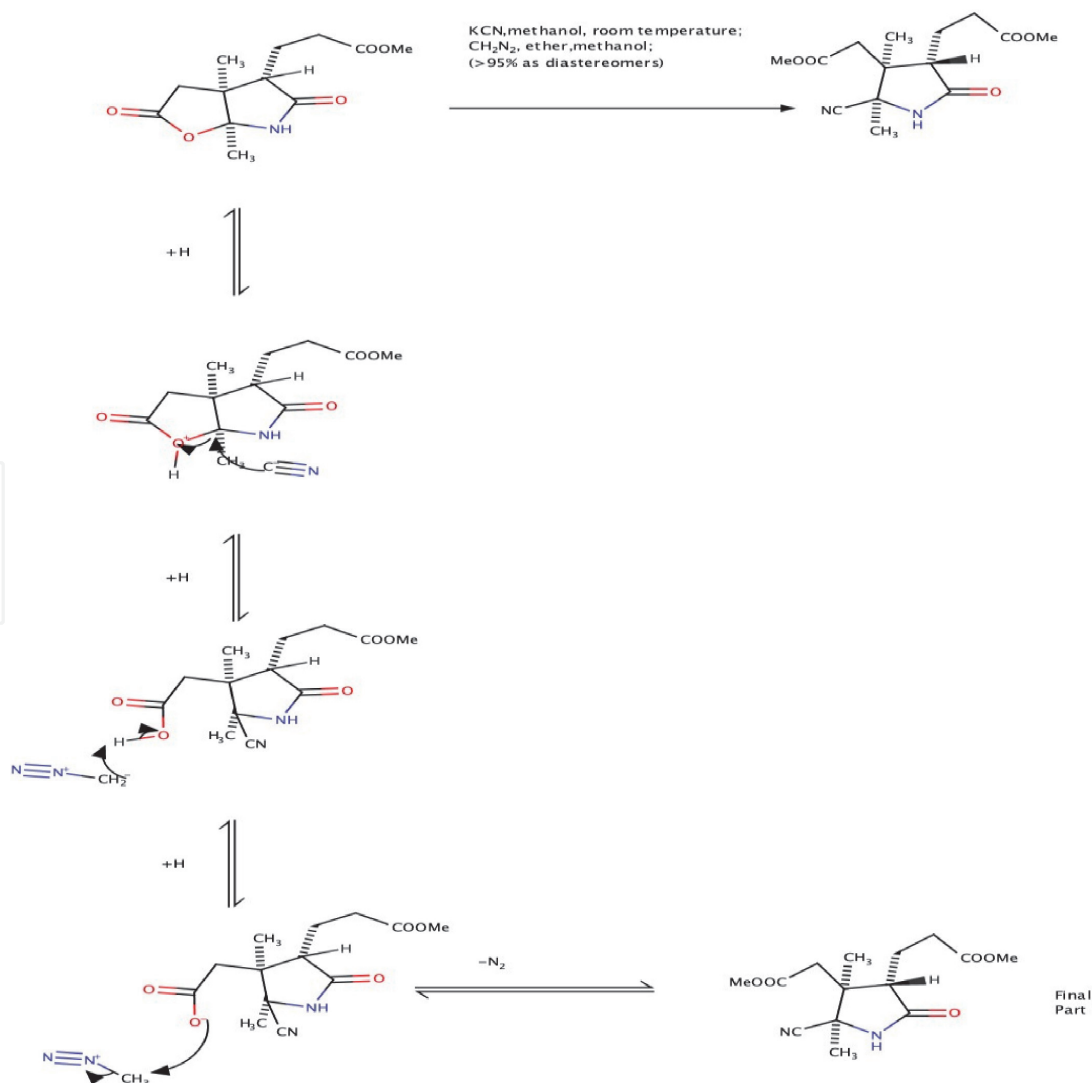
Mechanism:



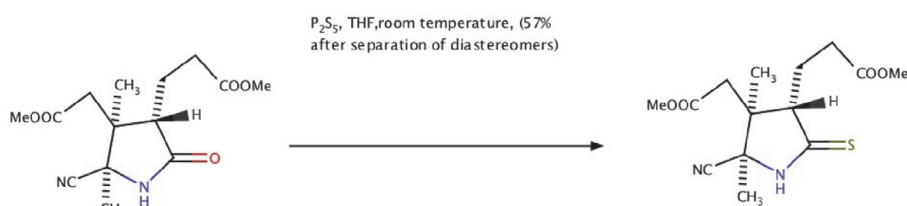
7. Ring opening (step 11 in Eschenmoser's overall schema)



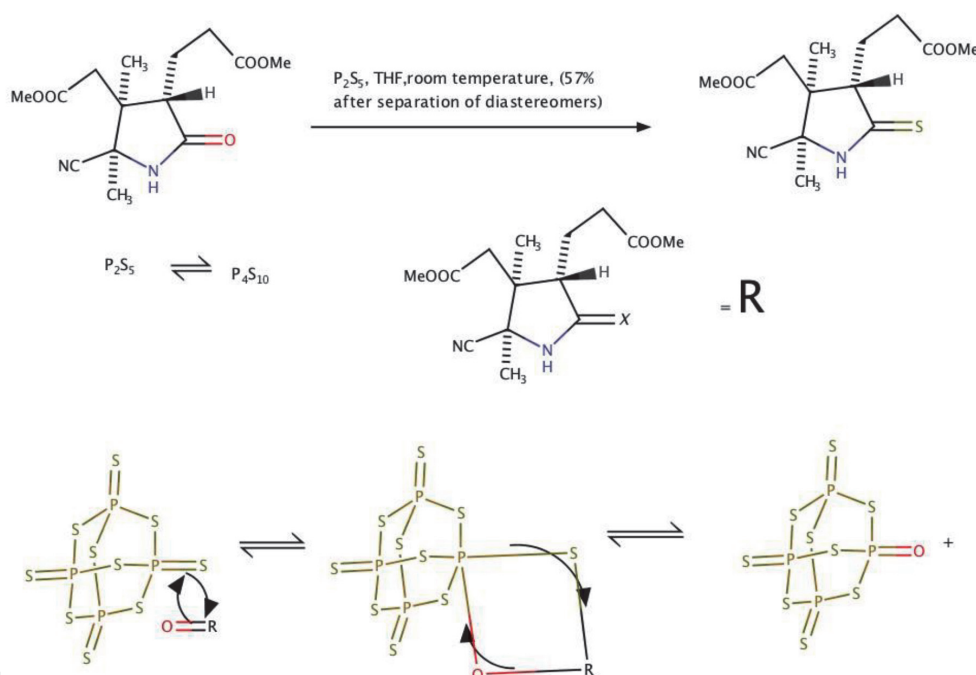
The eleventh reaction in the B12 reaction schema involves compound 6A reacting with potassium cyanide in methanol at room temperature, followed by a reaction with diazomethane in ether and methanol. This resulted in 95% being diastereomers. From this reaction we can see that a lactone ring is opened and a respective ester and cyano group are on the ends. Based on observation this appears to have gone through acid-catalyzed (methanol) ring opening, followed by nucleophilic attack by the cyanide anion from the potassium cyanide. Stated simply this involves the conversion of a 12-carbon-dicarbonyl-bicyclic compound to a cyclic compound with the other ring being cleaved to form an ester and a cyanide at the ends where the ring broke.

Mechanism:

8. Thionation (step 12 in Eschenmoser's overall schema)

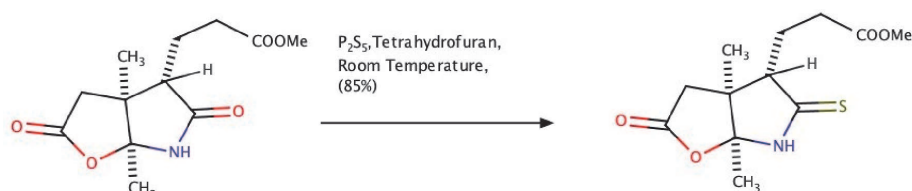


The twelfth reaction in the B12 reaction schema involves compound 11A reacting with diphosphorus pentasulfide and tetrahydrofuran at room temperature to form compound 12 A. Based on the observation of compound 11A, a 14 carbon-monocyclic compound going through a thionation of the carbonyl to form compound 12A, a 14 carbon-monocyclic compound. Stated simply this involves the conversion of a carbonyl to a thio-carbonyl on a 14-carbon monocyclic compound.



Ring B:

7. Thionation



The seventh reaction in the B12 reaction schema involves compound 6A reacting with diphosphorus pentasulfide in tetrahydrofuran at room temperature. The seventh reaction had a yield of 85%. From the reaction compound, 6A is converted to

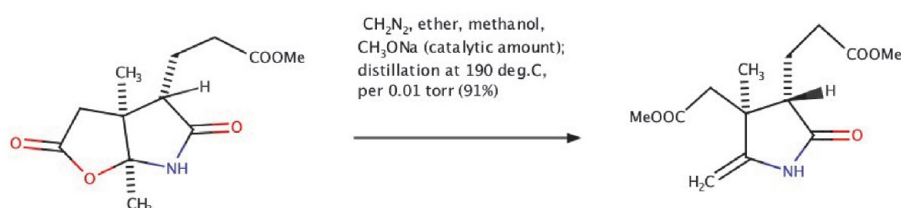
compound 7A with a subsequent thionation in which the carbonyl is converted to a thiocarbonyl. Thionation is the conversion of the carbonyl group to thiocarbonyl, which is a commonly used procedure for the preparation of organosulfur compounds. In many instances with thionations, both the ketone and ester carbonyl groups of the oxoester can be affected by P_4S_{10} but typically in rather low yield. This thionation was specific in that both carbonyl groups were not thionated to thiocarbonyls. Simply put the seventh reaction involved the conversion of one of the carbonyls in the C10-dilactone-ester to a thiocarbonyl using thionating reagents at room temperature. An interesting fact to note is that compound 7A was a precursor for ring B of the macrocyclic corrin that composes the cyanocobalamin.

Mechanism:

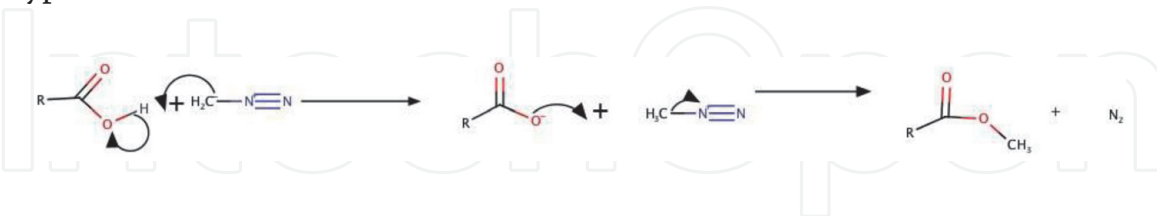
(See thionation mechanism above)

Ring C:

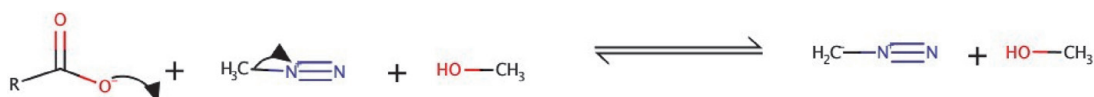
7. Esterification and methanolysis (step 8 in the reference)



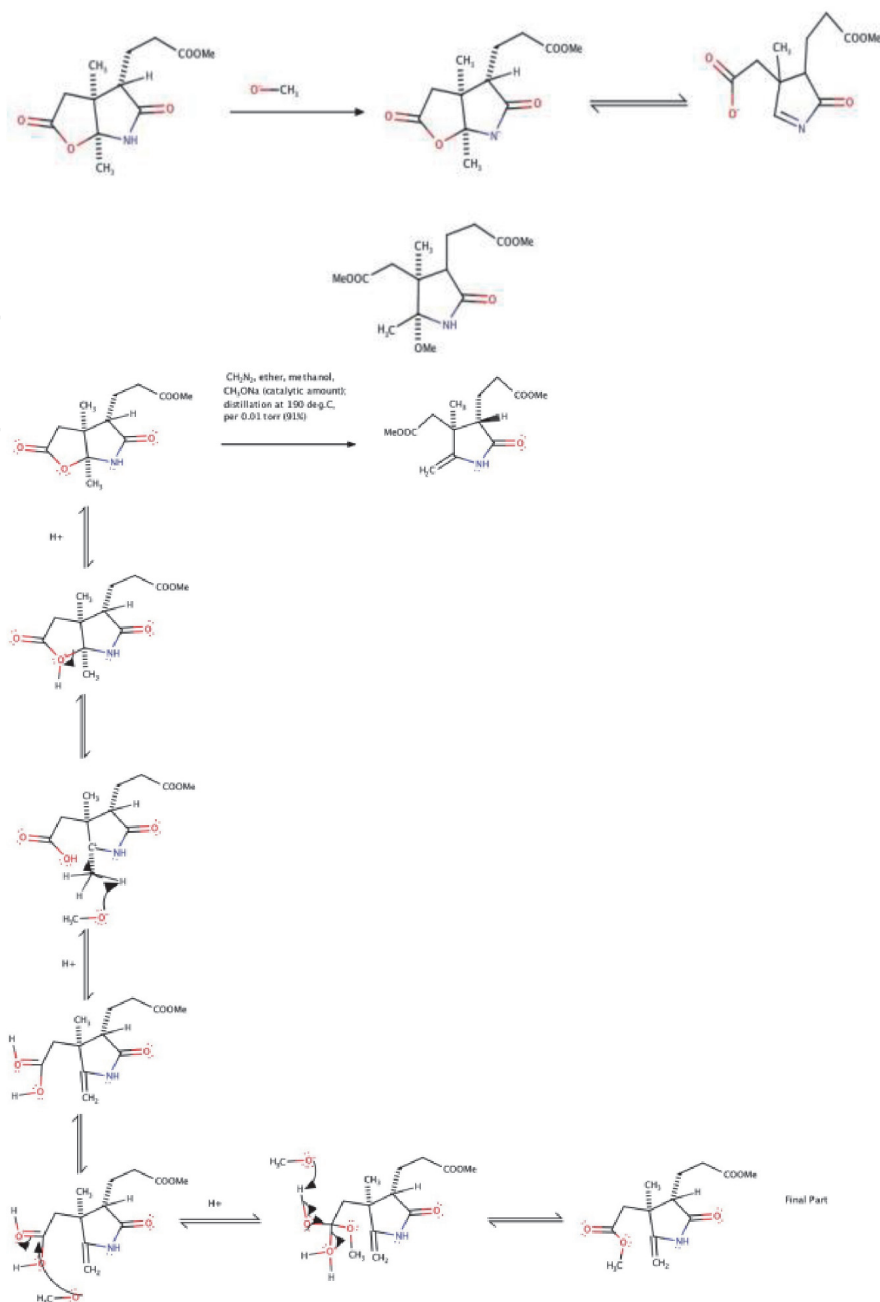
The eighth reaction in the B12 reaction schema involves compound 6A reacting with diazomethane in ether with methanol and a catalytic amount of sodium methoxide, after which is the distillation at $190^\circ C$ at a pressure of 0.01 torr. This reaction had a yield of 91%. From the reaction compound, 6A is converted to compound 8A in which an esterification occurs, resulting in the formation of a methoxy-ester and the formation of a double bond with a methene. Through the use of Dr. Albert Eschenmoser's 1973 ETH Zurich German lecture notes, we gain a better understanding. It states that "Normally when diazomethane is esterified, the free carboxylic acids are transformed with an ethereal solution of CH_2N_2 " and the hypothetical mechanism can be seen below:



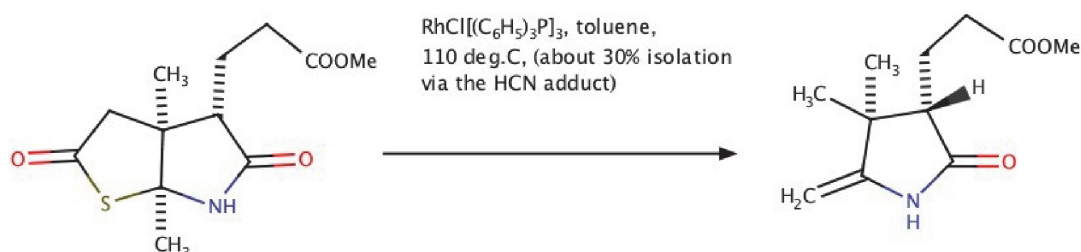
Conversion of compound 6A to compound 8A is "one of the rare examples of esterification in a basic mechanism."



The catalytic amount of sodium methoxide serves to adjust the following equilibrium.



9. Reductive decarbonylation (step 10 in Eschenmoser's overall schema)

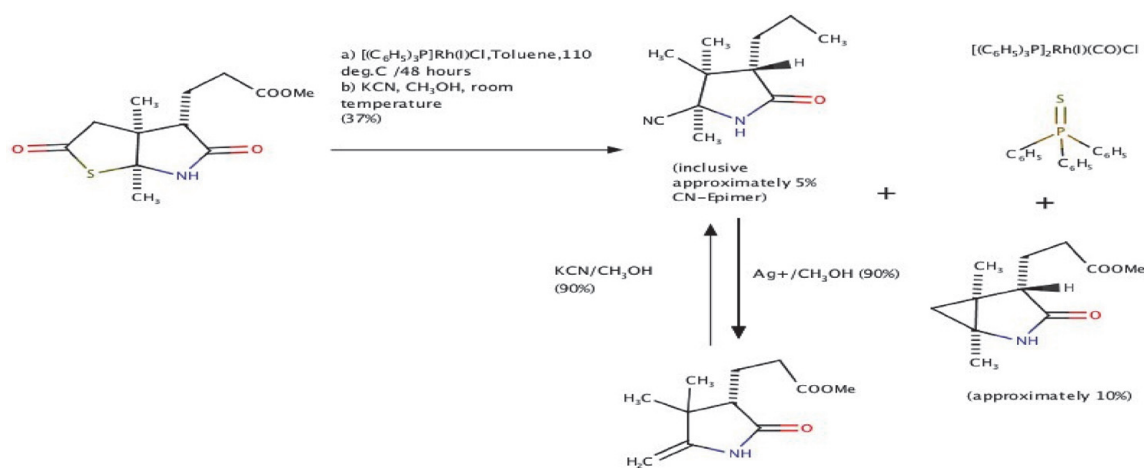


The tenth reaction in the B₁₂ reaction schema involves compound 9A reacting with a rhodium-based catalyst in toluene at 110°C, which resulted in about 30%

isolation through the use of an HCN adduct. From the reaction a thiolactam ring is opened, resulting in a separate methyl and ethylene. As seen the remainder of the bicyclic reactant structure remains the same. However it is worth noting that in Eschenmoser's 1973 lecture notes, it includes that there are several products including the two cyclic structures, a phosphor-sulfuryl and a rhodium-based compound, all of which are reflective of the reagents, the reactants react with. Added to that, one of the groups of products is reacted again with silver ions in the presence of methanol ($\text{Ag}^+/\text{CH}_3\text{OH}$) to form the final pyrrolidine-like product, which is a precursor to ring C for the vitamin B12 synthesis. Additionally the ring precursor can be converted back to the reactant by the use of potassium cyanide in methanol (KCN , methanol). Both the conversion of ring C from the intermediate group of products to the final product and the reversed conversion back to the reagent in the group of products have yields of 90%. Stated simply this reaction involves the conversion of a bicyclic dicarbonyl-12-carbon ester to a cyclic 8 carbon pyrrolidine-like molecule using a catalyst in organic solvent. In other words, the "corresponding thiolactone is ran through reductive decarbonylation brought about by the chloro-tris-trisphenyl-phosphine complex of rhodium (I)" [6]. Then through the use of HCN, there was about 30% isolation. The entire reaction scheme for this step can be seen below:

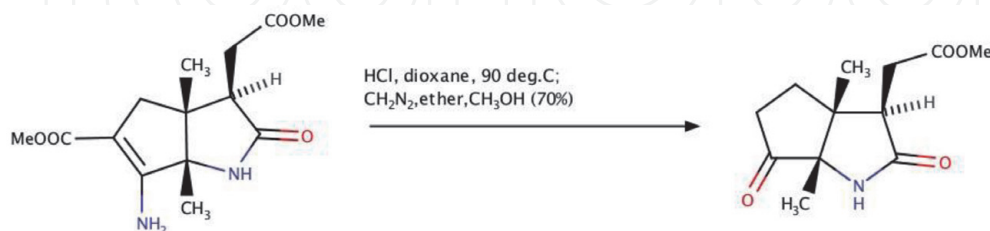
Steps:

Note: In ten some insight was gained from Eschenmoser's German lecture.



Ring D:

8. Hydrolysis, decarboxylation, and esterification (step 16 in the reference)



The general reaction involves compound 15B reacting with hydrochloric acid in dioxane at 90°C. This is followed by the reaction with diazomethane in ether and methanol. Compound 15B is a 12-carbon-bicyclic system with one of the cycles having a unit of unsaturation, i.e., a double bond, and an ester moiety and an amine moiety are attached to the cycle with the unit of unsaturation. Based on observation the two esters on compound 15B are hydrolyzed to acids, followed by the hydrolysis of anexamine to a ketone and then the decarboxylation of the beta-ketoacid, and finally the diazomethane is used to convert the remaining acid to an ester. Stated simply, this

involves the conversion of a 12-carbon-cyclic compound to an 11-carbon dicarbonyl-bicyclic compound, by hydrolysis, decarboxylation, and then esterification.

Note: Some insight was gained from Dr. S. S.

4. Section 4

Final steps in the synthesis of cyanocobalamin.

1. Iminoester condensation and sulfide contraction (step 24 in Eschenmoser's overall schema).
2. Thionation (step 25 in Eschenmoser's overall schema).
3. Sulfide contraction via alkylative coupling (step 26 in Eschenmoser's overall schema).
4. Ammonolysis (step 27 in Eschenmoser's overall schema).
5. Iodination (step 28 in Eschenmoser's overall schema).
6. Elimination (step 29 in Eschenmoser's overall schema).
7. Photochemical A/D cycloisomerization (step 30 in Eschenmoser's overall schema).
8. Metal complexation (step 31 in Eschenmoser's overall schema).
9. Lactonization (iodolactonization) (step 32 in Eschenmoser's overall schema).
10. Alkylation (step 33 in Eschenmoser's overall schema).
11. Reduction and esterification (step 34 in Eschenmoser's overall schema).
12. Reduction (step 35 in Eschenmoser's overall schema).
13. Hydrolysis and ammonolysis (steps 36 and 37 in Eschenmoser's overall schema).
14. Final step: cobyric acid to cyanocobalamin (step 38 from K. Bernhauer and Eschenmoser's lecture).

5. Section 5

Characteristics of the cobyric acid molecule complex

Altogether the entire molecule "contains all peripheral carboxy functions in the primary amide form, except that of the propionic side chain in ring D."

Common steps in the entire synthesis:

The first four steps in the synthesis

- The Claisen-Schmidt condensation
- Diels-Alder (steps 2 and 3)
- Oxidation

Common problems in the synthesis of cobyric acid:

- Introduction of cobalt
- Closure of the macrocyclic ring
- Ester differentiation
- Introduction of methyl groups at bridges
- Restoration of lost stereochemistry [13]

Problems that had to be solved

- For rings A and B they are:
- Elongation of the free acetic acid chain by one methylene unit
- Specific replacement of one lactone oxygen by NH
- Conversion of the potential methylketone group into the enamide form

General approaches to problems

The sources especially Eschenmoser's and Woodward's lecture notes listed the general approaches involved:

1. Collaboration with other scientists.
2. Exhaustive study of the relationships between thioethers.
3. Purifications using analytic instrumentations such as high-performance liquid chromatography.
4. Use of pure reagents, exclusion of oxygen and moisture [14].

Possible future studies

Some possible future studies may involve the role of sulfur-aromatic interactions in certain mechanistic steps as well as carbocation-conjugate base interactions or stabilization. Added to this are variations of Markovnikov rules in the context of heterocycles. Additionally, whether through computation chemistry and/or experimental evidence, hypothesized organic chemistry mechanism testing can be done, considering how the plausibility of the mechanism is tied to the reality of the reaction.

6. Conclusion

Indeed "the emergence of the Woodward-Hoffman rules out of such a situation is an extreme example and its impact on chemistry" is significant, albeit "the very existence of these rules had stimulated, encouraged and assisted experimental involvement in a research project which eventually led to a new type of corrin synthesis" [14].

Added to that persistence in scientific research is very important given that there were many obstacles notably with the photochemical cyclo-isomerization. “In short, those transition-metal ions that quench luminescence of the excited corrin chromophore by virtue of their unfilled d-shells, also seem to thwart photochemical cycloisomerization of the corresponding A/D-seco-corrinoid complexes.” However amidst the new challenge, new approaches and ideas developed in that it became “increasingly clear that the A/D-seco-corrin to corrin system offers an optimal opportunity to study relationships between the nature of the metal ion complexation centers and the photochemical behavior of excited porphinoid ligand chromophores.”

Also there was “an essentially analogous reaction sequence starting from the enantiomeric form of the C10-dilactone acid leads to the skeleton of the ring D precursor, provided that not the free, but the lactonized ($-\text{CH}_2-\text{COO}-$) chain is lengthened by one methylene unit.” Additionally, the conversion of ring B to the precursor of ring C requires a method for specific removal of the carbomethoxy group of acetic acid side chain and its replacement by hydrogen.


As Eschenmoser [6] wrote in his lecture, “but I should perhaps propose that we enjoy the figure just from an aesthetic point of view, by watching the corrinoid chromophore system evolve, like a bud blooming into a flower.”

Author details

David Joshua Ferguson
Taylor University, Upland, Indiana, United States of America

*Address all correspondence to: davidfergusonwarrior@gmail.com

IntechOpen

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Peters RA. The vitamin B complex. *British Medical Journal*. 1936;2(3957): 903-905. DOI: 10.1136/bmj.2.3957.903
- [2] Homologation Reactions. Available from: https://en.wikipedia.org/wiki/Homologation_reactions [Accessed: 23 November 2019]
- [3] Corrin Explanations. Available from: <https://en.wikipedia.org/wiki/Corrin> [Accessed: 23 November 2019]
- [4] Stephenson NA, Gellman SH, Stahl SS. Ammonolysis of anilides promoted by ethylene glycol and phosphoric acid. *RSC Advances*. 2014; 4(87):46840-46843. DOI: 10.1039/C4RA09065A
- [5] Ranganathan S. A tale of two topologies: Woodward-Hoffmann rules at your fingertips! *Resonance*. 2011; 16(12):1211-1222. DOI: 10.1007/s12045-011-0136-7
- [6] Becker A. Research Collection: Theses. 2017. pp. 12-19. DOI: 10.3929/ethz-a-010782581
- [7] Vitamin B12 Total Synthesis. Available from: https://en.wikipedia.org/wiki/Vitamin_B12_total_synthesis [Accessed: 23 November 2019]
- [8] Adapted from: Lecture material from Dr. RB Woodward by Pure and Applied Chemistry; Lecture material from Dr. A. Eschenmoser from ETH Zurich Research Collection, The numbering of the reactions was adapted from Dr. Albert Eschenmoser's german lecture paper
- [9] Organic Synthesis Search. Available from: <https://www.organic-chemistry.org/synthesis/> [Accessed: 23 November 2019]
- [10] Maurya CK, Mazumder A, Gupta PK. Phosphorus Pentasulfide Mediated Conversion of Organic Thiocyanates to Thiols. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5496577/>
- [11] File:Arndt-Eistert-Homologation mechanism V2.svg. Available from: https://commons.wikimedia.org/wiki/File:Arndt-Eistert-Homologation_mechanism_V2.svg [Accessed: 23 November 2019]
- [12] Sudalai A, Kanagasabapathy S, Benicewicz BC. Phosphorus pentasulfide: A mild and versatile catalyst/reagent for the preparation of dithiocarboxylic esters. *Organic Letters*. 2000;2(20):3213-3216. DOI: 10.1021/ol006407q
- [13] Protection of Carbonyl Groups. Available from: <https://en.chem-station.com/reactions-2/2014/04/protection-of-carbonyl-groups.html> [Accessed: 23 November 2019]
- [14] Marini-Bettolo GB. Recent advances in the chemistry of natural products from Latin American Flora. *Svensk Farmaceutisk Tidskrift*. 1955;59(5): 130-136