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Natural Product Synthesis and Vitamin B_{12}

Total synthesis of vitamin B_{12} provided a framework for exploration in several areas of organic chemistry.

Albert Eschenmoser and Claude E. Wintner

Through the combined efforts of two groups, a 12-year period of research in organic natural product synthesis came to an end in 1972 with the completion of two total syntheses of cobyric acid and, hence, of vitamin B_{12}. The work was accomplished through the close collaboration of R. B. Woodward's group at Harvard and the group at the Eidgenössische Technische Hochschule (ETH). In addition to a series of published lectures (*1–3*) describing the syntheses, a lecture dealing with trends and objectives in natural products chemistry as seen from the vantage point of B_{12} synthesis has appeared in German (*4*). This article is a translated and modified version of that lecture and, in addition, includes the full scheme of the photochemical variant of the cobyric acid synthesis.

On the Role of Natural Product Synthesis

Research on the synthesis of natural products is part of the foundation of our knowledge about structure and reactivity in organic chemistry. To a large degree, our ability to prepare organic compounds, whether naturally occurring or not, has grown out of such research. The importance placed on the technological aspect of natural product synthesis has not changed substantially since the era of Adolf von Baeyer. On the other hand, its scientific function within organic and biological chemistry has altered considerably with the passage of time.

During the classical period of natural products chemistry, synthesis was an essential part of the process of structure determination. Von Baeyer's labors on indigo and Hans Fischer's on the porphyrins may stand as consummate examples. The potential ambiguity of degradative evidence made the complementary information of synthesis imperative. This classical summons of synthesis to the determination of constitution did come about, however, not because at that time there existed any greater certainty about the structural course of synthetic reactions than of degradative ones. Rather, it was the extremely high improbability that reciprocally compensating errors of interpretation would occur, which conferred the weight of proof of constitution on an identity of constitutional hypotheses derived from both degradation and synthesis. However, the development of organic natural products chemistry is characterized by the fact that the determination of constitution through chemical degradation, in principle stochastic in its methodology, yielded results far more swiftly than could the methods of synthesis, which, having specific targets, were consequently far more demanding. As the rapidly increasing number and accompanying complexity of constitutional hypotheses from degradation outstripped the possibilities of synthesis, the demand for final proof of constitution through synthesis could be satisfied in simple cases only, and then often merely in the limited form of a partial synthesis.

The gap between structure determina-

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tion and synthesis has never been closed; on the contrary, it has ever widened. To be sure, in the middle of the present century came the achievements of the great total syntheses of natural products chemistry: quinine, morphine, strychnine, cholesterol, the steroid hormones, chlorophyll, among others. However, this heroic period of modern natural product synthesis came as a result of the development of the concept of inference through mechanistic rather than constitutional analogy, of the arrival of conformational analysis, and of the introduction of empirical spectroscopic methods. These were changes in organic chemistry that were even more effective for degradation, and they therefore only accelerated the widening of the gap.

The scene was irreversibly altered when x-ray analysis became by the mid-1950's the unchallenged method of choice for the task of structure elucidation. In retrospect, chemical degradation stands as the method of the first hundred years in the history of organic natural products chemistry. Even in its hitherto indispensable role in the investigation of biosynthetic reaction pathways with the help of ^{14}C-labeled compounds, the method is today on the verge of becoming obsolete as a consequence of the arrival of ^{13}C nuclear magnetic resonance (NMR) spectroscopy. Thus, one of organic chemistry's sources of information and discovery, and in fact the true wellspring of much of our knowledge about organic chemical structure and reactivity, has run dry. At the same time the classical task of natural product synthesis, that is, to provide final verification of constitutional hypotheses, has lost its primacy.

In contrast to physical structure determination, the stepwise and often groping approach toward the constitution of natural products through chemical degradation led not merely to a constitutional formula, but to an intimate acquaintance with the chemical properties of new structures. Today it is synthesis, rather than chemical degradation, which must fulfill this role. While a thorough knowledge of the specific reactivity of a natural product structure was formerly a prerequisite for setting out on the venture of its synthesis, now it is our comparative ignorance of the chemical properties of a structural island discovered by means of physical methods that demands the venture and confers upon the synthesis a special weight. The execution of such a synthesis is not simply an experimental verification of a plan conceived in detail in advance. Rather, in its most important phases it is an inquiry, guided by a synthetic strategy, into the reactivity of structural types with respect to their potential as intermediates in a synthetic reaction sequence. What the synthetic target provides is stimulation and direction. Challenged by the necessity of moving toward a given structure, the synthesis often leads to problems that are complementary to those chosen in open-ended preparative research on reactivity. At the same time, the demise of the classical function of structure proof means freedom from the restrictive, although once valid, principle that the synthetic route must consist of structure proving steps of known reaction type. Now, natural product synthesis poses the challenge to consider and develop new pathways of structural transformation. Natural products as targets for synthetic research possess a special fertility in this regard, because the structural channels of biosynthesis are not necessarily the conduits of organic synthesis.

In the synthesis of vitamin B_{12} we can find exemplification of these points. To be sure, an event without parallel will always be associated with this endeavor. While exploring one part of the problem, R. B. Woodward hit on a puzzle whose analysis became the point of departure for the discovery of the Woodward-Hoffmann rules concerning the role of orbital symmetry in chemical reactions. This development, which ushered in a new era in the theory of organic chemistry, is too unique in scientific and personal circumstance to be designated as exemplary of the function and the importance of research in natural product synthesis. Nevertheless, it does illustrate, if in an extreme way, the potential for stimulation and discovery that natural products research holds for the whole of organic chemistry. We are reminded that the full significance of a theoretical model may only become appreciated in the light of a comprehensive knowledge of the empirical realm of chemical reactions. The research area of natural product synthesis requires and provides such knowledge in exceptional breadth. It is therefore particularly fitting that it was the protagonist of modern natural product synthesis who triggered the final

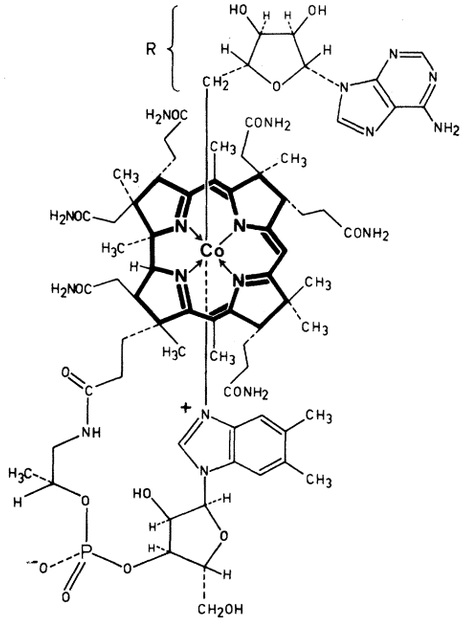


Fig. 1 (left). Vitamin B_{12} (R = CN) and coenzyme B_{12}.

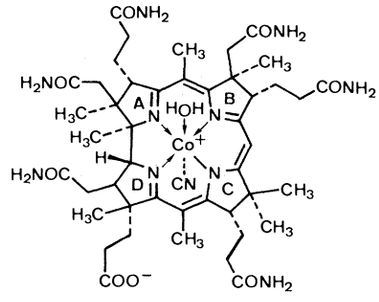


Fig. 2 (right). Cobyric acid.

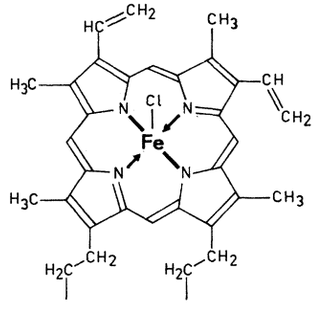


Fig. 3. Hemin.

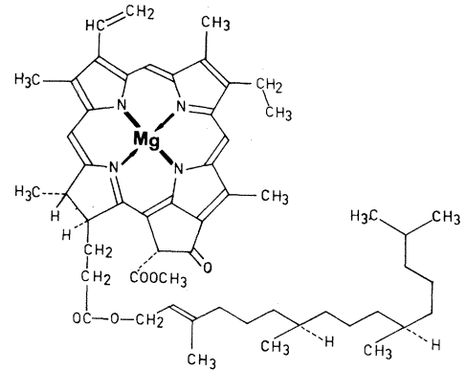


Fig. 4 (left). Chlorophyll a.

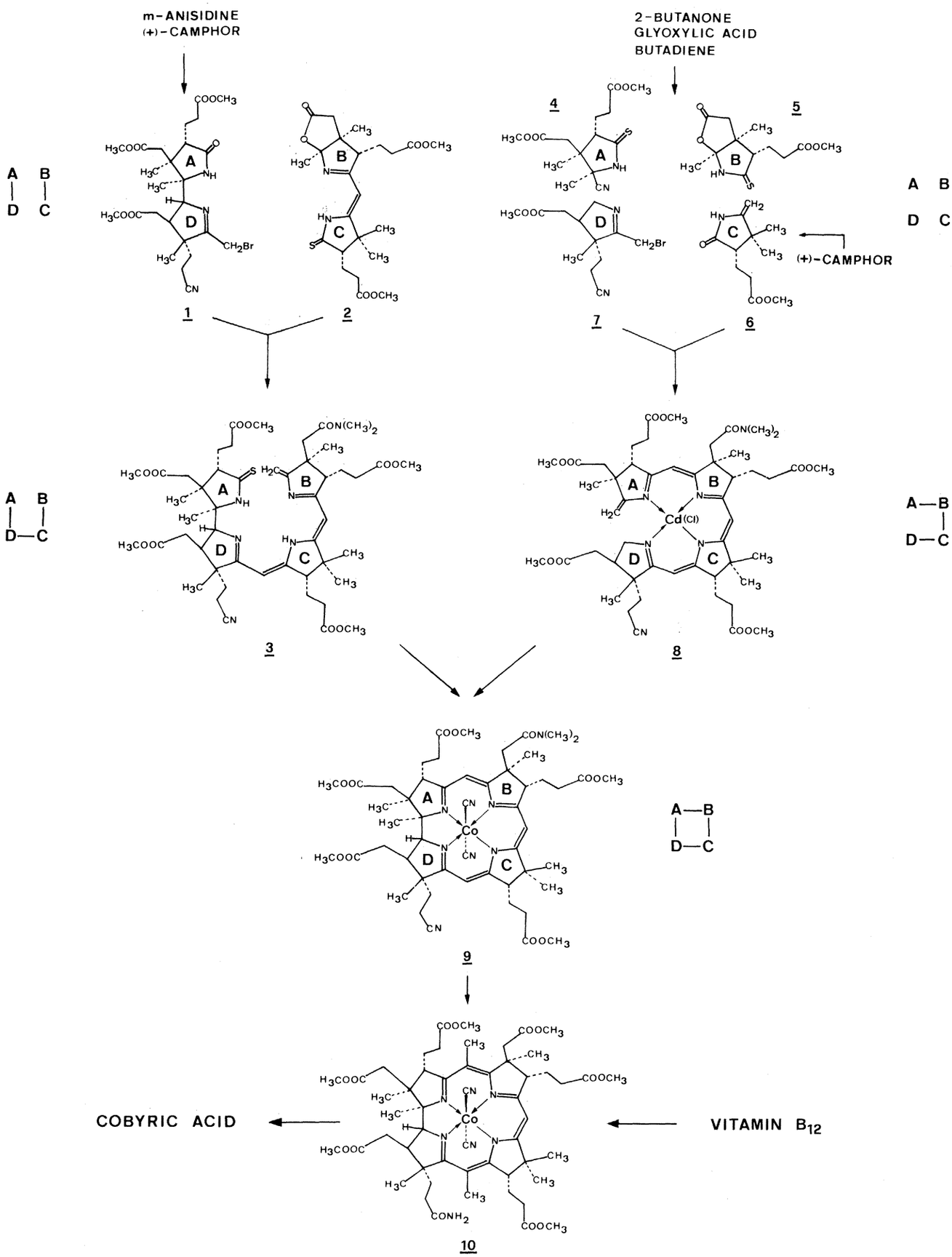


Fig. 5. The two approaches to cobyric acid.

breakthrough of the use of the quantum mechanical model of structure and reactivity in organic chemistry, an advance that parallels the establishment of the classical structure theory, the tetrahedral model of carbon, the octet rule, and conformational analysis.

Target: Vitamin B_{12}

When Hodgkin announced (*5*) the complete structural formula of vitamin B_{12} (Fig. 1) in 1956, it was clear that this natural product presented an ideal objective for organic synthetic research. It is a compound of great biochemical significance. Its molecular architecture is complex and had not previously been encountered in natural products chemistry. Its structural nucleus had resisted elucidation by means of chemical methods of degradation and had been solved by x-ray crystallographic analysis. The synthetic investigation of vitamin B_{12} would involve a host of new problems in the realms of planning and method and would link "x-ray island B_{12}" with the mainland of chemical experience. Vitamin B_{12} provided an opportunity to extend the frontiers hitherto established by organic synthesis in the area of low-molecular-weight natural products.

In building up a low-molecular-weight natural product, the construction of the carbon framework generally governs the planning of the synthesis. Indeed, the central problem of organic synthesis has always been the formation of the carbon-carbon bond. If a natural product is composed of carbon fragments that are joined together by heteroatoms, the strategy of the synthesis is essentially predetermined; proteins and polynucleotides may stand as examples. In the case at hand, cobyric acid is the compound that embodies the carbon core of vitamin B_{12}, and the problem of the total synthesis of the vitamin was, by 1960, that of the synthesis of cobyric acid (Fig. 2). This structurally "least complex" representative of the corrinoid natural products had already been linked to the vitamin by the partial synthesis of Friedrich, Gross, Bernhauer, and Zeller (*6*). In addition, the research groups of Johnson (*7*) and of Bernhauer (*8*) had shown how vitamin B_{12} can be transformed into the coenzyme (Fig. 1). Thus, through the synthesis of cobyric acid, one would gain synthetic entry into the entire sphere of corrinoid natural products.

The number and nature of chiral centers on the carbon framework are further determinants of the degree of difficulty of a chemical synthesis. An agglomeration of such centers categorically requires the use of stereospecific methods, and certainly no other aspect of natural product synthesis makes the (present) disparity between enzymatic and chemical synthesis so evident as this one. The struggle of the chemist to progress in this direction can be followed by inspection of the increasing stereochemical content of the three porphinoid natural products hemin [total synthesis 1929 (*9*)] (Fig. 3), chlorophyll [total synthesis 1960 (*10*)] (Fig. 4), and cobyric acid. Within the three-dimensional structure of cobyric acid, whose complication in the family of porphinoid natural products is without precedent, lies a major part of its challenge and potential as a target.

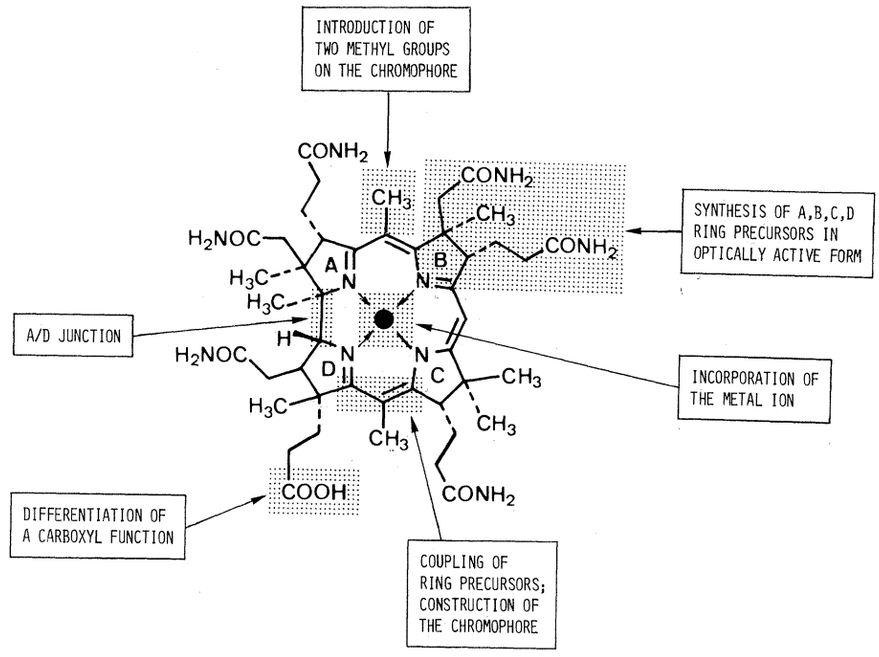


Fig. 6. Problems to be solved in a cobyric acid synthesis.

A summary of the two routes to synthetic cobyric acid (*11*) is given in Fig. 5. The goal was simultaneously attained by paths which met in their end phases in a common intermediate, the corrin cobalt complex **9**; from there the final ascent via hexamethylcobyrinate-f-amide **10** was collaboratively accomplished in both laboratories. The f-amide was also prepared from natural vitamin B_{12}, providing at this point the first opportunity for identification. Here we discuss just two problems which were generated by the synthesis.

Construction of the Chromophore: The A/D Junction Problem

The development of methods for the construction of the corrin chromophore, indeed related to, yet characteristically different from, that of the porphyrins, was central among the catalog of problems that a synthesis of cobyric acid had to overcome (Fig. 6). Such methods were worked out during the course of extensive model studies (*12*) parallel with the work on cobyric acid. The results of these studies shaped the planning and execution of the synthesis of the natural product.

The two variants of the formation of the corrin nucleus differ above all in the manner in which they deal with the task of linking rings A and D (Fig. 5). The concept that was originally set, and for years exclusively adhered to, locates the solution of this problem at the start, namely, in the synthesis of an A/D component. This is then to be linked with a B/C component, with the final closing of the ring to a macrocyclic corrin system following between rings A and B (the A/B variant). The elaboration of the A/D component was entirely the work of the Harvard group; their stereospecific 37-step conquest of compound **1** is an outstanding testimony to organic synthetic art. The Woodward-Hoffmann rules issued from one of the approaches studied at that time, and the history of that discovery in 1965 has been described by Woodward (*13*). The work that led to the cobalt complex **9**, through the coupling of the Harvard component **1** with the ETH component **2** via condensation product **3**, followed by A → B cyclization, has also been discussed (*1*, *2*); here we glance at the other variant (*3*).

The heart of this synthesis (the A/D variant) is the ring closure between rings A and D through photo-induced cyclo-

isomerization of secocorrin metal complexes of type **8**. This reaction, induced by visible light, takes place very smoothly and creates the natural configuration at the A/D junction with 95 percent stereoselectivity in the case of the cadmium complex (Fig. 7). The reaction was developed and then studied in detail in a model system (**11** → **12**) (Fig. 8). To be sure, it was sought primarily with a view toward its use for the construction of the corrin ring. However, it subsequently has also proved to be of interest in the study of the photochemistry of corrinoid metal complexes (*14–17*).

The rate-limiting structural transformation is the photo-induced shift of a hydrogen atom from the methylene group in ring D to the exocyclic methylidene group on ring A. Whether the π system **13** (Fig. 9) thus produced—formally it has two nonbonded electrons—achieves the status of an intermediate remains unknown. At any rate, this energy-rich π system is a ($\pi \rightarrow \sigma$) valence isomer of the corrin complex **12**. In the case of the palladium secocorrin complex (**11**; M, the metal is Pd^{+}) dideuterated at the ring D reaction center, the 1,16-hydrogen transfer is documented by NMR spectroscopy; the cyclization shows a kinetic isotope effect of about 7. The reaction runs excellently with electronically inert coordination centers, such as lithium, magnesium, zinc, and cadmium (*14*); it goes more slowly with the heavy transition metals palladium and platinum (*14, 15*); and it has not been observed at all with the light transition metals cobalt, nickel, and copper (*14*), which are evidently effective in quenching the excitation (*16*) (see Fig. 8). Action spectra as well as kinetic analyses show that the cyclization of the zinc and cadmium complexes occurs predominantly via sensitization of the educt **11** by photoexcited product **12** (*17*). Oxygen and specific triplet quenchers (*18*) effectively prevent these two cyclizations, suggesting that the hydrogen transfer departs from the triplet state of the educt (*17*). In conspicuous contrast to the corrin complexes (**12**; M is Li, MgCl, ZnCl, or CdCl), the secocorrin complexes (**11**; M is MgCl, ZnCl, or CdCl) show no fluorescence (*15, 16*), apparently because of loss of their initial excitation energy via nonradiative decay. Their photochemically productive triplet state seems to be populated effectively only by way of sensitization.

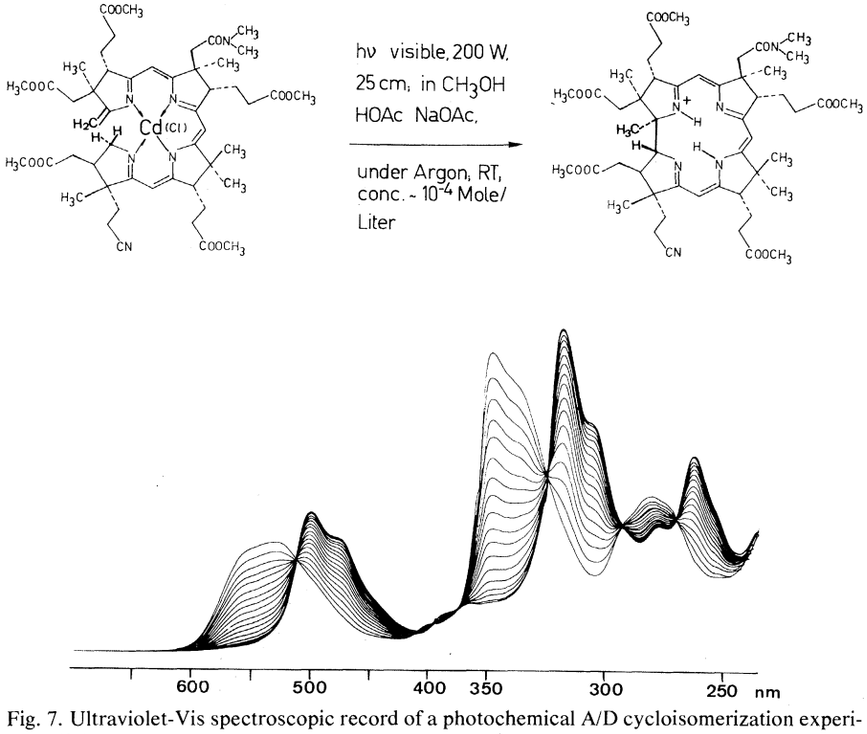


Fig. 7. Ultraviolet-Vis spectroscopic record of a photochemical A/D cycloisomerization experiment (*35*).

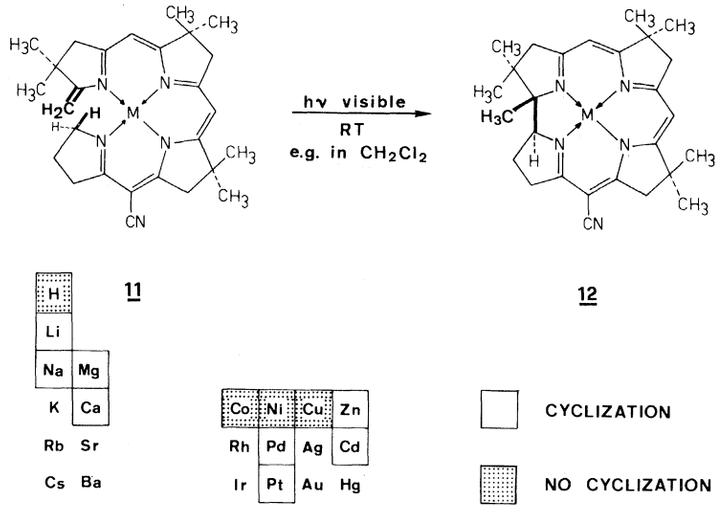


Fig. 8. Photochemical A/D cycloisomerization in the model system: dependence on the complexed metal ion (*14*).

Dunitz and his group have contributed x-ray crystallographic structure analyses of a series of secocorrin complexes (see *19*), thereby clarifying some of the stereochemical aspects of the cyclization process. The structures, for example that of the chlorocadmium complex **11** (M is CdCl) in Fig. 10 (*20*), show the secocorrin chromophore in a helical arrangement and the two reaction centers C-19 (ring D methylene) and C-24 (exocyclic methylidene on ring A) in spatial proximity. Cyclization is not observed with the metal-free ligand system, and a metallic coordination center is probably a necessary but certainly not sufficient condition for the occurrence of the cycloisomerization. In addition, there is the previously mentioned requirement that the central metal ion be inert with respect to the quenching of the excitation of the chromophore. The structure analysis of the noncyclizing nickel complex shows (in the ground state!) a seemingly ideal spatial arrangement of the two reaction centers.

The helical arrangement of the ligand system in the secocorrin complexes sets crucial boundary conditions for the stereochemical course of the cycloisomerization. The nonreactivity of the system in the ground state can oe interpreted as an indication that the hydrogen shift in such a helical structure must occur antarafacially (between the top of one end of the π system and the bottom of the other end), a process forbidden by the

Woodward-Hoffmann rules in respect to its taking place in the ground state. Given the (allowed) photochemical antarafacial hydrogen transfer (**11** → **13**, Fig. 9), collapse of the resulting system **13** in the same helical arrangement leads to *trans*-configuration between rings A and D in the product **12** via a ground state allowed antarafacial process.

Fortunately, the stereochemical reef which came into view with the use of the A/D cyclization for the cobyric acid problem could be circumnavigated. For the cobyroid ligand system there exist two diastereomeric helical arrangements. (In the model system, the same duality simply results in enantiomerism.) Thus, two diastereomeric *trans*-cyclization paths

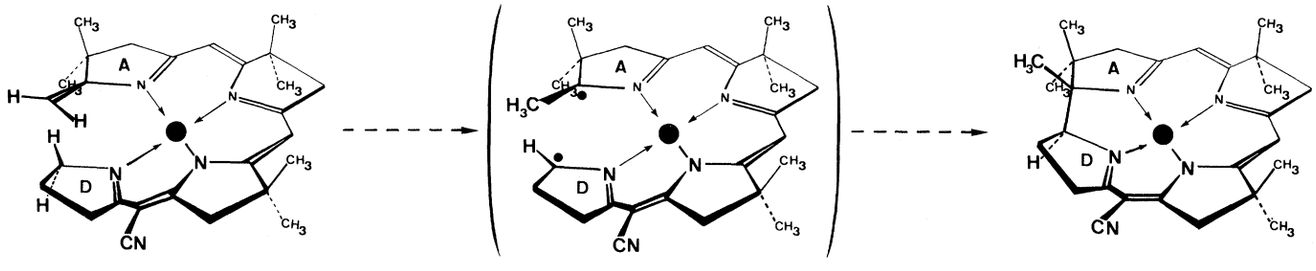


Fig. 9. Photochemical A/D cycloisomerization: presumed reaction path.

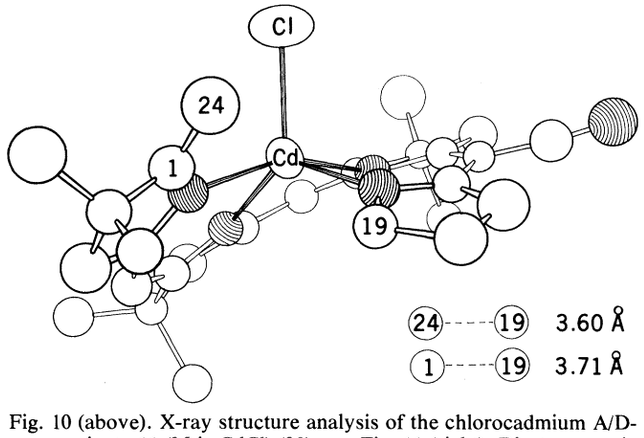


Fig. 10 (above). X-ray structure analysis of the chlorocadmium A/D-secocorrinate **11** (M is CdCl) (*20*).

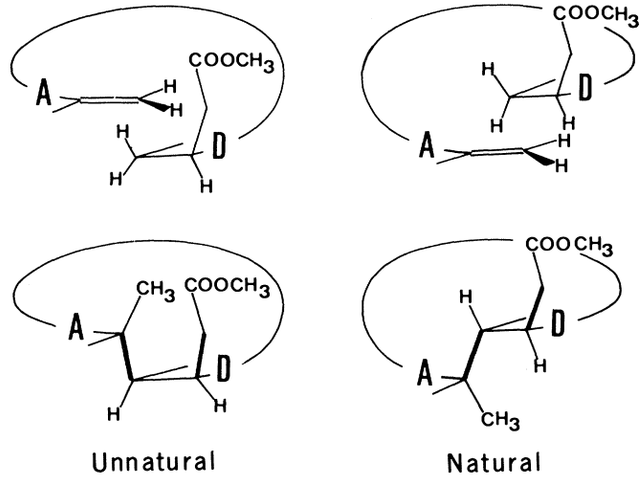


Fig. 11 (right). Diastereomeric reaction paths for the photochemical cycloisomerization of cobyroid A/D-secocorrin complexes.

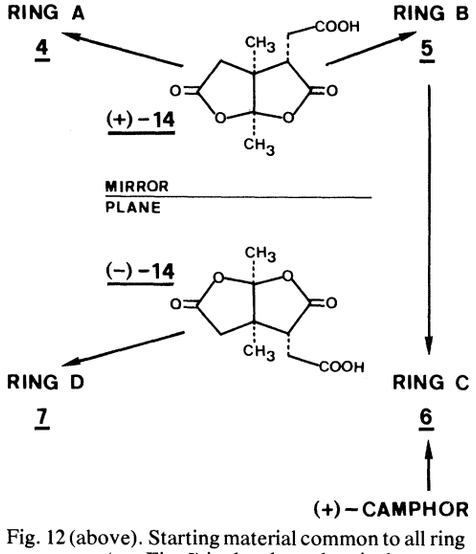


Fig. 12 (above). Starting material common to all ring precursors (see Fig. 5) in the photochemical route to cobyric acid.

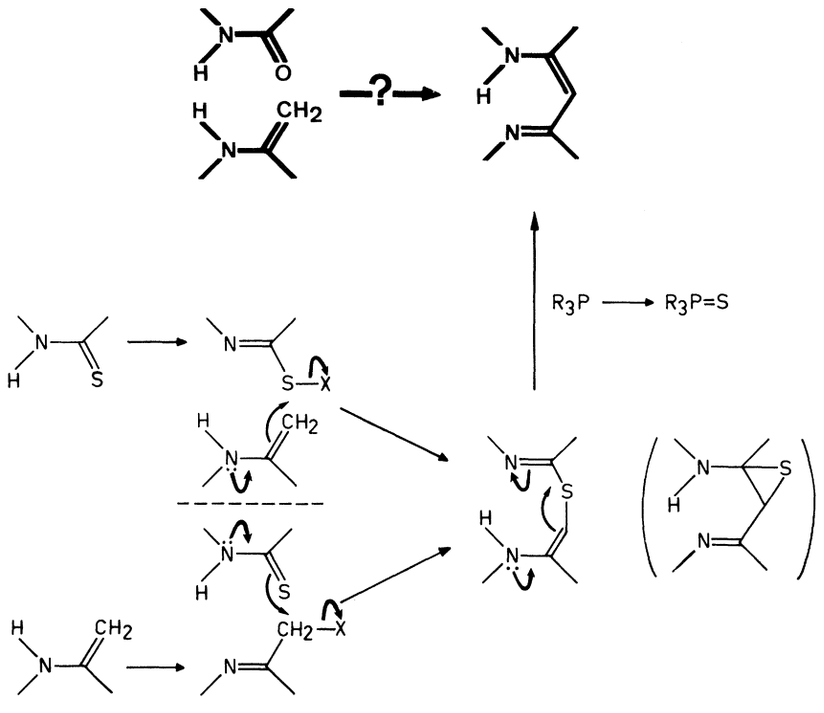


Fig. 13 (right). Corrin chromophore construction by the sulfide contraction method.

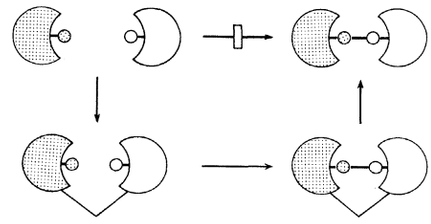


Fig. 14. "Whenever in the synthesis of complex organic molecules one is confronted with a situation where the success of an intermolecular synthetic process is thwarted by any type of kinetically controlled lack of reactivity, one should look out for opportunities of altering the structural stage in such a way that the critical synthetic step can proceed intramolecularly rather than intermolecularly."

are possible (Fig. 11). Only one of these leads to the natural A/D configuration of the corrin ring of cobyric acid. The natural arrangement is presumably the thermodynamically more stable, and in practice it is achieved almost exclusively when one works with the ("helically labile?") cadmium complex.

Normally, in the design of a multistep synthesis it is hazardous to plan an unknown all-or-nothing reaction as the concluding step. Almost certainly the idea of a secocorrin → corrin cycloisomerization would have been rejected as wishful thinking, had not the newly established principle of the conservation of orbital symmetry provided the impetus for the investigation of this alternative solution to the very same A/D junction problem which had generated the principle in the first place.

The realization of the secocorrin → corrin cycloisomerization in the model system allowed the fruition of a strategy of cobyric acid synthesis that had only seemed utopian until then, a strategy of making all four ring precursors of the molecule in optically active form from a single racemic starting material, and of then connecting these precursors in a stepwise fashion to set the stage for a final metal template controlled A/D coupling step (*21*). In practice, the single starting material became the racemate of the dilactone carboxylic acid **14**, rings A, B, and C (*22*) being prepared from its (+)-enantiomer, and ring D from its (−)-enantiomer (Fig. 12) (*23*).

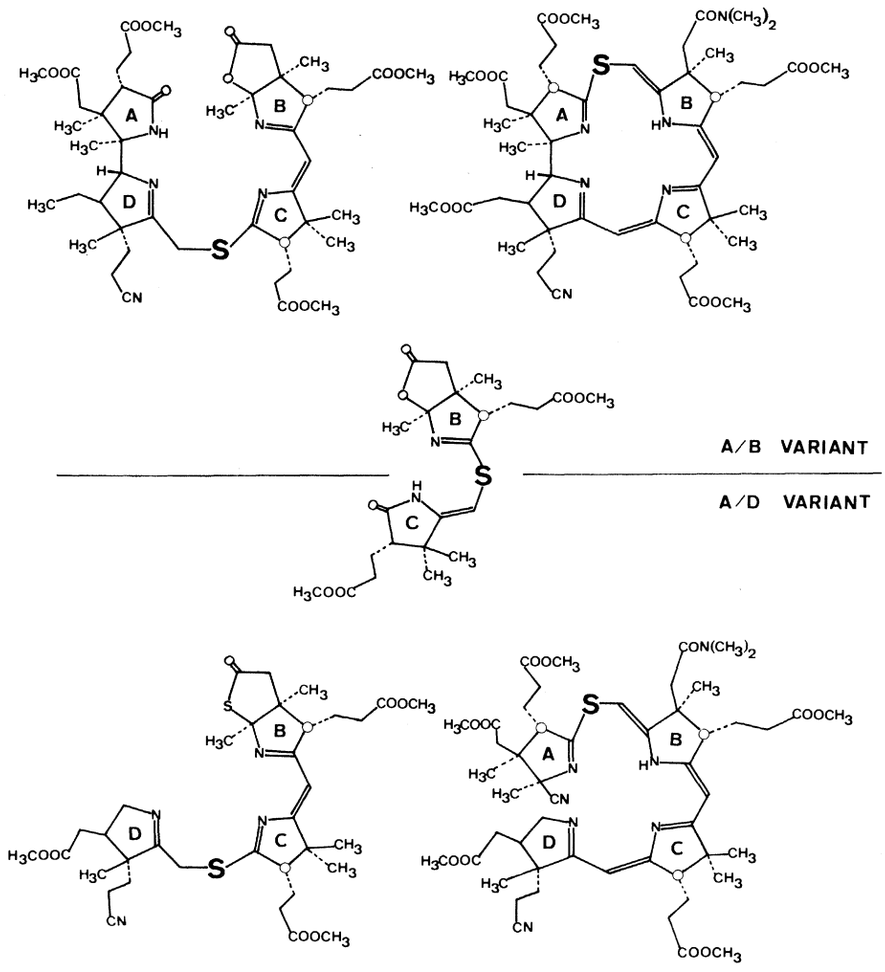


Fig. 15. Application of the sulfide contraction method in the two approaches to cobyric acid.

Construction of the Chromophore: The Sulfide Contraction Method

The A/D junction problem illustrates how research in natural product synthesis can unite the pursuit of a synthetic goal with the discovery of new paths of structural transformation. The problem of coupling for the remainder of the chromophore π system and the solution, which led to a general method of synthesis of β-dicarbonyl systems, may be taken as another case of the guiding effect of the cobyric acid structure. Moreover, it illustrates how simplification of a synthetic goal from the complex target structure to a model can at the same time lead to impoverished potential for discovery and invention. The most fruitful method for synthesis of the corrin chromophore (*24*) resulted from work on the natural products itself and not on simpler models.

Both variants of the synthesis, grounded on the concept of joining prefabricated optically active ring building blocks, required a general method for condensing lactam carbonyl groups with enamide or enamine systems to form the vinylogous amidine system, the characteristic element of ring juncture of the corrin chromophore (Fig. 13). The process of iminoester-enamine condensation, developed and found repeatedly successful for the synthesis of model corrins, failed when used in the attempt to reach cobyric acid itself, for which the required ring building blocks are laden with space-filling substituents. It was fundamental for the solution that one not strive for a direct intermolecular C-C condensation of the reaction partners, but that one first link these through a temporary bridge, achieve the critical formation of the C-C bond in an intramolecular condensation step, and finally expel the assisting bridge from the intermediate product. This is a principle of synthesis which has general significance for the tactics of building complex organic structures (Fig. 14).

Such a sequence, with the use of sulfur as the bridging atom (Fig. 13), was originally developed for the B/C coupling in the A/B variant (*25*, *26*). It proved to be an efficient method for building the corrinoid π system, and, as Fig. 15 indicates through the formulas of the appropriate sulfide-bridged intermediates, it provided the solution for all chromophore ring coupling problems that appeared in both variants of the cobyric acid synthesis. Today the condensation exists in a palette of experimental modifications (*27*), and its use is not limited to corrins; vinylogous amidines are aza analogs of β-dicarbonyl enols, and in fact the reaction provides a general method for building such and analogous systems (*28*).

Summary and Outlook

In this survey we deal with the solutions to only two of the problems which arose on the photochemical route to cobyric acid. What is left out is made evident by Fig. 16, which gives the complete scheme of this variant. Also, the reaction sequence of the A/B variant, including most of the work of the Harvard group, remains undiscussed here (*29*). Among the reactions of Fig. 16 (*25, 26, 30–47*), it is the critical coupling steps (operations 24–31) which are the subject of the previous sections. Entirely omitted is discussion both of the stereospecific preparation of the optically active ring precursors (operations 1 to 23) and of the problems and instructive difficulties met in both laboratories during the regioselective introduction of the two methyl groups at the meso positions of the corrin chromophore (operations 32–34) and during the structural differentiation of the single carboxyl function of ring D (operations 35–37). Nevertheless, it would be misleading to omit mention of the unexpected experience which threw the synthesis from the path that was to have been stereospecific throughout. Three of the centers of chirality (marked by rings in Figs. 15 and 16) proved to be configurationally labile in the intermediates of the chromophore syntheses. Because of this lability, it was not possible to maintain the stereochemical integrity of these intermediates. It is true that this presented difficulties not of principle, but rather of an experimental nature. That these difficulties were successfully overcome with the aid of high-pressure liquid chromatography, which appeared at precisely the right moment, proved to be one of the first illustrations of the efficacy of this new chromatographic separation procedure in organic synthesis (*48*).

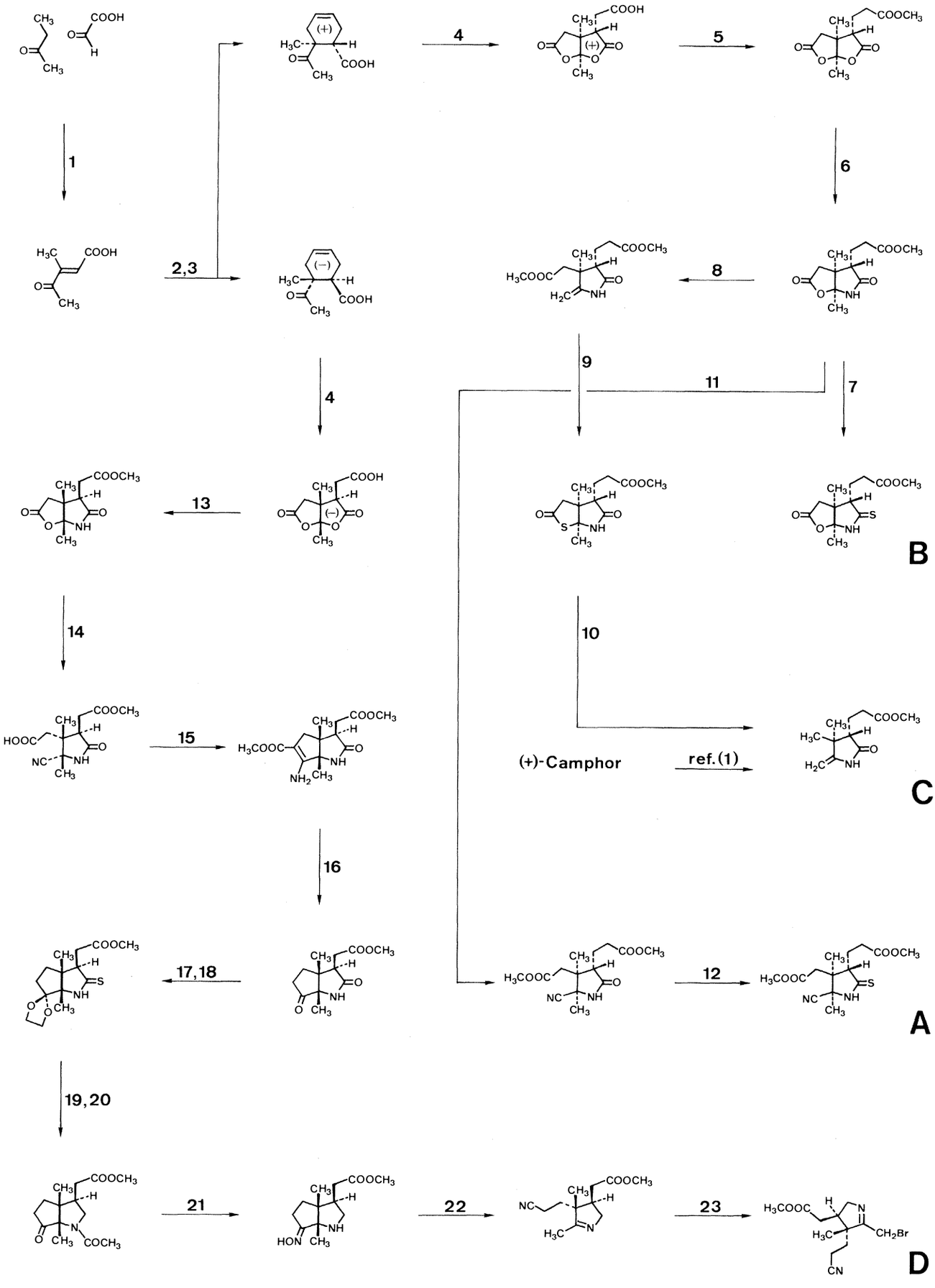
To deal with the state of today's organic natural product synthesis through the example of vitamin B_{12} of course implies a drastically narrowed perspective. The structural variation of synthetic objectives, the intensity of the search for new preparative methods, and the abundance in which these methods are being uncovered, have never been greater than today. Since structure elucidation can now be carried out with spectrometers and diffractometers, the way is clear for concentration on problems of structure transformation; strongly intensified activity in the realm of natural product synthesis is a consequence. With that activity comes the increased possibility of creating, through chemical synthesis, a starting point for biological research, long one of the important motives for the total synthesis of biologically active natural products, most particularly of those that, in contrast to vitamin B_{12}, are only obtainable with great difficulty from natural sources. What is probably the most comprehensive recent undertaking of this sort, the development of syntheses of the prostaglandins (*49*), testifies to the fertility of this motivation for synthetic chemistry.

That we only mention the event of the chemical synthesis of a gene (*50*) or concepts such as solid-phase synthesis (*51*) and automated synthesis (*52*) serves to indicate how much we have narrowed the field of view in this article on the state of natural product synthesis today, in that we restrict ourselves here to the area of low-molecular-weight natural products. Since biopolymers are of repetitive structure, the problem of their synthesis appears to lack the abundance of chemical challenge that has always attracted organic chemists to the field of low-molecular-weight natural products (and, in doing so, has spoiled them!). However, such matters of attitude are minor in the light of the chemical and biological significance of the biopolymers, whose synthesis is one of the great problems for chemistry in our time.

Research on the synthesis of natural products operates in an area bordering artistic creation on one side and technological development on the other. Man's effort to emulate Nature will not cease to inspire him on either frontier; and, to conclude with just one hope, we can look forward to the day when computer assistance in the design of synthesis—to date a visionary idea and a fascinating problem (*53*)—will come of age. More sharply than we can today, we would then be able to discern from the limits of the performance of the computer program what *research* in natural product synthesis really is or must be.

The contributions of the Zürich group to the synthesis of cobyric acid were

Fig. 16 (pages 1418 and 1419). The photochemical route to synthetic cobyric acid. Reaction conditions. Circled carbon atoms indicate mixtures epimeric at those carbon atoms. Percentages indicate yields. **1** Concentrated H_3PO_4, 80°C (82 percent) (*30*). **2** Butadiene, $SnCl_4$, benzene, room temperature (73 percent) (*31*). **3** Resolution with (−)- and (+)-phenylethylamine (*31, 32*). **4** CrO_3, H_2SO_4, acetone, room temperature (75 percent) (*31*). **5** $SOCl_2$, 77°C; CH_2N_2, ether, dioxane, room temperature; Ag_2O, methanol, 65°C (69 percent) (*31, 33*). **6** NH_3, methanol, room temperature (55 percent) (*26, 32*). **7** P_2S_5, tetrahydrofuran, room temperature (85 percent) (*26*). **8** CH_2N_2, ether, methanol, CH_3ONa (catalytic amount); distillation at 190°C per 0.01 torr (92 percent) (*33, 34*). **9** H_2S, CF_3COOH, room temperature (78 percent) (*33, 34*). **10** $RhCl[(C_6H_5)_3P]_3$, toluene, 110°C (about 30 percent; isolation via the HCN adduct) (*34*) **11** KCN, methanol, room temperature; CH_2N_2, ether, methanol (> 95 percent as diastereomers) (*35*). **12** P_2S_5, tetrahydrofuran, room temperature (57 percent after separation of diastereomers) (*35*). **13** NH_3, methanol, room temperature; CH_2N_2, ether, methanol (64 percent) (*33, 36*). **14** KCN, methanol, room temperature (72 percent) (*33, 36*). **15** $SOCl_2$, tetrahydrofuran, room temperature; CH_2N_2, tetrahydrofuran, room temperature; Ag_2O, methanol, 65°C (68 percent) (*33, 36*). **16** HCl, dioxane, 90°C; CH_2N_2, ether, methanol (70 percent) (*33*). **17** $(CH_2OH)_2$, $CH(OCH_3)_3$, toluene sulfonic acid, methanol, 80°C (76 percent) (*36*). **18** P_2S_5, tetrahydrofuran, room temperature (81 percent) (*36*). **19** Raney nickel, methanol, room temperature; Ac_2O, pyridine, room temperature (89 percent) (*36*). **20** 40 percent acetic acid, 60°C; aceticanhydride, pyridine (94 percent) (*36*). **21** HCl, methanol, 65°C; $H_2NOH{\cdot}HCl$, sodium acetate, methanol, 65°C (> 95 percent as diastereomers) (*36*). **22** HCl (gas), chloroform; $SOCl_2$, room temperature; piperidinomethylpolystyrene, chloroform, room temperature (74 percent) (*36*). **23** Br_2, methanol, phosphate buffer, *p*H 7.5, −10°C (69 percent) (*35*). **24** $(C_6H_5COO)_2$, trace of HCl (gas), methylene chloride, room temperature; $(C_2H_5O)_3P$, xylene, 125°C (85 percent as diastereomers, 51 percent as crystalline β isomer) (*25, 26, 37*). **25** P_2S_5, 4-methylpyridine, xylene, 130°C (*38*) (84 percent as diastereomers) (*35*). **26** Potassium *t*-butylate, *t*-butanol, tetrahydrofuran, room temperature; $P(CH_2CH_2CN)_3$, CF_3COOH, sulfolane, 60°C (64 percent as diastereomers) (*1, 2, 35*). **27** $(CH_3)_2NH$, methanol, room temperature (product not isolated) (*35, 37*). **28** *N*-iodosuccinimide, methylene chloride, 0°C (iodination of methylidene group); ring A precursor, $[(CH_3)_3Si]_2NNa$, benzene, *t*-butanol, room temperature (A/B coupling); $Cd(ClO_4)_2$, methanol, room temperature (complexation); $(C_6H_5)_3P$, CF_3COOH, benzene, 80°C (contraction); $Cd(ClO_4)_2$, ethyldiisopropylamine, benzene, methanol, room temperature, NaCl workup (recomplexation); (overall yield of operations **27** and **28**: 46 percent as diastereomers) (*35*). **29** 1,8-diaza-bicyclo[5.4.0]-7-undecene, sulfolane, 60°C; acetic acid, $Cd(ClO_4)_2$, methanol, room temperature, NaCl workup [labile product normally not isolated (*39*)] (*35*). **30** *hν*, visible, reaction mixture from operation **29**, under argon, 60°C [product not isolated (*39*)] (*35*). **31** $CoCl_2$, (*1, 2*), reaction mixture from operation **30**, 58°C; KCN, air, H_2O, methylene chloride, 0°C; thick-layer chromatography; [overall yield of operations **29–31**: 46 percent as diastereomers (*40*)] (*35*). **32** I_2, acetic acid, *N,N*-dimethylacetamide, 95°C; HPLC separation of diastereomers [56 percent diastereomers having natural configuration of side chain at ring A (*41*)] (*36*). **33** $C_6H_5CH_2OCH_2Cl$, LiCl, acetonitrile, 88°C; C_6H_5SH, 0°C (55 percent as diastereomers) (*42*). **34** Zn(Hg), acetic acid, room temperature; CH_2N_2, ether, methylene chloride [40 to 51 percent (*43*)] (*42, 44*). **35** Concentrated H_2SO_4, room temperature (*43*); HPLC separation and identification of diastereomers (19 percent diastereomer having natural side chain configuration at ring C, 43 percent having unnatural but reequilibratable *neo* configuration at ring C) (*42*). **36** *N*-cyclohexyl-α-chloropropionaldonitrone, $AgBF_4$, 1,2-dichloroethane, 0°C; 0.01*N* HCl, dioxane, H_2O, room temperature; $(CH_3)_2NH$, isopropanol, room temperature [$CONH_2 \rightarrow COOH$; 57 percent (*45*)] (*46*). **37** NH_3, NH_4Cl, ethylene glycol, 75°C (*2, 44*) (uncrystallized dicyano form; 64 percent); crystallization from H_2O, acetic acid, acetone, 3°C [84 percent (*45*)] (*36, 47*).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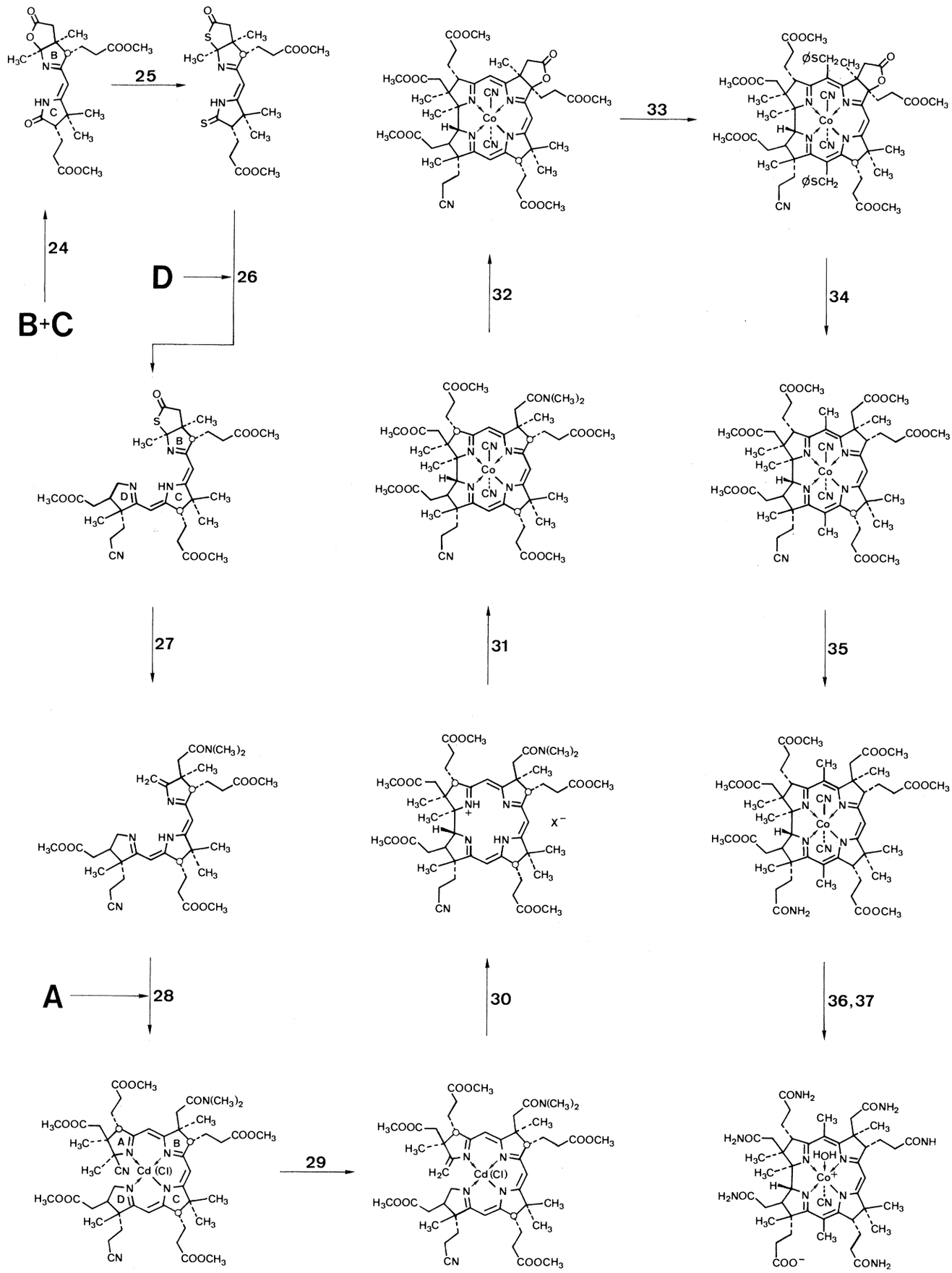
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made by (in chronological order): U. Locher (*31*), J. Wild (*30*), A. Wick (*32*), J. Muchowski, J. Sims, H. Gschwend, D. Coffen, R. Keese, T. Bogard, L. Werthemann (*45*), R. Wiederkehr (*33*), P. Dubs (*34*), P. Löliger (*26*), B. Golding, W. Huber (*38*), P. Schneider (*37*), D. Becker, F. Karrer, N. Hashimoto, J. Gleason, N. Obata, W. Fuhrer (*35*), H. Maag (*42*), W. Schilling (*36*), A. Holmes, W. Hunkeler, and J. Schreiber.

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22. It should be noted that the ring C precursor used in both variants has in practice been prepared via the camphor route (*1*).
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38. The C/D coupling was originally carried out (*35*) with the corresponding *S*-lactam-*O*-lactone, which also served as the B/C component in the A/B variant (Fig. 5, formula 2). For the preparation of this mono-thio derivative, see W. Huber, thesis, Eidgenössische Technische Hochschule, No. 4298 (Juris Verlag, Zürich, 1969); (*26*); (*37*).
39. The experiment recorded in Fig. 7 (*35*) was run on a sample of the purified (workup and high pressure liquid chromatography in the dark) single diastereomer of the secocorrin complex having the natural configuration. The duration of the reaction was 8 minutes. Under the conditions used, the spectroscopically observed cyclization product is the decomplexed corrin ligand.
40. Further analysis (TLC, HPLC) of material from operation 31 shows it to consist of about 95 percent of the eight diastereomers having the natural A/D configuration. All eight have been isolated in pure form; the four diastereomers with natural side chain configuration at ring A comprised 66 to 77 percent of the mixture (*35*), (*36*).
41. The spectroscopic yield of lactone diastereomers was 88 percent; 75 percent of this lactone mixture had the natural configuration at ring A (*36*).
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43. Operations 34 and 35 were carried out with the separated diastereomers. The sulfuric acid treatment of operation 35 reequilibrates the side chain configuration at ring C (*42*).
44. The procedure is based on work of the Harvard group.
45. The starting material used in operations 36 and 37 was prepared from vitamin B_{12} via partial ammonolysis (*42*) of heptamethyl cobyrinate [R. Keese, in L. Werthemann, thesis, Eidgenössische Technische Hochschule, No. 4097 (Juris Verlag, Zürich, 1968)]. See, however, (*11*). For identifications, see (*42*, *36*, *37*).
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54. We thank Dr. F. Boschke, Springer-Verlag, Heidelberg, for permission to use material from the article in *Die Naturwissenschaften* in (*4*). We also thank Prof. J. D. Dunitz, ETH, Zürich, for allowing us to present unpublished work from his laboratory in Fig. 10. M. G. Bonetti prepared Fig. 16. C.E.W. thanks the American-Swiss Foundation for Scientific Exchange for a grant. The work carried out in the Zürich laboratory on the synthesis of corrinoids and vitamin B_{12} was supported by the Swiss National Science Foundation.