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STUDIES ON THE SYNTHESIS OF CORRINS AND RELATED LIGANDS

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Abstract—The development of a plan for the synthesis of the corrin and corphin ligands (**5** and **6**) together with experimental execution thereof is presented.

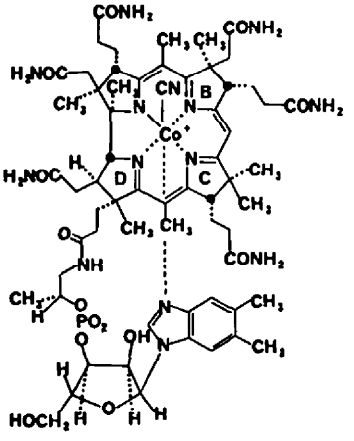
INTRODUCTION

The fascinating structure of vitamin B-12 was first revealed to the world through the brilliant X-ray crystallographic studies of Crowfoot–Hodgkin.[1] In retrospect, this outstanding contribution may be regarded as a turning point in the history and development of natural products chemistry, since prior to the event knowledge about the *chemistry* of new structural types was secured frequently as a "by-product" of extensive classical degradation. However, now, with an ever expanding array of powerful physical weapons at our disposal, we find ourselves in the rather enviable position of often being able to ascertain even the most intimate *structural* details without ever having performed a single chemical transformation! Although we may all be grateful for these exciting developments, we must also realize they create a void in our knowledge of the *chemistry* of new structural types, and, regretably, this is not a small price to pay. It is within this void that Synthesis may be called upon to play an even more prominent role. In the present case this challenge has been accepted in a number of laboratories of which the accomplishments of Eschenmoser,[2] Inhoffen,[3] Johnson,[4] and Woodward[5] are already legendary.[6]

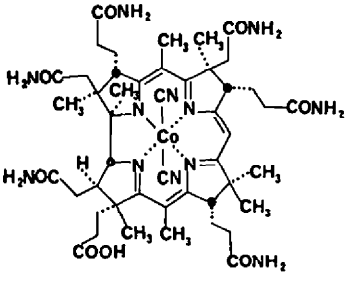
With these thoughts in mind it is perhaps appropriate to comment on what we feel are the broad objectives of synthesis. In certain respects the answer to this inquiry is that they defy any precise definition, for as many of the Grand Masters have made abundantly clear in both word and deed, there is an incalculable element of creative art and imagination in organic synthesis. Indeed, to a large extent, one might assert that it is only in the imaginations of those engaged in the profession which places any limits on its potential accomplishments. As a major partner of chemistry, synthesis has contributed impressively to at least two of the most essential elements of any chemical activity, mainly, in discovering new chemistry and in understanding. Thus, one prominent view of the role of synthesis is that it is an effective means for the discovery of new chemical transformations and to foster and improve upon old ones. Insofar as the major emphasis of chemistry continues to be on chemical reactions and their utility in creating new substances, the necessity of discovering new ones or in revealing new aspects of old ones becomes apparent. It is within this role of being able to provide the means within which discovery can be made which is certainly one of the most important functions of synthesis. And of course, ultimately, discovery leads to a better understanding. As such we find in synthesis an inviting, almost unparallelled, opportunity for expanding our knowledge of the science as a whole.

GENERAL PRINCIPLES WHICH GUIDE THE SYNTHETIC PLAN

Although there have been impressive and vast advances in the precision of our knowledge and understanding of organic chemistry, it is still largely an experimental science and is likely to remain so for some time to come. One discovers this fact rapidly and not infrequently brutally when attempting to reduce to practice even a well



Vitamin B_{12}



Cobyric Acid

documented series of transformations aimed at a relatively modest synthetic target. For this reason, the task of analyzing and understanding organic synthesis may appear rather formidable. The impressive and ever growing number of reactions which are at our disposal and the often justified uncertainty as to their scope and limitations often creates the impression that the decisive formulation of a synthetic plan is at best problematical. This lack of confidence is largely a consequence of the fact that, although a number of definite operations may be identified in the synthesis of intricate molecules, they are not strictly independent of one another. This helps to explain, in part, why the use of artificial intelligence in synthetic planning has been so slow in evolving.[7] Nevertheless, the impressive quantity and quality of successful syntheses which have succumbed to the chemist's imagination and skill serve as a monument to the fact that worthy and reliable synthetic plans can be devised. There can be no doubt that such efforts have already led to a more meaningful comprehension of synthesis and provide the means for its continued growth and development. Nevertheless, the greatest limitation on the art and science of organic synthesis is the degree to which sound planning is possible.

Some of the broad general principles which have served to guide the synthetic investigation outlined in the Report will now be dealt with explicitly and in the sequel implicitly.

(A) The synthesis of complex molecules (and even some that appear deceptively simple) most often requires the employment of carefully selected sequences of chemical transformations defined in a rather specific order. A relatively large number of possible approaches to the synthesis of such substances can usually be derived. Indeed, the number of posible approaches can be anticipated to increase with increasing molecular size and complexity. Obviously, failure of even one of these steps may doom an entire synthetic plan.

(B) An integral part of the planning stage is a thorough evaluation of the *molecular history* of the target molecule, since the results of earlier investigations may play an important role in the ultimate selection of a particular scheme. For example, during the elucidation of structure or as a result of previous synthetic efforts, certain decisive molecular characteristics may reveal themselves. Such history often will be useful in planning the attack, since prospective problems may be anticipated before they arise in the actual execution of the plan. Also, occasionally as part of degradative studies, partial syntheses will have been achieved, thus providing attractive alternate objectives.

(C) Synthetic organic chemistry, perhaps more than any other subdiscipline, demands the application of the knowledge and technical developments of the science as a whole. There can be no doubt that an intimate and broad knowledge of organic reactions and their mechanisms is of primary importance in conceiving of and executing organic syntheses. The acquisition of powerful physical tools and refined methods of analysis and purification has armed us for the attack as never before. In fact, as we have already noted, these exciting developments are modifying the very nature of synthesis. *Truly significant synthetic programs must now either cope with problems not amenable to trivial solution or accept the responsibility and challenge of developing and/or employing new methods of approach which test and expand the very principles upon which the science is founded.*

(D) There are distinct but not unequivocal criteria which may be employed to evaluate the utility or virtues of alternative contemplated syntheses. Quite often the selection of a preferred synthetic approach is forced to be arbitrary if there are a number of unknown factors. However, even in such cases these criteria allow the dismissal of inferior possibilities. The diagnostic criteria by which potentially competitive approaches may be evaluated are of a routine nature to the practicing organic chemist; nevertheless, the following comments should be made:

1. *The most satisfactory solutions to even complex synthetic problems are usually, at least in retrospect, relatively simple.* Excessively lengthy possible routes should be suspiciously and critically evaluated before their execution, and alternatively hopefully shorter possibilities sought.

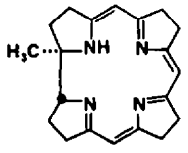
2. It is desirable to employ and/or develop new reactions in chemical synthesis, especially if it is possible that this will enhance the efficiency of the synthesis and/or provide new chemical principles. However, the number of such speculative transformations and their position in the overall plan must obviously be carefully considered. The execution of doubtful steps should, in general, be reserved for the first stages of the synthesis and, conversely, abhored in the latter stages. Of course, the proper selection of known chemical transformations of proven dependability and mechanistically sound interpretation occupies a central role in sound synthetic planning.

3. Alternative means of achieving required transformations in the synthetic plan are desirable especially where certain steps may be the subject of some doubt.

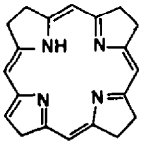
With these thoughts in mind we turn our attention to vitamin B-12. In contemplating the total synthesis of this intriguing substance, it should be noted that a closely related natural product, cobyric acid, had been transformed previously[8] into the vitamin itself. Thus, we may consider cobyric acid to be the ultimate synthetic target. In evaluating potential approaches to this substance, it is apparent that a number of interacting considerations must be taken into account. Of these, we regarded four as truly fundamental. First, a reliable method for construction of the macrocyclic (corrin) ligand itself must be developed. Second, regardless of the chemistry utilized to achieve this initial consideration, it must be compatible with the various functional groups which adorn the periphery of the molecule. Third, the methodology developed must be capable of handling the nine chiral centers present. Finally, the synthesis should be convergent. It is the purpose of the rest of this Report to outline a strategy and experimental support thereof which we believe is capable of satisfying each of these criteria.

A NEW APPROACH TO THE SYNTHESIS OF CORRINS AND RELATED LIGANDS

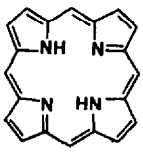
It is instructive to compare the corrin ligand (1) with certain other macrocyclic nuclei incorporated by Nature into some of her most important natural products:



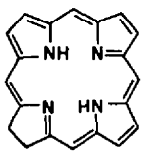
1
Corrin



2
Corphin



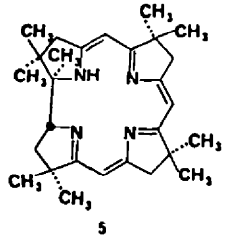
3
Porphin



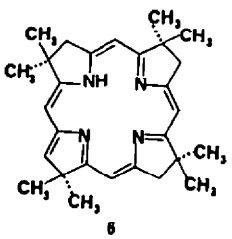
4
Chlorin

It has been known for many years that simple chlorins, **4**, are easily oxidized to porphyrins, **3**, (even though chlorophyll itself does not behave accordingly). In view of this fact the problems associated with preventing oxidation (or tautomerization) of an unsubstituted corrin, **1**, may be regarded as serious. Inspection of the vitamin B-12 molecule (or its chemical equivalent, cobyric acid) reveals how Nature defends itself against such oxidative or tautomeric disaster, i.e. we note that the alternate peripheral carbons bear quaternary, hence non-enolizable, centers. However, even this substance is not entirely immune to oxidative and tautomeric transformations. Thus, oxidative substitution reactions at the monosubstituted position of ring B have been observed to occur with relative ease (a fact actually employed to advantage in the Eschenmoser–Woodward synthesis). Furthermore, we also know from these synthetic investigations that the electronically equivalent positions of rings A and C can be epimerized.[2,5] For these and other reasons the incorporation of quaternary centers at corresponding positions on the corrin periphery fully defines octamethylcorrin **5** as our initial synthetic goal.

When we initiated this study very little was known about the biosynthesis of vitamin B-12. However, Eschenmoser[9] made the intriguing suggestion that quite possibly yet another macrocyclic ligand intermediate in structure between the well established corrinoid and porphinoid types might be involved in this process and which he termed "corphin" (**2**). The corphin ligand differs from the corrin one by a reductive ring contraction wherein one of the "meso" ring-bridging methylene carbons eventually becomes the "angular" methyl group found in the latter ligand. Although more recent biosynthetic studies[10] cast doubt on this suggestion, the possibility of effecting such a transformation *in vitro* was sufficiently attractive for us to include octamethylcorphin (**6**) as a synthetic objective.

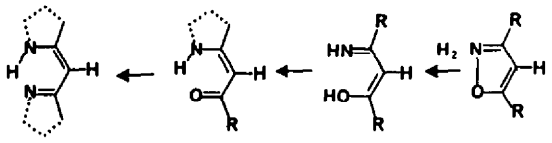


5
Corrin



6
Corphin

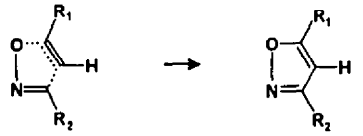
Having thus defined **5** and **6** as our targets, the central problem of any corrin synthesis comes into focus, and that is the question of how to elaborate the ringbridging vinylogous amidine systems. Of course, vinylogous amidines, **7**, are simply aza-analogs of vinylogous amides **8** which we regarded as attractive equivalent synthons. Amongst the various methods of synthesis of vinylogous amides which we considered (see later), the catalytic hydrogenation of an appropriately substituted isoxazole **10** captured our imagination and, in fact, provides a suitable heuristic on which the strategy of our corrin synthesis is based.[11,12]



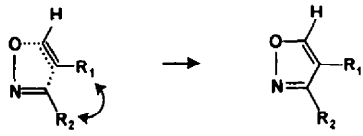
7 8 9 10

One particular feature of this method of approach warrants additional comment. Although the mechanistic details of isoxazole reduction remain obscure, **9** may be postulated as a reasonable intermediate in the ultimate production of the vinylogous amide. If we further assume that tautomerization of this intermediate proceeds via intramolecular proton transfer, then the required *cisoid*-arrangement of the vinylogous amide **8** is virtually assured.

A number of methods are available for the synthesis of isoxazoles.[13] However, only the rather well defined cycloaddition of nitrile oxides to terminal acetylenes appeared suitable for our purposes. Although two different regioselective possibilities exist for the cycloaddition step (**11** vs **12**), prior technology, coupled with steric and electronic considerations, led us to conclude that the desired orientation (**11**) should be favored. The question was—by how much?



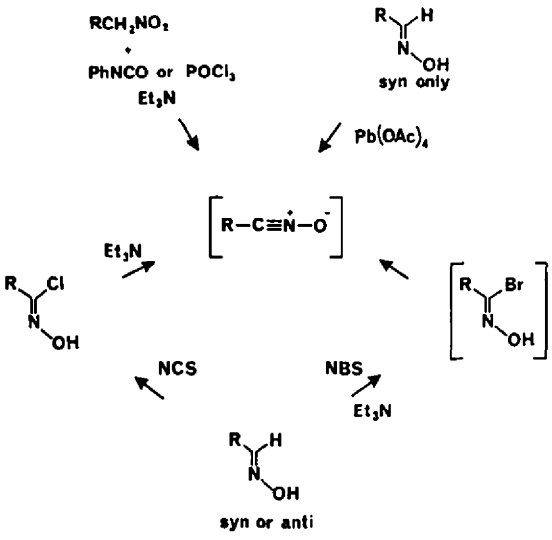
11



12

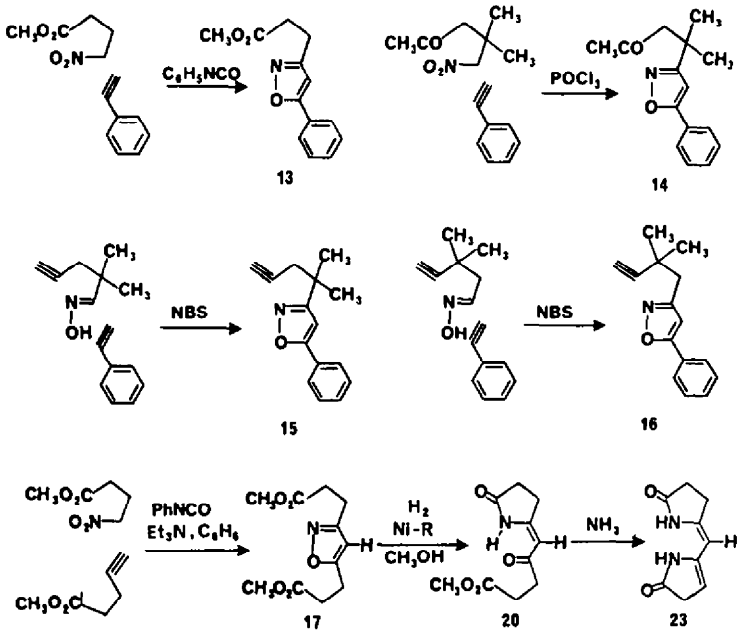
The nitrile oxides employed in this study are all unstable and must be generated *in situ* in the presence of the appropriate acetylenic partner. Therefore, the conditions used to generate these reactive intermediates and their compatibility with the various functional groups present became a question of a crucial nature which had to be tested experimentally. In practice, we have employed three different general methods: phosphorous oxychloride or phenyl isocyanate induced dehydration of primary nitro compounds; lead tetraacetate catalyzed dehydrogenation of *syn*-aldoximes (*anti*-aldoximes fail to yield nitrile oxides with this reagent); and by the reaction of either *syn*- or *anti*-aldoximes with N-bromosuccinimide, N-chlorosuccinimide or t-butyl hypochlorite in the presence of triethylamine. These methods are shown schematically below.

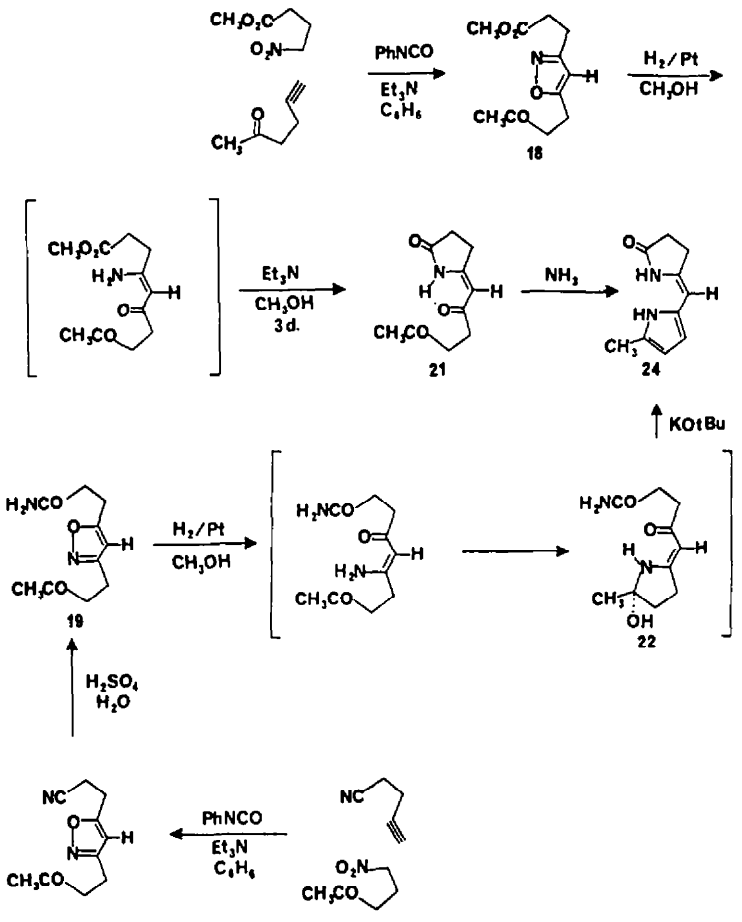
We, therefore, initiated a systematic model study to probe the potential generality and/or limitations for the generation and employment of isoxazole nuclei as latent synthons for combining the essential elements of corrinoid substances.[14] As will soon become apparent the substrates and products of this stage of the investigation were slected carefully to incorporate features which we felt would be useful in more precisely defining an actual corrin synthesis.



Our initial experiments dealt with two fundamental questions. First, what functional groups in the nitrile oxide partner can be tolerated? Subsequent studies required that ketones, esters, nitriles, and acetylenes be stable not only to the conditions used to generate the nitrile oxide but also to this dipolarophile itself. Second, what effect, if any, does the site of incorporation of the quaternary centers cited above have on the yield of isoxazole? The experimental answers to these questions were gratifyingly informative (see **13–16**). Thus, it was found that these functional groups in the nitrile oxide could be tolerated without any deleterious effects. Of course, in the case of **15** and **16** a generous five-fold excess of phenylacetylene was employed to prevent intermolecular cycloaddition. The crucial point here was that these nitrile oxides were stable to intramolecular cyclization. Furthermore, in all cases studied only the required 3,5-disubstituted isoxazole (**11**) was formed. None of the 3,4-isomer was detected. The fact that under identical conditions isoxazole **15** was isolated in about twice the yield of **16** strongly suggested that the most serious factor in these cycloaddition steps was not steric hindrance toward isoxazole formation but rather steric suppression of furoxan formation, i.e. self-condensation.

Armed with these encouraging results our attention focused on the acetylenic partner. Once again, substrates and products were carefully selected to incorporate certain features vital to subsequent manipulations. As in the preceding cases no difficulty was observed in the formation of isoxazoles **17–19**. Furthermore, catalytic reduction of these substances led cleanly to the required *cisoid* vinylogous amides **20–22** (it should be noted, however, that the catalyst and solvent of choice inexplicably vary widely with the particular isoxazole being reduced). Prior to these experiments we had anticipated that upon exposure to ammonia ester **20** would yield the simple "semicorrin" **23** (or a tautomeric equivalent thereof). Similarly, ketone **21** was expected to provide **24**. However, attempts to effect these transformations were uniformly unsuccessful. Thus, **20** proved to be a surprisingly inert substance and could be recovered unscathed when treated with ammonia (or one of its equivalents) under a variety of standard conditions. It was clear, therefore, that in future experiments we could not rely on such a system as a means for introducing one of the required rings of the corrin ligand. The problem in the conversion of **21** to **24** was not one of lack of reactivity. On the contrary, even under the mildest of conditions only polymeric-like materials were obtained. Although negative, these results were informative, nevertheless, for the design and execution of subsequent experiments. Thus, the failure of ester **20** to undergo an intermolecular reaction with ammonia was of some concern with regard to future plans and prompted investigation of an alternative method. In this connection, the possibility of altering the structure of our intermediates in such a way that this step could be achieved by an intra-rather than an inter-molecular reaction presented itself as a logical solution to what is, in fact, a common problem in organic synthesis. Thus, reduction of isoxazole **19** provided carbinolamide **22** which, not surprisingly, proved to be very labile. Immediate treatment with potassium t-butoxide induced cyclodehydration to **24**.

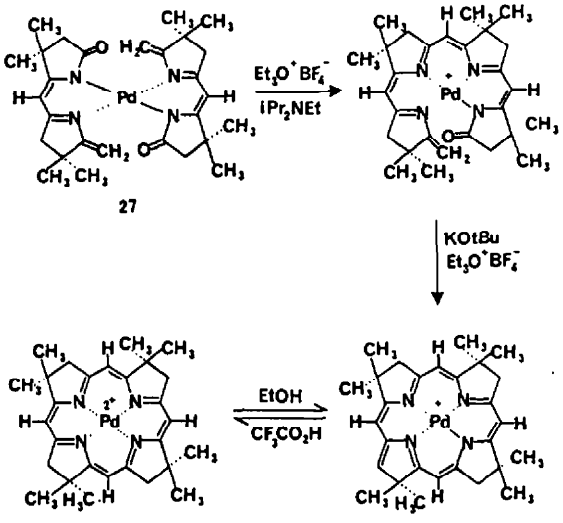




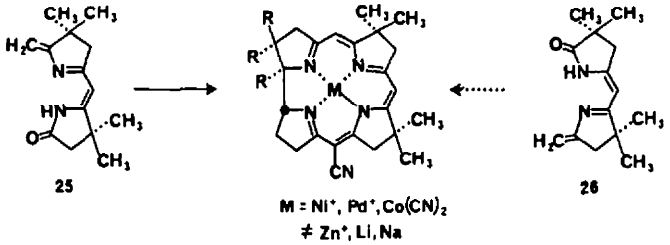
SYNTHESIS OF "SEMICORRIN E" AND "SEMICORRIN S"

The above model studies now allowed us to more clearly define an approach to corrins and/or corphins and our attention focused on the feasibility of employing isoxazoles as a reliable and efficient method for synthesizing semicorrins **25** and **26**. This goal was dictated by the fact that Eschenmoser[15] had incorporated previously **25** into various corrin systems. The ingenious employment of certain transition metal elements as templates played an important role in this outstanding achievement. The possibility of employing isomeric semicorrin **26** in this process captured our imagination.

In yet another brilliantly conceived and executed study,[9] it was found that semicorrin **25** could serve as both halves of the symmetrically substituted octamethylcorphin ligand. Thus, treatment of **25** with methoxide and palladium acetate provided the square-planar complex **27** together with the corresponding "head-to-head" isomer. Subsequent conversion to the palladium complex was accomplished as outlined below. Once again the possibility of employing isomeric semicorrin **26** in this sequence appeared potentially attractive.



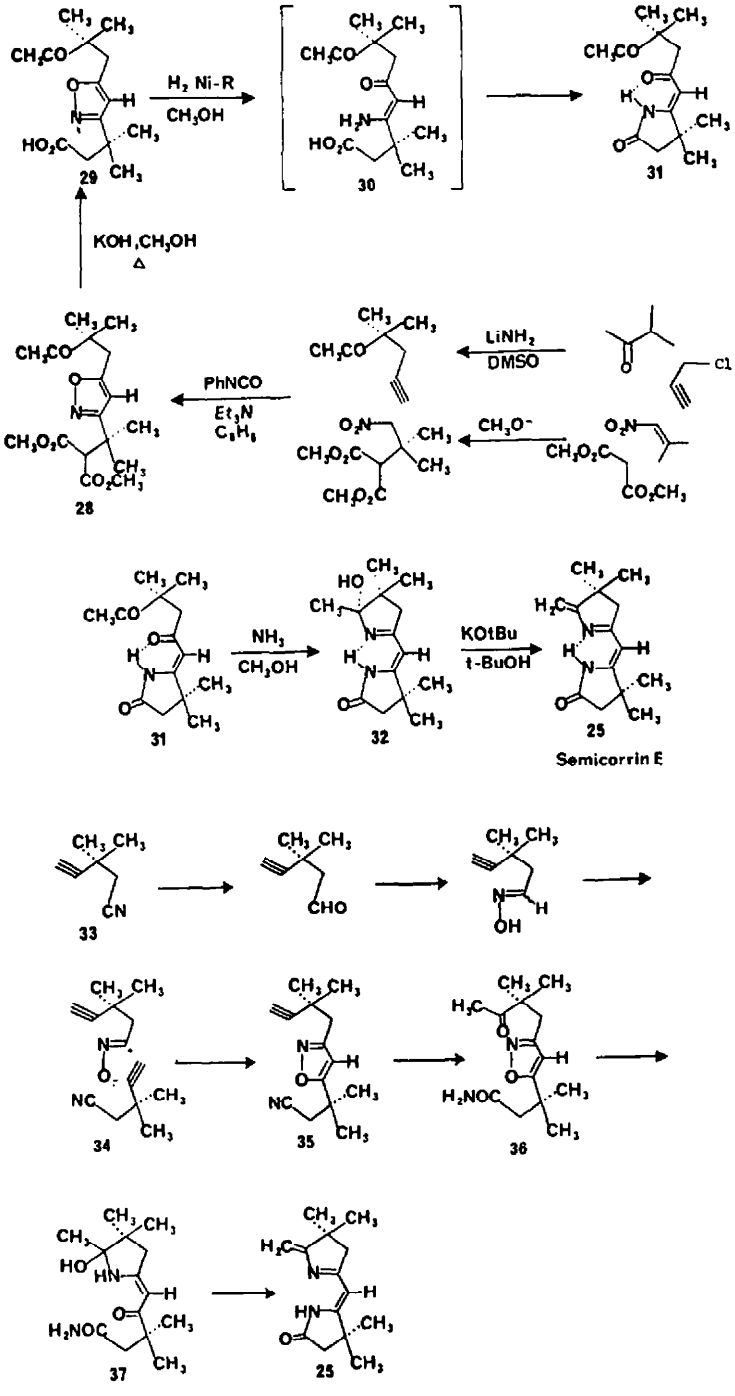
The isoxazole scaffold **28**, hopefully destined to become semicorrin **25**, was obtained by the now standard



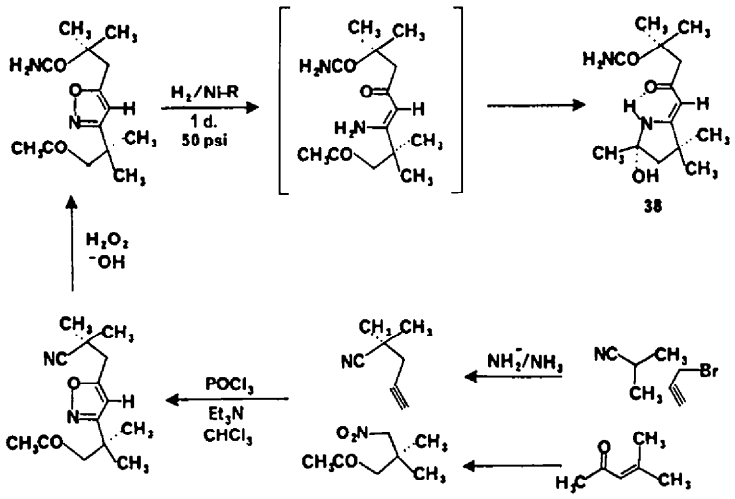
way and is outlined below. It is interesting to note that by suitable adjustment of the reaction conditions a 95% yield of this isoxazole could be obtained. Saponification and decarboxylation yielded keto ester **29**. Hydrogenation of this isoxazole over Raney nickel catalyst yielded vinylogous amide **30** which could be detected spectroscopically. However, by simply allowing the methanolic solution to stand over the basic catalyst spontaneous ring closure to **31** occurred. We were somewhat surprised by the apparent ease of this cyclization, but in any event it was a pleasant surprise indeed.

Exposure of diketone **31** to a saturated methanolic solution of ammonia yielded the vinylogous amidine chromophore **32** without any difficulty (compare this result to the unsubstituted simple model **21**). Subsequent potassium t-butoxide induced dehydration of this substance yielded the desired semicorrin **25** identical in all respects with the Eschenmoser compound.

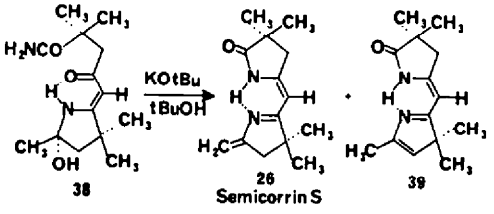
For reasons which will become apparent as this theme is developed, an alternative synthesis of this particular semicorrin is worthy of serious consideration. Cycloaddition of nitrile oxide **34** to its own acetylene precursor, **33**, provided isoxazole **35**.[16] Markovnikov hydration of the terminal acetylene and hydrolysis of the nitrile to an amide function proceeded smoothly to **36**. Reduction of this isoxazole yielded vinylogous carbinolamide **37**. Finally, potassium t-butoxide catalyzed cyclization and dehydration produce sermicorrin **25**.



Synthesis of the isomeric semicorrin **26** was accomplished in an analogous fashion:



In contrast to the unsubstituted model **22**, cycloelimination of two equivalents of water from **38** was easily achieved in 90% yield by exposure to 2 equivalents of Kot-Bu in boiling t-BuOH. The crude product was conveniently purified by sublimation, and the resultant green–yellow needles appeared homogeneous by tlc using a number of solvent systems. However, spectral analysis revealed the presence of the two tautomeric semicorrins **26** and **39** in an approximate ratio of 1:3.5.



Attempts to affect the separation of **26** and **39** were uniformly unsuccessful. However, this separation proved to be academic since methoxide induced deprotonation of the tautomeric mixture and subsequent complexation with Pd(II) yielded a *single* complex of structure **40**. Extensive spectral analysis of this complex reveals that the double bond is exclusively endocyclic, a fact which also accounts for the exclusive formation of the antisymmetric orientation rather than a mixture of both possible isomers as observed in the identical transformation of semicorrin **25**. Although we cannot precisely define its magnitude, steric compression of the terminal sp^3 hybridized opposing methyl functions in the alternative symmetric combination is apparently sufficiently large to resist this as a stable mode of orientation.

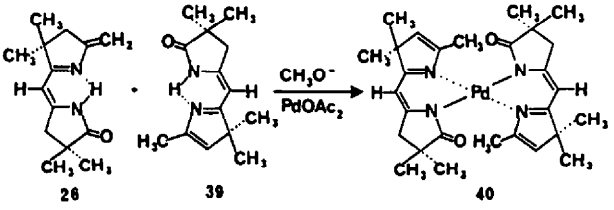
CONSTRUCTION OF THE MACROCYCLIC LIGAND

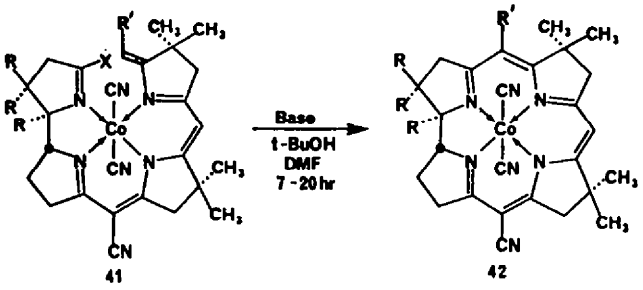
Mention should be made at this point that the employment of palladium (or nickel and cobalt) templates in a truly versatile corrin synthesis suffer from certain disadvantages. These have been enumerated by Eschenmoser and include:

1. "The method seems to be strictly confined to the preparation of corrin compelxes of those transition metal ions which form robust complexes with corresponding precorrinoid ligands. Experiments aiming at a cyclization of the labile precorrinoid complexes of sodium, lithium or zinc have failed (see diagram below). This limitation precludes in particular the preparation of metal-free corrins since neither under acidolytic nor reductive conditions (cyanidation included) was it possible to remove metal ions, such as nickel, palladium or cobalt from their very stable corrin complexes without concomitant destruction of the ligand".

2. "A further limitation of the method concerns the influence of the substitution pattern in the precorrinoid ligand on the ease of cyclization of dicyano cobalt (III)—complexes **41–42**. Whereas, in the least substituted series R = R′ = H (and likewise in the case of the corresponding 19-methyl derivative) the cyclization proceeds smoothly at room temperature in over 90% yield, a vitamin B_{12}-like substitution by methyl groups in ring A (R = CH_3, R′ = H) necessitates a somewhat higher reaction temperature and tends to have an adverse effect on the cyclization yield. Not surprisingly, an additional methyl group at the critical methylidene reaction center (R = R′ = CH_3) hampers the cyclization step to such an extent that the outcome may rather be called a 'mode of formation' of 5-methyl corrin complexes than a synthesis of them".

With these unfortunate restrictions in mind we em-

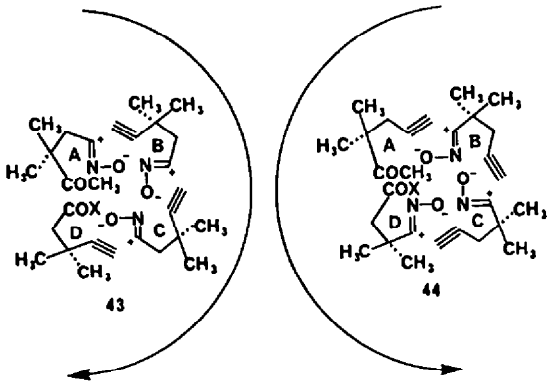




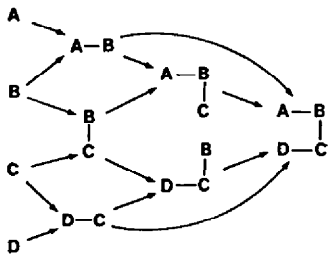
41 42

		X	R'	R	Yield
t-BuOK	20°	OC_2H_5	H	H	90
t-BuOK	50°	OC_2H_5	H	CH_3	65
NaH diglyme	120°	OC_2H_5	CH_3	CH_3	10
i-Pr_2NEt	150°	OC_2H_5	H	CH_3	5
i-Pr_2NEt	150°	SCH_3	H	CH_3	50

barked on a program to investigate the feasibility of employing multiple isoxazole nuclei in a *metal-free* corrinoid synthesis, a challenge also solved with typical elegance by Eschenmoser.[17] As mentioned in the discussion of simple model systems, we had considered very early in our investigation the possibility of incorporating more than one isoxazole scaffold into the same molecule as a means of establishing a network of ring-bridging vinylogous amidine chromophores. In principle, all of the structural features of octamethylcorrin **5** (or octamethylcorphin **6**) can be incorporated into an appropriately substituted triisoxazole system which, in turn, could be elaborated from carefully selected nitrile oxides and terminal acetylenes in either of the two modes suggested by the following diagram, i.e. either in a clockwise or counterclockwise fashion. Within each mode these combinations could be executed in a variety of ways as illustrated.

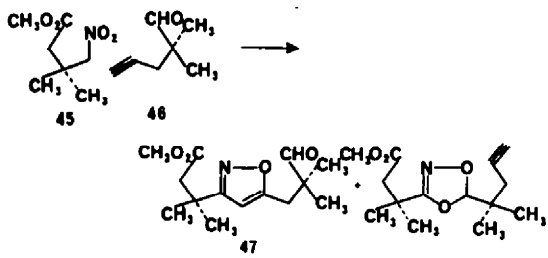


43 44



The counterclockwise approach[18]

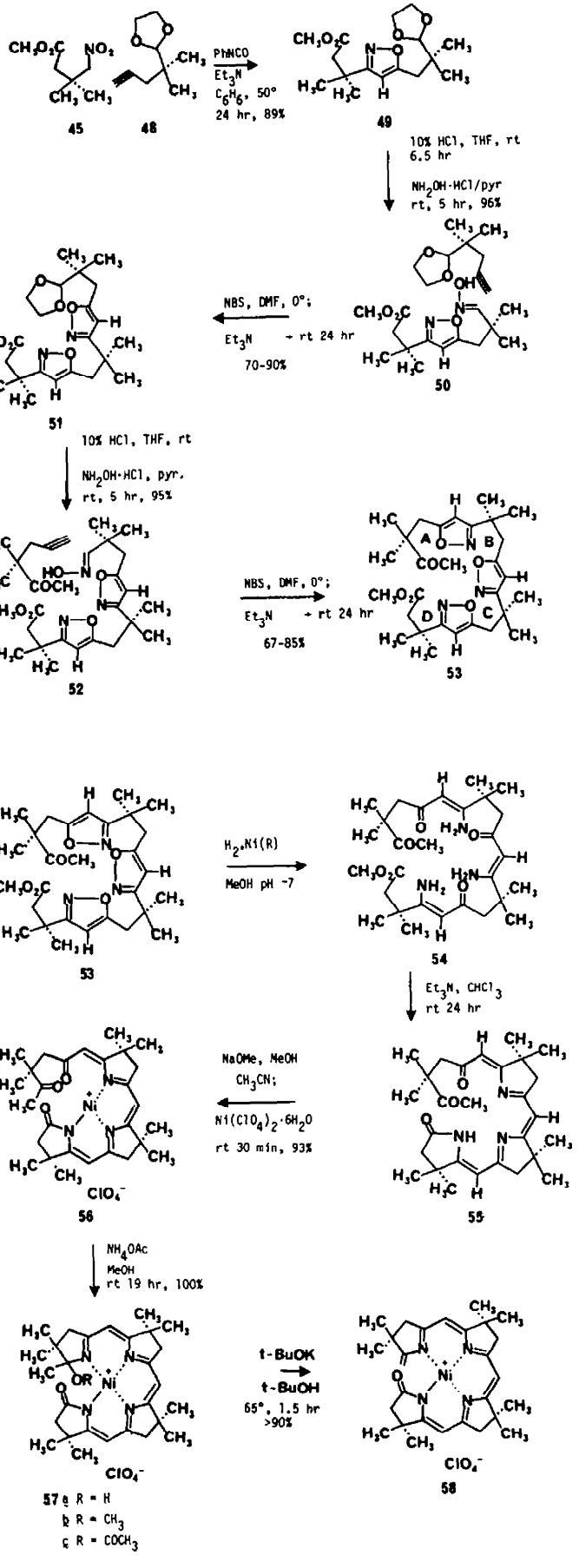
Our first experiments in this connection uncovered a new aspect of the cycloaddition step not encountered previously, and that is that nitrile oxide derived from **45** not only adds to the acetylenic function of **46** but also the aldehyde group and at a competitive rate:



45 46 47

Of course the solution to this problem was trivial, requiring only that we protect the aldehyde function. Thus, cycloaddition of **45**–**48** gave monoisoxazole **49**. Mild acid hydrolysis of the acetal function and treatment of the resultant aldehyde with hydroxylamine provided oxime **50**. Conversion of this intermediate to bisisoxazole **51** was achieved in the usual manner. Repetition of the sequence (cf. **51**→**52**→**53**) afforded the desired triisoxazole **53** in an overall yield (starting with **45** and **48**) of nearly 40%. In short, we were able to produce without too much difficulty as much as ten grams of the triisoxazole at a time.

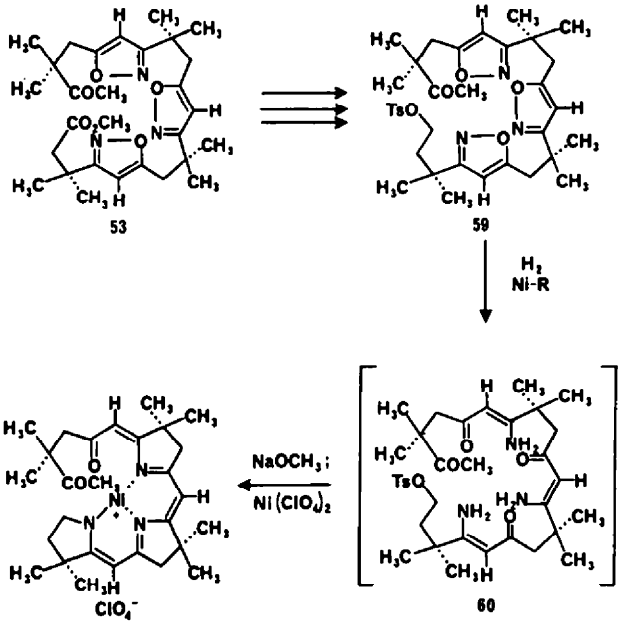
With more than adequate supplies of **53** on hand, we began to investigate its catalytic hydrogenolysis. At first, this proved to be more arduous than we had anticipated, until it was discovered that adjustment of the pH of the Raney nickel solution to about 7 with acetic acid resulted in smooth and virtually quantitative reduction to the corresponding tris-vinylogous amide **54** as a labile white crystalline solid. Upon exposure to triethylamine a yellow-orange gummy solid was produced whose PMR and mass spectra were consistent with the conjugated ligand structure **55**. However, due to its lability it was immediately treated with one equivalent of sodium methoxide followed by 1.1 equivalents of $Ni(ClO_4)_2$ in acetonitrile. This sequence provided the beautifully crystalline orange nickel complex **56** in essentially quantitative yield. The fourth nitrogen was incorporated by simply stirring a methanolic solution of **56** with excess ammonium acetate. This produced a solid whose PMR spectrum indicated was a mixture of products **57a-c**


PhNCO
Et3N
C6H6, 50°
24 hr, 89%
45
48
49
10% HCl, THF, rt
6.5 hr
NH2OH·HCl/pyr
rt, 5 hr, 96%
50
NBS, DMF, 0°;
Et3N + rt 24 hr
70-90%
51
10% HCl, THF, rt
NH2OH·HCl, pyr,
rt, 5 hr, 95%
52
NBS, DMF, 0°;
Et3N + rt 24 hr
67-85%
53
H2,Ni(R)
MeOH pH ~7
54
Et3N, CHCl3
rt 24 hr
55
NaOMe, MeOH
CH3CN;
Ni(ClO4)2·6H2O
rt 30 min, 93%
56
NH4OAc
MeOH
rt 19 hr, 100%
t-BuOK
t-BuOH
65°, 1.5 hr
>90%
57 a R = H
b R = CH3
c R = COCH3
58

which, without purification, was treated with potassium t-butoxide in t-butyl alcohol to provide the known[19] nickel precorphin complex **58**. The overall yield for this sequence starting with triisoxazole **53** was 30–50%. The conversion of nickel precorphin complex **58** into a variety of metal complexes of octamethylcorphin has been recorded recently.[19]

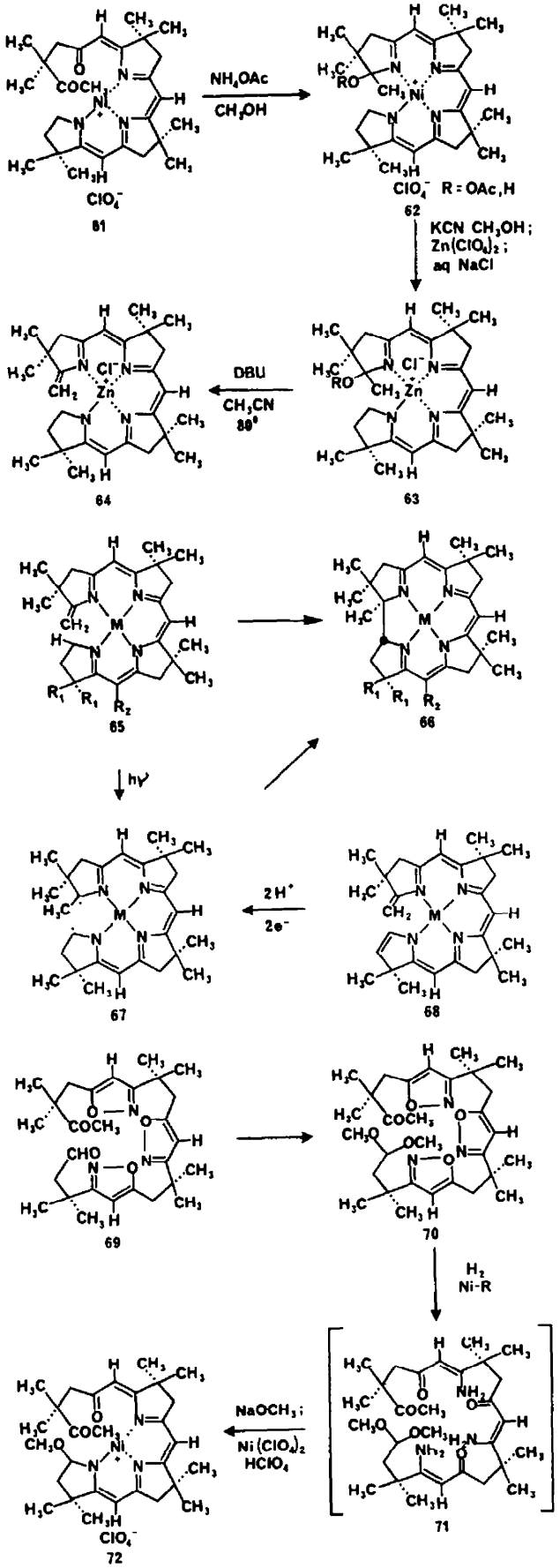
Triisoxazole **53** also serves as a latent synthon for the corrin ligand. Thus, protection of the ketone as its ketal, followed by reduction of the ester with lithium aluminum hydride gave a crystalline alcohol which reacted with p-toluenesulfonyl chloride in pyridine at room temperature to provide the crystalline tosylate **59** in 90% overall yield. Hydrogenolysis of this triisoxazole over a Raney-nickel catalyst adjusted to a pH of about 7 with acetic acid proceeded smoothly. The product of this reduction (presumably **60** or various ring-chain tautomers thereof) was too unstable for characterization and was treated directly with triethylamine to induce cycloelimination followed by deprotonation with sodium methoxide and finally complexation with nickel perchlorate. This sequence of reactions provided ligand **61** as beautiful red needles.

whereas carefully degassed solutions of the palladium, platinum, zinc, cadmium and magnesium complexes readily cyclize in essentially quantitative yield, the corresponding nickel and dicyanocobalt complexes do not. Furthermore, of those metals which can be utilized successfully, only the zinc and cadmium corrin complexes are sufficiently labile to allow subsequent removal and replacement by other metals, especially cobalt. Our own observations concerning the photochemical cycloisomerization are fully in accord with those reported. Provided care is taken to remove oxygen, a dilute benzene solution of A/D seco-corrin complex **65** [$R_1 = CH_3$, $R_2 = H$, M = Zn(Cl)] is smoothly transformed into the corresponding *trans*-octamethylcorrin **66**.[21] Even the crudest type of photochemical apparatus can be employed—a 250 watt sunlamp suffices. The mechanism of this fascinating transformation is believed to involve photochemically allowed antarafacial [1, 16]-sigmatropic shift of a hydrogen from ring D to the methylene carbon of ring A. The product of such a transformation would be a 15-center 16π-electron system (**67**) whose thermally allowed antarafacial 1,15-($\pi \rightarrow \sigma$)-electrocyclic ring clos-



Introduction of the fourth nitrogen into **61** was accomplished by the same method employed in the corphin series (cf. **56** to **57**) and provided ligand **62** in high yield as a mixture of carbinolamide and the corresponding ester. The nickel was then removed via cyanide induced ligand exchange and replaced with zinc to afford **63**. It should be noted that attempts to utilize zinc in the **60** to **61** transformation were uniformly unsuccessful necessitating this alternate course. Elimination of the elements of water or acetic acid from **63** was accomplished with DBU in refluxing acetonitrile to provide the crucial seco-corrin complex **64**. The importance of employing zinc in this ligand now comes more sharply into focus. In a truly inspired and extensive study of the photochemically induced cycloisomerization of various A/D seco-corrin complexes (**65**, $R_1 = H$, $R_2 = CN$) to A/D *trans*-corrin complexes (**66**), Eschenmoser and his collaborators[17,20] found that the nature of the metal was decisive. Thus, ure would provide the observed *trans*-corrin complex **66**.

The generation of intermediate **67** from the electrochemical reduction of **68** in acidic solution constitutes yet another exciting entry into *trans*-corrin complexes[22] and provides us with an additional synthetic target for the employment of triisoxazole **53**. Initial experiments[23] along these lines appear promising. Thus, after protection of the ketone as its ethylene glycol ketal, the terminal ester function was selectively reduced with diisobutylaluminum hydride to the corresponding aldehyde (**69**). Treatment of **69** with trimethyl orthoformate and toluene sulfonic acid in methanol provided acetal **70**. Based on our previous experiments with **56** and **61**, we anticipate that reduction of **70** over Raney nickel catalyst will produce **71**. Exposure of this substance to base followed by treatment with nickel perchlorate should provide ligand **72**. We further anticipate that exposure of **72** to ammonium acetate in methanol followed by treatment

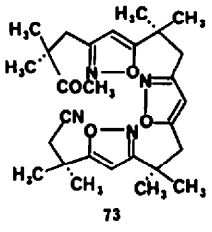

NH4OAc
CH3OH
R = OAc, H
KCN CH3OH;
Zn(ClO4)2;
aq NaCl
DBU
CH3CN
80°
hν
2H+
2e−
H2
Ni-R
NaOCH3;
Ni(ClO4)2
HClO4

with an appropriate base will provide the alternate seco-corrin complex **68**.

The "clockwise" approach

As noted above, all of the structural features of the corrin and/or corphin ligands can also be incorporated into the isomeric triisoxazole **73** which, in turn, can be assembled in various ways from the nitrile oxides and terminal acetylenes shown in diagram **74**. It should be noted that all four subunits (**74A-D**) are, in fact, derivatives of acetylenic nitrile **74D**. The possibility of constructing both macrocyclic ligands from this single starting material was, of course, irresistible and prompted further investigation. Unlike the "counterclockwise" approach, a tactical decision was made in this case to assemble the triisoxazole scaffold by joining together a "Northern" or AB subunit (**78**) and a "Southern" or CD-subunit (**79**). Such an approach would have the additional advantage of allowing us to test the feasibility of employing a convergent synthesis in the case of vitamin B-12 itself. This has now been achieved with partially gratifying results.[24]

The "Northern" subunit was prepared from the same acetylenic aldoxime (**75**) employed in the alternate synthesis of semicorrin E (cf. 33→25). Thus, protection of the terminal acetylene function as its trimethylsilyl derivative followed by careful chlorination of the oxime with N-chlorosuccinimide gave hydroxamic chloride **76** in high yield. Treatment of this substance with triethylamine in the presence of its own precursor (**75**) provided monoisoxazole **77** in about 80% yield. Repetition of the chlorination procedure on this substance afforded the necessary hydroxamic chloride **78**. The "Southern" subunit (**79**) was readily prepared by reduction of **35** with lithium aluminum hydride and acylation of the resultant amine with methyl chloroformate. 1,3-Elimination of hydrogen chloride from **78** was induced by heating it in the presence of **79** in benzene until gas evolution ceased. The desired triisoxazole (**80**) was obtained as a nice white crystalline substance in about 50% yield. After removal of the trimethylsilyl group with sodium hydroxide in methanol, the resultant terminal acetylene was hydrated with mercuric chloride in acid to provide the desired triisoxazole **81**. Although some of the yields in this sequence are still in need of improvement, the relative success of these experiments strongly suggests that the "clockwise" approach also has considerable merit.



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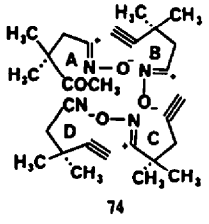

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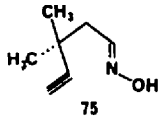
Further important models

In our discussion of general principles which guide the synthetic plan following the introduction of this Report, we noted that at least four fundamental problems must be solved before the synthesis of vitamin B-12 can be achieved. The first of these was concerned with developing a reliable method for construction of the macrocyclic ligand. We believe the experiments outlined above



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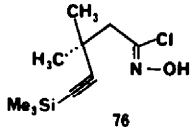

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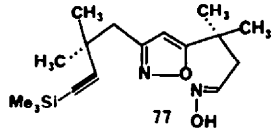

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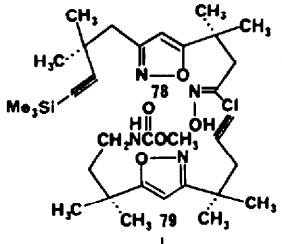
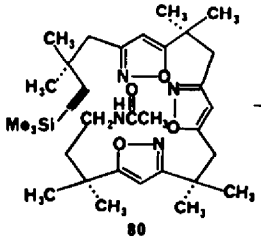


78 **79**



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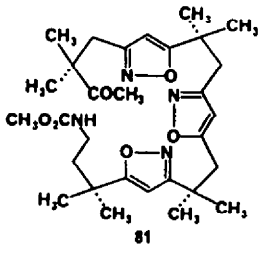
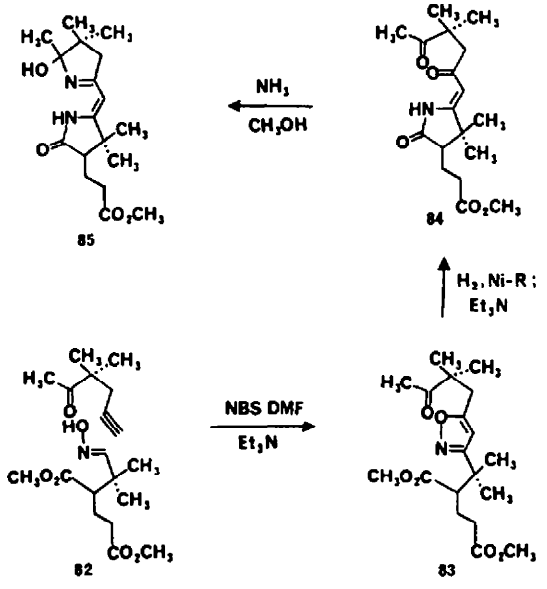
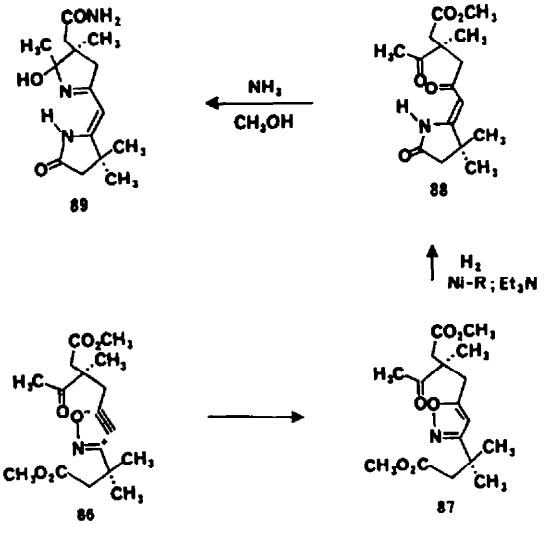


81

provide just such a method. It was further noted that the methodology must be compatible with the various functional groups which adorn the periphery of the ligand. In order to further test this important consideration, two additional model studies were executed. In the first of these[25] isoxazole **83** was prepared in the usual manner from aldoxime **82**. Reduction of **83** and ring closure provided vinylogous urethane **84** without incident. Treatment of **84** with ammonia in methanol then led to semicorrin **85**.

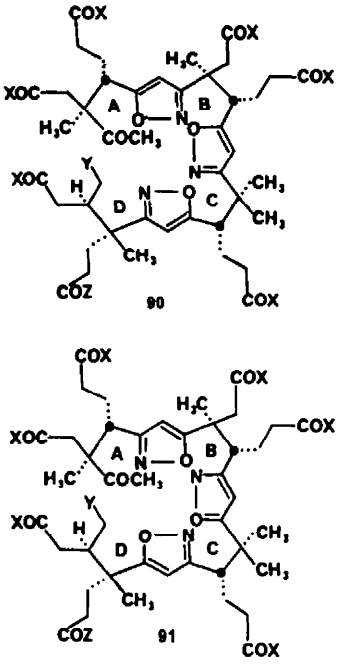


In a similar fashion[26] isoxazole **87** was prepared from **86**. Reduction and cyclization afforded **88**. Treatment of **88** with ammonia in methanol afforded semicorrin **89** in which the acetic ester side chain had suffered ammonolysis. At first this appeared surprising in view of the fact that the less hindered propionic ester side chain in **84** survived identical treatment. We attribute this difference to neighboring group participation initiated by facile addition of ammonia to the unconjugated methyl ketone group in **88**. The resultant carbinolamine is then ideally constituted for intramolecular transfer of the amine to the ester function.



On to vitamin B-12

With the acquisition of methodology which is satisfactory not only for construction of the macrocyclic corrin ligand, but also for dealing with the anticipated functionality problem, we now briefly turn our attention to the ultimate prize—vitamin B-12. As in the case of "simple" corrins, we can envisage two different triisoxazole nuclei (**90** and **91**) which incorporate all of the essential features of this substance. Here, then, we are brought face to face with the third fundamental problem—stereochemistry in the relative and absolute sense. Although many hurdles undoubtedly block our way, initial experiments in our laboratory have uncovered an apparently viable solution to this aspect of the problem—but, that will have to be the subject of a future report.



Acknowledgements—It remains only for me to acknowledge with heartfelt thanks the splendid efforts of my collaborators without whose skill and devotion this project would most certainly have failed several times over. Their names are cited in the appropriate footnotes and references. We also wish to express our gratitude to the National Science Foundation and The Robert A. Welch Foundation for providing generous financial support. Finally, I wish to express my gratitude to Professor Albert Eschenmoser for his prompt and generous assistance in providing us with analytical data for many of the substances prepared in his laboratory and for providing inspirational leadership for achieving our goals.

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[10]*Cf.* A. I. Scott, *Tetrahedron* **31**, 2639 (1975) and refs therein.
[11]Simultaneously with our own work a somewhat less broadly based model study was reported by Prof. G. Traverso. See G. Traverso, A. Barco, G. P. Pollini, M. Anastasia, V. Sticchi and D. Pirillo, *Il Farmaco, Ed. Sci.* **24**, 946 (1969); G. Traverso, A. Barco and G. P. Pollini, *Chem. Comm.* 926 (1971).
[12]Although we had no knowledge of it, the concept of employing isoxazole nuclei in the synthesis of vitamin B-12 itself had been advanced earlier in various lectures by Prof. J. W. Cornforth. The results of his investigations have now appeared in Ref. 6. However, in a private conversation with Prof. Cornforth (5 Nov. 1973), it became apparent that his method of approach was *entirely* different and encouraged us to continue our studies. We are most grateful to Prof. Cornforth for communicating with us the results of his investigation.
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[25]Unpublished work of J. M. Fitzpatrick, Ph.D. Thesis, Rice University (1973) and Dr. Paul Germeraad.
[26]Unpublished work of Dr. Boyd Harrison and Mr. Richard Cherpeck.