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AN APPROACH TO THE SYNTHESIS OF PEDERIN

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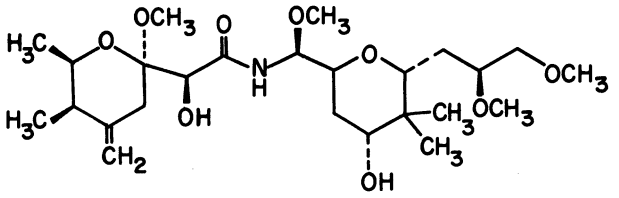
Abstract - Pederin, the vesicant component found in the haemolymph of many species of the staphylinid beetle of the genus Paederus, is a powerful inhibitor of protein synthesis in eucaryotic cells. With its nine chiral centers and its unusual functionality, it is also the most complex, non-proteinaceous insect defensive compound known. This paper describes our progress toward a total synthesis of this fascinating natural product.

Nature's use of organic chemicals for defensive purposes is one of the most intriguing areas of "applied organic chemistry". Arthropods are particularly skillful chemists (1); their defensive agents range from the elegant simplicity of single carbon compounds such as hydrogen cyanide and formic acid, through a variety of simple aliphatic compounds, to quinones, terpenes and "alkaloids" (2). Probably the most complex, non-proteinaceous defensive compound so far characterized is produced by staphylinid beetles of the genus Paederus (known in East Africa as the "Nairobi Eye Fly"). The dramatic vesicant properties of these beetles were first described in 1912 (3), although the isolation of pederin (the haemolymph component responsible for the vesicant effect) in crystalline form and the demonstration that pederin is different from the notorious insect product cantharidin (another vesicant of considerable interest) are more recent (4).

Extensive chemical and spectral studies were carried out on pederin in Italy (5) and in Japan (6), culminating in X-ray crystallographic studies (7) which resulted in the determination of both its structure and absolute stereochemistry.

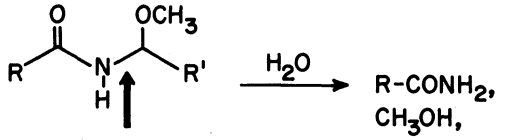


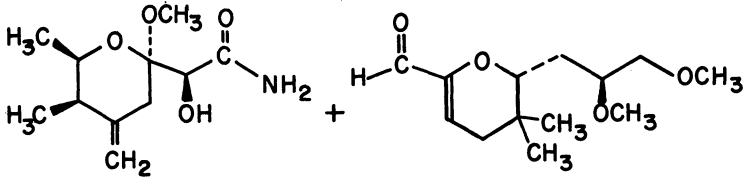
PEDERIN

This structure bears little resemblance to those of other known animal products, and its unique character is associated with several particularly dramatic biological activities. Pederin inhibits mitosis in intact HeLa cells at concentrations of 1-10 ng/ml (8). In cell-free systems, it has been shown to block protein synthesis at similar concentrations, making it the most powerful antimetabolite known (9). Pederin's ability to induce cell fusion in human skin fibroblasts represents quite another type of biological activity which may be a valuable tool in the field of cell biology (10).

Despite pederin's varied biological activities, the number of studies dealing with this remarkable substance has been rather limited. This is due in part to the fact that a single beetle contains only about a microgram of the toxin. In addition, the isolation procedure is far from simple (5). Because of the scarcity of the natural material, because of the challenge offered by its unique structure and because of our long-standing interest in the chemical defense mechanisms of arthropods, we have set out to synthesize pederin. While we are still some distance from our goal, we would like to use this opportunity to describe our approach, and to report in a preliminary way the progress we have made.

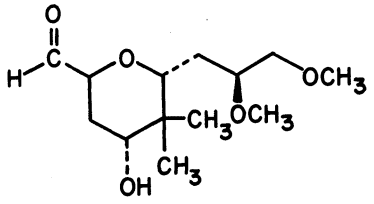
Examination of pederin's structure reveals the presence of a aza-acetal function in the chain of atoms connecting the two tetrahydropyran rings. We might expect



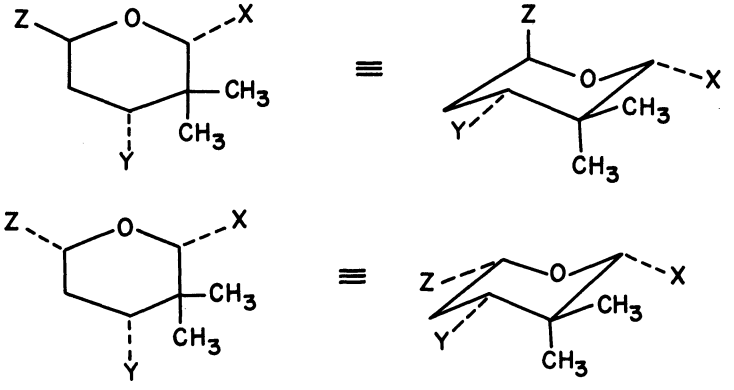


pederenal

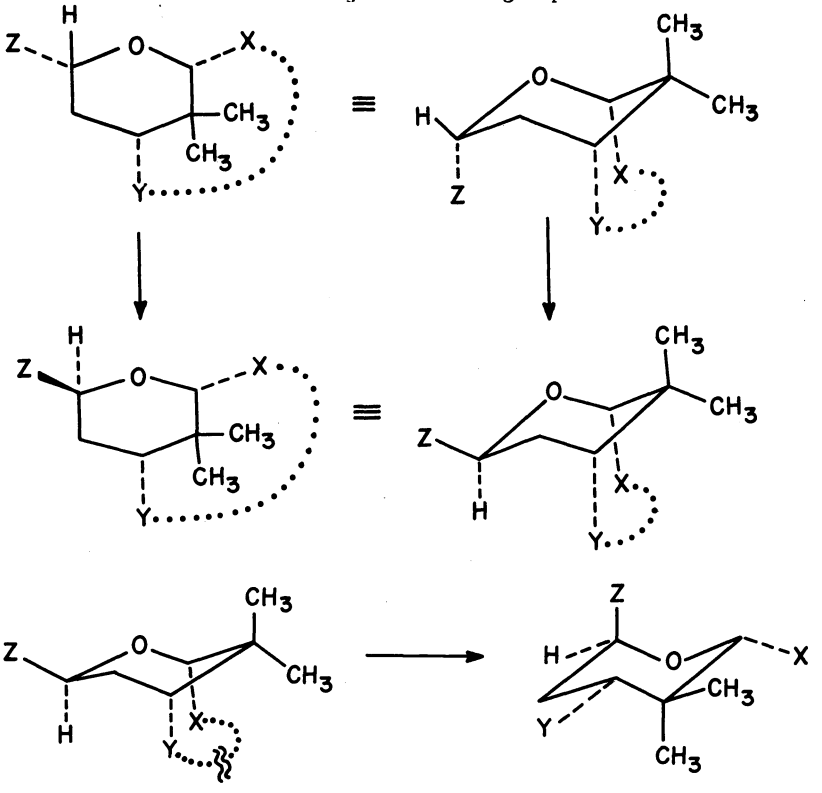
treatment with aqueous acid to result in cleavage at this site to give an amide, an aldehyde and methanol. Acid, in fact, does cleave pederin to the expected amide and methanol, although the aldehyde fragment is obtained as a dehydration product, "pederenal" (5,6). Our overall synthetic plan aims at (a) the synthesis of the undehydrated aldehyde corresponding to pederenal, (b) the synthesis of the amide constituting the other major portion of the pederin molecule and (c) the joining of these two large fragments to give pederin itself.



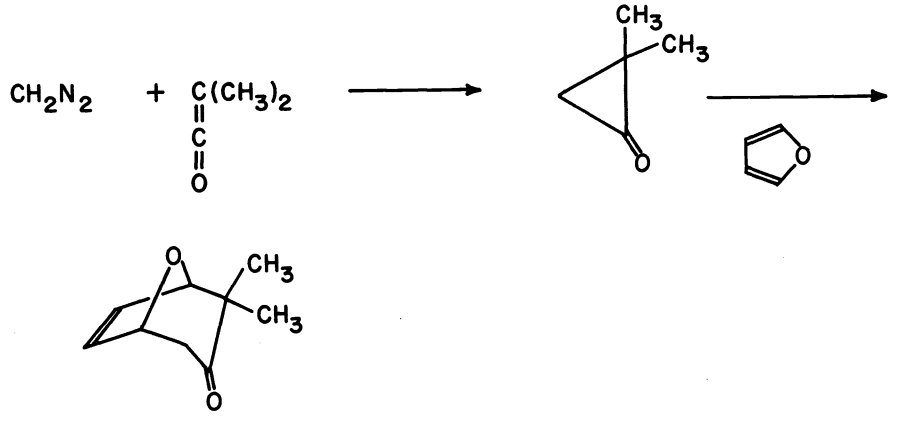
Let us begin by considering the structure and stereochemistry of the aldehyde unit. It is a multiply substituted tetrahydropyran bearing geminal methyl substituents, a dimethoxypropane side chain (X) cis to a hydroxyl group (Y) with a formyl group (Z) trans to the latter two substituents. This structure may be generally represented as shown below; a conformational formula suggests that the aldehyde function will occupy an axial position. We hoped



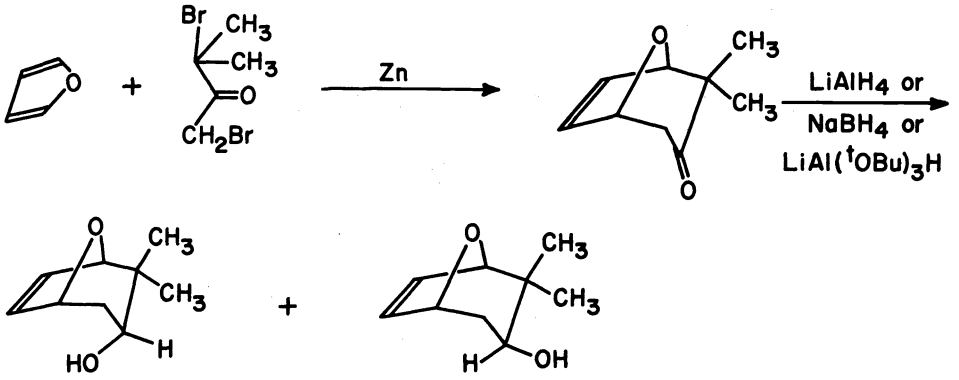
that this stereochemical pattern could be obtained by starting with a precursor in which the 2,4 and 6-substituents on the tetrahydropyran ring were all cis (equatorial). If two of these substituents (X and Y) were joined to each other, then a triaxially substituted tetrahydropyran would result. Epimerization of the remaining free axial group (Z) to the equatorial position would then yield a product which can relax into the required stereochemistry when the connection between the two joined axial groups is severed.



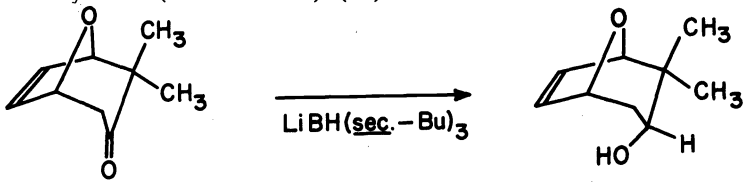
An attractive starting material for this synthesis is the known 2,2-dimethyl-8-oxabicyclo-[3.2.1]oct-6-ene-3-one, first prepared by reaction of 2,2-dimethylcyclopropanone (from dimethylketene and diazomethane) with furan (11). Since this synthesis of the desired starting material appeared impractical on a large scale, we sought a more convenient



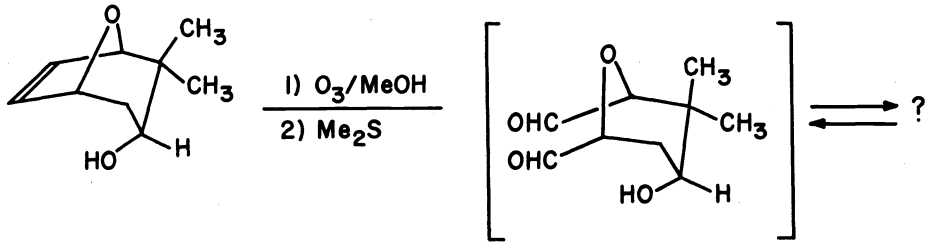
procedure. The reaction of an α,α'-dibromoketone with furan in the presence of sodium iodide has given the expected bicyclic product (12), but in the case of 1,3-dibromo-3-methylbutan-2-one, this technique was unpromising. In the presence of zinc and acetic acid, however, this dibromoketone and furan gave the desired adduct smoothly in ca. 50% yield (13).

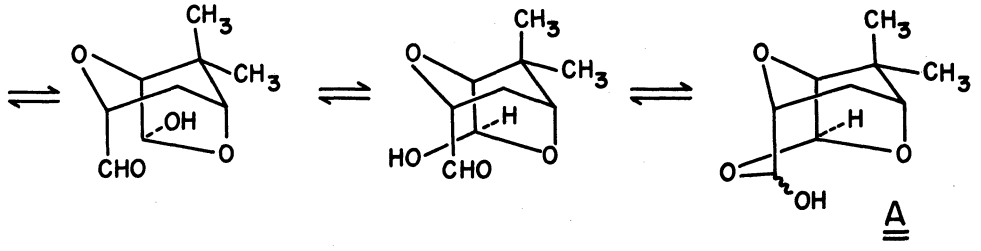


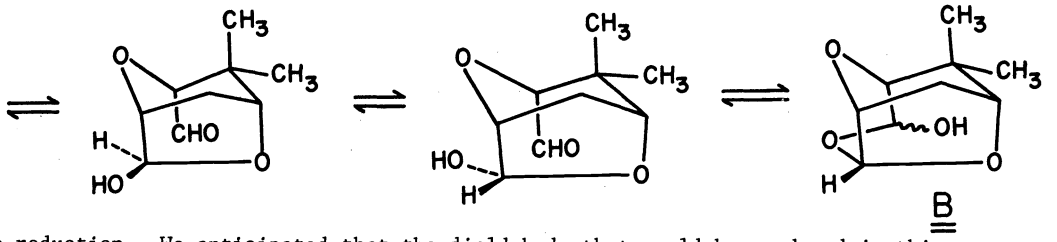
Our next objective was to reduce this ketone to the corresponding endo alcohol in order to establish the all cis tri-substituted tetrahydropyran system. Only the slightest selectivity could be obtained using either lithium aluminum hydride or sodium borohydride, but lithium tri-t-butoxyaluminum hydride gave an 85:15 ratio of endo and exo alcohols. Completely unidirectional reduction in favor of the desired product was finally obtained with lithium tri-sec-butylborohydride (L-Selectride) (14).



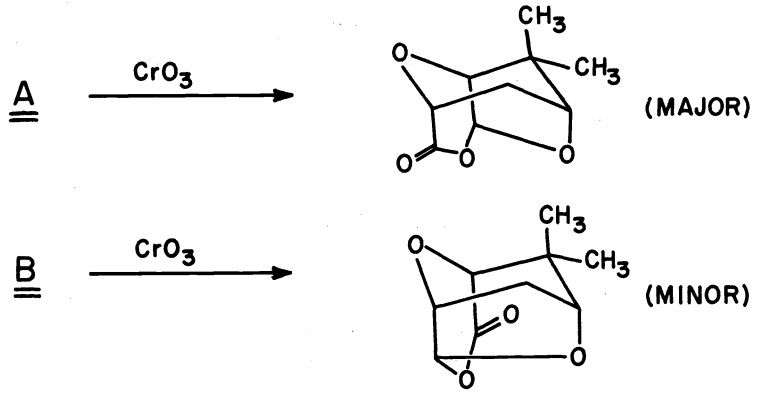
We have now come to the point at which the olefinic double bond in our bicyclic intermediate must be cleaved in order to generate functionality appropriate for elaboration of the final structure. The reaction selected for this purpose was ozonolysis followed by dimethyl







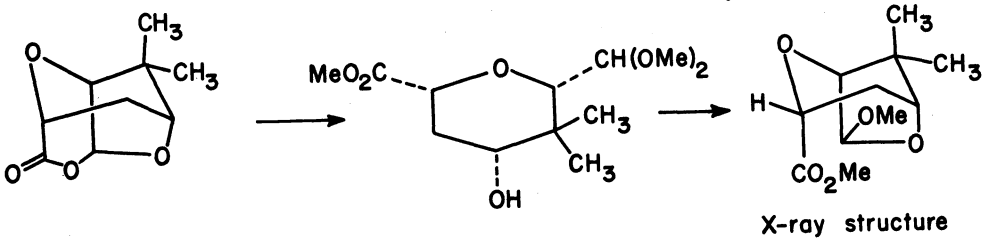
sulfide reduction. We anticipated that the dialdehyde that would be produced in this way might well exist as a somewhat complex mixture of intramolecularly generated bicyclic hemiacetal-aldehydes and tricyclic acetal-hemiacetals (A and B, see accompanying formulae). In fact, the infrared spectrum of the reduced ozonide showed only weak carbonyl absorption, indicating that mainly tricyclic products were formed. In order to convert this equilibrating mixture into something more stable, while at the same time producing a product in which the original aldehyde groups would be differentiated from each other, a chromic acid oxidation was carried out. This gave a mixture of two tricyclic lactones, the ratio of



which depended on the exact procedure followed in working up the ozonolysis reaction mixture. Under appropriate experimental conditions, the lactone labeled as "major" in the accompanying formulae constituted at least 95% of the reaction mixture; this lactone was readily purified by recrystallization. (The structures of the two isomeric lactones were apparent from an examination of their proton NMR spectra.)

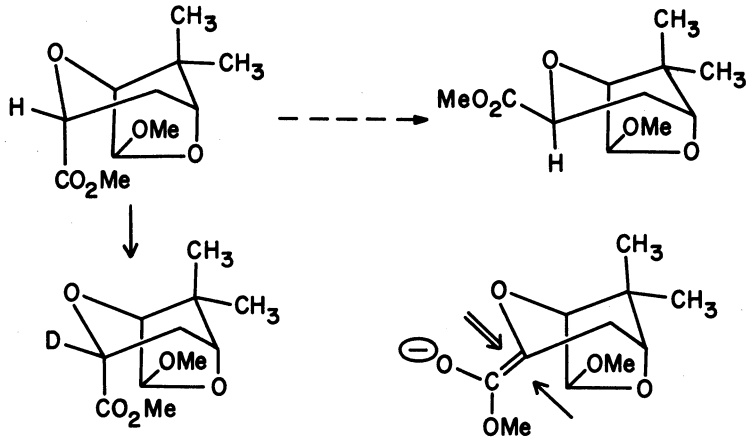
We should note that our synthetic plan was not dependent on which of the two possible tricyclic lactones would be the major one, since it is not difficult to envisage reaction sequences by which either isomer could be converted into the desired aldehyde. We did hope, however, that one lactone would predominate over the other, and fortunately the geminal methyl groups generated enough dissymmetry to bring about the desired result.

Our next step was to open up the lactone ring (along with the cyclic acetal), in order to provide an opportunity to epimerize the carbon atom bearing the carboxylic substituent. Acidic methanol gave the expected monocyclic methyl ester dimethyl acetal, and treatment of this intermediate with p-toluenesulfonic acid in dry benzene at reflux brought about a recyclization to give the corresponding bicyclic methylester-acetal. In this key intermediate, we have forced the ester group into an axial position, so that equilibration to a more stable equatorial epimer could be expected to proceed readily.

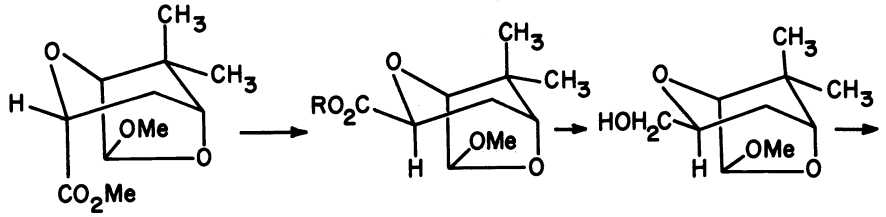


X-ray structure

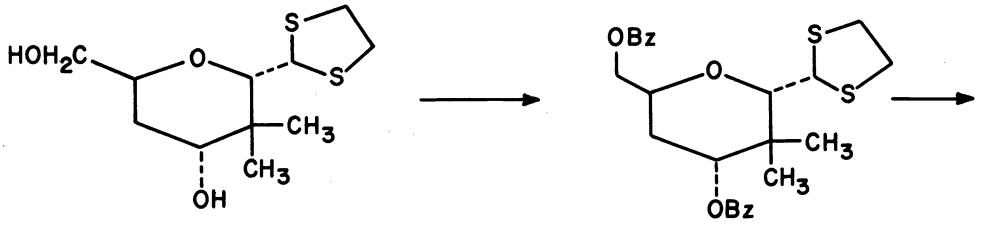
This ester epimerization, however, proved surprisingly difficult. Treatment of the ester with sodium methoxide in methanol under a variety of experimental conditions failed to bring about any reproducible conversion to the equatorial ester. That the problem was not with the removal of the α-proton to produce the desired enolate intermediate was demonstrated by the fact that this proton was readily exchanged for deuterium in CH_3OD/CH_3ONa. To confirm that the original methyl ester actually had the assigned structure and stereochemistry, a



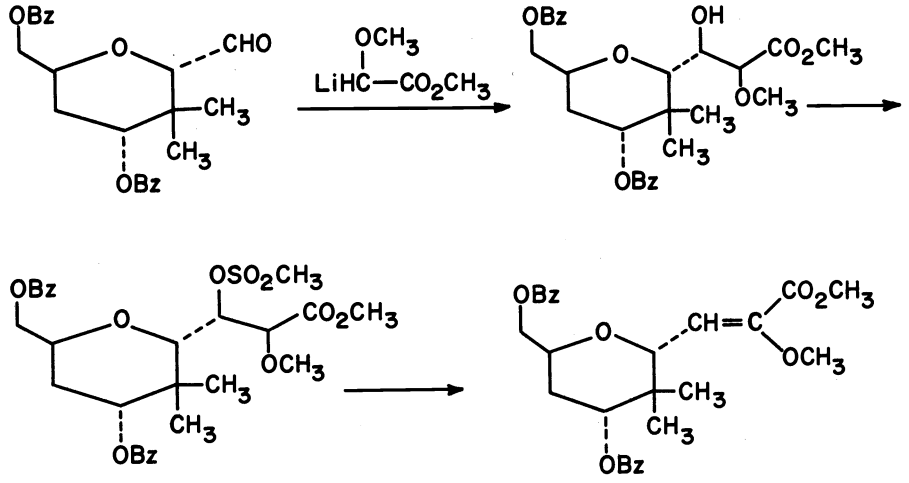
sample was submitted to Prof. Andrew McPhail at Duke University for X-ray crystallographic study. He ascertained that the ester did indeed have the assigned structure and stereochemistry (and incidentally that the methoxy group of the cyclic acetal had the exo-configuration). Our difficulty in performing this stereochemical transformation is most easily attributed to the fact that after the α-proton is removed, the resultant enolate ion is more easily approached by the proton donor from the less hindered exo face than from the endo face, so that the less stable endo ester is regenerated most of the time. By using potassium t-butoxide in t-butyl alcohol under appropriate conditions, however, the desired epimerization proceeded smoothly. Although the resultant product was a mixture of exo methyl and exo t-butyl esters, the following step was a sodium bis-(2-methoxyethoxy)aluminum hydride reduction to give the corresponding primary alcohol, so that this incidental ester interchange caused no difficulties.



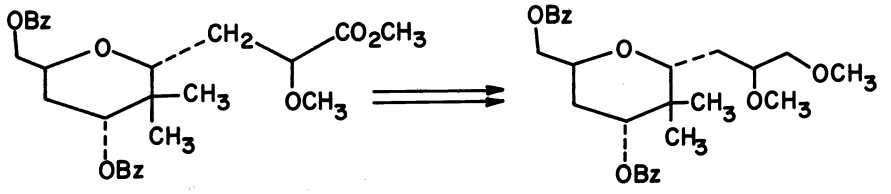
At this point, the correct relative stereochemistry of the three chiral centers on the tetrahydropyran ring is established, and the chief remaining task is the elaboration of the dimethoxypropane side-chain. A number of possible routes were explored, but only two were successful. One started with the boron triflouride etherate catalyzed cleavage of the cyclic acetal in the presence of ethanedithiol, to give the corresponding diol. The free hydroxyl groups were then converted into their benzyl ethers in the (unrealized) hope



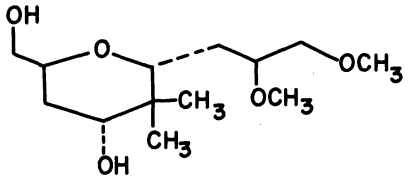
that selective cleavage of these protecting groups would be possible at a later stage, or that selective oxidation of the deprotected diol could be achieved. Treatment of the dithiolane bis-benzyl ether with mercuric oxide and mercuric chloride gave the expected aldehyde. The lithium enolate of methoxyacetic ester added smoothly to this aldehyde to give the corresponding aldol product, which was dehydrated to give the α-methoxy-α,β-unsaturated ester by conversion to its methanesulfonate ester followed by elimination of the elements of methanesulfonic acid by treatment with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). As anticipated, this ester was obtained as a mixture of about equal amounts of the E and Z



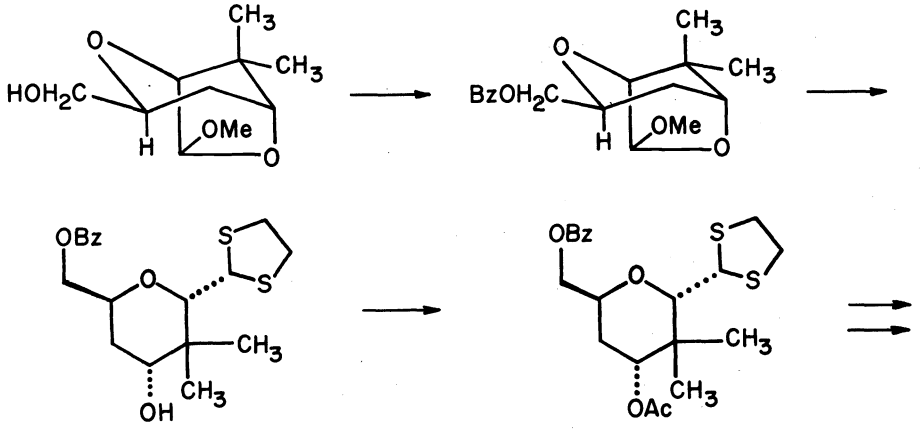
isomers, which could be separated by thin layer chromatography. Since reduction of either of these pure isomers gave a similar mixture of epimeric, saturated α-methoxy esters upon treatment with sodium borohydride and nickel chloride (15), there was no advantage to be gained by first separating the geometric isomers. Thus, the fourth chiral center is introduced in this scheme in an uncontrolled way, giving both the product whose stereochemistry must be the same as that of pederin, and an epimer. The conversion of this mixture into the ultimately required dimethoxypropane was accomplished smoothly by sodium bis-(2-methoxyethoxy)aluminum hydride reduction of the ester function to the primary alcohol, followed by methylation with sodium hydride and methyl iodide.



We now had to address the task of generating an aldehyde function selectively. To our disappointment, no conditions could be found for partial debenzylation by catalytic hydrogenolysis of the less hindered, primary benzyl ether. Selective Lewis acid deprotection procedures were also unrewarding. One especially attractive debenzylation procedure involves hydride ion transfer to the triphenylmethyl cation (16); we thought this method would show particular sensitivity to steric hinderance because of the bulk of the reagent. Again, results were disappointing. In view of this experience, the dibenzyl ether was completely hydrogenolized to give the corresponding 1°,2°-diol. However, no selective oxidation of the primary alcohol could be achieved, so that this route had to be modified in order to provide a reliable differentiation between the two hydroxylic centers. This in fact posed no particular problems; since the two hydroxyl groups were generated at different points in the reaction sequence, it was simply necessary to protect each one in a different manner as it was generated.

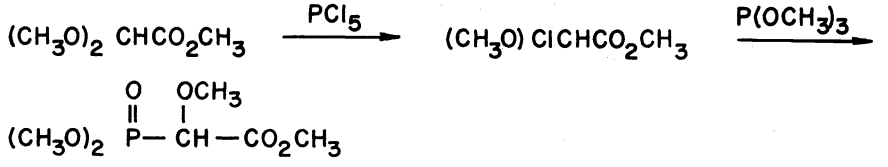


To do this, we have to return to the original reduction product of the epimerized ester, which was now converted into its benzyl ether by treatment with sodium hydride and benzyl bromide. Opening of the acetal ring with ethanedithiol was carried out as previously

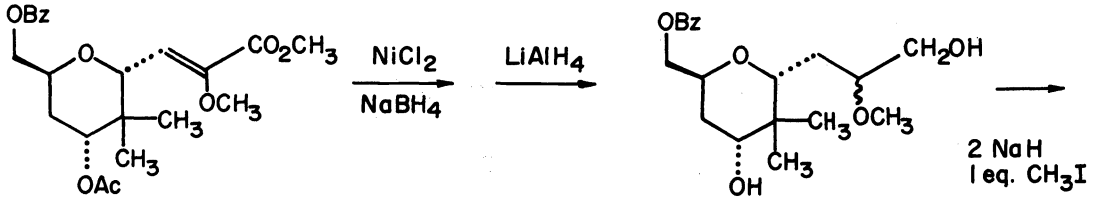


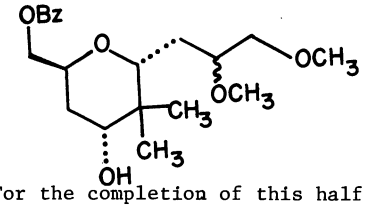
described and the secondary hydroxyl group thus liberated was acetylated. Hydrolysis of the dithiolane ring then gave the desired differentially protected tetrahydropyran aldehyde.

For the elaboration of the side chain, we developed a somewhat more efficient route. Methoxychloroacetic ester (17) was treated with trimethyl phosphite to give the corresponding phosphonate ester, which condensed smoothly with the aldehyde to give the desired

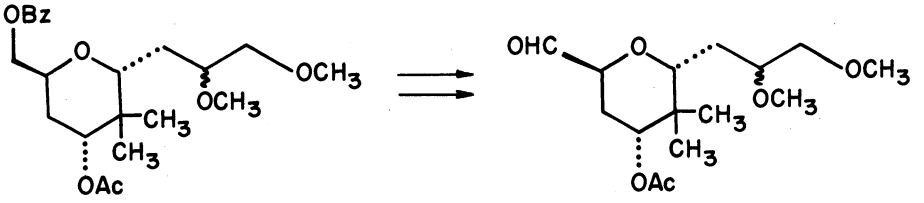


α-methoxy-α,β-unsaturated ester in one step. As before, sodium borohydride-nickel chloride reduction gave the saturated ester and complex hydride reduction converted the ester function into the primary alcohol while at the same time removing the acetate from the secondary hydroxyl group. In spite of the presence of two hydroxyl groups in this intermediate, selective methylation at the primary site using two equivalents of sodium hydride and one equivalent of methyl iodide proceeded well.



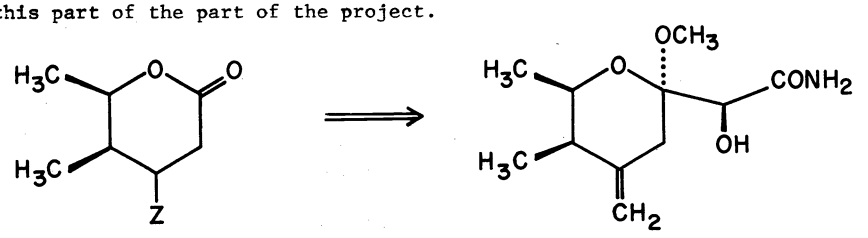


For the completion of this half of the pederin molecule, it remained only to remove the benzyl protecting group and to oxidize the resulting primary alcohol to an aldehyde. After reacetylating the secondary hydroxyl group to give a product whose epimers could be separated by TLC, catalytic hydrogenolysis and chromium trioxide-pyridine oxidation gave the final aldehyde. The intermediate we will need for coupling experiments to give pederin itself is therefore in hand.

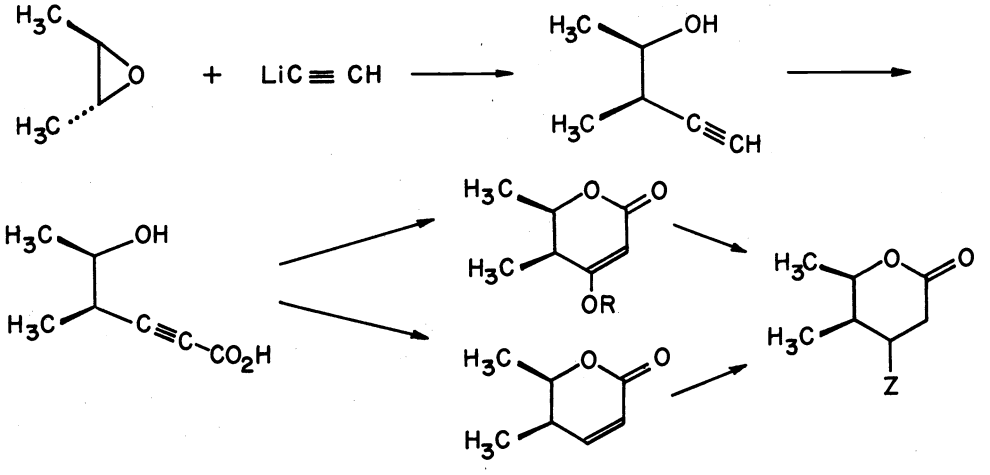


TLC separation of epimers

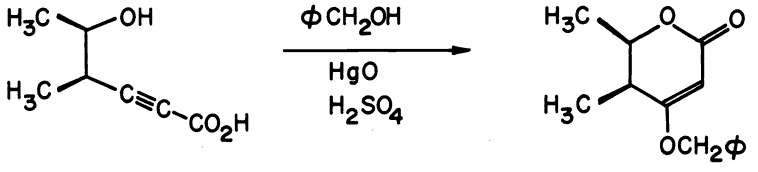
Our plan for the synthesis of the amide portion of the pederin molecule was based on the expectation that if a suitably substituted δ-valerolactone were prepared, a method for replacing the lactonic carbonyl group by geminal methoxy and hydroxyacetamido substituents could be developed. Although some key steps remain to be carried out, we are close to our goal with this part of the part of the project.



Starting with trans-2- butene epoxide, (which can be prepared optically active and with the appropriate absolute configuration from natural, optically active butane-2,3-diol), nucleophilic opening of the epoxide ring with lithium acetylide, followed by carboxylation of the acetylenic anion, gives the expected acetylenic acid (19). We have used this intermediate in two ways to produce two promising δ-lactones.



Mercuric ion catalyzed addition of benzyl alcohol to the triple bond of the acetylenic acid, followed by lactonization, gives the δ-benzyloxy-α,β-unsaturated δ-valerolactone. While treatment with hydrogen over palladium on carbon results in hydrogenolysis of the benzyl



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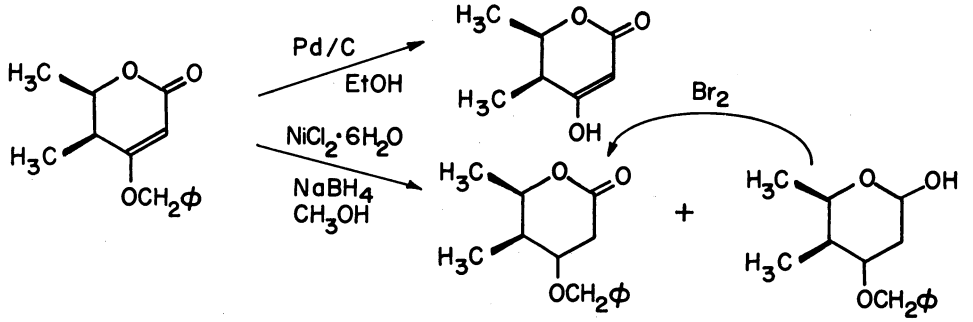
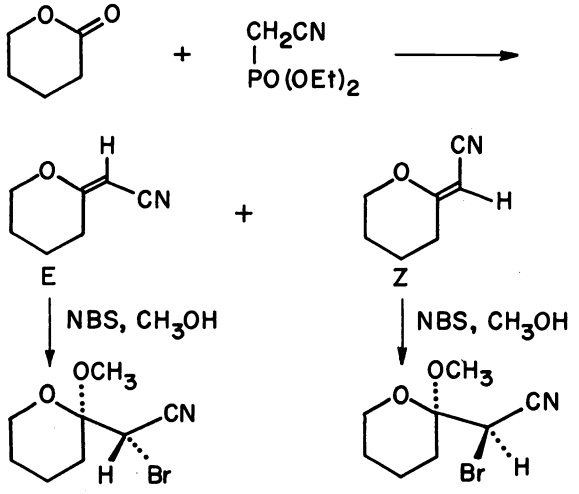
group, reduction with sodium borohydride and nickel chloride gave a mixture of the saturated lactone and the over-reduced saturated hemiacetal. Treatment of the mixture with bromine resulted in a smooth oxidation of the hemiacetal, giving the pure saturated lactone.

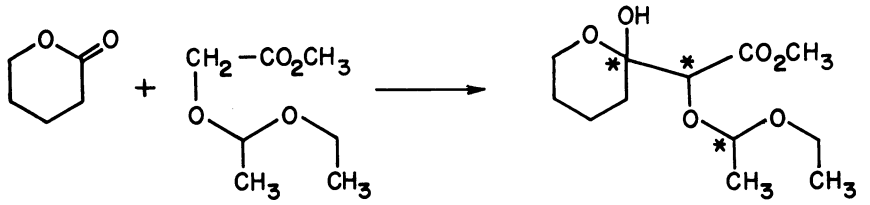


The task of elaborating the necessary side-chain was first studied using δ-valerolactone itself as a model compound. We were very pleased to find that the anion of the diethyl ester of cyanomethylphosphonic acid condensed readily with this lactone to give a mixture consisting chiefly of the E and Z isomers of the hoped for α,β-unsaturated nitrile. These isomers could be separated by thin-layer chromatography, and each gave, with about 85% stereospecificity, the anticipated bromo-methoxy adduct upon treatment with N-bromosuccinimide in methanol. Most disappointingly, however, no conditions were found under

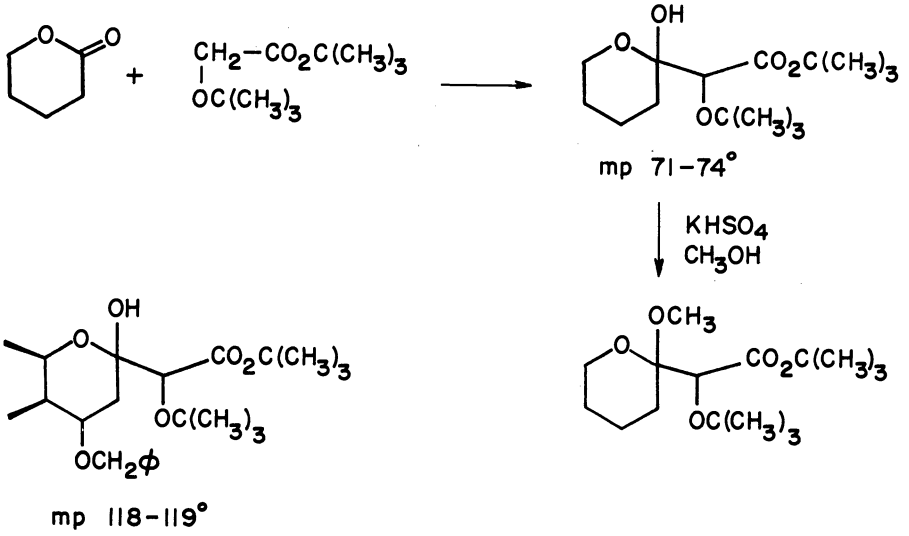


which the bromine in these adducts could be replaced by hydroxy or acetoxy substituents. Neither crown ethers nor phase transfer catalysts were helpful, and ultimately this simple approach to the hydroxy-amide side-chain had to be given up. Other approaches toward advantageous use of these unsaturated nitriles were similarly frustrating. Thus attempts to form the epoxy-amide by treatment with hydroperoxide anion were unrewarding, and oxygen trapping (20) of the nitrile anion generated by Michael addition of methoxide ion to the conjugated system also failed.

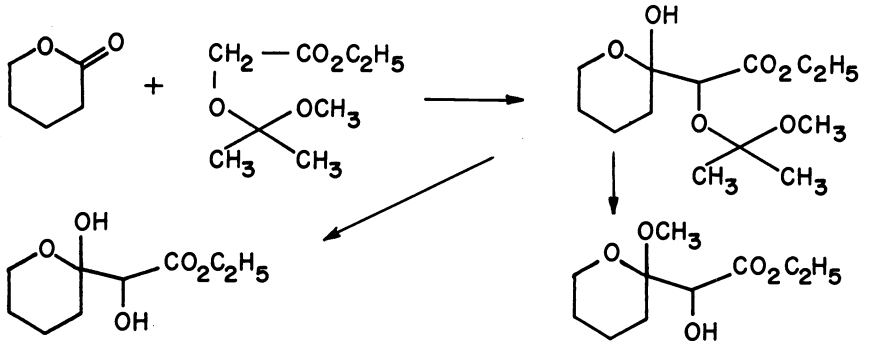
In view of these results, the possibility of adding a protected glycolic acid derivative (21) to δ-valerolactone was explored. Initial experiments with the base-catalyzed condensation of the ethyl vinyl ether adduct of methyl glycolate and δ-valerolactone were encouraging. An 85% yield of crude aldol product was obtained by addition of the lithium enolate



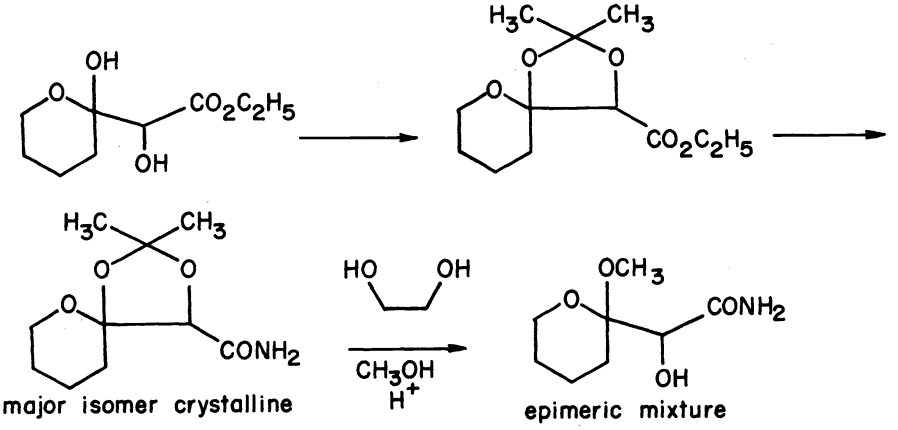
of this ester to δ-valerolactone. However, the desired aldol was contaminated by a self-condensation product derived from the methyl glycolate, and proton NMR spectral analysis was made unduly complicated by the presence of both a chiral and a prochiral center in the protected ester. To discourage self condensation and to simplify spectral analysis, the t-butyl ether of t-butyl glycolate was examined next. The corresponding enolate was found to add to δ-valerolactone at -78°C to give a good yield of crystalline adduct, which enchanged its angular hydroxyl group for a methoxyl group readily upon heating at reflux with potassium hydrogen sulfate in methanol. An analogous, crystalline adduct could also be prepared in excellent yield from our saturated benzyl lactone. Unfortunately, conditions could not be found for the conversion of this t-butyl ester into the corresponding amide,



and cleavage of the t-butyl ether function also proved more difficult than anticipated. Other protecting groups seemed to be called for, and we turned to the adduct of ethyl glycolate and isopropenyl methyl ether. The anion of this ester condensed readily with

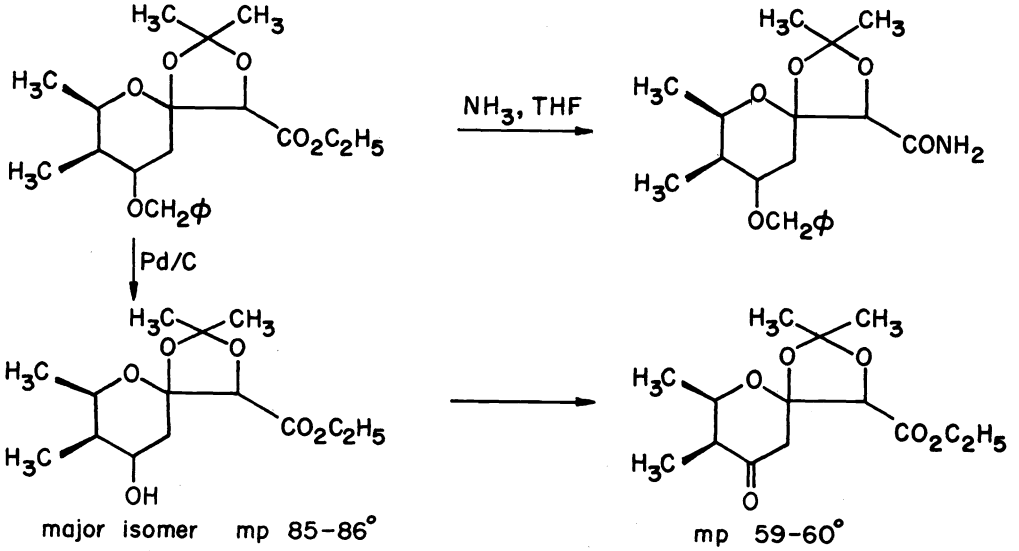


δ-valerolactone to give an adduct which was readily deprotected to give either the α-hydroxy ester or its angularly methoxylated analog. Because complications (not unexpectedly) were encountered in converting either of these esters into the corresponding amide, we decided to tie up the two adjacent oxygenated carbon atoms as their acetonide before carrying out ammonolysis of the ester function. The hydroxy hemiketal ester was transformed into a spiroacetonide using acetone with either phosphorous pentoxide or anhydrous copper (II) sulfate and p-toluenesulfonic acid. Treatment of the acetonide with aqueous ammonia then



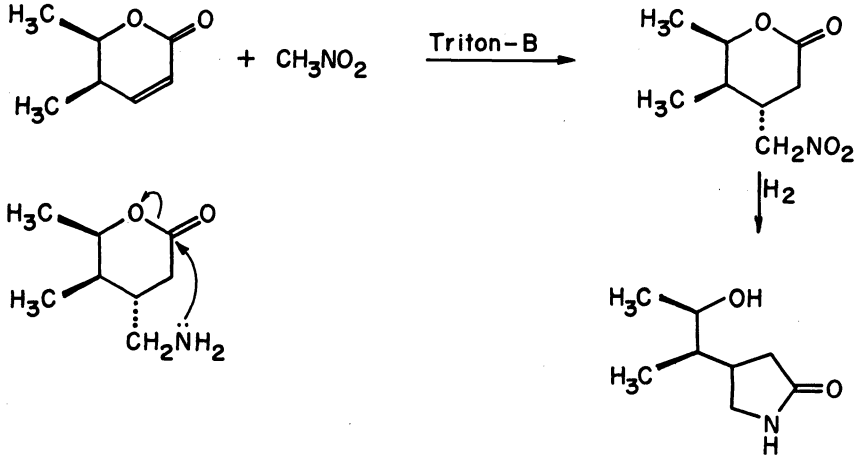
gave the anticipated amide. This amide was obtained as a mixture of stereoisomers, from which the major isomer was readily crystallized. The removal of the acetonide group was not a facile process, but in the presence of ethylene glycol, refluxing acidic methanol gave the angularly methoxylated hydroxy acetamide as a mixture of epimers, completing this phase of our model study.

The above-described reaction sequence was next carried out using the saturated cis-dimethylbenzyloxy lactone itself. In this way, the desired acetonide ethyl ester and acetonide amide were prepared without difficulty. Hydrogenolysis of the benzyl group in the ethyl



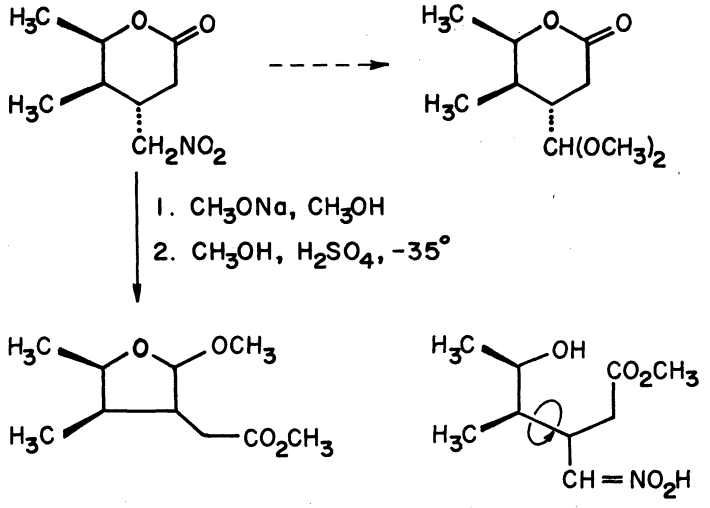
ester was accomplished in quantitative yield using 5% palladium on carbon in ethanol. The major stereoisomer of the resulting alcohol was obtained crystalline; pyridinium chlorochromate (22) in methylene chloride at room temperature gave the corresponding ketone as a single, crystalline stereoisomer. We are hopeful that there will not be insurmountable barriers in the steps that remain to convert this key intermediate into the amide moiety of pederin itself.

Another approach to the same target amide diverged from the route just described at an early stage. Partial hydrogenation of the original hydroxy acetylenic acid over Lindlar catalyst gives the cis olefinic acid, which lactonizes upon distillation. The resulting α,β-unsaturated lactone undergoes a Michael addition with the anion of nitromethane, thus giving an intermediate which would seem especially promising for generation of the ultimately required exocyclic methylene group. As a step in this direction, the reduction of

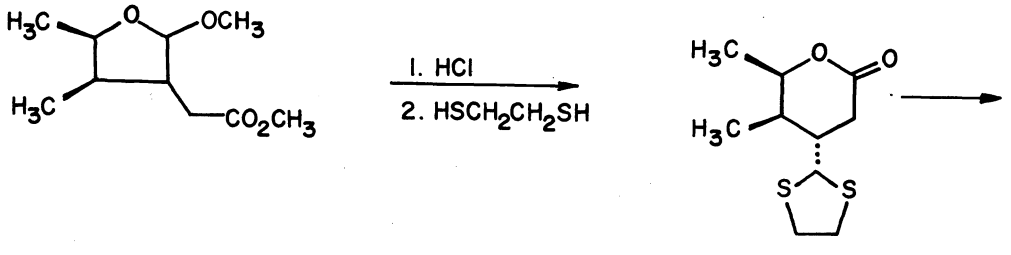


the nitro group to an amino group was investigated, but even in the presence of reagents which we hoped would convert the initially formed primary amine into its tertiary dimethyl derivative, an intramolecular displacement occurred to give an unwanted pyrrolidone.

In spite of this difficulty, we found that the Nef reaction provided a way in which we could make use of our nitromethylated lactone. Generation of the aci-nitro anion with sodium methoxide, followed by quenching in acidic methanol at low temperature (23), gave



a good yield of a rearranged cyclic acetal methyl ester. Treatment of this product with hydrogen and ethanedithiol then gave the desired δ-lactone dithiolane. This lactone, when



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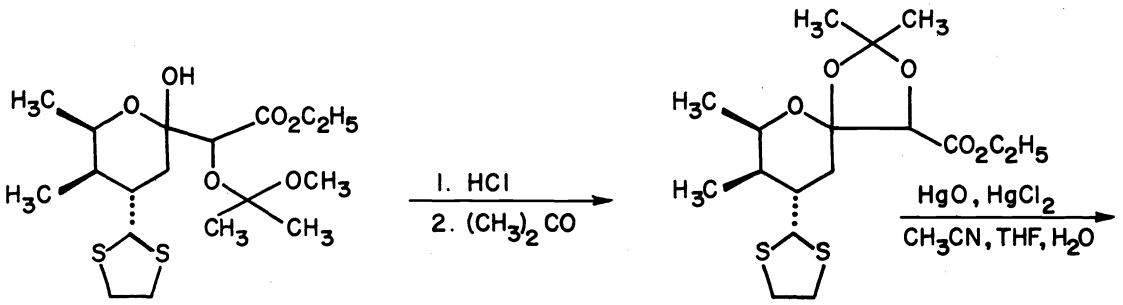
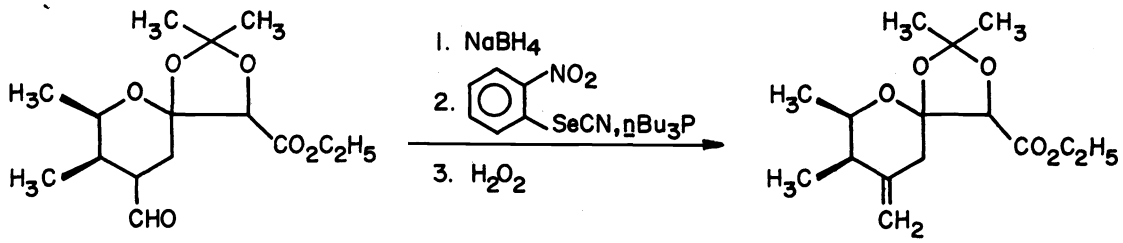
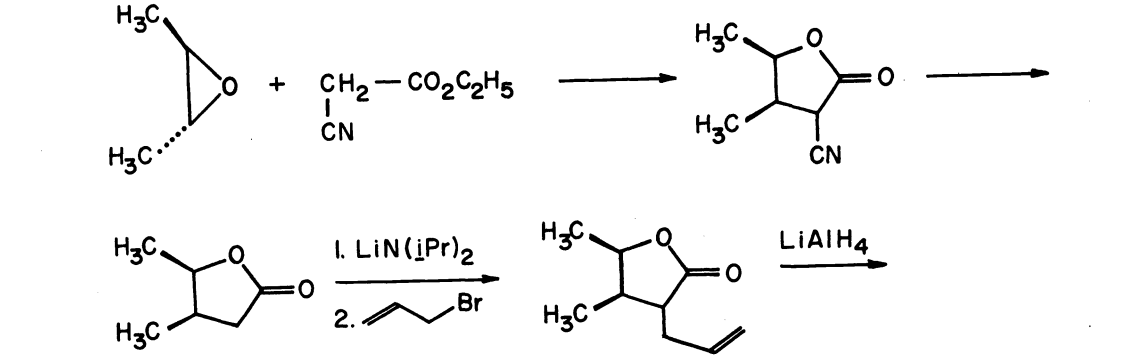
subjected to the reaction sequence already described for introduction of the necessary side-chain, yielded an acetonide ester bearing the additional dithiolane substituent on its tetrahydropyran ring. Mercuric ion catalyzed removal of the sulfur-containing protecting



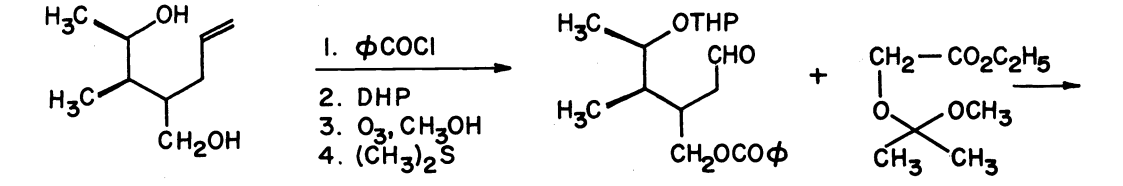


group led to the expected aldehyde, which could be reduced and then dehydrated (24) to give an exomethylenic acetonide ethyl ester. Once more, we are optimistic about being able to carry out the necessary remaining operations on the side chain of this intermediate.

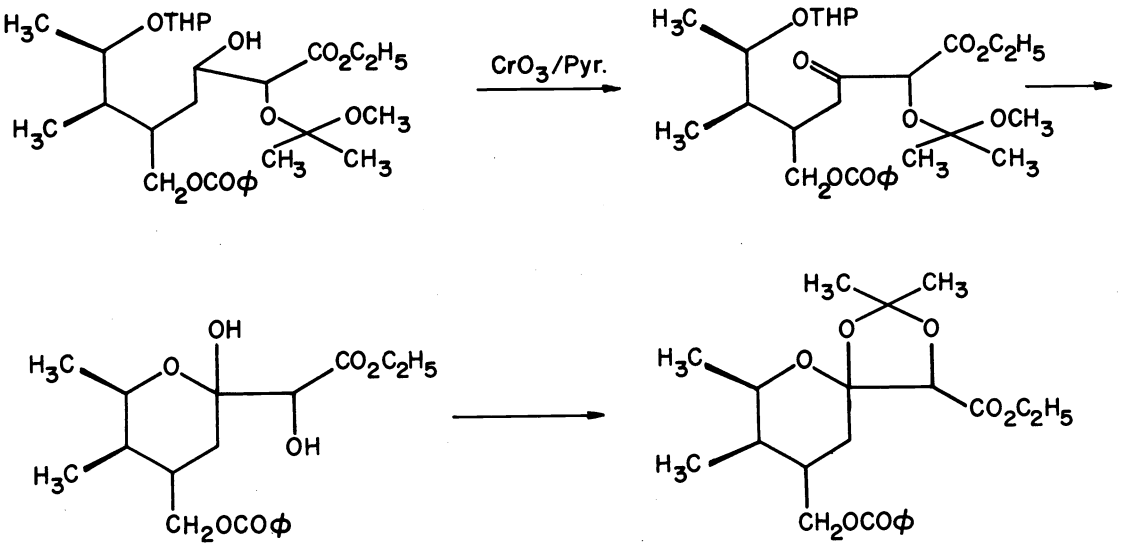
A third approach to the amide moiety of pederin also starts from trans-2-butene epoxide. Nucleophilic opening of this epoxide with ethyl cyanoacetate anion followed by hydrolysis and decarboxylation, gives a cis-β,γ-dimethylbutyrolactone, which is smoothly alkylated by treatment with lithium diisopropyl amide followed by allyl bromide. Lithium aluminum



hydride reduction gives a diol which is selectively benzoylated at the primary site by treatment with benzoyl chloride. Protection of the secondary alcohol as its tetrahydropyranyl ether, followed by ozonolysis, gives the anticipated aldehyde. The previously described adduct of methyl isopropenyl ether and ethyl glycolate adds smoothly to this



aldehyde and the resulting β-hydroxy ester is oxidized by chromium trioxide in pyridine to the corresponding ketone. Acid-catalyzed removal of the two acid-labile protecting groups gives an α-hydroxy ester as its cyclic hemiketal, and acetonide formation gives the desired spiroacetonide, closely related to our two previously described spiroacetonide intermediates. Which of these three approaches to the amide moiety of pederin finally



proves the most useful will depend on a detailed comparison of the reaction sequences, once each of the routes has reached its goal.

The problem of joining the two major pederin fragments to give pederin itself is a challenging one. Fortunately, however there are precedents for the construction of the required type of aza-acetal functionality (25). We should soon be at a stage where it will be appropriate to examine in detail how the coupling of the two tetrahydropyran moieties can be accomplished. We look forward to reaching the final stages of this effort, as well as to being able to simplify some of our reaction sequences. We also hope to develop a greater degree of stereochemical control in several of the reaction steps. While any synthesis we may be able to devise is hardly likely to compete in elegance with the still largely unraveled biosynthetic pathway followed by the beetles themselves (26), we should have an advantage in being able to prepare structural and stereochemical variants of natural pederin, as well as specifically labelled pederin. We hope these materials may be of utility in exploring the structural requirements for the diverse biological activities associated with this intriguing molecule, and in studying the mechanisms underlying its biological activities.

It remains for me to acknowledge the extensive contributions made to this project by my co-workers, who have not only carried out all of the experimental work, but also participated intimately in the planning of the approaches which we followed. Paul Brynes and Joshua Chong initiated the project, and their efforts were continued by Allan Wissner, Rawls Frazier, Joel Smolanoff, Angelina Duggan, C.Y. Ho, and Michael Adams. Marie-Claire Lasne made contributions both to the synthetic work and to the study of the ^{13}C spectra of our intermediates. I am also grateful to Tappey Jones and to Jonathan Zweig for their participation in this undertaking. Most recently, the pederin team has been joined by Ralph Volante, whose contributions have been substantial, although they have not been described in this account.

As every chemist knows, the pursuit of the synthesis of a complex natural product requires not only careful planning, skilled execution, and adequate facilities, but also money. I should like to conclude by thanking the American Cancer Society for their generous financial support of our pederin work, the National Institutes of Health for the post-doctoral fellowship awards which have provided us with substantial additional help, and our industrial-scientific friends at Hoffmann-La Roche, Upjohn and Eli Lilly for grants-in-aid which have made possible a most appreciated flexibility in our overall research program.

I dedicate this paper, on the occasion of his sixtieth birthday, to Professor R.B. Woodward, whose exemplary teaching and tenaciously inquiring spirit have served as models without peer.

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