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RECENT STUDIES ON THE SYNTHESIS OF NATURAL PRODUCTS

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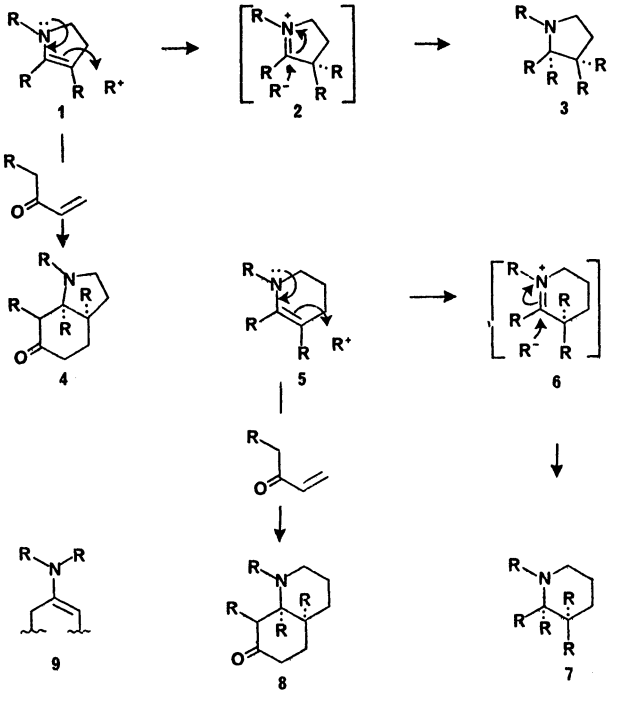
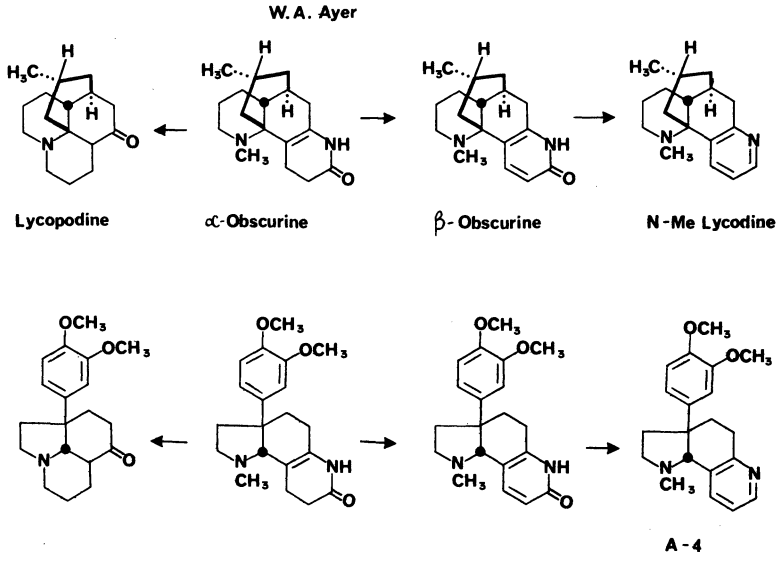
Synthetic chemists have always marveled at Nature's ability to elaborate a fantastic variety of structurally diverse and frequently very complex substances from a few relatively simple starting materials. Plants, for example, manufacture thousands of alkaloids from CO_2 -- a one carbon synthon! The total synthesis of alkaloids has occupied a central role in natural products chemistry for many years. Landenberg is credited with having synthesized the first alkaloid, coiine in 1886. This was followed at the turn of the century by nicotine, papaverine and the famous Robinson-Schöpf synthesis of atropine. Subsequent progress in alkaloid synthesis was rather slow to develop until 1944, when Woodward announced his landmark synthesis of quinine. In 1952, Gates published the first synthesis of morphine, and shortly thereafter Woodward announced that strychnine had been conquered. These accomplishments served as milestones for contemporary organic synthesis and have been followed by many other notable achievements which have contributed to "the art and science" of organic chemistry as a whole.

Our own program in alkaloid synthesis was initiated over a decade ago and was concerned with the development of general methodology for the facile elaboration of a whole host of structurally quite diverse families of alkaloids. In particular we were able to demonstrate the utility of endocyclic enamine synthons such as 1 and 5. Although the synthesis and

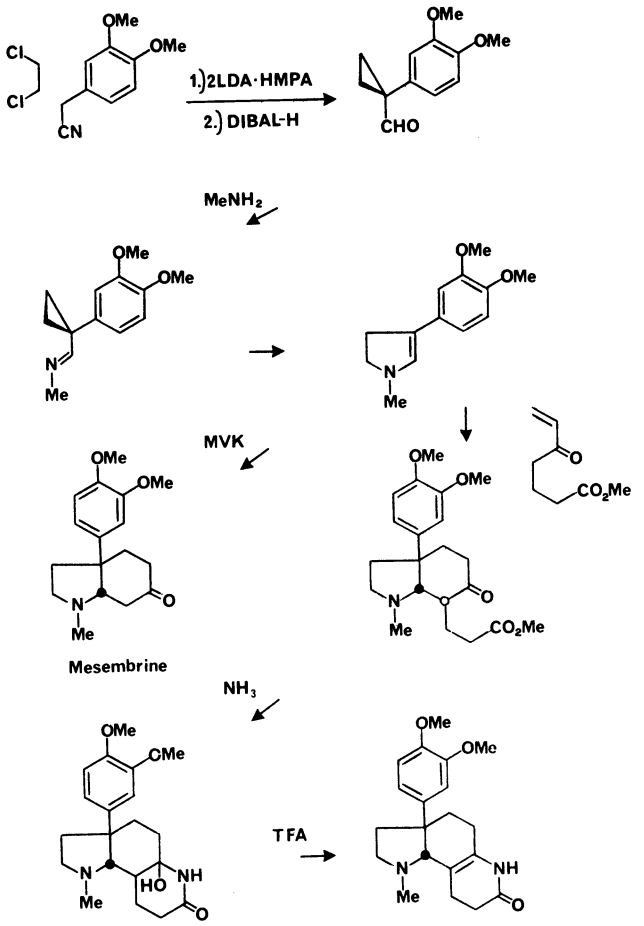


chemistry of exocyclic enamines (9) had been developed continuously for well over two decades, it seemed remarkable to us that from the standpoint of alkaloid synthesis their endocyclic counterparts (1 and 5) had been largely ignored. It is interesting to note that in those alkaloids where a pyrrolidine (or pyrroline) ring is discernible, one almost invariably finds nuclear "substitution" on only one side of the molecule; the other side is usually devoid of any substituents (see 3). By analogy with their exocyclic counterparts, we reasoned that endocyclic enamines 1 and 5 should react with electrophilic reagents on the β-carbon. It should be noted further that such a process simultaneously renders the α-carbon electrophilic and therefore susceptible to capture by nucleophilic reagents as depicted in 2 and 6. In this fashion we anticipated that the substitution pattern noted above might readily be elaborated. Further scrutiny of these alkaloids reveals that many of them incorporate either a hydroindolone (4) or hydroquinolone (8) moiety into their nucleus. We felt that annulation of endocyclic enamines 1 and 5 with methyl vinyl ketone, or derivatives thereof, might provide a facile entry into these fused ring systems. These thoughts set the stage for a remarkably general approach to alkaloid synthesis.

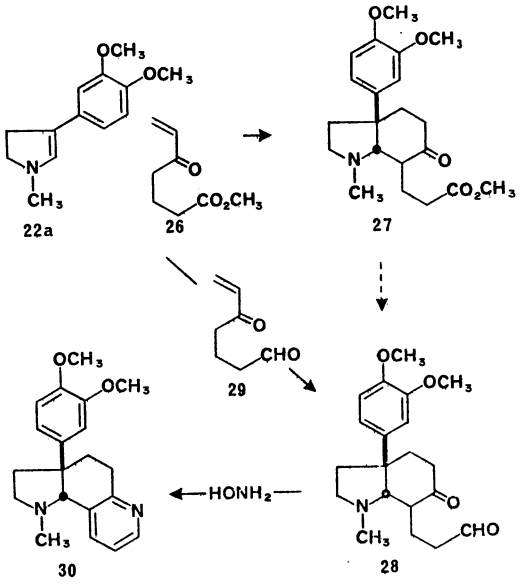
To illustrate the utility of these concepts I would like to turn your attention to the Sceletium alkaloids -- particularly one designated as A-4. By analogy with the biosynthetically unrelated lycopodine family we reasoned that in addition to A-4 one might also find pyridone rings or quite possibly even structurally rearranged isomers. Our synthetic plan took this possibility into account.



The requisite endocyclic enamine was prepared efficiently by means of the acid catalyzed cyclopropylimine rearrangement. Annulation with methyl vinyl ketone affords the prototype Sceletium alkaloid-mesembrine. Alternatively, annulation with the substituted enone shown provided an intermediate which incorporates all of the necessary carbons. This substance was readily converted to the corresponding dihydropyridone. As a footnote, as we had anticipated, this substance was subsequently found in the plant by Professor Jeffs of Duke University -- an interesting case where total synthesis preceded structure elucidation.



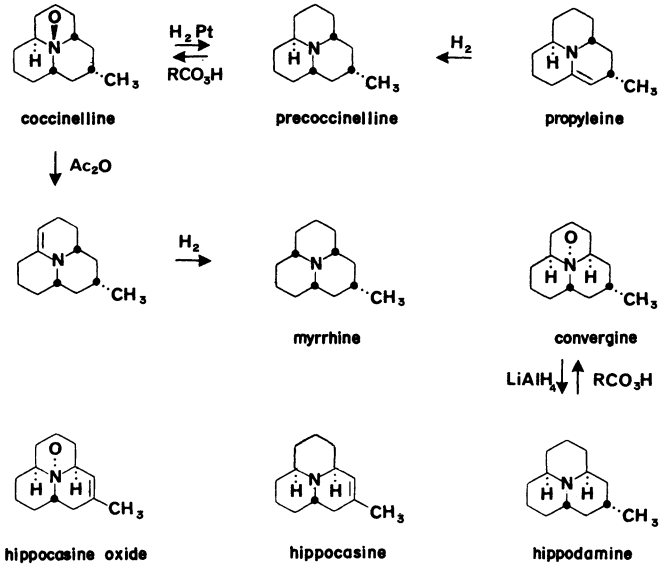
The synthesis of Sceletium A-4 itself required adjustment of the ester function to an aldehyde, and this was achieved by protection of the ketone as a dimethyl ketal followed by controlled reduction with i-Bu_2AlH. Treatment of the ketal aldehyde with $NH_2OH \cdot HCl$ in ethanol-water afforded the natural product.



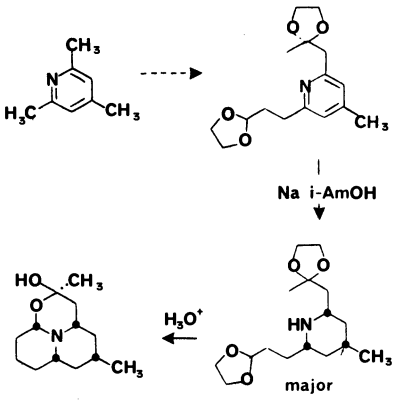
Although we are continuing to exploit this new methodology, I should like to turn our attention to some very old methodology and its application to a very contemporary problem in alkaloid chemistry -- insect pheremones. The Coccinellidae family (ladybugs) have long been valued by farmers and children throughout the world which lead to the old English rhyme:

"Ladybug, ladybug,
fly away home,
Your house is on fire,
and your children will burn!"

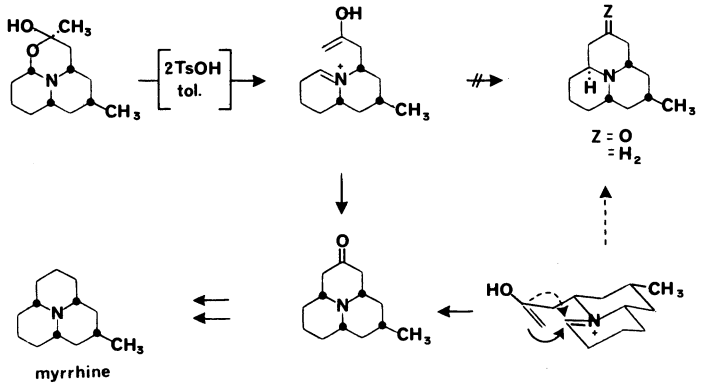
The various species of ladybugs play an important role in controlling plant pest populations. A dramatic example occurred in California in the late 1800's when the Australian cottony cushion scale insect (Icerya purchasi) was accidentally introduced and threatened to destroy the valuable citrus orchards. Entomologists them imported its natural predator the Australian ladybug Rodolia cardinolis which conquered the menace within two years. When alarmed, ladybugs exude a yellowish, bitter fluid which serves as an effective defense mechanism against predators. Recently, the structures of several new alkaloids has emerged. The structures of those bases which are known to date and some of their chemical interconversions are shown below.



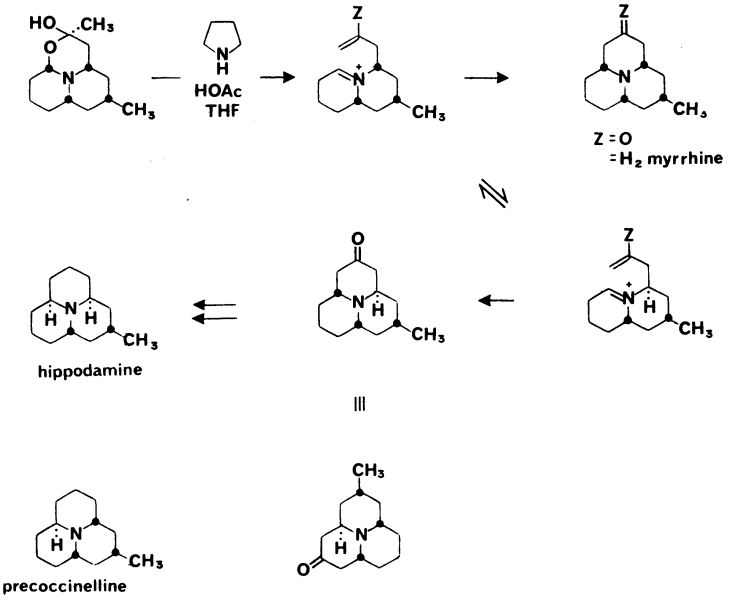
The synthesis of each of the saturated alkaloids has been reported recently by Professor Ayer's group of Alberta. A key intermediate was prepared from 2,4,6-collidine by the convenient sequence outlined:



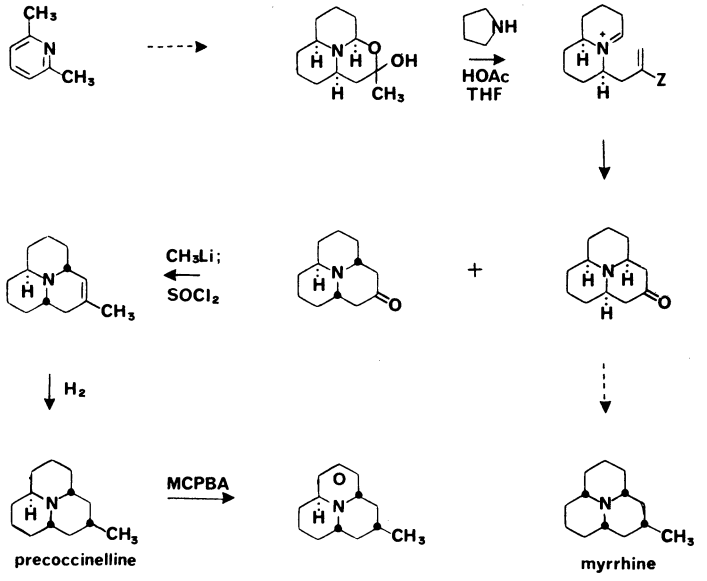
When exposed to TsOH in hot toluene this intermediate cyclized to a ketone possessing the myrrhine stereochemistry. Clearly this is the result of a thermodynamically controlled reaction.



Under less vigorous conditions the myrrhine ketone was also produced together with an isomeric ketone which turned out to have the hippodamine stereochemistry resulting from a subtle epimerization of the iminium salt. Professor Ayer astutely realized that the hippodamine ketone incorporates the same relative stereochemistry as that found in precoccinelline except for the methyl group:



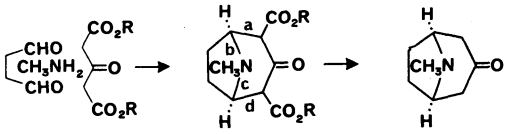
By employing 2,6-lutidine rather than 2,4,6-collidine in the same sequence of reactions he was able to generate a mixture of two ketones possessing the myrrhine and precoccinelline stereochemistry:

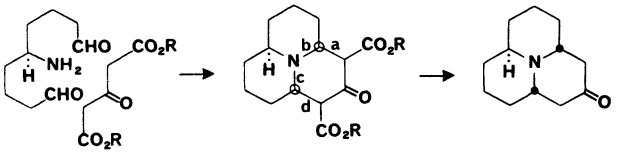


Our own interest in these alkaloids came from a consideration of one of the oldest reactions in alkaloid synthesis -- mainly, the famous Robinson-Schöpf reaction. This remarkable reaction generates four new bonds in a single process which I have designated as a,b,c,d. Now, inspection of these tricyclic alkaloids reveals four virtually identical bonds could be generated from an amine dialdehyde and acetone dicarboxylic ester. It seemed to us that such

a reaction should occur with almost mathematical certainty and for that reason very nearly abandoned such an approach until we realized that there was a much more fundamental question to be raised -- stereochemistry.

Robinson - Schöpf Reaction





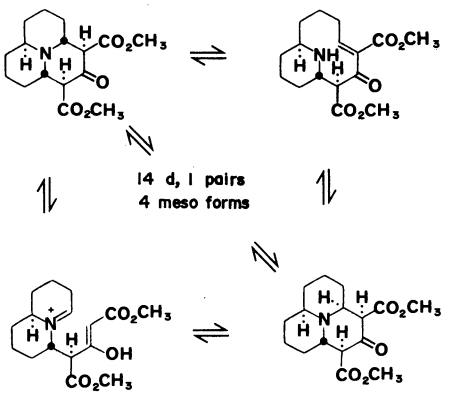
As Professor Ayer's studies clearly demonstrated -- the precoccinelline skeleton is the thermodynamically least stable of the saturated bases:

precoccinelline
meso

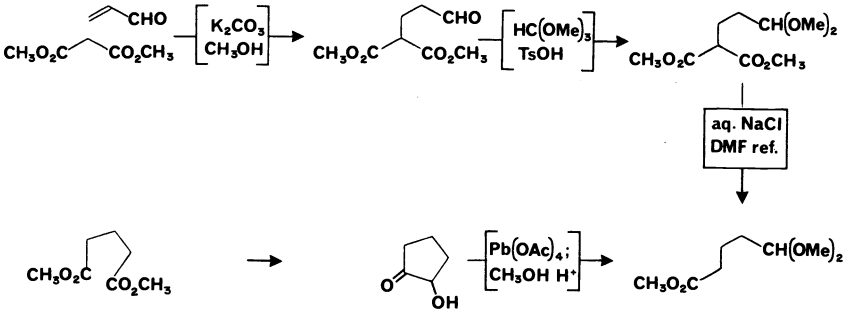
myrrhine
meso

hippodamine
(dl)

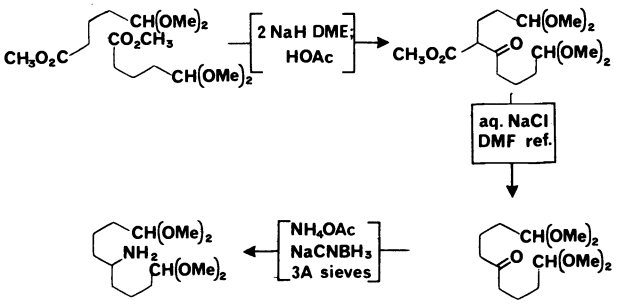
Furthermore, in the approach we envisaged there is the distinct possibility that all of the chiral centers will be scrambled by either retro-Mannich or retro-Michael reactions. Therefore, what appeared at first glance to be a method which could not fail, on reflection, became a method in which many potential perils were clearly discernible. We therefore initiated a study to determine the stereochemical course of the Robinson-Schöpf reaction under kinetically controlled conditions.



The necessary starting material we selected was an acetal-ester which had been prepared previously from $Pb(OAc)_4$ oxidation of α-hydroxycyclopentanone. We prepared this substance by the alternate method shown:

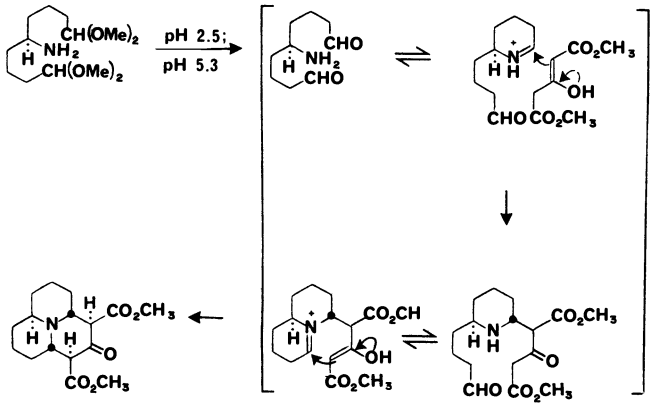


Self-Dieckmann condensation and decarbomethoxylation afforded a ketone which was reductively aminated via the Borch procedure:



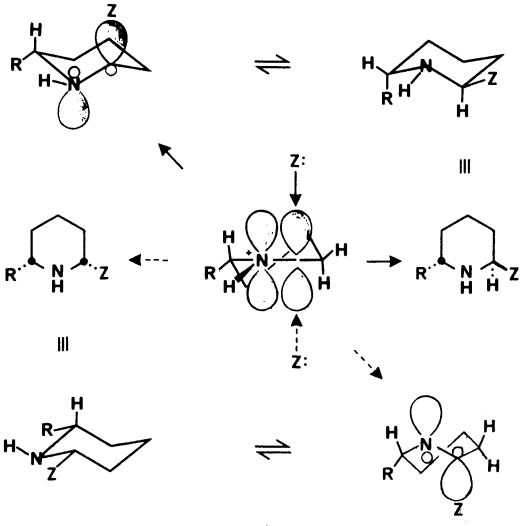
With the amine acetal in hand we were ready for the crucial experiment which I can only describe as one of the most delightful in my career. After acidification with hydrochloric acid to hydrolyze the acetal moieties the pH of the solution is adjusted to 5.3 and buffered. Addition of methyl acetone dicarboxylic ester produces a clear aqueous solution which slowly turns cloudy and after a period of time crystals appear. Without extraction the aqueous solution was filtered to collect the crystals which corresponded to a greater than 70% yield of a single product! In view of the potential hazards documented above you can imagine our

delight in securing this result which also suggested something of fundamental interest concerning the stereochemistry of the Robinson-Schopf reaction. With the aid of spectral data, especially the infrared spectrum which was devoid of trans-quinolizidine bands in the 2700 - 2800 cm^{-1} region and the CMR spectrum which showed the compound was meso, we were able to assign the stereochemistry as indicated.



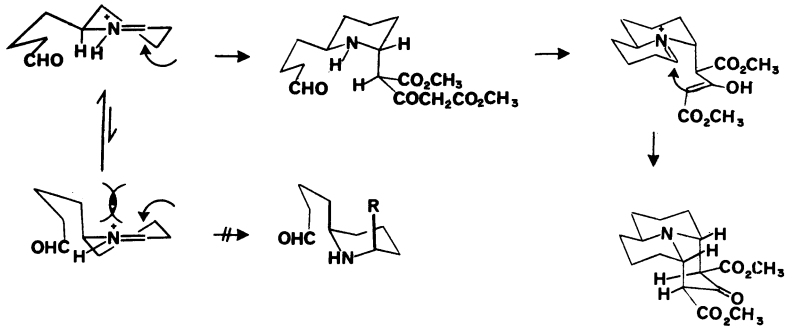
We believe the stereochemical course of this reaction is determined by the fundamental principle of maximum orbital overlap in the transition for this kinetically controlled process. Inspection of models reveals that nucleophilic addition to cyclic imminium salts of this type can occur via two possible pathways both of which maximize orbital overlap. However, one must proceed via a boat-like transition state and in the absence of other considerations it is necessarily one of higher energy:

Principle of Maximum Obital Overlap - kinetic control

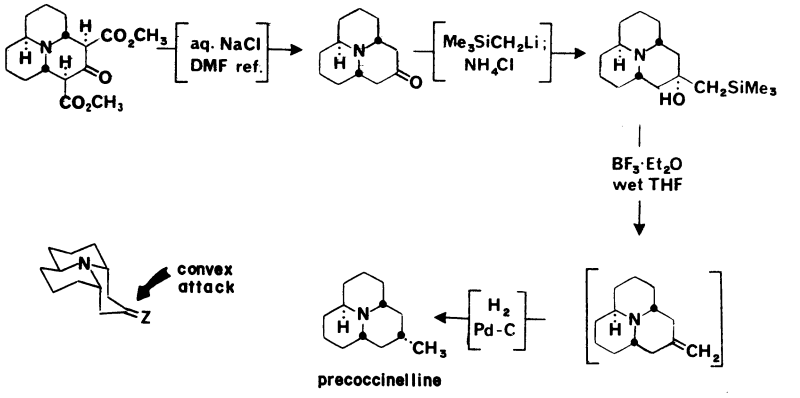


A complete analysis in the case at hand is shown below. It should be noted that there are two possible half-chair conformations for this intermediate. Even though the one with an equatorially disposed side chain will undoubtedly be favored, the other (less populated)

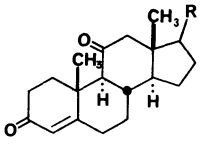
conformation should not be dismissed from consideration a priori for it might react faster kinetically. However, such a possibility could be ruled out in this case when coupled with the additional requirement for a chair-like transition state. Clearly, such attack is hindered in this case.



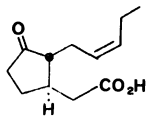
The final stages of our synthesis are outlined below. The esters were removed under essentially neutral conditions to minimize any possible epimerizations. The tricyclic ketone was sluggish to react with Wittig reagents but reacted smoothly with the silyl lithium reagent to generate an intermediate which we assume has the stereochemistry shown (convex attack). In view of Professor Ayer's observations concerning the lability of olefins in this series we decided to generate the double bond in situ under reducing conditions. In this fashion we were able to generate the methyl group of precoccinelline in one flask.



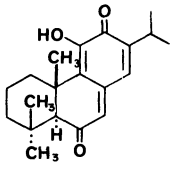
I would like now to turn our attention to rather different methodology which we have been investigating for the synthesis of natural products of the type shown below. In principle, one could employ the concept of homoconjugate addition to each of these targets. However, a serious problem encountered frequently in such reactions is a competing or predominant 1,2-carbonyl addition process.



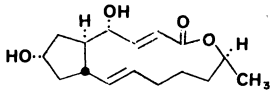
CORTICOSTEROIDS



JASMONIC ACID

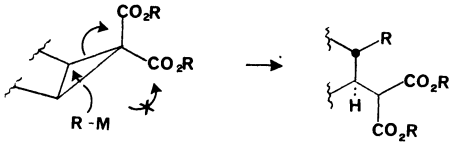


TAXODIONE

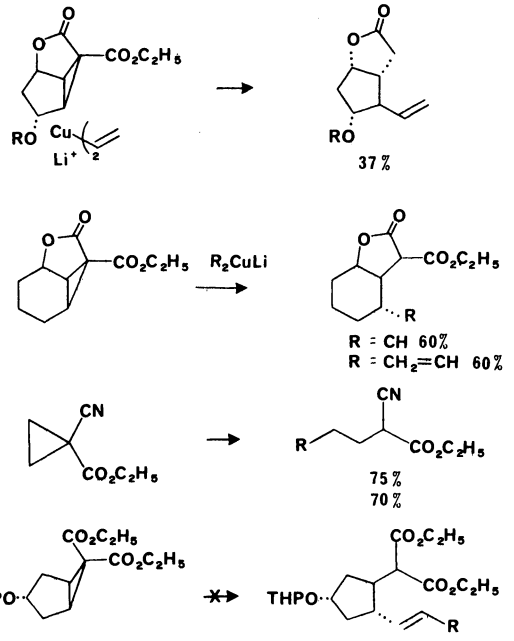


BREFELDIN A

"HOMOCONJUGATE ADDITION"



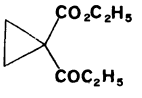
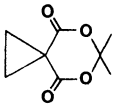
I have outlined below a few well-known examples of homoconjugate additions. You will note that in some cases the reaction proceeds in modest yield. Of special interest to us is the last entry where the reaction failed entirely.



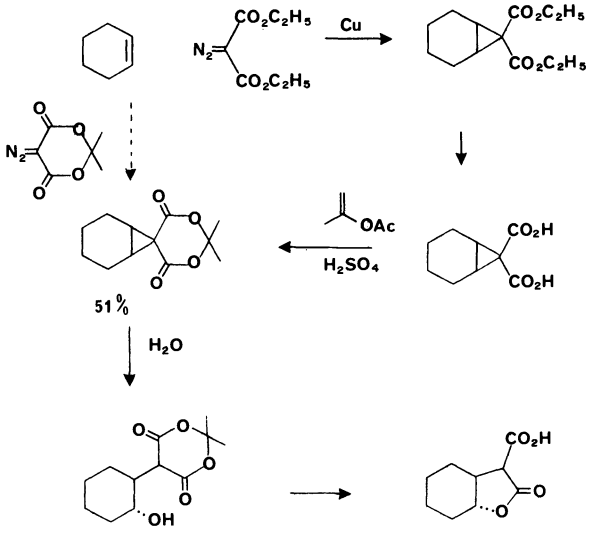
E. J. COREY ET AL., J. AM. CHEM. SOC., 94, 4014 (1972);
TETRAHEDRON LETT., 4705 (1976).

It occurred to us that desirable homoconjugate additions involving organometallic reagents might benefit substantially from the concept of "spiroactivation" introduced recently by Professor Danishefsky at the University of Pittsburgh. This group has convincingly demonstrated the enhanced reactivity of cyclic acylals towards a variety of nucleophiles other than organometallic ones. The following results are typical:

"SPIROACTIVATION" DANISHEFSKY

NUCLEOPHILE		
H_2 PD-C	NO REACTION	100%
PIPERIDINE	VERY SLOW	100% (5-10°, 30 MIN)
PYRIDINE	NO REACTION	92% (RT, 48 HR)

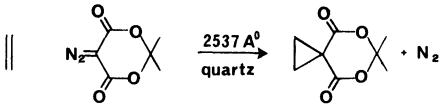
Nearly all of the cyclic acylals studied by this group were prepared by the indirect method outlined below. The conditions required to convert the malonate moiety into the spiroactivated cyclopropane were ill-suited for our purposes. Unfortunately, the direct copper catalyzed method fails.



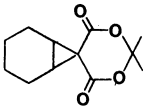
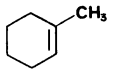
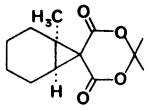
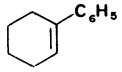
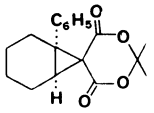
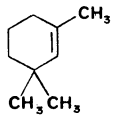
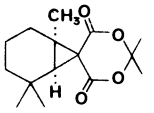
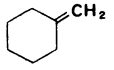
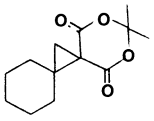
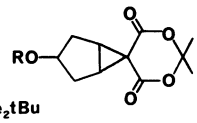
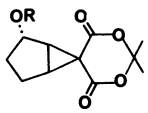
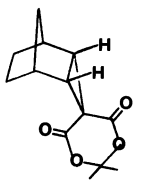
DANISHEFSKY AND SINGH, J. ORG. CHEM., 41, 1668 (1976)

We have now examined in some detail the photochemical decomposition of diazo Meldrum's acid in the presence of a variety of olefins:

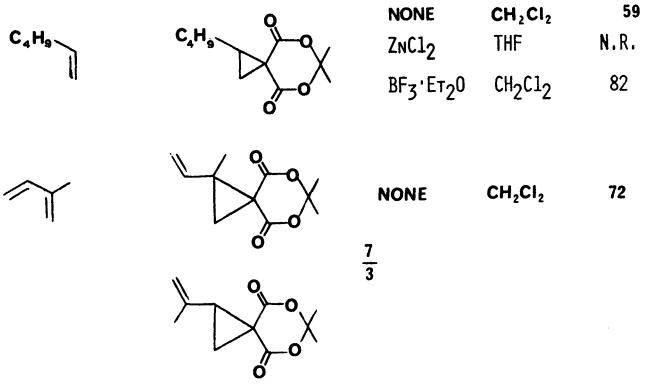
PHOTOCHEMICAL CYCLOPROPANATIONS



We have found the reaction to be quite general as the following tables indicate. In some cases the yields of cycloadduct can be improved substantially by the employment of a Lewis acid catalyst (either $ZnCl_2$ or BF_3). The precise nature of the catalytic effect remains unknown but in some cases can be quite dramatic. In other cases the catalyst had a deleterious effect presumably due to the lability of some of the cycloadducts themselves.

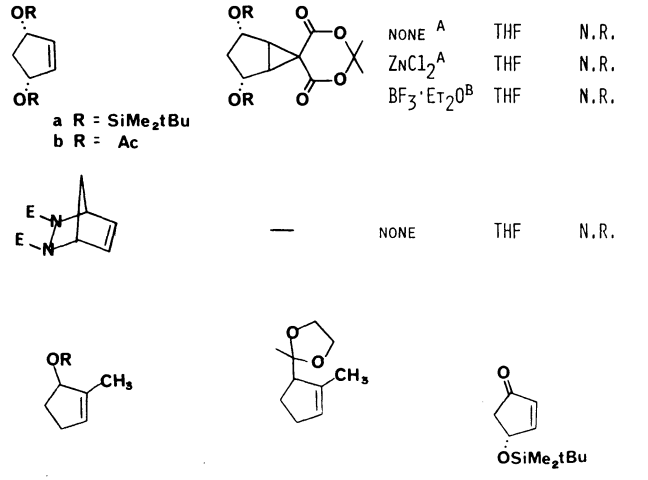
Olefin	Product	Catalyst	Solvent	% Yield
		NONE	CH_2Cl_2	66
		$ZnCl_2$	THF	84
		NONE	CH_2Cl_2	76
		$ZnCl_2$	THF	POLYMER
		NONE	CH_2Cl_2	54
		NONE	CH_2Cl_2	64
		NONE	CH_2Cl_2	87
 R = $SiMe_2tBu$		$ZnCl_2$	THF	70 ANTI 13 SYN
		NONE	CH_2Cl_2	73
		NONE	THF	40 Exo-Endo

It is interesting to note that in the case of isoprene, attack on the more substituted hence more nucleophilic double bond occurs preferentially. Quite possibly then, selective additions may be possible in systems containing isolated double bonds of different types although this has yet to be tested.

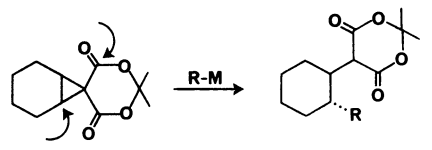


It should also be noted that olefins which are electronically deficient, either by direct conjugation or via inductive effects, fail to react further -- underscoring the electronically deficient character of the species undergoing reaction:

Olefins Which Fail to React



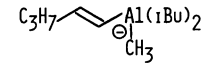
In spite of the above limitations it is clear that an impressive number of olefins can be induced to undergo cyclopropanation to produce these activated systems. With this foundation securely laid we turned our attention to homoconjugate openings with various organometallic reagents. Initial attempts were very frustrating. As the following table illustrates either no reaction was observed or complex mixtures were generated from a variety of organometallic reagents:



(1) R_2CuLi OR RMgBr + CuBr (CAT.) IN ETHER GIVE A COMPLEX MIXTURE

(2) RMgBr IN THF — NO REACTION

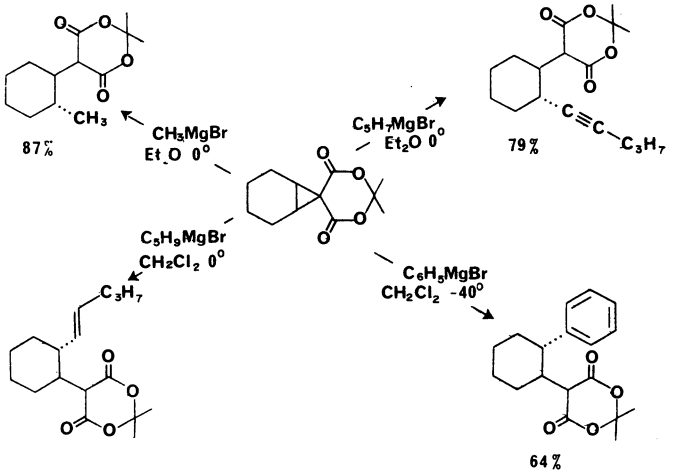
(3) RLi IN ETHER OR THF GIVE A COMPLEX MIXTURE

(4)  IN HEPTANE-ETHER REACTS VERY SLOWLY BUT PROVIDES A COMPLEX MIXTURE

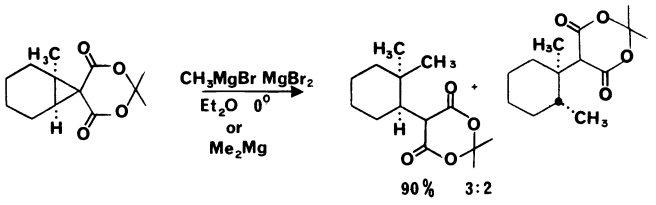
(5) $C_3H_7C{\equiv}C{-}Al(iBu)_2$ IN BENZENE GIVES A COMPLEX MIXTURE

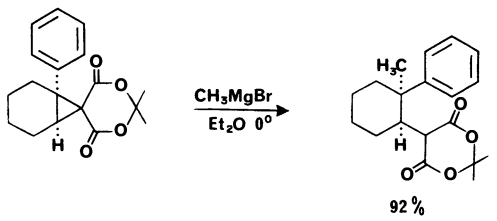
(6) RLi IN THF — HMPA GIVES EXCLUSIVELY 1,2 ADDITION

After considerable effort we discovered that simple Grignard reagents either in ether or in CH_2Cl_2 cleanly react in the desired homoconjugate manner. In this fashion we succeeded in adding alkyl, aryl, and acetylenic Grignard reagents. Curiously, we have been unable to add smoothly vinyl Grignard reagents under similar conditions.



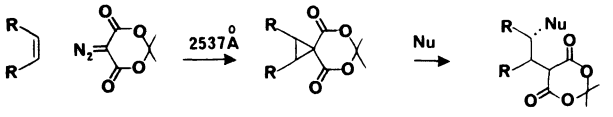
Addition to unsymmetrical systems proved to be interesting. Whereas most nucleophilic openings of unbiased three-membered rings occur <u>via</u> attack on the least substituted carbon, in the two cases shown below we observed that the major product was one of attack at the <u>most</u> substituted site -- an observation which played a role in our subsequent plans.



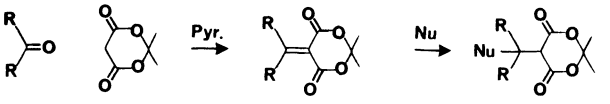


With these results in hand let us review the scope of this methodology in broad terms. By means of the photochemical addition process we are able to generate from olefins a variety of spiroactivated cyclopropanes. These intermediates, in turn, undergo homoconjugate addition reactions with various Grignard reagents (or other nucleophiles) to produce cyclic acylals substituted on the γ-carbon. A much older procedure involving simple conjugate addition can be employed to prepare derivatives substituted on the β-carbon. This brings us to the next consideration. Aside from their trivial hydrolysis and decarboxylation to substituted acetic acid derivatives, what other functional groups can be derived from this moiety.

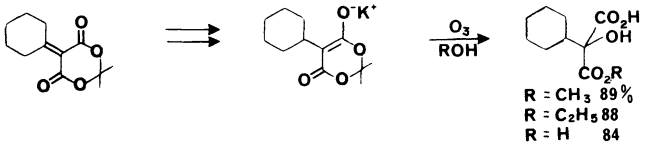
HOMOCONJUGATE ADDITION

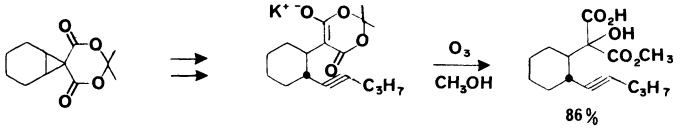


CONJUGATE ADDITION

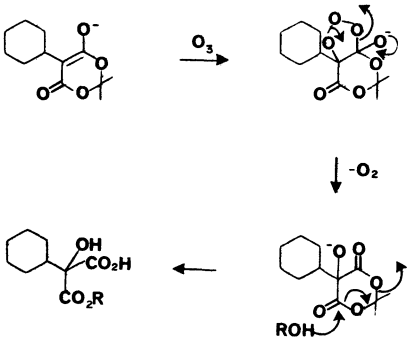


We have recently addressed ourselves to this question with some partially gratifying results. For example, we have found that the enolates react quite smoothly with ozone in hydroxylic solvents to insert a hydroxyl group between the two carboxyl groups. As the second example illustrates, this can be achieved even in the presence of an acetylene moiety which is of importance to our subsequent plans.

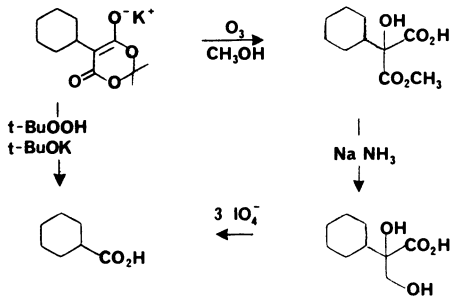




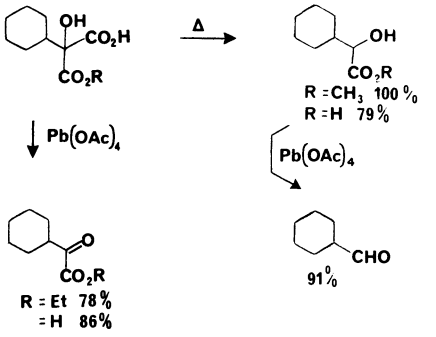
We suspect that the initial ozonide decomposes in the manner shown to produce an alkoxide intermediate which then undergoes hydrolysis to the acid derivative with ejection of acetone. Alternatively, the alkoxide intermediate may eject acetone by formation of an α-lactone derivative which would then suffer facile hydrolysis.



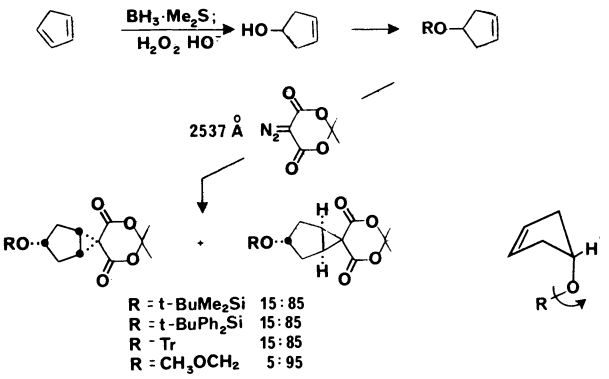
The hydroxyester can be reduced with Na/NH_3 to the corresponding acid diol and cleaved with periodate to a carboxylic acid. Alternatively, we discovered this can be achieved by direct treatment with basic t-BuOOH.



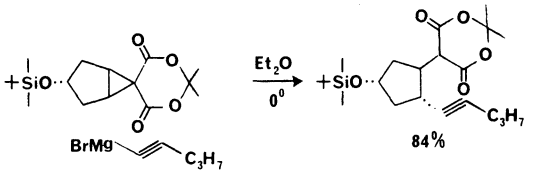
Other functional groups which can be generated readily from this intermediate include α-hydroxyesters, pyruvates and aldehydes:

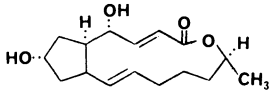


Having demonstrated the homoconjugate opening of these spiroactivated systems with organometallic reagents and several functional group manipulations of the resultant Meldrum's acid moiety we turned our attention to applications in the field of natural products synthesis. Brefeldin A was an obvious candidate. Photochemical cyclopropanation of various cyclopentenol derivatives proceeded in high yield to provide a mixture of regioisomers. Although the one we desired proved in all cases to be the major product, it was not until we employed the smaller methoxymethylene protecting group that a highly favorable ratio was produced. In short, the concept of increasing the size of the protecting group to shield against attack from that side failed -- the ratio seemed to be independent of the size of these very bulky protecting groups. In retrospect, this is precisely what one could have predicted with the aid of models. I have shown the conformation in which protection of the double bond would be maximized. However, when R becomes too bulky it can simply rotate away from the double bond leaving it partially exposed.

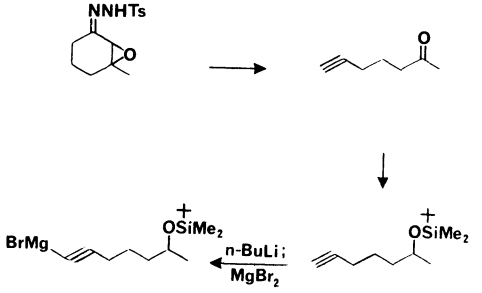


We were pleased to observe that homoconjugate addition occurred smoothly to open the cyclopropane with complete inversion of configuration. If we now compare this product with our target we see what is required for the synthesis of this substance. The Grignard reagent must incorporate a protected hydroxyl and the Meldrum's acid moiety must be transformed to an appropriate functional group for elaboration of the lactone ring.

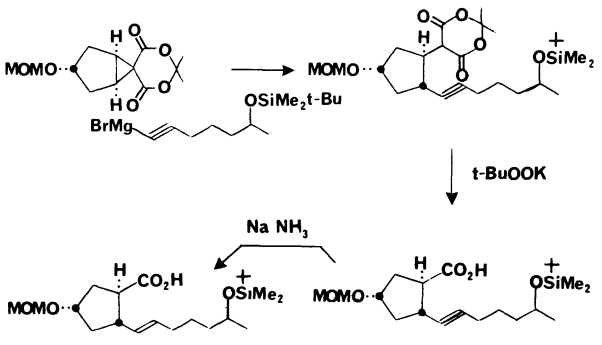




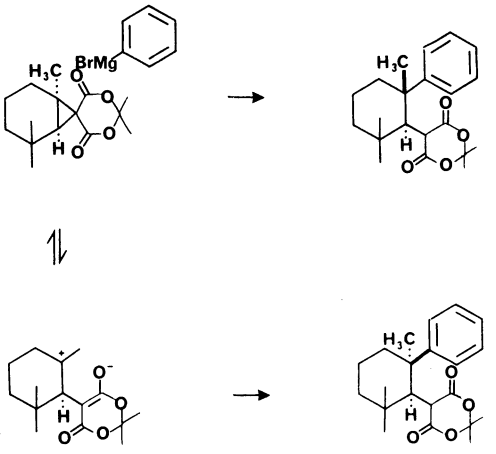
The requisite acetylenic Grignard reagent had already been prepared by the Crabbé group using the Tanabe-Eschenmoser fragmentation as a key step.



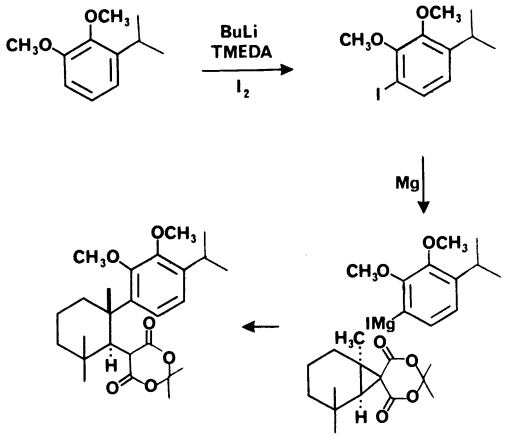
The crucial combination of synthons proceeded without incident. Further deployment of this intermediate could proceed along several lines. At the time of this writing we have simply degraded the side chain to a carboxylic acid by means of basic t-BuOOH. This substance has just been reported by Professor Bartlett at the University of California, Berkeley as an intermediate in his elegant synthesis of Brefeldin A. Thus we have in the formal sense demonstrated the utility of this methodology in a total synthesis. Alternative deployment of this intermediate is also being pursued.



A second application to natural products total synthesis is also being pursued and has already brought some interesting surprises. In principle, many diterpenoids can be assembled efficiently by homoconjugate addition of various aryl Grignards with the highly substituted spiroactivated system shown. We have prepared this substance and observed that reaction with phenyl Grignard itself produces two products. These two substances proved to be epimeric at the newly generated quaternary center. It is apparent, therefore, that in this highly congested system prior opening to a zwitterionic intermediate had occurred to some extent. Fortunately, the ratio was found to be temperature dependent varying from 9:1 at low temperatures to 3:2 at room temperature.



Our approach to taxodione relies on the assumption that a more sterically demanding Grignard reagent might capture the zwitterionic intermediate to produce exclusively the correct stereochemistry. At the time of this writing we have just prepared the requisite Grignard reagent by the path shown below and await its reaction with the spiroactivated cyclopropane.



It is a pleasure for me to acknowledge the splendid efforts of three graduate students: Mr. Tom Livinghouse, Mr. Albert Lee, and Mr. Greg Bisacchi. The work was supported by the NSF and a grant from Merck, Sharp and Dohme.