TRANSITION METAL TEMPLATES FOR SELECTIVITY IN ORGANIC SYNTHESIS

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Abstract - Palladium templates offer new avenues of selectivity as exemplified by four disparate problems in allylic alkylation. In the first, control of absolute and relative stereochemistry on conformationally non-rigid systems is considered in the context of the side chains of Vitamins E and K. The second problem deals with reorientation of the [3.3] sigmatropic rearrangement of alkylidenevinyltetrahydro-furans, readily available via three different routes, which produces cycloheptenones to a [1.3] rearrangement which produces vinylcyclopentanones, including prostanoid analogs. A cycloaddition approach to cyclopentane synthesis constitutes the subject of the third problem. Palladium(0) complexes of trimethylenemethanes, which form from 2-trimethylsilylmethylallyl acetates, cycloadd to electron deficient olefins to give methylenecyclopentanes in both inter- and intramolecular versions. The fourth section deals with macrocyclization. Palladium initiated cyclizations exhibit a remarkable degree of control of ring size - not available in non-transition metal reactions. Applications to the cytochalasin and erythrynolide familes of compounds are discussed.

A key aspect of synthetic design is efficiency - the ability to transform readily available starting materials to particular target compounds via the shortest route. Synonymous with efficiency is selectivity which may be grouped into three major classes - 1) chemoselectivity or functional group differentiation, 2) regioselectivity or orientational control in the reaction of an unsymmetrical functional group and/or an unsymmetrical reagent and 3) stereo-control or control of relative stereochemistry (diastereoselectivity) and/or control of absolute stereochemistry (enantioselectivity).

The unique position of the carbonyl group in synthetic design stems from the selective for-mation of bonds at the carbonyl carbon atom or the alpha carbon atom according to equation 1.

$$\qquad (1)$$

$$\qquad (2)$$
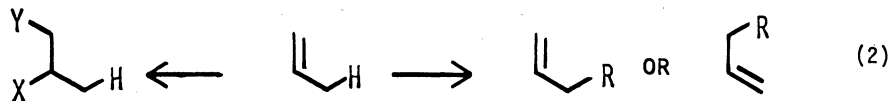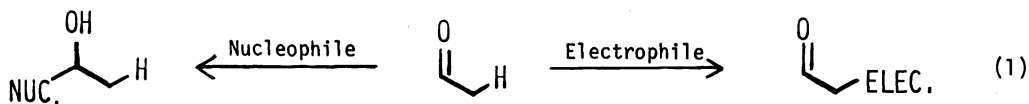
The corresponding reactions of the π-isoelectronic olefin, especially with respect to allylic functionalization, has proven much less useful because low selectivity frequently plagues such processes. In our search for chemoselective allylic alkylation procedures, we focused on the ability of palladium salts to achieve activation of the allylic system and permit subsequent alkylation in the presence of other functional groups - especially the carbonyl group. In the course of these studies, we delved into the palladium catalyzed alkylation of allylic systems in which palladium templates exercise an extraordinary degree of control over the behavior of organic molecules (1). In this report, I wish to consider the appli-cation of these concepts in four different problems, but first to outline the basic princi-ples.

GENERAL CONSIDERATIONS

As a general introduction of the basic process, we can consider the alkylation of 2-methyl-cyclopentan-1,3-dione. Such systems are notorious for their tendency to suffer O versus C


(3)

CORIOLIN   HIRSUTIC ACID C
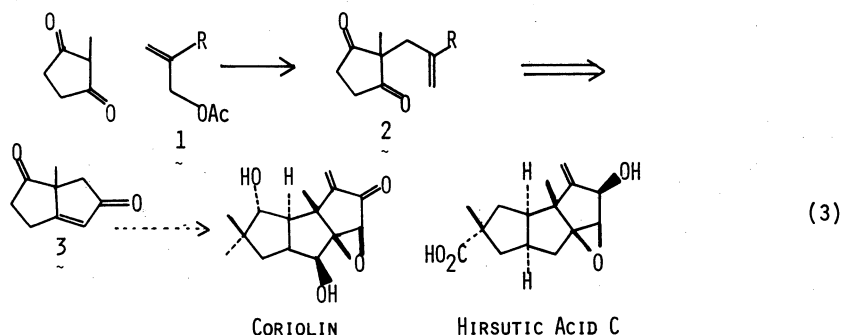
alkylation. Allylation of 2-methylcyclopentan-1,3-dione with allyl bromide proceeded in only 30% yield; however, with allyl acetate and a palladium(0) catalyst, the yield of 2 (R=H) jumped dramatically to 94%(2). Use of 1(R=OC$_2$H$_5$) gave 2(R=OC$_2$H$_5$) which permitted development of cyclopentenone annulation as illustrated in equation 3. The bicyclic ketone 3, a bis-nor analogue of the Wieland-Miescher ketone can prove pivotal as a general intermediate towards polycondensed cyclopentanoid natural products - such as coriolin and hirsutic acid C - in a fashion similar to the pivotal role the Wieland-Miescher ketone has played in cyclohexanoid natural products. A total synthesis of coriolin using this strategy nears completion (3).

Equation 4 illustrates the reordering of reactivity of two functional groups (4). In the absence of the transition metal catalyst, only the bromide would be expected to react - as

E = CO$_2$CH$_3$ S = PhSO$_2$

(4)
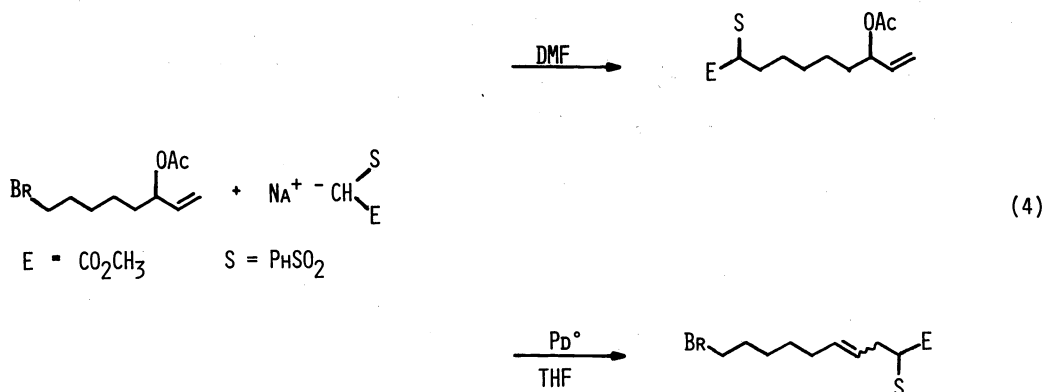
is observed. However, addition of a Pd(0) catalyst allows selective alkylation of the allylic acetate without any attack at the bromide.

Normally, displacement reactions in organic chemistry are synonymous with inversion of configuration. As is shown in equation 5, this alkylation involved displacement with retention of configuration (4). Equation 6 represents a convenient working hypothesis. When coordination of the Pd(0) catalyst occurs on the face of the double bond opposite the acetate, it induces ionization of the acetate to give a π-allylpalladium intermediate. The positional identity of the acetate - ie, whether it originally was located at C(a) or C(b) is lost at this stage. Thus, the choice of substrate with acetate at either C(a) or C(b) can depend only on synthetic expediency - a real benefit of this methodology. The regioselectivity depends upon: 1) the nature of the nucleophile, 2) the nature of the substitution of the allyl unit, and 3) the nature of the ligands on Pd.

$$(5)$$

$$(6)$$
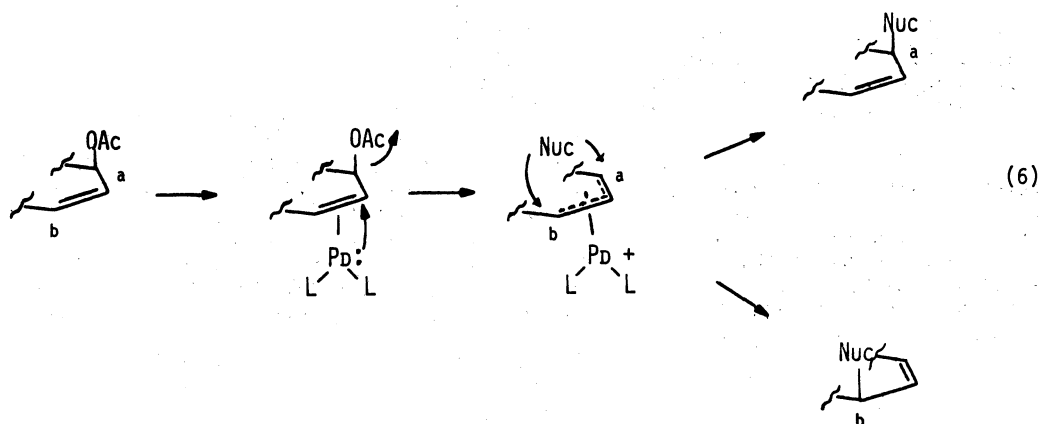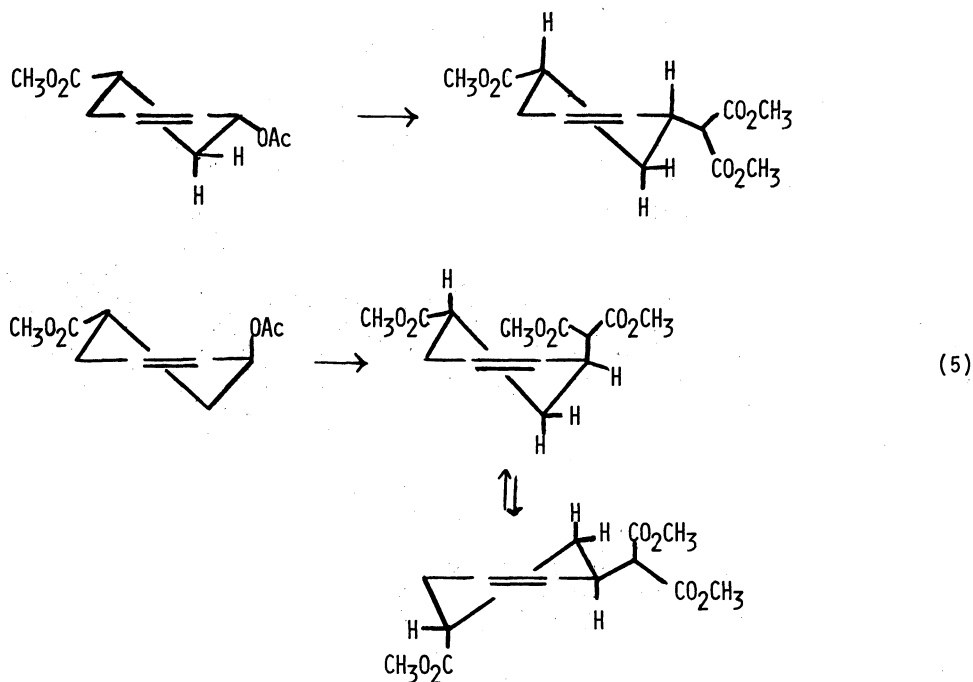
CATALYSTS

Pd(0) is required as a catalyst for these reactions. Soluble palladium catalysts which are sensitive to oxygen normally bear phosphine ligands. The most common catalysts are 4 (5) and 5 (6,7). In some cases, to preserve catalyst lifetime and increase turnover, 1-2
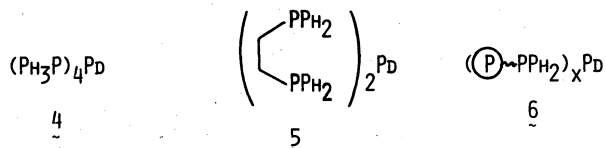

equivalents of additional phosphines are added. A rate retardation normally accompanies such a modification. To avoid handling such oxygen sensitive materials, the catalyst can be generated *in situ* from Pd(+2) salts by reduction with DIBAL or in the case of Pd(OAc)$_2$, with an olefin (typically the substrate) in the presence of phosphine ligands. For small scale reactions, 1-10 mol% of catalyst has been employed. The amount of catalyst decreases as the scale of the reaction increases - as little as 0.01 mol% has been employed.

An insolubilized version of the catalyst has been produced (8,9). Either silica gel or
crosslinked polystyrene can be phosphinylated and the modified support exchanged with 4 to
give 6. Besides facilitating recovery and recycling of the catalyst, such insolubilized
versions do show modified selectivities as a result of the modified ligands.

STEREO-RELAY

In Chart 1, we consider the question of control of stereochemistry at a reaction site
relative to a remote chiral center. In a conformationally well defined system, such as a
six membered ring, this problem is minimized. The presence of substituents on the ring
normally fixes the conformation in one of the two possible chair forms as shown in 7.
Thus, the two faces of the carbonyl group are quite distinct and reaction is expected to
occur preferentially on one of the two faces - most frequently from the equatorial direction
as shown. Cleaving bond "a" in 7 creates 8, where the interconnecting chain between the
chiral center and the reaction site no longer exhibits a conformational bias. Here,
reaction on the two faces of the carbonyl group occurs with equal probability. Thus,
in conformationally non-rigid systems - acyclic or macrocyclic ones - a mechanism to
communicate between these two sites needs to be found. One approach is to design a substrate
that permits temporary complexation of a normally non-rigid chain onto a template and,

CHART 1. Problem of Stereo-relay
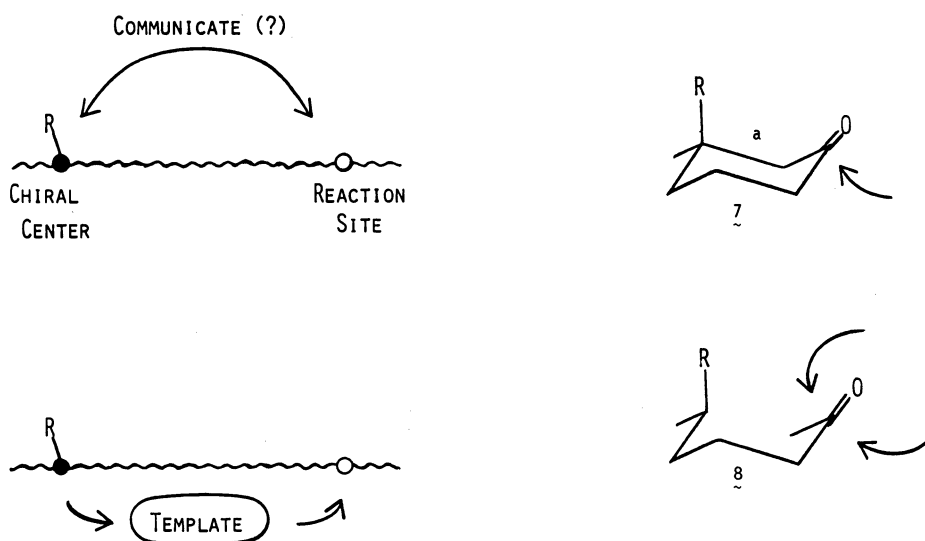
thereby, induce conformational rigidity. We chose to examine this question in terms of the
creation of the side chains of Vitamins E and K for which 9, which possesses the two chiral
centers, provides a logical target (10). In terms of allylic alkylation, 9 translates into
10, in which bond "a" creates the second chiral center relative to the existing one (11,12).
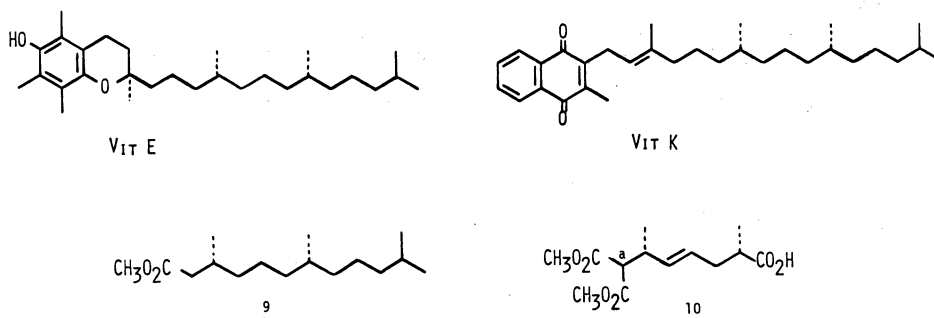

Vinyllactones represent ideal choices for this stereo-relay process in which the ring
geometry will be transmitted down the chain. Equations 7 and 8 illustrate the success of
this approach where Pd(0) catalyzed alkylation leads to S_N2' reaction with clean *retention*
of configuration regardless of the olefin geometry (11). This reaction complements cuprate
chemistry, as shown in equations 7 and 8, too, which proceeds with allyl inversion but
inversion of configuration (12). Unfortunately, the cuprate chemistry does not exhibit
as high a degree of stereochemical control with the *E* olefin series (equation 8) as does

$$ (7) $$

$$ (8) $$
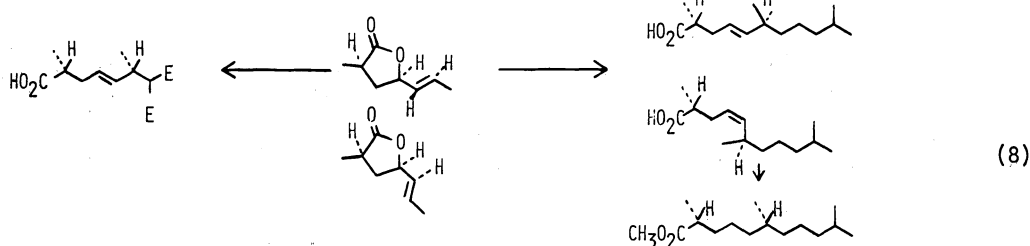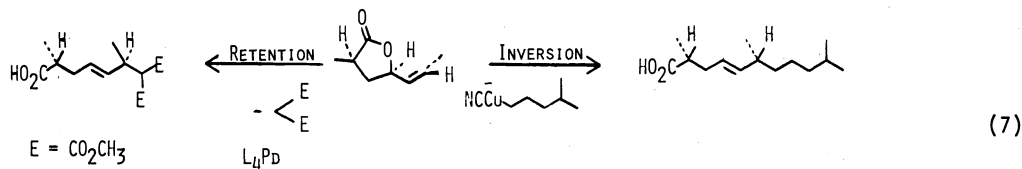
the palladium templates - demonstrating the superiority of the palladium reaction in this case.

Variation of the separation between the chiral centers as in 11 can be achieved by varying the position of the substituents on the vinyl lactone or, as shown in equation 9, by varying

$$ \underset{11}{} $$
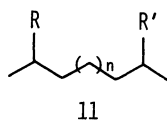
the size of the lactone ring (13). Here, too, the higher degree of control exhibited by the palladium template is obvious.

$$ (9) $$
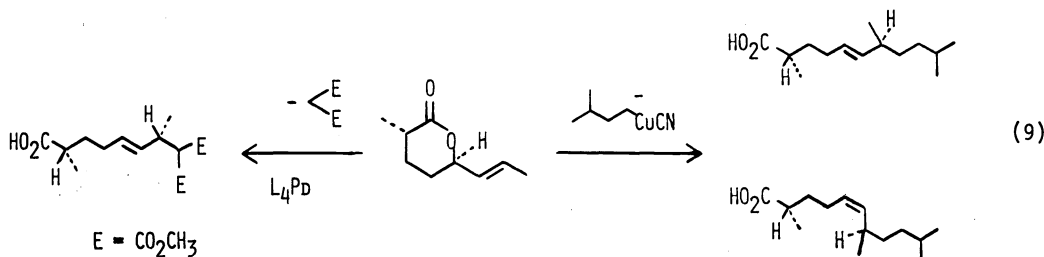
While the products of the reactions illustrated in equations 7 and 8 have been converted into the target for the vitamin side chains, this approach only controls relative stereo-chemistry. One reason for choosing such substrates was the use of carbohydrates as a potential optically pure raw material. Indeed, glucose is converted to lactone 12 (equation 10) by straightforward chemistry and the latter smoothly participated in the palladium

$$ (10) $$
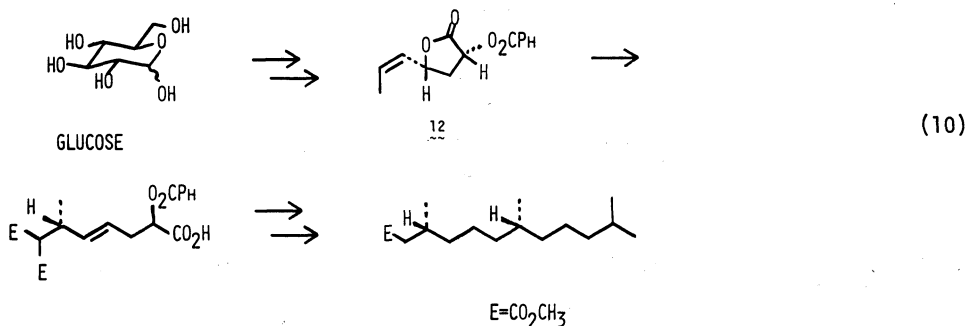
initiated reaction (95% yield) to give a single homogeneous product which is converted into the side chain fragment where both relative and absolute stereochemistry have been fully controlled (14).

[1.3] REARRANGEMENT

The chemistry of allylvinyl ethers invariably becomes integrated with [3.3] sigmatropic
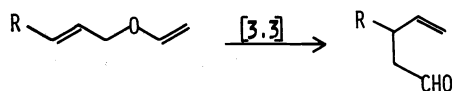
rearrangements. In cases such as 13, such a process produces the cycloheptenone 14. For many natural products, an alternative pathway, a [1.3] rearrangement, to produce a 3-vinyl-cyclopentanone would be the desired course. Indeed, a reordering of the "expected" reactivity profile of 13 is available using a palladium template in which the exclusive product is, indeed, the cyclopentanone 15 (6).
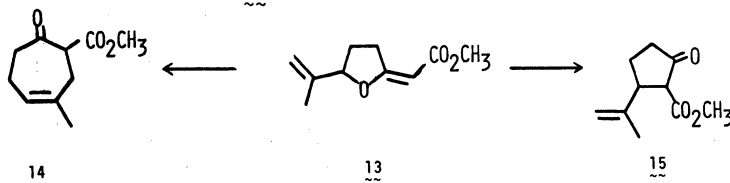

This process takes on added importance due to the cyclization proclivity of β-ketoesters such as 16 (equation 11) for O rather than C alkylation. Indeed, all attempts to cyclize


$$(11)$$
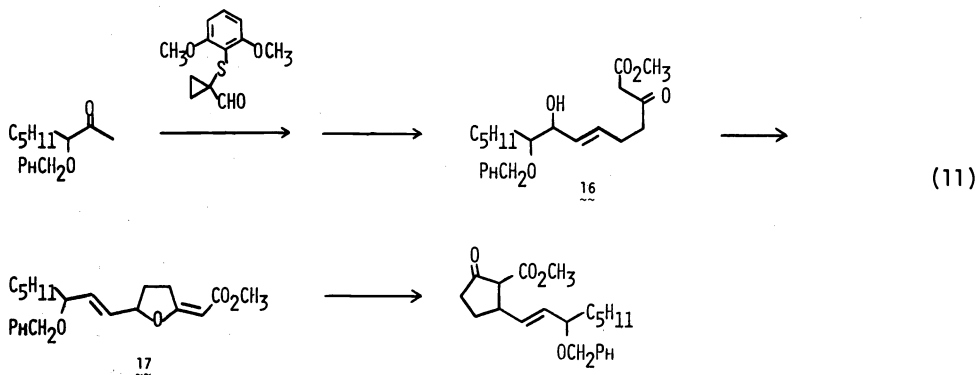
16 lead only to the alkylidenevinyltetrahydrofuran 17. However this tendency no longer presents a problem, since 17 smoothly isomerizes to the desired cyclopentanone with a Pd(0) catalyst - in this case, an approach to prostaglandin analogues.

The utility of this cyclopentanone synthesis depends upon the availability of the requisite alkylidenetetrahydrofurans. Equation 11 illustrates their accessibility from ketones through use of a new conjunctive reagent 1-(2,6-dimethoxyphenylthio)cyclopropanecarboxaldehyde (15). Especially valuable are vinyllactones such as 18 (equation 12) and 19 (equation 13) which are

$$(12)$$
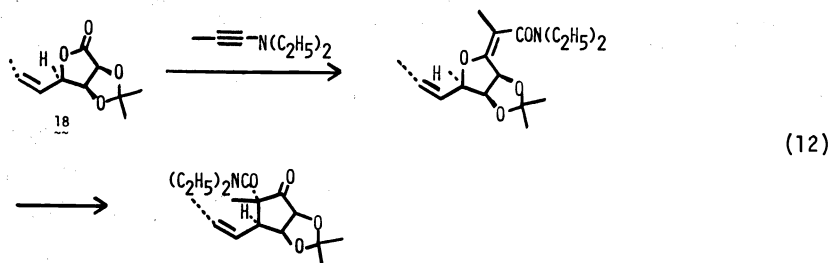
available from carbohydrates (16). Ynamines smoothly effect olefination of a lactone (87% yield) and the product rearranges to the cyclopentanone in 93% yield with complete regio- and stereocontrol upon subjection to 5 as the palladium template. Alternatively, 19 reacts with t-butyl lithioacetate followed by dehydration to give 20 in 91% yield. In this case, rearrangement can be controlled to give either the cycloheptenone 22, or the cyclopentanone 23, by judicious choice of catalyst. The regioselectivity depends upon the rate of syn-anti interconversion in the intermediate 21. With the sterically demanding polymeric catalyst,

(13)
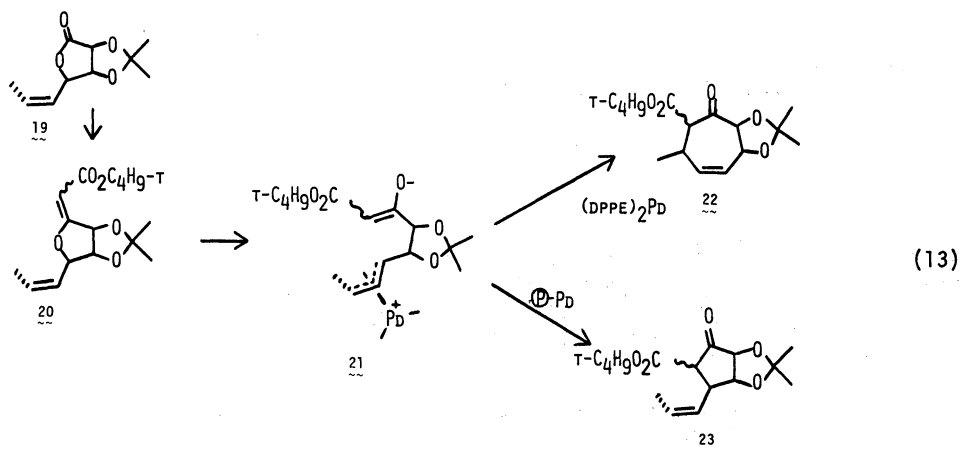
such interconversion is inhibited and only the normal [1.3] product is seen. With a sterically small ligand, such interconversion is fast and only the seven membered ring is observed. Such rational control of reactivity is a decided advantage of transition metal catalyzed reactions.

An alternative approach employs methyl 6-oxo-2-pentynoate as a conjunctive reagent for cyclopentanone synthesis (17). Chemoselective addition of vinyl organometallics produces the alcohol 24 (equation 14). Surprisingly, conjugate addition of the alcohol proved


(14)
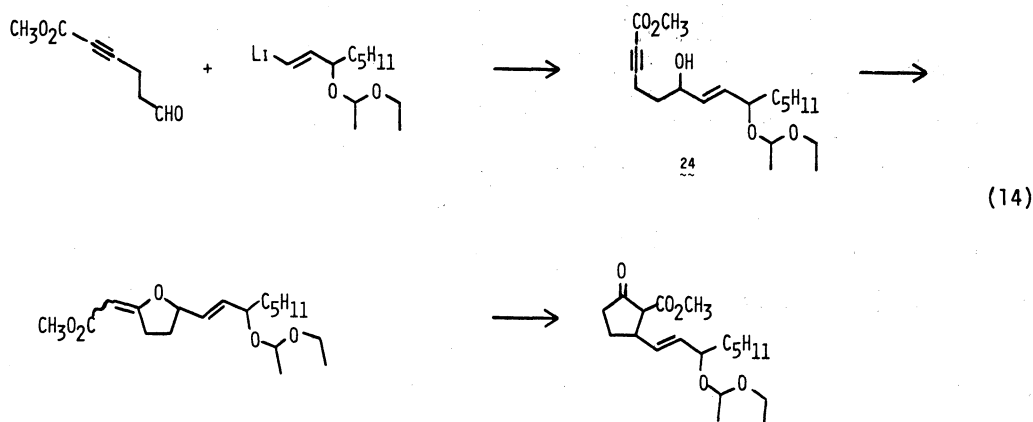
particularly troublesome. An efficient solution to this perplexing problem evolved from organosulfur chemistry. Addition of sodium benzenesulfinate to a warm alcoholic solution of 24 smoothly triggered cyclization to the desired alkylidenevinyltetrahydrofuran. Isomerization with the palladium catalyst completed an additional entry into the family of
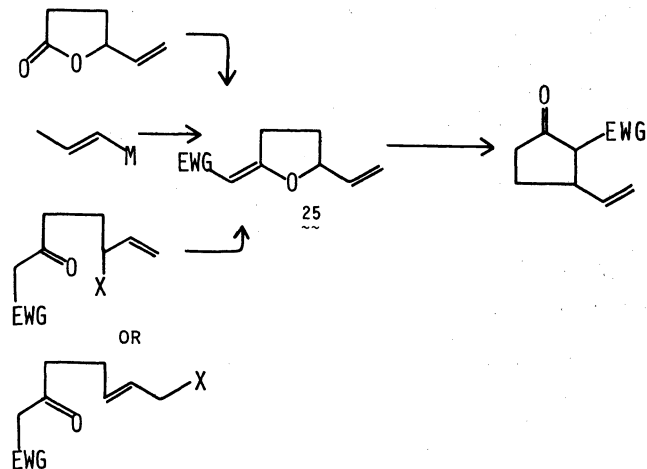
prostanoids. Thus, the availability of alkylidenevinyltetrahydrofurans of type $\underset{\sim}{25}$ from many different types of substrates suggests great versatility for this cyclopentanone synthesis.

CYCLOPENTANE ANNULATION

The increasing frequency of cyclopentanoid natural products heightens the demand for increased flexibility in synthetic approaches to them. The [1.3] isomerization of alkylidenevinyltetrahydrofurans contributes to that flexibility. In cyclohexanoid chemistry, the Diels-Alder reaction (equation 15) holds a special position. The virtues of such a cycloaddition approach are lacking for the case of five membered carbon rings for which the analogue might be a 1,3-dipolar cycloaddition as illustrated in equation 16. Initiating
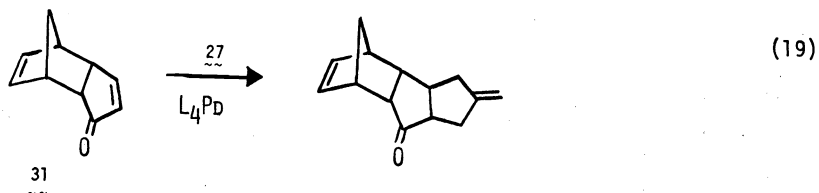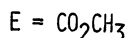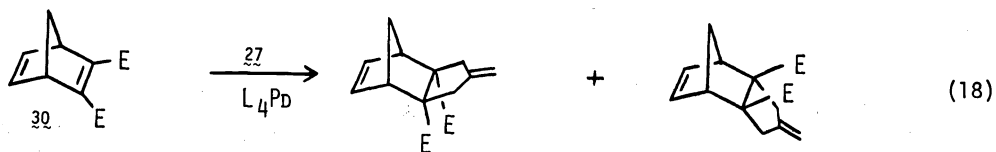
$$\text{(15)}$$

$$\text{(16)}$$

$$\underset{\sim}{26}$$
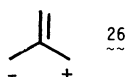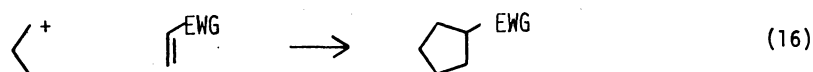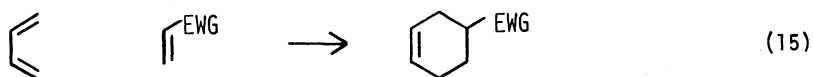
an investigation into such an area draws our attention to trimethylenemethane, shown in a dipolar form in $\underset{\sim}{26}$, a reactive intermediate which has been studied from a physical point of view but whose use in synthesis is precluded because of very low yields.

Combining the virtues of organosilicon chemistry with palladium templates led us to propose that a bifunctional conjunctive reagent such as $\underset{\sim}{27}$ (equation 17) would be ideal since the

$$\text{(17)}$$

$$\underset{\sim}{27} \qquad \overset{\ominus}{} OAc \quad \underset{\sim}{28} \qquad \underset{\sim}{29}$$
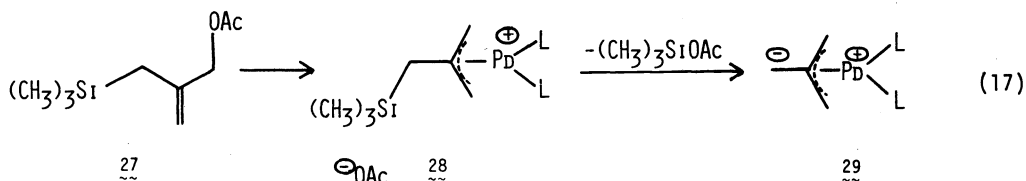
π-allylpalladium intermediate $\underset{\sim}{28}$ could suffer desilylation by acetate to generate, not trimethylenemethane itself, but its palladium complex $\underset{\sim}{29}$ where the only by-product is trimethylsilyl acetate (18-20). Of course, the reactivity of an intermediate such as $\underset{\sim}{29}$ was not known (21). For example, iron complexes of trimethylenemethane are notorious for their lack of reactivity (22). Hoping that cycloaddition would indeed occur, leads to the employment of traps such as $\underset{\sim}{30}$ and $\underset{\sim}{31}$ (equation 18 and 19) which contain both electron rich

$$\xrightarrow[L_4 Pd]{\underset{\sim}{27}} \qquad + \qquad \text{(18)}$$

$$\underset{\sim}{30}$$

$$E = CO_2CH_3$$

$$\xrightarrow[L_4 Pd]{\underset{\sim}{27}} \qquad \text{(19)}$$

$$\underset{\sim}{31}$$

and electron poor olefins. Both reacted smoothly and chemoselectively with $\underset{\sim}{27}$ in the presence of a Pd(0) catalyst to give cycloaddition-like products to the electron poor olefin. The cycloaddition to methyl E,E-muconate produces a methylenecyclopentane (equation 20) which possesses structural features that naturally lead to application of this methodology
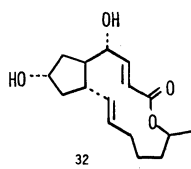
$$
\text{(20)}
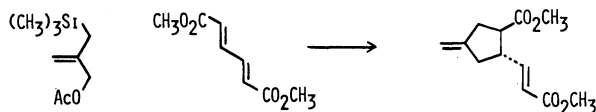$$

to a total synthesis of brefeldin A, $\underset{\sim}{32}$. The chemistry as well as Fenske-Hall calculations (20,23,24) lead to the conclusion that this complex indeed behaves as a zwitterion as represented in structure $\underset{\sim}{29}$ (equation 17). Thus, the cycloaddition can be generalized as in equation 21, in which the trap must bear at least one electron withdrawing group (EWG).

$$
\text{(21)}
$$

The utility of such a cycloaddition approach depends upon the accessibility of the requisite bifunctional reagents such as $\underset{\sim}{27}$ and the extension to substituted analogues. Such an extension is non-trivial. Consider the case of the methyl derivative $\underset{\sim}{33}$ where, at every stage, proton transfer can compete with the desired process as illustrated.
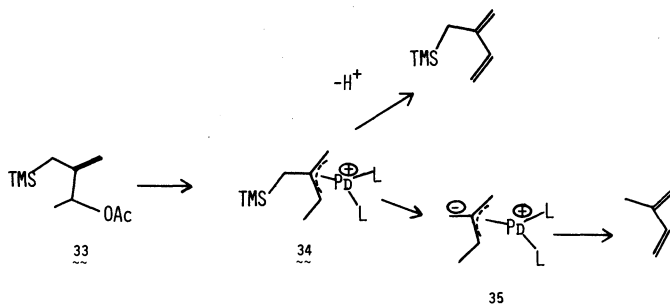
Scheme 1 outlines three of the four approaches we have developed to the requisite substrates (25). The direct metallation (path a) is very general for methallyl alcohols. 2-Trimethylsilylmethylpropenal, available from methallyl alcohol by the metallation-silylation procedure of path a followed by oxidation, represents an acceptor conjunctive reagent where

SCHEME 1. Synthetic approaches to bifunctional conjunctive reagents for cycloaddition
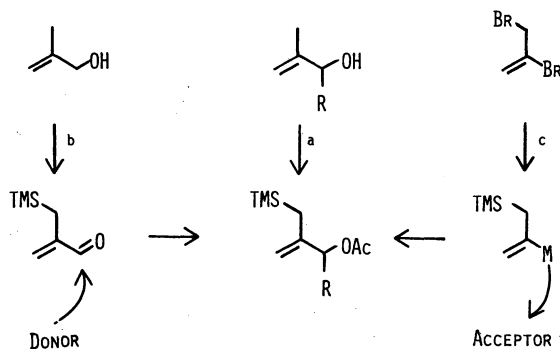
organometallics serve as the source of the R group (path b). Alternatively, the lithium or magnesium derivative of 2-bromoallyltrimethylsilane, available from 2,3-dibromopropene, represents a donor conjunctive reagent where electrophiles such as aldehydes serve as the source of the R group (path c).

The aspirations for the generality of this cycloaddition were fulfilled. Using coumarin as a trap (equation 22), a single major product resulted. Thus an extraordinary event occurred.


$$(22)$$
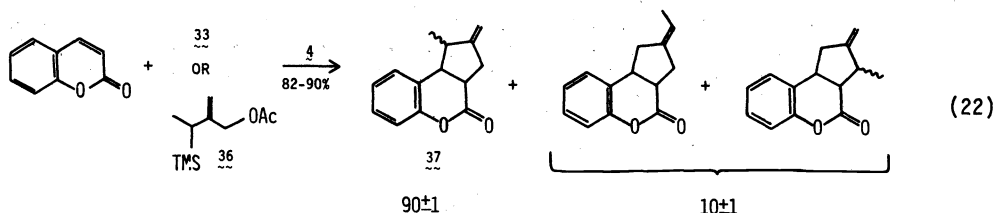
Desilylation of 34 to give a reactive intermediate 35 competes favorably with simple proton loss to give a stable molecule (equation 21)! Whereas use of 33 initially generates 35, the regioisomer 36 generates 38. Yet the same product mixture emerges. Using the simple
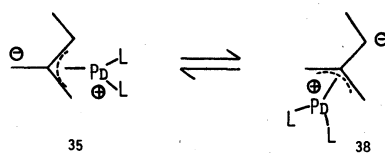
notion that the reaction is initiated by nucleophilic attack of the most anionic carbon of the complex, the predominant cycloadduct 37 derives from 38. Indeed, calculations predict 38 to be more stable than 35. The electron releasing methyl group prefers to be on the most electron rich carbon - the antithesis of normal behavior in organic chemistry! Thus, the transition metal template imposes a level of control that leads to new selectivity. The factors that lead to placing the electron donating group (EDG) on the most electron rich carbon of the TMM system, ie 39a, can suggest that the EWG be placed on the least electron rich carbon as in 39b.
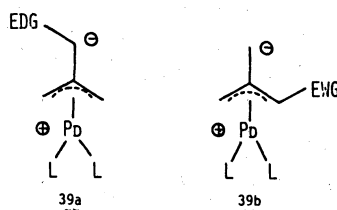
Cyclopentenone smoothly reacts with either 33 or 36 to give virtually exclusively 40 (>20:1 in regioisomers) - an intermediate towards loganin (26) as well as the insect pheromones dehydroiridodial and chrysomelidial (27) as shown in equation 23. The availability of a

$$(23)$$

DEHYDROIRIDODIAL   CHRYSOMELIDIAL
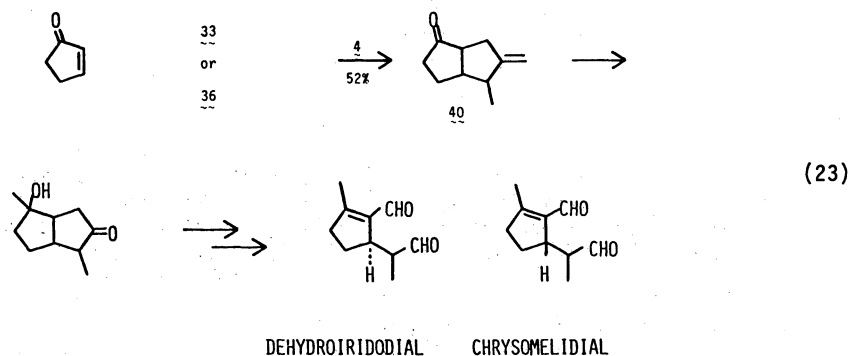
donor reagent to create the requisite structural unit particularly facilitates the synthesis of a substrate for an intramolecular reaction as shown in equation 24. The promise of a family of reagents for cycloaddition-like approaches to cyclopentanoid natural products appears fulfilled.

(24)
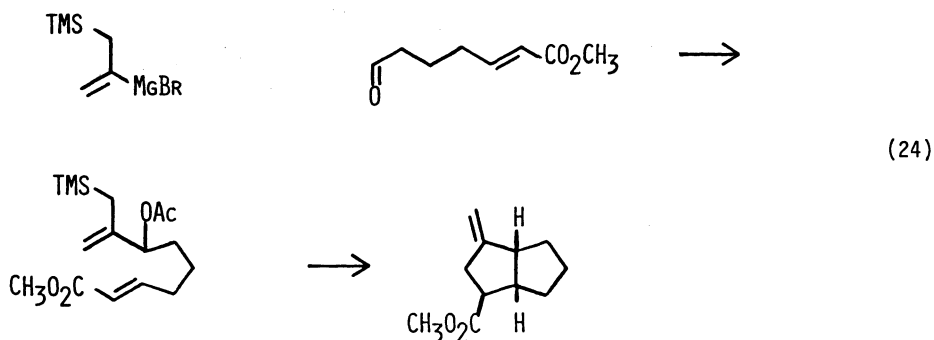
MACROCYCLIZATION

Thus far, the utility of these templates for ring formation dealt only with the more normal ring sizes - five, six and seven membered rings. Macrolides and all carbon macrocycles represent major synthetic challenges. Techniques that focus on formation of such rings by C-C bond formation represent the most flexible methods. Our initial attention (28) focused on macrolides where palladium initiated cyclization to rings of ten or more members culminated in syntheses of phoracantholides I and J (28,29), recifeiolide (28,30), and exaltolide (28,31). Most striking is the regioselectivity in formation of medium size rings. For example, cyclization of the substrate shown in Scheme 2 can proceed to either a six or an

SCHEME 2. Formation of 7-Heptanolide
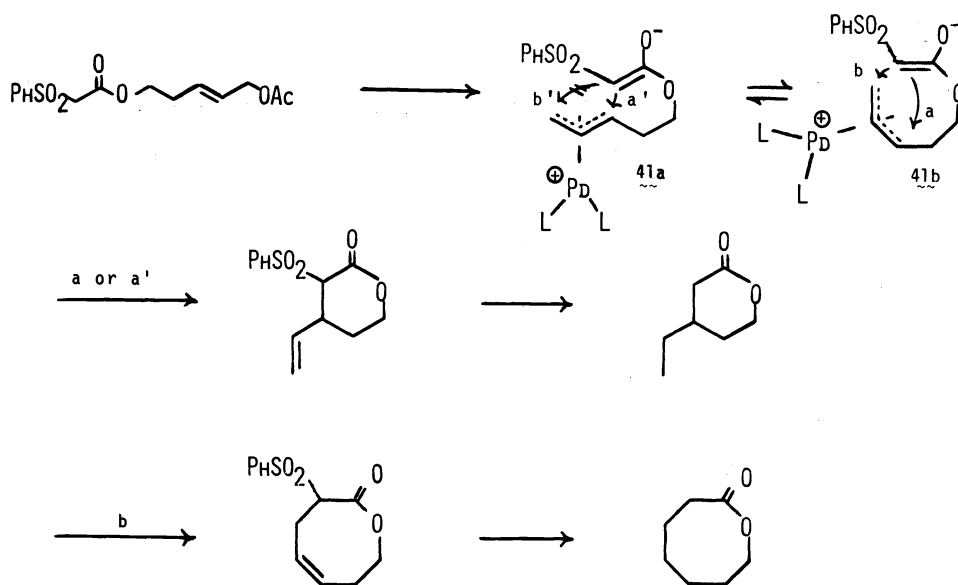
eight membered ring. In addition to the 10^5 kinetic preference for formation of six membered rings, the higher stability of *syn* complexes such as 41a over *anti* complexes such as 41b should reinforce the preference for six membered ring formation. In spite of all this, eight membered ring formation dominates (93%). As shown in equation 25, nine membered ring formation dominates over seven. Once again, the normal rules for reactivity are violated - the normally difficultly available eight and nine membered rings are now preferred! As equation 25 summarizes, variation in the nature of the nucleophiles, of the substitution in the chain, and of the ligands on palladium permits complete control of regiochemistry and thus ring size - truly a remarkable level of control of reactivity (32).

(25)

S	R	X	Y	CAT.		
PhSO$_2$	CO$_2$CH$_3$	C=O	O	(PH$_3$P)$_4$Pd	----	ONLY
PhSO$_2$	CO$_2$CH$_3$	CH$_2$	CH$_2$	(PH$_3$P)$_4$Pd	ONLY	----
PhSO$_2$	PhSO$_2$	CH$_2$	CH$_2$	(PH$_2$PCH$_2$CH$_2$PPH$_2$)$_2$Pd	----	ONLY

The challenge of the synthesis of complex natural products offers an ideal testing ground for this method. The cytochalasin family of natural products consists of a highly substituted cyclohexyl ring fused to a macrolide as in cytochalasin B or to an all carbon macrocycle as in aspochalasin B. A common feature of both is the highly oxygenated pattern in the

ASPOCHALASIN B   CYTOCHALASIN B

macrocycle - a type of pattern found in other natural products such as antibiotic A26771B (see Scheme 3). An ideal precursor to all of these is the fragment shown in structure 42,

42

where the enol ether can serve as a simple entry into the simple alcohol as in cytochalasin B or an α-hydroxyketone as in aspochalasin B and antibiotic A26771B. This fragment becomes an obvious target of allylic alkylation.

Scheme 3 illustrates the ready availability of the requisite substrate 43 from 10-undecenal.

SCHEME 3. Synthesis of Antibiotic A26771B

ANTIBIOTIC A 26771 B

Treatment of 43 with a Pd(0) catalyst and *O,N*-bis(trimethylsilyl)acetamide in refluxing THF gave the requisite macrocycle in 55-61% yield - a much higher yield than obtained by any lactonization approach (33). Hydroxylation using a catalytic amount of osmium tetraoxide followed by esterification with succinic anhydride completes the sequence. The soundness of this strategy for cytochalasin synthesis is established.

Equally challenging targets are the erythrynolides A (44, X=OH) and B (44, X=H) as shown in Scheme 4. The retrosynthetic analysis utilizing this macrocyclization principle converges to 45 and 46 - a pair of enantiomers! Thus the problem of control of absolute as well as

SCHEME 4. Retrosynthetic analysis for erythrynolide synthesis
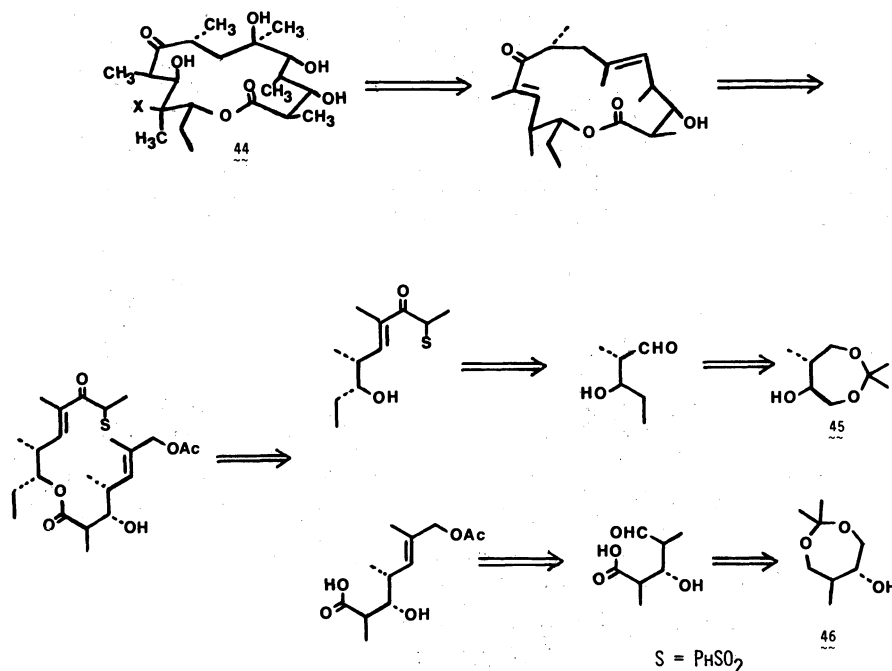
relative stereochemistry is resolved as long as both enantiomers are available in a simple operation. A simple solution emerged. The *O*-methylmandelate esters 47 and 48 revealed two well-resolved peaks by HPLC and permitted large scale separation on a Waters Prep 500

instrument (34). A second advantage of this approach is the ability to assign stereochemistry. Using the Mosher model, the stereochemistry depicted in 47 and 48 corresponds to the less and more polar isomers respectively. Further correlation was provided by comparison of the regenerated optically pure 45 and 46, whose absolute configuration was established by Horeau's method.

With the strategy developed, the elaboration of 45 into the requisite alcohol is complete, and the corresponding elaboration of 46 into the carboxylic acid is nearing completion. However, establishment of the critical ring closure remains. Comfortingly, subjection of model 49 (equation 26), which possesses a fully elaborated alcohol half and

(26)

$S = PhSO_2$
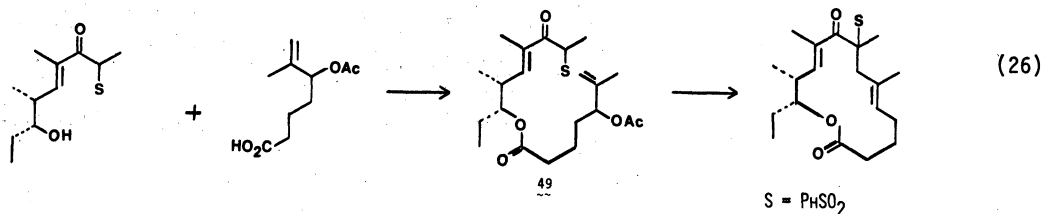
a stripped version of the carboxylic acid portion, to the normally cyclization conditions creates the correct fourteen membered macrolide ring of the erythrynolides.

CONCLUSIONS

An appreciation of the intracacies of transition metal chemistry in the design and applications of new reactions is emerging. The fact that insight based upon traditional thinking is challenged offers an unprecedented opportunity to expand the rules of selectivity. Indeed, such an expansion is critical if we are to mount a successful campaign to make chemistry better serve the needs of man by instilling efficiency and thereby bringing to application more sophisticated materials. We hope the above will contribute to this task.

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