

TETRAHEDRON REPORT

A REVIEW OF ANNULATION†

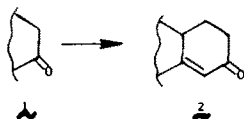
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INTRODUCTION

Annulation‡, derived from the Latin work *annulatus* (ringed) means "the formation of rings".¹ In organic chemistry this term is used to describe the process of building a ring onto a pre-existing system, cyclic or non-cyclic. The added ring may be of any size, although 5- and 6-membered rings are most commonly formed. This broad definition includes in a general sense many reactions that are not normally thought of as annulation reactions, such as Diels-Alder reactions,² acid-catalyzed polyolefinic cyclizations,³ photochemical,⁴ radical,⁵ and thermal⁶ cyclizations. This discussion will be concerned mainly with those processes of annulation which involve construction of a cyclohexenone ring onto a pre-existing ketone; e.g. 1 → 2. These processes normally involve the



attachment of an actual or potential 3-ketoalkyl chain to a carbon adjacent to a carbonyl function (e.g. 3 → 4), although other methods (e.g. enol lactone-Grignard) will also be discussed.

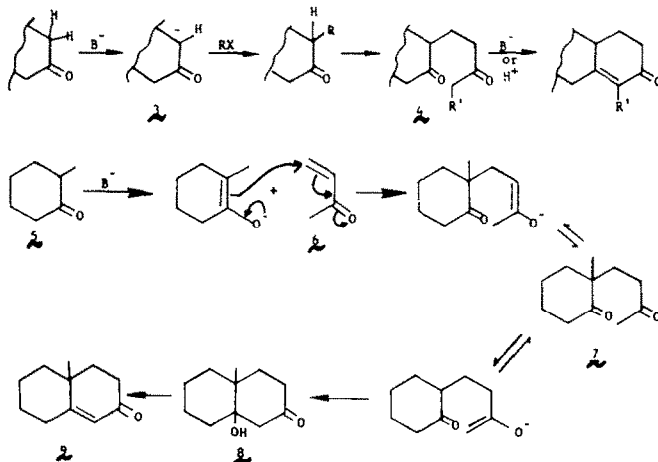
The methods of annulation have proved themselves to be invaluable aids to the synthetic organic chemist in the syntheses of such complex natural products as steroids, terpenes, and alkaloids. This is especially true of the use of the cyclohexenone system. Several factors justify the importance of this ring system, and these include ease of formation, control of ring-juncture and side-chain stereochemistry, introduction of functionality, and attachment of additional rings.

In general, annulation reactions can be divided into three basic categories depending on the method of attachment of 3-ketoalkyl chain: Michael reactions,⁷ nucleophilic additions (Grignards, ylides, etc.), and alkylations. Furthermore, annulation reagents can be subdivided into those designed to add one ring at a time (mono-annulation reagents) and those which result in several ring segments being added at once, the so-called bis- or tris-annulation reagents.

1. MICHAEL REACTION

(1) Mono-annulation

(a) *Robinson annulation*. The first example of this type of annulation reaction is the classical "Robinson annulation", which involves the base-catalyzed Michael addition of a ketone to methyl vinyl ketone 6, followed by base- or acid-catalyzed aldol condensation.⁸ The method is useful only in a very few simple cases, such as 2-methylcyclohexanone 5 where the availability of starting materials compensates for the low yield of octalone 9 produced. By proper adjustment of conditions, the reaction can be used to produce any one of the three possible products: the diketone 7, the ketol 8, or the enone 9. Both intermediate products 7 and 8 can be converted to



†Contribution No. 3503.

‡There has been some discrepancy in the spelling of this word with two forms, annulation and annelation, being used, the latter somewhat more often than the former. In this review, however, the correct spelling (cf. *Webster's Third New International Dictionary Unabridged*) annulation will be employed.

the enone **9** by treatment with either acid or base. With relatively acidic carbonyl compounds such as β -dicarbonyl compounds, e.g. **10**,⁹ or β -tetralones, e.g. **13**,¹⁰ the Robinson annulation gives good yields. With ordinary carbonyl substances the Robinson annulation is poor mainly because of polymerization of the vinyl ketone, initiated by strongly basic enolates, and also because of the inability of controlling the site of anion formation. Furthermore, unusual products are sometimes obtained^{9a,11,12} which result from the base- or acid-catalyzed cleavage of the β -diketone to a diketo acid which then cyclizes to an enone acid, e.g. **15** $\rightarrow$ **17**¹¹ and **10** $\rightarrow$ **18**.^{9a}

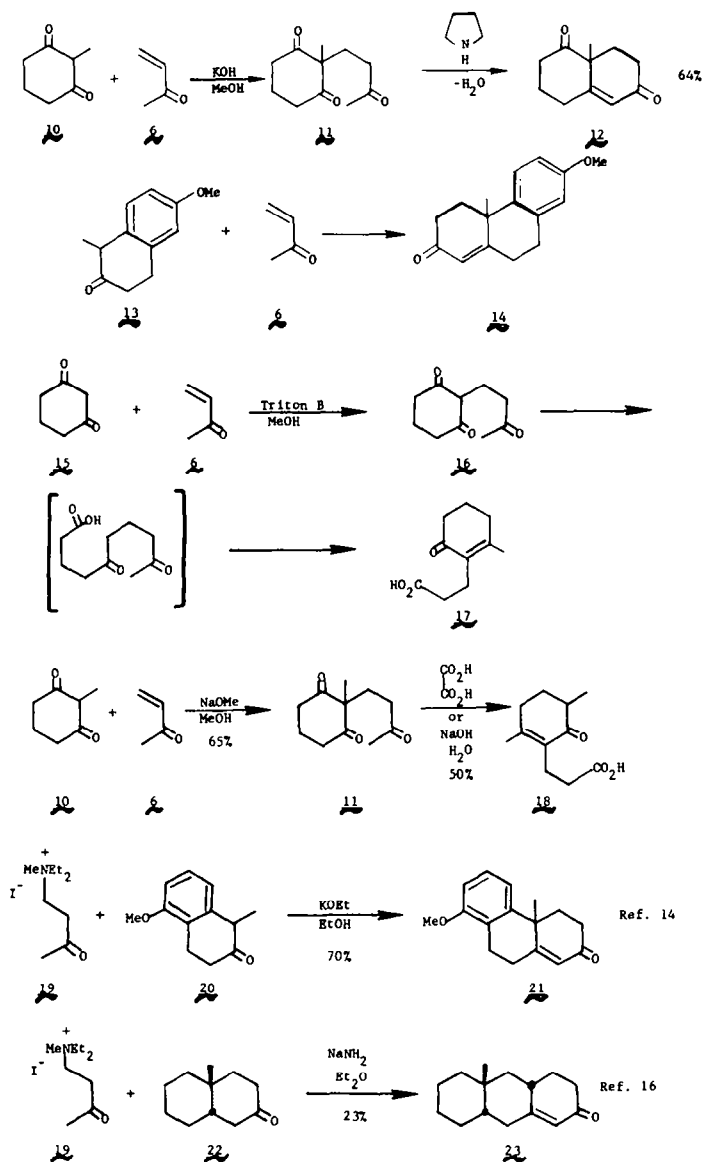
(b) *Mannich base and methiodide*. The problem of polymerization was overcome in part by the use of the Mannich base **19**.¹³ Treatment of the methiodide of the Mannich base with strong base converts it to methyl vinyl ketone *in situ*. This method can improve the yields of cyclohexenone formed; however, unexpected products are sometimes formed. The reaction of the methiodide **19** with *cis*-10-methyl-2-decalone **22** gives only the unexpected anthracene-type product **23** resulting from attack at C-3 rather than attack at C-1, although it has been

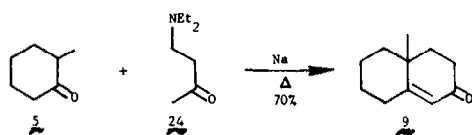
inferred that the anion at C-1 may be the more stable of the two anions.¹⁵

Marshall was unable to improve the yields of the Robinson annulation with a simple cyclohexanone system by varying the solvent, ratio of reagent, temperature or base.¹⁷ However, a Japanese group has reported a method which sometimes results in high yields for unactivated ketones. Treatment of the amine **24** and the ketone **5** with a trace of metallic sodium at 135°C gives a 70% yield of octalone **9**.¹⁸

The problem of unusual cyclization products mentioned earlier (cf. **15** $\rightarrow$ **17**) also occurs when the Mannich base **24** is used. For example, the dienone acid **27** is formed via the intermediates shown in 45–50% yield when one equivalent of compound **24** is employed and in 90–95% yield when two equivalents of **24** are used.¹¹

The choice of solvent for the reaction can have a direct bearing on the stereochemistry of the products.¹⁹ Scanio has recently shown that a change of solvents causes a dramatic shift in the stereochemical course of the annulation reaction between methyl propenyl ketone **28** and 2-methylcyclohexanone **5**.²⁰





An intriguing, though unproved, mechanism has been proposed to explain the unusual result in dimethylsulfoxide. This involves an initial aldol reaction in the inverse sense with the enone anion attacking the ketone carbonyl. A thermally allowed disrotatory cyclization of the derived enolate ion **31** would then lead to the observed product **30**.

Homologues of methyl vinyl ketone or their Mannich base methiodides have been prepared and used in the annulation sequence, e.g. ethyl vinyl ketone **32**²¹ and 1-*bis*(diethylaminomethyl)-acetone **33**.²²

(c) β -Halo ketone. The use of β -halo ketones, e.g. **40** and **41**, as alternatives to the above methods has also been investigated.²³ The reagents release the vinyl ketones slowly under base treatment as do the Mannich base methiodides and give comparable yields.

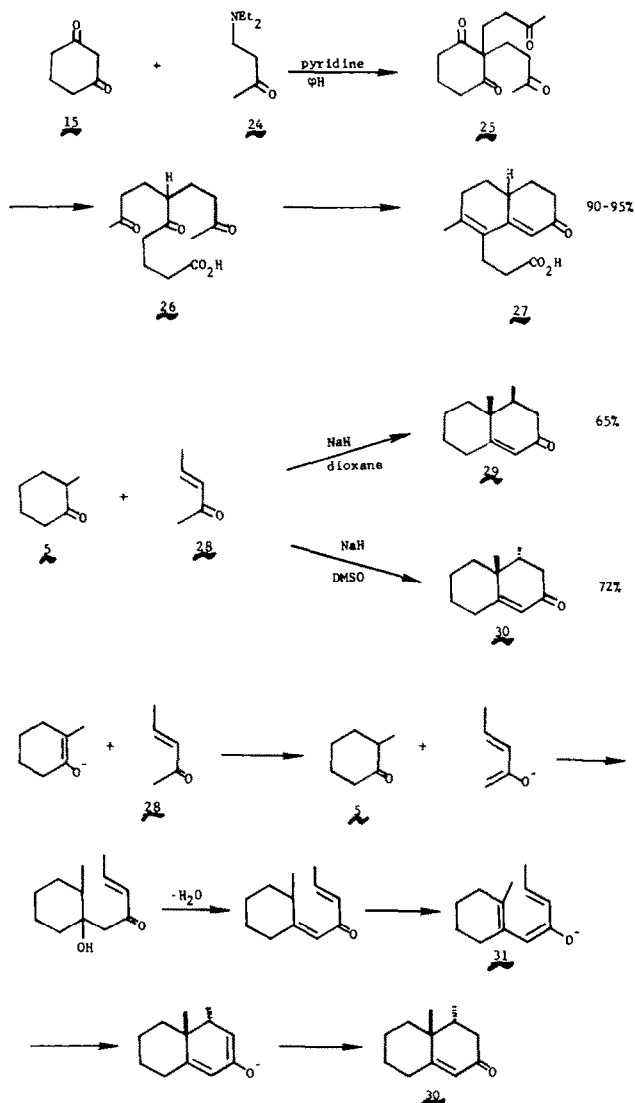
(d) *Enamine*. The use of enamines²⁴ with their relatively low basicity and high nucleophilicity often produces good yields in annulation reactions with vinyl

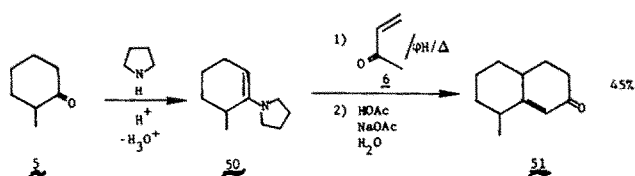
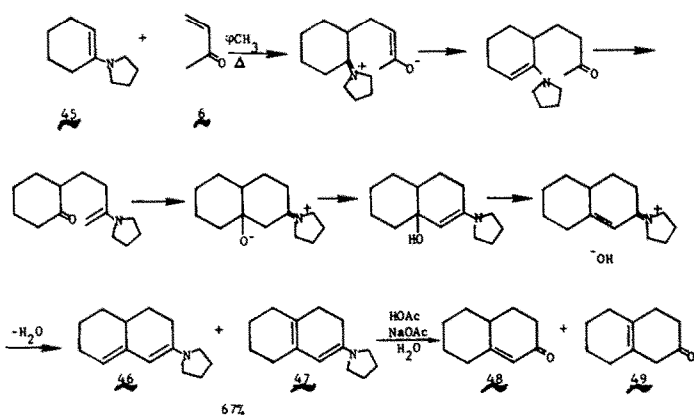
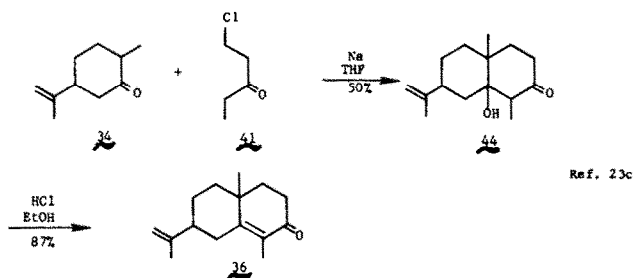
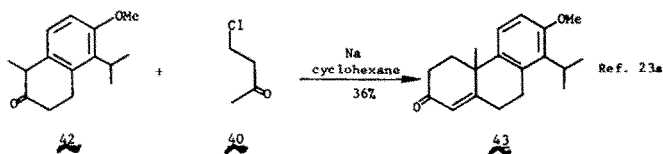
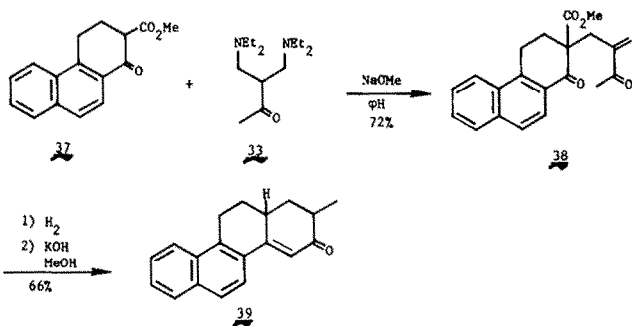
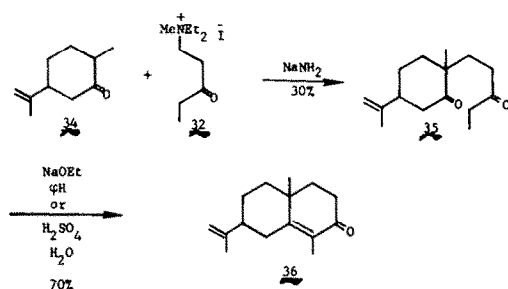
ketones in those cases where reaction with the corresponding carbonyl compound fails, due either to self-condensation of the carbonyl compound or to the polymerization of the vinyl ketone by the very basic enolates. The enamine of cyclohexanone, **45**, adds to methyl vinyl ketone to give directly the enamine of octalone as a mixture of double bond isomers, **46** and **47**, in 67% yield. This enamine mixture can be hydrolyzed to a mixture of the octalones **48** and **49**, or can be used directly in the alkylation or further Michael reactions. Moreover, the use of an enamine can alter the course of annulation by causing the addition to occur at the unsubstituted position of an α -substituted cyclic ketone. e.g. **5** $\rightarrow$ **51**.²⁴

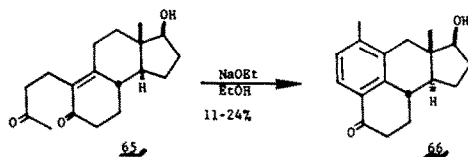
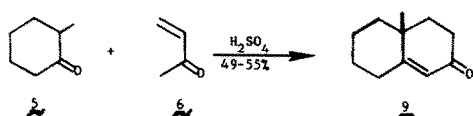
There is a recent report that the Robinson annulation gives improved yields of octalones and cyclohexenones under catalysis by sulfuric acid rather than base.²⁵

Also it has been observed that the vapor-phase introduction of the vinyl ketone into the solution of the ketone and base can often help improve the procedure, e.g. **52** $\rightarrow$ **53**.²⁶

(e) *Functionalized products.* All of the examples given thus far have resulted in the production of cyclohexanones with no other functionality in the 6-membered ring. Several reagents have been developed to synthesize

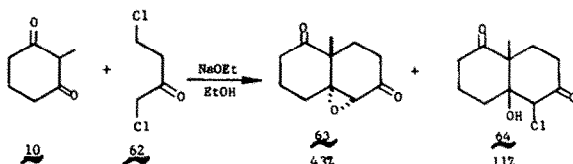
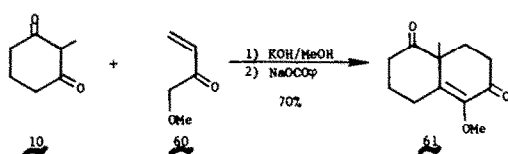
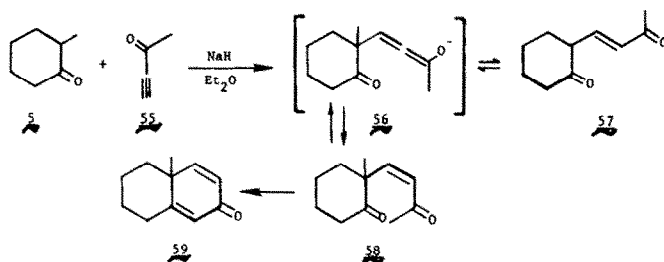
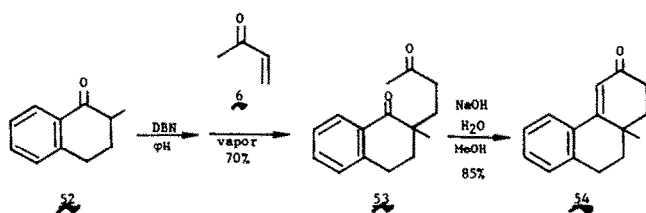
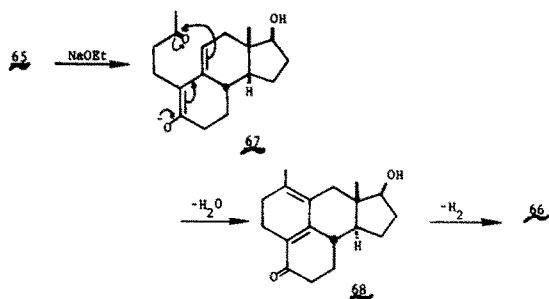






more functionalized rings. Woodward²⁷ has introduced methyl ethynyl ketone **55** as a reagent for the construction of cyclohexadienones although in rather low yields.

This is possibly due to the fact that the enedione intermediate may be largely the *E*-isomer **57** (which cannot cyclize to **59**) rather than the desired *Z*-isomer **58**. Oxygen functionality can also be introduced into the cyclohexenone ring. The enol ether of an α -diketone **61** is produced directly by the use of methoxymethyl vinyl ketone **60**.²⁸ The α -epoxide of the enedione **63** is the major product when 1,4-dichloro-2-butanone **62** is used as an annulation reagent.²⁹



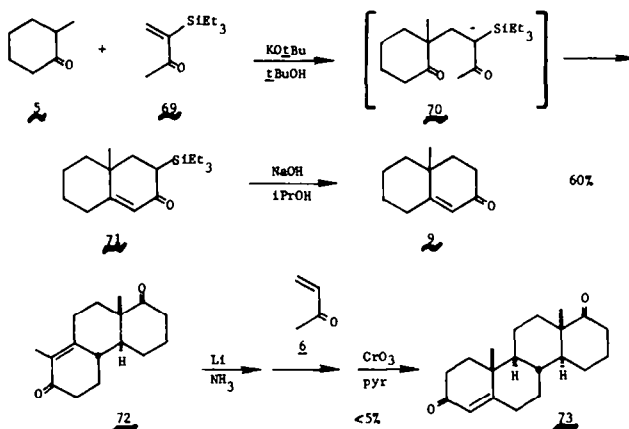
The Michael sequence can also be used with α,β -unsaturated ketones, but again the relatively low acidity of the enones (compared to β -diketones or β -tetralones) causes the yields to be low. Another problem is that the intermediate 1,5-diketone produced may cyclize in an abnormal manner to give undesired products, e.g. **65** $\rightarrow$ **66**.³⁰ In the proposed mechanism, the anion of the enone system, e.g. **67**, acts as the nucleophilic component in the aldol reaction with the saturated ketone to yield an unexpected cyclization product, e.g. **68**, which then aromatizes giving **66**.

(f) α -Silyl enone. In order to allow the use of vinyl ketones with regioselectively formed ketone enolates, α -silyl enones such as **69** were introduced by Stork.³¹ The silyl group in **70** stabilizes somewhat the initial negative charge formed by addition of the enolate ion to the enone, and, most importantly, provides strong steric hindrance which slows down anionic polymerization. Once annulation is complete, the silyl group is removed from the α' -silyl enone **71** with base. This method gives improved yields (70–75%) in a number of cases and most important,

allows for the first time the general use of the Michael addition with vinyl ketones under aprotic conditions.

The major drawback of the Michael sequence in general is that the reactions are usually not compatible with specifically generated enolate ions under aprotic, non-equilibrating conditions. The reagents are generally not reactive enough to trap the enolates generated by reduction of enones by lithium in liquid ammonia³² or those generated by attack of methylolithium on an enol acetate or silyl enol ether.³³ For example, reduction of the tricyclic enedione **72** with lithium in liquid ammonia followed by addition of methyl vinyl ketone, cyclization, and final chromic acid oxidation (to reconvert the alcohol in ring D in steroid nomenclature to the saturated ketone) gave the tetracyclic product **73** in very poor yield (less than 5%).³⁴

The problem in this case is probably polymerization of the enone by the strongly basic enolate, a result also observed in the attempted reduction-annulation of the octalone **9**. The specifically-formed enolate **74** cannot be annulated directly in the ammonia solution, but must first



be converted via a proton source into the decalone **75**. Reaction of this ketone with base in a protic medium gives rise to a mixture of the two equilibrating enolates, **74** and **76**, which on treatment with **6** gives the enone **78** as the major product with the desired isomer **77** being the minor product.

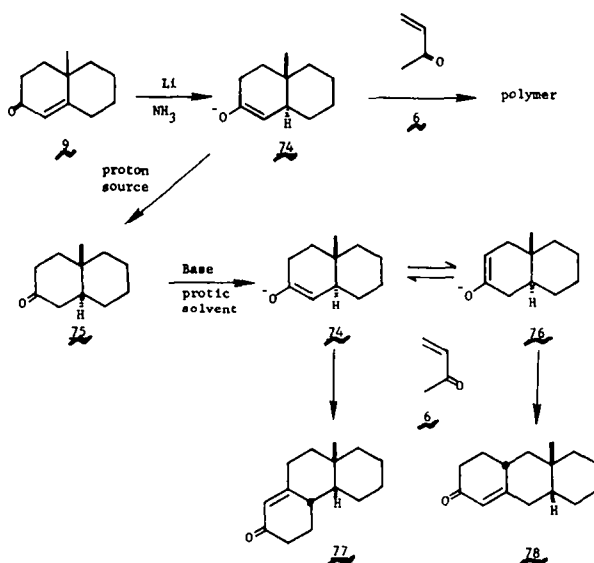
However, Boeckman³⁵ and Stork³⁶ have recently shown that the use of stronger Michael acceptors, namely α -silyl vinyl ketones such as **79**, circumvents these problems since now Michael addition is faster than polymerization and, provided that precautions are taken to insure that the medium is truly aprotic, it is also faster than equilibration of the enolates. For example, the reductive trapping-cyclization sequence using the silyl derivative **79** furnishes cleanly the tricyclic compound **77** in 60% yield, uncontaminated by isomer **78**. Again base treatment removes the silyl group from the intermediate silyl ketone **80** during cyclization. As indicated in the figure, the initial enolate **74** can be trapped as the silyl enol ether **81** and later regenerated in ethereal solution, thus allowing one to examine the purified intermediate spectrally before continuing, if need be.

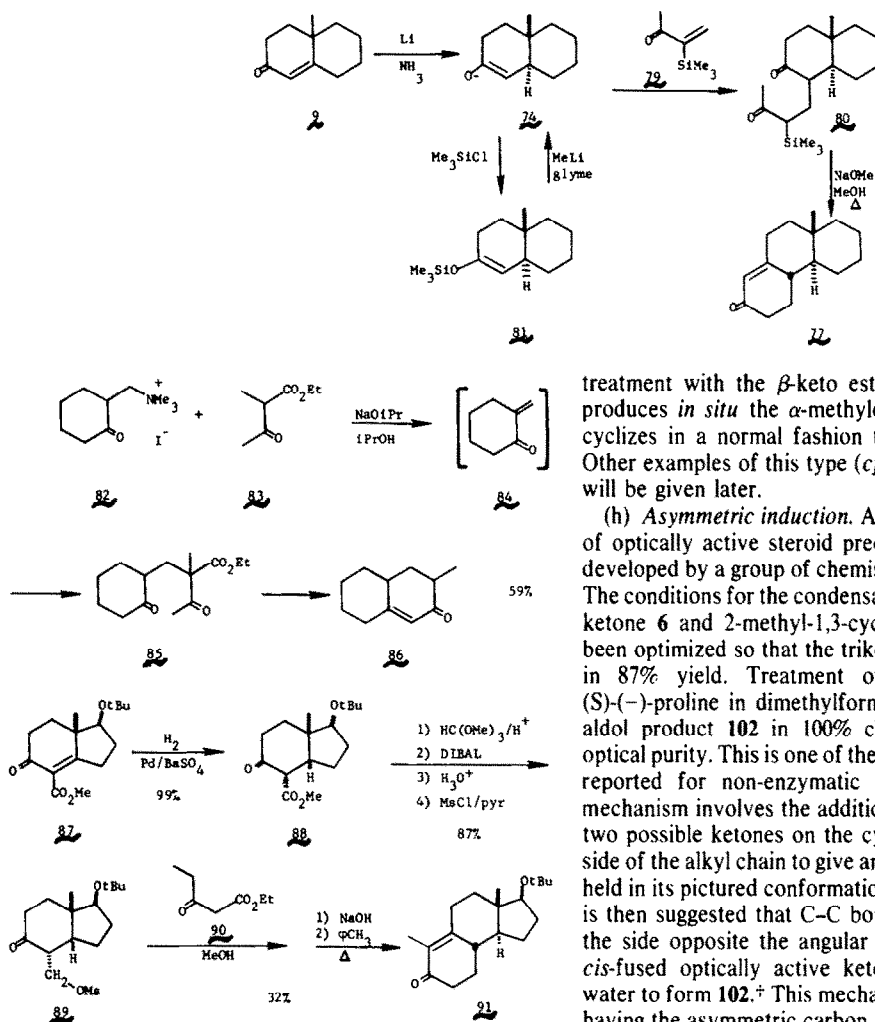
This is the first instance of the successful trapping of a regioselectively generated, less stable enolate ion without equilibration by an appropriate Michael acceptor and thus this result greatly increases the potential usefulness of the Michael reaction annulation sequence.

(g) α -Methylene cyclanone. Annulation sequences have also been reported in which the cyclic ketone functions as the Michael acceptor. In some cases a Mannich base methiodide **82** is the precursor of the α -methylene ketone **84**, which then acts as a Michael acceptor for a β -keto ester **83**.³⁷

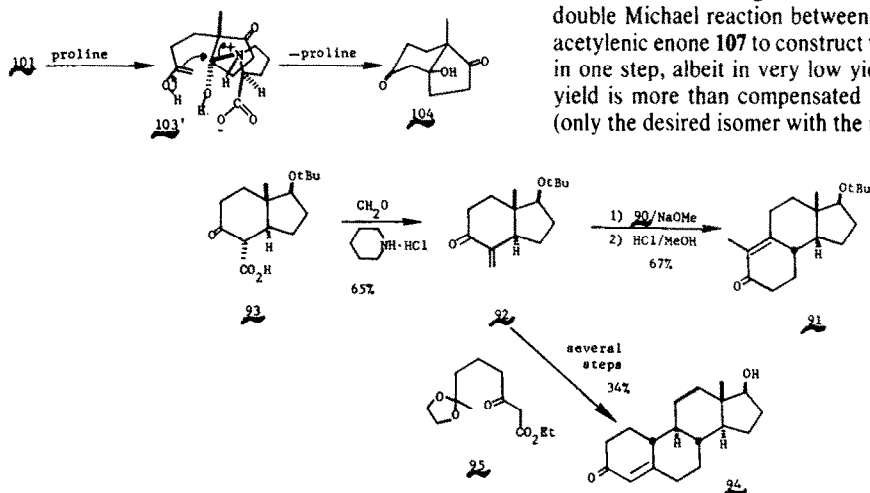
Hajos has recently reported sequences designed for steroid synthesis³⁸ which utilize an α -methylene ketone. In the first sequence the hydrindanone ester **88**, produced quantitatively from **87** by catalytic reduction, could be converted to the keto mesylate **89** in good yield. Addition of the β -keto ester **90** followed by cyclization, saponification, and decarboxylation yielded the tricyclic compound **91**, via the α -methylene ketone **92** as an intermediate produced *in situ*. This compound could be isolated in the second reported procedure by treatment of the keto acid **93** with formaldehyde and piperidine hydrochloride. Addition of the β -keto ester **90** followed by acid-catalyzed cyclization and decarboxylation gave the tricyclic **91** in higher yield. Tetracyclic products, e.g. **94**, can also be produced.

A method of forming an α -methylene ketone by a reductive trapping process has recently been developed by Stork.³⁹ Reduction of an enone with lithium in liquid ammonia leads to a specific enolate which can then be trapped as the hydroxymethyl compound **96** by the introduction of gaseous formaldehyde. Tosylation and





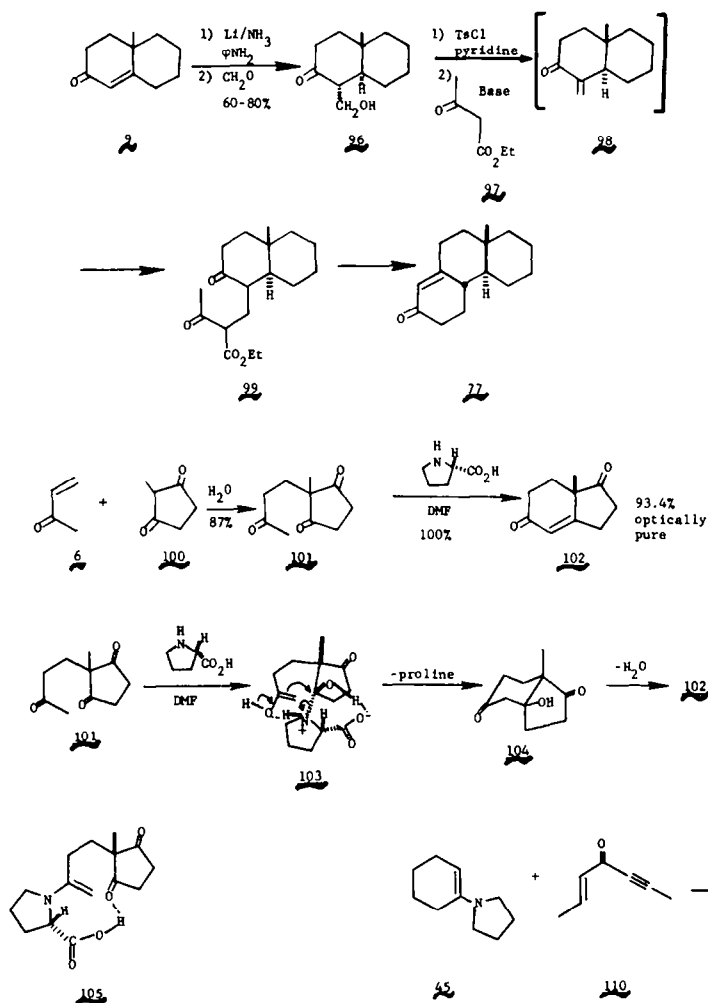
†The reaction $103 \rightarrow 104$ is formally a substitution reaction proceeding with *retention* which can occur only if there is a large amount of S_N1 character in the reaction. Perhaps a better mechanism of this type (via a carbinolamine such as 103) would be the following: attack of the bulky proline molecule *trans* to the alkyl chain (*cis* to the smaller methyl group) to give an intermediate $103'$ which is then displaced by the enol function in an S_N2 type reaction with *inversion* of configuration to give the ketol 104 .



treatment with the β -keto ester 97 in a basic medium produces *in situ* the α -methylene ketone 98 which then cyclizes in a normal fashion to the tricyclic enone 77 . Other examples of this type (*cf* compounds 135 and 156) will be given later.

(h) *Asymmetric induction*. A very interesting synthesis of optically active steroid precursors has been recently developed by a group of chemists at Hoffman-LaRoche.⁴⁰ The conditions for the condensation between methyl vinyl ketone 6 and 2-methyl-1,3-cyclopentanedione 100 have been optimized so that the triketone 101 is now available in 87% yield. Treatment of 101 with a trace of (S)-(-)-proline in dimethylformamide gives the cyclized aldol product 102 in 100% chemical yield and 93-4% optical purity. This is one of the highest optical yields ever reported for non-enzymatic synthesis. The proposed mechanism involves the addition of proline to one of the two possible ketones on the cyclopentane ring from the side of the alkyl chain to give an intermediate 103 which is held in its pictured conformation by hydrogen bonding. It is then suggested that C-C bond formation occurs from the side opposite the angular methyl group to give the *cis*-fused optically active ketol 104 , which then loses water to form 102 .† This mechanism has the advantage of having the asymmetric carbon atom of proline only three carbons removed from the center of asymmetric induction, whereas other possible mechanisms involving the enamine of the acyclic ketone 105 would have the asymmetric C atom much farther removed. However, we will see later (compounds 138 and 139) other examples of asymmetric induction in which the asymmetric carbon is indeed far from the reaction site.

(i) *Double Michael annulation*. In an ingenious synthesis of the antibiotic griseofulvin 109 , Stork used a novel double Michael reaction between the ketone 106 and the acetylenic enone 107 to construct the desired spiro system in one step, albeit in very low yield.⁴¹ However, the low yield is more than compensated by the stereoselectivity (only the desired isomer with the methyl group *syn* to the

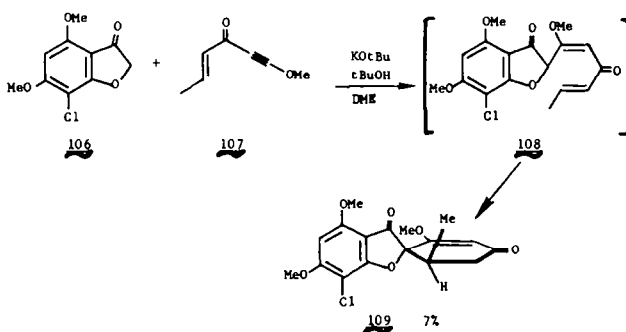


carbonyl is obtained) and the simplicity of the synthesis. The procedure has since been improved by Mulholland so that the yield of griseofulvin and its analogues can be raised to 20%.⁴² The initial Michael addition to the cross-conjugated acetylenic enone **107** occurred at the triple bond. This is due to the inductive effect of the methoxyl group which increases the electrophilicity of the acetylenic carbon β to the ketone function. In other cross-conjugated acetylenic enones only simple Michael addition to the double bond was observed, e.g. **110** $\rightarrow$ **111**.⁴³ The reason for the low yield in the griseofulvin annulation may be related to the reason for the low yields of cyclohexadienone formation mentioned earlier (**55** $\rightarrow$ **59**), that is, that the product of initial addition, **108**, may

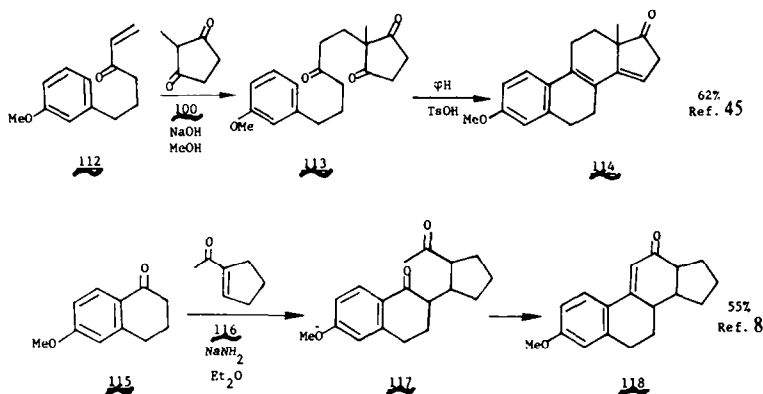
exist largely in the opposite geometric isomer, thus precluding further cyclization.

(2) Bis- and tris-annulation

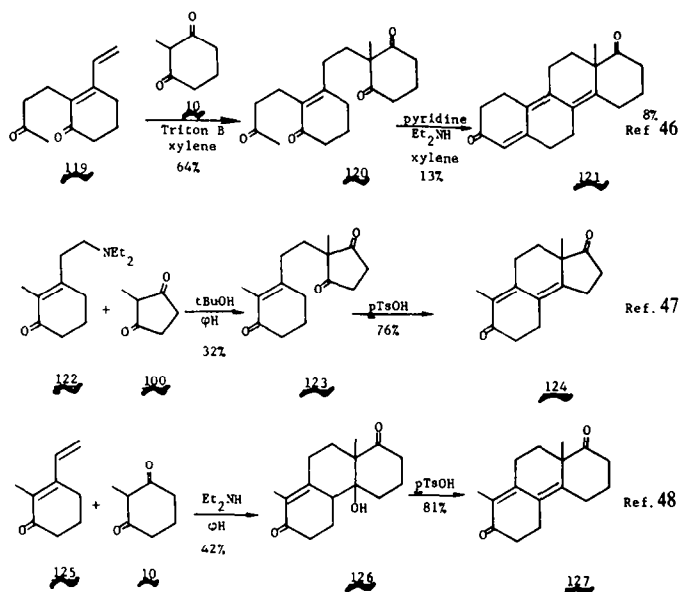
(a) *Vinyl ketone*. Thus far, all the examples cited have involved the construction of only one ring onto the existing system. There are also numerous instances of the addition of several rings at once via Michael reactions. The steroid literature is full of examples of additions of carbonyl compounds (usually β -diketones) to enones (1,4 addition) dienones (1,6 addition), and trienones (1,8 addition). An excellent survey of these methods has recently been published⁴⁴ and a few examples are appropriate.



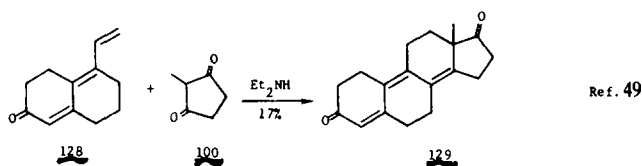
1,4 Addition



1,6 Addition



1,8 Addition



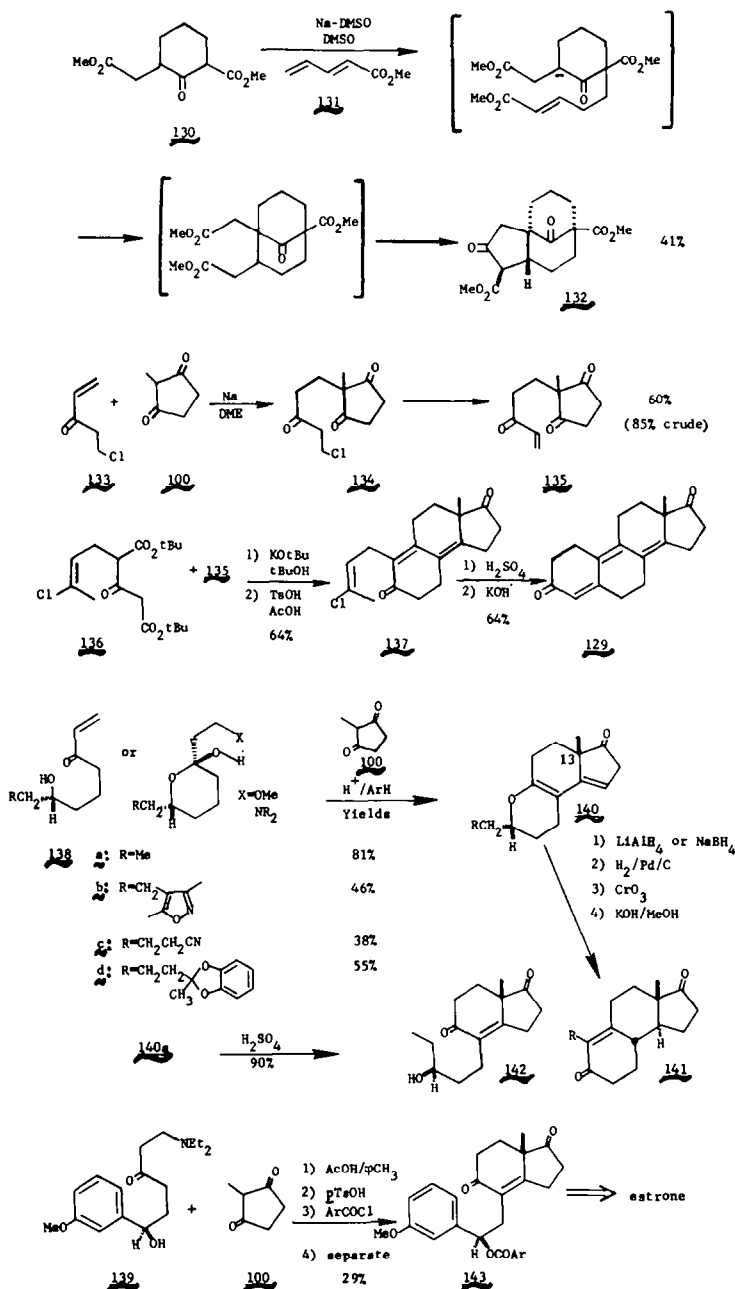
An interesting example of 1,6 addition followed by 1,4 addition and eventual Dieckmann cyclization has been reported recently.⁵⁰ The reaction of the diketone ester **130** with methyl β -vinylacrylate **131** produced the tricyclic compound **132** in 41% yield via a multi-step sequence involving an internal proton transfer.

Danishefsky has introduced the method shown below, which involves the Michael addition of the β -keto ester **136** to the enone **135** followed by acid treatment to construct the tetracyclic compound **129** containing the steroid backbone.⁵¹ The over-all yield from methylcyclopentan-1-one to the tetracyclic compound **129** is 34%. The hydrolysis of the vinyl chloride will be treated later.

(b) *Asymmetric induction.* Saucy *et al.* at Hoffman-LaRoche have developed a synthesis of optically active

steroids using an optically active enone, Mannich base, or β -alkoxy ketone in the key annulation step.⁵² A series of optically active compounds, **138(a-d)** and **139**, was synthesized and reacted with methylcyclopentan-1-one **100** as shown. The stereochemistry of the C-13 methyl group (steroid numbering) is determined by the absolute configuration of the hydroxyl group in the vinyl ketone. The intermediate optically active dienol ether **140** was then usually converted to the reduced and further cyclized enone **141** via several high-yield steps.^{52a} In one case the mono-annulated product was prepared in high yield, **140** $\rightarrow$ **142**. A modified sequence was utilized for the production of optically active estrone, **139** $\rightarrow$ **143**.^{53b}

The mechanism of this annulation sequence, which proceeds with high asymmetric induction (as high as 90%



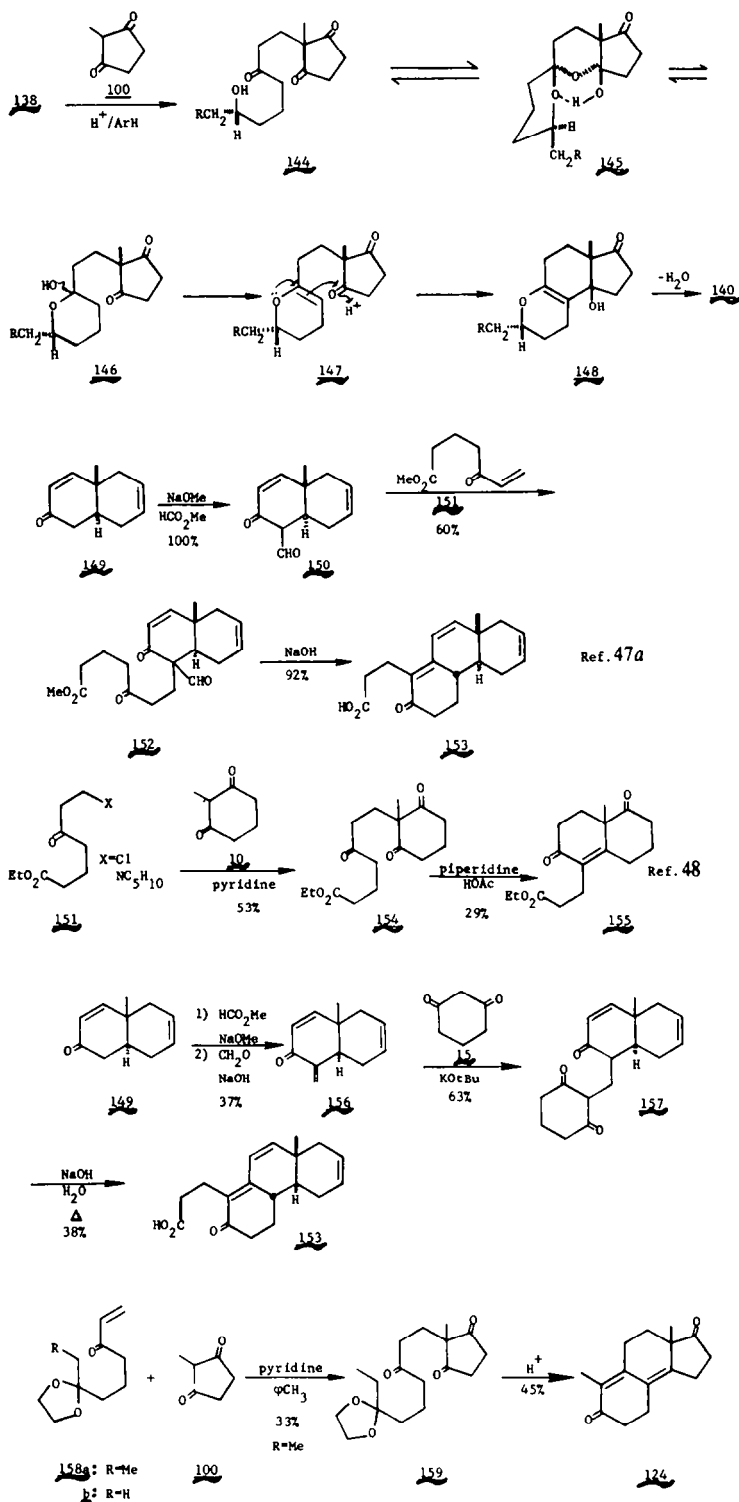
in some cases), is not known in detail. One suggested mechanism involves initial Michael addition to give the uncyclized hydroxytrione **144** which is in equilibrium with several hemiacetal forms (one of which, **145**, has been isolated from partial reaction mixtures). This mixture is converted to the cyclic enol ether **147** which then cyclizes as shown via ketol **148** to produce only compound **139** with the C-13 methyl group β (cf. compound **105**).

(c) *Vinyl ketone ester*. Other functionalized enones have been used in annulation. The methyl (or ethyl) ester **151** has been reacted with β -keto aldehydes,⁵³ e.g. **150**, or β -diketones,⁵⁴ e.g. **10**, and subsequently cyclized. In both cases, further elaboration of the next ring was accomplished by the enol lactone-Grignard method, which will be discussed later. The tricyclic intermediate **153** was also synthesized from **149** by an interesting but less efficient

method.^{53b} The enone **149** was converted to the cross-conjugated dienone **156**, which was then reacted with cyclohexanedione **15** to give trione **157**. Base catalyzed ring opening and subsequent cyclization led to the intermediate **153**. A similar type of operation has been mentioned previously, i.e. **92** + **95** $\rightarrow$ **94**.

(d) *Vinyl ketone ketal*. Other similar bis-annulation reagents are the ketal enones **158a**⁵⁵ and **158b**.⁵⁶ The major advantage with these is that the ketal can be converted to a ketone in one high-yield step. The yields are comparable to those obtained with the other enones mentioned in this section.

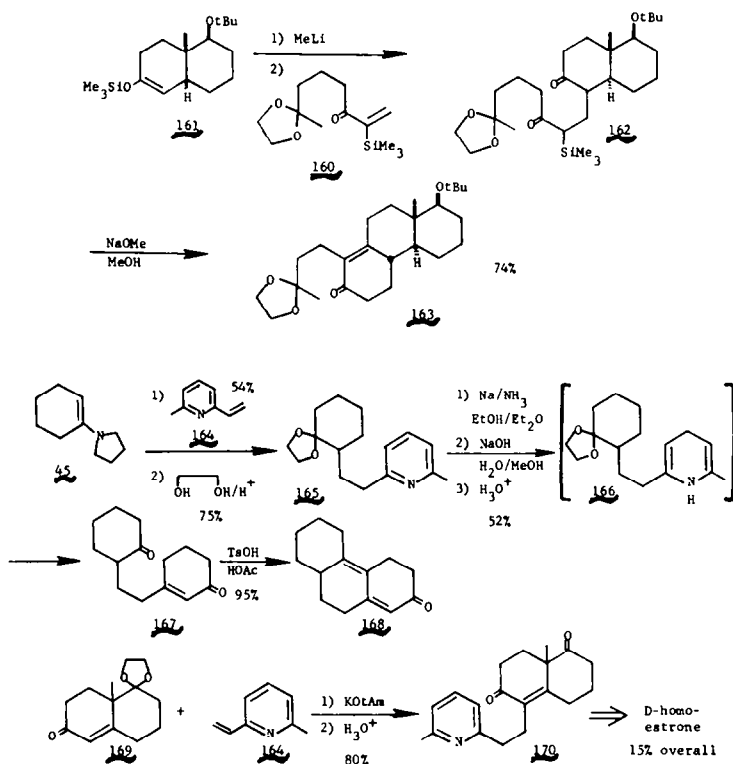
(e) *Silylvinyl ketone ketal*. Again in an attempt to make the enone a better Michael acceptor, the silyl derivative **160** was synthesized.⁵⁶ This reagent is also able to trap regioselectively generated enolates under non-equilibrating aprotic conditions, as was its lower analogue



79. The silyl group allows the use of kinetically generated enolate ions under aprotic conditions and is removed later by base. The overall yields, e.g. 161 $\rightarrow$ 163, are quite good.

(f) *Vinylpyridine*. An interesting bis-annulation reagent has been developed by Danishefsky in which a 2-vinylpyridine derivative 164 serves as the Michael acceptor.⁵⁷ After Michael addition and protection of the ketone, the pyridine ring in compound 165 is subjected to a Birch reduction to give the intermediate dihydropyridine

166, which is hydrolyzed and cyclized in acid to the keto enone 167. Acid-catalyzed cyclization affords the tricyclic dienone 168. This procedure has been used to synthesize D-homo estrone from 169 in 15% overall yield. This method suffers from the somewhat cumbersome, multi-step elaboration of the diketone function from the pyridine moiety and can lead to mixtures of products in varying overall yields, ranging from high (e.g. 169 $\rightarrow$ 170) to fair (e.g. 45 $\rightarrow$ 167).



(3) Conclusion

In general, then, one can see that the annulation sequence based on the Michael reaction has been used quite extensively and has achieved a moderate degree of success. In a number of cases the yields are relatively low but can be improved by several modifications. Considerable success has been obtained in the use of the method for adding more than one ring at a time. A major drawback of the sequence—that the vinyl ketones were not reactive enough to trap specifically generated enolate ions—seems to have now been surmounted with the advent of the silyl derivatives **79** and **160**.

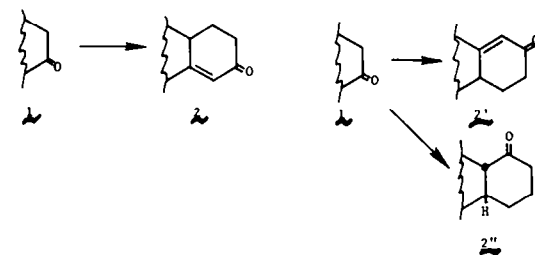
2. NUCLEOPHILIC ADDITION

The second basic category of annulation reactions can be grouped under the rather broad heading of nucleophilic additions. This title is meant to encompass essentially all annulation sequences which involve the addition of an organometallic reagent or ylide to a carbonyl derivative at some step.

Nucleophilic reagents can be used to form the same cyclohexanone system from a ketone or its derivative as is formed in a Michael reaction (e.g. **1** $\rightarrow$ **2**), that is, to give normal annulation. However several methods have recently been published which convert a ketone system into a different cyclohexanone system (e.g. **1** $\rightarrow$ **2'**), or into a saturated ketone of a different structural type altogether (e.g. **1** $\rightarrow$ **2''**). These types of conversions will be grouped under the heading of "Modified Annulation."

(1) Normal annulation

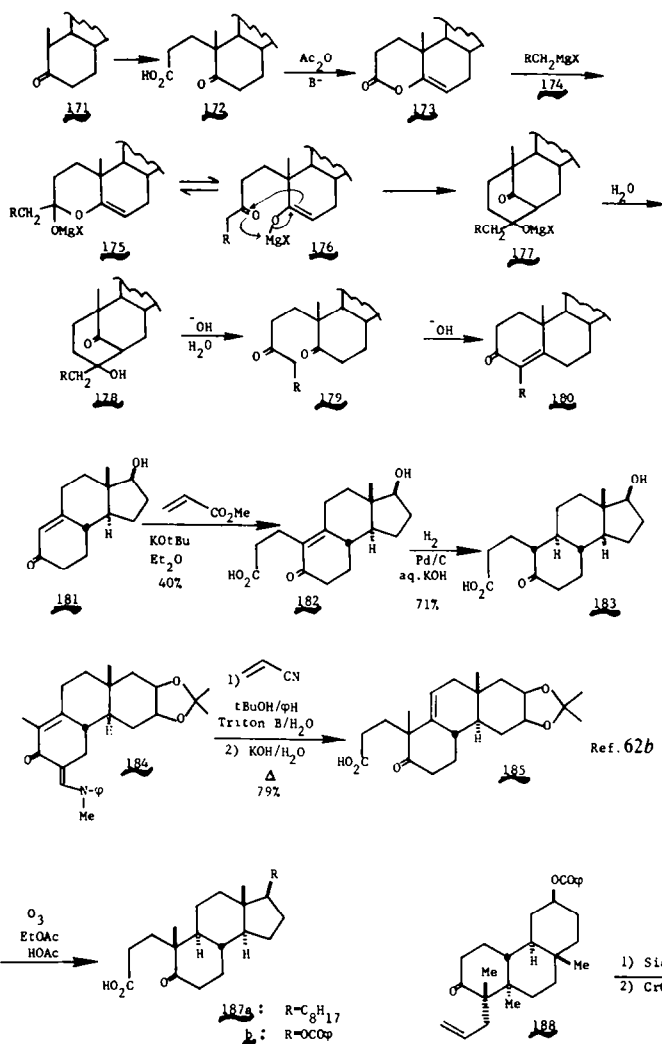
(a) *Enol lactone-Grignard*. The most common of the nucleophilic addition processes is the enol lactone-Grignard method developed by Turner and Fujimoto to introduce a labelled carbon at the 4-position of steroidal enones.⁵⁸ This method involves the addition of a Grignard reagent **174** to a 6-membered enol lactone **173** which



proceeds via the intermediates **175** and **176** as shown in the mechanism to give the bicyclic ketol salt **177**. The Grignard reaction stops at this stage since the normally reactive carbonyl function is now so sterically hindered that the Grignard reagent no longer adds to it. The ketol **178** obtained upon hydrolysis undergoes a base-catalyzed reverse aldol condensation to the 1,5-diketone **179**, which then cyclizes to the final enone product **180**.⁵⁹

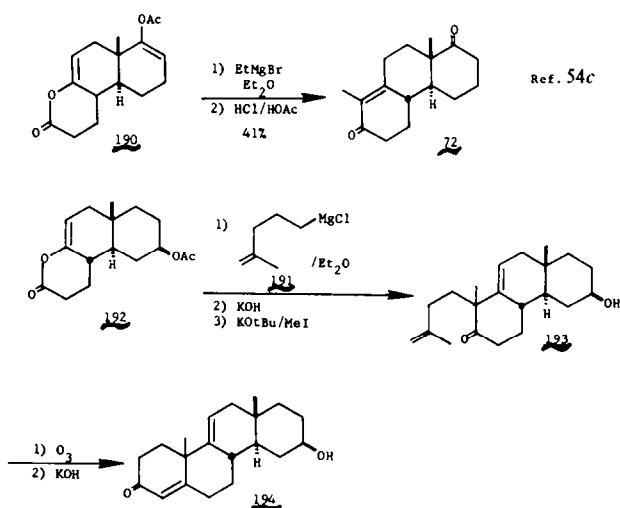
The enol lactone **173** is nearly always formed by the addition of basic acetic anhydride to the keto acid **172**, which is itself synthesized in a variety of ways.⁶⁰ The Michael addition of a ketone enolate to acrylic esters can lead to the acid directly,³⁰ e.g. **181** $\rightarrow$ **182**, or to the ester which can be hydrolyzed to the acid in base.⁶¹ Michael addition to acrylonitrile followed by base hydrolysis also yields the keto acid,⁶² e.g. **184** $\rightarrow$ **185**. The ozonolysis of a cyclohexenone system, one of the first methods developed,^{58a} has been used frequently.⁶³ A variant on this method employs ruthenium tetroxide as the oxidizing agent.⁶⁴ The keto acid can also be formed via the addition of a bis-annulation reagent such as **151**. Finally a multi-step but high-yield procedure has been developed involving alkylation with allyl bromide followed by hydroboration and oxidation,⁶⁵ e.g. **188** $\rightarrow$ **189**.

Several Grignard reagents have been used in this sequence with methylmagnesium bromide being the most



common.^{59,63} Ethylmagnesium bromide was used to give a methyl-substituted enone.^{54c,65} Several different Grignard reagents have been used to add the elements of an additional ring all at once. The first use of a functionalized Grignard reagent was that derived from 5-chloro-2-

methyl-1-pentene **191** which reacted with the enol lactone **192** to give a diketone.^{63a} After base-catalyzed cyclization and methylation, ozonolysis of compound **193** yielded a second diketone which was cyclized by base to yield enone **194** and complete the sequence.



A simpler Grignard reagent **195**, utilizing a ketal protecting group, was used successfully by French workers in the following sequence.⁶⁶ In this manner, the enol lactone **196** could be converted to the tetracyclic dienone **198** in moderate yield.

Aromatic A-ring steroids have been prepared by reacting the Grignard reagent **199** with the enol lactone **200** to give the bicyclic ketol **201** which is then cyclized to the bicyclic enone **202**.⁶⁷ When the optically active enol lactone **200** is employed, optically active steroids are obtained.

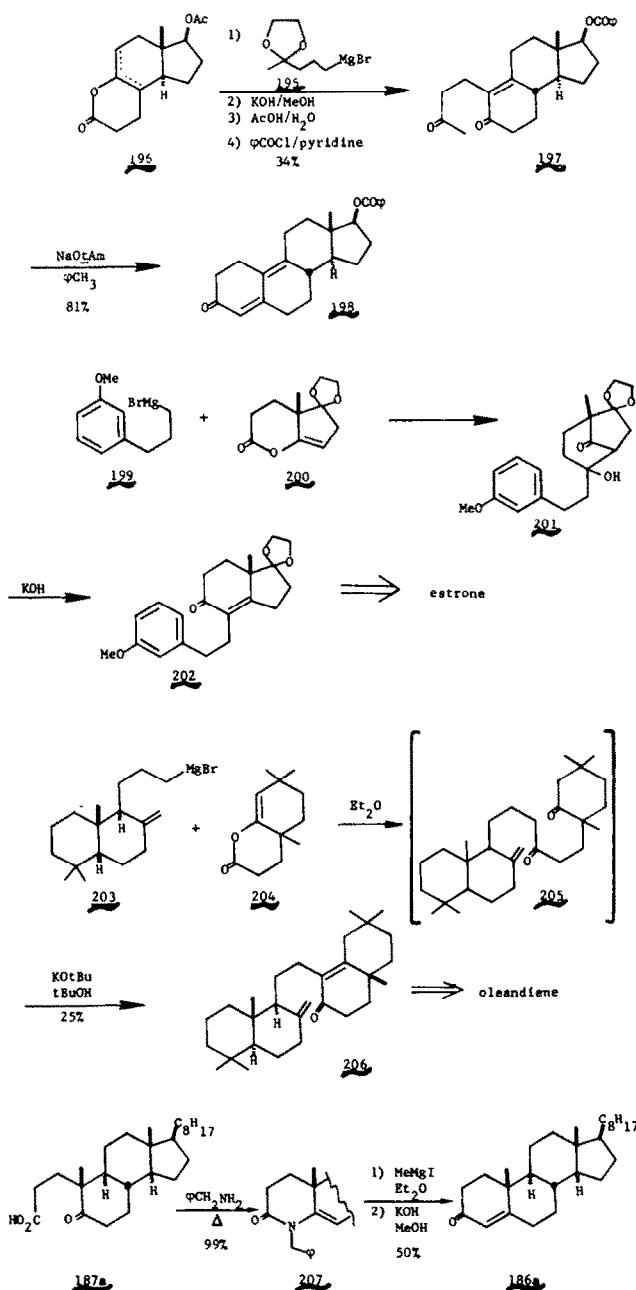
An application of this sequence to triterpene synthesis has been described.⁶⁸ The addition of the Grignard reagent **203** to the enol lactone **204** followed by base-catalyzed cyclization yields the enone **206**, which was then converted to oleandriene in very low yield.

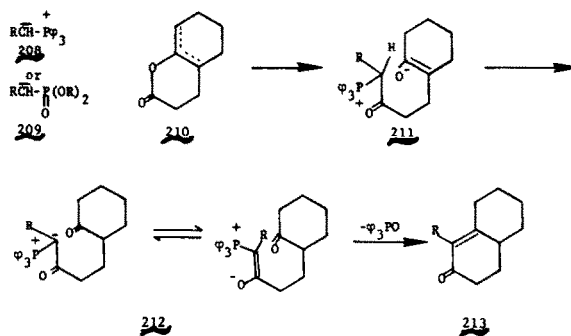
(b) *Enol lactam-Grignard*. An interesting variant on

this method has been reported by Woodward, involving the use of an enol lactam rather than an enol lactone.^{62b} The enol lactam **207**, formed in excellent yield from the keto acid **187a**, is reacted with methylmagnesium iodide and the resulting diketone cyclized to give cholestenone **186a** in 50% yield.

The yields for the enol lactone-Grignard method range from poor to good. It is a multistep process that can be somewhat limited by other functionality in the molecule which may be unstable to the Grignard reaction.

(c) *Enol lactone-phosphorane*. Fried *et al.*, have recently introduced a modification of this sequence which employs a phosphonium ylide **208** or phosphonate anion **209** rather than a Grignard reagent.⁶⁹ The carbanion adds to the enol lactone **210** to yield a keto phosphorane or keto phosphonate anion **212** formed via the initial enolate **211** by proton transfer. Cyclization then occurs by a normal

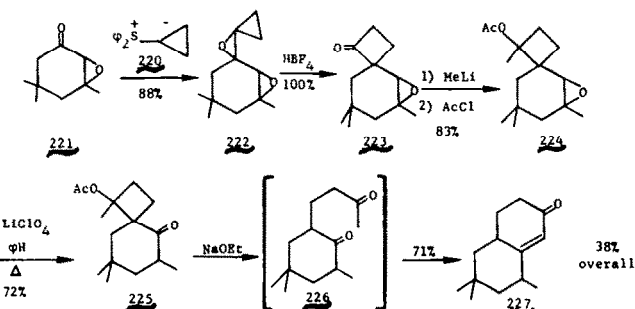
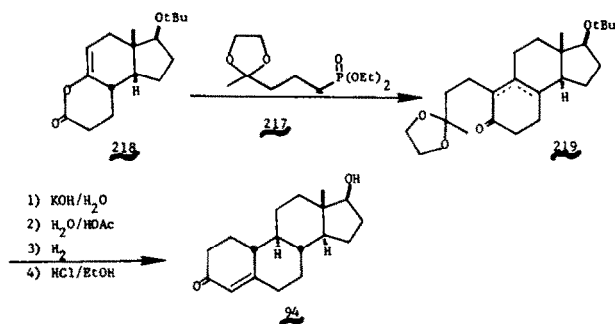
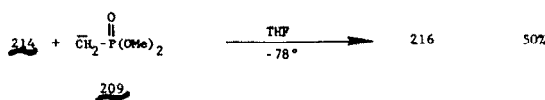
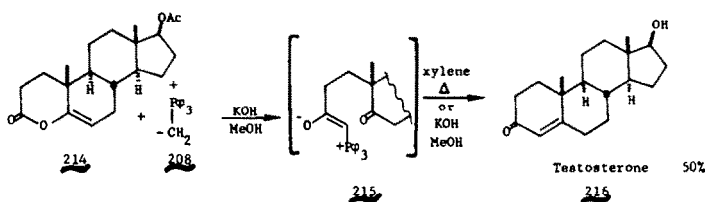




intramolecular Wittig or Wadsworth-Emmons reaction to give the enone **213**. This expands the scope of this annulation process since phosphoranes or phosphonate anions can be prepared with functional groups in other parts of the molecule whereas the corresponding Grignard reagents either cannot be formed or self-condense once formed. The yields are generally good, e.g. **214** $\rightarrow$ **216** and a bis-annulation reagent of this type **217** has been used successfully, e.g. **218** $\rightarrow$ **220**. In the case of enol lactone **214** the intermediate keto phosphorane **215** can be isolated and then converted to testosterone **216** either thermally or by treatment with base.

(2) Modified annulation

(a) *Sulfur ylide*. The first of the methods to convert a ketone into a cyclohexenone of modified structure was developed by Trost and involves initial attack of a sulfur ylide **220** on an α,β -epoxyketone **221** to give the diepoxide **222** in good yield.⁷⁰ A four-step sequence follows utilizing epoxide-ketone rearrangements at two key steps leading to the acetoxy ketone **225**, which upon treatment with base is cleaved and cyclized to the enone **227** via the diketone **226**. Although the yield of each step is good, the fact that it is a multi-step process forces the overall yield to be only 38%.



(b) *Ketal Grignard*. A simpler procedure for accomplishing the same general transformation (i.e. $1 \rightarrow 2'$) has been recently developed by Stork.⁷¹ Refluxing a solution of 2-benzoyloxycyclohexanone **228** and the bromo-ketal Grignard reagent **229** in tetrahydrofuran affords directly the ketal ketone **230** in 50% yield. Hydrolysis and cyclization give the enone **48** in 45% overall yield. The mechanism of this conversion is apparently similar to that of the Serini reaction⁷² and probably involves a hydride shift as was shown for 3-methyl-2-benzoyloxycyclohexanone **231**.

The initial Grignard adduct **232** undergoes a modified Serini reaction via the tetrahedral intermediate **233** to give the opposite benzoyloxy magnesium salt **234**. This compound then collapses with hydride transfer and loss of benzoate ion to the ketal ketone **235**, which could be cyclized to the enone **51**. None of the isomer resulting from alkyl migration from compound **232** was detected. However, the sluggish reactivity of the Grignard reagent **229** limits the applicability of this sequence to unhindered carbonyl compounds.

(c) *Organoborane*. A general method for the transformation of a cyclic ketone to a bicyclic ketone of totally different structure (cf $1 \rightarrow 2'$) has been developed by Brown.⁷³ Conversion of a simple cyclic ketone, e.g. cyclohexanone **236**, to the 1,4-diene **237** is easily accomplished by addition of allyl Grignard reagent followed by acid-catalyzed dehydration. Treatment of the diene with hexyl borane **238** affords the borane **239**, which can be carbonylated and oxidized to the bicyclic ketone **240** in 66% yield from the diene **237**. Substitution of the 1,3-diene **241** (prepared from cyclohexanone by acetylide ion addition, partial hydrogenation, and dehydration) into this sequence allows for the preparation of the

hydrindanone **242**. Due to *cis*-addition of the borane across the double bond and oxidation with retention to the carbonyl, only products with the *trans*-ring juncture are obtained in all cases. However, the application of this method to the construction of angularly substituted systems has not been reported.

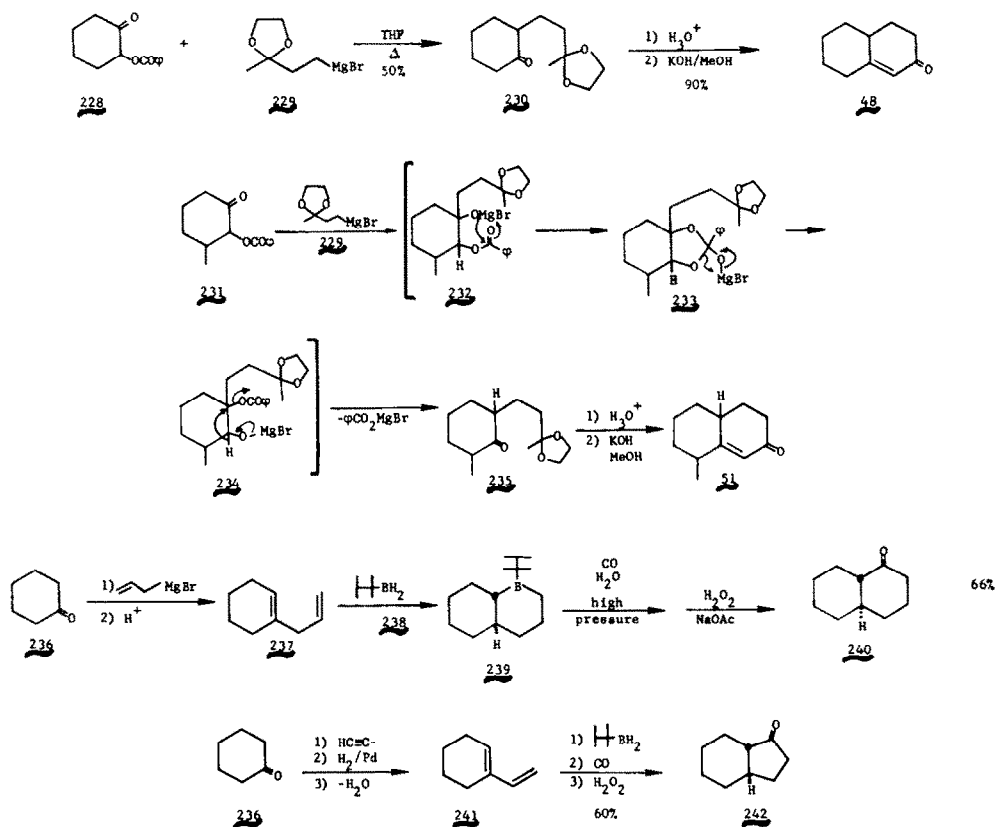
(3) Conclusion

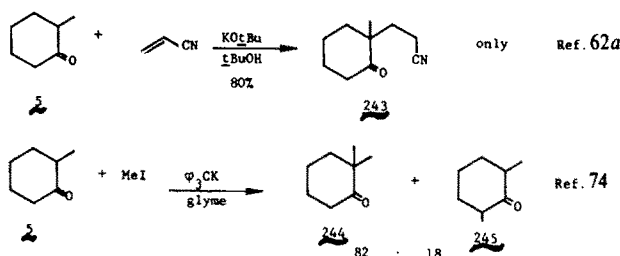
In general the nucleophilic reagents give fair yields in a multi-step process. They are useful, however, for adding the elements of a second ring all at once. In addition, they introduce the possibility of converting a ketone into a cyclic ketone of a different structure than that possible by Michael reaction or alkylation.

3. ALKYLATION

The third category of annulation reactions comprises all those reagents which are attached to the carbonyl compound by means of alkylation. These reagents have the greatest potential since they may be capable of trapping regioselectively generated enolate ions under aprotic, non-equilibrating conditions. They may be subdivided into alkyl halides (and sulfonates) and allylic (or benzylic) halides. A minor drawback of any reagent introduced by alkylation rather than by a Michael reaction is that some of the selectivity in the site of attachment may be lost. For example, the Michael addition of 2-methylcyclohexanone **5** to acrylonitrile affords only the 2,2-disubstituted product **243**, whereas an 82:18 mixture of the 2,2- and 2,6-disubstituted products, **244** and **245** respectively, is produced in the alkylation of **5** with methyl iodide.

However, this problem can generally be overcome by the use of highly reactive alkylating agents and the





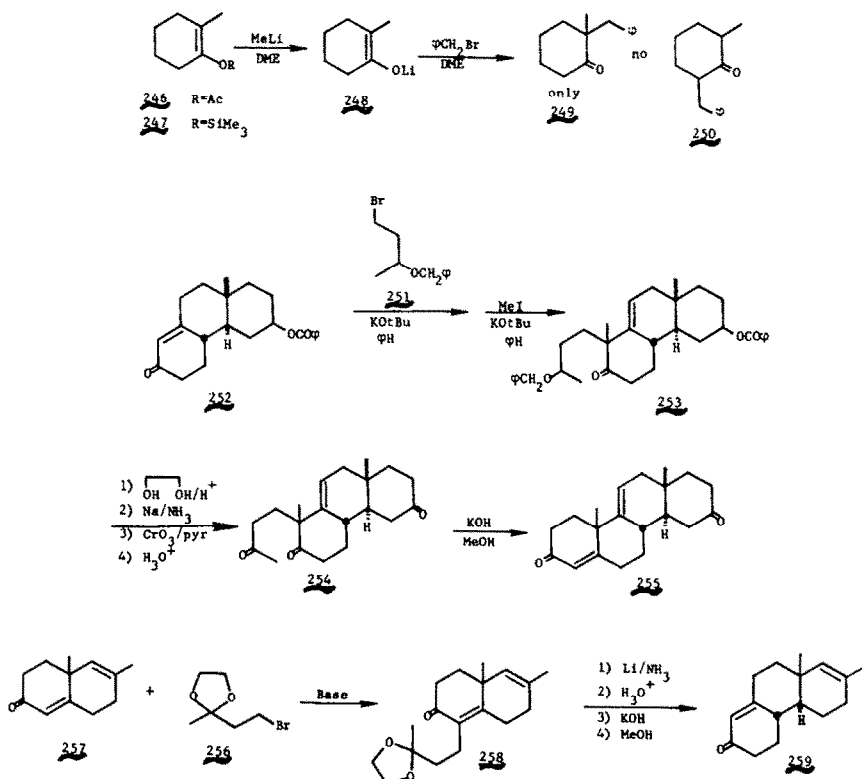
regiospecific enolate ions generated from either enol acetates or enol silyl ethers.³³ For example, treatment of the enol acetate **246** or the enol silyl ether **247** with methyl lithium generates the specific lithium enolate **248** (and an equivalent of lithium *t*-butoxide or tetramethylsilane, respectively). This enolate can be trapped with benzyl bromide to give only the 2,2-disubstituted product **249** with none of the 2,6-isomer **250** being formed. It should be stressed again, however, that this process works well only when very reactive alkylating agents (methyl iodide, allylic halides, benzylic halides, etc.) are employed.

(1) Alkyl halides

(a) *Halo ether*. Many alkyl halides have been tried in annulation reactions, with only a moderate degree of success. The first to be successfully employed was 1-bromo-3-benzyloxybutane **251**,^{63a} which was used to convert the tricyclic enone **252** with subsequent methylation into the dialkylated ketone **253**. The protected carbonyl function was then unmasked to the diketone **254** via several steps, namely, ketalization of the carbonyl, removal of the benzyl protecting group with sodium in liquid ammonia, oxidation, and deketalization. Base-

catalyzed cyclization of the diketone **254** smoothly afforded the tetracyclic enone **255**. This method suffers from two drawbacks. First, the alkylation step introduces a temporary asymmetric center into the molecule, e.g. **253**, and a mixture of diastereomers will be produced, adding complexity to the sequence. The asymmetry is eliminated in the following steps, so that this is more of a nuisance than a real problem: The second disadvantage is that the means by which the carbonyl function is unmasked is multi-step and somewhat cumbersome.

(b) *Halo ketal*. Perhaps the most desirable and the simplest reagent would be the ethylene ketal of 1-bromo-3-butanone **256** first introduced by Stork.^{75,18b} This compound has been used a few times but only with moderate success. The ease with which the ketal can be removed and its stability in highly basic media recommend its use. However, the yields of alkylation using **256** are only fair, e.g. **257** → **258**. Once alkylation is complete, hydrolysis and cyclization proceed quite well to furnish the enone **259**. The homologue of **256**, 1-bromo-3-pentanone ethylene ketal **260**, has also been employed with somewhat similar results.⁷⁶ Under optimum conditions, the enone **261** gave a 50% yield of the desired alkylated product **262**, with the O-alkylated product **263** accounting for 23% of the total product mixture. The



major disadvantages of both reagents **256** and **260** are the relatively low reactivity of the halides and their tendency to dehydrohalogenate (both presumably due to the strong electron withdrawing effect of the ketal oxygens) and the high proportion of O-alkylation in polar aprotic solvents.

The reactivity of two other similar alkylating agents has also been investigated. The ketal iodide **264**, although more difficult to prepare, is more reactive than the bromide. Its use in the alkylation of the unsaturated ketone **265** to afford enone **266** in fair yield has been described by Fried *et al.*⁷⁷

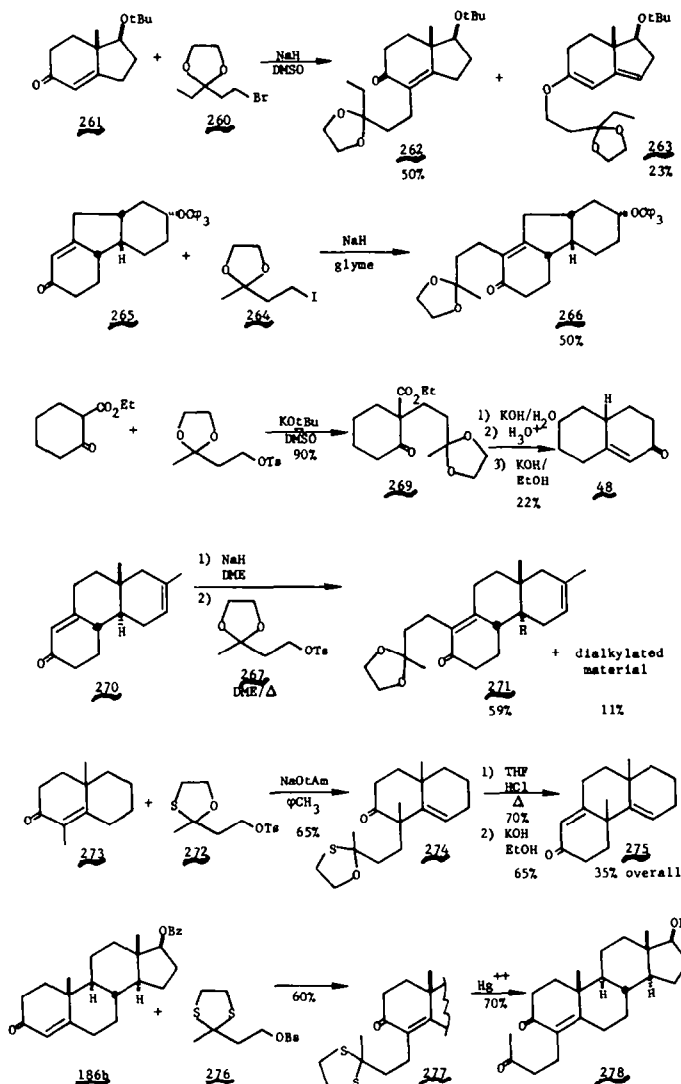
The corresponding tosylate **267** could also be prepared,⁷⁸ but initial results showed that it alkylated only acidic carbonyl compounds, e.g. **268** → **48**, in high yield.⁷⁹ However, recently Valenta has shown that alkylation of the tricyclic enone **270** with the tosylate **267** affords the ketal **271** in good yield along with a small amount of dialkylated material.⁸⁰

(c) *Hemithioketal and thioketal sulfonate*. If the electron withdrawing inductive effect of the ketal oxygens is the cause of the low reactivity of these reagents, then substitution of a less electronegative sulfur atom for one or more O atoms should render the resulting hemithioketal and thioketal more reactive. This is in fact the case. The hemithioketal tosylate **272** is capable of

alkylating saturated ketones and enones in moderate yield.⁷⁹ It, too, suffers from the problem of asymmetry previously discussed, in that upon alkylation a second center of asymmetry is produced, leading to a mixture of diastereomers. The reagent is useful primarily for α,β -unsaturated ketones having no α -hydrogens (so that the problems of dialkylation do not arise) such as **273**, where the overall yield of enone **275** is only about 35%. Other analogous sulfonates, e.g. brosylate and nosylate, gave somewhat poorer results.⁸¹

The thioketal brosylate **276** gives somewhat better results.⁷⁹ Alkylation of testosterone benzoate **186b** furnishes in good yield enone **277**, which is then converted to diketone **278** by mercuric ion catalyzed hydrolysis, again in good yield. Compounds analogous to **276**, e.g. the bromide, tosylate, and mesylate, give similar results.⁸¹

(d) *Unsaturated alkyl halides*. Several other alkyl halides which might seem to be obvious choices proved to be unsuitable. 2-Methyl-4-halo-1-butene **279** and 4-halo-1-butyne **280** are both dehydrohalogenated under basic conditions.⁷⁸ The former could have been converted to a 3-keto-alkyl chain after alkylation by ozonolysis, the latter via mercuric ion catalyzed hydration. Caine has developed a clever scheme which circumvents the problem of direct use of reagent **280**.⁸² Alkylation of 2,6-





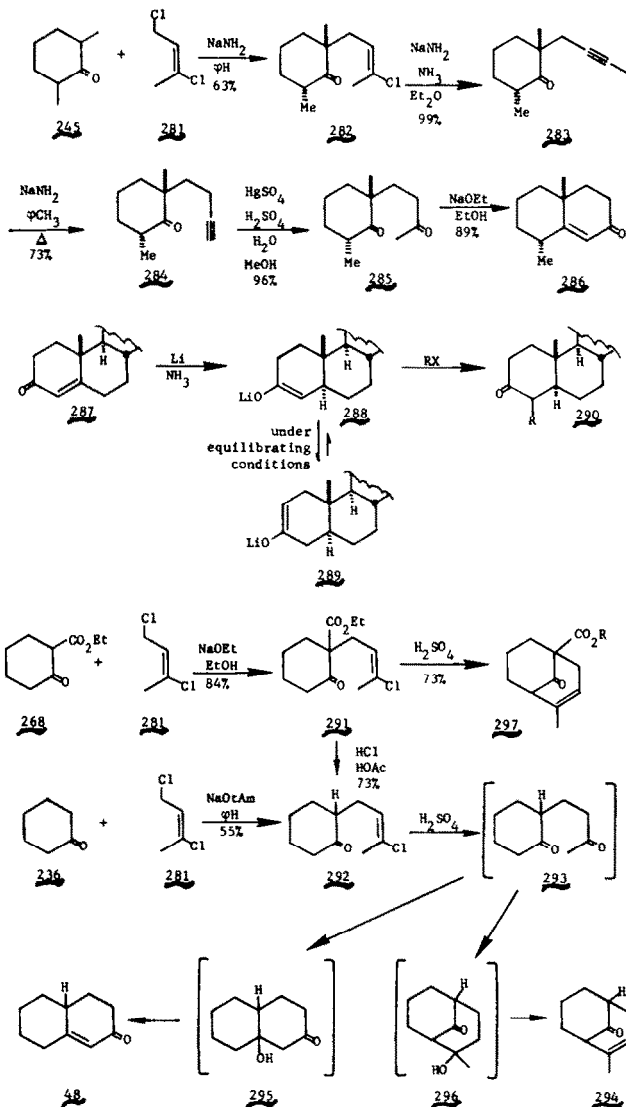
di-methylcyclohexanone **245** with 1,3-dichloro-2-butene **281** proceeds in good yield (as will be discussed later) to afford the ketone **282**. Base-catalyzed elimination to the internal acetylene **283** followed by base-catalyzed isomerization to the terminal acetylene leads to the intermediate **284** which would have been produced if alkylation with the halide **280** had been successful. Mercuric ion catalyzed hydration leads to the diketone **285** which is then cyclized as usual to the enone **286** in an overall yield of 29%. Internal acetylenes, such as **283**, which might have been expected to afford 1,5-diketones, e.g. **285**, directly upon hydration, have been shown to yield only 1,4-diketones under mercuric ion catalyzed hydration conditions.⁷⁵

(2) Allylic halides

One important quality of any truly general annulation reagent is that it be capable of trapping the regioselectively produced enolate ion formed by reduction of an enone with lithium in liquid ammonia. As the work of

Stork has shown,^{32,83} this reductive alkylation process accomplishes several difficult tasks: (1) formation of a *trans*-decalone system, from the starting octalone, e.g. **287**; (2) specific production, if need be, of the thermodynamically less stable enolate ion, e.g. **288** and **289**; and (3) monoalkylation of this enolate ion without accompanying dialkylation, giving only **290**. In addition to methyl iodide only allylic or benzylic halides have the reactivity required for this type of alkylation to proceed in high yields, and thus they have the greatest possibility of being successful, general annulation reagents.

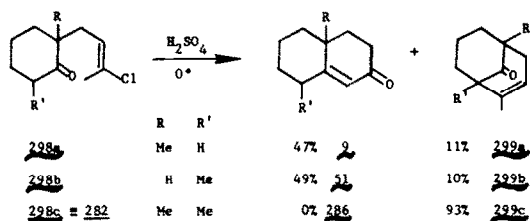
(a) *Wichterle reagent*. The most commonly used allylic halide is 1,3-dichloro-2-butene **281**, the Wichterle reagent.⁸⁴ Alkylation of acidic ketones, e.g. β -keto ester **268**, with **281** proceeds in high yield,⁸⁵ whereas alkylation of simple ketones, e.g. cyclohexanone **236**, affords the alkylated product **292** in only moderate yield.⁸⁶ The product from β -keto ester alkylation, **291**, can be hydrolyzed and decarboxylated to furnish a second route to compound **292**. Problems with this sequence arise at the stage of conversion of the intermediate vinyl chloride **292** to the diketone **293** and ultimately to the enone **48**, which requires concentrated sulfuric acid. The initial work on this system by Prelog⁸⁵ indicated the octalone **48**



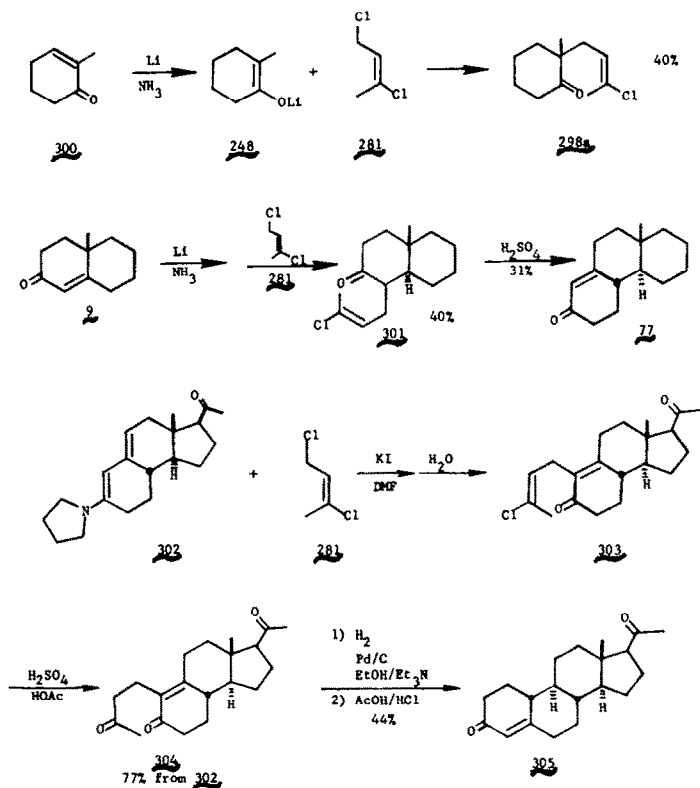
as the product, whereas Julia later found that under any similar conditions a mixture of the two enones **48** and **294** were formed, with the bicyclononene product **294** slightly predominating.⁸⁶ This implies that in strong acid the enol of the cyclic ketone adds to the acyclic carbonyl function leading, via bicyclic ketol **296**, to the enone **294**. The alternate procedure, attack of the enol of the acyclic ketone on the cyclic carbonyl function (analogous to the predominate mode of cyclization under basic catalysis), also occurs in the strongly acidic medium to yield the enone **48** via the ketol **295**. The early workers had also seen evidence of this unusual type of cyclization, since the vinyl chloride **291** yielded only bicyclononene products **297**. Marshall later confirmed that under some conditions the unusual cyclization products predominate, although by careful control of conditions one can force the reaction to yield the octalone as the major product.⁸⁷ For example, the methyl-substituted compounds, **298a-b**, afforded approx. 50% of the octalones **9** and **51** with only 10% bicyclic compounds **299a-b** being formed. However, the dimethyl compound **298c** afforded only the bicyclononene **299c** under all conditions in high yield. The Wichterle reagent **281** has been used to alkylate an enolate ion in liquid ammonia solution in fair yield, **300** → **298a**.¹⁴ It also has been shown to trap a regio-specifically generated, less stable enolate ion in fair yield, **9** → **301**.^{18b}

The major drawback of this sequence is that the conditions necessary for hydrolysis of the vinyl chloride are often too drastic for other functional groups in the molecule and often result in undesired cyclization products. However, the method has been used quite successfully in certain cases, e.g. **137** → **129**,³¹ and especially in total steroid synthesis.⁸⁸ For example, the group at Roussel-UCLAF has reported a high yield in the reaction of the Wichterle reagent **281** with the dienamine **302** in dimethylformamide containing an equivalent of potassium iodide.⁸⁹ The alkylating agent is the allylic iodide formed *in situ*. The intermediate vinyl chloride **303** is hydrolyzed by a sulfuric acid-acetic acid mixture to produce the diketone **304** in excellent overall yield. Reduction of the enone followed by acid-catalyzed cyclization yields nor-progesterone **305**. The use of vinyl chloride intermediates for the construction of annulated ketones of totally different structures will be described at the end of this section.

(b) *Halo ether and thioether*. Several possible reagents are too unstable to be of any use. Two such halides are 1-chloro-3-methoxy-2-butene **306** and 1-chloro-3-phenoxy-2-butene **307**, both of which undergo extremely facile E1 elimination of hydrochloric acid with subsequent



polymerization.⁷⁸ The enol ether **308** is more stable and proved to be a good reagent for α -substituted enones.⁷⁹ For example, the di-methyloctalone **273** was converted to the tricyclic dienone **275** via the intermediate enol ether **309** in good overall yield. However, when the use of enol

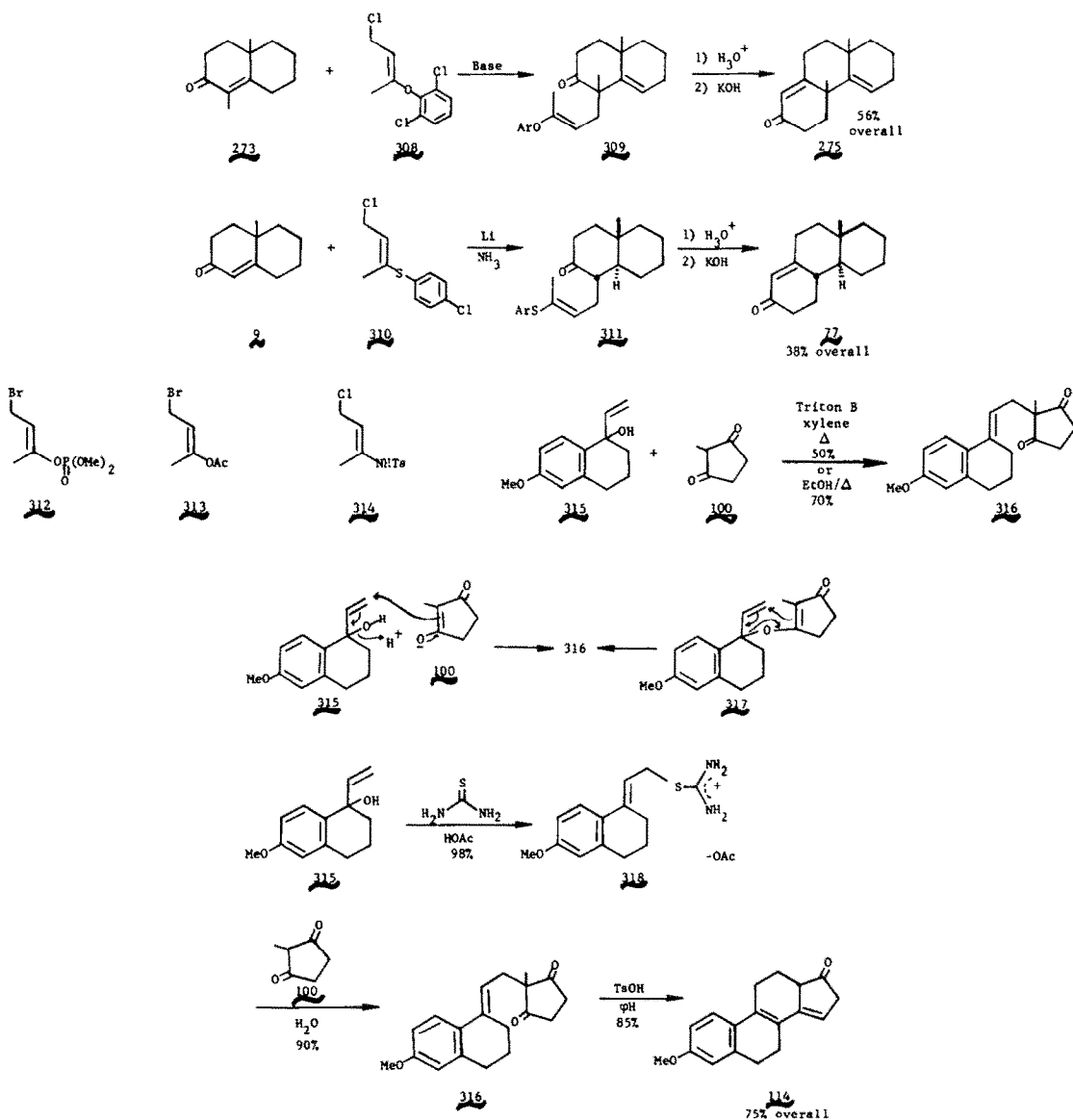


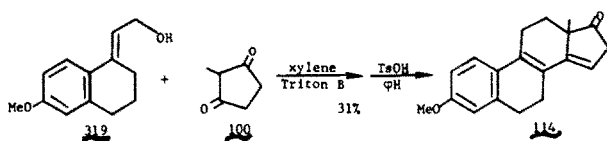
ether **308** was attempted in the reduction alkylation sequence, the reaction was unsuccessful, as the alkylating agent was converted to the corresponding diene. The somewhat more stable thio enol **310** was capable of reductive alkylation, trapping the enolate ion in fair yield, e.g. **9** → **311**.⁷⁹ The cleavage of the thio ether is sometimes unsatisfactory, however. The related halo enol derivatives, **312** → **314**, all give very poor yields in the alkylation step.⁸¹

(c) *Alcohol and thiouronium salt.* Although alcohols are not normally regarded as alkylating agents, certain very reactive alcohols have found use in several annulation methods designed for steroid total synthesis. The allylic benzylic alcohol **315** was condensed with 2-methylcyclopentane-1,3-dione **100** to afford the endione **316** in good yields.^{90,91} Although this reaction was first reported to proceed in a basic medium,⁹¹ it was later shown that the reaction was acid-catalyzed with the dione itself ($pK_a = 4.5$) acting as catalyst.⁹¹ Two mechanisms can be offered for the reaction, the first involving anionic allylic displacement of the hydroxyl function in which the proton is delivered by the acidic diketone.⁹² A second

possible mechanism involves formation of the enol ether derivative of the β -diketone **317** followed by a Claisen rearrangement to compound **316**. Treatment of the alcohol **315** with thiourea in acetic acid leads essentially quantitatively to the rearranged thiouronium salt **318**, which reacts with the β -diketone **100** in aqueous solution to furnish the product **316** in excellent yield. Acid catalyzed cyclization completes the sequence affording in high yield the tetracyclic compound **114**, which can also be obtained directly in one step in 65% yield from the reaction of the alcohol **315** with the β -diketone **100** in refluxing acetic acid-xylene solution.⁹¹ The isomeric allylic alcohol **319** has also been used in the sequence although the yields are much lower.⁹³

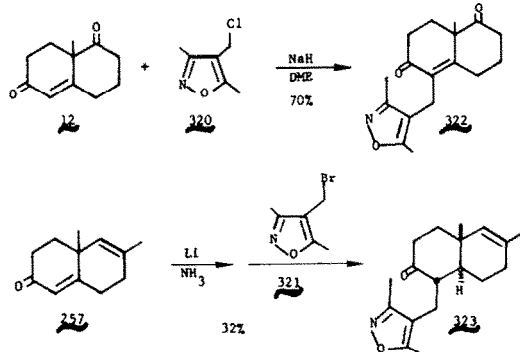
The following three annulation sequences—*isoxazole*, *tiglate*, and *vinylsilane*—are probably the most general yet developed. Each possesses to a greater or lesser extent most of the properties of an ideal annulation reagent, namely: (1) high reactivity so that normal alkylation occurs in high yield and enolate trapping in the reductive alkylation scheme is successful; (2) moderate stability and an efficient method of preparation; (3) the ability of





modifying the preparative scheme so that homologues (including bis-annulation reagents) can be readily produced and (4) an easily unmasked carbonyl function so that the conditions necessary for generating the ketone are neither too drastic nor too acidic (e.g. concentrated sulfuric acid which leads to undesired bicyclic products with the Wichterle reagent).

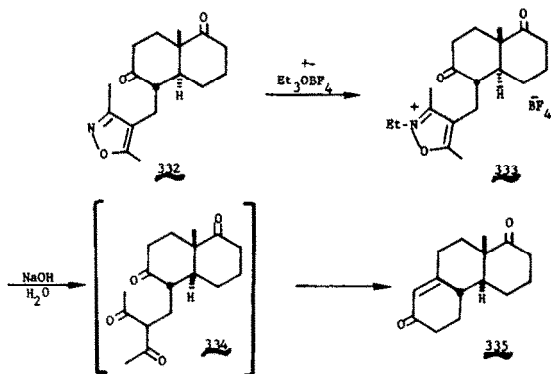
(d) *Isoxazole*. Some of the most successful annulation reagents are the 4-halomethylisoxazole reagents **320** and **321** introduced by Stork.⁹⁴ They alkylate saturated and α,β -unsaturated ketones well, e.g. **12** $\rightarrow$ **322**, and also can be used successfully in the enolate trapping required by the reductive alkylation process, affording the alkylated product, e.g. **257** $\rightarrow$ **323**, in low yield.⁸¹ The carbonyl function is unmasked by the following procedure: hydrogenolysis of the isoxazole **324** over Raney nickel



leads to the vinylogous carbinolamide **326**, which is cleaved by hot methoxide to the enamine **329**; this in turn is hydrolyzed by aqueous base to the 1,5-diketone **330** which then cyclizes to the enone **331** in the basic medium. The overall yield for this process is about 50–60%.

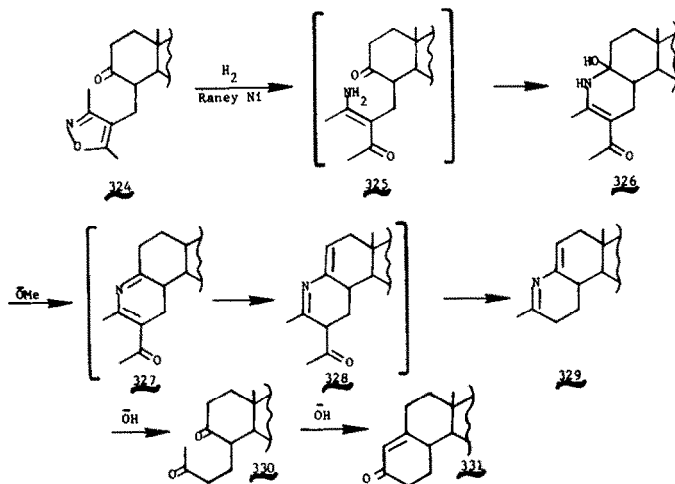
Two other methods of generating the carbonyl function have been reported. The first involves reaction of the isoxazole **332** (prepared by catalytic hydrogenation of

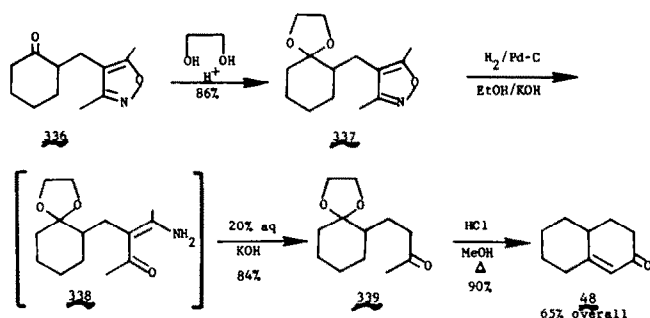
compound **322** in 70% yield) with triethyloxonium fluoroborate followed by treatment of the salt **333** with dilute aqueous base, which gives the desired enone **335** in yields of about 35%.^{94a}



The carbonyl can also be generated in somewhat higher yield by an improved sequence as is shown for the isoxazole **336**.⁹⁵ Ketalization affords the ketal **337** which is hydrogenated to the stable enamide **338** which can no longer form a vinylogous carbinolamide such as **326**. The enamide **338** is not isolated but is converted with aqueous base directly to the ketone **339** which is cyclized in acid to the enone **48** in an overall yield of 65%,⁹⁵ a moderate improvement on the 50% yield obtained by the simple hydrogenation-base catalyzed cyclization sequence.^{94a} The improved yields can probably be attributed to the suppression of the formation of the carbinolamines, e.g. **326**, which upon treatment with base, rapidly dehydrate to dihydropyridines, e.g. **327**, compounds which are known to be susceptible to oxidation and/or disproportionation to give undesired byproducts and lower yields.

With respect to carbonyl unmasking, the best isoxazole reagent is 3-methyl-4-chloromethylisoxazole, **340**.^{94a} For example, the alkylated octalone derivative **341** is converted to the tricyclic enone **335** in 70% yield by the





hydrogenation to the crystalline intermediate **342** followed by basic cyclization. The very serious drawback here is that monomethylisoxazoles such as **340** give very poor yields in the alkylation step for reasons not yet fully understood, and this poor reaction in the first step causes the overall yields to be only fair.⁹⁶

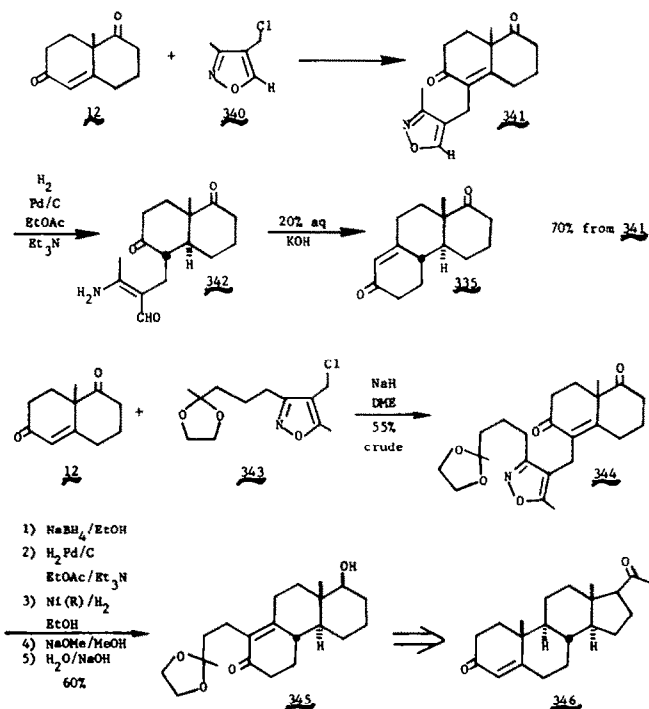
Examination of the mechanism of the conversion of the isoxazole to the 3-ketoalkyl chain leads to the observation that it is the alkyl group next to nitrogen which is retained in the final 3-ketoalkyl chain. This led to the use of the isoxazole **343** as a bis-annulation reagent, as in the synthesis of progesterone **346**.^{9b} Alkylation of the octalone **12** with **343** gave in moderate yield the isoxazole **344** which was converted by the usual method to the crystalline tricyclic enone **345** in 60% yield. A multi-step sequence was then employed to produce progesterone **346** from **345**.

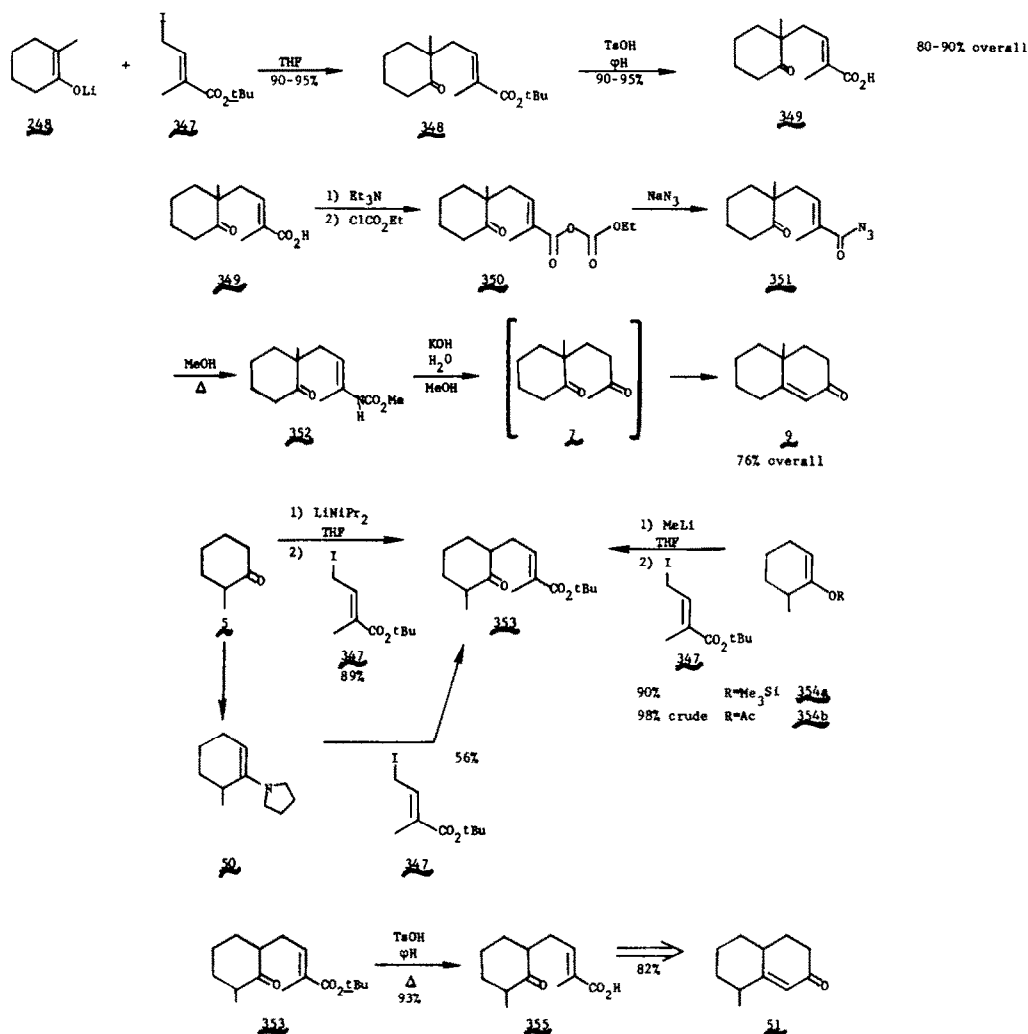
(e) **Tiglate.** The tiglate sequence, developed by Stotter, employs *t*-butyl γ -iodotiglate **347** as the annulation reagent.^{97,98} The general scheme is outlined for the annulation of 2-methylcyclohexanone. Alkylation of the enolate ion **248** derived from the enol acetate **246** by treatment with methylolithium gives a 90–95% yield of the alkylated product **348**. Refluxing the *t*-butyl ester **348** in benzene with *p*-toluenesulfonic acid gives the free acid **349** in 90–95% yield. This acid can be obtained directly in

yields of up to 90% by sequential alkylation and hydrolysis without isolation of any intermediates. The conversion of the α,β -unsaturated acid function in **349** to the ketone requires several steps and utilizes the Weinstock modification of the Curtius reaction. Addition of triethylamine to the acid **349** followed by ethyl chloroformate gives the mixed anhydride **350**, which was converted directly to the acyl azide **351** by addition of aqueous sodium azide. Heating of **351** in anhydrous methanol affords the vinyl urethane **352**, a readily hydrolyzable enamine derivative. Hydrolysis to the diketone **7** and cyclization to the octalone **9** occur upon refluxing the vinyl urethane **352** with potassium carbonate in methanol. Although this conversion is a multi-step process, the procedure is simple and the yields are generally good (70–80%).

Other alkylations can also be conducted.^{97,98} For example, the conversion of 2-methylcyclohexanone **5** to the 2,6-dialkyl compound **353** can be accomplished in several ways: via the enamine **50** (56%), by direct alkylation (89%), and via the enol silyl ether **354a** (90%) or enol acetate **354b** (>95% crude). Hydrolysis of the ester **353** gives in excellent yield the acid **355** which is then converted to the octalone **51** by the modified Curtius sequence in good yield.

The reagent **347** can be used in the reductive alkylation



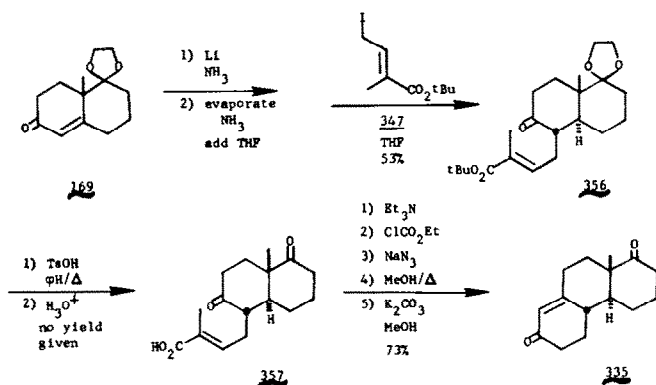


process although it is necessary to remove the ammonia and to replace it with tetrahydrofuran before adding the alkylating agent.⁹⁸ For example the ketal enone **169** could be converted in good yield to the ketone **356**, which was hydrolyzed in two steps to the diketone **357**. The tricyclic enone **335** was then produced from this compound in 73% yield by the usual process described earlier. The reagent is easy to prepare and homologues have been made although attempts to prepare a bis-annulation reagent have so far proved unsuccessful.⁹⁹

(f) *Vinylsilane*. We have recently developed a third

general annulation sequence, the vinylsilane method.^{100,101}

This procedure employs halomethyl vinylsilanes, and in particular *E*-3-trimethylsilyl-2-butenyl iodide **358**, as reactive alkylating agents. The general reaction scheme is illustrated for the annulation of 2-methylcyclohexanone **5** via its enol acetate **246**. Addition of the silylbutenyl iodide **358** to a solution of the lithium enolate of 2-methylcyclohexanone **248** in tetrahydrofuran (formed from the enol acetate **246** by addition of two equivalents of methyl lithium) affords the alkylated product **359** in 91% yield after purification by chromatography. Epoxida-

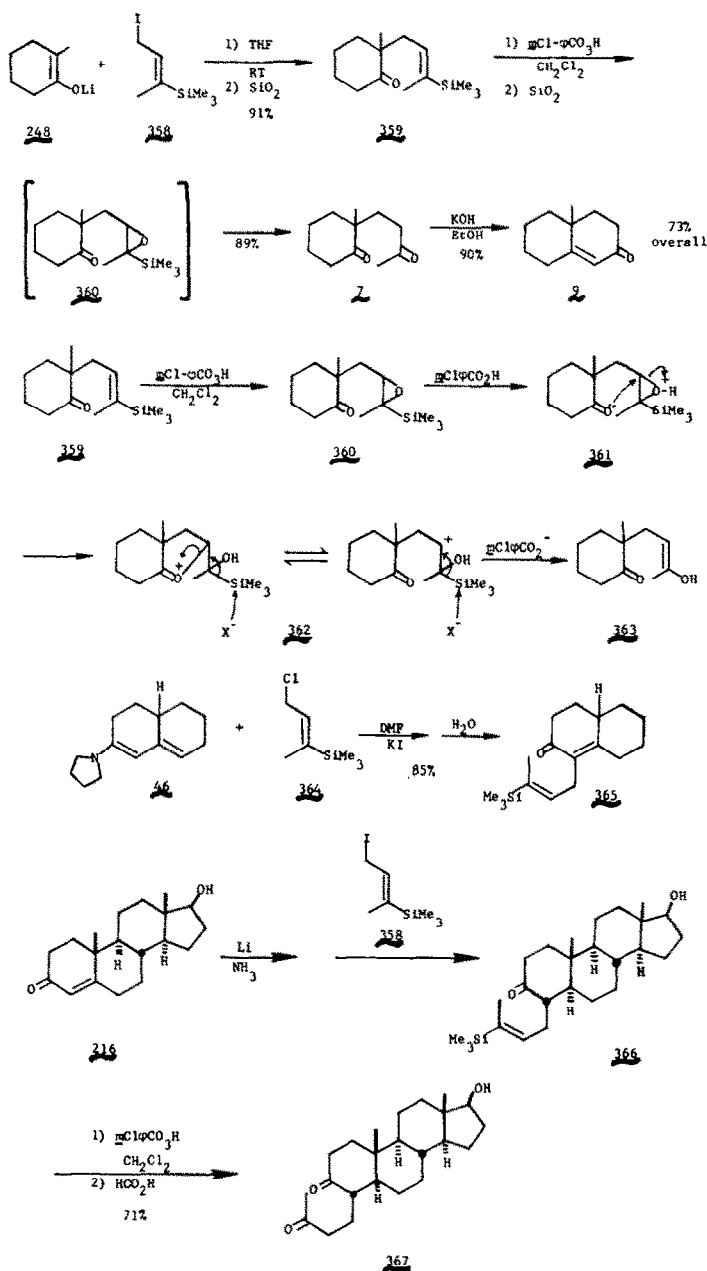


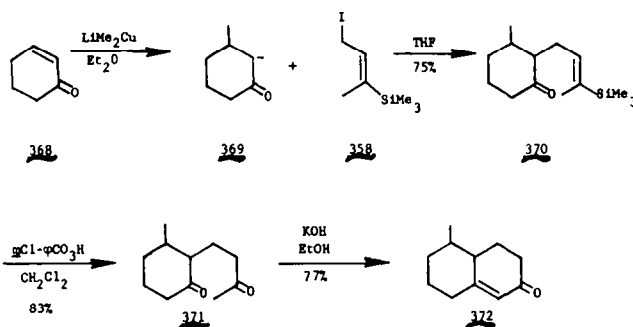
tion and opening to the diketone **7** is effected in 89% purified yield (94% based on recovered starting material) by treatment of the vinylsilane **359** with *m*-chloroperbenzoic acid in methylene chloride. Base-catalyzed cyclization completes the sequence, producing the octalone **9** in 90% yield, so that the overall yield of annulation is 73%. A possible mechanism of carbonyl formation involves protonation of the intermediate epoxysilane **360** by the meta-chlorobenzoic acid formed in the initial epoxidation to give **361** and then anchimeric assistance of the carbonyl group in opening the protonated epoxide function β to the silyl group. Finally, the meta-chlorobenzoate ion in solution then eliminates the silyl group in compound **362** via an S_N2 -type of attack to yield the enol **363** of the diketone **7**.

Several other types of alkylations were performed with iodide **358** and the analogous chloride **364**. The reaction of the pyrrolidine enamine of octalone **46** with the chloride

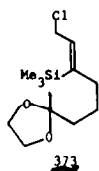
364 in dimethylformamide containing an equivalent of potassium iodide gave after hydrolysis the alkylated octalone **365** in 85% crude yield. The iodide **358** is most probably the alkylating agent, formed *in situ*. The reductive alkylation sequence with testosterone **216** was quite successful. Simple addition of the iodide **358** to the ammonia solution of the lithium enolate formed by enone reduction furnished after work-up and chromatography the crystalline vinylsilane **366** in 58% yield. Epoxidation and final treatment with formic acid gave the dione **367** in 71% yield.

Addition of the iodide **358** to a solution of the enolate ion **369** formed from the addition of lithium dimethylcuprate to cyclohexenone **368** afforded the 2,3-dialkyl product **370** in 75% yield after chromatography. Treatment of the vinylsilane **370** with *m*-chloroperbenzoic acid effected epoxidation and rearrangement to the dione **371** which has been cyclized to the enone **372**.⁸⁷

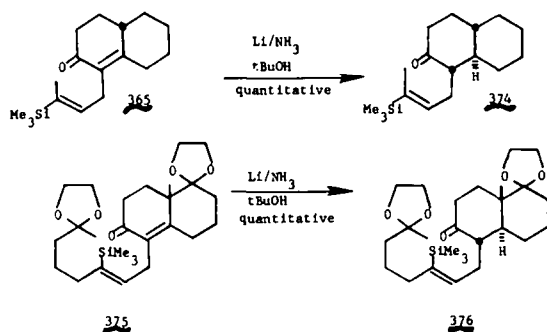




The vinylsilane reagents are easy to prepare and are quite stable, perhaps due to the inductive effect of the silyl group on the double bond which should decrease the tendency toward $E1$ 1,4-dehydrohalogenation. Also a bis-annulation vinylsilane reagent 373 has been prepared and used in annulation sequences.¹⁰¹



An important advantage of the vinylsilane reagents is the stability of the vinylsilane moiety to dissolving metal reductions. For example, addition of the vinylsilane octalone 365 to two equivalents of lithium in liquid ammonia affords the vinylsilane decalone 374 in quantitative yield. The similar system 375 (formed via the alkylation of the enone 169 with the bis-annulation reagent 373 in 52% yield) gives under the same conditions the analogous decalone 376 in quantitative yield. It should be pointed out that this type of reduction, which is quite often necessary for the synthesis of polycyclic compounds of the steroid or triterpenoid type, is not possible

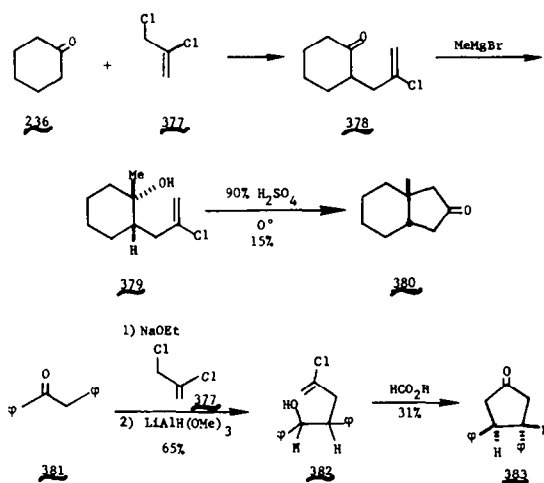


in the isoxazole or the tiglate sequences, since the masked carbonyl function in each contains easily reducible groups (namely, isoxazole and α,β -unsaturated ester). However, catalytic hydrogenation of an α,β -unsaturated ketone in the presence of the carbonyl protecting group can be successfully accomplished only in the isoxazole sequence,^{94b} since the vinylsilane moiety is reduced catalytically in competition with the enone functionality.¹⁰¹

(3) Modified annulation

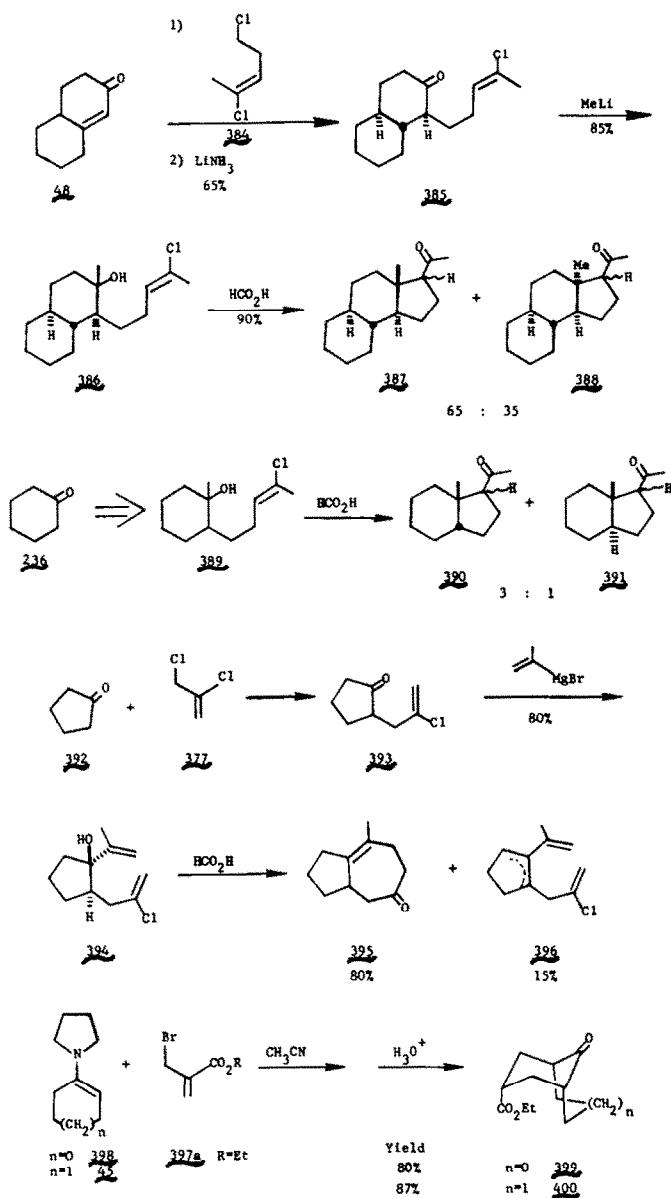
(a) *Chloro olefin cyclization*. Lansbury *et al.* have developed a scheme for the construction of cyclopent-

tanones and acetylcyclopentanes starting from ketones.¹⁰² Alkylation of cyclohexanone 236 with 2,3-dichloro-1-propene 377 affords the chloro ketone 378 which is converted to the tertiary alcohol 379 on reaction with a Grignard reagent. Acid-catalyzed cyclization then produces the *cis*-hydrindanone 380 in poor yield.^{103a} Somewhat higher yields are obtained from acyclic ketones, e.g. 381 $\rightarrow$ 382.^{103b} The conversion of the cyclic enone 48 into



the cyclopentyl methyl ketones 387 and 388 proceeds in much higher yield. Alkylation of 48 with 2,5-dichloro-2-pentene 384 followed by reduction furnishes the ketone 385 which reacts with methyl lithium to produce the tertiary alcohol 386 in good overall yield. Treatment of 386 with formic acid affords in 90% yield a 65:35 mixture of two sets of isomers with the *trans*-hydrindane ketones 387 being formed in preference to the *cis*-ketones 388. This is not a general result since the simple series derived from cyclohexanone yields the *cis*-hydrindane ketones 390 as the major isomers.^{103c} Recently, this procedure has been extended to allow for the synthesis of 7-membered ketones.^{103d} For example, cyclopentanone 392 was converted in good yield to the hydrazonone 395 via the intermediates 393 and 394 as shown.

(b) α,α' -Annulation. The synthesis of bicyclic keto esters can be easily effected via α,α' -annulation by the use of α -bromomethylacrylates, 397a-b, reagents which combine the properties of both allylic halides and α,β -unsaturated esters. Reaction of the ethyl ester 397a with the cyclic enamines 398 and 45 affords the bicyclic keto esters 399 and 400 in high yield.^{104a} The methyl ester 397b gives the spiro-annulated product 403 when reacted with the enamine of acetylcyclopentane 401.^{104b} The mechanism involves initial alkylation, either by a direct $\text{S}_{\text{N}}2$

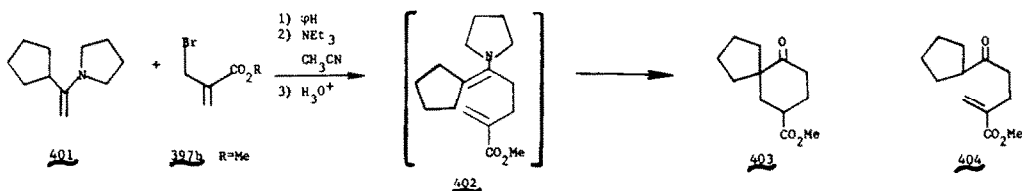


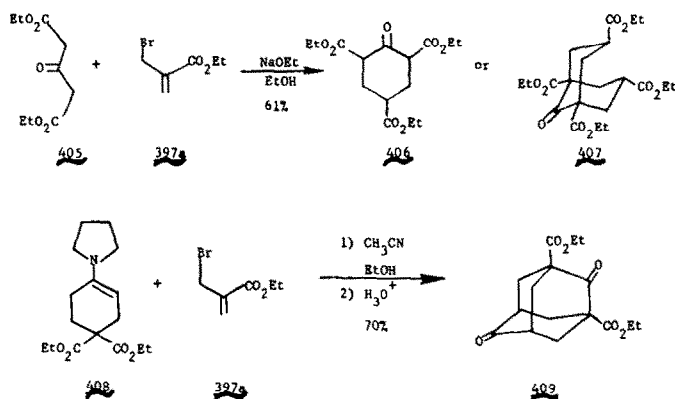
reaction or via Michael addition-elimination (a formal S_N2' process), which is then followed by Michael addition and hydrolysis. The product from simple alkylation, e.g. **404**, can sometimes be isolated. The keto diester **405** furnishes the cyclohexanone **406** when reacted with one equivalent of acrylate **397a** and the bicyclic ketone **407** when two equivalents of **397a** are used.^{105a} Reaction of the enamine **408** with **397a** affords the adamantanedione **409** directly in high yield.^{105b}

(4) Conclusion

Thus, alkylation annulation sequences have been used extensively with a high degree of success. The allylic

halide reagents have been shown to be quite general affording very high yields of annulation from several different carbonyl derivatives (ketones, enones, enamines, enol esters, enol ethers, diketones, etc.). A major advantage of the allylic halides is their ability to trap, in high yield, regioselectively generated, thermodynamically less stable enolate ions formed by several different methods (e.g. enone reduction, enol ester or enol ether cleavage, alkyl copper addition to enones). A disadvantage is that the annulation methods based on alkylation have not yet been shown to be as generally applicable to bis- or tris-annulation as have the Michael reaction or nucleophilic addition sequences. However, it





is possible to convert a ketone via an alkylation annulation method into a cyclic ketone of a structure unobtainable via the other two annulation sequences.

4. CONCLUSION

Thus, one can see that there exists today a broad range of possible annulation methods which permit the construction of a large number of different cyclic enones and ketones from a wide variety of starting structures. The Michael reaction annulation sequence is employed successfully mainly for acidic carbonyl compounds (β -diketones, β -keto esters, etc.) and for the addition of more than one ring at a time (bis- and tris-annulation). Annulation via nucleophilic addition is somewhat less useful in general, although in some cases it can proceed in fairly high yield. The annulation sequences involving alkylation, especially with allylic halides (e.g., isoxazole, tiglate, vinylsilane), are probably the most generally useful ones. They are particularly good for use in the trapping of regioselectively generated, thermodynamically less stable enolate ions under aprotic conditions. However, in general, these reagents have not yet been successfully utilized for bis- and tris-annulation.

REFERENCES

- ¹Recently a very short review of annulation methods has been published: B. P. Mundy, *J. Chem. Edn.* **50**, 110 (1973).
- ²For the exhaustive review of the Diels-Alder reactions, see Houben-Weyl, *Methoden der Organischen Chemie*, 997-1139. Kohlenwasserstoff-Verbindungen III.
- ^{3a}Acid-catalyzed polyolefinic cyclizations: see W. S. Johnson, *Accounts Chem. Res.* **1**, 1 (1968); ^bOlefinic-acid cyclizations: see M. F. Ansell and M. H. Palmer, *Quart. Rev.* **18**, 211 (1964); ^cOlefin-cyclopropane cyclizations: G. Stork, M. Gregson and P. Grieco, *Tetrahedron Letters*, 1391, 1393 (1969).
- ^{4a}G. S. Hammond and N. J. Turro, *Science* **142**, 1541 (1963); ^bO. L. Chapman, *Advan. Photochem.* **1**, 359 (1963); ^cW. L. Dilling, *Chem. Rev.* **66**, 373 (1966); **69**, 845 (1969); ^dP. E. Eaton, *Accounts Chem. Res.* **1**, 50 (1968); ^eP. de Mayo, *Ibid.* **4**, 41 (1971).
- ⁵M. Julia, *Rec. Chem. Prog.* **25**, 3 (1964).
- ⁶Ene Reaction: ^aH. M. R. Hoffmann, *Angew. Chem. Intl. Ed.* **8**, 556 (1969); ^bP. Beslin and J. M. Conia, *Bull. Soc. Chim. Fr.* 959 (1970); ^cW. Oppolzer, E. Pfenniger and K. Keller, *Helv. Chim. Acta* **56**, 1807 (1973); ^dJ. M. Conia and P. Le Perche, *Synthesis* **1** (1975). Oxy-Cope Rearrangement: ^eJ. A. Berson and M. Jones, Jr., *J. Am. Chem. Soc.* **86**, 5017, 5019 (1964); ^fJ. A. Berson and E. J. Walsh, Jr., *Ibid.* **90**, 4729, 4730, 4732 (1968); ^gD. A. Evans, W. L. Scott and L. K. Truesdale, *Tetrahedron Letters* **137** (1972).
- ⁷An extensive review of the Michael reaction has been published. E. D. Bergmann, D. Ginsburg and R. Pappo, *Organic Reactions*, Vol. X, pp. 179-555.
- ⁸W. S. Rapson and R. Robinson, *J. Chem. Soc.* 1285 (1935).
- ^{9a}I. N. Nazarov and S. I. Zav'yakov, *Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk* **300** (1952); ^bN. L. Wendler and H. L. Slates, U.S. pat. 2,542,223; [*Chem. Abstr.* **45**, 7599 (1951)]; ^c*Org. Syntheses*, Coll. **5**, 486 (1973).
- ¹⁰G. Stork, *Bull. Soc. Chim. Fr.* 256 (1955).
- ¹¹K. Balasubramanian, J. P. John and S. Swaminathan, *Synthesis* **51** (1974).
- ^{12a}J. W. Patterson, Jr. and W. Reusch, *Ibid.* **155** (1971); ^bA. M. Chalmers and A. J. Baker, *Ibid.* **539** (1974).
- ^{13a}E. C. du Feu, F. J. McQuillin and R. Robinson, *J. Chem. Soc.* **53** (1937); ^bA review of the use of Mannich base methiodides has been published: J. H. Brewster and E. L. Eliel, *Organic Reactions*, Vol. VII, pp. 99-197.
- ¹⁴J. W. Cornforth and R. Robinson, *J. Chem. Soc.* 1855 (1949).
- ^{15a}D. A. H. Taylor, *Chem. Ind.* 250 (1954); ^bL. Velluz, G. Nominé and J. Mathieu, *Angew. Chem.* **72**, 725 (1960); ^cL. Velluz, J. Valls and G. Nominé, *Angew. Chem. Intl. Ed.* **4**, 181 (1965).
- ¹⁶F. J. McQuillin and R. Robinson, *J. Chem. Soc.* 1097 (1938).
- ¹⁷J. A. Marshall and W. I. Fanta, *J. Org. Chem.* **29**, 2501 (1964).
- ^{18a}M. Yanagita and K. Yamakawa, *Ibid.* **22**, 291 (1957); ^bP. Rosen, Ph.D. Thesis, Columbia University, New York, New York (1962).
- ¹⁹J. A. Marshall and T. H. Warne, Jr., *J. Org. Chem.* **36**, 178 (1971).
- ²⁰C. J. V. Scanio and R. M. Starrett, *J. Am. Chem. Soc.* **93**, 1539 (1971).
- ²¹P. S. Adamson, F. J. McQuillin, R. Robinson and J. L. Simonsen, *J. Chem. Soc.* 1576 (1937).
- ²²A. L. Wilds and C. H. Shunk, *J. Am. Chem. Soc.* **65**, 469 (1943).
- ^{23a}D. A. H. Taylor, *J. Chem. Soc.* 3319 (1961); ^bA. R. Pinder and R. A. Williams, *Ibid.* 2773 (1963); ^cT. G. Halsall, D. W. Theobald and K. B. Walshaw, *Ibid.* 1029 (1964); ^dD. W. Theobald, *Tetrahedron* **22**, 2869 (1966).
- ²⁴G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *J. Am. Chem. Soc.* **85**, 207 (1963).
- ²⁵C. H. Heathcock, J. E. Ellis, J. E. McMurry and A. Coppolino, *Tetrahedron Letters* 4995 (1971).
- ²⁶C. D. DeBoer, *J. Org. Chem.* **39**, 2426 (1974).
- ²⁷R. B. Woodward and T. Singh, *J. Am. Chem. Soc.* **72**, 494 (1950).
- ^{28a}R. E. Ireland, D. R. Marshall and J. W. Tilley, *Ibid.* **92**, 4754 (1970); ^bD. Caine and F. N. Tuller, *J. Org. Chem.* **38**, 3663 (1973).
- ²⁹S. Danishefsky and G. A. Koppel, *Chem. Commun.* 367 (1971).
- ³⁰L. J. Chinn and H. L. Dryden, *J. Org. Chem.* **26**, 3904 (1961).
- ³¹G. Stork and B. Ganem, *J. Am. Chem. Soc.* **95**, 6152 (1973).
- ³²G. Stork, P. Rosen and N. L. Goldman, *Ibid.* **83**, 2965 (1961).
- ^{33a}H. O. House, M. Gall and H. D. Olmstead, *J. Org. Chem.* **36**, 2361 (1971); ^bFor enol acetates see: H. O. House and T. M. Barc, *Ibid.* **33**, 943 (1968); and refs therein; ^cFor enol silyl ethers see: G. Stork and P. Hudrik, *J. Am. Chem. Soc.* **90**, 4462, 4464 (1968); H. O. House, L. J. Czuba, M. Gall and H. D. Olmstead, *J. Org. Chem.* **34**, 2324 (1969).
- ³⁴J. Schreiber, Dissertation No. 2292, Eidgenössische Technische Hochschule, Zürich, Switzerland (1953).
- ^{35a}R. K. Boeckman, Jr., *J. Am. Chem. Soc.* **95**, 6867 (1973); ^bR. K. Boeckman, Jr., *Ibid.* **96**, 6179 (1974).
- ³⁶G. Stork and J. Singh, *Ibid.* **96**, 6181 (1974).

- ³⁷A. V. Logan, E. N. Marvell, R. LaPore and D. C. Bush, *Ibid.* **76**, 4127 (1954).
- ³⁸Z. G. Hajos and D. R. Parrish, *J. Org. Chem.* **38**, 3239, 3244 (1973).
- ³⁹G. Stork and J. D'Angelo, *J. Am. Chem. Soc.* **96**, 7114 (1974).
- ⁴⁰Z. G. Hajos and D. R. Parrish, *J. Org. Chem.* **39**, 1612, 1615 (1974).
- ⁴¹G. Stork and M. Tomasz, *J. Am. Chem. Soc.* **86**, 471 (1964).
- ⁴²T. P. C. Mulholland, R. I. W. Honeywood, H. D. Preston and D. T. Rosevear, *J. Chem. Soc.* 4939 (1965).
- ⁴³G. Stork and J. Hill, private communication.
- ⁴⁴A. A. Akhrem and Y. A. Titov, *Total Steroid Synthesis*. Plenum Press, New York (1970).
- ^{45a}C. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall and H. Smith, *J. Chem. Soc.* 5072 (1963); ^bG. A. Hughes and H. Smith, *Chem. & Ind.* 1022 (1960).
- ⁴⁶S. I. Zav'yalov, G. V. Kondrat'eva and L. F. Kudryavtseva, *Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk* 529 (1961).
- ⁴⁷J. J. Panouse and C. Sannie, *Bull. Soc. Chim. Fr.* 1429 (1956).
- ^{48a}T. D. Windholz, J. H. Fried, H. Schwam and A. A. Patchett, *J. Am. Chem. Soc.* **85**, 1707 (1963); ^bN. N. Gaidamovich and I. V. Torgov, *Steroids* **4**, 729 (1964).
- ⁴⁹A. Eschenmoser, J. Schreiber and S. A. Julia, *Helv. Chim. Acta* **36**, 482 (1953).
- ⁵⁰S. Danishefsky, W. E. Hatch, M. Sax, E. Abola and J. Pletcher, *J. Am. Chem. Soc.* **95**, 2410 (1973).
- ^{51a}S. Danishefsky, L. S. Crawley, D. M. Solomon and P. Heggs, *Ibid.* **93**, 2356 (1971); ^bS. Danishefsky and B. H. Migdalof, *Ibid.* **91**, 2806 (1969).
- ^{52a}N. Cohen, B. Banner, R. Borer, R. Mueller, R. Yang, M. Rosenberger and G. Saucy, *J. Org. Chem.* **37**, 3385 (1972); and refs therein; ^bN. Cohen, B. Banner, J. F. Blount, M. Tasi and G. Saucy, *Ibid.* **38**, 3229 (1973).
- ^{53a}L. B. Barkely, W. S. Knowles, H. Raffelson and Q. E. Thompson, *J. Am. Chem. Soc.* **78**, 4111 (1956); ^bU.S. Patent 2,786,836; [*Chem. Abstr.* **51**, 12163 (1957)].
- ^{54a}See ref. 5a; ^bI. N. Nazarov and S. I. Zav'yalov, *Zh. Obshch. Khim.* **25**, 508 (1955); ^cN. K. Chaudhuri and P. C. Mukharji, *J. Indian Chem. Soc.* **33**, 81 (1956).
- ⁵⁵G. Saucy, W. Koch, M. Müller and A. Fürst, *Helv. Chim. Acta* **53**, 964 (1970).
- ⁵⁶R. E. Ireland and U. Hengartner, *J. Am. Chem. Soc.* **94**, 3652 (1972).
- ^{57a}S. Danishefsky and R. Cavanaugh, *Ibid.* **90**, 520 (1968); ^bS. Danishefsky and A. Nagel, *Chem. Commun.* 373 (1972); ^cS. Danishefsky, A. Nagel and D. Peterson, *Ibid.* 374 (1972); ^dS. Danishefsky, P. Cain and A. Nagel, *J. Am. Chem. Soc.* **97**, 380 (1975).
- ^{58a}R. B. Turner, *Ibid.* **72**, 579 (1950); ^bG. Fujimoto, *Ibid.* **73**, 1856 (1951).
- ⁵⁹A review of the enol lactone-Grignard annulation sequence has been recently published: J. Weill-Raynal, *Synthesis* **1**, 49 (1969).
- ⁶⁰A recent review of the methods of enol lactone formation has appeared: N. P. Shusherina and R. Y. Levina, *Russ. Chem. Revs.* **37**, 198 (1968).
- ^{61a}H. J. Schneider, T. W. Rienner and H. A. Bruson, *J. Am. Chem. Soc.* **72**, 1486 (1950); ^bD. Stauffacher and H. Schinz, *Helv. Chim. Acta* **37**, 1223 (1954).
- ^{62a}R. L. Frank and R. C. Pierle, *J. Am. Chem. Soc.* **73**, 724 (1951); ^bR. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *Ibid.* **74**, 4223 (1952); ^cG. Stork, S. D. Darling, I. T. Harrison and P. S. Wharton, *Ibid.* **84**, 2018 (1962).
- ^{63a}G. Stork, H. J. E. Loewenthal and P. C. Mukharji, *Ibid.* **78**, 501 (1956); ^bJ. A. Hartman, A. J. Tomasewski and A. S. Dreiding, *Ibid.* **78**, 5662 (1956); ^cS. Kushinsky, *J. Biol. Chem.* **230**, 31 (1958); ^dM. Uskokovic and M. Gut, *J. Org. Chem.* **22**, 996 (1957).
- ⁶⁴D. M. Piatak, H. B. Bhat and E. Caspi, *Ibid.* **34**, 112 (1969).
- ⁶⁵G. Stork, S. Uyeo, T. Wakamatsu, P. Grieco and J. Labovitz, *J. Am. Chem. Soc.* **93**, 4945 (1971).
- ⁶⁶L. Velluz, G. Nominé, G. Amiard, V. Torelli and J. Cerede, *C.R. Acad. Sci., Paris* **257**, 3086 (1963).
- ⁶⁷R. Bucourt, M. Vignau and J. Weill-Raynal, *Ibid.* **265**, 834 (1967).
- ⁶⁸E. J. Corey, H.-J. Hess and S. Proskow, *J. Am. Chem. Soc.* **85**, 3979 (1963).
- ⁶⁹C. A. Henrick, E. Böhme, J. A. Edwards and J. H. Fried, *Ibid.* **90**, 5926 (1968).
- ⁷⁰B. M. Trost and M. J. Bogdanowicz, *Ibid.* **94**, 4777 (1972).
- ⁷¹G. Stork, A. A. Ponaras and G. A. Garcia, private communication.
- ^{72a}A. Serini, W. Logemann and W. Hildebrand, *Chem. Ber.* **72**, 391 (1939); ^bFor a discussion of the mechanism, see L. F. Fieser and M. Fieser, *Steroids*, p. 628ff. Reinhold, New York (1959).
- ⁷³E. Negishi and H. C. Brown, *Synthesis* 77 (1974).
- ⁷⁴H. O. House and V. Kramer, *J. Org. Chem.* **28**, 3362 (1963).
- ⁷⁵G. Stork and R. Borch, *J. Am. Chem. Soc.* **86**, 935 (1964).
- ⁷⁶Z. G. Hajos, R. A. Micheli, D. R. Parrish and E. P. Oliveto, *J. Org. Chem.* **32**, 3008 (1967).
- ⁷⁷M. J. Green, N. A. Abraham, E. B. Fleischer, J. Case and J. Fried, *Chem. Commun.* 234 (1970).
- ⁷⁸G. Stork, *Excerpta Medica, International Congress Series* No. 219, 101 (1970).
- ⁷⁹S. Stournas, Ph.D. Thesis, Columbia University, New York, New York (1970).
- ⁸⁰Z. Valenta and R. A. Dickinson, private communication.
- ⁸¹T. C. McKenzie, Ph.D. Thesis, Columbia University, New York, New York (1973).
- ⁸²D. Caine and F. N. Tuller, *J. Org. Chem.* **34**, 222 (1969).
- ^{83a}G. Stork and S. D. Darling, *J. Am. Chem. Soc.* **82**, 1512 (1960); *Ibid.* **86**, 1761 (1964); ^bG. Stork and J. Tsuji, *Ibid.* **83**, 2783 (1961); ^cG. Stork, P. Rosen, N. L. Goldman, R. V. Coombs and J. Tsuji, *Ibid.* **87**, 275 (1965).
- ⁸⁴O. Wichterle, J. Prochaska and J. Hoffman, *Coll. Czech. Chem. Commun.* **13**, 300 (1948); and refs therein.
- ⁸⁵V. Prelog, P. Barman and M. Zimmermann, *Helv. Chim. Acta* **32**, 1284 (1949).
- ⁸⁶S. Julia, *Bull. Soc. Chim. Fr.* **21**, 780 (1954).
- ⁸⁷J. A. Marshall and D. J. Schaeffer, *J. Org. Chem.* **30**, 3642 (1965).
- ⁸⁸For examples, see Ref. 15c and also Ref. 44, Schemes 72-74.
- ⁸⁹R. Bucourt, J. Tessier and G. Nominé, *Bull. Soc. Chim. Fr.* 1923 (1963).
- ⁹⁰S. N. Ananchenko and I. V. Torgov, *Tetrahedron Letters* 1553 (1963).
- ⁹¹C. H. Kuo, D. Taub and N. L. Wendler, *J. Org. Chem.* **33**, 3126 (1968); *Chem. & Ind.* 1340 (1966); *Angew. Chem.* **77**, 1142 (1965).
- ⁹²D. P. Strike, T. Y. Jen, G. H. Douglas and H. Smith, *Steroids* **8**, 309 (1966).
- ⁹³A. V. Zakharychev, S. N. Ananchenko and I. V. Torgov, *Izvest. Akad. Nauk SSSR, Ser. Khim.* 2056 (1963).
- ^{94a}G. Stork, S. Danishefsky and M. Ohashi, *J. Am. Chem. Soc.* **89**, 5459 (1967); ^bG. Stork and J. E. McMurry, *Ibid.* **89**, 5463, 5464 (1967).
- ⁹⁵J. W. Scott, B. L. Banner and G. Saucy, *J. Org. Chem.* **37**, 1664 (1972).
- ⁹⁶G. Stork, *Pure Appl. Chem.* **9**, 131 (1964).
- ⁹⁷P. L. Stotter and K. A. Hill, *J. Am. Chem. Soc.* **96**, 6524 (1974).
- ⁹⁸K. A. Hill, Ph.D. Thesis, University of Texas, Austin, Texas (1972).
- ⁹⁹K. A. Hill, private communication.
- ^{100a}G. Stork and M. E. Jung, *J. Am. Chem. Soc.* **94**, 3682 (1974); ^bG. Stork, M. E. Jung, E. Colvin and Y. Noel, *Ibid.* **94**, 3684 (1974).
- ¹⁰¹M. E. Jung, Ph.D. Thesis, Columbia University, New York, New York (1973).
- ¹⁰²P. T. Lansbury, *Accs. Chem. Res.* **5**, 311 (1972); and refs therein.
- ^{103a}P. T. Lansbury and E. J. Nienhouse, *J. Am. Chem. Soc.* **88**, 4290 (1966); ^bP. T. Lansbury, E. J. Nienhouse, D. J. Scharf and F. R. Hilfinger, *Ibid.* **92**, 5649 (1970); ^cP. T. Lansbury, P. C. Briggs, T. R. Demmin and G. E. Dubois, *Ibid.* **93**, 1311 (1971); ^dP. T. Lansbury, P. M. Workulich and P. E. Gallagher, *Tetrahedron Letters* 65 (1973).
- ^{104a}R. P. Nelson, J. M. McEwen and R. G. Lawton, *J. Org. Chem.* **34**, 1225 (1969); **35**, 690 (1970); ^bD. J. Dunham and R. G. Lawton, *J. Am. Chem. Soc.* **93**, 2074 (1971).
- ¹⁰⁵H. Stetter and K. Elfert, *Synthesis* 36 (1974); ^bH. Stetter and H. G. Thomas, *Chem. Ber.* **101**, 1115 (1968).