

AN ABSTRACT OF THE THESIS OF

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Title: SYNTHESIS OF LARGE-RING ANALOGS OF ESTRONE

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Richard W. Thies

Various ring expansion routes from benzo medium-ring ketones to large-ring analogs of estrone were explored. Initial efforts were directed towards a synthesis of a 1,2-divinyl substituted ring system which could undergo a four carbon ring expansion via the oxy-Cope rearrangement. A second approach involved the condensation of p-bromoanisole with cycloheptanone via the "Caubere reaction" to ultimately provide 2-methoxy-7, 8, 9, 10, 11-pentahydro-5(6H)-benzo-cyclononenone. One and two carbon ring expansions via the Tiffeneau-Demyanov rearrangement and the [1, 3] anionic rearrangement provided benzo twelve- and thirteen-membered rings which are analogs of estrone. A kinetic analysis of the [1, 3] anionic rearrangements of the potassium salts of 6-vinyl-7, 8, 9, 10, 11, 12-hexahydro-6(5H)-benzocyclodecenol as well as the para and meta methoxy analogs was undertaken to gain mechanistic insight into the rearrangement. Finally, a three-carbon ring expansion of β -benzocyclodecenone to an estrone analog via a cyclopentenone annulation-scission method was investigated.

Synthesis of Large-Ring
Analogues of Estrone

by

John Robert Pierce

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Associate Professor of Chemistry
in charge of major

Redacted for privacy

Chairman of Department of Chemistry

Redacted for privacy

Dean of Graduate School

Date thesis is presented March 11, 1980

Typed by Opal Grossnicklaus for John Robert Pierce

To

Kit and Mom

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The author wishes to express his sincere gratitude for the friendship, guidance, expertise, and support offered by Dr. Richard W. Thies, my wife, Kathryn, Dr. Gerald J. Gleicher, Dr. Ronald H. Chiarello, Dr. Dwight D. Weller, Mr. Brian Arbogast, and many other members of the Chemistry Department.

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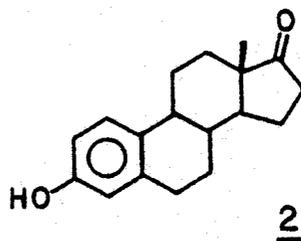
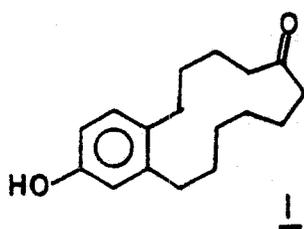
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SYNTHESIS OF LARGE-RING ANALOGS OF ESTRONE

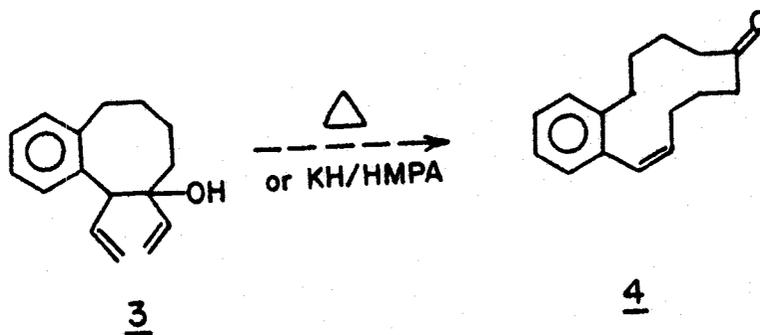
INTRODUCTION

As part of a program aimed at the synthesis of 8:9, 13:14-disecosteroid 1, various ring expansion reactions were examined. Disecosteroid 1 is a large ring analog of the female sex hormone estrone 2. Ultimately, the estrogenic activity of 1 or analogs of 1 will be investigated.



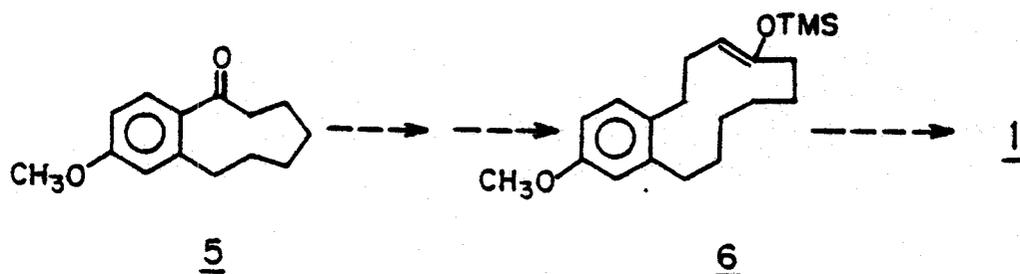
The initial general approach to the synthesis of 1 was the synthesis of a divinyl substituted ring system such as 3, followed by a four carbon ring expansion to give 4 (Scheme 1).

Scheme 1



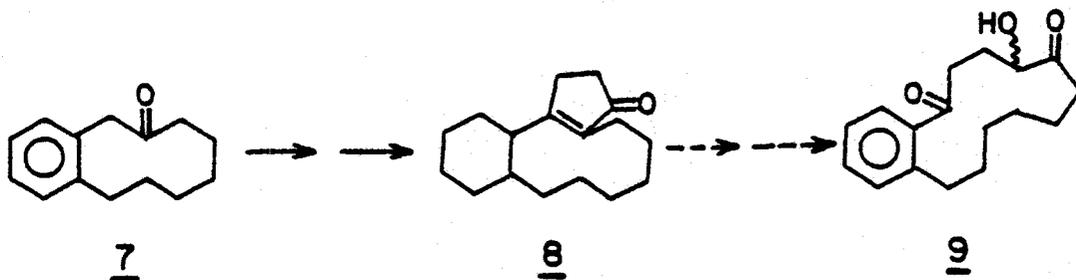
A second approach involved the condensation of p-bromoanisole with cycloheptanone in the Caubere reaction to ultimately provide 5. One and two carbon ring expansions were investigated to provide 6, which was to be converted ultimately to 1 as shown in Scheme 2.

Scheme 2



A third approach investigated the feasibility of a cyclopentenone annulation of 7, followed by cleavage of the double bond of 8 to provide 9 (Scheme 3).

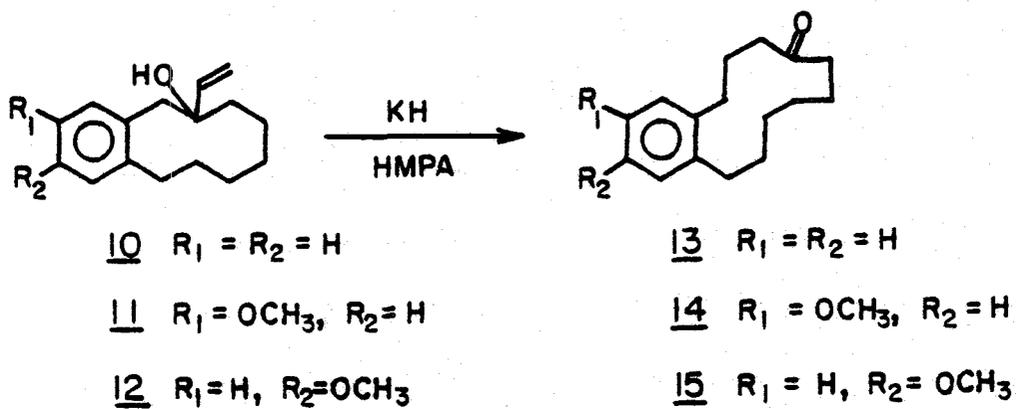
Scheme 3



An investigation of the kinetics of the two carbon ring expansion of the potassium salt of 10, 11, and 12 in hexamethyl phosphoramidate was also undertaken to provide insight into the mechanism of the

rearrangement (Scheme 4).

Scheme 4



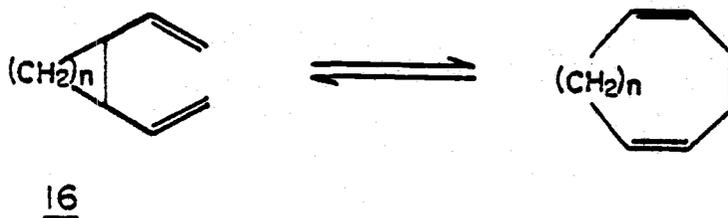
HISTORICAL

An excellent review of the synthesis of various disecosteroid systems can be found in the recent Ph. D. thesis of R. H. Chiarello (1), and will not be repeated here. Instead, the background of the various ring expansion reactions investigated in this thesis will be discussed.

Part I. Four Carbon Ring Expansion Via the Cope Rearrangement

The value of the Cope rearrangement¹ for ring enlargement by four carbons as illustrated in Scheme 5 was first realized for the cases where $n=1$ and 2 (3, 4). Here the inherent ring strain

Scheme 5



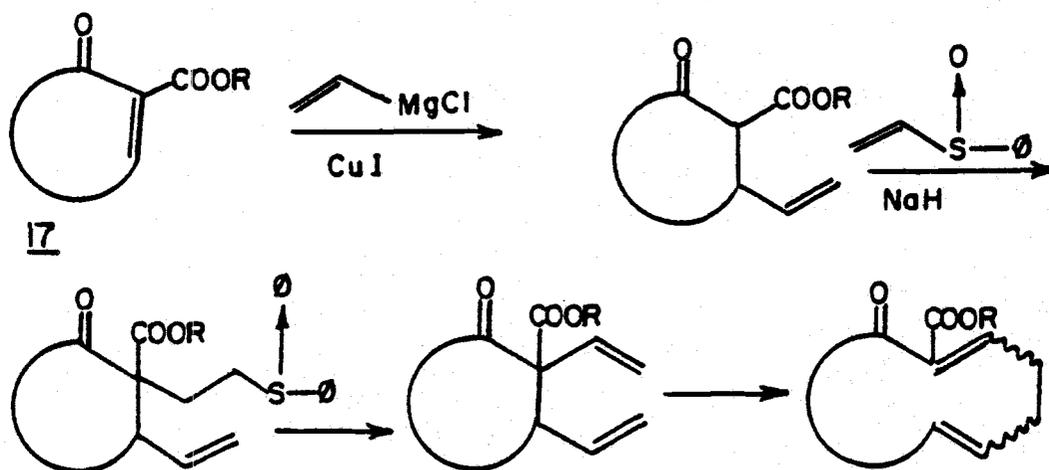
(Baeyer strain) of the cyclopropane and cyclobutane rings contributes to the facile rearrangements observed.

¹In this thesis the term "Cope rearrangement" will be used to describe [1, 3] and [3, 3] sigmatropic shifts of the following stoichiometric types, regardless of whether the mechanism is concerted or otherwise: $A=B-C-C'-B'=A' \rightarrow C=B-A-A'-B'=C'$ or $A=B-C-A'-B'=C'$. Hammond and DeBoer (2) have previously used the term "Cope rearrangement" in this manner.

In compounds of type 16 where n is larger than two, the rearrangement is far less favorable for forming medium sized rings. For example, cis-1,2,-divinylcyclopentane (n=3) has been shown to establish an equilibrium mixture at 300° which consists of only five percent 1,5-cyclononadiene (5). The even more unfavorable equilibrium value for the cyclohexane series is hinted by the fact that the attempt to prepare 1,5-cyclododecadiene via an N-oxide elimination reaction of the 1,6-diaminocyclodecane yields a mixture of cis- and trans-1,2-divinyl cyclohexane (6). In the latter two cases, it is the strain of the nine and ten membered cycloalkadienes that disfavor the ring expanded products.

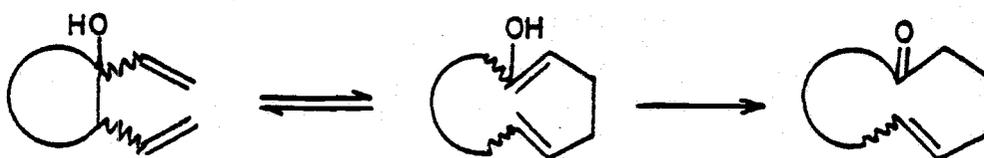
However, formation of a large ring compound from 16 has been more recently demonstrated for the case where n=6. Rienäcker (7) has shown that trans- and cis-5,6-divinyl-cis-cyclooctene rearrange above 200° to trans-1, trans-5, cis-9-cyclododecatriene and trans-1, cis-5, cis-9-cyclododecatriene, respectively.

Heimgartner and coworkers (8) have recently developed a ring expansion sequence starting with the unsaturated β -ketoester of type 17 that in principle would provide for an infinite number of ring expansions as shown in Scheme 6. Here the four carbon ring expansion product of the Cope rearrangement is itself an unsaturated β -ketoester which could again be ring expanded via the sequence

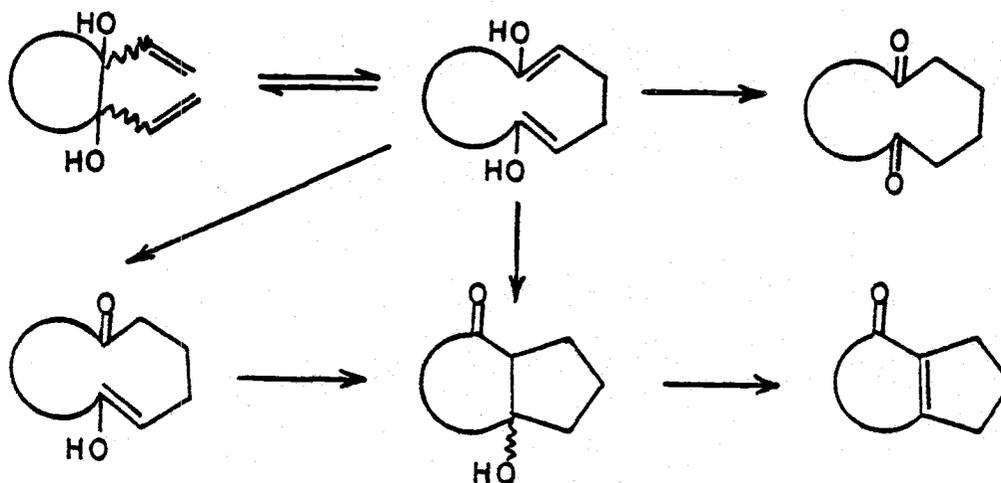
Scheme 6

shown. The above reaction sequence was utilized to ring expand the nine-, twelve-, and fifteen-membered ketoesters to the thirteen-, sixteen-, and nineteen-membered ring compounds respectively. Again, with the cyclohexane derivative, ring expansion could not be achieved.

A modification of the Cope rearrangement in which an oxygen functionality is attached to one or both of the positions bearing the vinyl substituents has been termed the oxy-Cope rearrangement (9), and is illustrated in Scheme 7 and Scheme 8 for the cyclic cases. In this

Scheme 7

Scheme 8

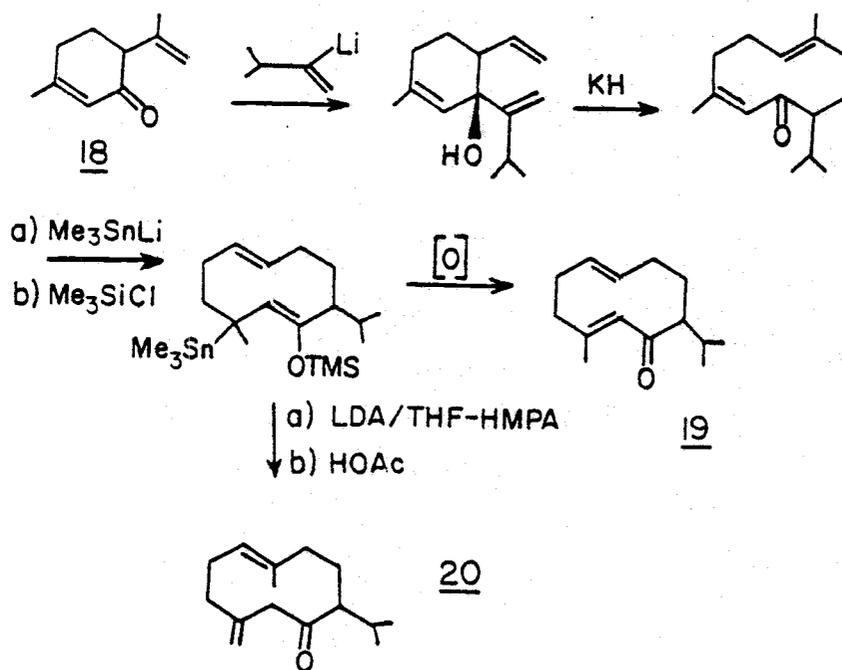


modification, enol formation is an important driving force for the reaction. Marvell *et al.* (10, 11), and Conia *et al.* (12, 13) have found Scheme 8 to provide a preparatively useful route for the synthesis of large ring ketones of twelve or more members. However, all attempts to prepare rings of nine to eleven members have been frustrated by intervention of aldo-like cyclization products. In contrast, Scheme 7 where only one oxygen functionality exists avoids the aldo cyclization routes and was shown by Marvell (14) to provide an efficient route to *trans*-5-cyclodecene-1-one from *trans*-1,2-divinylcyclohexanol. Nishino *et al.* (15) illustrated a facile route to the macrocyclic ketone 5-cyclohexadecen-1-one via the oxy-Cope rearrangement of 1,2-divinylcyclododecanol.

The Evans modification (17) of the oxy-Cope rearrangement in

which the alcohol is converted to the alkoxide in a strongly dissociating solvent (see Part II, page 11) was utilized by W. C. Still (16) to prepare the germacranes 19 and 20 starting with the monoterpene isopiperitenone (18) as outlined in Scheme 9.

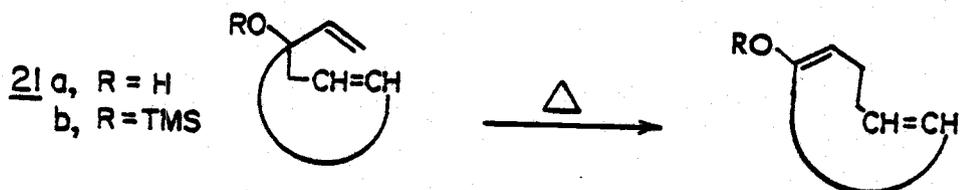
Scheme 9



Part II. Two Carbon Ring Expansions Via the Siloxy-Cope
and 1, 3 Anionic Rearrangements

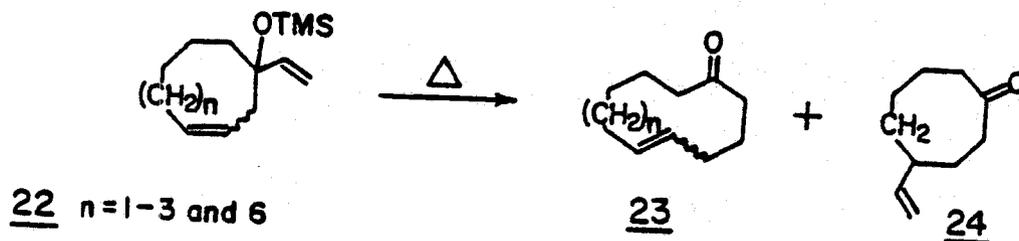
If part of a 3-hydroxy-1, 5-hexadiene system is linked together with a ring as in 21, then conceivably a thermolytic [1, 3]-sigmatropic shift could result in a two-carbon ring expansion (Scheme 10). The

Scheme 10



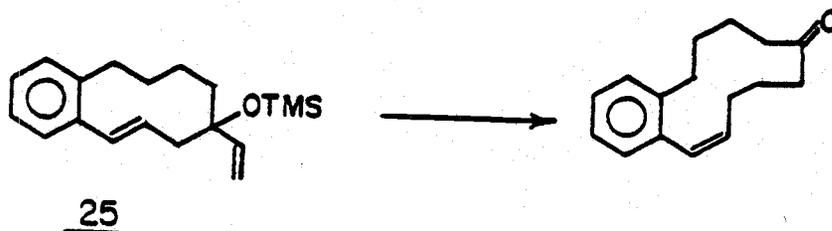
difficulty with this approach is that β -hydroxy olefin cleavage competes, and the ring simply fragments. In a series of papers, Thies and coworkers (18, 19, 20, 21) reported the use of a trimethylsilyl blocking group for systems like 22 which eliminated the cleavage and allowed, in most cases, an effective two-carbon ring expansion to occur (Scheme 11). For $n=1-3$, compound 23 was the major product,

Scheme 11



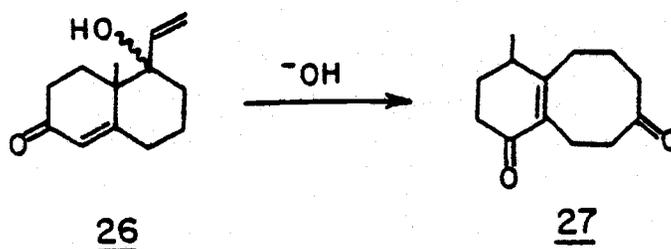
while for $n=6$, the [3, 3] rearrangement product 24 predominated.

Thies and Shih (22) have also utilized the siloxy-Cope reaction for ring expansion of 25 as part of a program to prepare a hormone model system as shown below.



It is important to note the rather high temperatures (ca. 300°) required to bring about the thermolytic ring expansions reviewed above. In contrast to the thermal rearrangements, certain anionic [1, 3] and [3, 3] sigmatropic rearrangements have been reported to proceed at much lower temperatures and at greatly enhanced rates.

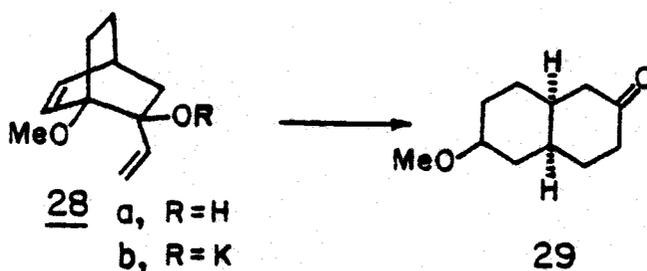
The first reported example in the literature of a formal anionic oxy-Cope rearrangement is the rearrangement reported by Swaminathan *et al.* (23) of the vinyl carbinol 26 to the diketone 27.



The authors felt this base induced rearrangement was best explained by a fragmentation-recombination mechanism, although a concerted oxy-Cope mechanism could not be disproven. In a later paper, Swaminathan *et al.* (24) reported the thermal rearrangement of 26

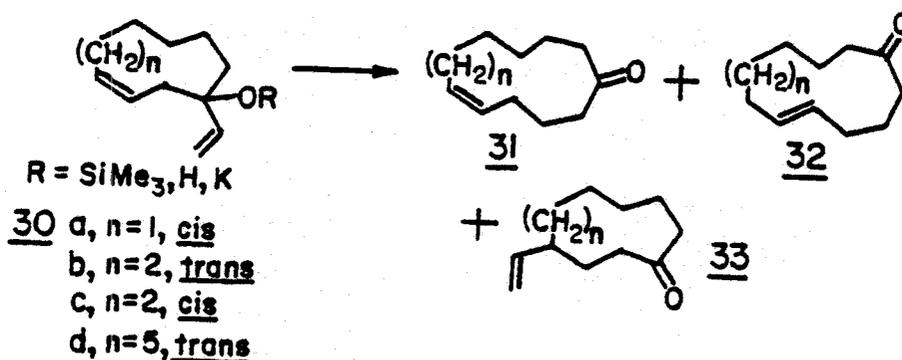
to 27 under more drastic conditions, which is believed to involve a concerted oxy-Cope mechanism.

A later paper by Evans and Golob (17) which reported 10^{10} - 10^{17} fold rate increase for the [3, 3] sigmatropic rearrangement of compound 28b to 29 in the highly dissociating media hexamethylphosphoramide (HMPA) or tetrahydrofuran (THF)/18:crown:6 when compared



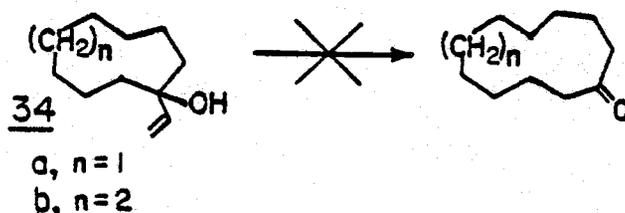
to the rearrangement rates of the parent alcohol (28a), prompted Thies and Sietz (25) to examine the possibility of using the related anionic [1, 3] sigmatropic rearrangements as a method for ring expansion as shown in Scheme 12. When alcohols 30 a-c were

Scheme 12



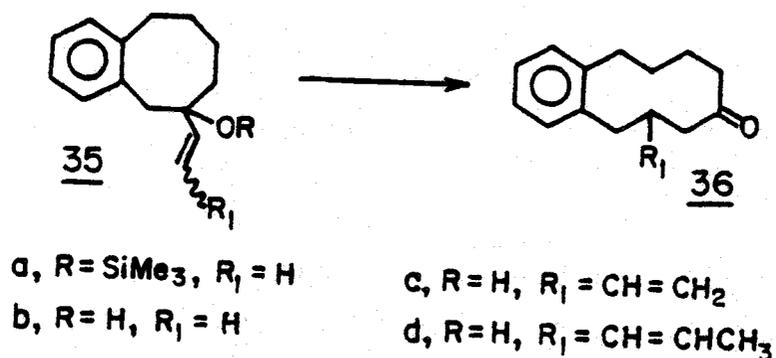
treated with KH in HMPA or dimethoxyethane (DME) or THF with

18:crown:6, the predominant process was the 1,3-shift ring expansion leading to 31 and/or 32. Similar treatment of compound 30d, however, resulted predominantly in a [3,3] process leading to 33. Comparison by the authors of the half life estimates for the alkoxides 30a-c in HMPA with earlier thermal rates for the trimethylsiloxy derivatives gave approximate rate enhancements for the alkoxide process in the range of 10^{15} - 10^{17} . Further studies of the scope of this reaction demonstrated the necessity of unsaturation homoallylic to the hydroxyl functionality. Treatment of compounds 34a and 34b with KH in HMPA failed to yield any ring expanded product.

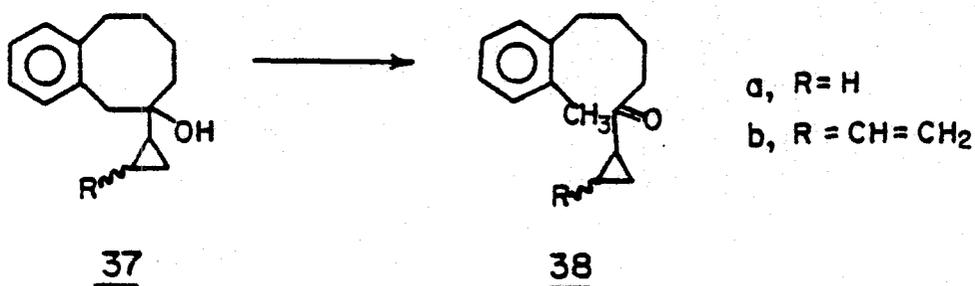


The utility of the above anionic [1,3] two-carbon ring expansion was also demonstrated for the synthesis of benzo-substituted ring systems by Thies (25) (Scheme 13). Treatment of compound 35b with KH in HMPA resulted in the ring expanded product 36 in somewhat better yield than the thermolysis of 35a. However, when compounds 35c and 35d were subjected to the same reaction conditions in an attempt to effect a four carbon ring expansion via a [1,5] sigmatropic rearrangement, only the [1,3] products were observed.

Scheme 13



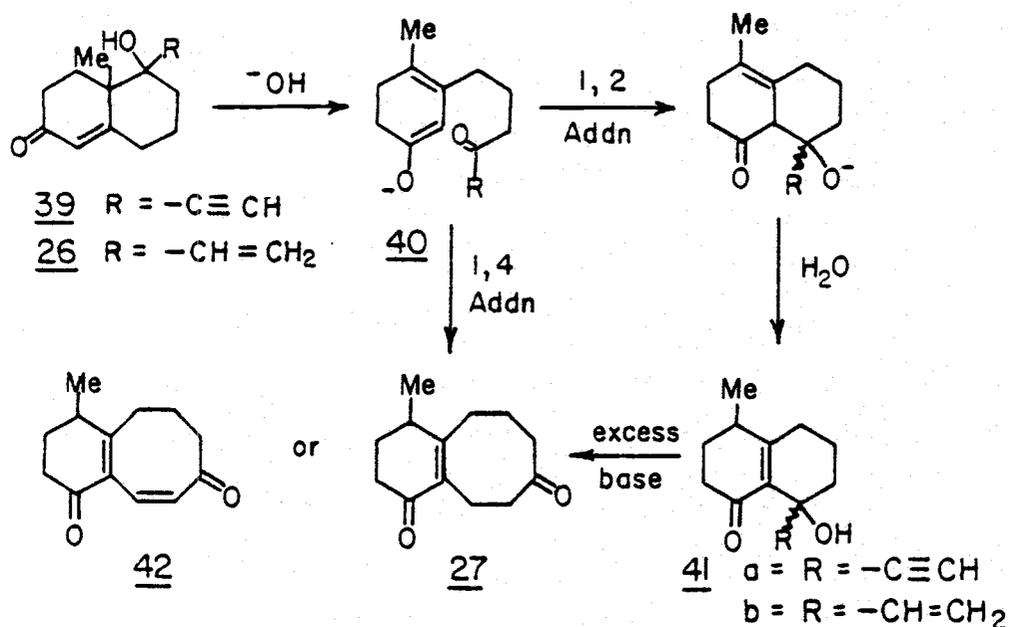
Finally, the possibility of a three or five carbon ring expansion was examined in compounds 37a and 37b. However, treatment of these compounds in the previously described manner resulted only in the isolation of ring cleaved products 38a and 38b.



The mechanism of these anionic [3, 3] and [1, 3] rearrangements is not clearly established. As previously mentioned, Swaminathan *et al.* (23) believed the mechanism of the rearrangement of the bicyclic- δ -hydroxy- α, β -enones (eg. compound 26) to be a fragmentation followed by a Michael addition. Swaminathan *et al.* (26) later reported the isolation of compound 41a and 41b in addition to starting material and 42 and 27 when compounds 39 and 26 were

treated with a catalytic amount of 0.1% solution of sodium methoxide in methanol. The author felt that the products could best be explained via the sequence shown in Scheme 14. A concerted [1,3] rearrangement of 39 and 26 to 41a and 41b was deemed to be unlikely in view

Scheme 14



of the unfavorable transoid location of carbon atoms 1 and 5. Compounds 41a and 41b were found to isomerize to the diones 42 and 27 more rapidly than the isomers 39 and 27 with base which could be explained by a favorable geometry for the [1,3] concerted reaction or due to an increased rate of fragmentation to species of the type 40.

In contrast, the results of Evans seem to disfavor a stepwise non-concerted mechanism for the systems he studied. In the initial

investigation of alkoxide rearrangements (17), Evans found that while the potassium salt of the endo compound 28 rearranged readily, the exo isomer of 28 showed no rearrangement under the same conditions. This observation does not rule out a non-concerted stepwise mechanism since single bond cleavage by a homolytic or heterolytic pathway could occur with 28 (endo or exo isomer), but the exo isomer may have a rotational barrier that is large relative to the recombination barrier, and thus does not achieve the desired geometry to proceed to 29.

In a stereochemical study of the [3, 3] sigmatropic rearrangement of the 1, 5-diene-3-alkoxides 44 a, b and 45a, b, Evans *et al.* (27, 28) found the rearrangement to be highly stereospecific and proceeded predominantly via a chair transition state to compounds 46 and 47. If the rearrangements were concerted, then dienols 44a and 45b should rearrange only to 46a and 47b via chair and boat transition states, while dienols 44b and 45a should afford only ketones 46b and 47a. The results are shown in Table I.

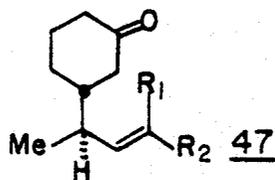
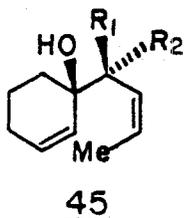
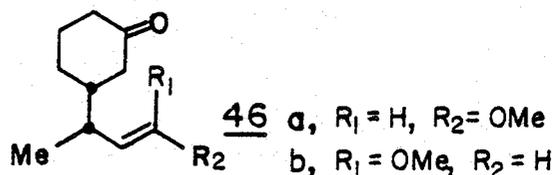
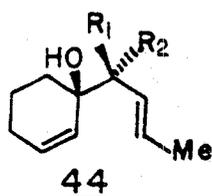
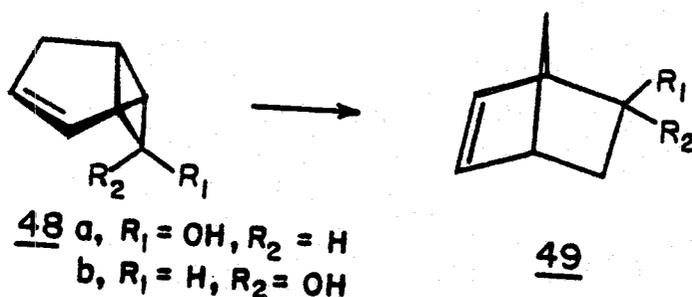


Table I. Rearrangement of Dienols 44a, 44b, 45a, and 45b

Alcohol	product composition %			
	<u>46a</u>	<u>47b</u>	<u>46b</u>	<u>47a</u>
<u>44a</u>	96	4	≤ 1	≤ 1
<u>45b</u>	30	70	≤ 1	≤ 1
<u>44b</u>	≤ 1	≤ 1	77	23
<u>45a</u>	≤ 1	0-2	2-0	98

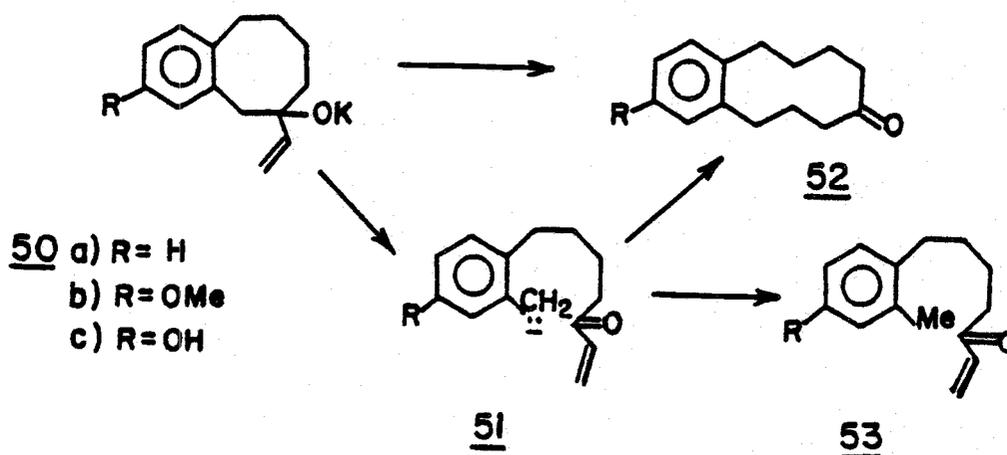
Evans states that the high stereospecificity and the absence of crossover products is unequivocal evidence for a concerted process. The fact that 44b and 45b are less stereospecific is accounted for by the fact that 44b and 45b possess a destabilizing pseudo-axial methoxy substituent in the chair transition state.

Wilson and Mao (29) reported the anionic [1, 3] rearrangement of the potassium salts of 48a and 48b to the norbornenols 49a and 49b to be consistent with a concerted mechanism. Compound 48a

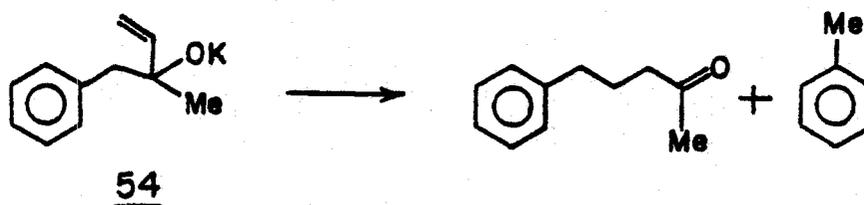


isomerized to a mixture of 67% 49a, 8% 49b, and 25% 48a after three hours at room temperature. Under the same conditions the endo alcohol 48b was stable. The clockwise rotation about C-6-C-7 of the endo isomer required by a concerted process would force the alkoxide substituent into the cyclopentane ring, and thus would disfavor the reaction. Under more vigorous conditions (refluxing THF/18:crown:6) compound 48b does isomerize, yielding 49a and 48b in a 6:1 ratio. A non-concerted mechanism still may not be ruled out since the thermodynamic ratio of 49a to 49b is 6:1.

The rearrangements of 50a and 50b to 52a and 52b were subjected to kinetic analysis by Thies *et al.* (30). The rearrangement of 50b was found to be three times faster than the rearrangement of the non-methoxy analog 50a. In contrast, compound 50c gave no evidence of rearrangement. The enhanced rate of the methoxy case, and the lack of reactivity of the hydroxy case (which would be a meta O^- under the reaction conditions) suggest that substantial negative charge builds up at the benzylic position as in the proposed intermediate 51.

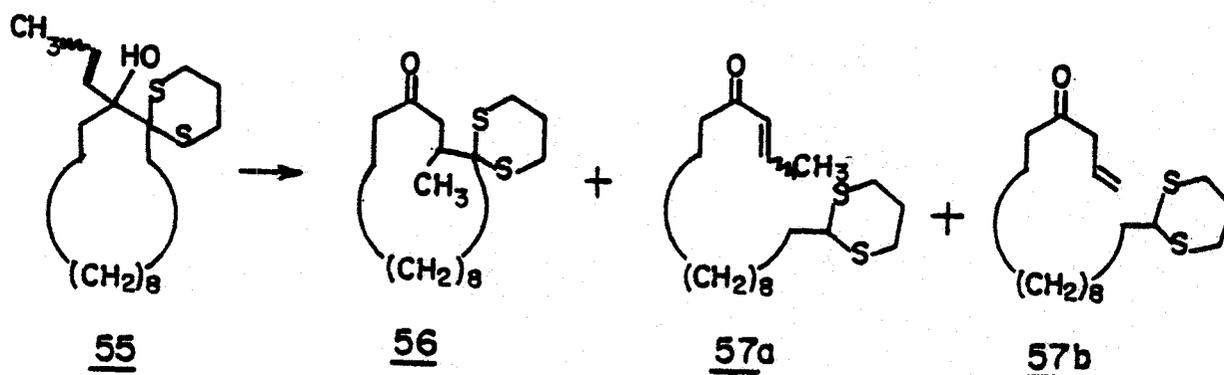


If an intermediate such as **51** is formed, one might expect to detect some **53** in the product mixture. No **53** was detected, however, the terminal α, β -unsaturated ketone moiety would be prone to polymerization under the reaction conditions. Also, cleavage was found to be a significant process for the acyclic analogue **54**.



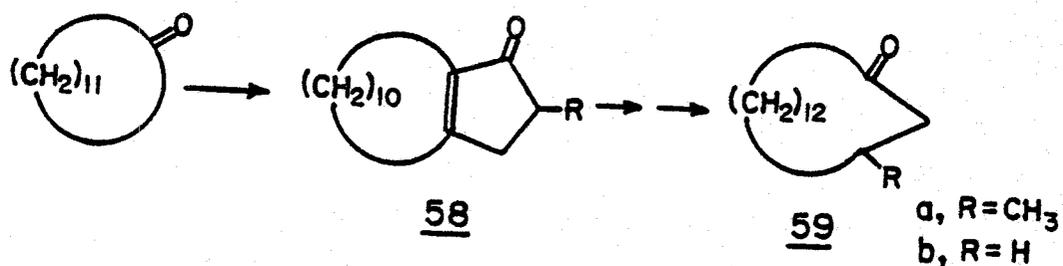
The results of Wilson and Misia (31, 32) while studying the applications of potassium alkoxide promoted [1, 3] rearrangements of dithianes also suggest a stepwise mechanism for the rearrangement. In a synthetic sequence aimed at the synthesis of d, l-muscone, compound **55** was rearranged with KH in tripyrrolidinylphosphoramidate (TPPA) to the ring expanded product **56** as well as the ring cleaved

product 57a and 57b.

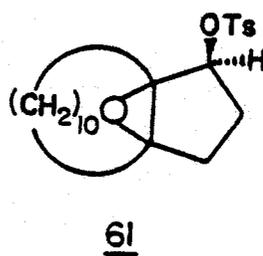
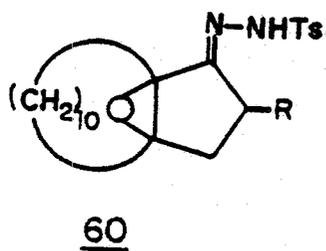


Part III. Ring Expansion Via a Cyclopentenone Annulation-Scission Method

A ring expansion sequence of considerable flexibility involves the addition of a new carbocyclic ring to a carbocyclic framework followed by a cleavage reaction. While there are many methods to effect this transformation, the one of particular interest in this thesis was a cyclopentenone annulation-scission of the type shown in Scheme 15, which has been utilized extensively by many researchers (33a-f) for the synthesis of Muscone (59a) and Exaltone (59b). These attempts mostly utilize the key intermediate 58, and numerous methods have been developed for fusing cyclopentenone units onto existing ring systems (33a-h). The key cleavage step in most of these synthesis of 59a and 59b is an ozonolysis, although Eschenmoser (34) and

Scheme 15

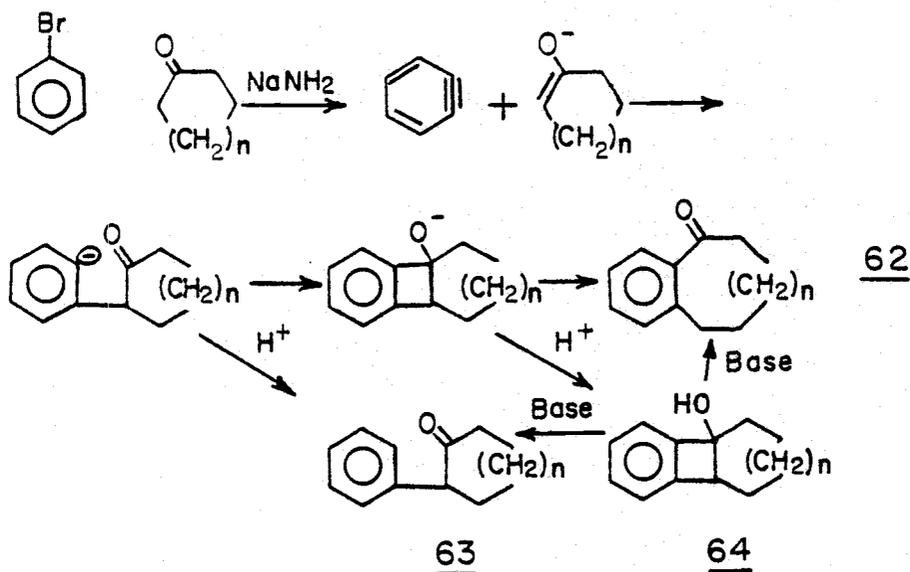
Dreiding (35) have reported cleavage via fragmentation reactions of compounds 60 and 61, respectively.



Part IV. Formation of Benzocycloalkenones via the "Caubere Reaction"

Methods of preparation of benzo medium-ring compounds are relatively few, and fewer still have been applied to systems with substituents on the benzo group. One recent innovation is the "Caubere reaction" (36) which has proven to be a method of great utility for the formation of benzo-substituted carbocyclic skeletons. The general reaction sequence is shown in Scheme 16. The relative

Scheme 16

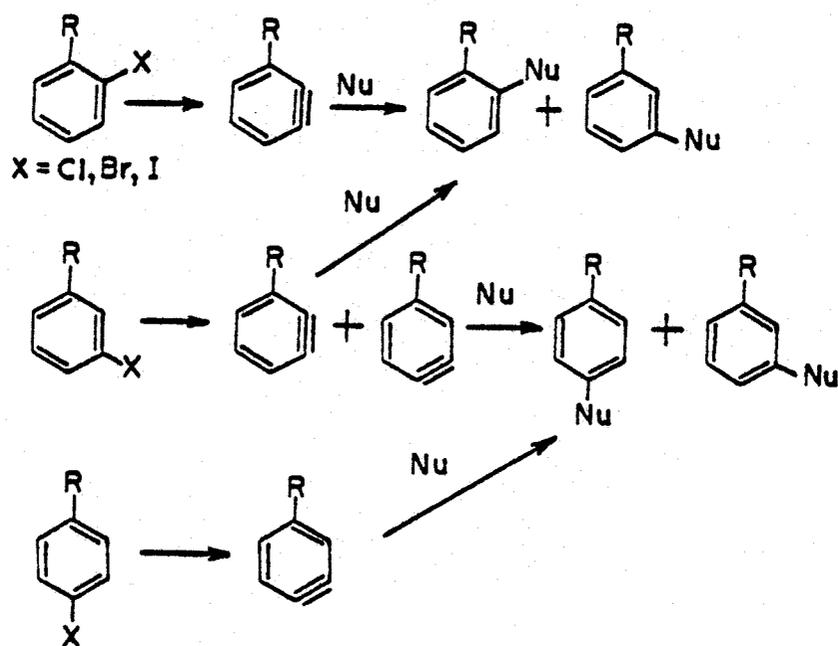


amounts of products 62, 63, and 64 formed is a function of n , temperature, base and solvent. Alcohols of type 64 have only been obtained for the cases where $n=1-3$. Although synthesized in basic media, these alcohols are unstable with bases and when treated with base

open to give the corresponding ketones 62 and 63. Again, the relative amounts of 62 and 63 are dependent upon n , temperature, and solvent, with HMPA strongly favoring formation of benzocycloalkenones of type 62.

If one generates the aryne from a substituted haloarene and reacts the aryne with a nucleophile, one would expect a mixture of positional isomers as shown in Scheme 17. The product mixture

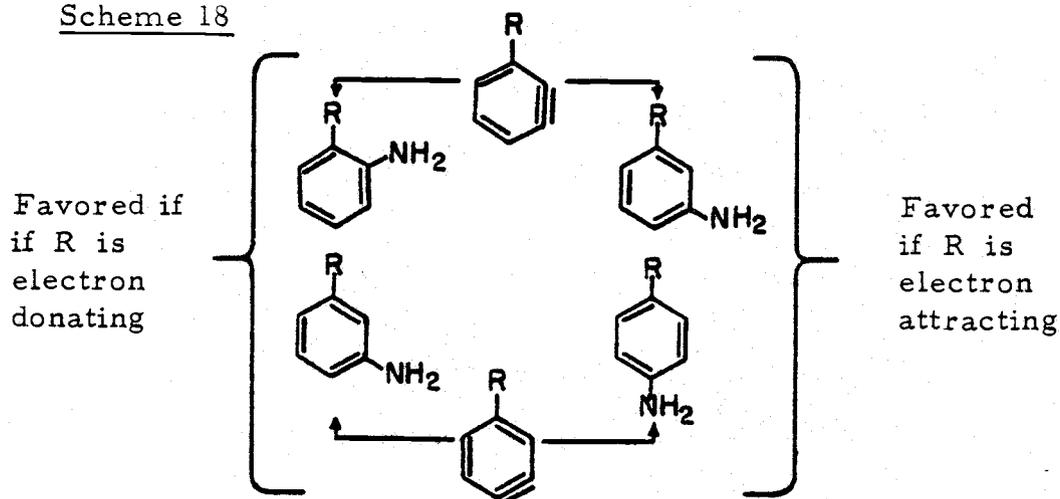
Scheme 17



would depend upon the steric and electronic properties of the substituent R, and the reaction is most useful if the substituent has a strong directing effect and forms predominantly one product. Roberts et al.

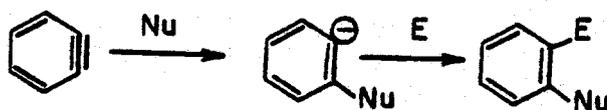
(37) have reported the results shown in Scheme 18 for the case where amide ion (NH_2^-) was the nucleophile. These results can be expected

Scheme 18



in terms of the "benzyne mechanism" in which after addition of the nucleophile a pair of electrons occupies an orbital that is orthogonal

Benzyne mechanism



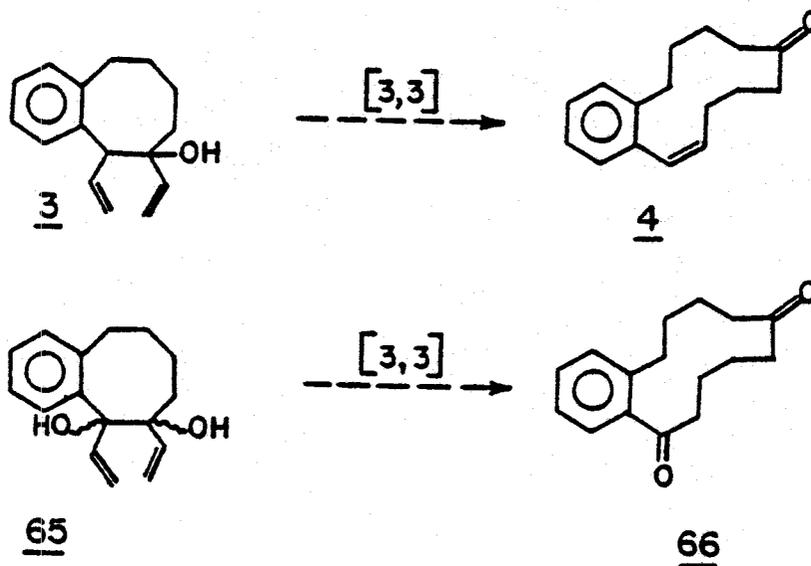
to the plane of the aromatic ring. Thus, the inductive effect of R can influence the addition of the nucleophile such that the resulting negative charge is most stabilized or least destabilized. However, preference in the case of 3-substituted arynes may be diminished by steric hindrance of the substituent. Also, less preference would be expected

for 4-substituted arynes where the inductive effects of R would be less due to the distance from the active site. Furthermore, for a highly exothermic process, which addition to an aryne is likely to be, little selectivity may actually be observed.

RESULTS AND DISCUSSION

Part I. Attempts Directed Towards Preparation of a 5,6-Divinyl-Benzocyclooctenol

The first approach directed towards the synthesis of a large ring analog of estrone was based on a [3,3] ring expansion of 3 to 4 or alternatively 65 to 66. Although oxygen functionality at the position analogous to the C-3 position in the steroid system is absent, once methodology was established on the model system, the methodology was to be applied to the C-3 oxygen functionalized analog of 3 or 65.

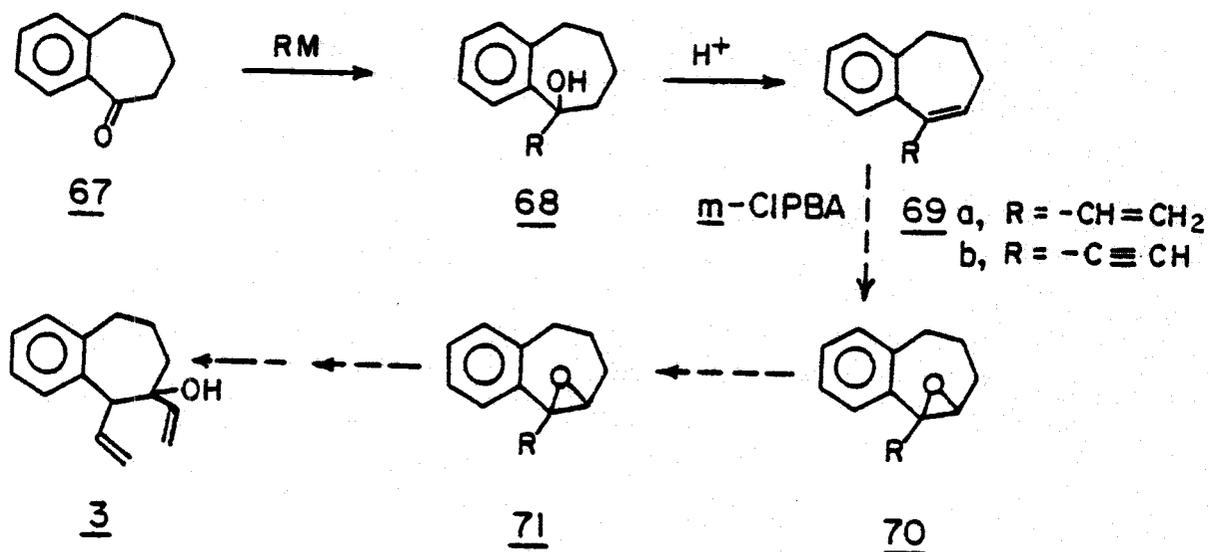


These type of oxy-Cope ring expansions have previously been explored by Conia (12, 13) and Marvell (10, 11, 14) for the thermal cases with the non-benzo substituted analogs of 3 and 65. Upon successful synthesis of 3 or 65, the Evans modification (17) of the oxy-Cope

rearrangement in which the alcohols were to be converted to the potassium alkoxides in HMPA was to be explored.

A previous investigation of the methodology of the synthesis of compound 3 was carried out by Seitz (38) on the commercially available model compound benzosuberone (67). The general approach is shown in Scheme 19. This scheme gave only a 12% yield of 69a or 69b,

Scheme 19



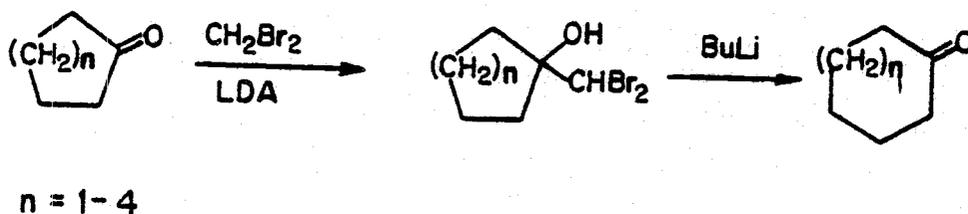
and was halted by the failure of both 69a and 69b to undergo the epoxidation reaction.

Partly due to the failure of the benzosuberone model system shown above, and for reasons which will be discussed later we decided to investigate the feasibility of using 6-benzocyclooctenone (73) as the starting point for our studies.

Huisgen and Seidl (39) had previously synthesized

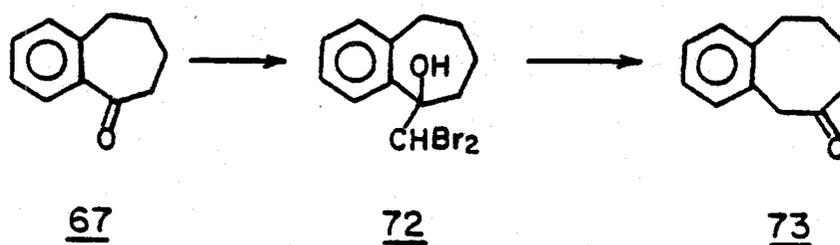
6-benzocyclooctenol in four steps from benzosuberone in overall low yield. Our first efforts were directed towards a more efficient synthesis of 6-benzocyclooctenone and were based on the work of Taguchi, Yamamoto and Nozaki (40), who had prepared cyclohexanone, cycloheptanone, cyclooctanone, and cyclononanone in two steps in good overall yields from the corresponding cycloalkanones. The method involved the addition of a dihalomethane carbanion to the cycloalkanone, followed by treatment of the dihalomethane adduct with butyl lithium as illustrated in Scheme 20 for the dibromomethane case. Application of

Scheme 20



the above method to benzosuberone (Scheme 21) resulted in a mixture

Scheme 21



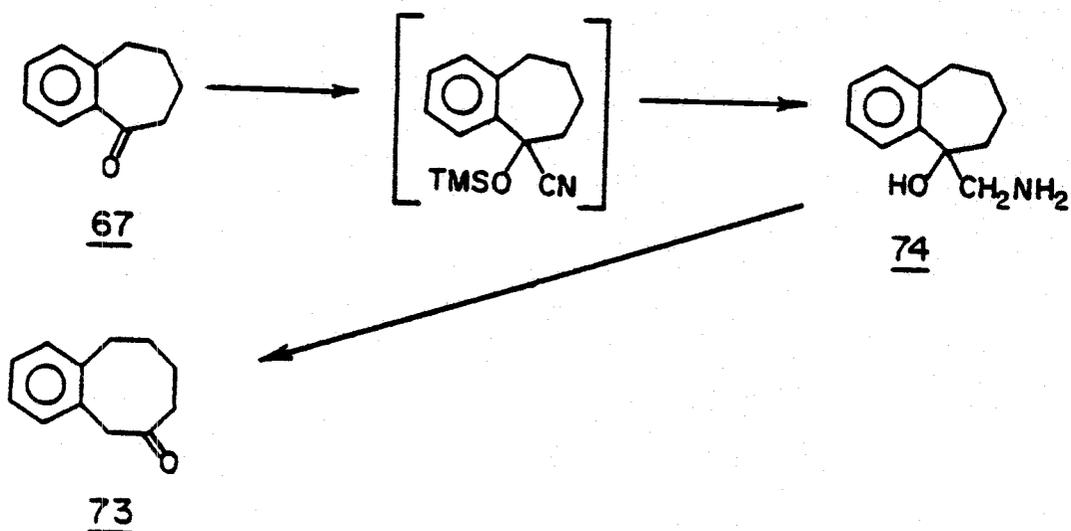
that contained 67% of the desired ketone 73 in only 27% overall yield.

Meanwhile, an improved synthesis of 73 via the trimethylsilyl cyanide

(TMSCN) ring expansion of benzosuberone was discovered in our laboratories (38) and Scheme 21 was abandoned.

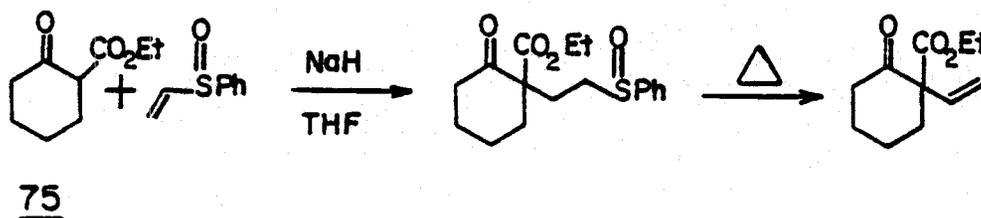
The TMSCN ring expansion of cycloalkanones was reported by Evans, Carrol, and Truesdale (41), and is shown for benzosuberone in Scheme 22. The improvement was in the substitution of potassium

Scheme 22



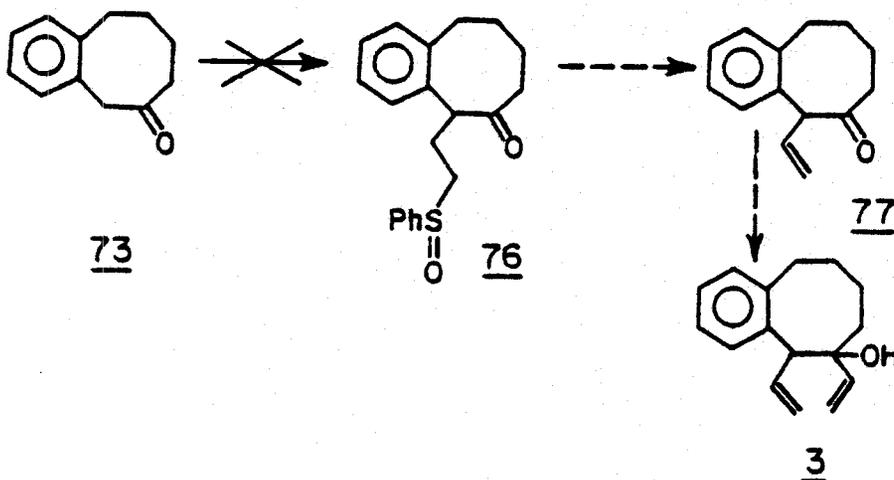
cyanide (KCN)/18:crown:6 catalyst for the zinc iodide catalyst originally reported by Evans. This improvement afforded consistently good yields of 74 following reduction of the TMSCN adduct with lithium aluminum hydride (LiAlH_4). Finally, a Tiffeneu-Demyanov rearrangement following diazotization of the amino alcohol 74 afforded the ring expanded product 73 in around 60% overall yield. The TMSCN ring expansion method became the method of choice in our laboratories to effect a one carbon ring expansion.

The first attempt at the preparation of a 5,6-divinylbenzocyclo-octenol derivative was based on work by Koppel and Kinnick (42) who illustrated a method for the overall introduction of a vinyl substituent to compound 75 at the doubly activated alpha position. It was hoped



that the same sequence could be applied to 6-benzocyclooctenone to introduce a vinyl substituent at the doubly activated benzylic position of 73 to ultimately produce 77 as shown in Scheme 23. Compound 77

Scheme 23

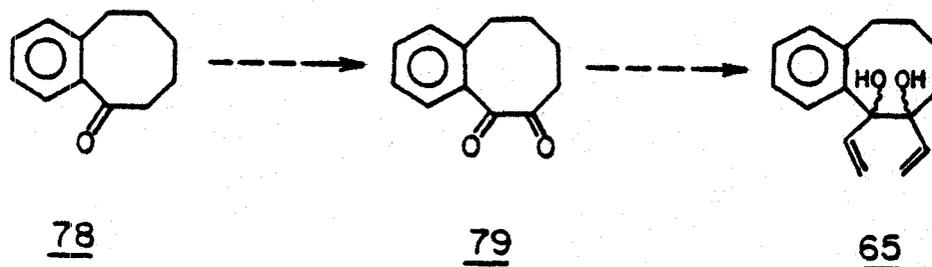


would then be reacted with vinyl Grignard reagent to prepare 3. Phenyl vinyl sulfide was prepared by the reaction of diphenyl disulfide with vinyl Grignard reagent (43), followed by oxidation with m-chloroperbenzoic acid (44). Preparation of the potassium enolate

of 73 by reaction with KH in THF followed by addition of phenyl vinyl sulfoxide failed to produce any significant amounts of 76 at temperatures ranging from -78° to 65° (refluxing THF).

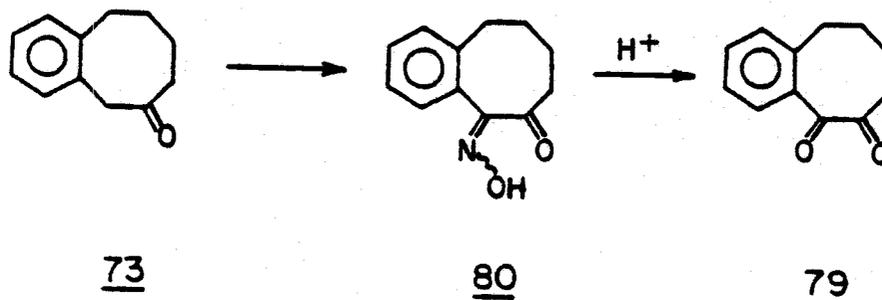
Having failed to prepare compound 3 via scheme 23, attempts were directed towards the preparation of compound 65 via the sequence shown in Scheme 24. Previously, compound 79 had been prepared in

Scheme 24



our laboratories by E. P. Seitz (45) via the selenium dioxide oxidation of 78. However yields and conversions were low. Compound 78 is available from the Caubere reaction (36) of bromobenzene with cyclohexanone. Alternatively, Seitz prepared 79 by hydrolysis of the isonitroso derivative 80 as shown in Scheme 25. The isonitroso

Scheme 25



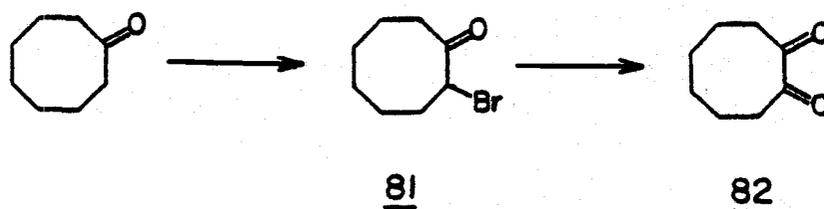
derivative was prepared by reaction of the potassium enolate of 73 with

isoamylnitrite. Again the yields and conversions were low, and we hoped to find a more efficient synthesis of 79.

Our initial efforts were based on results reported by Timms and Wildsmith (46) who reported the reduction of oximes with titanium trichloride (TiCl_3) to the corresponding ketone. Cyclooctanone was used as a model system and was converted to the α -oxime via the procedure of Litvan and Robinson (47). Unfortunately, reduction with TiCl_3 afforded no desired 1,2-cyclooctanedione.

During the course of this work a reference by Bauer and Macomber (48) was discovered in which the conversion of cyclooctanone to 1,2-cyclooctanedione was reported as shown in Scheme 26.

Scheme 26

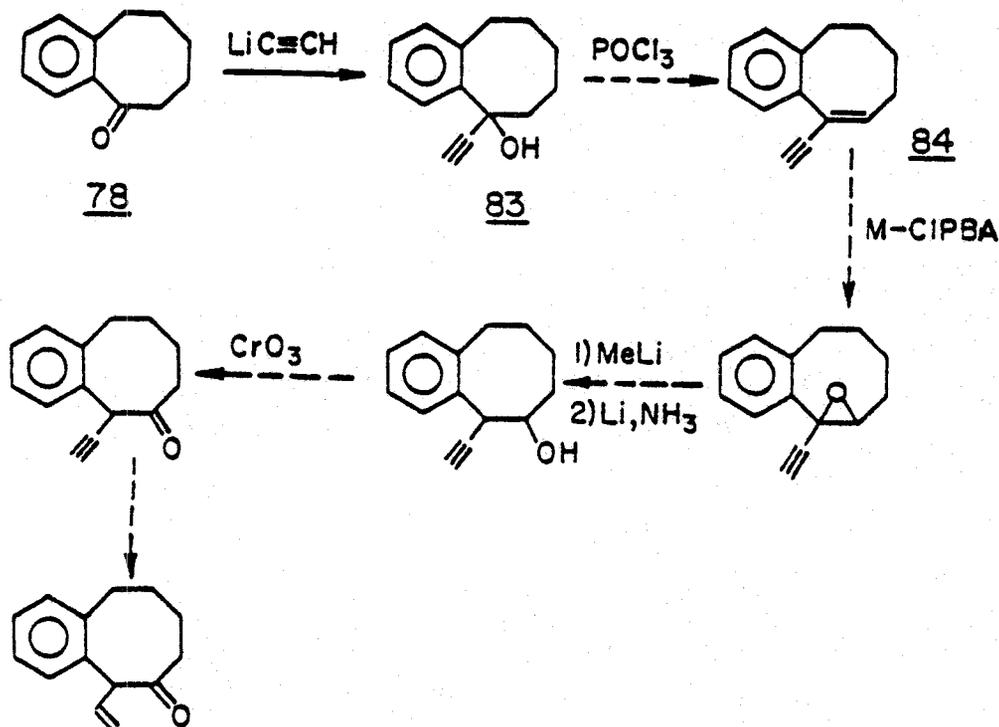


The 2-bromocyclooctanone (81) was readily synthesized according to the procedure of King and Ostrum (49). However, repeated attempts to convert 81 to the diketone 82 according to Macomber's procedure were frustratingly fruitless. A private communication with Macomber failed to reveal any error in my experimental technique or provide any insight which would lead to successful conversion of 81 to 82.

Attention was then turned to a more circuitous route for the

conversion of compound 78 to compound 77. This sequence is shown in Scheme 27 and is based on work by Carlson and Cox (50) who

Scheme 27

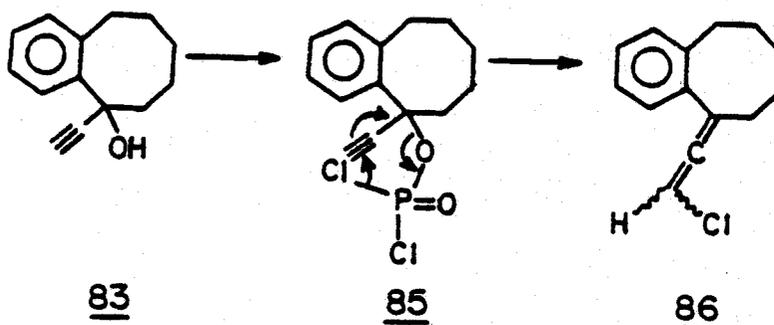


reported the conversion of cyclooctanone to 2-ethynylcyclooctanone via the same sequence using the reagents shown. Reaction of α-benzocyclooctenone with lithium acetylide failed to give any detectable amounts of the desired ethynyl adduct. However, treatment of the ketone with ethynyl Grignard reagent afforded a 50:50 mixture of product and starting material. The product to starting material ratio improved to 60:40 when lithium acetylide:ethylene diamine complex was used as the ethynyl reagent. Purification of the product with Girard's Reagent T afforded a 57% yield of compound 83 after correcting for recovered starting material.

Here the planned sequence went awry, when suitable conditions for the seemingly trivial dehydration of 81 to 84 could not be found. Conditions investigated included: 1) conversion of 83 to the acetate with acetic anhydride, followed by pyrolysis; 2) reacting 83 with a catalytic amount of p-toluene-sulfonic acid in refluxing benzene in a Dean-Starke trap apparatus; 3) pyrolysis of 83 in dimethyl sulfoxide; 4) reacting 83 with a catalytic amount of iodine in refluxing xylene in a Dean-Starke trap apparatus; and 5) conversion of 83 to the xanthate derivative, followed by pyrolysis. All of these methods gave recovered starting material or unidentified products (usually tars).

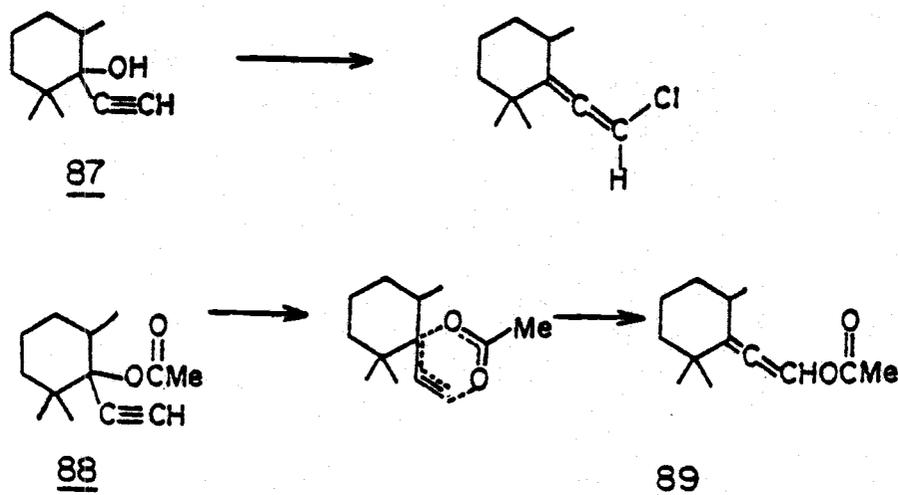
Attempted dehydration with phosphorous oxychloride in 75° pyridine as Carlson reports for the cyclooctanone analog failed to produce the desired ene-yene. The major products formed were the two isomers of the allene 86 shown in Scheme 28 based on the NMR spectrum of the product which showed loss of the acetylenic proton and a new triplet with a coupling constant of 1 Hz at δ 6.03; the IR

Scheme 28



spectrum which showed loss of the hydroxyl band and a new band at 1955 cm^{-1} indicative of an allene; and analysis of the GLC/mass

spectrum. This product presumably arises from an $\text{Sn1}'$ or $\text{Sn2}'$ reaction of the phosphate ester 85. The rearrangement of propargyl alcohols to allenes with thionyl chloride and phosphorous halide reagents is a known process (51), especially for hindered tertiary propargyl alcohols. Bhatia, Landor, and Landor (52) have reported this reaction for the propargyl alcohol 87 with thionyl chloride in pyridine. Landor and Landor (53) have reported the similar rearrangement of the propargyl acetate 88 to the allenyl acetate 89. It is suspected that one of the products of the pyrolysis of the acetate derivative of 83 was

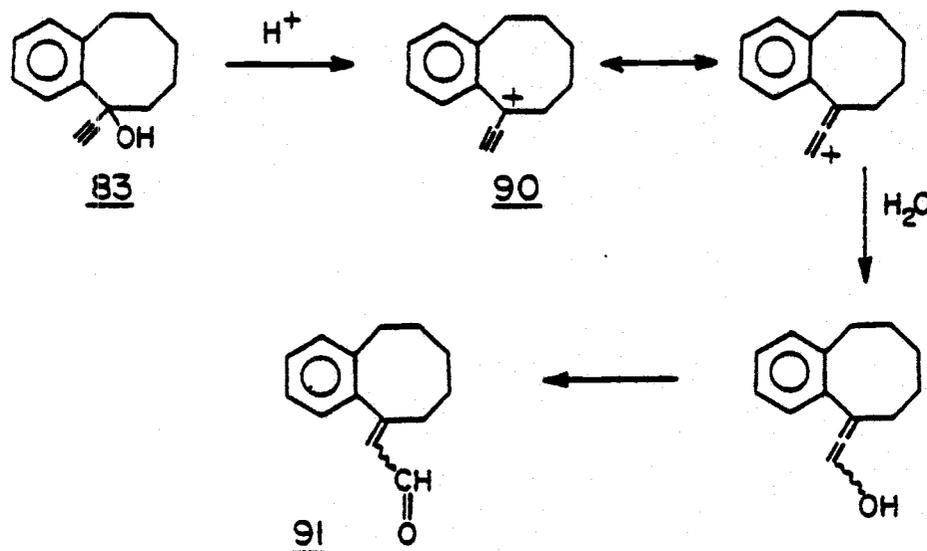


the analogous allenyl acetate, although a rigorous structural proof was not done.

Attempted dehydration with 50% aqueous sulfuric acid in THF as reported by Seitz (38) for the dehydration of the ethynyl carbinol derived from benzosuberone afforded a mixture of products that included compounds 91, 92, 93, and perhaps a small amount of

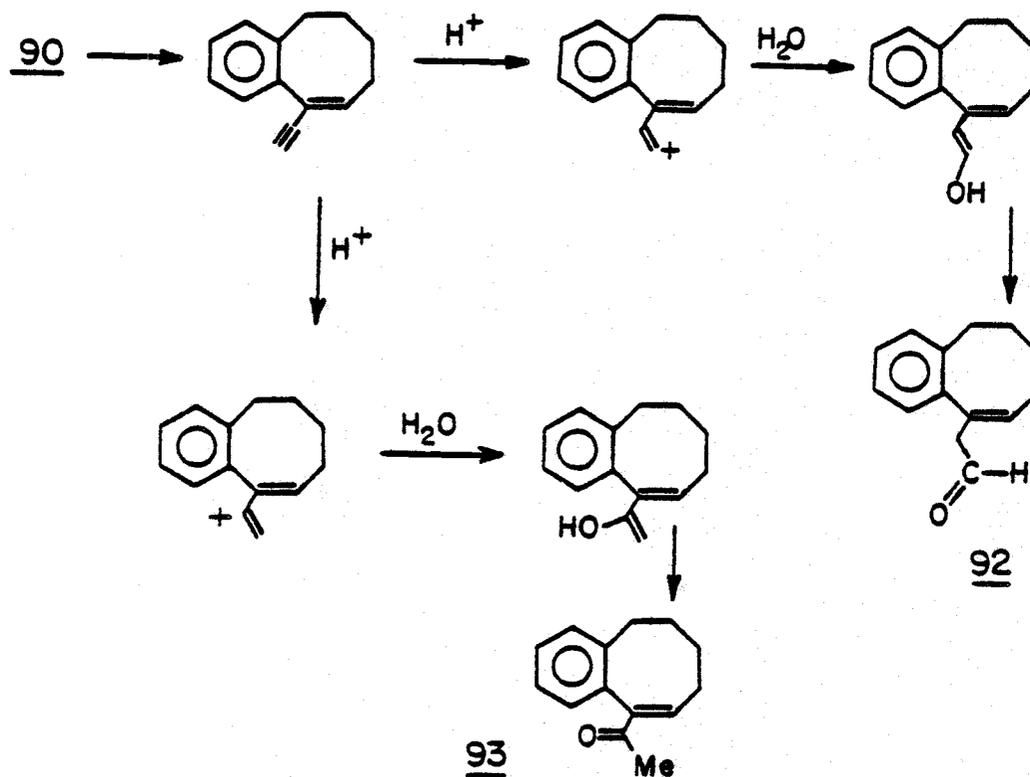
desired product 84 based on the spectral data. The spectral evidence included a doublet at δ 9.24 ($J=8$ Hz), a triplet at δ 9.58 ($J=2$ Hz), a doublet of triplets at δ 6.14 ($J=8, 1$ Hz), and singlets of relatively small intensity at δ 2.92, 2.30, and 2.14 in the NMR spectrum. The IR spectrum showed loss of the starting material hydroxyl band and carbonyl absorption at 1680 cm^{-1} (indicative of an α, β -unsaturated aldehyde) and at 1720 cm^{-1} . Absorption at 2750 and 2710 cm^{-1} is also indicative of an aldehyde. Absorption at 3290 , 2240 , and at 2100 cm^{-1} indicated that some acetylenic material was still present. The GLC/mass spectral analysis indicated the major component has a molecular weight of 200 consistent with structure 91. Compound 91 evidently arises from the Meyer-Schuster rearrangement (54) of 83 as shown in Scheme 29. The remaining compounds can be accounted for as

Scheme 29



shown in Scheme 30 by the similar Rupe rearrangement (54) of 83.

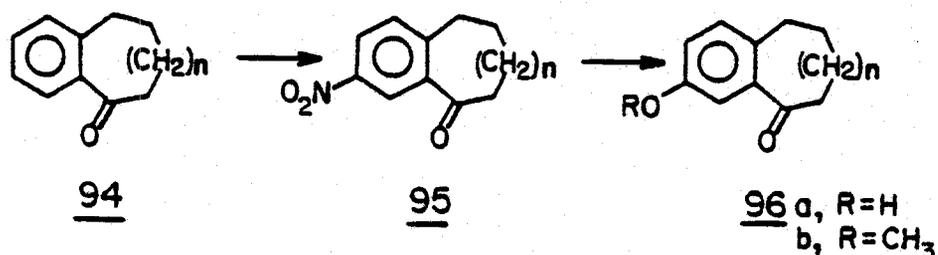
Scheme 30



While the preceding schemes discussed in this section by no means exhaust all of the possible routes to compounds of type 3 or 65, it was decided at this point to pursue a different approach.

Part II. The "Caubere Reaction" of *p*-Bromoanisole with Cycloheptanone and Ring Expansion of the Products

An examination of the target disecosteroid 1 reveals the requirement of an oxygen functionality at the position analogous to the C-3 position of the steroid ring system. Past attempts in our laboratories had mostly concerned themselves with the synthesis of a benzo-fused carbocyclic system of type 94. The directing effect of the carbonyl group of 94 was then taken advantage of in the electrophilic substitution



reaction with red fuming nitric acid to produce 95 predominantly.

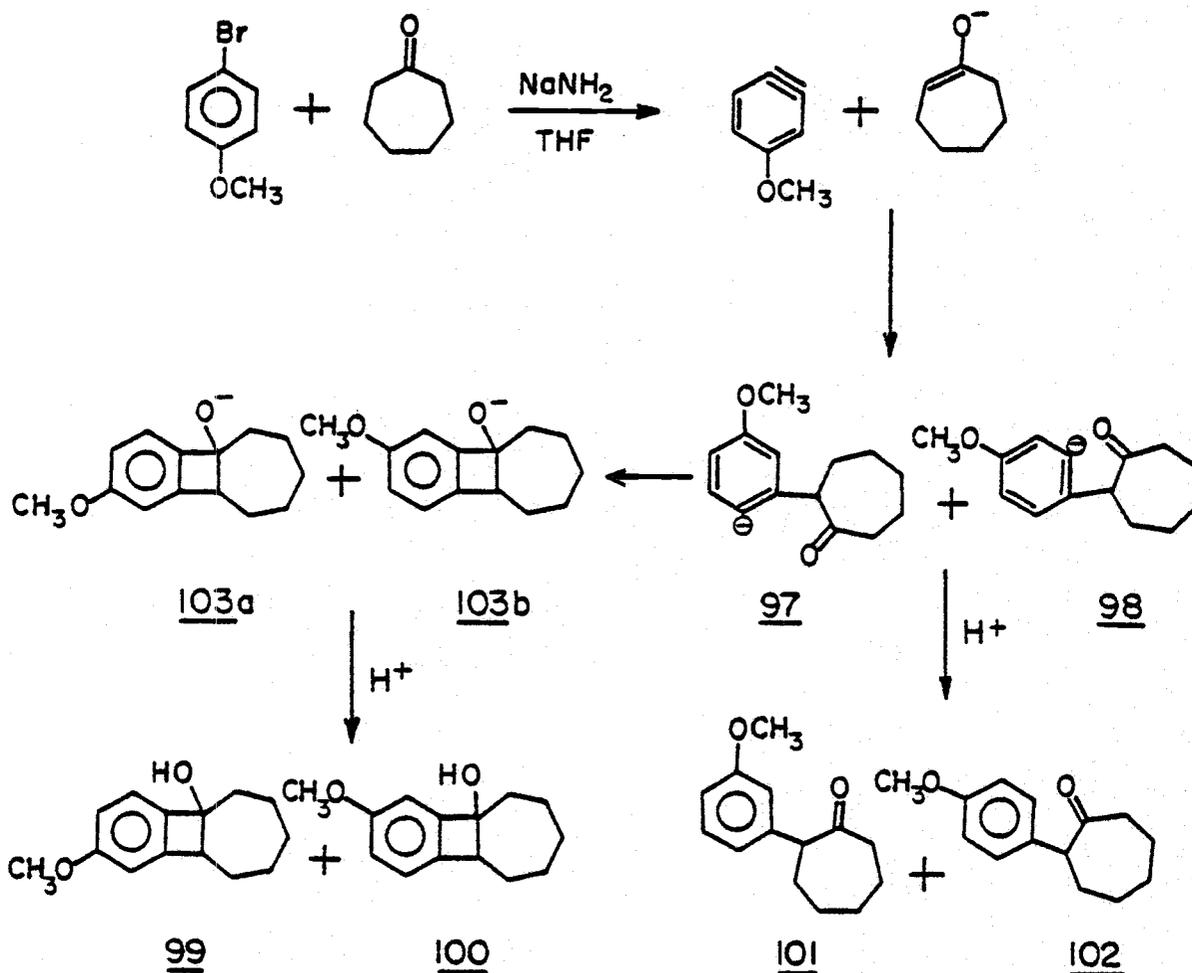
Ultimately, reduction and diazotization provided 96a. Treatment of 96a with dimethyl sulfate then afforded 96b, and thus a protected oxygen functionality at the desired position.

The problems with the above sequence were the number of steps required to prepare 96 from 94, the low yields for the nitration of certain homologs of 94 (e. g. $n=2$), and the formation of undesired products in some nitration reactions (e. g. a transannular reaction for the case where $n=6$ and a methoxy substituent occupied the C-10 position of the aliphatic ring (55)). Also, the nitro functionality had been shown to interfere with certain desired transformations that could be performed

on the system void of substitution on the aromatic ring (1).

It was reasoned that the "Caubere reaction" with *p*-bromoanisole and cycloheptanone as shown in Scheme 31 would provide

Scheme 31



an entry into an oxygen-functionalized benzocarabicyclic system provided the wrong isomer or isomers did not predominate excessively.

Compound 99 was the desired isomer in this case. An a priori examination of this reaction based on the directing effects of a methoxy substituted aryne (see Part IV of historical section) would lead to the

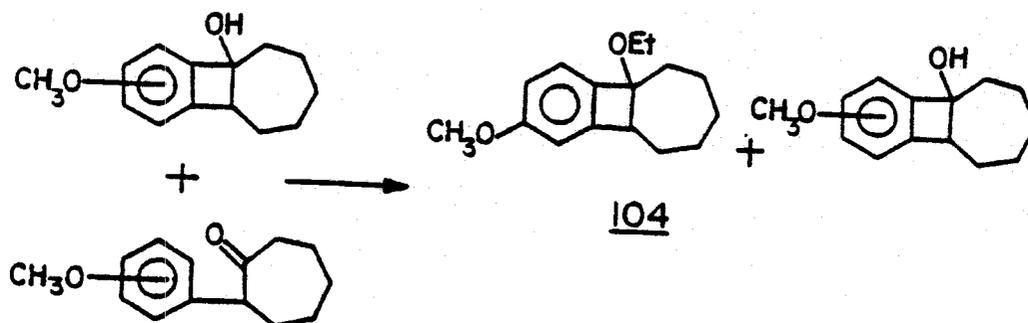
prediction that products 100 and 102 should be favored over products 99 and 101. Since the induction effect of a methoxy substituent is electron attracting, one would predict that para attack of the aryne by the enolate would be favored leading to the intermediate 98 (and ultimately 100 and 102) preferentially. However, benzyne are known to be highly reactive intermediates and are known to demonstrate low selectivity (56). Thus, we hoped to obtain a useful amount of 99 from the reaction.

When the reaction was actually carried out, an 87% yield of a mixture of alcohols 99 and 100, and ketones 101 and 102 was obtained. Analysis by GLC showed the alcohols to predominate over the ketones in about a 2:1 ratio. At this point, alcohols 99 and 100 could not be conveniently separated and the relative amounts of each could not be determined. However, a posteriori evidence indicated that alcohol 99 had been formed preferentially to alcohol 100 in about a 3:2 ratio. Although this result was somewhat fortuitous, it is not the expected result. No analysis was carried out on the relative ratio of ketones 101 and 102, and it is possible that intermediates 97 and 98 could have been formed in equal ratios, or perhaps 98 even predominated slightly. Intermediate 98 may have simply resulted in a higher proportion of ketone 102 relative to alcohol 100. Likewise, intermediate 97 may have resulted in a higher proportion of alcohol 99 relative to ketone 101. This is conceivable based on the inductive effect of the methoxy

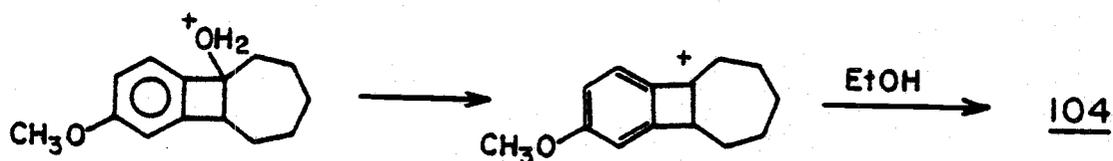
substituent. Intermediate 97 should be less stable than intermediate 98 and may have a greater preference to form the tricyclic alkoxide 103a.

The alcohols 99 and 100 could be separated from the ketones 101 and 102 by use of Girard's Reagent T. This separation is not quite as straightforward as the analogous separation of the non-aromatic substituted alcohol and ketone products obtained from the "Caubere reaction" with bromobenzene. Here a serious side reaction is the solvolysis of alcohol 99 to the diether 104 as illustrated in Scheme 32. The electron donating ability of the *p*-methoxy substituent apparently stabilizes the carbonium ion resulting from protonation of 99 followed by loss of

Scheme 32



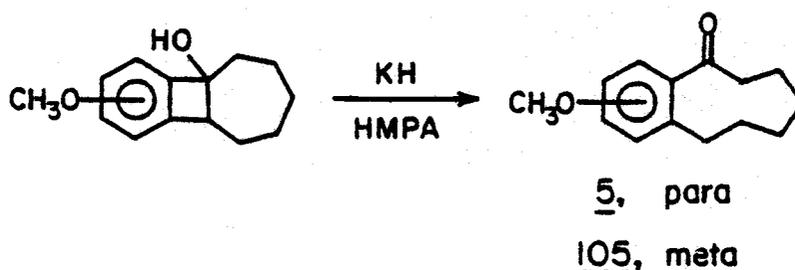
water and allows the solvolysis observed to occur. No such products



are observed with the m-methoxy alcohol or the non-substituted alcohols. If the Girard's Reagent T reaction is allowed to proceed for too long a period, all of alcohol 99 is converted to the diether 104. However, if the reaction is stopped after one hour at reflux, only about 20-25% of alcohol 99 is converted to diether 104, and effective removal of the ketones 101 and 102 was still obtained. Further, diether 104 could be converted back to alcohol 99 by hydrolysis with a catalytic amount of sulfuric acid in aqueous acetone.

Alcohols 99 and 100 were converted to the methoxybenzocyclo-nonenones 5 and 105 as shown in Scheme 33 by a reaction also reported

Scheme 33



by Caubere (36). No traces of ketones 101 and 102 were observed as a result of this reaction. The diether 104 was present in the reaction

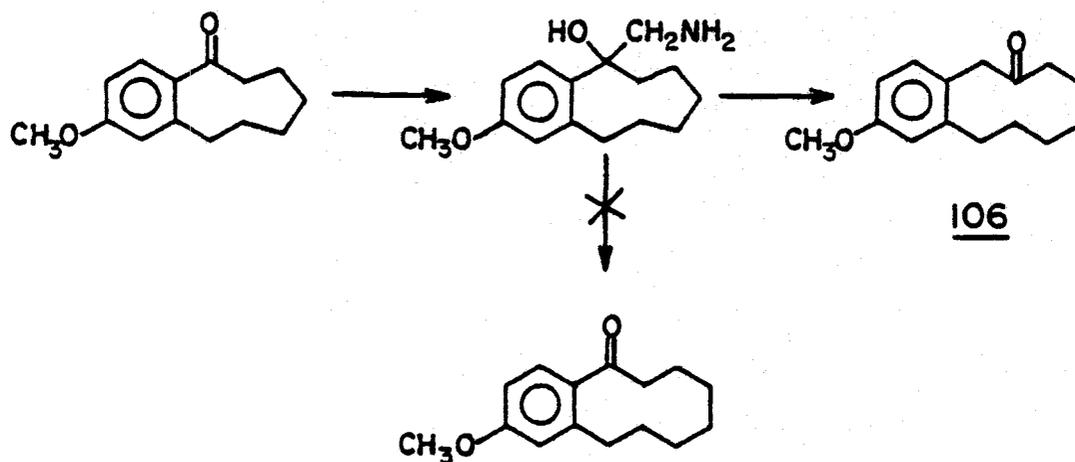
mixture and was unaffected by this treatment. The two ketones 5 and 105 along with the diether 104 could be separated conveniently by flash chromatography (57). Recycling of the overlapping fractions and conversion of the diether to the desired alcohol 5 as previously described provides ketone 5 in overall adjusted yield of about 24%. Although this yield is not high, the starting materials are relatively inexpensive and readily available and the reactions and separations are easily performed.

Positive identification of the two isomeric ketones 5 and 105 was reasonably obtained by comparison of the chemical shift and splitting patterns of the aromatic regions of the NMR spectra of the two isomers (see pages 44 to 47). The p-methoxy isomer 5 whose NMR spectrum has an ABX pattern in the aromatic region was especially distinguishable by the doublet at δ 7.41 ($J=8$ Hz) indicative of an ortho coupling constant and assigned to proton a; a doublet of doublets at δ 6.66 ($J=8, 2$ Hz) attributed to proton b; and a doublet at δ 6.59 ($J=2$ Hz) assigned to proton c. The m-methoxy isomer 105 whose NMR spectrum was not first order in the aromatic region was not as easily distinguishable. Comparison of the NMR spectra of 5 and 105 with the NMR spectra of 6- and 7-methoxy-1-tetralone (58) added further evidence to the assignment of structures. Finally, a shift reagent study gave final proof of structure assignment. The effect

of the shift reagent is shown in Figures 3 and 4 for each isomer. As can be seen by the spectra, for the *p*-methoxy isomer (5), addition of shift reagent causes proton a to shift the greatest amount as would be expected by the shielding effect of the shift reagent complexed with the carbonyl group of 5. For the *m*-methoxy isomer (105), the shift reagent caused the pattern of the aromatic region to become first order, and proton a is shifted the greatest amount consistent with the structure assigned to 105.

Having obtained 2-methoxy-7,8,9,10,11-pentahydro-5(6H)-benzocyclononenone (5) in pure form, attention was turned to a ring expansion sequence that would ultimately provide the desired disecosteroid system. The initial one-carbon ring expansion shown in Scheme 34 utilized the TMSCN method as previously described and afforded the methoxy benzocyclodecenone 106 in 81% overall yield.

Scheme 34



No trace of the alternative ring expanded product resulting from

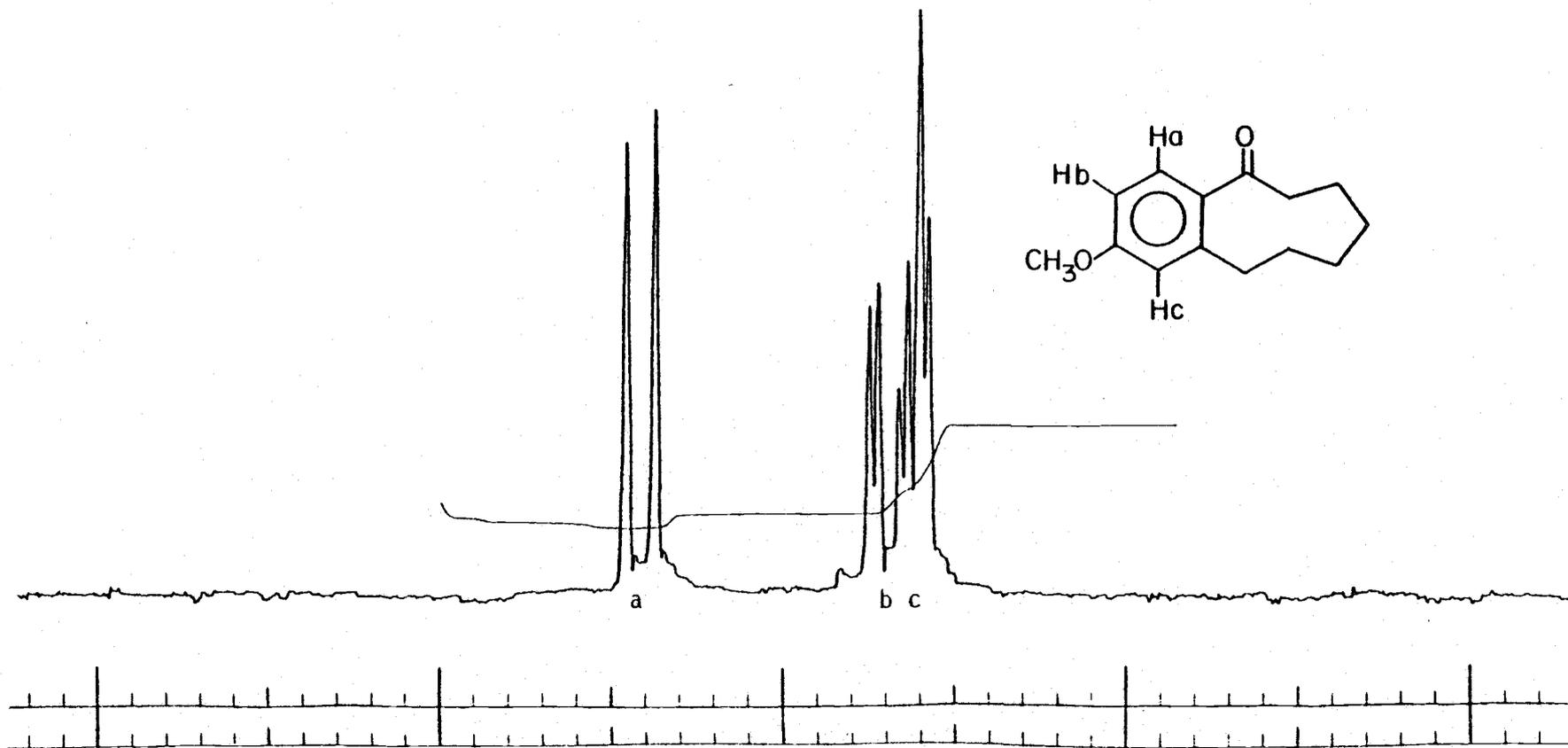


Figure 1. NMR spectrum of the aromatic region of 2-methoxy-7,8,9,10,11-pentathydro-5(6H)-benzocyclononenone (5).

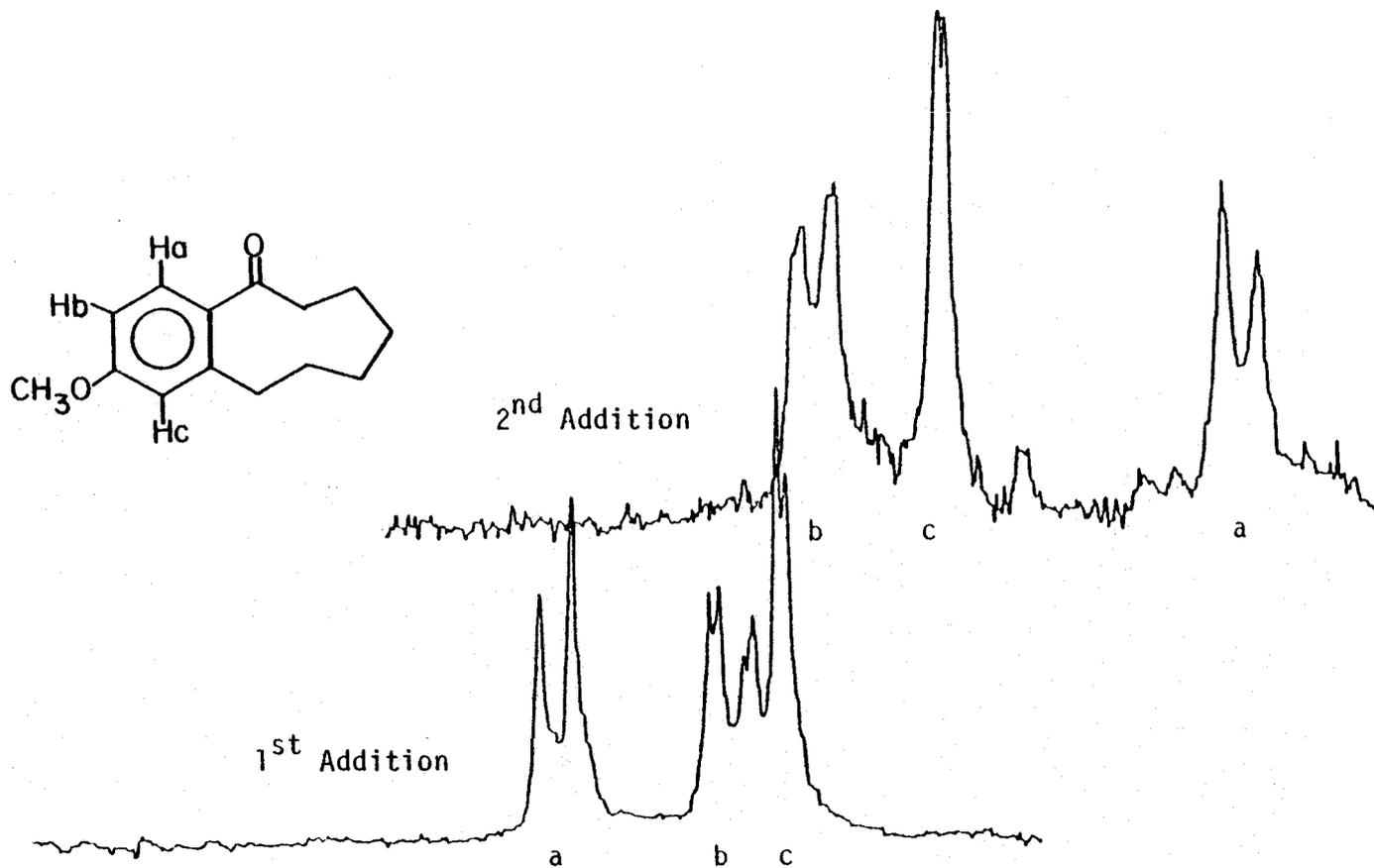


Figure 2. NMR spectrum of the aromatic region of 2-methoxy-7, 8, 9, 10, 11-pentahydro-5(6H)-benzocyclononenone (5) after addition of shift reagent.

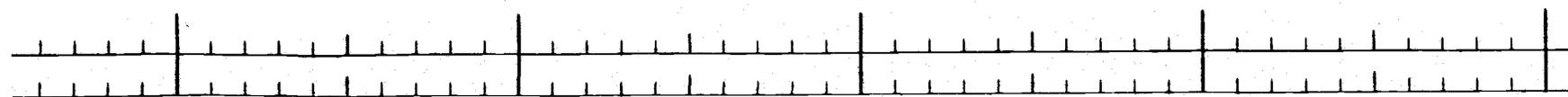
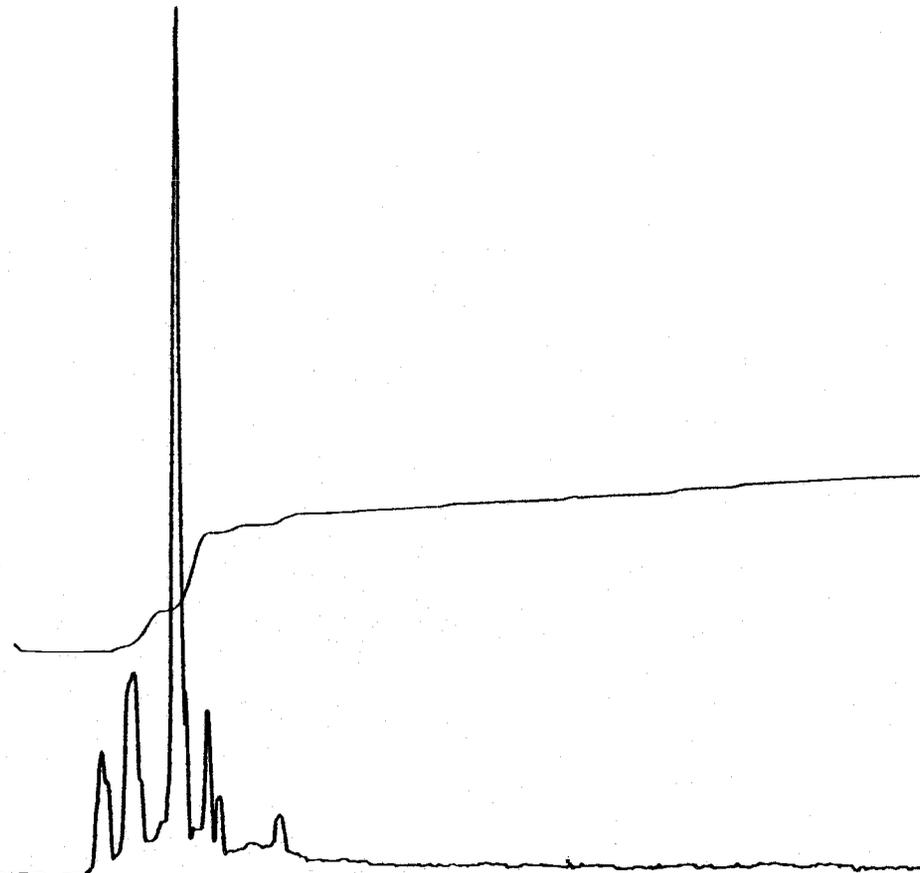
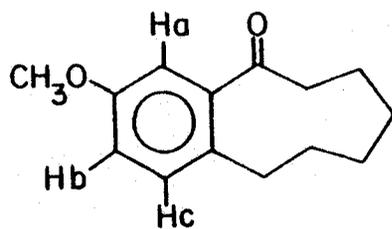


Figure 3. NMR spectrum of the aromatic region of 3-methoxy-7,8,9,10,11-pentahydro-5(6H)-benzocyclononenone (105).

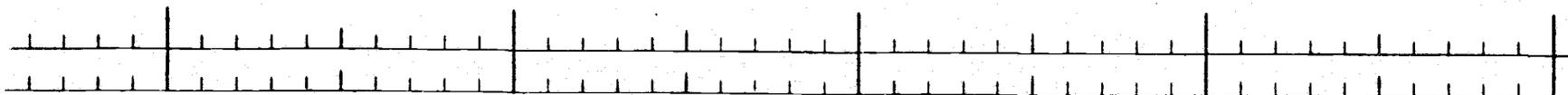
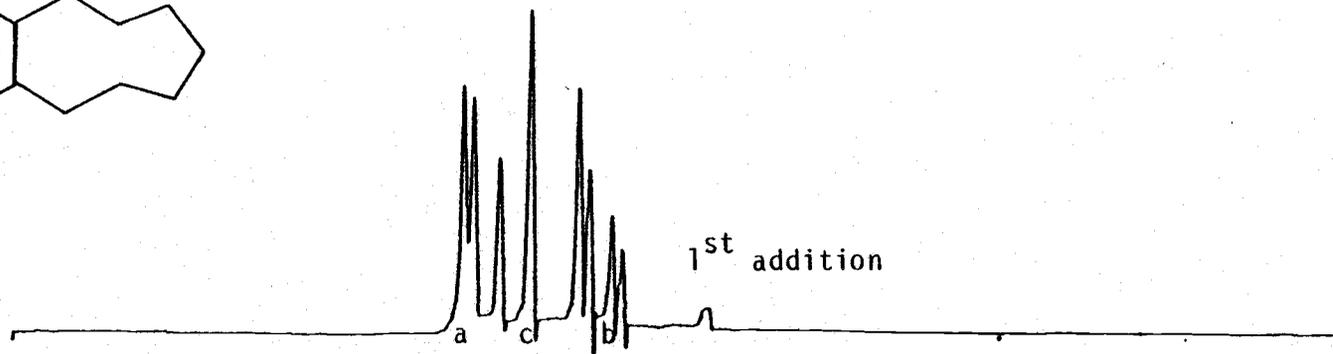
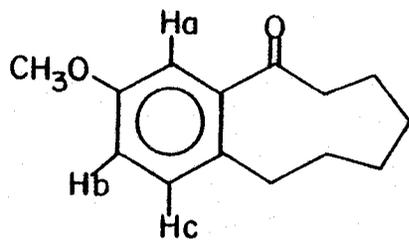
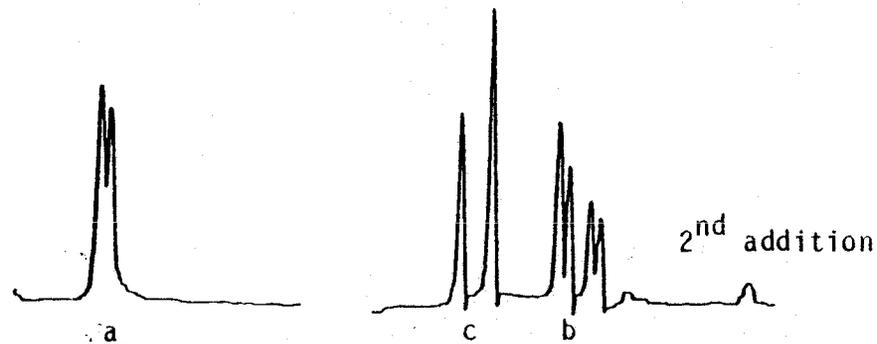
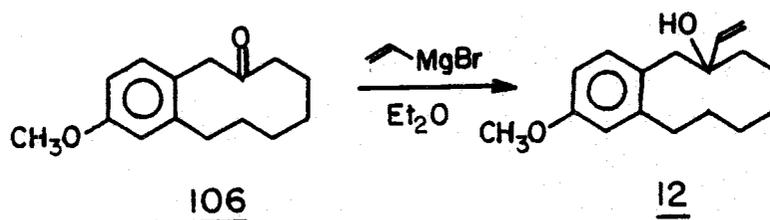


Figure 4. NMR spectrum of the aromatic region of 3-methoxy-7,8,9,10,11-pentahydro-5(6H)-benzocyclononenone (105) after addition of shift reagent.

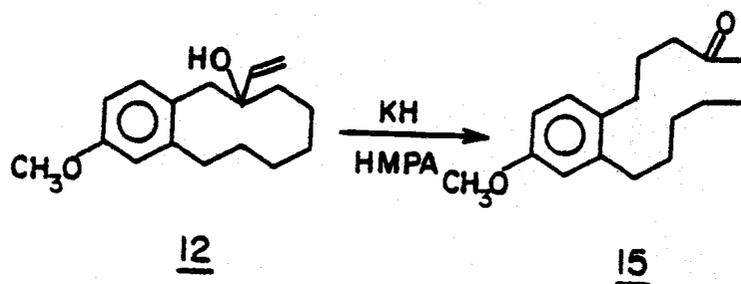
migration of the aliphatic carbon was observed.

The next step in the sequence is the addition of a vinyl substituent to 108 as shown below. While this is a seemingly trivial reaction,

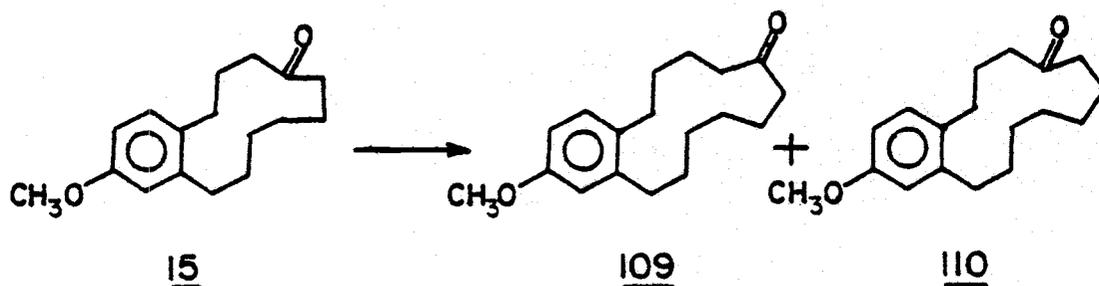


special conditions had to be devised to obtain reasonable yields and conversions. Addition of vinyl Grignard reagent to 106 in THF resulted in only about 25% conversion to the vinyl carbinol 12. Apparently, enolate formation is the primary reaction taking place with vinyl Grignard reagent in THF. The benzylic, alpha hydrogens in 106 are doubly labile and are likely more prone to abstraction than the protons alpha to a carbonyl without a beta phenyl group. Furthermore, medium sized rings are known to be resistant to reactions in which an sp^2 center is changed to sp^3 (59).

By working with β -benzocyclodecenone 107 as a model system, it was discovered that a less polar solvent such as toluene or diethyl ether resulted in higher conversion to the vinyl adduct. Vinyl Grignard reagent must be prepared in THF; therefore, after preparation of the Grignard in THF, the THF was removed under vacuum and replaced by the solvent of choice. Due to the low solubility of vinyl

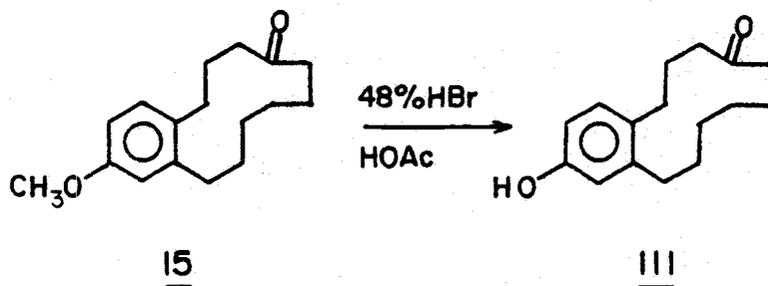
Scheme 35

Compound 15 is only one carbon short of the desired disecosteroid 1, and could be converted to a mixture of 109 and 110 by the previously discussed one carbon ring expansion method with TMSCN as shown in Scheme 36. The NMR spectrum of the product mixture from

Scheme 36

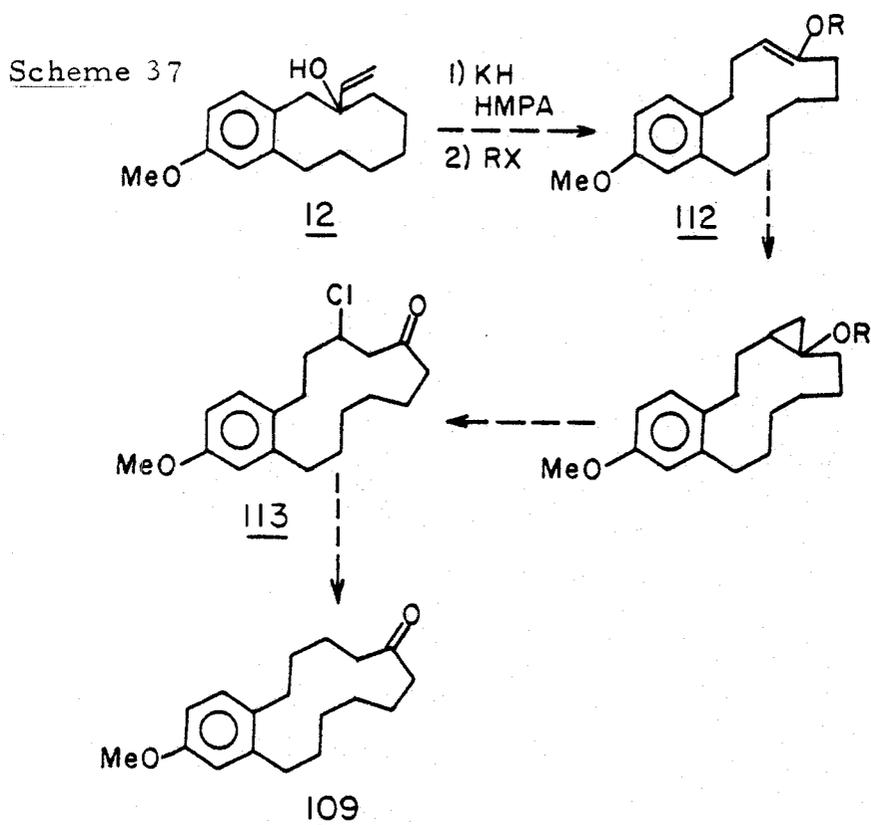
this reaction showed two methoxy peaks of approximately equal height, and the high resolution mass spectrum of a preparative GLC sample gave the correct molecular weight for 109 and 110. No convenient method for separating 109 from 110 was discovered, although little effort was made toward separating the two isomers since it was felt it would be a difficult and perhaps fruitless task.

If compound 109 could be isolated, then conversion of the methoxy group of 109 to a hydroxy group would result in disecosteroid 1. In anticipation of ultimately obtaining 109 in pure form, compound 15 was demethylated conveniently with a 50:50 mixture of refluxing hydrobromic acid and acetic acid to provide compound 111 in 71%

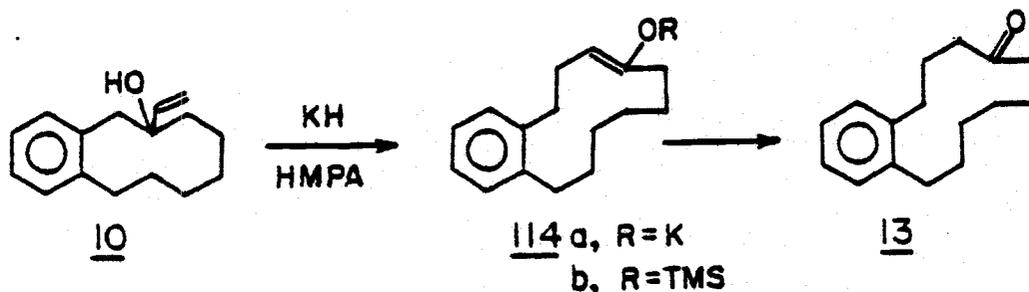


yield. Compound 109 is an analog of 1 and thus of 2, and it was reasoned that compound 109 might possibly exhibit some estrogenic activity. However, testing of compound 109 by the National Institute of Health failed to reveal any activity.

A selective route to compound 109 could possibly be provided by the sequence shown in Scheme 37. It was reasoned that the enolate intermediate resulting from the ring expansion of 2 with KH in HMPA could be trapped as 112 (although it should be pointed out that the enolate could equilibrate to the other side before it is trapped leading to two structurally isomeric products). If 112 could be formed, then addition of a Simmons-Smith reagent to the enol double bond, followed by the ring expansion reaction described by Ito, Fugii and Saegusa (60) could provide 113 and ultimately 109.



Preliminary work was again carried out on the model vinyl carbinol 10. The two carbon ring expansion to 13 with KH in HMPA



was found to be a facile reaction that gave a 70% yield of the benzo-cyclododecenone 13. Attempted trapping of the presumed enolate 114a with trimethylsilyl chloride failed to result in any detectable formation of 114b and only 13 was isolated. It was later discovered that TMSCl is reduced to trimethylsilyl hydride with metal hydrides (61), and this reduction is especially facile in polar solvents such as HMPA (62).

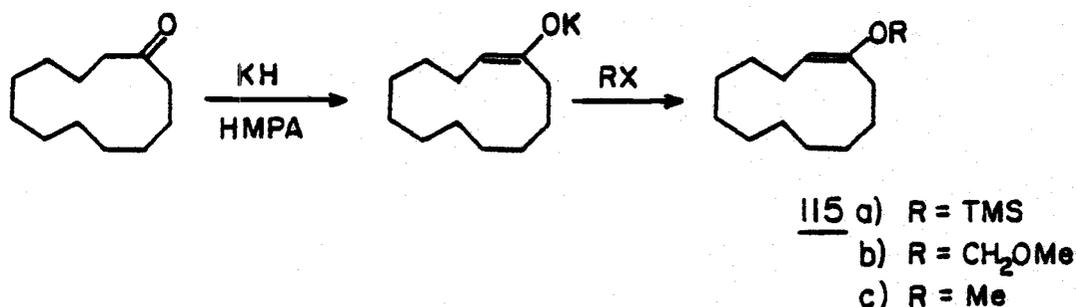
Coordination of the chlorosilane with the HMPA solvent is thought to be partly responsible for the reduction observed. In an effort to avoid the effect of the HMPA solvent, a reaction of 10 with KH was run in a minimal amount of HMPA solvent, and a large volume of dioxane was added to the HMPA mixture before adding the TMSCl to the enolate.

Hudrlik and Takacs (63) reported dioxane to be the most efficient solvent of several tested for the trapping of potassium enolates of various ketones with TMSCl, but again only 13 was isolated in our hands.

Using *t*-butyldimethylsilyl chloride in place of TMSCl also failed.

Trapping of the enolate 114a with acetic anhydride appeared to be partially successful, but not successful enough to be of use.

In an attempt to find a suitable trapping agent for 114a, the enolate of cyclododecanone was prepared from KH in HMPA. When

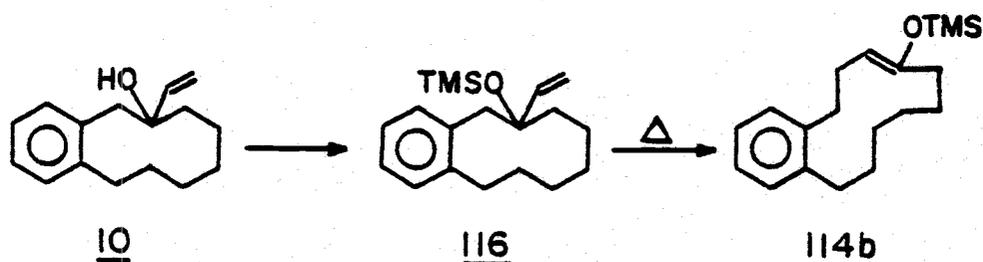


the enolate of cyclododecanone was reacted with freshly distilled TMSCl, only cyclododecanone was recovered. When freshly distilled TMSCl from a new bottle was used, a small amount of 115a was formed although cyclododecanone was still the major component of the product

mixture. When chloromethyl methyl ether was used as the trapping agent between 40% and 50% of the product appeared to be 115b. When methyl tosylate was used as the trapping agent a mixture of about 60% 115c and 40% cyclododecanone was recovered.

An alternative preparation of 114b was attempted as shown in Scheme 38. This procedure was based on the earlier discussed siloxy-Cope reaction reported by Thies et al. (17, 18, 19, 20, 21).

Scheme 38

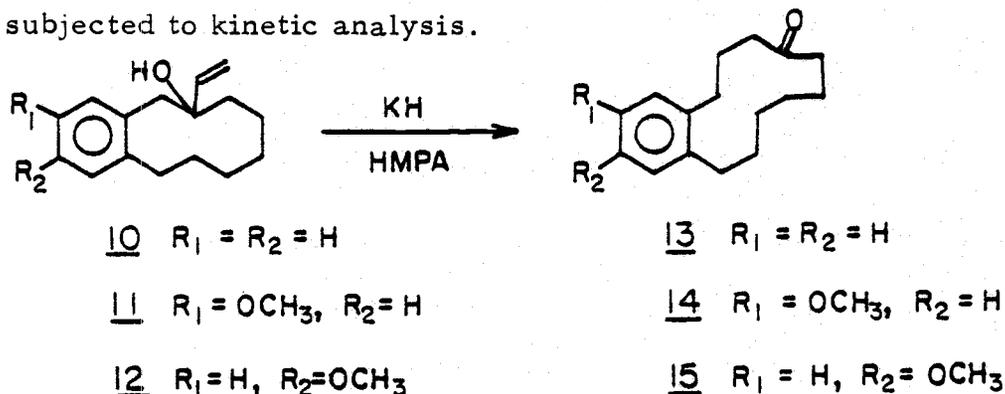


Compound 116 was prepared in 69% yield by the procedure reported by Sweeley, Bentley, Makita, and Wells (64). Pyrolysis of compound 116 at temperatures ranging between 306° and 313°, and again between 290° and 305° gave a low yield of product that could not be positively identified as 114b although it was obvious that 116 had disappeared. Hydrolysis of this product did give 13 which is consistent with 114b having been formed. Although these two attempts gave low yields of a product presumed to be 114b, perhaps better conditions (more dilute gas phase, solution, or lower temperatures and longer reaction times) might afford 114b in higher yield.

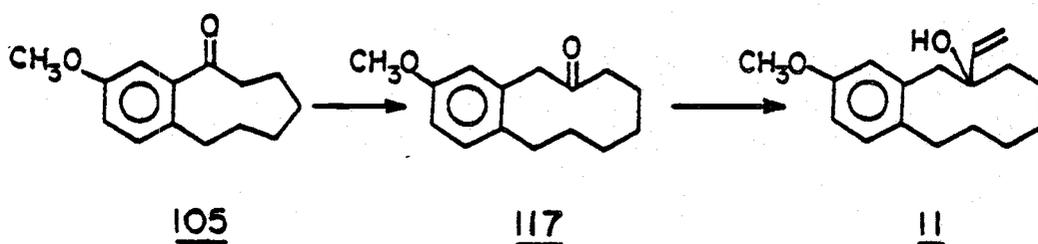
Although a selective route to 109 and thus 1 was not provided by the previously discussed routes, methodology has been established for the efficient synthesis of benzocyclododecenones from smaller ring compounds. Furthermore, more work could conceivably result in an efficient method for trapping of an enolate of type 114a. Alternatively, as just discussed conditions may yet be found for the thermal conversion of the TMS ether 116 to 114b. Also, it is possible that means could be found to separate compounds 109 and 110.

Part III. A Preliminary Kinetic Study of the Rearrangement of the Potassium Salts of 7, 8, 9, 10, 11, 12-hexahydro-6-vinyl-6(5H)-benzocyclodecenol (10), 3-methoxy-7, 8, 9, 10, 11, 12-hexahydro-6-vinyl-6(5H)-benzocyclodecenol (11), and 2-methoxy-7, 8, 9, 10, 11, 12-hexahydro-6-vinyl-6(5H)-benzocyclodecenol (12) in HMPA

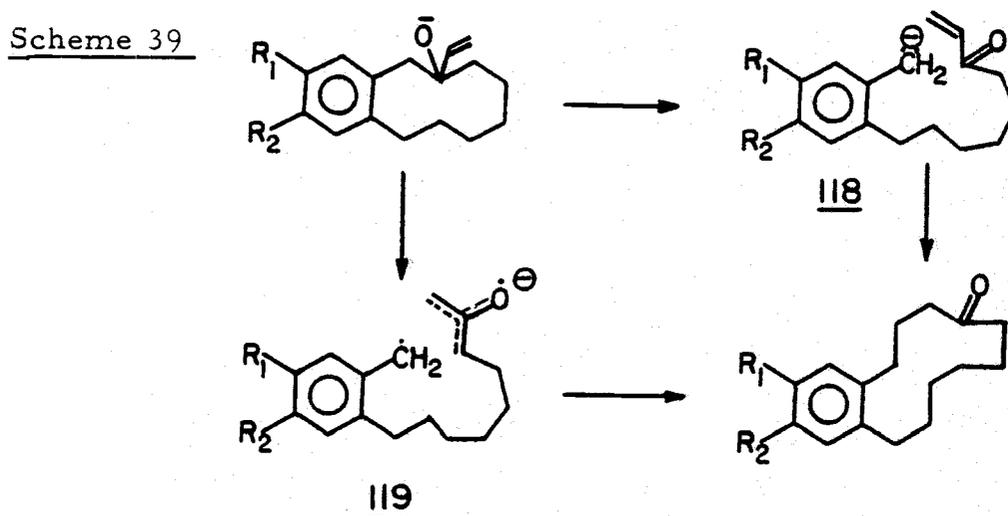
As discussed in the historical section, the mechanism of the anionic oxy-Cope rearrangements is not clearly established for all cases. For some cases, a concerted [i, j] sigmatropic shift seems to be operative, while for other cases a fragmentation-recombination mechanism appears to be operative. To gain further insight into the mechanism of the anionic [1, 3] shift utilized extensively in our laboratories to effect a two carbon ring expansion, the KH/HMPA rearrangements of compounds 10, 11, and 12 to 13, 14, and 15, respectively, were subjected to kinetic analysis.



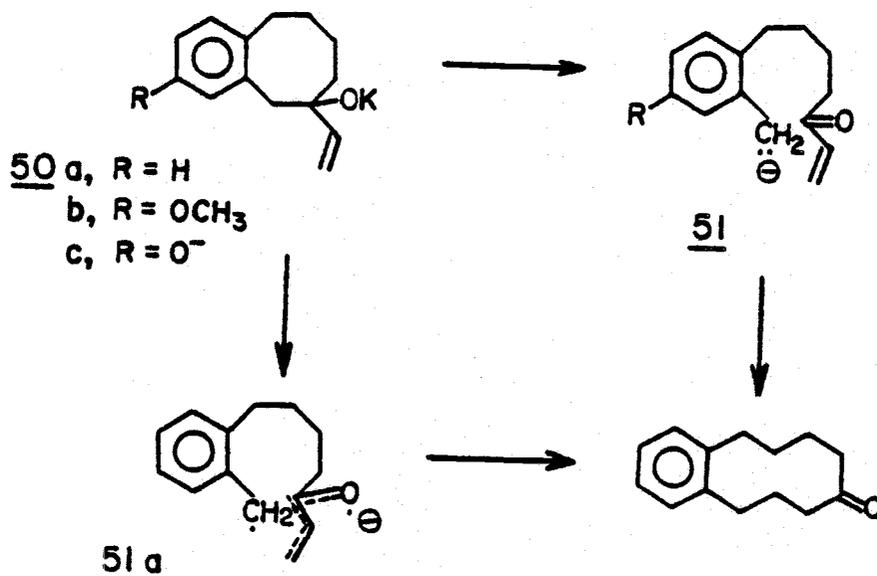
The synthesis of vinyl carbinols 10 and 12 have been previously discussed. Vinyl carbinol 11 was prepared in a like manner from ring expansion of 105 to ketone 117. Reaction of 117 with vinyl Grignard in ether afforded 11 in overall yield from 105 of 33%.



Two fragmentation-recombination type of mechanisms that can be envisioned are depicted in Scheme 39. These include cleavage to



the benzylic anion 118 followed by Michael addition, and homolytic cleavage to the radical, radical anion 119 followed by radical recombination. As discussed in the historical section, Thies et al. (29) while investigating the rearrangement of compounds 50a-c, found a three fold rate enhancement for 50b relative to 50a, and no reaction for 50c. These results are suggestive of an appreciable buildup of negative charge at the benzylic carbon as in structure 51. Though these results seem to preclude a rate determining formation of 51a, it may be possible that 51a is an intermediate included in the Michael addition of 51 arising from an electron transfer reaction (65).



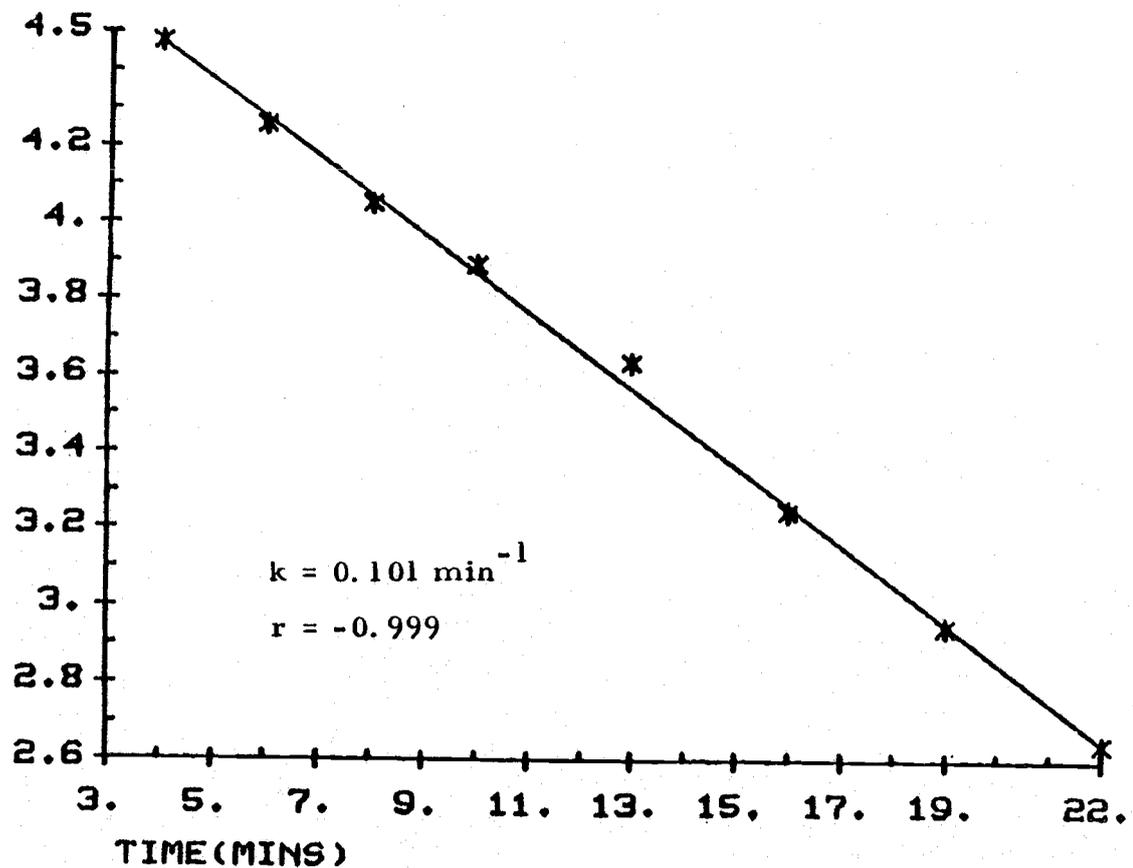
In contrast to the rearrangements of compounds 50a and 50b which were studied at 30°, compounds 10 and 11 were found to rearrange too rapidly at 30° to measure conveniently. The more facile rearrangements of alcohols 10 and 11 to ketones 13 and 14 might be attributable to the relief in strain in going from a ten to a twelve membered ring, while little relief in strain is realized in going from an eight to ten membered ring (66). It was discovered that the rearrangements of 10 and 11 could be conveniently studied at 0°, however, compound 12 gave no evidence of rearrangement at 0° even after several hours and therefore was studied at 30°. Since HMPA has a melting point of 7°C, the rearrangements were carried out in 80% HMPA/THF. One trial in a 50% HMPA/THF solution gave a four fold rate decrease for the potassium salt of 10 compared to the rate of the rearrangement in 80% HMPA/THF.

Compounds 10, 11, and 12 were each subjected to at least two kinetic runs, and compounds 10 and 11 were normally run concurrently

in the same ice bath. The conversions were determined by integration with a Hewlett-Packard 3373B Integrator of the starting material and product peaks. The relative percent of reactant remaining does not take into account the disappearance of starting material or product by other pathways, and the use of an internal standard might give a more accurate determination of the rate of disappearance of starting material. A representative graph of a kinetic run for each of the vinyl carbinols is depicted on pages 60 to 63, and kinetic runs for each compound are depicted in tabular form on pages 64 to 66. The rate constants were determined by use of the first order rate equation $\log \frac{x_0}{x} = \frac{k(t-t_0)}{2.3}$, and by least mean squares analysis of the reaction data. The initial points of the m-methoxy compound (11) rearrangement were not included in the tables although graphs with and without the initial data points are shown for one run. Data points that occurred after the reaction was more than 85%-90% complete were discarded.

For a first order reaction a plot of the logarithm of reactant concentration versus time must give a straight line. Also, the rate constant, k , should remain relatively constant throughout the reaction. The results from the graphs and tables indicate that the reactions appears to be first order with the possible exception of the case of the m-methoxy compound (11). However, if the first few data points are ignored in the m-methoxy case, it also takes on the appearance

2.3LOGA



* KINETIC ANALYSIS
— 4.876 - .1012XX

Figure 5. Rearrangement of the Potassium Salt of 6-vinyl-7,8,9,10,11,12-hexahydro-6(5H)-benzocyclodecenol (16) in 80% HMPA/THF at 0°.

2.3LOGA

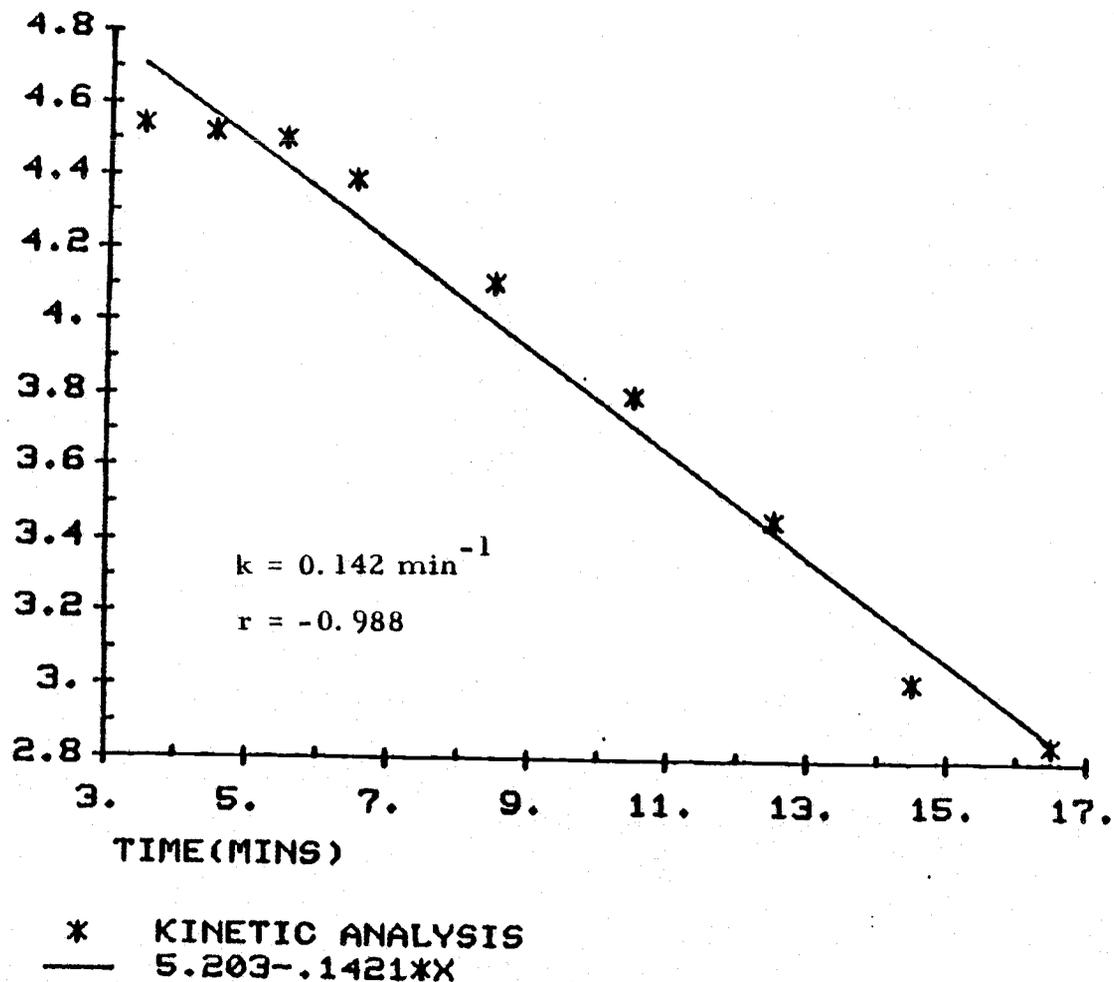
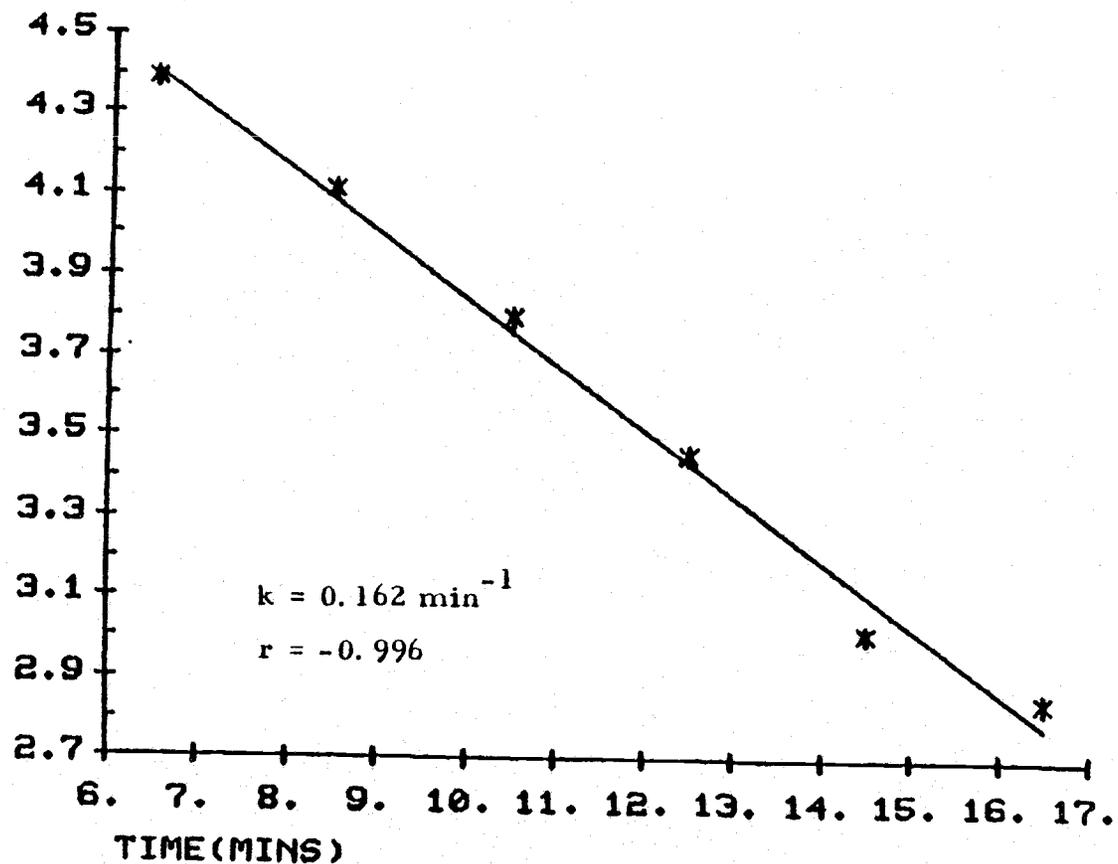


Figure 6. Rearrangement of the Potassium Salt of 3-methoxy-6-vinyl-7, 8, 9, 10, 11, 12-hexahydro-6(5H)-benzocyclodecenol (11) in 80% HMPA/THF at 0°, with initial data points.

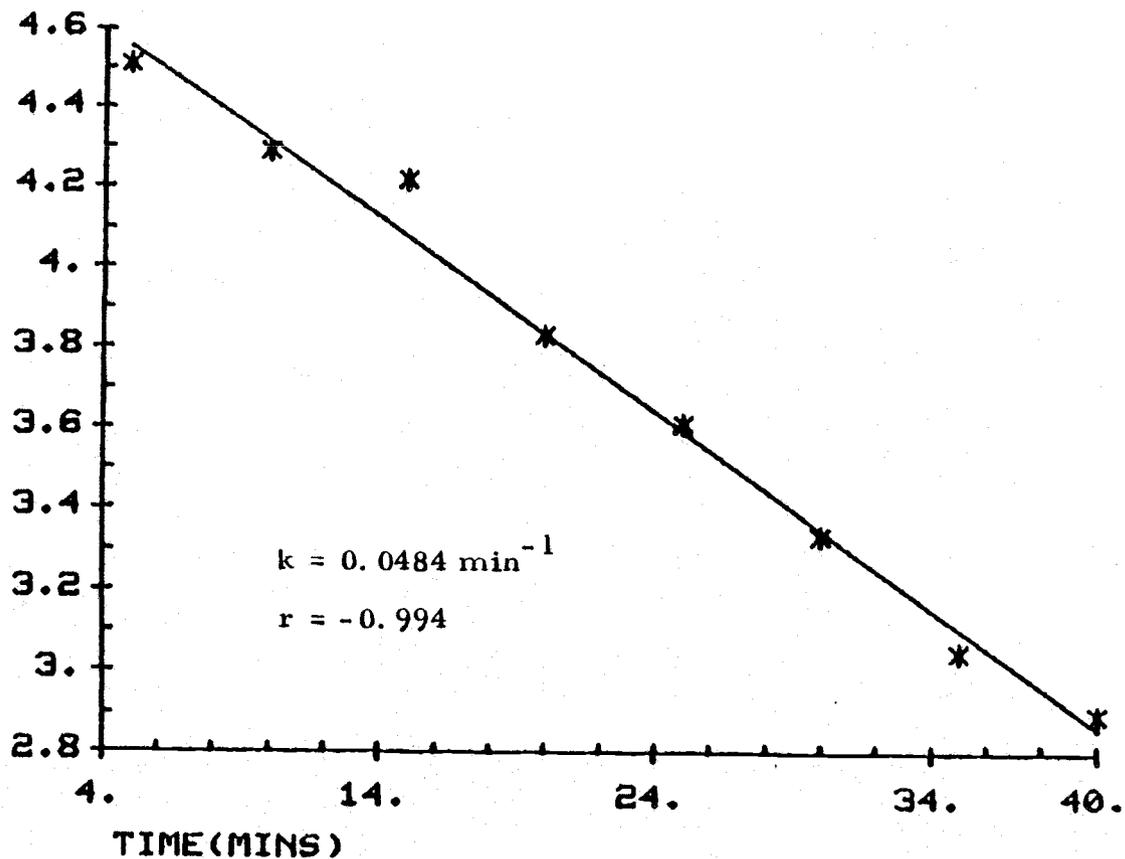
2.3LOGA



* KINETIC ANALYSIS
— 5.453 - .1616*X

Figure 7. Rearrangement of the Potassium Salt of 3-methoxy-6-vinyl-7, 8, 9, 10, 11, 12-hexahydro-6(5H)-benzocyclodecenol (11) in 80% HMPA/THF at 0°.

2.3LOGA



* KINETIC ANALYSIS
— 4.798 - .0484XX

Figure 8. Rearrangement of the Potassium Salt of 2-methoxy-6-vinyl-7, 8, 9, 10, 11, 12-hexahydro-6(5H)-benzocyclodecenol (12) in 80% HMPA/THF at 30°.

of a first order reaction. The anomalous results of the m-methoxy case may be due to an induction period or a mixing or solvent effect.

Table II. Kinetics run 1 for 10, $T = 0^\circ$

t (min)	% Reactant	2.3 log R	% Product	k (min ⁻¹)
3	89.4	4.49	10.6	
5	74.0	4.30	26.0	0.0944
7	61.4	4.11	38.6	0.0938
9	46.4	3.83	53.6	0.109
11	42.8	3.75	57.2	0.0921
14	32.7	3.48	67.3	0.112
17	24.3	3.19	75.7	0.0929
				ave = 0.099 ± 0.008

Table III. Kinetics run 2 for 10, $T = 0^\circ$

t (min)	% Reactant	2.3 log R	% Product	k (min ⁻¹)
4	87.5	4.47	12.5	
6	70.1	4.25	29.9	0.118
8	56.8	4.04	43.2	0.108
10	48.4	3.88	51.6	0.099
13	38.2	3.63	61.8	0.092
16	25.5	3.24	74.5	0.103
19	18.9	2.94	81.1	0.102
22	14.1	2.64	85.9	0.101
				ave = 0.102 ± 0.005

Table IV. Kinetics run 1 for 11, $T = 0^\circ$

t (min)	% Reactant	2.3 log R	% Product	k (min ⁻¹)
6.5	80.5	4.38	19.5	
8.5	60.7	4.10	39.3	0.141
10.5	44.5	3.79	55.5	0.148
12.5	31.5	3.45	68.5	0.156
14.5	20.3	3.01	79.7	0.172
16.5	17.2	2.84	82.8	0.154
				ave = 0.154 ± 0.008

Table V. Kinetics run 2 for 11, $T = 0^\circ$

t (min)	% Reactant	2.3 log R	% Product	k (min ⁻¹)
6	71.6	4.27	28.4	
8	57.9	4.05	42.1	0.106
10	42.8	3.75	57.2	0.128
12	29.5	3.38	70.5	0.148
15	16.0	2.77	84.0	0.166
				ave = 0.14 ± 0.02

Table VI. Kinetics run 3 for 11, $T = 0^\circ$

t (min)	% Reactant	2.3 log R	% Product	k (min ⁻¹)
6	74.5	4.31	25.5	
8	61.2	4.11	38.8	0.0982
10	39.0	3.66	61.0	0.161
12	26.8	3.28	73.2	0.171
15	13.8	2.62	86.2	0.187
				ave = 0.15 ± 0.03

Table VII. Kinetics run 1 for 12, T = 30°

t (min)	% Reactant	2.3 log R	% Product	k (min ⁻¹)
5	94.4	4.54	5.6	
10	76.3	4.33	23.7	0.0425
15	52.3	3.95	47.7	0.0590
20	46.6	3.84	53.4	0.0470
25	36.1	3.58	63.9	0.0480
30	27.2	3.30	72.8	0.0497
35	22.3	3.10	77.7	0.0480
				ave = 0.049 ± 0.004

Table VIII. Kinetics run 2 for 12, T = 30°

t (min)	% Reactant	2.3 log R	% Product	k (min ⁻¹)
5	90.1	4.50	9.9	
10	72.8	4.28	27.2	0.0426
15	68.0	4.21	32.0	0.0281
20	45.9	3.82	54.1	0.0449
25	36.7	3.60	63.5	0.0449
30	28.0	3.33	72.0	0.0467
35	21.0	3.04	79.0	0.0485
40	18.1	2.89	81.9	0.0458
				ave = 0.043 ± 0.004

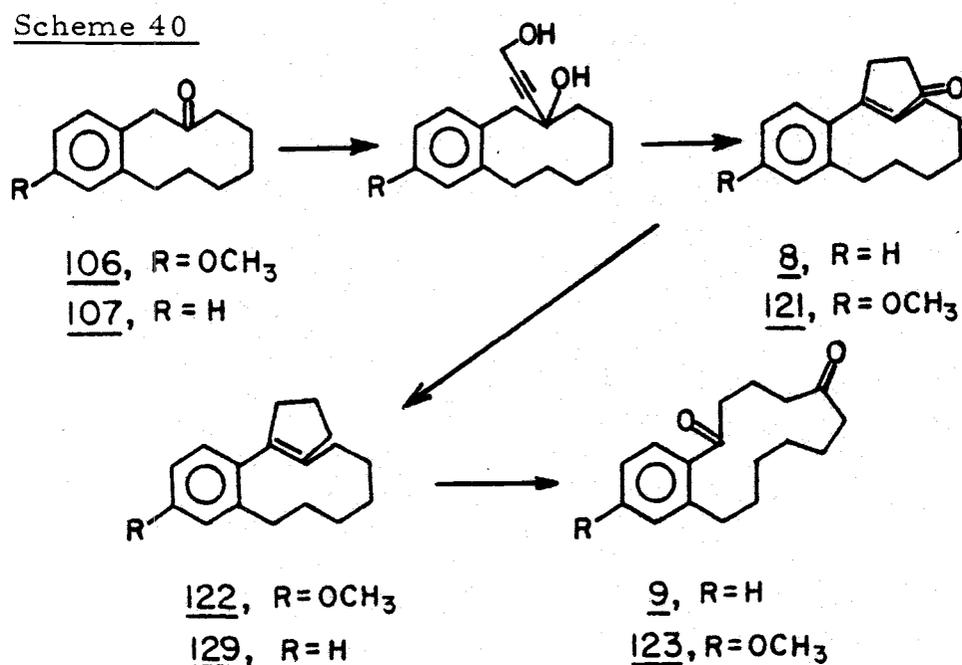
The facts that the p-methoxy compound (12) would not rearrange at 0° and the m-methoxy compound (11) rearranges ca. 1.5-2 times faster than the non-substituted compound (10) suggests a mechanism in which an electron rich center is created at the benzylic position in

the transition state as in intermediate 118 in Scheme 39. Of course, the p-methoxy compound cannot be directly compared with compounds 10 and 11 since the kinetic studies were run at different temperatures. A common temperature needs to be found at which the kinetics of the rearrangement of all three vinyl carbinols can be studied. Alternatively, a direct comparison of the rates could be made if each compound was studied at different temperatures and the Arrhenius equation was used to calculate the energy of activation for each of the vinyl carbinols, assuming that the energy of activation is constant over the temperature range. Although, the evidence suggests a mechanism that goes through a fragmentation-recombination via a carbanion intermediate, a concerted [1, 3] shift with a fair amount of charge in the transition state cannot be disregarded.

Finally, the difference in rates of rearrangement of the potassium salts of 11 and 12 suggests a means to improve the synthetic scheme from the mixture of meta and para methoxybenzocyclononones (105 and 5) to pure p-methoxy vinyl carbinol 12. Instead of using chromatography to separate 105 and 5, which is a tedious process and results in incomplete separation due to the similarity in R_f 's of the two ketones, compounds 105 and 5 could be carried through the reaction sequence together to the vinyl carbinol 11 and 12. The potassium hydride rearrangement of this mixture could be carried out at 0° resulting in a mixture of ketone 14 and vinyl carbinol 12. Presumably 12 could be easily separated from 14.

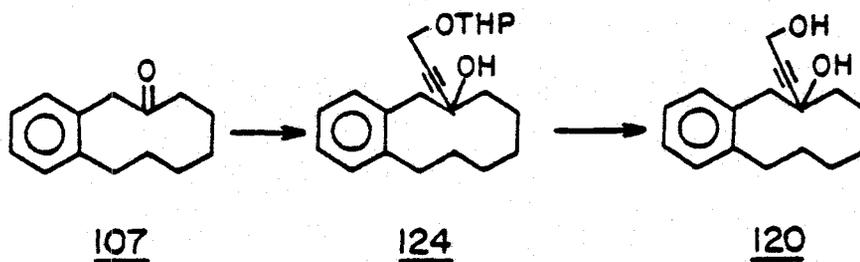
Part IV. Cyclopentenone Annulation of Benzocyclodecane

An alternative ring expansion route from compound 106 to the desired disecosteroid skeleton was suggested by the work of many researchers (33a-f) who utilized a cyclopentenone annulation-scission method to prepare Muscone and Exaltone. The proposed route is shown in Scheme 40, and again model studies were carried out with the non-methoxy substituted benzocyclodecenone 107.



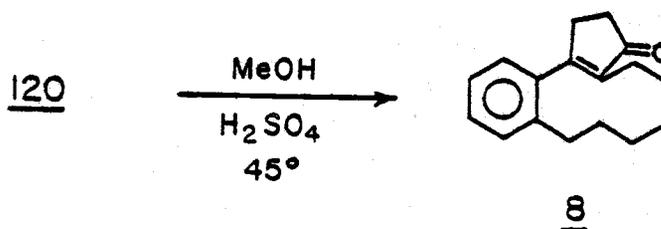
The addition of propargyl alcohol to compound 107 proved not to be as straightforward as the numerous methods described for addition of propargyl alcohol to cyclodecanone and other cyclic ketones (33). Use of the dilithio derivative of propargyl alcohol in THF gave only recovered starting material when reacted with 107. Apparently

enolate formation is again the predominant reaction as was the case for addition of vinyl Grignard in THF to 107. To effect addition of propargyl alcohol to 107 it was necessary to convert propargyl alcohol to the tetrahydropyran derivative. The tetrahydropyran derivative was then converted to the Grignard reagent by exchange with ethyl Grignard in ether according to the procedure of Jones (67). Addition of this Grignard reagent to ketone 107 resulted in a 70% conversion to 124 when carried out on a large scale. On a small scale the reaction went essentially to completion. Attempts to purify this material were unsuccessful, so the mixture was hydrolyzed with acetic acid in

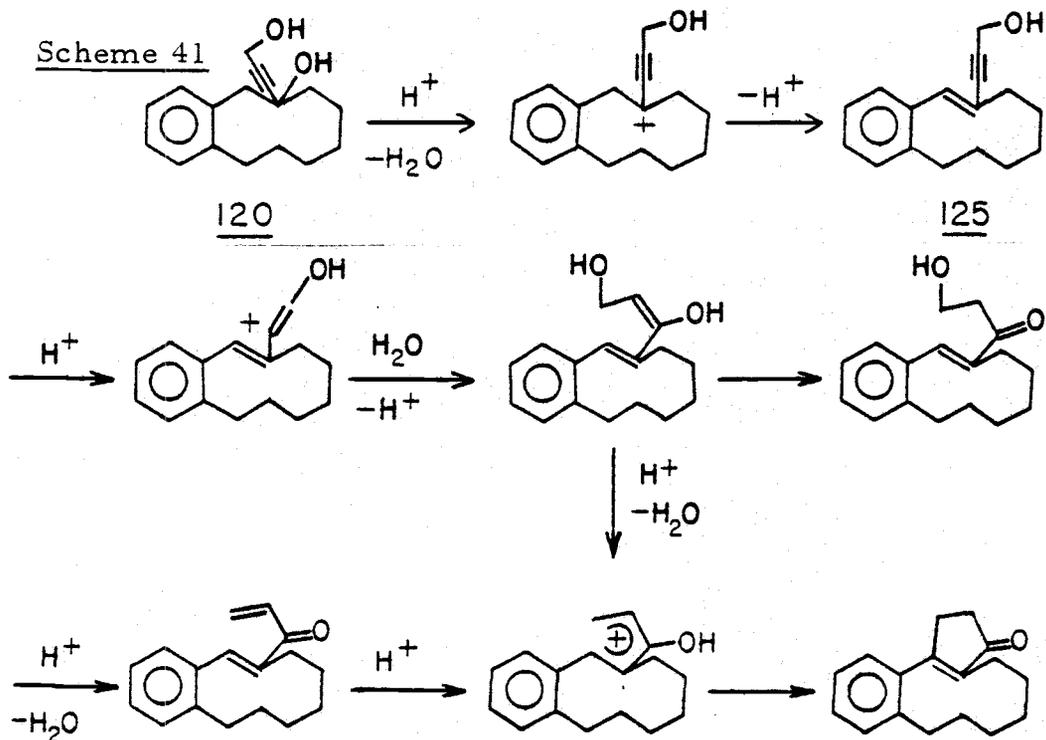


aqueous THF to impure 120. All volatile materials were removed from the crude diol (120) leaving an immobile wax that resisted attempts at recrystallization.

Cyclization of 120 to 8 was effected by reaction of the crude diol with concentrated sulfuric acid in methanol according to a



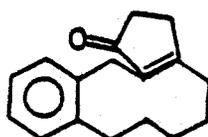
modified procedure of Hiyama, Shinoda, and Nozaki (33g). The reaction had to be carried out at 45° in contrast to the 0° reported by other researchers for cyclization of the propargyl alcohol adducts of other carbocyclic skeletons (33). This higher temperature may have resulted in the formation of the rather high amount of tar like materials observed in the reaction mixture. This cyclization is evidently the result of an acid catalyzed Rupe rearrangement (54) of 125 followed by a Nazarov cyclization (68) and is depicted in Scheme 41.



Indeed, one can follow the reaction by GLC analysis and observe a new peak of longer retention time than the product peak which diminishes with reaction time. The NMR, IR, and mass spectra of a preparative GLC sample of this peak were consistent with the structure of 125.

After purification and recrystallization compound 8 was obtained in 22% overall yield from 107.

Inspection of the mechanism in Scheme 41 reveals that elimination of the tertiary alcohol could proceed in the opposite direction shown to ultimately provide 126, although elimination should be

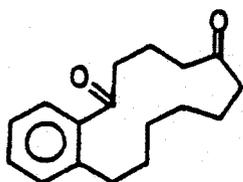
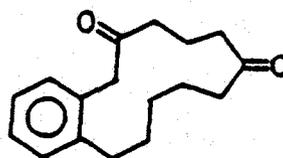


126

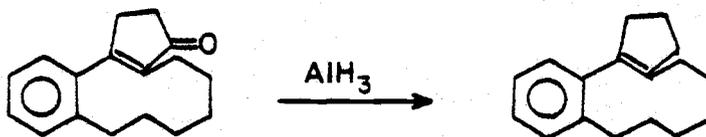
favored towards the aromatic ring. The assignment of structure 8 to the product was based primarily on the absence of any protons in the NMR spectrum attributable to the benzylic-allylic protons in 126. However, the UV spectrum which displayed a λ_{max} at 230 nm in EtOH with a small side shoulder at 288 nm is more consistent with structure 126. Application of Fieser's rules of enone absorption (69) predicts a λ_{max} of 284 nm for structure 8 and a λ_{max} of 236 nm for structure 126. The UV spectrum would still agree with structure 8 if the enone system were prevented from achieving coplanarity with the benzene nucleus. A model of compound 8 does indeed indicate that the most favorable conformation would result in the cyclopentenone group and benzene nucleus residing at or near 90° to each other. Huisgen (70) has observed this type of non-coplanarity between the carbonyl group and the benzene nucleus in the medium ring α -benzocycloalkenones.

A drop in the extinction coefficient of the λ_{max} was observed as the size of the ring changed from five to nine.

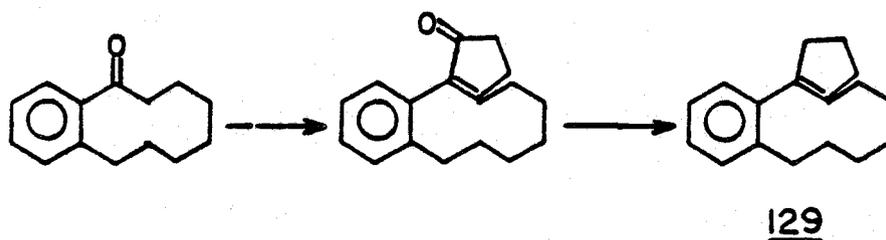
Positive identification of the structure should come from reduction of the tricyclic ketone to the alkene followed by careful ozonolysis. If 8 were the correct structure, ozonolysis of the alkene should result in structure 9, while 126 would ultimately result in structure 128.

9128

The absence or presence of benzylic- α protons would provide proof of structure. R. W. Thies carried out the reduction to the presumed alkene 129 with aluminum hydride (71) according to the method of Brown and White (72). Unfortunately, as of this writing, conditions for the ozonolysis of 129 have not been established. It should be

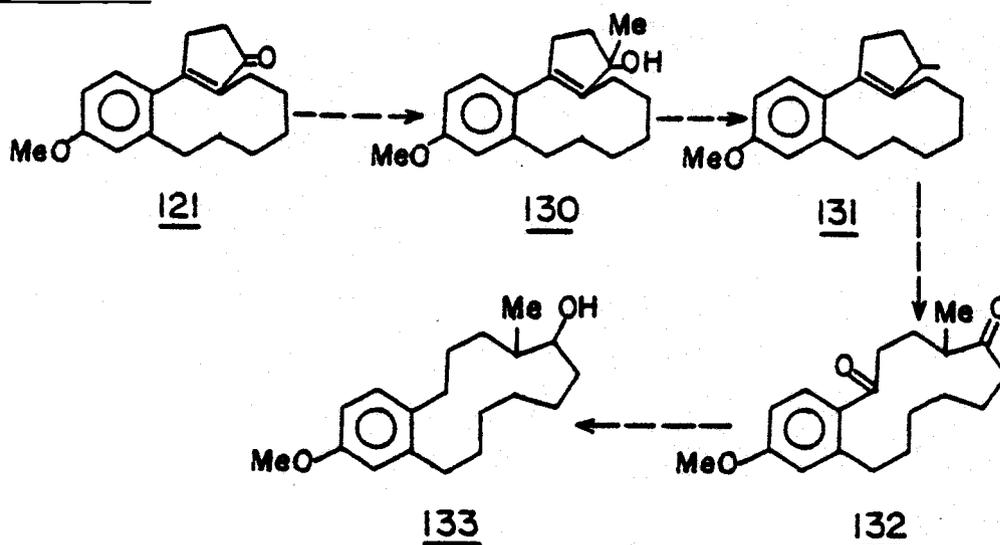
129

mentioned that even if the wrong tricyclic ketone were formed by this route, then application of the same methodology to α -benzocyclodec-
one would result in only one isomer, and eventually 129.



A further advantage of this cyclopentenone annulation route is the opportunity to introduce a methyl group at the position analogous to the C-13 position of the steroid system. Assuming the correct tricyclic ketone is formed one possible reaction sequence is depicted in Scheme 42. Addition of methyl lithium to 121 should give 130. Hydrogenolysis of the alcohol with aluminum hydride (73) or with

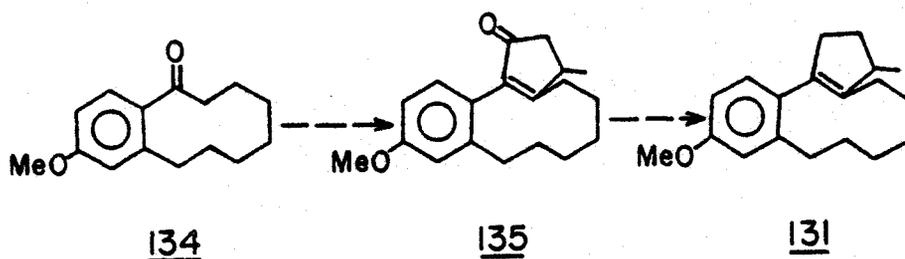
Scheme 42



triphenylsilane according to the procedure of Carey and Tremper (74) should give 131. Ozonolysis of 131, followed by selective hydrogenolysis of the benzylic carbonyl of 132 (71, 84) would result in the estradiol analog 133. The hydroxyl functionality could be oxidized to the

carbonyl to provide the estrone analog 133. The hydroxyl functionality could be oxidized to the carbonyl to provide the estrone analog; the methyl protecting group could be removed as previously described to provide an even closer analog of estrone than 1. Compound 131 could also be prepared by conversion of the carbonyl of 121 to an exo-methylene group followed by selective reduction to give 131. Completion of the lower half of Scheme 42 would provide 133.

Alternatively, one could begin with ketone 134 which is available from the "Caubere reaction" of cyclooctanone with p-bromoanisole. Reaction of ketone 134 with but-3-yn-2-ol instead of propargyl alcohol followed by cyclization should result in 135. Hydrogenolysis of the carbonyl group in 135 would provide 131 and completion of Scheme 42 as previously described would provide the large ring hormone analogs. The methodology up to the cleavage



reaction has been established for the model compound. Once suitable ozonolysis conditions or other cleavage methods are discovered this ring annulation-scission route provides an attractive route to a variety of large ring hormone analogs.

EXPERIMENTAL

General Laboratory Procedures and Conditions

All temperatures are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained on Varian EM-360 (60 MHz) and Varian HA-100 (100 MHz) spectrometers. Unless otherwise specified, tetramethylsilane was used as an internal reference, and the following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet. Infrared (IR) spectra were obtained on a Perkin-Elmer 727B infrared spectrophotometer, and polystyrene was used as a standard. Low resolution mass spectra were obtained from a Varian CH7 instrument using a 70 eV excitation potential. High resolution mass spectra were obtained from a CEC 110B instrument.

Gas-liquid chromatography (GLC) analyses were carried out on a Varian 920 (thermal conductivity detector, 0.25 in. columns) and Varian 1200 (flame ionization detector, 0.125 in. or less columns). The columns used will be referred to by the letter designation as defined below:

Column A 4' X 0.125" 3% AN600 on Chromosorb G, 60-80

Column B 4' X 0.125" 7% DEGS on Chromosorb G, 80-100

Column C 4' X 0.125" 7.4% OV101 on Chromosorb G, 80-100

Column D 2' X 0.25" 4.9% OV101 on Chromosorb G, 80-100

Column E 5' X 0.25" 1% stabilized DEGS on Chromosorb G,

80-100

Column F 5' X 0.25" 1.76% stabilized DEGS on Chromosorb G,

80-100

Thin layer chromatography (TLC) was conducted on precoated TLC sheets (EM Reagents).

Tetrahydrofuran (THF) and diethyl ether were distilled from the sodium benzophenone dianion under nitrogen. Hexamethylphosphoramide (HMPA) was dried by storing over 13X molecular sieves (pre-dried under nitrogen at 350° for four hours). Other solvents were dried according to standard published procedures (76, 77). All reactions involving air or moisture sensitive materials were conducted under a nitrogen atmosphere.

General Procedure for the Preparation of Benzobicycloalkenols

The procedure of Caubere (36) was followed using four equivalents of sodium amide (Fischer), two equivalents of cycloalkanone, and one equivalent of bromoarene.

In general, one or more 5 g or 20 g factory bottles of sodium amide (NaNH_2) (Fischer) is emptied into an Erlenmeyer flask under a nitrogen atmosphere in a dry bag. The Erlenmeyer flask is fitted with a rubber hose and clamped. The NaNH_2 is then transferred to a dry nitrogen purged three-necked round bottom flask by fitting the rubber hose over an inlet and releasing the clamp. About 200 mL of THF per 20 g of NaNH_2 is added to the round bottom flask.

Next, the cycloalkanone is dissolved in THF (30 mL/0.25 moles) and added dropwise to the NaNH_2 via an addition funnel. After complete addition, the mixture is allowed to stir for one to two hours.

The enolate mixture is brought to the appropriate temperature for the particular cycloalkanone, and then the bromoarene is added dropwise, while maintaining the appropriate temperature. The reaction mixture is then allowed to stir the appropriate length of time.

The reaction is quenched by pouring into an ice/hydrochloride (HCL) acid solution. After the ice melts, the aqueous layer is extracted with ether, and the combined organic layers are washed with saturated sodium bicarbonate (NaHCO_3) and brine. The organic layer is then dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. Further purification is obtained by Kugelrohr distillation.

Preparation of 7,8-Benzobicyclo-[4.2.0]-oct-7-ene-1-ol

The title compound was prepared by the standard procedure from 60 g (1.54 mol) NaNH_2 , 75.4 g (0.77 mol) cyclohexanone, and 60.9 g (0.388 mol) of bromobenzene. A two liter flask equipped with nitrogen inlet, mechanical stirrer, thermometer, and addition funnel was charged with the NaNH_2 and 250 mLs of THF. The cyclohexanone was taken up in 150 mLs of THF and added to the NaNH_2 over two hours, and the mixture was allowed to stir an additional two hours. The enolate mixture was cooled to -5° using an acetone bath containing copper coils

through which liquid nitrogen vapors were passed at a controlled rate. Bromobenzene was then added to the cooled mixture over a 45 minute period, while maintaining the reaction mixture at -5° . The reaction mixture was allowed to stir for 12 hours at -5° to -2° , and then quenched by pouring into 1.5 L of ice containing 150 mLs of concentrated HCL. The aqueous layer was extracted three times with 400 mL portions of ether, and the combined organic layers were washed two times with 400 mL portions of saturated NaHCO_3 and one time with brine. After drying and concentrating, 70.7 g of reddish brown oily crystals were obtained. GLC analysis (column B) indicated about a 3:2 ratio of the title compound to 2-phenylcyclohexanone. Kugelrohr distillation of this crude product up to 80° (0.5 mm) removed all excess cyclohexanone, and between 80° to 115° , 53.2 g of white crystals were collected. Girard's Reagent T was used to separate 2-phenylcyclohexanone from the title compound as described below (72).

The ketone/alcohol mixture was taken up in 500 mL absolute ethanol, and 27 g (0.16 mol) of 97% Girard's Reagent T (Aldrich) and 46 mL of acetic acid were added. The mixture was refluxed for two hours, and then allowed to cool. The mixture was concentrated by rotary evaporation, and then poured into a three L flask containing 200 g NaHCO_3 , 500 mL H_2O , one L ice, and 800 mLs ether. This mixture was stirred manually until most of the frothing had subsided, and then transferred to a four L separatory funnel. The aqueous and

organic layers were separated (the workup procedure to this point should be done as quickly as possible to minimize hydrolysis of the Girard's Reagent T adduct). The organic layer was washed two times with 500 mL portions of saturated NaHCO_3 , one time with 500 mLs brine, and dried over magnesium sulfate. GLC analysis (column B) still showed about 20% undesired 2-phenylcyclohexanone, so a second Girard's Reagent T separation was carried out on the 33.9 g of product isolated, which afforded 15.5 g of yellowish crystals (99% pure by GLC).

Preparation of 8,9-Benzobicyclo-[5.2.0]-non-8-ene-1-ol

The title compound was prepared from 40 g (1.0 mol) of NaNH_2 , 62.4 mL (0.51 mol) of cycloheptanone (Aldrich), and 27.0 mL (0.255 mol) of bromobenzene (MCB). A one liter flask equipped as before was used, and 250 mLs THF were added to the flask. The ketone was taken up in 60 mL of THF and added dropwise. After complete addition, an oil bath was used to bring the enolate mixture up to 45°. After two hours of stirring, the bromobenzene in 40 mL of THF was added slowly, while maintaining the reaction at 45°. The mixture was then allowed to stir for six hours at 45°, and then quenched by pouring into a mixture of 2500 mL of ice and 50 mL HCl. The aqueous layer was extracted with four 600 mL portions of ether and worked up as described in the previous experiment, yielding 75.8 g of dark mobile

oil. Kugelrohr distillation up to 95° (1 mm) gave 22.5 g of cycloheptanone; between 95° and 133° 39.9 g of yellow crystals were collected, and 9.9 g of dark brown tar remained in the pot. The fraction coming over between 95° and 133° showed two peaks in ca. 3:1 ratio of alcohol to 2-phenylcycloheptanone by GLC analysis (column C). The yield based on bromobenzene was 83%.

Girard's Reagent T separation of the alcohol/ketone mixture using 350 mL of absolute ethanol, 20.0 g (0.119 mol) of Girard's Reagent T, and 10 mL of acetic acid as described previously afforded 26.6 g of brownish white crystals which contained only a trace of 2-phenylcycloheptanone by GLC (column C).

Preparation of 8, 9-(5'-methoxybenzo)-bicyclo-[5.2.0]-non-8-ene-1-ol (99) and 8, 9-(4'-methoxybenzo)-bicyclo-[5.2.0]-non-8-ene-1-ol (100)

The title compounds were prepared from 20 g (0.51 mol) of NaNH_2 , 28.8 g (0.256 mol) of cycloheptanone, and 24.0 g (0.128 mol) of 99% p-bromoanisole (Aldrich). A one liter flask equipped as before was used, and 250 mL of dry THF were added to the flask. The cycloheptanone was taken up in 30 mL of THF and added dropwise over one hour and then allowed to stir for two hours. The p-bromoanisole was taken up in 30 mL of THF and added dropwise over one hour, and the reaction mixture was allowed to stir overnight at room temperature. The reaction was quenched as previously described and worked up in

the usual manner. After removal of ether and THF by rotary evaporation, 40.9 g of dark brown oil remained. Kugelrohr distillation of this oil afforded 9.0 g of cycloheptanone up to 95° (1 mm). A fraction coming over between 95° and 156° consisted of 24.2 g of dark yellow viscous oil which later partially recrystallized. This fraction contained a mixture of alcohols and ketones by IR. Analysis by GLC (column A) showed the alcohols to predominate over the 2-arylcycloheptanones in ca. a 2:1 ratio. The pot contained 4.0 g of a dark brown solid residue which contained material corresponding to the 2-arylcycloheptanones by GLC (column A). The crude yield of the 95° to 156° fraction based on p-bromoanisole was 87.0%: NMR (CCl₄) δ 7.08-6.56 multiplet, 3.71-3.67 (3 singlets), 3.26 (broad singlet), 2.18-1.36 (broad multiplet); IR (neat) 3600-3200, 3060, 3000, 2920, 2850, 1700, 1595, 1585, 1505, 1475, 1455, 1265, 1245, 1180, 1040, 1030, 820 (cm⁻¹).

Girard's Reagent T separation of the alcohol/ketone mixture must be carried out under somewhat less rigorous conditions than those previously described, to avoid excess solvolysis of 99 to 1-ethoxy-8,9-(5'-methoxybenzo)bicyclo-[5.2.0]-non-8-ene (104). Thus, a 300 mL flask was charged with 19.33 g of the alcohol/ketone mixture, 180 mL of absolute ethanol, 10 g (0.060 mol) of Girard's Reagent T and four mL of acetic acid. This mixture was refluxed for exactly one hour and allowed to cool until a precipitate had formed (ca. two and one-half hours). The ethanol layer was filtered from the

precipitate, and the precipitate was washed two times with absolute ethanol. The combined ethanol washings were then worked up as previously described, which yielded 10.53 g of oily crystals. GLC analysis (column A) showed four peaks in ratios of 11:88:1:0.5. The major peak corresponded to the benzobicyclic alcohols 99 and 100. The 11% peak corresponded to the solvolysis product 104, and the minor peaks corresponded to the 2-arylcycloheptanones. The mixture was used without further purification in a later step.

Preparation of 7,8,9,10-tetrahydro-5(6H)-Benzocyclooctenone (78)

An oven dried 500 mL round bottom flask equipped with nitrogen inlet and magnetic stirrer was charged with 19.4 g (0.116 mol) of 24% potassium hydride in oil (Ventron). The oil was removed by washing five times with 40 mL portions of hexane, 200 mL of HMPA were added, and the mixture was cooled to 0° in an ice bath. Next, 15 g (0.086 mol) of 7,8-benzobicyclo-[4.2.0]-oct-7-ene-1-ol were added portionwise over 20 minutes. During addition of the alcohol, the mixture went from orange to dark brown. An aliquot after one hour indicated no starting material remained by GLC (column A). The reaction mixture was then quenched cautiously with water, and transferred to a separatory funnel with 200 mL of ether. The aqueous layer was extracted three times with 100 mL portions of ether, and the combined ether layers were washed five times with 120 mL portions of

water, one time with 150 mL of saturated NaHCO_3 , and one time with 150 mL of brine. After drying over magnesium sulfate, filtering, and rotary evaporating, 14.1 g of mobile light brown oil was obtained. Bulb to bulb distillation of 8.9 g of this oil afforded 8.5 g of clear mobile oil which implies a 90% yield: NMR (CCl_4) δ 7.60 (m, 1H), 7.33-6.90 (m, 3H), 3.20-2.60 (m, 4H), 2.03-1.20 (broad m, 6H); IR (neat) 3050, 3000, 2925, 2850, 1680, 1660, 1600, 1490, 1480, 1440, 1340, 1330, 1310, 1290, 1260, 1190, 1160, 1140, 1130, 1040, 1000, 980, 750 (cm^{-1}).

Preparation of 7,8,9,10,11-pentahydro-5(6H)-Benzocyclononene

An oven dried flask was charged with 57.0 g (0.351 mol) of 24.7% potassium hydride in oil, and the oil was removed as described in the previous experiment. Next, 100 mL of THF were added to the flask, and the mixture was cooled to 0° in an ice bath. A 27.20 g portion (0.144 mol) of 8,9-benzobicyclo-[5.2.0]-non-8-ene-1-ol was taken up in 100 mL of THF and added dropwise to the potassium hydride over a two hour period. After stirring for five hours, the mixture was again cooled in an ice bath and quenched cautiously with water. The aqueous and organic layers were separated, and the aqueous layer was extracted two times with 100 mL portions of ether. The combined organic layers were washed one time with saturated NaHCO_3 , one time with brine, and dried over magnesium sulfate. Filtration and rotary

evaporation yielded 25.9 g of light brown oil (95% material yield).

Kugelrohr distillation (125°, 1 mm) afforded 22.27 g of clear mobile oil (78.2% yield). NMR (CCl_4 δ 7.56-6.60 (m, 4H), 3.10-2.52 (m, 4H), 2.20-1.02 (broad m, 8H); IR (neat) 3050, 3015, 2925, 2860, 2855, 1680, 1659, 1590, 1462, 1430, 1328, 1320, 1256, 1228, 1220, 1162, 1140, 1100, 1065, 1049, 1020, 1015, 955, (cm^{-1})

Preparation of 2-methoxy-7,8,9,10,11-pentahydro-5(6H)-benzocyclononenone (5) and 3-methoxy-7,8,9,10,11-pentahydro-5(6H)-benzocyclononenone (105)

A 500 mL flask equipped with nitrogen inlet and magnetic stirrer was charged with 31.9 g (0.197 mol) of 24.7% potassium hydride in oil and washed as usual with hexane. The flask was placed in an ice bath, and 100 mL of HMPA were added. A mixture of 19.5 g of alcohols 99 and 100 which contained some ethoxybenzobicyclononenone 104 was taken up in 75 mL of HMPA and added to the potassium hydride dropwise. The ice bath was removed, and the mixture was allowed to stir overnight. The reaction was then cooled to 0° and quenched cautiously with water. The aqueous layer was extracted four times with 200 mL portions of ether. The combined ether layers were washed four times with 150 mL portions of water, one time with 150 mL of saturated NaHCO_3 , one time with brine, and dried over magnesium sulfate. Filtering and rotary evaporating yielded 18.4 g of dark brown mobile oil. GLC analysis (column A) indicated three peaks, two of which

were not completely separated. The short retention time peak corresponded to 104. Spiking the GLC trace with pure p-methoxybenzocyclo-nonenone (5) (obtained by chromatography) indicated that the para isomer (5) predominated over the meta isomer (105) in ca. a 3:2 ratio. Flash chromatography of 10.0 g of this material according to the method of Still (57) with 10% ethyl acetate/pentane afforded 1.12 g of 104, 2.37 g of 105, a 2.31 g overlap fraction of 5 and 105, 3.51 g of 5, and 0.40 g of unidentified material, for a total recovery of 9.61 g: NMR of 104 (CCl_4) δ 6.96 (dd, $J=2,8$, 1H), 6.64 (m, 2H), 3.76 (s, 3H), 3.43 (q, $J=7$, 2H), 2.14-1.96 (m, 3H), 1.90-1.26 (broad m, 8H), 1.12 (t, $J=7$, 3H); IR (neat) 3060, 2980, 2930, 2850, 2755, 1605, 1590, 1475, 1440, 1390, 1350, 1325, 1270, 1240, 1215, 1190, 1125, 1090, 1065, 1020, 995, 970, 950, 930, 810, 780, 730 (cm^{-1}); mass spectrum m/e (rel %) 246 (26.1), 203 (81.1), 201 (100), 200 (31.9), 175 (47.6); m/e 246.161 (calcd for $\text{C}_{16}\text{H}_{22}\text{O}_2$; 246.162); NMR of 105 (CCl_4) δ 6.92 (m, 3H), 3.82 (s, 3H), 2.83 (m, 4H), 2.04-1.29 (broad m, 8H); IR (neat) 3060, 2990, 2910, 2840, 1680, 1650, 1595, 1560, 1480, 1450, 1400, 1310, 1270, 1250, 1225, 1175, 1020, 985, 920, 855, 810, 690 (cm^{-1}); mass spectrum m/e (rel %) 218 (51.8), 175 (100), 162 (28.4), 161 (30.8); m/e 218.130 (calcd for $\text{C}_{14}\text{H}_{18}\text{O}_2$; 218.131); NMR of 5 (CCl_4) δ 7.41 (d, $J=8$, 1H), 6.66 (dd, $J=8,2$, 1H), 6.59 (d, $J=2$, 1H), 3.80 (s, 3H), 2.96 (broad t, 2H), 2.74 (broad t, 2H), 2.02-1.25 (broad m, 8H); IR (neat) 3060, 3000, 2920, 2850, 1695, 1660, 1600, 1580,

1495, 1465, 1440, 1410, 1350, 1320, 1240, 1160, 1105, 1080, 1030, 1000, 990, 915, 810 (cm^{-1}); mass spectrum m/e (rel %) 218 (45.8), 175 (46.0), 162 (56.2), 161 (100); m/e 218.131 (calcd for $\text{C}_{14}\text{H}_{18}\text{O}_2$: 218.131).

Preparation of 8, 9-(5'-methoxybenzo)-bicyclo-[5.2.0]-non-8-ene-1-ol (99) from 1-ethoxy-8, 9-(5'-methoxybenzo)-bicyclo-[5.2.0]-non-8-ene (104)

A 100 mL flask was charged with 0.700 g (2.85 mmol) of the diether 104 and 20 mL of 80% aqueous acetone. Concentrated sulfuric acid (4 drops) was added causing a color change to amber. After stirring for 5.5 hours, an aliquot showed only about 20% reaction by GLC (Column C), so an additional 0.5 mL of sulfuric acid (H_2SO_4) was added, and the mixture was allowed to stir overnight. An aliquot taken then showed about 80% reaction, and an additional 0.5 mL of H_2SO_4 was added. After an additional 6 hours of stirring, no significant change was observed in the reaction mixture. The reaction mixture was then neutralized with saturated NaHCO_3 and extracted three times with 20 mL portions of ether. The combined ether layers were washed one time with saturated NaHCO_3 and one time with brine. After drying over magnesium, filtering, and rotary evaporating, 0.509 g of yellowish crystals were obtained. Flash chromatography with 10% ethyl acetate/pentane afforded 0.397 g of alcohol 99 as off white crystals, mp 94-95°, and 0.083 g of starting material 104, for

an adjusted yield of 72.6%: NMR (CCl_4) δ 6.94 (d, $J=8$, 1H), 6.70-6.50 (m, 2H), 3.72 (s, 3H), 3.40-3.16 (m, bridgehead H), 2.32-1.12 (broad m, 11H); IR (neat) 3600-3150, 3080, 3025, 2940, 2870, 1905, 1600, 1485, 1455, 1370, 1340, 1280, 1255, 1190, 1135, 1055, 1035, 980, 960, 865, 830 (cm^{-1}); mass spectrum m/e (rel %) 218 (15.7), 175 (100), 162 (21.7), 161 (19.1); m/e 218.131 (calcd for $\text{C}_{14}\text{H}_{18}\text{O}_2$: 218.131).

Preparation of trimethylsilyl cyanide

Procedure A of Evans, Carrol, and Truesdale (41) was followed. A 500 mL flask was charged with 50 g (0.37 mol) of silver cyanide (Aldrich) and 145 mL (1.20 mol) of chlorotrimethylsilane (Aldrich, freshly distilled), and the mixture was stirred for four days in the dark. The solid residue was washed and filtered with anhydrous ether, and the washings were subjected to careful fractional distillation, yielding 10.13 g of trimethylsilyl cyanide between 114° - 117° (760 mm) (lit (78) bp 114 - 118° , 760 mm).

Preparation of 7, 8, 9, 10, 11, 12-hexahydro-6(5H)-Benzocyclodecenone (107)

The procedure similar to that of Evans, Carrol, and Truesdale (41) was used. An oven dried 200 mL flask (equipped with nitrogen atmosphere and magnetic stirrer) was charged with 0.271 g of

18-crown-6:potassium cyanide catalyst (prepared by dissolving 18-crown-6 and potassium cyanide in anhydrous methanol and removing the methanol under vacuum), and 9.32 g (49.5 mmol) of 7, 8, 9, 10, 11-pentahydro-5(6H)-benzocyclononone. The mixture was stirred for one hour during which time it took on a light yellow color. Next, 9.4 mL (74.4 mmol) of freshly distilled trimethylsilyl cyanide (Petrach or prepared as described above) was added all at once. The reaction mixture took on a yellowish green color at first, and later turned light brown. After stirring for five hours, the mixture was cooled in an ice bath and 4.36 g (109 mmol) of 95% lithium aluminum hydride (LiAlH_4) was added cautiously via an anhydrous ether suspension. The reaction mixture took on a grayish-green color, and was allowed to stir for three hours. After cooling in an ice bath, the reaction was quenched cautiously with 4.4 mL of water, followed by 4.4 mL of 15% sodium hydroxide (NaOH), and finally another 13.2 mL of water. The whitish solid material which formed was extracted five times with 50 mL portions of refluxing ether. The combined ether extracts were washed eight times with 80 ml portions of 10% v/v of H_2SO_4 (until the ether layer went from cloudy to clear). The ether layer was washed two times with 100 mL portions of saturated NaHCO_3 , and one time with brine. After drying over magnesium sulfate, filtering, and rotary evaporating, 0.578 g of slightly cloudy oil was obtained. GLC (column C) analysis of this oil showed three

major peaks. The peak of largest area corresponded to starting material. The IR of this oil indicated the presence of both hydroxyl and carbonyl containing material.

The acidic extract from above was cooled in an ice bath and made basic with 15% NaOH, causing a cloudy white suspension to form. This basic solution was extracted three times with 250 mL portions of ether. The combined ether extracts were washed one time with 250 mL of saturated NaHCO_3 , one time with 250 mL of brine, and concentrated by rotary evaporation, yielding 9.60 g of white crystals.

The crystals were taken up in 150 mL 10% v/v acetic acid (HOAc), cooled to 0° in an ice bath, and 100 mL of 1.25 M sodium nitrite (NaNO_2) was added in four 25 mL portions. The solution turned creamy white after addition of the first portion, and a head of foam formed on top of the liquid layer. The mixture was allowed to stir overnight, at which time a solid layer was observed floating on top of a liquid layer. The reaction mixture was cooled in an ice bath and made basic with 10% NaOH. This basic material was extracted four times with 150 mL portions of ether. The combined ether extracts were washed one time with 150 mL of saturated NaHCO_3 , one time with 150 mL of brine, and dried over magnesium sulfate. Filtering and rotary evaporating yielded 8.18 g of light brown viscous oil. Kugelrohr distillation (136° , 1 mm) afforded 6.21 g of slightly yellow oily crystals, which contained 90.16% product 107 and 9.84% starting

material by GLC (column C). The pot contained 1.67 g of brown tar. The overall yield for two steps based on starting material consumed was 59.8%. A small amount of the oily crystals was recrystallized for analysis from cold pentane, affording white crystals: mp 41.5-42.5° (One peak by GLC); NMR (CCl_4) δ 7.13 (m, 4H), 3.63 (s, 2H), 2.64 (broad t, 2H), 2.31 (broad t, 2H), 1.84-1.24 (m, 6H), 1.22-0.86 (m, 2H); IR (CCl_4) 3080, 3040, 2940, 2870, 1705, 1610, 1500, 1475, 1455, 1355, 1225, 1175, 990, 930, 885 (cm^{-1}); m/e 202.136 (calcd for $\text{C}_{14}\text{H}_{18}\text{O}$: 202.136).

Preparation of 2-methoxy-7,8,9,10,11,12-hexahydro-6(5H)-benzocyclodecenone (106)

The procedure in the previous experiment was again used. A 100 mL round bottom flask was charged with 3.038 g (13.9 mmol) of p-methoxy- α -benzocyclononenone 5 and 0.108 g of 18-crown-6: potassium cyanide catalyst, and the mixture was stirred for 35 minutes, during which time it went from yellow to bright orange. Next, 2.50 mL (20.9 mmol) trimethylsilyl cyanide (TMSCN) was added, and the mixture was allowed to stir overnight. An anhydrous ether suspension of LiAlH_4 (1.225 g; 30.6 mmols) was added cautiously, and the mixture was allowed to stir for two hours, during which time it took on a gray-green color. The reaction mixture was quenched cautiously with 1.2 mL of water, followed by 1.2 mL of 15% NaOH, and finally 3.6 mL of water. The light brown precipitate which formed was extracted four

times with 30 mL portions of refluxing ether. The combined ether extracts were extracted with 10% H_2SO_4 until the ether layer turned clear (6 times, 60 mL portions). The ether layer was washed two times with 100 mL portions of saturated NaHCO_3 , and one time with 100 mL of brine. After drying over magnesium sulfate, filtering, and rotary evaporating, 0.088 g of light brown oil was obtained. Analysis by GLC (column A) of this oil indicated that this oil consisted mainly of starting material 5.

The acidic extract was cooled in an ice bath and made basic with 15% NaOH , which caused copious amounts of white crystals to form. The basic extract and crystals were extracted three times with 100 mL portions of ether, and the combined ether layers were washed one time with 100 mL NaHCO_3 , one time with 100 mL brine, and the ether was removed by rotary evaporation, leaving 4.272 g of white crystals.

The crystals were dissolved in 60 mL of 10% v/v HOAc , cooled to 0° , and 40 mL 1.25 M NaNO_2 was added in 10 mL portions. The mixture turned cloudy white and gas evolved. The mixture was allowed to stir overnight, and upon return several "popcorn" like balls of material were observed floating in a clear liquid layer. The contents of the reaction were made basic with 15% NaOH , and extracted three times with 100 mL portions of ether. The combined ether layers were washed one time with 100 mL NaHCO_3 , one time with 100 mL brine, dried over magnesium sulfate, filtered, and

concentrated by rotary evaporation, yielding 2.784 g of yellow crystals. Analysis by GLC (column A) indicated 94.6% product 106 and 5.6% starting material 5. An analytical sample was recrystallized from hexane, affording white crystals; mp 71-72°; NMR (CCl_4) δ 7.02 (d, J=9, 1H), 6.74-6.60 (m, 2H), 3.76 (s, 3H), 3.56 (s, 2H), 2.59 (broad t, 2H), 2.28 (broad t, 2H), 1.80-1.24 (broad m, 6H), 1.10-0.88 (broad m, 2H); IR (neat) 3060, 2940, 2860, 1710, 1610, 1575, 1505, 1475, 1425, 1350, 1320, 1295, 1260, 1215, 1205, 1190, 1180, 1090, 985, 880, 810 (cm^{-1}); m/e 232.145 (calcd for $\text{C}_{15}\text{H}_{20}\text{O}_2$: 232.146).

Preparation of 3-methoxy-7,8,9,10,11,12-hexahydro-6(5H)-benzocyclodecenone (117)

The procedure described in the previous experiment was again used. A 100 mL flask was charged with 0.813 g of catalyst and 2.047 g (9.39 mmol) of ketone 105. This mixture was stirred under nitrogen for 30 minutes, during which time it went from yellow to orange. A 1.70 mL portion (14.2 mmol) of freshly distilled TMSCN was added, and the mixture was stirred for 4.5 hours, while it took on a brownish orange color. Next, 0.83 g (20.7 mmol) of 95% LiAlH_4 was added cautiously via an ether suspension, and the mixture was stirred for four hours, while taking on a gray-green color. The mixture was quenched cautiously with 0.8 mL water, followed by 0.8 mL 15% NaOH, and finally 2.5 mL of water, and the solid material was extracted four

times with 30 mL portions of refluxing ether. The combined ether layers were extracted eight times with 25 mL portions of 10% H_2SO_4 (until ether layer turned clear). The ether layer was washed two times with saturated NaHCO_3 , one time with brine, dried over magnesium sulfate, filtered, and concentrated by rotary evaporating, yielding 0.090 g of slightly yellow oil. Analysis by GLC (column A) indicated that this oil was mainly starting ketone 105.

The acidic extract from above was made basic with 10% NaOH which caused a cloudy white suspension to form. This basic layer was extracted three times with 100 mL portions of ether and the ether was removed by rotary evaporation, leaving 2.26 g of oily crystals.

The crystals above were taken up in 40 mL of 10% v/v HOAc , cooled to 0° , and then 26 mL of 1.25 M NaNO_2 was added in four portions. The mixture turned cloudy white and foamed, and was allowed to stir overnight. Upon return, white crystals were observed in the reaction flask. The reaction mixture was made basic with 15% NaOH , and extracted three times with 80 mL portions of ether. The ether layers were washed with 80 mL of saturated NaHCO_3 , 80 mL of brine, and dried over magnesium sulfate. Filtering and rotary evaporating yielded 1.826 g of slightly yellow crystals (93.6% product by GLC analysis (column A)). A sample was recrystallized from hexane for analysis, affording off-white crystals: mp $72-73^\circ$; NMR (CCl_4) δ 7.10 (d, $J=8$, 1H), 6.92-6.74 (m, 2H), 3.83 (s, 3H), 3.63 (s, 2H), 2.56

(broad t, 2H), 2.32 (broad t, 2H), 1.87-1.30 (broad m, 6H), 1.26-1.05 (m, 2H); IR (CCl_4) 3010, 2945, 2870, 2845, 2765, 1715, 1620, 1555, 1505, 1475, 1450, 1325, 1300, 1255, 1215, 1160, 1110, 1050, 1010, 980, 875; m/e 232.147 (calcd for $\text{C}_{15}\text{H}_{20}\text{O}_2$: 232.146).

One carbon ring expansion of 2-methoxy-5,6,9,10,11,12,13,14-octahydro-8(7H)-Benzocyclododecenone (15)

A 25 mL round bottom flask was charged with 0.187 g (0.718 mmol) of ketone 15, a small spatula tip of catalyst, and 0.66 mL (5.21 mmol, essentially used as solvent) of TMSCN, and the mixture was allowed to stir overnight. A 0.110 g portion (2.75 mmol) of 95% LiAlH_4 was added via an ether suspension, and the mixture was stirred for 4.5 hours. The mixture was cooled in an ice bath, and quenched with 0.11 mL of water, followed by 0.11 mL of 15% NaOH, and finally 0.33 mL of water. This mixture was allowed to stir for two days (should have been worked up immediately; the precipitate turned black, and the ether layer turned brown). The black precipitate was washed three times with 20 mL portions of ether, and extracted three times with 20 mL portions of refluxing ether. The combined ether layers were washed seven times with 10 mL portions of 10% H_2SO_4 (until the ether layer turned clear). The ether layer was washed two times with 10 mL portions of saturated NaHCO_3 , one time with 10 mL brine, and dried over magnesium sulfate. Filtering and rotary

evaporating yielded 0.045 g of yellow oil (mostly starting material by GLC analysis (column C)).

The acidic layer was made basic with 15% NaOH, causing a cloudy suspension to form. This material was extracted three times with 50 mL portions of ether. The combined ether extracts were washed two times with saturated NaHCO_3 , one time with brine, and dried over magnesium sulfate. Filtering and rotary evaporating yielded 0.041 g of viscous cloudy oil.

This oil was taken up in 2 mL of 10% v/v HOAc, which caused a cloudy white mixture to form, and two mL of 1.25 M NaNO_2 was added, and the mixture was stirred overnight. After neutralization with saturated sodium bicarbonate, extraction with ether, and usual workup, 0.0293 g of viscous light brown oil was obtained. Analysis by GLC (column C) showed some starting material (ca. 9%), an uncharacterized component of longer retention time than starting material (ca. 18%), and the major component which corresponded to product and had the longest retention time (ca. 73%). The NMR spectrum of this mixture looked very similar to that of starting material, except there were two peaks of approximately equal height separated by about 1 Hz corresponding to the methoxy hydrogens. The IR also was similar (carbonyl at 1710 cm^{-1}). A GLC sample was collected for high resolution mass spectrum; m/e 274.193 (calcd for $\text{C}_{18}\text{H}_{26}\text{O}_2$: 274.193).

Preparation of 7,8,9,10-tetrahydro-6(5H)-
benzocyclooctenone (73)

A 50 mL flask was charged with 0.033 g of catalyst and 1.02 g (6.38 mmol) of benzosuberone (Aldrich, freshly vacuum distilled), and the mixture was stirred for 75 minutes. TMSCN (1 mL, 8.56 mmol) was added and the mixture was stirred for 135 minutes. An ether suspension of 0.48 g (12.6 mmol) of 95% LiAlH_4 in 25 mL of ether was added and the mixture was allowed to stir overnight. The reaction was quenched cautiously by addition of 1 mL of water, followed by 2 mL of 10% NaOH, and finally 3 more mL of water. The white slurry which had formed was extracted six times with 15 mL portions of refluxing ether. The ether layers were extracted with 10% H_2SO_4 until the ether layer turned clear (ca. 800 ml). The acidic extract was made basic with 10% NaOH, and extracted three times with 100 mL portions of dichloromethane (CH_2Cl_2), and then three times with 100 mL portions of ether. The organic layers were separately dried over magnesium sulfate, filtered, concentrated by rotary evaporation, and vacuum transferred. The CH_2Cl_2 layer afforded 0.60 g of white crystals, mp 73-75°, and the ether layer afforded 0.15 g of white crystals, mp 73-75°, for a combined yield of 63%.

The white crystals (0.72 g) were dissolved in 50 mL of 10% HOAc and cooled to 0°, and 30 mL of 1.25 M NaNO_2 was added dropwise. The mixture was allowed to stir for one hour at 0° and for two

hours at room temperature. The mixture was rechilled to 0° and made basic with 10% NaOH, and extracted four times with 50 mL portions of ether. The combined ether extracts were dried over magnesium sulfate, filtered, and concentrated by rotary evaporation, yielding 0.62 g of yellow oil. Kugelrohr distillation yielded 0.46 g (81%) of clear, mobile oil. NMR and IR spectra matched those in the literature (38).

Preparation of 5-dibromomethyl-6, 7, 8, 9-tetrahydro-5-benzocycloheptenol (72)

A 100 mL 3-necked round bottom flask equipped with a magnetic stirrer, nitrogen inlet, and rubber septum was charged with 1.6 g (10 mmol) of benzosuberone (Aldrich, freshly vacuum transferred), 2.1 mL (30 mmol) of dibromomethane (Aldrich), and 20 mL of dry THF, and cooled to -78° in a dry ice-acetone bath. A THF solution containing 30 mmol of lithium diisopropylamide (LDA) (prepared from dry Aldrich diisopropylamine, and Ventron butyl lithium in THF) was added dropwise via syringe to the above cooled mixture. The reaction mixture was stirred for one hour at -78° and then quenched by pouring the reaction mixture into a beaker containing 20 g of ice, 16 mL of conc. HCl, and 40 mL of ether. The organic and aqueous layers were separated, and the organic layer washed with two 20 mL portions of saturated NaHCO₃, and 20 ml of brine. After drying over magnesium

sulfate and concentrating, 3.7 g of a light brown solid was obtained. Recrystallization from ether yielded 2.0 g of a yellow solid, which contained about 75% desired product according to the NMR spectrum (δ 6.47 singlet), and exhibited a hydroxyl band in the IR. This material was used without further purification in the ring expansion step.

Preparation of 7,8,9,10-tetrahydro-6(5H)-benzocyclooctenone (73) from 5-dibromomethyl-6,7,8,9-tetrahydro-5-benzocycloheptenol (72)

A 25 mL 3-necked round bottom flask equipped with nitrogen inlet and magnetic stirrer was charged with 0.501 g of 75% pure 72 and five mL THF. The mixture was cooled to -78° in a dry ice-acetone bath, and 1.2 mL of 2.3 M butyllithium was added dropwise via syringe to the mixture. The reaction mixture was allowed to stir for 30 minutes at -78° , for five minutes at 0° , and then quenched by pouring into a mixture of ice, conc. HCl, and ether. The aqueous and organic layers were separated, and the organic layers were washed two times with saturated NaHCO_3 and one time with brine, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation, affording 0.325 g of brown oil. Kugelrohr distillation (130° , 1 mm) yielded 0.174 g of almost clear mobile oil. Comparison of the NMR spectrum of this oil with an NMR spectrum of 73 prepared by the TMSCN ring expansion route indicated that it contained ca. 67% desired product.

General Procedure for the Preparation of Solutions of vinyl magnesium bromide in THF

A 200 mL round bottom flask equipped with nitrogen inlet, 25 mL addition funnel, reflux condensor, and magnetic stirrer, was charged with 2.77 g (0.144 g-atom) of magnesium turnings (Mallinckrodt). The magnesium turnings were dried by heating the flask with a heat gun while passing nitrogen over the stirred turnings. A 60 mL portion of dry THF was added. Next, 7.2 mL of vinyl bromide (0.10 mol) (Aldrich, 98%; or condensed by cold finger from MCB lecture bottle) was added to the addition funnel which contained 15 mL dry THF. About five mL of the vinyl bromide/THF solution was added to the magnesium turnings, and the reaction was initiated by gentle heating with a heat gun. Once reaction was initiated, it was maintained by judicious addition of the remainder of the vinyl bromide/THF solution. The mixture was allowed to stir for an hour after the addition was complete. The solution was made ca. 1 M in concentration by addition of 25 mL of dry THF. The desired amount of vinyl magnesium bromide solution was transferred from the flask via syringe.

Preparation of Vinyl Phenyl Sulfide

The procedure of Jarvie and Skelton (43) was used to prepare the title compound. To a stirred solution of 3.5 g (16.0 mmol) of diphenyl-disulfide (Parrish) in 20 mL of dry THF was added 30 mL (ca. 30 mmol)

of vinyl magnesium bromide in THF in five mL portions. The reaction vessel warmed slightly, and the mixture was allowed to stir for two hours. The reaction was then quenched cautiously with six mL of water, washed three times with 15 mL portions of 5% NaOH, two times with 25 mL portions of saturated NaHCO₃, and one time with 25 mL of brine. After drying over magnesium sulfate and filtering, rotary evaporation gave 1.9 g of a dark yellow oil (87% yield): NMR (CDCl₃) δ 7.32 (m, 5H), 6.52 (dd, J=9, 17 Hz, 1H), 5.31 (d, J=17 Hz, 1H), 5.28 (d, J=9 Hz, 1H); Lit (79) NMR (CCl₄) δ 6.44 (dd, J=9.4, 16.4, 1H), 5.25 (d, J=9.4, 1H), 5.23 (d, J=16.4, 1H).

Preparation of Vinyl Phenyl Sulfoxide

The title compound was prepared according to the procedure of Trost, Salzmann, and Hiroi (44). A solution of 1.9 g (14 mmol) of vinyl phenyl sulfide in 200 mL of CH₂Cl₂ was cooled to -78°, and a solution of 3.2 g (16 mmol) of 85% m-chloroperbenzoic acid (Aldrich) in 90 mL of CH₂Cl₂ was added over a 10 minute period, during which time a white precipitate formed. The reaction mixture was allowed to stir an additional five minutes, and then filtered into a separatory funnel containing 800 mL of 10% sodium sulfite and 800 mL of ether. After shaking, the ether layer and the aqueous layer were separated, and the ether layer was washed two times with 500 mL portions of saturated NaHCO₃, and one time with 500 mL of brine. After drying over

magnesium sulfate, filtering, and rotary evaporating, 2.1 g of a cloudy yellow oil was obtained which showed four spots by TLC (CH_2Cl_2). Dry column chromatography with CH_2Cl_2 on a 20 inch column afforded 0.9 g of a dark brown oil: NMR (CDCl_3) δ 7.43 (m, 5H), 6.62 (dd, $J=9, 16$ Hz, 1H), 5.97 (d, $J=16$ Hz, 1H) 5.67 (d, $J=9, 1$ H).

Attempted preparation of 5-(2-phenylsulfinyl-1-ethyl)-7,8,9,10-6(5H)-Benzocyclooctenone (76)

The potassium enolate of β -benzocyclooctenone (73) was prepared by dripping in a 10 mL dry THF solution of 0.299 g (1.70 mmol) of 73 to a flask containing 1.90 mmol of potassium hydride (Ventron) in 5 mL of dry THF. The flask was cooled to -78° in a dry ice-acetone bath, and then 0.410 g (2.50 mmol) of vinyl phenyl sulfoxide in 10 mL of THF was added dropwise over 15 minutes. The reaction was followed by TLC, and no reaction was observed until the reaction mixture had warmed to -5° . After two hours at 0° , the reaction mixture was quenched with water. The quenched reaction mixture was extracted with three 10 mL portions of ether, and the combined ether layers were washed twice with 20 mL portions of saturated NaHCO_3 , and one time with 20 mL of brine. After drying over magnesium sulfate, filtering, and rotary evaporating, 0.488 g of a light yellow oil was obtained. The NMR spectrum of this material indicated no vinyl

protons were present, two types of aromatic protons were observed, and some new peaks in the 3.7 region were observed. The IR spectrum looked very similar to that of starting ketone 73, with a side band at 1750 and bands at 1150 and 1045 being the major difference. It was concluded that the reaction may have proceeded at least to a small extent, but the major product recovered was starting material. Preparative layer chromatography with ether as eluant failed to isolate any material of value. Other attempts at preparation of 76 were tried in which the temperature of the reaction was raised to refluxing THF, but were also unsuccessful.

Preparation of Isoamyl Nitrite

Isoamyl nitrite was prepared according to the procedure of Noyes (80). A 63 g (0.91 mol) portion of sodium nitrite (Mallinckrodt) was dissolved in 250 mL of water, cooled to 0° in an ice-brine bath, and stirred with a Herschberg stirrer. An ice-bath cooled solution of 18 mL water, 23.0 mL conc. H₂SO₄, and 91 mL (0.83 mol) of isoamyl alcohol was introduced slowly below the surface of the nitrite solution in 10 ml aliquots via a long stem dropping funnel, so as to maintain a temperature of ca. 0°. The addition took three hours. The mixture was allowed to stand and separate into layers. The liquid layer was decanted and filtered from the precipitate formed during the reaction. The aqueous and organic layers were separated, and the organic layer

was washed twice with a total of 100 mL of saturated NaHCO_3 , one time with 100 mL of brine, and dried over magnesium sulfate. After filtration, 46 g of a light yellow oil was obtained which was 82.5% pure by the NMR spectrum (isoamyl alcohol was the impurity). Distillation only improved purity to 85%.

Preparation of 2-hydroxyiminocyclooctanone

A 50 mL 3-necked round bottom flask was charged with 1.0 g (5.5 mmol) of 22.2% potassium hydride (Ventron) and washed as usual with hexane. The flask was equipped with a 25 mL addition funnel, and five mL of dry THF was added to the flask. Next, 0.506 g (4.00 mmol) of cyclooctanone (Aldrich) in 12 mL of dry THF was added dropwise over a 30 minute period and then allowed to stir for one hour. Next, 0.66 mL of 85% pure freshly distilled isoamyl nitrite was syringed into the mixture slowly. The mixture took on a reddish orange color. This mixture was allowed to stir for one hour at room temperature and then for two hours at 50° (oil bath), at which time a solid suspension was observed. The reaction was then allowed to stir overnight at room temperature, and then quenched with five mL of water. The reaction mixture was poured into 60 mL of 10% NaOH, and the basic layer was extracted three times with 50 mL portions of ether. The basic layer was then made acidic with about 60 mL of 6M HCl and the acidic layer was extracted five times with 50 mL portions of ether. The combined

ether extracts from the acidic layer were dried over magnesium sulfate, filtered, and rotary evaporated, yielding 0.65 g of brownish oil. Kugelrohr distillation yielded 0.34 g of cloudy yellow oil: NMR (CDCl_3) δ 10.67 (broad s, oxime H), 2.7-2.0 (broad m, 4H), 2.0-1.0 (broad m, 8H); IR (CCl_4) 3700-3100 (broad band), 2950, 2880, 1790 (weak), 1715, 1595, 1465, 1060, 1055, 1000, 880 (cm^{-1}) Matches lit. (81).

Attempted preparation of 1,2-cyclooctanedione (82)
from 2-hydroxyiminocyclooctanone

The procedure of Timms and Wildsmith (46) for the conversion of oximes to ketones was followed. Thus, about 1.77 g (11.5 mmol) of dry titanium trichloride (TiCl_3) was transferred under nitrogen atmosphere to a nitrogen purged solution of 25 mL of 10% HCl over granular zinc metal. A 50 mL three-necked round bottom flask was charged with 0.32 g (2.1 mmol) of 2-hydroxyiminocyclooctanone in 25 mL of dry THF and placed under nitrogen atmosphere. Next, 12 mL (5.5 mmol) of the TiCl_3 solution was added to the 2-hydroxyiminocyclooctanone over a 15 minute period. The color went from yellow to brown and finally brownish red during the addition. An additional one mL of TiCl_3 solution caused no change in color. After two hours, TLC indicated no oxime remained. The reaction mixture was extracted four times with 50 mL portions of ether. The combined ether

layers were washed one time with 50 mL of saturated NaHCO_3 , four times with 50 mL portions of water, and finally one time with 50 mL of brine. Drying over magnesium sulfate, filtering and rotary evaporating afforded only 0.09 g of oil. The NMR spectrum did not match literature (48) for 1,2-cyclooctanedione.

Preparation of 2-Bromocyclooctanone (81)

Cyclooctanone (Aldrich) (6.51 g, 50.0 mmol), chloroform (70 ml) and ethyl acetate (50 ml) were added to a 250 mL three-necked flask equipped with magnetic stirrer, reflux condensor, and fritted gas inlet tube. The mixture was warmed to 77° and refluxed while a constant stream of nitrogen gas was bubbled through the reaction solution. Powdered cupric bromide (22.3 g, 100 mmol) was added in small portions over a 3.5 hour period to the reaction mixture. The green color from each portion was allowed to disappear before addition of the next portion. After addition was complete, the solution was heated for an additional 1.5 hours, cooled, and filtered. The white cuprous bromide which formed during the reaction was washed with 25 mL of chloroform, and the combined filtrate and washings were concentrated by rotary evaporation. The dark oily residue was taken up in 200 mL of ether, and the ether layer was washed with water (50 mL), two times with 50 mL portions of 5% NaHCO_3 , and with 50 mL of brine. After drying over magnesium sulfate, filtering, and rotary evaporating, 7.25 g of slightly

darkened oil was obtained. Bulb to bulb vacuum distillation afforded 6.10 g of clear mobile oil. The NMR spectrum indicated 80% conversion. This oil darkened rapidly at room temperature: NMR (CDCl_3) δ 4.36 (t, 1H), 2.1-3.1 (m, 4H), 1.67 (m, 8H); IR (neat) 2940, 2870, 1710, 1470, 1450, 1350, 1330, 1265, 1240, 1210, 1195, 1150, 1125, 1095, 1085, 1060, 1020, 970, 875, 855, 840, 800 (cm^{-1}). The spectra agreed with those in the literature (48).

Attempted preparation of 1,2-Cyclooctanedione (82)
from 2-bromocyclooctanone (81)

The procedure described by Macomber (48) for preparation of the title compound was followed. A 100 mL three-necked flask was charged with 1.66 g (10 mmol) of potassium iodide, 1.06 g (10 mmol) of sodium carbonate, and 35 mL of dimethyl sulfoxide (distilled from calcium hydride, and stored over 4 Å molecular sieves), and placed under a nitrogen atmosphere. Next, 2.05 g (10 mmol) of 2-bromocyclooctanone (81) was added all at once and the mixture stirred for five minutes. The mixture was added to ice-cold brine (60 mL) and extracted two times with 25 mL portions of ether. The combined ether layers were washed three times with 25 mL portions of water, one time 25 mL of brine, one time with 25 mL of saturated NaHCO_3 , and one time 25 mL of brine again. After drying over magnesium sulfate, filtering, and rotary evaporating, 0.62 g of light yellow oil was

obtained, which was identical to starting material by NMR and TLC. Altering the time of the reaction to as long as five hours gave no observable product. The use of tetrabutylammonium iodide in place of potassium iodide gave no observable product. A check for all reagents used indicated proper purity.

Preparation of 5-ethynyl-7, 8, 9, 10-tetrahydro-5(6H)-benzocyclooctenol (83), Method A

The procedure of Jones (82) was used to generate ethynyl Grignard. Ethyl magnesium bromide was prepared from 0.48 g (20 mmol) of magnesium turnings and 1.6 mL (21 mmol) of ethyl bromide in 20 mL of THF. Meanwhile, a 50 mL three-necked flask equipped with gas inlet tube, calcium sulfate protected gas outlet, and magnetic stirrer was charged with 15 mL of dry THF. Acetylene gas was then passed through a drying train (consisting of a dry ice-acetone trap, safety trap, sulfuric acid scrubber, another safety trap, a potassium hydroxide trap, and finally a soda lime trap) and into the THF at a rapid rate. The ethyl magnesium bromide was then added slowly to the acetylene solution via an addition funnel. The first few drops caused the acetylene solution to turn purplish brown. After addition of about two thirds of the ethyl Grignard, a white precipitate was observed, which dissolved upon addition of 5 mL of THF. Towards the end of the addition of Grignard reagent, more precipitate formed, which again

dissolved upon addition of five mL of THF. Total time of addition of ethyl Grignard was four hours.

The acetylene gas inlet was replaced by a nitrogen inlet, and the ethynyl Grignard reagent was cooled to 0° in an ice bath. The α -benzocyclooctenone 78 (0.60 g, 3.4 mmol) in 10 mL THF was added to the ethynyl Grignard over a 20 minute period. The reaction mixture was then allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched by first cooling to 0°, cautiously adding 10% HCl until fizzing had ceased, and allowing the mixture to stir for 20 minutes. The aqueous layer was extracted two times with 25 mL portions of ether, and the combined organic layers were washed two times with 30 mL portions of saturated NaHCO₃, one time with 25 mL of brine, and dried over magnesium sulfate. After filtering and rotary evaporating, 0.53 g of a grainy light brown oil was obtained. GLC (column E) and NMR analysis indicated about a 50:50 mixture of product 83 and starting material 78. The NMR spectrum (CCl₄) of the mixture showed a new singlet at δ 2.62 (ethynyl H) and a new multiplet at δ 7.9-7.75. The IR spectrum (neat) showed bands at 3600-3200, 3300, and 2100 indicative of hydroxyl group and ethynyl group. Purification of the product by GLC (column D) gave a sample for mass spectral analysis: m/e 200.120 (calcd for C₁₄H₁₆O: 200.120).

Preparation of 5-ethynyl-7,8,9,10-tetrahydro-5(6H)-benzocyclooctenol (83), Method B

The title compound was prepared from commercially available (Aldrich) lithium acetylide ethylenediamine complex ($\text{LiC}\equiv\text{C}\cdot\text{EDA}$) according to a modified procedure of Beumel and Harris (75). A 500 mL three-necked round bottom flask equipped with mechanical stirrer, acetylene gas inlet, calcium sulfate drying tube, and addition funnel was charged with 250 mL of dry THF and 10.85 g (118 mmol) of $\text{LiC}\equiv\text{C}\cdot\text{EDA}$. Acetylene gas was bubbled through the solution for 30 minutes while stirring vigorously. Next, the ketone 78 (4.0 g, 23 mmol) was dissolved in 100 mL of dry THF and added to the acetylide mixture over a period of one hour at room temperature. The acetylene gas inlet was replaced by a nitrogen inlet after seven hours of reaction time. The reaction was followed by GLC (column F), which showed no improvement in starting material to product ratio after 24 hours. The reaction was quenched by adding 10% HCl cautiously and allowing the mixture to stir for 0.5 hours. The aqueous layer was extracted two times with 125 mL portions of ether, and the combined organic layers were washed two times with 125 mL portions of 10% HCl, one time with 200 mL of saturated NaHCO_3 , and one time with 250 mL of brine. After drying over magnesium sulfate, filtering, and rotary evaporating, 3.92 g of a viscous light brown oil was isolated. NMR and GLC analysis of this oil indicated ca. a 60:40 product to starting material ratio.

The above product mixture was subjected to Girard's Reagent T purification by refluxing 2.5 hours with 2.0 g of Girard's Reagent T, 40 mL of absolute ethanol, and three mL of HOAc. The mixture was cooled and concentrated by rotary evaporation until a precipitate was observed. The EtOH layer was decanted off, and the precipitate was washed twice with ethanol. The combined ethanol layers were then worked up in the usual way, affording 2.32 g of brown oil. GLC analysis (column F) indicated only product was present in this oil: NMR (CDCl_3) δ 7.90-7.74 (m, 1H), 7.36-7.02 (m, 3H), 3.74-3.40 (m, 1H), 3.12-2.82 (m, 1H), 2.65 (sharp singlet with broad base, 2H: broad base disappeared when D_2O was added), 2.38-1.12 (m, 8H); IR (neat) 3600-3200, 3520, 3300, 3060, 3010, 2940, 2875, 2100, 1600, 1495, 1450, 1355, 12275, 1205, 1080, 1030, 1010, 990, 970, 920, 900 (cm^{-1}); mass spectrum m/e (rel %) 201 (8.9), 200 (57.8), 157 (74.3), 144 (97.4), 115 (100); m/e 200.120 (calcd for $\text{C}_{14}\text{H}_{16}\text{O}$: 200.120). Hydrolysis of the aqueous layer from the workup of the Girard's Reagent T reaction, followed by standard workup afforded 0.48 g of α -benzocyclooctenone 78. The yield corrected for recovered starting material was 57.3%.

Attempted preparation of 5-ethynyl-7,8,9,10-benzocyclooctene (84) by dehydration of 5-ethynyl-7,8,9,10-tetrahydro-5(6H)-benzocyclooctenol (83) with sulfuric acid

A 25 mL round bottom flask equipped with nitrogen atmosphere,

magnetic stirrer, and reflux condenser was charged with 0.1045 g (0.5235 mmol) of the alcohol 83, three mL of THF, and 0.25 mL of 50% aqueous H_2SO_4 . The mixture was stirred in a 55° oil bath. GLC (column F) analysis of an aliquot showed no remaining starting material after one hour of reaction time. The reaction mixture was then cooled to 15° in a cold water bath, and quenched with saturated NaHCO_3 . The aqueous layer was extracted with ether, and the ether layer worked up with saturated NaHCO_3 and brine. After drying over magnesium sulfate, filtering, and rotary evaporating, 0.1008 g of an orange-red oil was isolated. GLC (column F) analysis showed three components. Kugelrohr distillation (74-94°, 1 mm) yielded 0.0794 g of a clear oil, which looked the same by GLC. The IR (neat) spectrum of this mixture showed loss of the hydroxyl band of starting material, carbonyl absorption at 1680 and 1720 cm^{-1} , and absorption at 2750 and 2710 cm^{-1} indicative of aldehydes. Absorption at 3290 and at 2240 and at 2100 cm^{-1} indicated some acetylenic material was still present. The NMR (CDCl_3) spectrum of this mixture showed a doublet at δ 9.24 ($J=8$ Hz), a triplet at δ 9.58 ($J=2$ Hz) of about one-fourth the area of the doublet, a doublet of triplets at δ 6.14 ($J=8, 1$ Hz), and three singlets at δ 2.92, 2.30, and 2.14 of relatively small area. GLC/mass spectral analysis on a 7% OV101 column of this mixture, showed that the major components of the mixture had m/e peaks at 200 and 199 indicative of aldehydes of molecular weight 200. It was concluded that

the major component of this mixture was the E and Z isomers of 5-formylmethylene-6H-7,8,9,10-tetrahydrobenzocyclooctenone (91), and a minor component was 5-ethanal-7,8,9,10-tetrahydrobenzocyclooctene (92). Some 7,8,9,10-tetrahydrobenzocyclooctene-methyl ketone (93) was probably present, and some desired product may have been formed.

Attempted preparation of 5-ethynyl-7,8,9,10-tetrahydrobenzocyclooctene (84) by dehydration of 5-ethynyl-7,8,9,10-tetrahydro-5(6H)-benzocyclooctenol (83) with phosphorous oxychloride

A 25 mL round bottom flask equipped with nitrogen inlet, magnetic stirrer, and septum, was charged with 0.1301 g (0.6505 mmol) of the alcohol 83 and one mL of dry pyridine. The mixture was cooled in an ice bath, and 0.10 mL (1.09 mmol) of phosphorous oxychloride (POCl_3) (freshly distilled) was introduced to the reaction mixture in 10 microliter aliquots over a 25 minute period. The ice bath was removed and the mixture was allowed to stir at ambient temperature. After two hours, GLC (column F) analysis of an aliquot showed mostly starting material. After six hours, GLC analysis of an aliquot still showed mostly starting material, so another 0.05 mL of POCl_3 was introduced as before, and the mixture was allowed to stir overnight. A little starting material still remained, so the mixture was heated to 75° (oil bath), and an aliquot taken after 30 minutes at this temperature showed no starting material by GLC analysis. The reaction was

quenched by cautious addition of ice, followed by water. The aqueous layer was extracted with three 50 mL portions of ether, and the combined ether layers were washed two times with 20 mL portions of 10% HCl, one time with 20 mL of water, one time with 20 mL of saturated NaHCO₃, and one time with 20 mL of brine. After drying over magnesium sulfate, filtering, and rotary evaporating only 0.0171 g of almost clear oil was isolated (some material was lost in the numerous aliquots taken, however). This oil consisted of two major peaks of roughly equal area by GLC analysis, and a minor third peak. The IR spectrum (neat) showed loss of the hydroxyl band of starting material and an absorption at 1955 indicative of an allene. The NMR spectrum (CDCl₃) showed loss of acetylenic proton and a triplet at δ 6.03 (J=1 Hz). GLC/mass spectral analysis of the two major peaks gave the following results: m/e (rel %) 220 (7.0), 218 (21.9), 183 (65.9), 141 (100), for peak of shorter retention time, and 220 (11.5), 218 (33.3), 183 (60.7), 141 (100) for peak of longer retention time. It was concluded that the major products from this reaction were the two isomers of 5-(chlorovinylidene)-6H-7,8,9,10-tetrahydrobenzocyclooctene (86).

Preparation of 6-vinyl-7,8,9,10,11,12-hexahydro-6(5H)-Benzocyclodecenol (10) in Toluene

An oven dried, nitrogen purged 250 mL three-necked round bottom flask was charged with 30 mL (39 mmol) of a 1.3 M vinyl

magnesium bromide solution (prepared as previously described) in THF. The nitrogen inlet was connected to a vacuum via a 3-way valve, and the THF was removed and collected in a dry ice-acetone trap over a period of three hours while vigorous stirring was maintained with a magnetic stirrer (until the stirrer "froze" in the solid yellow residue which formed).

The flask was fitted with a 25 mL addition funnel, and 125 mL of dry toluene was added. The flask was then fitted with a reflux condenser and oil bath, and the oil bath was warmed to 58°. The vinyl magnesium bromide was only sparingly soluble in the warm toluene.

Next, 1.5087 g of 94% pure β -Benzocyclodecenone (107) was dissolved in 25 mL of toluene and added slowly to the vinyl Grignard reagent over one hour. The progress of the reaction was followed by removing aliquots, working them up, and injecting them on a GLC (column D). After 11 hours at 55-58°, the ratio of product to starting material was about 1:1. The oil bath temperature was increased to 78°. After two hours at this temperature, the product to starting material increased to 3:2, and remained that way for three more hours. The oil bath temperature was then increased to 93°. After stirring overnight at this temperature, about a 3:1 ratio of product to starting material was observed. Finally, the toluene was brought to reflux briefly, then the temperature was brought back down to 105°. Final aliquot showed about 4:1 product to starting material ratio, but

a new product was observed as a minor component.

The reaction mixture was cooled and quenched after a total reaction time of 66 hours with saturated ammonium chloride (NH_4Cl) solution. The aqueous layer was extracted twice with toluene. The combined toluene layers were washed twice with 100 mL portions of saturated NaHCO_3 , one time with 100 mL of brine, dried over magnesium sulfate, filtered, rotary evaporated, and placed under vacuum to remove all toluene. This yielded 1.9797 g of a dark brown viscous oil.

Bulb to bulb distillation of the above oil (148° , 1 mm) afforded 0.9407 g of light yellow oil. Flash chromatography of this oil with 12% ethyl acetate/pentane gave the following fractions: 0.2360 g of light yellow oil which appears to be 6-vinyl-7, 8, 9, 10, 11, 12-hexahydrobenzocyclodecene (108): NMR (CCl_4) δ 7.36-6.72 (m, 4H), 6.55 (s, 1H), 6.35 (dd, $J=17, 11$, 1H), 5.23 (dd, $J=17, 1$, 1H), 5.03 (dd, $J=11, 1$, 1H), 2.94-1.96 (m, 4H), 1.92-0.92 (m, 8H); IR (CCl_4) 3130, 3090, 3060, 2960, 2890, 1650, 1620, 1500, 1470, 1450, 1425, 1380, 1360, 1310, 1285, 1120, 1050, 1000, 910, 865, 790, 750, 705 (cm^{-1}); mass spectrum, m/e (rel %) 213 (13.7), 212 (77.7), 155 (54.0), 142 (84.0), 141 (100.0); 0.0469 g of dark yellow oil with same retention time as starting material impurity; 0.0648 g of starting material; 0.0290 g of overlap between starting material and desired product; and 0.2704 g of off-white crystals of desired product (10); mp $58-60.5^\circ$; NMR (CCl_4)

δ 7.50-6.90 (m, 4H), 6.03 (broad dd, J=17, 11, 1H), 5.34 (broad d, J=17, 1H), 5.06 (dd, J=11, 2, 1H), 3.48-2.30 (m, 5H), 2.26-0.92 (m, 10H); IR (CCl₄) 3700-3200, 3580, 3090, 3040, 2950, 2890, 2740, 1970, 1940, 1860, 1660, 1620, 1595, 1510, 1495, 1465, 1435, 1365, 1310, 1290, 1280, 1180, 1150, 1130, 1075, 1015, 985, 940, 920, 885, 815, 805, 765, 740 (cm⁻¹); mass spectrum, m/e 230.167 (calcd for C₁₆H₂₂O: 230.167).

Preparation of 6-vinyl-7,8,9,10,11,12-hexahydro-6(5H)-benzocyclodecenol (10) in ether

Vinyl magnesium bromide was prepared in the usual way from 2.774 g (114.0 mmol) of magnesium and 7.2 mL (100 mmol) of vinyl bromide (Aldrich) in a total of 75 mL of THF. The Grignard reagent was transferred via syringe to a 250 mL 3-necked round bottom flask, and all the THF was removed under vacuum overnight as described in the previous experiment.

The vacuum was replaced by a nitrogen atmosphere, and the apparatus was equipped with a reflux condenser and 25 mL addition funnel. A 75 mL portion of anhydrous ether was added to the solid Grignard reagent and brought to reflux (the solid Grignard reagent is not very soluble in ether). Next, 4.03 g (19.9 mmol) of β-benzocyclodecenone (107) was dissolved in 50 mL of dry ether and added over a 2 1/2 hour period to the refluxing mixture. Aliquots taken at 30

minutes, 2 1/2 hours, five hours, and seven hours showed no significant change in reaction from first aliquot. The reaction mixture was cooled to room temperature and then quenched cautiously with saturated ammonium chloride solution.

Water was added to help dissolve the inorganic salts, and the cloudy aqueous layer was extracted three times with 50 mL portions of ether. The combined ether layers were washed two times with 75 mL portions of saturated ammonium chloride, one time with 75 mL of saturated NaHCO_3 , and one time with 75 mL of brine. The combined ether layers were dried over magnesium sulfate, filtered, and rotary evaporated to afford 3.97 g of viscous yellow oil.

The cloudy aqueous layer from above was treated with 10% sulfuric acid which caused the aqueous layer to turn clear. This acidic layer was extracted with four portions of 20 mL ether. The ether extracts were washed two times with 20 mL portions of saturated NaHCO_3 , and one time with 20 mL of brine. Drying over magnesium sulfate, filtering, and rotary evaporating afforded 0.38 g of yellow viscous oil. The total amount of organic material recovered was 4.35 g. GLC (column C) analysis indicated that the desired product predominated slightly over starting material, and revealed another minor product close in retention time to starting material.

Bulb to bulb distillation (140° , 1 mm) of 1.532 g of the yellow viscous oil afforded 1.420 g of very light yellow oil and 0.098 g of

brown tar which remained in the pot.

Flash chromatography of the 1.420 g of oil obtained above using 10% ethyl acetate/pentane and EM 60 silica gel afforded seven fractions when collected in 150 mm test tubes. Fractions 6-8 (0.0165 g of oil), 9-13 (0.085 g of oil), 27-40 (0.049 g of oil), and 41-58 (0.036 g of brown oil) were not characterized. Fractions 14-17 contained 0.339 g of starting material (107). Fraction 18 contained 0.024 g of mostly starting material and a small amount of desired product. Fractions 19-26 contained 0.781 g of desired product as a white solid. All spectral and analytical data matched that of the previous experiment. The yield of 10 based on recovery of starting material 107 was 65%.

Preparation of 2-methoxy-6-vinyl-7,8,9,10,11,12-hexahydro-6(5H)-benzocyclodecenol (12)

Vinyl magnesium bromide was prepared in the usual way, and approximately 56.2 mmol of the Grignard/THF was added to a 250 mL three-necked flask. The THF was removed under vacuum as previously described and replaced by 75 mL of ether. Next, 2.502 g (10.8 mmol) of ketone 106 was dissolved in 50 mL of anhydrous ether and added slowly over five hours. The reaction was followed by GLC (column C) analysis of aliquots. The first aliquot taken at 4.5 hours of reaction time indicated approximately a 1:3 product to starting material ratio when analyzed by GLC. GLC analysis of an aliquot taken after stirring overnight at room temperature showed no significant change of

the product/starting material ratio. The mixture was brought to reflux and stirred for 4.5 hours. GLC analysis of an aliquot indicated no change in the reaction mixture. The mixture was cooled to room temperature and quenched with saturated NH_4Cl , and the aqueous layer was extracted twice with 50 mL portions of ether. The combined ether layers were worked up as usual affording 2.821 g of yellow oil.

The 2.821 g of ketone/alcohol mixture obtained above was dissolved in 50 mL of ether and added to ca. 49.2 mmol of vinyl Grignard (freshly prepared as usual and removed of all THF) in 75 mL of refluxing anhydrous ether. Total addition time was 1.75 hours. The mixture was allowed to stir at reflux for seven hours and then at room temperature overnight (13 hours). The mixture was quenched with saturated NH_4Cl and the aqueous layer was extracted with ether. The combined ether layers were worked up as usual to yield 2.671 g of viscous brownish yellow oil. Kugelrohr distillation afforded 1.877 g of viscous yellow oil, with 0.746 g of brown tar-like material remaining in the pot. GLC analysis of the yellow oil indicated that the desired product predominated over starting material in ca. a 5:1 ratio, with some minor impurities present.

Flash chromatography of the above mixture with 10% EtOAc/pentane on EM 60 silica gel afforded six fractions when collected in 150 mm test tubes. Fractions 1-13 yielded 0.129 g of uncharacterized oil, 14-21 yielded 0.110 g of oil which consisted mainly of an

uncharacterized component and some ketone 106 by GLC analysis, 22-27 consisted of 0.156 g of white crystalline 106, 28-31 consisted of 0.073 g of 106 and 12, and 33-51 consisted of 1.089 g of 97% pure 12 as a viscous oil that later crystallized. Fractions 52-54 and the material that eluted with 100% EtOAc consisted of 0.268 g of light brown oil which contained some 12 but consisted mainly of uncharacterized material of long retention time by GLC analysis.

The 1.089 g fraction of 97% pure 12 was recrystallized twice from hexane to yield 0.680 g of pure white crystals, mp. 54-55°. NMR (CCl₄) δ 7.22 (broad d, 1H), 6.63 (m, 2H), 6.01 (dd, J=18, 10, 1H), 5.33 (broad d, J=18, 1H), 5.05 (dd, J=10, 2, 1H), 3.75 (s, 3H), 3.28-1.06 (broad m, 15H); IR (neat) 3650-3150, 3095, 3000, 2910, 2850, 2795, 2695, 1640, 1605, 1570, 1495, 1475, 1450, 1415, 1335, 1280, 1245, 1200, 1165, 1150, 1120, 1030, 985, 953, 910, 855, 840, 810, 790, 750, 715 (cm⁻¹); mass spectrum, m/e (rel %), 261 (10.0), 260 (91.1), 242 (25.1), 136 (100.0), 135 (88.5), m/e 260.177 (calcd. for C₁₇H₂₄O₂: 260.178).

The mother liquor from the recrystallizations consisted of 0.409 g of 95% pure 12. The overall yield based on recovered starting material was 40.2%.

Preparation of 3-methoxy-6-vinyl-7,8,9,10,11,12-hexahydro-6(5H)-benzocyclodecenol (11)

The title compound was prepared essentially as described in the

previous experiment. A 1.512 g (6.52 mmol) portion of ketone 117 was dissolved in 40 mL of anhydrous ether and added to 48 mmol of vinyl magnesium bromide in 75 mL of ether. Total time of addition was five hours. The reaction was followed by GLC (column C) analysis of aliquots. The first aliquot taken after 4.5 hours showed ca. a 3:1 starting material to product ratio. GLC analysis of an aliquot taken after stirring overnight (16 hours total), showed a 51:49 starting material to product ratio. Bringing the mixture to reflux for 4.5 hours gave no improvement in the product ratio. The mixture was quenched with saturated NH_4Cl and worked up as usual to yield 1.675 g of yellow oil.

The 1.675 g of ketone/alcohol mixture obtained above was taken up in 35 mL of dry ether and added to 39 mmol of vinyl magnesium bromide in 75 mL of refluxing ether over a period of 1.5 hours. The mixture was allowed to stir at reflux for seven hours and then overnight (13.5 hours) at ambient temperature. The mixture was quenched with NH_4Cl and worked up as usual to yield 1.642 g of viscous yellow oil. Kugelrohr distillation (145°, 1 mm) afforded 1.337 g of slightly yellow viscous oil. The pot contained 0.226 g of brown tar-like residue. GLC analysis of the yellow oil indicated that the product to starting material ratio was ca. 17:3 with some minor impurities present.

Flash chromatography of 1.308 g of the above mixture with 10% EtOAc/pentane on EM 60 silica gel afforded seven fractions when collected in 150 mm test tubes. Fractions 1-10 (0.067 g of light yellow

oil), 11-14 (0.036 g of viscous yellow oil), 15-18 (0.047 g of yellow oil), and 40-54 and the material that came off with 100% EtOAc (0.326 g of brown viscous oil) were not fully characterized. Fractions 19-24 contained 0.060 g of 117. Fractions 25 and 26 contained a mixture of 117 and 11. Fractions 27-40 contained 0.715 g of a viscous opaque oil that was 94% pure 11 by GLC analysis. Attempted recrystallization from hexane resulted in 0.384 g of this material oiling out of solution: NMR (CCl_4) δ 7.06-6.50 (m, 3H), 5.98 (dd, $J=18, 10$, 1H), 5.31 (broad d, $J=18$, 1H), 5.02 (d, $J=10$, 1H), 3.70 (s, 3H), 3.16-2.22 (m, 5H), 2.09-1.02 (m, 10H); IR (neat) 3650-3150, 3095, 3000, 2910, 2850, 2755, 2695, 1640, 1605, 1570, 1495, 1475, 1450, 1415, 1345, 1315, 1250, 1190, 1155, 1110, 1040, 990, 960, 915, 865, 815, 725 (cm^{-1}); mass spectrum, m/e (rel %), 261 (3.1) 260 (27.1), 242 (9.4), 136 (49.0), 135 (100.0), m/e 260.178 (calcd. for $\text{C}_{17}\text{H}_{24}\text{O}_2$: 260.178).

The mother liquor from the attempted recrystallization contained 0.331 g of ca. 90% pure 11. The overall yield based on recovered 117 was 41.3%.

Rearrangement of the potassium salt of 6-vinyl-7,8,9,10,11,12-hexahydro-6(5H)-benzocyclodecenol (10) in HMPA to 5,6,9,10,11,12,13,14-octahydro-8(7H)-benzocyclododecenone (13)

A 50 mL conical shaped flask was charged with 0.792 g (4.88 mmol) of 24.7% potassium hydride in oil (Ventron), and the KH was washed five times with five mL portions of hexane to remove the oil.

A 20 mL portion of HMPA was then added and the mixture cooled to 0° in an ice bath. Next, 0.284 g (1.23 mmol) of the alcohol 10 was dissolved (with some difficulty) in five mL of HMPA and added dropwise via syringe to the cooled KH/HMPA. A solid formed on the sides of the flask which disappeared upon removal of the ice bath, and the mixture took on an orange-red color. The mixture was stirred for 40 minutes, and was then allowed to sit for six hours, at which time it was again cooled in an ice bath. The cooled reaction mixture was quenched cautiously with two mL of water, which caused the solution to turn pale yellow. The mixture was made weakly acidic (ca. pH 6) with one mL of 10% sulfuric acid which caused the solution to turn colorless. About 60 mL of water were added, and this aqueous layer was extracted five times with 25 mL portions of ether. The combined ether layers were washed five times with 30 mL portions of water, one time with 30 mL of 5% NaOH, two times with 30 mL portions of saturated NH_4Cl , and one time with 30 mL of brine. After drying over magnesium sulfate and filtering, rotary evaporating gave 0.229 g (80.6% material yield) of yellow oil. Kugelrohr distillation (130°, 1 mm) yielded 0.198 g (69.7%) of yellow oil: NMR (CCl_4) δ 7.02 (s, 4H), 3.04-1.88 (m, 10H), 1.84-0.96 (m, 8H); IR (CCl_4) 3070, 3025, 2940, 2870, 1715, 1605, 1495, 1465, 1450, 1365, 1255, 1220, 1050, 825 (cm^{-1}); mass spectrum, m/e 230.165 (calcd for $\text{C}_{16}\text{H}_{22}\text{O}$: 230.167).

Rearrangement of the potassium salt of 2-methoxy-6-vinyl-7,8,9,10,11,12-hexahydro-6(5H)-benzocyclodecenol (12) in HMPA to 2-methoxy-5,6,9,10,11,12,13,14-octahydro-8(7H)-benzocyclododecenone (15)

A 200 mL round bottom flask was charged with 2.60 g of 24.7% potassium hydride in oil (16.0 mmol), and the KH/oil was washed five times with hexane as previously described. A 50 mL portion of HMPA was added to the KH. Next, 0.642 g (2.46 mmol) of the alcohol 12 was taken up in three 10 mL portions of HMPA (all of the alcohol did not dissolve in the first 10 mL portion of HMPA) and added slowly to the KH/HMPA. The reaction mixture took on a dark brown color. After stirring (magnetic stirrer) for eight hours at room temperature, an aliquot showed no starting material by GLC analysis (column C). The mixture was quenched cautiously with water, and the aqueous layer was extracted five times with 60 mL portions of ether. The combined ether extracts were washed five times with 80 mL portions of water, one time with 80 mL of saturated NaHCO_3 , and one time with 80 mL of brine. After drying over magnesium sulfate and filtering, rotary evaporation gave 0.604 g (94.0% material yield) of an orangish solid. GLC (column C) analysis of this solid indicated it was 96% pure 15. Preparative GLC (column D) gave a white solid, mp 67-68°, for analysis. NMR (CCl_4) δ 6.99 (d, $J=9$, 1H), 6.68-6.49 (m, 2H), 3.71 (s, 3H), 2.68-2.18 (m, 8H), 2.16-1.04 (m, 10H); IR (CCl_4) 3060, 2940, 2860, 1715, 1610, 1580, 1505, 1470, 1445, 1365, 1330, 1290, 1250,

1205, 1160, 1100, 1040, 995, 985, 855 (cm^{-1}); mass spectrum, m/e 260.179 (calcd. for $\text{C}_{17}\text{H}_{24}\text{O}_2$: 260.178).

Rearrangement of the potassium salt of 6-vinyl-7,8,9,10,11,12-hexahydro-6(5H)-benzocyclodecenol (10) in HMPA, followed by attempted trapping of the enolate with trimethylsilyl chloride

A 50 mL conical shaped flask under nitrogen atmosphere was charged with 0.373 g (2.30 mmol) of 24.7% KH (Ventron) and the KH was washed as usual with hexane. HMPA (15 mL) was added, and the mixture was cooled in an ice bath. Next, 0.240 g (1.04 mmol) of the alcohol 10 was dissolved in 10 mL of HMPA and added slowly to the KH/HMPA mixture via syringe. The mixture took on a bright orange color. The mixture was stirred for 10 hours, then cooled in an ice bath, and 0.5 mL (3.8 mmol) of trimethylsilyl chloride (TMSCl) was added in 0.1 mL aliquots. The solution went from orange-brown to pale yellow. The mixture was poured into a separatory funnel and washed three times with 40 mL portions of cold hexane. The combined hexane layers were washed eight times with 20 mL portions of cold 5% NaHCO_3 , dried over magnesium sulfate, filtered, and rotary evaporated, yielding 0.141 g of light yellow oil which contained no vinyl or trimethylsilyl protons in the NMR. All spectral and analytical data were identical to the corresponding data for 13. Other attempts to trap the enolates prepared similarly to that above were also unsuccessful. Adding dioxane (used by Hudrlik and Takacs (63) for trapping

of enolates with TMSCl) to the mixture before quenching with TMSCl failed to trap any enolate. Varying the workup procedure failed to alter the results. Attempted trapping with *t*-butyldimethylsilyl chloride also failed. Trapping of the enolate with freshly distilled acetic anhydride appeared to be partially successful (ca. 50% trapping by GLC analysis (column C)) as evidenced by a carbonyl band at 1760 cm^{-1} in the IR and a singlet at $\delta\ 2.31$ in the NMR. The vinylic proton of the enol-acetate was not clearly established, however.

Preparation of 6-trimethylsilyloxy-6(5H)-vinyl-7,8,9,10,11,12-hexahydrobenzocyclodecene (116)

A dry 10 mL round bottom flask under nitrogen atmosphere was charged with 0.0935 g (0.4065 mmol) of the alcohol 10 and three mL of the silylation formula of Sweeley, Bentley, Makita and Wells (64) consisting of trimethylsilyl chloride, hexamethyldisilazane, and pyridine in a 1:2:10 ratio. The mixture was allowed to stir for 23 hours, and was then taken up in 20 mL of hexane. The hexane layer was washed two times with 75 mL portions of water, two times with 15 mL portions of 10% H_2SO_4 , one time with 15 mL saturated NaHCO_3 , and dried over magnesium sulfate. After filtering and rotoevaporating, 0.0848 g of a viscous light yellow oil was isolated. The NMR spectrum of this oil looked very similar to starting material with the exception of the presence of trimethylsilyl protons. This oil was used without

further purification in the pyrolysis step. An attempt to prepare the t-butyldimethylsilyl ether according to the procedure of Olah, Gupta, Narang, and Malhatra (83) was unsuccessful.

Pyrolysis of 6-trimethylsilyloxy-6(5H)-vinyl-7,8,9,10,11,12-hexahydrobenzocyclodecene (116)

A five mL ampoule which had been washed with acetone, distilled water, 28% ammonium hydroxide, dried overnight in a 130° oven, and cooled in a desiccator was charged with 20 μ L of the TMS ether 116. The ampoule was placed under a 0.2 mm vacuum for five hours and then sealed. The ampoule was placed in a preheated 310° oven. The temperature of the oven quickly dropped to 260°, but gradually warmed up to 313° after one hour and 20 minutes. The temperature was adjusted to 306° for another two hours, and the sample was then allowed to cool to ambient temperature.

The ampoule was broken, and the sample was taken up in CCl_4 for NMR analysis. The NMR spectrum was weak, but the vinyl protons of the starting material had disappeared. However, it was difficult to determine positively that any of the desired TMS-enol derivative had been formed. The sample was stripped of the CCl_4 and stirred at 90° (oil bath) for 3.5 hours in a solution of pyridine, water, and hydrochloric acid in a 100:10:1 ratio to hydrolyze any TMS enol ether formed during pyrolysis. Extraction with five mL of ether, and workup with two portions of two mL of 10% H_2SO_4 , two mL of

saturated NaHCO_3 , and two mL of brine, gave 0.0122 g of light colored oil after drying over magnesium sulfate, filtering, and rotary evaporating. The spectra of this oil matched the spectra for 13.

In another experiment, 0.054 g of the TMS ether was pyrolyzed for exactly three hours between 290° and 305° . The NMR spectrum looked much the same as that above. GLC (column C) analysis of the product showed a mixture of at least seven products, with two peaks predominating. GLC analysis with a known weight of a standard indicated that the total material yield was ca. 6%.

Preparation and trapping of the potassium enolate of cyclododecanone in HMPA

A 50 mL conical shaped flask equipped with nitrogen inlet and magnetic stirrer was charged with 1.07 g (6.60 mmol) of 24.7% KH in oil (Ventron). The KH was washed as usual with hexane to remove the oil. Next, 10 mL of HMPA was added, followed by 1.02 g (5.48 mmol) of 98% cyclododecanone (Aldrich) dissolved in six mL of HMPA. The mixture took on a yellow color and was stirred for four hours at ambient temperature.

A. Trapping with chloromethyl methyl ether: A 25 mL flask under nitrogen atmosphere was charged with four mL (approx. 1.66 mmol) of the HMPA solution of cyclododecanone enolate prepared above. Next, 0.16 mL (ca. 1.25 molar excess based on KH) of

chloromethyl methyl ether (Aldrich, freshly distilled) was added slowly via syringe. The yellow solution became clear, and the mixture was allowed to stir for four hours, and was then poured into a separatory funnel containing 10 mL of ice cold saturated NaHCO_3 . Ten mL of ice cold water was added to the separatory funnel, and the aqueous layer was extracted four times with 10 mL portions of ether. The combined ether layers were washed four times with 10 mL portions of cold water and one time with brine, dried over magnesium sulfate, filtered, and rotary evaporated, yielding 0.209 g of viscous almost clear oil. GLC (column C) analysis showed the major fraction to be cyclododecanone (48.4%), with two peaks of longer retention time that partially overlapped of 9.8% and 41.8% respectively. The NMR spectrum appears to be a mixture of cyclododecanone and the desired enol ether.

B. Trapping with trimethylsilyl chloride: A 25 mL flask equipped as above was charged with four mL of the cyclododecanone enolate solution, and 0.26 mL (ca. 1.25 excess based on KH) of freshly distilled TMSCl was added slowly to the enolate via syringe. The mixture was allowed to stir for 2.5 hours, and then 0.29 mL (1 equiv. based on TMSCl) of triethylamine (Et_3N) was added. The mixture was poured into 15 mL of cold pentane, and the pentane was washed four times with cold water, one time with saturated NaHCO_3 , and one time with brine. After drying over magnesium sulfate,

filtering, and rotary evaporating, 0.160 g of crystals identical to cyclododecanone by GLC analysis and NMR spectra was isolated.

Another attempt at trapping the enolate of cyclododecanone with TMSCl was partially successful when freshly distilled TMSCl from a new bottle was used. The major component of the reaction mixture was still cyclododecanone, but some vinyl and TMS protons were observed in the NMR spectrum.

C. Trapping with benzyl chloride: To eight mL of the cyclododecanone enolate prepared above was added 0.48 mL (ca. 1.25 excess based on KH) of benzyl chloride. The mixture was allowed to stir overnight. After normal workup, 0.686 g of cyclododecanone was isolated.

D. Trapping with methyl tosylate (MeOTs): A solution of eight mL of cyclododecanone enolate prepared as above from 1.04 g of 24.7% KH and 1.00 g of cyclododecanone in 10 mL of HMPA was cooled to 0° in an ice bath. Next, 0.72 mL (ca. 1.25 excess based on KH) of freshly distilled (134-135°, 3.5 mm) methyl tosylate was added. This mixture was allowed to stir for 27 hours, and then poured into a separatory funnel containing cold saturated NaHCO_3 . The aqueous layer was extracted with four 60 mL portions of cold ether, and the combined ether layers were washed four times with 60 mL portions of cold water, one time with saturated NaHCO_3 , and one time with brine. Drying over magnesium sulfate, filtering, and rotary

evaporation yielded 0.659 g of oil which contained a fair amount of MeOTs. The mixture was taken up in ether and washed two times with Et_3N . After workup of the ether layer, 0.278 g of a dark yellow oil was isolated, which appeared to be ca. 60% methyl enol ether and 40% cyclododecanone by GLC (column C) analysis and as evidenced by the methyl singlet at δ 3.41 and a broad-triplet at δ 4.27 (vinyl proton).

Preparation of 2-hydroxy-5, 6, 9, 10, 11, 12, 13, 14-octahydro-8(7H)-Benzocyclododecenone (111)

A 10 mL round bottom flask was charged with 0.0296 (0.114 mmol) of the ketone 15 and fitted with a reflux condenser and nitrogen inlet. One mL of 48% hydrobromic acid and one mL of glacial acetic acid were added, and the mixture was stirred at reflux (magnetic stirrer) for five hours. The mixture was then allowed to cool to room temperature. A few crystals were observed on the side of the flask upon cooling. The reaction mixture was worked up by neutralizing with saturated NaHCO_3 , extracting with ether, and washing the ether layer two times with saturated NaHCO_3 , and one time with brine. After drying over magnesium sulfate and filtering, rotary evaporation gave 0.0199 g (71% material yield) of light yellow crystals: NMR (CDCl_3) δ 7.06 (d, $J=9$, 1H), 6.72-6.59 (m, 2H), 5.25 (broad s, 1H), 2.80-2.27 (m, 8H), 2.04-1.05 (m, 10H); IR (Neat) 3700-3100, 3040, 2950, 2875, 2705, 1705, 1620, 1595, 1510, 1475, 1455, 1375, 1355,

1290, 1250, 1170, 1135, 1115, 1035, 970, 920, 880, 830, 740 (cm^{-1}); mass spectrum, m/e (rel %) 246 (100.0), 213 (24.6), 173 (26.4), 159 (51.7).

Preparation of 2-prop-2-yn-1-yloxy-tetrahydropyran

The title compound was prepared according to the procedure of Henbest, Jones, and Walls (67). A 100 mL round bottom flask was charged with 13.7 mL (150 mmol) of dihydropyran (Aldrich) and 8.70 mL (149 mmol) of propargyl alcohol (Aldrich). Next, 0.08 mL of freshly distilled POCl_3 was added to the stirred mixture, and the mixture rapidly became warm and was moderated with an ice bath for the first ten minutes, and then allowed to stir at ambient temperature for two hours. The reaction was quenched with 20 mL of 10% potassium hydroxide and taken up in 60 mL of ether. The aqueous and organic layers were separated, and the aqueous layer was extracted two times with 20 mL portions of ether. The combined ether layers were washed one time with 40 mL of brine, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation to yield 17.5 g of clear, pine-smelling oil. This oil was distilled under reduced pressure (water aspirator) through a 15 cm vigreux column. The bulk of the material (16.4 g, 78%) came over between 76-80° (Lit. 78°/25 mm): NMR (CCl_4) δ 4.83 (broad t, 1H), 4.23 (d, $J=3$, 2H), 3.67 (m, 2H), 2.40 (t, $J=3$, 1H), 1.8-1.3 (m, 6H); IR (neat)

3260, 2920, 2850, 2830, 2100, 1435, 1380, 1250, 1190, 1175, 1110, 1070, 1040, 1015, 920, 890, 855, 800 (cm^{-1}).

Preparation of 6-[3'-(2-tetrahydropyranyloxy)-1-propynyl]-7,8,9,10,11,12-hexahydro-6(5H)-Benzocyclodecenol (124)

A 250 mL three-necked round bottom flask equipped with nitrogen atmosphere, magnetic stirrer, reflux condenser, and 25 mL addition funnel was charged with 1.913 g (79.4 mmol) of magnesium turnings. The magnesium was dried with a hot air gun while sweeping nitrogen over the turnings. A volume of 50 mL of anhydrous ether was added to the magnesium, and 6.5 mL (9.51 g, 87.3 mmol, 1.1 excess) of ethyl bromide (Baker, freshly distilled) and 10 mL of dry ether was added to the addition funnel. About three mL of the ethyl bromide/ether solution was added to the stirred magnesium solution, and within three to four minutes, a mild reaction was observed. The remainder of the ethyl bromide solution was dripped into the reaction pot at a rate so as to maintain a moderate reaction. An extra 10 mL of ether were used to rinse all of the bromoethane into the reaction mixture. The mixture was allowed to stir for one hour after the addition was complete, at which time all of the magnesium had been consumed, and the mixture had taken on a gray-black color.

Next, 11.12 g (79.5 mmol) of 2-prop-2'-yn-1-yloxy-tetrahydropyran (prepared as described above) in 15 mL of ether was added over

15 minutes. The solution gradually turned lighter during the addition, and within a few minutes a white precipitate was observed. An additional 25 mL of ether was added and the mixture was allowed to stir for one hour.

The mixture was brought to reflux and then 4.256 g (20.65 mmol) of 98% pure ketone 107 in 50 mL of ether was added over one hour. The mixture was allowed to stir at reflux for six hours, at which time GLC (column C) analysis of an aliquot showed starting ketone present. The mixture was allowed to stir at room temperature overnight (12 hours), and then quenched cautiously with saturated NH_4Cl . The organic and aqueous layers were separated, and the aqueous layer extracted two times with 100 mL portions of ether. The combined organic layers were washed one time with 100 mL of saturated NH_4Cl , one time with 100 mL of saturated NaHCO_3 , and one time with 100 mL of brine. Drying over magnesium sulfate, filtering, and rotary evaporating, followed by Kugelrohr distillation up to 95° (1 mm) to remove all excess tetrahydropyran derivative, afforded 6.178 g of a viscous gummy brown material. NMR and IR analysis of this crude reaction product indicated that the desired product had been formed, although it contained ca. 30% starting material in the NMR spectrum (Note: The same reaction carried out on a smaller scale (0.084 g of ketone), utilizing the same conditions went essentially to completion). Attempts to purify this mixture by recrystallization were

unsuccessful, so the mixture was used without further purification in the next experiment. Pertinent spectral data: NMR (CDCl_3) δ 7.47 (new peak), 4.91 (broad s), 4.36 (s); IR (neat) 3600-3140, 2230, carbonyl band of starting material is diminished.

Preparation of 6-(3-hydroxy-1-propynyl)-7,8,9,10,11,12-hexahydro-6(5H)-Benzocyclodecenol (120)

The title compound was prepared by hydrolysis of crude 124 (from the experiment above) according to the procedure of Karpf and Dreiding (33c). All of the crude reaction product from above was taken up in 20 mL of THF, 10 mL of water, and 10 mL of HOAc in a 100 mL round bottom flask, and refluxed with stirring for five hours. The reaction mixture was concentrated by rotary evaporation, leaving a gummy brown mass. Repeated attempts to recrystallize this material were unsuccessful, so the material was taken up in ether and washed two times with saturated NaHCO_3 and one time with brine. All volatile material was removed by rotary evaporation and Kugelrohr distillation up to 98° (1 mm), leaving a very viscous brown oil. The NMR spectrum of this crude reaction product showed loss of the tetrahydropyran protecting group. Repeated attempts to recrystallize the material at this stage were also unsuccessful. The material was again Kugelrohr distilled up to 110° (1 mm), and 0.562 g of oil was collected which was 68.9% 107 by GLC (column C) analysis. The pot contained

4. 805 g of a dark brown immobile wax-like material. This material was used without further purification in the next experiment.

Preparation of 8,3-benzobicyclo[8.3.0]-tridec-1(10),2-dien-11-one (8)

The title compound was prepared by cyclization of 4.478 g of crude 120 (from experiment above) according to a modified procedure of Nazaki, Shimada, and Hiyama (33g). The crude starting material was taken up in 25 mL of methanol (MeOH) and cooled in an ice bath. Next, 25 mL of concentrated H_2SO_4 was added with stirring over one hour and 40 minutes. The mixture turned dark brown and was allowed to warm to room temperature. An aliquot taken after 1.5 hours reaction time showed incomplete reaction by GLC (column D) analysis, so the mixture was cooled to 0° again, and an additional 10 mL of MeOH, followed by 10 mL of concentrated H_2SO_4 was added, and the mixture was allowed to warm to room temperature. After an additional 1.5 hours an aliquot still showed incomplete reaction, so an additional five mL of concentrated H_2SO_4 was added to the cooled solution. Another aliquot after one hour still showed incomplete reaction, so the mixture was warmed to 45° (oil bath). An additional four hours at this temperature showed essentially complete reaction by GLC analysis.

The reaction mixture was cooled to room temperature and ca. five g of ice and 20 mL of saturated $NaHCO_3$ were added. The reaction mixture was then extracted four times with 100 mL portions

of ether. A fair amount of black tar-like material that was insoluble in the ether or the aqueous layer was observed. The combined ether layers were washed two times with 120 mL portions of saturated NaHCO_3 , one time with 120 mL brine, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation, which yielded 3.326 g of brown oil. Kugelrohr distillation up to 155° (1 mm) afforded 1.794 g of slightly yellow oily crystals. GLC analysis (column C) of this product indicated that it consisted of 50.72% 8, 43.40% 107, 3.98% of a reaction intermediate (probably 6-(3-hydroxy-1-propynyl)-7, 8, 9, 10, 11, 12-hexahydrobenzocyclodecene (125), and 1.98% of uncharacterized material.

The oily crystals from above were recrystallized from hexane to afford 0.388 g of white crystals which were 97.4% 8 and 2.6% 107 when analyzed by GLC. A 61 mg portion of these crystals was recrystallized twice from hexane to yield 47 mg of pure white crystals for analysis; mp 108° . NMR (CCl_4) δ 7.18 (m, 3H), 6.86 (dd, $J=6, 2$, 1H), 3.62-1.08 (m, 16H); C^{13} NMR (CDCl_3) 209.44, 173.60, 141.57, 138.77, 138.52, 129.19, 128.35, 125.99, 125.92, 34.66, 33.45, 29.48, 29.07, 23.26, 21.98, 20.38, 19.69 (all proton decoupled); IR (CCl_4) 3160, 3105, 2920, 2850, 1695, 1635, 1590, 1480, 1455, 1440, 1355, 1315, 1285, 1265, 1180, 1145, 1005 (cm^{-1}); mass spectrum m/e (rel %), 242 (3.1), 241 (17.9), 240 (26.1), 184 (79.5), 183 (100); m/e 240.150 (calcd for $\text{C}_{17}\text{H}_{20}\text{O}$: 240.151). A second

recrystallization of the mother liquor from the first recrystallization yielded an additional 0.291 g of 96% pure 8. The mother liquor contained 1.115 g of a mixture consisting of 72.7% 107, 13.7% 8, 9.66% of the reaction intermediate 125, and 3.78% uncharacterized material. The implied yield of 8 based on consumed 107 for three steps was 21.8%.

Kinetics Study of the Rearrangement of the Potassium Salts of 6-vinyl-7,8,9,10,11,12-hexahydro-6(5H)-benzocyclodecenol (10), 3-methoxy-6-vinyl-7,8,9,10,11,12-hexahydro-6(5H)-benzocyclodecenol (11), and 2-methoxy-6-vinyl-7,8,9,10,11,12-hexahydro-6(5H)-benzocyclodecenol (12) in HMPA

Vinyl carbinols 10 and 11 were studied at 0° in an insulated ice bath. Vinyl carbinol 12 was studied in an insulated constant temperature oil bath equipped with a powerful mechanical stirrer, a Bailey temperature control, and a thermometer. The temperature of the oil bath was calibrated with a platinum resistance thermometer and maintained at 30.0°C.

In a typical kinetic run a 150 mm test tube was charged with 40-50 mg of the alcohol and one mL of 80% HMPA/THF. The test tube was equipped with a magnetic stirring bar, a rubber septum, and a nitrogen inlet. Another test tube (equipped as above) was charged with ca. 0.70 g of hexane washed potassium hydride and eight mL of 80% HMPA/THF. All of the test tubes were allowed to sit in the appropriate constant temperature bath and equilibrate for one hour. A four mL

portion of the KH-HMPA/THF mixture was injected into the vinyl carbinol mixture and allowed to react. Aliquots (0.1 mL) were removed at appropriate intervals with a syringe equipped with a long, large diameter needle. From trial runs it was established that intervals of two to three minutes were appropriate for sample taking of vinyl carbinols 10 and 11. For vinyl carbinol 12, five minute intervals were appropriate. All samples were immediately quenched upon removal by addition to a few mL of water and acidified with 10% H_2SO_4 . The aqueous layer was then extracted with ether. GLC analysis (column C) of this ether extract gave the relative amount of starting material and product. The kinetic results are summarized on pages 60 to 66.

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