AN ABSTRACT OF THE THESIS OF

Ronald Harry Chiarello for the degree of Doctor of Philosophy

in Chemistry presented on December 19, 1980

Title: EXPLORATORY STUDIES DIRECTED TOWARD THE SYNTHESIS OF LARGE RING HORMONE ANALOGS

Abstract approved: Redacted for privacy

Richard W. Thies

A variety of methodology was examined in exploratory work directed at the synthesis of large ring hormone analogs. In the initial approach several benzocycloalkenones were synthesized via condensation of benzynes with cycloalkanones. Required functionalization of the aromatic ring was accomplished either by electrophillic substitution of the benzocycloalkenone or the inclusion of an appropriate functional group on the benzyne. Methods examined for ring expansion of the intermediate benzocycloalkenones to the required thirteen membered ring included procedures leading toward cyclopropylcarbinyl rearrangements, Tiffeneau-Demyanov rearrangements, and ring expansion via cycloaddition of enamines with ethyl propiolate. In series of studies not directed toward the synthesis of the target compound, the reaction of a series of benzocycloalkyl oxirenes with lithium diisopropylamide was examined.

In addition to ring expansion approaches, several routes leading

to proposed ring closure of appropriately substituted benzenes were attempted. First examined was the synthesis of ortho substituted dialkyl benzenes containing terminal carbonyl groups on the alkyl side chains. Reductive coupling of such compounds with Ti(O) would lead to large ring benzocycloalkenes. As part of a scheme calling for ring closure via the acyloin condensation, 7-bromo-4-hydroxyheptanoic acid γ-lactone was synthesized and the synthesis of 3-(2-carboethoxy-5-methoxyphenyl) propanol was examined.

In related work, the mechanism of ring expansion via an anionic [1, 3] sigmatropic shift was examined. Also studied was the feasibility of the synthesis of zearalenone analogs via condensation of 3, 5-dimethoxybenzyne with cycloalkanones.

Exploratory Studies Directed Toward the Synthesis of Large Ring Hormone Analogs

by

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in charge of major

Redacted for privacy

Chairman of Department of Chemistry

Redacted for privacy

Dean of Graduate School

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Typed by Opal Grossnicklaus for Ronald Harry Chiarello

To

Ellen, Mom, Dad, Kevin and Michael

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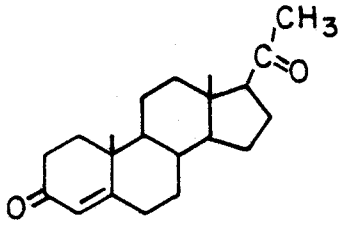
EXPLORATORY STUDIES DIRECTED TOWARD THE SYNTHESIS OF LARGE RING HORMONE ANALOGS

INTRODUCTION

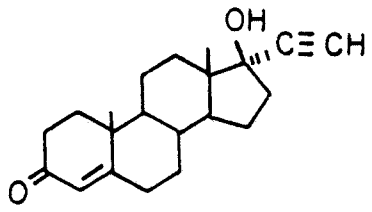
The history of the use of progestational and estrogenic compounds as antiovulation agents has been the subject of review by several authors (1). In preliminary work in the field, Beard and Prenot (1877-1898) postulated that a functional corpus luteum prevents ovulation in most mammalian species. Conformation of this theory by Loeb (1911-1925), followed by the demonstration by Corner and Allen (1928) that a hormone present in the corpus luteum was responsible for this activity, led to the isolation of progesterone 1 in 1934 by Allen and Wintersteiner; Butenandt, Westphal and Holweg; Hartman and Wettstein; and Stolta, Rushig and Fels.



1

Two years later Seyle, Brown, and Collip showed the daily injections of progesterone inhibited estrus in rats, thus opening the way for vast research in the area of antifertility drugs. The first

fruit of this labor came in 1938 with the synthesis by Inhoffen of the first orally active progestin, estisterone 2. Later that year Inhoffen



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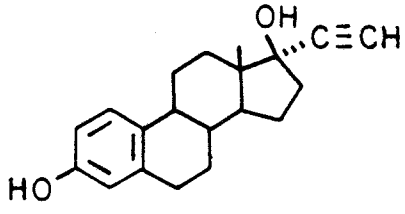


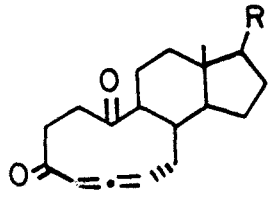
3

and Holweg also reported the first synthesis of an orally active estrogen, ethynyl estradiol 3. It was the availability of these orally active hormone analogs that led to the concept, developed by Sturgis and Allbright (1945), of producing anovulatory cycles by the administration of estrogen followed by doses of estrogen with progesterone.

In the years following this initial work a wide variety of structural modifications have been undertaken in hope of producing increased or modified activity. As conventional theory holds that a rigid steroid ring system is required for biological activity (2), most of the analogs examined contain an intact steroid nucleus. However, of more interest to the present work are various secosteroids where ring scission is the major structural modification.

The validity of the above mentioned rigid nucleus requirement has recently been questioned by the demonstration of biological activity in certain secosteroids. Apart from previously reported inhibition of

Δ^5-3-ketosteroid isomerase (3) and Δ^4-5α reductase (4, 5) activity, the 5, 10-secosteroids, 4 and 5, have been shown by Voight, Castro, Covey and Robinson (6) to exhibit strong antiandrogenic activity. However, it should be noted that the presence of the allene structure

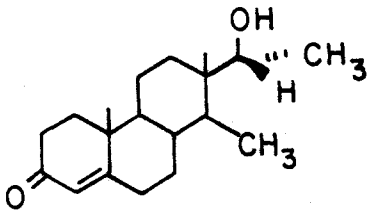


4, R = O ; 5, R = B-CH $-\overset{\overset{O}{\|}}{C}-$

in these molecules requires them to adopt a conformation very similar to that of a normal steroid.

A more drastic modification of this type is seen in various conformationally mobile secosteroids. Though examples of these compounds are relatively numerous, many were synthesized for reasons other than for biological testing. Compounds reported in this context include 1, 10-seco (7); 2, 5 and 3, 5-seco (8); 4, 5-seco (9); 5, 6-seco (10); 5, 10-seco (11); 8, 9-seco (12); 9, 10-seco (13); 9, 11-seco (14); and 13, 14-seco steroids (15).

There are, however, a significant number of conformationally mobile secosteroids which have been examined for biological activity. In a series of papers by Crossley (16) and Crossley and Dowell (17), the synthesis of several 14, 15-seco (compounds 6 and 7), 10-11-seco (compounds 8 and 9), and 5, 6-seco (compound 10a) progesterones



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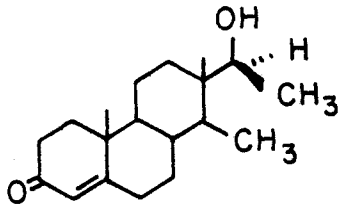

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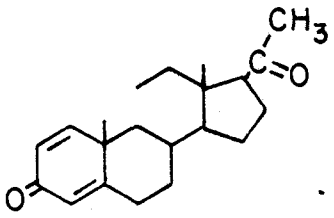

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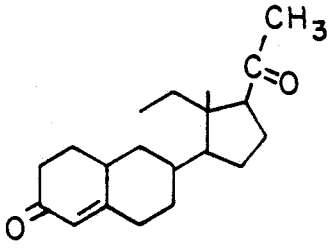

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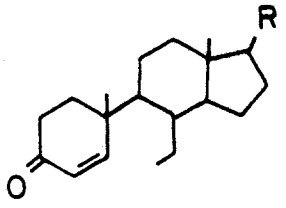


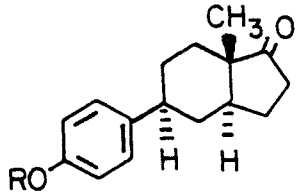
10

a, R = $-\overset{O}{\overset{\|}{C}}-CH_3$; b, R = OAc

has been reported. Of these compounds only 6 and 7 exhibited progestational activity. The extent of this activity was determined to be 1/50th and 1/5th that of progesterone, respectively. Interestingly, it is the compound with the opposite C-17 stereochemistry of progesterone that shows the greater activity. Furthermore, conversion of the inactive 5,6-secoprogesterone 10a to the 5,6-secotestosterone

10b gave a compound that showed 1/40th of the activity of testosterone propionate.

Similar work has also been carried out in the field of secoestrogens. In preliminary studies a number of 5, 8-secoestrogens (compounds 11 and 12) were prepared by Neyyarapally, Gupta, Srivastava,



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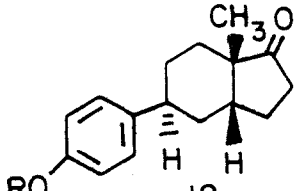
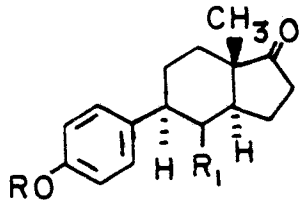


12

a, R = Me ; b, R = H ; c, R = $(CH_2)_2-N$

Bindra, Grover, Setty and Anand (18). Though all of the above compounds failed to prevent pregnancy in rats up to a dose of 20 mg/kg, some showed marked estrogenic activity. In tests measuring the increase in uterine weight in immature overectomized rats, compounds 12a and 12b showed significant activity at the 10 mg/kg level. Hopeful of increasing the activity, the related 5, 7-seco (compounds 13 and 14) and 5, 6-secoestrogens (compounds 15, 16, 17 and 18) were synthesized by Gupta and Anand (19) and Bindra, Neyyarapally, Gupta, Kamboj and Anand (20). Though no report was given of activity testing on compounds 13 and 14, significant antiimplantation and estrogenic activity was shown by compounds 15g, 16g, 17g and 18c.



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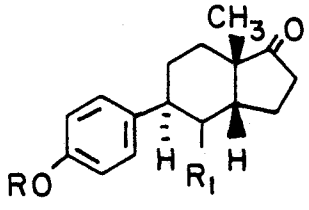
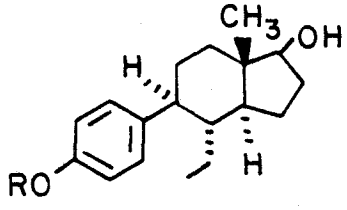


14

a, R = H, R_1 = α-CH_3 ; b, R = H, R_1 = β-CH_3 ;
c, R = CH_3, R_1 = α-CH_3 ; d, R = CH_3, R_1 = β-CH_3



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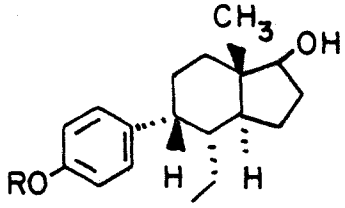

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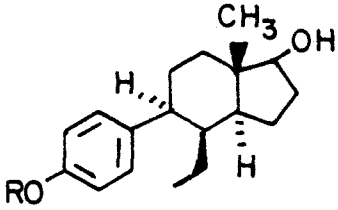

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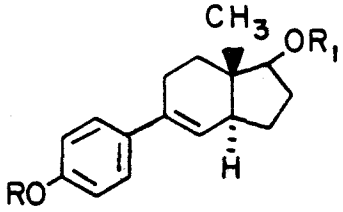
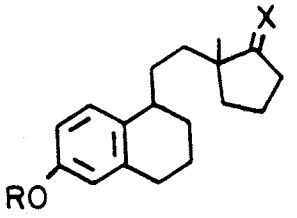


18

a, R_1 = H; b, R = $\overset{O}{\overset{\|}{C}}-CH_3$; c, R = R_1 = H; d, R = CH_3, R_1 = H;
e, R = CH_3, R_1 = $\overset{O}{\overset{\|}{C}}-CH_3$; f, R = CH_3 ; g, R_1 = H

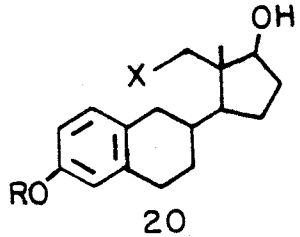
In addition to the above-mentioned ring B seco compounds, a number of ring C secoestrogens have also been examined. The first reported compounds in this class were the 8, 14-secoestrogens (compounds 19a-c) prepared by Ananthanarayanan, Rastogi and Anand (21a). These compounds failed to show any significant antiimplantation activity. However, of the 9, 10-secoestrogens; prepared by Kole,



19

a, R = Me, X = O; b, R = H, X = O;

c, R = H, X = OH; d, R = $(CH_2)_2$–N⟨ ⟩, X = O



20

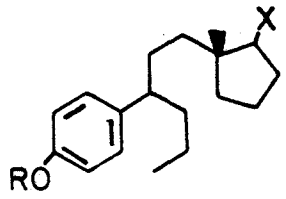
a, R = CH_3, X = CH_3; b, R = H, X = CH_3;

c, R = CH_3, X = $COOCH_3$; d, R = CH_3, X = COOH;

e, R = CH_3, X = CH_2OH; f, R = H, X = CH_2OH

Kamboj and Anand (21b); compounds 20e and 20c were found to be 100% effective in preventing implantation at the 10 mg/kg level, as was compound 20b when administered at 20 mg/kg.

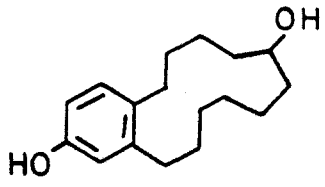
Finally, a single report exists in the literature of the synthesis of disecosteroids. Compounds 21a-e, 5,6, 8, 13-disecoestrogens, were synthesized by Anthanarayanan, Rastogi and Anand (22) and examined for activity. Unfortunately, none of these compounds were found to prevent pregnancy at a dose of 20 mg/kg, nor did they exhibit any noteworthy estrogenic activity.



21

a, R = H, X=OH; b, R=H, X=O; c, R = $(CH_2)_2$N⟨⟩, X=O

The conspicuous absence of any compounds with severed bonds between the B and C or C and D rings has led several workers in our laboratories to examine methodology necessary for the synthesis of such compounds. Specifically, these studies were directed toward the synthesis of compound 22, a 8,9,13,14-diseconorestrogen, by ring

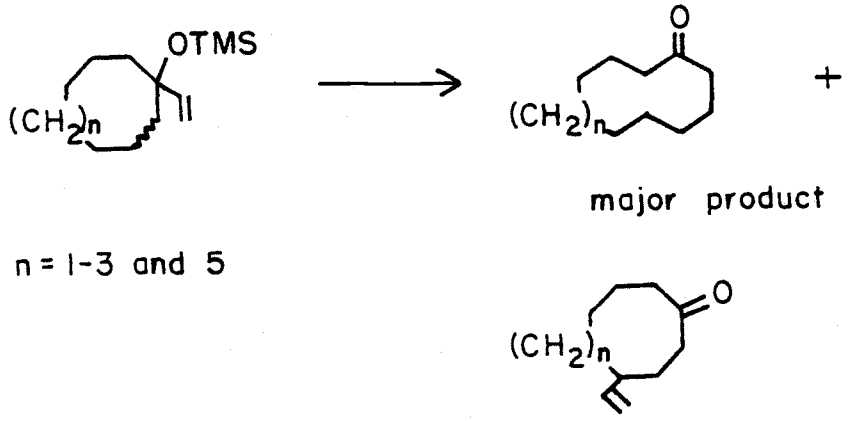


22

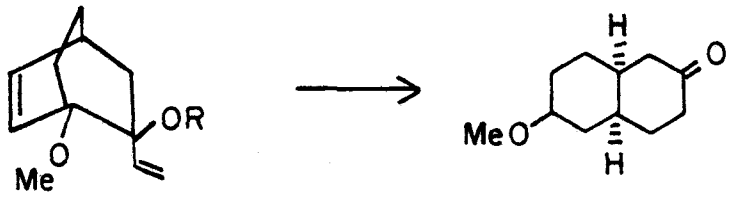
expansion of benzofused cyclic ketones.

In an early series of papers, Thies and coworkers (23-26) reported the use of the Siloxy Cope rearrangement (Scheme 1) as an effective 2 carbon ring expansion. The report by Evans and Golob (27) of enormously enhanced rates for the [3, 3] sigmatropic rearrangement

Scheme I



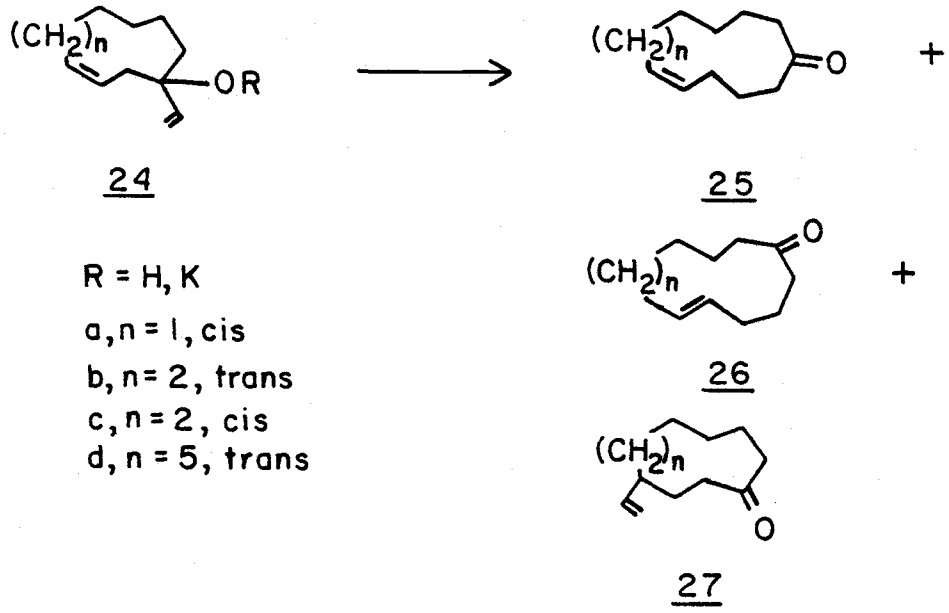
when compound 23 was treated with KH in hexamethyl phosphoramide (HMPA) or tetrahydrofuran (THF), stimulated Thies and Sietz (28)



23 a, R=H; b, R=K

to examine the possibility of using the related anionic [1, 3] sigmatropic shift as a method for ring expansion. Preliminary work in Scheme 2 tested the anionic rearrangement on compounds 24c-d. When alcohols 24a-c were treated with KH in HMPA or dimethoxyethane (DME) or THF with 18:crown:6, the predominant process

Scheme 2



24

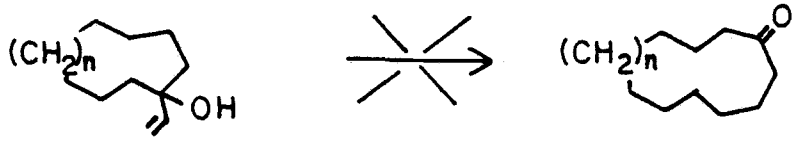
25

26

27

R = H, K
a, n = 1, cis
b, n = 2, trans
c, n = 2, cis
d, n = 5, trans

observed was a 1, 3 shift leading to products 25 and/or 26. Similar treatment of compound 24d, however, effects a [3, 3] sigmatropic shift yielding compound 27d. Further studies of the scope of this reaction demonstrated the necessity of unsaturation homoallylic to the hydroxyl functionality. Treatment of compounds 28c and 28c



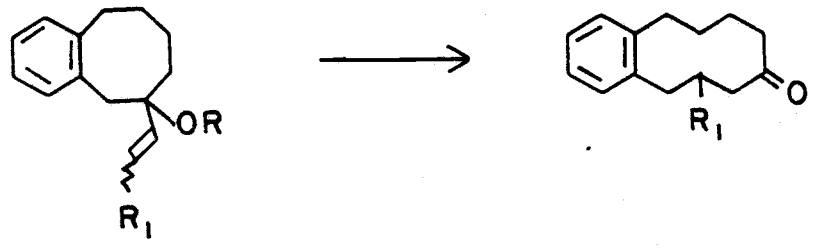
28

a, n = 1; b, n = 2

with KH in HMPA failed to yield any ring expanded product after 4h and 24h respectively.

Having demonstrated the utility of this method in the ring expansion of unsubstituted compounds, attention was turned toward rings expansion in benzo-substituted ring systems (Schemes 3 and 4).

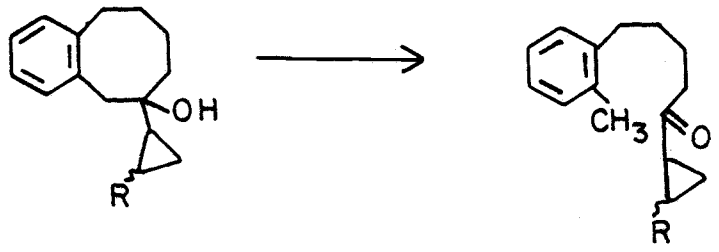
Scheme 3



29 30

a, R = TMS, R_1 = H; b, R = R_1 = H; c, R = H, R_1 = CH=CH_2; d, R = H, R_1 = CH = $CHCH_3$

Scheme 4



31 32

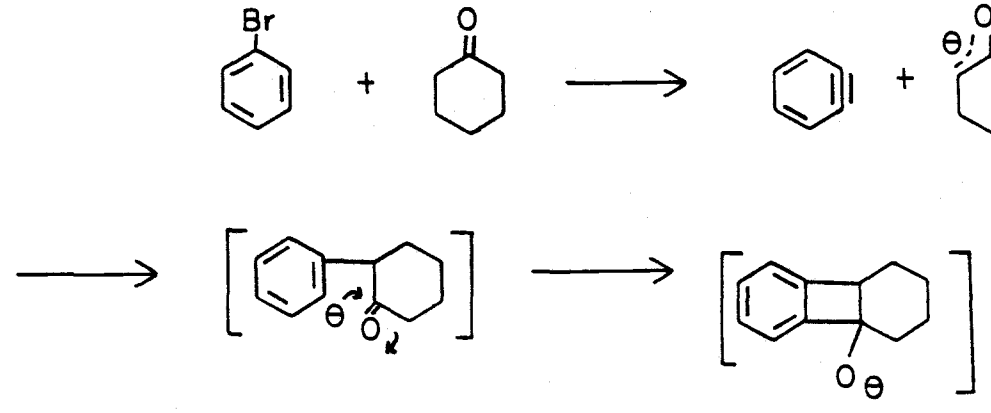
a, R = H; b, R = CH_3

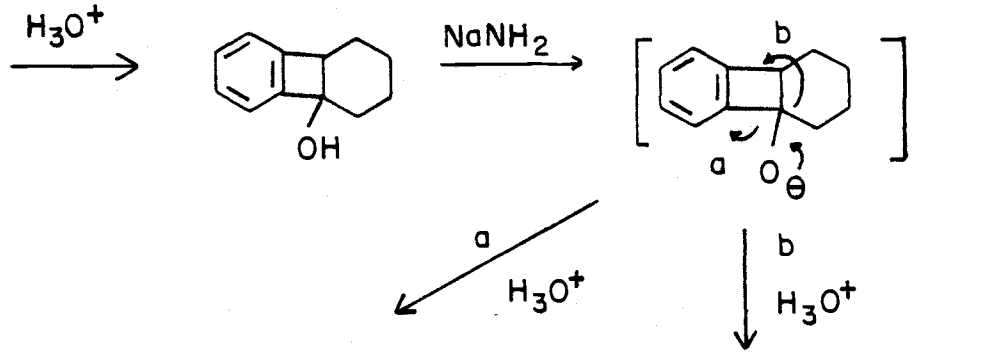
Treatment of compound 29b in the manner previously described led to the formation of the ring expanded product 30 in somewhat better yield than afforded by the thermolysis of 29a. The success of this reaction prompted investigation of a possible 4-carbon ring expansion resulting from a [1, 5] sigmatropic shift in compounds 29c and 29d. Unfortunately, only the 1, 3 products 30c and 30d were observed

in these systems. Finally, the possibility of 3 or 5-carbon ring expansion was examined in compounds 31a and 31b. However, treatment of these compounds in the manner described led only to the isolation of ring cleaved products 32a and 32b.

Further progress toward the synthesis of the target compound was made by Shih (28b) in the work outlined in Scheme 6. Synthesis of the starting ketone 33 was most conveniently accomplished by the reaction of benzyne with cyclohexanone as described by Caubere (29), who proposed the mechanism illustrated in Scheme 5. Reduction and elimination led to alkene 34, which was reacted with the carbenoid derived from ethyldiazo acetate yielding compound 35. Reduction of 35 to 36 followed by acid catalyzed rearrangement in the manner described by Thies and Billigmier (25) led to the formation of alcohol 37. Oxidation, treatment with vinylmagnesium bromide and preparation of the trimethylsilyl (TMS) ether afforded compound 38 which, upon thermolysis, successfully provided the ring expansion product 39. The completion of this work provided a compound which required only the inclusion of oxygen functionality on the aromatic ring and a one carbon ring expansion to complete a feasible synthesis of the target molecule.

Scheme 5





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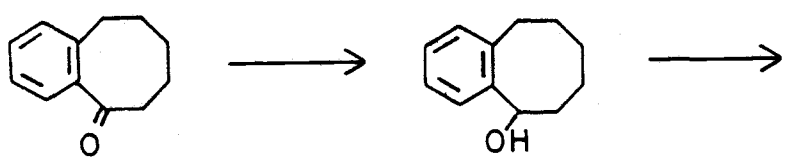
Scheme 6



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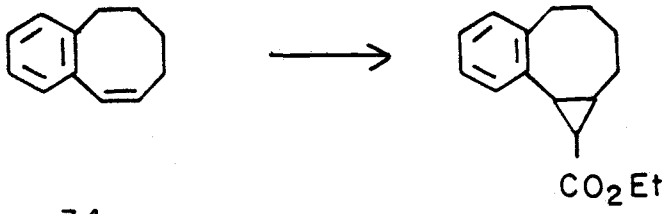
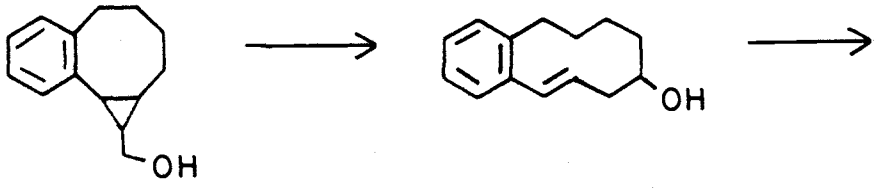
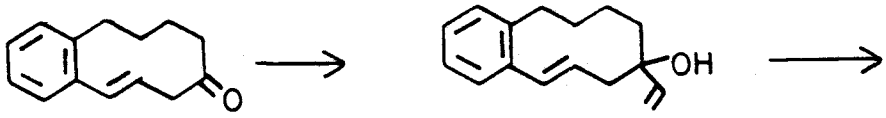


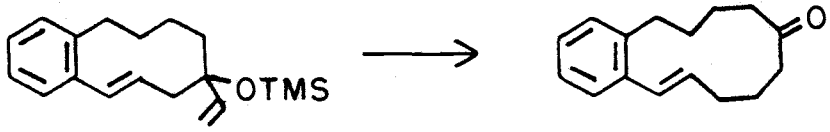
34 35



36 37a



37b



38 39

The purpose of the present work is to further examine methodology for use in the synthesis of the target molecule, 22. Apart from methods based on the preliminary work of Shih, alternate ring expansion methods were considered as well as methods based on ring

closure. Additionally, some mechanistic details of the anionic [1, 3] sigmatropic shift were examined.

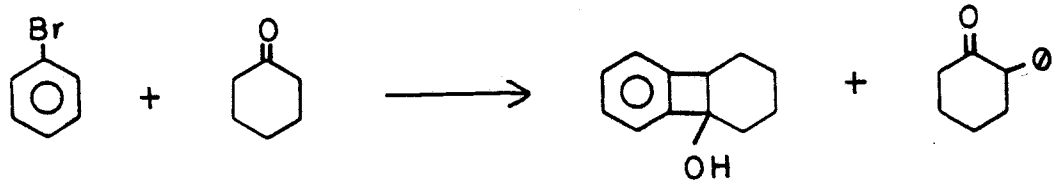
RESULTS AND DISCUSSION

Part 1: Synthesis based on ring expansions

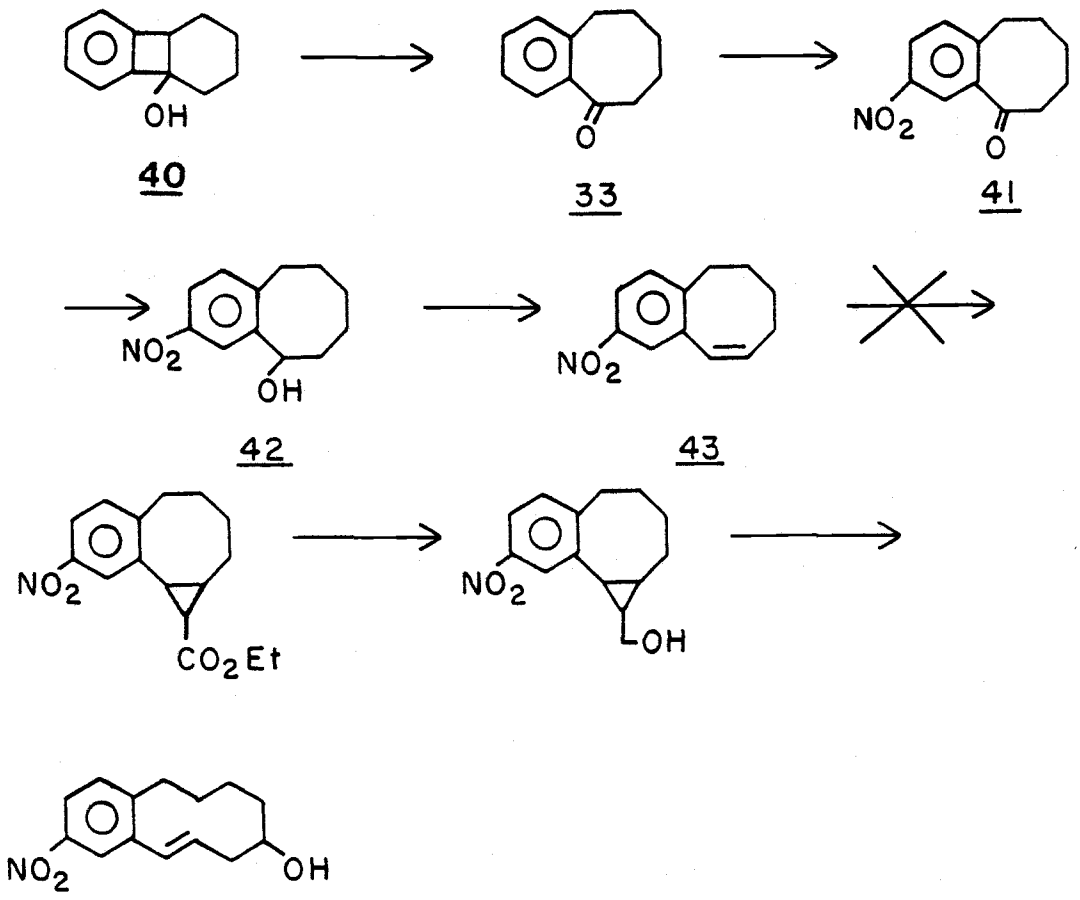
An examination of the structure proposed for synthesis reveals two requirements which must be considered in any synthetic approach. The first of these is the formation of the benzo fused carbocyclic ring, a requirement which may be met by the use of a relatively small number of reactions. First considered of the methods for the formation of the large ring were several approaches based on initial formation of medium ring compounds followed by ring expansion to the required 13-membered ring. Further constraints on the methods available are made by the second requirement which calls for hydroxyl substituents at the positions analogous to C_3 and C_{17} in the steroid ring system.

In previously discussed exploratory work conducted by Shih in our laboratories, a ring expansion route had been successfully completed using closely related model compounds. Thus, the initial approach shown in Scheme 7, was adopted extending Shih's preliminary work. A comparison of Scheme 7 with the work of Shih shows

Scheme 7



40 40a

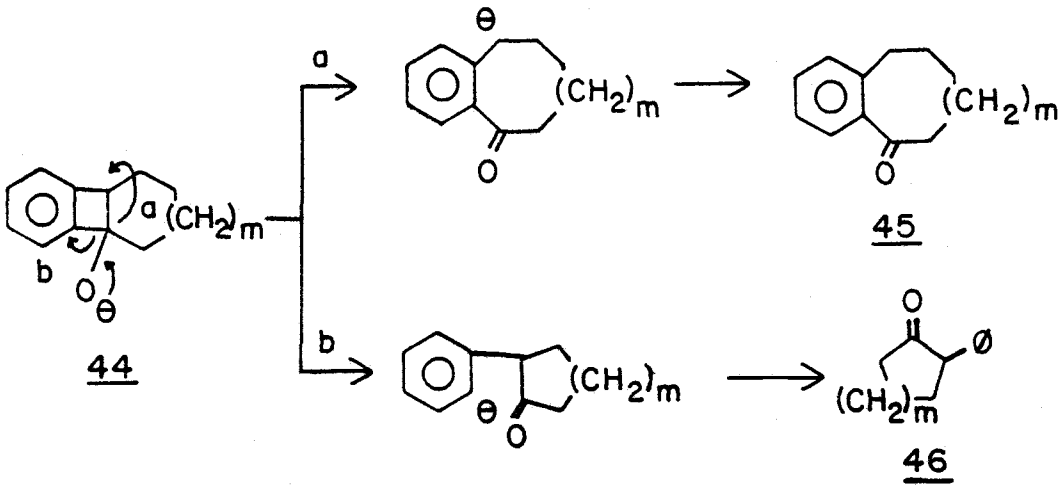


that it differs only in the introduction of a nitro group in the aromatic ring. This would ultimately allow for the inclusion of the oxygen functionality required in that position via a series of reactions that will be discussed later.

The first reaction of the synthetic scheme was the preparation of the benzobicyclo alcohol 40 by the previously described me thod of Caubere. As described by the author, the optimum yield of the desired compound was obtained when benzyne was condensed with the enolate of cyclohexanone in THF at -5 °C. Under these conditions a 30% yield

of the undesired 2-phenylcyclohexanone 40a was also formed. Fortunately, this material could be conveniently removed with Girards Reagent T leaving alcohol 40 as a white crystalline solid.

The opening of alcohol 40 to ketonic products 33 and 40a is a reaction also reported by Caubere (29). As shown below the benzobicyclo alkoxides 44 can open via two pathways, each leading to different products. Caubere found that treatment of the benzobicyclo alcohols with sodium amide in DME afforded 100% of type 45 ketone when



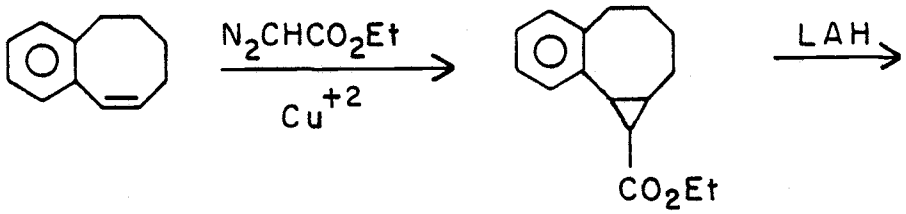
m=1 but gave both ketones in a 70:30 ratio of 45 to 46 when m=2. However, an improvement found in present work gave 85% of the desired ketone 33 when alcohol 40 was treated with KH in THF. Subsequent work in our laboratories (30) found the amount of undesired 2-phenylcyclohexanone could be further reduced to less than 10% using KH in HMPA. As further purification proved very difficult on a large scale, nitration was carried out on the mixture of compounds before

purification was affected.

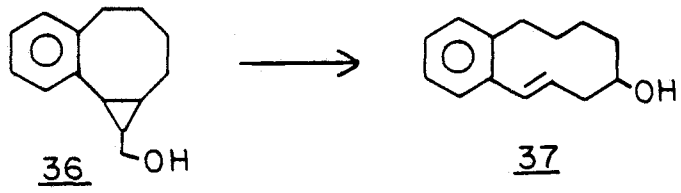
The nitration of ketone 33 was carried out at low temperature with red fuming nitric acid according to the procedure previously used by Thies (31). As would be predicted by considering the directing effect of the carbonyl functionality in electrophilic substitution, this reaction gave a predominance of product with the nitro group meta to the carbonyl (compound 41). Recrystallization from 50:50 ether/hexane, though often a difficult process, gave crystalline product that showed no evidence in the NMR spectrum of any undesired nitrated isomers or products from nitration of 2-phenylcyclohexanone.

Having successfully functionalized the aromatic ring in the desired position, attention was turned to the completion of the reaction sequence developed by Shih in model studies. Ketone 41 was reduced with $NaBH_4$ to the related alcohol 42 followed by dehydration as described by Traynelis and Love (32) affording alkene 43. It was at this point where the reactions of the model system failed to prove general.

As previously mentioned, Shih was able to affect the following two carbon ring expansion according to a procedure used by Thies and Billigmier (25). Though Shih was able to carry out the addition of the carbenoid derived from ethyldiazo acetate to alkene 34 in good yield, attempts to carry out this reaction on the analogous nitro alkene 43 led only to the recovery of carbene dimer.



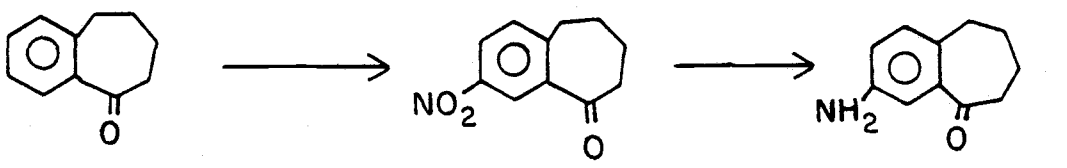
34 35



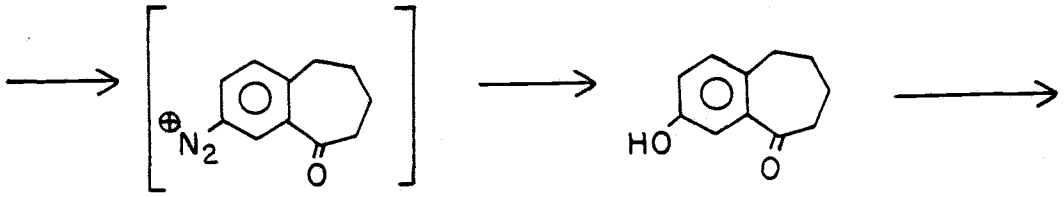
36 37

The failure of this reaction can be attributed to the electron withdrawing effect of the nitro group on the electrophilic carbenoid addition and it was hoped that the required reaction might proceed more favorably if a substituent with a more negative σ constant was used. Thus, attention was turned to the synthesis of alkene 57, where the required hydroxyl functionality was protected as the methyl ether. Though this compound could have been synthesized by an extension of the previous scheme, the alternative shown in Scheme 8 was employed due to the significantly greater yield obtained in the nitration. Initially the proposed sequence also included the synthesis of

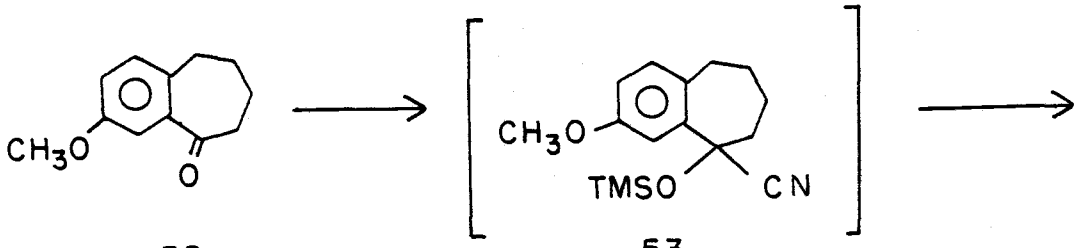
Scheme 8



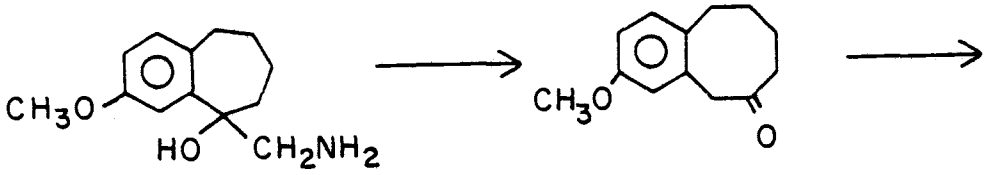
47 48 49



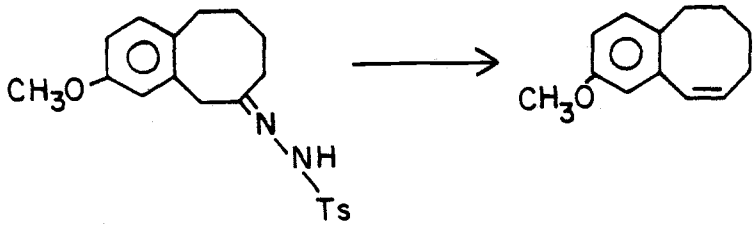
50 51



52 53



54 55



56 57

benzosuberone 47. However, attempts at its synthesis using the method of Caubere led to a mixture of products that could not be separated by preparative chromatography or distillation. A small amount of benzosuberone was conveniently synthesized by the cyclization of δ phenyl valeric acid as described by Gilmore and Horton (33), however, it was ultimately decided to use the commercially available material.

As previously mentioned, the nitration of benzosuberone 47 proceeded smoothly affording higher yield than experienced with the homologous compound. The nitro compound 48 was hydrogenated by the procedure of Smith and Berry (34) yielding the related amine 49. Diazotization followed by decomposition of the diazonium salt as described by Ungnade and Orwall (35) afforded the alcohol 51. Finally, the procedure of Hier and Hagen (36) was employed for methylation of the hydroxy compound to give 3-methoxybenzosuberone 52.

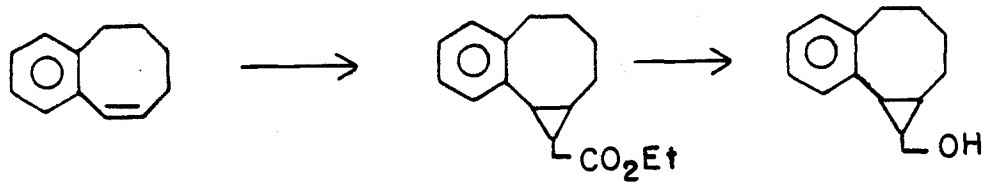
The methoxy functionality now in place, attention was turned to the expansion of the saturated ring and subsequent production of the 3-methoxybenzocycloöctene 57. The method of Evans, Carol and Truesdale (37) which employed ZnI_2 catalyzed addition of trimethysilyl cyanide (TMSCN) to cyclic ketones as the first step in the ring expansion process had previously been used in our laboratories (38) for the expansion of benzosuberone. In the present work, however, this reaction proved very inconsistent. As the intermediate trimethysilyl cyanohydrin 53 is reduced without isolation, failure of the

catalyst to effect addition of TMSCN resulted in isolation of reduced ketone. An improved procedure was found in the use of KCN/18: crown:6 catalyst which consistently afforded good yields of compound 54 following LAH reduction. This catalyst is apparently not sensitive to minute amounts of water as was the very hydroscopic ZnI_2. Finally, a Tiffineau rearrangement following diazotization of the amino alcohol 54 afforded the ring expanded product 55.

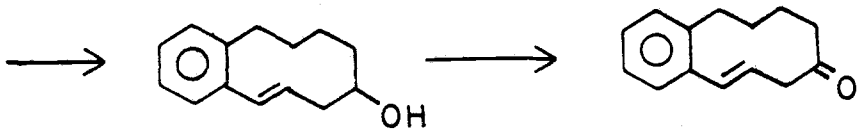
Although it is probable that alkene 57 could be formed by the reduction and elimination sequence previously used, the alternative method of Shapiro and Heath (39) seemed to hold promise of higher yields. Thus the methoxy benzocyclooctenone 55 was converted to the related tosyhydrazone 56 and eliminated with methyllithium affording the alkene 57 in good yield.

Though it had been hoped that this alkene would be as prone to carbenoid addition as its unsubstituted counterpart, this reaction, like that of the analogous nitro compound, failed. Thus, attention was turned to alternative methods of carrying out the required two carbon ring expansion compatible with the remainder of the reactions in the model studies.

A reexamination of a portion of the scheme used in the model studies shows several points where reentry into the synthetic scheme might be accomplished. Three schemes were decided upon that would allow reentry into Shih's scheme along the route from 34 to 37b.



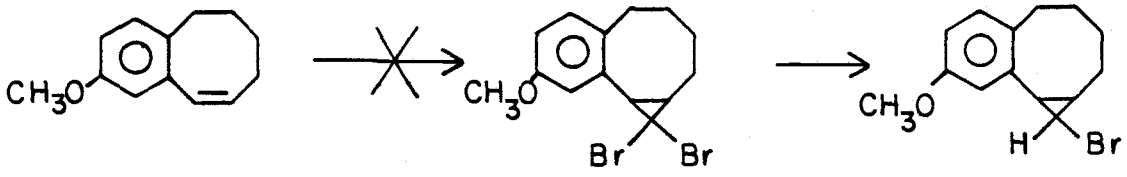
34 35 36



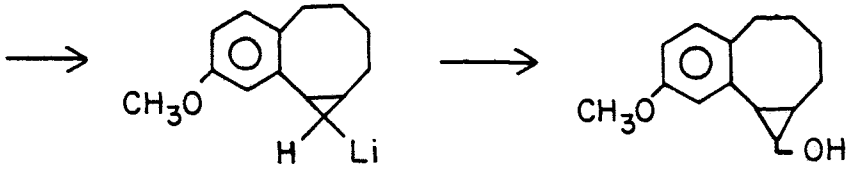
37a 37b

The first, shown in scheme 9, also involved addition of a carbenoid to an alkene and would give the methoxy compound 61

Scheme 9



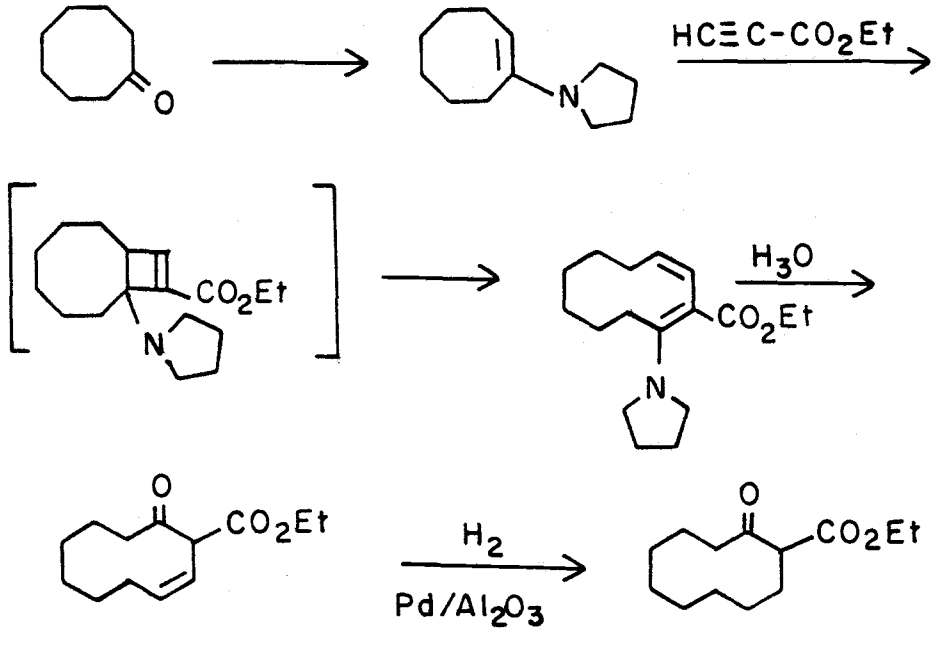
57 58 59

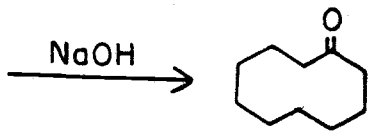


60 61

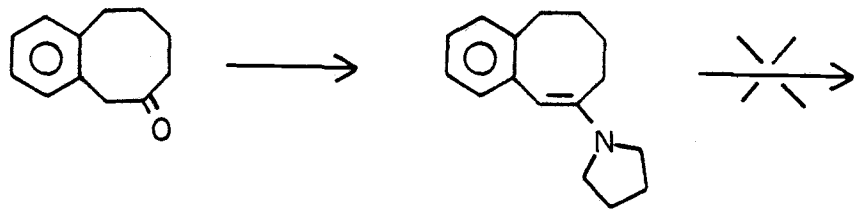
analogous to 36. The reactions leading to compound 60 had been successfully used in our laboratories in a synthesis of 2-vinylcyclopropyl lithium (40). The sequence proposed called for the addition of the carbenoid via a combination of the procedures described by Skattelbol (41) and Skell and Garner (42). Reduction to the monobromide 59 with $(n\text{-Butyl})_3SnH$ as described by Seyferth, Yamazaki and Alleston (43) followed by metal-halogen exchange and reaction of 60 with formaldehyde as described by Wender and Filosa (44) would have afforded the required compound. Unfortunately, addition of dibromocarbene to compound 57 proved just as difficult as the previously attempted carbenoid additions. It now seemed apparent that any method relying on carbene addition to compound 57 was predisposed to failure.

An alternative procedure for ring expansion had excellent analogy in the work of Burbitt and Thweatt (45) as illustrated below.

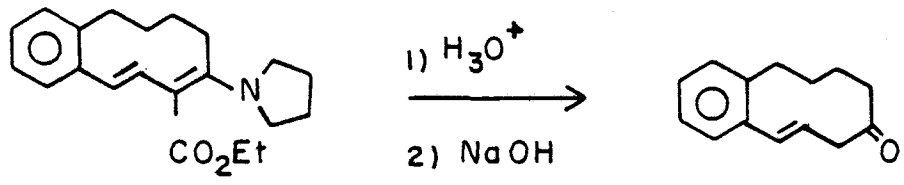




Scheme 10



62 63

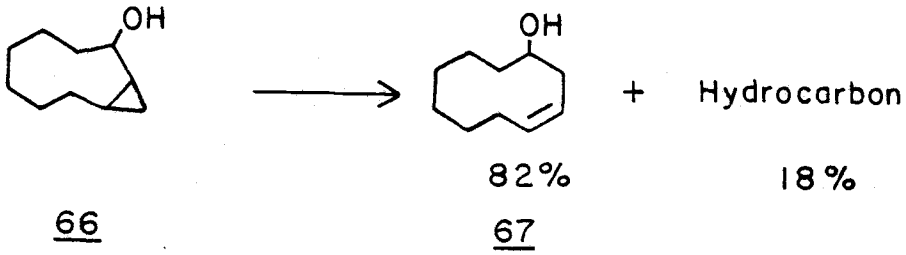


64 65

Clearly, as shown in Scheme 10, the substitution of ketone 62 for cycloöctenone and the elimination of the hydrogenation step should

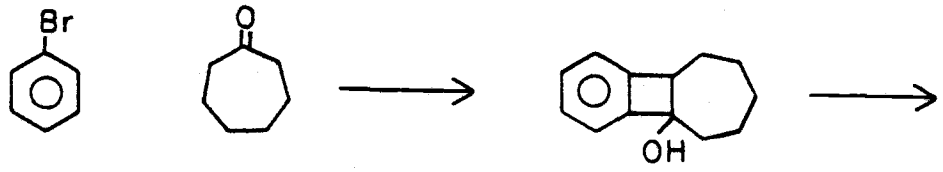
provide a convenient route to the β,γ unsaturated ketone 65 analogous to compound 37b in Shih's scheme. Unfortunately, though presence of enamine 63 was confirmed, no addition of the alkyne could be effected.

In a final attempt to reenter Shih's scheme several alternative syntheses of the compound 37a were devised. It was known from the work of Poulter and Winstein (46) that alcohol 66 gave mainly ring expanded product 67 when treated with perchloric acid in aqueous dioxane. Thus, the sequence illustrated in Scheme 11 was devised



66 67

Scheme 11



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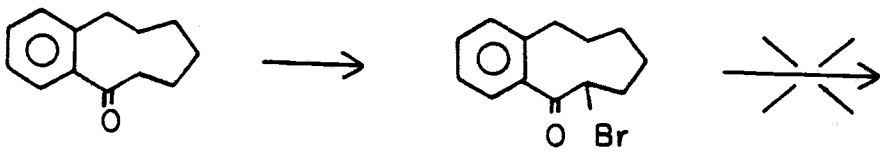
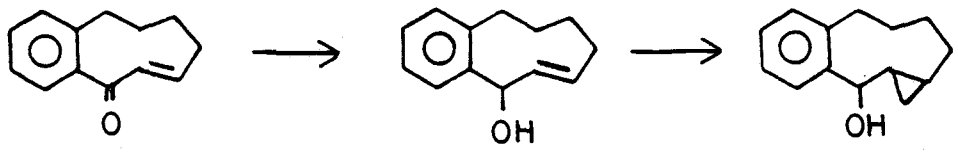


69 70



71 72 73

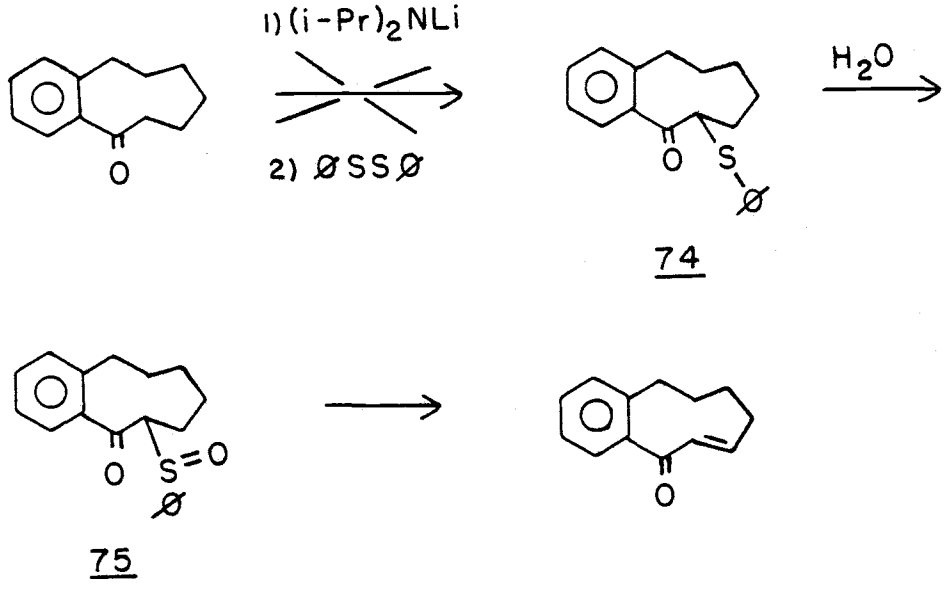
to make use of this ring expansion. It should be noted that synthesis of 73 from 72 requires a carbenoid addition, the very type of reaction that had previously proved so difficult. However, in the present case it was believed that the directing effect of an α-hydroxyl on the Simmons-Smith reaction would make this a much more favorable process.

This ring expansion, unlike that used by Shih, provides only a single extra carbon, however, the additional carbon was included by using cycloheptanone instead of cyclohexanone in the initial reaction. The required ketone 69 was thus synthesized, via alcohol 68, by methods previously described. Bromination as described by King and Ostrum (47) proceeded smoothly affording compound 70. Surprisingly, the dehydrohalogenation of 70 to 71 could not be effected though a variety of methods were attempted. Included in these attempts were the reaction of compound 70 with MgO/dimethyl formamide (DMF) (48), $AgNO_3$/ethanol/H_2O (49), KOt-Bu/dimethyl sulfoxide (50), 1,8-diazobicyclo[5.4.0]undec-7-ene/DMSO (51), LiCl/DMF (52). In every case except for the KOt-Bu reaction only starting material was obtained after prolonged reaction. In the case of KOt-Bu, a

compound whose NMR was identical to compound 69 was obtained.

An alternative procedure for the synthesis of alkenone 71 based on the work of Trost et al. (53) was devised following the failure of the dehydrohalogenation. As illustrated in Scheme 12, this procedure involves sulfenylation of 74, oxidation to sulfoxide 75 and finally thermal elimination. In our hands, however, only unacceptably small

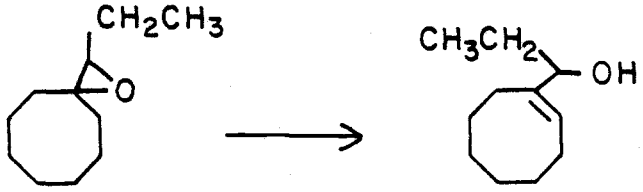
Scheme 12



amounts of 74 were obtained as evidenced by NMR upon integration of the downfield triplet due to the proton α to the sulfur and carbonyl. Several modifications suggested by Trost failed to improve this result.

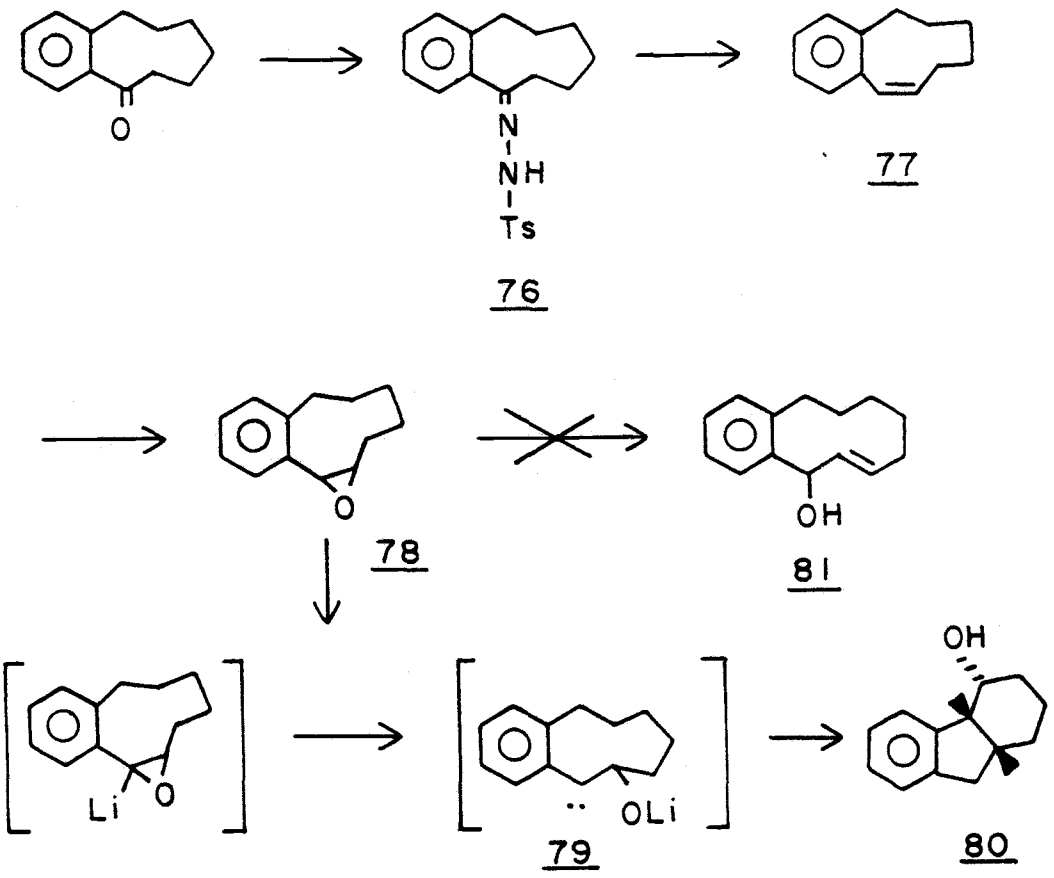
The failure of these attempts to synthesize alkenone 71 led us to seek another alternative in the literature. The work of Thummel and

Rickborn (54) shown below suggested a possible solution. It was



reasoned that the α, β unsaturated alcohol 72 might be synthesized by similar treatment of the appropriate epoxide as shown in Scheme 13.

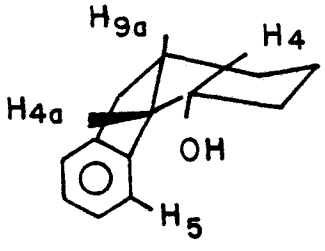
Scheme 13



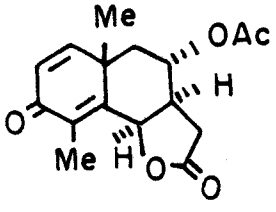
The cis alkene 77 was synthesized, via tosylhydrozone 76 as previously described and cleanly epoxidized affording compound 78. Unfortunately,

upon treatment of 78 with lithium diisopropylamide, none of the desired product 81 resulting from proton abstraction α to the epoxide was formed. Instead, preferential hydrogen abstraction occurred at the position α to the aromatic ring. Opening of the epoxide led to the formation of the intermediate carbene 79 and finally the production of the transannular ring insertion product 80, a result with some precedent in the literature (55, 56, 57). It should be noted, however, that at least some of the allylic alochol was noted in all the literature examples cited.

As indicated above, the formation of the insertion product is a highly stereospecific process. The structure of 80 was assigned from decoupling experiments with added $Eu(Fod)_3$, which demonstrated that the proton on the hydroxy bearing carbon is coupled to a benzilic proton, and this benzylic proton is coupled to another proton which, in turn, is coupled to the other benzilic protons. The cis, syn stereochemistry was assigned from the triplet pattern, J=5.5 Hz, for H_{4a}



82

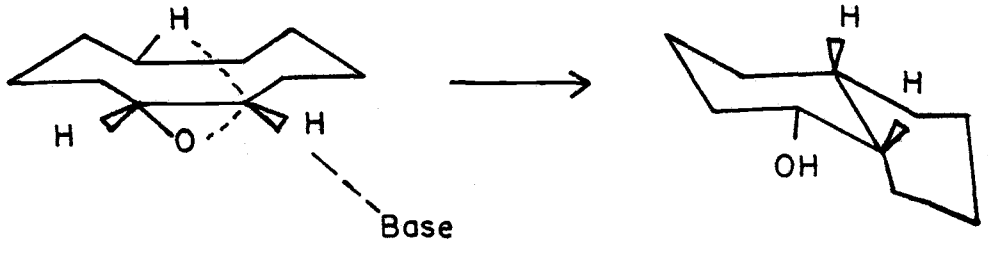


83

which is consistent with the structure 82, i.e., $J_{4,4a} = J_{4a,9a} = J_{ax,eq}$.

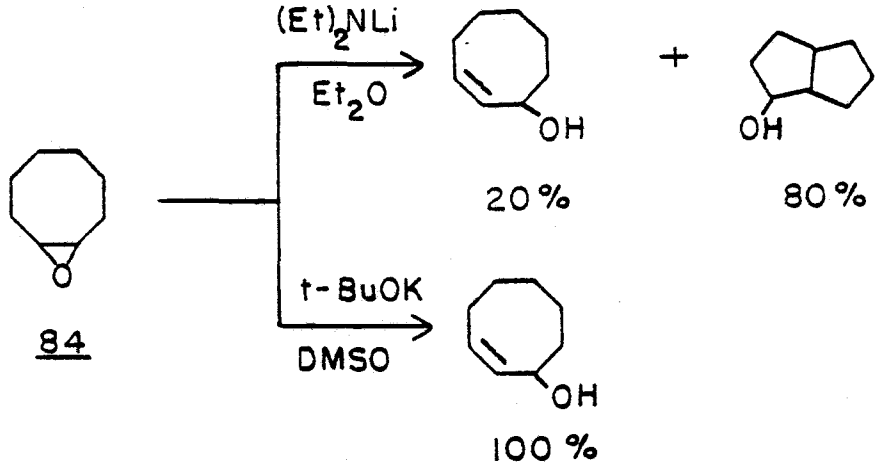
The coupling constant agrees with that of epiartemisin acetate 83, $J_{cis} = 5.7$, rather than that of artemisin acetate where $J_{trans} = 11.6$ Hz (58). The shift reagent studies are also consistent with the assigned structure showing a relative order of downfield movement of $H_4 > H_5 > H_{4a} > H_{9a}$. A comparison of the four possible isomers shows only the cis, syn isomer will give this order. Finally, additional support for the structural assignment was based on spectral and melting point comparisons with material synthesized by Kende and Goldschmidt (59) via an alternative route. In this synthesis the stereochemistry was tentatively assigned based on reduction steps used in the synthesis.

It should be noted that the cis, syn stereochemistry was also observed by Cope et al. (55) in the case of cis cyclodecene oxide. The following concerted mechanism was proposed to account for the stereospecificity of the reaction. This mechanism was differentiated



from an alternative mechanism calling for the abstraction of the transannular hydrogen with a concerted opening of the epoxide by studies where the epoxide hydrogens were replaced by deuterium.

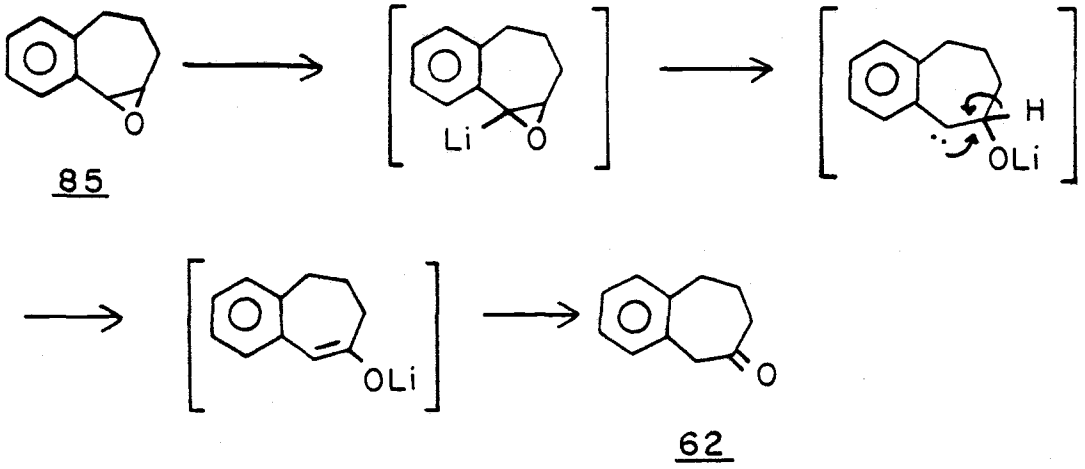
In addition to the examples cited above, ample precedent also exists for the formation of the desired allylic alcohol 81. It was observed in the work of Whittsell and White (60), Boeckman (61), and Sheng (62) that the relative amounts of transannular vs. allylic alcohol product could be influenced by the solvent, temperature, and base used. The most striking example was found in the work of Sheng where treatment of cycloöctene oxide 84 with lithium diethylamide in



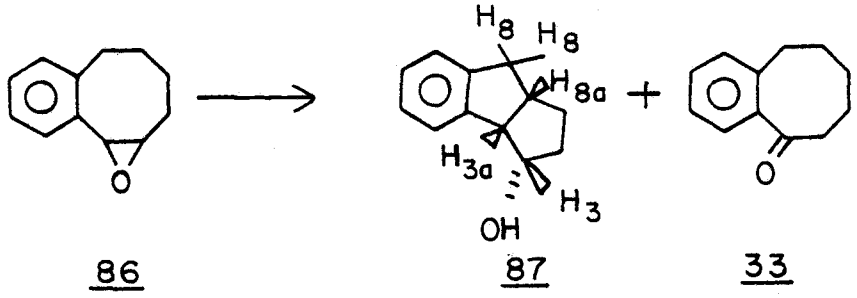
ether gave a predominance of transannular product, whereas treatment with t-BuOK in DMSO gave exclusive formation of the allylic alcohol. In the present work, however, treatment of expoxide 78 with t-BuOK in DMSO also gave transannular product, a result that can be attributed to the increased acidity of the proton α to the aromatic ring.

Though the above results proved of no direct value in the problem at hand, the reaction of benzocycloalkadiene oxides with strong base had not been reported in the litarature. Thus, it was decided to

examine the behavior of a homologous series of epoxides upon treatment with lithium diisopropylamide. Toward this end, epoxides 85 and 86 were synthesized from the appropriate ketone in the same manner described for epoxide 78. Treatment of these epoxides with lithium diisopropylamide led to the products depicted below.

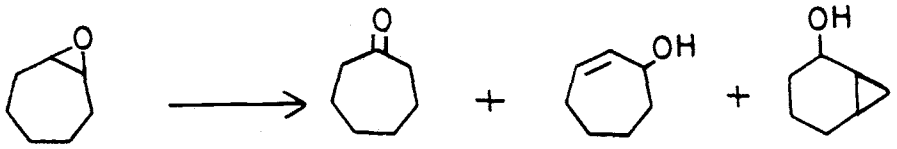


85 62



86 87 33

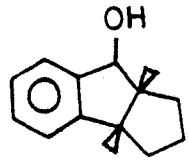
The rearrangement of epoxide 85 led cleanly to the β ketone 62, a surprising result in light of the products reported by Crandall and Chang (57) for cycloheptene oxide 88, which give the three primary products shown in comparable amounts. The difference in the behavior of the two systems can again be attributed to the enhanced acidity of



88

the epoxide proton α to the aromatic ring.

Finally, the rearrangement of epoxide 86 was carried out and found to give a majority of transannular product 87, though a minor amount of α ketone 33 could also be isolated. The structure of 87 was determined in a similar fashion to the assignment of 8a. Decoupling experiments demonstrated coupling between H_3, H_{3a} and H_{8a}, however the H_8 and H_{8a} protons were too close in chemical shift to demonstrate coupling even with added shift reagent. The clearly defined coupling pattern for the H_8 protons shows geminal coupling and indicates that each H_8 is coupled to only one other proton which must be H_{8a}. The magnitudes of the coupling constants are similar to those reported by Fohlisch and Schwaizer (63) for compound 89 where J_{syn} = 8.4 Hz and

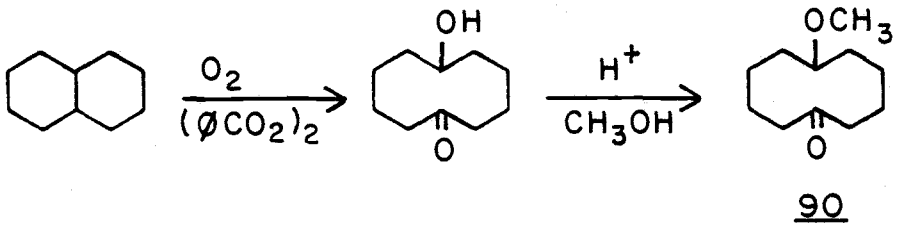


89

J_{anti} = 2.0 Hz. The ring juncture coupling constant, $J_{3a,8a}$ = 8 Hz, is somewhat larger than observed in compound 83, a fact attributable to a dihedral angle closer to 0°. Finally, the syn coupling constant,

$J_{3, 3a}$ = 7 Hz, is reasonably close to that observed in compound 80.

Having completed this work, attention was returned to the problem at hand. As we had been unsuccessful in our attempts to make use of the basic scheme developed by Shih, one final ring expansion method was attempted in hope of improving work that is currently in progress in our laboratories (64). The following depicts preliminary work carried out by Yue in this alternative route. Condensation of



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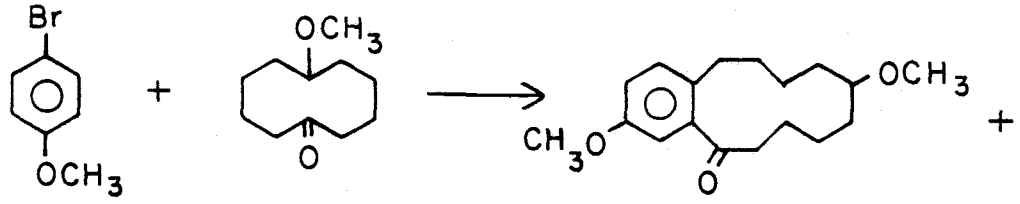
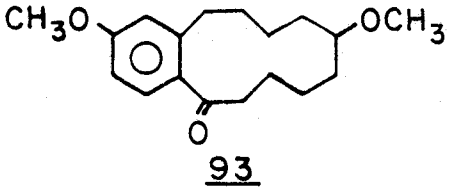
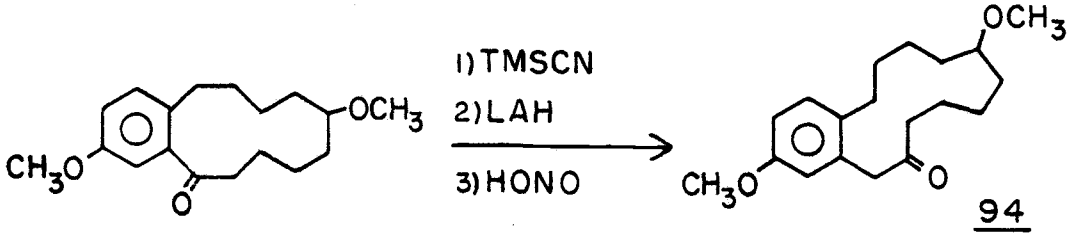


91 90 92



93



94

the benzyne derived from p-bromoanisole 91 with the enolate of

compound 90 afforded the predicted mixture of compounds 92 and 93. The desired isomer 92 was separated with some difficulty in approximately 20% yield via medium pressure chromatography.

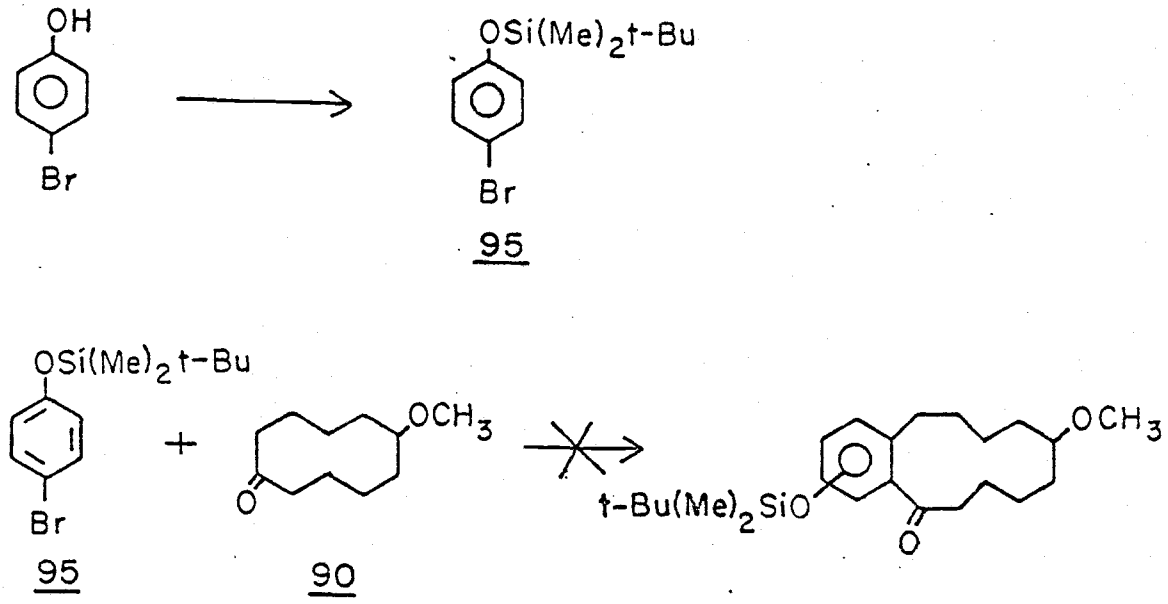
The room temperature ring expansion with TMSCN and 18:crown:6 in ether, which had proved so versatile with many other benzocycloalkanones, was unsuccessful in this case leading, instead, to the production of the -OTMS enol ether. It was ultimately discovered, however, that the reaction proceeded smoothly to yield compound 94 if the TMSCN addition was carried out at 0°C in toluene for several days. If the unwanted ketone functionality could be removed and the methyl ethers cleaved to the needed hydroxyl groups, the synthesis of the estradiol analog would be complete.

Though this synthesis appeared very promising, two difficulties were being encountered. First, even after the several chromatographic separations necessary to isolate isomers 92 and 93, the compounds were obtained only as colored oils which quickly darkened even when stored at low temperatures under argon. Second, the methoxy ethers used as protecting groups were proving much more difficult to cleave than anticipated. Though it seemed that any air or thermal instability of these compounds would have to be accepted, the replacement of the methoxy group with a more labile protecting group would certainly represent an improvement. Thus, while Yue continued to search for more effective conditions to cleave the methoxy group, the attention

of the present work was turned toward the use of alternative hydroxyl protecting groups.

For the preliminary work, shown in Scheme 14, it was decided to attempt the only replacement of the aromatic methoxy in order to test the compatibility of the t-butyldimethylsilyl ether with the various reaction conditions. Unfortunately, the attempted condensation of the

Scheme 14

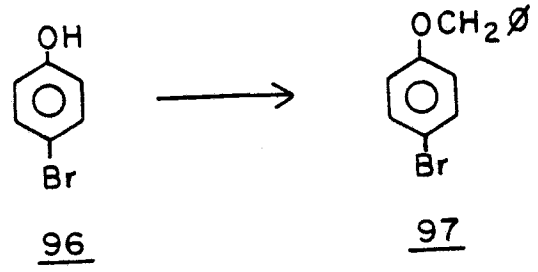


benzyne derived from compound 95 with the enolate of ketone 90 led only to the isolation of unreacted ketone 90. It seems probable that, under the reaction conditions, compound 95 is cleaved to p-bromo phenoxide, which failed to react and was lost to the basic water layer. In a further attempt to test the utility of the silyl protecting group in this reaction, p-bromo phenol was converted to its methyl diphenylsilyl ether and reacted with cyclooctanone. Again no condensation

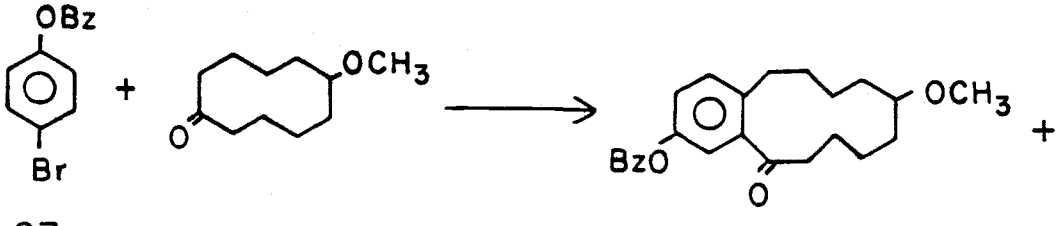
product or unreacted bromo compound could be isolated in the organic layer. However, the crude reaction mixture was found to contain a second product in addition to the unreacted ketone. Though not fully characterized, the NMR of this compound clearly indicates the presence of a methyl diphenylsilyl group. The absence of any other significant absorbtion in the NMR led to the tentative conclusion that this compound is derived from the displacement of p-bromo phenoxide by the amide anion. Having thus demonstrated the instability of silyl ethers under the reaction conditions, attention was turned to the use of alterative protecting groups.

The feasibility of using a benzyl protected alcohol was examined in the series of reactions illustrated in Scheme 15. The benzyl protected phenol 97 was prepared in DMF from benzyl chloride and the

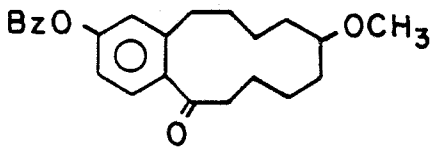
Scheme 15



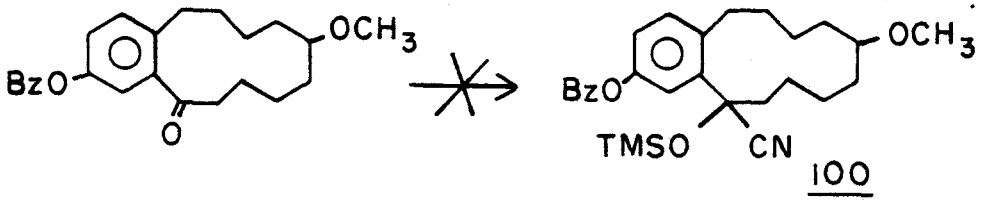
96 97



97 90 98

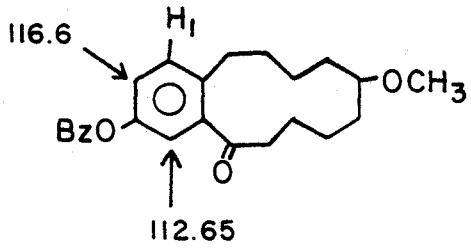


99

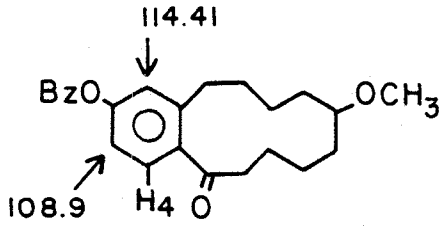


100

phenoxide generated by the action of NaH on p-bromophenol 96 (65). The reaction of the benzyne generated from compound 97 and the enolate of 90 produced the expected mixture of isomers 98 and 99. Determination of the structure of these two compounds was not as straightforward as for the dimethoxy analogs because the coupling pattern for the hydrogens on the fused aromatic ring is obscured by the aromatic protons of the protecting group. Some information could be gained from the C_{13} spectra where it was possible to compare the shifts for the carbons on either side of the benzoxy bearing carbon to the shifts observed for corresponding carbons in the methoxy compounds and calculated shifts for the model compounds 101 and 102 (66). While these values do not coincide exactly, a trend is observed showing the difference in chemical shift between the two



98



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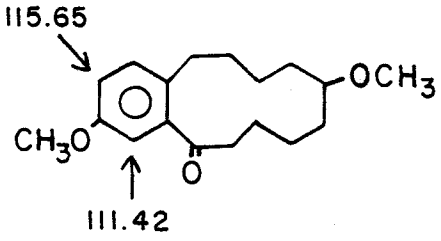
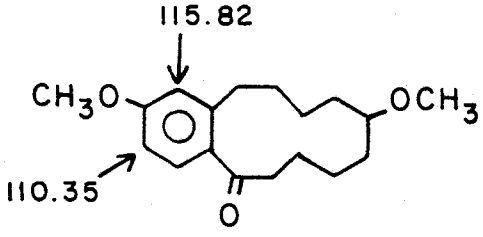
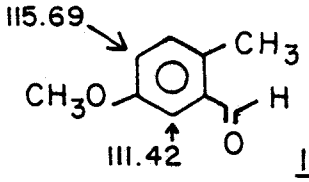


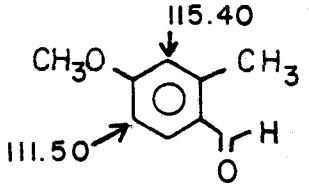
92



93



101



102

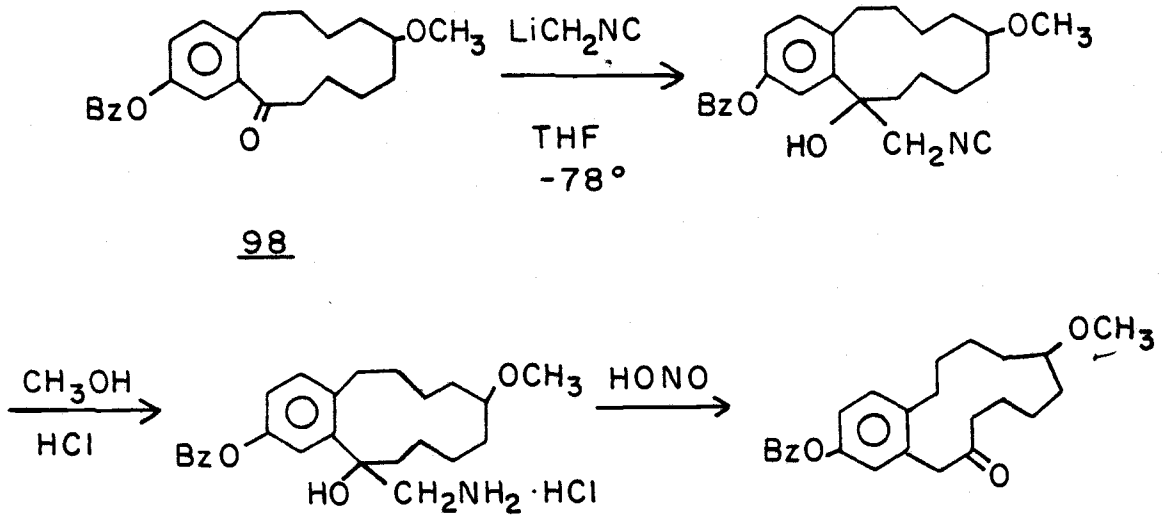
carbons is larger for the isomers with the oxygen functionality para to the carbonyl group. Final confirmation of structure, however, required removal of the protecting group. Hydrogenolysis over palladium on carbon in ethanol proved to be a very inefficient process, however enough material was collected to obtain a proton NMR spectrum. A doublet, J_{ortho} = 9Hz, centered at 7.1 ppm is indicative of

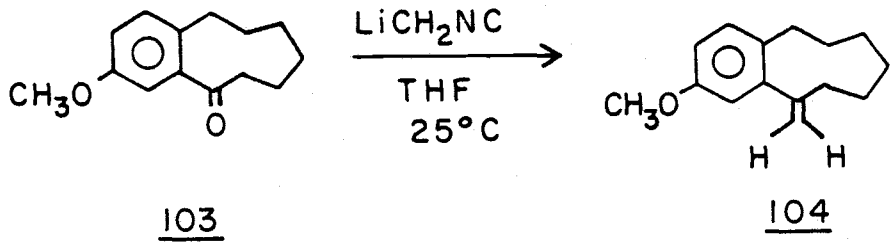
proton H_1 in 98 rather than proton H_4 in 99, which is observed at 7.5 ppm in the methoxy analog.

The fortuitous effect of replacing the methoxy group with the benzoxy group was that these compounds were more easily separated and the desired compound was obtained as a stable crystalline solid in slightly greater yield (20-25%) than that obtained by Yue. This seemed to be a significant improvement over the previous results. Unfortunately, the attempted reaction of ketone 98 with TMSCN and 18:crown:6 under conditions identical to those developed by Yue showed no significant addition after three weeks.

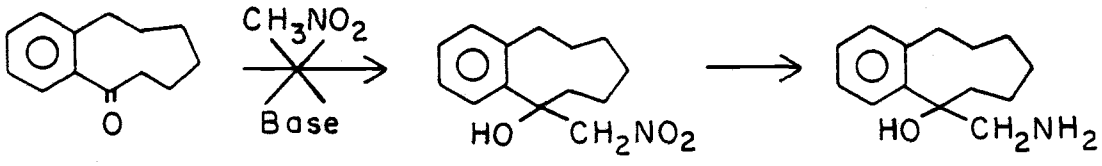
As the initial results had appeared so promising, several alternative ring expansions, shown in Scheme 15, were attempted. Methyl

Scheme 15



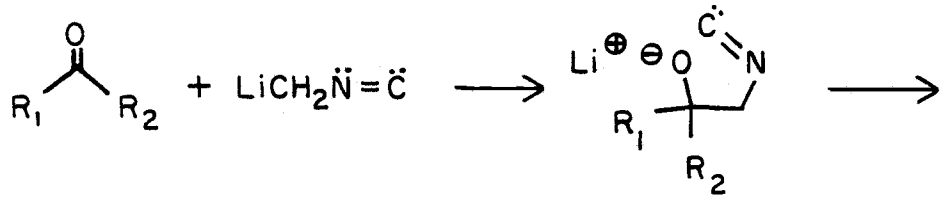


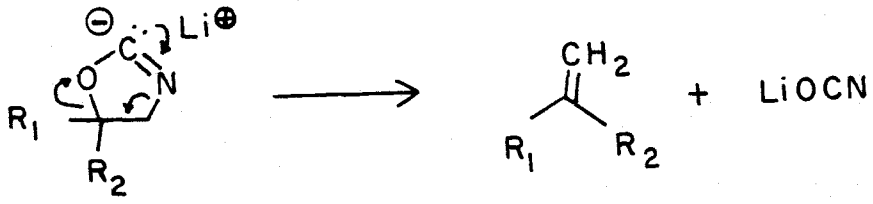
103 104



69 105

isocyanate was prepared as described by Schuster, Scott and Casanova (67) and the ring expansion described by Schollkopf and Bohme (68) was attempted. It was, however, impossible to effect any addition of the lithiated methyl isocyanate to ketone 98 at -78 °C. In further attempts to effect the desired addition, model compound 103 was used. Again no addition was observed at low temperatures, however, when allowed to proceed at ambient temperature, reaction occurred yielding the exomethylene compound 104. This result was not unexpected as similar products had been observed by Schollkopf and Gerhart (69) who proposed the following mechanism for their formation.

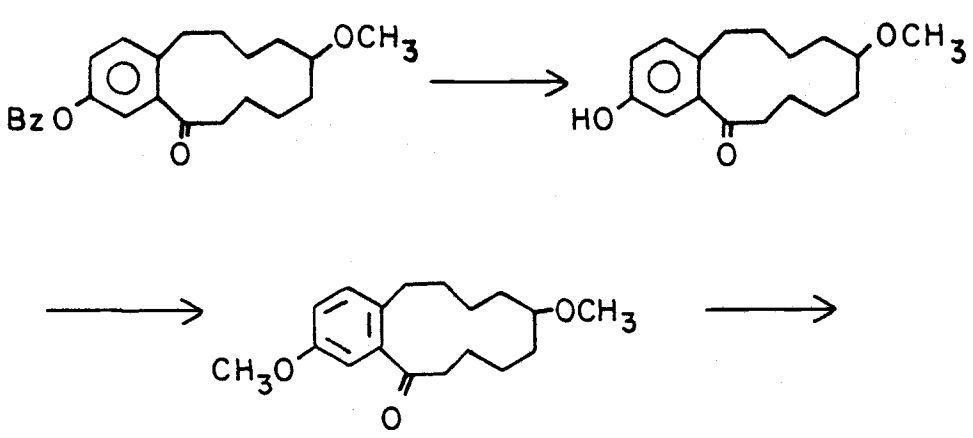


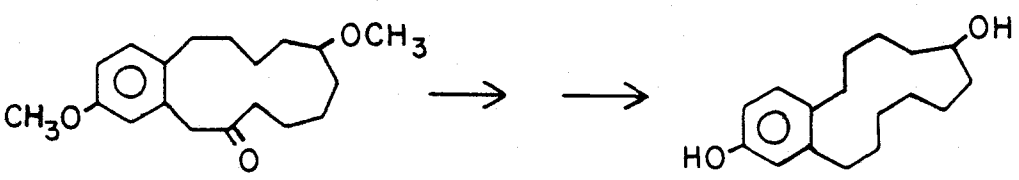


A similar ring expansion by Dauben, Ringold, Wade, Pearson, and Anderson (70) used the addition of nitromethane with sodium methoxide catalyst as the first step in the production of β-amino alcohols. However, when model compound 69 was treated under these conditions, none of the desired intermediate 105 was obtained. Similarly, treatment of 69 with nitromethane and KF/18:crown:6 as described by Wollenberg and Miller (71) failed to effect any addition.

Though no further work has been attempted on this system, two possible directions of additional investigation are indicated. First, the greater yield, ease of separation, and greater compound stability suggests the reaction sequence shown in Scheme 16. Though this

Scheme 16

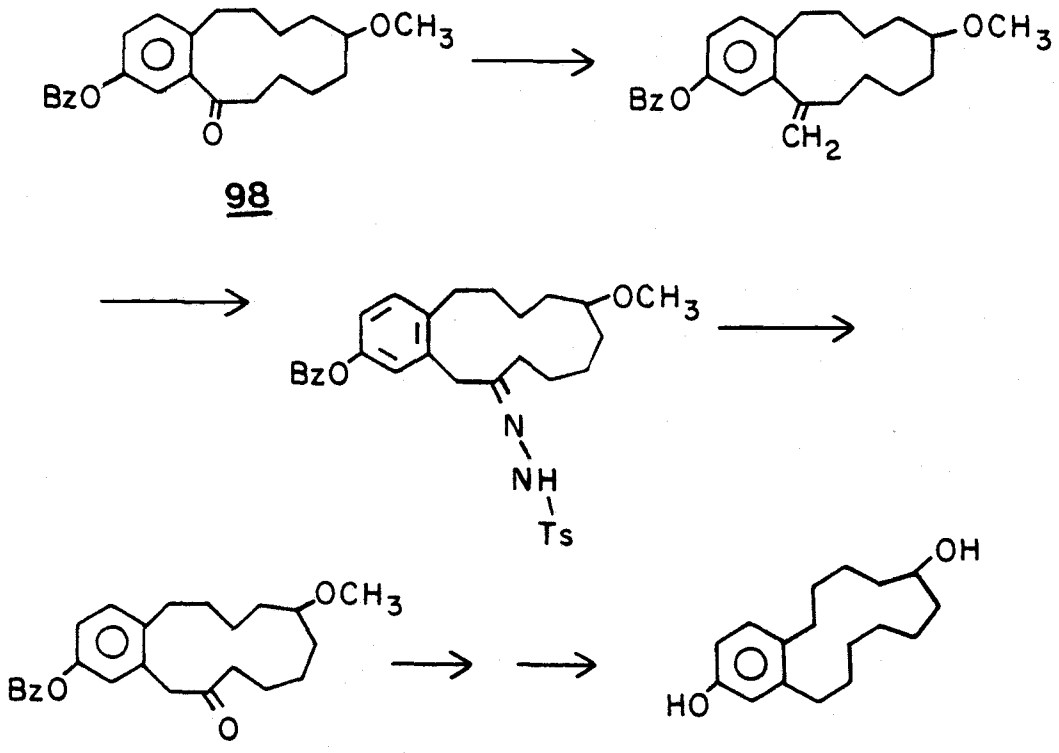




route involves more steps than the route employed by Yue, a greater overall yield may result from the above process.

A second possibility for additional work is suggested by the reaction of compound 103 with lithium methyl isocyanate. As shown in Scheme 17, if this reaction could be extended to ketone 98, treatment of the exomethylene compound with tosyl azide as described by Wohl

Scheme 17

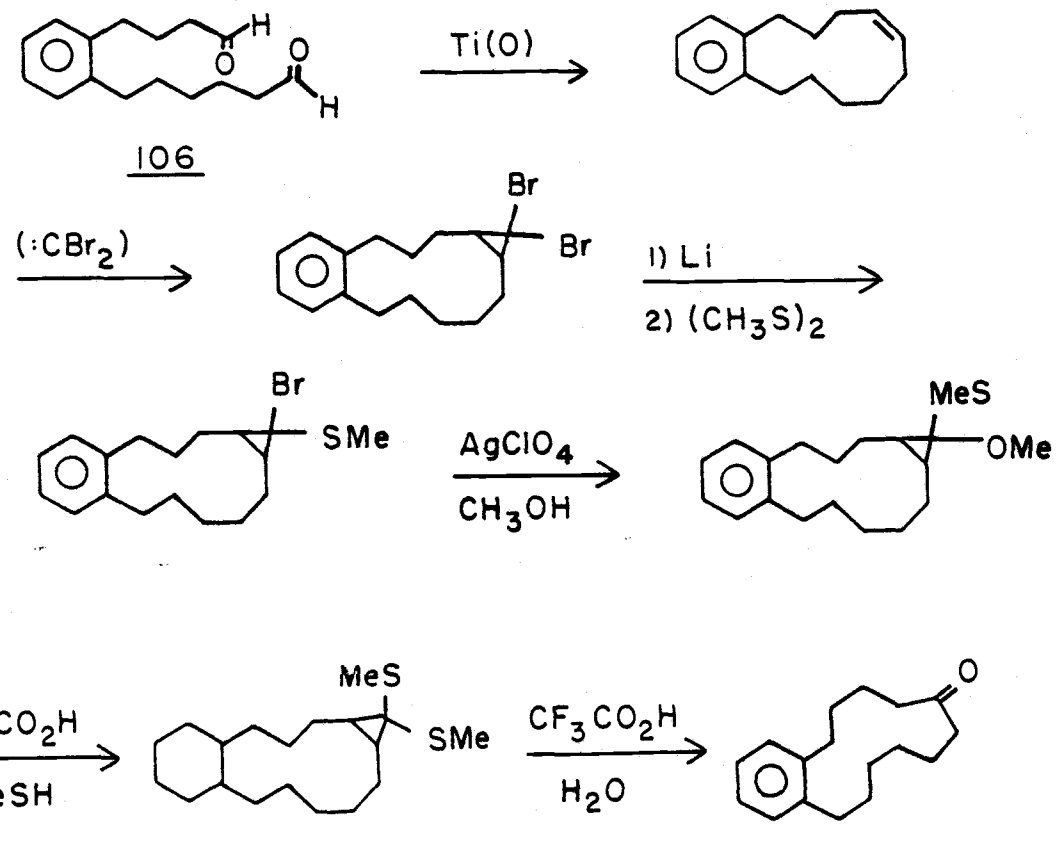


(72) may provide an alterative method of obtaining the required ring expansion. Similar results could also be obtained by treating the exomethylene compound with thallium(III) nitrate in the manner described by Taylor andChiang (73).

Part II - Methods based on ring closure

In addition to the approaches discussed in part I, several methods based on ring closure of side chains on appropriately substituted benzenes were also investigated. The first synthesis, shown in Scheme 18, was based upon a combination of the reductive coupling

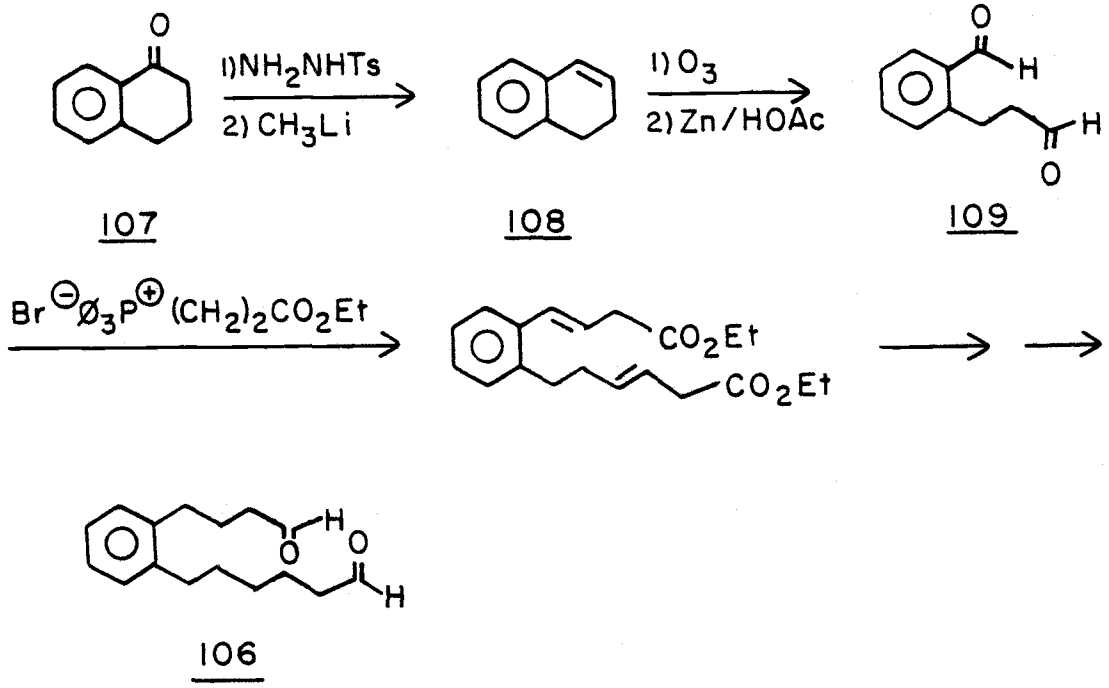
Scheme 18



procedure of McMurry and Kees (74), which was known to give medium

to large ring olefins in good yield from α,ω-dialdehydes, and the procedure of Seebach, Braun and DuPreez (75) for the insertion of a carbonyl grouping between the carbons of the double bond. As adequate precedent existed for these transformations, synthesis of the desired product rested on the efficient production of dialdehyde 106, which would be used in the preliminary work. The envisioned synthesis of 106, shown in Scheme 19, would later allow for the inclusion of the necessary oxygen functionality on the aromatic ring by starting with the commercially available methoxy tetralone.

Scheme 19



107 108 109

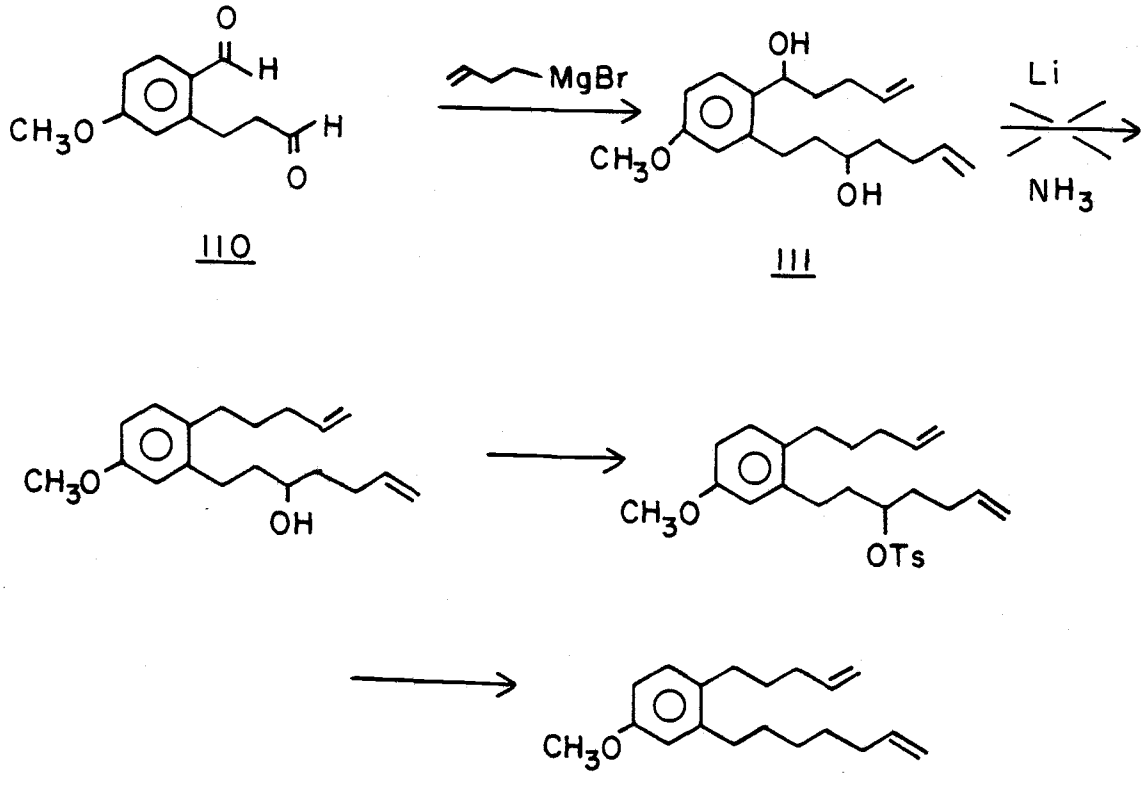
106

The synthesis of alkene 108 was accomplished as previously described via the tosylhydrozone of tetralone 107. Ozonolysis of 108,

as described by Warnell and Shriner (76), afforded a 97% crude yield of dialdehyde 109. Unfortunately, all attempts to add Wittig reagents to the dialdehyde afforded only small amounts of intractable material. However, it was discovered during the course of this work that the addition of Gignard reagents to 109 did proceed smoothly.

As addition of Wittig reagents to 109 continued to prove impossible, two syntheses were devised that utilized Grignard addition. The first, shown in Scheme 20, involved addition of a suitable Grignard

Scheme 20



110 111

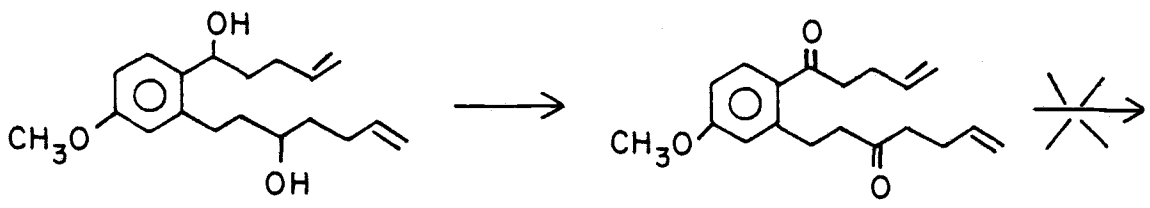
reagent to 110 followed by the removal of the unnecessary hydroxyl groups. For the initial studies, the Grignard reagent derived from

4-bromobutene was chosen because the terminal olefin could be ozonized to the desired dialdehyde, and it was feared that adding a Grignard reagent that contained a protected aldehyde would greatly restrict the methods available for the removal of the hydroxyls. Addition of the Grignard to dialdehyde 110 afforded a compound 111 as a dark oil. Since vacuum transfer of this material required high temperatures leading to substantial decomposition of the product, the next reaction was attempted using crude diol.

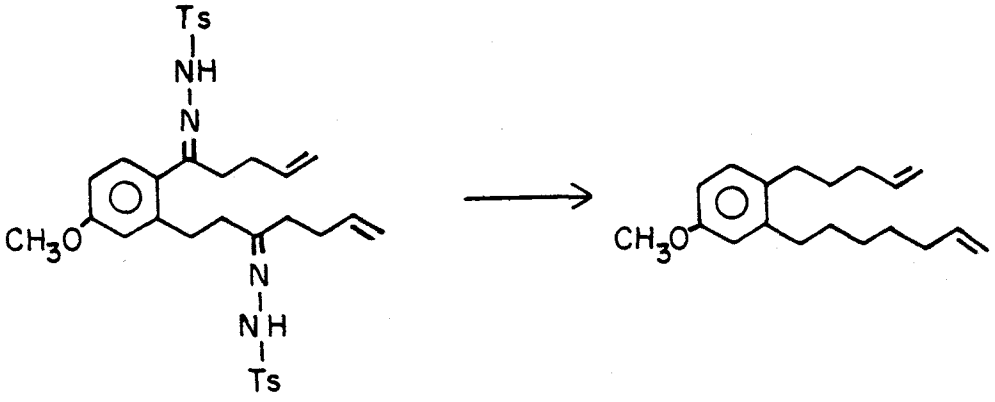
Removal of the benzilic hydroxyl as described by Small, Minnella, and Hall (77) failed to give the anticipated product. Instead, a product with a greatly reduced NMR signal in the aromatic region was isolated. Though not fully characterized, it was believed that this reaction was resulting in Birch reduction of the aromatic ring, possibly because the second hydroxyl was acting as an internal proton source. Attempts to remove this proton source by treating the diol with KH prior to Li/NH_3 reduction led only to the recovery of starting material.

A revised method for the removal of the unwanted functionality, shown in Scheme 21, called for oxidation of 111 to diketone 112, as

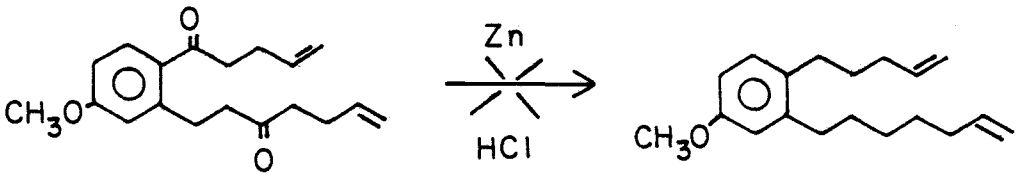
Scheme 21



111 112



113

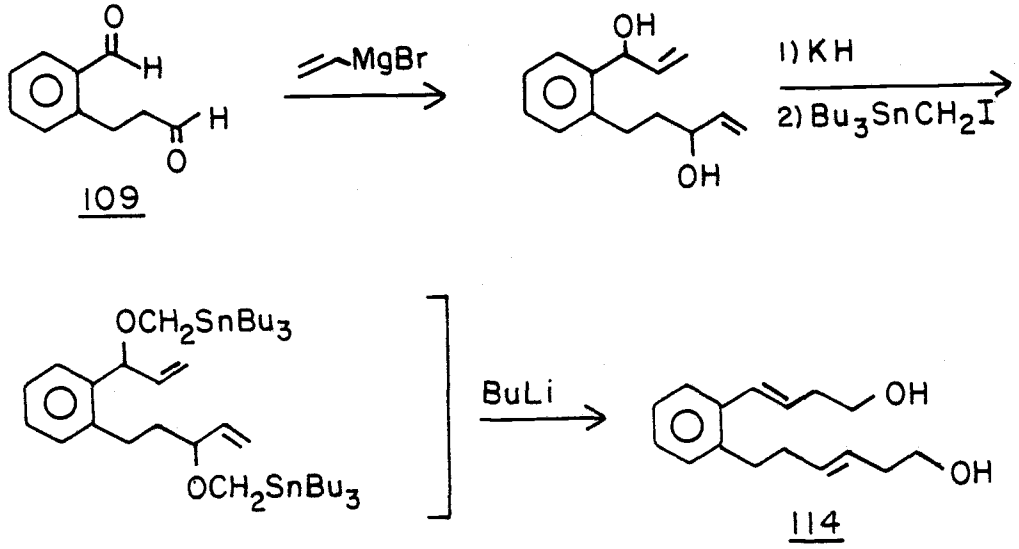


described by Collins, Hess, and Frank (78), and the subsequent reduction of the carbonyls. The first approach for the reduction of the carbonyls was that of Calgioti and Magi (79), which called for the conversion of 112 to the ditosylhydrazone 113 followed by reduction with $NaBH_4$. Unfortunately, treatment of 112 with tosylhydrazine afforded a complex mixture of products. It was later learned that similar difficulties had been encountered by Johnson (80) in the preparation of other ditosylhydrozones. An attempt at the direct reduction of the diketone using Zn and HCl, which had been used by Toda and Hirota (81) for reduction of steroidal diketones, also failed, yielding an intractable liquid.

The desirability of a method for homologation of dialdehyde 110 which produced no unnecessary functionality became increasingly clear

with the failure of each of the previous reactions. Such a method had been described by Stills et al. (82) and is shown as the final step in Scheme 22. The successful application of this reaction, which was

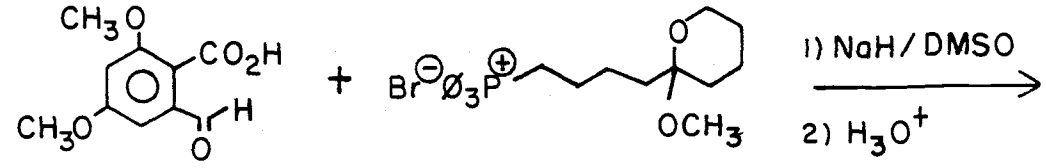
Scheme 22

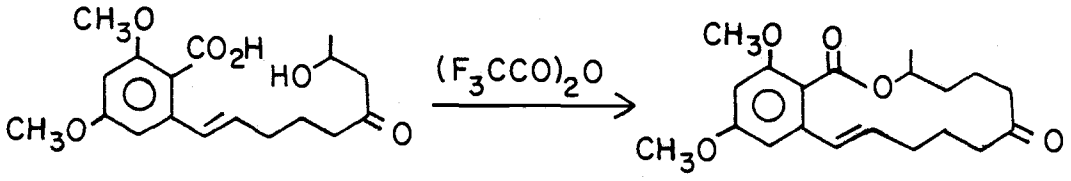


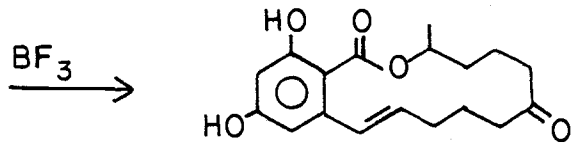
109 114

attempted on the model dialdehyde 109, would have afforded diol 114. Reduction of the double bond in 114 followed by oxidation to the dialdehyde would yield the compound required for ring closure. However, in our hands, Stills' reaction failed to produce any recognizable product.

Though the simultaneous homologation of both aromatic side chains attempted in the previous schemes appeared the more efficient process, in practice it now appeared unworkable. However, an alternative as suggested in the work of Taub, Girota, Hoffsommer, Kuo, Slates, Weber and Wendler (83) on the synthesis of zearalenone 115. In an adaption of this synthesis, shown in Scheme 23, the synthesis of 118 from the ester/aldehyde 116 and the phosphonium salt 117 was attempted. Reduction of the double bond and acyloin functionality in 118 would yield the ring system desired with oxygen functionality in the

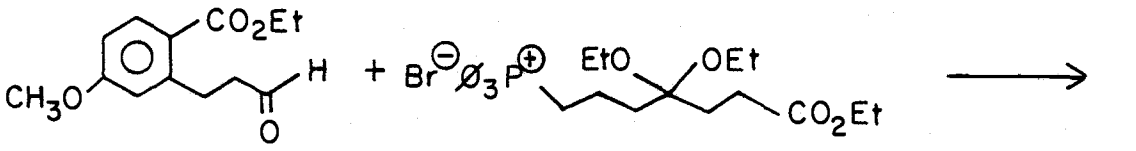




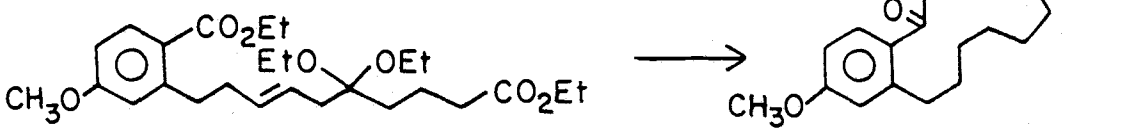


115

Scheme 23



116 117

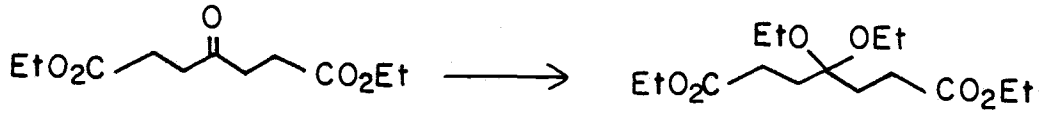


118

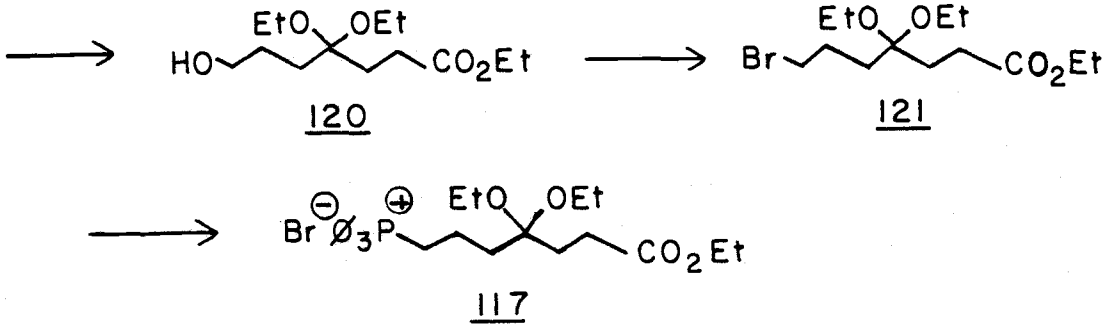
positions required. Thus attention was turned to the synthesis of the required synthons 116 and 117.

The initial method envisioned for the preparation of 117 is shown in Scheme 24. After protection of the ketone, this scheme requires

Scheme 24



119

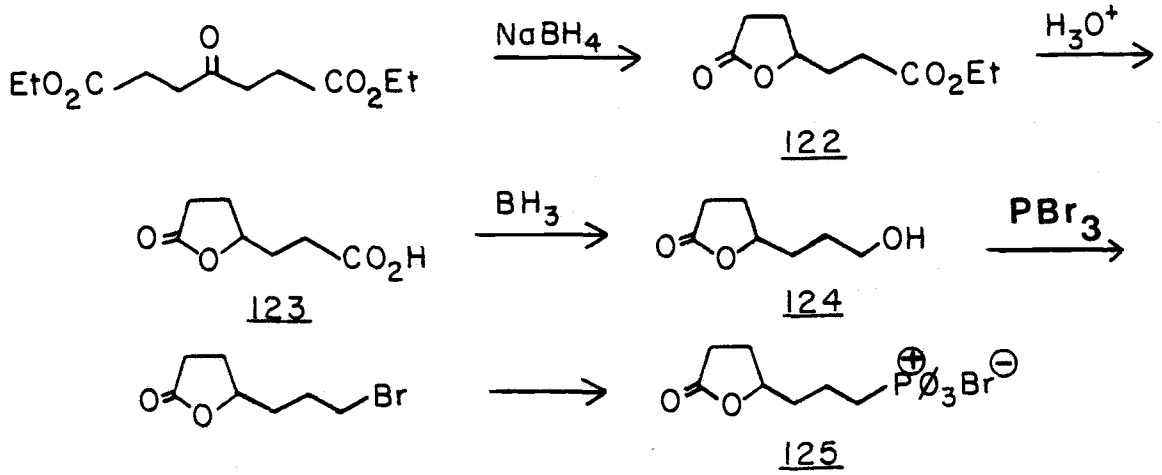


120 121 117

monoreduction of diester 119 to alcohol 120, conversion to the bromide 121 and formation of the phosphonium salt. However, this synthesis proved difficult in that attempted formation of the diethylketal consistently gave mixtures of product and starting material that could not be separated except by gas chromatography.

In view of this problem and the difficulties anticipated in obtaining clean monoreduction of diester 119, it was decided to make use of the alternative synthon 125. This synthon was seen to have advantages in that the central oxygen functionality is internally protected and would not require reduction following the ring closure. Thus, the synthesis of 125 was undertaken as shown in Scheme 25.

Scheme 25



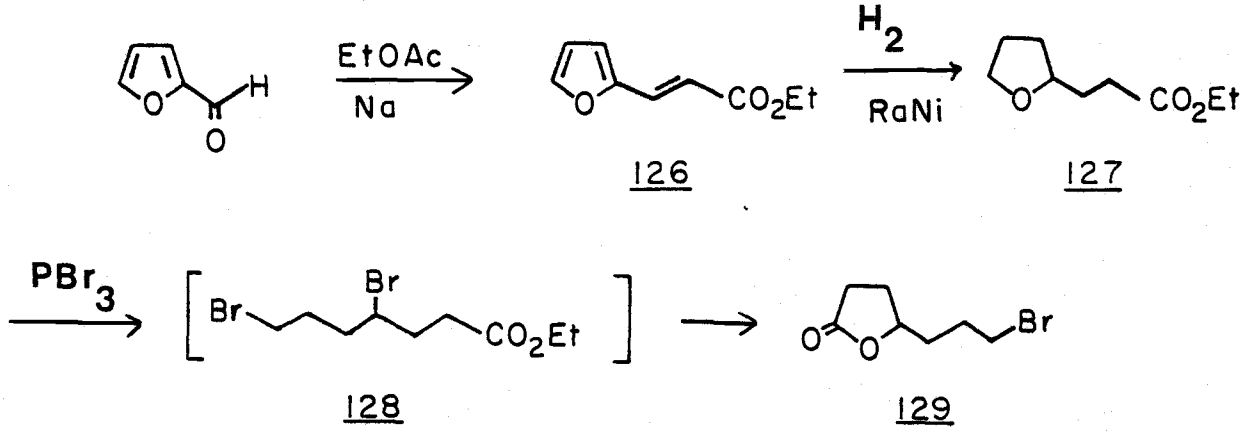
122 123 124 125

The reduction of the pimelate was known from previous work (84) to lead directly to lactone 122, reducing the ketone and protecting the

resulting hydroxyl in a single step. The aqueous hydrolysis of 122 to acid 123 and the reduction to alcohol 124 both proceeded as expected, however, isolation was difficult because of the extreme water solubility of these compounds.

Rather than devising hydrolysis and reduction methods that completely avoided aqueous conditions, it was decided to synthesize 125 by the route shown in Scheme 26, which had been reported in the

Scheme 26

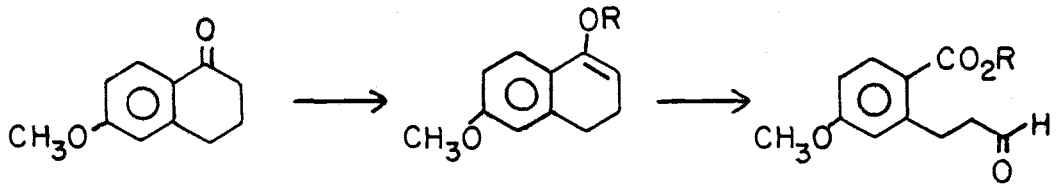


literature by Bel'skii, Shuikin, Grushco and Shostakovskii (85). The synthesis of 126 from furfural and ethylacetate was accomplished as described by Bel'skii, Shuikin, Shostakovskii and Khar'kov (86). Hydrogenation of 126 over Raney Nickel at 1500 psi and 100°C cleanly afforded the tetrahydrofuryl compound 127. Finally, ether cleavage with PBr_3 gave, along with a small amount of the intermediate dibromide 128, the desired bromo/lactone 129.

Having successfully prepared the halide required for the

production of the Wittig reagent, attention was turned to the synthesis of aldehyde 116 as outlined in Scheme 27. Similar procedures had been

Scheme 27



130 131 116

described by Schmidt and Grafen (87) for the ozonolysis of enol ethers to give α,ω aldehyde/esters and by Clark and Heathcock (88) for the ozonolysis of silyl enol ethers to give α,ω aldehyde/acids.

With the work of Schmidt and Grafen in mind, several attempts were made to synthesize the ethyl enol ether 130. These included the treatment of methoxy tetralone with triethylorthoformate and toluenesulfonic acid (89); triethylorthoformate, ethanol, and HCl (90); and triethylorthoformate and Amberlyst-15 (91). Though some reaction was observed in all of the above cases, the reaction appeared to proceed quickly to equilibrium after which no amount of additional stirring or refluxing would change the product ratio. Any attempts to drive the apparently unfavorable equilibrium or purify the resulting mixture via fractional distillation failed to improve this result.

Fortuitously, treatment of the methoxy tetralone 130 with trimethylorthoformate and toluenesulfonic acid in dry methanol as described by Miller and Gutierrez (92) afforded a good yield of

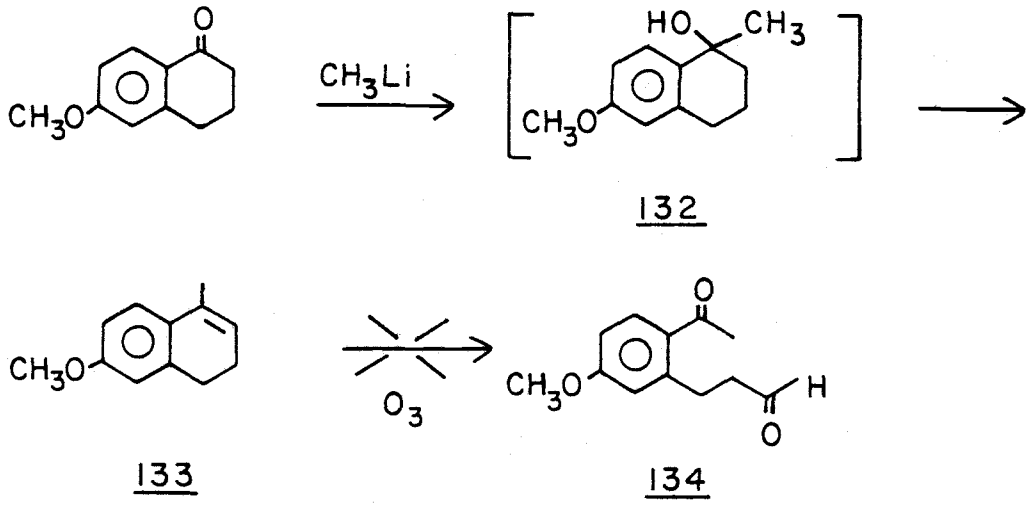
acceptably pure material. Attempted ozonolysis of this material, however, produced a complex mixture of products whose NMR spectrum indicated only a minor amount of aldehydic material.

The alternative procedure employing the ozonolysis of silyl enol ethers was foiled by inability to adequately prepare these compounds. In the work previously cited, Heathcock and Clark had produced silyl enol ethers with lithium diisopropyl amide and TMSCl or by refluxing a mixture of ketone, triethylamine and TMSCl in DMF. In the present work, however, both of these methods failed to yield more than 30% of the desired product, which proved too prone to hydrolysis to separate from unreacted starting material.

In a final attempt to employ ozonolysis as a means of cleaving the tetralone system, it was decided to try cleavage of the enol acetate. The enol acetate was formed via the exchange reaction with isopropenal acetate (93), which required removing the acetone produced as a means of driving the equilibrium. Alternatively, the formation of enol trifloroacetate, as described by Carter, Colyer, Hill, and Staunton (94), proved equally successful. Unfortunately, ozonolysis of either of these compounds gave a mixture of products which showed very little evidence of aldehyde in the NMR spectrum.

The failure of these reactions, combined with the success found in producing dialdehyde 109 via ozonolysis, led to the examination of the reactions shown in Scheme 28. It was hoped that, once prepared,

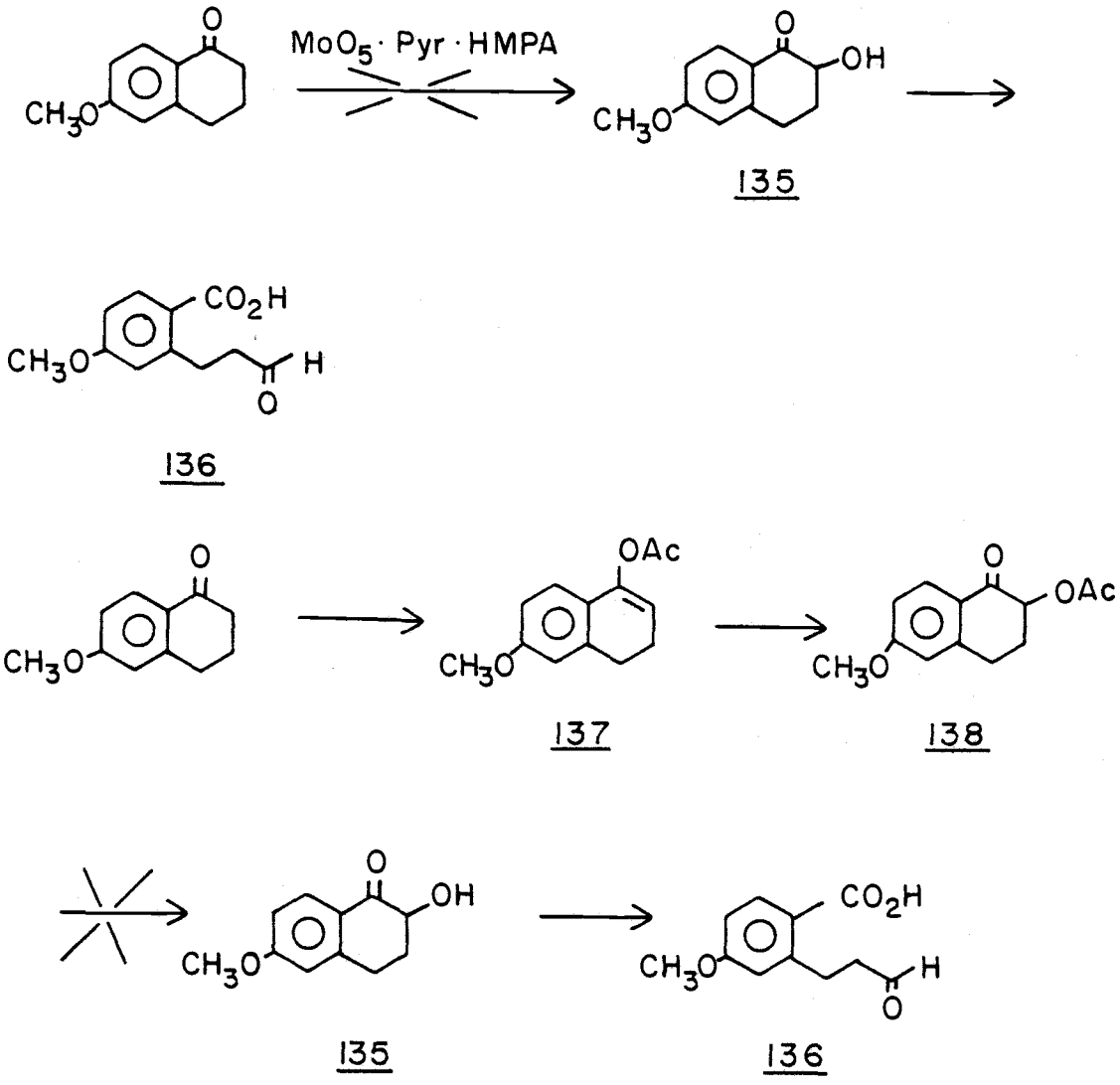
Scheme 28



compound 134 could be converted to the methyl ester via Baeyer-Villiger oxidation. Addition of methyllithium gave a mixture of the intermediate alcohol 132 and alkene 133 as a crude product but was converted entirely to alkene by vacuum transfer. Most unexpectedly, attempted ozonolysis failed to give appreciable quantities of ketone/aldehyde 134. Attempts to purify the product via flash chromatography gave low yield of material which was judged to be no more than 60% pure by NMR.

At this time a search of the literature suggested several other methods of affecting the required tetralone cleavage which were briefly examined. The first, shown in Scheme 29, called for a periodate cleavage of the α-hydroxyketone 135. Such a process had excellent precedent in the work of Schöpf and Kuhne (95), who was able to cleave the homologous α-hydroxyindanone in 72% yield.

Scheme 29



135 136 137 138 135 136

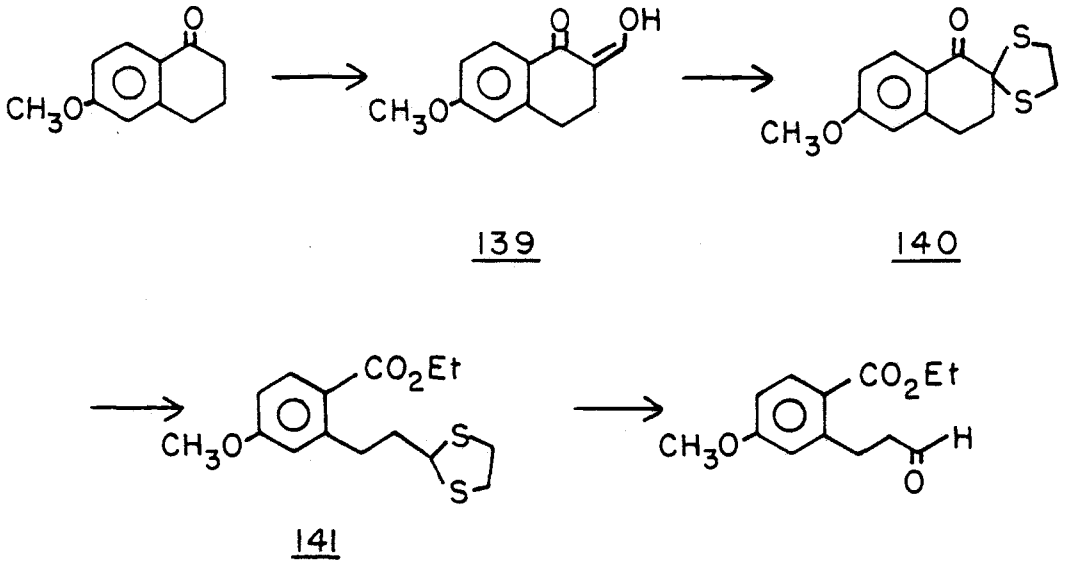
The initially attempted method for the preparation of 135 was a direct method described by Vedejs et al. (96). Treatment of methoxytetralone with lithium diisopropylamide followed by MoO_5·HMPA·Pyridine gave a dark oil that failed to show any down-field NMR signal expected for the proton on the hydroxyl-bearing

carbon. Further attempts at direct oxidation were abandoned after checking the reagent on camphor, which clearly gave the expected product.

A second, more indirect method was that reported by Barton, Evans, Hamlet, Jones and Walker (97). The enol acetate 137 was synthesized as previously mentioned and cleanly epoxided to yield 138 after rearrangement. Treatment of 138 with 10% H_2SO_4 in dioxane gave no reaction after 24 hours. Attempts to affect the desired hydrolysis in refluxing dioxane led to immediate decomposition of the starting material.

A final method of ring cleavage based on the work of Trost, Preckel and Leicher (98) is shown in Scheme 30, where reaction of

Scheme 30



139 140 141

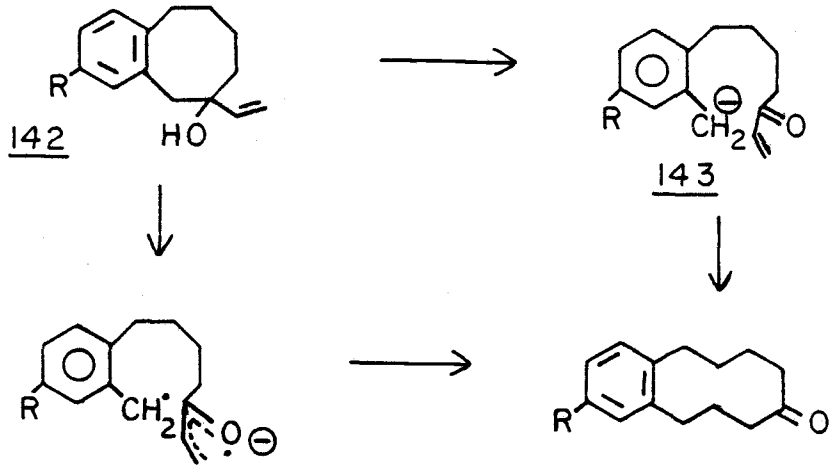
140 with sodium ethoxide would affect the desired cleavage yielding the protected aldehyde 141. Synthesis of the hydroxymethylene compound 139

was accomplished cleanly as described by Woodward, Pachter, and Scheinbaum (99), however, the attempted reaction of 139 with ethylene dithiotosylate gave a complex mixture of products that defied chromatographic separation.

The failure to obtain synthon 116 by the methods discussed certainly does not eliminate the possibility that the target molecule could be synthesized by the general method proposed. However, the principal advantage seen in such a method was its brevity and more convergent nature as compared to many of the previously discussed approaches. Though methods other than the cleavage of the methoxy tetralone system could be envisioned for the synthesis of 116, they lacked the brevity necessary to make this approach attractive as compared to other approaches currently being examined in our laboratories. Thus, the present work was laid aside pending the outcome of other approaches or the availability of an efficient synthesis of 116.

Part III - Mechanistic aspects of the anionic[1, 3] sigmatropic shift

As mentioned in the introduction, the anionic [1, 3] sigmatropic shift has been a reaction of significant importance in our laboratories as a means of effecting a two carbon ring expansion. In addition to the possibility of a concerted rearrangement, as postulated for the previously mentioned anionic [3, 3] sigmatropic rearrangement reported by Evans, two other mechanisms can be envisioned. These include cleavage to the benzylic anion 143 followed by Michael addition and homolytic cleavage to the radical, radical anion 144 followed by radical combination. Meshgini, in investigating the mechanism of this reaction, rearranged compounds 142a and 142b and found a threefold

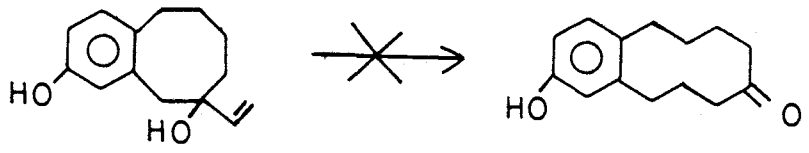


144 a,R = H; b,R = OCH_3

rate enhancement for the case where R = OCH_3. Such a rate enhancement suggests an appreciable buildup of negative charge at the benzylic carbon and the possible intermediacy of structure 143. Though these

results seem to preclude a rate determining formation of 144, it may be possible 144 is an intermediate in the Michael addition arising from a one electron transfer from 143 (100).

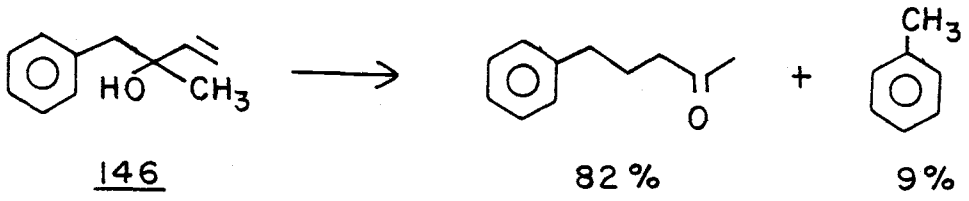
In order to further study the reaction mechanism, the rearrangement of a series of compounds with the general structure shown in 142 was of interest. Unfortunately, various limitations in the synthetic scheme made compound 145 the only example conveniently available for rearrangement. However, when compound 145 was treated with KH in HMPA no reaction was observed over several days. This fact



145

is consistent with the postulated mechanism as 145 is present as the phenoxide under the reaction conditions thereby disfavoring cleavage and the formation of a second negative change.

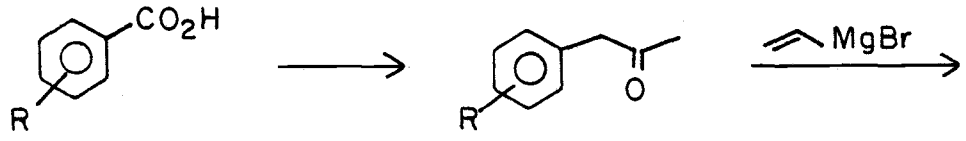
Further information suggesting a cleavage mechanism had been provided by Sietz (70), who had shown that the rearrangement of model compound 146 gave a 9% yield of toluene along with a 22% yield of the anticipated rearrangement product. It was therefore hoped that a series of substituted compounds related to 146 would provide a suitable system for more extensive rate studies. Such a series was synthesized as



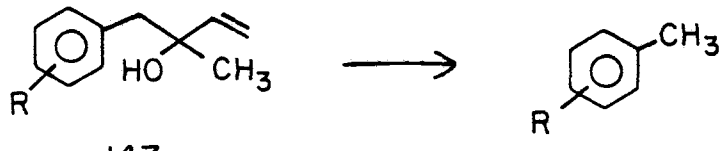
146 82 % 9 %

illustrated in Scheme 31. Treatment of the commercially available benzoic acid with excess methyllithium as described by Tegner (101),

Scheme 31



a, R = p-OCH_3 ; b, R = m-OCH_3 ; c, R = p-Cl
d, R = m-Cl; e, R = p-CH_3; f, R = m-CH_3



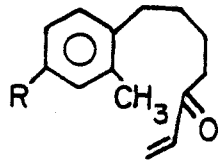
147

followed by addition of vinyl magnesium bromide afforded the compounds 147, which were required for rearrangement.

Unfortunately, those compounds which were found to react when

treated with KH in HMPA (p-Cl, p-CH_3, m-CH_3) gave substitued toluenes as the only volatile products. As any conclusions about the mechanism of rearrangement based on rate data for cleavage would be doubtful without proof of a common intermediate, no effort was made to determine the relative reaction rates for these compounds. Compound 147a, which contains the electron donating p-OCH_3 group, did not react when treated with KH, a result that was attributed to resonance destabilization of the benzylic anion. Finally, in a somewhat unexpected result, the m-OCH_3 compoung 147b also failed to react with KH in HMPA.

The fact that the cleavage products were observed in the examples cited above suggests the possibility that some quantity of compound 148 might be expected in the rearrangement of 142a and 142b. If 143 is an



148

intermediate, then such a product might arise from proton abstraction α to the carbonyl. Though an effort was made to isolate such compounds from the reaction of 142a and 142b, no material of this type could be found in the volatile products. The absence of these compounds, however, does not rule out the cleavage mechanism as such products would

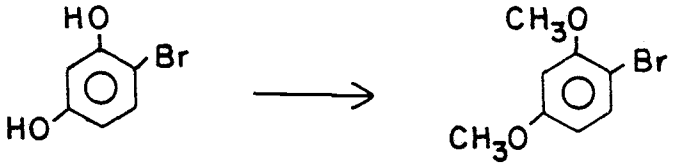
would be prone to polymerization under the reaction conditions. The NMR spectrum of the crude products from 142b did show a small extra singlet (< 10%) at δ2.22. Such a signal could be indicative of an aryl methyl in 148 or in polymerized material. It should be noted, however, that no corresponding peak was evident in the spectrum of the crude product from 142a.

To summarize, the rate data of Meshgini seems most consistent with a rate determining formation of 143. Though work on system 145 and 147 failed to provide the additional rate data hoped for, all findings were consistent with and, in that sense, are supportive of such a mechanism.

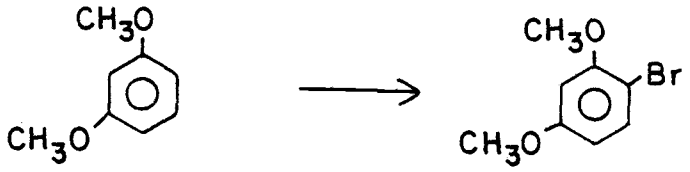
Part IV - Model studies directed at the synthesis of zearalenone analogs

In another related project, the utility of the Caubere reaction in the synthesis of a zearalenone analog was examined. The model reactions carried out toward this end are illustrated in Scheme 32.

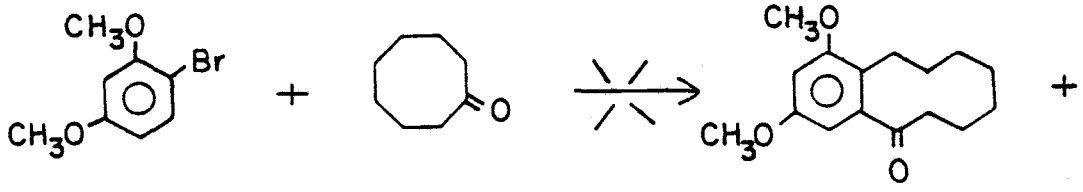
Scheme 32

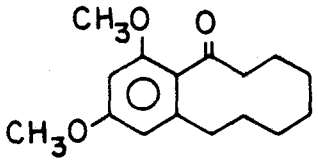


149 150

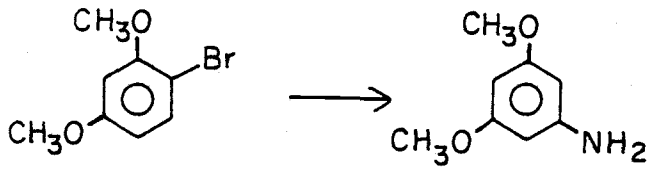


151





Synthesis of the required bromide 150 was accomplished via the two alternative routes shown. Dimethylation of bromoresorcinol 149 by



152

the method previously described did, indeed, afford the desired compound, but in unacceptably low yield. Thus bromide 150 was ultimately synthesized via the bromination of dimethoxybenzene 151 as described by Schlegel, Tipton, and Rinehart (102). Attempted reaction of the benzyne derived from 150 with the enolate of cyclooctenone failed to show any evidence of product formation in spite of the loss of starting bromide. Conformation of benzyne formation was made in the successful synthesis of compound 152 as reported by Benkesser, Hickner, Hoke and Thomas (103). The ease of formation of 152 suggests the possibility the dimethoxy benzyne is reacting with excess amide ion in preference to the enolate and the resulting aniline is lost in acidic work up. As excess amide has been shown by Caubere to be necessary for acceptable yields, this reaction was judged not to be useful in a synthesis of zearalenone analogs.

EXPERIMENTAL

General

The infrared spectra were obtained on a Perkin-Elmer 727B spectrophotomer with a polystyrene standard. NMR spectra were obtained on a Varian EM-360 (60 MHz) and HA-100 (100 MHz) with tetramethylsilane standard. High resolution mass spectra were obtained with a CEC 110B instrument at the University of Oregon. Gas-liquid chromatography (GLC) analyses were carried out on a Varian 920 (thermal conductivity detector) and a Varian 1200 (flame ionization detector) generally equipped with a OV101 on Chromosorb G, 80-100 column. Flash chromatography was carried out using the equipment and methods described by Still (104). Medium pressure chromatography was carried out on an Altex apparatus equipped with an Altex 150 UV detector. Solvents were dried according to standard procedures (105, 106).

Preparation of 7,8-benzobicyclo[4.2.0]oct-7-en-1-ol (40)

A solution of 125 g (1.28 mol) of cyclohexanone in 125 mL of dry THF was added dropwise to a vigorously stirred suspension of 100 g (2.56 mol) of $NaNH_2$ in 1L of dry THF. The addition rate was adjusted such that the internal temperature remained at 40°C. Upon completion of the addition, the reaction mixture was heated to 40°C and stirred an

additional 2 h. The resulting enolate solution was cooled to -5 °C and maintained at that temperature while 100 g (0.64 g mol) of bromobenzene was added dropwise. Following the addition of the bromobenzene the reaction was stirred for 18 h at -5°C.

The reaction was quenched by carefully pouring the resulting mixture into 2000 mL of ice and 320 mL of concentrated HCl. The aqueous layer was separated and extracted with three 100 mL portions of ether. The combined organic layers were washed with three 100 mL portions of saturated NaCl and dried over $MgSO_4$. Concentration by rotary evaporation yielded a brown semisolid.

Removal of the excess cyclohexanone was effected by Kugelrohr transfer of the volatile ketone at 50°C. The remaining material was then transferred at 100°C yielding a white solid. This material was refluxed 2 h in a solution of 2800 mL of 100% ethanol, 312 mL of acetic acid and 180 g of Girards Reagent T. The reaction was allowed to cool to room temperature and stand overnight. The ethanol solution was decanted off of the resulting white precipitate and divided into six equal portions. Each portion was concentrated to approximately 200 mL and poured into a mixture of 1000 mL of ice, 400 mL of H_2O, 800 mL of ether and 120 g of $NaHCO_3$. The resulting solution was stirred vigorously and the ether layer was separated taking care that the entire extraction procedure was completed within 5 minutes. The combined ether layers were dried over $MgSO_4$ and concentrated leaving 40.95 g

(37%) of white solid: mp 108-109°C; NMR ($CDCl_3$) δ 7.2 (s, 4H), 3.3 (t, J = 5 Hz, 1H), 0.9-2.1 (m, 9H); IR ($CDCl_3$) 3600, 3010, 2950, 1450, 1200, 1060, 920, 660 cm^{-1}.

Preparation of 7,8,9,10-tetrahydro-5(6H)-benzocyclooctenone (33)

An oven dried round bottom flask was charged with 33.32 g (0.18 mol) of 22% KH in mineral oil. The KH was washed with five 20 mL portions of dry hexane and suspended in 750 mL of dry THF. The resulting suspension was cooled in an ice bath to 0°C and treated dropwise with 29.12 g (0.17 mol) of 40 in 300 mL of dry THF. The reaction mixture was stirred at 0°C for 0.5 h then slowly quenched with 125 mL of H_2O. The aqueous layer was separated and extracted with four 125 mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated affording 29.11 g of yellow liquid. Kugelrohr transfer of this material yielded 27.48 g of clear liquid that was estimated by GC analysis to contain > 85% of the desired product. Further purification was accomplished by dry column chromatography of 4 g portions of the product on a 20" x 2" silica column with toluene elution which gave a 70% yield of pure 33: NMR ($CDCl_3$) δ 7.4-7.7 (m, 1H), 6.9-7.3 (m, 3H), 2.6-3.1 (m, 4H), 1.3-1.9 (broad m, 6H); IR (neat) 3050, 3000, 2925, 2850, 1680, 1660, 1600, 1490, 1480, 1440, 1340, 1330, 1310, 1290, 1260, 1190, 1160, 1140, 1120, 1040, 1000, 980, 750 cm^{-1}.

Preparation of 3-nitro-7, 8, 9, 10-tetrahydro-5(6H)-benzocyclooctenone (41)

A round bottom flask was charged with a 4.3 mL portion of red fuming nitric acid and cooled in a dry ice/acetone bath to -20°C. To the cooled acid was added a 1.04 g (6.0×10^{-3} mol) of 33 via dropwise addition from a pipet while maintaining the reaction of less than -15°C. Following addition of the ketone, the reaction was stirred for 0.5 h at -10 to -15°C and quenched by carefully pouring the reaction mixture into 150 mL of ice, 50 mL of H_2O and 150 mL of ether. The aqueous layer was separated and extracted with two 25 mL portions of ether. The combined ether extracts were washed with three 50 mL portions of 10% NaOH, 50 mL of saturated $NaHCO_3$ and dried over $MgSO_4$. Concentration by rotary evaporation afforded 1.10 g of yellow oil. Recrystallization from 50:50 ether/hexane gave 0.56 g (44%) of yellow crystals: mp 60-61°C; NMR ($CDCl_3$) δ 8.3 (d, J = 3 Hz, 1H), 8.1 (d of d, J = 9, 3 Hz, 1H), 7.3 (d, J = 9 Hz, 1H), 2.6-3.2 (m, 4H), 1.3-1.9 (m, 6H); IR ($CHCl_3$) 2975, 2925, 2850, 1680, 1610, 1520, 1440, 1380, 1340, 1250, 1110, 1070 cm^{-1}.

Preparation of 3-nitro-7, 8, 9, 10-tetrahydro-5(6H)-benzocyclooctenol 42

A solution of 6.91 g (0.032 mol) of 41 in 150 mL of 100% ethanol was added in a single portion to a suspension of 1.19 g (0.032 mol) of

$NaBH_4$ in 150 mL of 100% ethanol and the resulting mixture was stirred overnight at ambient temperature. The reaction was quenched with 50 mL of 10% HCl, the ethanol was removed by rotary evaporation and the resulting aqueous mixture was extracted with three 50 mL portions of ether. The combined ether extracts were washed with 75 mL of saturated $NaHCO_3$ and dried over $MgSO_4$. Removal of solvent by rotary evaporation gave 6.45 g (93%) of yellow liquid which solidifed on standing and was shown to be homogeneous by TLC: NMR ($CDCl_3$) δ 8.4 (d, J = 3 Hz, 1H), 8.0 (d of d, J = 3, 9 Hz, 1H), 7.2 (d, J = 9 Hz, 1H), 5.0-5.4 (m, 1H), 4.2-4.6 (m, 2H), 2.4-2.9 (m, 2H), 1.0-2.3 (m, 7H); IR (neat) 3400, 2925, 2850, 1600, 1580, 1510, 1450, 1350, 1280, 1270, 1250, 1210, 1170, 1130, 1090, 1070, 1030, 990, 940, 910, 870, 830, 820, 810, 770, 730 cm^{-1}.

Preparation of 3-nitro-7, 8, 9, 10-tetrahydrobenzocyclooctene (43)

A round bottom flask was charged with 6.94 g of P_2O_5 in 17 mL of H_3PO_4 and the resulting solution was heated to 100°C. In a separate flask 1.04 g (6.0×10^{-3} mol) of 42 was dissolved in 15 mL of H_3PO_4, and heated to 100°C. The resulting solution was treated by dropwise addition of the hot polyphosphoric acid and stirred 40 minutes at 100°C. The reaction was quenched by carefully pouring the resulting mixture in 50 mL of ice. The aqueous mixture was extracted with two 50 mL

portions of ether. The combined ether extracts were washed with two 75 mL portions of saturated $NaHCO_3$ and a 50 mL portion of H_2O; then dried over $MgSO_4$, and concentrated. Purification by column chromatography on a 2" x 5" silica column with toluene elution afforded 0.71 g (74%) of clear liquid: NMR ($CDCl_3$) δ 7.8-8.1 (m, 1H), 7.9 (m, 1H), 7.1-7.3 (m, 1H), 6.4 (d, J = 11 Hz, 1H), 5.4-6-2 (m, 1H), 2.7-3.0 (m, 2H), 2.0-2.4 (m, 2H), 1.2-2.0 (m, 4H); IR (neat) 3000, 2925, 2850, 1600, 1580, 1505, 1445, 1420, 1340, 1280, 1275, 1150, 1120, 1090, 910, 860, 830, 810, 750, 710 cm^{-1}.

Preparation of ethyldiazoacetate

A solution of 14.6 g of glycine ethylester hydrochloride and 0.36 g of NaOAc in 15 mL of H_2O was placed in a round bottom flask and cooled to -2° C. To the cooled solution was added 8.03 g of $NaNO_2$ in 10 mL of H_2O and the reaction was allowed to warm to 0°C. A mixture of 8 mL of ether and 0.3 mL of 10% H_2SO_4 was added and the reaction was stirred for 5 minutes at 0°C. The ether layer was separated and washed with a 10 mL portion of 10% Na_2CO_3. A second 8 mL portion of ether was added along with 1.5 mL of 10% H_2SO_4 and the reaction stirred an additional 3 minutes. The ether layer was separated and washed with a 10 mL portion of 10% $NaCO_3$. Treatment with ether and acid as described above was continued until the separated ether layer was no longer yellow. The combined ether extracts were dried over

$MgSO_4$ and concentrated leaving 2.74 g of yellow liquid. The product was stored in a solution with 75 mL of ether.

General procedure for attempted addition of the carboethoxy carbene to alkenes

A round bottom flask was charged with alkene along with catalytic amount of $CuSO_4$ and heated in a 100°C oil bath. To this mixture was slowly added 2 to 4 equivalents of ethyldiazoacetate via microsyringe and the reaction was allowed to proceed at 100°C for varying lengths of time. In all cases only carbene dimer could be isolated from the product mixtures.

Attempted preparation of benzosuberone (47)

A solution of 21 g (0.25 mol) of cyclopentanone in 50 mL of dry THF was added dropwise to a vigorously stirred suspension of 20 g (0.50 mol) of $NaNH_2$ in 250 mL of dry THF. The rate of addition was adjusted such that the internal temperature was maintained at 35°C. Upon completion of the addition, the reaction was heated to 35°C and stirred an additional 2 h. While carefully maintaining the reaction temperature at 35°C, a solution of 16.60 g (0.12 mol) of bromobenzene in 50 mL of dry THF was added dropwise to the enolate solution. The reaction was stirred an additional 3 h at 35° C and worked up as previously described. Removal of excess cyclopentanone by Kugelrohr

followed by Kugelrohr transfer of the remaining material afforded 17 g of yellow liquid which showed three components upon GC analysis. Spinning band distillation separated only one of the minor products whose IR indicated the presence of a hydroxyl group. The fraction containing the desired product remained contaminated with approximately 25% of an unknown material that defied chromatographic separation.

Preparation of benzosuberone (47)

A 15.30 g (0.10 mol) portion of P_2O_5 was dissolved in 10 mL of 85% H_3PO_4 and heated to 80-85 °C for 2 hr with occasional stirring. To the acid solution was added 0.49 g (2.7×10^{-3} mol) of δ phenylvaleric acid and the reaction mixture was heated to 95 °C for 2 h. The reaction was quenched by carefully pouring the mixture into 100 mL of ice. The aqueous mixture was extracted with three 50 mL portions of benzene. The combined benzene extracts were washed with two 50 mL portions of 5% NaOH, dried over $MgSO_4$ and concentrated affording 0.18 g (43%) of pale yellow liquid whose spectra matched that of the commercially available material.

Preparation of 3-nitro-6, 7, 8, 9-tetrahydro-5-benzocycloheptenone (48)

A round bottom flask was charged with 4 mL of red fuming nitric acid and cooled in a dry ice/acetone bath to -20°C. To the cold acid

was added 1.089 g (6.8×10^{-3} mol) of benzosuberone via dropwise addition by pipet while carefully maintaining the reaction temperature at -20°C. Following the addition, the temperature was allowed to raise to -15°C and the reaction was stirred for 0.5 h. The reaction was quenched by carefully pouring the vessel contents into a mixture of 100 mL of ether, 100 mL of H_2O and 100 mL of ice. The mixture was then neutralized with concentrated NH_4OH. The aqueous layer was separated and extracted with three 50 mL portions of ether. The combined ether extracts were washed with two 50 mL portions of 5% NaOH and one 50 mL portion of saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. Recrystallization from 50:50 ether/hexane afforded 0.81 g (59%) of pale yellow crystals: mp 91-92°C; NMR ($CDCl_3$) δ 8.5 (d, J = 3 Hz, 1H), 8.2 (d of d, J = 3, 8 Hz, 2H), 3.1 (broad t, J = 6 Hz, 2H), 2.8 (broad t, J = 6 Hz, 2H), 1.7-2.0 (m, 4H); IR (CCl_4) 2950, 2875, 1690, 1610, 1530, 1470, 1420, 1350, 1260, 1220, 1100, 1010, 980 cm^{-1}.

Preparation of 3-amino-6,7,8,9-tetrahydro-5-benzocycloheptenone (49)

A solution of 10 g (0.049 mol) of 48 in 250 mL of 95% ethanol was placed in a Parr apparatus along with 0.3 g of PtO_2 and hydrogenated at 40 psi. The reaction was periodically monitored via TLC (CH_2Cl_2) and was continued until no evidence of starting material could be observed.

The resulting reaction mixture was then filtered and concentrated yielding a yellow solid. This material was dissolved in a minimum amount of 10% HCl and the resulting solution was extracted with two 100 mL portions of ether. The aqueous layer was neutralized with saturated $NaHCO_3$ and extracted with five 100 mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated leaving 7.57 g (89%) of yellow crystals: mp 104-106° C; NMR ($CDCl_3$) δ 6.5-7.1 (m, 3H), 3.8 (broad s, 2H), 2.5-2.9 (m, 4H), 1.5-1.8 (m, 4H); IR (KBr) 3430, 3340, 3230, 3020, 2930, 2850, 1660, 1600, 1580, 1500, 1480, 1440, 1420, 1320, 1280, 1260, 1220, 1180, 1160, 980 940 cm^{-1}.

Preparation of 3-hydroxy-6,7,8,9-tetrahydro-5-benzocycloheptenone (51)

A 4.02 g (0.023 mol) of 49 was dissolved in 110 mL of 10% HOAc and the resulting solution was cooled to 8°C. To the cooled solution was added 1.64 g (0.024 mol) of $NaNO_2$ dissolved in 60 mL of H_2O at a rate such that the internal temperature remained at 8°C. After the addition was complete, the reaction was stirred an additional 15 minutes and poured into a boiling solution of 300 mL of saturated $CuSO_4$, 300 mL of H_2O, 30 mL of concentrated H_2SO_4 and 2 g of urea. The solution was stirred for 10 minutes, allowed to cool to room temperature and extracted with two 125 mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated. Kugelrohr transfer

of the crude product afforded 3.59 g (80%) of pale yellow solid: mp 98-99°C; NMR ($CDCl_3$) δ 7.4 (d, J = 2 Hz, 1H), 7.0 (d, J = 8 Hz, 1H); 6.9 (d of d, J = 2, 8 Hz, 1H), 6.7 (broad s, 1H), 2.7-3.0 (m, 4H), 1.7-2.0 (m, 4H); IR (neat) 3200 (broad H-bond OH), 2930, 1640, 1610, 1560, 1495, 1460, 1350, 1300, 1220, 1200, 980, 880, 830, 710 cm^{-1}.

Preparation of 3-methoxy-6,7,8,9-tetrahydro-5-benzocycloheptenone (52)

A 7.47 g (0.042 mol) portion of 51 was dissolved in a solution of 1.70 g (0.042 mol) of NaOH in 25 mL of H_2O and the resulting solution was cooled to 0°C in an ice bath. A 3.98 mL (0.042 mol) portion of $(CH_3)_2SO_4$ was added dropwise to the cooled solution over 0.5 h. The reaction was warmed to 50°C, stirred an additional 3 h, and quenched with 150 mL of saturated $NaHSO_4$. After stirring the quenched reaction for 5 minutes, the aqueous mixture was extracted with three 100 mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated. Kugelrohr transfer of the crude material afforded 5.92 g (74%) of yellow liquid: NMR ($CDCl_3$) δ 6.9-7.4 (m, 3H), 3.8 (s, 3H), 2.6-2.9 (m, 4H), 1.1-1.9 (m, 4H): IR (neat) 3000, 2940, 2860, 1670, 1610, 1580, 1495, 1415, 1410, 1320, 1290, 1270, 1240, 1205, 1180, 1170, 1160, 1110, 1090, 1040, 980, 860, 840, 740, 700 cm^{-1}.

Preparation of Potassium Cyanide/18:crown:6

A mixture of 0.71 g (3.0×10^{-3} mol) of 18:crown:6 and 0.81 g (3.0×10^{-3} mol) of KCN was dissolved in 30 mL of dry methanol and stirred briefly. The resulting solution was concentrated to approximately 5 mL via distillation and placed in a vacuum desiccator overnight. The white solid obtained was stored under nitrogen in a desiccator.

Preparation of 3-methoxy-5-aminomethyl-6,7,8,9-tetrahydro-5-benzocycloheptenol (54)

To a round bottom flask charged with 77 mg of KCN/18:crown:6 was added 2.43 g (0.013 mol) of 52 and the resulting mixture was stirred for 10 minutes. A 1.5 mL (0.013 mol) portion of freshly distilled TMSCN was added via syringe and the reaction was stirred for three hours at ambient temperature. Following the formation of the trimethylsilyl cyanohydrin, a 0.97 g (0.026 mol) portion of $LiAlH_4$ suspended in 25 mL of dry ether was slowly added via pipet and the reaction was stirred overnight. The reaction was quenched by careful addition of 1 mL of H_2O, 1 mL of 15% NaOH and 3 mL of H_2O. The resulting precipitate was refluxed with five 50 mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated affording 2.41 g (85%) of yellow solid which was used with further purification: NMR ($CDCl_3$) δ 7.4 (d, J = 2 Hz, 1H), 7.0

(d, J = 8 Hz, 1H), 6.7 (d of d, J = 2, 8 Hz, 1H), 3.8 (s, 3H), 3.1 (d of d, J = 2, 12 Hz, 2H), 2.7-3.0 (m, 2H), 1.7-2.3 (m, 9H); IR (neat) 3350, 3150, 2920, 2900, 2840, 1600, 1570, 1480, 1450, 1280, 1240, 1200, 1195, 1160. 1095, 1040, 920, 890, 840, 820, 740, 700 cm^{-1}.

Preparation of 3-methoxy-7, 8, 9, 10-tetrahydro-6(5H)-benzocyclooctenone (55)

A solution of 2.20 g (0.010 mol) of 54 in 75 mL of 10% aqueous acetic acid was cooled to 0°C and treated by dropwise addition with 50 mL (0.062 mol) of 1.25 M $NaNO_2$. The reaction was stirred 0.5 h at 0°C then allowed to warm to room temperature and stir overnight. The aqueous mixture was brought to pH = 10 with 15% NaOH and extracted with three 50 mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated yielding 1.72 g (85%) of yellow liquid: NMR (CCl_4) δ 7.0 (d, J = 8 Hz, 1H), 6.6-6.8 (m, 2H), 3.8 (s, 3H), 3.7 (s, 2H), 2.7-2.9 (broad t, 2H), 2.2-2.4 (broad t, 2H), 1.6-2.1 (m, 4H); IR (neat) 2930, 2850, 1700, 1610, 1580, 1500, 1460, 1320, 1250, 1160, 1105, 1040, 950, 810, 760, 700 cm^{-1}.

Preparation of 3-methoxy-7, 8, 9, 10-tetrahydro-6(5H)-benzocyclooctenone tosylhydrazone (56)

A mixture of 0.40 g (2.0×10^{-3} mol) of 55 and 0.35 g (2.0×10^{-3} mol) tosylhydrazine was dissolved in 5 mL of 100% ethanol containing one drop of concentrated HCl and the resulting solution was refluxed for 0.5 h. The reaction mixture was allowed to cool to room

temperature then placed in the refrigerator overnight. The resulting crystalline product was filtered and dried in vacuo yielding 0.51 g (73%) of product. NMR ($CDCl_3$) δ 7.9 (m, 2H), 7.2 (m, 2H), 6.9-7.2 (m, 1H), 6.6-6.9 (m, 1H), 6.2-6.6 (m, 1H), 3.8 (s, 2H), 3.7 (s, 3H), 3.5 (d, 1H), 2.4-2.8 (m, 2H), 2.4 (s, 3H), 1.8-2.2 (m, 2H), 1.3-1.7 (m, 4H); IR ($CDCl_3$) 3140, 2950, 2880, 1601, 1460, 1380, 1240, 1210, 1160, 1090, 1080, 900, 880, 850, 730, 710, 640 cm^{-1}.

Preparation of 2-methoxy-5,6,7,8-tetrahydrobenzocyclooctene (57)

A solution of 0.41 g (1.2×10^{-4} mol) of 56 in 25 mL of dry ether was placed in a round bottom flask and cooled to 0°C in an ice bath. A 1.9 mL (1.2×10^{-4} mol) portion of 1.8 M methyllithium was slowly injected, the ice bath was removed and the reaction was stirred overnight at ambient temperature. The reaction was quenched by slow addition of 50 mL of H_2O. The aqueous layer was separated and extracted with two 50 mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated affording 0.20 g (90%) of yellow liquid (as this material was shown by TLC to be homogenous, no further purification was attempted): NMR ($CDCl_3$) δ 6.7-7.2 (m, 3H), 6.4 (d, J = 11 Hz, 1H), 5.4-6.0 (m, 1H), 3.7 (s, 3H), 2.4-3.0 (m, 4H), 1.0-2.0 (m, 4H).

Attempted preparation of 1, 1-dibromo-8-methoxy-1a, 2, 3, 4, 5, 9b hexahydrobenzo[a]cyclopropa[c]cyclooctene (58)

A 0.64 g (3.4×10^{-3} mol) portion of 57 was dissolved in 1.5 mL of dry pentane and cooled to 0°C in an ice bath. To this solution was added 0.45 g (3.7×10^{-3} mol) of KOtBu followed by 0.27 mL (3.7×10^{-4} mol) of bromoform. The reaction mixture was allowed to come to room temperature and stir for 4 h. The reaction was quenched with 25 mL of H_2O and the aqueous layer was extracted with three 50 mL portions of ether. The combined organic layers were dried over $MgSO_4$ and concentrated yielding a dark brown oil which showed no evidence of the desired product in the NMR.

Preparation of 5-aminomethyl-6, 7, 8, 9-tetrahydro-5H benzocyclohepten-5-ol

The title compound was prepared by the previously described procedure from 5.0 g (0.031 mol) of benzosuberone and 3.7 mL (0.031 mol) of TMSCN. Reduction of the trimethylsilyl cyanohydrin with 2.37 g (0.062 mol) of $LiAlH_4$ gave 5.10 g of yellow solid which was used without further purification: NMR ($CDCl_3$) δ 7.6-7.8 (m, 1H), 7.0-7.35 (m, 3H), 2.7-3.36 (m, 4H), 1.5-2.5 (broad m, 9H); IR (KBr pellet) 3350, 3300, 3100, 2910, 2850, 1600, 1480, 1450, 1360, 1330, 1280, 1230, 1200, 1170, 1120, 1090, 1040, 1000, 990, 950, 860, 760, 740 cm^{-1}.

Preparation of 7,8,9,10-tetrahydro-6(5H)-benzocycloöctenone (62)

Diazotization of 5.0 g (0.026 mol) of 5-aminomethyl-6,7,8,9-tetrahydro-5-benzocycloheptenol was carried out by the previously described procedure. Kugelrohr transfer of the crude material afforded 3.90 g (86%) of pale yellow liquid: NMR (CCl_4) δ 7.1-7.2 (m, 4H), 3.7 (s, 2H), 2.7-2.9 (m, 2H), 2.2-2.3 (m, 2H), 1.6-2.0 (broad m, 4H); IR (neat) 3060, 3020, 2940, 2860, 1700, 1600, 1580, 1500, 1450, 1350, 1330, 1280, 1260, 1240, 1190, 1170, 1120, 1050, 1000, 960, 880, 760, 720, 710 cm^{-1}.

Attempted preparation of 9,10,11,12-tetrahydro-8(7H)-benzocyclodecenone (65)

A 1.02 g (6×10^{-3} mol) portion of 62 was dissolved, along with 10 mg of toluenesulfonic acid, in 6 mL of benzene and 6 mL of pyrrolidine. The solution was refluxed in a Dean-Stark apparatus for 5 h and concentrated by distillation. The resulting enamine was dissolved in 10 mL of dry hexane, treated with 0.6 mL (6×10^{-3} mol) of ethyl propiolate and refluxed overnight. The solvent was removed via rotary evaporation and the crude product was hydrolized in 10% HCl for 1 h at 50°C. The aqueous mixture was extracted with three 25 mL portions of ether. Concentration of the ether extracts followed by further hydrolysis of the product in refluxing 25% NaOH gave <400

mg of crude product. The NMR spectrum of this material, though not totally inconsistent with that expected for the desired product, indicated an unacceptably low yield of product.

Preparation of 8, 9-benzobicyclo[5.2.0]non-8-ene-1-ol (68)

The title compound was prepared by the previously described procedure with the exception that the entire reaction was carried out at 45 °C and stirred only 2 h following the addition of bromobenzene. Starting with 28.56 g (0.26 mol) of cyclohepanone, 40.25 g (0.26 mol) of bromobenzene and 20 g (0.52 mol) of $NaNH_2$, 29.10 g of white solid was obtained following vacuum transfer: NMR (d_6-acetone) δ 7.0 (s, 4H), 3.2-3.6 (m, 1H), 1.1-2.0 (m, 11H); IR ($CHCl_3$) 3550, 3400, 2950, 2900, 2825, 1590, 1510, 1470, 1450, 1410, 1360, 1320, 1200, 1100, 1040, 1010, 910, 840, 800 cm^{-1}.

Preparation of 6, 7, 8, 9, 10, 11-hexahydro-5-benzocyclononenone (69)

The title compound was prepared from 8.86 g (0.053 mol) of 22% KH in mineral oil and 10.00 g (0.053 mol) of 68 via the method previously described which gave, after Kugelrohr transfer, 9.59 g (96%) of clear liquid: NMR ($CDCl_3$) δ 7.1-7.4 (m, 4H), 2.7-3.0 (m, 4H), 1.2-2.1 (m, 8H); IR (neat) 3050, 2925, 2850, 1670, 1600, 1440, 1330, 1270, 1230, 1180, 1110, 1080, 1040, 1000, 940, 850, 780 cm^{-1}.

Preparation of 8, 9, 10, 11-tetrahydro-6(7H)-bromo-5-benzocyclononenone (70)

A 2.37 g (0.010 mol) portion of finely ground CuBr was suspended in 5 mL of ethyl acetate. The resulting mixture was brought to reflux and treated dropwise with 1.00 g (5×10^{-3} mol) of 69 in 5 mL of hot chloroform. The reaction was refluxed for 1.5 h, filtered, and the filter cake washed with two 25 mL portions of ethyl acetate. The combined organic layers were decolorized with Norit and concentrated affording 1.36 g (94%) of orange-brown liquid which appeared homogeneous upon TLC analysis: NMR ($CDCl_3$) δ 7.2 (s, 4H), 5.0 (t, J = 6 Hz, 1H), 2.5-2.9 (m, 2H), 1.9-2.3 (m, 2H), 1.0-1.9 (m, 6H).

Attempted preparation of 8, 9, 10, 11-tetrahydro-5-benzocyclononenone (71)

Method A: A 0.32 g (8×10^{-3} mol) portion of MgO was suspended in 4 mL of DMF and heated to 145 °C. The resulting solution was treated with 1.36 g (5×10^{-3} mol) of 70 and stirred at 145 °C for 1 h. The reaction was cooled in an ice bath and treated with 1.5 mL of dilute HCl in 20 mL of H_2O. The resulting aqueous mixture was extracted with three 25 mL portions of ether. The combined ether extracts were washed with two 10 mL portions of saturated NaCl, one 10 mL portion of saturated $NaHCO_3$, one 10 mL portion of saturated

NaCl, dried over $MgSO_4$ and concentrated. Analysis via TLC and NMR indicated only starting material.

Method B: A solution of 1.36 g (5×10^{-3} mol) of 70 and 0.87 g (5×10^{-3} mol) of $AgNO_3$ in 75 mL of ethanol and 4 mL of H_2O was stirred at ambient temperature for 12 h. The ethanol was removed via rotary evaporation and the resulting aqueous mixture was extracted with three 20 mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated. Analysis via TLC and NMR indicated only starting material.

Method C: A solution of 0.25 g (9×10^{-4} mol) of 70 in 3 mL of dry DMSO was injected into a round bottom flask charged with 0.10 g (9×10^{-4} mol) of KOtBu. The reaction was stirred for 2 h at amibent temperature and quenched with 50 mL of H_2O. The aqueous mixture was extracted with three 25 mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated yielding 0.18 g of product whose NMR spectrum was identical to 69.

Method D: A round bottom flask was charged with 0.25 g (9×10^{-4} mol) of 70, 0.14 g (9×10^{-4} mol) of diazobicycloundecene, and 2 mL of dry DMSO. The resulting solution was stirred for 20 h at ambient temperature. A 50 mL portion of H_2O was added and the aqueous mixture was extracted with three 25 mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated. Analysis via TLC and NMR indicated only starting material.

Method E: A solution of 1.01 g (4×10^{-3} mol) of 70 and 0.16 g (4×10^{-3} mol) of LiCl in 1.5 mL of dry DMF was stirred overnight at 100°C. A 10 mL portion of H_2O was added and the aqueous mixture was extracted with three 10 mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated. Analysis by NMR indicated only starting material.

Attempted preparation of 8, 9, 10, 11-tetrahydro-6(7H)-phenylthio-5-benzocyclononenone (74)

A round bottom flask was charged with a solution of 0.75 mL (0.018 mol) of diisopropyl amine in 15 mL of dry THF and cooled to -78°C in a dry ice/acetone bath. The cooled amine solution was treated by slow addition of 8.8 mL (0.018 mol) of 2.1 M butyllithium and the reaction was stirred for 15 minutes. A solution of 1.16 g (0.006 mol) of 69 in 5 mL of dry THF was slowly injected and the reaction was stirred for 1.5 h at -78°C. The enolate solution was allowed to warm to ambient temperature and was injected with a solution of 1.35 g (0.006 mol) of diphenyl disulfide in 5 mL of dry THF. The reaction was stirred overnight and quenched by pouring into a mixture of 50 mL of ether and 25 mL of 10% HCl. The aqueous layer was extracted with two 25 mL portions of ether. The combined organic layers were washed with one 25 mL portion of saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated. Analysis by TLC indicated two products

other than starting material. The NMR spectrum shows a triplet at 4.5 ppm indicative of the desired product, however, integration indicated that the desired product accounted for less than 20% of the product mixture. Similar results were obtained from a related procedure using phenyl phenylthiosulfonate as sulfenylating agent.

Preparation of 6, 7, 8, 9, 10, 11-hexahydro-5-benzocyclononenone tosylhydrazone (76)

A 5.21 g (0.028 mol) portion of 69 was dissolved, along with 4.82 g (0.031 mol) of tosylhydrazine, in 60 mL of anhydrous ethanol. The resulting solution was brought to reflux and stirred for 1.5 h. The reaction was allowed to cool to room temperature and placed in the refrigerator overnight. The resulting yellow solid was filtered and recrystallized from 100% ethanol affording 7.34 g (74%) of white crystalline product.

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

The title compound was prepared by the procedure described above with 4.00 g of 7, 8, 9, 10-tetrahydro-6(5H)benzocyclooctenone yielding 5.10 g (63%) of recrystallized product.

Preparation of 6, 7, 8, 9-tetrahydro-5-benzocycloheptenone tosylhydrazone

The title compound was prepared by the procedure described above with 10.01 g of 6, 7, 8, 9-tetrahydro-5-benzocycloheptenone yielding 15.89 g (84%) of recrystallized product.

Preparation of 6, 7, 8, 9-tetrahydro-5H-benzocyclononene (77)

A 5.14 g (0.016 mol) portion of 76 was dissolved in 125 mL of dry ether and cooled to 0°C in an ice bath. The cooled solution was slowly treated with 24.4 mL (0.044 mol) of 1.8 M methyllithium, allowed to warm to ambient temperature and stirred overnight. The reaction was quenched with 50 mL of H_2O and the aqueous layer extracted with three 25 mL portions of ether. The combined ether layers were dried over $MgSO_4$ and concentrated. Kugelrohr transfer of the crude product afforded 2.20 g (82%) of clear liquid: NMR ($CDCl_3$) δ 7.1 (m, 4H), 6.6 (d, J = 10 Hz, 1H), 5.8 (m, 1H), 2.4-2.8 (m, 2H), 1.7-2.4 (m, 8H); IR (neat) 3050, 3005, 2920, 2850, 1490, 1455, 1110, 1090, 850, 790, 745, 735 cm^{-1}; exact mass m/e 172.124 (calcd for $C_{13}H_{16}$: 172.125); Anal. calcd for $C_{13}H_{16}$: C, 90.64; H, 9.26, Found: C, 90.92; H, 9.10

Preparation of 5, 6, 7, 8-tetrahydrobenzocyclooctene

The title compound was prepared by the procedure described

above from 5.00 g (0.015 mol) of 6,7,8,9-tetrahydro-5-benzocyclooctenone tosylhydrazone. Kugelrohr transfer of the crude product gave 1.71 g (76%) of a pale yellow oil. The spectra of this material match those reported for the known compound (27b).

Preparation of 6,7-dihydro-5H-benzocycloheptene

The title compound was prepared by the procedure described above with 10.00 g (0.031 mol) of 6,7,8,9-tetrahydro-5-benzocycloheptenone tosylhydrazone yielding 6.8 g (76%) of clear liquid. The spectra of this material matched those reported for the known compound (107). NMR ($CDCl_3$) δ 7.1 (m, 4H), 6.3 (d of t, J = 2, 12 Hz, 1H), 5.2 (m, 1H), 2.6-2.9 (m, 2H), 2.1-2.4 (m, 2H), 1.6-2.1 (m, 4H).

Preparation of 1a,3,4,5,6,9b-hexahydro-2H-benzo[3,4]-cyclonon[1,2-b]oxirene (78)

A solution of 1.99 g (0.012 mol) of 77 in 60 mL of dry CH_2Cl_2 was cooled to 0°C in an ice bath. The cooled solution was treated with 2.59 g (0.013 mol) of 85% m-chloroperbenzoic acid, added in small portions over 10 minutes, and placed in the refrigerator overnight. The reaction mixture was filtered and the filtrate was washed with two 25 mL portions of CH_2Cl_2. The combined CH_2Cl_2 layers were washed with two 25 mL portions of saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated affording 2.09 g (96%) of clear oil. This

material appeared homogeneous on TLC and was used without further purification: NMR ($CDCl_3$) δ 6.9-7.3 (m, 4H), 3.9 (d, J=4 Hz, 1H), 3.05 (d of t, J = 4, 10 Hz, 1H), 2.5-2.9 (m, 2H), 1.0-2.3 (m, 8H); IR (neat) 3005, 2920, 2850, 1450, 1365, 1315, 900, 850, 840 cm^{-1}; exact mass m/e 188.119 (calcd for $C_{13}H_{16}O$: 188.120).

Preparation of 1a, 2, 3, 4, 5, 9b-hexahydrobenzo[3, 4]-cyclooct[1, 2-b]oxirene (86)

The title compound was prepared by the procedure described above with 0.41 g (2.5×10^{-3} mol) of 7, 8, 9, 10-tetrahydrobenzocyclooctene yielding 0.44 g (98%) of the known compound. This material was shown to be homogeneous by GC and used without further purification: NMR (CCl_4) δ 6.9-7.4 (m, 4H), 3.9 (d, J = 4 Hz, 1H), 3.05 (d of t, J = 4, 10 Hz, 1H), 2.6-2.8 (m, 2H), 1.1-2.1 (m, 6H).

Preparation of 1a, 3, 4, 8b-tetrahydro-2H-benzo[3.4]cyclohept [1, 2b]oxirene (85)

The title compound was prepared by the procedure described above with the exception that the reaction was buffered with 23 mL of 0.5 M $NaHCO_3$. A 1.11 g (7.7×10^{-3} mol) portion of 6, 7-dihydro-5H-benzocycloheptene afforded, after Kugelrohr transfer 0.91 g (73%) of the known compound 85: NMR (CCl_4) δ 6.8-7.5 (m, 4H), 3.9 (d, J = 4 Hz, 1H), 3.2 (d, J = Hz, 1H), 2.4-2.8 (m, 2H), 1.2-2.1 (m, 4H).

Rearrangement of epoxide 78

A solution of 0.14 mL (1.3×10^{-3} mol) of diisopropylamine in 5 mL of dry ether was cooled to -78°C in a dry ice/acetone bath and slowly injected with 0.58 mL (1.3×10^{-3} mol) of 2.3 M n-butyllithium. The reaction was stirred for 15 minutes at -78°C and allowed to warm to room temperature. The resulting solution was treated with 0.10 g (5.3×10^{-4} mol) of 78 dissolved in 1 mL of dry ether and stirred 4 h at ambient temperature. The reaction was quenched with 5 mL of H_2O and the aqueous layer was extracted with two 10 mL portions of ether. The combined ether layers were washed with 10 mL of 10% HCl and dried over $MgSO_4$. Removal of solvent by rotary evaporation afforded 0.093 g of crude 8,9-benzobicyclo[4.3.0]-non-8-ene-2-ol (80). A GC estimate based on integration of the product peak versus added internal standard indicated a 65% yield of 80: NMR ($CDCl_3$) δ 7.0-7.6 (m, 4H), 3.9-4.2 (m, 1H), 3.2-3.4 (t, J = 5 Hz, 1H), 2.6-2.9 (m, 2H), 2.4-2.6 (m, 1H), 1.2-1.9 (m, 7H); IR (CCl_4) 3600, 3450, 3070, 3020, 2930, 2850, 1450, 1230, 1055 cm^{-1}; exact mass m/e 188.120 (calcd for $C_{13}H_{16}O$: 188.120).

Rearrangement of epoxide 86

Treatment of the title compound in the manner described above gave, following Kugelrohr transfer, a 85:17 ratio (65%) of compound 86

and 7,8,9,10-tetrahydro-5(6H)-benzocyclooctenone: NMR (CCl_4) δ 7.1 (s, 4H), 4.1-4.4 (m, 1H), 3.5-3.8 (m, 1H), 2.5-3.4 (m, 3H), 1.3-2.1 (m, 5H); IR (CCl_4) 3570, 3450, 3060, 3010, 2930, 1480, 1460, 1440, 1170, 1075, 1000 cm^{-1}; exact mass m/e 174.104 (calcd for $C_{12}H_{14}O$: 174.104).

Rearrangement of epoxide 85

Treatment of the title compound in the manner described above gave, following Kugelrohr transfer, a 64% yield of 62: NMR ($CDCl_3$) δ 7.2 (s, 4H), 3.7 (s, 2H), 2.8-3.0 (m, 2H), 2.3-2.8 (m, 2H), 1.6-2.0 (m, 2H).

Preparation of p-bromo-(dimethyl-t-butylsiloxy)-benzene (95)

The title compound was prepared according to the procedure of Corey and Venkateswarlu (108). A 1.92 g (0.013 mol) portion of dimethyl-t-butylsilyl chloride and 1.73 g (0.013 mol) of imidazole were placed in a round bottom flask along with 20 mL of dry DMF. The resulting solution was treated dropwise with 2.00 g of p-bromophenol in 20 mL of DMF and stirred overnight at ambient temperature. An equal volume of ether was added and the resulting solution was stirred vigorously. The solution was extracted with one 100 mL portion of H_2O, two 100 mL portions of saturated $CuSO_4$ and one 50 mL

portion of saturated NaCl. The organic layer was dried over $MgSO_4$ and concentrated. Purification via flash chromatography with 5% ether in hexane afforded 2.59 g of clear liquid: NMR (CCl_4, external standard) δ 7.1 (d, J = 8 Hz, 2H), 6.5 (d, J = 8 Hz, 2H), 0.8 (s, 9H), 0.0 (s, 6H); IR (neat) 2975, 2950, 2925, 2890, 1600, 1500, 1410, 1330, 1275, 1180, 1110, 1080, 1020, 920, 840, 820, 800, 740 cm^{-1}.

Preparation of p-bromo-(diphenyl-t-butylsiloxy) benzene

The title compound was prepared by the procedure described above with 2.00 g (0.012 mol) of p-bromophenol, 3.31 g (0.013 mol) of diphenyl-t-butylsilyl chloride and 1.73 g (0.013 mol) of imidazole affording 4.53 g of clear liquid: NMR (CCl_4) δ 7.7 (m, 4H), 7.2 (m, 6H), 7.1 (d, J = 8 Hz, 2H), 6.5 (d, J = 8 Hz, 2H), 1.1 (s, 9H).

Preparation of 6-hydroxydecenone

A 1.6 L portion of decalin was placed in a round bottom flask equipped with an overhead stirrer, reflux condenser, thermometer and a sintered glass bubbler and heated to 130°C. While bubbling oxygen through the system, 18 g of benzoyl peroxide was aided in 2 g portions over 1.5 hr. The reaction was stirred an additional 20 minutes at 130°C, cooled to room temperature in an ice bath and extracted with three 200 mL portions of 10% NaOH. The organic layer was cooled to

15°C and treated with 1.5 L of 70% H_3PO_4 at such a rate that the temperature did not rise more than 2 or 3°C. After stirring an additional 1.5 h at 15°C, the acid layer was separated, diluted with 1.5 L of H_2O and extracted with three 350 mL portions of chloroform. The combined chloroform extracts were dried over $MgSO_4$ and concentrated. The crude reaction mixture was subjected to vacuum transfer at 80°C to remove excess decalin. Further purification by column chromatography with 50:50 ether/hexane afforded 4.5 g of light yellow crystals. NMR ($CDCl_3$) δ 3.6-3.9 (m, 1H), 2.2-2.7 (m, 4H), 1.2-2.0 (m, 13H); IR (CCl_3) 3550 3450, 3000, 2900, 2810, 1710, 1600, 1520, 1460, 1440, 1220, 1105, 1100, 1090, 1060, 1040, 100, 910, 900, 870, 750, 760, 740, 650 cm^{-1}.

Preparation of 6-(dimethyl-t-butylsiloxy) decanone

The title compound was prepared by the previously described procedure with 3.00 g (0.017 mol) of 6-hydroxydecanone, 2.92 g (0.018 mol) of dimethyl-t-butylsilyl chloride and 2.64 (0.018 mol) of imidazole yielding 4.69 g of crude product. Purification by flash chromatography with 30% ether in hexane afforded 3.91 g of clear liquid: NMR (CCl_4, external standard) δ 3.5-3.8 (m, 1H), 2.2-2.4 (m, 4H), 1.2-1.8 (m, 12H), 0.9 (s, 9H), 0.0 (s, 6H); IR (neat) 2950, 2940, 2850, 1710, 1480, 1470, 1460, 1375, 1260, 1190, 1110, 1080, 1040, 1020, 980, 940, 840, 780 cm^{-1}.

Attempted preparation of 3, 9-bis-(dimethyl-t-butylsiloxy)-7, 8, 9, 10, 11, 12, 13, 14-octahydro-5(6H)-benzocyclododecenone

Synthesis of the title compound from p-bromo-(dimethyl-t-butylsiloxy) benzene and 6-(dimethyl-t-butylsiloxy) decanone was attempted by the previously described procedure. Kugelrohr transfer of the excess ketone left only 0.85 g of material. The NMR spectrum of this residue showed what appeared to be unreacted ketone with a small amount of para substituted benzene.

Attempted reaction of p-bromo-(diphenyl-t-butylsiloxy) benzene with cycloheptanone

The condensation of p-bromo-(diphenyl-t-butylsiloxy) benzene and cycloheptanone was attempted via the previously described reaction. Kugelrohr transfer of the excess cycloheptane left of residue whose NMR was indicative of a dipphenyl-t-butylsilyl product resulting from cleavage of the protecting group. NMR ($CDCl_3$) 7.6 (m, 4H), 7.2 (m, 6H), 1.1 (s, 9H).

Preparation of benzyl p-bromophenyl ether (97)

A 2.72 g (0.063 mol) portion of 57% sodium hydride was placed in a round bottom flask, washed with three 20 mL portions of dry hexane and suspended in 50 mL of dry DMF. The resulting suspension was treated dropwise with a solution of 9.99 g (0.058 mol) of p-bromophenol

in 20 mL of dry DMF and the reaction was stirred for 10 minutes. A solution of 7.28 g (0.058 mol) of benzyl chloride in 20 mL of dry DMF was added dropwise and the reaction was stirred overnight at room temperature. The reaction was quenched by careful addition of 50 mL of H_2O and the resulting mixture was extracted with three 75 mL portions of ether. The combined ether extracts were washed with 50 mL of 5% NaOH, two mL portions of H_2O and dried over $MgSO_4$. Removal of solvent followed by recrystallization from ether/hexane afforded 9.5 g (63%) of white crystals: NMR ($CDCl_3$) δ 7.3 (m, 7H), 6.8 (d, J = 8 Hz, 2H), 4.9 (s, 2H).

Preparation of 3-benzyloxy-10-methoxy-7,8,9,10,11,12,13,14-octahydro-5(6H)-benzocyclododecenone (98)

Approximately 50 mL of anhydrous ammonia was condensed into a round bottom flask containing a few crystals of $Fe(NO_3)_3$. A 0.70 g (0.030 mol) portion of sodium metal was added in small pieces over 30 minutes. When the blue color had faded, the excess ammonia was blown off with N_2 and 20 mL of dry THF was added. The resulting $NaNH_2$ suspension was treated dropwise from 2.83 g (0.015 mol) of 6-methoxycyclodecanone (90) in 15 mL of dry THF. The reaction was stirred for 30 minutes at ambient temperature then heated to 45 °C. The warm enolate solution was then treated dropwise with 2.00 g (7.6×10^{-3} mol) of benzyl phenyl ether (97) in 15 mL of dry THF and

stirred overnight at 45°C. The reaction was quenched with 15 mL of H_2O and acidified with dilute HCl. The aqueous layer was separated and extracted with two 50 mL portions of ether. The combined organic layers were dried over $MgSO_4$ and concentrated. The excess layers were dried over $MgSO_4$ and concentrated. The excess ketone was removed by Kugelrohr transfer leaving 2.23 g of viscous liquid. Further purification was carried out by medium pressure chromatography on silica gel with 3:1 hexane/ether elution. The chromatographic separation yielded 0.52 g of a higher R_f material identified as 3-benzoxy-10-methoxy-7, 8, 9, 10, 11, 12, 13, 14-octahydro-5(6H)-benzocyclododecenone (98), 0.29 g of mixed fractions and 0.66 g of a lower R_f material identified as 2-benzyloxy-10-methoxy-7, 8, 9, 10, 11, 12, 13, 14-octahydro-5(6H)-benzocyclododecenone (99). Compound 98: NMR (CCl_4) δ 7.3 (m, 6H), 6.9 (m, 2H), 5.0 (s, 2H), 3.2 (s, 3H), 2.5-3.2 (m, 5H), 1.1-1.8 (m, 12H); IR (neat) 3100, 3060, 2910, 2850, 1680, 1600, 1560, 1490, 1460, 1450, 1370, 1280, 1230, 1190, 1020, 720, 690 cm^{-1}; C_{13} NMR ($CDCl_3$) 204.73, 156.10, 142.87, 138.70, 136.71, 131.70, 128.37, 127.78, 127.66, 127.16, 116.66, 112.68, 79.36, 69.97, 55.62, 39.25, 30.32, 29.44, 27.74, 27.27, 22.22, 20.17, 19.78. Compound 99: NMR (CCl_4) δ 7.3 (m, 6H), 6.9 (m, 2H), 5.0 (s, 2H), 3.2 (s, 3H), 2.5-3.2 (m, 5H), 1.1-1.8 (m, 12H); IR (neat) 3090, 3025, 2925, 2870, 2825, 1690, 1600, 1560, 1500, 1460, 1370, 1350, 1300, 1280, 1240, 1210, 1180, 1090, 1010, 990, 880, 740 cm^{-1};

C_{13} NMR ($CDCl_3$) 201.09, 157.79, 141.48, 134.19, 132.53, 126.38, 126.03, 125.45, 125.28, 124.81, 124.75, 114.56, 112.59, 108.95, 93.77, 77.00, 67.38, 57.34, 36.61, 27.80, 26.29, 26.14, 26.08, 25.79, 25.29, 20.25, 17.91, 17.41.

Attempted ring expansion of 3-benzyloxy-10-methoxy-7,8,9,10,11,12,13,14-octahydro-5(6H)-benzocyclododecenone (98)

A round bottom flask was charged with 0.52 g (1.4×10^{-3} mol) of 98, 0.036 mL of (2.8×10^{-3} mol) of TMSCN and 5 mL of dry toluene. The resulting solution was cooled to -78°C in a dry ice/acetone bath and approximately 50 mg of KCN/18:crown:6 was added. The vessel contents were placed under an argon atmosphere, tightly stoppered and placed in the freezer. After seven days, a comparison of the IR spectrum with that of the initial mixture showed no significant reduction in the carbonyl band. The vessel was returned to the freezer, however, longer reaction times failed to improve this result.

Preparation of methylisocyanide

A 57.2 g portion of recrystallized tosylchloride together with 100 g of quinoline (freshly distilled from zinc dust) were placed in a round bottom flask equipped with a distillation head, dropping funnel and collection vessel. The collection vessel was cooled in a dry ice/acetone bath and the system evacuated to approximately 200 mm using an aspirator. The reaction vessel was warmed to 75°C and 11.8 g of methylformamide was added at such a rate as to maintain boiling.

Upon completion of the addition, the reaction was stirred for 20 minutes at 75 °C. The collected distillate was redistilled at atmospheric pressure yielding 5.1 g of clear liquid; bp 60 °C (760 mm).

Attempted preparation of 3-benzyloxy-5-isocyanomethyl-10-methoxy-7, 8, 9, 10, 11, 12, 13, 14-octahydro-5(6H)-benzocyclododecenol

A round bottom flask was charged with 0.045 g (1.1×10^{-3} mol) of methylisocyanide in 5 mL of dry THF and cooled to -78 °C in a dry ice/acetone bath. The cooled solution was slowly injected with 0.68 mL (1.1×10^{-3} mol) of 1.6 M n-butyllithium and stirred for 20 minutes at -78 °C. The resulting lithium reagent was treated dropwise with 0.28 g of 98 in 8 mL of dry THF. The reaction was stirred at -78 °C and monitored by GC. No appreciable disappearance of starting material was observed after 4 h.

Attempted preparation 3-methoxy-5-isocyanomethyl-6, 7, 8, 9, 10, 11-hexahydro-5H-benzocyclononen-5-ol

Preparation of the title compound was attempted by the procedure described above using 0.25 g (1.1×10^{-3} mol) of 103, 0.047 g (1.1×10^{-3} mol) of 103, 0.047 g (1.1×10^{-3} mol) of methylisocyanide and 0.71 mL (1.1×10^{-3} mol) of 1.6 M n-butyllithium. After reacting 5 h at -78 °C, TLC analysis indicated no product formation. The reaction was allowed to warm to ambient temperature and was stirred for 48 h.

The reaction was quenched with 0.1 mL of acetic acid and diluted with 10 mL of H_2O. The aqueous layer was separated and extracted with two 20 mL portions of ether. The combined organic layers were dried over $MgSO_4$ and concentrated yielding 0.25 g of clear liquid. The NMR spectrum of this material indicated the formation of the exo-methylene compound 104: NMR ($CDCl_3$) δ 6.5-7.3 (m, 3H), 5.2 (d, J = 2Hz, 1H), 4.8 (d, J = 2Hz, 1H), 3.8 (s, 3H), 2.6-2.9 (m, 2H), 2.2-2.5 (m, 2H), 1.2-1.8 (m, 8H).

Attempted preparation of 5-nitromethyl-6,7,8,9,10,11-hexahydro-5H-benzocyclononen-5-ol (105)

Method A: A 12.5 mL portion of a stock solution containing 0.12 g (1.25×10^{-3} mol) of $KF \cdot 2H_2O$ and 0.33 g (1.25×10^{-3} mol) of 18:crown:6 in 50 mL of dry isopropanol was placed in a round bottom flask. To this solution was added 1 g (6.2×10^{-3} mol) of 69 and 0.34 mL (6.2×10^{-3} mol) of nitromethane. The reaction was stirred overnight at ambient temperature. Analysis by GC indicated no reaction had taken place.

Method B: A 0.34 g (6.3×10^{-3}) mol) portion of sodium ethoxide was dissolved in 25 mL of 100% ethanol and heated to 45°C. The warm solution was treated dropwise with 1 g (6.2×10^{-3} mol) of 69 and 0.34 mL of nitromethane in 25 mL of 100% ethanol. The reaction was stirred overnight at 45°C. Analysis by GC indicated no reaction had

taken place.

Preparation of 3,4-dihydro-1(2H)-benzocyclohexenone tosyhydrazone

The title compound was prepared by the previously described procedure with 5.00 g (0.034 mol) of 107 and 5.95 (0.037 mol) of tosylhydrazine affording 9.00 g (92%) of white crystals: NMR ($CDCl_3$) δ 7.8-8.2 (m, 4H), 7.0-7.4 (m, 5H), 2.3-2.7 (m, 4H), 2.3 (s, 3H), 1.5-1.9 (m, 2H); IR (KBr) 3070, 3030, 2960, 2950, 2925, 2875, 1620, 1600, 1490, 1460, 1440, 1400, 1340, 1320, 1310, 1290, 1180, 1080, 1060, 1020, 930, 910, 880, 860, 820, 800, 780, 710 cm^{-1}.

Preparation of 1,2-dihydrobenzocyclohexene (108)

The title compound was prepared by the previously described procedure with 3.00 g (0.011 mol) of 107 and 12.8 mL (0.024 mol) of 1.8 M methyllithium which afforded, after Kugelrohr transfer, 1.12 g (82%) of clear liquid: NMR ($CDCl_3$) δ 7.0 (s, 4H), 6.4 (d of t, J = 2.9 Hz, 1H), 5.9 (d of t, J = 4.9 Hz, 1H), 2.6-2.9 (m, 2H), 2.0-2.4 (m, 2H); IR (neat) 3050, 3010, 2910, 2875, 2810, 1480, 1470, 1430, 1420, 1120, 1270, 1220, 1200, 1150, 1110, 1030, 1020, 1000, 930, 880, 770, 740, 680 cm^{-1}.

Preparation of 3-(2-formylphenyl) propanal (109)

A 10.25 g (0.077 mol) portion of 108 was dissolved in 250 mL of dry methylene chloride and cooled to -78°C in a dry ice/acetone bath. Ozone was bubbled through the cooled solution with rapid stirring until a faint blue color was evident. The resulting solution was flushed with O_2 for 20 minutes, placed in an ice bath and allowed to warm to 0°C. The ozonide solution was treated with 4 g of zinc dust suspended in 20 mL acetic acid and stirred for 30 minutes at 0°C. This process was repeated until a total of five portions of zinc and acetic acid had been added. The excess zinc was removed by filtration and washed with three 50 mL portions of methylene chloride. The combined organic layers were washed with two 200 mL portions of H_2O, two 200 mL portions of saturated $NaHCO_3$ and dried over $MgSO_4$. Concentration via rotary evaporation afforded 9.96 g (80%) of clear liquid. Since previous attempts at Kugelrohr transfer caused significant decomposition of the product, this material was used immediately without further purification: NMR ($CDCl_3$) δ 10.1 (s, 1H), 9.7 (s, 1H), 7.6-7.8 (m, 1H), 7.0-7.1 (m, 3H), 3.3 (t, J = 7 Hz, 2H), 2.7 (t, J = 7 Hz, 2H).

Preparation of 6-methoxy-3,4-dihydro-1 (2H)-naphthalenone tosylhydrazone

The title compound was prepared by the previously described

procedure with 50 g (0.28 mol) of 6-methoxy-3,4-dihydro-1(2H)-naphthalenone and 52.84 g (0.30 mol) of tosylhydrazine which afforded, after recrystallization from 2:1 ethanol/methylene chloride, 73.2 g (75%) of white crystals: NMR ($CDCl_3$) δ 7.9 (overlapping d, J = 9 Hz, 3H), 7.6 (broad s, 1H), 7.3 (d, J = 9 Hz, 2H), 6.8 (d of d, J = 3 Hz, 9 Hz, 1H), 6.6 (d, J = 3 Hz, 1H), 3.8 (s, 3H), 2.7 (t, J = 6 Hz, 2H), 2.5 (t, J = 6 Hz, 2H) 2.4 (s, 3H), 1.8-2.1 (m, 2H); IR (neat) 3275, 3200, 3050, 2950, 2850, 1610, 1600, 1500, 1380, 1330, 1300, 1280, 1240, 1190, 1180, 1130, 1080, 1050, 1040, 1000, 940, 910, 890, 810 cm^{-1}.

Preparation of 7-methoxy-1,2-dihydro naphthalene

The title compound was prepared by the previously described procedure with 50 g (0.145 mol) of 6-methoxy-3,4-dihydro-1(2H)-naphthalenone tosylhydrazone and 169 mL (0.305 mol) of 1.8 M methyllithium which afforded, after Kugelrohr transfer, 17.71 g of clear liquid: NMR (CCl_4) 6.8 (d, J = 9 Hz, 1H), 6.5-6.7 (m, 2H), 6.3 (d of t, J = 2.8 Hz, 1H), 5.8 (d of t, J = 4, 8 Hz, 1H), 3.6 (s, 3H), 2.7 (t, J = 8 Hz, 2H), 2.1-2.3 (m, 2H); IR (neat) 3000, 2975, 2925, 2850, 2800, 1600, 1560, 1480, 1450, 1410, 1380, 1305, 1290, 1260, 1240, 1170, 1140, 1110, 1090, 1020, 1000, 920, 880, 860, 840, 800, 760, 740, 700, 670, 640 cm^{-1}.

Preparation of 3-(2-formyl-5-methoxyphenyl) propanal (110)

The title compound was prepared by the previously described ozonolysis procedure with 10.19 g of 7-methoxy-1, 2-dihydronaphthalene yielding 9.60 g (80%) of clear liquid. Since Kugelrohr transfer caused extensive product decomposition, this material was used without further purification: NMR (CCl_4) δ 9.8 (s, 1H), 9.6 (s, 1H), 7.6 (d, J = 8 Hz, 1H), 6.5-6.9 (m, 2H), 3.9 (s, 3H), 3.2 (t, J = 7 Hz, 2H), 2.7 (5, J = 7 Hz, 2H).

Preparation of 1-(1-hydroxy-4-pentenyl)-2-(3-hydroxy-6-heptenyl)-4-methoxybenzene (111)

A round bottom flask was charged with 1.18 g (0.049 mol) of magnesium turnings and 10 mL of dry THF. A small amount of solution containing 6.60 g (0.049 mol) of 4-bromobutene in 40 mL of dry THF was added and heat was applied to initiate reaction. The remainder of the bromide solution was added dropwise and the reaction was stirred 1 h at ambient temperature. The resulting Grignard reagent was treated dropwise with 8.50 g (0.044 mol) of 110 in 100 mL of dry THF. The reaction was stirred 2 h at ambient temperature and quenched with 20 mL of H_2O. The aqueous layer was separated and extracted with two 50 mL portions of ether. The combined organic layers were dried over $MgSO_4$ and concentrated affording 9.9 g (74%)

of crude product: NMR (CCl_4) δ 7.25 (m, 1H), 6.6 (m, 2H), 5.6-6.0 (m, 2H), 4.8-5.1 (m, 5H), 3.75 (s, 3H), 3.6-3.7 (broad s, 2H), 2.6-2.9 (m, 2H), 1.9-2.4 (m, 5H), 1.4-1.8 (m, 6H).

Attempted preparation of 1-(4-pentenyl)-2-(3-hydroxy-6-heptenyl)-4-methoxybenzene

A 0.62 g (0.090 mol) portion of lithium metal was placed in a round bottom flask containing 100 mL of dry THF. Approximately 200 mL of anhydrous ammonia was condensed into the reaction vessel and the mixture was stirred until all of the lithium had dissolved. The resulting solution was treated as rapidly as possible with a solution of 9.00 g (0.030 mol) of 111 in 50 mL of dry THF. The reaction was stirred for 10 minutes and quenched with solid NH_4Cl. The ammonia was allowed to evaporate and 100 mL of saturated NaCl was added to the remaining solution. The aqueous layer was separated and extracted with three 50 mL portions of ether. The combined organic layers were dried over $MgSO_4$ and concentrated affording 6.86 g of crude material. A 1 g portion of this material was subjected to flash chromatography with 30% ethyl acetate in pentane. Two main fractions were collected consisting of 0.36 g of material whose NMR was identical to that of the starting material and 0.21 g of product whose NMR showed a greatly reduced signal in the aromatic region and a methoxy singlet shifted 0.3 ppm upfield from that in the starting material.

Preparation of 1-(1-oxo-4-pentenyl)-2-(3-oxo-6-heptenyl)-4-methoxybenzene (112)

A round bottom flask was charged with 50 mL of dry methylene chloride, 3.2 mL (0.038 mol) of pyridine, and 1.97 g (0.019 mol) of CrO_3. The resulting solution was stirred for 15 minutes and treated with 0.50 g (1.6×10^{-3} mol) of 111 in 5 mL of dry methylene chloride. After an additional 15 minutes of stirring at ambient temperature, the solvent was decanted off of the resulting "tar" and the resinous material was extracted with two 50 mL portions of ether. The combined organic layers were washed with 50 mL of 5% NaOH, 50 mL of 5% HCl, and 50 mL of $NaHCO_3$. The washed solution was dried over $MgSO_4$, passed through a 2" silica column and concentrated affording 0.46 g (92%) of yellow liquid which was used without further purification: NMR (CCl_4) δ 7.8 (d, J = 8 Hz, 1H), 6.4-6.9 (m, 2H), 5.6-6.4 (m, 2H), 4.8-5.4 (m, 4H), 3.9 (s, 3H), 2.0-3.2 (m, 12H); IR (neat) 3050, 2990, 2950, 2905, 2825, 1720, 1675, 1610, 1600, 1580, 1490, 1440, 1410, 1350, 1310, 1280, 1240, 1200, 1180, 1120, 1030, 990, 900, 780 cm^{-1}.

Attempted preparation of 1-(1-oxo-4 pentenyl)-2-(3-oxo-6-heptenyl)-4-methoxybenzene ditosylhydrazone (113)

The synthesis of the title compound was attempted by the method previously described. TLC analysis of the resulting reaction mixture

indicated four major products which appeared to be present in equivalent amounts. Attempts to isolate the desired compound via recrystallization or column chromatography were uniformly unsuccessful.

Attempted preparation of 1-(4-pentenyl)-2-(6-heptenyl)-4-methoxybenzene

A 15 mL portion of dry ether was cooled to 0°C and saturated with dry HCl. The resulting solution was treated with 0.26 g (8.6×10^{-4} mol) of 112 and 0.10 g (0.015 mol) of zinc dust. The reaction mixture was stirred at 0°C for 1 h and poured into 50 mL of ice/H_2O. The liquid was removed by decantation, made basic with Na_2CO_3 and the ether layer was separated. The unreacted zinc was washed with three 20 mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated affording 0.22 g of black intractable liquid.

Preparation of 1-(1-hydroxy-2-propenyl)-2-(3-hydroxy-4-pentenyl) benzene

A round bottom flask was charged with 0.51 g (0.021 mol) of magnesium turnings and 5 mL of dry THF. A small amount of solution containing 1.5 mL (0.021 mol) of vinyl bromide in 20 mL of dry THF was added and heat was applied to initiate reaction. The remainder of the vinyl bromide solution was added dropwise and the reaction was stirred for 1 h at ambient temperature. A solution of 1.54 g

(0.010 mol) of 3-(2-formylphenyl) propanal 109 in 20 mL of dry THF was added dropwise to the Grignard reagent. The reaction was stirred for 2 h at ambient temperature and quenched with 20 mL of H_2O. The aqueous layer was separated and extracted with two 50 mL portions of ether. The combined organic layers were dried over $MgSO_4$ and concentrated. Kugelrohr transfer afforded 1.68 g (82%) of pale yellow liquid: NMR ($CDCl_3$) δ 7.1 (m, 4H), 5.5-6.0 (m, 2H), 4.8-5.5 (m, 4H), 3.2-4.2 (m, 4H), 2.7 (broad t, J = 6 Hz, 2H), 1.5-1.9 (m, 2H).

Attempted preparation of 1-(4-hydroxy-1-butenyl)-2-(6-hydroxy-3-hexenyl) benzene (114)

A 0.84 g (4.6×10^{-3} mol) portion of 22% KH in mineral oil was placed in a round bottom flask, washed with five 2 mL portions of dry hexane and slowly injected with 0.51 g (2.3×10^{-3} mol) of 1-(1-hydroxy-2-propenyl)-2-(3-hydroxy-4-pentenyl) benzene in 10 mL of dry THF. The reaction was stirred at ambient temperature for 15 minutes, injected with 1.98 g (4.6×10^{-3} mol) of iodomethyl tri-n-butyltin in 5 mL of dry THF and allowed to stir overnight. The resulting solution was cooled to -78°C, injected with 3.06 mL (4.6×10^{-3} mol) of 1.8 M n-butyllithium and stirred for 30 minutes. An aqueous work up as described above afforded a material whose NMR spectra showed no evidence of the desired product.

Attempted preparation of diethyl-4,4-diethoxylate (119)

A solution of 11.21 g (0.046 mol) of diethyl-4-oxopimelate and 11.22 g (0.076 mol) of triethylorthoformate in 40 mL of anhydrous ethanol was saturated with anhydrous HCl and stirred overnight at ambient temperature. The reaction mixture was neutralized with sodium ethoxide in ethanol and concentrated via rotary evaporation. Kugelrohr transfer afforded 11.52 g of product whose NMR indicated approximately 30% unreacted starting material along with the desired product. Attempts at separation via spinning band distillation failed to improve this result.

Preparation of 4-(2-ethoxycarbonylethyl)-4-hydroxybutanoic acid γ-lactone (122)

A 0.55 g (0.014 mol) portion of $NaBH_4$ was dissolved in 100 mL of 100% ethanol, cooled to 0°C and treated with 5.00 g (0.022 mol) of diethyl-4-oxopimilate in 10 mL of 100% ethanol. The resulting mixture was stirred for 2 h at 0°C, allowed to come to ambient temperature and was stirred overnight. The reaction was quenched with 20 mL of saturated NH_4Cl and the resulting salts were dissolved by addition of a minimum amount of H_2O. The ethanol was removed by rotary evaporation and the remaining aqueous mixture was extracted with two 100 mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated affording 3.70 g (91%) of pale yellow

liquid: NMR ($CDCl_3$) δ 4.4-4.8 (m, 1H), 4.2 (q, J = 7 Hz, 2H), 1.6-2.8 (m, 11H): IR (neat) 2900, 2850, 1780, 1720, 1475, 1450, 1430, 1380, 1350, 1260, 1180, 1100, 1040, 950, 920, 880, 800 cm^{-1}.

Attempted preparation of 4-(2-carboxyethyl)4-hydroxybutanoic acid γ-lactone (123)

A 1.17 g portion of 122 was stirred overnight in 15 mL of 10% NaOH, extracted with 50 mL of ether, reacidified and continuously extracted for 12 h with THF. Concentration of the THF by rotary evaporation failed to yield any product. Distillation of the aqueous layer left a mixture of sodium chloride and an organic product. Extraction of this mixture with acetone gave 1.05 g of yellow solid whose NMR spectrum was indicative of the desired product contaminated with an unknown organic material. Attempts to recrystallize the produce from various solvent mixtures containing acetone were uniformly unsuccessful.

Preparation of ethyl 3-(2-furyl) propenoate (126)

A 24 g (1.04 mol) portion of sodium metal was placed in a round bottom flask along with 600 mL of ethyl acetate (freshly distilled from Na) and the mixture was cooled to 0°C. The cooled mixture was treated dropwise with 100 g (1.04 mol) of furfural and allowed to warm to ambient temperature. The reaction was stirred for 24 h and quenched

with 300 mL of 10% acetic acid. The organic layer was separated, dried over $MgSO_4$ and concentrated. Kugelrohr transfer of the crude product afforded 101 g (59%) of yellow liquid. NMR (CCl_4) δ 7.2-7.7 (m, 2H), 6.1-6.6 (m, 3H), 4.1 (q, J = 7 Hz, 2H), 1.3 (t, J = 7 Hz, 3H); IR (CCl_3) 2950, 2900, 2850, 1700, 1620, 1560, 1480, 1380, 1360, 1300, 1260, 1200, 1160, 1100, 1080, 1000, 960, 880, 860, 800, 760, 660 cm^{-1}.

Preparation of ethyl 3-(2-tetrahydrofuryl) propanoate (127)

A solution of 10.00 g of 126 in 200 mL of 100% ethanol was hydrogenated over Raney-nickel at 1500 psi and 100°C. The solution was filtered and concentrated via rotary evaporation affording 10.2 g of crude product. Fractional distillation gave 8.5 g (85%) of clear liquid: bp 89°C (4 mm); NMR ($CDCl_3$) δ 4.2 (q, J = 7 Hz, 2H), 3.6-3.9 (m, 3H), 1.6-2.1 (m, 8H), 1.3 (t, J = 7 Hz, 3H): IR (neat) 2850, 1760, 1450, 1430, 1410, 1360, 1340, 1300, 1240, 1210, 1160, 1120, 960, 940, 900, 850, 790, 740 cm^{-1}.

Preparation of 7-bromo-4-hydroxyheptanoic acid γ-lactone (129)

A round bottom flask was charged with 1.01 g (6×10^{-1} mol) of 127 and 0.55 mL (6×10^{-3} mol) of PBr_3. The resulting mixture was stirred for 20 minutes at reflux, cooled to room temperature and

stirred an additional hour with three 20 mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated. Purification by flash chromatography with 50:50 ether/hexane afforded 400 mg (33%) of clear liquid: NMR ($CDCl_3$) δ 4.6 (m, 1H), 3.6 (t, J = 7 Hz, 2H), 1.6-2.7 (m, 8H); IR (neat) 2850, 1770, 1460, 1440, 1420, 1390, 1340, 1300, 1280, 1250, 1220, 1170, 1120, 1040, 980, 960, 910, 880, 800 cm^{-1}.

Attempted preparation of 7-methoxy-4-ethoxy-1, 2-dihydronaphthalene

Method A: A round bottom flask was charged with 5.0 g (0.028 mol) of 6-methoxy-3, 4-dihydro-1(2H)-naphthalenone, 0.025 g of toluenesulfonic acid and 4.72 mL (0.028 mol) of triethylorthoformate. The resulting mixture was stirred for 24 h at ambient temperature at which time GC analysis showed a substantial amount of unreacted starting material. An additional 2 mL of triethylorthoformate was added and the reaction was brought to reflux. The extent of reaction after 0.5 h at reflux was estimated to be no more than 50%. This result remained constant after an additional 12 h.

Method B: A solution of 0.50 g (2.8×10^{-3} mol) of 6-methoxy-3, 4-dihydro-1(2H)-naphthalenone and 0.47 mL (2.8×10^{-3} mol) of triethylorthoformate in 10 mL of 100% ethanol containing one drop of concentrated HCl was stirred at ambient temperature. After 0.5 h,

the extent of reaction as measured by GC analysis was estimated to be no more than 45%. As continued stirring produced no appreciable change in this result, some of the ethanol was distilled in hope of driving the equilibrium by azeotropic removal of H_2O. This procedure also failed to effect complete conversion of the starting material to product.

Method C: A solution of 0.50 g (2.8×10^{-3} mol) of 6-methoxy-3,4-dihydro-1(2H)-naphthalenone, and 0.47 mL (2.8×10^{-3} mol) of triethylorthoformate was stirred at 0°C with 0.12 g of Amberlyst-15. After 5 h of stirring, the extent of reaction was estimated to be no more than 25%. The reaction was stoppered and placed in the refrigerator. Analysis of the reaction mixture after 24 h showed no appreciable change.

Preparation of 4,7-dimethoxy-1,2-dihydronaphthalene

A solution of 10.01 g (0.056 mol) 6-methoxy-3,4-dihydro-1(2H)-naphthalenone, 20 mL (0.11 mol) of trimethylorthoformate and 0.2 g of toluenesulfonic acid in 150 mL of dry methanol was stirred overnight at ambient temperature. The reaction mixture was made basic with sodium methoxide and concentrated. The crude product was dissolved in ether and the resulting solution was extracted with H_2O until the aqueous layer remained neutral. The ether layer was dried over $MgSO_4$ and concentrated. Kugelrohr transfer afforded 7.51 g (73%)

of clear liquid: NMR (CCl_4) δ 7.4 (d, J = 9 Hz, 1H), 6.8 (m, 2H), 4.8 (t, J = 4 Hz, 1H), 3.6 (s, 3H), 3.5 (s, 3H), 2.5-2.9 (m, 2H), 2.2-2.5 (m, 2H) .

Preparation of 7-methoxy-4-trifloroacetoxy-1, 2-dihydro naphthalene

A round bottom flask was charged with 0.51 g of 6-methoxy-3, 4-dihydro-1(2H)-naphthalenone, in 10 mL of trifloroacetic acid and stirred at ambient temperature for 2 h. The excess trifloroacetic acid was blown off with dry nitrogen leaving a brown liquid. Kugelrohr transfer of the crude product afforded 0.73 g (94%) of pale yellow liquid: NMR (CCl_4) δ 6.9 (d, J = 9 Hz, 1H), 6.5 (m, 2H), 5.7 (t, J = 4 Hz, 1H), 3.7 (s, 3H), 2.6-2.9 (m, 2H), 2.2-2.5 (m, 2H).

Preparation of 7-methoxy-4-acetoxy-1, 2-dihydronaphthalene (137)

A round bottom flask equipped with a distillation head was charged with 0.20 g (1.1×10^{-3} mol) of 6-methoxy-3, 4-dihydro-1(2H)-naphthalenone, 10 mg of toluenesulfonic acid and 5 mL of isopropenyl acetate. The reaction mixture was heated such that isopropenol acetate was refluxing just below the distillation side arm and stirred for 2.5 h. The excess isopropenol acetate was removed by distillation and the crude product was dissolved in 50 mL of ether. The ether solution was washed with saturated $NaHCO_3$, dried over $MgSO_4$ and

concentrated. Kugelrohr transfer afforded 0.19 g (86%) of clear liquid: NMR ($CDCl_3$) δ 6.9 (d, J = 9 Hz, 1H), 6.6 (m, 2H), 5.5 (t, J = 4 Hz, 1H), 3.8 (s, 3H), 2.6-2.9 (m, 4H), 2.2 (s, 3H).

Ozonolysis of the 6-methoxy-3,4-dihydro-1(2H)-naphthalenone enol ether and enol acetates

Each of the three compounds described above were subjected to ozonolysis under the previously described conditions. In all cases, the NMR spectra of the crude product exhibited a singlet near 9.8 indicative of the desired product. However, integration of the signal showed that in no case did the amount of desired product exceed 20% of the crude mixture. Further purification of crude product was made impractical by the instability of these compounds.

Attempted preparation of 7-methoxy-4-trimethylsiloxy-1,2-dihydronaphthalene

Method A: A solution of 0.47 mL (3.4×10^{-3} mol) of diisopropyl amine in 50 mL of dry THF was cooled to -78°C and injected with 1.89 mL (3.4×10^{-3} mol) of 1.8 M of n-butyllithium. The reaction was stirred for 15 minutes and slowly injected with 0.50 g (2.8×10^{-3} mol) of 6-methoxy-3,4-dihydro-1(2H)-naphthalenone in 5 mL of dry THF. After an additional 30 minutes of stirring, the resulting enolate solution was treated with 0.43 mL (3.4×10^{-3} mol) of trimethylsilyl chloride. The reaction was allowed to warm to ambient temperature and

and stir overnight. Following dilution with cold pentane, the reaction was quenched by addition of 50 mL of cold saturated $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$ and concentrated. The NMR spectrum of the crude reaction mixture indicated only 33% conversion of the starting material to the desired product.

Method B: In an alternative procedure a mixture of 0.50 g (2.8×10^{-3} mol) of 6-methoxy-3,4-dihydro-1(2H)-naphthalenone, 0.78 mL (5.6×10^{-3} mol) of triethyl amine and 0.53 mL of trimethylsilyl chloride in 10 mL of dry DMF was stirred overnight at reflux. The NMR spectrum of the reaction mixture again indicated only partial conversion to product.

Preparation of 7-methoxy-4-methyl-1,2-dihydro naphthalene (133)

A round bottom flask was charged with 1.52 g (0.061 mol) of magnesium turnings and 50 mL of anhydrous ether. A small portion of a solution containing 3.89 mL (0.061 mol) of methyl iodide in 50 mL of anhydrous ether was added and heat was applied to initiate reaction. The remainder of the methyl iodide solution was added dropwise and the reaction was refluxed for 30 minutes. The resulting Grignard reagent was cooled to 0°C and treated dropwise with 10 g (0.056 mol) of 6-methoxy-3,4-dihydro-1(2H)-naphthalenone in 150 mL of anhydrous ether. The reaction was stirred overnight at ambient temperature and

quenched by slow addition of 100 mL of saturated NH_4Cl. The aqueous layer was extracted with two 50 mL portions of ether. The combined ether layers were dried over $MgSO_4$ and concentrated. Analysis of the crude product by NMR indicated a mixture of the expected alcohol and a large amount of the title compound. Kugelrohr transfer of the crude product affected complete dehydration of the alcohol leaving 7.40 g (74%) of the alkene (133): NMR (CCl_4) δ 7.0 (d, J = 9 Hz, 1H), 6.3-6.7 (m, 2H), 5.6 (m, 1H), 3.6 (s, 3H), 2.5-2.8 (m, 2H), 1.9-2.4 (m, 2H), 1.9 (s, 3H); IR (neat) 3000, 2975, 2925, 2850, 2800, 1600, 1560, 1480, 1450, 1410, 1380, 1305, 1290, 1260, 1240, 1170, 1140, 1110, 1090, 1020, 1000, 920, 880, 860, 840, 760, 740, 700, 670, 640 cm^{-1}.

Ozonolysis of 7-methoxy-4-methyl-1,2-dihydro naphthalene (133)

The title compound was subjected to ozonolysis under the previously described conditions. The NMR spectrum of the crude product indicated the reaction mixture contained about 40% of the desired compound. Attempts to further purify the product by flash chromatography yielded a clear liquid which contained only 60% of the desired product as judged by NMR.

Attempted Preparation of 6-methoxy-2-hydroxy-, 4-dihydro-1(2H)-naphthalenone (135)

Method A: A 0.11 g portion of 138 was placed in a round bottom

flask along with 1 mL of dioxane and 1 mL 10% H_2SO_4. The reaction was stirred overnight with no appreciable loss of starting material as evidenced by TLC. Further attempts at hydrolysis in refluxing dioxane/10% H_2SO_4 caused immediate decomposition of the starting material.

Method B: A solution of 0.59 mL (4.5×10^{-3} mol) of diisopropyl amine in 25 mL of dry THF was cooled to -78°C and slowly injected with 0.25 mL (4.5×10^{-3} mol) of 1.7 M n-butyllithium. The resulting solution was stirred for an additional 30 minutes and treated dropwise with 0.50 g (3.0×10^{-3} mol) of 6-methoxy-3,4-dihydro-1(2H)-naphthalenone in 25 mL of dry THF. After stirring 20 minutes at -78°C, the reaction was placed in a liquid nitrogen/CCl_4 slush bath. When the internal temperature had risen to -22°C, a 1.85 g (4.5×10^{-3} mol) portion of $MoO_5 \cdot HMPA \cdot$ pyridene was added via a solid addition tube. The reaction was stirred until all of the oxidant had dissolved and quenched with 25 mL of saturated Na_2SO_3. The organic layer was separated, washed with two 25 mL portions of 5% HCl, and dried over $MgSO_4$. Concentration by rotary evaporation gave a black liquid whose NMR spectrum showed no evidence of the desired product.

Preparation of 2-hydroxymethylene-6-methoxy-3,4-dihydro-1(2H)-naphthalenone (139)

A round bottom flask was charged with 3.07 g (0.056 mol) of

sodium methoxide, 4.55 mL (0.056 mol) of ethyl formate and 25 mL of dry toluene. The resulting mixture was cooled to 0°C and treated with 5.00 g (0.028 mol) of 6-methoxy-3,4-dihydro-1(2H)-naphthalenone dissolved in a minimum amount of toluene and allowed to warm to ambient temperature. The reaction was stirred overnight and quenched with 25 mL of ice/H_2O. The organic layer was separated and extracted with 0.1N NaOH. The basic layer was acidified with 6N HCl and extracted with three 50 mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated leaving 4.45 g (79%) of a tan solid which was used without further purification: NMR ($CDCl_3$) δ 7.8-8.0 (m, 3H), 3.8 (s, 3H), 2.7-2.9 (m, 2H), 2.2-2.6 (m, 2H); IR (CCl_3) 3600, 3000, 2900, 2800, 1700, 1620, 1580, 1410, 1430, 1400, 1360, 1320, 1270, 1220, 1200, 1110, 1090, 1040, 970, 920, 840, 800, 760, 660 cm^{-1}.

Preparation of the ethylenedithioketal of 6-methoxy-3,4-dihydro-1,2-naphthalenedione (140)

A mixture of 0.25 g (1.2×10^{-3} mol) of 139 0.51 g (1.2×10^{-3} mol) of ethylene dithiotosylate and 0.51 g of potassium acetate (recrystallized from H_2O/ethanol and vacuum dried) was placed in a round bottom flask and dissolved in 15 mL of dry methanol. The resulting solution was brought to reflux and stirred overnight. The methanol was removed by rotary evaporation and the residue was dissolved in 50 mL

of ether. The ether solution was washed with two 40 mL portions of cold 2N NaOH, one 30 mL portion of saturated NaCl and dried over $MgSO_4$. Concentration of the ether layer followed by purification via flash chromatography with 50:50 ether hexane afforded 0.20 g (61%) of clear liquid: NMR ($CDCl_3$) δ 8.1 (d, J = 9 Hz, 1H), 6.6-6.9 (m, 2H), 3.8 (s, 3H), 3.5 (s, 4H), 2.8-3.2 (m, 2H), 2.5-2.8 (m, 2H).

Attempted cleavage at 140

A stock solution of base was prepared by dissolving 0.41 g of powdered KOH in 6.6 mL of t-BuOH. A solution of 50 mg of 140 in 0.5 mL of base solution was placed in an NMR tube and heated to 60°C in an oil bath. The reaction was followed by NMR and TLC for 31 h with no apparent conversion of starting material to the desired product.

Preparation of p-methoxyphenyl-2-propanone

A solution of 6.01 g (0.036 mol) of p-methoxyphenylacetic acid in 300 mL of anhydrous ether was cooled to 0°C and treated dropwise with 51.6 mL (0.036 mol) of freshly titrated methyllithium. The reaction was allowed to warm to ambient temperature and was stirred an additional 2 h. The resulting suspension was slowly poured into a mixture of 300 mL of ice and 100 mL of 6N HCl. The acidic mixture was extracted with two 100 mL portions of ether. The combined ether

extracts were washed with two 100 mL portions of saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated affording 7.49 g of crude product.

The crude product was placed in a round bottom flask along with 8.4 mL of acetic acid, 84 mL of 95% ethanol and 8.40 g (1 eq. assuming complete conversion to the desired ketone) of Girard's Reagent T. The resulting mixture was refluxed 0.5 h and poured into a separatory funnel containing 500 mL of saturated NaCl, 6.4 g of NaOH, 250 mL of ether and 500 mL of ice. The aqueous layer was acidified with concentrated HCl, heated over a steam bath for 45 minutes and extracted with three 100 mL portions of ether. The combined ether extracts were washed with three 50 mL portions of saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated affording 4.8 g (80%) of pale yellow liquid: NMR ($CDCl_3$) δ 7.2 (d, J = 9 Hz, 2H), 6.9 (d, J = Hz, 2H), 3.7 (s, 3H), 3.6 (s, 2H), 2.1 (s, 3H); IR (neat) 2990, 2950, 2880, 1730, 1620, 1605, 1510, 1480, 1400, 1380, 1280, 1170, 1060, 890, 800, 760, 710 cm^{-1}.

Preparation of m-methoxyphenyl-2-propanone

The title compound was prepared as described above with 5.03 g (0.030 mol) of m-methoxyphenylacetic acid yielding 2.74 g (55%) of crude product. This material was shown to be homogenous by TLC and was used without further purification: NMR ($CDCl_3$) δ 7.0-7.4 (m, 4H), 3.7 (s, 3H), 3.6 (s, 2H), 2.1 (s, 3H).

Preparation of p-chlorophenyl-2-propanone

The title compound was prepared as described above with 5.00 g (0.029 mol) of p-chlorophenylacetic acid yielding 3.06 g (61%) of crude product: NMR ($CDCl_3$) δ 7.3 (d, J = 8 Hz, 2H), 7.1 (d, J = 8 Hz, 2H), 3.7 (s, 2H), 2.2 (s, 3H).

Preparation of m-chlorophenyl-2-propanone

The title compound was prepared as described above with 5.0 g of m-chlorophenylacetic acid yielding 3.06 g of crude material. Purification by reaction with Girard's Reagent T afforded 0.8 g (16%) of the desired product, however, the NMR spectrum of the "non-ketonic product" was also indicative of the desired product: NMR ($CDCl_3$) δ 7.3 (m, 1H), 7.1 (m, 3H), 3.7 (s, 2H), 2.2 (s, 3H).

Preparation of p-methylphenyl-2-propanone

The title compound was prepared as described above with 5.02 g (0.033 mol) of p-methylphenylacetic acid yielding 4.80 g (96%) of crude product: NMR ($CDCl_3$) δ 6.9-7.2 (m, 4H), 3.5 (s, 2H), 2.3 (s, 3H), 2.2 (s, 3H).

Preparation of m-methylphenyl-2-propanone

The title compound was prepared as described above with 5 g

(0.033 mol) of m-methylphenyl acetic acid yielding 3.05 g (61%) of crude product. This material was estimated to contain > 80% of the desired product and was used without further purification. NMR ($CDCl_3$) δ 6.8-7.4 (m, 4H), 3.5 (s, 2H), 2.3 (s, 3H), 2.2 (s, 3H); IR (neat) 3010, 2950, 2910, 2850, 1710, 1605, 1590, 1490, 1460, 1420, 1380, 1360, 1250, 1230, 1160, 1100, 1040, 1020, 910, 890, 790, 780, 730, 700 cm^{-1}.

Preparation of 1-(p-methoxyphenyl)-2-vinyl-2-propanol (147a)

A round bottom flask was charged with 0.18 g (7.0×10^{-3} mol) of magnesium turnings and 10 mL of dry THF. A small amount of solution containing 1 mL (1.3×10^{-2} mol) of vinyl bromide in 10 mL of dry THF was added and heat was applied to initiate reaction. The remainder of the bromide solution was added dropwise and the reaction was stirred for 1 h at ambient temperature. The resulting Grignard reagent was treated dropwise with 0.96 g (6×10^{-3} mol) of p-methoxyphenyl-2-propanone in 20 mL of dry THF. The reaction was stirred 2 h at room temperature and quenched with 25 mL of saturated NH_4Cl. The aqueous layer was extracted with three 75 mL portions of ether. The THF layer and combined ether extracts were dried over $MgSO_4$ and concentrated, yielding 1.05 g of yellow liquid. Kugelrohr transfer of the crude product afforded 0.82 g (70%) of clear liquid: NMR

($CDCl_3$) δ 7.2 (d, J = 8 Hz, 2H), 6.8 (d, J = 8 Hz, 2H), 5.9 (d of d, J = 17, 10 Hz, 1H), 5.1 (d of d, J = 17, 2 Hz, 1H), 4.9 (d of d, J = 10, 2 Hz, 1H), 3.7 (s, 3H), 2.7 (s, 2H), 1.8 (broad s, 1H), 1.2 (s, 3H).

Preparation of 1(m-methoxyphenyl)-2-vinyl-2-propanol (147b)

The title compound was prepared as described above with 1 g (6.1×10^{-3} mol) of m-methoxyphenyl-2-propanone yielding 0.69 g (85%) of yellow liquid: NMR ($CDCl_3$) δ 7.3 (m, 4H), 6.0 (d of d, J = 16, 9 Hz, 1H), 5.0 (d of d, J = 16, 2 Hz, 1H), 4.9 (d of d, J = 9, 2 Hz, 1H), 2.8 (s, 2H), 2.6 (broad s, 1H), 1.2 (s, 3H).

Preparation of 1-(p-chlorophenyl)-2-vinyl-2-propanol (147c)

The title compound was prepared as described above with 0.70 g (4.2×10^{-3} mol) of p-chlorophenyl-2-propanone yielding 0.67 g (85%) of yellow liquid: NMR ($CDCl_3$) δ 7.3 (d, J = 8 Hz, 2H), 7.1 (d, J = 8 Hz, 2H), 6.0 (d of d, J =9,16 Hz, 1H), 5.1 (d of d, J = 2, 16 Hz, 1H), 4.9 (d of d, J = 2, 9 Hz, 1H), 3.5 (s, 3H), 2.9 (broad s, 1H), 1.2 (s, 3H).

Preparation of 1-(p-methylphenyl)-2-vinyl-2-propanol (147e)

The title compound was prepared as described above with 3.00 g (0.020 mol) of p-methylphenyl-2-propanone yielding 2.92 g (82%) of

yellow liquid: NMR ($CDCl_3$) δ 7.0 (m, 4H), 6.1 (d of d, J = 18, 10 Hz, 1H), 5.1 (d of d, J = 18, 2 Hz, 1H), 4.9 (d of d, J = 10, 2 Hz, 1H), 2.7 (s, 2H), 2.2 (s, 3H), 2.0 (s, 1H), 1.1 (s, 3H).

Preparation of 1-(m-methylphenyl)-2-vinyl-2-propanol (147f)

The title compound was prepared as described above with 3.00 g of m-methylphenyl yielding 2.107 g (59%) clear liquid: NMR ($CDCl_3$) δ 7.0 (m, 4H), 6.1 (d of d, J = 10, 18 Hz, 1H), 5.1 (d of d, J = 15, 2 Hz, 1H), 4.9 (d of d, J = 10, 2 Hz, 1H), 2.7 (s, 2H), 2.2 (s, 3H), 2.1 (s, 1H), 1.1 (s, 3H); IR (neat) broad 3450, 3125, 3050, 3010, 2960, 1180, 1120, 1040, 1020, 940, 890, 810, 760, 720 cm^{-1}.

Attempted rearrangement of compound 145 and compounds 147a-c, e, f

In a typical procedure 300-400 mg of 22% KH was washed with several portions of dry hexane and suspended in 10 mL of dry HMPA. A 200 mg portion of the vinyl alcohol was dissolved in 10 mL of dry HMPA and added dropwise to the KH. The resulting solution was stirred at room temperature and quenched with 50 mL of H_2O. The aqueous layer was extracted with three 25 mL portions of ether. The combined ether extracts were washed with five 25 mL portions of H_2O, dried over $MgSO_4$ and concentrated. Analysis by GC comparison with

an authentic sample and NMR indicated fragmentation products from 147c, 147e, and 147f. Compounds 145, 147a, 147b failed to react under the conditions described.

Preparation of 2,4-dimethoxy bromobenzene (150)

Method A: To a solution of 0.50 g (2.6×10^{-3} mol) of 2,4-dihydroxy bromobenzene and 0.21 g (5.2×10^{-3} mol) NaOH in 10 mL of H_2O was added 0.49 mL (5.2×10^{-3} mol) of dimethylsulfate. The reaction was warmed to 48°C and stirred for 5 h. The reaction was quenched with 25 mL of saturated $NaHCO_3$ and extracted with two 25 mL portions of ether. The combined ether extracts were washed with two 25 mL portions of 10% NaOH and dried over $MgSO_4$. Removal of solvent gave 200 mg of product that was judged homogenous by NMR and GC.

Method B: A 10.00 g portion of 1,3 dimethoxybenzene was dissolved in 60 mL of ether and cooled to -20°C. The resulting solution was treated dropwise with 18.2 g of dioxane·Br_2 in 100 mL of ether. The reaction mixture was warmed to room temperature and extracted with two 75 mL portions of H_2O. The ether layers were separated, dried over $MgSO_4$ and concentrated. The crude product was fractionally distilled affording 10.99 g of clear liquid: bp 98°C (760 mm) NMR ($CDCl_3$) δ 7.3 (d, J = 9 Hz, 1H), 6.2-6.4 (m, 2H), 3.9 (s, 3H), 3.8 (s, 3H).

Attempted preparation of 1, 3-dimethoxy benzocycloalkanones

Several attempts were made to react the benzyne derived from 150 with the enolate of cyclooctanone by the previously described procedure. In all cases no product other than unreacted ketone could be isolated.

Conformation of the formation of the dimethoxy benzyne

A 50 mL portion of anhydrous ammonia was condensed into a round bottom flask containing a catalytic amount of $FeCl_3 \cdot 6\ H_2O$. A 0.21 g (9.2×10^{-3} mol) portion of sodium metal was added in small pieces to the liquid ammonia. The reaction was stirred until the blue color faded and was treated with 1.00 g (4.6×10^{-3} mol) of 150. The resulting solution was stirred at -78°C for 3 h and quenched with solid NH_4Cl. The ammonia was allowed to evaporate and the reaction product was dissolved in toluene. The toluene solution was washed with two 10 mL portions of 6N HCl. The acid layer was neutralized with 10% NaOH and extracted with two 10 mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated yielding 0.50 g of the known aniline 152.

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