AN ABSTRACT OF THE THESIS OF

STEPHEN T. YUE for the degree of DOCTOR OF PHILOSOPHY

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Title: SYNTHESES OF LARGE RING HORMONE ANALOGS

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The (±) 8,9:13,14-diseco-norestradiol, a large ring hormone analog, and its related derivatives, were prepared by a ring expansion approach. The key step of this approach is the establishment of the benzocyclododecenone system via the Caubere reaction. This step not only provides a favorable ring size, it also sets the necessary functionalities in their desired positions. The intermediate benzocyclodecenone was further expanded to the required thirteen membered ring skeleton via the Tiffeneau-Demyanov rearrangement. Reduction of the carbonyl followed by demethylation of the intermediate dimethyl ether yielded the large ring hormone analog.

In addition to the synthesis of the estradiol analog, methods directed towards the preparation of another large ring hormone analog, the 5,10:8,9-diseco steroid, were also investigated. The key intermediate is the 7-methoxy-4'-oxocyclohexenodecene, which conceivably can be cleaved by ozonolysis to generate the fourteen-membered ring with the essential oxygen functionalities in their desired positions. This intermediate was also employed as a starting material for the synthesis of the 5,10-seco, C-ring aromatic hormone analog, 4'-acetyl-7-methoxy-1,2-benzocyclodecene.

Syntheses of Large Ring Hormone Analogs

by

Stephen T. Yue

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Redacted for privacy

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Redacted for privacy

Dean of Graduate School

Date thesis is presented November 24, 1981

Typed by Opal Grossnicklaus for Stephen T. Yue

To

the glory of my Savior and Lord, Jesus Christ

ACKNOWLEDGMENTS

The author wishes to express his sincere gratitude for the friendship, guidance, expertise, and support offered by Dr. Richard W. Thies, my wife Teresa, Dr. John R. Pierce, Dr. Ronald H. Chiarello, and many other members of the chemistry Department.

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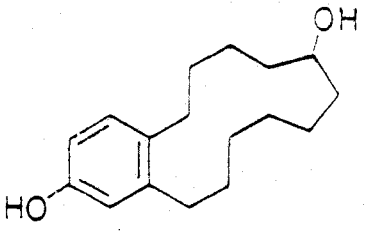
INTRODUCTION

Part I. Synthesis of 8,9:13,14-diseco-18-norestradiol

Since the application of hormones as antifertility agents, numerous structural modifications have been developed in the hope of producing the desirable estrogenic activity but reducing the risks from side effects. It was with this purpose in mind that the present project was undertaken to see if the target molecule, the 8,9:13,14-diseco-18-norestradiol 1, could potentially be used as a fertility control drug.



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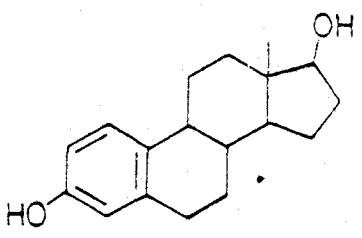

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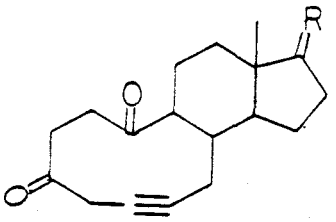
Estrogens, along with progesterones, are commonly administered orally in birth control pills. As one can see from the structures shown, the disecosteroid differs from the estradiol 2 in that a large ring is used to replace the B, C and D rings that are present in the parent steroid skeleton. Aside from its potential estrogenic activity, this large-ring flexible hormone analog is also of theoretical interest in testing the nature of binding of hormones to proteins.

Formation of an estrogen-protein complex is the first and essential step for the hormonal effects to be realized. One model of

hormone action (1) theorizes that in the estrogen-receptor complex, the steroid is tightly surrounded by the protein. In order to accommodate the steroid the protein has to be distorted and the deformation then dictates the further biological activities of the complex. This theory suggests that the rigid steroid skeleton and the placement of the oxygen groups both play essential roles in the formation of the estrogen-protein complex. The skeleton serves as a spacer to hold the two oxygen groups at the right distance for binding (2).

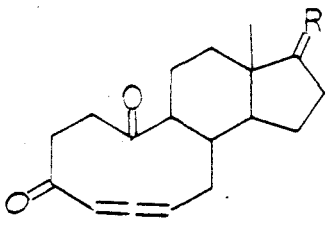
Recently several monoseco steroids (3) with a greater degree of flexibility than the parent steroid have been synthesized and show a considerable amount of progestational activity. Among other secosteroids, the strong biological activity of the 5,10-secosteroids 3 and 4 prepared by Robinson's (4) group are especially noteworthy -



3, R=O

4, R=β-CH_3CO , α-H

Compounds 3 and 4 show antiandrogenic activity (5) and are transformed enzymatically by Δ^5-3-keto steroid isomerase, an enzyme known for its action in transforming Δ^5-3-keto steroids to Δ^4-3-keto steroids, to their allenic isomers 5 and 6, which in turn were proved to be powerful irreversible inhibitors of the enzyme. Inactivation is thought to occur through covalent bond formation at the active site of the enzyme via Michael addition of a nucleophilic amino acid residue to the



5, R=O

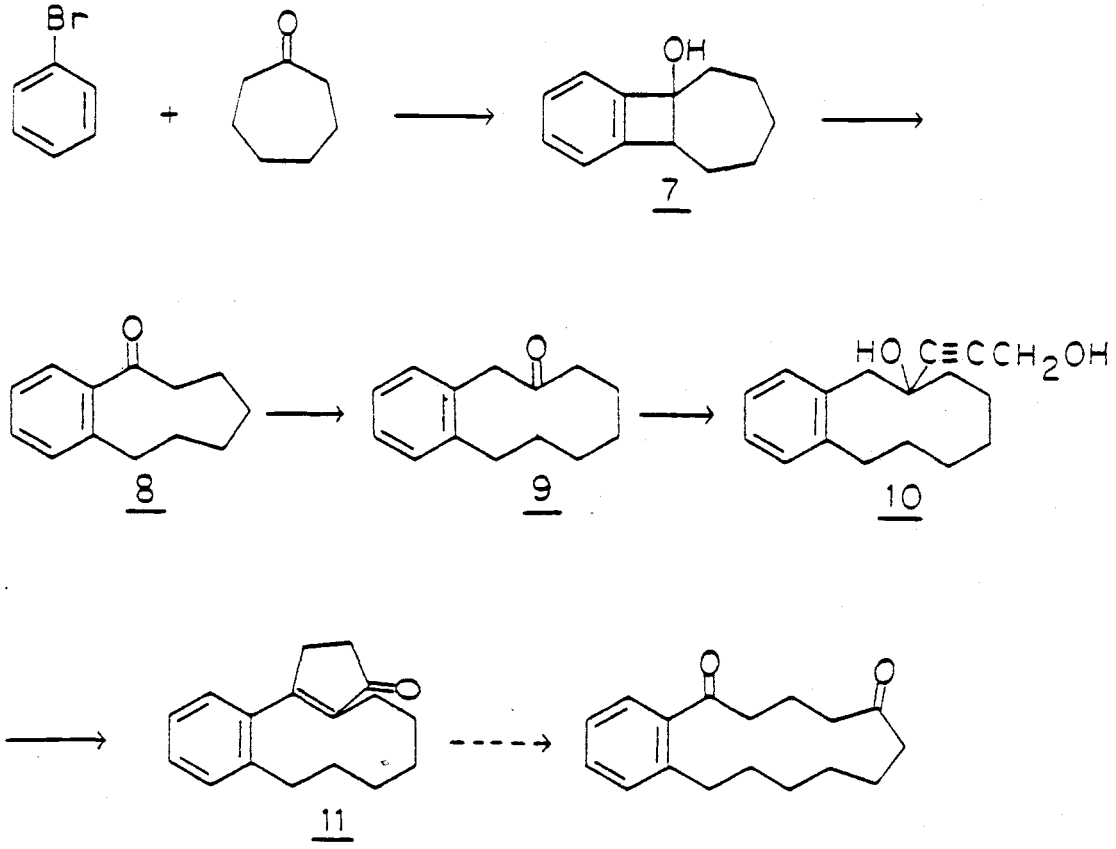
6, R=β-CH_3CO, α-H

conjugated allenic ketone group. Even though the acetylenic or the allenic groups in the ten-memebered ring may cause the molecule to adopt a conformation similar to that of a steroid, which in turn provides the required distance between the oxygen functionalities, the flexibilities of these compounds should still be greater than that of the parent steroid skeleton. This efficiency of the 5,10-seco compounds 3 and 4 as substrates and of 5 and 6 as irreversible inhibitors, and the estrogenic activity of other seco steroids, prompted some doubts on the validity of the postulated binding mode of hormones on their substrates. The observations demonstrate that monoseco deviations from the steroid prototype can still yield comparable biological activity. The proposed diseco steroid is of interest because it provides a much more flexible skeleton and yet at the same time provides the necessary placement of oxygen functionalities. Compounds like 1 should be able to adapt to the binding sites on the protein without causing the deformation of the receptor. Strong estrogenic activity would necessitate a change in the theory.

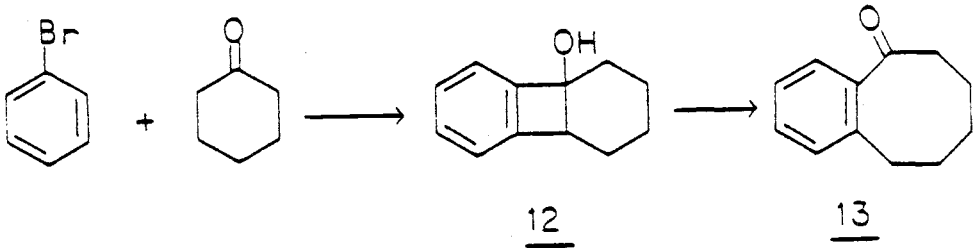
Considerable effort has been put into constructing the diseco steroid. The approaches have employed [1,3] and [3,3] sigmatropic shift ring expansions (6, 7), ring closure (8), and cyclopentenone annulation (9). Thus far, none of these approaches have successfully

led to the preparation of the target molecule. Among these approaches the two ring-expansion routes (6, 9) were the ones closest to being successful. These two approaches are outlines in Schemes I and II.

Scheme I: Cyclopentenone annulation



Scheme II: [1,3] Sigmatropic shift



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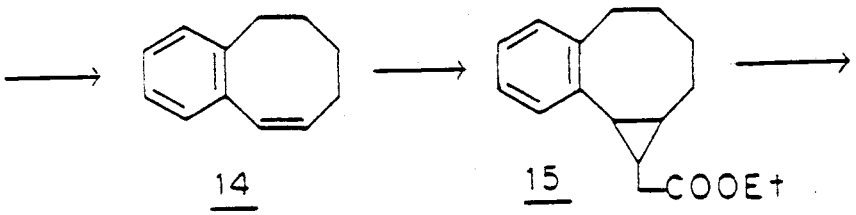

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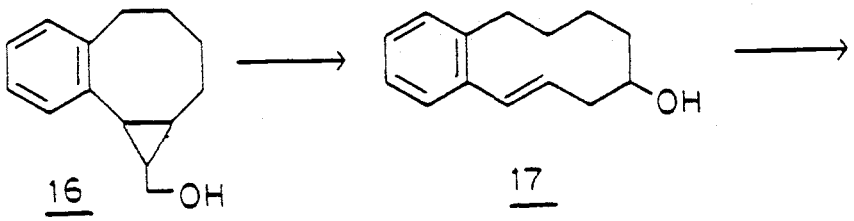

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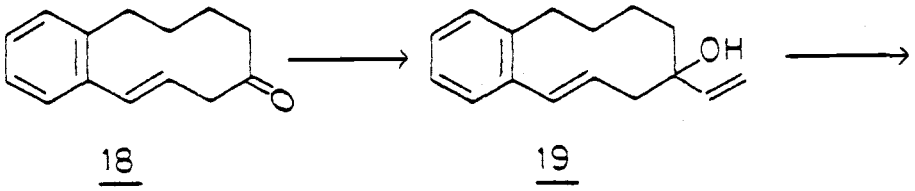

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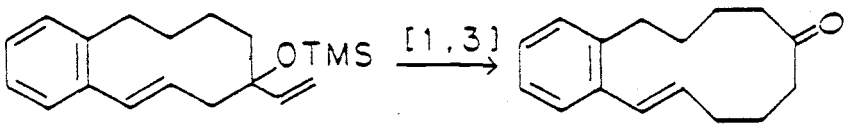

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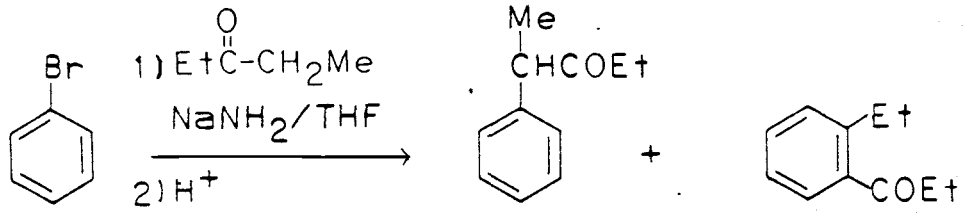
Note that in both approaches a benzo fused-ring system was constructed for the ring expansions that followed. These benzocycloalkenone

systems were all conveniently prepared via the Caubere reaction (10).

Caubere in his study of sodamide-containing complex base systems observed the following.



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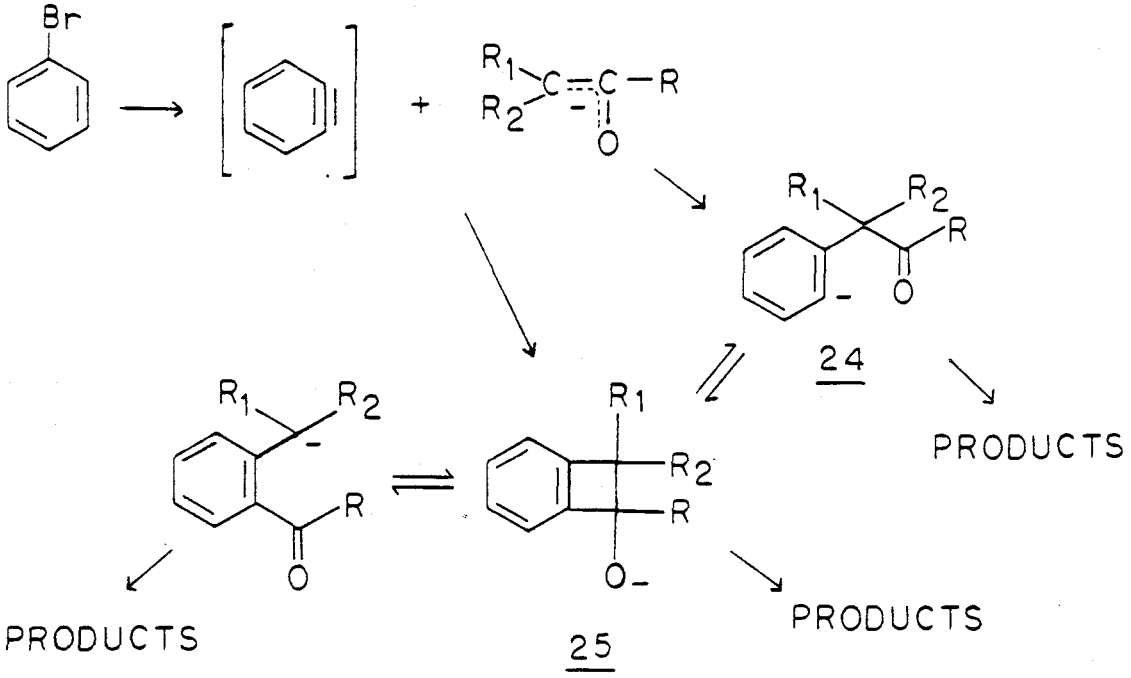
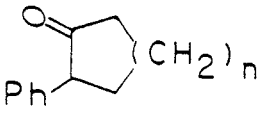
The proposed mechanism is shown in Scheme III.

Scheme III



When enolates from alicyclic ketones were reacted with the benzyne, three types of products 26, 27 and 28 resulted, depending on the

ring size of the starting enolates.



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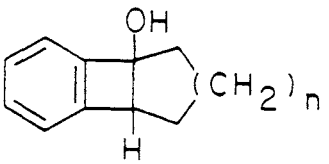

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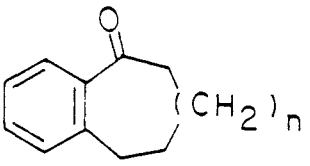

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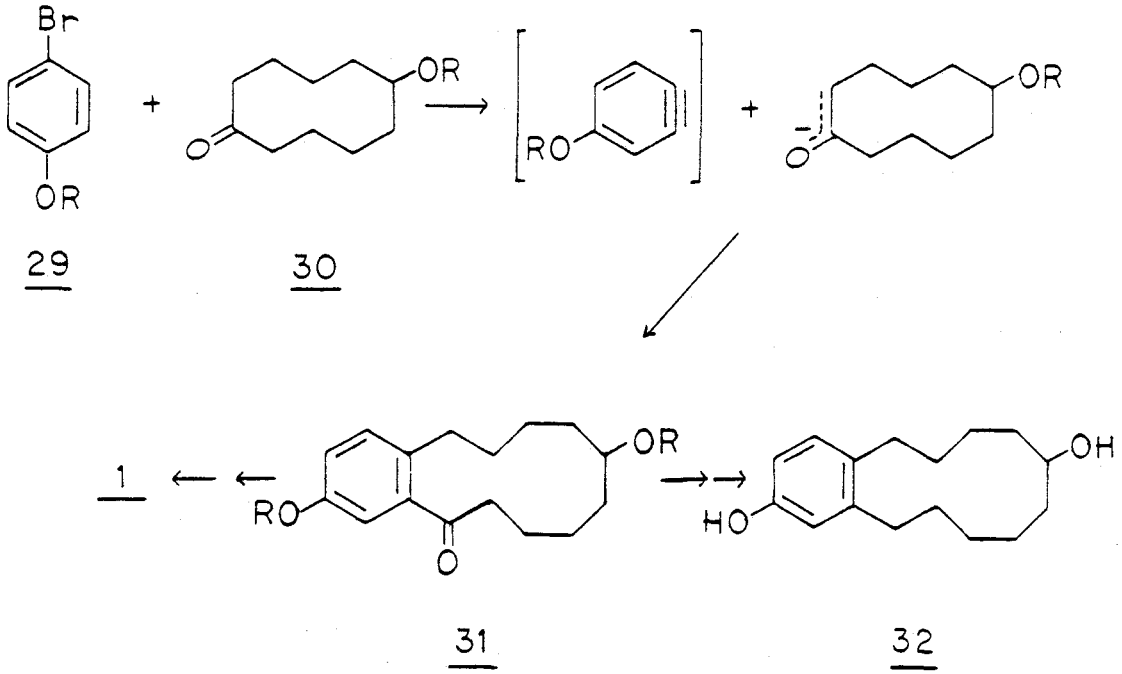
Benzocyclobutenols 27 were obtained only when n=1-3, whereas with larger alicyclic ketones, ketones 28 were generated. α-Aryl ketones 26 were present in all cases as minor products. The advantages of this reaction are at least three-fold. It constructs a benzo fused-ring system, simultaneously provides a two-carbon ring expansion, and sets up a ketone functionality for further reactions. The present approach is aimed at making use of all these advantages to construct the basic skeleton. Instead of starting with a small alicyclic ketone as before, a larger one (ten-membered ketone) was employed. It should be noted that even though Caubere had studied this reaction rather extensively, not too much effort had been put into the substituent effects either on the alicyclic ketone or on the bromobenzene or on both. If functional groups are placed properly in the starting materials, this reaction could conceivably incorporate the required functionalities in their desired positions as shown in Scheme IV.

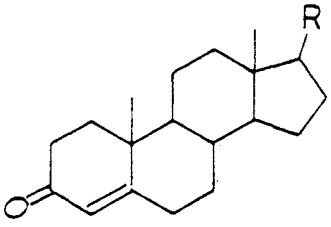
Scheme IV



The ketone 31 is only one carbon short from the required thirteen-membered skeleton of 1. This ketone can also be conveniently transformed into the twelve-membered homolog 32 of 1.

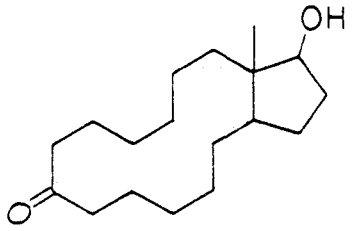
Part II. Synthesis of 5,10:8,9-diseco-19-nortestosterone

The therapeutic values of progesterone 33 and testesterone 34 have long been recognized (11). Like estrogens, derivatives of these



33, R=CH_3CO PROGESTERONE

34, R=OH TESTOSTERONE

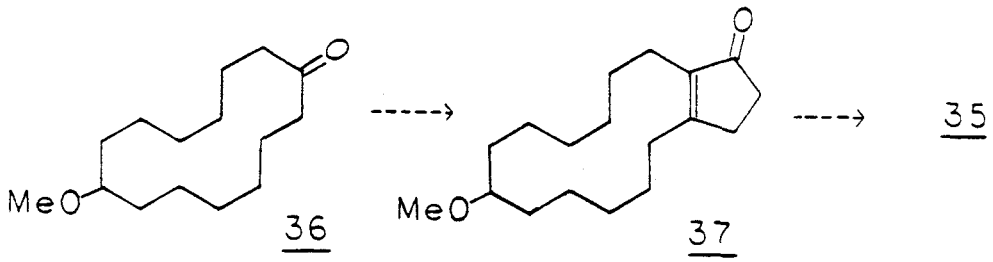


35

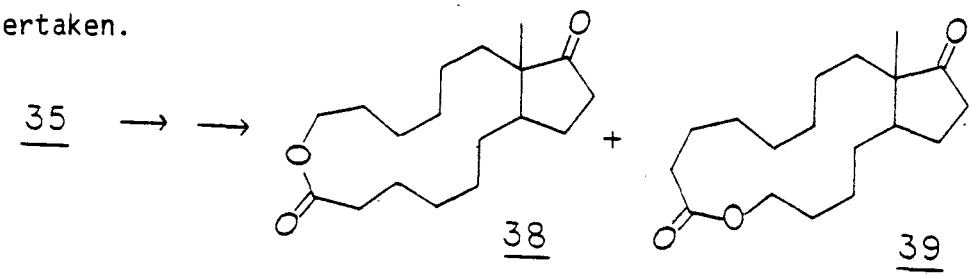
hormones are also commonly used in oral contraceptives. Progestins (compounds that exhibit progestational activity, primarily including progesterone and 19-nortestosterones) are used either with estrogens or by themselves in birth control pills.

As seen from the structures shown, the disecosteroid 35 differs from the androgen in that the A, B and C rings of the steroid skeleton are replaced by a fourteen-membered ring. Since the primary activity of 19-nortestosterone is progestational, it would be interesting to study the hormonal activity of this "flexible androgen."

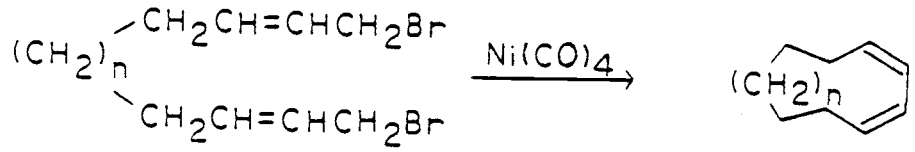
Brief examination of the structure of 35 suggests that a fourteen-membered carbocyclic ketone like 36 would be a very reasonable intermediae for the preparation of the disecosteroid. Cyclopentenone annulation (12) should give the required bicyclic skeleton 37.

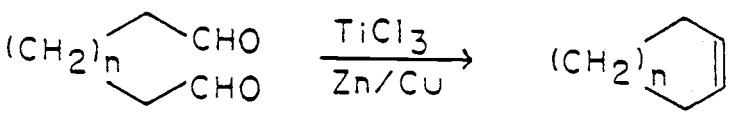


A somewhat related compound 38 that has been proposed earlier (13) but has not been made, could have in theory been prepared from 36; however, the final lactone forming step would be nonselective. No intermediate effort aimed toward the preparation of 38 has been undertaken.

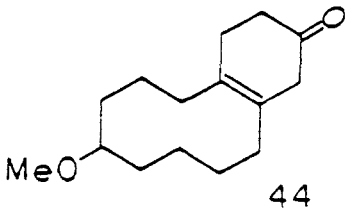


The purpose of the present work is to explore methodology leading to the preparation of this fourteen-membered ring intermediate. Several methods for preparing large carbocyclic rings were considered, e .g., the acyloin condensation (14) and the two more recent approaches which involve the use of Ni and Ti containing organometallic reagents (15, 16); however, no straightforward process was envisioned for these methods for putting the functional groups at the right positions.





The approach undertaken here is to apply a modified Robinson annelation (17) to the readily available 6-methoxycyclodecanone 30 ($R=CH_3$) to generate ketone 44. Subsequent cleavage of the ring fusion double



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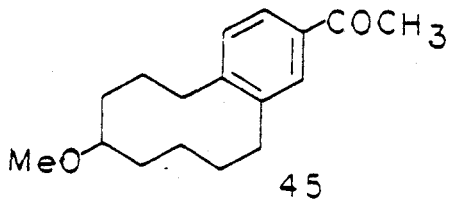
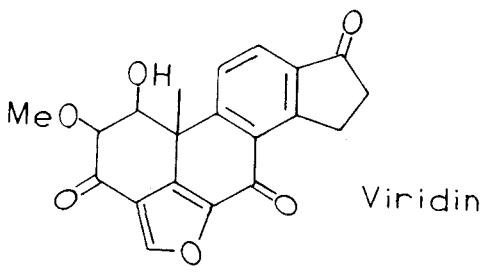
bond followed by some simple transformations should result in the preparation of 36.

Another interesting aspect of the above route is the versatility of intermediate 44 which could also serve as the precursor for the preparation of a 5,10-seco C-ring aromatic steroid analog 45. C-ring



45

aromatic steroids have been reported by several workers (18-25). The main interest was to evaluate the biological activities of this class of compounds. The impetus also comes from the isolation of viridin (26), the first natural C-ring aromatic steroid with remarkably high fungistatic activity. The synthesis of 45 was realized in four steps starting from 44.

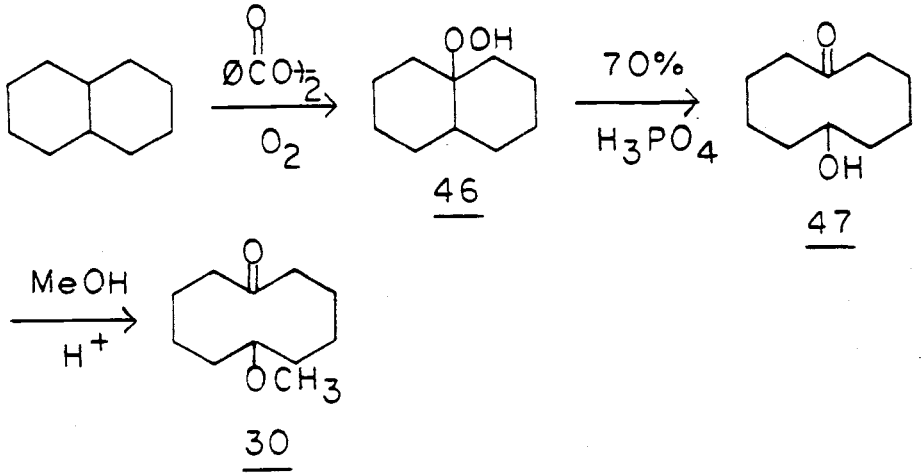


Viridin

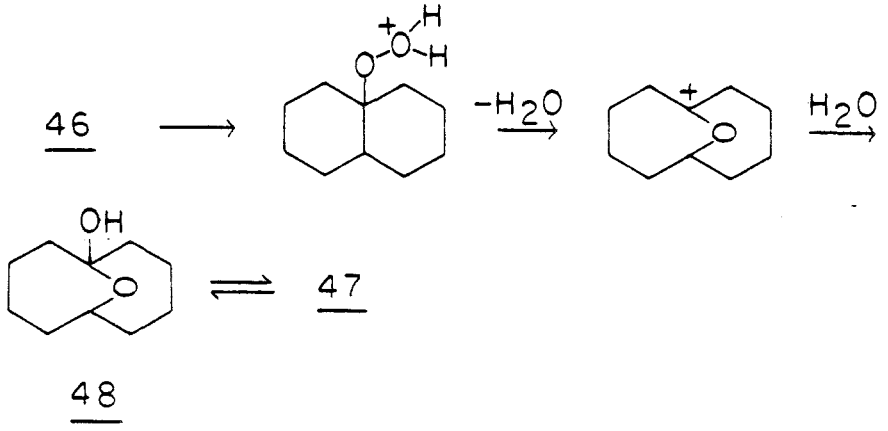
RESULTS AND DISCUSSION

Part I. Synthesis of 8,9:13,14-diseco-18-norestradiol

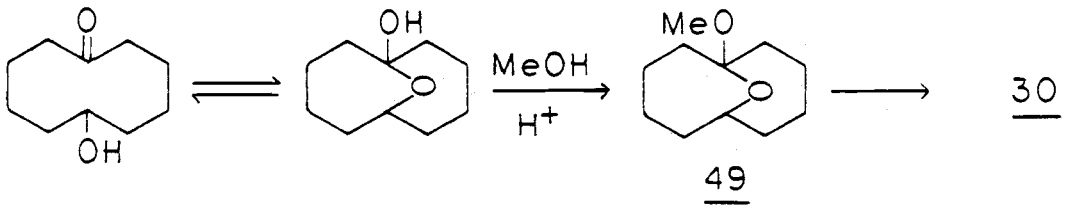
The required 6-methoxycyclodecanone 30 ($R=CH_3$) for the Caubere reaction was conveniently prepared by a modification of Cope's (27) procedure. The hydroperoxide 46 obtained from autoxidation of cis and trans decalin was not isolated, but was isomerized directly to the hydroxy ketone 47 by stirring with an equal volume of 70% H_3PO_4 (28). The hydroxy ketone 47 was then transformed readily into the methoxy ketone 30 by refluxing in acidic methanol (29).



The mechanism for the acid catalyzed isomerization of the hydroperoxide 46 is well established (30). The equilibrium between 48 and



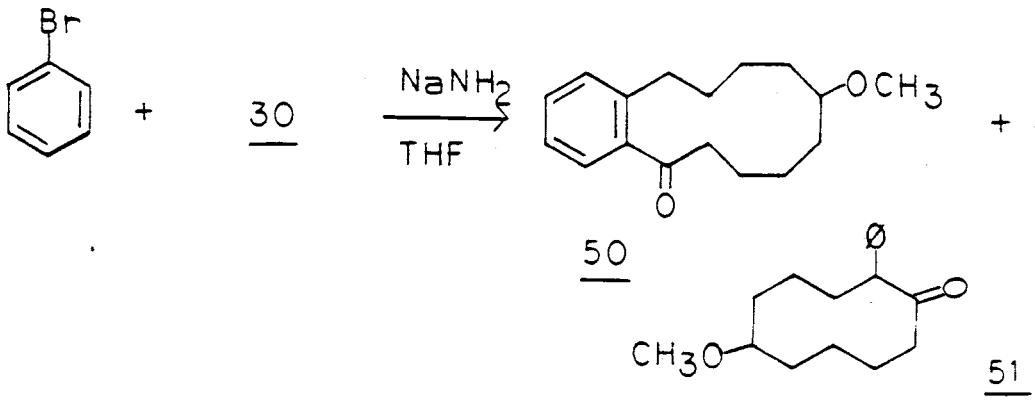
47 in different solvents has been studied by NMR (31). This transannular interaction is believed to play a major role in the transformation of the hydroxy ketone 48 to the desired methoxy ketone 30. The bicyclic ether 49 was observed if the methanolic solution was



allowed to stand at 0°C, but upon reflux, only ketone 30 was obtained.

With ketone 30 available, the Caubere reaction shown could be tried. The initial attempts were made on bromobenzene in THF as shown in Scheme V. Two compounds in a ratio of 85:15 were observed

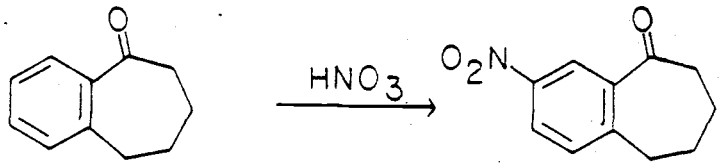
Scheme V



by GC analysis of the crude product. The minor component was presumably the α-phenyl ketone 51 which was never isolated. The crude product was purified by medium pressure HPLC to yield a thick light

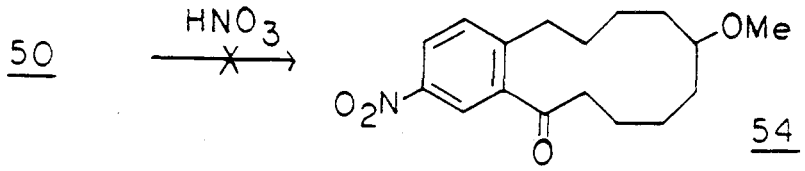
brown oily layer which could be further purified by triturating with pentane to give pure 50 in 44% yield as a white solid. Even though the yield was not high, the ease of acquisition of pure 50 made this route attractive.

Earlier work in this laboratory had shown that nitration of benzo ketone 52 leads predominantly to substitution meta to the carbonyl group because of its electron withdrawing effect. It was



52 53

therefore expected that nitration of 50 should yield a similar result;



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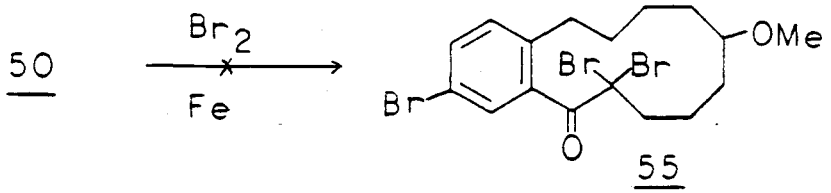
however this expectation was never realized. When the nitration was carried out at low temperature (-5 to 0°C) with fuming nitric acid, several products were observed by TLC analysis. Surprisingly, the NMR spectrum showed that the methoxy group had disappeared. Experiments described at the end of this section provide a rationale for the loss of the methoxy group under acidic condition. This approach was finally abandoned after several attempts with similar results. Another functional group that could ultimately be converted to the hydroxy group was then considered.

It has been known for a long time that Grignard reagents can be oxidized to their corresponding alcohols by molecular oxygen.

The mechanism proposed is the initial formation of the hydroperoxide which is subsequently reduced by another molecule of Grignard reagent to form the alcohol (32). This mechanism was further confirmed by the isolation of hydroperoxides when Grignard reagents were treated with molecular oxygen at low temperature (33). With this experimental evidence, Lawesson (34) conceived the possibility of using a hydroperoxide instead of oxygen in the oxidation of Grignard reagents to their alcohols. Excellent yields of phenols and alcohols were obtained by this route. Since bromination is a rather simple operation, it then seemed reasonable to consider it as a means of preparing the necessary Grignard reagent.

Because of the presence of the carbonyl group in 50, α bromo-substitution was also expected in a normal Lewis acid catalyzed bromination reaction; however, these bromo substituents should be readily



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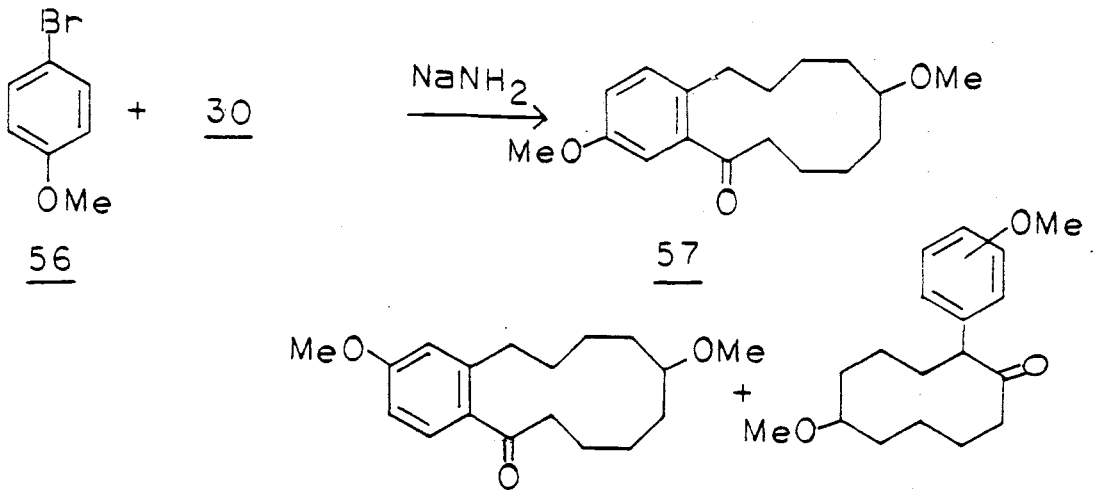
and selectively removed by treatment with zinc/acetic acid. Bromination was carried out with three equivalents of bromine in the presence of catalytic amount of iron powder in carbon tetrachloride at 65°C. Surprisingly, the NMR spectrum of the crude product obtained again did not show the methoxy protons.

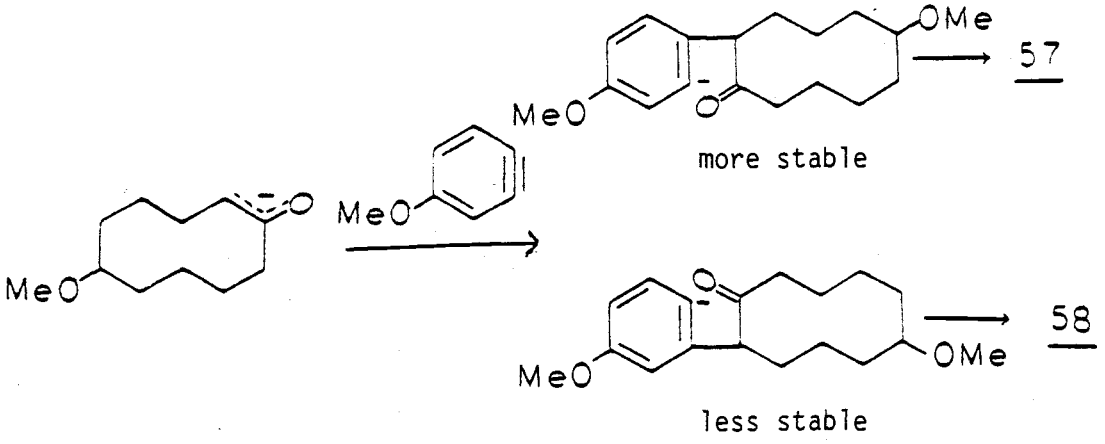
Inasmuch as this electrophilic substitution step had proved to be more troublesome than anticipated, it was then decided to take an approach where this step could be avoided. A feasible choice in

this direction was to select an aryl bromide where a para substituent was already present for the Caubere reaction. The drawback in this approach is the probable formation of isomers which could be difficult to separate. Since the ultimate compound contains an hydroxy group on its aromatic ring, the commercially available para-bromoanisole 56 appeared to be the reagent of choice. Preliminary work showed that the two isomers 57 and 58 could be separated by medium pressure



56 57 58

column chromatography, although the separation was not as clean as one would like. When the Caubere reaction was carried out under the same condition as before, 10% of 57 along with 5% of 58 were isolated after purification by medium pressure HPLC followed by trituration with pentane. The regiochemical disposition of the products can be rationalized by the electronic effect exerted by the aryl methoxy group; however, this analysis can be misleading since the seven-membered ring case shows the opposite regiochemistry (9). The two isomers were readily distinguished by their NMR spectra in the aromatic region: [57: δ 7.15 (1H, d, J=8 Hz) and 6.75-6.9 (2H, m);

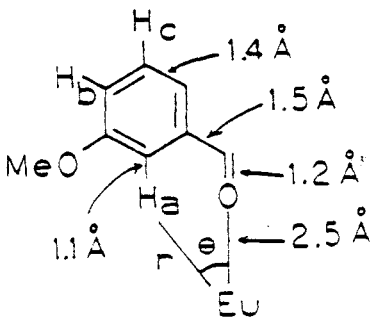


58: δ7.34 (1H, d, J=8 Hz), 6.74 (1H, d, J=2.5 Hz) and 6.64 (1H, dd, J=2.5, 8 Hz)]. The NMR assignments for the two isomers were further confirmed by Europium shift-reagent study.

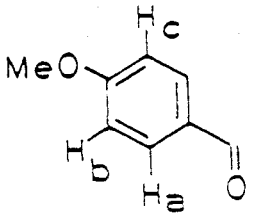
The theoretical prediction for the shifts of individual protons with the addition of shift reagent is formulated below.

$$\Delta\delta = \frac{k(3\cos^2\theta - 1)}{r^3}$$ Ref. 35

The terms r and θ are explained by the following models of 57 and 58.



57



58

The values for r and θ were obtained from direct measurement on the

models. It was found that for 57, individual k values agree best when the carbonyl has a 20° elevation from the aromatic ring while for 58, it is 40°. Theoretical shifts for individual protons

Table I: Predicted Lanthanide Induced Shifts for Ketone 57 for a Dihedral Angle of 20°

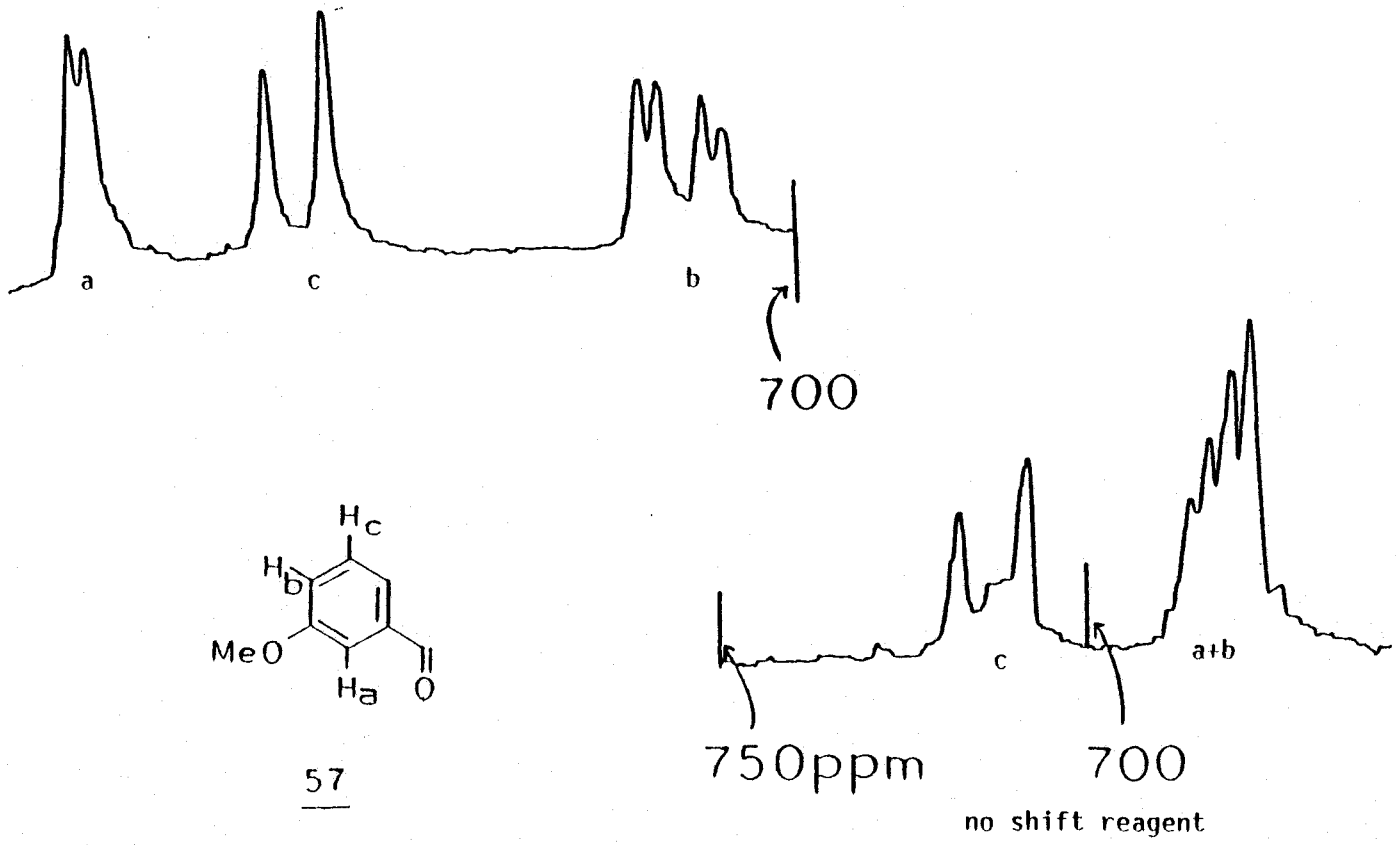
	r (Å)	θ (deg.)	k(Hz-Å^3)	Expt Δδ(Hz)	Calcd Δδ(Hz)
H_a	3.8	47	16000	115	118
H_b	8.0	34	16800	35	34
H_c	8.0	19	16700	55	54
		ave.	16500		

Table II: Predicted Lanthanide Induced Shifts for Ketone 58 for a Dihedral Angle of 40°

	r (Å)	θ deg.)	k(Hz-Å^3)	Expt Δδ(Hz)	Calcd Δδ(Hz)
H_a	4.1	45	20700	150	163
H_b	6.6	44	26000	50	43
H_c	7.9	20	20900	70	75
		ave.	22500		

were also calculated based on the averages of the k values. The emphasis though is not on the numerical values, since they are obtained very rudimentarily and also are subject to some prejudice, but rather on the splitting constants of the H_a's. The shift reagent should have the greatest effect on the H_a's owing to their proximities to the carbonyl groups. As expected, the most downfield aromatic proton (H_a) of 57 has a splitting constant of 2.5 Hz while for 58 it is 8 Hz (Figs. 1 and 2).

While the Caubere reaction was still under investigation, the



57

Figure 1. NMR spectrum of the aromatic region of 4',8-Dimethoxy-1,2-benzocyclododecen-3-one (57) after addition of shift reagent.

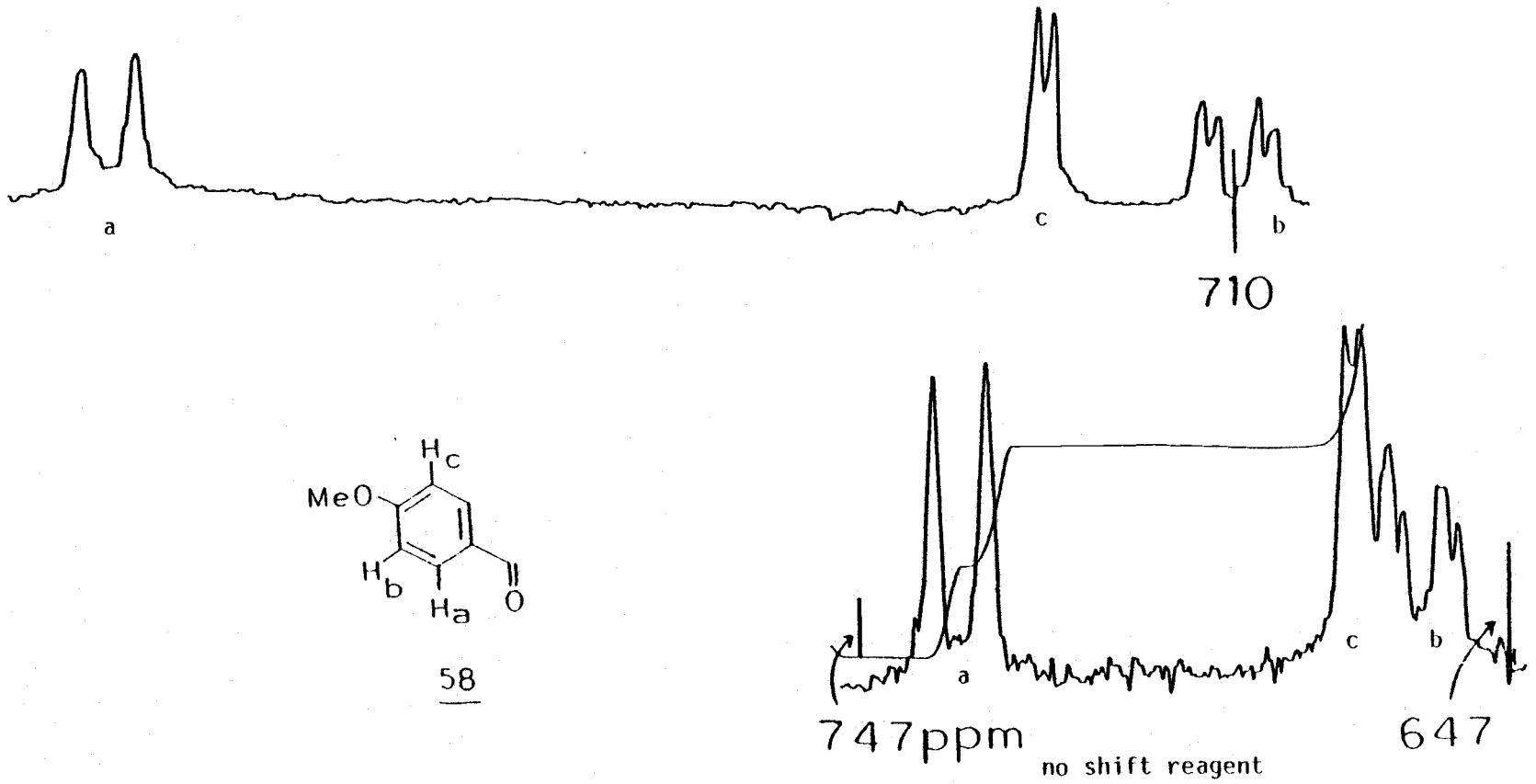
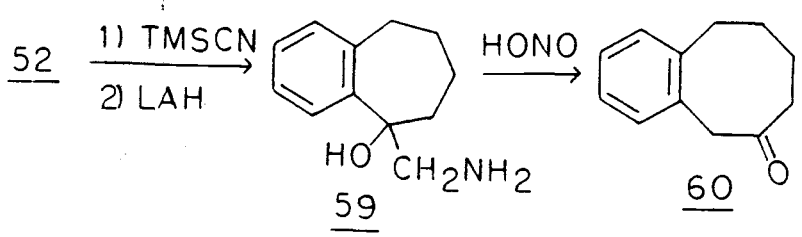
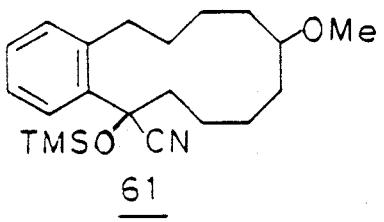


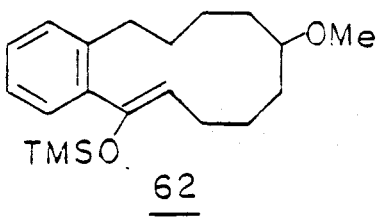
Figure 2. NMR spectrum of the aromatic region of 5',8-Dimethoxy-1,2-benzocyclododecen-3-one (58) after addition of shift reagent.

ring expansion step that would take the twelve-membered carbocyclic ring to its thirteen-membered homolog was tested on model system 50. Earlier work on benzosurberone 52 (7) with TMSCN (trimethylsilyl cyanide) and KCN/18:crown:6 or zinc iodide catalyst according to the procedure of Evans (36) gave promising results. Ketone 50 was



subjected to similar treatment at room temperature using ether as the solvent. The reaction course of the TMSCN addition step to the carbonyl was traced by GC analysis by monitoring the disappearance of the starting ketone. It was observed that when the starting material was all consumed, the major product was a compound with a retention time slightly shorter than the original ketone 50. This compound was isolated by GC and identified as the silyl enol ether 62

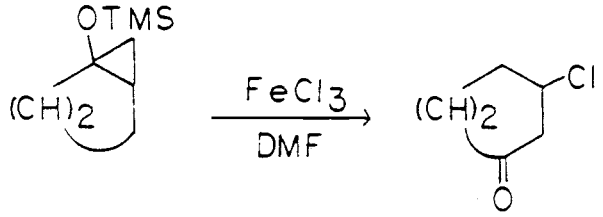




of the ketone 50. The other product with longer retention was also isolated and was found to be the expected trimethylsilyl cyanohydrin 61. Heating the mixture to elevated temperature for several hours did not change their ratio. Investigation was then undertaken to

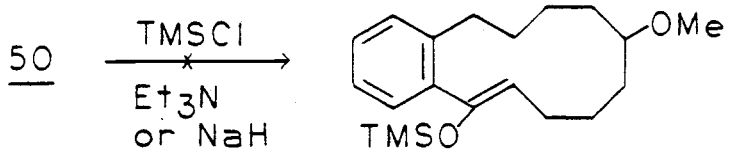
study the solvent and temperature effects on the ratio of the products. It was found that high temperature favored the formation of the silyl enol ether 62 while low temperature favored the cyano adduct 61. Non-polar solvent (pentane) on the other hand enhanced formation of the cyano adduct 61 relative to polar solvent (THF). These observations suggested that the yield of 61 could be improved by using a non-polar solvent at low temperature. Unfortunately the reaction rate in pentane was too slow at low temperature ($-8^{o}C$) to make this reaction practical. An attempt was then made to use ZnI_2 instead of KCN/18:crown:6 to investigate the catalyst effect. The reaction at room temperature did not improve the yield of the cyano adduct, and in addition an unknown product was observed with a much shorter retention time in the gas chromatogram. When the reaction was repeated in refluxing methylene chloride, this unknown compound, which showed no methoxy protons in the NMR spectrum, was almost the exclusive product. The TMSCN approach was temporarily set aside.

Since the silyl enol ether 62 could be prepared easily, it was then considered for use in an alternative route to expand the twelve-membered ring. The additional carbon needed conceivably could be introduced by a Simmons-Smith or dihalocarbene reaction on the double bond. The Simmons-Smith ring expansion route had been well worked out earlier (37) already and so attention was directed to a less



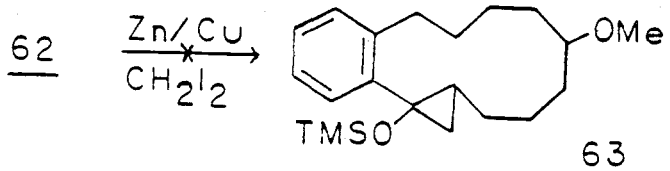
expensive way to prepare the silyl enol ether 62.

It was assumed that ketone 50 yielded the silyl enol ether as the major product in the presence of TMSCN because of the ease of formation of its enolate. It was therefore expected that other silylating agents such as TMSCl (trimethylsily chloride) should give similar results. Surprisingly both House's (38) and Hudrlik's (39) procedures failed to yield the silyl enol ether 62. TMSCN was used for the time being although it was more expensive.



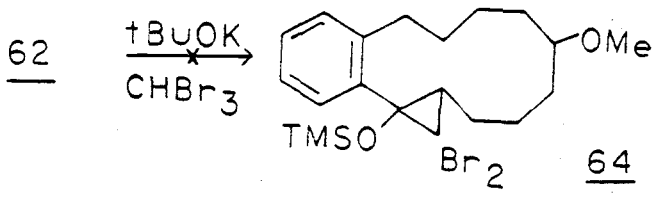
62

Silyl enol ether 62 was formed as nearly the exclusive product (≥95%) when ketone 50 was allowed to stir with TMSCN/18:crown:6 in refluxing toluene. The Simmons-Smith reaction (40) was carried out in a normal way with Zn/Cu couple prepared by the procedure of Harrison (41). To our surprise the methoxy group again disappeared in the product.



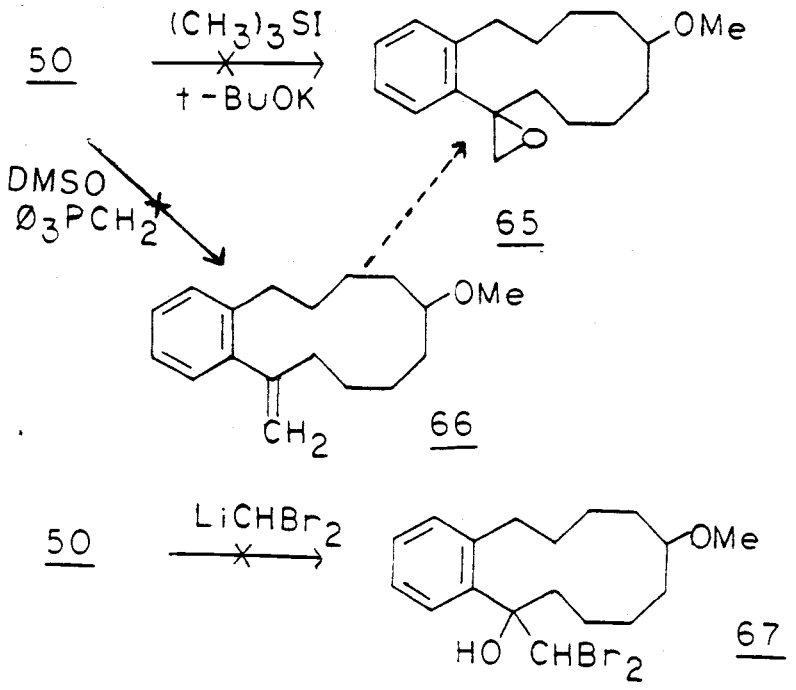
63

The dibromocarbene route was then attempted at low temperature according to the procedure of Miller (42). Excess carbene was generated for the reaction. Two products, which could be separated by



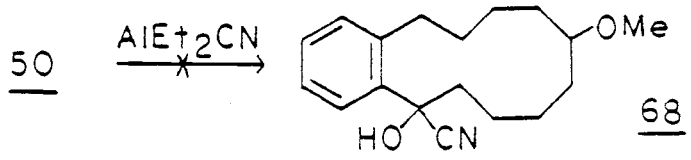
column chromatography were formed in rather small quantities. No idenfifications could be assigned for the products from routine NMR, IR and mass spectral data. This route was abandoned after two attempts because the product yield, if it was the expected product 64 at all, was too low to make this route useful.

Two other routes which sought to introduce this methylene group by nucleophilic attack on the carbonyl group were tried without success. The failure was believed to be due to the relative ease of enolization. An alternative route to prepare 65 through a Wittig reaction also failed. Another reagent, $AlEt_2CN$ (45), which should

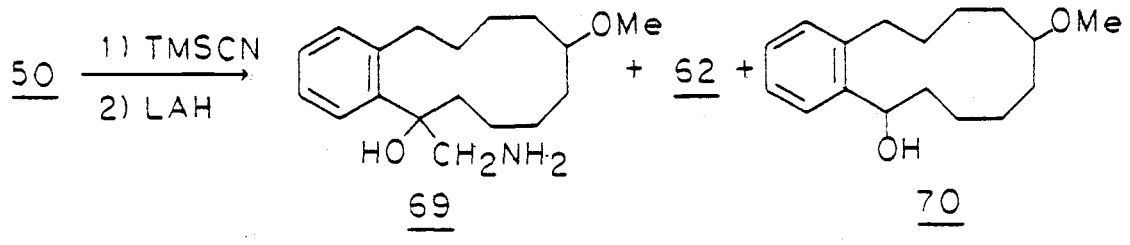


behave similarly to TMSCN was tested and failed to yield the

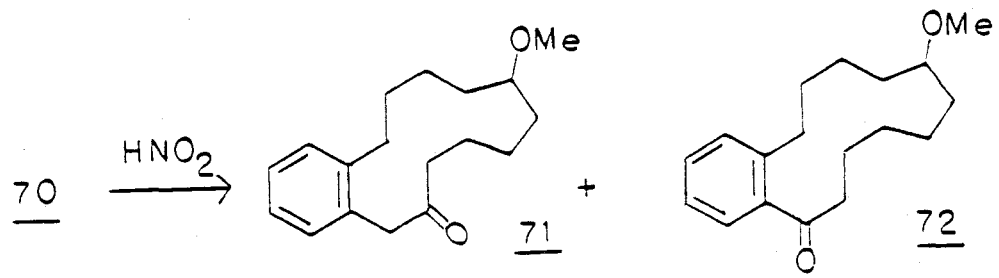
cyanohydrin 68. It was then decided to go back and further investigate the the TMSCN method.



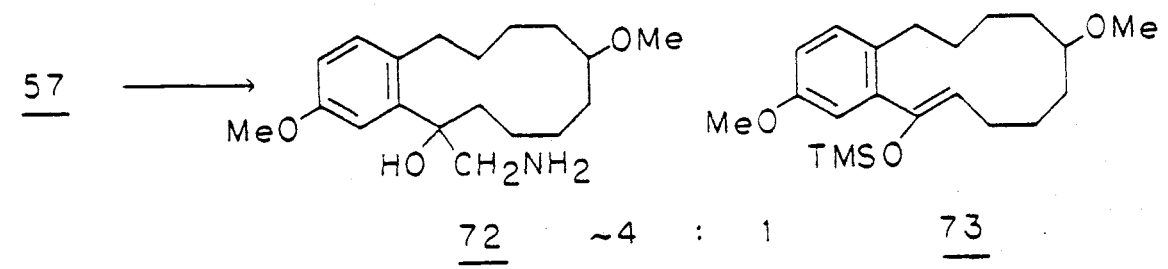
Early results had shown that the reaction rate in aliphatic non-polar solvent (pentane) was too slow to make the procedure practical; however, it was discovered while choosing a higher boiling solvent for the preparation of silyl enol ether 62 that toluene enhanced the rate of that reaction much more than the other non-polar solvents such as carbon tetrachloride and chloroform. When toluene was used as a solvent for the TMSCN reaction, a reasonable rate (about one week) was obtained at low temperatures (-25 to -15°C). The intermediate cyanohydrin 61 was reduced with $LiAlH_4$ directly prior to workup. The amino alcohol 69 and silyl enol ether 62 were obtained in a 2.5/1 mole ratio. The silyl enol ether 62 was transformed back to ketone 50 by stirring in THF/H_3O^+. Ketone 50, thus recovered was a thick oily layer which could not be recrystallized to its solid form. A small amount of alcohol 70, judging from the IR spectrum, was also present, presumably from the reduction by LAH



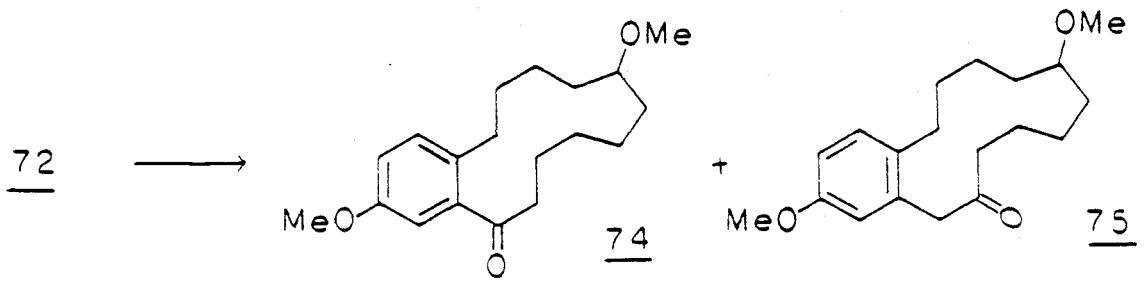
on the unreacted 50. The amino alcohol 69 obtained was diazotized without further purification by HONO in 10% HOAc. In initial trials, the crude product (a thick semi-solid layer) was recrystallized from pentane to yield a white fluffy solid identified as ketone 71, which is the expected aryl migration product, but the yield of this step was consistently only at the 30-40% range. The portion which was soluble in the pentane layer in the recrystallization was then examined by NMR, IR, MS and GC and found to be ketone 72, which corresponded to the unexpected alkyl migration in the ring expansion step.



The two ketones were formed in almost equal amounts. The same procedure was applied to ketone 59 and ketones 74 and 75 were obtained in

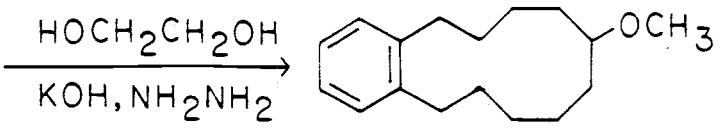


72 ~4 : 1 73



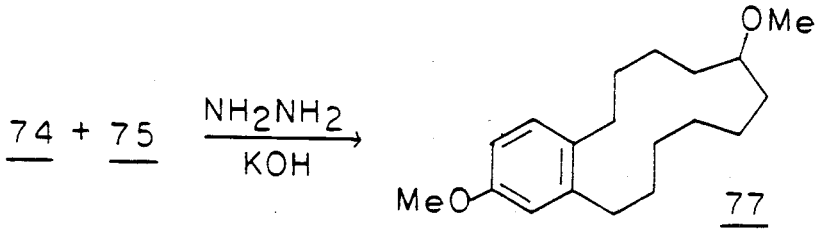
about 1:1 in 56% overall yield.

With ketones 74 and 75 in hand, success seemed imminent. Earlier work on the reduction of ketone 50 by Huang-Minlon's (45) modification of the Wolff-Kishner reaction gave a reasonable yield of the reduced product 76. However, applying the same procedure to ketones 74 and 75



76

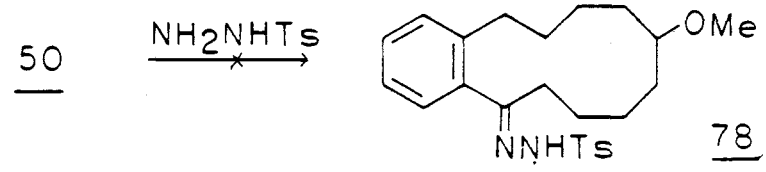
only gave a low yield of the expected 77 along with a considerable amount of dark brown impurity. A milder route was then explored



77

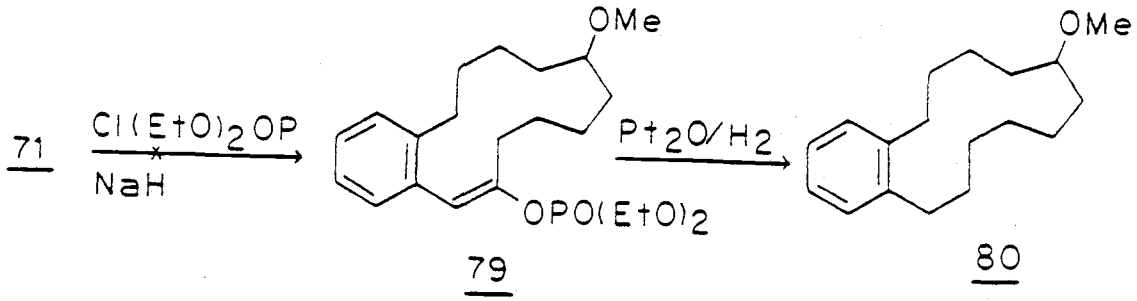
to reduce the ketones.

The tosylhydrazone seemed to be a promising intermediate because of its ease of formation and reduction by different reagents such as $NaBH_4$ (47), $NaCNBH_3$ (48), or RLi (49). Surprisingly when ketone 50 was refluxed with one equivalent of tosylhydrazine in ethanol or carbon tetrachloride (50), no solid tosylhydrazone 78 could be

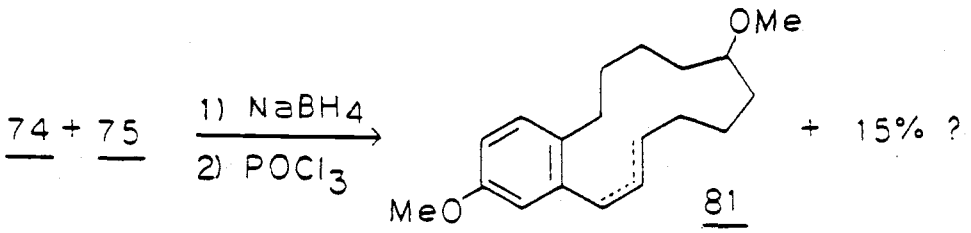


78

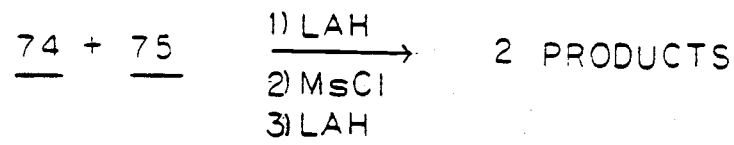
isolated. Other alternatives were explored and summarized as follows.

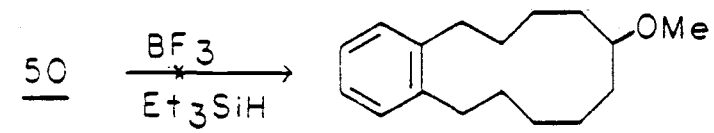


79 80



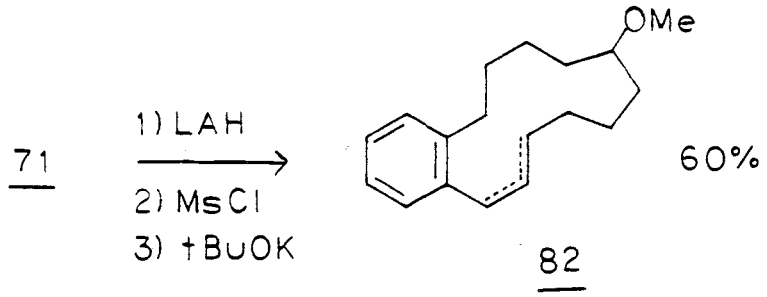
81



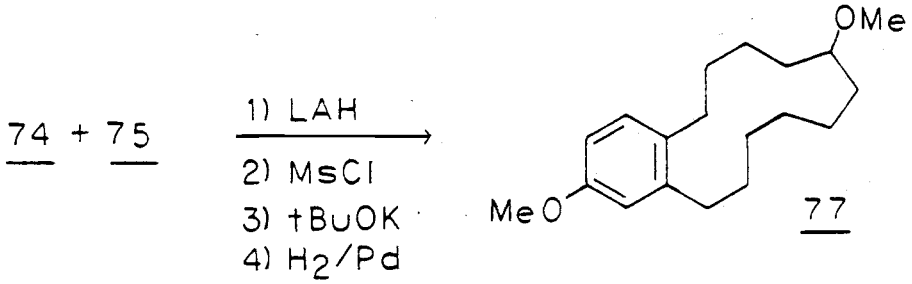


76

For the phosphonate procedure, only starting material was recovered when treated with chlorodiethylphosphate. The use of boron trifluoride and triethylsilane caused the disappearance of the methoxy group. The phosphorous oxychloride and the mesyl chloride worked for the twelve-membered homolog and yet on the thirteen-membered system, both of them yielded unexpected side products. Finally it was found that instead of displacing the intermediate mesylate directly with $LiAlH_4$, elimination with potassium t-butoxide/DMSO gave one clean product. This procedure was applied to reduce ketones 74 and 75

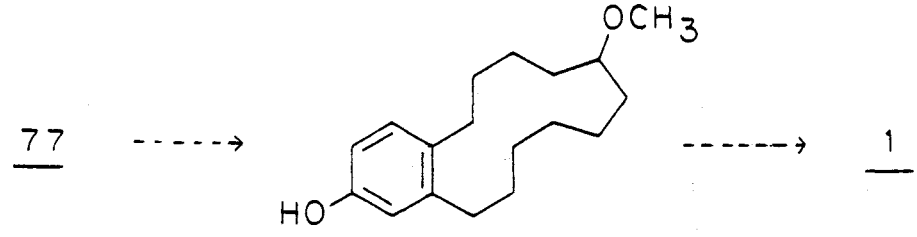


and gave dimethyl ether 77 in 51% yield.

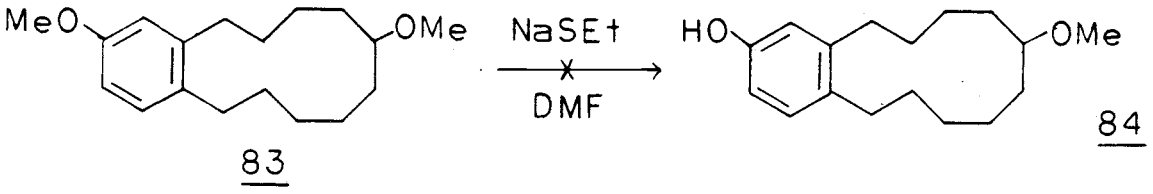


A satisfactory route to demethylate the ethers required considerable exploration. The original plan shown in Scheme VI was to remove

Scheme VI

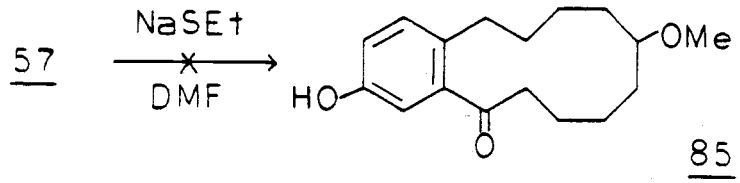


the methyl ethers one at a time, since they are of different types. It is known that the aryl methyl ether, because of the stability of the resulting phenolate, can be demethylated by NaSEt (54) through a S_N2 mechanism. When this procedure was employed to the model dimethyl ether 83, only starting material was recovered after



83 84

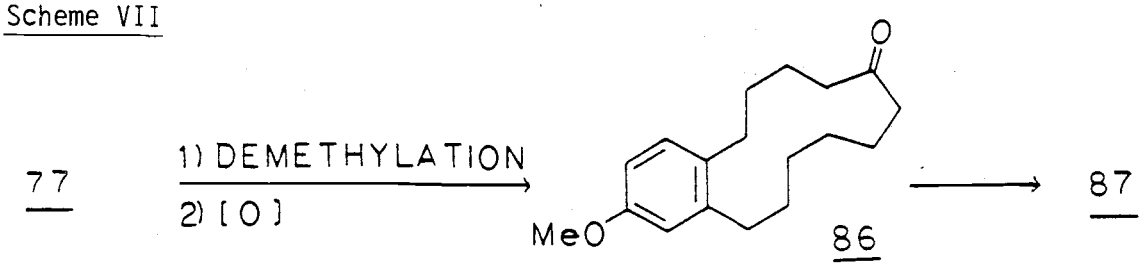
prolonged heating. It was thought that an electron withdrawing group might increase the stability of the resulting phenolate and so an attempt was made on ketone 59, but the result for this step was not reproducible.



85

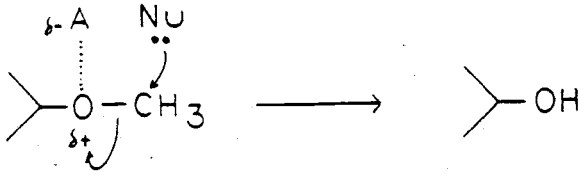
Not too much effort had been put into this nucleophilic displacement step of the aryl methyl ether before it was decided to change the sequence of demethylation as shown in Scheme VII. It was thought

Scheme VII

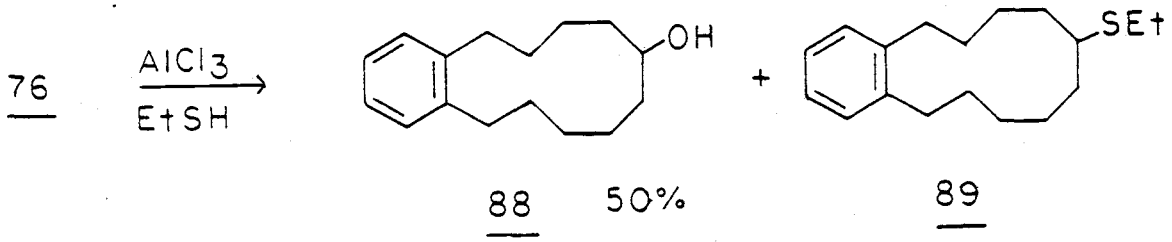


that if the aliphatic alcohol was converted to the ketone, it was then protected from subsequent demethylation of the aryl methyl ether, which could be removed by many other reagents.

Literature procedures for removing methyl ethers all utilized the same principle: the formation of a polarized bond between the oxygen and the methyl group through complexation of the reagent with oxygen and then attack on the methyl by a nucleophilic entity. The



reagents investigated were TMSI (55), BBr_3, $BF_3 \cdot Et_2O/HCl/HSCH_2CH_2SH$ (56), DIBAH (57), and $AlCl_3$/ ethanedithiol or thiol (58). Among all these reagents, only the $AlCl_3$/ thiol procedure gave a reasonable

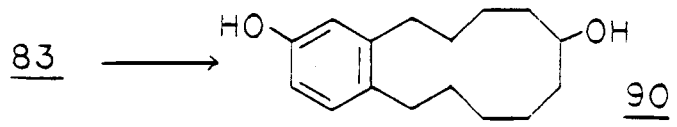


88 50% 89

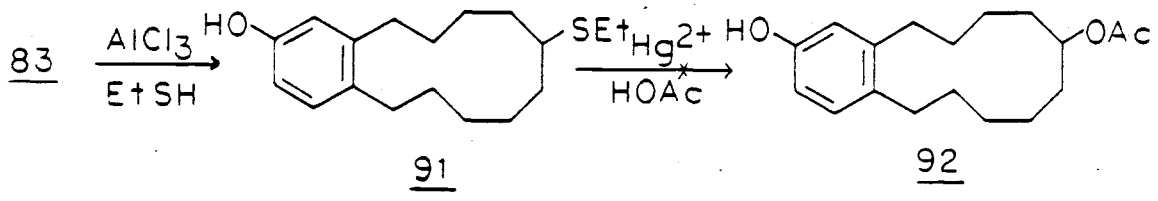
yield. The reactions were monitored by GC by observing the disappearance of the starting ether. The TMSI and BBr_3 both gave products with retention times considerably shorter than the starting ether. They were presumably products from elimination of the resulting iodide or bromide. The DIBAH yielded only the starting material even at elevated temperature. The $BF_3 \cdot Et_2O/HCl$-catalyzed reaction required longer reaction time than the $AlCl_3$ one and gave some alcohol product 88 along with impurities.

When $AlCl_3$/ thiol was applied to the model system 83, it was

found that a reasonable amount of the aryl methyl ether was also



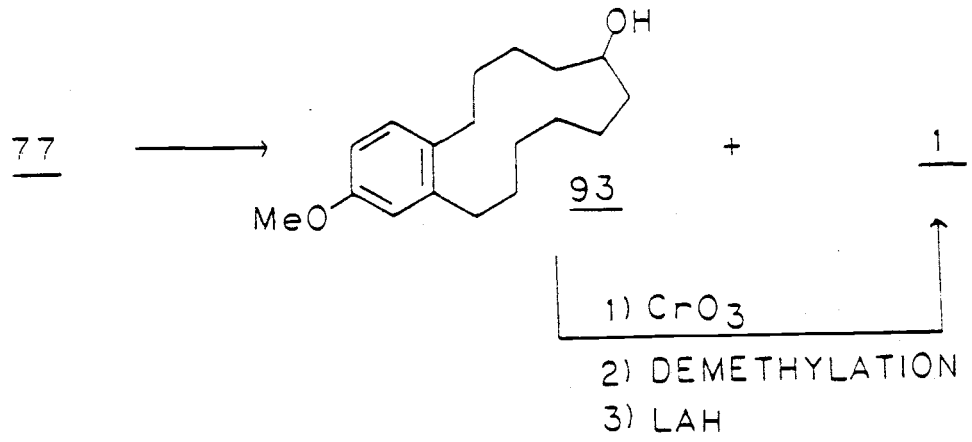
demethylated. This observation was different from the TMSI cases reported by Jung (55). When TMSI was used as the demethylation agent, Jung observed that removal of the aryl ethers was much slower than aliphatic ones, whereas in this case the rates were comparable. This phenomenon was initially considered to be an extra problem for this reacton since it was believed that there was still some difference in the demethyation rates. Prolonged reaction time for complete demethylation of the aryl methyl ether might mean ethyl sulfide formation at the aliphatic position. On the other hand, conversion of the sulfide to the alcohol (59) had been performed, and so it seemed easier to convert all the methyl ether to sulfide and then back to the alcohol than to optimize the temperature and reaction time to obtain the diol directly. The sulfide was obtained in good yield



(95%) but the subsequent step failed to yield the expected acetoxy

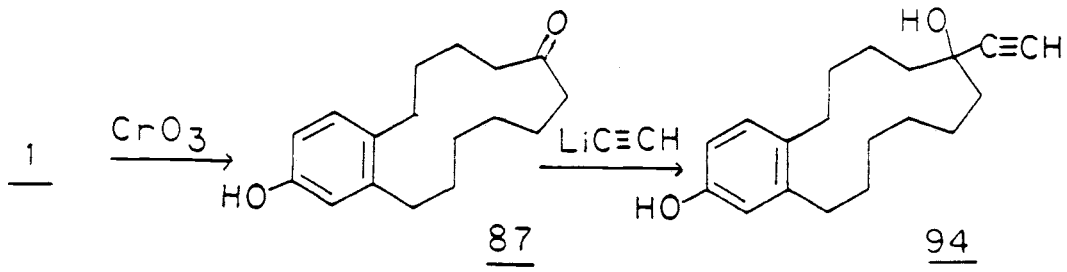
alcohol 92. The alternative route shown in Scheme VIII seemed more promising and only the starting sulfide was recovered.

Scheme VIII

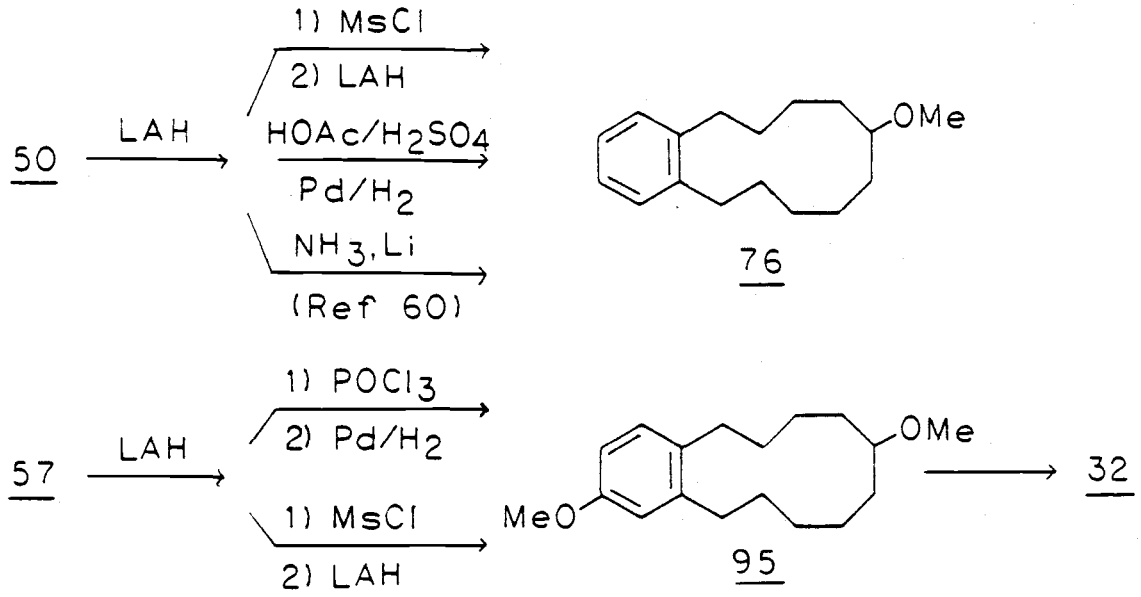


Diol 1 should be separated from 93 easily by aqueous NaOH extraction. The reaction was repeated several times at room temperature and in all attempts, judging from the NMR and IR spectra, only a very small amount of ether 93 was observed, which was never isolated. To our delight the diol 1 could be obtained in about 50% yield as the major product of the reaction. The synthesis of this large-ring hormone analog was thus accomplished in nine steps starting from 6-methoxy-cyclodecanone 30.

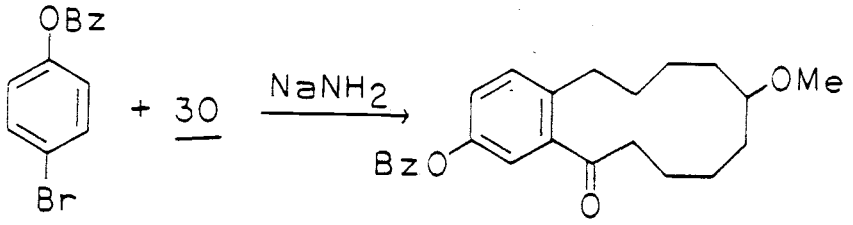
Other derivatives of 1 were synthesized from standard procedures. Diol 1 was oxidized with Jones reagent (60) to give the estrone analog 87 in 74% yield. The ethynyl derivative 94 was



obtained in 46% yield from 87 according to the procedure of Carlson (61). The twelve-membered ring diol 32 was also prepared from 57 by reduction of the ketone followed by demethylation with $AlCl_3$/ thiol. After testing several reduction methods on ketones 50 and 57, the mesylate method described earlier was found to give the best result (59% from ketone).



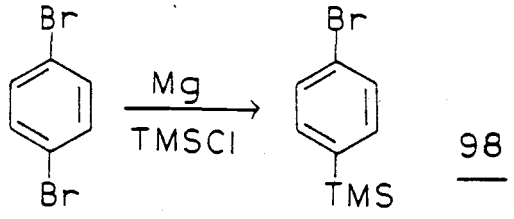
Although diol 1 was successfully synthesized, some steps, in particular the Caubere reaction, gave exceptionally low yield; modifications were therefore undertaken to improve the overall yield. A benzyl ether 96, instead of methyl, was prepared by Chiarello (8) and the yield for this step was improved to about 20%. Unfortunately the TMSCN ring expansion procedure used



96 97

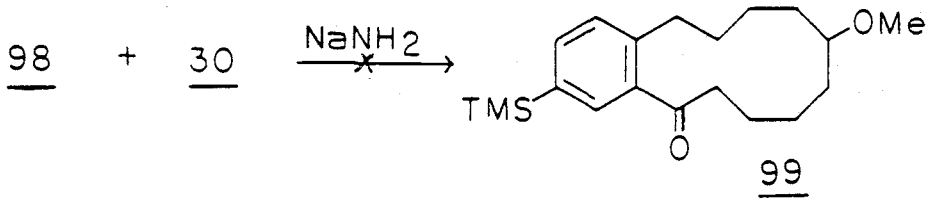
on the methoxy analog could not be achieved on 97. Other methods were used but also failed.

The trimethylsilyl group was also tested because of its easy transformation to an acetoxy group (63). The trimethylsilyl bromobenzene 98 was prepared in 50% yield according to the literature



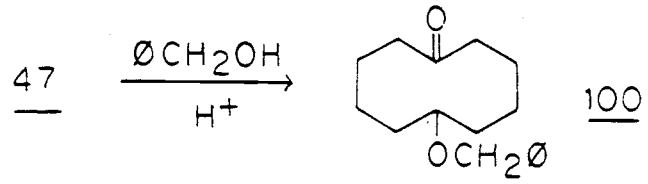
98

procedure (64). Unfortunately, the Caubere reaction did not yield the ketone 99. The product yield was low and there was partial loss of



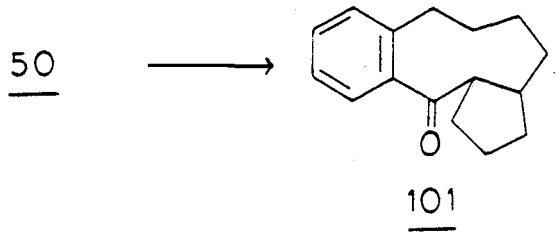
99

the TMS group. Another modification that might improve the yield would be to use the benzyl protecting group on the ten-membered ring component. Unfortunately, attempts to prepare the benzyl ketone 100

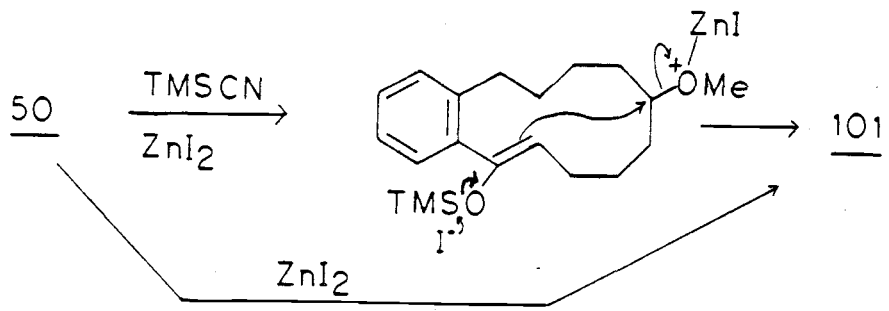


with a similar procedure to that of its methyl analog 30 only gave the desired product in low yield.

Finally, some effort was turned to the exploration of the disappearance of the methoxy group. It was noticed earlier that in the presence of various acids (Fe, ZnI_2, BF_3, Zn/Cu, HNO_3) the methoxy group on 50 disappeared. One reasonable postulate is that these acids catalyze an internal displacement of the methoxy group and caused the formation of ketone 101. This postulate was tested by



heating 50 with zinc iodide in toluene. A compound with smaller molecular weight was observed on GC analysis, yet only a small amount of starting material (~15%) was converted in 18 hours of heating. Upon the addition of TMSCN, almost all the starting material disappeared in about 16 hours. A possible mechanism is shown below.

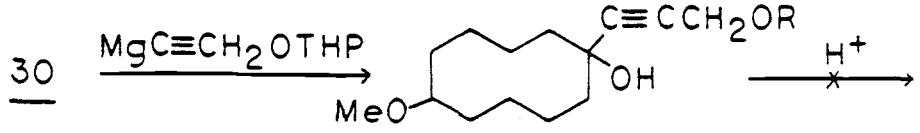


The spectral data which support the structure as shown are the presence of the carbonyl stretching band at 1695 cm^{-1} and the two peaks appearing at (δ56.13 and 46.79) in the ^{13}C NMR spectrum. These two peaks appear as doublets in the off resonance decoupled spectrum and are believed to be the two tertiary carbons of 101. Further confirmation of assignment was done by comparing with 2-cyclohexylcyclohexanone (65), which has a shift of δ56.4 for the α-tertiary carbon. When $AlCl_3$ was employed, reaction was completed within an hour. Besides 101, another product which has a higher R_f was observed on TLC analysis. This product has identical molecular weight as 101 and its NMR spectrum, which shows vinyl protons, suggests that it is probably an elimination product. No further identification was pursued.

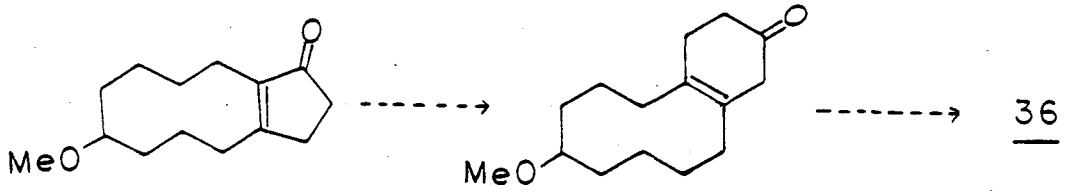
Part II. Methodology on the preparation of 5,10:8,9-diseco-19-nortestosterone

The present approach is designed to make use of the readily available 6-methoxycyclodecanone 30 to construct the specifically substituted fourteen membered-ring moiety of the 5,10:8,9-diseco-19-nortestosterone 35. The original plan to synthesize the fourteen-membered ring ketone 36 for further transformation is shown in Scheme IX. Alcohol 102 was obtained and hydrolyzed to the

Scheme IX



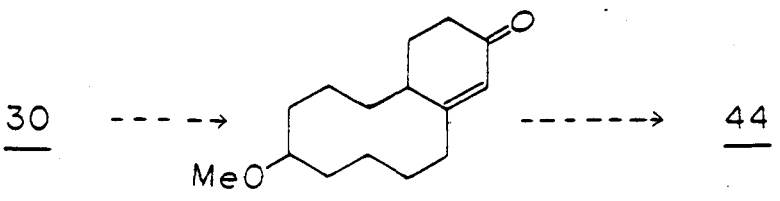
102, R=THP
103, R=H



44

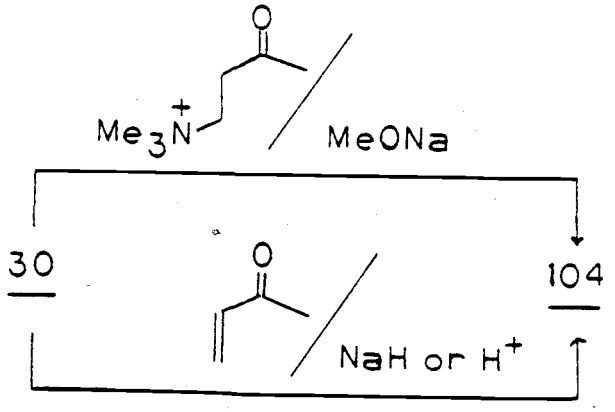
diol 103. Attempts to cyclize 103 with sulfuric acid:methanol (12) (1:1 or 1:2) yielded only tar. An alternative route was then pursued in which 44 would be prepared directly by a Robinson annelation (Scheme X) followed by an isomerization of the double bond to the β,γ position.

Scheme X



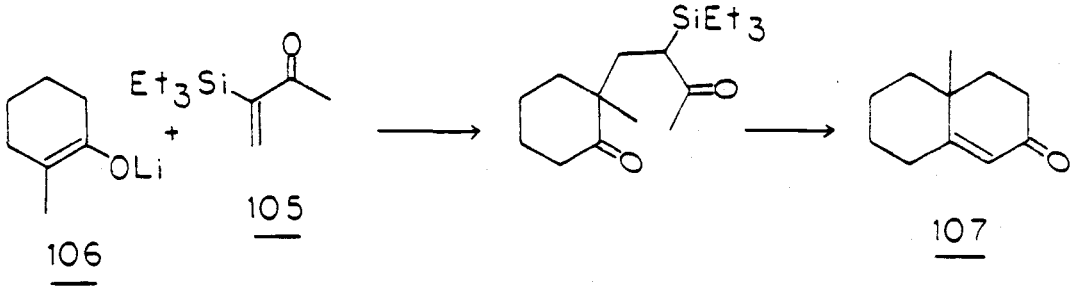
104

Early attempts with base (66) or acid (67) catalyst on 30 with methyl vinyl ketone gave back only the starting cyclodecanone. Generation of methyl vinyl ketone in situ from Mannich base (68) also



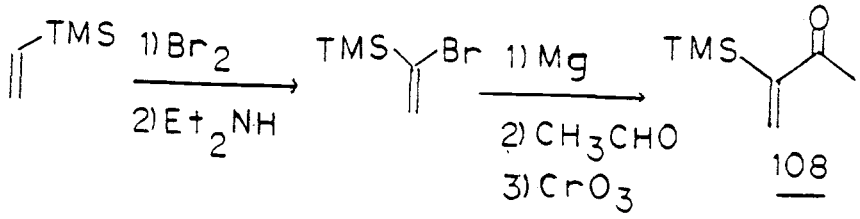
failed to yield the desired product. Presumably the methyl vinyl ketone polymerized at too fast a rate for any reaction to take place, so a more stable vinyl ketone was then sought.

Stork (17) had used an α-triethylsilyl substituted methyl vinyl ketone 105 which gave a very good overall yield (80%) for the

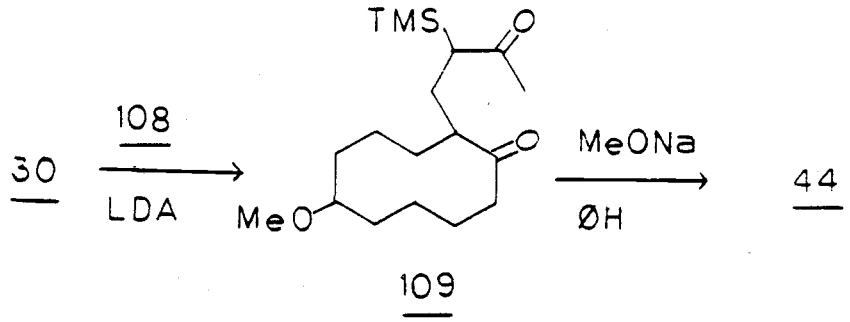


106 105 107

Robinson annelation. A procedure similar to that of Stork (69, 70) was used to prepare the vinyl ketone 106. The overall yield of 108 was not impressive (ca. 20%) but a large quantity of material could

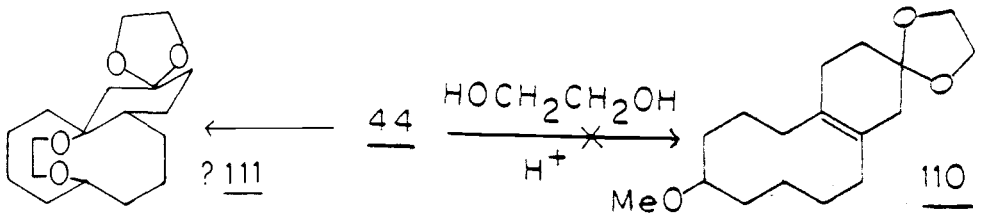


be handled at one time without difficulty. When 108 was allowed to condense with cyclodecanone 30, the diketone intermediate 109 was isolated. This intermediate 109 was not purified but was cyclized with sodium methoxide in benzene. Benzene was used in this case instead of methanol to avoid the possible formation of the bicyclic side product (71). Judging from the NMR spectrum, ketone 44 was formed exclusively; in particular, no vinyl proton was observed

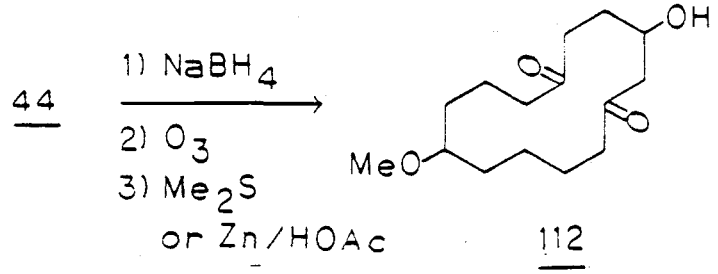


that would indicate the presence of 104. Cleavage of the double bond by ozonolysis should eventually give ketone 36.

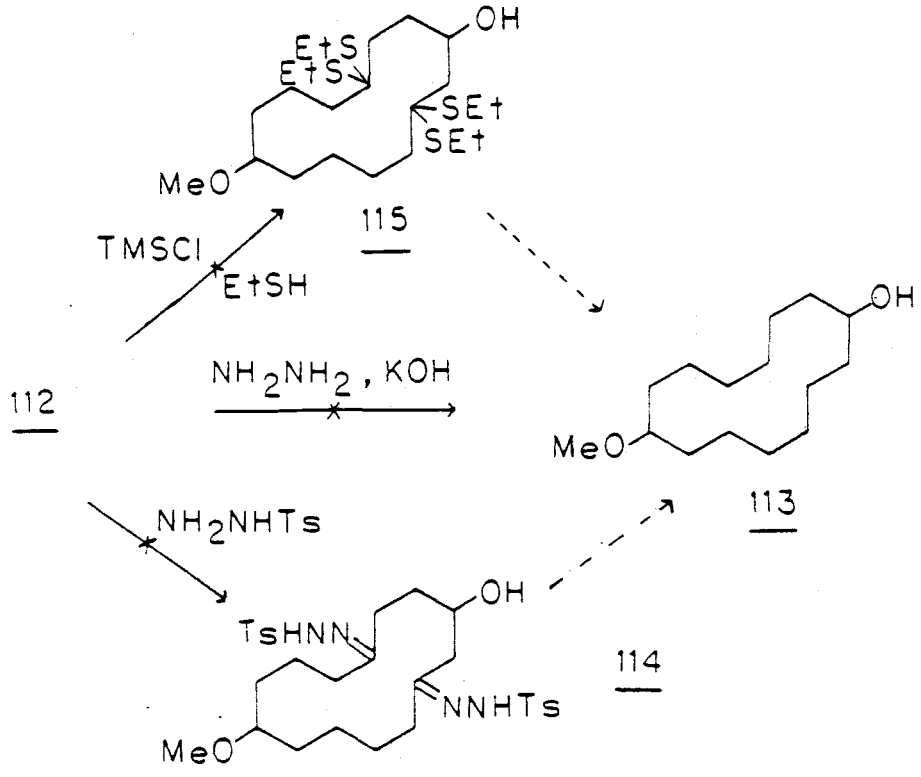
Attempts to protect the carbonyl with ethylene glycol failed to give the desired ketone 110. A yellow solid compound with a molecular weight of 310 was obtained which shows no methoxy protons and no carbonyl stretching band. It is postulated to be 111 but no further identification was done.



Several other attempts were made in which the carbonyl was protected as its alcohol or acetate. Ketone 44 was reduced by

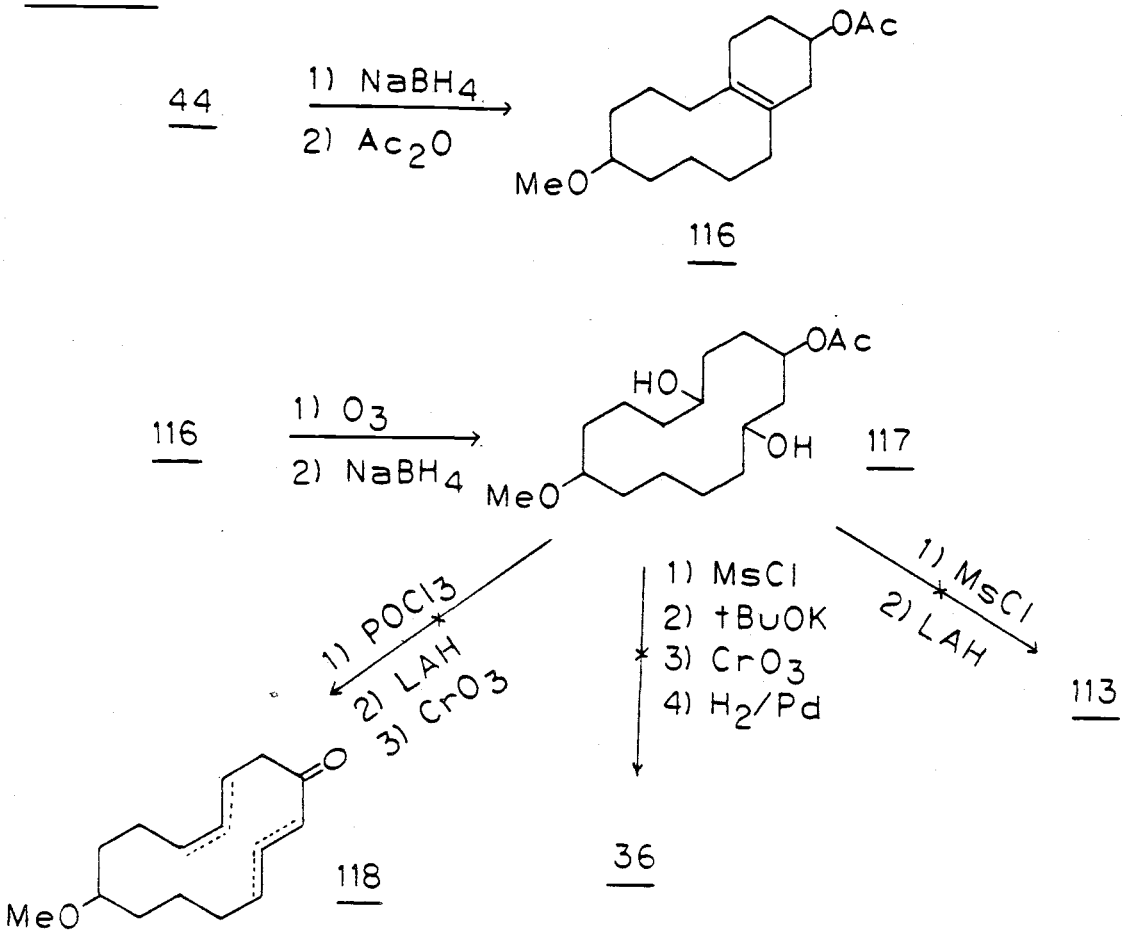


sodium borohydride and subjected to ozonolysis with zinc/acetic acid work-up which appeared to yield the diketone 112. Direct



Wolff-Kishner reduction failed to yield the alcohol 113. Heating with tosylhydrazine only gave a small amount of yellow crystalline product. No effort was invested to see if the solid product is the dihydrazone 114 since the yield was so poor. The TMSCl catalyzed thioketalization (72) only resulted in starting material attempts to reduce the diol 116 through a mesylate intermediate or with phosphorous oxychloride (Scheme X) only gave low yield of crude products

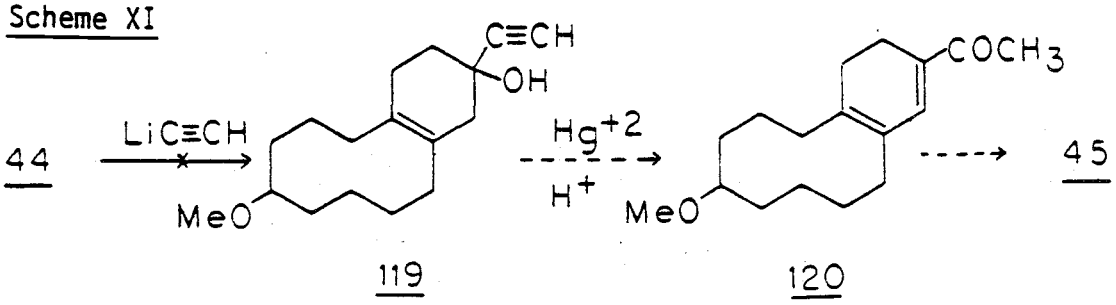
Scheme X



which contained large quantities of impurities. The cleavage of the double bond is still under investigation.

While working with ketone 44, its potential as a precursor of a C-ring aromatic hormone analog was discerned. Since the approach (Scheme XI) only called for a few steps and would constitute a new approach to benzo substituted medium-sized ring systems, some

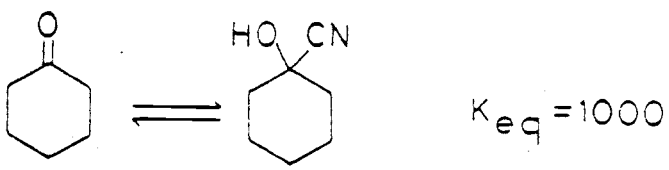
Scheme XI



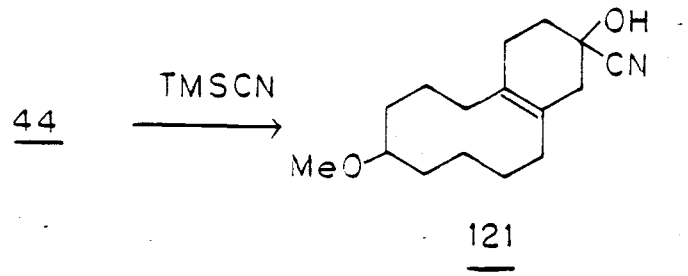
effort was put forth to test the viability of the scheme.

Excess lithium acetylide was generated with lithium diisopropyl amide and acetylene. In several attempts with THF or ether solvents at different temperatures only ketone was recovered. Presumably, the allylic protons alpha to the carbonyl are too acidic for a rather strong base like lithium acetylide. A neutral reagent was sought to introduce the necessary functionalities.

Our experience with TMSCN made it the reagent of choice in this case. A check on the equilibrium (73) between a six-membered ketone and its cyanohydrin gave more impetus for this approach.



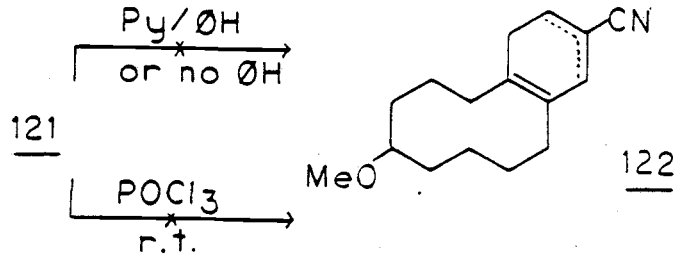
When TMSCN/KCN-18:crown:6 was allowed to stir with 44 in THF or ether at room temperature, the ketone disappeared in about two hours and cyanohydrin 121 was obtained after acidic workup. The rest of the



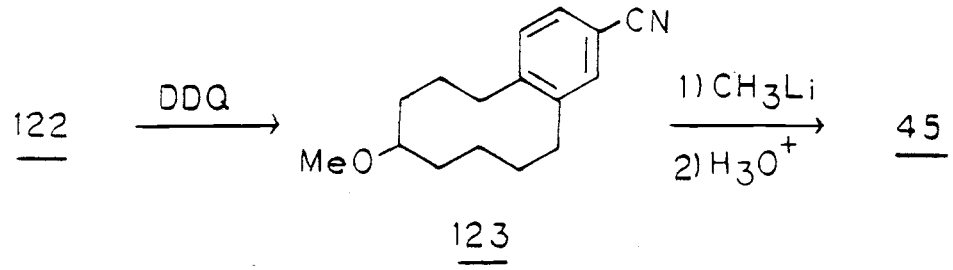
121

scheme then just called for the elimination of the hydroxy followed by aromatization and the conversion of the cyano group to the methyl ketone.

The resistance toward elimination of the cyanohydrin was more than expected. Refluxing 121 with pyridine in benzene with azeotropic removal of water or in pyridine alone only gave back the starting material, as did phosphorous oxychloride at room temperature.



Intermediate 122 was finally obtained by heating 121 with phosphorus oxychloride at 70-80°C. The remaining transformations to 45 were straightforward. Oxidation with DDQ (74) gave 123 which was converted to 45 with methyllithium. The seco C-ring aromatic hormone analog was thus completed in four steps from 44 in 12% overall yield.



123

Biological Test Results

Of the components prepared, 1, 32, 77, 87, 95 and 45 have been tested for uterotropic and post-coital activities (except for 77) at the Contraceptive Development Branch of the National Institute of Health Center for Population Research (see Table 3). When compared to estradiol which approximately doubles the uterine weight

Table III: Uterotropic Activity

Compound	Control	Dosage 1 µg	10 µg	100 µg	1000 µg
1	43.7 ± 3.7	44.9 ± 1.1	46.5 ± 3.4	49.0 ± 3.1	
32	43.4 ± 4.0	44.3 ± 3.2	46.8 ± 2.8	48.5 ± 4.9	
77	32.9 ± 1.0	46.0 ± 4.2	39.2 ± 2.4	36.7 ± 2.3	35.1 ± 2.5
87	25.9 ± 1.3	-----	30.1 ± 2.2	30.8 ± 2.2	
95	25.9 ± 1.3	-----	29.4 ± 2.5	31.4 ± 2.9	
45	38.3 ± 3.1	30.5 ± 1.3	32.7 ± 1.8	34.5 ± 2.0	

The table displays uterus wt (mg) vs. dosage of the compound indicated which was applied subcultaneously in sesame oil once daily for three days followed by sacrifice one day later.

at a 0.32 µg dose, all the analogs tested here, except 77, are extremely weak if active at all. The 40% increase in uterine weight at 1 µg dosage for 77 demonstrates that estrogen analogs without the rigid steroid backbone are capable of binding to the receptor and acting as an agonist. Cases in which the uterine weight increase falls off substantially with increasing dose have been observed previously for such compounds as nafoxidine which shows a 90% weight increase at 5 µg but only a 55% weight increase at 50 µg (75).

EXPERIMENTAL

General Laboratory Procedure and Conditions

All temperatures are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained on a Varian EM-360 (60 MHz) and a Varian HA-100 (100 MHz) spectrometers. Carbon 13 NMR was done on a Varian FT-80A machine. Unless specified, tetramethylsilane was used as the internal standard. Infrared spectra were obtained on a Perkin-Elmer 727B infrared spectrophotometer with polystyrene as a standard. Low resolution mass spectra were obtained from a Varian CH7 instrument using a 70 eV excitation potential. High resolution mass spectra were obtained from a CEC 110B instrument. Gas-liquid chromatography analysis were carried out on a Varian 1200 flame ionization detector GC using a 4' X 0.125" 7.4% OV101 on Chromosorb G, 80-100 column unless otherwise specified. Thin layer chromatography was done on precoated TLC sheets (EM reagents). Medium pressure high performance liquid chromatography (HPLC) was performed with a FMI laboratory pump and the Altex columns listed below.

Column A: 1.5 X 21 cm

Column B: 2.5 X 25 cm

Column C: 2.5 X 100 cm

The pressures employed were approximately 5 psi for column A, 10-15 psi for column B and 50-60 psi for column C. In all cases silica gel (EM Reagents Silica 60, 230-400 mesh) was used as the stationary phase. Preparative GC purifications were done on either a 2' X 0.25" 4.9% OV101 on Chromosorb G, 80-100 column or a 5' X 0.25" 10% OV101

on Chromosorb G, 60-80 column. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone under nitrogen.

General Procedure for the Preparation of 6-Hydroxy-cyclodecanone (47)

The modification of Cope was adapted for the preparation of the intermediate hydroperoxide. Thus practical grade decalin (Aldrich) was purified by passing through a column of silica gel (CC-7). The decalin solution was heated to 125±5°C in a three-necked flask equipped with a mechanical stirrer, a thermometer, a condenser and an oxygen inlet. After reaching the desired temperature, oxygen was bubbled through the solution at a rate of about 2 liter per minute and the solution was stirred vigorously. Benzoyl peroxide (a total of 11 gm per liter of decalin) was introduced in about ten equal portions at ten minute intervals. The temperature was maintained at about 125°C. The reaction was exothermic enough that only a small amount of external heat was needed. The total reaction time was 1.3 to 1.5 hours. The reaction mixture was then cooled quickly in an ice bath and washed with three 200 mL portions of 10% sodium hydroxide. The hydroperoxide intermediate thus obtained was then quickly isomerized into the title compound according to the procedure of Schnider (28). The organic layer was stirred vigorously with an equal volume of 70% phosphoric acid at 15°C in the presence of 200 mL of acetone. After 1.5 h, the layers were separated and the acid layer was extracted with water and chloroform. The combined organic layers were washed with water, sodium bicarbonate, and brine and then dried over magnesium sulfate. After

the chloroform was evaporated, a small amount of residual decalin was removed by Kugelrohr distillation at about 40°C and the crude product was then transferred over quickly at elevated temperature (120-150° C). The clear oily layer thus obtained was shaken with several hundred mL of hexane. White solid crystals settled out almost instantaneously. The majority of the hexane was evaporated under reduced pressure and the white crystals were filtered and recrystallized from hexane (mp 69-69.5° C; lit. (27) 70° C). This procedure yields about 10-15 gm of the product from one liter of decalin.

Recovered decalin (about 80%) was washed with water and sodium bicarbonate. The dried decalin ($MgSO_4$) can be used again one to two more times without further purification.

Preparation of 6-Methoxy-cyclodecanone (30)

The title compound was prepared according to the procedure of Creegee. Hydroxycyclodecanone 47 (14.8 gm) was dissolved in 150 mL of 0.1 N HCl/methanol and the resulting solution was refluxed for eight hours. At the end of that period the methanolic solution was diluted with three volumes of water and extracted with chloroform. The organic layer was washed with water, sodium bicarbonate, and brine and then dried over magnesium sulfate. After the chloroform was evaporated, 14.8 g (92%) of the desired product was obtained from Kugelrohr distillation which GC showed to be about 95% pure: ^{1}H NMR (CCl_4) δ3.4-3.0 (4H, singlet at 3.24), 2.7-2.18 (m, 4H), 2.04-1.06 (m, 12H); ^{13}C NMR ($CDCl_3$) δ214.4, 79.20, 56.37, 42.07, 39.76, 34.66, 33.64.

Preparation of 8-Methoxy-1,2-benzocyclododecen-3-one (50)

The Caubere reaction was adapted for the preparation of the title compound. Sodium amide was prepared *in situ* from metallic sodium and ammonia. Thus to 25 mL of liquid at -78°C with a catalytic amount of hydrated ferric nitrate, 3.2 g of sodium (0.14 mole) was added in small pieces within 5 min. The mixture was stirred at -78°C for 30 min and then at -33°C for an additional 30 min. The dry ice trap was removed and 100 mL of dry THF was introduced slowly and the result slurry was stirred at 45°C for about 2 h until excess ammonia was evaporated. To this sodium amide solution, 6-methoxycyclodecanone 30 (12.4 g, 0.067 mole) in 40 mL of dry THF was added dropwise over 10 min and the resulting mixture was stirred at 45°C for an additional h. Bromobenzene (5.0 g, 0.032 mole) in 30 mL of THF was added over 2 h and the solution was allowed to stir at 45°C for 24 h. The reaction was quenched by pouring into a mixture of 300 mL of ice and 20 mL of concentrated HCl. The aqueous layer was extracted with three portions of chloroform and the combined organic layers were washed with water, saturated $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and evaporated to yield a brown oily layer which was transferred by Kugelrohr distillation at about 90°C (1 mm) to give 6.8 g of the starting cyclodecanone and 6.15 g of the crude product at about 150°C. The crude product was purified by medium pressure HPLC eluting with ethyl acetate-pentane (1:4, v/v) on columns A and B. The oily layer obtained was triturated with 7 mL of pentane to yield 3.63 g (44%) of white solid product, mp 48-49°C. ^1H NMR (CCl_4) δ7.5-7.0 (m, 4H),

3.15-2.70 (m, 8H, singlet at 3.18), 1.94-0.78 (m, 12H); IR (CS_2) 2920, 2850, 2800, 1685, 1520, 1460, 1240, 1220, 1180, 1090, 980, 760 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ206.5, 141.83, 140.67, 130.73, 130.38, 126.07, 125.31, 79.41, 55.82, 39.59, 30.17, 28.38, 28.04, 27.83, 22.39, 20.24, 19.80; mass spectrum m/e 260.178 (calcd for $C_{17}H_{24}O_2$: 260.178).

Attempted Nitration of 8-Methoxy-1,2-benzocyclododecen-3-one (50)

Ketone 50 (0.797 g) was dissolved in several mL of ether and dripped into 10 mL of fuming HNO_3 at -10 - 0°C in about 15 min. After stirring for an additional 45 min at 0°C, the reaction was worked up with water and ether. The crude product collected amounted to 0.636 g; however, the NMR spectrum showed the disappearance of the methoxy protons (the IR still showed a band at 1690 cm^{-1}).

Attempted Preparation of 4',4,4-Tribromo-8-methoxy-1,2-benzocyclododecen-3-one (55)

The ketone 50 (1.10 g) was taken up in about 10 mL of carbon tetrachloride and stirred at 65°C for 18 h with 2.10 g of bromine in the presence of a catalytic amount of iron powder. The reaction mixture was then diluted with CCl_4 and the iron powder was filtered off. The organic layer was then washed with $NaHSO_3$, water, saturated $NaHCO_3$ and brine and then dried over magnesium sulfate. The NMR spectrum of the crude product (1.10 g) showed no methoxy protons.

Preparation of 4',8-Dimethoxy-1,2-benzocyclododecen-3-one (57)

The title compound was prepared from 3.2 g (0.14 mole) of sodium, 5.0 g (0.027 mole) of p-bromoanisole, and 11.2 g (0.061 mole) of 6-methoxycyclodecanone in a procedure similar to that for 50. After the Caubere reaction in 150 mL of dry THF at 45°C for 24 h, 6.2 g of starting 6-methoxy cyclodecanone was recovered from Kugelrohr distillation at about 90°C. At elevated temperature (about 150°C) 6.0 g of crude was obtained. The crude product was dissolved in about 10 ml of 1:4 (v/v) ethyl acetate-pentane and injected onto a medium pressure HPLC system consisting of 2 column B's and one column C in series. The mixed portion was chromatographed again on the two column B's. Ketone 57 has a slightly larger R_f value than 58. The separate portions were then triturated with several mL of pentane which gave 0.746 g (9.2%) of 57: mp. 71-74°C; ^{1}H NMR (CCl_4) δ7.15 (d, J = 9 Hz, 1H), 6.75-6.9 (m, 2H), 3.75 (s, 3H), 3.35-2.62 (m, 8H, singlet at 3.16), 1.9-0.85 (m, 12H); IR (mineral oil) 1680, 1615, 1510, 1295, 1260, 1210, 1180, 1100, 1040, 990, 870, 810 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ157.04, 142.34, 132.52, 131.97, 116.04, 111.59, 79.56, 55.97, 55.39, 39.65, 30.39, 28.49, 27.91, 27.40, 23.37, 20.30, 19.84; mass spectrum m/e 290.186 (calcd for $C_{18}H_{26}O_3$: 290.188) and 0.334 g (4.3%) of 58: mp 69.5-71.5°C; ^{1}H NMR (CCl_4) δ7.34 (d, J = 8, 1H), 6.74 (d, J = 2, 1H), 6.64 (dd, J = 8, 2 Hz, 1H), 3.8 (s, 3H), 3.26-2.6 (m, 8H, singlet at 3.16), 1.92-0.8 (m, 12H);

IR (mineral oil) 1670, 1605, 1585, 1290, 1260, 1220, 1190, 1100, 1060, 1040, 900, 800 cm^{-1}; ^{13}C NMR ($CCl_4/CDCl_3$) δ160.00, 143.79, 134.63, 129.38, 115.88, 110.38, 79.29, 55.57, 54.69, 38.03, 30.01, 28.52, 28.08, 27.60, 22.54, 20.33, 19.65; mass spectrum m/e 290.189 (calcd for $C_{18}H_{26}O_3$: 290.188). The carbonyl carbon was too weak to observe on ^{13}C NMR for both ketones.

Attempted Ring Expansion of the Silyl Enol Ether (62) of 8-Methoxy-1,2-benzocyclodecen-3-one (50) with Dibromo Carbene

The silyl enol ether was prepared from the corresponding ketone 50 with TMSCN. Thus 0.520 g of the ketone 50 was heated in 5 mL of toluene with 0.5 mL (4.1 mmole) of TMSCN. After reaching boiling temperature of toluene, a catalytic amount of KCN:18-crown-6 was added. The resulting mixture was refluxed for 5 h. The volatile components were evaporated under reduced pressure and 0.669 g of crude silyl enol ether was obtained.

Crude silyl enol ether was taken up in 20 mL of cyclohexane and stirred with 2.4 g of potassium t-butoxide. The mixture was then cooled in an ice bath and 2.2 mL of bromoform (in 3 mL of cyclohexane) was added and the resulting reddish brown solution was stirred at 0^oC for 15 min and then at room temperature for 24 h. Reaction was quenched with 30 mL of water and extracted with chloroform. The combined organic layers were washed by water and brine and then dried over magnesium sulfate. TLC of the crude product showed two major products which were separated by medium pressure HPLC on silica gel eluting with ethyl acetate-pentane (1:4, v/v)

to yield 0.23 g of the major product and 0.096 g of a minor product. GC of the major product thus obtained still contained a minor component with a shorter retention time. The mass spectrum of the major product has a molecular ion peak at 272 and IR of which shows a strong stretching at about 1660 cm^{-1}.

Attempted Preparation of Silyl Enol Ether (62) with TMSCl

Ketone 50 was heated to reflux in about 0.5 mL of DMF with 0.13 mL of TMSCl and 0.4 mL of triethylamine. even after 18 h a large amount of starting material was still present. Another attempt with 0.622 g of ketone 50 in 6 mL of refluxing dioxane with 0.3 mL of TMSCl and 0.7 g of potassium hydride (22% in oil slurry) also failed to yield significant amount of product after 18 h.

Attempted Simmon-Smith Reaction on Silyl Enol Ether (62)

The zinc-copper couple for the reaction was prepared according to the procedure of Harrison (41). Thus 0.13 g of zinc dust and 0.181 g of cuprous chloride (both oven dried) were refluxed in 5 mL of ether for 0.5 h. Silyl enol ether 62 (0.26 g, crude from TMSCN/KCN on ketone 50) in 5 mL of ether was then added to this zinc/copper couple followed by 0.14 mL of diiodomethane. After 16 h of reflux, several products (including the starting material) were observed on GC analysis and the prominent one had a retention time shorter than that of the starting material. After an additional 24 h, the crude product recovered showed no methoxy protons in the NMR spectrum.

Attempted Formation of 8-Methoxy-1,2-benzo-3-methylene (cyclododecene oxide (65) with a Sulfur Ylide

A 25 mL flask was charged with 0.14 g of sodium hydride which was then washed with two portions of pentane. Remaining pentane from washing was evaporated under reduced pressure. To this gray powder of sodium hydride, 3 mL of DMSO (distilled from CaH_2) was added and the mixture was heated to 60°C for 1 h under nitrogen to generate the methylsulfinyl carbanion. The solution was then cooled to room temperature and an equal volume of THF was added. The resulting solution was cooled to 0°C and 0.78 g of trimethylsulfonium iodide in 5 mL of DMSO was added in a rapid rate followed by the addition of ketone 50 in 5 mL of THF. The mixture was stirred at room temperature for 10 min and then at room temperature for 1 h. Reaction was quenched by water and extracted with pentane. The combined organic layers were washed with several portions of water and then brine. After drying over K_2CO_3 the crude product was analyzed by GLC and the majority of the product observed was just the starting ketone. The IR spectrum of the crude product showed very weak carbonyl stretching, but the NMR spectrum did not show any singlet corresponding to the methylene protons of the oxide.

Attempted Ring Expansion of 8-Methoxy-1,2-benzocyclodecen-3-one (50) with Methylene Bromide

Lithium diisopropyl amide was prepared from 1.8 mL of n-BuLi (1.7 M in hexane, 2 eq) and 0.45 mL of diisopropyl amine (2 eq) in 3 mL of THF at 0°C. The amide solution was added to a solution

of 0.406 g (1.56 mmole) of the ketone 0.22 mL of methylene bromide (2 eq) precooled in -78°C. The mixture was stirred at -78°C for 3 h and quenched with water. After normal work up, only starting material was recovered.

Attempted Ring Expansion of 8-Methoxy-1,2-benzocyclododecen-3-one (50) with Diethyl Aluminum Cyanide ($AlEt_2CN$)

The ketone 50 (0.155 g) was dissolved in 1 mL of toluene and cooled to -78°C. Diethyl aluminum cyanide (0.4 mL, Ventron, 1.57M in toluene) was added and the resulting mixture was allowed to stand at -15°C for several days. Only starting material was recovered. No attempts were made at higher temperature.

Preparation of 4',9-Dimethoxy-1,2-benzocyclotridecen-3-one (74) and -4-one (75)

The title compounds were prepared from ring expansion of 57 with trimethylsilyl cyanide (TMSCN). The starting ketone 57 (2.53 g, 8.7 mmole) was taken up in 25 mL of toluene (distilled and dried over molecular sieves) and cooled to -78°C. To this cold solution, 1.5 mL of TMSCN (12.9 mmole) was introduced followed by catalytic amount of 18-crown-6: KCN. The flask was then flushed with argon and sealed tightly with parafilm. The resulting mixture was allowed to wram up to -15°C in a refrigerator and left at that temperature for 7 days. At the end of this period a small amount of starting material was still detected by GC analysis. The reaction mixture was stirred at room temperature for 1 h. Toluene was evaporated and replaced by about 25 mL of anhydrous ether. This ether solution

was cooled to 0°C and 0.50 g of $LiAlH_4$ (Ventron 95%) was introduced in small portions. The resulting mixture was stirred at ice temperature for 15 min and then at room temperature for 3 h. At the end of the period, the reaction was cooled to 0°C and worked up by adding 0.48 mL of water and then 2.20 mL of 10% NaOH. The reagents were delivered carefully with the help of a buret. The mixture was stirred for 5 min and the ether layer was decanted and the light brown solid residue was washed with ether (2x25 mL). The combined ether layers were washed four times with 20 mL portions of 5% H_2SO_4. The aqueous acidic layer was then neutralized by 10% NaOH until basic and then extracted into ether. The ether was washed with saturated $NaHCO_3$ and dried over magnesium sulfate to yield 1.85 g of the amino alcohol 72 as a thick semi solid layer. The organic layer left behind from the H_2SO_4 washing yielded 0.510 g of the silyl enol ether 73. 72: IR (neat) 3400, 2940, 2860, 1610, 1580 cm^{-1}. 74 & 75: IR (neat) 2940, 2860, 1715, 1690, 1615, 1580, 1500, 1460, 1260, 1100, 1020 cm^{-1}.

The amino alcohol thus obtained was taken up in 70 mL of 10% HOAc in an Erlenmeyer flask. The solution was cooled to 0°C and 20 mL of 1.25 M $NaNO_2$ was added and stirred overnight. The mixture was extracted with water and ether. The combined ether layers were washed with saturated $NaHCO_3$ and dried over magnesium sulfate. Kugelrohr distillation yielded 1.46 g (56% overall) of products as a light yellow oily layer. GC analysis only showed one peak and TLC showed two spots.

Preparation of 8-Methoxy-1,2-benzocyclododecene (76) by Wolff-Kishner Reduction

The 8-methoxy-1,2-benzocyclododecen-5-one 50 (0.364 g) was refluxed in 4 mL of ethylene glycol with 1.9 mL of hydrazine (monohydrate) and 0.25 g of potassium hydroxide for 1.5 h. Excess hydrazine and water formed was then distilled and the resulting mixture was refluxed for additional 5 h. After cooling down to room temperature, reaction was poured into 5% H_2SO_4 and extracted with ether. The organic layer was washed with water and saturated $NaHCO_3$. The dried ($MgSO_4$) solution gave 0.185 g (54%) of crude product which analyzed as one peak on GC: ^1H NMR (CCl_4) δ7.2-6.96 (m, 4H), 3.34-3.04 (4H, singlet at 3.18), 2.88-2.3 (m, 4H), 1.94-1.10 (m, 14H); ^{13}C NMR ($CDCl_3$) δ140.19, 140.03, 129.50, 129.09, 125.62 (double intensity), 79.54, 55.74, 30.29, 29.26 (double intensity), 28.92, 28.61, 26.24, 22.14, 20.35. (76 appears one carbon short but the demethylated form shows all sixteen carbons).

Attempted Reduction of 4',9-Dimethoxy-1,2-benzocyclotridecen-3-one (74) and 4-one (75) by Wolff-Kishner Reaction

The cyclotridecenones (0.99 g) were taken up by about 2 mL of ethylene glycol and refluxed with 4.4 mL of hydrazine (Baker, monohydrate 99-100%) and 0.69 g of KOH for 2 h. At the end of the period, water was distilled off and 2 mL of ethylene glycol was added and the resulting mixture was heated at 195^oC for 5 h. The reaction was then cooled, diluted with water and extracted with ether. After the ether layer was washed with water and saturated $NaHCO_3$ and dried over magnesium sulfate, 0.527 g of crude product

was obtained. GC analysis of the crude thus obtained showed one major peak. The high resolution mass spectrum of a GC isolated sample of the major peak had a molecular ion peak 290.225 (calcd for $C_{17}H_{30}O_2$: 290.225) which corresponded very well to the desired dimethyl ether. The IR spectrum of the crude product also showed no carbonyl stretching. But TLC analysis showed a lot of tailing. No purification by chromatography was attempted since it was expected that yield would even be lower after chromatography.

Attempted Reduction of 8-Methoxy-1,2-benzocyclodecen-3-one (50) via the Tosylhydrazone

The ketone 50 (0.118 g) and 91 mg (1.1 eq) of tosylhydrazine were refluxed in 0.5 mL of absolute ethanol with a catalytic amount of conc. HCl. After 3 h, TLC analysis still showed mainly the starting material. No tosylhydrazone crystals were observed settling out from the reaction mixture upon cooling down to room temperature. The reaction was repeated without acid catalyst and the same result was observed. Other attempts with nonpolar solvents (carbon tetrachloride, toluene) with or without acid catalyst also failed to give the desired tosylhydrazone derivative.

Attempted Reduction of 9-Methoxy-1,2-benzocyclotridecen-4-one (71) via the Phosphonate Enol Ether

Ketone 71 (83 mg) was stirred in 5 mL of benzene with 15 mg of soidum hydride (57.2% on oil dispersion) for 20 minutes. Diethylchlorophosphate (0.05 mL) was then introduced and the resulting mixture was stirred at room temperature for 3 h and then at reflux

temperature for an additional 0.5 h. After cooling down to room temperature an equal volume of pentane was added and the inorganic precipitate was removed by suction filtration. Only starting material was recovered after removal of solvent. Another trial with longer reaction time and more chlorophosphate yielded the same result.

Attempted Reduction of 4',9-Dimethoxy-1,2-benzocyclotridecenones (74) and (75) with Phosphorous Oxychloride

Ketones 74 and 75 were taken into 15 mL of 95% ethanol and stirred with 0.19 g of soium borohydride at room temperature for 1.5 h and then at reflux temperature for anothe 1.5 h. Reaction was quenched with dilute sulfuric acid and extracted with ether. The organic layer was washed with $NaHCO_3$ and dried ($MgSO_4$). The crude alcohols thus obtained were dissolved in 15 mL of pyridine and chilled to 0^oC and then 1.2 mL of phosphorous oxychloride was introduced and the resulting mixture was stirred at 0^o C for about fifteen minutes and then at room temperature overnight. At the end of this period, water was added dropwise until the vigorous bubbling stopped and the resulting solution was then diluted with water and extracted with ether. The ether layer was washed and dried as before and 0.465 g of crude product was obtained. The GC analysis of the crude product showed one major peak and a minor peak (about 15%) with longer retention time. Hydrogenation of the crude product in 15 mL of 95% ethanol with 30 mg of 10% palladium on carbon did not change the ratio of the peaks. Purification by

medium pressure HPLC gave back only 0.229 g of product in about 90% purity.

Attempted Reduction of 4',9-Dimethoxy-1,2-benzocyclotridecenones (74) and (75) via Displacement of Intermediate Mesylate with $LiAlH_4$

The ketones (0.292 g) were stirred at room temperature in 10 mL of ether with 78 mg of $LiAlH_4$. After 3 hours, the reaction mixture was quenched with 0.08 mL of water and 0.34 mL of 20% NaOH. After drying ($MgSO_4$) and concentration 0.211 g of crude alcohol product was obtained.

The crude product was dissolved in 3 mL of pyridine and cooled to 0^oC. Methanesulfonyl chloride (0.6 mL) was added and the resulting mixture was left at -8^oC for 36 h. At the end of the period, pyridine and excess methanesulfonyl chloride was evaporated in vacuo at room temperature and residue was taken up in 30 mL of chloroform. The organic layer was washed with two portions of cold saturated copper sulfate and then by two portions of cold saturated sodium bicarbonate. The solution was dried and 0.4 g of crude product was obtained as a thick oily layer.

The crude product thus obtained was dissolved in 10 mL of ether and refluxed with 103 mg of $LiAlH_4$ for 3 days. After treatment with water (0.14 mL) and 10% NaOH (0.44 mL), drying ($MgSO_4$) and concentration gave 0.164 g of crude product. The GC analysis showed two products of very similar retention time. Hydrogenation with Pd/C (up to 70 mg of 10% catalyst) did not change the pattern in the GC analysis.

Attempted Reduction of 8-Methoxy-1,2-benzocyclododecen-3-one (50) with Boron Trifluoride and Triethylsilane.

Boron trifluoride (scrubbed by passage through a solution of 15 g of boric anhydride in 70 mL of conc H_2SO_4) was bubbled through 2 mL of methylene chloride at 0^oC. To this cold methylene chloride solution, the ketone (0.24 g) in 2 mL of methylene chloride was added slowly. Upon complete addition, 0.6 mL of triethylsilane (Silar) was added rapidly though a syringe and the mixture was stirred at 0^oC for 1 h with a constant slow stream of boron trifluoride passing through it. The reaction was quenched with brine and stirred at room temperature for several hours and worked up with ether. Removal of the ether gave 0.115 g of crude product which showed strong carbonyl stretching at about 1690 cm^{-1}, but the NMR spectrum showed that the methoxy group had disappeared.

Preparation of 4',9-Dimethoxy-1,2-benzocyclotridecene (77)

Crude 74 and 75 (1.46 g) was reduced by 0.18 g of $LiAlH_4$ in 35 mL of dry ether. After stirring at room temperature for 2 h, the reaction was worked up with 0.17 mL of water and then 0.79 mL of 10% NaOH. After the ether was decanted, the white precipitate was washed with three 25 mL portions of ether. The combined ether layers were washed with saturated $NaHCO_3$ and dried over magnesium suflate to yield 1.33 g of crude alcohols.

The crude alcohols obtained were taken up in 20 mL of dry pyridine (over BaO) and cooled to 0^oC and 3 mL of methanesulfonyl chloride (Aldrich) was then introduced. The mixture was stirred

at 0°C for 5 min and then left to stand at -15°C for 16 h. The majority of the pyridine and excess methanesulfonyl chloride was then removed in vacuo at room temperature. The residue was taken up in 100 mL of methylene chloride and the organic layer was washed with cold 5% H_2SO_4 (3x50 mL) and cold saturated $NaHCO_3$. The dried solution ($MgSO_4$) yielded 2.18 g of crude mesylates.

The crude mesylates were eliminiated by stirring with 1.55 g of potassium t-butoxide in 30 mL of dry DMSO (over CaH_2) at room temperature for 8 h. The reaction mixture was then partitioned between pentane and water and the aqueous layer was further extracted with two portions of pentane. The combined organic layers were washed with two portions of water and saturated $NaHCO_3$ and then dried over magnesium sulfate. After the pentane was evaporated, 1.6 g of crude product was obtained which was filtered through a short column of silica gel to yield 0.71 g of light oily material.

The crude products from elimination were taken up in 20 mL of 95% EtOH and hydrogenated with 45 mg of 5% Pd/C at room temperature and atmospheric pressure. At the end of 5 h, a stream of nitrogen was bubbled through the solution and the solution was further diluted with 20 mL of 95% EtOH. The catalyst was removed by suction filtration and after the ethanol was evaporated 0.71 g (51% overall) of product was obtained as a clear oil. GC and TLC analysis only showed one peak and one spot respectively. ^1H NMR (CCl_4) δ6.93 (d, J = 9 Hz, 1H), 6.77-6.4 (m, 2H), 3.72 (s, 3H), 3.40-3.00 (4H, singlet at 3.25), 2.95-2.5 (m, 2H), 2.5-2.1 (m, 2H), 1.90-1.0 (m, 16H); IR (neat) 2950, 2870, 1620, 1580, 1505, 1470, 1260, 1215,

1160, 1100, 1055, 790 cm^{-1}; ^{13}C NMR ($CCl_4/CDCl_3$) δ141.03, 130.14, 115.19, 110.98, 78.09, 55.83, 54.52, 31.71, 30.89, 30.71 (double intensity), 28.99, 27.94, 26.38, 25.18, 23.53, 21.81 (2 quaternary carbons were not observed); mass spectrum m/e 290.225 (calcd for $C_{19}H_{30}O_2$: 290.225).

Attempted Demethylation of 4',8-Dimethoxy-1,2-benzocyclododecen-3-one (57) with Sodium Thioethoxide

Sodium hydride (0.13 g, dispersion in mineral oil) was washed three times with pentane and after the final wash the residual pentane was evaporated under reduced pressure. This sodium hydride was then stirred in about 4 mL of DMF (over CaH_2) with 0.21 mL of ethanethiol at room temperature for about 5 minutes. Ketone 57 (0.48 g in about 4 mL of DMF) was added to this sodium thioethoxide solution and the resulting mixture was refluxed for 24 h. The reaction was quenched with dilute acid and extracted with ether. The ether layer was in turn extracted with 5% NaOH. The aqueous layer was then neutralized by concentrated hydrochloric acid and extracted with ether to give 0.433 g of starting material after washing with $NaHCO_3$ and NaCl and drying ($MgSO_4$). Another attempt yielded 60% of yellow crystalline crude product which was believed to be the phenol 85; however several other attempts gave back only the starting material.

Attempted Demethylation of Methyl Ether (76) via the Sulfide Intermediate

The methyl ether 76 (56 mg) was taken up in 2 mL of EtSH and cooled to 0^oC before 90 mg (3 eq) of $AlCl_3$ was added. The reaction

mixture was then stirred at room temperature overnight. Ethanethiol was evaporated and the residue was taken up in dilute acid and ether. The organic layer was washed with water and saturated $NaHCO_3$ and then dried over magnesium sulfate. The crude sulfide obtained (only 42 mg due to some mechanical loss during workup) was dissolved in 2 mL of glacial HOAc and stirred with 45 mg of mercuric acetate. No reaction was observed after 2 days at 65°C.

Attempted Demethylation of 7-Methoxy-1,2-benzocyclododecene (76) with BBr_3

The methyl ether 76 (0.16 g) was taken up in 1 mL of methylene chloride and cooled to 0°C. BBr_3/CH_2Cl_2 (0.15 mL, 50%, w/w) which had been cooled to -4°C was added and reaction mixture was stirred at -4°C. Aliquot samples were withdrawn at 5 minute intervals for GC analysis. Each aliquot was quenched with water and organic layer was taken up in a small amount of ether and dried over magnesium sulfate. Even after 5 min of reaction time, the starting ether had almost all disappeared and a compound with a lower retention time than the expected alcohol became the predominant product. No attempt was carried out again at lower temperature.

Attempted Demethylation of Methyl Ether (76) with Boron Trifluoride Etherate and Ethanethiol in the Presence of Hydrogen Chloride

Methyl ether 76 (59 mg) was taken up in 1 mL of EtSH and stirred with 0.4 mL of $BF_3 \cdot Et_2O$ (freshly distilled from ether and

CaH_2). The reaction mixture was cooled in an ice bath and a stream of HCl (from NaCl and conc H_2SO_4) was bubbled through the solution for about 10 min. The resulting mixture was then stirred at room temperature and reaction was monitored periodically by GC for the disappearance of the starting ether. After 2 days, the volatile components were evaporated under reduced pressure and the residue was dissolved in methylene chloride and washed with saturated $NaHCO_3$ and dried over magnesium sulfate. The crude product collected was put through a flash chromatography column eluting with ethyl acetate-pentane (1:4, v/v) and 41 mg of material was obtained. The IR spectrum shows a weak OH stretching band and TLC has at least 3 to 4 spots. No further purification was done on this material.

Attempted Demethylation of 8-Methoxy-1,2-benzocyclododecene (76) with Diisobutyl Aluminum Hydride (DIBAH)

To a 25 mL flask charged with 0.216 g of the methyl ether, 0.6 mL of DIBAH (Aldrich, 25% in toluene) was added and the reaction mixture was stirred at 70°C (bath temperature). After several hours, only starting material was observed by GC analysis. The reaction mixture was stirred for six more days but still no desired product was observed. Another attempt at refluxing toluene temperature also produced no results.

Preparation of 4',9-Dihydroxy-1,2-benzocyclotridecene (1)

The dimethyl ether 77 (0.71 g, 2.45 mmole) was taken up in 8 mL of ethanedithiol and chilled to 0°C. To this cold solution, 1.0 g of aluminum chloride (Mallinckrodt) was introduced in small

portions and upon complete addition, the reaction was stirred at $0^{o}C$ for 5 min and then at room temperature for about 1.2 h. Excess ethanedithiol was evaporated at room temperature in vacuo and collected in a trap cooled to $-78^{o}C$. The catalyst was destroyed by addition of water and the product was taken up in 75 mL of ethyl acetate. The time span between the addition of aluminum chloride to its destruction should not exceed 1.7 h. The ethyl acetate was washed with water (3x30 mL) and then extracted with 5% NaOH (6x30 mL). After further washing with saturated $NaHCO_3$ and drying ($MgSO_4$), the solvent was removed to give a semi-solid product. The crude product obtained was stirred with 15 mL of pentane to yield 0.361 g (56%) of product as a white solid. Further washing (0.250 g) with a small amount of ether-hexane (1:2, v/v) yielded 0.234 g of product, mp 142-145 ^{o}C. Pure diol (mp 149-150^{o}C) was obtained by washing with small amount of ether. ^{1}H NMR (d_6-DMSO/$CDCl_3$) δ6.86 (d, J = 8 Hz, 1H), 6.66-6.38 (m, 2H), 3.82-3.54 (m, 1H), 2.82-2.62 (m, 2H), 2.44-2.04 (m, 2H), 2.04-1.04 (m, 16H); IR (mineral oil) 3420, 3200, 1610, 1270, 1240, 1160, 1090, 1010, 980 cm^{-1}, ^{13}C NMR (d_6-acetone) δ142.92, 131.88, 117.71, 114.17, 68.61, 37.71, 34.61, 32.79, 32.04, 30.39, 29.38, 27.92, 36.37, 24.94, 23.48 (2 quaternary carbons were not observed); mass spectrum m/e 262.192 (calcd. for $C_{17}H_{26}O_2$: 262.193).

The NaOH extracted portion was neutralized with dilute acid and extracted with ether to yield 0.335 g of a yellow liquid product which was purified by chromatography. Analysis by TLC showed that the product obtained has a much higher R_f than that of the expected diol. The NMR spectrum of the product did not show any aromatic

protons at all. This portion was discarded without further characterization.

Preparation of 4'-Hydroxy-1,2-benzocyclotridecen-9-one (87)

The title compound was prepared by oxidation of the diol 1 with Jones reagent. Jones reagent was prepared by dissolving 7.0 g of CrO_3 in small amount of water followed by addition of 6.1 mL conc H_2SO_4. The resulting solution was then diluted to 50 mL with water.

The diol (0.234 g, mp 142-145°C) was taken up in 30 mL of acetone and Jones reagent was added dropwise at room temperature until a definite brown color persisted. Excess isopropanol was then added until the brown color disappeared. The solution was decanted and the acetone was evaporated under reduced pressure and replaced with 50 mL of ethyl acetate. The green chromium salt left behind from the decantation was dissolved in water and extracted with ethyl acetate. The ethyl acetate layers were combined and washed with two protions of water and saturated $NaHCO_3$ and dried over magnesium sulfate. After solvent was removed, the crude product was Kugelrohr distilled to yield 0.172 g (74%) of product; mp 94.5-96°C. ^{1}H NMR ($CDCl_3$) δ6.98 (d, J = 8 Hz, 1H), 6.74-6.44 (m, 2H), 4.8 (s, 1H), 2.84-2.4 (m, 8H), 2.4-1.2 (m, 12H); IR ($CDCl_3$) 3600, 2940, 2860, 1705, 1610, 1500 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ153.9, 142.17, 132.35, 130.54, 116.29, 112.91, 42.03, 40.62, 31.77, 30.65, 29.72, 28.94, 26.46, 25.47, 23.14, 23.08 (the carbonyl was too weak to observe); mass spectrum 260.179 (Calcd for $C_{17}H_{24}O_2$: 260.178).

Preparation of 4',9-Dihydroxy-9-ethynyl-1,2-benzocyclotridecene (94)

Acetylene (conc H_2SO_4 washed) was bubbled through 20 mL of dry THF at -78°C for 5 min. n-BuLi (3 mL of 1.27 M in hexane, 3.81 mmole) was added to this cold solution and stirred at -78°C for an additional 10 min with the continuous bubbling of acetylene. 4'-Hydroxy-1,2,benzocyclotridecen-9-one 87 (0.150 g, 0.576 mmole) in 10 mL of THF was added and the resulting mixture was stirred at -78°C for 20 min and then at room temperature for 1.5 h. The reaction was then poured into saturated NaCl and extracted with ether. The combined layers were washed with water and brine and dried over magnesium sulfate. Purification by chromatography on florisil eluting with ethyl acetate-hexane (40:60, v/v) followed by Kugelrohr distillation yielded 76 mg (46%) of product: mp indefinite, 45-60°C. ^{1}H NMR ($CDCl_3$) δ7.02 (d, J = 8 Hz, 1H), 6.7-6.52 (m, 2H), 4.7 (s, 1H), 2.76-2.3 (m, 5H, singlet at 2.43), 2.04-1.15 (m, 16H); IR ($CDCl_3$) 3600, 3310, 3160, 2940, 2870, 2350, 1820, 1800, 1710, 1610, 1590, 1500, 1420, 1380, 1220, 1100 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ153.46, 142.23, 132.57, 130.34, 116.57, 112.87, 88.18, 71.67, 71.24, 38.48, 37.25, 32.92, 31.28, 31.06, 28.66, 26.40, 25.87, 22.47, 20.56 (the carbonyl was too weak to observe); mass spectrum m/e 286.194 (Calcd for $C_{19}H_{26}O_2$: 286.193).

Preparation of 7-Methoxy-1,2-benzocyclododecene (76) through the Mesylate Intermediate

Ketone 50 (0.206 g) was reduced with 40 mg of LAH at room temperature in about 7 mL of ether. After 2.5 h, the reaction was

quenched with water and sodium hydroxide as before to yield 0.133 g of crude alcohol. This crude alcohol was then taken up in 4 mL of pyridine and chilled to $0^{o}C$. To this cold solution, 0.4 mL of methanesulfonyl chloride was introduced through a syringe and the reaction mixture was left at $-8^{o}C$ for 40 h. Pyridine and excess sulfonyl chloride was evaporated *in vacuo* at room temperature and the residue was taken up in 25 mL of chloroform. The chloroform layer was washed with cupric sulfate and $NaHCO_3$ and dried over magnesium sulfate. After the chloroform was evaporated, the crude mesylate was refluxed with 55 mg of LAH in ether for 5 days (reaction was completed in about 50 h already). After normal workup, 64 mg of crude 76 (51% from alcohol) was collected. The GC analysis only showed on peak.

Preparation of 8-Methoxy-1,2-benzocyclodecene (76) via Hydrogenolysis of 8-Methoxy-1,2-benzocyclodecen-3-ol

The alcohol was prepared from the reduction of the corresponding ketone with either $LiAlH_4$ or $NaBH_4$ in refluxing ethanol. The crude alcohol (0.814 g) was subjected to hdrogenolysis under 50 psi at room temperature in 15 mL of glacial acetic acid with 80 mg of 10% Pd/C in the presence of catalytic amount of conc H_2SO_4. After 2 days of reaction time, the mixture was diluted with ethanol, filtered and extracted with ether and water. The crude product obtained (0.621 g) was purified by HPLC eluting with ethyl acetate-pentane (1:4, v/v) and 0.254 g (33% from the alcohol) of product was obtained. The GC analysis showed a major product with the correct retention time for 76 and a 5% impurity.

Preparation of 8-Methoxy-1,2-benzocyclodecen (76) via Lithium Reduction of 8-Methoxy-1,2-benzocyclodecen-3-ol

The crude alcohol (0.331 g; from reduction of 0.367 g of the corresponding ketone with $LiAlH_4$) in 5 mL of THF was added slowly to a solution containing 5 mL of NH_3 and 90 mg of lithium in 5 mL of THF at -78°C. Upon complete addition, reaction mixture was stirred at -78°C for 5 min and then 15 more min with the dry ice bath removed. The blue color was discharged with granular ammonium chloride. After the NH_3 was evaporated, the residue was taken up by ether and the organic layer was washed by water and saturated $NaHCO_3$ and then dried over magnesium sulfate. The crude product (0.246 g) was purified by HPLC on silica gel eluting with ethyl acetate-pentane (1:4,v/v) to give 0.125 g (36% from ketone) of product. The GC analysis showed about 10% of impurities.

Preparation of 4',8-Dimethoxy-1,2-benzocyclododecene (96) from Ketone 57 with Phosphorous Oxychloride

Ketone 57 (0.604 g) was stirred in 15 mL of 95% ethanol with 0.106 g of sodium borohydride for 5 h. At the end of the period, the reaction was quenched with dilute acid and extracted with ether to yield 0.541 g of crude product after the normal washing and drying. Crude product was then taken up by 10 mL of dry pyridine and cooled to 0°C followed by the addition of 1.5 mL of phosphorous oxychloride. The reaction was warmed up to room temperature and

allowed to stir for an additional 12 h. At the end of that period, water was added dropwise carefully to get rid of the excess reagent and resulting mixture was extracted with water and pentane and 0.328 g of crude product was obtained. The crude material was hydrogenated with 18 mg of 10% palladium on carbon in 15 mL of 95% ethanol at room temperature under atmospheric pressure for 5 h. The solution was purged of hydrogen by bubbling nitrogen through it for a few minutes. The ethanolic solution was then suction filtered and 0.311 g of crude dimethyl ether 95 was obtained. Chromatography on Column A eluting with 20% ethyl acetate-hexane yielded 0.21 g of 95 (37% overall).

Preparation of 4',8-Dihydroxy-1,2-benzocyclododecene (32)

The title compound was prepared from the reduction of the 4',8-dimethoxy-1,2-benzocyclodecene-3-one 57. The starting ketone (0.318 g) was reduced with 63 mg of $LiAlH_4$ in 10 mL of ether. After 12 h (usually 2 h is enough) the reaction was quenched with 0.06 mL of water followed by 0.28 mL of 10% NaOH. The organic layer was decanted and the precipitate was washed with ether (3x20 mL). The combined ether layers were washed with satureated $NaHCO_3$ and dried over magnesium sulfate. After the ether was removed, 0.292 g of crude product was obtained.

The crude alcohol obtained was dissolved in 4 mL of dry pyridine and cooled to 0^oC before 0.3 mL of methanesulfonyl chloride was added and the resulting mixture was left at -8^oC for 7 days (one day should be enough). Pyridine and excess methanesulfonyl

chloride was removed in vacuo at room temperature and residue was taken up by 30 mL of chloroform. The organic layer was washed by copper sulfate (2x25 mL) and saturated $NaHCO_3$ (3x25 mL). The dried solution ($MgSO_4$) yielded 0.383 g of mesylate as a thick oily layer.

The crude mesylate was dissolved in 20 mL of ether and refluxed with 66 mg of $LiAlH_4$ for 2 days. After normal workup with water (0.07 mL) and 10% NaOH (0.30 mL), 0.180 g (59%) of 95 was obtained. Analysis by GC and TLC showed only one peak and one spot respectively. 95: ^1H NMR (CCl_4) δ6.94 (d, J = 8 Hz, 1H), 6.74-6.4 (m, 2H), 3.7 (s, 3H), 3.36-3.0 (4H, singlet at 3.2), 2.9-2.2 (m, 4H), 2.1-1.04 (m, 14H); IR (neat) 2940, 2860, 1610, 1590, 1500, 1470, 1260, 1200, 1160, 1100, 1040 cm^{-1}, ^{13}C NMR ($CCl_4/CDCl_3$) δ130.46, 114.39, 111.52, 79.76, 56.0, 54.77, 30.51, 29.15 (about twice the intensity), 28.66, 28.57, 26.21, 21.99, 20.28 (the carbonyl and the quaternary carbons were too weak to observe); mass spectrum m/e 276.208 (Calcd for $C_{18}H_{28}O_2$: 276.209).

The crude dimethyl ether (0.152 g) was dissolved in 5 mL of ethanethiol and stirred with 0.3 g of $AlCl_3$. After 1.5 h at room temperature, the mixture was stirred for an additional 10 min at 0^oC. The reaction was quenched by 15 mL of 10% H_2SO_4 and the excess ethanethiol was evaporated overnight. The aqueous acid layer was extracted by ether and the ether was then washed by several portions of 10% NaOH. The aqueous NaOH layer was then neutralized by 10% H_2SO_4 until acidic and extracted with ether again. The combined ether layers were washed with water and saturated $NaHCO_3$ and dried over magnesium sulfate. After solvent was removed 73 mg of crude

was obtained as a sticky solid. TLC analysis of the crude product showed only one spot with R_f<0.05 (eluting with 20% EtOAc-pentane) was purified by chromatography on silica gel eluting with ethyl acetate/pentane (1:4, v/v). It was evident later that the crude product could be purified by simply washing with pentane or hexane. 32: mp 173.5-174.5°C; ^{1}H NMR (d_6-acetone) δ7.0 (d, J = 8 Hz, 1H), 6.7-6.52 (m, 2H), 3.9-3.6 (m, 1H), 2.9-2.3 (m, 4H), 2.0-1.2 (m, 14H); IR (mineral oil) 3400, 3200, 1580, 1260, 1245, 1160, 1100, 1000, 800 cm^{-1}; ^{13}C NMR (acetone/$CDCl_3$) δ155.02, 141.7, 131.33, 130.37, 115.62, 112.03, 69.21, 34.17, 31.30, 30 23, 29.38, 29.06, 28.32, 26.31, 21.81, 20.48; mass spectrum m/e 248.178 (calcd for $C_{16}H_{24}O_2$: 248.178).

Preparation of p-Trimethylsilyl-bromobenzene (98)

The title compound was prepared from p-dibromobenzene. The mono Grignard reagent of the dibromobenzene was formed from 10.3 g (44 mmole) of the dibromobenzene (Aldrich) and 1.08 g (44 mmole) of magnesium turnings. To this Grignard reagent (in about 50 mL of THF), 6.2 mL of TMSCl (2 eq) was added and the resulting mixture was maintained at 45°C overnight. The magnesium salts were removed by filtration and the organic layer was diluted with about 100 mL of ether and washed with water and brine and then dried over magnesium sulfate. Purification by distillation (68-70°C, 1 mm) yielded 5.0 g (50%) of product: ^{1}H NMR (CCl_4) δ, 7.47-7.2 (m, 4H), 0.23 (s, 9H).

Preparation of 6-Benzylcyclodecanone (100)

The hydroxy ketone 47 (1.07 g) was heated up to 75°C in 5 mL of benzyl alcohol in the presence of several drops of hydrochloric acid. After 15 h, the reaction was diluted with water and extracted with ether. The ether layer was washed with $NaHCO_3$ and dried over magnesium sulfate. After the ether was stripped off, excess benzyl alcohol was evaporated by Kugelrohr distillation. The crude product was chromatographed on column A eluting with 15% ethyl acetate-hexane and only 0.425 g of product was obtained. The GC analysis showed about 30% of impurities. Another trial at elevated temperature (90-110°C bath temperature) yielded a better result (ca. 50%) after chromatography; but the product collected still showed considerable impurities. ^{1}H NMR (CCl_4) δ7.15 (s, 5H), 4.4 (s, 2H), 3.5-3.2 (m, 1H), 2.48-2.12 (m, 4H), 1.96-1.18 (m, 12); IR (neat) 2930, 2870, 1700, 1455, 1365, 1095, 1070, 735, 695 cm^{-1}.

Preparation of 3,4-Benzobicyclo[7.3.0]dodec-3-ene-2-one (101)

Ketone 50 (62 mg) was stirred in 2 mL of toluene with 90 mg of zinc iodide at reflux temperature for 3 days and reaction was then quenched with dilute acid and extracted with ether. The ether layer was washed with $NaHCO_3$ and dried over magnesium sulfate. After the ether was evaporated the crude product was chromatographed on column A eluting with 5% ethyl acetate-hexane to yield 47 mg of 101: ^{7}H NMR (CCl_4) δ7.4-6.92 (m, 4H), 3.14-2.42 (m, 3H), 2.42-1.04 (m, 13H); IR (neat) 2940, 2870, 1695, 1600, 1450, 1360, 1240, 1215, 1050, 755 cm^{-1}; ^{13}C NMR ($COCl_3$) δ129.82, 129.59, 126.00, 125.29,

56.13 (d) 46.79 (d), 36.48, 35.07, 32.52, 32.24, 30.28, 26.33, 23.36 (the carbonyl and the two quaternary carbons were too weak to observe); mass spectrum m/e 228.149 (Calcd for $C_{16}H_{20}O$: 228.151).

Preparation of 3-Trimethylsilybuten-2-one (108)

The title compound was prepared according to the method of Stork. Thus 40.5 g of vinyltrimethylsilane (Silar) was cooled to -78°C and stirred vigorously while 20 mL of bromine was added slowly. A large amount of yellow crystals were observed close to the end of addition and a reddish brown color persisted. The reaction mixture was warmed to room temperature slowly and stirred for an additional hour. The solution was then diluted with about 300 mL of pentane and washed with dilute sodium bisulfite until the brown color was discharged. The organic layer was then washed with saturated $NaHCO_3$ and brine and dried over magnesium sulfate. This yielded 88 g of crude dibromo silane. The dibromo silane was eliminated with diethyl amine according to literature procedure (31). This crude intermediate was shaken with 75 mL (2.2 eq) of dry diethyl amine (over calcium hydride) at room temperature for two days. Ether (about 150 mL) was then added and the resulting solution was filtered and 50 g of ammonium bromide salt was collected (theoretical 52 g). The ether was distilled off under atmospheric pressure and 43 g (59%) of bromo vinylsilane was obtained by distillation at reduced pressure (25 mm, 34°C).

The Grignard reagent of the α-bromo-vinyltrimethylsilane was prepared by dripping 25 g of the silane in 30 mL of dry THF into 4 g of magnesium turnings in 150 mL of THF. The Grignard solution

was then cooled to 0°C and 16.8 g of acetaldehyde (about 2.5 eq) in 30 mL of THF was added slowly and the resulting mixture was stirred at 0°C for 0.5 h and then at room temperature overnight. The reaction was quenched with 5% H_2SO_4 and extracted with water and ether. The combined organic layers were washed with saturated $NaHCO_3$ and dried over magnesium sulfate. Most of the solvent was removed at atmospheric pressure and the residual THF was then removed under slightly reduced pressure (100 mm); 21.7 g of crude alcohol was collected.

The crude alcohol was taken up in 90 mL of methylene chloride and added slowly to a slurry of 41 g of pyridinium chlorochromate (26) (Aldrich) in 200 mL of methylene chloride. The reaction mixture was slightly cooled by an ice bath during the addition of the alcohol and upon complete addition it was stirred at room temperature for 1.5 h. The reaction mixture was then diluted with about 2 volumes of ether and stirred at room temperature for 20 min. The organic layer was decanted and the residual black sticky solid was further washed with two portions of ether. The combined organic layers were filtered rapidly through a small florisil column with the help of an aspirator. The solvent was distilled at atmospheric pressure and 7.6 g of the desired ketone was obtained from distillation (13 mm, 42°C; lit. (71) 50 mm, 72°C). The overall yield for the last three steps was 34-48%.

Attempted Preparation of Ketone (104) by Acid Catalyzed Robinson Annelation

Cyclodecanone 30 (1.235 g) and 0.59 g of freshly distilled

methyl vinyl ketone was refluxed in 5 mL methanol in the presence of one drop of concentrate sulfuric acid. The solution turned dark very rapidly and only starting ketone 30 was recovered after 24 h.

Attempted Preparation of Ketone (104) by a Base Catalyzed Robinson Annelation

Sodium hydride (0.23 g, 57.2% in oil dispersion) which had been washed twice with pentane, was stirred with 1.00 g of cyclodecanone 30 and 0.6 mL of methyl vinyl ketone in 8 mL of dry DMSO for 2 h. The reaction turned dark very rapidly and only starting ketone 30 was recovered after workup.

Preparation of 7-Methoxy-4'-oxo-1,2-cyclohexenocyclodecene (44)

The title compound was prepared by the modified Robinson annelation according to Stork. Lithium diisopropylamide was formed by stirring 27 mL of nBuLi (1.55 M in hexane, 42 mmole) with 6.2 mL of diisopropyl amine (43 mmole) in 120 mL of THF at $0^{o}C$. To this cold LDA solution, 6-methoxycyclodecanone 30 (7.77 g, 42 mmole) in 20 mL of THF was added and stirred for 30 min. The resulting mixture was then cooled to $-78^{o}C$ and 3-trimethylsilyl-buten-2-one 108 (6.00 g, 42 mmole) in 20 mL of THF was introduced in a slow dropwise manner. The reaction was stirred at $-78^{o}C$ for 2 h and then at room temperature overnight. After quenching with water and extracting with ether, the combined ether layers were washed with brine and dried over magnesium sulfate. Solvent was evaporated under reduced pressure and unreacted 6-methoxycyclodecanone was recovered by

Kugelrohr distillation (1 mm, 60°C). The resultant 9.89 g of undistilled 109 was then refluxed in 80 mL of dry benzene (acid washed and then distilled over sodium) with 8.5 g of soidum methoxide in the presence of several drops of methanol. After 10 h, the reaction was quenched with water and extracted with ether. The combined layers were washed with saturated $NaHCO_3$ and dried over magnesium sulfate. The crude product (7.31 g, 70%) thus obtained showed about 85% purity when analyzed by GC. Analytic sample was obtained by GC purification on the 5' column. ^1H NMR ($CDCl_3$) δ3.42-3.16 (4H, singlet at 3.27), 2.76 (bs, 2H), 2.66-1.98 (m, 8H), 1.98-1.08 (m, 10H); IR (neat) 2940, 2860, 1720, 1670, 1480, 1460, 1270, 1200, 1100 cm^{-1}; ^{13}C NMR ($CCl_4/CDCl_3$) δ80.23, 56.03, 42.94, 38.42, 30.54, 29.45, 29.30, 28.37, 26.21, 24.26, 21.06, 19.32 (the carbonyl carbon and the quaternary carbons were too weak to observe); mass spectrum m/e 236.178 (calcd for $C_{15}H_{24}O_2$: 236.178)

Preparation of 3-Hydroxy-10-methoxycyclotetradecan-1,6-dione (112)

The title compound was prepared by ozonolysis of the ketone 44. Thus 0.800 g of ketone 44 was reduced at room temperature with 0.13 g of $NaBH_4$ in 20 mL of 95% EtOH. After 4 h, the reaction was quenched by 5% HOAc and extracted with ether to yield 0.789 g of crude alcohol.

The crude alcohol thus obtained was subjected to ozonolysis in 20 mL of methylene chloride at -78°C until a light blue color was observed (about 1 hour). Nitrogen was then bubbled through the solution until the blue color disappeared and the resulting solution was warmed to room temperature and poured into a slurry of 0.5 g of granular zinc in 10 mL of glacial acetic acid. After stirring

at room temperature for 1.5 h, the solution was extracted with water and methylene chloride. The combined organic layers were washed with saturated $NaHCO_3$ and brine. The dried solution yielded 0.742 g (81%) of crude product as a thick oily layer. The product would not go through the analytical GC column even at 190°C. The IR spectrum showed strong carbonyl stretching at 1720 cm^{-1}. The mass spectrum has m /e 252, presumably from the loss of the β-hydroxy group as water.

Attempted Reduction of Diketone (112) by Wolff-Kishner Reaction

Crude ketone 112 (0.180 g) was heated to 150°C with 0.2 mL of hydrazine (99-100%, monohydrate) in 4 mL of ethylene glycol. After 1.5 h, water and excess hydrazine was distilled off. The reaction mixture was cooled to room temperature and 0.12 g of KOH was added. The mixture was then heated to 180°C for 1 h. Workup in the normal way only yielded 38 mg of crude product which still showed the carbonyl stretching band in the IR.

Attempted Reduction of Diketone (112) via the Tosylhydrazone

Crude diketone 112 (0.54 g) was refluxed in 5 mL of 95% EtOH with 0.74 g of tosylhydrazine. After 3 h of reaction time, only 0.227 g of yellow crystals was collected. The crystals were not characterized because the yield was too low to be useful.

Attempted Reduction of Diketone (112) via a Thioketal Intermediate

The diketone (0.209 g, crude) was taken up into 6 mL of methylene chloride and to this solution, 0.23 mL of ethanethiol (ca. 4 eq) was

added followed by 0.4 mL of TMSCl (4 eq). The resulting mixture was stirred at room temperature for 4 h and worked up with water and methylene chloride. When the organic solvent was stripped off, 0.196 g of crude material was recovered which still showed a strong carbonyl band.

Preparation of 7-Methoxy-4'-acetoxycyclohexenocyclodecene (116)

7-Methoxy-4'-oxocyclohexenocyclodecene 44 (0.875 g) was reduced by 0.15 g of $NaBH_4$ in 20 mL of 95% EtOH at room temperature. Normal workup after 3 h yielded 0.794 g of alcohol.

The crude alcohol was acetylated by stirring with 2 mL (6 eq) of acetic anhydride in 15 mL of dry pyridine at room temperature for 12 h. The volatile components were evaporated under reduced pressure and the residue was taken up in ether. The ether layer was then washed with 5% H_2SO_4 (2x30 mL), water and saturated $NaHCO_3$. The dried solution ($MgSO_4$) yielded 0.742 g of crude product. A sample for analysis was obtained by GC on the 2' column: ^1H NMR (CCl_4) δ5.0-4.67 (m, 1H), 3.33-2.97 (4H, singlet at 3.18), 2.59-1.03 (m, 23H, singlet at 1.94); IR (neat) 2940, 2855, 1735, 1480, 1455, 1365, 1240, 1100, 930 cm^{-1}.

Attempted Preparation of 1-Hydroxy-8-methoxycyclotetradecanone (113)

Crude 116 (0.14 g) was subjected to ozonolysis in 10 mL of methylene chloride at -78°C. After a blue color was observed (about 1 h), nitrogen was bubbled through the solution until the color was discharged. The organic layer was warmed to room temperature and

0.15 g of $NaBH_4$ (77) in 10 mL of 50% EtOH was added and stirred at room temperature overnight. The reaction was worked up with dilute H_2SO_4 and extracted with methylene chloride to yield 87 mg of crude product. The IR spectrum of the crude product showed strong OH stretching.

The crude product thus obtained was dissolved in 4 mL of pyridine and stirred with 0.12 mL of mesyl chloride at room temperature for 6h. Workup as before yielded 0.147 g of crude, which was immediately taken up into 10 mL of ether/THF (1:1, v/v) and refluxed with 45 mg of $LiAlH_4$. No expected product was isolated by medium pressure HPLC after 36 h of reaction time.

Attempted Preparation of 8-Methoxycyclotetradecanone (36)

Acetate 116 was subjected to ozonolysis in 10 mL of methylene chloride at -78°C until a blue color was observed. Sodium borohydride (77) (0.35 g in 20 mL of 50% aqueous ethanol) was then added and stirred with the methylene chloride layer for two days (about 15 h should be enough). Acidic workup and extraction with ether yielded only 0.218 g of crude product. The IR spectrum showed the carbonyl stretching and the OH band and so it was assumed that this was the expected diol. Crude product was then dissolved in 4 mL of pyridine and chilled to 0°C before 0.3 mL of methanesulfonyl chloride was introduced and the resulting mixture was kept at -15°C for 12 h. Pyridine and excess sulfonyl chloride was evaporated *in vacuo* and residue was taken up into chloroform and washed and dried. The mesylate thus obtained was dissolved in 5 mL of DMSO (over calcium hydride) and stirred with 0.35 g of potassium t-butoxide at room

temperature for 3 h. The reaction was then worked up with water and pentane. The organic layer was washed with water and dried ($MgSO_4$) and 0.102 g of crude product was obtained. The IR spectrum of this eliminated product still showed an OH stretching band but no carbonyl stretching band as expected. It was assumed that the acetoxy group had been converted to its alcohol during the process of elimination with potassium t-butoxide. The crude product was then oxidized with Jones reagent (78 mg yield) and hydrogenated with 24 mg of 10% palladium on carbon under atmospheric pressure for 3 h and 71 mg of product was recovered. The GC analysis of this crude product showed one major peak (ca. 60%) along with at least four other minor ones. HPLC eluting with 15% ethyl acetate-hexane failed to isolate the major component. Purification by the 5 ft. column yielded a product with spectral properties which suggested that it could be the desired product, viz, the mass spectrum showed a m/e peak at 207 which was one mass unit short of the expected parent minus methanol (the m/e counter on the instrument occasionally reads one unit low). The NMR spectrum clearly showed the methoxy group in the product. Another earlier attempt also resulted in several components in the final product mixture.

Another attempt was made to eliminate the intermediate diol 117 with phosphorous oxychloride. Thus 0.111 g of the crude diol was stirred with 0.15 mL of phosphorous oxychloride in 5 mL of pyridine at room temperature for 4 h to yield 57mg of crude product. $LiAlH_4$ (12 mg) reduction followed by Jones reagent yielded a crude product which contained a large amount of impurities, judging by the mass spectrum. No GC analysis was done since the yield and

the purity were so discouraging.

Attempted Preparation of 4'-Hydroxy-4'-ethynyl-7-methoxy-cyclohexenocyclodecene (119)

Lithium acetylide was generated by passing acetylene (H_2SO_4 washed) through a solution n-BuLi (4.4 mL of 1.55 M in hexane) in 10 mL of THF at -78°C. After 30 min, 0.409 g of crude ketone 44 in 5 mL of THF was added to the resulting solution at -78°C for 30 min and then stirring was continued at room temperature for 1 h. The reaction was quenched with dilute H_2SO_4 and extracted into ether. The majority of the crude product obtained was just the starting ketone. Another trial of longer reaction time (overnight at room temperature) gave a similar result, and so did a third trial with a change of solvent from THF to ether.

Preparation of 4-Acetyl-7-methoxy-1,2-benzocyclodecene (45)

The title compound was prepared from 7-methoxy-4'-oxo-1,2-cyclohexenocyclodecene 44. Crude 44 (0.663 g) was stirred with 0.5 mL of TMSCN in 15 mL of dry ether in the presence of a catalytic amount of KCN:18-crown-6. After 5 h at room temperature, the reaction was worked up with dilute acid and ether to yield the crude cyanohydrin 121.

The cyanohydrin was taken up in about 4 mL of dry pyridine and dehydrated with 1 mL of $POCl_3$ at 70-80°C. After 12 h, reaction was cooled to room temperature and quenched by slow addition of water. Extraction with water and ether followed by acid washing (2x25 mL of 5% H_2SO_4) of the combined organic layers yielded 0.421 g of crude product.

The crude product thus obtained was aromatized by refluxing with 0.6 g of DDQ (75) (MCB) in 5 mL of dry benzene (acid washed and then over sodium) for 20 h. The mixture was cooled to room temperature, diluted with pentane and filtered. The organic layer was washed with 5% H_2SO_4, 5% NaOH (2x20 mL and brine and then dried over magnesium sulfate. The crude yield of the aryl nitrile 103 was 0.179 g. The IR spectrum showed stretching of the nitrile at 2310 cm^{-1}. GC analysis of the crude material showed predominantly one peak. Medium pressure HPLC purification of a sample from a different batch eluting with ethyl acetate-hexane (1:9, v/v) gave a pure sample of 123: ^1H NMR (CCl_4) δ7.54-7.06 (m, 3H), 3.42-2.98 (4H, singlet at 3.2), 2.98-2.58 (m, 4H), 2.28-0.88 (m, 10H); IR (neat) 2940, 2860, 2820, 2230, 1610, 1570, 1495, 1480, 1455, 1450, 1100, 900, 830 cm^{-1}; ^{13}C NMR ($CCl_4/CDCl_3$) δ145.53, 141.34, 132.89, 129.43, 129.00, 110.12, 79.63, 55.91, 29.62, 29.20, 28.88, 28.11, 25.50, 24.31, 19.81 (the nitrile carbon was too weak to observe); mass spectrum m/e 243.161 (calcd for $C_{16}H_{21}NO$: 243.162).

This crude aryl nitrile was refluxed with 4.3 mmole (about 6 eq) of methyllithium (78) in 10 mL of ether for 24 h. The reaction mixture was cooled to room temperature and quickly extracted with two 25 mL portions of 5% H_2SO_4. The aqueous acidic layer was then stirred heterogeneously with 25 mL of ether at room temperature for 12 h. The layers were separated and the aqueous layer was extracted with ether. The combined ether layers were washed with saturated $NaHCO_3$ and dried over magnesium sulfate to yield 0.113 g of crude product. Purification by HPLC on silica gel eluting with

ethyl acetate-hexane (20:80, v/v) yielded 84 mg of the desired product as a clear oily layer. Analysis by GC showed about 95% purity with some lower boiling components. The overall yield from 44 was 12%. 45: ^{1}H NMR (CCl_4) δ7.7-7.43 (m, 2H), 7.11 (d, J = 8 Hz, 1H), 3.36-3.02 (4H, singlet at 3.2), 2.96-2.7 (m, 4H), 2.47 (s, 3H), 2.3-0.72 (m, 10H); IR (neat) 3100, 2930, 2855, 2820, 1680, 1600, 1570, 1480, 1440, 1410, 1360, 1295, 1260, 1090 cm^{-1}; ^{13}C NMR (CCl_4/$CDCl_3$) δ145.77, 140.34, 135.06, 129.16, 128.90, 125.76, 79.94, 55.97, 29.74, 29.15, 29.00, 28.31, 26.34, 25.61, 24.48, 19.16 (the carbonyl carbon was too weak to observe); mass spectrum m/e 260.178 (calcd for $C_{17}H_{24}O_2$: 260.178).

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