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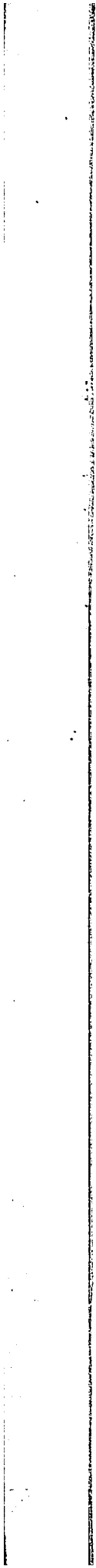
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7-(PHENYLSULFONYL)-BICYCLO[4.2.0]OCTA-1,3,5-TRIENE AS A  
SYNTHETIC INTERMEDIATE

by

Barbara D. Gowland, B.Sc.

A thesis submitted to the School of Graduate Studies  
in partial fulfillment of the requirements for  
the degree of  
Master of Science  
in the  
Department of Chemistry  
University of Ottawa  
Ottawa, Canada

April, 1978



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The undersigned hereby recommend to the Faculty of Graduate Studies acceptance of this report by Barbara D. Gowland in partial fulfillment of the requirements for the degree of Master of Science.

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Chairman, Department of Chemistry

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The role of 7-(phenylsulfonyl)-bicyclo[4.2.0]octa-1,3,5-triene (benzocyclobutene phenylsulfone (83)) as a synthetic intermediate is investigated. Attempts were made to prepare this compound by several new routes. Cyclization of 1-(chloromethyl),2-(phenylsulfonylmethyl)-benzene (127) was attempted with LDA, MeLi, and phase transfer conditions, as well as flash vacuum thermolysis. None of these modifications were successful.

The synthesis of phenyl 2-(o-chlorophenyl)ethyl sulfone (80) was approached by a new route in moderate yields by condensation of the anion of methyl phenyl sulfone with o-chloro-benzyl bromide, followed by oxidation. Cyclization of (80) via a benzyne intermediate proved possible with only four equivalents of  $\text{KNH}_2$ . Hindered bases such as 2,2,6,6-tetramethylpiperidide gave intractable tars.

The o-quinodimethane intermediate of (83) could not be efficiently trapped with maleic anhydride; instead, adducts with toluene and anisole were obtained. A rationale is proposed for this transformation.

The anion of (83) was found to be an efficient nucleophile, trapping alkyl bromides, iodides, ketones, and epoxides in high yields. Desulfonylations of the alkylated parent compound were carried out easily and in excellent yields to give the alkyl species.

Thermolysis of 7-(phenylsulfonyl)-7-(5'- $\eta$ -hexenyl)-bicyclo[4.2.0]octa-1,3,5-triene (161) resulted in 1,5 hydrogen abstraction to yield styrenes, whereas the desulfonylated species of (161) and (102) were transformed smoothly to tricyclic compounds.

Novel approaches to 7-(hydroxy)-bicyclo[4.2.0]octa-1,3,5-triene (benzocyclobutenol (77)) were investigated by intramolecular attack of an aromatic halide on an epoxide via the Grignard or halogen-metal exchange. These attempts did not lead to the desired compound, but instead, gave bromohydrins and olefins.

ACKNOWLEDGEMENTS

I would like to thank my husband, Fred, for his infinite encouragement and enthusiasm throughout this project. I would also like to thank my family for their moral support and confidence in me. A very special thanks to my supervisor, Professor T. Durst, whose constant interest, discussions, and patience made this project worthwhile..

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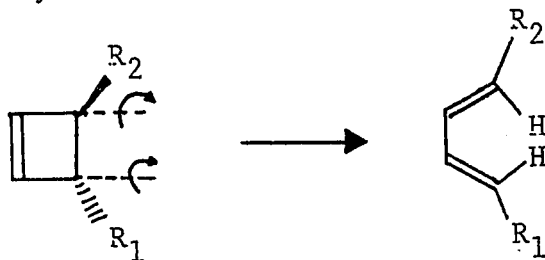
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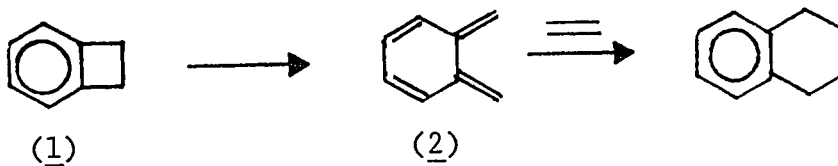
## INTRODUCTION

### The Use of Benzocyclobutene Derivatives in the Synthesis of Natural Products

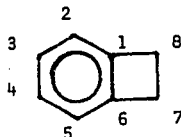
Cyclobutenes are known to isomerize thermally to 1,3 dienes. This reaction has been classified by Woodward and Hoffmann<sup>1</sup> as an electrocyclic ring opening which occurs in the conrotatory sense.



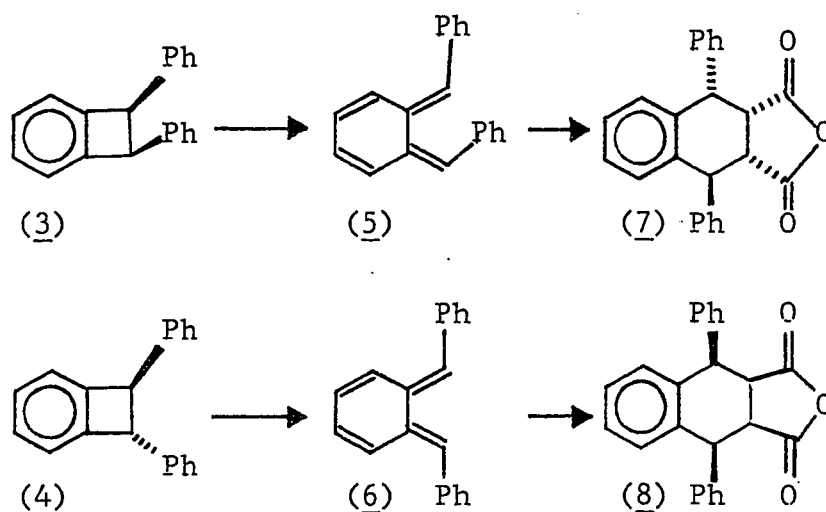
Benzocyclobutene (1)\* and its derivatives behave in a similar manner yielding an o-quinodimethane intermediate (2). This diene is extremely reactive, even towards unreactive dienophiles since the Diels-Alder reaction regenerates the aromatic ring.



\* The following nomenclature is currently being used by Chemical Abstracts: Bicyclo[4.2.0]octa-1,3,5-triene.

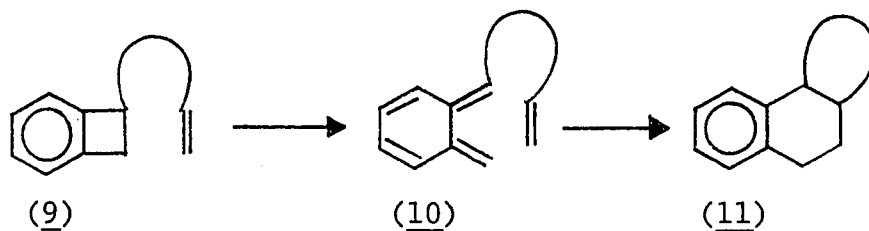


The conrotatory direction of the ring opening of benzocyclobutene derivatives has been indicated by the stereospecific trapping with a dienophile via an intermolecular cycloaddition.<sup>2</sup> Thus, heating of the cis and trans-6,7-diphenylbenzocyclobutenes (3) and (4) at 50° in the presence of maleic anhydride afforded the tricyclic products, (7) and (8) respectively, in greater than 90% yields. These products were explained as the result of stereospecific ring opening to the intermediates (5) and (6), followed by a Diels-Alder reaction.



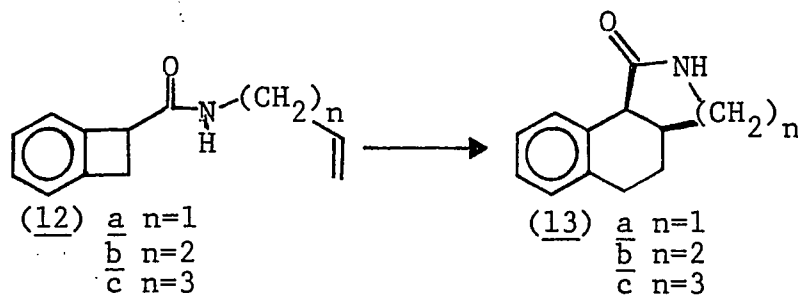
In the early 1970's, a number of workers recognized the synthetic potential of the above cycloreversion-Diels-Alder sequence. Thus, if a dienophile were incorporated into the benzocyclobutene, for example (9), thermolysis should generate the tricyclic product (11) with high stereoselectivity via the o-quinodimethane intermediate (10).

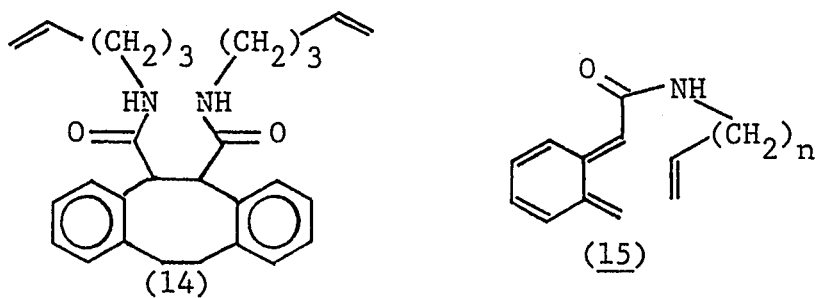
Oppolzer reported the first total synthesis of the alkaloid (dl)-chelidonine (26) based on the above route.<sup>3</sup>



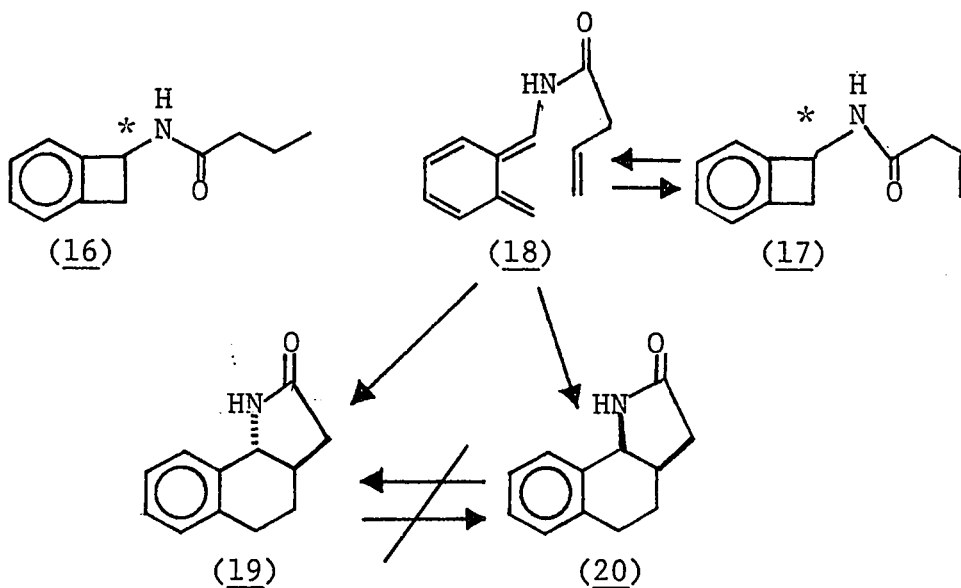
A decoction of the plant, Chelidonium majus L., from which chelidonine was first isolated, was a traditional remedy for tumors.<sup>4</sup> Prior to describing this synthesis, it is considered appropriate to discuss the model experiments performed by the Oppolzer group which illustrate the possible cyclic products obtainable.<sup>5, 6</sup>

For example, thermolysis of the propenylamide (12a) at 190° for 16 hours yielded the cis-benz[e]isoindole (13a) in 85% yield.<sup>5</sup> Thermolysis of the homologous butenylamide (12b) in boiling o-dichlorobenzene afforded the cis-benz[h]isoquinoline (13b) in the same high yield. When the pentenylamide (12c) was refluxed under the same conditions, the expected naph[1,2-c]azepine (13c) was isolated in only 20% yield together with the dimer (14) in 6% yield. This supports the hypothesis that o-quinodimethanes of type (15) are intermediates in the reaction.

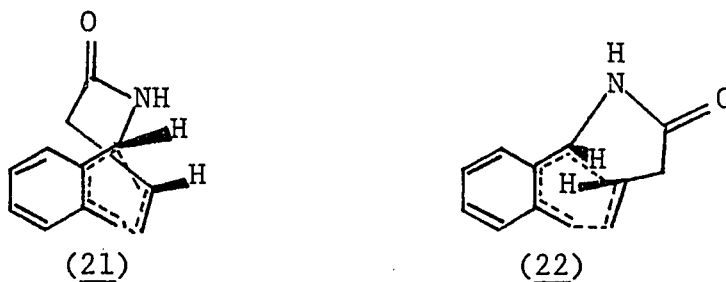




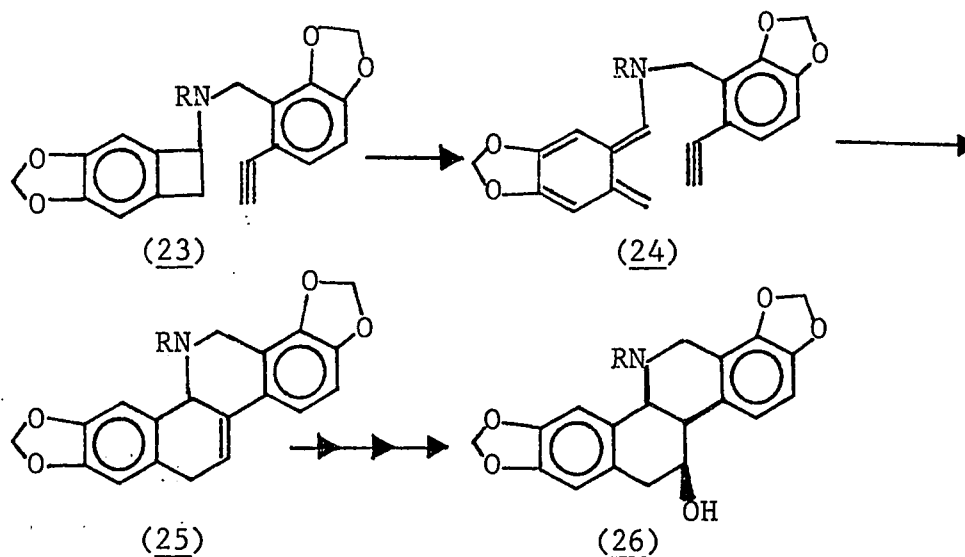
Further proof for the existence of these intermediates was presented by Oppolzer.<sup>6</sup> The thermal rearrangements of optically pure butenylamide (17) and optically pure butyramide (16) in boiling toluene were monitored polarimetrically, as well as by NMR analysis. The rate of disappearance of their optical activities under identical conditions were found to be similar. Hence it was concluded that the olefinic double bond of (17) was not involved to any major extent in the opening of the benzocyclobutene. Evidence for an achiral intermediate such as (18) was provided by the racemic nature of the products (19) and (20) isolated at an early stage of the reaction.



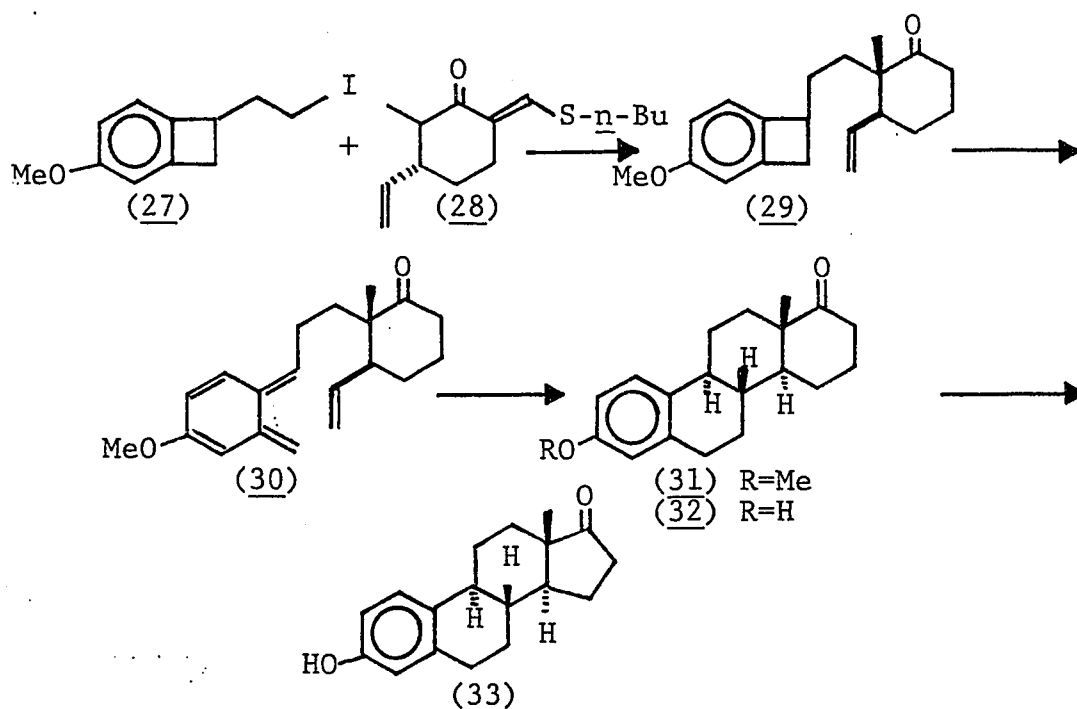
Assuming that the four-membered ring in (17) opens preferentially to form the sterically favored o-quino-dimethane (18), Oppolzer rationalized that the cis-fused product (20) was formed via the endo-transition state (21) and the trans product (19) from the exo-transition state (22).



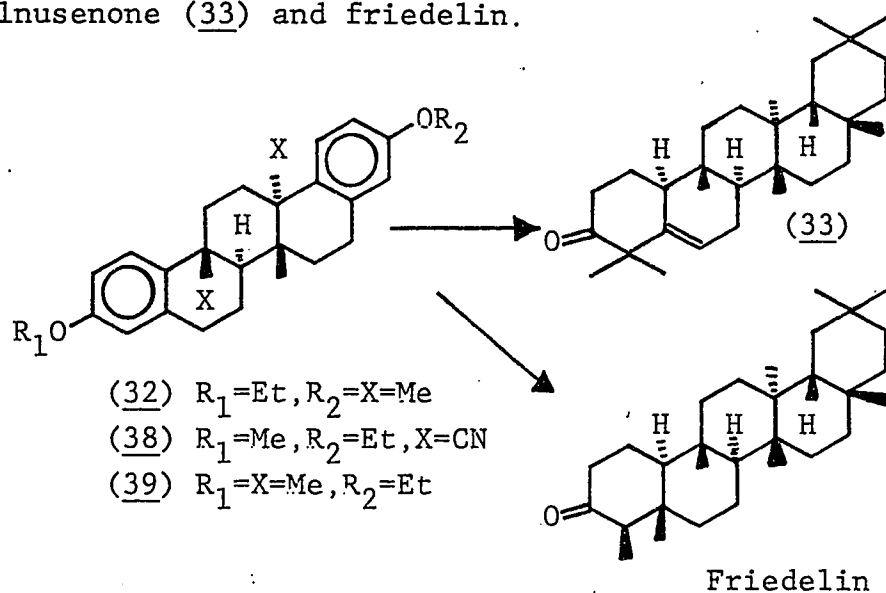
In the synthesis of (dl)-chelidonine (26), the required ring system (25) was obtained in 73% yield upon thermolysis of the acetylene (23). The intermediate (24) was elaborated to the final target molecule via hydroboration, Jones oxidation, and finally, reduction with sodium borohydride. The latter two steps were necessary since hydroboration gave the wrong stereochemistry of the alcohol.



Recently, Kametani *et al.*<sup>7</sup> reported a stereoselective total synthesis of estrone (33) utilizing the intermolecular cycloaddition reaction of the olefinic *o*-quinodimethane (30) generated from the thermolysis of the benzocyclobutene derivative (29). Estrone has held special interest for organic chemists due to its importance as a precursor in the production of 19-norsteroids which have been used as oral contraceptives.<sup>8</sup> The required benzocyclobutene derivative (29) was obtained by a condensation of  $\beta$ -(4-methoxybenzocyclobutenyl) ethyl iodide (27) with 6-*n*-butylthiomethylene-2-methyl-3-vinylcyclohexanone (28) followed by removal of the *n*-butylthiomethylene group. Thermolysis of (29) for 4 hours in *o*-dichlorobenzene, followed by demethylation of (31) yielded 95% of the *D*-homoestrone (32). This compound was converted by known procedures to estrone (33).<sup>8</sup>

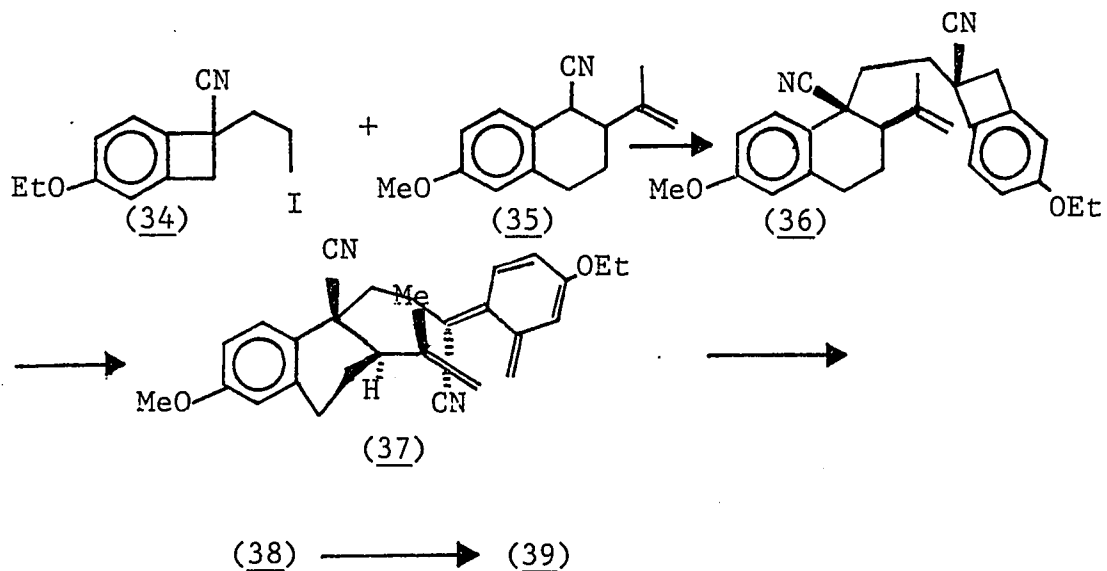


Kametani et al.<sup>9</sup> have reported a simple and stereoselective synthesis of the key intermediate, 10-ethoxy-3-methoxy-6 $\beta$ , 12 $\alpha$ , 14 $\alpha$  $\beta$ -trimethyl-5,6,6 $\alpha$ ,6 $\beta$ ,7,8,12 $\beta$ ,13,14,14 $\alpha$ -decahydropicene (39) for the synthesis of pentacyclic triterpenoids. The crucial step in the synthesis was the introduction of the methyl groups at angular positions with the required stereochemistry. This was accomplished by an intramolecular cycloaddition of the o-quinodimethane (37) to give the corresponding cyclized material (38). The pentacyclic aromatic ethers, (32) and (39), having the trans, anti, trans-BCD ring system and the correct array of angular methyl groups, are important intermediates in the total synthesis of the unsymmetrical pentacyclic triterpenes, alnusenone (33) and friedelin.

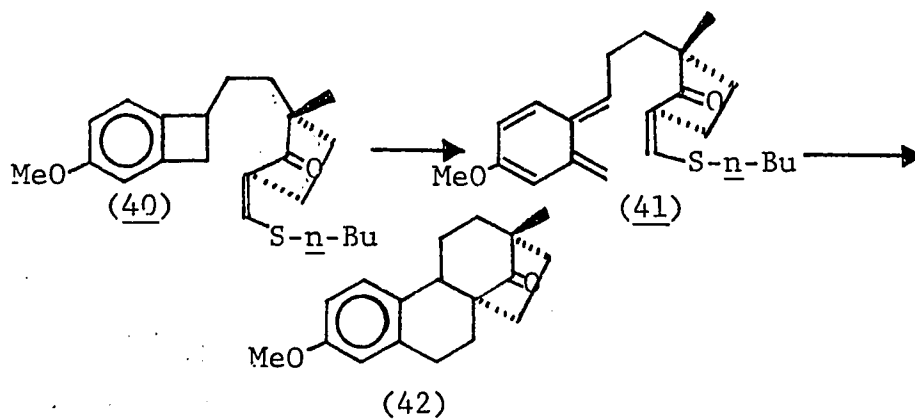


Condensation of (34) with (35) yielded (36) in 88% yield. Thermal rearrangement of (36) at 210-215 $^{\circ}$  for 3 hours afforded 58% of the cyclized material (38) via the o-quinodimethane intermediate (37). Reduction of (38) with

di-isobutylaluminum hydride, followed by further Wolff-Kishner reduction yielded the desired product (39).



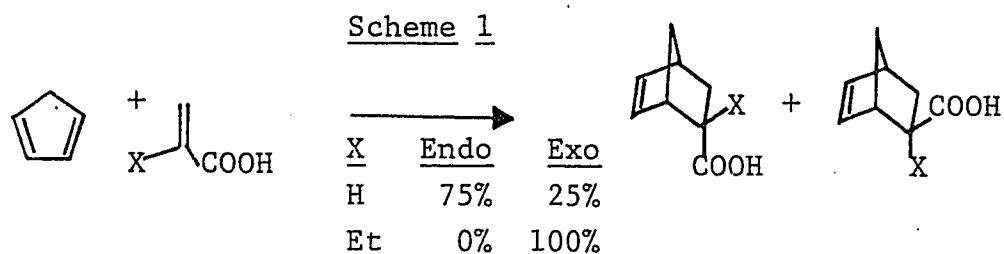
Further work in this area was pursued in order to stereospecifically synthesize the potential intermediate, the ethano-octahydromethoxymethylphenanthrenone (42), for the synthesis of tetracyclic diterpenoids.<sup>10</sup> This route again proceeded via an intramolecular cycloaddition of the o-quinodimethane (41) derived thermally from 5-n-butylthiomethylene-2-[-2-(4-methoxydihydrobenzocyclobutenyl)ethyl]-2-methylcyclopentanone (40) followed by desulfurization to yield (42).



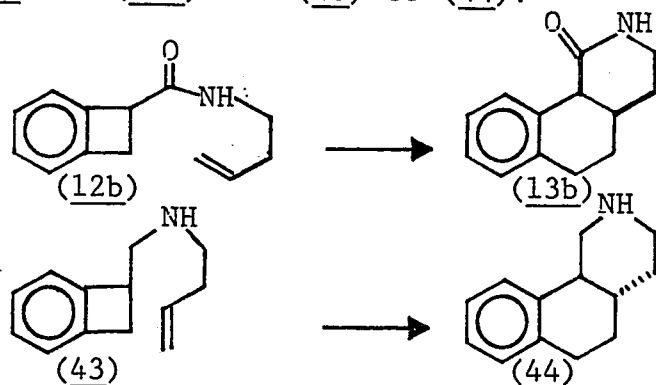
Based on the above examples, it is evident that benzocyclobutenes are effective intermediates for the construction of natural products such as estrone, chelidonine, alnusenone, friedelin, and others having complicated ring systems.

### Stereochemistry of Cycloaddition

Endo-adducts normally predominate in typical Diels-Alder reactions, for example, when X is H. However, non-bonding interactions of substituents may force the reaction towards exo-products, for example when X is an ethyl group (Et). (Scheme 1).<sup>11</sup>

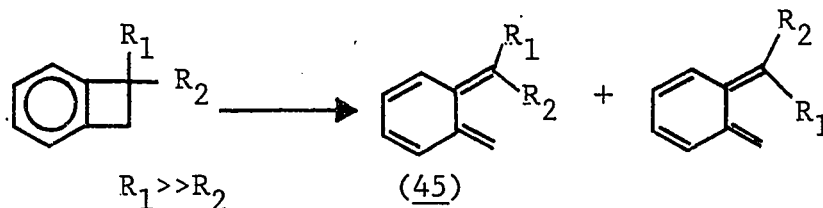


A simple and effective control of the endo to exo ratio is exemplified by the intramolecular cycloadditions (12b) to (13b) and (43) to (44).<sup>12</sup>



As discussed earlier, thermolysis of the butenyl amide (12b) in refluxing dichlorobenzene yielded the cis-fused lactam (13b) in 85% yield via the endo transition state, while reflux of the butenylamine (43) for 16 hours resulted in 62% of the trans-fused benz(h)isoquinoline (44) via the exo orientation. The fact that amides react predominantly via the endo transition state, whereas amines by the exo, may be explained by favorable secondary orbital interactions of the amide carbonyl with the diene.

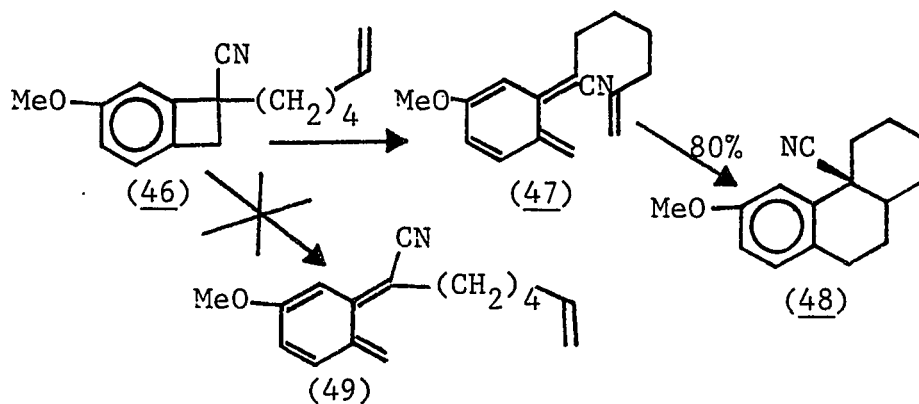
In the case of 7,7-disubstituted benzocyclobutenes, the direction of the ring opening occurs in a conrotatory sense. The larger substituent would be expected to rotate toward the outside to avoid steric interactions with the syn hydrogen in the diene intermediate.



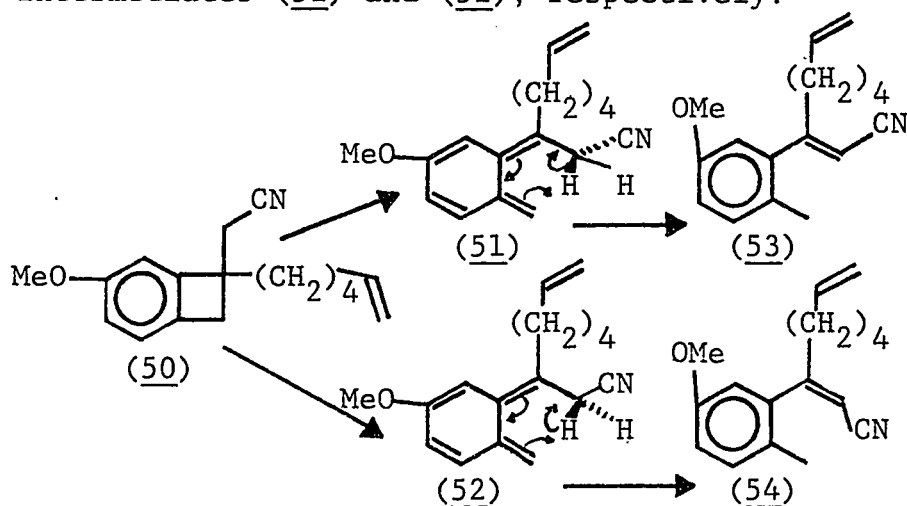
In the previously discussed examples,  $R_2$  is H, and thus, all products were rationalized as proceeding via (45).

Kametani has investigated the direction of ring opening in a number of geminally substituted benzocyclobutenes.<sup>13</sup>

Thermolysis of (46) in boiling o-dichlorobenzene for 6 hours gave, in 80% yield, the cycloaddition product octahydrophenanthrene (48). Thus, the benzocyclobutene (46) had been transformed preferentially into the Z-diene (47) rather than the E-intermediate (49).

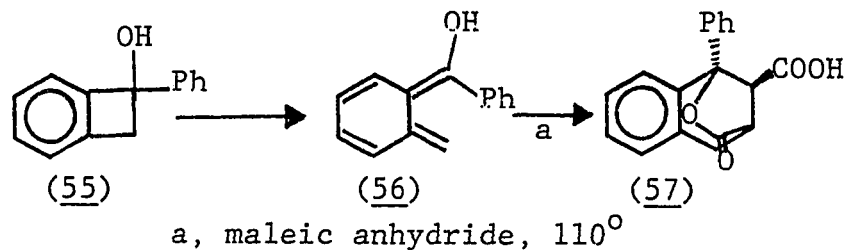


Thermolysis of (50) gave a separable mixture of styrenes (53) and (54).<sup>13</sup> These products can be rationalized as proceeding via a 1,5 hydrogen shift from the intermediates (51) and (52), respectively.

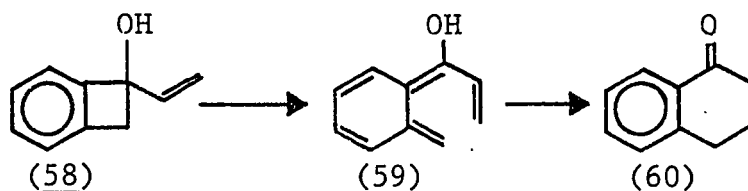


On the other hand, the benzocyclobutenol derivative (55) bearing an oxygen substituent at position 7 was found to undergo conrotatory thermal ring opening to yield the reactive diene species (56) in which the oxygen substituent preferentially adopts the outside position.<sup>13</sup> This observation was based on trapping experiments. In the

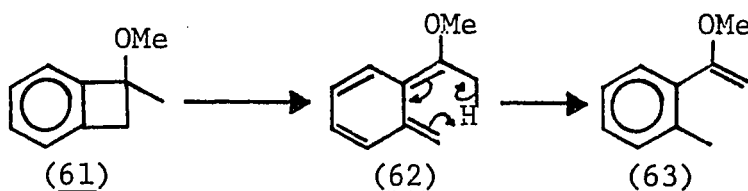
presence of maleic anhydride, the intermediate (56) gave 75% of the compound (57).



The stereoselective nature of the above conrotatory process was confirmed by 7-vinylcyclobut-7-ol (58), which on heating, gave a quantitative yield of  $\alpha$ -tetralone (60).<sup>14</sup> The reaction can again be visualized as proceeding via the E-dienol (59), followed by thermal cyclization.

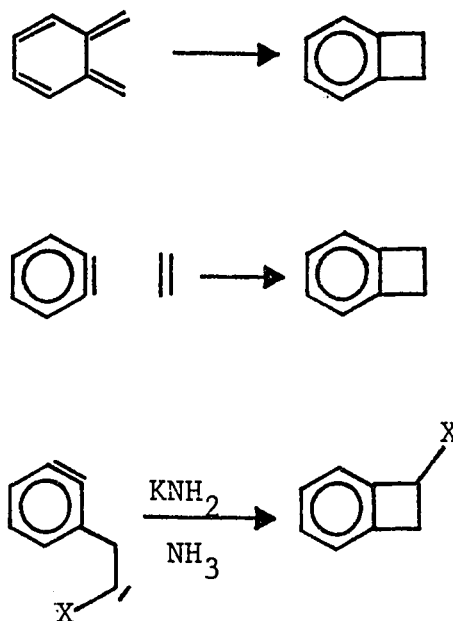


However, 7-methoxy-7-methylbenzocyclobutene (61) has been shown to rearrange thermally to give the styrene derivative (63) via intramolecular hydrogen transfer (62).<sup>14</sup> Since the size of a hydroxy group is smaller than that of a methyl group,<sup>15</sup> electronic effects of substituents, such as the presence or absence of unshared electrons, must be important in the above transformations.



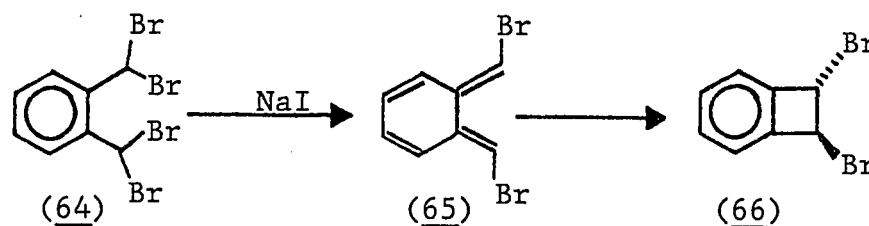
Previous Approaches to Benzocyclobutenes

The two most general approaches to benzocyclobutenes involve the generation of an *o*-quinodimethane followed by subsequent cyclization and the formation of a benzyne followed by either a cycloaddition with an alkene, or intramolecular addition of a carbanion intermediate (Scheme 2). Several syntheses which do not fall in these categories are mentioned at the end of this discussion.

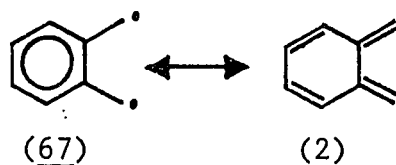
Scheme 2

The first synthesis of a benzocyclobutene was reported by Finkelstein<sup>16</sup> in 1910; it involved the reaction of

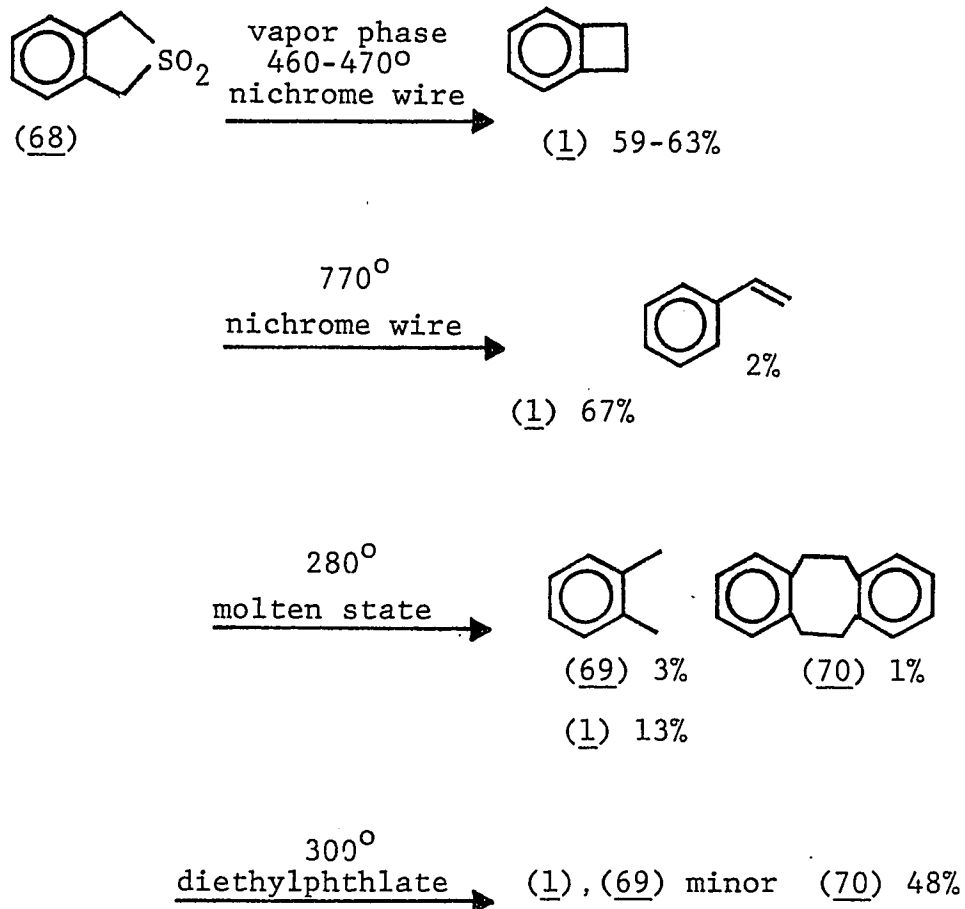
$\alpha, \alpha, \alpha', \alpha'$ -tetrabromo-o-xylene (64) with sodium iodide. This synthesis has been proposed to involve the o-quino-  
dimethane (65). The very poor yield of this dibromide (66) has been greatly improved to over 90%.<sup>17</sup>



Cava and coworkers<sup>18</sup> have studied the thermolysis of 1,3-dihydroisothianaphthalene-2,2-dioxide (68), and shown that under various conditions benzocyclobutene can be obtained in reasonable yield. However a number of by-products are also generally obtained (Scheme 3). All products can be rationalized as arising from the o-quino-  
dimethane (2) or its diradical equivalent (67). However, these routes have not yet been shown to be useful on a preparative scale.

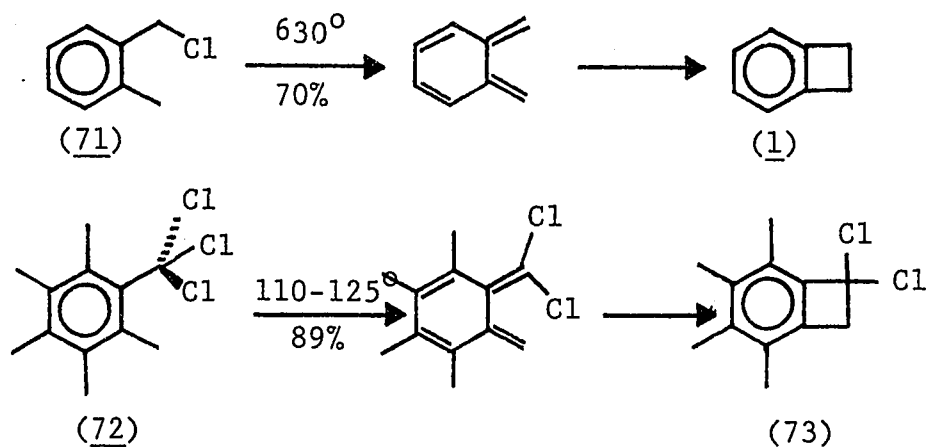


## Scheme 3

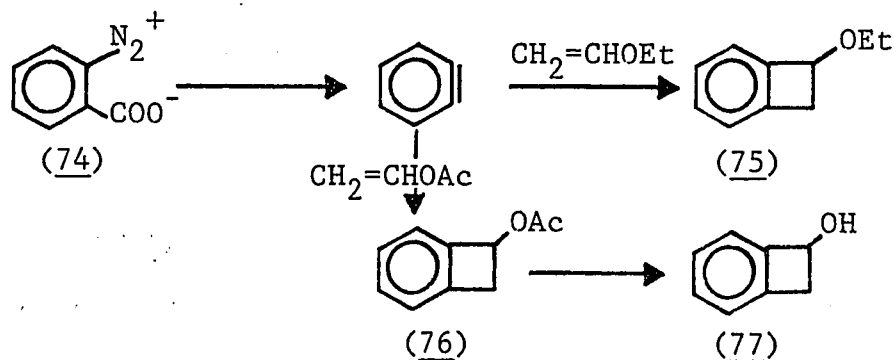


Thermolysis of  $\alpha$ -chloro-*o*-xylene (71)<sup>19</sup> and the trichloromethyl derivative (72)<sup>20</sup> resulted in the formation of (1) and (73) respectively. In both examples, elimination of HCl followed by electrocyclic ring closure of the *o*-quinodimethane intermediate was suggested to account for the products. It was interesting to note that the temperature required for elimination of HCl from (72) was only

110°-125°.

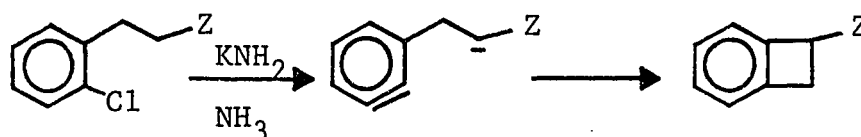


Electron-rich alkenes such as ethyl vinyl ether and vinyl acetate have been reacted with benzenes to form derivatives of benzocyclobutenol.<sup>21</sup> For example, decomposition of benzenediazonium-2-carboxylate (74), in the presence of excess vinyl ether, yielded 40% of the ethyl benzocyclobutenyl ether (75), whereas reaction with vinyl acetate gave benzocyclobutenyl acetate (76) in 45% yield. Hydrolysis of (76) yielded the benzocyclobutenol (77). These preparations, while novel, would be difficult to carry out on a large scale due to the hazardous nature of the benzenediazonium-2-carboxylate.



Bunnett and Skorcz<sup>22</sup> have prepared a series of electronegatively substituted benzocyclobutene derivatives (81)-(83) via intramolecular addition of a carbanion to a benzyne. The intermediate was generated by the use of excess potassium amide in liquid ammonia (Scheme 4).

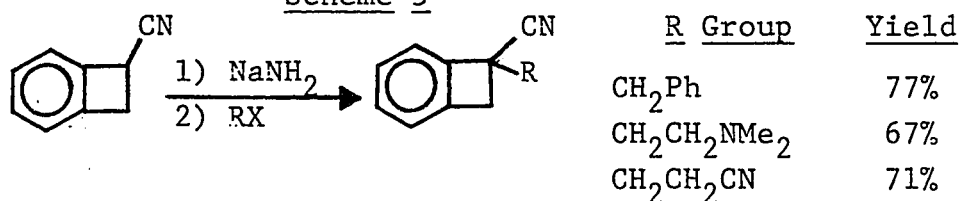
Scheme 4



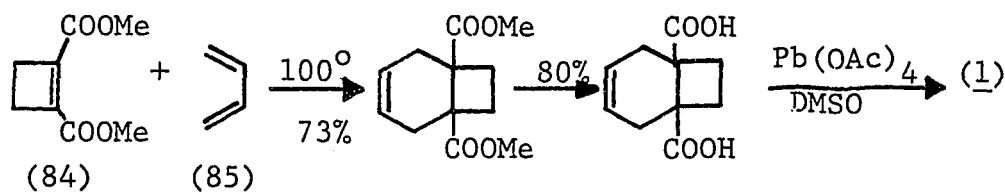
<u>Z-Group</u>	<u>Yield of Product</u>
(78) carboethoxy	(81) 10%
(79) cyano	(82) 61%
(80) phenylsulfonyl	(83) 47%

This method of benzocyclobutene formation is also the most versatile for the preparation of compounds having substituents on the aromatic ring. Both Kametani and Oppolzer have made extensive use of this approach in their total syntheses of natural products, the 7-cyanobenzocyclobutene (82) being their key reagent. This compound has been converted into a variety of useful derivatives via reaction of the  $\alpha$ -nitrile anion<sup>23</sup> (Scheme 5).

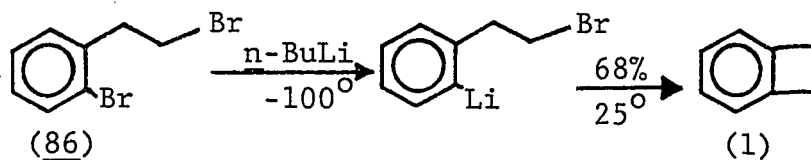
Scheme 5



A Diels-Alder approach<sup>24</sup> has been reported to give benzocyclobutene (1) in undetermined yield by addition of dimethylcyclobut-1-ene, 2-carboxylate (84) to the diene (85) followed by hydrolysis and subsequent aromatization.

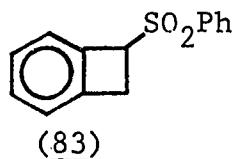


Parham, Sayed, and Jones<sup>25</sup> have recently described a highly efficient synthesis of the parent benzocyclobutene by halogen-metal exchange. In this reaction, the aromatic bromine of (86) was necessarily first replaced yielding (1) in 68% yield.



Since a simple and efficient route to a variety of new ring systems, as well as to certain natural products, has been provided via conrotatory ring opening of benzocyclobutene derivatives, it is essential to have a high yield preparation of the desired derivative. Even more important, the compound or synthesis must be flexible to the introduction of a variety of substituents.

Benzocyclobutene phenylsulfone (83) was considered an interesting alternative to the cyano derivative.



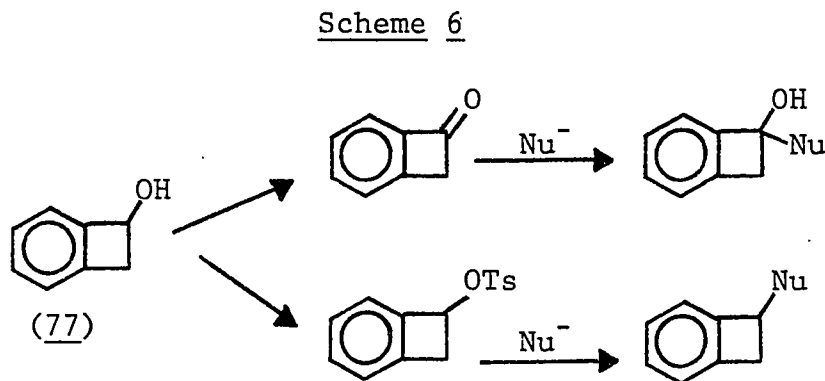
Attempts to find a high yield route to the synthesis of this compound were made for several reasons:

- (i) its carbanion should be easily generated, thereby allowing functionalities to be easily introduced
- (ii) the phenylsulfonyl moiety is easily reduced without disturbing other common functionalities present in the molecule<sup>26</sup>
- (iii) it would seem possible to obtain Diels-Alder adducts regardless of the presence of the phenylsulfonyl moiety.

## RESULTS AND DISCUSSION

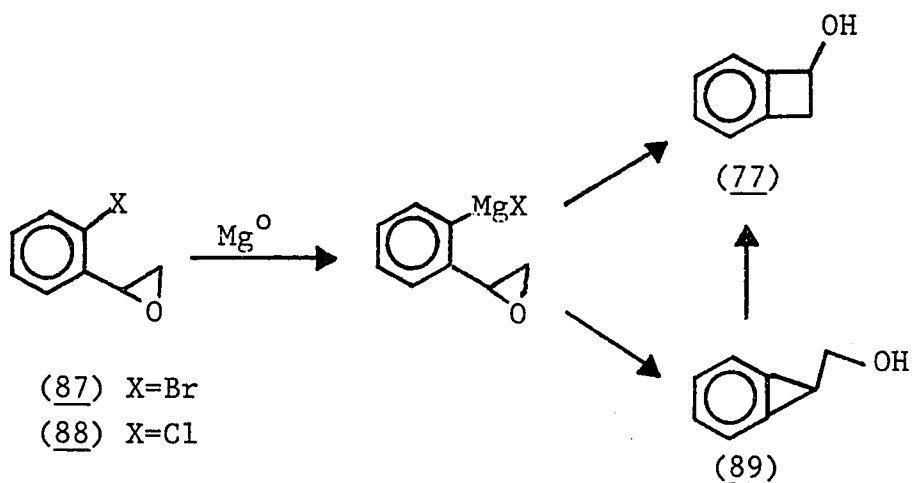
### Approaches to Benzocyclobutenol

Benzocyclobutenol may be considered a key intermediate to the synthesis of a variety of benzocyclobutenes (Scheme 6). Presently, it is most easily available from the benzenediazonium-2-carboxylate. Due to the hazardous nature of this material it was decided to investigate possible new approaches to the synthesis of this alcohol. Once synthesis of the benzocyclobutenol is achieved, oxidation to the ketone<sup>27</sup> occurs readily making introduction of a variety of nucleophilic substituents possible.

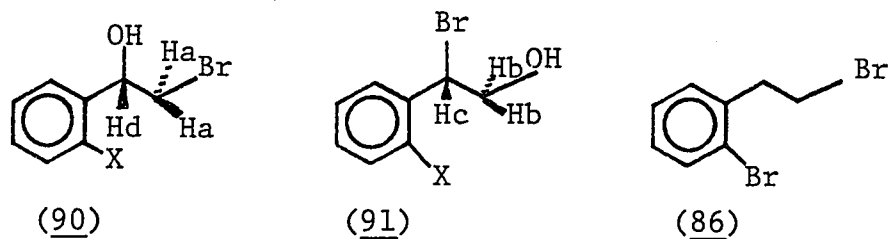


The first approach envisaged formation of the Grignard of *o*-bromo and *o*-chloro-styrene oxide, (87) and (88), followed by ring closure to (77). If attack occurred at the benzylic carbon, rearrangement of the cyclopropyl

carbinol (89) to the benzocyclobutenol (77) might be possible.



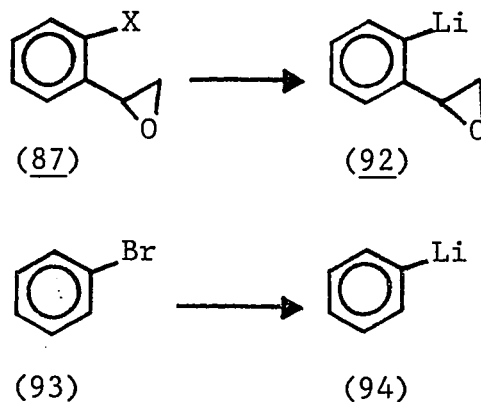
Alternatively, it was considered possible that the epoxide might be opened to the bromohydrin (90) by  $MgBr_2$ . Grignard formation at the aromatic position could then result in benzocyclobutenol formation. In analogy, Parham and coworkers have prepared benzocyclobutene by  $n$ -BuLi treatment of (86) at  $-100^\circ$ .



However, no Grignard formation was observed with (87) or (88) either in refluxing tetrahydrofuran or diethyl ether, nor on addition of iodine. When ethylene dibromide was added in an attempt to activate the magnesium, formation

of a bromohydrin was observed. Addition of the epoxide to  $\text{MgBr}_2$  and  $\text{Mg}^0$  gave the same result. Unfortunately the proton NMR of the product showed exclusive formation of the undesired bromohydrin (91). The regiochemistry of the epoxide opening was clearly defined by the proton NMR of the bromohydrin. An unresolved triplet was present at  $\delta 4.00$  (2H, Hb), and as well, a clean triplet at  $\delta 5.48$  (1H, Hc) indicated compound (91). On deuterium oxide exchange the hydroxyl proton disappeared and the unresolved triplet at  $\delta 4.00$  collapsed to a two proton doublet. Had the bromohydrin (90) been formed, a one proton triplet due to Hd should have been observed after  $\text{D}_2\text{O}$  exchange.

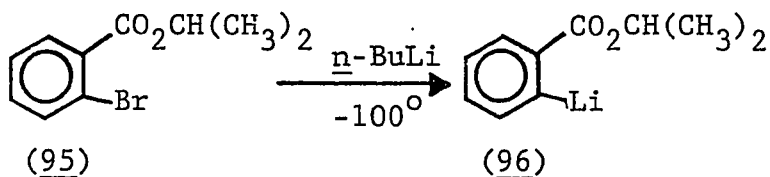
Another route, using lithium metal to effect metal-halogen exchange of (87) to (92), was investigated since Danishefsky<sup>28</sup> had accomplished metal-halogen exchange with bromobenzene, (93) to (94).



Refluxing the *o*-bromo-styrene oxide in dry ether under anhydrous conditions in the presence of clean lithium

ribbon gave no apparent reaction by NMR on workup. To confirm this, a sample was quenched with deuterium oxide. NMR indicated only the presence of starting material, and hence it was concluded that no metal-halogen exchange had taken place ortho to the epoxide, nor had lithiation occurred on the epoxide.<sup>29</sup>

More closely related are the results of Parham *et al.*<sup>25</sup> who utilized *n*-BuLi at  $-100^{\circ}$  to effect halogen-metal exchange in the synthesis of the parent benzocyclobutene (1). However, even more important, the same workers successfully effected halogen-metal exchange of (95) to (96) with the bromine ortho to the ester on the aromatic ring.<sup>30</sup>



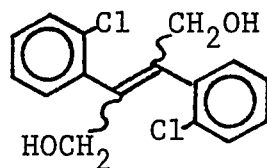
Again, generation of the halogen-metal exchange derivative of (88) with the halogen ortho to the epoxide was unsuccessful due to other types of reactions between *n*-BuLi and (88). The main product isolated in 22% yield was a colorless solid, melting point  $121^{\circ}$ . The structure assigned was the tetrasubstituted olefin (97). This material was characterized by spectral analysis and derivatization.

Acetylation of (97) with pyridine and acetic anhydride

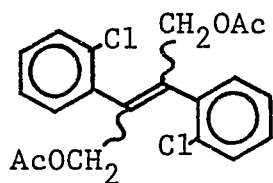
at room temperature afforded (99) as a white crystalline product in 65% yield. The proton NMR of the acetylated material proved the presence of two hydroxyls in the starting material due to the incorporation of two acetates. This is shown in the NMR by the singlet at  $\delta 2.84$  (6H,  $2\text{COCH}_3$ ) and the multiplet at  $\delta 4.32-4.90$  (4H,  $2\text{CH}_2$ ).

Oxidation of (97) with chromium-trioxide in pyridine yielded the yellow crystalline 1,4 dialdehyde (100) as indicated by the singlet at  $\delta 9.83$  (2H,  $2\text{COH}$ ). Eight aromatic protons were also present at  $\delta 7.23-7.73$ . The IR showed the presence of an aldehyde by a strong peak at  $1680-1685\text{ cm}^{-1}$ .

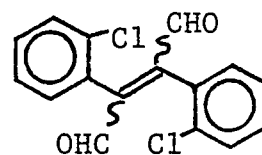
Another product of similar polarity to (97), melting point  $103-105^\circ$ , was also obtained and shown by NMR, IR, and elemental analysis to be the isomer (98). The proton NMR of (97) indicated a singlet (2H, OH) at  $\delta 1.42$  and a multiplet at  $\delta 3.83-4.23$  (4H,  $2\text{CH}_2$ ), while compound (98) had a singlet at  $\delta 3.28$  (2H, OH) and a broad singlet at  $\delta 4.56$  (4H,  $2\text{CH}_2$ ). On deuterium oxide exchange the hydroxyl protons were removed and the methylene resonances sharpened slightly. The infrared spectrum for (97) had a sharp band at  $3600\text{ cm}^{-1}$  due to a free hydroxyl while (98) showed only a hydrogen bonded alcohol at  $3400\text{ cm}^{-1}$ ; since these two spectra were run at comparable concentrations, the trans configuration is indicated for (97) and the cis for (98). However the stereochemistry of these two isomers is a question which is still in doubt. The NMR spectra for these isomers are presented in Figures 1 and 2 of the Appendix.



(97), (98)

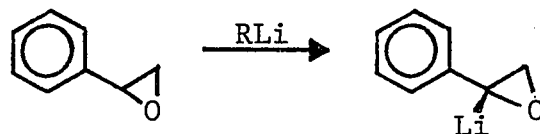


(99)



(100)

Eisch and coworkers have shown that styrene oxide lithiated with *t*-butyllithium, but interestingly *n*-BuLi failed to yield the  $\alpha$ -lithioepoxide.<sup>29</sup>

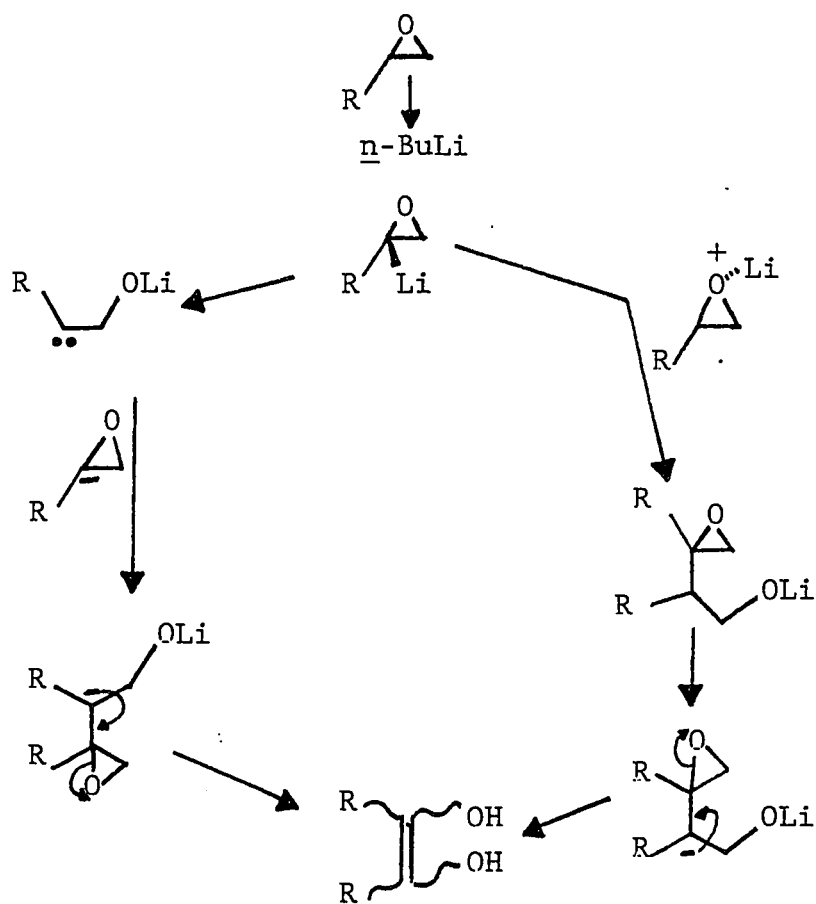


It was found, in the present study, that attention to reaction temperature was critical, the products (97) and (98) being produced only when the temperature was  $-100^{\circ}$ ; warmer conditions yielded only starting material.

Alpha-lithioepoxides are known to react in a nucleophilic fashion with electrophiles or rearrange to carbene intermediates.<sup>29, 32</sup> These carbene intermediates may also

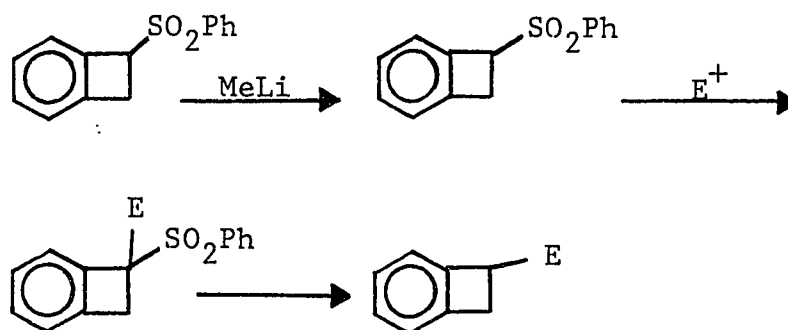
be trapped by nucleophiles to yield olefinic products. In this experiment, the  $\alpha$ -chloro-styrene oxide may act as an electrophile or the  $\alpha$ -lithioepoxide may act as the nucleophile in the carbene reaction. Either or both of these mechanisms could be operative in this system. The two likely modes of product formation are illustrated in Scheme 7.

Scheme 7

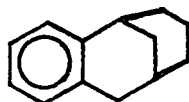


Since attempts to prepare the benzocyclobutenol by an efficient new route were unsuccessful, attention was next focused on benzocyclobutene phenylsulfone. This compound was considered synthetically more useful for a variety of reasons. A variety of substituents should be easily introduced alpha to the phenylsulfone moiety via the anion. Also, the phenylsulfonyl can be readily removed in one step in the presence of a variety of functionalities<sup>26</sup> (Scheme 8). The compound most frequently used is the 7-cyanobenzocyclobutene. However, removal of the nitrile group requires several more steps or fairly severe reaction conditions. For example, the use of lithium in liquid ammonia<sup>33</sup> to reduce the nitrile may be too severe for many functionalities and activated aromatic rings. Even more important, it was hoped that different polycyclic systems may be obtained by thermolysis of compounds such as (101) and the desulfonylated analogue (118).

Scheme 8



Based on an inspection of molecular models one would predict the formation of only the 3.3.1 ring system (113) if the thermolysis of (101) to an o-quinodimethane intermediate and subsequent internal Diels-Alder is carried out prior to desulfonylation. The electrocyclic ring opening of the benzocyclobutene (101) occurs in a conrotatory manner with the large phenylsulfonyl group preferentially rotating toward the outside<sup>1</sup> thereby giving (112) in preference to (103). Cyclization of (112) can lead only to (113), desulfonylation of which would give (125).

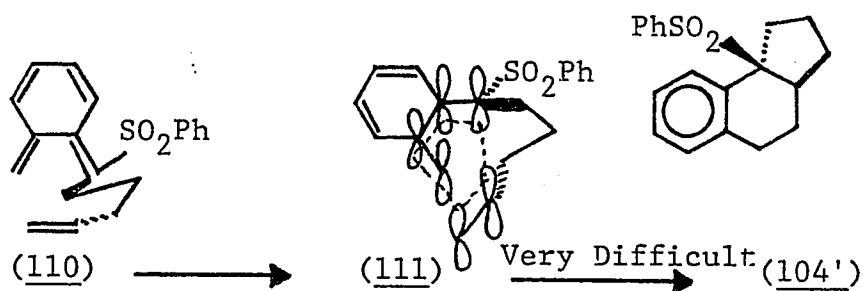
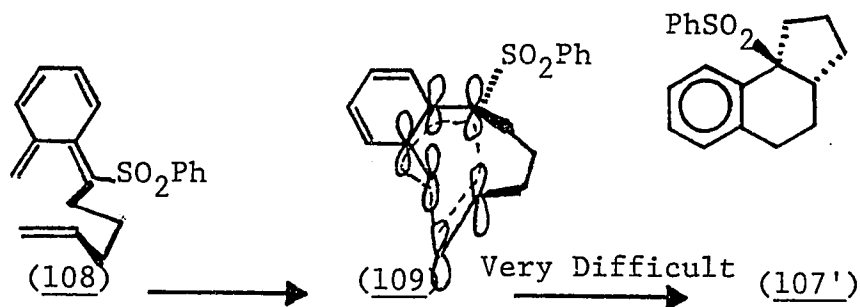
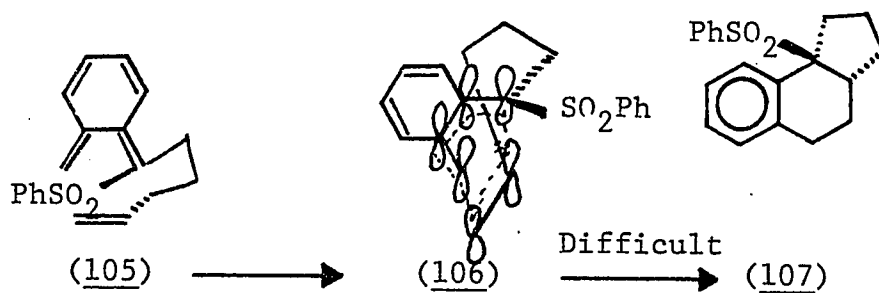
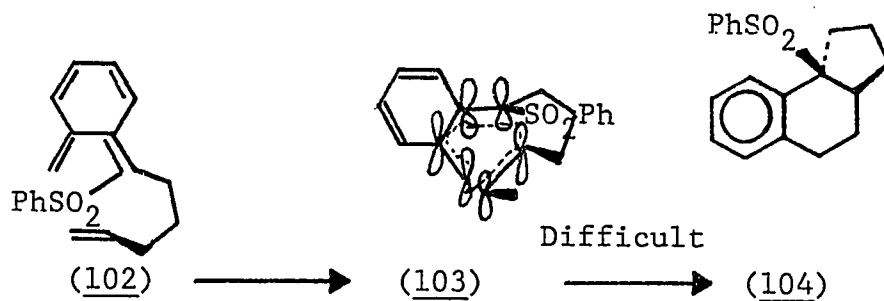
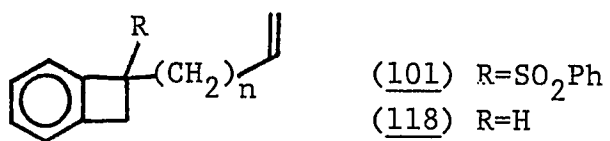


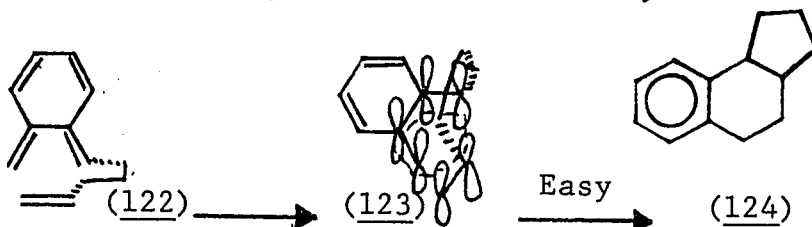
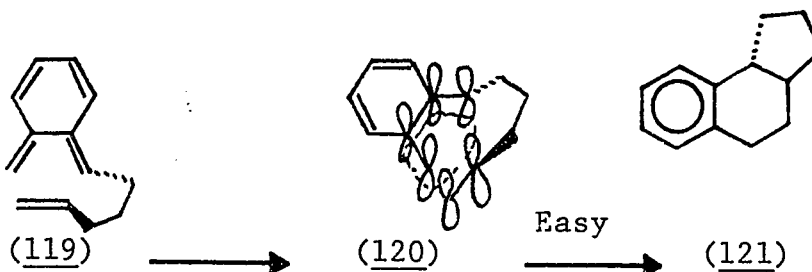
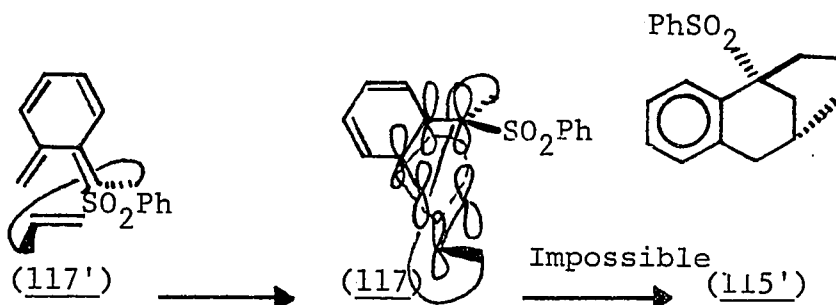
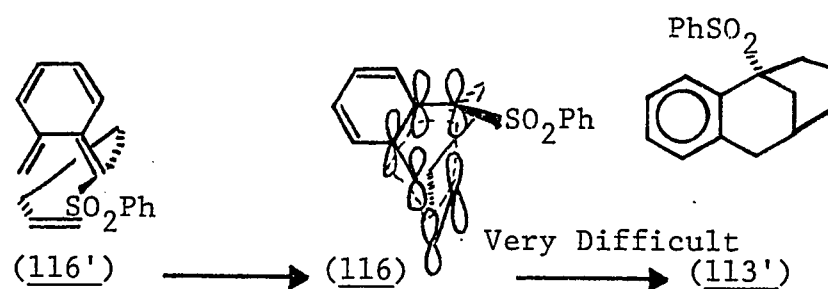
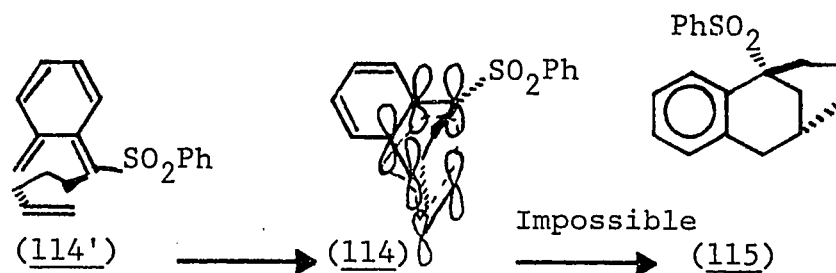
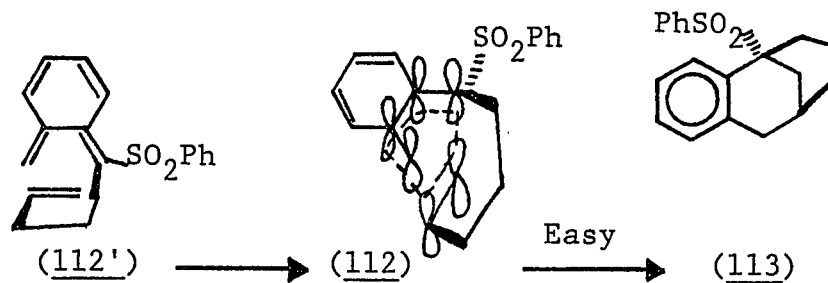
(125)

On the other hand, desulfonylation of (101) followed by thermolytic ring opening of the benzocyclobutene and subsequent intramolecular trapping would give either of the polycyclics (121) or (124). The homologues of (101) and (118) can be similarly analyzed, and are predicted to behave in a similar manner.

The various starting materials, transition states, and final products are shown in Scheme 9. For the sake of completeness, the processes which are sterically difficult (or impossible) are also shown. The ability to obtain the correct geometry for a Diels-Alder reaction is classified in the scheme as easy, difficult, and impossible.

## Scheme 9

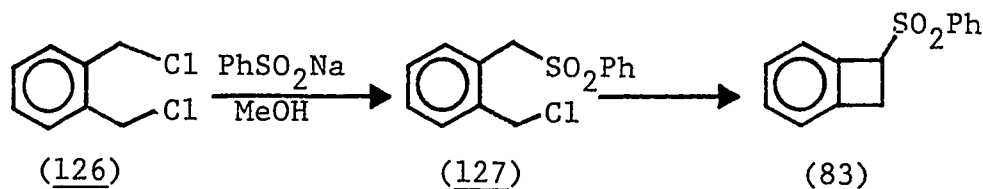




Approaches to Benzocyclobutene Phenylsulfone

Although the benzocyclobutene phenylsulfone has been prepared by Bunnett and coworkers<sup>22</sup>, the route requires several steps. The last step, an intramolecular benzyne cyclization, was achieved in 47% yield. Since benzyne reactions are difficult to carry out on a large scale, the synthesis of this potentially advantageous compound was approached by a variety of other pathways.

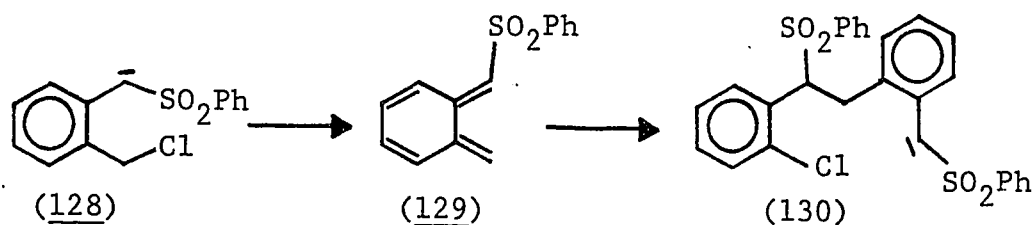
One approach involved the intramolecular cyclization of the compound (127) to the benzocyclobutene phenylsulfone (83) by elimination of HCl. This cyclization was based on the reported reaction of  $\alpha,\alpha,\alpha',\alpha'$ -tetrabromo-*o*-xylene (64) with sodium iodide, which afforded the 1,2-dibromo-benzocyclobutene (66) in good yield.<sup>17</sup> The compound (127) was synthesized in 42% yield by refluxing 1,2-bis-(chloromethyl)benzene (126) and the sodium salt of benzene sulfinic acid in methanol for 23 hours.



The NMR of the chlorosulfone (127), m.p. 75-77<sup>o</sup>, had two methylene singlets at  $\delta$ 4.57 and 4.70. The IR indicated the presence of the sulfone by peaks at 1120 cm<sup>-1</sup> and 1305 cm<sup>-1</sup>. The elemental analysis for C<sub>14</sub>H<sub>13</sub>ClO<sub>2</sub>S was also

consistent with the assigned structure (127).

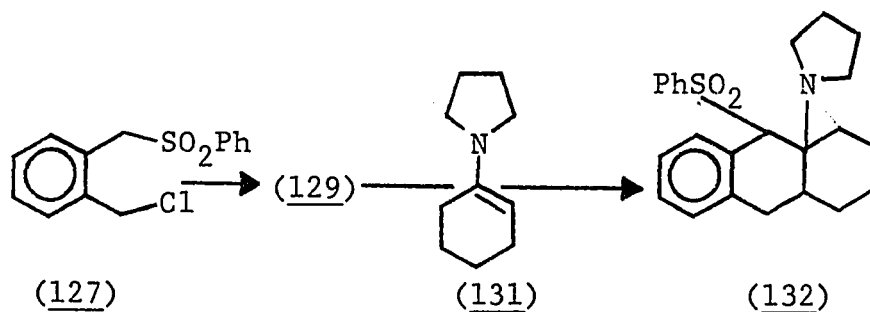
The base induced cyclization of (127) was attempted with lithium diisopropyl amide, methyl lithium, and sodium hydroxide. Addition of (127) to the LDA at  $-78^{\circ}$  gave a yellow color which turned orange-red on warming. This reaction appeared to yield polymer as suggested by the broad nature of the proton NMR. The formation of the *o*-quinodimethane intermediate (128) $\rightarrow$ (129) followed by ring closure of (129) may have been slow at the low temperature utilized, causing reaction of the anion (128) with the very reactive electrophilic diene (129) to form (130). This may have easily oligomerized by further reaction with (129).



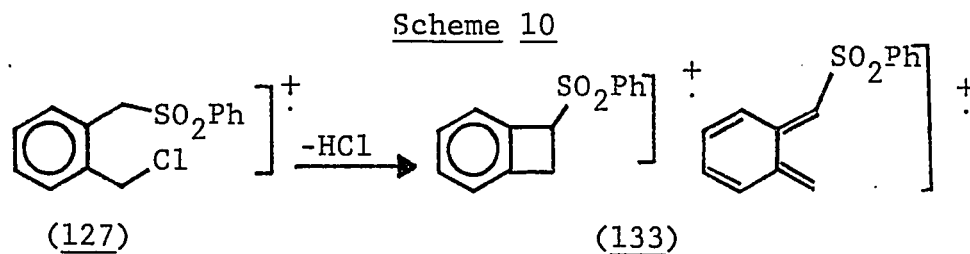
Reaction of (127) with MeLi (at  $0^{\circ}$  or  $25^{\circ}$ ) or under phase transfer conditions also yielded polymeric material. No trace of (83) was seen in these reactions.

Attempts to trap the *o*-quinodimethane intermediate (129) with 1-pyrrolidinocyclohexene (131) to obtain (132) were futile. The reaction was carried out with (127) and (131) under phase transfer conditions. After stirring for 24 hours at room temperature the reaction had turned yellow and all the starting material was absent by TLC and NMR.

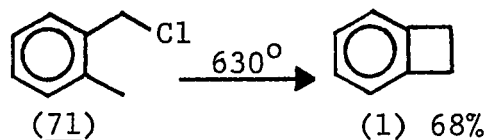
However, when purification was attempted on silica gel, a series of compounds was present. None of these could be isolated in pure form for characterization.



The mass spectrum of (127) showed a significant peak at  $m/e$  244, consistent with the loss of  $\text{HCl}$  from the parent ion ( $m/e$  280), suggesting possible formation of a charged benzocyclobutene phenylsulfone (133) (Scheme 10).



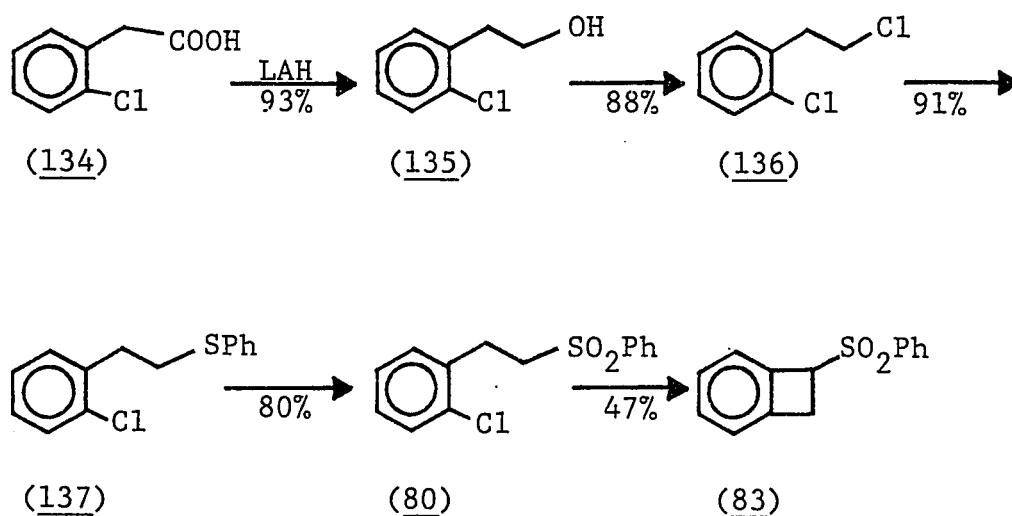
Furthermore, thermolysis of  $\alpha$ -chloro-*o*-xylene (71) has been reported to give the benzocyclobutene (1) via loss of  $\text{HCl}$ .<sup>19</sup>



Hence, it was decided to investigate the flash vacuum pyrolysis (FVP) of (127). The FVP involves the volatilization of a compound by use of a bulb-to-bulb heater, followed by passage through a furnace for a short period of time. The product is collected by a liquid nitrogen cooled trap. A series of experiments at different furnace temperatures were attempted using this flash pyrolysis apparatus. The pressure was .06 mm for all runs, but increased to .20 mm as the material volatilized through the hot furnace into the trap. At a furnace temperature of 300<sup>o</sup>, starting material was completely recovered. At 400<sup>o</sup>, both starting material and an inseparable mixture of products were formed. The substance collected on the trap was yellow. At 500<sup>o</sup>, a mixture of inseparable material was again obtained. An increase in the rate of volatilization of (127) resulted in only decomposition giving a dark yellow material on the trap. The proton NMR of the crude products indicated the absence of the desired benzocyclobutene phenylsulfone under any of the conditions tried.

Since the above approaches to the benzocyclobutene phenylsulfone (83) were unsuccessful, and a good supply of this material was essential to continue further research, attention was focused on Bunnett's route<sup>22</sup> to this compound. The pathway consisted of four steps, the first being reduction of the acid (134) to the alcohol (135), followed by chlorination. The chloride (136) was then reacted with

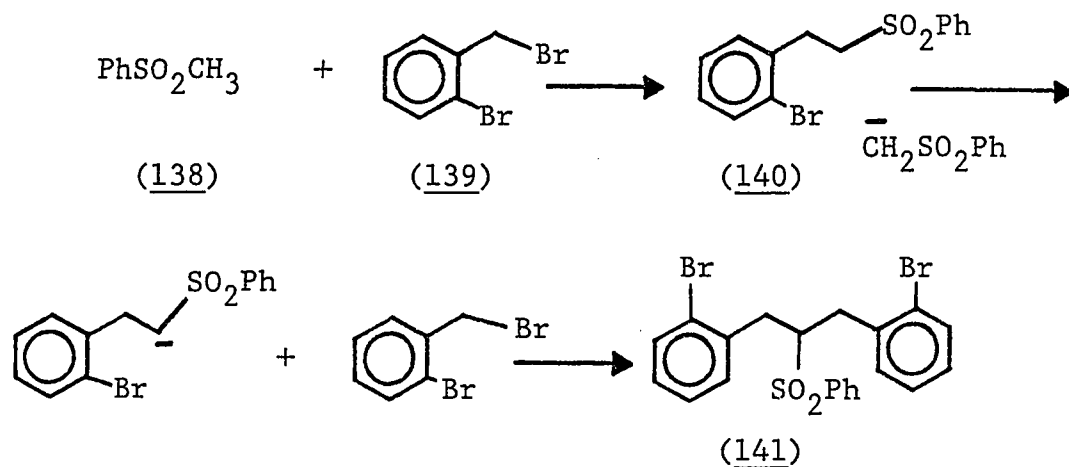
equimolar amounts of thiophenol and sodium ethoxide in refluxing ethanol to yield the 2-(*o*-chlorophenyl)ethyl sulfide (137) in 91% yield. Oxidation of the sulfide (137) to the sulfone (80) was accomplished in 80% yield. Conversion of (80) to (83) was carried out with potassium amide ( $\text{KNH}_2$ ) in liquid ammonia in 47% yield.



Since conversion of (80) to (83) was shown possible, alternate approaches to (80) were attempted. In the first attempt, the condensation of the anion of methyl phenyl sulfone (138) with *o*-bromo-benzyl bromide (139) was found to be unsuccessful. Small amounts of monoalkylated (140) and dialkylated (141) products were observed; large quantities of unreacted methyl phenyl sulfone were also recovered. The formation of the dialkylated product (141)

is explained in Scheme 11.

Scheme 11



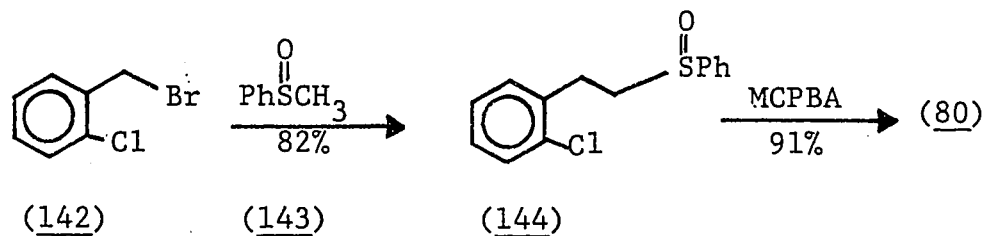
The monoalkylation of (138) with (139) was repeated under a variety of reaction conditions. Neither variation of the alkylating reaction time, temperature, addition of hexamethylphosphoramide, or inverse addition of the reagents significantly increased the amount of desired product. Similar results were obtained with benzyl bromide, thus suggesting that the ortho group was not the source of the problem. These results could be explained by the sulfone anion not reacting quickly enough with the alkylating agents.

The more reactive anion of the methyl phenyl sulfoxide (143), on the other hand, was alkylated by the o-chloro-

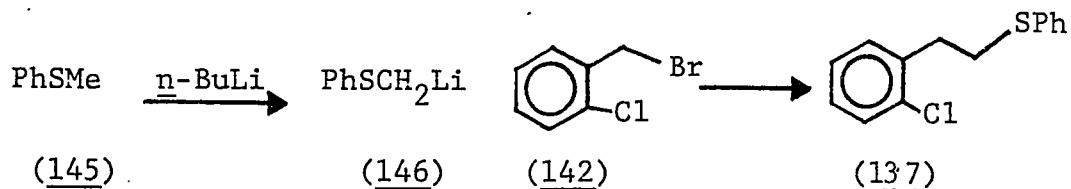
benzyl bromide (142) affording pure isolated phenyl 2-(o-chlorophenyl)ethyl sulfoxide (144) in 82% yield. Oxidation of the sulfoxide to the sulfone (80) was achieved in 91% yield. This two-step route afforded (80) in 75% overall yield from readily available starting materials. This compares favorably with Bunnett's overall yield of 60% via four steps, vide supra. Furthermore, when the crude sulfoxide was purified by column chromatography on silica, the unreacted methyl phenyl sulfoxide crystallized on top of the sand, and was easily recovered.

The proton NMR of the sulfoxide (144) indicated the presence of the four aliphatic protons as an  $A_2B_2$  multiplet at  $\delta$ 2.8-3.4, and the nine aromatic protons as a multiplet at  $\delta$ 7.0-7.8. The IR showed a strong peak at  $1030\text{ cm}^{-1}$  indicative of a sulfoxide.

The phenyl 2-(o-chlorophenyl)ethyl sulfone was isolated as a colorless solid, m.p.  $44-46^\circ$  (lit. value  $45-47^\circ$ ).<sup>22</sup> The NMR spectrum of the four aliphatic protons also gave an  $A_2B_2$  multiplet at  $\delta$ 3.0-3.6. The IR showed the presence of a sulfone by two strong peaks at  $1065\text{ cm}^{-1}$  and  $1305-1310\text{ cm}^{-1}$ .

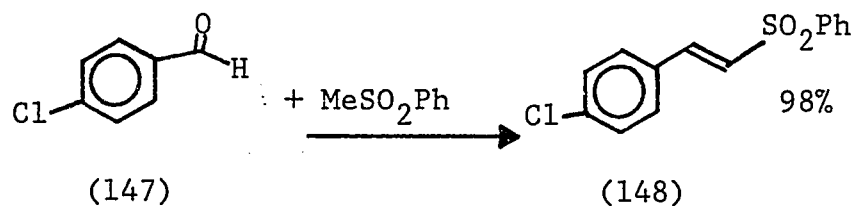


The reaction of (142) with the lithio derivative of methyl phenyl sulfide was also investigated with the hope that (137) would be formed in high yield.



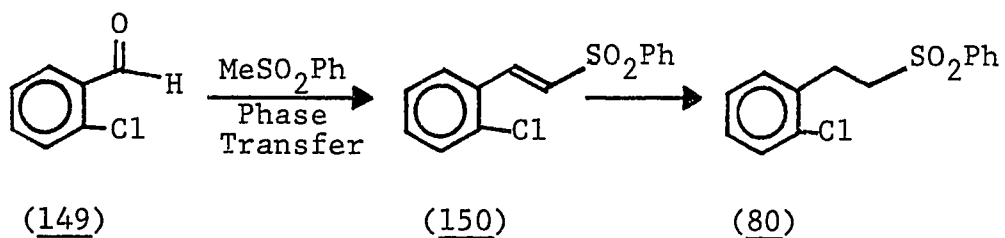
The lithio species (146) was generated according to the method of Corey and Seebach<sup>34</sup> utilizing 1,5-diazabicyclo [4.3.0] non-5-ene to activate the *n*-BuLi. However, a very exothermic reaction ensued, resulting in a black mixture. No *o*-chloro-benzyl bromide remained in the crude product. The phenylthiomethyl lithium may have acted as a base rather than a nucleophile towards (142), giving only regenerated sulfide and tars.

Cardillo and coworkers<sup>35</sup> have reported a facile synthesis of (148) starting with methyl phenyl sulfone and the corresponding aromatic aldehyde (147) under phase transfer conditions.



Such a procedure when applied to the *o*-chloro-benzaldehyde (149), should afford the  $\alpha,\beta$ -unsaturated

sulfone (150), hydrogenation of which would give (80).



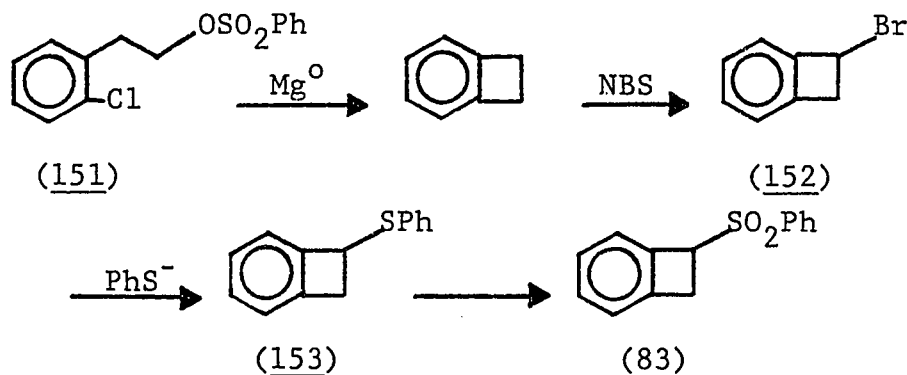
However, when the typical reaction conditions were employed with *o*-chloro-benzaldehyde, none of the desired product was formed. Instead, the reaction appeared to undergo a Cannizzaro reaction giving a mixture of the *o*-chloro-benzyl alcohol and the corresponding carboxylic acid, as well as unreacted methyl phenyl sulfone. Apparently, the ortho chloro substituent sufficiently hinders the addition of the methyl phenyl sulfone anion to the aldehyde thus allowing alternate reactions to occur.

One of the minor modifications in Bunnett's route involved conversion of the alcohol (135) to the mesylate (151) in 95% yield by the use of methanesulfonylchloride and triethylamine in methylene chloride. However, the reaction with thiophenol in a 50% potassium hydroxide/methanol mixture resulted in 76% of the sulfide (137) and 24% of *o*-chloro-styrene. Thus this modification did not constitute any improvement in the overall yield of (80). This was unfortunate as the mesylate could be considered equivalent to the chloride (136), and was obtained in a better yield.

A final new approach to the benzocyclobutene phenyl-

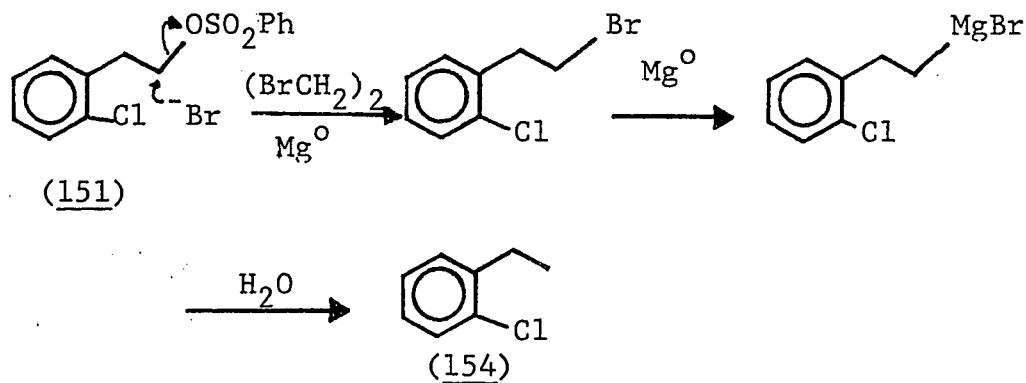
sulfone was envisaged (Scheme 12).

Scheme 12

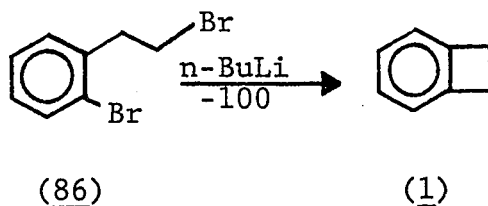


The reaction of (151) with magnesium metal was attempted in refluxing ether, but as with *o*-bromo-styrene oxide, no Grignard formation occurred. Only starting material was recovered. When dibromoethane was added, a reaction was observed. The proton NMR spectrum of the crude reaction was suggestive of *o*-chloro-ethylbenzene (154) being formed due to the presence of a triplet at  $\delta 1.24$  and a quartet at  $\delta 2.79$ . The formation of (154) may be explained by Scheme 13.

Scheme 13



Parham and coworkers have synthesized the parent benzocyclobutene (1) in 68% yield by halogen-metal exchange with  $n\text{-BuLi}$  at  $-100^\circ$  from (86).<sup>25</sup>

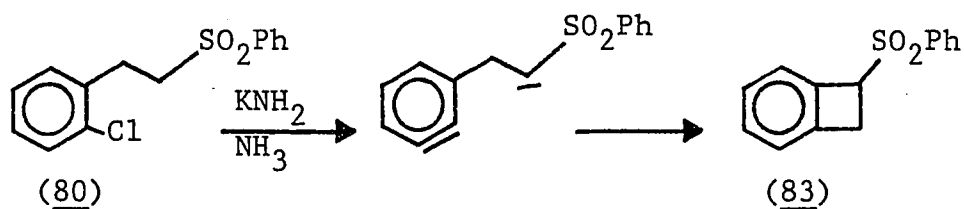


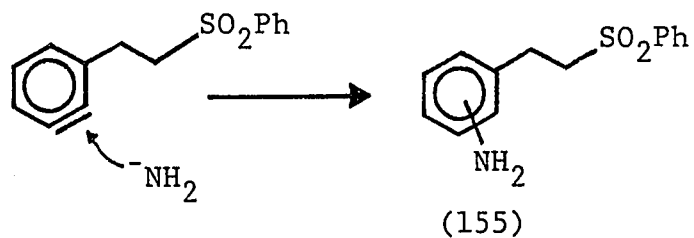
Perhaps these conditions may have worked for the tosylate of (135) providing the  $\text{CH}_2\text{CH}_2\text{OSO}_2\text{PhCH}_3$  protons are not too acidic. If they are abstracted, elimination will occur.

Had the parent benzocyclobutene been prepared by reaction of the mesylate (151) with magnesium, it was planned to brominate the benzocyclobutene to (152), followed by displacement of the bromide with the anion of thiophenol to obtain (153). The benzocyclobutene nitrile (82) has been prepared by an analogous reaction.<sup>36</sup>

Conversion of Phenyl 2-(o-chlorophenyl)ethyl sulfone to Benzocyclobutene Phenylsulfone via a Benzyne Intermediate

Bunnett's method of ring closure using four equivalents of  $\text{KNH}_2$  in liquid ammonia was achieved in 30-40% yield. This percentage range was consistent over eight benzyne reactions. When the ammonia was twice distilled and the sulfone was added very quickly as a solid, the reaction gave the upper range of yield of the product (83). The reported yield was 46%.<sup>22</sup> The desired benzocyclobutene phenylsulfone was isolated by column chromatography on silica gel, followed by recrystallization or sublimation. It was obtained as pure colorless needles, m.p. 102-103° (lit. value 103.5-104.5°).<sup>22</sup> The proton NMR showed a doublet at  $\delta$ 3.52 (2H,  $\text{CH}_2$ ) and a triplet at  $\delta$ 4.92 ( $\text{CHSO}_2\text{Ph}$ ), as well as the nine aromatic protons between  $\delta$ 6.9 and  $\delta$ 8.0. The IR indicated the presence of the sulfone by two strong peaks at 1120 and 1290  $\text{cm}^{-1}$ . The main contaminant in the crude reaction mixture was the amine (155) generated by addition of the amide to the benzyne. The NMR spectrum of (83) is presented as Figure 3 of the Appendix.



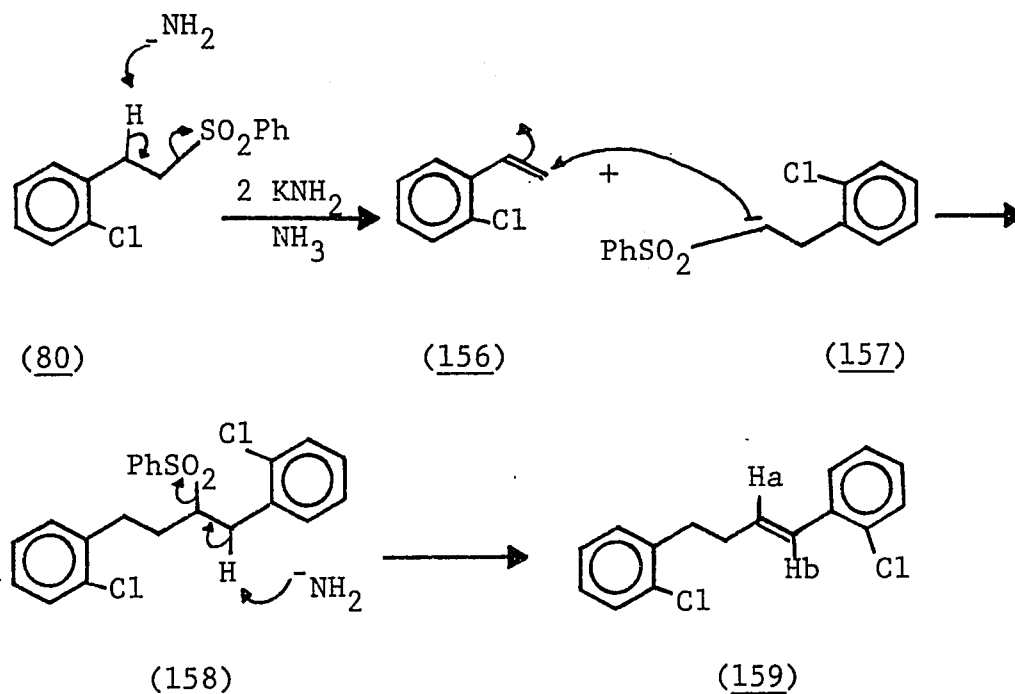


When only two equivalents of  $\text{KNH}_2$  were utilized, the reaction took a completely different course. None of the desired product (83) was obtained. Examination of the crude reaction mixture by NMR indicated the presence of mainly *o*-chloro-styrene by comparison with the spectrum of an authentic sample.<sup>31</sup> When the reaction mixture was subject to silica gel chromatography, the *o*-chloro-styrene was lost, presumably by polymerization. However, a second product was obtained in crystalline form. This product, m.p. 51-53 $^\circ$ , gave an analysis in agreement with  $\text{C}_{16}\text{H}_{14}\text{Cl}_2$ . The NMR showed a ratio of 8:2:4 of aromatic versus olefinic versus aliphatic hydrogens. The structure of this compound was assigned (159). The detailed NMR analysis, which supported the trans assignment of the double bond, is discussed below.

The NMR spectrum showed, in addition to the eight aromatic protons which occurred as a multiplet,  $\delta$ 6.97-7.55, four sets of triplets in the  $\delta$ 6.0-7.0 ppm region due to the two olefinic hydrogens,  $\text{H}_\text{A}$  and  $\text{H}_\text{B}$ . Two multiplets,  $\delta$ 2.4-2.7 and  $\delta$ 2.8-3.1, each integrating for two protons, were also present. The four sets of triplets are the

result of an ABX<sub>2</sub> pattern due to a CH<sub>2</sub>CHCHPh structure fragment. The assignment and coupling patterns are shown in Figure 4.

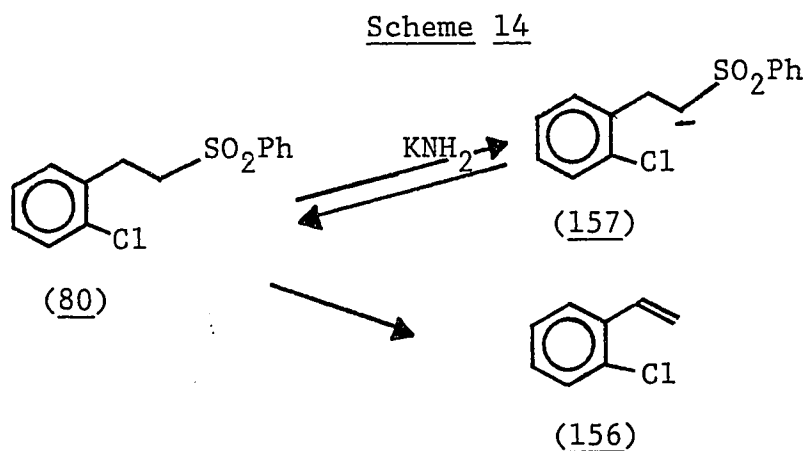
A reasonable mechanism for the formation of the compound (159) is shown below.



The first step, a  $\beta$ -elimination of phenylsulfonic acid, results in the formation of *o*-chloro-styrene (156), whose presence was shown in the crude product. Addition of the  $\alpha$ -phenylsulfonyl anion (157) to the styrene gives the sulfone (158), from which, again by  $\beta$ -elimination, (159) is obtained. Each step in the above mechanism has

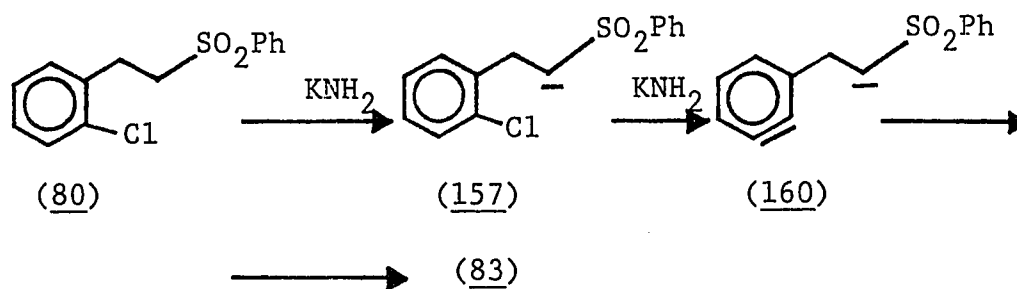
literature precedence. A number of  $\beta$ -eliminations of phenylsulfonic acid in the presence of strong base have been described.<sup>37</sup> The addition of  $\alpha$ -sulfonyl carbanion to conjugated aromatic systems is also known.<sup>38</sup>

The different behavior of the sulfone (80) in the presence of either 2 or 4 equivalents of  $\text{KNH}_2$  can be explained in the following manner. In the presence of one or somewhat more than one equivalent of base, the  $\alpha$ -sulfonyl anion (157) would be expected to form preferentially. The anion should be stable under the reaction conditions, and in equilibrium with the starting material (80) and  $\text{KNH}_2$ . A slow competitive reaction due to the formation of (156) may be  $\beta$ -elimination of phenylsulfonic acid from the starting material by action of  $\text{KNH}_2$ . Under these reaction conditions, benzyne formation would be expected to be slow (Scheme 14).



As the amount of base is increased, most of the starting material (80) would be present as the monoanion

(157), and the excess base could now react with (157) at a reasonable rate to produce the benzyne intermediate (160), and eventually the benzocyclobutene phenylsulfone (83). Apparently, when four equivalents of base are used, the optimum yield of benzocyclobutene phenylsulfone is obtained.



The use of more than four equivalents of  $\text{KNH}_2$  was not investigated since it was felt that intermolecular trapping of the benzyne with amide would reduce the yield of desired product, especially since 15-20% of the crude reaction product was, in fact, the amines (155). Reactions with three equivalents were also not attempted because it was feared that mixtures would be formed. However, further work in this area may prove interesting.

In order to avoid formation of amination products, the ring closure was attempted using lithium tetramethylpiperidide, which has been reported to generate benzyne successfully without any additions by the amide.<sup>39</sup> However, neither the use of two nor four equivalents of this base yielded the desired product as shown by the NMR. TLC analysis indicated the formation of a large number of

products.

Lithium diisopropylamide was also utilized as a base. Three equivalents of this base yielded only unreacted starting material, whereas four equivalents gave an inseparable mixture of compounds. None of the desired product was present in the NMR spectrum.

#### Alkylations of Benzocyclobutene Phenylsulfone

Alkylations were carried out in order to prepare substituted benzocyclobutene phenylsulfones containing a terminal alkene. It was then hoped that thermolysis of these compounds would yield a variety of polycyclic materials.

These alkylations were prepared via the sulfone anion, which was generated by reaction of (83) with MeLi at  $-78^{\circ}$  in dry tetrahydrofuran (THF) under a nitrogen atmosphere. On addition of the MeLi to (83), a bright yellow solution was obtained. Further proof that the anion had been formed in quantitative yield was obtained by quenching the yellow anion with  $D_2O$ . The NMR spectrum of the product (162) showed complete disappearance of the  $CHSO_2Ph$  proton at  $\delta 4.92$ . Furthermore, the doublet at  $\delta 3.52$  (2H,  $CH_2$ ) collapsed to a singlet at  $\delta 3.51$  (2H,  $CH_2$ ). During the course of the alkylation experiments, it was observed that the anion would displace only a bromide or an iodide, but not a chloride.

Model alkylations were carried out with iodomethane and allyl bromide. Reaction of the benzocyclobutene phenylsulfone with 1.1 equivalents of MeLi and 1.0 equivalent of the alkylating reagents afforded the 7-methyl and 7-allyl derivatives in 82 and 81 % yields, respectively, after chromatography on silica.

The NMR of 7-methyl benzocyclobutene phenylsulfone (163) showed an AB quartet,  $\delta A=3.74$ ,  $\delta B=3.12$ ,  $J_{AB}=14\text{Hz}$ , due to the methylene group, and a singlet at  $\delta 1.84$  assigned to the methyl group.

In the allyl derivative (164), the methylene protons again occurred as an AB quartet,  $\delta A=3.54$ ,  $\delta B=3.23$ ,  $J_{AB}=14\text{Hz}$ . The complete spectral details of these compounds are given in the experimental section. See Table 1 also.

The compounds containing the remote terminal alkenes (102) and (161) were synthesized in 79 and 62% yields respectively by reaction of the benzocyclobutene anion with 5-iodo-1-pentene and 6-bromo-1-hexene. See Figures 5 and 6 of the Appendix for the NMR spectra of these compounds.

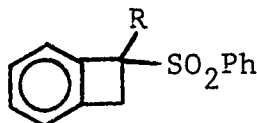
Reaction of the anion with styrene oxide was also attempted. Purification on silica gel yielded the alcohol (167) formed by anion attack at the least hindered site of the epoxide. However, the NMR of this material also contained some unreacted benzocyclobutene phenylsulfone.

In addition to the alcohol, a small amount of non-polar, crystalline material was also isolated. This same substance was isolated whenever the alkylation reactions

took some time to complete. Furthermore, when the benzocyclobutene phenylsulfone was allowed to stir overnight in the presence of one equivalent of MeLi followed by workup, the same material was obtained. Two singlets at  $\delta$ 3.52 and  $\delta$ 3.80 were present in the proton NMR, as well as the aromatic protons at  $\delta$ 7.06-7.40. The IR indicated the absence of any sulfonyl moiety, and was suggestive of a hydrocarbon. Both NMR and VPC indicated that this material contained two very similar components. The melting point was broad, 103-112<sup>o</sup>, again indicative of an impure material or of decomposition. The mass spectrum of the mixture showed a very strong peak at m/e 204, indicating that at least one of these two products was a dimer of benzocyclobutadiene. The properties of this material were not consistent with any of the previously reported dimers.

18,49,50,51

TABLE 1

Alkylations of Benzocyclobutene Phenylsulfone

<u>COMPOUND</u>	<u>R GROUP</u>	<u>% ALKYLATED</u>	<u>J<sub>AB</sub> Hz.</u>	<u>δA</u>	<u>δB</u>
<u>162</u>	D	98 *	—	3.51	3.51
<u>163</u>	Me	82	14.0	3.74	3.12
<u>164</u>	CH <sub>2</sub> CH=CH <sub>2</sub>	81	14.0	3.54	3.23
<u>165</u>	(CH <sub>2</sub> ) <sub>2</sub> CH=CH <sub>2</sub>	67	14.0	3.58	3.25
<u>102</u>	(CH <sub>2</sub> ) <sub>3</sub> CH=CH <sub>2</sub>	79	15.0	3.54	3.22
<u>161</u>	(CH <sub>2</sub> ) <sub>4</sub> CH=CH <sub>2</sub>	62	14.0	3.52	3.22
<u>166</u>	(CH <sub>3</sub> ) <sub>2</sub> CHOH	58 *	16.0	3.67	3.55
<u>167</u>	CH <sub>3</sub> CHPhOH	78 **	14.0	3.62	3.31

Calculations for the above AB systems are carried out as by Williams and Fleming.<sup>40</sup> The error for  $J_{AB} = \pm 0.2$  Hz. The error for  $\delta = \pm .03$  ppm.

\* yield based on NMR

\*\* contains 40% starting material

Desulfonylations of Substituted Benzocyclobutene  
Phenylsulfones

Desulfonylations of the substituted derivatives were achieved in excellent yields. These were carried out by a modified Trost procedure<sup>43</sup>, the sodium-mercury amalgam being added at room temperature until no liquid mercury was observed to precipitate. It was then concluded that the reaction was complete. This was confirmed by TLC due to the presence of a less polar product, and absence of the starting material. The only by-product, the very polar phenylsulfonic acid, was easily separable from the desired product by chromatography.

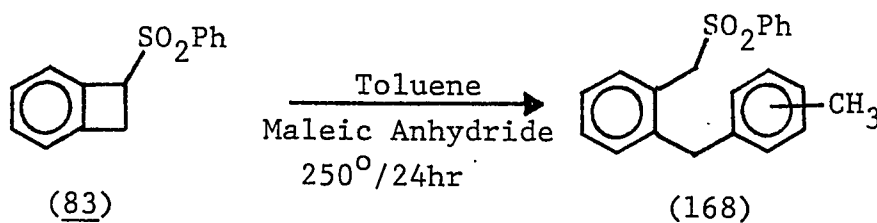
The structures of the desulfonylated products were established by NMR, IR, and elemental analysis or mass spectra. In this series of compounds, the two protons,  $H_A$  and  $H_B$ , give rise to the AB portion of the ABX pattern. Because of further coupling of  $H_X$  with the side chain protons, the coupling constants for the AB portion were not obtainable. However, the apparent coupling constants for this system are easily measured, the geminal coupling being 14 Hz and the apparent vicinal couplings being 2 Hz and 6.5 Hz. The NMR spectra of (173) and (174) are presented as Figures 7 and 8 of the Appendix.  $J_{CIS}$  was assigned to be 6.5 Hz and the  $J_{TRANS}$  to be 2.0 Hz in agreement with values reported for similar compounds.<sup>43,44</sup>

Thermolysis of Benzocyclobutene Phenylsulfone in the Presence of External Dienophiles

Trapping of the benzocyclobutene phenylsulfone was attempted with maleic anhydride in toluene in an evacuated sealed tube. The conditions chosen were similar to those used by Kametani *et al.*<sup>13</sup> who reported that thermolysis of the 7-methyl 7-cyano benzocyclobutene in the presence of maleic anhydride gave 65% of Diels-Alder adducts and 12% styrene. Reaction of the benzocyclobutene phenylsulfone occurred on heating for 24 hours at 250°. After cooling and breaking of the sealed tube, the reaction mixture was filtered to remove unreacted maleic anhydride. The crude product was then chromatographed on preparative thin layer chromatography. Several bands were observed after development in 3:1 hexanes to ethyl acetate. The major product was isolated as a slightly yellow solid, m.p. 116-118°. This material was also obtained when benzocyclobutene phenylsulfone was thermolyzed in toluene in the absence of maleic anhydride. The IR showed no carbonyl stretching frequencies, further indicating that the maleic anhydride was not incorporated into this product. Also, all the maleic anhydride employed, had been recovered by filtration.

The NMR of this isolated material showed two peaks at  $\delta$ 2.18 and  $\delta$ 2.28 integrating for a total of three protons, assignable to aromatic methyls. In addition, two singlets, equal to two protons each, were present at  $\delta$ 3.80 and  $\delta$ 4.29.

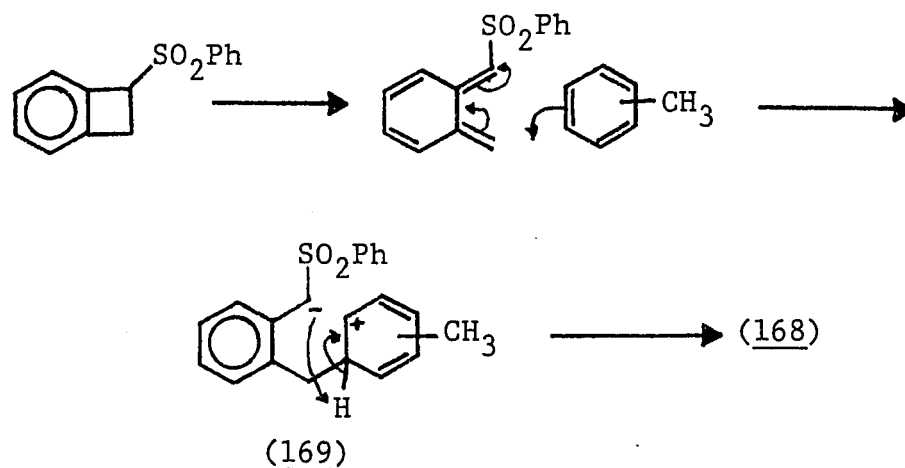
Finally, a total of 13 aromatic protons were observed. These data are in agreement with structure (168). The correct molecular formula was confirmed by the mass spectrum and elemental analysis. Strong peaks at  $1300\text{ cm}^{-1}$  and  $1125\text{ cm}^{-1}$  in the IR proved the presence of the sulfone group. In the crude reaction mixture, the two aromatic methyls were present in different ratios, suggestive of an isomeric mixture. Recrystallization from hexanes caused enrichment of the isomer having its aromatic methyl group at  $\delta 2.28$ . The yield of (168) after recrystallization was 25%. The NMR spectrum is given in Figure 9.



Two different pathways may be proposed to possibly account for the formation of (168). In the first (Scheme 15), the phenylsulfonyl substituted *o*-quinodimethane serves as an electrophile, and is attacked by toluene in a typical aromatic electrophilic substitution reaction to give the zwitterionic intermediate (169). This compound rearomatizes by transferring a proton to give the product. Nucleophilic attack on the *o*-quinodimethane intermediate might be expected to be relatively easy because such a reaction causes rearomatization, and also generates a benzylic carbanion further stabilized by a phenylsulfonyl

group. Such a mechanism would be expected to give rise to a mixture of isomers due to ortho and para attack by the toluene.

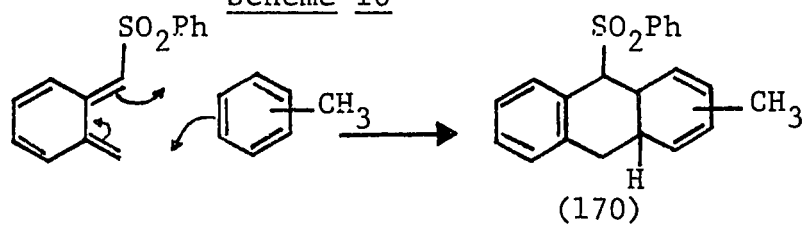
Scheme 15

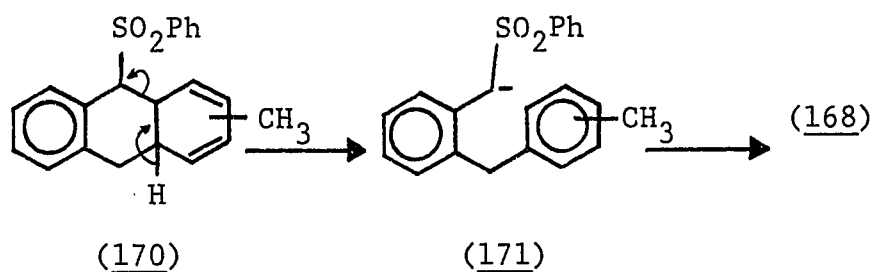


Another conceivable route for the formation of (168) involves a Diels-Alder reaction between toluene and the  $o$ -quinodimethane intermediate, followed by rearomatization (170) and opening to form the benzylic anion (171) (Scheme 16).

It was not possible to find any literature precedence for toluene acting as a dienophile in either of the above two cases.

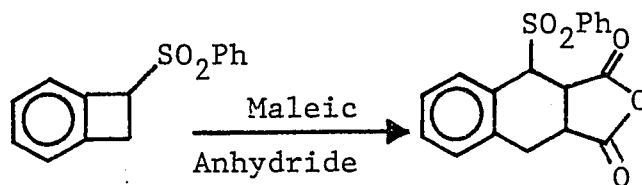
Scheme 16





In another experiment, the benzocyclobutene phenylsulfone was thermolyzed in the presence of anisole. After careful evacuation of the solvent, the NMR was suggestive of anisole incorporation. However, the product was not isolated in pure form due to difficulties in separation from the starting material.

In order to avoid reaction of the benzocyclobutene phenylsulfone with an aromatic solvent, it was heated with maleic anhydride in cyclohexane at 250° for 24 hours. Many products, resulting from the decomposition of (83), were obtained, the only isolable product being diphenyl disulfide. None of the products appeared to be the Diels-Alder adduct.



In view of the fact that Kametani was able to observe a Diels-Alder with the 7-methyl-7-cyano substituted *o*-quinodimethane, it was expected that the phenylsulfonyl analogue

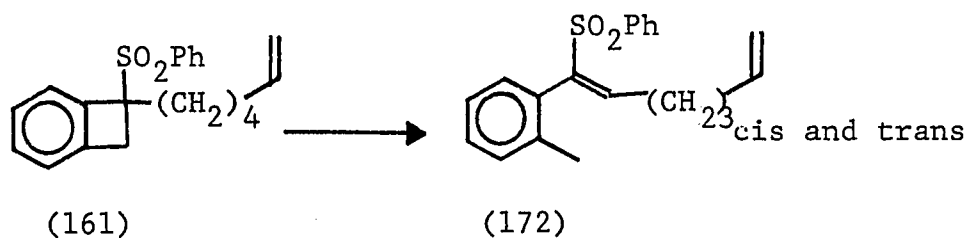
would behave likewise since a nitrile and a phenylsulfonyl have similar electron withdrawing power.<sup>41</sup> No simple explanation can be offered or is apparent to explain this difference of behavior.

#### Thermolysis of Substituted Benzocyclobutenes

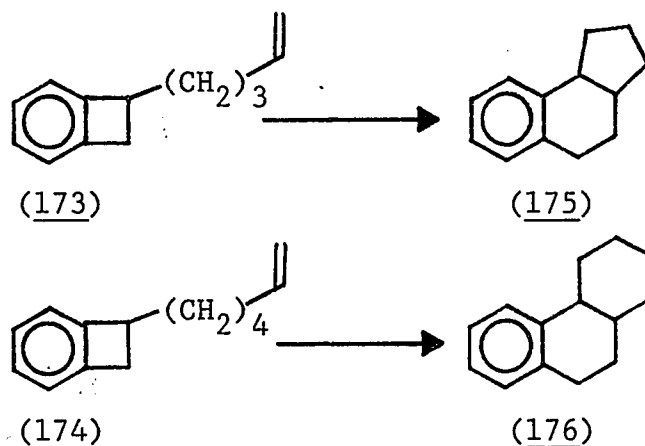
Despite the fact that no external dienophiles were capable of trapping the phenylsulfonyl substituted *o*-quinodimethane, it was nevertheless decided to attempt intramolecular trapping with a remote terminal vinyl group.

Thus, the alkylated benzocyclobutene phenylsulfone (161) was heated at 250° for 24 hours. Molecular models appeared to favor a Diels-Alder geometry used to obtain the 3.3.1 system, for example (113), assuming the phenylsulfonyl to be on the outside. However, the NMR spectrum of the product (Fig. 10) completely ruled out any possibility that the desired ring system was obtained. It showed that the terminal vinyl group had been retained (2H,  $\delta$ 4.80-5.07, CH=CH<sub>2</sub>) and (1H,  $\delta$ 5.22-5.9, CH=CH<sub>2</sub>), and that a fourth vinyl proton had been generated. Its low field position ( $\delta$ 6.67-6.88, C=CH) is in agreement with the shift of a proton on a double bond bearing the electron withdrawing phenylsulfonyl group. These results, together with the presence of two aromatic methyl groups, point to a mixture of geometrical isomers having the structure (172) formed via 1,5 hydrogen shift. Such shifts have been reported by

Kametani<sup>13</sup> as discussed in the introduction.



In a final series of experiments, the desulfonylated benzocyclobutenes (173) and (174) carrying terminal alkenes, were thermolyzed at 250<sup>o</sup> in cyclohexane. Clean isomerization to the tricyclic materials (175) and (176), respectively, was observed. The NMR spectrum of these polycyclic products (Figures 11 and 12) showed the absence of olefinic protons, and the correct ratio of aliphatic to aromatic protons. The stereochemistry of the ring junctions could not be determined with the available data. In the case of (176), VPC on two different columns showed a very symmetrical peak, suggestive of only one isomer, in contrast to (175), where the VPC results were suggestive of two closely related isomers due to the presence of a single unsymmetrical peak.



EXPERIMENTAL

Melting points (m.p.) were taken on a Thomas Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained as films on sodium chloride plates, and in chloroform ( $\text{CHCl}_3$ ) solution for solids on the Beckman IR-20A and Unicam SP1100 Spectrophotometers. Absorptions are reported in  $\text{cm}^{-1}$ , and are noted as strong (s), medium (m), weak (w), or shoulder (sh). Nuclear magnetic resonance (NMR) spectra were taken on Varian Associates Model HA-100 and a Model T-60A with deuteriochloroform as solvent (unless otherwise indicated), and tetramethylsilane (TMS) as internal standard. Peak positions are reported in  $\delta$  units as parts per million (ppm) from TMS. The following designations are used in characterizing NMR signals: singlet (s), doublet (d), triplet (t), doublet of doublets (dd), multiplet (m), and broadened (br). Combustion analyses were performed by Spang Microanalytical Laboratory of Eagle Harbor, Michigan. Mass spectra were courtesy of the University of Ottawa, Ottawa.

Thin-layer and preparative thin-layer chromatography (TLC and PTLC, respectively) were carried out on Merck 60 F-254 precoated silica plates of 0.25 mm thickness. Bands were visualized by (i) viewing under an ultraviolet source or (ii) stained with iodine vapour. The adsorbant used for column chromatography was 60-200 mesh Baker Silica Gel.

When used as a reaction solvent, tetrahydrofuran (THF)

was always distilled from lithium aluminum hydride under a nitrogen atmosphere immediately prior to use. Ethyl acetate and hexanes were distilled before using.

The term 'work-up' refers to quenching the reaction with excess H<sub>2</sub>O, extraction with methylene chloride (CH<sub>2</sub>Cl<sub>2</sub>), drying the organic extracts over MgSO<sub>4</sub>, and evaporation of the solvent under reduced pressure.

#### o-chloro-styrene oxide (88)

A 50% NaOH solution (40g NaOH; 40 ml H<sub>2</sub>O) was added dropwise to a stirred solution of o-chloro-benzaldehyde (7.99g 57mmol), trimethylsulfonium chloride (8.0g; 71mmol), and triethylbenzyl ammonium chloride (.5g) in CH<sub>2</sub>Cl<sub>2</sub> (50 ml). After stirring (.5h), the mixture was quenched with H<sub>2</sub>O (100 ml), extracted with CH<sub>2</sub>Cl<sub>2</sub> (2X50 ml), backwashed with H<sub>2</sub>O (2X50 ml), dried (MgSO<sub>4</sub>), and evacuated to yield the desired product (8.3g; 95%) as a yellow oil. Further purification to give a clear colorless oil (6.1g; 70%) was obtained by distillation (.04mm; 36°).

NMR: 2.63 (m, 1H, CH<sub>2</sub>), 3.17 (m, 1H, CH<sub>2</sub>), 4.19 (m, 1H, CH),  
7.23 (m, 4H, aromatic H). IR: CO, 1250 (w), 760 (s),  
890 (s).

#### o-bromo-styrene oxide (87)

The same procedure was used as for the preparation of

o-chloro-styrene oxide (88). The crude epoxide (12.9g; 91%) was further purified to give a colorless oil (10.9g; 78%) by distillation (0.8mm; 42°).

NMR: 2.62 (m, 1H, CH<sub>2</sub>), 3.16 (m, 1H, CH<sub>2</sub>), 4.20 (m, 1H, CH), 7.37 (m, 4H, aromatic H). IR: CO, 1250 (w), 760 (s), 890 (s).

Attempted Syntheses of 7-(hydroxy)-bicyclo[4.2.0]octa-1,3,5-triene (Benzocyclobutenol) (77)

(A) To Mg (0.47g; 19 mmol) in anhydrous ether (20 ml) was added ethylene dibromide (1.8g; 10 mmol) dropwise. When no further reaction was observed, the epoxide (87) (2.0g; 10 mmol) was added. A fine white precipitate appeared. The reaction was stirred (.5h) and then poured into saturated ammonium chloride (30 ml), extracted with CH<sub>2</sub>Cl<sub>2</sub> (3X20 ml), dried (MgSO<sub>4</sub>), and evacuated. The crude product (2.7g; 96%) was purified on silica gel (120 g) with increasing percentage of ethyl acetate in hexanes to yield 2.2g (80%) of 2-bromo-2-(o-bromophenyl)ethanol (91).

NMR: 2.48 (unresolved t, 1H, OH), 4.00 (unresolved t, 2H, CH<sub>2</sub>OH), 5.48 (t, 1H, CHBr), 6.91-7.69 (m, 4H, aromatic H). D<sub>2</sub>O: 4.00(d, 2H, CH<sub>2</sub>OH), 5.52 (t, 1H, CHBr). IR: OH, 3400 (s).

Anal. Calcd. for C<sub>8</sub>H<sub>8</sub>Br<sub>2</sub>O: C, 34.32%; H, 2.87%. Found: C, 34.35%; H, 2.91%.

(B) O-chloro-styrene oxide (1.1g; 71 mmol) in THF (150 ml) was added dropwise to magnesium (.18g; 71 mmol) in THF (50 ml) under nitrogen. No reaction was apparent, and hence ethylene dibromide and iodine were added. After stirring (3h), the reaction was worked up as in (A) and found to yield 2-bromo-2-(o-chlorophenyl) ethanol. The NMR spectrum was found to be identical to that of (91).

(C) To anhydrous ether (50 ml) and clean metal lithium ribbon (.11g; 16 mmol) under nitrogen was added the o-bromo-styrene oxide (87) (1.5g; 7.6 mmol). The mixture was refluxed (48 h), but no reaction was apparent. After 24 hours, part of the solution was withdrawn, quenched with D<sub>2</sub>O, extracted with ether, dried (MgSO<sub>4</sub>), and evacuated. Only starting material (87) was recovered as indicated by the NMR.

(D) n-BuLi (5.6 ml; 8.9 mmol; 1.6M) was added dropwise to a cold mixture of o-chloro-styrene oxide (1.24g; 8.1 mmol) and THF (75 ml). The external temperature of the liquid nitrogen-ether bath was maintained between -95° to -105°. A light yellow color was observed. The reaction was allowed to warm to room temperature (2 h), during which time a series of vivid color changes were observed. Work-up involved quenching with H<sub>2</sub>O (100 ml), extracting with CHCl<sub>3</sub> (4X20 ml), drying (MgSO<sub>4</sub>), and evacuating to yield 1.3 g of crude material. Recrystallization with CCl<sub>4</sub> gave

a white product (.60g; 22%), m.p. 121.0-121.5°, characterized to be the olefin (97).

NMR: 1.24-1.64 (unresolved t, 2H, 2OH), 4.0-4.38 (unresolved d, 4H, 2CH<sub>2</sub>), 7.20-7.52 (m, 8H, aromatic H). D<sub>2</sub>O: 4.0-4.38 (m, 4H, 2CH<sub>2</sub>), 7.20-7.52 (m, 8H, aromatic H). IR: free OH, 3600.

Anal. Calcd. for C<sub>16</sub>H<sub>14</sub>O<sub>2</sub>Cl<sub>2</sub>: C, 62.15%; H, 4.56%; Found: C, 61.84%; H, 4.50%.

The remaining oil was eluted with increasing proportions of ethyl acetate in hexanes on silica (120 g) to give several 25 ml fractions. Fractions 14-19, eluted with 85% ethyl acetate in hexanes yielded a crystalline material still containing some impurity. Recrystallization from hexanes:ether gave a product, m.p. 103-105°, characterized as (98).

NMR: 3.28 (s, 2H, OH), 4.56 (s (br), 4H, 2CH<sub>2</sub>), 6.72-7.40 (m, 8H, aromatic H). D<sub>2</sub>O: 4.56 (m, 4H, 2CH<sub>2</sub>), 6.72-7.40 (m, 8H, aromatic H). IR: hydrogen-bonded OH, 3400.

Anal. Calcd. for C<sub>16</sub>H<sub>14</sub>O<sub>2</sub>Cl<sub>2</sub>: C, 62.15%; H, 4.56%; Found: C, 61.98%; H, 4.72%.

#### Acetylation of (97)

Compound (97) (.18g; 58 mmol) was stirred with acetic anhydride (.13g; 1.3 mmol) in pyridine (3 ml) at 25° for

24 hours.  $\text{H}_2\text{O}$  (5 ml) was added, followed by stirring (1 h). The reaction was worked up by washing the organic layer with 15% HCl (3X10 ml), and extracting the water layers with ethyl acetate (5X15 ml). The product was dried ( $\text{MgSO}_4$ ) and evacuated to yield .28 grams of crude material. Re-crystallization with 2:1 hexanes to ethyl acetate yielded a pure white crystalline solid (.15g; 65%) with a m.p. 85-86°.

NMR: 2.84 (s, 6H,  $2\text{CO}_2\text{CH}_3$ ), 4.32-4.90 (m, 4H,  $2\text{CH}_2$ ), 7.0-7.58 (m, 8H, aromatic H). IR:CO, 1740 (s).

Anal. calcd. for  $\text{C}_{20}\text{H}_{18}\text{O}_4\text{Cl}_2$ : C, 61.08%; H, 4.61%; Found: C, 61.15%; H, 4.59%.

#### Oxidation of (97)

Chromium trioxide-pyridine complex (Sarett's reagent) was prepared by the method of Ratcliffe and Rodehorst.<sup>4 5</sup> The chromium trioxide (.70g; 7.0 mmol) was added to a stirred solution of pyridine (1.1g; 14 mmol) in  $\text{CH}_2\text{Cl}_2$  (15 ml). The flask was stoppered with a drying tube, and the deep burgandy solution was stirred (.3h) at room temperature. The alcohol (97) (.36g; 1.2 mmol) was added quickly in a small volume of  $\text{CH}_2\text{Cl}_2$ . A tarry black deposit separated immediately. After stirring (.3 h), the solution was decanted from the residue, which was washed with  $\text{CH}_2\text{Cl}_2$  (50 ml). The solution was filtered to remove insoluble

chromium salts, washed with  $\text{NaHSO}_3$ , extracted with  $\text{CH}_2\text{Cl}_2$  (5X15 ml), dried ( $\text{MgSO}_4$ ), and evacuated. The crude product was chromatographed on silica (55 g) with increasing proportions of ethyl acetate in hexanes. A yellow crystalline material (.11g; 30%) was obtained as the major fraction (m.p.  $115-117^\circ$ ) by elution with 25% ethyl acetate in hexanes.

NMR: 9.83 (s, 2H, 2COH), 7.23-7.73 (m, 8H, aromatic H).

IR: CO, 1680-1685 (s).

Anal. Calcd. for  $\text{C}_{16}\text{H}_{10}\text{Cl}_2\text{O}_2$ : C, 63.15%; H, 3.29%; Found: C, 63.22 %, H, 3.45%.

Attempts to Synthesize 7-(phenylsulfonyl)-bicyclo[4.2.0]octa-1,3,5-triene (Benzocyclobutene Phenylsulfone) (83)

1-(chloromethyl), 2-(phenylsulfonylmethyl)-benzene (127)

The sodium salt of benzene sulfinic acid (2.8g; 17 mmol) and 1,2-bis-(chloromethyl)-benzene (3.0g; 17 mmol) were refluxed in methanol (100 ml) for 23 hours. The reaction was poured into  $\text{H}_2\text{O}$  (100 ml), extracted with  $\text{CH}_2\text{Cl}_2$  (4X20 ml), dried ( $\text{MgSO}_4$ ), and evacuated to yield 3.9 grams of crude material. Chromatography on silica gel (100 g) by elution with 25% ethyl acetate in hexanes yielded the desired product (2.02g; 42%) as white crystals, m.p.  $75-77^\circ$ .

NMR: 4.57 (s, 2H,  $\text{CH}_2\text{SO}_2\text{Ph}$ ), 4.70 (s, 2H,  $\text{CH}_2\text{Cl}$ ), 6.87-7.97 (m, 9H, aromatic H); IR:  $\text{SO}_2$ , 1120 (s) and 1305 (s); m/e: 280, 282, 244 (-HCl).

Anal. Calcd. for  $\text{C}_{14}\text{H}_{13}\text{ClO}_2\text{S}$ : C, 60.00%; H, 4.64%; Found: C, 59.94%; H, 4.70%.

Attempts to cyclize 1-(chloromethyl), 2(phenylsulfonylmethyl)-benzene to benzocyclobutene phenylsulfone (127)→(83)

(A) Lithium diisopropylamide (LDA) was made by addition of MeLi (1.1 ml; 1.9 mmol; 1.84M) to diisopropylamine (.18g; 1.8 mmol) at  $-78^\circ$  in THF under nitrogen. Compound (127) (.50g; 1.8 mmol) was then added quickly. The reaction turned yellow, and then orange-red. After stirring (.5 h), the mixture was poured into  $\text{H}_2\text{O}$  (100 ml), extracted with  $\text{CH}_2\text{Cl}_2$ , dried ( $\text{MgSO}_4$ ), and evacuated. The NMR was suggestive of a polymer due to its very broad, unresolved nature.

(B) Compound (127) (.20g; .71 mmol) in  $\text{CH}_2\text{Cl}_2$  (25 ml) was poured on to a 50% NaOH/ $\text{H}_2\text{O}$  mixture. Triethylbenzyl ammonium chloride (.062 g) was then added followed by stirring (3 h). The reaction turned bright yellow on addition of the phase transfer catalyst. Work-up involved pouring into  $\text{H}_2\text{O}$  (50 ml), extraction with  $\text{CH}_2\text{Cl}_2$  (3X15 ml), drying ( $\text{MgSO}_4$ ), and evacuating to yield .16 grams of crude product. Purification on silica (12 g) by elution with ethyl acetate yielded one major product.

NMR: 4.40 (s, 1H), 6.6-8.0 (m, 16-18H); IR: SO<sub>2</sub>, 1125 (s), 1290-1295 (s).

(C) To 1-(chloromethyl), 2(phenylsulfonylmethyl)-benzene (127) (.21g; .76 mmol) in THF (20 ml) under nitrogen at 0° was added MeLi (.45 ml; .84 mmol; 1.84M) dropwise. During the addition, the reaction turned from dark to light yellow. After stirring (24 h), the mixture was added to H<sub>2</sub>O (50 ml), extracted with CH<sub>2</sub>Cl<sub>2</sub> (3X15 ml), dried (MgSO<sub>4</sub>), and evacuated to give .16 grams of crude product. Purification on silica with ethyl acetate yielded the same spectral data as obtained in procedure (B). This reaction was repeated at 25°, but the same results were obtained.

(D) All flash vacuum pyrolysis experiments were carried out in an apparatus designed by Dr. David Smith of the University of Leicester. The apparatus consisted of a bulb-to-bulb heater, a furnace, and a liquid nitrogen cooled trap (Fig. 13). The vacuum was about 0.06 mm for all runs, but decreased to 0.20 mm as the material passed through the hot furnace into the trap. The time taken to pass a sample through the furnace varied between 20-30 minutes. When the temperature of the furnace was 300° or lower, only the starting material was recovered, whereas at 400° small amounts of (127) remained, accompanied by an inseparable mixture of products. At 500°, an inseparable mixture of products was again formed. NMR indicated

the absence of the desired benzocyclobutene phenylsulfone at any of the temperatures utilized. At higher volatilization temperatures, only a yellow-black material was collected on the trap. This consisted of an inseparable series of compounds.

Attempts to trap 1-(chloromethyl), 2(phenylsulfonylmethyl)-benzene (127) with N-1-cyclohexenylpyrrolidine.

(A) The N-1-cyclohexenylpyrrolidine was prepared by refluxing (1.5 h) cyclohexanone (9.8g; 100 mmol) with pyrrolidine (7.8g; 110 mmol), p-toluenesulfonic acid (0.1g), and toluene (60 ml) in a Dean Stark apparatus. The starting materials were distilled prior to use. When the reaction was complete, the excess pyrrolidine was removed by distillation (105-108°). The residual enamine was used without further purification.

To (127) (.20g; .71 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 ml) was added the enamine (.12g; .79 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml). This was stirred at room temperature (1 h) giving a yellow color. Triethylamine (.179g; .79 mmol) was added, and the reaction was stirred (24 h). TLC and NMR indicated that no reaction had taken place; only unreacted starting material (127) was present.

(B) To (127) (.20g; .71 mmol) and the enamine (.12g; .79 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 ml) and 50% NaOH (15 ml) was added triethylbenzyl ammonium chloride. After stirring (24 h)

at room temperature, the reaction had turned yellow, and (127) was absent on TLC and NMR. Attempts to purify the crude material (.30 g) were made on PTLC, and developed in 3:1 hexanes to ethyl acetate. However, a series of products were actually present, and only small amounts of impure material could be isolated.

#### methyl phenyl sulfoxide (143)

Methyl phenyl sulfoxide was prepared by oxidation of thioanisole.<sup>46</sup> Sodium metaperiodate (28.5g; 128 mmol) was dissolved in H<sub>2</sub>O (260 ml), and cooled in an ice-bath. Thioanisole (15.0 ml; 15.9g; 127 mmol) was added, and the reaction was stirred (15 h). It was then filtered through a Buchner funnel, the sodium iodate cake was washed with CH<sub>2</sub>Cl<sub>2</sub> (3X30 ml), and the H<sub>2</sub>O-CH<sub>2</sub>Cl<sub>2</sub> filtrate was transferred to a separatory funnel. The H<sub>2</sub>O layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3X100 ml), dried (MgSO<sub>4</sub>), and evacuated to give 17.1 grams (96%) of crude sulfoxide. Distillation (.22 mm; 90°) yielded pure methyl phenyl sulfoxide (15.7g) in 88% yield.

NMR: 2.67 (s, 3H, CH<sub>3</sub>), 7.3-7.8 (m, 5H, aromatic H); IR: SO, 1040 (s).

#### methyl phenyl sulfone (138)

The same procedure, to obtain methyl phenyl sulfone (86%), was used as in the synthesis of methyl phenyl

sulfoxide, only using 2.1 equivalents of sodium metaperiodate.

NMR: 3.07 (s, 3H, CH<sub>3</sub>), 7.6-8.1 (m, 5H, aromatic H); IR: SO<sub>2</sub>, 1120 (s), and 1290 (s).

o-chloro-benzyl bromide (142)

The procedure used to prepare this compound was similar to that of Barnes and Gordon.<sup>47</sup> O-chloro-toluene (4.9g; 39 mmol), n-bromosuccinimide (7.6g; 43 mmol) and CCl<sub>4</sub> (50 ml) were refluxed (4 h) in the presence of light to give the desired product (98% by NMR). The reaction was worked up by filtering, washing the filtrate with H<sub>2</sub>O (60 ml), extracting with CH<sub>2</sub>Cl<sub>2</sub> (4X20 ml), drying (MgSO<sub>4</sub>), and evacuating. The o-chloro-benzyl bromide was distilled (3.4 mm; 30°) giving pure product (7.4g; 93%).

NMR: 4.43 (s, 2H, CH<sub>2</sub>), 6.8-7.4 (m, 4H, aromatic H).

o-bromo-benzyl bromide (139)

This material was obtained in the same manner as the o-chloro-benzyl bromide. The crude product was obtained in 98% yield, the NMR indicating quantitative conversion of o-bromo-toluene to o-bromo-benzyl bromide.

NMR: 4.53 (s, 2H, CH<sub>2</sub>), 6.9-7.6 (m, 4H, aromatic H).

phenyl 2-(o-bromophenyl)ethyl sulfone (140)

(A) To methyl phenyl sulfone (4.0g; 25 mmol) in THF (80 ml) at 0° was added MeLi (16ml; 28 mmol; 1.84M) giving a bright yellow solution. After stirring (5 min), o-bromobenzyl bromide (6.4g; 25 mmol) was added resulting in a dark brown solution. The reaction was stirred (24 h), followed by pouring into H<sub>2</sub>O (100 ml), extracting with CH<sub>2</sub>Cl<sub>2</sub> (5X20 ml), drying (MgSO<sub>4</sub>), and evacuating to give the crude material (8.45 g). Purification was attempted on silica (130 g) with increasing proportions of ethyl acetate in hexanes. Elution with 25% ethyl acetate in hexanes yielded 1,3 di-(o-bromophenyl)2-(phenylsulfonyl) propane (141) (.68 g). Further elution yielded 1.3 grams (16%) of the desired phenyl 2-(o-bromophenyl)ethyl sulfone (140). Large amounts of unreacted methyl phenyl sulfone were also isolated.

NMR (140): 2.63-3.67 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>), 6.73-8.13 (m, 9H, aromatic H); IR: SO<sub>2</sub>, 1130 (s), and 1290 (s).

NMR (141): 2.76-3.51 (m, 4H, CH<sub>2</sub>CHSO<sub>2</sub>PhCH<sub>2</sub>), 4.11-4.30 (m, 1H, CHSO<sub>2</sub>Ph), 6.41-8.12 (m, 13H, aromatic H); IR: SO<sub>2</sub>, 1290 (s) and 1130 (s).

(B) The above reaction was repeated at -78° inverting the order of addition. The anion of the methyl phenyl sulfone in THF was added dropwise to the o-bromobenzyl bromide. The solution slowly turned yellow. After stirring

(1 h), the reaction was worked up as in (A). Unfortunately, the amount of desired product (140) was not significantly increased in the crude NMR.

(C) The reaction via (A) was repeated in the presence of hexamethylphosphoramide, again with no success in obtaining higher yields of (140).

(D) Alkylating reaction times, quenching times, and temperature were also altered, but the desired phenyl 2-(o-bromophenyl)ethyl sulfone was still not obtained in good yields.

(E) Methyl phenyl sulfone (1.0g; 6.5 mmol) and a catalytic amount of triethylbenzyl ammonium chloride in 50% aqueous NaOH (20 ml) and  $\text{CH}_2\text{Cl}_2$  (20 ml) were stirred (.5h) under phase transfer conditions. The o-chloro-benzaldehyde (3.0g; 22 mmol) was added dropwise and the reaction was stirred (24 h). Work-up involved pouring into  $\text{H}_2\text{O}$  (50 ml), extracting with  $\text{CH}_2\text{Cl}_2$  (3X15 ml), drying ( $\text{MgSO}_4$ ), and evacuating to yield a yellow oil. The products appeared to be o-chloro-benzyl alcohol and o-chloro-benzoic acid, arising from a Cannizzaro reaction. The above reaction was repeated using 1:1 equivalents of the methyl phenyl sulfone to the o-chloro-benzaldehyde, but the same results were obtained.

NMR: 2.94 (s, 2H, CH<sub>2</sub>), 2.12 (s, 1H, OH); IR: OH, 3600 (m), 3400 (m).

phenyl 2-(o-chlorophenyl)ethyl sulfoxide (144)

Lithium diisopropylamide was made by addition of MeLi (20 ml; 37 mmol; 1.84M) to diisopropylamine (3.41g; 33mmol) in THF (160 ml) at -78° under nitrogen. The dry ice-acetone bath was removed after ten minutes, and replaced by an ice-bath. The freshly distilled methyl phenyl sulfoxide (4.74g; 34 mmol) was added neat giving a bright yellow anion. After 5 minutes, the o-chloro-benzylbromide (6.93g; 34 mmol) was added quickly giving a bright purple solution. The reaction was stirred (.25 h), poured into H<sub>2</sub>O (150 ml), extracted with CH<sub>2</sub>Cl<sub>2</sub> (4X20 ml), dried (MgSO<sub>4</sub>), and evacuated to yield the crude product (11.5g). Purification was attempted by elution with increasing proportions of ethyl acetate in hexanes on silica (230 g). The desired product (144) was isolated as an oil (7.3 g; 82%) by elution with 35-40% ethyl acetate in hexanes.

NMR: 2.76-3.38 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>), 6.96-7.76 (m, 9H, aromatic H); IR: SO, 1030 (s).

phenyl 2-(o-chlorophenyl)ethyl sulfone (80)

Metachloroperoxybenzoic acid (3.5g; 20 mmol) was added slowly as a solid to phenyl 2-(o-chlorophenyl)ethyl sulfoxide (5.27g; 20 mmol) in refluxing CH<sub>2</sub>Cl<sub>2</sub> (50 ml).

The reaction was followed by TLC. When the more polar sulfoxide was absent, the reaction was cooled, filtered to remove the insoluble benzoic acid, poured into H<sub>2</sub>O (30 ml), backwashed with sodium sulfite (2X20 ml), extracted with CH<sub>2</sub>Cl<sub>2</sub> (3X25 ml), dried (MgSO<sub>4</sub>), and evacuated to yield the desired sulfone (5.1g; 91%). The m.p. of this colorless solid was determined to be 44-46° (lit. value 45-47°).<sup>22</sup>

NMR: 2.98-3.56 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>), 7.02-8.1 (m, 9H, aromatic H); IR: SO<sub>2</sub>, 1125 (s), and 1305 (s).

phenyl 2-(o-chlorophenyl)ethyl sulfide (137)

A solution of phenylthiomethyl lithium was prepared by the route of Corey and Seebach.<sup>34</sup> To a solution of 1,5-diazabicyclo[4.3.0]non-5-ene (4.8g; 43 mmol) and thioanisole (5.3g; 43 mmol) in THF (65 ml) under nitrogen at 0° was added n-BuLi (21 ml; 48 mmol; 2.3M) within 12 minutes. After stirring (2 h), the o-chloro-benzyl bromide (8.7g; 43 mmol) was added. A very exothermic reaction occurred giving a black solution. The reaction was worked up by pouring into H<sub>2</sub>O (80 ml), extracting with CH<sub>2</sub>Cl<sub>2</sub> (4X20 ml), drying (MgSO<sub>4</sub>), and evacuating. The black material was eluted through a silica column with hexanes. The NMR indicated only the presence of thioanisole; no o-chloro-benzyl bromide was present in the crude NMR. A small amount of this reaction product was oxidized with

metachloroperoxybenzoic acid in  $\text{CH}_2\text{Cl}_2$ . The oxidized product was methyl phenyl sulfoxide, indicative that only thioanisole was present in the crude reaction product, and not the desired phenyl 2-(o-chlorophenyl)ethyl sulfide.

Attempts to cyclize o-chlorophenethyl alcohol methylsulfinate (151)

o-chlorophenethyl alcohol (135)

The o-chlorophenyl acetic acid (5.0 g; 29 mmol) in THF (25 ml) was added dropwise to lithium aluminium hydride (4.5 g; 117 mmol) in THF (30 ml), and refluxed (2 h). Work-up involved addition of 10% HCl until the gelatinous mass was dissolved, extraction with  $\text{CH}_2\text{Cl}_2$ , drying ( $\text{MgSO}_4$ ) and evacuating to yield the o-chlorophenethyl alcohol (4.4 g; 95%).

NMR: 2.87 (unresolved t, 2H,  $\text{CH}_2\text{CH}_2\text{OH}$ ), 3.67 (unresolved t, 2H,  $\text{CH}_2\text{CH}_2\text{OH}$ ), 6.7-7.3 (m, 4H, aromatic H); IR: 3400 (s).

o-chlorophenethyl alcohol methylsulfinate (151)

To o-chlorophenethyl alcohol (3.5 g; 22 mmol) dissolved in  $\text{CH}_2\text{Cl}_2$  (50 ml) at  $0^\circ$  was added triethylamine (2.71 g; 27 mmol). Freshly distilled methanesulfonyl chloride (2.8 g; 25 mmol) was added dropwise, giving a white precipitate. The reaction was stirred (24 h), and poured into 5% HCl (25 ml), extracted with  $\text{CH}_2\text{Cl}_2$  (20 ml), dried ( $\text{MgSO}_4$ )

and evacuated to yield 5.0 g (95%) of the desired mesylate.

NMR: 2.77 (s, 3H, CH<sub>3</sub>), 3.07 (t, 2H, J=6 Hz, CH<sub>2</sub>CH<sub>2</sub>SO<sub>2</sub>),  
4.37 (t, 2H, J=6 Hz, CH<sub>2</sub>CH<sub>2</sub>SO<sub>2</sub>), 7.0 (s, 4H, aromatic  
H); IR: 1150 (s), 1340 (s).

7-(phenylsulfide)-bicyclo[4.2.0]octa-1,3,5,-triene (153)

The mesylate (151) was added to magnesium (.12 g, 4.7 mmol) in THF (15 ml). No reaction with the magnesium was apparent. Work-up involved pouring into water, and extracting with ether, drying (MgSO<sub>4</sub>), and evacuating. Only starting material was present in the NMR. This reaction was repeated and ethylene dibromide was added in attempts to activate the magnesium in refluxing ether. A white precipitate was observed. Work-up was carried out as above. NMR of the crude product was suggestive of o-chloro-ethylbenzene being formed.

NMR: 1.24 (t, 3H, CH<sub>3</sub>), 2.79 (q, 2H, CH<sub>2</sub>).

Attempts to cyclize phenyl 2-(o-chlorophenyl)ethyl sulfone (80).

(A) The ring closure of (80) was done by the method of Bunnett<sup>22</sup> via a benzyne intermediate. A three-neck litre flask was fitted with a dry-ice condenser and a nitrogen inlet. A soda lime drying tube was attached to the top of the condenser. The system was first flamed with nitrogen flowing through the system. The condenser

was then filled with dry-ice/acetone and the nitrogen inlet was replaced with an  $\text{NH}_3$  inlet. When the flask contained 600 ml of liquid  $\text{NH}_3$ , the nitrogen inlet was substituted for the  $\text{NH}_3$  inlet. Potassium metal (2.8 g; 73 mmol, 4 equivalents) was added slowly to the  $\text{NH}_3$  until a deep blue color persisted. A trace of powdered ferric nitrate was added as a catalyst. The remaining potassium was added slowly. The mixture turned from blue to grey, after complete reaction of the potassium with the  $\text{NH}_3$ . When all the potassium was consumed, the phenyl 2-(*o*-chlorophenyl)ethyl sulfone (5.0 g; 18 mmol) was added quickly, giving an orange-brown solution. The reaction was stirred (10 min) and  $\text{NH}_4\text{NO}_3$  (5 g) was then added to quench any unreacted  $\text{KNH}_2$ . The  $\text{NH}_3$  was allowed to evaporate overnight. Extraction with methylene chloride and water gave crude product. Elution with 20% ethyl acetate in hexane on silica gel (40 g) yielded the crude product (2.1 g; 48%), melting point  $100-102^\circ$ . Further purification by recrystallization from benzene:hexane gave white needles, (1.16 g; 37%), melting point  $102-103^\circ$  (literature value  $103.5-104.5^\circ$ ).<sup>22</sup> Eight benzyne reactions were carried out with the yields ranging from 30-40%. The upper range of the yield was obtained only when the ammonia was doubly distilled, and the sulfone added quickly as a solid. Sublimation ( $135^\circ$ ; .05 mm) was often used to purify the benzocyclobutene phenylsulfone after chromatography.

NMR: 3.52 (d, 2H,  $J=4$  Hz,  $\underline{\text{CH}}_2$ ), 4.92 (t, 1H,  $J=4$  Hz,  $\underline{\text{CH}}\text{SO}_2\text{Ph}$ ), 6.88-8.02 (m, 9H, aromatic H); IR:  $\text{SO}_2$ , 1120 (s) and 1290 (s); m/e: 244, 103 ( $-\text{SO}_2\text{Ph}$ ).  
 Anal. Calcd. for  $\text{C}_{14}\text{H}_{12}\text{O}_2\text{S}$ : C, 68.85; H, 4.86. Found; C, 68.94; H, 4.92

The slightly more polar amines (155) were eluted with 20-25% ethyl acetate in hexane.

NMR: 2.81-3.57 (m, 4H,  $\underline{\text{CH}}_2\underline{\text{CH}}_2$ ), 3.70 (s, 2H,  $\underline{\text{NH}}_2$ , exchanges with  $\text{D}_2\text{O}$ ), 6.53-8.07 (m, 9H, aromatic H).

This material was desulfonylated to give the ortho and meta ethyl anilines.

NMR: 1.25 (t, 3H,  $J=8$  Hz,  $\underline{\text{CH}}_3$ ), 2.52 (q, 2H,  $J=8$  Hz,  $\underline{\text{CH}}_2$ ), 3.54 (s, 2H,  $\underline{\text{NH}}_2$ ), 6.52-7.32 (m, 4H, aromatic H).

(B) The (A) procedure was used, the only change being the number of  $\text{KNH}_2$  equivalents employed, 2 instead of 4. The crude NMR spectrum indicated the presence of o-chloro-styrene. Purification on silica gel resulted in the loss of the styrene and isolation trans-1,4-di(o-chlorophenyl) butene (159), melting point  $51-53^\circ$ .

NMR: 2.41-3.09 (m, 4H,  $\underline{\text{CH}}_2\underline{\text{CH}}_2$ ), 6.03-6.38 (dt, 1H,  $J=16,6$  Hz), 6.65-6.91 (dt, 1H,  $J=16,2$  Hz, olefinic H), 6.97

-7.55 (m, 8H, aromatic H); IR; trans-alkene, 960(m).  
Anal. Calcd. for  $C_{16}H_{14}Cl_2$ : C, 69.32; H, 5.09. Found  
C, 69.25; H, 5.04.

(C) Lithium 2,2,6,6-tetramethylpiperidide (LiTMP) was prepared just before use from 2,2,6,6-tetramethylpiperidine (Aldrich, dried over KOH and distilled) under anhydrous conditions. The purified amine (.21 g; 1.5 mmol) was syringed into the reaction vessel followed by THF (10 ml). MeLi (.87 ml; 1.6 mmol; 1.8 M) was then added at ambient temperature. The reaction was allowed to stir (10 min) followed by cooling to  $-78^{\circ}$ . The phenyl 2-(o-chlorophenyl) ethyl sulfone (.20 g; .73 mmol) was added quickly resulting in a red-brown solution. After stirring (.5 h), this reaction was worked up by pouring into  $H_2O$  (20 ml), acidifying with 40% HCl (20 ml), extracting with  $CH_2Cl_2$  (3X15 ml) drying ( $MgSO_4$ ) and evacuating to give .19 g of crude material. None of the desired benzocyclobutene phenyl-sulfone was present in the NMR. Hence the reaction was repeated using 4 equivalents of LiTMP. The reaction was also allowed to stir longer. Again, none of the desired product was present in the NMR of the crude reaction, and TLC showed a large number of products present, as in the first reaction.

(D) LDA was prepared by addition of MeLi (3.5 ml; 2.1 mmol; 1.6 M) to diisopropylamine (.54 g; 5.3 mmol) at  $-78^{\circ}$  in THF (30 ml) under nitrogen and allowed to stir (15 min). The sulfone (80) (.50 g; 1.8 mmol) was added quickly at  $0^{\circ}$ . The reaction turned from orange to pink. It was stirred (15 min), poured into water (30 ml), extracted  $\text{CH}_2\text{Cl}_2$  (3X15 ml), dried ( $\text{MgSO}_4$ ), and evacuated. NMR and TLC indicated the presence of only unreacted starting material. The reaction was attempted again using 4 equivalents of LDA. Only an inseparable mixture of compounds was obtained.

Alkylations of 7-(phenylsulfonyl)-bicyclo[4.2.0]octa-1,3,5-triene

7-(phenylsulfonyl)-7-d-bicyclo[4.2.0]octa-1,3,5-triene

To crystalline (83) (.10 g; .41 mmol) dissolved in THF (8 ml) under nitrogen at  $-78^{\circ}$  was added MeLi (.24 ml, .45 mmol; 1.84 M). A bright yellow anion was observed. After stirring (15 min) the reaction was quenched with deuterium oxide (>99% D). The yellow color disappeared and the reaction was worked up by adding  $\text{H}_2\text{O}$  (10 ml), extracting with  $\text{CH}_2\text{Cl}_2$  (2X10 ml), drying ( $\text{MgSO}_4$ ), and evacuating to give 98 mg of product (98%).

NMR: 3.51 (s, 2H,  $\text{CH}_2$ ), 6.89-8.03 (m, 9H, aromatic H).

7-(phenylsulfonyl)-7-(methyl)-bicyclo[4.2.0]octa-1,3,5-triene (163)

To (83) (.21 g; .85 mmol) in THF (13 ml) at  $-78^{\circ}$  under nitrogen was added MeLi (.59 ml, .94 mmol; 1.6 M) giving a bright yellow anion. After stirring (15 min), the reaction was quenched with excess iodomethane. After 10 minutes the yellow color disappeared and the reaction was worked-up to give .21 g of crude product. Purification on silica gel (12 g) with increasing proportions of ethyl acetate in hexane yielded the product, mp  $61-63^{\circ}$ , as a slightly clored solid (.18 g; 82%).

NMR: 1.84 (s, 3H,  $\text{CH}_3$ ), 3.74, 3.12 (q, 2H, benzylic H,  $J=14$  Hz), 6.86-7.88 (m, 9H, aromatic H); IR:  $\text{SO}_2$  1120 (s), 1290 (s); m/e: 258, 117(- $\text{SO}_2\text{Ph}$ ).

Anal. Calcd. for  $\text{C}_{15}\text{H}_{14}\text{SO}_2$ ; C, 69.74; H, 5.46, Found C, 68.53; H, 5.53.

7-(phenylsulfonyl)-7-(2'-n-propenyl)-bicyclo[4.2.0]octa-1,3,5-triene (164)

To (83) (.16 g, .65 mmol) in THF (15 ml) under nitrogen at  $-78^{\circ}$  was added MeLi (.47 ml; .75 mmol) to give a yellow anion. After stirring (15 min), allyl bromide (.16 g; .65 mmol) was added. The reaction was stirred overnight followed by usual work-up to give .16 g of crude material. Elution with increasing proportions of ethyl acetate in hexane on silica (13 g) yielded the product (.15 g; 81%).

NMR: 2.57-3.09 (m, 2H,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 3.54, 3.23 (q, 2H, benzylic H,  $J=14$  Hz), 4.85-5.25 (m, 2H,  $\text{CH}=\text{CH}_2$ ), 5.35-5.83 (m, 1H,  $\text{CH}=\text{CH}_2$ ), 6.83-7.87 (m, 9H, aromatic H); IR:  $\text{SO}_2$ , 1295 (s) and 1130 (s); terminal olefin, 975 (m) and 905 (m); m/e: 284, 143(- $\text{SO}_2\text{Ph}$ )

Anal. Calcd. for  $\text{C}_{17}\text{H}_{16}\text{SO}_2$ : C, 71.80; H, 5.67. Found C, 71.82; H, 5.57.

7-(phenylsulfonyl)-7-(3'-n-butenyl)bicyclo[4.2.0]octa-1,3,5-triene (165)

To (83) (.20 g; .82 mmol) in THF (15 ml) under nitrogen at  $-78^\circ$  was added MeLi (.59 ml; .94 mmol). After stirring (15 min), an excess of 4-bromo-butene (.16 g; 1.2 mmol) was added. The reaction was left overnight, followed by workup to yield .21 g of crude material. Purification by elution on silica (13 g) with increasing proportions of ethyl acetate in hexane yielded the product (.15 g; 67%).

NMR: 1.94-2.66 (m, 4H,  $\text{CH}_2\text{CH}_2$ ), 3.58, 3.25 (q, 2H, benzylic H,  $J=14$  Hz), 4.80-5.12 (m, 2H,  $\text{CH}=\text{CH}_2$ ), 5.52-5.98 (m, 1H,  $\text{CH}=\text{CH}_2$ ), 6.82-7.92 (m, 9H, aromatic H); IR:  $\text{SO}_2$ , 1295 (s) and 1135 (s); terminal olefin 985 (m) and 900 (m).

Anal. Calcd. for  $\text{C}_{18}\text{H}_{18}\text{SO}_2$ : C, 72.45; H, 6.08. Found C, 72.38; H, 6.05.

7-(phenylsulfonyl)-7-(4'-n-pentenyl)-bicyclo[4.2.0]octa-1,3,5-triene (102)

Sodium iodide (6.5 g; 43 mmol) was added to 5-chloro-1-pentene in acetone (20 ml). The solution was refluxed (24 h) followed by cooling, filtration and evacuation. Quantitative conversion to the iodide was indicated by NMR and the compound was used without further purification.

NMR: 1.7-2.7 (m, 4H,  $\text{CH}_2\text{CH}_2\text{CH}=\text{}$ ), 3.1 (t, 2H,  $\text{CH}_2\text{I}$ ), 4.8-5.2 (m, 2H,  $\text{CH}_2=\text{CH}$ ), 5.3-6.1 (m, 1H,  $\text{CH}_2=\text{CH}$ ).

To (83) (.10 g; .41 mmol) in THF (20 ml) under nitrogen at  $-78^\circ$  was added MeLi (.29 ml; .47 mmol; 1.6M). The reaction was stirred (.5 h) and the 5-iodo-pentene (.12 g; .61 mmol) was added. Stirring overnight, followed by work-up gave crude product (.12 g; 93%). Purification on silica with increasing percentages of ethyl acetate in hexane yielded pure product (.10 g; 79%).

NMR: 1.13-1.66 (m, 2H,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 1.91-2.54 (m, 4H,  $\text{CH}_2\text{SO}_2\text{Ph}$  and  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 3.54, 3.22 (q, 2H, benzylic H,  $J=15.0$  Hz), 5.45-5.95 (m, 1H,  $\text{CH}=\text{CH}_2$ ), 4.81-5.15 (m, 2H,  $\text{CH}=\text{CH}_2$ ), 6.79-7.83 (m, 9H, aromatic H); IR:  $\text{SO}_2$ , 1290 (s) and 1130 (s); terminal olefin, 905 (m) and 980 (m).

Anal. Calcd. for  $\text{C}_{19}\text{H}_{20}\text{SO}_2$ : C, 73.04; H, 6.45. Found, C, 73.06; H, 6.50.

7-(phenylsulfonyl)-7-(5'-n-hexenyl)-bicyclo[4.2.0]octa-1,3,5-triene (161)

To (83) (.76 g; 3.1 mmol) in THF (25 ml) was added MeLi (2.3 ml; 3.6 mmol; 1.6 M) at  $-78^{\circ}$  under nitrogen. After stirring (.5h), 6-bromo-hexene (.67 g; 4.1 mmol) was added and stirred overnight. Purification on silica (12 g) with 15% ethyl acetate in hexane yielded pure product (.12 g; 62%), mp  $57-58^{\circ}$ .

NMR : 1.12-1.80 (m, 4H,  $\text{CH}_2\text{CH}_2$ ), 1.82-2.56 (m, 4H,  $\text{CH}_2\text{SO}_2\text{Ph}$  and  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 3.52, 3.22 (q, 2H, benzylic H,  $J=14.0$  Hz, 4.80-5.12 (m, 2H,  $\text{CH}=\text{CH}_2$ ), 5.48-6.00 (m, 1H,  $\text{CH}=\text{CH}_2$ ), 6.80-7.86 (m, 9H, aromatic H). IR:  $\text{SO}_2$ , 1295 (s) and 1130 (s); terminal olefin, 900 (m) and 980 (m); m/e 326.

Anal. Calcd. for  $\text{C}_{20}\text{H}_{22}\text{SO}_2$ ; C, 73.58; H, 6.79. Found: C, 73.13; H, 6.69.

7-(phenylsulfonyl)-7-(2'-hydroxy, 2'-phenyl ethane)bicyclo[4.2.0]octa-1,3,5-triene (167)

To (83) (.19 g; .77 mmol) in THF (20 ml) under nitrogen at  $-78^{\circ}$  was added MeLi (.55 ml; .88 mmol). After stirring (.5 h), styrene oxide (.078 g; .80 mmol) was added. The solution was stirred (24 h) followed by work-up to give .26 g of crude material. Purification was attempted with increasing proportions of ethyl acetate in hexane on silica (13 g) giving 78% product which contained 40% of (80).

NMR: 2.55-2.79 (m, 2H,  $\text{CH}_2\text{CH}$ ), 3.62, 3.31 (q, 2H, benzylic H,  $J=14.0$  Hz), 5.03-5.23 (m, 1H,  $\text{CHOH}$ ), 6.80-7.01 (m, 1H,  $\text{CHOH}$ , exchanges with  $\text{D}_2\text{O}$ ), 7.13-7.80 (m, 14 H, aromatic H). IR: OH, 3510 (m),  $\text{SO}_2$ , 1125 (s) and 1285 (s).

7-(phenylsulfonyl)-7-(1'-methyl, 1'-hydroxyl)bicyclo[4.2.0]octa-1,3,5-triene (166)

To (83) (.20 g; .80 mmol) in THF (15 ml) at  $-78^\circ$  under nitrogen was added MeLi (.55 ml; .88 mmol; 1.6 M). The yellow anion was stirred (15 min) and acetone (.046 g; .80 mmol) was then added. The solution became colorless immediately, and the reaction was quenched with water (10 ml), extracted (2X10 ml), dried ( $\text{MgSO}_4$ ). The NMR of the crude product consisted of both starting material and 58% of the desired product. These had similar polarities and purification of (166) could not be effected. Quenching of the reaction at room temperature gave only starting material.

NMR: 1.67 (s, 3H,  $\text{CH}_3$ ), 1.37 (s, 3H,  $\text{CH}_3$ ), 3.67, 3.55 (q, 2H, benzylic H,  $J=16.0$  Hz), 6.43-7.87 (m, 9H, aromatic H).

7-(phenylsulfonyl)-bicyclo[4.2.0]octa-1,3,5-triene (83) in the presence of 1 equivalent of MeLi.

To (83) (.20 g; .82 mmol) at  $-78^{\circ}$  under nitrogen in THF (15 ml) was added MeLi (.56 ml; .90 mmol). The reaction was stirred (24 h), followed by work-up. Elution of the crude product through silica (12 g) with hexanes yielded .06 g of a nonpolar material, mp  $103-112^{\circ}$ . VPC analysis on SE-30 indicated the presence of two compounds of similar retention times.

NMR: 3.52 (s), 3.80 (s), 7.06-7.40 (m, aromatic H). m/e: 204 . IR: no sulfone, sulfoxide.

Desulfonylations of 7-(Phenylsulfonyl)-7-(alkyl)-bicyclo[4.2.0]octa-1,3,5-trienes

All desulfonylations were carried out by treating the sulfone (1 equivalent) in dry methanol, in the presence of disodium hydrogen phosphate, with excess Na-Hg amalgam at room temperature. Na-Hg amalgam was added to the stirred reaction until no liquid mercury was observed to precipitate out. Hence an excess of amalgam was present and the reaction complete. This was confirmed by TLC due to the presence of a faster moving material and the absence of starting material. All reactions were complete within .5 h and were done with 10 ml of MeOH. They were worked up by pouring into saturated NaCl solution (10 ml), extracting

with ether (4X10 ml), drying ( $\text{MgSO}_4$ ) and evacuating. The only by-product, phenylsulfonic acid, was easily separated from the product by silica gel filtration or PTLC. The spectral properties of the desulfonylated materials are given below with their yields.

bicyclo[4.2.0]octa-1,3,5-triene (1) 96%

NMR: 2.97 (s, 4H, 6.6-7.5 (m, 4H, aromatic H)<sup>48</sup>

7-(2'-n-propenyl)-bicyclo[4.2.0]octa-1,3,5-triene (177) 95%

NMR: 2.46 (t(br), 2H,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 2.80 (dd, 1H, benzylic  $\text{CH}_2$ ,  $J=14.0, 2.0$  Hz), 3.35 (dd, 1H, benzylic  $\text{CH}_2$ ,  $J=14.0, 6.5$  Hz), 3.35-3.78 (m, 1H, benzylic CH), 4.96-5.26 (m, 2H,  $\text{CH}=\text{CH}_2$ ), 5.70-5.22 (m, 1H,  $\text{CH}=\text{CH}_2$ ), 6.97-7.30 (m, 4H, aromatic H). m/e: 144.

7-(4'-n-pentenyl)bicyclo[4.2.0]octa-1,3,5-triene (173) 93%

NMR: 1.4-1.94 (m, 4H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 1.96-2.30 (m, 2H,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 2.74 (dd, 1H, benzylic  $\text{CH}_2$ ,  $J=14.0, 2.0$  Hz), 3.35 (dd, 1H, benzylic  $\text{CH}_2$ ,  $J=14.0, 6.5$  Hz), 3.3-3.6 (m, 1H, benzylic CH), 4.83-5.18 (m, 2H,  $\text{CH}=\text{CH}_2$ ), 5.51-6.08 (m, 1H,  $\text{CH}=\text{CH}_2$ ), 6.97-7.33 (m, 4H, aromatic).  
Anal. Calcd. for  $\text{C}_{13}\text{H}_{16}$ : C, 90.64; H, 9.36. Found: C, 90.84; H, 9.41.

7-(5'-n-hexenyl)-bicyclo[4.2.0]octa-1,3,5-triene (174) 96%

NMR: 1.2-1.9 (m, 6H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$ ), 1.9-2.3 (m, 2H,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 2.75 (dd, 1H, benzylic  $\text{CH}_2$ ,  $J=14.0$ , 2.0 Hz), 3.25 (dd, 1H, benzylic  $\text{CH}_2$ ,  $J=14.0$ , 6.5 Hz), 3.25-3.60 (m, 1H, benzylic CH), 4.83-5.18 (m, 2H,  $\text{CH}=\text{CH}_2$ ), 5.60-6.08 (m, 1H,  $\text{CH}=\text{CH}_2$ ), 6.96-7.40 (m, 4H, aromatic H)

Anal. Calcd. for  $\text{C}_{14}\text{H}_{18}$ : C, 90.26; H, 9.74. Found: C, 89.95; H, 9.69.

Thermolysis of 7-(phenylsulfonyl)-bicyclo[4.2.0]octa-1,3,5-triene in the Presence of External Dienophiles

(A) Benzocyclobutene phenylsulfone (83) (.13 g; .51 mmol), maleic anhydride (.087 g; .89 mmol), and toluene (3 ml) were heated together at  $250^\circ$  (15 h) in an evacuated sealed tube. After cooling, the remaining solid (maleic anhydride; .078 g) was filtered, and the remains evacuated. The crude product was purified on two silica gel plates, developed in 3:1 hexane to ethyl acetate. The five bands present were extracted with ether. One main fraction was isolated, recrystallization of which yielded a solid material (.043 g; 25%), mp  $116-118^\circ$ , characterized to be 1-(phenylsulfonylmethyl), 2-(tolyl)-benzene (168).

NMR: 2.18, 2.28 (2s, 3H,  $\text{CH}_3$ ), 3.80 (s, 2H,  $\text{CH}_2\text{PhMe}$ ), 4.29

(s, 2H,  $\text{CH}_2\text{SO}_2\text{Ph}$ ), 6.56-7.80 (m, 13H, aromatic H)

IR:  $\text{SO}_2$ , 1300 (s) and 1125 (s); m/e 336.

Anal. Calcd. for  $\text{C}_{21}\text{H}_{20}\text{O}_2\text{S}$ : c, 74.97; H, 5.99. Found  
C, 74.78; H, 6.11.

(B) Thermolysis of (83) (.10 g; .42 mmol) in the presence of toluene (2 ml) at  $250^\circ$  for 24 h in an evacuated tube yielded compound (168) as the major product by NMR.

(C) (83) (.15 g; .61 mmol), maleic anhydride (.87 g; .89 mmol) and cyclohexane (2 ml) were heated at  $250^\circ$  for 10 h. All crude material soluble in ethyl acetate was purified on silica with hexane/ethyl acetate. Diphenyl-disulfide, mp  $53-55^\circ$ , (lit.  $62^\circ$ )<sup>49</sup>, was the major fraction isolated (m/e 218).

(D) (83) (.10 g; .40 mmol) was heated in the presence of anisole (2 ml) in a sealed tube at  $250^\circ$  for 26 h. Purification of the anisole adduct from the starting material (83) was not effected.

NMR: 3.68-3.92 (m,  $\text{OCH}_3$  and benzylic  $\text{CH}_2$ ), 4.28-4.48 (m,  $\text{CH}_2\text{SO}_2\text{Ph}$ ), 6.68-8.05 (m, aromatic H).

Thermolysis of Alkylated Bicyclo[4.2.0]octa-1,3,5-trienes

(A) The 7-(phenylsulfonyl)-7-(5'-n-hexenyl)-bicyclo[4.2.0]octa-1,3,5-triene (.07 g; .22 mmol) was heated in cyclohexane (3 ml) in an evacuated sealed tube at 250° for 20 h. Purification of the crude product (.06 g; 75%) on silica gel plates in 3:1 hexane to ethyl acetate, followed by extraction with ether (3X) yielded a mixture of the styrenes (172) in 59 % yield (.041 g)

NMR: 1.50-2.1 (m, 9H, aliphatic H), 4.8-5.0 (m, 2H, CH=CH<sub>2</sub>), 5.22-5.9 (m, 1H, CH=CH<sub>2</sub>), 6.67-6.9 (m, 1H, styrene H) 6.9-7.7 (m, 9H, aromatic H).

Anal. Calcd. for C<sub>20</sub>H<sub>22</sub>O<sub>2</sub>S: C, 73.58; H, 6.79. Found: C, 73.12; H, 6.62.

(B) The desulfonylated benzocyclobutenes (173) and (174) were thermolyzed at 250° for 24 h. in cyclohexane. Compound (173) (.031 g) was isomerized to (175). Purification by PTLC in hexane, followed by extraction with ether (3X) yielded 74% (.023g) of the cyclized product (175).

NMR: 1.20-3.22 (m, 12H, aliphatic H), 7.00-7.22 (m, 4H, aromatic H).

Anal. Calcd. for C<sub>13</sub>H<sub>16</sub>: C, 90.64; H, 9.36. Found: C, 91.10, H, 8.96.

Thermolysis of (174) (.082 g) gave (176) in 77% yield (.063 g).

NMR: .98-3.0 (m, 14H, aliphatic H), 6.98-7.38 (m, 4H, aromatic H)

Anal. Calcd. for  $C_{14}H_{18}$ : C, 90.26; H, 9.74. Found:  
C, 89.96; H, 9.61.

Vapor phase chromatography on a 2.0 meter SE-30 column suggested that (175) was a mixture of closely related isomers due to the presence of a single unsymmetrical peak. In contrast, analysis of (176) gave only a single symmetrical peak, suggestive of one isomer.<sup>52</sup>

SUMMARY

The role of benzocyclobutene phenylsulfone (83) as a synthon in organic synthesis is still a question. This bicyclic sulfone is easily alkylated in high yields with a variety of alkylating agents. Desulfonylations occur in excellent conversion, and the compounds rearrange smoothly to cyclic materials. The serious drawback to the versatility of (83) lies in its preparation. The benzyne conversion from phenyl 2-(o-chlorophenyl)ethyl sulfone to (83) is too low for synthetic exploitation. Future research in this area should concentrate on higher yield, preparative approaches to benzocyclobutene phenylsulfone. One consideration would be the synthesis of 1-(chloromethyl),2-(phenylthiomethyl)-benzene. It is conceivable that the use of the sulfide in this series rather than the sulfone, may give an o-quinodimethane bearing an electron donating substituent (PhS) in contrast to the electron withdrawing group (PhSO<sub>2</sub>), resulting in the formation of benzocyclobutene phenylsulfide. This material could then be readily oxidized to the sulfone.

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52. VPC used was a GOW-MAC SERIES 550, Thermal Conductivity Detector.

CLAIMS TO ORIGINAL RESEARCH

1. A number of novel routes to the synthesis of benzocyclobutene phenylsulfone (83) and benzocyclobutenol (77) were investigated.
2. The reaction of n-BuLi at  $-100^{\circ}$  with o-chloro-styrene oxide resulted in the formation of the tetrasubstituted olefins (97) and (98).
3. Benzocyclobutene phenylsulfone was alkylated with a variety of alkylating reagents including iodomethane, allyl bromide, 4-bromo-butene, 5-iodo-pentene, 6-bromohexene, styrene oxide, and acetone.
4. The 7-(phenylsulfonyl)-7-(alkylated) benzocyclobutenes were desulfonylated with Na-Hg amalgam in excellent yields.
5. Benzyne cyclization to (83) was investigated and it was found that four equivalents of potassium amide were required to obtain a 30% yield; two equivalents yielded the trans-1,4-di(o-chlorophenyl)butene (159).
6. Attempts to trap the o-quinodimethane intermediate with maleic anhydride in toluene failed, resulting only in formation of 1-(phenylsulfonylmethyl)-2-(tolyl)-benzene (168).

7. Attempts to cyclize 7-(phenylsulfonyl)-7-(5'-n-hexenyl)-bicyclo[4.2.0]octa-1,3,5-triene failed, resulting in a mixture of styrenes (172).
  
8. Thermolysis of 7-(5'-n-hexenyl)-bicyclo[4.2.0]octa-1,3,5-triene resulted in the formation of 2,3,4,5,3a,9b-hexahydro-benz[e]-indene (175).
  
9. Thermolysis of 7-(4'-n-pentenyl)-bicyclo[4.2.0]octa-1,3,5-triene yielded 1,2,3,4,9,10,11,12-octahydrophenanthrene (176).

Figure 1. NMR Spectrum of (97)

100 MHz NMR, 1000 Hz SW

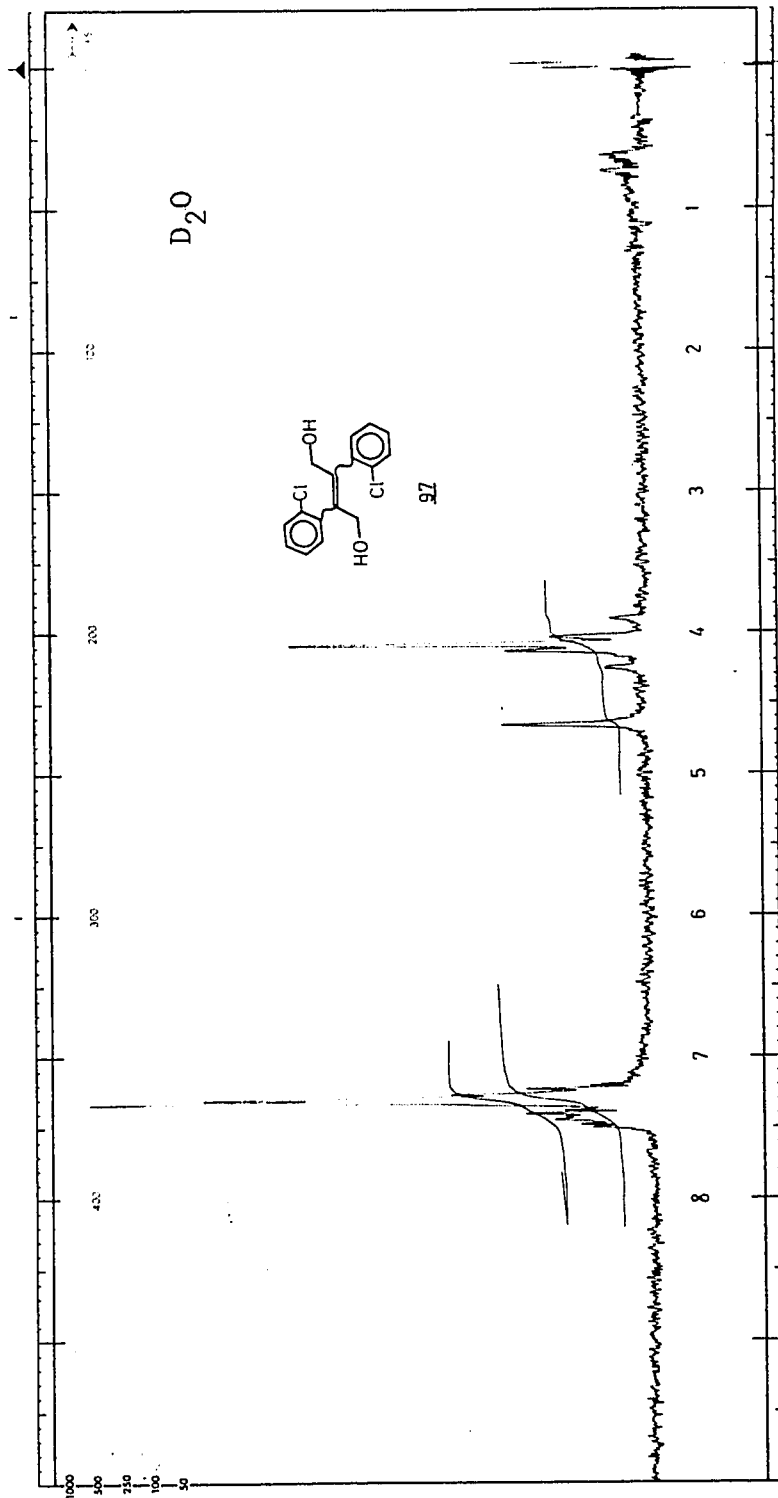


Figure 2. NMR Spectrum of (98)

100 MHz NMR, 1000 Hz SW

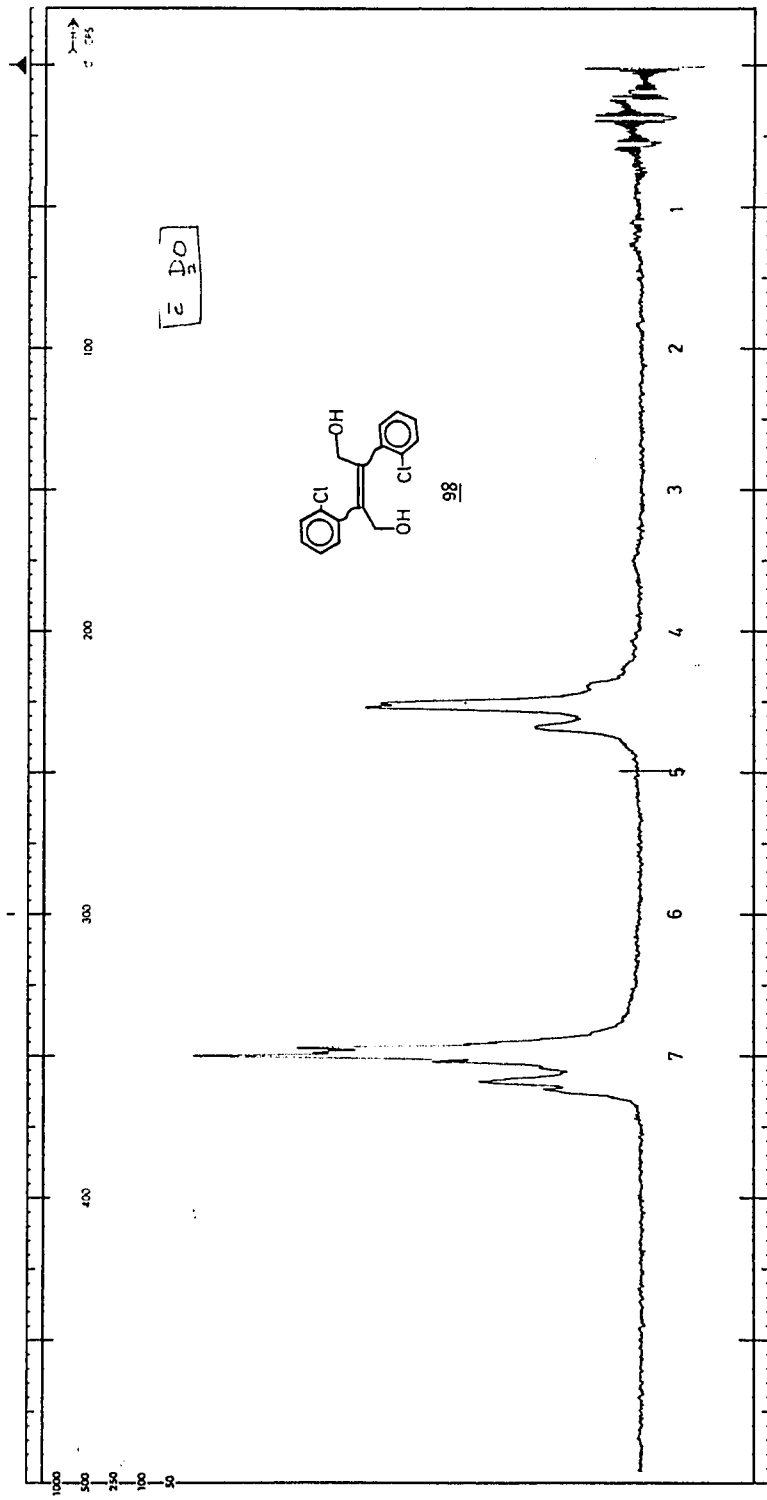


Figure 3. NMR Spectrum of (83)  
100 MHz NMR, 1000 Hz SW

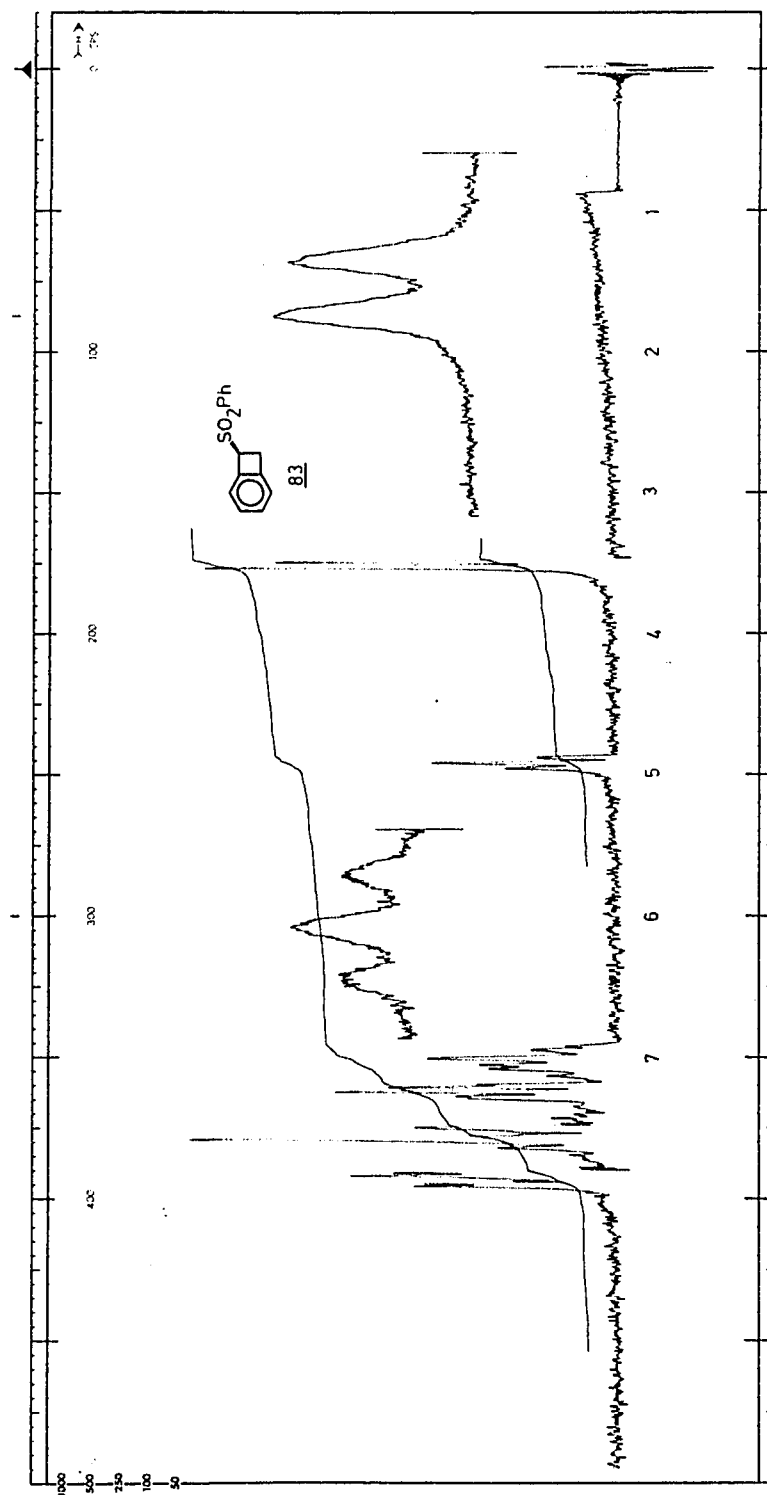


Figure 4. NMR Spectrum of (159)  
100 MHz NMR, 1000 and 250 Hz SW

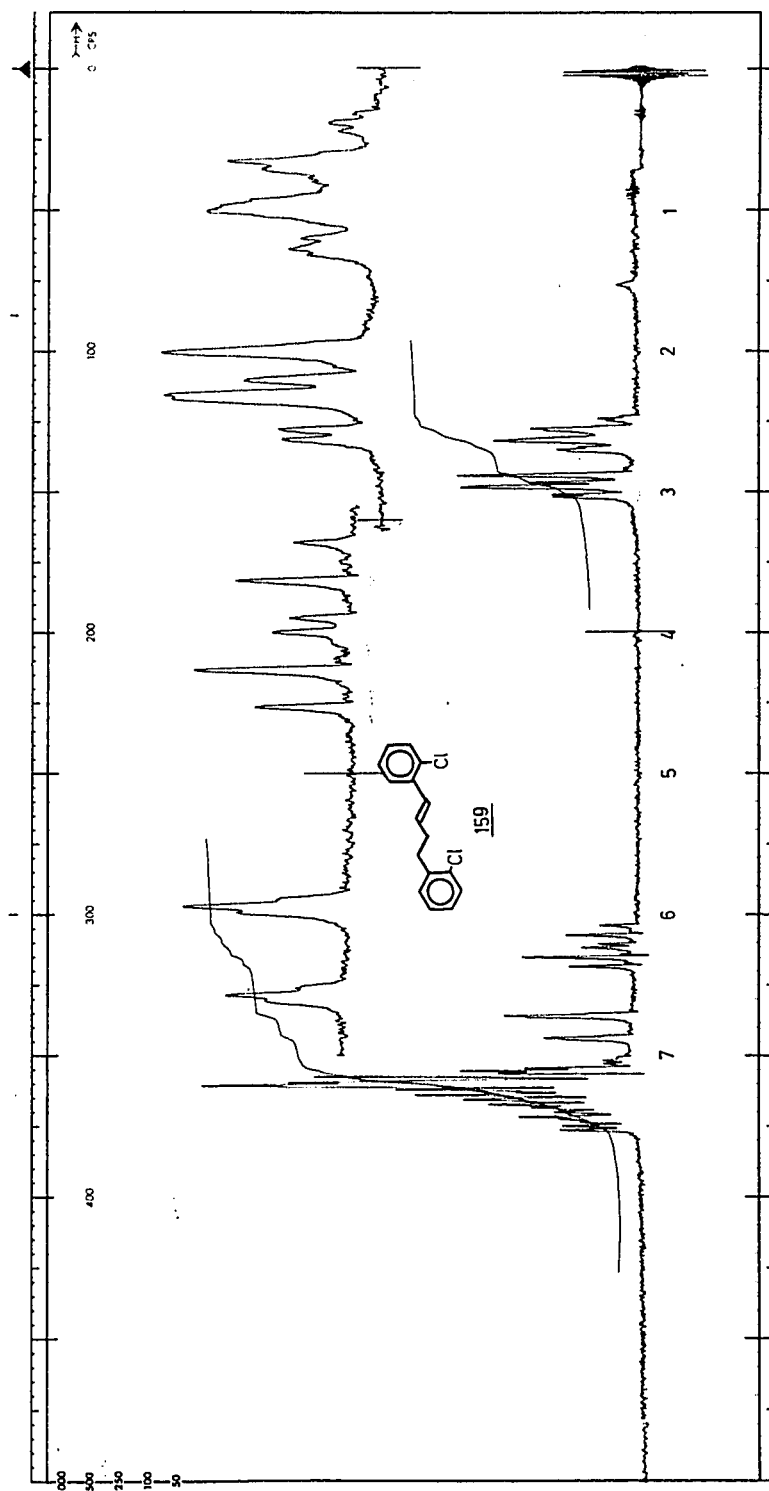


Figure 5. NMR Spectrum of (102)  
100 MHz NMR, 1000 and 250 Hz SW

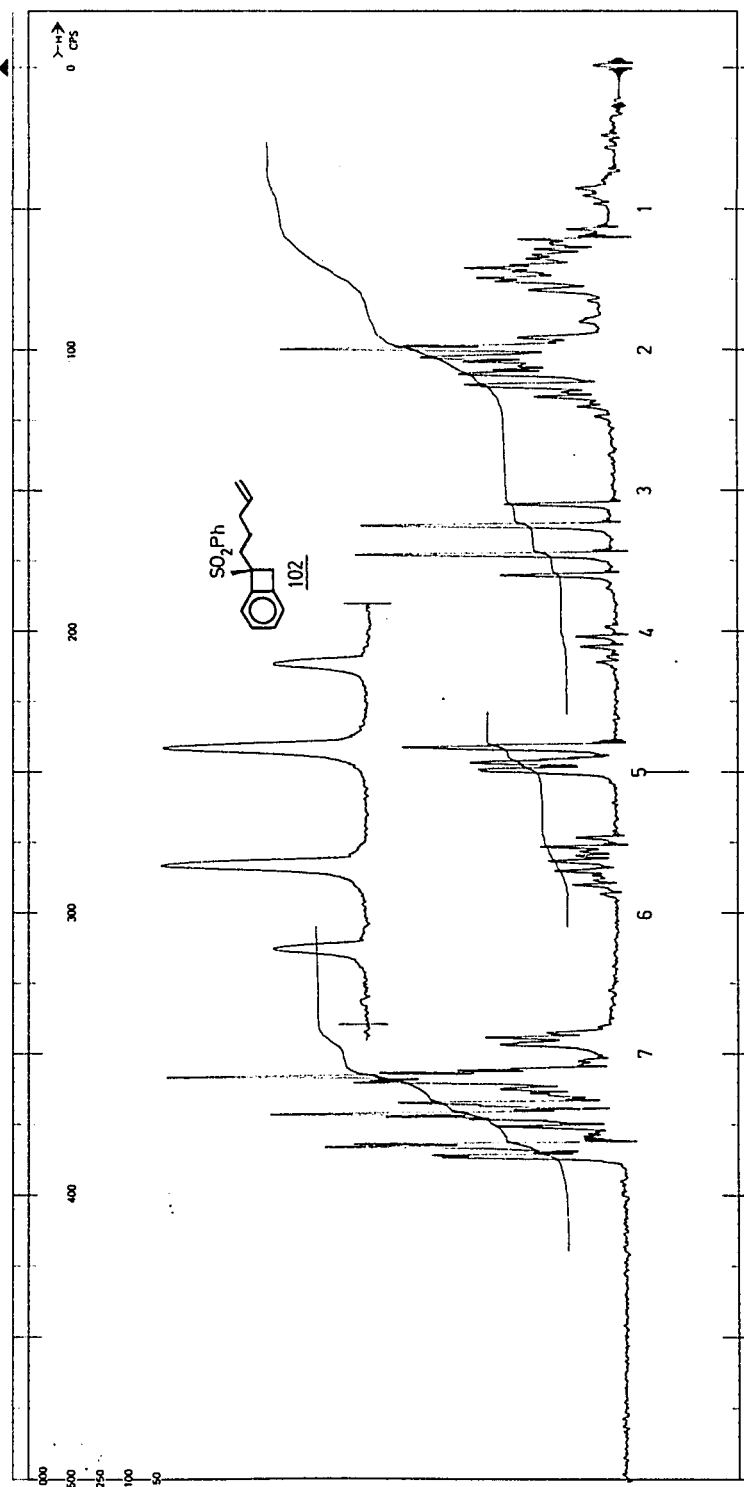


Figure 6. NMR Spectrum of (161)  
100 MHz NMR, 1000 Hz SW

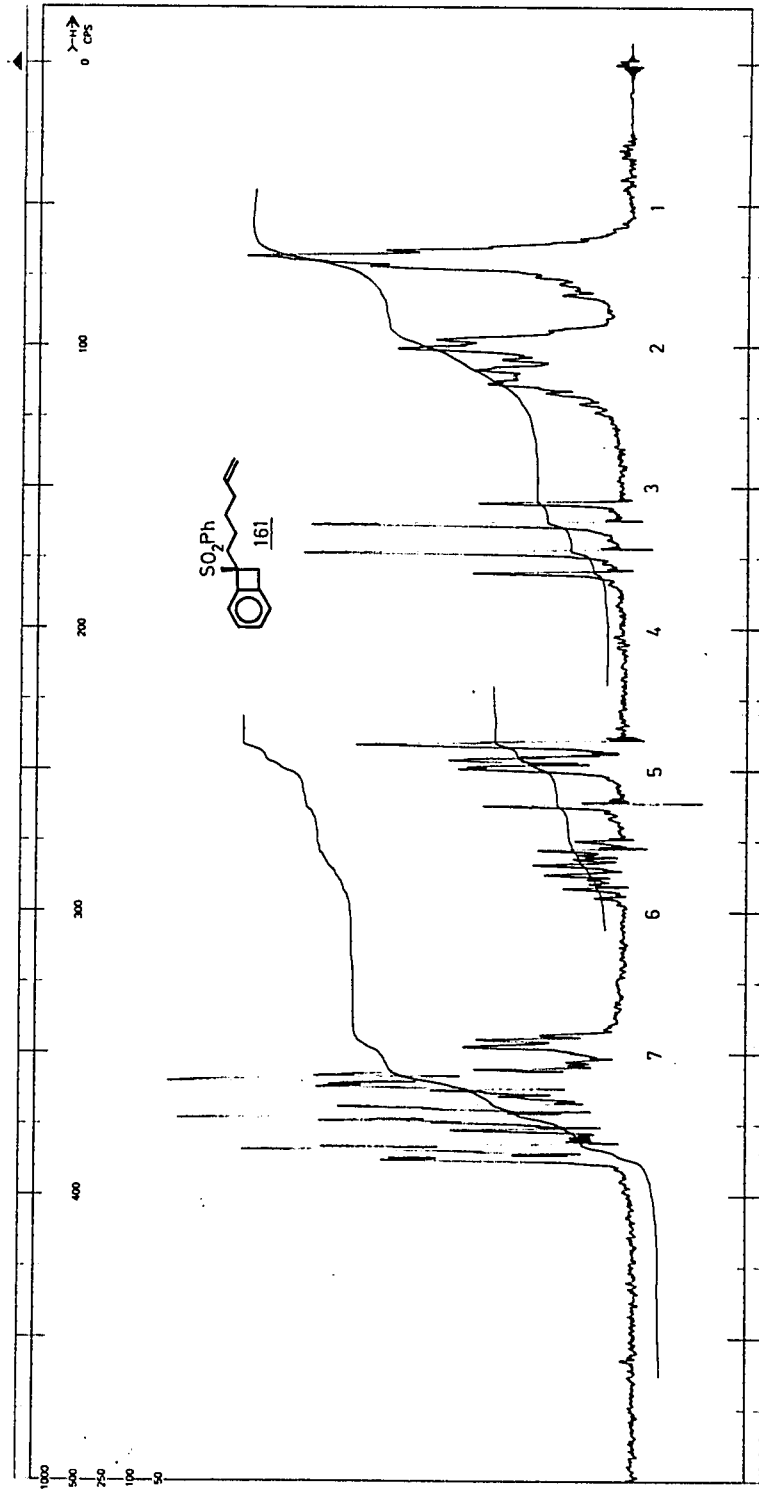


Figure 7. NMR Spectrum of (173)  
100 MHz NMR, 1000 Hz SW

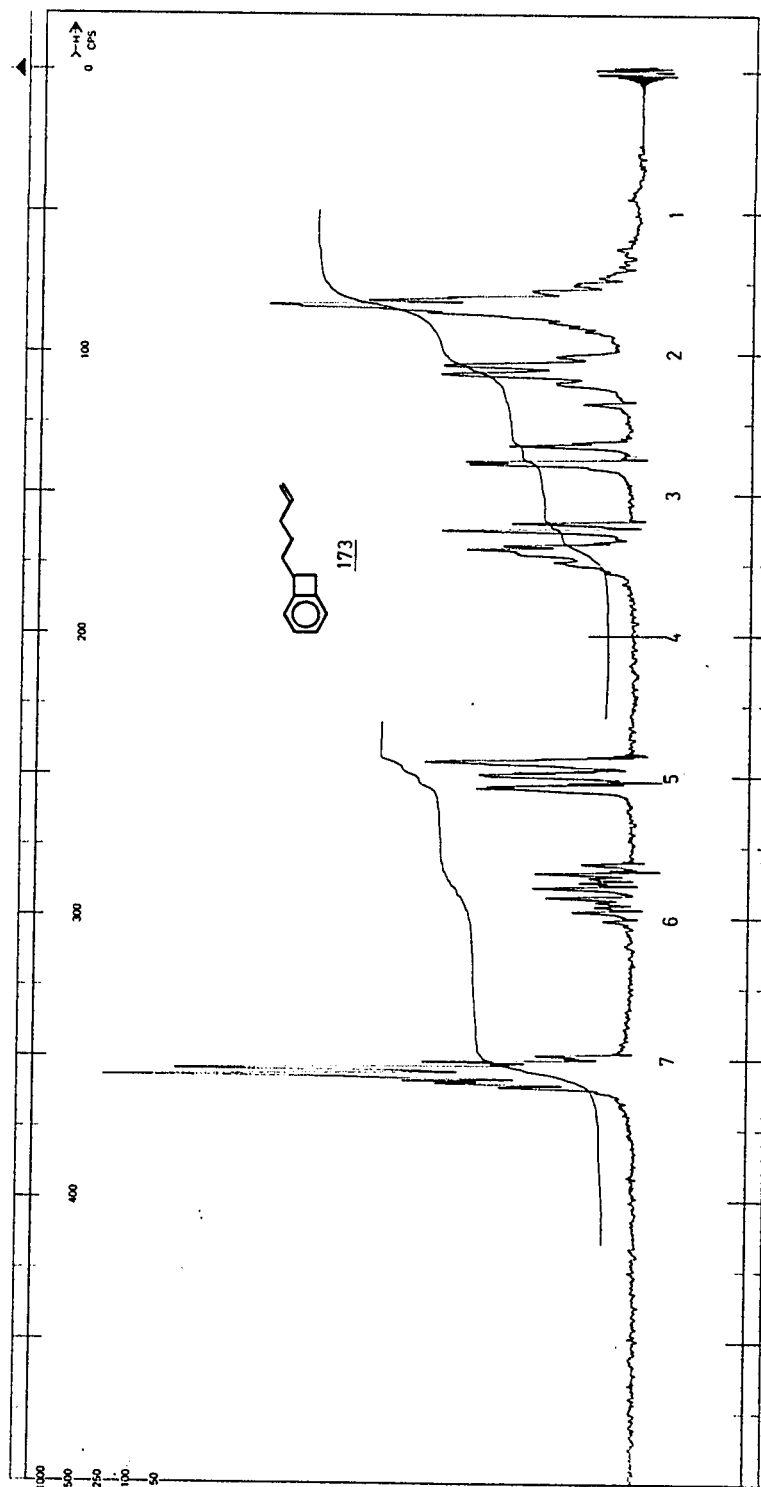


Figure 8. NMR Spectrum of (174)  
100 MHz NMR, 1000 Hz SW

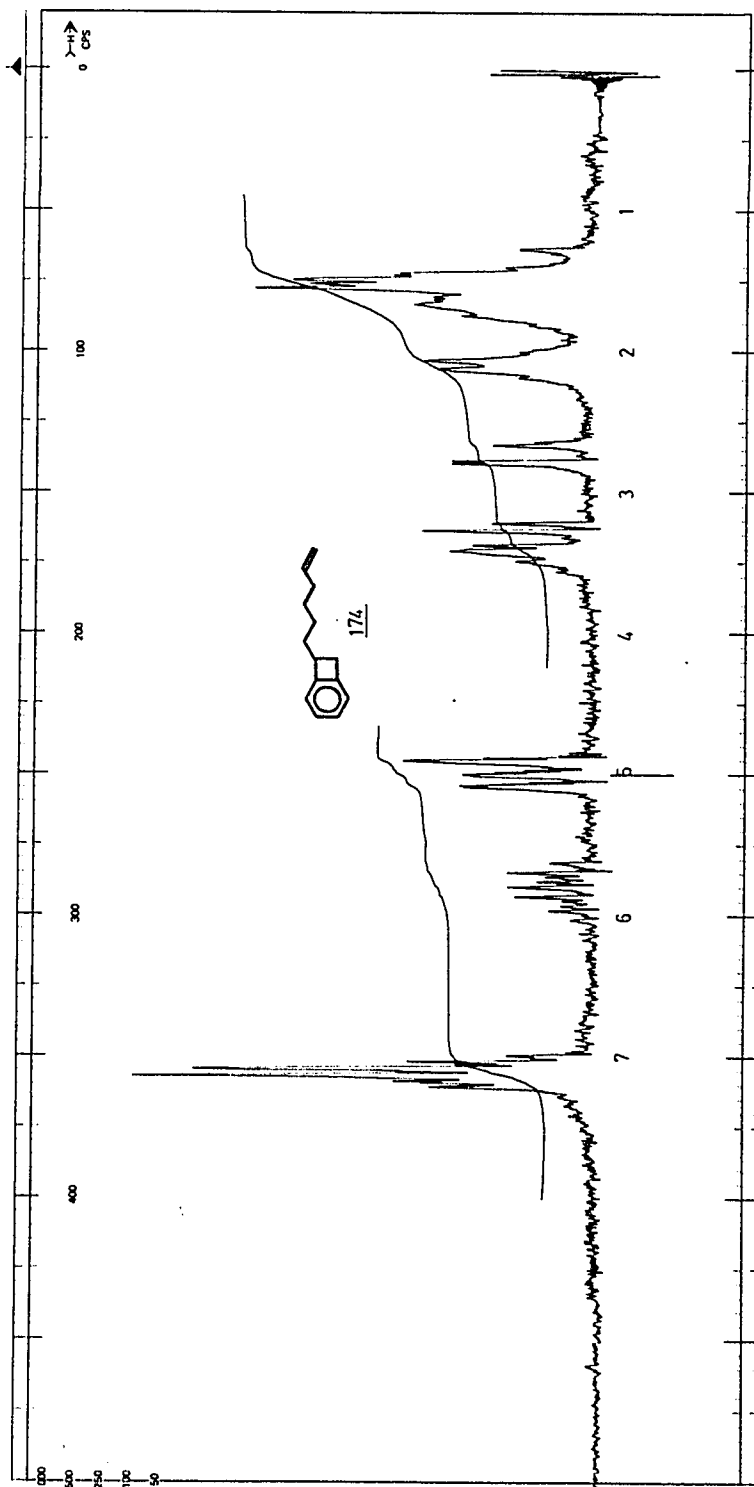


Figure 9. NMR Spectrum of (168)

100 MHz NMR, 1000 Hz SW

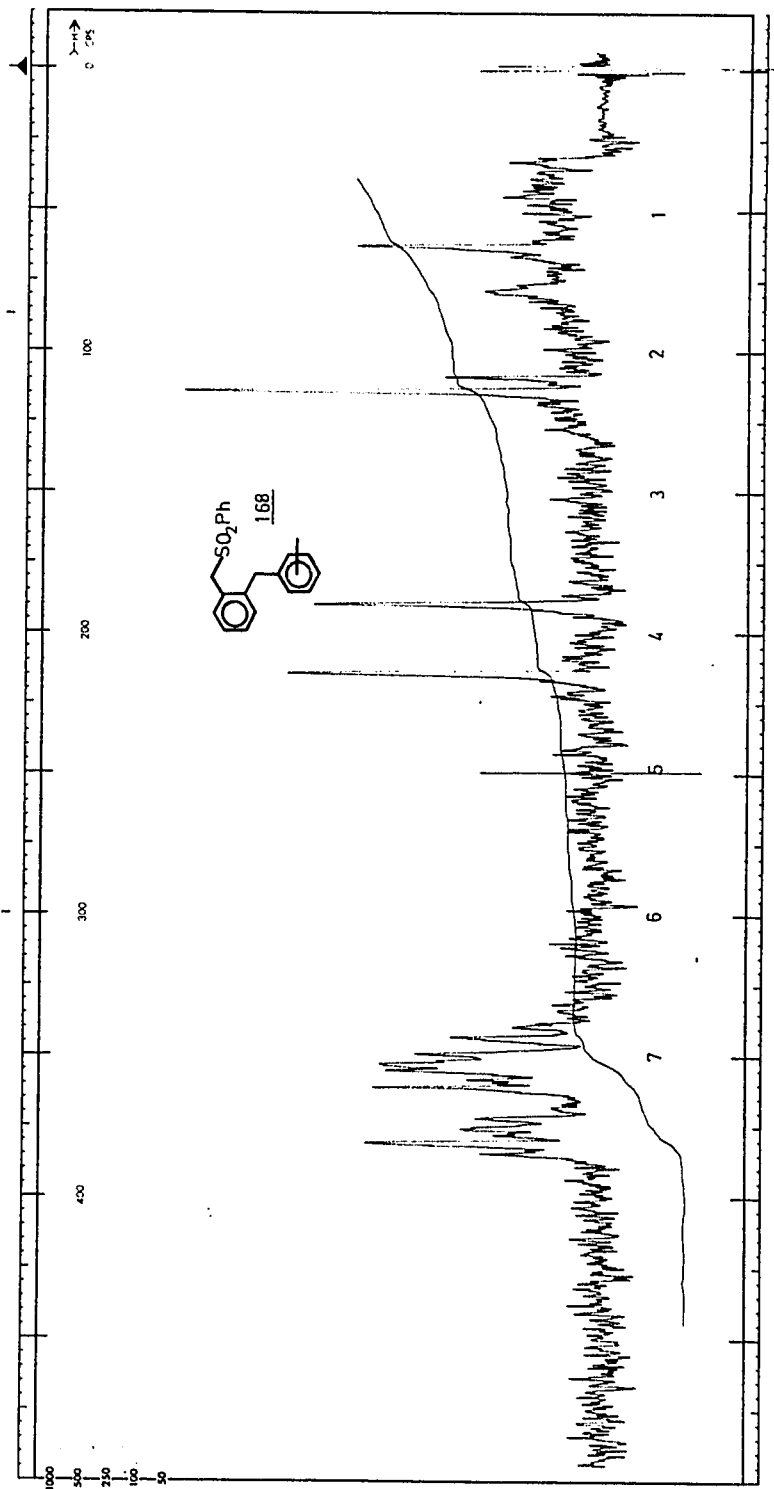


Figure 10. NMR Spectrum of (172)  
100 MHz NMR, 1000 Hz SW

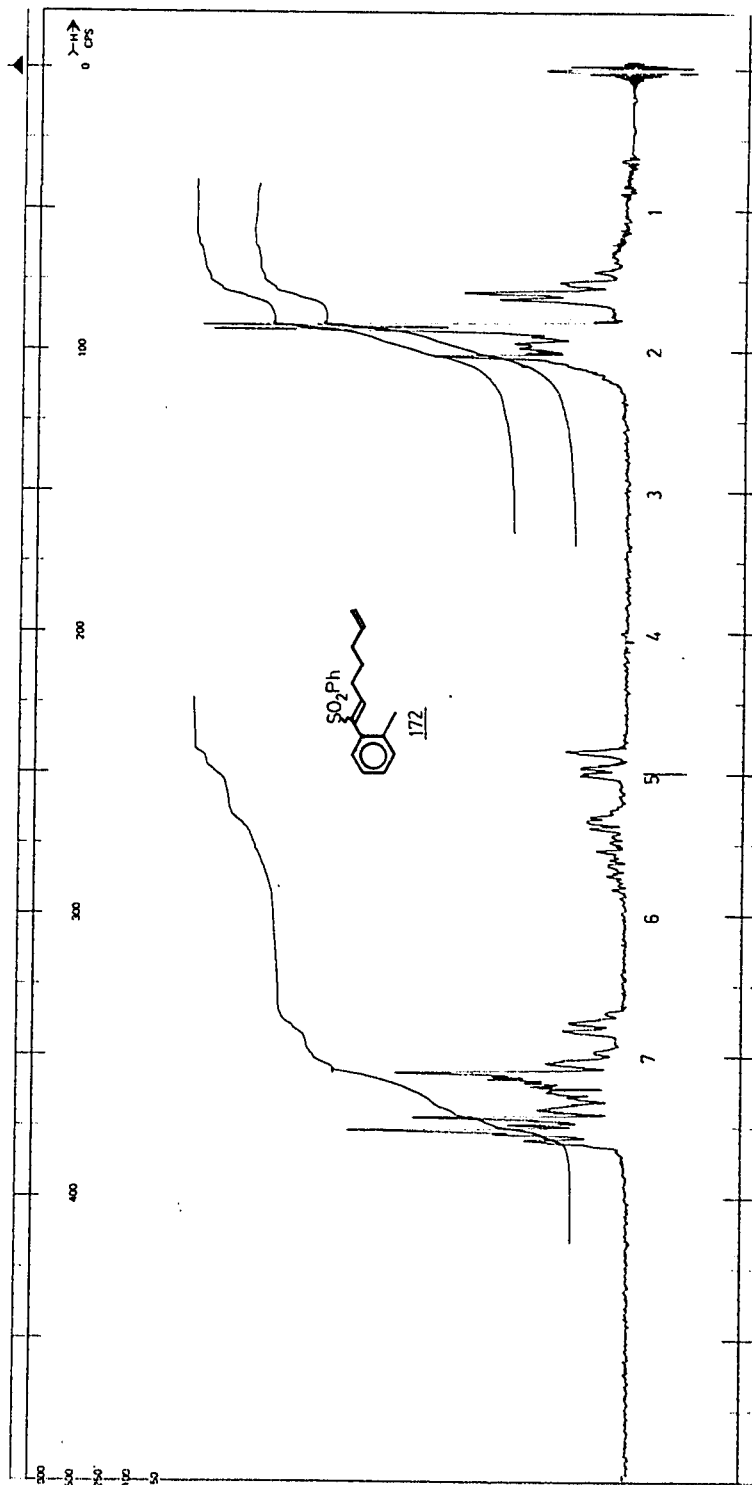


Figure 11. NMR Spectrum of (175)  
100 MHz NMR, 1000 and 250 Hz SW

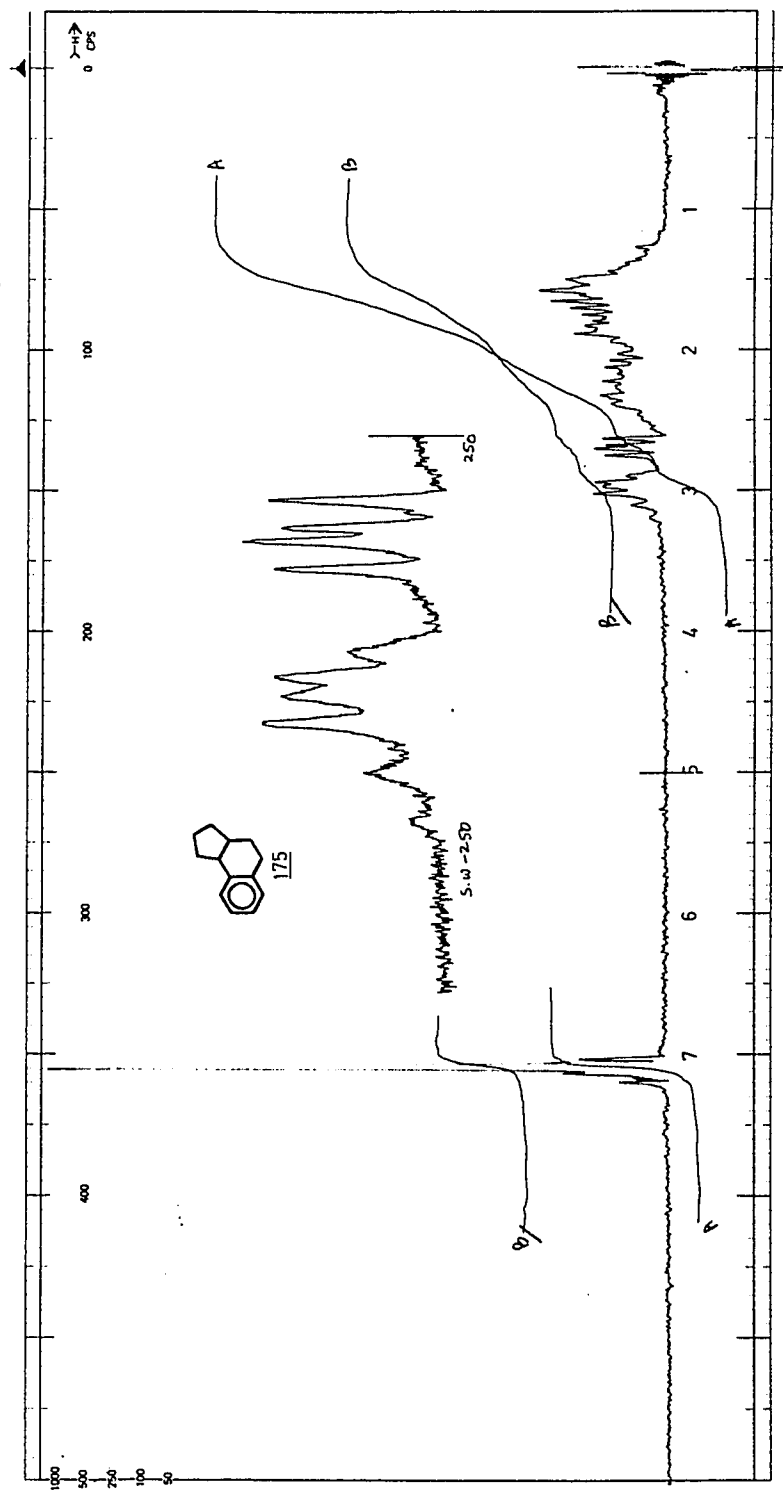


Figure 12. NMR Spectrum of (176)  
100 MHz NMR, 1000 Hz SW

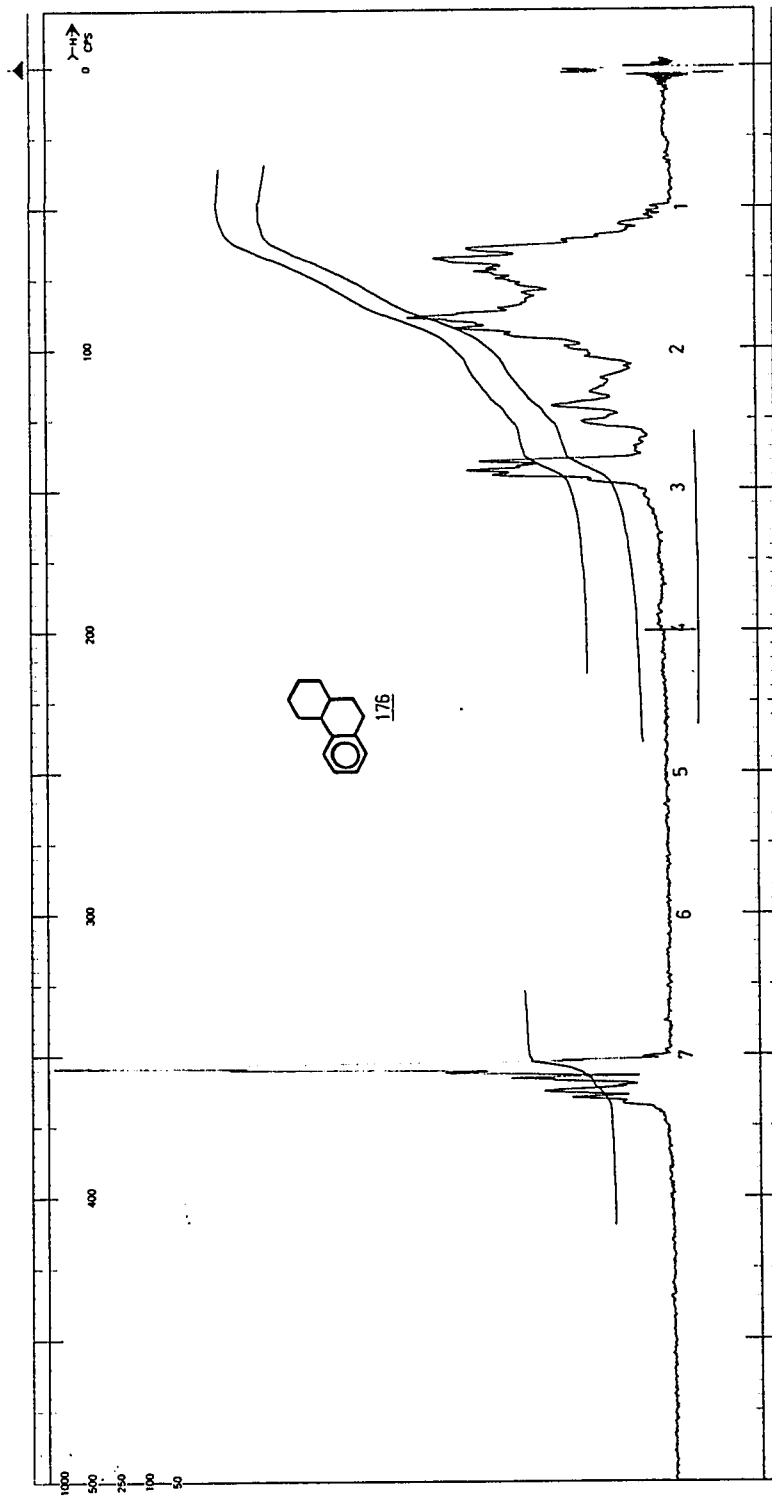


FIGURE 13

## Flash Vacuum Thermolysis Apparatus

