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SYNTHESIS AND REACTIONS OF POTENTIAL BENZOCYCLOBUTENOL PRECURSORS

by

Eva Iversen-Hasselrot, civ. ing.

A thesis submitted to the School of Graduate Studies
in partial fulfillment of the requirments for
the degree of
Master of Science
in the
Department of Chemistry
University of Ottawa
Ottawa, Canada
August, 1981

ABSTRACT.

PART I.

The reactions of 3-(*ortho*-bromophenyl)-1,2-epoxypropane with *n*-BuLi and *n*-BuLi/MgBr$_2$, to yield respectively cinnamyl alcohol and 2-indanol, are described and mechanisms are suggested. In the *n*-BuLi reaction no evidence of an intramolecular attack of the aryl anion at the internal epoxide carbon was observed.

PART II.

Attempts to cyclize styrene oxides, bearing carbanion stabilizing groups such as phenylsulfonylmethyl, cyanomethyl or benzyl groups in the *ortho* position, to benzocyclobutenes via 1,4-elimination of the respective carbanion and subsequent cyclization of the *ortho*-quinodimethane intermediates, were not successful. The products obtained appeared to be polymeric in nature.

Flash vacuum thermolysis of *ortho*-methyl- and *ortho*-benzylstyrene oxide at 770°C/0,1 mmHg gave the rearranged aldehydes as a major product. The aldehydes were accompanied with several deoxygenated, possibly dimeric, products.

PART III.

The cyclization reactions of the carbanion generated from methyl *ortho*-(phenylsulfonylmethyl)-benzoate with dienophiles and simple carbonyl compounds are described and mechanisms are suggested. In the case of benzaldehyde

the cyclization was followed by an elimination to yield the unsaturated sulfone (93).

The reaction between the dianion derived from ortho-(phenylsulfonymethyl)-benzyl alcohol with dimethyl fumarate, diiodomethane and dichlorodimethylsilane were also investigated, with dimethyl fumarate a novel seven-membered lactone (97) was formed.

ACKNOWLEDGEMENTS

I am indebted to my supervisor, Professor Tony Durst for his advice and support throughout this work. Many thanks are due to my colleagues for their cooperation, Margaret Glinski for assistance and useful advices, Raj Capoor for his help with the NMR spectra and Dr John Kraus for help with the Mass spectra. I also wish to thank the technical and administration staff at our department.

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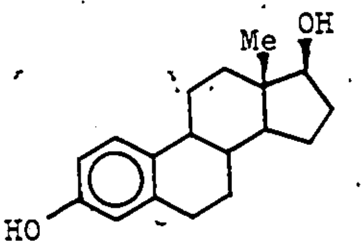
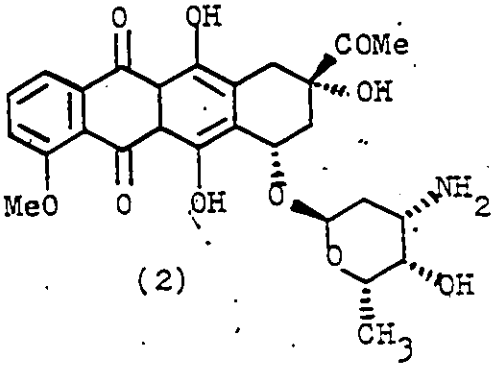
GENERAL INTRODUCTION.

The aglycon portion of many biologically significant natural products consist of polycyclic systems containing aromatic rings. Such systems include steroids, antibiotics and antitumor agents. Well known examples are the female sex hormone estradiol (1) which exists in the body in equilibrium with esterone, another example is dauorubicin[1] (2) which is an antibiotic tried in the treatment of many types of human cancer.



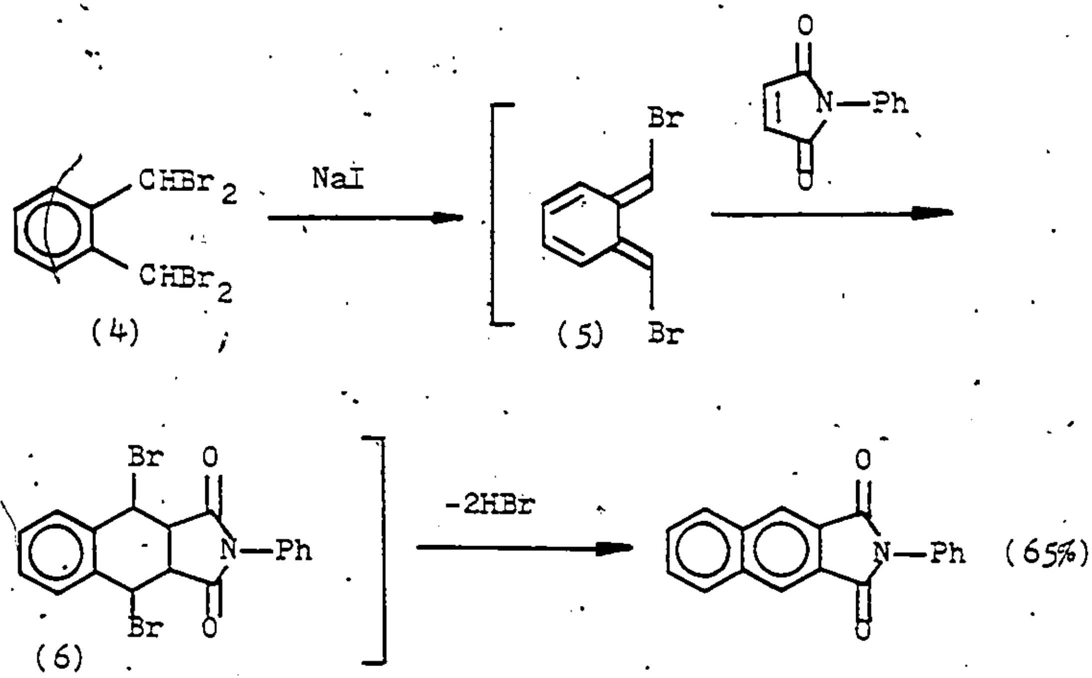
(1)



(2)

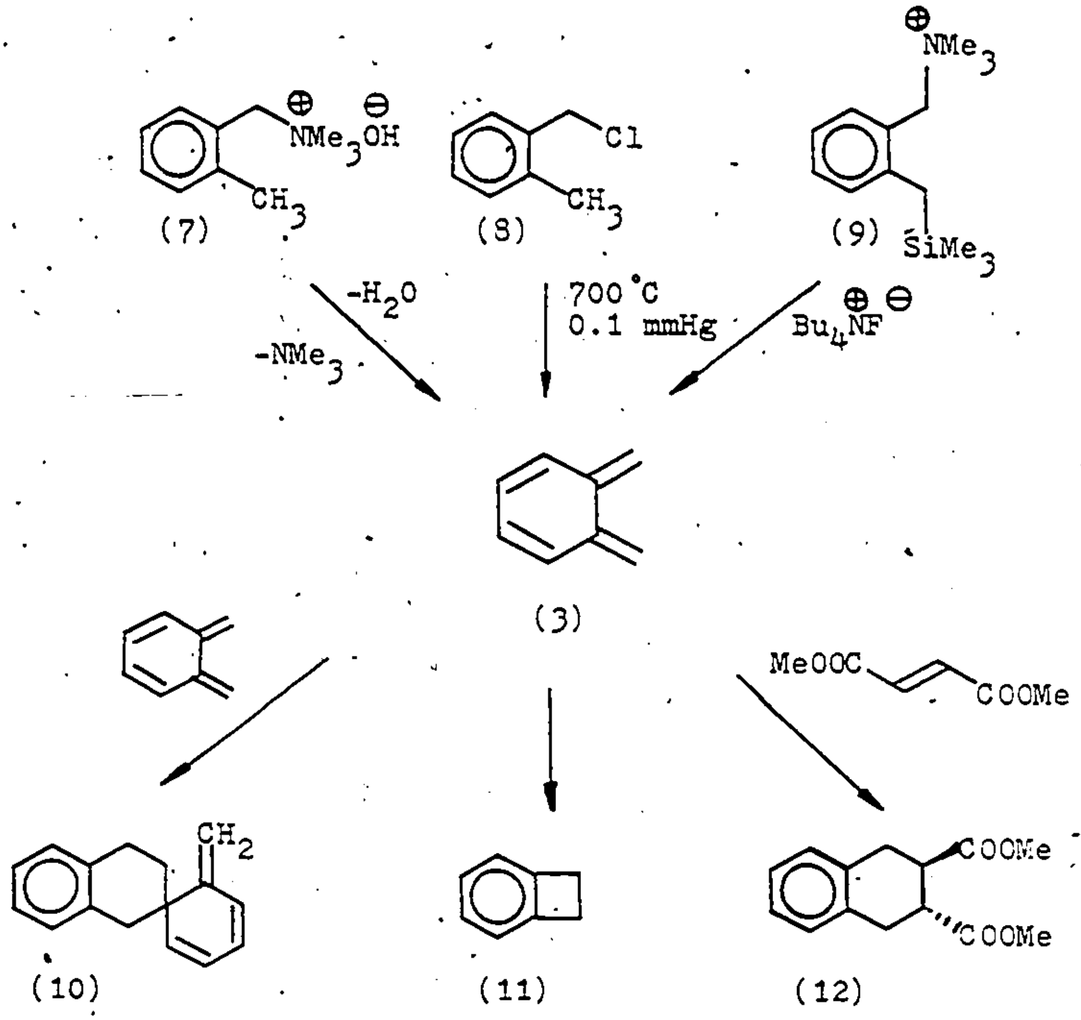
In a review article in 1978 W. Oppolzer[2] described reactions of <u>ortho</u>-quinodimethanes (3). These highly reactive dienes can be generated in a number of ways:

a) By a 1,4-elimination reaction from suitably substituted <u>ortho</u>-xylene derivates. This method represented the first described route to <u>ortho</u>-quinodimethanes and was originally carried out by H. Finkelstein in 1910 and later studied more carefully by M. P. Cava[1]. Cava showed that treatment of the dibromide (4) with NaI generated the intermediate (5) which was trapped with N-phenylmaleimide to yield the tricyclic derivative (6).



In recent years many interesting variations of this 1,4-elimination have been carried out. These have included the thermolysis of the ammonium hydroxide (7)[3], flash vacuum thermolysis of <u>ortho</u>-chloromethyl toluene (8)[4] and most recently the fluoride ion-catalysed elimination of the SiMe$_3$ and NMe$_3$ groups from (9)[5].

As can be seen in Scheme 1 the <u>ortho</u>-quinodimethanes exist only as intermediates and rapidly react in a variety of ways. These include dimerization to (10) via a $4\pi + 2\pi$ cycloaddition, conrotatory electrocyclic ring closure to (11) and trapping with external dienophiles such as dimethyl fumarate to give (12).

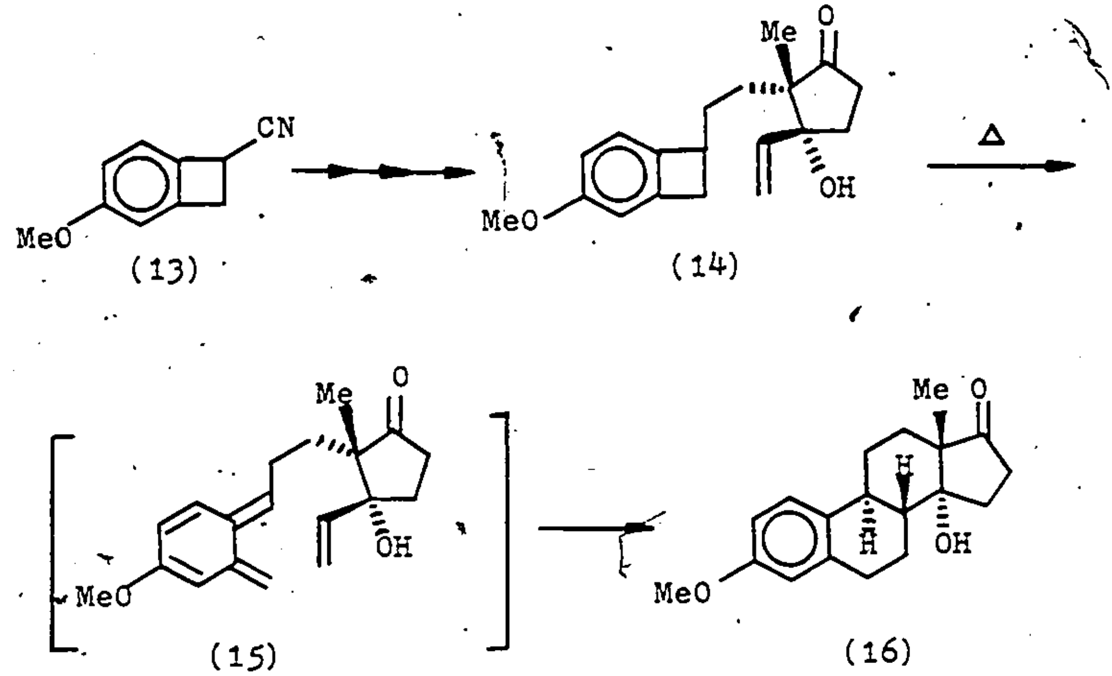


Scheme 1

Related to the above elimination reaction are a series of thermal or photolytic extrusions which have been shown to yield (3). Among these are the loss of SO_2 from benzothiophene-2,2-dioxide at 300°C[2,6], elimination of CO_2 from homophthalic lactones[7], photochemical extrusion of C=O from

2-indanones[2,8] and by loss of N_2 from 3,4-dihydrophthalazines[2,9].

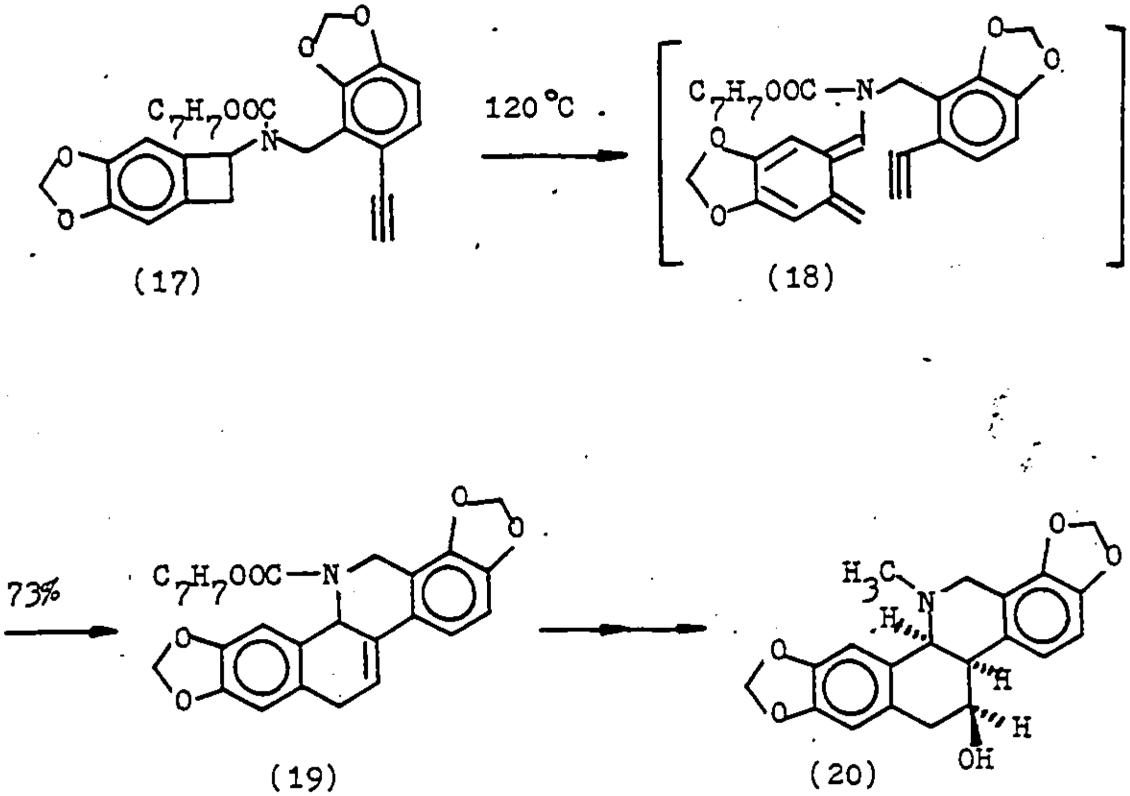
b) By thermal reaction of benzocyclobutenes. Benzocyclobutenes when heated undergo ring opening to ortho-quinodimethanes. Early kinetic and stereochemical studies of 1,2-diphenylbenzocyclobutene addition reactions gave evidence that the opening of the four membered ring (11→3) was a reversible conrotatory opening[10].The intermediate dienes thus generated have been trapped by a variety of dienophiles both inter- and intramolecularly. A number of effective synthesis of important natural products have been reported using the intramolecular trapping of ortho-quinodimethanes as the key step in generation of complex ring systems. These applications have been reviewed by W. Oppolzer[2] and only two examples are briefly described here.



Scheme 2

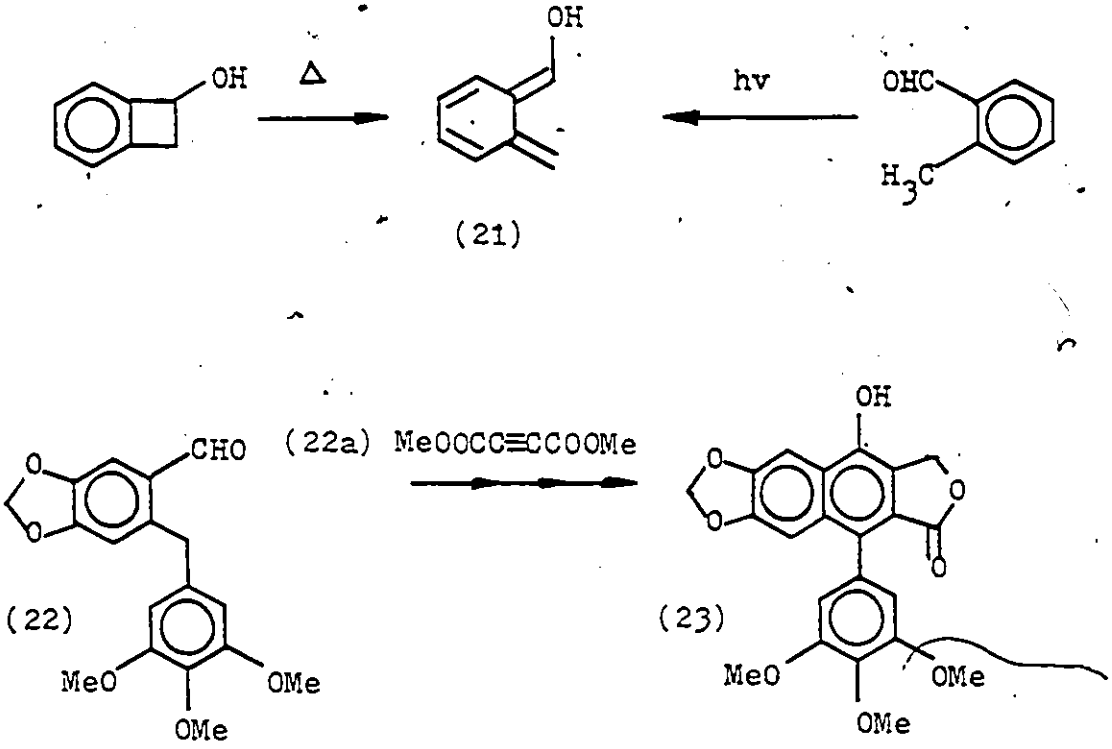
In 1979 T. Kametani et. al.[11] reported a stereoselective total synthesis of 14-α-hydroxyestrone methylether (16). In this synthesis the important step is the opening of the functionalized benzocyclobutene (14), derived from the 1-cyano-4-methoxybenzocyclobutene (13) in a "multistep reaction", to give the ortho-quinodimethane (15) followed by an intramolecular trapping to afford (16) in 45% yield. See Scheme 2.

The key step in a pioneering total synthesis of the alkaloid (±)-chelidonine (20)[12], involved the thermal conversion of the acetylene (17) at 120°C to the ortho-quinodimethane (18) before cyclization to yield (19) in 73%. Subsequent functionalization of the new double bond resulted in a racemic mixture of (20). See Scheme 3.



Scheme 3

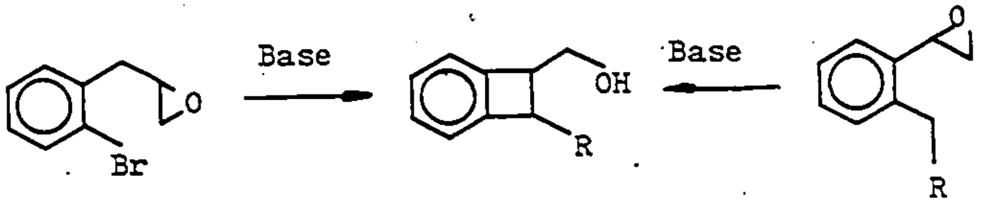
The reactive dienol (21) can be generated either by heating benzocyclobutenol in refluxing toluene or via photoenolization of ortho-tolulaldehyde[13]. Scheme 4. Typically these dienes (21) can be trapped with reactive dienophiles such as acetylenic ester (22a) to give the cycloadducts (22) via an endocyclic addition process. Ortho-substituted benzaldehydes such as (23) have been used as starting material for the synthesis of lignan lactone derivatives[13].



Scheme 4

These results show the importance of cyclobutene derivatives and ortho-quinodimethanes in synthesis. Our intension was to prepare compounds of the type (25). Such compounds occure as intermediates in the conversion (13—14) in Kametani's steroid synthesis[11]. For this we envisaged two approaches.

In Part I we describe our efforts to convert (24) to (25) via an intramolecular opening of the epoxide ring while in Part II the use of the styrene oxides (26) as a route to (25) is investigated. Scheme 5.

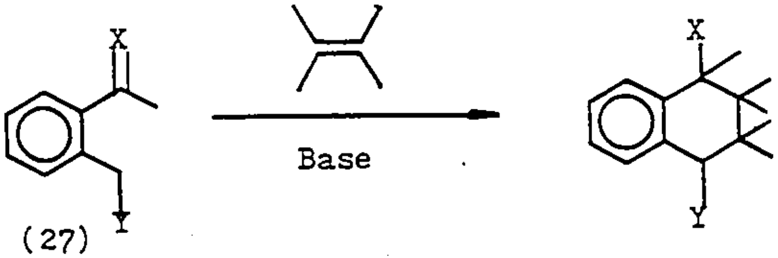


(24) (25) (26)

R=(H,SO_2Ph,CN,Ph,I)

Scheme 5

Finally, in Part III we describe a brief investigation of the reaction of carbanions of the type (27) with Michael-acceptors and electrophiles such as aldehydes, ketones and 1,1-dihalo derivatives. Scheme 6.



(27)

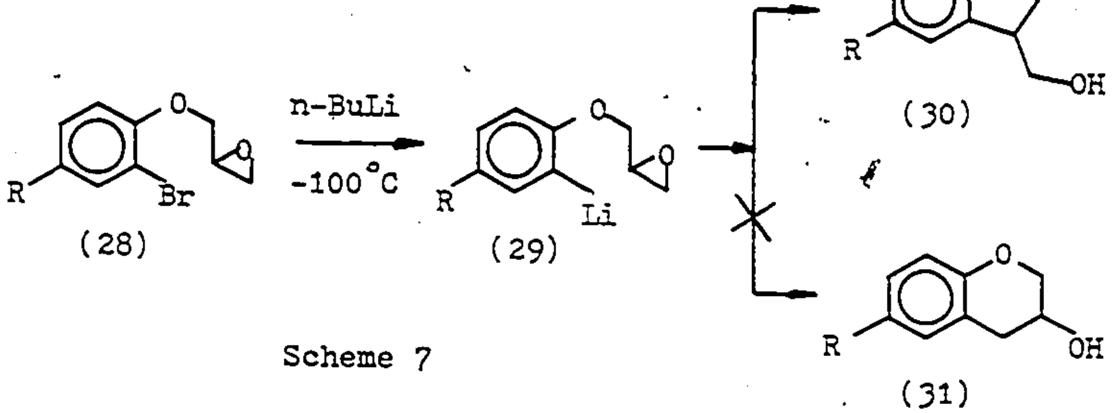
Scheme 6

Part I.

REACTIONS OF 3(ORTHO-BROMOPHENYL)-1,2-EPOXYPROPANE.

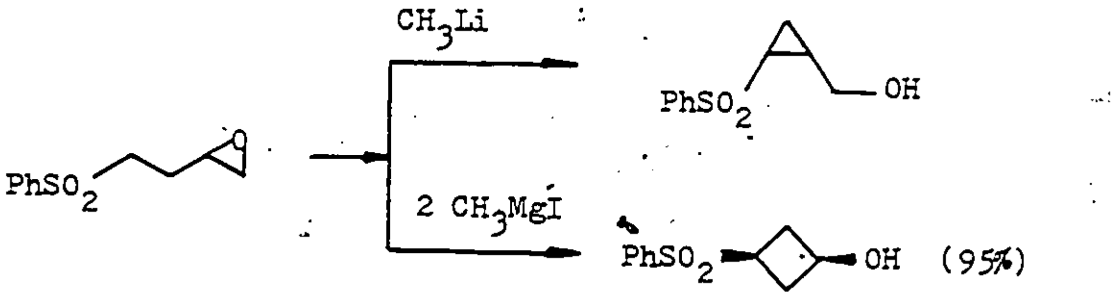
Introduction.

In 1976 C. K. Bradsher and D. C. Reames[14] reported that the ortho-bromo epoxides (28) undergo bromine-lithium exchange at -100°C in a mixture of THF and hexane (4:1) upon treatment with n-butyllithium. The intermediates (29) thus formed cyclize to the five-membered rings (30) but not the six-membered rings (31) following J. F. Baldwin's "rules for ring closure".[10] See Scheme 7.



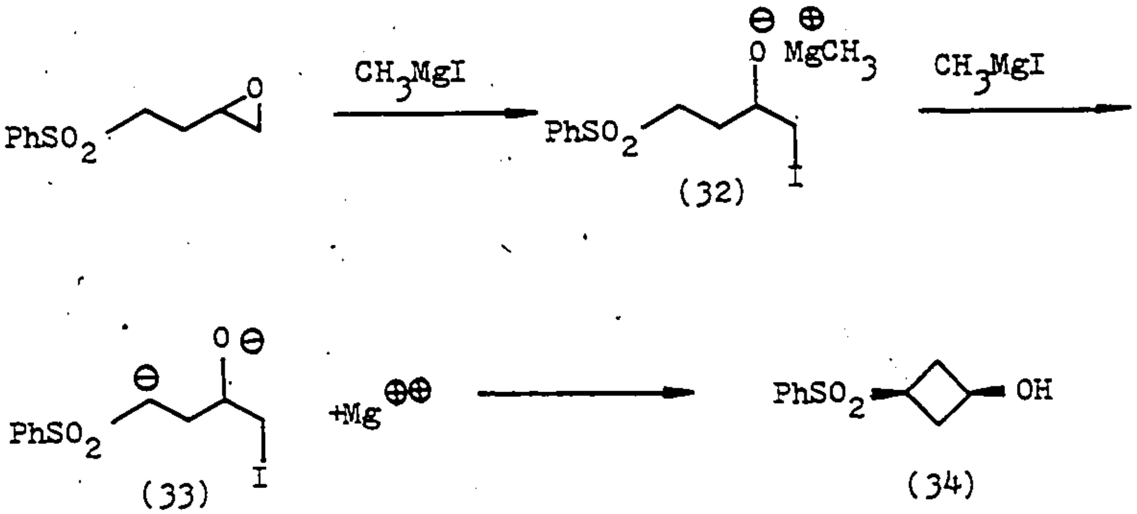
Scheme 7

It has also been reported that the regiochemistry of the intramolecular epoxide opening of epoxysulfones can be altered to favor formation of the larger ring by use of a Grignard reagent rather than an alkyllithium as the base.[15, 16, 17] Scheme 8.



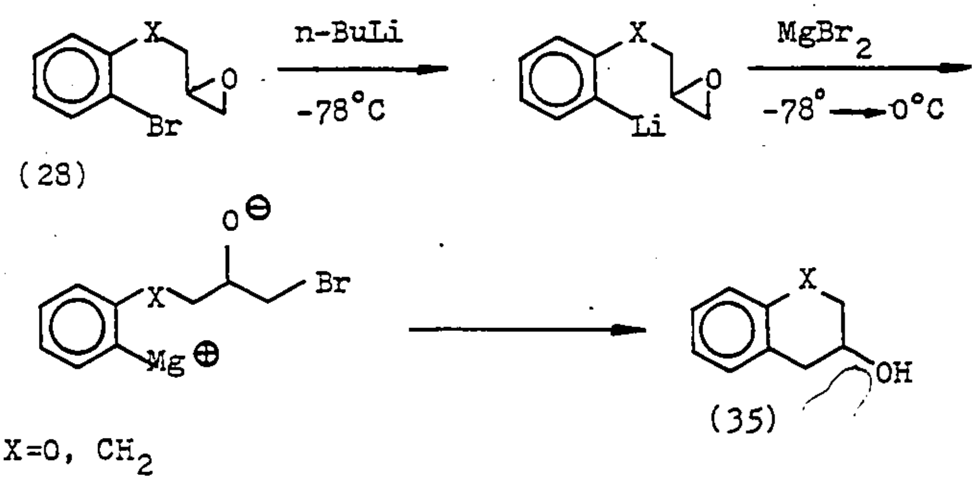
Scheme 8

The Grignard mediated reaction was shown to involve internal opening of the epoxide to an iodoalkoxide (32), formation of an α-sulfonyl Grignard (33) and finally cyclization to (34). Scheme 9.



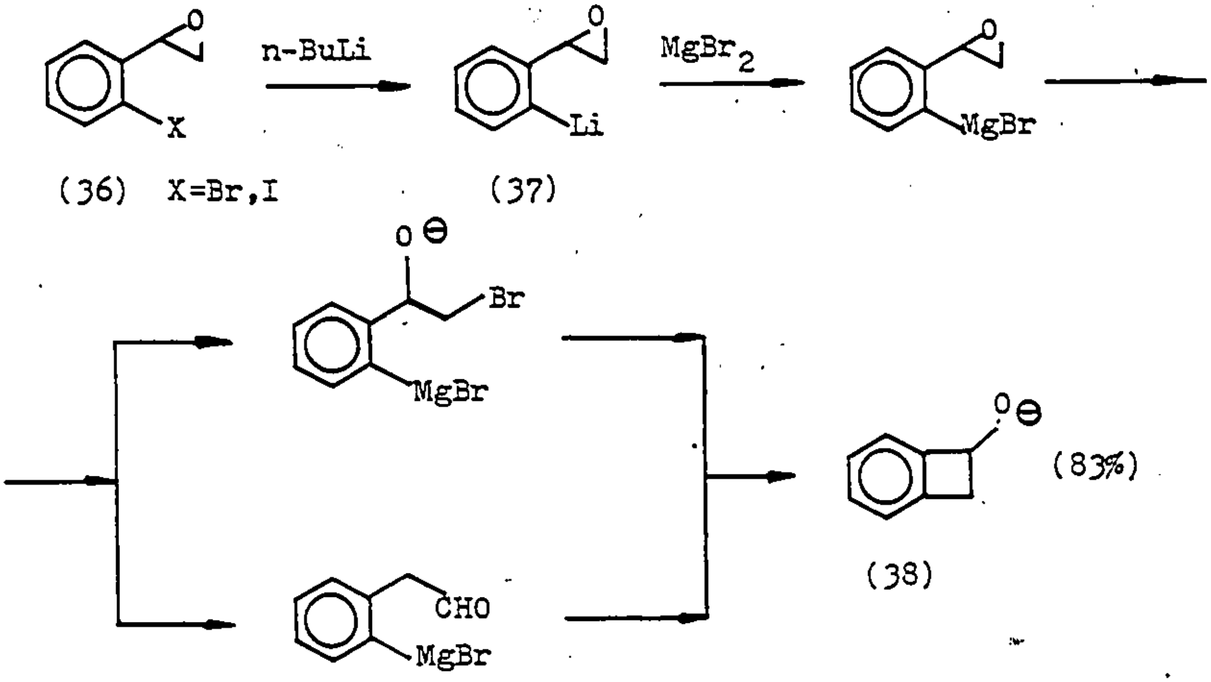
Scheme 9

Application of this idea to the compounds (28) enabled K. L. Dhawan *et. al.*[18] to synthesize the six-membered ring derivatives (35) in good yield. Scheme 10.



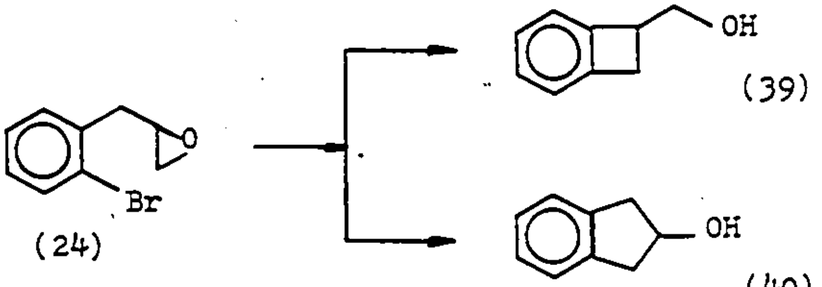
Scheme 10

Halogen-metal exchange without opening of the epoxide ring has also proved possible for a series of ortho-bromo or ortho-iodo styrene oxides (36). The ortho-lithiated epoxides (37) when treated with excess $MgBr_2$ were converted into benzocyclobutenols (38) in excellent yields via the two concurrent pathways shown in Scheme 11.[18]



Scheme 11

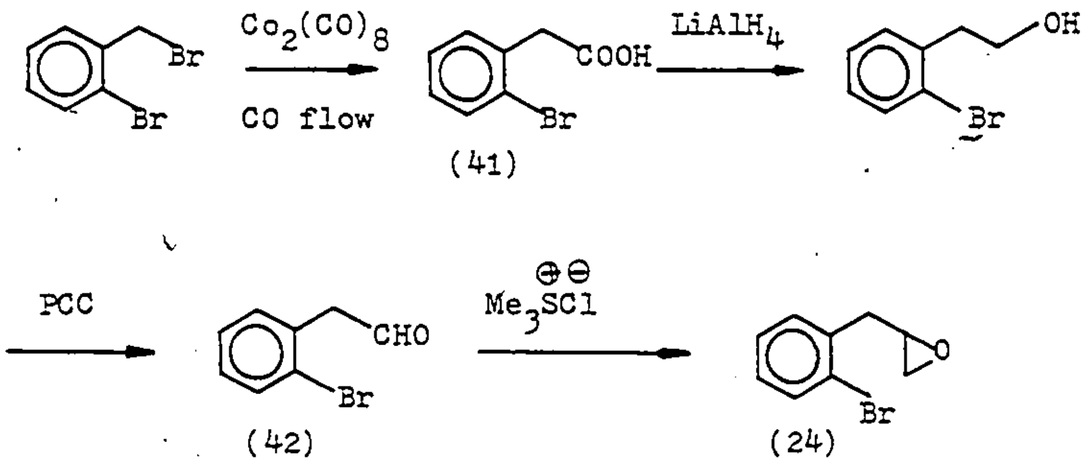
These results suggested the possibility of obtaining either the benzocyclobutene derivative (39) or the benzocyclopentene (40) starting from the epoxide (24) depending on the reaction conditions. See Scheme 12.



Scheme 12

Results and discussion.

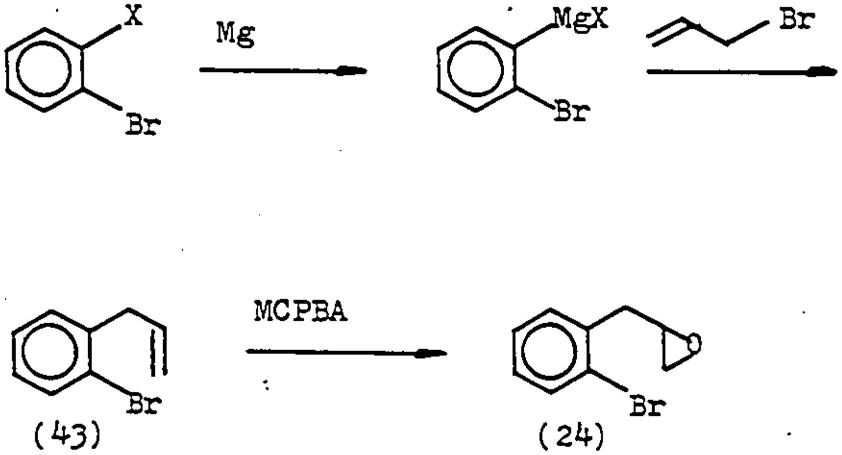
The epoxide (24) was prepared via two different routes. In the first *ortho*-bromophenylacetic acid (41) was generated from *ortho*-bromobenzyl bromide by using $Co_2(CO)_8$ and carbon-monoxide flow in a phase-transfer reaction[i]. The acid was converted to the corresponding aldehyde (42) by reduction with $LiAlH_4$ followed by oxidation with pyridinium chlorochromate. The overall yield was 22%. The aldehyde (NMR: -CHO at δ=9,63 as a triplet J=2 Hz and $-CH_2$ as a doublet at δ=3,83 J=2 Hz) was treated with trimethylsulfonium chloride in a phase-transfer reaction to give the epoxide (24) in 33% yield.[18] The epoxide (24) had in the NMR aliphatic H's at δ =2,25-3,50 as a complex multiplet, integrating for 5 H, aromatic H's at δ =6,75-7,60 as a multiplet, integrated as 4H. Scheme 13.



Scheme 13

i) The author would like to thank S. Amaratunga for the $Co_2(CO)_8$ and technical help in preparation of (41).

A second route to the epoxide (24) involved epoxidation of o-allylbromobenzene[19,20]. To prepare additional quantities of (24) this route was followed starting either with 1,2-iodobromobenzene or with 1,2-dibromobenzene and magnesium metal[21]. Scheme 14.

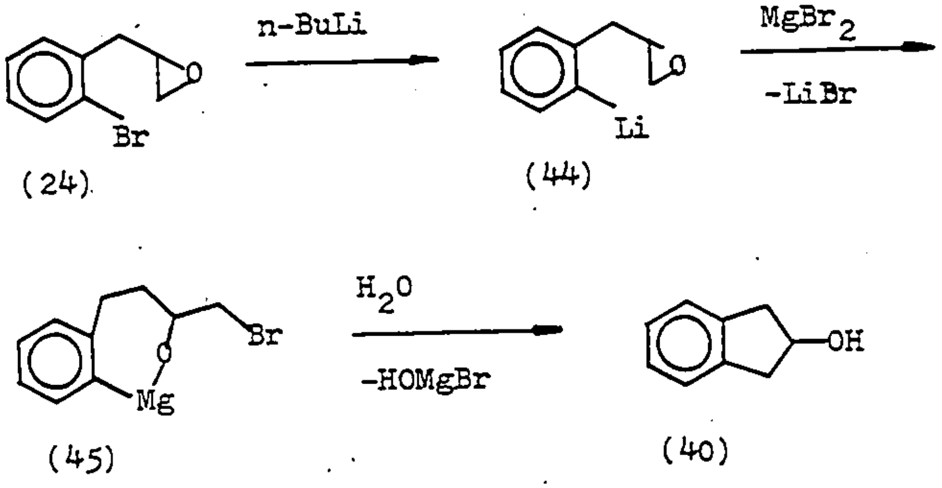


Scheme 14

The Grignard reagent (43a) was reacted with allylbromide to form ortho-allylbromobenzene (43) which was epoxidized with meta- chloroperoxybenzoic acid to give after purification the epoxide (24). The overall yield, starting from either of the dihalogenated benzenes, was only 11%. The low yield was mainly due to unreacted starting material which was impossible to separate from the ortho-allylbromobenzene (43), despite the use of home-made medium pressure chromatography columns[22]. The NMR spectra of (24) prepared via both routes were identical.

Treatment of the epoxide (24) with n-BuLi at -78°C for 2 minutes followed by the addition of $MgBr_2$ and subsequent warming to room temperature, resulted in the formation of one major product, which was purified by chromatography and recrystallization from ether/hexane to give 59% yield of white needlelike crystals identified as 2-indanol. (m.p. 68 -70°C, Aldrich: m.p. 68 -71°C) NMR: -OH at δ=1,72 as a singlet, $2H_B$ at δ=2,92 doublet of doublets J_{BX}=4 Hz J_{AB}=16 Hz, $2H_A$ at δ=3,26 doublet of doublets J_{AX}=6 Hz J_{AB}=16Hz, $1H_X$ at δ=4,69 multiplet and 4 aromatic H's at δ=7,10-7,30 multiplet. The published NMR-spectra for 2-indanol[23] is: -OH at δ=1,80, $2H_B$ at δ=2,85 doublet of doublets J_{BX}=4 Hz J_{AB}=16 Hz, $2H_A$ at δ=3,20 doublet of doublets J_{AX}=6 Hz J_{AB}=16 Hz, $1H_X$ at δ=4,65 multiplet and 4 aromatic H's at δ=7,10-7,30 multiplet.

The mechanism for the formation of 2-indanol (40) is shown in Scheme 15 and is based on earlier work.[15, 16, 17, 18]

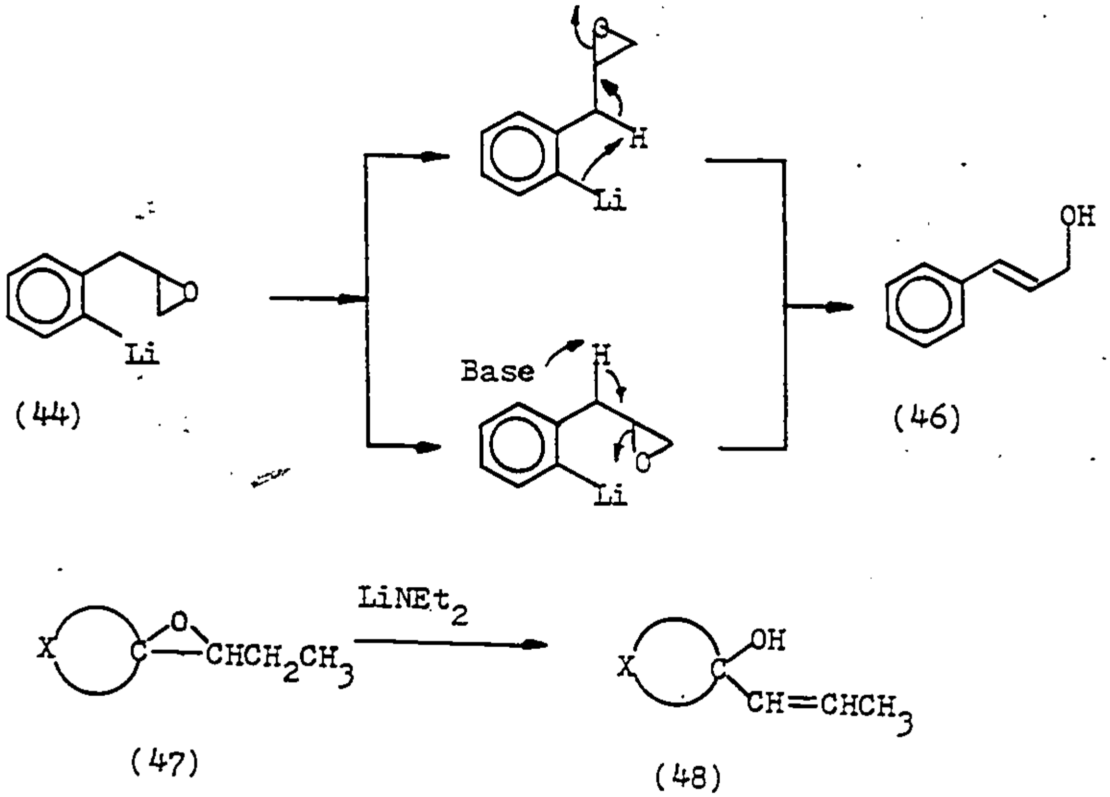


Scheme 15

In this mechanism lithium replaces bromine followed by metal exchange upon addition of excess $MgBr_2$, the epoxide ring is opened preferentially to (45) followed by intramolecular cyclization to give (40), after quenching with water.

When the lithioepoxide (44) was warmed to room temperature the major reaction product was isolated by silica gel column chromatography and identified as cinnamyl alcohol (46) in 27% yield. No other materials could be identified and and none of the desired benzocyclobutene derivative (25) was apparently formed as judged by a NMR-examination of the crude reaction product.

The mechanism of the conversion of (24) to cinnamyl alcohol could be either via an intra- or intermolecular pathway. The reaction of substituted epoxides with lithium diethylamide (47) gives allylic alcohols[24, 25] (48). The conversion (44→46) appears to be related to this general reaction. Scheme 16.



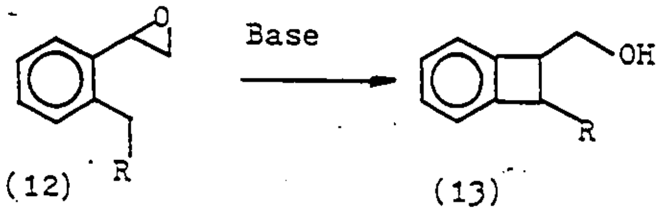
Scheme 16

Part II.

REACTIONS OF ORTHO-SUBSTITUTED STYRENE OXIDES.

Introduction.

The goal of the research described in this part of the thesis was to investigate the possibility of effecting the reaction shown in Scheme 17.

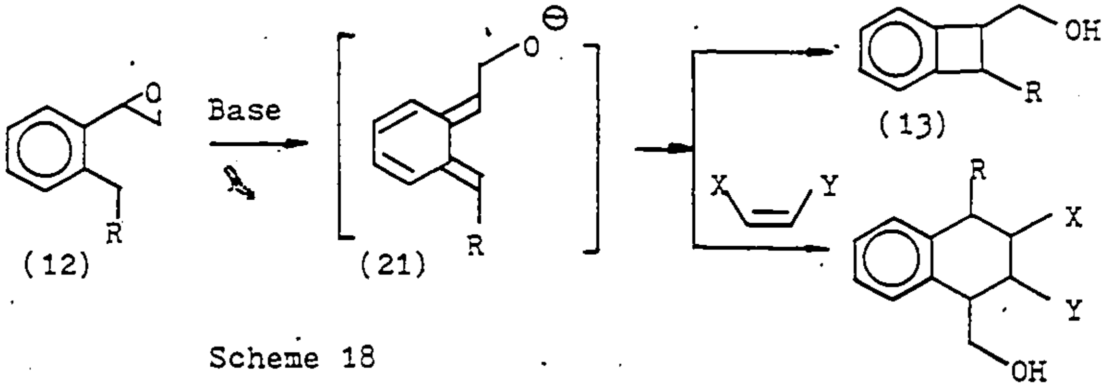


Scheme 17

R:

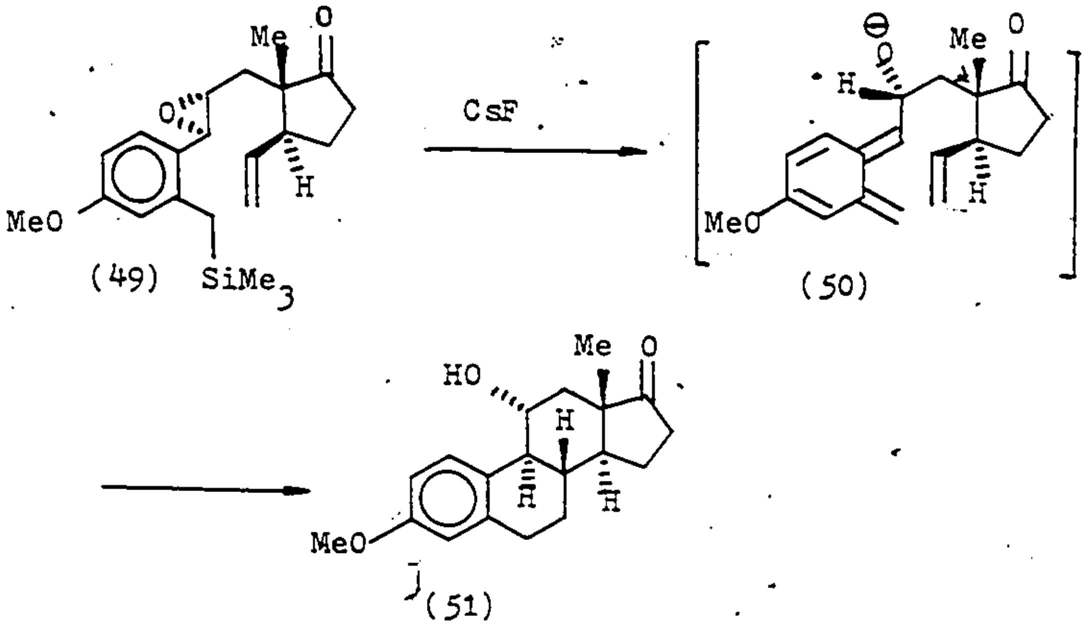
a = Br
b = SPh
c = SO_2Ph
d = CN
e = Ph
f = H
g = I

It has been mentioned in the introduction that an easy acess to compounds of the type (13) would be of considerable synthetic importance[11]. The interconversion was expected to occur via a base-catalysed 1,4-elimination from (12) to give the intermediate (21) which might either cyclize to (13) or be trapped by a dienophile. Scheme 18.



Scheme 18

During the course of this research S. Djuric <u>et.</u> <u>al.</u>[26] reported a sucessful application of the above reactions. These workers were able to show that reaction of the <u>ortho-</u> (trimethylsilylmethyl)-styrene oxide derivative (49) with CsF in diglyme at 27 °C gave 70% yield of 11α-hydroxyesterone methylether (51).



Scheme 19

The high affinity of F^- for silicon (Si-F 540-570 kJ/mol) is the key to this reaction. Attack of F^- at the trimethylsilyl group generates the electron pair which can cause the 1,4-fragmentation reaction to yield the intermediate (50). See Scheme 19.

In our work we investigated the reactions of the derivatives of (12) where R= SO_2Ph, CN, Ph, H and I. The choice of sulfone was based on it's:

a) carbanion stabilizing effect. Thereby allowing the generation of (21).

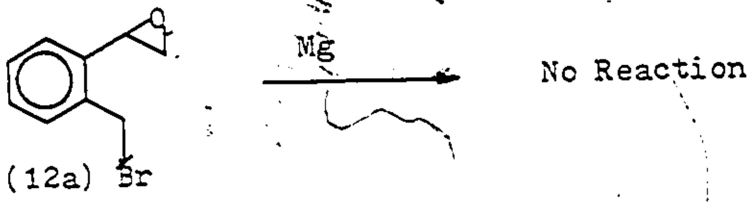
b) ability to introduce electrophiles α to it via the α-sulfonyl carbanion.

c) ability to be hydrogenolyzed by Na/Hg to give derivatives with no sulfur.

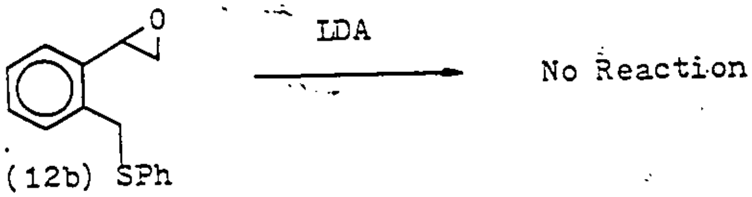
d) ready-availability.

The nitrile derivative has similar properties to the sulfone. In addition it represents a carbon substituent in (13) which could easily be modified into -COOH, -CHO and $-CH_2NH_2$ functions.

Prior to this work M. Glinski was investigating the reactions of (12a) and (12b) which turned out to be unsuccessful.



(12a)

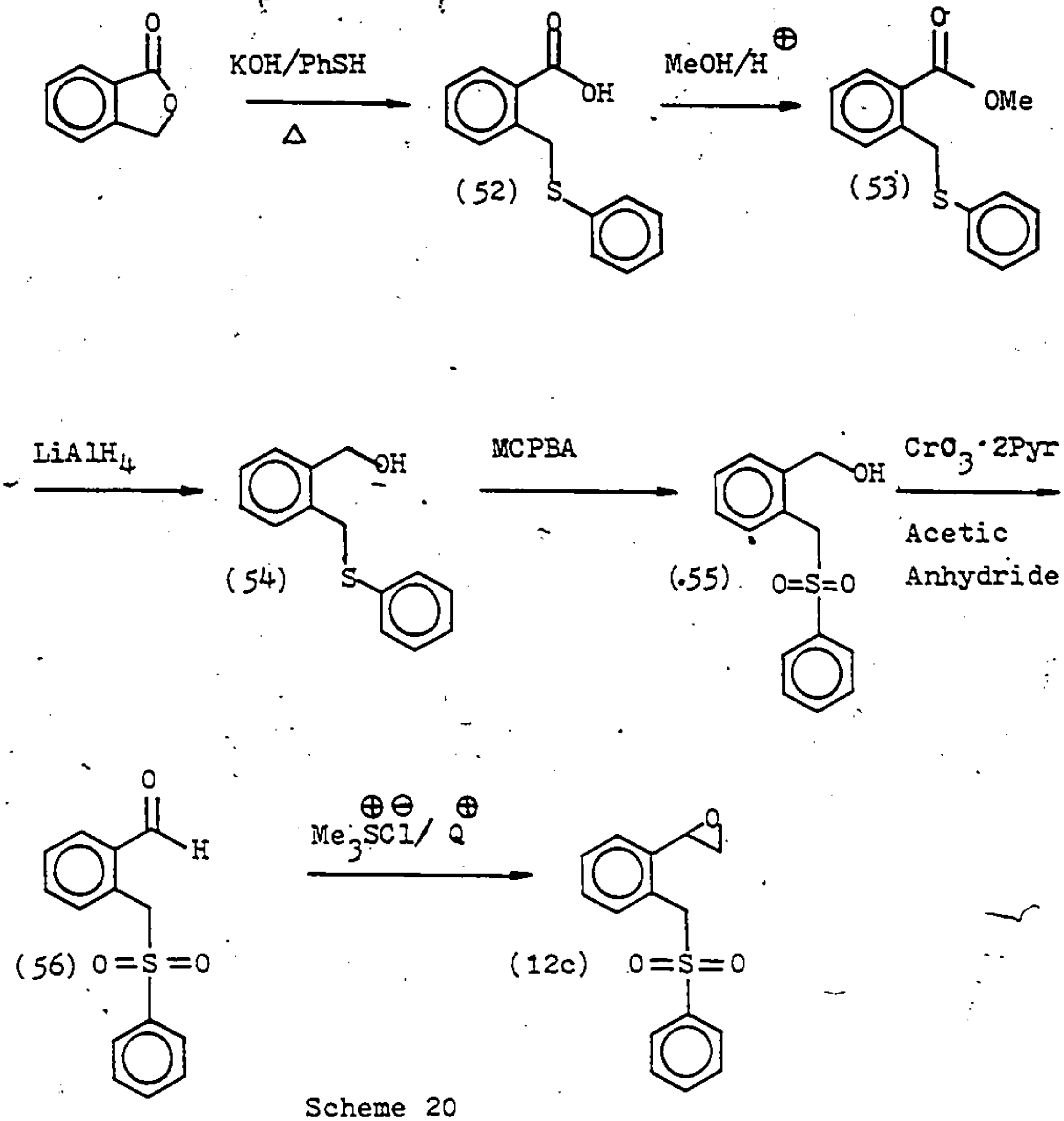


(12b)

The probable reason for these results is that in the case of the sulfide (12b) the carbanion is not formed, because the sulfide does not sufficiently stabilize a benzylic carbanion. The use of the sulfone should increase electron withdrawal from the carbanion and therefore stabilize it. In the case of the bromide (12a) it appears that it is simply not reactive enough to form the Grignard reagent, possibly due to the steric hindrance of the <u>ortho</u>-substituent.

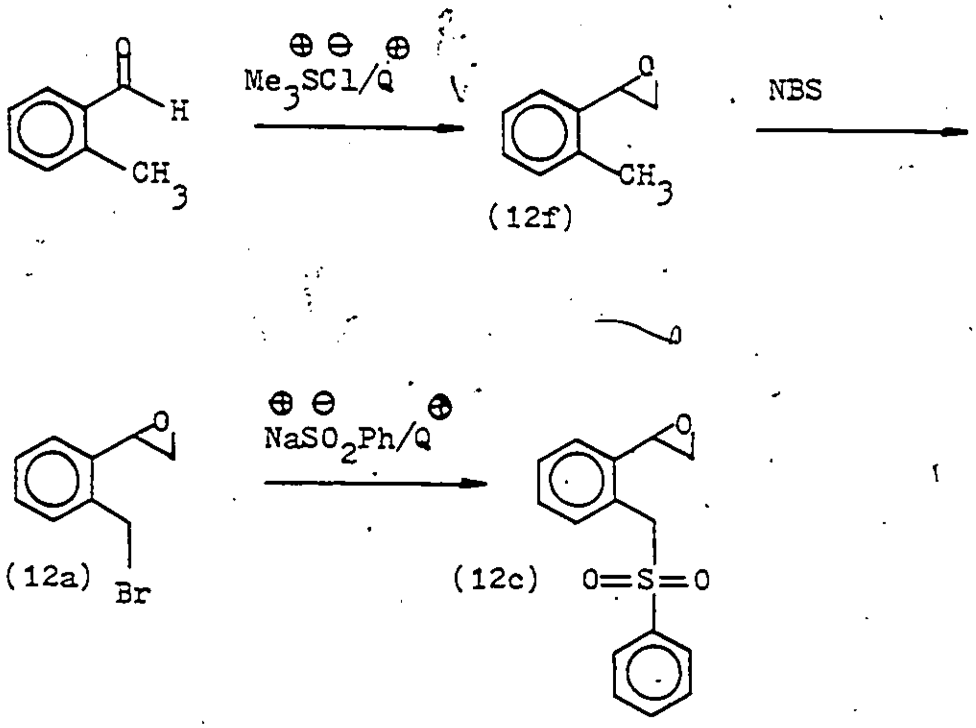
-Results and discussion.

Ortho-(phenylsulfonylmethyl)-styrene oxide (12c) was prepared via two different routes. In the first ortho-(phenylthiomethyl)-benzoic acid (52) was generated in 87% yield from phthalide by refluxing with KOH and thiophenol in 2-propanol. The acid was converted to the corresponding alcohol in 77% over-all yield via esterification to the methylester (53) followed by reduction with $LiAlH_4$. This alcohol (54) (m.p. 66-67°C, and NMR; $-OH$ δ=2,68, $-CH_2SPh$ δ=4,14, $-CH_2OH$ δ=4,68) was oxidized with 2 equivalents of meta-chloroperoxybenzoic acid to the ortho-(phenylsulfonylmethyl)-benzyl alcohol (55) in quantitative yield (m.p. 136-138°C, and NMR: $-OH$ δ=3,07, $-CH_2SO_2Ph$ δ=4,51, $-CH_2OH$ δ=4,57). Oxidation of this alcohol with pyridinium chromate and acetic anhydride^{27} gave the aldehyde (56) (m.p. 140-142°C, and NMR: $-CH_2SO_2Ph$ δ=5,06, $-CHO$ δ=9.93) in 63% yield. The epoxidation with trimethylsulfonium chloride was carried out under phase-transfer conditions (CH_2Cl_2/ 50% NaOH and $PhCH_2\overset{\oplus}{N}Et_3\overset{\ominus}{Cl}$) to afford the styrene oxide (12c) in 69% yield. The over-all yield of (12c) (m.p. 79-80°C) from phthalide was 33%. The styrene oxide (12c) had a NMR spectrum that showed the typical ABX pattern for the epoxide function: H_A δ=2,50 J_{AB}=5,6 Hz J_{AX}=2,6 Hz, H_B δ=3,03 J_{AB}=5,6 Hz J_{BX}=4.1 Hz, H_x δ=3,90 J_{AX}=2,6 Hz J_{BX}=4.1 Hz; the benzylic CH_2 showed an AB pattern because of the chiral center on the epoxide ring δ=4.42 and δ=4.59 J_{AB}=14,1 Hz (see Appendix 1 Figure 1). Scheme 20.



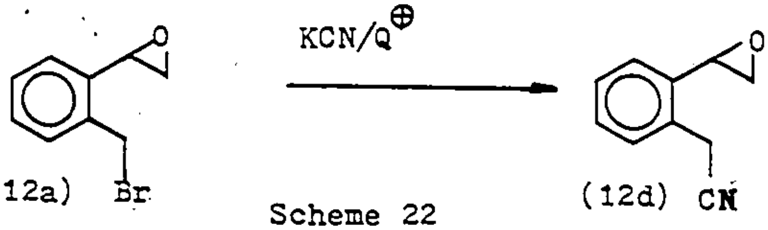
Scheme 20

In the second route *o*-tolualdehyde (commercially available) was epoxidized with trimethylsulfonium chloride to give the *ortho*-methyl-styrene oxide (12f) in 88% yield (b.p. 57-59°C/ 0,32 mmHg, NMR: $-CH_3$ $\delta=2,50$ singlet, and the epoxide ABX pattern with H_A $\delta=2,73$ $J_{AB}=5,8$ Hz $J_{AX}=2,7$ Hz, H_B $\delta=3,20$ $J_{AB}=5,7$ Hz $J_{BX}=3,7$ Hz and H_X $\delta=4,05$ $J_{AX}=2,70$ Hz $J_{BX}=3,7$ Hz). The methyl group was brominated with N-bromosuccinimide to give *ortho*-(bromomethyl)-styrene oxide (12a) in 92% yield (b.p. 122-124°/0,75 mmHg, the NMR spectrum showed the typical ABX pattern for the epoxide portion and the benzylic -CH_2Br showed an AB pattern similar to that described for (12c)). The compound (12a) has the very unpleasent qualities of a strong lachrymator and skin irritant. In the conversion of (12f) to (12a) little or no hydrogen abstraction occured from the benzylic epoxide position. The bromine was exchanged for a phenylsulfonyl group via a phase-transfer reaction (CH_2Cl_2/H_2O, $PhSO_2^{\ominus}\,Na^{\oplus}$ and $PhCH_2\overset{\oplus}{N}Et_3\overset{\ominus}{Cl}$) to give the styrene oxide (12c) in 68% yield. The NMR spectrum was identical with that obtained from the first route. Scheme 21.



Scheme 21

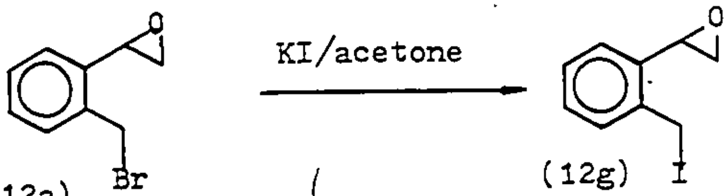
The ortho-(cyanomethyl)-styrene oxide (12d) was prepared by treatment of (12a) with potassium cyanide in a phase-transfer reaction (CH_2Cl_2/H_2O and $PhCH_2\overset{\oplus}{N}Et_3\overset{\ominus}{Cl}$) to give (12d) (42 %).The NMR spectrum again showed the expected ABX pattern for the epoxide hydrogens but in this case the benzylic hydrogens in the CH_2CN group appeared as a singlet in contrast to the comparable $-CH_2SO_2Ph$ group in (12c) where they occured as a AB system.



(12a) (12d)

Scheme 22

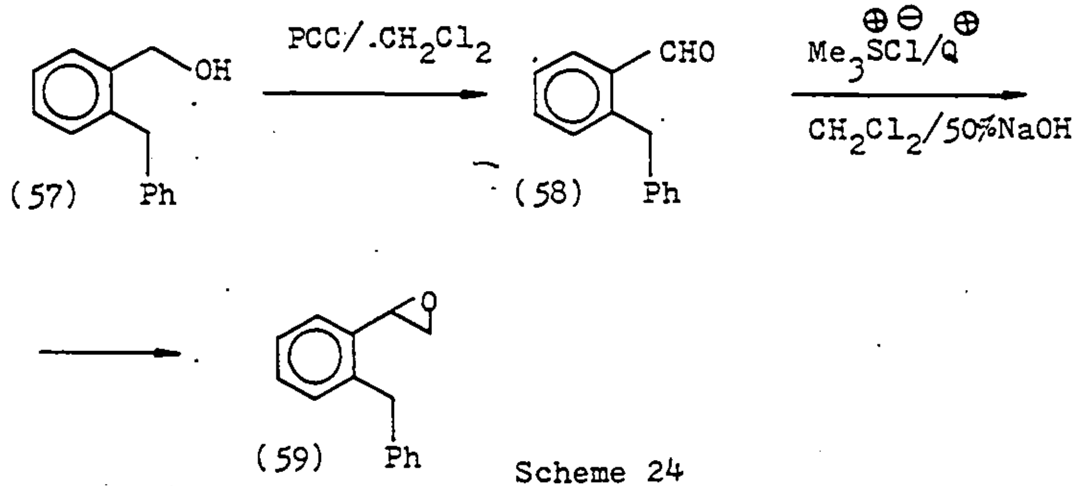
The ortho-(bromomethyl)-styrene oxide (12a) was transfered into the iodo derivative (12g) (crystals melting at room temperature) in 42% yield, by treatment with potassium iodide in refluxing acetone for 26 hours. Scheme 23. The NMR spectrum of (12g) showed the characteristic ABX pattern for the epoxide protons and an AB pattern for the benzylic $-CH_2I$ protons.



(12a) (12g)

Scheme 23

The ortho-benzyl-styrene oxide (12e) was prepared from ortho-benzyl-benzyl alcohol (57)[27] by oxidation with pyridinium chlorochromate in CH_2Cl_2 to the aldehyde (58) in 88% yield (NMR: $-CH_2Ph$ δ=4.40 singlet, -CHO δ= 10,57 singlet). The aldehyde (58) was reacted with trimethylsulfonium chloride in a phase-transfer reaction (CH_2Cl_2/50% NaOH and $PhCH_2\overset{\oplus}{N}Et_3\overset{\ominus}{Cl}$) to give the ortho-benzyl-styrenoxide (12e) in 50% yield (slightly yellow oil, NMR: the epoxide protons showed the usual ABX pattern and the benzylic $-CH_2Ph$ protons showed up as a singlet, see Appendix 1 figure 2). The over-all yield from (57) to the styrene oxide (12e) was 44%. Scheme 24.

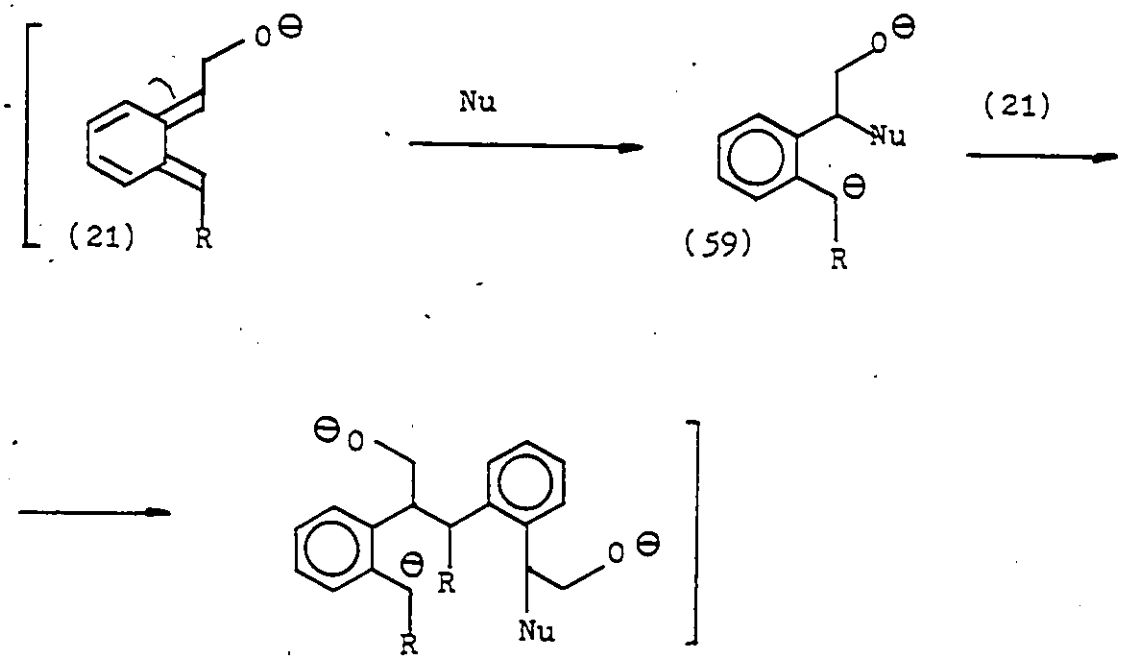


Scheme 24

The styrene oxides (12e→12g) were each treated with either LDA or n-BuLi. The reactions were generally kept at -78°C for various periods of time and then allowed to warm to room temperature prior to quenching with a saturated aqueous ammonium chloride solution. The quenching was generally carried out after TLC examination of the reaction mixture had indicated the disappearance of starting material or that no change of the reaction occured after an extended period of time. In the case of the sulfone (12c) and nitrile (12d) addition of a solution of LDA in THF at -78°C gave an immediate dark brown solution. This was taken as an indication that the desired carbanion had been generated. During the reaction period this colour tended to persist or lighten to almost yellow. Examination of the reaction mixture obtained from the nitrile (12d) by TLC with various solvent systems showed a very large number of spots stretching from the base-line to the solvent front. The NMR spectrum of the crude product showed only very broad signals in several regions including the aromatic part (δ=6,20-8,20). In addition there was evidence for the incorporation of diisopropylamine (doublet at δ=1,27). Both the NMR and TLC were suggestive of the formation of series of oligomeric/polymeric products. Since no product seemed to be formed in major proportions this reaction was not further investigated.

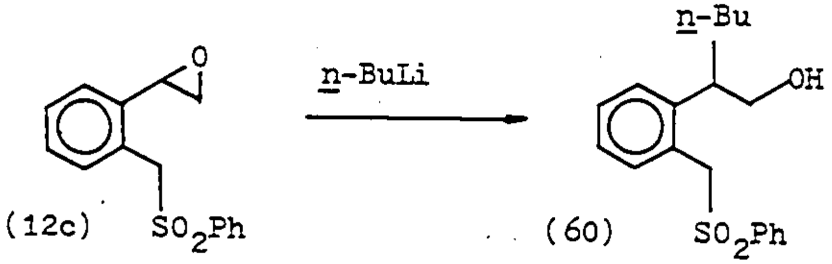
The reaction of the sulfone (12c) with LDA (a/ 45 min. at -78°C, → room temperature; b/ 30 min. at -78°C; followed by quenching with aqueous NH_4Cl) looked more promising. TLC investigation of the crude reaction mixture indicated the absence of starting material and the formation of two major products, both more polar than the starting material. Despite considerable efforts no pure product could be separated by silica gel chromatography, in spite of the reasonable separation which appeared on analytical TLC. The "products" were eluted in only very small quantities and never as pure samples.

In these cases also the NMR spectra of both the crude product and the various chromatography fractions could not be interpreted. The reason for formation of very complicated mixtures from (12c) and (12d) is possibly due to the expected high reactivity of the intermediates (21, R=SO_2Ph, CN). The electron withdrawing character of the -SO_2Ph and -CN groups should make these dienes highly susceptible to any nucleophile present in the reaction mixture. Such an addition would generate the intermediate (59), which itself could add to any (21) present in the mixture. A number of such reactions would lead to a variety of oligomeric products. Scheme 25.



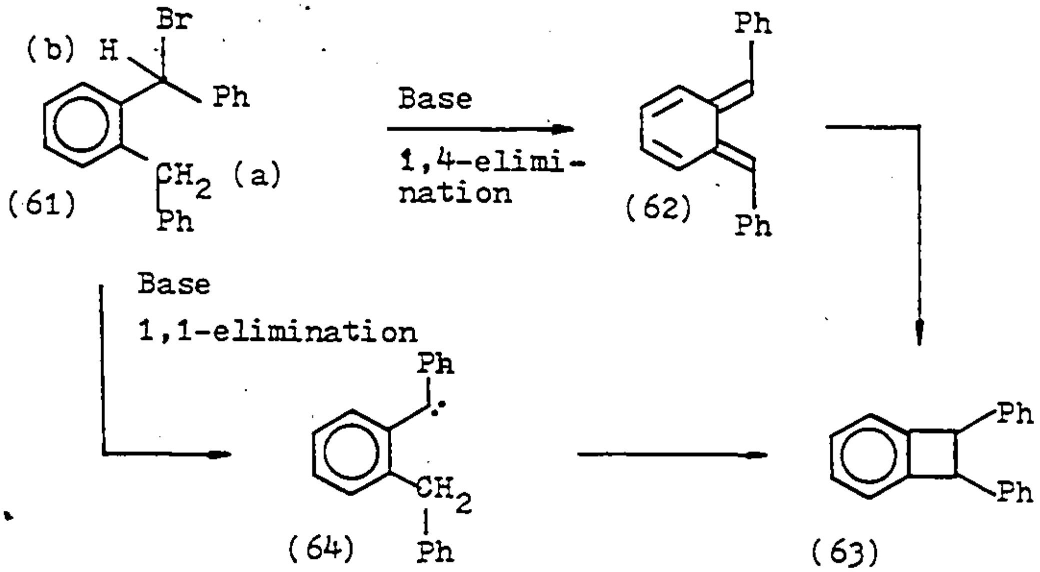
Scheme 25

A similar result was observed by B. Gowland[28]. The reaction of (12c) with n-BuLi in THF at -78°C immediately produced a yellow coloured solution. The reaction mixture was kept at -78°C for 5 min., then warmed to room temperature and quenched with aqueous NH_4Cl. The NMR spectrum of the crude product indicated considerable incorporation of butyl groups, possibly via direct opening of the epoxide, or by addition of n-butyl lithium to the intermediate (21) thereby generating (59), or a combination there of. The former possibility is considered less likely since such a reaction should yield a single product, namely the alcohol (60) (Scheme 26), and epoxide opening by n-BuLi is not expected to be as rapid as the formation of a benzylic-α-sulfone carbanion. From earlier work in this laboratory it had been shown that (36) underwent Br—Li exchange with n-BuLi without epoxide cleavage[18]. The TLC of the above reaction mixture showed many products, again suggesting polymeric material as described in Scheme 25.



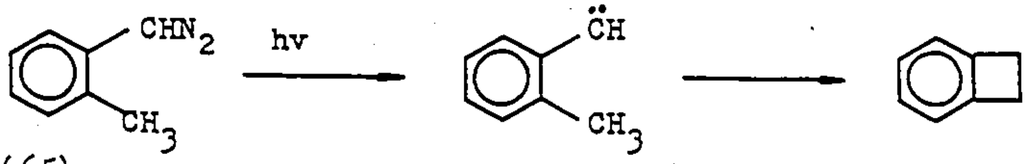
Scheme 26

In a communication in 1958 F. R. Jensen and W. E. Coleman[29] reported (without experimental details) that α-bromo-α,α'-diphenyl-ortho-xylene (61) cyclizised to the 1,2-diphenyl-ortho-cyclobutene (63) when treated with base. This result initially suggested to us that the benzylic hydrogens (a) in (61) might be acidic enough to allow an 1,4-elimination to (62). We felt that a similar elimination could result from (61) to give (63). Further consideration of the mechanism for the the formation of (63) from (61) indicated the possibility that (63) might be formed over the carbenoid (64). The benzylic hydrogen (b) α to Br, would certainly be more acidic than the hydrogens of the CH_2 group. Abstraction of this hydrogen followed by loss of Br would generate (64). Intramolecular hydrogen abstraction would then give the benzocyclobutene (63). See Scheme 27.



Scheme 27

The photolysis of ortho-methylphenyldiazomethane (65) has been reported[30] to yield benzocyclobutanes. Scheme 28.



(65)

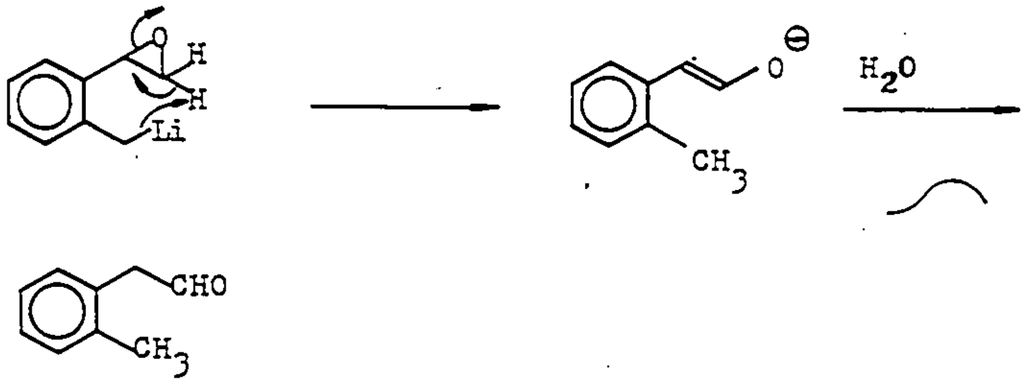
Scheme 28

Despite the possibility that the formation of (63) from (61) might not proceed via 1,4-elimination we carried out the reactions of (12e) both with LDA and n-BuLi following the same reaction conditions as described for (12c) and (12d).

In the case of the LDA reaction the NMR of the crude product indicated that 55%of the starting material (12e) was left together with several products containing the diisopropylamine function. No evidence for cyclobutene formation was found.

When the styrene oxide (12e) was treated with n-BuLi at -78°C in THF a brown solution developed. The reaction was slowly warmed to room temperature and quenched as usual. TLC showed no trace of starting material but once again many small spots ranging from the baseline to the solvent front. (4:1 hexane/ethyl acetate). The NMR of the crude reaction mixture showed considerable n-butyl group incorporation. The poor resolution in the spectrum suggested probable polymer formation.

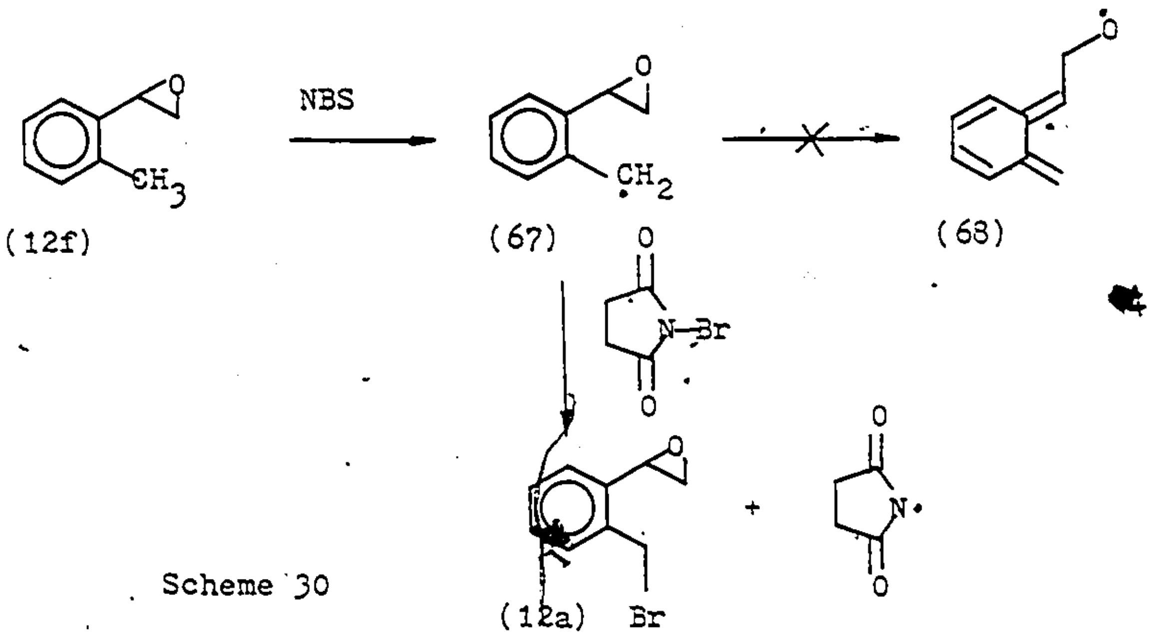
Finally, reaction of ortho-methyl-styrene oxide (12f) with respectively LDA or n-BuLi gave results similar to those obtained for (12e). With LDA the major isolated product was recovered starting material, while n-BuLi treatment gave some recovered starting material but mainly polymeric products and a small amount (13% by NMR) of material which surprisingly showed the presence of an aldehyde function. This was tentatively identified as <u>ortho</u>-methylphenylacetaldehyde (66) (NMR $-CH_3$ δ=2,23, $-CH_2-$ δ=3,63 doublet J=2 Hz and -CHO δ=9,66 triplet J=2 Hz). The formation of such a product is totally unexpected but a possible mechanism is shown in Scheme 29.



(66)

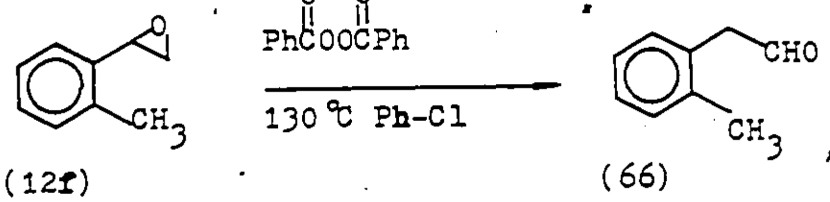
Scheme 29

It had earlier been found that bromination of (12f) with NBS gave abstraction of a benzylic methyl hydrogen rather than the benzylic hydrogen of the epoxide. Under the bromination conditions the radical (67) abstracted Br from NBS rather than opening the epoxide fuction to the diene radical (68). Scheme 30.



Scheme 30

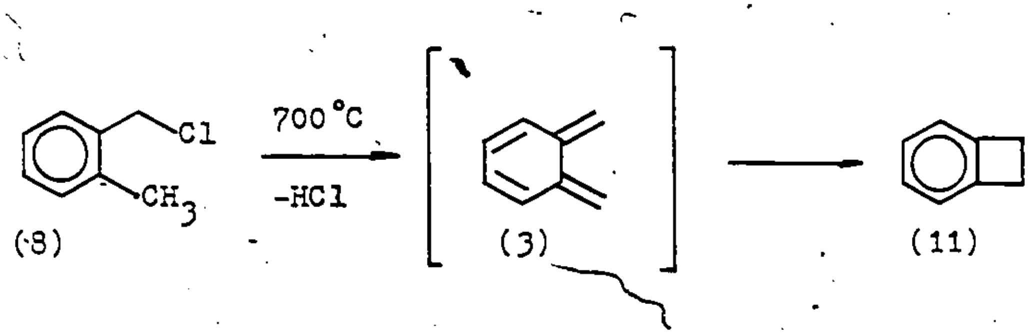
In absence of NBS, and at high temperature there should be a possibility of forming (68). The styrene oxide (12f) was therefore refluxed in chlorobenzene together with a catalytic amount of benzoyl peroxide at 130°C for 12 hours. During the reaction time additional amounts of benzoyl peroxide were added. The crude product mixture obtained on evaporation of the solvent was examined by TLC and NMR, this indicated the presence of two compounds, namely starting material (12f) and <u>ortho</u>-methylphenylacetaldehyde (66) in a ratio of 5:1. Scheme 31.



Scheme 31

Probably the aldehyde is obtained by acid catalysis, the acid being generated from decomposition of the peroxide.

In the introduction the flash vacuum thermolysis of ortho-chloromethyl toluene was described. This compound lost HCl at 700°C and afforded benzylcyclobutene in 70% yield.[4]

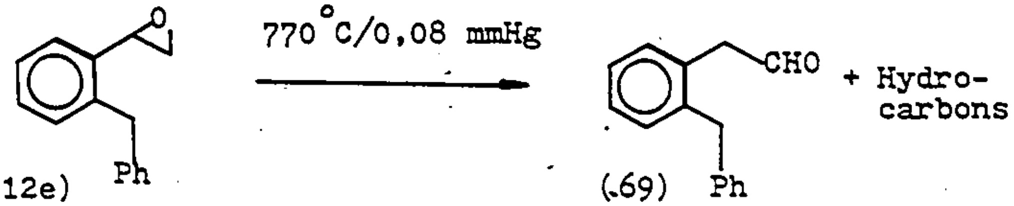


Again we hoped that thermolysis of the styrene oxide (12f) might occur via an analogous 1,4-elimination to give (21) which under the high vacuum thermolysis conditions should cyclize to (13f). The ortho-methylstyrene oxide (12f) was thermolysed at different temperatures and different pressures in a flash vacuum apparatus containing a heating zone 13,5 x 2,5 cm. The apparatus (see Figure 1 Appendix 2) was made partly of quartz to tolerate the high temperatures. The trapping of the substances was done on a cold finger positioned before the outlet to the vacuum pump. The thermolysis were made at 450°C/0,025 mmHg, 765°C/0,1 mmHg and 770°C/12 mmHg. The starting material was preheated in a oven to 60°C before exposure to the high temperatures. At 450°C/0,025 mmHg only starting material (12f) was trapped and identified. When the temperatures was raised to 765°C/0,1 mmHg all starting material disappeared (observation made by interpretation of the NMR spectrum of the crude reaction product). The ortho-methylphenylacetaldehyde (66) could be identified from the above NMR spectrum and the yield estimated at 33% based on the integrations of the aromatic and the aldehyde hydrogens. When the pressure was increased to 770°C/12 mmHg, which means longer exposure times, little or no aldehyde could be detected by NMR.

GC analysis (10% DEGS on Chromasorb I column) of the product mixtures indicated five products with respective retention times 37,5; 49; 105; 146 and 195 seconds. The first peak corresponded to the starting material, which could be detected in a small amount in the product mixture from the reaction at 765°C/0,1 mmHg and of course in the first 450°C/0,025 mmHg reaction. The second peak was very intence in the 765 C/0,1 mmHg product mixture, but absent in the others. The peaks having the retention times 105, 146 and 195 seconds were present in all samples except in the 450°C/0,025 mmHg case.

Column chromatography of the product mixture (765°C/0,1 mmHg) on silica gel with hexane as eluant gave two fractions one which was very non-polar and consisted of more than one component, and a second fraction which was pure aldehyde (66). (colourless oil) in 14% yield (NMR: $-CH_3$ $\delta=2,23$, $-CH_2$ $\delta=3,62$ doublet J=2 Hz and -CHO $\delta=9,63$ triplet J=2 Hz). GC analysis of the first non-polar fraction (59 mg from 450 mg starting material) gave again the three peaks (105,146 and 195 seconds) mentioned above. The NMR spectrum of this mixture was complex and could not be assigned to any specific compound. The aromatic signals occured at $\delta=7,06$ and $\delta=7,16$, while the major aliphatic hydrogens were found as three peaks near δ=2,85 and a singlet at δ=2,25. Since the fraction is extremely non-polar and since no aliphatic signals occured below δ=2,9 it is appearant that the material no longer contained oxygen and is thus a mixture of hydrocarbons. The long retention times on the GC could only be reasonably explained if the mixture contained structures based on "dimerization" of the starting material coupled with loss of the oxygen function. Time did not permit re-examination of the reaction and identification of the products. Surprisingly, a search of the litterature yielded no reports on thermolysis of <u>ortho</u>-methylstyrene oxide or of styrene oxides in general.

In a last attempt the styrene oxide (12e) was thermolyzed at 770°C/0.08 mmHg. The starting material was preheated at ca 120°C before exposure to the high temperature. NMR examination of the crude product obtained showed results similar to the above thermolysis of (12f). The <u>ortho</u>-benzylphenylacetaldehyde (69) could be identified and the yield estimated at 16% based on integration of the aromatic and aldehyde hydrogens. Purification of the reaction mixture by preparative TLC (hexane/ethyl acetate 20:1) gave a major fraction in 41% "yield". The NMR spectrum of this fraction indicated the same type of "dimerization" of starting material to hydrocarbons as observed for the thermolysis of (12f) at 765°C/0,1mmHg (NMR: aromatic protons δ=7,4-7,0, $-CH_2Ph$ δ=3,9 and two singlets at δ=2,9 and δ=2,4). See Scheme 32.



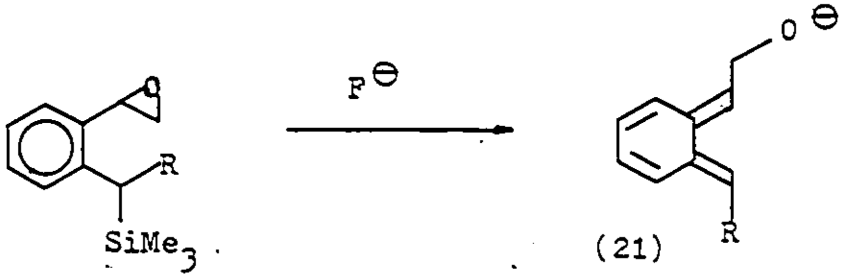
(12e) (69)

Scheme 32

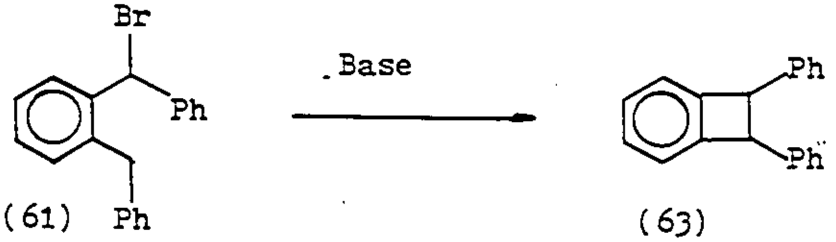
The <u>ortho</u>-(iodomethyl)-styrene oxide (12g) was reacted with magnesium in refluxing THF for 5 hours. After quenching of the reaction four major products were observed by TLC. Chromatography on a silica gel column with hexane/ethyl acetate (10:1) as eluant was not successful, but NMR examination of the different impure fractions showed that no (13g) was obtained. Further investigation of this reaction was not possible due to lack of material and time.

Conclusion.

It is quite obvious that none of the epoxides (12a→12g) are convertible into the desired benzocyclobutylmethanol derivatives (13). The reason for our failures were discussed in several instances. Obviously the modification due to S. Djuric *et. al.*[26], i.e. the fragmentation of *ortho*-trimethylsilylmethyl styrene oxide is the method of choice for the preparation of intermediates of the type (21).



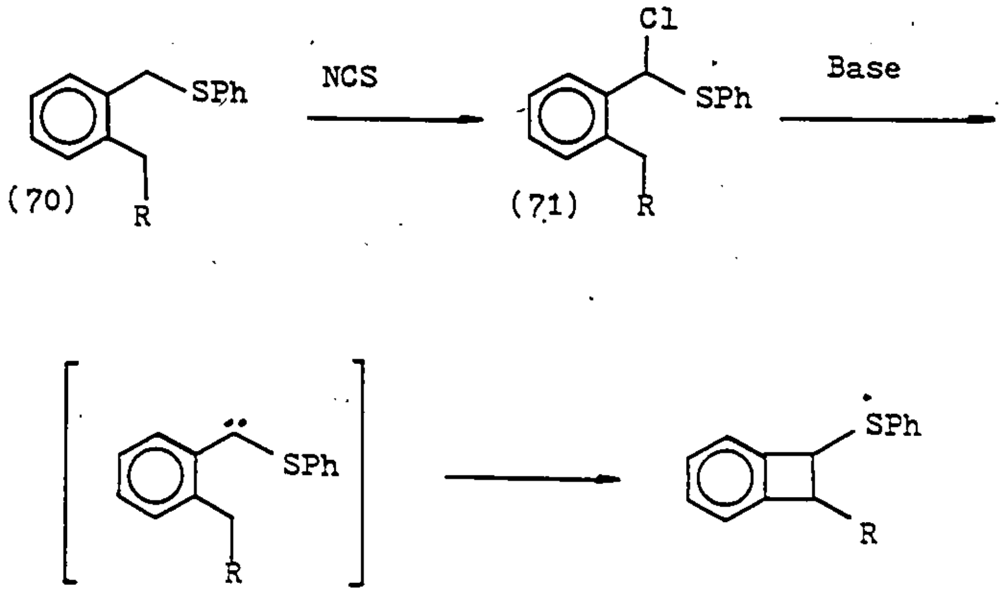
(21)



(61)

(63)

We left several unresolved problems. In particular the most intriging is the thermolysis of the *ortho*-substituted styrene oxides. Also a consideration of the results from F. R. Jensen and W. E. Coleman[28], regarding the base-induced conversion of (61) to (63) possibly via a carbenoid intermediate suggest that compounds such as the bromo- or chlorosulfide (71), readily available by halogenation of (70), might serve as useful precursors to substituted benzocyclobutenes. Scheme 33.



(70)

(71)

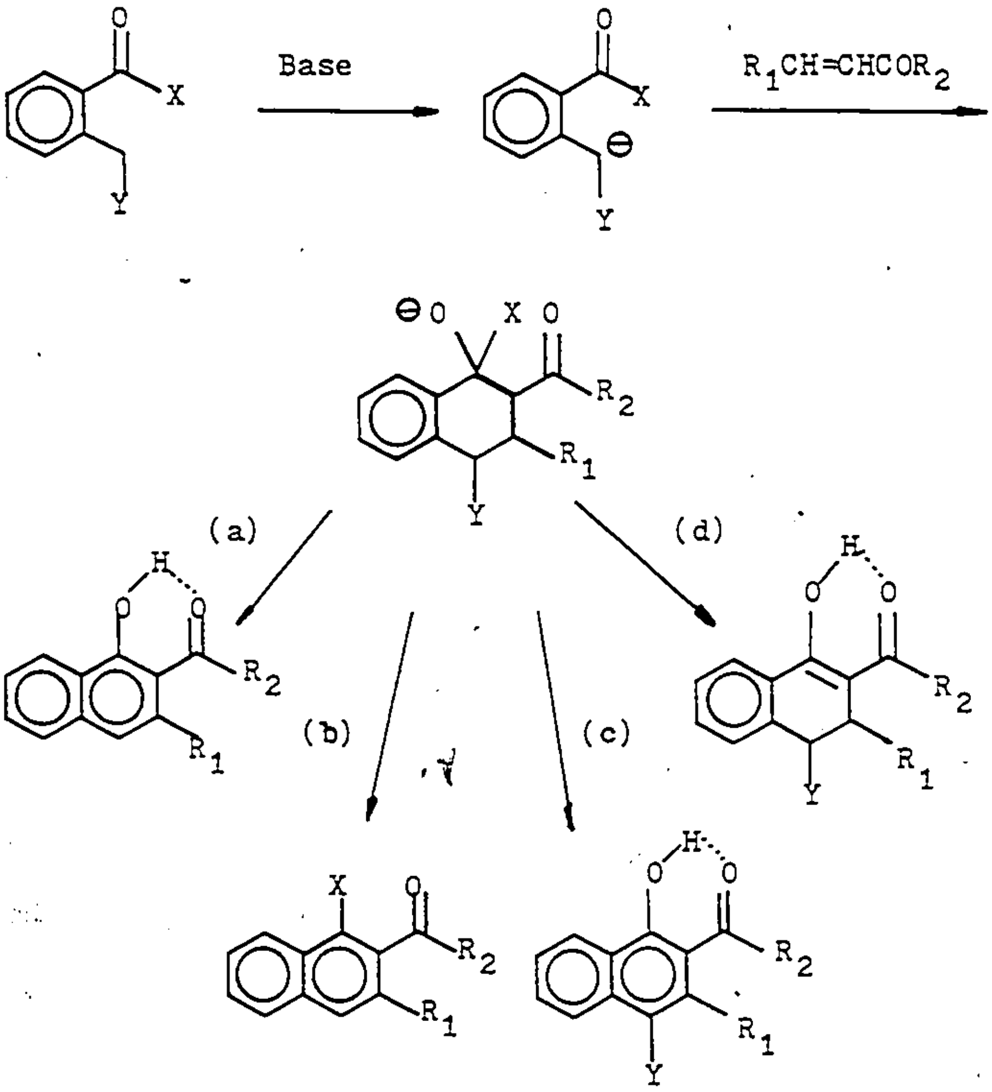
Scheme 33

Part III.

REACTIONS OF 2-CARBOMETHOXYBENZYL PHENYL SULFONE.

Introduction.

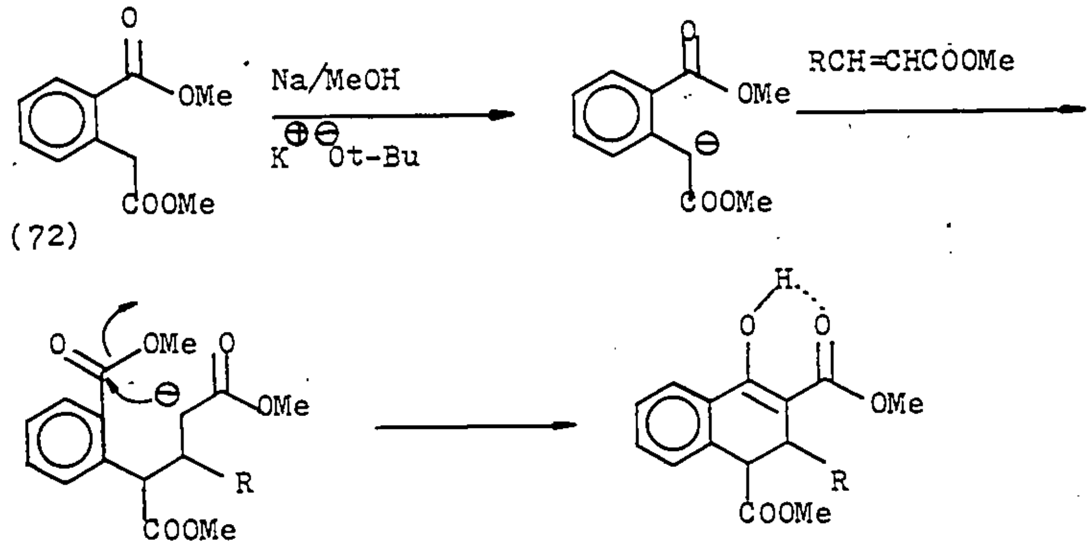
A number of recent publications have dealt with the concept of building polycyclic systems based on the reactions of *ortho*-substituted benzyl derivatives with Michael acceptors. Scheme 34.



Scheme 34 (a) -X,-HY; (b) $-H_2O$, -Y; (c) -HX; (d) -X.

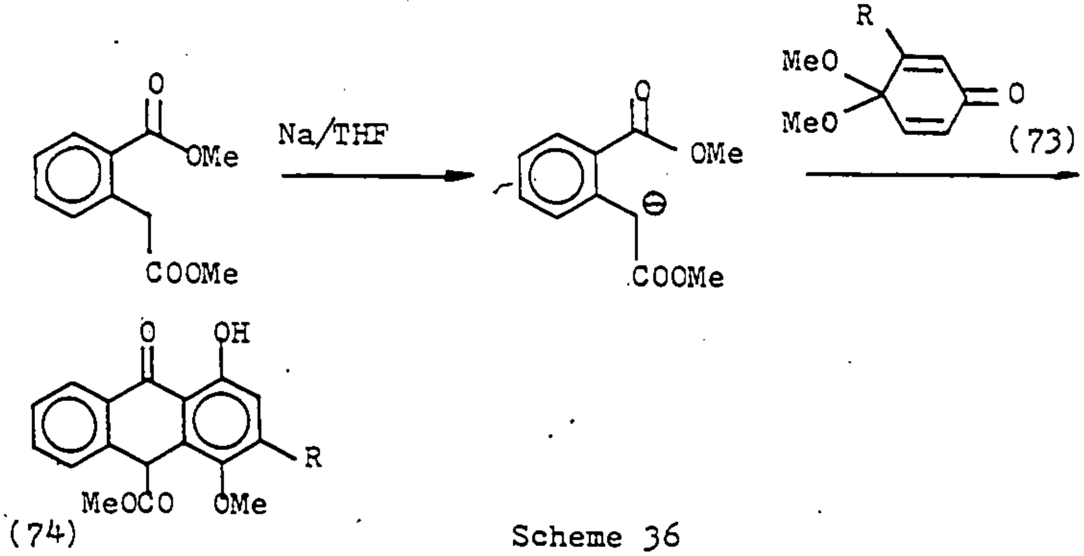
In particular such a scheme should be valuable in the synthesis of naphthol and naphthaquinone derivatives, assuming that the X- or Y-group can be either eliminated or exchanged for an oxygen function. Depending on the nature of the substituents, the process can in principle be repeated to give anthracene derivatives.

In 1965 W. Eisenhuth <u>et</u>. <u>al</u>.[31] reported the first example of such an annelation utilizing homophthalacid dimethylester (72) as the starting material. Base-catalysed condensation of (72) with α,β -unsaturated carbonyl derivatives gave dihydronaphthol derivatives in 40-55%. The mechanism is shown in Scheme 35.



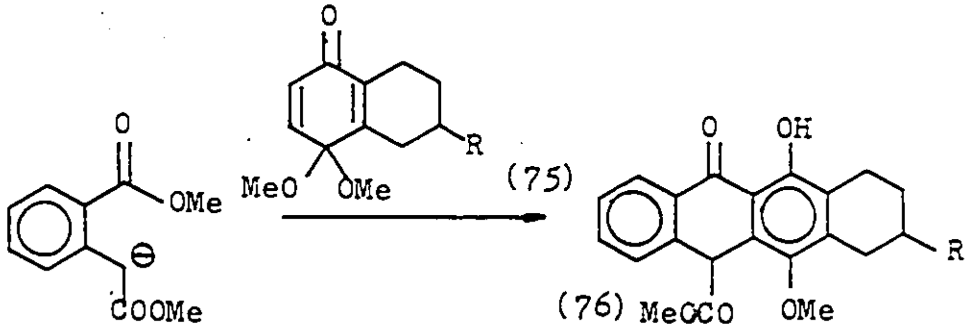
Scheme 35

B. L. Chenard <u>et. al.</u>[32] expanded the above reaction and used quinone monoacetals (73) as Michael-acceptors to produce anthrone derivatives (74) in 20-60% yield. Scheme 36.



Scheme 36

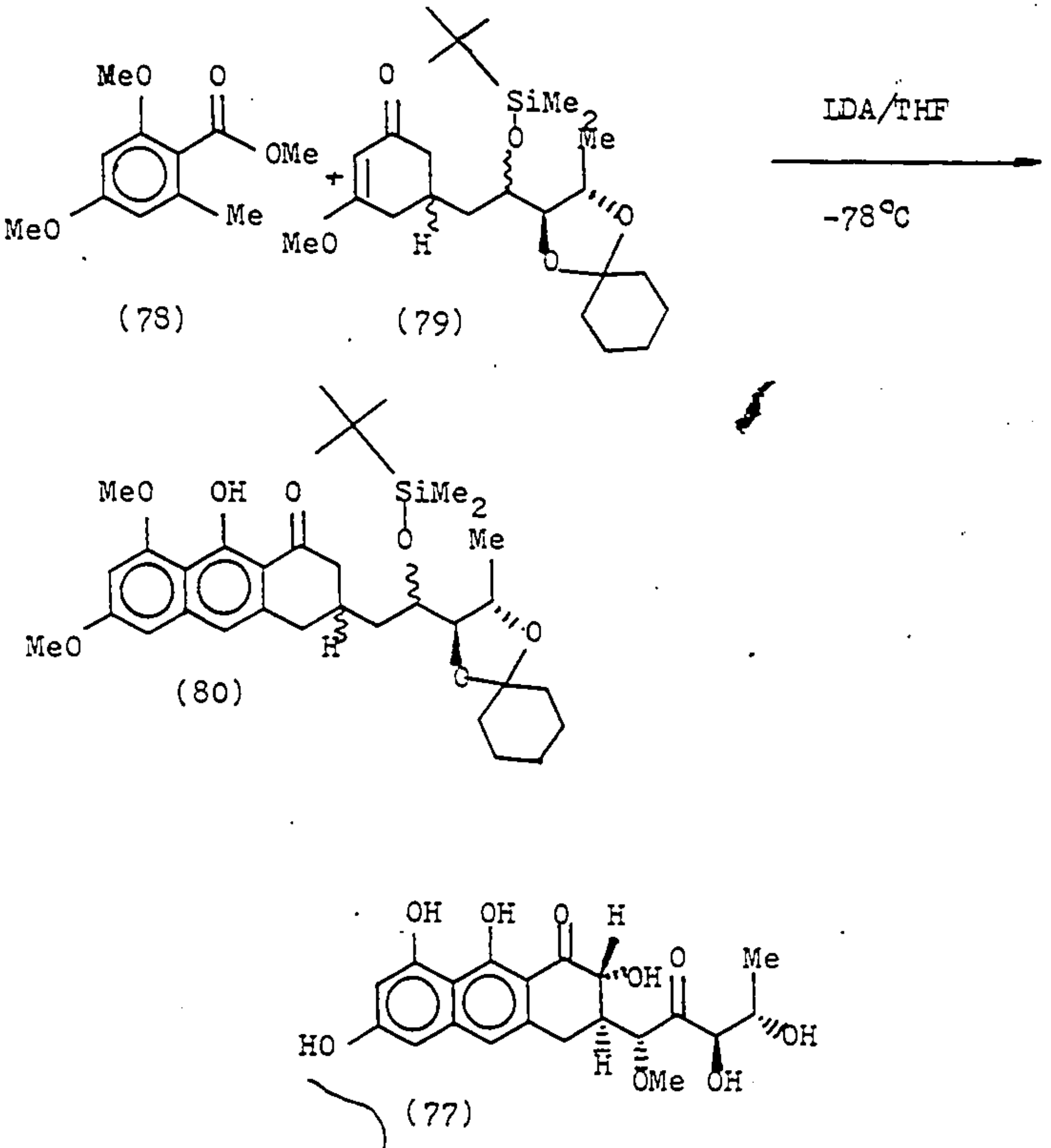
When the naphthaquinone acetal (75) was used as the electrophile the tetracyclic products (76) were obtained in 60% and 41% yield, respectively. Scheme 37.



Scheme 37

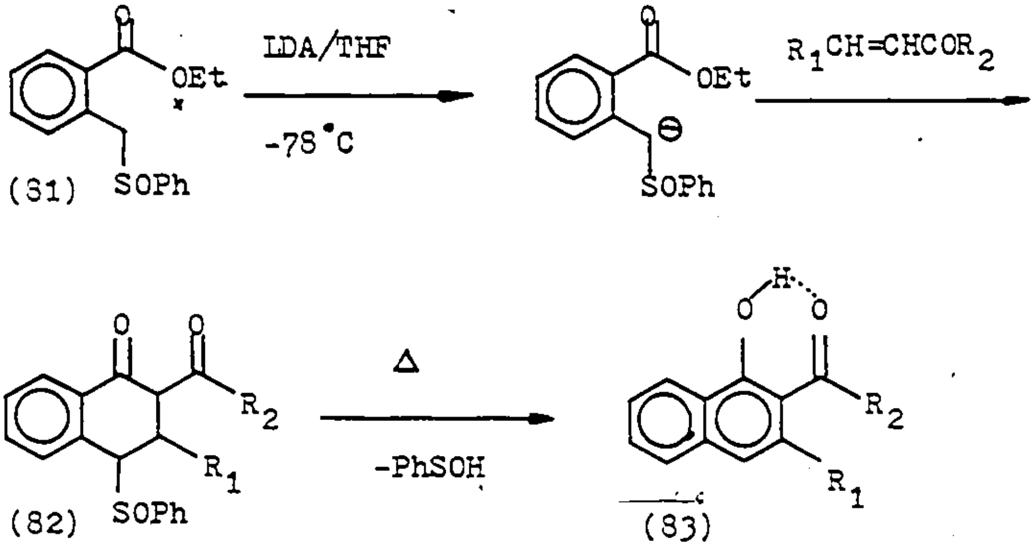
This condensation product shows considerable similarity to the adriamycin aglycone and suggests that such compounds might be accesible via this general route.

One example is the synthesis of the framework of olevine[33] (77) where one of the critical steps was the condensation between the carbanion derived from orsellinate (78) and the β-methoxyenone (79) to afford the tricyclic derivative (80) as a mixture of diastereoisomers in 40% yield. Scheme 38.



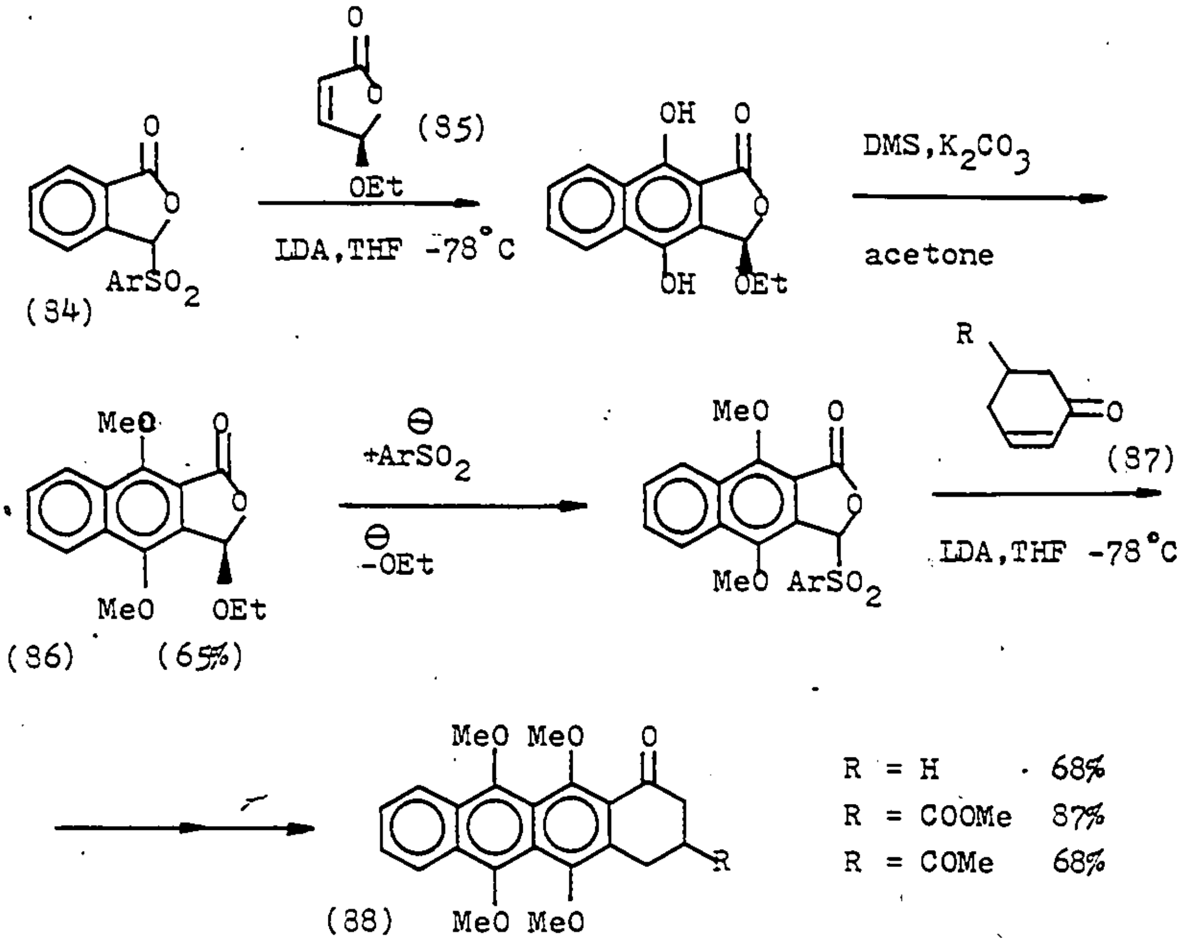
Scheme 38

The use of aromatic sulfones and sulfoxides as anion stabilizing groups has been investigated by F. M. Hauser et. al.[34]. The carbanion generated from the sulfoxide (81) with LDA at -78°C was condensed with α,β-unsaturated carbonyl derivatives to yield first the tetralone (82). Aromatization of (82) to the 1-hydroxy-2,3-disubstituted naphthalene (83) was accomplished by thermal elimination of phenylsulfenic acid. Scheme 39.



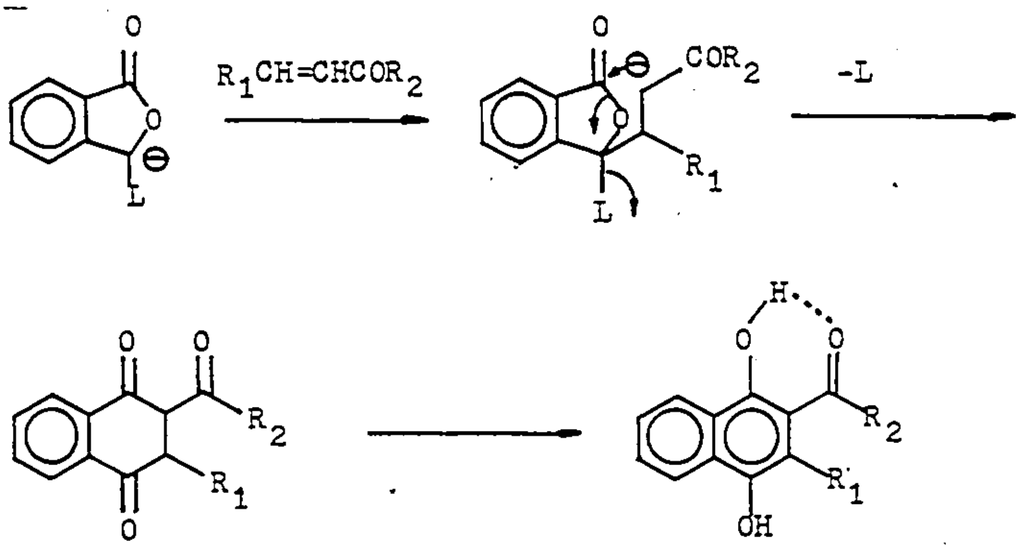
Scheme 39

Later F. M. Hauser et. al.[34, 35] found that the arylsulfonyl substituted lactone (84) behaved similary but offered considerable advantages in allowing repetitive cyclizations. For example a number of tetracyclic hydronaphtacene derivatives of the type (88) could be readily generated according to Scheme 40.



Scheme 40

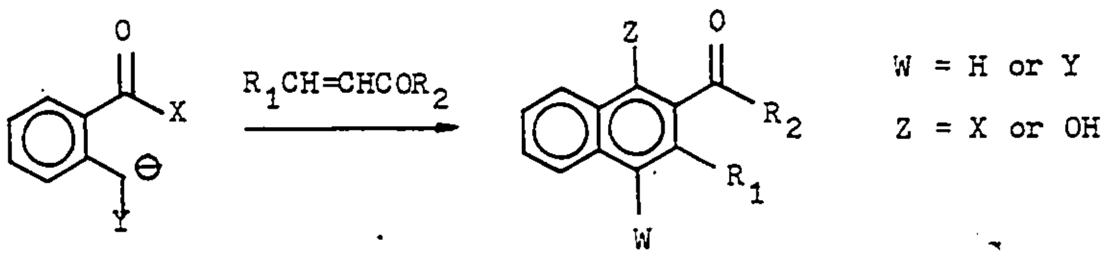
The carbanion of 3-phenylsulfonyl-1(3H)-isobenzofuranone (84) was generated with LDA at -78°C and condensed with 5-ethoxy-2(5H)-furanone (85) to afford after methylation 3-ethoxy-4,9-dimethoxynaphtho(2,3-C)-furan-1(3H)-one (86) in 65% yield. The ethoxy-group on (86) is replaced by an arylsulfonyl group to allow the second annelation step. The introduction of the terminal saturated ring was carried out by condensation between the carbanion derived from (86) with LDA and 2-cyclohexene-1-one derivatives (87) to give the tetracyclic ketones, which after methylation could be isolated in yields between 68% and 87% for different R-groups. The mechanism of these annelations[34, 35, 36, 37] is shown in Scheme 41.



Scheme 41

In 1978 J. Wildeman et. al.[38] reported an extensive study of the general reaction described in Scheme 34, these authors utilized a varity of X-groups (H, CH_3, Ph, OEt) in combination with Y equivalent to tosyl or nitrile (see scheme 42). A number of typical Michael acceptors, among them α,β -unsaturated ketones, aldehydes, esters and nitriles, were studied. In these reactions, the arylsulfonyl group was lost under the reaction conditions and typically 1,2,3-trisubstituted naphthalenes were obtained in 10-78% yield. Again the use of the corresponding naphthalene rather than the benzene substituted starting material provided a route to phenanthrenes.

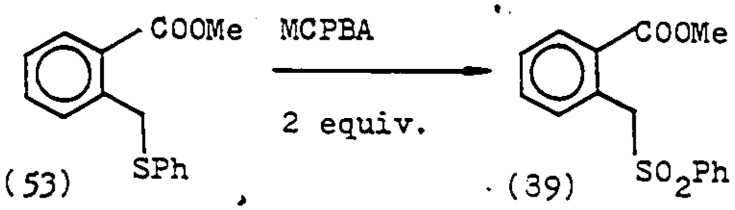
We have studied the reaction of o-(phenylsulfonylmethyl)-styrene oxide (12c) and its potential as a source of ortho-quinodimethanes. The preparation of (12c) is shown in Scheme 20. A number of intermediates, eg. ester (53), alcohol (55) and aldehyde (56) have structural requirments necessary for a potential annelation reaction as described above. Since these were available it was decided to investigate the several possible cyclizations.



Scheme 42

Results and discussion.

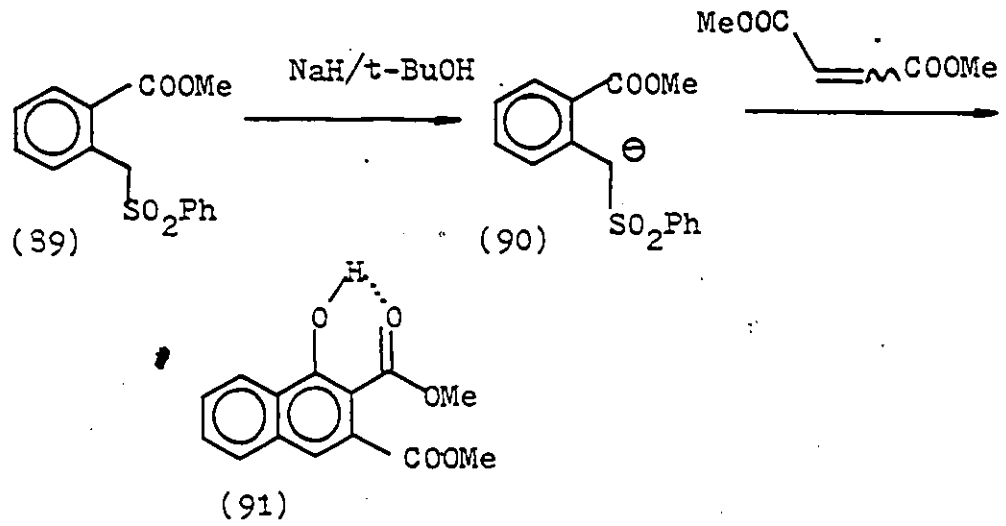
The methyl ortho-(phenylsulphonylmethyl) benzoate (89) was prepared from methyl ortho-(phenylthiomethyl) benzoate (53) by oxidation with two equivalents of meta-chloroperoxybenzoic acide to give (89) as white crystals (m.p. 101-102°C) in 99% yield. Scheme 43.(NMR: $-OCH_3$ δ=3,73 and $-CH_2Ph$ δ=5,05)



Scheme 43

To investigate the reaction described in the introduction we repeated the reaction between (89) and two Michael acceptors. As Michael accptors we used dimethyl fumarate and dimethyl maleate. When the sulfone (89) was added to a mixture of NaH/t-BuOH in THF at room temperature, a purple colour change occured immediatly. The Michael acceptor was added and the reaction was kept at room temperature for 20 hours prior to quenching with aqueous ammmonium chloride. Both Michael acceptors yielded the dimethyl-

1-hydroxynaphthalene-2,3-dicarboxylate (91) (m.p. 102-103°C, lit. m.p. 145-160° C[39]) in 60% and 74% yield, respectively for the dimethyl fumarate and dimethyl maleate (lit. yield for the condensation between ortho-tosyl-methyl-ethylcarboxylate and diethyl maleate is 76%[38]). The NMR spectrum of (91) showed singlets at δ=3,91; δ=3,94 and δ=11,88 (-OH), and multiplets at δ=7,38-7,80 4 aromatic hydrogens and δ=8,28-8,46 1 aromatic hydrogen*. Scheme 44.



Scheme 44

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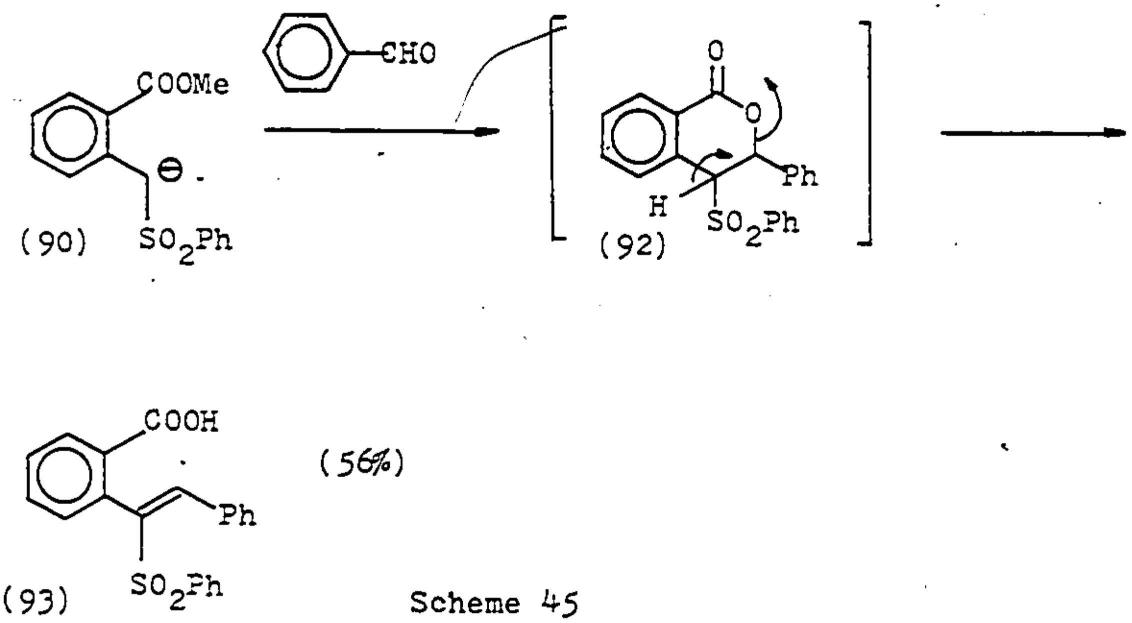
* Footnote: B. J. Arnold et. al.[39] reported the NMR spectrum of (91) which differs from ours. Their methoxygroups have the shifts τ=6,16 and τ=6,70, whilst ours are at τ=6,07 and τ=6,10. The reason for this difference could be due to typing errors or impure material, lit. m.p. 145-160° C decomp.; our m.p. 102-103° C.

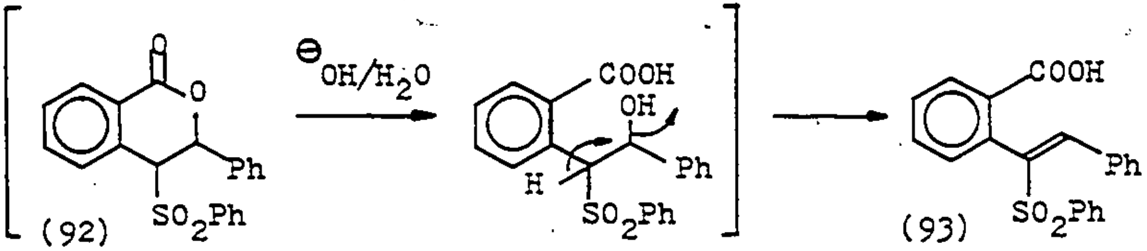
Since we had succesfully repeated the trapping of the carbanion (90) with Michael acceptors we decided to expand the reaction to include simple electrophiles such as aldehydes and ketones. Such reactions should lead to lactones of the type (92). Scheme 45.

When benzaldehyde was reacted with (90) in THF containing t-BuOK for 20 hours a white solid (m.p. 158-160° C) was obtained in 56% yield. The analytical and spectroscopic data (IR: -OH 2800-3500 cm^{-1}, -C=O 1700 cm^{-1}, $-SO_2$ asymetric 1320 cm^{-1} and symetric 1150 cm^{-1}) was consistent with the structure (93). The formation of (93) most likely occured via ring opening of the intermediate (92). This reaction is somewhat surprising since it represents an example of a reverse 6-endo trigonal cyclization, a process disfavored by Baldwin's rules.



Scheme 45

Another possible mechanism is hydrolysis of the lactone ring due to the presence of residual KOH, followed by elimination of the hydroxyl group from the produced intermediate to give the product (93). This path is more unlikely because the same result was obtained when the reaction was repeated in THF with LDA as base. Finally the hydrolysis of the lactone ring could have occured during the workup of the reaction, but the following elimination of water is unlikely since β-hydroxy sulfones generally do not undergo loss of water[40]. Scheme 46.

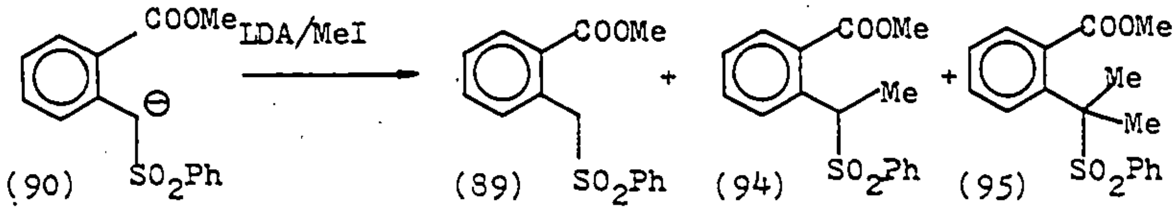


Scheme 46

V

In order to obtain a δ-lactone of the type (92) which would not undergo direct elimination we decided to prepare the monomethyl derivative (94). Methylation of the carbanion (90) in THF with methyl iodide gave a product whose NMR spectrum indicated a 2:2:1 mixture of (89), (94) and the dimethyl derivative (95) based on the integration of the $-CH_2-$, $-CH-$ and the two added methyl groups in the dimethylated compound. Unfortunately separation by chromatography on silica gel was not feasible since analytical

TLC showed only one spot in several solvent systems. Problems in the mono alkylation of sulfone carbanions have previously been reported[40].

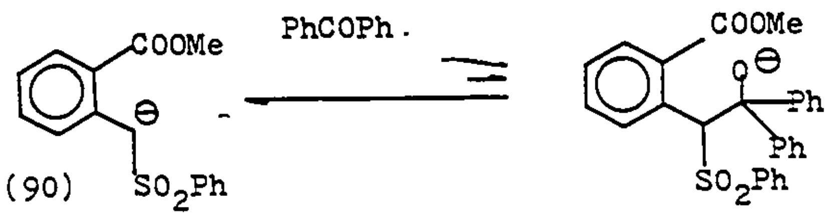


(90) (89) (94) (95)

The methylation of the sulfide ester (53) was also briefly investigated. Treatment of (53) with LDA in THF at -78°C gave an imediate violet coloured solution. Addition of methyl iodide followed by warming to room temperature and subsequent work up gave a product (0,29 g) whose NMR spectrum indicated a 5:1 mixture of mono- and dimethylated products. Because of separation difficulties and lack of time this aspect was not futher persued.

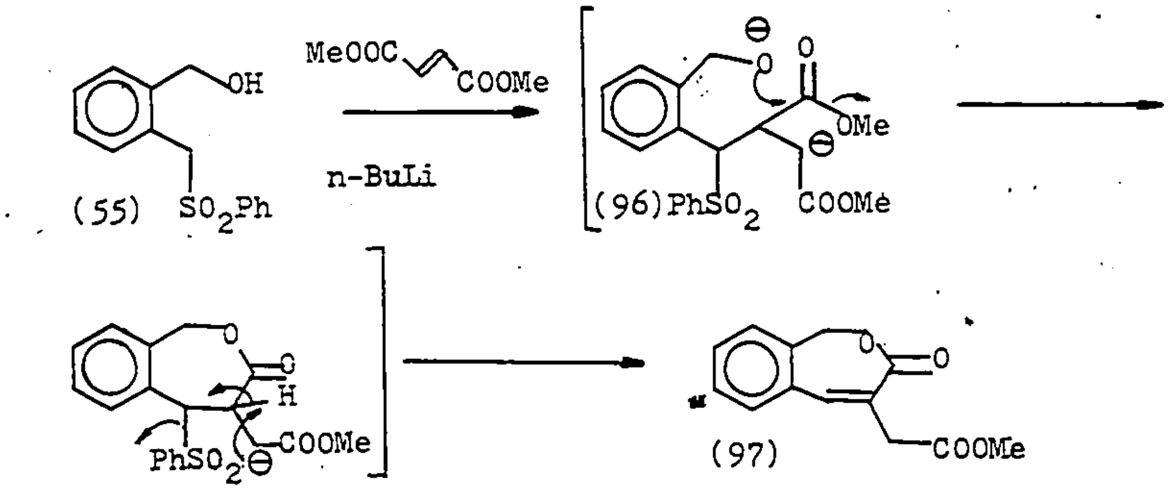
The carbanion (90) was also reacted with benzophenone and cyclohexanone under the usual conditions. In the case of benzophenone the two starting materials were recovered (37% for (89)) after 4 days reaction time. No other products could be isolated.

It appears that the initial adduct formation is not favorable (cheme 47). This was confirmed in the cyclohexanone case, were the appearently slow condensation of the carbanion (90) with the carbonyl compound allowed the self condensation reaction of cyclohexanone to occur.



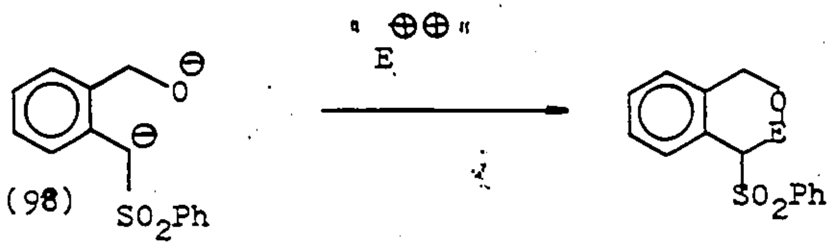
Scheme 47

In order to synthesize heterocyclic compounds we investigated the condensation reactions of the <u>ortho</u>-(phenylsulfonylmethyl)-benzyl alcohol (55) with different electrophiles. When (55) was treated with 2 equivalents of <u>n</u>-BuLi in THF and dimethyl fumarate at -78°C followed by warming to room temperature, a seven membered lactone (97) could be isolated in 43% yield as a white solid (m.p. 115-117°C, for NMR see Appendix 1 Figure 3). The mechanism of this reaction is shown in Scheme 48, and is possible because it allows the largest distance between the two anions in (96).



Scheme 48

The cyclization reaction between diiodomethane and the carbanion (98) under phase-transfer conditions (CH_2Cl_2/50% NaOH and $PhCH_2\overset{\oplus}{N}Et_3\overset{\ominus}{Cl}$) was also attempted, but after 5 days reaction time the only detectable compounds were the starting materials. Instead the carbanion (98) was generated by treatment with n-BuLi in THF at -78°C and treated with dichlorodimethylsilane, followed by warming to room temperature and work up. Product analysis by TLC showed the presence of starting material and a complex mixture of products and in the NMR spectrum of the crude reaction product no cycloadduct could be detected. See Scheme 49.



Scheme 49

Conclusion.

The cyclization reaction between carbanions of the type (90) and different Michael acceptors leads to the anticipated cycloadducts. When instead simple carbonyl compounds are used as electrophiles the chosen reaction route is harder to predict. The character of the electrophile is obviously very important, for example steric effects can inhibit the reaction as in the case with benzophenone (Scheme 47). Also the presence of more than one acidic α-hydrogen on the sulfone leads to the possibility of subsequent elimination reactions as seen in the condensation between (90) and benzaldehyde (Scheme 45).

The reaction of the dianion (98) with Michael acceptor dimethyl fumarate led to the formation of the seven-membered lactone (97).

EXPERIMENTAL.

General methods.

Concentrations were preformed at reduced pressure. NMR spectra were recorded using Varian HA-100, CFT-20, T-60A or EM360A instruments with deuteriochloroform as solvent unless otherwise stated. IR spectra were obtained on a Unicam SP 1100 instrument with chloroform as solvent. Mass spectra were recorded on a Varian MS902 instrument. Melting points were taken on a Gallenkamp instrument and are uncorrected. Analytical TLC were preformed on "Merk DC-Fertigplatten, kieselgel F 254" and preparative TLC on "Merk PSC-Fertigplatten, kieselgel F 254". Column chromatography was preformed on 60-200 mesh Baker silica gel. For microanalytical data see Figure 1 Appendix 3.

ortho-(Bromophenyl)-acetic acid (41)

ortho-bromobenzyl bromide (1,00 g, 4,0 mmol), aqueous sodium hydroxide (20 ml, 5 M) and benzyltriethylamonium chloride (0,09 g, 0,4 mmol) in benzene (20 ml) were stirred under CO for 1 hour at room temperature. $Co_2(CO)_8$ (0,14 g,0,4 mmol) was then added. The reaction was stirred over night under a slow strem of CO. The reaction mixture was filtered through glasswool and diluted with water (100 ml). The aqueous layer was acidified with 6 M HCl and extracted several times with diethylether. The combined organic extractions was dried over anhydrous $MgSO_4$ and evaporated. The crude product was recrystallized from ether/hexane to give pure (41) (0,74 g,86%) as white crystals m.p.97-98°C (lit. m.p. 105-106°C[41]).

^1H NMR: $-\underline{CH_2}-COOH$ $\delta=3,73$ singlet; 4 aromatic H $\delta=6,87-8,07$ multiplet; $-COOH$ $\delta=10,87$ singlet.

^{13}C NMR: $-CH_2-$ $\delta=42,3$; $-COOH$ $\delta=174,3$.

IR: $-OH$ 2400-3200 cm^{-1}; $-COOH$ 1712 cm^{-1}.

ortho-Bromophenethyl alcohol

A solution of (41) (0,63 g, 2,9 mmol) in ether (3ml) was dropwise added to a suspension of $LiAlH_4$ (0,12 g, 3,0 mmol) in ether (7ml) at room temperature. The reaction was stirred for 20 minutes before work-up, as described in reference 42, to give the product (0,49 g, 83%) as a slightly yellow oil.[42]

^1H NMR: $-OH$ $\delta=2,63$ singlet; $-\underline{CH_2}Ph$ $\delta=3,00$ triplet J=7 Hz; $-\underline{CH_2}OH$ $\delta=3,87$ triplet J=7 Hz; 3 aromatic H $\delta=7,0-7,6$ multiplet; 1 aromatic H $\delta=7,6-7,9$ multiplet.

IR: $-OH$ 2750-3100 cm^{-1}.

ortho-Bromophenylacetaldehyde (42)

ortho-Bromophenethyl alcohol (0,49 g, 2,4 mmol) was added to a mixture of pyridinium chlorochromate (1,1 g, 5,0 mmol) and sodium carbonate (1,1 g, 10mmol) in dichloromethane (10ml) and the reaction was stirred at room temperature for 1 hour. Filtration through Florasil and evaporation of the solvent left a residue that was purified on a silica gel column (hexane/ethyl acetate 15:1) to give pure aldehyde (42) (0,15 g, 31%) as a light yellow oil.

^1H NMR: $-C\underline{H_2}CHO$ $\delta=3,83$ doublet J=2 Hz; 3 aromatic H $\delta=6,9-7,4$ multiplet; 1 aromatic H $\delta=7,4-7,7$

multiplet; -CHO δ=9,63 triplet J=2 Hz.

3-(<u>ortho</u>-Bromophenyl)-1,2-epoxypropane (24)

To a solution of (42) (0,15 g, 0,7 mmol), trimethylsulfonium chloride (0,13 g, 1,0 mmol) and benzyltriethylammonium chloride (50 mg, 0,2 mmol) in dichloromethane (2ml) was dropwise added aqueous sodium hydroxide (50%, 1ml). The reaction was stirred for 1 hour at room temperature prior to dilution with water and extraction with dichloromethane (3 x 5ml).The combined organic layers were dried over anhydrous magnesium sulfate and evaporated to give the crude product. Purification on a silica gel column (hexane/ethyl acetate 20:1) gave pure (24) (52 mg, 33%) as a colourless oil.

^{1}H NMR: 5 aliphatic H δ=2,25-3,50 multiplet; 4 aromatic H δ=6,75-7,60 multiplet. See Figure 4 Appendix 1.

<u>ortho</u>-Allylbromobenzene (43)

The Grignard reagent obtained from <u>ortho</u>-dibromobenzene21 (14,9 g, 63 mmol) and magnesium turnings (1,75 g, 72 mmol) in dry ether (115ml) was added to a solution of allyl bromide (6,1ml, 72 mmol) in dry ether (15ml). The reaction was stirred at room temperature overnight, quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. The crude residue obtained on evaporation of the solvents was separated on a silica gel column (hexane) to give a 3:4 mixture of <u>ortho</u>-dibromobenzene and (43) (3,2 g).[19]

The reaction was repeated with the alternation that ortho-iodobromobenzene (7,0 g, 25 mmol) was used as the starting material, but according to the same procedure and proportions as above, to give after work-up, distillation (the fraction with b.p. 44-46°C/0,1 mmHg was collected) and purification on a silica gel column (hexane) a 1:2 mixture of ortho-iodobromobenzene and (43) (0,97 g).

^{1}H NMR: -C$\underline{H}_2$Ph δ=3,50 doublet; =CH_2 δ=4,90-5,20 multiplet; -CH= δ=5,75-6,25 multiplet; 4 aromatic H δ=6,75-7,75 multiplet.

3-(ortho-Bromophenyl)-1,2-epoxypropane (24)

The above mixture of ortho-dibromobenzene and (43) (3,2 g) was refluxed for 6 hours together with meta-chloroperoxybenzoic acid (5,25 g, 26 mmol) in dichloromethane (50ml). Work-up included washing with aqueous sodium sulfite (10%) and aqueous potassium hydroxide (10%) before drying over anhydrous magnesium sulfate and evaporation. The crude product was purified on a silica gel column (hexane) to give ortho-dibromobenzene (0,98 g) and pure (24) (1,49 g).[20] The overall yield calculated from ortho-dibromobenzene was 11%.

2-Indanol (40)

To a stirred solution of (24) (0,32 g, 1,5 mmol) in dry THF (3ml) at -78°C under nitrogen, was added n-BuLi (0,62ml, 1,5 mmol, 2,4 M) and two minutes later $MgBr_2$ (1,20ml, 3,0 mmol, 2,5 M). A yellow colour change occured. The reaction was slowly warmed to room temperature before quenching with saturated aqueous ammonium chloride and extraction with dichloromethane (3x15ml). The combined organic extractions were dried over anhydrous magnesium sulfate and evaporated to give a residue, which was separated on a silica gel column (hexane/ethyl acetate 1:3) to give pure (40) (0,12 g, 59%) as white needles; m.p. 68-70° C from hexane/ether (Aldrich m.p. 68-71°C).

^{1}H NMR: -OH δ=1,73 singlet; 2 benzylic $-CH_2$ and -CH ABX pattern: $2H_B$ δ=2,92 doublet of doublets J_{AB}= 16 Hz J_{BX}=4 Hz; $2H_A$ δ=3,26 doublet of doublets J_{AB} =16 Hz J_{AX} =6 Hz; H_X δ=4,69 multiplet; 4 aromatic H δ=7,10-7,30.

Cinnamyl alcohol (46)

To a stirred solution of (24) (0,41 g, 1,9 mmol) in dry THF (5ml) at -78°C under nitrogen, was added n-BuLi (0,80ml, 1,9 mmol, 2,4 M) which caused a immediate colour change to yellow. The reaction was allowed to reach room temperature before quenching with saturated aqueous ammonium chloride and extraction with dichloromethane (3x15ml). The combined organic extractions were dried over anhydrous magnesium sulfate and evaporated to give a residue, which was separated on a silica gel column (hexane/ethyl acetate 10:1) to afford (46) (70 mg, 27%) as the major product (identical with authentic material).

ortho-(Phenylthiomethyl)-benzoic acid (52)

A mixture of phthalide (67,0 g, 0,5 mol), thiophenol (55,0 g, 0,5 mol) and potassium hydroxide (31 g, 0,55 mol) in 2-propanol (300ml) was refluxed under nitrogen overnight. The reaction mixture was diluted with water (500ml), acidified with conc. HCl and extracted with dichloromethane (4x100ml). Evaporation of the solvents left a crystalline residue which was recrystallized from hexane/ether to give pure (52) (106,2 g, 87%) as white crystals:m.p. 114-115°C. (Lit. m.p. 109-112°C[43]).

^{1}H NMR: $-CH_2-$ δ=4,59 singlet; 8 aromatic H δ=7,1-7,5 multiplet; 1 aromatic H δ=8,0-8,15 multiplet; -COOH δ=12,30 singlet.

^{13}C NMR: -COOH δ=173,1; $-\underline{C}H_2Ph$ δ=38,1.

IR: CO 1700 cm^{-1}; -OH 2400-3400 cm^{-1}.

MS: m/e 244

Methyl ortho-(phenylthiomethyl)-benzoate (53)

A solution of (52) (50,0 g, 0,2 mol) and conc. sulfuric acid (25 ml) in methanol (300 ml) was refluxed over night. The reaction mixture was diluted with aqueous sodium carbonate (10%, 150 ml) and extracted with dichloromethane (4x100 ml). The combined organic layers were washed with aqueous sodium hydroxide (10%, 100 ml), water (100 ml), dried over anhydrous magnesium sulfate and evaporated to give the crude product

(53) (53,0 g, 96%), which was used in the following step without further purification. A small amount was purified on a silica gel column (hexane/ethyl acetate 13:1) to yield (53) as a colourless oil.

^{1}H NMR: -OCH$_3$ δ=3,80 singlet; -CH$_2$Ph δ=4,47 singlet; 8 aromatic H δ=7,0-7,7 multiplet; 1 aromatic H δ=7,75-7,94 multiplet.
IR: CO 1720 cm^{-1}.

<u>ortho</u>-(Phenylthiomethyl)-benzyl alcohol (54)

A solution of (53) (25,0 g, 0,10 mol) in dry ether (150ml) was added dropwise to a stirred suspension of LiAlH$_4$ (2,8 g, 74 mmol) in dry ether (100ml). The reaction was stirred at room temperature overnight. Work-up was made as described in reference 42. The crude product was crystallized from ether/hexane to give pure (54) (20.5 g, 92%) as white needles: m.p. 66-67°C (lit. m.p. 67-68°C)[43].

^{1}H NMR: -OH δ=2,68 singlet; -CH$_2$PH δ=4,14 singlet; -CH$_2$-O δ=4,68 singlet; 9 aromatic H δ·7,0-7,5 multiplet.
^{13}C NMR: -CH$_2$SPH δ=36,7; -CH$_2$-OH δ=62,9.
IR: -OH 3100-3600 cm^{-1}; free -OH 3590 cm^{-1}.
MS: m/e 230

ortho-(Phenylsulfonylmethyl)-benzyl alcohol (55)

Meta-peroxybenzoic acid (9,7 g, 44 mmol) in dichloromethane (50ml) was slowly added to a stirred solution of (54) (5,0 g, 22 mmol) in dichloromethane (10ml) at 0°C. The reaction mixture was stirred at 0 C for further 1 hour, washed with aqueous sodium sulfite (10%, 25ml), aqueous sodium hydroxide (10%, 2x25ml) and water (25ml). The organic layer was dried over anhydrous magnesium sulfate and evaporated to give the crude product which was recrystallized from CH_2Cl_2/hexane to give pure (55) (5,63 g, 99%) as white crystals: m.p. 136-138° C.

^{1}H NMR: -OH δ-3,07 singlet; $-CH_2SO_2Ph$ δ=4,51 singlet; $-C\underline{H}_2OH$ δ=4,57 singlet, 9 aromatic H δ=6,9-7,8 multiplet.

^{13}C NMR: $-CH_2SO_2Ph$ δ=59,1; $-CH_2OH$ δ=62,2.

IR: -OH 3300-3550 cm^{-1}; free -OH 3580 cm^{-1}; $-SO_2-$ 1155 cm^{-1} and 1325 cm^{-1}.

MS: m/e 262

ortho-(Phenylsulfonylmethyl)-benzaldehyde (56)

Chromium trioxide (3,1 g, 31 mmol) was added to a stirred solution of pyridine (5ml, 62 mmol) in dichloromethane (20ml). After 15 min. a solution of the alcohol (55) (2,2 g, 7,8 mmol) and acetic anhydride (3ml, 32 mmol) in dichloromethane (5ml) was added and stirring continued for 15 min.. The reaction mixture was filtered through a short silica gel column with ethyl acetate as eluant, followed by evaporation of the solvents to give the crude product. Recrystallization from ethyl acetate/hexane gave (56) (1,3 g, 63%) as slightly red crystals: m.p. 140-142°C.

^{1}H NMR: $-CH_2SO_2Ph$ δ=5,06 singlet; 9 aromatic H δ=7,3-8,0 multiplet; -CHO δ=9,93 singlet.
^{13}C NMR: $-CH_2SO_2Ph$ δ=59,5; -CHO δ=191,9.
IR: CO 1730 cm^{-1}; $-SO_2-$ 1150 cm^{-1} and 1320 cm^{-1}.

<u>ortho</u>-(Phenylsulfonylmethyl)-styrene oxide (12c)

Aqueous sodium hydroxide (50%, 2,5ml) was added dropwise to a stirred solution of (56) (1,0 g, 3,8 mmol), trimethylsulfonium chloride (0,65 g, 5mmol) and benzyltriethylammonium chloride (50 mg, 0,2 mmol) in dichloromethane (4ml). The reaction was stirred at room temperature overnight, diluted with water (5ml) and extracted with dichloromethane (3x5ml). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated to yield a residue which was purified on a silica gel column (hexane/ethyl acetate 3:1) to give pure (12c) (0,72 g, 69%) as white crystals: m.p. 79-80°C from CH_2Cl_2/hexane.

^{1}H NMR: See figure 1 Appendix 1; epoxide ABX pattern H_A δ=2,50; H_B δ=3,03; H_X δ=3,90 J_{AB}=5,6 Hz J_{AX}=2,6 Hz J_{BX}=4,1 Hz doublets of doublets; $-CH_2SO_2Ph$ AB pattern H_A δ=4,42; H_B δ=4,59 J_{AB}= 14,1 Hz doublets; 9 aromatic H δ=6,75-7,75 multiplet.

^{13}C NMR: epoxide C: CH δ=50,1; CH_2 δ=50,4; $-CH_2SO_2Ph$ δ=59,4.

IR: $-SO_2-$ 1150 cm^{-1} and 1325 cm^{-1}.

MS: m/e 274

ortho-Methylstyrene oxide (12f)

The same procedure as above was used for the preparation of *ortho*-methyl-styrene oxide (12f). Starting from *ortho*-tolualdehyde (20,2 g, 0,16 mmol) the reaction yielded pure (12f) (14,8 g, 83%) as a colourless oil: b.p. 57-59°C/0,32 mmHg. (lit. b.p. 89°C/10 mmHg[44]).

^{1}H NMR: $-CH_3$ δ=2,50 singlet; epoxide ABX pattern H_A δ=2,73; H_B δ=3,20; H_X δ=4,05 J_{AB}=5,8 Hz J_{AX}=2,7 Hz J_{BX}=3,7 Hz doublets of doublets; 4 aromatic H δ=6,75-7,75 multiplet.

^{13}C NMR: $-CH_3$ δ=18,8; epoxide C: CH_2 δ=50,1; CH δ=50,5.

MS: m/e 134

ortho-(Bromomethyl)-styrene oxide (12a)

A mixture of (12f) (14,7 g, 0,11 mol), *N*-bromosuccinimide (20 g, 0,11 mol), benzoylperoxide (0,2 g, 0,8 mmol) and $CaCO_3$ (1,0 g, 0,01 mol) in carbon tetrachloride (60ml) was refluxed over night. Filtration and evaporation of the solvent left a crude product, which was distilled under vacuum to give pure (12a) (23,5 g, 92%) as a colourless oil: b.p. 122-124°C/0,75 mmHg.

^{1}H NMR: epoxide ABX pattern H_A δ=2,70; H_B δ=3,20; H_X δ=4,13 J_{AB}=6 Hz J_{AX}=3 Hz J_{BX}=4 Hz doublets of doublets; -CH_2Br AB pattern H_A δ=6,11; H_B δ=6,22 J_{AB}=11 Hz doublets; 4 aromatic H δ=7,30 broad singlet.

ortho-(Phenylsulfonylmethyl)-styrene oxide (12c)

To a solution of (12a) (1,56 g, 7,3 mmol), benzenesulfinic acid sodium salt (1,25 g, 7,4 mmol) and benzyltriethylammonium chloride (75 mg, 0,3 mmol) in dichloromethane (15ml) was added water (10ml). The reaction was stirred at room temperature overnight, extracted with dichloromethane (4x10ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvents left a residue that was purified on a silica gel column (hexane/ethyl acetate 3:1) to give pure (12c) (1,37 g, 68%) as a colourless oil. The analytical and physical data were identical with those obtained following the first route.

ortho-(Cyanomethyl)-styrene oxide (12d)

(12a) (12,0 g, 56 mmol), potassium cyanide (9,0 g, 0,11 mol) and benzyltriethylammonium chloride (0,5 g, 2mmol) were dissolved in dichloromethane (30ml). Water (50ml) was added, and the mixture was stirred for 36 hours at room temperature. The reaction was extracted with dichloromethane (3x30ml), dried over anhydrous magnesium sulfate and evaporated to give a crude product (7,5 g). A part of this crude product (1,0 g) was separated on a silica gel column (hexane/ethyl acetate 5:1) to give pure (12d) (0,50 g) and pure starting material (12a) (0,21 g), this corresponds to a yield of 42% (12d).

^{1}H NMR: epoxide ABX pattern H_A δ=2,63; H_B δ=3,10; H_X δ=3,95 J_{AB}=6 Hz J_{AX}=3 Hz J_{BX}=4 Hz doublets of doublets; $-CH_2CN$ δ=3,77 singlet; 4 aromatic H δ=7,27 broad singlet.

IR: -CN 2250 cm^{-1}

<u>ortho</u>-(Iodomethyl)-styrene oxide (12g)

A solution of <u>ortho</u>-(bromomethyl)-styrene oxide (12a) (1,50 g, 7mmol) and potassium iodide (1,4 g, 8 mmol) in acetone (20ml) was refluxed for 26 hours. Evaporation of the solvent left a crude product, which was taken up in dichloromethane (30ml) and washed with aqueous sodium thiosulfate (10%, 2x15ml). The organic phase was dried over anhydrous magnesium sulfate and evaporated to give a crude oil. Separation on a silica gel column (hexane/CH_2Cl_2 5:1) yielded pure (12g) (0,77 g, 42%) as slightly yellow coloured crystals that melted at room temperature.

^{1}H NMR: epoxide ABX pattern H_A δ=2,73; H_B δ=3,25; H_X δ=4,10 J_{AB}=6 Hz J_{AX}=3 Hz J_{BX}=5 Hz doublets of doublets; $-CH_2I$ AB pattern H_A δ=4,48; H_B δ=4,65 J_{AB}=10 Hz. 4 aromatic H δ=7,10-7,80 multiplet

<u>ortho</u>-Benzylbenzaldehyde (58)

A mixture of pyridinium chlorochromate (5,7 g, 26 mmol) and sodium carbonate (5,4 g, 51mmol) in dry dichloromethane (30ml) was stirred at room temperature for 15 min.. <u>ortho</u>-Benzylbenzyl alcohol (2,50 g, 12,6 mmol) in dry dichloromethane (20ml) was then added dropwise and the reaction stirred for further 2 hours at room temperature. Filtration through a short silica gel column with ether as eluant and evaporation yielded the aldehyde (58) (2,18 g, 88%) as a colourless oil.[39]

^{1}H NMR: -CH_2Ph δ=4,40 singlet; 8 aromatic H δ=6,90-7,60; 1 aromatic H δ=7,60-8,00 multiplet; -CHO δ=10,57 siglet.

<u>ortho</u>-Benzylstyrene oxide (12e)

Aqueous sodium hydroxide (50%, 7ml) was added dropwise to a stirred solution of the aldehyde (58) (2,0 g, 10,2 mmol), trimethylsulfonium chloride (1,7 g, 13 mmol) and benzyltriethylammonium chloride (0,10 g, 0,4 mmol) in dichloromethane (10ml). The reaction was stirred at room temperature for 1,5 hours, diluted with water (15ml) and extracted with dichloromethane (3x15ml). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated to yield a residue, which was purified on a silica gel column (hexane/ethyl acetate 20:1) to give pure (59) (1,1 g, 50%) as a slightly yellow oil. For ^{1}H and ^{13}C NMR spectra see Figure 2 a,b Appendix 1.

^{1}H NMR: epoxide ABX pattern H_A δ=2,60; H_B δ=3,03; H_X δ=4,03 J_{AB}=5,8 Hz J_{AX}=2,7 Hz J_{BX}=4,1 Hz doublets of doublets; -CH_2Ph δ=4,22 singlet; 9 aromatic H δ=7,16-7,41 multiplet.

^{13}C NMR: -$\underline{C}H_2$Ph δ=39,0; epoxide C: δ=50,5 (2C)

MS: m/e 210

Attempts to cyclize the styrene oxides (12c→12g).

(**A**). Reaction of <u>ortho</u>-(cyanomethyl)-styrene oxide (12d) with LDA.

Lithium diisopropyl amide (LDA) was prepared by addition of <u>n</u>-BuLi (1,25ml, 3,0 mmol, 2,4 M) to a solution of diisopropyl amine (0,3 g, 3,0 mmol) in THF (1ml) at room temperature, under nitrogen. The mixture was stirred for further 5 min. at roomtemperature before cooling to -78°C. A solution of the styrene oxide (12d) (0,50 g, 2,8 mmol) in THF (6ml) was then added quickly. The reaction was slowly warmed to room temperature (1 hour) before quenching with saturated aqueous ammonium chloride (5ml) and extraction with dichloromethane (3x5ml). The combined organic extractions were dried over anhydrous magnesium sulfate and evaporated to give a residue (0,55 g), as a brown foam. Examination of the product mixture by analytical TLC with various solvent systems showed a very large number of small spots. The ^{1}H NMR spectrum of the crude mixture showed very broad signals in several regions including a doublet at δ=1,27 and aromatic signals at δ=6,20-8,20.

(B). Reaction of ortho-(phenylsulfonylmethyl)-styrene oxide (12c) with LDA.

The styrene oxide (12c) (0,28 g, 1,1 mmol) in dry THF (5ml) was quickly added to a solution of LDA (1,2 mmol) in THF (2ml) at -78 °C, under nitrogen. The colour immediately changed to dark brown. The reaction was stirred at -78 °C for further 45 min. and was then allowed to reach room temperature (1 hour). Workup, as described above, yielded a crude product (0,31 g) as a brown foam. Examination of the product mixture by analytical TLC (hexane/ethyl acetate 3:2) showed two major spots, both more polar than the starting material. Separation on a silica gel column (gradient hexane/ethyl acetate 1:1 ethyl acetate) gave only small amounts of impure materials.

The reaction was repeated, (12c) (0,65 g, 2,4 mmol), with the change that it was stirred at -78 C° for 30 min. and then quenched at that low temperature. Workup left a crude product (0,68 g) as a light yellow foam. Analytical TLC (hexane/ethyl acetate 3:2) again showed the presence of two major spots. Separation of the product mixture on a silica gel column (gradient as above) again gave only small amounts of impure materials. The ^{1}H NMR spectra of the crude products and the different impure fractions showed all very broad signals in several regions including a doublet at δ=1,27 and aromatic signals.

(C). Reaction of ortho-(phenylsulfonylmethyl)-styrene oxide (12c) with n-BuLi.

n-BuLi (0,8ml, 1,9 mmol, 2,4 M) was added to a solution of (12c) (0,43 g, 1,6 mmol) in dry THF (10ml) at -78°C, under nitrogen. A yellow colour appeared instantly. The reaction was stirred for 5 min. at -78°C and was then allowed to reach room temperature (1 hour), followed by workup, as described above, to give the crude product (0,42 g) as a brown oil. Examination of the mixture by analytical TLC showed the presence of many products in small quantities. The ^{1}H NMR spectrum of the crude product showed very broad signals including aliphatic protons at δ=0,8-2,0 and aromatic protons at δ=6,80-8,70.

(D). Reaction of ortho-benzylstyrene oxide (12e) with LDA.

The styrene oxide (12e) (0,20 g, 1,0 mmol) in dry THF (2ml) was quickly added to a solution of LDA (1,1 mmol) in THF (1ml) at -78°C, under nitrogen. The reaction was stirred at -78°C for 30 min. and was then allowed to reach room temperature (1 hour). Workup, as described above, left a crude product (0,21 g) as a brown oil. Examination by analytical TLC (hexane/ethyl acetate 4:1) showed starting material as the major spot. The ^{1}H NMR spectrum indicated 55% of (12e) (based on integration) and had a doublet at δ=1,27.

(E). Reaction of ortho-benzylstyrene oxide (12e) with n-BuLi.

n-BuLi (0,5ml, 1,2 mmol, 2,4 M) was added to a solution of (12e) (0,22 g, 1,0 mmol) in dry THF (5ml) at -78°C, under nitrogen. A brown colour appeared instantly. The reaction was stirred for 5min. at -78°C and was then allowed to reach room temperature (1 hour), followed by workup, as described above, to give the crude product (0,26 g) as a brown oil. Examination of the product mixture by analytical TLC (hexane/ethyl acetate 4:1) showed that all the starting material had been consumed, but once again many small spots were present, ranging from the base-line to the solvent front. The ^{1}H NMR spectrum of the crude product had bad resolution and broad signals, including aliphatic signals at δ=0,70-1,90 and aromatic signals at δ=6,50-7,90.

(F). Reaction of ortho-methylstyrene oxide (12f) with LDA.

The styrene oxide (12f) (0,49 g, 3,7 mmol) in dry THF (4ml) was quickly added to a solution of LDA (4,0 mmol) in dry THF (1ml) at -78°C, under nitrogen. The reaction was stirred at -78°C for 1 hour and was then allowed to reach room temperature (1 hour). Workup, as described above, left a crude product (0,52 g) as a brown oil. Examination by analytical TLC (hexane/ethyl acetate 4:1) showed starting material as the main component.

(G). Reaction of ortho-methylstyrene oxide (12f) with n-BuLi.

n-BuLi (1,6ml, 3,8 mmol, 2,4 M) was added to a solution of (12f) (0,50 g,3,7 mmol) in dry THF (5ml) at -78°C, under nitrogen. A dark red colour appeard instantly. The reaction was stirred at -78°C for 15 min. and was then allowed to reach room temperature (1 hour). Workup, as described above, yielded a crude oil (0,51 g). Examination of the crude mixture by analytical TLC (hexane/ethyl acetate 3:2) showed the presence of starting material and base-line spots. The ^{1}H NMR spectrum of the crude product showed starting material (12f) (23%, based on integration over the $-CH_3$ signal and the aromatic protons), and also that an aldehyde derivative had been generated, tentatively identified as ortho-methylphenylacetaldehyde (66) ($-CH_3$ δ=2,33 singlet; $-CH_2-$ δ=3,63 J=2 Hz doublet; -CHO δ=9,66 J=2 Hz triplet ; 13% based on integration). There were also broad signals in the aliphatic region δ=0.70-2,0.

(H). Reaction of ortho-methylstyrene oxide (12f) with benzoyl peroxide.

Benzoyl peroxide (0,05 g, 0,2 mmol) was added to a solution of the styrene oxide (12f) (0,49 g, 3,7 mmol) in freshly distilled chlorobenzene (5ml) and the reaction was refluxed for 12 hours (130°C). Additional amounts of benzoyl peroxide (2x0,05 g, 0,4 mmol) were added during the reaction time. Evaporation of the solvent gave a crude product (0,61 g) as a lightly yellow oil. Examination of the crude mixture by analytical TLC (hexane/ethyl acetate 3:1) showed the presence of the starting material (12f) and a second more polar compound. The ^{1}H NMR spectrum of the crude product showed that the two compounds namely (12f) and (66) were present in a ratio of 5:1.

(I). Reaction of ortho-(iodomethyl)-styrene oxide (12g) with magnesium.
The styrene oxide (12g) (0,53 g, 2,0 mmol) and magnesium turnings (70 mg, 2,9 mmol) were refluxed in dry THF (5ml) for five hours. Workup, as described above, yielded the crude product (0,27 g) as a dark brown oil. Examination of this mixture by analytical TLC revealed the presence of four major products. Separation on a silica gel column (hexane/ethyl acetate 10:1) gave two impure fractions (160 mg and 90 mg). The ^{1}H NMR spectra of the crude product and the two fractions, respectively, showed the absence of any cycloadduct (13g) and no further interpretation could be made.

Thermolysis of the styrene oxides (12e and 12f)

All the flash vacuum thermolysis experiments were carried out in an apparatus (see Figure 1, Appendix 2) consisting of a bulb to bulb heater, a furnace and a cold finger before the outlet to the high vacuum pump.

(A). The styrene oxide (12f) (0,13 g, 1,3 mmol) was preheated to 60°C/0,025 mmHg before exposure to 450°C/0,025 mmHg. The material trapped on the cold finger was recovered by washing with dichloromethane followed by evaporation of the solvent to give back the starting material (0,15 g, 33%) as shown by GC and NMR.

(B). The styrene oxide (12f) (0,45 g, 1,3 mmol) was preheated to 60°C/0,1 mmHg before exposure to 765°C/0.1 mmHg. A crude product (0,32 g) was recovered from the cold finger. Separation of the crude product on a silica gel column (hexane) gave pure aldehyde (66) (60 mg, 14%) and a very non-polar fraction (60 mg). GC-analysis of the non-polar fraction indicated the presence of three products (retention times: 105, 146 and 195 seconds) and the ^{1}H NMR spectrum showed signals at δ=2,25 singlet; three peaks near δ=2,35; and aromatic protons at δ=7.06 and 7,16 singlets; integrating as 1:1:2.

(C). The styrene oxide (12f) (30 mg, 0,6 mmol) was preheated to 60°C/12 mmHg before exposure to 770°C/12 mmHg. A crude product (60 mg) was recovered from the cold finger. GC and NMR analysis showed the absence of the aldehyde (66), and gave the same results as for the non-polar fraction in the experiment (B).

(D). The styrene oxide (12e) (0,21 g, 1,0 mmol) was preheated to 120°C/0.08 mmHg before exposure to 770°C/0,08 mmHg. A crude crystalline product (0,16 g) was recovered from the cold finger. Attempts to recrystallization failed. Examination of the crude product by analytical TLC (hexane/ethyl acetate 10:1) showed the presence of one major product less polar than the starting material. Separation by preparative TLC (hexane/ethyl acetate 20:1) gave the major fraction (85 mg, 41 % recovery) as a white solid. The ^{1}H NMR spectrum of the crude product showed that an aldehyde derivative had been generated, tentatively identified as <u>ortho</u>-benzylphenylacetaldehyde (69) ($-C\underline{H}_2CHO$ δ=3,53 J=2 Hz doublet; $-CH_2Ph$ δ=3,93 singlet; -CHO δ=9,40 J=2 Hz triplet; 16% based on integration). The ^{1}H NMR spectrum of the major fraction showed signals at δ=2,4 singlet; δ=2,9 singlet; $-CH_2Ph$ δ=3,9 singlet; and aromatic protons at δ=7,0-7,4 multiplet.

Methyl <u>ortho</u>-(phenylsulfonyl)-benzoate (39)

<u>meta</u>-Chloroperoxybenzoic acid (16,8 g,78.mmol) in dichloromethane (10ml) was dropwise added to a stirred solution of (53) (9,9 g, 38 mmol) in dichloromethane (160ml) at room temperature. The reaction was then refluxed for 1 hour, washed with aqueous sodium sulfite (10%, 100ml), aqueous sodium hydroxide (10%, 2x100ml) and water (100ml). The organic layer was dried over anhydrous magnesium sulfate and evaporated to give a crude crystalline product. Recrystallization from hexane/CH_2Cl_2 gave pure (39) (11,0 g, 99%) as white crystals: m.p. 101-102°C.

^{1}H NMR: $-OCH_3$ δ=2,73 singlet; $-CH_2SO_2Ph$ δ=5,05 singlet; 8 aromatic H δ=7,20-7,70 multiplet; 1 aromatic H δ=7,80-7,90 multiplet.

^{13}C NMR: $-OCH_3$ δ=52,1; $-CH_2SO_2Ph$ δ=59,2.
IR: CO 1720 cm^{-1}; $-SO_2-$ 1315 cm^{-1} and 1150 cm^{-1}.
MS: m/e 290

Dimethyl 1-hydroxynaphthalene-2,3-dicarboxylate (91)

A mixture of methyl ortho-(phenylsulfonylmethyl)-benzoate (39) (0,47 g, 1,6 mmol), dimethyl fumarate (0,27 g, 1,9 mmol), sodium hydride (0,16 g ,6,7 mmol) and t-butyl-alcohol (0,13 g, 1,8 mmol) in dry THF (5ml) was stirred at room temperature for 20 hours. The reaction was quenched with saturated aqueous ammonium chloride (5ml) and extracted with dichloromethane (3x5ml). The combined organic extractions were washed with water (5ml), dried over anhydrous magnesium sulfate and evaporated to give a residue. Purification on a silica gel column (hexane/ethyl acetate 4:1) yielded pure (91) (0,25 g, 60%) as white needles: m.p. 102-103°C from hexane/CH_2Cl_2 (lit. m.p. 145-160°C decomp.[39])

^{1}H NMR: 2 $-OCH_3$ δ=3,91 and δ=3,94 singlets; 4 aromatic H δ=7,38-7,80 multiplet; 1 aromatic H δ=8,28-8,46 multiplet; -OH δ=11,88 singlet.
^{13}C NMR: 2 $-OCH_3$ δ=52,6 and δ=52,8; COH δ=161,0; 2CO δ=169,7, δ=170,4
IR: CO 1720 cm^{-1} and 1670 cm^{-1}
MS: m/e 260

The reaction was repeated following the same procedure and quantities as described above , with exception that dimethyl maleate was used instead of dimethyl fumarate.

After workup the naphthol (91) (0,33 g, 74%) was obtained, all analytical and physical data were identical with the above described. For ^{1}H and ^{13}C NMR see Figure 5 a,b Appendix 1.

Synthesis of the unsaturated sulfone (93) with potassium *tert*-butoxide as base

A mixture of (39) (0,47 g, 1,6 mmol), benzaldehyde (0,20 g, 1,9 mmol) and potassium *tert*-butoxide (0,22 g, 2.0 mmol) in dry THF (5ml) was stirred at room temperature for 20 hours. The reaction mixture was diluted with water (5ml), extracted with dichloromethane (3x5ml), dried over anhydrous magnesium sulfate and evaporated. The residue crystallized from hexane/ethyl acetate to give pure (93) (0,33 g, 56%) as white crystals: m.p. 153-160°C.

^{1}H NMR: (DMSO-d_6) 15 H δ=6,95-8,10 multiplet.
^{13}C NMR: (DMSO-d_6) δ=CH-Ph δ=138,7; -COOH δ=167,5.
IR: (KBr pellet) -OH 2800-3500 cm^{-1}; CO 1700 cm^{-1}; -SO$_2$- 1320 cm^{-1} and 1150 cm^{-1}.
MS: m/e 364

Synthesis of the unsaturated sulfone (93) with LDA as base

A solution of (39) (0,50 g, 1,7 mmol) and benzaldehyde (0,20 g, 1,9 mmol) in dry THF (5ml) was added to LDA (1,7 mmol) in THF (2ml) at -78°C, under nitrogen. The reaction was stirred at room temperature for 2 days, quenched with saturated aqueous ammonium chloride (5 ml), extracted with dichloromethane (3x5ml), dried over anhydrous magnesium sulfate and evaporated. The crude product was filtered through a short silica gel column with ethyl acetate as eluant. Crystallization from hexane/ethyl acetate gave pure (93) (0,23 g, 37%) with the same analytical and physical data as described above.

Attempt to monomethylate methyl ortho-(phenylsulfonylmethyl)-benzoate (89)

A solution of (89) (0,49 g, 1,7 mmol) and methyl iodide (0,27 g, 1,9 mmol) in THF (4ml) was added to LDA (1,9 mmol) in THF (1ml) at -78°C, under nitrogen. The reaction was allowed to reach room temperature (1 hour) and was then stirred at room temperature for 1 hour. The reaction was quenched with saturarated aqueous ammonium chloride (5ml), extracted with dichloromethane (3x5ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvents left a brown oil (0,54 g). The ^{1}H NMR spectrum of the crude product showed a ratio of 2:2:1 for (89), monomethylated product (94) and dimethylated product (95).

^{1}H NMR (94): -CH_3 δ=1,65 J=7 Hz doublet; -OCH_3 δ=3,65 singlet; -CH δ=5,93 J=7 Hz quartet.

^{1}H NMR (95): 2 -CH_3 δ=1,73 singlet; -OCH_3 δ=3,65 singlet.

Attempt to monomethylate methyl ortho-(phenylthiomethyl)-benzoate (53)

A solution of (53) (0,5 g, 1,9 mmol) and methyl iodide (0,28 g, 2 mmol) in THF (4ml) was added to LDA (2,1 mmol) in THF (1ml) at -78°C, under nitrogen. The reaction was stirred at -78°C for 15 min. before it was allowed to reach room temperature (1 hour) and was then stirred at room temperature for 1 hour. The reaction was quenched with saturated aqueous ammonium chloride (5ml), extracted with dichloromethane (3x5ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvents left a crude product which was purified on a silica gel column (hexane/ethyl acetate 4:1) to give a colourless oil (0,29 g). The ^{1}H NMR spectrum showed a ratio of 5:1 for monomethylated product and dimethylated product.

^{1}H NMR (monomethylated product): $-CH_3$ δ=1,60 J=7 Hz doublet;
$-OCH_3$ δ=3,77 singlet; -CH δ=5,53 J=7 Hz quartet.
^{1}H NMR (dimethylated product): 2 $-CH_3$ δ=1,75 singlet;
$-OCH_3$ δ=3,77 singlet.

Reaction of methyl ortho-(phenylsulfonylmethyl)-benzoate (89) with benzophenone

A mixture of (89) (0,39 g, 1,3 mmol), benzophenone (0,30 g, 1,6 mmol), sodium hydride (0,04 g, 1,7 mmol) and t-butyl alcohol (0,12 g, 1,7 mmol) in dry THF (4ml) was stirred at room temperature for 4 days. The reactiom was quenched with saturated aqueous ammonium chloride (5ml), extracted with dichloromethane (3x5ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvents gave a residue, which was separated on a silica gel column (hexane/ethyl acetate 10:1) to afford (89) (0,15 g, 37% recovery) and benzophenone (0,11 g, 38% recovery). No other products were isolated.

Reaction of methyl ortho-(phenylsulfonylmethyl)-benzoate (89) with cyclohexanone

The above reaction was repeated with the exception that cyclohexanone (0,15 g, 1,5 mmol) was used instead of benzophenone. Workup yielded a brown oil (0,56 g). Examination by analytical TLC (hexane/ethyl acetate 4:1) showed many small spots, ranging from the base-line to the solvent front. The ^{1}H NMR spectrum of the crude product had bad resolution and broad signals, including aliphatic signals at δ=0,8-2,3 and aromatic signals at δ=5,8-7,9.

Synthesis of the seven membered lactone (97)

To a solution of ortho-(phenylsulfonylmethyl)-benzyl alcohol (55) (1,00 g, 3,8 mmol) in dry THF (20ml) at -78°C under nitrogen was added n-BuLi (3,5 ml, 3,4 mmol, 2,4 M). The reaction was stirred at the low temperature for 1 hour before it was allowed to reach room temperature (1 hour). Dimethyl fumarate (0,57 g, 4,0 mmol) was then added and the reaction stirred for another 15 min. at room temperature prior to quenching with saturated aqueous ammonium chloride

(10ml), extraction with dichloromethane (3x15ml) and drying over anhydrous magnesium sulfate. Evaporation of the solvents left a residue, which after crystallization gave pure (97) as white crystals: m.p.115-117°C.

^1H NMR: $-C\underline{H}_2-COOCH_3$ $\delta=3,63$ singlet; $-OCH_3$ $\delta=3,74$ singlet;
$-CH_2-OCO-$ $\delta=5,10$ singlet; $-CH=$ $\delta=7,08$ singlet;
4 aromatic H $\delta=7,40$ broad singlet.

^{13}C NMR: $-\underline{C}H_2-COOCH_3$ $\delta=40,7$; $-OCH_3$ $\delta=52,2$; $-\underline{C}H_2-OCO-$
$\delta=68,5$; 2 CO $\delta=163,3$ and 171,4.

IR: $-COOCH_3$ 1730 cm^{-1} and , -unsaturated CO
1705 cm^{-1}.

MS: m/e 232

Attempt to cyclize <u>ortho</u>-(phenylsulfonylmethyl)-benzyl alcohol (55) with diiodomethane

Aqueous sodium hydroxide (50%, 3ml) was added dropwise to a stirred solution of the alcohol (55) (0,20 g, 0,8 mmol), diiodomethane (0,49 g, 1,5 mmol) and benzyltriethylammonium chloride (0,01 g, 0,04 mmol) in dichloromethane (3ml). The reaction was stirred at room temperature for 5 days before dilution with water (4ml) and extraction with dichloromethane (3x4ml). The combined organic extractions were dried over anhydrous magnesium sulfate and evaporated to yield a crude product (0,53 g). The ^1H NMR spectrum of the crude product showed only the presence of starting materials.

Attempt to cyclize ortho-(phenylsulfonylmethyl)-benzyl alcohol with dichlorodimethylsilane

n-BuLi (1,7ml, 4,1 mmol, 2,4 M) was added to a solution of (55) (0,48 g, 1,8 mmol) and freshly distilled dichlorodimethylsilane (0,25 g, 1,9 mmol) in dry THF (5ml) at -78°C, under nitrogen. The reaction was stirred at that low temperature for 15 min. before it was allowed to reach room temperature (1 hour). The reaction was quenched with saturated aqueous ammonium chloride (3ml) and extracted with dichloromethane (3x5ml). The combined organic extractions were dried over anhydrous magnesium sulfate and evaporated to give a crude product (0,68 g). Examination of the crude product by analytical TLC (hexane/ethyl acetate 1:1) showed the presence of the starting material (55) as the major spot and also many small spots, ranging from the base-line to the solvent front. The ^{1}H NMR spectrum showed the presence of (55) (43%, based on integration over the benzylic and aromatic protons), and also of products that gave raise to broad signals with bad resolution, including signals in the aliphatic region δ=0-2.0 and the aromatic region δ=6,8-8,0.

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CLAIMS TO ORIGINAL RESEARCH.

1. The reactions of 3-(*ortho*-bromophenyl)-1,2-epoxypropane with *n*-BuLi and *n*-BuLi/$MgBr_2$ were studied. The products were cinnamyl alcohol and 2-indanol respectively.

2. The possibility of converting several electronegatively substituted *ortho*-styrene oxide derivatives via carbanions, generated with LDA, *n*-BuLi or Grignard reaction, into benzocyclobutyl methanol derivatives was studied. It was concluded that this does not represent a viable route.

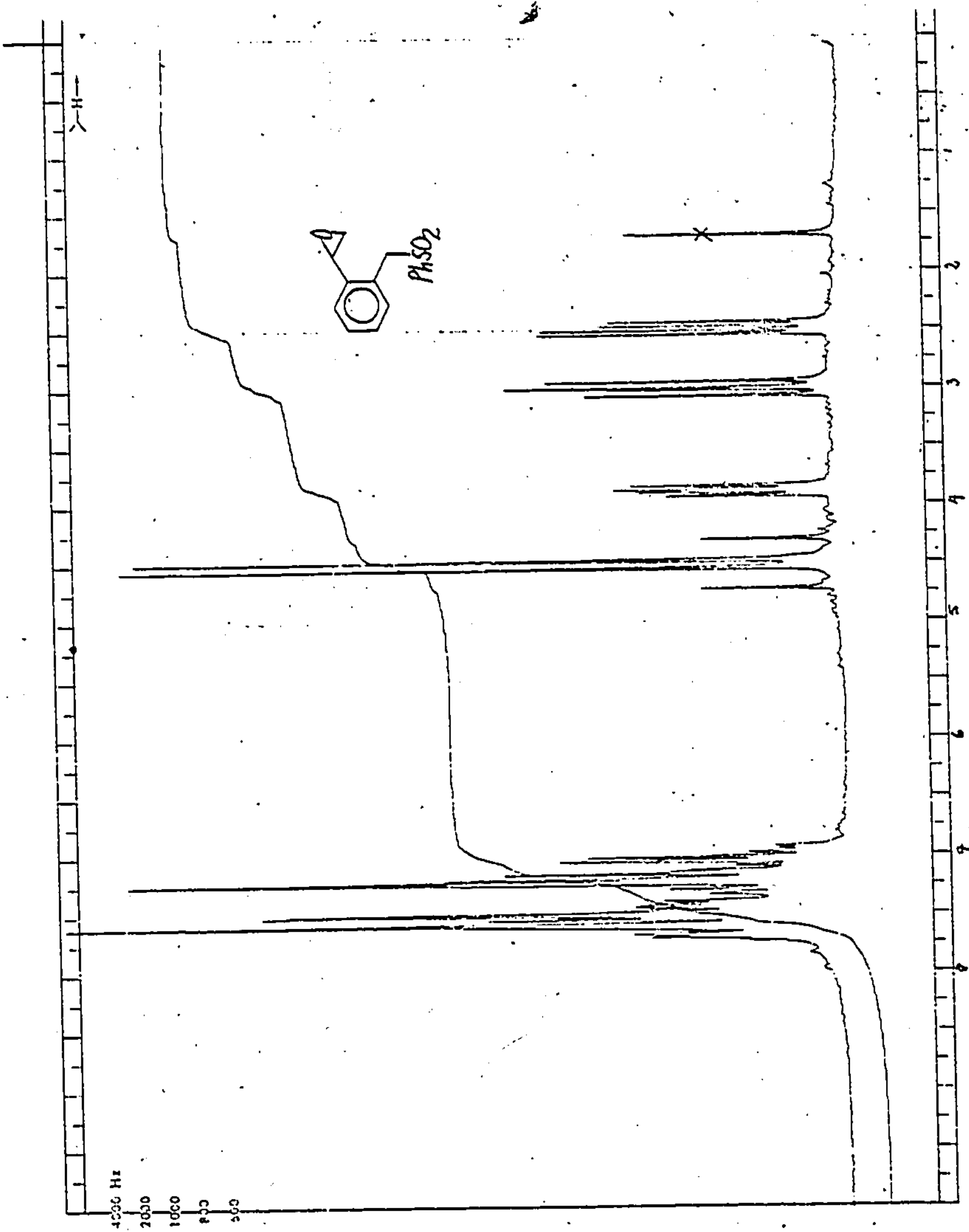
3. The flash vacuum thermolysis (770°C/0,1 mmHg) of *ortho*-methyl- and *ortho*-benzylstyrene oxide was briefly investigated and shown to yield the rearranged *ortho*-substituted phenylacetaldehyde as a major product. Several other, as yet unidentified, deoxygenated products were also found.

4. The reactions of the carbanion derived from methyl-*ortho*-(phenylsulfonylmethyl)-benzoate with dienophiles and simple carbonyl compounds were investigated.

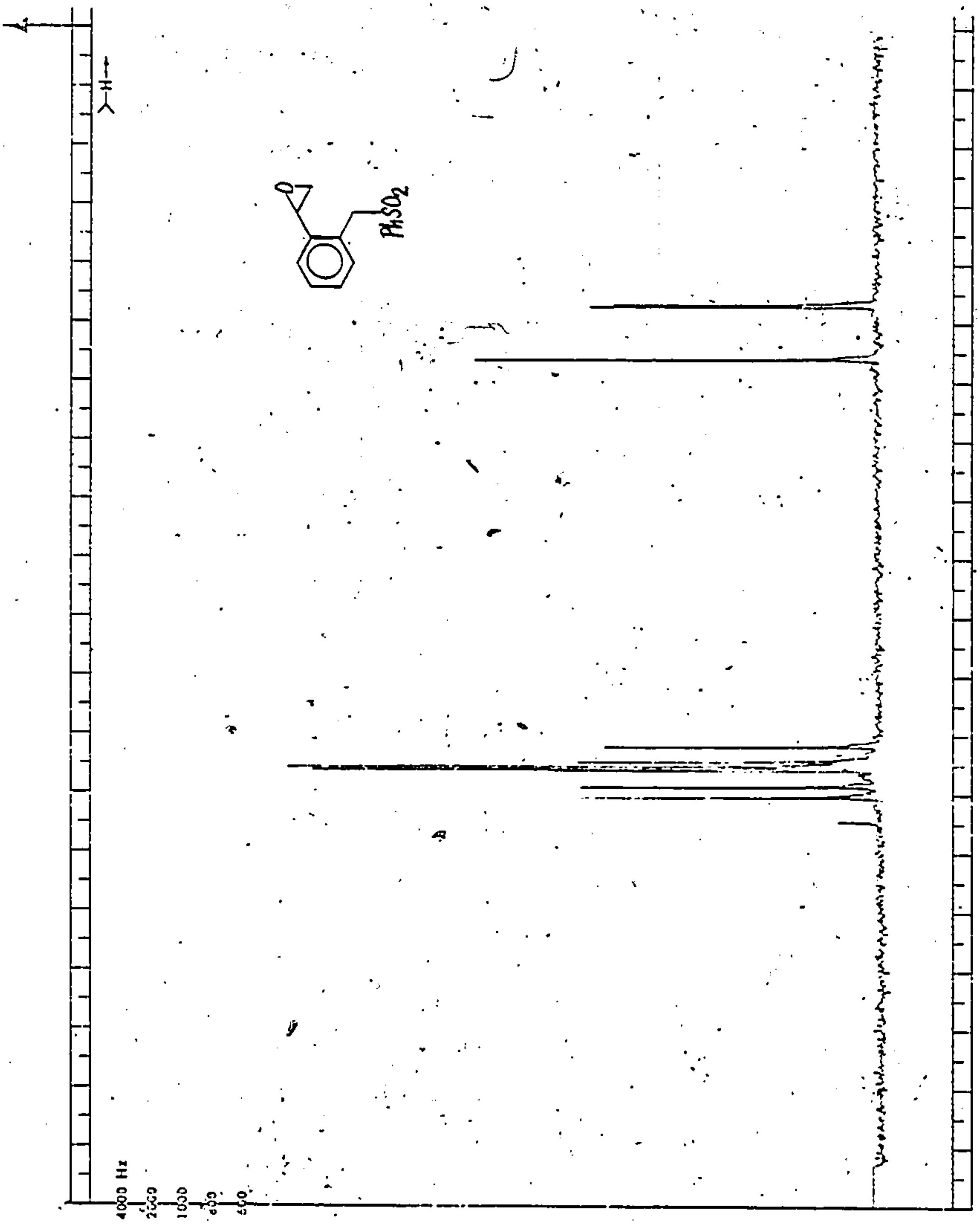
5. The dianion generated from *ortho*-(phenylsulfonylmethyl)-benzyl alcohol reacted with dimethyl fumarate to give the seven-membered lactone (97).

6. In the course of these investigations 16 new compounds were synthesized.

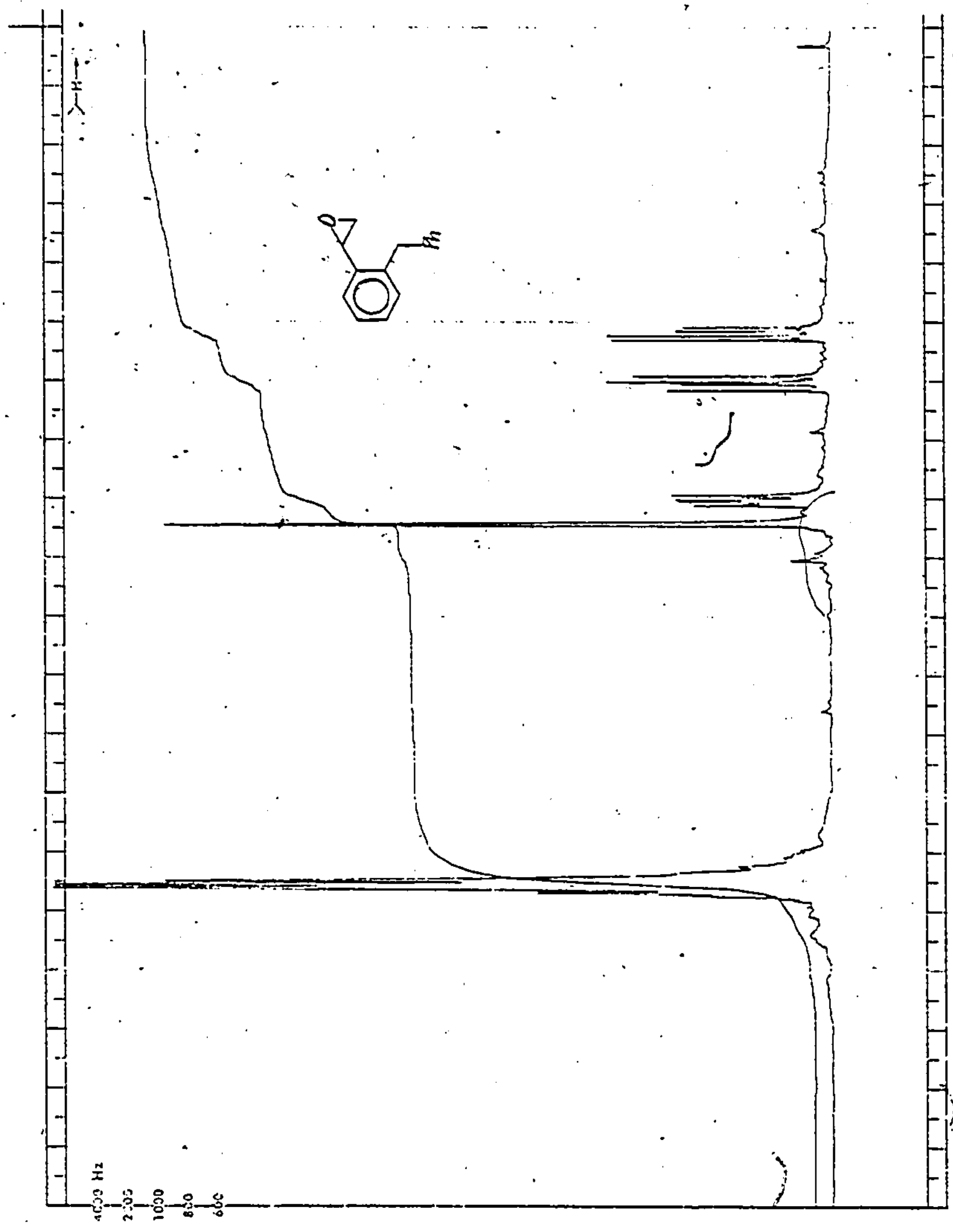
Appendix 1; Figure 1 a), ^1H NMR spectrum of <u>ortho</u>-(phenylsulfonylmethyl)-styrene oxide (12c), 80 MHz NMR



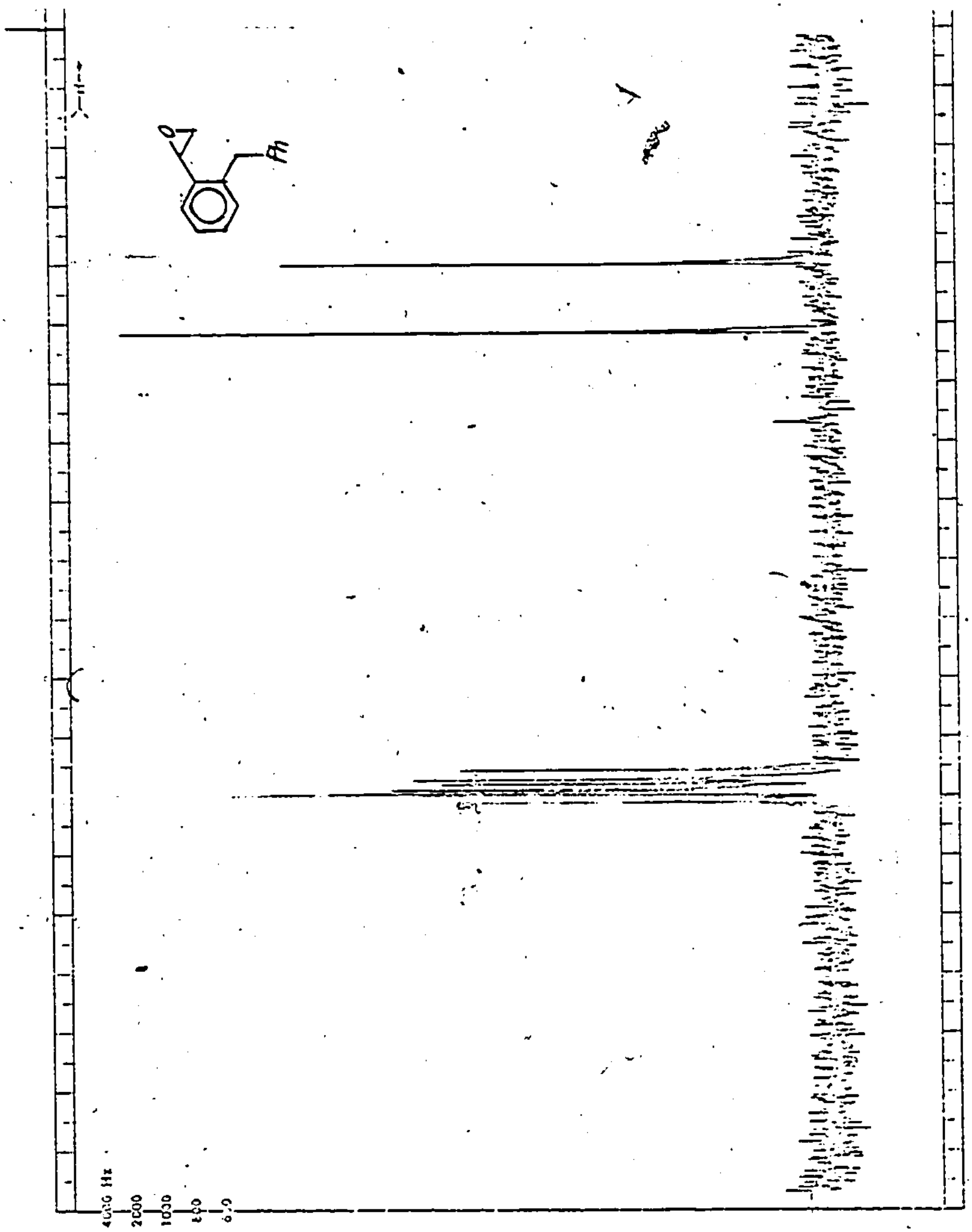
Appendix 1; Figure 1 b), ^{13}C NMR spectrum of ortho-(phenylsulfonylmethyl)-styrene oxide (12c), 80 MHz NMR



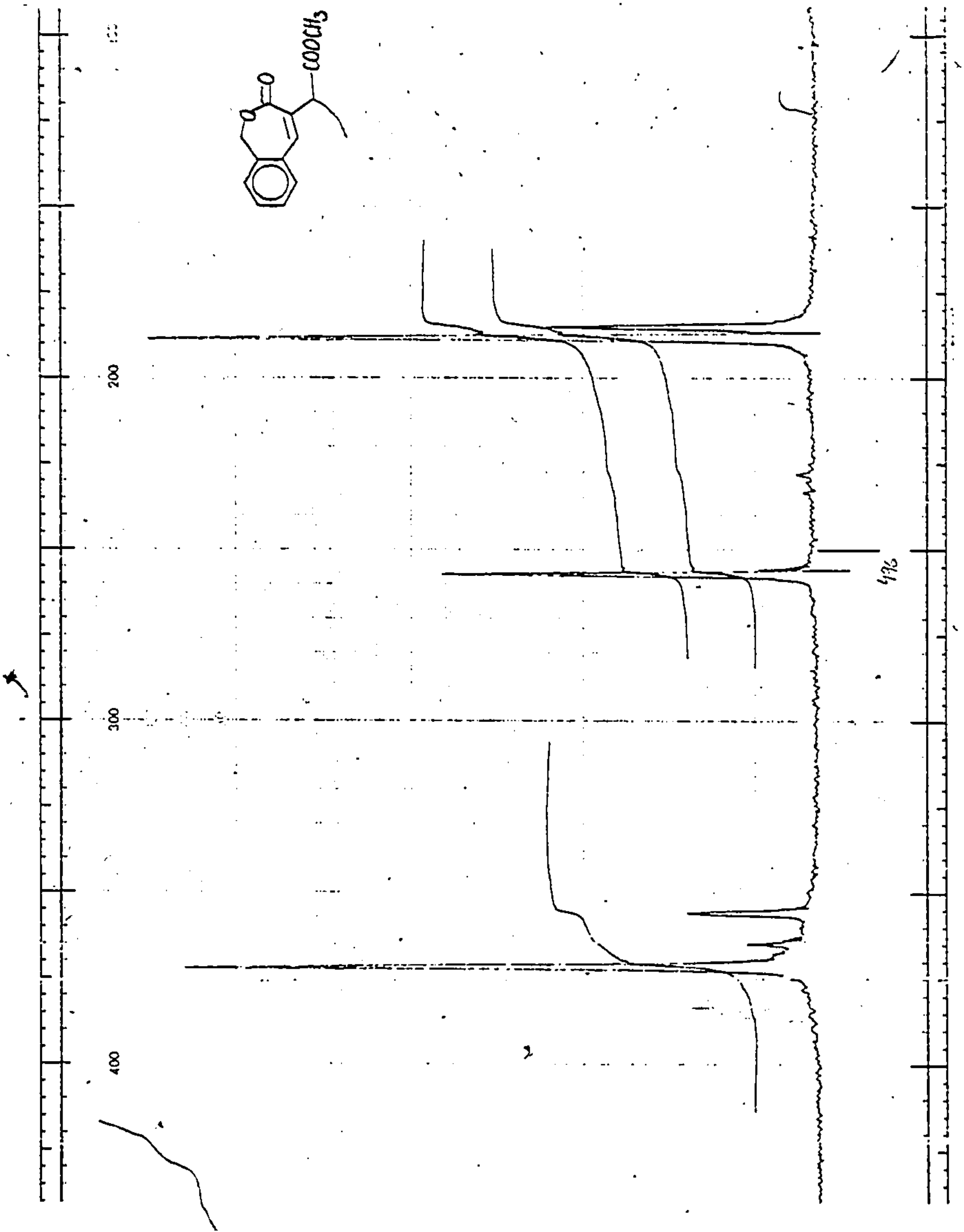
Appendix 1; Figure 2 a), ^{1}H NMR spectrum of <u>ortho</u>-benzylstyrene oxide (12e), 80 MHz NMR

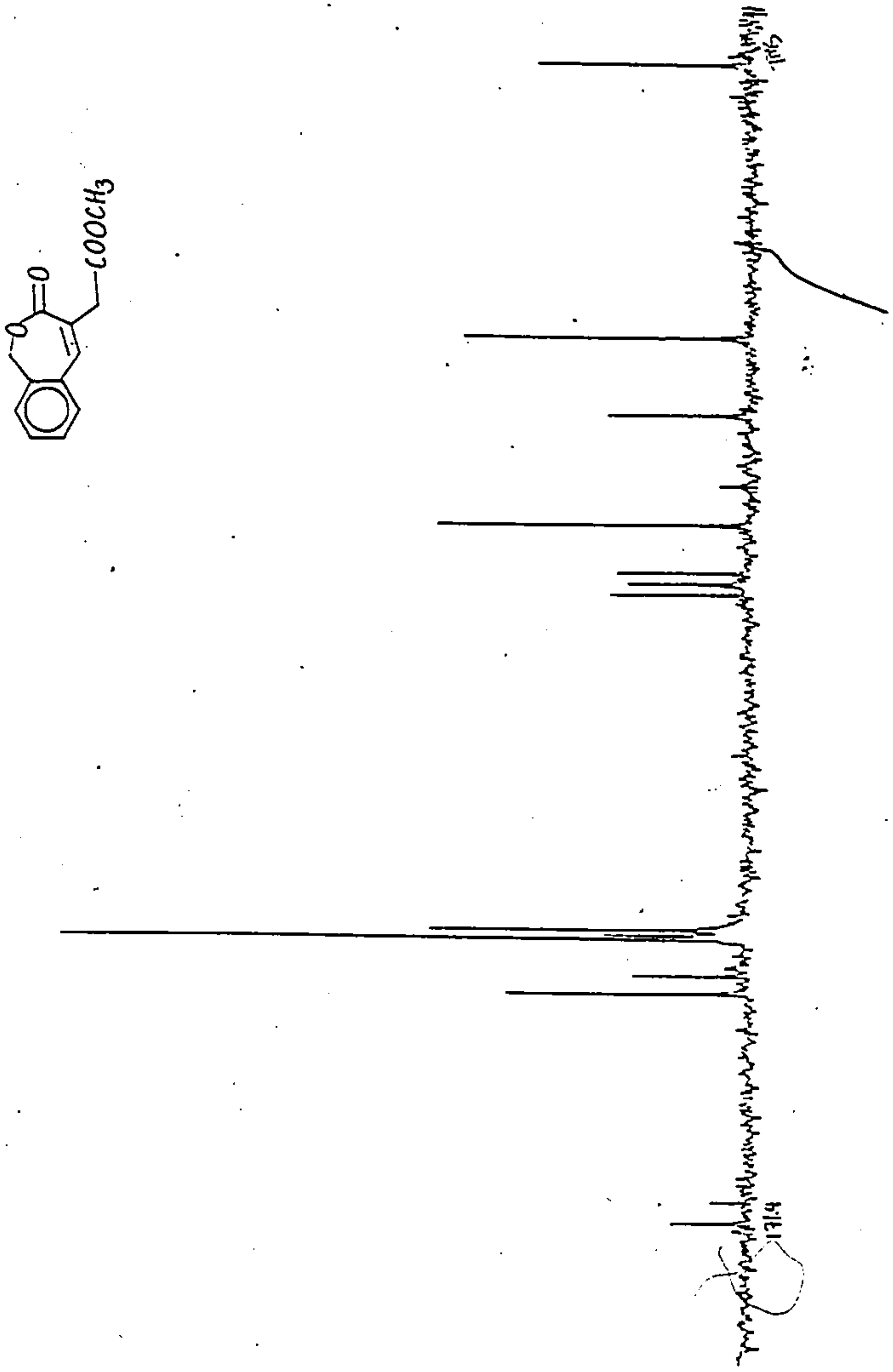


Appendix 1; Figure 2 b), ^{13}C NMR spectrum of <u>ortho</u>-benzylstyrene oxide (12e), 80 MHz NMR



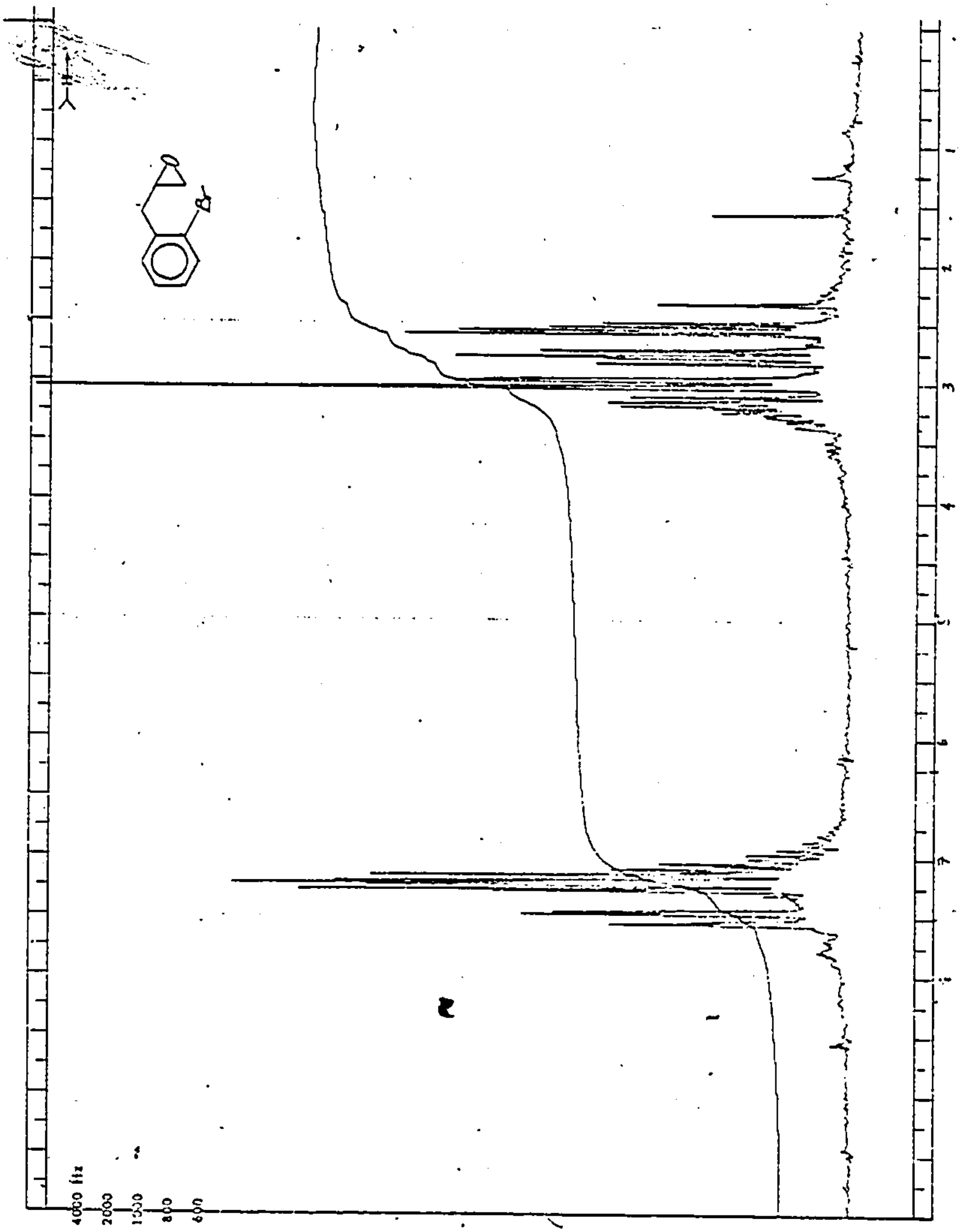
Appendix 1; Figure 3 a), ^{1}H NMR spectrum of the seven-membered lactone (97), 100 MHz NMR



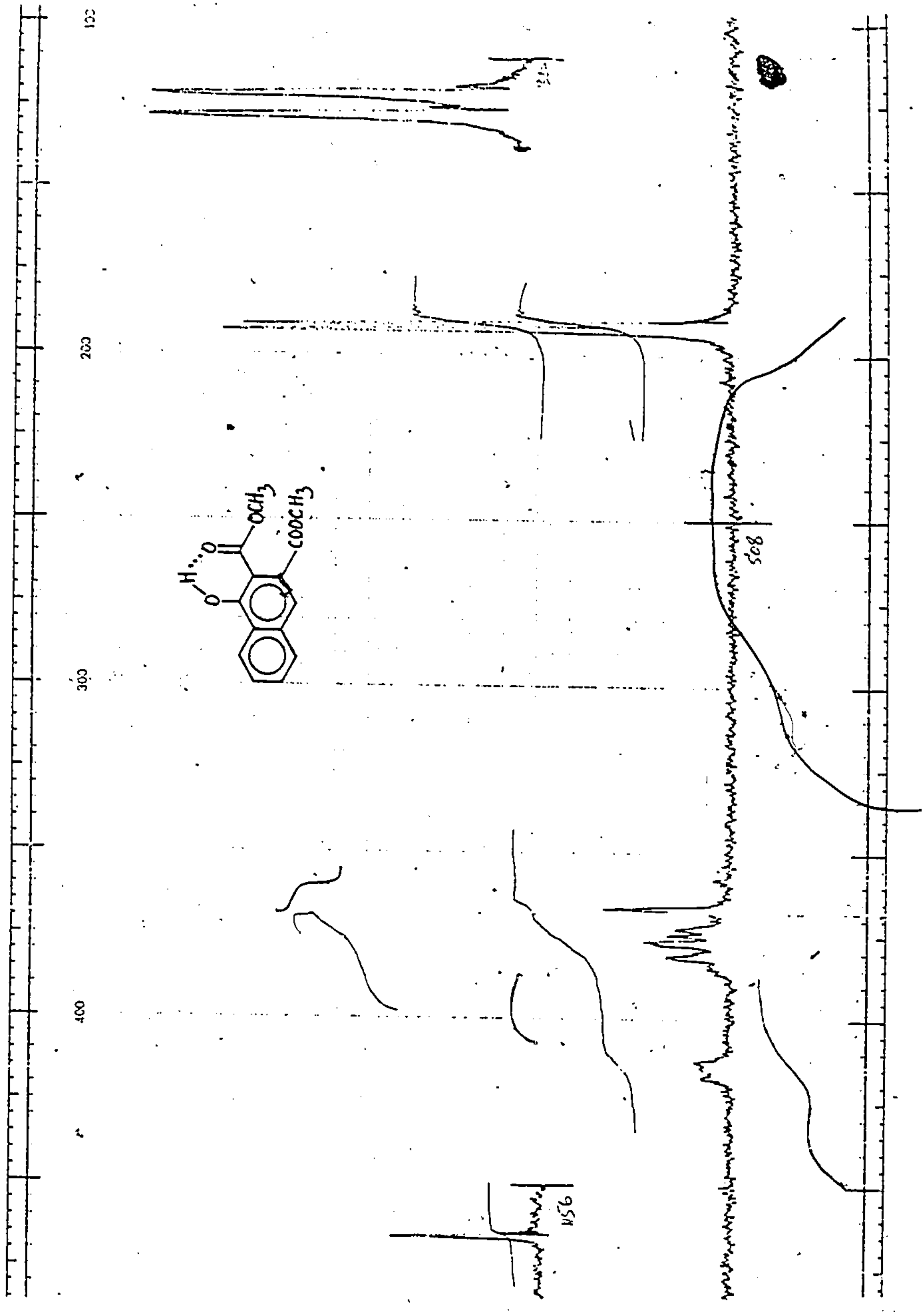


Appendix 1; Figure 3 b), ^{13}C NMR spectrum of the seven-membered lactone (97), 80 MHz NMR

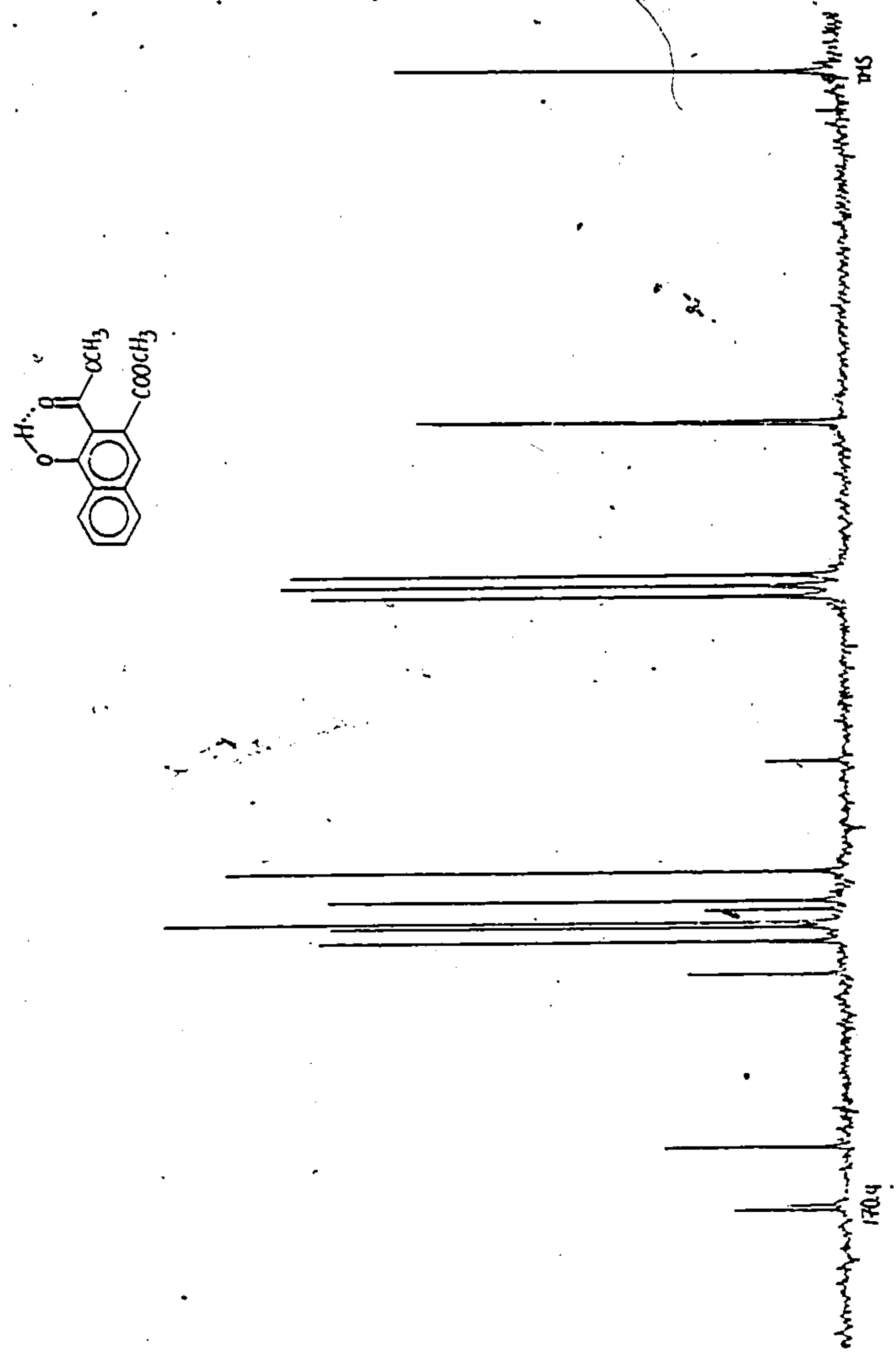
Appendix 1; Figure 4, ^{1}H NMR spectrum of 3-(<u>ortho</u>-bromophenyl)-1,2-epoxypropane (24), 80 MHz NMR



Appendix 1; Figure 5 a), ^1H NMR spectrum of (91), 100 MHz NMR

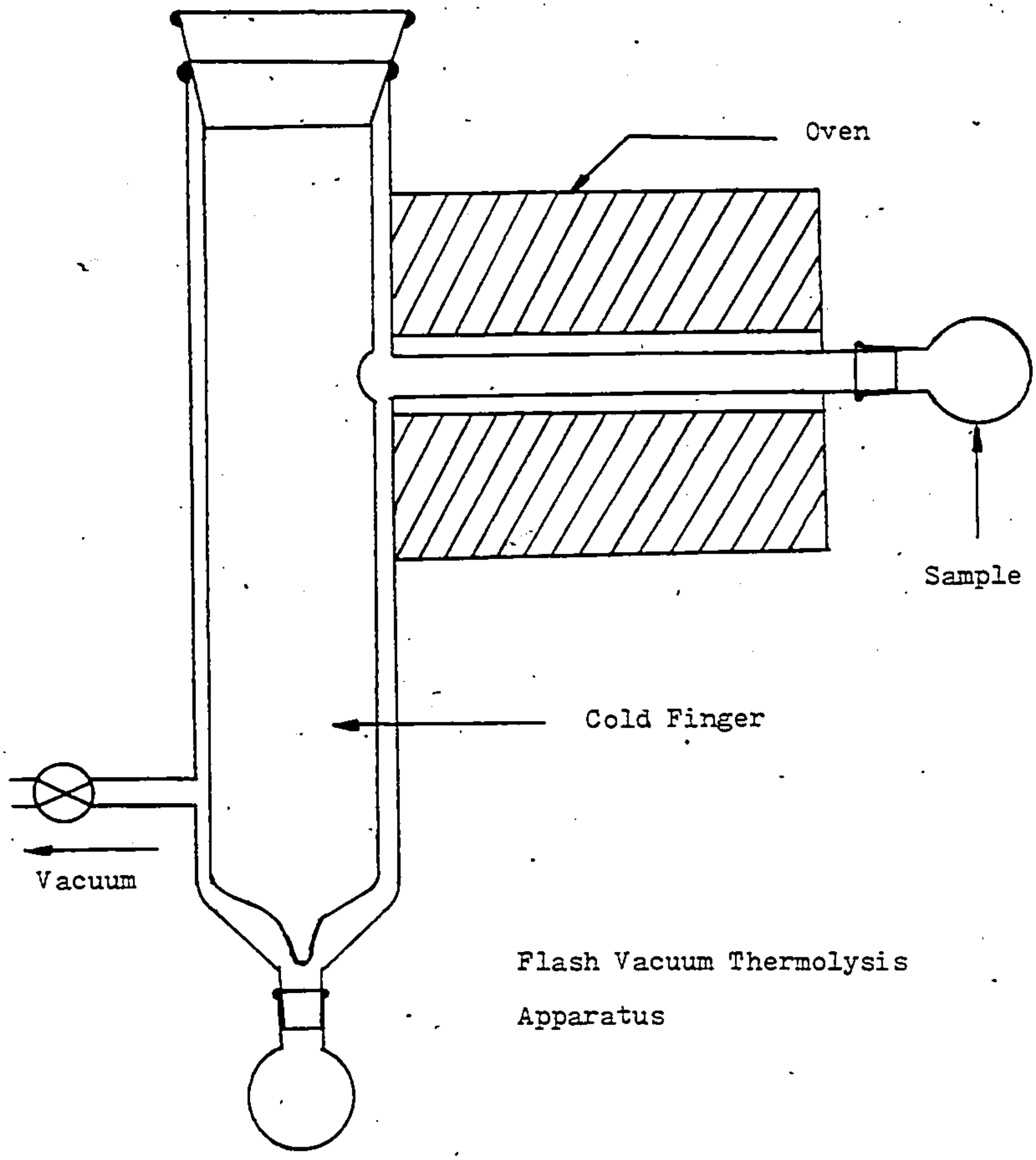


Appendix 1; Figure 5 b), ^{13}C NMR spectrum of dimethyl
1-hydroxynaphthalene-2,3-dicarboxylate (91),
80 MHz NMR



Appendix 2

Figure 1.



Flash Vacuum Thermolysis Apparatus

Appendix 3

Figure 1,

Compound	Calculated value		Found	
	C %	H %	C %	H %
(53)	69,74	5,46	70,17	5,53
(12c)	65,67	5,14	65,68	5,35
(12e)	85,68	6,71	85,65	6,53
(12f)	80,56	7,51	80,72	7,72
(89)	62,05	4,86	61,89	4,52
(93)*	69,21	4,43	69,11	4,59
(97)	67,23	5,21	66,66	5,29

* Calculated value S % = 8,80 ; Found S % = 8,73