SYNTHETIC STUDIES ON HETEROCYCLES OF BIOLOGICAL INTEREST
AND
REARRANGEMENT STUDIES ON CYCLOPROPYL KETONES

By

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Thesis

DEDICATED IN THE MEMORY OF MY LATE UNCLE,

GRANDFATHER AND GRANDMOTHER

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The work described in this thesis is original and has not been submitted for any other degree or diploma in this or any other university.

H. JUNJAPPA
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Date: 20th February, 1997

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2. SPS-629	Numerical Methods with Application to Computers.	A
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PREFACE

The α-oxoketene dithioacetals are a versatile group of 3-carbon fragments having ambident 1,3-electrophilic centres thus permitting to design various methodologies for both carbocyclic and heterocyclic syntheses. The differential electrophilicity of 1,3-carbon centres of these compounds has been exploited thoroughly by our group's continued efforts for the construction of new C-N and C-C bonds involving either 1,2- or 1,4- nucleophilic additions leading to a number of general synthetic routes for a wide range of organic molecules.

The work presented in this thesis is a part of our ongoing investigations on α-oxoketene S,S-, S,N- and O,S-acetals and cyclopropyl substituted oxoketene dithioacetal.

The first chapter brings a brief review on the reactivity of oxoketene dithioacetals. The use of oxoketene dithioacetals for a range of heterocycles, carbocycles, aromatics and heteroaromatics as well as construction of cyclopentanoids through acid catalyzed ring opening of cyclopropyl ketone is given.

A new efficient route to substituted carbazoles particularly having C-ring regiocontrolled substituents through the reaction of 1-alkylindole-3-acetonitrile with various α-oxoketene S,S-, N,S- and O,S-acetals is presented in second chapter.

Third chapter deals with aromatic annelation studies on S,S- acetal derived from 1,2,3,4-tetrahydro-N-benzenesulfonylquinol-4- one. The synthesis of a large variety of phenanthridines and benzo[j]phenanthridines is carried out following this route.

The acid catalyzed rearrangement studies on styryl cyclopropyl ketones via tandem carbocationic cyclization affording cyclopentanoids are described in the last chapter.

CONTENTS

CHAPT - 1

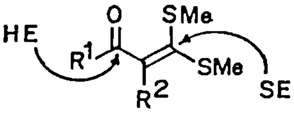
POLARIZED KETENE DITHIOACETAL AS VERSATILE INTERMEDIATE IN ORGANIC SYNTHESIS: A BRIEF REVIEW

The versatile synthon family of polarized ketene dithioacetal has been proved to be among the simplest and potential synthetic intermediates in various synthetic transformations.[1] This family of compounds can be prepared conveniently from a wide variety of active methylene compounds by condensation of the corresponding enolate with carbon disulfide or trithiocarbonate followed by alkylation of the intermediate dithiolate species often in one pot operation in moderate to good yield.[2-9] They exhibit well defined physical properties either as crystalline solids or distillable liquids and can be purified by conventional chromatographic methods. They are stable at room temperature and can withstand mild acidic and alkaline conditions.

1.1 The polarized ketene dithioacetal

Kelber and co-workers reported the first synthesis of α-oxoketene dithioacetal in 1910.[10-11] However, the chemistry of these intermediates remained unexplored until Thuillier and co-workers prepared these compounds in higher yields using sodium amylate as base.[2-5] Subsequently, these reaction conditions have been greatly improved using different bases and careful manipulation of reaction conditions.[4,6-9] A large number of α-oxoketene dithioacetals have now been reported and they have emerged as very useful synthetic intermediates over the last two decades.[1]

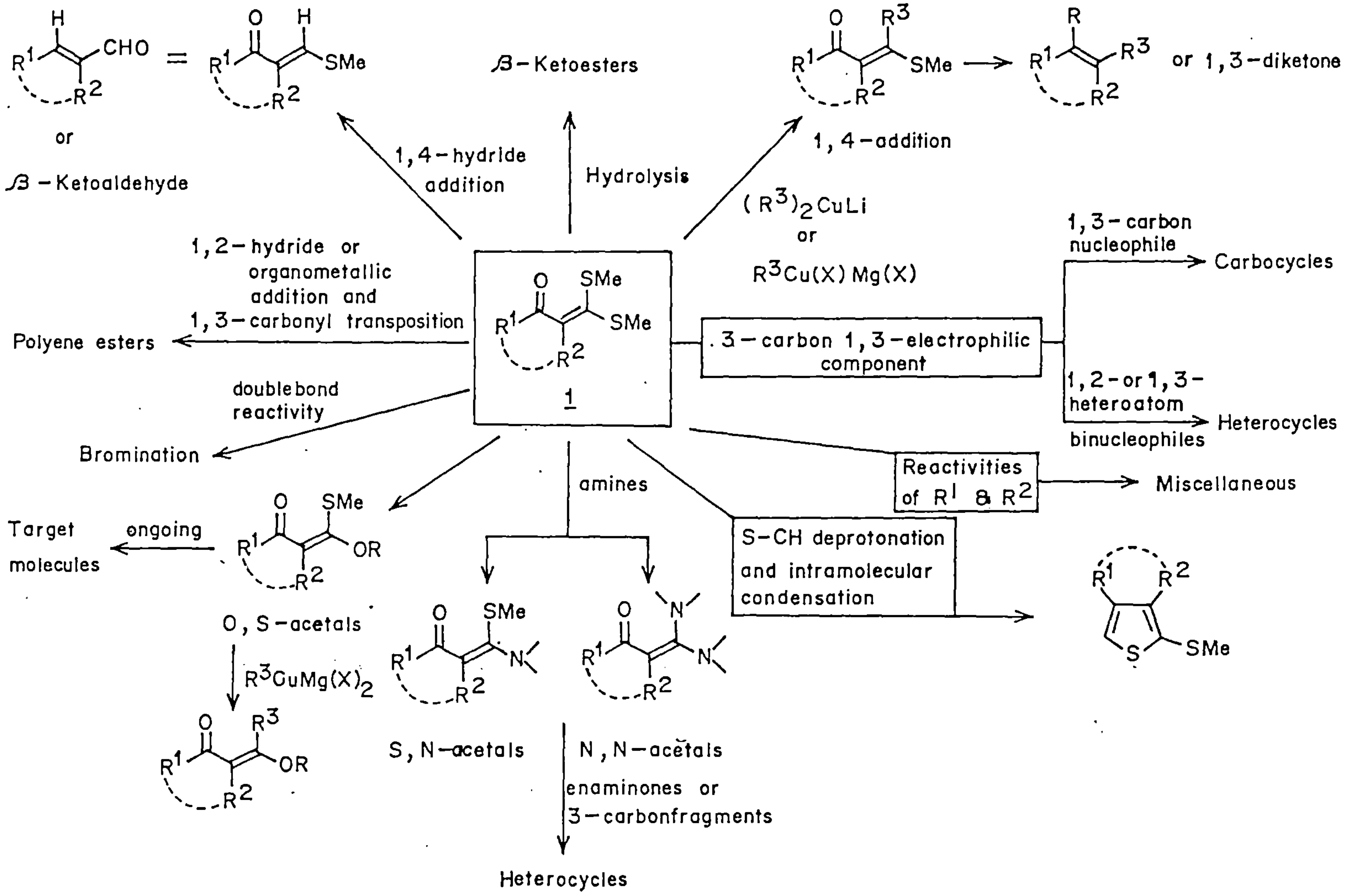
The oxoketene dithioacetals which can be prepared by easier methods in one pot and in high yields exhibit greater stability than the corresponding O,O-acetals,[12] which are moisture sensitive and undergo hydrolysis under mild conditions. They can be further converted to the corresponding ketene dihalogenides[13,14], N,S-[15], N,N-[16] and O,S-[17]acetals making them more important as precursors for a large variety of functionalized acetals. The oxoketene dithioacetals can also be visualized as masked ß-ketoester in which the ester functionality is manifested as a ketene dithioacetal moiety. Alternatively, they may be considered as α,ß-unsaturated ketones containing a highly functionalized carbon. The α-oxoketene dithioacetals have been shown to be excellent three carbon fragments possessing 1,3- electrophilic centres with differing electrophilic properties.[1]



HE = Hard electrophile
SE = Soft electrophile

Taking advantage of this difference, they have been exploited to construct stereo and regioselective bonds in various transformations. The oxoketene S,S-, N,S- N,N- and O,S-acetals have been extensively utilized in this laboratory for the synthesis of both heterocyclic and carbocyclic compounds.

Various reactivity profiles of α-oxoketene dithioacetals of general formula **1** are outlined in Scheme-1. Hydrides and organometallic reagents give 1,2-addition product characteristic of carbonyl function reactivity[18] but this sequence can be altered to the 1,4-path by suitably manipulating the reaction conditions and reagents.[18-20] Further transformations after the initial 1,2- or 1,4-addition have also been investigated extensively.[18] The α-oxoketene dithioacetal possess typical 1,3- electrophilic centres. These intermediates react with 1,2- and 1,3-heteroatom binucleophiles to give 5- and 6-membered heterocyclic compounds. The 1,3-carbon nucleophiles have been similarly used in the synthesis of carbocycles. The enolate anion formed by the deprotonation (when R=alkyl) can undergo condensation with aldehydes to give α-enoyl ketene dithioacetals.[3b,21] An allylic anion formation has been reported when R^2 is a methyl group leading to rearranged products.[22] Deprotonation of thiomethyl group followed by intramolecular aldol type condensation to afford thiophene is also reported.[23] As discussed, the α-oxoketene dithioacetal can be easily converted to O,S-, N,S- and N,N-acetals. They (R^2=H) also undergo bromination at α-position with N-bromosuccinimide.[24] Thus it is apparent that the α-oxoketene dithioacetal of general formula **1** constitute an important class of synthons with reactive electrophilic as well as nucleophilic centres distributed in various centres of its skeleton permitting



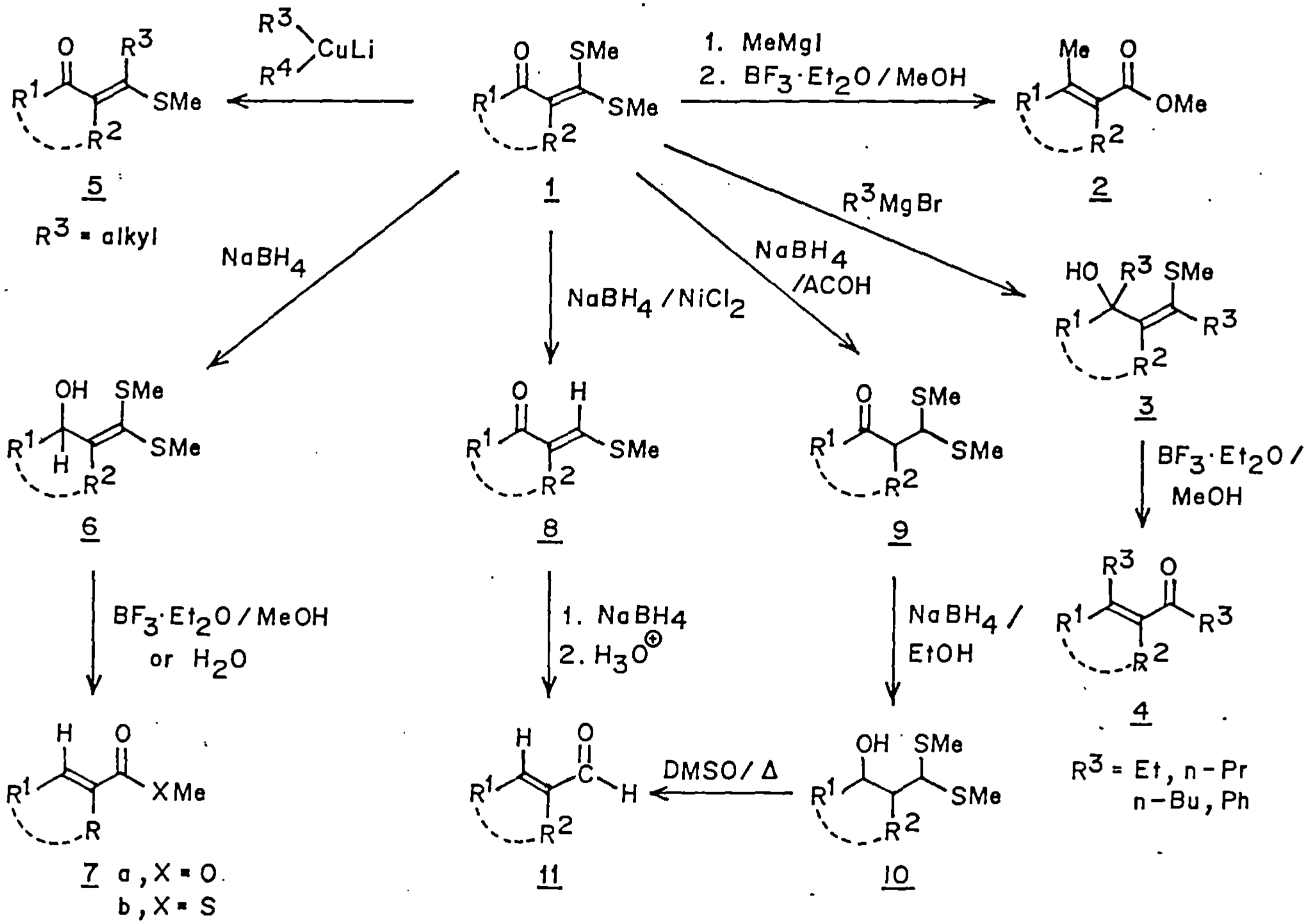
or
β – Ketoaldehyde
β – Ketoesters
or 1,3 – diketone
1,4 – hydride addition
Hydrolysis
1,4 – addition
(R^3)_2CuLi or R^3Cu(X)Mg(X)
1,2 – hydride or organometallic addition and 1,3 – carbonyl transposition
Polyene esters
double bond reactivity
Bromination
1
3 – carbon 1,3 – electrophilic component
1,3 – carbon nucleophile
Carbocycles
1,2 – or 1,3 – heteroatom binucleophiles
Heterocycles
Reactivities of R1 & R2
Miscellaneous
amines
S–CH deprotonation and intramolecular condensation
Target molecules
ongoing
O,S – acetals
R3CuMg(X)2
S,N – acetals
N,N – acetals
enaminones or 3 – carbonfragments
Heterocycles

Scheme – 1

reactions of great synthetic importance. Some of the important transformations are briefly summarized below.

The oxoketene dithioacetal **1** have been reported to undergo chemoselective 1,2-reduction with sodium borohydride to give the corresponding carbinol acetal **6**[25,26], which was shown to undergo smooth methanolysis in the presence of $BF_3.Et_2O$ to afford α,β- unsaturated methyl ester **7a**[26] in quantitative yield (Scheme-2). The overall transformation can be viewed as the homologation of active methylene ketones at the α-position, involving 1,3- carbonyl transposition.

The Grignard and organolithium reagents undergo either regioselective 1,2-addition or a sequential 1,4- and 1,2- addition[18-20] to afford the α-hydroxy vinyl sulfides **3**. The borontrifluoride-etherate catalyzed solvolysis or the hydrolysis of these carbinols yield[18] either ß-substituted α,β-unsaturated esters **2** or the corresponding ketenes **4** (Scheme 2). Dieter and co-workers[19,20] have reported the chemo and stereo selective addition of organocuprates to dithioacetals **1**. Thus organocuprates are shown to undergo conjugate addition to give ß- alkylthio-ß-substituted α,β-unsaturated ketones **5**. The oxoketene dithioacetals were also shown to undergo $NaBH_4/NiCl_2$ reduction to the corresponding ß-methylthioalkenyl ketones **8** which are further transformed to the corresponding α,β-unsaturated aldehydes **11**.[27]The exclusive regiospecific 1,4-addition of hydride ion to the α- oxoketene dithioacetal was accomplished by using excess $NaBH_4$ in the presence of strong proton donor solvent[28] like acetic acid to afford the ß-oxodithioacetal **9** in moderate yield which on further borohydride treatment in ethanol affords the carbinol acetal **10**. The carbinolacetal was further heated in DMSO to afford the corresponding α,β-unsaturated aldehyde **11** in high yield.[29]


R^3 CuLi R^4
1. MeMgI
2. BF3·Et2O / MeOH
R^3MgBr
NaBH4
NaBH4 / NiCl2
NaBH4 /ACOH
BF3·Et2O / MeOH
BF3·Et2O / MeOH or H2O
1. NaBH4
2. H3O⊕
NaBH4 / EtOH
DMSO / Δ
1
2
3
4
5
6
8
9
10
11
R^3 = alkyl
7 a, X = O
b, X = S
R^3 = Et, n-Pr
n-Bu, Ph

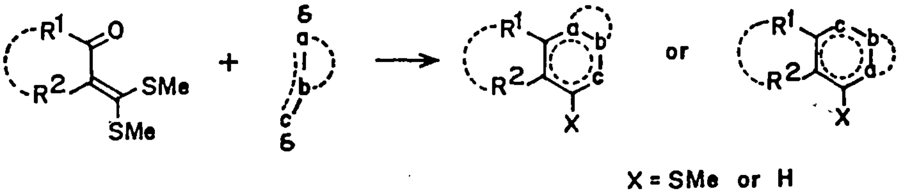
Scheme – 2

Like oxoketene S,S-acetals, the S,N- and N,N-acetals also possess 1,3-electrophilic centres and undergo a number of reactions with various binucleophiles to yield various heterocycles and carbocycles. They can be considered as vinylogous amides if they are derived from ketones and as vinylogous amines if derived from other methylene compounds. They are stable and exhibit property identical to enamines. The α-oxoketene S,N-and N,N-acetals were considered as suitable alternatives to enamines in the Nenitzescu indole synthesis.[30] The chemistry and synthetic applications of the α-oxoketene S,N- and N,N-acetals have been reviewed[1b] and a number of synthetic methods have been developed in this laboratory.

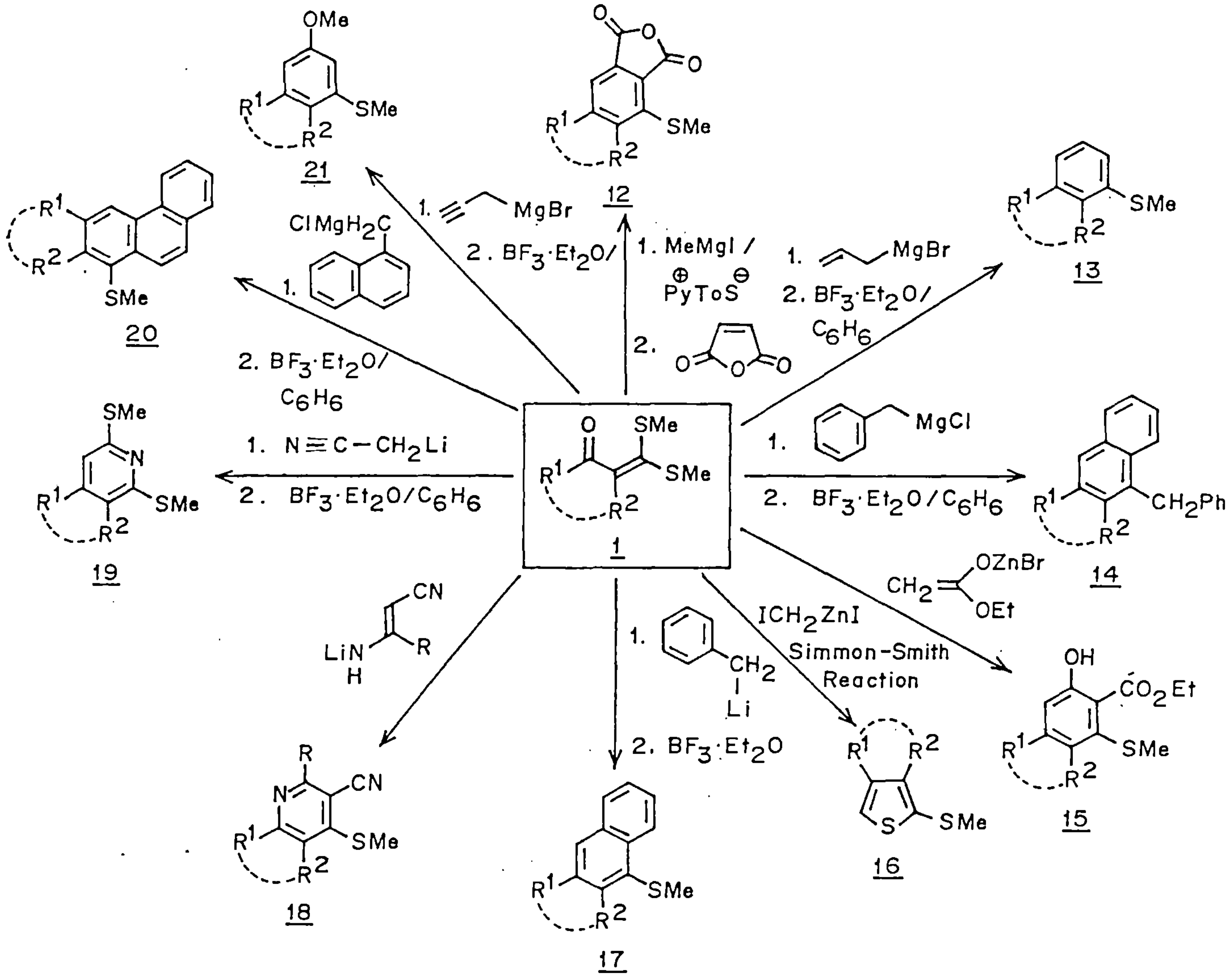
The α-oxoketene O,S-acetals were conveniently prepared[17] either directly from the corresponding S,S-acetals by quarternization of the methylthio group to give the corresponding activated sulphonium salt which undergoes smooth displacement with alkoxides or by alkoxythiocarbonylation of active methylene ketones in the presence of base to afford the corresponding ß- oxothionoesters followed by base catalyzed alkylation.

I.2 α-Oxoketene dithioacetals: Precursor for aromatic annelation

The aromatic annelation strategy developed from our laboratory has emerged as an area of great synthetic potential.[61] The discovery of our aromatic and heteroaromatic annelation involving the reaction of allyl anions with α-oxoketene dithioacetals has been shown to be of general application to yield the corresponding benzenoids, naphthalenes, polycyclic aromatic and heteroaromatic compounds in good yields. The overall process was aimed at creating an aromatic (or heteroaromatic) system with diverse structural features from the easily available acyclic aliphatic precursors. The method offers for the first time a one pot reaction process for the construction of aromatic rings from the open chain precursors involving the combination of two 3-carbon fragments of which one possesses 1,3-dielectrophilic centres and the other 1,3-binucleophilic centres.



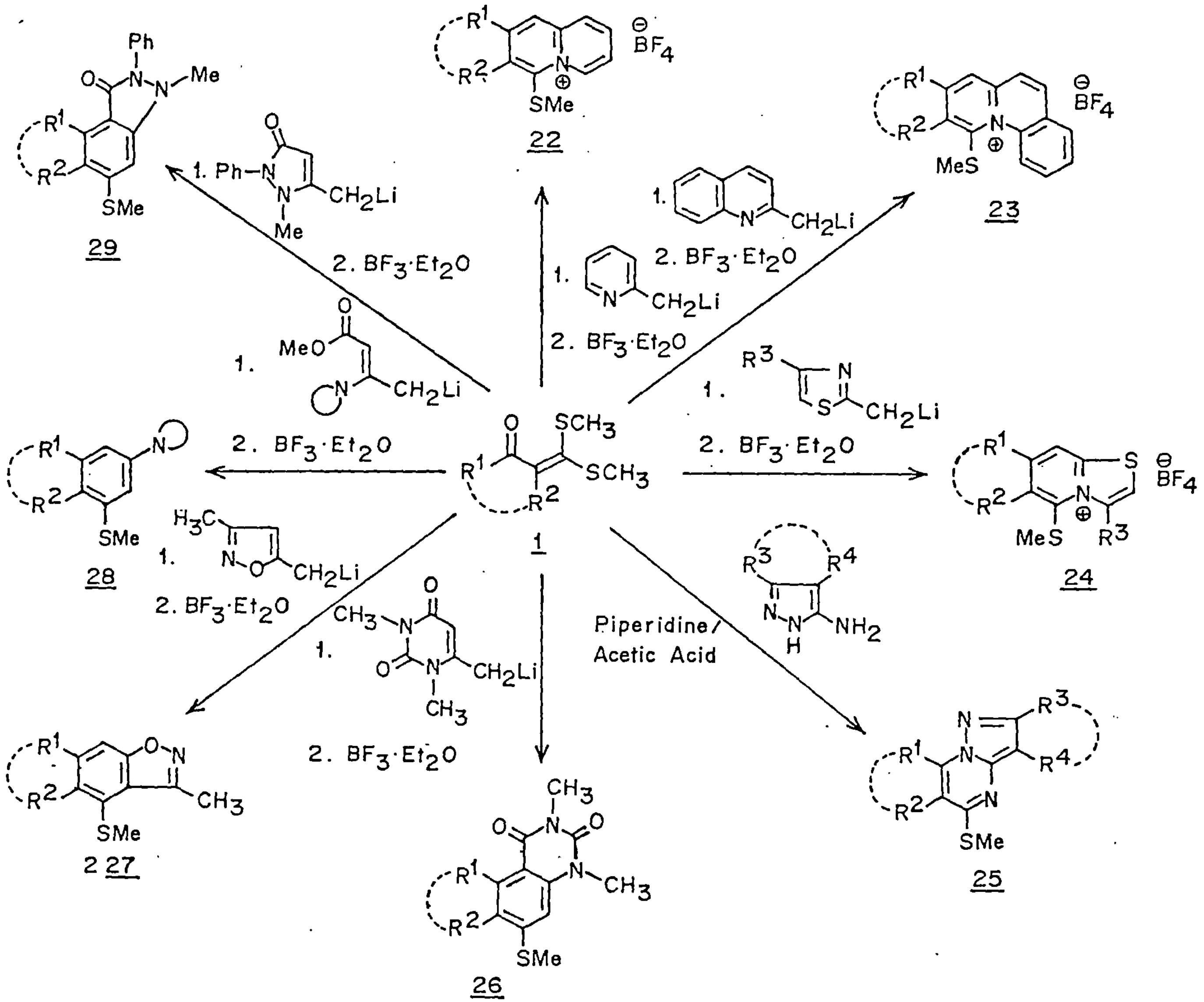
The α-oxoketene dithioacetals **1** derived from a variety of active methylene ketones and aldehydes constitute a large number of 1,3-electrophilic fragments that lend scope for liberal structural variation in the product aromatics. Similarly a variety of allyl anions have been shown to undergo facile 1,2-addition (Scheme-3 & 4) to the α-oxoketene dithioacetals to give the corresponding carbinolacetals in nearly quantitative yields. The carbinolacetals were then subjected insitu with Lewis acid catalyzed cyclization to afford the corresponding benzoannelated product. Thus a large variety of benzenoids, naphthalenes, phenanthrenes, anthracenes, benzanthracenes and many other condensed aromatics were synthesized by choosing appropriate allyl, benzyl, 1-(or 2-) naphthylmethyl anions and α-oxoketene dithioacetals. For the synthesis of substituted benzenes this approach is novel since the literature methods follow the substitution on the preconstructed aromatic ring. Such an approach suffers some limitations due to rigid aromatic orientation. In the present method the desired


OMe
SMe
R1
R2
21
SMe
R1
R2
12
SMe
R1
R2
13
R1
R2
SMe
20
1. ≡ MgBr
2. BF3·Et2O/
ClMgH2C
1.
2. BF3·Et2O/
C6H6
1. MeMgI /
⊕PyToS⊖
2.
1. MgBr
2. BF3·Et2O/
C6H6
SMe
N
R1
SMe
R2
19
1. N≡C—CH2Li
2. BF3·Et2O/C6H6
O
SMe
R1
SMe
R2
1
1. MgCl
2. BF3·Et2O/C6H6
R1
CH2Ph
R2
14
CN
LiN
H
R
1. CH2 Li
2. BF3·Et2O
ICH2ZnI
Simmon-Smith
Reaction
CH2 OZnBr OEt
OH
CO2Et
R1
SMe
R2
15
R
N
CN
R1
SMe
R2
18
R1
SMe
R2
17
R1
R2
S
SMe
16

Scheme-3

substituents could be placed either in the open chain dielectrophilic fragment or in the binucleophilic fragment or in both, if required. Thus we can exercise control on the substituent pattern in the product aromatics. Also a variety of 1- or 1,3-heteroatom binucleophiles can be used so that an heteroatom or atoms can be incorporated in the aromatic ring. Another important variation is the successful construction of aromatic ring over the preconstructed heterocyclic ring which provides a new route for benzoheterocycles and related condensed heteroaromatics. Some of the important synthetic outcome of this methodology is depicted in Scheme-3 and 4.

The reaction of allylmagnesium bromide with α-oxoketene dithioacetal **1** has been shown to undergo exclusive 1,2-addition[31] to yield the corresponding carbinolacetals in high yields, which on $BF_3.Et_2O$ assisted cationic cyclization yield the substituted and fused benzene derivatives **13**. The approach is extended for the synthesis of other benzenoids **14**,[32]**20**,[33]**21**.[34] Interestingly, benzylmagnesium chloride reacts 1,4-addition followed by 1,2-addition sequence leading to benzyl substituted[32,33] naphthalenes **14** on cycloaromatization. This method is further shown to be extremely versatile and found general application for the synthesis of pyridines **18** and **19**. The ß-lithioaminocrotonitriles react in 1,4-fashion with α- oxoketene dithioacetal **1** yielding highly substituted and functionalized pyridines[35] **18**. Similarly the lithioacetonitrile[36] follows 1,2-addition mode with **1** affording the corresponding carbinolacetals in high yield which on further cyclization with H_3PO_4 gave pyridines **19**. Interestingly the product pyridines contain methylthio unsubstituents at 2- and 6- positions, and participation of the external nucleophile was not observed. The Diels-Alder cycloadditions of vinylketene dithioacetals derived from the corresponding oxoketene dithioacetal **1** with maleic anhydride afforded the phthalic anhydride **12** in moderate


1
22
23
24
25
26
2 27
28
29
1. 2-pyridyl-CH2Li
2. BF3·Et2O
1. 2-quinolyl-CH2Li
2. BF3·Et2O
1. R3-thiazolyl-CH2Li
2. BF3·Et2O
Piperidine/
Acetic Acid
CH2Li
2. BF3·Et2O
1. H3C-isoxazolyl-CH2Li
2. BF3·Et2O
1. MeO
CH2Li
2. BF3·Et2O
1. Ph
CH2Li
Me
2. BF3·Et2O
SMe
MeS
BF4
NH2
R1
R2
R3
R4

Scheme -4

yield[37]. The synthesis of thiophenes **16** by Simmon-Smith reaction on **1** is an very important synthetic outcome from our laboratory[38,39]. The Reformatsky reaction on α-oxoketene dithioacetals afforded the corresponding regiospecifically substituted and annelated 6-methylthio benzoates **15** in good yields.[40,41] The reaction of benzyllithium with α-oxoketene dithioacetal **1** follows exclusive 1,2-addition[42] (unlike benzylmagnesium chloride) and yield the corresponding naphthalenes **17** which has been reported recently describes further importance of our aromatic annelation methodology.

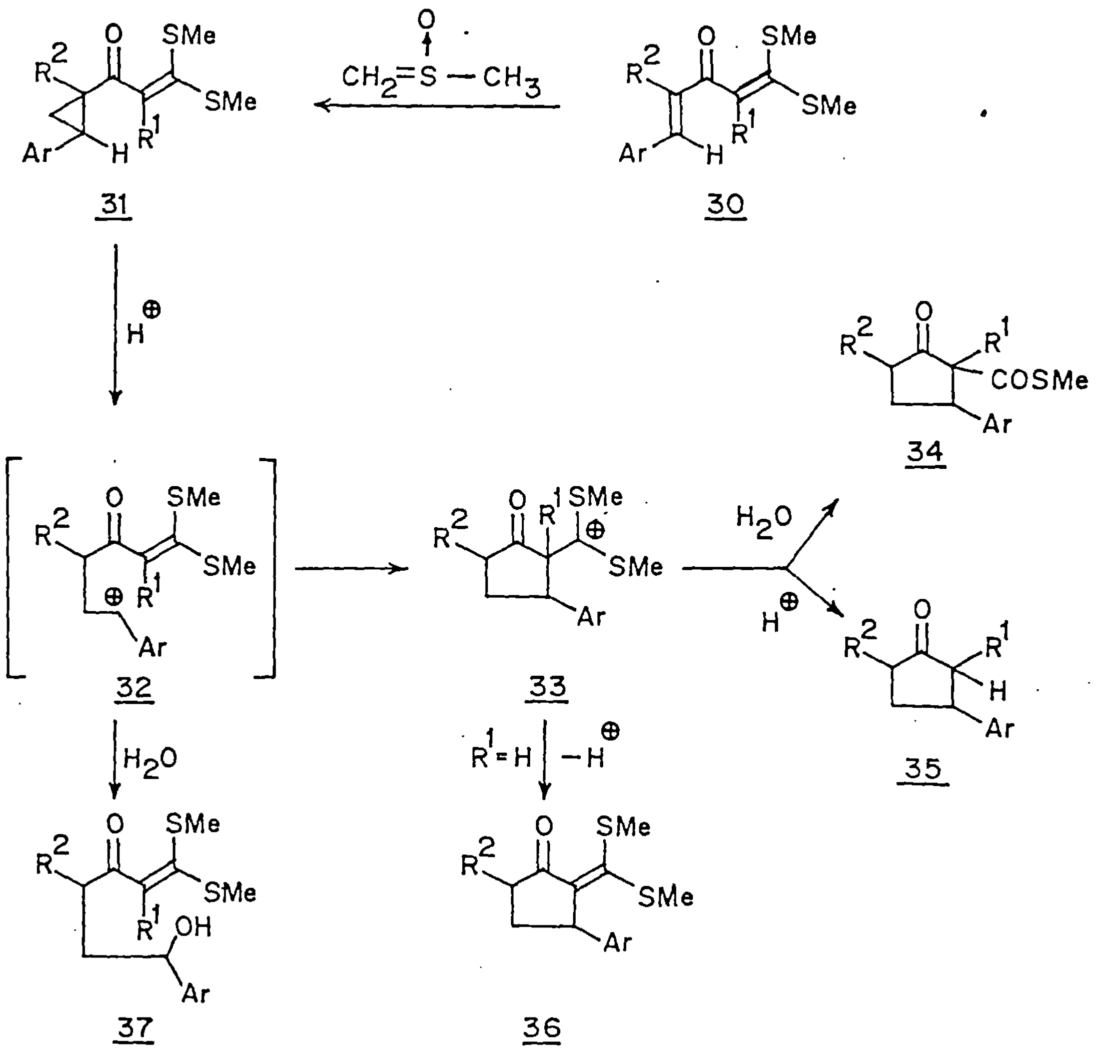
With a view to enhance the scope of aromatic annelation methodology for the synthesis of benzoheterocycles, heteroaromatic annelation methodology was developed in our laboratory by reacting appropriately substituted heteroallyl systems with α-oxoketene dithioacetals.

Thus the reaction of 2-picolyllithium with α-oxoketene dithioacetal at -30°C afforded the carbinolacetal in high yield which on further treatment with $BF_3.Et_2O$ in refluxing benzene gave the quinolizinium salt **22** in quantitative yield.[43a] Similarly, 2-lithiomethylquinoline[43b] reacted with α-oxoketene dithioacetal under identical reaction conditions to afford the corresponding quinolizinium tetrafluoroborates **23** in good yields. The 2-lithiomethylthiazole[44] reacted with **1** afforded the corresponding thiazolopyridinium salt **24** under the same reaction condition. This methodology developed as considerable synthetic importance due to the fact that, a large number of azallyl anions could be used to construct various synthetically important heterocyclic compound. The cycloaromatization of α-oxoketene dithioacetals **1** with 3-aminopyrazoles yielded the corresponding highly regioselectively substituted and condensed pyrazolo[a]- pyrimidines **25** in very good yields.[45] The reaction of 6-lithiomethyluracil and 1-phenyl-2-methyl-3-lithiomethyl pyrazolin -5-one reacted with α-oxoketene dithioacetal **1** in 1,4-fashion yielding the corresponding quinazolines[46] **26** and indazoles[62] **29** respectively. The regioselectivity was analysed by various spectral and analytical data. Similarly the lithiomethyl isoxazoles[47,48] and lithiomethyl aminocrotonates[46] reacted with **1** to afford the corresponding benziosoxazoles **27** and aminobenzenes **28** respectively in high yields.

The α-oxoketene dithioacetals therefore with a wide ranging functional group variation and many easily accessible reagents and reactive intermediates manifestly hold many new synthetic possibilities leading to diverse product range, including carbocyclic, heterocyclic and benzoheterocyclic systems.

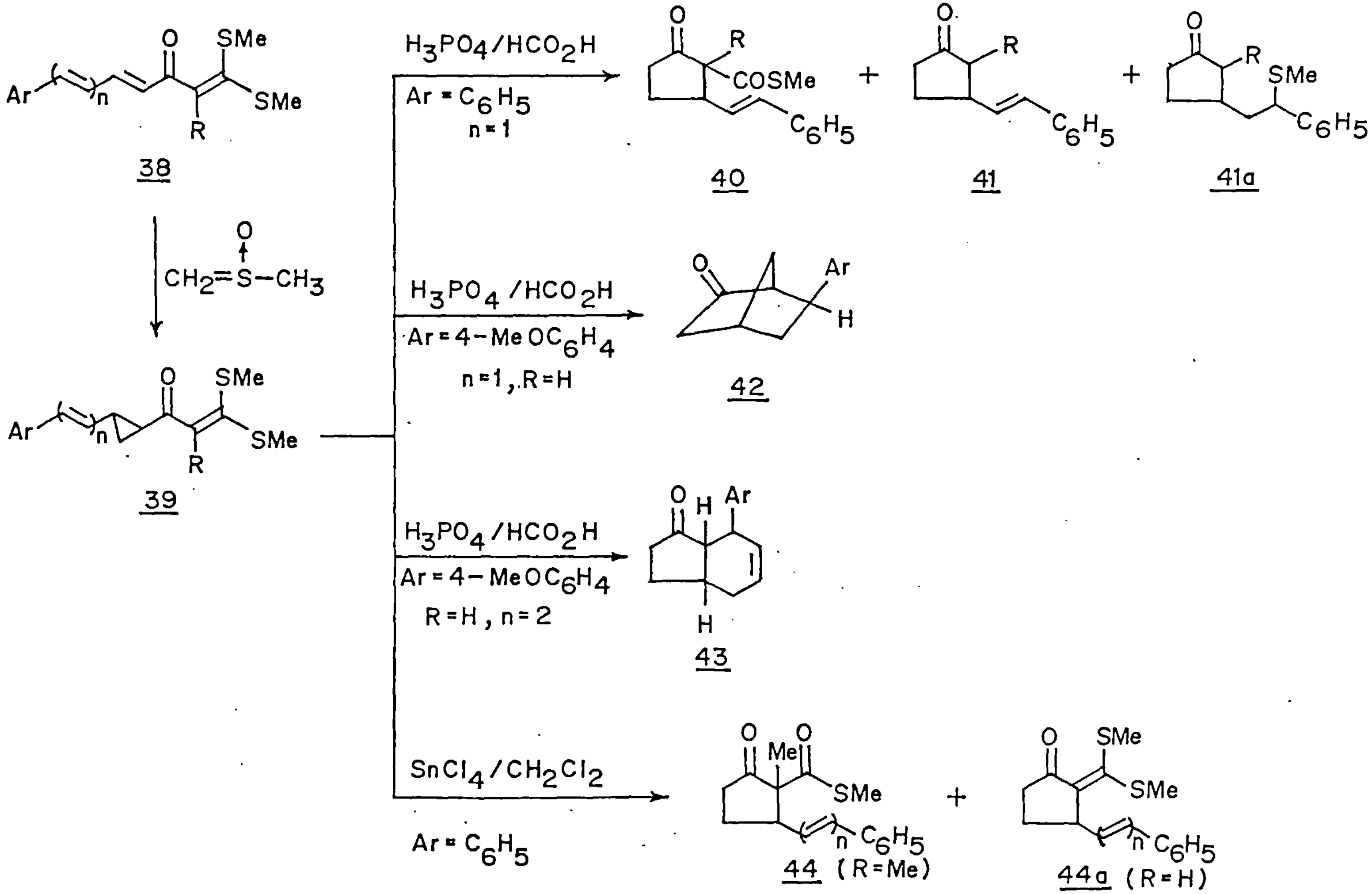
I.3 α-Oxoketenedithioacetal: Precursor for cyclopentannelation

The development of newer synthetic strategies for the construction of five membered ring has been very active area of research in recent years.[49] Particularly impressive are a number of approaches involving cyclopropane ring expansion reactions.[50] A major contribution to these area has been Hudlicky's [4+2][51] annulation approach based on cyclopropanation of dienes and subsequent 1,3-sigmatropic rearrangement of the resulting vinylcyclopropanes to cyclopentene derivatives. The acid assisted rearrangement of cyclopropyl ketones has long been a subject of synthetic and mechanistic interest.[52] The carbocation generated in the presence of suitable acid catalyst is often intercepted either by an external nucleophile or by intramolecular participation of a neighbouring aryl or olefinic double bond.[53] This prompted us to


30
31
32
33
34
35
36
37
CH2=S—CH3
O
H⊕
H2O
H⊕
R1=H
−H⊕
H2O
SMe
COSMe
Ar
R1
R2

Scheme-5

synthesize cyclopropyl ketone of the general formula **31** and study their acid-catalyzed ring opening. The bis(methylthio)methylene group in **31**, as masked ester-functionality is expected to undergo intramolecular π- participation with the developing carbocation during ring opening and the new C-C bond thus formed lead to cyclopentanone. Apparently, the reaction condition should be so governed that the intermediate carbocation should not be intercepted by any external nucleophiles such that the intramolecular new C-C bond should prevail over other processes. We successfully developed a very efficient method for the synthesis of cyclopentanones and other cyclopentanoids using this general structural frame of cyclopropyl substituted α-oxoketene dithioacetal **31**. A series of communications have been published[54] on the rearrangement of **31** to the corresponding cyclopentanoids in the presence of a number of acid catalysts. The key intermediate **33** formed via trapping of carbocation **32** (Scheme-5) by the mercapto double bond was proposed for the formation of thioester **34**, ketone **35** (H_3PO_4/HCO_2H),[55] and thioacetal **36** ($SnCl_4/C_6H_6$). The isolation of open chain carbinol **37** (Ar=4-$MeOC_6H_4$) could prove the intermediacy of carbocation **32** in support of a stepwise mechanism for the transformation. Thus the ketenedithioacetal moiety in **31** not only serves as an efficient cationic cyclization terminator[56] but also retains the original α-oxoketenedithioacetal functionality in the product cyclopentanones. However, the cyclopentanone ring formation was successful only with cyclopropyl ketones carrying substituents capable of stabilizing the developing benzyl carbocation **32**. This limitation became a constraint on this methodology for side chain elaboration at the 3-position of the product cyclopentanones. It was therefore considered of interest to explore further structural changes so that the overall transformation results in the formation of cyclopentanones. The cyclopropyl ketones **39** (Scheme-6) were considered suitable precursors to meet these requirements. The

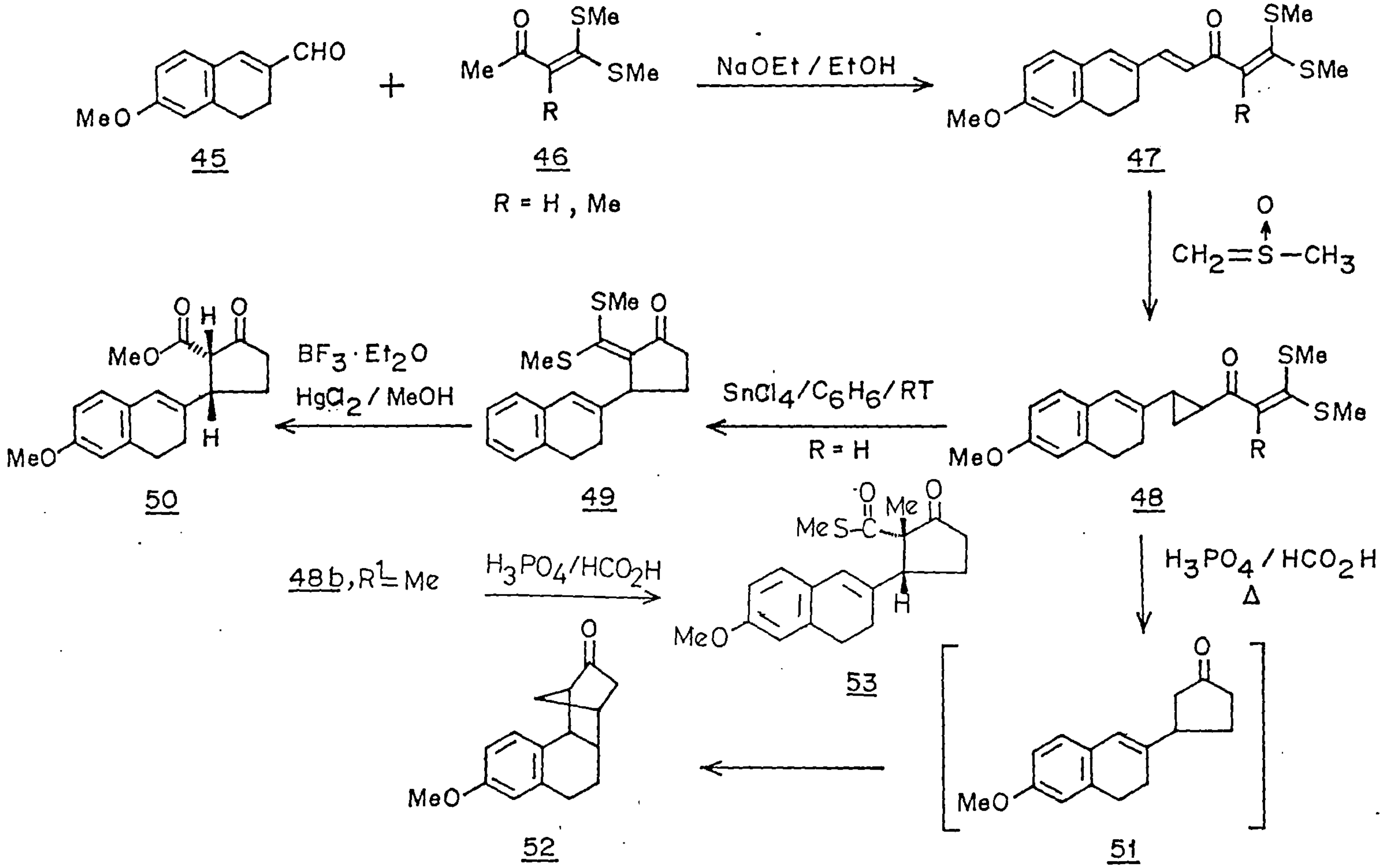

Ar
n
O
SMe
SMe
R
38
$CH_2=S-CH_3$
O
Ar
n
O
SMe
SMe
R
39
H_3PO_4/HCO_2H
$Ar = C_6H_5$
n = 1
R
COSMe
C_6H_5
40
+
41
+
41a
H_3PO_4/HCO_2H
$Ar = 4-MeOC_6H_4$
n = 1, R = H
Ar
H
42
H_3PO_4/HCO_2H
$Ar = 4-MeOC_6H_4$
R = H, n = 2
O H Ar
H
43
$SnCl_4/CH_2Cl_2$
$Ar = C_6H_5$
Me
SMe
44 (R = Me)
+
44a (R = H)

Scheme-6

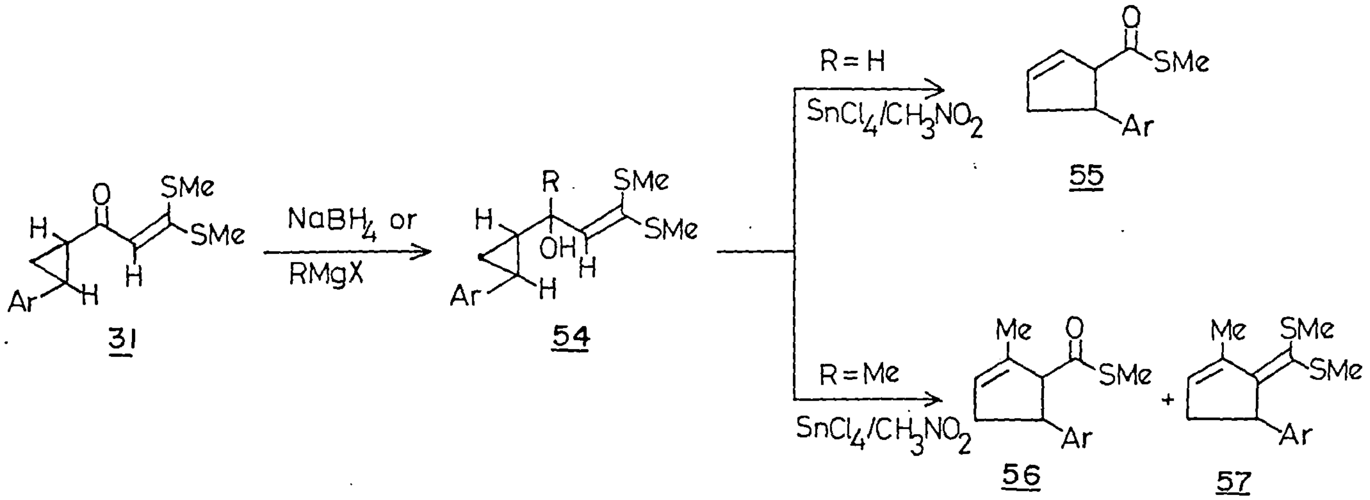
resulting 3-styryl cyclopentanones could be of further interest since they can be utilized as potential synthons for 11- oxostereoids. The regio- and chemoselective cyclopropanation of **38** was achieved by treating them with dimethyloxosulfonium methylide in the presence of phase transfer catalyst in very good yields. The styryl cyclopropyl ketone **39** when treated with H_3PO_4 in formic acid at variable temperature afforded the corresponding thioester **40**, thiomethylated ketone **40a** and cyclopentanone **41** in moderate yields. Interestingly, **39** (Ar=4-MeOC_6H_4,R=H,n=1) did not yield any product under the same condition but on heating at 80°C (1-4 hr) yielded oxobicyclo[2.2.1]heptane **42**.

The cyclopropyl ketone **39** (Ar=4-MeOC_6H_4, R=H, n=2) rearranged in the presence of H_3PO_4 in formic acid at 80°C (1-4hr) to the corresponding bicyclic ketone **43** in good yield. However, in the presence of $SnCl_4$ in CH_2Cl_2, the styryl cyclopropyl ketone **31** (R=Me) afforded the thioester **44** and dithioacetal **44a** in the absence of an α-proton i.e. R=H at room temperature (Scheme-6).

As an application of these cyclizations, the synthesis of 11- oxosteroid precursors was investigated (Scheme-7).[55] The ene aldehyde **45** was condensed with α-acetyl ketene dithioacetals **46** to afford the corresponding dienoyl ketenedithioacetals **47** in high yields. Subsequent cyclopropanation under phase transfer condition as described in Scheme-8 gave the desired cyclopropyl ketones **48** in quantitative yields. The ß-ketoester **50** could be obtained in 78% overall yield by treating **48** initially with $SnCl_4$ in benzene at room temperature. The resulting dithioacetal **49** on subsequent methanolysis ($BF_3.Et_2O/HgCl_2/MeOH$) gave the expected cyclopentanone **50**, which was found to be a single trans substituted isomer. The assignment of ring stereochemistry was based on spectral datas which were in accordance with the


CHO
MeO
45
+
O
SMe
Me
SMe
R
46
R = H , Me
NaOEt / EtOH
O
SMe
SMe
MeO
R
47
O
CH$_2$=S−CH$_3$
O
SMe
SMe
MeO
R
48
SnCl$_4$/C$_6$H$_6$/RT
R = H
SMe
O
MeS
49
BF$_3$·Et$_2$O
HgCl$_2$ / MeOH
O
H
O
MeO
H
MeO
50
48b, R^1= Me
H$_3$PO$_4$/HCO$_2$H
O
Me
O
MeS-C
H
MeO
53
H$_3$PO$_4$ / HCO$_2$H
Δ
O
MeO
51
O
MeO
52

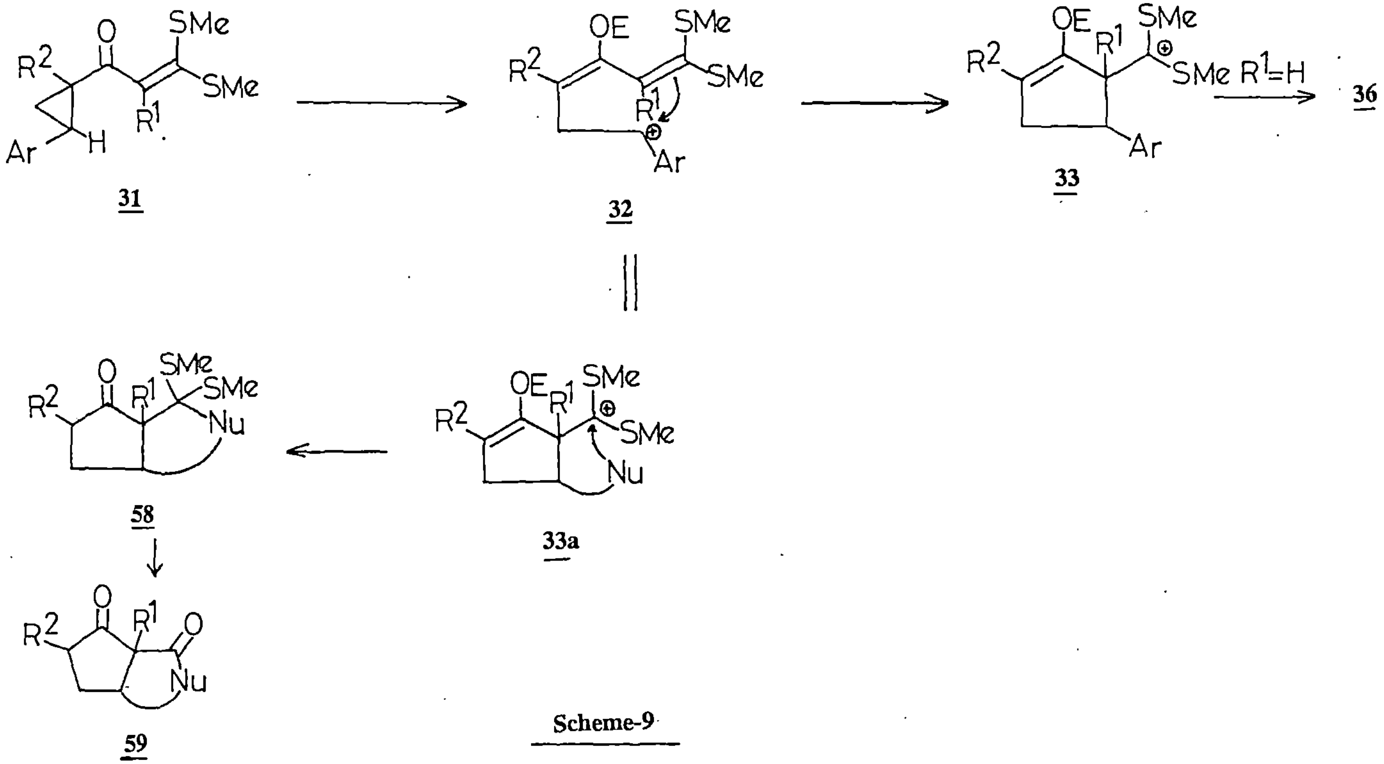
Scheme -7



Scheme-8

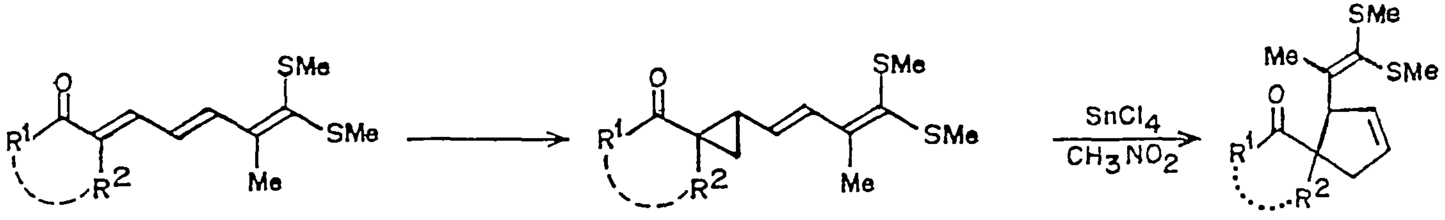
corresponding 6-bromo analogue reported by Trost and co- workers.[57] However, the cyclopropyl ketone **48** (R=H) when treated with H_3PO_4/HCO_2H yielded a product characterized as bicyclic ketone **52**,(cyclopentanone **51**) the precursor of **52** was not detected. The ketone **48** (R=Me) in H_3PO_4/HCO_2H afforded the expected thioester **53** in very good yield which was found to be a single stereoisomer.

Cyclopropyl carbinols like their carbonyl counterparts are well recognized as a class of important precursors in organic synthesis and the chemistry of their rearrangements have been extensively studied both from synthetic and mechanistic point of view. The bis(methylthio)cyclopropyl propen-1-ols **54** (R=H) under Lewis acid ($SnCl_4/CH_3NO_2$) assisted rearrangement afforded the corresponding cyclopentene carbothioates **55** as exclusive product. However, the cyclopropyl methyl carbinols (R=Me) afforded the methyl substituted cyclopentene carbothioates **56** as major product (55%) and bis(methylthio) cyclopentanones **57** as minor product (15-25%) (Scheme-8). The cation stabilizing ability[56] of sulfur has promoted the ketene dithioacetals as initiator in the intramolecular electrophilic cyclization. In addition to this they have proved to be excellent cationic cyclization terminators.[56d,e] During our earlier report on cyclopentanoid synthesis,[54] we have examined the characteristic d^2 step through 5-exotrig process to give the sulfur stabilized carbocation **33a** (R^1=Me, Ar=Nu) in the presence of Lewis acid and subsequent intramolecular trapping of these carbocations by suitably substituted aryl cyclopropyl ketones (Scheme-9). However, the cyclopropyl ketones having R^1=H undergone rapid deprotonation to afford the corresponding bis(methylthio) cyclopentanones as described in Scheme-5. The aryl ring having electron donating groups and the cyclopropyl ketone having α- substituent (R^1=Me) afforded the corresponding doubly annulated cyclopentanone rings of general formula



O
SMe
R2
SMe
R1
Ar
H
31
OE
SMe
R2
SMe
R1
Ar
32
OE
SMe
R2
R1
SMe
R1=H
Ar
33
36
O
SMe
R2
R1
SMe
Nu
58
OE
SMe
R2
R1
SMe
Nu
33a
O
R2
R1
O
Nu
59

Scheme-9



60 61 62

Scheme-10

58 (Scheme-9). These thioketals were hydrolysed in $HgCl_2$/aqCH_3CN to afford the corresponding diketones **59**. It was also extended to the corresponding carbinols. It was shown that Tandem[59] two-stage annulation could be achieved in the systems where the cyclopropyl ring carries a highly oxygenated aryl group. It was then considered of interest to examine the ability of the bis(methylthio) functionality to function as a cationic cyclization terminator group if it is flanked by conjugation of double bonds with cyclopropyl ketones. The vinylogous ketene dithioacetals **60** underwent highly regio and stereoselective cyclopropanation with oxodimethylsulphonium methylide in presence of PTC to afford the novel 1-aroyl (or 1,1-spiro) cyclopropanes **61** (Scheme-10). Lewis acid ($SnCl_4$/CH_3NO_2) induced rearrangement of these dienyl cyclopropyl ketones afforded the corresponding cyclopentenes or spiro derivatives **62** in good yields.[60] Then subsequent reactions were done on these. Encouraged by all these results, we were interested to examine the rearrangement studies on styryl cyclopropyl ketones in the same Lewis acid condition ($SnCl_4$/CH_3NO_2) and the results are described in Chapter -4.

In conclusion, in this laboratory, we have achieved the elegant synthesis of aromatics, heteroaromatics, heterocycles as well as cyclopentanoids by exploiting the open chain oxoketene dithioacetal. The versatility of all these methodologies are being examined further and will be reported in due course.

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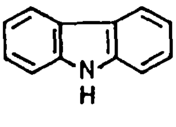
CHAP-2

An Expediant New Synthesis of Substituted Carbazoles via α-Oxoketene Acetals through Heteroaromatic Annelation Methodology

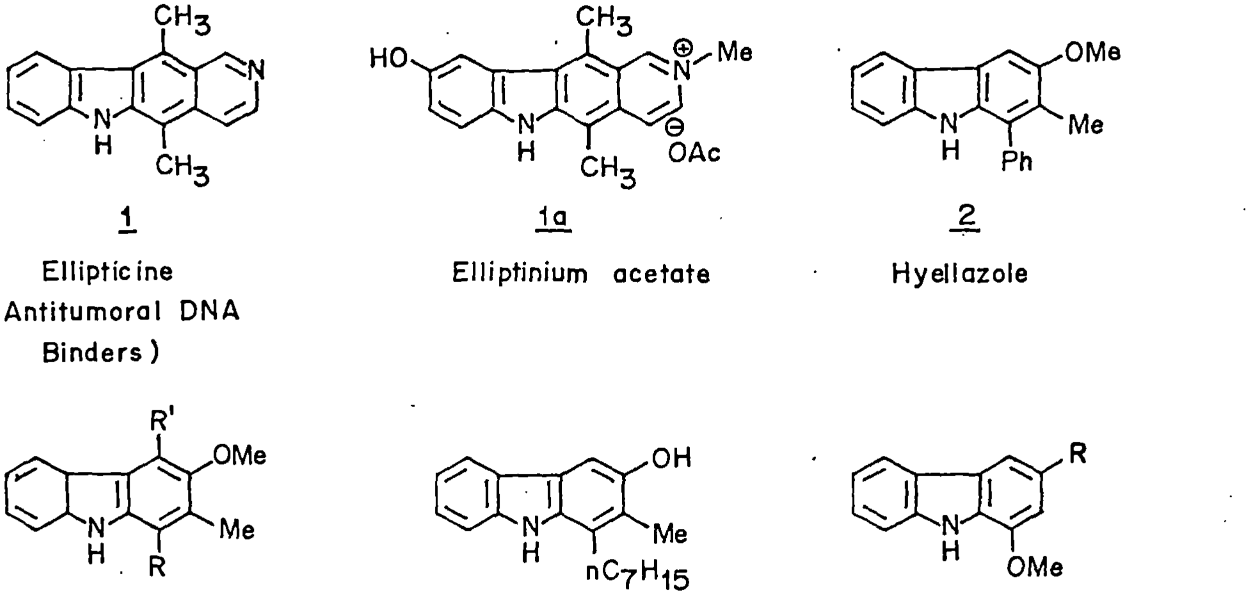
The carbazole **A** was first isolated from coaltar in 1872 by Grabe and Gleaser and a number of synthetic approaches have been developed[1] for the synthesis of these groups of compounds.



A

The major methods employed for the synthesis of these carbazole derivatives include the one developed by (i) dehydrogenation of 1,2,3,4-tetrahydrocarbazole which are generally prepared by Fischer-Borsche cyclization[2] (ii) reductive cyclization[3] of 2-nitrobiphenyls (iii) thermal,[4] photolytic[5] and palladium assisted cyclization[6] of diphenylamines (IV) iron mediated oxidative coupling[7] of 1,3-cyclohexadiene and arylamines and (V) [b]-annulation[8] of indole skeletons. The enormous synthetic activity in the area of carbazole chemistry is evidently due to the fact that a number of carbazole alkaloids were discovered as late as 1960 for the first time by D.P. Chakraborty.[9] Subsequently other new carbazole alkaloids were isolated with interesting biological activity.[10] Thus these novel naturally occuring carbazole derivatives (Scheme-1) have catalysed enormous synthetic activity in recent years.[11] The group belonging to benzo and pyrido annelated carbazoles[12,13] as represented by a naturally occuring substance ellipticine **1** which displays antitumor activity and intercalates with DNA and inhibits topoisomerase II.[12,14] The compound is currently used clnically to inhibit the growth of several human tumors. A very important derivative of this is 2-methyl-9-hydroxy elliptinium acetate **1a** which is frequently used in the therapy of breast, kidney and thyroid cancer.[12,15] Also carbazoles with hydroxy or methoxy group at 1-or 3-position constitute a group of carbazole alkaloids belonging to hyellazole **2**[16] isolated from the marine blue green algae *hyella caespitosa*, cytotoxic koenoline **3a**,[17] murrayafoline-A **3b**,[18] carbazomycins[19] **4a,b** & **c** produced by *streptoverticellium ehimense*, carazostatin **5** which is a free radical scavanger,[20] and carbazomycinal **4d**.[21] Besides the listed carbazomycins **4a-c**, there are other isomeric products which are reported in the literature belong to this class.[22]

The carbazomycins isolated by Nakamura in 1980 possess antibiotic, antibacterial and antiyeast activity.[23] Therefore there is considerable interest in recent years by chemists to develop effecient synthetic routes for these compounds. Also many of the classical approaches pose difficulty in placing the required substituents in C-ring of carbazoles. Looking at the structures of these alkaloids and antibiotics, the classical approaches will definitely require multistep synthetic schemes with drastically reduced overall yields of both target intermediates and carbazoles and thus are less attractive to be choosen for their synthesis. Among them the most important carbazoles and their synthesis involving [b]-annulation on preconstructed indole skeleton are of special importance.[8] There are many approaches utilizing this strategy reported in the literature which may include (a) thermally induced and photochemical electrocyclizations of 2,3-divinyl



1
Ellipticine
(Antitumoral DNA
Binders)

1a
Elliptinium acetate

2
Hyellazole

4
4a, R' = H, 4-Deoxy-carbazomycin-B
b, R' = OH; Carbazomycin-B
c, R' = OMe; Carbazomycin-A
d, R' = OH, R = CHO; Carbazomycinal
Antibacterial, Antiyeast etc.

5
Carazostatin
(Freeradical Scavanger)

3
3a, Koenoline; R = CH_2OH
b, Murraya-folline-A; R = Me

Scheme - 1

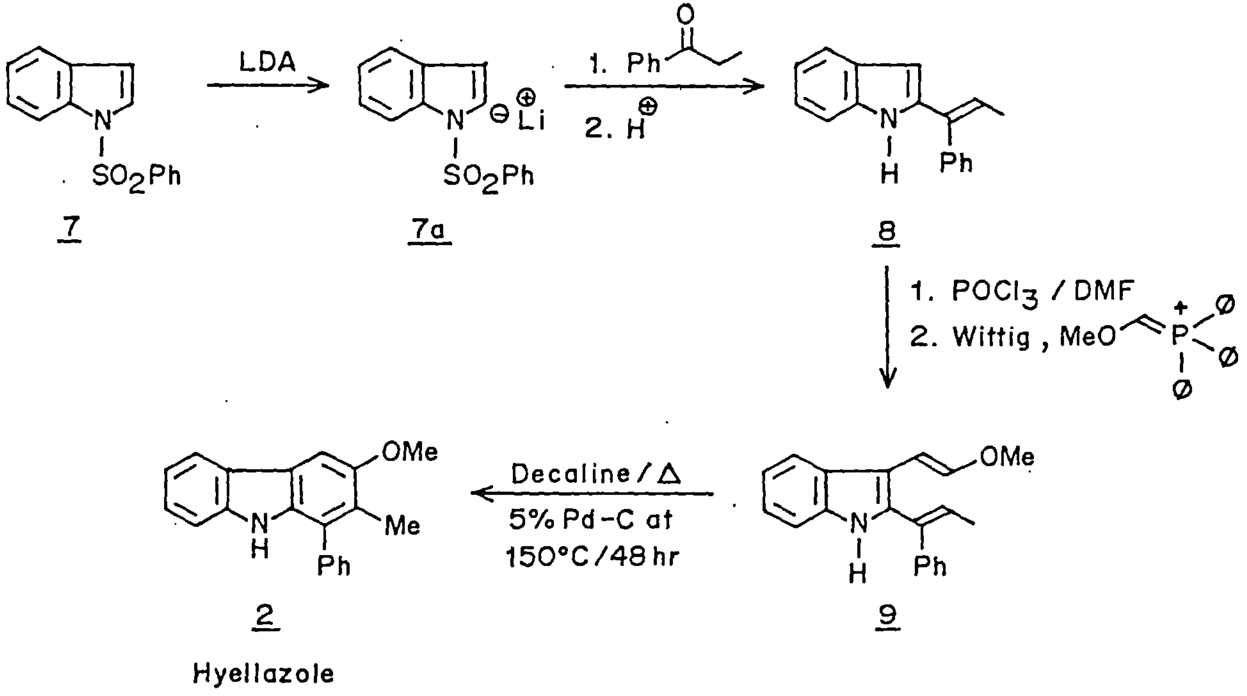
indoles[8h] (b) [4+2]-cycloadditions of indolo-2,3-quinodimethanes[8a,e] and of vinyl indoles with dienophiles.[8g] In the third category (c) addition of α-methyl carbanions at C-2 of indoles to Michael acceptor followed by intramolecular cyclization with the ester group at the 3-position.[8b,f] In the fourth category (d) a number of miscellenous approaches have been used which will be briefly stated.

The methods covering synthesis of carbazoles are too many to be listed and can not be included in a single brief introduction of this kind. Therefore attention is drawn to the reviews[1] for comprehensive coverage on this class of compounds. In the present review we will be briefly discussing few selected reports that might fall into the four categories stated above.

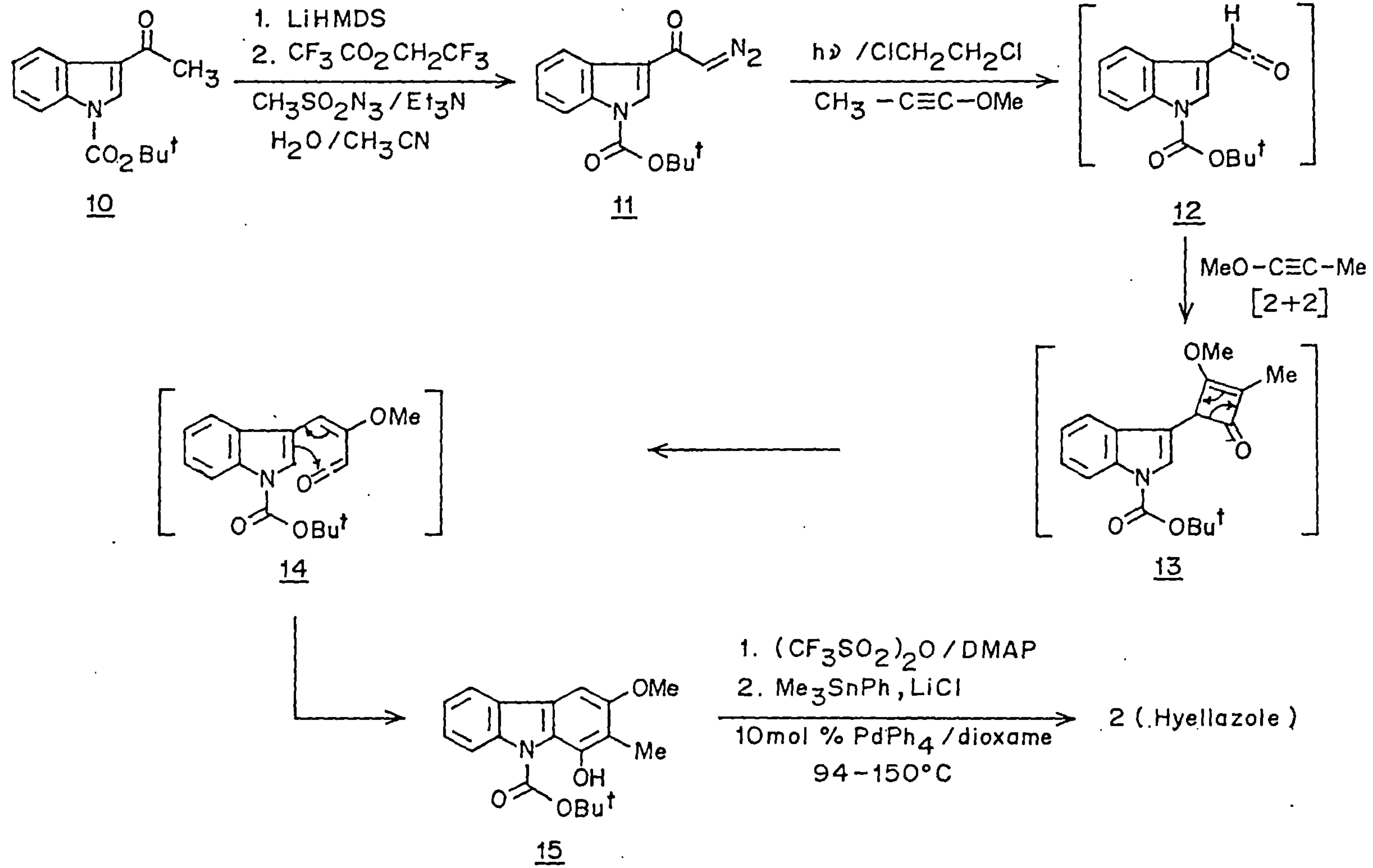
Kano and co-workers[24] developed a new synthetic strategy for [a]- annelated carbazoles and reported the synthesis of hyellazole and its chloro analog. The strategy involves deprotonation of α-proton of indole to yield the corresponding carbanion **7a** (Scheme-2) which was reacted with various ketones followed by dehydration to yield the corresponding 2-vinylindoles **8** in good yields. These on subjecting to Vielsmeir and Haack reaction yielded the corresponding indole-3-carboxaldehydes which were reacted with methoxymethyl triphenyl phosphirane to yield the corresponding trienes **9** which on heating with Pd-C in xylene at 150°C yielded the corresponding hyellazole in 21% yield. And they have used many modified approaches to convert **9** to **2** with a view to increasing the yield of **2**.

A novel approach is developed by Danheiser and co-workers[25] for the synthesis of hyellazole and many related derivatives. They developed a general strategy involving irradiation of a mixture of indole-3-α-diazoketone **11** and methoxy acetylene to yield N- Boc-1-hydroxy-2-methyl-3-methoxycarbazole **15**. The hydroxy group at 1-position was displaced by phenyl group as indicated in Scheme-3 to yield the corresponding hyellazole **2**.

Kawasaki and co-workers[26] reported an interesting route for the synthesis of hyellazole


LDA
1. Ph
2. H⊕
1. POCl3 / DMF
2. Wittig , MeO
Decaline / Δ
5% Pd-C at
150°C / 48 hr
SO2Ph
⊖ Li⊕
Ph
OMe
Me
7
7a
8
9
2
Hyellazole

Scheme – 2


1. LiHMDS
2. $CF_3CO_2CH_2CF_3$
$CH_3SO_2N_3/Et_3N$
H_2O/CH_3CN
hν / $ClCH_2CH_2Cl$
$CH_3-C\equiv C-OMe$
MeO−C≡C−Me
[2+2]
1. $(CF_3SO_2)_2O$ / DMAP
2. Me_3SnPh, LiCl
10mol % $PdPh_4$ / dioxame
94−150°C
2 (Hyellazole)
10
11
12
13
14
15

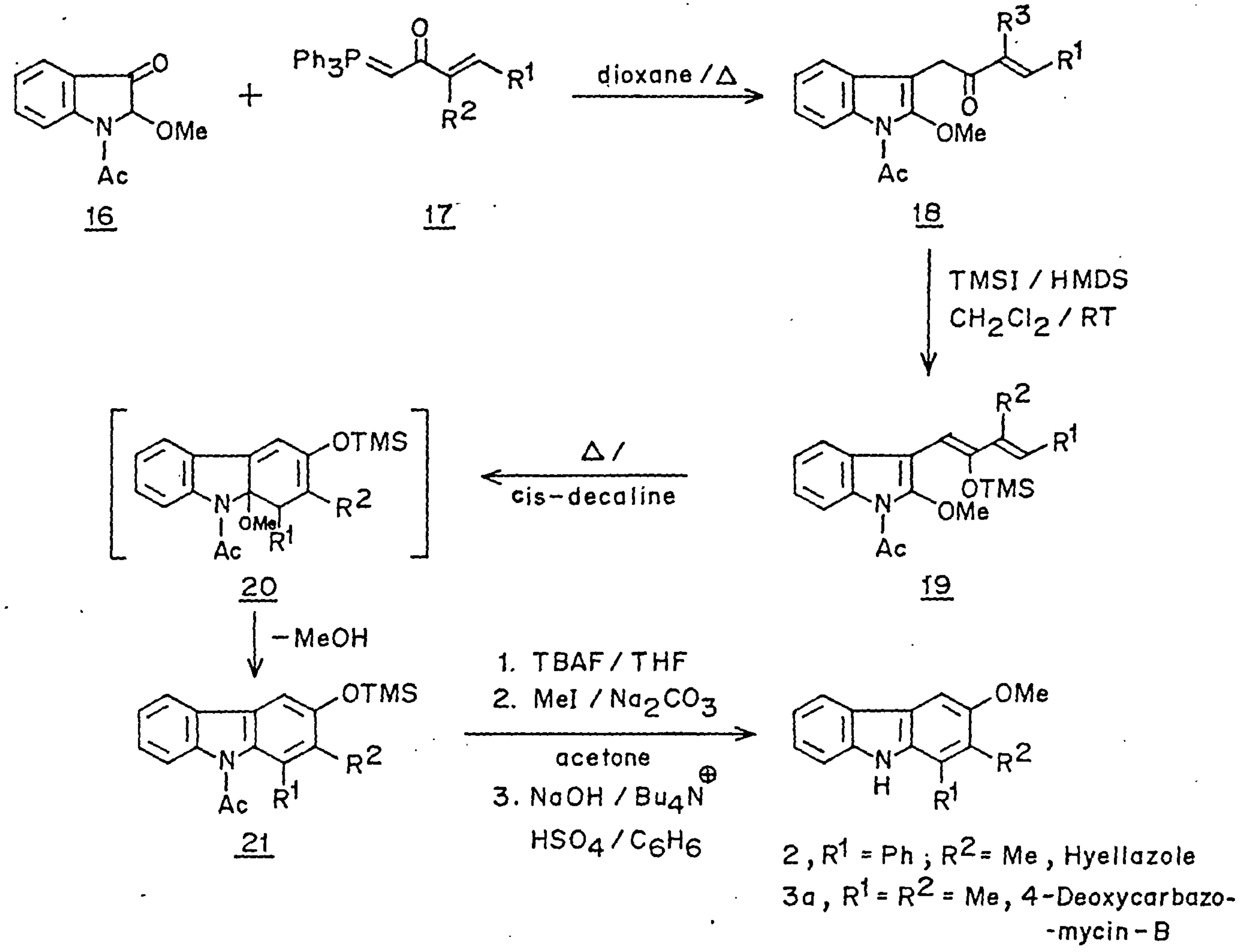
Scheme - 3

and carbazomycin (Scheme-4). 1-acetyl-2- methoxyindoxyl **16** was their starting point on which they conducted Wittig reaction to yield the corresponding 2-methoxy indole **18**. The keto group in the side chain of **18** was conveniently transformed to the corresponding trimethyl silylether **19** there by creating a triene system which on thermolysis yielded the corresponding hyellazole precursor **21** in 53% yield which was then transformed into the corresponding hyellazole as formulated.

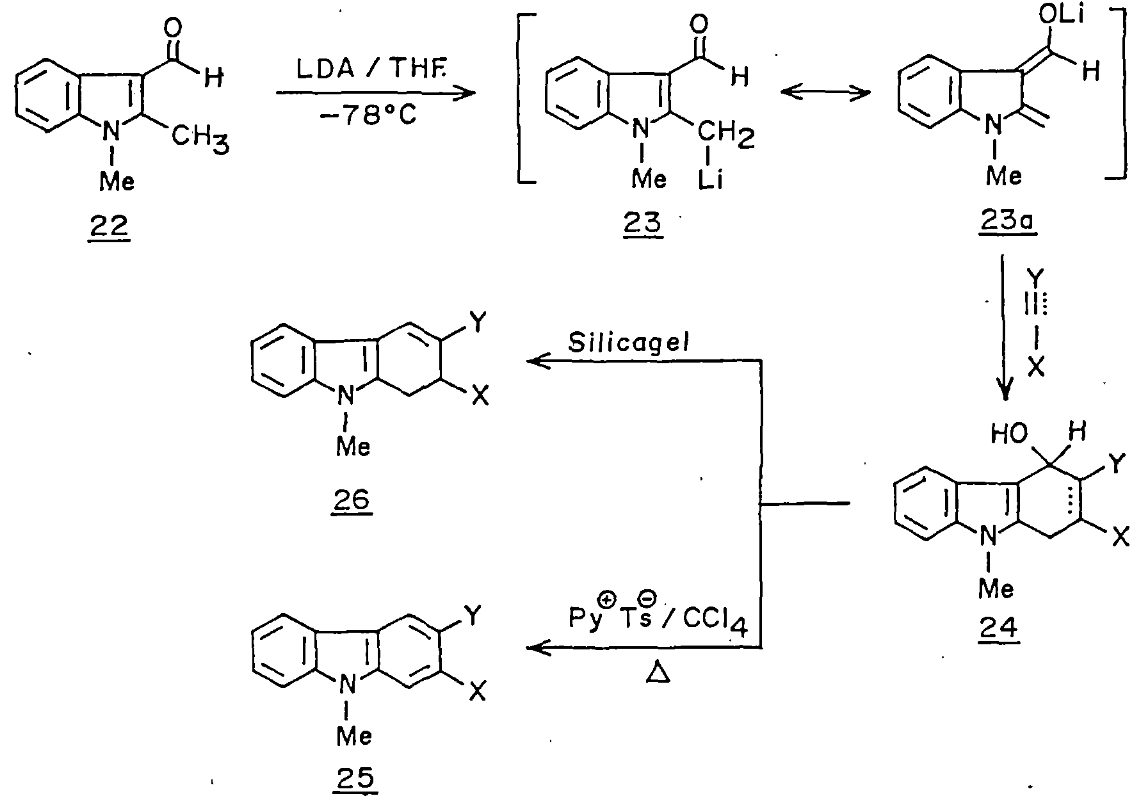
Recently a novel carbazole synthesis based on the principles of [4+2]-cycloaddition involving indolo-2,3-quinodimethane as diene *insitu* with various dienophiles (Scheme-5) has been reported from our laboratory.[8a] Thus the indolo-2,3-quinodimethane was *insitu* generated by treating 1,2-dimethylindole-3-carboxaldehyde **22** with LDA at -78°C to yield the desired anion **23** in the presence of different dienophiles when the corresponding dihydrocarbazoles **24** were obtained in moderate to good yields. The dihydrocarbazoles were subsequently converted into the corresponding carbazoles **25** as depicted in Scheme-5. A number of dienophiles have been reacted with **23** to yield the corresponding carbazoles.

Gribble and co-workers[27,28] used 4H-furo[3,4-b]indoles **27** as stable neutral 2,3-quinodimethanes which are potential dienes for making [b]-annelated carbazoles. Thus they have achieved ellipticine synthesis by reacting **27** with piperidinone to get the intermediate **32** which subsequently converted to ellipticine. Similarly they made other carbazoles **30** by reacting **27** with various dienophiles **28**. The benzyne intermediate is also added to **27** to yield the corresponding [b]-annelated carbazole **34** (Scheme-6).

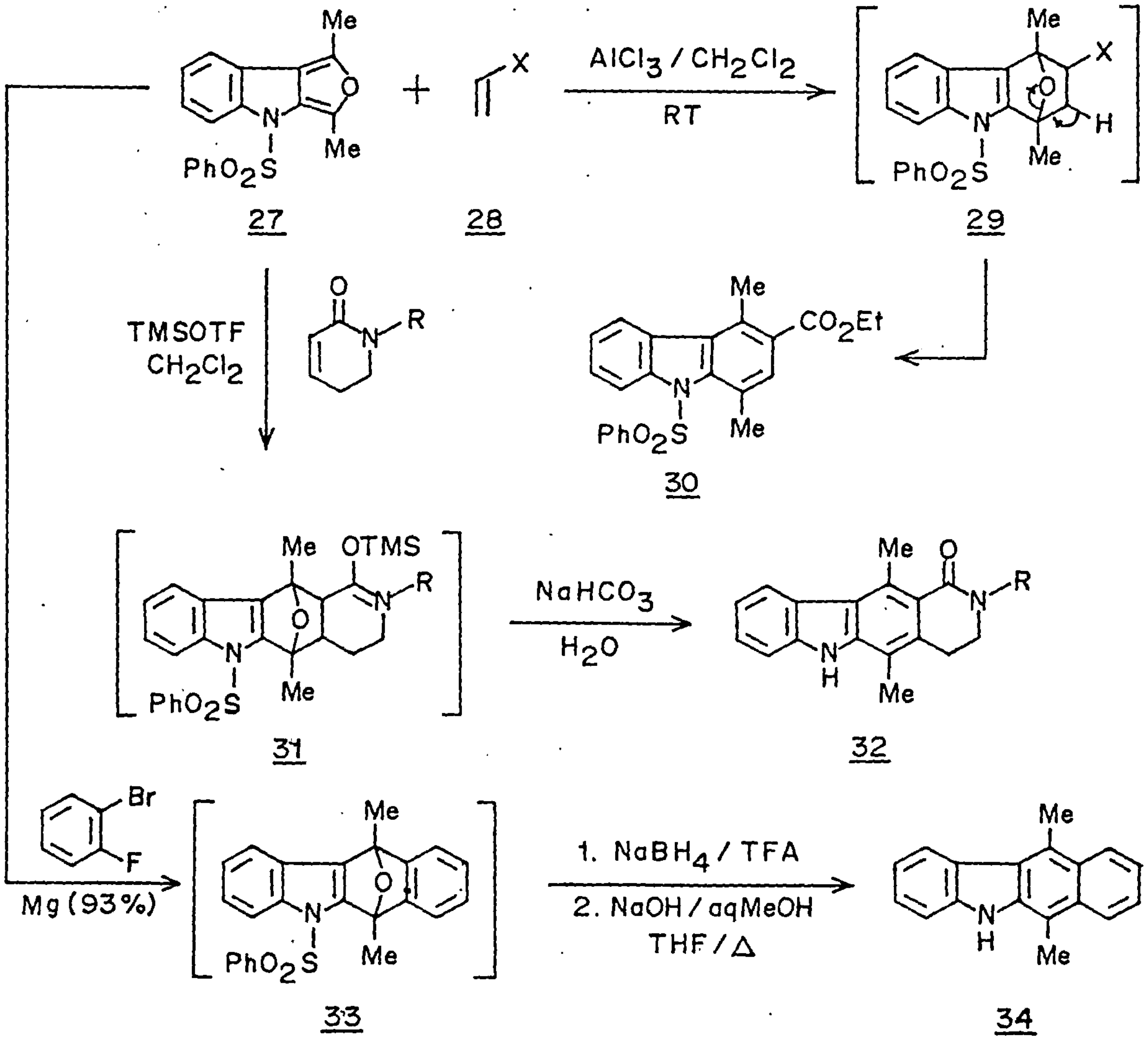
Srinivasan and co-workers[8b] used the intermediate **35** and michael acceptors **36** in the presence of NaH at 0°C and obtained the corresponding 4-methoxycarbazoles **37** in good yields. Similarly Tamura and co-workers[29] used the anhydride **38** which was deprotonated with NaH in the presence of various dienophiles when the corresponding carbazoles **40** were obtained in good yields (Scheme-7).


16
17
18
19
20
21
Ph_3P
OMe
Ac
R^1
R^2
R^3
OTMS
dioxane / Δ
TMSI / HMDS
CH_2Cl_2 / RT
Δ / cis-decaline
−MeOH
1. TBAF / THF
2. MeI / Na_2CO_3 acetone
3. NaOH / $Bu_4N^{\oplus}$ HSO_4 / C_6H_6
2, R^1 = Ph ; R^2 = Me, Hyellazole
3a, R^1 = R^2 = Me, 4-Deoxycarbazo-mycin-B

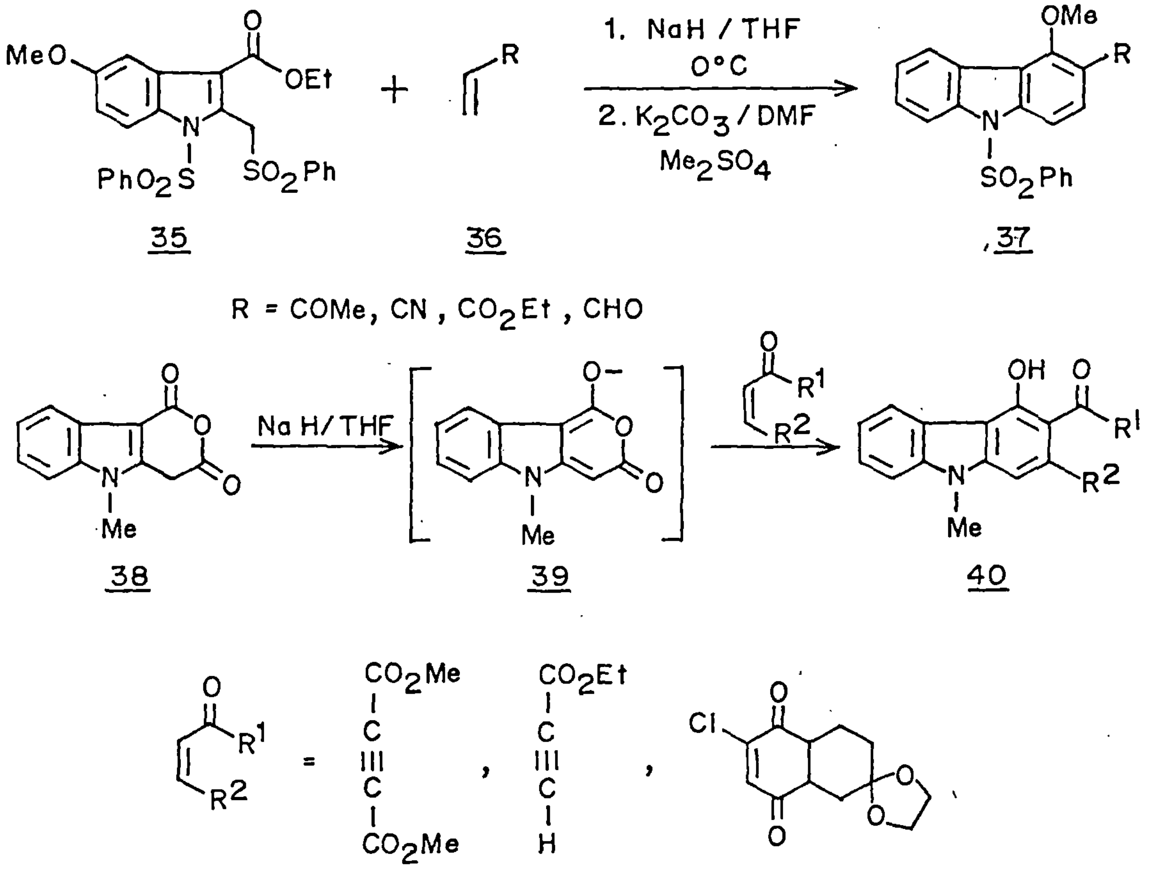
Scheme – 4



Scheme−5


Me
Me
PhO2S
27
28
X
AlCl3 / CH2Cl2
RT
Me
X
H
Me
PhO2S
29
TMSOTF
CH2Cl2
O
R
Me
CO2Et
Me
PhO2S
30
Me
OTMS
R
PhO2S
Me
31
NaHCO3
H2O
Me
O
R
H
Me
32
Br
F
Mg (93%)
Me
PhO2S
Me
33
1. NaBH4 / TFA
2. NaOH / aqMeOH
THF / Δ
Me
H
Me
34

Scheme - 6


MeO
OEt
PhO$_2$S
SO$_2$Ph
35
R
36
1. NaH / THF
0°C
2. K$_2$CO$_3$ / DMF
Me$_2$SO$_4$
OMe
R
SO$_2$Ph
37
R = COMe, CN, CO$_2$Et, CHO
Me
38
Na H/ THF
O−
Me
39
R^1
R^2
OH
R^1
R^2
Me
40
R^1
R^2
CO$_2$Me
CO$_2$Me
CO$_2$Et
H
Cl

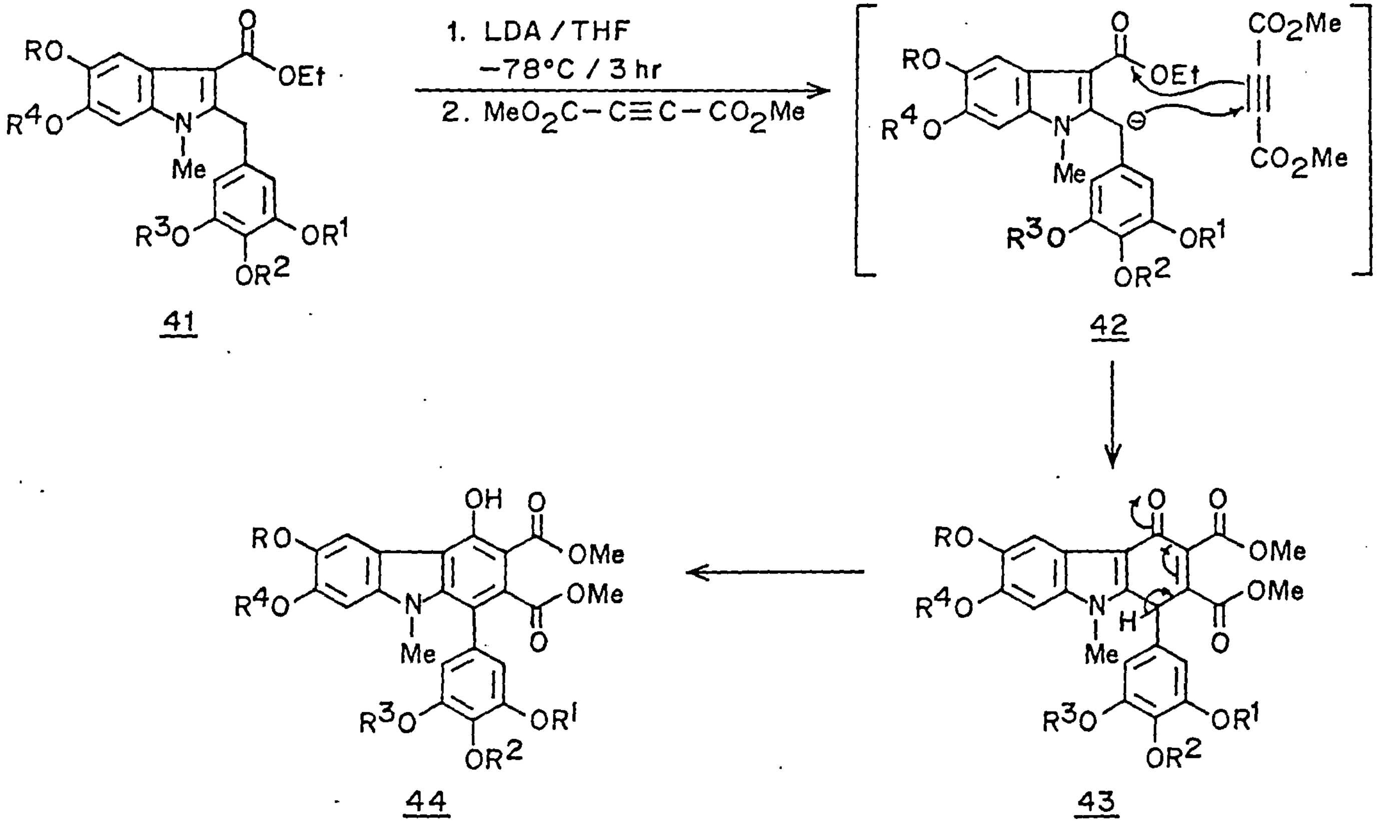
Scheme—7

Mali and co-workers[8f] (Scheme-8) extended the michael addition approach by taking 2-benzyl-3-carbomethoxy indole analogs which were subjected to deprotonation with LDA in the presence of dimethyl acetylinic ester when the corresponding 1-aryl-2,3-dicarbomethoxy-4-hydroxy carbazoles **44** were obtained.

Knolker and co-workers[30] have developed a highly convergent synthesis for hyellazoles as formulated in Scheme-9. Their approach included the formation of tricarbonyl iron complexed cyclohexadienylium cation and approptiately functionalized arylamines to yield the corresponding biphenyl **47** through electrophilic substitution which on subsequent oxidation by MnO_2 underwent coupling reaction to yield **49** which on further treatment with trimethyl-N-oxide and subsequent methylation of 3- hydroxy group yielded the desired hyellazole in overall 59% yield.

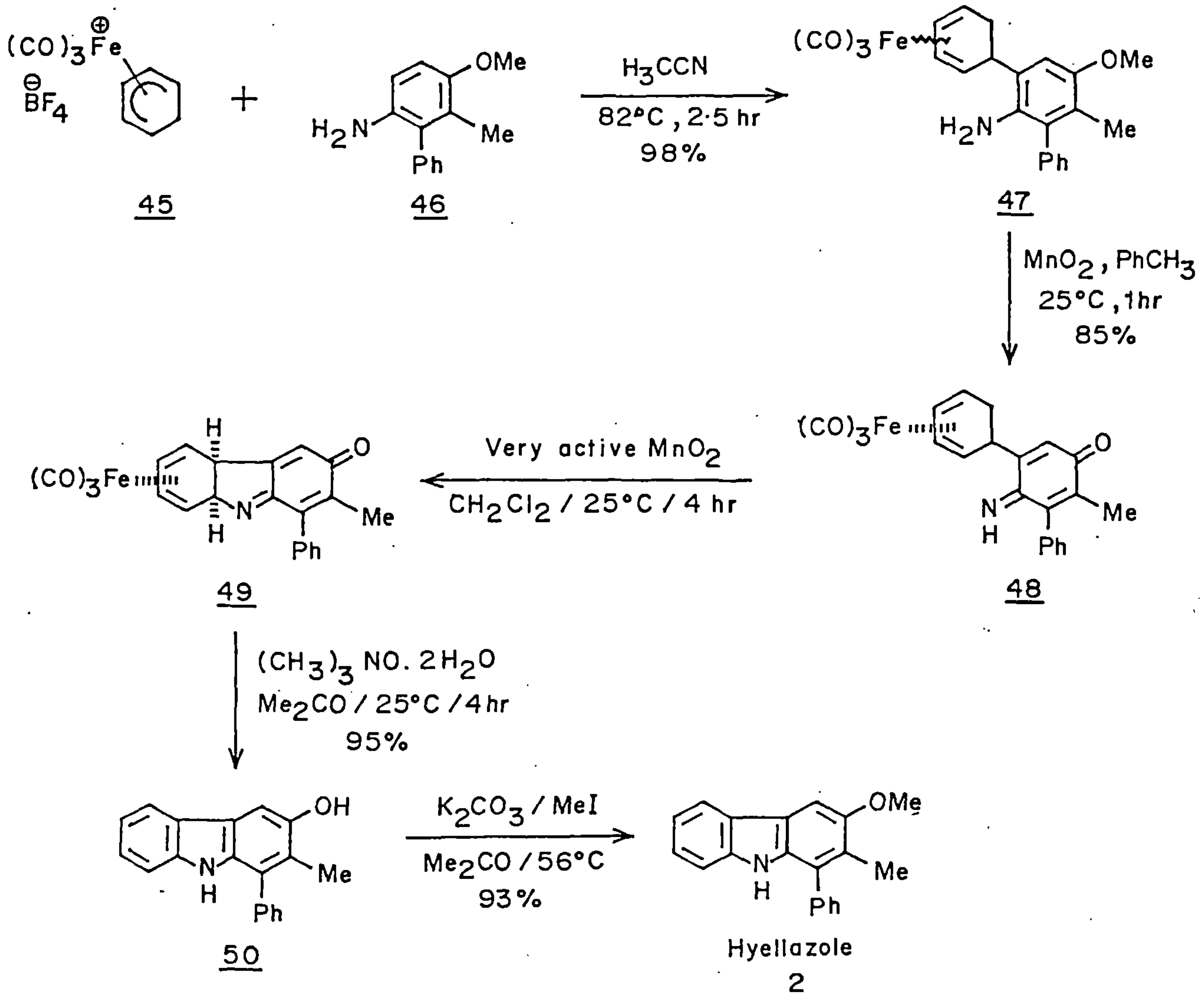
Sainsbury and co-workers[31] developed a synthesis for unsymmertically 1,4-disubstituted carbazoles and applied it for the synthesis of 6H-pyrido [4,3-b] carbazoles. Thus 3-N,N'-dialkylaminoalkylmethyl indoles **53** were the starting materials, which were conveniently prepared from appropriate indole **51** as indicated in Scheme-10. When **53** was reacted with carbanion derived from cyanoacetate derivative to yield the intermediate **54** which on treatment with acetic acid yielded the corresponding dihydro-3,3-cyanocarboethoxy-4-methylcarbazoles **55** in good yields. These dihydrocarbazoles on subsequent treatment with lithium chloride in DDQ yielded the fully aromatic 3-cyano carbazoles having different alkyl group at 1-and 4-positions. The 3-cyanocarbazoles **56** were then transformed into its ellipticine derivatives **57**.

Katritzky and co-workers[11] recently developed an efficient synthesis of carbazoles using 1-methyl-3-benzotriazole-1-yl methyl indole **58** which on deprotonation with n-BuLi underwent 1,4-addition to a variety of α,β-unsaturated ketones and aldehydes **59** to yield the corresponding addition product **60**. These 1,4-adducts on subsequent treatment with acidic resins in refluxing dioxane underwent cyclization to yield the corresponding carbazoles **62** in moderate to excellent yields. A number of carbazoles having substitution at 1,3-di, 2,3-di, 1,2, 3-tri, have been prepared by this method.

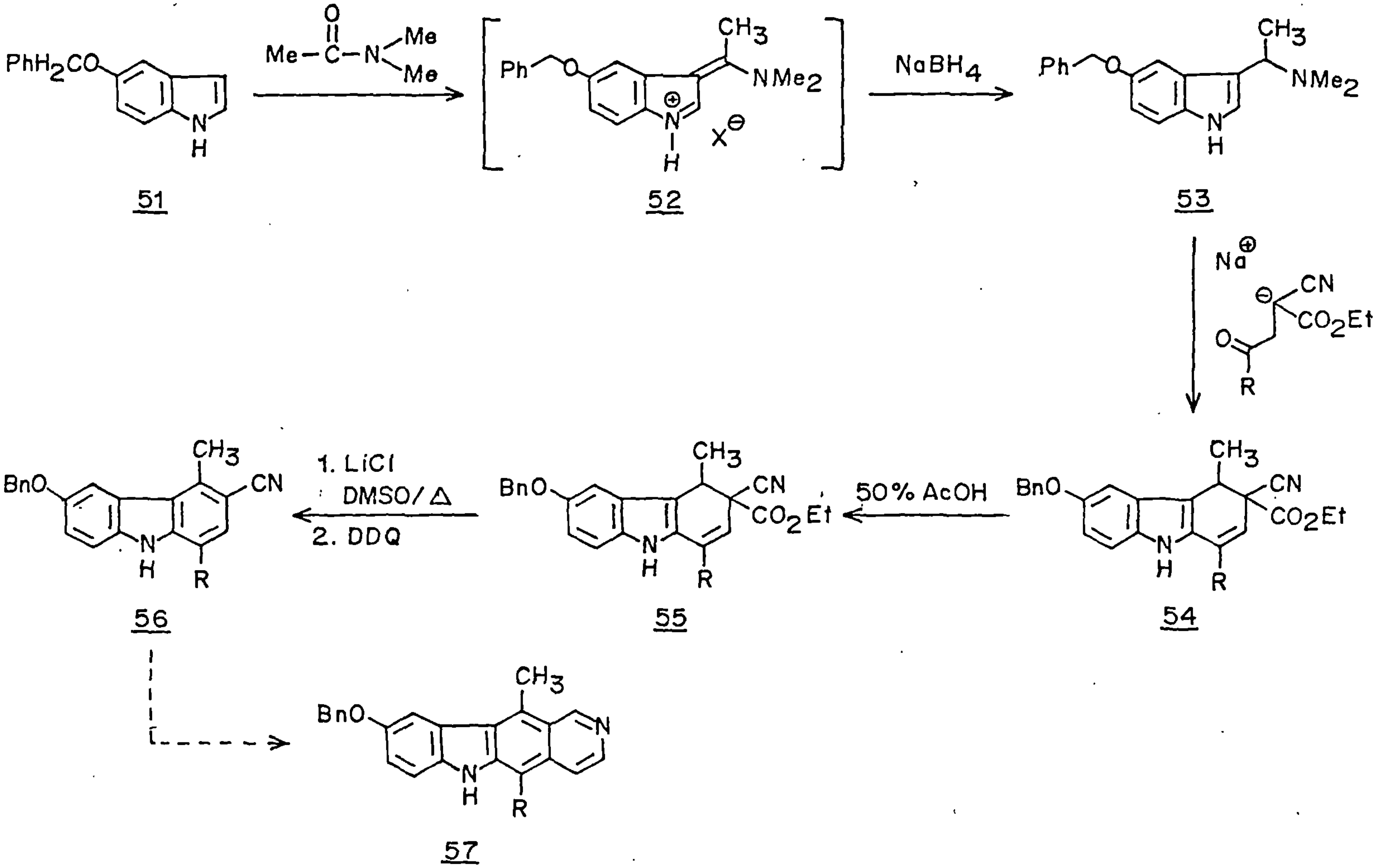


R , R^1, R^2, R^3, R^4 = Me or $-CH_2-$

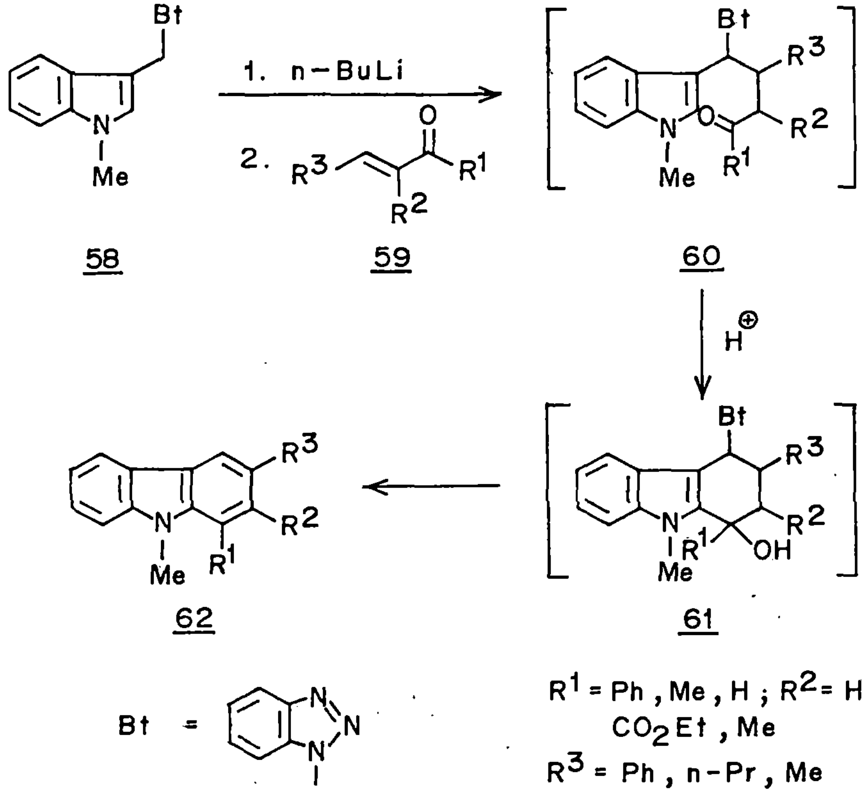
Scheme − 8


(CO)$_3$Fe$^{\oplus}$
$^{\ominus}$BF$_4$
45
+
OMe
H$_2$N
Me
Ph
46
H$_3$CCN
82°C, 2·5 hr
98%
(CO)$_3$Fe
OMe
H$_2$N
Me
Ph
47
MnO$_2$, PhCH$_3$
25°C, 1hr
85%
(CO)$_3$Fe
O
N
H
Me
Ph
48
Very active MnO$_2$
CH$_2$Cl$_2$ / 25°C / 4 hr
(CO)$_3$Fe
H
O
N
H
Me
Ph
49
(CH$_3$)$_3$ NO. 2H$_2$O
Me$_2$CO / 25°C / 4 hr
95%
OH
N
H
Me
Ph
50
K$_2$CO$_3$ / MeI
Me$_2$CO / 56°C
93%
OMe
N
H
Me
Ph
Hyellazole
2

Scheme – 9


51
Me–C(=O)–NMe2
52
NaBH4
53
Na⊕
CN
CO2Et
R
54
50% AcOH
55
1. LiCl
DMSO/Δ
2. DDQ
56
57

Scheme-10



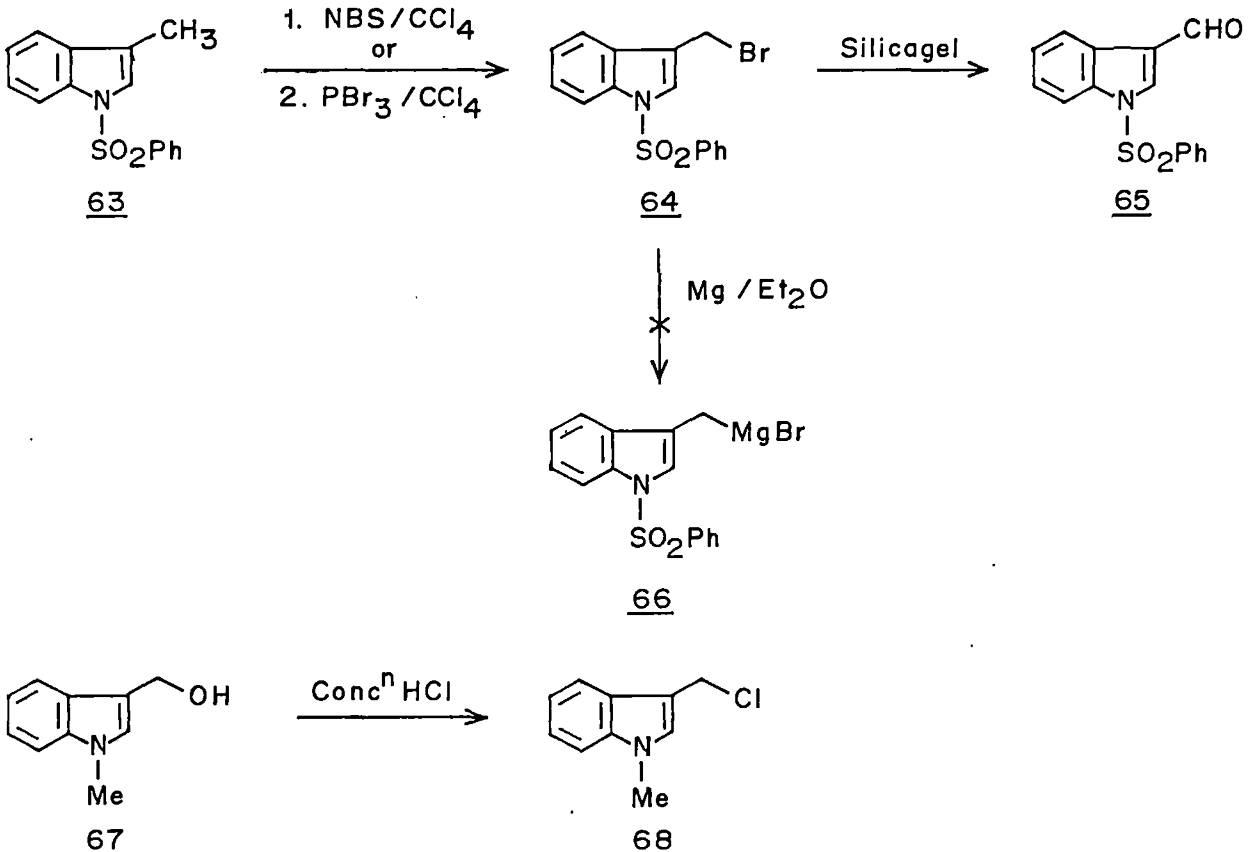
R^1 = Ph , Me , H ; R^2= H , CN , Ph , CO_2Et , Me
R^3 = Ph , n-Pr , Me

Scheme—11

Many new novel approaches for the synthesis of carbazoles and their biologically active derivatives have been recently reported which are reviewed in this section. These carbazoles, appeared to be molecules of simple structure carrying regioselectively substituted molecular fragments have proved more difficult for synthesis as can be seen from different strategies adopted by various groups with overall poor yields. Efforts to develop new synthetic routes are being ceaselessly made in recent years with a view to developing improved yields of these carbazoles. The enormous biological importance of these molecules is drawing increasing attention of many chemists all over the world to design new synthesis due to their broad range of biological activities.

Results and Discussion

In the preceding section we have presented brief outlines on the recent methods of carbazole syntheses. We became interested to extend our heteroaromatic annelation approach to the synthesis of C-ring substituted carbazoles with full regiocontrol. We considered of interest to start with 1-benzenesulphonyl-3- bromomethyl indole **64** (Scheme-12) which could be converted to the corresponding Grignard reagent **66** for use as allyl anion in creating C-ring through our aromatic annelation methodology and enter into carbazole chemistry. However **64**, though reported in the literature our efforts to purify it resulted in its hydrolytic oxidation to yield the corresponding indole-3- aldehyde **65**. Attempts to prepare Grignard reagent from the crude **64** were not successful. Since the desired Grignard reagent **66** was not formed even in small quantitities, it was then considered that the corresponding chloro compound could be more stable than **64** and attempts were made to prepare **68**. The corresponding indole-3-methyl alcohol **67** was prepared by subjecting 1-methylindole-3-carboxaldehyde to $NaBH_4$ reduction when the alcohol **67** was formed in quantitative yield. The alcohol then was treated with concentrated HCl to get the corresponding 1-methyl- 3-chloromethylindole **68**, which underwent decomposition as the bromo compound. Thus the corresponding 1-methyl-3-chloromethyl indole **68**

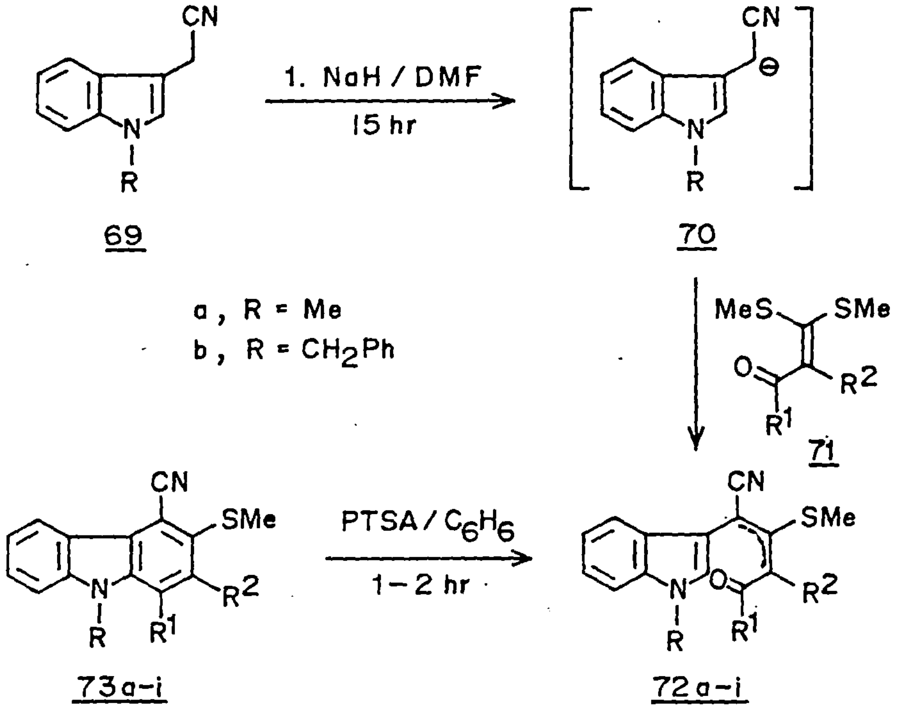


Extremely Sensitive
Could not be purified

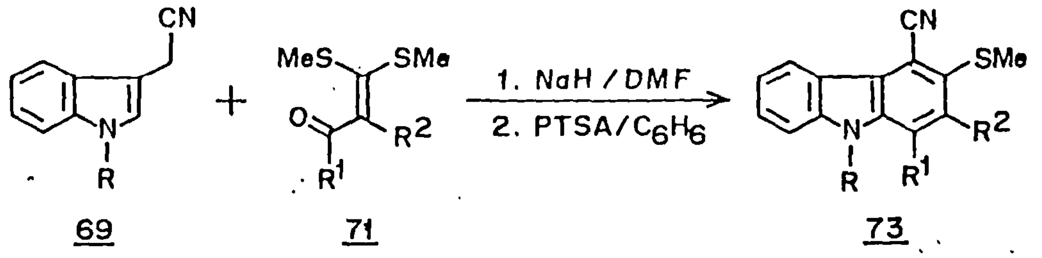
Scheme – 12

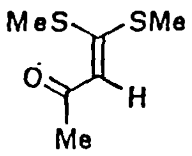
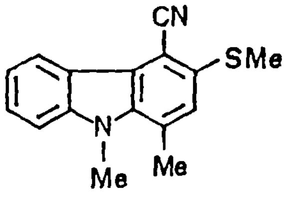
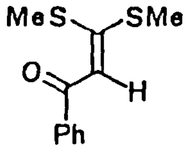
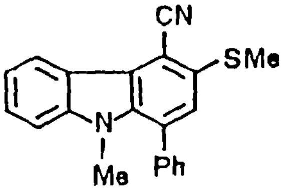
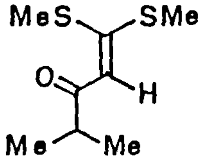
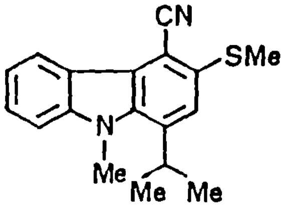
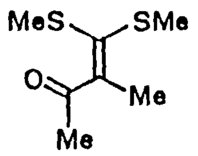
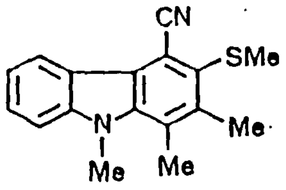
could not be obtained in pure form. Our efforts to use either **64** or **68** to convert them into the corresponding organo Grignard reagents were disappointingly unsuccessful. Many attempts to purify these intermediates ended only in failure.

After having failed to generate indole-3-methylmagnesium halide as formulated in Scheme-12, we considered to use easily accessible indole-3-acetonitriles as allyl anion precursors to react with various α-oxoketene dithioacetals. The nitrile group will certainly go as a C-4 substituent in the product carbazoles which can be either removed or transformed into different functional groups. Thus when 1-methyl-3-indole acetonitrile was reacted with α-oxoketene dithioacetal **71a** derived from acetone in the presence of NaH in dimethyl formamide at room temperature. After 10-15hr the reaction mixture was worked up to yield a product characterized as 3-[(2'-acetonyl)-2'-methylthio-1'- cyano)ethenyl]-N-methyl indole **72a** as colourless needles (chloroform-ether), m.p. 112-113°C in 93% yield. The structure was confirmed by its spectral and analytical data (see the NMR spectrum). The data are described in experimental section. The ketone **72a** when refluxed in benzene in the presence of p-toluene sulphonic acid, underwent smooth ring closure to yield the corresponding 1,9-dimethyl-3-methylthio-4-cyanocarbazole **73a** in 98% yield. The carbazole was obtained as colourless needles (chleroform-hexane) had m.p.146-147°C. Its structure was consistent with its analytical and spectral data. It was analysed for $C_{16}H_{14}N_2S$ (266.354). And its molecular weight was confirmed by its mass spectrum with a molecular ion peak at m/z, 266 (M^+,100). In its IR (KBr) spectrum a strong band at 2206cm^{-1} was assigned to the CN group. Other bands observed are reported in the experimental section. The structure was further confirmed from its ^{1}H NMR (300 MHz, $CDCl_3$) spectrum, the singlet (3H) at δ 2.52 was assigned to 3-methylthio protons. The other singlet at δ 2.74 (3H) was assigned to N-methyl protons. The singlet at δ 6.98 (1H) was assigned to the lone aromatic proton of C-ring. The multiplet (2H) between δ 7.18 to 7.25 were assigned to A ring, H_6 & H_7-protons. The peri proton (H_5) appeared as a double doublet at δ 8.45 (J=9,3Hz). The other multiplet at δ 7.43-7.49was assigned to H_8 of A ring. The structure was also confirmed from its ^{13}C NMR (75MHz) spectrum. The δ values are listed in the experimental


CN
1. NaH / DMF
15 hr
N
R
69
70
a , R = Me
b , R = CH$_2$Ph
MeS
SMe
O
R^2
R^1
71
SMe
PTSA / C$_6$H$_6$
1 – 2 hr
73a–i
72a–i

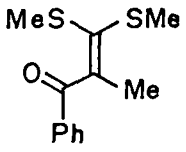
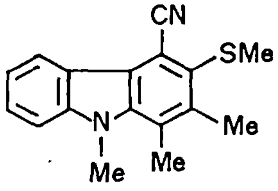
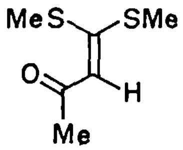
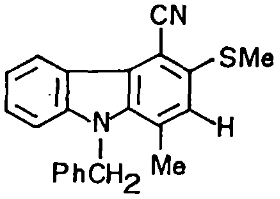
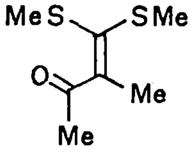
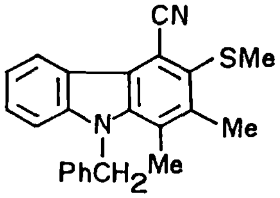
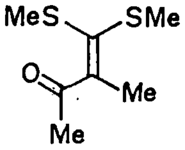
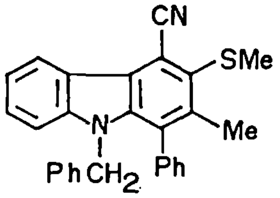
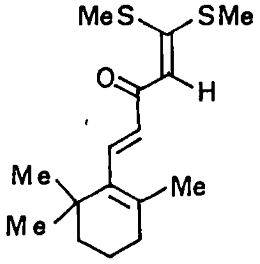
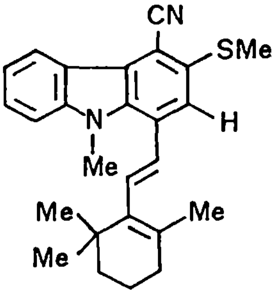
Scheme – 13



Entry	R	Mercaptal 71	Product 73	% Yield
1.	Me	 a	 a	98
2.	Me	 b	 b	69
3.	Me	 c	 c	85
4	Me	 d	 d	92

Scheme – 14

Table contd.

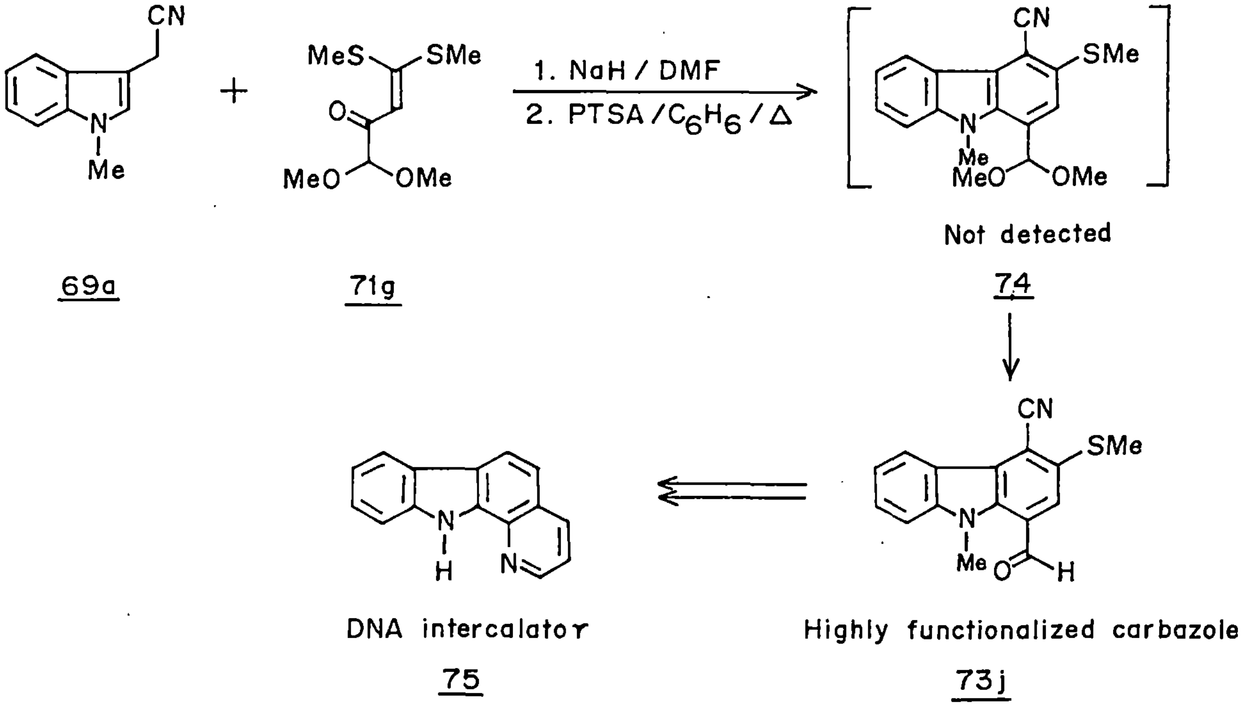
Entry	R	Mercaptal 71	Product 73	% Yield
5.	Me	 e	 e	72
6.	PhCH$_2$	 a	 f	82
7.	PhCH$_2$	 d	 g	81
8.	PhCH$_2$	 e	 h	82
9.	Me	 f	 i	82

Scheme-15

section. From these experimental data, the method we have developed is not only simple but is capable of yielding a large number of carbazoles with substituent variations possibly on all carbon atoms of the C-ring. We may compare this approach to the similar method recently published by Katritzky and co- workers using benzotriazole ring in place of CN group. The anion obtained by treating the benzotriazolylindole **58** with n-BuLi was reacted with α,β-unsaturated ketones and aldehydes followed by cyclization to yield the corresponding carbazoles in moderate to excellent yields (Scheme-11). However the present method is much more simpler and versatile in terms of choice of the α- oxoketenedithioacetals which can be made from any active methylene ketone or aldehyde. This has been amply demonstrated by reacting various α-oxoketene dithioacetals **71b-f** with 1-alkyl-3- indoleacetonitrile to yield the corresponding carbazoles **73b-i** in 69-92% overall yields. The structures of all these carbazoles were fully established by their analytical and spectral data which are explained in the experimental section.

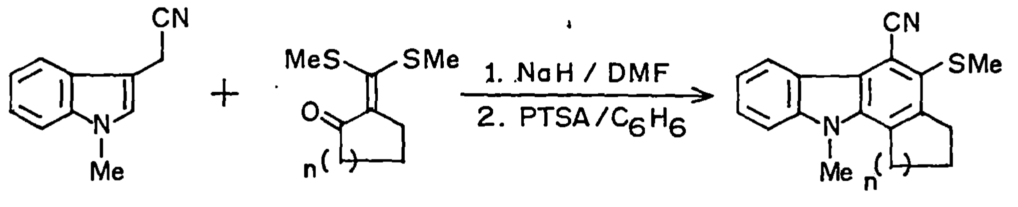
The reaction of **69a** with α-oxoketene dithioacetal derived from pyruvaldehyde dimethylacetal **71g** underwent displacement and cyclization under the described reaction conditions to yield the corresponding 1-formyl-3-methylthio-4-cyano-9-methylcarbazole **73j** in 67% yields. This aldehyde is important because it can be easily carried from its oxoketene dithioacetal component directly and regioselectively at 1- position in the product carbazole. It is a potential intermediate for the construction of pyrido[1,2-a] carbazole **75** and its condensed variants (Scheme-16). The structure of **73j** which was crystallized from ether as light yellow needles (m.p. 186-188°C) was established by its analytical and spectral data (Experimental section).

The oxoketene dithioacetals derived from three cyclic ketones **71h,i&j** similarly reacted with **69a** under the described reaction conditions to yield the corresponding open chain ketones in high yields (tlc) which were cyclized as described earlier to yield the corresponding 1,2-cycloalkano-3-methylthio-4-cyano-9-methyl carbazoles **73k-m** in 78-91% overall yields (Scheme-17). The structures were established by their analytical

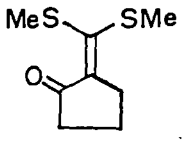
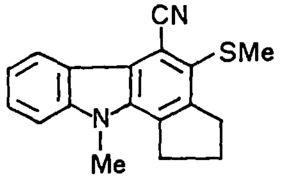
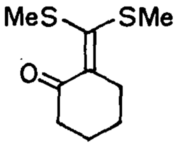
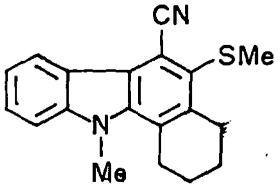
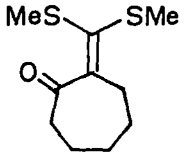
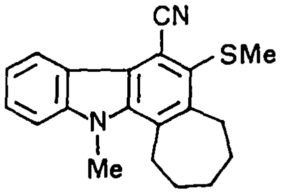

CN
MeS
SMe
O
MeO
OMe
N
Me
1. NaH / DMF
2. PTSA / C_6H_6 / Δ
Not detected
69a
71g
74
H
DNA intercalator
75
Highly functionalized carbazole
73j

Scheme – 16

Sythesis of a annelated carbazole :—



69a 71h, i, j 73k, l, m (n = 1, 2, 3)

Entry	Mercaptal 71	Product 73	% Yield
1.	 h	 k	78
2.	 i	 l	91
3.	 j	 m	83

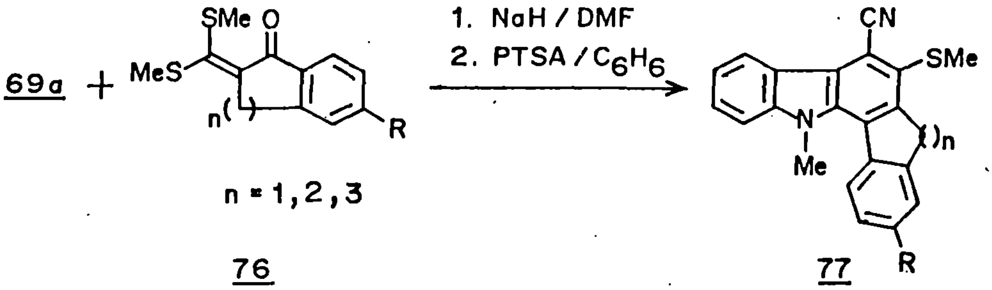
Scheme — 17

and spectral data which are described in the experimental section.

The acetonitrile **69a** was then reacted with various α-oxoketene dithioacetals derived from indanone **76a**, tetralones **76b&c** and benzo subrerone **76d** to yield the corresponding carbazoles **77a, b, c & d** in high yields under the described reaction conditions (Scheme-18). The structure of these compounds were in agreement with the analytical and spectral data.(Experimental)

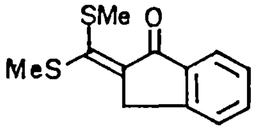
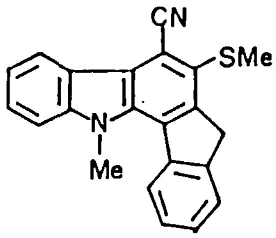
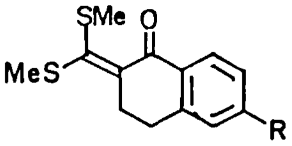
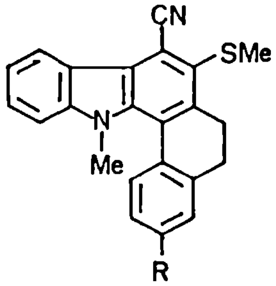
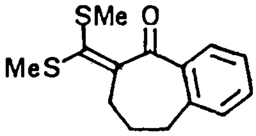
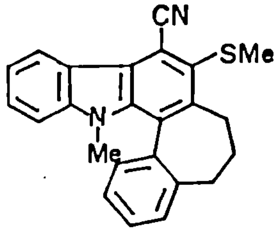
Interestingly the oxoketenedithioacetal **78** derived from an optically active natural product estrone-3-methylether as reported[34] from this laboratory is also shown to react smoothly with **69a** (Scheme-19). It gave the open chain intermediate in very high yield following the same conditions described and the intermediate was then cyclized in the presence of PTSA in refluxing benzene to yield the corresponding 1,2-annelated carbazole **80** in 78% yield, m.p. 235°C (dichloromethane) as colourless needles $[\alpha]_D^{13}$ +49° (c=1, dioxane). The analytical and spectral data were in confirmity with the assigned structure (Experimental). Thus the method is extremely suitable to make optically active carbazoles which are pure enantiomers. We were tempted to call this compound as man made alkaloid, which are to be screened for various biological activities. The scope of this reaction is quite evident that any new such carbazole can be made provided the corresponding α-oxoketenedithioacetal is derived from naturally occuring optically active methylene ketones. The work is in progress along these directions.

The versatility of this method can be visualized by its general application to the corresponding S,N-acetals which are most attractive precursors for the synthesis of 3-aminocarbazoles. Only three S,N-acetals **81a-c** (Scheme-20) have been selected in the present work though the choice of these S,N-acetals is too large. The intermediates thus obtained were cyclized under similar reaction conditions to yield the corresponding 3- pyrrolidino **82a**, 3-piperidino **82b** and 3-morpholino **82c**, in 62, 68 and 71% yields respectively. The structures of these carbazoles **82a-c** were in accordance with the analytical and spectral data (Experimental section).

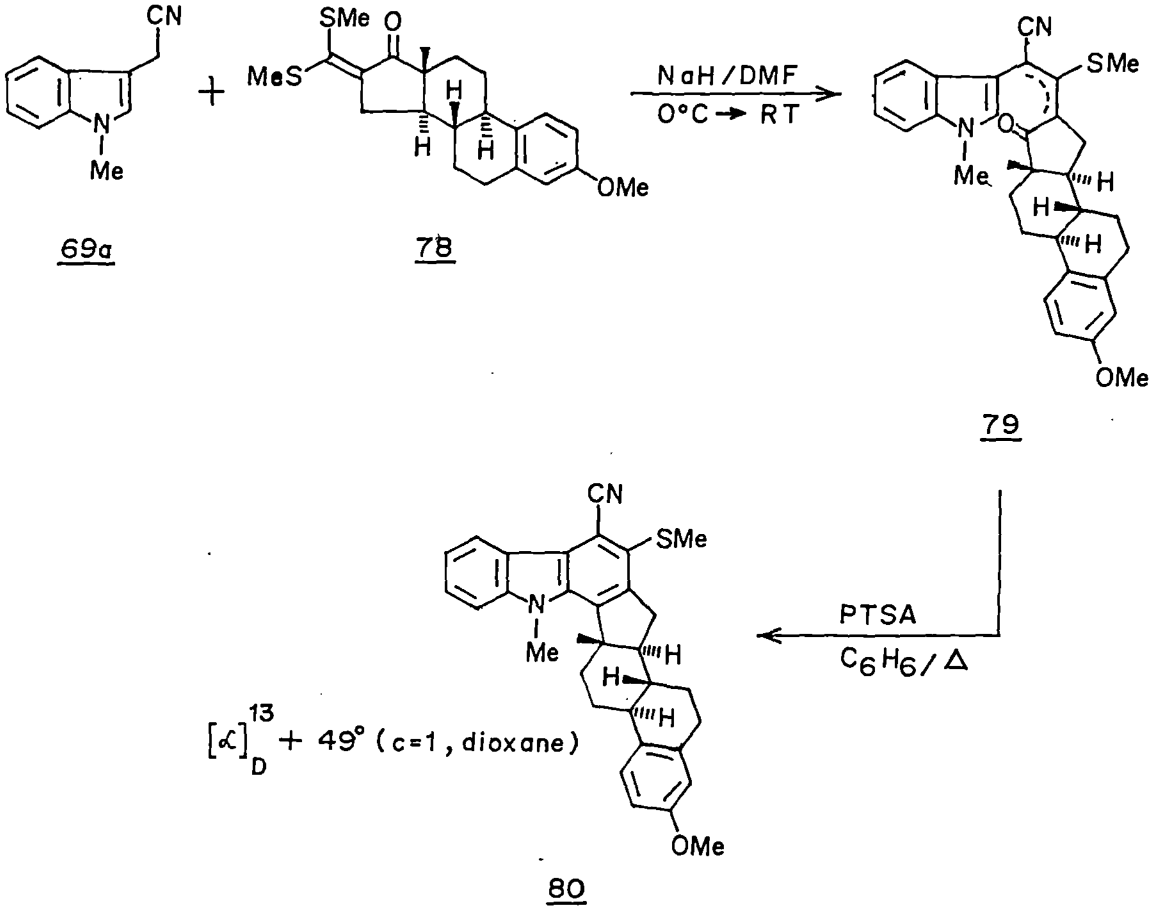


76

77

Entry	76	77	%Yield
1.	 a	 a	92
			
2.	b, R = H	b, R = H	68
3.	c, R = OMe	c, R = OMe	72
4.	 d	 d	72

Scheme – 18


CN
N
Me
69a
+
SMe
O
MeS
H
H
H
OMe
78
NaH/DMF
0°C → RT
CN
SMe
N
Me
O
H
H
H
OMe
79
PTSA
C6H6/Δ
CN
SMe
N
Me
H
H
H
[α]13D + 49° (c=1, dioxane)
OMe
80

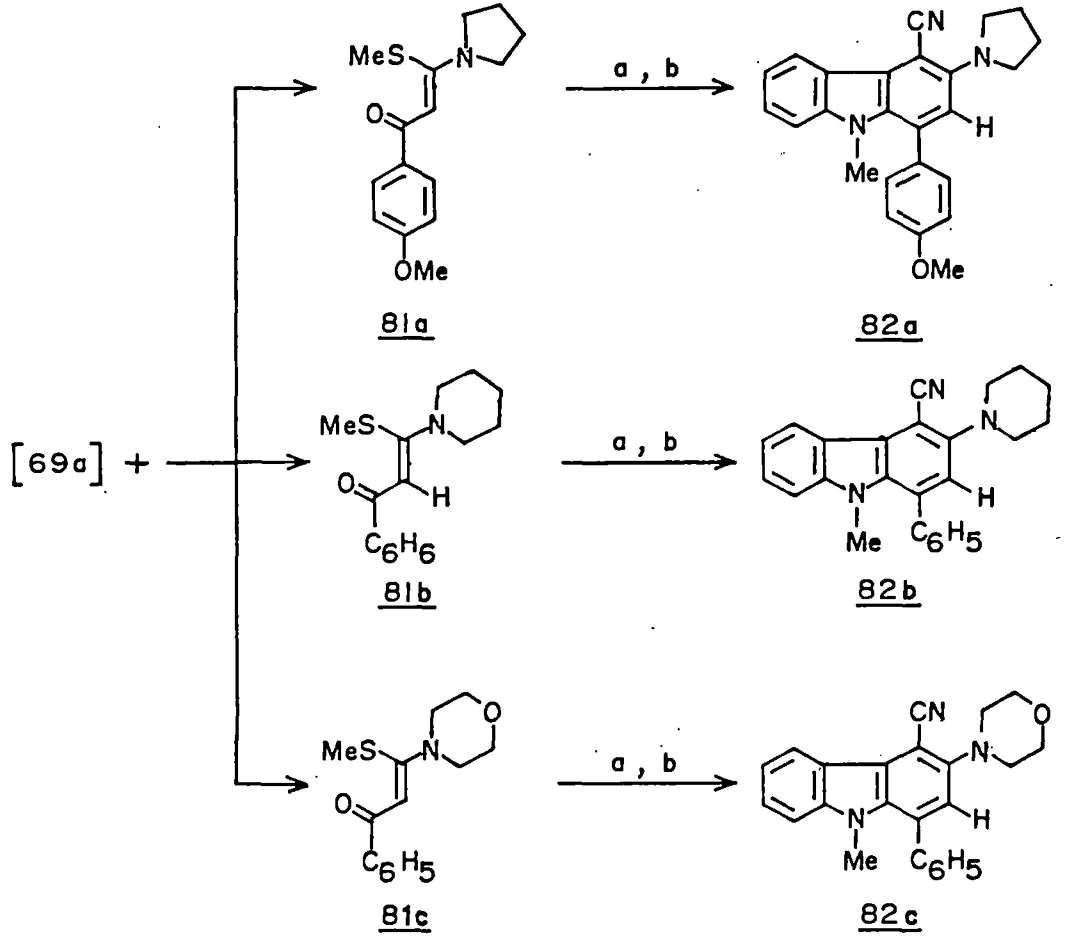
Scheme – 19

After having successfully utilized the α-oxoketene dithioacetals and the corresponding S,N-acetals for the synthesis of 3- methylthio and 3-aminocarbazoles, it was felt to extend this method to the corresponding α-oxoketene O,S-acetals so that the methodology can be extended to the synthesis of 3-methoxy carbazoles which are widely present in many natural products of this class. Thus the two O,S-acetals **83a,b** of interest to us were prepared according to our reported method in moderate yields. The hitherto unknown O,S-acetals **83a** derived from ethylmethyl ketone was obtained by reacting enolate of the ethylmethyl ketone with dimethylxanthate followed by alkylation to yield the desired O,S- acetal **83a** in very low yield. The structure of this compound was in agreement with its analytical and spectral data given in the experimental section. The two O,S-acetals **83a** and **b** were reacted with **69a** to yield the corresponding 3-methoxycarbazoles **84a** and **84c** in 92 and 85% yields respectively. The O,S-acetal **83a** was also reacted with **69b** to yield the corresponding 3-methoxy carbazole **84b** in 72% yield. All the carbazoles thus obtained were confirmed for their structures from their analytical and spectral data (Experimental section).
A number of recently discovered naturally occuring carbazoles **85a-e** are listed in Scheme-22 to demonstrate the closeness of our method to the naturally occuring carbazoles. Some efforts were made to transform the cyano group to other functional groups including its removal and their results are being currently investigated.

In one of the experiments, the effect of Raney-Nickel assisted desulfurization on 3-methylthio and CN group was examined. Thus **73a** on desulfurization in the presence of Raney-Ni yielded the corresponding carbazole having N,N'-diethylaminomethyl group through reduction of the CN functionality with complete removal of 3-methylthio group. The structure of **86** was confirmed from its analytical and spectral data (see experimental). When we used very active Raney-Nickel (freshly prepared), the cyanogroup in **73k** was conveniently transformed into the corresponding methyl group to yield the carbazole **87** in high yield. Its structure was confirmed from its analytical and spectral data (Experimental).

Two experiments were carried out as an attempt to hydrolyse the 4-cyano group in

Reaction with S,N-acetals :— Synthesis of 3-amino carbazoles



a, NaH / DMF ; RT / 15 hr
b, PTSA / C_6H_6 ; 65°C / 1-2 hr

Scheme-20

these carbazoles. It may be however said that the cyano group did not undergo any hydrolytic change both under acidic and alkaline conditions even on prolonged refluxing condition. However when **73a** was heated with 20% ethanolic NaOH in sealed tube 230°C for 7-12 hrs, the nitrile group was found to be partly hydrolysed to the corresponding amide **88**. The structure of **88** was confirmed by its analytical and spectral data. Similarly the amide **89** was prepared from the corresponding **77c** under the described reaction condition. Further attempts to transform the carboxamide into free acid and decarboxylation to yield the carbazoles having no substituents at 4-position are in progress.

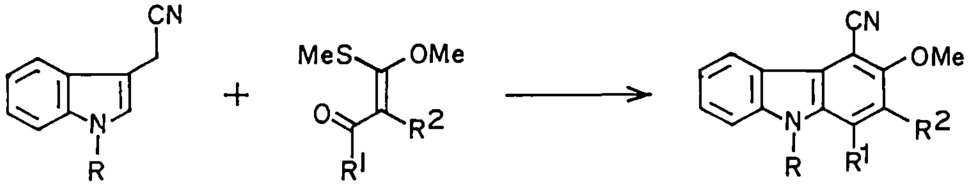
In conclusion, it is to be noted that a very practical, efficient and facile method for the synthesis of regioselectively substituted carbazoles has been developed as an extension of our heteroaromatic annelation methodology. The reaction examined are only illustrative of what further can be done to achieve the synthesis of more important carbazoles. As an initial step, we have made a maiden effort to standardize the methodology for the family of carbazole molecules and their synthesis which will now be more rigorously applied for the synthesis of the target molecules of the carbazole group. The indole-3-acetonitrile has been shown to be attractive precursor to generate our desired allyl anion which undergoes exclusive 1,4-addition elimination sequence with all the α-oxoketene S,S-,S,N-and O,S-acetals to yield the desired regiochemistry in terms of C-ring substituents. Further work in these directions is being continued.

Experimental Section

General

M.Ps were obtained on a "Thomas Hoover" melting point (capillary method) apparatus and are uncorrected. The Infrared spectra were recorded on Perkin-Elmer 983 spectrometer. ^{1}H NMR (90 MHz) were recorded on Varian EM-390 spectrometer. High resolution ^{1}H NMR (300 MHz), ^{13}C NMR (75.43 MHz) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shifts (δppm) and the coupling

Reaction with O, S–acetals : Synthesis of 3-methoxy carbazoles

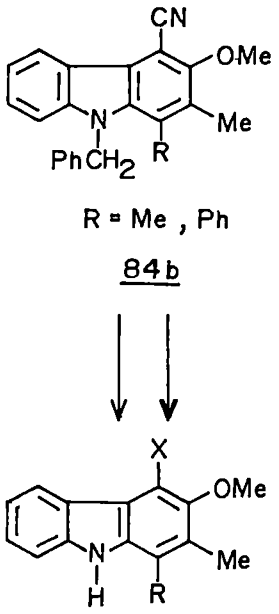


69a, R = Me
b, R = CH$_2$Ph

83a, R^1 = Me, R^2 = Me
b, R^1 = Ph, R^2 = H

84a, R = R^1 = R^2 = Me
b, R = CH$_2$Ph; R^1 = R^2 = Me
c, R = CH$_3$, R^1 = Ph, R^2 = H

Scheme – 21



R = Me , Ph

84b

85a , X = H ; R = Me 4-deoxy carbazomycin-B
b, X = OH ; R = Me carbazomycin-B
c, X = OMe ; R = Me carbazomycin-A
d, X = H ; R = Ph Hyellazole
e, X = OH ; R = CHO carbazomycinal

Scheme-22

constants (Hz) are reported in the standard fashion with reference to either TMS as internal lock (for ^{1}H NMR), the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C NMR) Mass spectra (MS) were obtained on a Jeol JMS-D 300 Mass spectrometer. Masses are reported in units of mass over charge (m/z), the molecular and base peaks are indicated by "M^+" and "%" respectively. Elemental analysis were carried out on a Heraeus CHN-O-Rapid analyzer.

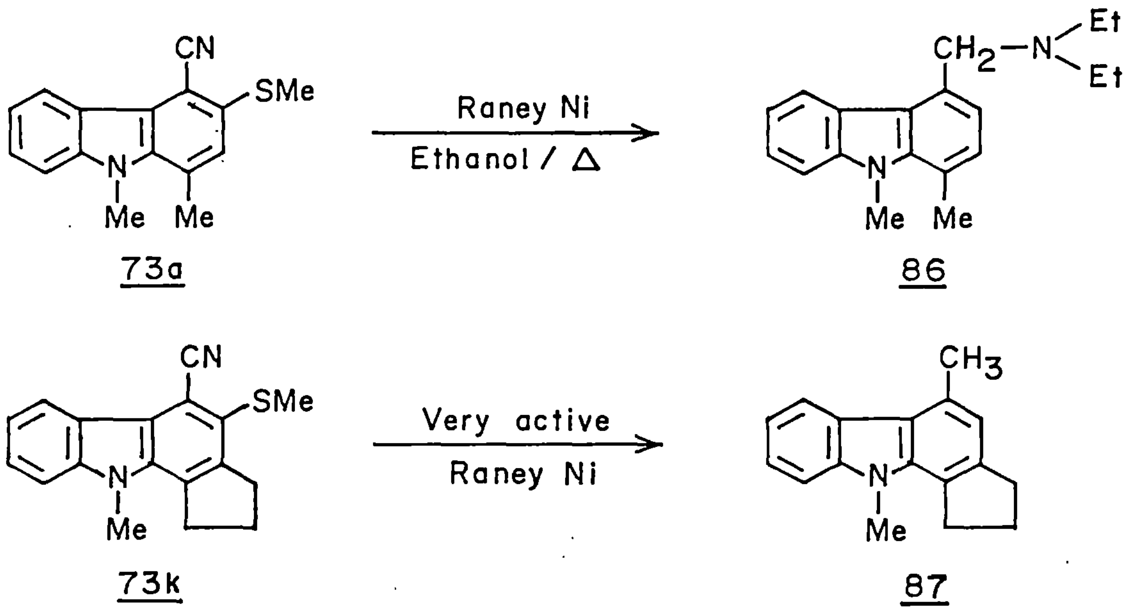
All reactions were performed in oven dried (120°C) glasswares under a positive dry argon/nitrogen atmosphere. Analytical thin layer chromatography (tlc) were performed on glass plates coated with ACME's silicagel containing 13% calcium sulfate as binder and various combination of visualization of spots was accomplished by exposure to iodine vapour or potassium permanganate (acidic) solution. ACME's silicagel (60-120 mesh) is used for coloumn chromatography, eluents for coloumn chromatography were used after simple distillation of commercial materials. All solvent evaporations were done using a steam bath.

Chemicals and Reagents

Commercially available NaH, 50% suspension (SISCO,SPECTRO-CHEM) was used. N,N-dimethyl formamide (Aldrich) was purchased bottle grade and dried over calcium hydride, distilled and stored over molecular sieves (4A). Anhydrous p-toluene sulfonic acid (PTSA) was purchased from Aldrich. Tetrahydrofuran (THF) was obtained anhydrous by keeping the deperoxidised THF over sodium- benzophenone. Anhydrous ether was obtained by keeping the bottle grade over calcium chloride over night and finally stored over sodium wire. Dry benzene was obtained by washing with concentrated sulphuric acid followed by azeotropic distillation and stored over sodium wire. Raney Ni[35] (W4) was prepared according to the reported procedure.

Starting Materials

The commercial sample of ß-ionone, acetone, 2-butanone, acetophenone, cyclopentanone, cyclohexanone, cycloheptanone, isopropyl methyl ketone, 4-methoxy


CN
SMe
N
Me
Me
73a
Raney Ni
Ethanol / Δ
CH2—N
Et
Et
N
Me
Me
86
CN
SMe
N
Me
73k
Very active
Raney Ni
CH3
N
Me
87

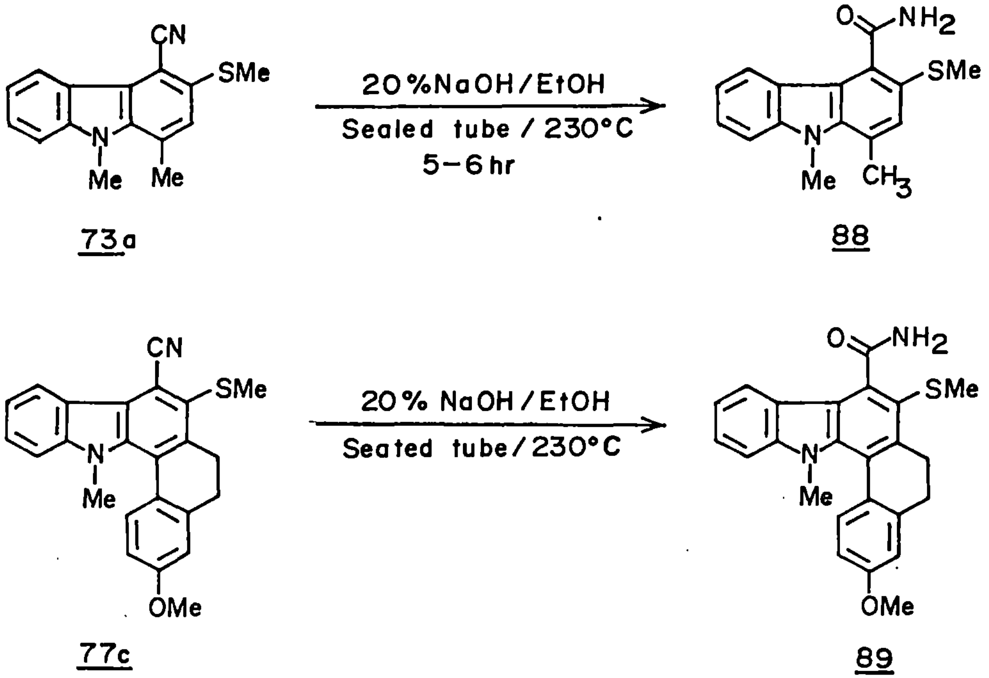
Scheme-23

acetophenone, pyruvaldehyde dimethylacetal were purified by distillation under reduced pressure before use. 1-tetralone,[36] 1-indanone,[37] benzosuberone,[38] propiophenone[39] were prepared according to the reported procedure. Estrone was gifted by Organon Research Centre, Calcutta. The 6-methoxy tetralone (Aldrich) was used. For the preparation of α-oxoketene S,N-acetals, commercially available, pyrrolidine, piperidine and morpholine (secondary amines) were used which were purified by simple distillation. Dimethyl trithiocarbonate bp 225°C (760 mm) was prepared according to the earlier reported procedure.[40] The methyl xanthate[41] was prepared according to the literature procedure for the preparation of O,S-acetals. The indole-3-acetonitrile was prepared as per the reported procedure.[42] α-Oxoketene S,S- acetals, S,N-acetals and O,S-acetals required for the present investigation were prepared according to the earlier reported general procedures which are given below.

General procedure for the preparation of oxoketene dithioacetals

A mixture of ketone (0.2 mol) and carbondisulphide (0.2 mol) was added dropwise to an ice-cold and well stirred suspension of sodium t-butoxide (0.4 mol) in dry benzene (200 ml) and the reaction mixture was allowed to stir at ambient temperature for 5-6 hrs. Acid free dimethyl sulphate (0.2 mol) was then gradually added with stirring and cooling and the reaction mixture was allowed to stir at room temperature for 6-10 hrs. The reaction mixture was poured over aqueous saturated ammonium chloride solution (250 ml) and the layers were separated. The aquous layer was extracted with benzene (100 ml) and combined benzene extracts were washed with water (4x250 ml), dried over anh.sodium sulphate and evaporated. Trituration of the oily residue with hexane gave the dithioacetals as light yellow crystalline solids in good yields. Liquid dithioacetals were purified by passing through silicagel coloumn using hexane-ethylacetate as eluent.

All the known dithioacetals were characterized by comparision of their melting points, NMR, IR spectra with those of reported data and of authentic samples.



73a 88

77c 89

Scheme – 24

General procedure for the preparation of 4,4-bis(methylthio)-1,1-dimethoxy-3-buten-2-one (<u>71g</u>)

To a suspension of NaH (0.4mol) in dry THF (50ml), was added dropwise a solution pyruvaldehyde dimethylacetal (0.2mol) in dry THF (25ml) followed by the addition of carbon disulfide (0.2mol) at 0°C for 30-45min. Neutral dimethyl sulphate (0.13mol) was added dropwise to the reaction mixture at the same temperature and stirred for 5-6 hours at room temperature. Poured slowly to crushed ice (200gms), allowed to remain for 2 hrs and then extracted with ether (3 x 75 ml), dried over anh.Na_2SO_4, concentrated to give the crude dithioacetal which on further purification using coloumn chromatography yielded pure dithioacetal in 67% yield as viscous liquid;IR (KBr): 2989, 2829, 1642 (CO), 1428cm^{-1}; ^{1}H NMR (300 MHz, CCl_4): δ 2.47 (s, 3H, SCH_3), 2.50 (s, 3H, SCH_3), 3.38 (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3), 4.44 (s, 1H, CH), 6.30 (s, 1H, olefinic); ^{13}C NMR (75 MHz, CCl_4): δ 14.56, 16.93, 53.96 (2 OCH_3), 104.01, 107.83, 166.00, 187.48 (CO). Anal. Calcd. for $C_8H_{14}O_3S_2$ (222.31): C 43.2; H 6.34. Found: C 43.24; H 6.31.

Preparation of oxoketene S,N-acetals: General procedure:

(i) Preparation of methyl ß-oxodithiocarboxylate: To a well stirred suspension of NaH (5g, 0.01 mol, 50% suspension) in dry benzene (100 ml), dimethyl trithiocarbonate (7.60 gm) was refluxed with stirring for 10 min. A solution of the appropriate ketone (0.05 mol) in dry benzene (50 ml) was slowly added dropwise over a period of 3.5-4 hrs, the mixture was further refluxed for 2 hr, then allowed to cool and poured into ice-cold water (250 ml). The aqueous layer is separated, washed with benzene (200 ml), acidified with 3N HCl or 20% acetic acid, and extracted with chloroform (2x150 ml). The combined organic extracts were dried over sodium sulphate and evaporated to give the product (single spot on tlc which is pure enough 95% purity according to NMR analysis) for the reactions.

(ii) Preparation of ß-oxodithioacetamide: A solution of methyl ß- oxodithiocarboxylate and the appropriate secondary amine (0.01 mol) in ethanol (25 ml) was refluxed for 5-7 hr (monitored by tlc), ethanol was distilled off, residue triturated with hexane and the crude thiamides thus obtained were crystallized from ether-hexane as yellow crystalline solids.

(iii) Preparation of oxoketene S,N-acetals: A suspension of thiamide (0.004 mol) and anhydrous potassium carbonate (0.56g, 0.004 mol) in acetone (30 ml) was refluxed for 3 hr with stirring, it was then cooled and to this was added methyliodide (0.71g, 0.005 mol) with stirring and the mixture was further stirred for 3 hr at room temperature. It was then poured over crushed ice, acidified with 20% acetic acid (150 ml) and extracted with chloroform (2x100 ml), dried over sodium sulphate and concentrated to give oxoketene S,N-acetals which were purified by passing through silicagel coloumn using hexane- ethylacetate as eluent.

All the known S,N-acetals were characterised by comparison of their NMR, IR spectra with those of reported data and of authentic samples.

Preparation of α-oxoketene O,S-acetals: General procedure

(i) Preparation of ß-oxothionoesters: To an ice cold stirring suspension of sodium t-butoxide (38.4g, 0.4 mol, prepared from 9.2g, 0.4 atom of sodium) in t-butanol (150 ml), a mixture of dimethyl xanthate (0.2 mol) and respective ketone (0.2 mol) was added dropwise and the resulting mixture was stirred at room termperature for 8-10 hr (monitored by tlc). It was then poured on to crushed ice (200g), acidified with 50% HCl (50 ml), extracted with benzene (3x100 ml) and the combined extracts were washed with water (3x150 ml), dried over Na_2SO_4 and concentrated to give the crude thionoesters, which were purified by coloumn chromatography over silicagel using hexane as eluent.

(ii) Preparation of α-oxoketene O,S-acetals A suspension of ß- oxothionoesters (0.2 mol) and anhydrous K_2CO_3 (52.59g, 0.4 mol) in dry acetone (100 ml) was refluxed with stirring for 3 hr, and then cooled to room temperature. Iodomethane (0.25 mol) was added dropwise with stirring at 0-5°C and the resulting reaction mixture was further stirred at room temperature for 5-6 hrs (monitored by tlc). It was then put to crushed ice (250gm) and extracted with chloroform (3x150 ml). The combined extracts were washed thoroughly with water (3x100 ml), dried over Na_2SO_4 and evaporated to give crude O,S-acetals which were purified by coloumn chromatography over silicagel using EtOAc/hexane as eluent.

4-Methoxy-4-methylthio-3-methyl-3-buten-2-one(83a).

Light yellow liquid; yield 32%; IR (CCl_4): ^1H NMR (90 MHz, CCl_4): δ 2.00 (s, 3H, CH_3), 2.45 (s, 3H, SCH_3), 2.50 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3). Anal.Calcd.for $C_7H_{12}O_2S$ (160.234): C 52.46; H 7.55. Found: C 52.58; H 7.56.

3-Methoxy-3-methylthio-1-phenyl-2-propene-1-one (83b) used for this reaction was compared with the reported data.

General procedure for N-alkylation of indole-3-acetonitrile

To a well stirred suspension of anh.K_2CO_3 (0.06mol) in acetone (100ml), was added a solution of indole-3-acetonitrile (0.02mol) in acetone (50ml) and the reaction mixture was refluxed for 3-5hr. Cooled to 0°C and appropriate alkyl halide (0.03mol) was slowly added and kept stirring for another 2-3hr. Poured into crushed ice (200gms), extracted with chloroform (3x50ml), concentrated to give viscous residue which on trituration with hexane afforded pure colourless crystalline solid. Data are compared with the reported values.

General procedure for the reaction of N-alkylindole-3- acetonitrile with α-oxoketene S,S-, O,S- and N,S-acetals.

To a well stirred suspension of NaH (0.04 mol) in dry DMF (10 ml), N-alkylindole-3-acetonitrile (0.02 mol) dissolved in dry DMF (10 ml) was added dropwise at 0°C. After keeping for 45 min to 1 hr the appropriate α-oxoketene acetal

(0.02 mol) was added dropwise to the reaction mixture at 0°C and kept stirring for further 10-15 hrs at room temperature. Poured into crushed ice (200 g) and extracted with chloroform (3x100 ml). The combined extracts were thoroughly washed with water (3x250 ml), evaporated to give crude 1,4-addition elimination product in quantitative yields.

The 1,4-adduct formed by the reaction of 1-methylindole-3- acetonitrile with **71a** was characterized by its analytical and spectral data as given below.

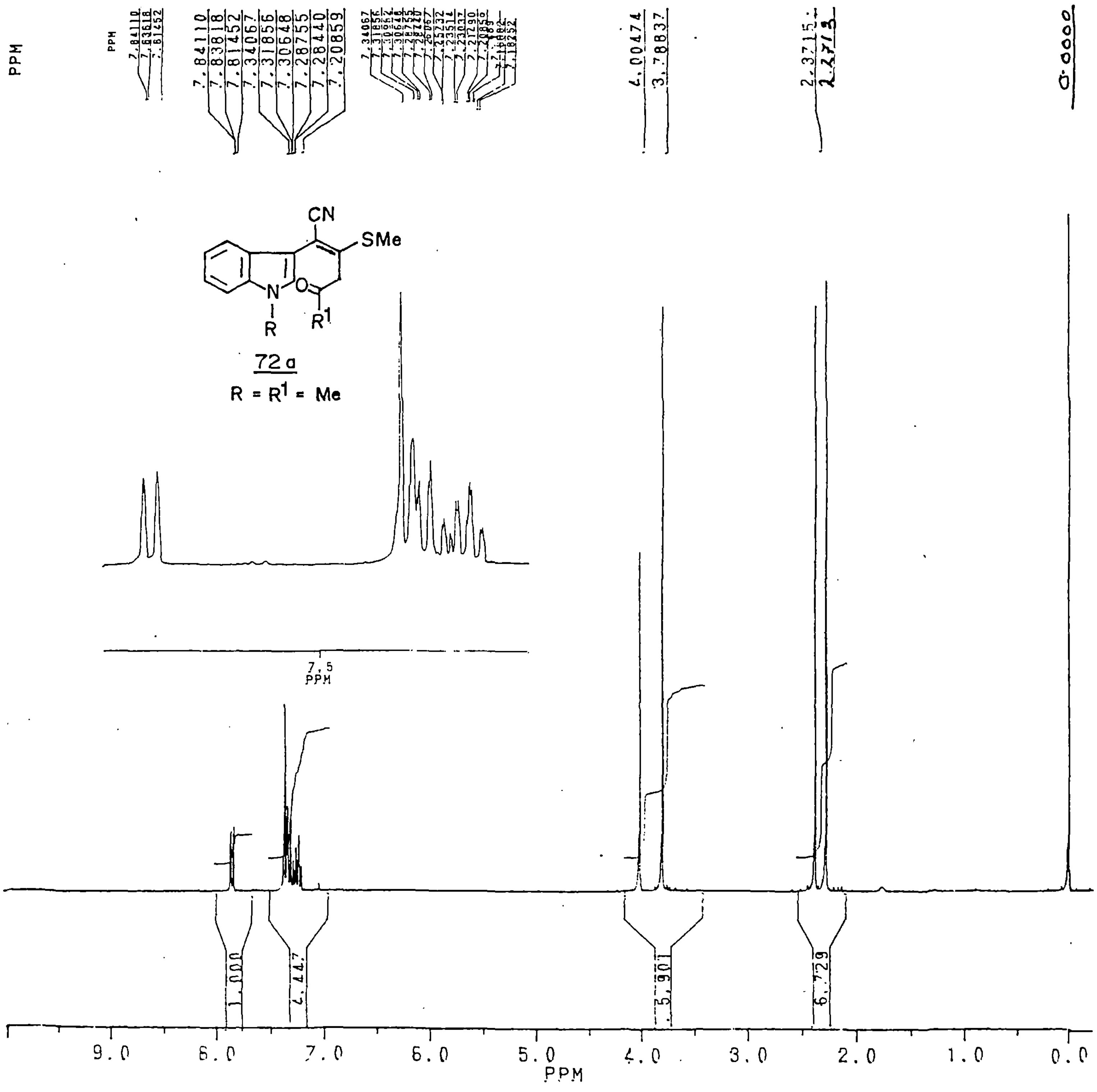
3-[(2'-Acetonyl-2'-methylthio-1'-cyano)ethenyl]-N-methylindole 72a

Colourless crystals (chloroform-ether); mp. 112-113°C; yield 93%; IR (KBr): ν_{max} 2927, 2201 (CN), 1712 (CO), 1525, 1474 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H, CH_3), 2.37 (s, 3H, SCH_3), 3.78 (s, 3H, NCH_3), 4.00 (s, 2H, CH_2), 7.18-7.31 (m, 3H, ArH), 7.34 (s, 1H, ArH), 7.82 (dd, 1H, J = 9, 3Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.12 (CH_3), 29.27 (SCH_3), 33.10 (CH_2), 49.15 (NCH_3), 103.33, 106.75, 109.62, 118.35, 120.13, 120.29, 122.55, 125.74, 130.25, 136.38, 149.58, 202.72 (CO); MS (m/z, %): 284 (M^+, 38.5). Anal. Calcd. for $C_{16}H_{16}N_2OS$ (284.374): C 67.57; H 5.67; N 9.85. Found: C 66.72; H 5.63; N 9.82.

The rest 1,4-addition elimination products **72** were cyclized directly without purification and characterization.

General procedure for PTSA induced cyclization of 1,4-addition elimination products to carbazoles (73, 77, 80, 82, 84).

To the crude 1,4-addition elimination product (0.01 mol) dissolved in dry benzene (25 mol), anhydrous PTSA (one pinch) was added and refluxed for 1-2 hrs. Poured to aq $NaHCO_3$ solution (250 ml) and extracted with chloroform (2x150 ml), dried over Na_2SO_4, evaporated and coloumn chromatographed using hexane-ethyl acetate (18:2) as eluent, to yield pure carbazoles in nearly quantitative yields.



72a

R = R^1 = Me

CN
SMe
N
R
O
R1
PPM
7.84110
7.83618
7.81452
7.84110
7.83818
7.81452
7.34067
7.31856
7.30648
7.28755
7.28440
7.20859
7.34067
7.31856
7.30648
7.28755
7.28440
7.26067
7.25232
7.23514
7.23037
7.21290
7.20850
7.16082
7.18252
4.00474
3.78837
2.37151
2.2713
0.0000
7.5
PPM
1.000
4.447
5.901
6.729
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

4-Cyano-1-methyl-3-methylthio-N-methylcarbazole (73a)

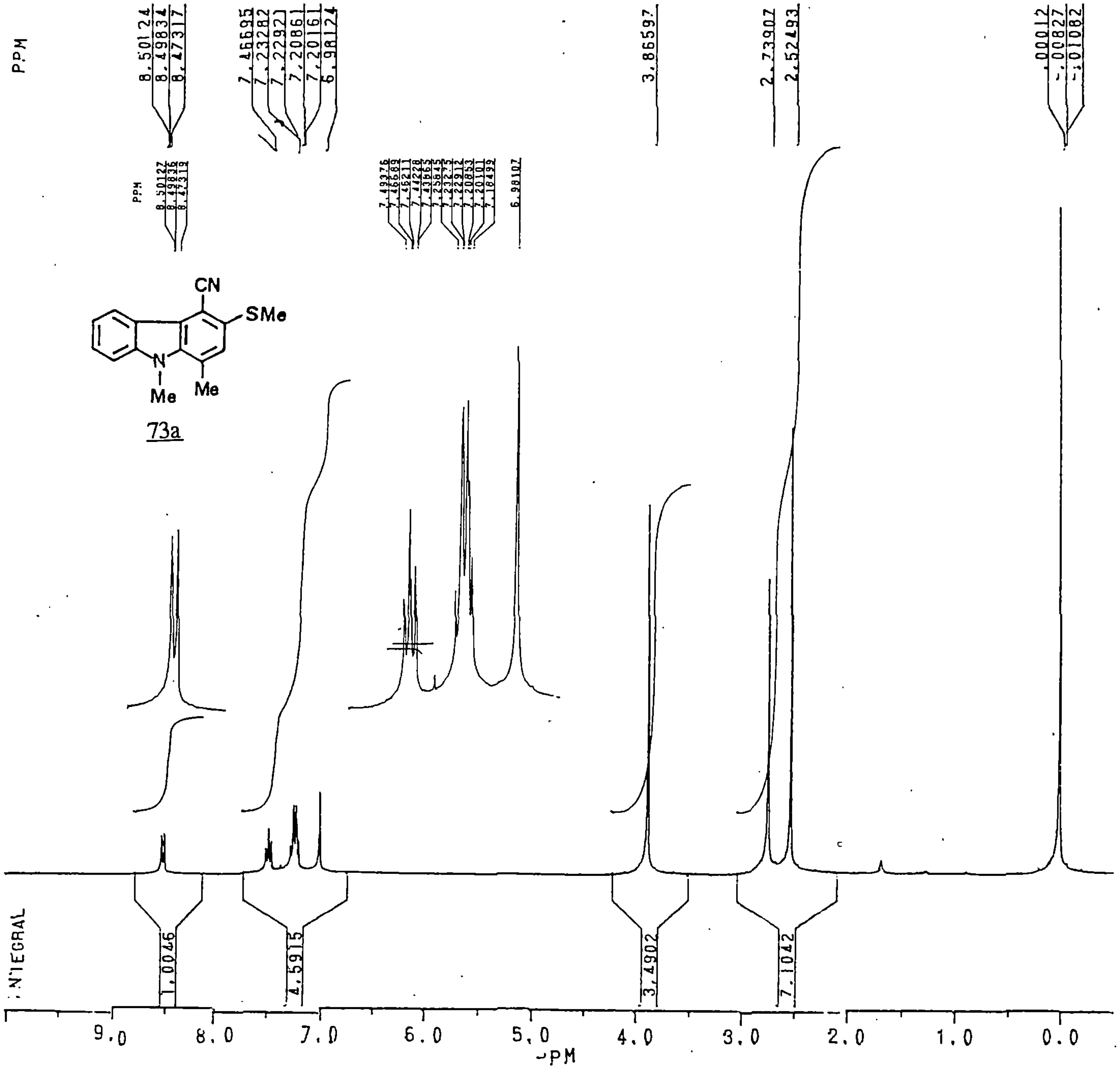
Colourless crystals (Chloroform-hexane); mp. 146-147°C; yield 98%; IR (KBr): 3414, 2923, 2206 (CN), 1642, 1609 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.52 (s, 3H, SCH_3), 2.74 (s, 3H, CH_3), 3.86 (s, 3H, NCH_3), 6.98 (s, 1H, ArH-H_2), 7.18-7.25 (m, 2H, ArH), 7.43-7.49 (m, 1H, ArH), 8.49 (dd, 1H, J = 9, 3Hz, ArH-H_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.45 (SCH_3), 20.69 (CH_3), 32.09 (NCH_3), 102.98, 108.76, 117.47, 119.78, 121.39, 124.08, 126.09, 127.36, 129.56, 132.17, 137.67, 141.93; MS (m/z, %): 266 (M^+, 100), 267 (M^++1, 16.9). Anal. Calcd. for $C_{16}H_{14}N_2S$ (266.354): C 72.14; H 5.29; N 10.52. Found : C 72.02; H 5.27; N 10.48.

4-Cyano-3-methylthio-1-phenyl-N-methylcarbazole (73b)

Colourless crystals (ether); mp. 138-139°C; yield 69%; IR (KBr): 3054, 2921, 2218 (CN), 1611, 1569; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.56 (s, 3H, SCH_3), 3.26 (s, 3H, NCH_3), 7.17-7.26 (m, 2H, ArH), 7.29 (s, 1H, ArH-H_2), 7.42-7.49 (m, 6H, ArH), 8.57 (d, 1H, J = 9Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.49 (SCH_3), 32.79 (NCH_3), 109.12, 117.25, 119.79, 120.06, 121.51, 125.19, 127.72, 128.26, 128.31, 129.12, 129.49, 130.57, 131.99, 136.68, 138.30, 142.72; MS (m/z, %): 328 (M^+, 100), 329 (M^++1, 30.2). Anal. Calcd. for $C_{21}H_{16}N_2S$ (328.424): C 76.79; H 4.91; N 8.53. Found: C 76.68; H 4.87; N 8.49.

4-Cyano-1-isopropyl-3-methylthio-N-methylcarbazole (73c)

Colourless crystals (hexane-ether); mp. 135°C; yield 85%; IR (KBr): 2963, 2217 (CN), 1565, 1483cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.38 (d, 6H, J = 9Hz, 2CH_3), 2.52 (s, 3H, SCH_3), 4.01 (hept, 1H, J = 9Hz, CH), 4.05 (s, 3H, NCH_3), 7.13-7.62 (m, 4H, ArH), 8.66 (d, 1H, J = 8.75Hz, ArH-H_5); ^{13}NMR (75 MHz, $CDCl_3$): δ 19.07 (SCH_3), 24.04 (2CH_3), 28.38 (CH), 33.06 (NCH_3), 103.99, 108.96, 117.58, 120.09, 120.19, 121.69, 125.37, 127.63, 132.61, 137.15, 137.65, 142.70; MS (m/z, %): 294 (M^+, 100), 295 (M^++1, 10.3). Anal. Calcd. for $C_{18}H_{18}N_2S$ (294.404): C 73.43; H 6.16; N 9.51. Found: C 72.49; H 6.14; N 9.57.


PPM
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8.49834
8.47317
7.46695
7.23282
7.22921
7.20861
7.20161
6.98124
3.86597
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1.0
0.0
PPM

73a

4-Cyano-1,2-dimethyl-3-methylthio-N-methylcarbazole(73d)

Colourless crystals (ether); yield 92%; mp. 177-178°C; IR (KBr): 2976, 2216 (CN), 1608, 1564; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, CH_3), 2.56 (s, 3H, SCH_3), 2.64 (s, 3H, CH_3), 3.86 (s, 3H, NCH_3), 7.19 (t, 2H, J = 9Hz, ArH-$H_{6\&7}$), 7.43 (td, 1H, J = 9, 0.9Hz, ArH-H_8), 8.49 (d, 1H, J = 9Hz, ArH-H_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.96 (CH_3), 18.40 (CH_3); 20.25 (SCH_3), 33.29 (NCH_3), 108.02, 108.81, 118.31, 119.86, 121.20, 122.63, 125.12, 127.17, 130.04, 138.83, 139.89, 142.47; MS (m/z, %): 280 (M^+, 100); 281 (M^++1, 18.9), 265 (M^+-15, 70.3). Anal. Calcd. for $C_{17}H_{16}N_2S$ (280.384): C 72.81; H 5.75; N 9.99. Found: C 72.76; H 5.71; N 9.93.

4-Cyano-2-methyl-3-methylthio-1-phenyl-N-methylcarbazole(73e)

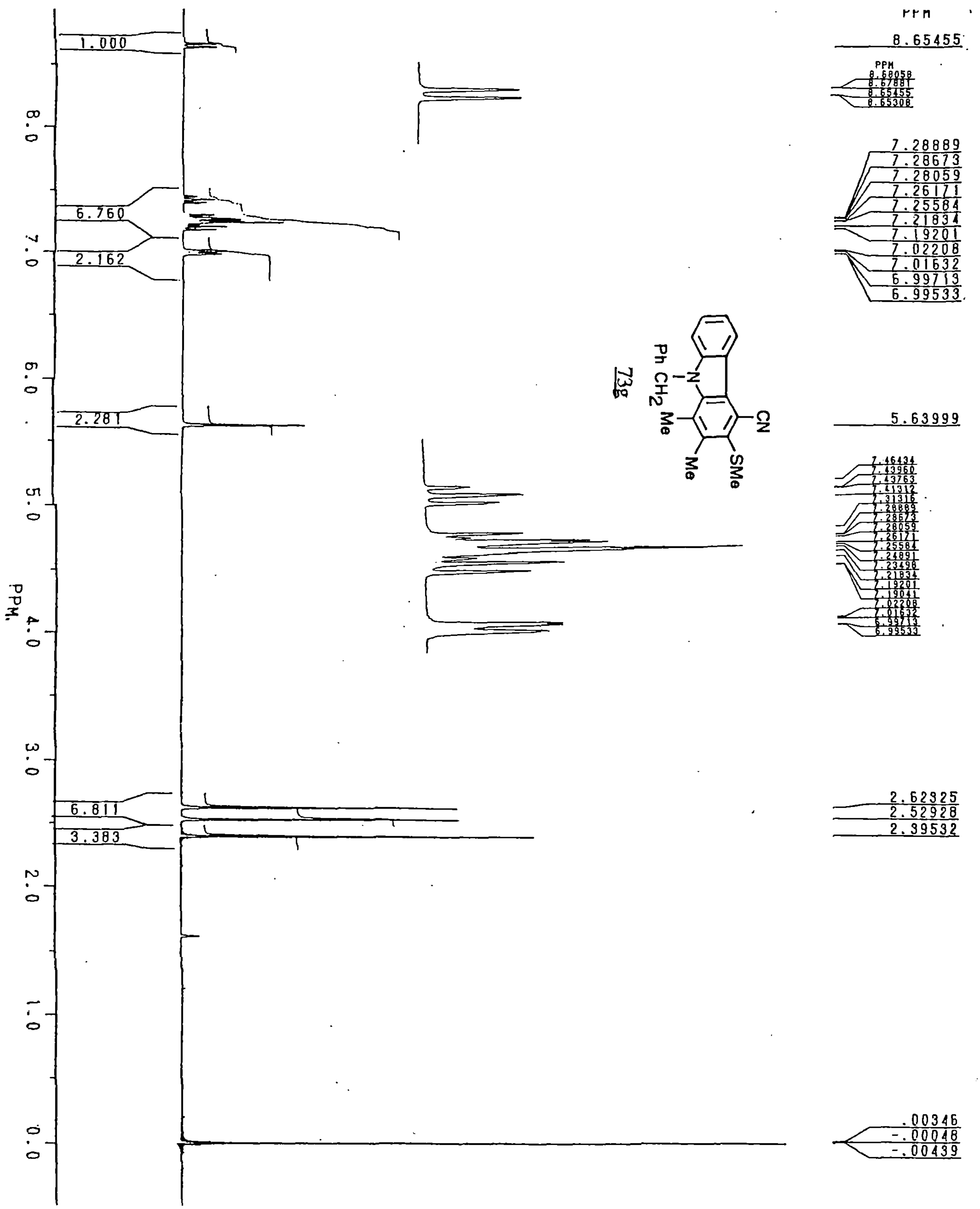
Colourless crystals (ether); mp. 176-177°C; yield 72%; IR (KBr): 3056, 2219 (CN), 1612 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H, SCH_3), 2.48 (s, 3H, CH_3), 3.10 (s, 3H, NCH_3), 7.25-7.33 (m, 4H, ArH), 7.50-7.53 (m, 4H, ArH), 8.69 (d, 1H, J = 9Hz, ArH-H_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.28 (SCH_3), 20.15 (CH_3); 31.77 (NCH_3), 108.90, 118.08, 119.89, 120.21, 121.58, 123.22, 127.43, 128.24, 128.63, 129.86, 129.93, 138.03, 138.68, 142.54; MS (m/z, %): 342 (M^+, 100), 294 (M^+-48, 90.8). Anal. Calcd. for $C_{22}H_{18}N_2S$ (342.444): C 77.15; H 5.29; N 8.18. Found: C 77.38; H 5.22; N 8.16.

4-Cyano-1-methyl-3-methylthio-N-benzylcarbazole(73f)

Colourless crystals (chloroform-ether); mp. 146-147°C; yield 82%; IR (KBr): 2857, 2204 (CN), 1644, 1607 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57 (s, 3H, SCH_3), 2.61 (s, 3H, CH_3), 5.67 (s, 2H, NCH_2), 6.88-6.91 (m, 2H, ArH), 7.13 (s, 1H, ArH-H_2), 7.21-7.32 (m, 5H, ArH), 7.43-7.49 (m, 1H, ArH), 8.67 (dd, 1H, J = 9, 3Hz, ArH-H_5); ^{13}C NMR (75MHz, $CDCl_3$): δ 18.58 (CH_3), 20.18 (SCH_3); 103.66, 109.28, 117.46, 120.24, 120.49, 121.80, 124.82, 125.22, 126.16, 127.55, 127.85, 129.04, 130.23, 132.87, 137.67, 137.83, 142.06; MS (m/z, %): 354 (M^+, 100). Anal. Calcd. for $C_{23}H_{18}N_2S$ (354.454): C 77.93; H 5.11; N 7.90. Found: C 78.19; H 5.07; N 7.82.

4-Cyano-1,2-dimethyl-3-methylthio-N-benzylcarbazole(73g)

Colourless crystals (ether); mp. 129-130°C; yield 81%; IR (KBr): 2923, 2213 (CN),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73g

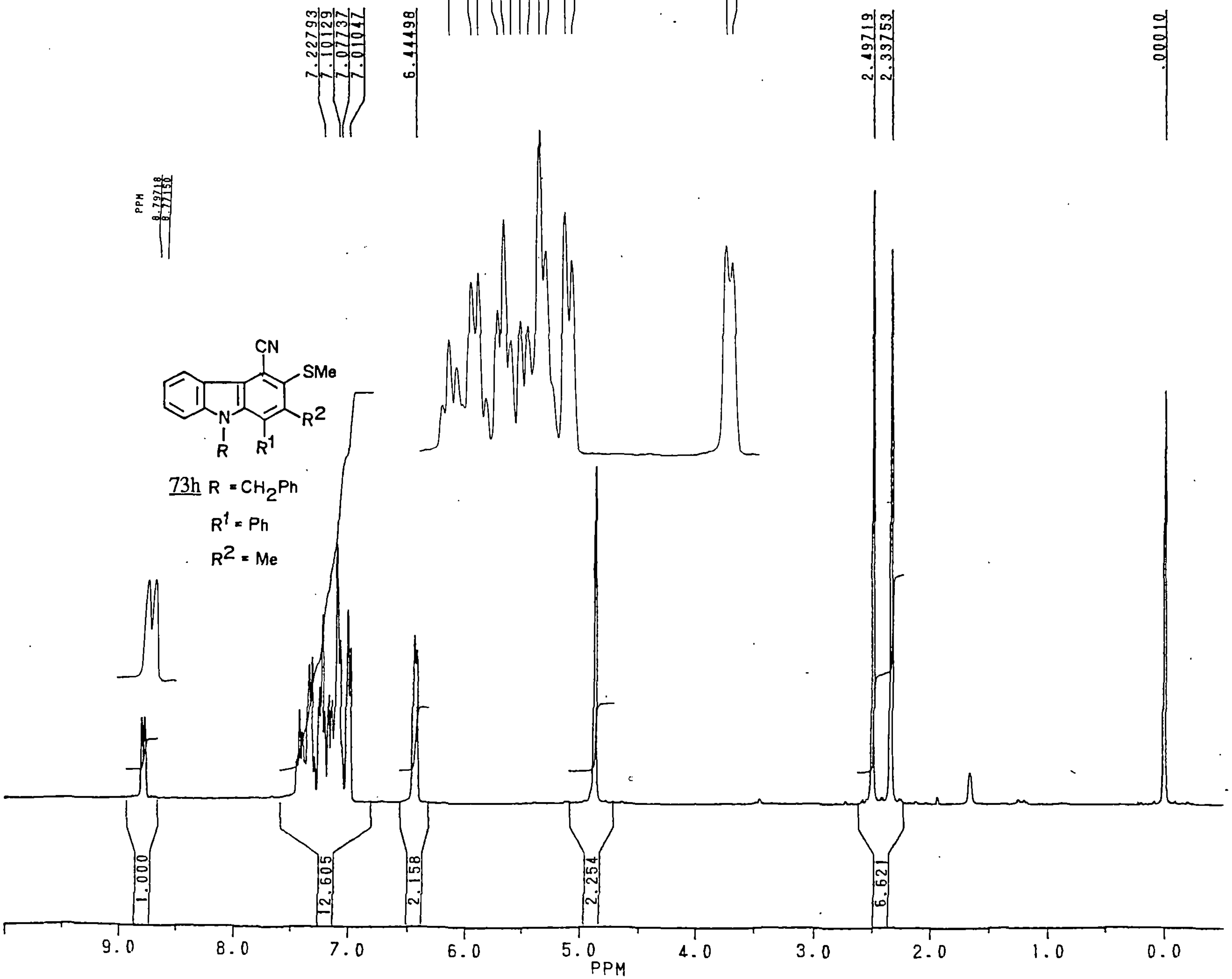
1604, 1560 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39 (s, 3H, SCH_3), 2.52 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 5.63 (s, 2H, NCH_2), 6.99-7.02(m, 2H, ArH), 7.19-7.28(m, 5H, ArH), 7.43 (m, 1H, ArH), 8.66 (d, 1H, J = 9Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.49 (CH_3), 18.56 (CH_3), 20.23 (SCH_3), 49.02 (CH_2), 108.51, 109.30, 118.29, 120.35, 120.55, 121.57, 123.27, 125.21, 125.39, 127.47, 127.63, 128.99, 130.74, 137.78, 139.27, 139.87, 142.68; MS (m/z, %): 356 (M$^+$, 100). Anal. Calcd. for $C_{23}H_{20}N_2S$ (356.474): C 77.49; H 5.65; N 7.86. Found: C 77.35; H 5.58; N 7.78.

4-Cyano-2-methyl-3-methylthio-1-phenyl-N-benzylcarbazole(73h)

Colourless crystals (Chloroform-hexane); mp. 176-177°C; yield 82%; IR (KBr): 2220 (CN), 1610, 1554, 1492 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, CH_3), 2.49 (s, 3H, SCH_3), 4.87 (s, 2H, NCH_2), 6.44 (m, 2H, ArH), 7.01-7.22(m, 11H, ArH), 8.76 (d, 1H, J = 7.7Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.28 (CH_3), 20.03 (SCH_3), 47.19 (CH_2), 109.58, 110.37, 117.96, 120.13, 120.66, 121.70, 123.62, 125.06, 126.84, 127.70, 128.01, 128.17, 128.46, 129.24, 130.10, 130.35, 136.91, 137.23, 138.03, 139.10, 142.28; MS (m/z, %): 418 (M$^+$, 62.3); 419 (M$^+$+1, 12.8). Anal. Calcd. for $C_{28}H_{22}N_2S$ (418.544), C 80.34; H 5.29; N 6.69. Found: C 80.15; H 5.25; N 6.59.

4-Cyano-3-methylthio-1-[ß-2',6',6'-trimethylcyclohexenyl)] ethenyl-N-methylcarbazole (73i)

Light yellow crystals (ether); mp. 132-133°C; yield 82%; IR (KBr): 2921, 2858, 2212 (CN), 1611, 1569cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (s, 6H, $2CH_3$), 1.52-1.56(m, 2H, methylene), 1.67- 1.73 (m, 2H, methylene), 1.85 (s, 3H, CH_3), 2.09 (t, 2H, J = 5.7Hz, methylene), 2.61 (s, 3H, SCH_3), 3.99 (s, 3H, NCH_3), 6.64 (d, 1H, J = 15.9Hz, olefinic), 7.06 (d, 1H, J = 15.9Hz, olefinic), 7.22-7.33 (m, 2H, ArH), 7.44 (s, 1H, ArH-H_2), 7.47- 7.52 (m, 1H, ArH), 8.57 (d, 1H, J = 7.8 Hz, ArH-H_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.96 (CH_3), 19.20 (CH_3), 21.80 (SCH_3), 23.30, 29.02 (CH_2), 32.94 (CH_2), 33.01 (CH_2), 34.55 (CH_2), 39.48 (CH_3), 55.19, 108.93, 117.47, 119.98, 120.10, 121.69, 121.97, 125.08, 127.19, 127.65, 128.32, 128.88, 130.80, 132.25, 133.77, 136.77, 137.52, 137.94, 142.36; MS (m/z, %): 400 (M$^+$, 100), 401 (M$^+$+1, 68). Anal. Calcd. for $C_{26}H_{28}N_2S$ (400.569): C 77.95; H 7.04; N 6.49. Found: C 77.81; H 7.06; N 6.82.



73h R = CH_2Ph

R^1 = Ph

R^2 = Me

4-Cyano-1-formyl-3-methylthio-N-methylcarbazole(73j)

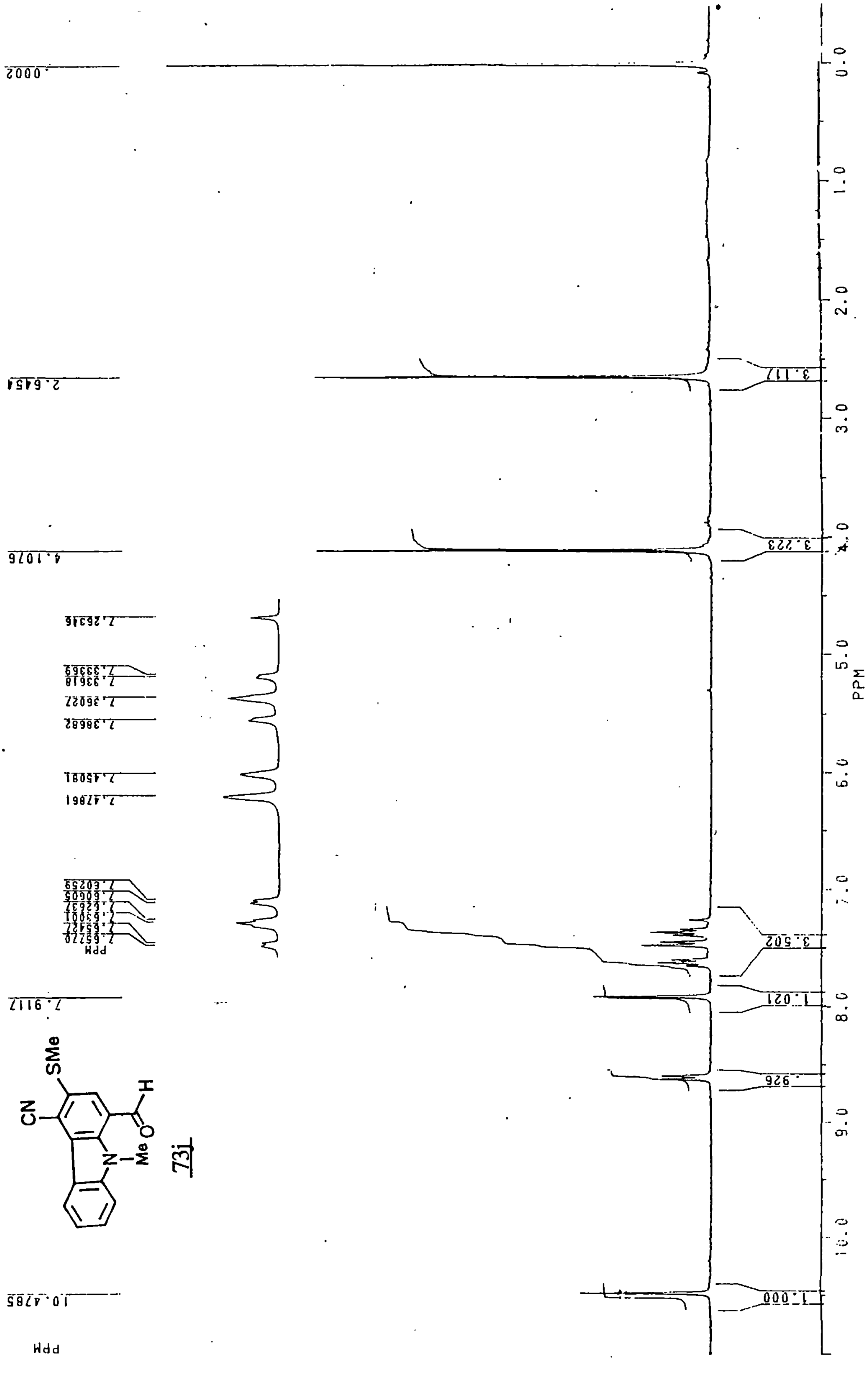
Yellow. crystals (ether); mp. 187-188°C; yield 67%; IR (KBr): 2892, 2217 (CN), 1673 (CO), 1473 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.64 (s, 3H, SCH_3), 4.10 (s, 3H, NCH_3), 7.33-7.38 (m, 1H, ArH), 7.46 (d, 1H, J = 8.34Hz, ArH), 7.60-7.65 (m, 1H, ArH), 7.91 (s, 1H, ArH-H_2), 8.59 (d, 1H, J = 8.07Hz, ArH-H_5), 10.47 (s, 1H, aldehydic); ^{13}C NMR (75 MHz, $CDCl_3$): δ *18.43* (SCH_3), 34.88 (NCH_3), *109.66*, *110.19*, 116.15, 119.58, 121.41, 121.90, 123.95, 127.89, 128.95, 130.39, 131.84, 137.72, 142.98, 188.97 (CO); MS (m/z, %): 280 (M^+, 100), 281 (M^++1, 5.8). Anal. Calcd. for $C_{16}H_{12}N_2OS$ (280.324): C 68.55; H 4.31; N 9.98. Found: C 68.41; H 4.29; N 9.94.

5-Cyano-4-methylthio-N-methylcyclopenta[a]carbazole (73k)

Light yellow crystals (ether; mp. 179-180°C; yield 78%; IR (KBr): 2951, 2921, 2213 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.19 (pent, 2H, J = 7.8Hz, CH_2); 2.40 (s, 3H, SCH_3), 3.05 (t, 2H, J = 7.8Hz, CH_2), 3.39 (t, 2H, J = 7.8Hz, CH_2), 3.75 (s, 3H, NCH_3), 7.14-7.22 (m, 2H, ArH), 7.43 (t, 1H, J = 8.4, 0.9 Hz, ArH), 8.45 (d, 1H, J = 9Hz, ArH-H_6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.66 (SCH_3), 24.38 (CH_2), 30.86 (CH_2), 32.72 (NCH_2), 33.02 (CH_2), 107.39, 108.63, 118.15, 119.80, 120.25, 121.22, 123.46, 126.35, 127.01, 129.73, 137.28, 141.48, 147.34; MS (m/z, %): 292(M^+, 100), 293 (M^++1, 10). Anal. Calcd. for $C_{18}H_{16}N_2S$ (292.394): C 73.93; H 5.51; N 9.58. Found: C 74.22; H 5.48; N 9.52.

6-Cyano-5-methylthio-N-methyl-1,2,3,4-tetrahydrobenzo[a]carbazole (73l)

Colourless crystals (ether); mp. 158-159°C; yield 91%; IR (KBr): 2922, 221 (CN), 1563, 1480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.84 (brs, 4H, $2CH_2$), 2.36 (s, 3H, SCH_3), 3.02 (brs, 2H, CH_2), 3.27 (brs, 2H, CH_2), 3.91 (s, 3H, NCH_3), 7.18 (td, 2H, J = 9Hz, 1.2Hz, ArH-$H_{8\&9}$), 7.38-7.43 (m, 1H, ArH-H_{10}), 8.46 (dd, 1H, J = 9, 1.2Hz, ArH-H_7); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.85 (CH_2) 22.39 (SCH_3), 27.81 (CH_2), 29.43 (CH_2), 33.30 (NCH_3), 108.31, 108.79, 118.18, 119.80, 119.86, 120.98, 121.71, 126.82, 126.87, 130.26, 138.84, 139.43, 142.07; MS (m/z, %): 306 (M^+, 100), 307 (M^++1, 29.8), 291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O
H

73j

(M^+-15, 45.5). Anal. Calcd. for $C_{19}H_{18}N_2S$ (306.414): C 74.47; H 5.92; N 9.14. Found: C 74.38; H 5.89; N 9.11.

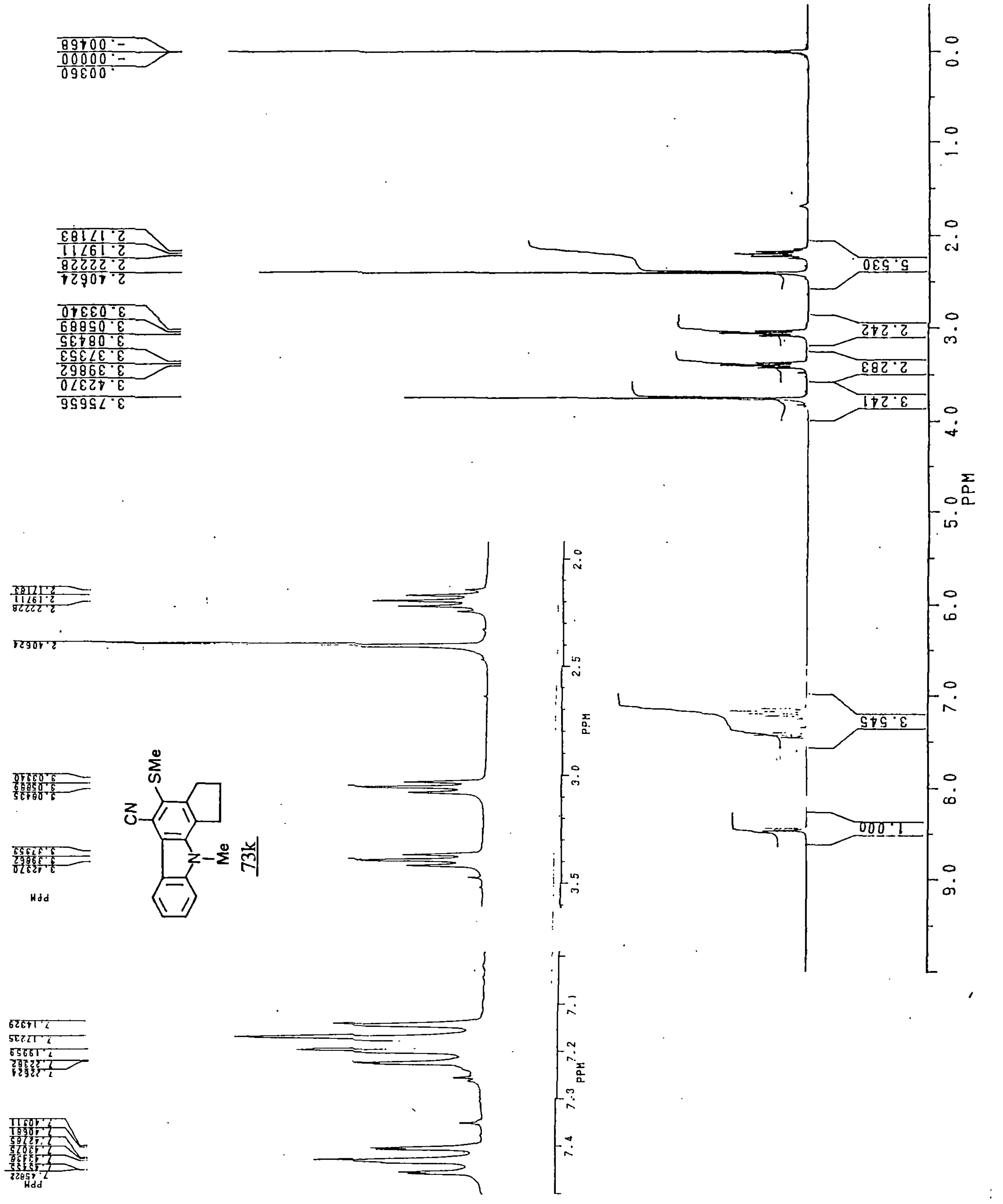
7-Cyano-6-methylthio-N-methylcyclohepta[a]carbazole (73m)

Green colour crystals (chloroform-hexane); mp. 173-174°C; yield 83%; IR (KBr): 2920, 2219 (CN), 1477 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66-1.67 (m, 2H, CH_2), 1.77-1.788(m, 2H, CH_2), 1.84- 1.86 (m, 2H, CH_2), 2.36 (s, 3H, SCH_3), 3.29-3.32(m, 2H, CH_2), 3.40-3.44 (m, 2H, CH_2), 3.89 (s, 3H, NCH_3), 7.20-7.27 (m, 2H, ArH), 7.44-7.50 (m, 1H, ArH), 8.57 (d, 1H, ArH), 8.57 (d, 1H, J = 9Hz, ArH-H_8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.08 (SCH_3), 26.98 (CH_2), 27.61 (CH_2), 29.13 (CH_2), 31.06 (CH_2), 31.60 (CH_2), 33.92 (NCH_3), 108.20, 108.90, 118.43, 119.98, 120.09, 121.44, 123.85, 127.43, 129.20, 132.04, 139.61, 143.13, 146.16; MS (m/z, %): 320 (M^+, 100). Anal. Calcd. for $C_{20}H_{20}N_2S$ (320.444): C 74.95; H 6.29; N 8.74. Found: C 74.82; H 6.25; N 8.68.

7-Cyano-6-methylthio-N-methylindeno[a]carbazole (77a)

Dark red crystals (chloroform-ether); mp. 185-186°C; yield 92%; IR (KBr): 2917, 2208 (CN), 1613, 1574 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50 (s, 3H, SCH_3), 4.00 (s, 2H, CH_2), 4.08 (s, 3H, NCH_3), 7.23-7.29 (m, 1H, ArH), 7.34-7.44 (m, 3H, ArH), 7.51-7.59 (m, 2H, ArH), 8.07 (d, 1H, J = 7Hz, ArH-H_4), 8.56 (d, 1H, J = 9Hz, ArH-H_8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.50 (SCH_3), 35.57 (CH_2), 38.65 (NCH_3); 107.56, 109.69, 117.87, 120.75, 120.99, 121.49, 124.19, 125.22, 126.24, 126.91, 127.06, 127.28, 127.70, 129.01, 137.13, 139.10, 143.45, 144.21, 146.62; MS (m/z, %): 340 (M^+, 37.9), 341 (M^++1, 10.3), 325 (M^+-15, 14.5). Anal. Calcd. for $C_{22}H_{16}N_2S$ (340.434): C 77.61; H 4.73; N 8.23. Found: C 77.53; H 4.69; N 8.18.

8-Cyano-5,6-dihydro-7-methylthio-N-methylnaphtho-[1,2-a]carbazole (77b) Colourless crystals (ether); mp. 203-204°C; yield 68%; IR (KBr): 2911, 2216 (CN), 1611, 1545 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$): δ 2.45 (s, 3H, SCH_3), 2.90 (brm, 2H, methylene), 3.18-3.42 (brm, 2H, methylene), 7.31-7.55 (m, 7H, ArH), 8.66 (d, 1H, J = 8.3Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.90 (SCH_3), 28.23 (CH_2), 29.24 (CH_2), 35.62 (NCH_3), 109.08, 110.10, 118.02, 120.83, 121.05, 121.66,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125.11, 125.85, 125.94, 127.30, 127.83, 128.20, 128.74, 129.32, 132.08, 138.86, 139.37, 142.23, 144.67; MS (m/z, %): 354 (M^+, 100), 355 (M^++1, 27.4). Anal. Calcd. for $C_{23}H_{18}N_2S$ (354.454): C 77.93; H 5.11; N 7.90. Found : C 77.82; H 5.15; N 7.87.

8-Cyano-5,6-dihydro-3-methoxy-7-methylthio-N-methylnaphtho[1,2-a]carbazole(77c)

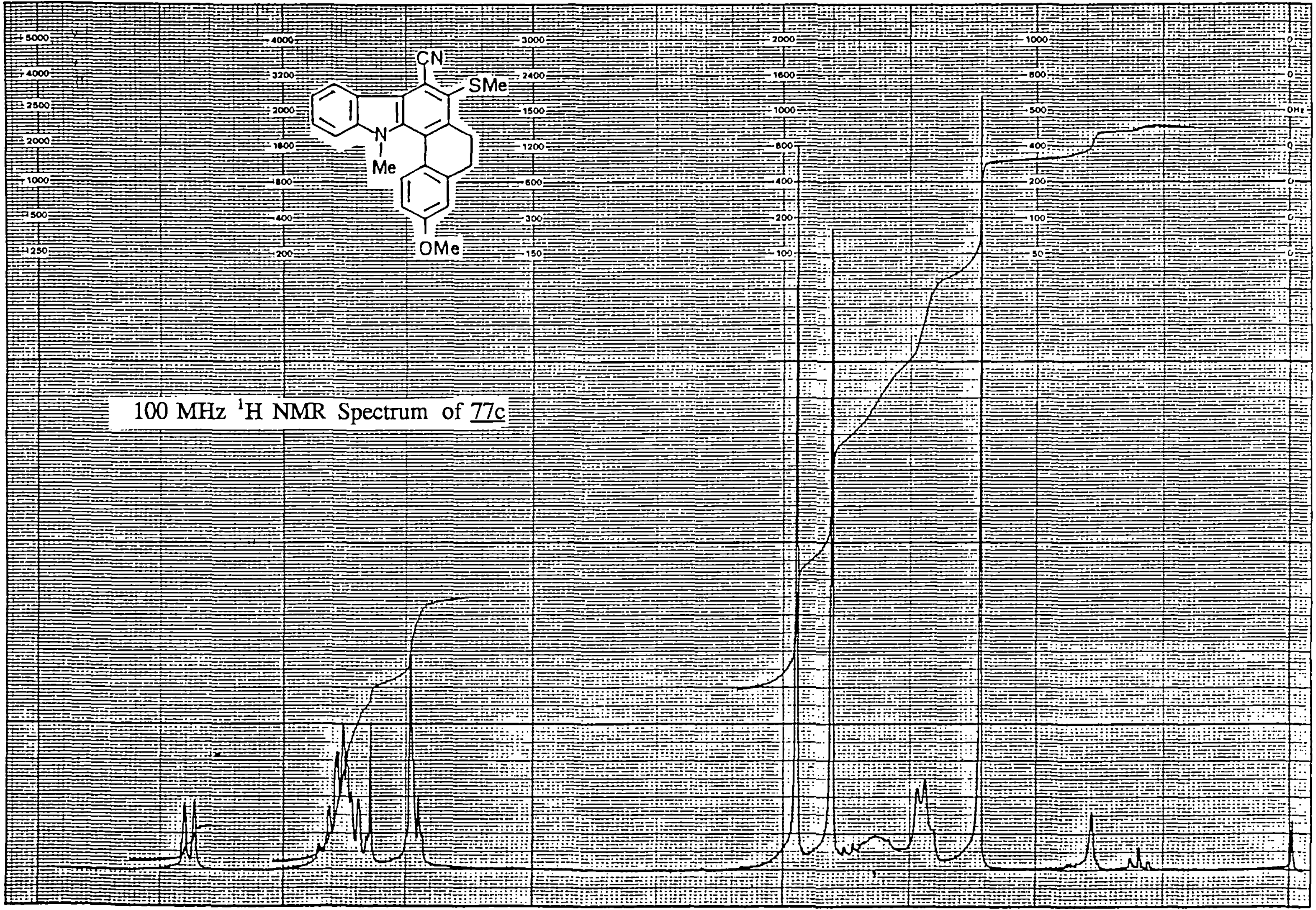
Colourless crystals (ether); mp. 149-150°C; yield 72%; IR (KBr): 2937, 2214 (CN), 1608 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 2.45 (s, 3H, SCH_3), 2.89 (brm, 2H, methylene), 3.19-3.42 (brm, 2H, methylene), 3.61 (s, 3H, NCH_3), 3.89 (s, 3H, OCH_3), 6.91 (m, 2H, ArH), 7.33-7.56 (m, 4H, ArH), 8.68 (d, 1H, J = 8.5Hz, ArH-H_9); ^{13}C NMR (75MHz, $CDCl_3$): δ 19.95 (SCH_3), 28.16 (CH_2), 29.72 (CH_2), 35.40 (NCH_3), 55.39 (OCH_3), 108.28, 110.15, 111.39, 112.80, 118.20, 120.83, 122.24, 121.75, 124.88, 125.37, 125.91, 127.80, 129.45, 130.13, 139.15, 140.81, 141.34, 144.85, 159.56; MS (m/z, %): 384 (M^+, 100), 385 (M^++1, 30.5), 369 (M^+-15, 6.2). Anal. Calcd. for $C_{24}H_{20}N_2OS$ (384.484): C 74.96; H 5.24; N 7.28. Found : C 74.98; H 5.18; N 7.23.

9-Cyano-8-methylthio-N-methylbenzosubereno[1,2-a]carbazole (77d)

Colourless crystals (ether); mp. 142-143°C; yield 72%; IR (KBr): 2920, 2219 (CN), 1612, 1575 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 2.14- 2.22 (m, 3H, methylene H_d), 2.48-2.56 (m, 1H, methylene H_c), 2.49 (s, 3H, SCH_3), 2.68 (dd, 1H, J = 6, 4.5Hz, methylene H_b), 3.30 (s, 3H, NCH_3), 3.79 (dd, 1H, J = 4.2, 3Hz, methylene H_a), 7.25-7.39 (m, 6H, ArH), 7.50-7.56 (m, 1H, ArH), 8.71 (d, 1H, 7.9Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.28 (SCH_3), 28.47 (CH_2), 30.81 (CH_2), 32.79 (CH_2), 33.93 (NCH_3), 109.36, 110.15, 118.11, 120.33, 120.43, 121.66, 124.84, 125.76, 127.72, 128.07, 128.77, 128.85, 129.95, 136.29, 138.66, 140.26, 141.22, 143.57; MS (m/z, %): 368 (M^+, 100), 369 (M^++1, 38.9). Anal. Calcd. for $C_{24}H_{20}N_2S$ (368.484): C 78.22; H 5.47; N 7.60. Found : C 78.09; H 5.41; N 7.63.

3-Methoxy-4'-cyano-3'-methylthio-9'-methylcarbazolo[16,17-b]estra-1,3,(5)-triene (80)

Colourless crystals (CH_2Cl_2); mp. 235°C; yield 78%; $[\alpha]_D^{13}$ +49° (C=1, dioxane); IR (KBr): 2978, 2217 (CN), 1607, 1495 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 3H, CH_3), 1.45-1.52 (m, 1H, CH), 1.70-1.86 (m, 4H), 2.07-2.11 (m, 1H, CH), 2.22 (brm, 1H,



100 MHz ^{1}H NMR Spectrum of 77c

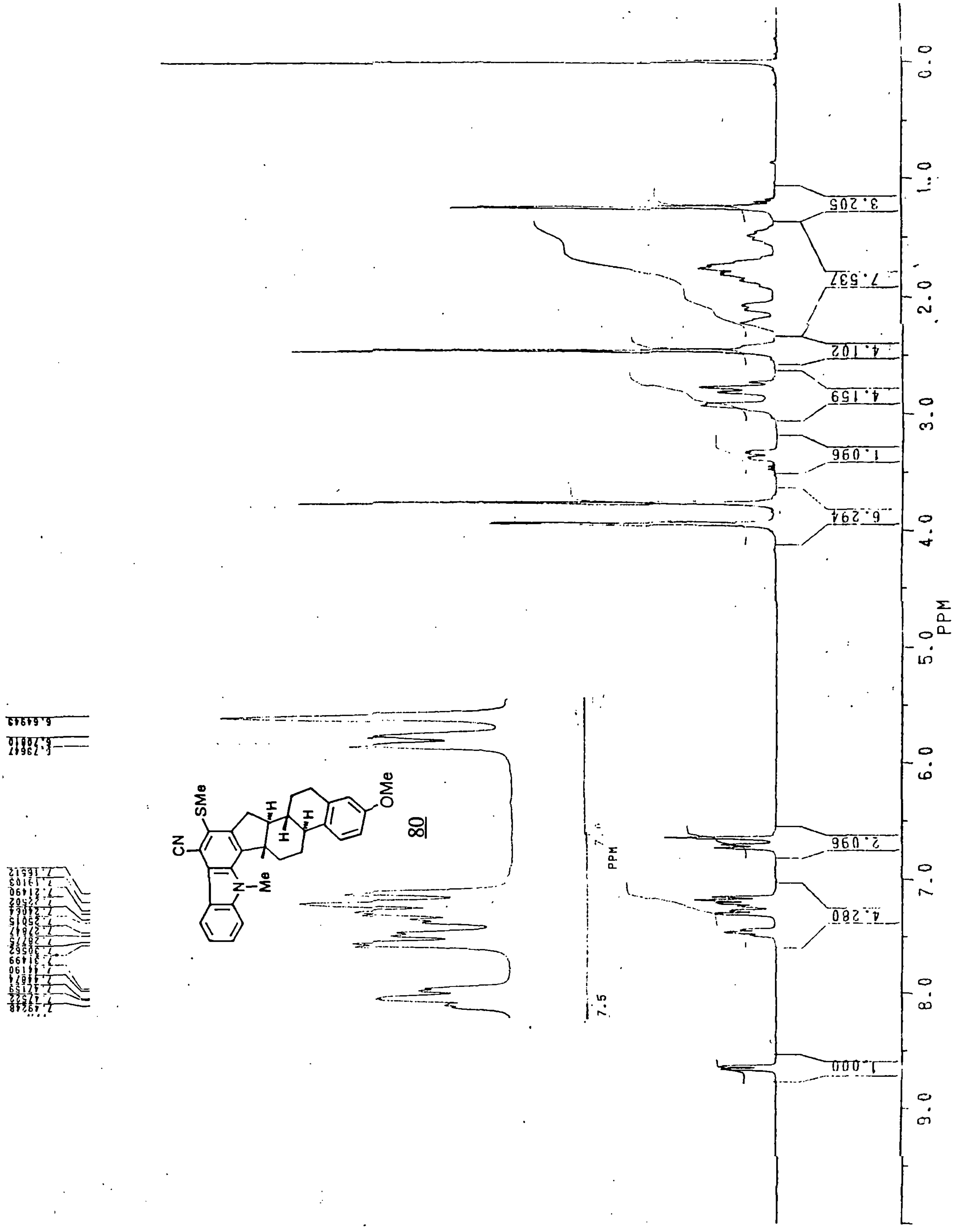
CH), 2.46 (s, 3H, SCH_3), 2.73-2.93(m, 4H, $2CH_2$), 3.32-3.38(m, 1H, CH), 3.77 (s, 3H, NCH_3), 3.95 (s, 3H, OCH_3), 6.65 (s, 1H, ArH), 6.72 (d, 1H, J = 8.4Hz, ArH), 7.16-7.31 (m, 3H, ArH), 7.44-7.49 (m, 1H, ArH), 8.56 (d, 1H, J = 6Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.64 (CH_3), 19.70 (SCH_3), 26.83, 27.48, 29.61, 33.10, 35.20, 37.13, 37.51, 43.23, 48.52 (NCH_3), 55.14 (OCH_3), 56.48, 107.52, 109.16, 111.55, 113.77, 118.04, 120.16, 120.65, 121.37, 125.76, 125.92, 127.28, 127.48, 131.99, 137.61, 137.81, 140.55, 142.65, 146.47, 157.56; MS (m/z, %): 492 (M^+,100), 493 (M^++1, 76.3), 477 (M^+-15, 11.3). Anal. Calcd. for $C_{32}H_{32}N_2OS$ (492.664): C 78.00, H 6.54; N 5.68. Found: C 77.82; H 6.59; N 5.62.

4-Cyano-1-(1'-methoxyphenyl)-3-(1-pyrrolidinyl)-N-methylcarbazole (82a)

Light red crystals (hexane-ether); mp. 158-159°C; yield 62%; IR (KBr): 2937, 2198 (CN), 1608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.06 (brs, 4H, CH_2), 3.29 (s, 3H, NCH_3), 3.69 (brs, 4H, NCH_2), 3.88 (s, 3H, OCH_3), 6.99 (dd, 2H, J = 6, 1.8Hz, ArH), 7.20-7.27 (m, 2H, ArH), 7.30 (s, 1H, ArH), 7.36 (dd, 2H, J = 6, 1.8Hz, ArH), 7.46 (t, 1H, J = 7.2Hz, ArH), 8.74 (d, 1H, J = 8.1Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) : δ 25.84 (CH_2), 32.73 (NCH_3), 51.47 (NCH_2), 55.34 (OCH_3), 108.98, 120.85, 124.80, 113.61, 119.25, 121.97, 126.84, 130.48, 131.36, 131.60, 142.91, 159.50; MS (m/z, %): 381 (M^+, 100); 382 (M^++1, 13.8). Anal. Calcd. for $C_{25}H_{23}N_3O$ (381.45): C 78.71; H 6.07; N 11.01. Found: C 78.62; H 6.16; N 11.06.

4-Cyano-1-phenyl-3-piperidinyl-N-methylcarbazole (82b)

Orange crystals (ether-hexane); mp. 189-191°C; yield 79%; IR (KBr): 2205(CN), 1601, 1410^{cm-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.6- 1.9 (m, 6H, CH_2), 3.1-3.2 (m, 4H, NCH_2), 3.29 (s, 3H, NCH_3); 7.01 (s, 1H, ArH_2), 7.25-7.52 (m, 8H, ArH), 8.8 (s, 1H, ArH_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.06 (CH_2), 26.35 (CH_2), 32.72 (NCH_3), 54.53 (NCH_2), 108.98, 118.19, 119.53, 119.67, 120.59, 121.71, 124.94, 127.30, 128.06, 128.17, 129.44, 130.81, 134.05, 139.04, 143.02, 150.75. Anal. Calcd. for $C_{25}H_{23}N_3$ (365.45): C 82.16; H 6.34; N 11.49. Found: C 82.51; H 6.36; N 11.38.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1.000
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
PPM

80

4-Cyano-1-phenyl-3-(1'-morpholinyl)-N-methylcarbazole(82c)

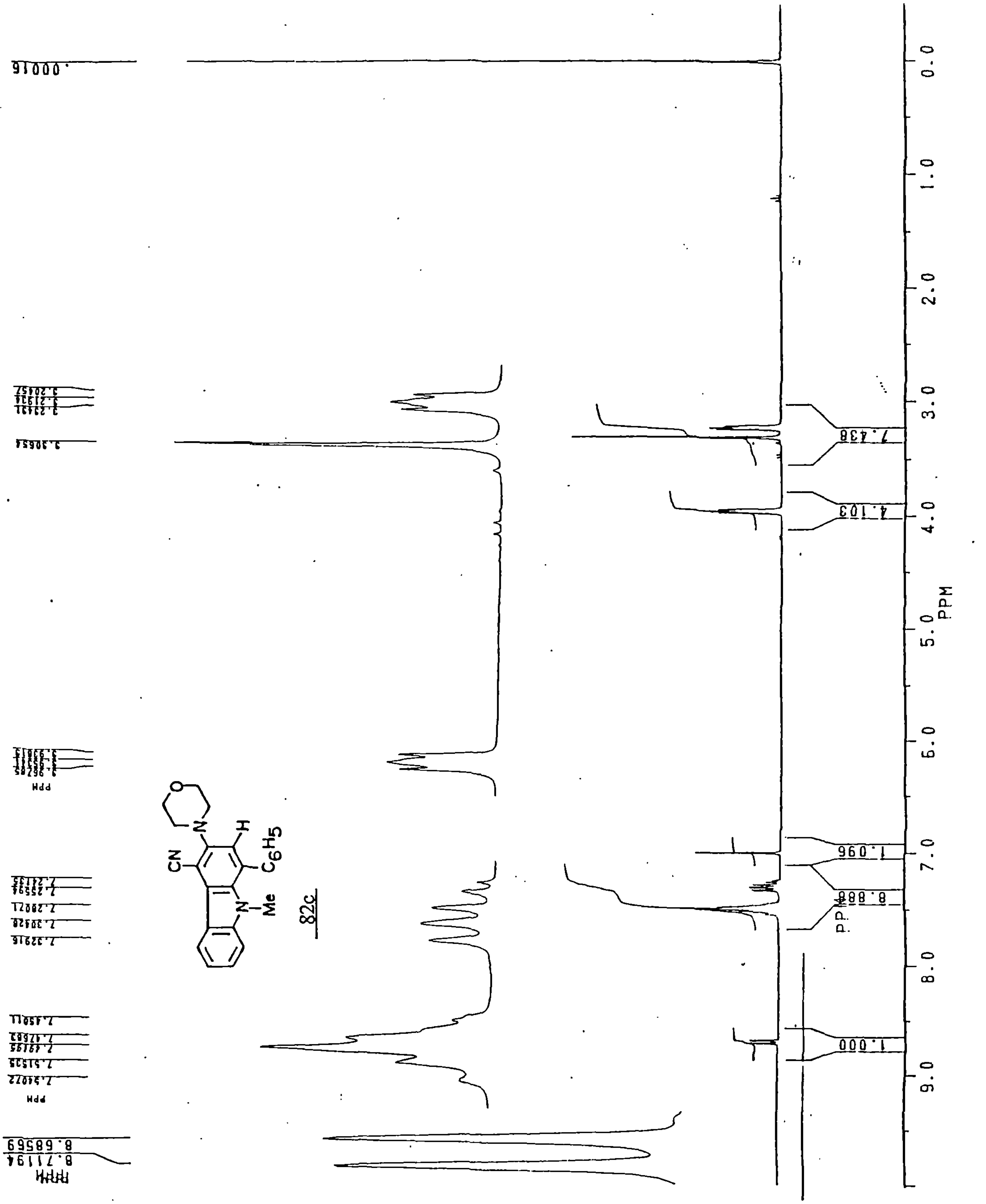
Dark red crystals (hexane); mp. 120-121°C; yield 71%; IR (KBr): 2924, 2208 (CN), 1616, 1582 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.21 (t, 4H, J=4.5Hz, NCH_2), 3.30 (s, 3H, NCH_3), 3.95 (t, 4H, J = 4.3Hz, OCH_2), 6.99 (s, 1H, ArH-H_2), 7.24-7.33 (m, 2H, ArH), 7.45-7.54 (m, 6H, ArH), 8.70 (d, 1H, J = 7.8Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.81 (NCH_3), 53.16 (NCH_2), 67.25 (OCH_2), 109.12, 117.96, 119.29, 119.82, 120.59, 121.88, 125.23, 127.63, 128.24, 128.29, 129.49, 131.03, 134.52, 138.96, 143.20, 149.28; MS (m/z, %): 367 (M^+,100); 368 (M^++1, 33.2). Anal. Calcd. for $C_{24}H_{21}N_3O$ (367.43): C 73.44, H 5.76, N 11.43. Found: C 73.52; H 5.69; N 11.45.

4-Cyano-1,2-dimethyl-3-methoxy-N-methylcarbazole(84a)

Colourless crystals (ether); mp. 138-140°C; yield 92%; IR (KBr): 2932, 2215 (CN), 1566, 1485, 1456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.19 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.71 (s, 3H, NCH_3), 3.87 (s, 3H, OCH_3), 7.09-7.16 (m, 2H, ArH), 7.34-7.40 (m, 1H, ArH), 8.36 (dd, 1H, J = 9, 3Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.73 (CH_3), 16.00 (CH_3), 32.90 (NCH_3), 62.16 (OCH_3), 108.70, 116.88, 119.26, 120.36, 120.83, 121.00, 126.37, 126.66, 128.36, 136.20, 142.45, 155.05; MS (m/z, %): 264 (M^+, 100). Anal. Calcd. for $C_{17}H_{16}N_2O$ (264.32): C 77.24; H 6.10; N 10.60. Found: C 77.33; H 6.06; N 10.52.

4-Cyano-1,2-dimethyl-3-methoxy-N-benzylcarbazole(84b)

Colourless crystals (ether); mp. 155°C; yield 85%; IR (KBr): 2217 (CN), 1566, 1478, 1448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.21 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 5.43 (s, 2H, NCH_2), 6.90-6.92 (m, 2H, ArH), 7.10-7.35 (m, 5H, ArH), 8.54 (d, 1H, J = 9Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.86 (CH_3), 15.57 (CH_3), 48.53 (CH_2), 62.25 (OCH_3), 109.20, 116.20, 116.97, 119.89, 120.64, 120.99, 121.44, 125.28, 126.60, 127.12, 127.30, 127.54, 128.86, 135.96, 137.98, 142.52, 155.39; MS (m/z, %): 340 (M^+, 56.3); 341 (M^++1, 13.8). Anal. Calc. for $C_{23}H_{20}N_2O$ (340.41): C 81.14; H 5.92; N 8.23. Found: C 79.98; H 5.86; N 8.18.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6.0
7.0
8.0
9.0
PPM
CN
N
O
H
C_6H_5
N
Me

82c

4-Cyano-3-methoxy-1-phenyl-N-methylcarbazole(84c)

Colourless crystals (ether); mp. 165°C; yield 72%; IR (KBr): 2217 (CN), 1558, 1475cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.31 (s,3H,NCH_3), 4.01 (s, 3H, OCH_3), 7.00 (s, 1H, ArH_2), 7.31-7.65(m, 8H, ArH), 8.79 (d, 1H, J=8Hz, ArH_5); ^{13} NMR (75 MHz, $CDCl_3$): δ 32.81 (NCH_3), 56.88 (OCH_3), 109.13, 112.04, 119.64, 120.41, 121.97, 127.73, 127.91, 128.30, 129.46, 129.54, 131.38, 132.12, 133.13, 138.90, 143.44, 155.72. Anal. Calcd. for. $C_{21}H_{16}N_2O$ (312.36): C 80.74; H 5.16; N 8.97. Found: C 80.89; H 5.11; N 8.93.

Procedure for the Raney-Ni desulfurization/reduction of carbazoles 73a & 73k.

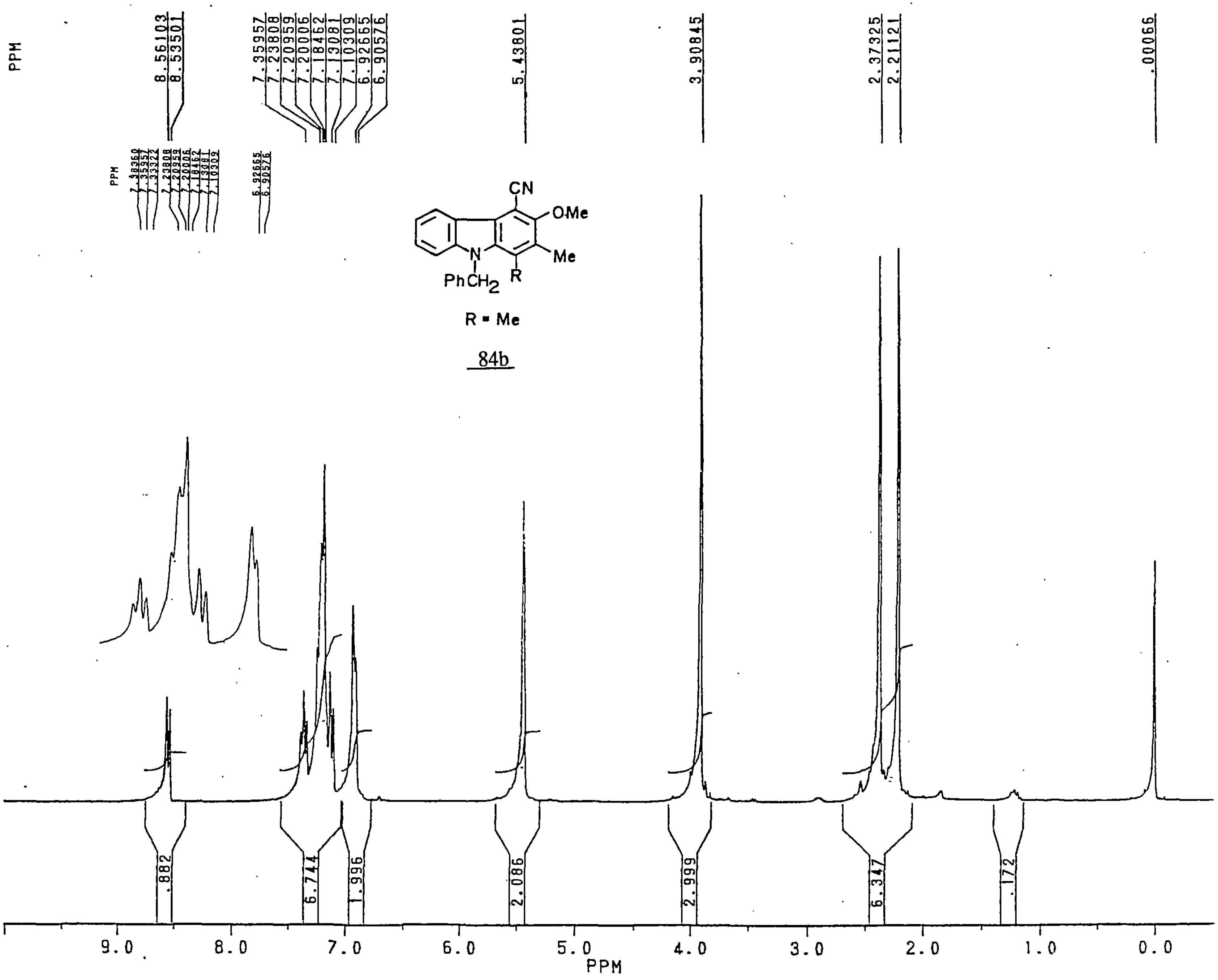
To a solution of appropriate carbazole (0.01mol) in ethanol (10ml), was added a spoon of Raney-Ni and refluxed for 6-7hr. The reaction mixture was filtered and concentrated to afford crude solid which on coloumn chromatography (EtOAc-hexane) afforded pure desulfurized/reduced carbazole.

1-Methyl-4-(N,N-diethylaminomethyl)-N-methylcarbazole (86)

Colourless crystals (ether); mp. 70.71°C; yield 62%; IR (KBr): 2832, 1540, 1438 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (t, 6H, J = 7.2Hz, CH_3), 2.56 (s, 3H, CH_3), 2.62 (quart, 4H, J = 7.2Hz, $2NCH_2$), 3.67 (s, 3H, NCH_3), 4.04 (s, 2H, NCH_2), 6.98 (d, 1H, J = 7.5Hz, ArH-H_2), 7.08 (t, 2H, J = 7.2Hz, ArH), 7.15 (d, 1H, J = 7.5Hz, ArH-H_3), 7.30 (t, 1H, J = 7.8Hz, ArH), 8.22 (d, 1H, J = 7.8Hz, ArH-H_5); MS (m/z, %): 280 (M^+, 21.9), 208 (M^+-72, 100). Anal. Calcd. for $C_{19}H_{24}N_2$ (280.400): C 81.38; H 8.62; N 9.99. Found: C 81.22; H 8.68; N 9.91.

5,10-Dimethylcyclopenta[1,2-a]carbazole (87)

Colourless crystals (hexane-ether); mp. 101-103°C; yield 63%; IR (KBr): 1598, 1580, 1487, 1330cm^{-1}; ^{1}H NMR (90MHz, $CDCL_3$): δ 2.20 (pent, 2H, J=7Hz, CH_2), 2.8 (s, 3H, CH_3), 3.0 (t, 2H, J=7Hz, CH_2), 3.4 (t, 2H, J=7Hz, CH_2), 3.95 (s, 3H, NCH_3), 6.92 (s, 2H, ArH_4), 7.28-7.45 (m, 3H, ArH), 8.2 (d, 1H, J=6.5Hz, ArH_6). Anal Calcd. for $C_{17}H_{17}N$ (235.317): C 86.76; H 7.28; N 5.95. Found: C 86.83; H 7.31; N 5.92.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6.0
5.0
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3.0
2.0
1.0
0.0
PPM

Procedure for the hydrolysis of carbazoles 73a & 77c via sealed tube: Synthesis of carbazole-4-amide.

A solution of appropriate carbazole (0.001mol), NaOH (0.005mol) in ethanol (8ml) was heated in a sealed tube for 6-7hr. Cooled, poured to water (20ml), extracted by DCM (2x15ml), dried over Na_2SO_4, concentrated to give pure crystals on trituration with hexane.

1-Methyl-3-methylthio-N-methylcarbazole-4-amide (88)

Colourless crystals (hexane); mp. 215°C; yield 76%; IR (KBr): 3439, 2921, 1666, 1607cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ 2.49 (s, 3H, SCH_3), 2.79 (s, 3H, CH_3), 4.02 (s, 3H, SCH_3), 5.97 (brs, 1H, NH), 6.51 (brs, 1H, NH), 7.15-7.20 (m, 1H, ArH), 7.26 (s, 1H, ArH), 7.30 (d, 1H, J = 8Hz, ArH), 7.41-7.47 (m, 1H, ArH), 8.18 (d, 1H, J = 8Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.33 (CH_3), 20.73 (CH_3), 32.22 (NCH_3), 108.57, 119.67, 119.95, 120.46, 121.88, 121.94, 122.30, 126.27, 131.49, 132.69, 139.03, 141.95, 171.01 (CO); MS (m/z, %): 284 (M^+, 100). Anal.Calcd. for $C_{16}H_{16}N_2OS$(284.374): C 67.57; H 5.67; N 9.85. Found: C 67.82; H 5.62; N 9.88.

8-Cyano-5,6-dihydro-3-methoxy-7-methylthio-N-methylcarbazole-9-amide(89)

Colourless crystals; mp. 153-154°C; yield 75%; IR (KBr): 2920, 1654 (CO), 1606, 1495cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ 2.26 (s, 3H, SCH_3), 2.51 (m, 2H, CH_2), 2.82 (m, 2H, CH_2), 3.54 (s, 3H, NCH_3), 3.83 (s, 3H, OCH_3), 6.15 (brs, 1H, NH, exchangeable with D_2O), 6.78-6.83 (m, 2H, ArH & NH exchangeable with D_2O), 7.17-7.22 (m, 1H, ArH), 7.33-7.43 (m, 3H, ArH), 8.19 (d, 1H, J = 7.8Hz, ArH); ^{13}C NMR (75MHz, $CDCl_3$): δ 20.73 (SCH_3), 28.01 (CH_2), 29.96 (CH_2), 35.43 (NCH_3), 55.30 (OCH_3), 109.95, 111.09, 112.64, 120.35, 120.51, 121.20, 121.59, 121.67, 121.80, 125.66, 126.49, 129.40, 134.54, 139.79, 140.33, 141.69, 144.58, 158.70, 171.65 ($CONH_2$); MS (m/z, %): 386 (M^+, 100). Anal. Calcd. for $C_{24}H_{22}N_2OS$ (386.504): C 74.57; H 5.73; N 7.25. Found: C 74.72; H 5.71; N 7.29.

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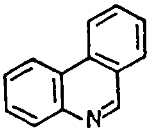
CHAPT-3

A Simple Regiospecific Route for Substituted Phenanthridines and Benzo[j]phenanthridines via Aromatic Annelation.

Phenanthridine of general formula 1 (Scheme-1) was first reported by Pictet[1] in 1889 and Grabe[2] in 1884 independently. The basic phenanthridine and its derivatives remained unattracted until useful therapeutic activity was discovered in some quarternary phenanthridinium compound.[3] A substantial number of substituted phenanthridine and their salts were then reported in the literature and are described in the reviews.[4,5]

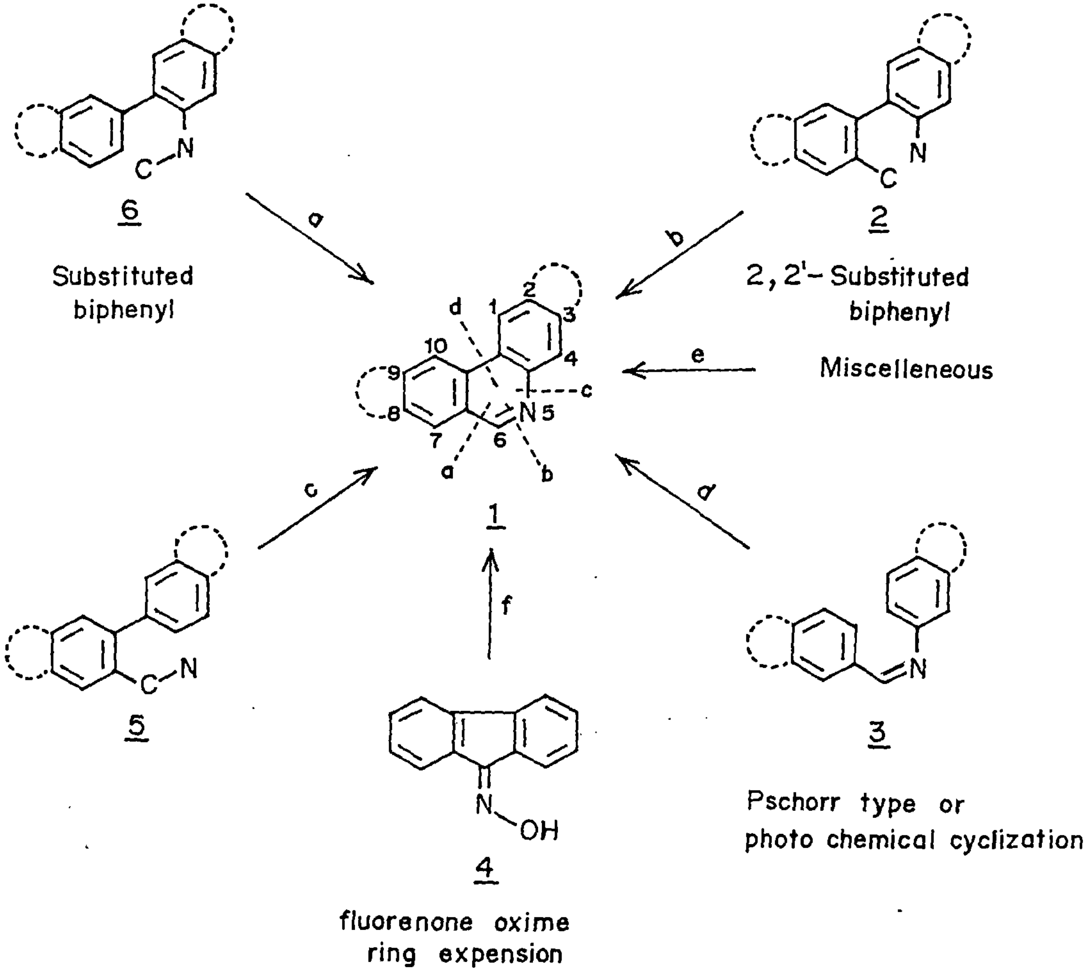


1

Even then phenanthridines have received less attraction despite theoritical interest in these systems due to unusual nonequivalent 9-carbon atoms present in the molecule. Many naturally occuring derivatives containing phenanthridine ring have now been discovered largely containing benjo[c]phenanthridine frame work. They are an important class of alkaloids belonging to isoquinoline group, which have been described in the recent reviews.[6,7]

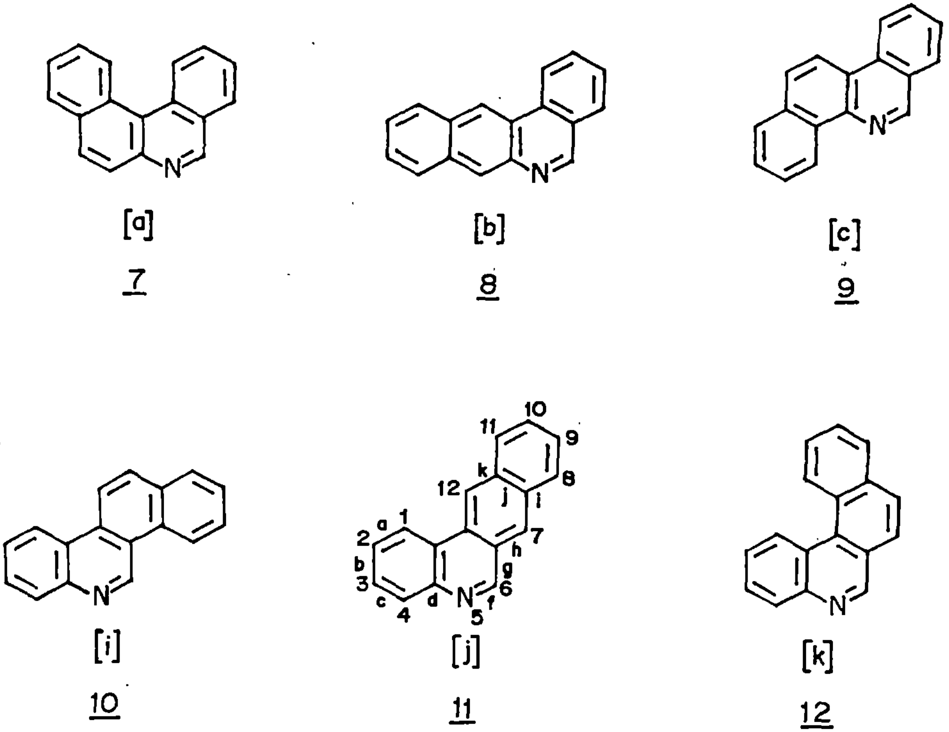
The phenanthridine ring system is also an integral part of many synthetic dyes, antibacterials, antileukemic agents.[6,8] Several diverse synthetic routes are reported for the construction of phenanthridines and its derivatives generally following the cyclization approach from functionalized biphenyl derivatives (path a, b and c; Scheme-1). Other methods include photochemical cyclization of intermediate **3** (Path-d) and the fluorenone oxime **4** involving ring transformation under Beckmann rearrangement (Path-f). Most of the methods describe till the first review[4] appeared in 1950, dealt largely with the ring closure approach a, b and c types, particularly using 2-acylamino biphenyls as potential intermediates for the synthesis of **1**. These are the possible approaches for the synthesis of phenanthridine and can be classified depending on the nature of the intermediates used as described in Scheme-1, which involve suitably substituted biphenyls or fluorene derivatives or those systems which do not contain biphenyl structural units.

There are excellent reviews available on phenanthridines till 1984[9] and therefore a brief survey on the methods of synthesis of phenanthridine is given. It may be mentioned here that most of the benzophenanthridines both natural and synthetic described in the literature belong to the structural group of benzo[a] **7**, benzo[b] **8**, benzo[c] **9**, benzo[i] **10**, benzo[j] **11** and benzo[k] **12**, (Scheme-2). Among these different types of phenanthridines, the largest occuring benzo[c]phenanthridine **9** have been widely studied. There are only sporadic studies on the benzo[i], benzo[j] & benzo[k]phenanthridines. Also there are no reports on the biological activities of these latter categories probably due to the lack of availability of these compounds for biological screening. In the present investigation, we have developed a facile new general method for the synthesis of benzo[j]phenanthridine which, in our opinion is by far the most efficient route for the synthesis of this class of compounds. A brief survey of the methods employed for the synthesis of various phenanthridines is presented as follows:


6
Substituted biphenyl
C
N
a
2
2,2'– Substituted biphenyl
b
e
Miscelleneous
1
2
3
4
N 5
6
7
8
9
10
d
c
a
b
c
5
f
4
N
OH
fluorenone oxime ring expension
d
3
Pschorr type or photo chemical cyclization

Scheme – 1

Benzophenanthridines



Scheme – 2

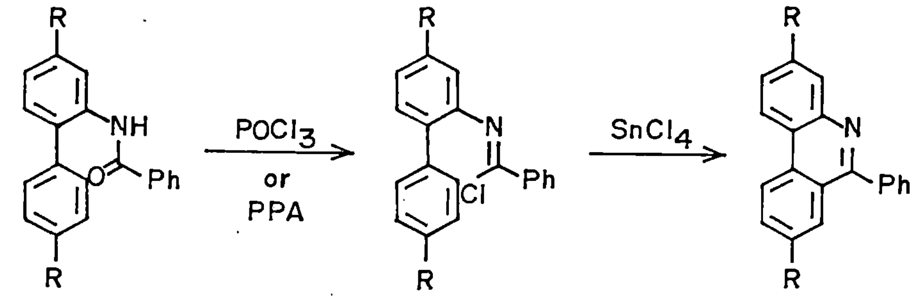
Type "a":Cyclizationof 2-substituted biphenyls

Cyclization of 2-acyl amino biphenyls (type-a) has been one of the most established routes for the synthesis of phenanthridine derivatives. Morgan & Walls[3] used phosphoryl chloride to achieve the ring closure of these acetamidobiphenyls **13** (Scheme-3) either alone or in the presence high boiling solvents such as nitrobenzene. The transformation was mechanistically studied by Ritchie[10] involving the formation of the carbocation intermediate which was subsequently confirmed by Barber and co-workers.[11] The intermdeiate iminochloride **14** was confirmed by Barber's work which was conveniently cyclized in the presence of Friedel-Craft reaction condition. Particularly $SnCl_4$ was found to be more efficient than $POCl_3$. A number of phenanthridines **15** carying both alkyl and aryl substititients at 6-position were then reported in the literature.[12-14] Initially the aminobiphenyls failed to cyclize under these reaction conditions which were subsequently achieved more conveniently by treating the formamido compound with a mixture of phosphoryl chloride and $SnCl_4$. Also the formamides underwent cyclizations in the presence of polyphosphoric acid at 142-160°C. These methods were employed insitu by heating aminobiphenyls and carboxylic acids in the presence of PPA to yield the corresponding phenanthridines in good yields.[15]

Smith has reported[16] an interesting phenanthridine synthesis unequivocally under a novel Beckmann reaction condition. Thus o- phenylbenzophenone oxime **18** underwent cyclization to give the corresponding 6-phenylphenanthridine **20** in 89% yield in PPA. The cyclization did not give the phenanthridine **20**, when o- benzamidobiphenyl was treated under similar reaction conditions.

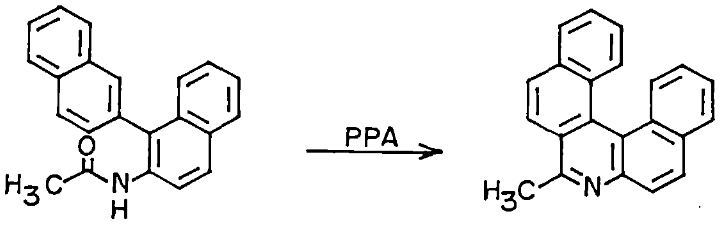
Lete and co-workers in their efforts[17] to construct isoquinoline alkaloids related to benzo[c]phenanthridines, utilized the type-a approach and prepared the intermediate **23** as shown in Scheme-4 and cyclized in the presence of $POCl_3$ and CH_3CN to yield the corresponding 11-acetoxy-N-benzyl-6-methyl-2,3,8,9-tetramethoxy-benzo[c]phenanthridinium chloride **24**. The other intermediate **22** similarly underwent

Type 'a' approach

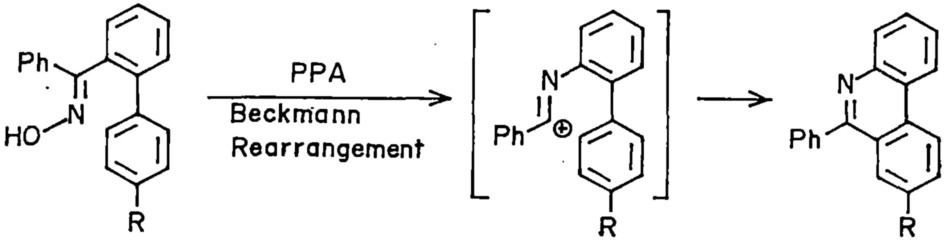


13 14 15

Application of Morgan-Walls Reaction :-

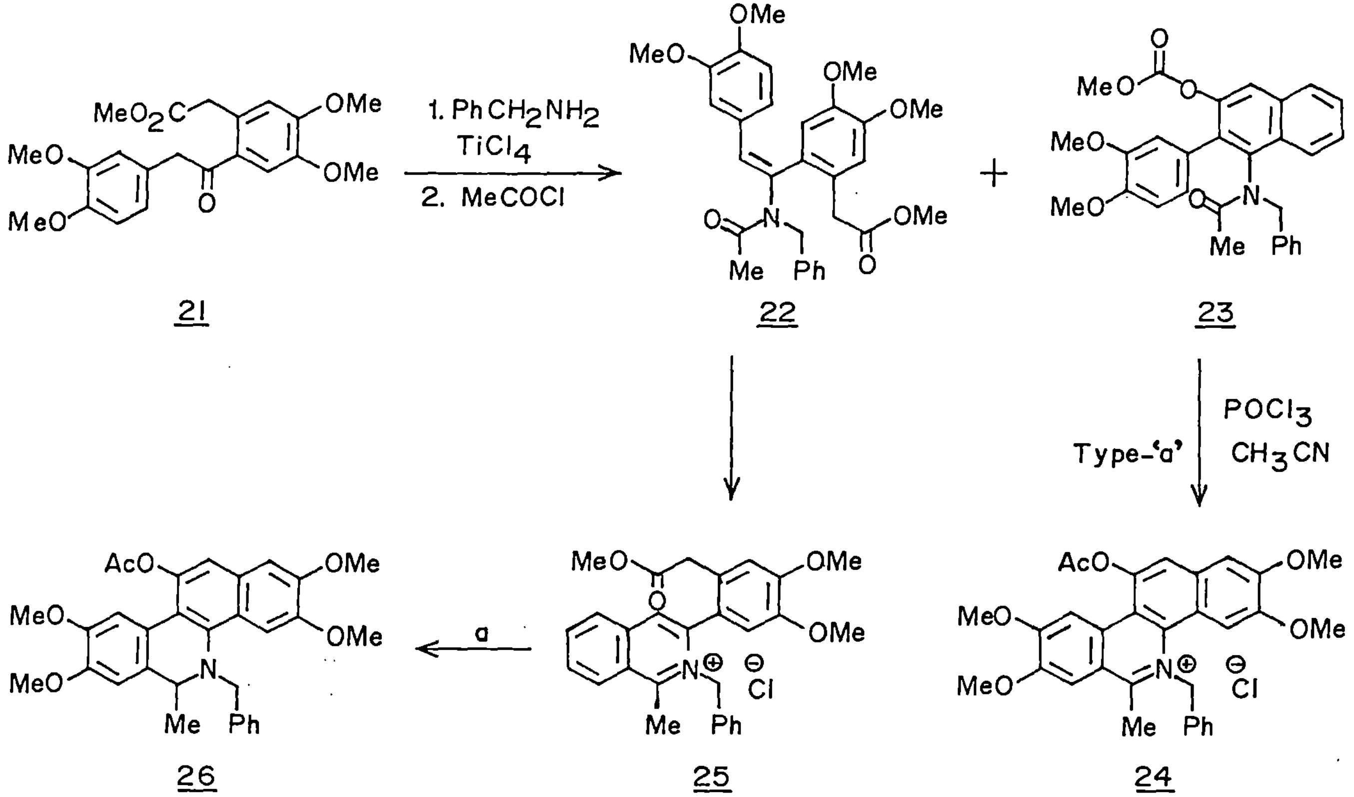


16 17



18 19 20

Scheme - 3



a (i) $NaBH_4$ / THF (ii) 12M HCl, MeOH (iii) $(AcO)_2$, Pyridine

Scheme – 4

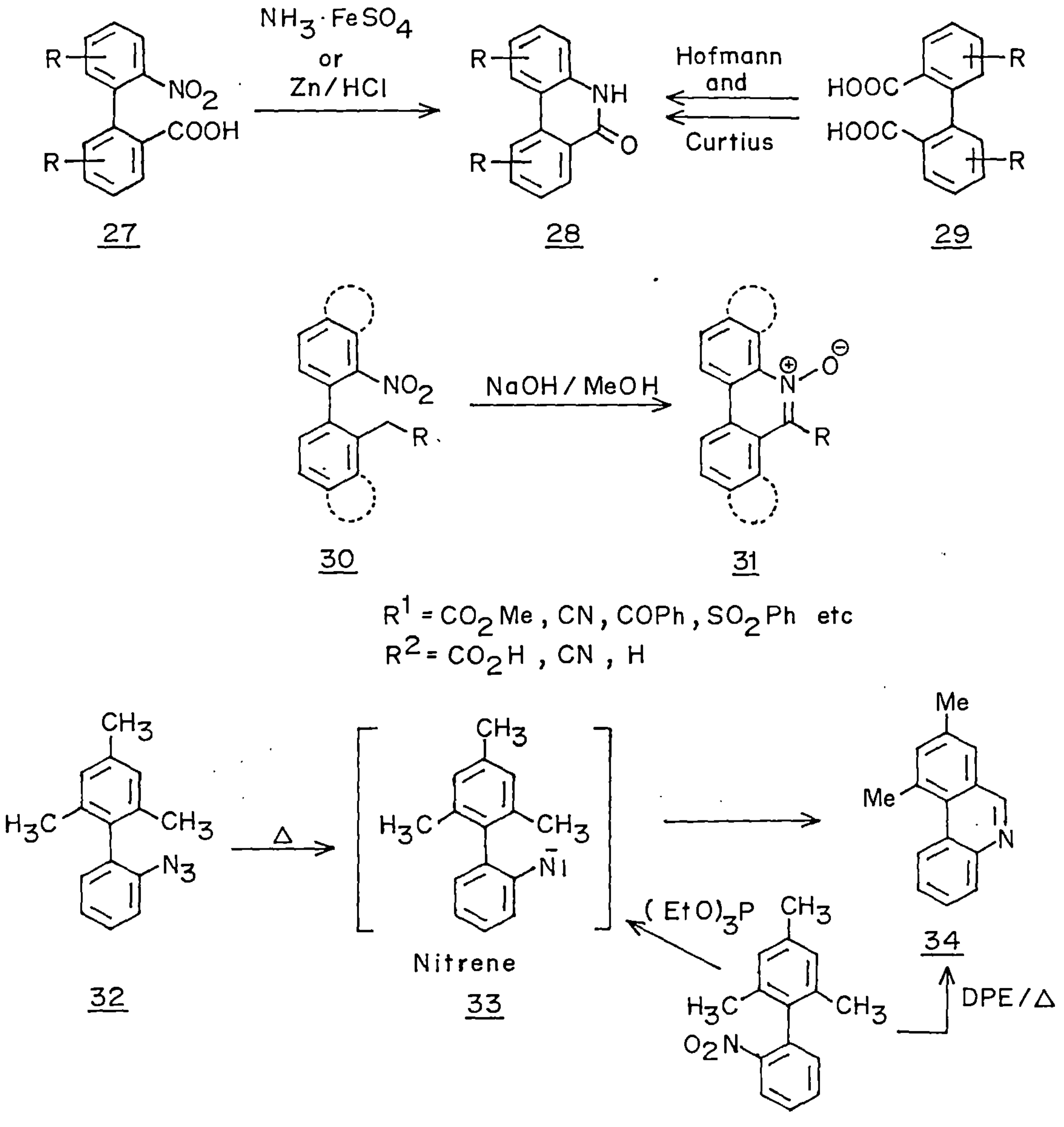
Bischler-Napieralski cyclization in the presence of $POCl_3$ and CH_3CN to yield the isoquinolinium salt **25** which was subsequently transformed to the corresponding dihydro phenanthridine **26** as shown in Scheme-4.

Type "b":Cyclization involving 2,2' biphenyls

Phenanthridines have also been prepared from 2,2'-disubstituted biphenyls **27,30** and **32** using various reaction conditions. In all these cases substituents from both the phenyl groups interact intramolecularly to form the heterocyclic ring. The oldest example of these type synthesis involve Hofmann[18] and Curtius[19] reaction and biphenic acid **29** (Scheme-5),[20] and have been explained in terms of intermediate formation of 2-aminobiphenyl- 2'-carboxylic acid, which undergoes spontaneous cyclization to yield the corresponding phenanthridone. Similarly the reduction of 2'-nitrophenyl-2-phenylcarboxylic acid **27** with ammoniacal $FeSO_4$[21] or with Zn/HCl[22] also yields the corresponding phenanthridone **28**.

Also 2'-nitro-2-substituted biphenyl **30** represents an interesting example of the participation of an aromatic nitrogroup involving an aldol type condensation.[23] The reaction was generally carried out in the presence of NaOH/alcohol when the carbanion generated attacked the nitrogroup followed by elimination of water to yield the corresponding phenanthridinium oxide **31**. Smolinsky has shown that 2-azido-2'-methyl biphenyl[24] of general formula **32** yields the corresponding phenanthridine **34**. The mechanism is proposed through nitrene intermediate **33** in its triplet state interacting with methyl group through radical mechanism giving rise to benzyl and imino radicals which will couple to yield the corresponding phenanthridine **34**. Similarly 2-nitro-2'-methyl biphenyl **35** has been examined by Smolinsky and co-workers[25] in the presence of triethylphosphite presumably involving the formation of a nitroso derivative and then to the nitrene **33** followed by ring closure to **34** (Scheme-5). However Smolinsky has also demonstrated the formation of phenanthridine **34** by heating the nitro compound **35** at 350°C in diphenylether. They therefore concluded that it is not necessary that the ring closure is going through

Type -'b'- approach :-



$R^1 = CO_2Me$, CN, COPh, SO_2Ph etc
$R^2 = CO_2H$, CN, H

Scheme - 5

nitrene intermediate as proposed by Abramovitch.[26]

Type "f":Ring expansion approach:

Phenanthridones have been obtained from the oximes of fluorenones **36** by subjecting them to either Schmidt or Beckmann reaction conditions. However with unsymmetrically substituted fluorenones, isomeric mixtures of the corresponding phenanthridones are generally formed. The first reaction of this transformation (Scheme-6) was reported[27] by Beckmann and co-workers using a mixture of PCl_5 and $POCl_3$, although reaction under these conditions resulted in ring chlorination. However when PPA was used the corresponding phenanthridone was obtained in quantitative yield. The benzo[j]phenanthridone **37** was subsequently converted to benzo[j]phenanthridine **11** following reduction elimination sequences.[28]

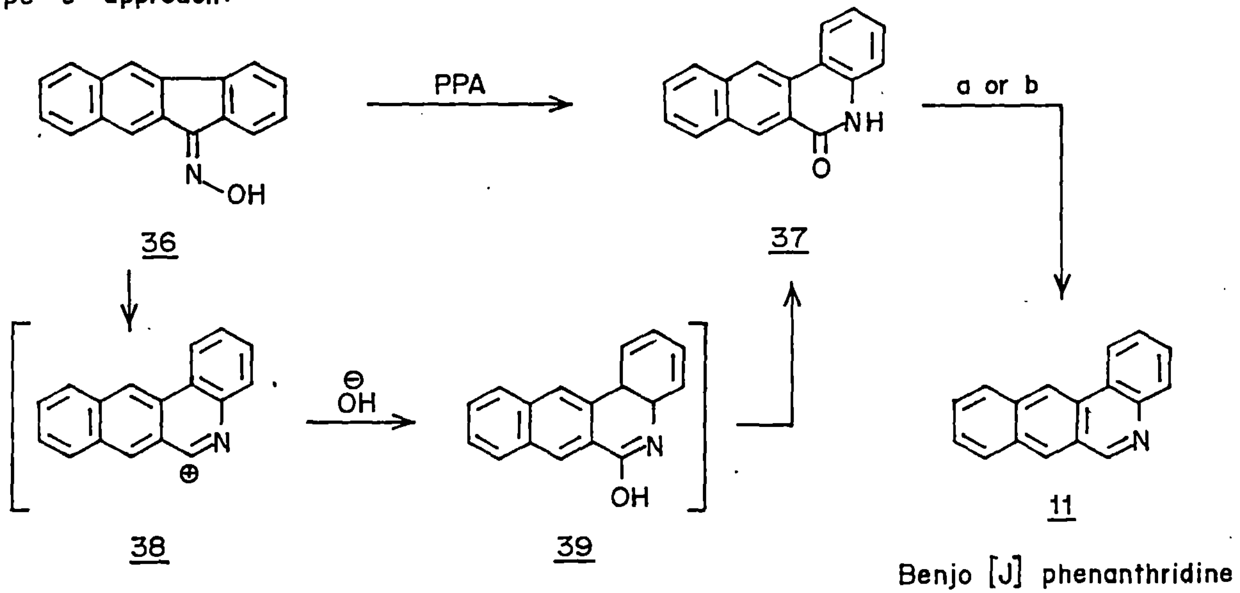
Type "d"approach: Pschorr and related cyclization approach:

N-methylphenanthridone **42** can be obtained from diazonium sulphate of aminobenzanilide **40** usually as its fluoroborate salt **41** in the presence of Cu-powder in boiling acetone.[29] The reaction however yields other undesirable biproducts. When diazonium salt is decomposed thermally[31] often differ from those reactions under copper catalyzed conditions. Thus in a typical reaction the fluoroborate **41** yields spirocyclohexene dione **43** and the spirocyclohexadiene dimer **44**. A number of examples have been studied using these types, which are reviewed in the literature. Decomposition[31] of 3,4-dihydro-4-oxo-3-phenyl-1,2,3-benzotriazene **45** opens up when treated with phosphoric acid to give the diazonium salt **46** followed by ring closure with the loss of nitrogen (Scheme-7).

Type "d":Cyclodehydration:

Hollingworth and co-workers[32,33] have shown that the trans anil **48** (Scheme-8) obtained by condensation of aniline and 2-hydroxy methylene cyclohexanone underwent

Type -'c'- approach:-

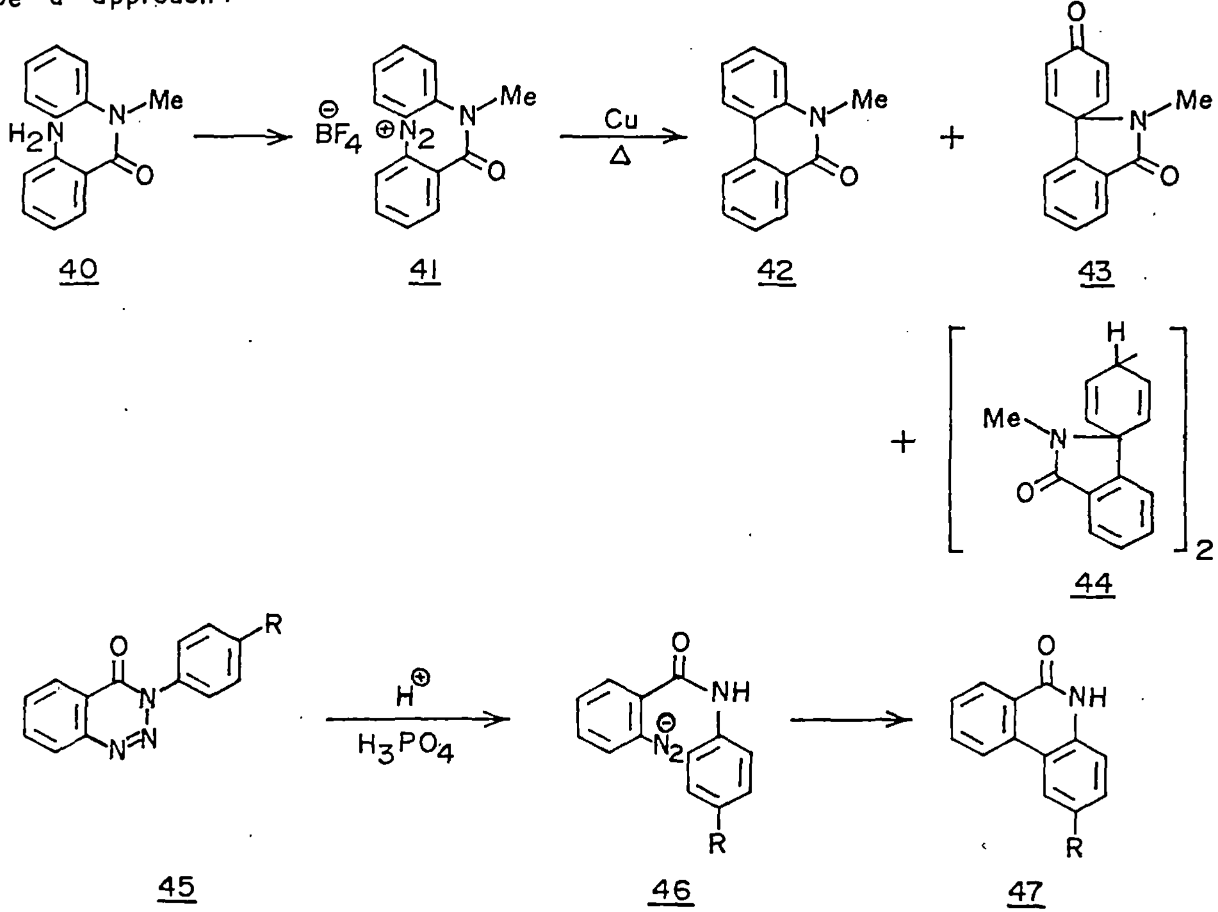


a, 1. LAH ; 2. Pd (c), 190°C

b, 1. $POCl_3$ / Ø $N(CH_3)_2$; 2. LAH

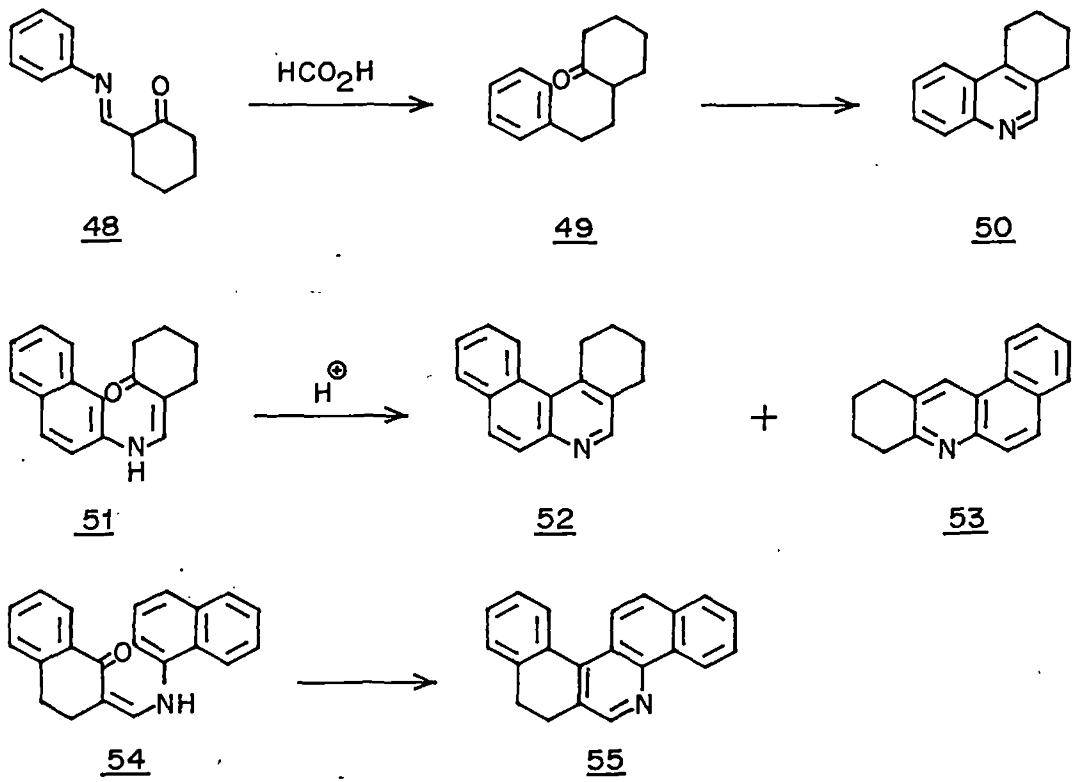
Scheme – 6

Type -'d'- approach :-



Scheme-7

Type-'d'-approach :- Cyclodehydration



Scheme-8

reduction followed by cyclodehydration in the presence of formic acid to yield the corresponding 7,8,9,10-tetrahydrophenanthridine **50**. The enamine reductions with formic acid are well known in the literature which in this case yielded the corresponding secondary amine **49** followed by cyclodehydration to yield **50**. Similarly treatment of 2-(2'-naphthylaminomethylene)cyclohexanone[34] **51** was also shown to give phenanthridine **52** in 39% yield along with benzacridine **53** (12%) when the reaction was carried out in hot formic acid. However **51** when heated with latic acid at 130°C yielded the corresponding benzacridine **53** exclusively in 60% yield. No benzophenanthridine was formed. Similarly **54** in the presence of HCO_2H yielded the corresponding 7,8-dihydro-3,4:9,10- dibenzophenanthridine **55**.

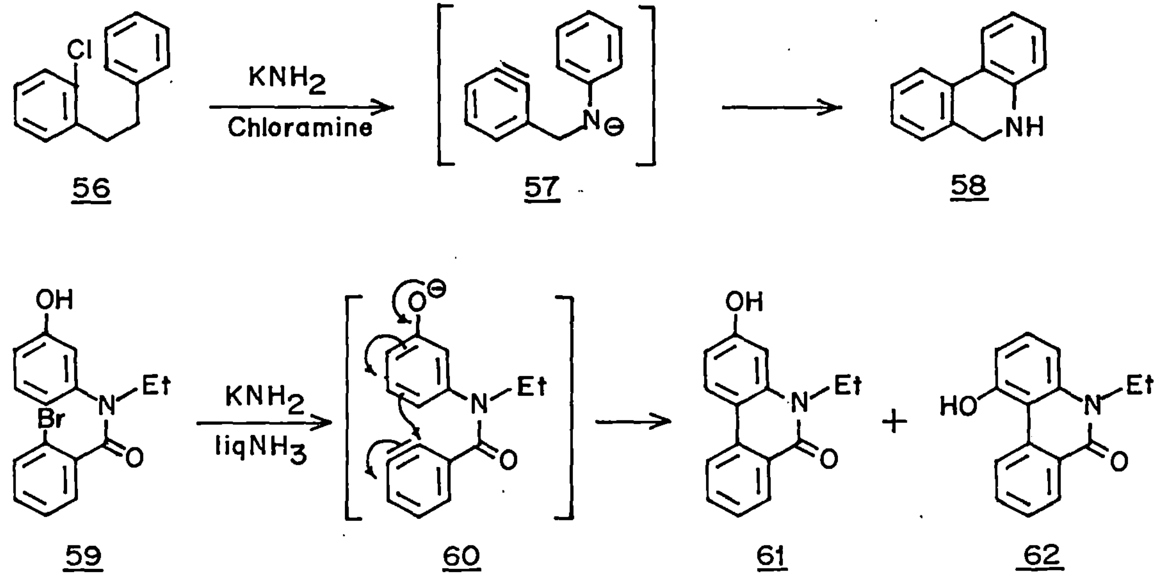
Type "d":Benzyne approach

Kessar and Co-workers[35] have reacted chlorobenzylidene **56** (Scheme-9) in the presence of KNH_2 and liquid ammoina to yield corresponding dihydrophenanthridine **58** through the possible intermediacy of benzyne **57** followed by its ring closure. Similarly Rees and co-workers[36] have studied intramolecular cyclization of 2-bromo-3'-hydroxy-N-ethylbenzanilide **59** in the presence of potassium in liquid ammonia and obtained the corresponding hydroxyphenanthridones **61** and **62** as mixtures. Again the reaction involves through the benzyne intermediate **60** under the described conditions.

Quinoline, isoquinoline annulation approach:

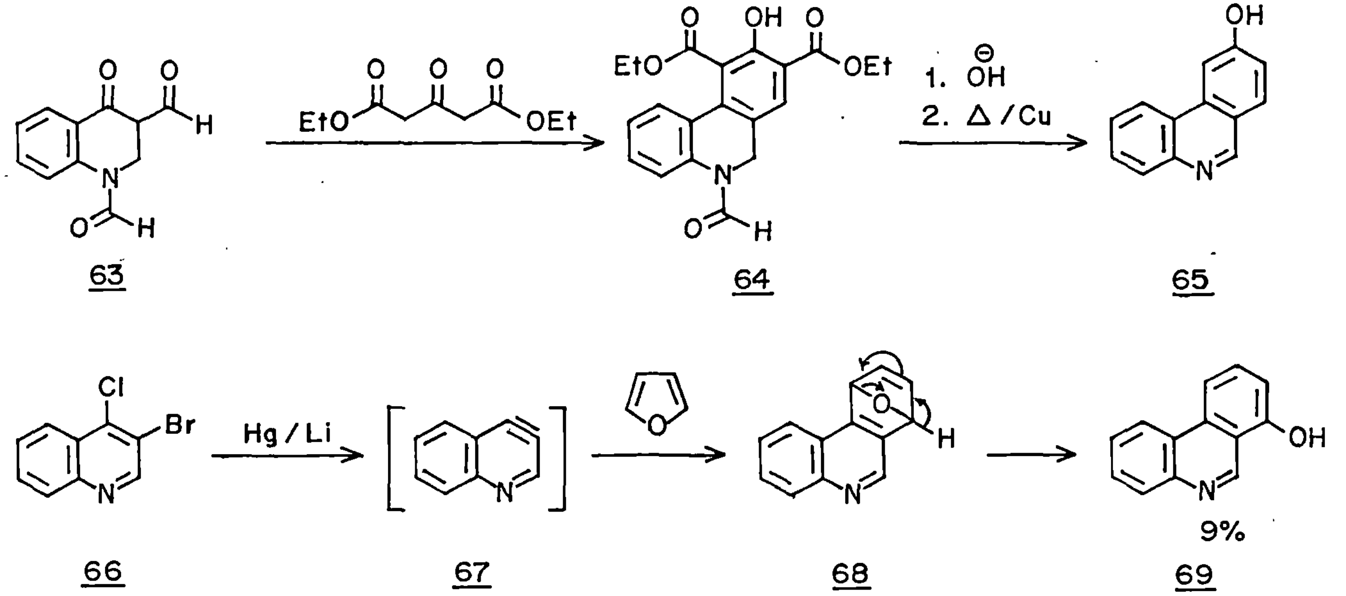
This type of phenanthridine synthesis though potentially important has been less extensively investigated. There are however few papers where preconstructed quinoline or isoquinoline derivatives have been used as precursors for the synthesis of phenanthridines. Thus condensation[37] of 1,3-diformyl-4-oxo- tetrahydroquinoline **63** was condensed with ethylacetonedicarboxylate to yield the corresponding 5-formyl-9-hydroxy-5,6-dihydrophenanthridine-8,10-dicarboxylate **64** (Scheme- 10) which on subsequent hydrolysis and decarboxylation yielded the corresponding

Type–'d'– approach :– Through Benzyne Intermediate



Scheme – 9

Annulation of quinoline / isoquinoline



Scheme – 10

hydroxyphenanthridine **65** in very low yield. Similarly the 3-bromo-4-chloro quinoline **66** was used as potential intermediate to. generate the corresponding 3,4-dehydroquinoline using lithium amalgam[38] in the presence of furan as dienophile to yield the corresponding 7-hydroxyphenanthridine **69** in 9% yield (Scheme-10).

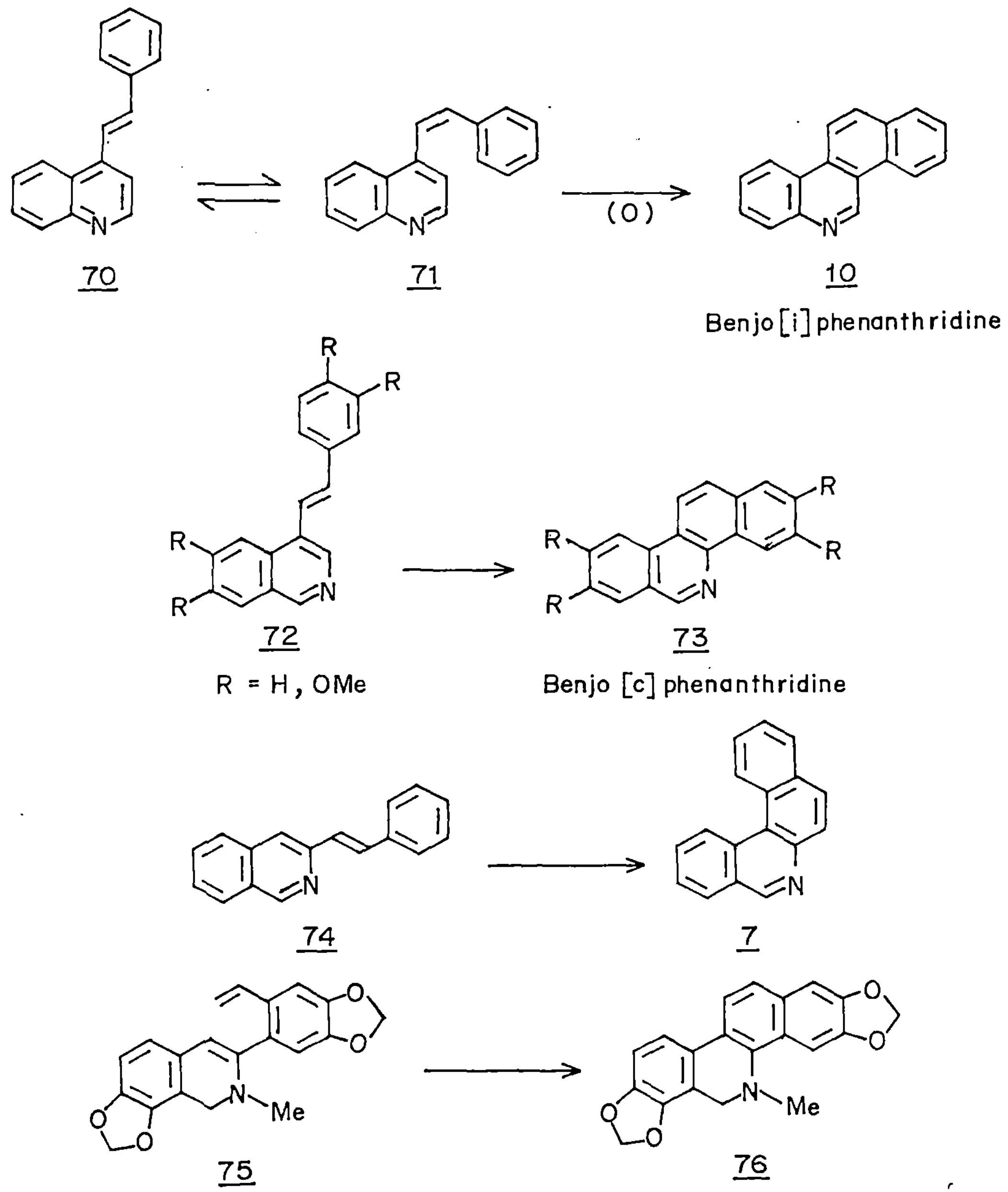
Using this approach 4-styrylquinoline[39,40] **70**, 4-styryl isoquinoline[41] **72**, 3-styrylisoquinoline[40] **74** have been studied under photolytic conditions.Thus **70** on photolysis yielded benzo[i]phenanthridine **10**. Similarly **72** yielded the corresponding benzo[c]phenanthridine **73**. The styrylisoquinoline **74** also yielded on photolysis the benzo[a]phenanthridine **7**. This approach was successfully extended to the synthesis[42] of naturally occuring benzo[c]phenanthridine **76** by photolysis of the corresponding isoquinoline derivative **75** (Scheme-11).

Duval and co-workers have developed a novel benzo[c] phenanthridine synthesis in overall 52-58% yields involving five steps. The intermediate vinyl alcohol **78** (Scheme-12) was obtained by reacting vinylmagnasium bromide with tetrahydroisoquinolone **77** which was subsequently treated with methane sulphonic acid in nitromethane in the presence of I_2 when the corresponding phenanthridine **80** was obtained in moderate yields.[43]

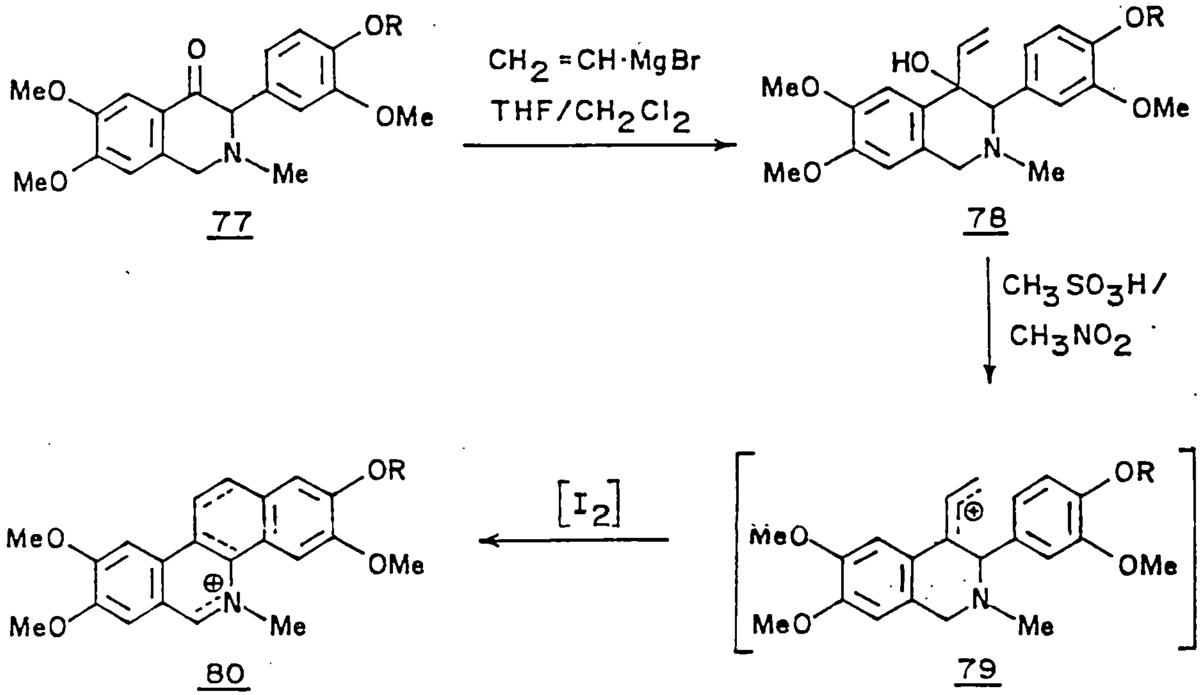
Recently, an interesting phenanthridine synthesis has been reported by Reuter et al. Halogenated benzaldimines **83** were shown to react with lithiated N-Boc-aniline **81** to yield the corresponding binary amines involving SN^{Ar} reaction,[44] which undergo cyclization under hydrolytic condition to yield the corresponding phenanthridines **84** in good yields. The reaction is found to be general with many benzaldimines to yield the corresponding phenanthridines. Yoshida and group[45] have also shown the phenanthridine **86** synthesis by reacting benzyne with N- benzylideneaniline **85** (Scheme-13).

The phenanthridine chemistry though 100 years old appears not fully developed as compared to other heterocyclic ring systems. Most of the earlier synthesis used

Photochemical approach:—



Scheme – 11


MeO
MeO
O
OR
OMe
N
Me
77
CH$_2$=CH·MgBr
THF/CH$_2$Cl$_2$
HO
78
CH$_3$SO$_3$H/
CH$_3$NO$_2$
⊕
79
[I$_2$]
⊕
80

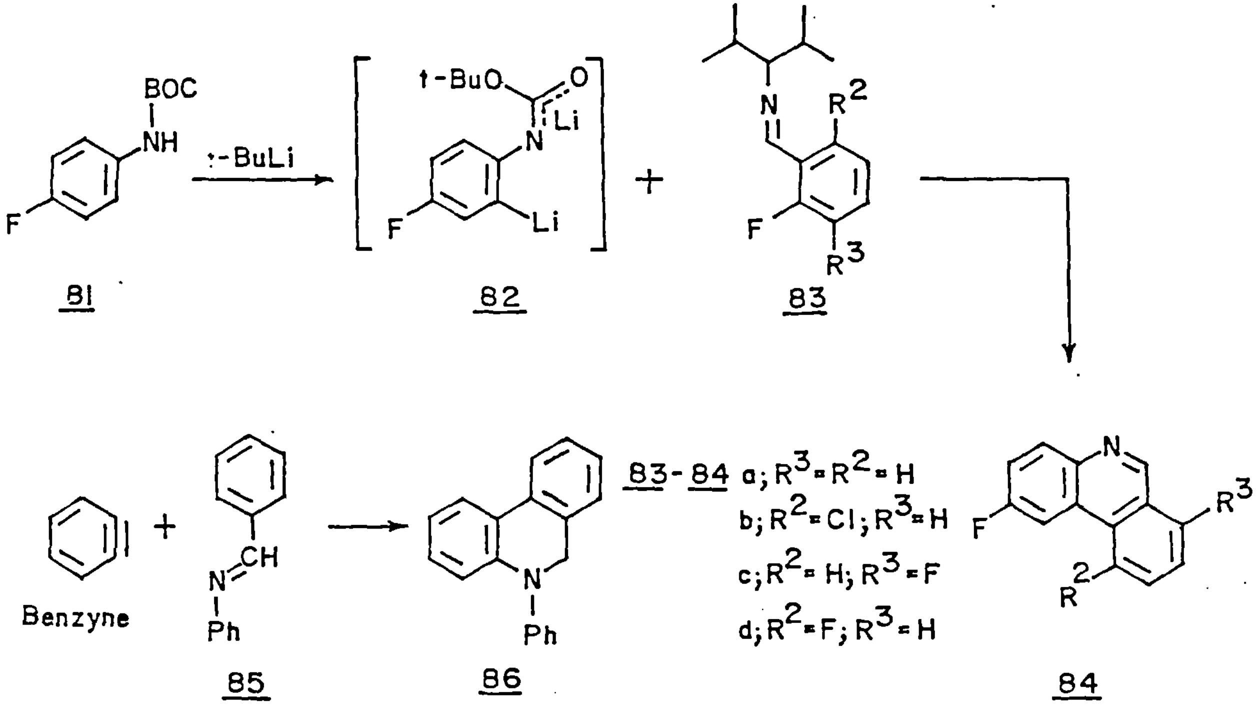
Scheme-12

functionalised biphenyls to create the desired heterocyclic ring. Two major approaches have been used using biphenyl, N-acylbiphenyl cyclization which are by far the most extensively studied group to yield the corresponding phenanthridines. The other group involving 2,2'- disubstitution on biphenyl is comparatively less vigorously investigated. There are other approaches described in the literature which are reviewed briefly in this section. Thus benzyne approach involving intramolecular ring closure has been used with good success in some cases yielding the phenanthridines in high yields though these yields from different workers are often quoted as moderate. Also the popular approach of photolytic cyclization of appropriate styryl quinolines and isoquinolines is also limited to very few reports in the literature. The methodology using preconstructed quinoline and isoquinoline suffers serious problems associated with poor yields. Apparently there is no single method for the synthesis of phenanthridines in high yields other than the developed by Morgan & Walls . It is therefore important that more efficient methods with improved yields for the synthesis of various phenanthridine ring systems are still needed. The chemistry of benzo[c]phenanthridine became attractive only when some of the phenantridinium salts displayed good antileukemic properties. However the biological properties of the corresponding benzo[j], benzo[b], benzo[i] and benzo[k] types have been little studied for their biological activities. This lack of interest in these compounds we primarily attribute due to non-availability of these compounds since the existing methods are totally inadequate to achieve this goal. It is therefore necessary to discover efficient methods for the synthesis of these rare phenanathridine types. We have made a very successful attempt to develop a facile general route for the synthesis of benzo[j]phenanthridine starting from easily available 4-quinolone **91** utilizing our heteroaromatic annelation methodology.[46,47] These results are presented in the following section.

RESULTS AND DISCUSSION

In the preceding section, a brief survey on the methods of synthesis of phenanthridines described in the recent literature is presented. It is to be noted that there are only few reports on the synthesis of phenanthridines using preconstructed tetrahydroquinoline,

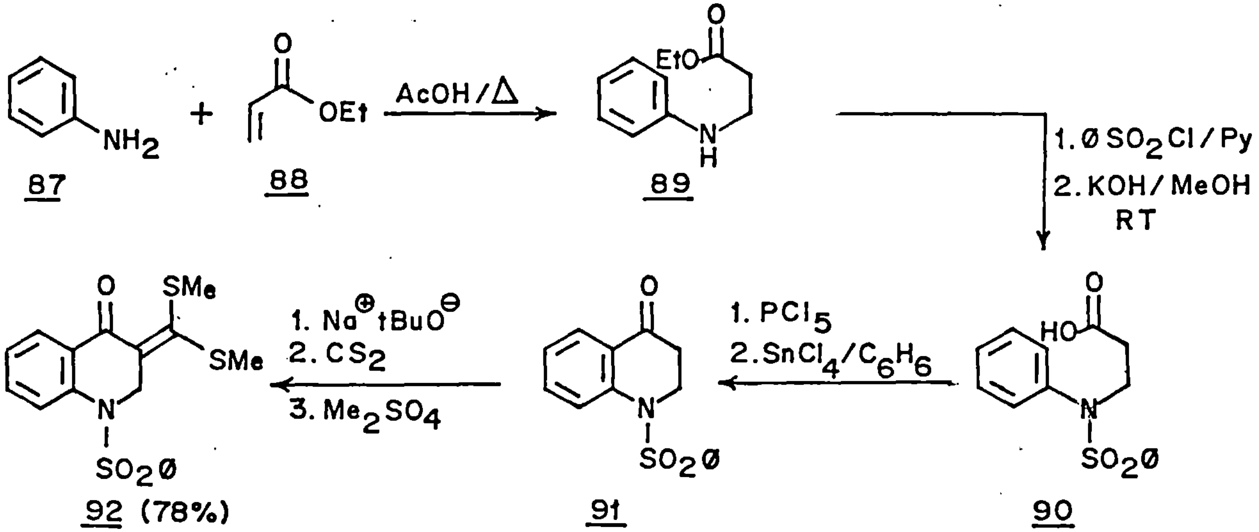
SN^{Ar} Methodology: Synthesis of Substituted Phenanthridines.



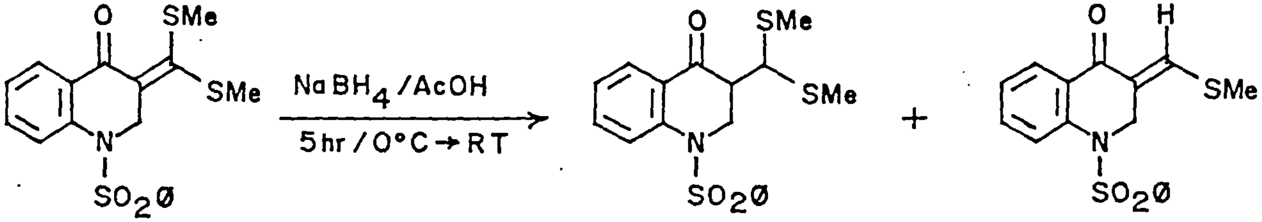
83-84 a; $R^3 = R^2 = H$
b; $R^2 = Cl$; $R^3 = H$
c; $R^2 = H$; $R^3 = F$
d; $R^2 = F$; $R^3 = H$

Scheme-13

isoquinoline and tetrahydro isoquinolones. All other methods have employed generally the functionalized biphenyls as starting materials and the methods have been extensively investigated. It is therefore of interest that the easily accessible tetrahydro-4-quinolone[48] should be attractive intermediate for constructing a large number of phenanthridines and benzo[j]phenanthridines through reverse heteroaromatic annelation, which has been extensively investigated[50,51] in our laboratory. To achieve this goal 1,2,3,4-tetrahydro-N- benzenesulphonyl-4-quinolone **91** (Scheme-14), was taken as a typical example which was converted easily to the corresponding 3-[bis(methylthio)methylene]-N-benzenesulphonyl-1,2,3,4-tetrahydro-4-quinolone as reported in our earlier work.[49] 3-[bis(methylthio)methylene]-1,2,3,4-tetrahydro-N-benzenesulphonyl -4-quinolone **92** was subjected to sodium borohydride reduction in acetic acid to achieve the corresponding ß-oxodithioacetal **93** as reported in our earlier work.[52] Under this condition after workup a mixture of the corresponding 3-[bis(methylthio)methyl]-1,2,3,4-tetrahydro-N-benzenesulphonyl-4-quinolone **93** and the corresponding 3-[(methylthio)methylene]-1,2,3,4-tetrahydro-N- benzenesulphonyl-4-quinolone **94** was obtained in 45 and 51% yields respectively. The compounds **93** and **94** were separated using silicagel coloumn eluting with mixture of hexane and ethylacetate (98:2). The first fractions contained **93** (r_f=0.6) which has higher r_f value than **94**. The other compound **94** was isolated then in 51% yield. Both the compounds were characterised to confirm the assigned structures. Thus **93** as pale yellow needles (hexane- ether); mp. 80-81°C; yield 45% displayed molecular ion peak at m/z 393 (M^+), and analysed for $C_{18}H_{19}NO_3S$ thus confirming the molecular weight. In its IR (KBr) spectrum, the characteristic band at 1680cm^{-1} was assigned to carbonyl group. Other prominent bands are described in the experimental section. The structure was further confirmed from its ^{1}H NMR spectrum (300MHz, $CDCl_3$). The two signals as singlets at δ 2.12 and 2.14 integrating for 3H each were assigned to the six methylthio protons. The signal at δ 2.65 appeared as broad doublet (J=12.9Hz) was assigned to the $H_d(C_3)$ proton which had a coupling with $H_b(C_2)$ proton and a signal at δ 3.98 appeared as a triplet (J=13Hz) was assigned to $H_b(C_2)$ proton. The signal at δ 4.30 (1H) appeared as a broad singlet which was assigned to H_c (exocyclic methylthio carbon proton), which


NH2
87
+
O
OEt
88
AcOH/Δ
EtO
O
N
H
89
1. ØSO2Cl/Py
2. KOH/MeOH
RT
HO
O
N
SO2Ø
90
1. PCl5
2. SnCl4/C6H6
O
N
SO2Ø
91
1. Na⊕ tBuO⊖
2. CS2
3. Me2SO4
O
SMe
SMe
N
SO2Ø
92 (78%)

Scheme-14

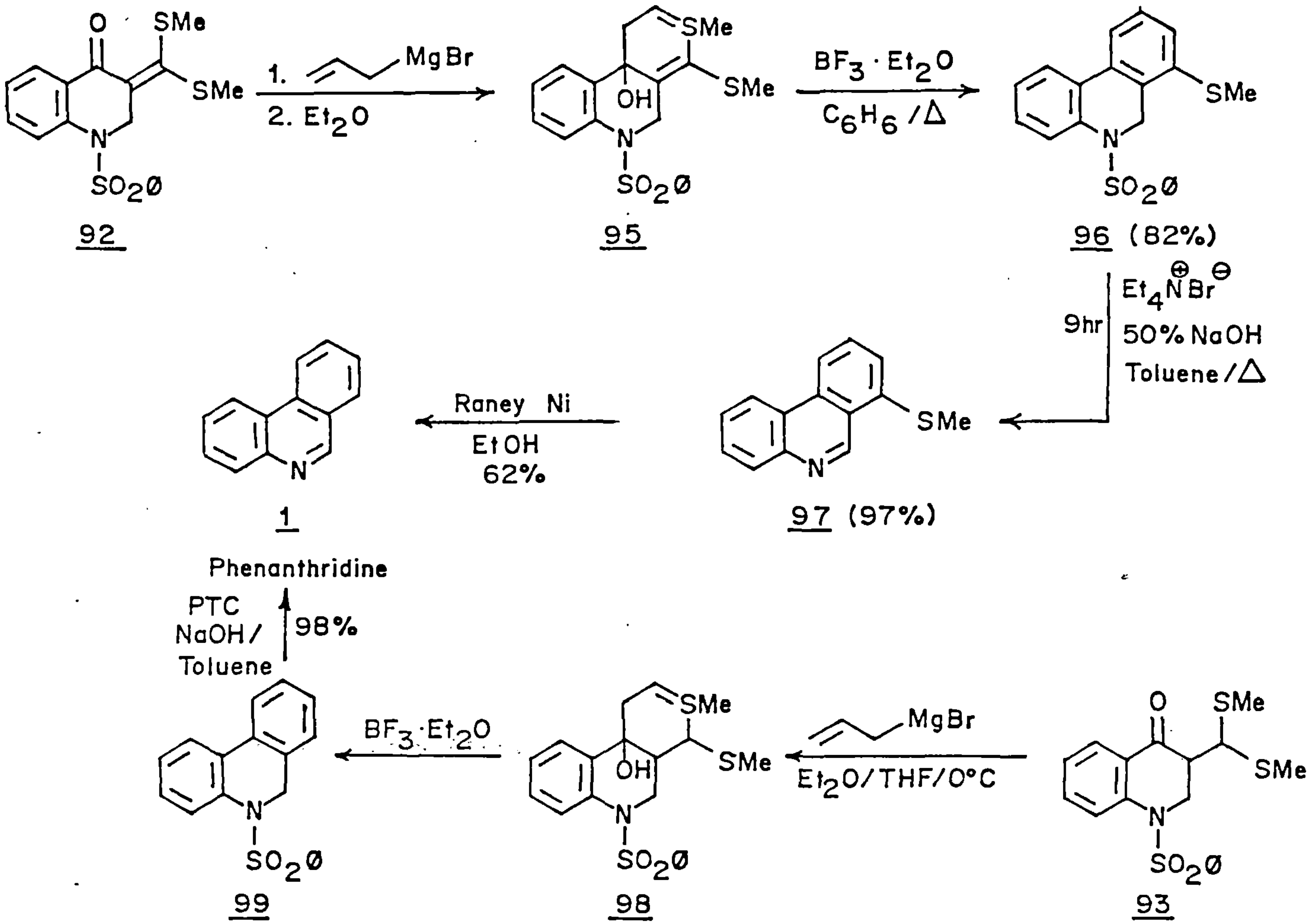


92 93 (45%) 94 (51%)

Scheme-15

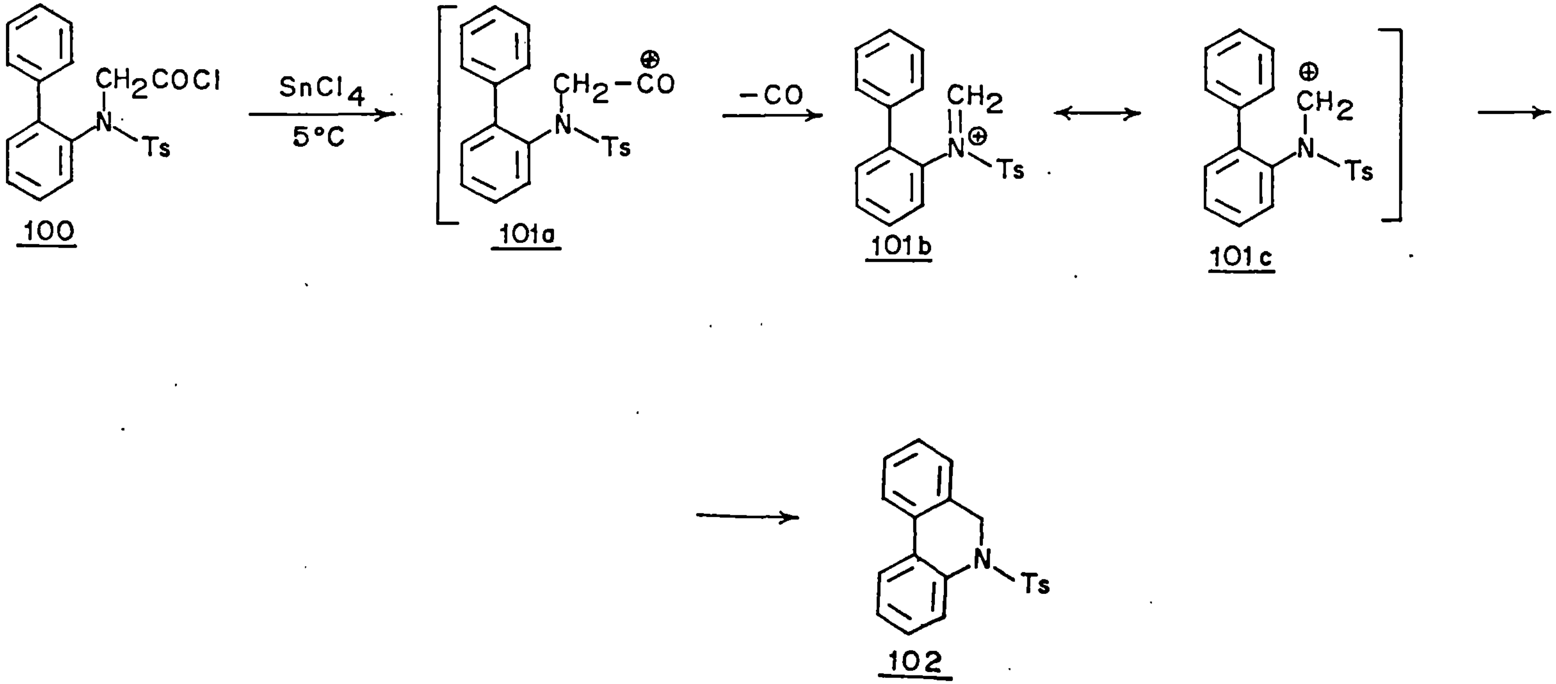
did not couple clearly with $H_d(C_3)$ (see spectrum). The double doublet ($J=3.6,14.7Hz$) at δ4.63 was assigned to $H_a(C_2)$. The other data are described in the experimental section. The structure was further confirmed from ^{13}C NMR spectrum as shown in the experimental section. The structure of **94** was also confirmed by its spectral and analytical data, the compound was analysed for molecular formula $C_{16}H_{15}NO_3S$ for a molecular weight 345. In its IR spectrum, the charecteristic C=O band appeared at $1651cm^{-1}$. The other bands are reported in the expeprimental section. It was further confirmed from ^{1}HNMR (90MHz, $CDCl_3$) spectrum, a singlet at δ 2.50 was assigned to three-methylthio protons. The ring C_2 protons appeared as singlet at δ4.70. The aromatic protons which were less clearly resolved appeared as multiplet around δ7.50-8.30 (10H) accounting for nine protons merging with the vinylic proton in the aromatic region.

The proposed aromatic annelation studies were then carried out on **92** and **93**. Thus when allylmagnesium bromide was reacted with **92**, the corresponding carbinolacetal **95** was formed in quantitative yield as observed by tlc. The carbinolacetal **95** in situ without further purification was treated with $BF_3.Et_2O$ in refluxing benzene for 45 minutes and the reaction mixture after work up yielded the corresponding 7-methylthio-5,6-dihydro-N- benzenesulphonylphenanthridine **96** as colourless needles, mp. 160- 161°C in 82% yield. The structure was established on the basis of its analytical and spectral data. It was analysed for the molecular formula $C_{20}H_{17}NO_2S_2$ and its molecular weight (367) was confirmed by its mass spectrum with a peak at m/z 367 (M^+, 30.8%) and a peak at m/z 226 (M^+-141) accounting for the loss of benzene sulphonyl group appeared as 100% base peak. IR spectrum displayed bands at 2413, 1573 and $1439cm^{-1}$. In its ^{1}H NMR (300MHz) spectrum the methylthio protons appeared at δ 2.49 as a singlet. The methylene protons appeared as singlet at δ 4.46. The multiplet between δ 6.89-6.94 for two protons were assigned to $C_{2',6'}$ protons of the aromatic ring of SO_2Ph and the other multiplet (3H) between δ 7.01-7.07 was assigned to the other three $C_{2,3\&4}$ protons of the same ring. The multiplet between δ 7.30-7.42 was assigned to $ArH_{8\&9}$. The double doublet (J=9Hz) at δ 7.55 was assigned to ArH_{10} proton. The other double doublet at δ 7.79 (J=9Hz) was assigned to ArH_1.



92
1. MgBr
2. Et$_2$O
95
BF$_3$ · Et$_2$O
C$_6$H$_6$ / Δ
96 (82%)
Et$_4$N$^{\oplus}$Br$^{\ominus}$
50% NaOH
Toluene / Δ
9hr
97 (97%)
Raney Ni
EtOH
62%
1
Phenanthridine
PTC
NaOH/
Toluene
98%
99
BF$_3$·Et$_2$O
98
MgBr
Et$_2$O/THF/0°C
93
SMe
OH
SO$_2$Ø

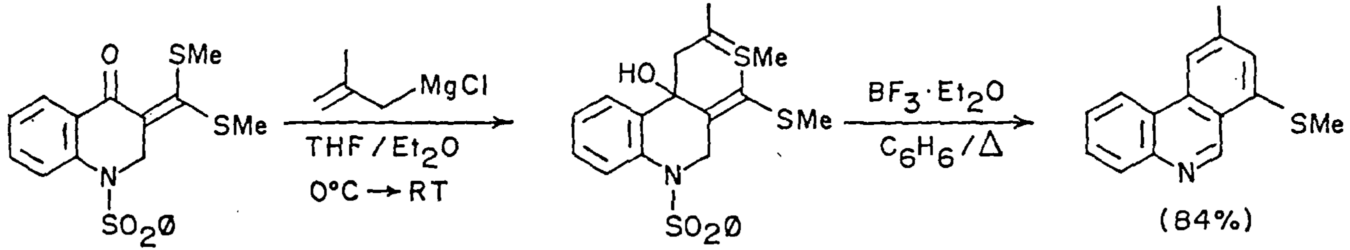
Scheme-16



Scheme-17

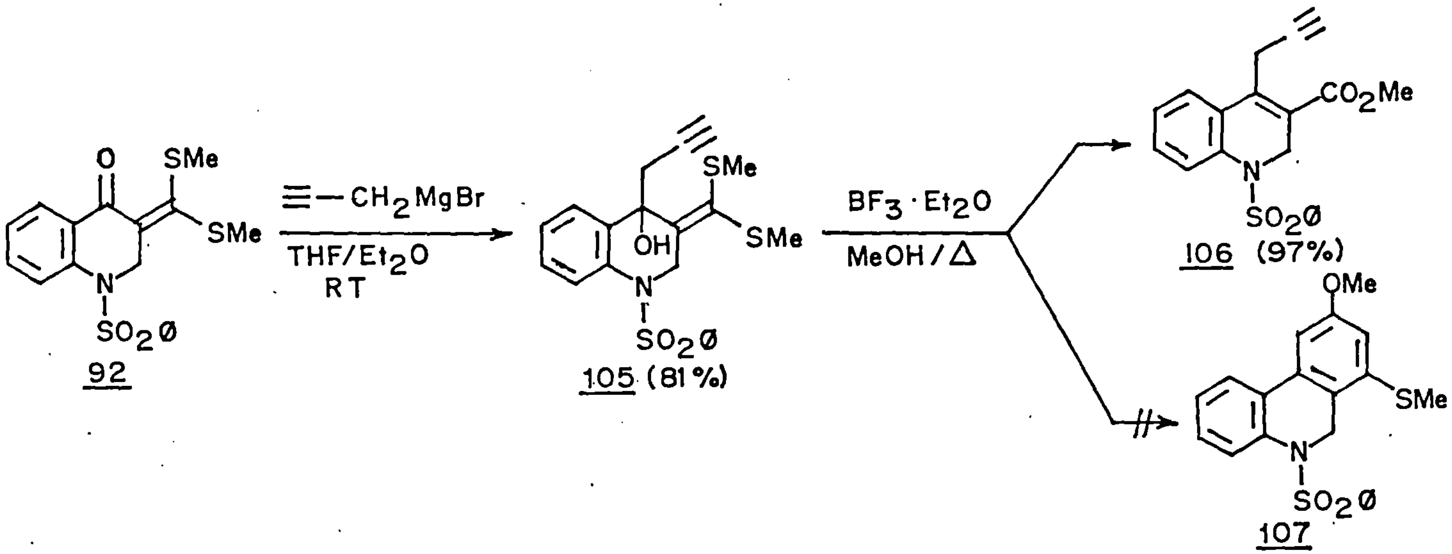
The structure was further confirmed from its ^{13}C NMR spectrum analysis and various signals observed are listed in the experimental section. The dihydro phenanthridine **96** when refluxed with phase transfer catalyst ($Et_4N^+Br^-$), 50% NaOH in toluene yielded the corresponding 7- methylthiophenanthridine in 97% yield as colourless needles (ether), mp. 123-124°C. In its IR (KBr) spctrum, there were no bands for -NH stretching and therefore the desulphonylation was accompanied with aromatization. The presence of methylthio protons was confirmed from its ^{1}HNMR (300MHz,$CDCl_3$) spectrum which appeared as singlet at δ 2.53. All other signals which were in the aromatic region are listed in the experimental section. However the characteristic singlet at δ 9.69 (1H) was assigned to H_6 which distinguishes the phenanthridine structure assigned. The structure was also confirmed by its ^{13}C NMR spectrum. The structure of **97** was further confirmed by subjecting it to Raney- Ni desulphurization to yield the parent phenanthridine **1** in 62% yield as colourless needles from hexane-ether (mp. 105-106°C) reported mp. 104°C). Its ^1H NMR spectral data were in agreement with that reported in the literature. The ^{13}C NMR spectrum was recorded (75MHz, $CDCl_3$). Interestingly the phenanthridne **1** was alternatively prepared in two steps without involving the desulfurization, thus the intermediate **93** prepared as described above was reacted with allylmagnesium bromide followed by $BF_3.Et_2O$ treatment in refluxing benzene to yield the corresponding N-benzenesulphonyl-5,6-dihydrophenanthridine **99** in quantitative yield. It may be interesting to note that the corresponding N-tosyldihydrophenanthridine **102** (Scheme-17) was reported by Proctor and co-wrokers in unspecified yield.[53] The compound **99** yielded the corresponding phenanthridine **1** in phase transfer catalyst condition in quantitative yield. The compound thus obtained mp. 105-106°C was confirmed by its mmp. It was superimposable with IR spectrum obtained by phenanthridine prepared from **92**. It is therefore to be inferred that even for the synthesis of simple unsubstituted phenanthridine **1** this is perhaps one of the most efficient route.

Similarly when **92** was reacted with methacrylylmagnesium chloride, the carbinolacetal **103** (Scheme-18) obtained in quantitative yield (tlc) yielded directly



92 103 104

Scheme-18

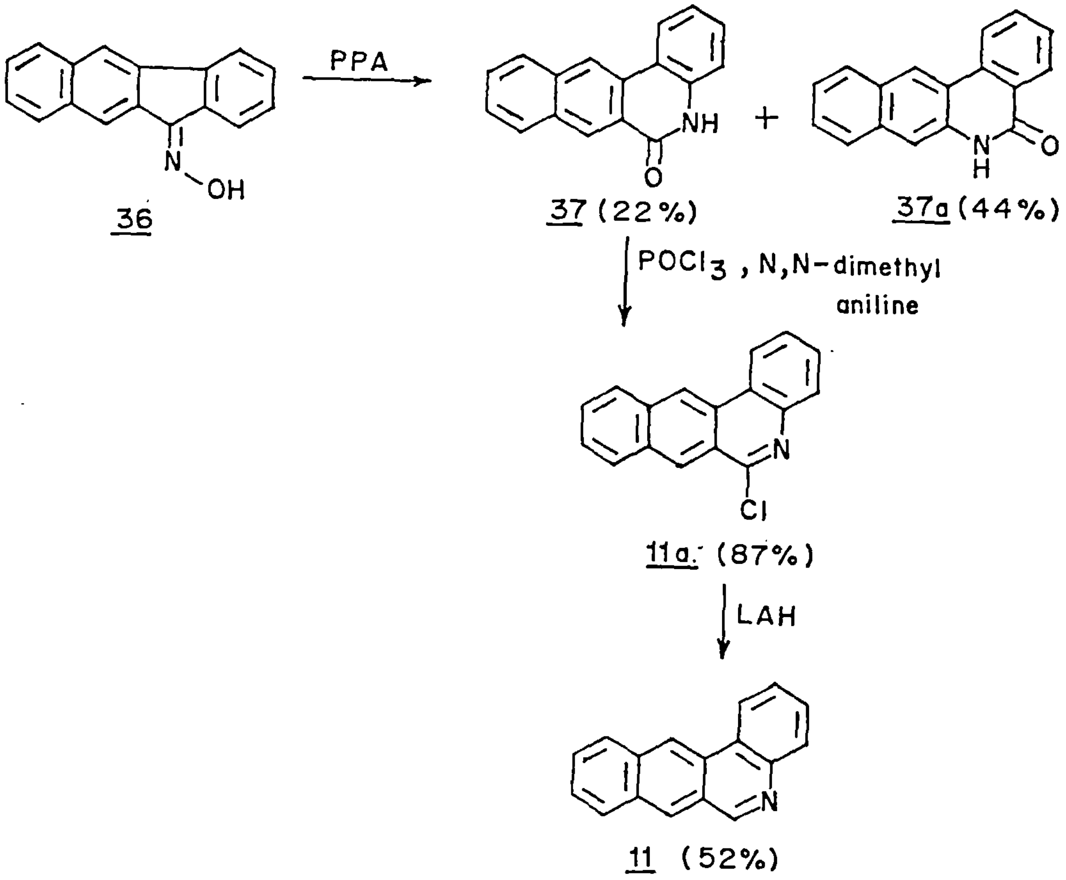

92
≡—CH2MgBr
THF/Et2O
RT
105 (81%)
BF3·Et2O
MeOH/Δ
106 (97%)
107
O
SMe
OH
OMe
CO2Me
N
SO2Ø

Scheme-19

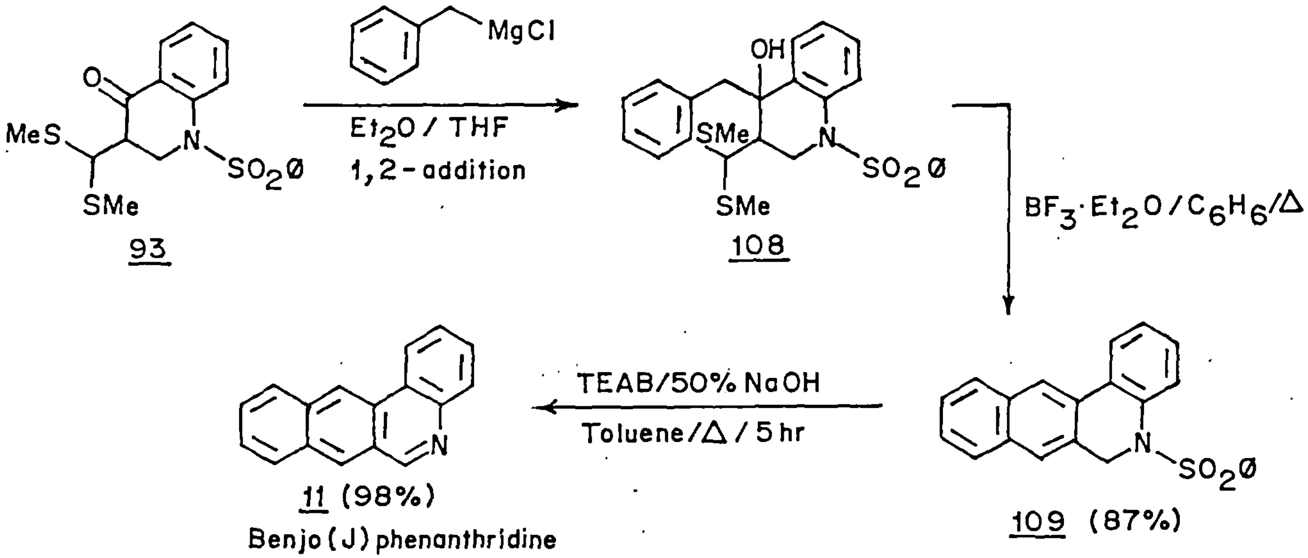
7-methylthio-9-methylphenanthridine **104** in 84% yield. It was obtained as colourless crystals (mp. 103- 104°C). It is again interesting to note that carbinolacetal **103** on treatment with $BF_3.Et_2O$ gave directly the phenanthridine and the observed dihydro-N-benzenesulphonyl derivatives in the preceding example was not detected in this reaction. The phenanthridine **104** was in accordance with the assigned structure from its analytical and spectral data which are described in the experimental section.

In the next experiment, it was considered of interest to react **92** with propargylmagnesium bromide to examine whether the intermediate carbinolacetal **105** (Scheme-19) would undergo cyclization in the presence of methanolic $BF_3.Et_2O$ with the participation of the solvent to yield the 9-methoxy dihydro phenanthridine **107**. However the intermediate carbinolacetal **105** under the described conditions yielded the open chain dihydro quinoline **106** as colourless needles (ether) in 97% yield. The structure was assigned on the basis of its analytical and spectral data. It was analysed for $C_{20}H_{17}NO_4S$ for a molecular weight 367. In its IR (KBr) spectrum a strong band at 1718cm^{-1} was assigned to the ester carbonyl group. However the IR band of acetynylic group in the region around 2100cm^{-1} was too weak to be observed. Same was true for carbinolacetal **105**. The structure was further confirmed from its ^{1}H NMR (300MHz) sectrum. The signal at δ 1.88 as triplet (J=3Hz) was assigned to the characteristic acetynylic proton. Doublet at δ 3.36 (J=3Hz) was assigned to two exocyclic methylene protons. The singlet (3H) at δ 3.82 was assigned to the ester methyl protons. The ring NCH_2 protons appeared at δ 4.63. The aromatic protons appeared as multiplets between δ 7.22-7.76 accounting for all the nine protons.

The method was next extended to the synthesis of benzo[j] phenanthridines. It is interesting to note that there are very few methods described in the literature for the synthesis of benzo[j]phenanthridines. The parent benzo[j]phenanthridine **11** has been reported by Klenn and Weisert as formulated in Scheme- 20.
The starting benzo[b]fluorenone oxime **36** itself is not easily accessible, which is subjected to Beckmann rearrangement in the presence of PPA to yield a mixture of isomeric phenanthridones **37** and **37a** of which **37** was obtained in 22% yield. Which


N
OH
36
PPA
NH
O
37 (22%)
+
N
H
O
37a (44%)
POCl3 , N,N-dimethyl aniline
N
Cl
11a. (87%)
LAH
N
11 (52%)

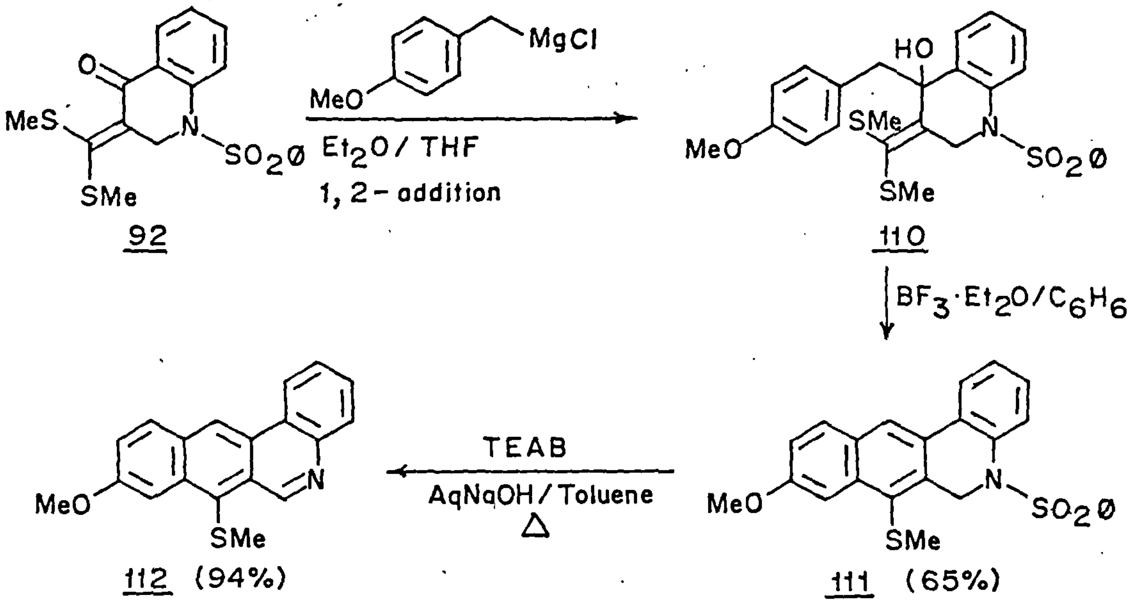
Scheme-20


O
MeS
SMe
N
SO2Ø
93
MgCl
Et2O / THF
1,2-addition
OH
SMe
SMe
N
SO2Ø
108
BF3·Et2O / C6H6 / Δ
N
SO2Ø
109 (87%)
TEAB/50% NaOH
Toluene / Δ / 5 hr
N
11 (98%)
Benjo (J) phenanthridine

Scheme- 21

was then converted to the corresponding chloro compound **11a** followed by $LiAlH_4$ reduction to remove the chlorine resulting in the formation of benzo[j]phenanthridine **11** in overall 10% yield. It is therefore interesting to compare our method for the synthesis of **11** which is formulated in Scheme-21. The starting ß- oxodithioacetal **93** which has been described was reacted with benzylmagnesium chloride to yield the corresponding carbinolacetal **108** in nearly quantitative yield. It was then cyclized in the presence of $BF_3.Et_2O$ in refluxing benzene to yield the corresponding N-benzenesulphonyl-5,6- dihydrobenzo[j]phenanthridines **109** in 87% yield, which was then converted to the parent benzo[j]phenanthridine **11** in 98% yield as colourless needles (hexane-ether), mp. 143°C (reported mp.141- 143°C). The spectral and analytical data of **109** and **11** have been in accordance with the assigned structure which are described in the experimental section. The data for **11** are in agreement with those reported in the literature.

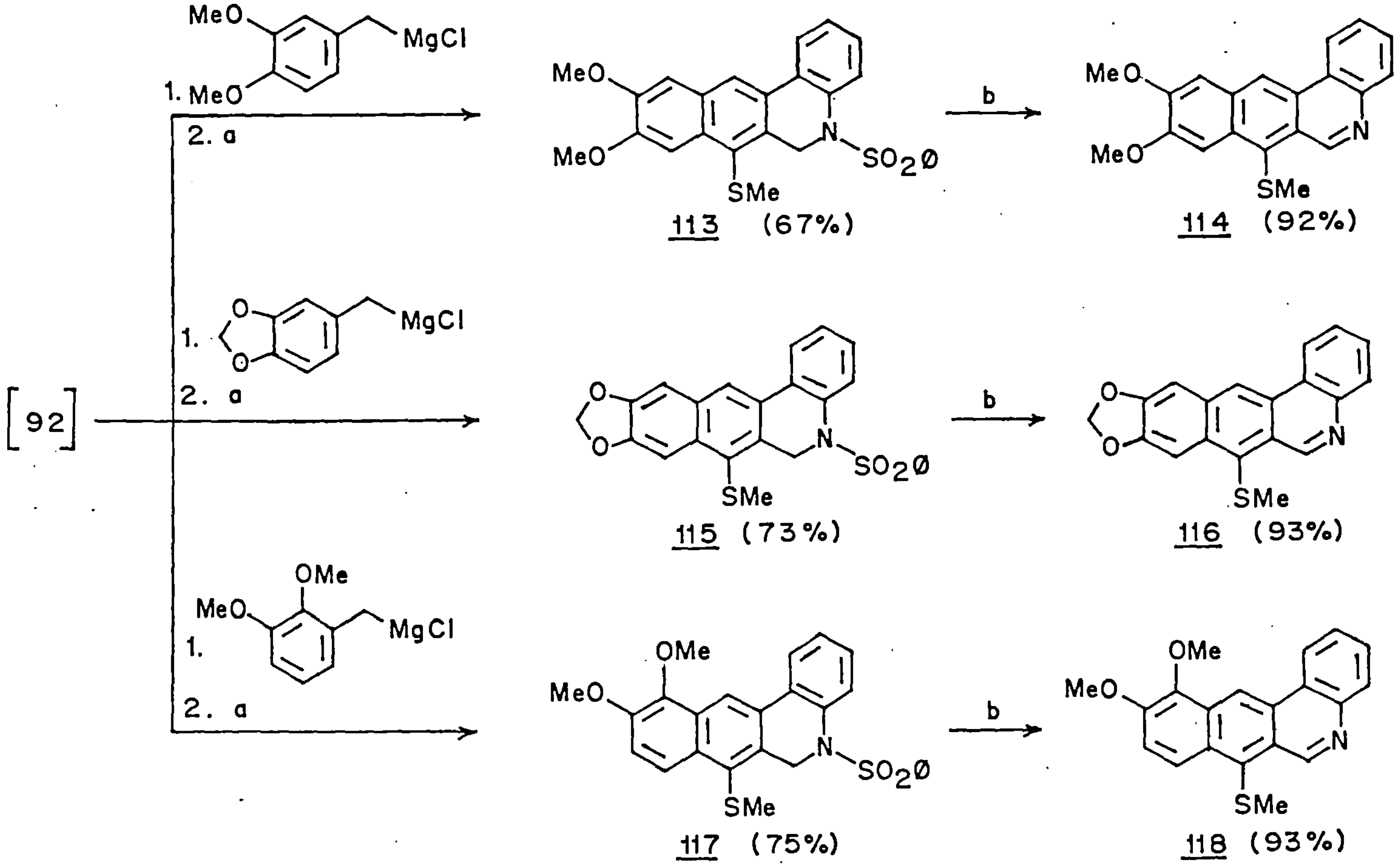
The mercaptal **92** was reacted with p-methoxy benzylmagnesium chloride with a view to prepare 9-methoxybenzo[j]phenanthridine **112**. It has been demonstrated in our labrotary that the alkoxy substituted benzylmagnesium halides undergo preferentially 1,2- addition unlike sequential 1,4- followed by 1,2-additon by benzylmangneisum chloride as observed in our earlier studies. This 1,2-selectivity was attributed due to the presence of methoxy group which inhibits the benzene ring participation in the exocyclic anionic electrons thus making the alkoxy benzylmagnesium halides behave more close to hard nucleophiles. We indeed observe this trend when the carbinolacetal thus formed showed 1,2-exclusive selectivity (crude NMR data), which on $BF_3.Et_2O$ assisted cyclization yielded the correspending 5,6-dihydro-7-methylthio-9-methoxy-N-benzenesulphonylbenzo[j]- phenanthridine in 65% yield. The structure of **111** was established on the basis of its analytical and spectral data which are given in experimental section. When **111** was treated with phase transfer catalyst as described earlier, the corresponding 7-methylthio-9-methoxybenzo[j]phenanthridine was formed as dark red needles (m.p. 175°C) from ether in 94% yield. The structure of **112** was established on the basis analytical and spectral data (Experimental section).


MgCl
MeO
Et$_2$O / THF
1, 2 - addition
HO
SMe
MeS
SMe
O
N
SO$_2$Ø
92
110
BF$_3$·Et$_2$O/C$_6$H$_6$
111 (65%)
TEAB
AqNaOH / Toluene
Δ
112 (94%)

Scheme- 22

After this successful experiment it was decided to examine dimethoxy benzyl Grignard reagents with a view to preparing the corresponding dialkoxy benzo[j]phenanthridines. Thus 3,4- dimethoxy benzylmegnasium chloride (Scheme-23) reacted with **92** to yield the corresponding 7-methylthio-9,10-dimethoxy-N-benzene sulphonyl-5,6-dihydrobenzo[j]phenanthridine **113** in 67% yield under the conditions described earlier, which underwent facile deprotection and dehydrogenation in the presence of PTC to yield the corresponding benzo[j]phenanthridine **114** in 92% yield as dark red prisms, m.p. 179-180°C (ether). The structure of **114** was confirmed from its analytical and spectral data (Experimental section). Similarly piperonyl benzyl Grignard reagents reacted with **92** to yield the corresponding 5,6-dihydro-7-methylthio-9,10- methylenedioxybenzo[j]phenanthridine in 73% yield. The analytical and spectral data for this compound were in agreement with the assigned structure (Experimental section).It was similarly deprotected and dehydrogenated using PTC to yield the corresponding 7-methylthio-9,10-methylenedioxybenzo[j]phenanthridine **116** in 93% yield as light yellow needles, m.p. 235°C (ether). The analytical and spectral data confirm the structure assigned (Experimental section). In the same sequence 7- methylthio-10,11-dimethoxybenzo[j]phenanthridine **118** was obtained in 93% yield as colourless needles, m.p. 143°C (ether) from the corresponding dihydro phenanthridine **117** which was obtained in 75% yield by reacting 2,3-dimethoxy benzyl Grignard reagent with **92**. The structure of **117** and **118** were confirmed from the analytical and spectral data which are described in the experimental section.

2,5-dimethoxy benzyl Grignard reagent was similarly reacted with **92** under the described reaction conditions to yield the corresponding 5,6-dihydro-7-methylthio-8,11-dimethoxybenzo[j]phenanthridine **119** in 78% yield which on deprotection and dehydrogenation yielded the corresponding 7-methylthio-8,11-dimethoxybenzo[j]phenanthridine **120** in 98% yield as bright yellow needles m.p. 169-170°C (ether).The structure of both **119** and **120** were established by their analytical and spectral data (Experimental section). The phenanthridine **120** is an excellent precursor for the preparation of the corresponding quinone **121**. Also, 8-methoxy or 11-methoxy phenanthridines are important precursors for the preparation



113 (67%)

114 (92%)

115 (73%)

116 (93%)

117 (75%)

118 (93%)

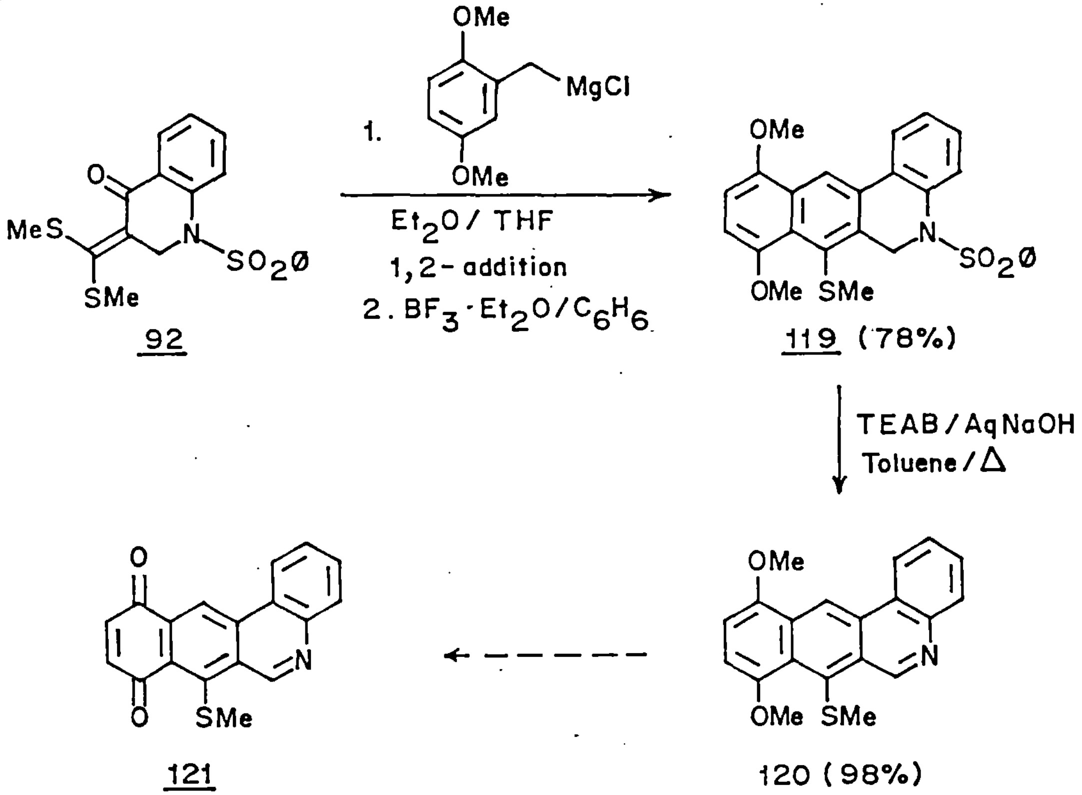
a, $BF_3 \cdot Et_2O/C_6H_6/\Delta$; b, TEAB / AqNaOH / Toluene /Δ

Scheme - 23

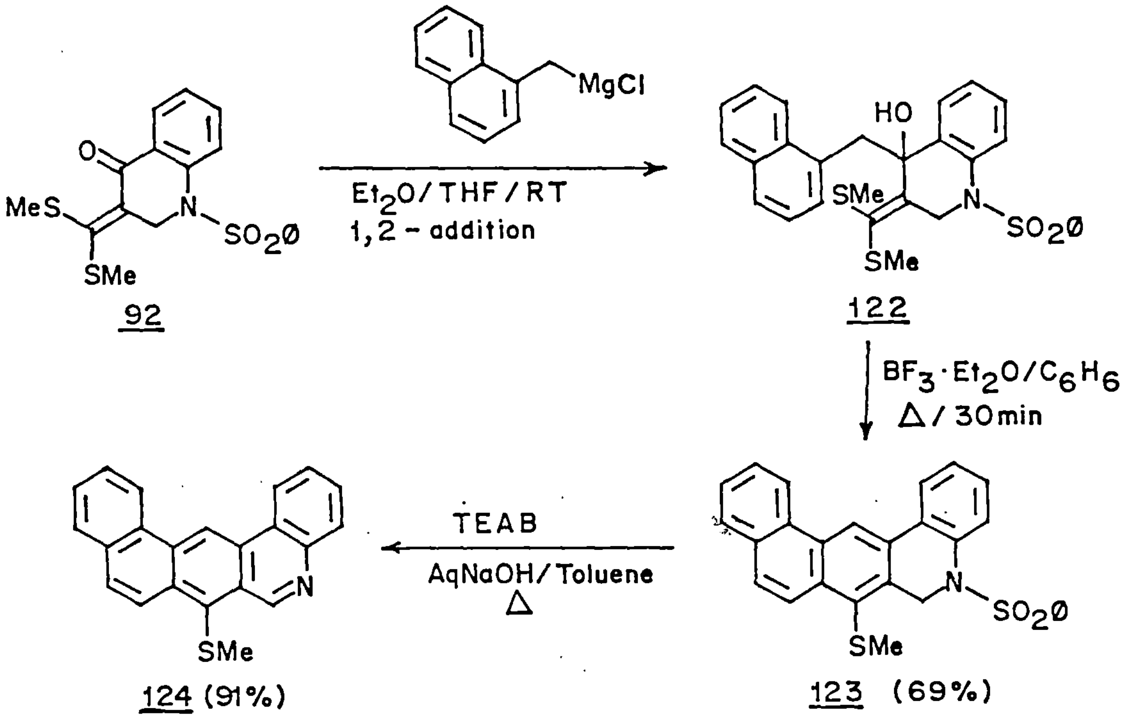
of the corresponding quinones which are excellent likely candidates as DNA intercalators. This work is in progress.

In the earlier studies, we have shown that the α-methylmagnesisum naphthalene displays a remarkable 1,2-selectivity which is explained on the basis of steric reasons. Thus the exocyclic charge if delocalized over the aromatic ring, will push the two hydrogen atoms in the plane of the ring which is resisted sterically the peri hydrogen atom and therefore charge remains largely exocyclic so that it displays a clear hard nucleophilic character. Taking advantage of this experience, it was decided to react naphthyl-1-methylmagnesium chloride with **92** which yielded the corresponding carbinolacetal **122** in near quantitative yield. It was then cyclized under the described reaction conditions to yield the corresponding 5,6-dihydro-7-methylthio naphtho[1,2-j]phenanthridine **123** in 69% yield. The compound was fully characterised as confirmed by its analytical and spectral data (Experimental section). It was deprotected and dehydrogenated as described earlier to yield the corresponding 7-methylthionaphtho[1,2-j]phenanthridine **124** in 91% yield as light yellow needles, m.p. 188-190°C (ether). The basic skeleton of this naphthophenanthridine itself is not known to date and the current work will continue to make the final naphthophenanthridine by both the routes.

From the preceding discussion of our results on the development of new synthetic strategy involving our heteroaromatic annelation methodology, it is apparent that the method constitutes one of the most facile routes for the synthesis of phenanthridine and its derivatives. The method is unique in its extension to the synthesis of benzo[j]phenanthridine and their condensed analogs. The literature methods described for the synthesis of these compounds generally involve more difficult starting materials with overall poor yields. The present method involves tetrahydroquinol-4-ones as starting material whose preparations are well documented with excellent yields. In the present investigation only the basic molecule tetrahydroquinol-4-one has been examined to demonstrate the generality of the method. Also the selection of allyl anions in the present investigation was restricated to few in numbers though the range of availability of these anions is quite wild. With the combination of these two


1.
OMe
MgCl
OMe
Et2O / THF
1,2- addition
2. BF3·Et2O/C6H6
TEAB / AqNaOH
Toluene / Δ
O
MeS
N
SO2Ø
SMe
92
OMe
N
SO2Ø
OMe SMe
119 (78%)
O
O
N
SMe
121
OMe
N
OMe SMe
120 (98%)

Scheme-24


MgCl
Et$_2$O/THF/RT
1,2 - addition
O
MeS
N
SO$_2$Ø
SMe
92
HO
SMe
N
SO$_2$Ø
SMe
122
BF$_3$·Et$_2$O/C$_6$H$_6$
Δ/30min
TEAB
AqNaOH/Toluene
Δ
SMe
N
124 (91%)
N
SO$_2$Ø
SMe
123 (69%)

Scheme - 25

components it is possible to achieve the synthesis of a large structural variants of phenanthridines, benzo[j]phenanthridine and their condensed analogs. It is also possible to extend this methodology for other phenanthridine analogs, starting from appropriate tetrahydroisoquinolones which are likely to yield more important group of benzo[c]phenanthridines which forms basic skeleton in a large no of phenanthridine alkaloids. These studies are in progress. It may be noted that the entire benzo[j]phenanthridine group have not been tested for their biological activities. It is appearently due to the fact that these compounds were unavailable for such screening due to lack of efficient synthetic methods. These compounds should therefore manifest as good DNA intercalators and for such studies often the polycyclic heterocycles found to be insolu-ble thus cannot be tested. However the benzo[j]phenanthri-dines display excellent solubility in both ether and alcohol and their screening as DNA intercalators will pose no difficulty. The screening of these compounds as DNA intercalators as well as topoisomerase inhibitors will be carried out in due course.

Experimental Section

General

M.Ps were obtained on a "Thomas Hoover" melting point (capillary method) apparatus and are uncorrected. The Infrared spectra were recorded on Perkin-Elmer 983 spectrometer. ^{1}H NMR (90 MHz) were recorded on Varian EM-390 spectrometer. High resolution ^{1}H NMR (300 MHz), ^{13}C NMR (75.43 MHz) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shifts (δppm) and the coupling constants (Hz) are reported in the standard fashion with reference to either TMS as internal lock (for ^{1}H NMR), the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C NMR) Mass spectra (MS) were obtained on a Jeol JMS-D 300 Mass spectrometer. Masses are reported in units of mass over charge (m/z), the molecular and base peaks are indicated by "M^+" and "%" respectively. Elemental analysis were carried out on a Heraeus CHN-O-Rapid analyzer.

All reactions were performed in oven dried (120°C) glasswares under a positive dry argon/nitrogen atmosphere. Analytical thin layer chromatography (tlc) were performed on glass plates coated with ACME's silicagel containing 13% calcium sulfate as binder and various combination of visualization of spots was accomplished by exposure to iodine vapour or potassium permanganate (acidic) solution. ACME's silicagel (60-120 mesh) is used for coloumn chromatography, eluents for coloumn chromatography were used after simple distillation of commercial materials. All solvent evaporations were done using a steam bath.

Chemicals & Reagents

Magnesium turnings (SISCO) were used for all the Grignard reactions, which were carried out under a stream of dry nitrogen. Anhydrous ether was obtained by keeping the bottle grade di-ethyl ether (QUALIGEN's) over fused calcium chloride and finally stored over sodium wire. Anhydrous THF was obtained by keeping the deperoxidised THF over sodium-benzophenone. Sodium borohydride (Aldrich) was used for the conjugate 1,4-reduction of quinolone dithioacetal. Raney Nickel (W-4) was prepared according to literature procedure from Nickel-Aluminium Alloy.

Starting Material

N-benzenesulfonyl-1,2,3,4-tetrahydro-4-quinolone was prepared according to the literature procedure.[48] Allylbromide (Aldrich), 3-chloro-2-methyl-1-propene (Aldrich), benzyl chloride (SD's), 1-chloromethyl naphthalene (Aldrich) were used as supplied. The Alkoxy benzyl halides were prepared from their corresponding alkoxy benzaldehydes as per the reported methods. 4-Methoxybenzyl chloride, 3,4-dimethoxy benzyl chloride, 2,5-dimethoxybenzyl chloride, 2,3-dimethoxy benzyl chloride and 3,4-dimethoxy benzyl chloride were prepared from their corresponding benzyl alcohols treated with either concentrated HCl or thionyl chloride. Propargyl bromide was prepared according to the reported procedure from propargyl alcohol treated with

PBr_3.

Preparation of N-benzenesulphonyl-3-[bis(methylthio)methylene] 1,2,3,4-tetrahhydro-4-quinolone92

A mixture of N-benzenesulphonyl-1,2,3,4-tetrahydroquinolone 14.3g (0.05 mol) and carbondisulphide 3 ml (0.05 mol) in dry benzene (100 ml) was added to an ice cooled and well stirred suspension of sodium-t-butoxide (0.10 mol) in dry benzene (150 ml). The reaction mixture was stirred for 4-5 hr. Methyliodide 6.3 ml (0.1 mol) was then gradually added with cooling and the reaction mixture was further stirred for 6 hr. Poured into ice cold water (200 ml) and extracted with benzene (2x100 ml) and the combined benzene extracts were washed thoroughly with water (3x150 ml). Dried over sodium sulphate and evaporated to give only residue which on trituration with hexane/benzene afforded yellow crystalline needles, 78% yield, mp. 111-112°C.

General procedure for the reaction of the dithioacetal 92 with 1-(naphthylmethyl), allyl, proprgyl and alkoxysubstituted benzylmagnesium halides

The reaction of oxoketene dithioacetal **92** with allyl magnesium bromide is representative. To an ice cooled solution of allyl magnesium bromide (0.03 mol) prepared from magnesium turnings (1.0g) and allyl bomide (0.03 mol)] in dry ether (60 ml), the oxoketene dithioacetal, 7.8g (0.02 mol) in dry THF (25 ml) was added dropwise (2-3 min) under N_2 atmosphere. The reaction mixture was further stirred for 1 hr to 1.5hr and the temperature was raised to room temperature. It was then decomposed by pouring over saturated aquous ammonium chloride solution (100 ml), extracted with ether (2x50 ml) and the combined ether extracts were washed with water (2x100 ml), dried over sodium sulphate and evaporated to give the crude carbinol **95** which was used as such for cycloaromatization step.

The reaction of ß-oxodithioacetal with benzyl and allylmagnesium chloride were carried out in the similar manner and all the crude carbinols were subjected to cycloaromatization step without further purification.

General procedure for $BF_3.Et_2O$ assisted cycloaromatization of carbinols

Cycloaromatization of carbinol **95** is representative. To a solution of crude allylic carbinol (0.015 mol) obtained from the reaction of **92** with allyl magnesium bromide, in dry benzene (50 ml), borontrifluoride etherate (2 ml) was added and the reaction mixture was refluxed for 45 min. It was then cooled, poured into saturated $NaHCO_3$ solution (50 ml), extracted with chloroform (2x100 ml) washed with water (2x100 ml), dried over Na_2SO_4 and evaporated to give a viscous residue which on coloumn chromatography over silicagel (hexane-ethylacetate as eluent) afforded colourless crystalline solid **96**.

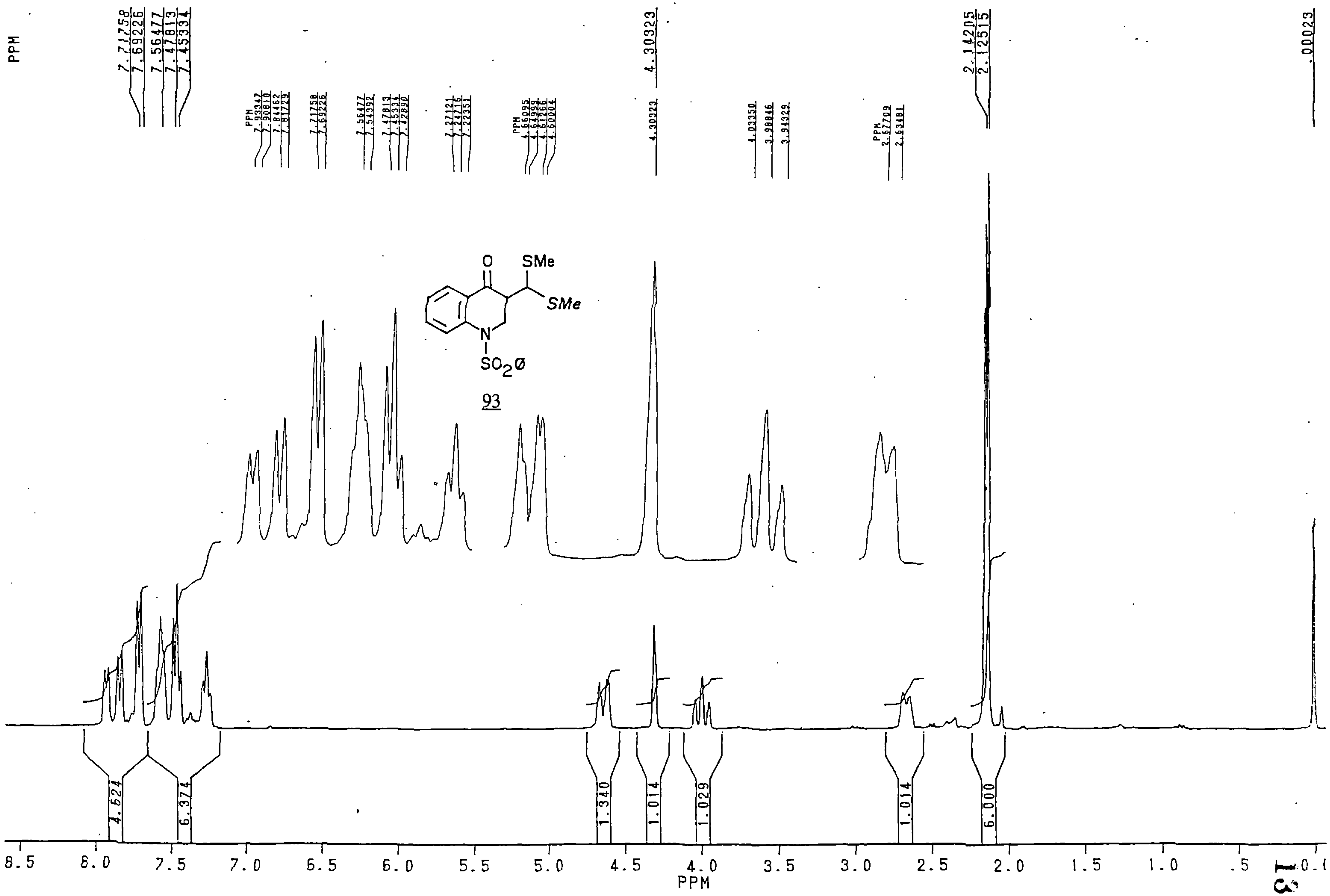
General procedure for the debenzenesulphonylation followed by aromatization of dihydrophenanthridines

The dihydrophenanthridine **96** is representative. To **96** (0.005 mol)) in toluene (20 ml), were added a catalytic amount of tetrabutyl ammonium bromide (Phase Transfer Catalyst) and 50% aquous NaOH (15 ml). The mixture was heated to reflux for 10 hr, cooled, diluted with water (250 ml) and extracted with chloroform (3x50 ml) dried over Na_2SO_4, concentrated and on trituration with hexane afforded nearly quantitative yields of phenanthridine **97**.

The desulfurization reaction via Raney Nickel on 7-thiomethylphenanthridine 97 : Synthesis of parent phenanthridine 1

To a solution of **97** (0.001mol) in ethanol (10mL) was added Raney Nickel (one spoon) and refluxed for 5 hr, cooled, filtered by cintered funnel (G-3), concentrated to give the parent phenanthridine 1 in 62% yield. Mp. and spectral and analytical data are in agreement with the reported values.

The 1,4-conjugate reduction of 3-[Bis(methylthio)methylene]-


PPM
7.71758
7.69226
7.56477
7.47813
7.45334
PPM
7.93347
7.90810
7.84462
7.81729
7.71758
7.69226
7.56477
7.54392
7.47813
7.45334
7.42890
7.27121
7.24716
7.22351
PPM
4.66095
4.64999
4.61266
4.60004
4.30323
4.30323
4.03350
3.98846
3.94329
PPM
2.67709
2.63481
2.14205
2.12515
.00023
O
SMe
SMe
N
SO2Ø
93
4.524
6.374
1.340
1.014
1.029
1.014
6.000
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

1,2,3,4-tetrahydro-N-benzenesulphonyl-quinol-4-one 92 : Synthesis of 3-[Bis(methylthio)methyl]-1,2,3,4-tetrahydro-N-benzenesulphonylquinol-4-one 93 and 3-(methylthio)methylene-N-benzenesulphonylquinol-4-one 94.

To a well stirred solution of **92**, 3.91g (0.01 mol) in glacial acetic acid (60 ml), sodium borohydride 1.5g (0.04 mol) was added slowly (portion wise) in 30 minute at 5-10°C. The reaction mixture was further stirred at room temperature for 3 hr (monitored by tlc) and then poured into ice-cold water (100 ml) followed by extraction with chloroform (3x50 ml). The combined chloroform extracts were washed with water (3x100 mol), dried over sodium sulphate and concentrated to give a viscous residues, which on coloumn chromatography over silicagel (hexane and EtOAc as eluent) gave pure **93** and **94**.

The spectral data of all the compounds are given below.

3-[Bis(methylthio)methylene]-1,2,3,4-tetrahydro-N-benzenesulphonyl-4-quinolone (92)

Light yellow crystals; mp. 111-112°C; yield 73%; IR (KBr): 3267, 1620, 1589, 1469, 1345 cm^{-1}; ^{1}H NMR (90 MHz, CDCl$_3$): δ 2.29 (s, 3H, SCH$_3$), 2.47 (s, 3H, SCH$_3$), 5.19 (s, 2H, NCH$_2$), 7.30-8.20(m, 9H, ArH); MS (m/z, %): 391 (M$^+$, 21), 250 (M$^+$-141, 100). Anal. Calcd. for $C_{18}H_{17}NO_3S$ (391.517): C 55.21; H 4.37; N 3.57. Found: C 55.30; H 4.38; N 3.53.

3-[Bis(methylthio)methyl]-1,2,3,4-tetrahydro-N-benzenesulphonyl-4-quinolone (93)

Light yellow crystals (hexane,ether); mp. 80-81°C; yield 45%; IR (KBr): 2917, 1680 (CO), 1596 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.12 (s, 3H, SCH$_3$), 2.14 (s, 3H, SCH$_3$), 2.65 (dd, 1H, J = 3.6, 12.9Hz, CH$_d$), 3.98 (t, 1H, J = 13.5 Hz, CH$_b$), 4.30 (brs, 1H, CH$_c$), 4.63 (dd, 1H, J = 3.6, 14.7Hz, CH$_a$), 7.24 (brt, 1H, J = 7.2 Hz, ArH$_{4'}$), 7.45 (t, 2H, J = 7.5Hz, ArH$_{6\&7}$), 7.54-7.56(m, 2H, ArH$_{3'\&5'}$), 7.70 (d, 2H, J = 7.5Hz, ArH$_{2'\&6'}$), 7.83 (d, 1H, J = 8Hz, ArH$_8$), 7.92 (d, 1H, J = 7.5Hz, ArH$_5$); ^{13}C NMR (75 MHz, CDCl$_3$): δ

15.33 (SCH_3), 16.69 (SCH_3), 47.03 (NCH_2), 49.93 (CH), 52.14 (CH), 124.08, 125.26, 126.77, 127.01, 127.50, 127.98, 128.31, 129.22, 133.02, 134.35, 139.84, 141.97 (CO); MS (m/z, %): 393 (M^+, 82.3), 252 (M^+, 89.08). Anal. Calcd. for $C_{18}H_{19}NO_3S_3$ (393.527): C 54.93; H 4.86; N 3.56. Found: C 54.81; H 4.78; N 3.51.

3-(Methylthio)methylene-1,2,3,4-tetrahydro-N-benzenesulphonyl-4-quinolone(94)

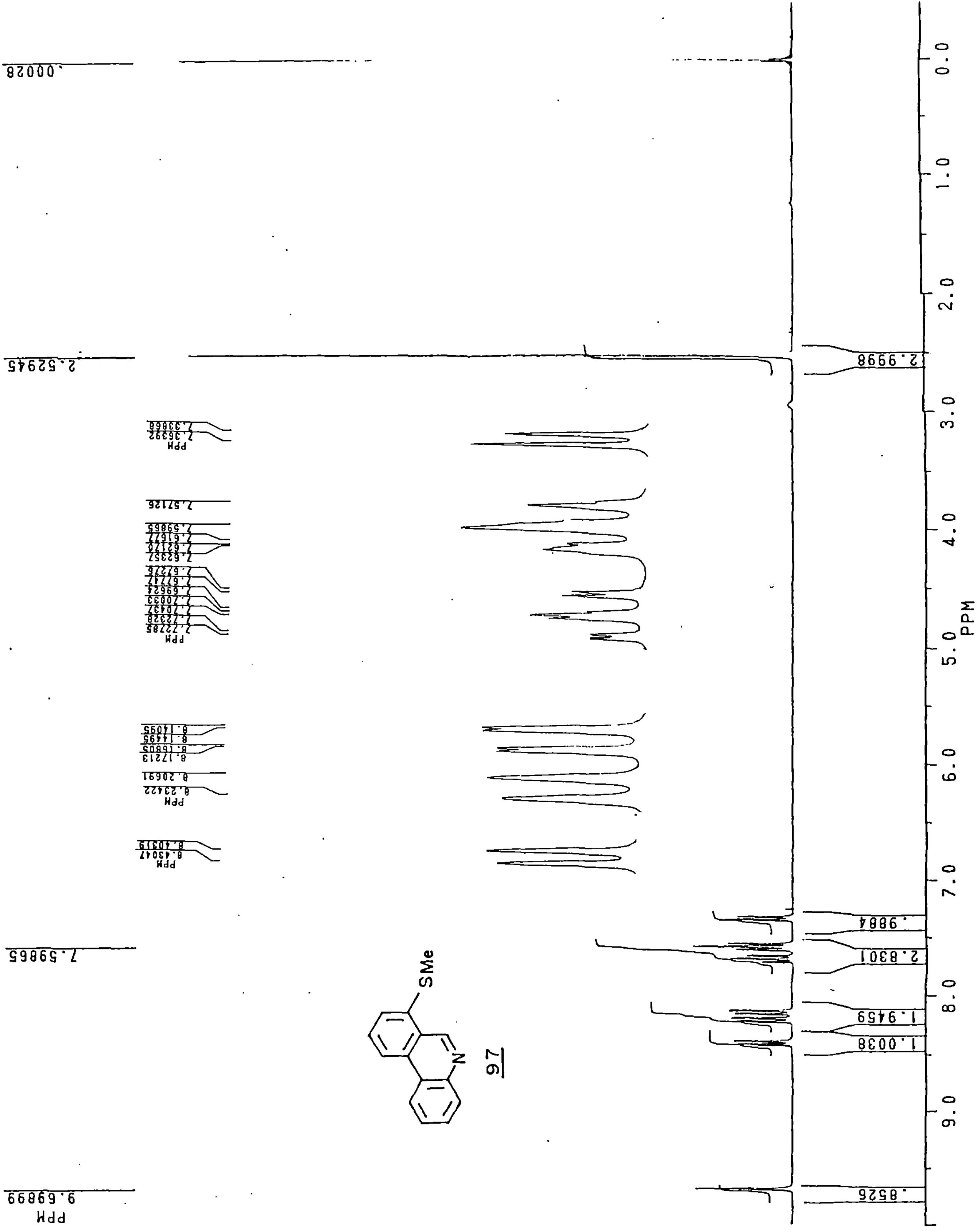
Light yellow crystals; mp. 164-166°C; yield 51%; IR (KBr): 2898, 1651, 1596, 1550 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 2.51 (s, 3H, SCH_3), 4.63 (s, 2H, NCH_2), 7.30-8.10(m, 10H, ArH & olefinic H); (m/z, %): 345 (M^+, 11.9), 204 (M^+-141, 97.2). Anal. Calcd. for $C_{17}H_{15}NO_3S$ (345.415): C 59.10; H 4.37; N 4.05. Found: C 58.93; H 4.38; N 4.07.

5,6-Dihydro-7-methylthio-N-benzenesulphonylphenanthridine (96)

Colourless crystals (ether); mp. 160-161°C; yield 82%; IR (KBr): 2413, 1573, 1439 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.49 (s, 3H, SCH_3), 4.46 (s, 2H, NCH_2), 6.89-6.94(m, 2H, ArH), 7.01-7.07 (m, 3H, ArH), 7.11-7.17(m, 2H, ArH), 7.30-7.42(m, 2H, ArH-$H_{2\&3}$), 7.55 (dd, 1H, J = 9, 3Hz, ArH-H_{10}), 7.79 (dd, 1H, J = 9Hz, 3Hz, ArH-H_1); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.41 (SCH_3), 46.17 (NCH_2), 120.20, 124.07, 125.89, 126.67, 127.50, 127.80, 128.00, 128.18, 128.53, 129.67, 130.35, 131.29, 132.23, 135.44, 135.63, 137.58; MS (m/z, %): 367 (M^+, 30.8), 368 (M^++1, 7.3), 226 (M^+-141, 100). Anal. Calcd. for $C_{20}H_{17}NO_2S_2$ (367.467): C 65.36; H 4.66; N 3.81. Found: C 65.12; H 4.61; N 3.79.

7-Methylthiophenanthridine (97)

Colourless crystals (ether); mp. 123-124°C; Yield 97%; IR (KBr): 2986, 1595, 1563 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.53 (s, 3H, SCH_3), 7.35 (d, 1H, J = 7.8 Hz, ArH_8), 7.57-7.62(m, 2H, ArH-$H_{9\&3}$), 7.67-7.72(m, 1H, ArH-H_2), 8.15 (dd, 1H, J = 8Hz, 1.2Hz, ArH-H_{10}), 8.22 (d, 1H, J = 8.4Hz, ArH-H_4), 8.41 (d, 1H, J = 9Hz, ArH-H_1), 9.69 (s, 1H, ArH-H_6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.93 (SCH_3), 118.66, 122.41, 123.68, 123.73,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1.0038
.8526
0.0
1.0
2.0
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4.0
5.0
6.0
7.0
8.0
9.0
PPM

97

124.32, 127.02, 128.77, 129.91, 130.53, 133.02, 138.72, 144.13, 149.45; MS (m/z, %): 225 (M^+, 100), 226 (M^++1, 22.9), 210 (M^+-15, 40.3). Anal. Calcd. for $C_{14}H_{11}NS$ (225.301): C 74.63; H 4.92; N 6.21. Found : C 74.57; H 4.89; N 6.18.

Phenanthridine (1)

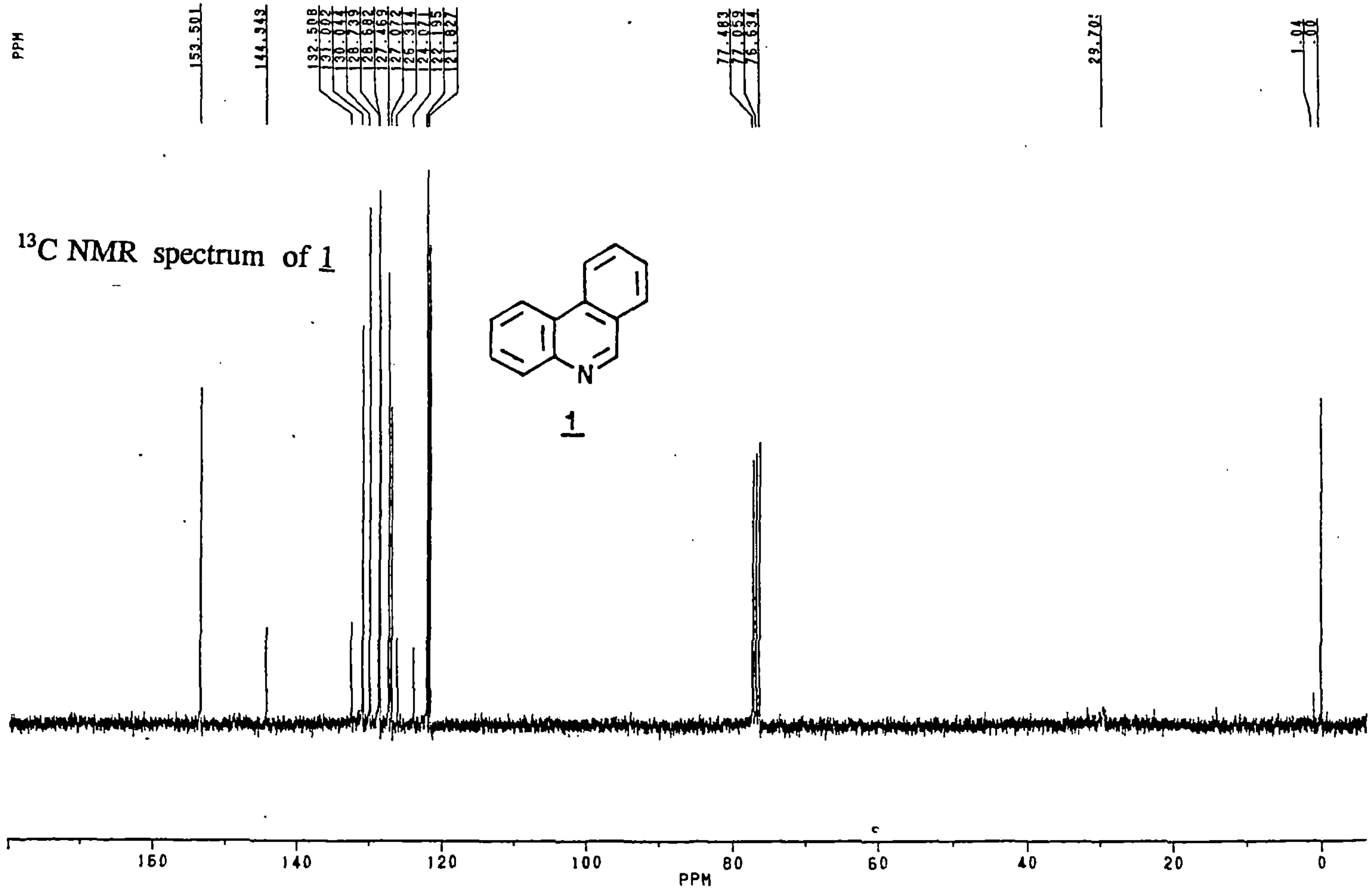
Colourless crystals (ether); mp. 105-106°C, ^{lit}104°C; Yield 62%; IR(KBr): superimposable; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59-7.81 (m, 4H, ArH), 7.96 (d, 1H, J = 7.86Hz, ArH), 8.17 (d, 1H, J = 7.86Hz, ArH), 8.17 (dd, 1H, J = 8Hz, 1.32Hz, ArH), 8.49 (t, 2H, J = 9Hz, ArH), 9.23 (s, 1H, ArH-H_6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 121.73, 122.10, 123.99, 126.27, 126.97, 127.35, 128.59, 128.63, 130.04, 130.87, 132.43, 144.34, 153.39.

9-Methyl-7-methylthiophenanthridine (104)

Colourless crystals (ether); mp. 103-104°C; yield 84%; IR (KBr): 2673, 1563, 1440 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.60 (s, 6H, SCH_3, CH_3), 7.45 (s, 1H, ArH-H_8), 7.60-7.92 (m, 2H, ArH), 8.30 (s, 1H, ArH-H_{10}), 8.30-8.35 (m, 1H, ArH), 8.52-8.70 (m, 1H, ArH), 9.91 (s, 1H, ArH-H_6); MS (m/z, %): 239 (M^+, 100), 240 (M^++1, 36.9), 224 (M^+-15, 78.6). Anal. Calcd. for $C_{15}H_{13}NS$ (239.321): C 75.27; H 5.47; N 5.85. Found : C 75.16; H 5.42; N 5.81.

3-[Bis(methylthio)methylene]-4-hydroxy-4-(2'-propargyl)-1,2,3,4-tetrahydro-N-benzenesulphonylquinoline (105)

Colourless crystals (ether); mp. 144°C; yield 71% ; IR (KBr): 2976, 1578, 1441, 1369cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.84 (t, 1H, J = 3Hz, methyne proton), 2.27 (s, 3H, SCH_3), 2.36 (s, 3H, SCH_3), 2.79 (qd, 2H, J = 18, 3Hz, CH_2), 4.39 (d, 1H, J = 16.3Hz, methylene proton), 5.36 (d, 1H, 16.3Hz, methylene proton), 7.24-7.38 (m, 4H, ArH), 7.46-7.57 (m, 4H, ArH), 7.67 (dd, 1H, J = 7.8Hz, 1.8Hz, ArH); ^{13}C NMR (75 MHz,



^{13}C NMR spectrum of 1

$CDCl_3$): δ 16.96 (SCH_3), 17.69 (SCH_3), 33.87 (NCH_2), 52.27 (OCH_3), 71.52, 74.18, 79.44, 124.68, 126.49, 127.23, 127.41, 128.27, 128.70, 132.78, 134.59, 136.28, 139.09, 143.41. Anal. Calcd. for $C_{21}H_{21}NO_3S_3$ (417.57): C 60.34; H 5.07; N 3.35. Found: C 60.21; H 4.98; N 3.36.

1,2-Dihydro-3-methoxycarbonyl-4-(2'-propargyl)-N-benzenesulphonylquinoline(106)

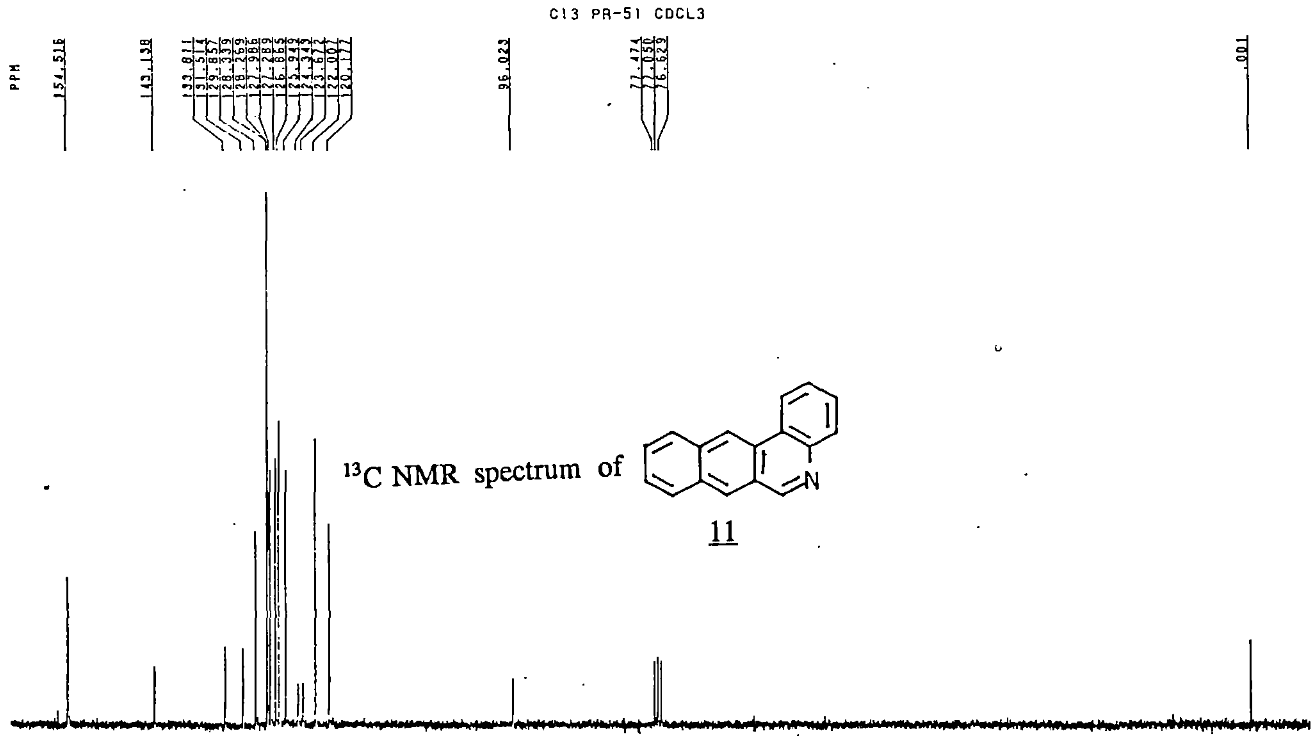
Colourless crystals (ether); mp. 107-108°C; yield 97%; IR (KBr): 2952, 1718 (CO), 1616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.88 (t, 1H, J = 3Hz, CH), 3.36 (d, 2H, J = 3Hz, CH_2), 3.82 (s, 3H, OCH_3), 4.63 (s, 2H, NCH_2), 7.22-7.47 (m, 7H, ArH), 7.60 (dd, 1H, J = 1.5Hz, 8 Hz, ArH), 7.76 (dd, 1H, J = 8, 1.3Hz, ArH). Anal. Calcd. for $C_{20}H_{17}NO_4S$ (367.411): C 65.37; H 4.66; N 3.81. Found: C 65.13; H 4.58; N 3.79.

5,6-dihydro-N-benzenesulphonylbenzo[J]phenanthridine (109)

Colourless crystals (hexane,ether); mp. 141°C; yield 87%; IR (KBr): 2910, 1443, 1345, 1165cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.93 (s, 2H, NCH_2), 6.56-6.61 (m, 2H, ArH), 6.80-6.85 (m, 1H, ArH) 7.00-7.03 (m, 2H, ArH), 7.33-7.43 (m, 4H, ArH) 7.46 (s, 1H, ArH), 7.60-7.71 (m, 4H, ArH) 7.81-7.83 (m, 1H, ArH); ^{13}C NMR (75MHz, $CDCl_3$): δ 50.40 (NCH_2), 122.21, 124.25, 124.54, 126.07, 126.40, 127.03, 127.20, 127.48, 127.67, 127.85, 128.18, 128.46, 128.73, 129.38, 130.78, 131.91, 132.49, 132.87, 136.22, 137.06; MS (m/z, %): 371 (M_+, 32.4), 230 (M^+-141, 99.1). Anal. Calcd. for $C_{23}H_{17}NO_2S$ (371.441): C 74.36, H 4.61; N 3.77. Found: C 74.21; H 4.59; N 3.72.

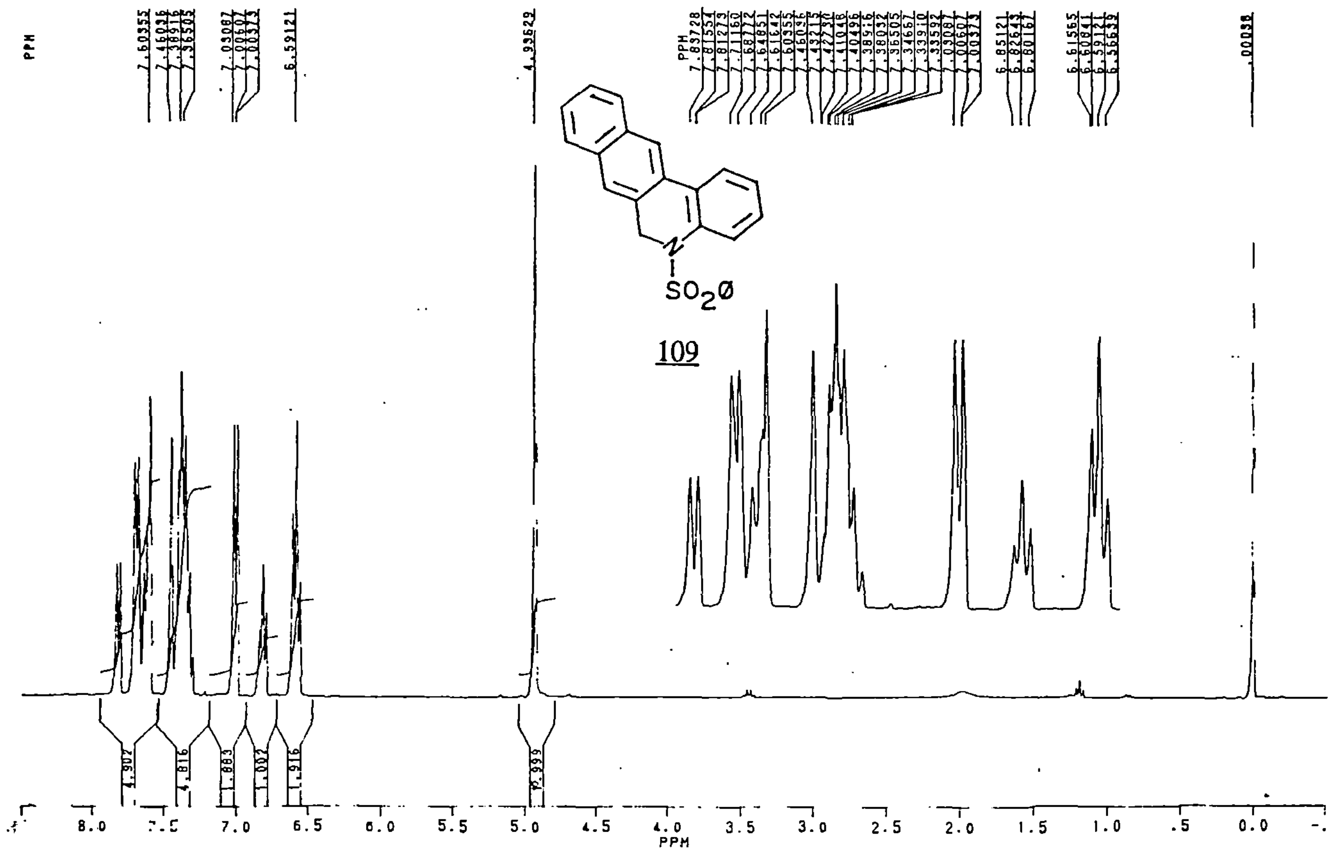
Benzo[j]phenanthridine (11)

Colourless crystals (hexane-ether); mp 143°C; yield 98%; IR (KBr): 1949, 1622, 1603, 1492 cm^{-1}; 1 H NMR (90 MHz, CDC13): δ 7.41-8.50 (m, 8H, ArH), 8.20 (s, 1H, ArH_7), 8.70 (s, 1H, ArH_{12}), 9.20 (s, 1H, ArH_6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 120.177, 122.007, 123.67, 124.34, 125.95, 126.86, 127.29, 127.98, 128.27, 128.34, 129.85, 131.51, 133.81,



^{13}C NMR spectrum of

11



109

143.13, 154.51. Anal. Calc. for $C_{17}H_{11}N$ (229.267): C 89.05; H 4.83; N 6.11. Found: C 89.24; H 4.81; N 6.10.

5,6-Dihydro-7-methylthio-9-methoxy-N-benzenesulphonylbenzo[J]phenanthridine (111)

Light yellow crystals (ether); mp. 191°C; yield 65%; IR (KBr) : 2918, 1617, 1496 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H, SCH_3), 4.01 (s, 3H, OCH_3), 5.41 (s, 2H, NCH_2), 6.65-6.71 (m, 2H, ArH), 6.87-6.92 (m, 1H, ArH), 7.02-7.05 (m, 2H, ArH), 7.12 (dd, 1H, J = 9, 2.5Hz, ArH), 7.34-7.45 (m, 2H, ArH), 7.58 (s, 1H, ArH- H_{12}), 7.59 (d, 1H, J = 8.7Hz, ArH), 7.67 (dd, 1H, J = 9Hz, 3Hz, ArH), 7.82 (dd, 1H, J = 9, 3Hz, ArH), 7.91 (d, 1H, J = 3Hz, ArH); ^{13}C NMR (75MHz, $CDCl_3$): δ 18.95 (SCH_3), 48.85 (NCH_2), 55.38 (OCH_3), 104.38, 119.08, 123.42, 124.01, 126.80, 127.15, 127.54, 128.09, 128.26, 128.48, 129.05, 130.17, 131.07, 131.93, 135.46, 135.52, 135.99, 137.33, 158.93; MS (m/z, %): 447 (M^+, 24.8), 306 (M^+-141, 57.4). Anal. Calcd. for $C_{25}H_{21}NO_3S_2$ (447.547): C 67.08; H 4.73; N 3.13. Found: C 66.87; H 4.69; N 3.08.

7-Methylthio-9-methoxybenzo[J]phenanthridine (112)

Dark red crystals; mp. 175°C; yield 94%; IR (KBr): 2928, 1619, 1490, 1463 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.34 (s, 3H, SCH_3), 3.92 (s, 3H, OCH_3), 7.18 (dd, 1H, J = 9,2.4Hz, ArH-H_{10}), 7.55 (t, 1H, J = 7.8Hz, ArH-H_2), 7.63 (t, 1H, J = 7.8 Hz, ArH-H_3), 7.76 (d, 1H, J = 9Hz, ArH-H_{11}), 7.98 (s, 1H, ArH-H_8), 8.09 (d, 1H, J = 7.8Hz, ArH-H_4), 8.40 (d, 1H, J = 7.8Hz, ArH-H_1), 8.65 (s, 1H, ArH-H_{12}), 10.17 (s, 1H, ArH-H_6); ^{13}C NMR (75MHz, $CDCl_3$): δ 20.40 (SCH_3), 55.36 (OCH_3), 103.18, 121.83, 121.97, 122.03, 123.68, 126.21, 127.14, 127.55, 128.20, 129.87, 130.09, 130.54, 132.34, 135.44, 142.68, 153.36, 158.81; MS (m/z, %): 305 (M^+,100), 306 (M^++1, 22.5), 290 (M^+-15, 76). Anal. Calcd. for $C_{19}H_{15}NOS$ (305.381): C 74.72; H 4.95; N 4.58. Found : C 74.67; H 4.91; N 4.61.

5,6-Dihydro-9,10-dimethoxy-7-methylthio-N-benzenesulphonylbenzo[J]phenanthridine (113)

Light yellow crystals (ether); mp. 192°C; yield 67%; IR(KBr): 1616, 1497, 1488, 1468 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H, SCH_3), 3.99 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 5.36 (s, 2H, NCH_2), 6.66-6.71 (m, 2H, ArH), 6.88-6.94 (m, 1H, ArH), 6.98 (s, 1H, ArH-H_{11}), 7.04 (dd, 2H, J = 8.49,3Hz, ArH), 7.32-7.42 (m, 2H, ArH-$H_{2\&3}$), 7.52 (s, 1H, ArH-H_8), 7.66 (dd, 1H, J = 7.7,3Hz, ArH-H_4), 7.81 (dd, 1H, J = 7.4,3Hz, ArH-H_1), 7.90 (s, 1H, ArH- H_{12}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.05 (SCH_3), 48.68 (NCH_2), 55.88 (OCH_3), 55.97 (OCH_3), 104.97, 106.84, 122.11, 124.03, 126.79, 127.53, 127.56, 127.68, 128.02, 128.18, 128.75, 128.84, 130.17, 131.18, 131.90, 133.06, 135.98, 137.41, 149.63, 150.58; MS (m/z, %) : 477 (M^+, 10.7), 336 (M^+-141, 13.1). 289 (M^+-141-47, 18.6). Anal. Calcd. for $C_{26}H_{23}NO_4S_2$ (477.567): C 65.38; H 4.85; N 2.93. Found : C 65.23; H 4.80; N 2.91.

9,10-Dimethoxy-7-methylthiobenzo[J]phenanthridine (114)

Dark red crystals (ether); mp. 179-180°C; yield 92%; IR (KBr): 2907, 1619, 1482, 1458 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H, SCH_3), 3.99 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 6.96 (s, 1H, ArH- H_{11}), 7.52 (t, 1H, J = 7.5Hz, ArH), 7.61 (t, 1H, J = 7.8 Hz, ArH- H_2), 7.91 (s, 1H, ArH-H_8), 8.06 (d, 1H, J = 7.8Hz, ArH-H_4), 8.32 (d, 1H, J = 7.8Hz, ArH-H_1), 8.41 (s, 1H, ArH-H_{12}), 10.05 (s, 1H, ArH-H_6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.44 (SCH_3), 55.78 (two OCH_3), 104.01, 105.71, 119.58, 121.62, 123.42, 124.42, 126.71, 128.00, 128.07, 129.69, 130.68, 131.79, 142.67, 150.98, 151.07, 152.92; MS (m/z, %): 335 (M^+, 100), 336 (M^++1, 23.2). Anal. Calcd. for $C_{20}H_{17}NO_2S$ (335.411): C 71.61; H 5.11; N 4.17. Found : C 71.48; H 5.08; N 4.13.

5,6-Dihydro-9,10-methylenedioxy-7-methylthio-N-benzenesulphonyl-

benzo[J]phenanthridine (115)

Light yellow crystals (ether); mp. 199-200°C; yield 73%; IR(KBr): 2916, 1489, 1460, 1348 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, SCH_3), 5.35 (s, 2H, NCH_2), 6.07 (s, 2H, OCH_2O), 6.68-6.73(m, 2H, ArH), 6.91 (m, 1H, ArH), 6.94 (s, 1H, ArH-H_{11}), 7.03 (d, 2H, J = 6Hz, ArH), 7.35-7.40(m, 2H, ArH-$H_{2\&3}$), 7.45 (s, 1H, ArH-H_8), 7.64 (dd, 1H, J = 6, 1.8Hz, ArH-H_4), 7.81 (dd, 1H, J = 6, 1.8Hz, ArH-H_1), 7.92 (s, 1H, ArH-H_{12}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.17 (SCH_3), 48.68 (NCH_2), 101.40 (CH_2), 102.86, 104.25, 122.70, 124.03, 126.82, 127.54, 127.59, 127.92, 128.06, 128.33, 129.47, 130.26, 130.97, 131.85, 131.93, 133.44, 136.08, 137.47, 147.78, 149.13; MS (m/z, %): 461 (M^+, 49.7), 320 (M^+-141, 80.8), 273 (M^+- 141-47, 100). Anal. Calcd. for $C_{25}H_{19}NO_4S_2$ (461.527): C 65.05; H 4.15; N 3.03. Found : C 64.89; H 4.12; N 2.97.

9,10-Methylenedioxy-7-methylthiobenzo[J]phenanthridine (116)

Colourless crystals (ether); mp. 235°C; yield 93%; IR (KBr): 2920, 1612, 1592, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H, SCH_3), 6.12 (s, 2H, OCH_2O), 7.25 (s, 1H, ArH-H_{11}), 7.63-7.73 (m, 2H, ArH-$H_{2\&3}$), 8.15 (d, 1H, J = 7.8Hz, ArH-H_4); 8.21 (s, 1H, ArH-H_8); 8.58 (d, 1H, J = 8Hz, ArH-H_1), 8.76 (s, 1H, ArH-H_{12}); 10.25 (s, 1H, ArH-H_6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.75 (SCH_3), 101.75 (CH_2), 102.36, 103.65, 120.92, 121.99, 123.57, 125.13, 127.13, 128.46, 128.70, 129.93, 132.57, 132.72, 133.20, 143.05, 149.47, 149.80, 153.44; MS (m/z, %): 319 (M^+, 100), 320 (M^++1, 22.9). Anal. Calcd. for $C_{19}H_{13}NO_2S$ (319.361): C 71.45: H 4.10; N 4.38. Found: C 71.38; H 4.08; N 4.35.

5,6-Dihydro-10,11-dimethoxy-7-methylthio-N-benzenesulphonyl benzo[J]phenanthridine (117)

Colourless crystals (ether); mp. 164°C; yield 75%; IR(KBr): 3070, 1598, 1463, 1060 cm^{-1};

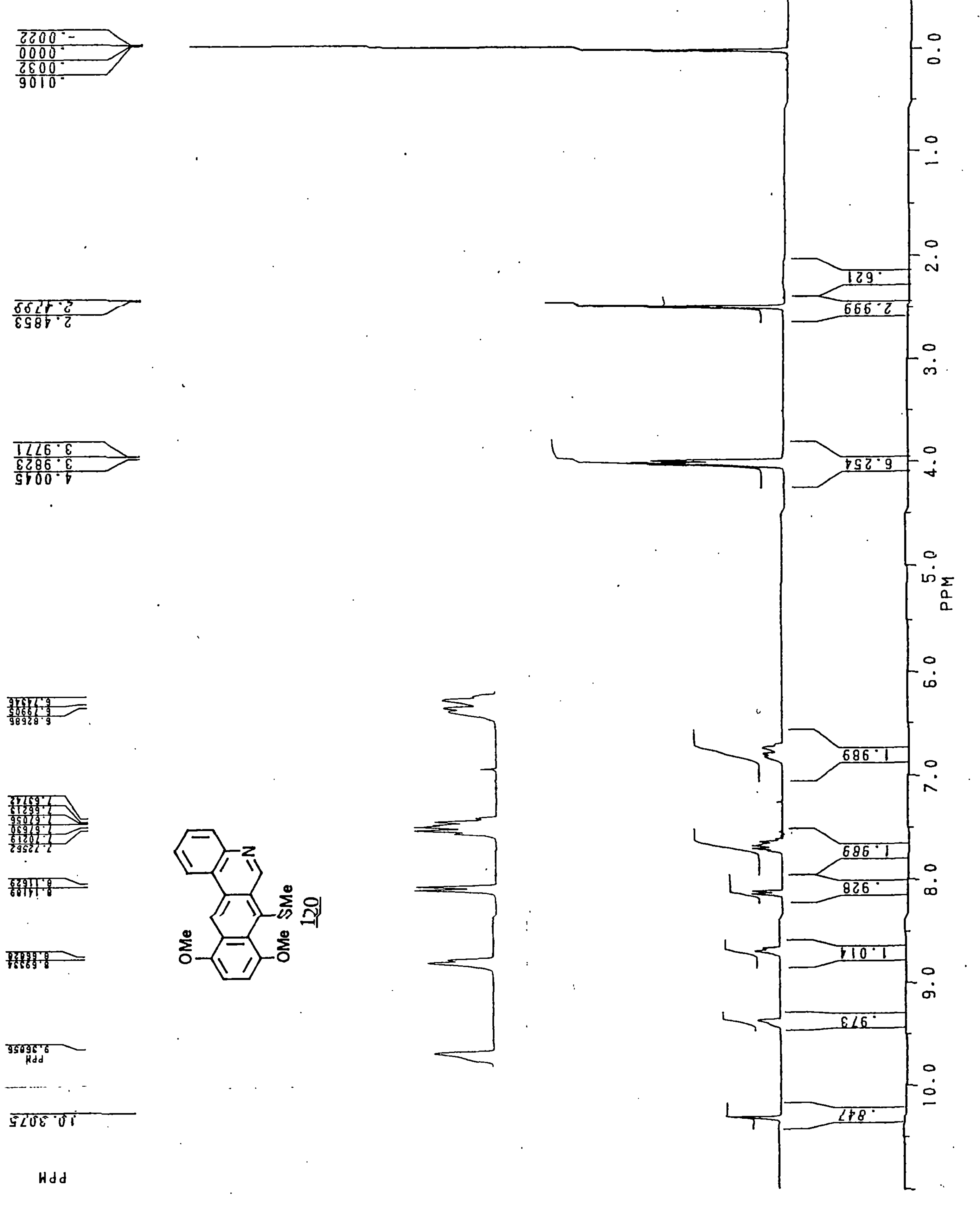
^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H, SCH_3), 3.93 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 5.37 (s, 2H, NCH_2), 6.64-6.69(m, 2H, ArH), 6.88 (m, 1H, ArH-H_2), 7.02 (d, 1H, J = 9Hz, ArH-H_8), 7.05 (d, 1H, J = 9Hz, ArH-H_9), 7.33 - 7.46 (m, 3H, ArH), 7.76-7.86 (m, 2H, ArH-H_3), 7.95 (s, 1H, ArH-H_{12}), 8.32 (d, 1H, J = 9Hz, ArH-H_1); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.40(SCH_3), 48.76(OCH_3), 56.5(OCH_3), 61.11(NCH_2), 115.60, 116.92, 122.63, 124.71, 126.80, 127.57, 127.6, 128.0, 128.65, 128.8, 129.5, 130.66, 131.3, 131.8, 133.21, 136.4, 137.46, 142.91, 148.46; MS (m/z, %): 477 (M^+, 97.9), 336 (M^+-141, 87.0), 289 (M^+- 141-47, 100). Anal. Calcd. for $C_{26}H_{23}NO_4S_2$ (477.567): C 65.38; H 4.85; N 2.93. Found: C 65.21; H 4.81; N 2.89.

10,11-Dimethoxy-7-methylthiobenzo[J]phenanthridine (118)

Colourless crystals (ether); mp. 143°C; Yield 93%; IR (KBr): 3500, 1530, 1384 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H, SCH_3), 4.08 (s, 3H, OCH_3), 4.13 (s, 3H, OCH_3), 7.51 (d, 1H, J = 9Hz, ArH-H_9), 7.64-7.74(m, 2H, ArH); 8.13 (d, 1H, J = 9Hz, ArH- H_8); 8.75 (m, 2H, ArH-$H_{1\&4}$), 9.36 (s, 1H, ArH-H_{12}), 10.26 (s, 1H, ArH-H_6); ^{13}C NMR (75MHz, $CDCl_3$): δ 21.10 (SCH_3), 56.70 (OCH_3); 61.10 (OCH_3), 115.29, 117.09, 122.4, 123.6, 123.7, 123.8, 125.0, 127.10, 127.20, 128.70, 129.70, 129.80, 129.90, 130.31, 143.23, 148.76, 153.56; MS (m/z, %): 335 (M^+, 100); 320 (M^+-15, 47.4). Anal. Calcd. for $C_{20}H_{17}NO_2S$ (335.411): C 71.61; H 5.11; N 4.17. Found: C 71.52; H 5.08; N 4.18.

5,6-Dihydro-8,11-dimethoxy-7-methylthio-N-benzenesulphonylbenzo[J]phenanthridine (119)

Yellow crystals (ether); mp. 160-161°C; yield 78%; IR (KBr): 2915, 2832, 1613, 1489 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H, SCH_3), 3.92 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 5.42 (s, 2H, NCH_2), 6.66-6.71 (m, 3H, ArH), 6.85-6.92 (m, 2H, ArH-$H_{1\&4}$), 7.03-7.07(m, 2H, ArH), 7.33-7.44(m, 2H, ArH-$H_{2\&3}$), 7.73-7.83 (m, 2H, ArH-$H_{9\&10}$), 8.07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7.67056
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7.70219
7.72562
8.11629
8.14109
8.66828
8.69334
9.36056
10.3075
PPM
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2.999
6.254
1.989
1.989
.928
1.014
.973
.847
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
PPM
N
OMe
SMe
OMe
120

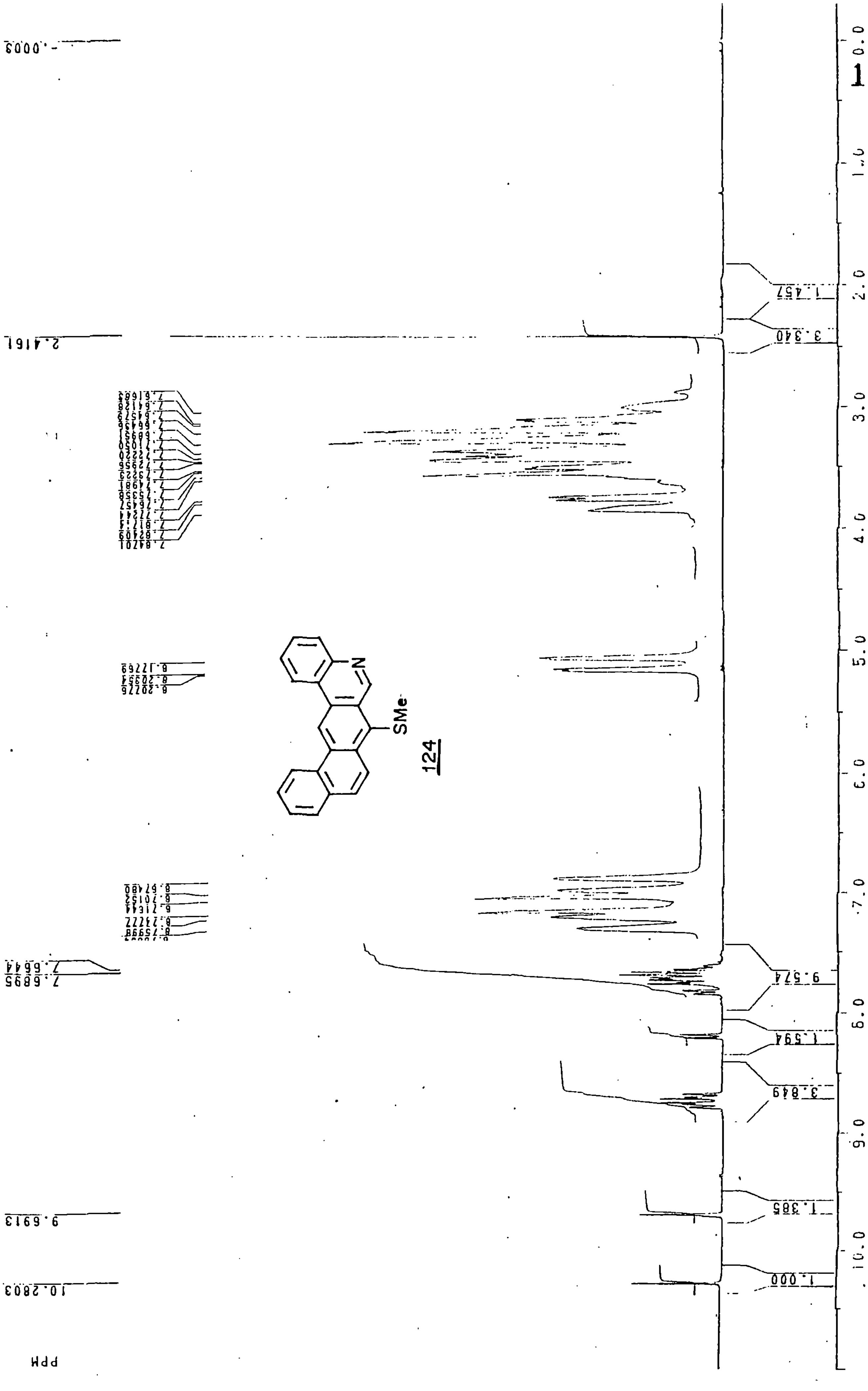
(s, 1H, ArH-H_{12}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.97 (SCH_3), 48.76 (NCH_2), 55.82 (OCH_3), 57.38 (OCH_3), 104.01, 109.33, 117.50, 124.67, 126.62, 126.79, 126.84, 127.47, 127.65, 127.85, 128.50, 128.66, 129.43, 131.21, 131.88, 135.81, 136.33, 137.37, 150.02, 150.48; MS (m/z, %): 477 (M^+, 32.2%); 336 (M^+-141, 98.0). Anal. Calcd. for $C_{26}H_{23}NO_4S_2$ (477.567): C 65.38; H 4.85; N 2.93. Found: C 65.31; H 4.82; N 2.89.

8,11-Dimethoxy-7-methylthiobenzo[J]phenanthridine (120)

Yellow crystals (ether); mp. 169-170°C; yield 98%; IR (KBr): 2916, 1615, 1594, 1335, 1259 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.48 (s, 3H, SCH_3), 3.98 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 6.47-6.82 (m, 2H, ArH), 7.63-7.72 (m, 2H, ArH), 8.12 (d, 1H, J = 9Hz, ArH_{10}), 8.68 (d, 1H, J = 9Hz, ArH_1), 9.36 (s, 1H, ArH-H_{12}), 10.30 (s, 1H, ArH-H_6); ^{13}C NMR (75 MHz): δ 23.15 (SCH_3), 55.81 (OCH_3), 56.75 (OCH_3), 104.02, 107.36, 115.77, 122.67, 123.92, 126.45, 127.14, 127.40, 128.24, 128.72, 129.28, 129.69, 135.85, 143.05, 149.62, 151.15, 153.99; MS (m/z, %): 335 (M^+, 100), 336 (M^++1, 23.9), 320 (M^+-15, 52.4). Anal. Calcd. for $C_{20}H_{17}NO_2S$ (335.411): C 71.61; H 5.11; N 4.17. Found: C 71.58; H 5.07; N 4.21.

5,6-Dihydro-7-methylthio-N-benzenesulphonylnaphtho[1,2-J] phenanthridine (123)

Light yellow crystals (ether); mp. 184-186°C; yield 69%; IR (KBr): 1595, 1578, 1508, 1436, 1345 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, SCH_3), 5.37 (s, 2H, NCH_2), 7.37-7.41 (m, 2H, ArH); 7.52-7.61 (m, 3H, ArH), 7.73-7.76 (m, 2H, ArH), 7.81-7.85 (m, 2H, ArH), 8.41 (s, 1H, ArH), 8.48-8.52 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.48 (SCH_3), 48.55 (NCH_2), 116.40, 118.02, 122.35, 124.30, 126.67, 126.76, 126.93, 127.48, 127.54, 128.04, 128.29, 128.42, 128.52, 128.63, 129.43, 130.06, 130.09, 131.08, 131.62, 132.78, 135.21, 136.34, 137.27; MS(m/z, %): 467 (M^+, 18.2), 326 (M^+-141, 53.7), 279


-.0003
2.4161
7.61685
7.64128
7.64529
7.66496
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7.72220
7.72956
7.73223
7.74981
7.75358
7.76452
7.77244
7.81214
7.82409
7.84201
8.17269
8.20354
8.20276
8.67480
8.70152
8.71644
8.74722
8.75998
7.6895
7.6644
9.6913
10.2803
PPM
1.457
3.340
9.574
1.594
3.849
1.385
1.000
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
PPM
N
SMe

124

(M^+-141-47, 100). Anal Calcd. for $C_{28}H_{21}NO_2S_2$ (467.577): C 71.92; H 4.52; N 2.99. Found: C 71.87; H 4.20; N 2.81.

7-methylthionaphtho[1,2-J]phenanthridine (124)

Light yellow crystals (ether); mp. 188-190°C; yield 91%; IR (KBr): 2997, 1635, 1505, 1214 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H, SCH_3), 7.61-7.84 (m, 6H, ArH), 8.19 (dd, 1H, J = 9.02, 1.26Hz, ArH), 8.67-8.78 (m, 3H, ArH), 9.69 (s, 1H, ArH-H_{14}), 10.28 (s, 1H, ArH-H_6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.13 (SCH_3), 114.71, 116.49, 122.08, 122.80, 123.18, 123.75, 124.69, 125.90, 126.01, 126.45, 127.17, 127.24, 128.08, 128.68, 128.82, 128.92, 130.00, 130.06, 132.21, 133.40, 135.17; MS (m/z, %): 325 (M^+, 17.4), 310 (M^+-15, 13.6), 326 (M^++1,5); Anal. Calcd. for $C_{22}H_{15}NS$ (325.411): C 81.19; H 4.64; N 4.30. Found : C 80.84; H 4.52; N 4.21.

5,6-Dihydro-N-benzenesulphonylphenanthridine (99)

Colourless crystals (ether); mp. 146°C; yield 79%; IR (KBr): 2489, 1439, 1310 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 4.52 (s, 2H, NCH_2), 6.92-7.83 (m, 13H, ArH). Anal. Calcd. for $C_{20}H_{17}NO_2S_2$ (367.467): C 65.36; H 4.66; N 3.81. Found: C 65.12; H 4.61; N 3.79.

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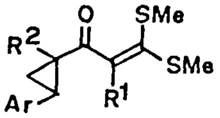
CHAPTER - 4

Tandem Carbocationic cyclization Studies on 1-[2-Bis(methylthio)methylene]propanoyl]-2-styrylcyclopropanes.

The interest in the chemistry of cyclopentanoids continues to attract the attention of many synthetic chemists due to wide spread occurrance in many natural products containing cyclopentane ring[1-7]. A number of efficient methods have already been developed involving the synthesis of many important natural products and the literature in the subject have increased enormously in recent years with the appearance of many excellant reviews covering major development in this area[8-20]. Few years back a new intramolecular alkylation approach leading to substituted cyclopentanones was developed in our laboratory,[21] through acid induced ring opening and rearrangement of cyclopropyl ketone **7** carrying bis(methylthio)methylene moiety.

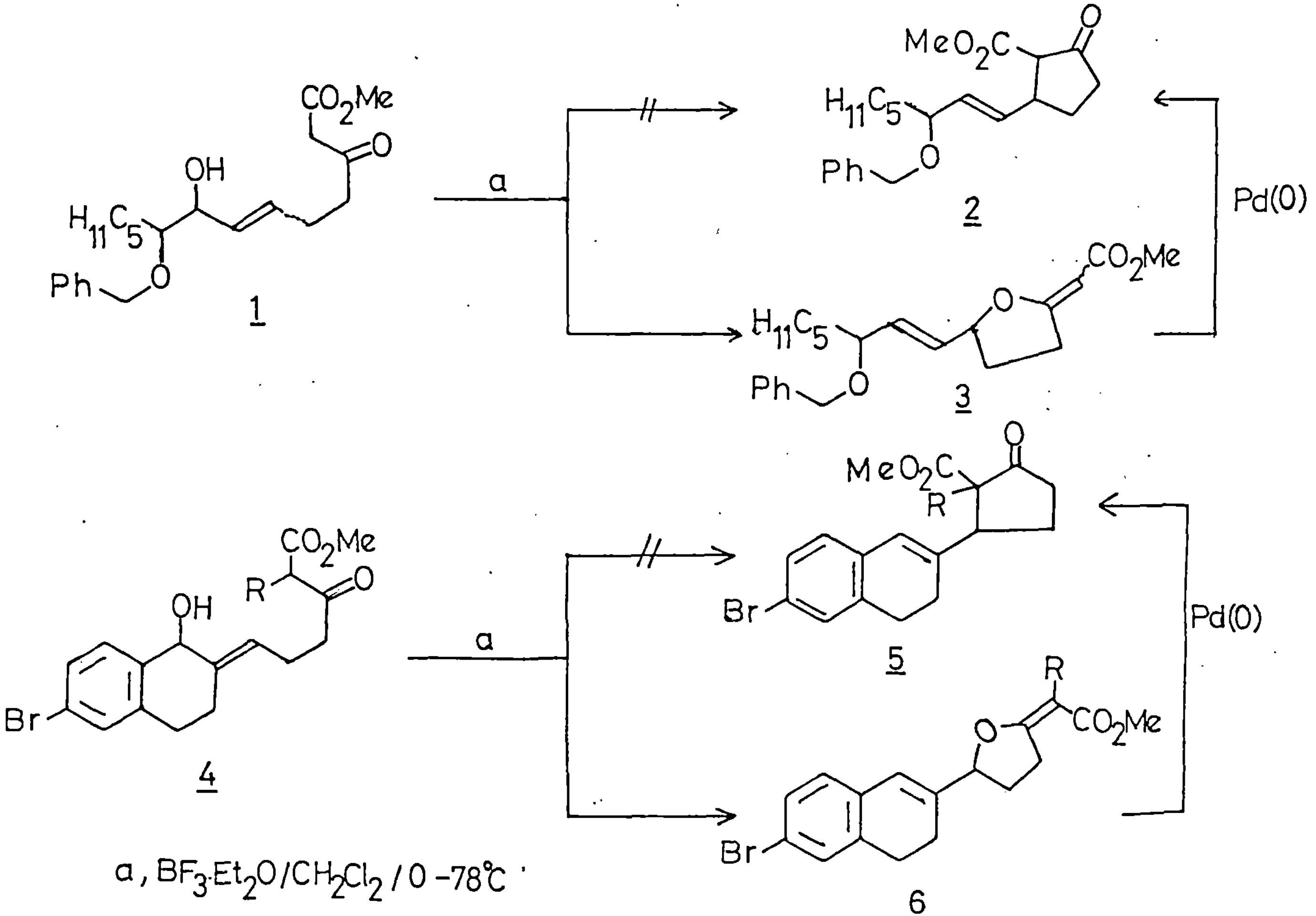


7

Thus these ketones were shown to undergo facile acid assisted cyclopropyl ring opening and subsequent intramolecular participation of mercapto double bond to the corresponding cyclopentanoids. This new general method for the synthesis of cyclopentanoids has been extensively investigated in our laboratory[22] and the scope of the reaction is defined. The present approach was important in the light of earlier findings for the synthesis of cyclopentanone ring through popular approach involving intramolecular cyclization[8,23] of the enolate anion of τ-haloketones or the corresponding ß-ketoesters which led to the corresponding alkylidine tetrahydrofurans through O-alkylative process instead of cyclopentanones. This propensity of O-alkylation to yield alkylidine tetrahydrofurans was attributed to stereoelectronic factors associated with the formation of 5-membered cyclopentanone ring involving disfavoured 5-endotrig process, according to Baldwin Rule[24]. However these difficulties were circumvented by Barry M.Trost through developing an efficient method to convert these easily accessible alkylidine tetrahydrofurans **3** and **6** to the desired cyclopentanones **2** and **5** respectively by using Pd(0) as catalyst[23] (Scheme-1).

In our approach, the initially generated carbocation through acid induced ring opening of cyclopropyl ring is intramolecularly trapped by mercapto double bond, which is a masked ß-Ketoester functionality. Thus a series of communications[21,22a-c] have been published on the rearrangement of **7** to the corresponding cyclopentanoids in the presence of a number of acid catalylsts. In the forgoing section a brief review of the earlier works in this area from our laboratory has been described.

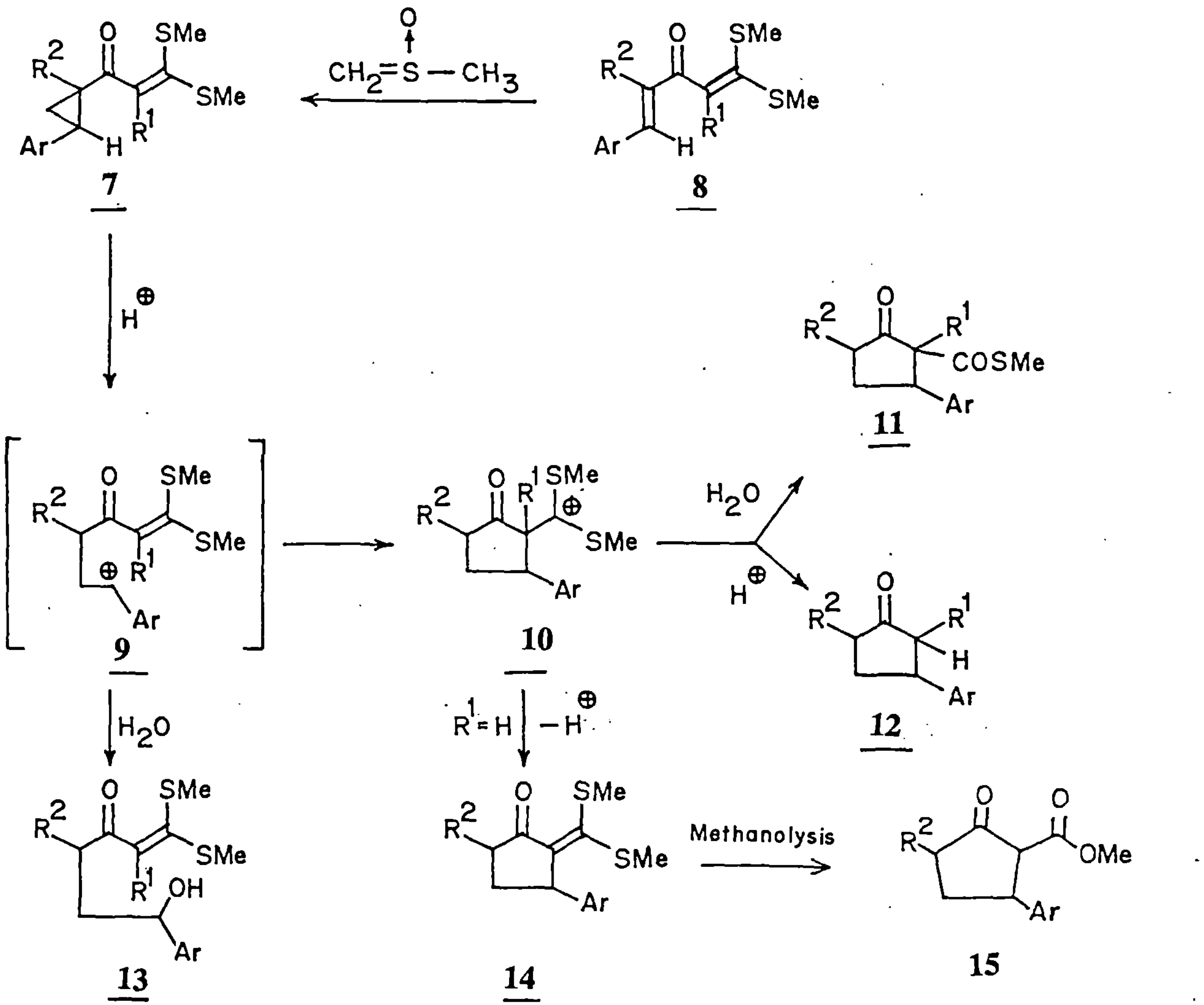
The application of cyclopropyl ketone of the general formula **7** having mercapto functionality for the synthesis of cyclopentanoids is first reported from our laboratory[21a] in 1988 as a new alternative model to τ-haloketones and the



a, $BF_3 \cdot Et_2O/CH_2Cl_2/0$ -78°C

Scheme 1

corresponding ß-ketoesters having the molecular configuration suitable for allowed 5-exotrig ring closure. The bis(methylthio)methylene cyclopropyl ketone **7** on treatment with a mixture of H_3PO_4 and formic acid (HCO_2H) yielded the ß-ketothioester **11** or the ketone **12** depending on the reaction conditions (Scheme-2). When **7** was treated with $SnCl_4$ in dry benzene the α-bis(methylthio)methylene cyclopentanone derivative **14** was obtained. The mercapto functionality in **14** could be transformed into the corresponding carbomethoxy group by treatment with methanolic $BF_3.Et_2O$. The mechanism governing this transformation involved the initial formation of the carbocation **9** which is intercepted by the mercapto double bond in the 5-exotrig fashion to yield the cyclopentanone **10** with a cation being stabilized on the exocyclic bis(methylthio) carbon which leads to the product cyclopentanones chain carbinol **13** obtained on treatment of **7** with $SnCl_4$ in nitromethane at -20°C. However when Ar = phenyl group, the envisaged cyclopentanone ring did not take place and only the open chain carbinol was isolated as the major product. Further attempts to introduce carbocation stabilizing substituents led to the investigation[22a] of α-bis(methylthio)methylene cyclopropyl ketones with olefinic double bond of general formula **17** (Scheme-3). Thus when **17** was treated with H_3PO_4/HCO_2H for 1hr at RT, the corresponding thiolester **21** was found in 73-77% yield. However when the reaction temperature was raised to 80°C (1hr), the thiomethylated product **22** was obtained in 81% yield. When the reaction was prolonged for more than one hour at 80°c the corresponding dethiocarbonylated product **23** was obtained as exclusive product. Interestingly when Ar=4-methoxyphenyl, **17** did not yield any of the expected product instead, the bicyclic ketone **19** was found in 60% yield. Similarly the bicyclic ketone **20** was formed when Ar = 4-methoxy phenyl group and n = 2 (Scheme- 3). The rearrangement was applied for the synthesis of 11- oxosteroid precursors **31** and **32** respectively (Scheme-4). The required cyclopropyl ketones **27a** and **27b** were synthesized as shown in Scheme-4. Thus when **27a** was treated with a mixture of H_3PO_4/HCO_2H, the bicyclic ketone **29** was obtained as only product while treatment of **27a** with $SnCl_4/C_6H_6$ gave the cyclopentanone **30a** with intact bis(methylthio)methylene moiety which subsequently yielded the α-carbomethoxy cyclopentanone on methanolysis in the presence of $BF_3.Et_2O/HgCl_2/MeOH$. The cyclopropyl Ketone **27b** on the other hand yielded the carbothioate **32**, a precursor for 11-oxosteroid[23b,c] on treatment with a mixture of H_3PO_4/HCO_2H (Scheme-4). In an another experiment the cyclopropyl ketones **7** were reduced with $NaBH_4$ to afford the corresponding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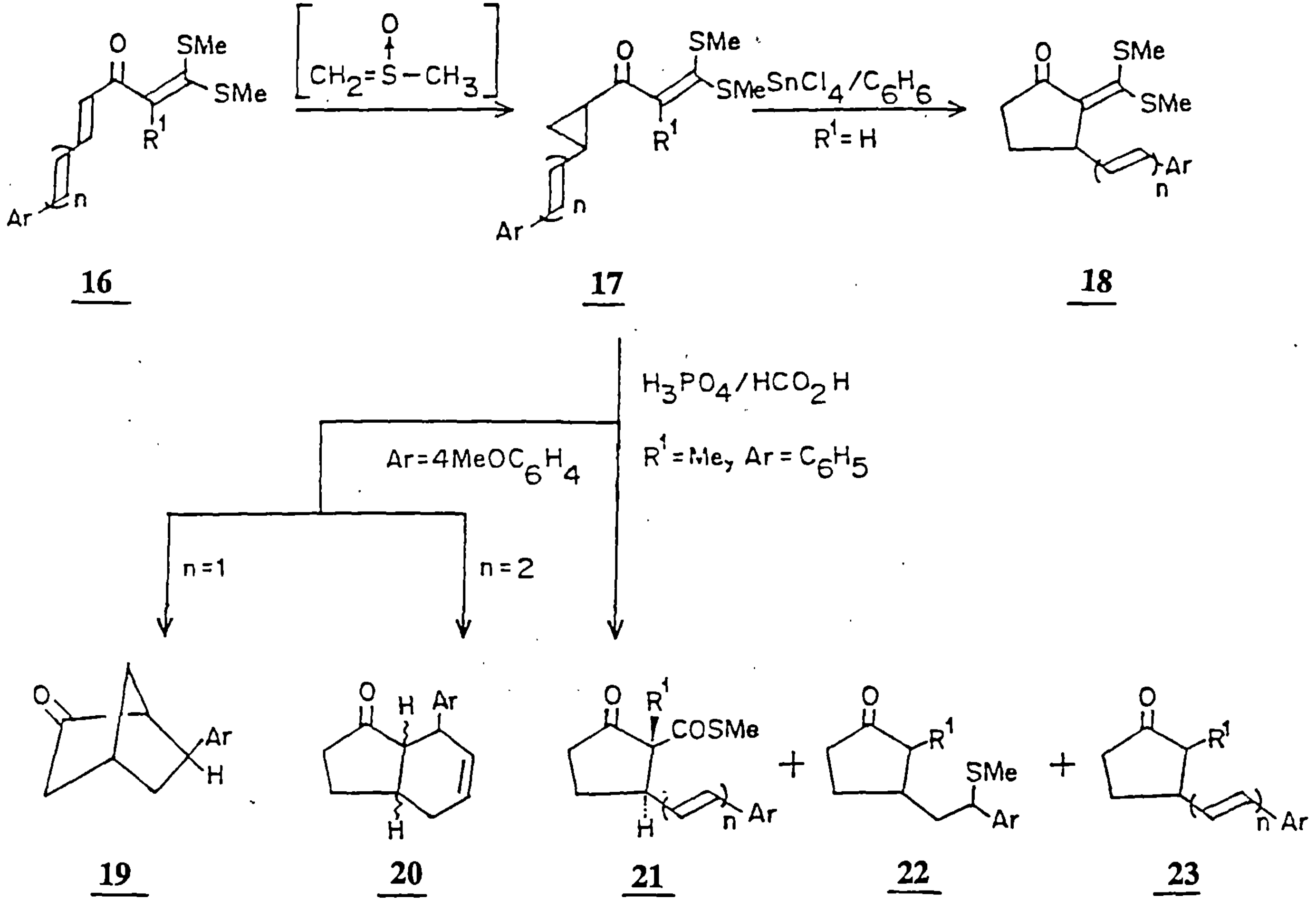
8
9
10
11
12
13
14
15
CH2=S—CH3 (O)
H⊕
H2O
H⊕
H2O
R1=H
−H⊕
Methanolysis
SMe
COSMe
OMe
Ar

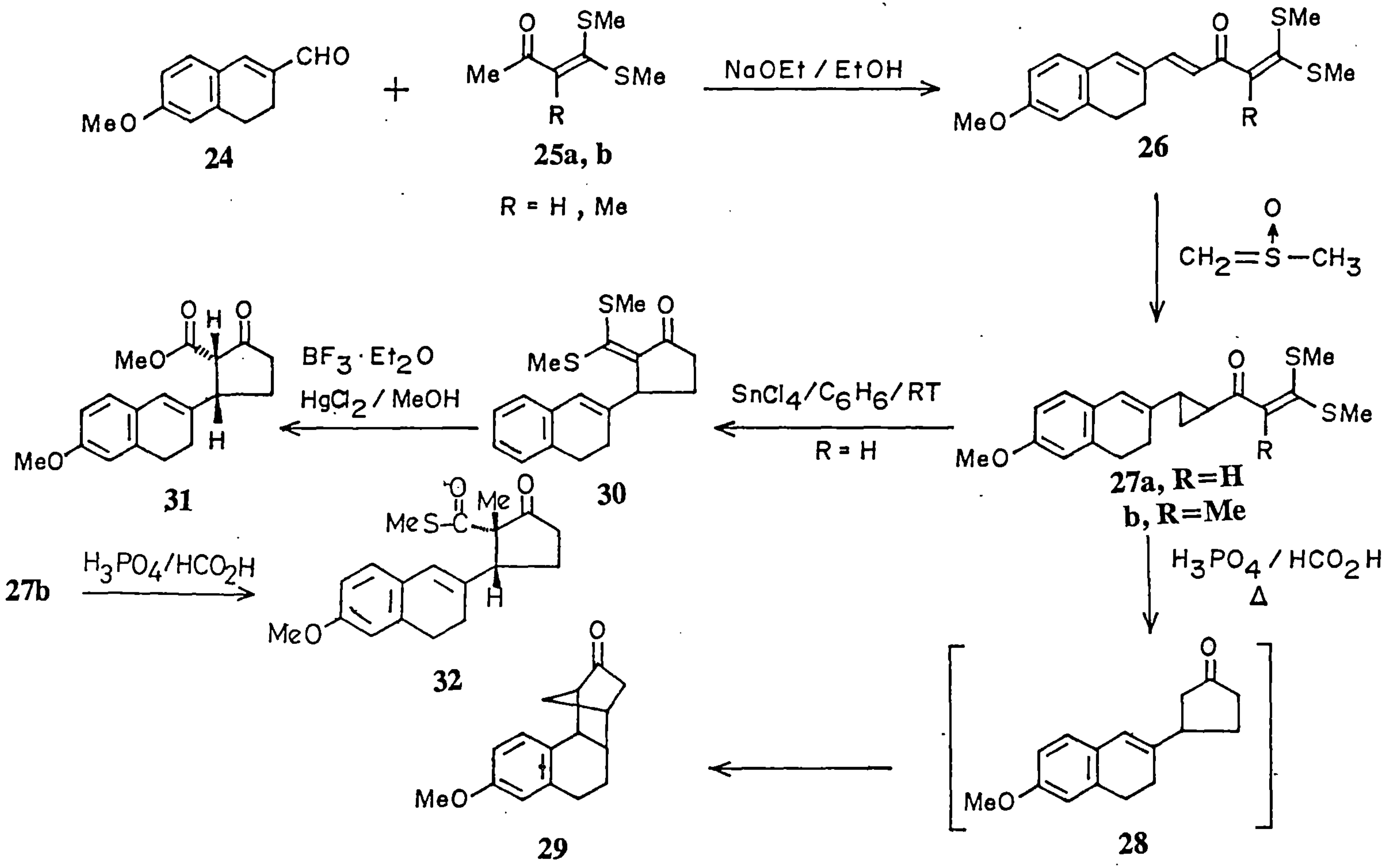
Scheme-2

carbinol **33** quantitatively in highly regiospecific manner.[22b] These carbinols on treatment with $SnCl_4$ in CH_3NO_2 yielded various products(i.e. either **34**,**35** or **36**) depending on the substituents R_1,R_2 and R_3 as illustrated in Scheme-5. Similarly the carbinol **33** on treatment with pyridinium tosylate in CCl_4 yielded either the cyclopentene **36** or the corresponding triene **37** depending on the substituent R_1, R_2 and R_3. The mechanism governing the above transformation is depicted in Scheme-6. The initially formed carbocation **38a** rearranged to homohexadienylic cation **39a** through the cleaveage of cyclopropane bond. In highly ionic medium like nitromethane, the thermodynamically more stable 2E, 3E configuration **39c** may predominate which would slowly isomerise to 2E,3Z configuration **39a** having favourable geometry for 5-exotrig cyclization to give carbocation **39b** that leads to products having cyclopentene ring (**35**, **36**). Under less polar reaction conditions (Pyridinium tosylate in CCl_4), the 2E, 3E carbocation **39c** undergoes fast deprotonation to give trienes **37** and their higher homologues (when R = styryl or 4-aryl-1,3-butadienyl). In systems where R_1, and R_2 are methyl, the dienylic cation **39e** having U-configuration undergoes 6-endotrig cyclization to give the carbocation **41** which affords the aromatic product **34** via dethiomethylation and deprotonation (Scheme-6).

In the preceding examples, the bis(methylthio)methylene functionality has been shown to be an effective cationic cyclization terminator during the formation of cyclopentanones. It was further considered of interest that in the presence of Lewis acid, the sulfur stabilized carbocation in the cyclopentane and cyclopentanone ring could be suitably trapped by an appropriate nucleophilic terminal situated on the adjacent carbon atom so that further annulated derivatives of cyclopentanones **42** could be synthesized (Scheme-7). This was elegantly achieved in our laboratory[22c] by subjecting cyclopropyl ketones **43** carrying aryl group with electron donating substituents, which were subjected to ring opening and cyclization in the presence of Lewis acid. Thus when **43** were cyclized in the presence of $SnCl_4/CH_3NO_2$ at room temperature, corresponding 1-oxocyclopent[a]indenes **45** (Scheme-8) were obtained in high yields with intramolecular trapping of carbocation **44** by aryl group at position para to the alkoxy group. The dithioketal group of **45** were subsequently hydrolysed to the corresponding ketones **46a** & **b** respectively in the presence of aquous acetonitrile and $HgCl_2$.


O
SMe
SMe
R1
Ar
n
16
O
CH2=S−CH3
O
SMe
SMe
R1
Ar
n
17
SnCl4/C6H6
R1=H
O
SMe
SMe
Ar
n
18
H3PO4/HCO2H
R1=Me, Ar=C6H5
Ar=4MeOC6H4
n=1
n=2
O
Ar
H
19
O
H
Ar
H
20
O
R1
COSMe
H
n
Ar
21
+
O
R1
SMe
Ar
22
+
O
R1
n
Ar
23

Scheme-3



24
25a, b
R = H , Me
NaOEt / EtOH
26
CH2=S(O)−CH3
27a, R=H
b, R=Me
SnCl4/C6H6/RT
R = H
30
BF3·Et2O
HgCl2 / MeOH
31
H3PO4/HCO2H
Δ
28
29
27b
H3PO4/HCO2H
32

Scheme-4

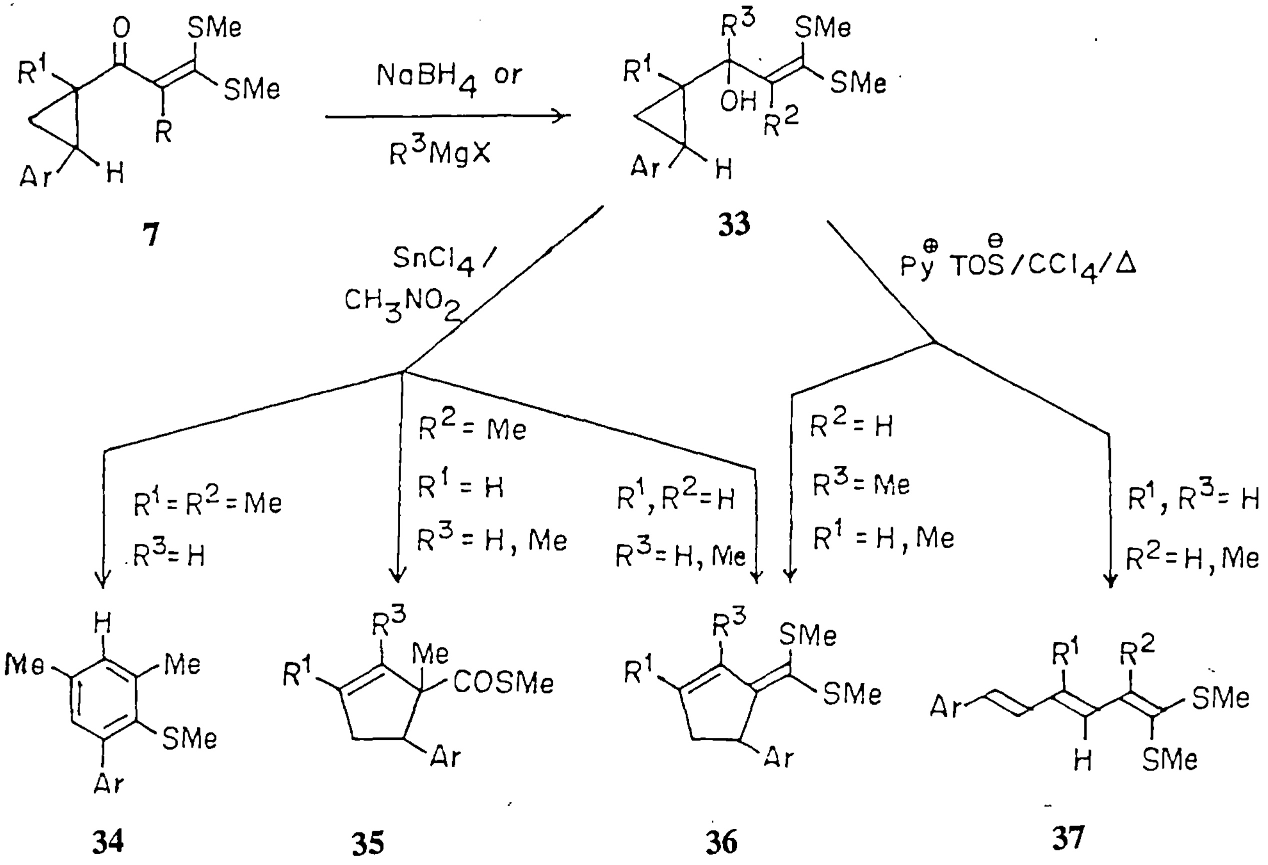
In an another experiment[22c] the bis(methylthio)methylene cyclopropyl ketones **43** carrying dialkoxy aryl substituents were reduced with $NaBH_4$ to afford the corresponding carbinols **47a** & **b** respectively in quantitative yields. There again these carbinols underwent expected double annulation through tandem carbocationic cyclization to afford the corresponding cyclopent[a]indene derivatives **49** respectively in good yields (Scheme-9). Both **49a** & **b** were hydrolysed to the corresponding ketones **50a** & **b** respectively in the presence of $HgCl_2$/aqCH_3CN. Similarly the reductive desulfurization of **49a** & **b** with Raney Nickel afforded the parent cyclopent[a]indene derivatives **51a** and **51b** respectively in good yields.

The work described in this chapter is further elaboration of this strategy of tandem carbocationic cyclization on styryl cyclopropyl ketones and the corresponding carbinols of the general structures **125** (Scheme-24) and **132** (Scheme-29) respectively. Results of our studies on Lewis acid assisted rearrangement of these ketones, structure assignments of the product formed and the mechanisms of various transformations are described in this chapter (Results and discussion). Before coming to the actual discussion of the outcome of this work a brief account of the role of ketene dithioacetal moiety as terminator and initiator in carbocationic cyclizations and some of the literature examples of the synthesis of annelated cyclopentane derivatives through tandem cyclization has been described.

4.I The role of Ketene dithioacetal functionality in carbocationic cyclizations.

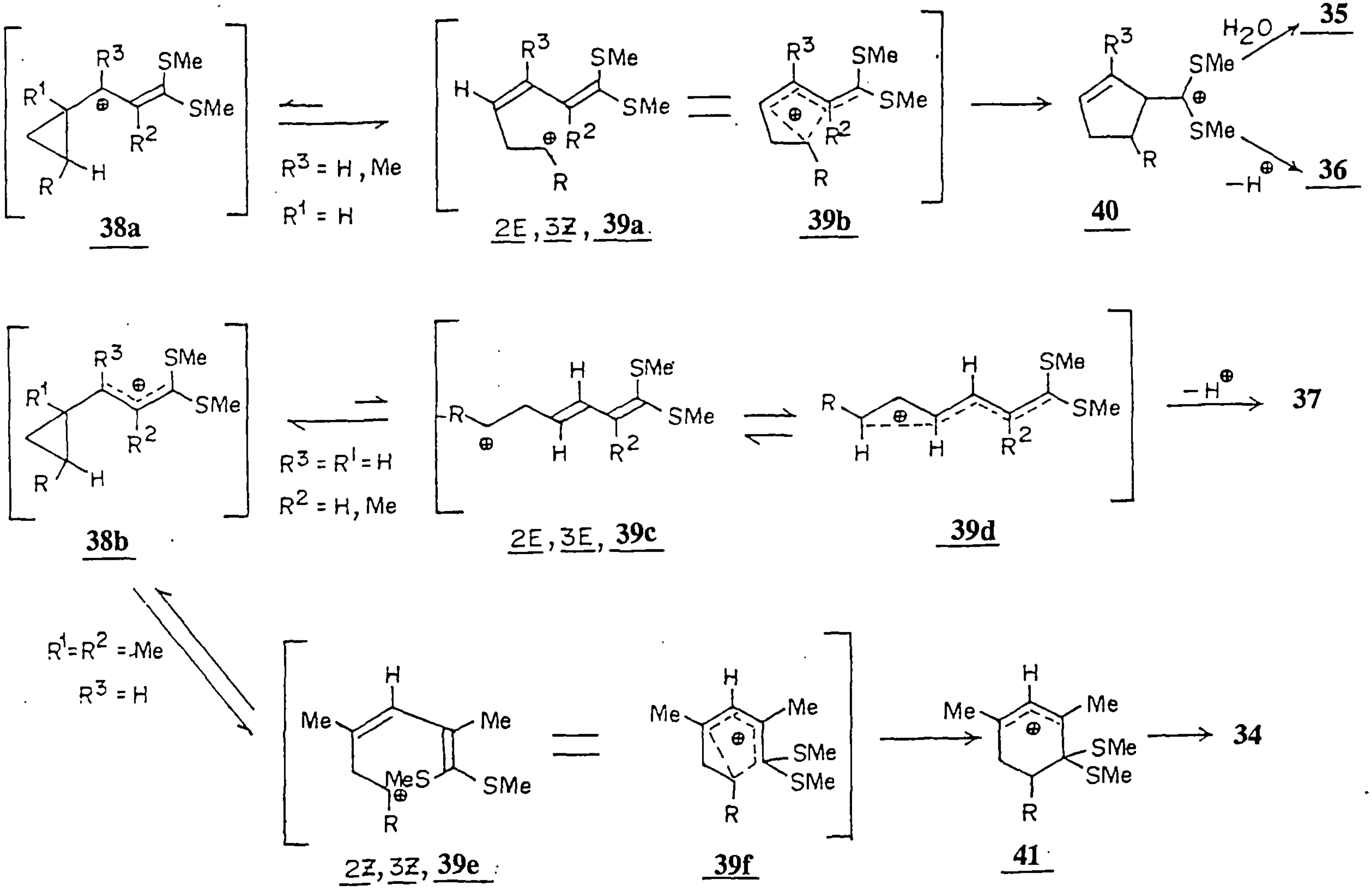
The versatile reactivity of ketene dithioacetal functionality stems from the presence of two sulfur atoms which exercise stabilizing effect on the neighbouring positive as well as negative charges. This makes the double bond in ketene dithioacetals sensitive towards both nuleophilic as well as electrophilic reagents and it is this reactivity of these intermediates which makes them versatile useful intermediate in Organic Syntheses. Application of ketene dithioacetal of general formula **52** have been discussed partly in Chapter-1 and also in several papers.

The normal reactivity of ketene dithioacetal **52** categorized as a^1, d^2 reactivity involves attack by the double bond to the appropriate electrophile to give sulfur stabilized carbocation **53** which on solvolytic interaction gives either the ketone **54** or ester **55** in good yields (Scheme-10).

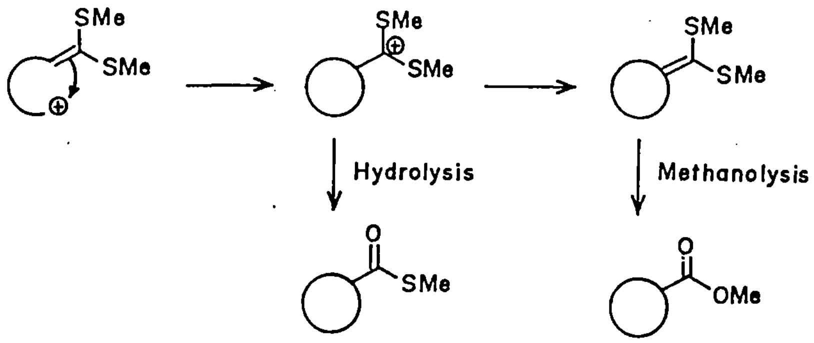


7
NaBH4 or
R3MgX
33
SnCl4 / CH3NO2
Py⊕ TOS⊖/CCl4/Δ
R1 = R2 = Me, R3 = H
R2 = Me, R1 = H, R3 = H, Me
R1, R2 = H, R3 = H, Me
R2 = H, R3 = Me, R1 = H, Me
R1, R3 = H, R2 = H, Me
34
35
36
37

Scheme-5


38a
R^3 = H, Me
R^1 = H
2E, 3Z, 39a
39b
40
H2O
35
−H⊕
36
38b
R^3 = R^1 = H
R^2 = H, Me
2E, 3E, 39c
39d
−H⊕
37
R^1 = R^2 = Me
R^3 = H
2Z, 3Z, 39e
39f
41
34
SMe
Me
R

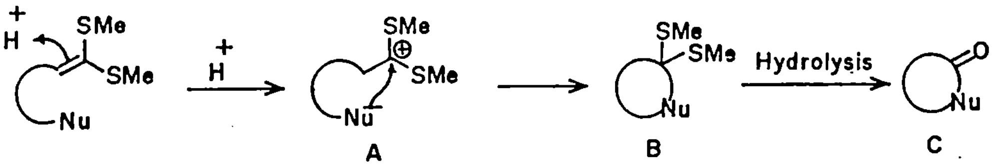
Scheme-6



(KETENE DITHIOACETALS as **Cationic Cyclization Terminator)**

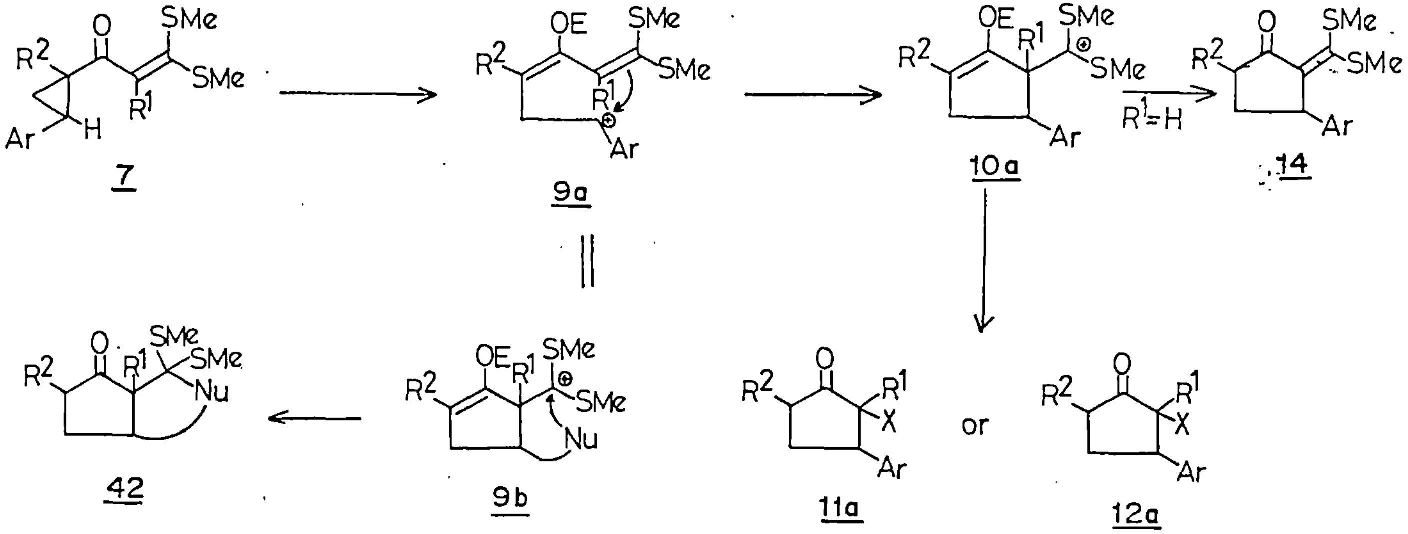
When the electrophile is a carbocation situated on same carbon chain terminal (as shown above) ring formation takes place with the product having ketene dithioacetal functionality intact which can be either converted to carbomethoxy or aldehydic functionality after reduction. Thus ketene dithioacetal functionality acts as cationic cyclization terminator in such kinds of reactions.

On the other hand the carbocation **A** obtained after the protonation of double bond can be attacked intramolecularly by a nucleophile yielding a cyclic ring **B** in which thioketal moiety can be hydrolysed to give cyclic ketone **C**. Thus, ketene dithioacetal group now acts as cationic cyclization initiator in this reaction. The examples of both kind of reactivity has been reported in the literature which are discribed below.

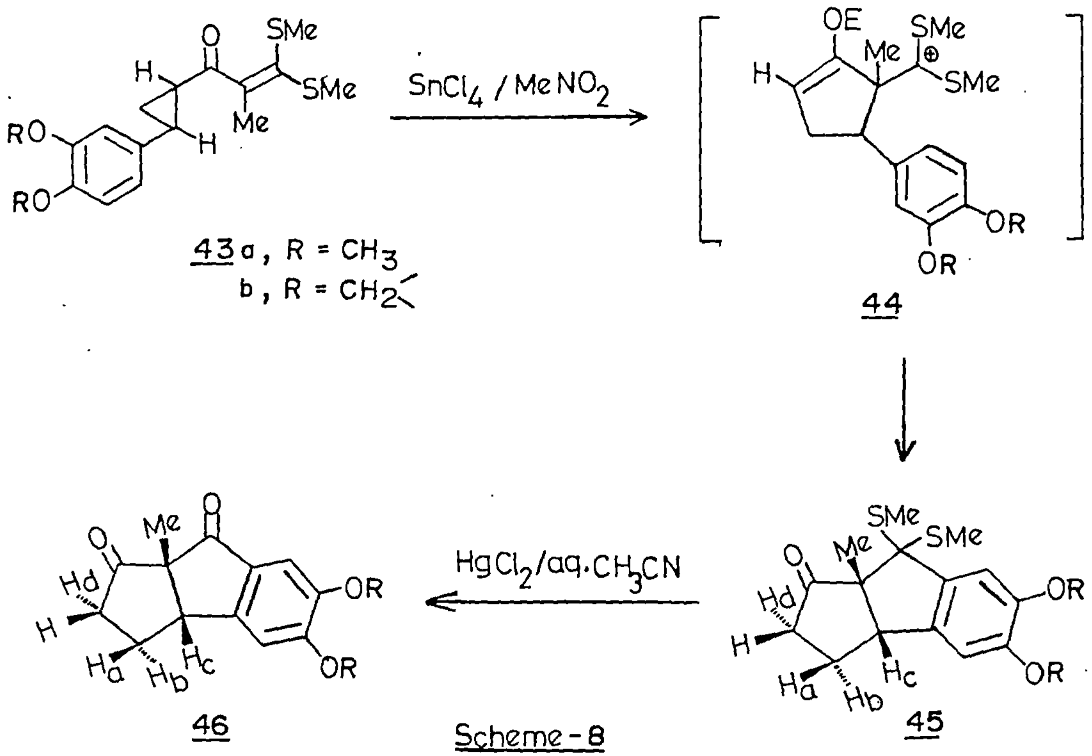


(KETENE DITHIOACETALS as **cationic cyclization initiator)**

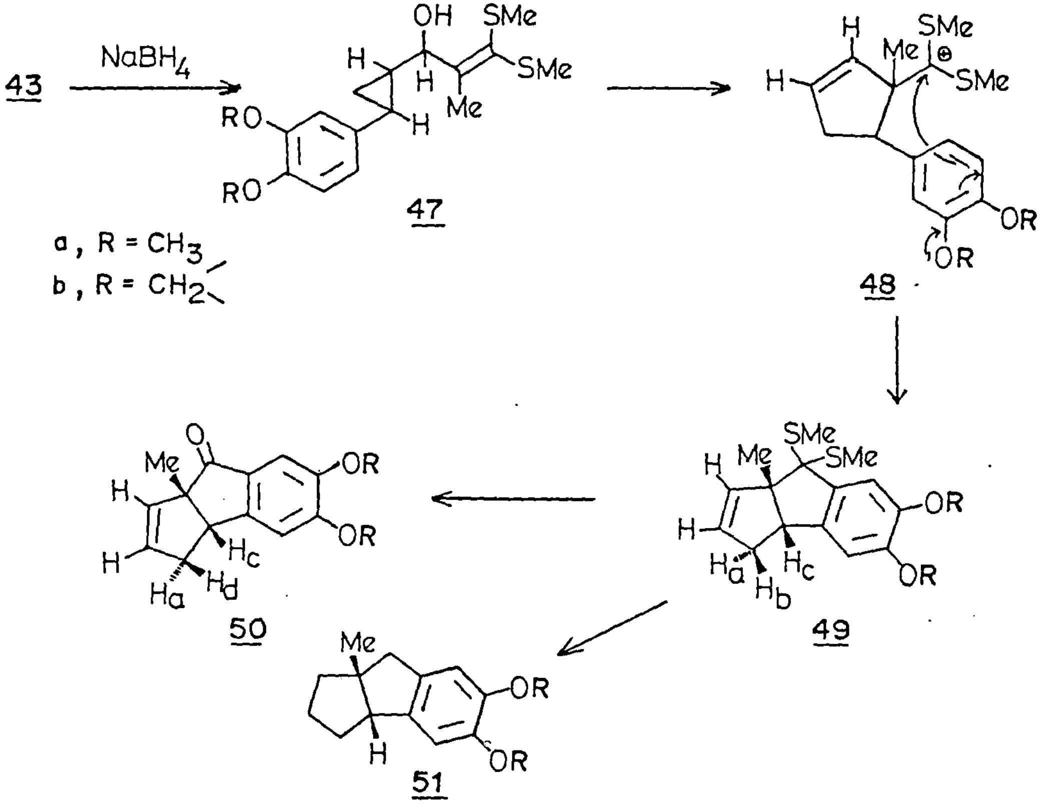
An interesting example of mercapto functionality[25] being used as a source of carbonyl function is in the synthesis of seven membered lactone **59** (Scheme-11). Thus the ketene dithioacetal **57** on treatment with PPTS in dichloromethane afforded the corresponding thioketal **58** in 88% yield. The free carbonyl function



Scheme-7


SMe
SMe
Me
H
H
RO
RO
43a, R = CH3
b, R = CH2<
SnCl4 / MeNO2
OE
SMe
Me
⊕
SMe
H
OR
OR
44
SMe
SMe
Me
O
Hd
H
Ha
Hb
Hc
OR
OR
45
HgCl2/aq.CH3CN
O
Me
O
Hd
H
Ha
Hb
Hc
OR
OR
46

Scheme-8


43
NaBH$_4$
OH
SMe
SMe
H
H
H
Me
RO
RO
47
a, R = CH$_3$
b, R = CH$_2$
H
H
SMe
Me
SMe
OR
OR
48
SMe
Me
SMe
H
H
OR
OR
Ha
Hb
Hc
49
O
Me
OR
H
H
OR
Hc
Ha
Hd
50
Me
OR
OR
H
51

Scheme-9

was generated from **58** in the presence of silver ion assisted phase transfer catalyst to afford the seven membered lactone **59**. Here an oxygen atom instead of double bond can also be used as trapping agent. Thus the cationic stabilizing ability of sulfur has promoted the use of ketenedithioacetal as initiator in the intramolecular electrophilic cyclizations.

Similarly in an another example of streospecific synthesis[26] of (+)Naptolactone **62** (Scheme-12), the intermediate **61** undergoes intramolecular cyclization in the presence of $BF_3.Et_2O$ to give **62** in highly sterospecific manner. Thus the mercapto functionality behaves both as cationic cyclization terminator and initiator.

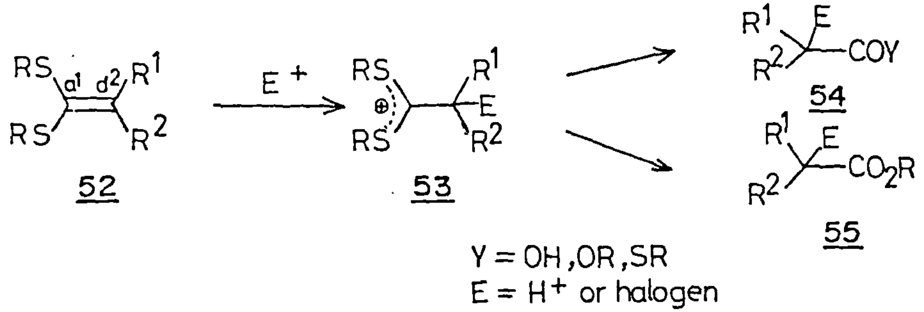
In an another example shown in Scheme-13, the protonated mercapto double bond[27] of **63** is rapidly attacked by the olefinic double bond in the presence of triflouroethanol and methane sulfonic acid to afford the corresponding cyclic thioketal **64** which on hydrolytic cleavage yielded the corresponding cyclic enone **65** (Scheme-13). Similarly the sulfur stabilized cation was intercepted by the double bond in a tandem ring closure sequence[28] to afford decaline dione **68** in high yield.

Sulfur stabilized carbocations have also been elegantly cyclized with the participation of aryl ring through a double bond to give tricyclic ketone **71** in high yield.[27] Similar approaches were extended for the synthesis of tetralone **74** and tetraline **75** (Scheme-14).[29]

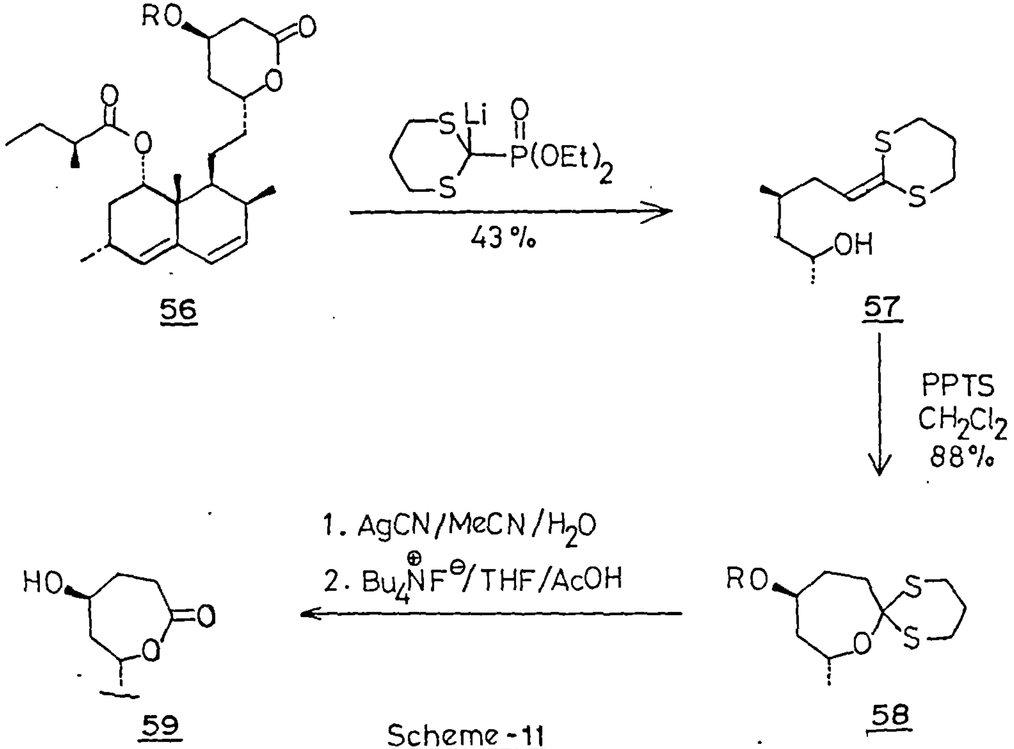
4.II Few examples of Tandem cyclization to cyclopentanoids from Literature.

Several approaches have been employed in the literature for the construction of annelated carbocyclic system among them the tandem ring closure approach which is closed to our studies, has been highlighted here with the few related examples described in the literature.

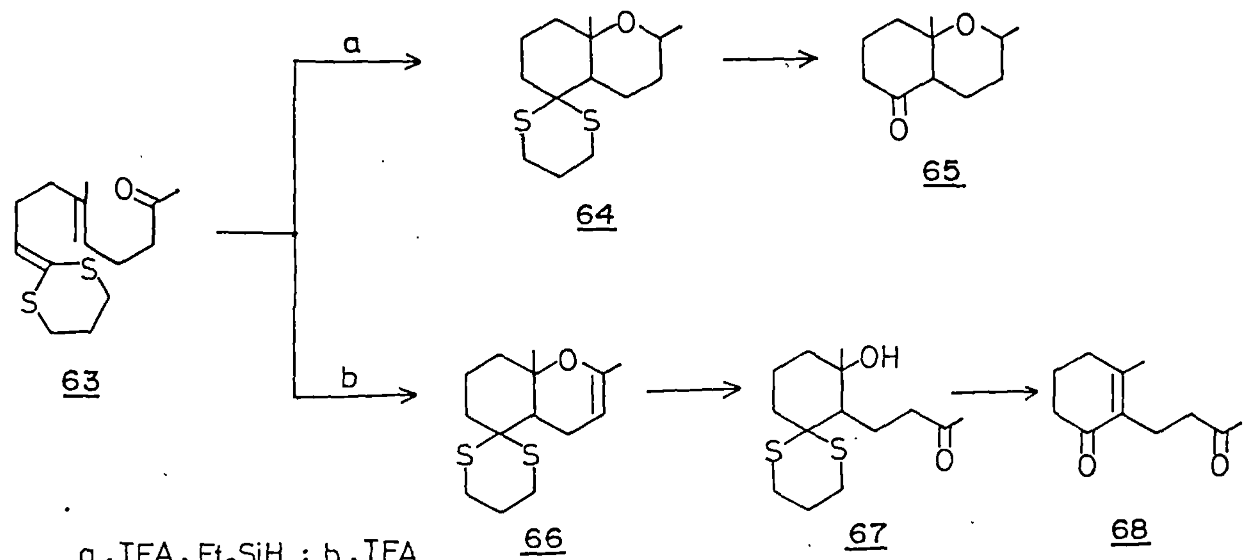
In a series of paper, Murphy and co-workers[30,31] showed the utility of cyclopropyl ketones to construct tetralines as well as cyclopentanoids with great success. They have reported an unexpected synthesis of tricyclic carbocyclic compound **81** obtained from cyclopropyl ketone **76** through $SnCl_4$ assisted rearrangement. They have shown that when the dimethoxy groups are present on both aryl rings, the


RS
RS
a1
d2
R1
R2
52
E +
RS
RS
R1
E
R2
53
R1
E
R2
COY
54
R1
E
R2
CO2R
55
Y = OH, OR, SR
E = H+ or halogen

Scheme 10

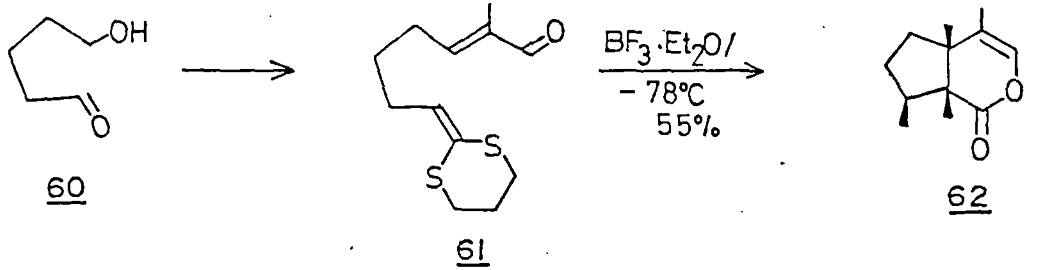

RO
O
O
O
O
56
S
Li
O
P(OEt)$_2$
S
43 %
S
S
OH
57
PPTS
CH$_2$Cl$_2$
88%
1. AgCN/MeCN/H$_2$O
2. Bu$_4$N$^{\oplus}$F$^{\ominus}$/THF/AcOH
HO
O
O
59
RO
S
S
O
58

Scheme-11



a, TFA, Et_3SiH ; b, TFA

Scheme -13



Scheme -12

intermediate ketone **79** underwent insitu cyclization through aromatic ring participation to give the corresponding ß-hydroxy tricyclic compound **80** (Scheme-15). The hydroxy group in **80** was knocked off slowly to afford the corrosponding carbocation which on intramolecular hydride abstraction yielded the tricyclic compound **81**.

An interesting example of olefinic bond participation in the acid catalyzed ring opening of the acyl cyclopropanes to afford bicyclo[2.2.1]heptane is reported.[32] The endo bicyclo[3.1.0]hexane **82** underwent $SnCl_4$ assisted rearrangement to afford the cation **83** which on intramolecular enole double bond participation as in **84** afforded the ketone **85** (Scheme-16). Similarly a tricyclic ketone **88** has been synthesized[33] from cyclopropyl ketone **86**, thus **86** on treatment with $SnCl_4/CH_2Cl_2$ underwent cyclopropyl ring cleavage to afford the corresponding enolate carbocation **87** which followed intramolecular tandem ring closure to afford natural product cedrene **88** (Scheme-16)

4.III Conclusion

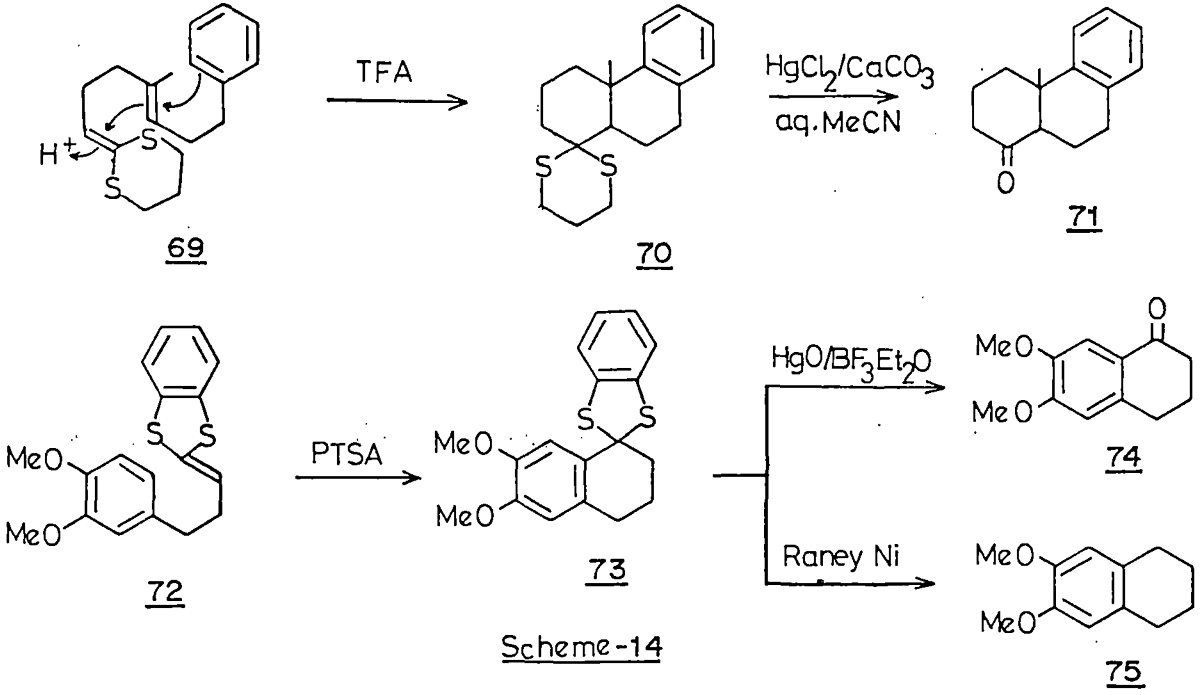
The acid induced rearrangement of ketones and carbinols described in the present work provide a new route to diquinane system. Some of them constitute basic framework for many naturally occuring sesquiterpenoids. Because of the importance of this ring system, several strategies have been developed for their synthesis. Some of the important ones involving

(A) **Pauson-Khand reaction**[34,35] involving a (2+2+1) intramoleuclar cycloaddition between alkene, alkyne and carbon monoxide (from $Co(CO)_8$) (Scheme-17).

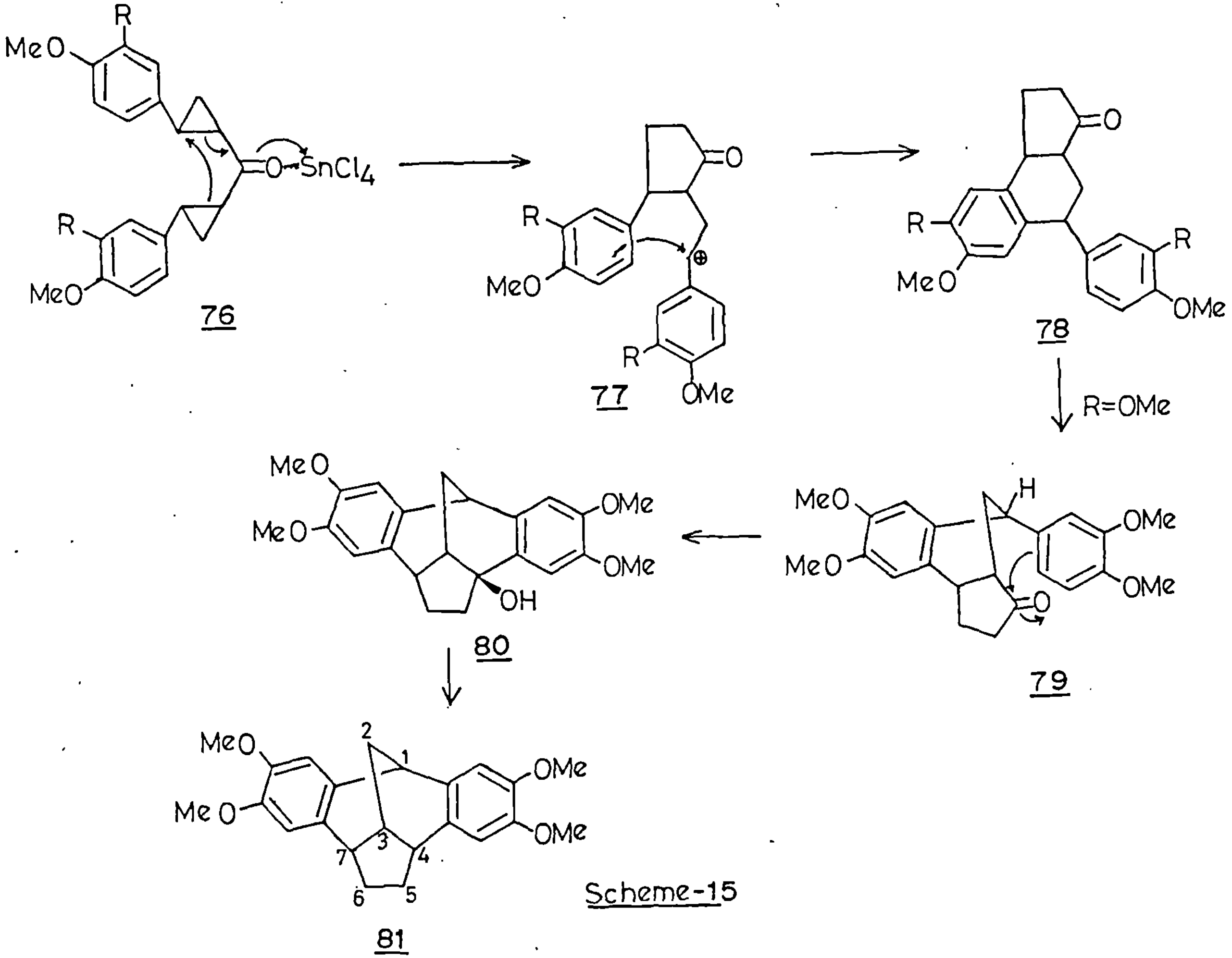
(B) **In Corioline Synthesis**,[36,37] the intermediate diquinane **95** was obtained by intramolecular Pauson Khand reaction of enyne (Scheme-18).

(C) **Through addition of vinyl anion**[38] to squarate esters (Scheme-19). Thus the two fold addition of vinyl anion to squarate esters and its congeners led to ring eleavage at low temperature and there by to charged reactive intermediates amenable to trans annular bonding. The ensuing bond reorganization results in direct formation of diquinane and polyquinane systems.

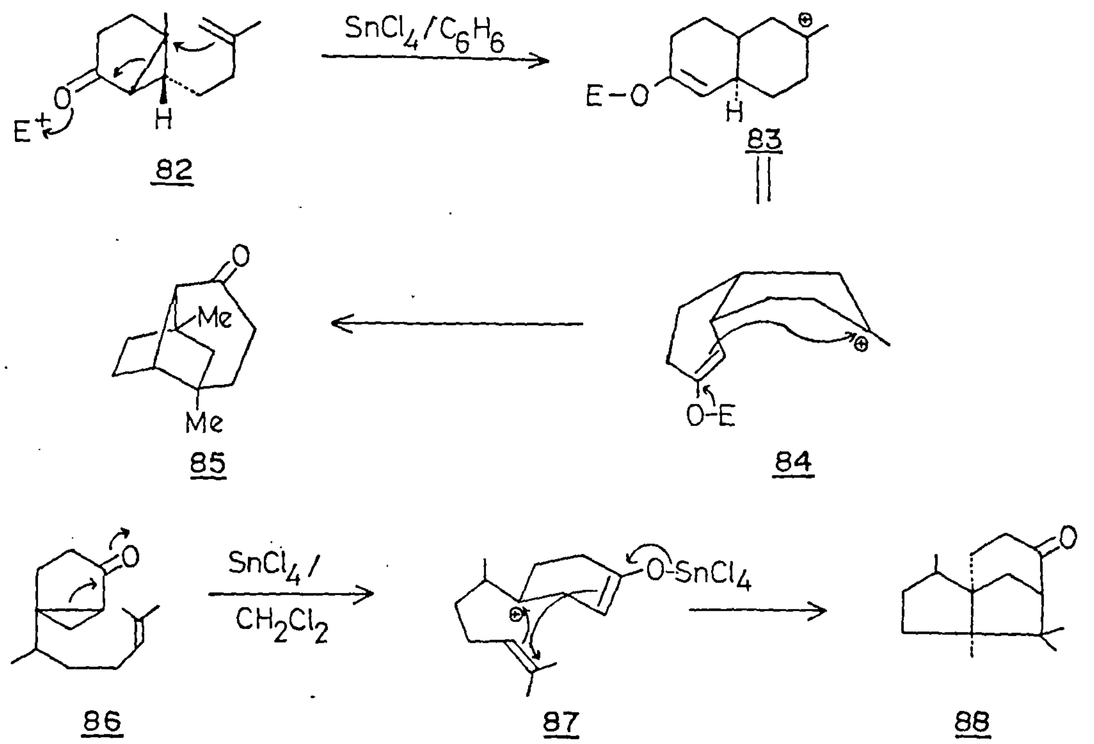
(C) **Photocycloaddition fragmentation** approach[39] involving intramolecular Paterno-Buchi reaction for construction of diquinanes (Scheme-20). Thus Paterno-Buchi reaction of the Norbornene skeleton of type **104** generates an Oxetane **105** which on subsequent ring cleavage and oxidation gives a strained


H$^+$
S
S
69
TFA
S
S
70
$HgCl_2/CaCO_3$
aq.MeCN
O
71
MeO
MeO
S
S
72
PTSA
MeO
MeO
S
S
73
HgO/BF_3Et_2O
O
MeO
MeO
74
Raney Ni
MeO
MeO
75

Scheme-14


MeO
R
O→SnCl4
R
MeO
76
R
MeO
O
R
OMe
77
O
R
MeO
R
OMe
78
R=OMe
MeO
MeO
H
OMe
OMe
O
79
MeO
MeO
OMe
OMe
OH
80
MeO
MeO
OMe
OMe
1
2
3
4
5
6
7
81

Scheme-15


E⁺
O
H
82
SnCl4/C6H6
E–O
H
83
85
Me
Me
O
O–E
84
86
O
SnCl4/
CH2Cl2
87
O-SnCl4
88
O

Scheme- 16

ketoalkene **106**. The succeptibility of ketoalkene to fragmentation due to inherent strain energy gives the radical **107** which rearranges via the path A and B to quinane **108** & **109**.

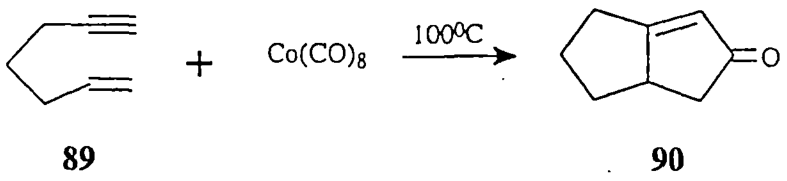
(D) **Weiss-Cook Condensation** :- A versatile method for the synthesis of polyquinane[40] by acid catalyzed condensation of two molecules of dimethyl-3-oxoglutarate with one molecule of glyoxal followed by subsequent hydrolysis and decarboxylation under acidic condition (Scheme-21).

The present approach on the Lewis acid induced cyclization of styryl cyclopropyl carbinols **132a** and **132b** via complex tandem carbocationic rearrangement represents another interesting approach to cyclopent[a]indene ring system (Scheme-29). The classical methods for cyclopent[a]indene ring sytem involve (a) through intramolecular cyclization[41] of indane carboxylic acid and Fridel Craft cyclization (b) by intramolecur PPA induced cyclization of 2-benzylidene cyclopentanone, cyclopent[a]indene was reported to be formed[42] in poor yields (c) through intramolecular aldol condensation[43] of benzocitanedione in the presence of sodium ethoxide (d) pyrolytic rearrangement[44] of 1,4-bridged-1,2,3,4-tetrahydronaphthalene derivative through a biradical intermediate. Another interesting classical approach to cyclopent[a]indene system involving acid catalyzed cyclization is shown in Scheme-22.

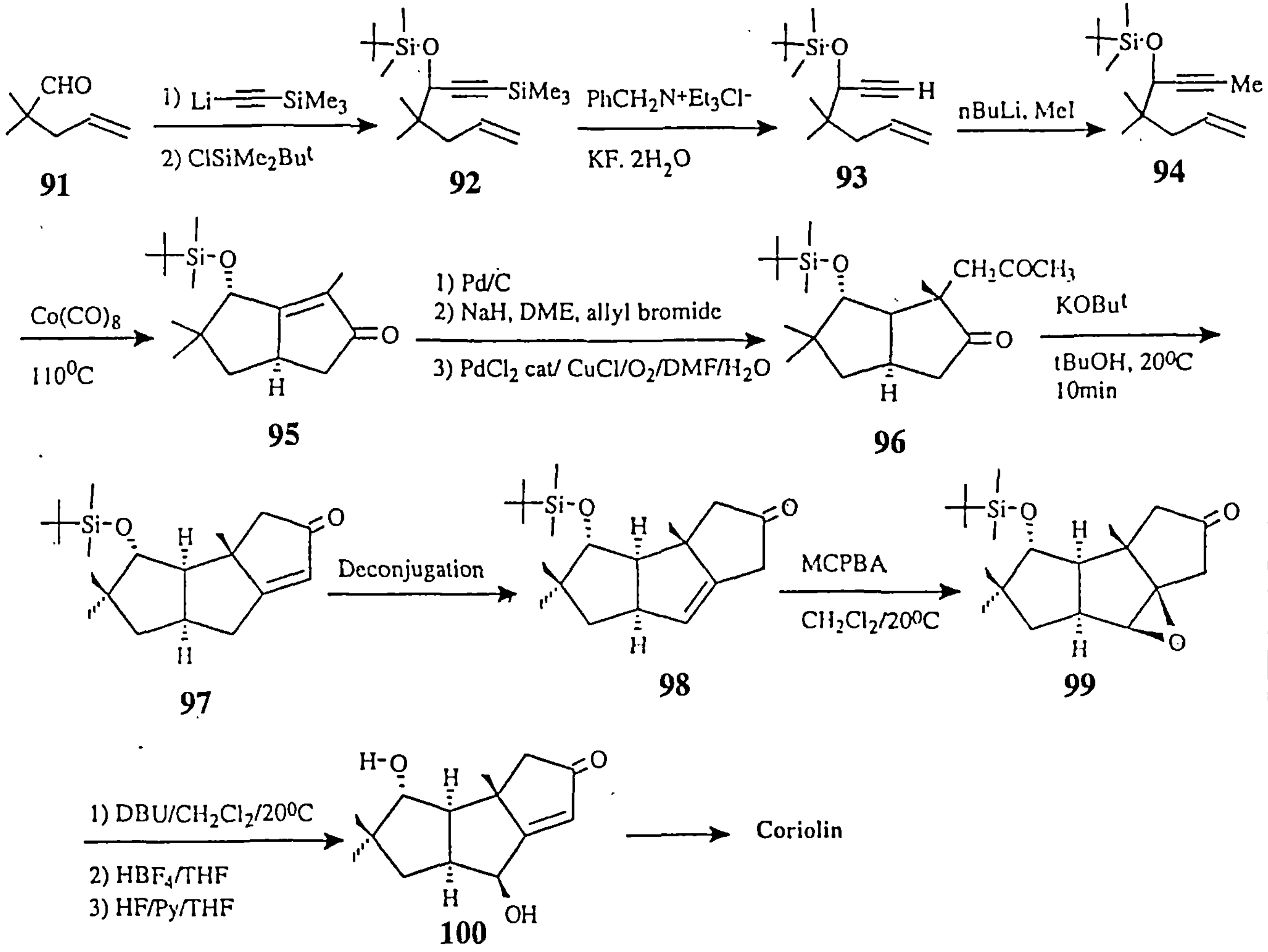
Hart and co-workers reported the synthesis[45] of cyclopent[a]indene **119** through a very interesting unusual synthesis in their studies on carbocation rearrangement. Benzbicyclo[2.2.0]octanol **114** with an anta hydroxy group on treatment with strong acid yielded **119** in 80% yield. The mechanism of the formation of **114** (anta epimer) through a series of rearrangements is shown in Scheme-22.

4.IV RESULTS AND DISCUSSION

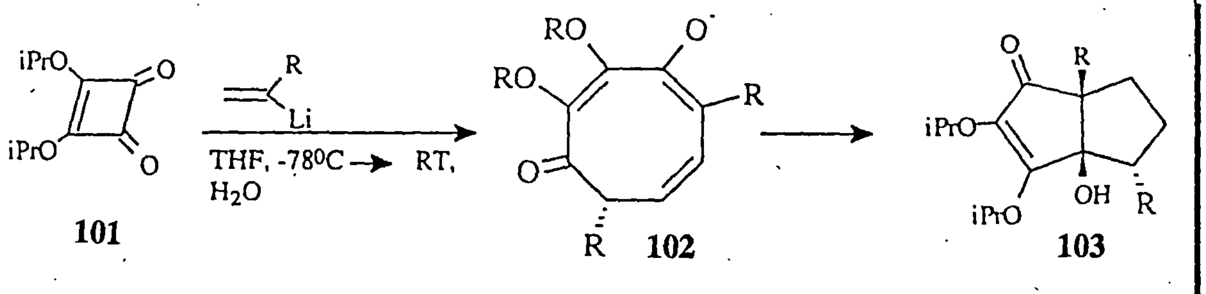
In the preceding section, a brief description on the role of bis(methylthio)methylene double bond as cationic cyclization terminator and initiator has been highlighted. We further envisaged that a bicyclo[3.3.0]octene system can be constructed via tandem carbocationic process by intramolecular trapping of carbocation **9b** when a double bond as a nucleophile is present (Scheme-23). In the following sections an attempt has been made in this direction



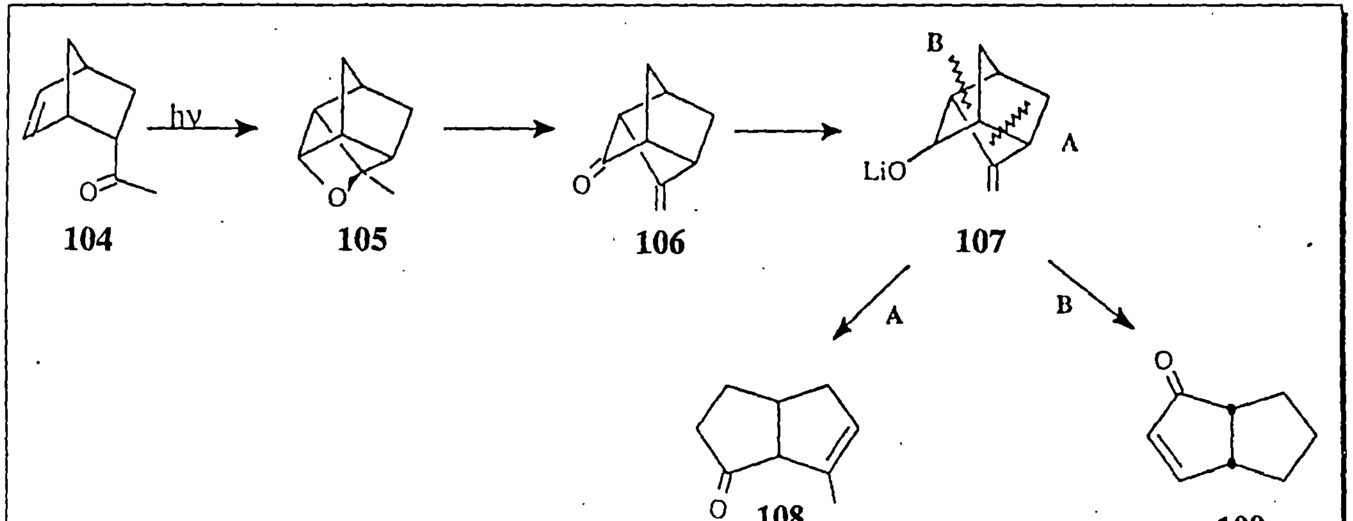
Scheme-17



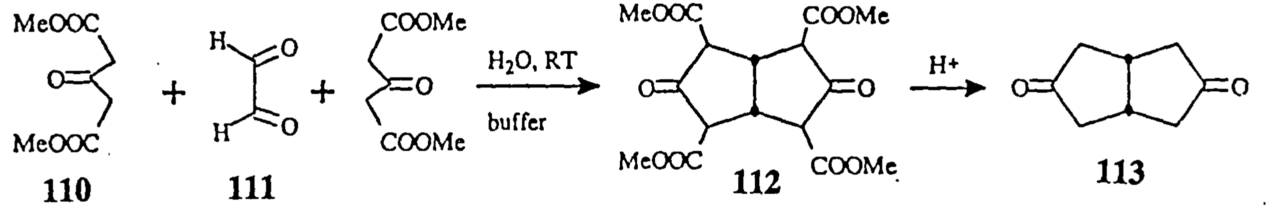
Scheme-18



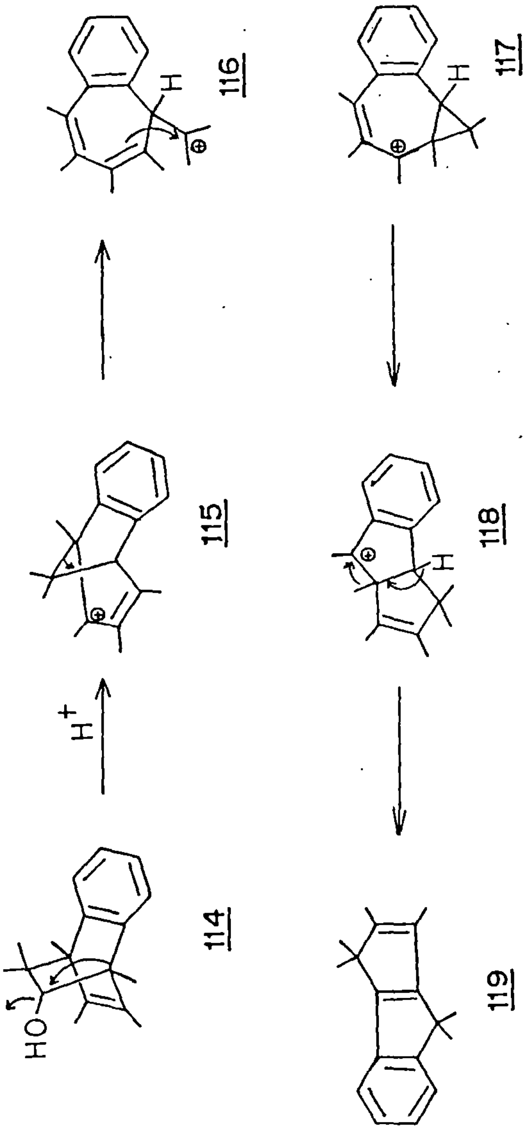
Scheme-19



Scheme-20



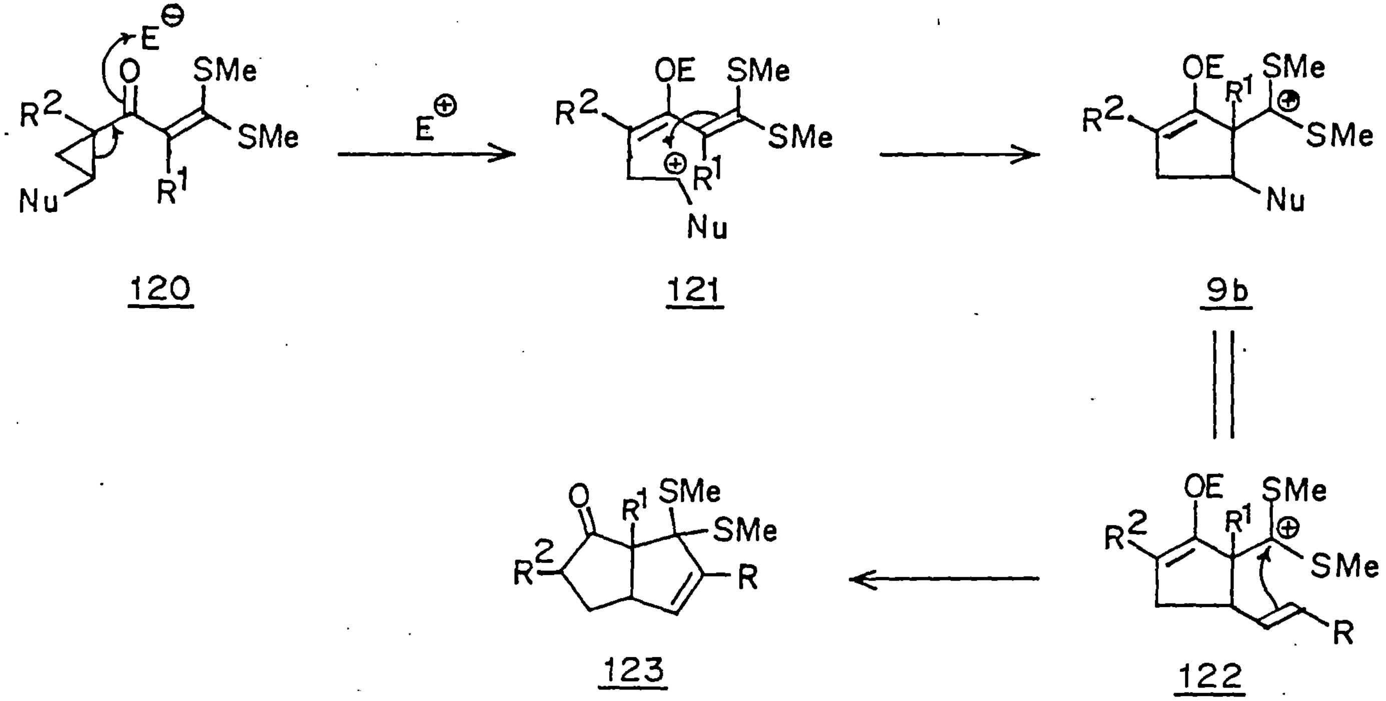
Scheme-21



Scheme-22

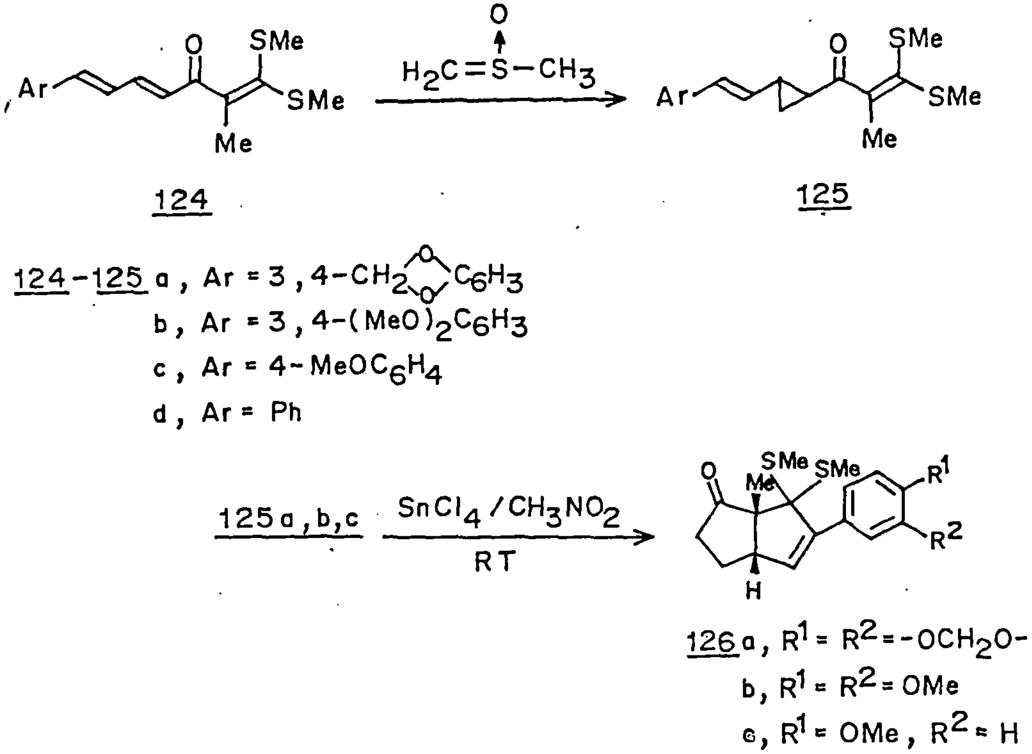
and a few selected examples of cytopentannelation has been presented via Lewis acid induced tandem carbocationic cyclizations of cyclopropanes **125** (Scheme-2) having a vicinal styryl and oxoketene dithioacetal moiety, and the corresponding carbinols.

The desired cylopropyl ketones **125a-d** were prepared by our earlier reported procedure through regiospecific cyclopropanation of α-(4-aryl-1, 3-butadienyl)oxoketene dithioacetal **124** with oxodimethylsulphonium methylide under phase transfer conditions[46] in good yields. The cyclopropyl ketone **125a** was first investigated under Lewis acid conditions. Thus when **125a** was treated with $SnCl_4$ in nitromethane at room temperature for twelve hours, tlc showed the quantitative conversion to a new product. Work up of the reaction mixture afforded a viscous liquid which was characterized as substituted bicyclo[3.3.0]oct-2-ene-6-one **126a**. Thus **126a** displayed molecular ion peak at m/z 348(M^+, 26%) besides peaks at m/z 301 (M^+-SMe, 100%) and 253 (M^+-2SMe, 88%). Its elemental analysis confirmed its molecular formula as 348.46. The infrared spectrum shows 1750 and 1605 cm^{-1} due to cyclopentanone carbonyl group and styryl olefinic double bond. The ^1H NMR spectrum (300 MHz, $CDCl_3$) exhibited three singlets (3H each) at δ 1.68, 2.21 and 2.24 due to two methylthio and a methyl group. The methylenedioxy protons appeared at δ 5.98 while the aromatic protons were present as doublet (J = 10Hz, 1H, H_a), doublet (J = 3Hz, IH, H_b) and a double doublet (J = 10, 3Hz, 1H, H_c). The presence of a doublet at 7.40 (J = 3Hz, 1H) was assigned as olefinic proton further supported the assigned structure. The methylene protons of cyclopentanones appeared merged as wide envelope between δ 2.20 to δ 2.40, while the signal due to bridged methyne proton appeared at lower field at 5.02 (double triplet, J = 7.8,2.5Hz, 1H) further confirming the structure of **126a**. The stereochemistry at ring junction was arbitrarily assigned as *cis* on the basis of similar reported system and also by differential NOE experiment. Further support of the structure of **126a** was obtained from ^{13}C analysis, which showed peaks at δ 16.69, 17.04 and 18.51 confirm the presence of two methylthio and bridged methyl groups. Peaks due to methyne and methylene carbons appeared at δ 26.56, 36.88 and 45.76. A peak at δ 101.46 confirmed the methylenedioxy carbon. The aromatic (Ar-CH) carbons were present at δ 135.04, 127.21 and 109.47 besides the vinylic carbon at δ 108.26. The three aromatic quarternary carbons appeared at δ 148.88, 147.64 and 146.62 further confirmed the structure. The other quarternary peaks at δ 128.63, 128.83 and δ 207.27 (CO) confirmed the structure of **126a**. The corresponding


E⊖
O
SMe
SMe
R2
Nu
R1
120
E⊕
OE
SMe
SMe
R2
R1
Nu
121
OE
R1
SMe
SMe
R2
Nu
9b
OE
R1
SMe
SMe
R2
R
122
O
R1
SMe
SMe
R2
R
123

Scheme – 23

3,4-dimethoxy styryl **125b** and 4-methoxy styryl **125c** cyclopropyl Ketones also yielded the respective bicyclooctenes **126b** and **126c** under identical conditions in 65 and 72 % yield respectively. The spectral and analytical data of **126b** and **126c** were in confirmity with the assigned structure. The probable mechanism of formation of **126a-c** is shown in Scheme-25. Thus Lewis acid induced ring opening of cyclopropyl ketone **125** and subsequent trapping of carbocation by bis(methylthio)methylene moiety afforded the stable bis(methylthio)methyl carbocation **127a** which is further trapped by styryl double bond in tandem fashion to give the bicyclic carbocation **127b** which on deprotonation yields the observed product bicyclooctenes **126**. It is pertinent to note that the corresponding unsubstituted styryl cyclopropyl ketone **125d** did not yield the expected bicyclooctene-6-one **126d** under identical conditions and the product obtained (59%) was characterized as 1-oxo-3-styryl-2-carbothioate **128a** (Scheme-26). Also we had earlier observed that the corresponding 4-methoxy styrylcyclopropyl ketone **125c** afforded similar product **128b** when rearrangement of **125c** was carried out in $SnCl_4$ using dichloromethane as solvent. Thus the solvent nitromethane plays a crucial role in the formation of bicyclooctene framework through intramolecular trapping of carbocation **127a**. Further as we have observed this cyclization takes place only when electron donating groups are present on the aryl ring of the styryl double bond (i.e. **125a-c**). It appears that in a highly polar solvent like nitromethane, the carbocation **127a** is stable enough to be trapped by electron rich styryl double bond to afford the bicyclooctene **126** through tandem carbocationic cyclizations. Where as in a relatively nonpolar solvent like benzene, dichloromethane this cyclization does not take place and the carbocation **127a** undergoes hydrolysis during workup to give the corresponding carbothioate **128b** (Scheme-25). The same pathway is also followed in the absence of electron donating group on styryl group to afford the unsubstituted-3-styrylcarbothioate **128a** (scheme-26).. In the absence of electron donating group on the aryl ring of cyclopropyl ketone **125d**, the double bond of styryl moiety is not enough electron rich to trap the bis(methylthio)carbocation **127a** intramolecularly to a give bicyclooctene **126d** (Scheme-26) and the carbothioate **128a** formed by hydrolysis of **127** (Ar=ph) was obtained. Our attempts to obtain bicyclooctenedione **129** by dethioactalization of **126a** with various reagents under different conditions ($HgCl_2$, AqCH_3CN; DMSO; HCl, DMSO; NBS, $AgNO_3$) were not successful and in most of the cases either intractable reaction mixture of several products were obtained (Scheme-27).



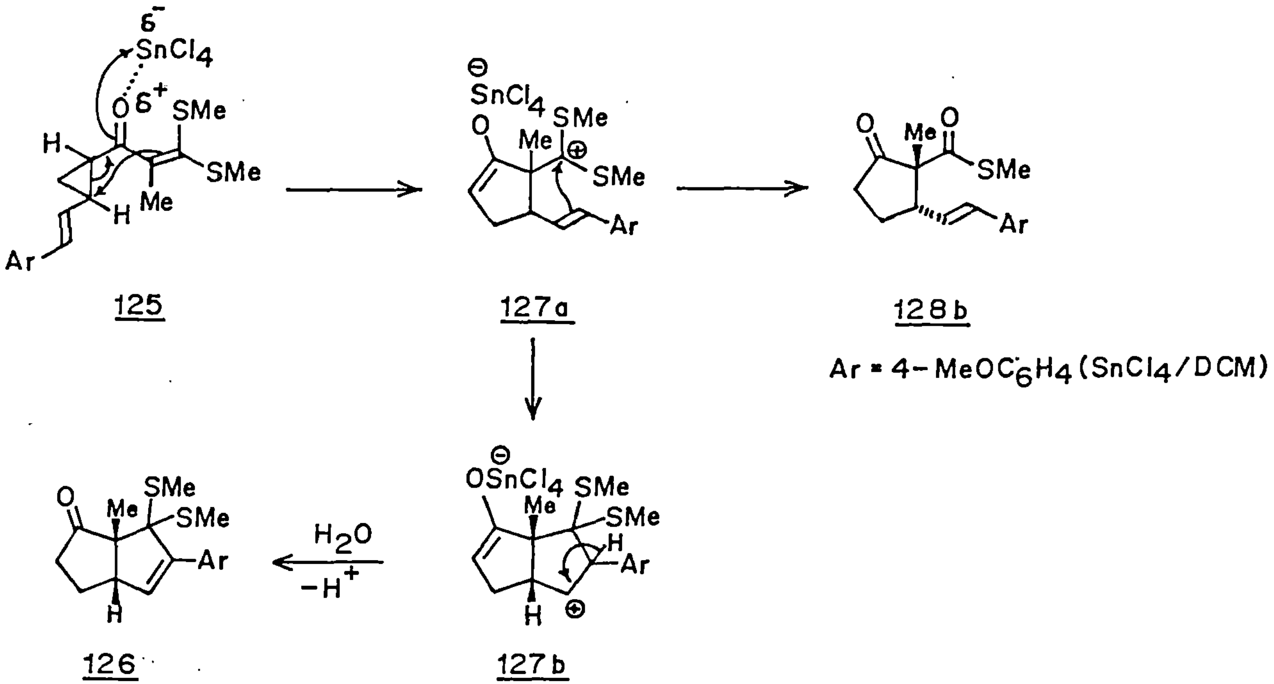
124

125

124–125 a, Ar = 3,4-$CH_2O_2C_6H_3$
b, Ar = 3,4-$(MeO)_2C_6H_3$
c, Ar = 4-$MeOC_6H_4$
d, Ar = Ph

126 a, $R^1 = R^2 = -OCH_2O-$
b, $R^1 = R^2 = OMe$
c, $R^1 = OMe$, $R^2 = H$

Scheme-24


SnCl4
SMe
SMe
H
H
Me
Ar
125
SnCl4
O
Me
SMe
SMe
Ar
127a
O
Me
O
SMe
Ar
128b
Ar = 4-MeOC6H4 (SnCl4/DCM)
OSnCl4
Me
SMe
SMe
H
Ar
H
127b
H2O
-H+
O
Me
SMe
SMe
Ar
H
126

Scheme-25

We also carried out the desulphurization reaction (Scheme-28) on the bicyclo[3.3.0]octene **126a** by subjecting it with Raney-Nickel in refluxing ethanol. After 5-6hr, the reaction yielded a colourless viscous oil which was characterized as 2-methyl-3-[2'-(3,4-dimethoxyphenyl)]propyl-1-cyclopentanol **131** instead of bicyclooctene **130**. Its IR spectrum showed the absence of carbonyl functionality. Its ^{1}H NMR showed two equivalent doublets (J=6Hz) in the high field region at δ 0.83 and δ 0.94, (3H each) confirming the presence of two methyl groups. The dimethoxy protons (6H) appeared as two singlets at δ 3.85 & 3.87. The other aliphatic and aromatic protons were present and have been explained in the experimental section. It was also confirmed by ^{13}C NMR and DEPT analysis, which were in aggrement with the assigned structure and are reported in the experimental section.

We further studied $SnCl_4$ induced ring opening and rearrangement of cyclopropyl carbinols **132a** and **b** obtained by sodium borohydride reduction of the ketones **125a** and **b** respectively. It was anticipated in line with our earlier studies that the initially formed bis(methylthio)methyl cyclopentenyl carbocation **135** obtained by Lewis acid induced and intramolecular cyclization of the carbinol **132** may yield the strained bicyclo octadiene framework **133** as shown in Scheme-29. However when the carbinol **132a** was treated with $SnCl_4$ in nitromethane under identical condition the product isolated as colourless crystalline compound (78%), was found to be not the expected bicyclo octadiene **133** but the cyclopent[a]indene **134a** on the basis of spectral and analytical data. The product **134a** analysed for exhibited molucular ion peak m/z 332 (M^+, 47%) besides other significant peaks at m/z 286 (M^+- SMe, 19%), 269 (M^+-SMe-Me, 68%) and 237 (M^+-2SMe, 86%). The structure of **134a** was strongly supported by its ^{1}H NMR (300 MHz, $CDCl_3$), which showed two singlets at δ 6.31 (1H) and δ 6.68 (1H) due to two aromatic protons thus confirming the participation of aromatic ring during cyclization. The two olefinic protons* of cyclopentene were present as two singlets at δ 5.84 and δ 5.88 respectively besides signals due to methylenedioxy proton δ 5.70 (singlet, 2H) in the low field region. In the high field region the three singlets (3H each) at δ 1.79 and δ 2.27 and δ 2.31 were assigned to the methyl and two methylthio groups respectively while two broad doublets at δ 4.85 (1H, J = 6Hz) and δ 4.16 (1H, J = 9Hz) were assigned to be benzylic methyne protons H_a and H_b respectively

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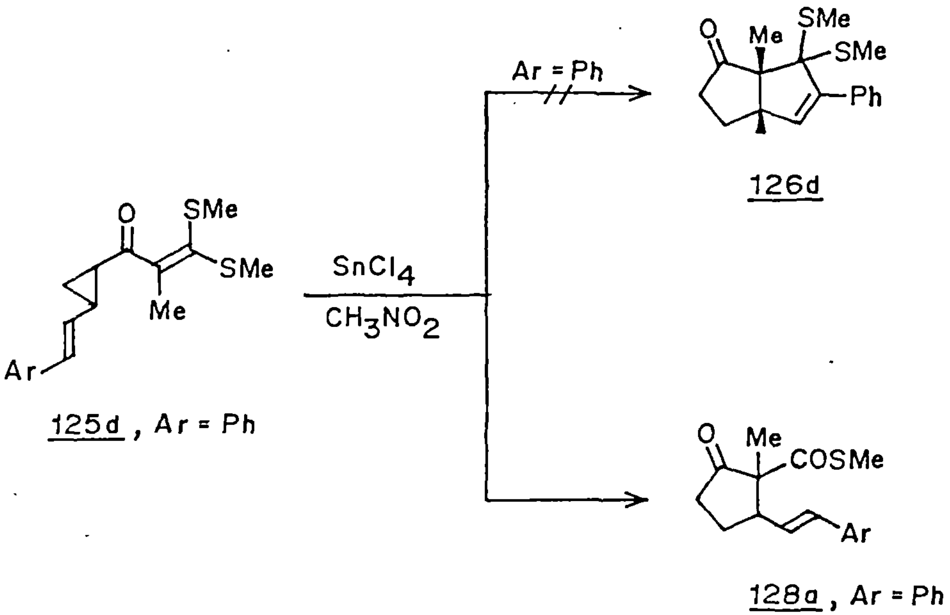
* *Cis* coupling of two olefinic protons (8-10Hz) was not observed as expected.

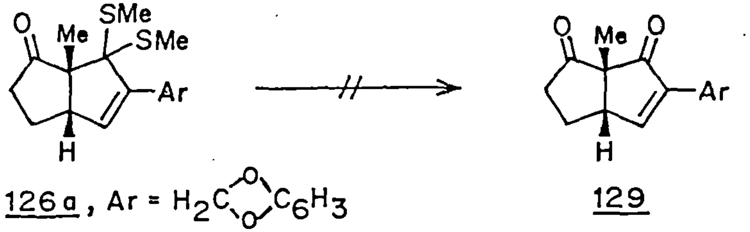


125d, Ar = Ph

126d

128a, Ar = Ph

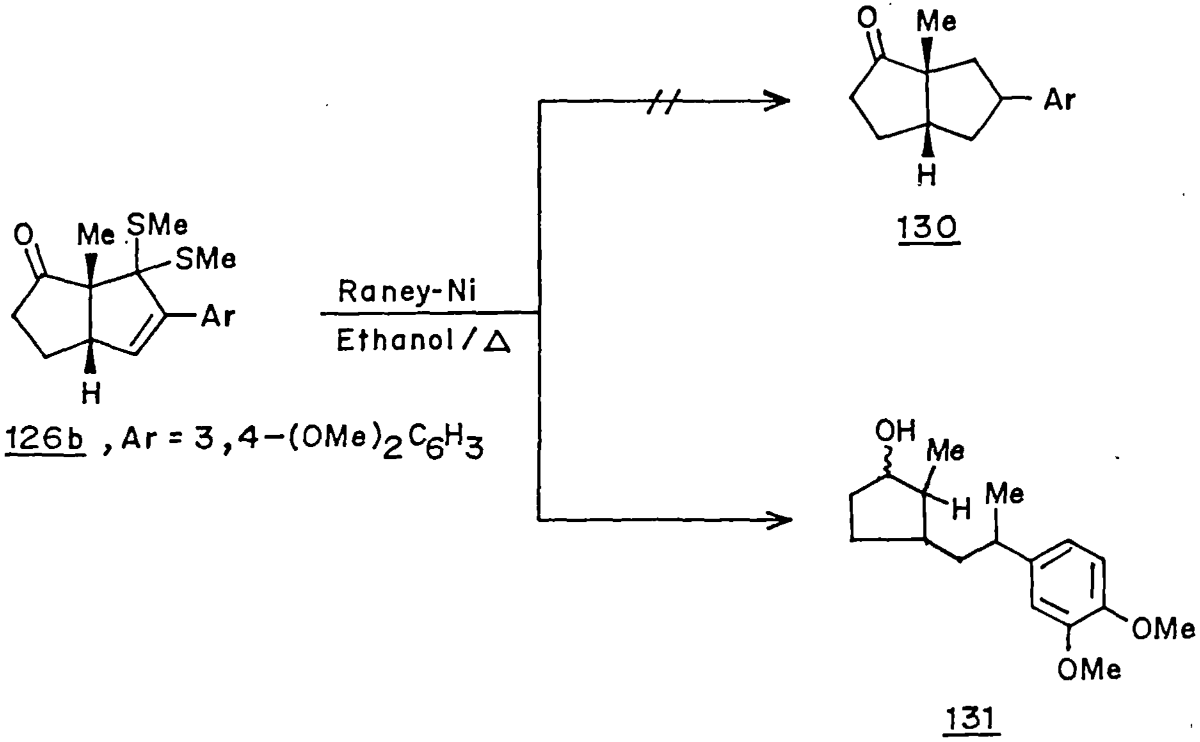
Scheme—26



126a, Ar = $H_2C\langle O O \rangle C_6H_3$

129

Scheme —27

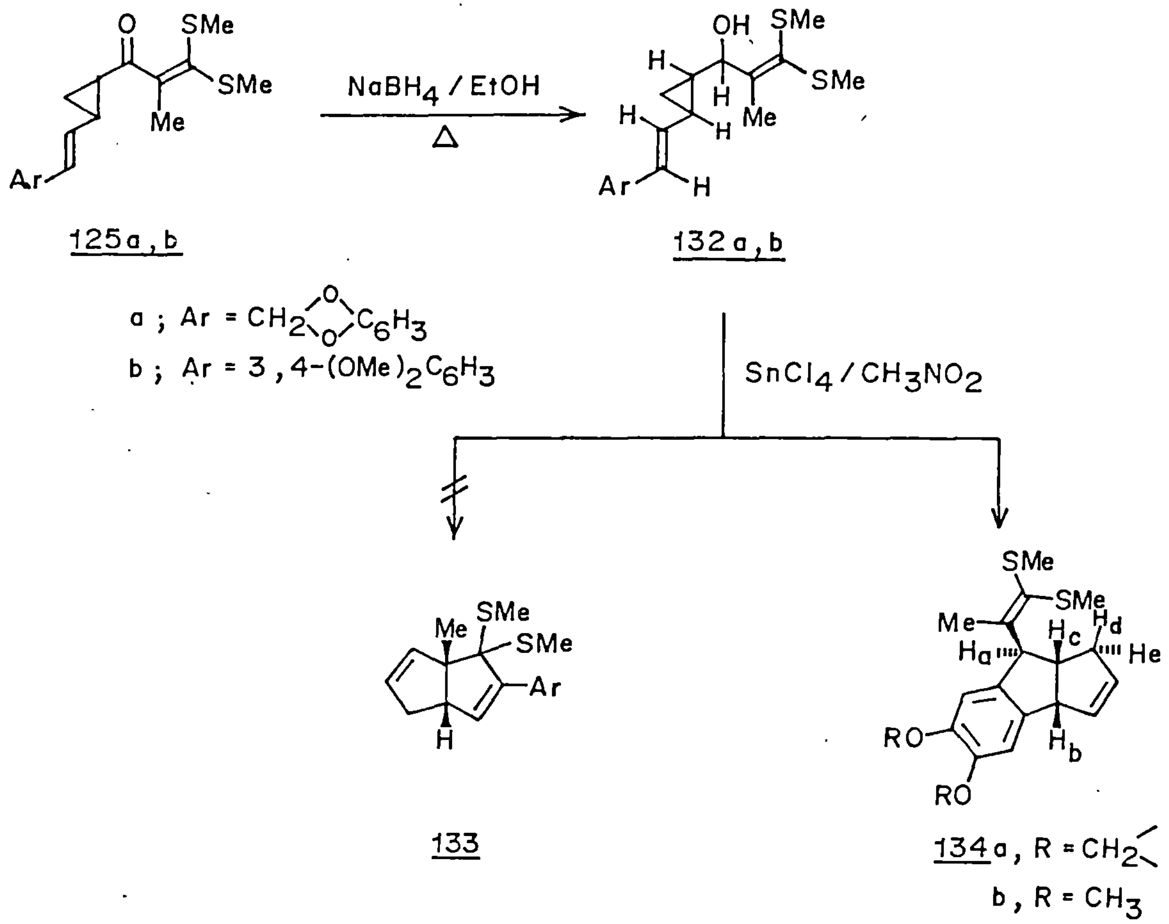

Raney-Ni
Ethanol / Δ
126b , Ar = 3,4–(OMe)$_2$C$_6$H$_3$
130
131
O
Me
SMe
SMe
Ar
H
OH
OMe

Scheme – 28

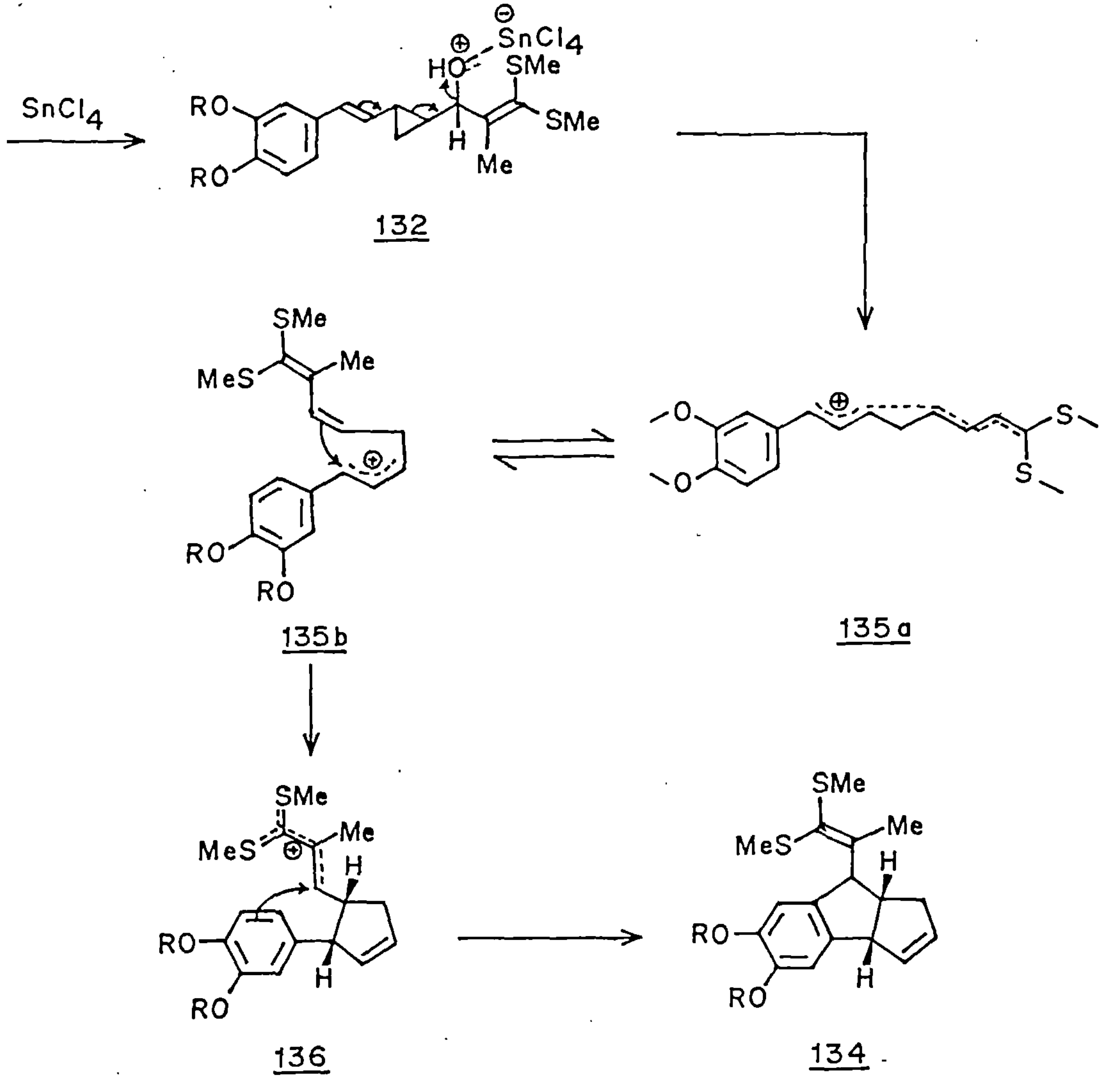
and the bridged methyne proton H_c appeared as broad multiplet between δ 2.94 to 3.01 due to its coupling with H_a and H_b, and two methylene protons H_d and H_e appeared at δ 2.61 (dd, 1H, J = 17, 9Hz) and δ 2.43 (d, 1H, J = 16.8Hz) respectively. These assignments of methyne and methylene protons were derived from decoupling experiment. Thus the irradiation of signal due to H_c proton at δ 2.94 to 3.01 reduced the doublet due to H_a to a singlet and H_b to a broad singlet and H_d to a broad doublet (J = 17Hz). Similarly irradiation of doublet (J=6Hz) due to H_b proton simplified the multiplet besides the broad double doublet due to H_d proton was converted to a sharp signal showing W-coupling between the two (H_b & H_d). Further irradiation of H_d signal at δ 2.61 reduced the multiplet due to H_c proton to a double doublet (J = 6, 8Hz) while H_b signal was appeared as sharp doublet. The stereochemical assignments of three methyne protons were attributed by differential NOE experiment. Thus irradiation of H_b proton at δ 4.16 caused 9.03% enhancement of H_c signal and olefinic signal (δ 5.84). The aromatic signal H_h at δ 6.68 showed enhancement by 5.52 and 6.11% respectively. The corresponding 3,4-dimethoxy styryl carbinol **132b** obtained by borohydride reduction of ketone **125b** gave the corresponding cyclopent[a]indene **134b** in 71% yield under identical condition. The structure of **134b** was also thoroughly assigned with the help of spectral and analytical data. The probable mechanism for the formation of cyclopent[a]indenes is shown in Scheme-30. The acid induced ring opening and rearrangement of cyclopropyl carbinols are very well documented in the literature. Few examples related to these have alredy been discussed.

Thus Lewis acid assisted ring opening of **132** gives highly stabilized carbocation **135a** which does not undergo intramolecular cyclization to give bis(methylthio)methyl cyclopentenyl carbocation **122** (Scheme-23). On the other hand **135a** (Scheme-30) exists in equillibrium with its geometrical isomer **135b** (U shape) having favoured conformation for cyclization through electron rich dienyl double bond to give another cyclic stablized carbocation **136**. The carbocation **136** is trapped by electron rich aromatic ring (para to alkoxy group) to afford bicyclic cyclopent[a]indene framework **134** over bicyclooctenes **133** play a crucial role, responsible for the observed rearrangement of the carbinols **132a, b** to the products **134a & b**.

The bis(methylthio)methylene side chain of the cyclopent[a]indene **134a & b** could be transformed to the corresponding α-methyl carboxylate **137** (Scheme-31) in the


O
SMe
SMe
Me
Ar
125a, b
NaBH$_4$ / EtOH
Δ
OH
SMe
H
H
SMe
H
Me
H
Ar
H
132a, b
a ; Ar = CH$_2$ O O C$_6$H$_3$
b ; Ar = 3, 4-(OMe)$_2$C$_6$H$_3$
SnCl$_4$ / CH$_3$NO$_2$
Me
SMe
SMe
Ar
H
133
SMe
SMe
Me
H$_c$
H$_d$
H$_a$
He
RO
H$_b$
RO
134a, R = CH$_2$
b, R = CH$_3$

Scheme – 29

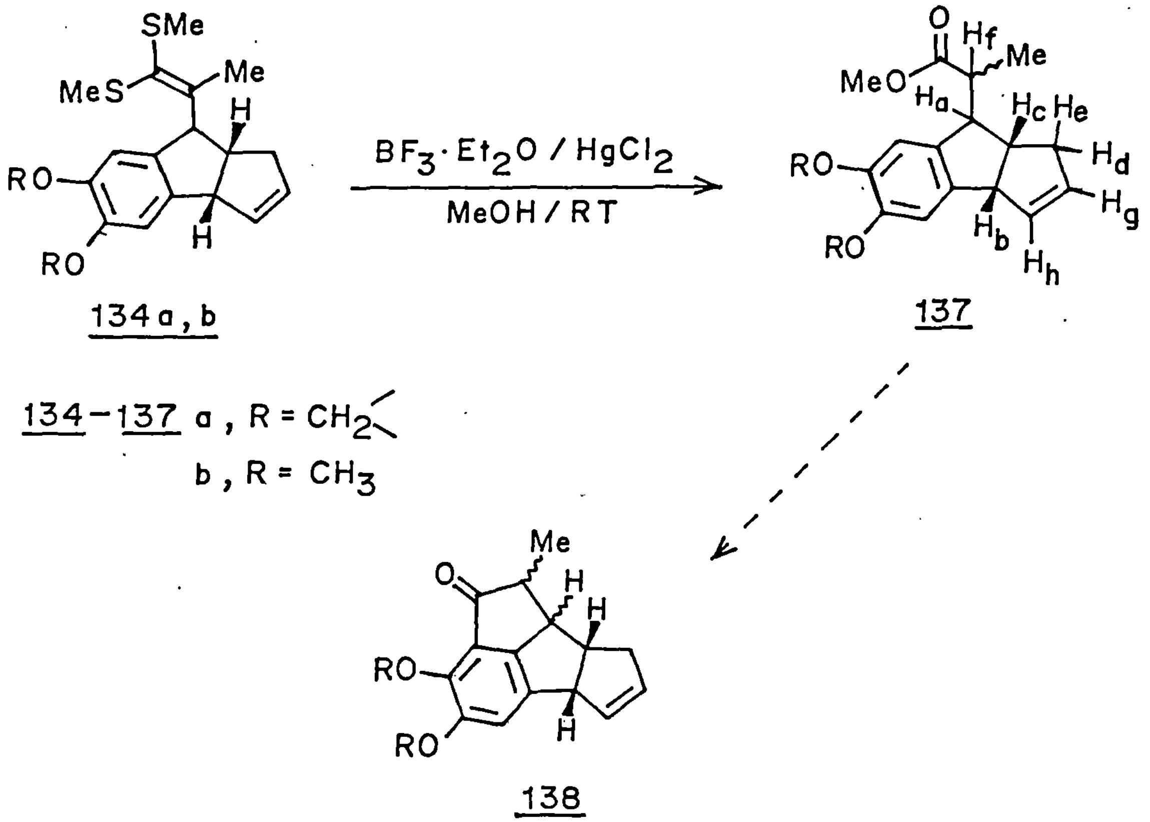

SnCl4
RO
RO
HO
SnCl4
SMe
SMe
H
Me
132
SMe
MeS
Me
RO
RO
135b
O
O
S
S
135a
SMe
MeS
Me
H
H
RO
RO
136
SMe
MeS
Me
H
H
RO
RO
134

Scheme - 30

presence of $BF_3.Et_2O/HgCl_2/MeOH$ in 93% yield. The structure of **137a & b** was established with the help of analytical ^1H and ^{13}C NMR data which showed it to be a mixture of two diastereomers [60:40]. The IR spectra displayed a strong peak at 1727cm^{-1} due to carbomethoxy group besides in the NMR spectrum methyl protons present at α- position appeared as doublet doublet (two diastereomers, J = 7.2Hz) and two methoxy peaks at δ 3.64 and δ 3.71 absolutely confirming the transformation. We are further attempting to cyclize the carbomethoxy side chain on aromatic ring to give the annelated triquinane **138**. Our efforts in this direction are in progress *(Scheme-31)*.

We had also observed that in the absence of α-proton on the cyclopropyl carbinol **140**, the rearrangement under similar reaction condition yielded a product which was characterized as 3-piperonyl-4-[(2'-methylthiocarbonyl)ethenyl]cyclopentene **141** instead of cyclopent[a]indene **142** (Scheme-32). The initial steps appeared to be same as in the case of cyclopropyl carbinol **132** (Scheme-30). The second cyclization did not take place in tandem fashion as expected, may be because of the unstability of carbocation **135d** more succeptible to hydrolysis. The compound was characterized with the help of IR, ^1H & ^{13}C NMR, COSY and other analytical data which were in aggrement with the assigned structure and are presented in the experimental section.

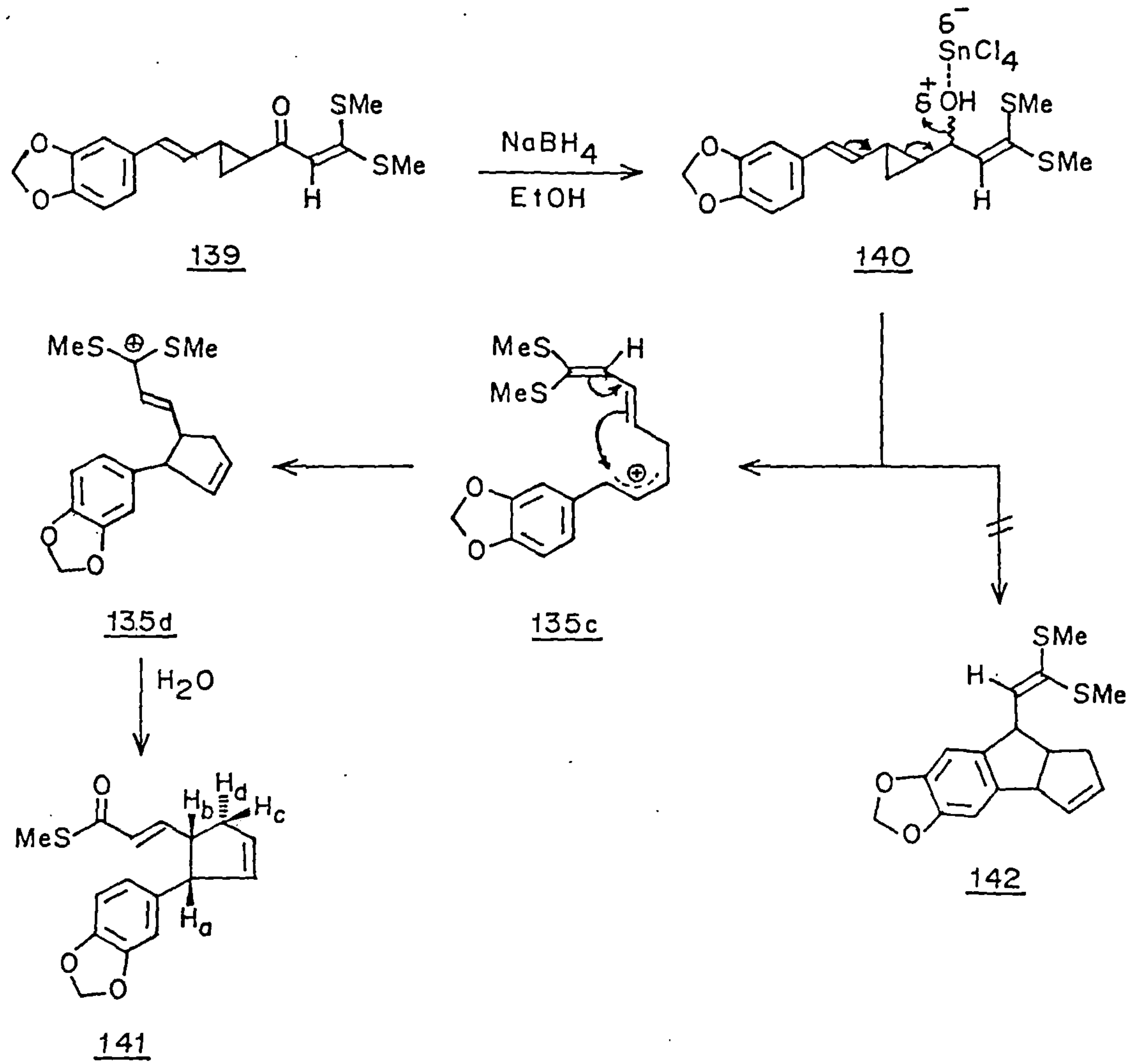
Finally we had attempted the acid induced cyclization studies on carbinol **143** obtained by regiospecific addition of methylmagnesium iodide on the cyclopropyl ketone **125a** (Scheme-33). The product isolated was not the expected rearranged cyclopent[a]indene **145** but it was characterized as bridged bicyclo[3.2.1]octadiene **144** by spectral and analytical data. The probable mechanism of formation of **144** is shown in Scheme-34. The initial step appears to be the same like the formation of cyclopent[a]indene obtained by treatment on cyclopropyl carbinol. Thus the carbocation **147** does not undergo cyclization at position-1 of allyl carbocation **147** to give **145** probably due to steric crowding on **147**. On the other hand the carbocation **147** exists in 1Z,2Z configuration and undergo intramolecular participation of olefinic double bond to give initially the bridged bicyclo[3.2.1]octadiene **148** which appears to undergo homo 1,5-sigmatropic shift through intermediate **149** to give another intermediate **150**. Further reorganisation and rearrangement of proton in **150** affords the observed product **144** having less steric crowding as compared to **148**. The mass spectra of **144** exhibited molecular


SMe
MeS
Me
H
RO
RO
H
134a,b
BF3·Et2O / HgCl2
MeOH / RT
O
MeO
Hf
Me
Ha
Hc
He
Hd
Hg
RO
RO
Hb
Hh
137
134–137 a, R = CH2<
b, R = CH3
Me
O
H
H
RO
RO
H
138

Scheme – 31

ion peak m/z 346 (M^+, 90) besides other important peak at m/z 251 (M^+-95, 100). The IR spectra shows peaks at 2922, 1482, 1433, 1254 cm^{-1}. The structure of **144** was established mainly with the help of ^1H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR data. The ^1H NMR showed absenced of any olefinic proton in the low field region and only three aromatic protons were present as double doublet (J = 8, 1.5Hz), broad singlet and doublet (J = 1.5 Hz) at δ 6.69 to 6.77, while methylenedioxy protons were present as singlet at δ 5.93. In the higher field region the two singlets at δ 1.75 and δ 1.78 were assigned two olefinic methyl groups. Where as another two singlets at δ 1.94 and δ 2.38 were assigned to two methylthio groups attached to sp^3 and sp^2 carbons respectively. The three methyne and two methylene protons appeared as broad singlet at δ 3.39(H_a, 1H), doublet at δ 2.97 (J = 4.8Hz, 1H, H_b) and another doublet at δ 2.42 (J = 4.8Hz, 1H, H_c) assigned to the bridged methyne protons while two methylene protons were merged at δ 1.92 and δ 1.75 with signals due to methyl groups. The geminal coupling of H_d & H_e was not observed. Further confirmation of structure **144** were obtained from its ^{13}C NMR spectra which showed signals at δ 11.35, 13.12, 14.95, 15.09 due to two methyl and two methylthio carbons while the four signals at δ 34.73, 47.39, 47.42 and 53.71 confirmed the presence of three methyne carbons and one methylene carbon. The signals at δ 107.96, 108.83, 121.24 (Ar-CH) and 100.65 (methylenedioxy), 125.13 (Ar-quarternary), 145.70, 147.41 (Ar- quarternary) confirm the presence of aryl group besides other four signals at δ 132.98, 138.14, 142.67, 143.38 due to four olefinic quarternary carbons supported the presence of two olefinic double bond. Finally the structure of **144** will be confirmed by X-rays.

In conclusion, it has been demonstrated that the substituent on cyclopropyl ring as well as substitution on mercapto double bond and also on styryl double bond play a vital mole for the formation of various products through tandem carbocationic cyclization to provide bicyclic or tricyclic ring. The presence of electron donating substituents on aromatic ring is necessary so as to facilitate the ring formation through intramolecular electrophilic rearrangement.


O
SMe
SMe
H
NaBH4
EtOH
139
δ−
SnCl4
δ+ OH
SMe
SMe
H
140
MeS
SMe
135d
MeS
MeS
H
135c
H2O
MeS
O
Hb
Hd
Hc
Ha
141
H
SMe
SMe
142

Scheme – 32

EXPERIMENTAL SECTION

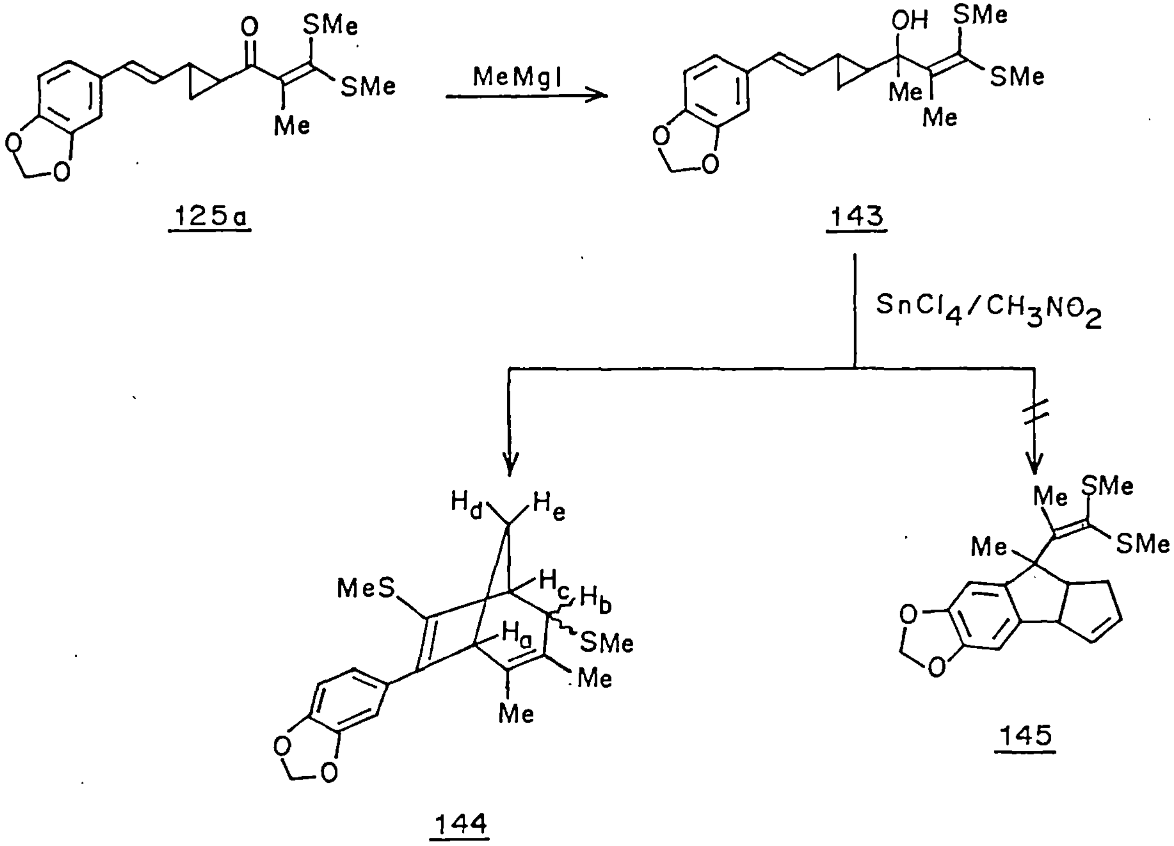
General

M.Ps were obtained on a "Thomas Hoover" melting point (capillary method) apparatus and are uncorrected. The Infrared spectra were recorded on Perkin-Elmer 983 spectrometer. ^{1}H NMR (90 MHz) were recorded on Varian EM-390 spectrometer. High resolution ^{1}H NMR (300 MHz), ^{13}C NMR (75.43 MHz) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shifts (δppm) and the coupling constants (Hz) are reported in the standard fashion with reference to either TMS as internal lock (for ^{1}H NMR), the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C NMR) Mass spectra (MS) were obtained on a Jeol JMS-D 300 Mass spectrometer. Masses are reported in units of mass over charge (m/z), the molecular and base peaks are indicated by "M^+" and "%" respectively. Elemental analysis were carried out on a Heraeus CHN-O-Rapid analyzer.

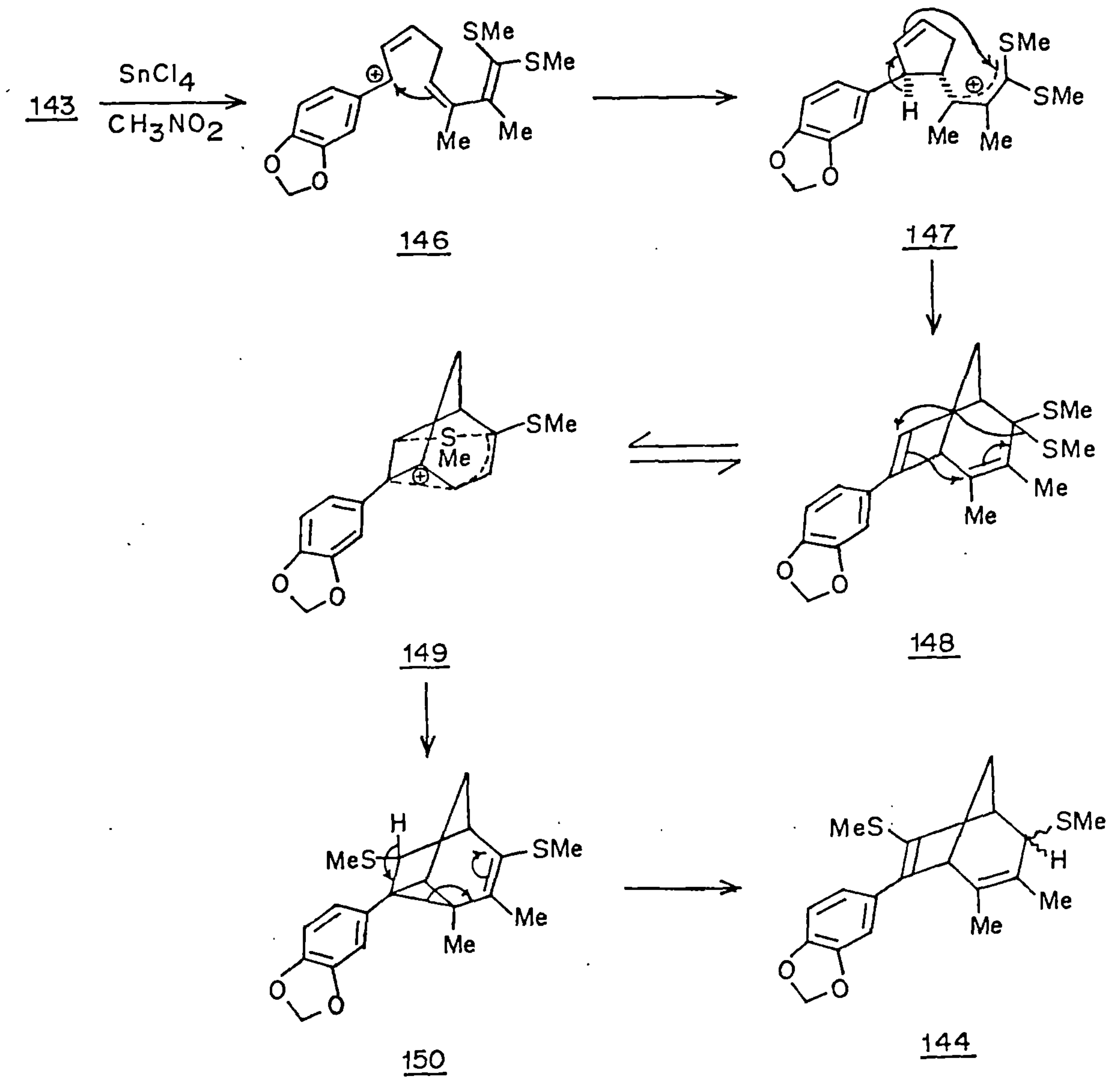
All reactions were performed in oven dried (120°C) glasswares under a positive dry argon/nitrogen atmosphere. Analytical thin layer chromatography (tlc) were performed on glass plates coated with ACME's silicagel containing 13% calcium sulfate as binder and various combination of visualization of spots was accomplished by exposure to iodine vapour or potassium permanganate (acidic) solution. ACME's silicagel (60-120 mesh) is used for coloumn chromatography, eluents for coloumn chromatography were used after simple distillation of commercial materials. All solvent evaporations were done using a steam bath.

Chemicals and Reagents

The commercial samples of 3,4-dimethoxy benzaldehyde, 3,4- methylenedioxy benzaldehyde and 4-methoxy benzaldehyde were used as such for the preparation of corresponding cinnamaldehydes as per reported procedure.[48] Cinnamaldehyde was distilled before use. Solvents used for the reaction were dried before use. Stannic chloride and nitromethane were purchased from SPECTRO-CHEM and used as such. Trimethylsulphoxonium iodide was prepared by reported method[47] and PTC (tetrabutylammonium bromide) was purchased from Aldrich.



Scheme-33


143
SnCl4
CH3NO2
SMe
SMe
Me
Me
146
SMe
SMe
H
Me
Me
147
SMe
S
Me
149
SMe
SMe
Me
Me
148
H
MeS
SMe
Me
Me
150
MeS
SMe
H
Me
Me
144

Scheme - 34

General procedure for the condensation of α-acylketene dithioacetals with cinnamaldehydes: Synthesis of cinnamoyl ketene dithioacetals 124a-d.

To a cooled and stirred solution of sodium ethoxide (1gm in 10ml ethanol) in ethanol (25ml), a solution of α-acyl ketene dithioacetal (0.02mol) and the appropriate cinnamaldehyde (0.02mol) in ethanol (15ml) was added dropwise over a period of 5min. The reaction mixture was brought to room temperature within 20min. and further stirred for 4-5hr. Poured to ice cooled water (200ml). The crude solid was filtered off and washed thoroughly with water (4x500ml), which were pure enough for cyclopropanation. the liquid condensed products were extracted with chloroform (3x50ml),washed thoroughly with water (4x75ml),dried and coloumn chromatographed (EtOAc-hexane) to give pure cinnamoyl ketene dithioacetals in quantitative yields.

General procedure for cyclopropanation of 124a-d: Synthesis of cyclopropylketones 125a-d.

A suspension of the appropriate cinnamoyl ketene dithio acetal (0.01mol), trimethylsulphoxonium iodide (0.013mol), tetrabutylammonium bromide[46] (0.015mol) in aq.NaOH (50%, 50ml) and dichloromethane (70ml) was stirred at 50°C for 7-20hr (monitered by tlc). The organic layer was separated, concentrated and diluted with ethyl acetate to precipitate the PTC (TBAB) which was filtered off. The filtrate was evaporated to give crude cyclopropyl ketones, purified by coloumn chromatography over silicagel using EtOAc-hexane as eluents. The cyclopropyl ketone **139** was also prepared following this method.

1-[2-[Bis(methylthio)methylene]propanoyl]-2-(3,4-methylenedioxy-styryl)cyclopropane (125a)

Viscous liquid; yield 86%; IR (CCl_4): 2920, 1660 (CO), 1497, 1249cm^{-1}; ^{1}H NMR (90MHz, CCL_4): δ 0.94-1.3(m, 1H, CH), 1.5-1.82(m, 1H, CH), 2.15 (s, 3H, CH_3), 2.14-2.4(m, 2H, CH_2), 2.20 (s, 3H, SCH_3), 2.30 (s, 3H, SCH_3), 5.68 (dd, J=16, 8Hz, 1H, =CH), 5.98 (s, 2H, methylenedioxy), 6.43 (d, J=16Hz, 1H, =CH), 6.75 - 6.90 (m, 3H, ArH). Anal. Calcd. for $C_{18}H_{20}O_3S_2$ (348.46): C 62.03; H 5.78. Found: C 62.29; H 5.73.

1-[2-[Bis(methylthio)methylene]propanoyl]-2-(3,4-dimethoxy- styryl)cyclopropane (125b)

Viscous liquid; yield 82%; IR (CCl_4): 2828, 1658 (CO), 1545, 1509cm^{-1}; ^{1}H NMR (90MHz, CCl_4): δ 0.91-1.13(m, 1H, CH), 1.40-1.61(m, 1H, CH), 1.98-2.24(m, 2H, H_2), 2.00 (s, 3H, CH_3), 2.15 (s, 3H, SCH_3), 2.26 (s, 3H, SCH_3), 3.70 (s, 6H, OCH_3), 5.55 (dd, J=16,8Hz, 1H, =CH), 6.40 (d, J=16Hz, =CH), 6.68-6.77 (m, 3H, ArH). Anal. Calcd. for $C_{19}H_{24}O_3S_2$ (364.5): C 62.60; H 6.63. Found: C 62.92; H 6.40.

1-[[Bis(methylthio)methylene]acetyl]-2-(3,4-methylenedioxy- styryl)cyclopropane (139)

Light yellow solid; mp. 72-73°C; yield 83%; IR (KBr): 2911, 1663 (CO), 1489cm^{-1}; ^{1}H NMR (90MHz, CCl_4): δ 0.92-1.20 (m, 1H, CH), 1.51-1.75 (m, 1H, CH), 1.9-2.16 (m, 2H, CH_2), 2.50 (s, 6H, SCH_3), 5.65 (dd, J=16, 8Hz, 1H, =CH), 5.92 (s, 2H, methylenedioxy), 6.24 (s, 1H, =CH), 6.43 (d, J=16Hz, 1H, =CH), 6.72-6.88 (m, 3H, ArH). Anal. Calcd. for $C_{17}H_{18}O_3S_2$ (334.43): C 61.05; H 5.42. Found: C 61.29; H 5.46.

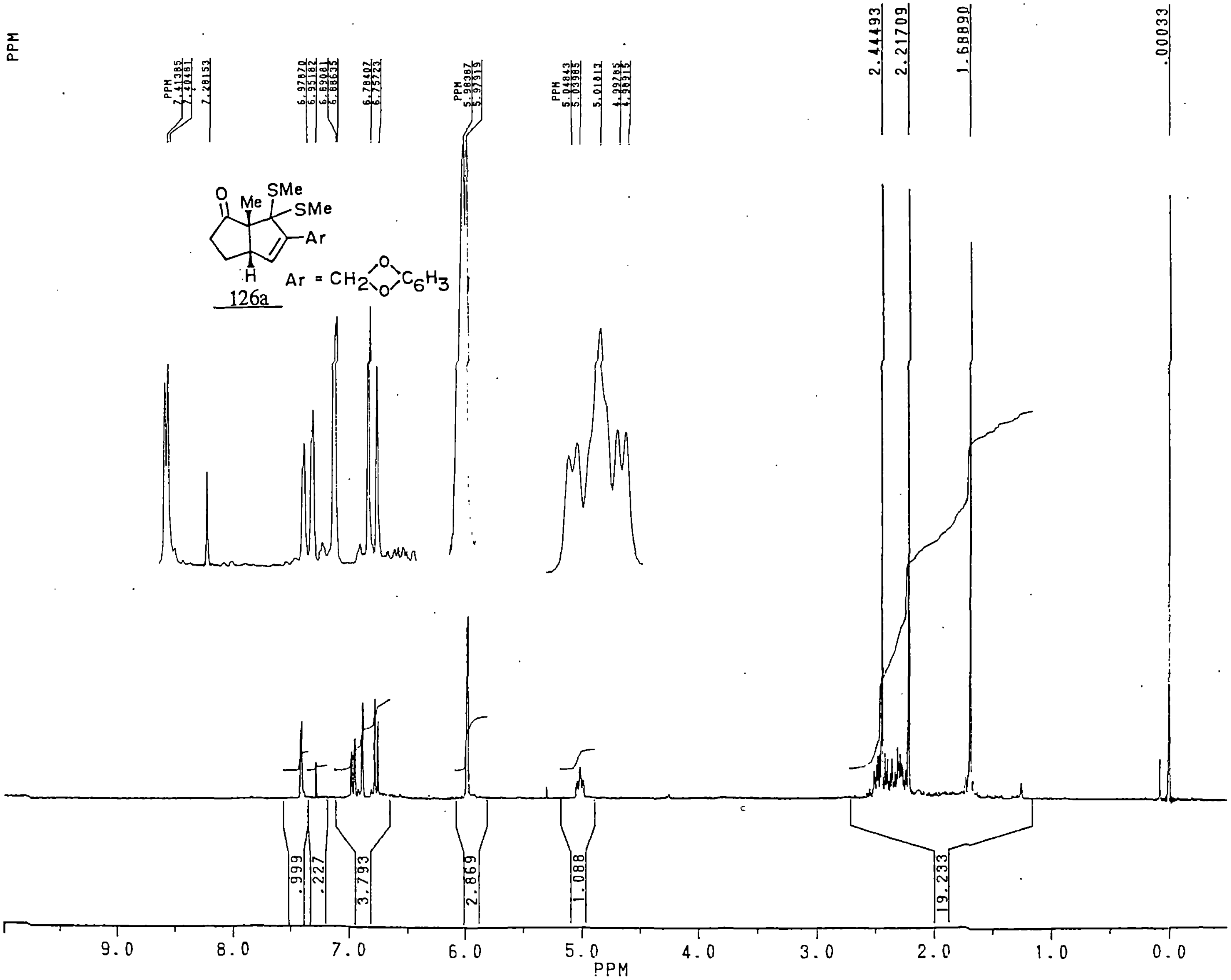
The cyclopropyl ketones **125c & d** were prepared as reported and compared with spectral and analytical data of reported ones.[22a]

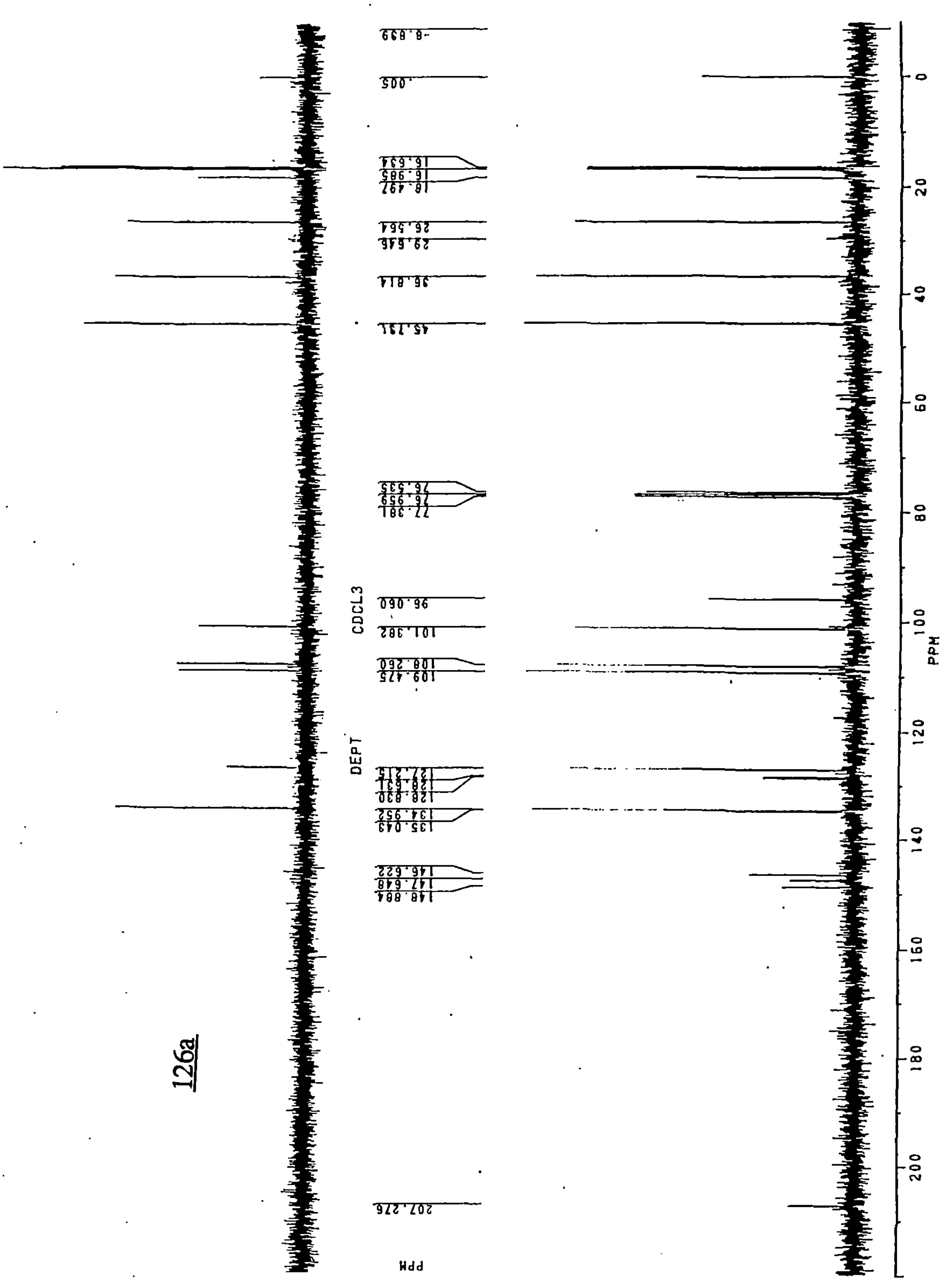
General Procedure for the Cyclization of Cyclopropyl Ketones (125a-d) and Carbinols (132a, b, 140 & 143) in the Presence of Stannic Chloride in Nitro Methane.

A solution of appropriate cyclopropyl ketone or carbinol (0.01mol) in nitromethane (25ml) was treated with $SnCl_4$ (1.5eqv), and the reaction mixture was stirred at rt for 2hr. It was then poured into cold aq$NaHCO_3$ solution (200ml), extracted with chloroform (3x60ml), washed with water (3x100ml), dried (Na_2SO_4) and evaporated to afford crude products, which were purified by coloumn chromatography over silicagel using EtOAc-hexane as eluents.

1-Bis(methylthio)-2-piperonyl-6a-methylbicyclo[3.3.0]oct-2-ene-6-one (126a)

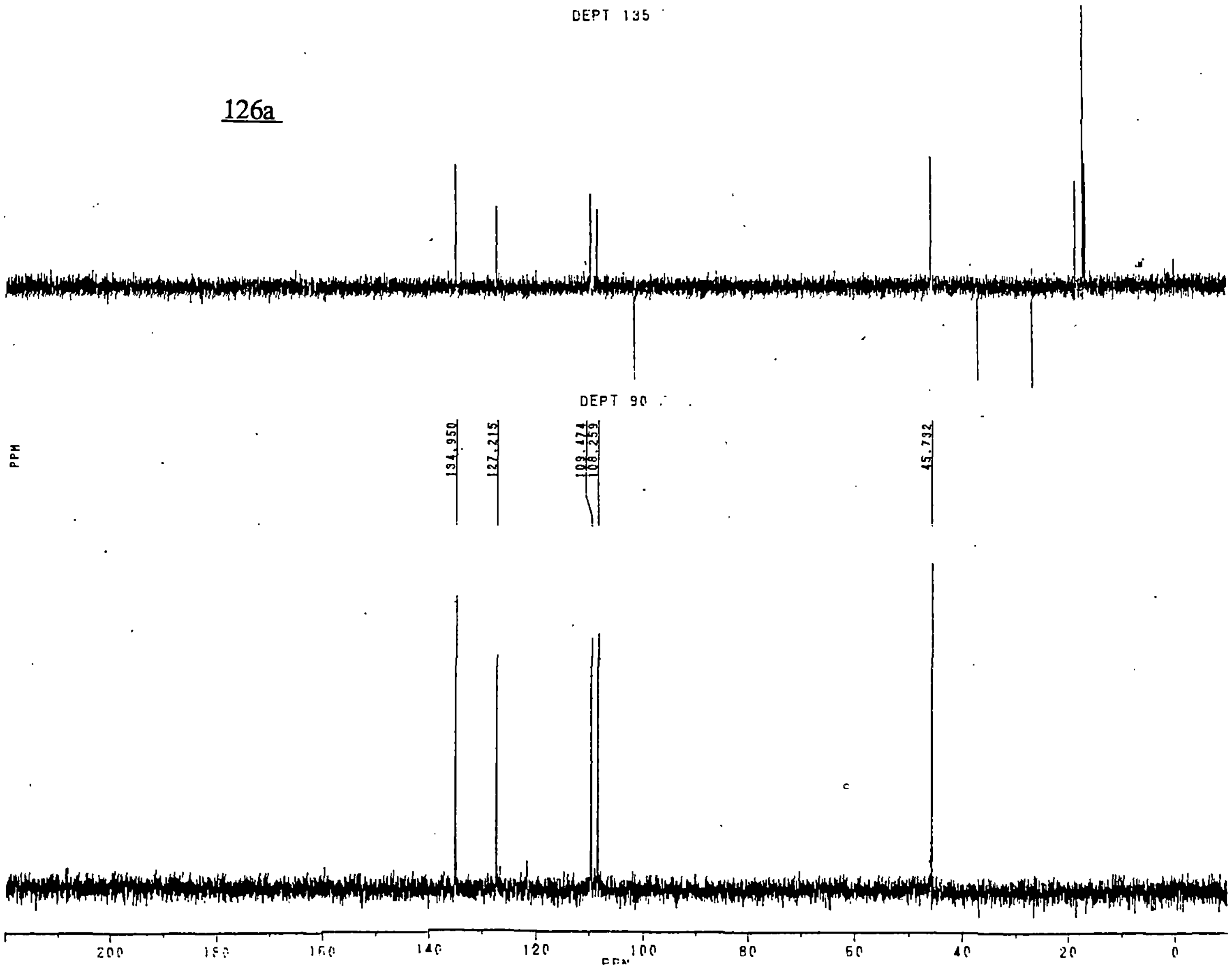
Viscous liquid; yield 61%; IR (CCl_4): 2901, 1740 (CO), 1610, 1501cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ 1.68 (s, 3H, CH_3), 2.21 (s, 3H, SCH_3), 2.22-2.50 (m, 4H, CH_2), 5.02 (dt, J=7.8,2.5Hz, 1H, C_{3a}-H), 5.98 (s, 2H, OCH_2O), 6.77 (d, J=8Hz, 1H, ArH_a), 6.88 (d, J=3Hz, ArH_b), 6.96 (dd, J=8, 3Hz, 1H, ArH_c), 7.40 (d, J=3Hz, 1H, =CH); ^{13}C NMR (75MHz, $CDCl_3$): δ 16.63 (SCH_3), 16.98 (SCH_3), 18.49 (CH_3), 26.56 (CH_2), 29.64, 36.81 (CH_2), 45.73 (CH), 101.38 (OCH_2O), 108.26, 109.47, 127.21, 128.63, 128.83, 135.04, 146.62, 147.64, 148.88, 207.27 (CO); MS (m/z, %): 348 (M^+, 26), 301 (M^+- SMe, 100), 253 (M^+-2SMe, 88); Anal.Calcd. for $C_{18}H_{20}O_3S_2$ (348.46): C 62.03; H 5.78. Found: C 62.18; H 5.75.


126a
O
Me
SMe
SMe
Ar
H
Ar = CH2O2C6H3
PPM
7.41385
7.40481
7.28153
6.97870
6.95182
6.89081
6.88635
6.78407
6.75723
PPM
5.98387
5.97919
PPM
5.04843
5.03985
5.01813
4.99785
4.98915
2.44493
2.21709
1.68890
.00033
.999
.227
3.793
2.869
1.088
19.233
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM


-8.899
.005
16.634
16.985
18.492
26.564
29.646
36.814
45.131
76.535
76.959
77.381
96.060
101.382
108.260
109.475
127.215
128.631
128.830
134.952
135.045
146.622
147.648
148.884
207.276
CDCL3
DEPT
PPM
0
20
40
60
80
100
120
140
160
180
200
PPM

126a

126a


DEPT 135
DEPT 90
PPM
134.950
127.215
109.474
108.259
45.732
200
180
160
140
120
100
PPM
80
60
40
20
0

1-Bis(methylthio)-2-(3,4-dimethoxybenzyl)-6a-methyl-bicyclo[3.3.0]oct-2-ene-6-one (126b)

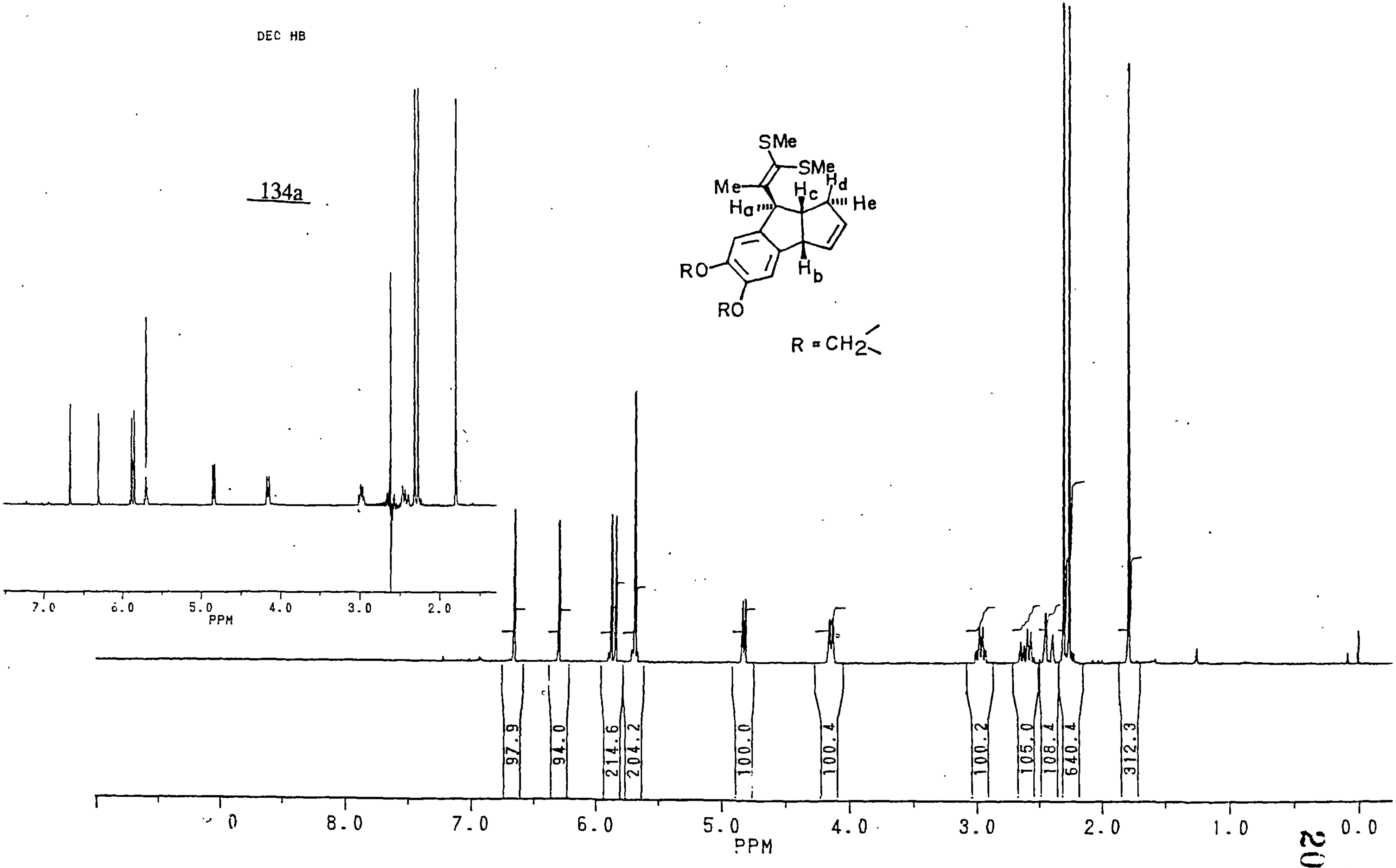
Colourless solid (hexane); mp. 105°C; yield 65%; IR (KBr): 2881, 1740 (CO), 1605, 1512cm^{-1}; ^{1}H NMR (90MHz, $CDCl_3$): δ 1.75 (s, 3H, CH_3), 2.26 (s, 3H, SCH_3), 2.27-2.25(m, 4H, CH_2), 2.24 (s, 3H, SCH_3), 3.76 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.82 (dt, J=7.8, 2.5Hz, 1H, C_{3a}-H), 6.79-7.10 (m, 3H, ArH), 7.43 (d, J=3Hz, 1H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.89 ($2SCH_3$), 18.30 (CH_3), 26.82 (CH_2), 31.23, 36.85 (CH_2), 45.74 (CH), 56.41 (OCH_3), 56.42 (OCH_3), 110.21, 113.10, 125.01, 127.41, 128.03, 130.00, 147.50, 148.11, 150.06, 211.56 (CO); MS (m/z, %): 364 (M^+, 9.2), 317 (M^+- SMe, 33.5), 269 (M^+-2SMe). Anal. Calcd. for $C_{19}H_{24}O_3S_2$ (364.5): C 62.60; H 6.63. Found: C 62.88; H 6.64.

1-Bis(methylthio)-2-(4'-methoxyphenyl)-6a-methyl- bicyclo[3.3.0]oct-2-ene-6-one (126c) Viscous liquid; yield 72%; IR (CCl_4): 2948, 1740 (CO), 1618, 1530cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (s, 3H, CH_3), 2.14 (s, 3H, SCH_3), 2.18-2.43 (m, 4H, CH_2), 2.35 (s, 3H, SCH_3), 3.75 (s, 3H, OCH_3), 4.96 (dt, J=8, 3Hz, CH), 6.75 (d, J=9Hz, 2H, ArH), 7.30 (d, J=9Hz, 2H, ArH), 7.40 (d, J=3Hz, 1H, =CH); ^{13}H NMR (75 MHz, $CDCl_3$): δ 16.65 (SCH_3), 16.81 (SCH_3), 18.32 (CH_3), 24.96, 29.47 (CH_2), 36.71 (CH_2), 45.76 (CH), 55.13 (OCH_3), 113.63, 113.83, 132.41, 134.66, 147.06, 160.61, 207.25 (CO); MS (m/z, %): 334 (M^+, 8.4), 287 (M^+-SMe, 84.12), 239 (M^+-2SMe, 100). Anal. Calcd. for $C_{18}H_{22}O_2S_2$ (334.48): C 64.63; H 6.63. Found: C 64.75; H 6.60.

S-Methyl-trans-1-methyl-5-styryl-2-oxocyclopentane-r-1thiocarboxylate (128a) was compared with that of reported data.[22a]

8-[2'-[Bis(methylthio)methylene]propenyl]-5,6- methylenedioxycyclopent[a]ind-2-ene (134a)

Colourless solid (hexane); mp. 59-60°C; yield 82%; IR (KBr): 1470, 1360, 1290cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.79 (s 3H, CH_3), 2.27 (s, 3H, SCH_3), 2.31 (s, 3H, SCH_3), 2.43 (d, J=16.8Hz, 1H, H_e), 2.61 (dd, J=16.8, 9Hz, 1H, H_d), 2.94-3.01 (m, 1H, H_c), 4.16 (d, J=9Hz, 1H, H_b), 4.85 (d, J=6Hz, 1H, H_a), 5.70 (s, 2H, OCH_2O), 5.84 (d, J=1.5Hz, 1H, =CH_g), 5.88 (d, J=1.5Hz, 1H, =CH_f), 6.32 (s, 1H, ArH), 6.68 (s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.85 (CH_3), 18.12 ($2SCH_3$), 38.91, 47.33, 57.05, 58.37, 100.92 (OCHO), 104.32, 104.53, 128.99, 129.65, 132.11, 137.16, 138.05, 146.93, 147.37; MS (m/z, %): 332 (M^+, 47.1), 286 (M^+-SMe, 18.5), 269 (M^+-63, 68.2), 237 (M^+-95, 86.1). Anal. Calcd. for $C_{18}H_{20}O_2S_2$ (332.46): C 65.02; H 6.06. Found: C 65.21; H 6.02.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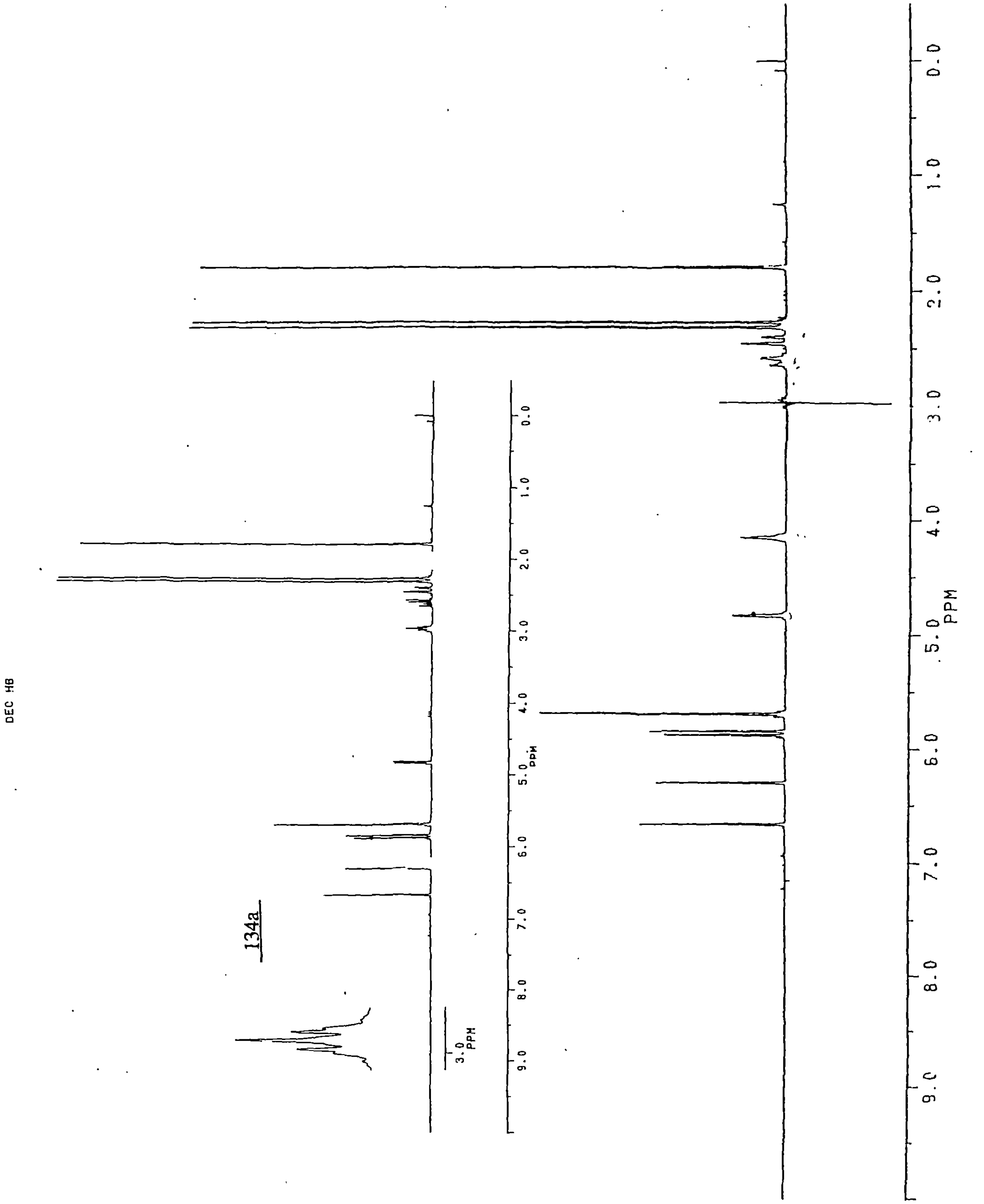
7.0
6.0
5.0
4.0
3.0
2.0
PPM
SMe
SMe
Me
Hd
Hc
Ha
He
RO
RO
Hb
R = CH2
97.9
94.0
214.6
204.2
100.0
100.4
100.2
105.0
108.4
640.4
312.3
0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

134a



134a

8-[2'-[Bis(methylthio)methylene]propenyl]-5,6- dimethoxycyclopent[a]ind-2-ene (134b) Viscous liquid; yield 67%; IR (CCl_4): 1468, 1240, 1220cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82 (s,3H, CH_3), 2.34 (s, 3H, SCH_3), 2.37 (s, 3H, SCH_3), 2.45 (tt, J=17, 1.5Hz, 1H, H_e), 2.65 (dddd, J=17, 9, 1.5Hz, 1H, H_d), 2.98 (dttd, J=17, 9, 6, 1.5Hz, 1H H_c), 3.80 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.25 (tt, J=9, 1.5Hz, 1H, H_b), 4.92 (d, J=6Hz, 1H, H_a), 5.69-5.75 (m, 1H, =CH), 5.75-5.83 (m, 1H, =CH), 6.38 (s, 1H, ArH), 6.78 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.97 (CH_3), 18.23 ($2SCH_3$), 39.06 (CH_2), 47.52 (CH), 56.06 (CH), 56.15 (OCH_3), 57.39 (CH), 58.77 (OCH_3), 107.02, 107.35, 128.64, 129.78, 132.31, 136.00, 137.26, 148.00, 148.66. Anal. Calcd. for $C_{19}H_{24}O_2S_2$ (348.5): C 65.47; H 6.94. Found: C 65.58; H 6.93.

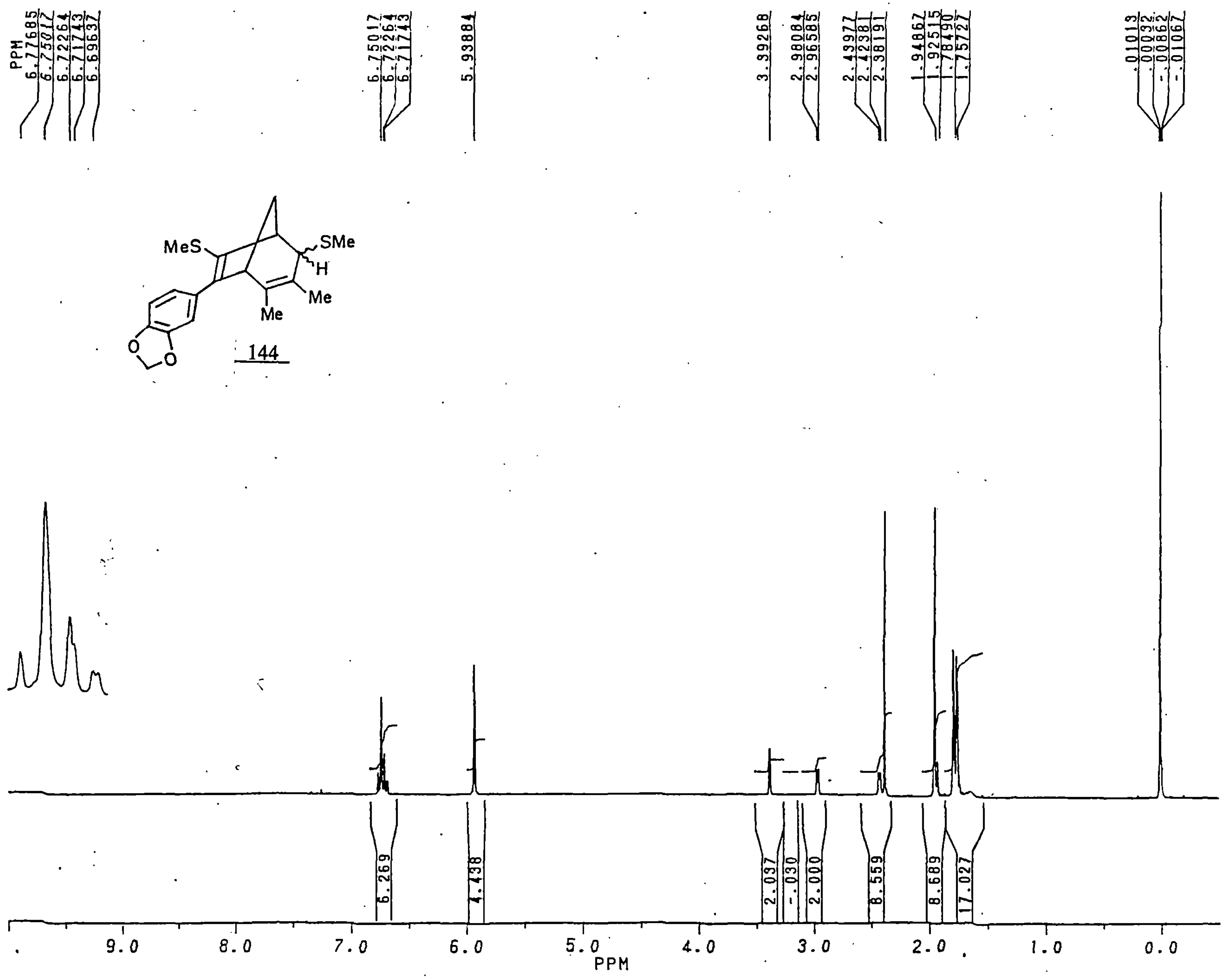
3-(3,4-methylenedioxy)-4-[(2'-methylthiocarbonyl)ethenyl]- cyclopentene (141) Viscous liquid; yield 75%; IR (CCl_4): 2917, 1651 (CO), 1499cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H, SCH_3), 2.26-2.29 (m, 1H, H_c), 2.69-2.78 (m, 1H, H_d), 3.28 (pent, J=6Hz, 1H, H_b), 3.59-3.62 (m, 1H, H_a), 5.68 (dd, J=4, 1.5Hz, 1H, =CH), 5.89 (s, 2H, OCH_2O), 5.88-5.93 (m, 1H, =CH), 6.04 (dd, J=15, 9Hz, 1H, =CH), 6.34 (d, J=15Hz, 1H, =CH), 6.70-6.73 (m, 2H, ArH), 6.88 (s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.49 (SCH_3), 39.26 (CH_2), 46.04 (CH), 65.72 (CH), 100.86 (OCH_2O), 105.47, 108.17, 120.64, 127.96, 129.69, 130.35, 131.45, 133.88, 146.79, 147.83, 200.77 (CO). Anal. Calcd. for $C_{16}H_{16}O_3S$ (288.354): C 66.64; H 5.59. Found: C 66.59; H 5.62.

1,5-Bis(methylthio)-2,3-Dimethyl-4-(3,4-methylenedioxy)-bicyclo[3.2.1]octa-2,4-diene (144)

Colourless crystals; mp. 102-103°C; yield 72%; IR (KBr): 2922, 1482, 1433, 1254cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.75 (s, 3H, CH_3), 1.76 (m, 1H, H_d, merged with CH_3), 1.78 (s, 3H, CH_3), 1.93 (m, 1H, H_e, merged with SCH_3), 1.94 (s, 3H, SCH_3), 2.38 (s, 3H, SCH_3), 2.42 (d, J=4.8Hz, 1H, H_c), 2.97 (d, J=4.8Hz, 1H, H_b), 3.39 (brs, 1H, H_a), 5.93 (s, 2H, OCH_2O), 6.70 (dd, J=8, 1.5Hz, 1H, ArH), 6.75 (brs, 1H, ArH), 6.77 (d, J=1.5Hz, 1H, ArH), 6.75-6.77 (brs, d, J=1.5Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.35 (CH_3), 13.12 (CH_3), 14.94 (SCH_3), 15.09 (SCH_3), 34.73, 47.39, 47.42, 53.71, 100.65, 107.96, 108.83, 121.24, 125.13, 132.98, 138.14, 142.67, 143.38, 145.70, 147.41; MS (m/z, %): 346 (M^+, 90), 299 (M^+-SMe, 10.3), 251 (M^+-95, 100). Anal. Calcd. for $C_{19}H_{22}O_2S_2$ (346.49): C 65.85; H 6.40. Found: C 65.71; H 6.44.

Boron Trifluoride Catalyzed Methanolysis of cyclopent[a]indenes 134a & 134b

A suspension of the required cyclopent[a]indene (0.01mol) and $HgCl_2$ (0.1mol) in anhydrous methanol (10ml) was stirred at rt (10min) followed by addition of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6.75017
6.72264
6.71743
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6.72264
6.71743
5.93884
3.39268
2.98084
2.96585
2.43977
2.42381
2.38191
1.94867
1.92515
1.78490
1.75727
.01013
.00032
-.00862
-.01067
MeS
SMe
H
Me
Me
O
O
144
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4.438
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2.000
8.559
8.689
17.027
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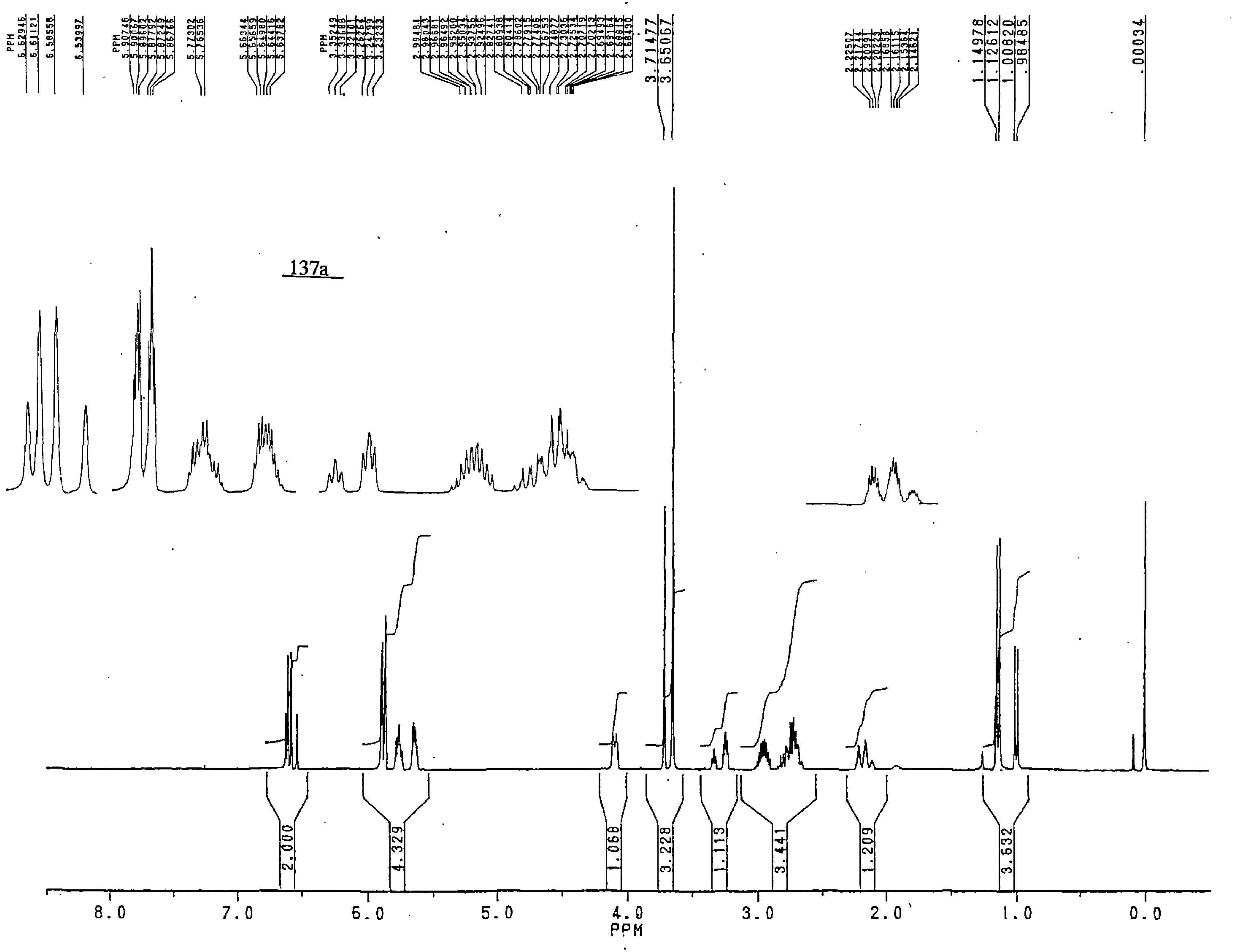
8.0
7.0
6.0
5.0
PPM
4.0
3.0
2.0
1.0
0.0



137a

PPM
6.62946
6.61121
6.58558
6.53997
PPM
5.90746
5.90067
5.89602
5.87792
5.87249
5.86766
5.77302
5.76536
5.66344
5.65659
5.64980
5.64416
5.63782
PPM
3.35249
3.33688
3.32101
3.26264
3.24799
3.23233
2.99481
2.98043
2.96681
2.96492
2.95200
2.95034
2.93756
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2.77915
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2.76753
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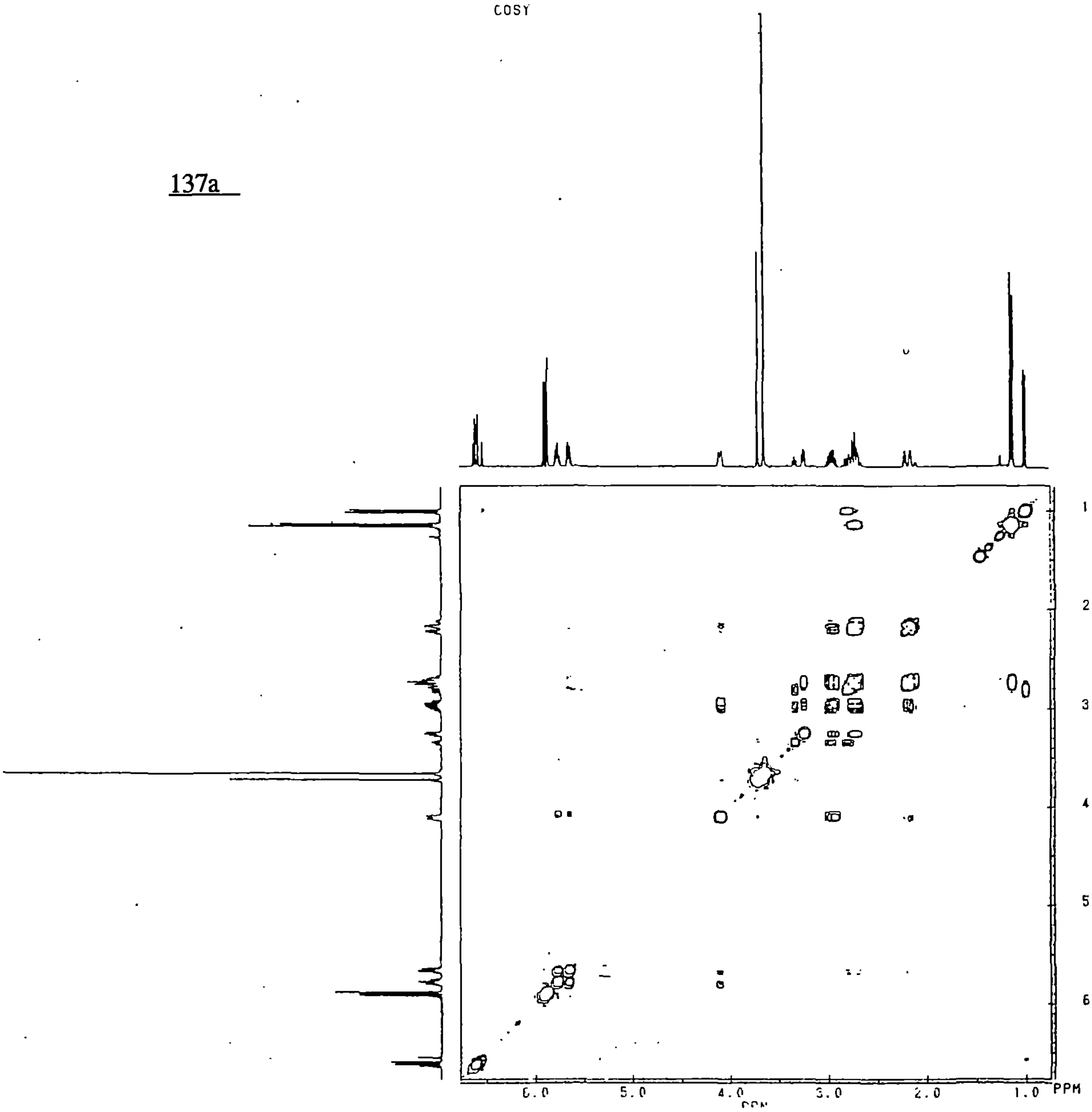
2.72534
2.70719
2.70213
2.69493
2.69164
2.68815
2.68430
3.71477
3.65067
2.22507
2.21744
2.20991
2.20223
2.16858
2.16115
2.15364
2.14621
1.14978
1.12612
1.00820
.98485
.00034
2.000
4.329
1.068
3.228
1.113
3.441
1.209
3.632
8.0
7.0
6.0
5.0
4.0
PPM
3.0
2.0
1.0
0.0

137a



$BF_3.Et_2O$ (1.5ml). The reaction mixture was refluxed (3h), cooled and filtered. The filtrate was poured into saturated $NaHCO_3$ solution (50ml) followed by extraction with chloroform (3x30ml). The combined extracts were washed with water (50ml), dried (Na_2SO_4), and evaporated to give a viscous residue which on coloumn chromatography over silicagel (EtOAc/hexane) afforded pure ester in quantitative yield.

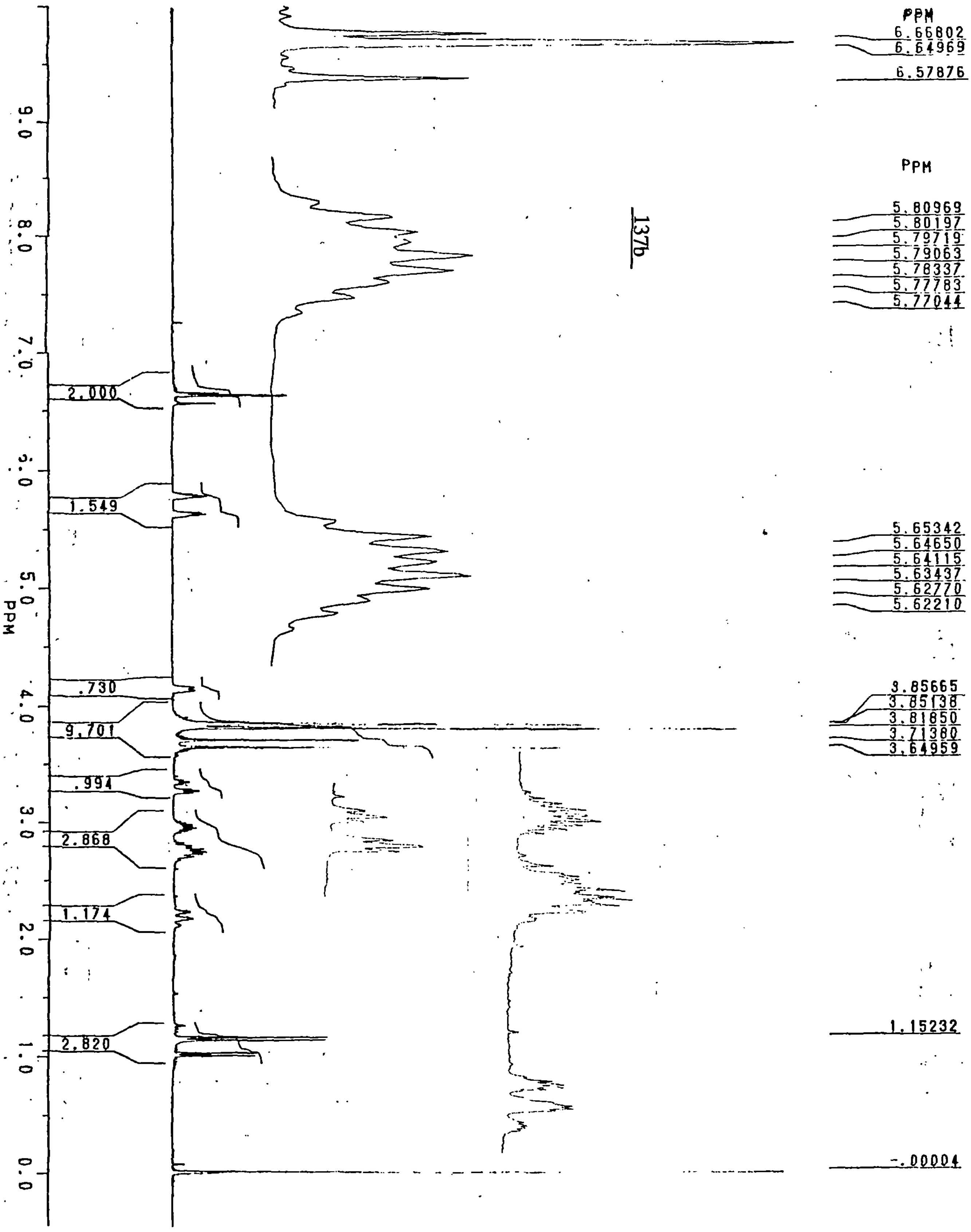
8-[(1'-methoxycarbonyl)ethyl]-5,6-methylenedioxycyclopent[a]ind- 2-ene. (137a) (Diastereomers 60:40)

Colourless viscous liquid; yield 93%; IR (CCL_4): 1727 (CO), 1469, 1038cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 1.00 (d, J=7Hz, 1H of CH_3), 1.13 (d, J=7Hz, 2H of CH_3), 2.09-2.22(m, 1H, H_e), 2.67-2.82(m, 2H, $H_{c\&d}$), 2.95 (two overlapped quintets, J=4Hz, 1H, H_f), 3.24 (t, J=4Hz, 0.66H of H_a), 3.33 (t, J=4Hz, 0.33H of H_a), 3.64 (s, 2H of OCH_3), 3.71 (s, 1H of OCH_3), 4.09 (d, J=6Hz, 1H, H_b), 5.63-5.65 (m, 1H, $=CH_g$), 5.75-5.78 (m, 1H, $=CH_h$), 5.86 (s, 0.6H of OCH_2O), 5.89 (s, 1.3H of OCH_2O), 6.53-6.62 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.85, 13.60, 40.19, 40.43, 43.45, 43.54, 44.02, 46.46, 51.56, 54.42, 55.82, 56.63, 100.98, 101.03, 104.29, 104.44, 105.67, 130.02, 130.19, 132.15, 132.21, 134.95, 135.81, 138.57, 146.58, 147.26, 175.99 (CO); MS (m/z, %): 286 (M^+, 38.2). Anal. Calcd. for $C_{17}H_{18}O_4$ (286.31): C 71.31; H 6.33. Found: C 71.22; H 6.31.

8-[(1'-Methoxycarbonyl)ethyl]-5,6-dimethoxycyclopent[a]ind-2-ene. (137b) (Diastereomers 60:40)

Colourless viscous liquid; yield 91%; IR (CCl_4): 2947, 1733 (CO), 1604, 1497cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (d, J=7Hz, 1H of CH_3), 1.13 (d, J=7Hz, 2H of CH_3), 2.16-2.24 (m, 1H, H_e), 2.70- 2.82 (m, 2H, $H_{c\&d}$), 2.95 (two overlapped quintets, J=4Hz, 1H, H_f), 3.27 (t, J=4Hz, 0.66H of H_a), 3.35 (t, J=4Hz, 0.33H of H_a), 3.64 (s, 2H of OCH_3), 3.71 (s, 1H of OCH_3), 3.81 (s, 2H of Ar- OCH_3), 3.85 (s, 4H of Ar-OCH_3), 4.20 (d, J=6Hz, H_b), 5.62-5.65 (m, 1H, =CH), 5.77-5.81 (m, 1H, =CH), 6.57-6.66 (m, 2H, ArH); MS (m/z, %): 302 (M^+, 29.9), 215 (M^+-87, 100). Anal.Calcd. for $C_{18}H_{22}O_4$ (302.36): C 71.49; H 7.33. Found: C 71.58; H 7.33. Found: C 71.58; H 7.30.

Raney Nickel desulphurization reaction of 126b. 2-Methyl-3-[2'-(3,4-dimethoxyphenyl)]propylcyclopentanol (131) To a suspension of Raney-Ni (1 spoon) in ethanol (10ml), was added **126b** (0.7g, 0.002mol) and refluxed for 6-7hr. Filtered, concentrated to give a viscous residue which on coloumn chromatography (EtOAc/hexane) affored pure cyclopentanol **131** as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6.64969
6.57876
PPM
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5.79719
5.79063
5.78337
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5.64650
5.64115
5.63437
5.62770
5.62210
3.85665
3.85138
3.81850
3.71380
3.64959
1.15232
-.00004
2.000
1.549
.730
9.701
.994
2.868
1.174
2.820
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

137b

colourless liquid: yield 0.28g (51%); IR (neat): 2919, 1608, 1506, 1439cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (d, J=6Hz, 3H, CH_3), 0.94 (d, J=6Hz, 3H, CH_3), 1.36-1.82 (m, 8H, CH_2, CH), 2.66-2.68 (m, 2H, CH & OH exchangeable with D_2O), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.01-4.04 (m, 1H, $CH_{benzylic}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.93 (CH_3), 22.09 (CH_3), 23.47 (CH_2), 28.87 (CH), 33.56 (CH_2), 34.12 (CH_2), 47.27 (CH), 49.66 (CH), 55.78 (OCH_3), 55.83 (OCH_3), 74.40 (CH), 111.03 (ArCH), 111.95 (ArCH), 120.43 (ArCH), 134.36, 147.01, 148.72 ($Ar_{quarternary}$); MS (m/z, %): 273 (M^+, 89). Anal. Calcd. for $C_{17}H_{21}O_3$ (273.34): C 74.69; H 7.74. Found: C 74.58; 7.71.

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