# SYNTHETIC AND MECHANISTIC STUDIES ON POLARIZED KETENE DITHIOACETALS

ABSTRACT

By

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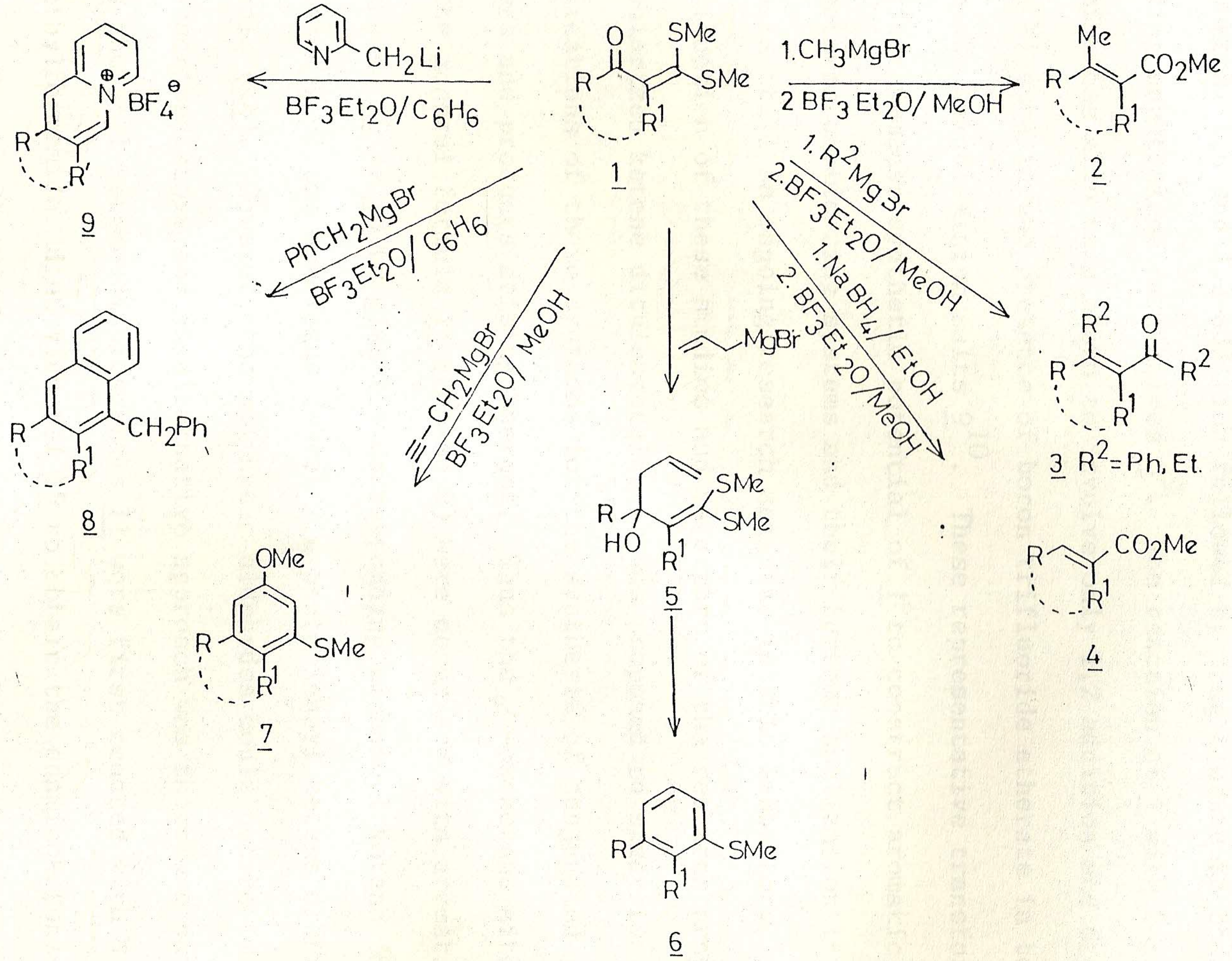
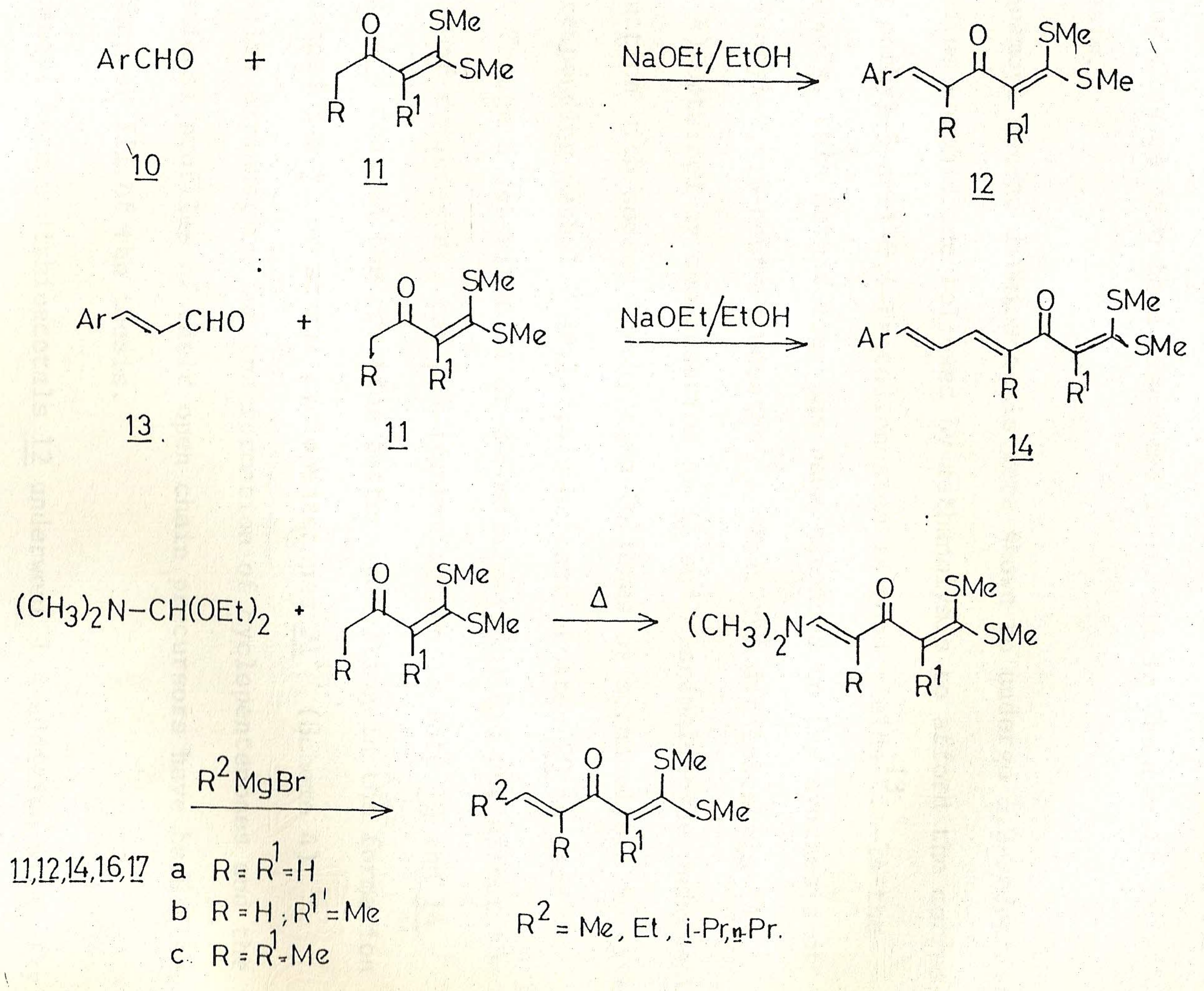
The synthesis of α-oxoketene dithioacetals of the general formula 1 were first reported in 1910, by Kelber and co-workers[1]. A number of these compounds have been subsequently prepared by reacting active methylene ketones with carbon disulphide, in the presence of suitable base followed by alkylation. Many experimental variations of this method have been developed[2-4] in order to improve the yields of dithioacetals 1 evolving the overall process to a one pot transformation. It is therefore now possible to prepare large structural variants of 1 from widely occuring active methylene ketones. The α-oxoketene dithioacetals possess 1,3-electrophilic centers with differing electrophilicity thus making them excellent class of 3-carbon synthons. Their 1,3-electrophilic reactivity has been extensively exploited for the regioselective construction of new C-C-bonds involving either 1,2 or 1,4 nucleophilic additions leading to a number of new synthetic methodologies for a wide range of organic molecules. For example, the dithioacetals 1 have been shown to undergo exclusive 1,2-reduction with sodium borohydride followed by boron trifluoride etherate assisted methanolysis to afford highly stereoselective eneesters 4 (Scheme 1)[5]. This method is of particular interest since it provides a convenient transformation of easily available active methylene ketones to corresponding eneesters *via* α-oxoketene dithioacetals. Similarly methyl magnesium iodide is also shown to add to ketene dithioacetal 1 in a 1,2 fashion, while the bulkier Grignard reagents undergo a sequential 1,4-addition followed by a 1,2-addition, resulting in the formation of regioselectively substituted α,β-unsaturated esters (2) and ketones (3) respectively[6]. The allyl magnesium bromide undergoes exclusive 1,2 addition and the resultant carbinol acetals 5 underwent smooth aromatization with a new C-C-bond formation to yield the corresponding


1.CH3MgBr
2 BF3 Et2O/ MeOH
1. R2MgBr
2.BF3Et2O/ MeOH
1. NaBH4/ EtOH
2. BF3Et2O/MeOH
MgBr
CH2Li
BF3Et2O/C6H6
PhCH2MgBr
BF3Et2O/ C6H6
≡—CH2MgBr
BF3Et2O/ MeOH
3 R2=Ph, Et.
1
2
3
4
5
6
7
8
9

Scheme 1

benzenoids 6[7]. Similarly propargyl magnesium bromide underwent 1,2-addition followed by ring closure to the corresponding methoxy benzenoids 7[8], with the participation of the solvent methanol. The reaction of the S,S-acetal 1 with benzyl magnesium bromide however underwent sequential 1,4 and 1,2-addition followed by ring closure to the corresponding naphthalene derivatives 8[9]. The reaction of 1 with 2-picolyllithium has also been shown to involve only 1,2 addition and their ring closure in the presence of boron trifluoride etherate in benzene gave the quinolizinium salts 9[10]. These representative transformations manifest immense synthetic potential of 1 to construct aromatic as well as heteroaromatic ring systems and their further application in this area is still an ongoing research activity in this laboratory. In continuation of these studies and as a part of the research programme on polarized ketene dithioacetals, it was proposed to study further applications of these synthons for the synthesis of conjugated polyene esters and products arising thereof. Thus the $\alpha$-oxoketene dithioacetals of the general formula 11 (Scheme 2) were condensed with aromatic aldehydes 10 or 13 to give the corresponding cinnamoyl ketene dithioacetals 12 or the homologus 5-aryl 2,4-pentadienoyl ketene dithioacetals (14). However, the aliphatic aldehydes could not be condensed as described above and an alternative approach was therefore developed. Thus the acyl ketene dithioacetals 11 were first reacted with N,N-dimethylformamide diethylacetal 15 to obtain the enaminoketones 16 which underwent 1,4-addition with various alkyl magnesium halides to afford the corresponding alkenoyl ketene dithioacetals 17 in good yields[11]. The above intermediates 12 and 14 were shown to undergo methanolysis in the presence of boron trifluoride etherate and mercuric chloride to yield the $\gamma$, $\delta$-unsaturated $\beta$-ketoesters 18 which are



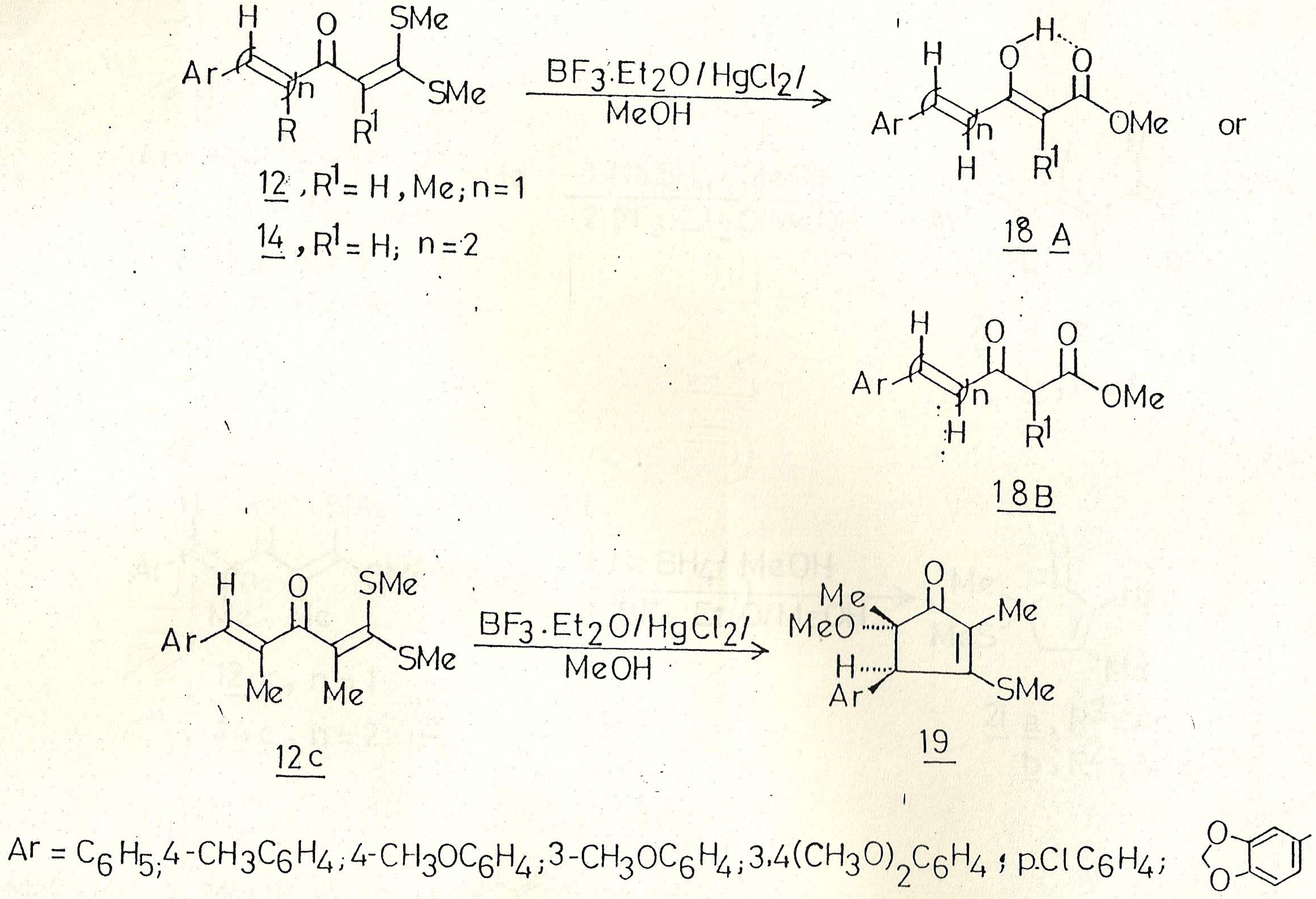
Scheme 2

16, 17 missing in Scheme 2

potential precursors in various synthetic transformations[12]. The cinnamoyl ketene dithioacetals 12c having substituents at the 2 and 4 positions underwent boron trifluoride etherate assisted Nazarov cyclization to give substituted cyclopentenone 19[12]. The generality of this cyclopentenone synthesis and the structural requirement for such ring closure have been discussed in detail in Chapter II of the thesis.

The cinnamoyl ketene dithioacetals were shown to undergo 1,2-reduction with sodium borohydride followed by methanolysis to afford the corresponding methyl 5-aryl-2,4-pentadienoates in good yields[13]. In the present work, this methodology has been extended to the synthesis of methyl 7-aryl-2,4,6-heptatrienoates[14]. Thus the dithioacetals 14 (Scheme 4) obtained by condensation of 11 and cinnamaldehyde underwent 1,2-reduction with sodium borohydride followed by methanolysis to give the corresponding methyl 7-aryl-2,4,6-heptatrienoates 20 in good yields. Though a substitution at 2-position (14b) did not affect the formation of trieneester, the 2,4-disubstitution in both 12 and 14 (12c and 14c) changed the reaction pattern resulting in the formation of rearranged 2-aryl or styryl cyclopentenones 21[15] (Scheme 4). The detailed explanation for the formation of cyclopentenones and the conformational profiles of their open chain precursors have been discussed in the Chapter III of the thesis.

The cinnamoyl ketene dithioacetals 12 underwent 1,4-addition with alkyl and aryl grignard reagents resulting in the formation of corresponding $\delta$-substituted $\beta$-ketoesters 22 in high yields after subsequent methanolysis of the Michael adduct. However allyl magnesium bromide exhibited preference for 1,2-addition to give the corresponding styryl



12, $R^1$ = H, Me; n = 1

14, $R^1$ = H; n = 2

18 A

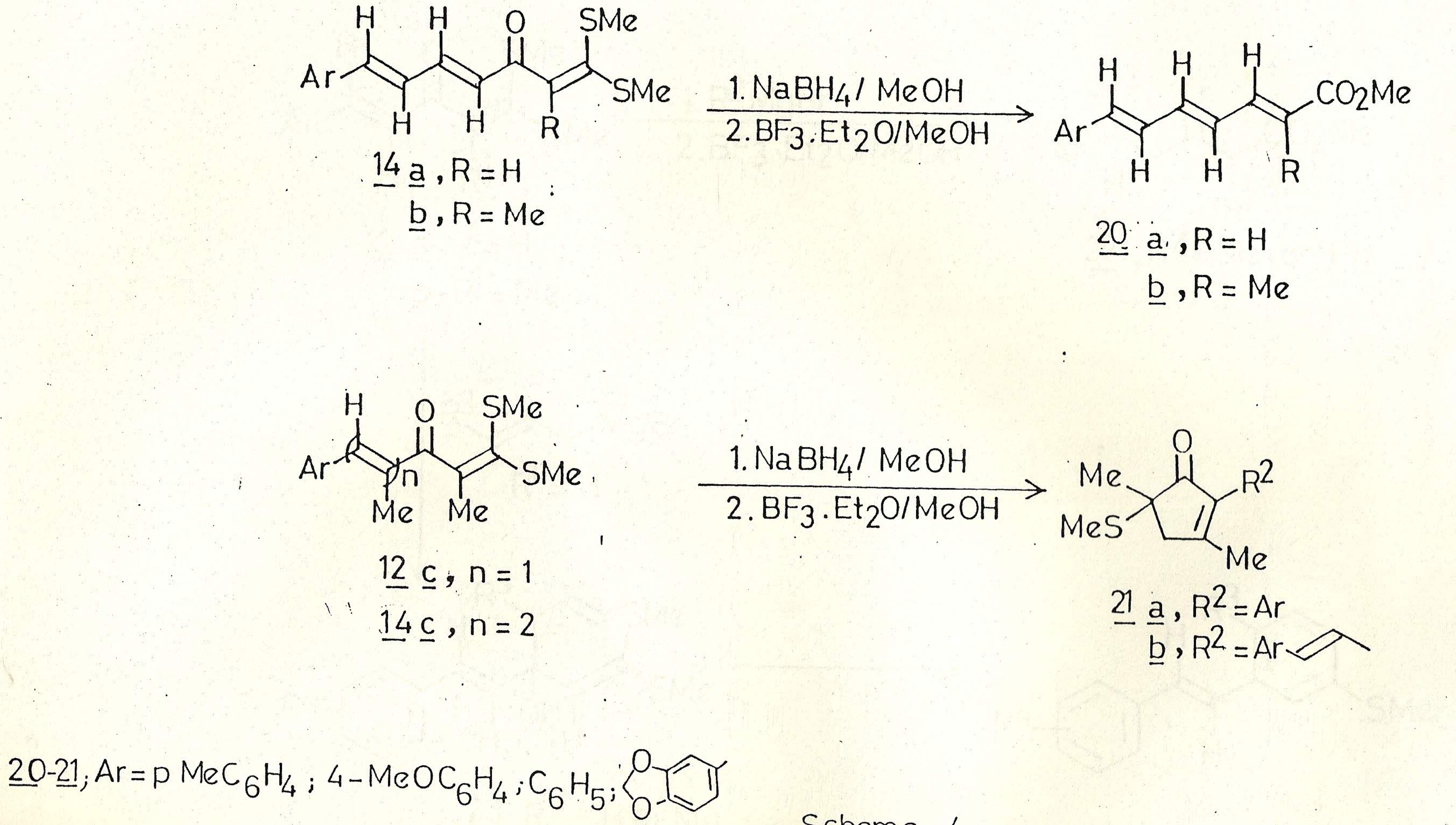
18 B

12c

19

Ar = $C_6H_5$; 4-$CH_3C_6H_4$; 4-$CH_3OC_6H_4$; 3-$CH_3OC_6H_4$; 3,4$(CH_3O)_2C_6H_4$; p.Cl$C_6H_4$;

Scheme 3



14 a, R = H
b, R = Me

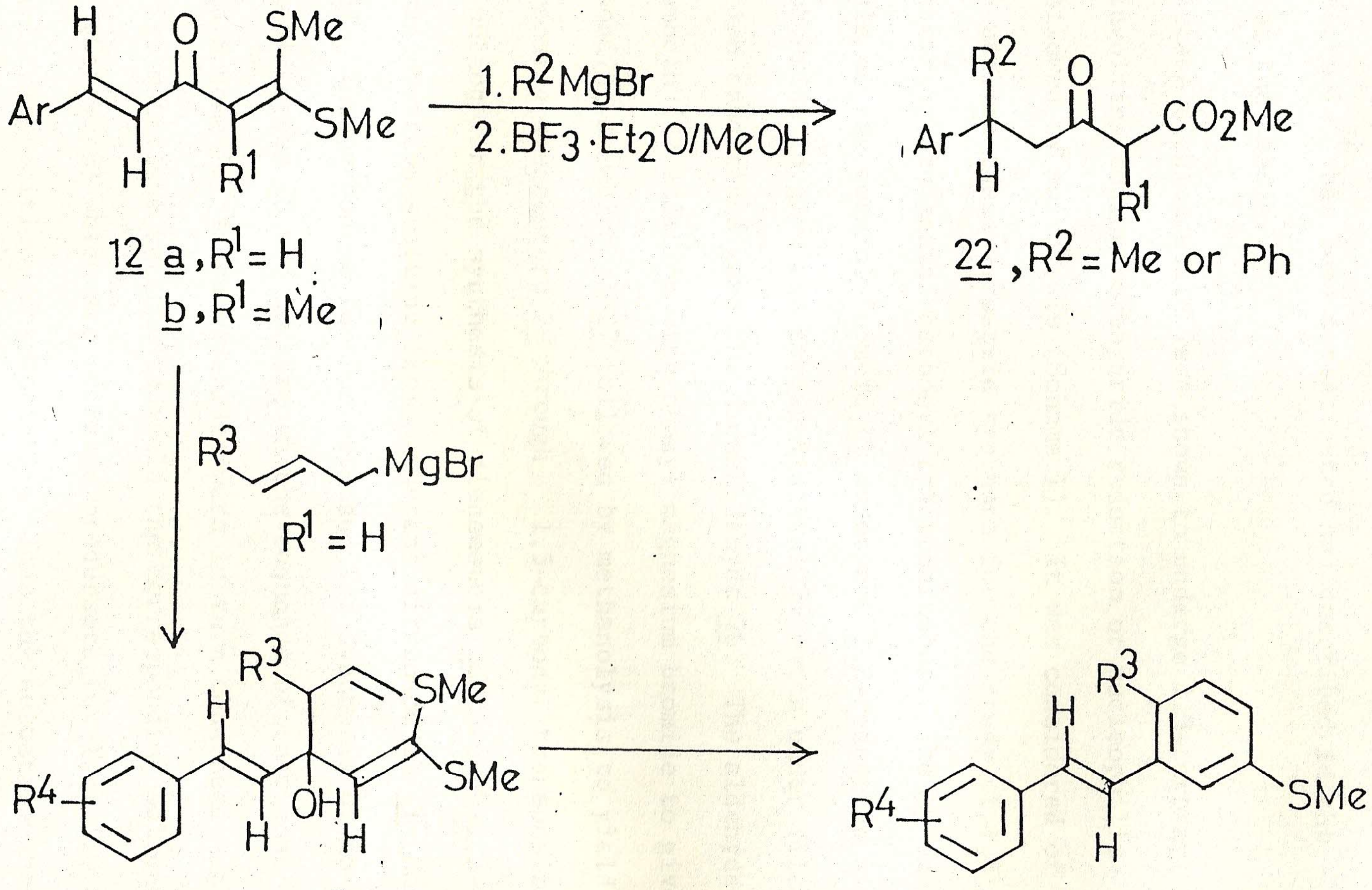
20 a, R = H
b, R = Me

12 c, n = 1
14 c, n = 2

21 a, R$^2$ = Ar
b, R$^2$ = Ar–CH=CH–

20-21; Ar = p MeC$_6$H$_4$ ; 4-MeOC$_6$H$_4$ ; C$_6$H$_5$ ;

Scheme -4



12 a, $R^1 = H$
b, $R^1 = Me$

22, $R^2 = Me$ or Ph

23 $R^3 = H$ or Me

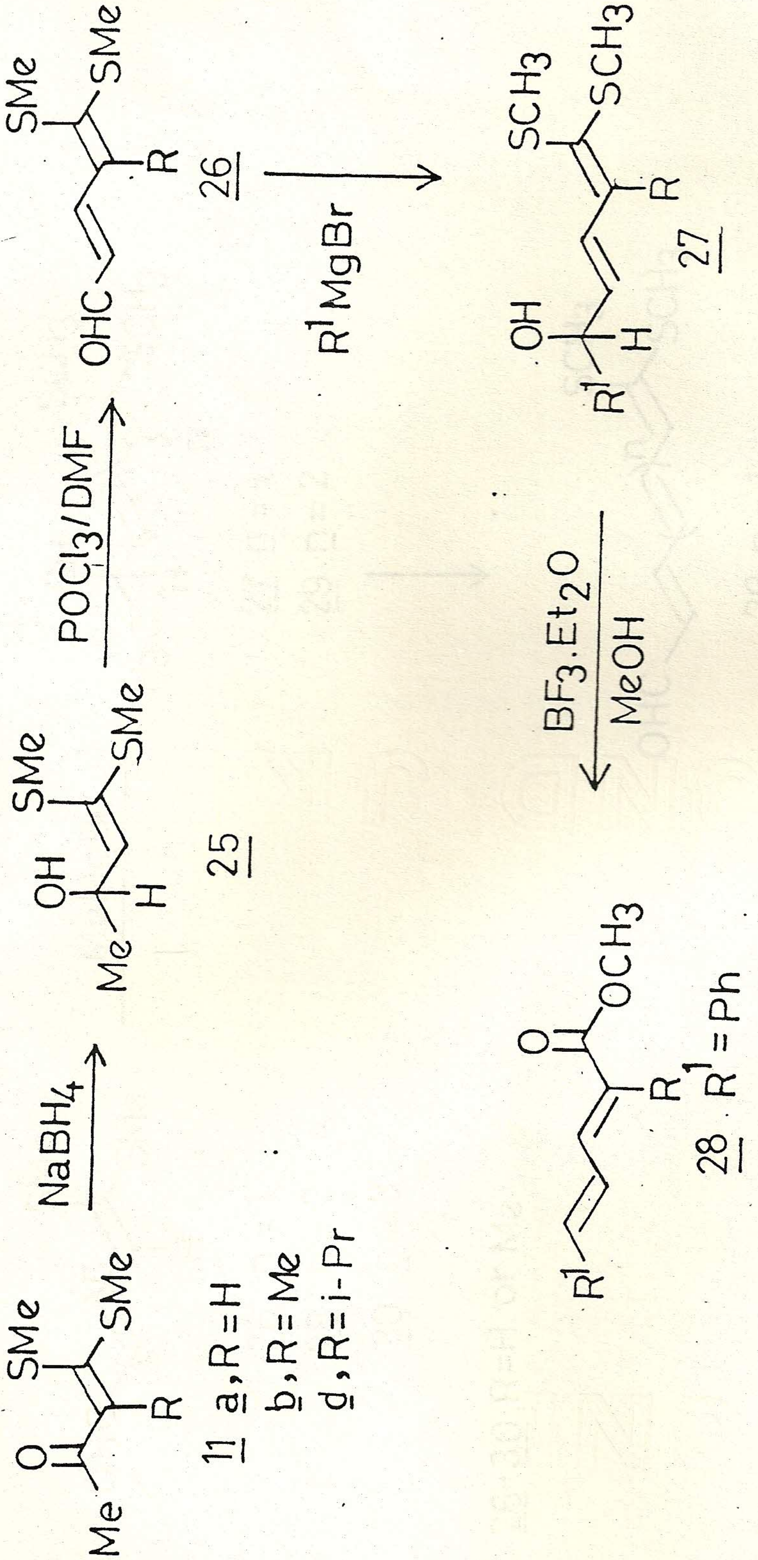
24

23, 24; R=H; 4-Me; 4-Cl; 3-MeO; 2,4-$Cl_2$; 3,4-$Cl_2$.

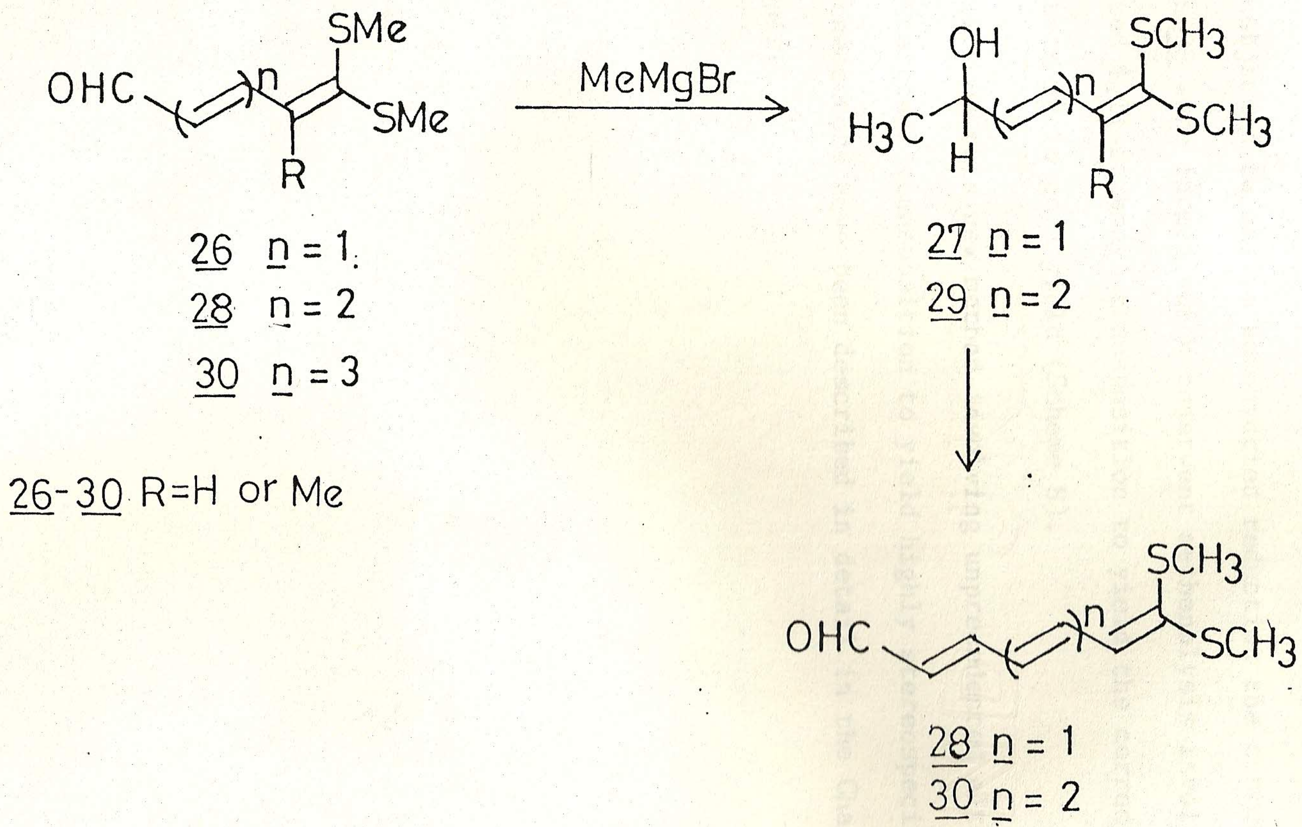
Scheme-5

carbinol acetals 23 which underwent cycloaromatization to yield the corresponding stilbenes 24 (Scheme 5). The generality of this new stilbene synthesis[16] has been investigated and described in the Chapter IV of the thesis.

The $\alpha$-oxoketene dithioacetals were shown to undergo 1,3-carbonyl transposition involving sodium borohydride reduction or nucleophilic addition followed by solvolysis (Scheme 1). It was considered of interest to utilize these versatile synthons for the study of 1,5 to 1,11 alternatively sequential carbonyl transpositions. The $\alpha$-oxoketene dithioacetals of the general formula 11 underwent 1,2-reduction with sodium borohydride to give the carbinol acetal 25 which under Vilsmeier-Haack reaction conditions gave the dienealdehyde 26. The aldehyde 26 underwent smooth 1,2 addition with phenyl magnesium bromide to give the corresponding dienealcohol 27 followed by methanolysis to yield the corresponding dieneesters 28 through 1,5-carbonyl transpositions. Thus a new method for the synthesis of dieneesters 28 through 1,5-carbonyl transposition starting from oxoketene dithioacetal 11 (Scheme 6) is developed. The method is further extended for synthesis of homologous polyenealdehydes 28 and 30 through the sequence of reactions described in Scheme 7. These aldehydes were in turn condensed with various active methylene ketones to yield the corresponding polyeneketones 31, 34 , 37 (Scheme 8) which are suitable precursors for 1,7; 1,9 and 1,11 carbonyl transpositions respectively. Thus the heptatrienones 31 (n=1) after sodium borohydride reduction or methyl magnesium iodide addition yielded the corresponding trienol acetals 32 which underwent smooth 1,7 carbonyl transposition to give the corresponding trieneesters


Me
O
SMe
SMe
R
11 a, R = H
b, R = Me
d, R = i-Pr
NaBH4
Me
OH
H
SMe
SMe
25
POCl3/DMF
OHC
SMe
SMe
R
26
R1MgBr
R1
OH
H
SCH3
SCH3
R
27
BF3.Et2O
MeOH
R1
O
OCH3
R
28 R1 = Ph

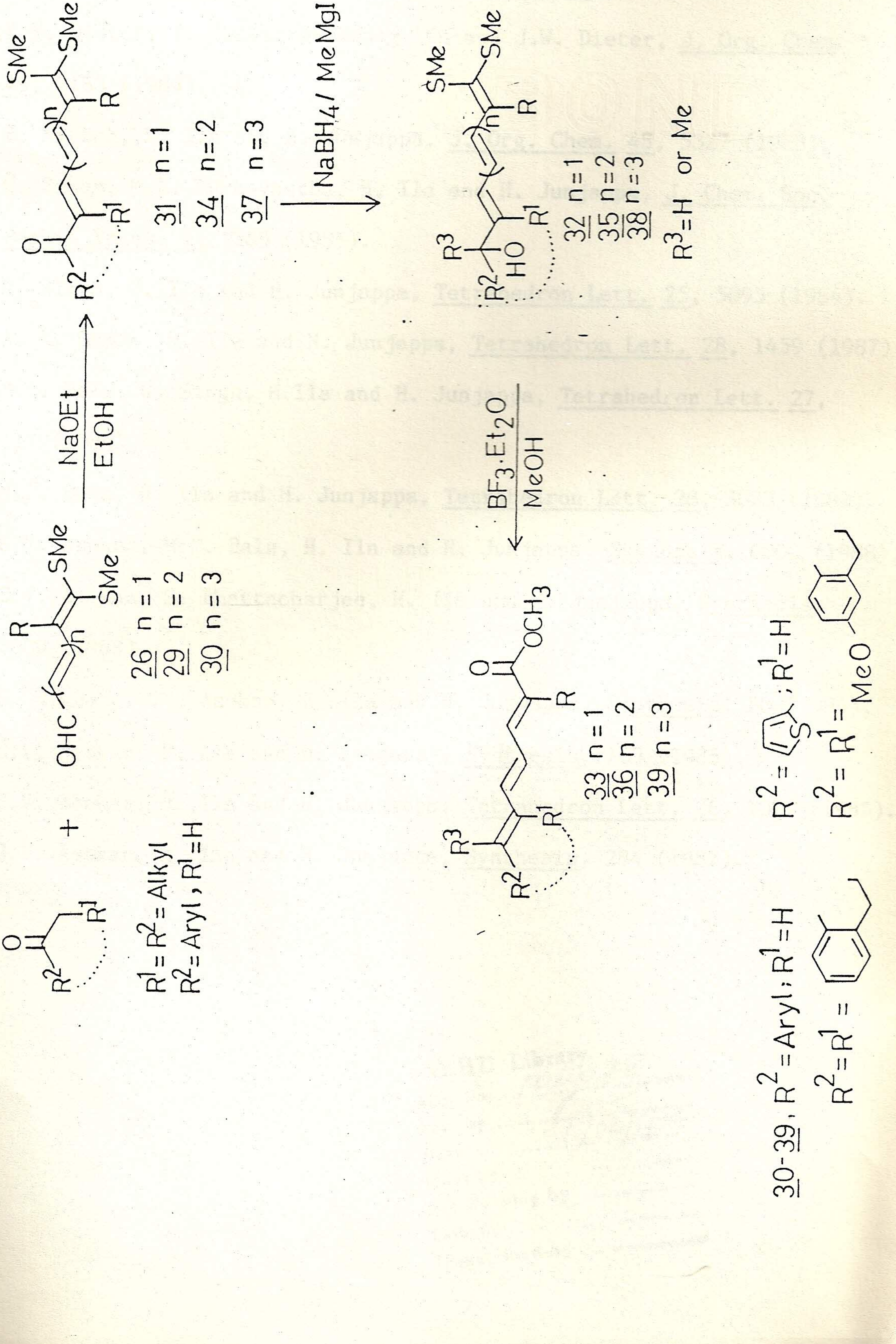
Scheme-6


OHC
SMe
SMe
n
R
26 n = 1
28 n = 2
30 n = 3
26-30 R=H or Me
MeMgBr
OH
H3C
H
SCH3
SCH3
n
R
27 n = 1
29 n = 2
OHC
SCH3
SCH3
n
28 n = 1
30 n = 2

Scheme-7

33 in good yield. Similarly tetraenyl ketones 34 (n=2) (Scheme 8) were shown to undergo the described reaction sequence (Scheme 8) to give the corresponding tetraeneesters 36 (n=2) in good yields. The overall process involves an unprecedented 1,9-carbonyl transposition. When 37 (n=3) was subjected to sodium borohydried reduction the corresponding enolacetals 38 were formed, which underwent methanolysis involving an unprecedented 1,11-carbonyl transposition to yield the corresponding pentaeneesters 39 in good yield (Scheme 8).

The generality of this new method involving unprecedented alternatively sequential carbonyl transposition to yield highly stereospecific all trans polyenesesters have been described in detail in the Chapter V of the thesis.


R¹ = R² = Alkyl
R² = Aryl , R¹ = H
OHC
SMe
SMe
R
26 n = 1
29 n = 2
30 n = 3
NaOEt
EtOH
31 n = 1
34 n = 2
37 n = 3
NaBH4 / MeMgI
32 n = 1
35 n = 2
38 n = 3
R³ = H or Me
HO
BF3.Et2O
MeOH
OCH3
33 n = 1
36 n = 2
39 n = 3
30-39, R² = Aryl ; R¹ = H
R² = R¹ =
R² = ; R¹ = H
R² = R¹ =
MeO

Scheme.8

## REFERENCES

1. C. Kelber, *Chem. Ber.* *43*, 1252 (1910).
2. A. Thuillier and J. Vialle, *Bull. Soc. Chim. Fr.* 2182 (1962).
3. S.M.S. Chauhan and H. Junjappa, *Tetrahedron* *32*, 1779 (1976).
4. R.K. Dieter, Y. Jenkitkasemwong Lin and J.W. Dieter, *J. Org. Chem.* *49*, 3183 (1984).
5. B. Myrboh, H. Ila and H. Junjappa, *J. Org. Chem.* *48*, 5327 (1983).
6. G. Singh, M.L. Purkayastha, H. Ila and H. Junjappa, *J. Chem. Soc. Perkin Trans. I*, 1289 (1985).
7. G. Singh, H. Ila and H. Junjappa, *Tetrahedron Lett.* *25*, 5095 (1984).
8. A. K. Gupta, H. Ila and H. Junjappa, *Tetrahedron Lett.* *28*, 1459 (1987).
9. M.P. Balu, G. Singh, H.Ila and H. Junjappa, *Tetrahedron Lett.* *27*, 117 (1986).
10. M.P. Balu, H. Ila and H. Junjappa, *Tetrahedron Lett.* *28*, 3023 (1987).
11. C.V. Asokan, M.P. Balu, H. Ila and H. Junjappa, *Synthesis*, 0000 (1988).
12. C.V. Asokan, S. Bhattacharjee, H. Ila and H. Junjappa, *Synthesis*, 0000 (1988).
13. B. Myrboh, C.V. Asokan, H. Ila and H. Junjappa, *Synthesis*, 50 (1984).
14. C.V. Asokan, H. Ila and H. Junjappa, *Synthesis*, 163 (1985).
15. C.V. Asokan, H. Ila and H. Junjappa, *Tetrahedron Lett.* *26*, 1087 (1985).
16. C.V. Asokan, H. Ila and H. Junjappa, *Synthesis*, 284 (1987).