# TOTAL SYNTHESIS OF (±)-4-DEMETHOXYDAUNOMYCINONE



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BY

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*Dedicated To*
*My Parents*

Certified that the work incorporated in the thesis "Total Synthesis of (±)4-demethoxydaunomycinone" submitted by Mr. S.M. Jaweed Mukarram was carried out by the candidate under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

(A. V. RAMA RAO)
Supervisor

C O NT E N T S


| | | Page |
|---|---|---|
| CHAPTER I : | SYNTHESIS OF (+)4-DEMETH0XY-DAUNOMYCINONE - A GENERAL REVIEW | 1 - 3 5 |
| CHAPTER II : | SYNTHESIS OF (+)4-DEMETH0XYDAUNO-MYCINONE STARTING FROM QUINIZARIN (DIELS-ALDER APROACH) | 36 - 116 |
| Section I | 1,4-Anthraquinone and napthalene precursors as dienophiles | 36 - 79 |
| | Experimental | 80 |
| | References | 102 |
| Section II | l-Acetoxy-10-chloro-4,9-anthra-quinone as a dienopnile. | 105 - 116 |
| | Experimental | 113 |
| | References | 116 |
| CHAPTER III : | SYNTHESIS OF (+)4-DEMETHOXYDAUN0-MYCINONE BY FRIEDEL-CRAFTS REACTION | 117 - 158 |
| Section I | Synthesis starting from hydro-quinone. | 117 - 139 |
| | Experimental | 131 |
| | References | 139 |
| Section II | Synthesis starting from Methyl-quinizarin | 140 - 158 |
| | Experimental | 151 |
| | References | 158 |
| SUMMARY .. | .. .. | 159 |
| ACKNOWLEDGEMENTS | | 172 |

# CHAPTER - I

## SYNTHESIS OF (±) 4-DEMETHOXYDAUNOMYCINONE

## A GENERAL REVIEW

## INTRODUCTION

About 20 per cent of the deaths in Western countries are currently ascribed to neoplastic diseases, i.e. those associated with growth of new abnormal body tissues commonly referred as "cancer". This disease has engaged the world-wide attention of a variety of research workers.

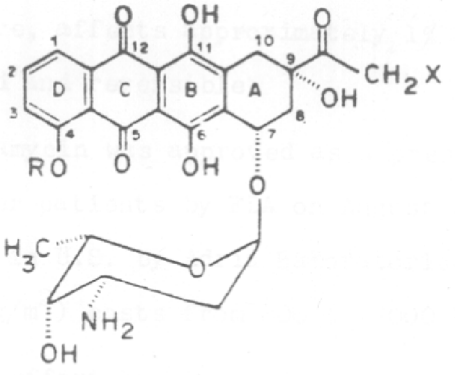
Radiation and surgery have certainly a curative effect as long as it is detected at an early stage and localized. But unfortunately by the time it is detected, the disease often spreads to other organs of the body and then the answer lies in chemotherapy either exclusively or in combination with surgery and radiation.

A large number of anti-cancer drugs are now being used in medical practice which have been approved by the National Cancer Institute (USA). Further many are undergoing clinical trials. All these drugs can be broadly classified into (1) alkylating agents (2) antimetabolites, (3) antibiotics, and (4) miscellaneous compounds.

Among the various compounds which are promising as antitumor agents, natural products, either of plant or microbial origin, are showing much more specificity in their anti-cancer properties. Many of them possess structures and clinical properties which suggest that they may act by selective alkylation of growth regulatory macromolecules.

The usefulness of certain anthracyline antibiotics as anti-neoplastic agents are now widely accepted. Both daunomycin[1] (1a) and adriamycin[2] (1b) produced by Streptomyces pencelius (Family: Streptomycetacea) and a mutant strains respectively, have shown pronounced anticancer activity in some types of human cancer[3]. However, their use is restricted by a dose limiting cardiotoxicity (congestive heart failure). Recently, carminomycin[3,4] (1c), isolated from Actinomadura carminata sp.nov. and streptosporangium sp. has shown to be more effective than other two antibiotics (1a and 1b) in inhibiting DNA synthesis[5]. Further, carminomycin is found to suppress the growth of a murine brochogenic lung carcinoma to indicate that it has less severe cardiotoxicity and is better absorbed from gastro-intestinal tract than daunomycin[3].

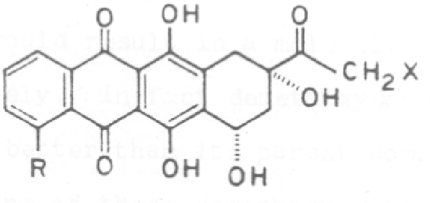
The biological activity of the antitumor anthracyclines is related to their ability to bind with DNA. Adriamycin displayed a more favourable therapeutic index than daunomycin in different experimental tumors in laboratory animals and particularly an impressive broad spectrum of activity. Adriamycin however is not devoid of serious side effects such as dose limiting myelosuppressia and cardiomyopathy etc. All toxic effects, with the exception of cardiotoxicity which in its fatal form, congestive



(Ia) R = $CH_3$ ; X = H Daunomycin

(Ib) R = $CH_3$ ; X = OH Adriamycin

(Ic) R = H ; X = H Carminomycin



(IIa) R = H ; X = H 4-Demethoxydaunomycinone

(IIb) R = $OCH_3$; X = H Daunomycinone

(IIc) R = $OCH_3$; X = OH Adriamycinone

heart failure, affects approximately 1% of patients, are dose related and reversible.

Adriamycin was approved as a prescription drug for use in cancer patients by FDA on August 5, 1974. It is distributed in U.S. by Adria Laboratories. A full course of drug (550 $mg/m^2$) costs from 800 to 2000 U.S. dollars.

Much effort has been directed to obtain either new derivatives or develop new dose regimes that show decrease in undesirable side effects and/or increased anticancer activity and selectivity. Such goals are common to many areas of cancer chemotherapy; however, in the case of daunomycin and adriamycin, it is now possible to take account of recent knowledge concerning their mode of action.

A detailed examination of the daunomycin-DNA model reveals that intercalation of the chromophore is only partial and one might speculate the removal of bulky methoxy group which would result in a molecule that could intercalate more effectively. In fact demethoxydaunomycin binds to DNA somewhat better than its parent compound. Significantly, in vivo testing of these demethoxy derivatives in mouse cancer shows that it is as effective as daunomycin itself, but at dose levels four to eight times lower[6].

Total synthesis of these compounds by itself is a major line of research directed towards the exploration of

structural modification on different parameters of anthracycline antitumor activity.

The intact antibiotic consists of a glycone and an aglycone portion. The synthesis of the sugar part and its coupling with the aglycone has been achieved[7]. A number of organic chemists from well known groups in USA are intensively involved in the synthesis of daunomycinone (IIb) and demethoxydaunomycinone (IIa). This problem is now being increasingly tackled by many more chemists throughout the world. Apparently, this is next to prostaglandins as a single largest group of chemists involved in one problem, but unfortunately, all the synthetic routes so far appeared are unable to achieve the coveted objective i.e. Development of a synthetic procedure which can be adopted at least upto a large bench scale resulting in gram amounts of the desired aglycone.

The principal synthetic challenge posed by the aglycones include generation of the tetracyclic skeleton, introduction of the A-ring functionality and achievement of the "correct" (i.e. natural) regiochemical juxtaposition of the substituents in the A- and D-rings. The demonstration[8-10] that the natural, cis orientation of the 7-and 9-hydroxyl groups is thermodynamically preferred ( 6:1 ratio) and that epimerization of the C-7 position is effected by

$CF_3COOH$ has decreased the need to address aglycones/stereochemistry directly. The recent finding[6] that the 4-demethoxy analogues of (1a) and (1b) are ca. ten times as potent as (1a) and (2a) (they are also more toxic) may well have diminished the practical need for finding an efficient solution to the problem of regiochemistry. Nonetheless, efforts to achieve regiochemically controlled routes have led to a number of new methods of anthraquinone synthesis.

In the following lines a brief survey of efforts towards the synthesis of 4-demethoxydaunomycinone will be given.

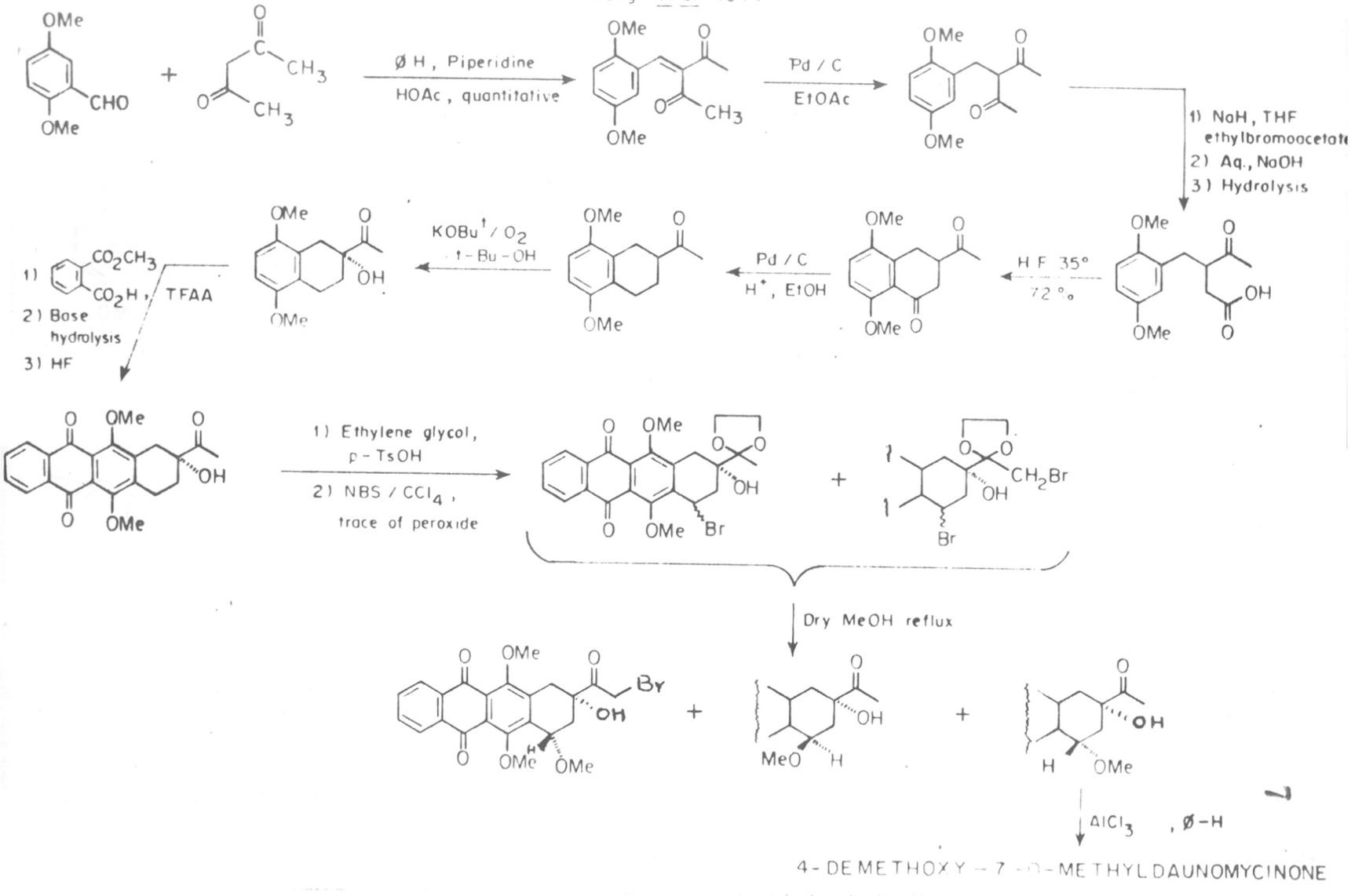
In general the syntheses of aglycone have relied on the employment of one (or more) of three named reaction classes: Friedel-Crafts alkylation or acylations, nucleophilic condensations, and Diels-Alder reactions. The various routes can be conveniently discussed under these three headings.

A. Friedel-Crafts-type Routes:

In 1971 Wong et al.[11] were the first to report the synthesis of 4-demethoxydaunomycinone (Scheme-1). Subsequently in 1973 the same group has reported the synthesis of daunomycinone itself[8]. Both the methods suffer various drawbacks including numerous steps with low yields. The selective bromination (NBS) of C-7 (and not C-10 attributed

SCHEME – I

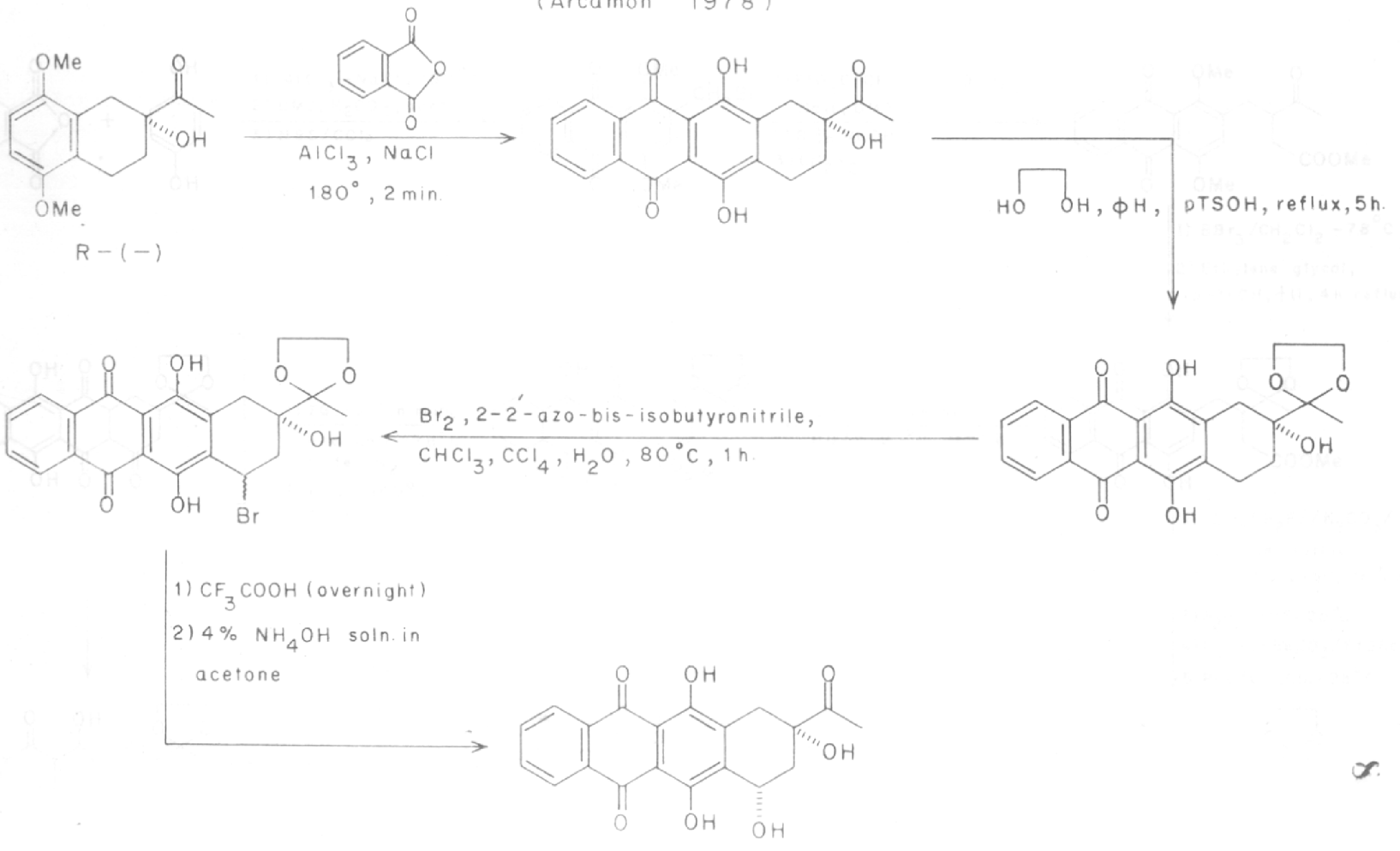
Wong et al 1971



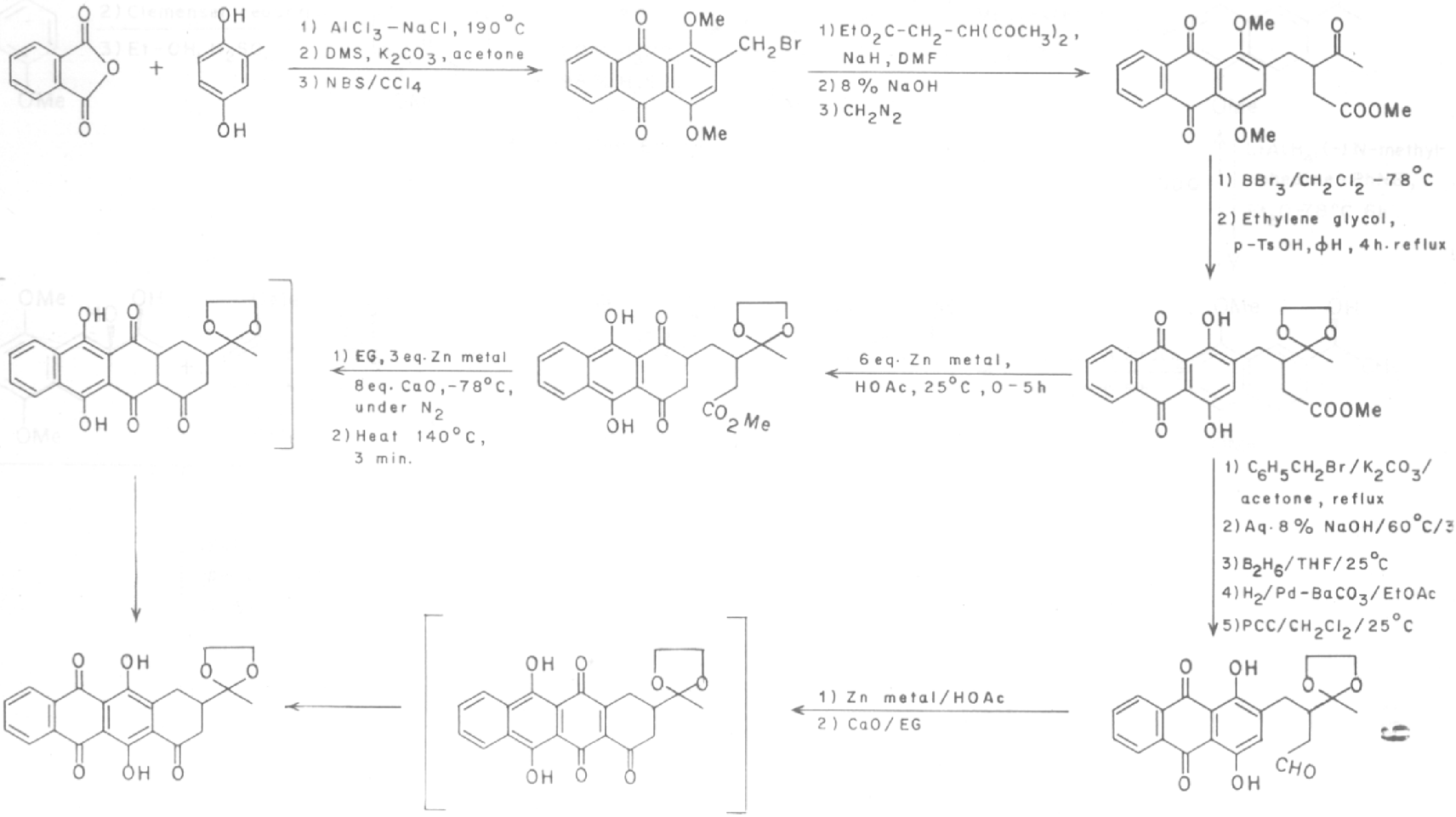

4-DEMETHOXY-7-O-METHYLDAUNOMYCINONE

## SCHEME-2

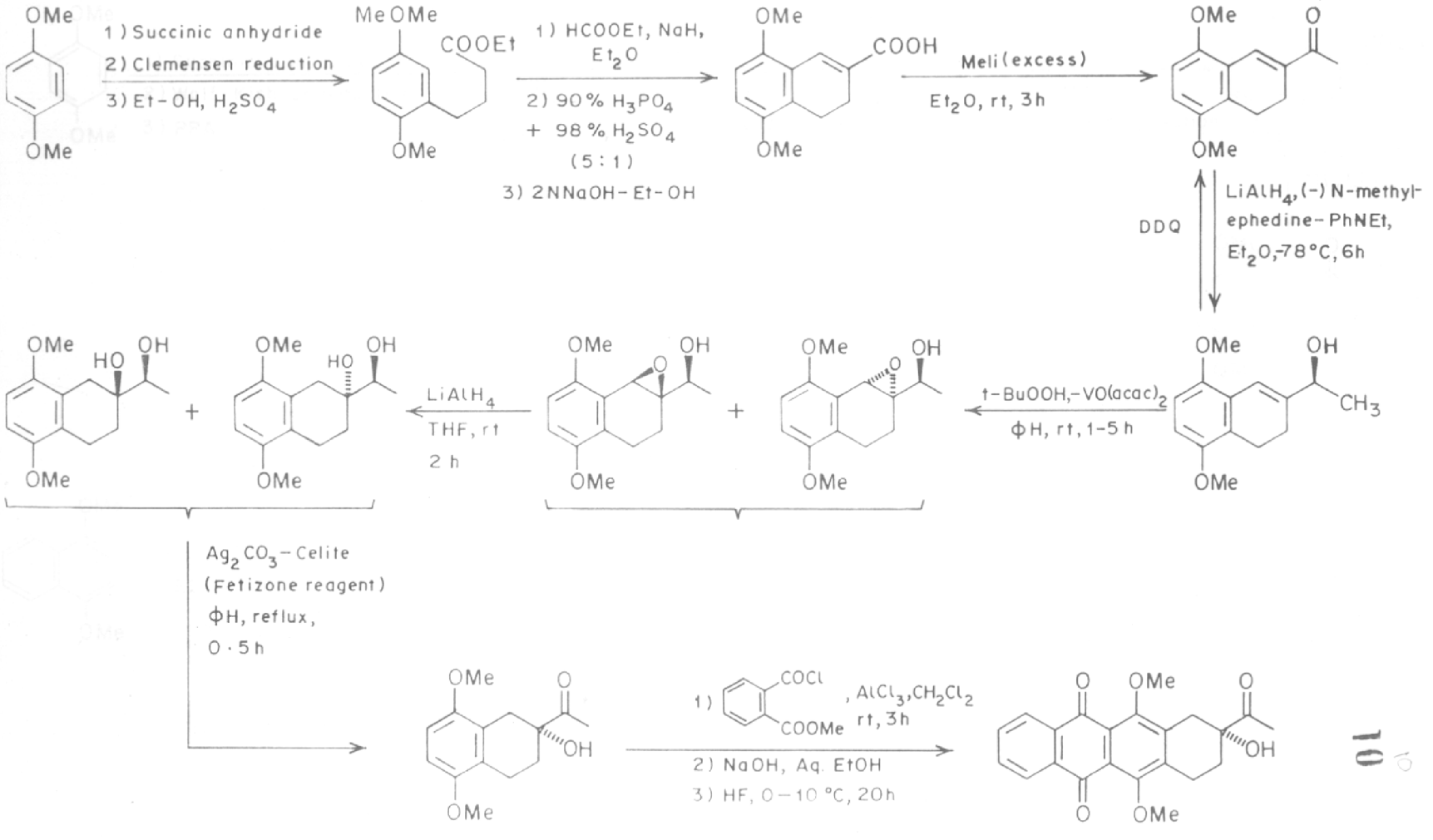
(Arcamon 1978)



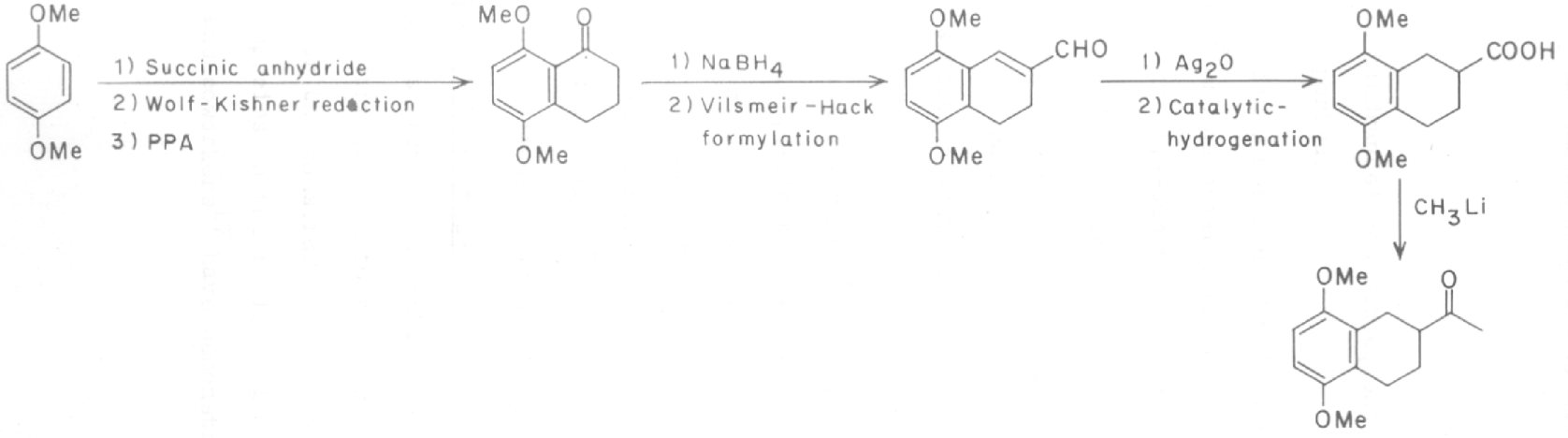
# SCHEME-3 (Sih, 1977)



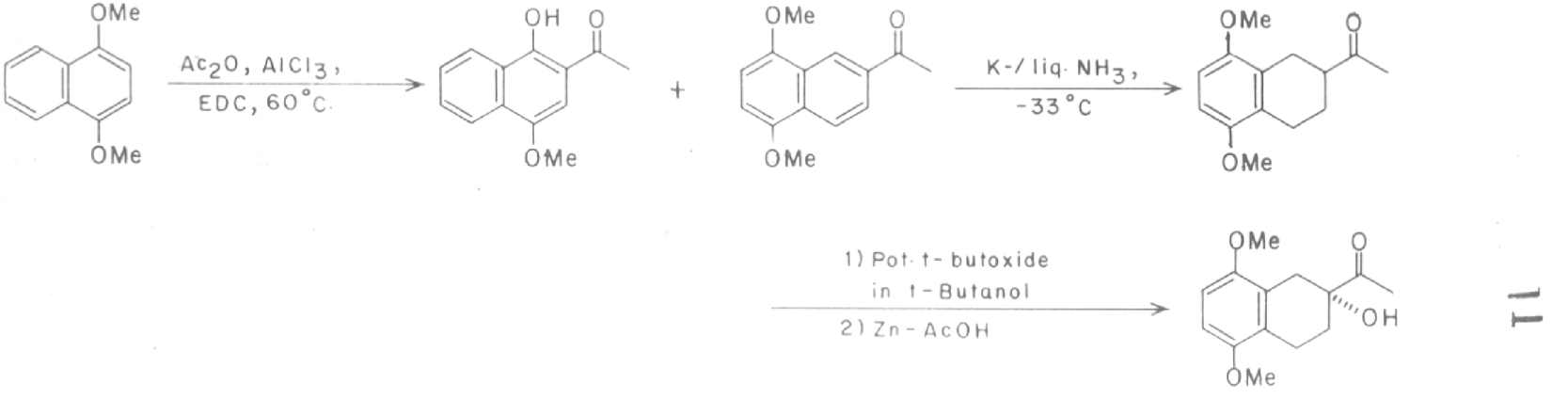
## SCHEME 4 (Terashima et al 1980)



## SCHEME 5 (Rao, 1981)




## SCHEME 6 (Rama Rao, 1982)



to steric hindrance) and subsequent conversion to 7-hydroxyl has been reported.

A refined version of this approach was reported by Arcamone[12] and associates employing phthalic anhydride and R-(-)-6-acetyl-1,4-dimethoxy-6-hydroxy tetralin (Scheme-2).

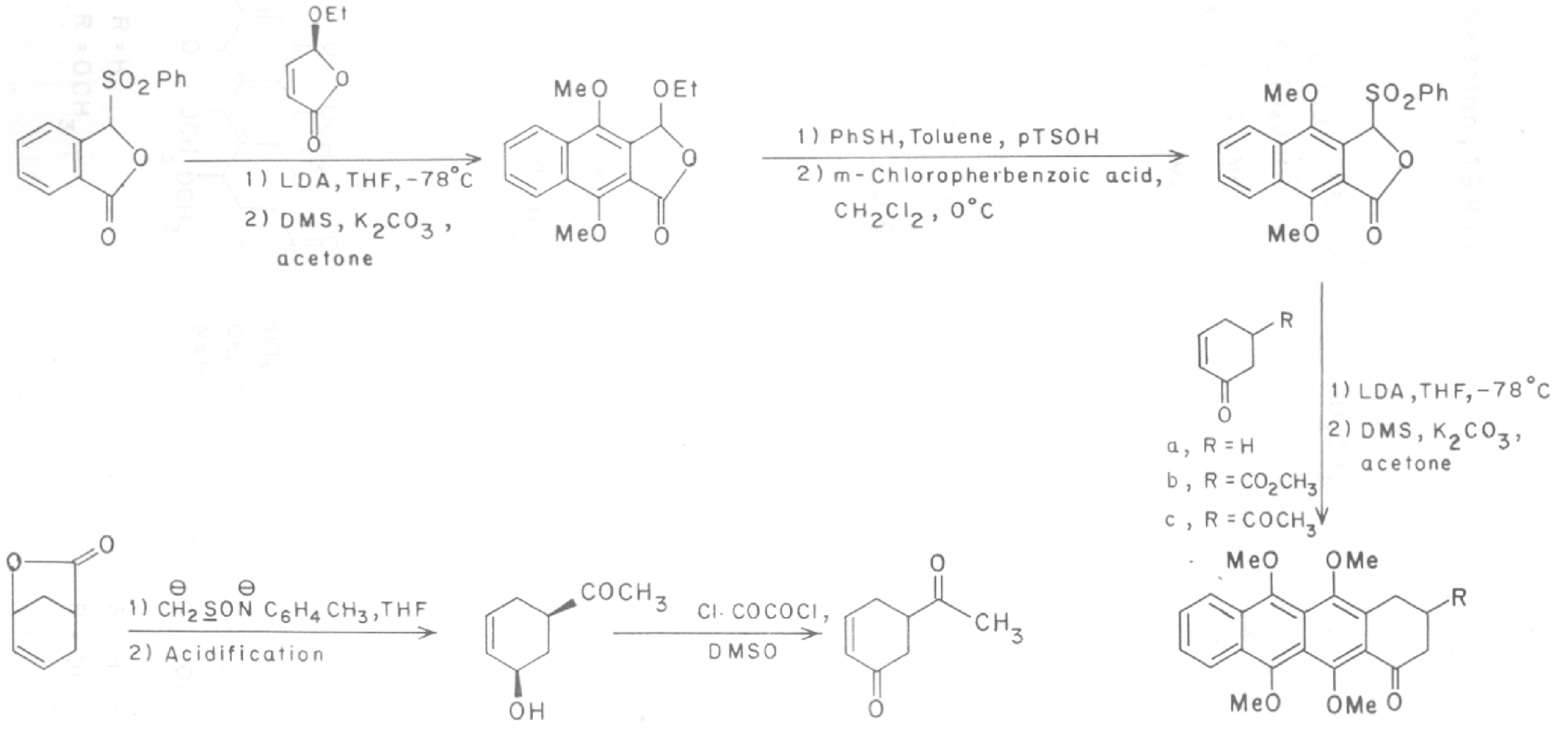
Sih and coworkers[13] have reported the regiospecific synthesis of anthracyclinones *via* base catalysed cyclization (Scheme-3). Terashima and coworkers[14] successfully carried out an asymmetric synthesis by Friedel-Craft approach (Scheme-4).

Rao and coworkers[15] have reported the synthesis of (±)-6-acetyl-1,4-dimethoxy-6-hydroxy tetralin, a key intermediate, in seven steps starting from 1,4-dimethoxy benzene (Scheme-5). A short route to 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol, a key intermediate, was reported by Rama Rao and coworkers[16] in three steps by metal ammonia reduction of 2-acetyl-5,8-dimethoxynaphthalene (Scheme-6).

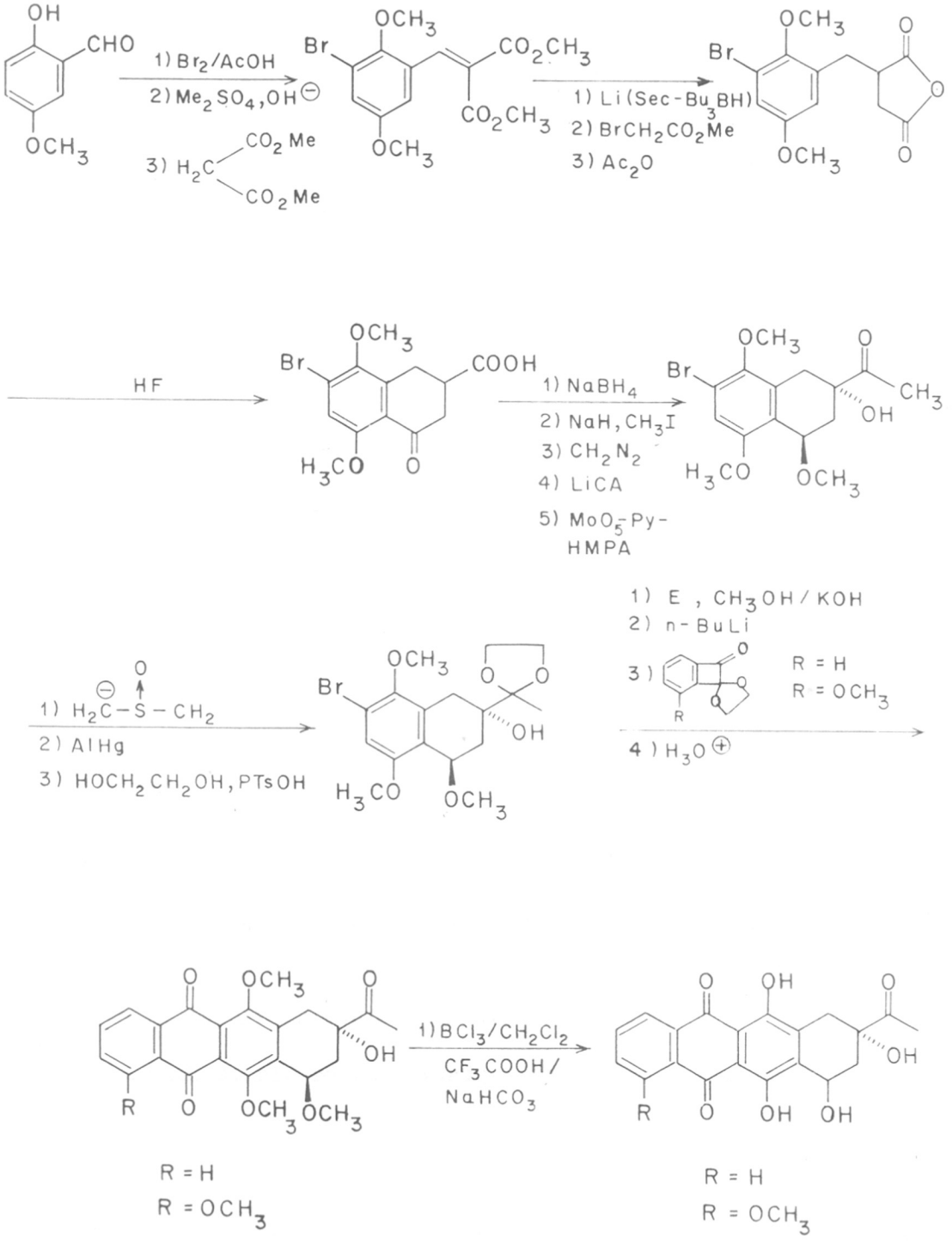
B. Nucleophilic Routes:

The search for effective solutions to aglycone regiochemistry has led to the development of a number of new methods for the construction of anthraquinones which involve anionic species in the regiochemically determining step. Hauser and coworkers[17] have demonstrated that by repeated

## SCHEME 7 ( Hauser, 1979)



Scheme 8 (Swenton, 1981)



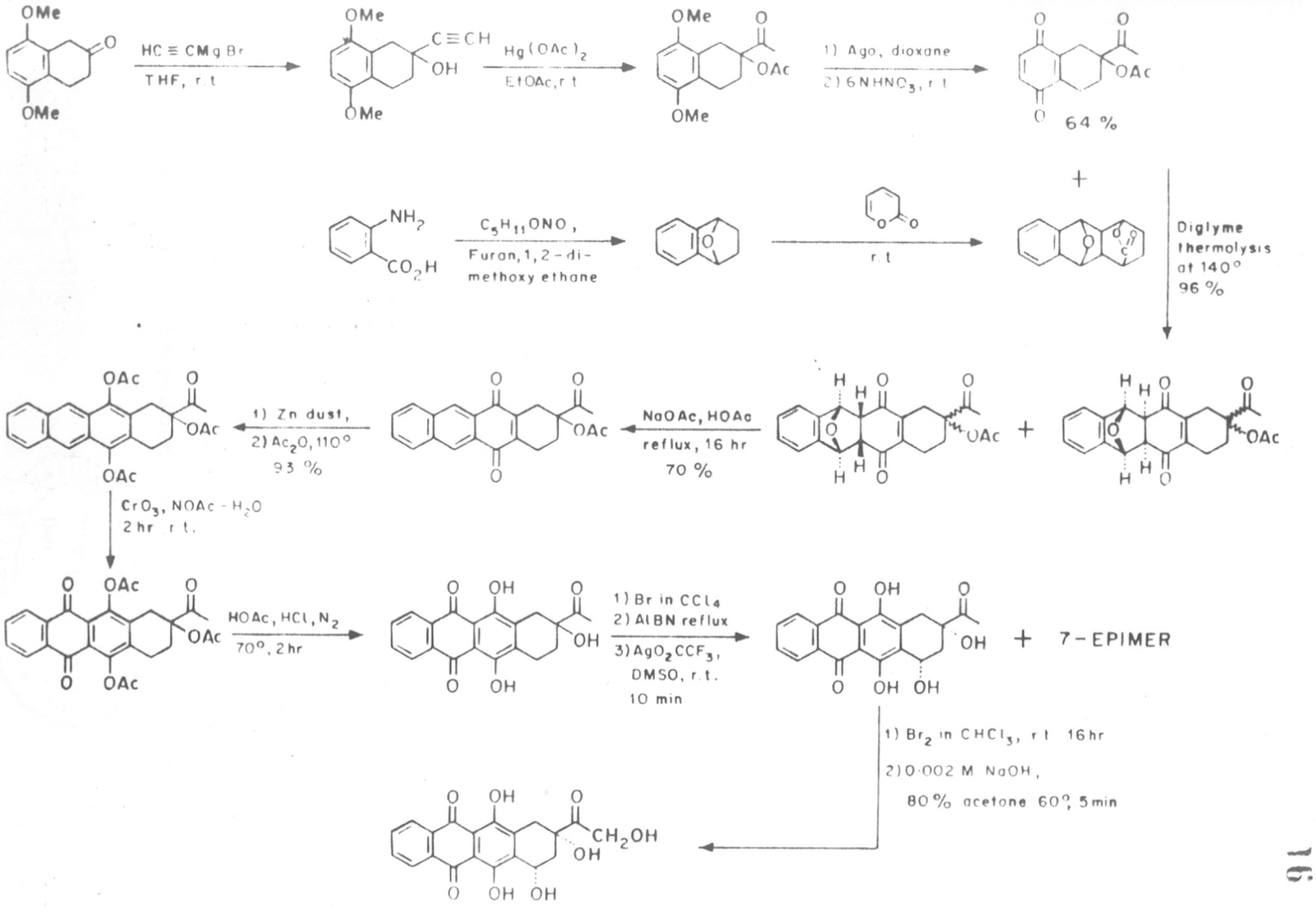
annelation and adjunct ring construction methodology, the anion of 3-phenylsulfonyl-1(3H)-isobenzofuranone can be condensed with Michael acceptors such as 5-ethoxy-2(5H)-furanone and substituted 2-cyclohexen-1-ones to provide the tetracyclic structures with A-ring functionalized (Scheme-7). One of the more thoroughly implemented approaches is due to Swenton and associates[18]. Their strategy for total synthesis of anthracyclinone consists a benzocyclobutenedione monoketal serving as a 1,4-dipole equivalent and its reaction with a lithiated quinone bis-ketal, serving as a metalated quinone equivalent, affords in one step a fully functionalized tetracyclic ring system (Scheme-8).

C. Diels-Alder Routes: The power of the Diels-Alder reaction for the expeditious construction of complex carbocycles has not escaped the notice of practitioners of anthracycline synthesis.

A relatively practicable synthesis of daunomycinone involving the Diels-Alder additions was first reported by Kende et al.[19] in 1976 starting from 1,4,5-trimethoxy-anthraquinone. The major drawback in this method is the loss of an equivalent quantity of the other regio isomer (1-methoxy adduct). In their later attempt Kende et al.[20] have built C-ring on AB-synthon using isobenzofuran as the diene which itself is tedious to make (Scheme-9).

A much simple route towards tetracyclic triketone was

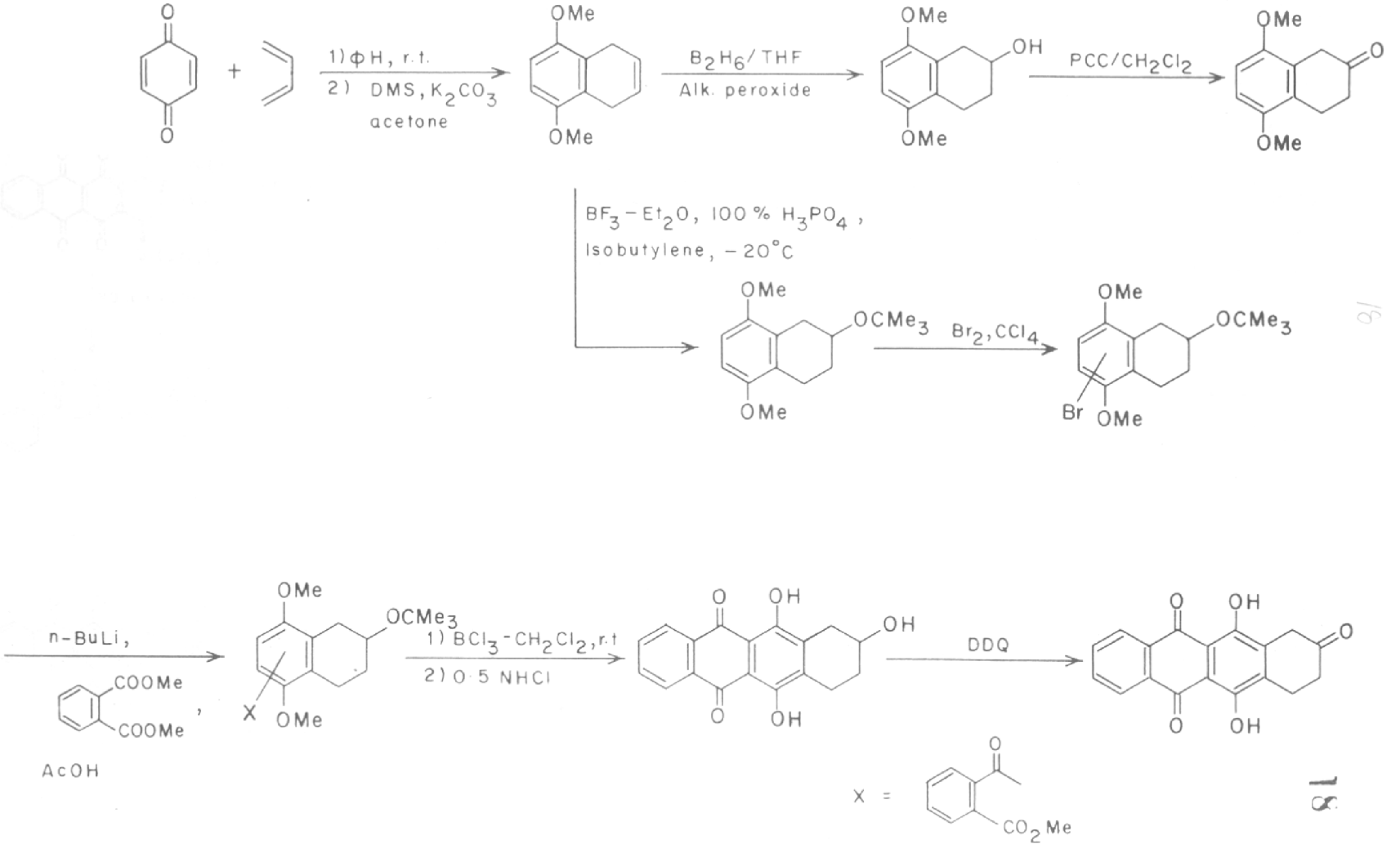
KENDE et al 1977 SCHEME-9



reported by Alexander et al.[21] starting from benzoquinone and butadiene but further elaboration and introductions of the C-7 and C-9 oxygens were not reported (Scheme-10). A stereoselective demethoxydaunomycinone has been reported by Garland et al.[22] employing trans-4-(trimethylsilyl)-3-butene -2-one as a diene and quinizarin quinone as a dienophile (Scheme-11).

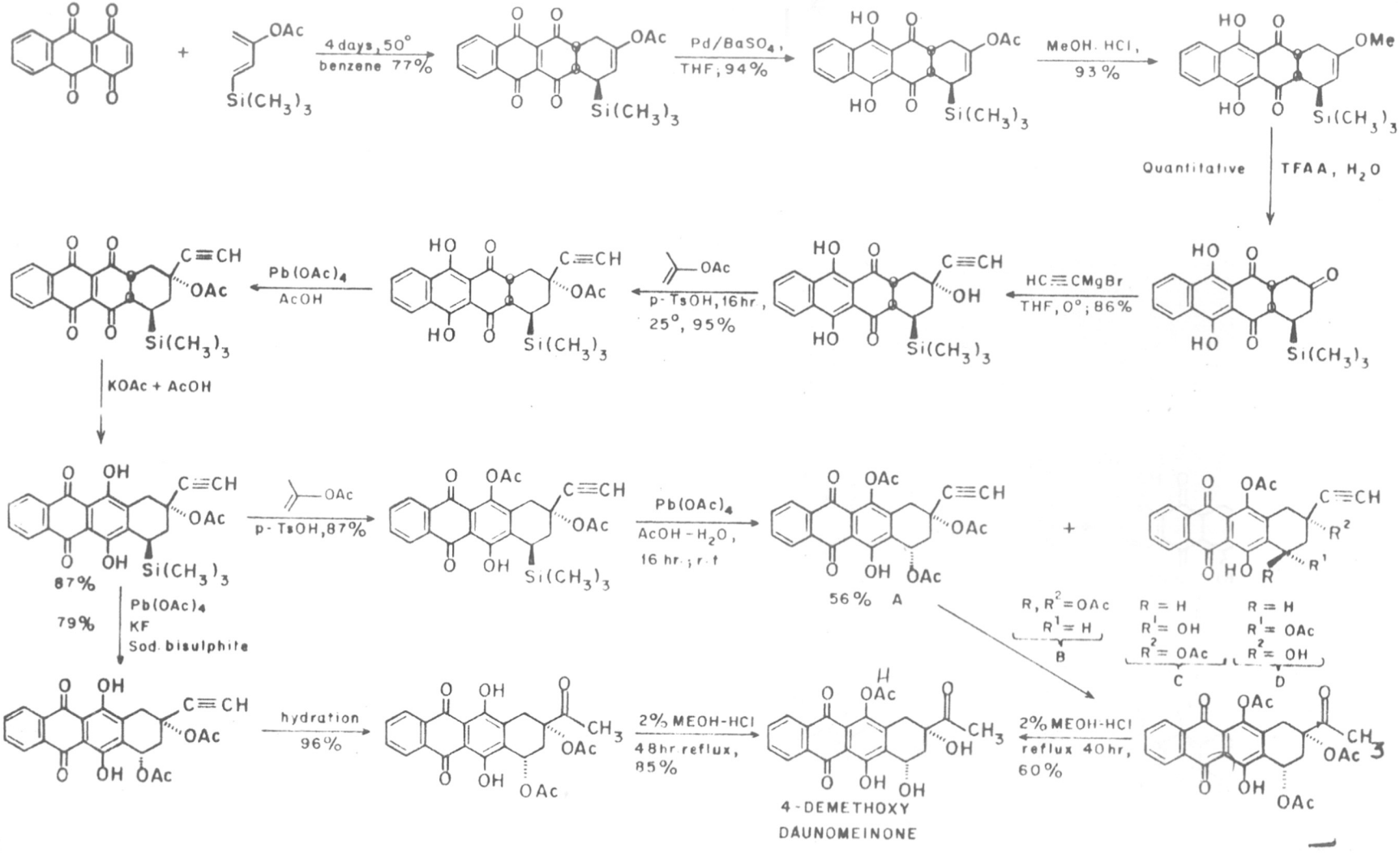
Wiseman et al.[23] made a slightly different approach. The key feature in the synthetic strategy is the construction of tetracyclic nucleus by a Diels-Alder reaction between an appropriately substituted quinone and a reactive O-quinodimethane (Scheme-12). A similar approach was reported by Krohn and Talkiehn[24] employing napthazarin quinone and 1,3-disubstituted diene (Scheme-13). Starting from quinizarin quinone A-ring was added with masked preformed acetyl group by Kelly et al.[25] (Scheme-14). Relatively a simple approach has been made by Kerdesky and Cava[26] whereby A-ring was constructed from O-quinodimethane by Diels-Alder addition to the olefinic portion of an $\alpha,\beta$-unsaturated ketone (Scheme-15). Farina and associates[27] found that substituted naphthazarins and their diacetates exist in tautomeric equilibrium and that tautomers can be selectively trapped by Diels-Alder reaction (Scheme-16). One more approach towards anthracyclinone aglycone analogues by Diels-Alder reaction was reported by

## SCHEME 10 ( Alexander et al , 1978 )

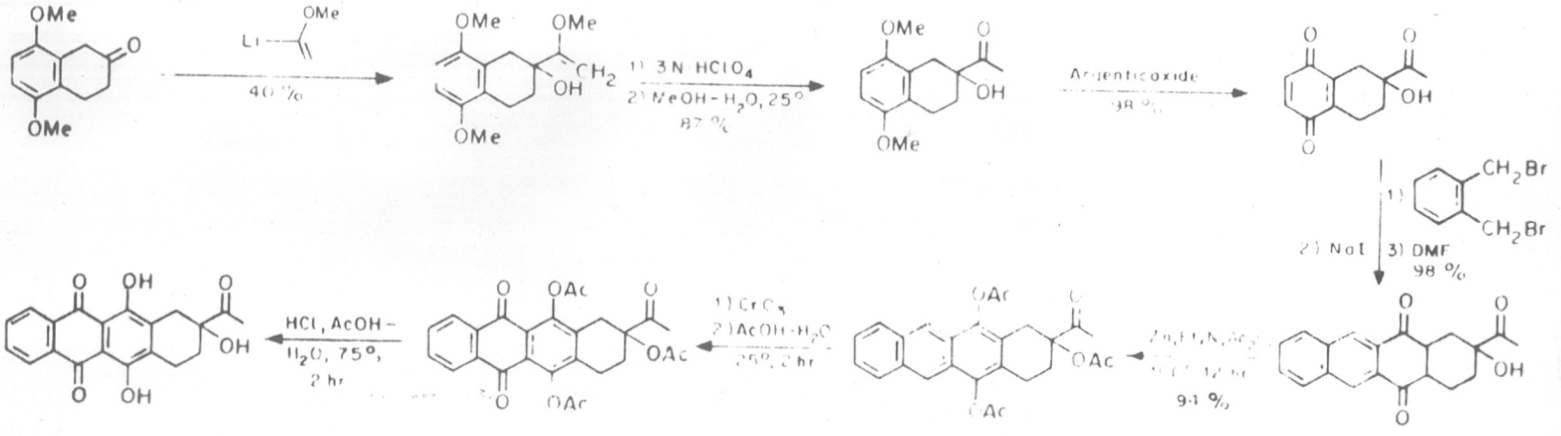


## SCHEME – 11

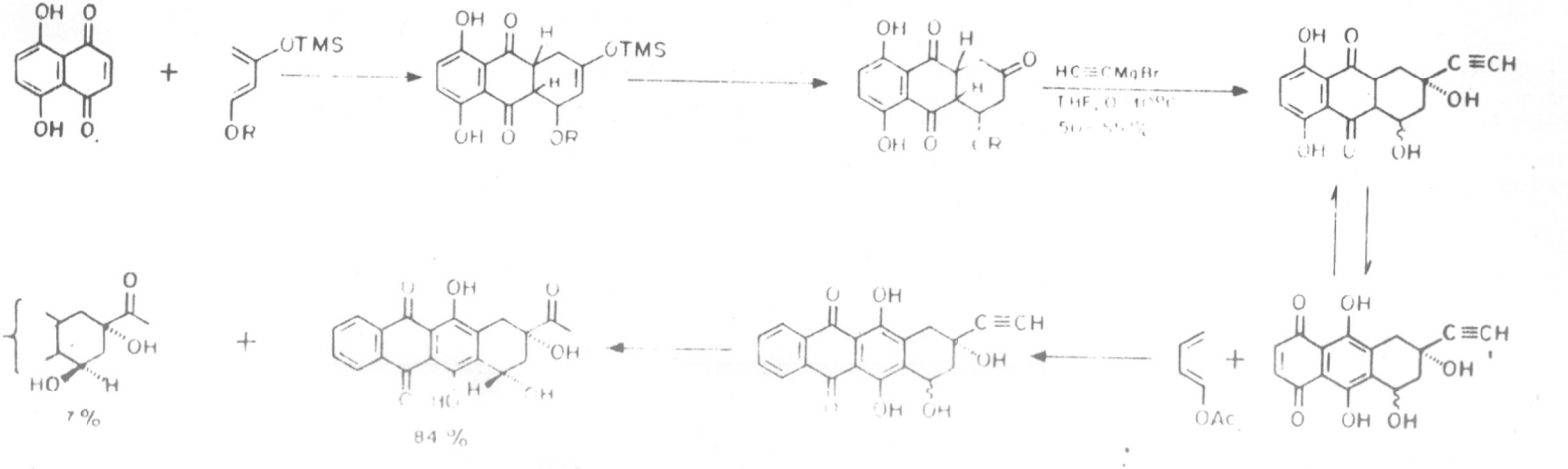
Garland et al, 1978



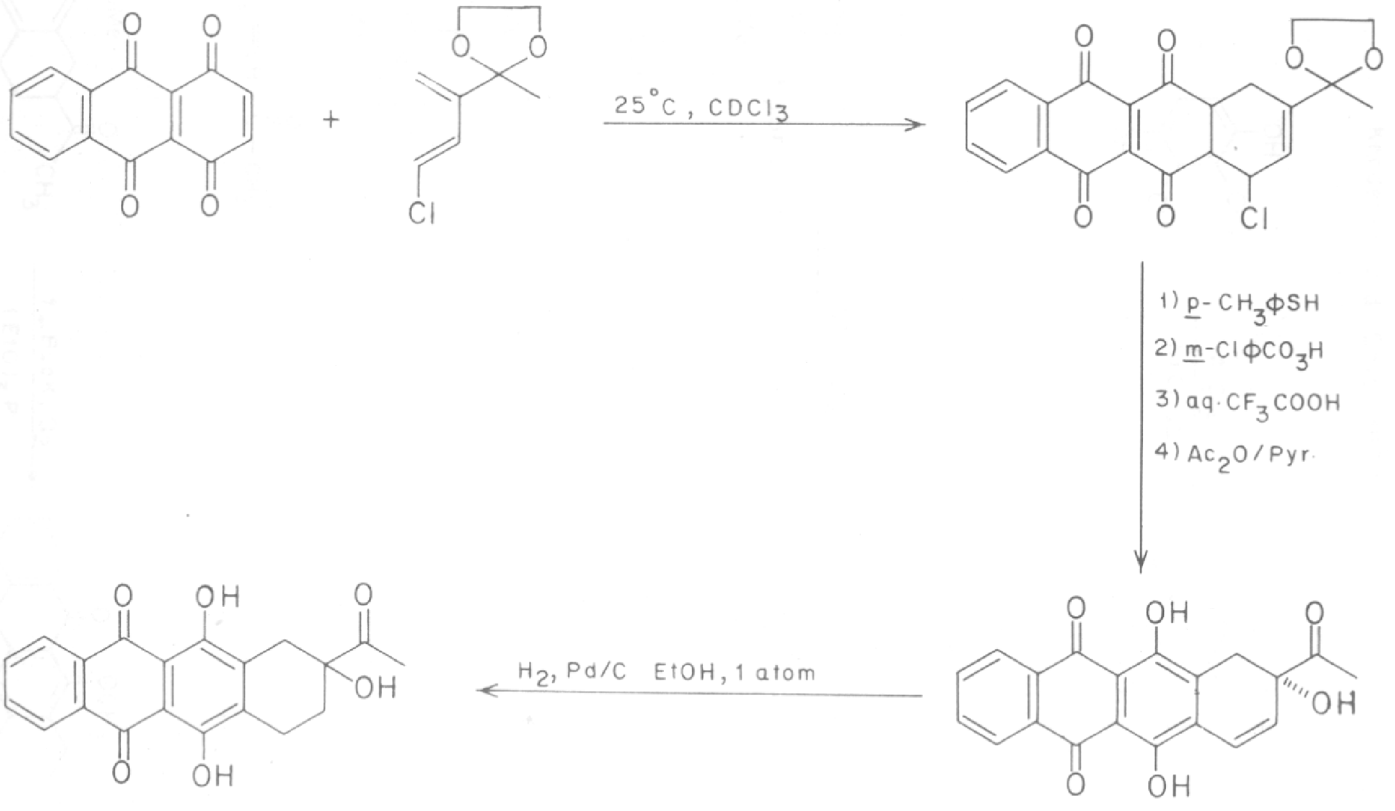
WISEMAN et al. 1978 SCHEME - 12



KROHN and TALKIEHN, 1978 SCHEME - 13

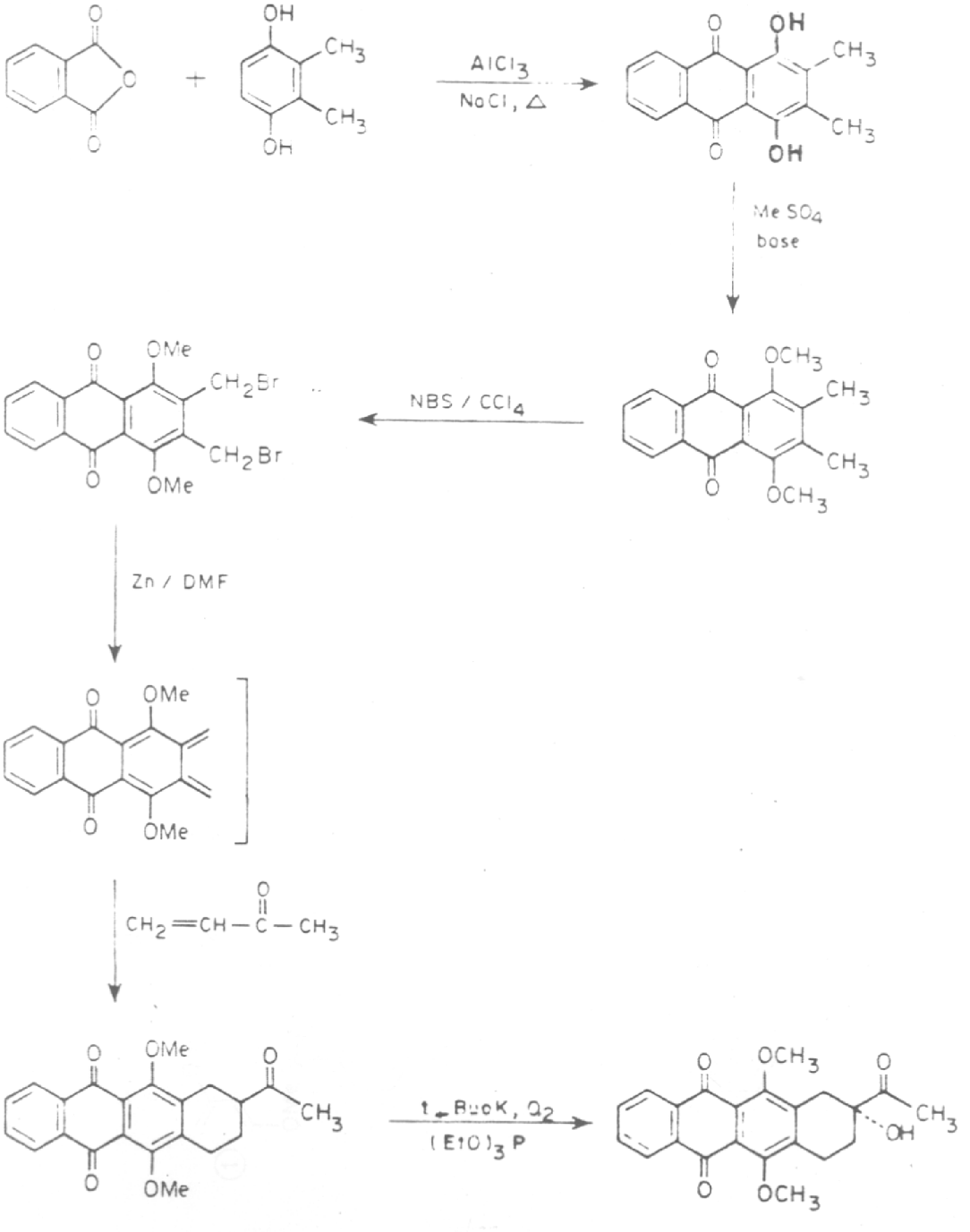


SCHEME 14 ( Kelley et al 1978)

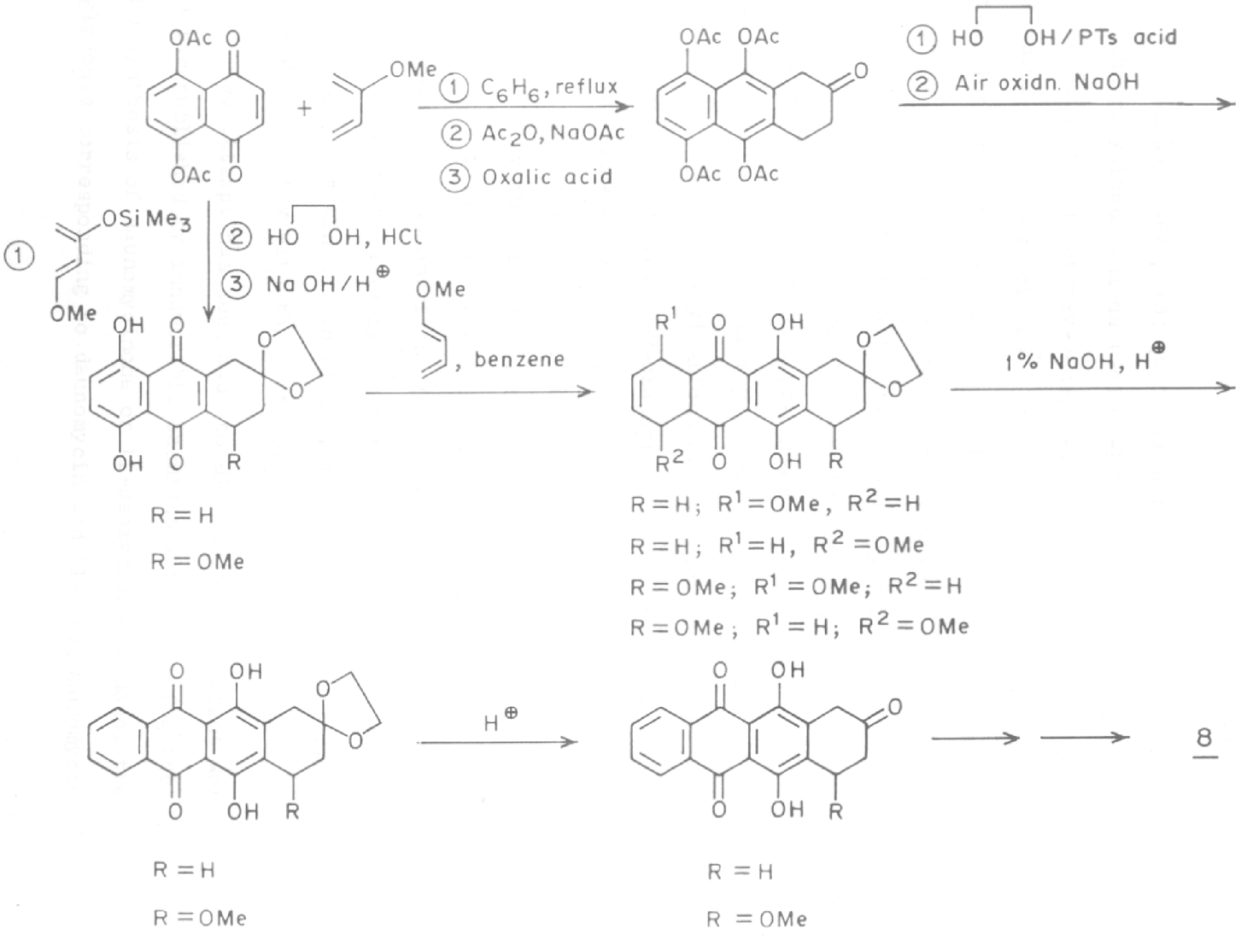


# SCHEME – 15

Kendesky and Cava, 1978



SCHEME 16 (Farina 1979)

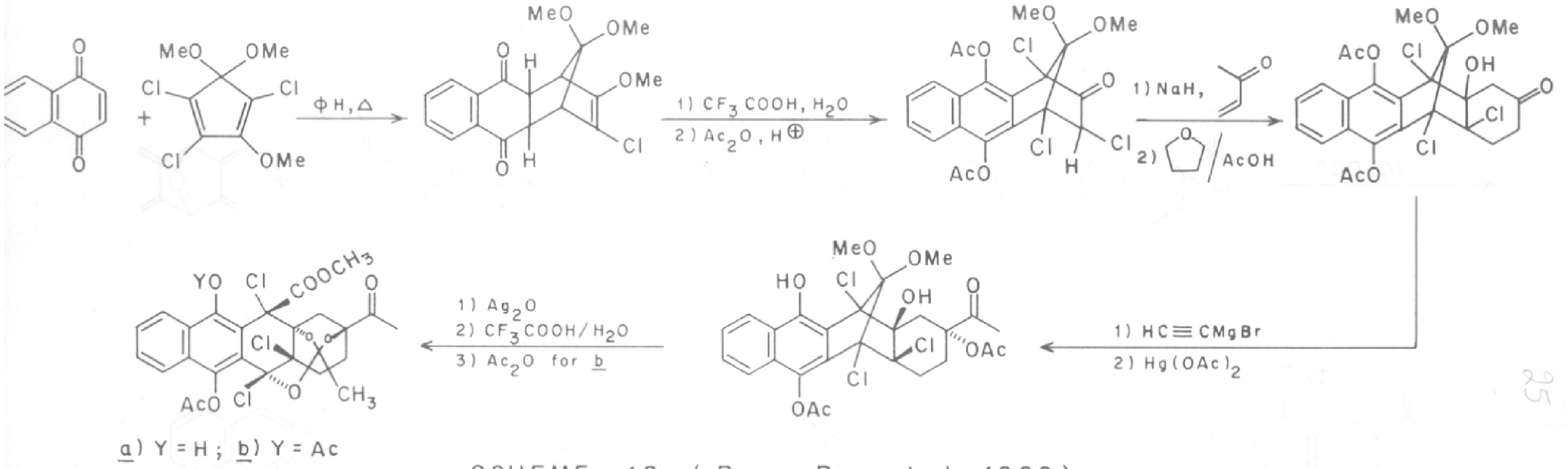


24

Rosen et al.[28] involving quinones and 1,1,3-trimethoxy-2,4,5-trichlorocyclopentadiene (Scheme-17). A simple and short synthesis of 4-demethoxy-7-deoxy-daunomycinone was reported by Rama Rao and associates[29] starting from 1,4,-dimethoxy-6-tetralone and its two carbon homologation by using an acyl anion equivalent such as 2-lithio-2-methyl-1,3-dithiane and transforming the resultant intermediate by conventional operations to get required product (Scheme-18). Vogel and coworkers[30] have reported a precursor of (±)-4-demethoxy-daunomycinone in a simpler way by sequential Diels-Alder additions of methyl vinyl ketone and dehydrobenzene to 2,3,5,6-tetramethylidene-7-oxanorbornane and followed by oxidation (Scheme-19). Hassall and coworkers[31] have reported that the Diels-Alder adduct prepared from the optically active, fully functionalized bicyclic precursor and O-benzo-quinone dimethide can be converted in good yield into (+)-4-demethoxydaunomycinone (Scheme-20). The above discussion is confined to exclusively for the total synthesis of (±)-4-demethoxydaunomycinone, in view of the fact that the present work deals mostly with the synthesis of this aglycone.

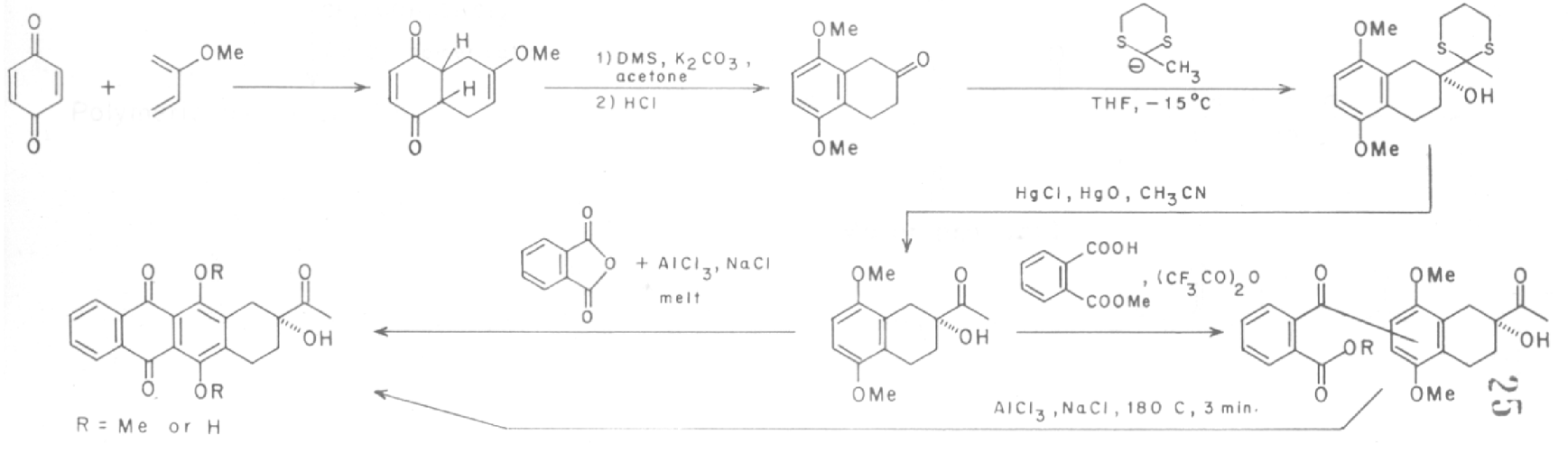
No attempt has been made to discuss the excellent work so far published by innumerable chemists world over for the the synthesis of daunomycinone or 11-deoxydaunomycinone, the aglycones corresponding to daunomycin and 11-deoxydaunomycin

## SCHEME-17 ( Rose et al, 1979 )



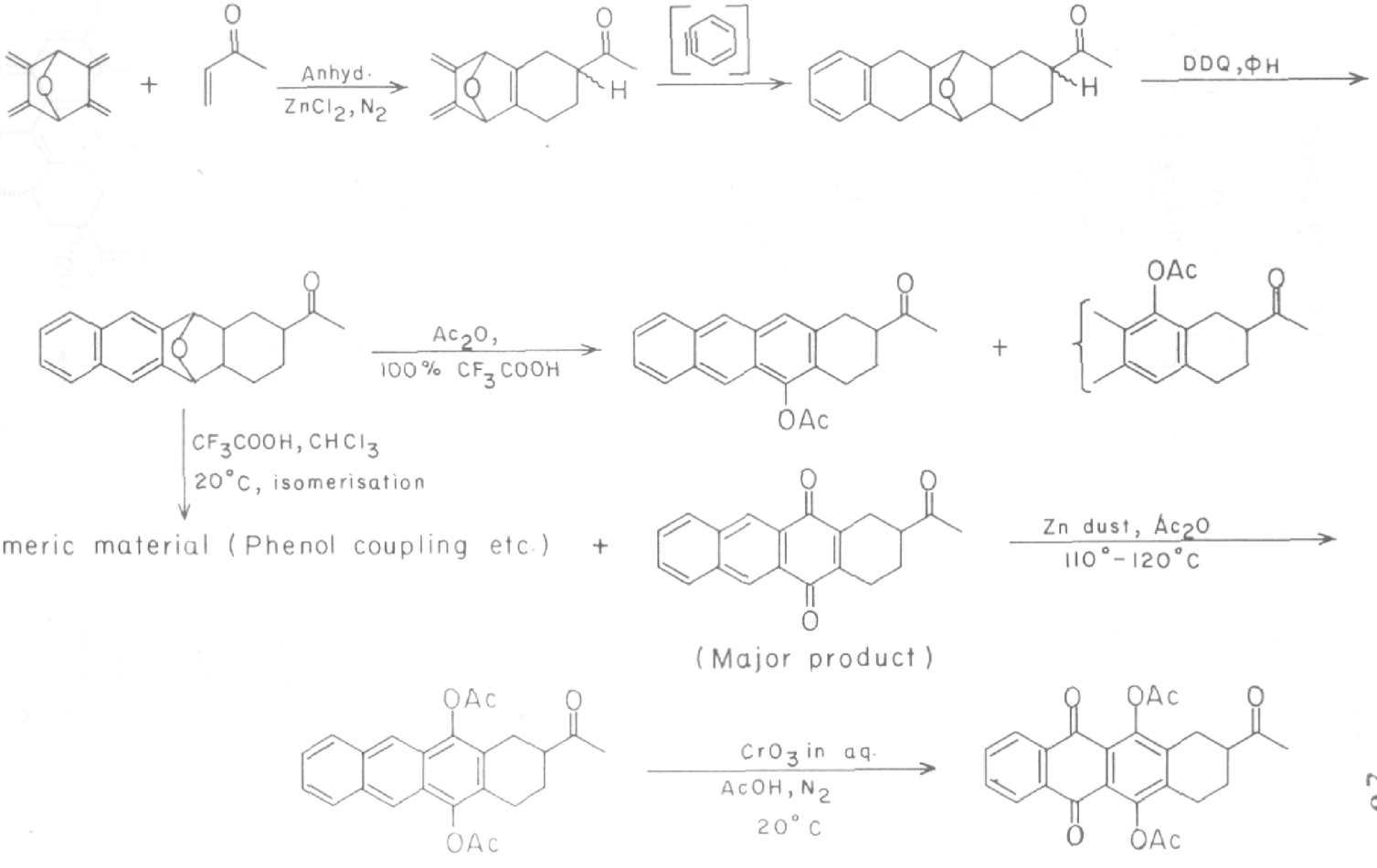

a) Y = H ; b) Y = Ac

## SCHEME - 18 ( Rama Rao et al , 1980 )




R = Me or H

SCHEME 19 ( Vogel et al 1980 )



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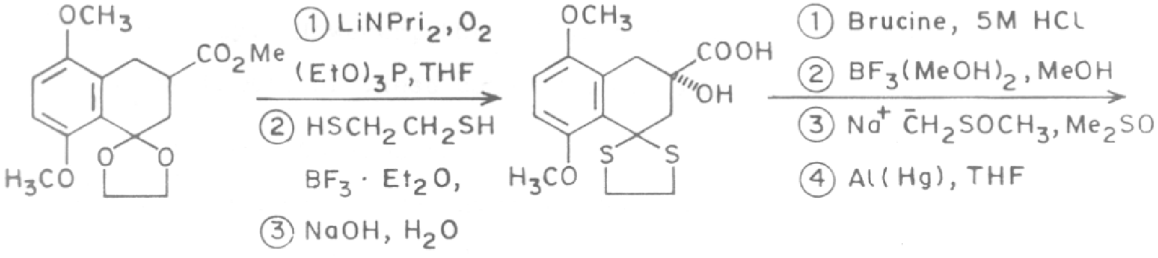
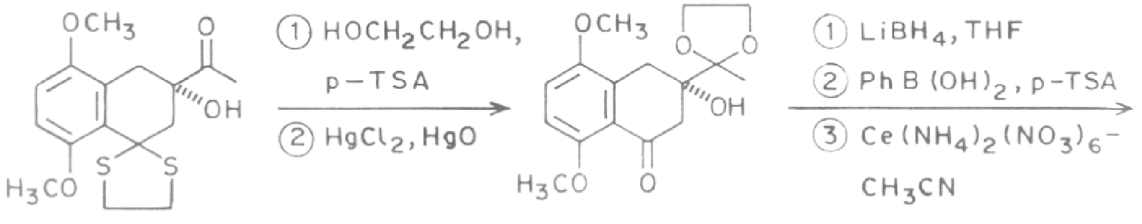
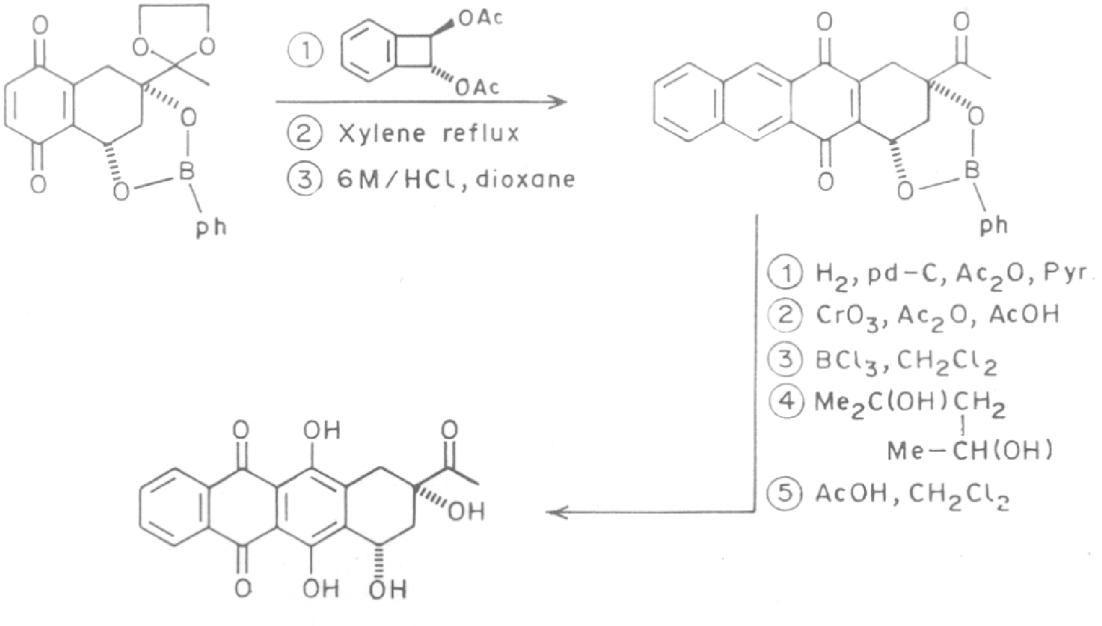
## SCHEME 20 (Hassal et al 1982)




WONG'S COMPD



28

respectively. However, the relevant references for the total synthesis of these compounds are listed in the appendix.

Efforts towards the synthesis of the anthracyclines have provided a chemical harvest which is already bounteous and continues to be reaped. Overall yields for the total synthesis of the intact, chiral natural products (1a) and (1b) as well as their demethoxy analogues are now on the order of 5% in the best cases. Whether total (or partial) synthesis will emerge as the practical solution for the future is, however, a question whose ultimate answer depends on many as yet incompletely resolved factors which include the relative economics of fermentative and total synthesis, the potential therapeutic superiority of non-natural anthracyclines, and future advances in total synthesis.

29

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# CHAPTER - II

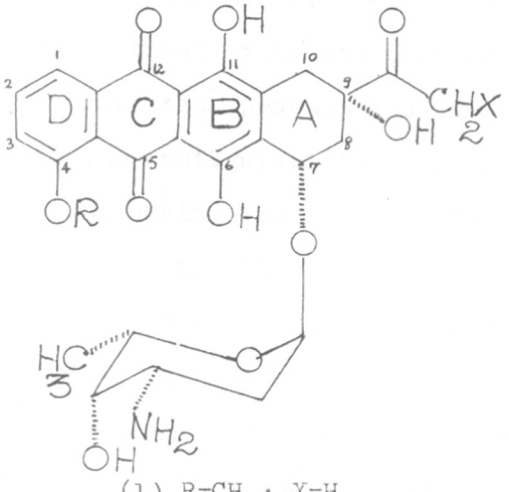
## SYNTHESIS OF (±) 4-DEMETHOXYDAUNOMYCINONE STARTING FROM QUINIZARIN (DIELS-ALDER APPROACH)

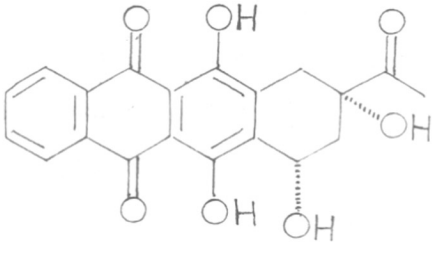
# SECTION – I

## 1,4–ANTHRAQUINONE AND NAPHTHALENE PRECURSORS AS DIENOPHILES

36

It has been discussed in the introductory part that daunomycin (1), adriamycin (2) and carminomycin (3) are useful anti-tumor antibiotics and are formally related structurally to the glycoside antibiotics which are designated with the generic name of anthracyclines.




(5)

(1) R=$CH_3$; X=H

(2) R=$CH_3$; X=OH

(3) R=H; X=H

(4) OR=H; X=H

The structures of these compounds have been well established by spectral studies[1] coupled with chemical degradations[2] and further confirmed by X-ray crystallography[3]. These studies

37

indicated that these molecules consist of a tetracyclic aglycones attached to the aminosugar "daunosamine" via ∝-O-glycosidic linkage. The stereochemistry of both chiral centres present at C-7 and C-9 positions of the aglycone is S and the daunosamine exists as L isomer.

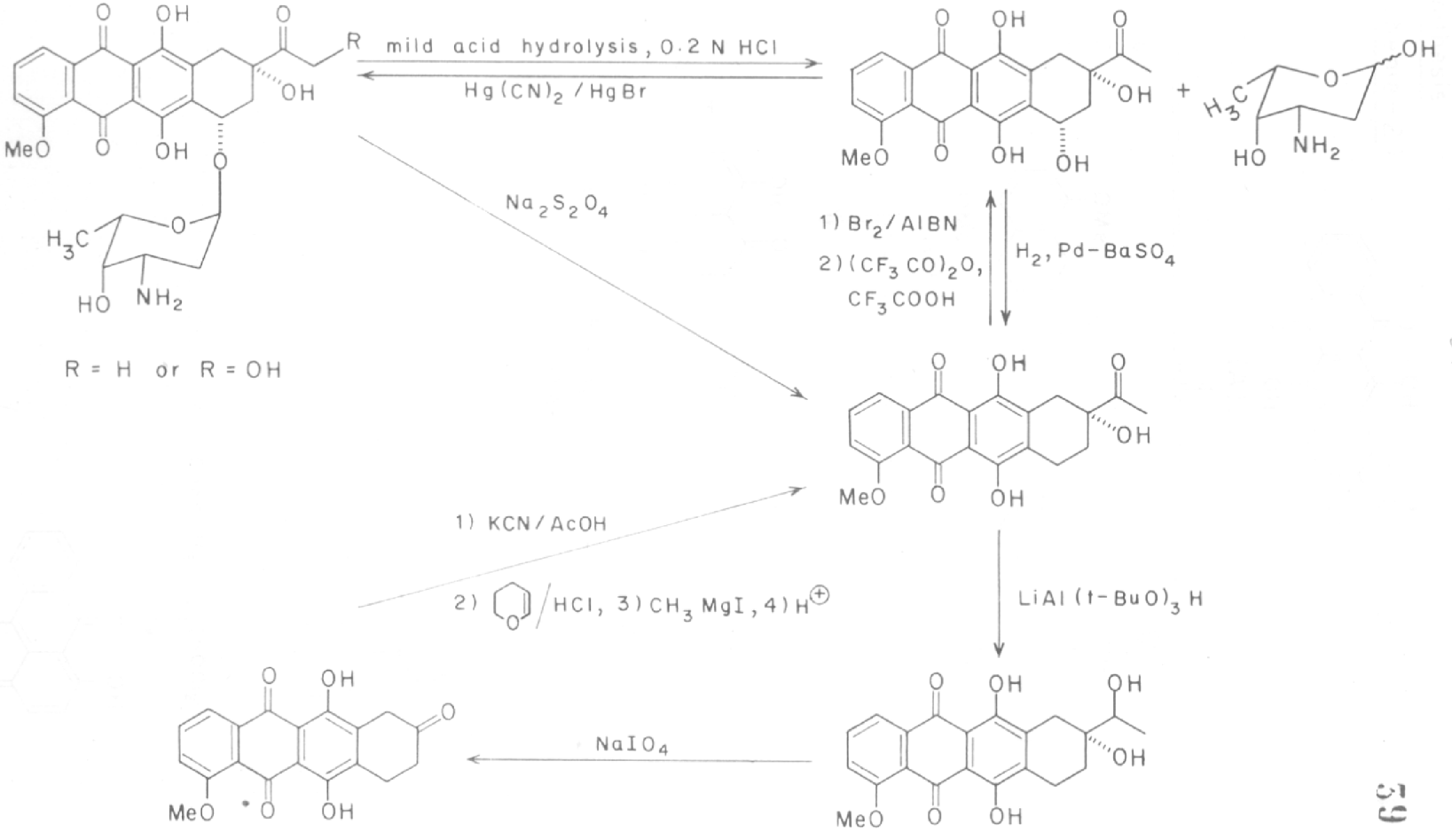
Their scarcity and certain undesirable side effects[4] which are common to many antitumor drugs, have limited their broad utilization in chemotherapy. These aspects have led to continual chemical interest aimed at the development of an efficient total synthesis that would be more advantageous than the fermentation process and more importantly offer a way to provide configurationally and/or functionally modified analogues having improved therapeutic indices. For example it has been shown that 4-demethoxydaunomycine (4) is eight times more effective compared to daunomycin (1) and adriamycin (2) and the results of its clinical trials are reported to be promising[5]. As there is no way of obtaining 4 by fermentation, numerous synthetic approaches have appeared[6]. It is well established that the treatment of daunomycin with sodium dithionite resulted in the reductive cleavage of the O-glycoside bond to afford 7-deoxydaunomycinone and L-daunosamine in quantitative yields. The same aglycone can also be obtained by mild acid-hydrolysis of 1 followed by partial reduction[7]. Same authors have

38

reported the degradation of daunomycin to a nonasymmetric tetracyclic ketone and the refunctionalization of its A-ring to daunomycin and adriamycin (Scheme-1). Several syntheses[8] of L-daunosamine are known and it is noteworthy to mention that its coupling with an aglycone (4-demethoxy-daunomycinone) under given condition proceeds stereospecifically giving exclusively the required α-L-isomer[9]. Therefore, the main interest centered around the synthesis of 4-demethoxydaunomycinone. The methods so far reported for its synthesis are not practicable. This thesis mainly concerns with new synthesis of 4-demethoxydaunomycinone starting from cheap and easily accessible synthons.

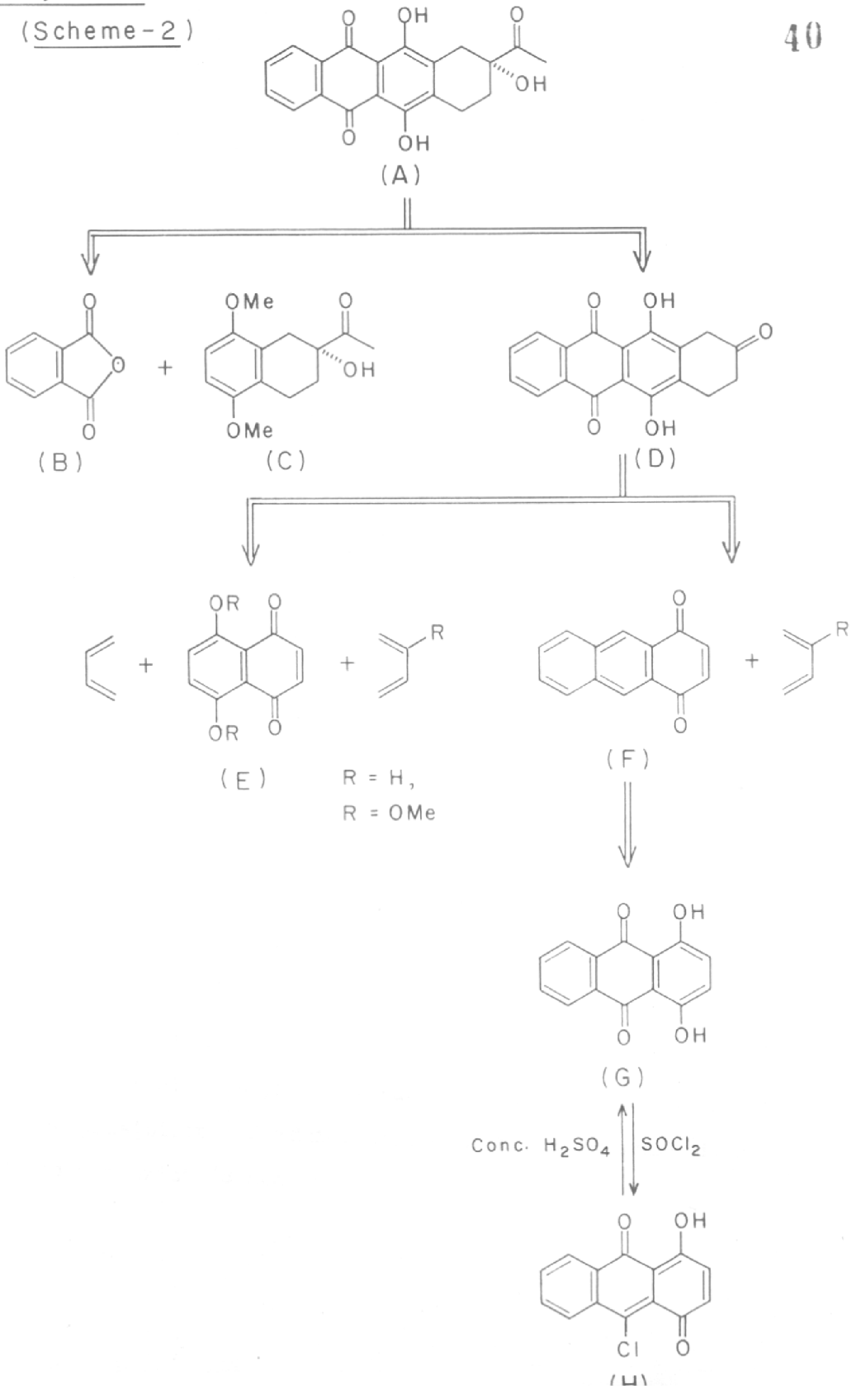
The retrosynthesis of the key intermediate A (as shown in Scheme-2) led us to believe that anthraquinone precursors could act as a plausible starting material for its synthesis. Anthraquinone derivatives could be easily obtained from microbial[10] or plant sources[11] or as dye intermediate[12], and more importantly could be converted into suitably substituted derivatives. Moreover, in anthraquinones the rings B, C and D of anthracyclinones are already present and the A-ring could be generated by Diels-Alder reaction (D.A. reaction) with suitably substituted butadiene.

Scheme – 1


mild acid hydrolysis, 0.2 N HCl
Hg(CN)2 / HgBr
Na2S2O4
1) Br2/AIBN
2) (CF3CO)2O, CF3COOH
H2, Pd-BaSO4
1) KCN/AcOH
2) HCl, 3) CH3MgI, 4) H⊕
LiAl(t-BuO)3H
NaIO4
R = H or R = OH

Retrosynthesis

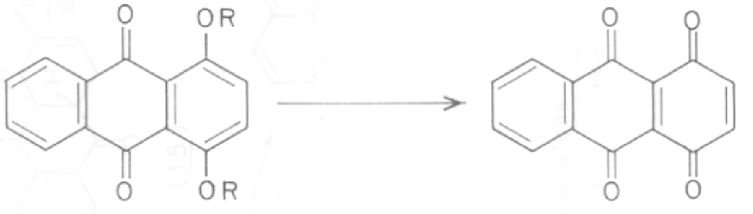
(Scheme-2)



Inhoeffen et al.[13] studied the Diels-Alder reaction of quinizarinquinone[14] (dienophile) (8) with substituted butadienes (Scheme-3). They observed that since quinizarinquinone (8) was bifunctional, the D.A. reaction occurred at both internal and terminal double bonds. Later Sauer[15] suggested a hypothesis based on Inhoeffen's work as well as on his own work that the internal addition was favoured with electron-rich dienes whereas terminal addition occurred with unsubstituted or slightly electron-poor dienes. Thus, with 1-acetoxybutadiene and 2-methoxy- or 2-ethoxybutadiene addition to quinizarin quinone (8) predominantly took place at the internal double bond giving rise to 10a and 10b, whilst with 1,3-butadiene or 2-acetoxybutadiene addition at the terminal double bond predominated to afford 9a and 9b respectively. Although in the latter case addition at the terminal bond did occur, the yields were not significant and moreover, the reaction were reported to be sluggish. Thus it was concluded that quinizarinquinone (8) was not particularly suited dienophile for the present requirements.

Hence, it was though that 1,4-anthraquinone[16] (11) would be an ideal dienophile, because in 1,4-anthraquinone (11) the possibility of addition of a diene to internal double bond did not exist (Scheme-4).

## Scheme - 3

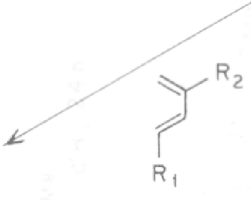


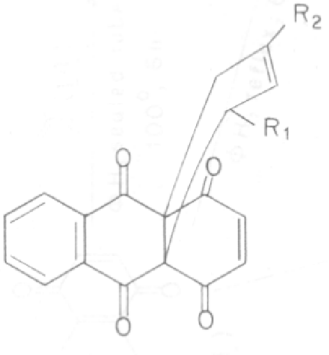
(6) R = H

(7) R = $CH_3$



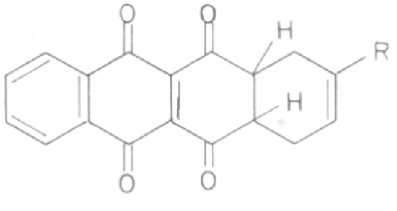
(8)





(10 a) $R_1$ = OAc ; $R_2$ = H

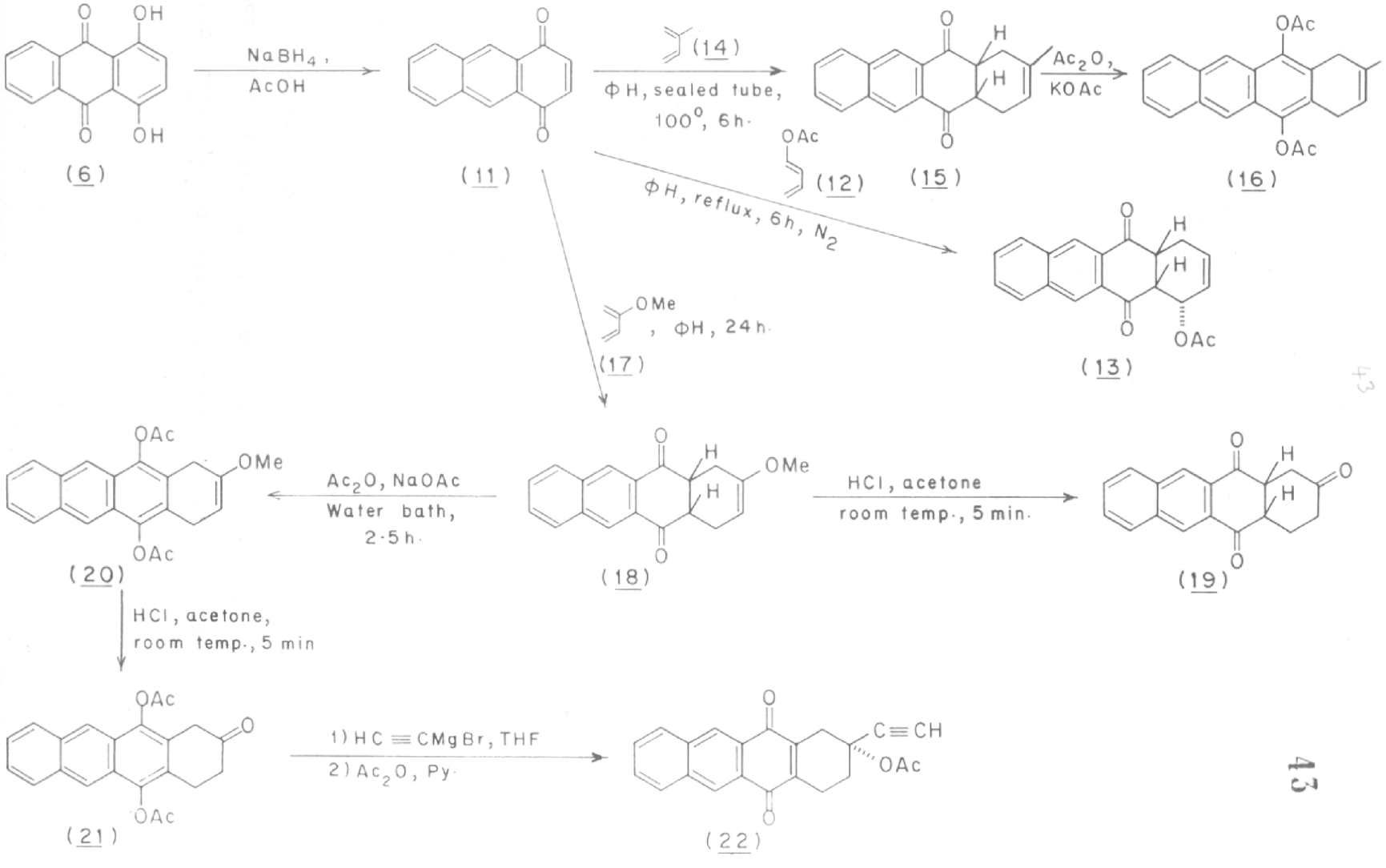
(10 b) $R_1$ = H ; $R_2$ = OMe / OEt



(9 a) R = H

(9 b) R = OAc

## Scheme-4


NaBH4, AcOH
(6)
(11)
(14)
ΦH, sealed tube, 100°, 6h.
(15)
Ac2O, KOAc
(16)
(12)
ΦH, reflux, 6h, N2
(13)
(17), ΦH, 24h.
(18)
Ac2O, NaOAc, Water bath, 2-5h.
(20)
HCl, acetone, room temp., 5 min.
(19)
HCl, acetone, room temp., 5 min
(21)
1) HC≡CMgBr, THF
2) Ac2O, Py.
(22)

Although 1,4-anthraquinone was known for a long time, it had not been exploited as a dienophile in D.A. reactions and it was felt worthwhile exploring its dienophilicity.

The strategy adopted for the synthesis of 4-demethoxy-daunomycinone from 1,4-anthraquinone (11) consisted of following steps:

1) Explore the D.A. reaction of 1,4-anthraquinone with butadienes in particular with 2-methoxybutadiene.
2) O-alkylation or O-acylation of the adduct.
3) Ethynylation of the ketone to ethynyl carbinol.
4) Hydrolysis of ethynyl function to acetyl group.
5) Oxidation to tetracyclinone.

1,4-Anthraquinone (11) could be easily obtained from quinizarin (6) by sodiumborohydride reduction in acetic acid[16]. Its D.A. reaction was first attempted with 1-acetoxy-butadiene (12) in refluxing benzene. The adduct (13) was obtained in high yield (87.5%), whose structure was demonstrated as 1-acetoxy-1,4-dihydro-5,12-naphthacenequinone (13) by $^1$H-NMR spectrum in which a singlet for acetoxy group appeared at $\delta$1.16 and a triplet for vinylic proton at $\delta$6.04, signals due to other protons were in agreement with the proposed structure (13). The appearance of acetyl signal at such a high field ($\delta$1.16) was abnormal because in this region normally resonances due to the alkyl group was expected.

45

This high field shift could be ascribed to the shielding effect of the π-electron cloud of the benzene ring. Indeed examination of molecular model of 13 revealed that the acetoxy group directly fell under the benzene ring and therefore appeared at high field.

The D.A. reaction of 1,4-anthraquinone was then carried out with isoprene (14) in a sealed tube at 100° for 6 hr when 2-methyl-1,4,13,14-tetrahydro-5,12-naphthacene-dione (15) was obtained in 98% yield. The structure of 15 was confirmed by $^1$H-NMR spectrum where the expected signals due to methyl group and vinyl proton were located at 1.73 and 5.36 ppm respectively. For further confirmation of structure of 15, it was converted into the diacetate (16) with potassium acetate-acetic anhydride. The $^1$H-NMR spectrum of the diacetate (16) showed three C-methyl resonances, one at $\delta$ 1.73 due to methyl group at C-2 and and two due to those of acetoxy groups at $\delta$ 2.50 and 2.52. The vinyl proton was observed at $\delta$ 5.36 as a triplet indicating that A-ring did not undergo aromatization. The other protons appeared at the expected chemical shifts.

With 2-methoxybutadiene[17] (17) (prepared from methyl vinyl ketene), 1,4-anthraquinone (11) underwent D.A. reaction giving the adduct (18) in 96% yield. $^1$H-NMR

46

spectrum indicated the signal due to methoxy group and vinylic proton at $\delta$ 3.30 and 4.63 respectively. Further confirmation of 18 was achieved by treating 18 with a trace of HCl in acetone and isolating the resulting trione (19). Comparison of $^1$H-NMR spectrum of 19 with 18 revealed that the signals due to methoxy group and vinylic proton had disappeared. The three methylene protons of A-ring appeared as a multiplet around 2.5 ppm.

The second step of the sequence was effected first by acetylation of 18 with sodium acetate and acetic anhydride (20) followed by treatment with a trace of HCl in acetone. The resulting diacetoxy ketone (21) was obtained in almost quantitative yield. The structure of 21 was assigned on the basis of $^1$H-NMR spectrum. The Grignard reaction was carried out by treatment of 21 with ethynylmagnesium-bromide in THF at $-5^{\circ}$ followed by conventional acetylation. A mixture of products was obtained as judged by TLC. The mixture was subjected to chromatographic purification. One of the products was quinone (22) whose structure was suggested on the basis of $^1$H-NMR spectrum. For example, the resonances due to acetoxy group and due to acetylynic proton appeared as singlets at 2.05 and 2.60 ppm respectively, confirming the assigned structure (22). Other fractions afforded the decomposed products in insignificant amounts,

47

and therefore not characterised.

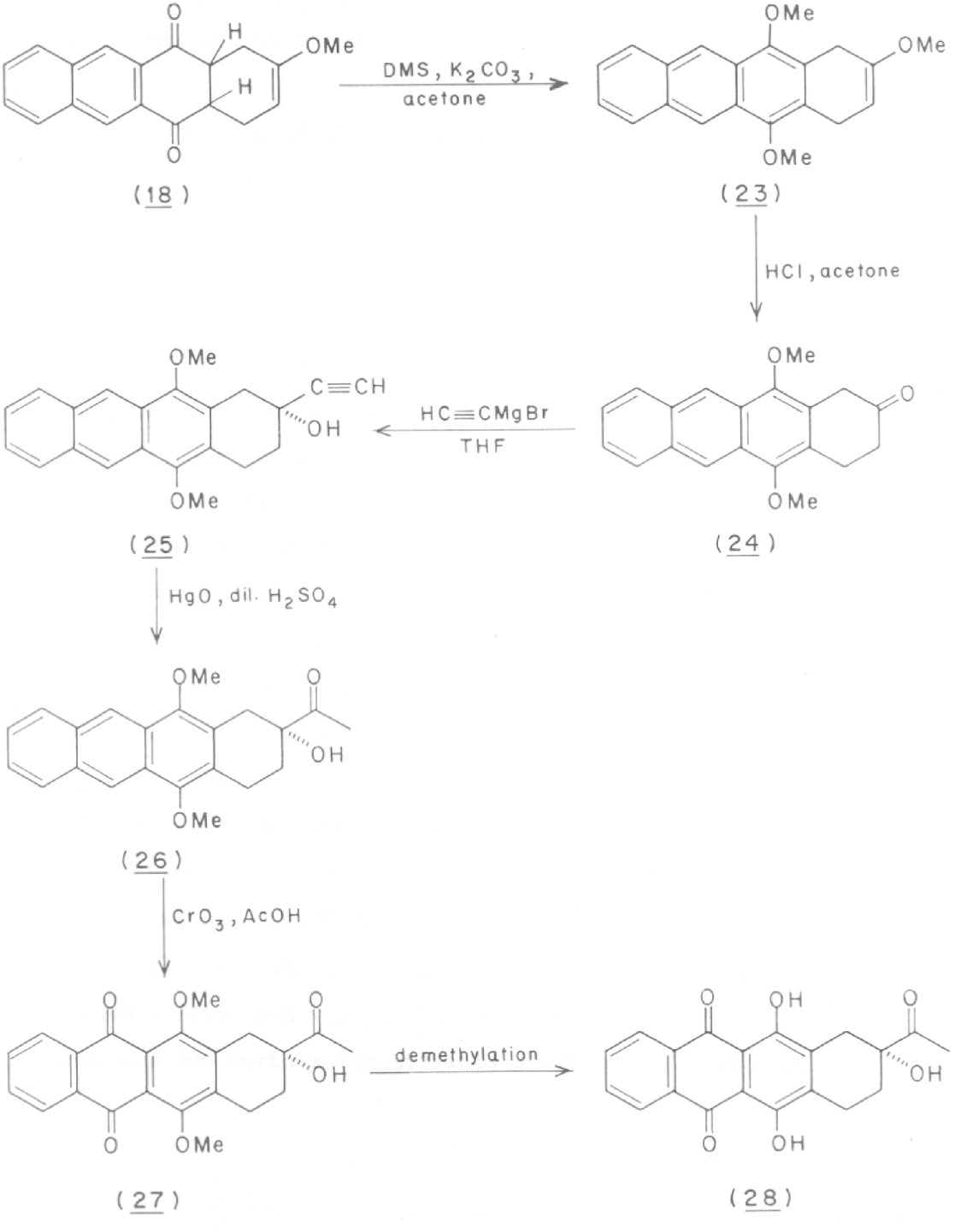
In order to circumvent the formation of side products (probably due to partial de-O-acetylation) during Grignard reaction, it was thought essential to block the hydroxyl groups with base-stabilised substituents. The most convenient group was undoubtedly the O-methyl group since it could be easily introduced and more importantly easily removed at the final stages of the sequence (Scheme-5).

Accordingly the dimethylether (24) was prepared from 18 using conventional methylation procedure (DMS, potassium carbonate) followed by acid hydrolysis. Treatment of 24 with ethynylmagnesium bromide in tetrahydrofuran at $-10^{\circ}$ gave a mixture of products as judged by TLC. Because of the complexity of mixture, this approach was abandoned.

Having failed to do the Grignard reaction between ethynyl-magnesiumbromide and 24, attention was directed to utilise 2-lithio-2-methyl-1,3-dithiane. Ironically with the latter reagent, ketone (24) did not react smoothly and this approach was also given up.

Failure of 24 to undergo reactions either with ethynylmagnesiumbromide or with 2-lithio-2-methyl-1,3-dithiane may be ascribed to the position of carbonyl group in 24. In the presence of a base the ketone function

## Scheme – 5



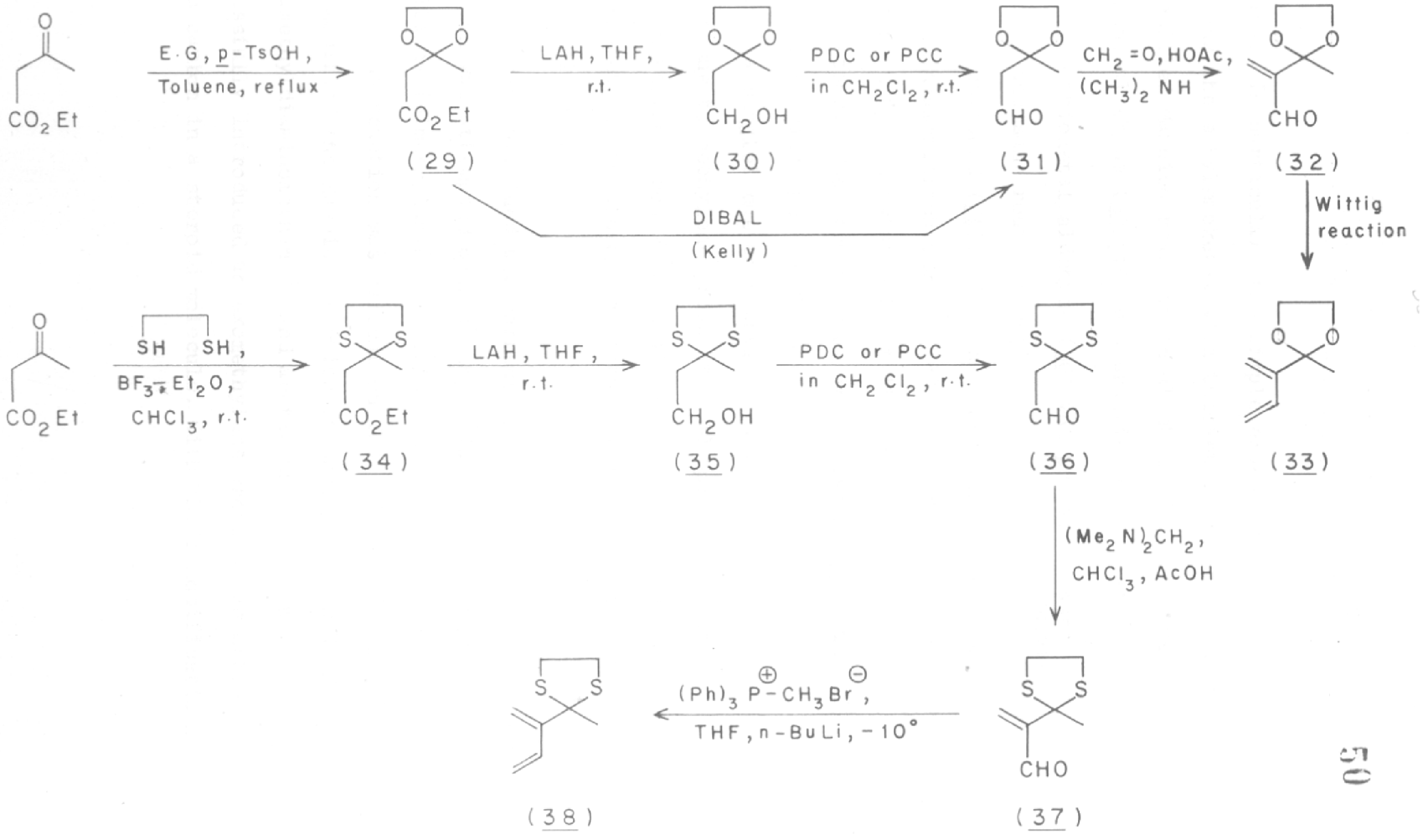

(18) (23) (24) (25) (26) (27) (28)

49

immediately forms a stabilized enolate and under drastic conditions may lead to unwanted side-reactions whereby impeding the expected reaction.

From the preceding work it was concluded that 1,4-anthraquinone (11) could act as a good dienophile, with butadienes it underwent D.A. reactions generating A-ring of the anthracyclinone in high yields[18]. The problem encountered was during the elaboration of the A-ring side-chain because of the base catalyzed degradation. With this problem in mind an another synthetic route for 4-demethoxydaunomycinone (5) was designed (as shown in Scheme-7). The major feature of the route involved the use of ketal or thioketal protected acetyl butadiene (33 or 38 respectively) so that the protective group could be conveniently removed at later stage. It was thought that the synthesis of 33 could be achieved by a simple Wittig reaction on 32. Compound 32 was already prepared by Kelly *et al.*[19] starting from ethylacetoacetate (Scheme-6). However, in our hands the Mannich reaction of aldehyde 31 failed to provide the desired product (32), a polymeric material was always obtained. Modification with wide range of conditions did not bring any improvement. This finding initially provided a less than welcome incentive to explore alternative approaches but further investigations afforded a favourable

## Scheme - 6


E·G, p-TsOH, Toluene, reflux
LAH, THF, r.t.
PDC or PCC in $CH_2Cl_2$, r.t.
$CH_2$=O, HOAc, $(CH_3)_2$NH
DIBAL (Kelly)
Wittig reaction
SH SH, $BF_3$·$Et_2O$, $CHCl_3$, r.t.
LAH, THF, r.t.
PDC or PCC in $CH_2Cl_2$, r.t.
$(Me_2N)_2CH_2$, $CHCl_3$, AcOH
$(Ph)_3P^{\oplus}-CH_3Br^{\ominus}$, THF, n-BuLi, -10°
(29)
(30)
(31)
(32)
(33)
(34)
(35)
(36)
(37)
(38)

51

solution. In particular, the simple expedient of replacing the ethyleneketal with thioketal group allowed the modified Mannich reaction on aldehyde (36) to have methylene-aldehyde (37) in less drastic conditions.

The thioketal aldehyde (36) was prepared essentially by the same route starting from ethylacetoacetate as shown for ketal compound (31). It was interesting to note that the pyridiniumchlorochromate[20] (PCC) or pyridiniumdichromate[21] (PDC) reaction on 35 underwent without the oxidation of the sulphur atoms. The structure of the aldehyde (36) was confirmed by mass and $^1$H-NMR spectroscopy. In the $^1$H-NMR spectrum a singlet due to methyl group at 1.83 ppm, a doublet due to methylene group at 2.90 ppm, a singlet due to two methylene groups of dithiolane ring at 3.40 ppm and the triplet due to aldehydic proton at 9.80 ppm were distinctly visible.

Having obtained the correct aldehyde (36) Mannich reaction was attempted over it employing the reported conditions (dimethylamine, formaldehyde, acetic acid), however, no reaction was evident on TLC. Taylor and Shov[22] have modified the Mannich reaction by employing N,N,N',N'-tetramethyldiaminomethane[23] and acetic anhydride and successfully introduced an exomethylene group on an activated carbon in a steroid molecule. With their modification

52

also, compound (36) failed to undergo condensation, and a polymeric material was obtained. Later it was found that with the combination of N,N,N',N'-tetramethyldiaminomethane and acetic acid in methylene chloride at $0^{\circ}$, the aldehyde (36) underwent Mannich reaction to yield the methylene-aldehyde (37) in 54% yield, after chromatographic purification. Compound (37) was found to be unstable but could be stored in solutions. The $^{1}$H-NMR spectrum (Fig. 1 ) showed two distinct signals for terminal methylene protons resonating at 5.96 and 6.46 ppm. The aldehydic proton appeared as a singlet at 9.83 ppm while the remaining protons appeared at the expected chemical shifts, confirming the assigned structure (37).

Compound (37) was subjected, without delay, to Wittig reaction using methyltriphenylphosphonium bromide[24] and n-butyl-lithium in THF under $N_2$ at $-10^{\circ}$ to give 2-(2-methyl-1,3-dithiolanyl)-1,3-butadiene (38) in 60% yield, confirmed by $^{1}$H-NMR spectrum (Fig. 2 ).

The diene (38) readily reacted with 1,4-anthraquinone (11) in refluxing toluene to give the corresponding adduct (39) in 85% yield (Scheme-7). The vinylic proton was distinctly visible as a triplet at 6.0 ppm in $^{1}$H-NMR spectrum (Fig. 3 ).

Although the preparation of the diene (38) was

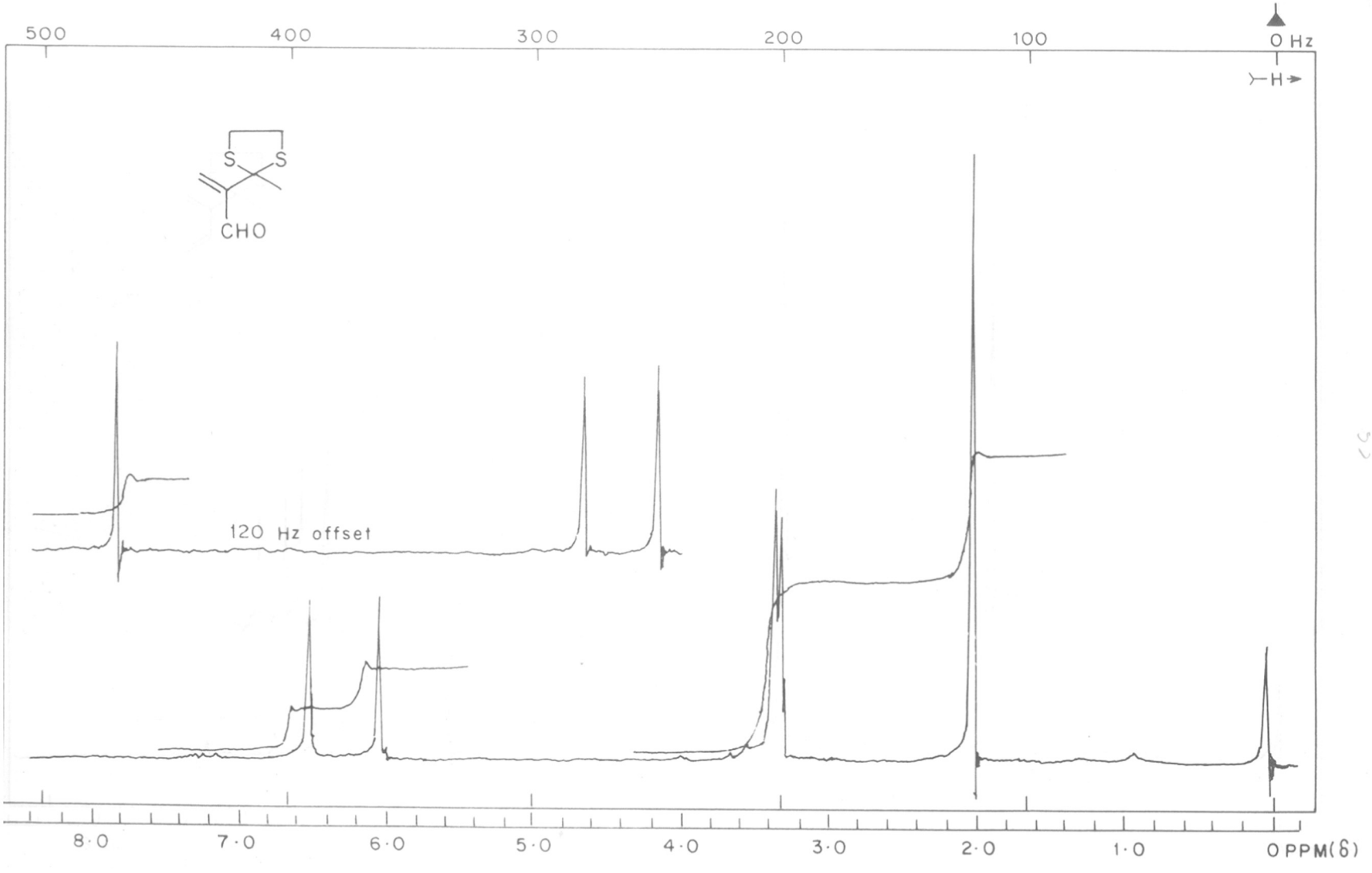



FIG. 1 $^{1}H$-NMR SPECTRUM OF COMPOUND (37) IN $CDCl_3$

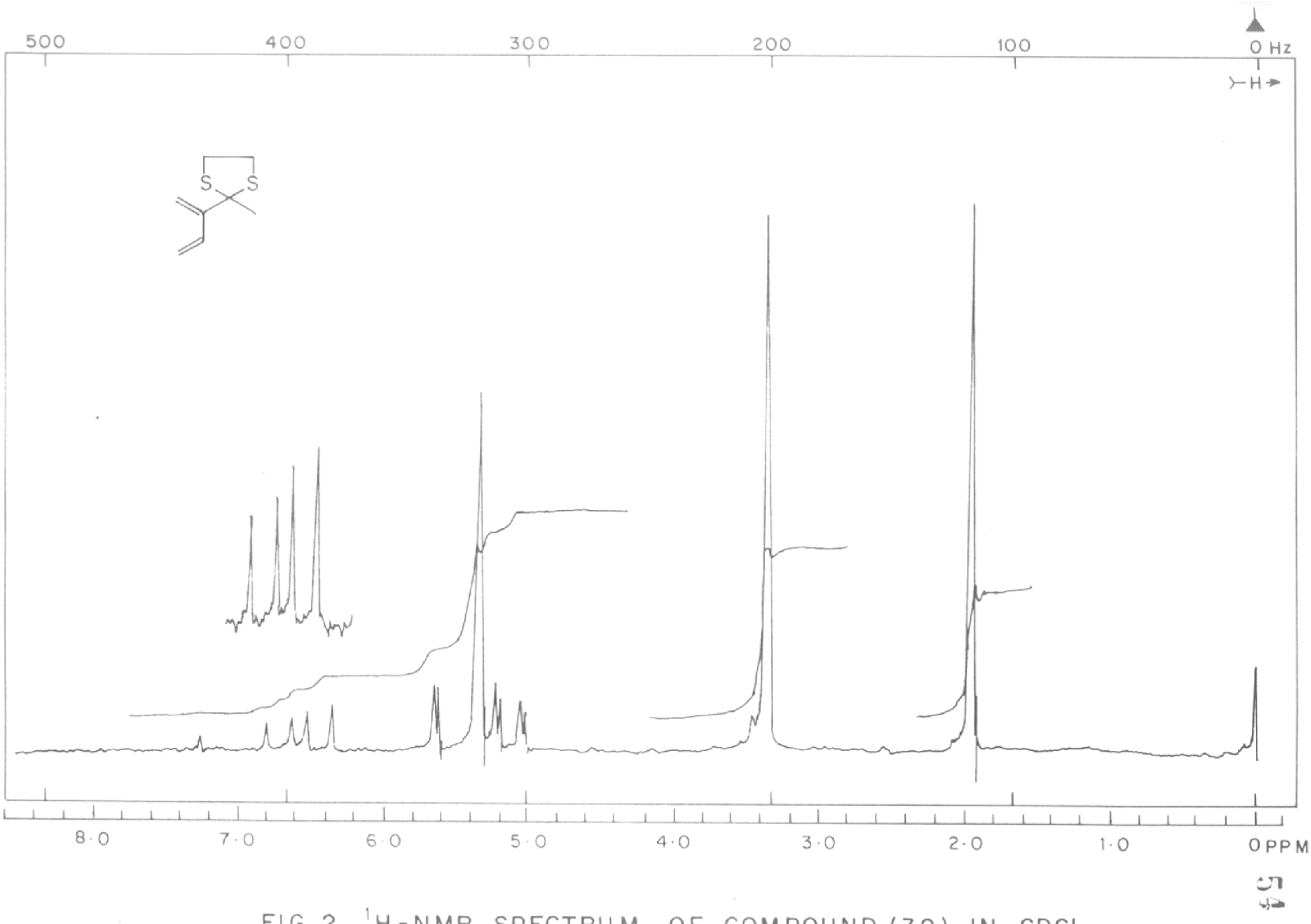
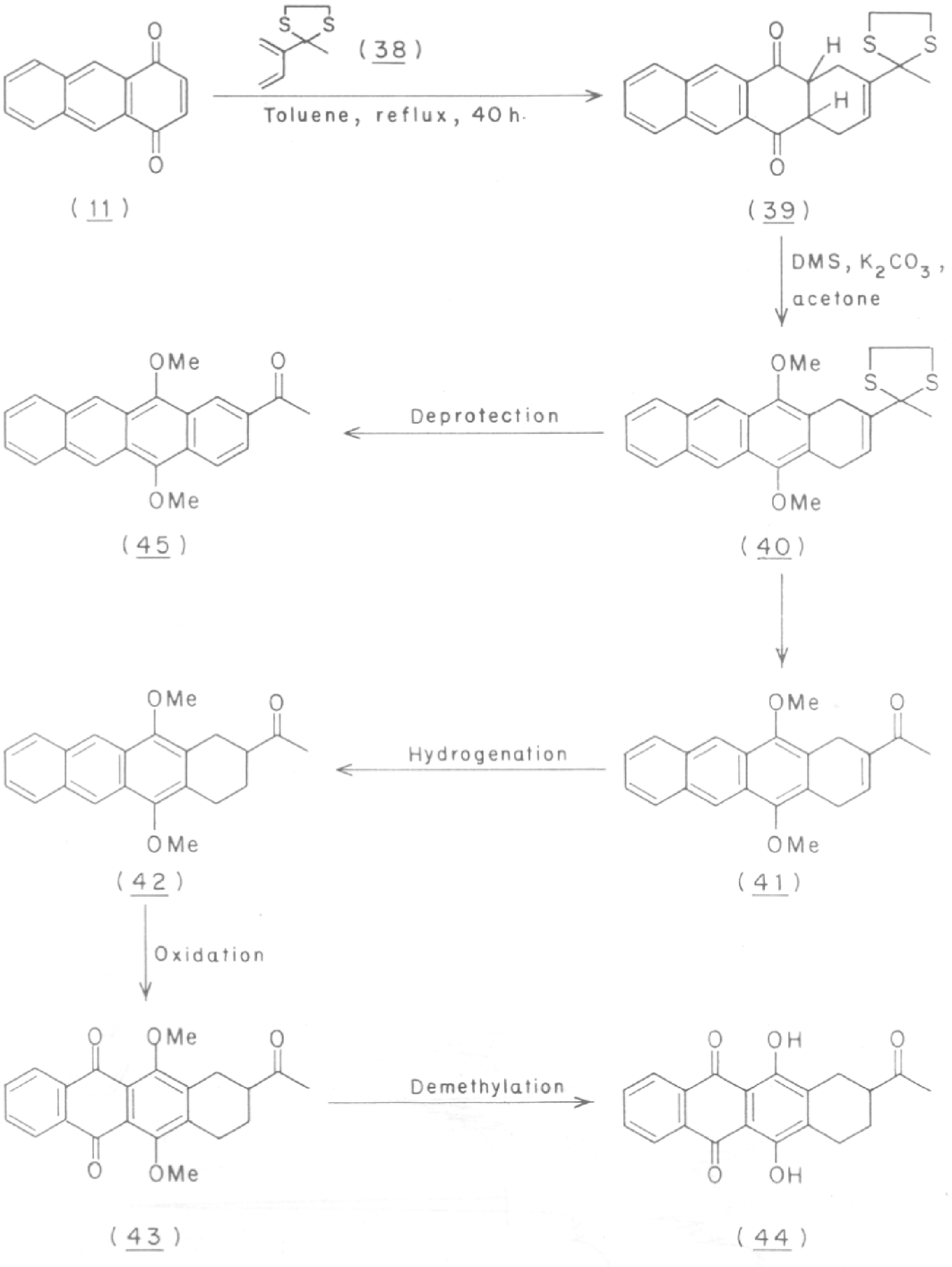



FIG. 2 $^{1}$H-NMR SPECTRUM OF COMPOUND (38) IN $CDCl_3$

Scheme - 7


(38)
Toluene, reflux, 40 h
(11)
(39)
DMS, $K_2CO_3$, acetone
(40)
Deprotection
(45)
Hydrogenation
(41)
(42)
Oxidation
(43)
Demethylation
(44)

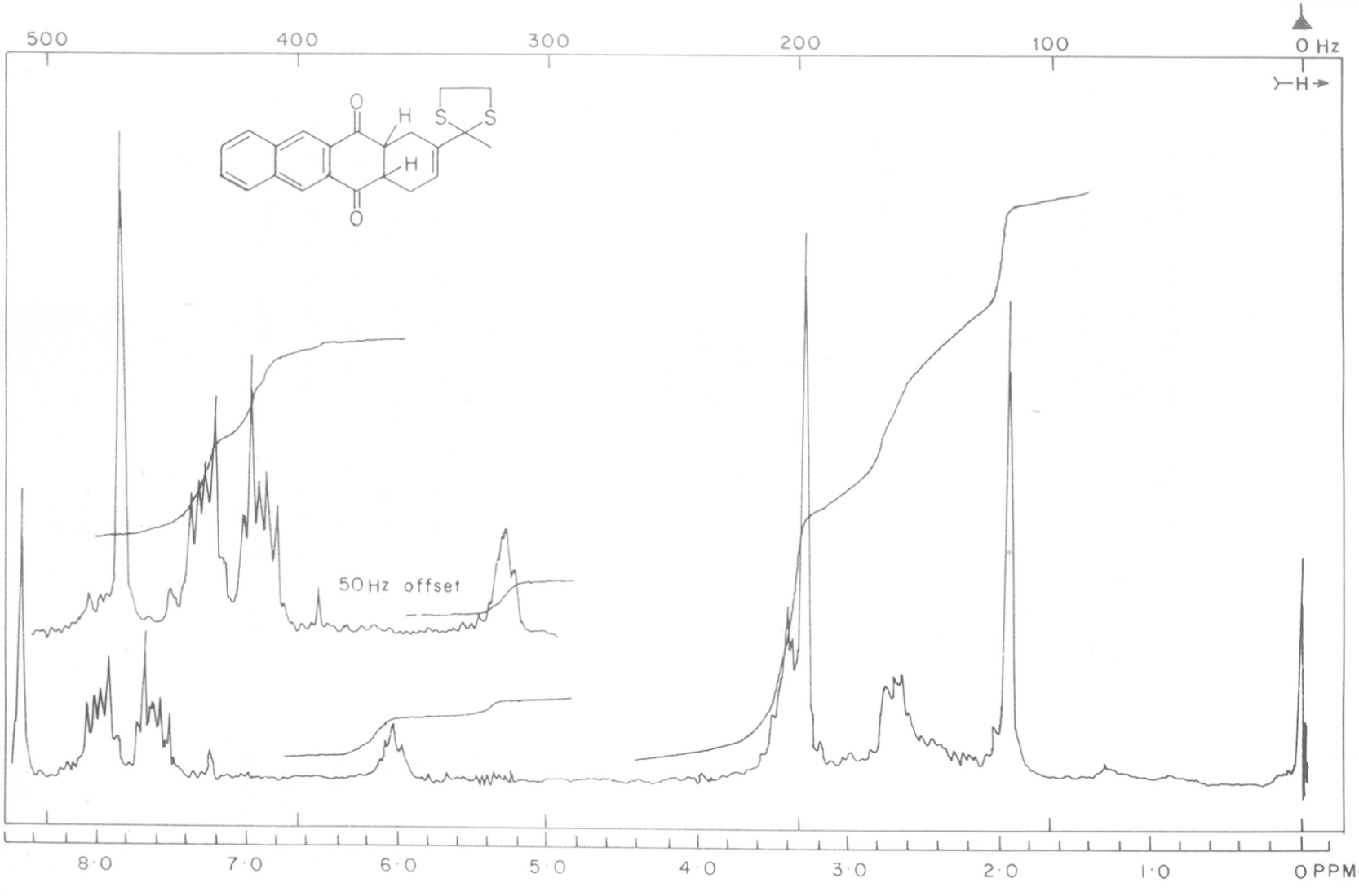



FIG. 3. $^{1}$H-NMR SPECTRUM OF COMPOUND (39) IN $CDCl_3$

58

best be achieved by converting alcohol (48) to O-mesylate followed by elimination of methanesulfonic acid with triethylamine at $0^{o}$, 49 was isolated in 60% yield. Its structure (49) was supported by $^{1}$H-NMR spectrum (Fig.4 ) in which the characteristic multiplet pattern for $CH_2=CH-C=CH_2$ appeared in between $\delta$ 5.0 to 6.1, other protons resonated at the expected chemical shifts.

The D.A. reaction of 49 with 1,4-anthraquinone (11) was attempted under wide range of conditions but surprisingly no reaction was observed, the quinone (11) was recovered quantitatively. Attempts to add the diene (49) even to reactive dienophiles such as 1,4-benzoquinone and 1,4-naphthoquinone met with failure.

It is important to point out that although the difference in the substituents at 2-position of the dienes (38) and (48) seemed to be insignificant (the former having a dithiolane while the latter was having dithiane group) their marked difference in the D.A. reaction with quinones (11) was not clearly understood.

Compound (39), prepared earlier (page ) was methylated with dimethylsulphate, in presence of potassium carbonate and acetone to give the dimethylether (40) (Scheme-7). Its structure (40) was supported by $^{1}$H-NMR (Fig.5). Dethioketalization of 40 was attempted with HgO, $HgCl_2$ in aqueous acetonitrile, a mixture of products

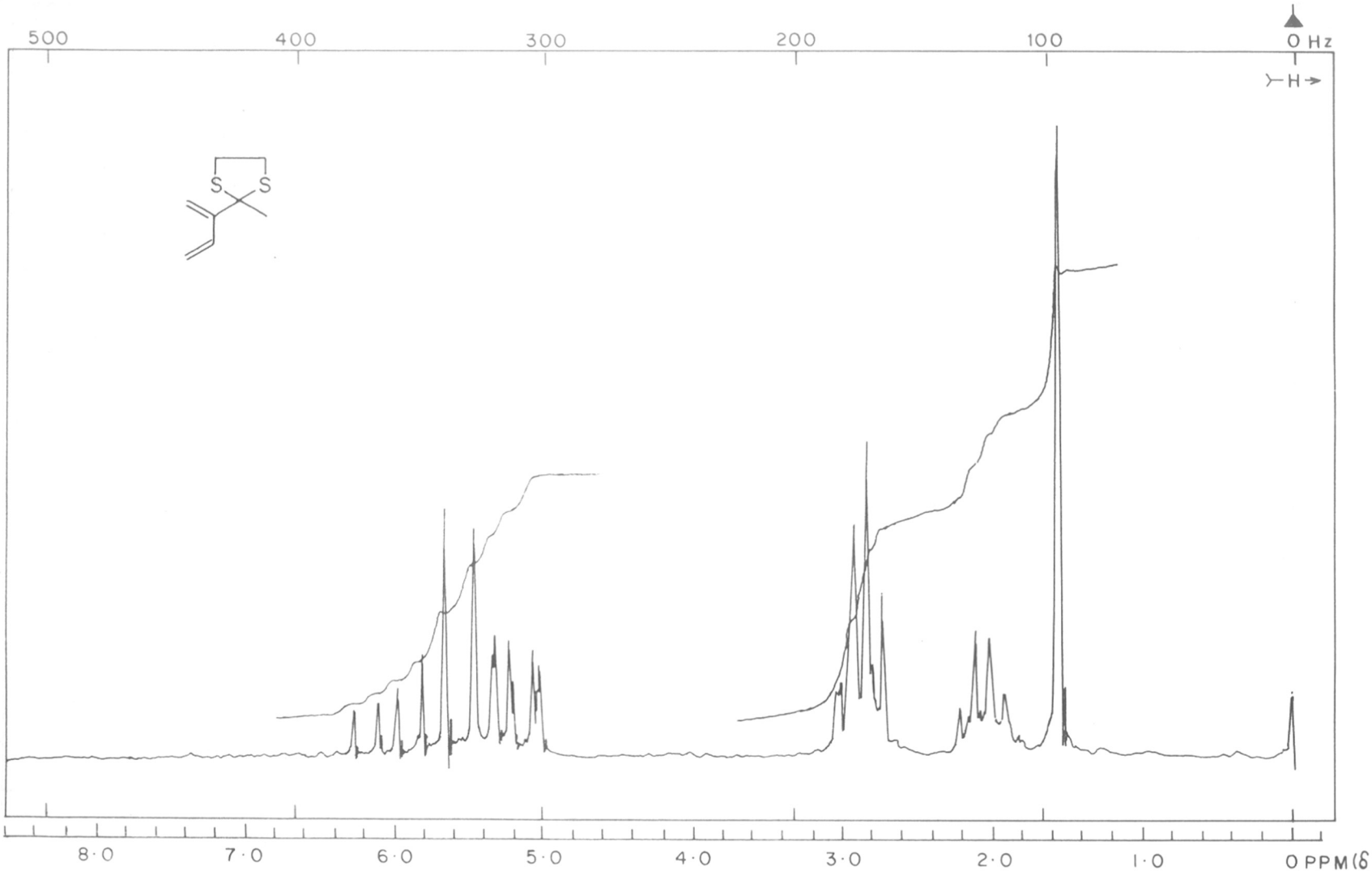



FIG. 4. $^{1}H$-NMR SPECTRUM OF COMPOUND (49) IN $CCl_4$

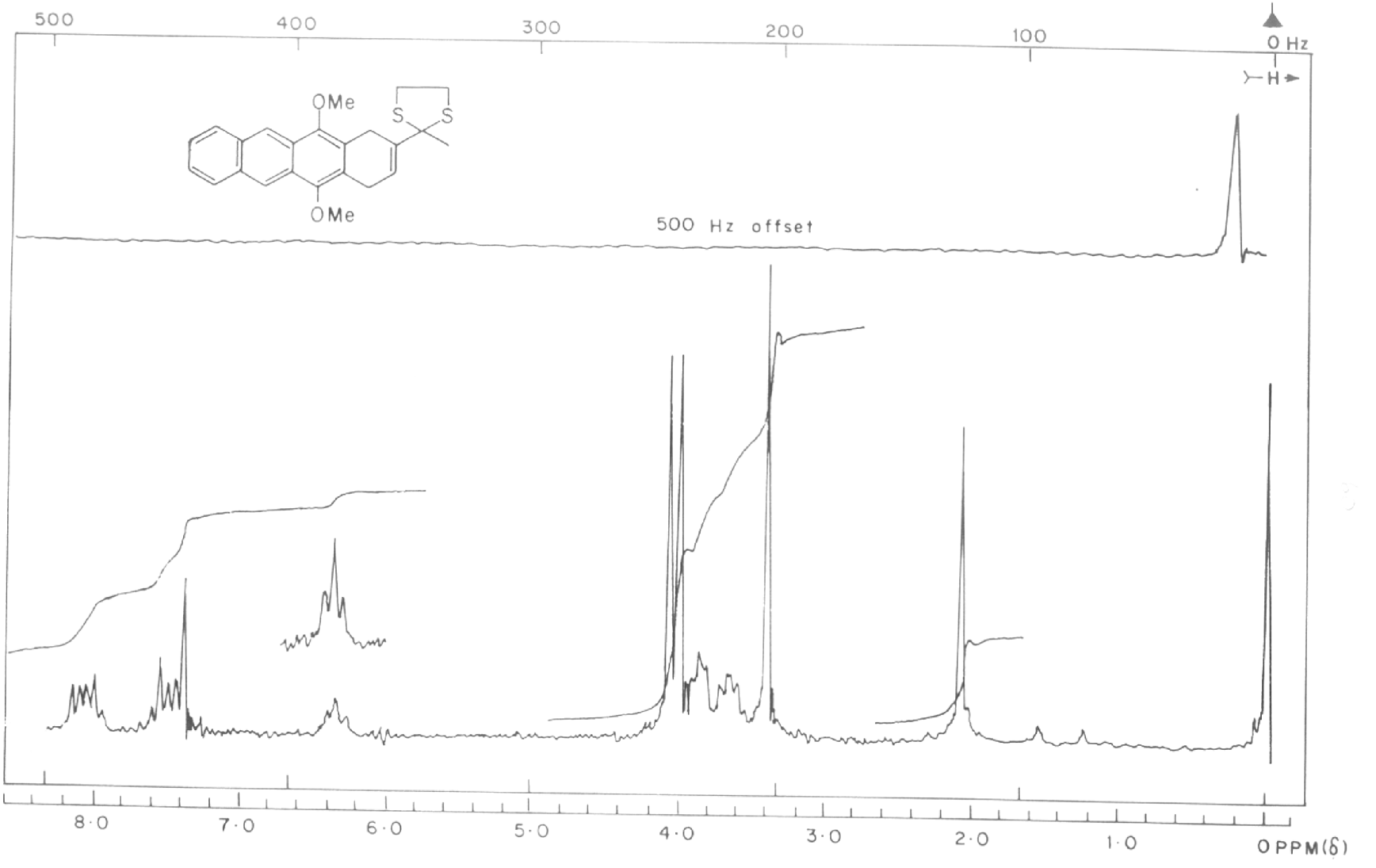



FIG. 5. $^{1}H$-NMR SPECTRUM OF COMPOUND (40) IN $CDCl_3$

was obtained (TLC), containing one major and several minor products. The major product was isolated after column chromatography in 20% yield whose $^1$H-NMR spectrum suggested the structure (45) (in which the A-ring had aromatized). Later dethioketalization with N-chlorosuccinimide, silver-nitrate and aqueous acetonitrile was attempted but a similar reaction viz. aromatization of A-ring was observed. This could be attributed to the extended conjugation of the tetra-cyclic system.

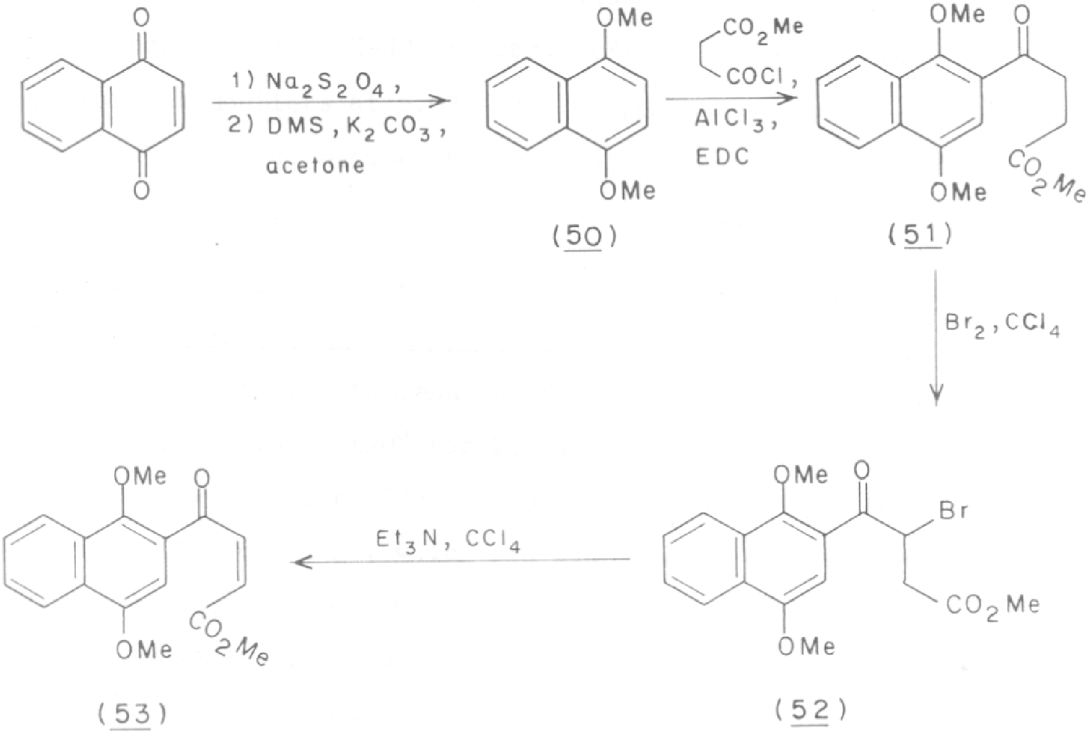
Naphthalene precursors as a dienophile:

It was anticipated that in order to avoid the process of aromatization, A-ring should be built first on a dieno-phile such as methyl 4-(1,4-dimethoxy-2-naphthyl)-4-keto-butyrate-2-ene (53) (Scheme-8) and ultimately bridged to B-ring of the anthracyclinone moiety. With this view in mind a synthetic route was planned (as shown in Scheme-9).

α,β-Unsaturated ester (53) was prepared as follows:

Friedel-Craft reaction[25] of 1,4-dimethoxynaphthalene (49) was carried out with β-carbomethoxypropionyl chloride in presence of $AlCl_3$ and ethylene dichloride at room temp. to afford methyl 4-(1,4-dimethoxy-2-naphthyl)-4-ketobutyrate (51) in 85% yield (while acylation of 1,4-dimethoxynapthalene with succinic anhydride afforded only 50% yield). Bromination

Scheme – 9


1) $Na_2S_2O_4$,
2) DMS, $K_2CO_3$,
acetone
OMe
OMe
(50)
$CO_2Me$
COCl,
$AlCl_3$,
EDC
OMe
O
OMe
$CO_2Me$
(51)
$Br_2$, $CCl_4$
OMe
O
Br
$CO_2Me$
OMe
(52)
$Et_3N$, $CCl_4$
OMe
O
OMe
$CO_2Me$
(53)

63

of 51 occurred exclusively at the carbon atom α- to carbonyl group giving rise to the bromide(52) which was then subjected, without delay, to dehydrobromination using triethylamine. The resulting α,β-unsaturated ketoester (53) showed in its 'H-NMR spectrum (Fig.6 ) two olefinic protons as doublets at 6.07 and 8.10 ppm, the coupling constant of 16 Hz between the olefinic protons was indicative of the fact that they were trans to each other.

Diels-Alder reaction between methyl 4(1,4-dimethoxy-2-naphthyl)-4-ketobutyrate-2-ene (53) and 2-methoxybutadiene:

2-Methoxybutadiene and 53 were heated in benzene in a sealed tube at 120° for 12 hours after which time the reaction was complete (Scheme-10). The adduct (54) was isolated in 96% yield, which was found to be a regio-isomeric mixture in 2:1 ratio(54a and 54b) (TLC and 'H-NMR). No attempts were made to separate these isomers, because subsequent hydrolysis and cyclization, would lead to a single symmetrical product.

The major isomer was considered to be 54a and the minor 54b, based on the assumption that carbonyl is more electron withdrawing compared to a carboxyl group.

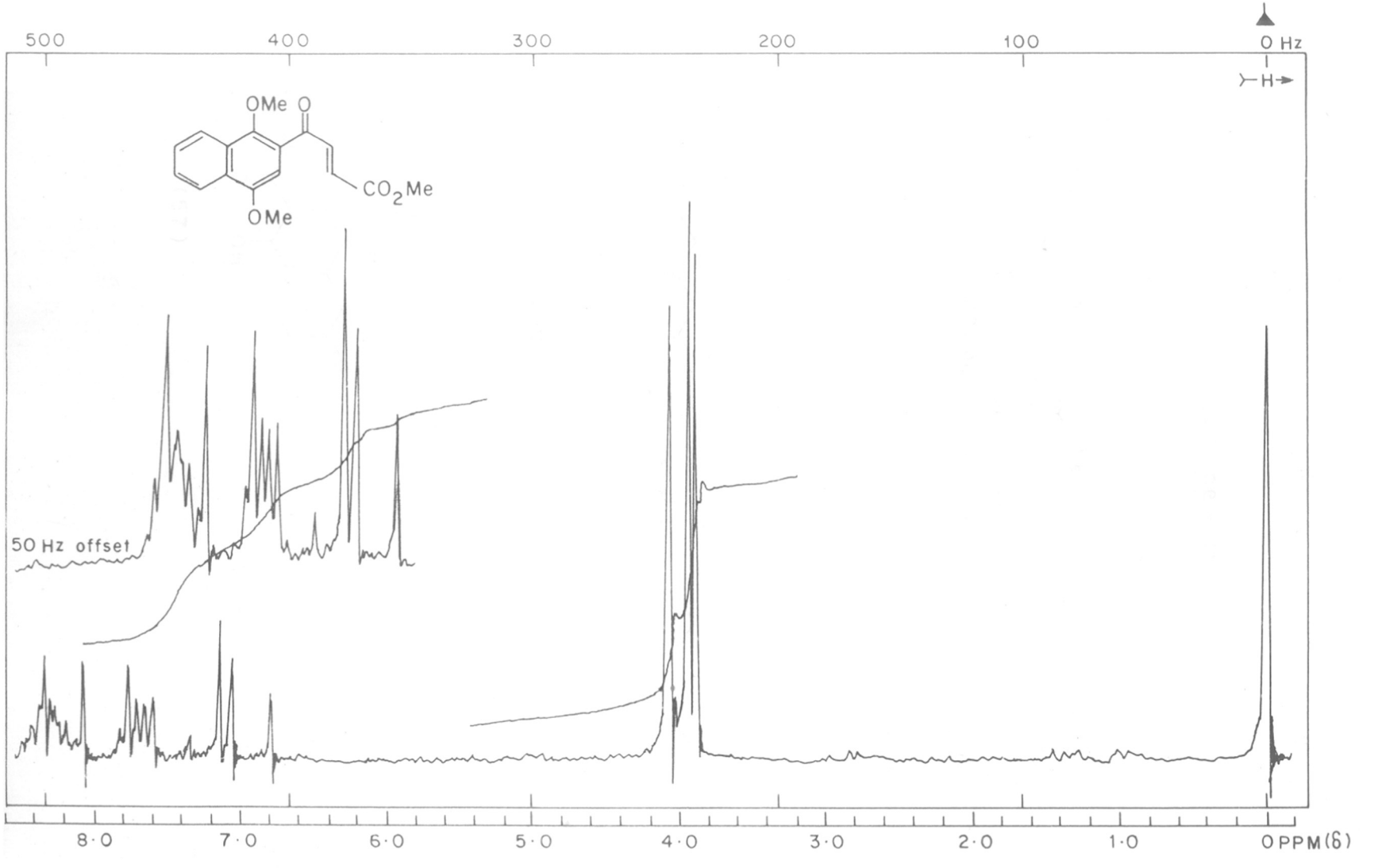
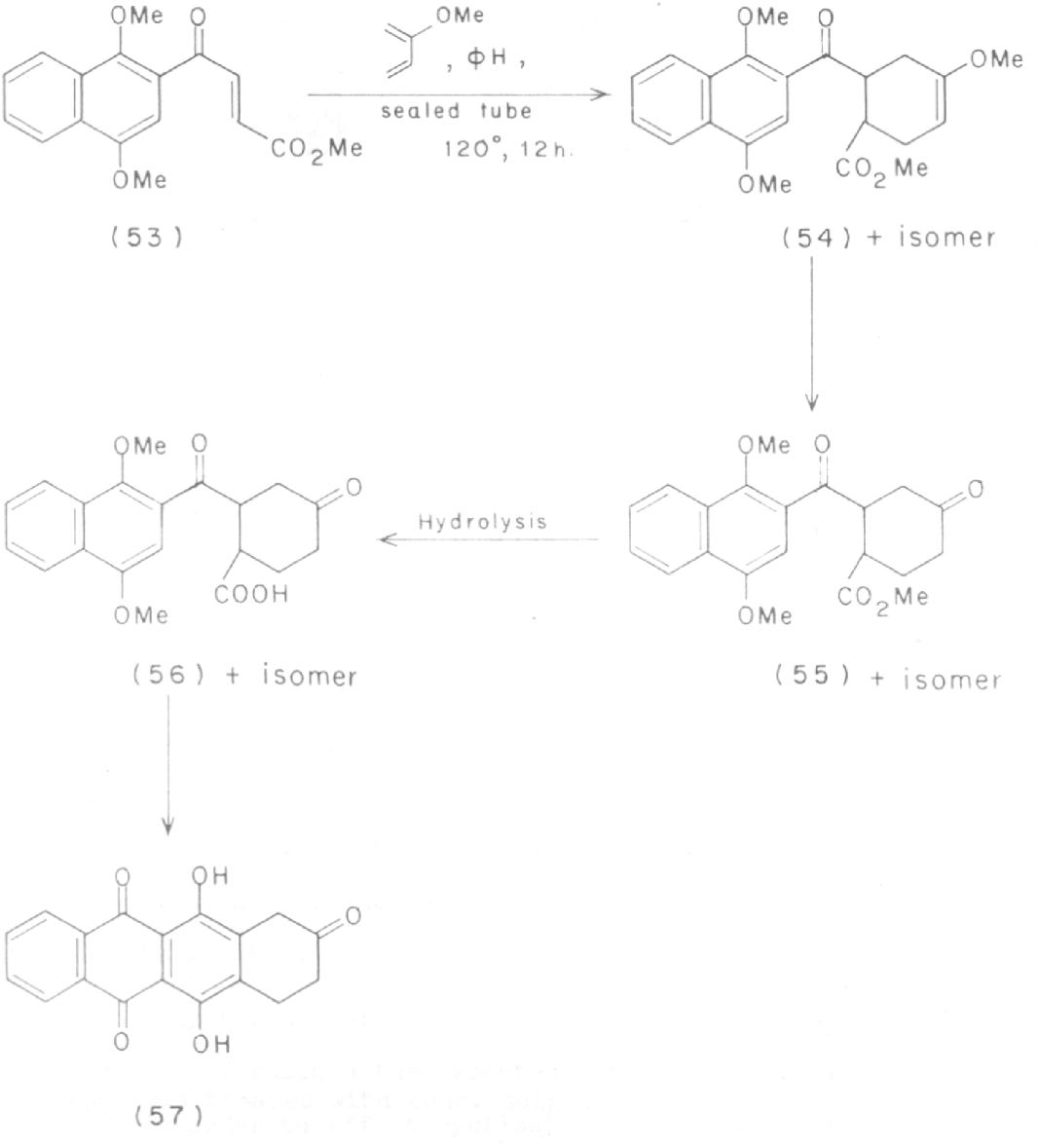
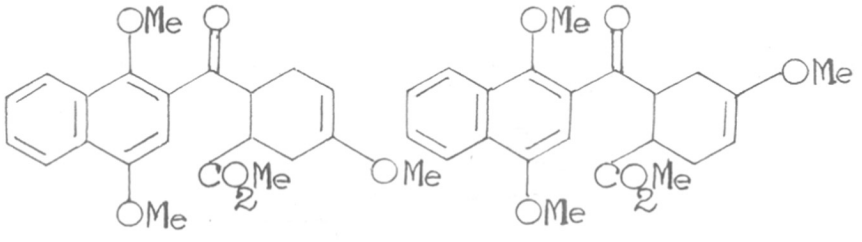



FIG. 1 $^1$H-NMR SPECTRUM OF COMPOUND (53) IN $CDCl_3$

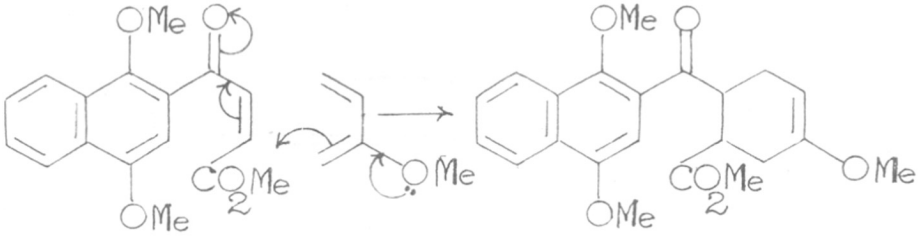
## Scheme – 10


OMe
O
CO2Me
OMe
(53)
OMe
, ΦH ,
sealed tube
120°, 12h.
OMe
O
OMe
OMe
CO2Me
(54) + isomer
OMe
O
O
OMe
CO2Me
(55) + isomer
Hydrolysis
OMe
O
O
COOH
OMe
(56) + isomer
O
OH
O
O
OH
(57)



(54a) (54b)

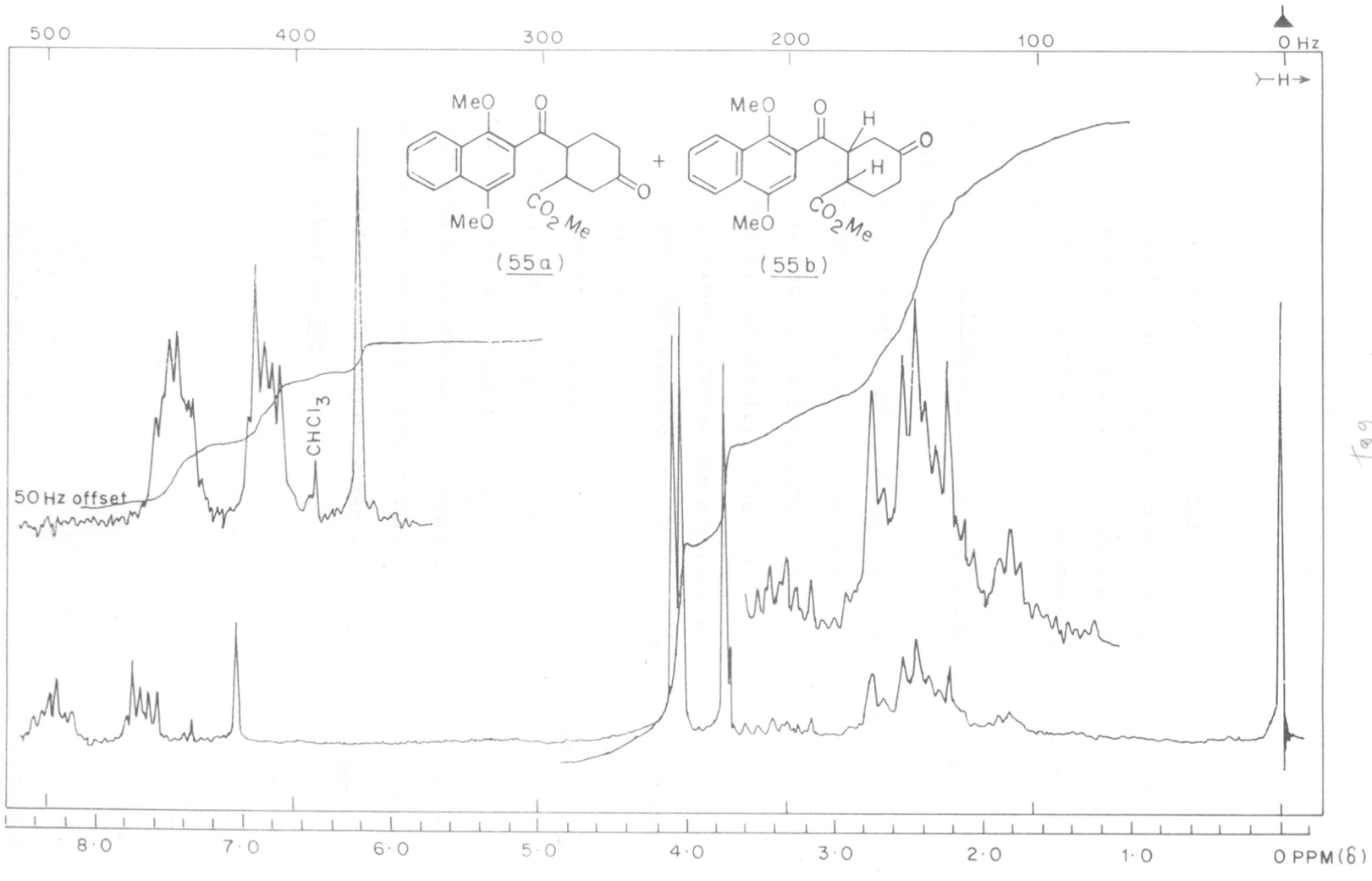
Mechanism



(54a)

Conversion of 54 to 55 was achieved with a trace of HCl in acetone. Although the $^1$H-NMR spectrum (Fig.7) of 55 was not amenable for first order analysis because of overlapping of methylenes and methine protons, the signals due to two methoxyls, one carbomethoxy and three aromatic protons were clearly located.

Hydrolysis of 55 with aqueous methanolic-sodium hydroxide furnished the expected ketoacid (56). The keto acid (56) was treated with conc. sulphuric-acid in order to effect cyclization but unfortunately a




FIG·7· $^{1}H$-NMR SPECTRUM OF COMPOUND (55) IN $CDCl_3$

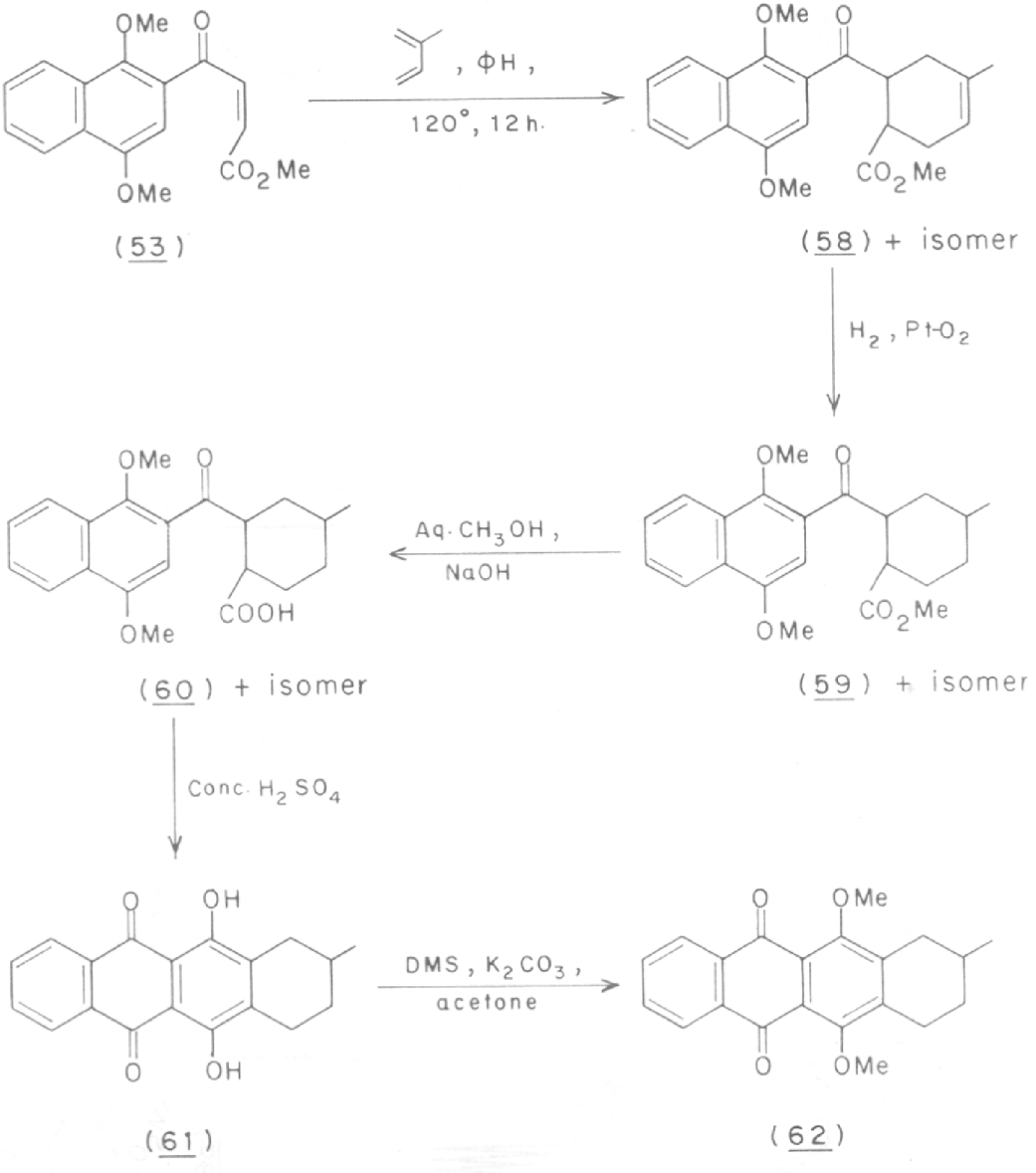
68

complex mixture was obtained (TLC). Cyclisation was then attempted with hydrofluoric acid when only the starting material was recovered. With polyphosphoric acid also, no cyclization was observed as the starting material was obtained.

Diels-Alder reaction of α,β-unsaturated ester (53) with isoprene:

When a mixture of α,β-unsaturated keto-ester (53) and isoprene in benzene in a sealed tube was heated at 120° for 12 hours, the D.A. adduct (58) was formed almost quantitatively (Scheme-11). The $^1$H-NMR spectrum (Fig.8) of the adduct (58) clearly showed the presence of two isomers in 2:1 ratio. For example the methyl group was expected to resonate as a singlet but it appeared as a broad doublet. The shoulder ($\delta$ 1.63) to the singlet ($\delta$ 1.70) could be attributed to the methyl group of the other isomer. Similarly broad multiplet for $A_2B_2$ pattern for aromatic protons at $\delta$ 7.5 and 8.1 also confirmed the presence of two isomers. The remaining signals were not amenable to first order analysis. The major isomer was considered as 58a and the minor as 58b.

## Scheme – 11


OMe
O
CO2Me
OMe
(53)
, ΦH ,
120°, 12 h.
OMe
O
OMe
CO2Me
(58) + isomer
H2 , Pt-O2
OMe
O
OMe
CO2Me
(59) + isomer
Aq. CH3OH ,
NaOH
OMe
O
OMe
COOH
(60) + isomer
Conc. H2SO4
O
OH
O
OH
(61)
DMS , K2CO3 ,
acetone
O
OMe
O
OMe
(62)

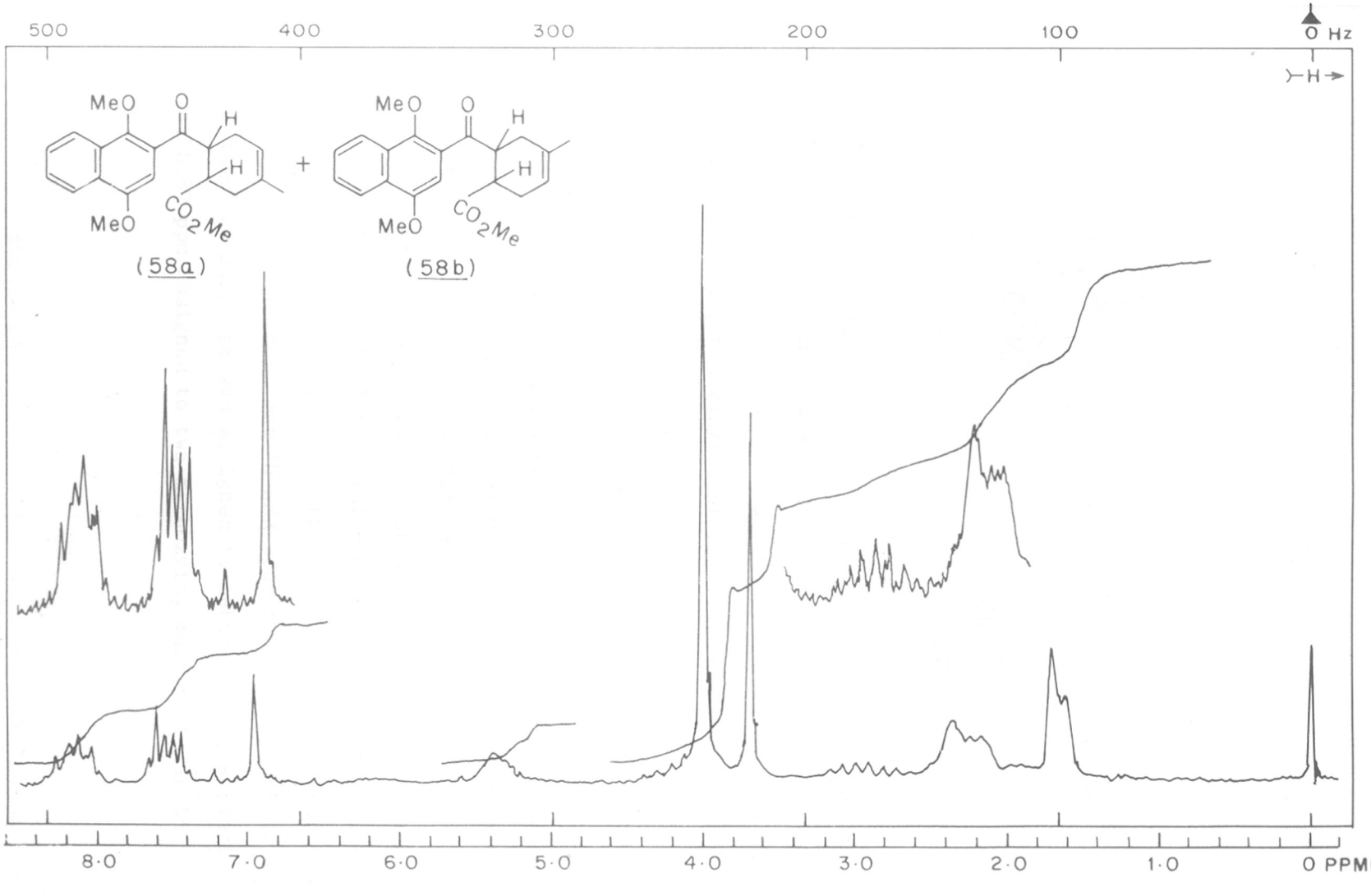
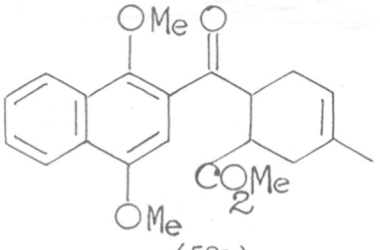
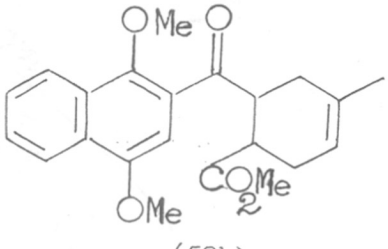



FIG. 8. $^{1}$H-NMR SPECTRUM OF COMPOUND (58a) and (58b) IN $CDCl_3$

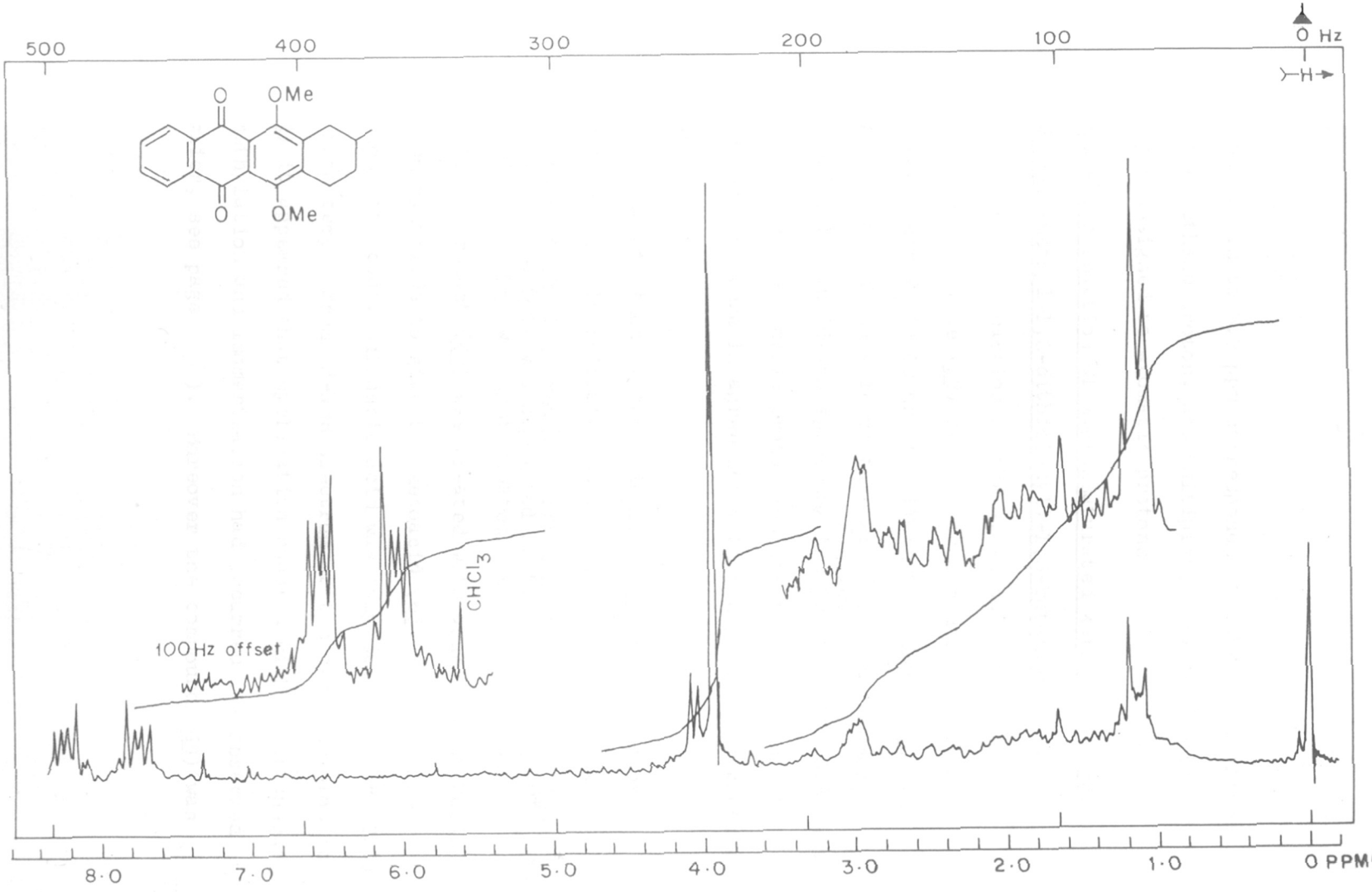


(58a)



(58b)

Their separation was not attempted, as hydrogenation followed by hydrolysis of the adduct and its cyclization would afford a single symmetrical product. Hydrogenation of 58 in the presence of $PtO_2$ as catalyst gave 59. In the $^1$H-NMR spectrum, the vinylic proton triplet disappeared indicating that the reduction had occurred. Hydrolysis of 59 to 60 with aqueous methanolic sodium hydroxide occurred to afford 60 in 67% yield. The ketoacid 60 in concentrated sulphuric acid afforded a product (61) in 87% yield, whose $^1$H-NMR spectrum indicated that cyclization with concommitant demethylation and isomerization had taken place in one step. Further support for the structure of 61 was gleaned by conventional methylation (dimethylsulphate, potassium-carbonate and acetone) which afforded the dimethylether (62) and confirmed by mass and $^1$H-NMR spectrum (Fig.9). For example, a doublet at 1.13 ppm was assigned to methyl group, a singlet at 3.87 ppm assigned to two methoxyls, multiplets in the




FIG·9. $^1$H-NMR SPECTRUM OF COMPOUND (62) IN $CDCl_3$

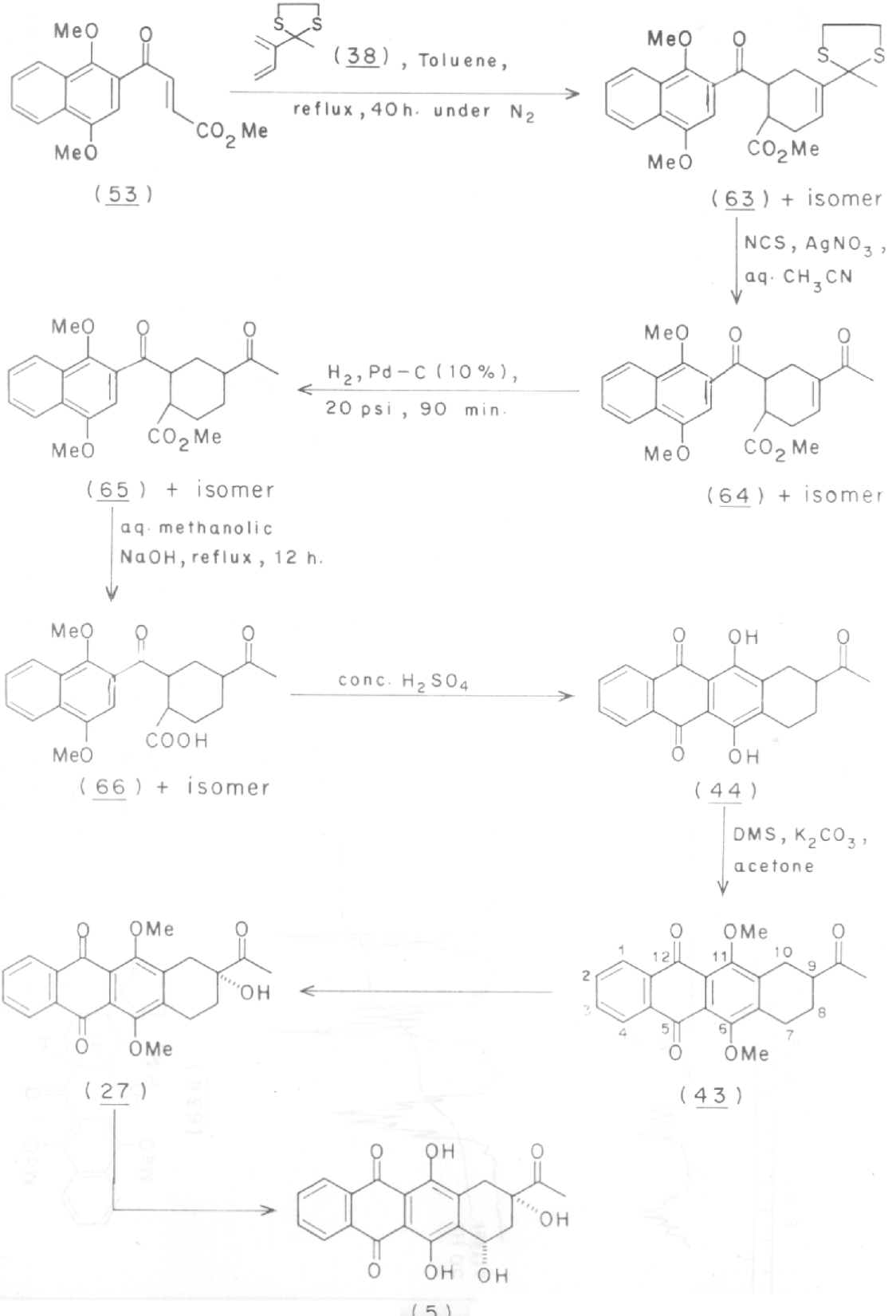
region of 1.3 to 3.3 ppm corresponded to three methylenes and one methine proton, and multiplets between 7.5 to 8.5 ppm assigned to aromatic protons.

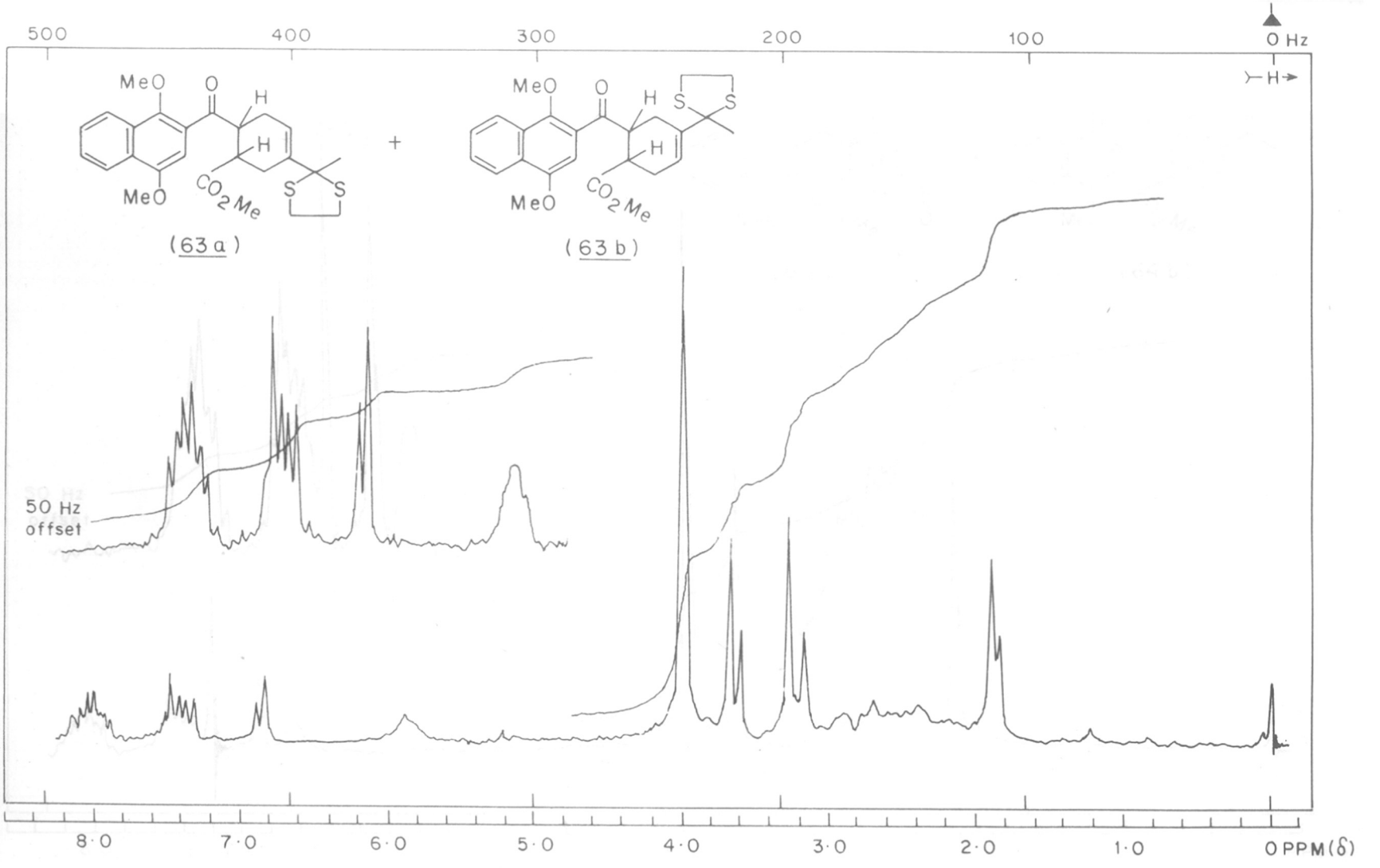
Diels-Alder reaction of α,β-unsaturated keto-ester (53) with 2-(2-methyl-1,3-dithiolanyl)-1,3-butadiene (38):

The D.A. reaction of the α,β-unsaturated ester (53) with the diene (38) readily occurred in refluxing toluene under $N_2$ in 60 hr, to afford the adduct (63) in 79% yield as an isomeric mixture 2:1 (TLC and $^1$H-NMR) (Scheme-12). In $^1$H-NMR spectrum (Fig.10), the triplet at δ 5.83 was assigned to the vinylic proton and the resonances due to other protons were in agreement with the proposed stfucture (63).

Deprotection of the thioketal (63) with N-chloro-succinimide, silvernitrate and aqueous acetonitrile at room temp. took place readily affording the compound (64) in 65% yield. (Its structure (64) was supported by $^1$H-NMR spectrum (Fig.11). 64 was hydrogenated over 10% Pd-C and the resulting product (65) was treated with aqueous methanolic sodium hydroxide to give the ketoacid (66). Its cyclization with conc. sulphuric acid was complete in 36 hr (TLC) at room temp. From $^1$H-NMR spectrum of the cyclized product (44) it appeared that cyclization coupled with simultaneous demethylation and isomerisation had occurred (as observed earlier, see page ). Moreover the compound (44) was

## Scheme – 12


MeO
O
CO2Me
MeO
(53)
(38), Toluene,
reflux, 40h. under N2
MeO
O
S
S
CO2Me
MeO
(63) + isomer
NCS, AgNO3,
aq. CH3CN
MeO
O
O
CO2Me
MeO
(64) + isomer
H2, Pd–C (10%),
20 psi, 90 min.
MeO
O
O
CO2Me
MeO
(65) + isomer
aq. methanolic
NaOH, reflux, 12 h.
MeO
O
O
COOH
MeO
(66) + isomer
conc. H2SO4
O
OH
O
O
OH
(44)
DMS, K2CO3,
acetone
O
OMe
O
1
12
11
10
9
2
3
4
5
6
7
8
O
OMe
(43)
O
OMe
O
OH
O
OMe
(27)
O
OH
O
OH
O
OH
OH
(5)




FIG·10. $^{1}$H-NMR SPECTRUM OF COMPOUND (63a) and (63b) IN $CDCl_3$

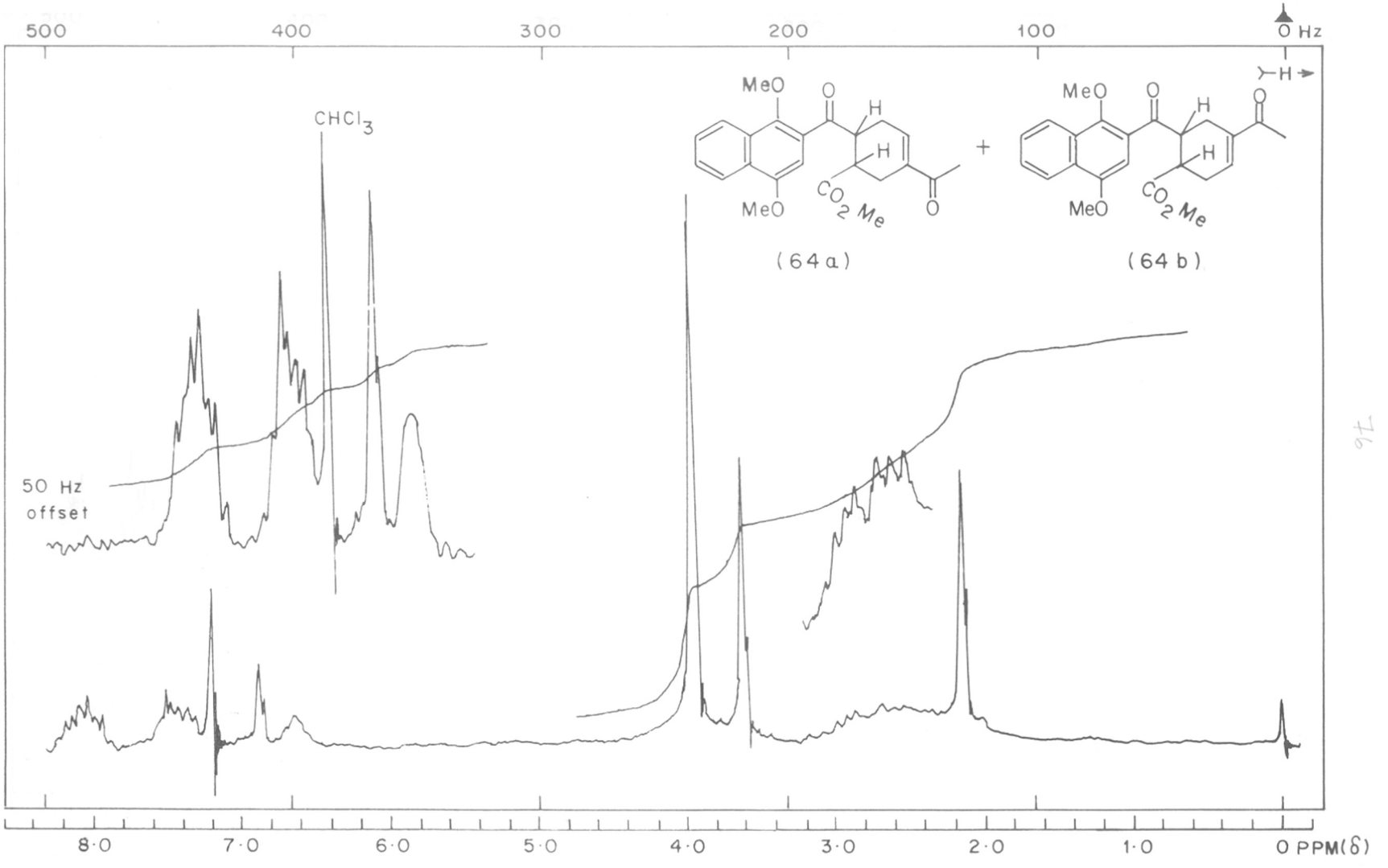



FIG. 11. $^1$H-NMR SPECTRUM OF COMPOUNDS (64 a) and (64 b) IN $CDCl_3$

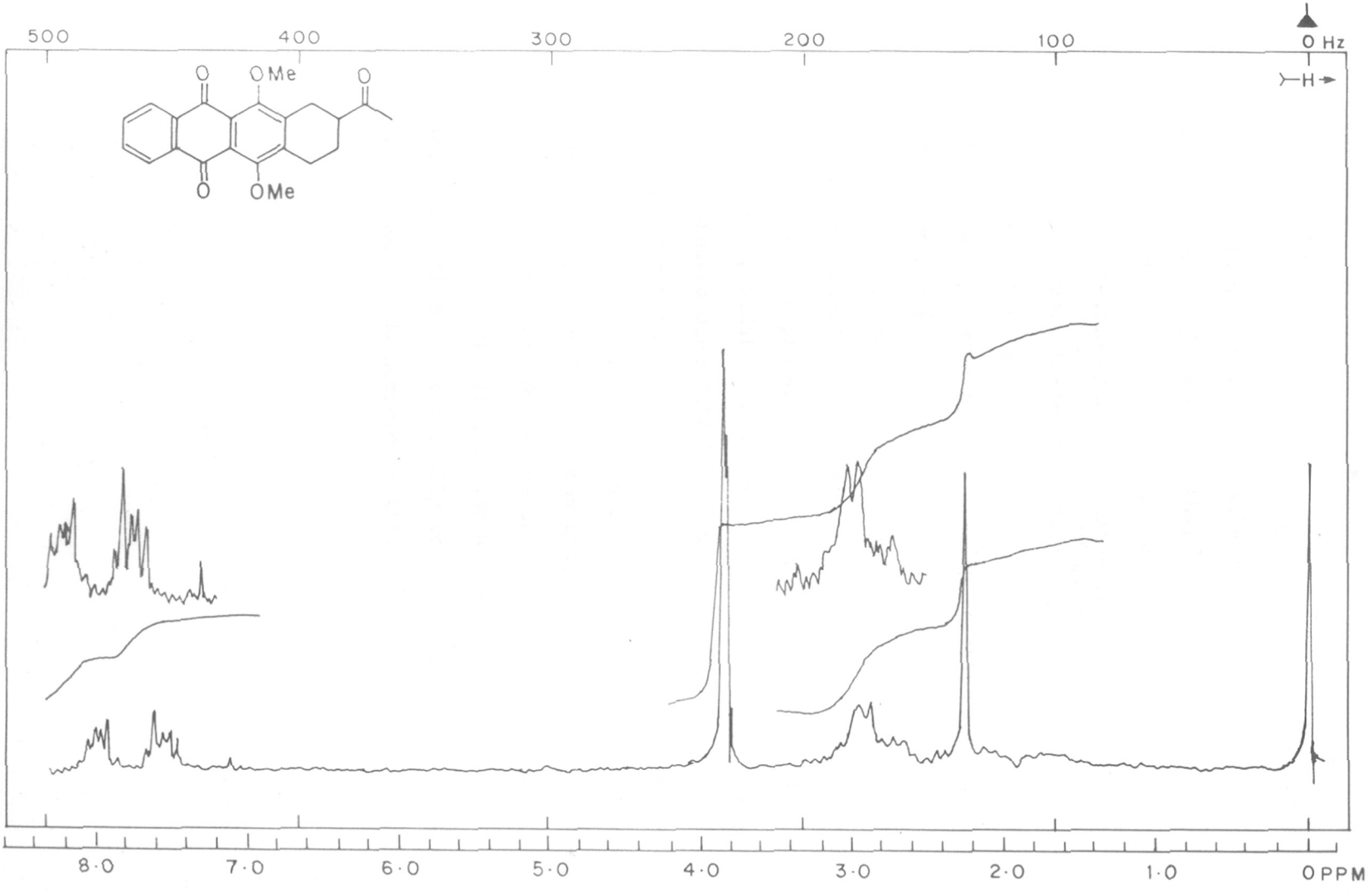



FIG. 12. $^1$H-NMR SPECTRUM OF COMPOUND (43) IN $CDCl_3$

found to be identical in all respects with the reported[26] one. Treatment of 44 with dimethylsulphate in presence of potassium carbonate in boiling acetone afforded 4-demethoxy-7,9-dideoxydaunomycinone-5,12-dimethyl ether (43) in 83% yield. $^1$H-NMR spectrum (Fig.12) of 43 was found to be identical with the reported[27] spectrum. Hydroxylation of C-9 in 43 was achieved *via* a four-step reaction sequence which was commonly employed for the introduction of C-17 hydroxyl group in steroids[28] and the same was adopted by Sih and colleagues[29] for the synthesis of 7-deoxydaunomycinone. This involved the preparation of enol acetate (PTS acid, $Ac_2O$), followed by epoxidation and the resultant epoxy acetate was then treated successively by base and acid to ensure complete hydrolysis and rearrangement to give (±)7-deoxy-4-demethoxydaunomycinone dimethyl ether (27), which after chromatographic purification resulted in 55% overall yield from 43. As the method for the demethylation of 27 and introduction of hydroxyl function at C-7 have already been described[29], this route formally constitutes a total synthesis of (±)4-demethoxydaunomycinone (5).

GENERAL REMARKS AND EXPERIMENTAL MEMORANDA

Melting points were determined in open capillaries and are uncorrected.

Unless otherwise stated:

a) Infrared spectra were recorded in nujol on a Perkin-Elmer model 683 spectrometer with sodium chloride optics. The maxima are recorded in $cm^{-1}$.

b) Proton magnetic resonance spectra were recorded in $CDCl_3$ containing TMS as internal standard on Varian T-60 or Varian FT-80A or Bruker WH-90 Spectrometer. Chemical shifts ( ) expressed in ppm downfield from TMS.

c) Column chromatography was performed using silica gel (100-200 mesh, Acme make).

d) Progress of the reactions was checked by TLC on 0.2 mm layers of silica gel, using iodine chamber for visualisation.

e) Solvents were removed rotary evaporator at temperature between 40-50°.

Mass spectra were recorded on a CEC 21-110B double focussing mass spectrometer operating at 70 eV using direct inlet system.

# EXPERIMENTAL

## 1-Acetoxybutadiene[30]

Freshly distilled crotonaldehyde (30 g) was added dropwise to a refluxing mixture of acetic anhydride (55 g) and fused potassium acetate (30 g) under nitrogen. After the addition was complete, the reaction mixture was refluxed for additional one hour, cooled, and poured over crushed ice, extracted with ether. The ether layer was washed with 10% sodium carbonate, just to neutralize acetic acid, then washed with 40% sodium bisulphite solution (150 ml) and finally with 10% sodium carbonate solution (40 ml). After each extraction the aqueous layer was extracted with ether. The combined ether solution was dried on anhydrous sodium sulphate. The solvent was distilled off, and the product distilled under reduced pressure to yield 31.0 g (65%) of 1-acetoxybutadiene, b.p. 54-56°/32 mm, lit.[27] b.p. (53-55°/32 mm).

## 2-Methoxybutadiene[17]

p-Toluenesulphonic acid (20 mg) was added to the mixture of freshly distilled methyl vinyl ketone (35 g), methyl orthoformate (88 g) and anhydrous methanol (48 ml). The reaction mixture became exothermic and developed dark green colour. The stoppered reaction flask was allowed to

stand at room temperature for 12 days. Then anhydrous sodium carbonate (1 g) was added and stirred magnetically for 3 days, filtered off the solids. The excess methyl orthoformate and methanol were removed by simple distillation, and filtered once again to remove the solids, and then distilled under reduced pressure to yield 65 g (88%) of 1,3,3-trimethoxybutane, b.p. 62-65°/30 mm.

Potassium bisulphate (10 mg) was placed into a 3-necked flask with a 20 cm distillation column and condenser system, protected with calcium chloride guard tube. Trimethoxybutane (5 ml) was added initially and heated the pot flask at 150°, with preheated oil bath. The decomposed product (distilled at 62°) was collected by cooling the receiver to -10°. The remaining methoxybutane was added dropwise at such a rate as to keep approximately 5 ml of the material in the pot flask.

The distillate was washed with ice cold water (25 x 4 ml) and then filtered over anhydrous sodium sulphate (2 g), added a pinch of hydroquinone and fractionated through 20 cm column at atmospheric pressure. The yield of 2-methoxy-1,3-butadiene at 72-73°/710 mm was 21.6 g (53%).

1,4-Anthraquinone (11)

1,4-Anthraquinone was prepared from quinizarin by following the reported procedure[16].

82

1-Acetoxy-1,4,13,14-tetrahydronaphthacene-5,12-dione (13)

The mixture of 1,4-anthraquinone (11, 0.20 g, 0.001 mole), 1-acetoxy-1,3-butadiene (12 0.20 g, 0.002 mole) and dry benzene (5 ml) were refluxed under $N_2$ for 6 hours. The solvent was removed under reduced pressure and the residue crystallised from the mixture of acetone-pet.ether as pale yellow needles to give 13 (0.280 g, 87.5%), m.p. 176°. $^1$H-NMR ($CDCl_3$): $\delta$ 1.16 (s, 3H, OAc), 2.0 - 2.4 (m, 2H, $CH_2$), 3.21 (bd, 1H, 4H), 3.53 (m, 2H, 13-H, 14-H), 5.4 (t, 1H, 2-H), 6.04 (t, 1H, vinylic), 7.9 ($A_2B_2$ pattern, 4H, 7,8,9,10-H), 8.60 and 8.62 (s x2, 2H, 6-H, 11-H). $M^+$ 320.

Analysis: Calculated for $C_{20}H_{16}O_4$: C, 75.0; H, 5.0; Found: C, 74.6; H, 5.2%.

2-Methyl-1,4,13,14-tetrahydronaphthacene-5,12-dione (15)

The mixture of 1,4-anthraquinone (11, 2.0 g, 0.01 mole), isoprene (14, 2.0 g, 0.03 mole), and dry benzene (30 ml) was sealed in a thick corning tube and heated at 98-100° for 6 hours. The product was transferred into a flask, treated with a pinch of norite, boiled and filtered. Solvent removal gave a syrup which was crystallized from benzene-pet.ether (2:1) to afford 15 (2.5 g, 98%) as pale yellow needles, m.p. 175°; $^1$H-NMR ($CDCl_3$); $\delta$ 1.73 (s, 3H, $CH_3$), 2.31 (m, 4H, $CH_2$ x2), 3.3 (m, 2H, 13-H, 14-H), 5.36 (bt, 1H, vinylic), 7.76 ($A_2B_2$ pattern, 4H, 7,8,9,10-H), 8.40 (s, 2H,

83

6-H, 11-H); $M^+$ 276.

Analysis: Calculated for $C_{19}H_{16}O_2$: C, 82.6; H, 5.8. Found: C, 82.4; H, 5.9%.

Preparation of 5,12-diacetoxy-1,4-dihydro-2-methyl-naphthacene (16)

Compound (15, 0.50 g), potassiumacetate (0.50 g) and acetic anhydride (5 ml) were mixed together and heated on steam bath for 5 min. and then stirred at room temperature for 3 hr poured over crushed ice and filtered off the pale yellow residue. The residue was crystallised from benzene as pale yellow needles (0.60 g, 96%), m.p. 230° ($C_{23}H_{20}O_4$, $M^+$ 360).

2-Methoxy-1,4,13,14-tetrahydronaphthacene-5,12-dione (18)

The solution of 1,4-anthraquinone (11, 2.0 g, 0.01 mole) in dry benzene (40 ml) was treated with 2-methoxy-1,3-butadiene (17, 2.50 g, 0.03 moles) for 24 hours at room temperature. After usual work up, the product 18 was isolated and crystallized from benzene-pet. ether (2:1) (2.80 g, 96%); m.p. 192-193°; $^1$H-NMR ($CDCl_3$): $\delta$ 2.51 (m, 4H, $CH_2$ x2), 3.32 (m, 2H, 13-H, 14-H), 3.53 (s, 3H, OMe), 4.63 (t, 1H, vinylic), 7.91 ($A_2B_2$ pattern, 4H, 7,8,9,10-H), 8.63 (s, 2H, 6-H, 11-H); $M^+$ 292.

Analysis: Calculated for $C_{19}H_{16}O_3$: C, 78.0; H, 5.48; Found: C, 77.77; H, 5.93%.

84

Preparation of trione (19)

To the acetone (10 ml) solution of the dione (18, 0.30 g), conc. hydrochloric acid (3 drops) was added, and stirred for 5 minutes. Pet. ether (10 ml) was added to the acetone solution and filtered off the colourless crystalline product, recrystallized from methanol as colourless needles (0.27 g, 92%), m.p. 199-200° and characterised as trione (20). $M^+$ 278.

Analysis: Calculated for $C_{18}H_{14}O_3$: C, 77.7; H, 5.04. Found: C, 78.0; H, 5.3%.

5,12-Diacetoxy-2-methoxy-1,4-dihydronapthacene (20)

The mixture of the dione (18, 0.30 g, 0.003 moles), sodium acetate (1.50 g, 0.018 moles), acetic anhydride (10 ml) was heated on water bath for 2.5 hours and poured over crushed ice. The yellow precipitate was filtered, and crystallized from methanol to yield the diacetate (20, 1.10 g, 95%) as light yellow needles, m.p. 182°; $^1$H-NMR ($CDCl_3$): $\delta$ 2.5 (s, 6H, OAc), 3.5 (m, 4H, $CH_2$ x2), 3.6 (s, 3H, OMe), 4.8 (bt, 1H, 3-H), 7.77 ($A_2B_2$ pattern, 4H, 7,8,9 and 10-H), 8.5 (s, 2H, 6-H and 11-H). $M^+$ 376.

Analysis: Calculated for $C_{23}H_{20}O_5$: C, 73.4; H, 5.32. Found: C, 73.80; H, 5.20%.

Diacetoxy ketone (21) from 20

A mixture of compound (20, 0.60 g), acetic acid (8 ml) and

three drops of concentrated hydrochloric acid was stirred for 5 minutes at room temperature and then poured over crushed ice, the precipitate was filtered, washed with water, dried and recrystallised from methanol to yield the ketone (21) as pale yellow needles (0.52 g, 90%), m.p. 220° (decomp.); $M^+$ 362.

Analysis: Calculated for $C_{22}H_{18}O_5$: C, 72.9; H, 4.97. Found: C, 72.5; H, 5.20%.

Ethynyl magnesiumbromide:

This compound was prepared following the procedure of Skattebol et al.[31].

Preparation of quinone (22):

A solution of the ketone (21, 0.36 g, 0.001 mole) in dry tetrahydrofuran (10 ml) was added dropwise to a stirred solution of ethynyl magnesiumbromide (1.30 g, 0.01 moles) at -5°. The reaction mixture was allowed to come to room temperature. It was then poured slowly to a saturated ammonium chloride solution (20 ml) and extracted with ether (3 x 15 ml). The combined etheral layer was washed with water, dried ($Na_2SO_4$) and concentrated to yield a gummy mixture of three compounds (TLC). The mixture was acetylated with acetic anhydride-pyridine (1:1, 4 ml) on waterbath for 3 hours. After usual processing, the resulting residue was chromatographed on a column of silica gel using

benzene as an eluent. The polarity of the eluent was gradually increased. The major fraction (eluted with benzene-acetone 95:5) afforded the compound (22, 0.063 g, 20%) crystallised from ethanol, m.p. 202°. $^1$H-NMR ($CDCl_3$): $\delta$ 2.05 (s, 3H, 2-OAc), 2.4 (m, 2H, H-3), 2.6 (s, 1H, C=CH), 2.9 (m, 2H, H-4), 3.3 (s, 2H, 1-H), 7.8 ($A_2B_2$ pattern, 4H, 7,8,9 and 10-H), 8.53 (s, 2H, 6-H, 11-H). $M^+$ 344.

Analysis: Calculated for $C_{22}H_{16}O_4$: C, 76.74; H, 4.65. Found: C, 76.43; H, 4.80%.

The other fractions were not analysed.

Preparation of trimethyl ether (23)

The mixture of the dione (18, 0.30 g), dry acetone (30 ml), anhydrous potassium carbonate (2.0 g) and dimethyl-sulphate (0.30 g) were refluxed for 6 hours. Usual work-up gave a product (24, 0.30 g), which was subjected to demethylation in the following step.

Preparation of dimethyl ether (24) from 23:

To a solution of trimethylether (23, 0.30 g) in acetone (10 ml) was added a drop of concentrated hydrochloric acid. After 5 minutes pet. ether (5 ml) was added to the solution and the precipitate filtered, and crystallized from methanol to afford (24, 0.27 g, 95%), m.p. 142-3°. $^1$H-NMR ($CDCl_3$): $\delta$ 2.6 (t, 2H, $CH_2$), 3.3 (t, 2H, $CH_2$), 3.83 (s, 2H, $CH_2$), 3.93 (s, 3H, OMe), 3.96 (s, 3H, -OMe), 7.9 ($A_2B_2$ pattern

4H, 7,8,9 and 10-H), 8.53 (s, 2H, 6-H, 11-H). $M^+$ 306.

Analysis: Calculated for $C_{20}H_{18}O_3$: C, 78.43; H, 5.91; Found: C, 78.2; H, 6.0%.

Ethyl 2-(2-methyl-1,3-dithiolanyl)-acetate (34):

To a stirring mixture of ethyl acetoacetate (60 g, 0.461 mole) in chloroform (500 ml) and ethanedithiol (43.2 ml, 0.513 mole) was added dropwise $BF_3$-etherate (66 ml; 0.536 mole). The reaction mixture was stirred for 12 hr. at room temp. and then washed successively with water, 5% aq. KOH solution, brine, dried over anhydrous $Na_2SO_4$ and concentrated. The residue was distilled under reduced pressure (135°/15-18 mm Hg) to give title thioketal (85.5 g, 90%) as colourless liquid. $^1$H-NMR ($CCl_4$): $\delta$ 1.26 (t, 3H, $CO_2Et$), 1.86 (s, 3H, Me), 3.26 (s, 4H, $-S(-CH_2)_2-S$), 4.06 (q, 2H, $CO_2Et$). $M^+$ 206.

Analysis: Calculated for $C_8H_{14}O_2S_2$: C, 46.6; H, 6.79. Found: C, 46.4; H, 6.80%.

2-(2-methyl-1,3-dithiolanyl)-ethanol (35)

To a stirring suspension of lithium aluminium hydride (2 g, 52.6 m.mole) in dry THF (20 ml) at room temp. was added a solution of the thioketal ester (10 g, 48.5 m.mole) in dry THF (70 ml) over 3 hr. The reaction mixture was further stirred for 5 hr, excess of LAH decomposed by successive addition of water (2 ml), 15% NaOH solution (2 ml) and water (6 ml). The reaction mixture was filtered and

washed with ether. The filterate was extracted with ether, washed with water and dried over $Na_2SO_4$. The residue on removal of the solvent was distilled at 140°/15-18 mm of Hg gave pure thioketal alcohol (35, 7 g, 88%). $^1$H-NMR ($CCl_4$): δ 1.76 (s, 3H, $-CH_3$), 2.2 (t, 2H, $CH_2$), 2.86 (s, 1H, -OH, exchanges with $D_2O$), 3.3 (s, 4H, $-S-CH_2-CH_2-S$), 3.83 (t, 2H, $CH_2$). $M^+$ 164.

Analysis: Calculated for $C_6H_{12}OS_2$: C, 43.9; H, 7.31. Found: C, 44.0; H, 7.33%.

2-(2-Methyl-1,3-dithiolanyl)-acetaldehyde (36)

To a stirring suspension of pyridinium dichromate (30 g, 79.7 m.mole) in dichloromethane (50 ml), the solution of the above alcohol (35, 8 g, 48.7 m.mole) in dichloromethane (25 ml) was added. After 40 hr, dry ether (125 ml) was introduced and the solid was filtered and the filterate concentrated, passed through a short silica gel column (benzene-pet.ether, 1:1) to afford pure (36, 4.25 g, 54%), $^1$H-NMR ($CCl_4$): δ 1.83 (s, 3H, $CH_3$), 2.9 (d, 2H, $-CH_2$), 3.4 (s, 4H, $-SCH_2CH_2-S$), 9.8 (t, 1H, -CHO), $M^+$ 162.

Analysis: Calculated for $C_6H_{10}OS_2$: C, 44.44; H, 6.17. Found: C, 44.5; H, 6.2%.

2-(2-Methyl-1,3-dithiolanyl)-1,3-butadiene (38):

To an ice cold solution of the aldehyde (36, 1 g, 6.17 m.mole) in methylene dichloride (8 ml), N,N,N',N'-

tetramethyldiaminomethane (1.5 g, 14.7 m.mole) was added dropwise followed by acetic acid (2 ml, 33.3 m.mole), and kept in deep freeze for 18 hr. Solid sodium bicarbonate (2 g) was added, the liquid decanted and passed through a small silica gel column (pet. ether-acetone, 99:1) to give (37, 0.531 g, 50%) as a yellow oil, which was unstable at room temperature. $^1$H-NMR ($CDCl_3$): $\delta$ 1.96 (s, 3H, $-CH_3$), 3.36 (m, 4H, $-SCH_2CH_2S-$) 5.96 and 6.46 (s, 1H each, $>C=CH_2$), 9.83 (s, 1H, -CHO). This product was used immediately for further reaction.

In a 3-necked round bottom flask, triphenylphosphonium-methyl bromide (3.7 g, 10.36 m.mole) was suspended in THF (25 ml) under $N_2$. It was cooled in ice bath and while stirring, n-BuLi (2N, 5.5 ml, 11 m.moles) was added dropwise in 10 min. After stirring for 15 min. at 0° a solution of 37 (1.14 g, 6.55 m.mole) in THF (5 ml) was introduced dropwise. After 3 hr of stirring followed by usual work up and chromatographic purification (silica gel, benzene-pet.ether, 20:80) afforded the pure 38 (0.672 g, 60%) as colourless oil. $^1$H-NMR ($CDCl_3$); $\delta$ 1.93 (s, 3H, $CH_3$), 3.33 (s, 4H, $-SCH_2CH_2-S$), 5.0 to 6.9 (complex pattern of 5H, $CH_2=\overset{1}{C}-CH=CH_2$). $M^+$ 172.

Analysis: Calculated for $C_8H_{12}S_2$: C, 55.81; H, 6.97. Found: C, 55.88; H, 7.01%.

2-(2-Methyl-1,3-dithiolan-2-yl)-1,4,13,14-tetrahydro-naphthacene-5,12-dione (39):

A mixture of 1,4-anthraquinone (11, 0.30 g, 1.4 m.mole) and the diene (38, 0.30 g,1.7 m.mole) in toluene (20 ml) was refluxed under $N_2$ for 40 hr. The solvent was distilled off and the residue purified (silica gel, pet. ether:acetone, 98:2) to get the title adduct (39, 0.47 g, 85%) as a syrupy liquid. $^1$H-NMR ($CDCl_3$): $\delta$ 1.90 (s, 3H, $CH_3$), 2.3 to 2.9 (broad m, 4H, 2 x $CH_2$), 3.2 - 3.63 (broad m, 6H, -S-$(CH_2)_2$-S and 2 x CH), 6.0 (t, 1H, vinylic H), 7.63 (m, 2H, aromatic), 8.0 (m, 2H, aromatic), 8.66 (s, 2H, aromatic), $M^+$ 380.

Analysis: Calculated for $C_{22}H_{20}O_2S_2$: C, 69.47; H, 5.26. Found: C, 69.51; H, 5.22%.

5,12-Dimethoxy-2-(2-methyl-1,3-dithiolan-2-yl)-1,4-dihydronaphthacene (40):

A mixture of the adduct (39, 0.76 g, 2 m.mole), dimethylsulphate (0.63 g, 5 m.mole), potassium carbonate (5 g) and acetone (30 ml) was refluxed for 4 hr. Usual work up and chromatographic purification (silica gel, pet.ether: acetone, 99:1) afforded dimethyl ether (40, 0.73 g, 90%), crystallised from methanol, m.p. 185°. $^1$H-NMR ($CDCl_3$): $\delta$ 2.1 (s, 3H, $CH_3$), 3.46 (s, 4H, -S-$CH_2$-$CH_2$-S), 3.5 - 3.9 (broad m, 4H, 2 x $CH_2$), 4.0 and 4.06 (2s, 3H each, 2 x $OCH_3$), 6.4 (t, 1H, vinylic H), 7.53 (m, 2H, aromatic H), 8.13 (m, 2H,

aromatic H), 8.7 (s, 2H, aromatic H), $M^+$ 408.

Analysis: Calculated for $C_{24}H_{24}S_2O$: C, 70.58; H, 5.88; Found: C, 70.61; H, 5.92%.

2-(2-Methyl-1,3-dithian-2-yl)-3-buten-2-ol (48):

To a solution of 2-methyl-1,3-dithiane (4.02 g, 30 m.mole) in THF (30 ml) was added dropwise n-BuLi (2.5 N, 12.6 ml, 30 m.moles) at -15°. The reaction mixture was stirred for 3 hrs at -15° and then methyl vinyl ketone (2.1 g, 30 m.mol) in THF (5 ml) was added dropwise. After stirring for 2 hr at -15°, the reaction mixture was kept in deepfreeze overnight. The solvent was removed, diluted with water and extracted with ether. The combined organic layer after washing with water, was dried over $Na_2SO_4$ and concentrated. The residue was purified (silica gel, pet.ether) to get 48 (4.6 g, 75%) as pale yellow liquid. $^1$H-NMR ($CCl_4$). δ 1.4 (s, 3H, $CH_3$), 1.63 (s, 3H, $-CH_3$), 1.8 - 2.2 (m, 3H, OH and $-CH_2$) 2.5 - 3.1 (m, 4H, 2 x $SCH_2$), 5.0 - 6.6 (m, 3H, $_{H}>C=C<_{H}$ ); $M^+$ 204.

Analysis: Calculated for $C_9H_{16}S_2O$: C, 52.94; H, 7.84; Found: C, 52.86; H, 7.79%.

2-(2-Methyl-1,3-dithian-2-yl)-1,3-butadiene (49):

To a solution of (48, 1.37 g, 6.75 m.mole) in $CH_2Cl_2$ (20 ml) was added triethylamine (11 ml, 78.2 m.mole) under $N_2$ at -20°. Mesyl chloride (2.24 ml, 30.74 m.mole) was added

92

in two equal portions with an interval of 2 hr. The reaction mixture was washed with water, dried over $Na_2SO_4$ and the residue chromatographed (basic alumina, pet. ether) to give diene (49, 0.753 g, 60%) as a colourless liquid. $^1$H-NMR ($CCl_4$): $\delta$ 1.63 (s, 3H, $CH_3$), 2.06 (q, 2H, $-S-CH_2-CH_2-CH_2-S$), 2.73 (q, 4H, $-SCH_2-CH_2-CH_2-S$), 5.0 - 6.16 (m, 5H, diene-H), $M^+$ 186.

Analysis: Calculated for $C_9H_{14}S_2$: C, 58.06; H, 7.52; Found: C, 57.43; H, 7.67%.

Methyl 4-(1,4-dimethoxy-2-naphthyl)-4-ketobuterate (51):

To an ice cold solution of 1,4-dimethoxynaphthalene (50, 3.76 g, 20 m.mole) [prepared from 1,4-naphthoquinone] in ethylenedichloride (100 ml) was added aluminium chloride (4.0 g, 29.96 m.mole) and β-carbomethoxypropionyl chloride (3.47 g, 23 m.mole) [prepared from succinic anhydride]. After further stirring at 0° for 4 hours, it was left overnight at room temperature. The reaction was worked up in conventional manner and the crude product on chromatographic purification (silica gel, 5% acetone-pet. ether) afforded 51 (5.10 g, 85%) m.p. 58-60°, $^1$H-NMR ($CDCl_3$): $\delta$ 2.81 (t, 2H, $CH_2-CO_2Me$), 3.50 (t, 2H, $\overset{O}{\overset{\|}{C}}-CH_2$), 3.71 (s, 3H, $CO_2CH_3$), 4.06 (s, 6H, $OCH_3$ x 2), 7.1 (s, 1H, aromatic H), 7.6 (m, 2H, aromatic H), 8.3 (s, 2H, aromatic ); $M^+$ 302.

Analysis: Calculated for $C_{17}H_{18}O_5$: C, 67.54; H, 5.96; Found: C, 67.51; H, 6.01%.

93

Methyl 4-(1,4-dimethoxy-2-naphthyl)-4-ketobuterate-2-2-ene (53):

To a stirred solution of 51 (6.0 g, 19.86 m.mol) in $CCl_4$ (60 ml) benzoylperoxide (50 mg) was added followed by bromine solution (1 ml of $Br_2$ in 20 ml $CCl_4$) added over a period of 1 hour. After 1 hour the reaction mixture was washed with water, dried over $Na_2SO_4$. To the $CCl_4$ solution of 52 a solution of triethylamine (6.0 g in 30 ml $CCl_4$, 59.8 m.mole) was added dropwise and stirred for 5 hours. It was then washed with dilute HCl, water and dried ($Na_2SO_4$) concentrated to yield the residue, purified (silica gel, 80% acetone-pet. ether) to give 53 (5.60 g, 95%), m.p. 72-74° (methanol). $^1$H-NMR ($CDCl_3$): 3.83 (s, 3H, $CO_2Me$), 3.90 (s, 3H, -OMe), 4.03 (s, 3H, OMe), 6.07 and 8.10 (two ds, J = 16 Hz $\alpha$ and $\beta$-H), 7.07 (s, 1H, Ar-H), 7.6 (m, 2H, Ar-H), 8.16 (m, 2H, Ar-H). $M^+$ 300.

Analysis: Calculated for $C_{17}H_{16}O_5$: C, 68.0; H, 5.33. Found: C, 67.79; H, 5.23%.

Preparation of diketo ester (55):

A mixture of $\alpha,\beta$-unsaturated keto ester (53, 1.20 g, 4.0 m.mol), 2-methoxybutadiene (0.403 g, 4.8 m.mol) in benzene (12 ml) was sealed and heated in an oven at 120° for 12 hours. Benzene was removed under reduced pressure and the enol-ether (54) was obtained as a gummy product (1.48 g, 96%).

94

The above gummy enol-ether (54, 1.48 g) was dissolved in acetone (20 ml) containing concentrated hydrochloric acid (2-3 drops). After 1 hour of stirring, water (2 ml) was introduced and acetone was removed under reduced pressure. The resulting residue was extracted with methylene chloride, dried over $Na_2SO_4$, concentrated to a product which was purified on a silica gel column (10:90 acetone-pet. ether) to afford the pure keto-ester (55, 1.30 g, 88%) as a syrup. $^1$H-NMR spectrum clearly showed the presence of isomeric mixture of products in 2:1 ratio. $^1$H-NMR of major isomer ($CDCl_3$) $\delta$ 1.6 - 2.9 (bm, 8H, $CH_2$ x 3 + -CH x 2), 3.75 (s, 3H, $CO_2\underline{CH}_3$), 4.05 (s, 3H, OMe), 4.08 (s, 3H, OMe), 7.03 (s, 1H, aromatic), 7.6 - 8.2 (m, 4H, Ar$\underline{H}$), 7.6 (m, 2H, aromatic), 8.2 (m, 2H, aromatic). $M^+$ 370.

Analysis: Calculated for $C_{21}H_{22}O_6$: C, 68.10; H, 5.94. Found: C, 68.18; H, 6.01%.

Preparation of Diels-Alder adduct (58):

$\alpha,\beta$-unsaturated keto ester (53, 0.350 g, 1.16 m.mol) and isoprene (0.095 g, 1.4 m.mol) in benzene (10 ml) were heated for 12 hours at 120° in a sealed tube. Removal of the solvent in vacuo afforded the adduct (58, 0.41 g, 96%) as a syrup. $^1$H-NMR ($CDCl_3$, major isomer): $\delta$ 1.5 to 3.3 (bm, 9H, $CH_3$ + $CH_2$ x 2 + CH x 2), 3.7 (s, 3H, $CO_2CH_3$), 4.0 (s, 6H, OMe x 2), 5.4 (bt, 1H, vinylic), 6.9 (s, 1H, aromatic),

7.5 (m, 2H, aromatic), 8.1 (m, 2H, aromatic). $M^+$ 368.

Analysis: Calculated for $C_{22}H_{24}O_5$: C, 71.74; H, 6.52. Found: C, 71.68; H, 6.60%.

Hydrogenation product of 58 (59)

The solution of unsaturated adduct (58, 1.30 g, 3.53 m.mol) in ethanol (30 ml) was hydrogenated (30 p.s.i.) in the presence of platinum oxide (60 mg) at room temperature for 4 hours. It was filtered and concentrated to a residual mass which was chromatographed on a column of silica gel using benzene as eluent to give 59 (1.17 g, 90%) as a syrup. $^1$H-NMR of major isomer ($CDCl_3$): $\delta$0.8 - 3.0 (m, 12H, $CH_3$ + $CH_2$ x 3 + CH x 3), 3.61 (s, 3H, $CO_2CH_3$), 4.0 (s, 6H, OMe x 2), 6.9 (s, 1H, aromatic), 7.5 (m, 2H aromatic), 8.2 (m, 2H, aromatic). $M^+$ 370.

Analysis: Calculated for $C_{22}H_{26}O_5$: C, 71.35; H, 7.02. Found: C, 71.41; H, 7.05%.

Hydrolysis of ketoester (59) to 60:

The keto ester (59, 0.332 g, 0.892 m.mol) in methanol (4 ml) was boiled with 5% aqueous sodium hydroxide (2 ml) for 3 hours after which time the hydrolysis was complete (TLC). Methanol was removed under reduced pressure and the residual aqueous portion was acidified with hydrochloric acid to give the crude acid which was extracted

with methylene chloride and concentrated. The crude residue was purified over silica gel using pet. ether-acetone (95:5) to afford the pure keto acid (60, 0.215 g, 67%).

Cyclisation of keto acid (60) to 61:

To the keto acid (60, 0.20 g, 0.56 m.mol) concentrated sulphuric acid (2.0 ml) was added, and then left at room temperature overnight. It was poured over crushed ice and extracted with methylene chloride which was dried over anhydrous $Na_2SO_4$ and concentrated to yield the cyclised product (61, 0.150 g, 87%) as red coloured solid. M.p. 250°. $M^+$ 308.

Preparation of dimethyl ether (62):

The dihydroxy compound (61, 0.150 g, 0.487 m.mol), dimethylsulphate (0.12 ml, 1.2 m.mol) and anhydrous potassium carbonate (2.0 g) in acetone (dry, 20 ml) were refluxed on a waterbath for 6 hours followed by usual work up to give the dimethylether (62, 0.120 g, 73%). $^1$H-NMR ($CDCl_3$) $\delta$ 1.0 to 3.3 (bm, 10H, $CH_2$ x 3 + CH + $CH_3$), 3.87 (s, 6H, OMe x 2), 7.7 (m, 2H, aromatic), 8.2 (m, 2H, aromatic). $M^+$ 336.

Analysis: Calculated for $C_{21}H_{20}O_4$: C, 75.0; H, 5.95. Found: C, 75.04; H, 5.92%.

Diels-Alder adduct (63):

$\alpha,\beta$-Unsaturated ester (53, 0.44 g, 1.46 m.mol) and

the diene (38, 0.28 g, 1.62 m.mol) were dissolved in toluene (5 ml) and refluxed for 60 hours under $N_2$. The solvent was removed under reduced pressure and the residue purified (silica gel, acetone-pet. ether, 3:97) to give the adduct (63, 0.55 g, 79%) as a gummy product. IR (Nujol): 1750, 1670, 1600 $cm^{-1}$. $^1$H-NMR spectrum clearly showed the presence of two isomers in 2:1 ratio. $^1$H-NMR of major isomer ($CCl_4$): $\delta$ 1.86 (s, 3H, $CH_3$), 2.0 - 3.0 (m, 6H, $CH_2$ x 2 and CH x 2), 3.23 (s, 4H, -S-$CH_2$-$CH_2$-S), 3.63 (s, 3H, $CO_2$Me), 3.96 (s, 6H, OMe x 2), 5.83 (t, 1H, vinylic H), 6.76 (s, 1H, Ar-H), 7.33 (m, 2H, Ar-H), 7.93 (m, 2H, Ar-H), $M^+$ 472.

Analysis: Calculated for $C_{25}H_{28}O_5S_2$: C, 63.55; H, 5.93. Found: C, 63.67; H, 6.00%.

Dethioketalization of 63 (64)

Silver nitrate (0.621 g, 3.65 m.mol) in aqueous $CH_3CN$ (80%, 10 ml) was treated with N-chlorosuccinimide (0.435 g, 3.24 m.mol). After 5 minutes 63 (0.383 g, 0.811 m.mol) in aq. $CH_3CN$ (5 ml) was added. The mixture was stirred for 20 minutes and treated successively with saturated solutions of sodium sulfite (3 ml), sodium carbonate (3 ml), brine (3 ml) and mixture of pet. ether and $CH_2Cl_2$ (1:1). After 10 min. solid was filtered, washed with a mixture of pet. ether and methylenechloride (1:1)

98

and organic layer separated, dried over $Na_2SO_4$, concentrated and the residue purified by chromatography (silica gel pet.ether-acetone, 85:15) to give 64 (0.21 g, 65%) as yellow gummy mass. IR (Nujol): 1740, 1670, 1600 $cm^{-1}$. $^1$H-NMR (of the major isomer) ($CDCl_3$) $\delta$2.1 (s, 3H, $COCH_3$), 2.2 - 3.2 (bm, 6H, $CH_2$ x 2, CH x 2), 3.6 (s, 3H, $CO_2Me$), 3.9 (s, 6H, OMe x 2), 6.6 (bt, 1H, vinylic H), 6.9 (s, 1H, aromatic H), 7.5 (m, 2H, Ar-H), 8.1 (m, 2H, Ar-H). $M^+$ 396.

Analysis: Calculated for $C_{23}H_{24}O_6$: C, 69.69; H, 6.06. Found: C, 69.72; H, 6.10%.

Hydrogenation product of 64 (65):

63 (0.4 g, 1.01 m.mole) in EtOH (10 ml) was hydrogenated at 20 psi for 90 min. in the presence of Pd-C (10%, 0.1 g). Filtration and chromatographic purification (silica gel, pet.ether-acetone 80:20) afforded 65 (0.380 g, 94%). $^1$H-NMR of the major isomer ($CDCl_3$): $\delta$2.13 (s, 3H, $CH_3$), 2.0 - 3.0 (m, 9H, 3 x $CH_2$ and 3 x CH), 3.6 (s, 3H, $CO_2Me$), 3.93 (s, 6H, 2 x $OCH_3$), 6.73 (s, 1H, Ar-H), 7.3 (m, 2H, Ar-H), 7.9 (m, 2H, Ar-H). $M^+$ 398.

Analysis: Calculated for $C_{23}H_{26}O_6$: C, 69.34; H, 6.5. Found: C, 69.44; H, 5.56%.

2-(1,4-Dimethoxy-2-naphthoyl)-4-acetyl-cyclohexane-1-carboxylic acid (66):

A mixture of 65 (0.350 g, 0.88 m.mol), 2N aqueous

99

sodium hydroxide (1.5 ml) and methanol (15 ml) was refluxed on water bath for 12 hr. Methanol was removed, diluted with water (15 ml) and extracted with $CH_2Cl_2$ to remove any unhydrolysed product. The alkaline solution was acidified with dil. HCl and the solid filtered, washed with water and dried to give the acid 66 (76%) which was used as such without further purification.

4-Demethoxy-7,9-dideoxydaunomycinone (44):

The crude acid (66, 0.30 g, 0.78 m.mole) was treated with conc. $H_2SO_4$ (5 ml) at room temperature for 36 hr. The reaction mixture was poured over crushed ice, solid filtered, washed with water, dried and crystallised from methanol to give 44 (0.22 g, 84%) as orange red needles, m.p. 187°. IR ($CHCl_3$): 3300, 1700, 1680, 1600 $cm^{-1}$. $^1$H-NMR ($CDCl_3$): $\delta$ 2.25 (s, 3H, $COCH_3$), 1.5 - 3.3 (m, 7H, 3 x $CH_2$ and CH), 7.75 (m, 2H, Ar.H), 8.29 (m, 2H, Ar-H), 13.35 (s, 1H, OH), 13.40 (s, 1H, OH). $M^+$ 336.

Analysis: Calculated for $C_{20}H_{16}O_5$: C, 71.42; H, 4.76. Found: C, 71.50; H, 4.81%.

4-Demethoxy-7,9-dideoxydaunomycinone-6,11-dimethyl ether (43):

A mixture of 44 (0.22 g, 0.66 m.mole), dimethyl sulphate (0.208 g, 1.65 m.mole), potassium carbonate (2 g) in acetone (20 ml) was refluxed for 16 hr. Usual work up

100

and chromatographic purification (silica gel, pet.ether-acetone 9:1) afforded the dimethyl ether (43, 0.2 g, 83%) as yellow crystals, m.p. 145-146°. IR (Nujol): 1710, 1680, 1600 $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ2.2 (s, 3H, $COCH_3$), 2.5 - 3.3 (m, 7H, 3 x $CH_2$ and CH), 3.8 and 3.83 (s, 3H each, 2 x $OCH_3$), 7.6 (m, 2H, Ar-H), 8.03 (m, 2H, Ar-H). $M^+$ 364.

Analysis: Calculated for $C_{20}H_{20}O_5$: C, 72.52; H, 5.49. Found: C, 72.41; H, 5.86%.

4-Demethoxy-7-deoxydaunomycinone dimethyl ether (27):

To a mixture of 43 (0.20 g, 0.55 m.mol) in acetic anhydride (50 ml), p-toluenesulphonic acid (670 mg, 4.9 m.mol) was added. Continuous slow distillation of acetic anhydride and acetic acid was carried out over 6-7 hr. A further quantity of p-toluenesulphonic acid (0.120 g) was added and the distillation continued over 3-4 hr. The residual acetic anhydride was removed in vacuo and the brownish yellow mass was partly purified over silica gel column. This yellow solid (0.200 g) was epoxidised with m-chloro-perbenzoic acid in dichloromethane. After stirring for 1 hr at room temperature (25°C), it was worked up to give 0.180 g (90%) of the crude epoxide as a yellow viscous oil. The latter was treated with ethanolic sodium hydroxide (0.3N, 7.5 ml) in ethyl alcohol (50%) for 35 min. at room temperature. After acidification and extraction with

dichloromethane, the residue was treated with a solution of glacial acetic acid (6 ml), conc. $H_2SO_4$ (1 ml) and water (3 ml) for 1 hr. After dilution with water, the reaction mixture was extracted with dichloromethane, washed with water, dried and evaporated to yield the crude red solid (0.180 g). Silica gel column chromatography (hexane: acetone, 97:3) gave 4-demethoxy-7-deoxydaunomycinone dimethyl ether (27) which was crystallised from methanol: hexane as yellow needles (0.110 g, 55%), m.p. 187-8° (lit.[27] m.p. 184-6°); NMR ($CDCl_3$): δ 8.25 (m, 2H, 1,4-H), 7.75 (m, 2H, 2,3-H), 4.0 (s, 3H, OMe), 3.90 (s, 3H, OMe), 2.25 (s, 3H, OMe). $M^+$ 380.

Analysis: Calculated for $C_{22}H_{20}O_6$: C, 69.47; H, 5.26. Found: C, 68.95; H, 5.13%. The sample was identical in all respects with an authentic[6] sample.

102

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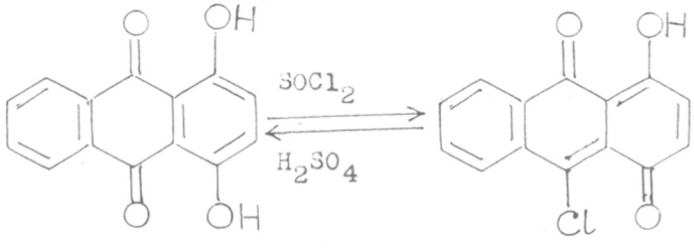
# SECTION – II

## 1–ACETOXY–10–CHLORO–4,9–ANTHRAQUINONE AS A DIENOPHILE

In the preceding chapter it was discussed that why quinizarinquinone could not be a suitable dienophile due to its bifunctionality undergoing both the internal as well as terminal Diels-Alder reactions with butadienes. Although with 1,4-anthraquinone the Diels-Alder reactions of butadiene has been shown to proceed smoothly, unexpected difficulties were encountered during the elaboration of the side-chain. In particular deprotection of the dithiane ring resulted in the aromatization of ring-A.

It was felt that chloroquinizarin (2) could act as a



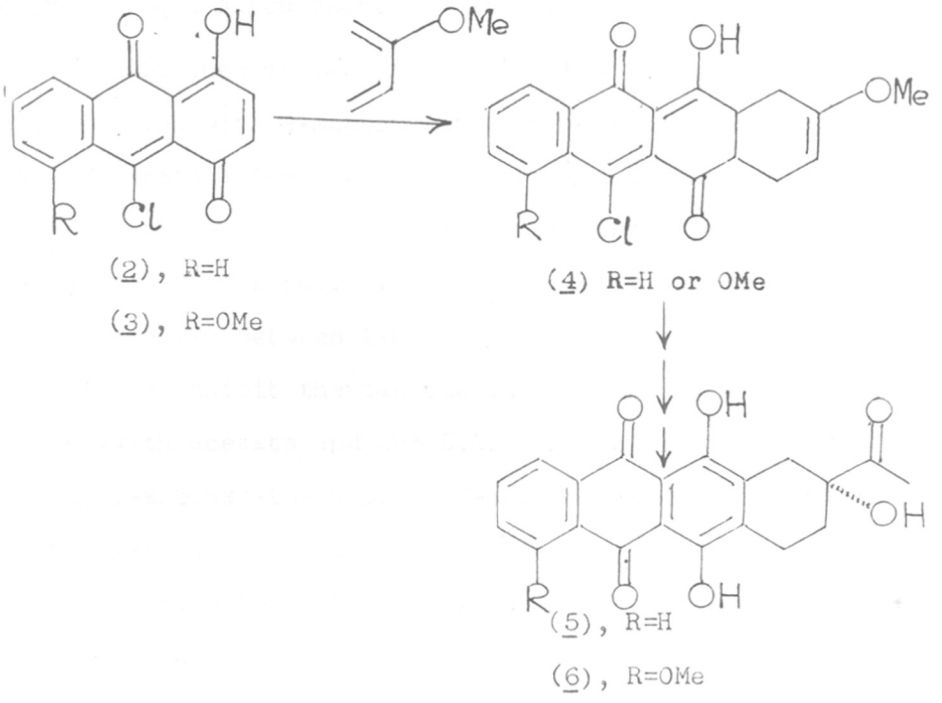

(1) (2)

suitable synthon because firstly it contained only one terminal double bond for D.A. reactions to go; and secondly it could be converted back conveniently to quinizarin[1] (1). With this view in mind it was thought that with suitable butadienes such as 2-methoxybutadiene, 2 would give the anticipated

106

regioselective Diels-Alder adduct (4) which in turn could be

Scheme-1




(2), R=H

(3), R=OMe

(4) R=H or OMe

(5), R=H

(6), R=OMe

elaborated to 4-demethoxydaunomycinone (5) by the known[2] set of reactions. Similarly 5-methoxy analogue (3) of 2 with above sequence of reactions would lead to a regio-specific synthesis of daunomycinone (6) (Scheme-1).

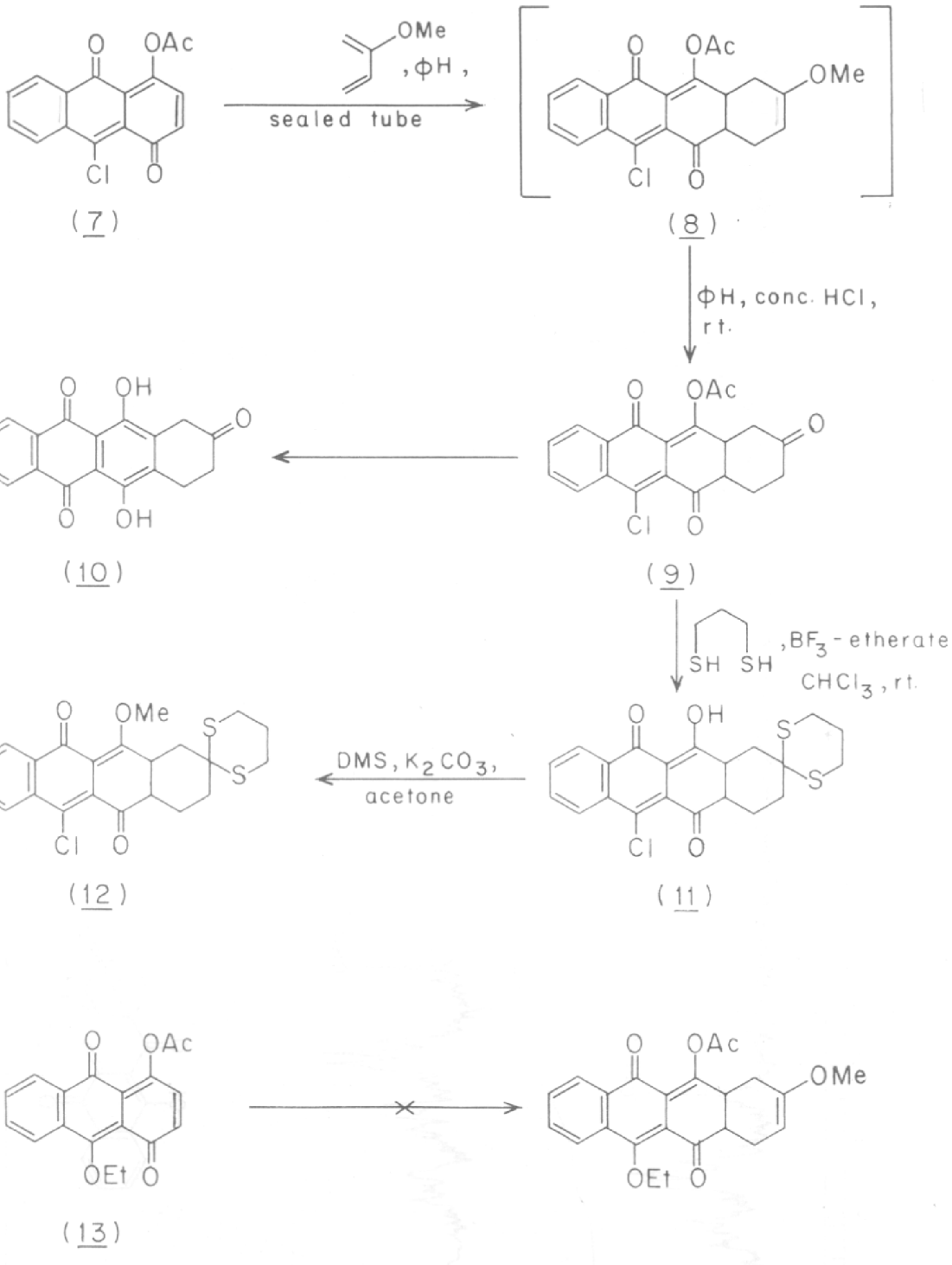
Earlier Winkler[3] had studied the D.A. reaction of chloroquinizarin (2) with isoprene and 2-chlorobutadiene and indeed obtained the regioselective adduct. Treatment of 2

with 2-methoxybutadiene in benzene in a sealed tube at 100° for 40 hr resulted in no reaction as judged by TLC. Even after employing drastic conditions and catalyst ($BF_3$-etherate) no desired reaction was observed.

Although it was anticipated that 2 should undergo D.A. reaction with 2-methoxybutadiene faster than isoprene and 2-chlorobutadiene because of strong electron donating behaviour of 2-methoxy function surprisingly no reaction was noticed. This failure could be partly attributed to the tautomerism between 1-hydroxy and 9-ketone. Therefore in order to inhibit the tautomerism, 1-hydroxy group was blocked with acetate and the D.A. reaction of the corresponding 1-acetoxy-10-chloro-4,9-anthraquinone (7)[1] with 2-methoxy-butadiene was conducted (Scheme-2). It was gratifying to note that the desired adduct (8) was obtained in good yield.

Conversion of 8 to 9 was effected in benzene containing a few drops of concentrated HCl. The $^1$H-NMR spectrum of 9 (Fig.1) showed a complex multiplet in the region of 2.1 - 4.1 ppm. for methylenes and methine protons, a singlet at 2.50 ppm for acetoxy group. The aromatic protons appeared as a multiplet between 7.0 - 8.2 ppm. Transformation of compound (9) to the trione (10) was

Scheme 2


OAc
Cl
O
OMe
,φH,
sealed tube
OMe
(7)
(8)
φH, conc. HCl,
r.t.
OH
(10)
(9)
SH SH
,BF3 - etherate
CHCl3, r.t.
S
(12)
(11)
DMS, K2CO3,
acetone
OEt
(13)

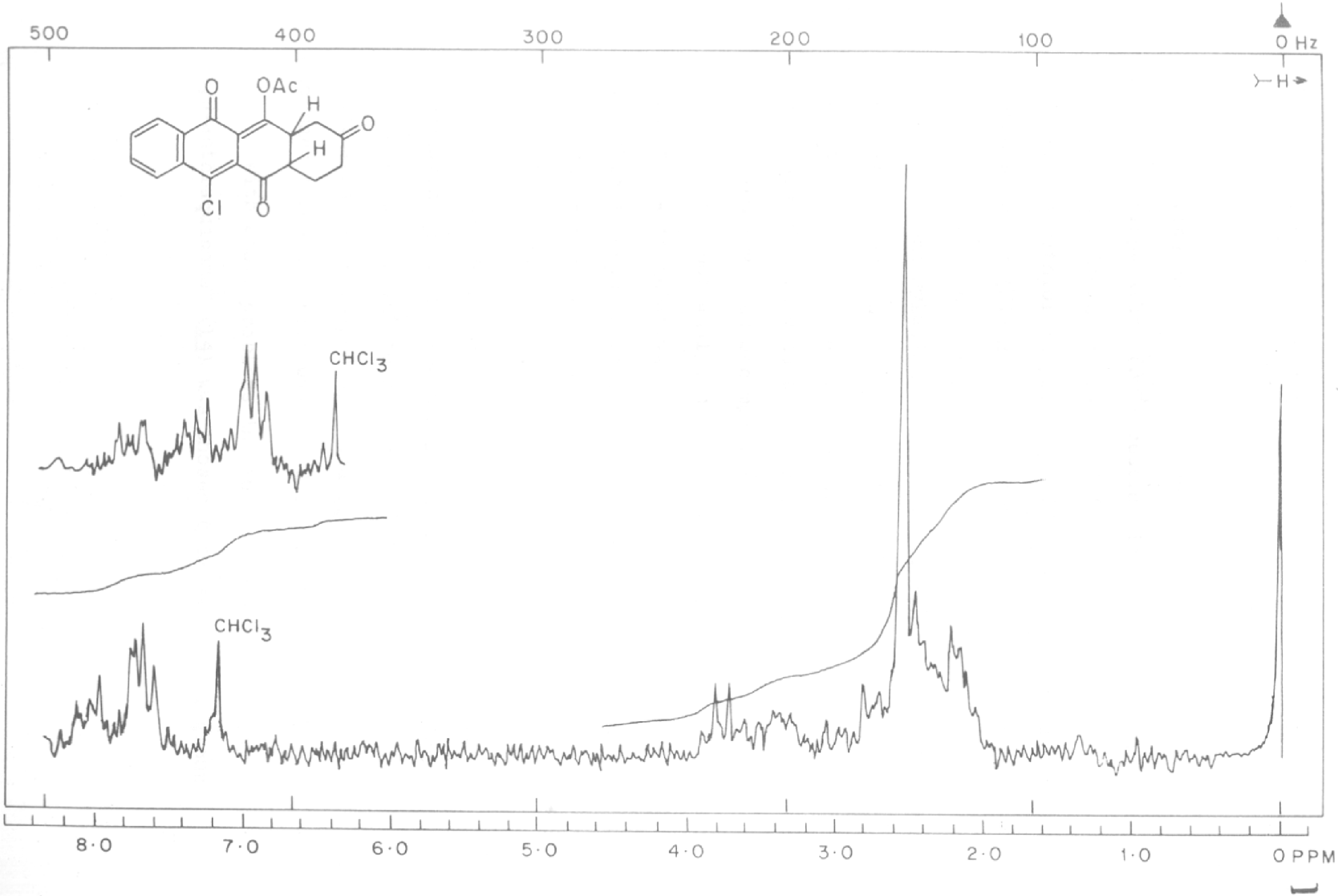



FIG. 1. $^{1}$H-NMR SPECTRUM OF COMPOUND (9) IN $CDCl_3$

attempted with conc. $H_2SO_4$ but no reaction was observed. At higher temperature ($90^{o}$) destructive decomposition was seen on TLC. Therefore compound (2) was protected with 1,3-propane dithiol in presence of $BF_3$-etherate in chloroform. $^1H$-NMR spectrum (Fig.2 ) of the resulting compound (11) indicated that the acetoxy substituent had hydrolysed. Subsequent O-methylation with dimethylsulphate and potassium carbonate in acetone gave the methyl ether (12), which was subjected to concentrated $H_2SO_4$ treatment hoping that acid hydrolysis will lead to the corresponding quinone derivative. However TLC revealed decomposition of the reaction mixture and therefore not analysed. The desired transformation was attempted with relatively milder reagents such as ethanolic hydrochloric acid or acetic acid to displace chlorine with OEt or OAc but no reaction was observed and the starting material was recovered.

It was surprising to note that although chloroquinizarin (2) and 1-acetoxy-10-chloro-4,9-anthraquinone (7) have been shown[1] to undergo smooth transformation to quinizarin, with compounds 9 and 11 under identical conditions no such transformation was found to occur.

With above problems in mind 1-acetoxy-10-ethoxy-4,9-anthraquinone[1] (14) was chosen because O-ethyl group

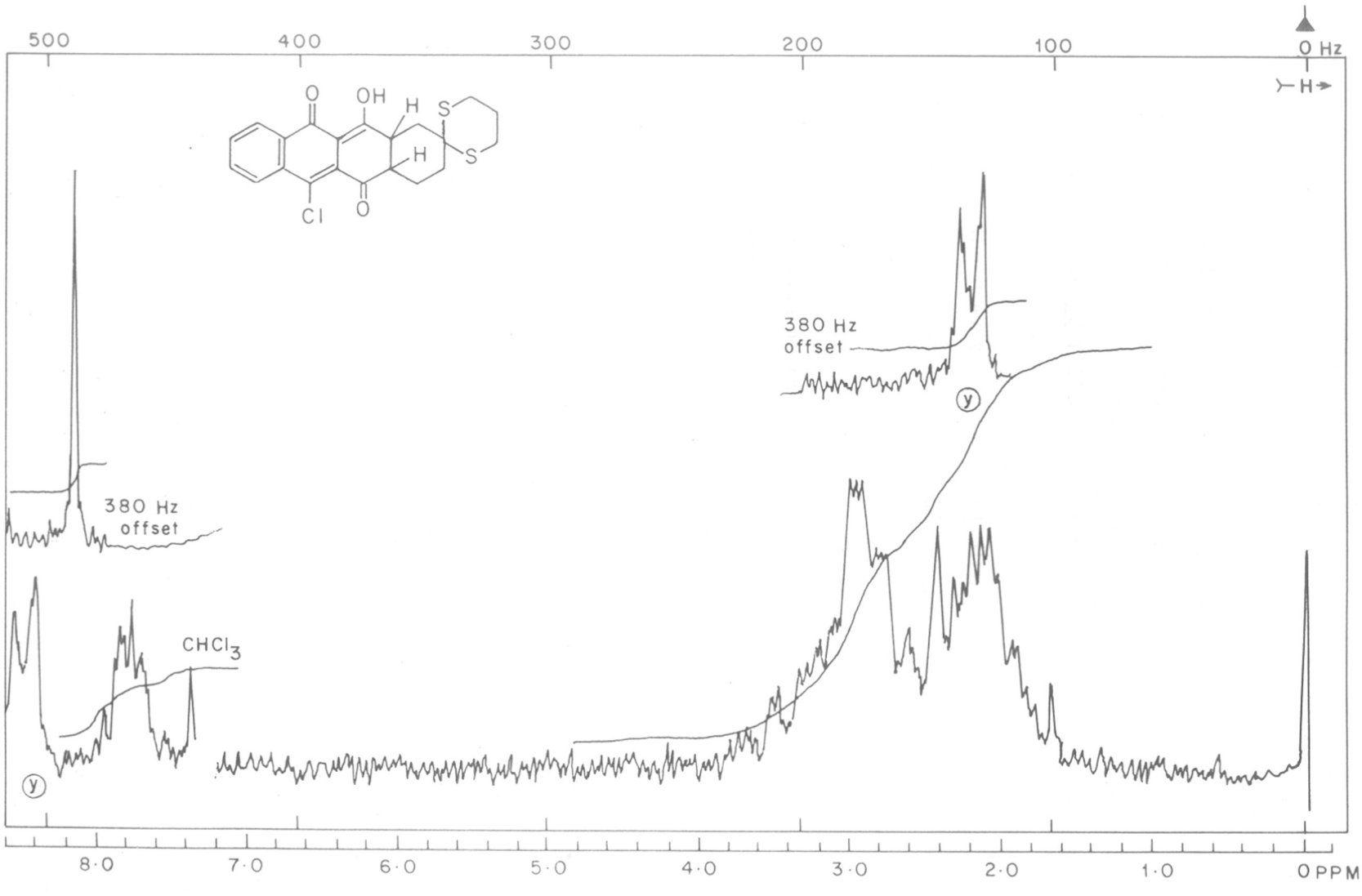



FIG. 2. $^1$H-NMR SPECTRUM OF COMPOUND (11) IN $CDCl_3$

112

could be easily hydrolysed under mild conditions as compared to chloro group. Accordingly ethoxy derivative (14) was prepared from chloroquinizarin (2) with 3% HCl in absolute ethanol to give 13 followed by acetylation to afford acetyl derivative (14).

The D.A. reaction of 14 with 2-methoxybutadiene was attempted but no reaction was observed. Change of conditions such as using $BF_3$-etherate as catalyst did not bring any success as the starting material was recovered.

Because of the above mentioned problems this route was abandoned.

# EXPERIMENTAL

## 1-Acetoxy-10-Chloro-4,9-anthraquinone (7)

Quinizarin (3.0 g, 12.5 m.mol) was refluxed with freshly distilled thionylchloride (12.0 ml) for 12 hr. The deep red coloured reaction contents were concentrated to half bulk. On cooling it deposited dark red needles. Product was filtered and washed with benzene and ether and was recrystallized from methanol to get pure chloro-quinizarin (2, 2.60 g, 80%) in form of dark red needles m.p. 226-228° (lit.[1] m.p. 225-226°).

The above product (2, 0.50 g, 1.93 m.mol) was heated with acetic anhydride (5 ml) and pyridine (5 ml) at 60-70° till a clear solution was obtained. It was cooled and poured over crushed ice. The precipitated solid was filtered dried and recrystallised from benzene-hexane to afford 7 (0.50 g, 86%) m.p. 196-197° (lit.[1] m.p. 197-8°).

## Preparation of the trione (9)

10-Chloro-1-acetoxy-4,9-anthraquinone (7, 0.30 g, 0.998 m.mol), 2-methoxybutadiene (0.24 g, 2.85 m.mol) and dry benzene (5.0 ml) were sealed in a glass tube and kept in an oven at 80-90° for 6 hr. Dark coloured contents were treated with charcoal and filtered. Solvent was removed at lower temperature (35°) to give the adduct (8, 0.372 g,

98%) as a yellow coloured syrup. Since the product decomposed on prolonged keeping, it was submitted as such for demethylation.

The crude adduct (8, 0.372 g, 0.967 m.mol) in benzene (5 ml) was treated with concentrated hydrochloric acid (one drop) for 2 hr at room temperature. The solid was separated filtered, washed with benzene, water, dried and recrystallized from benzene to give 9 (0.184 g, 51%), m.p. 210-4°. $^1$H-NMR ($CDCl_3$): δ 1.9 - 2.8 (bm, 6H, $CH_2$ x 3), 2.5 (s, $COCH_3$), 3.2 - 3.9 (bm, 2H, >CH x2), 7.5 - 7.8 (m, 2H, aromatic), 7.9 - 8.2 (m, 2H, aromatic), $M^+$ 370.

Analysis: Calculated for $C_{20}H_{15}ClO_5$: C, 64.77; H, 4.05; Cl, 9.6. Found: C, 64.09; H, 4.04; Cl, 10.5%.

Thioketalisation of 9 to 11

To a stirring solution of the keto compound (9, 0.80 g, 2.159 m.mol) in dry chloroform (20 ml), was added propanedithiol (0.30 g, 2.77 m.mol) followed by $BF_3$-etherate (0.350 g, 2.46 m.mol). Contents were stirred at room temp. for 4 hr, poured into a saturated solution of sodium acetate (10 ml) and further stirred for 30 min. It was extracted with chloroform, dried over anhydrous $Na_2SO_4$ concentrated to a crude product which was purified on a silica gel column using benzene to afford the compound (11, 0.40 g, 44%) as a crystalline solid, m.p. 228-9°. $^1$H-NMR ($CDCl_3$): δ 1.6 - 3.9

(bm, 14H, $S(C\underline{H}_2)_3S$, $C\underline{H}_2$ x3, $>C\underline{H}$ x2), 7.6 - 8.1 (m, 2H, aromatic), 8.2 - 8.7 (m, 2H, aromatic), 14.31 (s, 1H, OH). $M^+$ 418.

Analysis: Calculated for $C_{21}H_{19}S_2ClO_3$: C, 60.21; H, 4.54; Cl, 8.48. Found: C, 60.58; H, 4.50; Cl, 8.69%.

Preparation of methyl ether (12)

The compound (11, 0.50 g, 1.19 m.mol), dimethylsulphate (0.180 g, 1.4 m.mol), anhydrous potassium carbonate (2.0 g) and acetone (30 ml) were refluxed on water-bath for 8 hr. Usual work up gave the crude product which was purified by column chromatography (silica gel, benzene) to give the methyl ether (12, 0.464 g, 90%), m.p. 220-221° (decomposition). $^1$H-NMR ($CDCl_3$) $\delta$ 1.6 - 3.7 (bm, 14H, $S(CH_2)_3S$, $CH_2$x3, CH x2) 4.0 (s, 3H, $OCH_3$), 7.5 - 7.9 (m, 2H, aromatic), 8.1 - 8.5 (m, 2H, aromatic). $M^+$ 432.

Analysis: Calculated for $C_{22}H_{21}S_2ClO_3$: C, 61.04; H, 4.85; Cl, 8.20. Found: C, 61.35; H, 4.89; Cl, 8.64%.

10-Ethoxy-1-hydroxy-4,9-anthraquinone (13)

10-Chloro-1-hydroxy-4,9-anthraquinone (2, 2.50 g, 9.67 m.mol) was refluxed with absolute ethanol (200 g) containing 3% of dry hydrogen-chloride for 3.5 hr. It was filtered and on concentration and cooling gave reddish brown needles which was recrystallized from ethyl alcohol to the desired ethoxy quinizarin (13, 2.10 g, 81%), m.p. 133-4° (lit.[1] m.p. 135°).

116

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# CHAPTER – III

## SYNTHESIS OF (±) 4-DEMETHOXYDAUNOMYCINONE BY FRIEDEL-CRAFTS REACTIONS

# SECTION – I

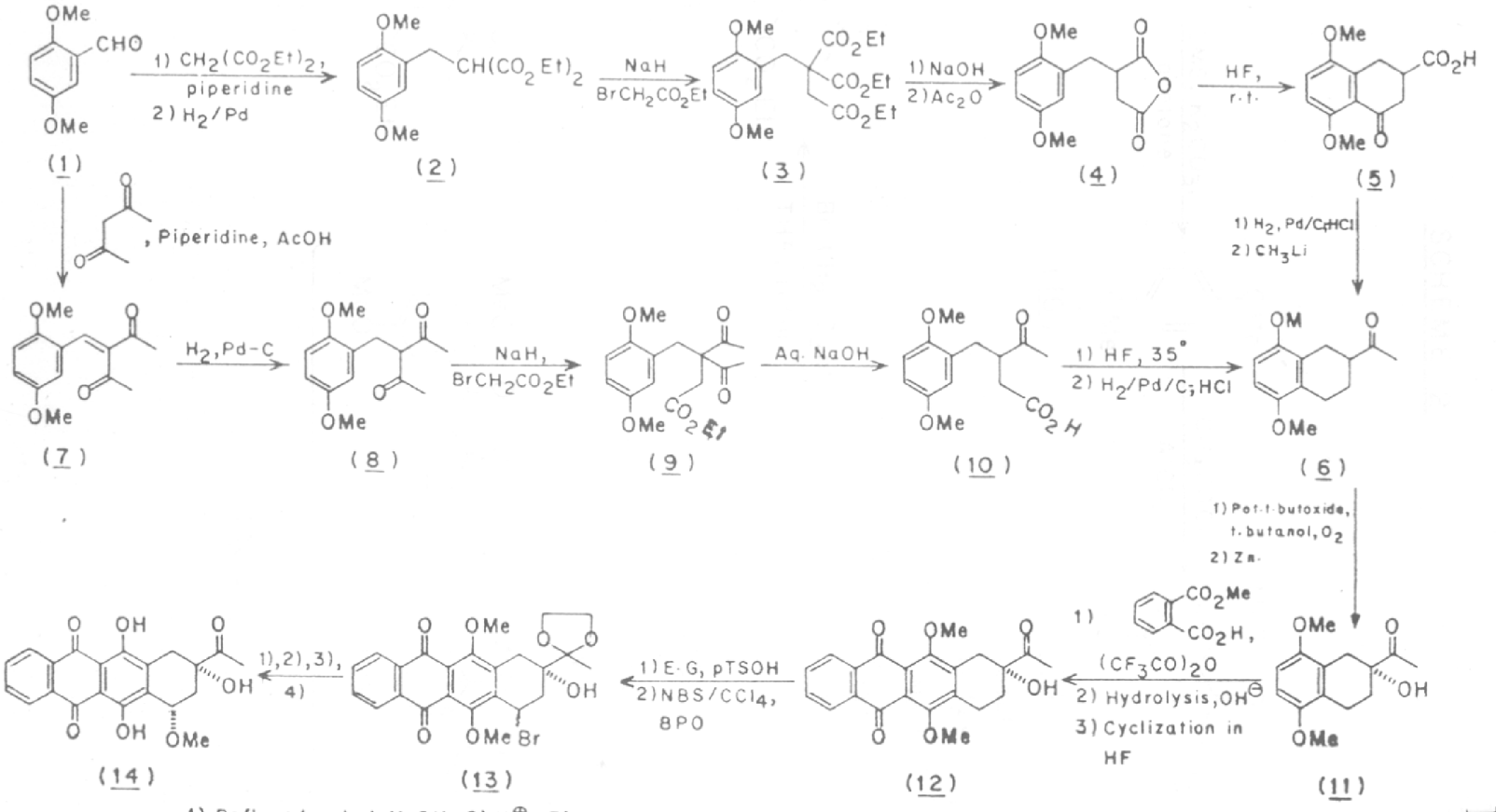
## SYNTHESIS STARTING FROM HYDROQUINONE

Several synthetic approaches have been described in literature for the synthesis of 4-demethoxydaunomycinone. Earlier in this thesis the Diels-Alder approach utilising quinizarin derivatives (having BCD rings already incorporated) had been exploited to build ring-A. A number of unexpected problems were faced during the elaboration of the side-chain because of extended aromatic conjugation.

Yet the method of Wong et al.[1] who had employed for the assemblage of the tetracyclic system AB + CD coupling seemed to be most attractive. It involved the preparation of a tetralin derivative (AB rings) and its condensation with phthalic acid monoester (CD rings). They have successfully converted the hydroxy-ketone (11) (Scheme-1) into (±)4-demethoxy-7-O-methyl daunomycinone (14) utilising AB and CD coupling. Compound (11) was prepared from tetralin (6) which in turn was synthesised by two different synthetic sequences (Scheme-1). In the present work, attempts were made to synthesise the key intermediate (6) from an altogether new approach (Scheme-2) starting from cheap and easily accessible starting material, 2,5-dimethoxyacetophenone (17).

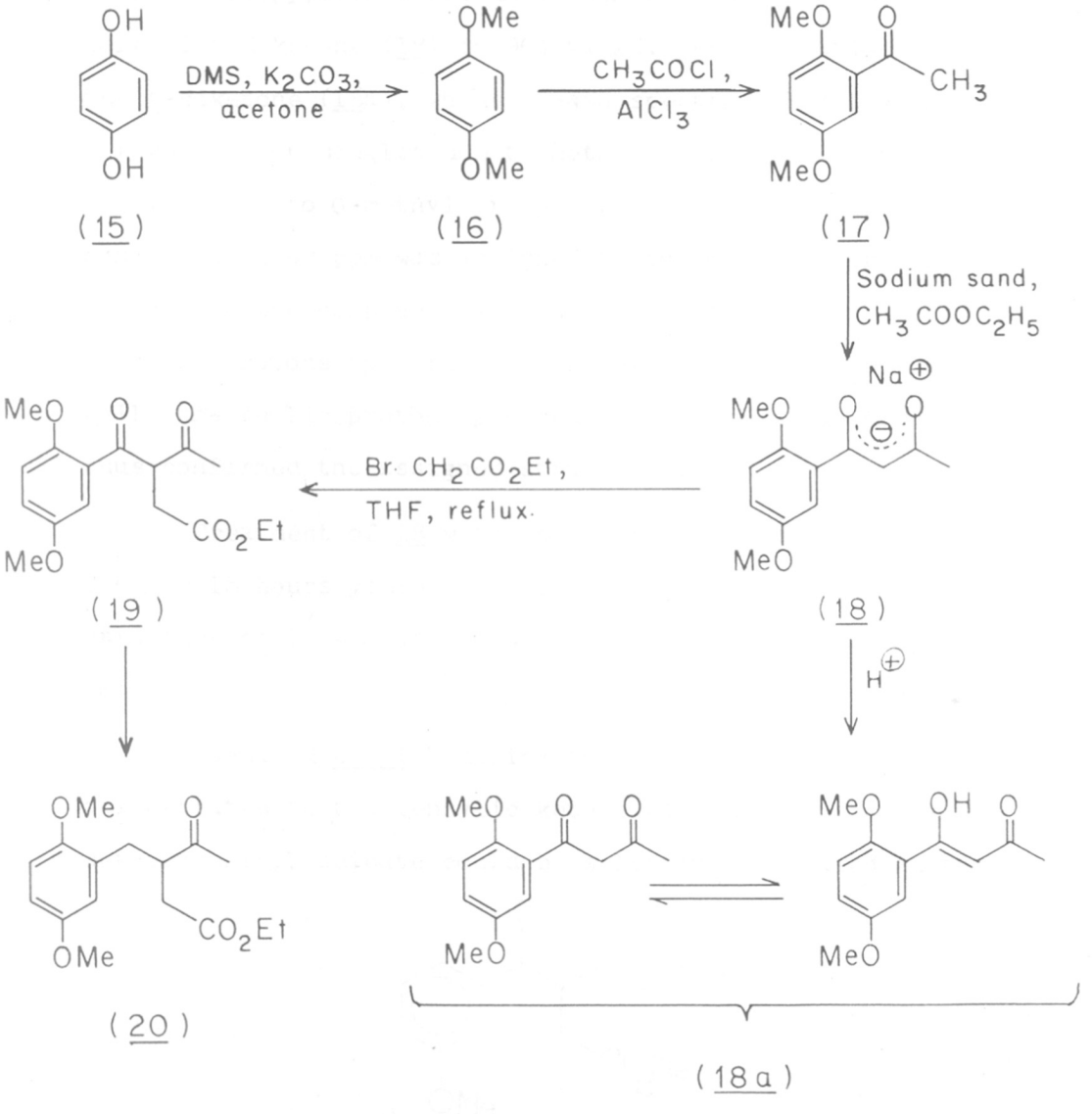
2,5-Dimethoxyacetophenone (17) was prepared starting from hydroquinone (15) by the known route[2] in quantitative

## SCHEME 1




1) Refluxed anhyd. MeOH; 2) $H^{\oplus}$; 3) Chromatographic separation of isomers; 4) Demethylation with $AlCl_3$.

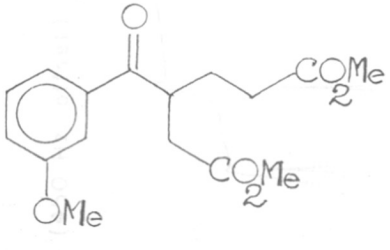
## SCHEME 2


OH
OH
(15)
DMS, $K_2CO_3$,
acetone
OMe
OMe
(16)
$CH_3COCl$,
$AlCl_3$
MeO
O
$CH_3$
MeO
(17)
Sodium sand,
$CH_3COOC_2H_5$
Na⊕
MeO
O
O
⊖
MeO
(18)
Br·$CH_2CO_2Et$,
THF, reflux.
MeO
O
O
$CO_2Et$
MeO
(19)
H⊕
OMe
O
$CO_2Et$
OMe
(20)
MeO
O
O
MeO
MeO
OH
O
MeO
(18a)

yield. Its (17) condensation with ethylacetate in the presence ofpulverized sodium in ether offered the sodium salt of β-diketone (18) in 96% yield. Acidification afforded the β-diketone (18a), whose $^1$H-NMR spectrum (Fig.1 ) showed a three proton singlet due to methy group at 2.10 ppm, two singlets due to O-methyl groups at 3.76 and 3.83 ppm. A singlet at 6.40 ppm was assigned to the olefinic proton indicating the compound existed in its enolic form. The aromatic protons appeared as multiplets between 6.9 and 7.5 ppm while the enolic proton appeared as a singlet at 16.0 ppm, thus confirmed the assigned structure (18a).

Treatment of 18 with ethyl bromoacetate in refluxing THF for 15 hours yielded the ester (19) in 80% yield. The structure of 19 was assigned on the basis of $^1$H-NMR spectrum (Fig.2 ).

Woodward et al.[3] during the synthesis of tetracyclin, demonstrated that a benzylic ketone viz. dimethyl β-(3-methoxybenzoyl)adipate could be selectively reduced in the




presence of other carbonyl functions using 10% Pd-C at 200 psi

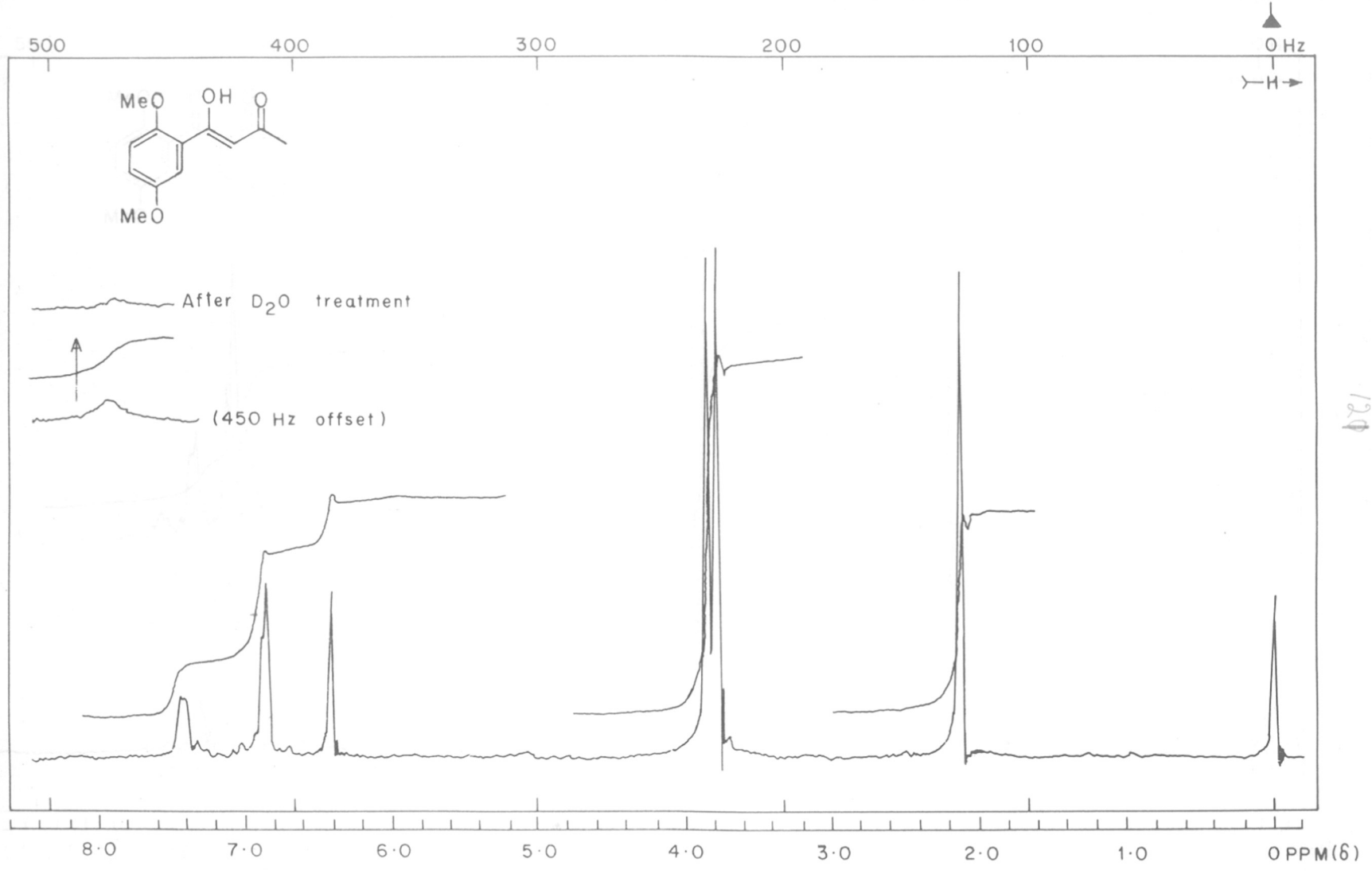



FIG. 1. $^1$H-NMR SPECTRUM OF COMPOUND (18a) IN $CCl_4$

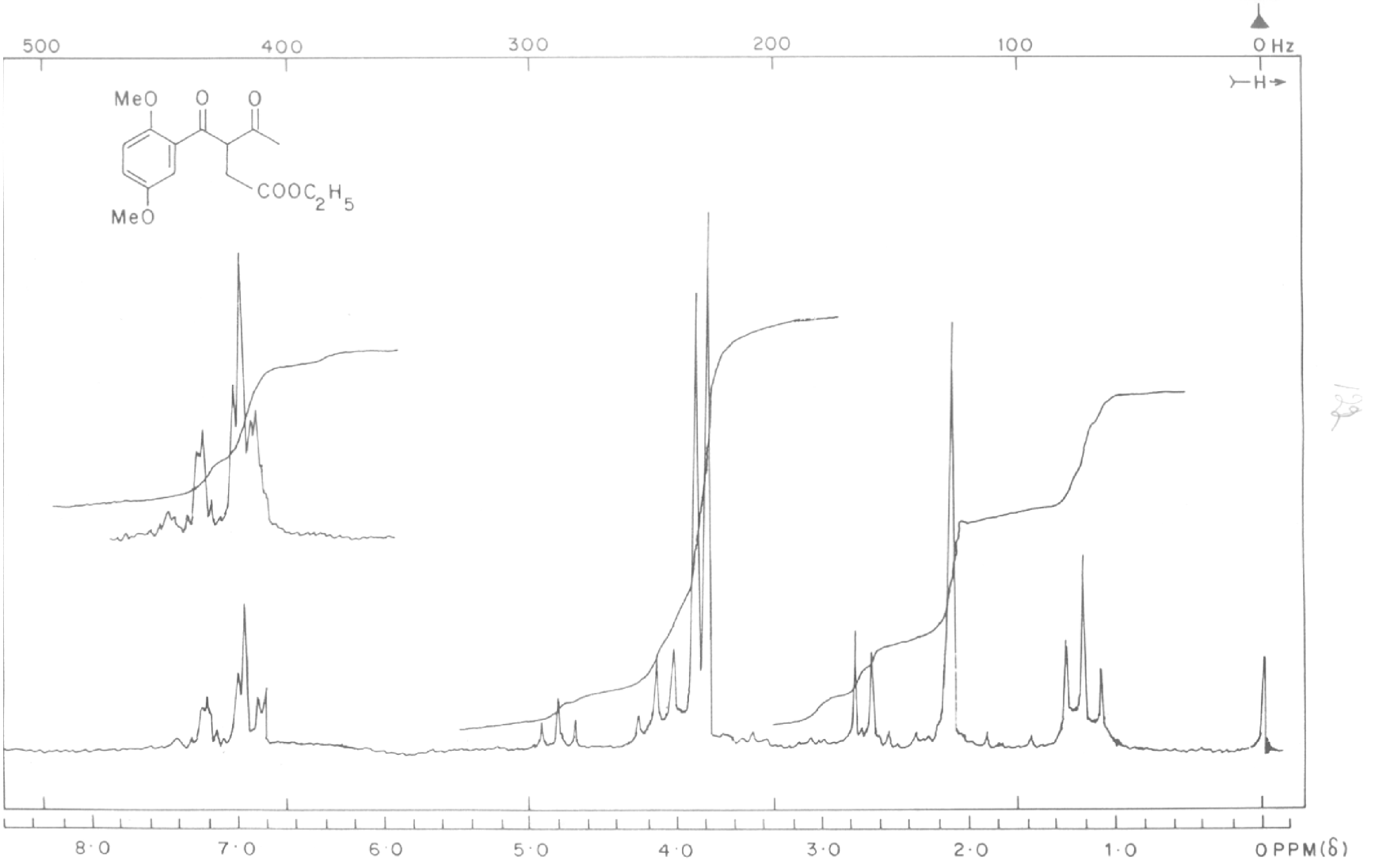


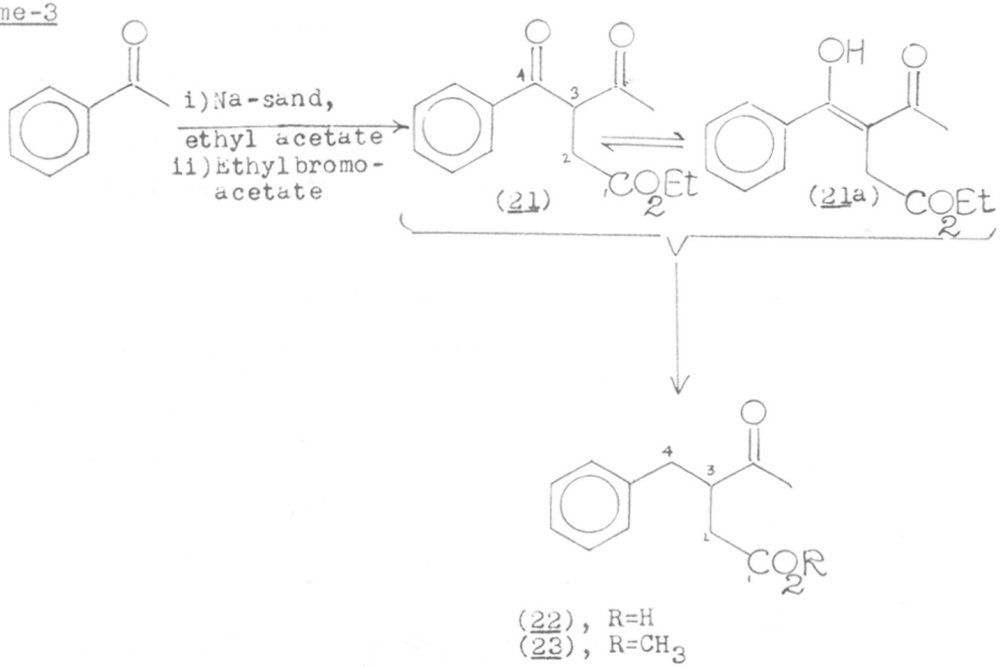

FIG. 2. $^1$H-NMR SPECTRUM OF COMPOUND (19) IN $CCl_4$

123

at ambient temperature in acetic acid. Under similar conditions, compound (19) failed to undergo hydrogenation as the starting material was recovered quantitatively. Change of solvent (ethyl acetate, ethanol), did not bring any success. Even with perchloric acid in ethanol, no reaction was observed.

This failure could be attributed to the presence of O-methyl group causing a steric hindrance. In order to prove this, the reduction of diketoester (21) (Scheme-3) was attempted under Woodward's conditions (instead of acetic acid catalytic amount of perchloric acid in ethanol was used). The

Scheme-3




(22), R=H
(23), R=$CH_3$

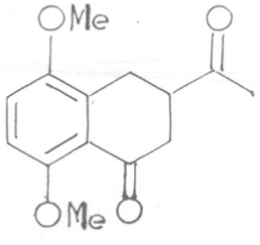
expected reduced product (22) was obtained in 80% yield. The

124

structure of 22 was proved by comparison of its $^1$H-NMR spectrum (Fig. 3) with that of 21 (Fig. 4). The methine at C-3 which appeared as a triplet in 21 at 4.80 ppm was observed as a multiplet at 2.93 ppm in 22. The resonances due to two methylenes at C-2 and C-4 appeared as multiplet at 2.2 - 2.8 ppm. The other protons had comparable chemical shifts.

Further confirmation of structure 22 was gleaned by converting it into its methyl ester (23) with diazomethane.

It is worthwhile mentioning here that the drastic conditions had to be employed for the reduction of benzylic ketone of 21 because of the keto enol tautomerism of the 1,3-diketone. As it has been observed from $^1$H-NMR studies (page ) that enol form predominated in solutions. In case of the methoxy analogue (19) the reduction failed because of steric hindrance due to O-methyl substituent in the aromatic ring. However, no such difficulty was encountered by Wong et al.[1] in reducing the benzylic ketone of 10a inspite of the presence of O-methyl group at C-8.




(10a)

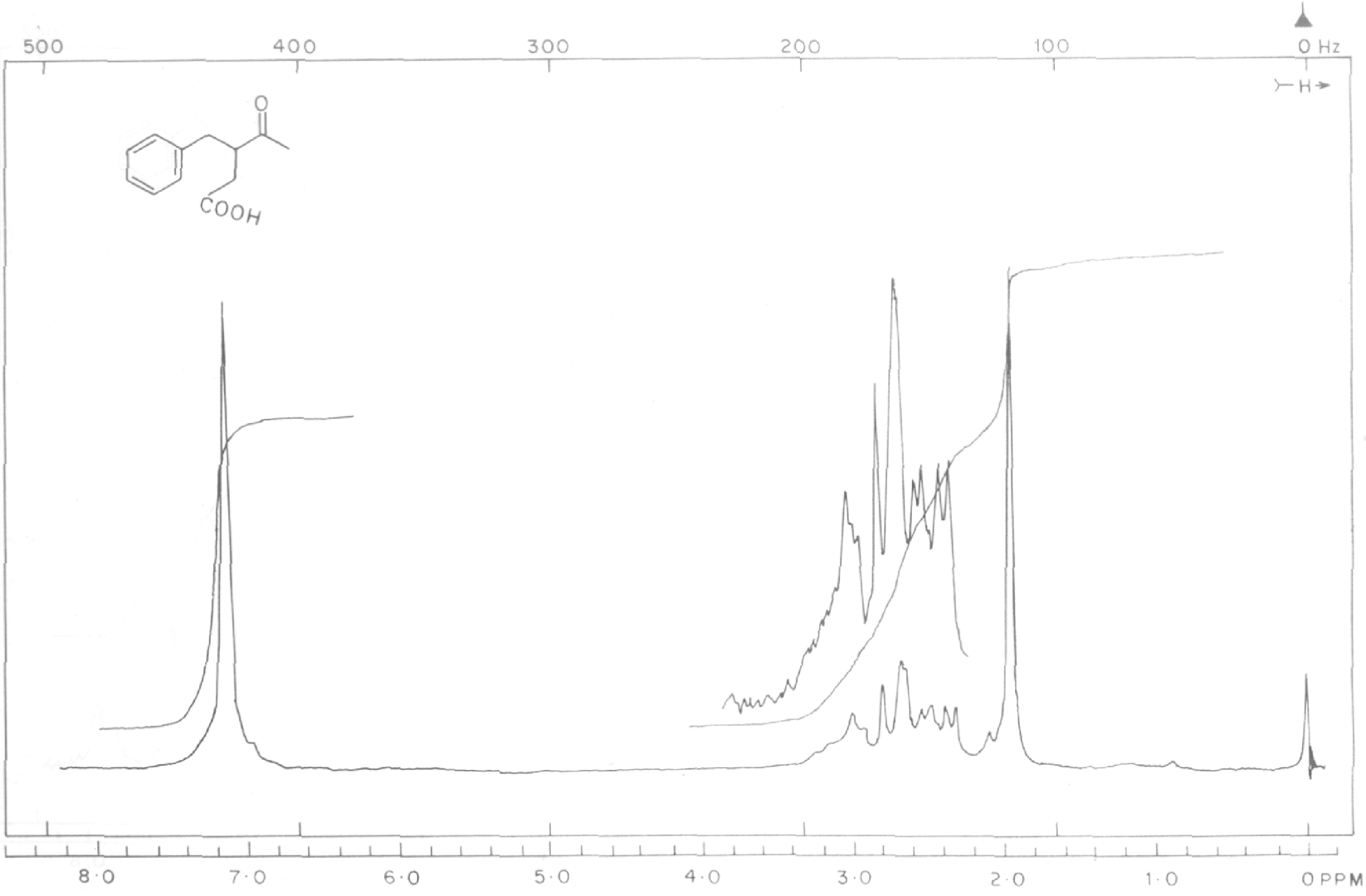



FIG. 3. $^{1}$H-NMR SPECTRUM OF COMPOUND (22) IN $CCl_4$

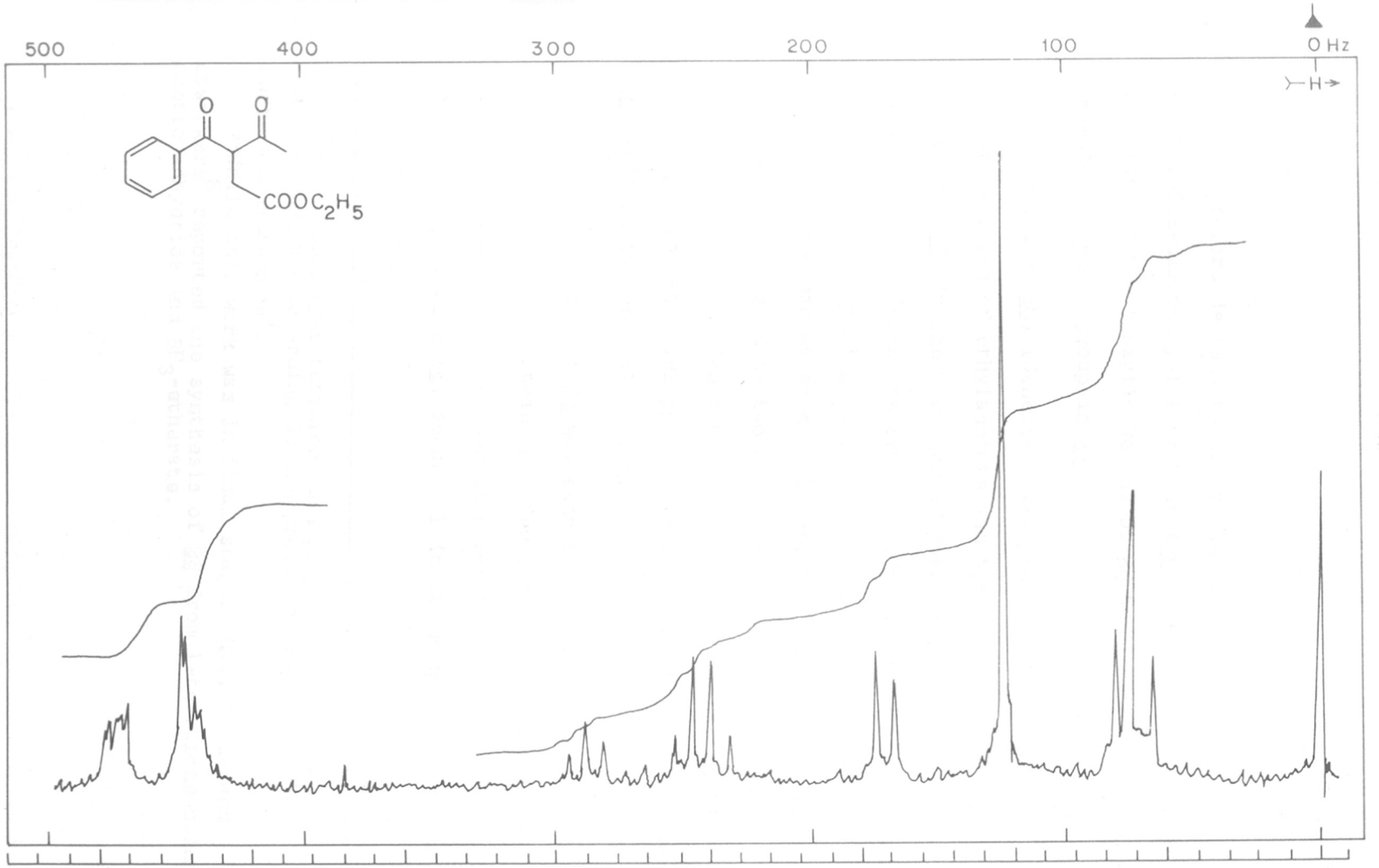



FIG. 4.. $^{1}$H-NMR SPECTRUM OF COMPOUND (21) IN $CCl_4$

It was therefore decided to study the hydrogenation of 2-acetyl-5,8-dimethoxy-1-tetralone (28) because of the close similarity of the benzylic ketone of 28 and 5, except for the presence of β-keto group in 28.

Compound (28) (Scheme-4) was prepared by Claisen-Schmidt reaction of ethylacetate and 5,8-dimethoxy-1-tetralone* (27) in the presence of pulverized sodium (80% yield). In the $^1$H-NMR spectrum (Fig. 5) the peak at 2.33 ppm was assigned to acetyl group, the multiplet in the region 2.3 - 3.0 ppm assigned to methylenes, two singlets at 3.80 and 3.83 ppm assigned to two methoxyls and two doublets at 6.66 and 6.96 ppm assigned to two aromatic protons, enolic proton appeared at 15.82 ppm, indicating that the β-diketone (28)** existed in the enolic form.

Hydrogenation of 28 was executed in the presence of 10% Pd-C in ethanol containing a few drops of conc. hydrochloric acid at 30 psi at room temperature to give 2-acetyl-5,8-dimethoxytetralin (6) identical in all respects with the reported[1] compound.

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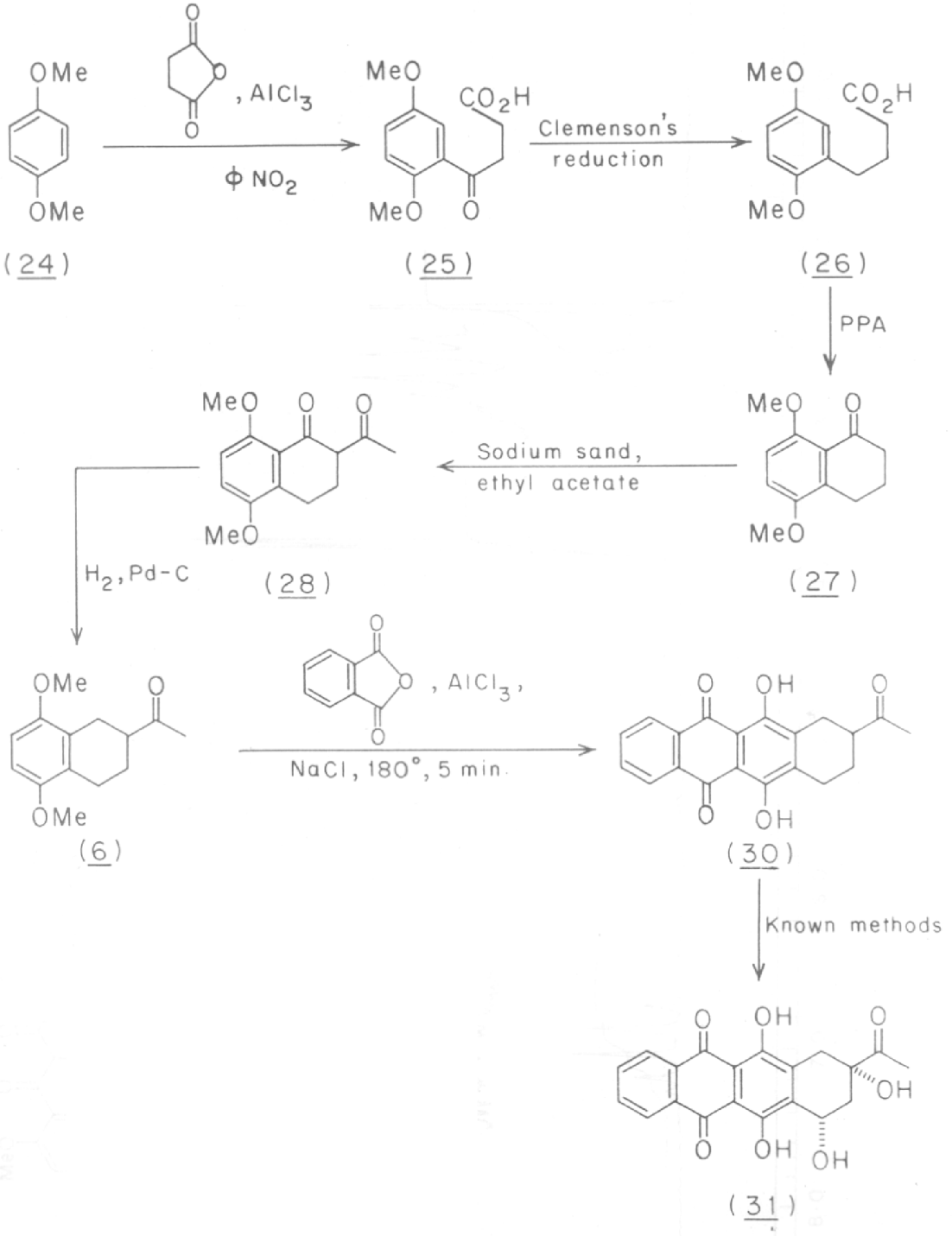
*5,8-Dimethoxy-1-tetralone was prepared from 1,4-dimethoxybenzene according to the procedure reported by Moore and coworkers[4].

**While this work was in final stages, R.J. Blade and coworkers[8] reported the synthesis of 28 from 1-tetralone using acetic anhydride and $BF_3$-etherate.

SCHEME 4


OMe
OMe
(24)
, AlCl3
φ NO2
MeO
CO2H
MeO
O
(25)
Clemenson's
reduction
MeO
CO2H
MeO
(26)
PPA
MeO
O
MeO
(27)
Sodium sand,
ethyl acetate
MeO
O
O
MeO
(28)
H2, Pd-C
OMe
O
OMe
(6)
, AlCl3,
NaCl, 180°, 5 min.
O
OH
O
O
OH
(30)
Known methods
O
OH
O
OH
O
OH
OH
(31)

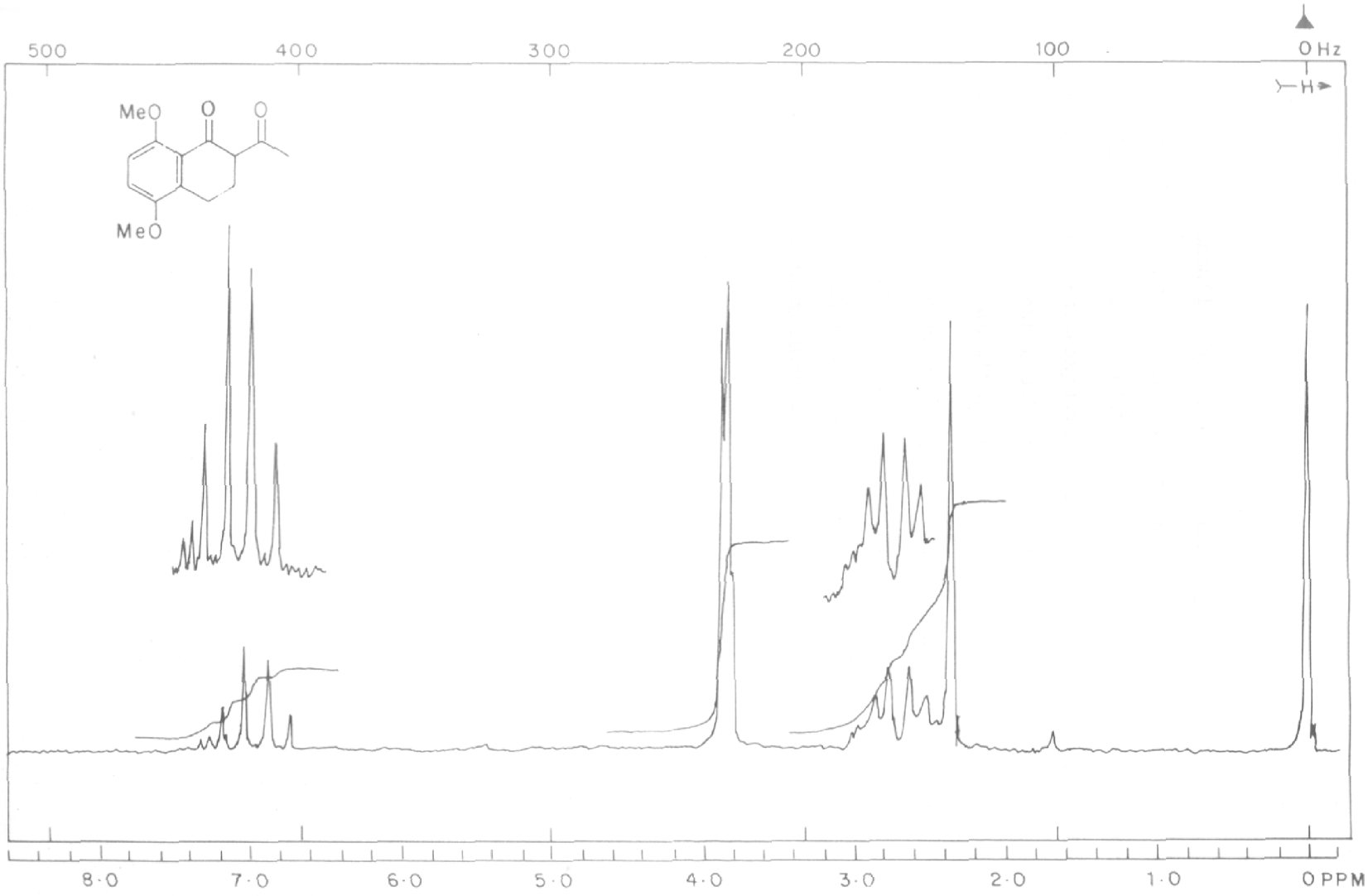



FIG. 5. $^{1}$H-NMR SPECTRUM OF COMPOUND (27) IN $CDCl_3$

Condensation of acetyltetralin (6) with phthalic anhydride in the presence of sodium aluminium chloride ($AlCl_3$, NaCl melt) at 180° for 5 minutes afforded the expected 4-demethoxy-7,9-dideoxydaunomycinone (30) in 95% yield. The physical and spectral data of 30 were identical with the compound made by an alternate route in this laboratory[5].

Since conversion of 30 to 4-demethoxydaunomycinone (31) has already been done by several groups[1,6,7], the preparation of 30 constituted a complete synthesis of 4-demethoxydaunomycinone.

131

# EXPERIMENTAL

2,5-Dimethoxy acetylacetophenone (18)

A mixture of 2,5-dimethoxyacetophenone (17, 7.0 g, 38.8 m.mol) and ethyl acetate (75.0 ml) was added dropwise to an ice-cold suspension of pulverized sodium (2.0 g, 0.08 atom) in dry ether (10 ml) with mechanical stirring. The mixture was refluxed for 5 hours, then allowed to stir at room temperature overnight.

Solvent was distilled out at reduced pressure and the solid was filtered, washed to remove organic impurities with benzene. The crystalline sodium salt (18, 9.1 g, 96%) was submitted as such for further condensation.

A small amount of sodium salt was acidified with acetic acid to give 18a. $^1$H-NMR ($CCl_4$) $\delta$ 2.10 (s, 3H, $-\overset{O}{\overset{\|}{C}}-CH_3$), 3.76 (s, 3H, -OMe), 3.83 (s, 3H, OMe), 6.36 (s, 1H, CH), 6.8 - 7.5 (m, 3H, aromatic). $M^+$ 222.

Analysis: Calculated for $C_{12}H_{14}O_4$: C, 69.36; H, 6.30. Found: C, 69.44; H, 6.39%.

Ethyl 3-(2,5-dimethoxybenzoyl)levulinate (19)

To a refluxing suspension of sodiobenzoyl acetone (18, 5.0 g, 20.5 m.mol) in dry tetrahydrofuran (60 ml), ethyl bromoacetate (4.1 g, 24.5 m.mol) was added. After 15 hours

132

of refluxing, it was cooled and filtered. The filtrate was concentrated and the residue was vacuum distilled to afford the product (19, 5.0 g, 80%), b.p. 240-5°/2.5 mm of Hg. $^1$H-NMR ($CCl_4$): δ 1.20 (t, 3H, $CH_2$-$CH_3$), 2.10 (s, 3H, $COCH_3$), 2.76 (d, 1H, CH-$CH_2$-$CO_2Et$), 3.8 - 4.3 (m, 8H, OMe x2, $CH_2$.$CH_3$) 4.76 (t, 1H, CO-CH-CO), 6.7 - 7.4 (m, 3H, aromatic) $M^+$ 308.

Analysis: Calculated for $C_{16}H_{20}O_6$: C, 62.33; H, 6.49; Found: C, 62.52; H, 6.52%.

Ethyl 3-benzoyl levulinate (21)

To an ice-cold suspension of pulverised sodium (2.50 g, 0.108 atom) in absolute ether (5 ml) a mixture of acetophenone (6.0 g, 50 m.mol), ethylacetate (dry, 8 ml) in ether (20 ml) was added dropwise with stirring at room temperature. After complete addition mixture was refluxed for four hr. then allowed to stir at room temperature overnight. Solvent was distilled out and the separated salt (7.0 g, 76%) was filtered and washed with chloroform to remove organic impurities.

The above salt (2.0 g, 10.87 m.mol) in dry THF (25 ml) was treated with ethylbromoacetate (1.27 ml, 11.41 m.mol). Contents were refluxed for 12 hr, worked up as given earlier to give 21, (2.10 g, 74%), b.p. 140-141°/0.3 mm. $^1$H-NMR($CCl_4$):

δ 1.26 (t, 3H, $CH_2$-$C\underline{H}_3$), 2.06 (s, 3H, $\overset{O}{\overset{\|}{C}}$-$CH_3$) 2.86 (d, 2H, CH-$C\underline{H}_2$-$CO_2Et$), 4.06 (q, 2H, $C\underline{H}_2$-$CH_3$), 4.76 (t, 1H, $\overset{O}{\overset{\|}{C}}$-$C\underline{H}$-$\overset{O}{\overset{\|}{C}}$ ), 7.4 (m, 3H, aromatic), 7.9 (m, 2H, aromatic).
$CH_2CO_2Et$

$M^+$ 248.

Analysis: Calculated for $C_{14}H_{16}O_4$: C, 67.74; H, 6.45. Found: C, 67.81; H, 6.49%.

3-Benzyllevullinic acid (22)

A mixture of the diketo ester (21, 10.0 g, 40.3 m.mol) in perchloric acid (8 ml), ethanol (120 ml) and palladium on carbon (10%, 0.50 g) was hydrogenated in a Parr hydrogenator at 200 psi at 30° for 3 hr. Catalyst was filtered, diluted with water and ethanol, was removed under reduced pressure, and the aqueous layer was extracted with chloroform and dried over anhydrous $Na_2SO_4$. Solvent was removed and the residue was chromatographed over a silica gel column acetone:pet.ether, (2:98) to give the acid (22, 6.60 g, 80%) as a syrup $^1$H-NMR ($CCl_4$): δ 1.96 (s, 3H, $\overset{O}{\overset{\|}{C}}$-$C\underline{H}_3$), 2.2 - 3.4 (bm, 5H, $CH_2$ x2, >$C\underline{H}$), 7.1 (s, 5H, aromatic). $M^+$ 206.

Analysis: Calculated for: $C_{12}H_{14}O_3$: C, 69.90; H, 6.79. Found: C, 70.25; H, 6.81%.

Methyl 3-benzyllevullinate (23)

The ketoacid (22, 3.0 g, 14.5 m.mol), in ether (30 ml)

134

was treated with excess of etheral diazomethane at 0°. After 1 hr excess of diazomethane was decomposed with acetic acid, solvent was removed and the resulting product was chromatographed over a column of silica gel using acetone-pet. ether (5:95 as eluent) to get the methyl ester (23, 2.60 g, 81%). $^1$H-NMR ($CCl_4$) δ 2.0 (s, 3H, $\overset{O}{\overset{\|}{C}}$-$CH_3$), 2.2 - 3.4 (bm, 5H, $CH_2$ X2, C-H), 3.6 (s, 3H, $CO_2CH_3$), 7.3 (s, 5H, aromatic). $M^+$ 220.

Analysis: Calculated for: $C_{13}H_{16}O_3$: C, 70.90; H, 7.27. Found: C, 71.40; H, 7.21%.

2-[2',5'-Dimethoxybenzoyl]propionic acid (25)

To an ice-cold solution of p-dimethoxybenzene (24, 10.5 g, 76 m.mol), succinic anhydride (8.8 g, 88 m.mol) in nitrobenzene (65.0 ml), aluminium chloride (22.5 g, 168 m.mole) was added and the contents were stirred for 3.5 hr at room temperature. The reaction mixture was poured over crushed ice, containing conc. HCl and the organic layer was separated. Solvent was removed by steam distillation. The crude keto acid was purified by dissolving it in 10% sodium bicarbonate solution and extracted with ethyl acetate. The aq. layer was neutralized by conc. HCl and solvent separated was filtered and keto acid (25, 17.5 g, 94%) was obtained. Melting point 100-103° (lit.[4] 101-2°).

Analysis: Calculated for $C_{12}H_{14}O_5$: C, 60.50; H, 5.88. Found: C, 60.71; H, 5.93%.

135

4-[2',5'-Dimethoxyphenyl]Butyric acid (26)

Zinc wool (7.5 g), mercuric chloride (0.5 g) conc. HCl (0.5 ml) and water (8 ml) were shaken efficiently. Contents were decanted and to the zinc amalgum so obtained, the keto acid (25, 2.4 g, 10.1 m.mol) toluene (30 ml), conc.HCl (7.0 ml) and water (5.0 ml) was added. Contents were heated on water-bath for 30 hrs. Conc.HCl (7 ml) added after 6 hr. The organic layer was separated, washed with water, dried over anhydrous $Na_2SO_4$, and solvent was removed under reduced pressure to get 4-[2',5'-Dimethoxyphenyl]butyric acid as a low melting solid (26, 2.0 g, 88%), m.p. 67-68° (lit.[4] 68-69°) $M^+$ 224.

Analysis: Calculated for: $C_{12}H_{16}O_4$: C, 64.28; H, 7.14. Found: C, 64.45; H, 7.28%.

5,8-Dimethoxy-1-tetralone (27)

Polyphosphoric acid (PPA) was prepared from $P_2O_5$ (90 g) and syrupy phosphoric acid (40 ml) by heating at 80°C for 1 hr and the dimethoxy acid (26, 2.50 g, 11.16 m.mol) was added in one lot. This was thoroughly stirred at this temperature for 5 minutes and the homogeneous reaction mixture was left aside at 80° for another 45 min. without stirring. The reddish brown product, while still hot, was at once poured on crushed ice. The material was left aside overnight to

136

decompose the complex. The product was taken up in chloroform (30 ml), washed with water, aqueous NaOH and brine dried over anhydrous $Na_2SO_4$ and concentrated to give 27 (1.374 g, 60%) as a low melting solid (60-62°) (lit.[4] m.p. 58-62°). $^1$H-NMR ($CCl_4$): δ 1.8 - 2.9 (m, 6H, 3 x $CH_2$), 3.66 (d, 6H, 2 x $OCH_3$), 6.33 (m, 2H, aromatic).

Analysis: Calculated for $C_{12}H_{14}O_3$: C, 55.34; H, 6.79. Found: C, 55.62; H, 6.84%.

2-Acetyl-5,8-dimethoxy-1-tetralone (6)

A mixture of α-tetralone ( 27, 0.400 g, 1.94 m.mol) and ethyl acetate (2.0 ml) was added to an ice-cold suspension of pulverised sodium (0.400 mg, 0.017 atom) in dry ether (2 ml). Contents were stirred for 24 hr at room temperature under Nitrogen. Water (10 ml) was added and acidified with acetic acid and extracted with chloroform, washed with water and dried over anhydrous $Na_2SO_4$, and chromatographed over silica gel column (5% acetone-benzene) to give the acetyl tetralone (28 ) which was crystallized from benzene-pet. ether as yellow crystalline compound (0.337 g, 70%), m.p. 130-133° (lit.[8] m.p. 131-2°). NMR ($CDCl_3$): δ 2.20 (s, 3H, $COCH_3$), 2.3 - 2.9 (m, 4H, 2 $XCH_2$), 3.81 (s, 3H, OMe), 3.88 (s, 3H, OMe), 6.7 - 7.1 (m, 2H, aromatic), 17.55 (s, 1H, enolic OH), $M^+$ 248.

137

Analysis: Calculated for $C_{14}H_{16}O_4$: C, 67.74; H, 6.45. Found: C, 67.89; H, 6.59%.

Hydrogenation

A mixture of diketone (28, 0.250 g, 1.008 m.mol), palladium-carbon (0.200 g), conc. HCl (0.75 ml), water (1.75 ml) and ethanol (25 ml) was shaken under pressure of hydrogen (40 lb/in$^2$) for 3 hr. Catalyst was filtered off. Ethanol was removed under reduced pressure diluted with water, extracted with methylene chloride and dried over anhydrous $Na_2SO_4$. Chromatography of the product on silica gel column (5% acetone-pet. ether) gave the desired product (29, 0.141 g, 60%) as low melting solid m.p. 80-81°(lit.[1] 81-82°). $^1$H-NMR ($CDCl_3$): δ 2.20 (s, 3H, $COCH_3$), 2.2 - 3.2 (m, 7H, 3X $-CH_2$ , CH), 3.73 (s, 6H, 2 X $OCH_3$), 6.46 (s, 2H, H-6 and H-7). $M^+$ 234.

Analysis: Calculated for $C_{14}H_{18}O_3$: C, 71.79; H, 7.69 Found: C, 71.83; H, 7.72%.

Friedel-Craft reaction of 29 with phthalic anhydride

To a melt of aluminium chloride (0.500 g, 3.74 m.mol) and sodium chloride (0.100 g, 1.71 m.mol) at 180°C, a mixture of tetralin (29, 0.050 g, 0.213 m.mol) and phthalic anhydride (0.100 g, 0.675 m.mol) was added, contents were stirred for 5 min. Reaction mixture was digested with a saturated solution of oxalic acid (20 ml), extracted with methylene chloride and dried over anhydrous $Na_2SO_4$. Removal

of the solvent afforded the quinone (0.064 g, 90%) as red needles, m.p. 198-202° (lit.[6] m.p. 198-202°). NMR($CDCl_3$): δ 1.90 (m, 2H, $CH_2$), 1.95 (m, 1H, CH), 2.31 (s, 3H, $COCH_3$), 2.75 (m, 2H, benzylic), 3.10 (m, 2H, benzylic), 7.80 (m, 2H, aromatic), 8.30 (m, 2H, aromatic), 13.49 (s, 1H, OH), 13.52 (s, 1H, OH).

Analysis: Calculated for $C_{20}H_{16}O_5$: C, 71.42; H, 4.76. Found: C, 71.33; H, 4.82%.

139

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# SECTION – II

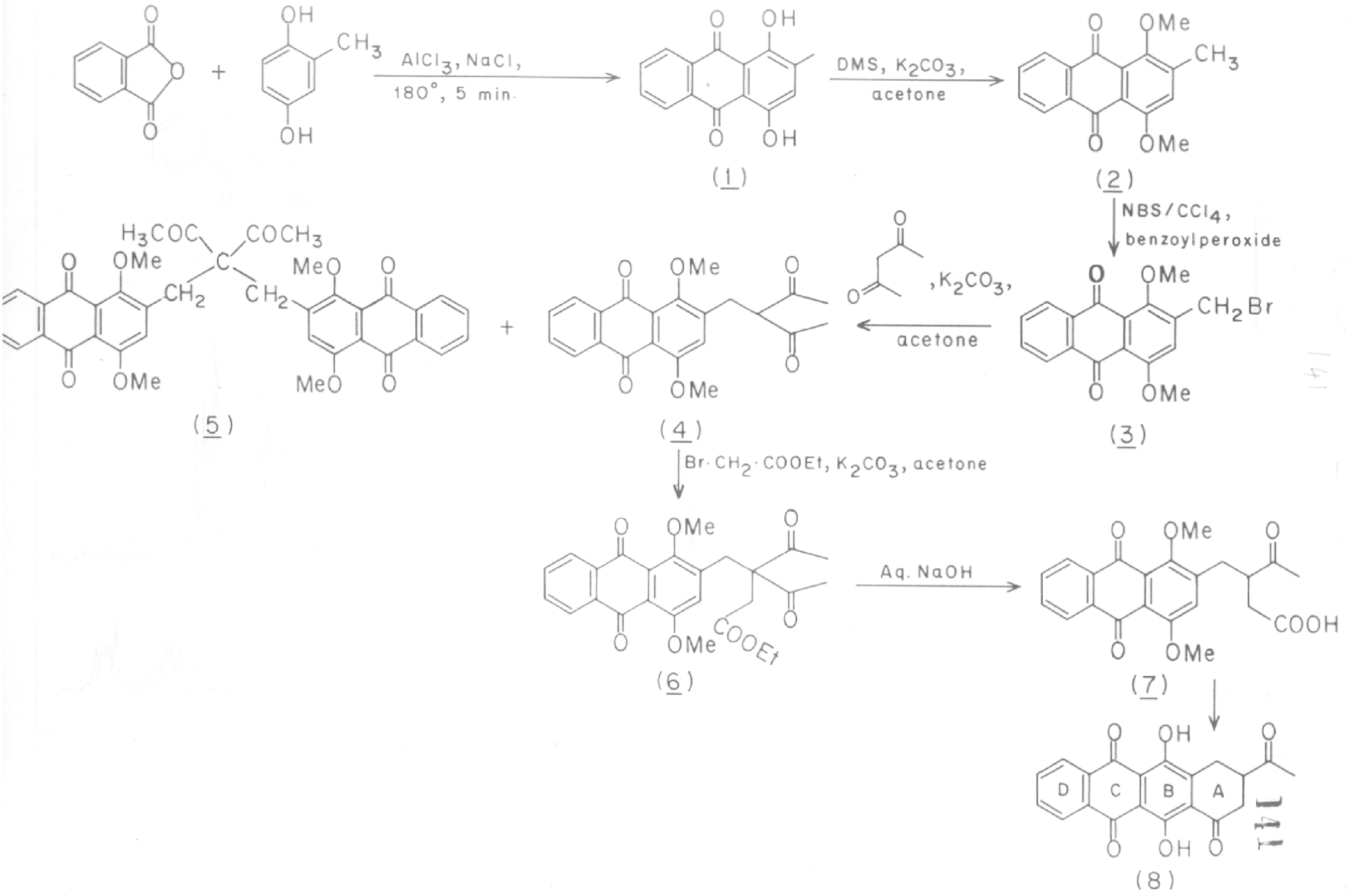
## SYNTHESIS STARTING FROM METHYLQUINIZARIN

In the previous chapter studies were made towards the synthesis of (±)4-demethoxydaunomycinone using quinizarin derivatives as precursors. In this chapter methyl qunizarin was chosen as the starting material with a view in mind that the methyl function could be successfully transformed into ring-A (Scheme-1). Methylquinizarin has been prepared by fusion of methyl hydroquinone with phthalic anhydride[1].

O-Methylation with dimethylsulphate and potassium carbonate in acetone followed by treatment of the resulting dimethyl ether (2) with N-bromosuccinimide in the presence of catalytic amount of benzoylperoxide in refluxing carbon tetrachloride gave the 2-bromomethyl-1,4-dimethoxyanthraquinone (3) in 60% yield. Its structure was supported by $^1$H-NMR spectrum.

Condensation of the ω-bromide (3) with 2,4-pentanedione was effected in the presence of anhydrous potassium carbonate[2] in acetone at room temperature giving a mixture of 3-acetyl-4-(1',4'-dimethoxyanthraquinonyl)butanone (4) and the dicondensed product (5) in 47 and 40% yield respectively. They were separated by fractional crystallization. The $^1$H-NMR spectrum of 4 (Fig.1) revealed two acetyl signals at 2.06 and 2.16 ppm, a singlet for two O-methyl groups at

SCHEME 1


AlCl3, NaCl,
180°, 5 min.
DMS, K2CO3,
acetone
NBS/CCl4,
benzoylperoxide
,K2CO3,
acetone
Br·CH2·COOEt, K2CO3, acetone
Aq. NaOH
(1)
(2)
(3)
(4)
(5)
(6)
(7)
(8)
D
C
B
A

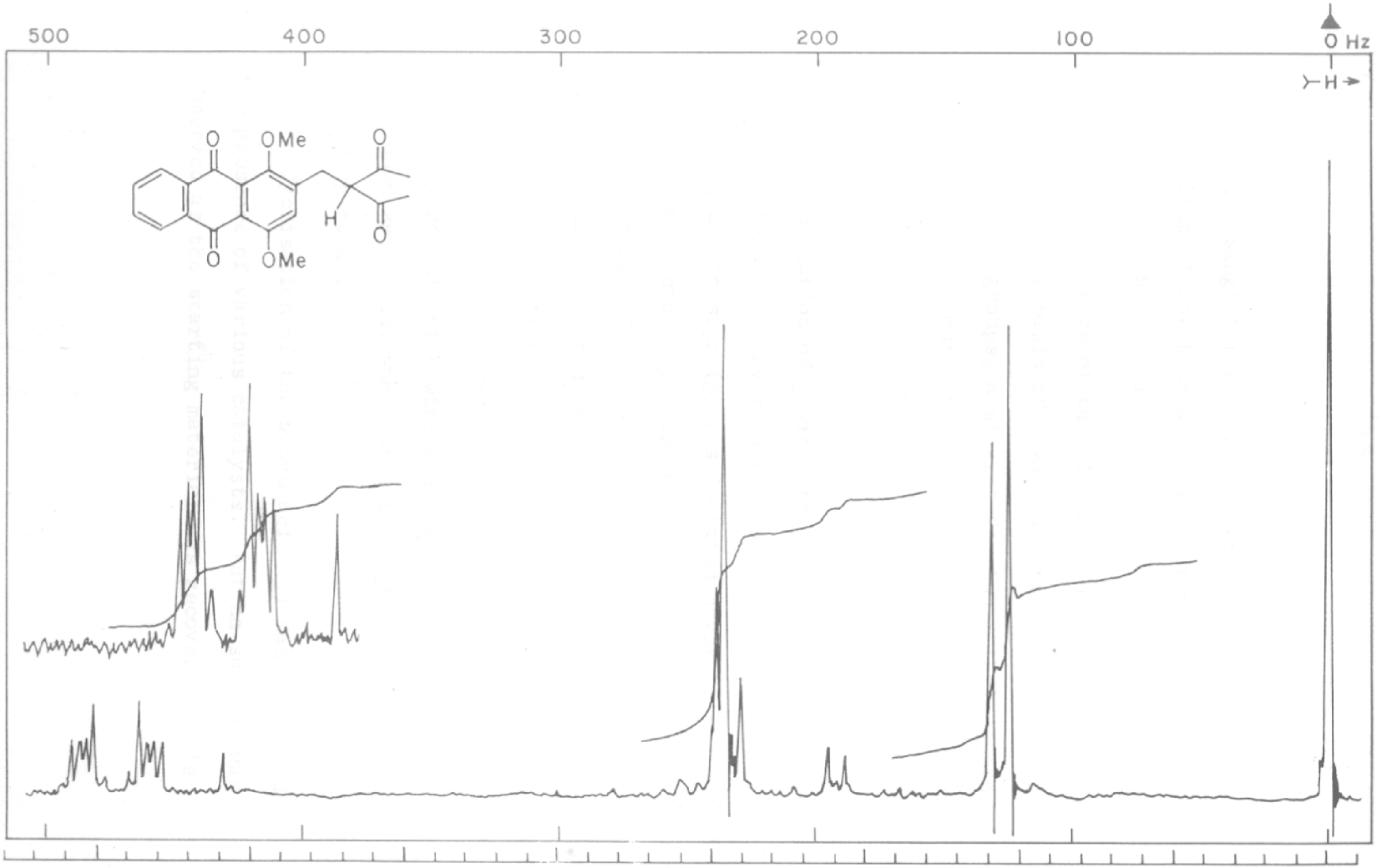



FIG. 1. $^{1}$H-NMR SPECTRUM OF COMPOUND (4) IN $CDCl_3$

143

3.83 ppm, a singlet for benzylic methylene at 3.90 ppm and a multiplet for four aromatic protons in the region 6.9 - 8.2 ppm thus confirmed the assigned structure (4).

The structure of the dicondensed product (5) was suggested on the basis of $^1$H-NMR spectrum, where a singlet for two acetyl groups, a singlet for two methylene groups two singlets for four methoxy groups and multiplets for eight aromatic protons were in conformation with the dimeric structure (5).

Condensation of 4 with ethylbromoacetate was carried out in acetone and anhydrous potassium carbonate and the resulting diketoester (6) was isolated crystalline in 30% yield. Its structure (6) was supported by $^1$H-NMR spectrum (Fig.2) where the triplet for methyl group appeared at 1.2 ppm, two acetyl groups resonated as a singlet at 2.10 ppm, methylene appeared as a singlet at 2.90 ppm and the remaining signals were in complete agreement with the assigned structure (6).

Hydrolysis of 6 with aqueous sodium hydroxide gave the known 3-keto acid, whose structure (7) was supported by $^1$H-NMR spectrum.

Cyclisation of the above acid (7) was attempted in the presence of various catalysts. But no success was observed as the starting material was recovered. This

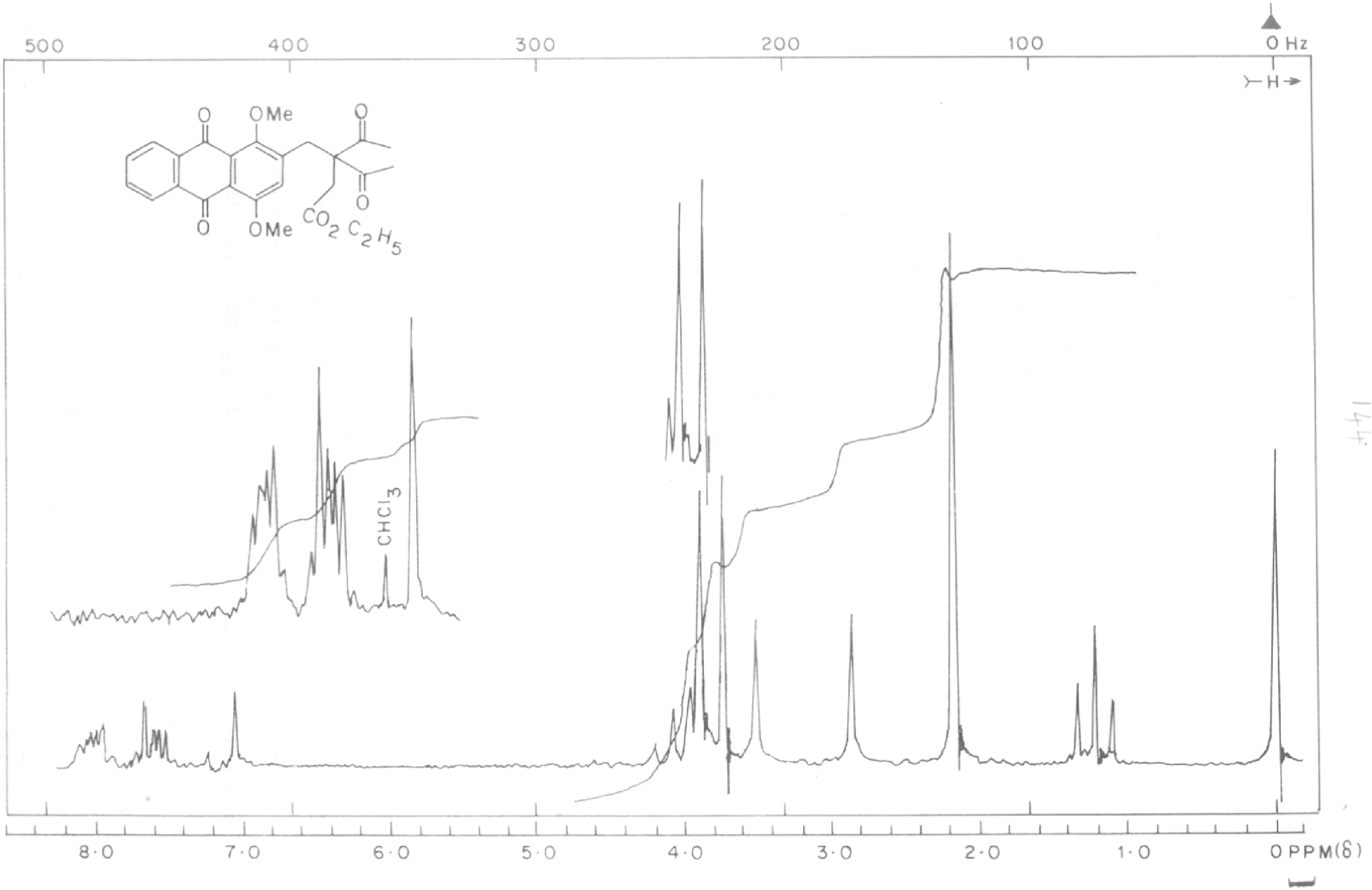
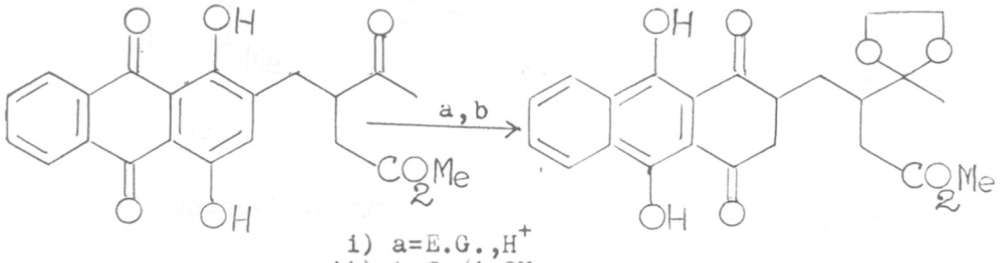


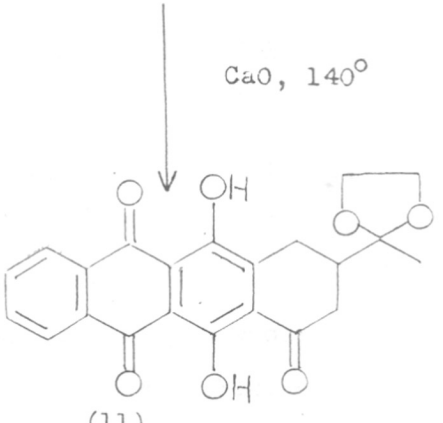

FIG. 2. $^1$H-NMR SPECTRUM OF COMPOUND (6) IN $CDCl_3$

failure was attributed to strong electron withdrawing properties of the anthraquinone system. Similar difficulties were encountered by Sih and coworkers[1] during cyclisation of (9). However, after ketalisation and reduction with zinc



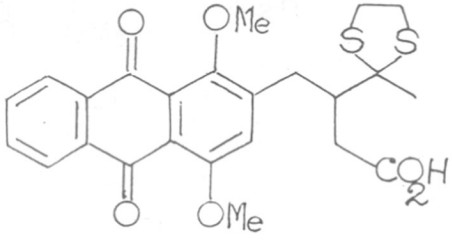

i) a=E.G.,$H^+$
ii) b=Zn/AcOH

(9) (10)




(11)

and acetic acid the cyclisation occurred in very poor yield. Likewise Whitlock et al.[3] successfully cyclised the tetramethoxy acid (13) in good yield. However, with the

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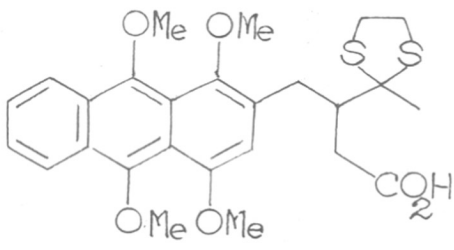



(13)

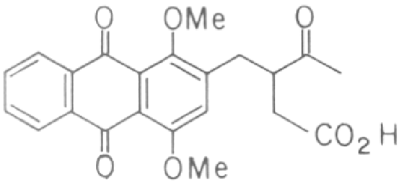
parent compound (12) cyclization under various conditions failed.

It was therefore decided to transform the keto acid (7) into the tetramethoxy compound (13) by the following sequence of reaction (Scheme-2).

Methylation of ketoacid (7) with dimethylsulphate and potassium carbonate in acetone gave the methyl ester (14) which was protected with ethane-dithiol in the presence of $BF_3$-etherate to afford thioketal ester (15), whose structure was demonstrated by $^1H$-NMR spectrum (Fig. 3 ) in which the expected signals for methyl group, methoxy group, methylenes and aromatic protons appeared at the expected chemical shifts. Protected ester (15) was reductively methylated using sodiumdithionite and dimethyl-sulphate in acetone and aqueous potassium hydroxide to give

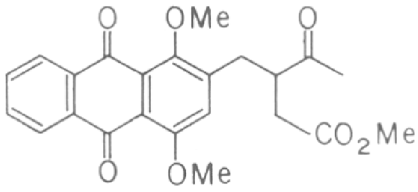
SCHEME 2





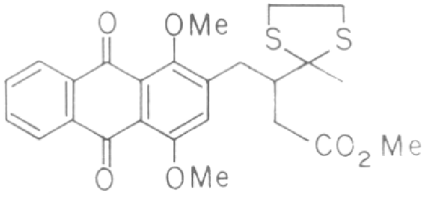

(7)

DMS, $K_2CO_3$, acetone



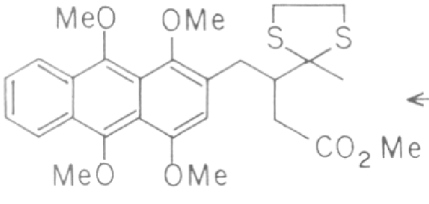

(14)

SH SH, $BF_3$ - etherate, $CHCl_3$



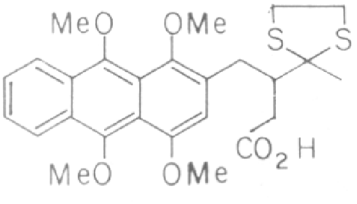

(15)

$Na_2S_2O_4$, DMS, aq. KOH, acetone




(16)

Aq. NaOH, r.t.

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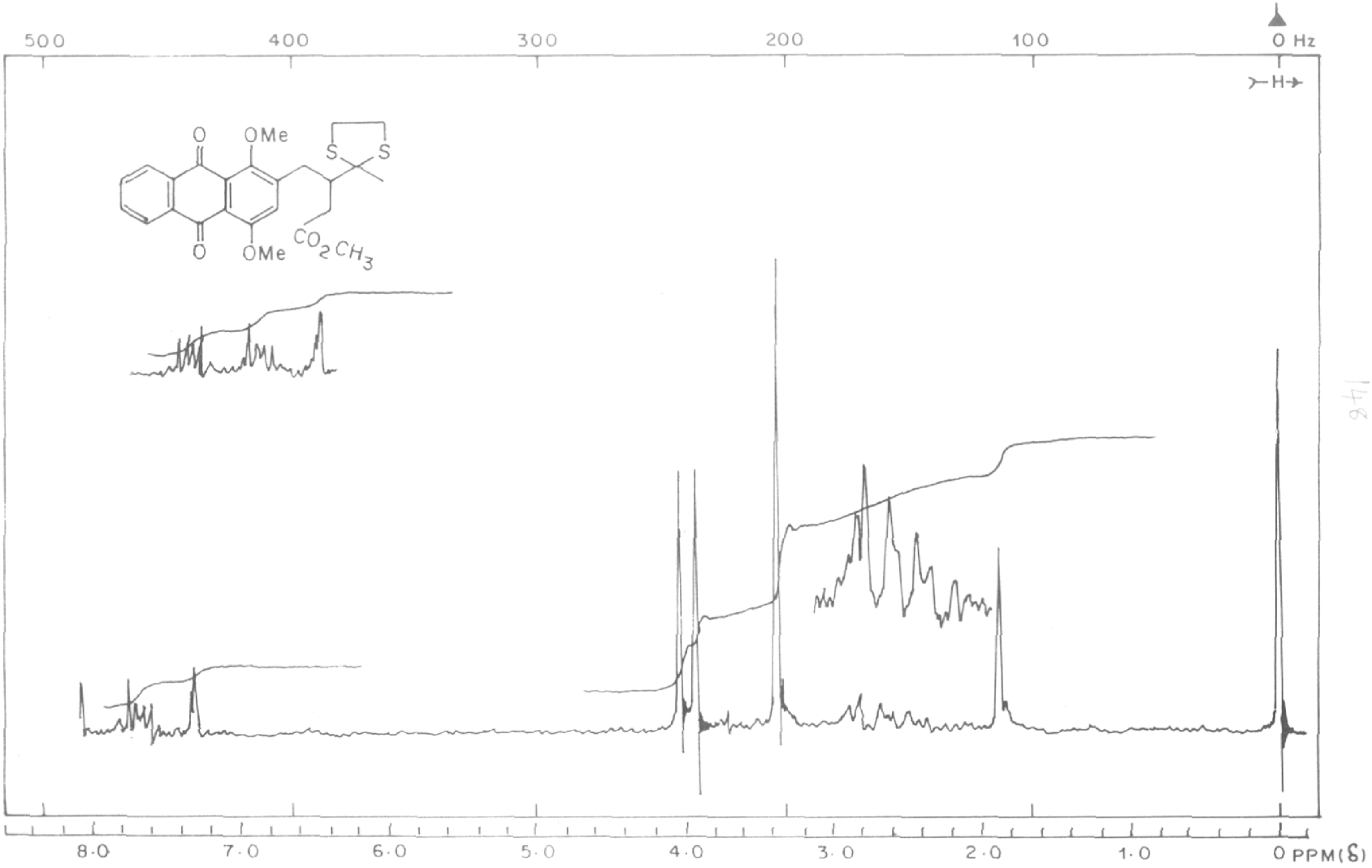


FIG. 3. $^1$H-NMR SPECTRUM OF COMPOUND (15) IN $CDCl_3$

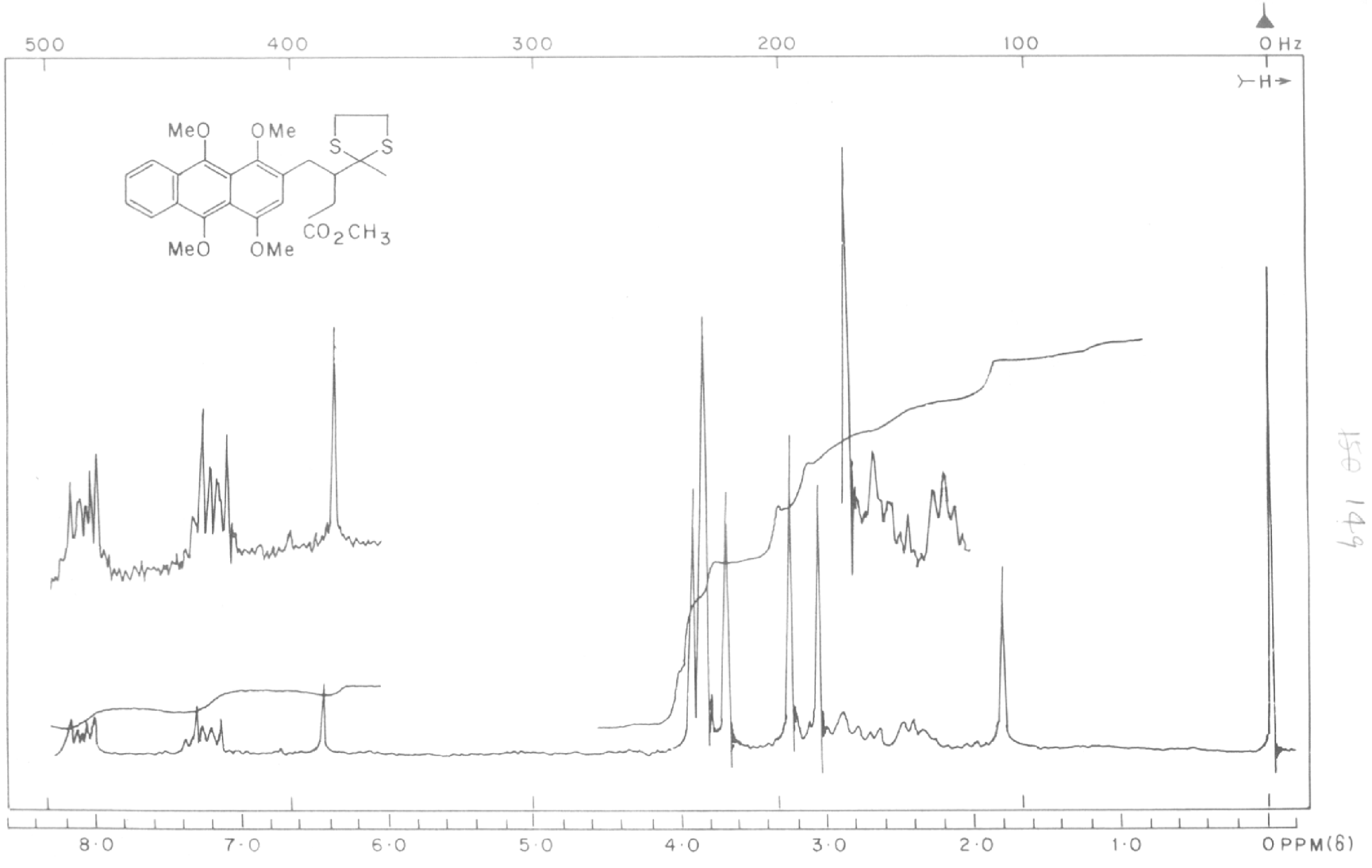


FIG. 4. $^1$H-NMR SPECTRUM OF COMPOUND (16) IN $CCl_4$

the tetramethoxyester (16) in 70% yield. In its (16) $^1$H-NMR spectrum (Fig. 4 ) methyl group resonated as a singlet at $\delta$ 1.80, the methylenes and methine protons appeared as multiplets in the region $\delta$ 2.2 - 3.0, the methyl of the carbomethoxy group appeared as a singlet at $\delta$ 3.26, the four methoxyls appeared as three singlets at $\delta$ 3.70, 3.86 (2X-$OCH_3$), 4.03 and the aromatic proton at C-3' appeared as a singlet at $\delta$ 6.50, while other aromatic protons appeared as multiplets in the region $\delta$ 7.0 - 8.2 thus confirming the assigned structure (16).

Hydrolysis of 16 gave the known tetramethoxy acid (13), whose spectral analysis was in complete agreement with the reported structure[3].

Attempted cyclisation of the above acid under the similar conditions reported by Whitlock et al.[3] did not work in the author's hands. Therefore further work on this approach was abandoned.

# EXPERIMENTAL

## 2-Methyl-1,4-dihydroxy anthraquinone (1)

A mixture of anhydrous aluminium chloride (18.4 g, 0.138 mol) and sodium chloride (3.60 g, 0.062 mol) was taken in a 1 L. beaker and heated in an oil bath with stirring at 180-190° till a homogenous melt was formed. To this melt phthalic anhydride (2.0 g, 0.013 mol) and methyl hydroquinone (1.70 g, 0.013 mol) were added and stirred for 10 minutes at 180-190°. After cooling to room temperature the reaction mixture was quenched with 75 ml of ice-water containing concentrated HCl (15 ml) then heated on water-bath for 1 hr and extracted repeatedly with chloroform. The combined chloroform extract was washed with 5% $NaHCO_3$ solution, brine, dried and concentrated to dryness. The residue was recrystallized from $CHCl_3$-$CCl_4$ to afford the pure anthraquinone (1, 2.70 g, 79%), m.p. 178-180° (Lit.[1] m.p. 178-179°). IR (KBr): 1628, 1583, 1460, 1483, 1350, 1273, 1260, 1249, 1218, 726 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) δ 2.30 (s, 3H, $CH_3$), 7.1 (s, 1H, aromatic), 7.75 (m, 2H, aromatic), 8.25 (m, 2H, aromatic), 12.83 (s, 1H, OH), 13.21 (s, 1H, OH), $M^+$ 254.

Analysis: Calculated for $C_{15}H_{10}O_4$: C, 70.86; H, 3.96. Found: C, 70.33; H, 4.13%.

## 2-Methyl-1,4-dimethoxyanthraquinone (2)

A mixture containing dihydroxyanthraquinone (1, 2.70 g,

152

10.62 m.mol), fused potassium carbonate (3.60 g) and dimethyl-sulphate (3 ml, 32.0 m.mol) in dry acetone (150 ml) was refluxed for 24 hr. After usual work up the yellow solid was filtered, washed with water, dried and recrystallised from $CHCl_3$-$CCl_4$ to get dimethoxyanthraquinone (2, 2.70 g, 92%), m.p. 134-135° (lit.[1] m.p. 132.5 - 133.5°). IR (KBr): 1668, 1592, 1330, 1248, 975, 730 $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 2.42 (s, 3H, $C\underline{H}_3$), 3.89 (s, 3H, $OC\underline{H}_3$), 4.01 (s, 3H, $OC\underline{H}_3$), 7.15 (s, 1H, aromatic), 7.69 (m, 2H, aromatic), 8.17 (m, 2H, aromatic), $M^+$ 282.

Analysis: Calculated for $C_{17}H_{14}O_4$: C, 72.33; H, 5.0. Found: C, 71.86; H, 4.93%.

2-Bromomethyl-1,4-dimethoxyanthraquinone (3)

A mixture of dimethoxyanthraquinone (2, 2.56 g, 0.1 m.mol) N-bromosuccinimide (1.70 g, 0.1 m.mol) and benzoylperoxide (5 mg) in carbontetrachloride (310 ml) was refluxed with stirring under nitrogen with the heat of a sun lamp for 2 hr. After cooling, the precipitated succinimide was removed by filtration and the filtrate was evaporated under reduced pressure. Crystallisation of the residue from acetone gave monobromoquinone (3, 1.90 g, 60%), m.p. 184-185° (lit.[1] m.p. 184-186°). IR: 1670, 1590, 1323, 1266, 1240, 1038, 1008, 972, 731 $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 4.00 (s, 6H, $OC\underline{H}_3$ x2),

153

4.61 (s, 2H, $C\underline{H}_2Br$), 7.38 (s, 1H, aromatic), 7.70 (m, 2H, aromatic), 8.15 (m, 2H, aromatic), $M^+$ 362.

Analysis: Calculated for $C_{17}H_{13}O_4Br$: C, 56.53; H, 3.63. Found: C, 56.44; H, 3.71%.

The mother liquor contained a mixture of starting material, monobromo and dibromo compounds.

Acetylacetone product (4)

A mixture containing bromo compound (3, 1.140 g, 3 m.mol), acetylacetone (0.4 ml, 4 m.mol), anhydrous potassium carbonate (2.0 g) and dry acetone (100 ml) was stirred at room temperature for 16 hr. Contents were filtered and washed thoroughly with acetone and the filtrate was concentrated under vacuum in order to remove excess of acetylacetone. The residue was crystallized from acetone hexane to afford the dimer (5, 0.3 g). Removal of the solvent from the mother liquor gave the product (4, 0.70 g, 47%) as a syrupy liquid. $^1$H-NMR ($CDCl_3$): $\delta$ 2.06 (s, 3H, $COC\underline{H}_3$), 2.18 (s, 3H, $COC\underline{H}_3$), 3.90 (m, 8H, $OC\underline{H}_3$ x2, $C\underline{H}_2$), 7.2 (s, 1H, aromatic), 7.7 (m, 2H, aromatic), 8.16 (m, 2H, aromatic), $M^+$ 380.

Analysis: Calculated for $C_{22}H_{20}O_6$: C, 69.47; H, 5.26. Found: C, 69.51; H, 5.31%.

2-(2'-Acetyl-2'-carboethoxymethyl-3'-oxobutyl)-1,4-dimethoxy-anthraquinone (6)

A mixture containing the product (4, 0.380 g, 1 m.mole),

ethylbromoacetate (0.12 ml, 1.1 m.mol), anhydrous potassium carbonate (0.165 g, 1.5 m.mol) in dry acetone (10 ml) was stirred for 20 hr at room temperature. The mixture was filtered and the residue was washed thoroughly with acetone. Solvent was removed and the crude product was crystallized from benzene-hexane to afford the ester (6, 0.14 g, 30%), m.p. 163-164° (Lit.[1] m.p. 163-163.5°). IR: 1724, 1700, 1670, 1281, 1262, 1242, 1157, 1042 $cm^{-1}$. $^1H$-NMR ($CDCl_3$): δ 1.2 (t, 3H, $CO_2CH_2\underline{CH_3}$), 2.1 (s, 6H, $COC\underline{H_3}$ x 2), 2.9 (s, 2H, $C\underline{H_2}$-$CO_2Et$), 3.56 (s, 2H, benzylic $C\underline{H_2}$), 3.76 (s, 3H, $OC\underline{H_3}$), 3.93 (s, 3H, $OC\underline{H_3}$), 4.00 (q, 2H, $CO_2C\underline{H_2}CH_3$), 7.0 (s, 1H, aromatic), 7.6 (m, 2H, aromatic), 8.0 (m, 2H, aromatic), $M^+$ 466.

Analysis: Calculated for $C_{26}H_{26}O_8$: C, 66.95; H, 5.58. Found: C, 66.91; H, 5.61%.

2-(2'-carboxymethyl-3'-oxobutyl)-1,4-dimethoxyanthraquinone (7)

A mixture of ester (6, 2.42 g, 5.19 m.mol) and 8% aqueous sodium hydroxide (10 ml) was stirred under nitrogen at 60° for 3 hr. Contents were diluted with water (5 ml) and extracted with methylenechloride. Aqueous layer was acidified with dil. HCl to give a solid which was filtered, dried and crystallized from benzene-hexane to afford the acid (7, 1.87 g, 91%) as pink coloured solid, m.p. 200-201° (lit.[1] m.p. 200-201.5°. IR: 3300-2800 (broad), 1715, 1668, 1592,

155

1330, 1260, 1243, 1039 $cm^{-1}$. $^1H$-NMR ($CDCl_3$): $\delta$ 2.22 (s, 3H, $COC\underline{H}_3$), 2.4 - 3.6 (m, 5H, $CH_2$ x2, $C\underline{H}$), 3.97 (s, 3H, $OC\underline{H}_3$), 4.0 (s, 3H, $OC\underline{H}_3$), 7.16 (s, 1H, aromatic), 7.76 (m, 2H, aromatic), 8.21 (m, 2H, aromatic), 8.73 (broad, 1H, $COO\underline{H}$, $D_2O$ exchangeable), $M^+$ 396.

Analysis: Calculated for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 66.69; H, 5.11%.

2-(2'-Carbomethoxymethyl-3'-oxobutyl)-1,4-dimethoxyanthraquinone (14)

The acid (7, 1.80 g, 4.5 m.mol) was treated with dimethyl sulfate (0.5 ml, 5 m.mol) and anhydrous potassium carbonate (5 g) in dry acetone (50 ml) under reflux for 1 hr. After usual work up the product was crystallized from benzene-hexane to afford the methyl ester (14, 1.70 g, 91%), m.p. 129-130° (Lit.[1] m.p. 129-130°). IR: 1726, 1703, 1669, 1329, 1314, 1260, 1242, 1039 $cm^{-1}$. $^1H$-NMR ($CDCl_3$): $\delta$ 2.19 (s, 3H, $CO_2C\underline{H}_3$), 2.4 - 3.6 (m, 5H, $C\underline{H}_2$ x2, $C\underline{H}$), 3.61 (s, 3H, $CO_2C\underline{H}_3$), 3.93 (s, 3H, $OC\underline{H}_3$), 4.00 (s, 3H, $OC\underline{H}_3$), 7.13 (s, 1H, aromatic), 7.71 (m, 2H, aromatic), 8.19 (m, 2H, aromatic), $M^+$ 410.

Analysis: Calculated for $C_{23}H_{22}O_7$: C, 67.31; H, 5.40. Found: C, 67.25; H, 5.42%.

Preparation of thioketal ester (15) from 14.

A mixture of ester (14, 0.466 g, 0.958 m.mol),

156

$BF_3$-etherate (0.460 g, 3.24 m.mol), ethanedithiol (0.224 g, 2.4 m.mol) in dry chloroform (15 ml) was stirred overnight at room temperature. Contents were washed with water, potassium hydroxide solution, water and dried over anhydrous $Na_2SO_4$, concentrated and chromatographed over silica gel column (benzene-acetone, 9:1) to get the thioketal ester (15, 0.20 g, 36%) as a syrupy liquid. $^1$H-NMR ($CDCl_3$): $\delta$ 1.86 (s, 3H, $COCH_3$), 2.4 - 2.9 (bm, 5H, $CH_2$ x2, CH), 3.36 (s, 7H, $SCH_2$-$CH_2$-S-, $CO_2CH_3$), 3.90 (s, 3H, $OCH_3$), 4.0 (s, 3H, $OCH_3$), 7.26 (s, 1H, aromatic), 7.7 (m, 2H, aromatic), 8.3 (m, 2H, aromatic), $M^+$ 486.

Analysis: Calculated for $C_{25}H_{26}S_2O_6$: C, 61.72; H, 5.35. Found: C, 61.78; H, 5.39%.

Reductive methylation of 15 to 16.

Quinone (15, 0.20 g, 0.411 m.mol) was dissolved in acetone (10 ml) and 5% aqueous potassium hydroxide (20 ml) was added followed by dimethylsulphate (1.20 g, 9.523 m.mol) and sodiumdithionite (2.0 g, 10.41 m.mol). The mixture was vigorously shaken at room temperature for 45 minutes. Acetone was removed under reduced pressure, diluted with water (20 ml) and kept at room temperature for 1 hr to decompose excess of dimethylsulphate. The reaction mixture was extracted with methylenechloride, washed with water and dried over anhydrous

157

$Na_2SO_4$. Evaporation of solvent gave the crystalline product (16, 0.15 g, 70.6%), m.p. 80-85°. $^1$H-NMR ($CCl_4$): $\delta$ 1.83 (s, 3H, $COCH_3$), 2.1 - 2.9 (bm, 5H, $CH_2$ X2, CH), 3.10 (s, 3H, $CO_2CH_3$), 3.26 (s, 4H, S-$CH_2$-$CH_2$-S), 3.7 - 4.0 (bm, 12H, $OCH_3$ x4), 6.50 (s, 1H, aromatic), 7.3 (m, 2H, aromatic), 8.1 (m, 2H, aromatic), $M^+$ 516.

Analysis: Calculated for $C_{27}H_{32}S_2O_6$: C, 62.79; H, 6.20. Found: C, 62.83; H, 6.17%.

Hydrolysis of tetramethoxythioketal ester 16 to 13.

Ester (16, 0.080 g, 0.155 m.mol) was treated with 8% aqueous sodiumhydroxide (5 ml) and methanol (5 ml) at room temperature for 6 hr. Methanol was removed under reduced pressure, the resulting solution diluted with water and extracted with methylene chloride. The aqueous layer was acidified with acetic acid, extracted with methylene chloride. The methylene chloride layer was washed with water and dried over $Na_2SO_4$. Removal of solvent gave (13, 0.050 g, 65%) as a crystalline solid, m.p. 157-159° (lit.[3] m.p. 158-160°), $M^+$ 502.

Analysis: Calculated for: $C_{26}H_{31}S_2O_6$: C, 62.15; H, 6.17. Found: C,62.43; H, 6.25%.

158

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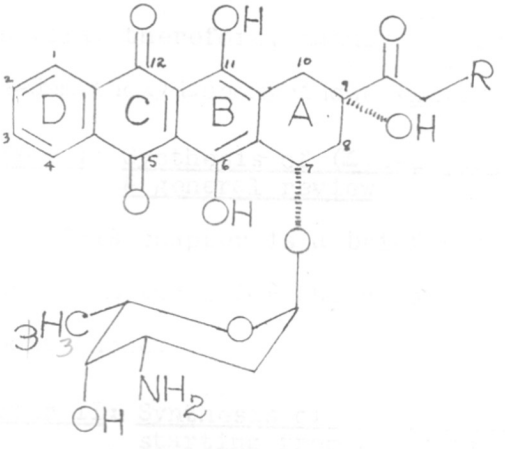
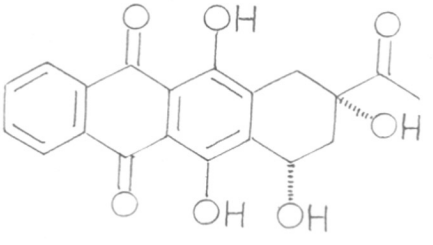
# SUMMARY

159

## S U M M A R Y

The usefulness of certain anthracycline antibiotics as neoplastic agents are now widely accepted. Both daunomycin (1a) and adriamycin (1b) have shown pronounced




(1d)

1a = R=H; R'=OMe

1b = R=OH; R'=OMe

1c = R=R'=H

anticancer activity in a variety of human cancers. However, their use is restricted by dose-limiting cardiotoxicity. Much effort has been directed in recent years to obtain either new derivatives or develop new dose regime that show decrease in undesirable side effects and/or increased anti-cancer activity. Based on extensive studies, it has been shown that 4-demethoxydaunomycin (1c) is eight times more

160

effective as anticancer agent than daunomycin (1a). As there is no way of obtaining 4-demethoxydaunomycin by a fermentation process, several synthetic routes have been developed in various laboratories for its synthesis. It has been established that 4-demethoxydaunomycinone (1d) is a valuable precursor for 4-demethoxydaunomycin and its coupling with L-daunosamine has also been demonstrated. This work, therefore, mainly concerned with the new synthesis of 4-demethoxydaunomycinone (1d).

Chapter I: Synthesis of (±)4-demethoxydaunomycinone - A general review

This chapter is a brief review dealing with various synthetic methods for the preparation of (±)4-demethoxy-daunomycinone.

Chapter II: Synthesis of (±)4-demethoxydaunomycinone starting from quinizarin (Diels-Alder approach)

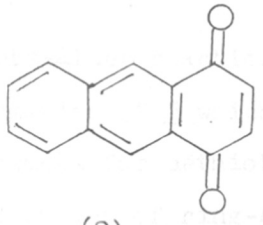
Section I: 1,4-Anthraquinone and napthalene precursors as dienophiles

The methods so far adopted for the synthesis of 4-demethoxydaunomycinone (1d) are not practicable. In the present Chapter new synthetic routes have been considered for the synthesis of 1d starting from easily accessible and commercially available intermediates.

First attempt was to look into the feasibility of utilizing quinizarin (1,4-dihydroxyanthraquinone) and

building the ring-A of the anthracyclinone moiety by the Diels-Alder reaction. Many groups have investigated this approach by first converting qunizarin to quinizarin quinone which served as the dienophile, but the main limitation was that most of the dienes add preferentially to the 'internal' double bond. Although several methods to resolve this difficulty had been devised including the preparation of a few dienes with substituents which were likely to promote the addition at the "terminal" double bond, the most attractive one was to make use of 1,4-anthraquinone (2) in the Diels-Alder reaction by which any diene could be added to build the tetracyclic system. Further, it was easy to oxidize the 9,10-positions of anthracene system to the corresponding anthraquinone derivative.

Accordingly the D.A. reaction between 2 (prepared from quinizarin by sodiumborohydride reduction in acetic acid) and 2-methoxy-1,3-butadiene gave the adduct (3) which was converted to the tetracyclic ketone (4). The side-chain elaboration on the ketone of 4 by a two carbon homologation either by reacting with ethynyl magnesium bromide or with 2-lithio-2-methyl-1,3-dithiane met with failure probably



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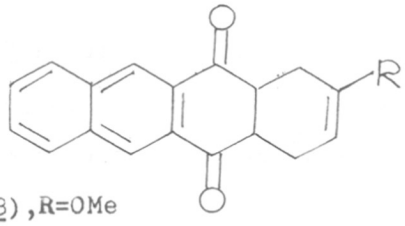
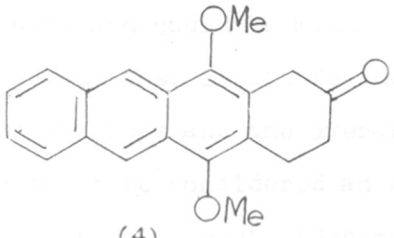



(3), R=OMe

(5), R = 

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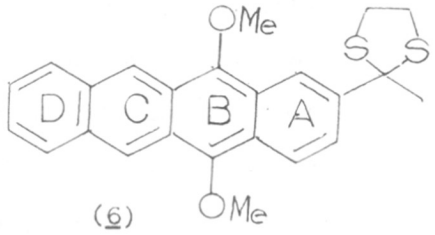
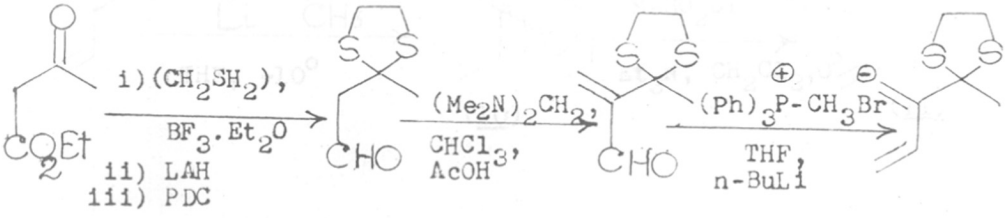



(6)

due to base-catalyzed decomposition via enolisation.

Next attempt was to prepare a suitably protected (as ketal or thioketal) 2-acetyl-1,3-butadiene, which on D.A. reaction with 2 was expected to give the desired product 5. The diene (9) was made starting from ethyl acetoacetate as shown in Scheme-1.

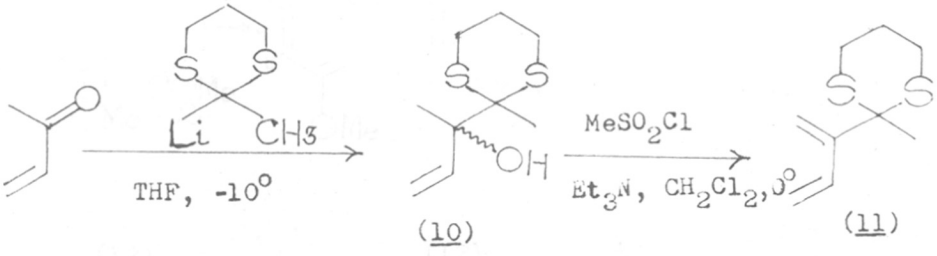
Scheme-1



Diels-Alder reaction between 2 and 9 resulted in the formation of 5 which was converted to 6. However, all attempts for dethioketalization of 6 resulted in the aromatisation of ring-A.

While the preparation of the diene (3) was straightforward and could be made starting from readily available intermediates, it had few drawbacks. Its synthesis involved several steps and the overall yield was not satisfactory for it to be considered an efficient synthesis. Therefore, an alternative route (Scheme-2) was considered for obtaining 2-acetyl-1,3-butadiene in which the ketone group was protected by thioketalisation with 1,3-propanedithiol. Addition of methyl vinyl ketone to 2-lithio-2-methyl-1,3-dithiane in THF at -30° and usual work up gave the alcohol (10) which was dehydrated to give the diene (11). The D.A. reaction between 2 and 11 however did not proceed even in refluxing

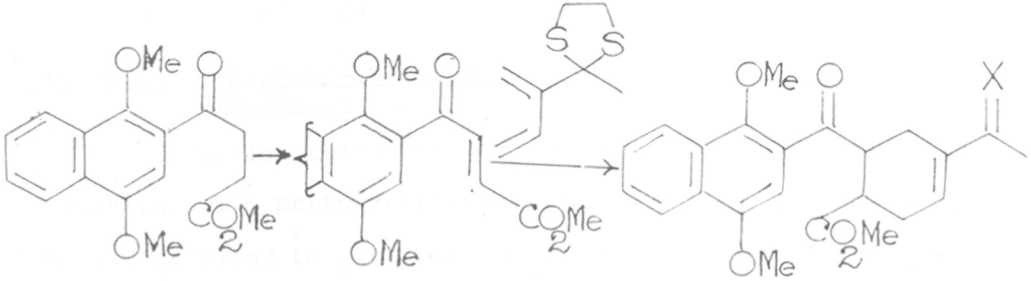
Scheme-2




(10) (11)

toluene and the quinone (2) was recovered. Attempts to add the diene (11) even with reactive dienophiles such as 1,4-benzoquinone and 1,4-napthoquinone did not proceed. Although the difference in the substituents at 2-position of the dienes 9 and 11 seems to be insignificant (the former was having a dithiolane while the latter was having a dithiane group) their marked difference in the D.A. reaction with 2 was not clearly understood.

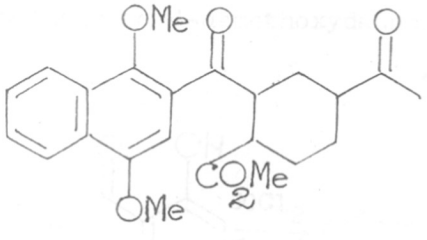
The observation that the ring-A of 6 was prone to easy aromatization during dethioketalisation could be attributed to the extended conjugation of the tetracyclic system. This unexpected trouble could be avoided if the ring-A was built first on a dienophile such as 13 and bridged ultimately to form the ring-B of the anthracyclinone moiety. Compound 13 had been made by bromination of methyl-3-[1,4-dimethoxy-2-napthoyl]-propionate 12 followed by dehydrobromination. D.A. reaction between 13 and 9 resulted in the formation of 14a.

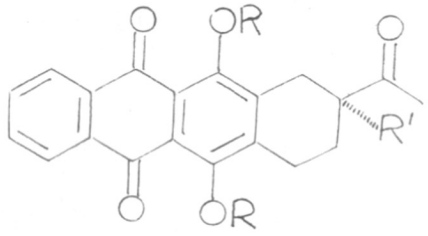



(12) (13)

14a: X = S, S

14b: X = O




15a: R=Me

15b: R=H

16a: R=R'=H; 16b: R=Me R'=H

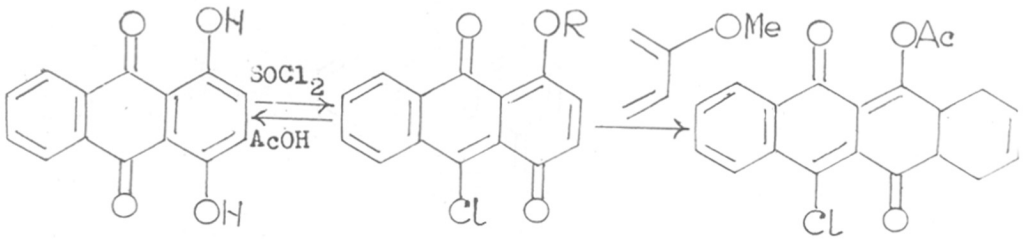
16c: R=Me; R'=OH

Dethioketalization of 14a gave 14b which was subjected to hydrogenation to yield 15a. Alkali hydrolysis of 15a and ring closure of the resultant acid (15b) with conc. $H_2SO_4$ gave 4-demethoxy-7,9-dideoxydaunomycinone (16a). Methylation of 16a gave 16b which was converted to 16c. As the conversion of 16c to 4-demethoxydaunomycinone (1d) had already been described, this new synthesis of 16c in effect constituted a total synthesis of 1d.

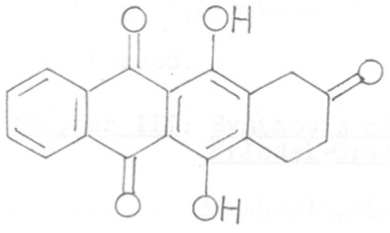
Section II: 1-Acetoxy-10-chloro-4,9-anthraquinone as a dienophile

This section deals with the attempted synthesis of 1d starting with acetoxychloroquinizarin (19b). 19b had been demonstrated to give back quinizarin (18) with mild reagents such as ethanolic HCl acetic acid or conc. $H_2SO_4$. It was felt that on similar treatment, the compound (21a) should

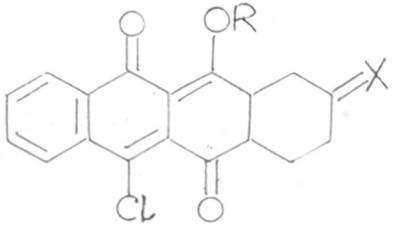
give rise to the required intermediate (22) which had been elaborated to 4-demethoxydaunomycinone (1d).




(18) 19a: R=H 19b: R=Ac (20) X=OMe




(22)



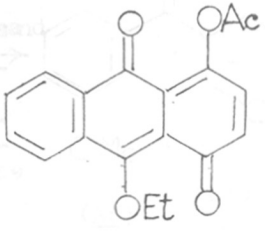

21a: R=Ac, X=O

21b: R=H, X= S S

21c: R=Me, X= S S

Accordingly, 21a was prepared by D.A. reaction of 19b with 2-methoxy-1,3-butadiene followed by demethylation. Unfortunately conversion of 21a → 22 with aforementioned reagents did not occur. The desired transformation of the

derivatives 21b or 21c into 22 also met with failure. Later the ethoxyquinizarin (23) was chosen as a dienophile because



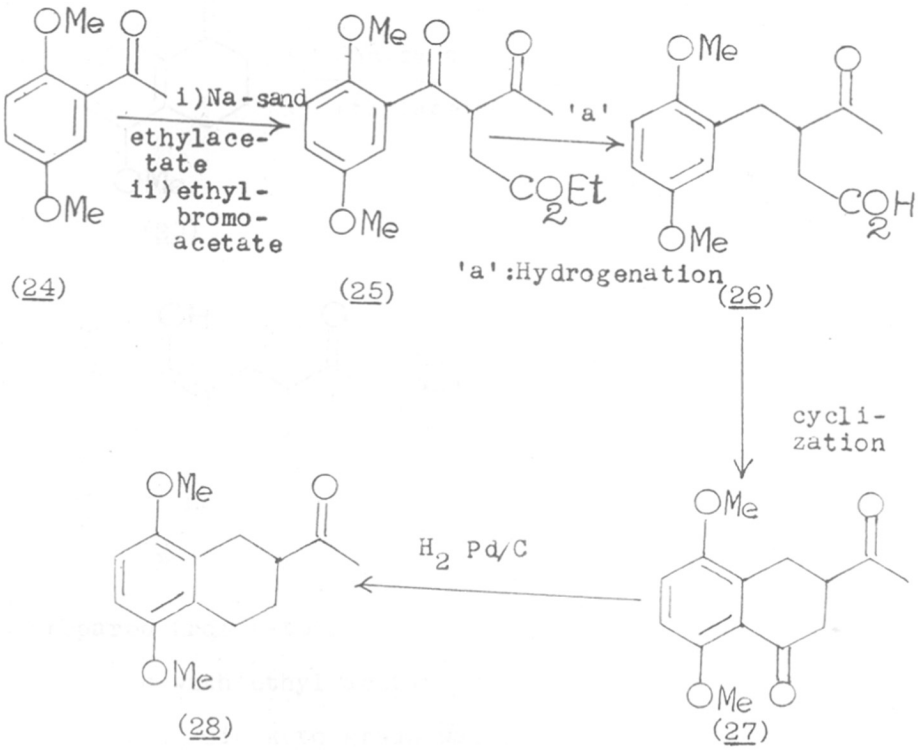

23

of the ease with which ethyl substituent could be removed in the final stages. Surprisingly its D.A. reaction with 2-methoxy-1,3-butadiene under wide range of conditions did not proceed.

Chapter III: Synthesis of (±)4-demethoxydaunomycinone by Friedel-Crafts reaction.

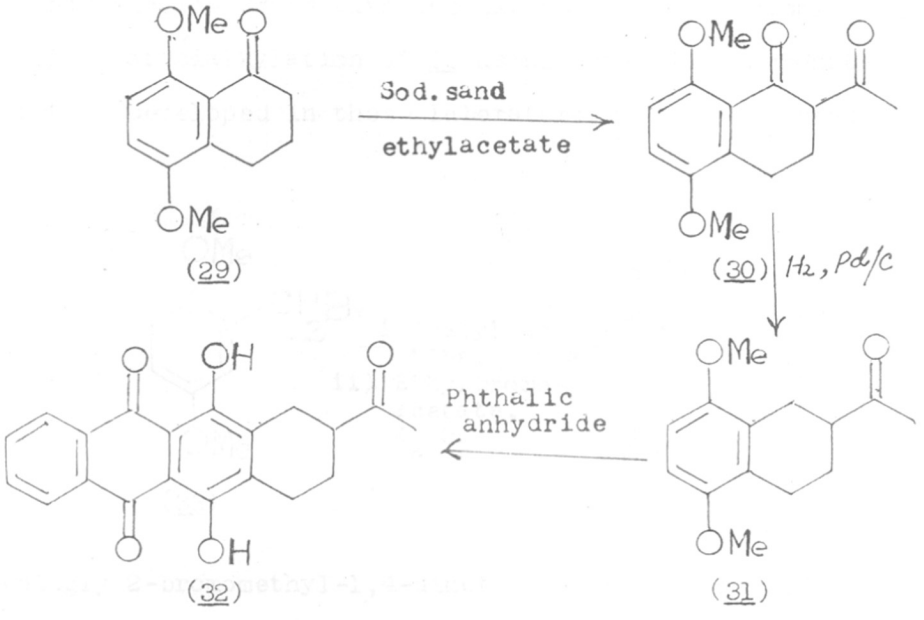
Section I: Synthesis starting from hydroquinone

In this section, the synthesis of the key intermediate (28) is dealt with. Earlier the same intermediate was prepared by Wong et al. and was successfully transformed into 4-demethoxydaunomycinone (1d). A new route starting from 2,5-dimethoxyacetophenone (24) was attempted as follows.




(24) (25) (26) (27) (28)

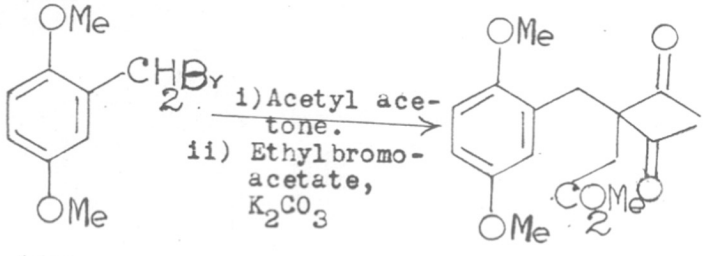
The diketo ester (25) was obtained by Claisen-Schmidt reaction of 24 with ethyl acetate in presence of pulverized sodium followed by alkylation with ethyl bromoacetate. A selective reduction of the benzylic keto group using Pd-C did not proceed. In a similar approach the acetyl tetralone (30)




was prepared from 1-tetralone (29) by Claisen-Schmidt condensation with ethyl acetate in the presence of sodium sand. The benzylic keto group was reduced in presence of Pd-C to give the required key intermediate (31). Its coupling with phthalic anhydride in presence of sodium aluminium chloride melt gave 4-demethoxy-7,9-dideoxy-daunomycinone (32) whose conversion to 4-demethoxydaunomycinone (1d) had been well demonstrated.

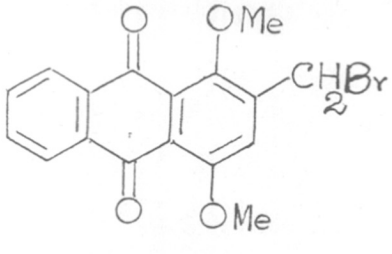
Section-II: Synthesis starting from methyl quinizarin

This section deals with the extension of the simple methodology of dialkylation of 33 using potassium carbonate and acetone developed in these laboratories for the synthesis of 1d.

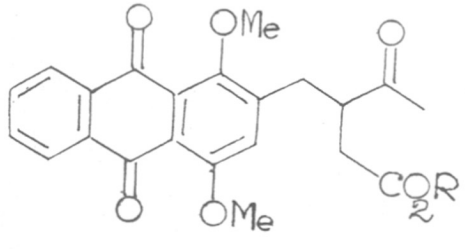



(33) (34)

Accordingly 2-bromomethyl-1,4-dimethoxyanthraquinone (35) was condensed with 2,4-pentanedione in the presence of




(35)




(36a): R=H

(36b): R=$CH_3$

anhydrous potassium carbonate and acetone, and the resulting monoalkylated product was further condensed with ethyl bromoacetate using the same base. Alkaline hydrolysis afforded the keto acid (36a) which was earlier prepared by Sih et al. from 35 and ethyl acetyllevulinate with sodium hydride in DMF and was converted into 4-demethoxy-daunomycinone (1d).

172

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