SYNTHESIS OF ANALOGUES OF ANTHRACYCLINES

A THESIS
SUBMITTED TO THE
UNIVERSITY OF POONA

FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN CHEMISTRY

BY

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Dedicated to my Respected Father In Law

MR. J. P. KULKARNI

CERTIFICATE

Certified that the work incorporated in the thesis entitled "SYNTHESIS OF ANALOGUES OF ANTHRACYCLINES" by Mrs. Kulkarni Asavari Deepak was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

A. V. RAMA RAO
Supervisor

ACKNOWLEDGEMENTS

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(A. D. KULKARNI)

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CONTENTS

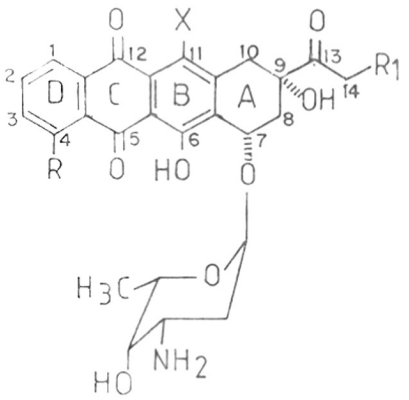
SUMMARY

The thesis is divided into two sections. Section A describes the synthesis of anthracyclines while Section B deals with the synthesis of pheromones.

Section A: Anthracyclines

The anthracyclines are a group of structurally related antibiotics that produce a wide variety of effects and have a rather broad spectrum of antineoplastic activity. They are comprised of a variable lengths and are isolated from cultures of various Streptomyces. Adriamycin (1), daunomycin (2), carminomycin (3), 11-deoxyadriamycin (4), 11-deoxydaunomycin(5) have been evaluated clinically and are proved to be potent antitumor agents, but the acute dose limiting toxicity of 1 or 2 is found cardiotoxic and myelosuppressing. The very significant clinical activity of 1 or 2 and the obvious deficiencies of the drug have resulted in several extensive analogue programmes which consist of developing new analogues with equivalent clinical activity but reduced cardiotoxicity. These aspects have led to the development of efficient syntheses that would be more advantageous than fermentation process. They also offer methods to obtain functionally modified analogues which may have improved therapeutic indices. Recently it has been shown that 4-demethoxydaunomycin (6) is 8 to 10 times more active than daunomycin.

Keeping in mind the profound pharmacological importance of anthracyclines and their analogues, the syntheses of a few anthracyclinones were undertaken and the results are discussed in the present thesis. There are a number of reports about L-daunosamine and coupling of the amino sugar and an aglycone part is well established. Therefore, efforts were mainly directed towards the syntheses of various aglycones.



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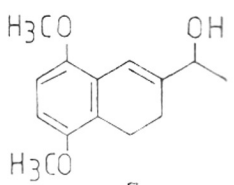
6	H	OH	H



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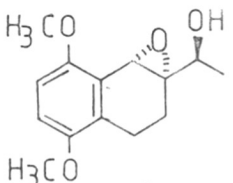

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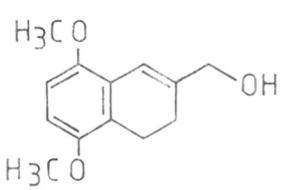

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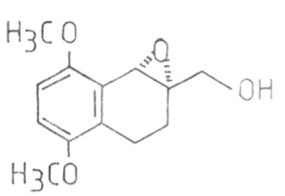

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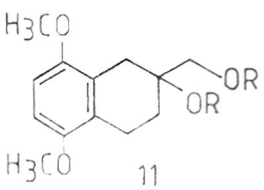

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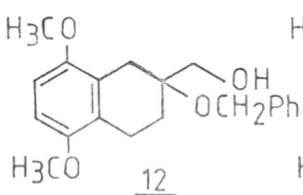
11 R, R = H
11a R,R = CHPh



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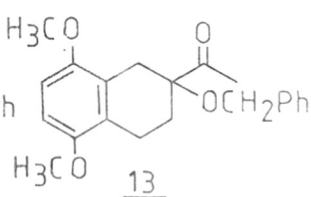

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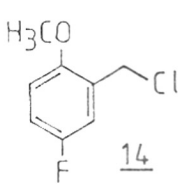

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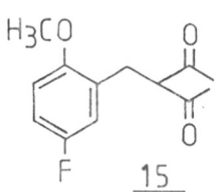

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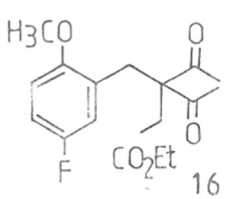

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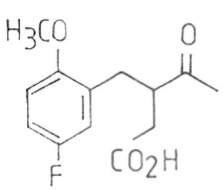

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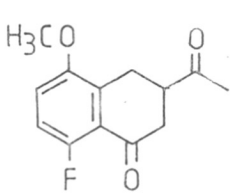

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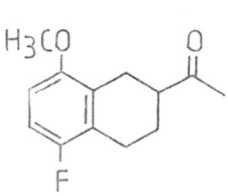

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For convenience, the Section A is divided into two Chapters.

CHAPTER I:

This chapter comprises of a review on the various synthetic approaches to the anthracyclinones and their analogues.

CHAPTER II:

Part I: Synthesis of 4-demethoxydaunomycinone

Earlier reports from these laboratories indicated that the allylic alcohol 7 by Sharpless kinetic resolution could be converted into optically active epoxide 8 which in turn could be elaborated into optically active (+)4-demethoxydaunomycinone. However, in this process, the theoretical yield of this product could be only 50% as 50% of the precious material is either discarded or recycled involving a number of reactions. Practically the yield of 8 could only be optimised upto 35%. In order to prepare 4-demethoxydaunomycinone in substantial amount, it was felt that a scheme should be devised in which optically active epoxide could be obtained in almost quantitative theoretical yield. This could best be achieved by Sharpless asymmetric epoxidation of the allylic alcohol 9 in which kinetic resolution would be omitted. In order to establish methodologies for the preparation of compound 10 and of course, for its elaboration to 4-demethoxydaunomycin, some model studies were performed on racemic compounds.

Diels-Alder reaction of benzoquinone and butadiene followed by subsequent methylation afforded dihydronaphthalene derivative which was converted into allylic alcohol derivative 9 by three step sequence involving isomerisation of double bond, Vilsmeier-Haack formylation and reduction of the resulting aldehyde. The compound was subjected to epoxidation in the presence of tertiary butylhydrogenperoxide to yield the

epoxide 10 in 90% yield which on lithium aluminium hydride reduction gave the diol 11. Protection of the diol with α,α-dimethoxytoluene in the presence of catalytic amount of acid gave the benzylidene derivative 11a which on hydrogenolysis with a mixture of lithium aluminiumhydride and aluminium chloride gave exclusively tertiary o-benzyl derivative 12. Oxidation of primary alcohol followed by Grignard reaction with methylmagnesium iodide and oxidation gave the AB ring synthon 13 which was fused with phthalic anhydride in the presence of sodium chloride and aluminium chloride mixture to give (±)4-demethoxy-7-deoxydaunomycinone which has been converted to (±)4-demethoxydaunomycinone by the known route. The work on Sharpless asymmetric epoxidation of allylic alcohol 9 is being pursued in these laboratories.

Part II: Attempts for the synthesis of 6-fluoro-7-deoxydaunomycinone

There are ample evidences in literature especially in steroid chemistry that replacement of hydroxyl group with fluorine can lead to derivatives having more activity than the parent compound. Therefore, it was felt to make an attempt and synthesize fluoro derivatives of daunomycinone.

p-Anisidine was converted into p-fluoroanisole by the reported procedure. Subsequent chloromethylation then gave 14 which was converted into 17 by a procedure developed in these laboratories. For instance, 14 was reacted with 2,4-pentanedione in the presence of potassiumcarbonate, potassium iodide and acetone to give rise to product 15 which *in situ* was treated with ethylbromoacetate to provide diketo ester 16. Reverse Claisen condensation was effected in the presence of sodium hydroxide to give the keto acid 17. All the attempts to cyclise the keto acid 17 into tetralone derivative 18 failed to give the satisfactory yield. In case of sulfuric acid as a cyclising agent, the compound 18 was obtained in only 5% yield.

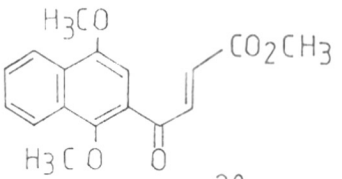
This problem of cyclisation was not expected, however, the small amount of 18 was reduced to give 19 in moderate yield. The introduction of tertiary hydroxyl group at C-9 was attempted according to the procedure reported by Wong ($KtBuO/O_2$). The product isolated from the reaction was not the required hydroxytetralin, but fully aromatised naphthalene derivative. In view of the poor yield of cyclisation step, introduction of tertiary hydroxyl at C-9 was not attempted again and 18 could not be elaborated to 6-fluoro-7-deoxydaunomycinone.

Part III: Synthesis of 4-demethoxyfeudomycinone

This part consists of attempted synthesis of (±)4-demethoxy-7-deoxyfeudomycinone. The dienophile 20 was prepared by Friedel-Crafts reaction of 1,4-dimethoxynaphthalene and halfchloride of methyl succinate followed by bromination-debromination reaction. 20 was subjected to Diels-Alder reaction with isoprene and subsequent hydrolysis gave a mixture of acid 21a+21b. The mixture as such was subjected to iodolactonisation in the presence of potassium iodide, sodium bicarbonate, iodine, dioxane and water. The γ-iodolactone 22 was the exclusive product. Reductive deiodination of 22 was carried out with tri-n-butyltinhydride in the presence of methylene chloride under reflux. It is interesting to note that when the reduction was carried out in benzene under reflux, reduction of the benzylic ketone also occurred. Opening of γ-lactone with ethanolic potassium hydroxide furnished hydroxyacid 23 whose cyclisation was attempted under various conditions. However, the starting γ-lactone was the only product isolated. In case of drastic conditions such as conc. sulfuric acid, aromatisation of the product resulted. Therefore, this route was abandoned.

Part IV: Synthesis of 3-methoxyphthalic anhydride

3-Methoxyphthalic anhydride logically represents C and D rings of anthracyclinones. Although several methods are available for its synthesis including the classical one from



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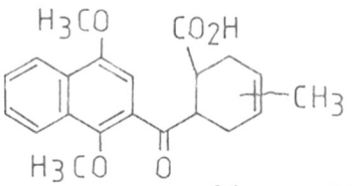
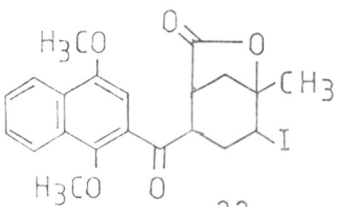


21a + 21b



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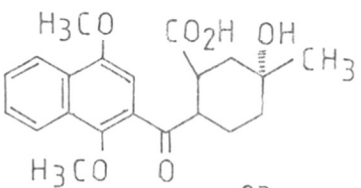

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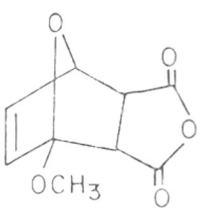

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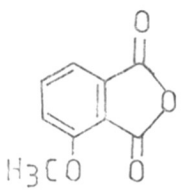

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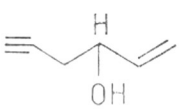

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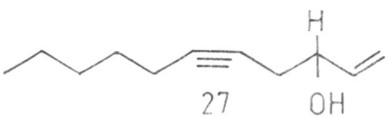

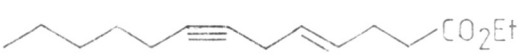

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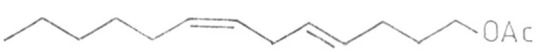

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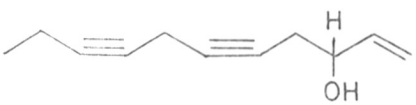

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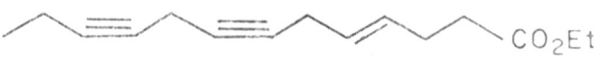

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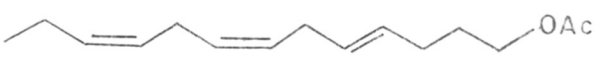

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3-nitrophthalic acid, all involve either tedious work up or several number of steps. Therefore, it was warranted to have a simpler route for its synthesis which can give the product in substantial amount. Herein, a novel method for 25 is described. 2-Methoxyfuran and maleic anhydride were subjected to Diels-Alder reaction to give an adduct 24 which was hydrolysed in the presence of acetic anhydride and trifluoro-acetic acid to give 3-methoxyphthalic anhydride in overall 70% yield.

Section B - Pheromones

Synthesis of (4E,7Z)-4,7-tridecadienylacetate (30) and (4E,7Z,10Z)-4,7,10-tridecatrienylacetate (33)

The current interest in the synthesis of pheromones for pest management in agriculture and forestry may be attributed to the health hazards caused by pesticides. The pheromones are specifically used in small quantities, biodegradable and therefore produce no environmental catastrophe. The potato tuberworm Phthorimaea operculella (Zeller) (Lepidoptera Gelechiidae) has been considered as widely distributed pest on a solanaceous crops and thrives best in areas with hot dry summer all over the world. The compounds (4E,7Z)-4,7-trideca-dienylacetate 30 and (4E,7Z,10Z)-4,7,10-tridecatrienylacetate 33 have been isolated from female species. 1:1 mixture of 30 and 33 has been found to be more attractive to male moths. Because of its importance in potato crop protection, coupled with the unusual odd-carbon chain, a number of syntheses have been reported. Herein a novel route towards their synthesis has been described.

The intermediate 26 which is a six carbon acetylinic moiety was common for both the pheromones and was prepared from propargyl bromide and acrolein. 26 was alkylated with

1-bromopentane to give 27 which was subjected to Claisen rearrangement in the presence of triethylorthoacetate and catalytic amount of propionic acid to give a 12 carbon ester 28. Reduction of acetylinic bond in 28 with poisoned catalyst gave 29 whose ester functionality was reduced with lithium aluminiumhydride. Acetylation of the resulting alcohol afforded the required compound 30.

Similarly, the pheromone 33 was prepared from 26 and 1-bromo-2-pentyne according to the procedure reported above.

SECTION I

ANTHRACYCLINES

CHAPTER I

SYNTHESIS OF ANTHRACYCLINONES

A REVIEW

INTRODUCTION

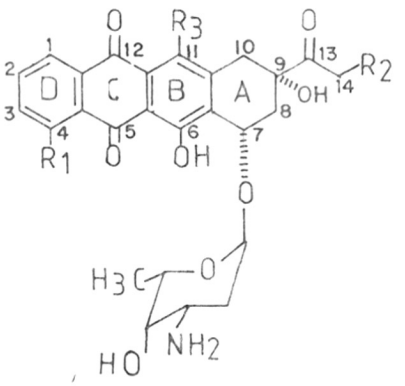
Cancer, the abnormal growth of body tissues, is the foremost killer disease in the western countries and is also ranked as the third most dreaded disease in India. This disease has attracted world-wide attention and search for reliable methods to cure it is continuously going on. Presently, radiation, surgery and chemotherapy are some of the methods being used in the treatment of cancer. 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 anticancer 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: (i) alkylating agents, (ii) antimetabolites, (iii) antibiotics and (iv) miscellaneous compounds.

The usefulness of certain anthracycline antibiotics as antineoplastic agents is now widely accepted. Adriamycin (1)[2] and daunomycin (2)[2] have become established as one of the most useful weapons in the oncologist's

armamentarium and their targets include lymphomas (Hodgkin's and non-Hodgkin's), acute leukaumia, osteogenic and soft tissue carcinomas and solid tumors (particularly of the breast and ovaries and to a lesser extent of bladder and lung).[3] Their potent anticancer activity has made them the subject of interest of many synthetic chemists all over the world and extensive work has been carried out with regard to their isolation, structure determination, physical and chemical properties and preparation on large scale. As a result, some more anthracyclines like carminomycin (3),[4] 11-deoxyadriamycin (4)[5] and 11-deoxy-daunomycin (5)[6] have been isolated. A number of synthetic analogues have also been prepared and screened for activity against different types of cancer. Among synthetic analogues, the most promising activity has been shown by 4-demethoxydaunomycin (6) which is 8-10 times more active than daunomycin. Likewise new analogues such as 4-demethoxy-11-deoxydaunomycin (7) have been found to be more active against different types of cancer.

Isolation and structure elucidation

Anthracyclines are produced by various Streptomyces species. Daunomycin was first isolated in 1963 simultaneously from Streptomyces peucetius by Farmitalia group[2b]



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2	OCH_3	H	OH
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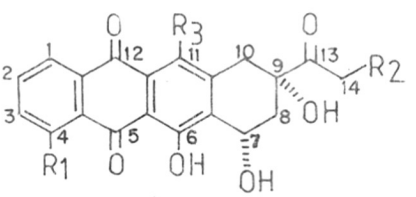
5	OCH_3	H	H
6	H	H	OH
7	H	H	H



	R_1	R_2	R_3
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9	OCH_3	H	OH
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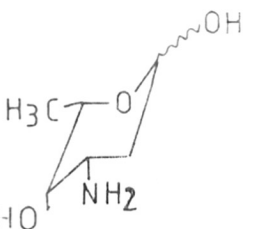

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in Italy and from Streptomyces coeruleorubidus by Rhone-Poulenc in France.[7] Exposure of S. peucetius to the mutagen N-nitroso-N-methylurethane by the group at Farmitalia gave a variant organism (S. peucetius var. caecius) which was found to produce adriamycin (1). Carminomycin (3) has been isolated in Russia from Actinomadura carminata.[4]

The structures of these anthracyclines were determined by spectral analyses,[6] chemical degradations,[2,8] X-ray analysis[9] and were confirmed by their syntheses and comparison with natural products. Anthracyclines usually occur as glycosides. Mild acidic hydrolysis affords the tetracyclic aglycone part and sugar part. The aglycones, termed anthracyclinones, are polyhydroxylated and differ in the hydroxylation pattern, the degree of saturation in ring A and the presence or absence of carboxyl function at C-10. The difference in structures can be explained by considering the biosynthesis of anthracyclinones. Ring A of the anthracyclinones contains asymmetric centres and the absolute configuration of daunomycinone has been determined by degradation.[8] Comparison of the circular dichroism spectra of other anthracyclinones with that of daunomycinone led to the assignment of configuration for most of other anthracyclinones.[10] The configuration at 7 and 9 position is 'S'. Last feature of the structure is

that adriamycin, daunomycin and carminomycin are 7-glycosides of the appropriate aglycone with the sugar L-daunosamine (2,3-dideoxy-3-amino-L-fucose) (16). L-daunosamine was synthesised by Marsh et al.[11] in 1967 from L-rhamnose while the first synthesis of daunomycinone (9) was reported by Wong et al.[12] in 1973. Acton et al.[13] successfully coupled daunomycinone (9) with daunosamine (16) in 1974 to afford daunomycin (2) identical with the natural product, thus proving the structure to be (2).

Biological Activity

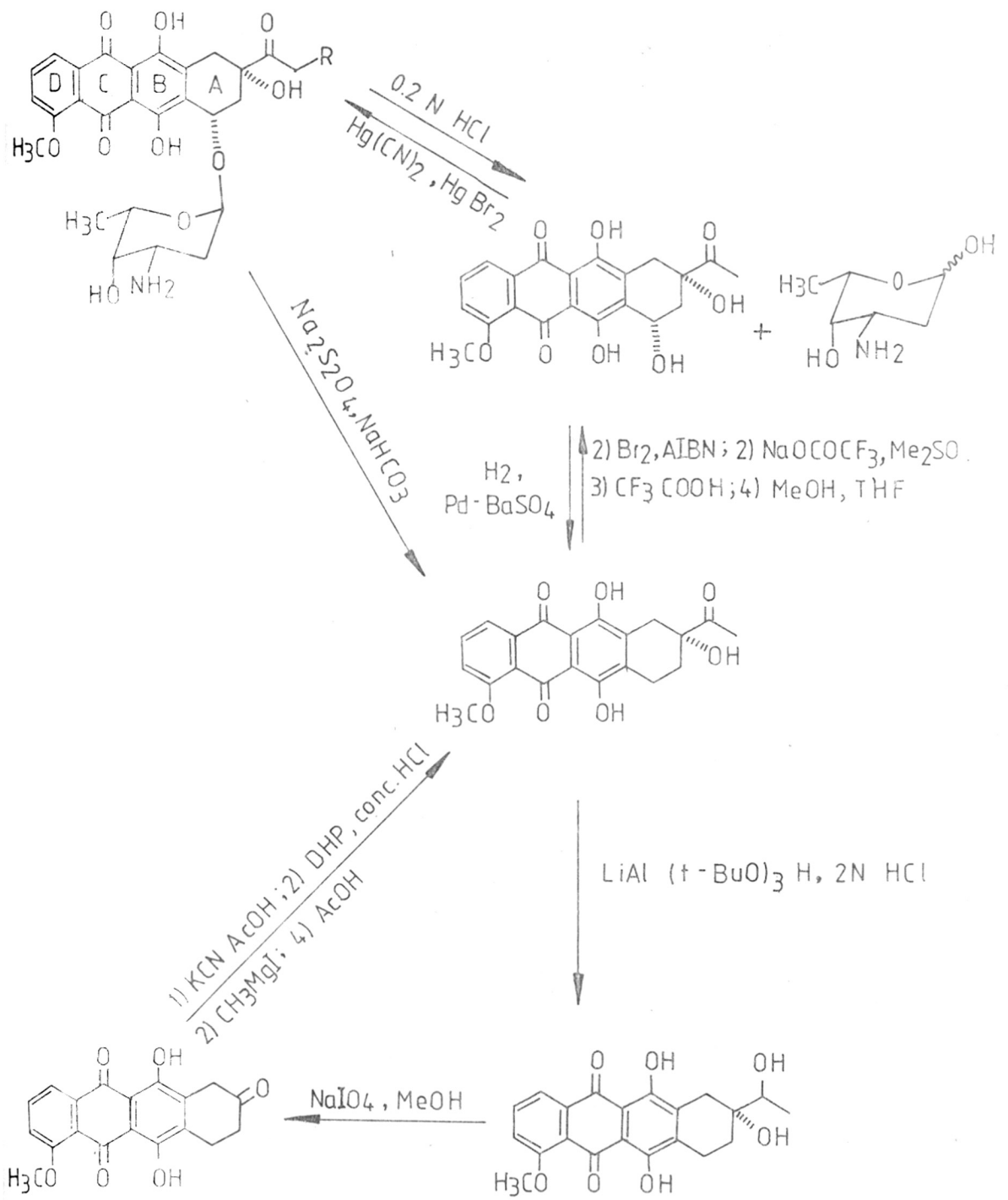
Different theories have been put forward to explain the antineoplastic activity of anthracyclines out of which DNA intercalation is the first and certainly the best documented one.[14] The interaction has been investigated by physiochemical techniques such as ultraviolet, visible and fluorescence spectroscopy, T-jump, stopped flow, unwinding of closed circular DNA, electrochemical methods, spin-labelling and transient electric dichroism.[15-17] NMR studies of anthracyclines with polynucleotides clearly demonstrated the rings B and C to be stacked with the base-pairs whereas ring D is not, suggesting the drug is oriented anti-parallel to the basepairs between which it intercalates.[18] By the finding that the binding still occurs with nucleotides with blocked major grooves, it has been shown that the sugar residue lies in the minor

groove.[19] An X-ray crystallography study of daunomycin/d (CpGpTpCpG) complex has confirmed the orientation of the drug perpendicular to the plane of the basepairs with insertion from the minor groove.[20] There are several stabilizing H-bonding interactions but, surprisingly, there is no interaction between the charged amino group and a phosphate residue. A resonance Raman spectroscopy study supports this new model of the binding[21] and insertion from the minor groove has also been suggested from a molecular mechanics energy study.[22] The biological significance of the anthracycline-DNA interaction is the inhibition of DNA and RNA synthesis. Certainly the extent of DNA damage in cancerous cell from patients correlates with the response to drug treatment.[23] This damage to DNA plus the condensation of chromatin argue that the nuclear effects of the drug are the important effects. Adriamycin and daunomycin produce the toxic effect typical of drugs which inhibit nucleic acid synthesis like alopecia, stomatitis, depression of the bone-marrow leading to leukopenia, nausea and vomiting.[24,25] The most serious toxic effect, however, and the effect which limits the total dose, is the cardiotoxicity.[26]

Degradation

Smith *et al.*[27] have carried out the degradation studies of daunomycin (2) (Scheme-1). In this report the degradation

SCHEME 1 Smith et al, J. Org. Chem. 42, 3653 (1977)



of daunomycin to the nonasymmetric tetracyclic ketone and refunctionalization of A ring to daunomycin and adriamycin has been described. Thus, mild acidic hydrolysis of daunomycin (2) yielded daunomycinone (9) and daunosamine (16). Hydrogenolysis of benzylic hydroxyl of daunomycinone afforded 7-deoxy-daunomycinone which on reduction with lithium tri-t-butoxy-aluminium hydride followed by cleavage of the resulting glycol with sodium periodate yielded the tetracyclic ketone. They were successful in converting this ketone back into 7-deoxydaunomycinone in four steps which was further elaborated to daunomycin (2). Bromination of daunomycinone (7) followed by alkaline hydrolysis yielded adriamycinone which permitted conversion of daunomycin into adriamycin (1).

Synthesis

Total synthesis of these molecules by itself is a major line of research directed towards the exploration of structural modification on different parameters of anthracycline antitumor activity. The problems which arise here are: (a) development of a synthetic procedure which can be adopted at least upto a large bench-scale resulting in gram amounts of the aglycone, (b) synthesis of the amino sugar, L-daunosamine from an easily accessible natural sugar, (c) development of suitable methods for the synthesis of the glycosidic bond and

(d) the necessity of obtaining these products in substantial quantities in optically pure form. A number of organic chemists from well known groups throughout the world are involved in the syntheses of these anthracycline antibiotics. In the year 1979, Kelly has published a comprehensive review,[28] on synthetic approaches to anthracyclines, in which it was discussed under three parts: (i) syntheses of anthracyclinones such as daunomycinone (9), 4-demethoxy-daunomycinone (14) etc., (ii) syntheses of L-daunosamine (16) and (iii) glycosidation of aglycone with the sugar moiety.

As there are several practicable methods for the synthesis of L-daunosamine[9] from sugar and non-sugar precursors and the coupling of aglycone with L-daunosamine is well established,[13] much efforts were directed to develop a preparative method for the synthesis of anthracyclinones, the aglycones of anthracyclines. In consequence, there appeared a good number of methods for the synthesis of aglycones.

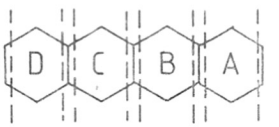
In the present review, the recent synthetic methods (appeared after 1979) are dealt with and the emphasis is being placed on general strategies rather than operational details. For convenience, the methods of synthesis of anthracyclinones are classified into five sections: (1) Diels-Alder Routes, (2) Nucleophilic Routes,

(3) Friedel-Craft and Fries Routes, (4) Syntheses of chiral aglycones and finally (5) Syntheses based on different principles.

1. Diels-Alder Routes:

The obvious application of the Diels-Alder reaction to build up the tetracyclic ring system of the anthracyclinones has been widely explored and it represents one of the most attrative and economical routes.

The possible constructions are shown by vertical lines in the following tetracyclic system and most of them have appeared.

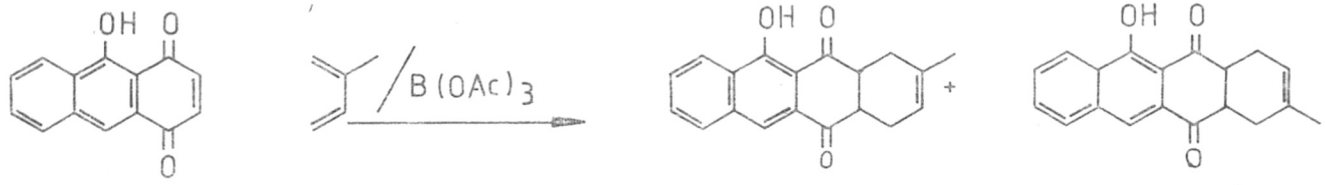


Kende et al.[29] reported the synthesis of daunomycinone in which bisquinone was subjected to Diels-Alder reaction with 2-acetoxybutadiene to yield an isomeric mixture of adduct which was separated to obtain the desired adduct and was further elaborated to daunomycinone. Hodge and coworkers[30] reported the synthesis of 4-demethoxy-7-deoxydaunomycinone in which the key step was the Diels-Alder reaction of 1,4-anthraquinone and butadiene. The 9-hydroxy-1,4-anthraquinone upon Diels-Alder reaction with isoprene in the presence of borontriacetate yielded

regioselective adduct (Scheme-2).[31] Scheeren et al.[32] developed a tailor-made 1,3-diacetoxybutadiene for the site-selective cycloaddition with quinizarinquinone which led to a promising synthon for the preparation of 4-demethoxydaunomycinone (Scheme-3). But, the cycloadduct on hydrolysis under various conditions yielded aromatic product exclusively.

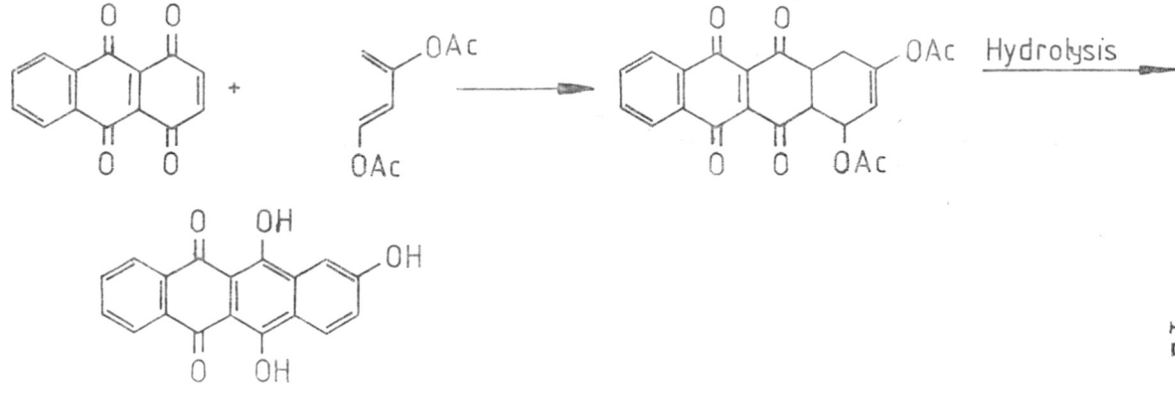
Stoodley et al.[33a] elaborated the tetracyclic carbon skeleton by a Diels-Alder strategy in which 6a, 7 and 10, 10a bonds were constructed. The epoxytetrone[33a] and the appropriate diene[33b,c] served as precursors. Epoxytetrone was obtained by a method where quinizarinquinone was oxidised with m-chloroperbenzoic acid to give an internal 4a,9a epoxide. Interestingly, the cycloaddition reaction of epoxytetrone and (E)-1-[(2',3',4',6'-tetra-O-acetyl- -D-glucopyranosyl)oxy]-3-trimethylsilyloxybuta-1,3-diene yielded exclusively the desired cycloadduct, revealing a notable diastereo-facial reactivity of the diene. The cycloadduct was further elaborated to optically active (+)-4-demethoxydaunomycinone by reaction sequence in which no resolution step or chromatography was involved. Preston et al[34] reported the synthesis for the intermediate of (±)-4-demethoxy-11-deoxydaunomycinone (Scheme-5). 4a,9a-Epoxy-4a,9a-dihydroanthracene-1,4,9,10-tetrone and 2-trimethylsilyloxybuta-1,3-diene gave the Diels-Alder

SCHEME 2 Russell et al Tetrahedron Lett, 4229 (1979)

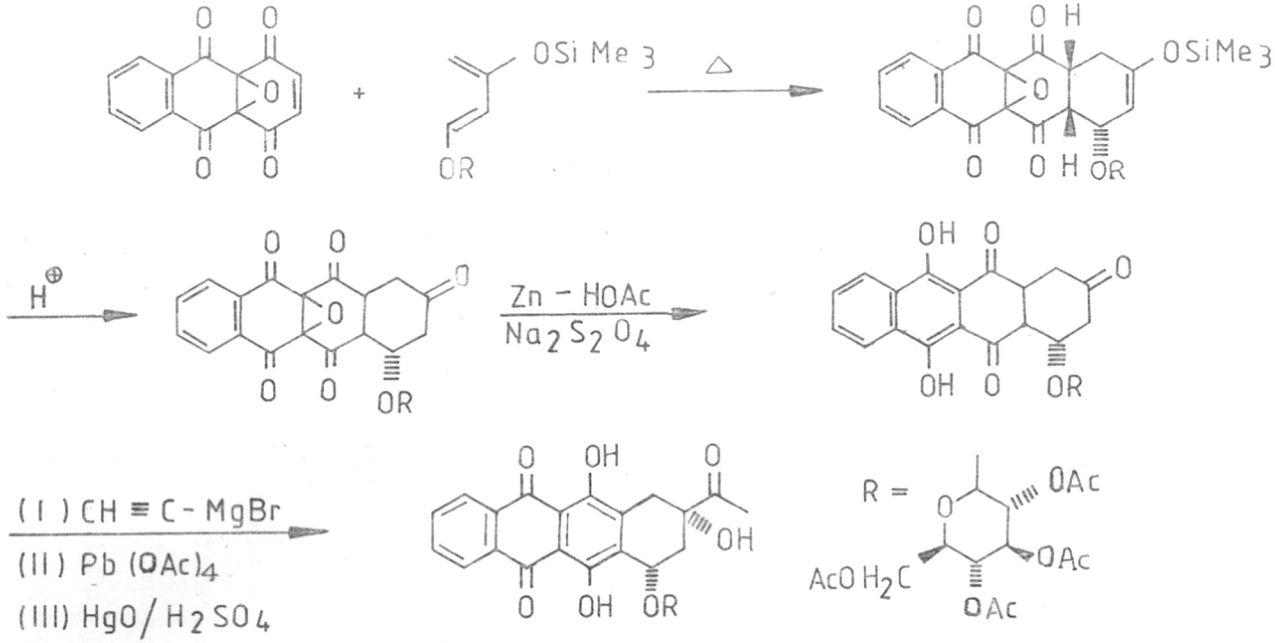


Major Minor

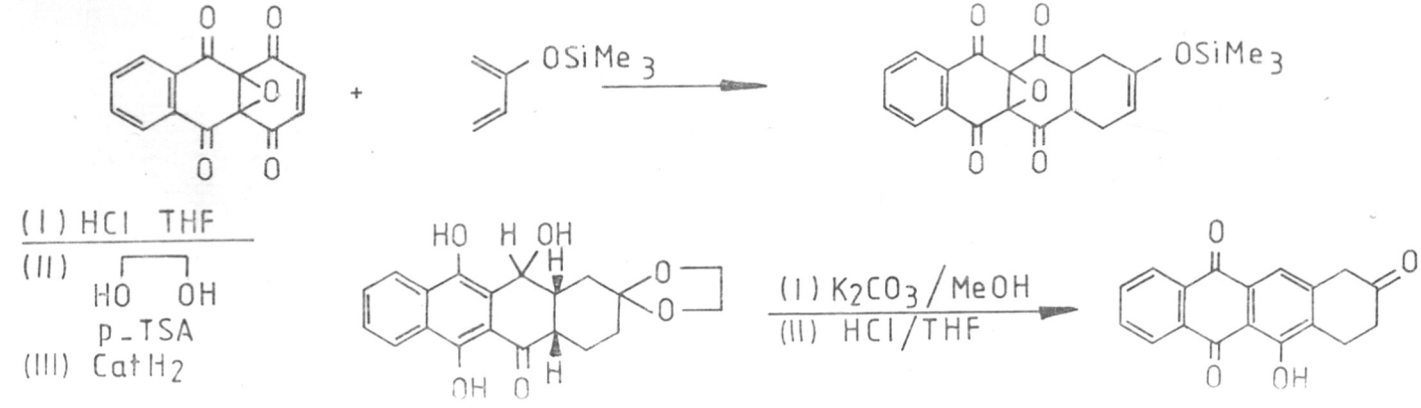
SCHEME 3 Scheeren et al J.Org. Chem 50 1955 (1985)



SCHEME 4 R.J. Stoodley et al, Tetrahedron, 40, 4657 (1984)



SCHEME 5 Preston et al J. Chem Soc. Perkin Trans. I, 39 (1985)

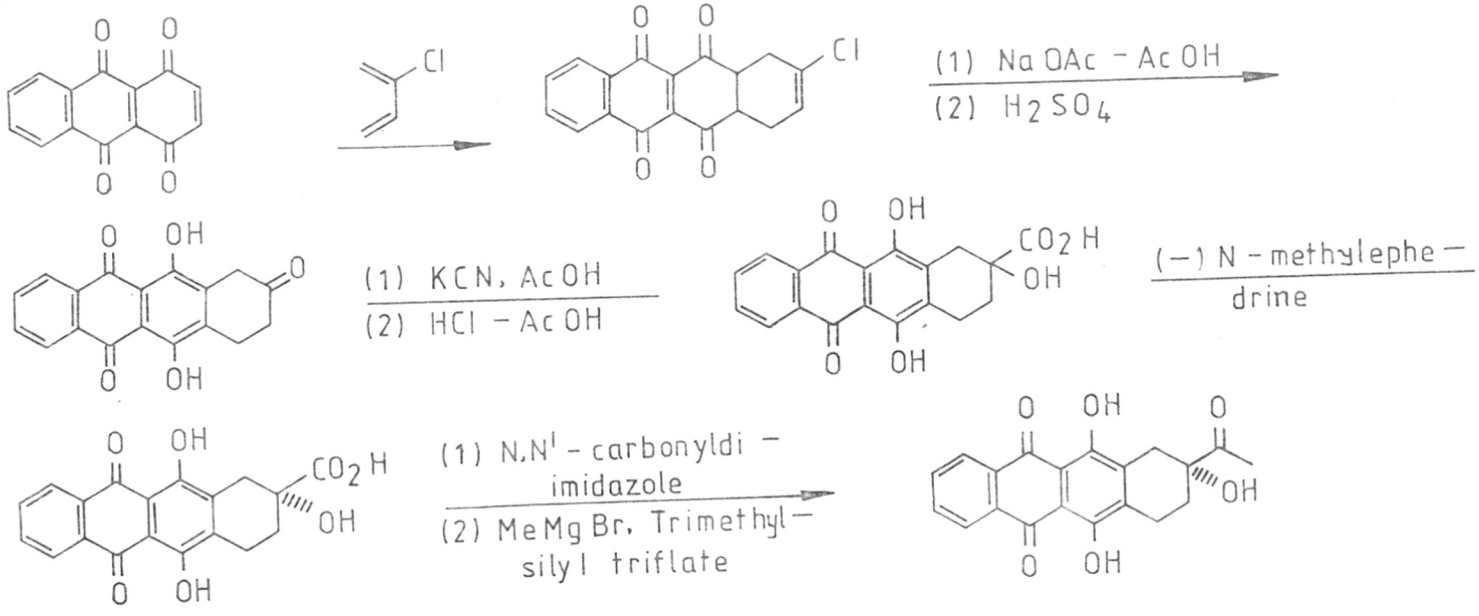


adduct whose conversion to naphthacene-5-one derivative afforded the above said compound.

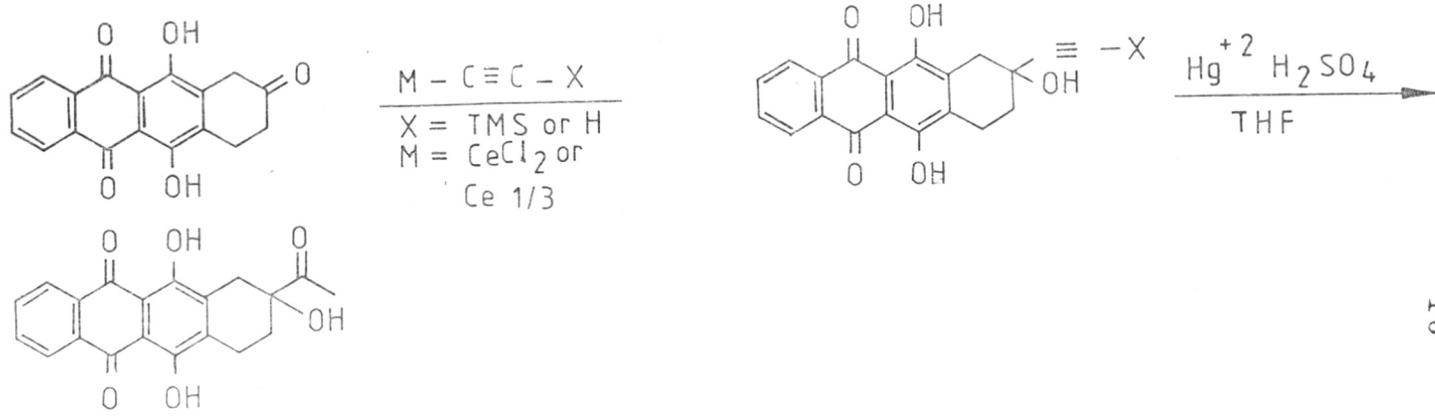
Terashima et al[35a] reported Diels-Alder reaction of 2-chloro-1,3-butadiene with quinizarinquinone which was found to occur exclusively at C-2, C-3 double bond, giving the adduct in excellent yield. The adduct was readily converted into (±)-4-demethoxy-7-deoxydaunomycinone as shown in Scheme 6a. The same reaction sequence gave the optically active (-)-4-demethoxy-7-deoxydaunomycinone[35b] when (R)-(-)-2-carboxylic acid was obtained via resolution of racemic carboxylic acid by (-)N-methylephedrine. Later on, Terashima et al.[35c] modified the conversion of trione to (±)-4-demethoxydaunomycinone by Grignard reaction of trione with 2-trimethylsilylethynylcerium (III) reagent (Scheme 6b).

The work published by Sih et al[36] was concerned with a naphthalene route to anthracyclinones. According to this approach, the 6,11-dihydroxy-4-methoxy-7,8,9,10-tetrahydro-5,11-naphthacenedione-9-carboxylic acid methyl ester was synthesised by using a Diels-Alder adduct as a key intermediate (Scheme-7). Rama Rao et al.[37a] described an elegant regiospecific approach for the synthesis of 11-deoxydaunomycinone involving the Diels-Alder reaction of 2-methoxybutadiene with a suitably substituted naphthalene CD ring synthon (Scheme-8a).[37b] They further carried out the

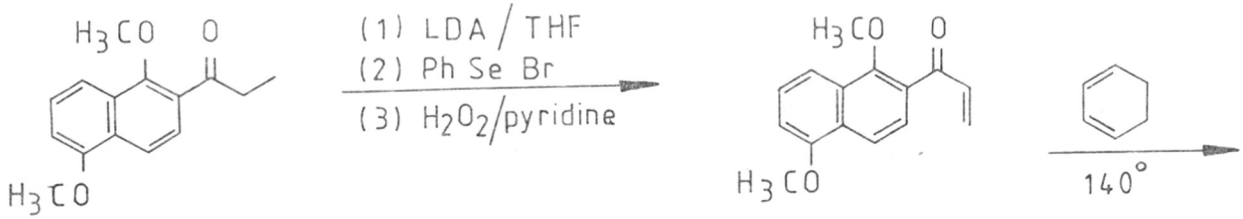
SCHEME 6a Terashima et al., Chem. Lett, 57 (1985)
" " " , " " , 473 (1984)

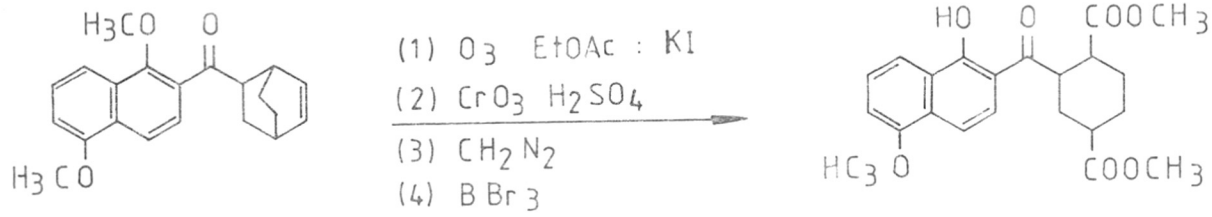


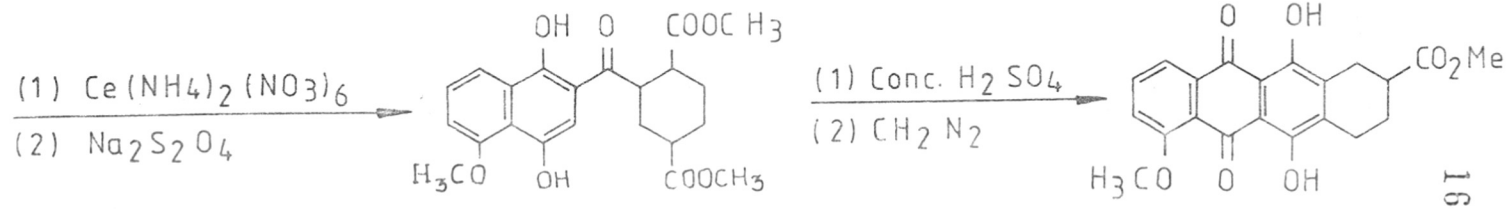
SCHEME 6b Terashima et al., Chem. Lett, 1543 (1984)



SCHEME 7 Sih *et al.*, Tetrahedron Lett, 1285, (1979)







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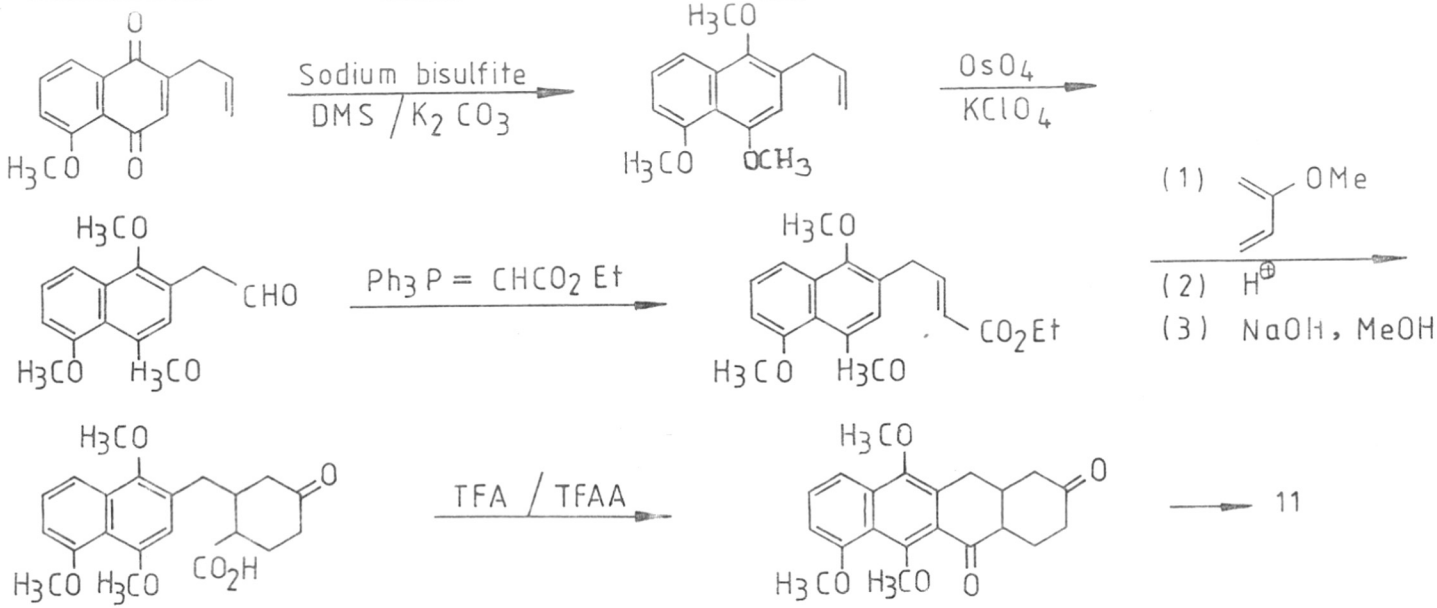
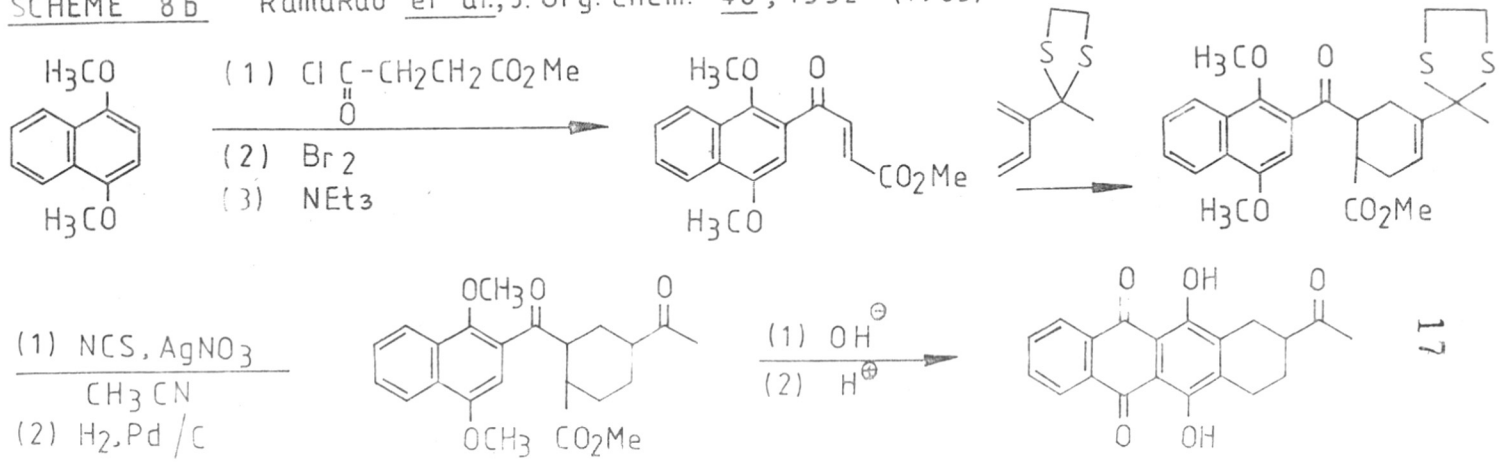
SCHEME 8 a RamaRao et al., Tetrahedron Lett 23, 775 (1982)



SCHEME 8 b RamaRao et al., J. Org. Chem. 48, 1552 (1983)

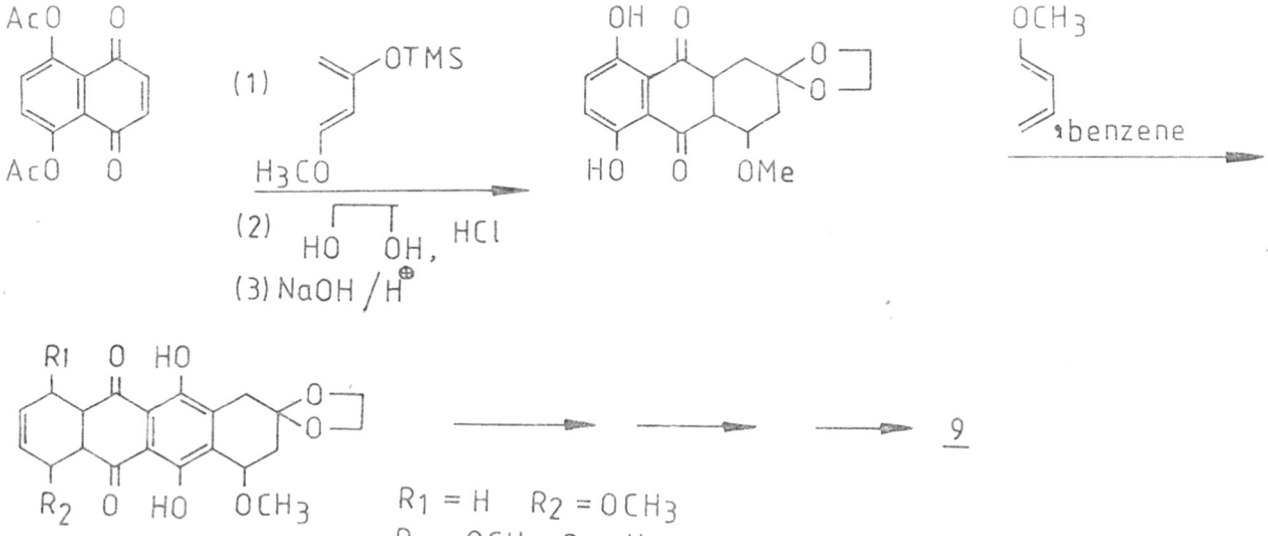


Diels-Alder reaction of a suitable dienophile with appropriate diene to give after four steps (±)-4-demethoxy-7,9-dideoxydaunomycinone (Scheme-8b), a late stage precursor to (±)-4-demethoxydaunomycinone.

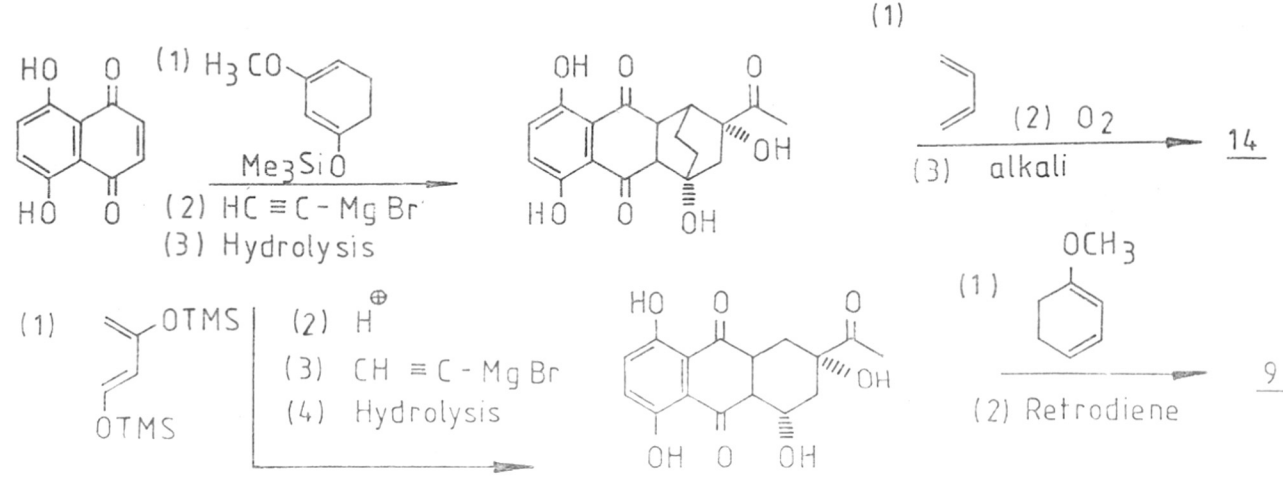
The construction of rings A and D starting from a precursor representing rings B and C was reported by Farina and Pardos[38] (Scheme-9a). According to their study, the successive Diels-Alder reactions of naphthazarin diacetate with (E)-1-methoxy-3-trimethylsiloxy-1,3-butadiene and (E)-1-methoxy-1,3-butadiene furnished (±) daunomycinone. The similar method was developed independently by Krohn et al.[39] in which the synthesis of 4-demethoxydaunomycinone and daunomycinone was reported by successive Diels-Alder reactions on naphthazarin with appropriate dienes (Scheme-9b).

The problem of regioselectivity was solved by the remarkable synthetic study by Kelly et al.[40] According to this study (Scheme-10), (±)-daunomycinone was regioselectively obtained in ten steps in 36% yield from commercially available naphthazarin. The results obtained by Farina et al.[41] confirmed the utility of the halogenated naphthazarins to control the orientation of remote substituents in the elaboration of tetracyclic systems by cycloaddition reaction. They described the regioselective route to a late stage precursor of (±) daunomycinone via a succession of Diels-Alder reactions from 2,7-dichloronaphthazarin (Scheme-11).

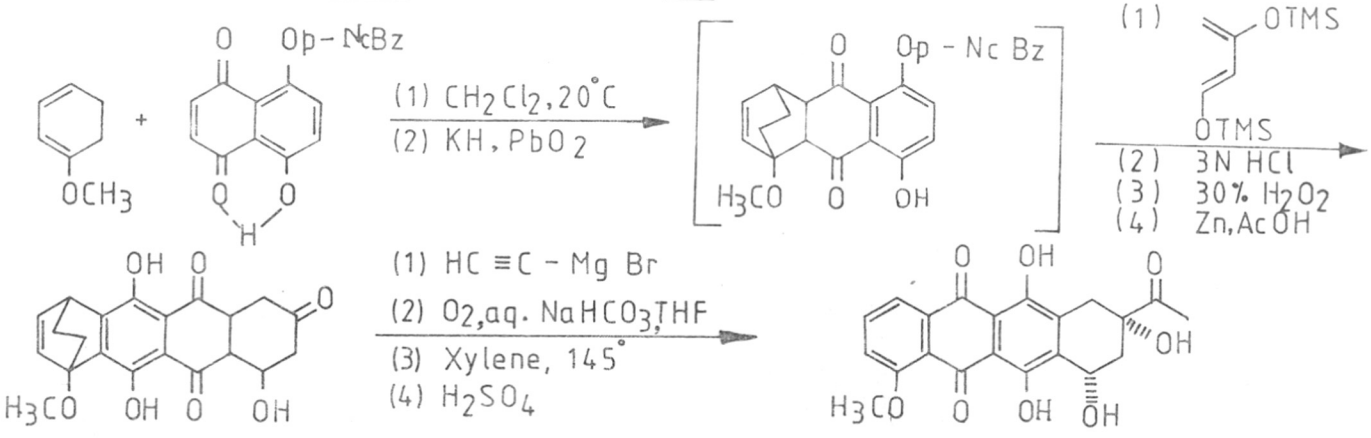
SCHEME 9a Farina et al., Tetrahedron Lett. 477 (1979)



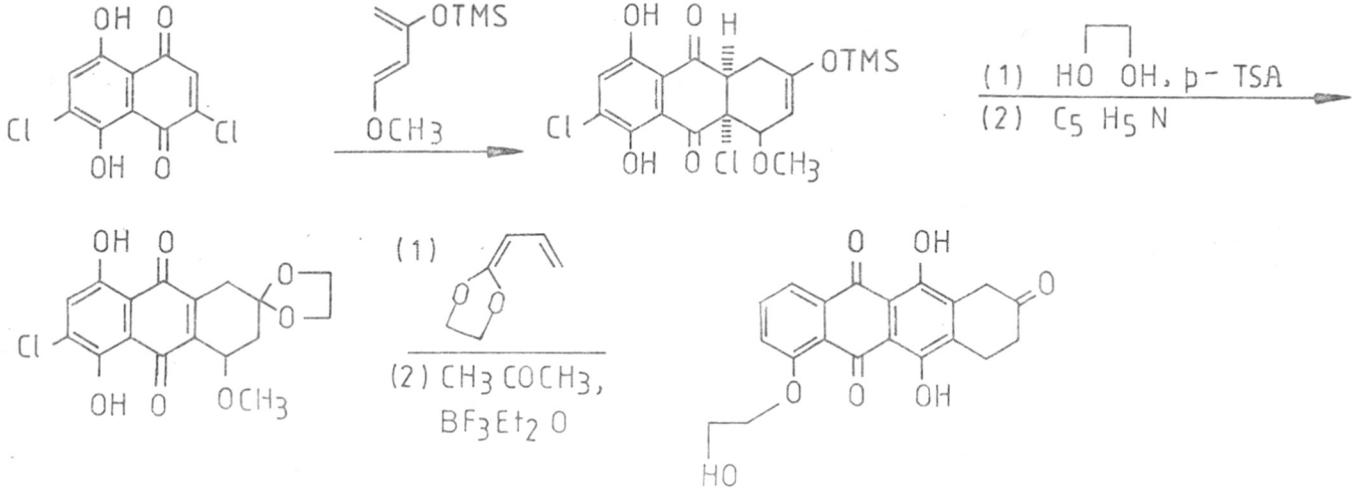
SCHEME 9b Krohn, Chem. Ber., 112, 2640 (1979)



SCHEME 10 Kelly et al., J. Am. Chem. Soc. 102, 5983 (1980)



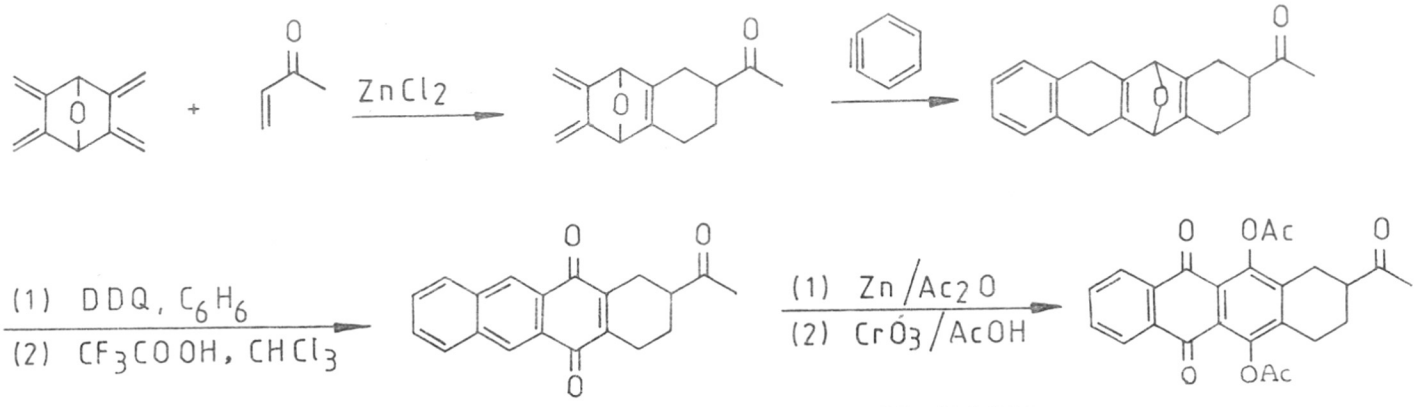
SCHEME 11 Farina et al., Tetrahedron, 40, 4561 (1984)



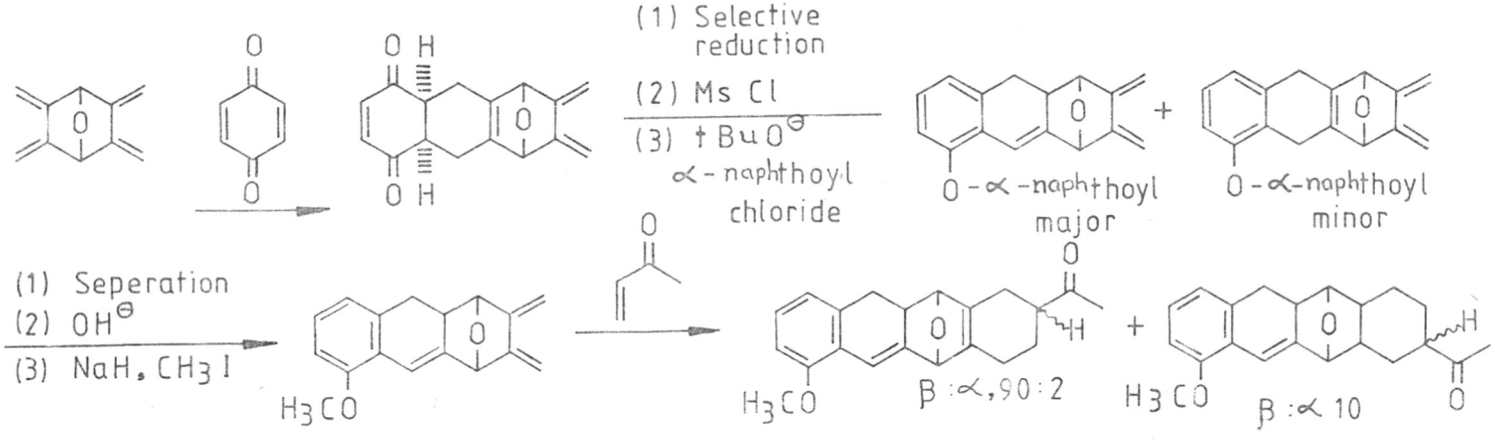
Vogel et al.[42a] reported sequential Diels-Alder addition of methyl vinyl ketone and dehydrobenzene with 2,3,5,6-tetrahydroethylidene-7-oxanorbornane to give the adduct which was oxidised and further elaborated to a precursor of (±)-4-demethoxydaunomycinone (Scheme-12a). Later, they[42b] extended the strategy for the synthesis of (±)-7,9-dideoxydaunomycinone inolving the sequential Diels-Alder reaction of 2,3,5-tris(methylene)norbornane and benzoquinone and methyl vinyl ketone with para regioselectivity (Scheme 12b). By applying the same strategy, Vogel et al[42c] synthesised 7,11-dideoxydaunomycinone (Scheme-12c) in which precursors were 2,5-dimethylidene-3,6-bis[(2)-[2-nitrophenyl]sulfenylmethylidene]-7-oxabicyclo[2.2.1]heptane and 2,3-didehydroanisole and methyl vinyl ketone.

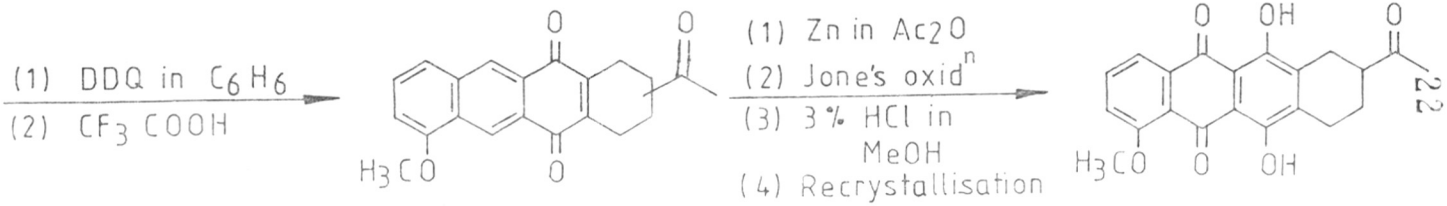
Various studies have shown that o-quinodimethane substituents on dienes and dienophiles impart good selectivity to Diels-Alder reactions. This was exploited by Farina et al.[43] for the preparation of the key intermediate in the synthesis of anthracyclinone in which the key step was the construction of the C-ring of the tetracyclic system by the Diels-Alder reaction (Scheme-13). The strategy of constructing ring-A of an anthracyclinone

SCHEME 12a Vogel et al., Helv Chim Acta, 63, 232 (1980)

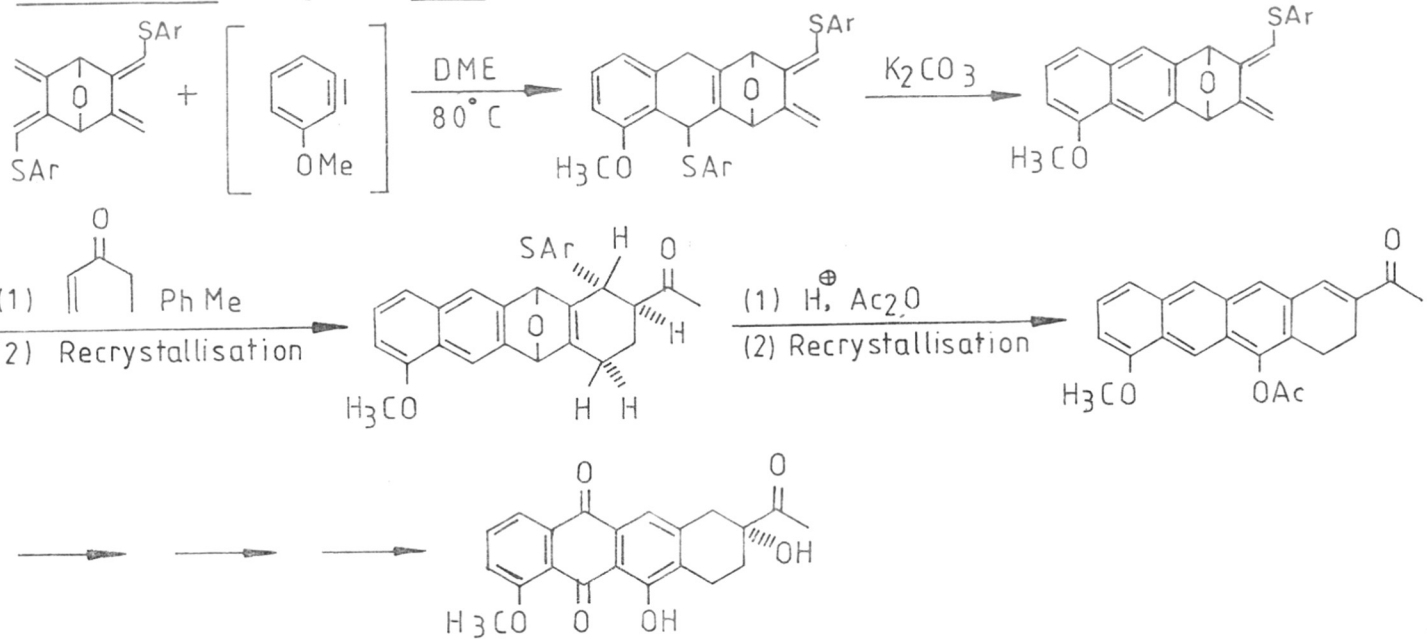


SCHEME 12b Vogel et al., TetrahedronLett, 24, 1497 (1983)

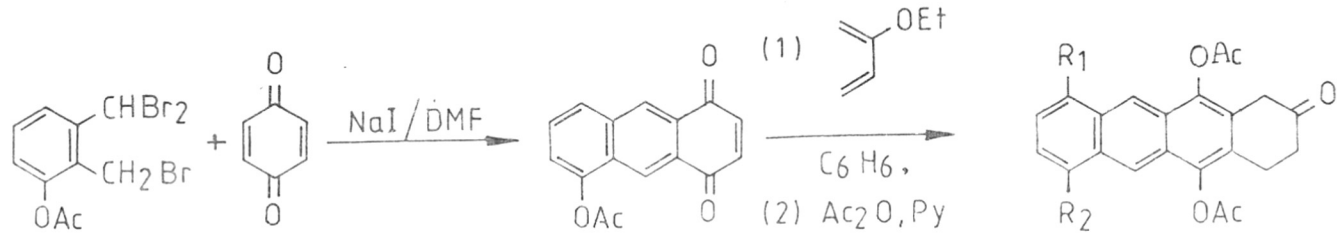




SCHEME 12c Vogel P. et al., Helv. Chim.Acta, 68 1067 (1985)



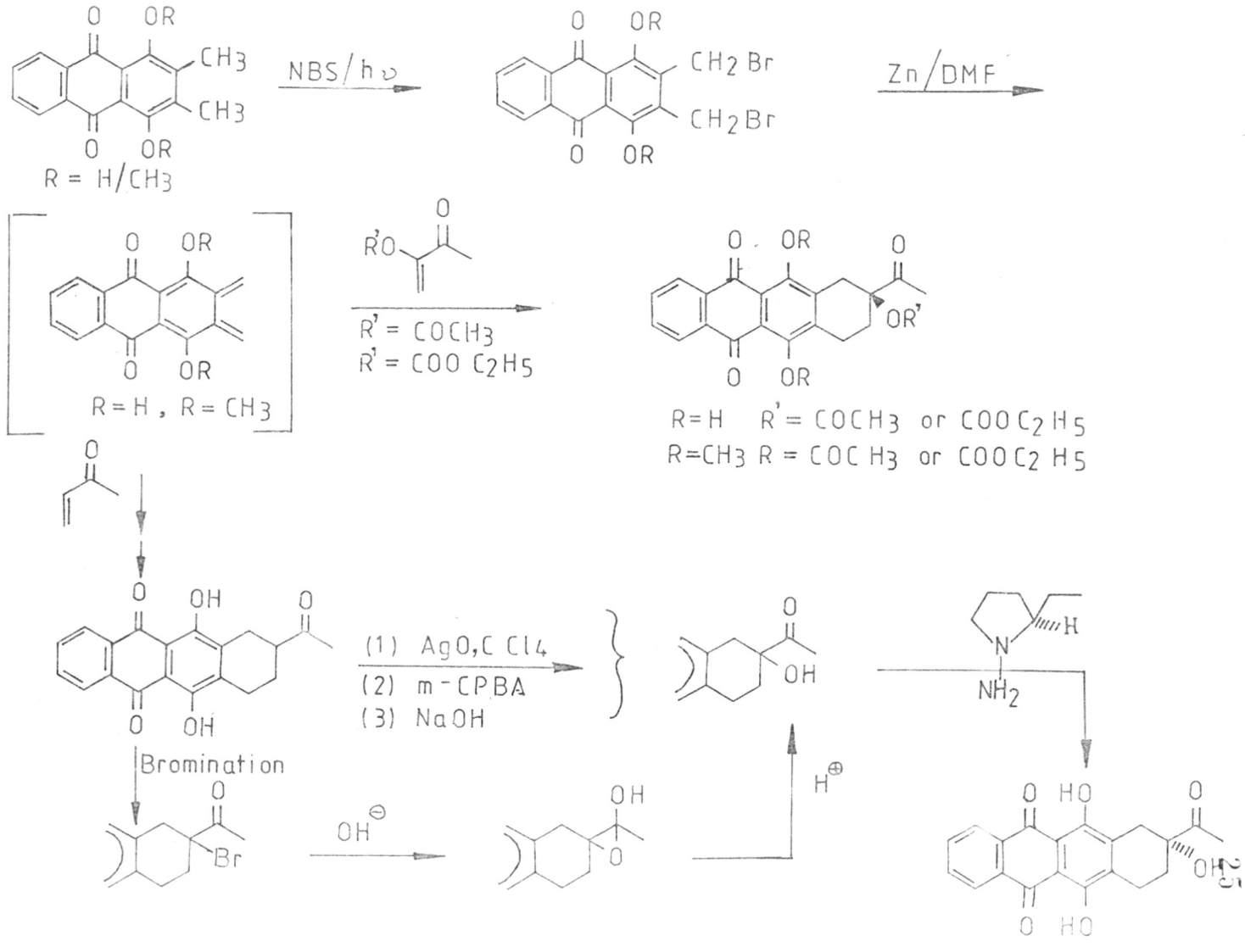
SCHEME 13 Farina et al., Chem. Lett, 77, (1980)



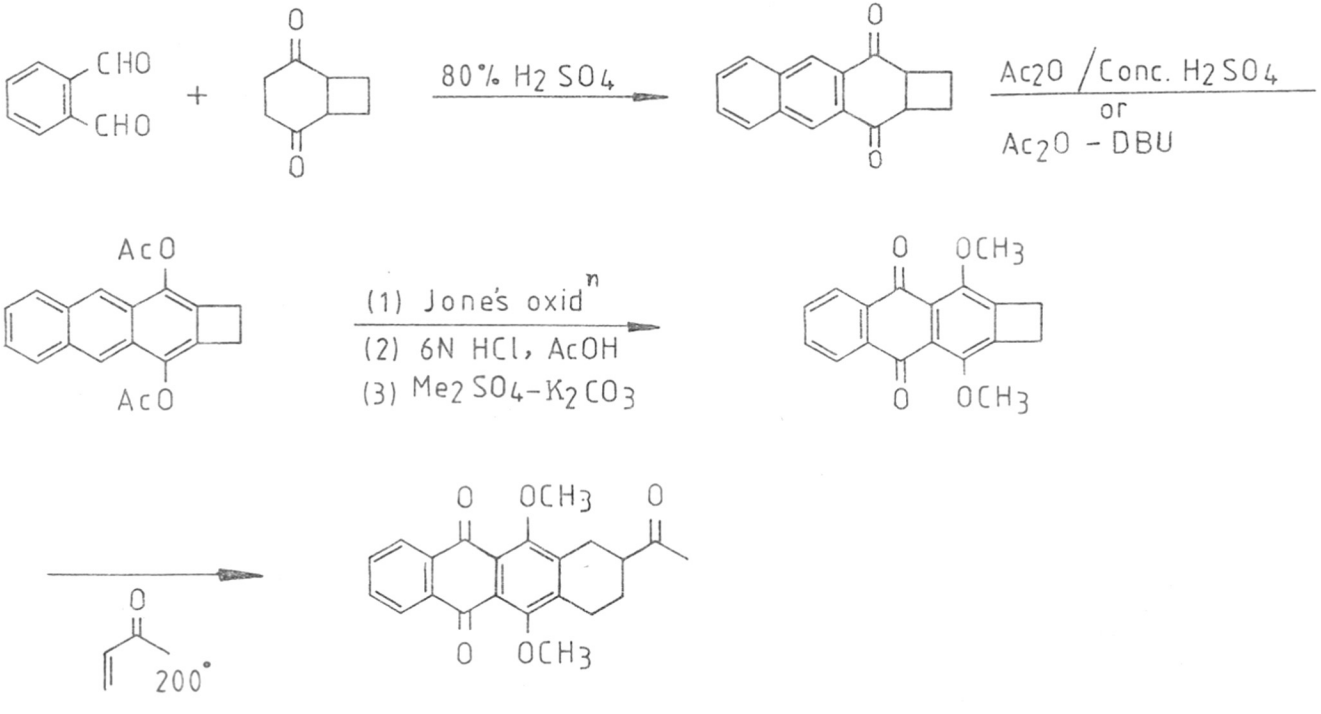
system was reported by Cava et al.[44a,b] A comparative study was made of the dienophiles with related transient anthraquinone-o-quinodimethanes which are readily available from 2,3-dimethylquinizarin. The yield of the tetracyclic adduct obtained was highly dependent upon the structures of dienophiles and dienes. Later on, they[44c] reported the introduction of 9-hydroxyl substituent in (±) 4-demethoxy-7,9-dideoxydaunomycinone via enol-acetate method and subsequent alkaline hydrolysis. They[44d] modified the procedure for introduction of C-9 hydroxyl group. (±)-4-Demethoxy-7,9-dideoxydaunomycinone was brominated at 9 position and was subjected to react rapidly with cold dilute sodium hydroxide to give 4-demethoxy-7-deoxy-daunomycinone in high yields. They also reported the procedure for optically active 4-demethoxy-7-deoxydaunomycinone via resolution of racemic compound with Enders' reagent (Scheme-14).

The regiospecificity of the reactions of several juglone derivatives with complex dienes derived from bicyclic dimethoxy cyclobutenes was examined as a model study leading towards the synthesis of anthracyclinone systems.[45] Oda et al.[46] synthesised the compound 1,2-dihydro-3,10-dihydro-cyclobut(b)-anthracene-4,9-dione, a key intermediate for 4-demethoxydaunomycinone in four steps from bicyclo(4.2.0)-octane-2,5-dione and o-phthaldehyde undergoing clean

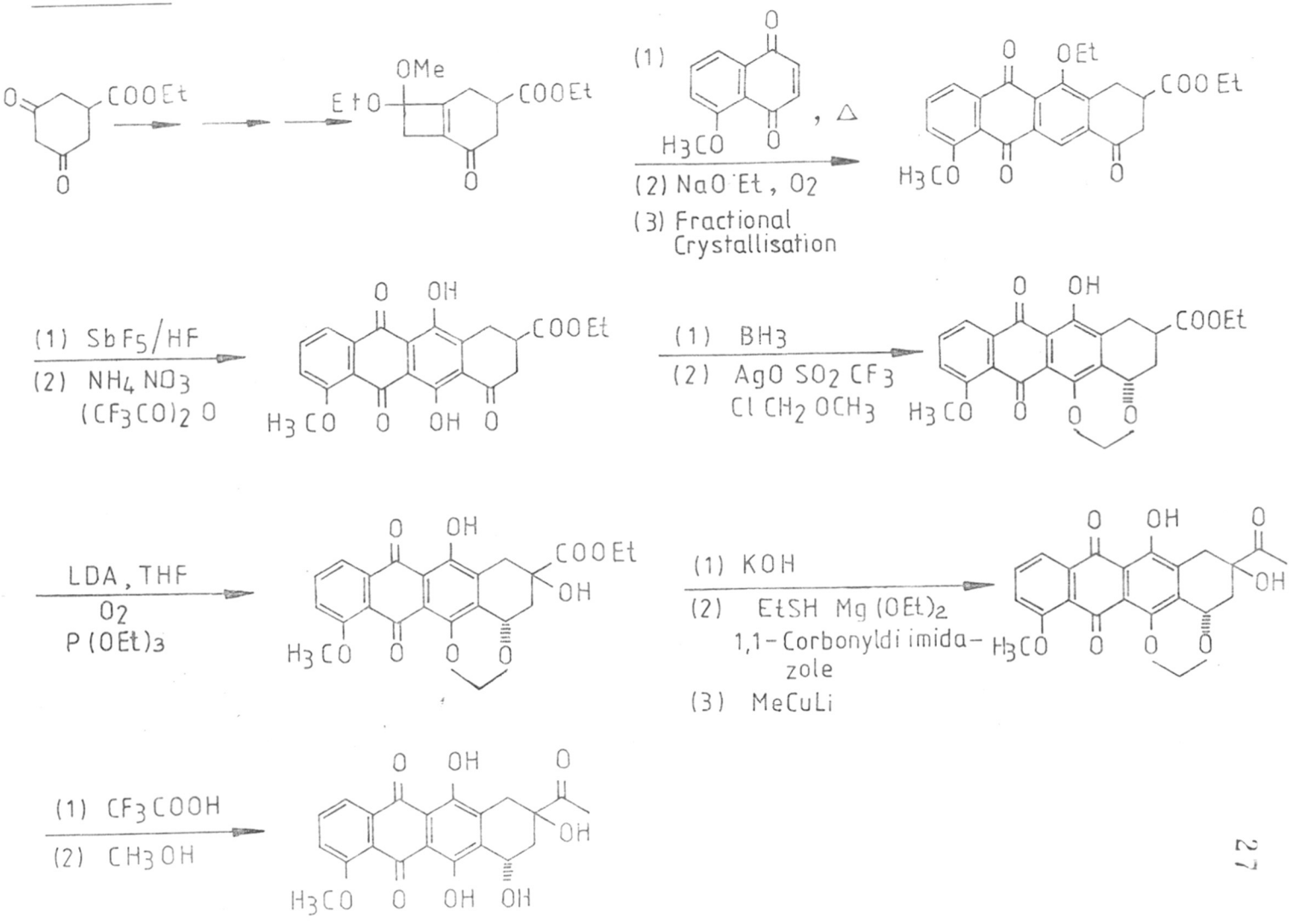
SCHEME 14 Cava et al., Tetrahedron Lett, 26, 4703 (1985)



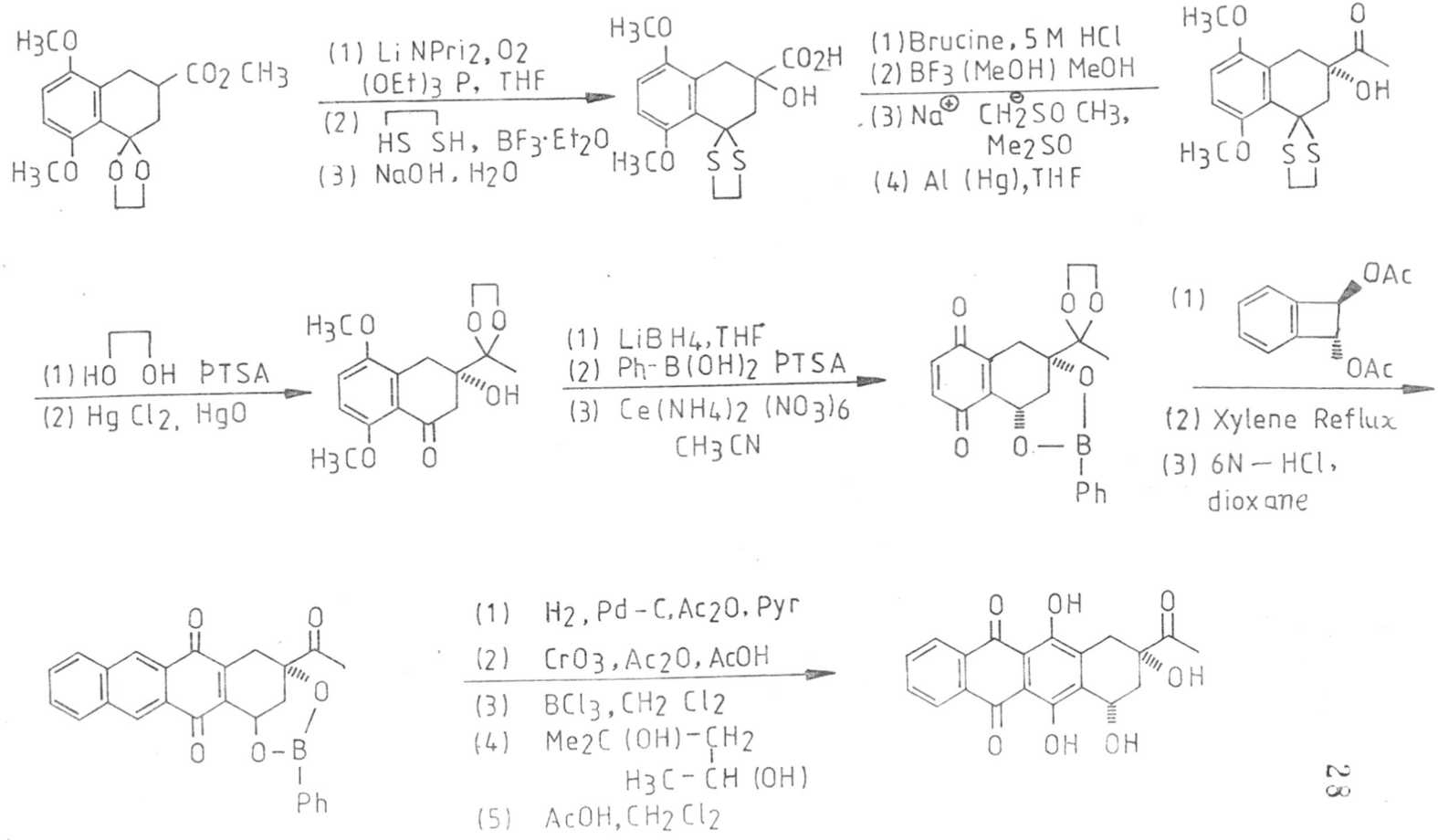
SCHEME 15 Oda et al., Tetrahedron Lett, 24, 5623 (1983)



SCHEME 16 Boeckman & Cheon, J. Am. Chem Soc., 105, 4112 (1983)



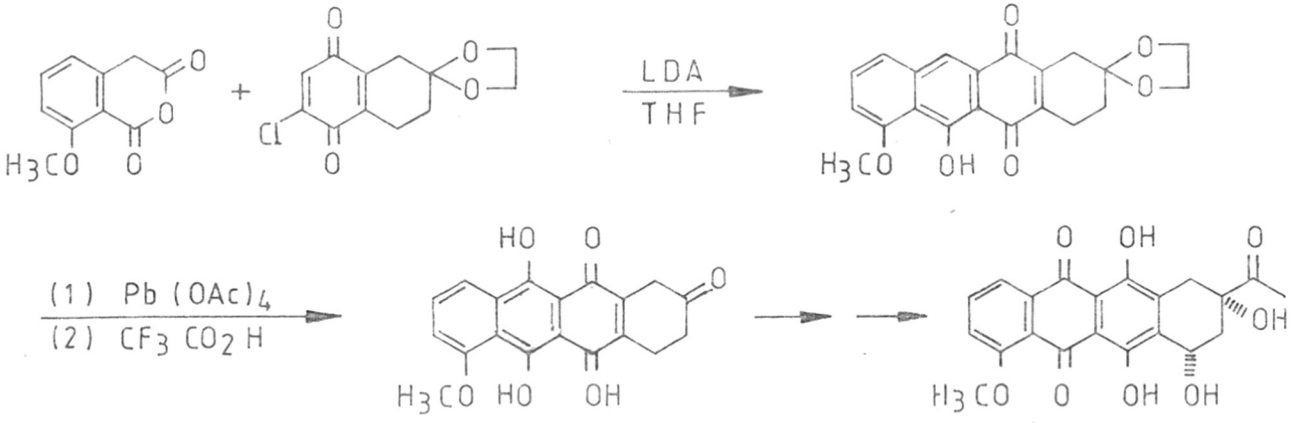
SCHEME 17 Broadhurst et al., J. Chem. Soc. Chem. Commu, 158 (1982)



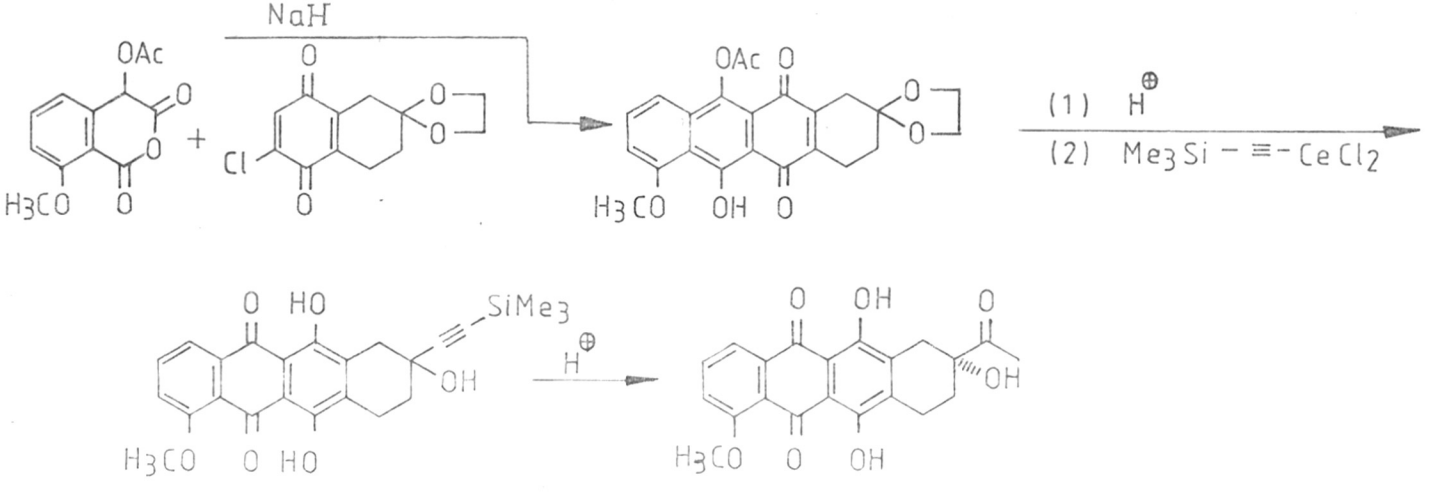
thermolytic intermolecular Diels-Alder reaction providing a general synthesis of 7,8,9,10-tetrahydro-6,11-dihydro-5,12-naphthacenediones (Scheme-15). Boeckmann and Cheon[47] reported a flexible, synthetic sequence for the preparation of daunomycinone, adriamycinone and their 6-deoxy analogues by employing Diels-Alder reaction between juglone and the diene equivalents which were obtained from dihydroresorcinol derivatives (Scheme-16). The special feature of this synthesis was the incorporation of C-7 hydroxyl group at early stage. Broadhurst et al.[48] reported the synthesis of (+) 4-demethoxydaunomycinone (Scheme-17) by a Diels-Alder reaction of optically active fully functionalised bicyclic system with o-benzoquinone-dimethide which on glycosidation with the daunosamine derivative afforded (+) 4-demethoxydaunomycin.

Tamura et al[49a] reported the strong base induced cycloadditons of homophthalic anhydrides and related compounds with halo-1,4-naphthaquinone derivatives to provide short, convergent synthesis of daunomycinone (Scheme-18a). Later, they[49b] modified the reaction design by using C-4 acetoxyl derivatives of homophthalic anhydride (Scheme-18b). They[49c] applied the same strategy for the synthesis of 11-deoxydaunomycinone (Scheme-19a). Further, they[49d] reported the regiospecific synthesis of 11-deoxydaunomycinone by using the anhydride in which

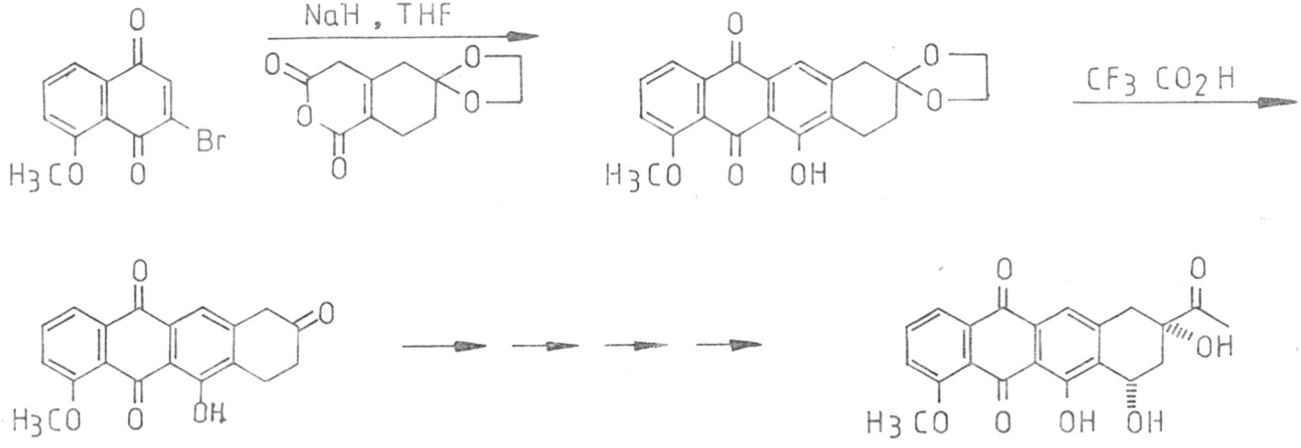
SCHEME 18a Tamura et al., J. Org. Chem., 47, 4376 (1982)



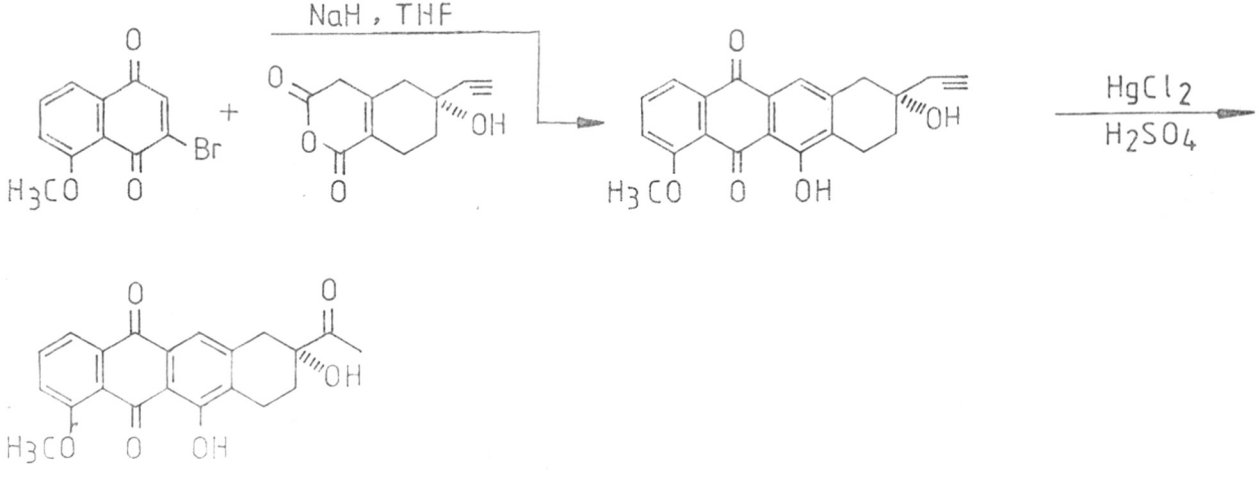
SCHEME 18 b Tamura et al., Tetrahedron Lett, 27, 195 (1986)



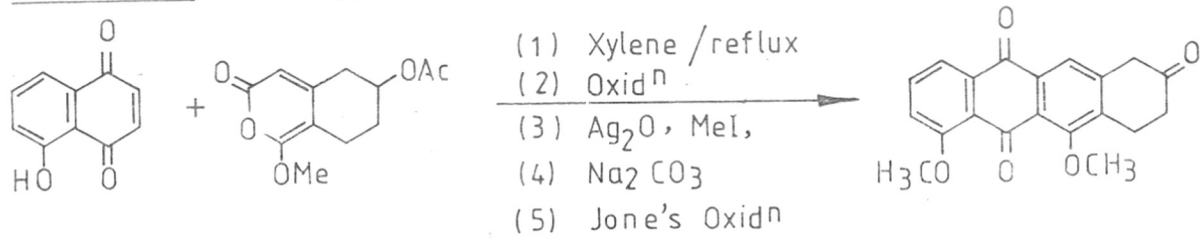
SCHEME 19 a Tamura et al., Tetrahedron 40, 4539 (1984)



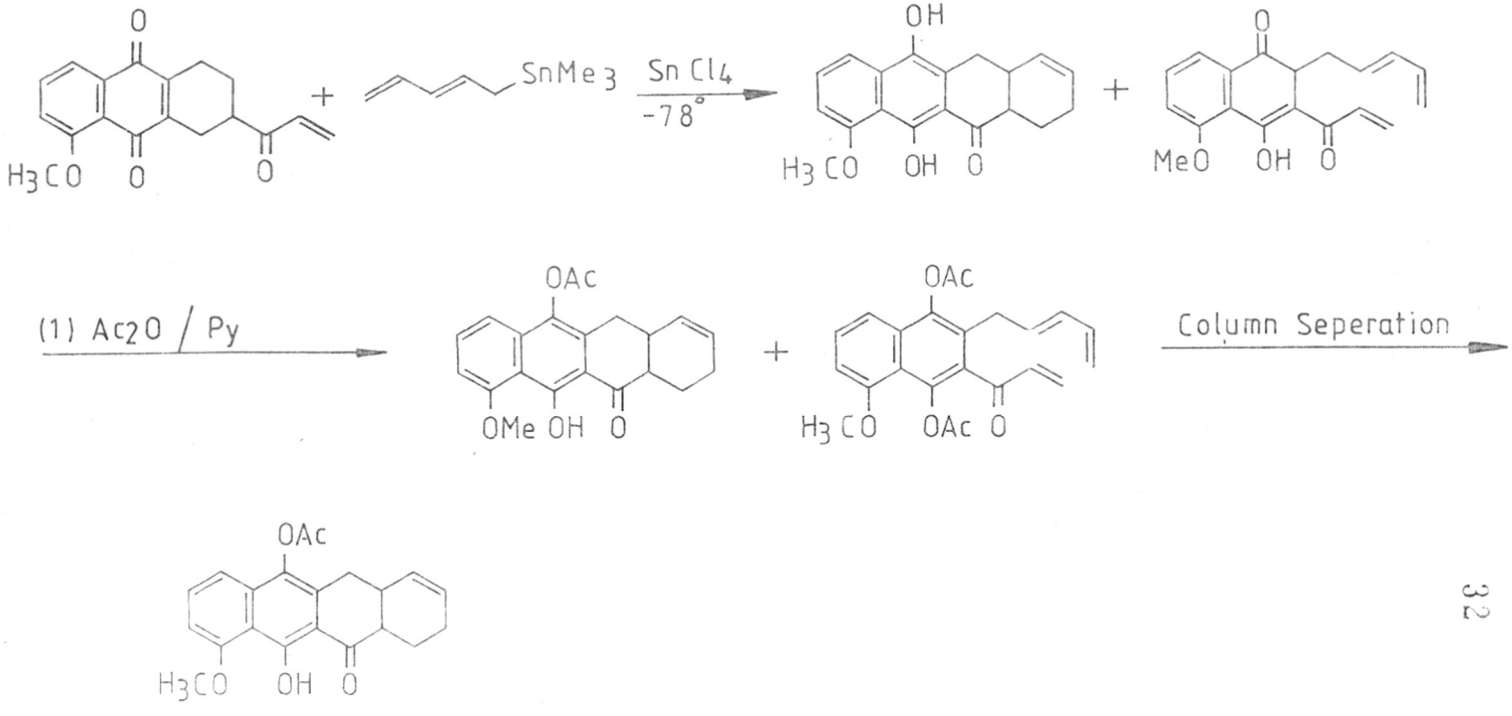
SCHEME 19 b Tamura et al., Tetrahedron Lett, 26, 1549 (1985)



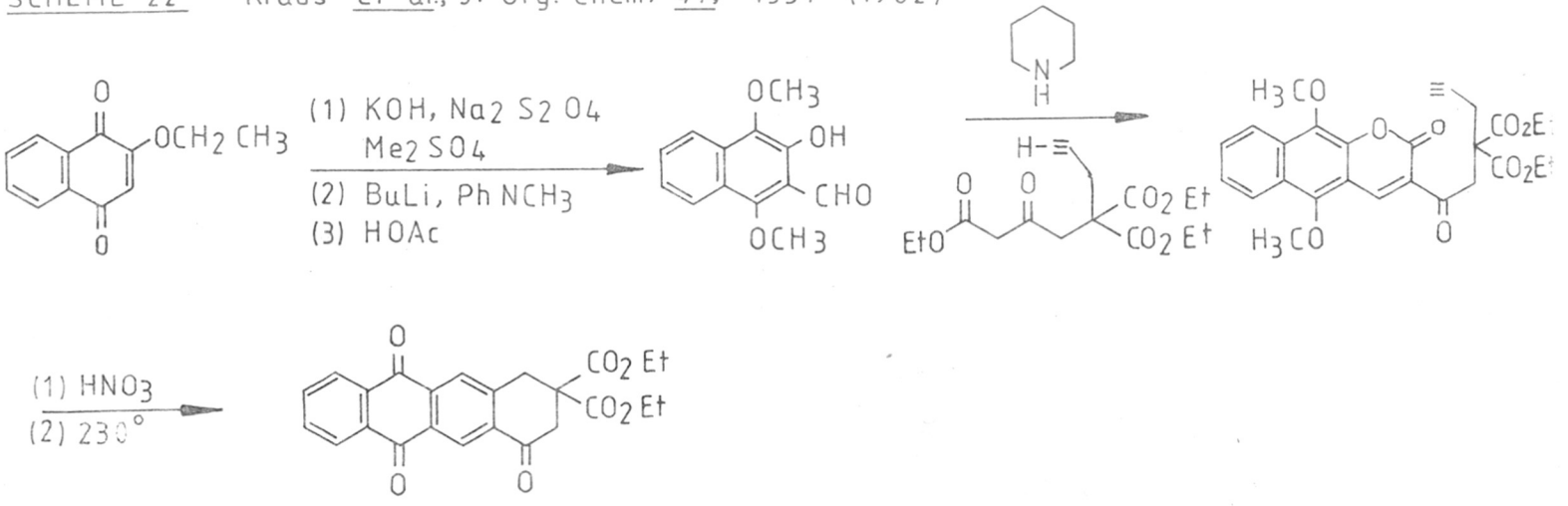
SCHEME 20 Jung et al., J. Org. Chem. 47, 1150 (1982)



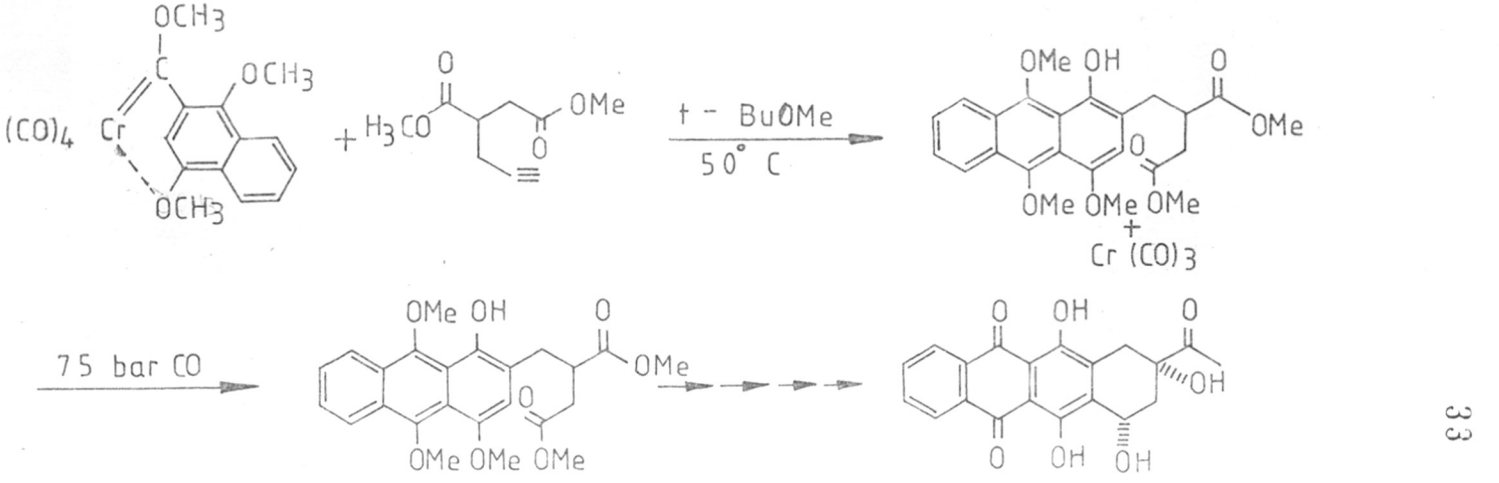
SCHEME 21 Natura, Chem. Lett, 18, 1687 (1983)



SCHEME 22 Kraus et al., J. Org. Chem. 47, 4337 (1982)



SCHEME 23 Dotz H.& Popall M. J. Orgmet. Chem, 291, C4 (1985)



ring A of anthracyclinone was functionalised in advance (Scheme-19b).

Jung et al[50] have used substituted alkoxypyrones as dienes in the synthesis of 11-deoxyanthracyclinones (Scheme-20). Natura et al[52] reported a general synthetic route to 11-deoxy type tetracyclic intermediate by one step construction of AB rings via tandem 1,4/(4+2) addition of conjugated diene and activated bond (Scheme-21). Kraus et al.[52] described a synthesis in which the key reaction was the cyclisation of acetylenic coumarin to anthraquinones. Dotz et al.[53] developed the cycloaddition of Cr-Co-ordinated alkyne, carbene and carbonyl ligands to provide a variable route to the anthracyclinone skeleton. The key step of a formal total synthesis of 4-demethoxy-daunomycinone was based on the reaction of carbonylcarbene complex used as a CD ring synthon and alkyne leading to the formation of ring B (Scheme-23).

2. 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 regiochemistry determining step. A regioselective synthesis of tetracyclic ketone was carried out by Kende et al.[54] which was based on the Michael addition of 1,4,5-trimethoxynaphthylacetonitrile

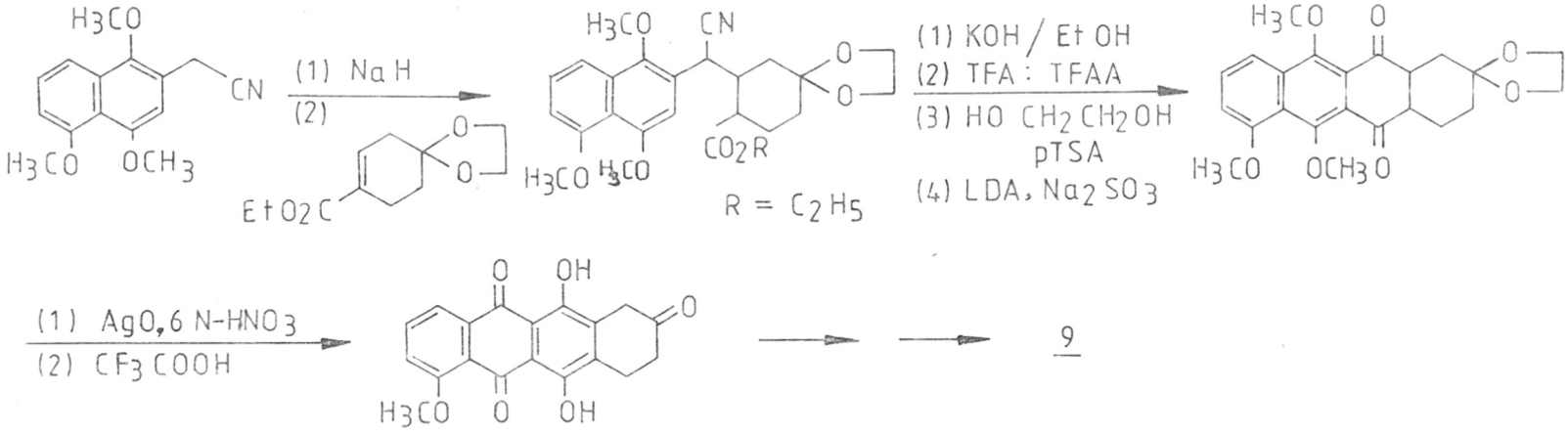
to the readily available cyclohexane ester ketal (Scheme-24). The similar approach was independently developed by Parker and Kallmerten.[55]

The phthalic anhydrides are attacked by the Grignard reagent in tetrahydrofuran almost exclusively at carbonyl group which is situated at the meta position of methoxyl substituent. This highly regioselective reaction was used as the key step in the synthesis of (±)-daunomycinone by Braun[56] (Scheme-25). The ortho-lithiated benzamides were used in the regiospecific synthesis of 11-deoxycarminomycinone by Kende et al.[51] (Scheme-26). Broadhurst et al[58] reported the synthesis of (±)-daunomycinone (Scheme-27a) by a mild procedure using phthalide intermediate for annelation. The 7,9-dideoxydaunomycinone (Scheme-27b) was also prepared[58] by reaction of 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene with 2-carbomethoxy-6-methoxy benzaldehyde in the presence of benzene boronic acid.

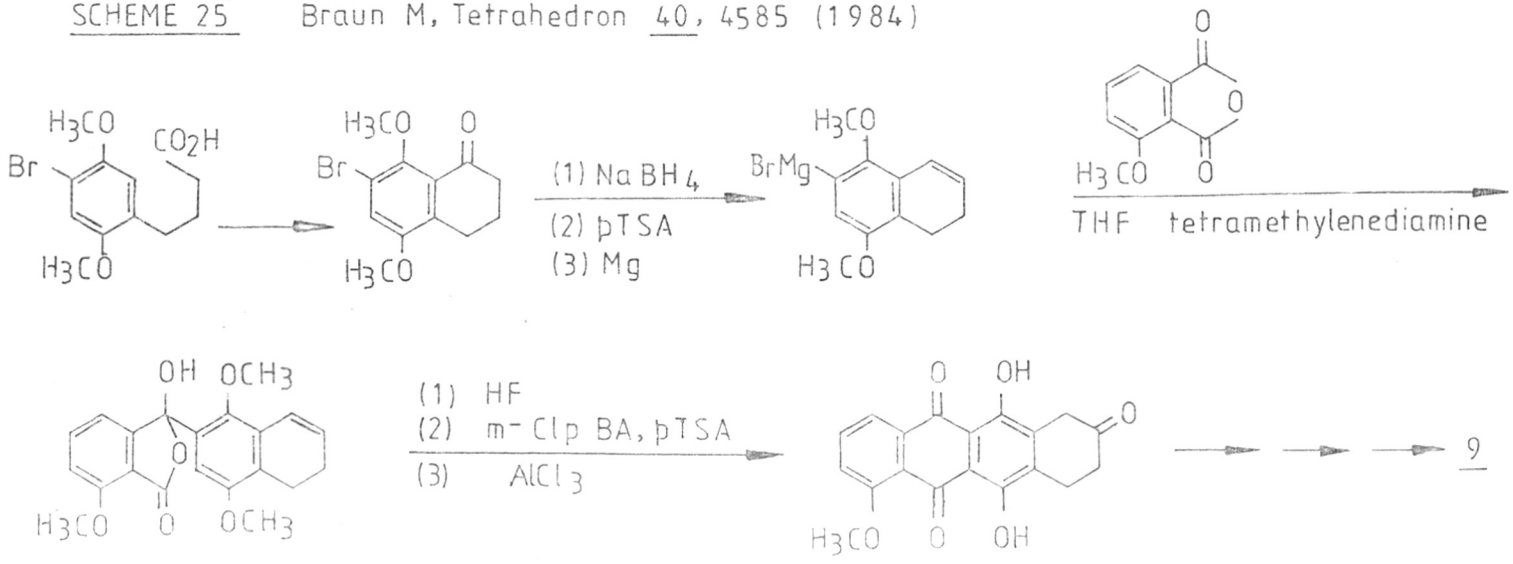
Hauser et al[59] reported the regiospecific synthesis of (±)-7-deoxydaunomycinone through repetitive ring annelations. The oxygenated B,C rings were formed through annelations from an initial and subsequently regenerated (phenyl sulfonyl) isofuranone fragment. To accomplish this initial annelation in an efficient manner 5-ethoxy-2-furanone was utilised as a synthon. Use of either

NUCLEOPHILIC ROUTES

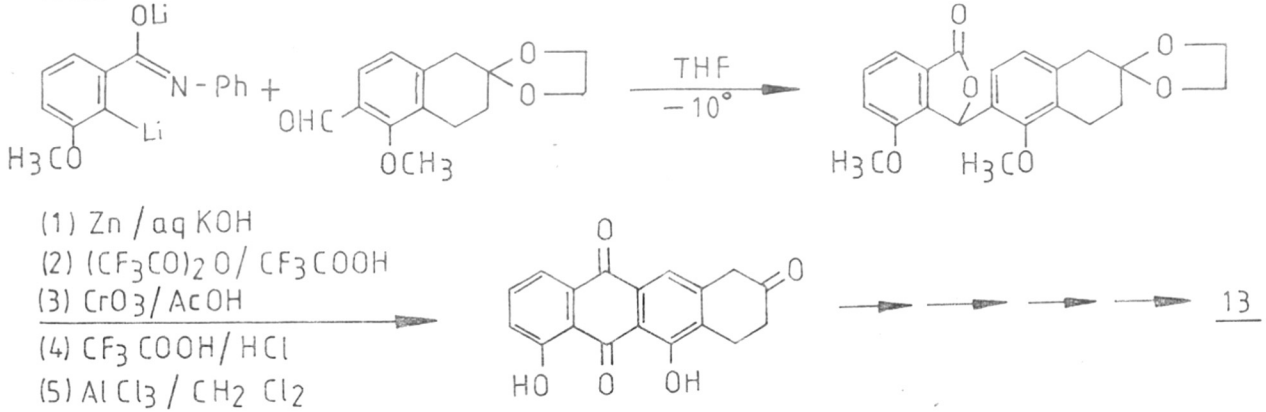
SCHEME 24 Kende et al., Tetrahedron Lett, 1201 (1979)



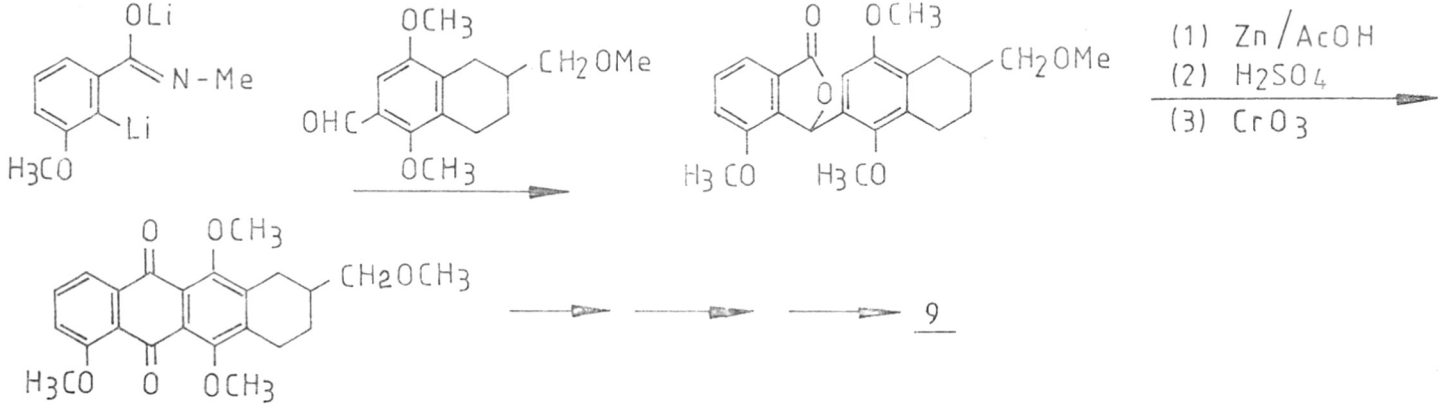
SCHEME 25 Braun M, Tetrahedron 40, 4585 (1984)



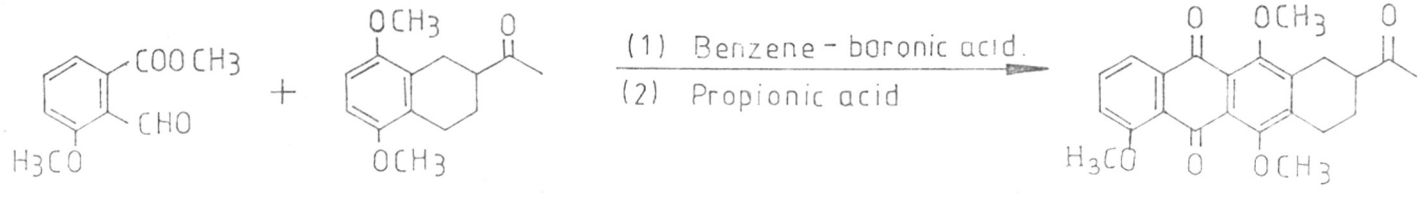
SCHEME 26 Kende et al., J. Org. Chem. 46, 2699 (1981)



SCHEME 27a Broadhurst et al., J. Chem. SOC, Perkin Trans I, 2227 (1982)



SCHEME 27b Broadhurst et al., J. Chem. SOC. Perkin Trans I, 2227 (1982)

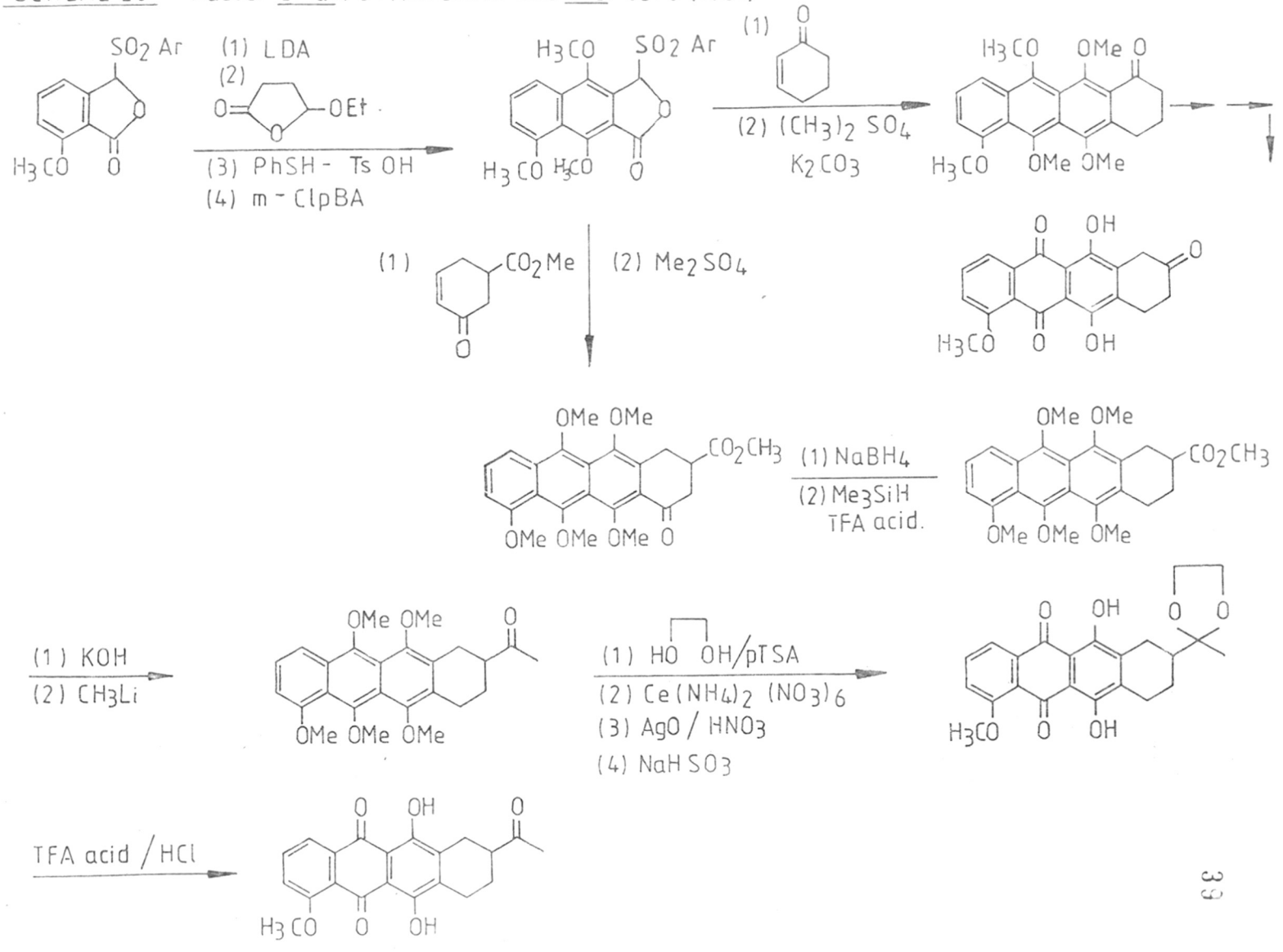


2-cyclohexene-1-one or 5-substituted 2-cyclohexene-1-one opened two ways for elaboration of ring A and generated the two routes to (±)-7-deoxydaunomycinone as shown in Scheme-28. Later on, they[60] reported a regiospecific synthesis of 7-11-dideoxydaunomycinone. The key element bicyclo-octanol was converted into suitably functionalised AB ring synthon. Condensation of AB ring synthon with the anion of methoxy-(phenylsulfonyl)-isobenzofuranone furnished the tetracyclic product. It was transformed into 7,11-dideoxydaunomycinone in single step (Scheme-29).

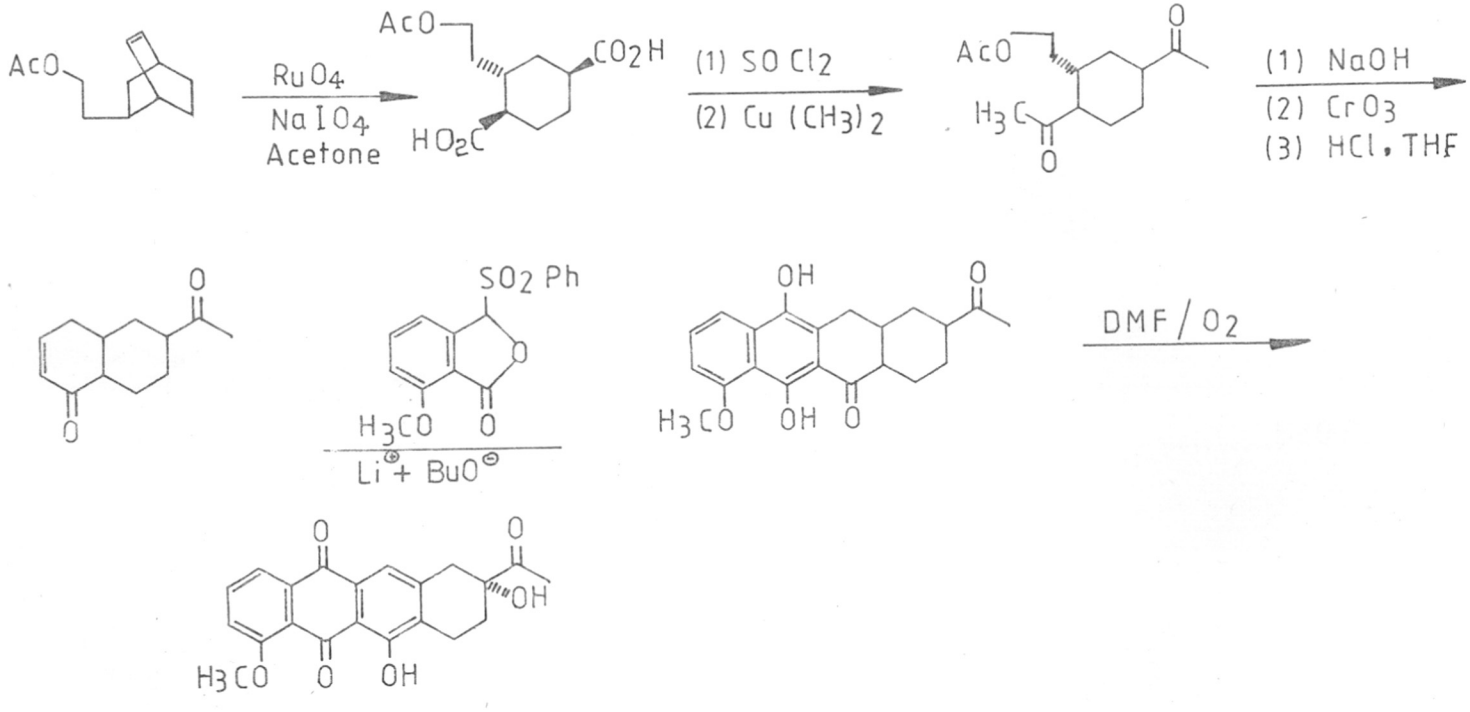
Regiospecific and efficient synthesis of anthracyclinones had been achieved by using directed metalation strategy by Furukawa et al.[61] The phthalides were prepared by the condensation of metalated N,N-diethylbenzamide derivatives with dihydronaphthalene carbaldehydes or by the reaction of metalated dihydronaphthalene with a phthalaldehydic amide derivative (Scheme-30).

The exploratory studies have established the utility of quinone-monoketals in the regiospecific sysnthesis of anthrones and anthraquinones. This strategy was exploited by Swenton et al[62a, b] for a convergent, regiospecific synthesis of daunomycinone (Scheme-31a) in which the combination of 1,4-dipole equivalents with an appropriate quinone monoketal effected a one step synthesis of an anthracyclinone fully functionalised in the ring A. Another

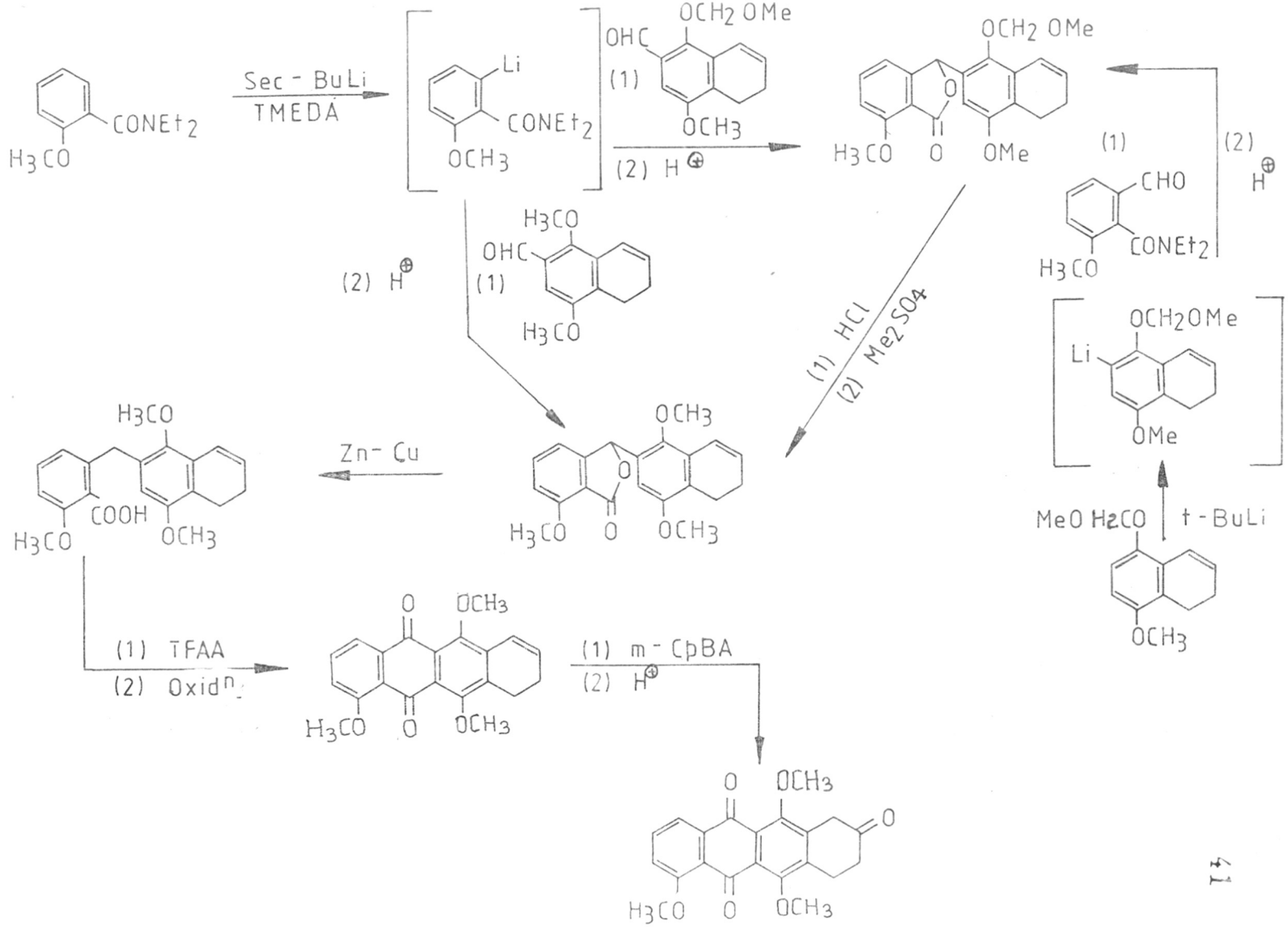
SCHEME 28 Hauser et al., J. Am. Chem. Soc. 103, 6378 (1981)



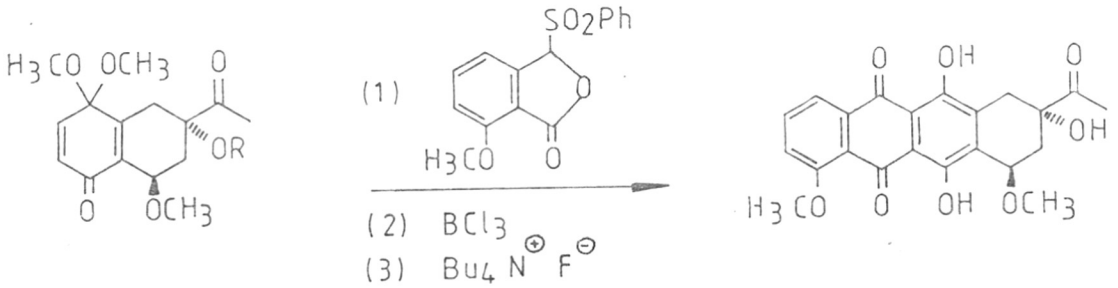
SCHEME 29 Hauser et al., J. Am. Chem. Soc. 105, 5688 (1983)



SCHEME 30 Furukawa et al., Chem. Pharm. Bull., 2662 (1983)



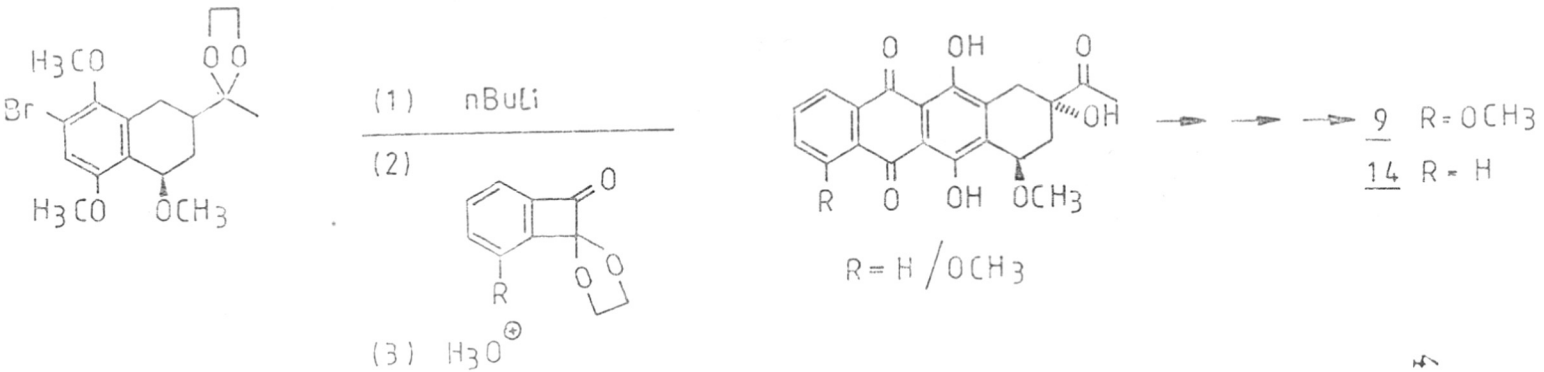
SCHEME 31a Swenton et al., J. Am. Chem. Soc 103, 5263 (1981)
Swenton et al., J. Am. Chem. Soc Chem Commu, 932 (1980)



R : $SiMe_3$

R : $SiMe_2$ tBu

SCHEME 31b Swenton et al., J. Org. Chem. 46, 4825 (1981)



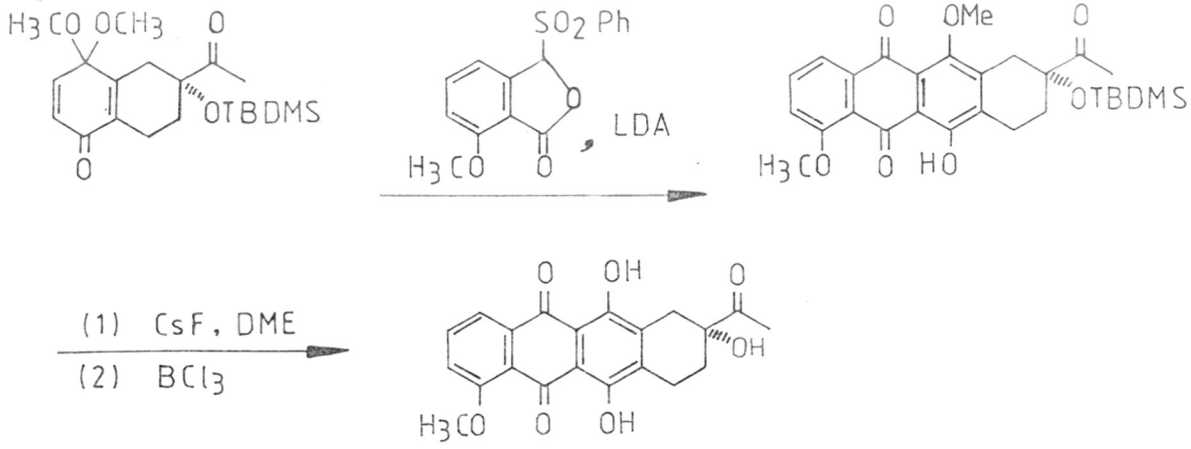
regiospecific route to 9 and 14 was also developed by them[62c] (Scheme-31b) in which a benzocyclobutenedione monoketal serving as a 1,4-dipole equivalent was reacted with a lithiated quinone bis-ketal serving as a metallated quinone equivalent to afford in one step a fully functionalised tetracyclic ring system. Russell et al.[63] reported a high yielding enantiospecific synthesis of 7-deoxydaunomycinone (Scheme-32) employing the regio-specific condensation between quinone monoketal and 1,4-dipole equivalent to afford tetracyclic skeleton in one step.

Rutledge et al [64] have described the synthesis in which benzyl bromide of 1,4-dihydroxy-2-methylanthraquinone was elaborated to (±)-4-demethoxy-7-deoxydaunomycinone via condensation with acetylbutyrolactone (Scheme-3). Synthetic strategy of 7,11-dideoxydaunomycinone developed by Sih et al[65] involved the nucleophilic condensation of CD ring synthon to a suitably functionalised ring A intermediate, followed by subsequent cyclisation of the ring B to give the tetracyclic system (Scheme-34).

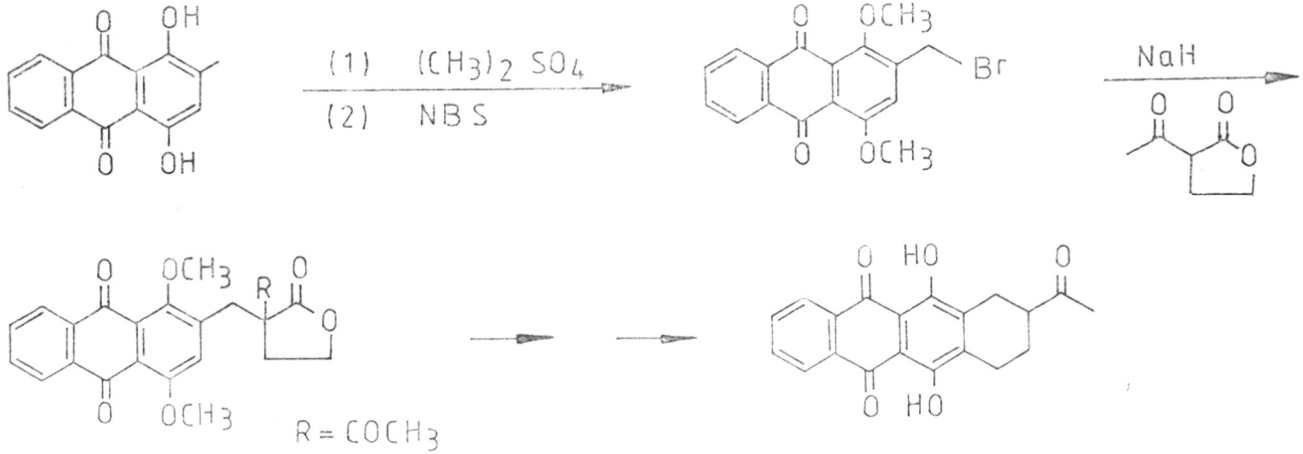
3. Friedel Crafts and Fries Routes

Friedel-Crafts reactions and especially photofries rearrangements have taken a suitable role in the regiospecific syntheses of many anthracyclinones. As Kelly already

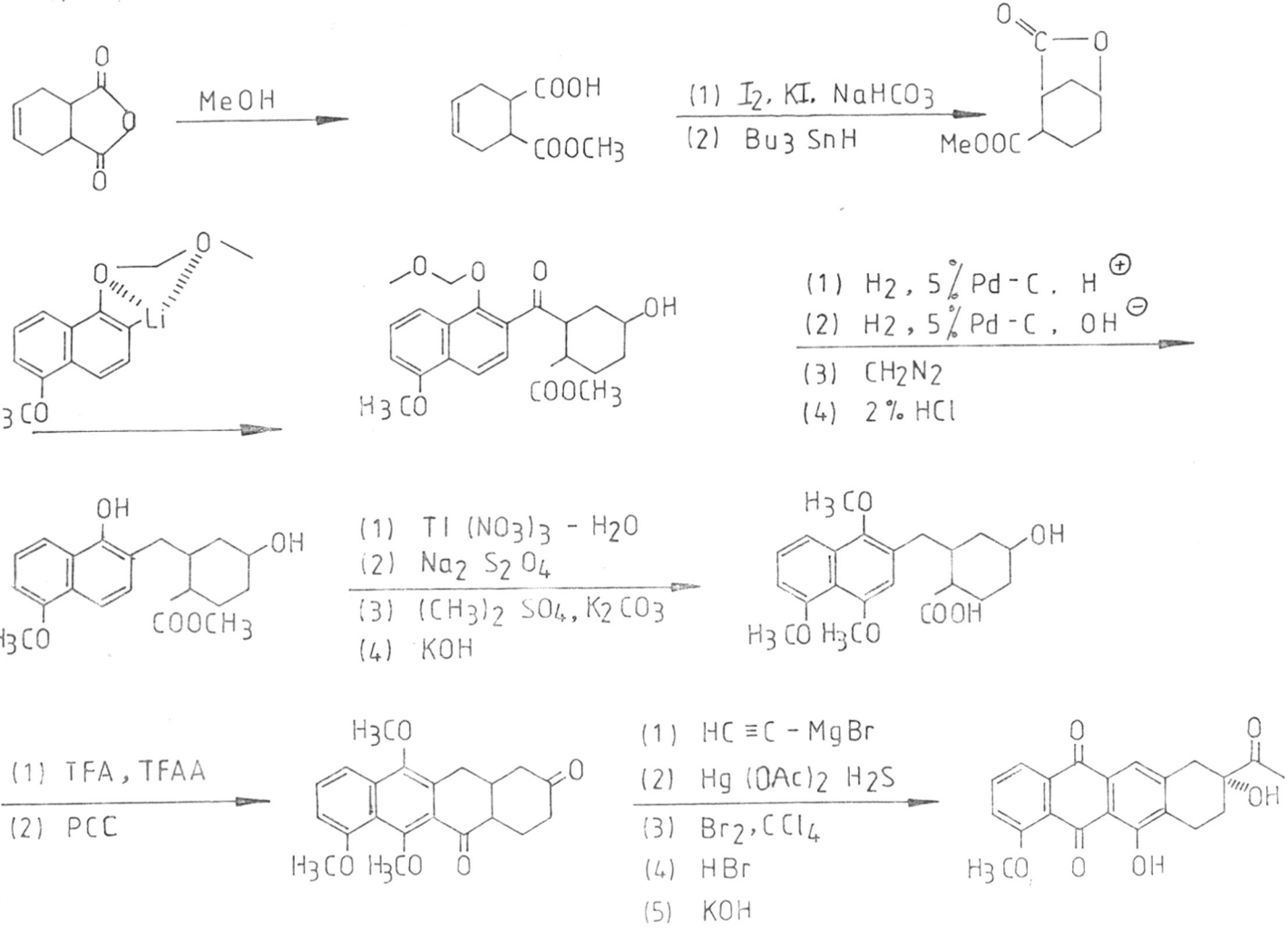
SCHEME 32 Russell et al., Tetrahedron Lett, 1517 (1984)



SCHEME 33 Rutledge et al., Syn. Commu, 15, 1081 (1985)



SCHEME 34 Sih et al., Tetrahedron Lett 22, 811 (1981)



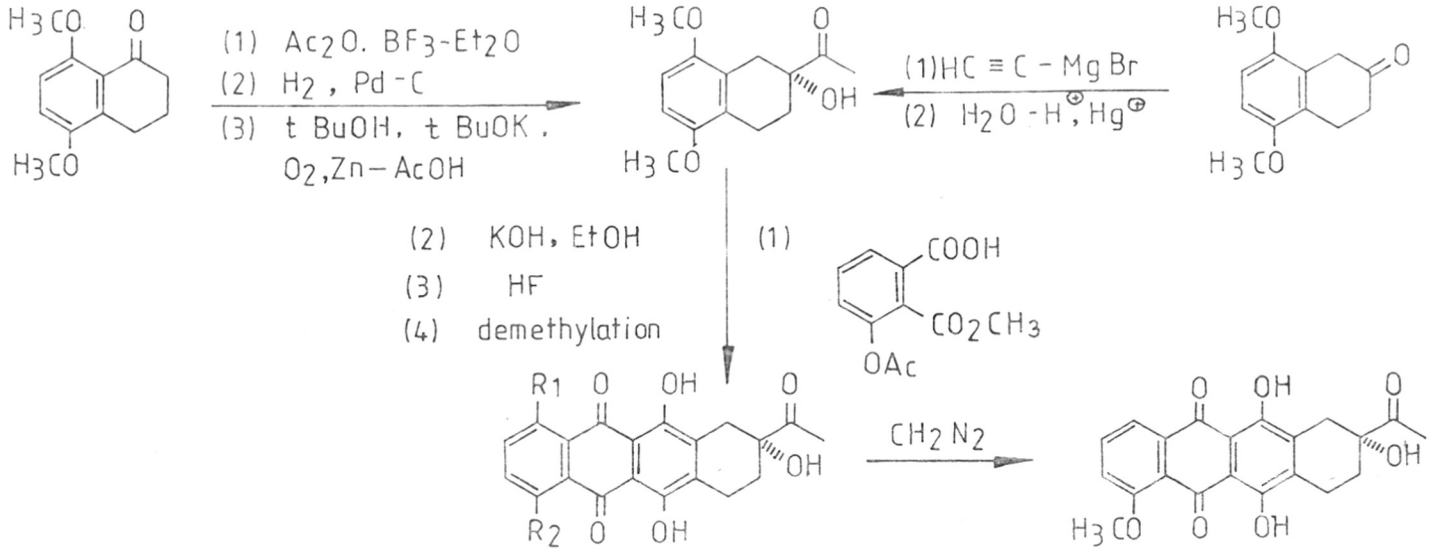
reviewed[28] many of these syntheses, only the recent reports are discussed here. The versatile method first employed by Wong et al[66] for the assemblage of tetracyclic system, AB+CD coupling seems to be the most appropriate. It involves the preparation of a tetralin derivative representing AB rings and its condensation by acylation with a phthalic acid derivative, corresponding to CD rings in tetracyclic system. Later, Arcamone et al.[67] developed a one step method for tetracyclic system by fusion of tetralin derivative with phthalic anhydride.

Hodge et al.[68] reported the Friedel-Crafts reaction of 5,8-dimethoxy-2-acetyl-1,2,3,4-tetrahydro-2-naphthol with 2-methoxy carbonyl benzoylchloride and 3-acetoxyphthalic acid half ester to give (±)-4-demethoxydaunomycinone and (±)-daunomycinone (Scheme-35) respectively. The key intermediate 5,8-dimethoxy-2-acetyl-1,2,3,4-tetrahydro-2-naphthol was prepared by two methods starting from corresponding α-tetralone as well as from β-tetralone. The attractive feature of this synthesis was that the carminomycinone was selectively methylated with diazomethane to give daunomycinone.

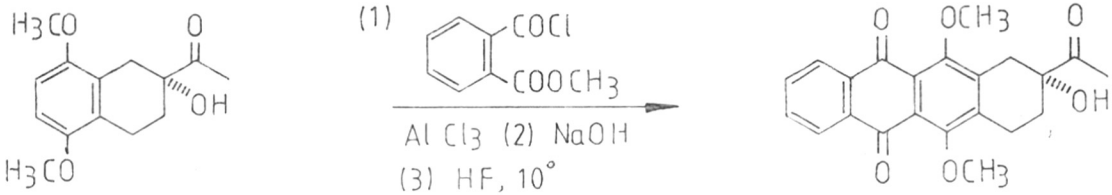
Terashima et al.[69] reported the synthesis of (±)-4-demethoxy-7-deoxydaunomycinone dimethyl ether (Scheme-36) by Friedel-Crafts reaction of tetralin (prepared from 1,4-dimethoxy benzene) with o-methoxy

FRIEDEL - CRAFTS AND FRIES MIGRATION ROUTES

SCHEME 35 Hodge et al., J. Chem. Soc. Chem. Commu, 85 (1979)



SCHEME 36 Terashima et al., Tetrahedron Lett, 2749 (1980)



carbonyl benzoyl chloride in the presence of aluminium chloride followed by cyclisation with anhydrous hydrogen fluoride.

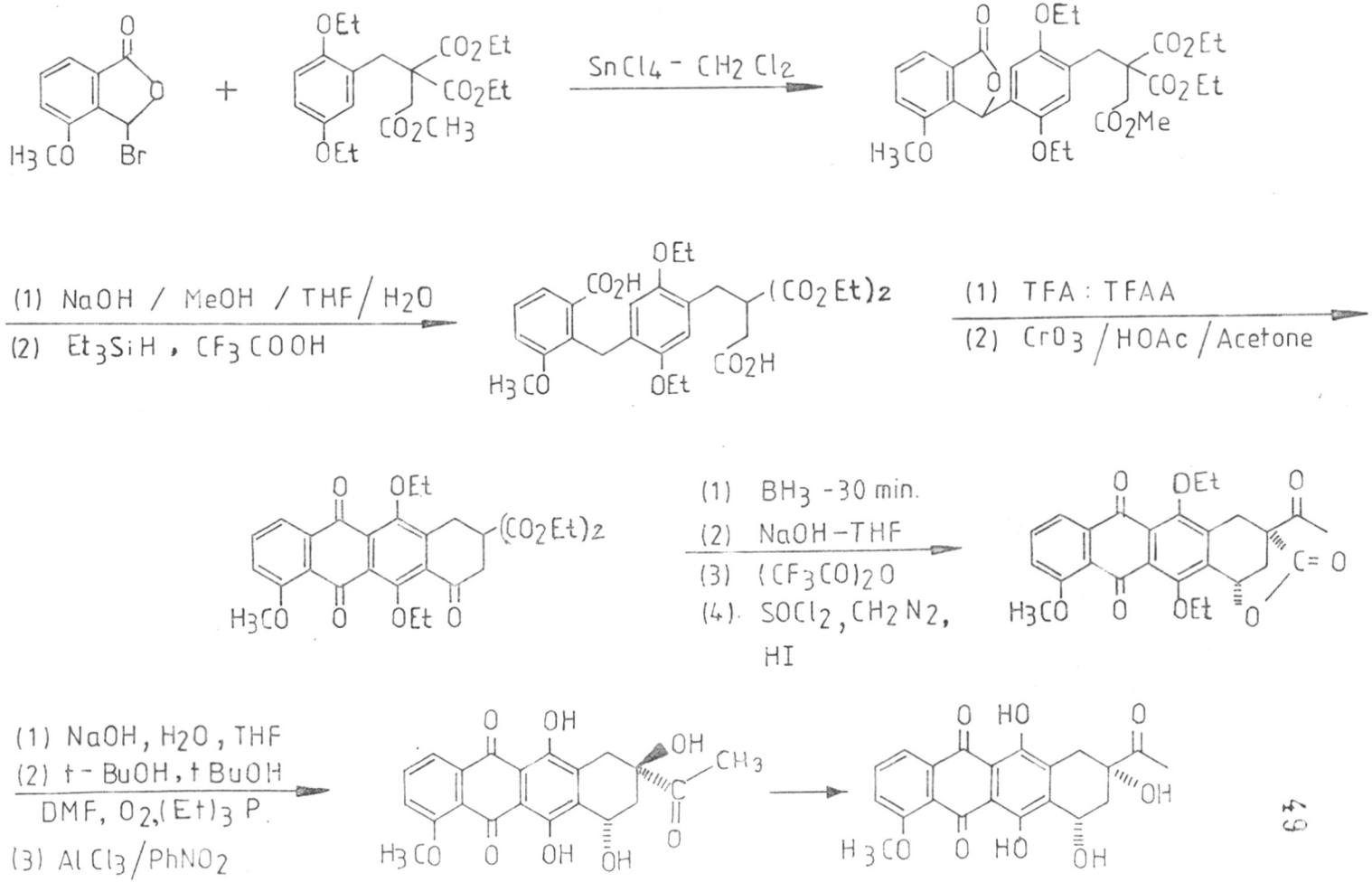
Rama Rao et al.[70a,b,c] reported the synthesis of (±)-4-demethoxydaunomycinone and (±)-4-demethoxy-11-deoxy-daunomycinone. Properly substituted AB ring synthons were fused with phthalic anhydride to give tetracyclic structures which were smoothly elaborated to the above said compound in moderate yields. (See chapter II for preparation of AB ring synthons).

According to the study of Broadhurst et al.[71] the Friedel-Crafts annelation of AB ring synthon with mono-methylphthalate afforded the tetracyclic system which was further transformed to (±)-4-demethoxydaunomycinone by conventional methods.

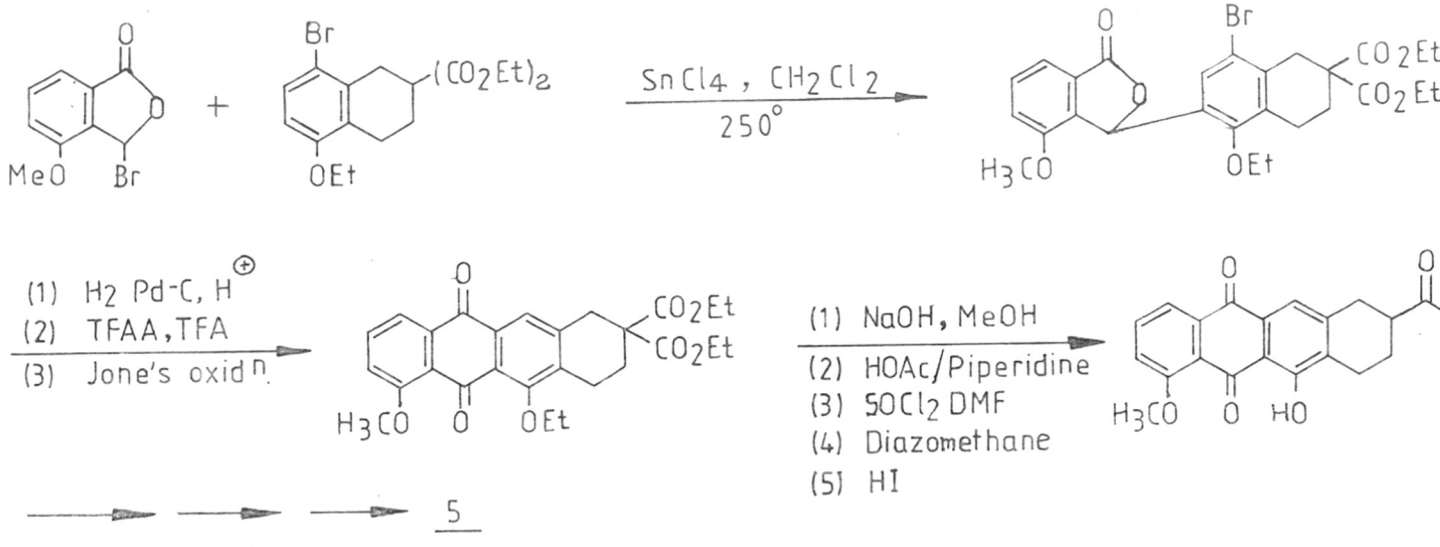
A new type of Friedel-Crafts alkylation which directly introduced a phthalide residue into the aromatic nucleus destined to be the ring B of anthracyclinone was reported by Johnson et al. for the synthesis of (±)-daunomycinone (Scheme-37)[72a,b] & (±)-11-deoxydaunomycinone (Scheme-38).[72c]

Aloe-emodin was converted in six steps to 1,4,5-trihydroxy-2-(2,3-dicarboxypropyl)-9,10-anthraquinone, a synthon for further regiospecific elaboration to daunomcyin, adriamycin analogues. A method for Friedel-Crafts

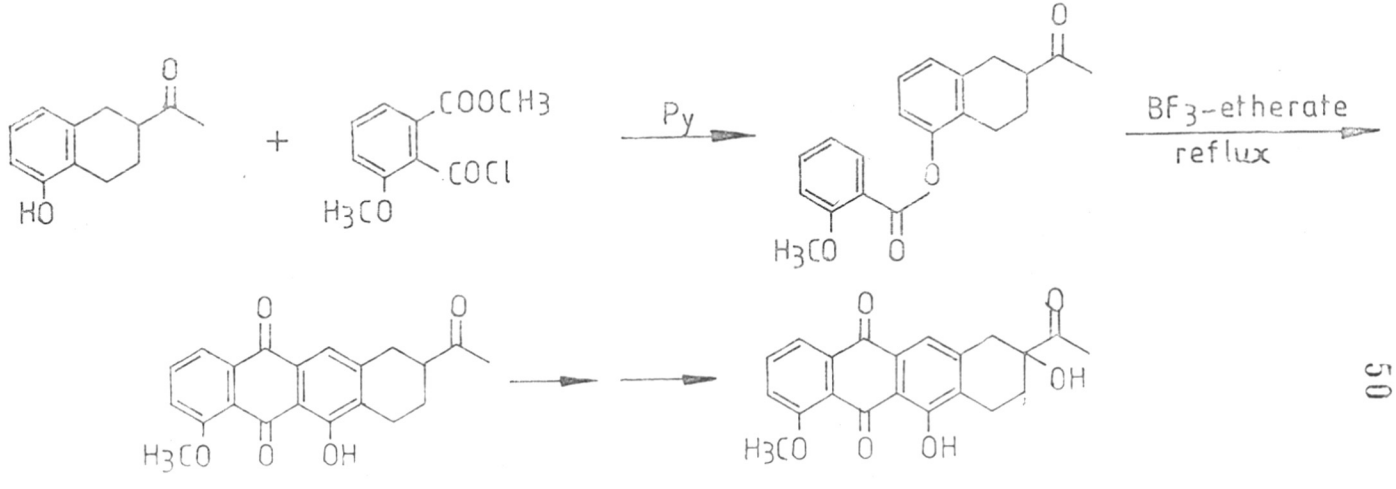
SCHEME 37 Johnson et al., Tetrahedron Lett, 3871 (1982)



SCHEME 38 Johnson et al., J. Am. Chem. Soc. 103, 1561 (1981)



SCHEME 39 RamaRao et al., Tetrahedron Lett, 2415 (1982)



acylation of anthraquinone by reduction to the anthracenone cyclisation and reoxidation was developed as a key feature of this synthesis.[73]

Rama Rao et al.[74] reported the synthesis of 7,9,11-trideoxydaunomycinone by a Fries rearrangement of a benzoyl ester which was prepared from substituted tetralin by treatment with 2-carbomethoxy-6-methoxy benzoyl chloride (Scheme 3a).

4. Syntheses of Chiral Aglycones

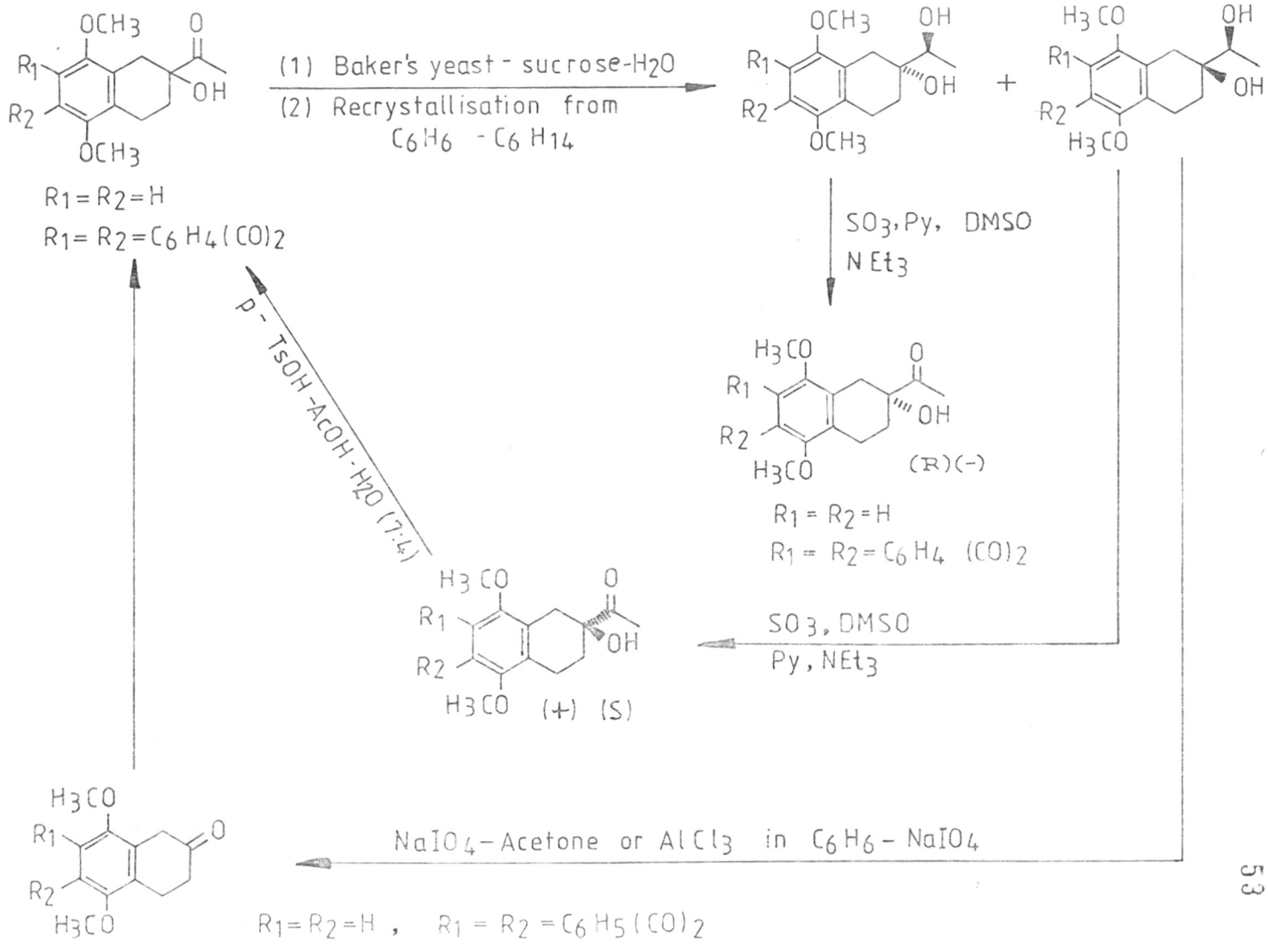
Although various syntheses of the anthracyclinones, aglycones of the anthracyclines, have been reported in racemic modifications, efficient methods to produce optically active anthracyclinones seem quite limited. Optically active anthracyclinones can be achieved either by developing an asymmetrically induced synthesis of chiral aglycones or by resolution of racemic aglycones.

Terashima et al[75] reported the reduction of racemic α-hydroxy ketone with fermenting baker's yeast followed by fractional recrystallisation and oxidation to give pure anthracyclinone intermediates (Scheme-40) and their partially optically active antipodes. The attractive feature of this synthesis was that the useless enantiomers were recycled to racemic form by racemization. Further,

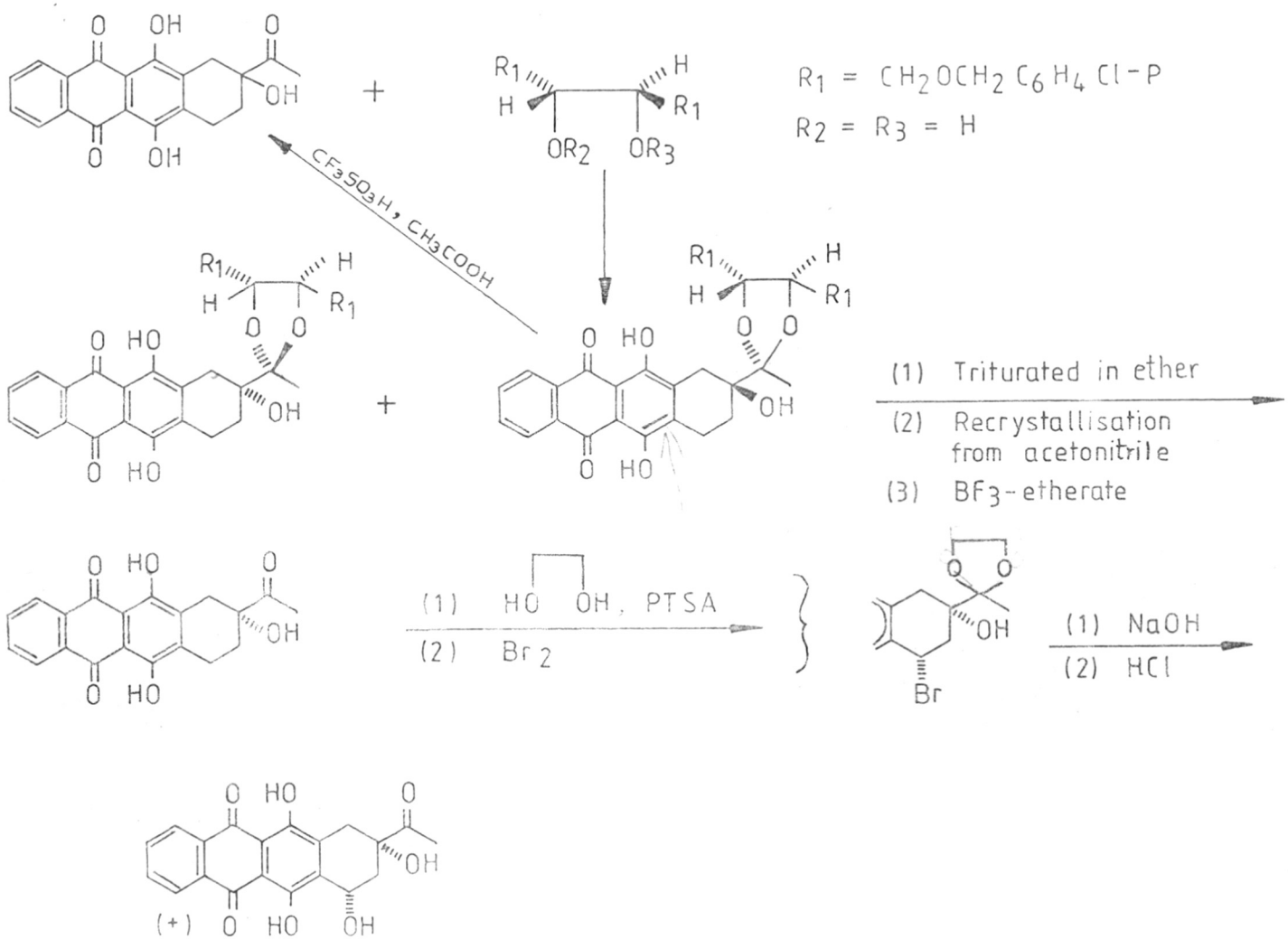
they developed[76] an alternative method for the desired optically active anthracyclinone by the resolution of racemic aglycone. According to this study, (±)-7-deoxy-4-demethoxydaunomycinone was found to be cleanly resolved by forming a mixture of the diastereomeric acetals with the C-2 symmetric (2R,3R) (+)-1,4-bis-(4-chlorobenzyloxy) butane-2,3-diol. It was further elaborated to optically pure (+)-4-demethoxydaunomycinone by employing a highly stereoselective introduction of the C-7 hydroxyl function. The method for racemising the undesired enantiomer (+)(S) was also explored (Scheme-41). Later on, they reported[77] an asymmetric synthesis of anthracyclinones by featuring bromolactonisation of (-) acetals derived from 2-acetyl-3,4-dihydro-naphthacene-6,11-diones and (2R,3R) (+)-N,N-N',N'-tetra-alkyl tartaric acid diamide,as a key diastereo-selective reaction (Scheme-42). The produced bromolactone mixtures could be readily converted to the highly optically active key synthetic intermediates of 4-demethoxydaunomycinone and 4-demethoxy-11-deoxydaunomycinone.

Kishi et al[18] reported a general procedure for optically active 11-deoxyanthracyclinones namely 11, 12, 13 and 15 (Scheme-43). The key step of synthesis involved a crossed asymmetric aldol reaction of acetal derivative with $CH_3\text{-}\underset{\underset{CH_2}{|}}{C}\text{-}COCH_2Si(CH_3)_3$. The acetals corresponding to 12, 13 and 15 were synthesised from bromojuglone and furandiene

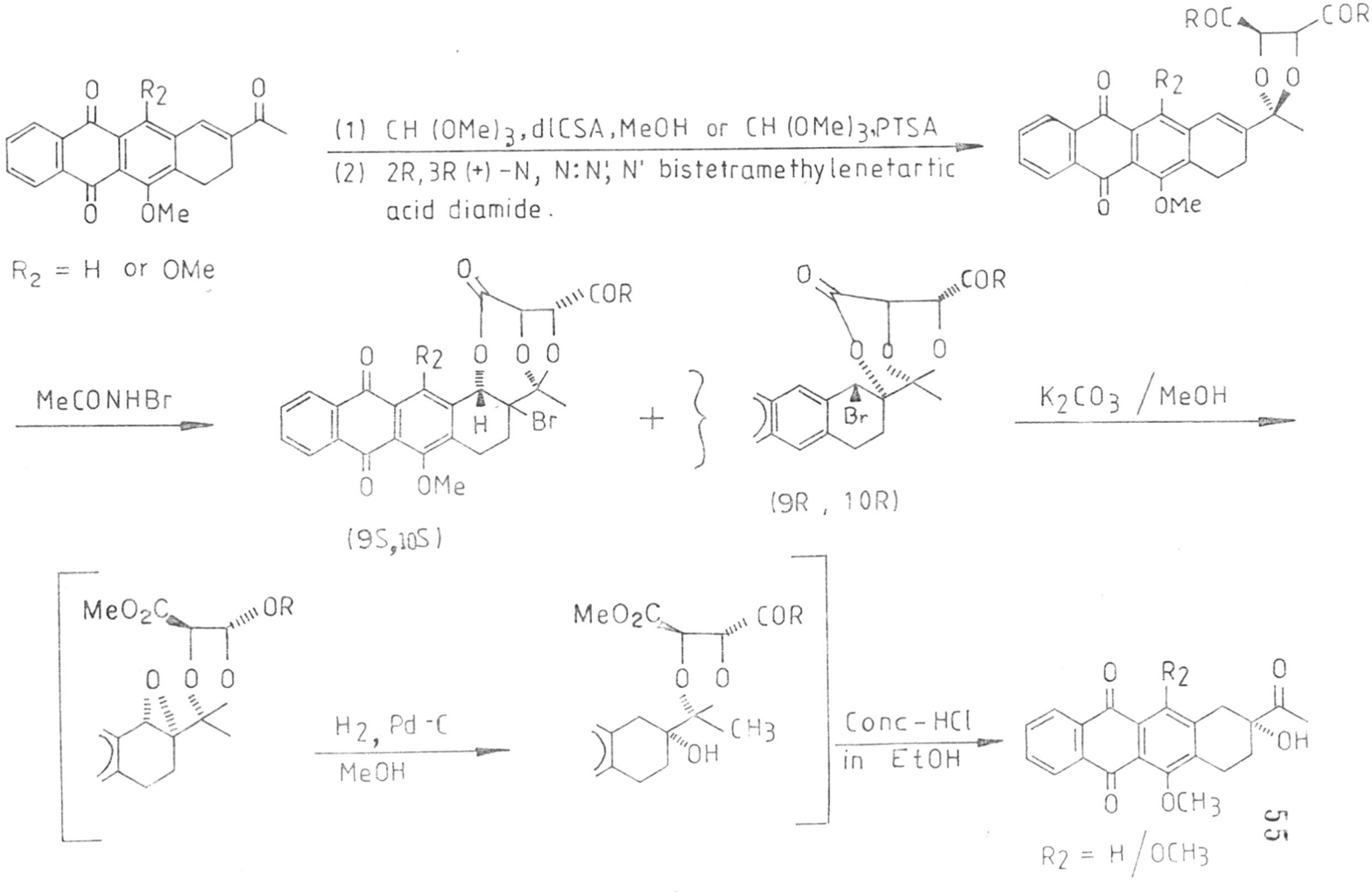
SCHEME 40 Terashima et al., Tetrahedron Lett, 23, 3715 (1982)



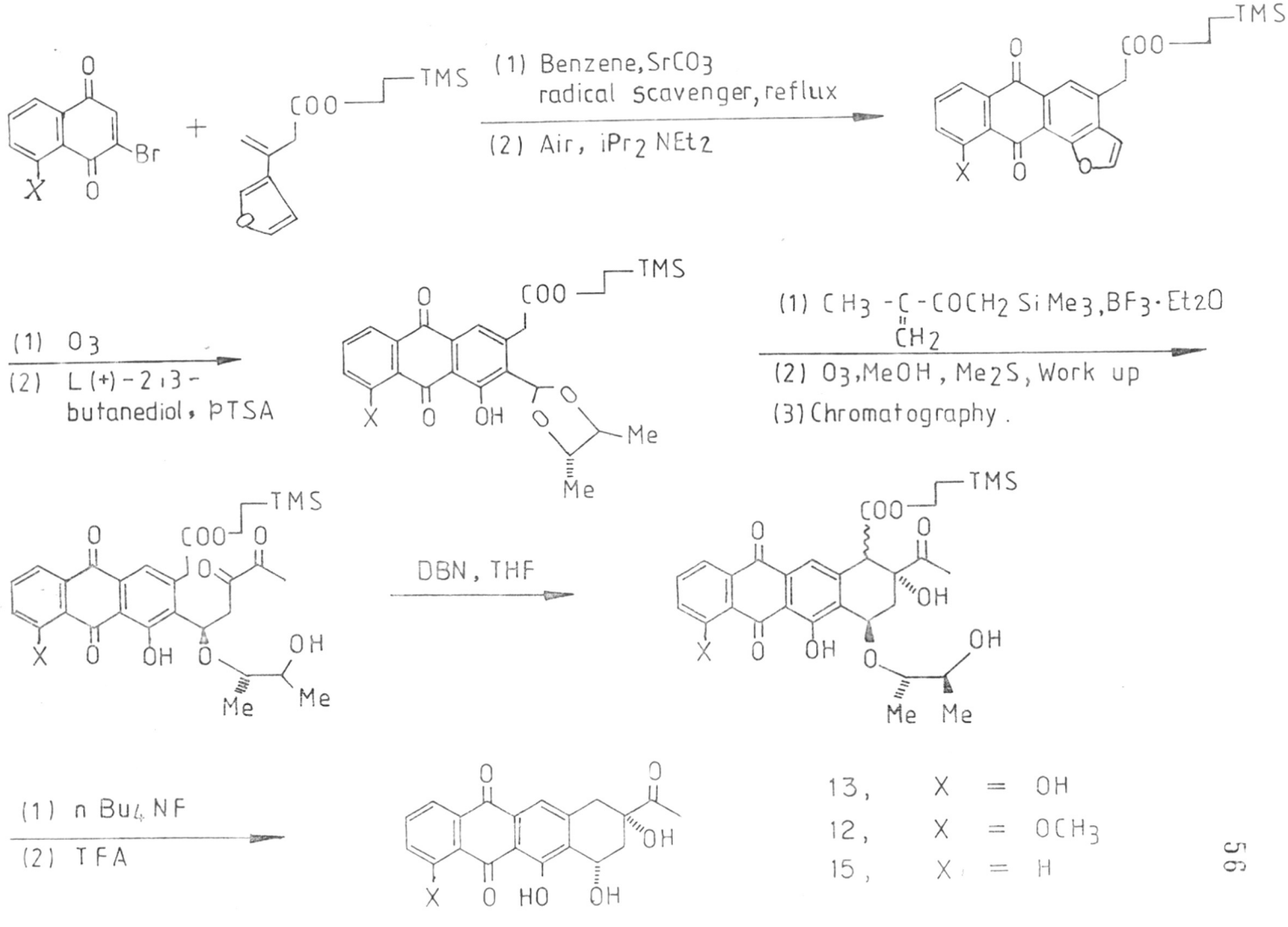
SCHEME 41 Terashima, Tetrahedron, 40, 4617 (1984)



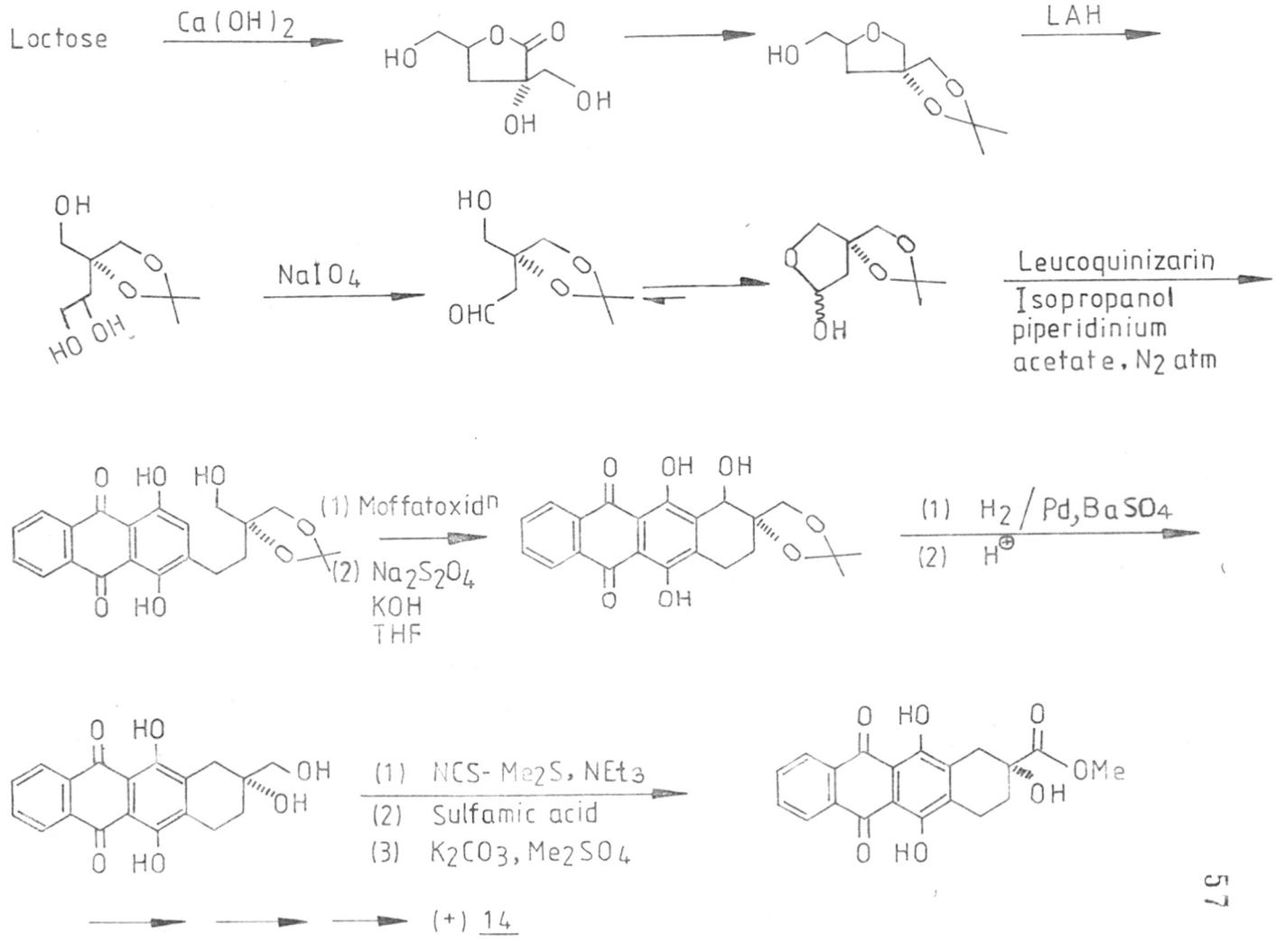
SCHEME 42 Terashima et al., Tetrahedron Lett, 6481 (1985)



SCHEME 43 Kishi et al., J. Am. Chem. Soc. 104, 7372 (1982)



SCHEME 44 Monneret et al., Tetrahedron Lett 25, 3975 (1984)



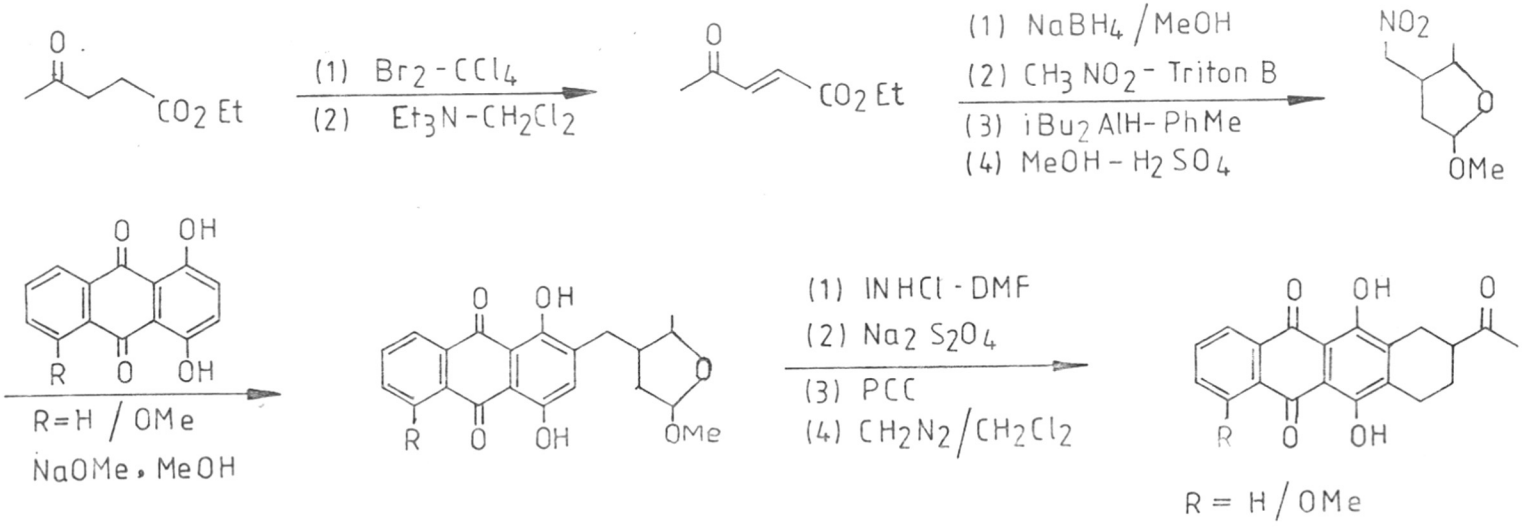
and they generated chiral oxonium ion. The nucleophile derived from $CH_3-\underset{\underset{CH_2}{\|}}{C}-COCH_2Si(CH_3)_3$ reacted with chiral oxonium ion from either of its diastereomeric faces producing potentially unequal amounts of two possible diastereomeric aldols which were separated.

Monneret et al[79] described the synthesis of optically active 4-demethoxydaunomycinone which was synthesised in several steps from lactose as a chiral precursor of ring A and from leucoquinizarin as precursor of rings B, C and D (Scheme-44).

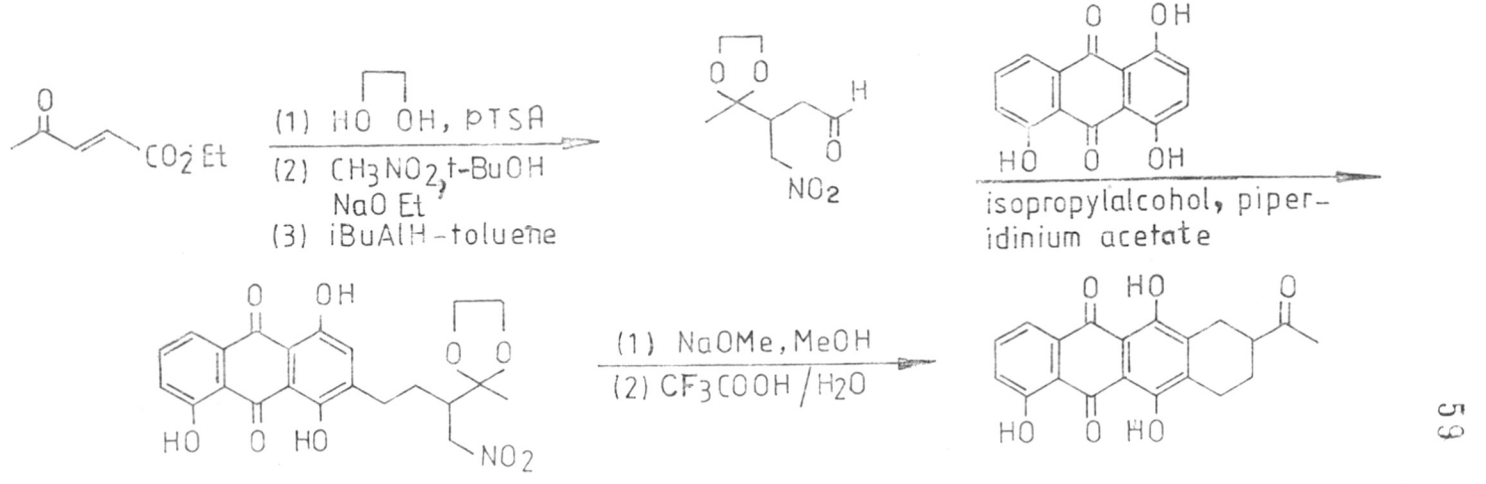
5. Syntheses Based on Different Principles

Various types of chemical reactions were exploited to achieve the regioselectivity in the syntheses of anthracyclinones. According to the study of Sutherland et al.[80a] a regiospecific synthesis of 7,9-dideoxydaunomycinone (Scheme-45a) was reported from 5-hydroxyquinizarin. Their strategy was to form the initial C-C bond by regiospecific nitronate addition to C-2 of 5-hydroxyquinizarin and the second one by Marschalk condensation. Later, they[80b] reported the synthesis of 7,9-dideoxycarminomycinone (Scheme 45b) from 5-hydroxyquinizarin by reverse strategy using the regioselective piperdinium acetate catalysed Marschalk-Lewis condensation to form the first C-C bond, followed by nitronate cyclisation. An improved Marschalk

SCHEME 45a Sutherland et al, J.Chem. Soc. Chem. Commu., 1075 (1981)



SCHEME 45b Sutherland et al., Tetrahedron Lett, 519 (1983)

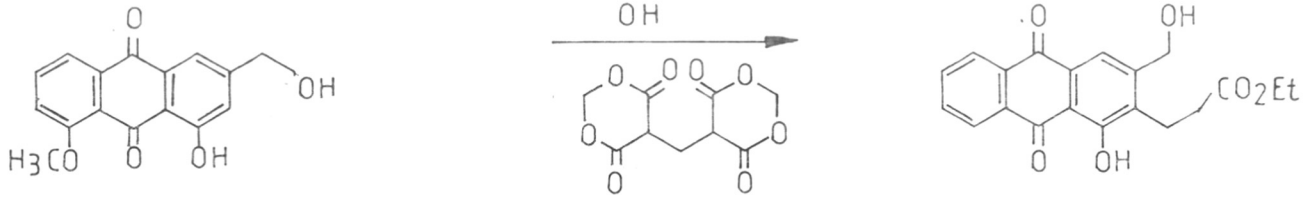


reaction between leucoquinizarin and more reactive Michael acceptor di-isoporpylidene methylenedimalonate was used in the synthesis of 11-deoxydaunomycin and its analogues by Mitscher et al.[81] (Scheme-46).

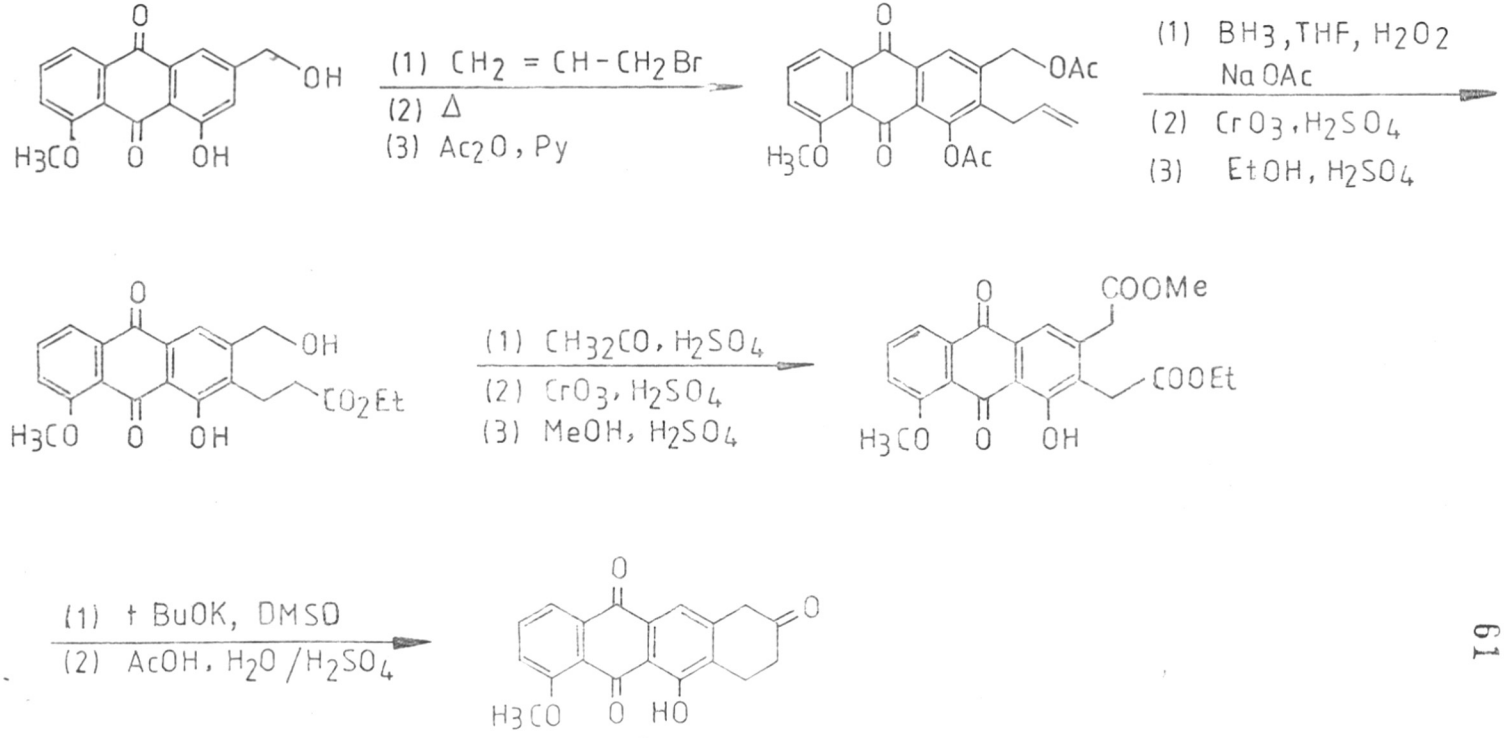
Mitscher et al.[82] utilised naturally occurring aloe-emodin as BCD ring precursor and built the ring A by utilising Claisen rearrangement to form C-C bond (Scheme-47). Rutledge et al.[83] also reported a synthesis of the key intermediate of 4-demethoxydaunomycinone by making use of Claisen rearrangement of anthrafuran (Scheme-48). Kraus et al.[84] have reported the synthesis of 11-deoxydaunomycinone and 4-demethoxy-11-deoxydaunomycinone by coupling the Claisen rearrangement with an intramolecular Diels-Alder reaction as shown in Scheme-49

Wulff and Tang[85] demonstrated the importance of Fischer carbene complexes in the regiospecific synthesis of anthracyclines (Scheme-50). Thus, the benzannulation reaction of acetylene derivative and the chromium complex afforded the lactone regiospecifically. Protection of phenolic hydroxyl and reductive cleavage of lactone resulted in the formation of an acid which was cyclised, oxidised and demethylated to afford the known tetracyclic ketone.

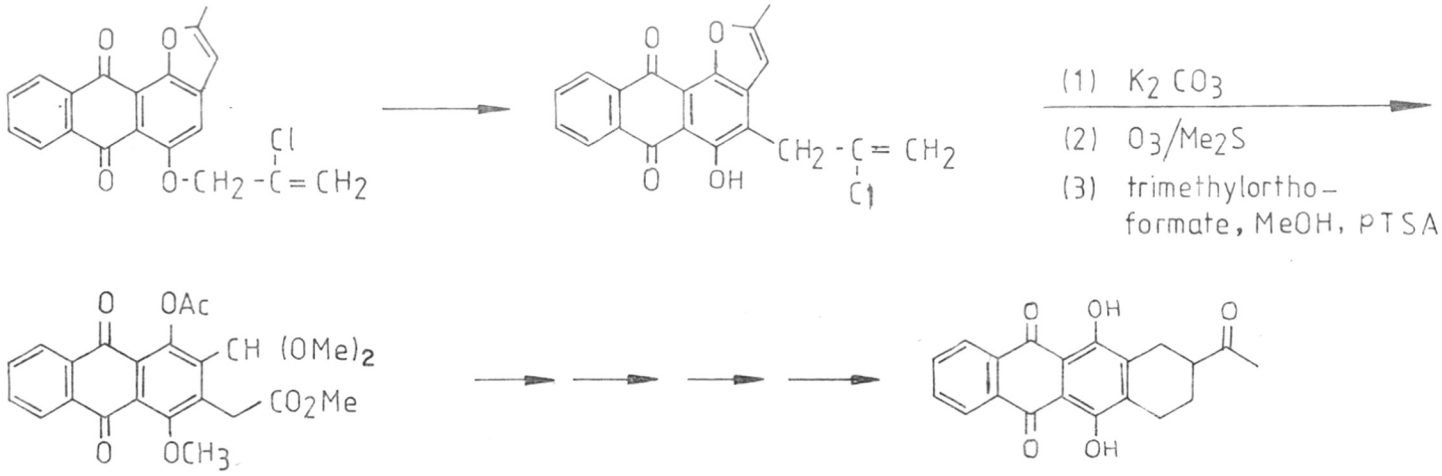
SCHEME 46 Mitscher et al, Tetrahedron Lett., 4809 (1983)



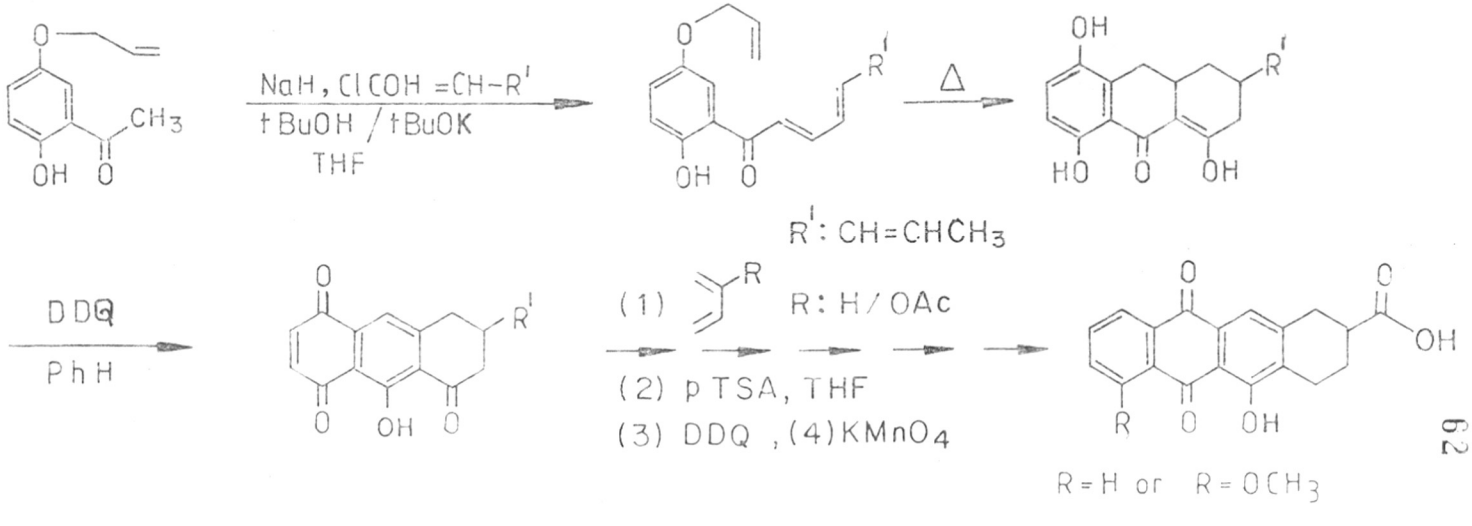
SCHEME 47 Mitscher et al., Tetrahedron Lett, 22, 3771 (1981)



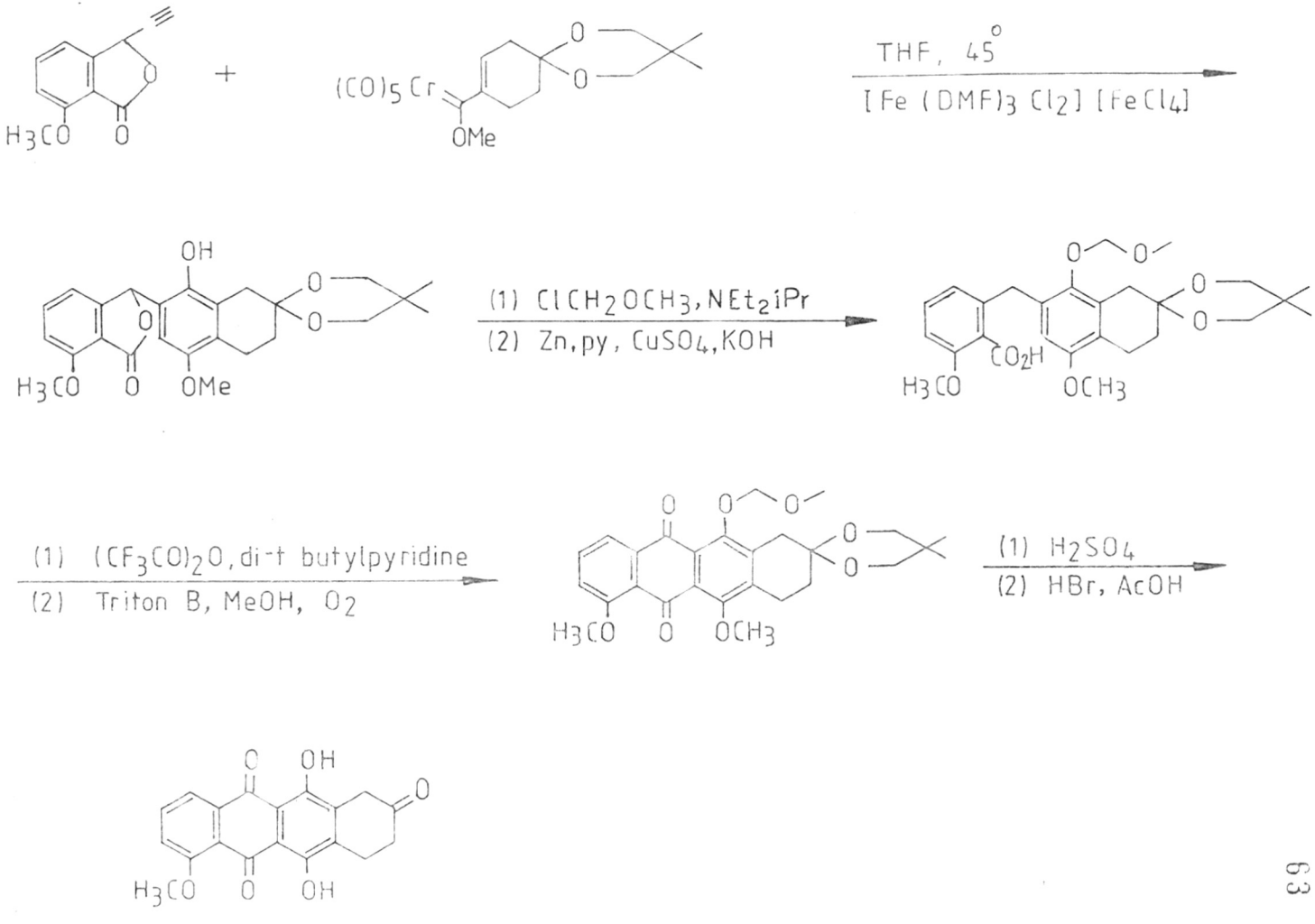
SCHEME 48 Rultedge et al, Tetrahedron Lett., 2319 (1984)



SCHEME 49 Kraus et al., J. Org. Chem. 50, 1782 (1985)



SCHEME 50 Wulff and Tang. J. Am. Chem. oc., 106, 434 (1984)



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J. Org. Chem., 50, 1782 (1985).

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J. Am. Chem. Soc., 106, 434 (1984).

CHAPTER II

PART I

SYNTHESIS OF

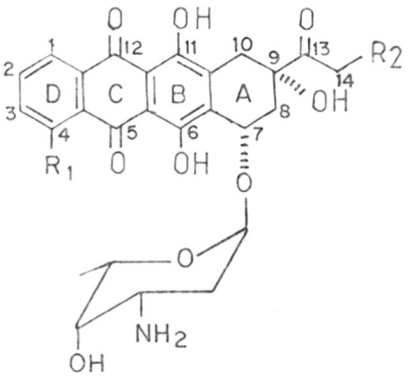
4-DEMETHOXYDAUNOMYCINONE

INTRODUCTION

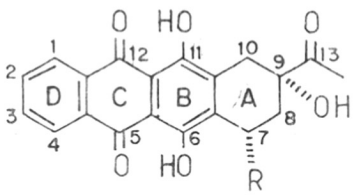
The anthracycline antibiotics, adriamycin (1), daunomycin (2) and carminomycin (3) are of topical interest in view of their activity against various experimental tumors, as well as their clinical effectiveness in the treatment of many types of human cancers.[1] Their primary site of action is considered to be at the tumor cell level through an interference with DNA synthesis and functionality. However, the chemotherapy employing these drugs is hampered by a number of undesirable side effects such as myelosuppression, cardiomyopathy etc.[2] This prompted the search for new derivatives that show decreased side effects and/or increased anticancer activity. Recently it has been shown that 4-demethoxydaunomycin (4) is 4-8 times more active than daunomycin (2) and the initial results of its clinical trials are reported to be very promising.[3] Non-feasibility of 4 by fermentation process coupled with the improved therapeutic value of 4 has attracted the attention of many organic chemists to attempt its total synthesis.

DISCUSSION

(±)-4-Demethoxydaunomycin (4) consists of a tetracyclic aglycone part, 4-demethoxydaunomycinone (5), attached to the amino sugar L-daunosamine via an α-glycosidic bond.[4] The



	R_1	R_2
1	OCH_3	OH
2	OCH_3	H
3	OH	H



4	R	=	O - daunosaminyl
5	R	=	OH
6	R	=	H

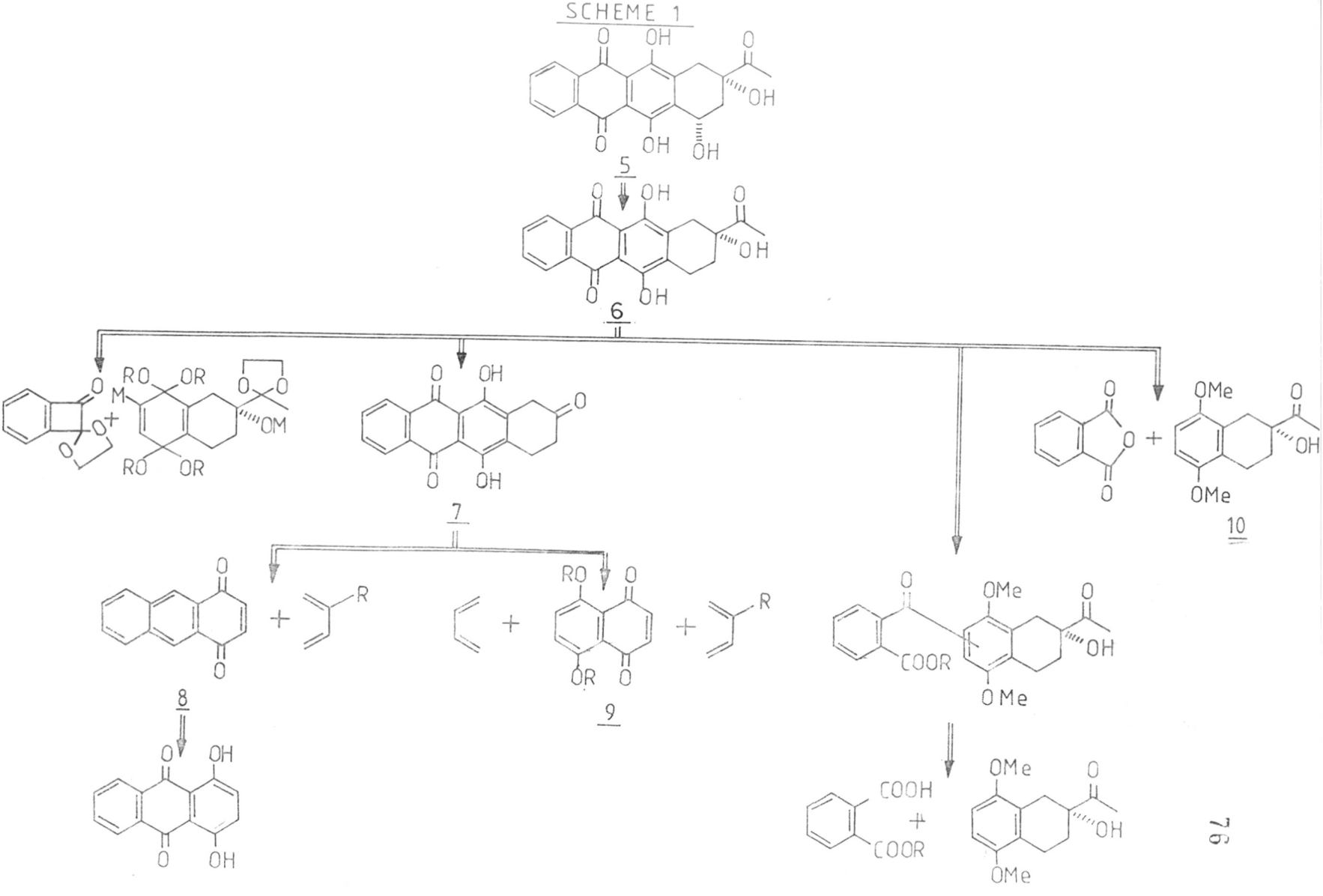
stereochemistry of both the asymmetric centres of the aglycone is 'S' and amino sugar is of the 'L' configuration.

As several suitable syntheses of L-daunosamine[5] and its coupling[6] with 4-demothoxydaunomycinone (4) have been accomplished, research efforts have been mainly directed towards the synthesis of the aglycone moiety, 4-demethoxy-daunomycinone (5).

Synthetic Approaches

The retrosynthetic approach outlined in Scheme-1 demonstrates that the key intermediates involved in the synthesis of 4-demethoxy-7-deoxydaunomycinone (6) and in turn the synthesis of 4-demethoxydaunomycinone (5) can be broadly classified into three categories: i) anthraquinone derivative 8 representing B, C and D rings, ii) naphthaquinone derivative 9 representing B and C rings and iii) the substituted tetralin derivatives like 10 representing A and B rings of the anthracyclinones. It is pertinent to mention that if one desires to elaborate anthraquinone derivative 8 or the naphthaquinone derivative 9 to the anthracyclinones, there will be a number of steps involved which will finally result in overall low yields. On the other hand, the substituted tetralin derivative 10 which can be fused with phthalic anhydride in a single step to afford 4-demethoxy-7-deoxydaunomycinone (6) in high yield will be a suitable

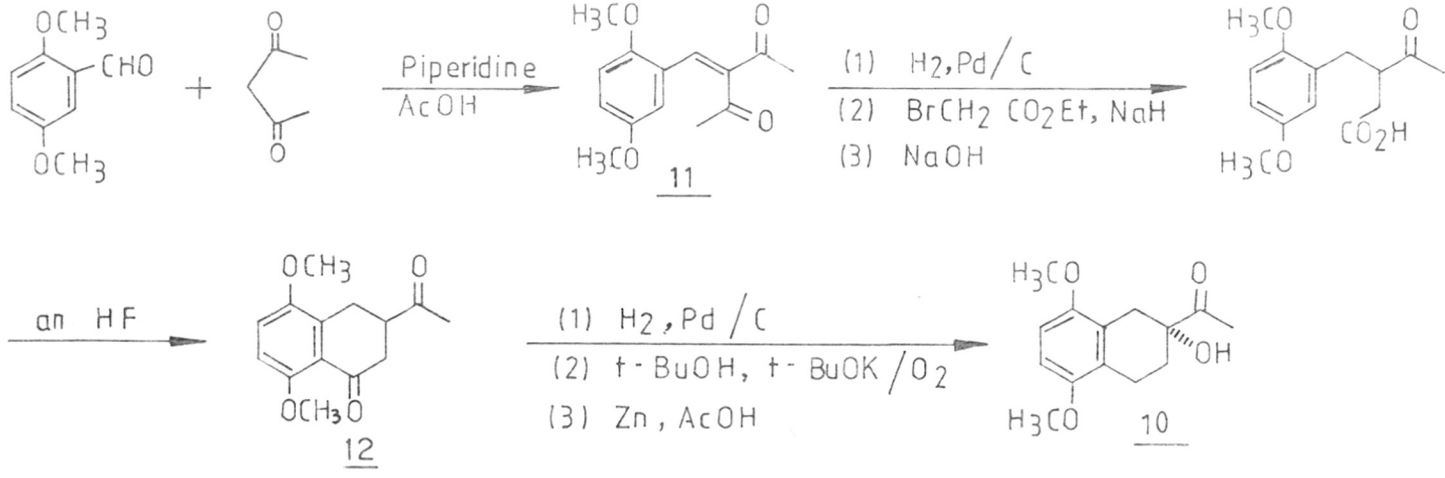
SCHEME 1



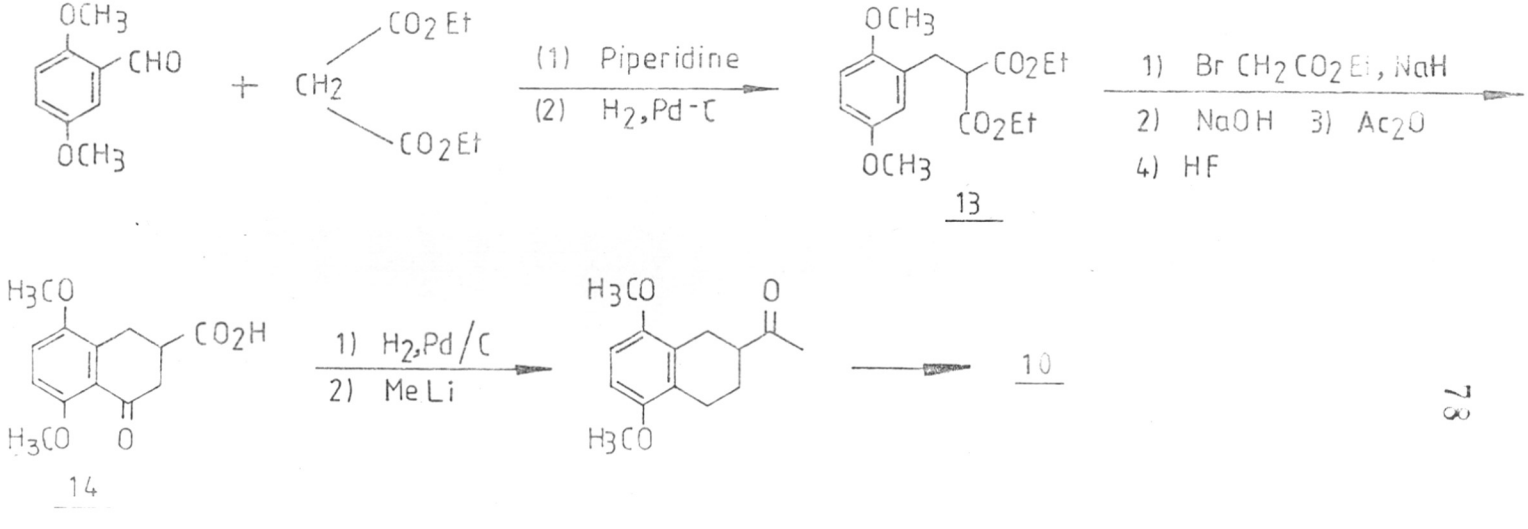
precursor provided a simple and efficient process for its generation is available. Owing to the importance of 10, different synthetic procedures for the preparation of this intermediate (±)10 have been reported. Some of the important approaches for the synthesis of 10 are outlined below. In fact in many cases 10 was further converted to anthracyclinones.[7]

Among these, Wong et al.[8a] reported the first synthesis of 10 in the year 1971 (Scheme-2a). 2,5-Dimethoxybenzaldehyde on condensation with 2,4-pentanedione gave the diketone 11 which was transformed to the 3-acetyl-4-(2,5-dimethoxyphenyl)-butanoic acid. Cyclisation of this ketoacid was achieved with anhydrous hydrofluoric acid to produce the tetralone (12). Hydrogenolysis of 12 with Pd/C in acidic ethanolic solution gave the tetralin which upon oxidation with butanolic potassium t-butoxide and oxygen followed by reduction with zinc-acetic acid afforded the desired hydroxy ketone in good yield. Wong et al.[8b] further reported another synthesis (Scheme-2b) in which 2,5-dimethoxybenzaldehyde was condensed with dimethylmalonate followed by reduction with H_2 over Pd/C to give the diester 13. Ketotetralone 14 was obtained from 13. Hydrogenolysis of 14 with Pd/C gave the tetralin which upon treatment with methyllithium produced the acetyl tetralin which was oxidised by the above method to give 10.

SCHEME 2a Wong et al, Can J. Chem. 49, 2712 (1971)

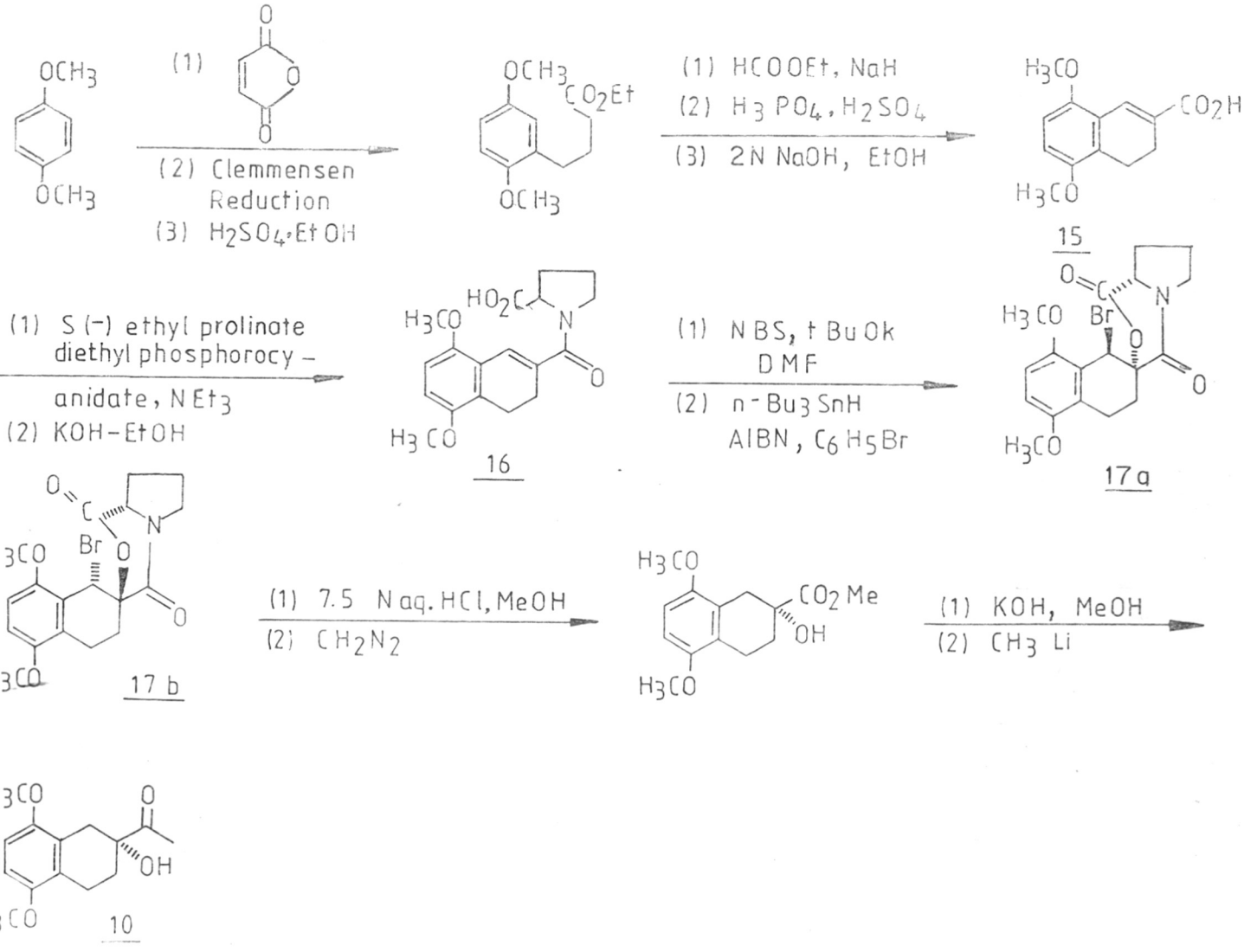


SCHEME 2b Wong et al., Can. J. Chem. 51, 466 (1973)

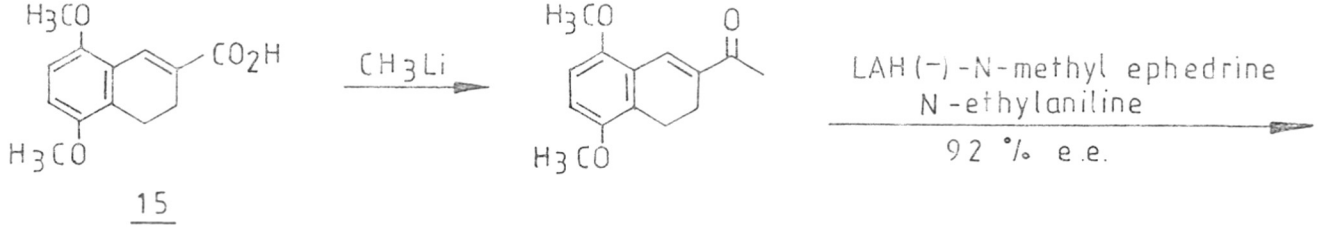


Terashima et al. reported a series of syntheses of optically active AB ring synthons. In 1978, Terashima et al.[9a] reported a synthesis of optically active (10), starting from 1,4-dimethoxybenzene. Ethyl-4-(2,5-dimethoxyphenyl)-butanoate was obtained in three steps from 1,4-dimethoxybenzene whose conversion to 15 was accomplished by condensation with ethyl formate followed by acid promoted cyclisation and alkaline hydrolysis. Treatment of 15 with (S)(-)ethyl prolinate and alkaline hydrolysis yielded 16. The asymmetric bromolactonisation of 16 was found to occur stereoselectively to give the bromolactones in which one diastereomer was predominant. Debromination of 7a followed by acidic hydrolysis afforded the optically active ∝-hydroxy acid which was converted to R(-)10 by methyl lithium. Later, they[9b,9c] prepared R(-)10 by using the intermediate 15 (Scheme-3b). 15 on treatment with methyl lithium gave 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene and the asymmetric reduction of the same with the lithium aluminiumhydride partially decomposed with (-)-N-methyl ephedrine and N-ethyl aniline afforded the optically active allylic alcohol (18) which was smoothly elaborated to (R)(-) 10 by three step sequence consisting of epoxidation of double bond, opening of epoxide by lithium aluminium hydride and oxidation of secondary alcohol by Fetizon's

SCHEME 3a Terashima et al., Tetrahedron Lett, 4937, (1978)



SCHEME 3b Terashima et al., Tetrahedron Lett, 2753 (1980)
" " " , Chem. Pharm. Bull, 31, 821 (1983)



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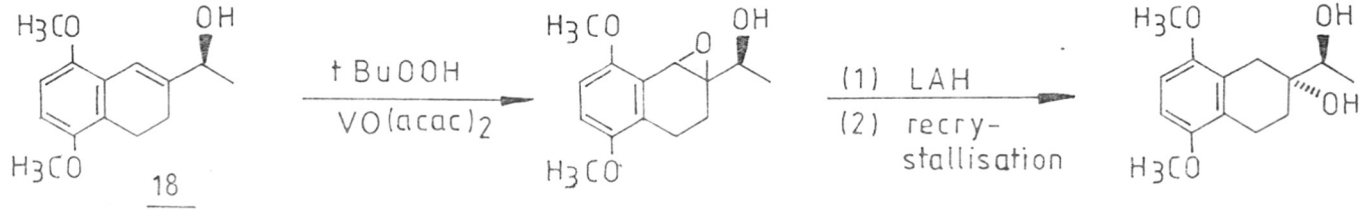


18

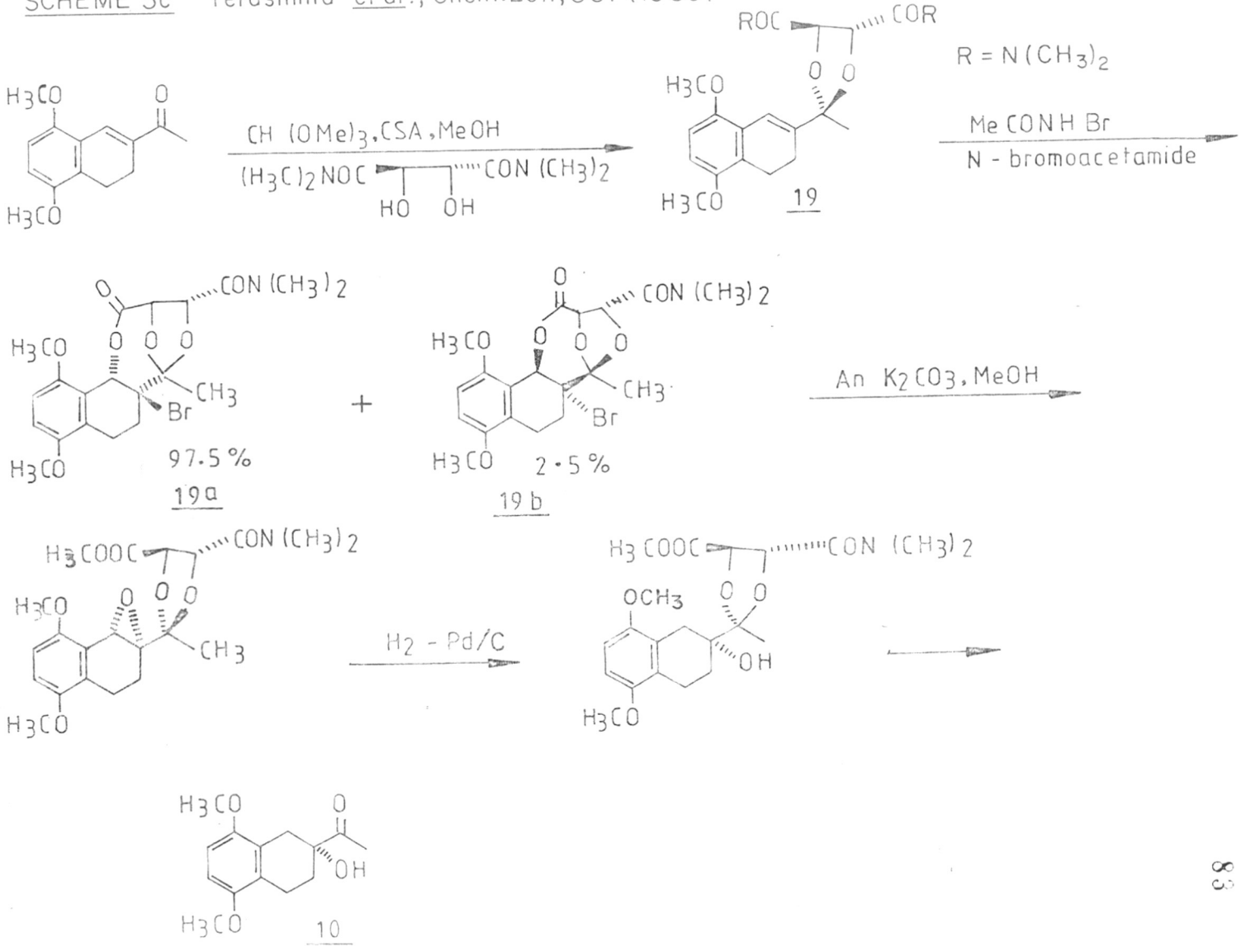
R (−) − 10

reagent. Recently, Terashima et al.[9d] modified the asymmetric bromolactonisation reaction in which the bromolactonisation of (-)acetal 19 prepared from readily available 2-acetyl 5,8-dimethoxy-3,4-dihydronaphthalene and (1R,2R)-(+)-tartaric acid diamide was found to proceed with high diastereoselectivity giving the 7-membered bromolactones 19a and 19b in 97.5:2.5 ratio. The 19a was efficiently converted to R(-) 10 (Scheme-3C).

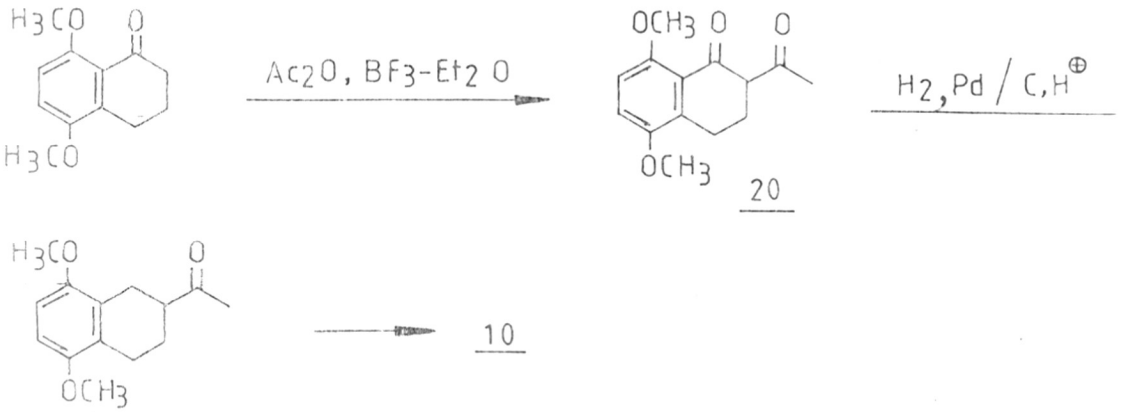
A new approach was developed by Hodge et al.[10] starting from 5,8-dimethoxy-1-tetralone (Scheme-4) which on Friedel-Crafts acylation with acetic anhydride and BF_3 etherate gave the diketone 20. Selective hydrogenolysis on Pd-C afforded the tetralin whose conversion to (±)-10 was carried according to Wong's procedure.

The ketone functionality in 5,8-dimethoxy-2-tetralone was exploited by many chemists for side chain elaboration to give 10. In general, these methods could be classified as two carbon homologations or two sequential one carbon homologations. Smith et al.[11] converted the 5,8-dimethoxy-2-tetralone into its cyanohydrin derivative (21) which after THP protection was treated with excess methyl magnesiumiodide and subsequently hydrolysed to produce the desired hydroxy ketone (±)-10 in good yield (Scheme-5). Ethylation of above tetralone with ethyl magnesium bromide was reported by Kende et al[12] to give 22 which on treatment with mercuric acetate in ethyl acetate afforded 10 (R=Ac) (Scheme-6). Wiseman et al.[13] treated

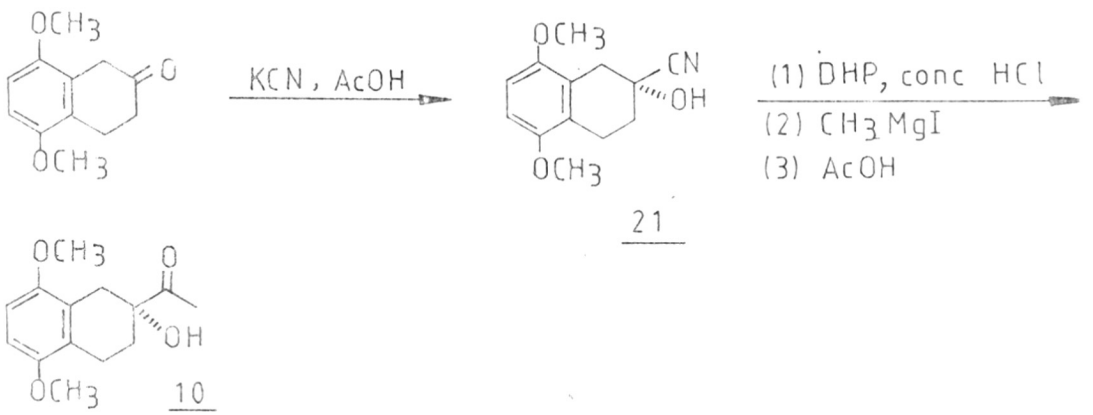
SCHEME 3c Terashima et al., Chem.Lett, 367 (1985)



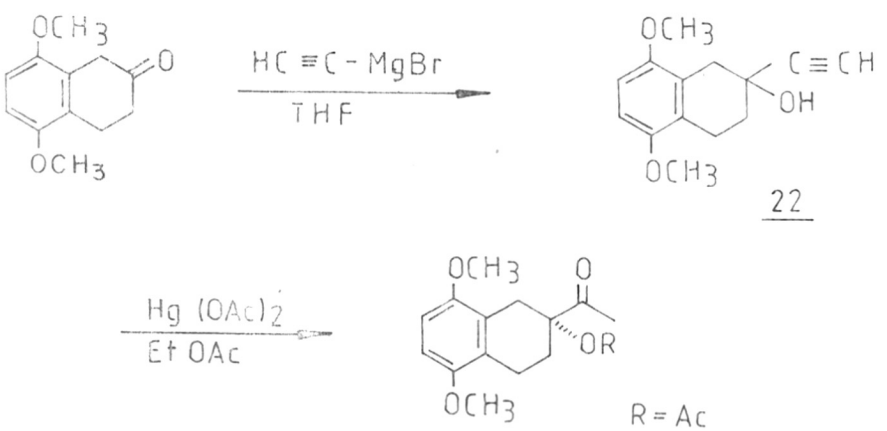
SCHEME 4 Hodge et al., J. Chem. Soc. Chem. Commu, 85 (1979)



SCHEME 5 Smith et al., J. Org. Chem. 42, 3653 (1977)



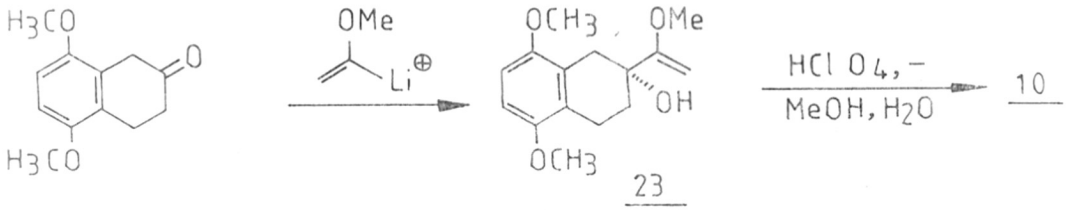
SCHEME 6 Kende et al., Tetrahedron Lett, 3537 (1977)



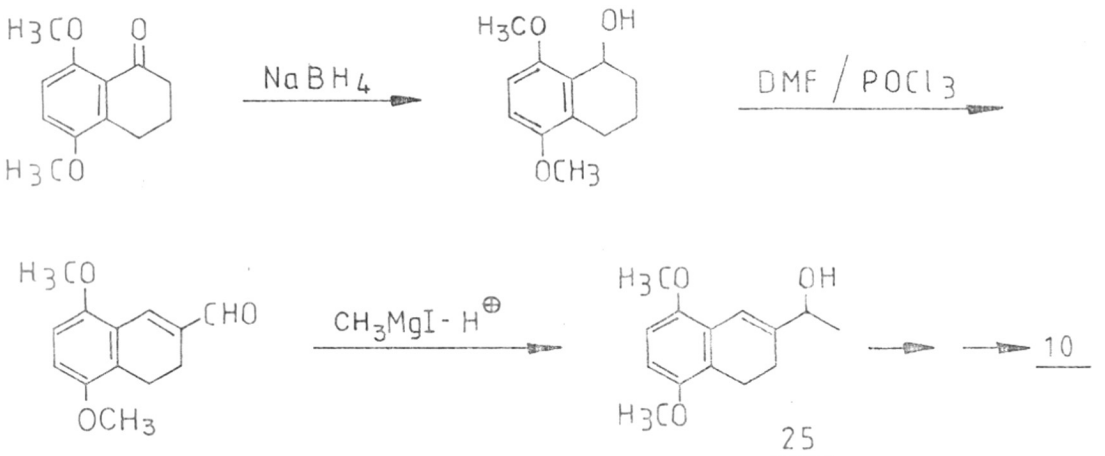
5,8-dimethoxy-2-tetralone with methoxyvinyllithium, followed by aqueous work up to give 23 which on hydrolysis with perchloric acid gave (±)10 (Scheme-7). Krishna Rao et al.[14] reported the synthesis of 2-(2-ℓ-hydroxyethyl)-5,8-dimethoxy-,3,4-dihydronaphthalene (25), a late stage precursor to 10, starting from 5,8-dimethoxy-1-tetralone (Scheme-8). The above tetralone on reduction with sodium borohydride yielded 5,8-dimethoxy-1,2,3,4-tetrahydro-1-naphthol. It was subjected to Vilsmeier reaction with dimethyl formamide and phosphorous oxychloride to give dihydroaldehyde 24 which on reaction with methyl magnesium iodide afforded 25. Cava et al.[15] reported a two step synthesis of 10 (Scheme-9) by a Diels-Alder reaction. The o-quinodimethane, derived from 9 substituted benzylbromide by treatment of zinc, was treated with substituted methyl vinyl ketone to give hydroxy ketone 10, after hydrolysis, in poor yield.

Arcamone et al.[16] reported the synthesis of the key intermediate 10 by three different routes. According to the first approach (Scheme-10a) the 5,8-dimethoxy-1-tetralone was treated with ethyl formate in the presence of a base to give, after acid catalysed addition of n-butyl thiol, compound 26. The dihydroaldehyde 24, obtained in two steps from the compound 26, was treated with methyl magnesium iodide followed by hydrolysis to give 27 in good yield. Epoxidation of 27 , followed by reductive opening of epoxide and finally oxidation

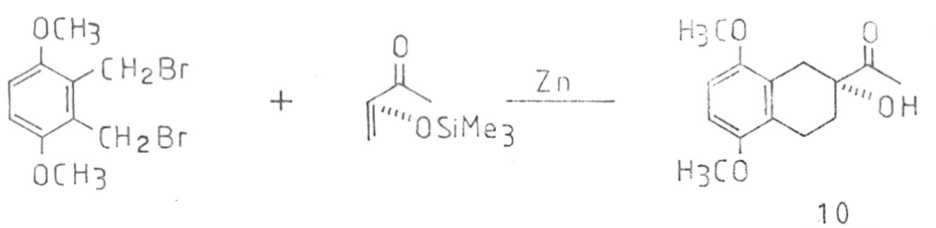
SCHEME 7 Wiseman et al., Tetrahedron Lett, 3765 (1978)



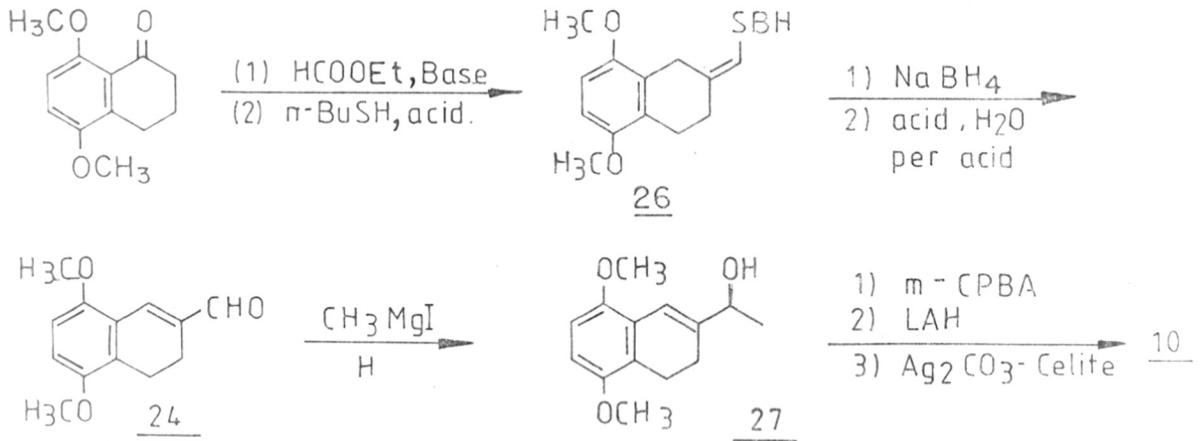
SCHEME 8 KrishnaRao et al., Tetrahedron Lett, 3549 (1981)



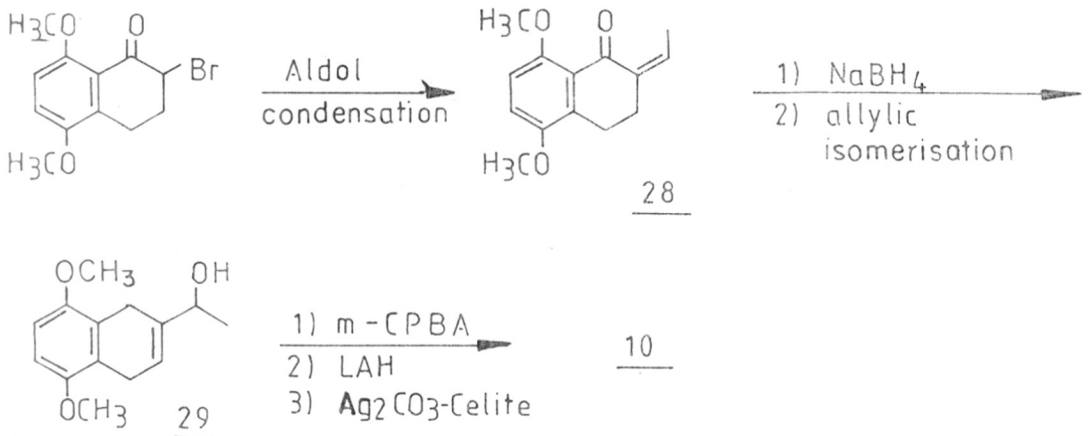
SCHEME 9 Cava et al., J. Org Chem. 46, 1483 (1981)



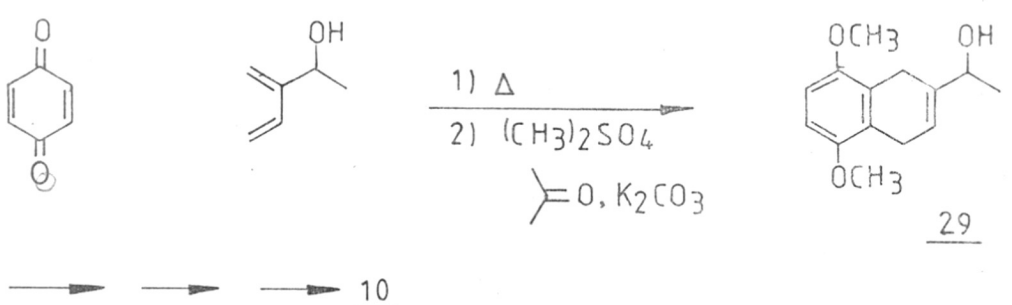
SCHEME 10a Arcamone et al., Bull Soc. Chim. Belg., 1003 (1982)



SCHEME 10 b Arcamone et al., Bull Soc. Chim. Belg. 91, 1003 (1982)



SCHEME 10c Arcamone et al., Bull. Soc. Chim. Belg. 91, 1003 (1982)

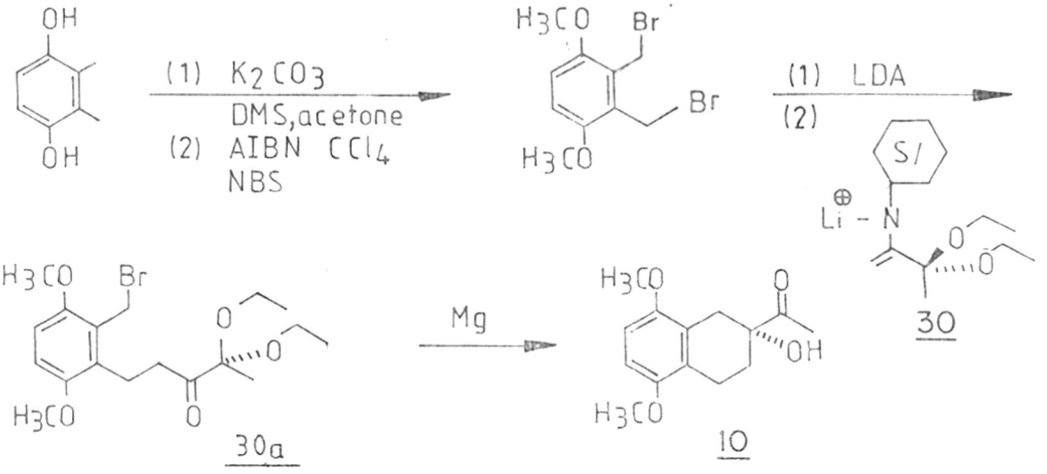


afforded 10 in 55% overall yield. The second synthesis of 10 (Scheme-10b) involved the aldol condensation of 5,8-dimethoxy-2-bromo-1-tetralone which on acid treatment afforded 28. Reduction of 28 by sodium borohydride followed by allylic isomerisation gave 29 which on epoxidation followed by reductive opening of epoxide and finally oxidation yielded 10 in 56% overall yield. The third route (Scheme-10c) involved the Diels-Alder reaction between p-benzoquinone and 2-α-hydro-γ-ethyl butadiene to give the same adduct 29 after methylation.

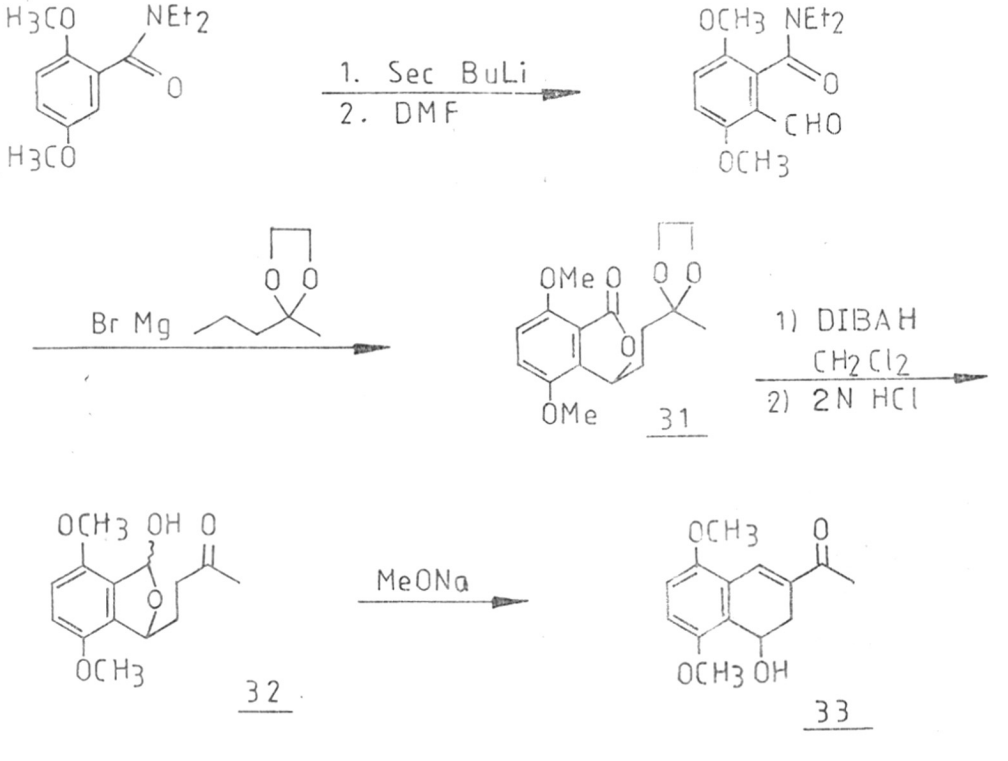
Belleau et al.[17] reported the synthesis of 10 by an altogether different route starting from 2,3-dimethylhydroquinone (Scheme-11). Protection of hydroxyl groups followed by bromination afforded the dibromide which on treatment with lithium enamine derivative (30) followed by intramolecular Grignard reaction afforded the desired intermediate 10.

Snieckus et al.[18] reported the preparation of AB ring synthon 33 by using benzamide directed ortho metalation strategy (Scheme-12). The salient features were: the incorporation of a four carbon Grignard unit, 1-bromobutan-3-one-ethyleneketal into N,N-diethyl-2-formyl-3,6-dimethoxybenzamide, DIBAH reduction of 31 and intramolecular aldol condensation of the resulting product 32 to give the dihydronaphthalene 33.

SCHEME 11 Belleau et al., Tetrahedron Lett., 257 (1983)



SCHEME 12 Snieckus et al., Tetrahedron 40, 4593 (1984)

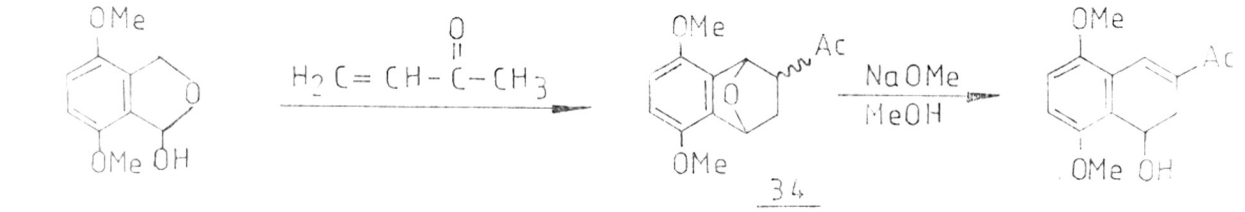


Rodrigo et al.[19] described the synthesis of AB ring synthon (±) 36 (Scheme-13). Treatment of 4,7-dimethoxy-isobenzofuran (generated from hydroxyphthalan) with methyl vinyl ketone produced a (3:1) endo-exo mixture of bridged adducts 34 from which endo isomer was crystallised. 34 suffered a reverse Michael cleavage with methanolic sodium methoxide to afford enone which was reduced with 2% sodium amalgam in ethanol to the hydroxyketone 35a as a single diastereomer. Silylation then provided a single silyl ether 35b. Oxygenation under the Gardner conditions yielded the required AB ring synthon 36 as a single stereoisomer.

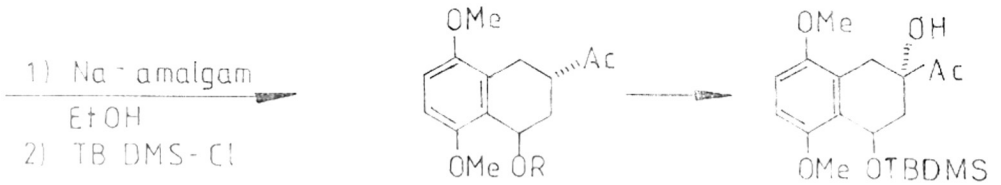
Swenton et al.[20] reported the synthesis of optically active AB ring synthon (S)(+)(38) without recourse to chromatography(Scheme-14). The intermediate 1,2,3,4-tetrahydro-5,8-dimethoxy-4-oxo-2-acetyl-2-hydroxynaphthalene cyclic-4-(ethylene mercaptole) (37) was prepared from 2,5-dimethoxybenzaldehyde in eleven steps. Resolution of (±)37 with (-)∝-methylbenzylamine followed by recrystallisation and acidic hydrolysis afforded (S) (-)37. Ketalisation of (S)(-)37, followed by hydrolysis of thioketal and potassium tri-secbutylborohydride reduction furnished almost exclusively the required cis diol (S) (+)38.

The synthesis of optically active AB ring synthon 41 starting from optically active 3-C-hydroxymethyl-3,3'-isopropylidene-D-glycerotetrose was described by

SCHEME 13 Rodrigo et al., Tetrahedron 40, 4597 (1984)



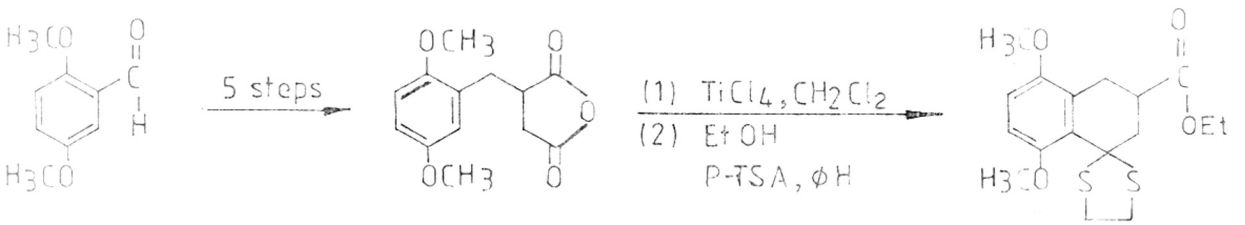
34

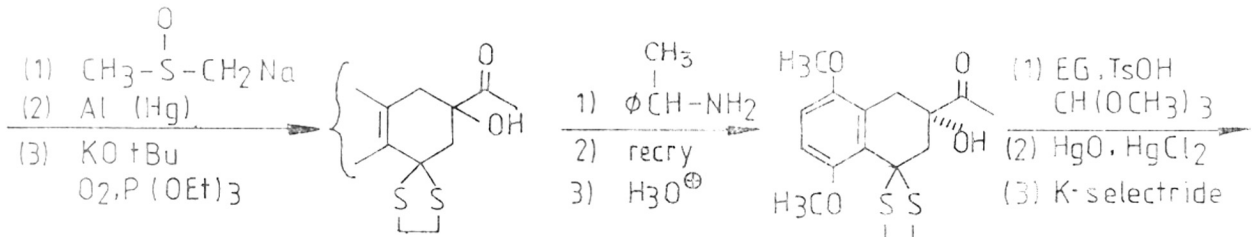


35 a : R = H
b : R = TBDMS

36

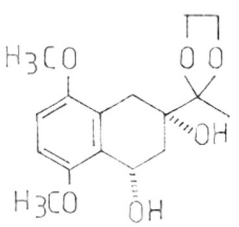
SCHEME 14 Swenton et al., Tetrahedron 40, 4625 (1984)





(±) 37

S (−) 37



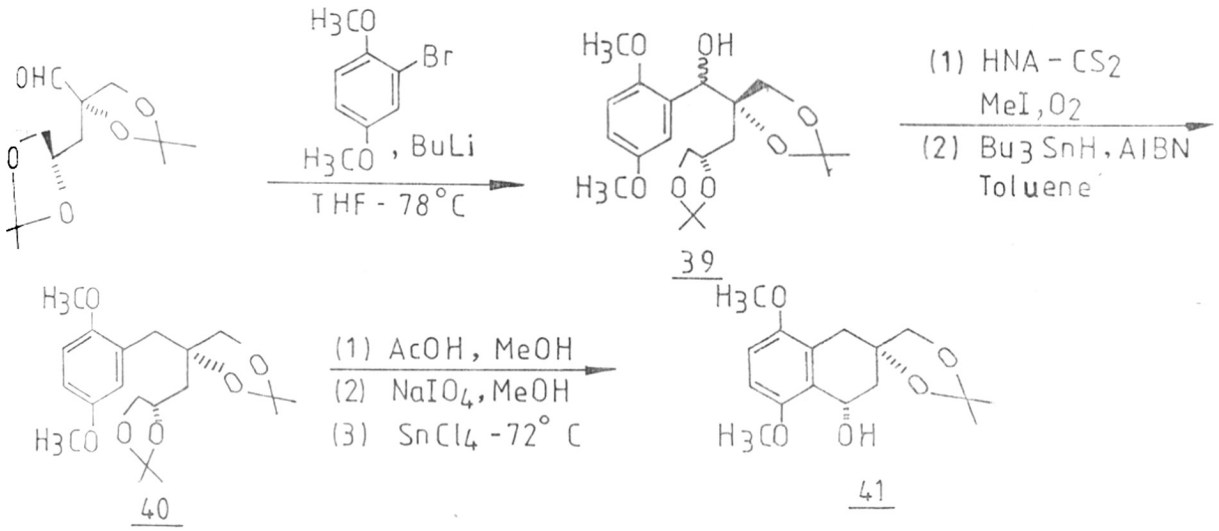
S(+) 38

Monneret et al.[21] (Scheme-15). Ortho alkylation of 2,5-dimethoxybromobenzene with the aldehyde followed by a sequence of standard reactions gave the required compound 41.

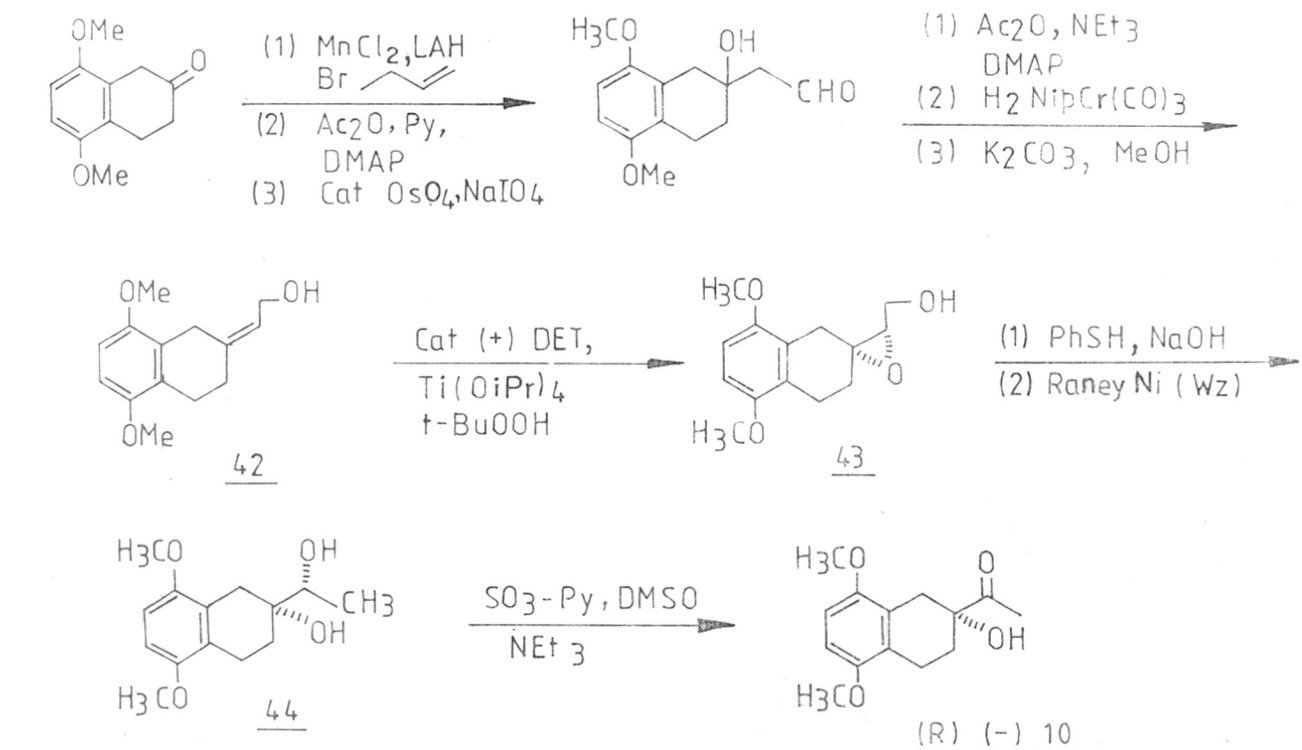
Shibasaki et al.[22] reported the synthesis of R(-)10 (Scheme-16). Exo allylic alcohol 42 was prepared in six steps from 5,8-dimethoxy-β-tetralone. 42 under Sharpless asymmetric epoxidation conditions afforded the optically active epoxide 43. Treatment of 43 with thiophenol under the basic conditions followed by hydrogenolysis of the carbon-sulfur bond with Raney Nickel yielded the diol 44 which on oxidation furnished (R)(-)10.

Rama Rao et al.[23] reported a series of synthesis of AB ring synthons. The main strategy to prepare the desired tetralin 10 (Scheme-17), involved 2-carbon homologation of 5,8-dimethoxy-2-tetralone by using an acyl anion equivalent such as 2-lithio-2-methyl-1,3-dithiane and transforming the resultant thioketal intermediate 45 by hydrolysis to get the required product 10. Later, they reported the non-Diels-Alder approach for the synthesis of AB ring synthon 47 (Scheme-17b). Diketo ester 46 was obtained from 2-bromo-5-acetyl benzylbromide. Alkaline hydrolysis of 46 and subsequent cyclisation of resulting acid with sulfuric acid afforded (±)47. They also developed the synthesis of (±) 10 starting from 5,8-dimethoxy-1-tetralone

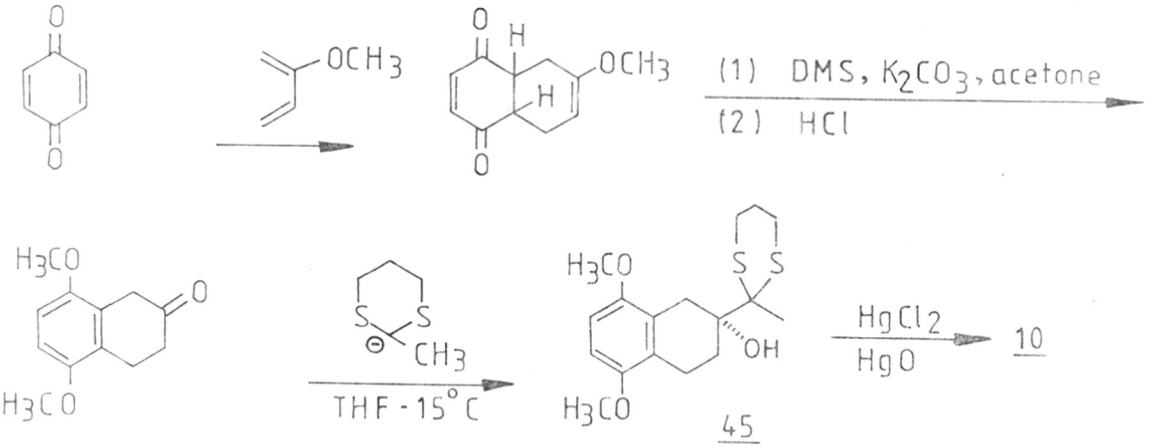
SCHEME 15 Monneret Tetrahedron Lett 26, 5295 (1985)



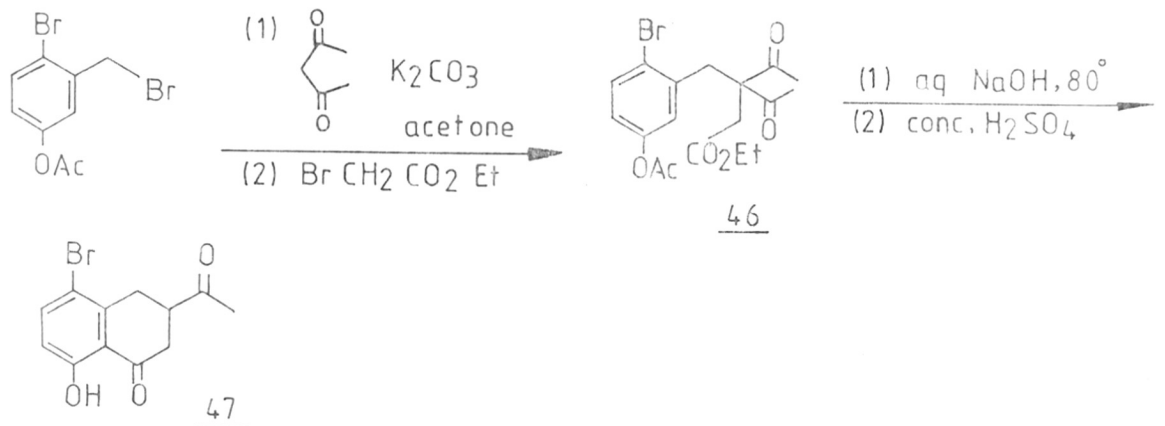
SCHEME 16 Shibasaki et al, Tetrahedron Lett 26, 6497 (1985)



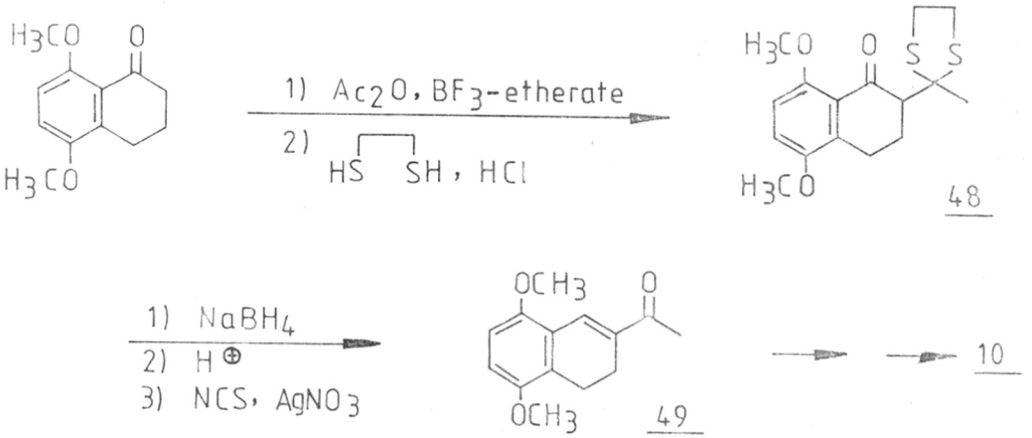
SCHEME 17a RamaRao et al., Tetrahedron Lett, 2661 (1980)



SCHEME 17b RamaRao et al., Tetrahedron Lett, 2415 (1982)



SCHEME 17c RamaRao et al., Tetrahedron Lett., 1015 (1982)



(Scheme-17c). Acylation of tetralone followed by selective protection with 1,2-ethane-dithiol afforded 48. Compound 48 on reduction, dehydration and finally dethioketalisation produced 49 in excellent yield. Conversion of 49 or 50 into racemic (±)10 or optically active (-)10 has been well established.

PRESENT WORK

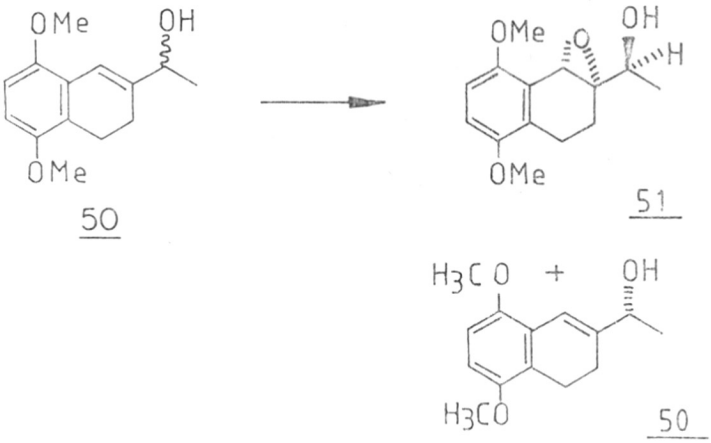
In spite of the fact that only 7S,9S[24] anthracyclinones show biological activity, very little efforts have been made to synthesise them in optically active form. There is no doubt that these compounds would be of immense interest as crucial separations of diastereomers during glycosidation step could be avoided, thereby helping to save the loss of valuable sugar unit. The optically pure anthracyclinones can be obtained by resolution of racemates in which case more than 50% anthracyclinones will be wasteful, it would therefore be appropriate to venture into the chiral synthesis of these molecules. This can be achieved either by obtaining optically active AB ring synthon followed by its extension into tetracyclic ring system or by obtaining optically active tetracyclic ring system itself.

There are some syntheses reported for optically active anthracyclinones either by resolution of racemates or by asymmetric syntheses. The approach reported from

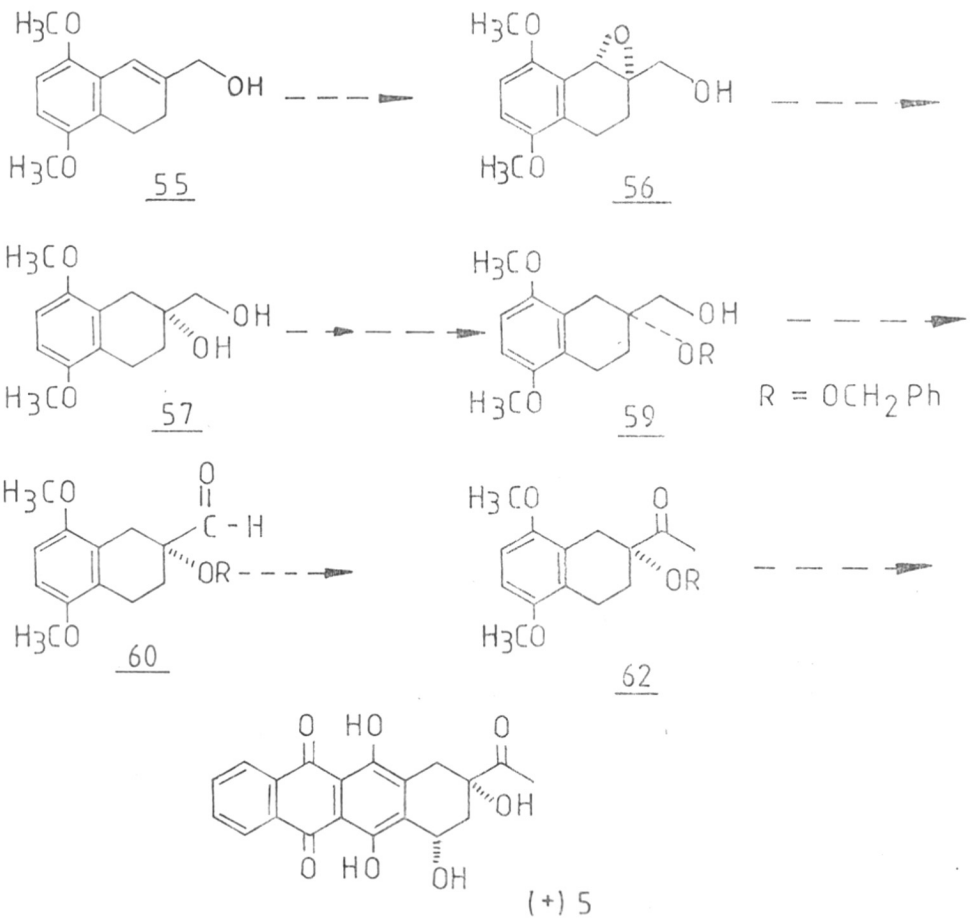
these laboratories[25] involving Sharpless kinetic resolution is by and large the most suitable. For example, the dl-allylic alcohol intermediate 50 on epoxidation under Sharpless kinetic resolution conditions would give the required optically active epoxide 51 at the most in 50% yield. However, in practical terms, the yield of the epoxide 51 could be optimised upto 35%. This leads to the loss of 50% precious material, although recycling of the unwanted material can boost overall yield. It has been seen that during the epoxidation reaction and recycling the undesired alcohol, considerable amount of efforts are required coupled with extensive chromatographic purification. Therefore, what was felt essential was to devise a scheme in which kinetic resolution by Sharpless epoxidation could be completely avoided. This can only be done if one has the allylic alcohol 55. Before venturing into optically active synthesis of (+)-4-demethoxydaunomycinone (Scheme-19), it was felt necessary to carry out the entire sequence with a racemic mixture and overcome unforeseen difficulties which may be encountered in due course of the synthesis (Scheme-20, 21, 22).

The allylic alcohol 55 was synthesised as follows. Diels-Alder reaction of benzoquinone with butadiene in glacial acetic acid at room temperature afforded the adduct 52[26] in 89% yield. Methylation of the adduct (52)

SCHEME 18



SCHEME 19

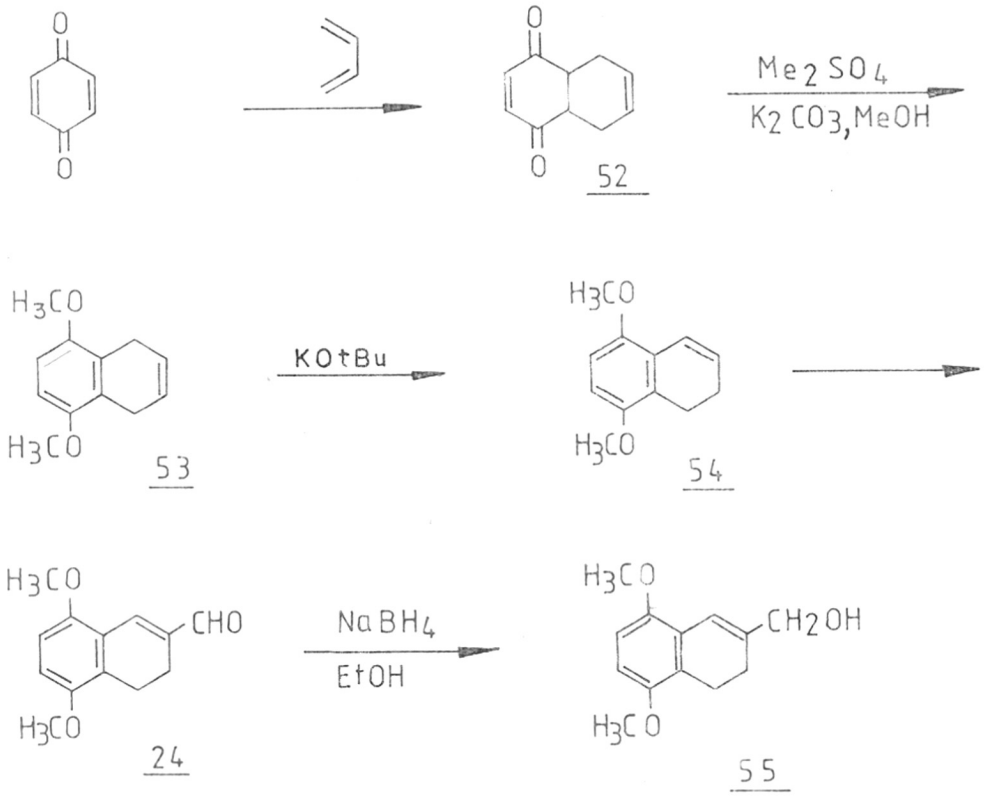


with dimethylsulfate in presence of potassium carbonate in refluxing acetone afforded 5,8-dimethoxy-1,4-dihydronaphthalene(53)[27] as a colourless solid (m.p. 57°). 53 was subjected to base catalysed isomerisation in the presence of potassium tertiarybutoxide in dimethylsulfoxide at room temperature under nitrogen to afford 5,8-dimethoxy-3,4-dihydronaphthalene(54)[28] in almost quantitative yield. Vilsmeier Haack formylation of 54 with phosphorous oxychloride and dimethyl formamide at 80° gave 5,8-dimethoxy-3,4-dihydro-2-naphthaldehyde (24)[14] as a crystalline product, m.p. 91-92°.

Reduction of the aldehyde 24 with sodium borohydride in ethanol and catalytic amount of potassium hydroxide gave the required allylic alcohol, namely 2-hydroxymethyl-5,8-dimethoxy-3,4-dihydronaphthalene (55)[29] in 91% yield. The PMR spectrum of 55 showed the characteristic triplet at 6.75 ppm for the vinylic proton at C-1. The hydroxymethyl and hydroxyl protons appeared respectively at 4.25 ppm ($\underline{CH_2}OH$) and 1.50 ppm ($CH_2\underline{OH}$, D_2O exchangeable). Other protons resonated at the expected chemical shifts. The IR and mass spectra were in agreement with the structure 55.

Epoxidation of this allylic alcohol 55 under non-asymmetric Sharpless conditions[30] using t-butyl hydroperoxide (TBHP) in the presence of vanadyl acetylacetonate [$VO(acac)_2$] in benzene at room temperature yielded the epoxide 56 in

SCHEME 20

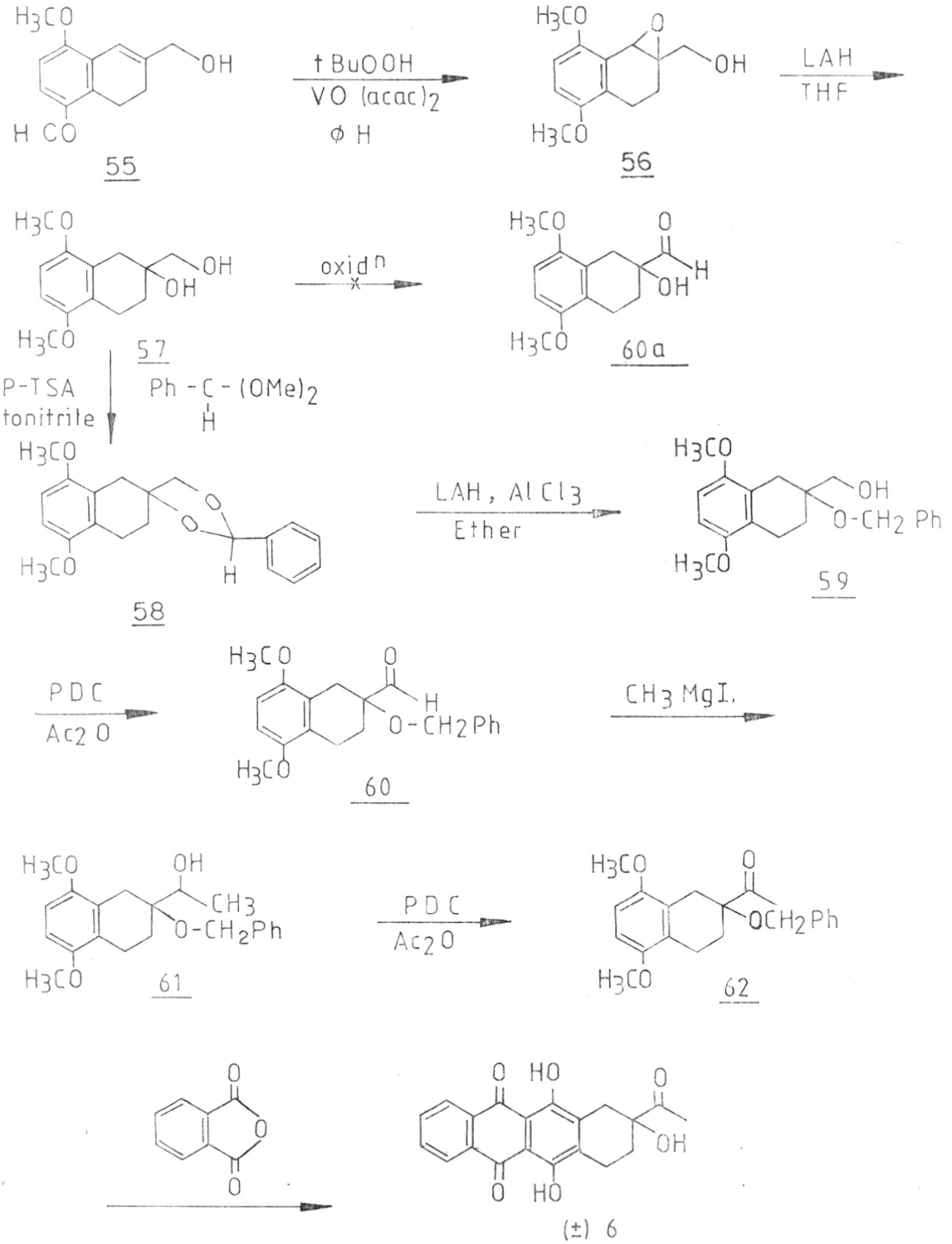

O
O
O
O
52
Me2 SO4
K2 CO3, MeOH
H3CO
H3CO
53
KOtBu
H3CO
H3CO
54
H3CO
CHO
H3CO
24
NaBH4
EtOH
H3CO
CH2OH
H3CO
55

90.6% yield. The proton H-1 appeared at 4.26 ppm in the PMR spectrum of 56. As the epoxide 56 was unstable at room temperature, it was reduced with lithium aluminium hydride in tetrahydrofuran to 2-hydroxymethyl-2-hydroxy-5,8-dimethoxytetralin (57)[29] without delay. The IR spectrum of 57 showed the absorption at 3200 cm^{-1} (OH). PMR spectrum of the diol 57 showed that singlet at δ4.37 due to H-1 proton was disappeared. Multiplet in the region of 1.53-2.3 corresponding to H_a-3,H_b-3 and hydroxyl group was located. Benzylic protons resonated as a multiplet at δ2.41-2.91. The broad singlet at δ3.6 corresponding to three protons was due to hydroxymethyl protons and hydroxyl group. Two methoxyl groups appeared as a singlet at δ3.84 while singlet at δ6.73 was assigned to two aromatic protons (Fig. 1).

In accordance with the plan, the next step involved the oxidation of primary alcohol 57 to the hydroxy aldehyde 60a. Theoretically, the oxidation can be directly achieved. However, the reaction generally proceeds further to afford a tetralone system, thereby giving the required aldehyde in very poor yield. Therefore, in order to circumvent this problem, the oxidation of primary alcohol was achieved by an indirect method as follows.

Protection of the diol 57 with α,α-dimethoxytoluene in the presence of catalytic amount of p-toluene sulfonic

SCHEME 21


H3CO
OH
H CO
55
t BuOOH
VO (acac)2
φ H
O
56
LAH
THF
OH
oxidn
60a
57
P-TSA
acetonitrile
Ph - C - (OMe)2
H
58
LAH, Al Cl3
Ether
O-CH2 Ph
59
PDC
Ac2 O
60
CH3 MgI.
CH3
61
62
(±) 6

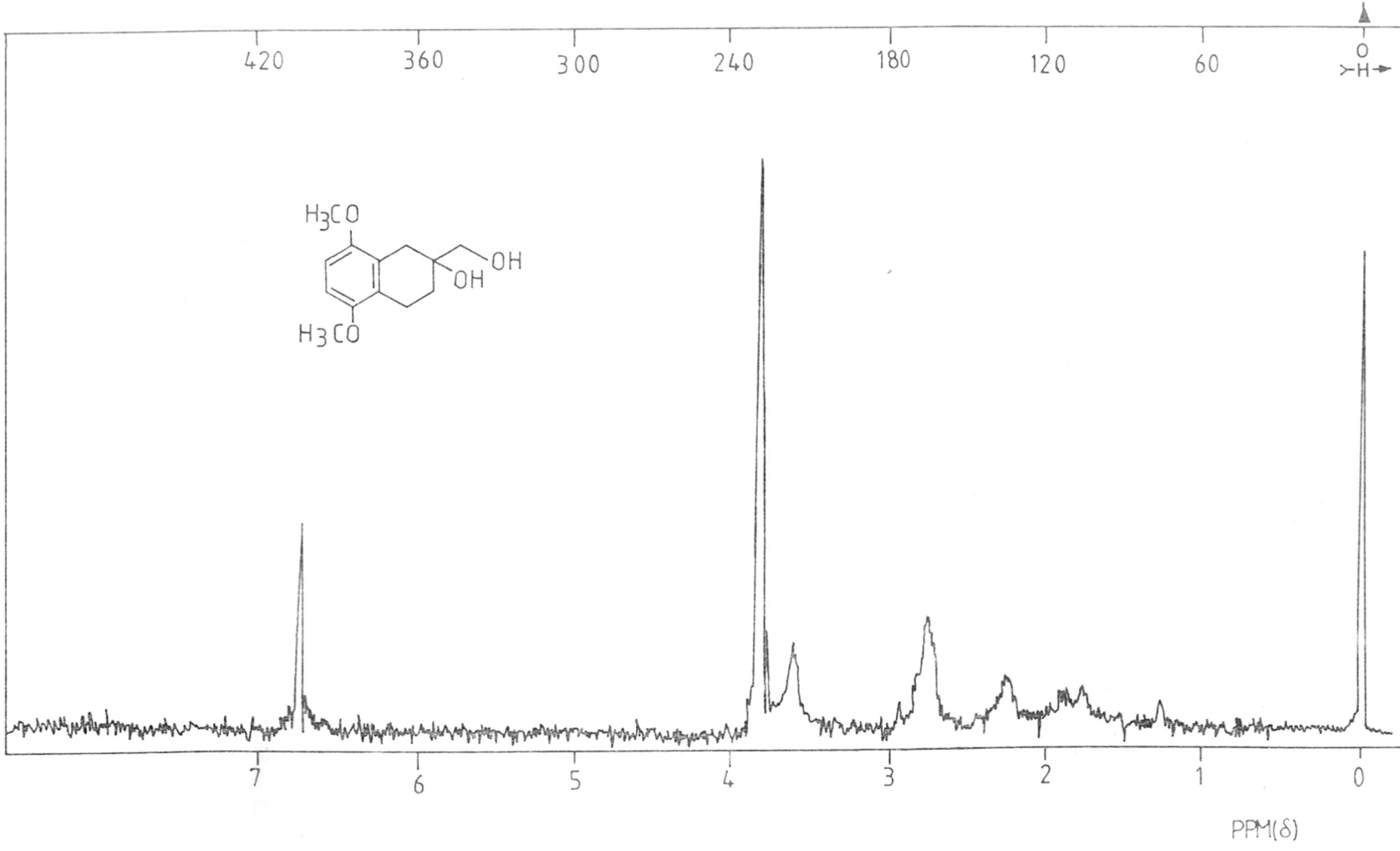


FIG.1: PMR SPECTRUM OF THE COMPOUND (57) IN $CDCl_3$

acid gave the benzylidine derivative 58 in 70% yield. The IR spectrum of 58 showed absence of hydroxyl absorption. The PMR spectrum of 58 showed the presence of two singlets at δ 5.93 and δ 6.0 corresponding to isomeric benzylidine proton. This clearly suggested the structure 58. Other protons had comparable chemical shifts. Hydrogenolysis of 58 with lithium aluminium hydride - aluminium chloride ($LAH-AlCl_3$) gave a product whose structure was suggested on the basis of ample evidences as 2-hydromethyl-2-O-benzyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (59). The final confirmation that the benzyl group was present on tertiary hydroxyl and not on primary hydroxyl group came from the PMR studies in $DMSOd_6$ solvent (Fig. 2 and Fig. 2a). The appearance of a triplet for hydroxyl group (D_2O exchangeable) clearly suggested that the primary hydroxyl group was free.[31] The chemical shifts of other protons were consistent with the structure assigned. In addition, the IR spectrum showed the absorption at 3480 cm^{-1} due to hydroxyl moiety.

Oxidation of the primary alcohol 59 by pyridinium dichromate (PDC) in the presence of acetic anhydride in boiling dichloromethane afforded 2-formyl-2-O-benzyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (60) in 67% yield. The IR spectrum of 60 showed absorption at 1720 cm^{-1} due to aldehyde group. Absorption due to hydroxyl group was

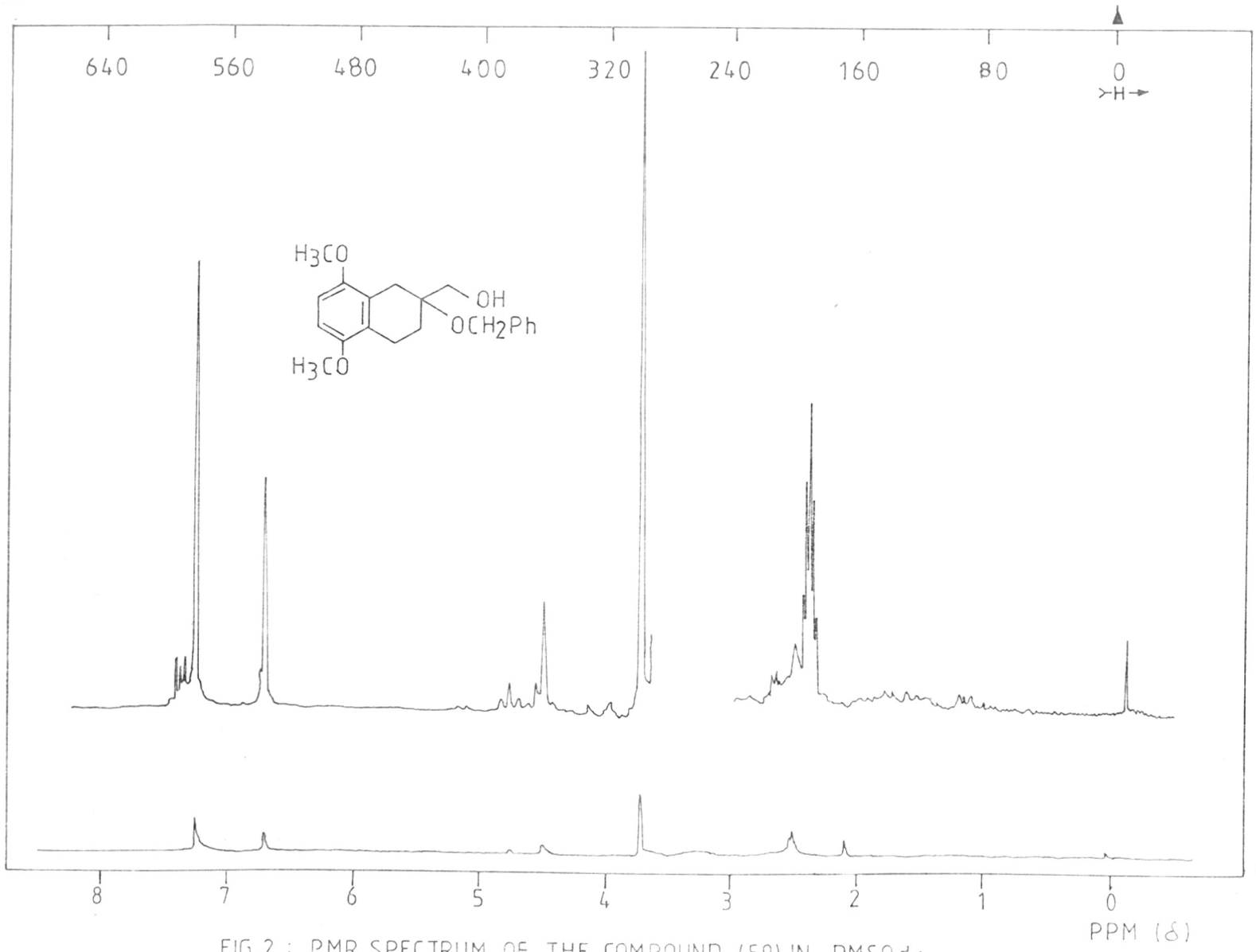


FIG. 2 : PMR SPECTRUM OF THE COMPOUND (59) IN DMSOd_6

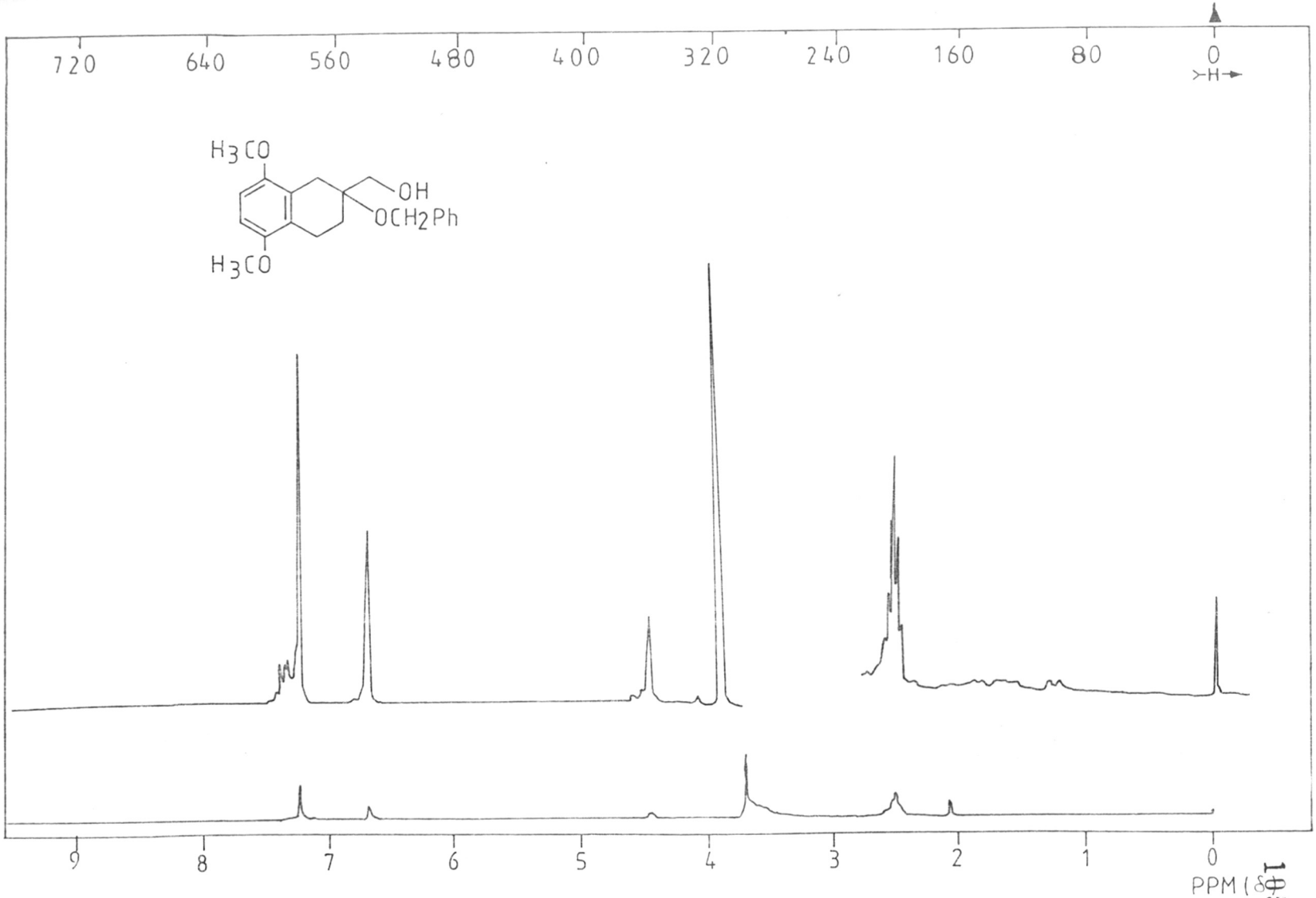


FIG. 2a : PMR SPECTRUM OF THE COMPOUND (59) IN DMSOd6 after D2O exchange

absent. The PMR of 60 (Fig. 3) showed the characteristic singlet at δ9.72 corresponding to the aldehydic proton. Other protons resonated at the expected chemical shifts. Appearance of the aldehydic proton further confirmed our assignments that primary hydroxyl was free in structure 59.

The aldehyde 60 on Grignard reaction with methyl magnesium iodide in ether yielded 2-(1-hydroxyethyl)-2-O-benzyl-5,8-dimethoxy-1,2,3,4-tetrahydro naphthalene (61) in 82% yield. The IR of 61 showed absorption at 3400 cm^{-1} (OH) and absorption due to the aldehyde group was absent. The PMR of 61 showed the presence of doublet at δ1.2 for three protons revealing the presence of methyl group. H_a-3, H_b-3 appeared as a doublet at 2.12 ppm and benzylic protons resonated as multiplet at δ2.48-2.92. Two methoxyl groups appeared as a singlet at δ3.72. The methine proton appeared as a quartet at δ3.98. The remaining protons resonated at the expected chemical shifts.

The secondary alcohol 61 was oxidised with pyridinium dichromate in the presence of acetic anhydride in boiling dichloromethane to afford the expected AB ring synthon namely, 2-acetyl-2-O-benzyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (62) in 70% yield. The IR of 62 showed absorption at 1710 cm^{-1} (C=O). The PMR of 62 showed a singlet at δ2.15 for three protons. The downfield shift of the methyl

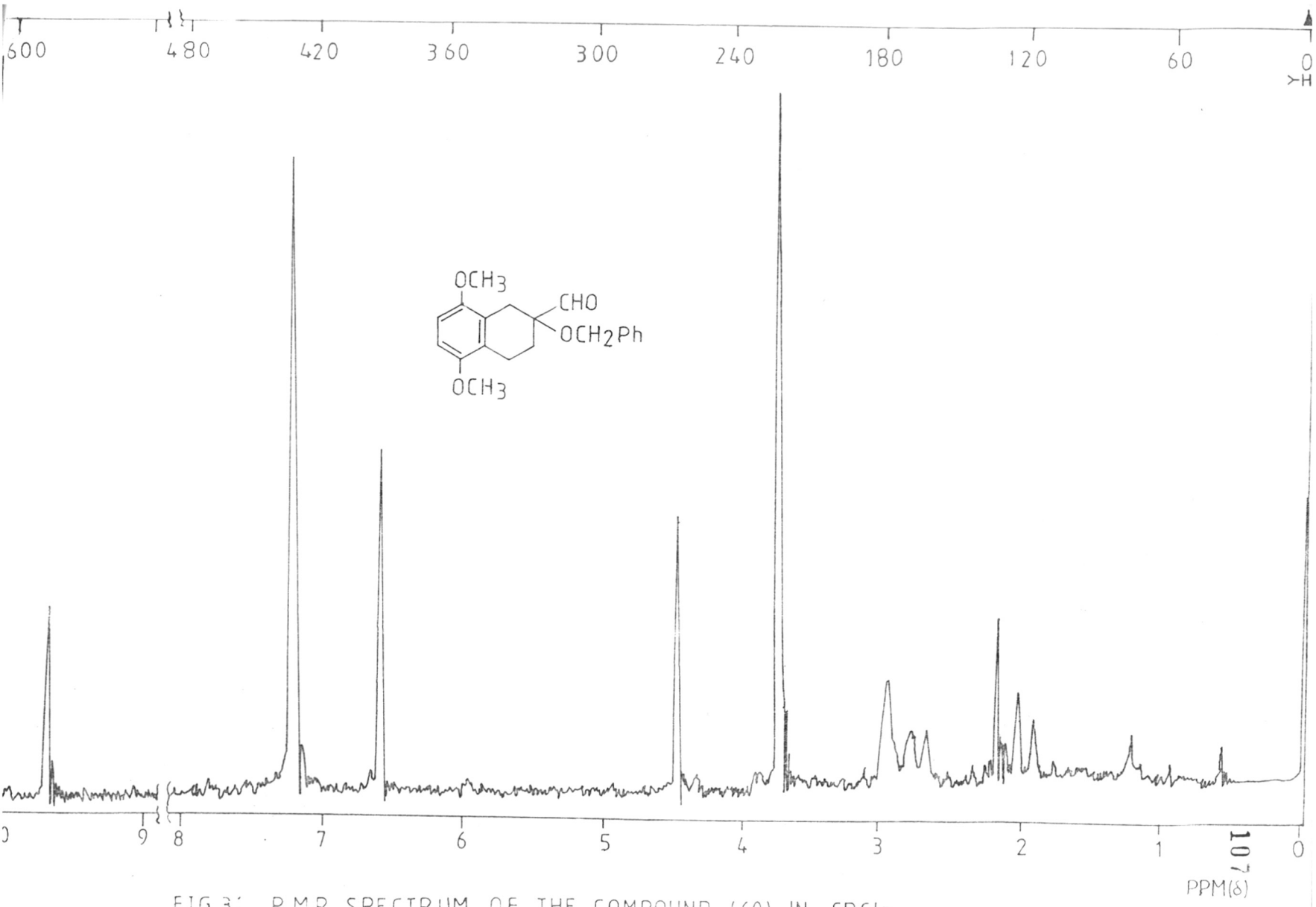


FIG.3: P M R SPECTRUM OF THE COMPOUND (60) IN $CDCl_3$

protons clearly indicated that it was adjacent to carbonyl group. H_a-3, H_b-3 and benzylic protons resonated at δ1.76-2.08 and δ2.57-3 as multiplets respectively. Both methoxyl groups appeared as a singlet at δ3.74. O-Benzyl protons resonated as AB quartet at δ4.33. The chemical shifts of other protons were consistent with the product.

The intimate mixture of 62, phthalic anhydride, aluminium chloride and sodium chloride was heated at 180-190° for 5 minutes. Work up afforded (±)-4-demethoxy-7-deoxydaunomycinone (6) in 74% yield. The IR of 6 showed the absorption at 3460 cm^{-1}, 1700 cm^{-1}, 1655 cm^{-1} and 1580 cm^{-1} due to the presence of hydroxyl, carbonyl, quinone and aromatic functionalities respectively. The PMR of 6 revealed the presence of three hydroxyl groups at δ3.72 and δ13.5. Singlet at δ2.46 was corresponding to acetyl methyl protons. Aromatic protons resonated as multiplets at δ7.6-7.8 and δ8.2 - 8.4. The remaining protons resonated as expected. The spectral data was in agreement with the reported one.[32] It is pertinent to note that during fusion reaction, the benzyl group fell apart which, however, in the present case, was advantageous as it saved one step of de-O-benzylation.

The total synthesis of (±)-4-demethoxydaunomycinone (5) would be effected by introduction of hydroxyl group in the C-7 position of 4-demethoxy-7-deoxydaunomycinone (6).

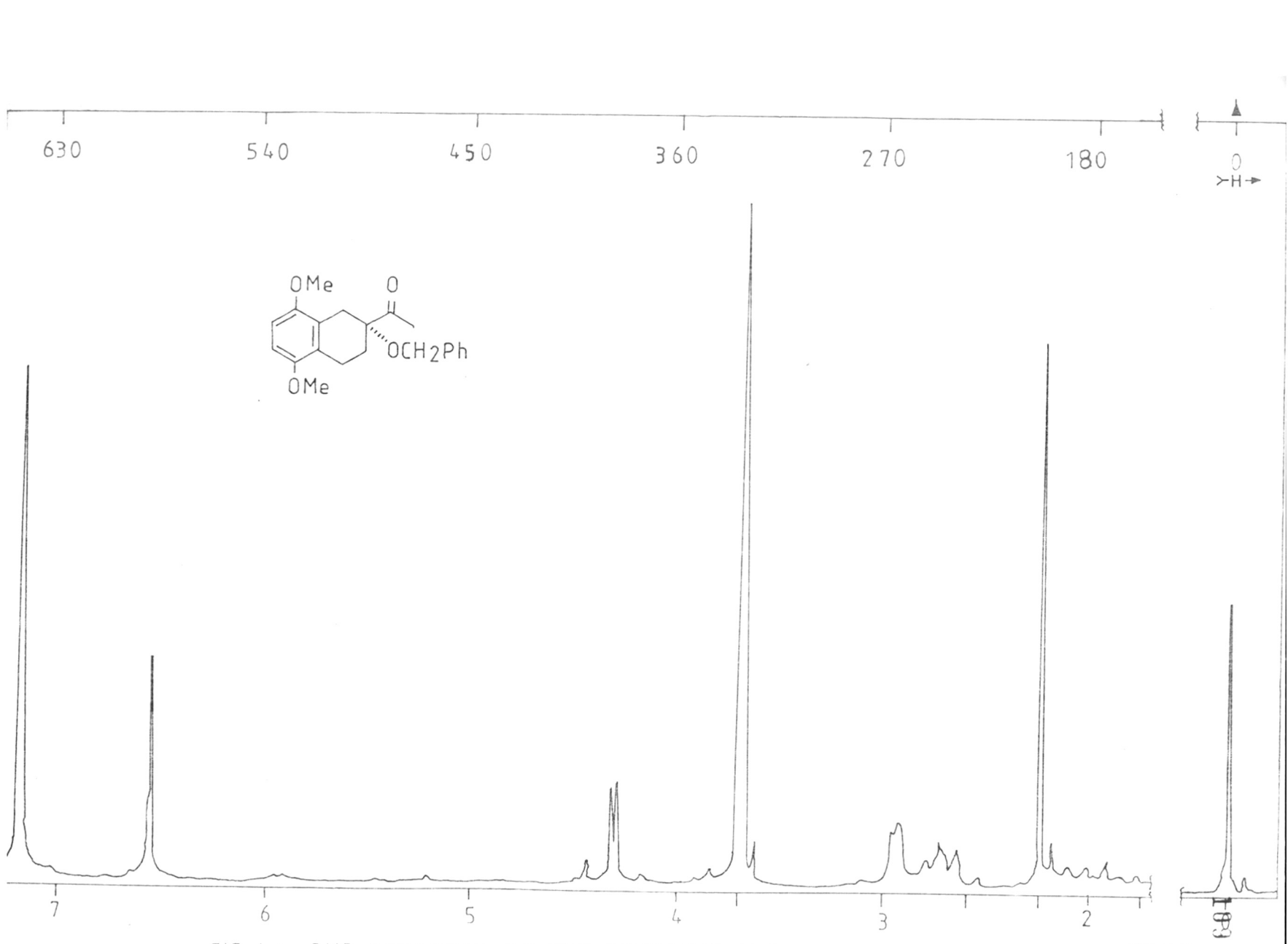


FIG. 4 : PMR SPECTRUM OF THE COMPOUND (62) IN $CDCl_3$

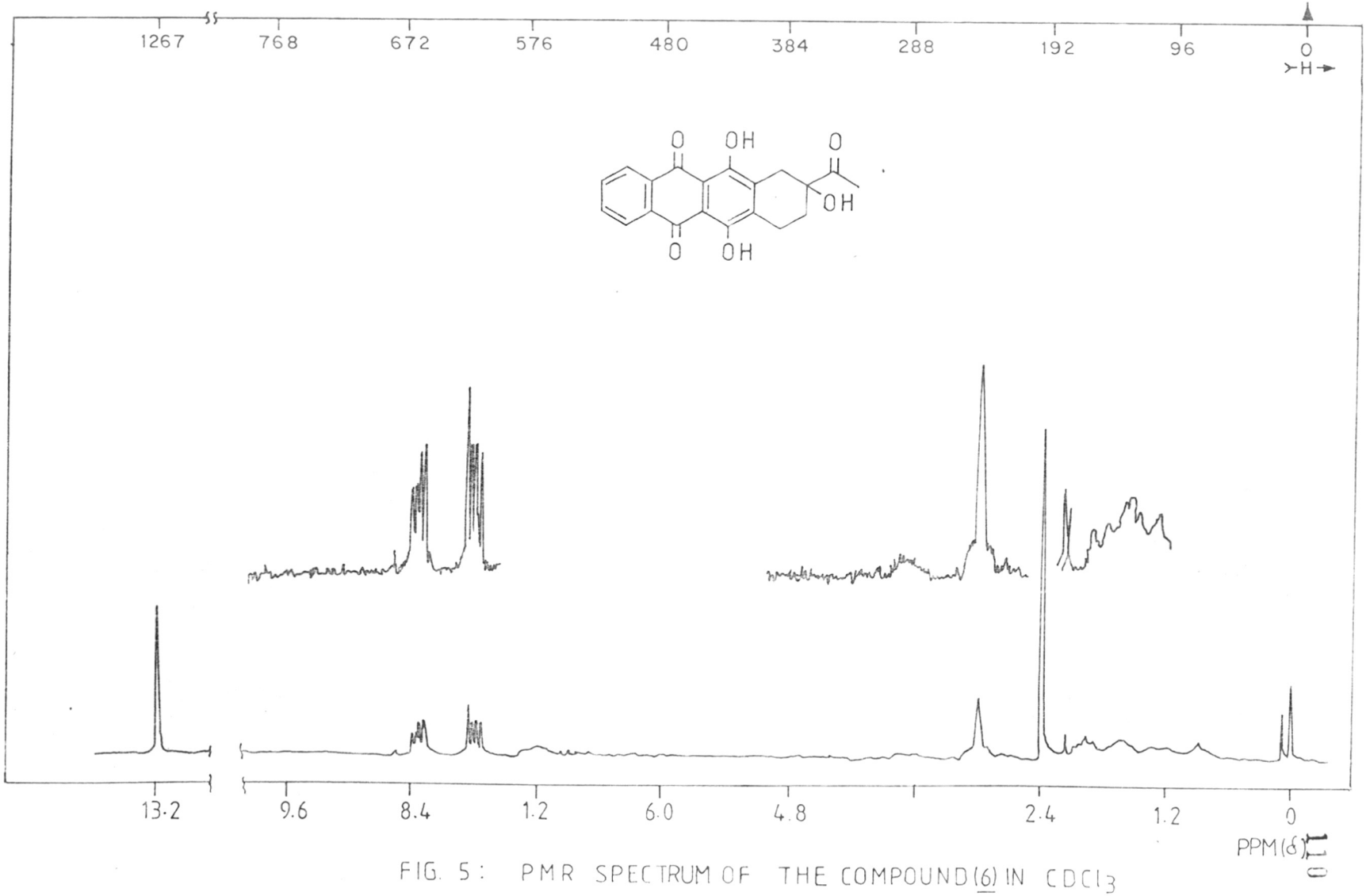


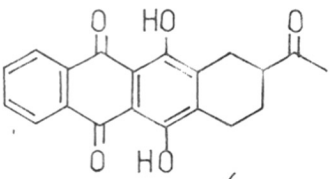
FIG. 5: PMR SPECTRUM OF THE COMPOUND (6) IN $CDCl_3$

Wong et al.[8a] were the first to study the introduction of hydroxyl function at C-7 wherein ethylene acetal of (±)-4-demethoxy-7-deoxydaunomycine dimethyl ether, was brominated with N-bromosuccinimide and a mixture of bromo-compounds obtained was methanolised to the corresponding 7-methoxy derivative. Later, this approach was utilised by others[12] with suitable modifications in the synthesis of different anthracyclinones.

Cava et al.[33] studied this problem in more details and reported a better procedure which was utilised in the present work for the introduction of C-7 hydroxyl group (Scheme-22). Thus, 4-demethoxy-7-deoxydaunomycinone (6) was converted into its triacetate 63 by treatment with acetic anhydride in the presence of catalytic amount of concentrated sulphuric acid. It was then brominated with 1,3-dibromo-5,5-dimethylhydantoin to obtain the required bromide (64) as a major product. The PMR of 64 revealed the presence of a broad triplet for one proton at δ5.70 corresponding to H-7 proton which was shifted downfield because of the presence of bromo group. H_a-8,H_b-8 & H_a-10,H_b-10 protons resonated as multiplets at δ2.70 and δ3.10 - 3.40 respectively. All other protons resonated at the expected chemical shifts.

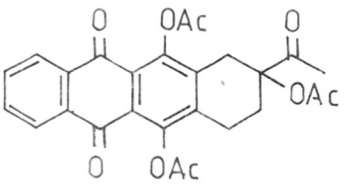
The bromide (64) was subsequently reacted with silver trifluoroacetate in trifluoroacetic acid followed by treatment

SCHEME 22



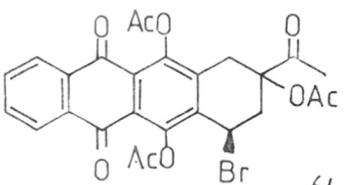
6

Ac_2O, H_2SO_4



63

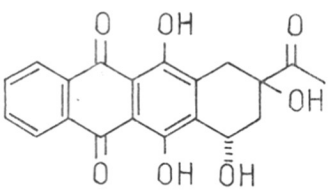
1,3- Dibroma-5,5 dimethyl-hydantoín, CCl_4, benzoyl-penoxide, $h\nu$.



64

(1) CF_3COOAg, CF_3COOH

(2) NaOH, THF



(±)5

with sodium hydroxide to afford the desired (±)-4-demethoxy-daunomycinone (5). The IR of 5 showed the absorption at 3368 cm^{-1}, 1710 cm^{-1}, 1632 cm^{-1} and 1590 cm^{-1} due to the presence of hydroxyl, ketone, quinone and aromatic moieties. The PMR of 5 showed the presence of singlet at δ2.39 corresponding to acetyl methyl group. H-7 proton appeared as a broad singlet at 5.31 ppm. Aromatic protons resonated as multiplets at 7.71 - 8.00 ppm and δ8.19 - 8.42 respectively. All other protons resonated at the expected chemical shfits. The spectral characteristic of 5 were in good agreement with reported values.[33]

From the above study, it could be suggested that the synthetic scheme outlined above works without any serious drawback and is suitable for asymmetric synthesis of 4-demethoxydaunomycinone. Initial studies on the Sharpless asymmetric epoxidation of the allylic alcohol 55 failed to give the desired optically active epoxide 56. However, a tetralone type of product whose structure was not unambiguously assigned was formed. These reactions were earlier observed in these laboratories.[25] This suggests that proper reaction conditions have to be optimised so as to prevent the epoxide to undergo further reactions. This work is being pursued in these laboratories.

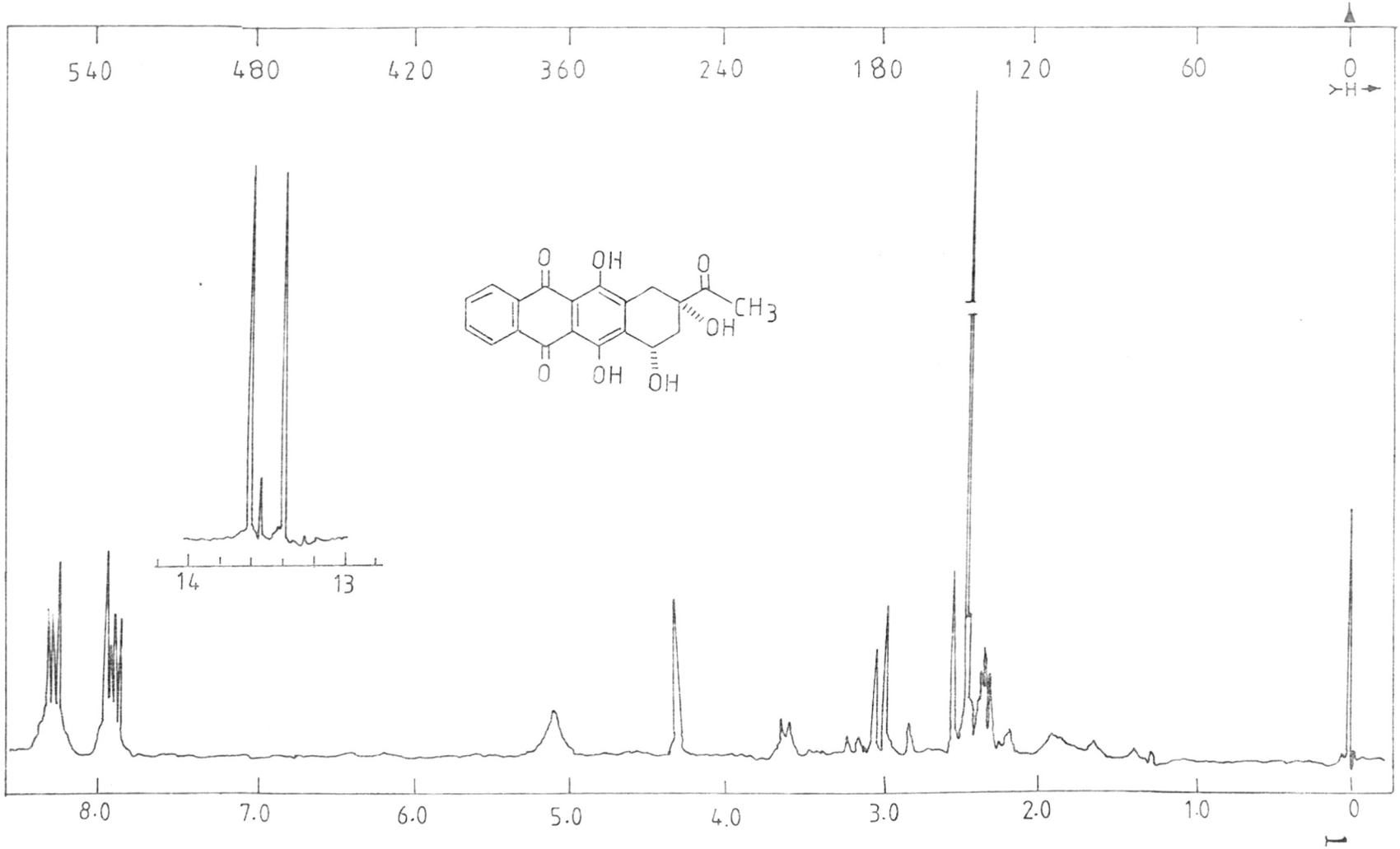


FIG 6 : PMR SPECTRUM OF THE COMPOUND (5) IN CDCl3

GENERAL REMARKS

Melting points are uncorrected. IR spectra ($\tilde{\nu}_{max}$ in cm^{-1}) were recorded in nujol or chloroform or neat on a Perkin-Elmer Model 683 spectrophotometer with sodium chloride optics.

PMR and ^{13}C-NMR were obtained on Varian T-60 or Varian FT-80A or Bruker WH-90 spectrometer in $CDCl_3$ or CCl_4 solutions containing tetramethylsilane (TMS) as an internal standard with chemical shifts (δ) expressed in ppm downfield from TMS.

Mass spectra were run on AEI MS 30 double beam mass spectrometer or CEC 21-110B mass spectrometer.

All solvents and reagents were purified and dried by standard techniques. All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 50°C.

EXPERIMENTAL

Diels-Alder adduct (52)

To a solution of p-benzoquinone (27g, 250 mmol) in glacial acetic acid (250 ml) in one litre round bottom flask, was introduced liquid butadiene (54g, 1000 mmol) at 0° to 5°. The flask was stoppered and the contents were allowed to stand at room temperature for 36 hr. Reaction mixture was poured over crushed ice with stirring. The colourless compound that precipitated was filtered and dried to obtain the Diels-Alder adduct 52[26] (36g, 89%).

5,8-Dimethoxy-1,4-dihydronaphthalene (53)

A mixture of adduct 52 (32.4g 200 mmol), dimethyl sulphate (53g, 500 mmol) and potassium carbonate (100 g) in dry acetone (500 ml) was heated under reflux for 6 hours. Acetone was distilled off and crushed ice added to reaction mixture. The separated solid was filtered and dried to give 53 (35.5g 93.4%) as colourless solid, m.p. 51° (lit.[27] 50°); PMR (CCl_4): δ 3.24 (bs, 4H, H_a-1, H_b-1 and H_a-4, H_b-4), 3.76 (s, 6H, 2X-OCH_3), 5.90 (bs, 2H, H-2 and H-3), 6.53 (s, 2H, aromatic). Mass: 190(M^+). Analysis: Calculated for $C_{12}H_{14}O_2$: C, 75.79; H, 7.36; Found: C, 75.86; H, 7.41%.

5,8-Dimethoxy-3,4-dihydronaphthalene (54)

To a solution of compound 53 (28.5 g, 150 mmol) in dry dimethylsulfoxide (125 ml) was added potassium t-butoxide

(2 g, 18 mmol). The contents were stirred under nitrogen atmosphere at room temperature for 6 hr. The reaction mixture was poured over crushed ice with stirring. The colourless solid was filtered and dried to afford 53[28] (27.6 g, 96.8%) which crystallised from hexane as colourless crystals, m.p. 70°. PMR (CCl_4): δ 2.1-2.7 (m, 1H, H_a-3, H_b-3 & H_a-4, H_b-4), 3.8 (s, 6H, 2X-OCH_3), 5.85 (m, 1H, H-2), 6.63 (s, 2H, aromatic), 6.83 (m, 1H, H-1); Mass: 190 (M^+); Analysis: Calculated for $C_{12}H_{14}O_2$: C, 75.79; H, 7.36; Found: C, 75.72; H, 7.42%.

2-Formyl-5,8-dimethoxy-3,4-dihydronaphthalene (24)

To a precooled (10°) solution of 5,8-dimethoxy-3,4-dihydronaphthalene (54) (19 g, 100 mmol) in dimethyl formamide (40 ml) was added Vilsmeier reagent (prepared from phosphorous oxychloride (23 g, 150 mmol) and dimethyl formamide (18 g, 250 mmol]. The reaction mixture was heated at 80° for 4 hr and poured over crushed ice. It was left at room temperature for 30 minutes. The solid, that separated, was filtered, washed with water, dried to give aldehyde 24 (20.8 g, 95.4%) as light yellow solid and crystallised from methanol to give light yellow crystals, m.p. 91-92°, (lit.[14] m.p. 92-93°). PMR ($CDCl_3$): δ 2.43-2.86 (m, 4H, H_a-3, H_b-3 & H_a-4, H_b-4), 3.76 & 3.83 (each s, each 3H, 2X-OCH_3), 6.60 & 6.82 (each d, J=8Hz,

each 1h, H-6 & H-7), 7.66 (s, 1H, H-1), 9.63 (s, 1H, -CHO), Mass: 218(M^+); Analysis: Calculated for $C_{13}H_{14}O_3$, C, 71.55; H, 6.42; Found: C, 71.69, H, 6.47%.

2-Hydroxymethyl-5,8-dimethoxy-3,4-dihydronaphthalene (55)

To a solution of aldehyde 24 (6.54 g, 30 mmol) in ethanol (120 ml) was added powdered potassium hydroxide (0.3 g, 5.35 mmol) followed by sodium borohydride (1.14 g, 30 mmol) in portions at 0°. The contents were stirred to room temperature for 1 hr. Water (2 ml) was added to the reaction mixture. Ethanol was removed under vaccum and water was added to the residue to give white solid which was filtered, washed with water and dried to afford 55 (6 g, 91%). Crystallisation from methanol gave colourless crystals, m.p. 93-95° (lit.[29] m.p. 93-95°). IR(nujol): 3200 cm^{-1} (OH); PMR ($CDCl_3$): δ 1.50 (s, 1H, $-CH_2\underline{OH}$, D_2O exchangeable), 1.87-2.31 (m, 2H, H_a-3 & H_b-3), 2.75 (t, J = 8Hz, 2H, benzylic). 3.75 (s, 6H, 2X-OCH_3), 4.25 (bd, 2H, $-\underline{CH_2}OH$), 6.62 (s, 2H, aromatic), 6.75 (t, 1H, H-1); Mass: 220(M^+), Analysis: Calculated for $C_{13}H_{16}O_3$; C, 70.90; H, 7.27; Found: C, 70.65, H, 7.32%.

2-Hydroxymethyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (57)

To a solution of allylic alcohol 55 (5.5 g, 25 mmol) in dry benzene (350 ml) was added vanadyl acetylacetonate

(60 mg) followed by t-butylhydroperoxide (TBHP) (30 ml, 70%) in portions at room temperature. The contents were stirred for 4 hr when the starting material disappeared (TLC). Benzene solution was then washed with water, dried over anhydrous sodium sulphate and evaporated to get a gummy product 56 (5.35 g, 90.6%); PMR ($CDCl_3$): δ 4.26 (s, 1H, epoxide H) which was immediately subjected to lithium aluminiumhydride reaction.

To the solution of epoxide 56 (5.35 g, 22.7 mmol) in dry tetrahydrofuran (30 ml) was added lithium aluminium hydride (0.863 g, 22.7 mmol) in portions in 10 minutes at room temperature. The contents were stirred at room temperature for 4 hr. Reaction was worked up by the addition of saturated sodium carbonate solution. A white solid was obtained which was filtered, washed with chloroform. The filtrate on evaporation gave a semi-solid which was crystallised from benzene to give colourless crystals of 57 (4.5 g, 83.3%), m.p. 129-132°C; IR (nujol): 3500 cm^{-1} (OH), 1600 (aromatic). PMR ($CDCl_3$): 1.53-2.3 (m, 3H, H_a-3,H_b-3 & OH), 2.41-2.91 (m, 4H, benzylic), 3.6 (bs, 3H, CH_2OH & OH), 3.84 (s, 6H, $2XOCH_3$), 6.73 (s, 2H, aromatic); Mass: 238 (M^+); Analysis: Calculated for $C_{13}H_{18}O_4$; C, 65.5; H, 7.56; Found: C, 65.25; H, 7.3%.

Benzylidine derivative of diol 57 (58)

To the diol 57 (2 g, 8.4 mmol) in acetonitrile (10 ml), $\alpha\alpha$-dimethoxytoluene (1.15 g, 7.56 mmol) and catalytic amount of p-toluenesulfonic acid (50 mg) were added at 0°. The reaction mixture was stirred at 0° to room temperature for ½ hr when the starting material almost disappeared (TLC). Powdered sodium bicarbonate was added and contents were stirred for ½ hr at 0°. Acetonitrile was decanted. Inorganic salts were washed with chloroform. Both organic layers were mixed, wahsed with water, dried over anydrous sodium sulphate and solvent removed under reduced pressure to afford 58 as a semisolid (1.9 g, 69.35%). 58 was crystallised from ether-pet. ether; m.p. 95-98°. IR (nujol): 1600 cm^{-1} (aromatic); PMR ($CDCl_3$): δ 1.76-2.13 (m, 2H, H_a-3,H_b-3), 2.85 (bs, 4H, benzylic), 4.74 (s, 8H, 2X-OCH_3+$\underline{CH_2}OR$), 5.93 & 6.0 (s, 1H, isomeric benzylidine proton), 6.54 (s, 2H, aromatic), 7.23-7.54 (m, 5H, aromatic); Mass: 326(M^+); Analysis: Calculated for $C_{20}H_{22}O_4$; C, 73.61; H, 6.74; Found: C, 73.82; H, 6.79%.

2-Hydroxymethyl-2-O-benzyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (59)

Anhydrous aluminium chloride (1.6 g, 12 mmol) was added to dry ether (20 ml) at 0°. After stirring for 10 minutes at 0°, lithium aluminiumhydride (0.115 g, 3 mmol)

was added and suspension was stirred till all the aluminium chloride dissolved (1 hr). To this aluminium chloride-lithium aluminiumhydride mixture, benzylidine derivative 58 (1.97 g, 6.04 mmol) in dry ether (20 ml) was added dropwise. Reaction mixture was further stirred for 1 hr till there was no starting material (indicated by TLC). The complex was decomposed by the addition of ethyl acetate and water. Reaction product was extracted extensively with chloroform. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate and evaporated to give 59 as a colourless solid which was crystallised from carbontetrachloride (1.7 g, 85.76%); m.p. 96-98°, IR (nujol): 3480 cm^{-1} (OH), 1600 cm^{-1} (aromatic), PMR ($CDCl_3$): δ1.88-2.06 (m, 2H, H_a-3, H_b-3), 2.64-2.94 (m, 4H, benzylic), 3.63 (s, 2H, $\underline{CH_2}OH$), 3.87 (s, 6H, 2X-OCH_3), 4.56 (s, 2H, $O\underline{CH_2}Ph$), 6.62 (s, 2H, aromatic), 7.23-7.36 (m, 5H, aromatic); PMR ($DMSOd_6$): δ 1.72-1.96 (m, 2H, H_a-3, H_b-3), 2.3-2.52 (m, 4H, benzylic), 3.56 (s, 8H, 2X-OCH_3+$\underline{CH_2}OH$), 4.56 (s, 2H, $O\underline{CH_2}Ph$), 4.74 (t, 1H, OH, vanishes after D_2O exchange), 6.64 (s, 2H, aromatic), 7.2 (s, 5H, aromatic); Mass: 328(M^+); Analysis: Calculated for $C_{20}H_{24}O_4$; C, 73.1; H, 7.32; Found: C, 72.96; H, 7.24%.

2-Formyl-2-O-benzyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (60)

To a stirred solution of pyridinium dichromate (PDC)

(0.361 g, 0.96 mmol) in dichloromethane (5 ml) and acetic anhydride (0.49 g, 4.8 mmol), alcohol 59 (0.525 g, 1.6 mmol) was rapidly added at room temperature. After 2 hr, the reaction mixture was diluted with ether (30 ml). The solvent was decanted and the reaction product was washed thoroughly with ether. The organic phase was concentrated and filtered through silica gel to give 2-formyl-2-O-benzyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene 60 (0.35 g, 67.3%) as semisolid which was pure enough for next step. IR (nujol): 1720 cm^{-1}; PMR ($CDCl_3$): δ 2.0 (t, J=8Hz, 2H, H_a3,H_b-3), 2.64 - 3 (m, 4H, benzylic), 3.74 (s, 6H, 2X OCH_3), 4.5 (s, 2H, -OCH_2Ph), 6.58 (s, 2H, aromatic), 7.26 (s, 2H, aromatic), 9.72 (s, 1H, CHO); Mass: 326 (M^+); Analysis: Calculated for $C_{20}H_{22}O_4$, C, 73.61, H, 6.74; Found: C, 73.38; H, 6.26%.

2-(1-Hydroxyethyl)-2-O-benzyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (61)

To a suspension of methyl magnesiumiodide (0.166 g, 1 mmol) in dry ether (5 ml) was added dropwise a solution of the aldehyde 60 (0.326 g, 1 mmol) in dry ether (5 ml) at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 1 hr at room temperature. The mixture was poured into a cooled saturated solution of ammonium chloride and the reaction product was extracted with ether (3 x 20 ml). The combined organic layer was

washed with water, dried over anhydrous sodium sulphate and evaporated under reduced pressure to yield 2-(1-hydroxyethyl-2-O-benzyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene 61 (0.290 g, 84.8%); IR ($CHCl_3$): 3400 cm^{-1} (OH); PMR ($CDCl_3$): δ 1.2 (d, J = 6Hz, 3H, CH_3), 2.12 (d, 10Hz, H_a-3, H_b-3), 2.48-2.92 (m, 4H, benzylic), 3.72 (s, 6H, 2X-OCH_3), 3.98 (q, J = 6Hz, 1H, $-\overset{OH}{\underset{H}{C}}-CH_3$), 4.41 (AB quartet, J = 7.5Hz, 2H, OCH_2Ph), 6.66 (s, 2H, aromatic), 7.24 (s, 5H, aromatic); Mass: 342(M^+); Analysis: Calculated for $C_{21}H_{26}O_4$; C, 73.68; H, 7.6; Found: C, 73.82; H, 7.52%.

2-Acetyl-2-O-benzyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (62)

To a stirred solution of pyridinium dichromate (PDC) (0.176 g, 0.47 mmol) in dichloromethane (4 ml) and acetic anhydride (0.24 g, 2.35 mmol), secondary alchol 61 (0.27 g, 0.78 mmol) was rapidly added at room temperature. After 2 hr, the reaction mixture was diluted with ether (20 ml). The solvent was decanted and reaction product was washed thoroughly with ether. The organic phase was filtered through silica gel and concentrated to give 2-acetyl-2-O-benzyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (62) as colourless solid which was crystallised from pet. ether (0.19 g, 70.8%); m.p. 106-8°; IR (nujol): 1720 cm^{-1} (C=O); PMR ($CDCl_3$): δ 1.77-2.08 (m, 2H, H_a-3, H_b-3), 2.24 (s, 3H, $COCH_3$), 2.57 - 3 (m, 4H, benzylic), 3.74 (s, 6H, 2XOCH_3),

4.33, (AB quartet, J = 11Hz, 2H, OCH_2Ph), 6.55 (s, 2H, aromatic), 7 (s, 5H, aromatic). Mass: 340 (M^+); Analysis: Calculated for $C_{21}H_{24}O_4$; C, 74.11; H, 7.05; Found: C, 74.32; H, 7.13%.

4-Demethoxy-7-deoxydaunomycinone (6)

A mixture of anhydrous aluminium chloride (0.707 g, 5.3 mmol) and sodium chloride (0.288 g, 4.93 mmol) was heated at 180-190° for 5 minutes. To this melt was added a mixture of phthalic anhydride (0.313 g, 2.12 mmol) and the tetralin 62 (0.18 g, 0.53 mmol) and the resulting mixture was stirred at 180-190° for 7 minutes. After cooling, the reaction mixture was digested with saturated oxalic acid solution on water bath for 1 hr, cooled and extracted with chloroform (4 x 10 ml). The chloroforom layer was successively washed with 5% sodium bicarbonate, brine, dried and evaporated to yield 4-demethoxy-7-deoxy-daunomycinone (6) (0.137 g, 74.5%) as red needles, m.p. 216-217° (lit.[32] m.p. 210-212°); IR (nujol): 3460 cm^{-1} (OH), 1710 cm^{-1} (keto), 1655 cm^{-1} (quinone), 1580 cm^{-1} (aromatic); PMR ($CDCl_3$): δ 1.5-1.9 (m, 2H, H_a-8, H_b-8), 2.46 (s, 3H, $COCH_3$), 3.12 (bs, 4H, benzylic), 3.72 (bs, 1H, OH), 7.6-7.8 (m, 2H, aromatic), 8.2-8.4 (m, 2H, aromatic), 13.5 (s, 2H, 2XOH); Mass: 352(M^+).

(±)-4-Demethoxydaunomycinone (5)

A mixture of 4-demethoxy-7-deoxydaunomycinone (6) (0.12 g, 0.34 mmol), acetic anhydride (4 ml) and a catalytic amount (2 drops) of conc. sulphuric acid was heated at 90° for 6 hr. The excess of acetic anhydride was removed under vaccuo and the residue was crystallised from methanol-methylene chloride to afford the triacetoxy ketone (63) (0.138 g, 85%) as pale yellow crystals, m.p. 235-7° (lit.[33] m.p. 242-43°); IR (KBr): 1772 cm^{-1} (Ar-$OCOCH_3$), 1740 cm^{-1} ($OCOCH_3$), 1722 cm^{-1} ($COCH_3$), 1670 cm^{-1} (quinone), 1587 cm^{-1} (aromatic); PMR ($CDCl_3$): δ 1.8-2.11 (m, 2H, H_a-8, H_b-8), 2.10 (s, 3H, $OCOCH_3$), 2.26 (s, 3H, $COCH_3$), 2.54 (s, 3H, Ar-$OCOCH_3$), 2.55 (s, 3H, Ar-$OCOCH_3$), 2.81-3.35 (m, 4H, benzylic), 7.65-7.83 (m, 2H, aromatic), 8.07-8.23 (m, 2H, aromatic).

A solution of above triacetoxy ketone (63) (0.119 g, 0.25 mmol) and 1,3-dibromo-5,5- dimethyl hydantoin (0.047 g, 0.165 mmol) in dry carbontetrachloride (12 ml) was refluxed with the help of an electric bulb in the presence of a catalytic amount of benzoyl peroxide for 3 hr. The residue obtained after removal of solvent was purified by column chromatography (silica gel; eluent 20% acetone in pet. ether) to yield the bromide (64) (0.07 g, 50.7%) as pale yellow needles, m.p. 210-14° (lit.[33] m.p. 216-17°); IR (KBr): 1785 cm^{-1} (Ar-$OCOCH_3$),

1735 cm^{-1} ($OCOCH_3$), 1718 cm^{-1} ($COCH_3$), 1685 cm^{-1} (quinone), 1585 (aromatic), PMR ($CDCl_3$): δ 2.11 (s, 3H, $-OCOCH_3$), 2.24 (s, 3H, $COCH_3$), 2.57 (s, 3H, Ar-$OCOCH_3$), 2.59 (s, 3H, Ar-$OCOCH_3$), 2.7 (m, 2H, H_a-8, H_b-8), 3.1-3.4 (m, 2H, H_a-10, H_b-10), 5.7 (br.t, 1H, H-7), 7.714 (m, 2H, aromatic), 8.17 (m, 2H, aromatic).

The bromide (64) (0.08 g, 0.14 mmol) was stirred with silver trifluoroacetate (0.106 g, 0.48 mmol) and trifluoroacetic acid (4 ml) at room temperature for 2 hr. After the removal of trifluoroacetic acid in vaccuo the residue was dissolved in a mixture of tetrahydrofuran (4 ml) and aqueous sodium hydroxide (3 ml. 0.5 N) and the contents were stirred at room temperature under nitrogen for 2 hr. The blue solution was diluted with water and acidified with dil. hydrochloric acid (10%) till the colour changed to red. It was then extracted with chloroform, dried (Na_2SO_4), evaporated and purified with column chromatography (silica gel; eluent - 10% methanol in chloroform) to afford 4-demethoxydaunomycinone (5) (0.021 g, 40%); m.p. 167-70° (dec.), (lit.[33] m.p. 167-70°); IR (nujol): 3368 cm^{-1} (OH), 1710 cm^{-1} ($-COCH_3$), 1632 cm^{-1} (quinone), 1590 cm^{-1} (aromatic); PMR ($CDCl_3$): δ 2.1-2.33 (m, 2H, H_a-8, H_b-8), 2.39 (s, 3H, $COCH_3$), 3.05 (AB quartet, J = 8 Hz, 2H, H_a-10, H_b-10), 3.72 (d, J = 6Hz, 2H, C_7 -OH), 4.52 (s, 1H, C_9-OH), 5.31 (bs, 1H, H-7), 7.71-8 (m, 2H, aromatic), 8.19-8.42 (m, 2H, aromatic), 13.33 (s, 1H, phenolic OH), 13.62 (s, 1H, phenolic OH).

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PART II

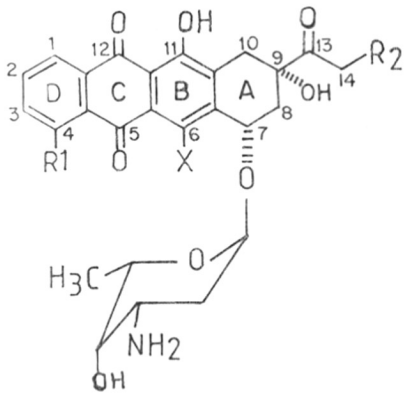
ATTEMPTED SYNTHESIS OF

(±) 6 FLUORODAUNOMYCINONE

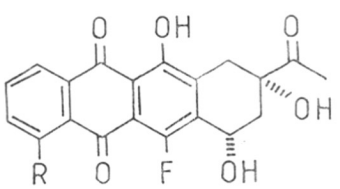
INTRODUCTION

As described in the earlier section, adriamycin (1), daunomycin (2) and carminomycin (3) have emerged as an important class of chemotherapeutic agents for the treatment of a broad spectrum of cancers.[1] With the use of the above mentioned anthracyclines, to treat cancer patients alone or in combination with surgery, increasing attention has been paid to the toxic effects of these drugs. The acute dose limiting toxicity of adriamycin is cardiotoxicity. Other toxicities include mucositis, alopecia, nausea and vomiting.[2]

The very significant clinical activities of adriamycin and obvious deficiencies of the drug have resulted in several extensive analogue programmes. The major goals of anthracycline development are to develop new analogues which are less toxic, orally active, active against adriamycin resistant tumors, equally or more clinically active and are cheaper. A number of modifications on the aglycone and the glycosidic side chain can be made without loss of activity but also more subtle molecular and clinical pharmacologic differences are induced by such modifications. The quinone appears to be essential for the antitumor activity of compounds. Modifications could be done at C-4, C-6, C-9 and C-11 positions. Among the synthetic analogues it has been shown that 4-demethoxydaunomycin[3] is eight times more effective than daunomycin.



	R_1	R_2	X
1	OCH_3	OH	OH
2	OCH_3	H	OH
3	OH	H	OH
4	H	H	OH
5	OCH_3	H	F
6	H	H	F



7 R = OCH_3

8 R = H

There are ample evidences to suggest that fluoro derivatives are more active than their parent compounds. For example, in steroid chemistry, several fluoro derivatives have been prepared by the replacement of hydroxyl group.[4] The former compounds exhibit activity sometimes far more superior than the parent compounds. In addition, recently it has been shown that the introduction of fluorine in sporaricin A[5] lowers the toxicity of this antibiotic. Therefore, it was thought worthwhile to prepare some fluoro analogues of anthracyclines with a view to hit an analogue which may have lower toxicity. Work in the field of sugar unit, the introduction of fluorine at C-2' position of L-daunosamine has been carried out in this laboratory.[6]

It has been mentioned earlier that anthracycline antibiotics can be logically synthesised from an aglycone and sugar unit by a suitable coupling reaction.[7] Therefore, the synthesis of aglycone is particularly important. In the present work studies related to the synthesis of 6-fluorodaunomycinone or 4-demethoxy-6-fluorodaunomycinone have been highlighted. The choice of making 6-fluoro derivative of anthracycline was because of the ease with which the fluoro substituted starting material can be prepared.

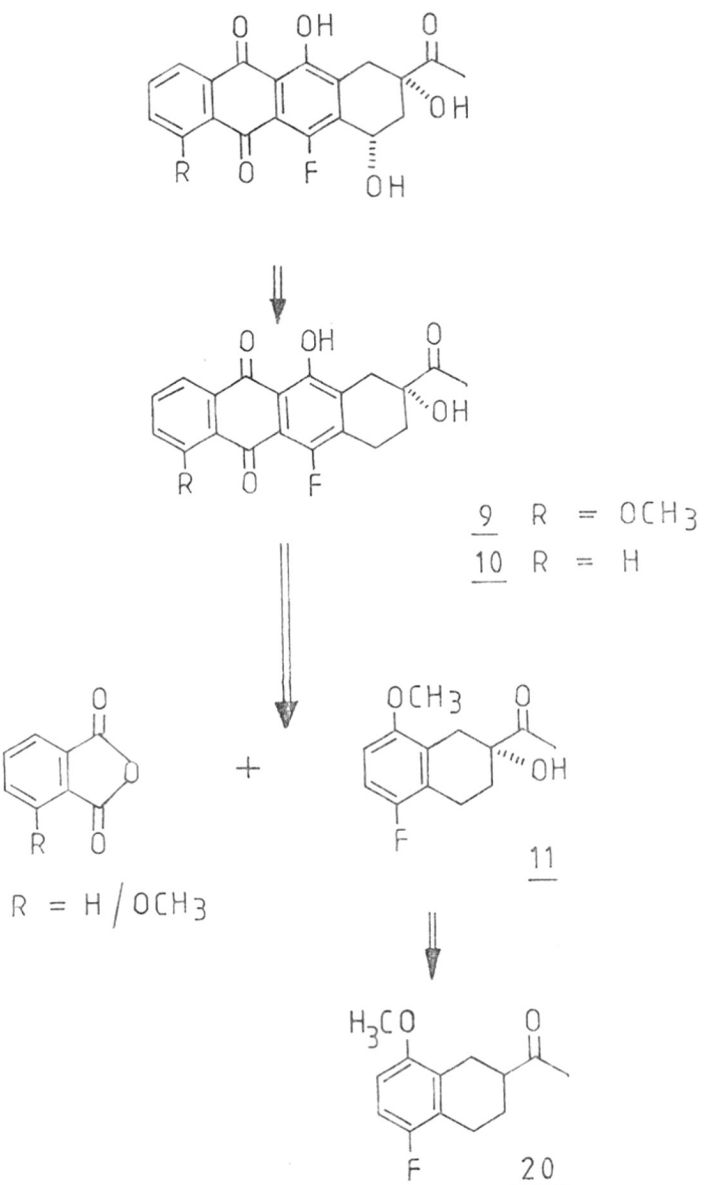
PRESENT WORK

Although there are several ways to prepare tetracyclic system, AB+CD fusion approach is by far most appropriate in the present situation. As depicted in retrosynthetic scheme-1, 2-acetyl-2-hydroxy-5-fluoro-8-methoxy-1,2,3,4-tetrahydronaphthalene (11) or its precursor 2-acetyl-5-fluoro-8-methoxy-1,2,3,4-tetrahydronaphthalene (20) represent AB ring synthon. The synthesis of 20 is described below (Scheme-2 and Scheme-5).

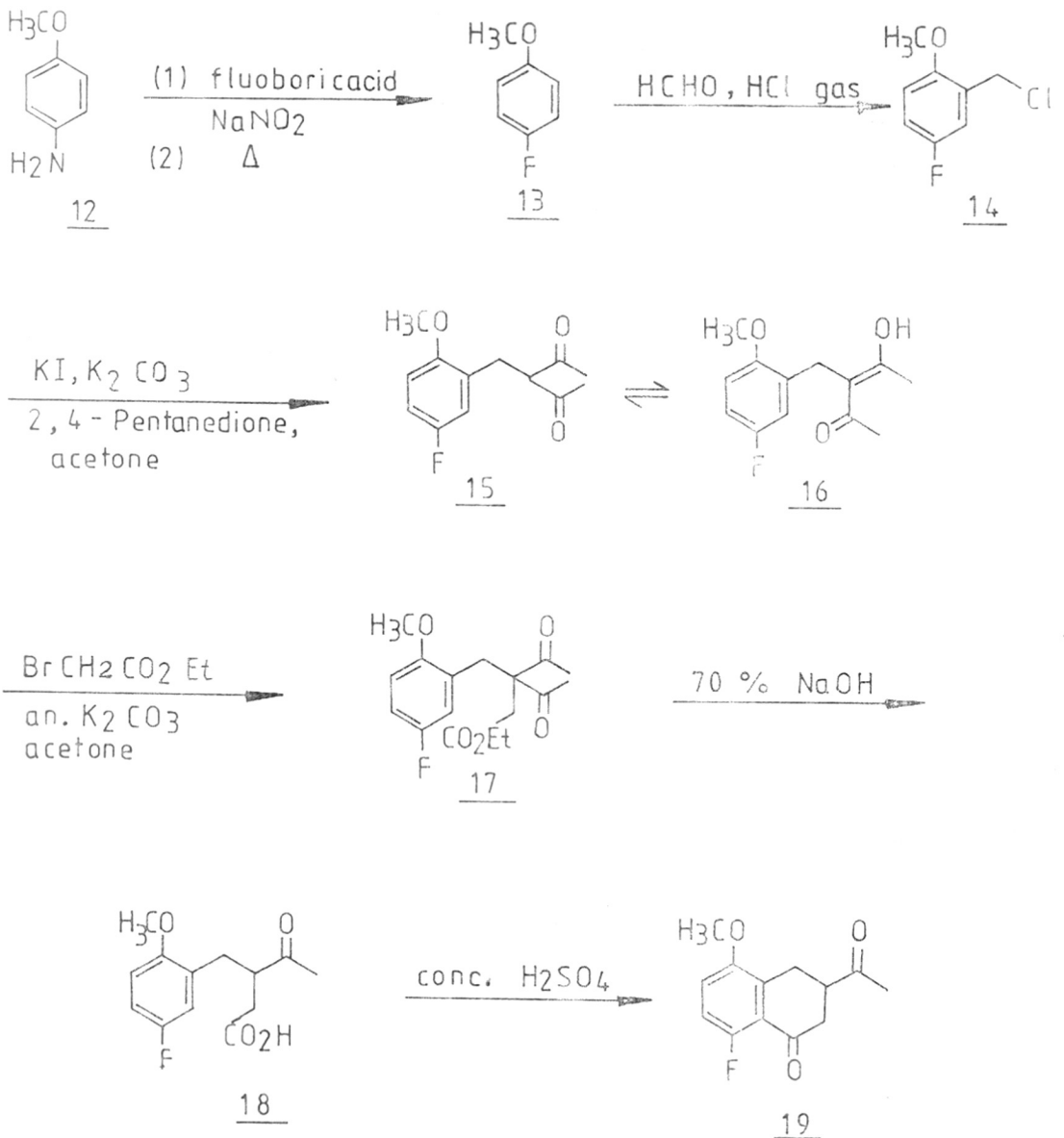
p-Anisidine (12) on treatment with fluoboric acid and sodium nitrite afforded diazoniumfluoborate salt which on decomposition yielded p-fluoroanisole (13).[8] Chloromethylation of 13 was carried out with p-formaldehyde and hydrogen chloride gas to yield 5-fluoro-2-methoxybenzyl chloride (14).[9]

The benzylic chloride (14) on stirring with potassium iodide, 2,4-pentanedione and anhydrous potassium carbonate in acetone furnished the alkylated product 3-acetyl-4 (5-fluoro-2-methoxyphenyl)-butan-2-one (15+16) in 75% yield. The PMR (Fig. 1) suggested that the product was a tautomeric mixture of 15 and 16, benzylic proton indicated doublet at 3 ppm and a singlet at 3.46 ppm for 15 and 16 respectively. Treatment of 15+16 with ethylbromoacetate, anhydrous potassium carbonate and acetone at room temperature afforded

SCHEME 1



SCHEME 2



12 13 14 15 16 17 18 19

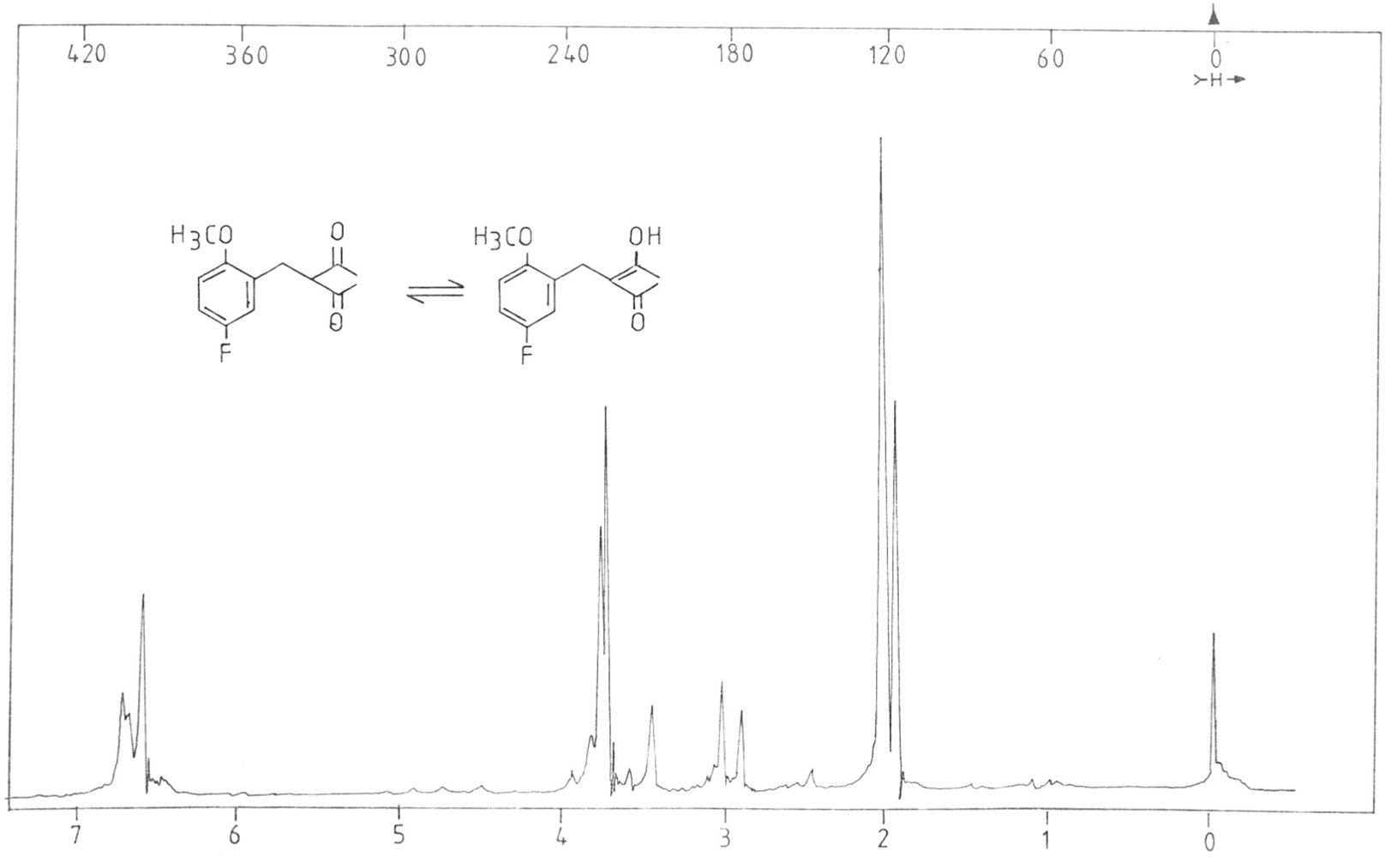


FIG.1 : PMR SPECTRUM OF THE COMPOUND (15+16) IN CCl_4

the crystalline ethyl 3,3-diacetyl-4-(5-fluoro-2-methoxyphenyl)-butanoate (17) whose structure was demonstrated by its PMR spectrum where peaks corresponding to ethyl ester were clearly observed, indicating that the alkylation had occured. Other protons resonated at expected chemical shifts.

It is pertinent to mention here that Wong et al.[10] reported a similar strategy earlier for the synthesis of ethyl-3,3-diacetyl-4-(2,5-dimethoxyphenyl)-butanoate where sodium hydride was being used in tetrahydrofuran under strictly anhydrous conditions. However, the present method in which anhydrous potassium carbonate is employed was found to be far superior than Wong's method with respect to yield and reaction conditions. It is gratifying to note that both the alkylations had been carried out in one pot by the sequential alkylation of 2,4-pentanedione by 14 and ethylbromoacetate without affecting the overall yield of the product.

The keto ester 17 was treated with aqueous sodium hydroxide (70%) to effect hydrolysis and reverse Claisen condensation to yield 3-acetyl-4-(5-fluoro-2-methoxyphenyl)-butanoic acid (18) in 91% yield. The proof for the structure of 18 was gleaned from its PMR spectrum (Fig. 2). It showed singlet for three protons at δ 2.1 which suggested

that singlet was due to one acetyl methyl group and other acetyl group was lost. A broad singlet for carboxylic proton was located at δ 10.21. Other protons resonated at expected chemical shifts.

Wong et al[10] had reported the cyclisation of 3-acetyl-4-(2,5-dimethoxyphenyl)-butanoic acid to the corresponding tetralone by using hydrofluoric acid. Thus, the cyclisation of keto acid 18 was attempted with hydrofluoric acid but reaction did not proceed to give the desired tetralone 19, starting keto acid 18 was recovered.

However, cyclisation of keto acid 18 to 2-acetyl-5-fluoro-8-methoxy-4-tetralone (19) was accomplished by using conc. sulphuric acid in 72 hr. IR spectrum of 19 showed absorption at 1710 cm^{-1} ($\overset{O}{\overset{\|}{C}}-CH_3$) and at 1680 cm^{-1} ($\overset{O}{\overset{\|}{C}}$). The PMR (Fig. 3) showed the presence of a singlet at δ 2.29 corresponding to methyl protons of acetyl group, methylenes and C-2 proton resonated as multiplet between δ 2.67 and 3.29, a singlet at 3.86 was due to methoxyl protons and aromatic protons appeared as AB quartet at δ 6.96. Though the desired tetralone 19 was obtained, the yield of cyclisation was extremely low (5%).

The low yield of cyclised product led to try some other cyclising reagents. For example, with boronfluoride etherate the cyclisation met with failure as the starting

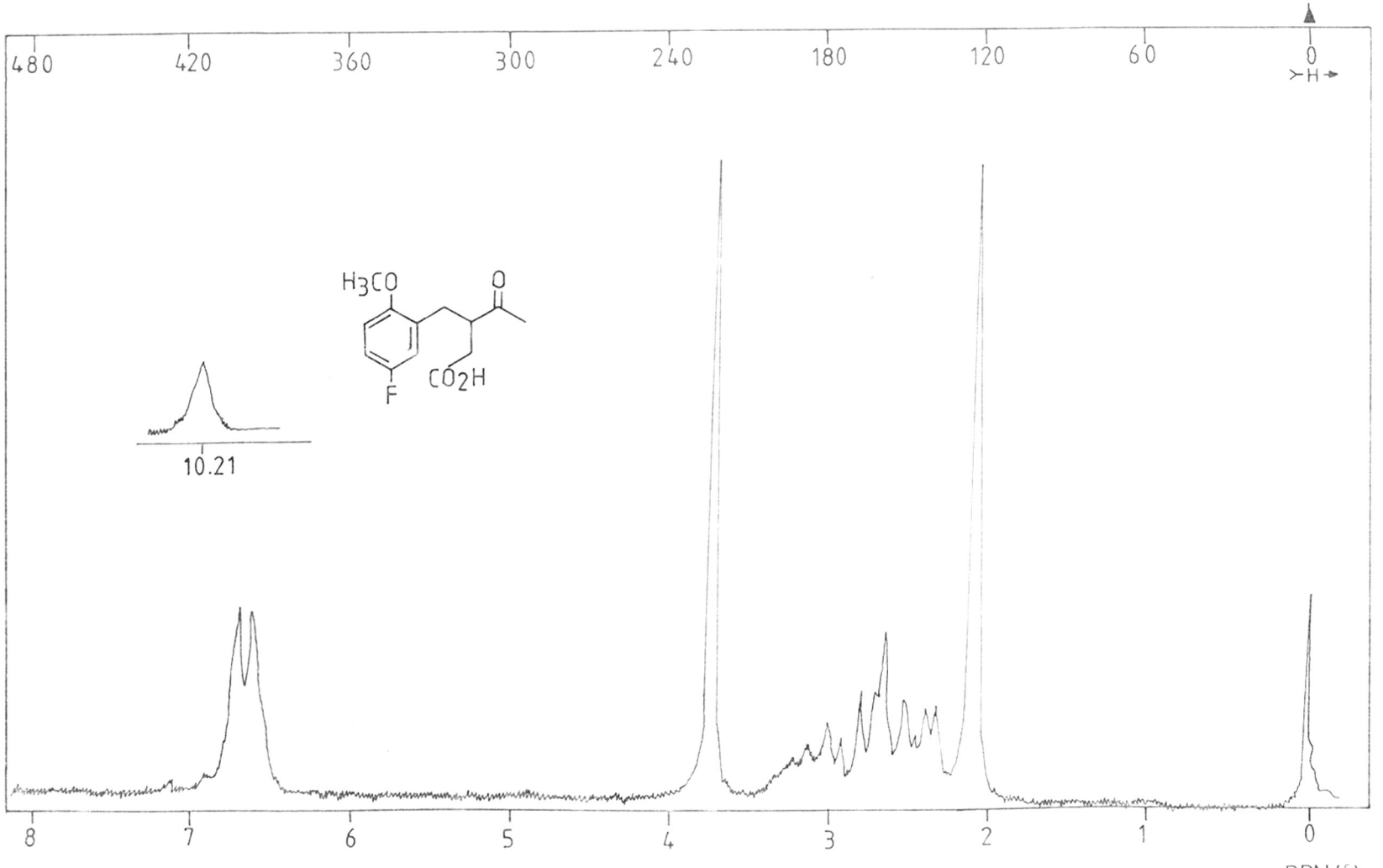


FIG. 2 : PMR SPECTRUM OF THE COMPOUND (18) IN $CDCl_3$

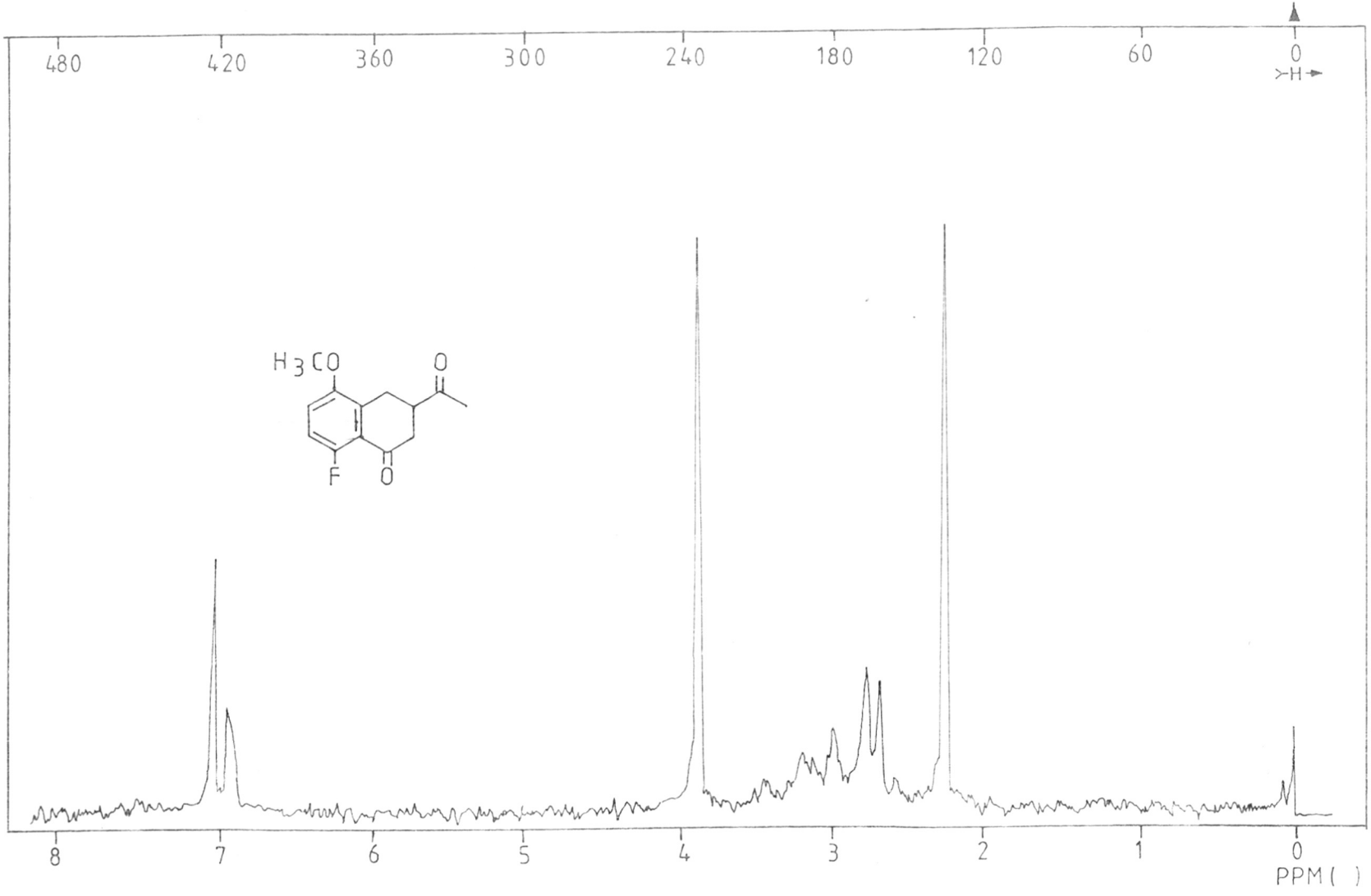
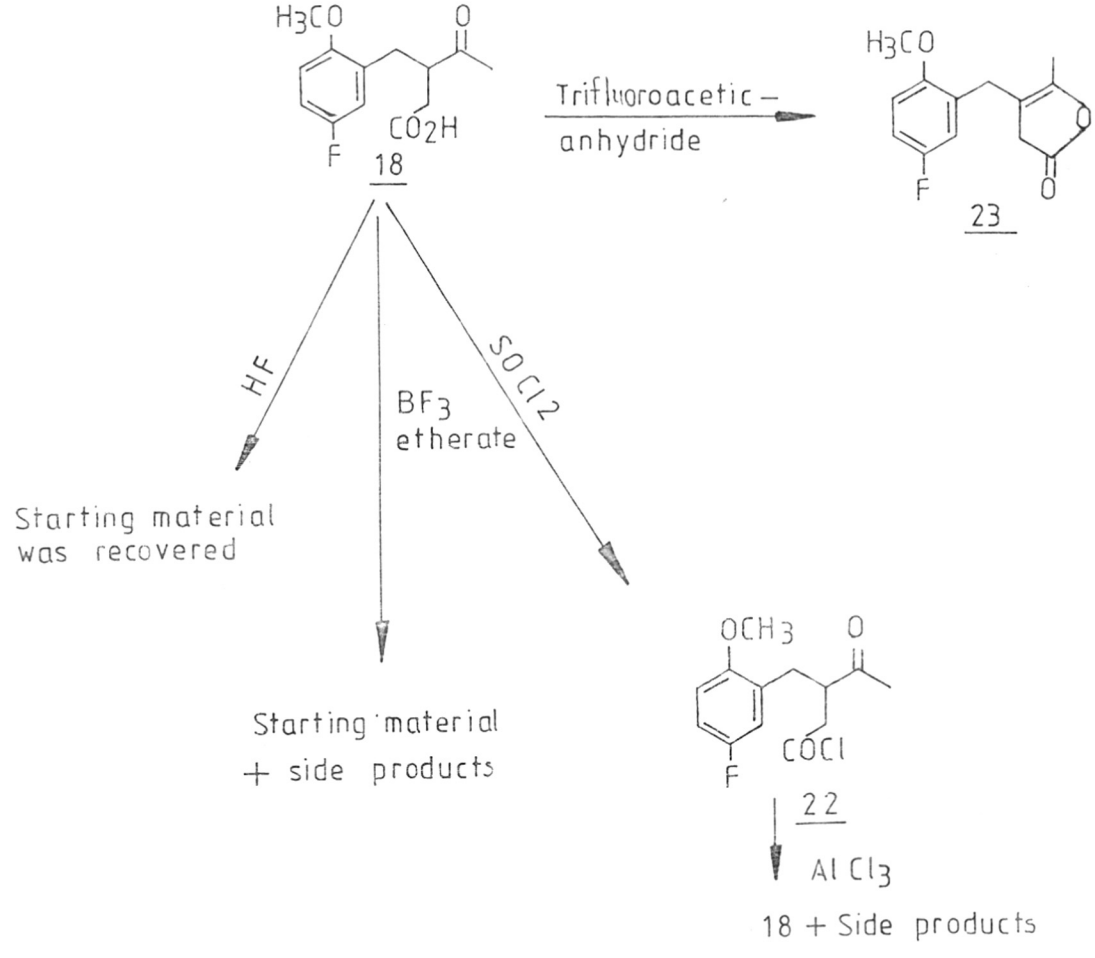


FIG 3 : PMR SPECTRUM OF THE COMPOUND (19) IN $CDCl_3$

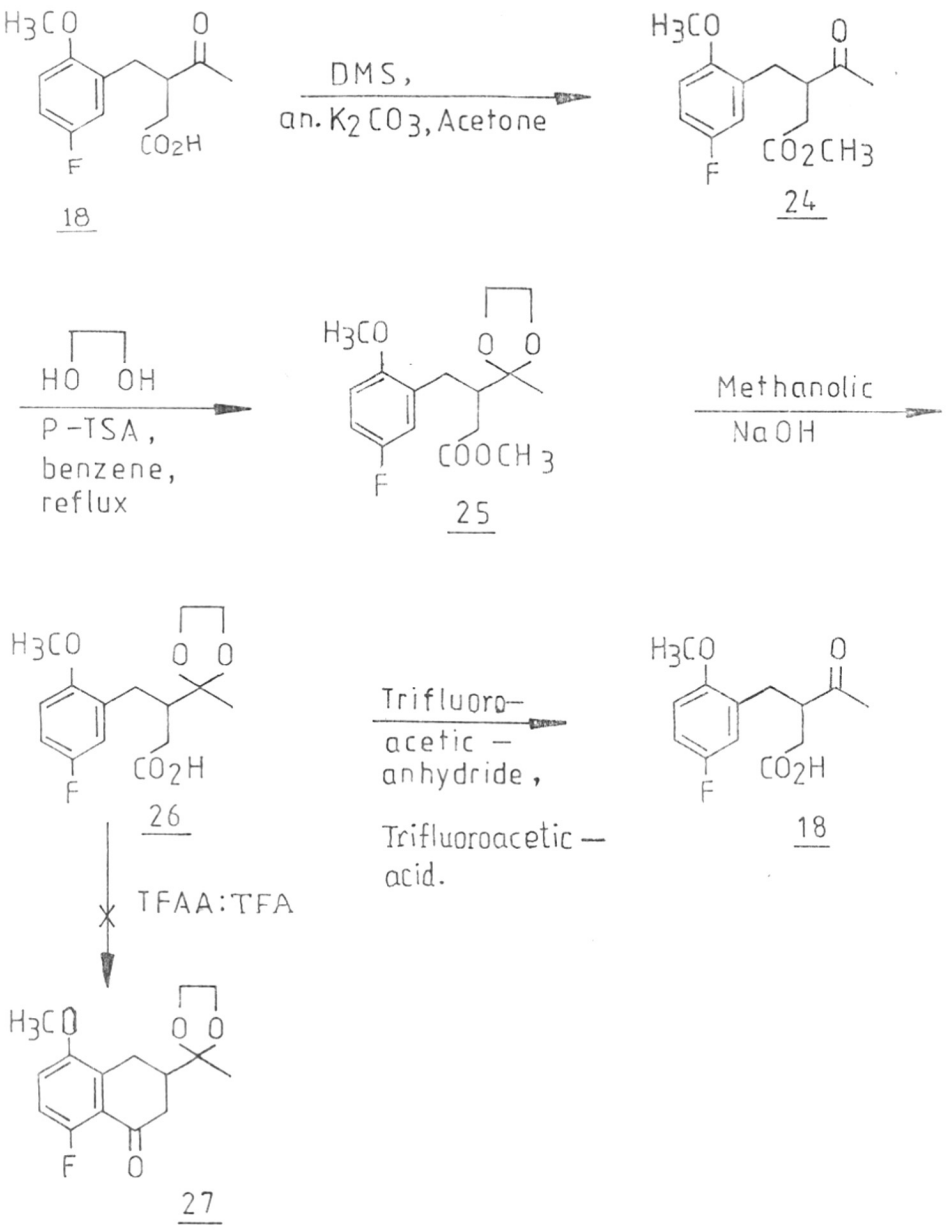
keto acid 18 and some other products of minor proportion were obtained. The acid chloride of 18, prepared by the treatment of acid with thionyl chloride, upon treatment with anhydrous aluminium chloride afforded no tetralone product but the corresponding acid was recovered. With trifluoroacetic anhydride, keto acid 18 gave a product which on the basis of PMR spectrum was assigned the structure as 23 because a singlet at δ2.1 for methyl group, a broad singlet for benzylic protons at δ3.3, multiplet for three protons in aromatic region indicated that cyclisation had not occured in desired way.

The failure to undergo cyclisation of acid 18 made to believe that the enolisation of the carbonyl functionality might be interfering. Therefore, ketone of the corresponding ester 24 was protected with ethanediol in the presence of catalytic amount of p-toluenesulfonic acid in refluxing benzene. The presence of ethylene ketal 25 was seen in the PMR spectrum as a singlet at 4 ppm. and singlet due to methyl proton was shifted upfield at δ1.45. The ester group in 25 was saponified and subsequently the acid 26 was treated with 1:1 mixture of trifluoroacetic anhydride and trifluoroacetic acid. The product isolated from the reaction mixture was keto acid 18 indicating cyclisation had not occured.

Attempted reagents for cyclisation of keto acid 18



SCHEME 3

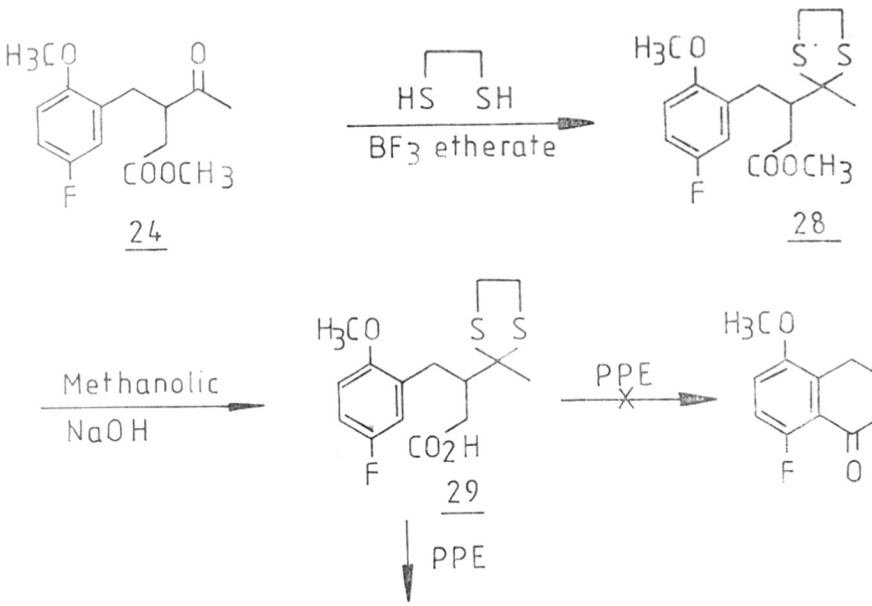

H3CO
O
CO2H
F
18
DMS,
an. K2CO3, Acetone
CO2CH3
24
HO OH
P-TSA,
benzene,
reflux
COOCH3
25
Methanolic
NaOH
26
Trifluoro-
acetic -
anhydride,
Trifluoroacetic -
acid.
TFAA:TFA
27

In addition to this, as thioketals are stable under acidic conditions, keto group in the ester 24 was protected as 1,3-dithiolane to get 28 by using ethanedithiol in the presence of borontrifluoride etherate. The structure of 28 was confirmed by spectral analysis. Hydrolysis of ester function in 28 followed by treatment with polyphosphate ester did not bring about required cyclisation to 30, however, a complex mixture was formed which was not further analysed.

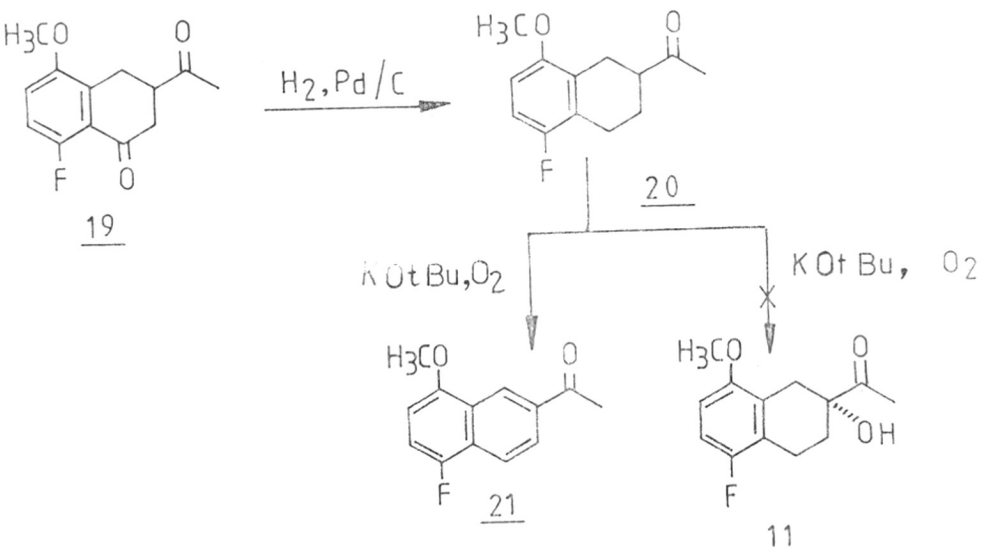
Having failed to get the cyclised product in a satisfactory manner, it was felt that whatever cyclised product was available, further reactions should be carried out. Therefore, 19 was hydrogenated in the presence of 5% Pd/C at normal pressure and temperature to give 2-acetyl-5-fluoro-8-methoxy-1,2,3,4-tetrahydronaphthalene (20) in 76% yield. The IR spectrum indicated absorption at 1710 cm^{-1} corresponding to keto group whereas absence of absorption at 1685 cm^{-1} indicated that benzylic ketone was reduced. The PMR spectrum of 20 (Fig. 4) indicated singlet at δ 2.13 for acetyl methyl, multiplet in the region of δ 2.03-3.55 for methylenes and C-2 proton, a singlet at δ3.69 for the methoxyl group and AB quartet at 6.6 for the two aromatic protons.

For the introduction of hydroxyl group at C-9 position, Wong's procedure was employed. For instance,

SCHEME 4



SCHEME 5



the compound 20 was treated with potassium tertiary-butoxide and oxygen gas was bubbled. The product isolated showed in its PMR spectrum, a singlet at δ2.55 for acetyl methyl, a singlet at δ3.8 for methoxyl protons and a multiplet for five protons in the aromatic region. Peaks in aliphatic region of δ2-3.5 were absent. This suggested that the product was fully aromatised derivative, namely, 2-acetyl-5-fluoro-8-methoxynaphthalene 21. This was substantiated by the mass spectrum which revealed the molecular ion peak at 218.

In conclusion, it could be mentioned that the attempted cyclisation of the keto acid 18 to the corresponding tetralone 19 did not occur under various cyclising conditions. However, in case of concentrated sulphuric acid, very poor yield of 5% resulted. This failure could be attributed due to the presence of strong electron-withdrawing fluorine atom which by virtue of inductive effect makes the aromatic ring electron-deficient. Therefore, it is mainly less reactive towards acylative cyclisation giving poor yield of tetralone 19. Hence, 19 was not further elaborated to 6-fluorodaunomycinone.

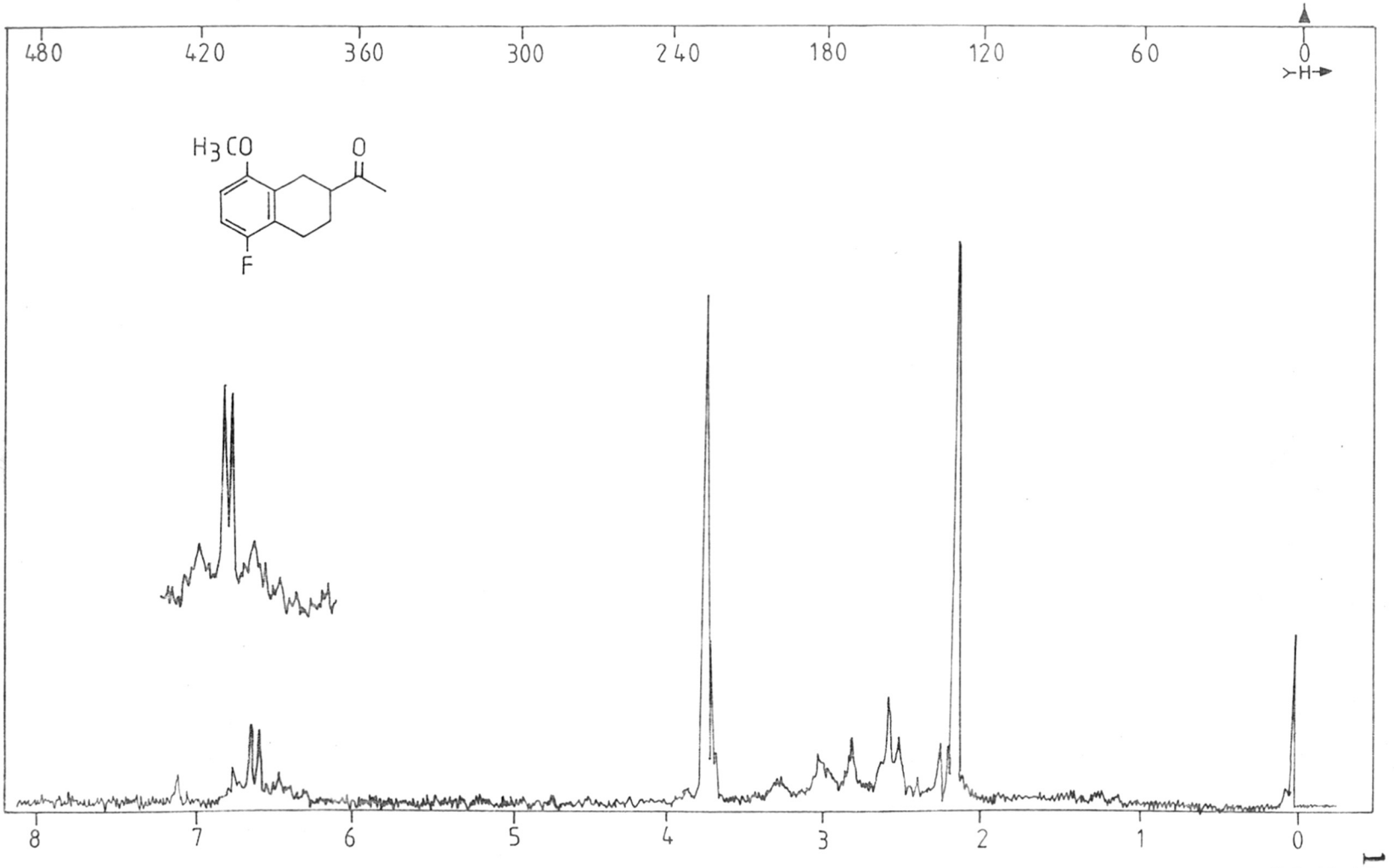


FIG. 4. : PMR SPECTRUM OF COMPOUND (20) IN CCl_4

EXPERIMENTAL

p-Fluoroanisole (13)

To 42% fluoboric acid (150 ml, 940 mmol) diluted with 150 ml of water, p-anisidine (46 g, 380 mmol) was added. The solution was cooled to -5° to -10°. To this cold solution, sodium nitrite (26 g, 380 mmol) in 50 ml of water was added with vigorous stirring at such a rate that the temperature being kept at -5°. The precipitate, p-methoxybenzenediazoniumfluoborate, was filtered, washed with 50 ml of ice-cold 5% fluoboric acid, 50 ml of ice-cold methanol and several 50 ml portions of ether and dried overnight on filter paper (74 g, 90%).

Dry p-methoxybenzenediazoniumfluoborate (74 g, 336 mmol) was placed in a 500 ml round bottom flask connected by a wide mouth condenser to three gas traps. The last trap was fitted with a tube leading to an absorption flask containing ice, water and soda solution. The salt was heated gently with a free flame until decomposition commences as indicated by evolution of white fumes. At the end of decomposition, the flask was heated vigorously until no more fumes were evolved. The crude reaction product was purified by steam distillation to give p-fluoroanisole (13) 13 was distilled through fractionating column (23.4 g, 53.4%), b.p. 150-52°, (lit.[8] 152-55°).

5-Fluoro-2-methoxybenzyl chloride (14)

To p-fluoroanisole (15.5 g, 123 mmol) in dry ether (250 ml), formalin (11 ml, 37%), anhydrous zinc chloride (1 g) and sodium chloride (200 mg) were added. Hydrogen chloride gas was then bubbled through the solution for 15-16 hr with stirring. After usual work up, 14 was obtained as white crystalline solid (18 g, 84%) which was pure enough for the use in next reaction, m.p. 43-5° (lit.[9] 44-45°).

3-Acetyl-4-(5-fluoro-2-methoxyphenyl)-butan-2-one (15+16)

A solution of 5-fluoro-2-methoxybenzyl chloride (14) (13.08 g, 75 mmol), potassium iodide (12.45 g, 75 mmol), 2,4-pentanedione (8.3 g, 83 mmol) and anhydrous potassium carbonate (20 g, 145 mmol) in acetone (400 ml) was stirred at room temperature for 12 hr with a mechanical stirrer. The acetone was then distilled off and water was added to dissolve the inorganic salts. It was then extracted with chloroform, washed with water and dried over anhydrous sodiumsulphate and concentrated under reduced pressure to give 3-acetyl-4-(5-fluoro-2-methoxyphenyl)-butan-2-one (15+16) as yellow coloured viscous oil which was purified by chromatography on silica gel by using pet. ether: acetone 5% as eluent to give pure (15+16) (13.5 g, 75.7%) IR (neat): 3410 cm^{-1} (OH), 1720 and 1700 cm^{-1} (C=O),

1610 and 1600 cm^{-1} (C=C), PMR (CCl_4): δ 1.93 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 3 & 3.46 (d, J = 8Hz and s, total 3H, two benzylic protons and one proton between acetyl groups), 3.78 (s, 3H, OCH_3), 6.55-6.78 (m, 3H, aromatic H). Mass: 238(M^+).

Ethyl-3,3-diacetyl-4-(5-fluoro-2-methoxyphenyl)-butanoate (17)

A solution containing 3-acetyl-4-(5-fluoro-2methoxyphenyl)-butan-2-one (15+16) (11.9 g, 50 mmol), ethylbromo acetate (9.75 g, 58 mmol) and anhydrous potassium carbonate (10.35 g, 75 mmol) in acetone (250 ml) was stirred at room temperature for 12 hr. Work up and recrystallization of the residue from hexane yielded ethyl-3,3-diacetyl-4-(5-fluoro-2-methoxyphenyl)-butanoate (17) (14 g, 86%), m.p. 106-8°C, IR (nujol): 1740 cm^{-1} (C-OEt), 1700 cm^{-1} (C-CH_3)

PMR (CCl_4): δ 1.25 (t, J = 7Hz, 3H, $OCH_2\underline{CH_3}$), 2.1 (s, 6H, $2XCOCH_3$), 2.66 (s, 2H, H_a-1, H_b-1), 3.3 (s, 2H, benzylic CH_2), 3.53 (s, 3H, OCH_3), 4 (q, J = 7Hz, 2H, $O\underline{CH_2}CH_3$), 6.35-6.8 (m, 3H, aromatic H); Mass: 324(M^+).

3-Acetyl-4-(5-fluoro-2-methoxyphenyl)-butanoic acid (18)

The keto ester 17 (13.6 g, 42 mmol) was heated in an aq. 70% sodium hydroxide solution (120 ml) at 65-70° for 3 hr. The reaction mixture was washed with benzene and then acidified by cold concentrated hydrochloric acid. The

precipitated keto acid 18 was filtered, dried and crystallised from methanol (9.8 g, 92%); m.p. 98-100°; IR ($CHCl_3$): 1725 cm^{-1} (C=O); PMR ($CDCl_3$): δ 2.1 (s, 3H, CH_3), 2.3-3.29 (m, 5H), 3.76 (s, 3H, OCH_3), 6.29-6.9 (m, 3H, aromatic), 10.21 (bs, 1H, OH, exchanges with D_2O); Mass: 254 (M^+).

2-Acetyl-5-fluoro-8-methoxy-4-tetralone (19)

To the keto acid 18 (7 g, 27.55 mmol), concentrated sulphuric acid was added dropwise (7 x 5 ml) at room temperature with shaking. After 72 hr, reaction was worked up by addition of cold water and extraction with chloroform. Chloroform was washed with saturated sodium bicarbonate solution, water, brine, dried (Na_2SO_4) and concentrated to yield a product which was purified on a silica gel column using pet. ether:acetone 3% as eluent to give 2-acetyl-5-fluoro-8-methoxy-4-tetralone (19), (0.33 g, 5%); IR (nujol): 1710 cm^{-1}, (C(=O)-CH_3), 1680 cm^{-1} (C=O); PMR (CCl_4): δ 2.29 (s, 3H, $COCH_3$), 2.67-3.29 (m, 5H), 3.86 (s, 3H, OCH_3), 6.96 (AB quartet, 2H, aromatic). Mass: 236 (M^+).

Methyl-3-acetyl-4-(2-methoxy-5-fluorophenyl)-butanoate (24)

The ketoacid 18 (1.5 g, 6 mmol) in methanol (5 ml) was treated with excess of an ethereal solution of diazomethane. Work up in the usual fashion and purification

of the residue over silica gel column yielded methyl-3-acetyl-4-(2-methoxy-5-fluorophenyl)-butanoate (24) (1.45 g, 92%); IR (neat): 1740 cm^{-1} ($COOCH_3$), 1720 cm^{-1}, ($COCH_3$); PMR (CCl_4): δ 2.1 (s, 3H, $COCH_3$), 2.2-3 (m, 5H), 3.52 (s, 3H, $COOCH_3$), 3.83 (s, 3H, OCH_3), 6.46-6.66 (m, 3H, aromatic); Mass: 268(M^+).

Ketal derivative of 24 (25)

A mixture of the ester 24 (0.98 g, 3.65 mmol), ethanediol (2.27 g, 36.5 mmol) and p-toluenesulphonic acid (100 mg) was heated under reflux for 40 hr. Benzene was distilled off under reduced pressure and the residue purified over silica gel column with pet. ether:acetone 2% as eluent to give 25 (0.87 g, 76%); PMR (CCl_4): δ 1.43 (s, 3H, CH_3), 2.06-3.12 (m, 5H), 3.52 (s, 3H, $COOCH_3$), 3.87 (s, 3H, OCH_3), 4 (s, 4H, ), 6.65-7 (m, 3H, aromatic).

Ketal derivative of 18 (26)

The protected ester 25 (0.65 g, 2.08 mmol) was hydrolysed with 8% methanolic sodium hydroxide solution (7 ml) at 65-70°C. After usual work up, 26 (0.5 g, 80%) was isolated. PMR ($CDCl_3$): δ 1.35 (s, 3H, CH_3), 2-3.06 (m, 5H), 3.63 (s, 3H, OCH_3), 3.87 (s, 4H, ), 10.1 (bs, 1H, COOH, exchanges with D_2O).

1,3-Dithiolane derivative of 24 (28)

The ketoester (24) (1.1 g, 4 mmol) in chloroform (10 ml) was stirred at 0° and then treated with ethanedithiol (0.45 g, 4.8 mmol) and BF_3-etherate (2 ml). The mixture was stirred at room temperature overnight, washed with 2% NaOH, water and dried (Na_2SO_4). Evaporation of the solvent yielded a viscous liquid which was purified on a column of silica gel to give 28 (1.1 g, 78%). IR (nujol): 1740 cm^{-1} ($COOCH_3$); PMR ($CDCl_3$): δ 1.79 (s, 3H, CH_3), 1.96-3 (m, 5H), 3.12 (s, 3H, $COOCH_3$), 3.19 (s, 4H, S S), 3.68 (s, 3H, OCH_3), 6.29-6.6 (m, 3H, aromatic). Mass: 344(M^+).

1,3-Dithiolane derivative of 18 (29)

The above protected ester 28 (1.1 g, 3.2 mmol) in methanol (10 ml) was heated with 8% methanolic sodium hydroxide (10 ml) under reflux for 4 hr. Methanol was removed, water added and the residue acidified with concentrated hydrochloric acid to yield the crude acid 29 which was crystallised from methanol, (0.83 g, 78%); m.p. 115-117°; IR (nujol): 3500 cm^{-1} (OH), 1720 ($COOCH_3$), PMR ($CDCl_3$): δ 1.83 (s, 3H, CH_3), 2.1-3.09 (m, 5H), 3.36 (s, 4H, S S), 3.79 (s, 3H, OCH_3), 6.48-6.87 (m, 3H, aromatic). Mass: 330(M^+).

2-Acetyl-5-fluoro-8-methoxy-1,2,3,4-tetrahydronaphthalene (20)

A solution of the tetralone 19 (0.32 g, 1.36 mmol), ethanol (3 ml), water (0.3 ml), concentrated hydrochloric acid (0.1 ml) and 5% Pd/C (80 mg) was hydrogenated at normal pressure and temperature for 6 hr. After the catalyst was removed, the solution was evaporated to dryness under reduced pressure to yield 2-acetyl-5-fluoro-8-methoxy-1,2,3,4-tetrahydronaphthalene (20) (0.23 g, 76%); IR (nujol): 1710 cm^{-1} (C=O); PMR (CCl_4): δ 2.13 (s, 3H, C-CH_3), 2.03-3.55 (m, 7H), 3.69 (s, 3H, OCH_3), 6.6 (AB quartet, (2H, aromatic H). Mass: 222(M^+).

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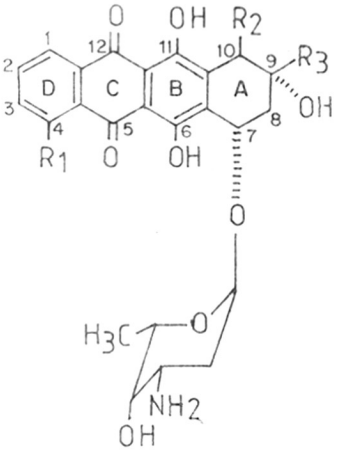
PART III

ATTEMPTED SYNTHESIS OF (±) 4-DEMETHOXYFEUDOMYCINONE C

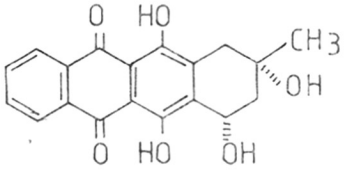
INTRODUCTION

As indicated in the earlier sections, for the treatment of various types of cancer, anthracycline antibiotics probably enjoy maximum attention. Various compounds related to daunomycin (1) have been isolated by fermentation processes and their anticancer activity evaluated. A new class of anthracyclines, termed as feudomycins, having novel aglycone unit were isolated from Streptomyces coeruteorabidus by Oki et al.[1] Feudomycins A-D have new aglycones which differ from each other as well as from daunomycin (1) mainly by the presence of different side chain at C-9 and/or C-10 position. For example, aglycones of feudomycin C and D have methyl group at C-9. However, in case of feudomycinone D, an additional hydroxyl group at C-10 is present.

It is interesting to know that feudomycin-A (3) was synthesised[2] much before than its isolation by sodium cyanoborohydride reduction of corresponding 13-tosylhydrazone of daunomycin. It was also proved that 3 inhibited nucleic acid synthesis and showed activity similar to that of daunomycin. In addition, it was also found that 3 showed high activity at lower doses. From these studies, it could be pointed out that the presence of carbonyl functionality at C-13 was not intrinsically required for biological activity.



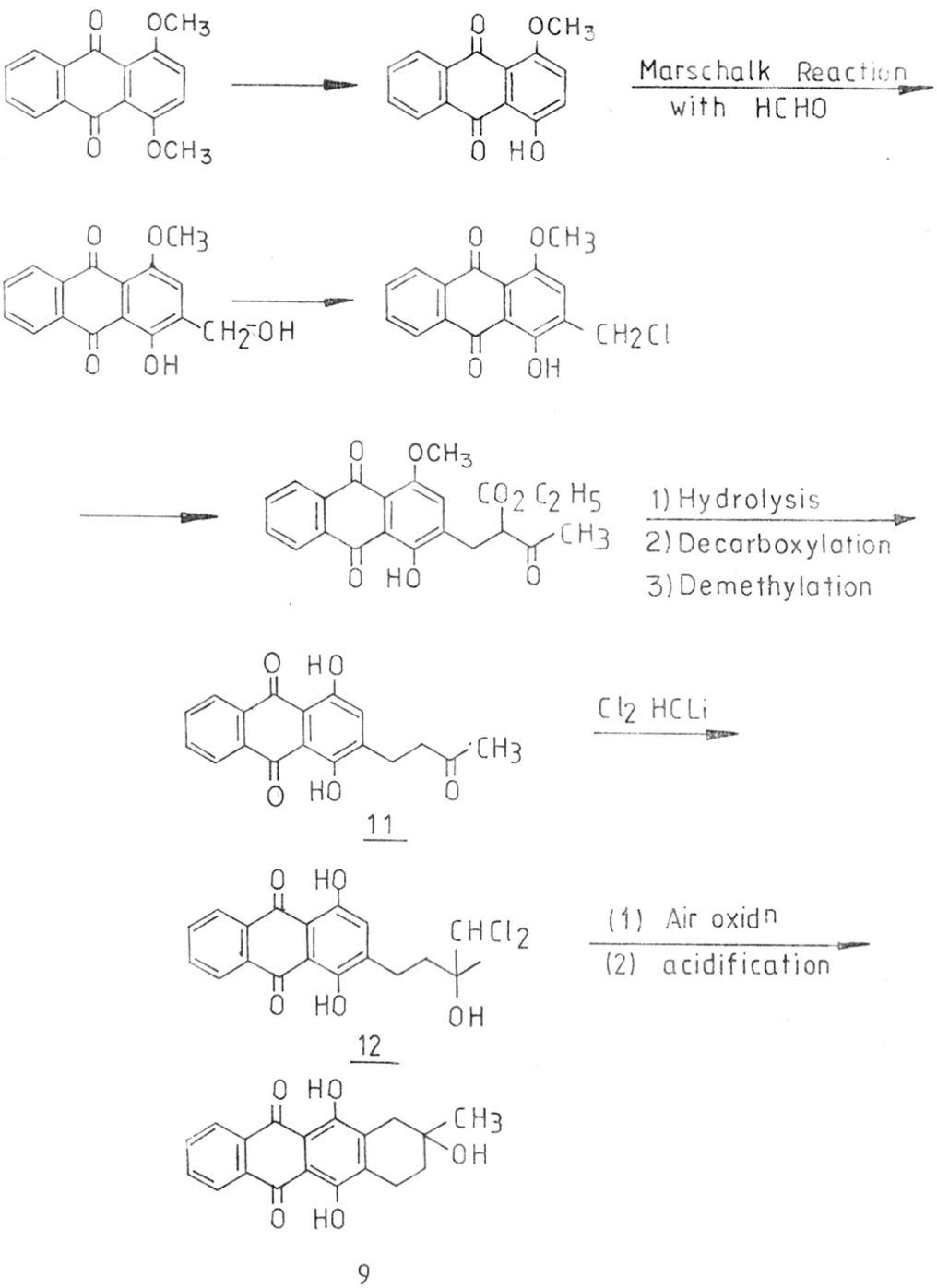
	R_1	R_2	R_3
1 Daunomycin	OCH_3	H	$COCH_3$
2 4-Demethoxydaunomycin	H	H	$COCH_3$
3 Feudomycin A	OCH_3	H	CH_2CH_3
4 Feudomycin B	OCH_3	H	CH_2COCH_3
5 Feudomycin C	OCH_3	H	CH_3
6 Feudomycin D	OCH_3	OH	CH_3
7 4-Demethoxyfeudomycin C	H	H	CH_3



8. 4- Demethoxyfeudomycinone C

SCHEME 1

Krohn & Behuke B, Liebigs Ann. Chem, 1818 (1983)



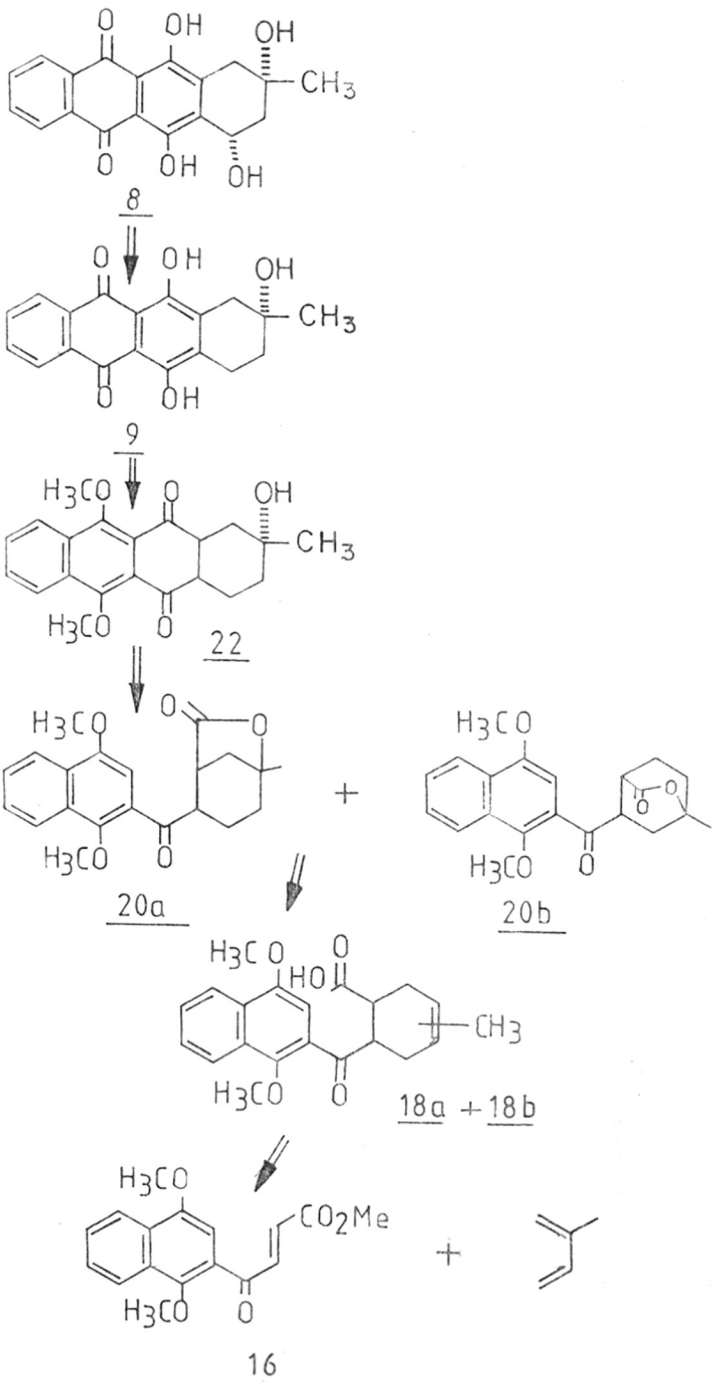
Since 4-demethoxydaunomycin[3] (2) has been proven to have activity 8-10 times more than the parent compound, it was felt worthwhile venturing into the synthesis of 4-demethoxyfeudomycin C(7). Moreover, the introduction of methyl group at C-9 as required for feudomycin C would be an easier attempt to carry out.

The glycosidation reaction of anthracyclinones with the sugar unit has been well established.[4] Hence, our attention was primarily focussed on the synthesis of 4-demethoxyfeudomycinone C(8). When the work was initiated in these laboratories, no synthesis of this aglycone was known. However, later Krohn et al.[5] reported the synthesis of 4-demethoxy-7-deoxyfeudomycinone C (9) starting from 1,4-dimethoxyanthraquinone (10). 10 was converted to the key intermediate 11 by a series of reactions. 11 was converted to 12 by dichloromethyl lithium reaction which on oxidation followed by acid treatment afforded 9.

PRESENT WORK

The retrosynthetic analysis of (±)-4-demethoxy-feudomycinone C (8) clearly established α,β-unsaturated ester 16 to be its starting material. Diels-Alder reaction with isoprene and subsequent hydrolysis in fact would lead to the formation of regioisomers 18a+18b.

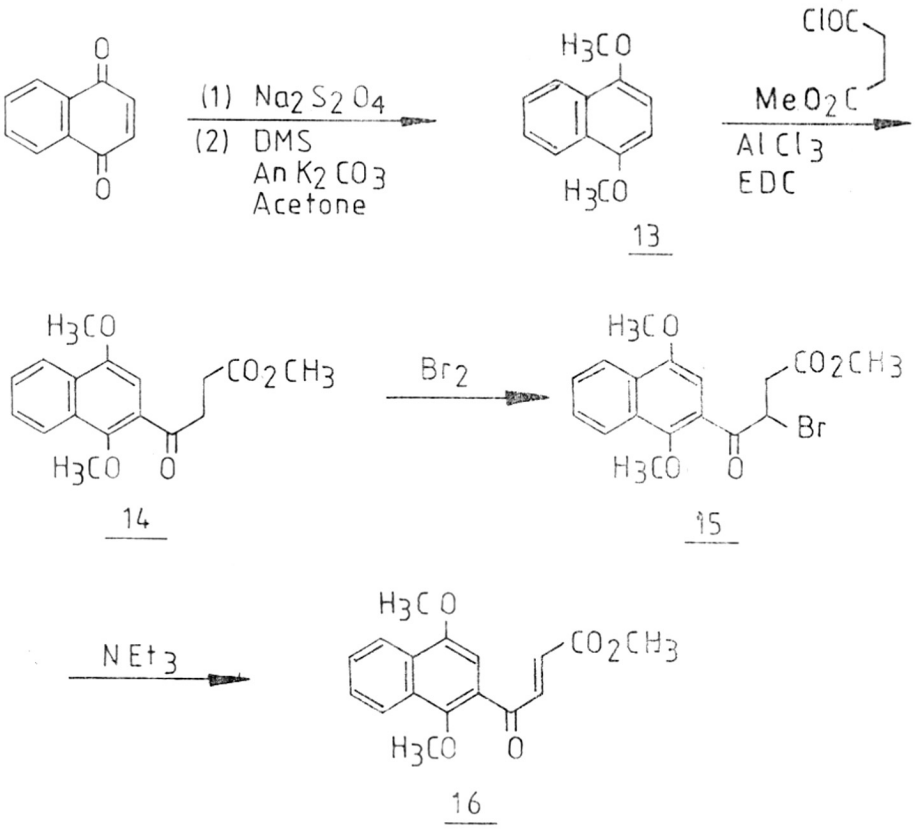
SCHEME 2



However, iodolactonisation followed by deiodination would give a mixture of γ-lactone 19a + δ-lactone 19b. The formation of regioisomers 18a + 18b and γ-lactone 19a + δ-lactone 19b do not affect the overall synthetic strategy. This is in view of the fact that after cyclisation the same product would result.

The synthesis presented in this section starts from 1,4-naphthaquinone which was converted to 1,4-dimethoxy-naphthalene by sodium dithionite reduction immediately followed by methylation with dimethyl sulphate in the presence of anhydrous potassium carbonate in boiling acetone. Friedel-Crafts acylation with methylsuccinoyl chloride in the presence of anhydrous aluminium chloride in 1,2-dichloroethane at room temperature afforded the γ-keto ester 14. Bromination of 14 at α- to carbonyl group was effected by the use of bromine in carbontetra-chloride to give the compound 15 which being unstable at room temperature was subjected, without delay, to dehydrobromination using triethylamine. The structure of 16[6] was demonstrated by PMR (Fig. 1) in which the presence of doublet at δ 6.93 corresponding to one olefinic proton was observed. Other olefinic proton was merged in a multiplet at δ 7.84-8.12 along with two aromatic protons. The coupling constant of 8Hz between olefinic protons suggested that they were trans to each other.

SCHEME 3



13

14

15

16

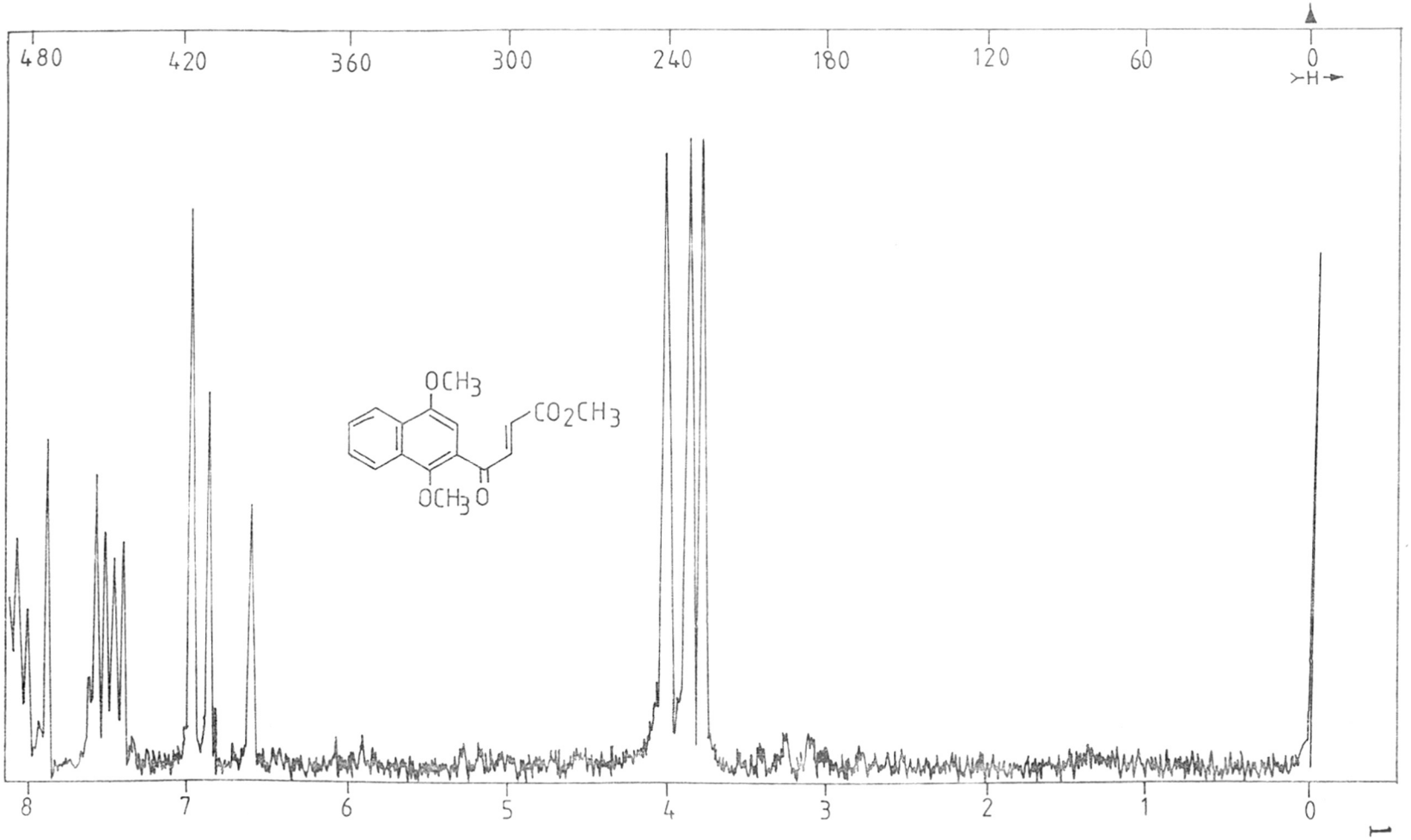
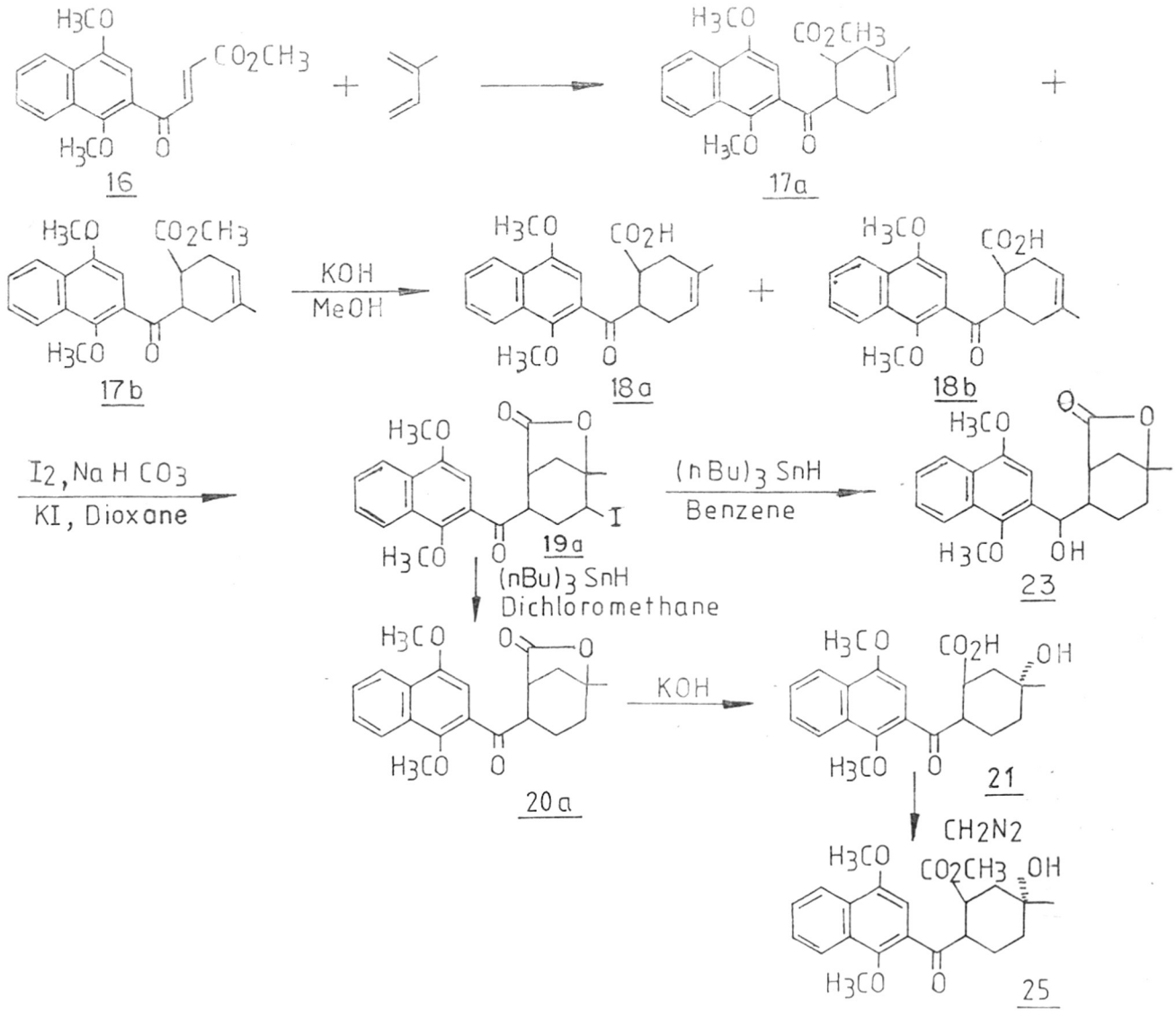


FIG.1: PMR SPECTRUM OF THE COMPOUND (16) IN CCl_4

The α,β-unsaturated ester 16 was treated with excess of isoprene in benzene in sealed tube at 120° for 12 hr to give the corresponding Diels-Alder adduct 17. From PMR of 17 it was clearly observed that this product was in fact a mixture of two isomers. For example, the methyl group was expected to resonate as a singlet but it appeared as two doublets at δ1.56 and δ1.65. Similarly, broad multiplet of A_2B_2 pattern for aromatic protons at δ 7.39-7.61 and δ 3.03-8.3 also confirmed the presence of two isomers. The remaining signals were not amenable to first order analysis. The mixture of Diels-Alder adduct was subjected to hydrolysis by methanolic potassium hydroxide to give the acid 18a+18b. The IR of the hydrolysis product showed the absorption at 1685 cm^{-1}, 1605 cm^{-1} and 1600 cm^{-1} due to the presence of keto, double bond and aromatic moieties. Appearance of methyl group as a broad singlet at 1.63 ppm and methoxyl group as broad singlet at 3.94 ppm in the PMR (Fig. 2) of acid clearly suggested that the hydrolysis product was also a mixture of isomers 18a+18b.

Iodolactonisation[7] of 18a+18b was effected in the presence of iodine, potassium iodide and sodium bicarbonate in aqueous dioxane. The reaction mixture afforded only one product whose structure was given as γ-lactone 19a on the basis of spectral data. The IR of 19 showed the

SCHEME 4


H3CO
CO2CH3
16
17a
17b
KOH
MeOH
18a
18b
I2, NaHCO3
KI, Dioxane
19a
(nBu)3 SnH
Benzene
23
(nBu)3 SnH
Dichloromethane
20a
KOH
21
CH2N2
25

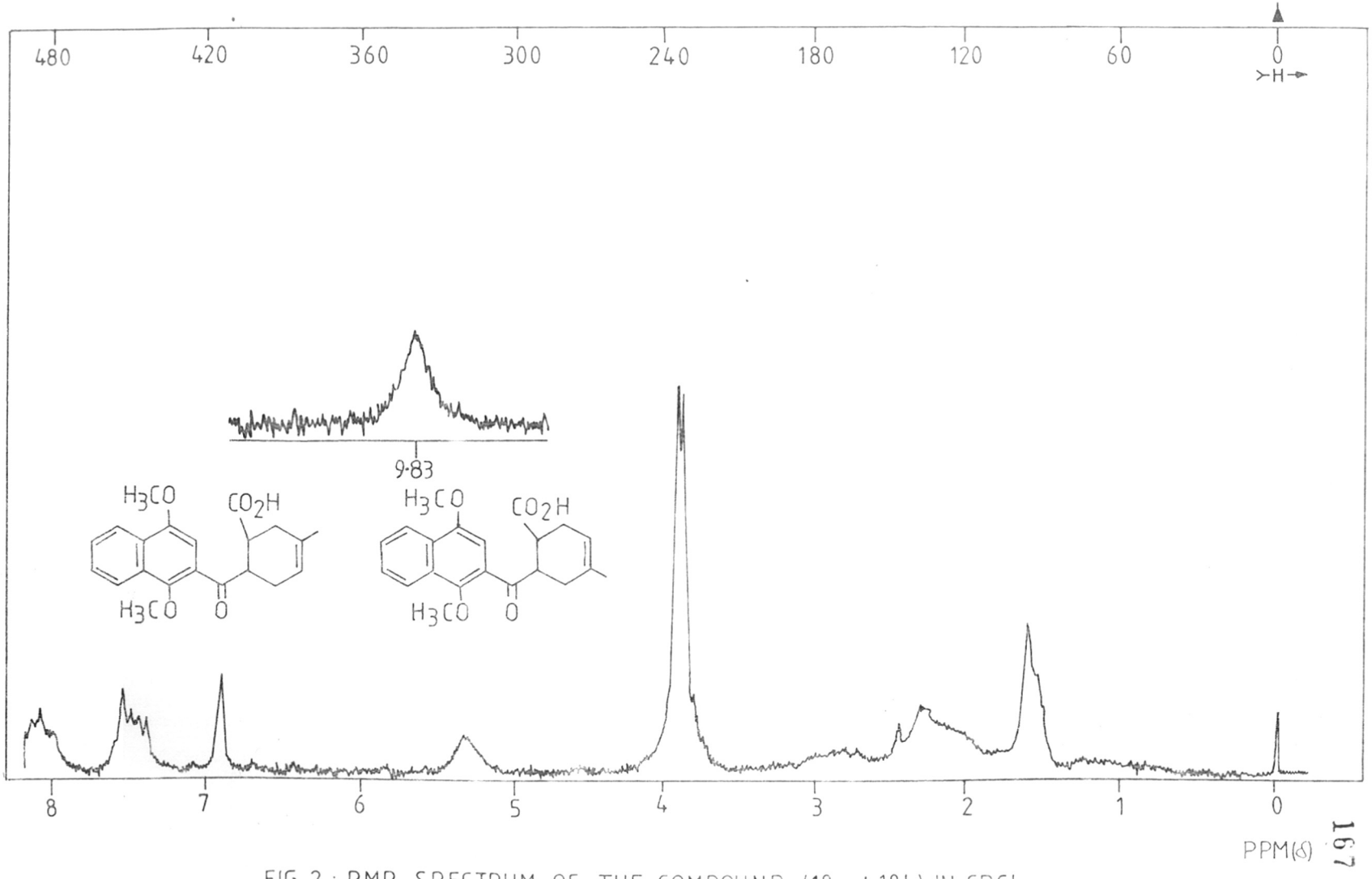


FIG. 2 : PMR SPECTRUM OF THE COMPOUND (18a + 18b) IN $CDCl_3$

presence of absorption at 1780 cm^{-1} corresponding to γ-lactone. PMR (Fig. 3) of 19 revealed the presence of methyl group as a sharp singlet at δ 1.63. H-8 proton appeared as distorted triplet at δ 4.2. The downfield shift of proton indicated the presence of iodo group. Structure 19a was also supported by its mass spectrum.

The exclusive formation of γ-lactone 19a with no traces of δ-lactone 19b was surprising. However, by drawing molecular models of the δ-lactone, it would be reasonably suggested that the [2:2:2] system present in δ-lactone was highly strained and therefore its formation was inhibited. Since γ-lactone 19a was in hand, the further synthetic reactions were performed on it.

Deiodination of 19a in the presence of tributyltin-hydride in dichloromethane gave the product 20a. The IR of 20a showed absorption at 1780 cm^{-1} corresponding to γ-lactone. Absorption at 1670 cm^{-1} indicated that the benzyl keto group was intact. PMR of 20a (Fig. 4) revealed the presence of singlet at δ 1.5 corresponding to methyl. The broad distorted triplet for H-8 proton was absent, instead H_a-8, H_b-8 and H_a-10, H_b-10 resonated as a multiplet at δ 1.73 - 2.03. Both methoxyl groups appeared as separate singlets at δ 3.97 and δ 4.07. The multiplets of A_2B_2

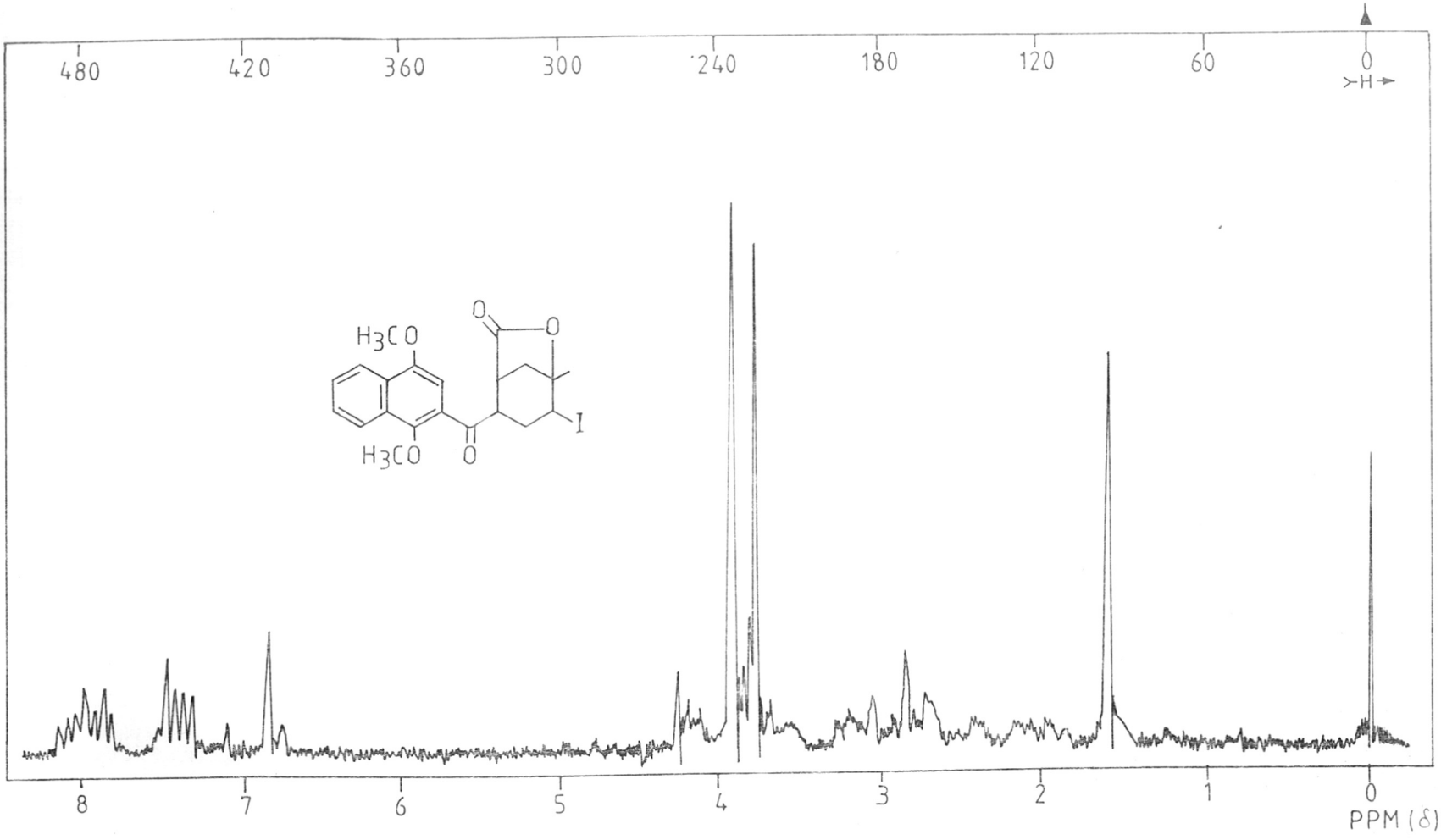


FIG. 3 : PMR SPECTRUM OF THE COMPOUND (19a) IN $CDCl_3$

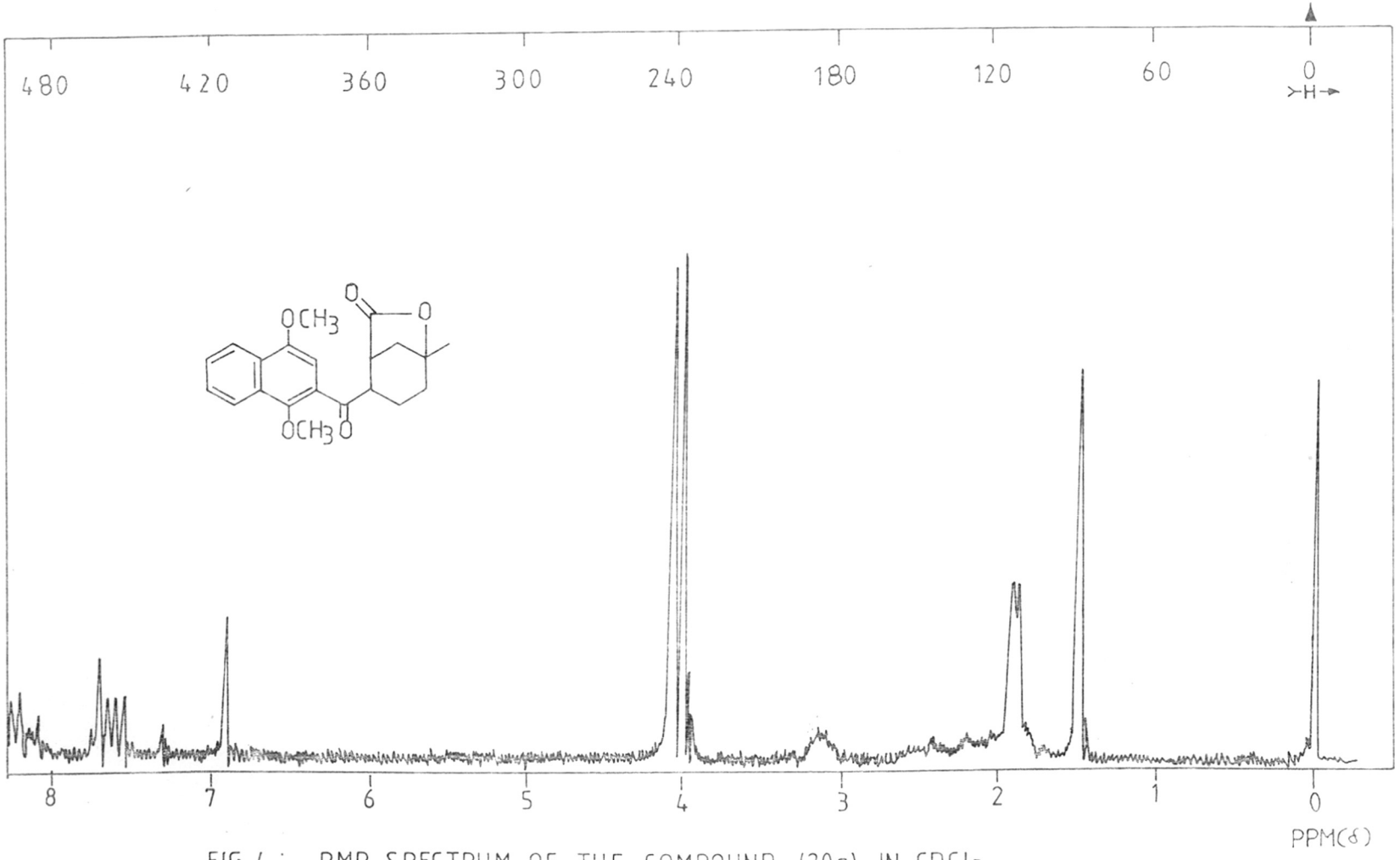


FIG. 4 : PMR SPECTRUM OF THE COMPOUND (20a) IN $CDCl_3$

pattern for aromatic protons were present at δ 7.56-7.74 and δ 8.06-8.28. All other protons resonated at expected chemical shifts. However, when 19a was subjected to reduction by tributyltinhydride in benzene,[7] the product obtained was 23 whose structure was determined by spectral data. The IR of 23 showed absorption at 3540 cm^{-1}, 1760 cm^{-1} and 1600 cm^{-1} corresponding to hydroxyl, γ-lactone and aromatic groups. Absorption at 1670 cm^{-1} due to benzylic keto group was absent. The PMR of 23 revealed the presence of a sharp doublet due to H-C-OH at δ 5.28 which emerged after D_2O exchange. All other protons resonated at the expected chemical shifts.

Opening of the γ-lactone ring to the hydroxyacid 20 was carried out by treatment with alkali[7] and the corresponding acid 21 was obtained in 80% yield. The IR of 21 showed the absorption at 3390 cm^{-1}, 1735 cm^{-1} and 1650 cm^{-1} corresponding to tertiary hydroxyl, acid and bezylic keto group. Mass spectrum of 21 supported the strcuture. For further proof for the structure of acid 21, it was converted to methyl ester 25 by diazomethane. The PMR of 25 (Fig. 5) showed the singlets at δ1.29, δ 3.69, δ 4 and δ6.96 due to methyl group, ester group, methoxyl groups and the aromatic proton. Remaining protons resonated at the expected chemical shifts.

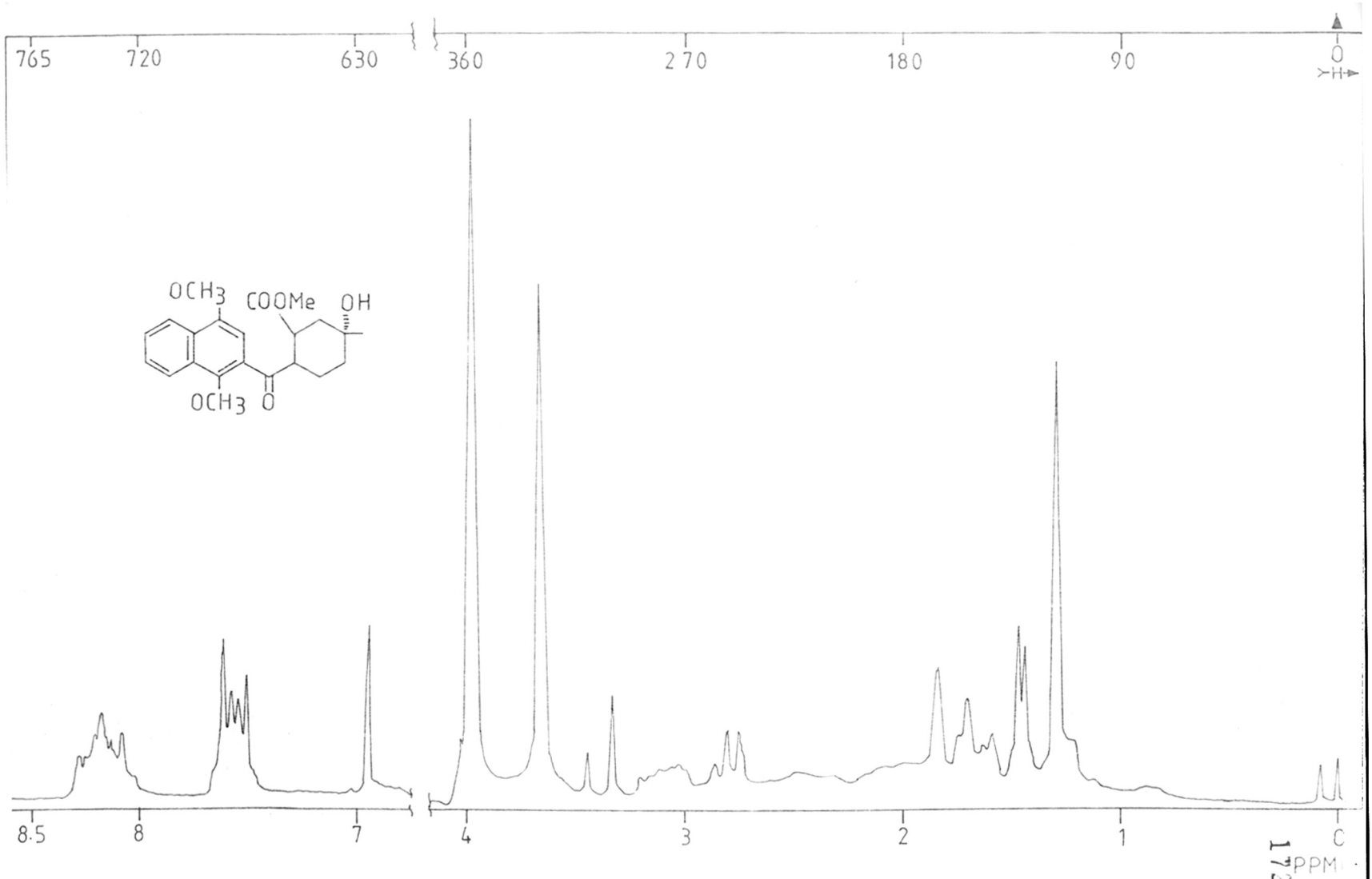
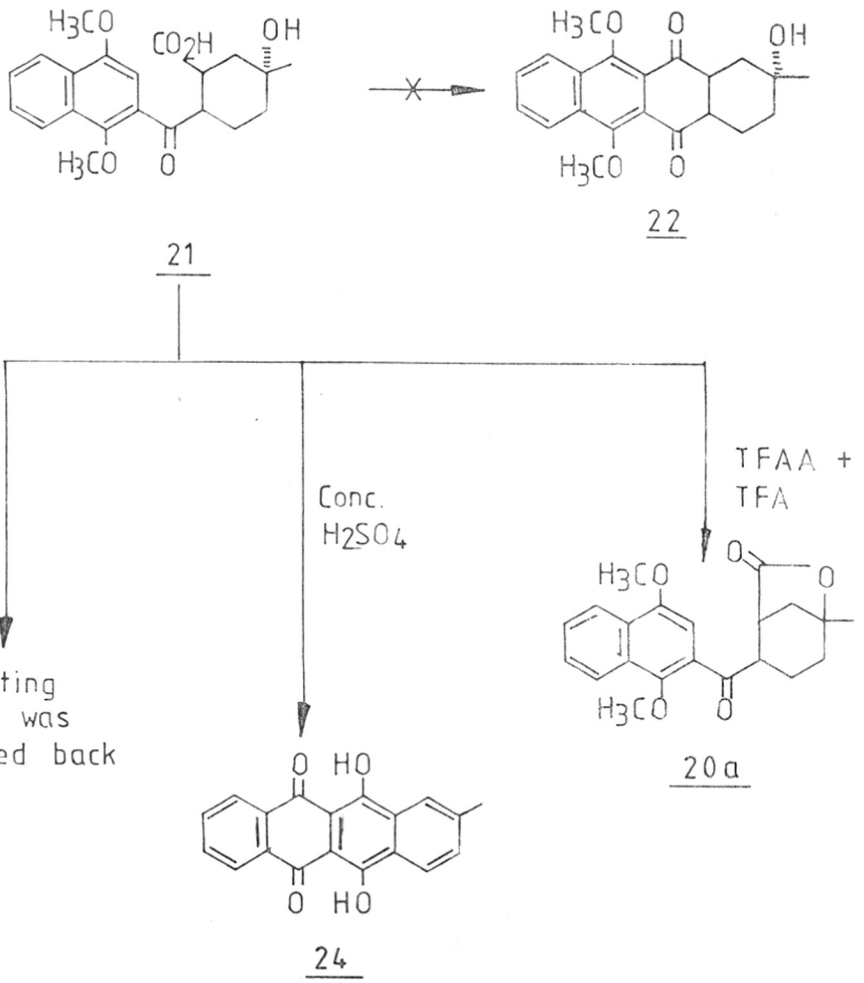


FIG.5 : PMR SPECTRUM OF THE COMPOUND (25) IN $CDCl_3$

After obtaining the required acid 21, the next concern involved the cyclisation. Initially, the acid was treated with anhydrous hydrofluoric acid at 5° to furnish a product which was identical to the starting material. This reaction clearly indicated that a strong cyclising agent was required. Therefore, the second attempt of cyclisation was carried out in the presence of concentrated sulphuric acid. Although the tlc indicated that a new product was formed, the mass spectrum revealed the molecular ion peak at 304 which corresponded with the product being 24. The formation of 24 may be attributed to the aromatisation of the required tetracyclic system 22. Treatment of the acid 21 with trifluoroacetic acid and trifluoroacetic anhydride gave a product whose PMR, IR and mass spectra corresponded well with γ-lactone 20a prepared earlier.

Failure on the part of the acid 21 to cyclise under different acidic conditions was rather discouraging. However, such type of cyclisations have been proved difficult in other cases and there are ample evidences to prove this fact.[8] The further work on the synthesis of this molecule was abandoned.

Attempts for cyclisation of 21



EXPERIMENTAL

Methyl-4(1,4-dimethoxy-2-naphthyl)-4-ketobutanoate (14)

To an ice cold solution of 1,4-dimethoxynaphthalene (18.8 g, 100 mmol) [prepared from 1,4-naphthaquinone] in dichloro-ethane (400 ml) was added aluminium chloride (20 g, 150 mmol) and β-carbomethoxypropionyl chloride (18 g, 120 mmol) [prepared from succinic anhydride]. After further stirring at 0° for 4 hr, 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 14 (24.3 g, 80%); m.p. 58-60°; PMR (CCl_4): δ 2.28 (q, 2H, $\underline{CH_2}$-CO_2Me), 3.35 (q, 2H, -$\overset{O}{\overset{\|}{C}}$-$CH_2$), 3.8 (s, 3H,-$COO\underline{CH_3}$), 4.05 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 7.05 (s, 1H, ArH), 7.4-7.6 (m, 2H, Ar-H), 8 - 8.4 (m, 2H, Ar-H), Mass: 302(M^+); Analysis: Calculated for $C_{17}H_{18}O_5$, C, 67.57; H, 5.96; Found: C, 67.40; H, 6.02%.

Methyl-4-(1,4-dimethoxy-2-naphthyl)-4-keto-2-butanoate (16)

To a stirred solution of 14 (15.1 g, 50 mmol) in dry carbontetrachloride (120 ml), benzoyl peroxide (100 mg) was added followed by bromine solution (8 g, 50 mmol) in 80 ml dry carbontetrachloride added over a period of 1 hr. The reaction mixture was further stirred for 1 hr and washed

with water and dried (Na_2SO_4). To this carbontetrachloride solution containing the bromo compound 15, a solution of dry triethylamine (5 g, 50 mmol) in 60 ml of dry carbontetrachloride was added dropwise and stirred for 5 hr. It was then washed with dilute hydrochloric acid, water, dried (Na_2SO_4) and concentrated to yield the residue which was purified (silica gel, 8% acetone-pet ether) to give 16, (13.2 g, 87.41%); m.p. 72-74°, (lit.[6] m.p. 72-74°); IR (nujol): 1750 cm^{-1} (C-OCH_3), 1695 (C), 1650 (-C=C-); PMR (CCl_4): δ 3.76 (s, 3H, $COOCH_3$), 3.85 (s, 3H, OCH_3), 4.0 (s, 3H, OCH_3), 6.64 (s, 1H, aromatic H), 6.93 (d, J = 8Hz, vinylic), 7.38-7.52 (m, 2H, aromatic), 7.84-8.12 (m, 3H, aromatic 2H and vinylic 1H); Mass: 300(M^+); Analysis: Calculated for $C_{17}H_{16}O_5$; C, 68, H, 5.33; Found: C, 67.89; H, 5.28.

Diels-Alder adduct (17a+17b)

α,β-Unsaturated keto ester (16) (6 g, 20 mmol) and isoprene (3.4 g, 50 mmol) in benzene (90 ml) were heated for 12 hr at 120° in a sealed tube. Removal of the solvent in vaccuo afforded the adduct 17a+17b (6.2 g, 84.2%) as a syrup; IR(nujol): 1730 cm^{-1} (COOMe), 1695 cm^{-1} (C), 1620 (C=C); PMR ($CDCl_3$): δ 1.56 and 1.65 (distorted d, 3H, CH_3), 2.09-2.36 (m, 4H, allylic H), 2.77-3.03 (m, 2H), 3.64 (s, 3H, $COOCH_3$), 4 (s, 6H, 2XOCH_3), 5.35 (bs, 1H, vinylic), 6.97 (s, 1H, aromatic), 7.39-7.61 (m, 2H, aromatic), 8.03-8.3 (m, 2H, aromatic); Mass: 368(M^+).

Ketoacid 18a+18b

The keto ester (5 g, 13.58 mmol) was hydrolysed by boiling in a methanolic sodium hydroxide solution (8%, 50 ml) for 3 hr. After removal of methanol under reduced pressure, the residue was diluted with water and extracted with benzene. The aqueous alkaline layer was acidified with cold conc. hydrochloric acid. The solid separated was filtered to give ketoacid 18a+18b (4.1 g, 85.4%); m.p. 130-33° (decomposes at melting point); IR(nujol): 1700 (COOH) 1685 cm^{-1} (C=O), 1605 cm^{-1} (double bond); PMR ($CDCl_3$) δ 1.63 (bs, 3H, CH_3), 2.06-2.51 (m, 4H, allylic H), 2.69-3.07 (m, 2H), 3.94 (broad s, 6H, $2XOCH_3$), 5.29 (bs, 1H, vinylic), 6.88 (s, 1H, aromatic), 7.36-7.56 (m, 2H, aromatic), 7.91-8.18 (m, 2H, aromatic), 9.83 (bs, 1H, COOH exchanges with D_2O); Mass: 354 (M^+).

γ-Iodolactone (19a)

To the ketoacid 18 (2.88 g, 8 mmol) in dioxane (180 ml), water (120 ml), potassium iodide (2 g, 12 mmol), iodine (2.64 g, 10.4 mmol) and sodium bicarbonate (0.84 g, 10.4 mmol) were added at room temperature. Reaction mixture was stirred under nitrogen atmosphere for 7 hr at room temperature. The aqueous solution was extracted with chloroform, washed with sodium thiosulphate, dried (Na_2SO_4) and distilled off the solvent under reduced pressure to give yellow solid which

was crystallised from acetone (1.68 g, 43%); m.p. 185-87°; IR: ($CHCl_3$); 1780 cm^{-1} (γ-lactone), 1670 (C=O); PMR ($CDCl_3$): δ 1.63 (s, 3H, CH_3), 2.03-3.51 (m, 6H), 3.79 (s, 3H, OCH_3), 3.9 (s, 3H, OCH_3), 4.26-4.19 (distorted triplet, 1H, H-8), 6.87 (s, 1H, aromatic H); 7.29-7.55 (m, 2H, aromatic), 7.78-8.132 (m, 2H, aromatic); Mass: 480(M^+). Analysis: Calculated for $C_{21}H_{21}O_5I$; C, 52.50; H, 4.37; I, 26.45; Found: C, 52.92; H, 4.54; I, 25.87%.

γ-Lactone (20a)

To the iodolactone (0.66 g, 1.375 mmol) dissolved in dichloromethane (10 ml), tri-n-butyltinhydride [freshly prepared from tri-n-butyltinchloride[9]] (0.6 g, 2.065 mmol) in dichloromethane (2 ml) was added dropwise with stirring at room temperature under N_2 atmosphere. Reaction mixture was heated to reflux for 2.5 hr. Dichloromethane was distilled off. Residue was extracted with dry acetonitrile, washed with dry hexane to remove tri-n-butyliodide and distilled off to give colourless solid (20a) which was crystallised from methanol (0.32 g, 66.6%); m.p. 155-56°; IR (nujol): 1770 (γ-lactone), 1670 (C=O); PMR ($CDCl_3$): δ 1.5 (s, 3H, CH_3), 1.73-2.03 (m, 6H), 3-3.24 (m, 2H), 3.97 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 6.93 (s, 1H, Ar-H), 7.56-7.74 (m, 2H, Ar-H), 8.06-8.28 (m, 2H, Ar-H); Mass: 354(M^+); Analysis: Calculated for $C_{21}H_{22}O_5$; C, 71.18; H, 6.21; Found: C, 71.35; H, 6.32%.

Keto-hydroxy acid (21)

The γ-lactone (20a) (0.320 g, 0.9 mmol) was hydrolysed by addition of ethanolic potassium hydroxide (10%, 6 ml). The reaction mixture was stirred at room temperature for 43 hr, then diluted with water, washed by benzene, aqueous layer acidified by cold concentrated hydrochloric acid, extracted with ethyl acetate, dried (Na_2SO_4) and evaporated to give 21 as colourless solid which was crystallised from chloroform (0.285 g, 84.82%); m.p. 195-97°; IR (nujol); 3390 cm^{-1}; 1735 (COOH), 1650 (C=O); Mass: 372(M^+), For PMR spectrum, ketohydroxy acid 21 (50 mg) was converted to ketohydroxy ester 25 by excess of diazomethane.

PMR of ketohydroxy ester (25)

$CDCl_3$: 1.29 (s, 3H, CH_3), 1.41-1.92 (m, 6H), 2.77-3.52 (m, 2H), 3.69 (s, 3H, $COOCH_3$), 4.00 (s,6H, $2XOCH_3$), 6.93 (s, 1H, aromatic H), 7.47-7.63 (m, 2H, Ar-H), 8-8.28 (m, 2H, Ar-H).

Hydroxy γ-lactone (23)

To the solution of iodolactone 19a (0.66 g, 1.375 mmol) in benzene (10 ml), tri-n-butyltinhydride (600 mg, 2.065 mmol) in benzene (2 ml) was added dropwise with stirring at room temperature under nitrogen atmosphere. Reaction mixture was heated to reflux for 2.5 hr. The solvent was distilled off.

Residue was extracted with dry acetonitrile, washed with dry hexane to remove tri-n-butyltiniodide and evaporated to give 23 (0.31 g, 63.3%). IR (nujol): 3540 cm^{-1} (OH). 1760 cm^{-1} (-lactone), 1600 (aromatic); PMR ($CDCl_3$): 1.5 (s, 3H, CH_3), 1.59-2.41 (m, 6H), 3.11-3.34 (m, 2H), 3.89 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 5.28 (bs, 2H, OH, exchanges with D_2O, after D_2O exchange bd — d, J = 11Hz, 1H, H-C-OH), 6.68 (s, 1H, Ar-H), 7.37-7.52 (m, 2H, Ar-H), 7.81-8.25 (m, 2H, Ar-H).

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PART IV

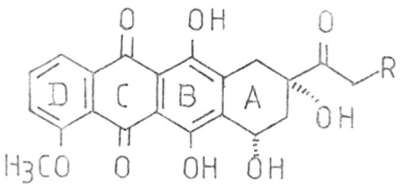
SYNTHESIS OF

3-METHOXYPHTHALIC ANHYDRIDE

DISCUSSION

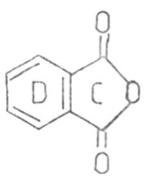
In the anthracycline chemistry (e.g. 1a and 1b) it is now well recognised that AB ring synthon (2) would be considered as key intermediate.[1] Its conversion into tetracyclic system can be realised by several approaches. However, fusion with phthalic anhydride is particularly employed in most of the cases.[2] Therefore, one can indicate that phthalic anhydride (3a) constitutes the CD ring system for anthracyclines. Because of the presence of methoxyl at 4 position of anthracycline, 3-methoxy-phthalic anhydride (3) logically constitutes the CD ring system. Though 3 is an essential reactant for many syntheses of anthracyclines, this relatively simple chemical is however not commercially available.

Although there are several syntheses reported for 3-methoxyphthalic anhydride (3) in literature,[3-18] most of them either give product in low yield or involve long sequence and not so accessible starting material. The classical method reported by Amstuz et al.[10] involved the use of 3-nitrophthalic acid (4) as a starting material which on reduction with stannous chloride and hydrogen chloride followed by diazotisation and alkali treatment afforded the 3-hydroxyphthalic acid (5). Subsequent anhydride formation in the presence of acetic anhydride followed by methylation afforded 3-methoxyphthalic anhydride (3).



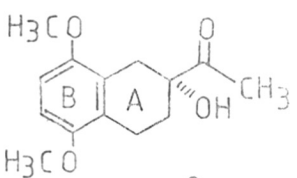
1a : R = H

1b : R = OH



3a

+



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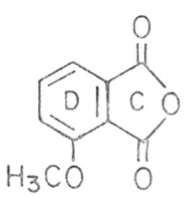

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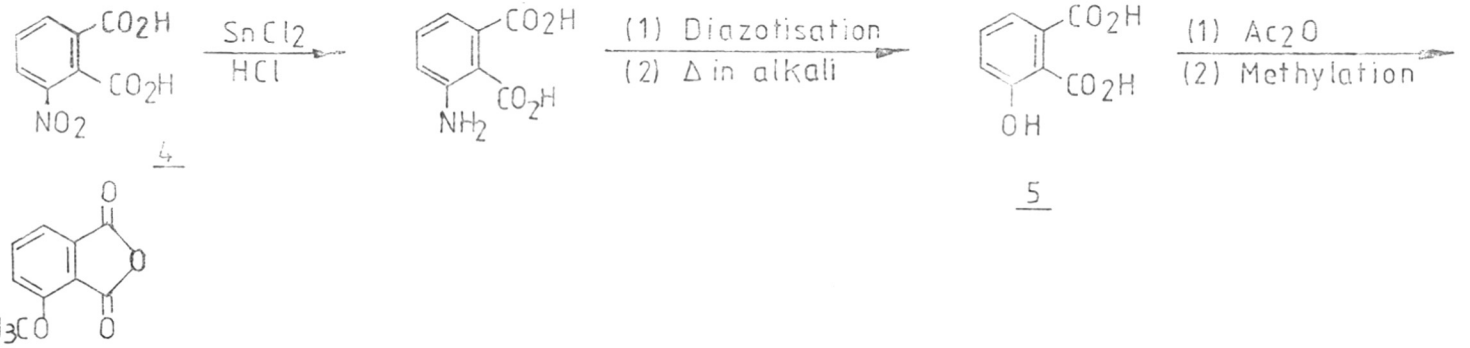
SCHEME 1 Amstutz et al., J.Am. Chem. Soc. 68, 349 (1946)



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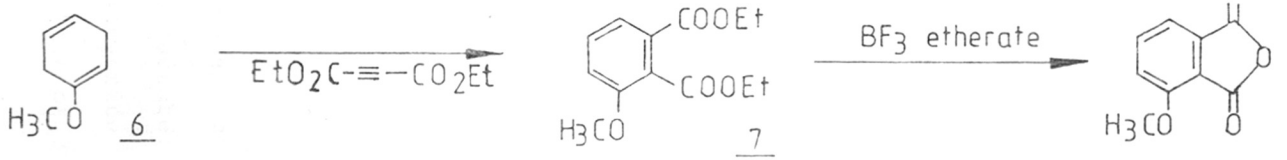
SCHEME 2 Newman et al., J. Org. Chem. 45, 3523 (1980)



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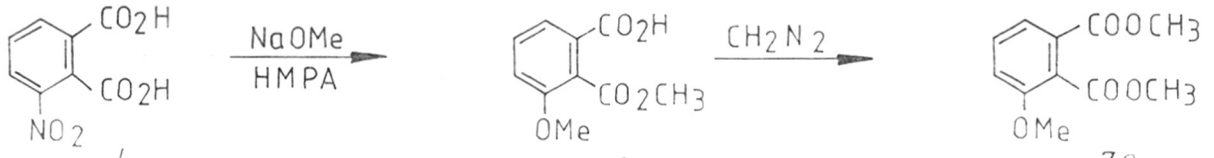
SCHEME 3 Mitscher et al, Org Prep & proc Int, 185 (1981)



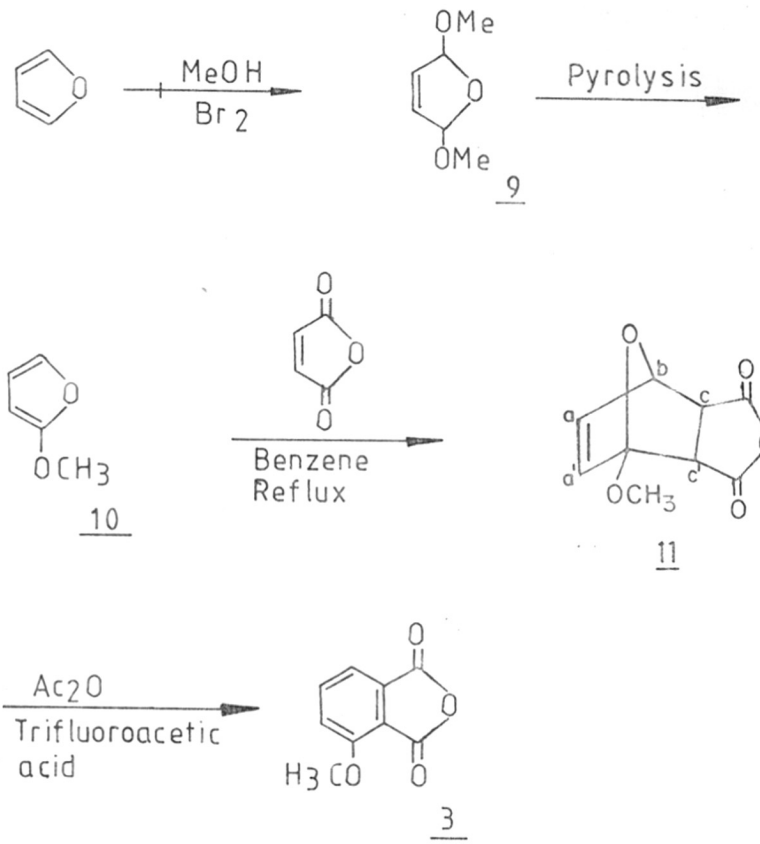
4 8 7a

When the work on the synthesis of 3 was undertaken in these laboratories two more syntheses of 3 appeared whose discussion is worthwhile to mention. For example, in Newman's procedure,[19] 2,5-dihydroanisole (6) and diethylacetylenedicarboxylate in the presence of catalytic amount of dichloromaleic anhydride were allowed to undergo Diels-Alder reaction to give diethyl-3-methoxyphthalate (7) which on heating with small amount of borontrifluoride etherate afforded 3. Later, Mitscher et al. demonstrated that 3-nitrophthalic acid in the presence of sodium methoxide and hexamethylphosphoramide formed 2-carbomethoxy-3-methoxybenzoic acid (8) which on esterification gave dimethyl-3-methoxyphthalate (7a). Conversion of 7a to 3 is well known.

The present synthesis of 3-methoxyphthalic anhydride (3) started from furan whose treatment with bromine in methanol afforded 2,5-dihydro-2,5-dimethoxyfuran (9)[21] which without any delay was treated under pyrolytic condition at 220-30° to give 2-methoxyfuran (10) whose physical and spectroscopic data was in agreement with the reported one.

Diels-Alder reaction of 2-methoxyfuran (10) with maleic anhydride in refluxing benzene afforded the Diels-Alder adduct 11 whose PMR spectrum and melting point was in agreement with the assigned structure. The Diels-Alder adduct was treated with acetic anhydride and trifluoroacetic acid which resulted in the formation of 3-methoxyphthalic anhydride (3) in excellent yield.

SCHEME 4


MeOH
Br 2
OMe
OMe
9
Pyrolysis
OCH3
10
Benzene
Reflux
a
b
c
a'
c'
OCH3
11
Ac2O
Trifluoroacetic
acid
H3CO
3

Thus, the versatility of the reaction is in the use of easily accessible intermediates, in employing new reagents for better yield and in eliminating problems for the large scale preparation of 3-methoxyphthalic anhydride.

EXPERIMENTAL

2,5-Dihydro-2,5-dimethoxyfuran (9)

A solution of methanol (100 ml), benzene (100 ml), anhydrous sodium carbonate (76 g) and furan (29.24 g, 43 mmol) was stirred vigorously at -5° to -10°. An ice-cold solution of bromine (64 g, 40 mmol) in methanol (200 ml) was added at such a rate to maintain the reaction temperature in between -5° and 0°. The reaction mixture was stirred for two more hours after the addition of bromine was over. The solid was filtered and washed with benzene (2 x 50 ml), the filtrate was concentrated on rotavapor upto 200 ml and anhydrous potassium carbonate was added to it. The slurry was stirred for ½ hr. Again the solid was filtered, washed with benzene and concentrated on rotavapor to 150 ml. The same procedure was repeated for two more times. The crude product was distilled to give 2,5-dihydro-2,5-dimethoxyfuran (9) (41 g, 73.3%), b.p. 83-5°/45 mm (lit.[21] b.p. 80-82°/50 mm).

2-Methoxyfuran (10)

To a mixture of dibutylphthalate (20 ml) and β-naphthalenesulfonic acid (catalytic amount) preheated to 220-50° (a dalda bath was used in the present case), was added 2,5-dimethoxy-2,5-dihydrofuran (33 g, 25.4 mmol) dropwise in such a manner as to minimise accumulation of

material in the pyrolysis flask containing a dropping funnel, Claisen head column, condenser and receiver. The distillate was washed with saturated calcium chloride solution and extracted with 2 x 75 ml of ether. Ether water dried over anhydrous sodium sulphate and distilled off to give 2-methoxyfuran (7.1 g, 29%) as colourless liquid; b.p. 100-105° (lit.[22] b.p. 108-9°).

Diels-Alder adduct of 2-methoxyfuran with maleic anhydride (11)

A solution of 2-methoxyfuran (10) (5.18 g, 52.85 mmol) and maleic anhydride (4.9 g, 50 mmol) in dry benzene was refluxed under nitrogen atmosphere for 2 hr. The solution was concentrated and cooled to give the adduct 11, (9.4 g, 91%); m.p. 116-17° (lit.[23] m.p. 117-19°); PMR ($CDCl_3$): 3.65 (m, 2H, H - a , H -a'), (m, 1H, H- b), 7.2 (m, H - c , H -c').

3-Methoxyphthalic anhydride (3)

A mixture of the adduct 11 (5.0 g, 25.5 mmol), acetic anhydride (50 ml) and trifluoroacetic acid (5 ml) was gently refluxed (1 hr). The excess acetic anhydride and trifluoroacetic anhydride were removed under reduced pressure,, the brownish residue dissolved in hot benzene

(200 ml), treated with norit and filtered. The solution on concentration gave colourless crystals of 3 (3.5 g, 77%); m.p. 161-63° (lit.[17] m.p. 161-63°). Mixed melting point with 3-methoxyphthalic anhydride prepared from 3-nitrophthalic acid remained undepressed. The IR and PMR spectra of both the samples were superimposable. IR (nujol): 1780 cm^{-1} (anhydride); PMR ($CDCl_3$): 4.06 (s, 3H, OCH_3), 7.37-7.66 (m, 2H, Ar-H), 7.76-7.94 (m, 1H, Ar-H).

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SECTION B

PHEROMONES

CHAPTER III

SYNTHESIS OF SEX PHEROMONES OF POTATO TUBERWORM *Phthorimaea operculella* (zeller):

(4E,7Z)-4,7 Tridecadienylacetate

(4E 7Z 10Z) - 4,7,10 - Tridecatrienylacetate

PREAMBLE

The development of cultural, technical and agricultural civilisation has been marked with increasing interference in hydrogeochemical cycles and the production of a growing number of chemicals; this is accompanied by a growing concern on the potential adverse effect on biological systems. Assessment of the potential toxicological and ecological effects of pollutants is of central importance.

The development of agricultural product means ensuring economic yield of food crops. To avoid low production level of food and natural fibre, it is essential to control the insect and other invertebrate pests by chemical agents. These chemical agents need to be effective because the food industry and consumers have come to expect unblemished agricultural produce. High effectiveness has been achieved mainly by developing compounds toxic to invertebrate pests. However, such compounds can affect non-target and beneficial organisms, including aesthetically and economically valuable vertebrates and even man. Increasing public concern has resulted in even more stringent regulatory and environmental requirements. To satisfy these and deal with the threat of increased pest resistance to insecticides, new chemical approaches must be explored.

During the past two decades tremendous search has been going on for such chemical approaches. Among these, insect attractant chemicals are giving promising results in the pest control programme. The interdisciplinary investigations of insect kingdom by biologists and chemists have established the importance and complexity of chemosensory communications among insects. Many facets of insect behaviour have been shown to be regulated by chemical stimuli. The current outcry over indiscriminate use of insecticides has provided much of the motivation for this work since the species specificity and high potency of many naturally occurring chemosensory substances hold great promise for manipulation and control of insect populations.

Natural insect attractants fall broadly into two categories: (i) Secretions of insect origin which produce responses for mating, aggregation and foraging within a single species: the term "pheromone" applies to this type of intraspecies attractant, (ii) Volatile constituents of plant or animal hosts utilized by insects in searching for food and egg laying sites.

The term "pheromone" coined by Karlson and Lusher[1] is derived from the Greek phreim, to transfer, and hormone to excite. Pheromones are defined as substances that are secreted to the outside by an insect and received by the

opposite sex of the same species in which they release a specific reaction, for example, a definite behaviour or developmental process. Pheromones are classified into two distinct types by Wilson[2] according to the response they elicit. Chemical stimuli that trigger an immediate and reversible change in the behaviour of the recipient are called releasers whereas those inducing delayed and lasting responses are referred to as primers.

A variety of chemicals have been identified by screening as attractive to one sex, but until these compounds have been isolated and identified from the opposite sex, they are called as sex attractants or parapheromones. In some species, particularly among beetles, the pheromone may attract both sexes and therefore serve more than one function and they are called as aggregation pheromones.

The potential economic and environmental importance of biological pest control is currently undergoing experimental evaluation and the successful use of natural insect attractants has been reported by several groups.[3] Insect sex pheromone attractants have been used to reduce pest populations by employing attractant-baited traps. Sex pheromone attractants have also been used in the "confusion technique" where normal mating behaviour is disrupted by premating the atmosphere with synthetic sex attractants.

These methods of pest control have considerable advantages over the use of conventional insecticides. The relatively small amounts of synthetic attractant required minimises the possibility of environmental pollution and the species specificity of many natural attractants reduces the risk of destroying beneficial insects such as predators, parasites and pollinators. Furthermore, the evolution of strains of pest populations resistant to natural attractants is very unlikely. The most general application of insect attractants probably lies in integrated control measures as population survey tools to probe the degree of infestation and the need for blanket spraying programmes throughout the season with its attendant hazards would be obtivated.

From the beginning the synthetic approach was very important in pheromone research because of the limited availability of natural pheromones from insects (usually less than several milligrams). Synthetic work in pheromones may be classified into three categories: (1) Synthesis as the final proof of the proposed structure including olefin geometry and relative as well as absolute stereochemistry, (2) Synthesis that provides sufficient material for biological study, such as field tests and (3) Synthesis of a number of isomers and analogues to clarify the structure-pheromone activity relationship.

Synthesis thus ensures ample supplies and facilitates the practical use in agriculture and forestry. Because of the importance of synthetic pheromones, a number of organic chemists from well known groups throughout the world are involved in this area of research.

INTRODUCTION: SEX PHEROMONES OF POTATO TUBERWORM MOTH

The potato tuberworm, Phthorimaea operculella (Zeller) (Lepidoptera Gelechiidae), is a widely distributed pest on solanaceous crops and thrives best in areas with hot dry summer. The larvae attack foliage and infest tubers in the field. It can be spread by potato shipments from infected to uninfected area. As potato is staple diet for many people in the world, this pest has attracted world-wide attention. The pest has done the damage for potatoes all over the world. For example, in some areas of California, tuber infestation may be so severe that portions of fields or occasionally entire fields must be abandoned at harvest time. Insecticide resistance and inadequate means for monitoring tuberworm populations have resulted in the excessive use of insecticides. The discovery that potent sex attractants are produced by the female suggested that these pheromones might be used to monitor and possibly control population of tuber moth.

The potato tuberworm moth was first found in Japan in a tobacco plant field at Kure city, Hiroshima Prefecture in May 1953. Since the end of 1960,[4] it has been known that the extracts of the terminal abdominal segments of of the virgin female potato tuberworm moth evolve the

characteristic response of male moths in the laboratory and lure them in the field. Kennedy[5] in 1975, knowing that an identification programme of the pheromone had been started, investigated the efficiency of eight different trap designs deployed at two different heights and two orientations with virgin females as lures. Mated females released little or no active pheromone, since they attracted no males. The pheromone PTM1 trap was superior to all others and its performance was independent of the heights tested (0.3 and 1.0 M above the ground). Fouda[6] (1975) extracted 100000 male and female potato tuberworm moths and concluded that the major component of the pheromone mixture could be an unsaturated C-13 acetate. Hindenlang et al.[7] (1975) extracted abdomens of adult virgin females and tried to find optimum conditions for a laboratory bioassay, since it had been found that two related species, also belonging to Gelechiidae, have doubly unsaturated C-16 acetates as their pheromones. Hindenlang and his coworkers first tested these and similar compounds without success. They concluded that a thorough fractionation of crude female extract was necessary to identify the active component.

At this stage, Roelofs et al.[8] (1975) succeeded in identifying one component of the pheromone system in extracts from female abdominal tips after performing a

(4E, 7Z)-4,7-tridecadienyl acetate

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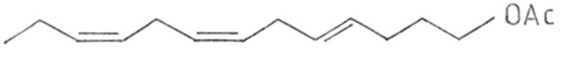
(4E, 7Z, 10Z)-4,7,10-tridecatrienyl acetate



2

classical identification programme. This compound (4E,7Z)-4,7-tridecadienyl acetate (1) was active in the laboratory bioassay and was also attractive in the field. In two of three field tests 100-300 µg of 1 on rubber dispensors were competitive with three living virgin females. Addition of (4E,7Z)-4,7-tridecadien-1-ol, the parent alcohol of 1 did not increase trap catch. The geometrical isomer of 1, (4E,7E)-4,7-tridecadienyl acetate was not attractive at all. In their opinion, 1 is potent enough to be used as an attractant in trap for monitoring purposes. They also found indications of a second component in the extract which could be a part of the pheromone system, but its chemical structure was not clarified. In the meantime, a joint effort of the laboratory for research on insecticides at Wageningen and the central laboratory TNO at Delft had independently led to the conclusions similar to those of Roelofs et al. In addition, these laboratories succeeded in isolating, identifying and synthesising the second component which proved to be the triunsaturated C-13 acetate, (4E,7Z,10Z)-4,7,10-tridecatrienyl acetate (2).[9] In a field trial, 200 µg of 1 lured 275 moths while 200 µg of 2 lured 123 moths. A trap baited with 1:1 mixture of 1 and 2 (100 µg of 1 + 100 µg of 2) lured 618 moths, demonstrating the mixture of both the pheromones is more attractive to moths.[10]

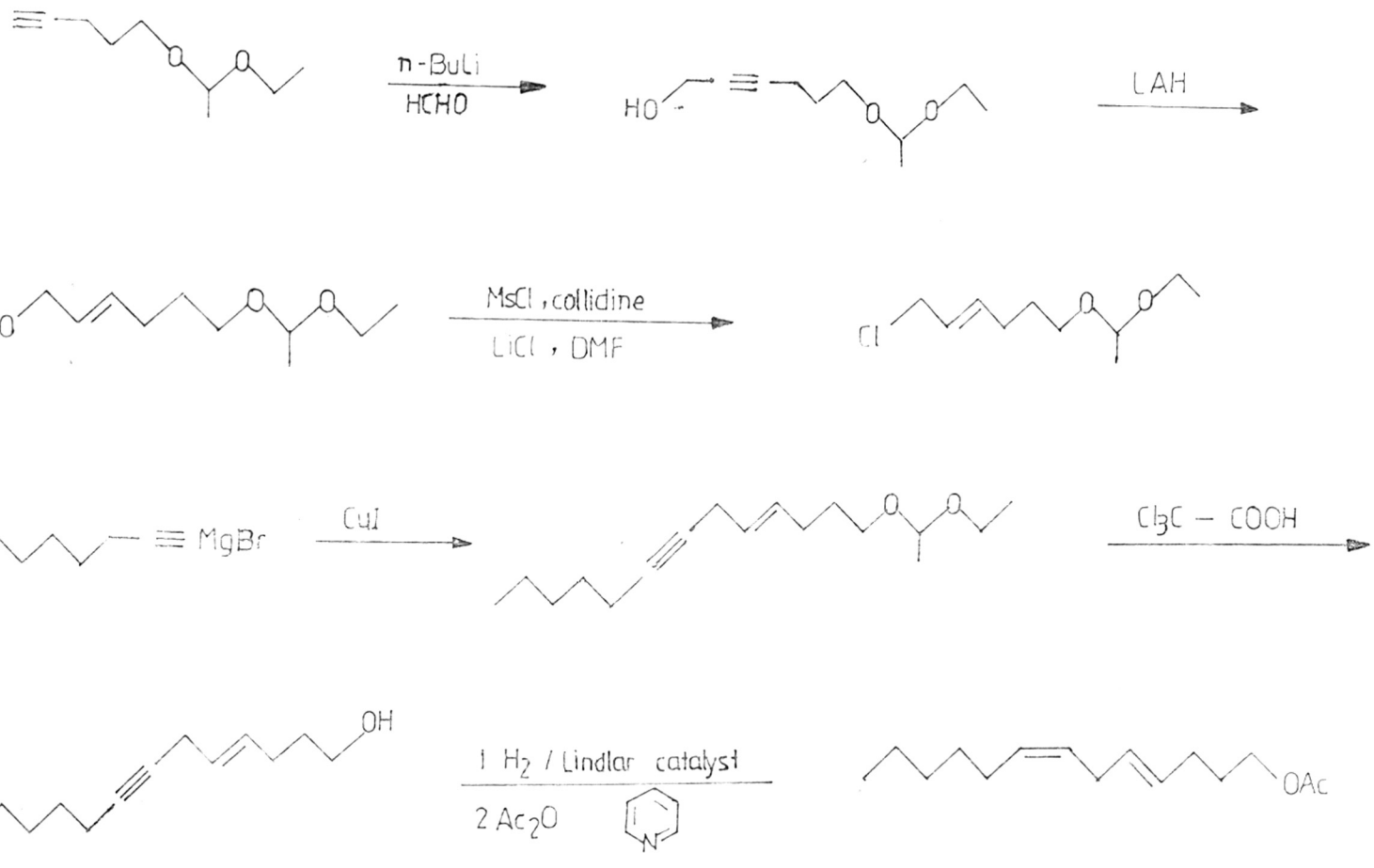
DISCUSSION

Synthetic approaches to (4E,7Z)-4,7-tridecadienyl acetate (1) and (4E,7Z,10Z)-4,7,10-tridecatrienyl acetate (2).

Due to the importance of pheromones (4E,7Z)4,7-tridecadienyl acetate (1) and (4E,7Z,10Z)-4,7,10-tridecatrienyl acetate (2) in potato crop protection coupled with unusual odd carbon chain structure, several syntheses of 1 have been reported. However, only one synthesis of the pheromone 2 was known. It is pertinent to discuss the reported syntheses of 1 and 2 because these syntheses are directly or indirectly related to the work reported in this chapter.

The first synthesis of 1 was reported by Roelofs et al.[8] starting from 4-pentyn-1-ol-ethoxy ethyl ether (3). Condensation of 3 with formaldehyde in the presence of n-butyl lithium, followed by reduction with lithium aluminiumhydride gave the alcohol 4 which was converted into allylic chloride 5. The coupling of 5 with heptanyl-magnesium bromide was effected in the presence of cuprous iodide to afford 6 which was hydrolysed with trichloroacetic acid and the resulting alcohol was reduced and then acetylated to afford the pheromone 1 (Scheme-1).

SCHEME 1 Roelfs et al, Life Sci, 17, 699 (1975)

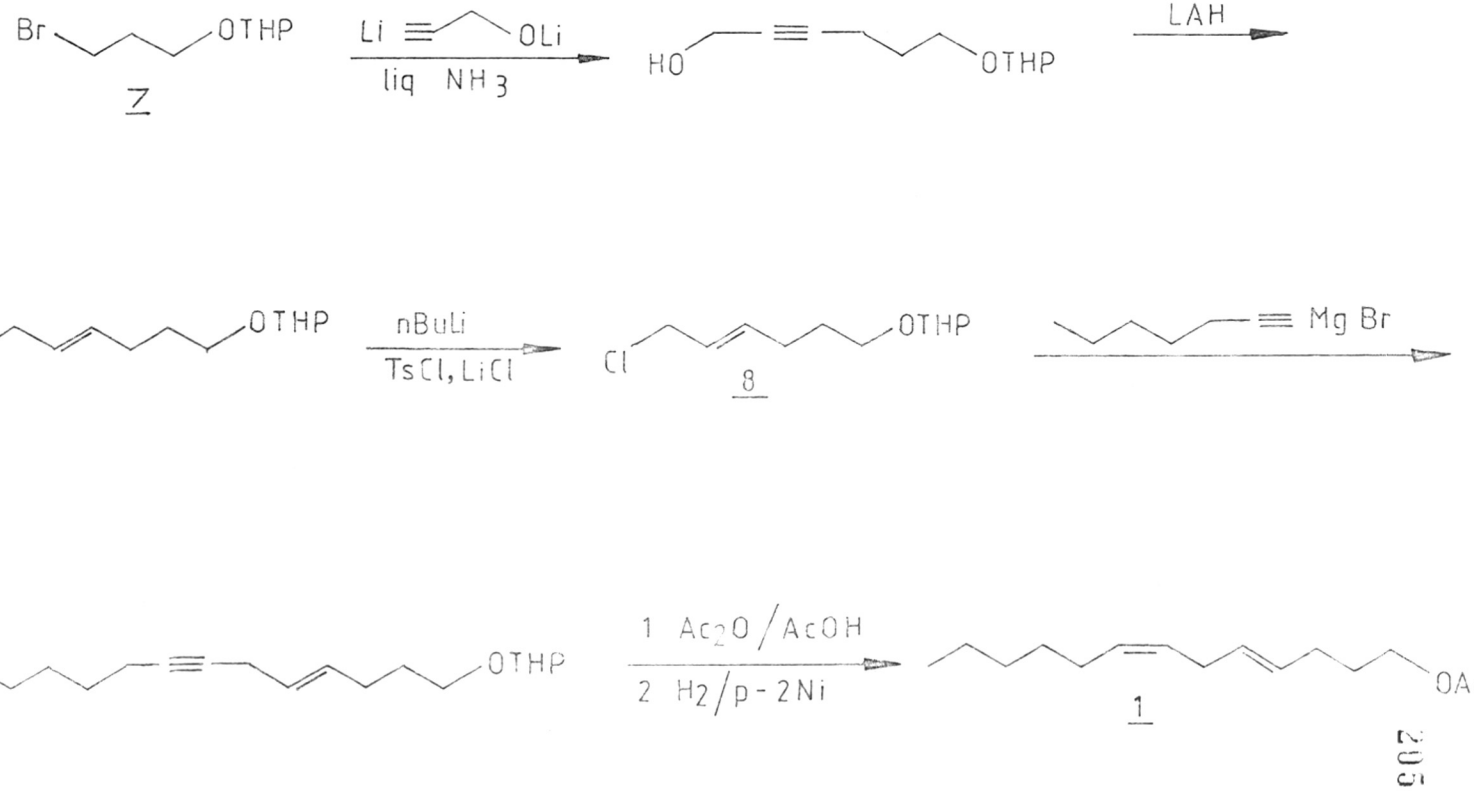


The synthesis reported by Voreman et al.[11] (Scheme-2) was similar to the one reported above. In the present case, the allylic chloride 8 was synthesised by the condensation of dianion of propargyl alcohol with tetrahydropyran protected bromopropanol 7. Subsequent reduction of the triple bond by lithium aluminium hydride, followed by chlorination afforded the required allylic chloride 8 which was then transformed into 1 by the reported procedure.

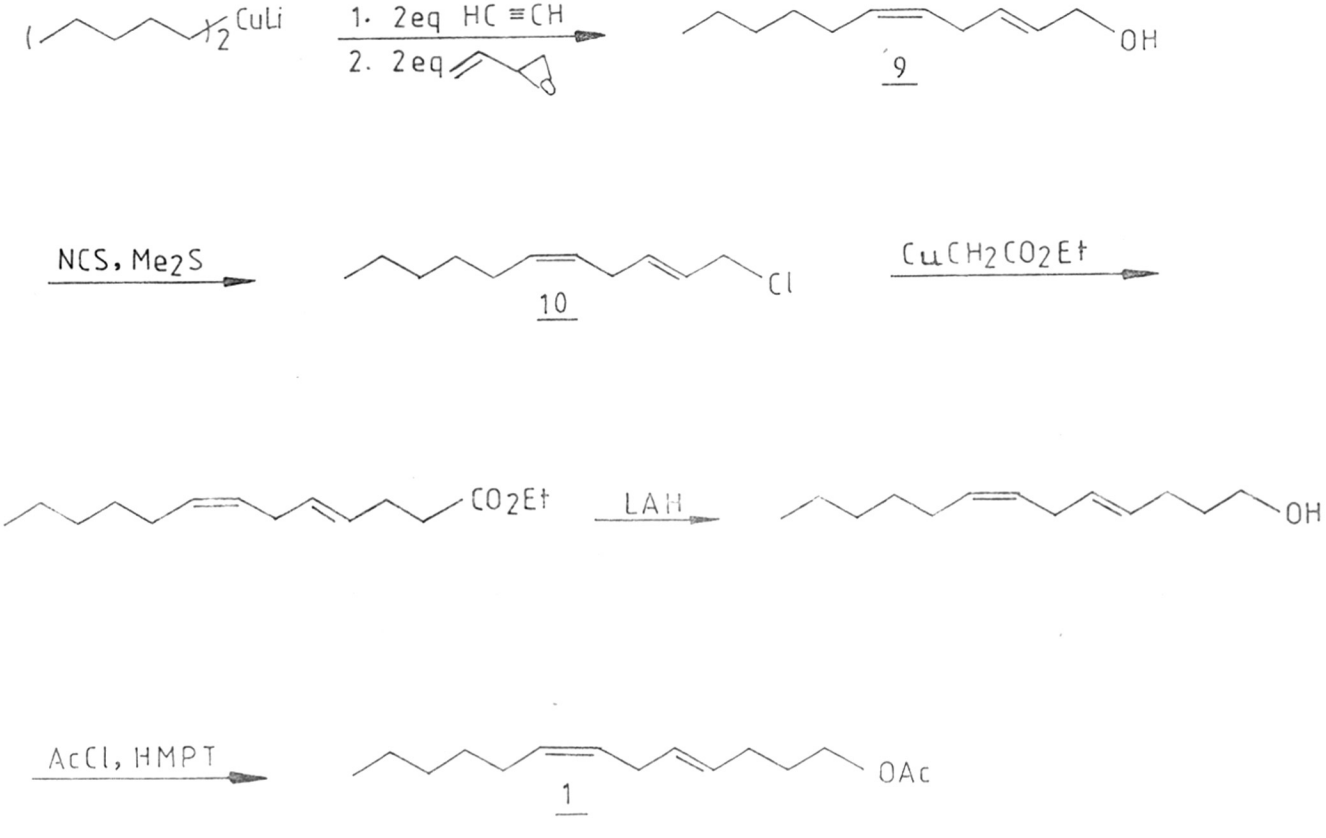
Normant et al.[12] reported the synthesis of 1 which was based on the use of organo-copper reagents. For example, dipentyl cuprate was treated with acetylene to give Z-heptanylcuprate which was subsequently treated with butadiene epoxide to form dienol 9. 9 was converted into the dienylchloride 10 and then treated with ethyl copper acetate followed by reduction and acetylation to give the pheromone 1 (Scheme-3).

Fuzisawa et al.[13] reported a synthesis of 1 (Scheme-4) based on the regio and stereoselective opening of γ-vinyl-γ-butyrolactone with diorganocuprate. (Z)-Heptanylcuprate (obtained from dipentylcuprate and acetylene) reacted with γ-vinyl-γ-butyrolactone to give the acid 11 which was successively esterified, reduced and acetylated to afford the required pheromone (1).

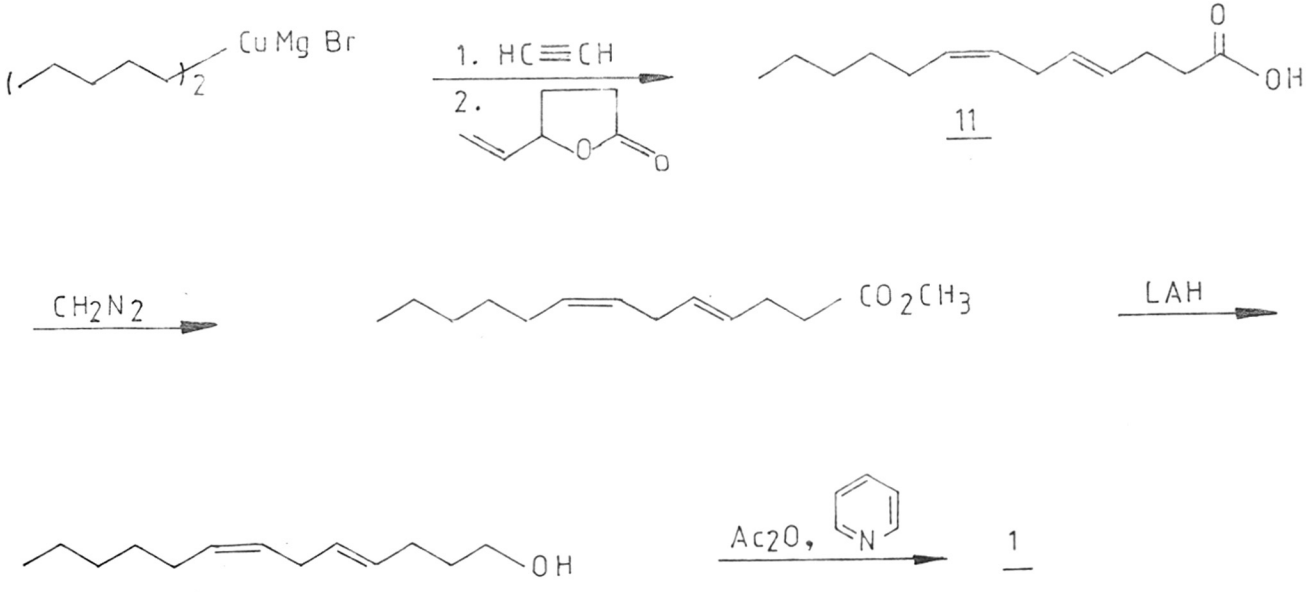
SCHEME 2 Voreman et al., J. Chem. Ecol, 4, 531 (1978)



SCHEME 3 Normant et al., Tetrahedron Lett, 2027 (1978)



SCHEME 4 Fujisawa et al., Tetrahedron Lett, 23, 3583 (1982)

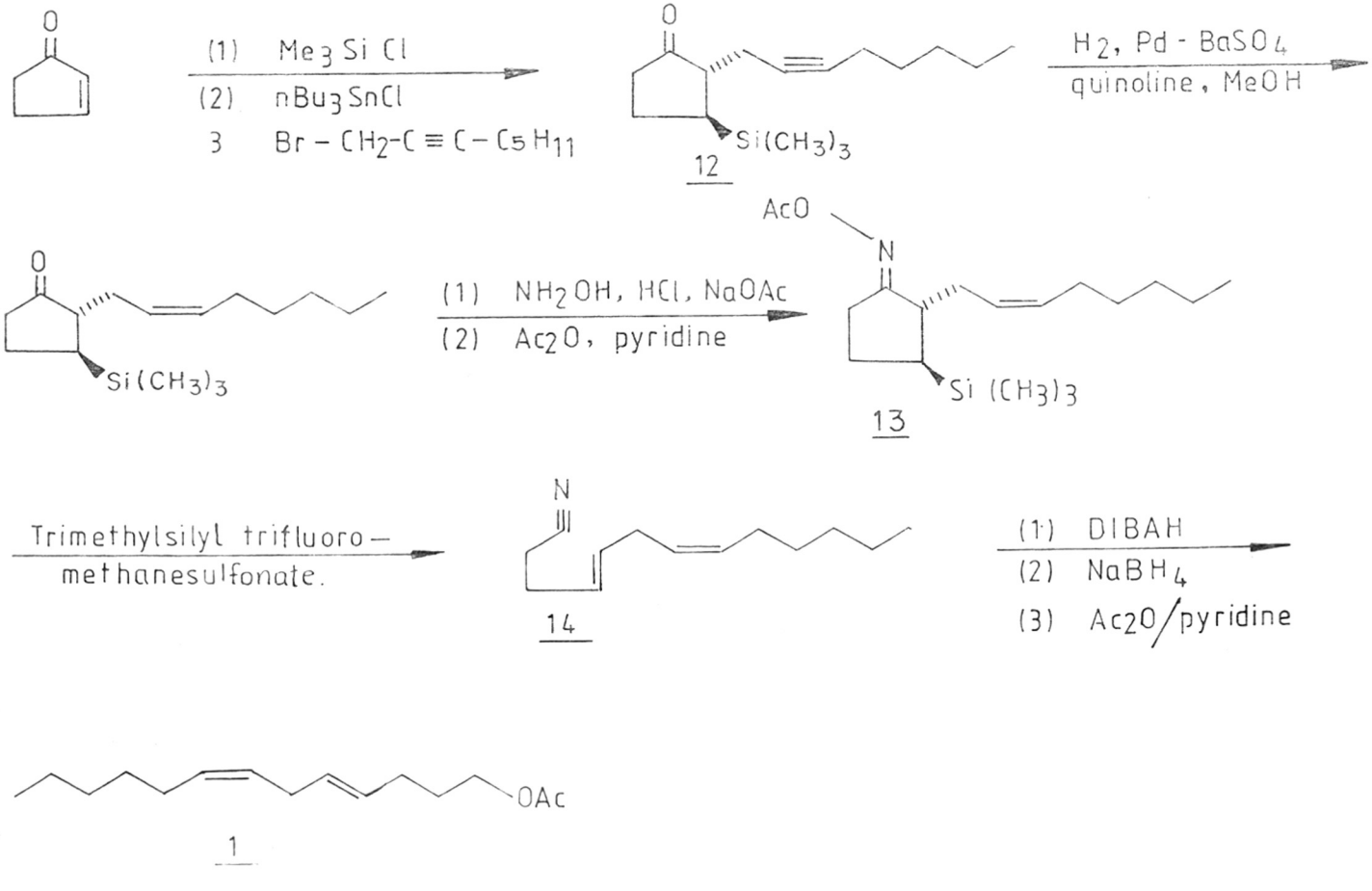


Based on silicon-directed Beckmann fragmentation Itoh et al.[14] reported the synthesis of 1 (Scheme-5). Thus, treatment of lithium enolate of 3-trimethylsilyl-cyclopentanone with tributyltin chloride at -78° followed by alkylation with 1-bromo-2-octyne afforded β-silyl ketone 12. Partial hydrogenation of 12 followed by oximation and acetylation gave the oxime acetate 13 which was treated with trimethylsilyltrifluoromethane sulfonate to give rise to nitrile 14. Reduction of 14 with diisobutylaluminium hydride at -78° and then with sodium borohydride at 0° followed by acetylation furnished the desired compound 1.

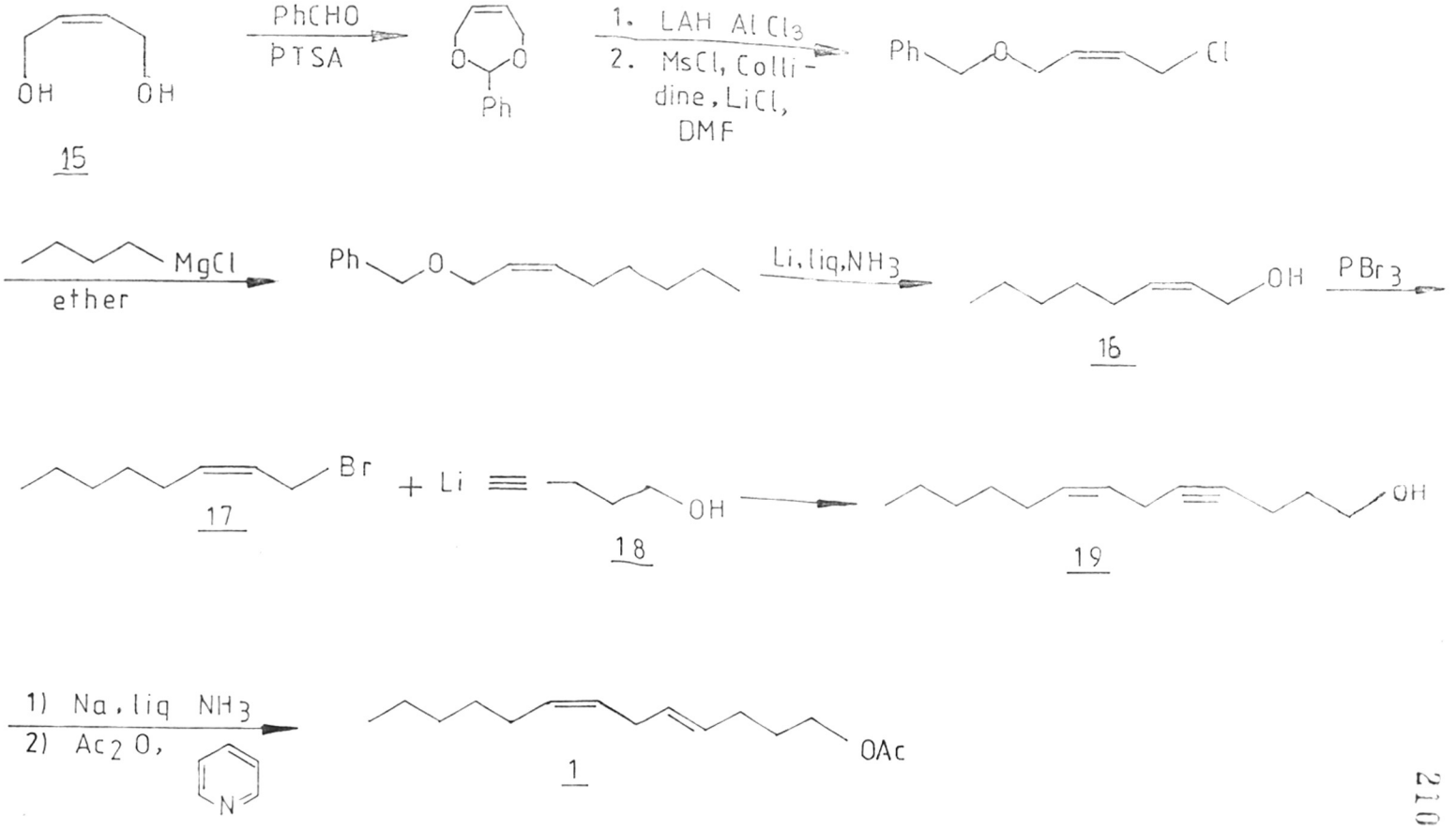
The pheromone 1 was earlier synthesised in these laboratories starting from cis-butenediol(15). Benzylidine protected cis-butenediol was hydrogenolysed in the presence of lithium aluminiumhydride and aluminium chloride mixture followed by removal of benzyl group gave the alcohol 16. Its bromide 17 and lithium salt of acetylenic intermediate 18 were condensed to give the compound 19 whose reduction with sodium in liquid ammonia followed by acetylation gave pheromone 1 (Scheme-6).[15]

The only synthesis of pheromone 2 was reported by Voreman et al.[11] in 1978 (Scheme-7). 3-Bromo-1-propanol (20) was protected as tetrahydropyran derivative 21 which was coupled with dianion of propargyl alcohol.

SCHEME 5 : Itoh et al., Tetrahedron Lett, 25, 223 (1984)

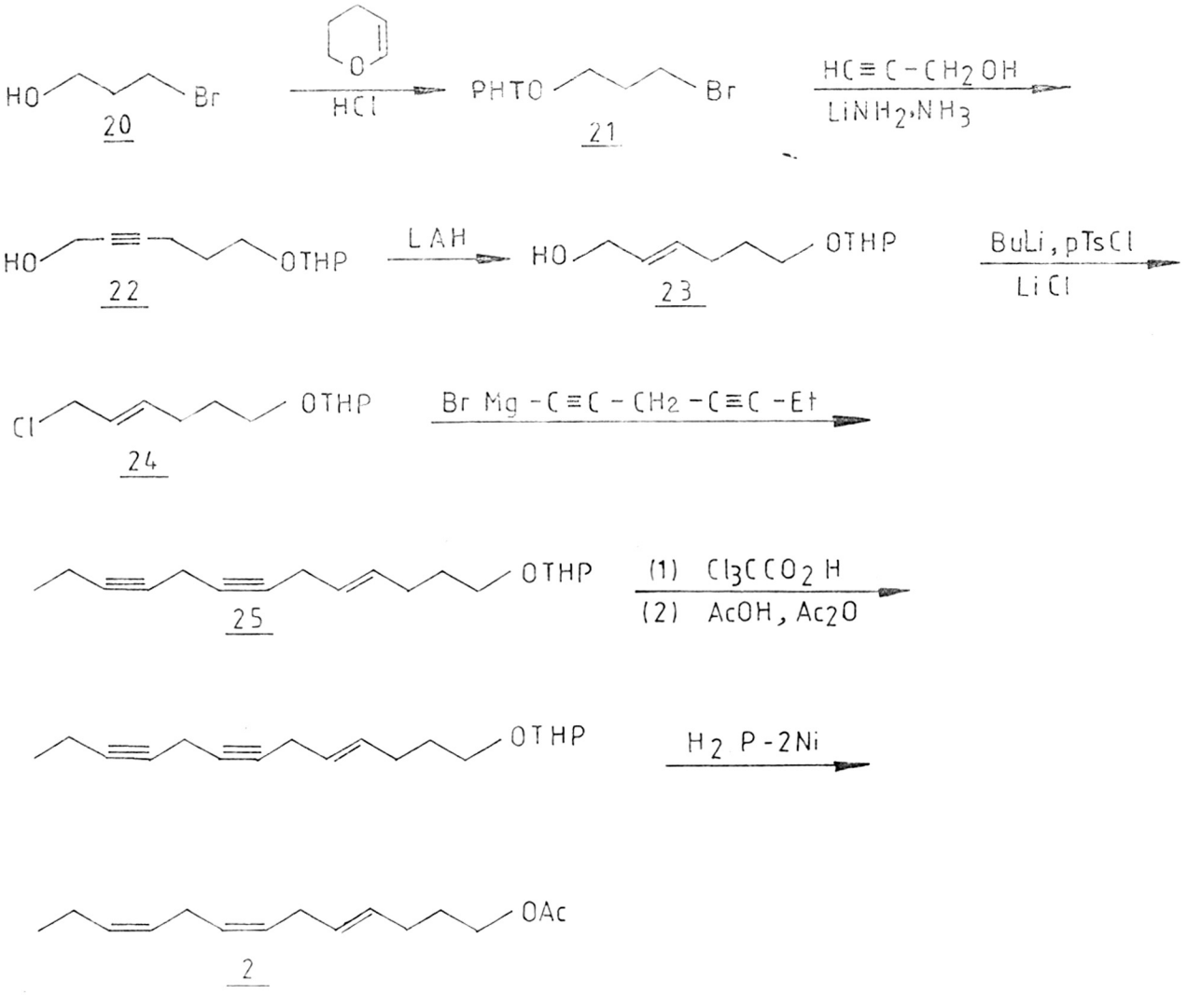


SCHEME 6 Yadav et al, Syn. Commu. (In Press)



The resulting alcohol 22 on reduction with lithium aluminium-hydride produced the trans allylic alcohol 23 whose chloride 24 and 1,4-heptadiyne were condensed together to give the enyne derivative 25. Subsequent acetolysis and reduction furnished the desired pheromone 2.

SCHEME 7 Voreman et al , J. Chem. Ecol., 4, 531 (1978)



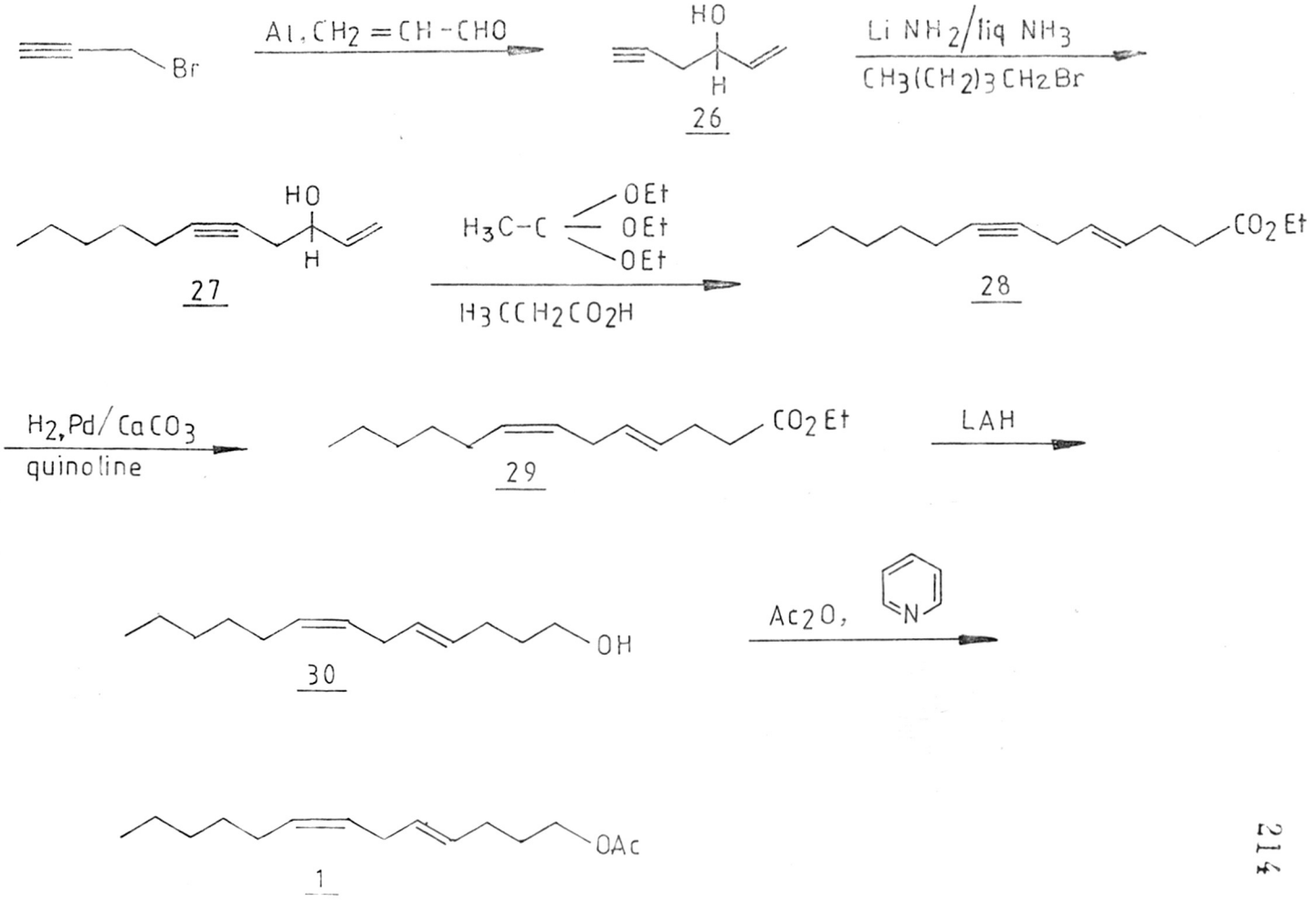
PRESENT WORK

As reported earlier for pest control of potato crop the pheromones (4E,7Z)-4,7-tridecadienyl acetate (1) and (4E,7Z,10Z)-4,7,10-tridecatrienyl acetate have considerable potential. Because of the fact that these pheromones are present in minute amounts, syntheses of these compounds have been undertaken by several groups. In addition, the salient features present in their structures involve cis and trans double bonds, acetyl group and of course, odd carbon atom chain. The present chapter deals with the synthesis of 1 and 2. The synthetic strategy reported here involved the use of properly functionalised intermediate, 1-hexen-5-yn-3-ol (26), common for both the pheromones 1 and 2. The acetylenic portion in 26 has been exploited for C-C bond formation as well as a source for cis double bond. While allylic alcohol portion of 26 rendered the generation of trans double bond coupled with two carbon homologation via Claisen rearrangement.

Synthesis of (4E,7Z)-4,7-tridecadienyl acetate (1) (Scheme-8).

The intermediate, viz. 1-hexen-5-yn-3-ol (26) was prepared by modified route[16,17] in which the propargyl-bromide was first treated with aluminium and resulting organoaluminium reagent was reacted with acrolein to give

SCHEME 8


Br
Al, CH2=CH-CHO
HO
H
26
Li NH2/liq NH3
CH3(CH2)3CH2Br
HO
H
27
H3C-C
OEt
OEt
OEt
H3CCH2CO2H
CO2Et
28
H2, Pd/CaCO3
quinoline
CO2Et
29
LAH
OH
30
Ac2O,
N
OAc
1

the intermediate 1-hexen-5-yn-3-ol (26) in 60% yield. It is pertinent to mention here that when magnesium was used, a considerable amount of undesired side products resulted along with required alcohol. It was found that with aluminium reaction was clean and yield was consistent. The structure of 26 was confirmed by spectroscopic evidences.

The dianion of 26 was obtained by treatment with lithum amide in liquid ammonia at -30°. Its treatment with 1-bromopentane afforded 1-undecen-5-yn-3-ol[17] (27) in 70% yield. The IR spectrum of 27 revealed an absorption for hydroxyl group at 3340 cm^{-1}. In PMR spectrum, the absence of triplet at 2.05 ppm for the acetylenic proton indicated that alkylation had occured. Distorted triplet due to terminal methyl group was observed at 0.9 ppm. The remaining protons were observed at expected chemical shifts.

The two carbon homologation via the Claisen rearrangement was effected by the treatment of 27 with triethylorthoacetate and catalytic amount of propionic acid under reflux resulting into ethyl(4E)-tridecene-7-ynoate (28) after 2 hr. The presence of a sharp absorption at 1730 cm^{-1} for carbonyl and 980 cm^{-1} for trans double bond were observed in the IR spectrum. The absorption corresponding to hydroxyl group was absent. Further confirmation of the strcuture of 28 was gleaned by its PMR spectrum (Fig.1). Though the presence of

trans double bond could not be unambigously proved by PMR spectrum because of the appearance of multiplet of olefinic protons, there are ample evidences[18] based on mechanistic aspects of the Claisen rearrangement which tend to show that trans double bond had resulted.

Partial hydrogenation of the triple bond in 28 over Lindlar catalyst[19] gave the skipped diene derivative, (4E,7Z)-4,7-tridecadienoate (29).[12,13] Its IR spectrum revealed absorption for carbonyl, trans double bond and a cis double bond at 1730, 960 and 735 cm^{-1} whereas its PMR spectrum revealed resonances due to four olefinic protons in the region of 5 to 5.3 ppm as multiplets, signals due to skipped methylene protons (H_a-6, H_b-6) at δ 2.4-2.7.

Reduction of ester function in 29 was effected with lithium aluminiumhydride and the corresponding alcohol (4E,7Z)-4,7-tridecadien-1-ol (30)[12,13] was obtained in whose IR spectrum absorption due to hydroxyl group, trans double bond and cis double bond were observed. The PMR spectrum was consistent with the structure of 30.

Conventional acetylation of 30 with acetic anhydride and pyridine gave the required pheromone (4E,7Z)-4,7-tridecadienyl acetate (1) in 90% yield. In the PMR spectrum (Fig.2) of 1 the four olefinic protons resonated in the

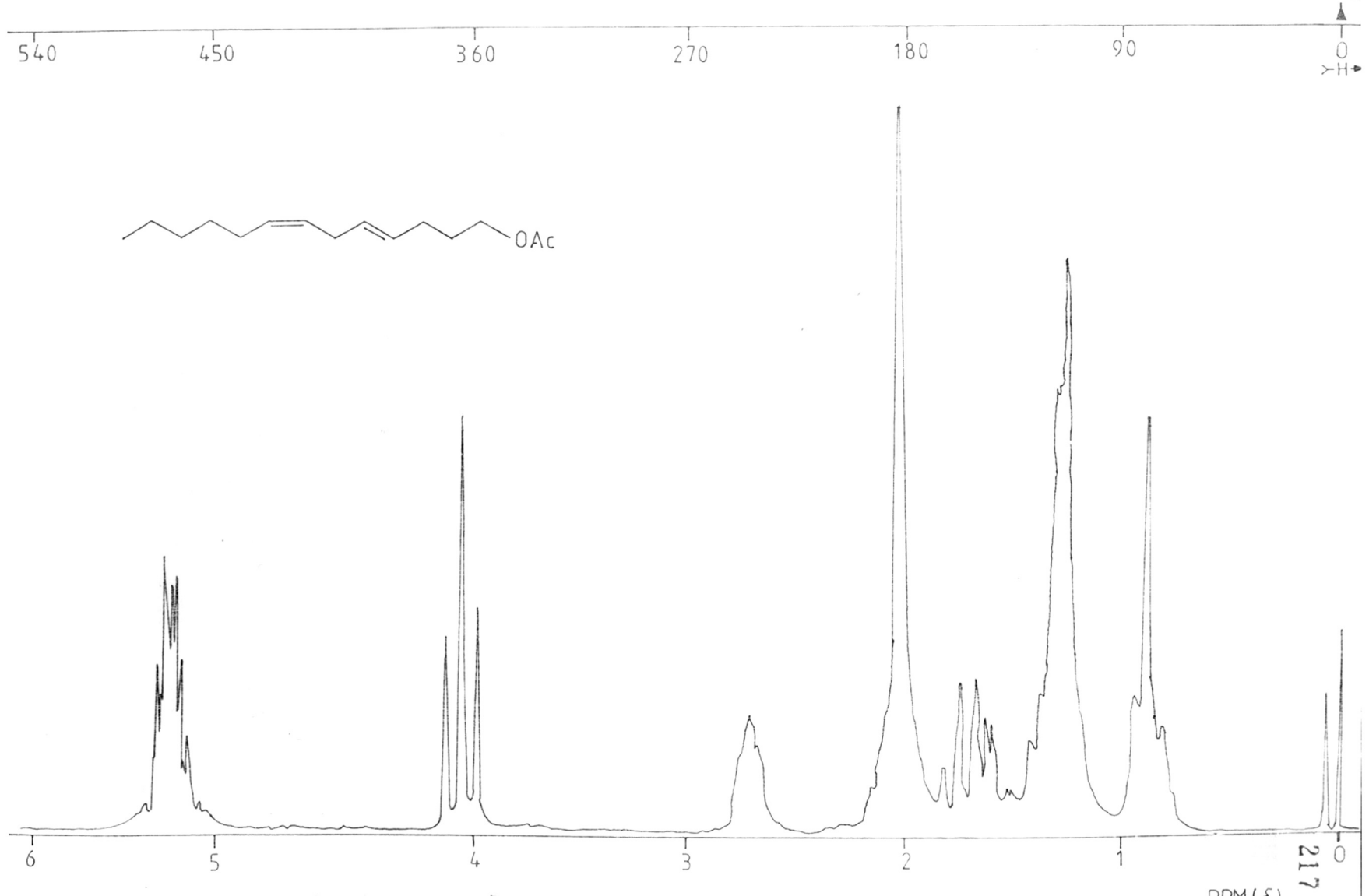


FIG. 2: PMR SPECTRUM OF THE COMPOUND (1) IN $CDCl_3$

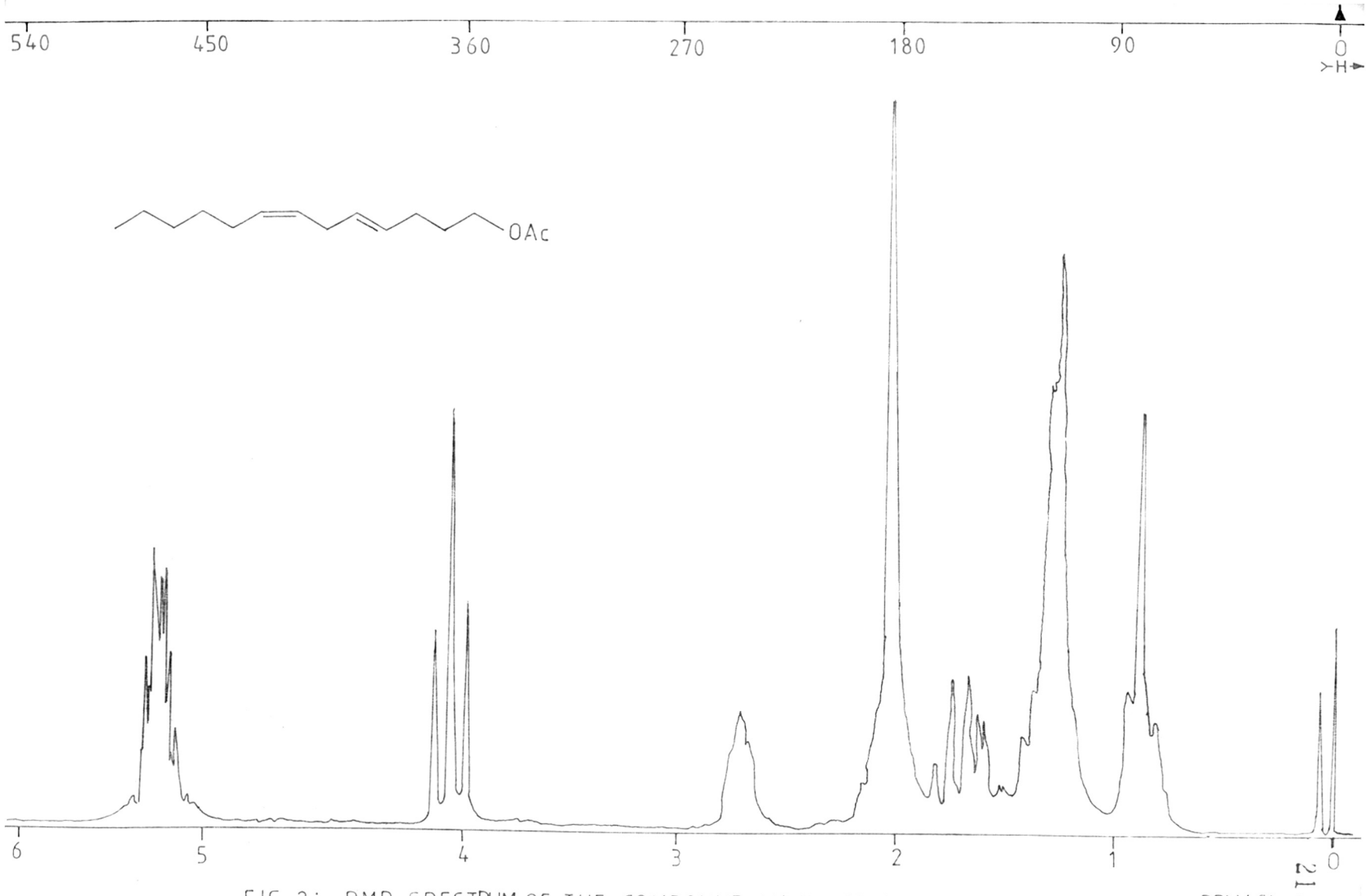


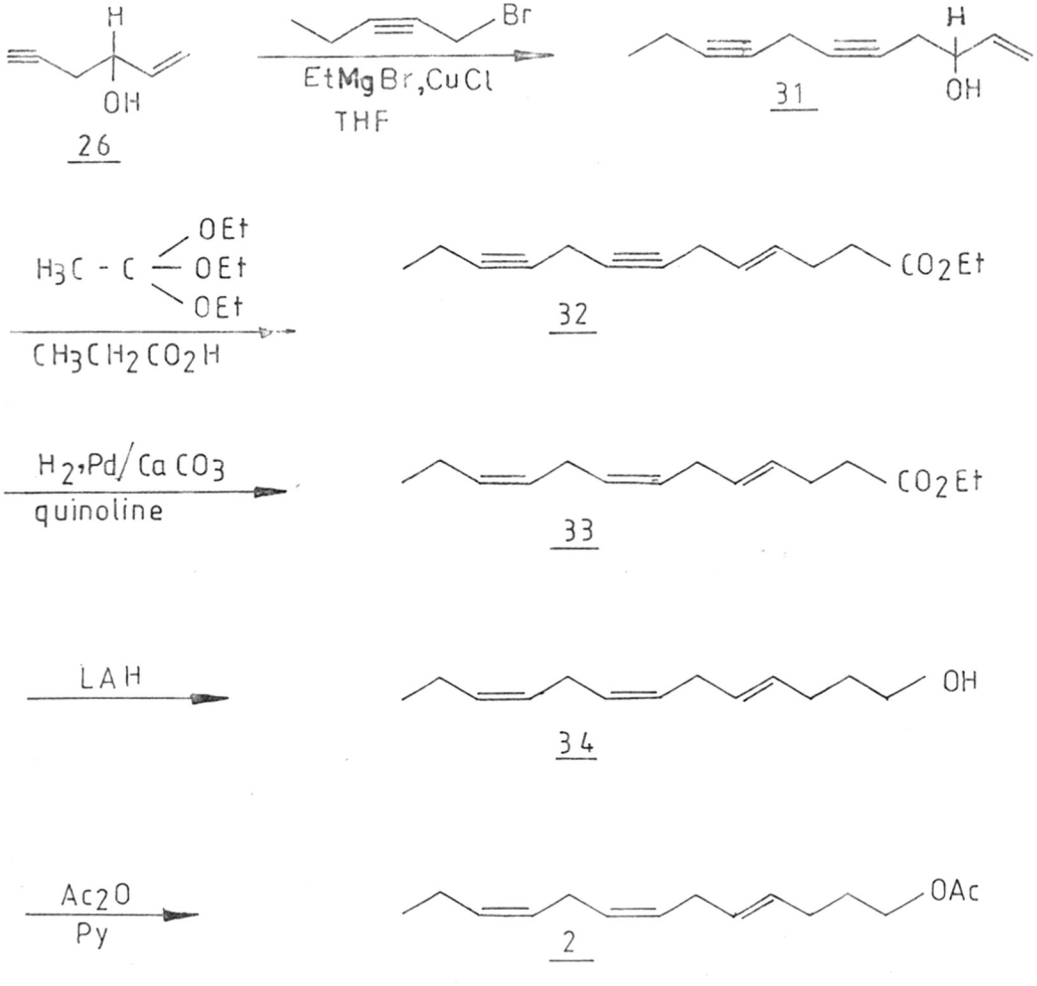
FIG. 2: PMR SPECTRUM OF THE COMPOUND (1) IN $CDCl_3$

region of δ 5.17-5.44 as a multiplet. The methyl protons of acetyl group appeared as a singlet at 2.02 ppm and the remaining protons resonated at the expected chemical shifts. In the ^{13}C NMR spectrum of 1, the carbonyl carbon appeared at 171.3, olefinic carbons appeared at 130.9, 129.8, 129.4, 127.4 and the skipped methylene carbon resonated at 31.7 ppm. All these spectral data were identical with the sample reported earlier.[15]

Synthesis of (4E,7Z,10Z)-4,7,10-tridecatrienyl acetate (2) (Scheme 9)

To synthesise the pheromone 2, attention was focussed on alkylation of 26, by using 1-bromopent-2-yne to obtain 5,8-undecadiyn-1-en-3-ol (31). The alkylation of 26 with 1-bromopent-2-yne in the presence of lithium amide in liquid ammonia could not give 31 in satisfactory yield. However, when 26 was reacted with two equivalents of ethylmagnesium bromide, followed by reaction with 1-bromopent-2-yne containing catalytic amount of cuprous chloride, yielded 5,8-undecadiyn-1-en-3-ol (31) in 60% yield. The IR spectrum of 31 showed the absorption at 3400 cm^{-1} indicating the presence of hydroxyl group and absorption at 2000 cm^{-1} suggested the presence of acetylenic moieties in the molecule. The PMR spectrum confirmed the structure of 31. Absence of triplet at δ 2.05 ruled out the possibility of the free acetylenic proton. The neat triplet at

SCHEME 9


H
OH
26
Br
EtMgBr, CuCl
THF
31
H
OH
OEt
H3C - C
OEt
OEt
CH3CH2CO2H
32
CO2Et
H2, Pd/CaCO3
quinoline
33
CO2Et
LAH
34
OH
Ac2O
Py
2
OAc

1.08 ppm proved the presence of terminal methyl group and multiplet at δ3 to 3.16 indicated the presence of skipped methylene protons (H_a-7,H_b-7). Remaining protons resonated at their respective chemical shifts (Fig.3).

When 31 and triethyl orthoacetate were heated under reflux in the presence of catalytic amount of propionic acid a Claisen rearrangement occurred to afford 32 as a single geometric isomer, confirmed by TLC and GLC analysis. The product was characterised as ethyl-7,10-tridecadiyn-4-(E)-enoate (32). This trans geometry was assigned on the basis of ample precedent. In addition, the given structure was suggested by IR spectrum in which the presence of a strong absorption at 960 cm^{-1} (for trans double bond) and absence of absorption in the region of 695-735 cm^{-1} (cis double bond) were revealed. The structure of 32 was further supported by PMR which showed the quartet at 4.08 ppm corresponding to methylene protons of ethyl ester groups. Signals due to skipped methylene protons (H_a-6,H_b-6) appeared between 2.76-2.96 ppm and the other pair of skipped methylene protons (H_a-9,H_b-9) appeared between 3-3.2 ppm. Remainging protons resonated in accordance with the expected chemical shifts (Fig.4).

The acetylenic bonds present in 32 were partially hydrogenated over Lindlar catalyst at atmospheric pressure to obtain ethyl-(4E,7Z,10Z)-tridecatrienoate (33). IR spectrum of 33 revealed absorption at 1745 cm^{-1} (carbonyl

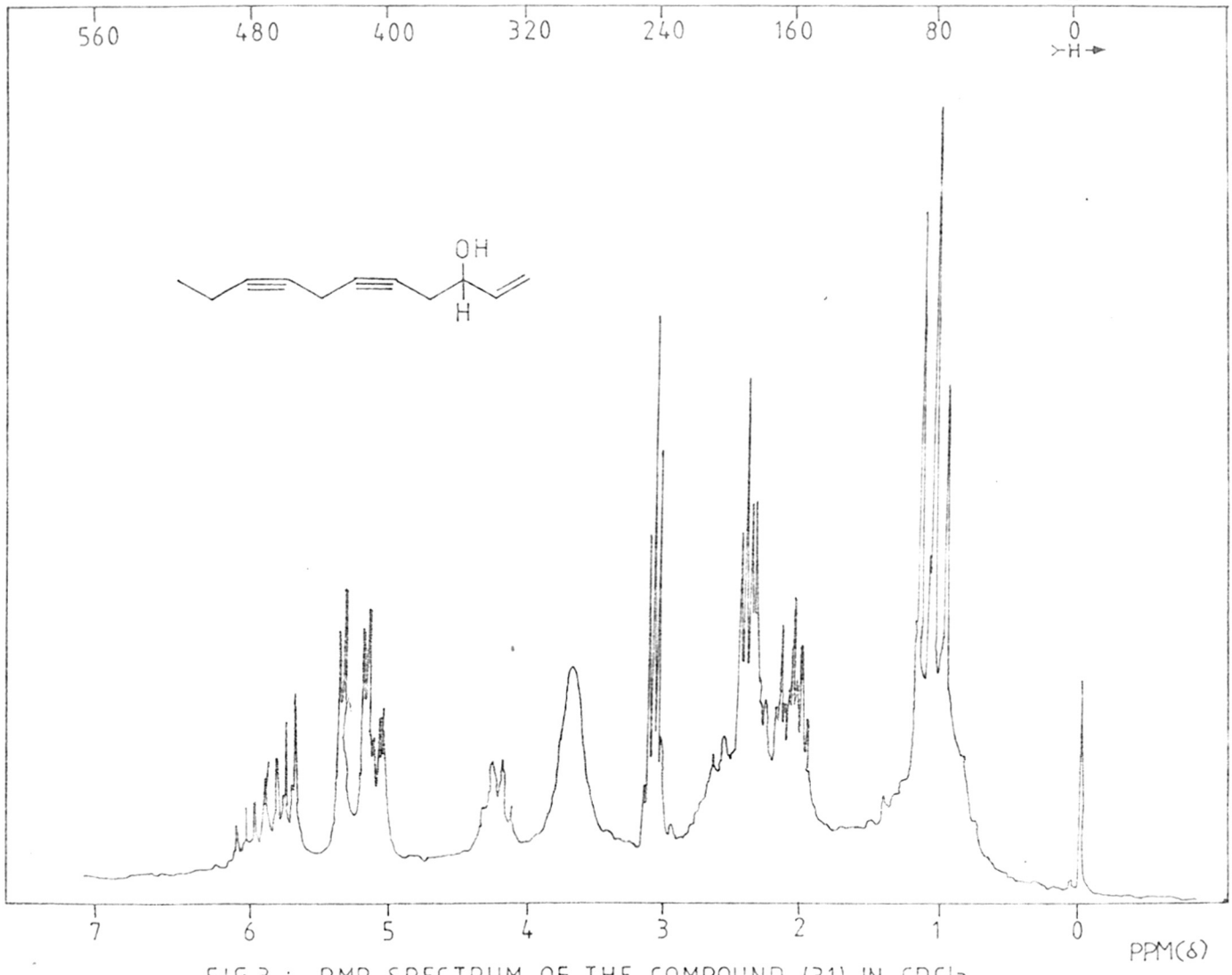


FIG.3 : PMR SPECTRUM OF THE COMPOUND (31) IN $CDCl_3$

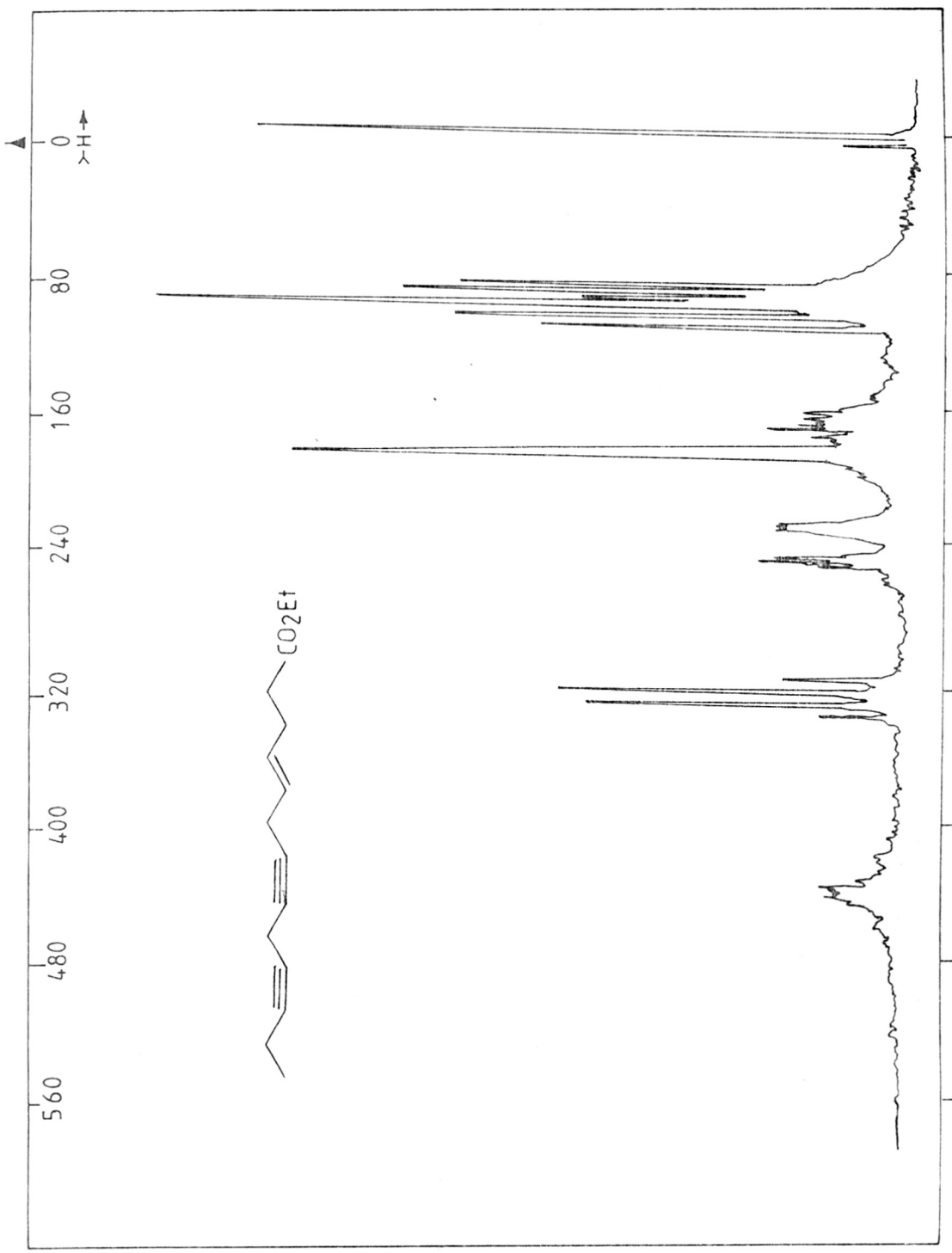


FIG.4: PMR SPECTRUM OF THE COMPOUND (32) IN $CDCl_3$

group), 980 cm^{-1} (trans double bond), 730 cm^{-1} (cis double bond). In addition, the given structure was suggested by PMR spectrum in which six olefinic protons resonated as a multiplet at δ 5.12 - 5.6 and all the four skipped methylene protons (H_a-6,H_b-6,H_a-9,H_b-9) appeared as multiplet at δ 2.52-2.88 (Fig. 5)

The compound 33 on treatment with lithium aluminium-hydride in ether at room temperature yielded the alcohol (4E,7Z,10Z)-4,7,10-tridecatrien-1-ol (34). The IR spectrum showed strong absorption at 3480 cm^{-1} (hydroxyl group). Absorption corresponding to ester group was absent. The PMR spectrum showed the triplet at δ 3.7 for the protons H_a-1,H_b-1. Remaining protons resonated in accordance with the expected chemical shifts.

(4E,7Z,10Z)-4,7,10-tridecatrien-1-ol (34) was acetylated by conventional procedure to furnish the desired pheromone (4E,7Z,10Z)4,7,10-tridecatrienyl acetate (2) in 90% yield. Its IR spectrum showed absorption at 1745 cm^{-1} (carbonyl) 965 cm^{-1} (trans double bond), 730 cm^{-1} (cis double bond). In the PMR spectrum (Fig. 6) of 2 the six olefinic protons resonated in the region of δ 5.12 - 5.44 as a multiplet. The methyl protons of acetyl group appeared as a singlet at 2.08 ppm and the remaining protons resonated at the expected chemical shifts. All these values were identical with the values reported for the natural product.[11]

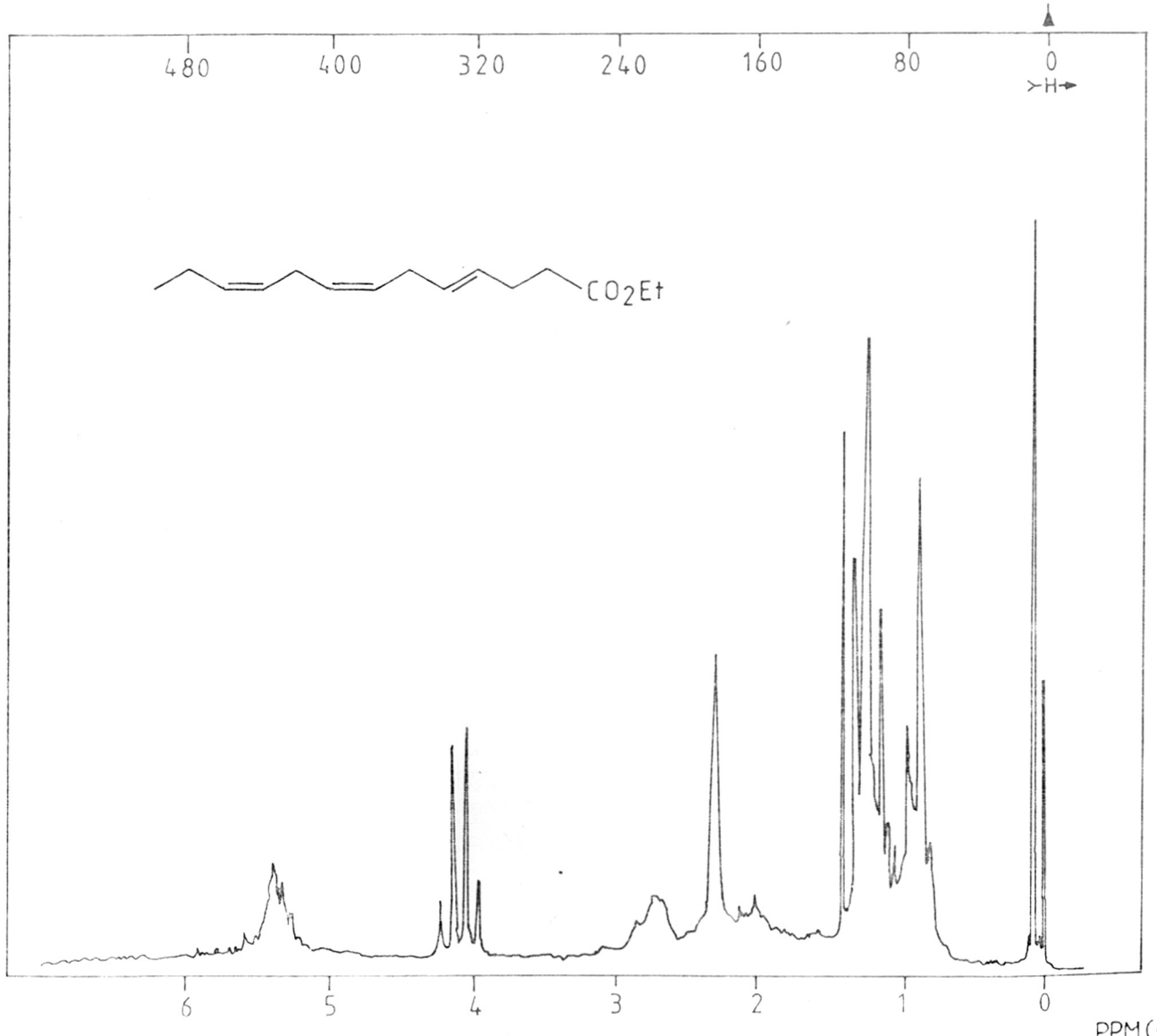


FIG.5 : PMR SPECTRUM OF THE COMPOUND (33) IN $CDCl_3$

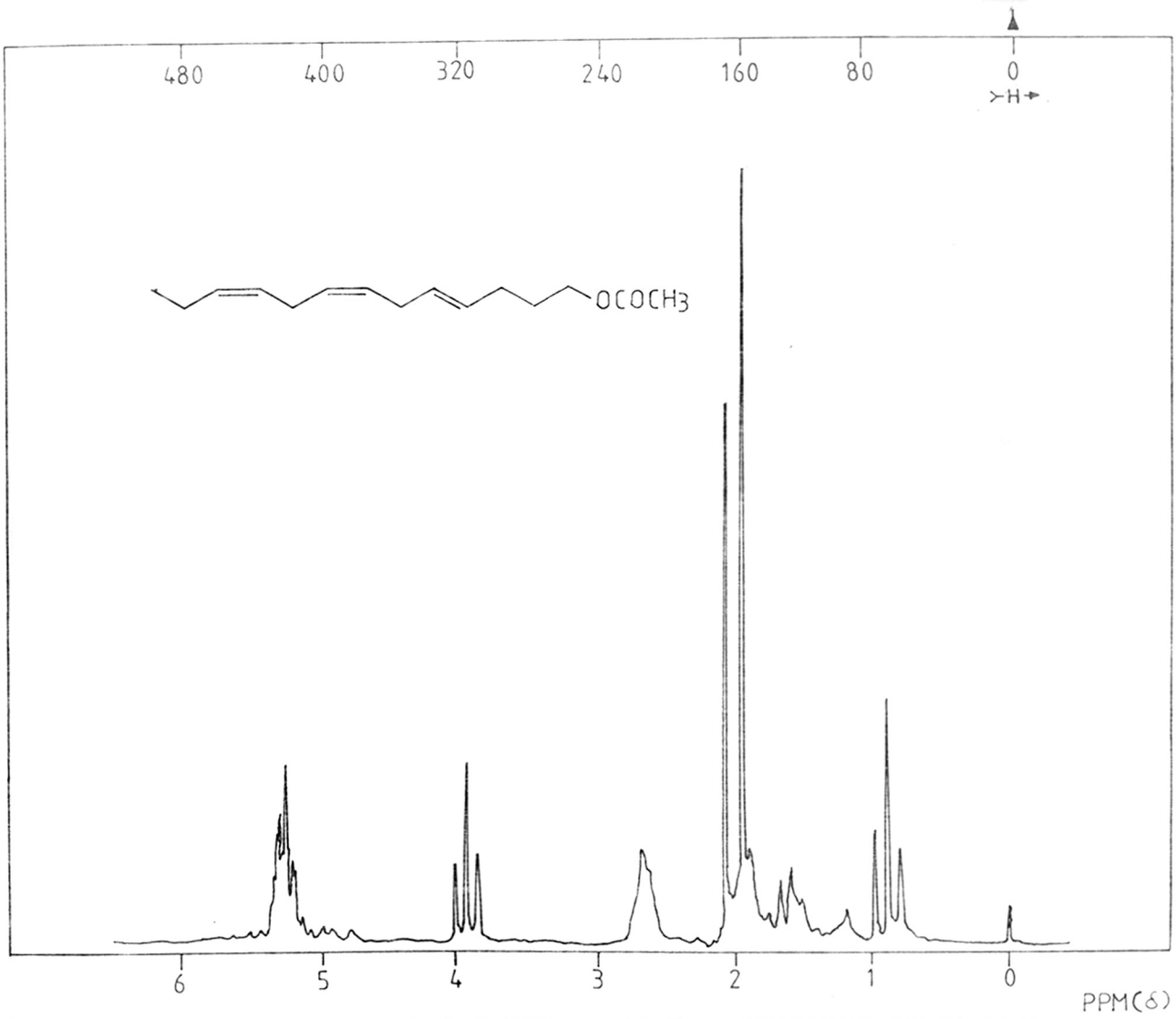


FIG.6: PMR SPECTRUM OF THE COMPOUND (2) IN $CDCl_3$

Apart from the fact that the intermediate 26 is bifunctional for elaboration at both ends of the molecule, it also appears to be an attractive intermediate for the synthesis of a variety of unsaturated fatty acids possessing skipped diene systems. Work in this regard is being pursued in our laboratory to produce them in order to understand their metabolism processes in the biological system.

EXPERIMENTAL

1-Hexen-5-yn-3-ol (26)

To a mixture of aluminium (2.25 g, 0.083 gatoms), mercuric chloride (0.1 g) in tetrahydrofuran (50 ml) was added 3-bromoprop-1-yne (15 g, 126 mmol) at 5° and the reaction mixture was heated at 50° for 30 min. Then acrolein (4.65 g, 83 mmol) was added dropwise to the reaction mixture at 0° and heated at 50° for 2 hr. It was cooled to room temperature and poured in dilute sulfuric acid. Aqueous layer was extracted with ether. All the combined ether extracts were washed with sodium bicarbonate solution, water, brine and dried over anhydrous sodium sulfate. Solvent was removed carefully and the residue was distilled under reduced pressure to afford 26 (7.26 g) in 60% yield, b.p. 75° / 40 mm (lit.[16] 49°/ 12 mm); IR (neat): 3350 cm^{-1} (OH), 3250 cm^{-1} (H-C≡C), 2100 (C≡C). PMR ($CDCl_3$): δ 2.05 (t, J = 3Hz, 1H, H-6), 2.5 (d, J = 3Hz, 2H, H_a-4, H_b-4), 3.7 (bs, 1H, OH exchanges with D_2O), 4.13-4.42 (m, 1H, H-3), 5.05-5.42 (m, 2H, H_a-1, H_b-1), 5.7-6.1 (m, 1H, H-2).

1-Undecen-5-yn-3-ol (27)

To a freshly prepared suspension of lithium amide [prepared from 1.1 g (0.157 gatoms) of lithium and liquid ammonia (150 ml)] in liquid ammonia (250 ml) was added 26

(6.0 g, 63 mmol) in 10 min. After 2 hr 1-bromopentane (9.44 g, 63 mmol) in tetrahydrofuran (20 ml) was added dropwise to the reaction mixture. After 0.5 hr ammonia was evaporated and the residue was treated with ammonium chloride solution. Aqueous layer was extracted with ether and the combined extract dried over anhydrous sodium sulfate. Solvent was removed and the residue was purified by column chromatography to afford 27 (7.2 g, 70% yield). IR (neat): 3340 cm^{-1} (OH). PMR ($CDCl_3$): δ 0.9 (distorted t, 3H, CH_3), 1.25-1.48 (m, 6H, $3XCH_2$), 2.0-2.26 (m, 2H, H_a-7, H_b-7), 2.5 (d, J = 3Hz, 2H, H_a-4, H_b-4), 4.07-4.34 (m, 2H, H-3 and OH), 5.0-5.5 (m, 2H, H_a-1, H_b-1), 5.7-6.1 (m, 1H, H-2). Mass: 166(M^+), 109, 95 (100%), 57.

Ethyl (4E)-tridecene-7-ynoate (28)

A mixture of 27 (4.98 g, 30 mmol), propionic acid (10 mmol) and triethylorthoacetate (34.1 g, 210 mmol) was heated at 138° for 2 hr with distillative removal of ethanol. The solution was poured into 100 ml of ether. The ether was separated and washed with sodium bicarbonate, water, brine and dried over anhydrous sodium sulfate. The excess triethylorthoacetate removed at 50 mm and the crude product was purified by column chromatography to afford pure 28 (4.58g) in 65% yield. IR (neat) 1730 cm^{-1} (carbonyl),

980 cm^{-1} (trans double bond). PMR ($CDCl_3$): δ 0.9 (distorted t, 3H, CH_3), 1.28 (t, J = 6Hz, 3H, $OCH_2\underline{CH_3}$), 1.33-1.51 (m, 6H, $3XCH_2$), 2.04-2.22 (m, 2H, H_a-2, H_b-2), 2.26-2.4 (m, 4H, H_a-3, H_b-3 and H_a-9, H_b-9), 2.8-2.94 (m, 2H, H_a-6, H_b-6), 4.13 (q, J = 6Hz, 2H, $O\underline{CH_2}CH_3$), 5.44-5.66 (m, 2H, olefinic); Mass: 236(M^+), 191, 179 (100%), 163. Analysis: Calculated for $C_{15}H_{24}O_2$; C, 76.27 ; H, 10.16 ; Found: C, 76.4 ; H, 10.31%.

Ethyl (4E,7Z)-4,7-tridecadienoate (29)

Compound 28 (3.6 g, 15 mmol) was partially hydrogenated over Pd-$CaCO_3$ (200 mg) in hexane (25 ml) containing one drop of quinoline at atmospheric pressure. Usual work up afforded 29 (2.9 g) in 80% yield. IR (neat); 1730 cm^{-1} (carbonyl), 960 cm^{-1} (trans double bond), 735 cm^{-1} (cis double bond), PMR ($CDCl_3$): δ 0.85 (distorted t, 3H, CH_3), 1.03-1.3 (m, 9H, $3XCH_2$ and $OCH_2\ \underline{CH_3}$), 1.8-2.04 (m, 2H, H_a-2, H_b-2), 2.13-2.28 (m, 4H, H_a-3, H_b-3 and H_a-9, H_b-9), 2.48-2.71 (m, 2H, H_a-6, H_b-6), 4.02 (q, J = 6Hz, 2H, $O\underline{CH_2}CH_3$), 5.08-5.36 (m, 4H, olefinic).

(4E,7Z)-4,7-tridecadien-1-ol (30)

To a cooled suspension of lithium aluminiumhydride (0.418 g, 11 mmol) in ether (10 ml) was added compound 29 (2.75 g, 11 mmol) in ether (25 ml). After 2 hr water

(0.5 ml), sodium hydroxide (10%, 0.5 ml) and water (1.5 ml) were added in succession. Ether was separated and washed with brine and dried over anhydrous sodium sulfate. Solvent was removed to afford pure 30 (2.25 g, 99%). IR (neat): 3320 cm^{-1} (OH), 965 cm^{-1} (trans double bond), 730 cm^{-1} (cis double bond). PMR ($CDCl_3$): δ0.95 (distorted t, 3H, CH_3), 1.1-1.54 (m, 8H, $4XCH_2$), 1.62-1.84 (m, 4H, H_a3, H_b-3 and H_a-9, H_b-9), 2.1 (bs, 1H, OH, D_2O exchangeable), 2.5-2.9 (m, 2H, H_a-6, H_b-6), 3.65 (t, J = 6Hz, 2H, H_a-1, H_b-1), 5.2-5.5 (m, 4H, olefinic).

(4E,7Z)-4,7-tridecadienyl acetate (1)

Alcohol 30 (1.96 g, 10 mmol), pyridine (2 ml) and acetic anhydride (3 ml) were stirred at room temperature during 12 hr. Usual work up afforded 1 (2.142 g) in 90% yield; b.p.112° / 1 mm (lit.[15] 93° / 0.05 mm). IR (neat): 1745 cm^{-1} (carbonyl), 960 cm^{-1} (trans double bond), 735 cm^{-1} (cis double bond). PMR ($CDCl_3$): δ 0.9 (distorted t, 3H, CH_3), 1.15-1.64 (m, 8H, $4XCH_2$), 1.55-1.77 (m, 4H, H_a-3, H_b-3 and H_a-9, H_b-9), 2.02 (s, 3H, $\underset{O}{C}$-CH_3), 2.66-2.8 (m, 2H, H_a-6, H_b-6), 4.05 (t, J = 6Hz, 2H, H_a-2, H_b-2), 5.17-5.44 (m, 4H, olefinic). ^{13}C NMR ($CDCl_3$/TMS) PPM 171.3, 130.4, 129.8, 129.4, 127.4, 64.2, 31.7, 30.5, 29.5, 29.0, 28.6, 27.2, 22.7, 20.9, 14.1; Mass: 238(M^+), 180, 152, 125, 96, 88. Analysis: Calculated for $C_{15}H_{26}O_2$: C, 75.63; H, 10.96; Found: C, 75.47; H, 10.89%.

5,8-Undecadiyn-1-en-3-ol (31)

To a freshly prepared ethyl magnesium bromide (12 g,90 mmol) in tetrahydrofuran (25 ml) was added 1-hexen -5-yn-3-ol (26) (4.32 g, 45 mmol) in tetrahydrofuran (25 ml) at room temperature. After stirring for 0.5 hr cuprous chloride (catalytic amount) was added and stirred for another 0.5 hr. To the yellow coloured solution,1-bromopent-2-yne (2.2 g, 15 mmol) in tetrahydrofuran (10 ml) was added dropwise at room temperature. Reaction mixture was stirred at 50° for 8 hr, cooled to 0° and treated with saturated ammonium chloride solution. Aqueous layer was extracted with ether. The combined ether extract was dried over anhydrous sodium sulfate. Solvent was removed and the crude product was purified by column chromatography to obtain 31 (1.45 g) in 60% yield (based on 1-bromopent-2-yne). IR (neat): 3400 cm^{-1} (OH), 2080 cm^{-1} (C≡C). PMR ($CDCl_3$): δ 1.08 (t, J = 6Hz, 3H, CH_3), 1.96-2.16 (m, 2H, H_a-10, H_b-10), 2.28-2.52 (m, 2H, H_a-4, H_b-4), 3-3.6 (m, 2H, H_a-7, H_b-7), 3.64 (bs,1H,OH,D_2O exchangeable), 4.04-4.36 (m, 1H, H-3), 5.0-5.44 (m, 2H, H_a-1, H_b-1), 5.68-6.08 (m, 1H, H-2).

Ethyl-7,10-tridecadiyn-4(E)-enoate (32)

A solution of 31 (1.0 g, 6 mmol), propionic acid (1 mmol) and triethylorthoacetate (6.9 g, 41 mmol) was heated at 138° for 2 hr with distillative removal of

ethanol. The solution was poured into 100 ml of ether and the organic layer was washed with sodium bicarbonate solution, water, brine and dried over anhydrous sodium sulfate. Solvent was removed and the excess triethyl-orthoacetate was removed at 50 mm . The crude product was purified by column chromatography to afford 32 (0.91 g) in 63% yield. IR (neat): 1740 cm^{-1} (carbonyl), 960 cm^{-1} (trans double bond). PMR ($CDCl_3$): δ 1.1 (distorted t, 3H, CH_3), 1.24-1.48 (distorted t, 3H, OCH_2-$\underline{CH_3}$), 1.96-2.16 (m, 4H, H_a-3, H_b-3 and H_a-12, H_b-12), 2.36-2.52 (m, 2H, H_a-2, H_b-2), 2.76-2.96 (m, 2H, H_a-6, H_b-6), 3-3.2 (m, 2H, H_a-9, H_b-9), 4.08 (q, J = 6Hz, 2H, $O\underline{CH_2}CH_3$), 5.36-5.72 (m, 2H, olefinic). Mass: 232(M^+), 129, 115, 91 (100%). Analysis: Calculated for $C_{15}H_{20}O_2$: C, 77.58; H, 8.6; Found: C, 77.42; H, 8.5%.

Ethyl-(4E,7Z,10Z)-4,7,10-tridecatrienoate (33)

Compound 32 (0.5 g, 2 mmol) was partially hydrogenated over Lindlar catalyst (0.1 g) in hexane (8 ml) containing one drop of quinoline at atmospheric pressure. Usual work up afforded 33 (0.43 g) in 86% yield. IR (neat): 1745 cm^{-1} (carbonyl), 980 cm^{-1} (trans double bond), 760 cm^{-1} (cis double bond). PMR ($CDCl_3$): δ 0.96 (distorted t, 3H, CH_3), 1.32 (t, J = 7.5 Hz, 3H, $OCH_2\underline{CH_3}$), 1.88-2.12 (m, 4H, H_a-3, H_b-3 and H_a-12, H_b-12), 2.16-2.41 (m, 2H, H_a-2, H_b-2), 2.52-2.88 (m, 4H, H_a-6, H_b-6 and H_a-9, H_b-9), 4.08

(q, J = 7.5Hz, 2H, OCH_2CH_3), 5.12-5.6 (m, 6H, olefinic). Mass: 236(M^+).

(4E,7Z,10Z)-4,7,10-Tridecatrien-1-ol (34)

To a cooled suspension of lithium aluminiumhydride (0.05 g, 1.3 mmol) in tetrahydrofuran (3 ml) was added 33 (0.3 g, 1.3 mmol) in tetrahydrofuran (5 ml). After 1 hr the reaction mixture was treated with 0.5 ml of water, 0.5 ml of 10% sodium hydroxide and 1.5 ml of water. The material was extracted with ether. The combined organic layers were washed with brine and dried over anhydrous sodium sulphate. Solvent was removed to afford 34 (0.225 g) in 91% yield. IR (neat): 3480 cm^{-1} (OH), 955 cm^{-1} (trans double bond), 770 cm^{-1} (cis double bond). PMR ($CDCl_3$): δ0.9 (distorted t, 3H, CH_3), 1.24-1.96 (m, 2H, H_a-2, H_b-2), 2.0-2.36 (m, 4H, H_a-3, H_b-3 and H_a-12, H_b-12), 2.72-2.9 (m, 4H, H_a-6, H_b-6 and H_a-9, H_b-9), 3.7 (t,J=6H_z,2H,H_a-1,H_b-1) 5.16-5.72 (m, 6H, olefinic).

(4E,7Z,10Z)-4,7,10-Tridecatrienyl acetate (2)

A mixture of alcohol 34 (0.12 g, 0.6 mmol), pyridine (0.5 ml) and acetic anhydride (0.5 ml) was stirred at room temperature during 12 hr. Usual work up and purification of the crude product through column chromatography afforded 2 (0.131 g) in 90% yield. IR (neat) 1745 cm^{-1} (carbonyl), 965 cm^{-1} (trans double bond), 760 cm^{-1} (cis double bond).

PMR ($CDCl_3$): δ 0.85 (t, J = 7.5Hz, 3H, CH_3), 1.41-1.68 (m, 2H, H_a-2, H_b-2), 1.72-2.0 (m, 4H, H_a-3, H_b-3 and H_a-12, H_b-12), 2.08 (s, 3H, $OCOCH_3$), 2.51-2.8 (m, 4H, H_a-6, H_b-6 and H_a-9, H_b-9), 3.9 (t, J = 6Hz, 2H, H_a-1, H_b-1), 5.12-5.44 (m, 6H, olefinic). Mass: 236(M^+). Analysis: Calculated for $C_{15}H_{24}O_2$: C, 76.27; H, 10.17; Found: C, 76.1; H, 10%.

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