THE TOTAL SYNTHESIS

OF

4-DEMETHOXY-10-NORDAUNOMYCIN

A Thesis

Submitted to the Faculty of Graduate Studies in

Partial fulfillment of the Requirements for the Degree

of Doctor of Philosophy

by

PATRICK M. GORDON

Department of Chemistry

University of Manitoba

CANADA

SEPTEMBER 1987

ISBN 0-315-44143-7

THE TOTAL SYNTHESIS OF 4-DEMETHOXY-10-NORDAUNOMYCIN

BY

PATRICK M. GORDON

A thesis submitted to the Faculty of Graduate Studies of the University of Manitoba in partial fulfillment of the requirements of the degree of

DOCTOR OF PHILOSOPHY

****

ONE MAY EDUCATE ONESELF, RECEIVE MANY ACCOLADES AND REACH UNIMAGINABLE HEIGHTS. BUT MEMORIES, I BELIEVE, REMAIN OUR MOST TANGIBLE AND PRECIOUS TREASURES. I HAVE MANY, MANY PLEASANT MEMORIES OF MY **MOTHER, MARY G,** WHOSE ALTRUISM WAS LIMITLESS AND I DARE SAY NOT EASY TO EMULATE. WITHOUT HER PARENTING, MY LIFE WOULD NOT HAVE BEEN AS RICH AS IT IS. IT IS WITH HUMILITY, THEREFORE, **I DEDICATE THIS THESIS IN HER MEMORY.**

****

ACKNOWLEDGMENTS

During the five years of my research, there were many people who gave me their time, co-operation, and confidence. Therefore, I would be less than grateful if I didn't acknowledge the contributions of those people who were truly instrumental in making the objective of this work a reality.

I would first like to extend my gratitude to Mr. Wayne Buchannon for recording the mass spectra for me. My sincere thanks goes to Mr. Kirk Marat and Mr. Terry Wolowiec for not only recording numerous NMR spectra, but also for doing so expeditiously at times. I would also like to thank my co-workers for their co-operation, over the years. Their friendship is also treasured. I would like to thank Dr. Francis Jay and Dr. Peter Lam for conducting the biological testing on the synthetic drugs.

My appreciation extends to the many friends and fellow graduate students who have made my stay here an enjoyable one. However, it would be remiss of me if I did not mention the names of some of the people who were extremely helpful to me in many ways. The Cupids, Pastor Linquist and family, Mrs. P. Peet, Violet and Rose White and Dr. L Morton. The financial sacrifices and encouragement of my parents made it possible for me to reach this far and I am, forever, indebted to them. The constant support of my family and relatives is greatly acknowledged, especially my brothers Ronald and Mervyn. More importantly, the

unending love and support of my wife Hermayne, during this period, will always be treasured. It is also pleasing to acknowledge her help in typing and collating the manuscript.

My sons, Paul and Peter, were not only a joy to come home to after leaving the laboratory but were also, unknowingly, very accommodating by allowing me to maintain my work schedule after they were born. For that I will always be grateful.

Without the help of Mr. Francois Lafortune in computer drawing the diagrams and transforming them to the final form, this thesis could not have been submitted for examination at the time it was. In addition, the instruction on the "cut and paste" method was invaluable. I will always be indebted to him. His friendship is also treasured and his hospitality appreciated.

The guidance of my advisory and examining committee through out this project, Drs. N. R. Hunter, D. M. McKinnon, J. F. Templeton is appreciated. In particular, the editorial comments, with regard to the manuscript, are greatly appreciated. I would also like to thank my external examiner Dr. Gary Flynn, of Merrell Dow Pharmaceuticals, for not only his editorial suggestions but also for taking the time to be present for the oral examination.

Last, but not least, it gives me great pleasure to acknowledge the supervision of my advisor, Dr. C. M. Wong. His guidance, suggestions and the freedom and independence to develop my own synthetic

manipulations are all greatly appreciated. The freedom to engage in extra curricula activities, which entailed spending crucial days, at times, away from the lab, is also appreciated.

ABSTRACT

The discovery of the antitumour properties of the anthracycline antibiotics and their subsequent successful clinical application has stimulated much interest in this area of research. The study of the nature of their cardiotoxicity and structure-activity relationships remains one of the most active areas of research into chemotherapy.

The challenge can be met, at least partially, by a new molecular structure, which exhibits a greater therapeutic efficacy against a broader neoplastic syndrome and is much less toxic than the first generation anthracyclines, daunomycin and adriamycin, which are currently in use. To that end, the synthesis of **4-demethoxy-10-nordaunomycin** was undertaken.

Nucleophilic addition of **ethynylmagnesium bromide** to **4,7-dimethoxy-1-indanone**, 3*, followed by **mercuric acetate** oxidation and **iron pentacarbonyl/tri-n-butyltin hydride** reduction gave **4,7-dimethoxy-1-acetylindane**, 19. Condensation of this product (19) with **phthalic anhydride** followed by methylation with **dimethyl sulphate** and oxidation, under strongly basic conditions, gave the diol, **6,10-di-O-methyl-4-demethoxy-10-nordaunomycinone**, 24. Epimerisation was achieved by preparing the **trifluoroacetate** of 24 (**trifluoroacetic acid/trifluoroacetic anhydride**) followed by the addition of water and aqueous sodium carbonate to give **6,10-di-O-methyl-4-demethoxy-7-epi-10-nordaunomycinone**, 25. Demethylation of the two stereoisomers 24 and 25 with **aluminium chloride** produced the aglycones, **4-demethoxy-10-nordaunomycinone**, 27 and **4-demethoxy-7-epi-10-nordaunomycinone**, 28.

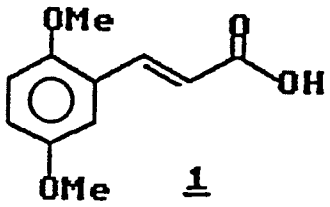
Coupling of these two aglycones with **2,3,6-trideoxy-1,4-di-O-p-nitrobenzoyl-3-trifluoroacetamido-alpha-L-lyxohexopyranose**, 30, with **silver trifluoromethanesulphonate** gave the protected glycosides 31 and 32 of **racemic** 27 and 28. Of the **four** possible diastereoisomers of 31 and 32 , two major compounds (31 A and 31 , 32 B and 32 C) in each series were isolated and characterised by ^{1}H NMR spectroscopy. From the multiplicity and shape of the glycosidic hydrogen, it was judged that both the alpha and beta glycosides were formed.

These compounds were deprotected in basic methanol to give the title compound **4-demethoxy-10-nordaunomycin**, its **C7 epimer**, **4-demethoxy-7-epi-10-nordaunomycin and the glycosidic epimers.** Preliminary biological testing results indicated that the glycosides corresponding to 31 were active against lung carcinoma with the alpha glycoside diastereoisomer being the more active of the two, in agreement with previous findings that the alpha glycoside is more active than its beta epimer. Quantitatively, daunomycin is about 60 times more active than the alpha glycoside of 31. The glycosides corresponding to 32 were completely inactive.

The results presented here represent the first total synthesis of a new class of antitumour compounds and it is envisaged that, with larger quantities available, a better insight into the structure activity relationships of these anthracyclines will be gleaned.

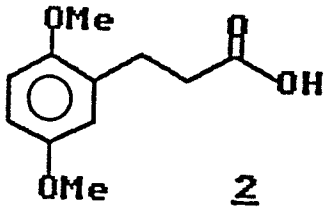
*The numbers here refer to the compound numbers in the **Results and Discussion and Experimental sections only.**

COMPOUND LIST WITH NAMES FOR THE RESULTS AND DISCUSSION AND EXPERIMENTAL SECTIONS



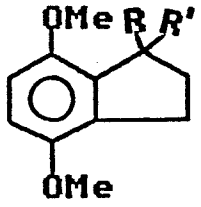
1

3-(2,5-dimethoxyphenyl)-propenoic acid.



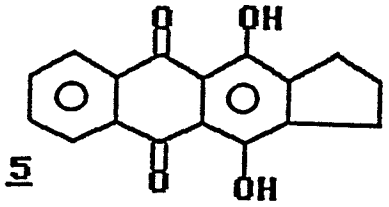
2

3-(2,5-dimethoxyphenyl)-propanoic acid.



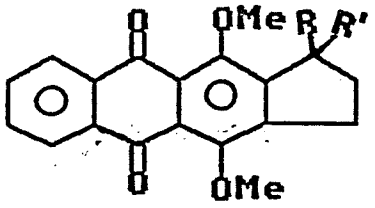
R=R'=O: 4,7-Dimethoxyindanone. 3

R=R'=H_2: 4,7-Dimethoxyindane. 4



5

4,11-Dihydroxycyclopenta[b]anthracene-5,10-dione.

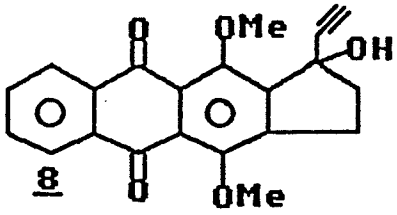


R=R'=H_2:

4,11-Dimethoxycyclopenta[b]anthracene-5,10-dione. 6

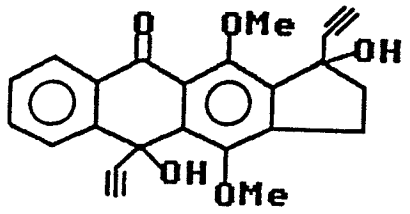
R=R'=O:

4,11-Dimethoxycyclopenta[b]anthracene-1,5,10-trione. 7



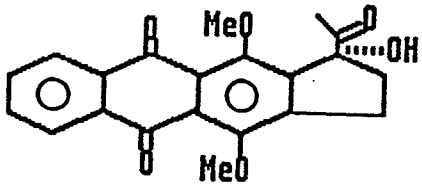
8

1-Hydroxy-1-ethynyl-4,11-dimethoxycyclopenta[b]anthracene-5,10-dione.



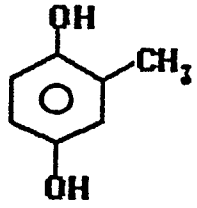
8A

1,5-Dihydroxy-1,5-diethynyl-4,11-dimethoxycyclopenta[b]anthracene-10-one.



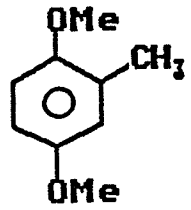
9

1-Acetyl-1-hydroxy-4,11-dimethoxycyclopenta[b]anthracene-5,10-dione.



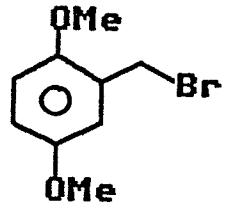
10

1-Methyl-2,5-dihydroxybenzene.



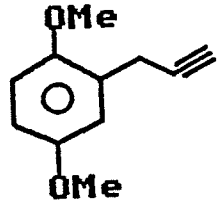
11

2,5-dimethoxytoluene.



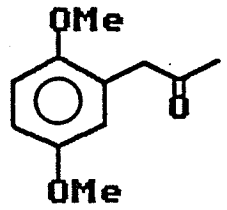
12

2,5-Dimethoxybenzyl bromide.



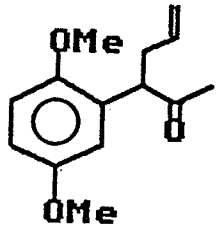
13

3-(2,5-Dimethoxyphenyl)-1-propyne.



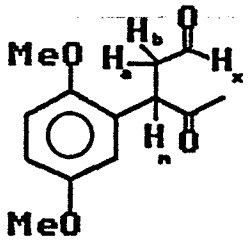
14

3-(2,5-Dimethoxyphenyl)-2-propanone.



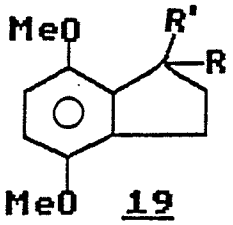
15

3-(2,5-Dimethoxyphenyl)-hex-5-ene-2-one.



16

3-(2,5-Dimethoxyphenyl)4-oxo-pentanal.



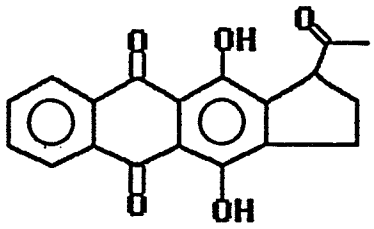
19

R=Ac, R'=H: 1-Acetyl-4,7-dimethoxyindane.

R=Ac, R'=OAc: 1-Acetyl-1-acetoxy-4,7-dimethoxyindane.

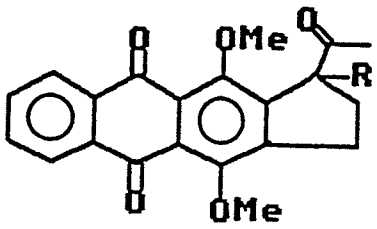
R=Et, R'=H: 1-Ethyl-4,7-dimethoxyindane.

R=-CHOH-CH_3, R'=H: 1-(1-Hydroxyethyl)-4,7-dimethoxyindane.



20

1-Acetyl-4,11-dihydroxycyclopenta[b]anthracene-5,10-dione.

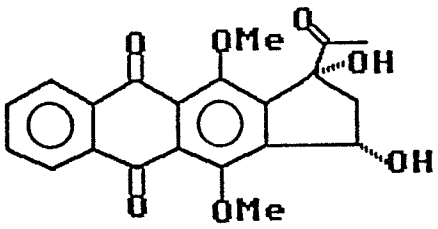


R=H:

1-Acetyl-4,11-dimethoxycyclopenta[b]anthracene-5,10-dione. **21**

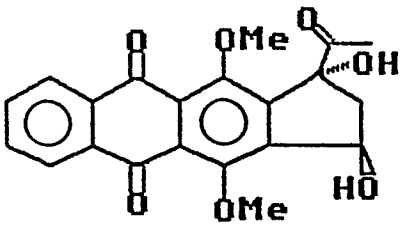
R=Me: **22**

1-Acetyl-1-methyl-4,11-dimethoxycyclopenta[b]anthracene-5,10-dione.



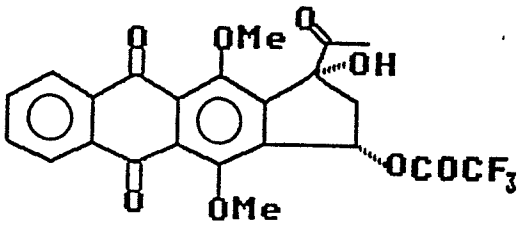
24

cis-6,11-Di-O-methyl-4-demethoxy-10-nordaunomycinone.

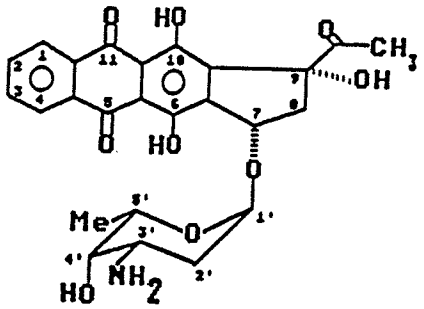


25

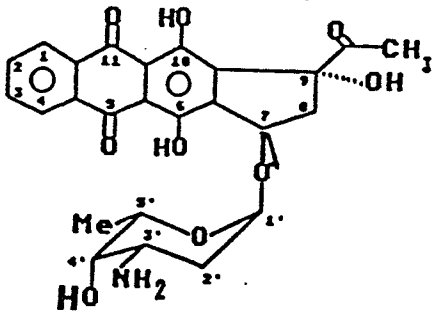
trans-6,11-Di-O-methyl-4-demethoxy-7-epi-10-nordaunomycinone.



cis-6,11-Di-O-methyl-4-demethoxy-7-O-trifluoroacetyl-10-nordaunomycinone. **26**



4-Demethoxy-10-nordaunomycin. **31**



4-Demethoxy-7-epi-10-nordaunomycin. **32**

TABLE OF CONTENTS

LIST OF FIGURES

INTRODUCTION

LIST OF FIGURES (cont'd)

RESULTS AND DISCUSSION

LIST OF SCHEMES

Introduction

The Chemical Basis and Synthesis of Anthracycline Drugs

The anthracycline drugs are one type of antineoplastic agents used in cancer chemotherapy and over the last twenty years or so, the field of anthracycline chemistry has blossomed tremendously. In this chapter, it is hoped that the reader will acquire an appreciation of the chemical basis of chemotherapy and the synthetic approaches to this very important class of chemotherapeutic agents and their analogues.

Before rational approaches towards the synthesis of possible anticancer drugs are undertaken, an understanding of the cellular basis of cancer chemotherapy is obligatory (1). Therefore, a general treatment of this area will be presented.

Cancer is a disease of cells characterised by the destruction of the normal controlling influences which regulate cellular organisation in tissues. These cancer cells have acquired characteristics which allow them to possess growth advantages over normal cells. Moreover, this ability to cause cell proliferation, locally, can also be transferred to remote sites; a condition known as **metastasis.** From the knowledge of cancerous and normal cells, the following differences can be extracted with regards to the former:

1) uncontrolled cell proliferation
2) a lack of cellular differentiation features
3) the ability to invade surrounding tissue
4) the ability to metastasise.

Currently, the major approaches to cancer treatment are:

1) surgical removal of the tumour which is frequently limited, not so much by the tumour size but, by its distribution

2) radiotherapy, which depends frequently on the degree of tumour dissemination , and

3) chemotherapy (2).

The need for surgery in conjunction with therapy can be exemplified by the following: A tumour weighing approximately 100 g contains approximately 10^{11} cells. By undergoing a single course of therapy with a cytotoxic drug to the patient's tolerance limit, one may be able to kill 99.9% of the tumour cells. However, this still leaves 10^{8} living tumour cells (2) , which would soon double and eventually regenerate the 100 g tumour in a matter of weeks. The most common rationale for the use of chemotherapy is the control of the growth of tumour cell populations by cell-kill mechanism. A severe limitation to this use is the lack of discrimination of chemotherapeutic agents. Therefore, an obvious goal of cancer chemotherapists is to discover a unique biochemical feature of the cancerous target tissue which is absent in the normal tissue. That goal is even more important when one realises that since cell-kill effects are dose dependent and theoretically a large enough dose of anticancer agent could eradicate the tumour, these are cytotoxins with severe, dose-limiting (toxic) side effects for the host.

The biochemical events encompassing cell division are best described in terms of a cell cycle. In this cycle, there are two basic states; the

mitotic state in which actual cell division occurs and an **intermitotic state or interphase state.** The latter state can be further subdivided into a period called the **S** phase (synthesis of deoxyribonucleic acids (DNA)). The period between the birth of a new cell and the **S** phase is classified as the G_1 (gap 1) phase and the period after the **S** phase but before mitosis is the G_2 (gap 2) phase. There is also a G_0 phase which is a resting or non-dividing phase (Fig. 1).

In the **S** phase, DNA and ribonucleic acids (RNA) synthesis occurs; in the G_1 phase many of the necessary enzymes for DNA synthesis and macromolecules are produced and the G_2 phase is characterised by macromolecules necessary for mitosis. The significance of the cell-cycle in chemotherapy relates to the cell-kill **specificity** or **non-specificity** of the therapeutic agents. Agents termed **cell phase specific** act specifically on one of the cell phases, e.g., **S**-phase inhibiting a particular reaction crucial to the cell's survival. The **cell phase non-specific** drugs have no toxic characteristics which are related to a specific part of the cell cycle but rather on their toxic effects following the cells' exposure to the drug as they prepare for DNA replication or repair. This class includes the antitumour antibiotics, e.g., anthracyclines.

Some important consequences of cell-cycle phase non-specific drugs are: 1) there is no preferred time during which the drug will be more effective and 2) these drugs are not expected to be dependent on a particular schedule of drug dosage.

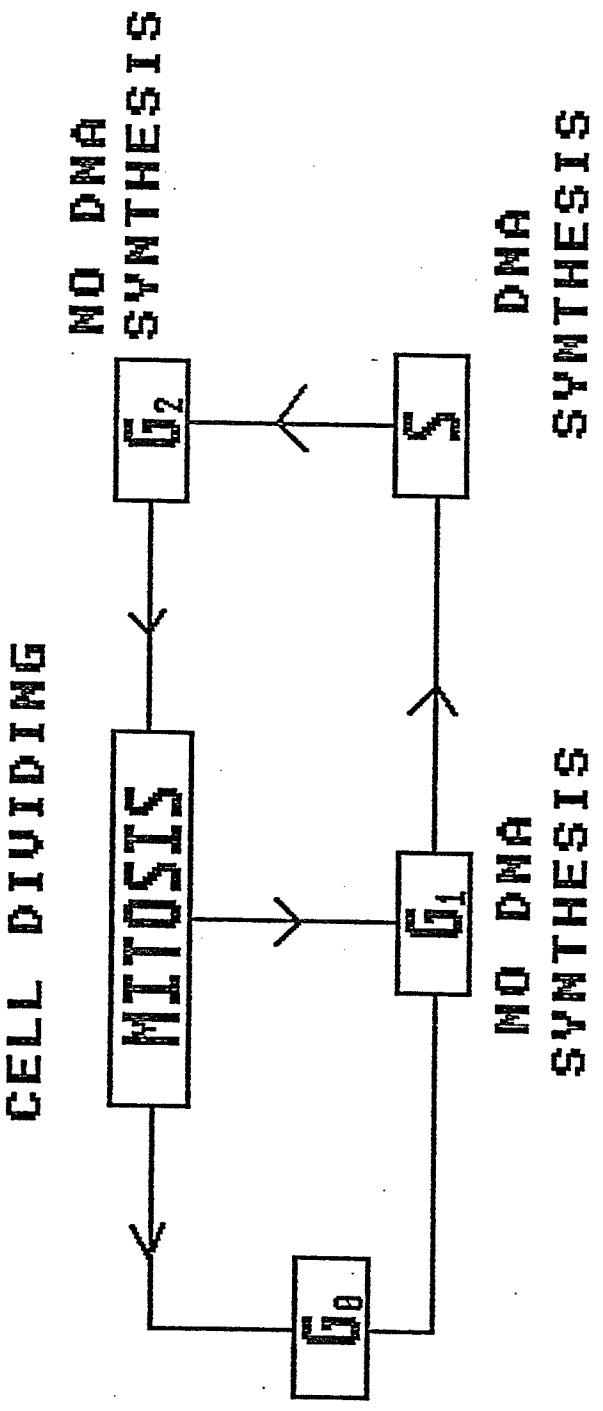
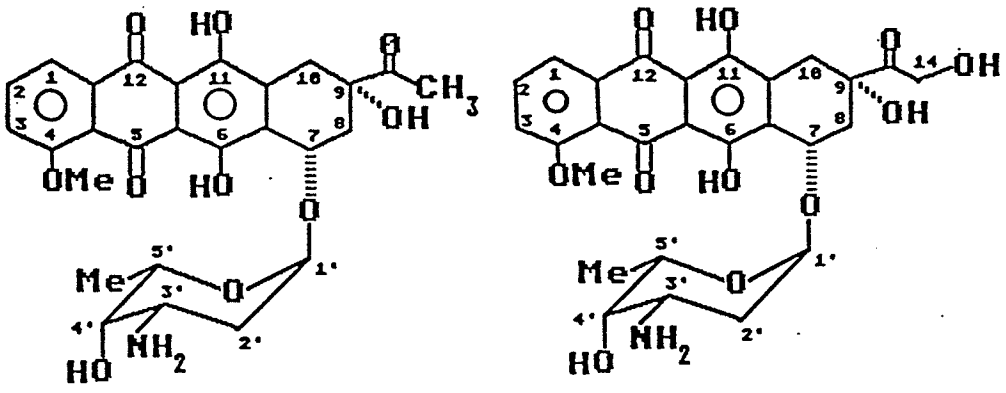

NO DNA SYNTHESIS
DNA SYMTHESIS
CELL DIVIDING
MITOSIS
NO DNA SYNTHESIS
G2
S
G1
G0

FIG. 1



Daunomycin Adriamycin

Fig. 2a

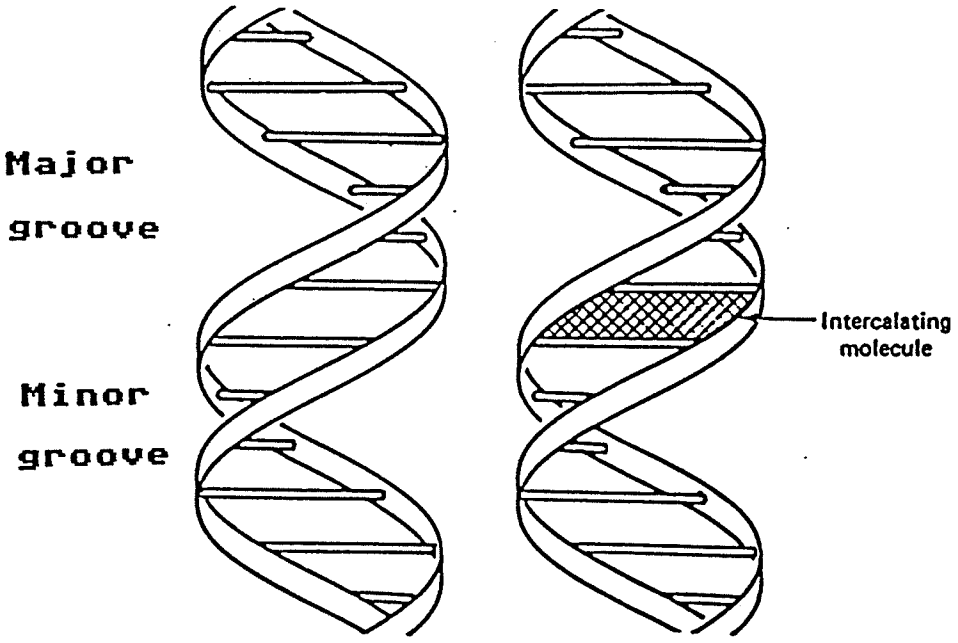


Fig. 2b

One important interaction of some antitumour agents with DNA is that of **intercalation.** This intercalation is in part responsible for the cytotoxic effect on the cell. Intercalation results from the insertion of flat polycyclic moieties between and parallel to stacked adjacent base pairs without changing the overall stacking of the bases (3). This process is characterised by the deoxyribose phosphate backbone of the helix unwinding partially to form a separation between adjacent base pairs. The intercalating agent then moves into this separation positioning itself perpendicular to the helical axis and binding above and below the base pairs by van der Waals and other non-covalent forces. Specifically, for adriamycin and daunomycin, the chromophore is inserted into the adjacent base pairs of cytosine and guanine. The chromophore is inserted head on, as opposed to edge on, intercalation with ring D entering the major groove and the sugar residue interacting with the minor groove which it nearly covers (Fig. 2, a & b).

The evidence for intercalation is based on the many changes in the properties of the DNA molecule. Owing to the unwinding, lengthening and stiffening of the helical structure, the viscosity increases, the bouyant density decreases and the denaturation temperature increases. Moreover, the intercalating molecule also undergoes changes as evidenced by inhibition of bathochromic shift on addition of base, hypochromicity and bathochromic shift in the visible region and quenching of fluorescence (4). Other indicators for the intercalation phenomenon are shifts in the NMR absorption for the base pairs and the drug, flow dichroism studies which show the plane of the drug perpendicular to the helical axis and X-ray patterns which show the DNA lengthened but not

thickened.

As a result of intercalation, the normal functions of DNA as a template are impaired and, in the absence of reversibility, cytotoxicity results. This impairment can be expressed by the inhibition of polymerases for example, daunorubicin inhibits DNA-dependent RNA polymerases from E. coli.

While the intercalation model is regarded as the principal mode through which the anthracyclines effect their toxicity, it is not the only way. The anthracyclines are known to bind to cell membranes thus changing their structure and function. The most important sites appear to be the phospholipids, cardiolipin and phosphatidylserine, and it is felt that this binding may also form the basis for both antitumour activity and cardiotoxicity (4).

Finally, upon reduction of anthracyclines, species can be produced which may be toxic or have an antitumour effect. These include, oxygen radicals and potentially alkylating drug radicals (4), (see Fig. 3).

In summary, the antitumour action and/or toxicity of anthracyclines can be grouped into three broad classes viz.,

1) effects related to complexation with DNA
2) effects related to direct membrane binding and
3) effects due to free radical formation.

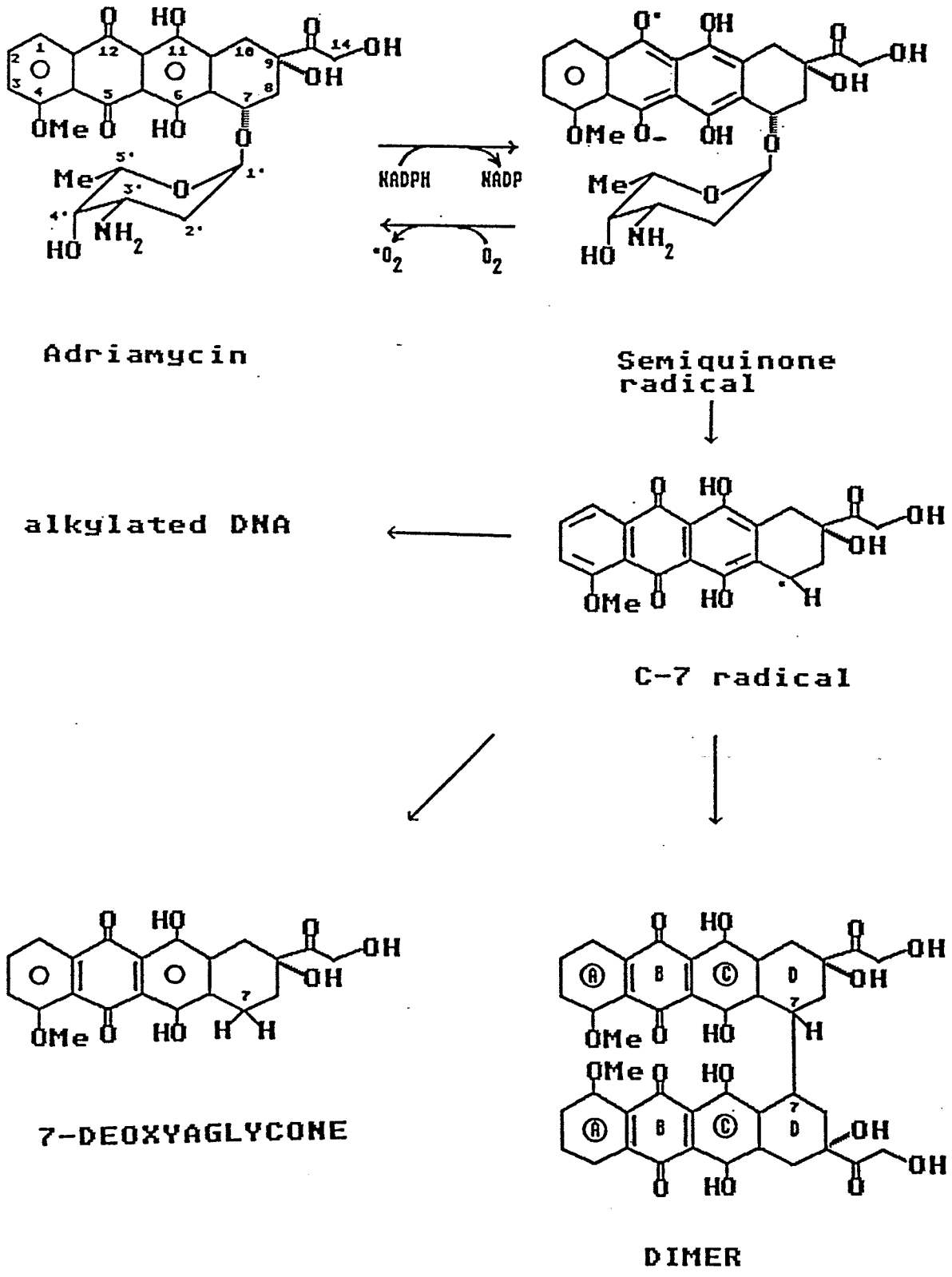
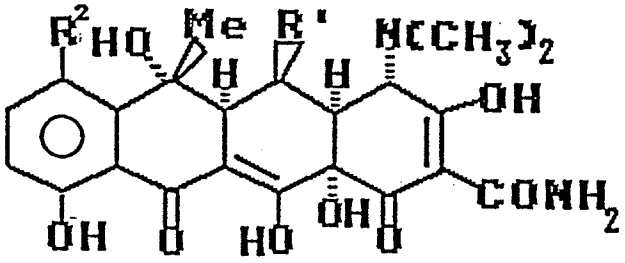

NADPH
NADP
$^{\bullet}O_2$
O_2
Adriamycin
Semiquinone radical
alkylated DNA
C-7 radical
7-DEOXYAGLYCONE
DIMER

Fig.3

R'=H, R^2=Cl
AUREOMYCIN

R'=OH, R^2=H
TERRAMYCIN

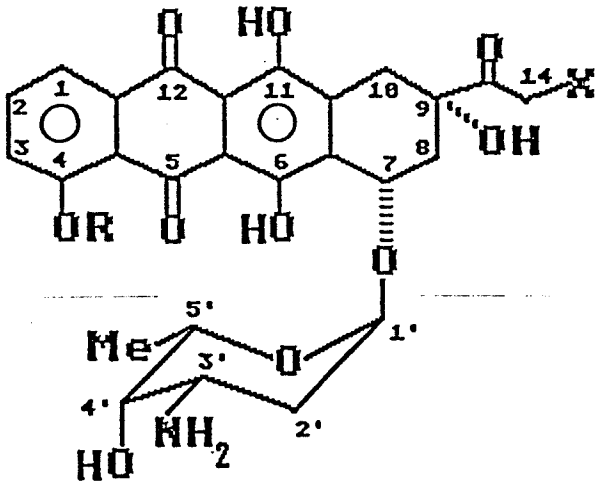


TETRACYCLINES

R=H, X=H
CARMINOMYCIN

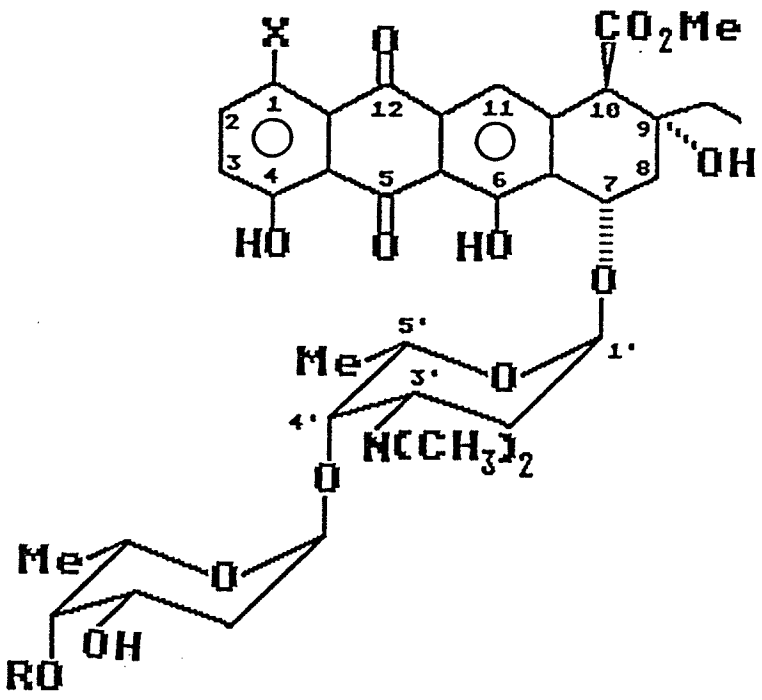
R=CH_3, X=H
DAUNOMYCIN

R=CH_3, X=OH
ADRIAMYCIN



ANTHRACYCLINES
(TYPE 1)

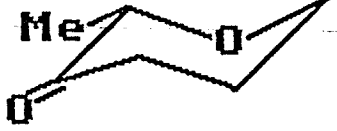
Fig. 4



CINERUBIN A

X=OH

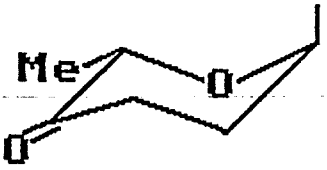
R=



ACLACINOMYCIN A

X=H

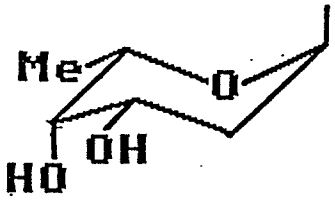
R=



MARCELLOMYCIN

X=OH

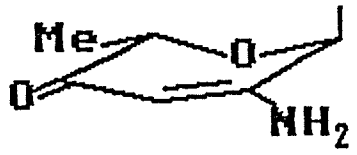
R=



RUDOLFOMYCIN

X=OH

R=



TYPE II ANTHRACYCLINES

Fig. 5

Structure-Activity Relationships

In this section some documentation of the structure-activity relationship of some of the analogs of daunomycin and adriamycin will be presented. However, for more comprehensive reviews, the reader should consult (5a, 5b, 5c).

The name anthracycline is derived from the structural feature common to members of the family having an anthraquinone chromophore contained within a linear carbon framework resembling the tetracyclines (Fig. 4).

They occur naturally both as the glycosides (anthracyclines) and the aglycones (anthracyclinones). The anthracyclines have been divided into two **classes** based on their selective effects on the inhibition of nucleic acid synthesis. **Type I** anthracyclines are exemplified by adriamycin and carminomycin and they inhibit DNA, whole cell RNA (transfer RNA, messenger RNA and ribisomal RNA) and nucleolar RNA (messenger RNA) synthesis at approximately comparable concentrations; **type II** anthracyclines, typified by aclacinomycin and marcellomycin, inhibit whole cellular RNA synthesis at 6-7 fold lower concentrations and nucleolar peribosomal synthesis at 170-1250 fold lower concentrations than those required for inhibition of DNA synthesis (6), (Fig. 5).

The presence of a carboxymethoxy group and the greater number of sugar residues present in the **type II** anthracyclines in noteworthy (Fig. 5).

TABLE 1 Activities of Daunorubicin Analogs Against Murine Leukemias[a]

Analog	P-388 Maximum Effect (% T/C)	L-1210 Maximum Effect (% T/C)
13-Dihydro		138(147)
13-Deoxy	160(167)	
9-Deacetyl	228(171)	
9-Epi-deacetyl	171(171)	
4-O-Demethyl (carminomycin)		162(162)
13-Dihydro-4-*O*-demethyl		168(162)
Benzoylhydrazone (rubidazone)	192(167)	
4-Cl-Benzoylhydrazone	211(167)	
4-CH_3O-Benzoylhydrazone	211(167)	
4′-Deoxy		162(162)
4′-*O*-Methyl	156(169)	
4′-*O*-Tetrahydropyranyl		>474(191)
N-Lauroyl	240(251)	
N-Glycinyl		194(183)
N-Leu		>325(183)
N-Leu-Leu		310(183)
N-Ala-Leu		293(183)
N,N-Dimethyl	214(160)	
N,N-Dibenzyl	259(160)	
7-$OCOCH_2CH_2NH_2$(Dedaunosaminyl)	169(160)	

[a]The maximum effect for each compound is given with the maximum effect of daunorubicin control in parentheses beside it. Optimal doses of analog and control are not necessarily the same. T/C = life span treated/life span control × 100.

TABLE 2 Activities of Doxorubicin Analogs Against Murine Leukemias[a]

Analog	P-388 Maximum Effect (% T/C)	L-1210 Maximum Effect (% T/C)
4-Demethoxy	261(>300)	
13-Deoxy	164(197)	154(157)
14-Valerate		125(154)
14-Octanoate	247(215)	
14-Nicitinoate	229(215)	
N-$COCF_3$	189(187)	
N-$COCF_3$, 14-valerate	221(195)	
4′-Deoxy	225(>300)	177(155)
4′-*O*-Methyl	270(254)	312(187)
4′-Epi	229(221)	150(166)
4′-Epi-4′-*O*-methyl		187(187)
4′-*O*-Tetrahydropyranyl		>800(>458)
N,N-Dimethyl	164(197)	
N,N-Diethyl	199(197)	

[a]The maximum effect for each compound is given with the maximum effect of doxorubicin control in parentheses beside it. Optimal doses of analog and control are not necessarily the same. % T/C = life span treated/life span control × 100.

For **type I** anthracyclines, Table 1 (7c) shows the activities of some daunomycin analogues against two types of leukemias. As can be gleaned from the table, the N-peptidyl derivatives and 4'-O-tetrahydropyranyl derivatives appear to have superior activities against L-1210 leukemias whereas, the benzoylhydrazone and derivatives, and some N,N-dialkyl derivatives appear to have superior activity against P-388 leukemias.

In the adriamycin analogue series (Table 2, (7c)), the 14-octanoate, N-$COCF_3$- 14-valerate, 4'-O-methyl and 4'-epi derivatives are more active against P-388 leukemias whereas the 4'-O-tetrahydropyranyl derivative seems to be far superior against L-1210 leukemias than its precursor. It should be noted here that only the maximum effect of each analog and the corresponding maximum effect of daunomycin and adriamycin in the same assay is presented (6).

The **type II** anthracyclines have not been well investigated. However, it is known that cytotoxicity is decreased by demethoxycarbonylation (at C10) of compounds such as aclacinomycin A, marcellomycin and rudolfomycin which all lack an 11-hydroxyl group. However, in aclacinomycin, this cytotoxicity was preserved by 4-O-methylation (7c).

Synthetic approaches to aglycones

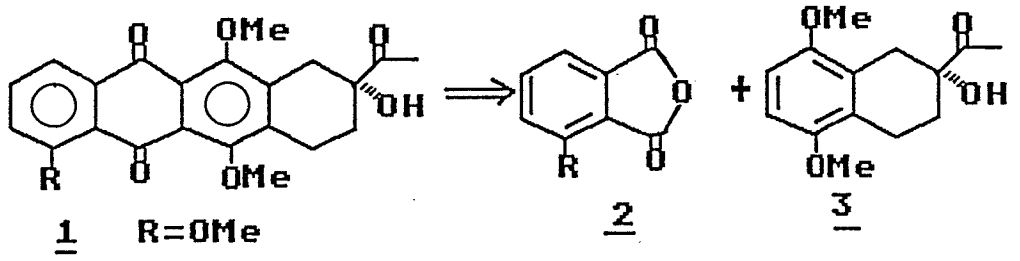
There have been a number of recent reviews which chronicle the synthetic approaches to anthracyclinones and this section will deal only with a summary of the approaches, by class, to the aglycones and any new strategies not mentioned in the reviews. For individual accounts, the

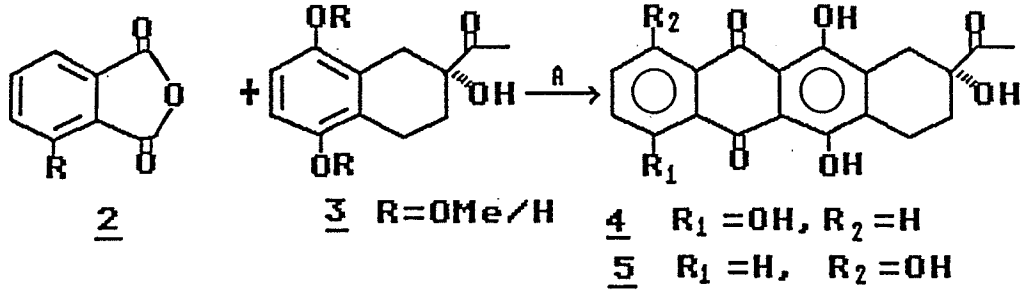
reader is directed to the reviews (7).

The synthetic methodology can be classified into Friedel-Crafts (cationic) reactions, Diels-Alder (concerted) reactions and carbanion (anionic) reactions.

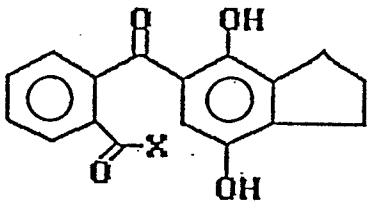
Friedel-Crafts Reactions

The most direct and rational approach for assembly of the aglycone skeleton via a Friedel-Crafts reaction is by disconnecting the molecule as shown in order to exploit the electron donating ability of the OMe(OH) group of the AB portion of the molecule.





When R=OH/OMe there is the regioselective problem in the D ring and therefore this Friedel-Crafts method is more suitable for the 4-demethoxy analogues. In addition, drastic conditions are necessary since this reaction proceeds in two steps, the first step deactivating the arene ring towards the second acylation as shown below.

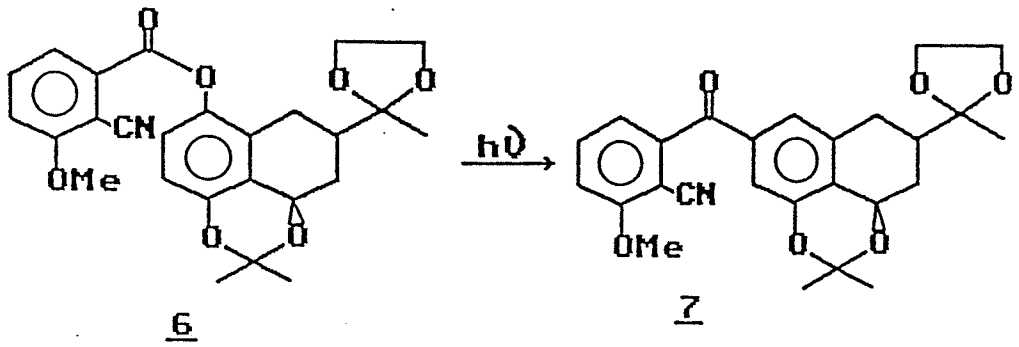


X=Cl, O-$\bar{A}lCl_3$

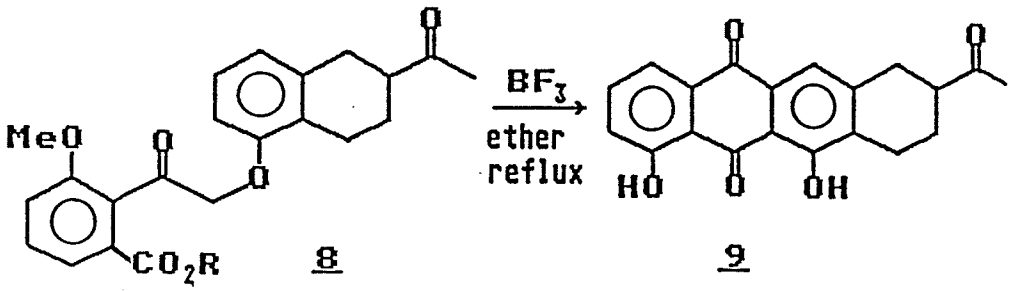
The harsh conditions prevent the incorporation of the C7 hydroxyl group (or a precursor) before the acylation and, therefore, the C7 hydroxyl group is then introduced via benzylic bromination followed by solvolysis.

One example of the way in which the regioselectivity can be obtained is by a photochemical Fries rearrangement of 6 to 7 or a Fries rearrangement of 8 to 9. This regioselectivity can also be achieved by using phenylboronic acid in the presence of 10 and 11 to give 12 (Fig. 6).

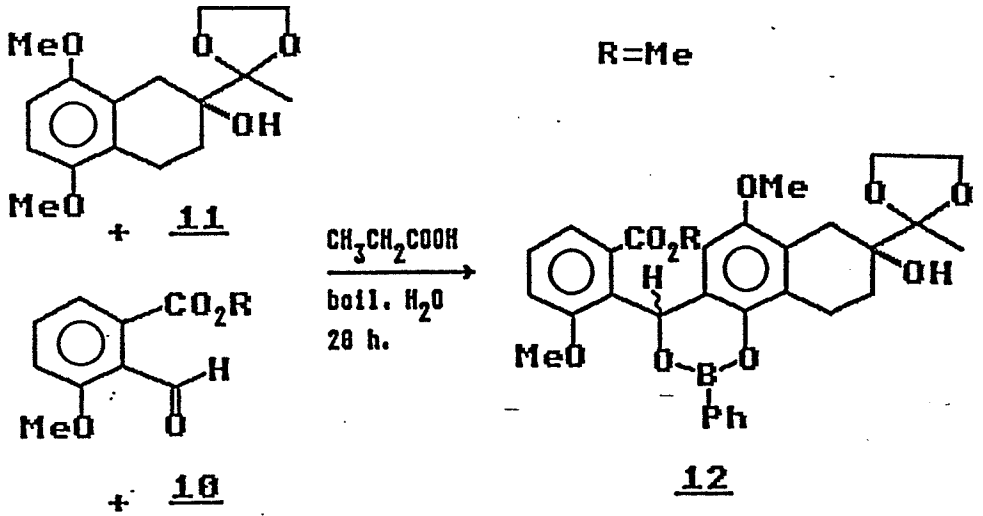
In addition, these vigorous conditions are not favourable to the construction of anthracyclines which have an alkyl (methyl or ethyl) side chain in contrast to those which possess a carbonyl (acetyl) side chain. This is due to the fact that an incipient positive charge will


CN
OMe
hν
CN
OMe

6 7


MeO
CO_2R
BF_3
ether
reflux
HO
OH

8 9


MeO
OH
MeO
+ 11
CO_2R
H
MeO
+ 10
$PhB(OH)_3$
CH_3CH_2COOH
boil. H_2O
20 h.
R=Me
OMe
CO_2R
H
OH
MeO
B
Ph

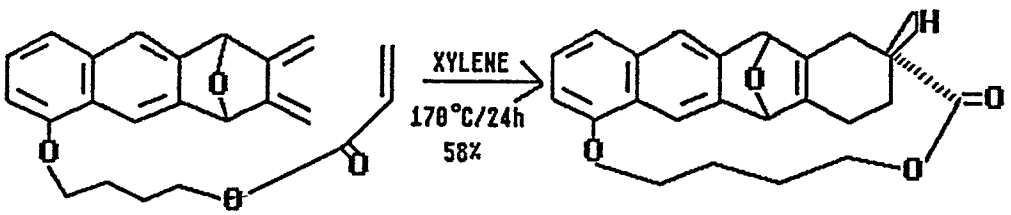
12

Fig. 6

be more stable in the former than in the latter and, consequently, the anthracyclinones like the rhodomycinones are easily dehydrated.

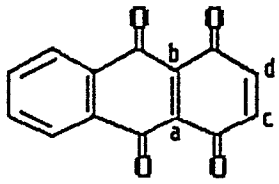
Diels-Alder Reactions

The Diels-Alder reaction has provided many solutions to the synthetic chemists working in the area of anthracycline synthesis with regard to regio, stereo and enantiocontrol.
One ingenious example of "remote" control in a Diels-Alder Reaction is shown below: 13 to 14 (8).



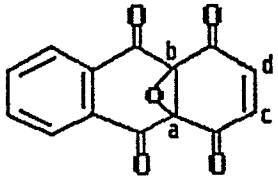
13 14

When using anthradiquinones of type 15, many electron rich, highly functionalised dienes add to the inner double bond ab rather than cd.



15

Exclusive addition to the cd double bond can be achieved, however, by first oxidising the ab double bond to produce 16.



16

Then by use of a chiral diene 17, an enantioselective synthesis of 4-demethoxydaunomycinone 20 can be achieved (9a), (Fig. 7).

An elegant way of introducing the C-7 functionality was that of Garland et al. (9b), shown in Fig. 8.

Krohn and Tolkiehn (10) have used naphthazarin 25 in sequential Diels-Alder reactions thus permitting functionalities to be introduced both in rings A and D. However, this reaction does not proceed regioselectively

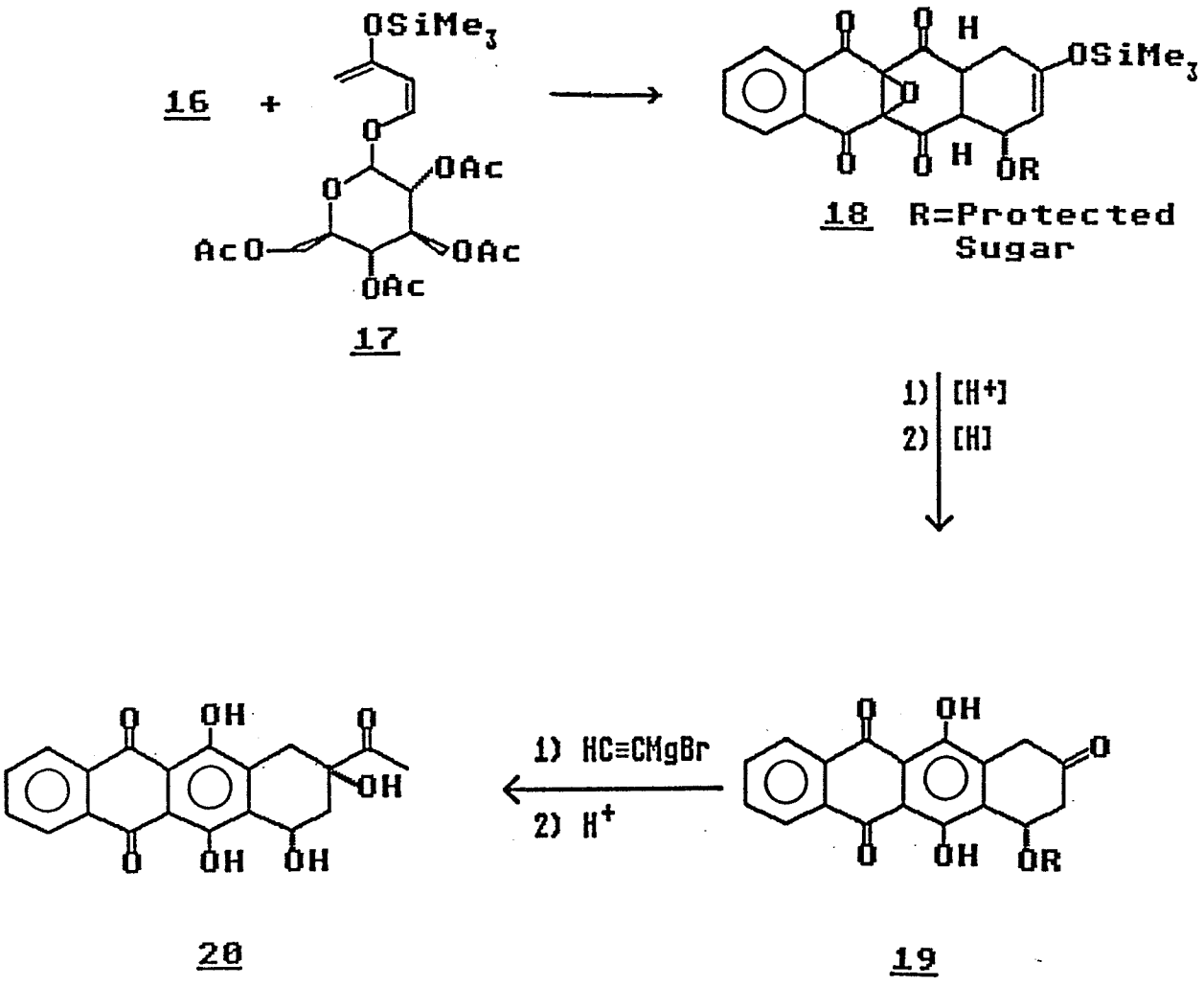
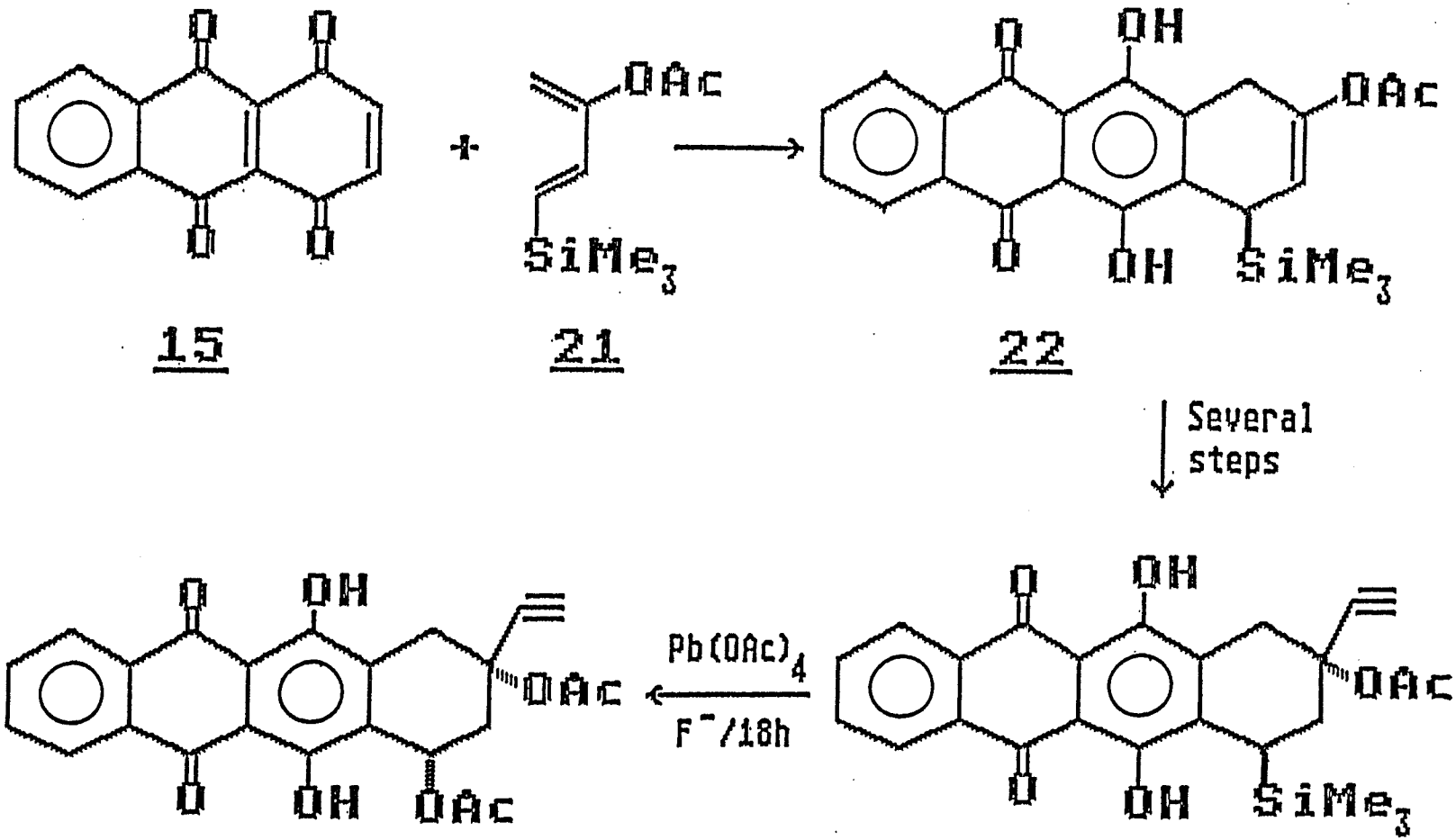

16
OSiMe3
OAc
AcO
OAc
OAc
17
H
OSiMe3
OR
18 R=Protected Sugar
1) [H+]
2) [H]
OH
OH
19
1) HC≡CMgBr
2) H+
OH
OH
OH
20

Fig.7



15 21 22

24 23

Fig.8

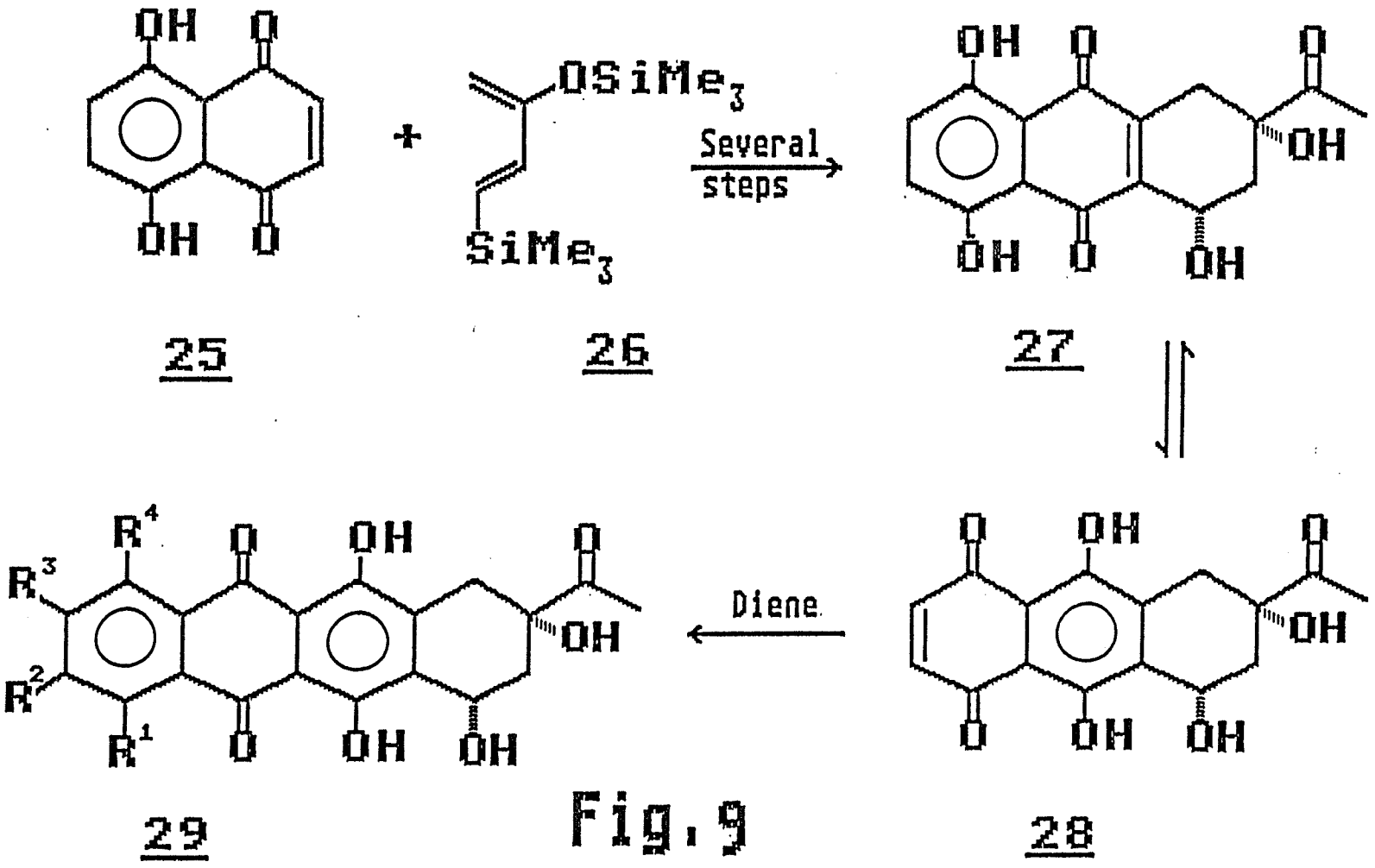

OH
O
OH
O
+
OSiMe3
SiMe3
Several steps
OH
O
OH
O
OH
OH
25
26
27
R4
R3
R2
R1
O
OH
O
OH
OH
Diene
O
OH
O
OH
O
OH
29
28

Fig. 9

Fig.10a

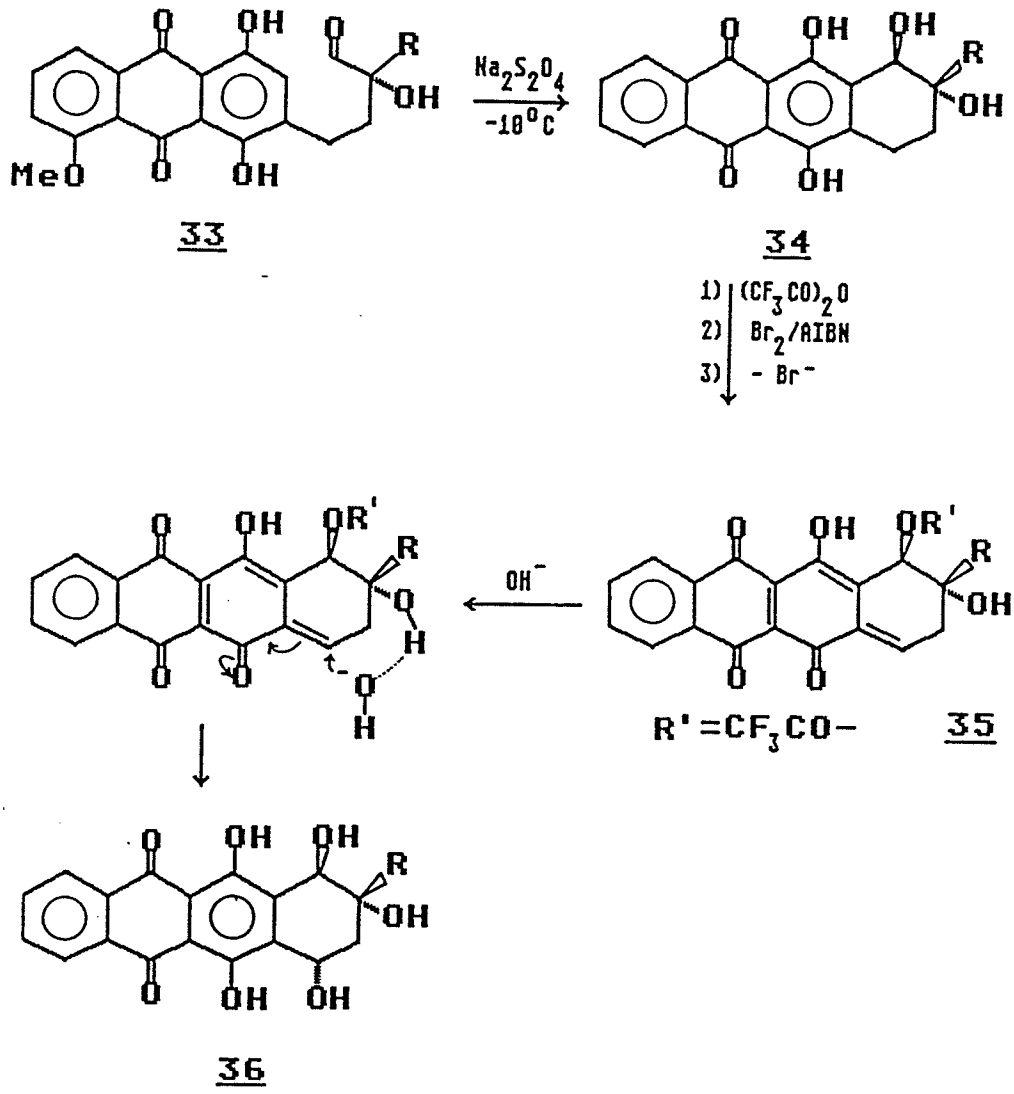

MeO
OH
R
$Na_2S_2O_4$
-10°C
33
34
1) $(CF_3CO)_2O$
2) Br_2/AIBN
3) - Br^-
OH^-
R'=CF_3CO-
35
36

Fig.10b

for ring D (Fig. 9).

CARBANION REACTIONS

The construction of the aglycone skeleton via carbanion reactions provide selective bond formation and thus provide a means for a high degree of control of the regiochemistry.

Marschalk conditions (11) ($Na_2S_2O_4$/NaOH) are one of the most popular ways of generating the aglycone skeleton from a hydroquinone and an aldehyde under the basic conditions stated above (Fig. 10a).

Under the original Marchalk conditions ($Na_2S_2O_4$/NaOH/high temperatures), the integrity of the newly formed C7 hydroxyl group is not preserved. However, Krohn and Hemme (12) have shown that C7 hydroxyl group can easily be preserved by decreasing the reaction temperature. The Marschalk conditions are especially useful for stereoselective syntheses and enantioselective syntheses when chiral auxiliaries are used (Fig. 10b).

Krohn and Muller (13) have incorporated (S)-lactic acid as the chiral auxiliary for anthracyclinones with methyl side chains at C9. Dialdedehyde 41, derived from glucose, can provide a chiral auxiliary with any desired R group which will eventually become a C9 functionality (Fig. 11).

Tamura et al. (14) have demonstrated that excellent regioselectivity can

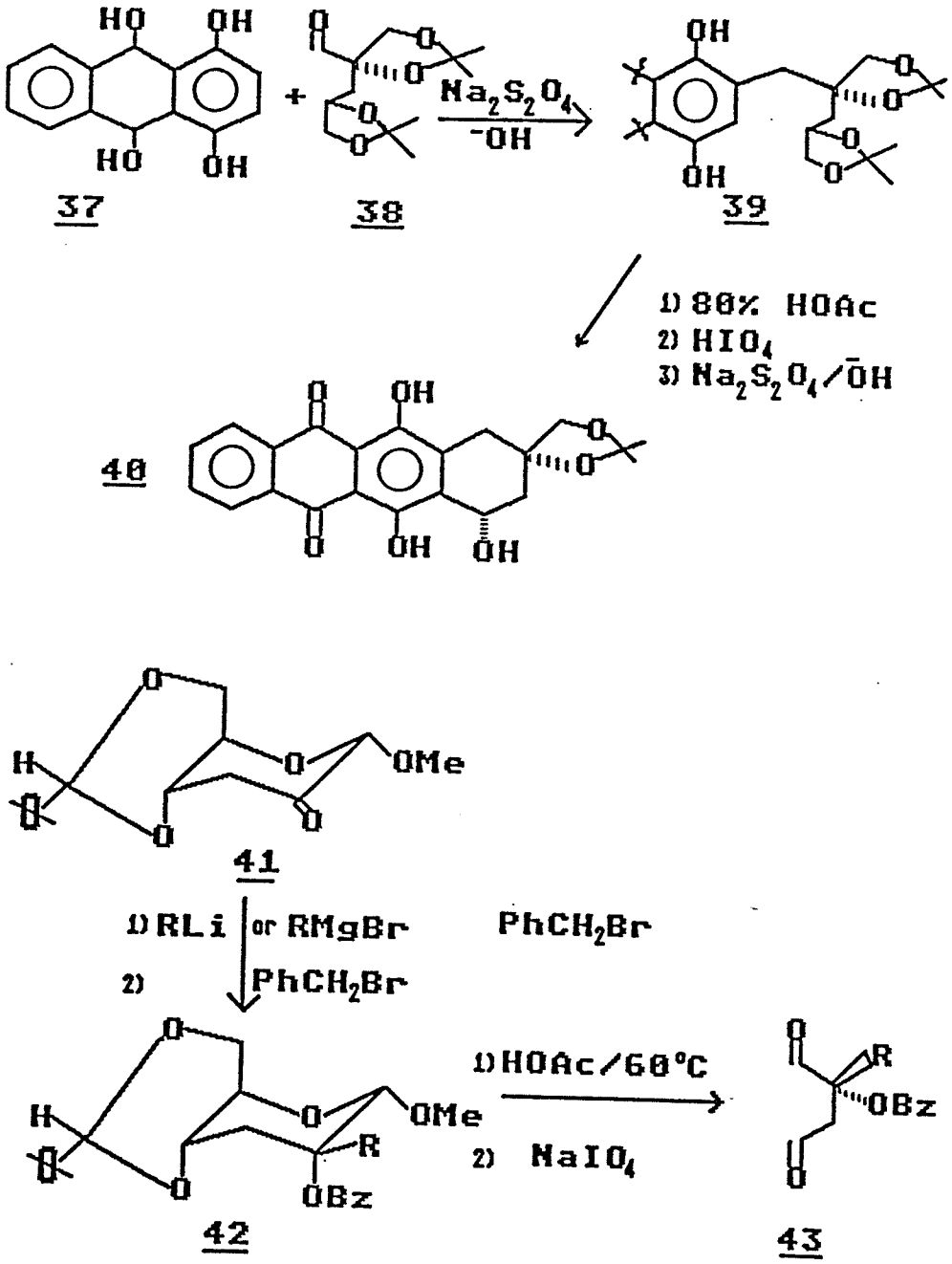
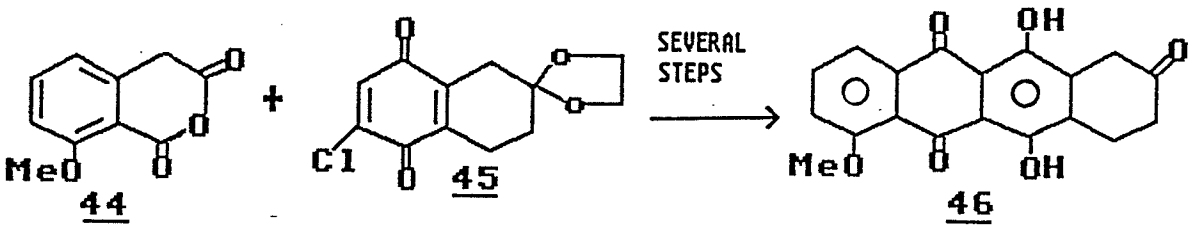
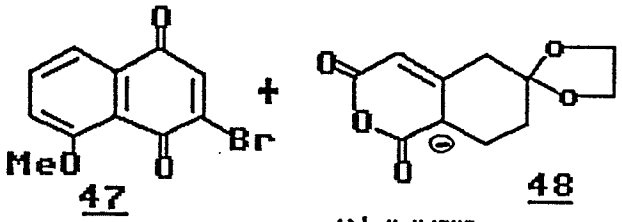
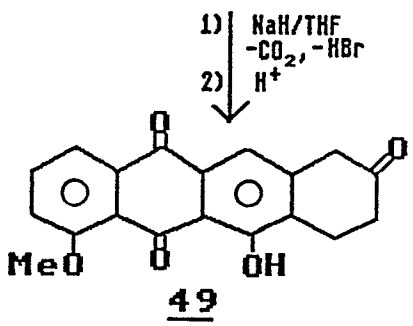

HO
OH
HO
OH
37
38
$Na_2S_2O_4$
^-OH
OH
OH
39
1) 80% HOAc
2) HIO_4
3) $Na_2S_2O_4/\bar{O}H$
40
OH
OH
OH
41
OMe
1) RLi or RMgBr
2) $PhCH_2Br$
$PhCH_2Br$
OMe
R
OBz
42
1) HOAc/60°C
2) $NaIO_4$
R
OBz
43

Fig. 11

be obtained by using 45 and 47 together with the respective homophthalic anhydride derivatives 44 and 48, under strongly basic conditions in their synthesis of daunomycinone and of 11-deoxyaglycones as shown below.

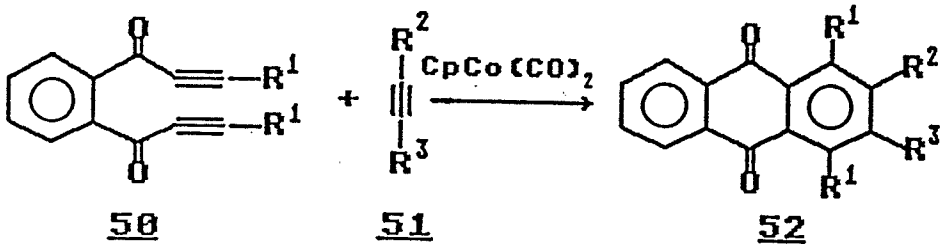






OTHER STRATEGIES

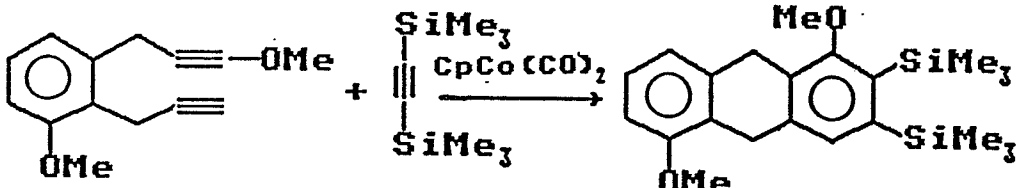
In a strategy, yet to be proven useful in anthracycline synthesis, Volhardt (15) has shown that the newly discovered (2+2+2) cobalt mediated cycloadditions can be applied to the construction of the aglycone skeleton (Fig. 12). These products can be transformed, by known methodology, to the basic aglycone skeleton.



50 51 52

R^1=H; $SiMe_3$

R^2, R^3=H; alkyl; $SiMe_3$



53 54 55

Fig. 12

In a recent communication, Kanematsu et al.(16) have suggested that regioselective Michael additions of O-silylated ketene acetates to quinzarinquinone 15, followed by sigmatropic rearrangements and reductive Claisen rearrangements can lead to linear tetracycles which can be transformed to anthracycline aglycones (Fig. 13).

In another recent communication, Sutherland and Mullah (17) have used a one pot addition-oxidation-aldol sequence, starting with known 63, to assemble anthracyclinone aglycones functionalised at C11 with a ester functionality (Rhomycinone type) (Fig. 14).

However, in these reactions, the diastereoselectivity was poor and, in addition, several by-products were obtained. Therefore, more experimentation seems appropriate before this type of approach can be satisfactorily applied to the construction of the aglycone skeleton of the Rhodomycinones.

The development of carbene (carbonyl) transition-metal complexes have found application in natural products synthesis, in general, and in anthracycline aglycones, in particular (for a review see (18)). Bond formations among carbenes, carbon monoxide and alkynes can occur to generate an aromatic six membered ring which is pi-bonded to the metal (Fig. 15).

The relative disposition of the carbons are as shown and a number of substituents can be tolerated on C5 and C6 i.e. the carbene ligand. e.g., polycyclic arene ligands. Thus, the following disconnections can

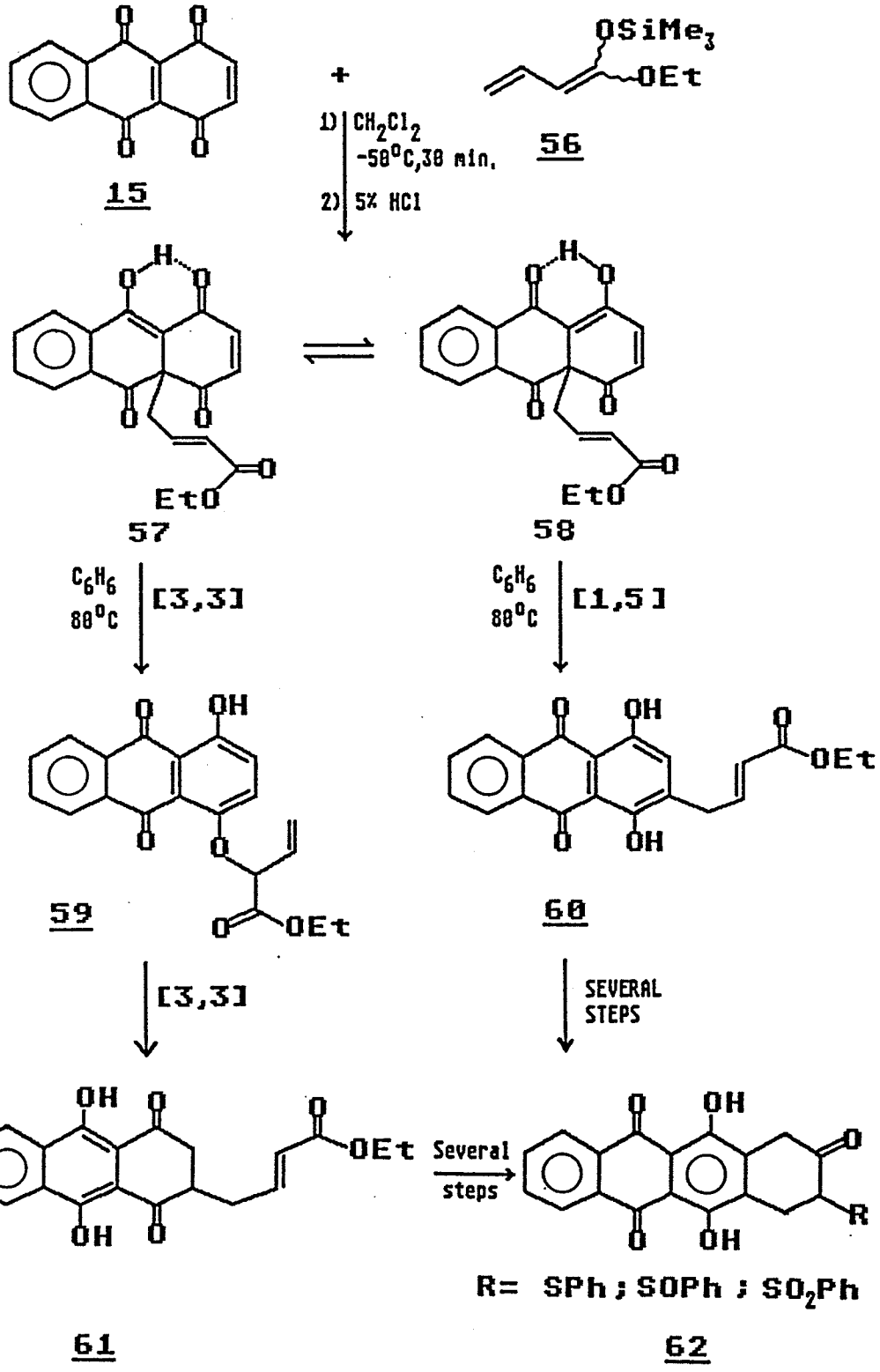

OSiMe3
OEt
1) CH2Cl2
-58°C,30 min.
2) 5% HCl
15
56
EtO
57
58
C6H6
80°C
[3,3]
[1,5]
OH
OEt
59
60
SEVERAL
STEPS
Several
steps
R= SPh ; SOPh ; SO2Ph
61
62

Fig.13

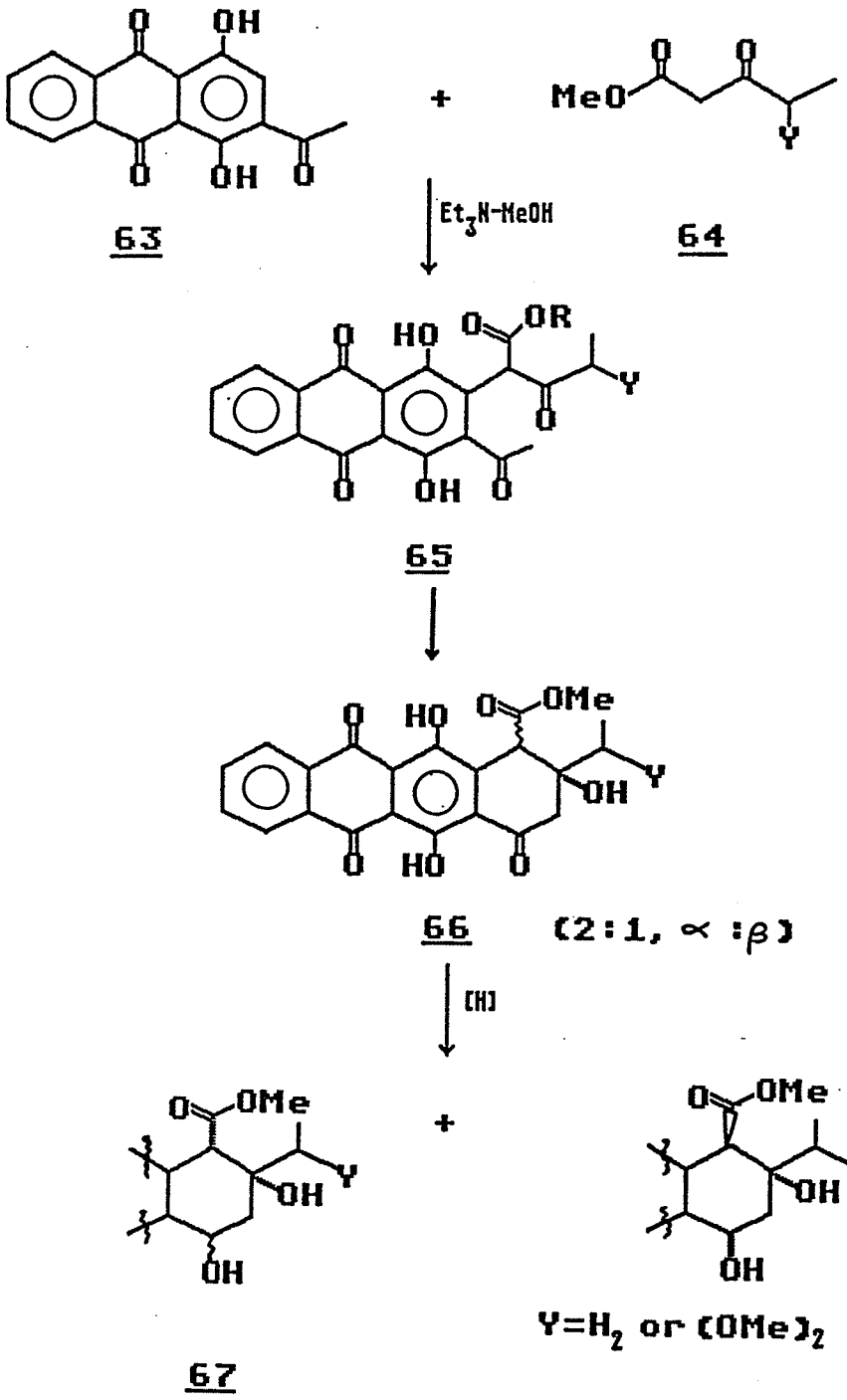


Fig.14

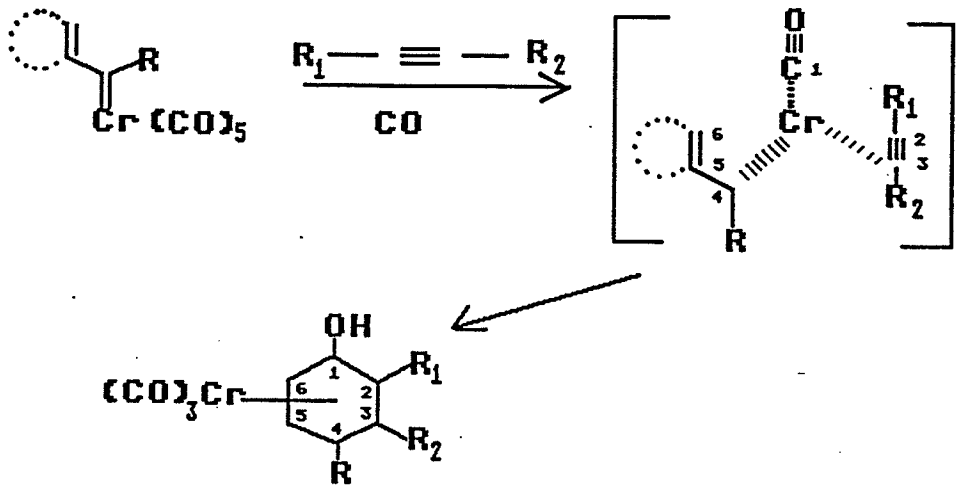


Fig. 15

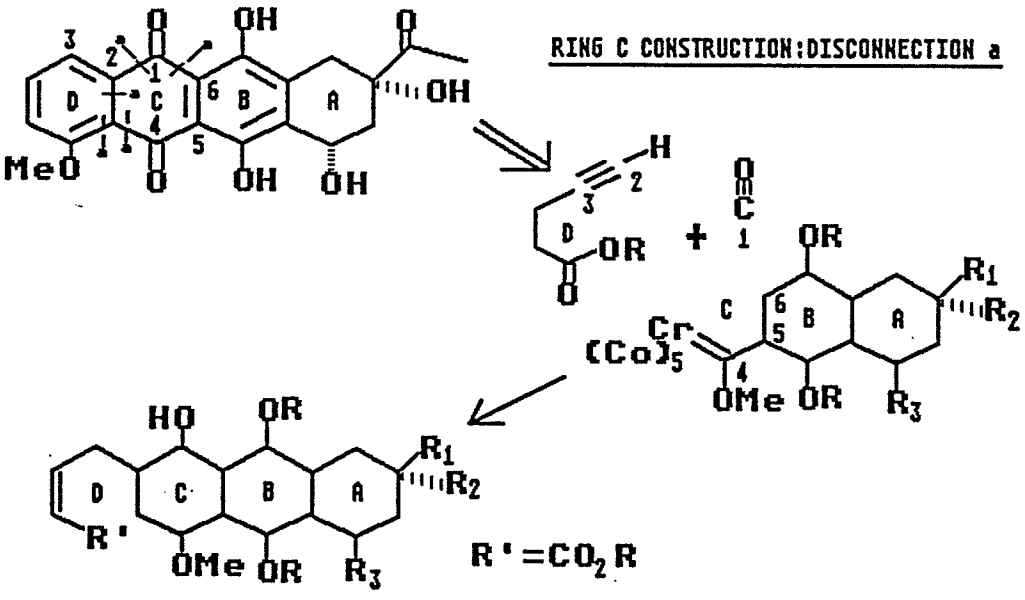


Fig. 16

be made providing four independent routes to the aglycone skeletons (Fig. 16 - 19).

Dotz and Popall (19) have used disconnection c to generate the anthracene derivative shown (Fig. 20).

These types of intermediates have been transformed into the fully functionalised aglycone of daunomycinone and 4-demethoxydaunomycinone.

Following the disconnection d (B ring formation) Wulff and Tang (20) have shown that this approach to the synthesis of the trione 75 is comparable in yield to other syntheses of this intermediate. Their approach is shown in Fig. 21.

More recently, Wulff et al. (21) have achieved a one pot tandem cycloaddition/annulation to the intermediate 75 in roughly the same yield (23%) as shown in Fig. 22.

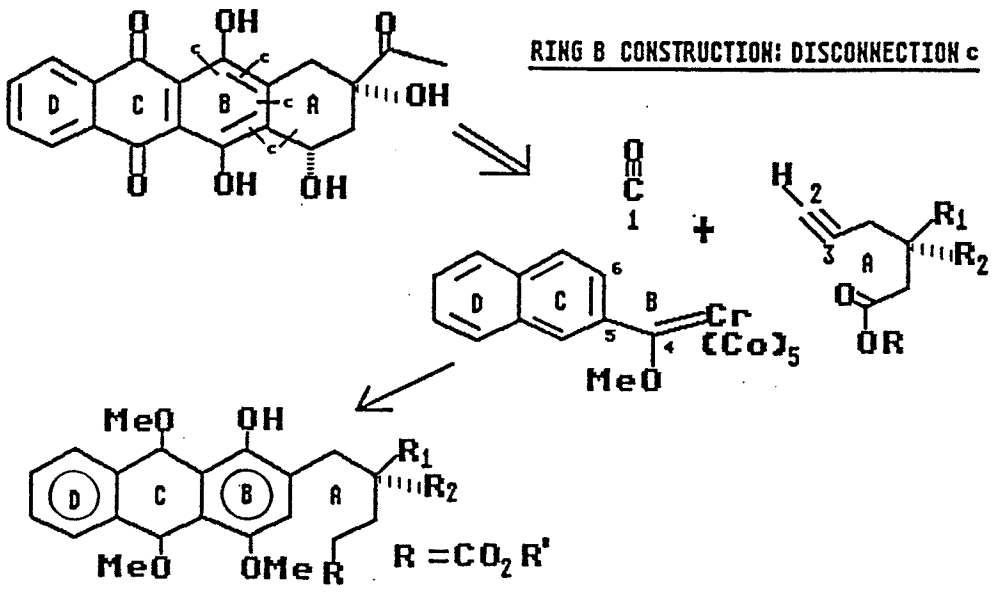

RING B CONSTRUCTION: DISCONNECTION c
MeO
OH
OMe
R
R =CO2 R'

Fig. 17

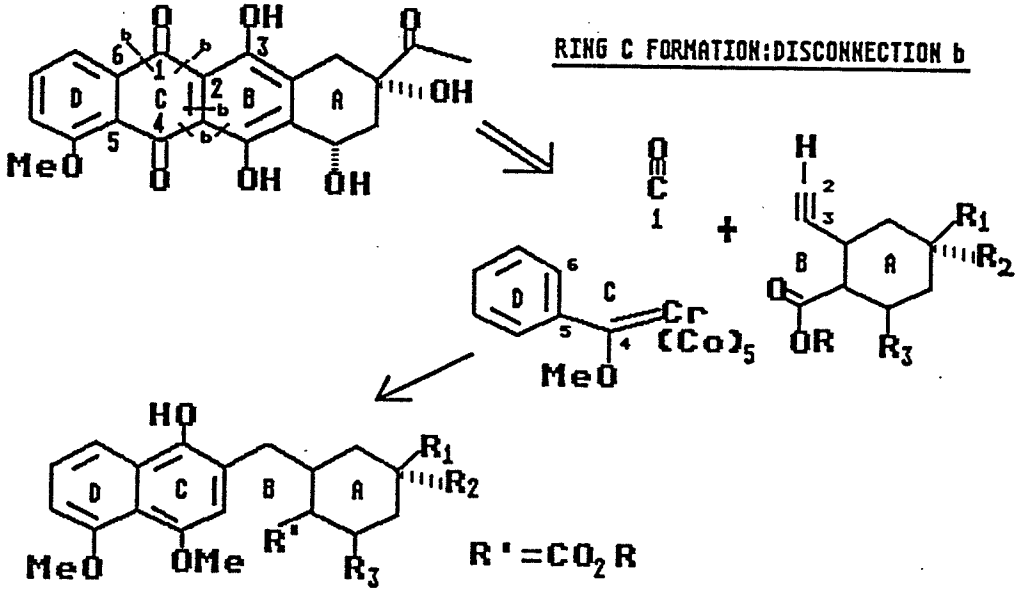

RING C FORMATION:DISCONNECTION b
MeO
OH
HO
OMe
R'
R' =CO2 R

Fig. 18

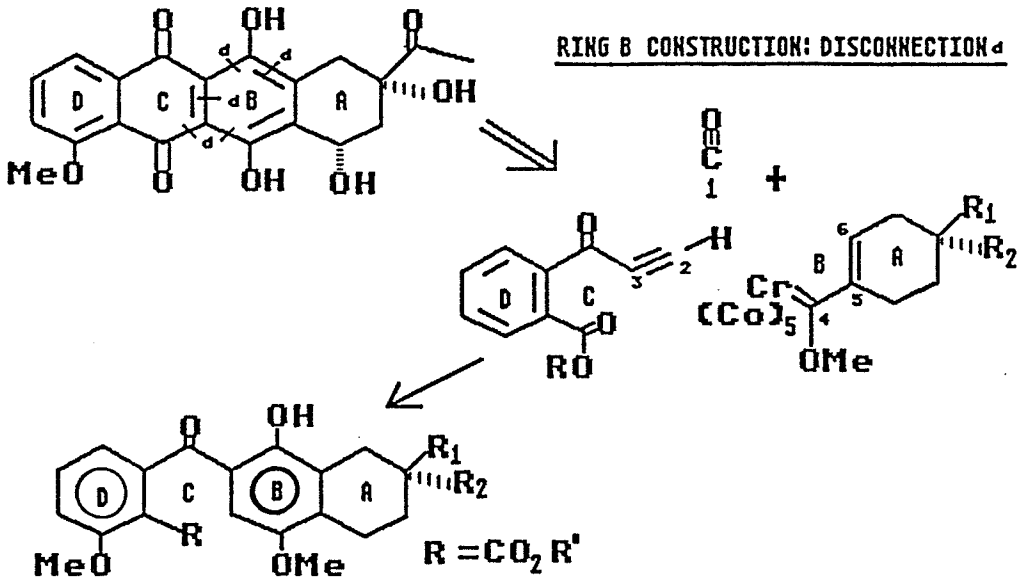

RING B CONSTRUCTION: DISCONNECTION
MeO
OH
OH
OH
OH
D
C
B
A
RO
OMe
R = CO2 R'

Fig. 19

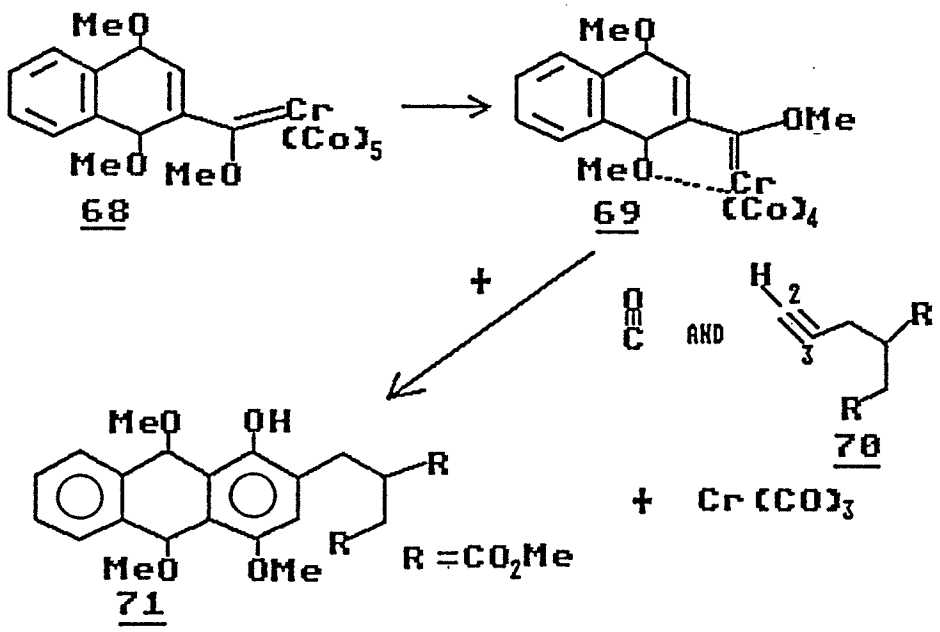

MeO
MeO
MeO
Cr
(Co)5
68
MeO
OMe
MeO
Cr
(Co)4
69
+
O
C
AND
H
2
3
R
R
70
+ Cr(CO)3
MeO
OH
R
R
MeO
OMe
71
R = CO2Me

Fig. 20

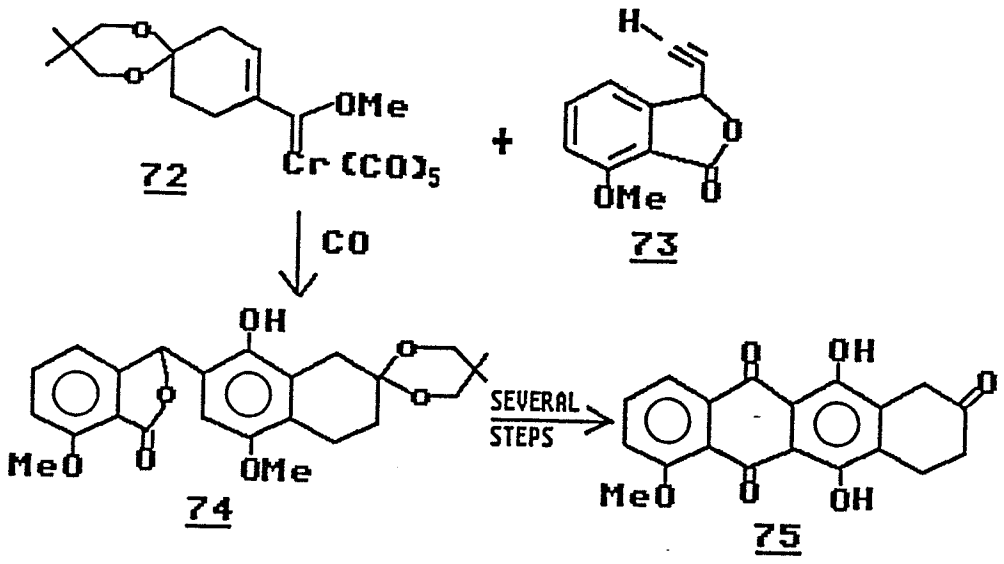

OMe
Cr(CO)5
72
+
H
O
OMe
O
73
CO
OH
MeO
O
OMe
74
SEVERAL
STEPS
O
OH
O
MeO
O
OH
75

Fig. 21

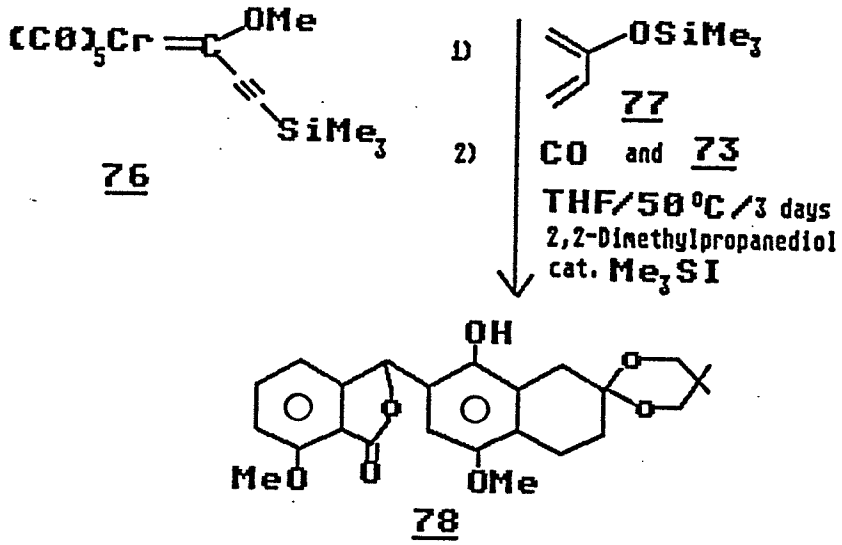
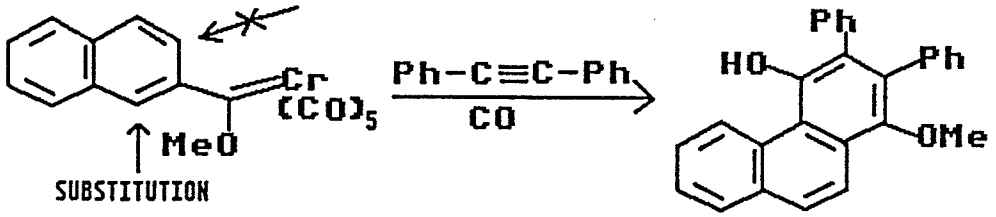
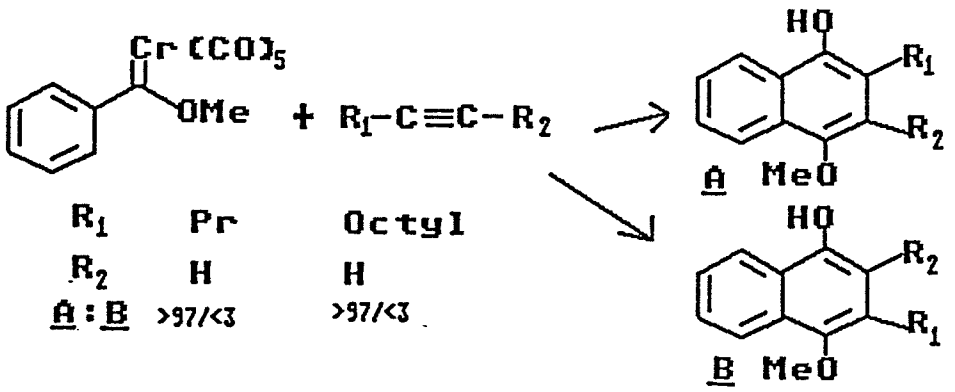

(CO)5Cr
OMe
SiMe3
76
1)
OSiMe3
77
2)
CO and 73
THF/50°C/3 days
2,2-Dimethylpropanediol
cat. Me3SI
OH
MeO
O
OMe
78

Fig. 22

There is high regioselectivity in these carbene, acetylene, carbon monoxide co-cyclisations both with respect to the carbene component if two sites are available, and with respect to an unsymmetrical alkyne as shown below.





Therefore, this approach to the construction of 4-hydroxy (methoxy) and 11-deoxy-aglycones holds much promise. It remains to be seen how easy it would be to incorporate A ring functionality into these intermediates.

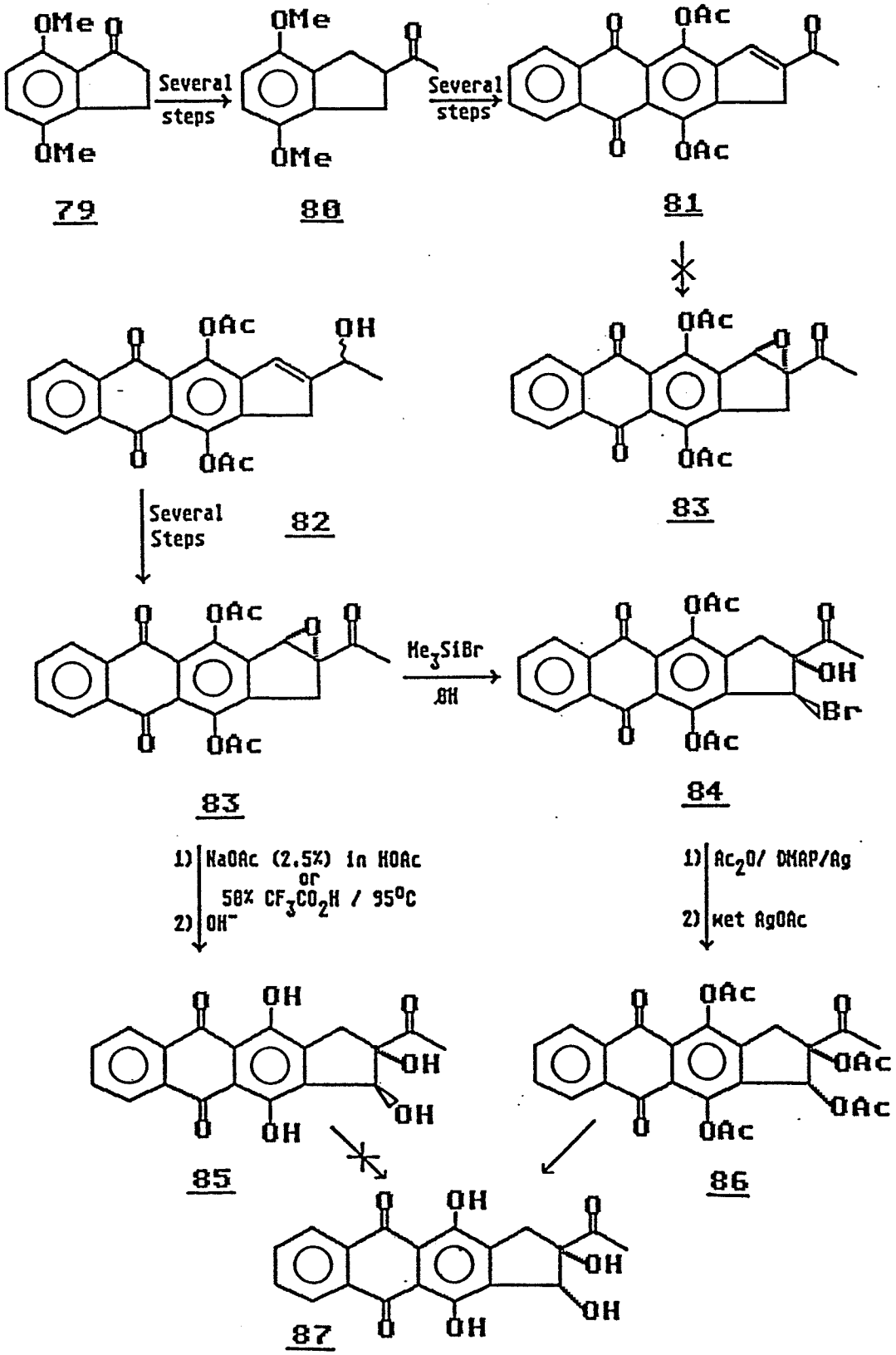

OMe
OMe
Several steps
OMe
OMe
Several steps
OAc
OAc
79
80
81
OAc
OH
OAc
OAc
OAc
OAc
Several Steps
82
83
OAc
OAc
Me3SiBr
OH
OAc
OH
Br
OAc
83
84
1) NaOAc (2.5%) in HOAc
or
58% CF3CO2H / 95°C
2) OH-
1) Ac2O/ DMAP/Ag
2) wet AgOAc
OH
OH
OH
OH
OAc
OAc
OAc
OAc
85
86
OH
OH
OH
OH
87

Fig. 23

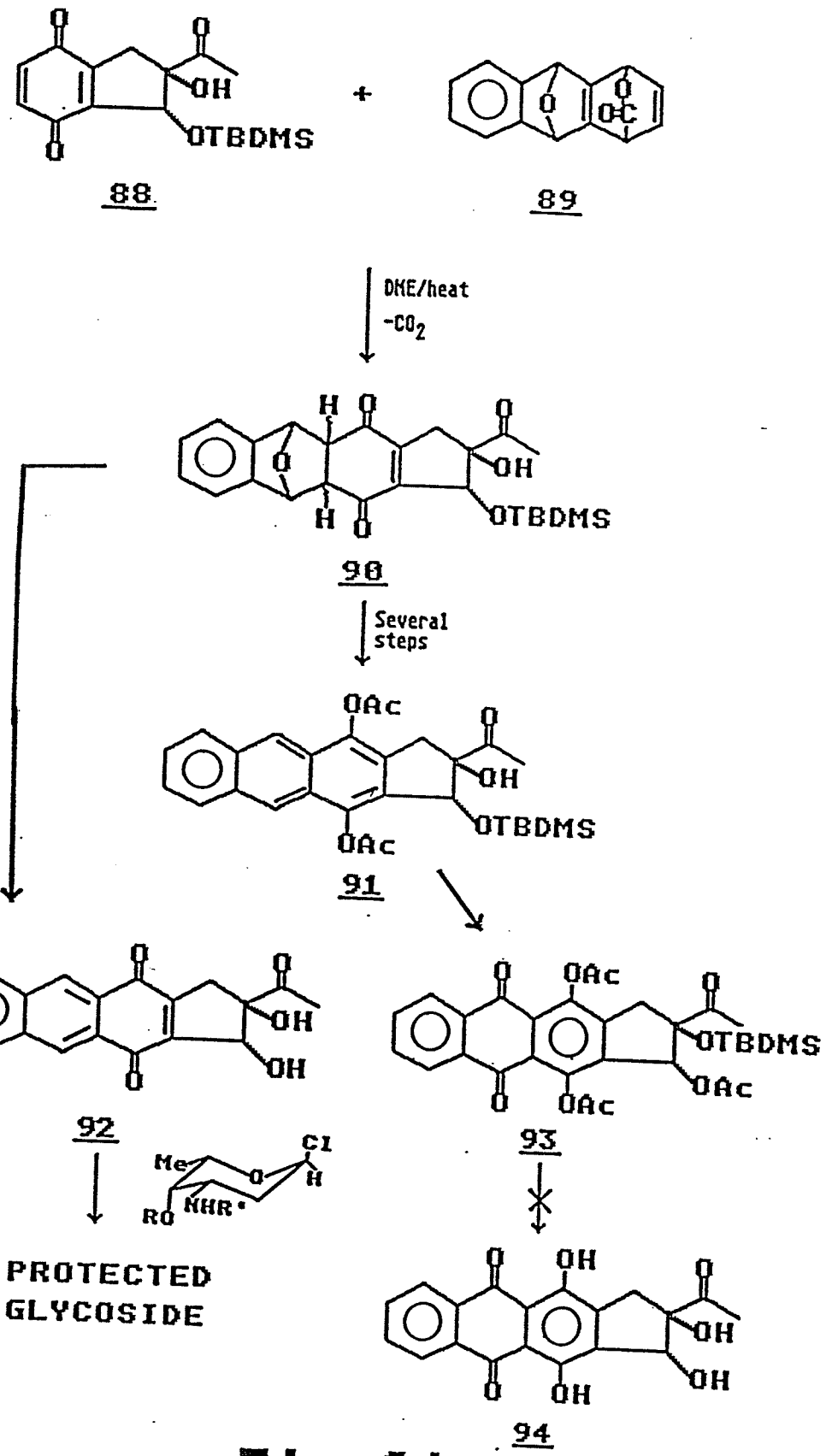

OH
OTBDMS
88
89
DME/heat
-CO2
H
OH
OTBDMS
96
Several steps
OAc
OH
OTBDMS
OAc
91
OH
OH
92
OAc
OTBDMS
OAc
OAc
93
Me
Cl
O
H
RO
NHR'
PROTECTED GLYCOSIDE
OH
OH
OH
OH
94

Fig. 24

In addition to the research described in this thesis, there have been two published syntheses concerning the **nor** analogues of 4-demethoxydaunomycinone (22).

Mitscher's approach closely parallels the independently conceived work described in this thesis in that a common starting material (79) was used to generate the structural isomeric compound 80 followed by a Friedel-Crafts reaction to generate the basic aglycone skeleton. This approach is outlined in Fig. 23.

In contrast to Mitscher's approach and our approach, Flynn et al.(22 b.) chose the Diels-Alder route utilising the izobenzofuran precursor 91 with a fully functionalised AB dienophile. Their approach is outlined in Fig. 24.

CONCLUSION

There are a number of ways to construct the aglycone skeleton of anthracycline analogues. However, there are few syntheses which are practical for large scale preparations and as a consequence it is envisaged that this problem will receive much attention in the near future. In addition, owing to a greater understanding of factors which govern high asymmetric induction, the number of published enantioselective syntheses in the anthracycline area is increasing and their accessibility is expected to aid in the overall efficiency of the agylcone syntheses.

REFERENCES

1. R. N. Buick in,

   Antineoplastic Agents: Chemistry and Pharmacology of Drugs, Vol., 3 Ed., W. A. Remers, John Wiley and Sons 1984.

2. K. T. Douglas,

   Anticancer Drugs, Chem. and Ind. (Lond.), 693 (1984).

3a. W. J. Pigram, W. Fuller and L. D. Hamilton,

   Nat. New Biol., 235, 17 (1972).

3b. M. J. Waring,

   Nature, 219, 1321 (1968).

3c. K. T. Douglas,

   Chem. and Ind. (Lond), 766 (1984).

4. L. Gianni, B.J. Corden and C. E. Myers,

   Rev. in Bio. Chem. Toxic., 5, 1 (1983).

5a. Anthracycline Antibiotics, Academic Press, 1982.,

   H. S. El Khadem Ed., (based on the ACS symposium on Anthracyclines, Aug., 24-25, 1981).

5b. T. Oki and T. Takeuchi,

   J. Synth. Org. Chem. (Japan) (Yuki Gosei Kaga Kyokai) 40, 21 (1982). CA #, 96, 115297 b.

5c. D. G. Strauss,

The Pharmacist (Die Pharmazie), Vol., 42, 289 (1987).

6. W. A. Remers in,

Antineoplastic Agents: Chemistry and Pharmacology of Drugs, Vol., 3; Ed., W. A. Remers, John Wiley and Sons 1984.

7a. F. Arcamone,

Doxorubicin anticancer antibiotics. Medicinal Chemistry. Vol., 17. Academic Press, N.Y. 1981.

7b. T. R. Kelly,

Ann. Rep. Med. Chem., 14, 288 (1979).

7c. W. A. Remers,

The Chemistry of the Antitumour Antibiotics, Vol., 1, Wiley, N. Y., 1979.

7d. T. Kametani and K. Fukumoto,

Med. Res. Rev., 1, 23 (1980).

7e. H. S. El Khadem Ed.,

Anthracycline Antibiotics, Academic Press, N. Y., 1982

7f. S. Terashima,

J. Synth. Org. Chem. Japan, (Yuki Gosei Kagarku Kyokaishi) 40, 21 (1982). CA #, 96, 142501 v.

7g. V. Sniekus and W. Altintas,

The Total Synthesis of Natural Products, Vol., 8. J. Apsimon Ed., Wiley-interscience.

7h T. R. Kelly Ed.,

Recent Aspects of Anthracyclinone Chemistry, Tetrahedron, 40, 4537-4792 (1984) .

7i. M. J. Broadhurst, C. H. Hassall and G. J. Thomas,

Chem. Ind. (Lond.), 106 (1985).

7j K. Krohn,

Angew. Chem. Int. Ed. Engl., 25, 790 (1986).

8. T. Tamirez and P. Vogel,

Angew. Chem. Int. Ed. Engl., 23, 74 (1984).

9a. R. C. Gupta, P. A. Harland and R. J. Stoodley,

Tetrahedron 40, 4657 (1984).

9b. R. B. Garland, J. R. Palmer, J. A. Schultz, P. B. Sollman and R. Rappo,

Tetrahedron Lett., 3669 (1978).

10. K. Krohn and K. Tolkiehn,

Chem. Ber., 112, 3453 (1979); **ibid.** 113, 2976 (1980).

11. C. Marschalk, F. Koenig and N. Ouroussoff,

Bull. Chem. Soc. Fr., 3, 1545 (1936); **ibid.** 6, 655 (1939).

12. K. Krohn and C. Hemme,

Liebigs Ann. Chem., 19 (1979); **ibid.**, 35 (1979).

13. K. Krohn and V. Muller,

Tetrahedron, 42, 6635 (1986).

14. Y. Tamura, M. Sasho, S. Akai, A. Wada and Y. Kita,
Tetrahedron, 40, 4539 (1984).

15. K. P. C. Volhardt,
Angew. Chem. Int. Ed. Engl., 23, 539 (1984).

16. K. Hayakawa, M. Aso and K. Kanematsu,
J. Chem. Soc. Chem. Commun., 102 (1987).

17. K. B. Mullah and J. K. Sutherland,
Tetrahedron Lett., 28, 2165 (1987).

18. K. H. Dotz,
Angew. Chem. Int. Ed. Engl., 23, 587 (1984).

19. K. H. Dotz and M. Popall,
Tetrahedron, 41, 5797 (1985).

20. W. D. Wulff and P. C. Tang,
J. Am. Chem. Soc., 106, 434 (1984)

21. W. D. Wulff , P. C. Tang, K. S. Chan, J. S. McCallum, D. C. Yang and S. R. Gilbertson,
Tetrahedron, 41, 5813 (1985).

22a. I. K. Khanna and L. A. Mitscher,
Tetrahedron. Lett., 26, 691 (1985).

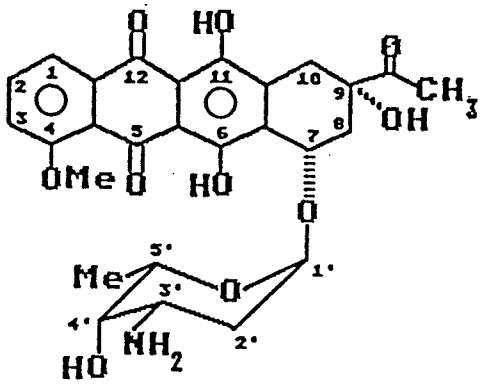
22b. G. A. Flynn, M. J. Vaal, K. T. Stewart, D. L. Wenstrup, D. W. Beight and E. H. Bohme, J. Org. Chem., 49, 2252 (1984).

Results and Discussion

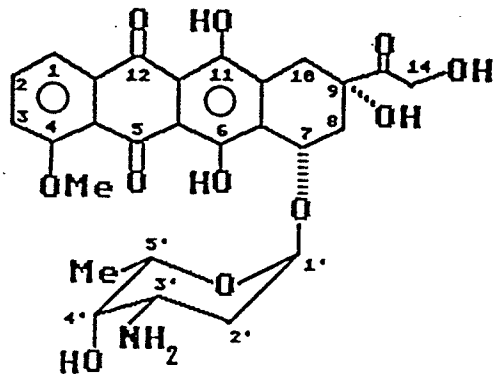
All important classes of natural products, in general, and antibiotics, in particular, have been and continue to be the focus of extensive research aimed at producing such products on a large scale and/or optimising their pharmacological properties. Part of that research usually deals with the partial syntheses of new analogs by chemical modification or total syntheses of natural or modified natural products. Our research has been concerned with the latter.

The anthracycline antibiotics which also exhibit antineoplastic properties are a class of natural products which has seen a great deal of synthetic effort devoted to viable total syntheses of both their natural and synthetic members. In particular, most of these synthetic ventures have been concerned with the syntheses of daunomycin (daunorubicin) and adriamycin (doxorubicin) shown in Fig. 1a. Adriamycin is the more popular of the two drugs because of its wider use and activity over a broader spectrum of neoplastic diseases. Structural modification of these drugs has led to the discovery that the 4-demethoxy analogue of daunomycin exhibits a higher degree of antitumour activity (1). In general, for the daunomycin series, the structure-activity relationship follows 4H > 4OH > 4OMe and for the adriamycin series 4H > 4OMe (2).

Several years ago, our laboratory initiated a program aimed at synthesising new analogues of the (±)-4-demethoxy series which will, predictably, have higher therapeutic properties and lower cardiotoxicities than the ones currently in use. Thus, we turned our

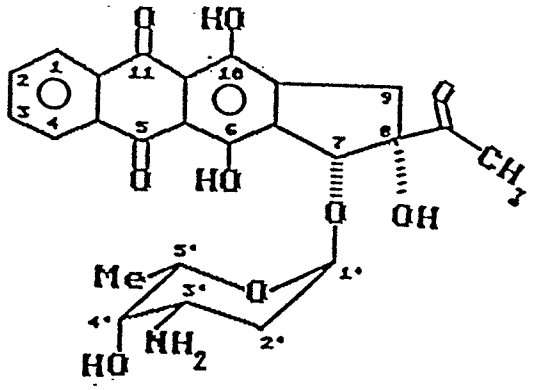


Daunomycin

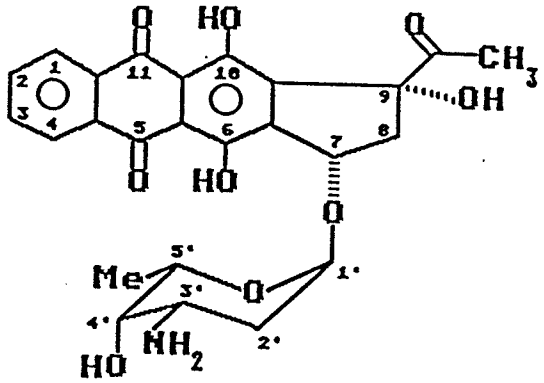


Adriamycin

Fig. 1a



4-DEMETHOXY-8-NOR-DAUNOMYCIN.



4-DEMETHOXY-10-NOR-DAUNOMYCIN.

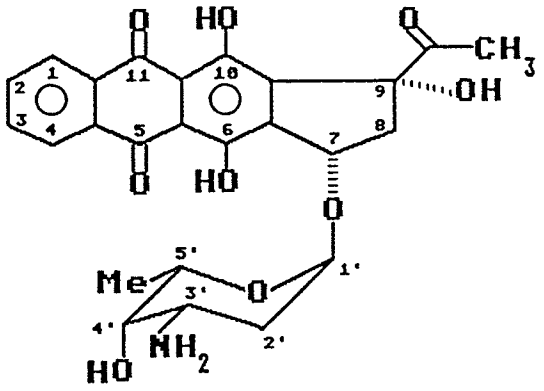
Fig. 1b

attention to modifying the basic aglycone skeleton. For example, the heteroanthracyclines where the carbon at C5 and/or C11 (anthracycline numbering) is replaced by O or S; the sulphur atom being present at varying oxidation levels (3). Moreover, since intercalation, a remarkable binding process to deoxyribonucleic acid (DNA), is purported to be one of the main ways in which these drugs exhibit their antitumor activity by inhibiting various aspects of DNA synthesis (see chapter 1), we also looked at modifying, in particular, the A ring portion of the molecule. Since it is known that a five membered ring has less flexibility than a six membered ring, it was felt that the more planar arrangement of a molecule with a five membered A ring would be more ideal for intercalation than its homologue. Therefore, if intercalation, in this instance, is of major importance for antitumour activity then it is expected that a higher response to activity against neoplastic cells will be exhibited.

Clearly, there are only two possibilities for a five membered A ring anthracycline, namely, the **8-NOR** and the **10-NOR** derivatives as shown in Fig. 1b, if one is to maintain the requisite functionality in that ring. Two other groups, led by Mitscher (4a) and Flynn (4b), have both successfully synthesised the **4-demethoxy-8-nordaunomycinone.** We chose the **10-NOR** series because we wanted to maintain the relative dispositions of the substituents on the A ring. This may have been a fortuitous choice as will be evident towards the end of the chapter.

This chapter, then, deals with the total synthesis of one of the modified natural members of this class, vide licet, (±)- 4-demethoxy-10-

nor-daunomycin shown below.



The synthesis of anthracycline antibiotics is divided into three parts:

1. the synthesis of the anthracyclinone (aglycone),

2. the synthesis of the amino sugar, and

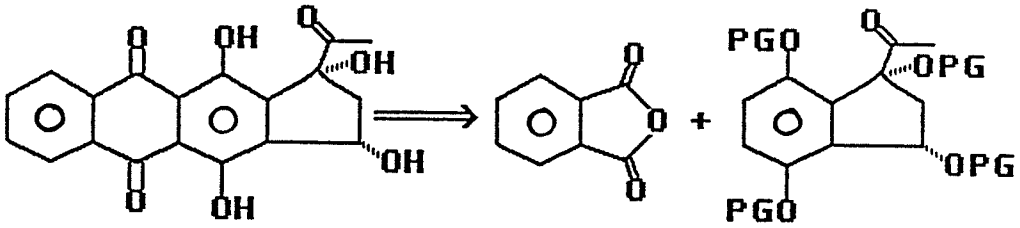
3. the coupling of the two (glycosidation).

Only parts 1 and 3 will be dealt with here. The optically active sugar L-daunosamine purchased from a commercial source or donated by Farmatalia was used as a starting material. However, mention will be made of our current synthetic efforts in the synthesis of the (±) 4-deoxy sugar from simple non-carbohydrate precursors but this will be documented elsewhere (5).

SYNTHETIC APPROACHES TO (±)-4-DEMETHOXY-10-NOR-DAUNOMYCIN.

The construction of the aglycone skeleton is based on three types of annulation reactions: Friedel-Crafts reactions, Diels-Alder reactions and carbanion annulations.

Since our work began on the synthesis of (±)-daunomycinone (6), we have adhered to the Friedel-Crafts method of achieving a convergent synthesis of the tetracyclic skeletons of these molecules. Thus a heuristic approach would be to, in a retrosynthetic fashion, dissect the molecule as shown below.

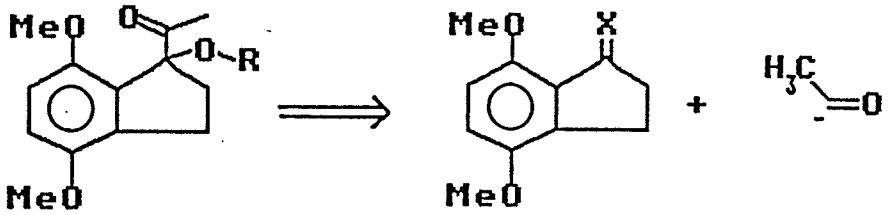


A B C

This retrosynthetic analysis is obviously the most direct approach but its success is, of necessity, limited by the type of Friedel-Crafts conditions needed to generate A from B and C. From experience, one might intuitively recognise that it would not be possible to condense such a highly functionalised fragment C with B and preserve the integrity of what would eventually become the C7 and C9 hydroxyl groups under the harsh Friedel-Crafts conditions (aluminium chloride, 180 ^{o}C,

5-10 min.) normally employed in this type of approach. Nevertheless, model studies were done on the 1-acetoxy-1-acetyl-4,7-dimethoxyindane (and 1-hydroxy-1-acetyl derivative) but these experiments proved fruitless, resulting only in polymeric unidentified material. That result was not at all unexpected since, under the harsh acidic conditions, the propensity to form a benzylic carbocation would be great despite the fact that it would be $\underline{\alpha}$ to a carbonyl group.

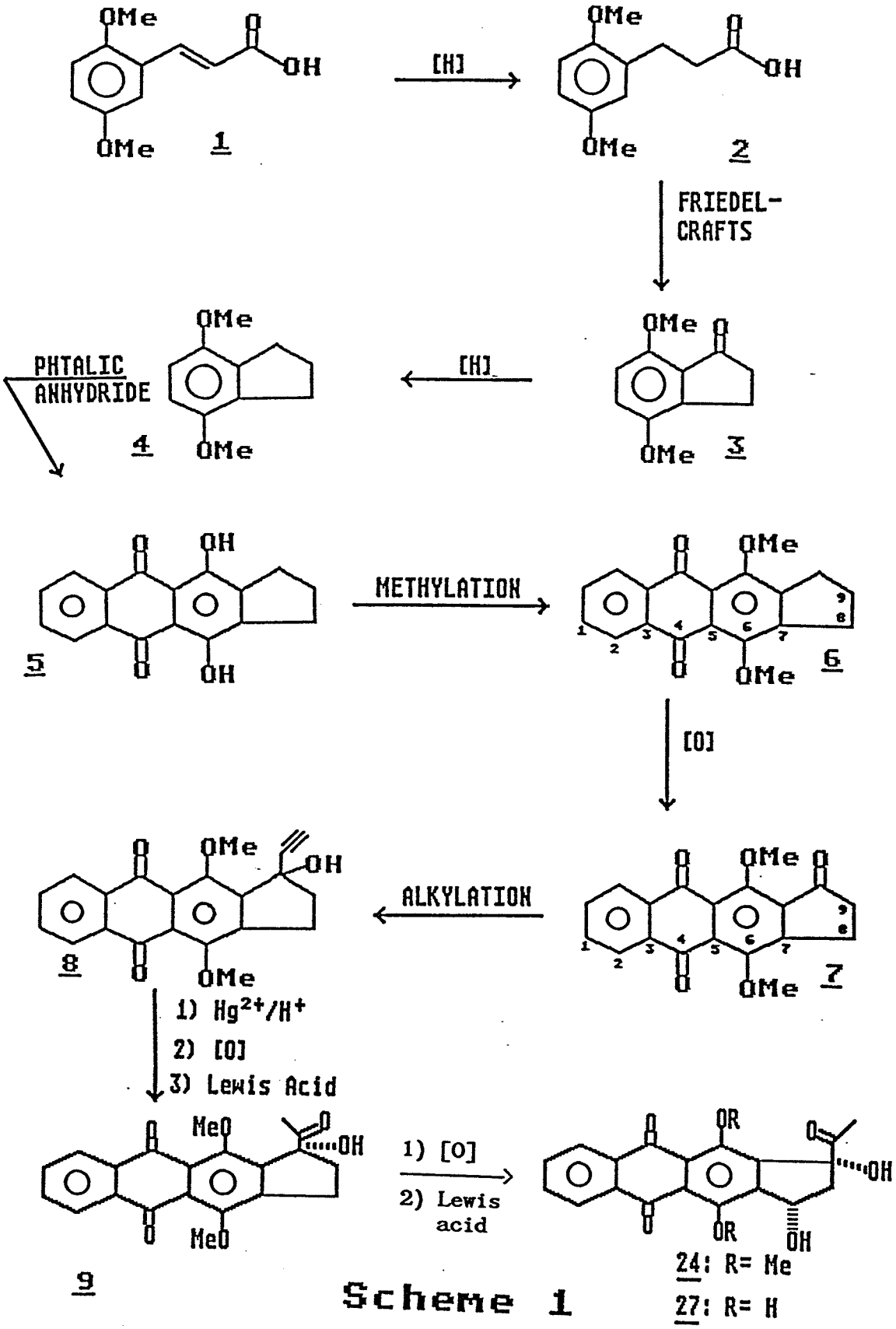
We then felt that since the introduction of the C7 hydroxyl functionality can, in principle, be achieved <u>via</u> radical bromination followed by solvolysis (6), we could focus our attention on the C9 functionalities. In fact, almost all the aglycone syntheses that are not highly convergent, i.e. having a functionalised (C7 and C9 hydroxyl groups) AB ring portion, do rely on Wong's method referenced above (6). The removal of the tertiary hydroxyl group should facilitate the Friedel-Crafts condensation in the retrosynthetic analysis shown below:



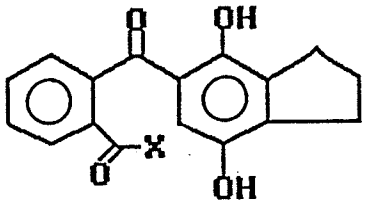
D E X=O, H_2

where the acyl anion equivalent is a metal acetylide, e.g., dilithium acetylide. However, the 1-indanone derivative E, (X=O), proved to be inactive to Friedel-Crafts condensations; presumably due to the

deactivation of the benzene ring by the carbonyl function. Presumably then, condensation of E ($X=H_2$) should reverse this inactivity. Indeed, this proved to be the case. The indane derivative E ($X=H_2$), condenses smoothly with phthalic anhydride to provide the tetracyclic skeleton. Thus, with that positive result, we proceeded as outlined in Scheme 1. 1,4-Dimethoxycinnamic acid was reduced catalytically with hydrogen and palladium on carbon to give the dihydrocinnamic acid derivative 2. It was anticipated that the reduction of the indanone derivative 3, to the indane derivative 4, would be achieved by triethylsilane in trifluoroacetic acid. Thus, it was decided to attempt the Friedel-Crafts intramolecular reaction in trifluoroacetic acid since, if this worked, the addition of triethylsilane can then effect the conversion of 2 to 4 essentially in one pot. However, the cyclisation in trifluoroacetic acid was not clean and was not pursued. A clean conversion to 2 to 3 was, however, effected in polyphosphoric acid and optimised to 80 % yield. The reduction of 3 to 4 proceeded without complications using triethylsilane and gave the indane derivative in high yield. The Friedel-Crafts acylation of 4 with phthalic anhydride also proceeded without any problems. The deep red to purple colour of the reaction of these substrates with aluminium chloride is indicative of the formation of, at least, some product. The harsh conditions (180-190 ^{o}C oil bath temp.) necessary for this condensation are due to the fact that this process consists of two steps. The initial adduct shown below deactivates the aromatic ring making the second condensation significantly more difficult than the first.


OMe
OH
OMe
1
[H]
OMe
OH
OMe
2
FRIEDEL-
CRAFTS
OMe
OMe
3
[H]
PHTALIC
ANHYDRIDE
OMe
4
OMe
OH
OH
5
METHYLATION
OMe
OMe
6
[O]
OMe
OH
OMe
8
ALKYLATION
OMe
OMe
7
1) Hg2+/H+
2) [O]
3) Lewis Acid
MeO
OH
MeO
9
1) [O]
2) Lewis
acid
OR
OH
OR
OH
24: R= Me
27: R= H

Scheme 1



X=Cl, O-$\bar{A}lCl_3$

Methylation 5 was achieved using a mixture of acetone/iodomethane/potassium carbonate at reflux for about 24 h. The colour change provides visible evidence of the progress of the reaction as it proceeds from red to yellow. It was certainly pleasing to see that the tetracyclic skeleton 6 could be generated rapidly and efficiently. We were quite anxious to have the tetracyclic indanone derivative 7 in hand since the conversion of 7 to 8 was viewed as the most challenging step. The benzylic oxidation was not as easy as had been anticipated. After an intensive search of the literature, it was decided to use chromium trioxide in acetic anhydride/acetic acid/H_2O as the oxidant. However, the conversion of 6 to 7 under various modifications as described (7), failed to give a worthwhile yield (about 15-20%). Nevertheless, the remaining starting material could be recovered. The oxidation was finally achieved, in modest yields (30-40%), by using chromium trioxide in acetic anhydride. Presumably, the reaction proceeds through the intermediate diacetate, which is hydrolysed upon aqueous workup.

With a workable amount of 7 in hand, the conversion to 8 was studied.

Although, the findings were disappointing, we learned something about the nature of the acetylide anion and its use in alkylation reactions.

The nucleophilic reagent, dilithium acetylide, was generated from acetylene and t-butyl lithium, initially at low temperatures (-78 ^{o}C) and later at 0 ^{o}C. Various stoichiometric ratios were used ranging from 1 equivalent to 8 equivalents and at various temperatures e.g. (-78 ^{o}C, -20 ^{o}C to room temperature, 0 ^{o}C to room temperature, room temperature) for varying reaction times ranging from 0.5 h to 4 days. Low reaction temperatures and small stoichiometric ratios favour recovery of unreacted material. Short reaction times with large excess of nucleophile initially favours the addition to the C5 and/or C11 carbonyl group. It was evident that the regioselectivity we had hoped for was going to be difficult to achieve. In one study, the reversibility of the addition to the quinone carbonyl group was demonstrated. When 8 equivalents of the acetylide was used, after about 0.5 h, it was clear that the quinone carbonyls were being attacked, in addition to the desired C9 carbonyl group as evidenced from the IR spectrum, Fig. 2 (a-e). After several days at room temperature, the intensity of the C5 and C11 carbonyl groups appeared stronger. By adjusting the pH to about 14 by adding varying amounts of tert-butyl alcohol, followed by acidification with hydrochloric acid to about pH=8 and allowing the reaction to stir for a total of seven days, it was seen that the reaction at the C5 and/or C11 carbonyl groups had been reversed significantly from that observed after 0.5 h (see Fig. 2, a).

Fig.2 (c) is an IR spectrum of 8 treated with the dilithium acetylide

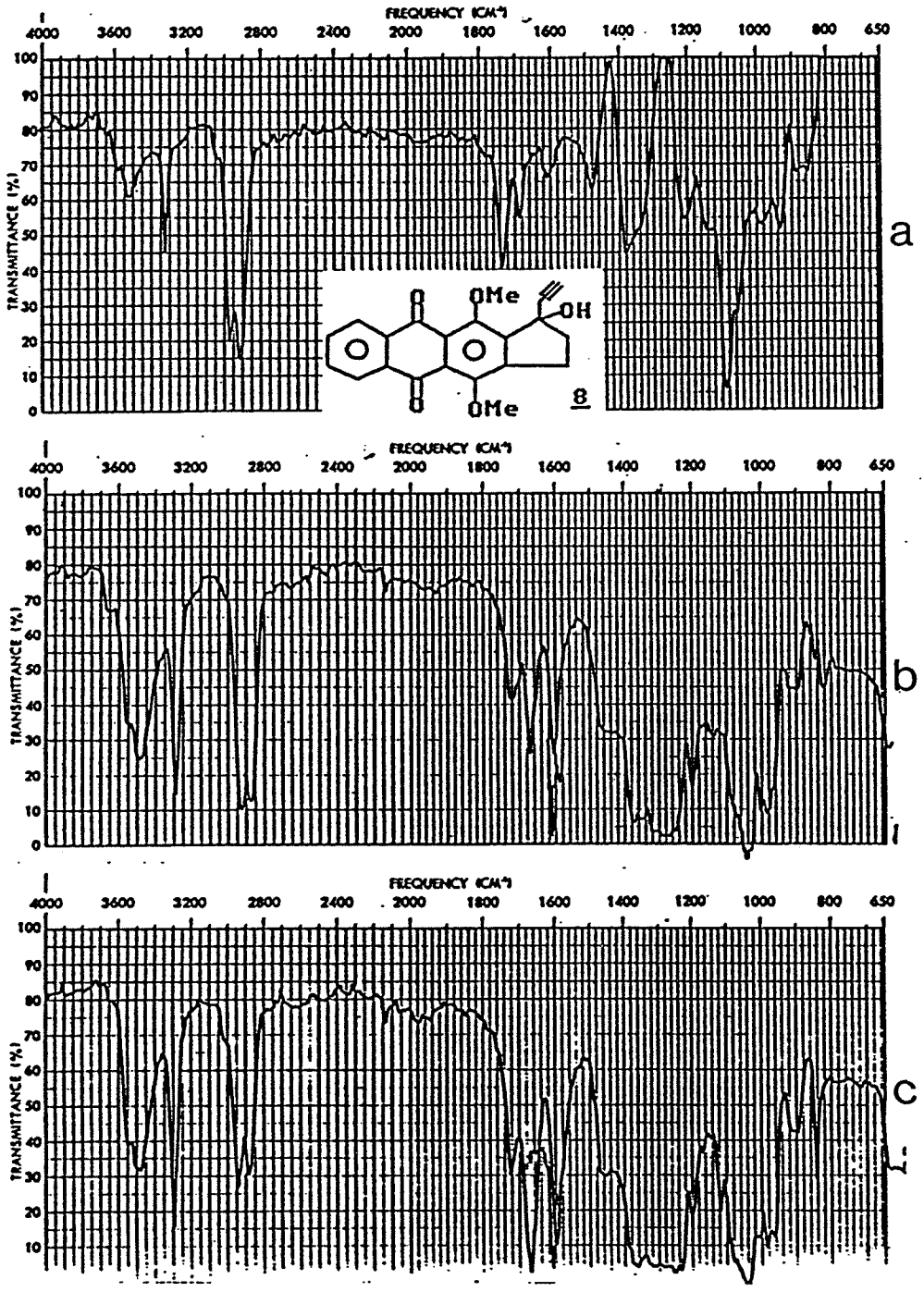


Fig. 2

a: 8 Molar excess/0.5 h

b: After 7 d

c: 2 Molar excess/22 h

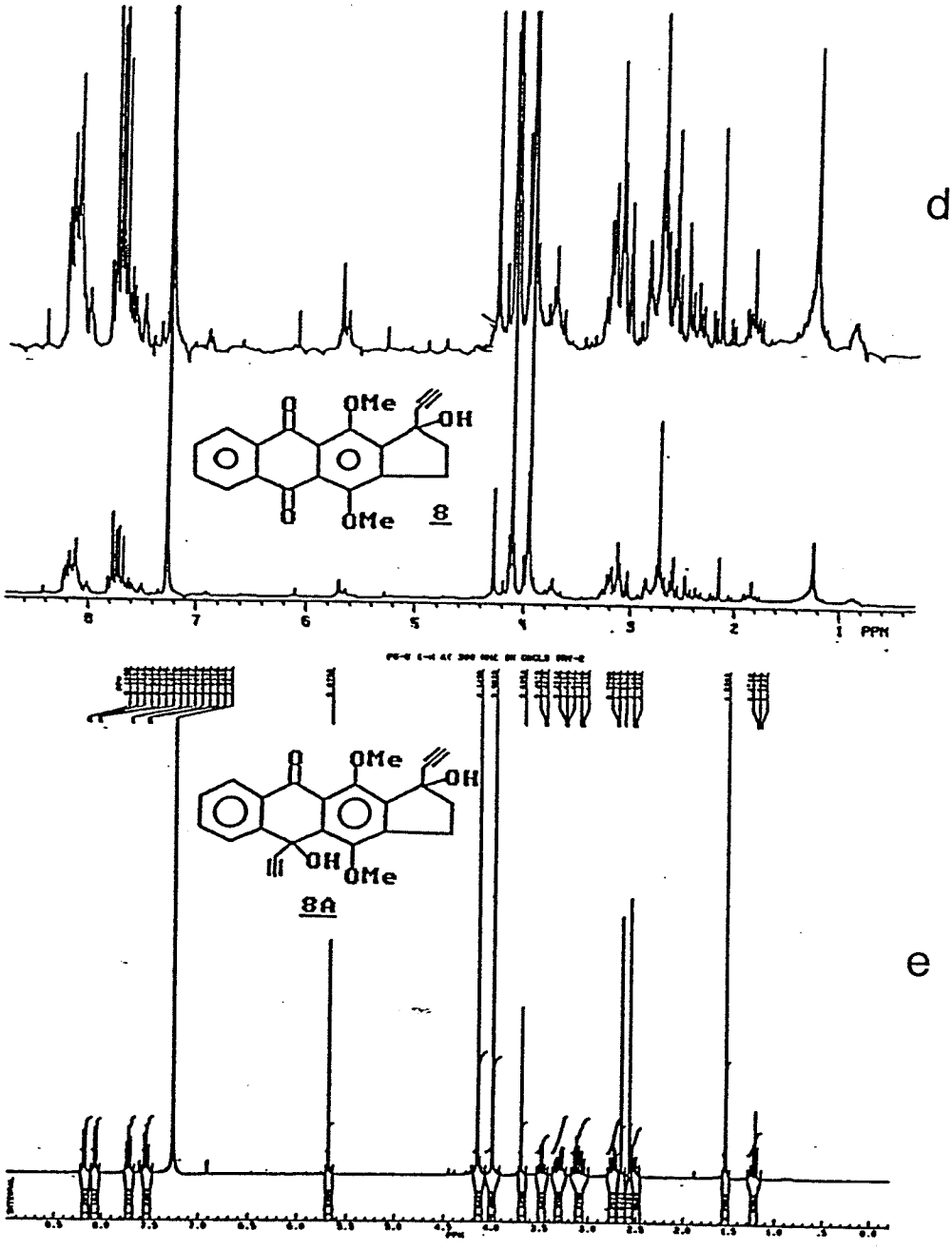
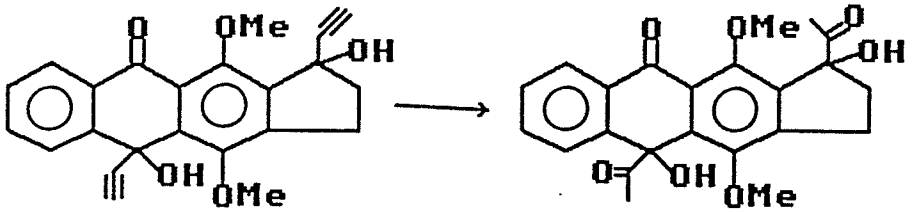


Fig. 2

reagent (2 equivalents) after 22 h. We found these conditions to be the "best" at that time. Since the reversibility of addition to the 5-membered carbonyl group appeared facile, the crude products from all the reactions were usually hydrolysed immediately to the stable hydroxy ketone 9. However, two preparative thin layer chromatographic (PTLC) samples from two of these experiments were procured for ^{1}H NMR analysis and their spectra are shown in Fig. 2 (d,e). Despite the fact that the ^{1}H NMR and IR spectra indicated that the acetylenic group was attached to the 5-membered ring in both samples, in one sample the mass spectrum ($M^{+\cdot}$ 374 amu) indicated the presence of another compound containing an additional acetylene functionality. The structure of this product, 8A, (proposed on the grounds of steric stability in the product and subsequently isolated as a solid (m.p., 220^o C)), was characterised by its ^{1}H NMR (see Fig. 2, e) and mass spectra. The ^{1}H NMR spectrum of the diacetylenic compound shows the two acetylene signals at 2.57 ppm and 2.66 ppm, and the two hydroxyl protons at 3.69 ppm and 5.68 ppm. The difference in the AA'BB' pattern between 7.50 ppm and 8.30 ppm is also noteworthy. It should be mentioned here that the hydrolysis product 9A, corresponding to the diacetylenic alcohol 8A, was not detected.



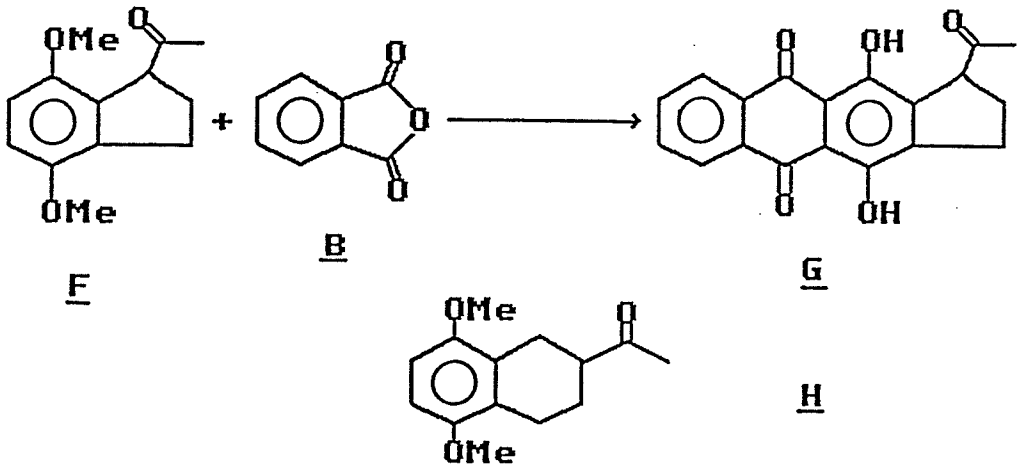
8A 9A

In light of the observations and the foregoing, it is reasonable to suggest that, during hydrolysis, the addition of dilithium acetylide to the quinone carbonyl group is partially reversed and that the desired monoacetylenic alcohol is most probably not the only precursor of the stable hydroxy ketone.

The reduction of 3 to 4 (Scheme 1) can be easily monitored by both the colour change (from red to colourless) and by IR spectroscopy (i.e., the disappearance of the carbonyl group frequency). The ^{1}H NMR spectrum reflects the symmetry of the molecule, thus showing a triplet at 2.91 ppm and quintet at 2.10 ppm, for the C1, C3, and C2 hydrogens respectively and the equivalency of the methoxyl and benzene ring hydrogens. The integrity of the methyl ethers is not preserved during the acylation reaction (4 to 5) as indicated by the appearance of the phenolic hydrogens at 13.13 ppm in 5. Here again, the symmetry of the molecule is evident from its ^{1}H NMR spectrum. Likewise, for the conversion of 5 to 6 the absorption of the phenolic hydrogens at 13.13 ppm disappears and the absorption of the new methoxyl hydrogens appear at 3.93 ppm as a singlet. It should be noted here that both compounds, 5 and 6, can be crystallised as beautiful red and yellow needles, respectively. The introduction of the C9 oxygen in 7 destroys the symmetry which was evident in 5 and 6 (cf 3 and 4) and the ^{1}H NMR spectrum of 7 reflects this.

In view of the problems which were encountered with regard to the regioselective addition of lithium acetylide to the 5-membered carbonyl of 7, an alternative approach was investigated. Obviously, one way to alleviate the problems encountered, in going from 7 to 8, is to have the

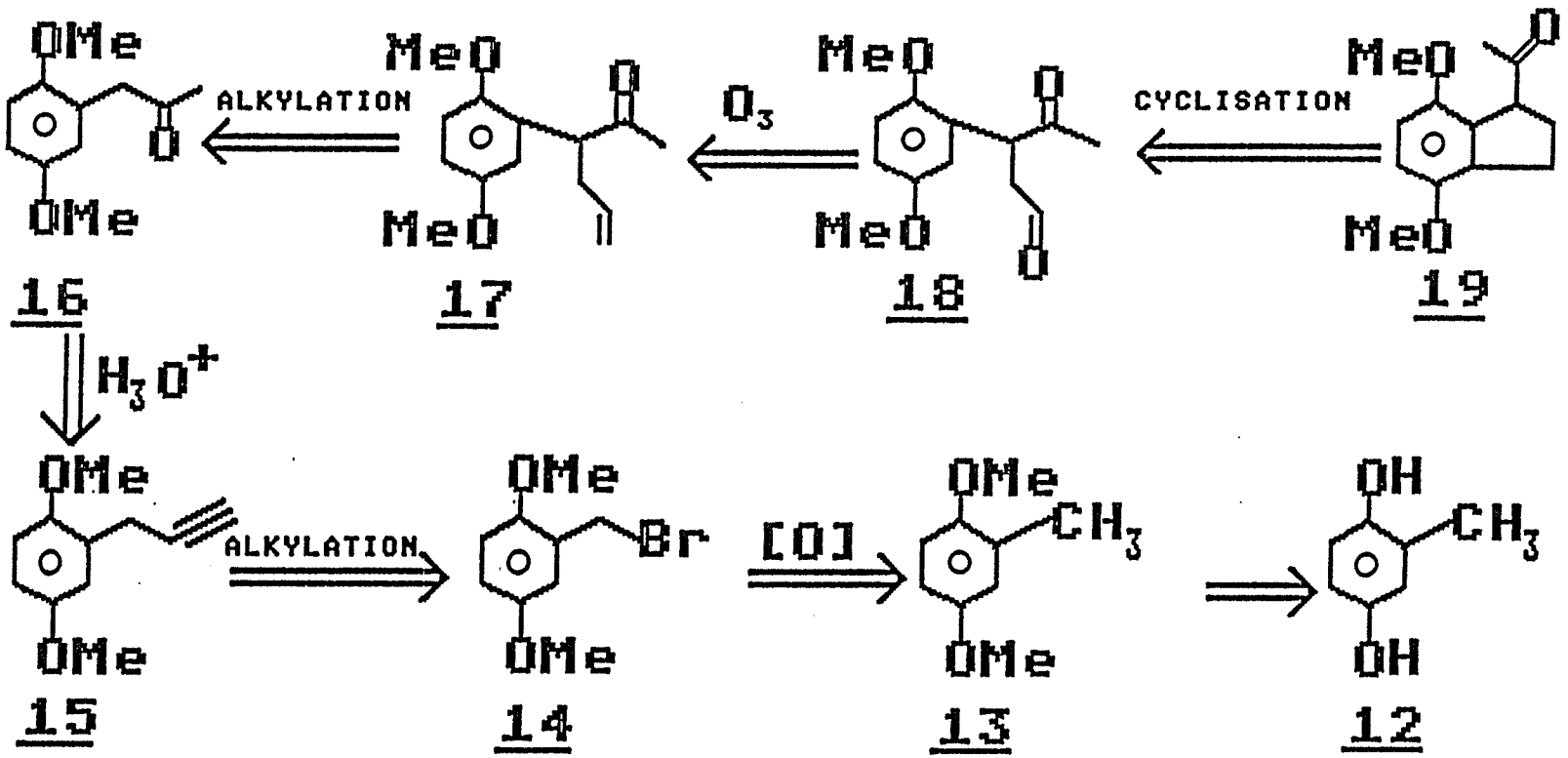
C9 acetyl functionality present at the time the Friedel-Crafts acylation is effected. i.e.



F B G H

It was expected that the carbonyl group in F would not deactivate the ring in the Friedel-Crafts acylation since the carbonyl function was not conjugated to the aromatic ring. The main focus was then to develop a feasible synthesis of the target molecule F. Owing to our experience with the synthesis of the six membered tetralin analogue H, a plan was devised as shown in Scheme 2, which closely parallels the synthesis of the six membered tetralin, H, (8).

2-Methyl-1,4-dihydroxybenzene 12, was efficiently methylated in toluene/sodium hydroxide (aqueous) with dimethyl sulphate to produce 1,4-dimethoxy-2-methylbenzene 13 (ca., 90%). The monobromo benzyl derivative was selectively produced using N-bromosuccinimide (1.1 equivalents) in boiling carbon tetrachloride while radiating with a Hanovia lamp under nitrogen. Under these experimental conditions, there did not appear to be any side products (e.g., ring bromination, which was effectively suppressed by passing nitrogen through the solution for the duration of the reaction time, or bis bromination). The reaction


OMe
OMe
ALKYLATION
MeO
MeO
O3
MeO
MeO
CYCLISATION
MeO
MeO
16
17
18
19
H3O+
OMe
OMe
ALKYLATION
OMe
Br
OMe
[O]
OMe
CH3
OMe
OH
CH3
OH
15
14
13
12

SCHEME 2

can be easily monitored as the clear suspension first becomes light yellow in colour then clear and the N-bromosuccinimide, which is denser than carbon tetrachloride, is transformed into succinimide, which is less dense and therefore rises to the top. Thus, the stirring and passage of nitrogen can be halted and the quantity of N-bromosuccinimide which remains at the bottom can be visually estimated.

The ethynylation of the benzyl bromide derivative 14, was first attempted using monolithium acetylide reagent prepared essentially according to Midland (9). The lithium acetylide reagent was generated in tetrahydrofuran at -72 ^{o}C with t-butyl lithium and the bromide added (substrate:reagent, 1:1.5) at that temperature. The solution was allowed to stir at -72 ^{o}C for 0.5 h then allowed to warm up to room temperature and stirred for 3 h. However, upon work up, IR spectroscopy did not indicate any product at all but mostly starting material. The reaction was repeated using three other conditions:

1. 3 equivalents of lithium acetylide and adding the solution of the bromide in tetrahydrofuran at -74 ^{o}C over 35 min., then allowing the solution to warm up to 10 ^{o}C,
2. using 5 equivalents of lithium acetylide and repeated as in 1., except anhydrous ether was used as the the solvent, and
3. 10 equivalents of lithium acetylide in dimethyl formamide/anhydrous ether (1:1) and after warming up to room temperature, the solution was allowed to stir for 4 h. In all three cases, little or no product but mostly starting material was observed by IR spectroscopy.

Since the sodamide/liquid ammonia method has always been an effective

method of generating one form of the acetylide reagent we decided to try that method. After generating the sodium acetylide reagent, the ammonia was allowed to evaporate and anhydrous ether was added. A solution of the bromide was added and the reaction mixture was refluxed overnight. On analysis, there was a small peak at approximately 3290 cm^{-1}. However, unlike previous attempts where starting material was recovered, this product was an oil which on distillation did not display the spectral properties consistent with the desired product. In view of that result, we did not pursue this method any further. Preparation of the Grignard reagent derived from the benzyl bromide derivative 14 was attempted and this reagent was treated with acetonitrile. This reaction also failed as IR spectroscopy again indicated only starting material. This method was also abandoned since work by Cannone et al. (10a), Alvernhe and Laurent (10b), and Chastrette et al. (10c) did not present an encouraging prognosis for this type of reaction, since yields quoted were low.

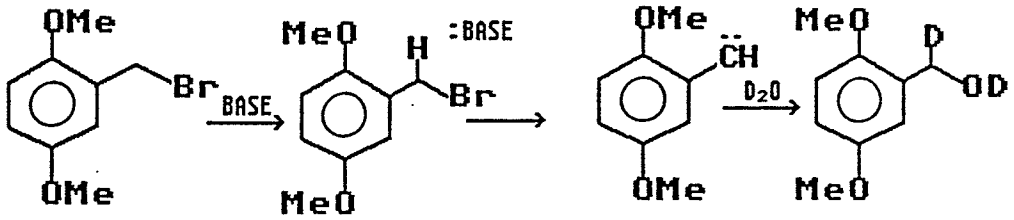
Next, the Grignard reagent of acetylene was made by adding methylmagnesium iodide to a solution of acetylene in dry tetrahydrofuran with continuous infusion of acetylene. The benzyl bromide derivative was added in one portion to the mono (or di?) acetylenic Grignard reagent and the reaction allowed to stir overnight. However, the IR spectrum was very similar to starting material. This reaction was repeated but instead the methylmagnesium iodide was filtered under nitrogen prior to addition to a solution of acetylene in anhydrous ether with continuous passage of acetylene. Again, spectroscopic analysis indicated only starting material.

It was at this point that the literature was consulted with regards to generating the acetylide reagent from an alkyl Grignard reagent. The information gleaned suggested that ethylmagnesium bromide is best for this purpose and that the acetylene needed to be purified (acetone being the major impurity). Acetylene was purified by passing the gas sequentially:

1. through a dry ice/acetone trap,
2. through concentrated sulphuric acid,
3. through a drierite filled tube, and
4. through activated alumina or soda lime (11).

Ethynylmagnesium bromide was prepared from ethylmagnesium bromide and acetylene according to Skattebol et al. (12). In this way, the bromide 14, was added to the ethynylmagnesium reagent (1:10 equivalents) and the reaction mixture allowed to stir for 6 h at room temperature. Again, only starting material was obtained. The reaction was repeated but the mixture was refluxed for 4 h then allowed to stir overnight. Both IR and ^{1}H NMR spectroscopy indicated that there was some product present. Despite the fact that the ^{1}H NMR spectrum indicated a substantial amount of starting material, the peaks at 2.2 ppm and 3.59 ppm were indicative of the resonances of the respective acetylene and methylene hydrogens of 15.

During the workup of this reaction, the mixture was quenched with D_2O because a possibility of carbene formation was suspected as indicated below:

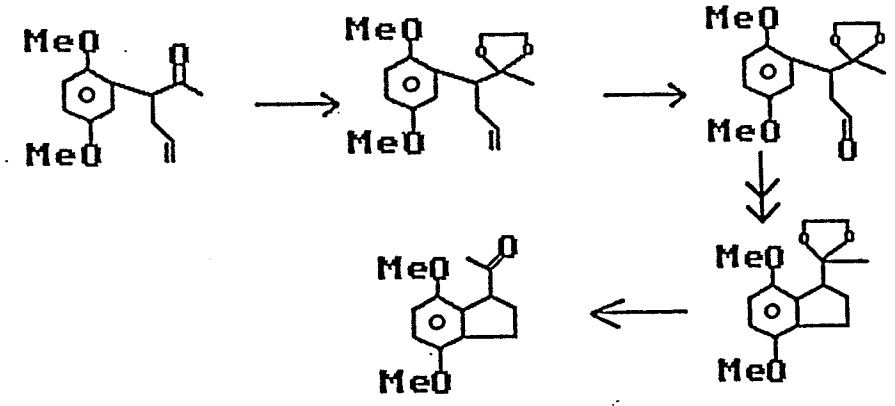


However, this did not result in any deuterated product. The result alluded to above indicated that one of the unsuccessful attempts was due to the lack of reactivity of the alkylating agent. Therefore, the experiment was repeated in which the reaction mixture was refluxed for about 22 h. The ^{1}H NMR analysis indicated about 35% of the product present. We were confident that we were on the right track and, indeed, refluxing the mixture for 3 days, then hydrolysing the product with aqueous sodium hydroxide gave a product that showed both a negligible hydroxyl stretch and a triple bond CH stretch in the IR spectrum. The former, however, was negligible. Hydrolysing the reaction mixture with aqueous base resulted in the benzyl alcohol derivative simplifying the chromatographic separation of the desired non-polar acetylene derivative. Thus, for large scale preparations (10 g) of 15, the mixture was refluxed (75–80 ^{o}C) for about 5 days and the yield (^{1}H NMR analysis) was typically 94%.

With the acetylene derivative 15, in hand, the hydrolysis of the crude product (catalytic amount of mercuric acetate/acetic acid (80%)) was straightforward and the propanone derivative 16 was purified by column chromatography. This ketone was alkylated with potassium carbonate/allyl bromide and the product separated from starting material by column chromatography. This allyl derivative, 17, was ozonised at -78 ^{o}C in methylene chloride, the progress of the reaction being monitored by IR spectroscopy for the disappearance of C=C stretch. Nitrogen was substituted for ozone when this was being done. When the reaction was complete, the ozonide was reduced by adding trimethylphosphite at reflux for 24 h. The keto aldehyde, 18, was usually purified from a small amount of unreacted alkene. On one occasion, the aromatic ring was destroyed due to over oxidation and therefore it was more desirable to have some unreacted alkene present since this presented no problems in purification.

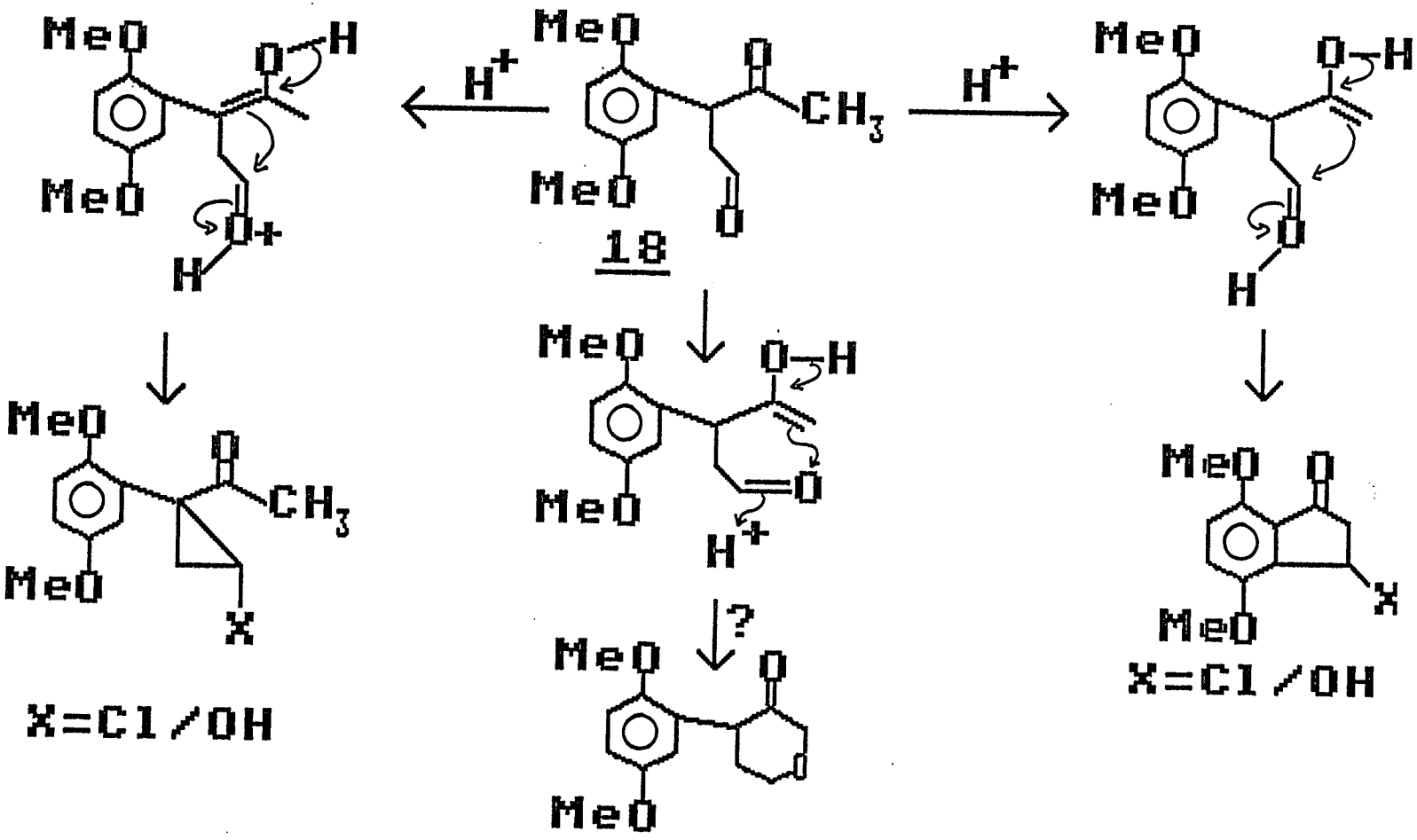
All attempts to cyclise the aldehyde, 3-acetyl-3-(2,5-dimethoxyphenyl)-butanal, 18, in methylene chloride saturated with gaseous hydrochloric acid at low temperatures followed by hydrogenolysis of the intermediate chloride (or alcohol) in ethanol in the presence of palladium on carbon failed. This is in direct contrast to our previous experience with the six membered analogue, H (see 8,13). Similarly, changing the acid from hydrochloric acid to trifluoroacetic acid did not produce the desired acetylindane derivative. In fact, by these methods we have not been able to isolate any of 19 in a pure state for analysis. In all but one of the cases, the disappearance of the CH stretch of the aldehyde 18 was evident in the IR spectrum and an absorption appeared in the region in

the region in which one might expect the acetyl frequency to appear. However, as the ^{1}H NMR spectra showed, in some cases, the acetyl absorption was sometimes absent and accompanied by other resonances which seem to belong to a different kind of methyl group. The ^{1}H NMR and IR results do not lend themselves to an easy interpretation and do not appear to be compatible with some of the pathways for undesirable side reactions (Scheme 3). The results are still a conundrum to us but one might speculate that the removal of one carbon (C4 in H) increases the activation barrier for cyclisation to form the desired five membered ring. It would be informative to see what results would be obtained if the ketone were protected before the ozonolysis step and the ketal aldehyde was used to perform the cyclisation as outlined below:



It should be noted here that these results support a major principle for organic synthesis which is directed towards a target molecule: that is, a versatile approach should be used which allows an intermediate to be converted into a target molecule by several ways. It can be absolutely disastrous to rely on **a single** approach.

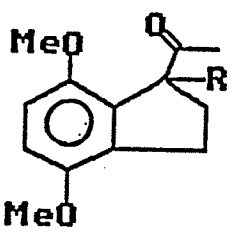
While we were having problems with the hydrochloric acid cyclisation of



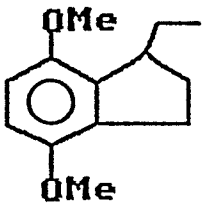
SCHEME 3

the keto aldehyde 18, we began looking for an alternative method of making the acetylindane derivative 19 in order to have an authentic sample of the material as a standard. Since we had some of the 1-acetoxy-1-acetylindane derivative, D (R=Ac), which was used in earlier model studies, we sought to reduce this compound to the desired material. Hydrogenolysis was chosen since this can be performed expeditiously. The reduction was conducted in ethanol containing a few drops of concentrated hydrochloric acid with 10% palladium on carbon for 10 h. IR spectra were taken at 2, 4, 9, and 10 h and showed that several reactions had occurred over those times.

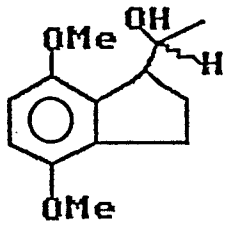
First, after 2 h, one could observe that the acetyl carbonyl group underwent reduction preferentially since the intensity of the carbonyl stretch diminished with concomitant appearance of the hydroxyl stretch at approximately 3450 cm^{-1}. However, after 4 h, the rate of reduction of the acetate seemed to increase but the increasing hydroxyl absorption indicated that the acetyl function was being reduced. After 9 h, the spectrum showed a stronger hydroxyl absorption and a single carbonyl group absorption and TLC indicated three spots, all of which were different in rf value from the starting acetate. Therefore, it was speculated that the three products were the completely reduced product, 19A, the hydroxyethyl indane derivative, 19B, and the desired acetylindane derivative, 19, shown below.



19 (R=H)



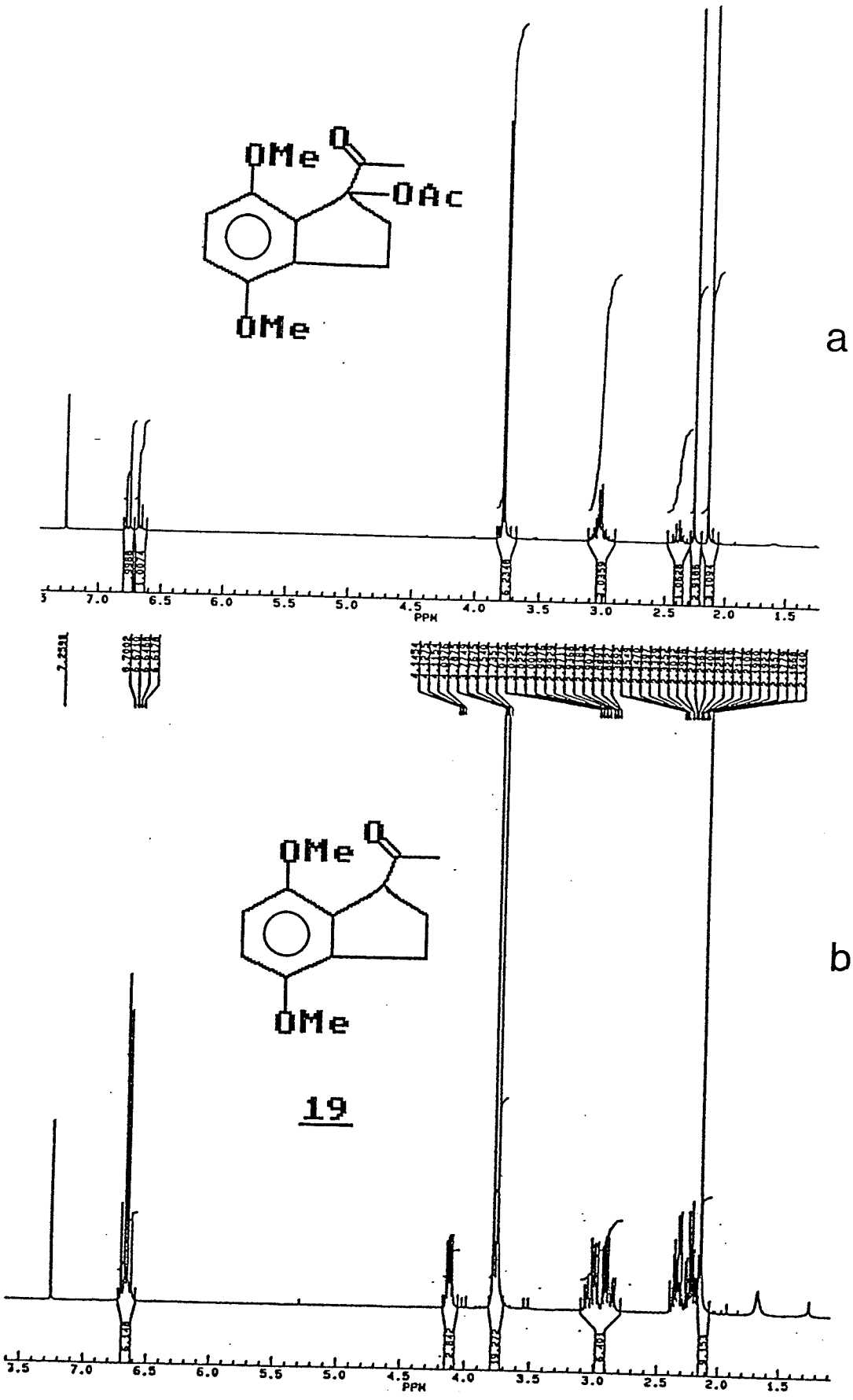
19A



19B

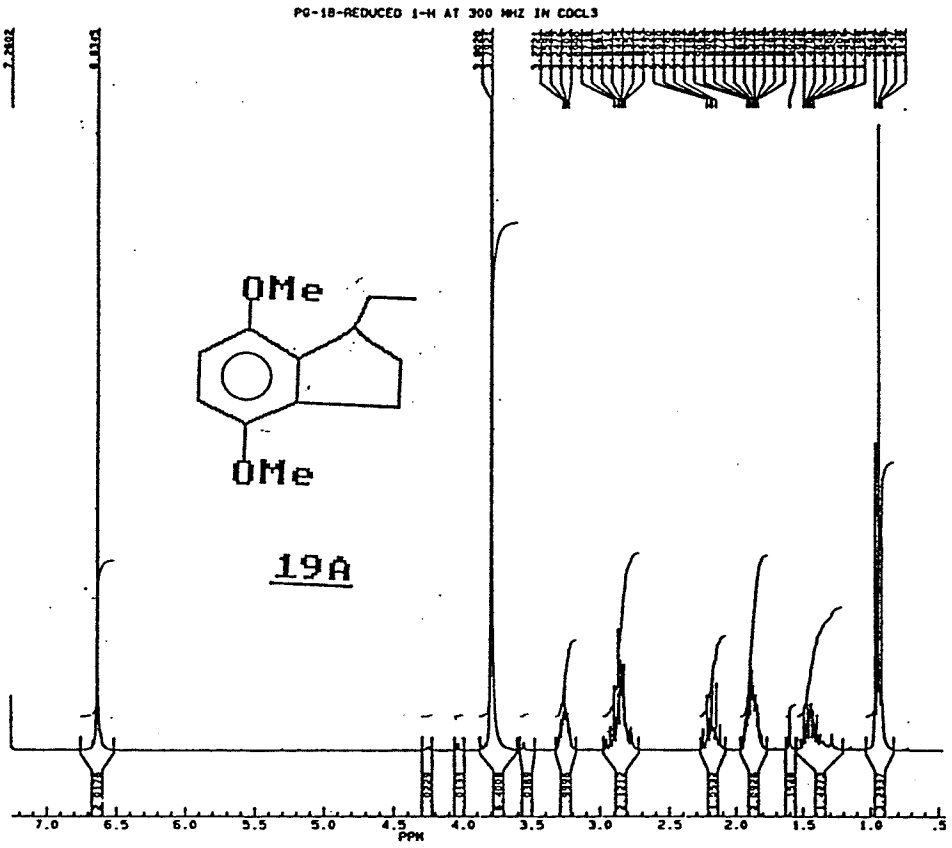
Preparative TLC afforded pure 19, 19A and 19B and ^{1}H NMR and IR spectroscopy confirmed the putative structures as assigned. The ^{1}H NMR spectra of these products together with D (R=Ac) are shown in Figs. 3 (a-d). Not unexpectedly, the hydroxyethyl derivative, 19B, (one spot by TLC) occurs as a mixture of diastereoisomers as evidenced by the ^{1}H NMR spectrum. The two doublets centered at 1.15 ppm and 1.05 ppm and the peaks centered at 3.82 ppm and 3.79 ppm are due to the methyl and methoxy protons respectively of the two diastereoisomers. With the aid of COSY-45 (COrrelation SpectroscopY) all the proton resonances were unambiguously assigned (see experimental section).

Despite the lack of chemoselectivity in the reduction of 1-acetoxy-1-acetyl-4,7-dimethoxyindane D, we were able to acquire, for the first time, an authentic sample of the desired 1-acetyl-4,7-dimethoxyindane 19 for mass spectrometric, infrared and nuclear magnetic resonance spectroscopic and melting point analysis. The compound was off white in appearance melting at 56-58 ^{o}C, with a carbonyl absorption at 1710 cm^{-1}. Its ^{1}H NMR spectrum displayed all the characteristic features that one would expect; viz the AB pattern for H_5 and H_6 (indane numbering) of the

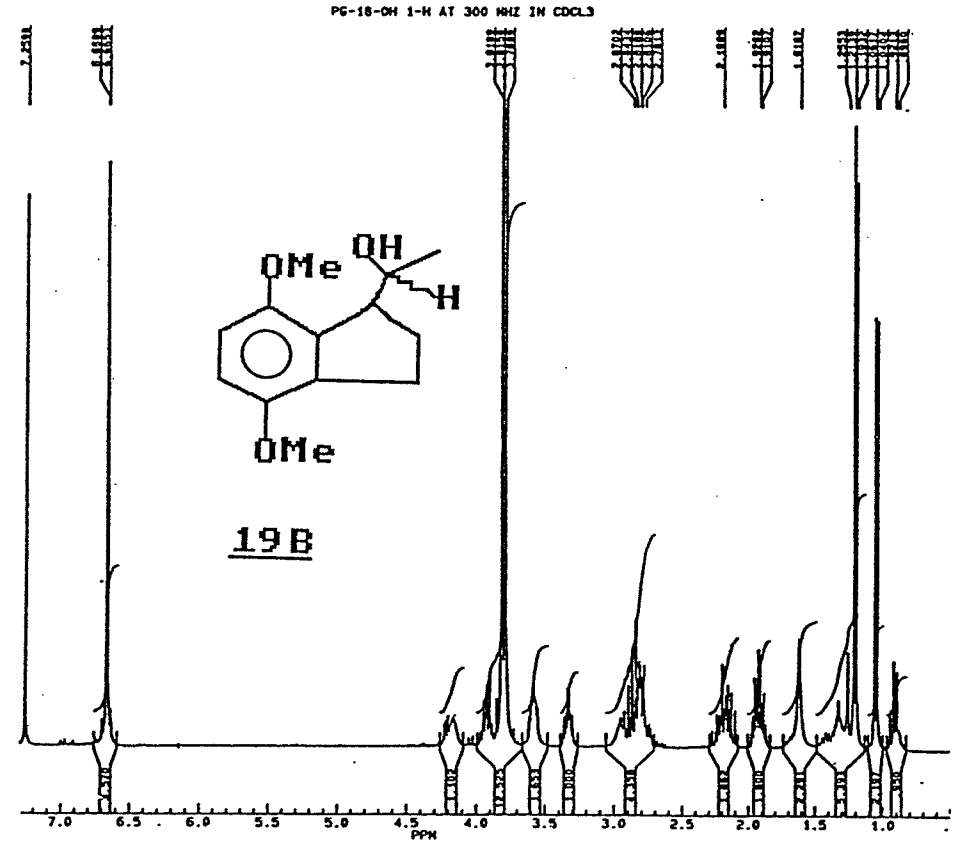


19

Fig. 3


PG-18-REDUCED 1-H AT 300 MHZ IN CDCL3
OMe
OMe
19A
PPM

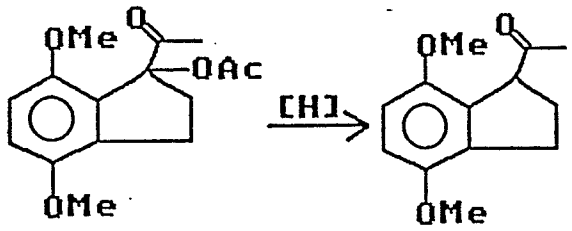
c


PG-18-OH 1-H AT 300 MHZ IN CDCL3
OMe
OH
H
OMe
19B
PPM

d

Fig. 3

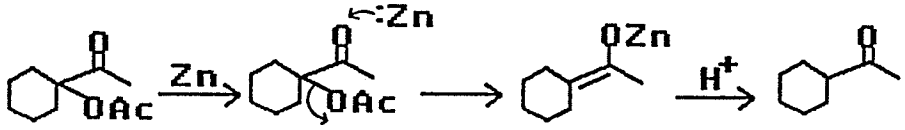
aromatic ring, the doublet of doublets for the C1 hydrogen and the ABX and the AB splitting pattern for the C2 and C3 hydrogens. Since the reduction of such systems, for example, $\underline{\alpha}$ bromoketones, α-hydroxyketones, $\underline{\alpha}$ acetoxy ketones, and hydrogenolysis of benzylic alcohols are well known (14), it was felt that a method to achieve the following transformation should not be too difficult to find.

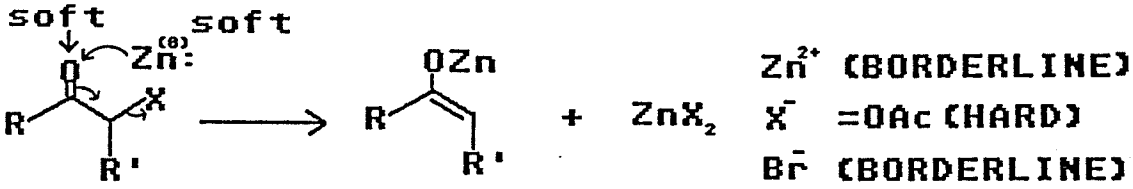


The simplest method attempted was the well known zinc/acetic acid reduction. However, under those conditions (zinc /acetic acid (90%)) the only product was the hydrolysed 1-hydroxy-1-acetyl-4,7-dimethoxyindane, D (R=H). However, this reaction was easily suppressed by using acetic anhydride/acetic acid mixture and heating between 120-130 ^{o}C for 24 h. This method produced the desired material but only in 40% yield. This low yield is due to the formation of an intractable dimer or polymer (based on mass spec. data) but yet to be identified. Its IR spectrum seems to suggest that a carbonyl group is still present. The IR spectrum also indicates that there is a medium intensity carbonyl group absorption at 1750 cm^{-1} suggestive of an ester (acetate?). Its ^{1}H NMR spectrum does not display an acetyl resonance and its ^{13}C NMR spectrum does not show any carbonyl group absorption. These data are

informative but not very helpful in interpreting what this product might be.

The accepted mechanism for the formation of the reductive product of an acetoxy ketone is shown below (14):

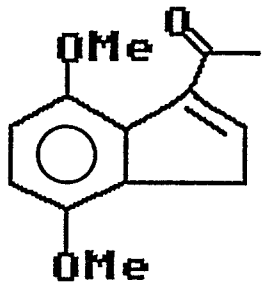




The zinc metal donates electron(s) to the carbonyl oxygen which results in displacement of the acetate anion to form the zinc enolate. Protonation of this enolate then results in the deacetoxylated product. This type of reduction may also be rationalised by the **Hard and Soft Acids and Bases Principle** (**HSAB**) (15a,b).

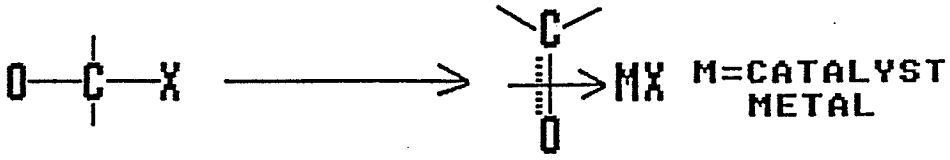
It seems reasonable ,based on the above mechanism, to suggest that the zinc enolate is not an intermediate in the formation of the dimer/polymer since that enolate should readily tautomerise to the acetylindane derivative which should be stable to the acidic conditions employed. The most likely intermediate in the formation of this by-product is the 1-hydroxy-1-acetylindane derivative, D (R=H), formed as a result of hydrolysis of the acetate. This hydrolysis and/or dimerisation/polymerisation are known to be facile, under other conditions where zinc has been used as a reducing agent (vide infra.).

Since it was felt that the acidic conditions were adverse to the formation of the desired material but seemed to facilitate the formation of the dimer (polymer?), it was decided to try neutral conditions for the reduction. To that end, we prepared zinc-copper couple in three different ways (16). The reduction was carried out in a number of different solvents, e.g. 95% ethanol and absolute ethanol and absolute methanol. However, the products obtained were mainly that of starting material and the 1-hydroxy-1-acetylindane derivative, D (R=H), resulting from hydrolysis accompanied by small amounts of the desired ketone, 19. In some cases, a product having an absorption at 1680 cm^{-1} in the IR spectrum was observed. We assigned the structure below solely on the basis that the 1680 cm^{-1} peak disappeared on hydrogenation with palladium on carbon in glacial acetic acid.



The stability of the acetoxy group in the 1-acetoxy-1-acetylindane derivative, D (R=Ac), towards catalytic hydrogenation under the conditions employed is most probably due to the fact that these sterically hindered compounds are not well adsorbed onto the catalyst's surface. One of the proposed mechanisms for hydrogenolysis of benzyl alcohol derivatives is the formation of a π benzyl intermediate with the

benzylic carbon undergoing a change of hybridisation from tetrahedral to planar, shown below (16).

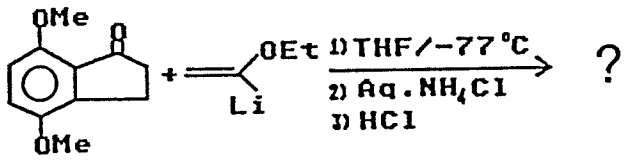


Based on the mechanism outlined above, and taking into account that the acetoxy group is expected to be a better leaving group than the hydroxyl group, it may be concluded that the resistance of the 1-acetoxy-1-acetylindane derivative, D (R=Ac), to hydrogenolysis is presumably the lack of effective adsorption on to the catalyst's surface, i.e. steric hindrance to adsorption.

Early in our synthetic efforts, parallel experiments were conducted to ascertain the feasibility of hydrogenolysing D (R=H) to the desired acetylindane derivative, 19. Thus, the aim was to synthesise D. The acyl anion equivalent, α ethoxyvinyllithium, was chosen for the introduction of the acetyl functionality (18).

Contrary to the findings of Baldwin et al. (18), it was observed that enolisation was the main reaction as evidenced by recovered starting material. However, a product (less than 100 mg) was isolated by thin layer chromatography (after hydrolysis in aqueous 0.02 M hydrochloric

acid) which displayed a hydroxyl and carbonyl adsorption. It was felt that this product was the expected 1-acetyl-1-hydroxy-4,7-dimethoxyindane; especially in view of the fact that its molecular weight (mass spectrum) was 236 amu corresponding to an empirical formula of $C_{13}H_{16}O_4$. However, as evidenced by its NMR spectrum, that prediction proved to be wrong. A doublet, centered at 1.29 ppm is indicative of a methyl resonance attached to a methine carbon. The structure elucidation of this product was as follows.



The ^{13}C-proton decoupled spectrum (Fig. 4j) confirmed that the molecule has thirteen carbons. Included in that number is one carbonyl carbon and four other carbons bearing no hydrogens. The DEPT (Distortionless Enhancement Polarisation Transfer) sequence shown in Fig. 4 (k) provides a method of determining the number of attached hydrogens to a given carbon. The traces (from bottom to top) give:

1. the normal spectrum,
2. all carbons bearing hydrogens,
3. all methine carbons up, and
4. methylene carbons down and methine and methyl carbons up.

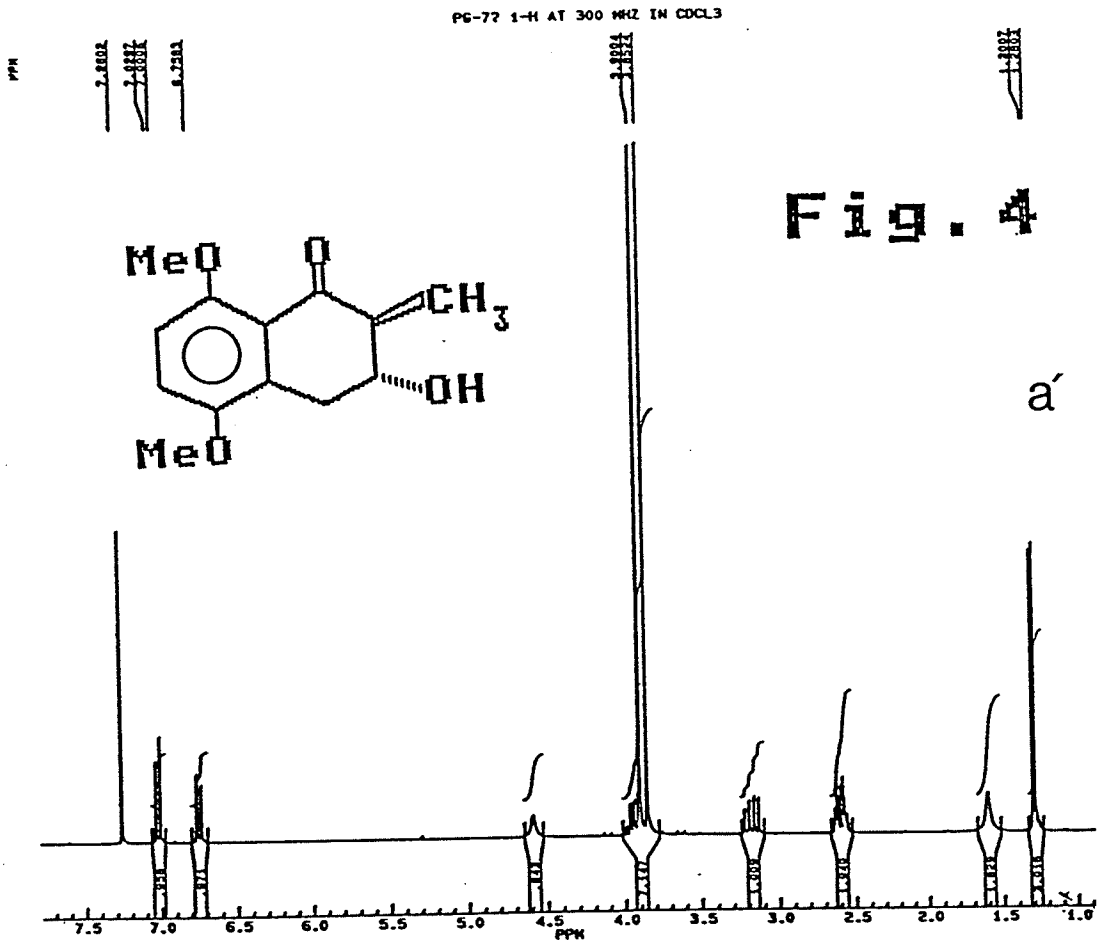
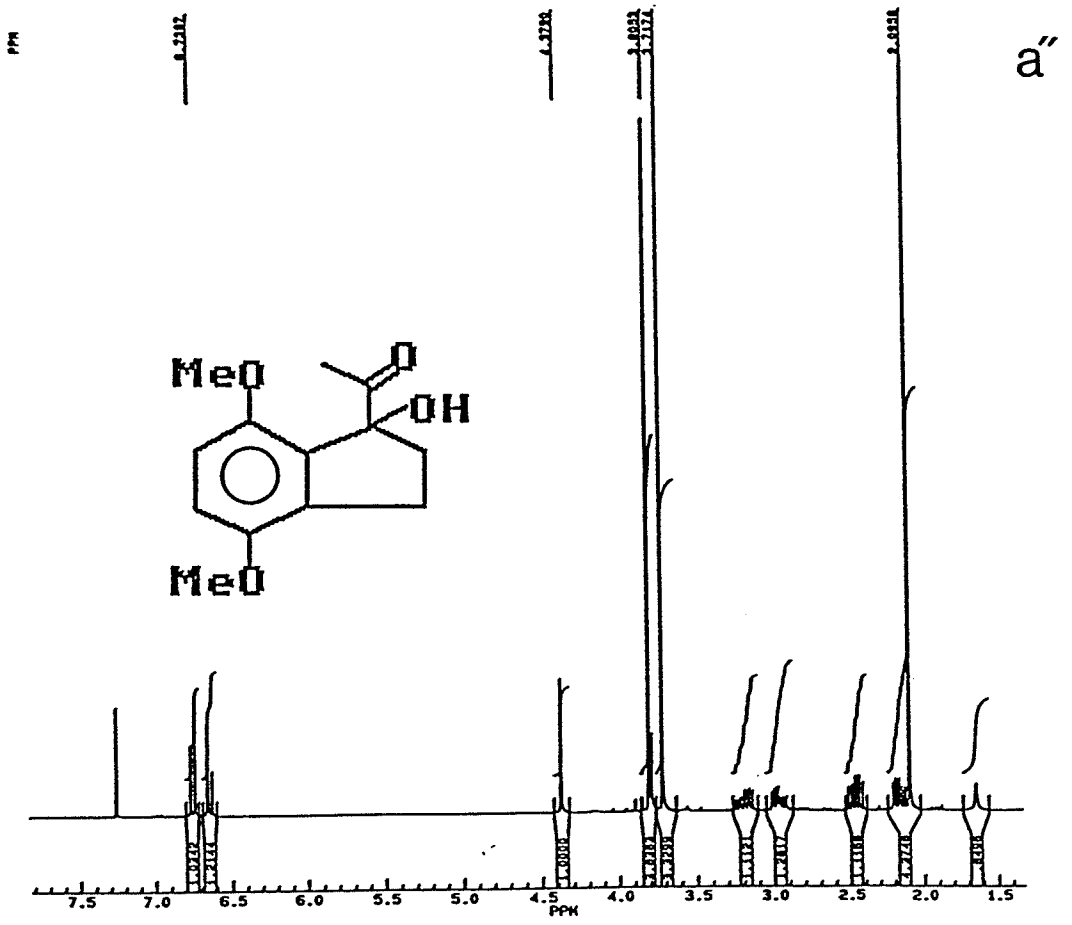

PG-77 1-H AT 300 MHZ IN CDCL3
PPM
MeO
O
CH3
OH
MeO
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
PPM

Fig. 4

a'


PPM
MeO
O
OH
MeO
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
PPM

a''

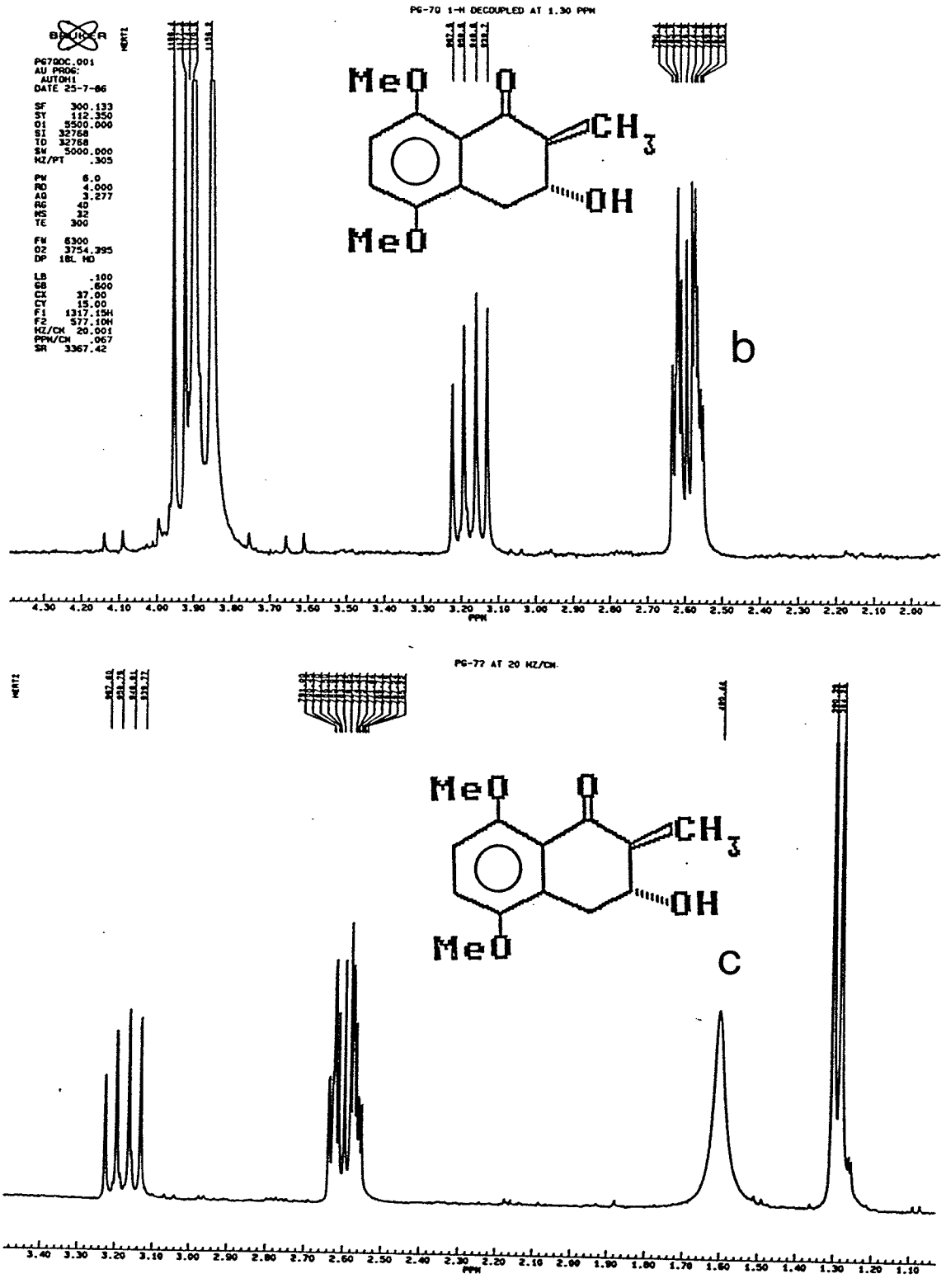
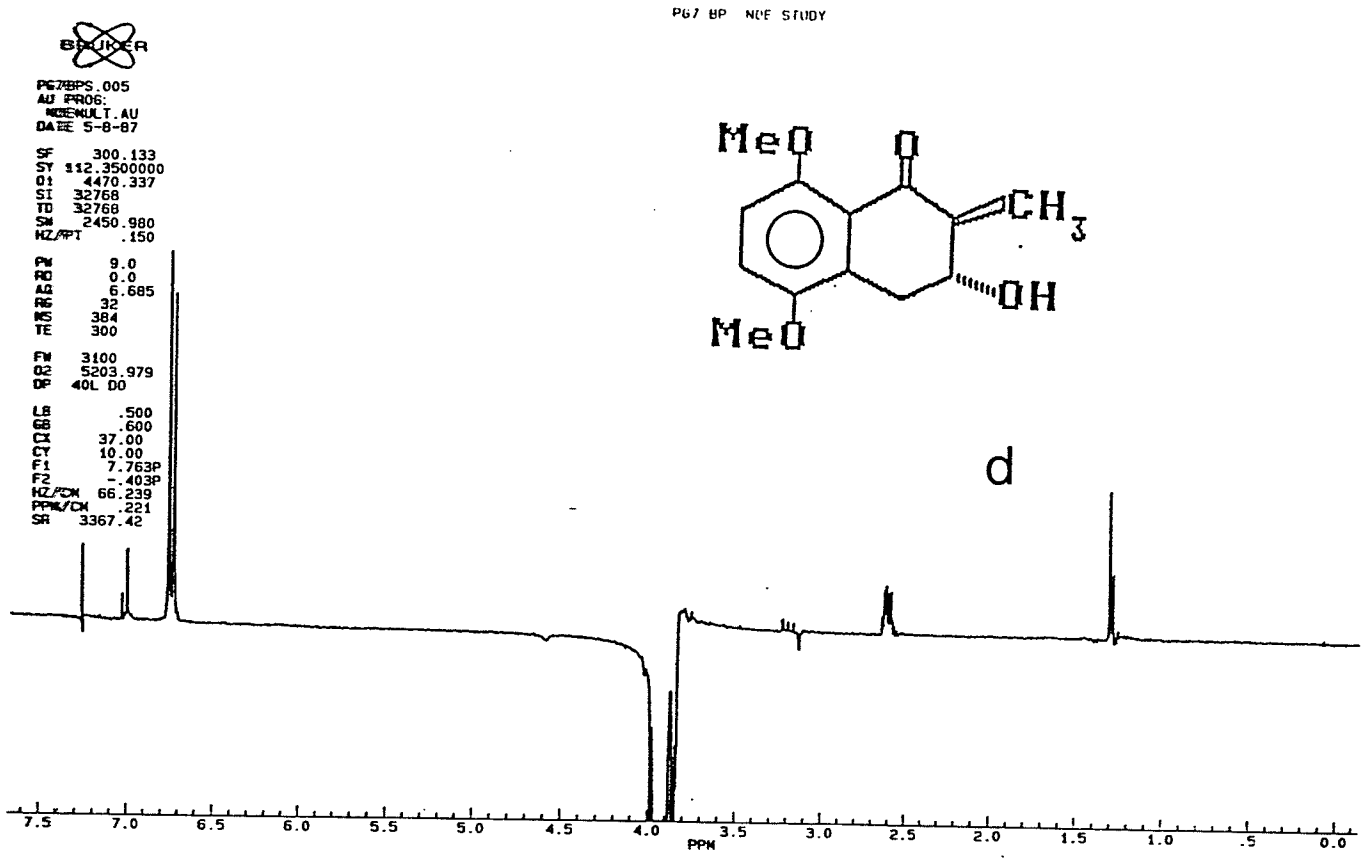

PG-70 1-H DECOUPLED AT 1.30 PPM
MeO
O
CH3
OH
MeO
b
PPM
PG-77 AT 20 HZ/CM
MeO
O
CH3
OH
MeO
c
PPM

Fig. 4


P67 BP NOE STUDY
PG7BPS.005
AU PROG:
NOEMULT.AU
DATE 5-8-87
SF 300.133
SY 112.3500000
O1 4470.337
SI 32768
TD 32768
SW 2450.980
HZ/PT .150
PW 9.0
RD 0.0
AQ 6.685
RG 32
NS 384
TE 300
FW 3100
O2 5203.979
DP 40L DO
LB .500
GB .600
CX 37.00
CY 10.00
F1 7.763P
F2 -.403P
HZ/CM 66.239
PPM/CM .221
SR 3367.42
MeO
O
CH3
OH
MeO
d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

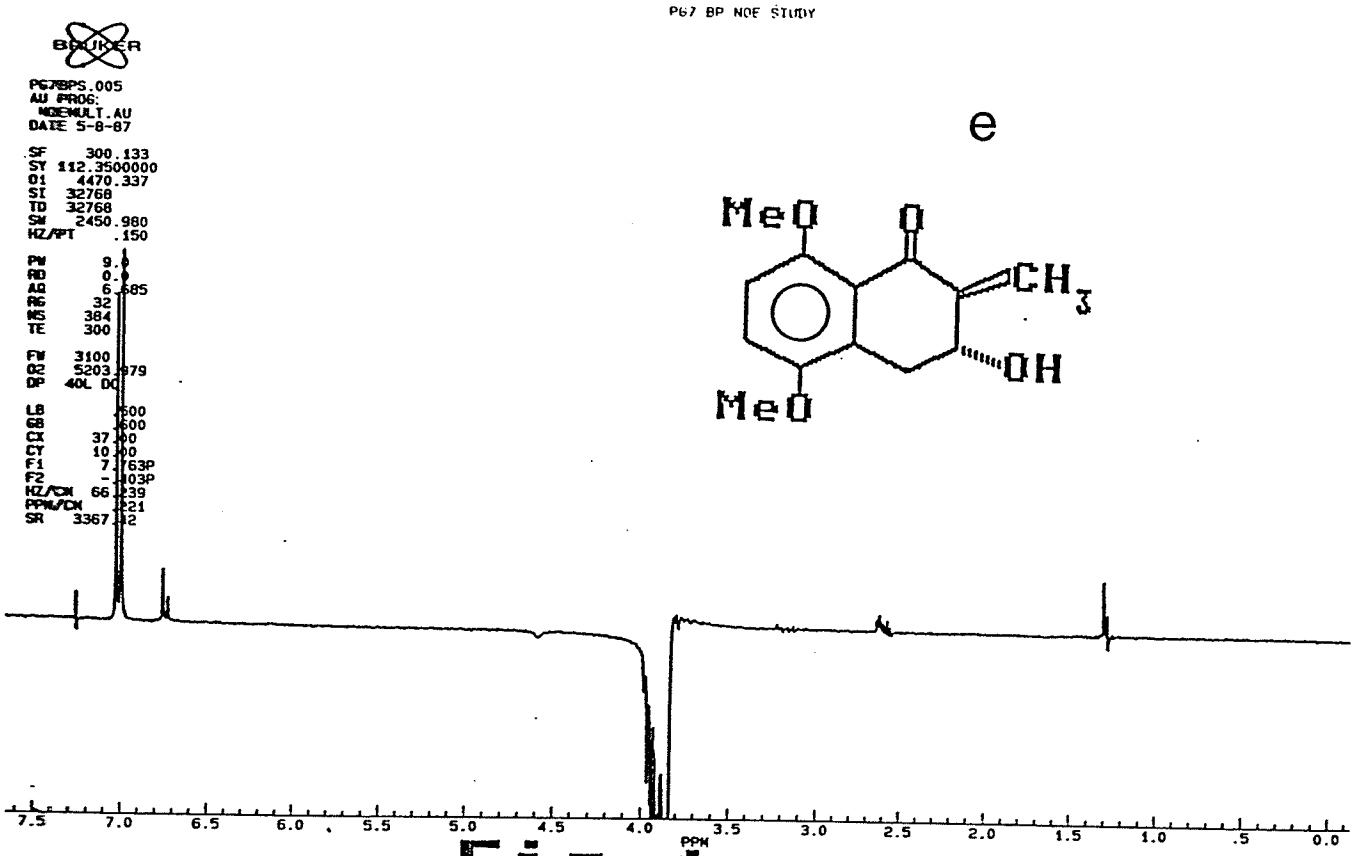
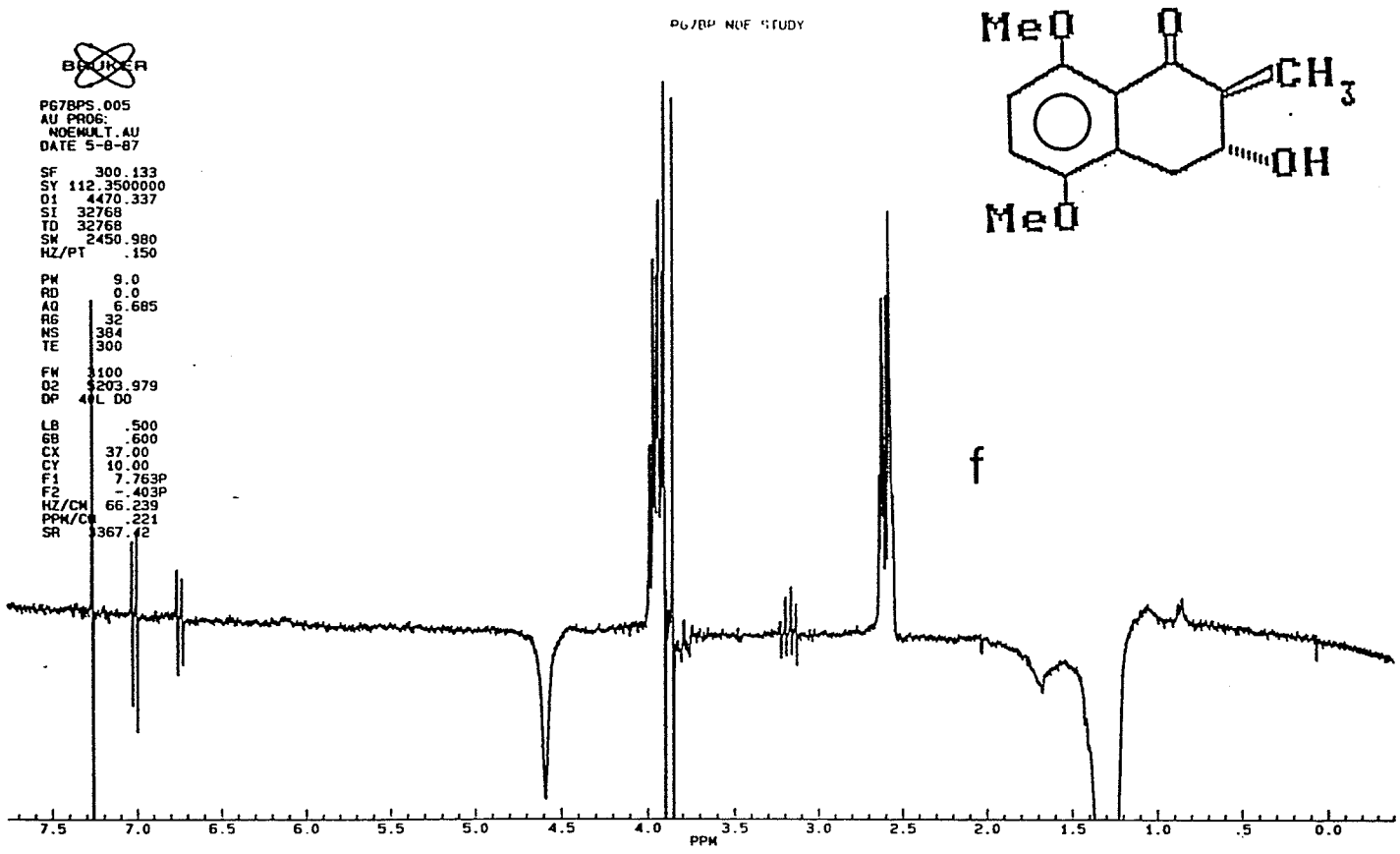

P67 BP NOE STUDY
PG7BPS.005
AU PROG:
NOEMULT.AU
DATE 5-8-87
SF 300.133
SY 112.3500000
O1 4470.337
SI 32768
TD 32768
SW 2450.980
HZ/PT .150
MeO
O
CH3
OH
MeO
e
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

Fig. 4


PG7BP NOE STUDY
PG7BPS.005
AU PROG:
NOEMULT.AU
DATE 5-8-87
SF 300.133
SY 112.3500000
O1 4470.337
SI 32768
TD 32768
SW 2450.980
HZ/PT .150
PW 9.0
RD 0.0
AQ 6.685
RG 32
NS 384
TE 300
FW 3100
O2 5203.979
DP 40L DO
LB .500
GB .600
CX 37.00
CY 10.00
F1 7.763P
F2 -.403P
HZ/CM 66.239
PPM/CM .221
SR 3367.42
MeO
O
CH3
OH
MeO
f
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

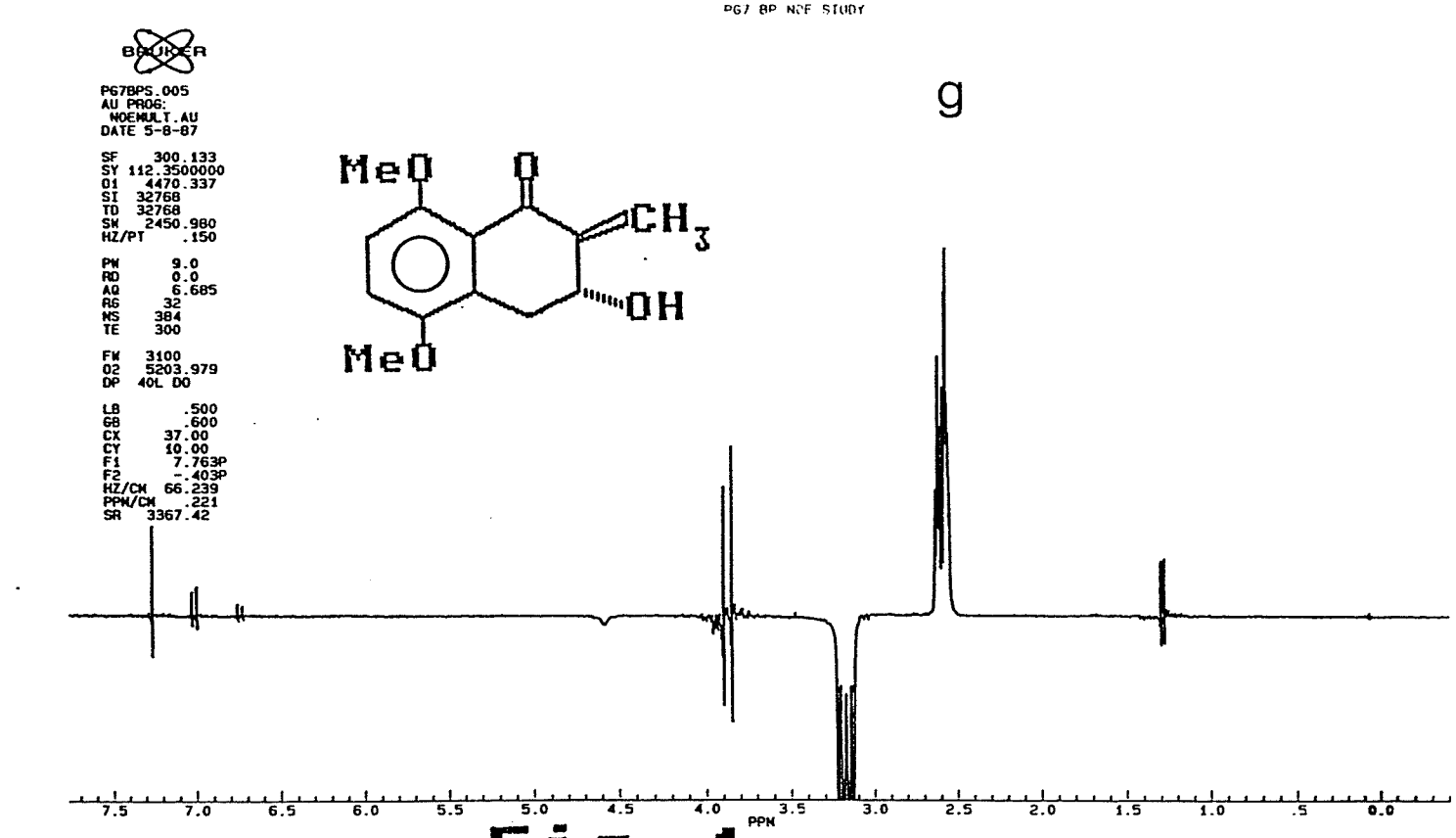

PG7 BP NOE STUDY
PG7BPS.005
AU PROG:
NOEMULT.AU
DATE 5-8-87
SF 300.133
SY 112.3500000
O1 4470.337
SI 32768
TD 32768
SW 2450.980
HZ/PT .150
PW 9.0
RD 0.0
AQ 6.685
RG 32
NS 384
TE 300
FW 3100
O2 5203.979
DP 40L DO
LB .500
GB .600
CX 37.00
CY 10.00
F1 7.763P
F2 -.403P
HZ/CM 66.239
PPM/CM .221
SR 3367.42
MeO
O
CH3
OH
MeO
g
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

Fig. 4

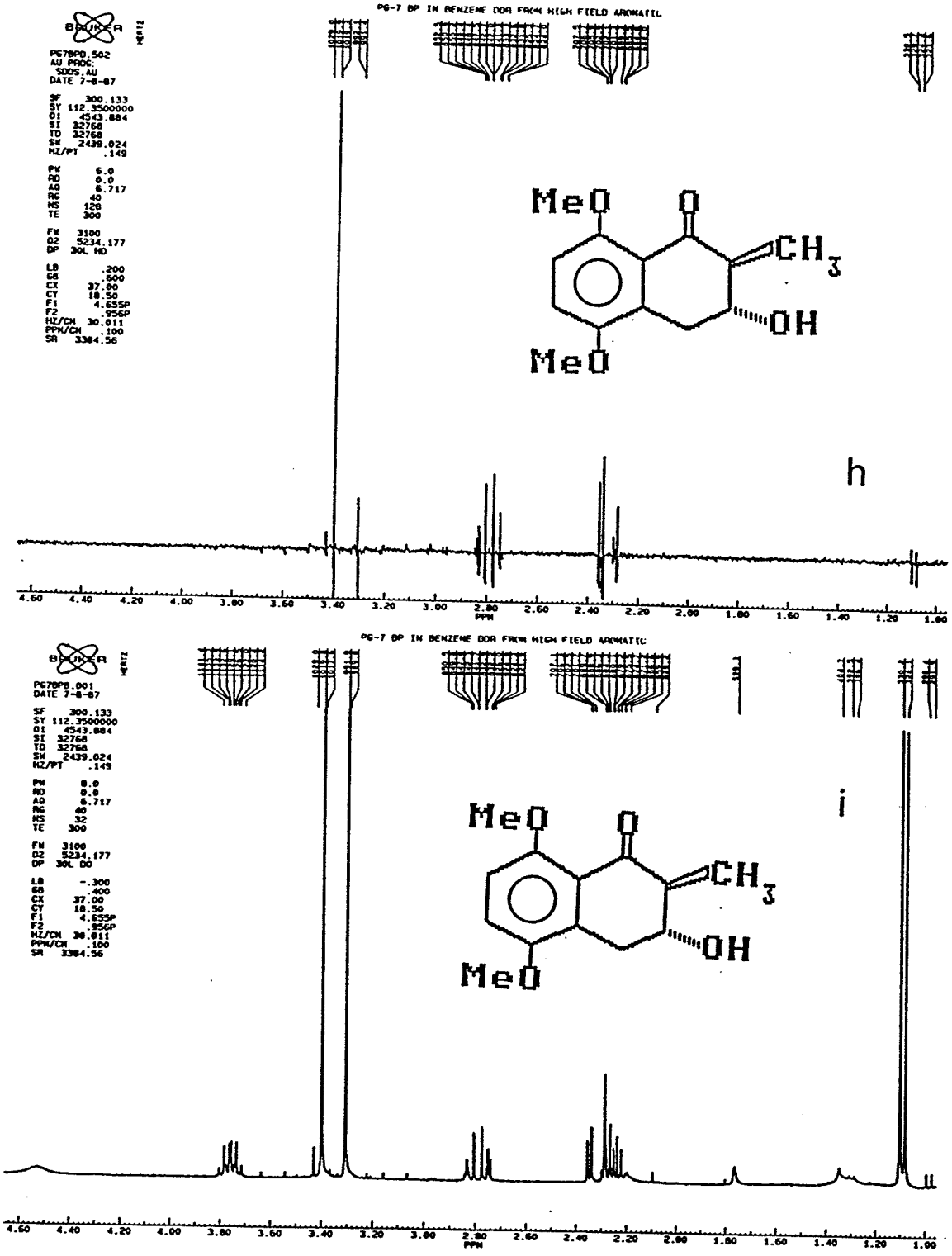

PG-7 BP IN BENZENE DDR FROM HIGH FIELD AROMATIC
PG7BPD.502
AU PROG.
SDDS.AU
DATE 7-8-87
MeO
O
CH3
OH
MeO
h
PPM
PG-7 BP IN BENZENE DDR FROM HIGH FIELD AROMATIC
PG7BPB.001
DATE 7-8-87
MeO
O
CH3
OH
MeO
i
PPM

Fig. 4

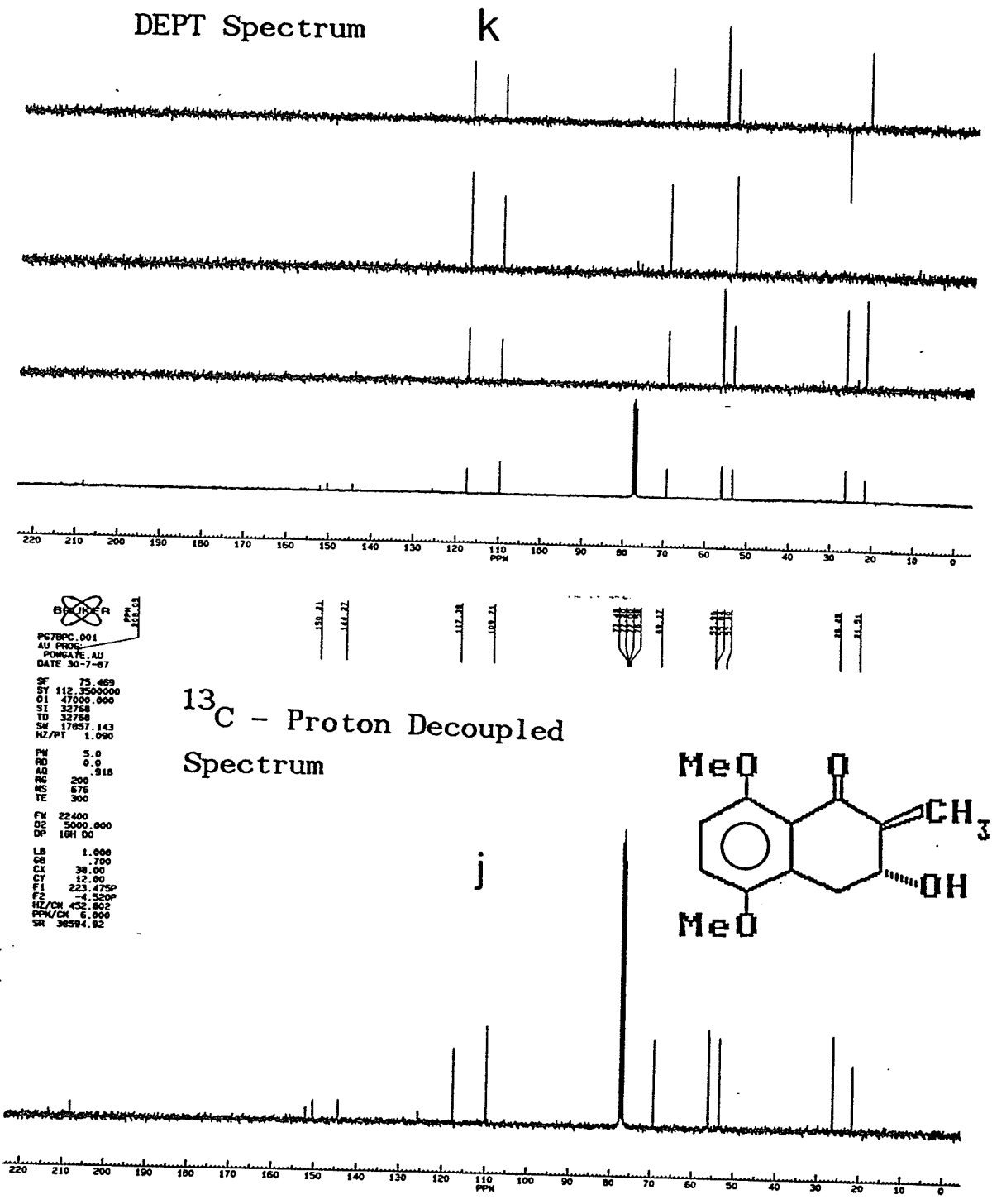
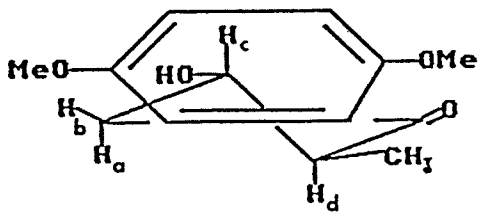

DEPT Spectrum
k
PS7BPC.001
AU PROG.
POWGATE.AU
DATE 30-7-87
^{13}C - Proton Decoupled
Spectrum
j
MeO
O
CH3
OH
MeO
PPM

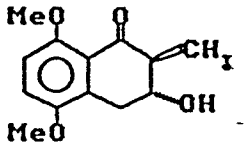
Fig. 4

Therefore, the peak at 21.51 ppm is a methyl carbon; the peak at 26.25 ppm is a methylene carbon; the peak at 53.30 ppm is a methine carbon; the peaks at 55.84 and 55.96 ppm are two methyl carbons (OCH_3); the peaks at 69.17, 109.71 and 117.38 are all due to methine carbons. In addition, the information above confirmed the number of hydrogens in the molecule (15 hydrogens + one OH as evidenced from the IR spectrum). That number was also confirmed from the ^1H NMR spectrum (Fig. 4, a'). With that information and the splitting pattern in ^1H NMR spectrum it was reasonable to assume that there was a six membered ring attached to a benzene ring.

Decoupling the signal at 1.30 ppm (CH_3, Fig. 4, b) resulted in the multiplet between 3.9 and 4.0 ppm collapsing to a doublet (J_{AX} = 9 Hz), implying that there is only one other neighbouring hydrogen i.e. -CH-CH_3 group. Nuclear Overhauser Enhancement (NOE) studies (Fig. 4, d-g) allowed us to decide on a structure. Irradiation of the low field methoxy resonance produces a NOE to the high field aromatic ring hydrogen and a NOE to one of the methylene hydrogens (axial?) adjacent to the aromatic ring since the hydrogen attached to the methyl group is not in that region. Similarly, irradiation of the high field methoxy causes an enhancement of the low field aromatic ring hydrogen. Those experiments also indicated that there were no NOE 's between the methyl group and either of the methoxy groups and therefore the methyl group cannot be in either of the benzylic positions. Irradiation of the resonance between 3.1 and 3.2 ppm showed a geminal NOE to one of the resonances between 2.5 and 2.65 ppm and to the CH-OH proton. Irradiation of the methyl resonance showed no NOE to the methoxy groups

but NOE's to the resonance between 3.9 and 4.0 ppm and a 'geminal' NOE to the $CH-CH_3$ hydrogen. Thus the most probable structure, with the stereochemistry indicated, is that shown below:

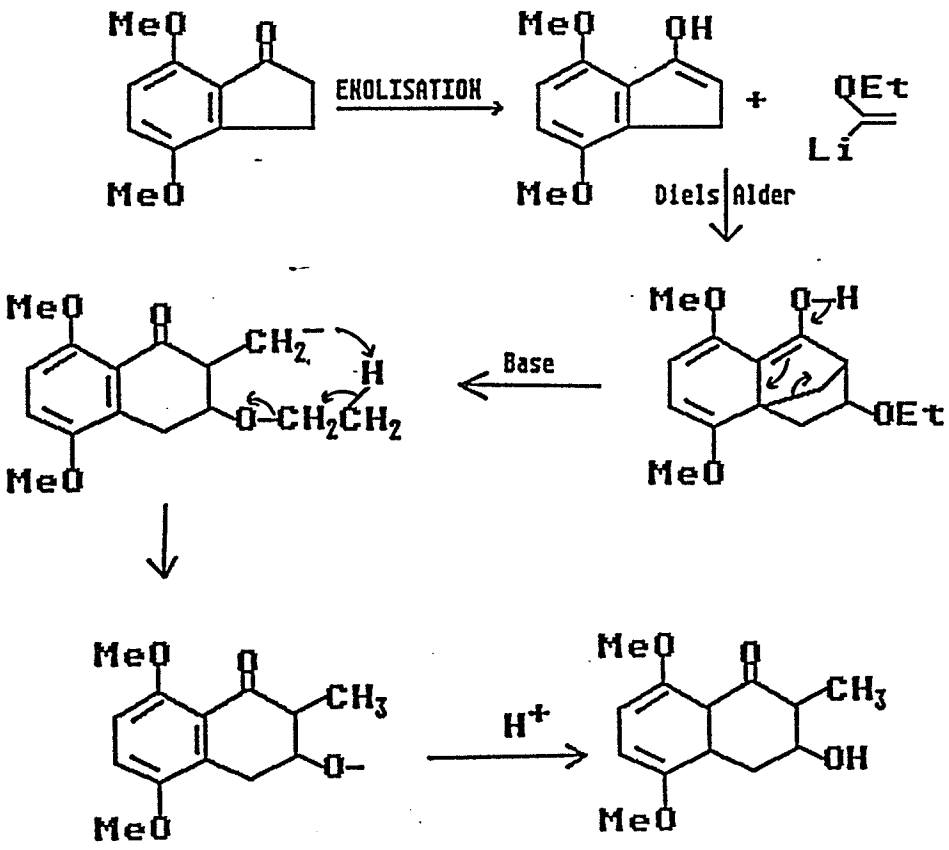




This is based, in part, on the coupling constants of H_a (18 and 9 Hz) and H_d (6 and 9 Hz) and on the NOE results when the methyl group was irradiated. The latter coupling constants (9 Hz) suggest a <u>trans</u> diaxial relationship between H_a and H_c and between H_c and H_d. The NOE enhancement when the methyl group was irradiated suggests also that H_c and the methyl group are on the same side of the aliphatic ring. Double resonance experiments from the high field aromatic ring hydrogen (Fig. 4, h,i) shows a coupling to the methylene hydrogens, again confirming that this group is benzylic. **COSY**-45 (**CO**rrelation Spectrosco**Y**) also is in agreement with the structure as suggested.

The ^1H NMR spectrum of 1-hydroxy-1-acetyl-4,7-dimethoxyindane <u>D</u> (R=H) is shown in Fig. 4 (a") for comparison with ^1H NMR spectrum of the tetralone derivative <u>3B</u>. The presence of the acetyl resonance and the splitting pattern of the four non-equivalent aliphatic hydrogens in Fig. 4 (a") are noteworthy.

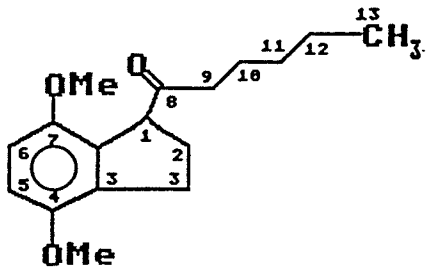
The mass spectra of these two compounds display significant differences too. The 1-hydroxy-1-acetyl-4,7-dimethoxyindane derivative mass spectrum is dominated by the loss of 15 and 43 amu, the latter being the base peak whereas in the mass spectrum of the tetralone derivative, the molecular ion has an intensity of approximately 98%. Other noteworthy losses are 218 amu ($M^{+\bullet}-H_2O$); 203 amu ($M^{+\bullet}-H_2O-CH_3$); 192 amu ($M^{+\bullet}-44(CH_3CHO?)$) and 177 amu ($M^{+\bullet}-44-15$). If a Diels-Alder reaction can take place between the 4,7-dimethoxy-1-indanone and α-ethoxyvinyllithium, the genesis of this product can then be rationalised as shown below.



From our experience, it was clear that acidic conditions were adverse to

the formation of 19 and thus we sought other methods to achieve this reduction. Following a report by Nelson et al. (19) we tried the deacetoxylation using ironpentacarbonyl in dibutylether. A number of experiments were tried by varying the conditions, e.g. at different temperatures (95-100, 130, 135, 136, 142, 144 ^{o}C) for different lengths of time (25, 48, 50, 51, 59, 72 h) and varying amounts of iron pentacarbonyl (10, 20 mole equivalents). The best conditions appeared to be using 20 mole equivalents of iron pentacarbonyl at 130 ^{o}C for 2-3 days. When the reduction was carried out for 2 days at 144 ^{o}C, a compound identified as having the structure shown in Scheme 4 was the major byproduct. However, the mass spectrum shows a $M^{+\cdot}$ of 276 amu and a base peak of 177 amu corresponding to the loss of 99 amu. There also appears to be a loss of 72 amu which is difficult to rationalise. The IR spectra of 19 and this undesired product appear very similar except for the peaks at 1170, 1210 and 1300 cm^{-1} of the acetylindane which are absent in the undesired product. However, the ^{1}H NMR spectrum (Fig. 5a) of this undesired product is quite different from the acetylindane but does suggest some similarity in structure. For example, a doublet of doublets appear in both spectra at 4.1 and 4.15 ppm (acetylindane and undesired product respectively). The α and β benzylic protons resonate in the same positions with the same splitting pattern. In addition, the absorption for the C-2 hydrogens of the acetylindane derivative appear in the same positions, with apparently the same multiplicity, as the undesired product. In other words, there appears to be a 5-membered ring in the undesired product. Since the acetyl resonance is missing in the spectrum of the undesired product and since there is what appears to be aliphatic resonances with a terminal CH_3 group between 0.8 and 1.6

ppm, the structure was tentatively identified as the following:



As alluded to above the mass spectrum indicates the loss of 97 amu, possibly $[CH_3CH_2CH_2CH_2CH_2C{=}O]^{\bullet}$ producing an ion at 177 amu as the base peak. The peak at 204 amu is difficult to rationalise except one invokes a loss of H $^{\bullet}$ followed by a loss of $[CH_3CH_2CH_2CH_2CH_2]^{\bullet}$ which would result in an odd electron ion going to an even electron ion and back to an odd electron ion, an uncommon occurrence.

The COSY-45 spectrum (Fig. 6) indicates that the methine benzylic hydrogen H1 is coupled to the hydrogens giving rise to the resonances between 2.0 and 2.4 ppm ($H2_a$ and $H2_b$). The C2 hydrogens are in turn coupled to the benzylic C3 hydrogens (2.7-3.1 ppm). The C9 hydrogens at about 2.5 ppm are only coupled to the C10 hydrogens at 1.6 ppm and the C11 and C12 hydrogens are, of course, coupled to the C10 and C13 hydrogens respectively. The ^{13}C NMR DEPT sequence spectrum (Fig. 5, b) can be used not only to firmly establish this structure but also to assign all the resonances in the ^{13}C NMR proton decoupled spectrum. Thus, there are 6 methylene carbons between 20 and 42 ppm. The resonance at 29.4 ppm is assigned to two carbons based on its intensity.

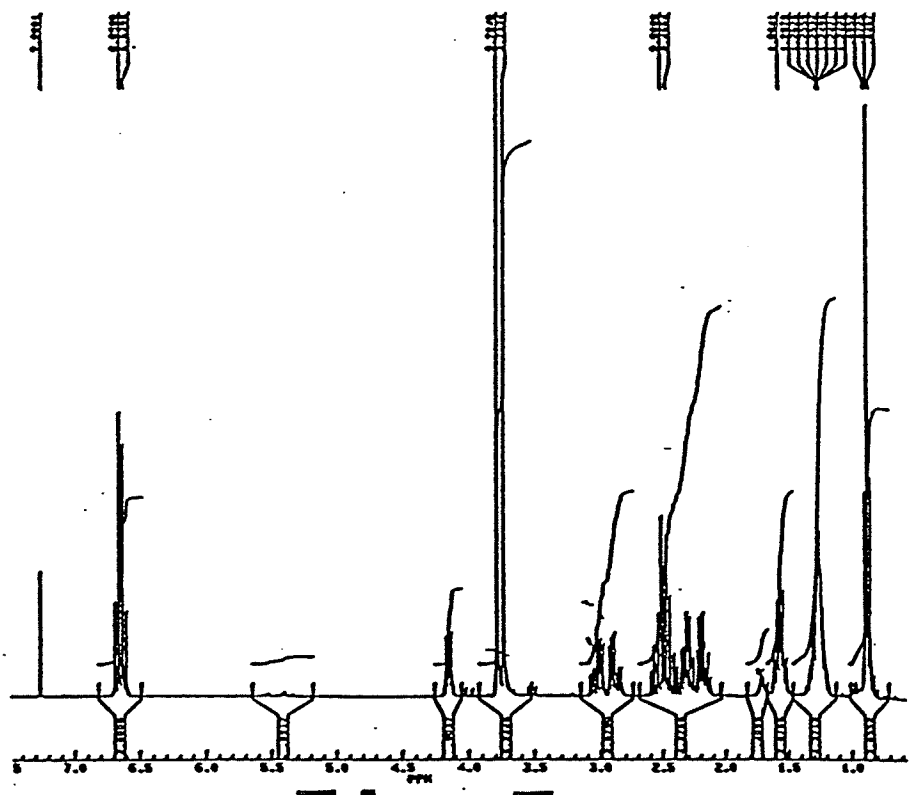


Fig. 5a

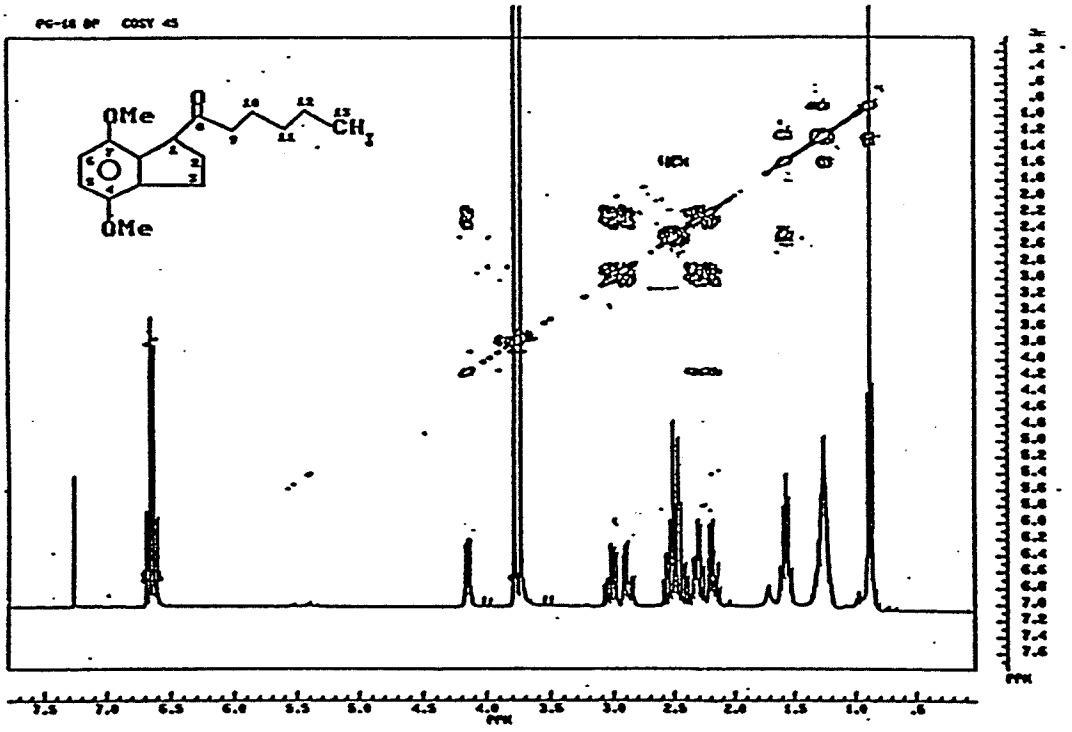


Fig. 6

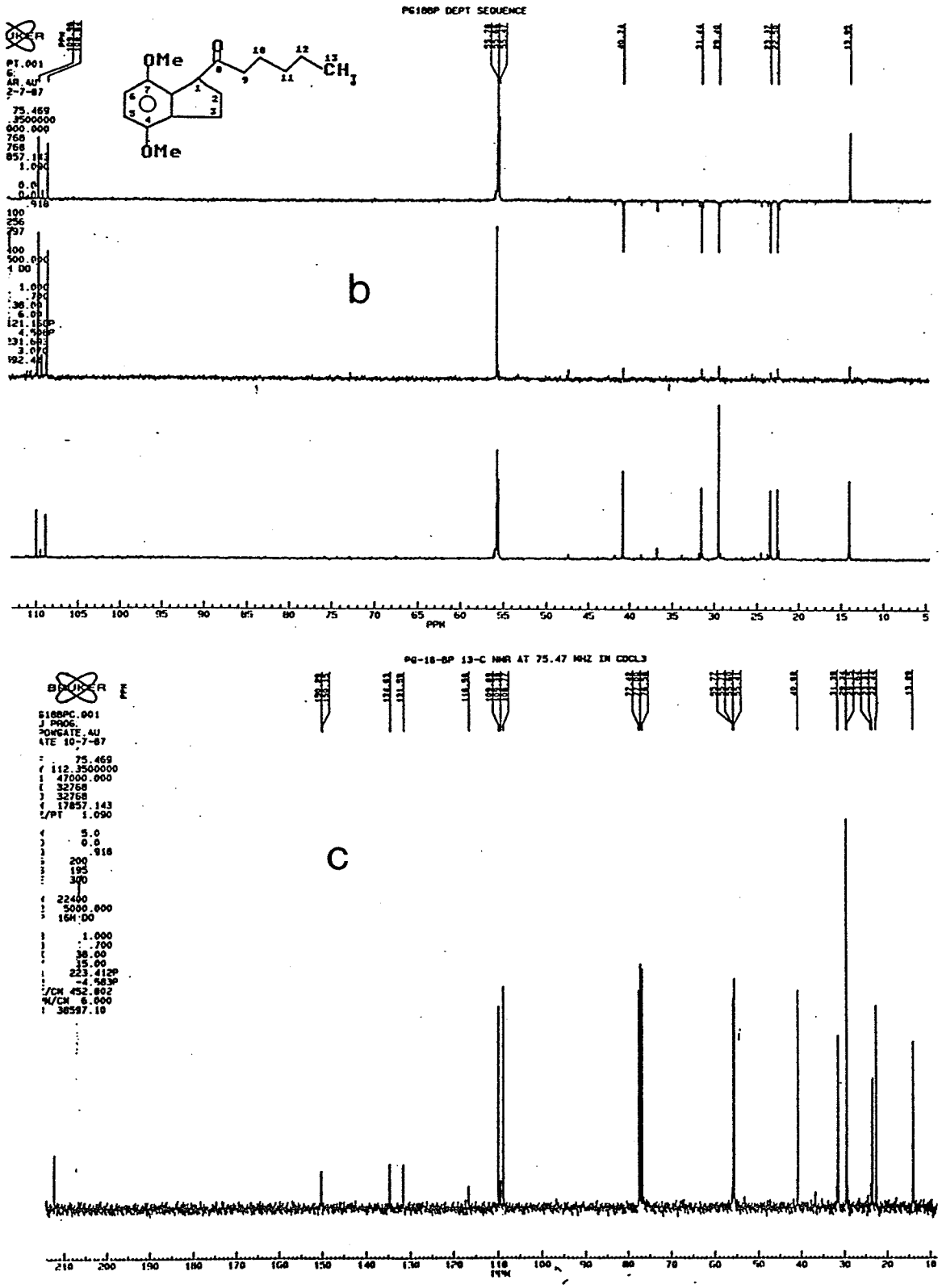
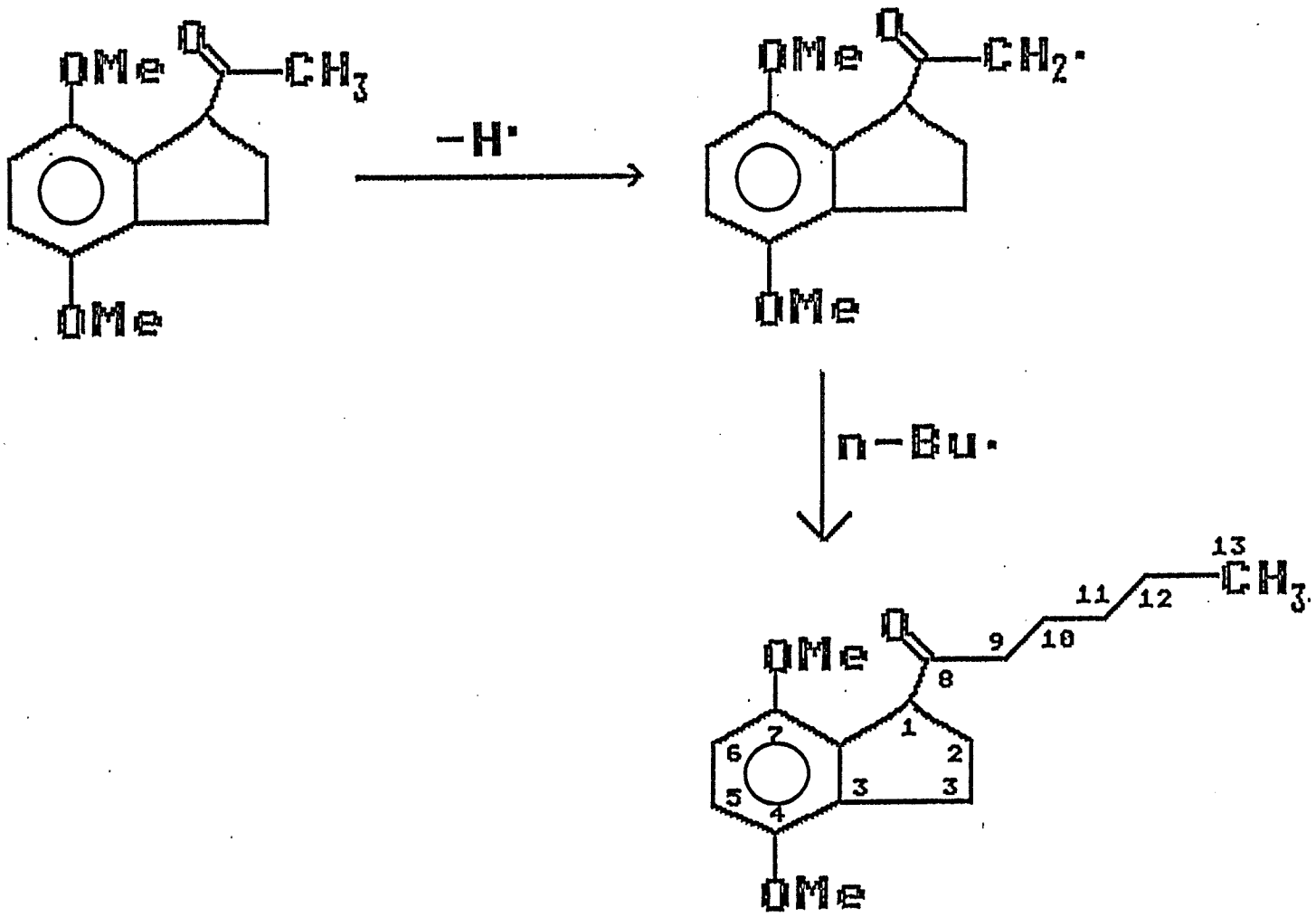

PG188P DEPT SEQUENCE
OMe
OMe
b
PPM
PG-18-BP 13-C NMR AT 75.47 MHZ IN CDCL3
c

Fig. 5

There are 3 methyl carbons (13.95 ppm (CH_3), 55.47 and 55.76 ppm (OCH_3)) and 3 methine carbons (55.66 ppm (C1), 108.84 ppm and 109.96 ppm (C6 and C7). Therefore, 12 of the 17 carbons are accounted for. The other 5 carbons can be assigned from the ^{13}C NMR proton decoupled spectrum: C9 (210.5 ppm) C5 and C8 (150.59 and 150.15 ppm) and the bridgehead carbons (134.63 and 131.59 ppm) The peaks at 116.56 and 109.38 ppm must be impurities. This product most probably arises from the free radical coupling of 19 with n-butyl radical as shown in Scheme 4.

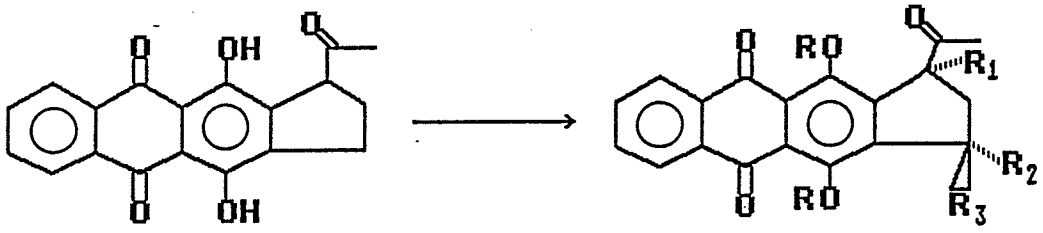
We found that using 20 equivalents of iron pentacarbonyl together with 2 equivalents of n-tributyltin hydride as a hydrogen atom source in xylene at 125 ^{o}C for three days gave the best results. It should be emphasised here that higher temperatures favour the undesired product discussed in the previous paragraph while lower temperatures (80-110 ^{o}C) favour unreacted material.

Therefore, having found an acceptable method of reducing the 1-acetyl-1-acetoxy indane derivative, it meant that we could arrive at the AB portion of the target molecule (with the C9 acetyl group in place) rapidly and fairly efficiently from the 1-indanone derivative 3. The 1-indanone derivative is reacted with about 4 equivalents of ethynylmagnesium bromide at room temperature for about 1-1.4 h then hydrolysed with 2 equivalents of mercuric acetate in ethyl acetate for 24-48 h followed by hydrogen sulphide addition. The 1-acetoxy-1-acetyl-4,7-dimethoxyindane can be crystallised in a pure state in about 60% yield.



SCHEME 4

Some of the acetylindane derivative 19 obtained from our efforts using the zinc/acetic anhydride/acetic acid reduction was used to effect the Friedel-Crafts acylation with phthalic anhydride according to the method of Arcamone et al. (20). As expected this proceeded without any complications in about 50-60% yield to give the tetracyclic phenol 20.



20

21 R=Me, R_1=R_2=R_3=H
22 R=R_1=Me, R_2 =R_3=H
23 R=Me, R_1 =OH, R_2 =R_3 =H
24 R=Me, R_1 =R_2 =OH, R_3 =H
25 R=Me, R_1 =R_3 =OH, R_2 =H
26 R=Me, R_1 =OH, R_2 =CO_2CF_3, R_3 =H

A small amount of this tetracyclic phenol was alkylated with iodomethane and the crude product was oxidised with potassium t-butoxide/oxygen in dimethyl formamide/t-butyl alcohol at -30 ^{o}C for 2 h to produce a compound whose ^{1}H NMR spectrum is shown in Fig. 7b, and which was assigned the structure 25. The equilibrium shown below was presumed to be in existence.

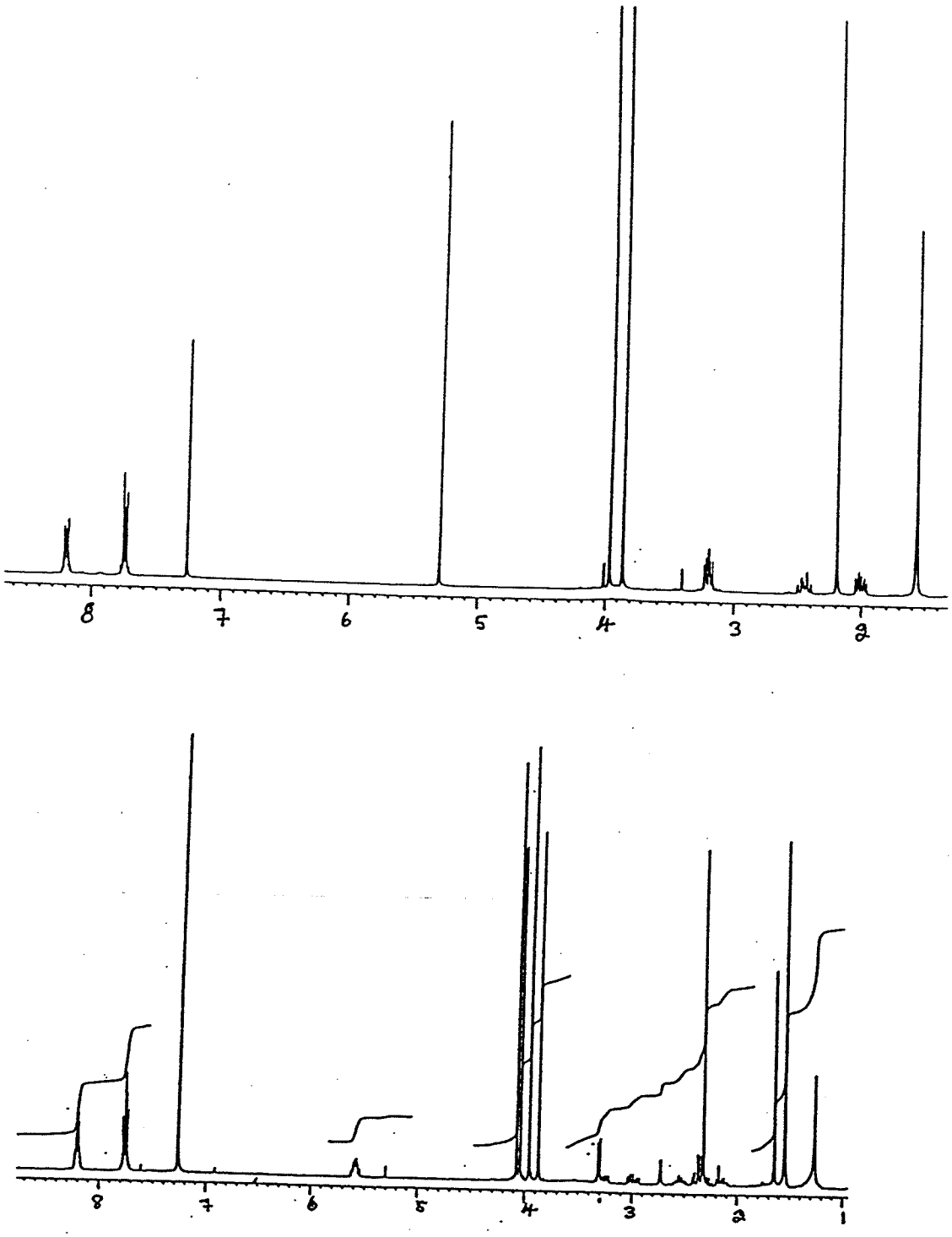
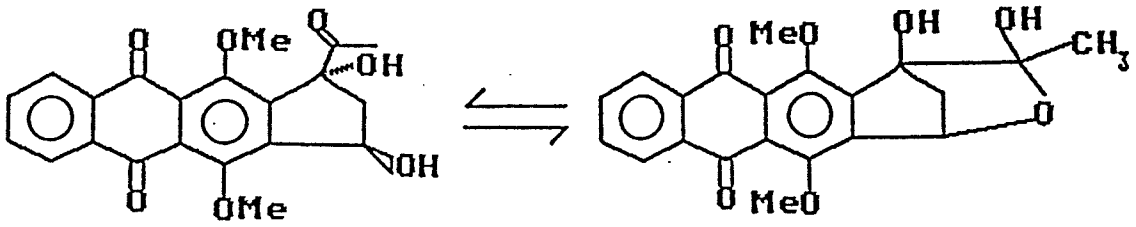
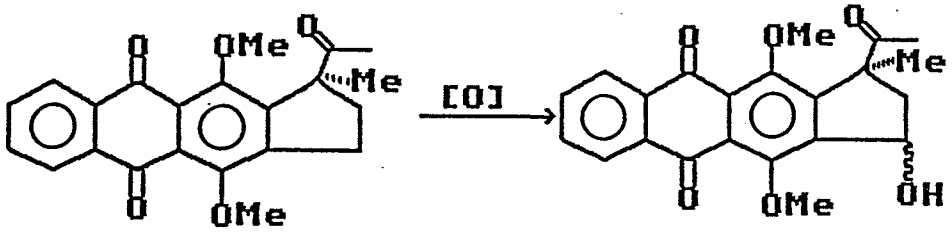


Fig. 7



This assignment was based on comparisons with the six membered analogues and the two sets of aromatic and methoxy resonances together with the resonance at 1.55 ppm assigned to the methyl group of the hemiketal. However, the mass spectrum of the starting material showed a $M^{+\cdot}$ of 364 amu compatible with the compound 22 (^{1}H NMR, Fig. 7a).

Thus, the ^{1}H NMR (Fig. 7b)spectrum of the compound which was assigned a mixture of the trans dihydroxy structure (25) and its hemiketal form was, in this case, really a mixture of cis and trans monohydroxy (C7) derivatives shown below in a 70:30 ratio.



The ^{1}H NMR spectrum of the trimethyl derivative 22 (Fig. 7a) clearly indicates the absence of the doublet of doublets expected for the C9

hydrogen (anthracycline numbering) and the presence of the methyl resonance. Moreover, the ^1H NMR spectrum of the monohydroxy derivative of 22, (Fig. 7b) shows the presence of the benzylic hydrogens (C7) at 5.6 ppm, the two hydroxyl resonances (two doublets at 3.3 and 2.72 ppm) and two sets of aromatic resonances, methoxy and methyl resonances indicating a mixture of diastereoisomers. Despite those observations, it did indicate that the one step conversion of 21 to 24/25, in principle, was possible.

The rf values and the IR spectra of 21 and 22 are very similar and thus 21 can easily be mistaken for 22.

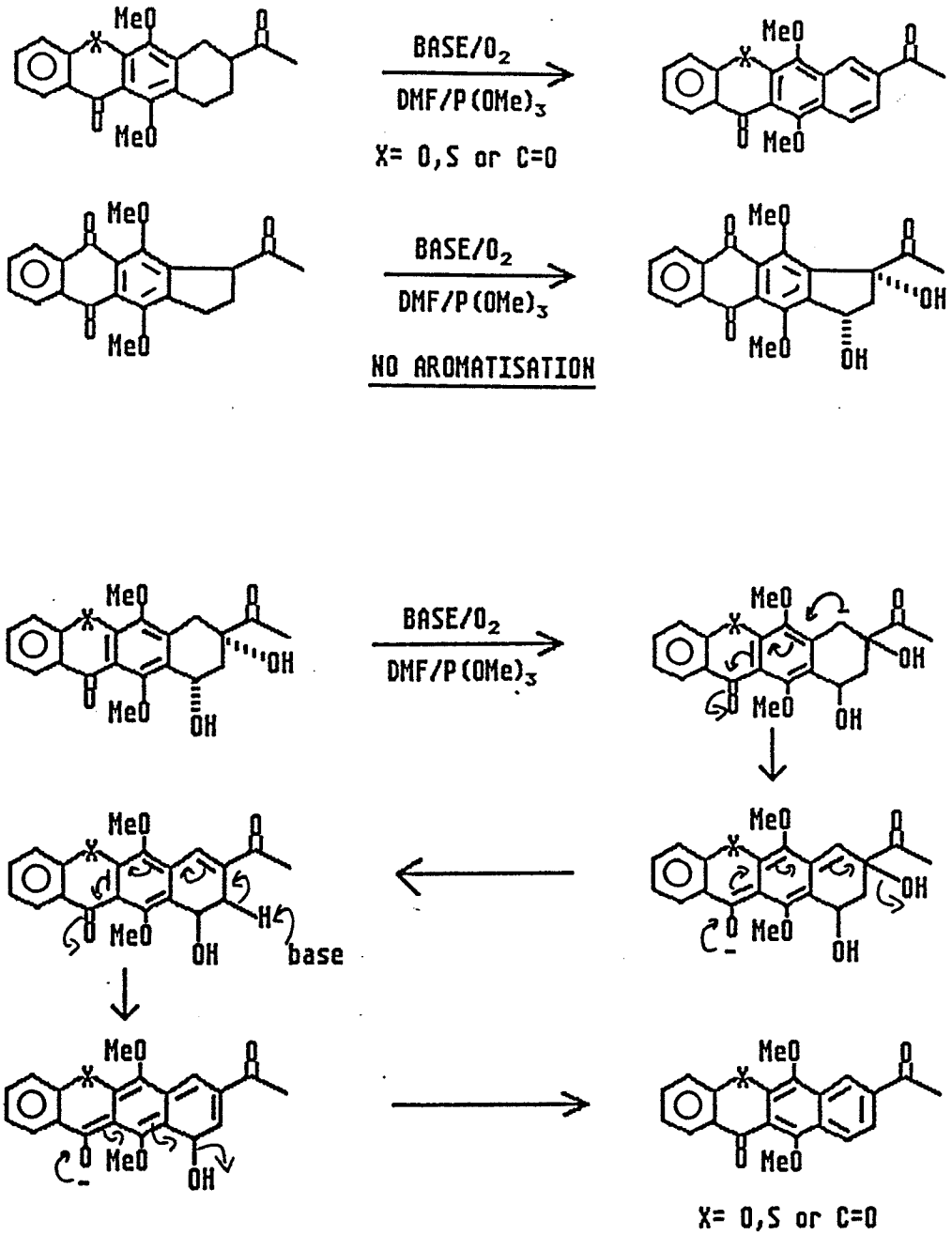
One principle which can be invoked to explain the lack of regioselectivity in the methylation of the tetracyclic phenol 20 is the **Principle of Hard and Soft Acids and Bases** (15). Briefly this theory states that a hard acid prefers to bind to a hard base and a soft acid prefers to bind to a soft base. Following the guidelines, a carbanion is considered a soft base and the methyl carbocation of methyl iodide ($CH_3^+ \ ^-I$) is considered a soft acid. Thus one would expect a favourable interaction between these two species. On the other hand, the methyl carbocation of dimethyl sulfate ($CH_3^+ \ ^-OSO_2 \ O^- \ ^+CH_3$) is considered a hard acid (or at least harder than CH_3^+ of methyl iodide) and thus an unfavourable interaction between the carbanion of the substrate and the methyl carbocation of dimethyl sulfate is expected to prevail.

Alkylation at C9 using dimethyl sulfate has never been observed. Even with 10 equivalents of alkylating agent, we have not observed any alkylation at C9. The only side product to be observed is the oxidised product at C9 in 23 when the system was not purged properly to remove

oxygen.

Having arrived at the tetracyclic protected phenol, 21, the only problem remaining is the crucial bis hydroxylation. Unlike the daunomycinone, xanthanone or thioxanthone series of aglycones, no aromatisation can occur under the standard conditions (potassium t-butoxide, t-butyl alcohol, dimethylformamide, trimethyl phosphite, low temperatures) employed. The reason for this problem is due to the delocalisation of the negative charge as outlined in Scheme 5. This kind of delocalisation is not possible with the **nor-series** and hence elimination of the hydroxyl group was not problematic. However, we did have problems achieving a clean conversion, under numerous conditions, of the C9 monohydroxy derivative to the C7, C9 dihydroxy derivative; ie. 23 to 24/25.

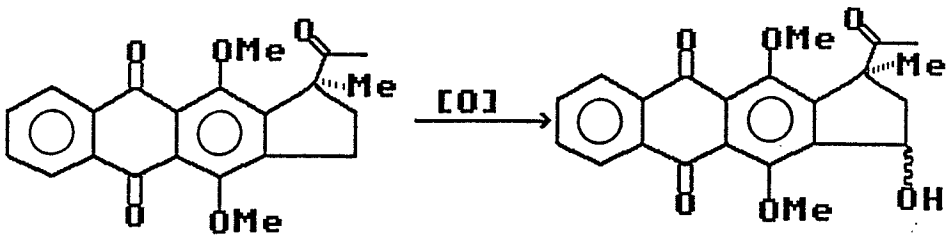
After those futile attempts, we decided to attempt the oxidation of 21 to 24/25. Indeed, after oxidation (potassium t-butoxide/oxygen in dimethylformamide/t-butyl alcohol/trimethyl phosphite at -30 ^{o}C for 1 h) and work up a solid readily separated on evaporation of the solvent. This solid showed one hydroxyl stretch in the IR spectrum which is to be expected from analogy to the six-membered series: one hydroxyl absorption due to H-bonding. However, the ^{1}H NMR spectrum and the mass spectrum clearly indicated that the monohydroxy derivative 23 was formed. A systematic variation of the experimental conditions allowed us to discover that it is essential that the reducing agent, trimethyl phosphite, be added not at the commencement of the reaction **but after** the oxidation is allowed to proceed for about 3 h. The reason, we


MeO
MeO
BASE/O2
DMF/P(OMe)3
X= O,S or C=O
MeO
MeO
BASE/O2
DMF/P(OMe)3
NO AROMATISATION
MeO
MeO
OH
MeO
OH
BASE/O2
DMF/P(OMe)3
MeO
OH
MeO
OH
MeO
OH
MeO
OH
base
MeO
OH
MeO
MeO
X= O,S or C=O

SCHEME 5

believe, is that the intermediate hydroperoxide is reduced immediately and for some yet undetermined steric (electronic?) reason, the resulting alkoxide ion prevents the oxidation of the C7 position. That fact has been demonstrated by one undesigned and two designed experiments all of which have lent credence to the above statement. They are as follows:

1. the oxidation of the trimethyl derivative 22 was facile,

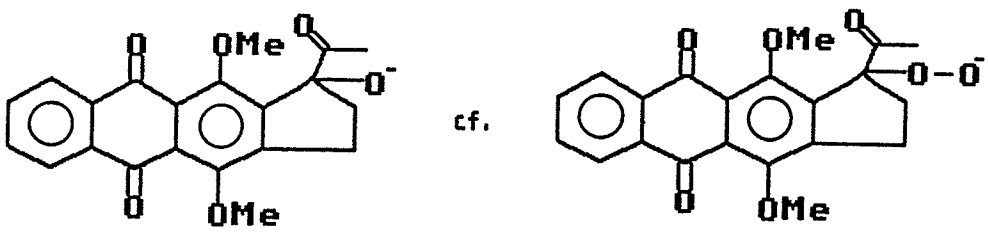


2. the oxidation of the C9 monohydroxy derivative, 23, under conditions which should produce the C7, C9 dihydroxy derivatives, 24/25, gives little or no dihydroxy compound(s), and

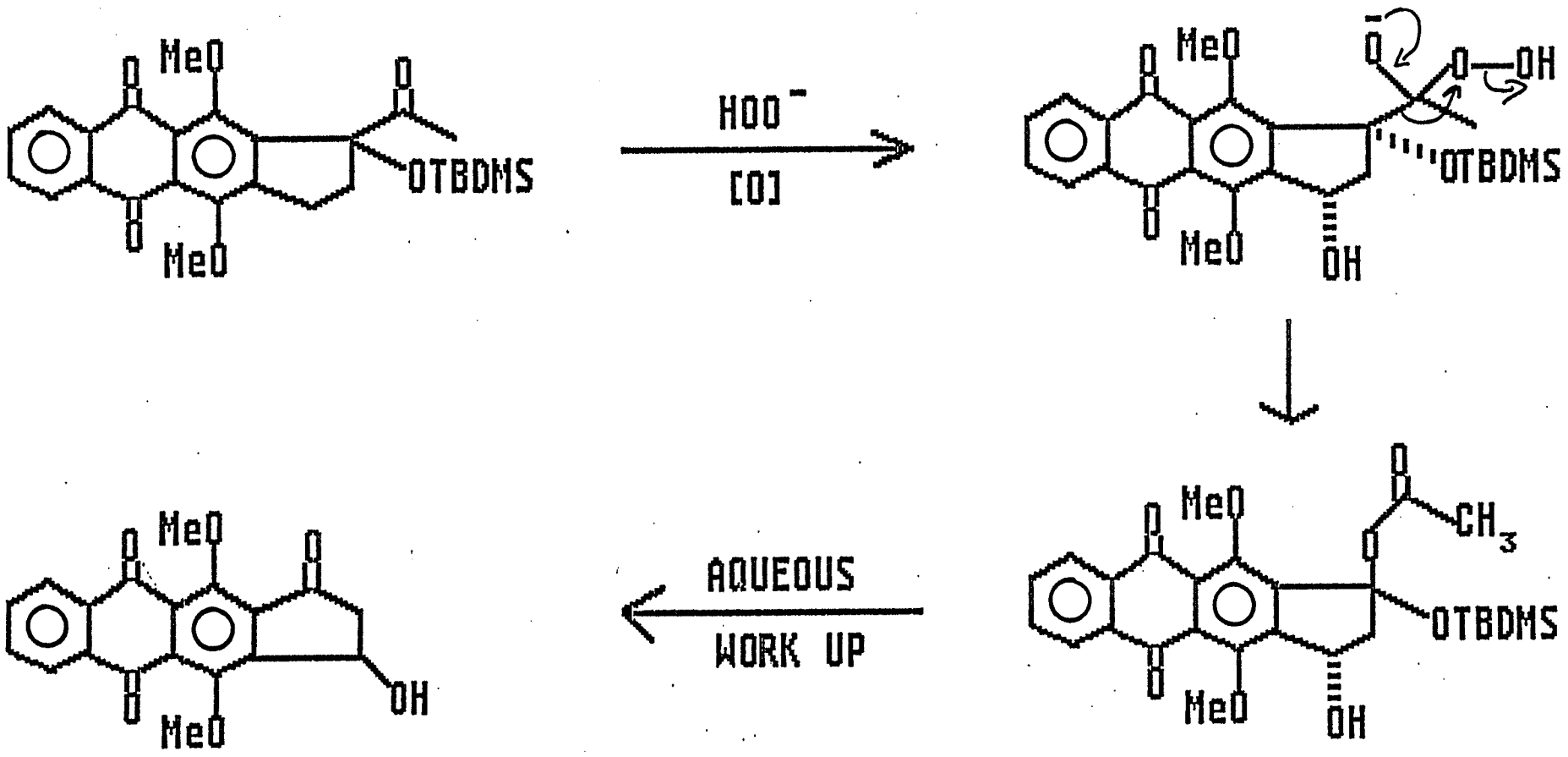
3. protection of the monohydroxy derivative as its t-butyl-dimethylsilyl ether (TBDMS) followed by oxidation does produce the C7 hydroxylated derivative. It should be emphasised that the oxidation of the TBDMS derivative was only performed once. It should also be noted here that there was a byproduct believed to be the result of a Baeyer-Villiger oxidation as outlined below in Scheme 6.

The yield of the dihydroxy derivative has been disappointing (30-40% at best) and it is felt that this is due to the extreme conditions necessary to produce the desired compound (approximately 10 equivalents

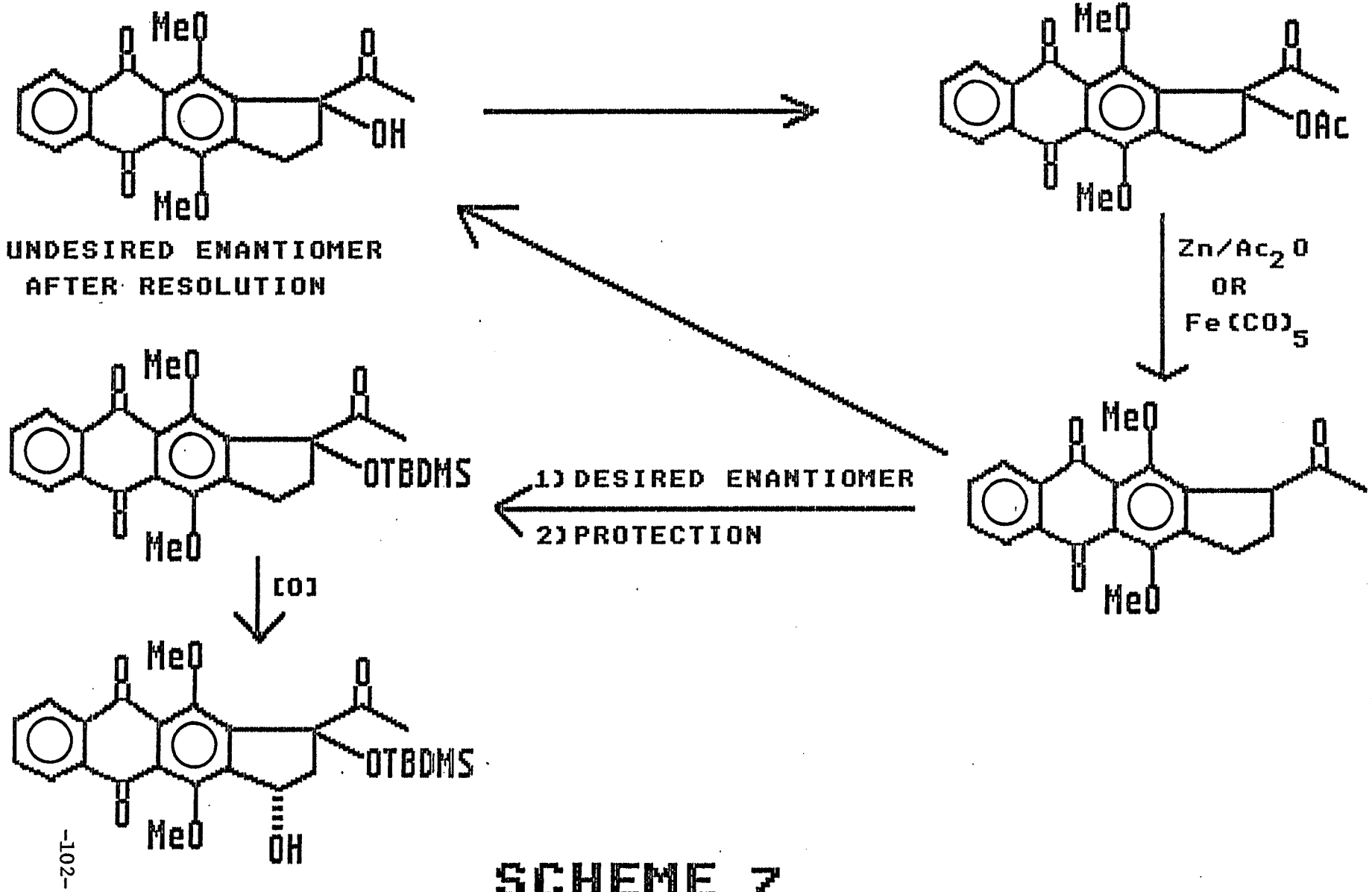
of base for about 3 h at low temperatures). However, the use of less base or shorter reaction times, leads to substantial amounts of the monohydroxy derivative. Although the results were disappointing it may be possible to exploit the facile synthesis of the monohydroxy derivative by devising a synthetic plan which may incorporate a resolution step at an appropriate stage. For instance, since it is possible to protect the monohydroxy derivative as its TBDMS ether and since the preliminary result indicates that it may be possible to oxidise the C7 position easily, then one can envisage a resolution at the monohydroxy stage and then elaboration as outlined in Scheme 7. However, that design would necessitate an easy conversion of the undesired enantiomer back to the tetracyclic acetylindane as suggested in Scheme 7. One explanation which might account for the lack of reactivity of the monohydroxy derivative 23 is as follows. It is believed that the alkyl hydroperoxide anion arising from C9 oxidation does not prevent sterically (or electronically) the deprotonation of the less acidic C7 hydrogen (less acidic than the C9 hydrogen), whereas the alkoxide anion arising from oxidation of that same position (C9) does.



Despite the problems with the bis hydroxylation, we did have enough


MeO
OTBDMS
MeO
HOO⁻
[O]
MeO
O
O—OH
OTBDMS
MeO
OH
MeO
CH3
OTBDMS
MeO
OH
AQUEOUS
WORK UP
MeO
OH
MeO

SCHEME 6


MeO
OH
MeO
UNDESIRED ENANTIOMER
AFTER RESOLUTION
MeO
OAc
MeO
Zn/Ac2O
OR
Fe(CO)5
MeO
OTBDMS
MeO
1) DESIRED ENANTIOMER
2) PROTECTION
MeO
[O]
MeO
OTBDMS
MeO
OH

SCHEME 7

material to proceed with the rest of the synthesis of the aglycones. The product from the oxidation was difficult to crystallise, more polar than its diastereoisomer (which is easily crystallised), displayed a broad doublet resonance at 5.5 ppm (C7), and was assigned the **trans** stereochemistry based on previous information gleaned from the six membered analogues. Therefore, our efforts were concentrated on changing the configuration at C7. In the six membered analogues, this is effected by the use of trifluoroacetic acid (6) at about 70 ^{o}C for 12-24 h followed by basic hydrolysis of the resulting C7 trifluoroacetate. This method usually produces about 60:40 mixture in favour of the desired **cis** isomer. We then felt that we would be able to invert the configuration as outlined above. However, to our surprise, even after 72 h at reflux, we could not detect any change by thin layer chromatography in the configuration at C7. However, we were able to produce some of the other isomer by using trifluoroacetic acid/2,2-dimethoxypropane/acetone at reflux for 24 h. The diastereoisomers were separated and we were able to crystallise the higher rf isomer to which we assigned the **cis** configuration based on:

1. its crystalline nature,
2. its higher rf value, and
3. the epimerisation presumably *via* the acetonide which is only expected to form with the **cis** configuration. This aspect of the assignment will be dealt with in detail shortly (*vide infra*). We were even more surprised to be faced with the difficulty of not being able to repeat the epimerisation under the above conditions. In view of those problems, we were forced to undertake a "systematic" investigation of the epimerisation. To that end, we tried a number of conditions as

delineated in Tables 1 and 2.

From the Entries outlined above, the only successes obtained were those in which the trifluoroacetate was made then epimerised by adding the nucleophile, water. It was also demonstrated that

1. low temperature (52-55 ^{o}C) and 27-35% of water (Entries 20 and 21), or

2. low and followed by high temperature 52-80 ^{o}C and 35% water (Entry 19) favors the hydrolysed product. IR spectroscopy and TLC also indicated that after approximately 4.5 hours (Entry 24) there was little unacylated starting material. This product could also be isolated and recrystallised but as a rule this was not done. The disappearance of the secondary (C7) hydroxyl stretch at 3550 cm^{-1} and the appearance of the carbonyl absorption of the triflouroacetate group at approximately 1790 cm^{-1} is indicative of the formation of the C7 trifluoroacetate (26). The ^{1}H NMR spectrum (Fig. 8) and mass spectrum also supports the structural integrity of this product. The disappearance of the C7 hydroxyl resonance at 2.9 ppm, the down field shift of the C7 hydrogen by about 0.75 ppm (OH vs. CF_3CO_2) and the $M^{+\cdot}$ at 478 amu are all in support of this structure. The high resolution mass spectrum also indicates that the molecule is unambiguously of that composition.

It is proposed that the mechanism of the epimerisation is via a S_N2 reaction pathway. This proposal is based on the observations that

1. under rather drastic conditions (72 h/reflux/trifluoroacetic acid) the starting diol was recovered. It is worth reiterating here that 70 ^{o}C/trifluoroacetic acid/12-24 h are usually the conditions employed for

TABLE 1

ENTRY	DMP(mL)	TFA(mL)	TFAA(mL)	H_2O(mL)	$(Me)_2CO$(mL)	TEMP.°C	RESULT
1	5	0.3			20	R/0	NC
2	5	0.1			10	R/0	NC
ADDED	5	0.2			1	R/6h	NC
3	5	3			1	R/10h	NC
ADDED	5	5		2	1	R/24h	C*
4		8		2	6	74/24h	NC
5	10	9		1	10	80/4d	
THEN						95/1d	
THEN						100/1d	C*
6	10	18		2	10	95/24h	NC
7	10	18		2	5	105/24h	NC
8[a]		1.5	3		3	105/5.5h	
THEN						base°/7h	C#
9		3	3			39/1h	
THEN						70/2h	
ADDED		3	3			90/6h	
THEN						base°/0	C#
10		3	3			60/17h	
THEN		3	3			90/6h	
THEN						base°/0	C#
11		3	3			60/17h	
THEN		3	3			90/6h	
THEN				5		80/4h	
THEN						base°/0	C#
12		6	4.5			60/9h	
THEN		1.5	3			82/5h	
THEN				5		82/0	C#

TABLE 1 cont'd

ENTRY	DMP(mL)	TFA(mL)	TFAA(mL)	H_2O(mL)	$(Me)_2CO$(mL)	TEMP.°C	RESULT
13		6	3			60/4h	
THEN		1.5	3			70/8h	
THEN				5		70/0	C#
14		6	4.5			60/12h	
THEN		1.5	3			80/3h	
THEN				5		80/24h	C#
15		6	3			60/1h	
THEN		1.5	3			70/3h	
THEN				5		70/12h	C#
16		6	3			60/8h	
THEN		1.5	3			80/2h	
THEN				5		80/24h	C#
17		9	6			50/4h	
THEN		1.5	3			74/7h	
THEN				9		80/0	C#
18		4.5	3			60/9h	
THEN		1.5	3			70/3h	
THEN				5		70/24h	C#
19		4.5	4.5			52/3.5h	
THEN		3	3			75/13h	
THEN				8		52/9h	C**
20		4.5	4.5			52/3h	
THEN		1.5	3			52/12h	
THEN				5		52/12h	C+
21		9	6			55/9h	
THEN				8		55/12h	C+
22		4.5	3			60/2h	
THEN			1.5			60/2h	
THEN				0.6		80/18h	C#
23		6	6.5			52/3.5h	
THEN				1.4		80/18h	C#

TABLE 1 cont'd

R reflux
NC no change
O overnight
* small amount detected by TLC
C# ratio estimated (TLC) around 60:40 ,trans:cis
** less than previously noted in earlier trials
C+ very little epimerised product detected (TLC).
o base refers to aqueous sodium carbonate (saturated)
a entries 8 to 23, the mixture was stirred with aqueous sodium carbonate at around 50 °C overnight.

TABLE 2

ENTRY	$PhB(OH)_2$(mg)	TsOH(mg)	XYLENE(mL)	TEMP.°C	RESULT
24	22	7	3	RT	NC
THEN				120/O	NC
25	40	132	T	R/24h	NC

R reflux
NC no change
T toluene
O overnight

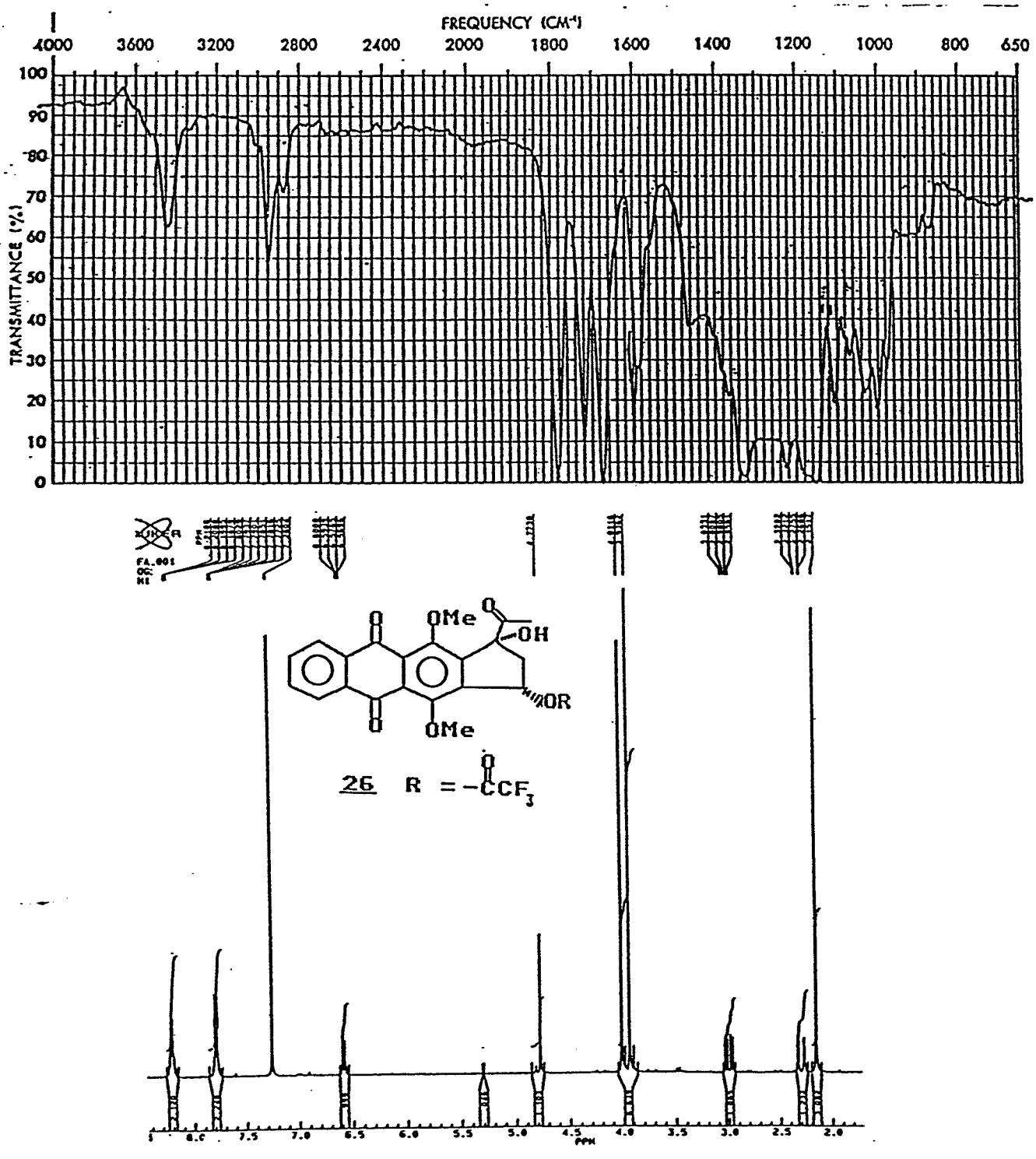
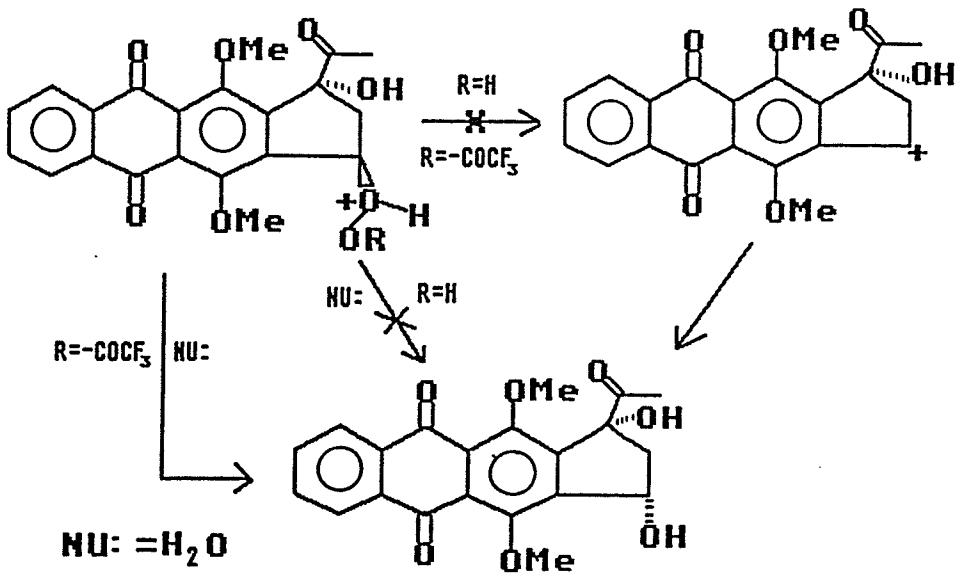

FREQUENCY (CM⁻¹)
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
650
TRANSMITTANCE (%)
100
90
80
70
60
50
40
30
20
10
0
OMe
OH
OR
OMe
26 R = -C(=O)CF3
PPM

Fig. 8

epimerisation of the six membered analogues and these are known to proceed through a carbocation ion intermediate, and

2. the formation of the trifluoroacetate should not have any influence on the formation of the benzylic carbocation but rather on the ability of a nucleophile (water) to effect an S_N2 displacement on a good leaving group. i.e., CF_3CO_2 vs, OH (see below).



This is supported by the Entries run under conditions (aqueous acid) which the trifluoroacetate was not formed (Entries 10–12), and

3. the competing reaction, the hydrolysis of the labile trifluoroacetate group once removed, prevents any further epimerisation (see Entries 24, 25 and 26).

The fact that in Entry 8 and in the epimerisation using 2,2-dimethoxypropane/acetone/trifluoroacetic acid at reflux (which we could not reproduce) some epimer was produced suggests to us that it plausible to assume that the intermediate was the trifluoroacetate which was epimerised, to some extent, during the aqueous work up. It is worth

noting here that the stability of the trans diol system towards acid and acetonide formation was also noted by Mitscher and Khanna (4a).

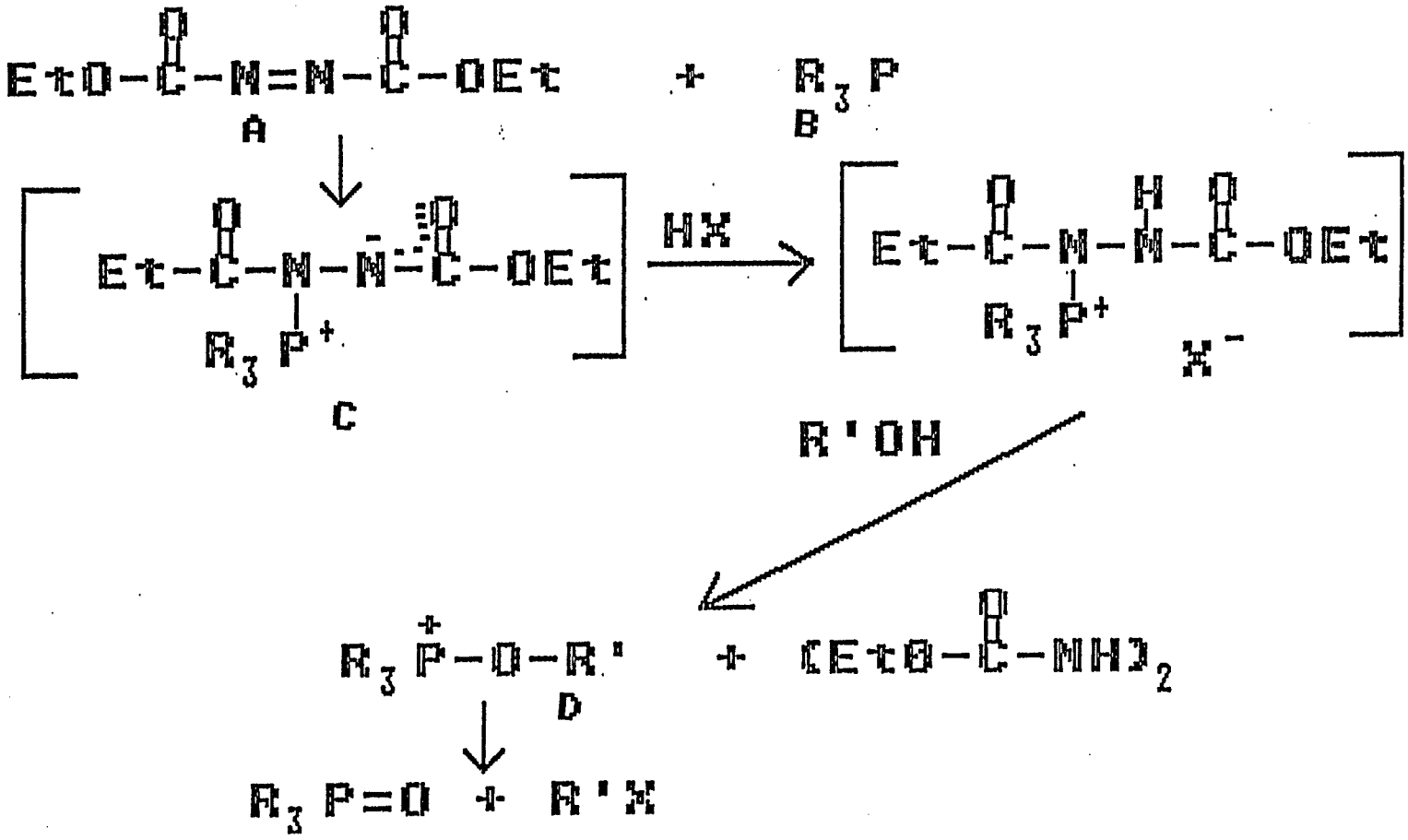
The stability of the diol towards S_N1 conditions may be a blessing in disguise. Since it appears that the findings alluded to above do suggest an S_N2 reaction then, theoretically, it is possible to achieve complete inversion of configuration at C7 thus making the synthesis less problematic with regards to a chromatographic separation. To that end, the Mitsunobu reaction (21) is probably a worthwhile alternative. Mitsunobu conditions consist of the use of diethylazidodicarboxylate(DEAD), triphenyl phosphine(TPP), an acid, and an alcohol. The accepted mechanism is outlined in Scheme 8.

The steps are

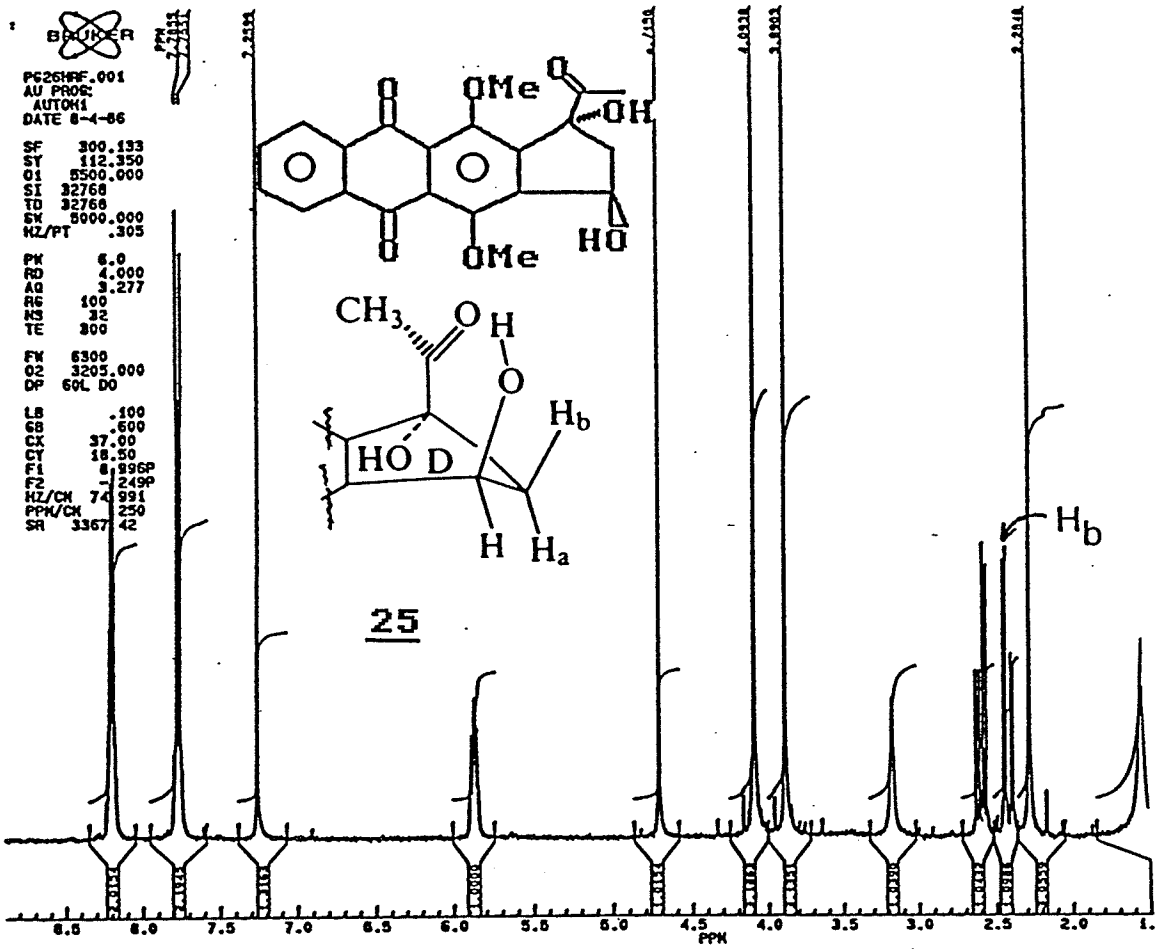
1. addition of A (DEAD) to B (TPP) resulting in a quaternary phosphonium salt C,
2. protonation of C by HX (e.g. $PhCO_2H$),
3. formation of an alkoxy phosphonium salt D as a result of attack by the alcohol R'OH, and
4. S_N2 attack on the activated carbon center of R' in D by the conjugate base of HX (X^-) giving R^2X.

The product R^2X is then saponified to produce the inverted alcohol.

The stereoselectivity of the bis hydroxylation discussed above may not be problematic after all. NOE experiments were performed on the two diasterisomeric diols 24 and 25. The results are shown in Fig. 9 (e-g) and they indicate, unambiguously, that we had misassigned the



SCHEME 8


PG26HRF.001
AV PROG:
AUTOH1
DATE 8-4-06
OMe
OH
HO
OMe
CH3
O
H
O
Hb
HO D
H
Ha
Hb
25
a
PPM

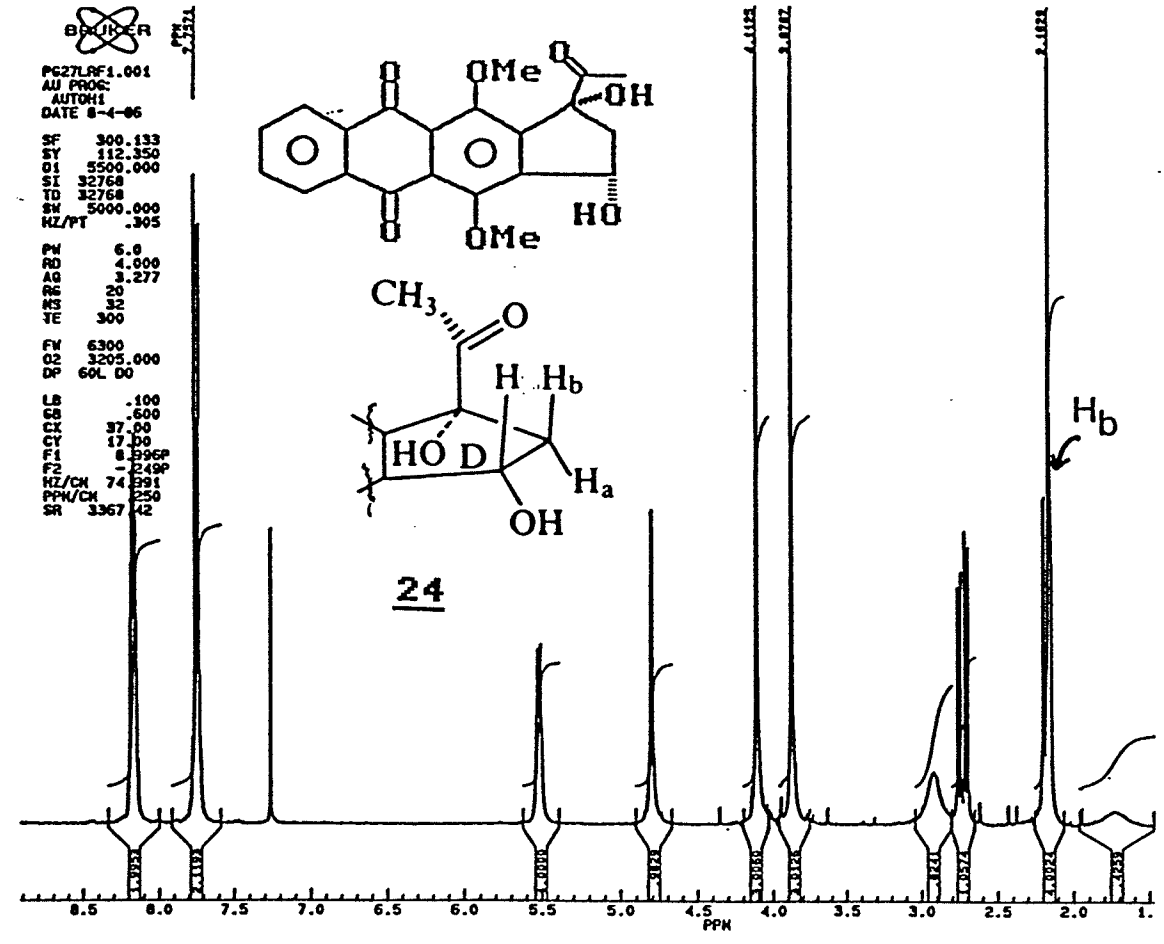

PG27LRF1.001
AV PROG:
AUTOH1
DATE 8-4-06
OMe
OH
HO
OMe
CH3
O
H
Hb
HO D
Ha
OH
Hb
24
b
PPM

Fig. 9

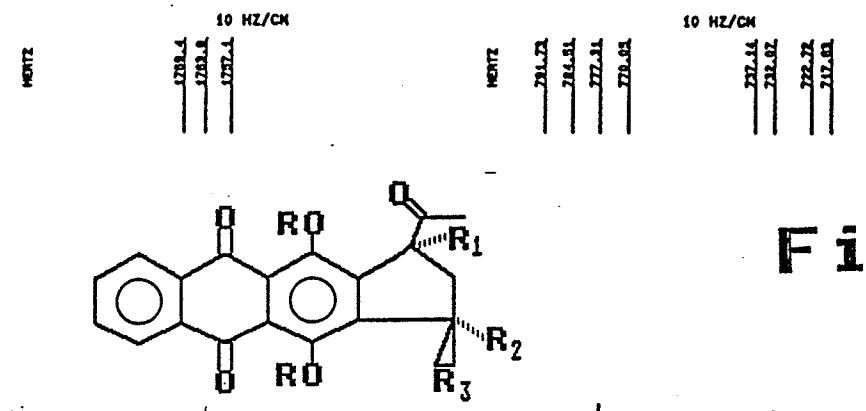
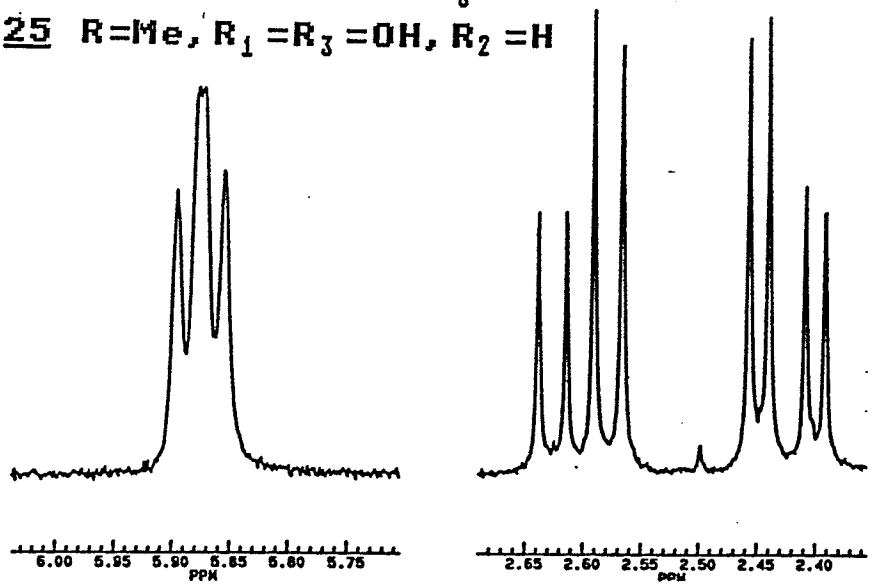
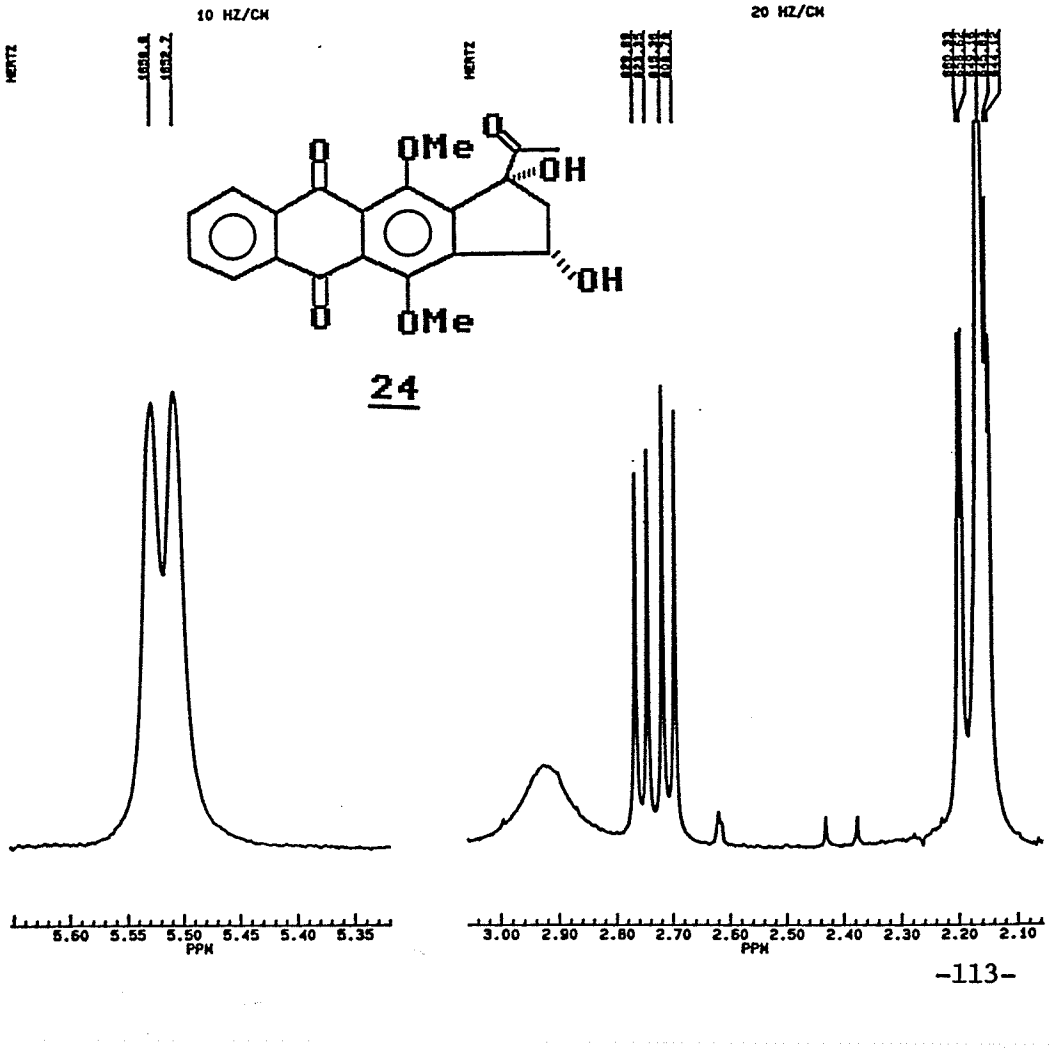


Fig. 9

25 R=Me, R_1 =R_3 =OH, R_2 =H



c



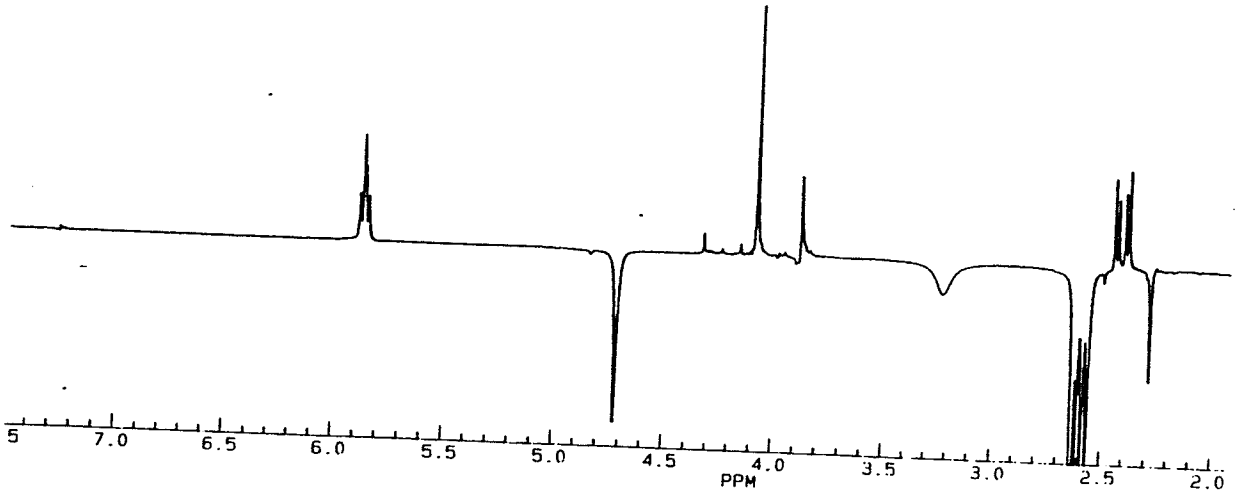
24

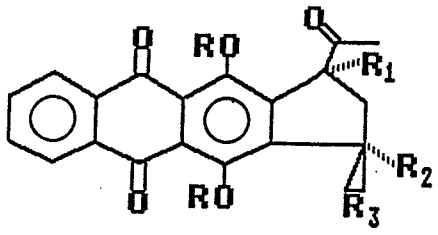
d

Fig. 9

NOE DIFF FROM PEAKS AT 2.5 PPM

e





NOE DIFF FROM GROUP AT 5.9 PPM

25 R=Me, R_1 =R_3 =OH, R_2 =H

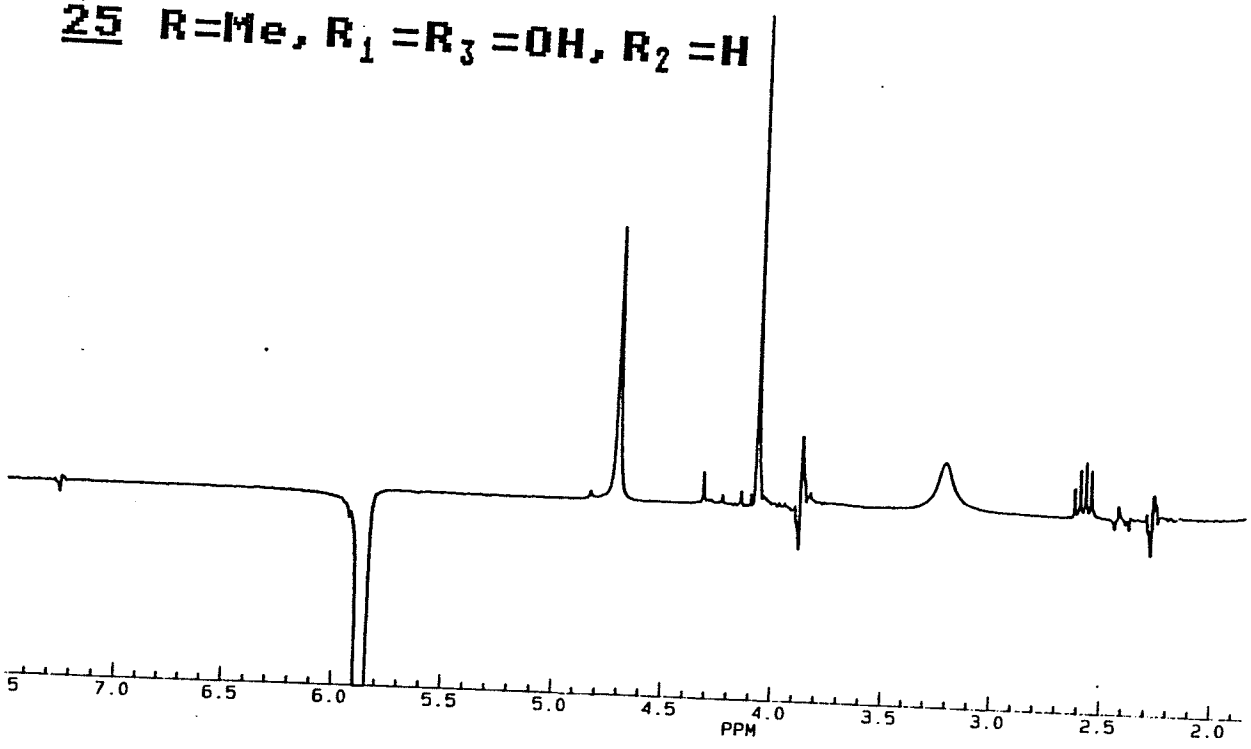


Fig. 9

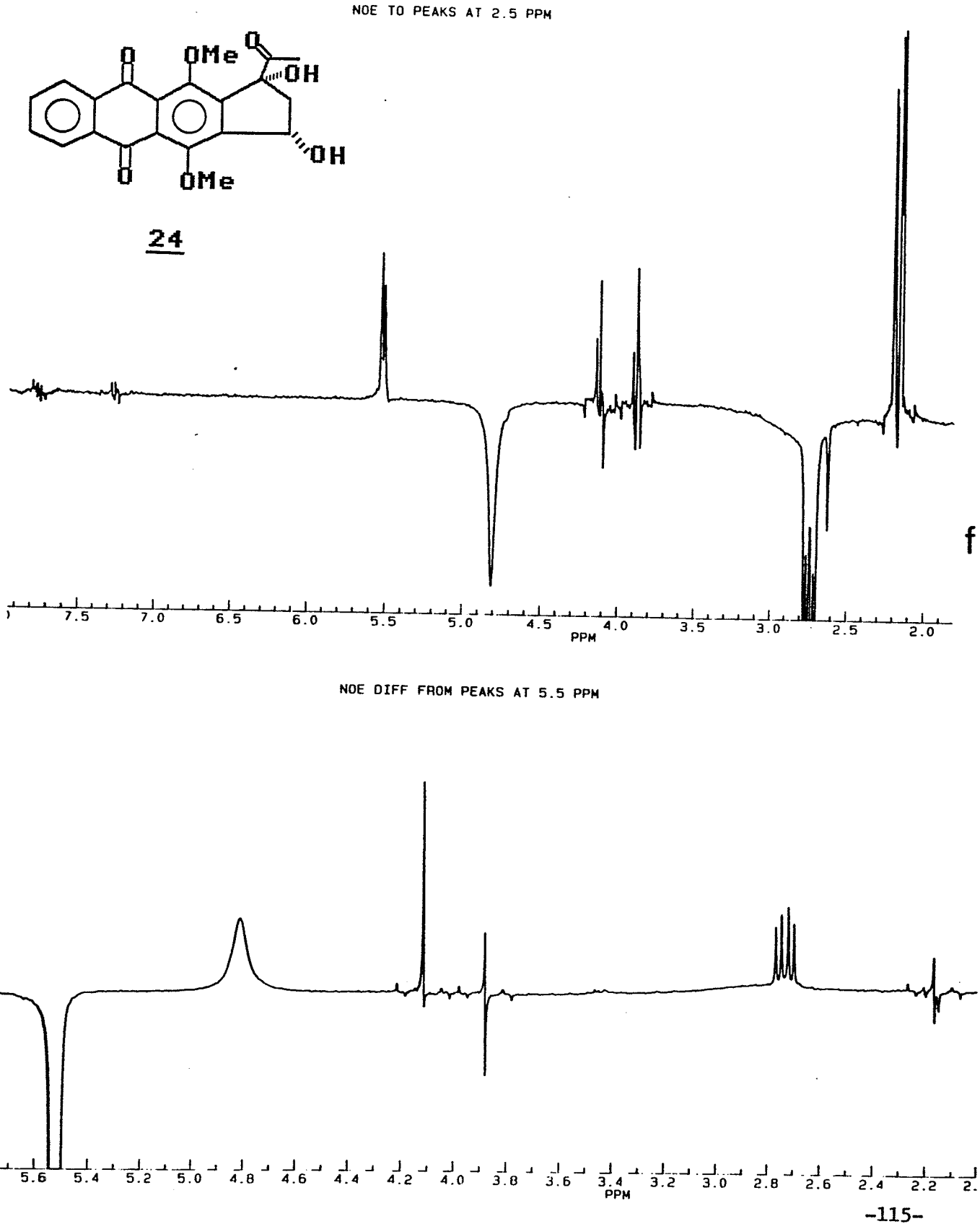
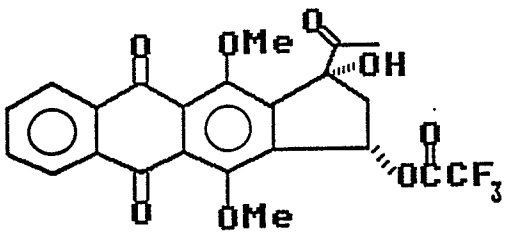

NOE TO PEAKS AT 2.5 PPM
O
OMe
O
OH
OH
O
OMe
24
f
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
PPM
NOE DIFF FROM PEAKS AT 5.5 PPM
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.
PPM

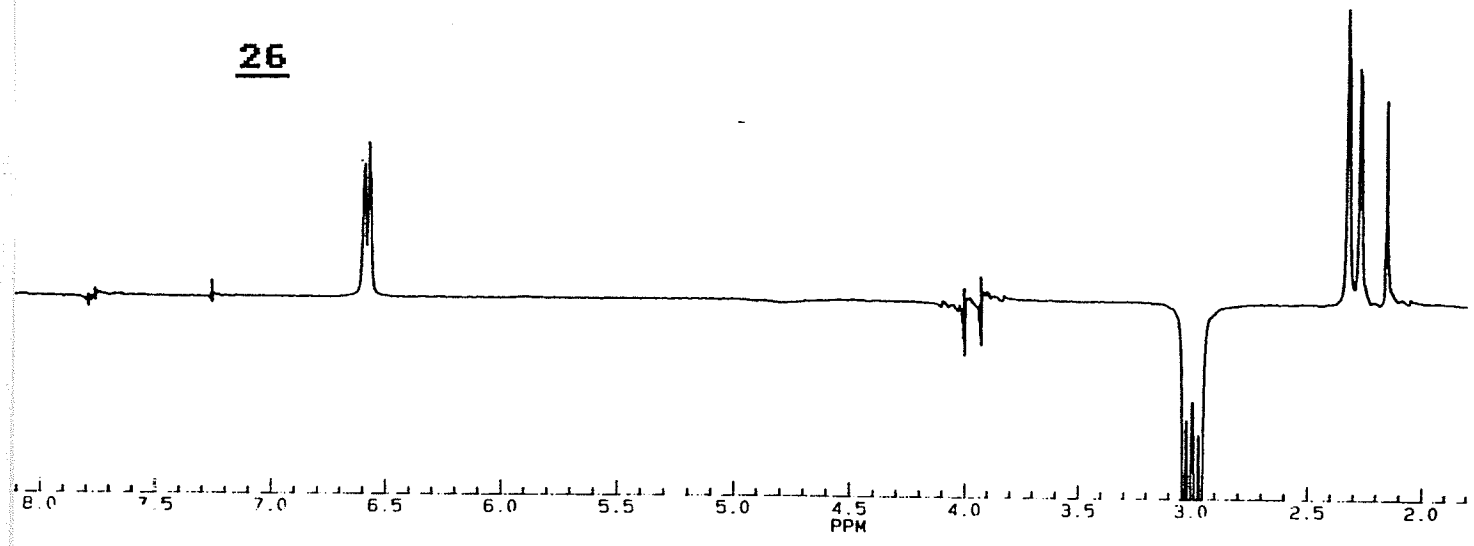
Fig. 9



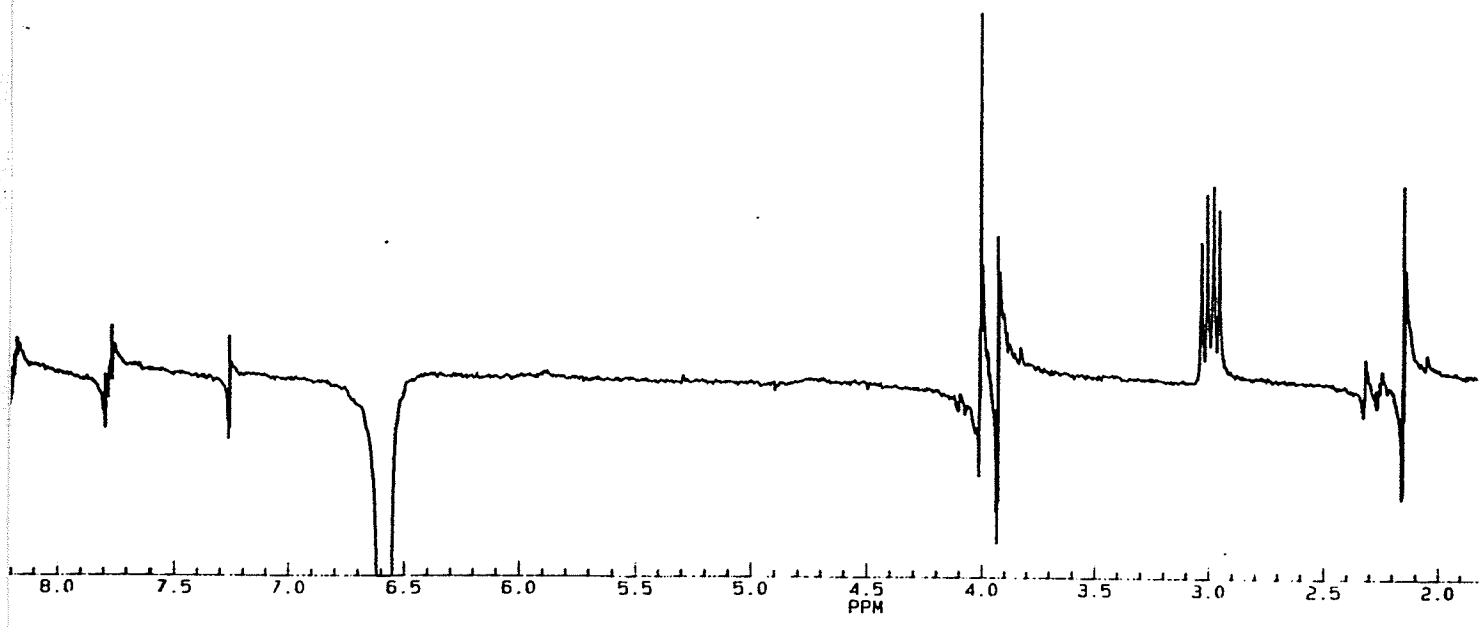
26

NOE DIFF FROM PEAKS AT 3 PPM

g



NOE DIFF FROM PEAKS AT 6.4 PPM



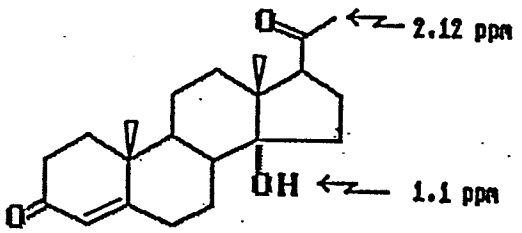
configuration at C7, i.e. the product from the bis hydroxylation is the **cis** stereoisomer 24 and the product from the trifluoroacetic acid epimerisation is the **trans** stereoisomer 25.

Irradiation of the peaks at 2.5 ppm (Fig. 9f) of the isomer previously assigned the **trans** configuration (of the two hydroxyl groups) results in an observed NOE to the methyl hydrogens of the acetyl group on C9 and to the C7 hydrogen. This would indicate that the hydrogen at C7, and the acetyl group are on the same side of the 5-membered ring placing the two hydroxy groups **cis** to each other. Similarly, a NOE from the C7 hydrogen causes an enhancement of the peak at 2.5 ppm (Fig. 9f). These results are also demonstrated more clearly by the NOE experiments on the trifluoroacetate derivative 26. (see Fig. 9g). Conversely, when NOE experiments were conducted on the stereoisomer assigned the **cis** configuration (i.e. 25) opposite and consistent results were obtained. Irradiation of C7 hydrogen caused an NOE to one of the protons at C8 (2.6 ppm). When this same hydrogen was irradiated, no NOE to the hydrogens of the acetyl group was observed (Fig. 9e). These experiments were not performed on the trifluoroacetate of 25 as we did not have any in hand. However, since the NOE method is a fairly reliable method, one has to take cognisance of the results. In view of these results, it is not clear whether or not the acetonide was formed (in our earlier efforts to epimerise the C7 center) or the trifluoroacetate (our latter, reproducible way of epimerising the C7 center).

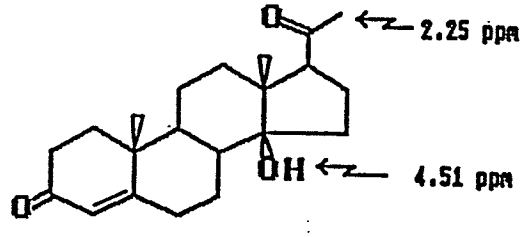
Before the NOE experiments were conducted on the two stereoisomers 24 and 25, the assignments of the cis and trans configuration to 25 and 24 respectively were based on the resonances, multiplicities coupling

constants of the acetyl, C7 and C8 hydrogens and other physical characteristics (22). However, in view of the NOE results, the following discussion is more compatible with the ^1H NMR spectra Fig. 9 (a-d) of these two stereoisomers.

In the trans stereoisomer 25 (by the NOE results), the free rotation of both the C7-OH and the C9-$COCH_3$ groups is impeded by the hydrogen bonding between these two groups. This hydrogen bonding thus decreases the electron density on the carbonyl carbon (as compared with its stereoisomer), making it more positive than 'normal' and hence exhibits a downfield shift of 0.122 ppm of the acetyl hydrogens relative to its diastereoisomer (2.28 vs. 2.16 ppm, Fig. 9a,b). That kind of downfield shift of an acetyl group with the same relative disposition to a hydroxy group is known (23). Some of the ^1H NMR data for two compounds in the progesterone series are shown below.

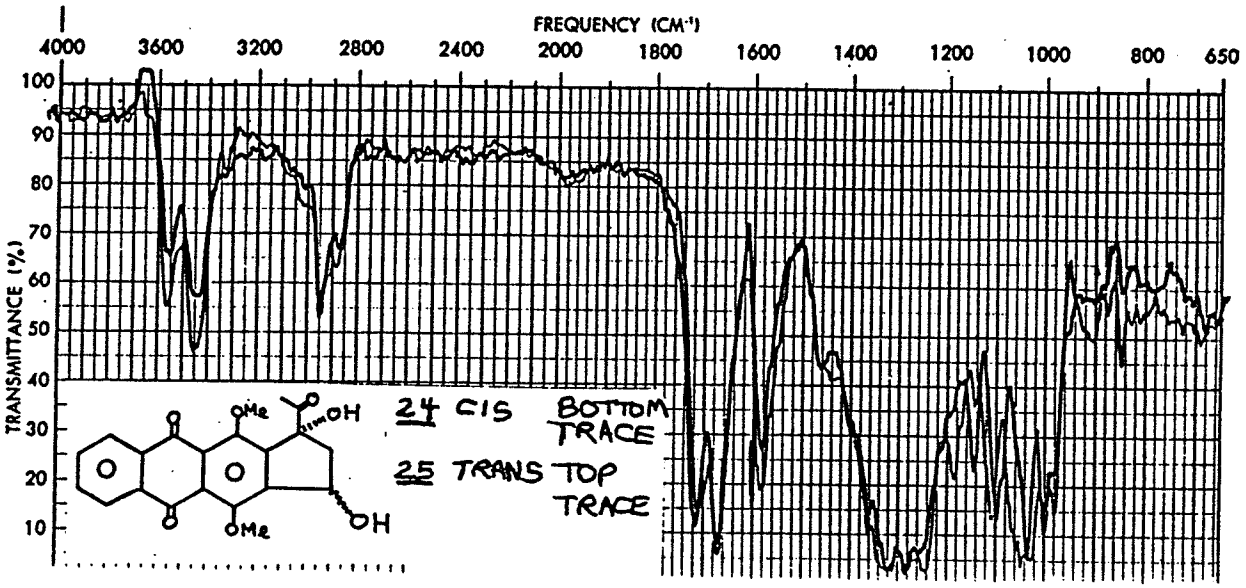


14α-Hydroxyprogesterone



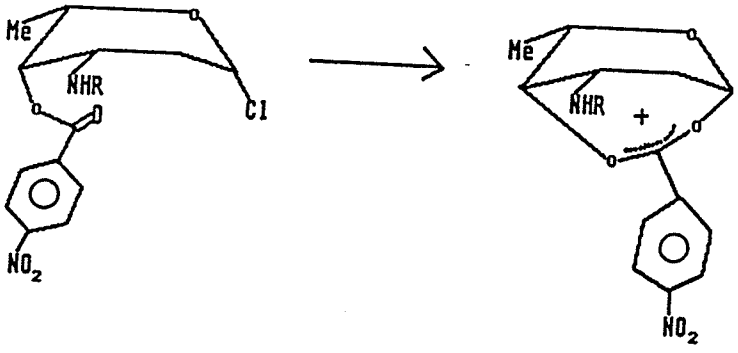
14-Hydroxy-14-β-pregn-4-ene-3,20-dione

The hydrogen bonding in the trans isomer 25, is also reflected in the value of the resonance of the C7–OH hydrogen shown by a downfield shift of 0.27 ppm relative to the cis isomer 24, (3.19 vs. 2.92 ppm, Fig. 9a,b). That relative downfield shift is also seen in the progesterone series (23) shown above. By extension and assuming that the ^{1}H NMR spectrum of the cis stereoisomer 24 is the 'normal' spectrum, then we can once again suggest that the hydrogen bonding in the trans stereoisomer 25 diminishes the shielding effect of the carbonyl group and, therefore, the C8 H_b hydrogen in 25, is deshielded relative to the C8 H_b hydrogen in 24 (2.428 vs. 2.173 ppm, Fig. 9a,b). The probable 1,3-'diaxial' interaction of C7–H and C9–OH is presumed responsible for the downfield shift of the C7 hydrogen in 25 compared with the C7 hydrogen in 24 (5.874 vs. 5.517 ppm, Fig. 9a,b). The similarity in the IR spectra of the compounds, 24 and 25, shown below is noteworthy.



In view of the NOE results, it was decided to couple **both** aglycones 27

and 28 to the protected sugar 30. Thus, both the **cis** and **trans** dihydroxy compounds 27 and 28 were demethylated at room temperature in chloroform by using aluminium chloride and after work up triturated with chloroform/diethyl ether or methylene chloride/diethyl ether. The ^{1}H NMR spectra are shown in Figs. 10 and 11 and are consistent with those of their precursors 24 and 25. The glycoside formation was performed under Koenigs-Knorr conditions (24). The stereoselectivity in the formation of the epimers at the glycosidic center in the absence of neighbouring group participation is dependent on, inter alia., the reaction conditions and the halosugar used. For example, it is known that a chlorosugar is more selective than a bromosugar. The p-nitrobenzoyl group seems to be the protecting group of choice for the hydroxyl group of the sugar moiety. The use of this group appears, in some cases, to favour exclusively the alpha anomer; presumably due to anchimeric assistance (25).



However, in other cases (24) and in our hands both the α and β anomers were isolated.

The N-trifluoroacetyl, 4'-O-nitrobenzoyl daunosamine was converted to

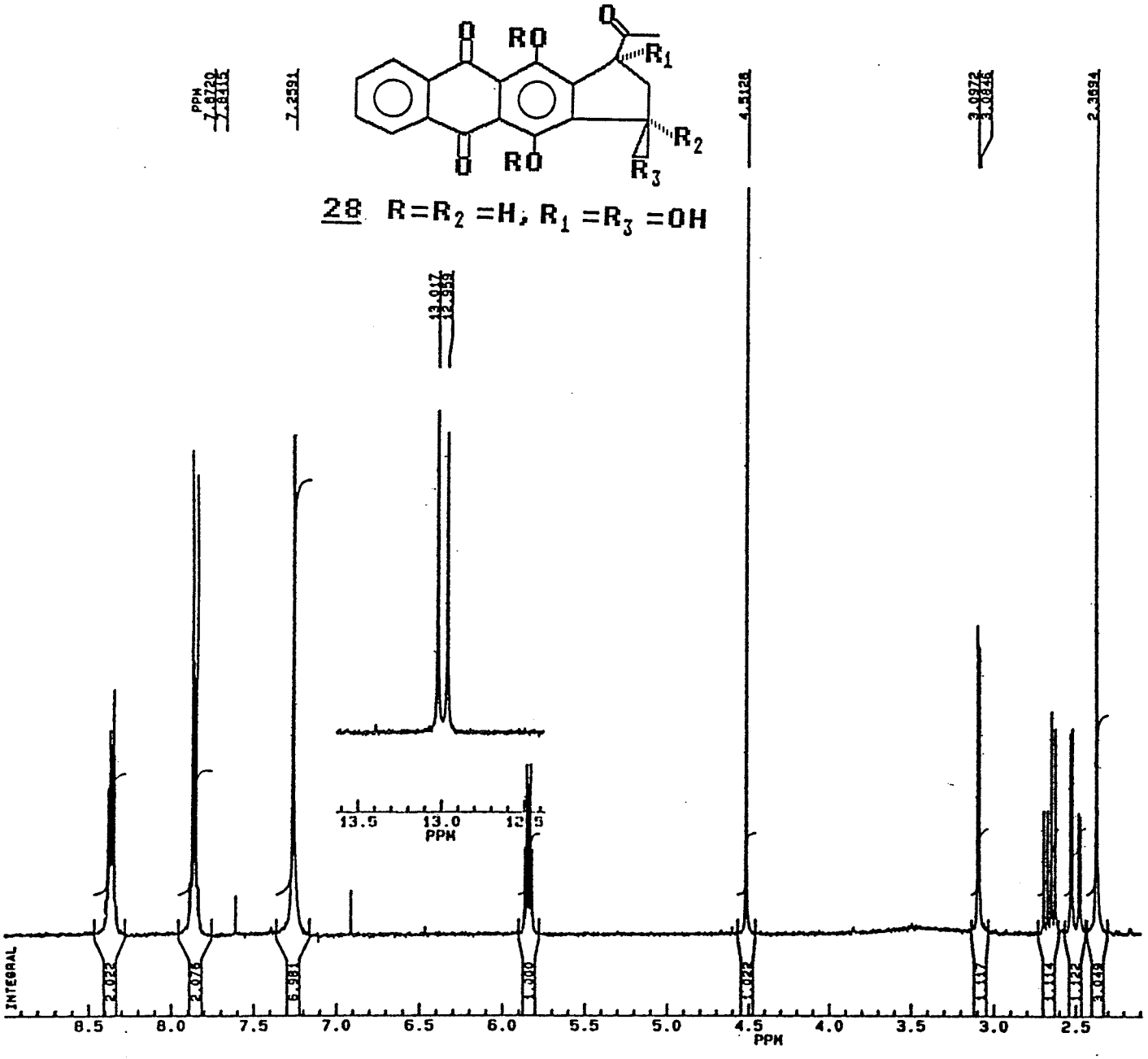

O
RO
O
RO
O
R1
R2
R3
28 R=R2 =H; R1 =R3 =OH
PPM
7.8729
7.8418
7.2591
4.5128
3.0972
3.0844
2.3694
13.017
12.959
13.5
13.0
PPM
INTEGRAL
2.022
2.026
5.981
1.000
1.022
3.117
1.114
1.122
3.048
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
PPM

Fig. 10

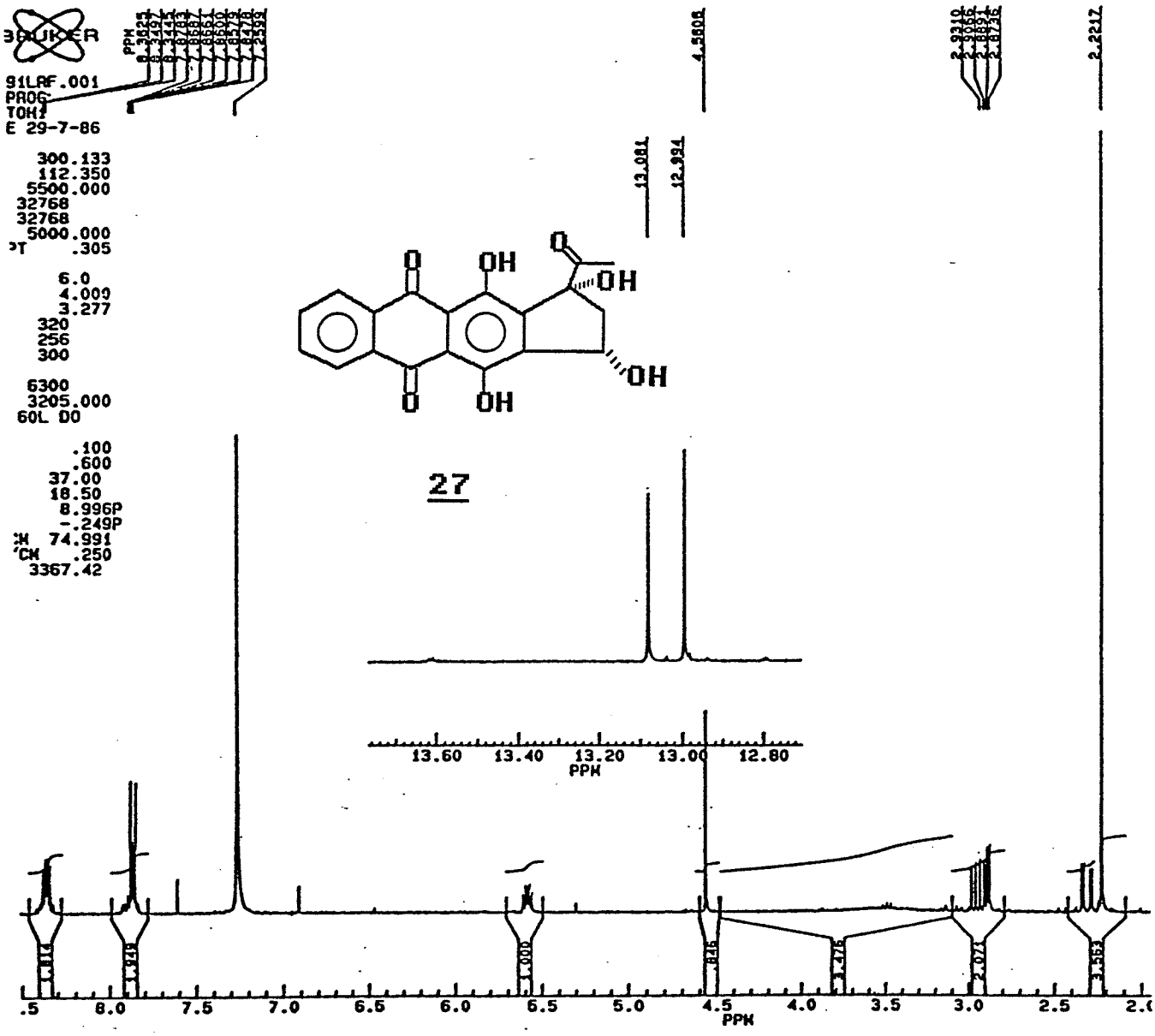

BRUKER
91LRF.001
PROC
TOH1
E 29-7-86
300.133
112.350
5500.000
32768
32768
5000.000
.305
6.0
4.009
3.277
320
256
300
6300
3205.000
60L DO
.100
.600
37.00
18.50
8.996P
-.249P
74.991
.250
3367.42
27
OH
OH
OH
OH
O
O
13.081
12.934
4.5808
2.9310
2.8891
2.8738
2.2212
13.60
13.40
13.20
13.00
12.80
PPM
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
PPM

Fig. 11

its chloride by treatment with HCl gas in methylene chloride. An ether solution of this chlorosugar was added to the aglycone in methylene chloride containing molecular sieves and silver trifluoromethane sulfonate. This method, in the case of the trans stereoisomer 28, gave one minor and two major compounds (^{1}H NMR spectra, Fig. 12 a-c, 32 A, 32 B and 32 C). The numbers are relative to their rf values (1 > 2 > 3). The ^{1}H NMR spectrum of 32 A shows the major resonances but is still rather impure. However, since it is a minor compound it will not be discussed any further. To date, we have only been able to purify 32 C to the extent where all the resonances can be assigned. The NH absorption is a doublet centered at 6.427 ppm. The doublet of doublets at about 5.90 ppm is due to the anomeric hydrogen H'1 of the sugar residue. The broad peak at 5.465 ppm is the resonance due to H_7. The other signals between 5.40 and 4.50 ppm are due to H'4, H'3, H'5 and C9 hydroxyl group respectively. The multiplets between 1.80 and 2.70 ppm are due to the C8 hydrogens and the C'2 hydrogens. The peak at 2.318 ppm is the absorption of the hydrogens of the acetyl group. The doublet centered at 1.295 ppm is due to the hydrogens of the methyl group of the sugar residue absorption. The peaks at 2.164 ppm, 1.551 ppm and 1.253 ppm are impurities due to acetone, water and grease respectively.

The resonances in the ^{1}H NMR spectrum of 32 B can be analogously assigned but the spectrum is complicated by a sugar impurity. Nevertheless, one can make the anomeric assignment of those hydrogens since these hydrogens are well resolved. Accordingly, 32 B displaying a broad peak (W_H about 6 Hz) and 32 C displaying a doublet of doublets are assigned the alpha and beta glycosides respectively (24, 25). The beta

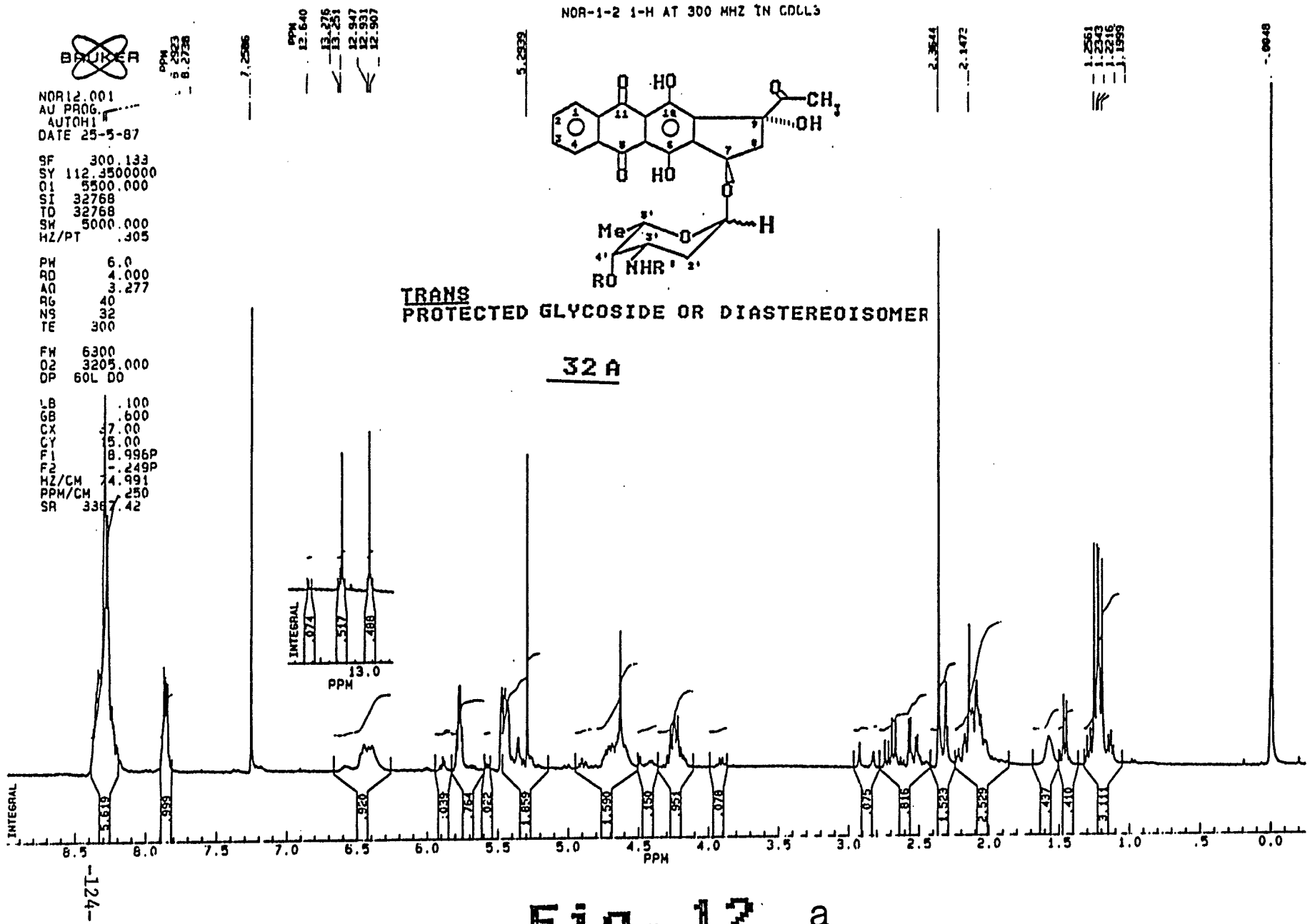

NOR-1-2 1-H AT 300 MHZ IN CDCL3
BRUKER
NOR12.001
AU PROG.
AUTOH1
DATE 25-5-87
SF 300.133
SY 112.3500000
O1 5500.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 6.0
RD 4.000
AQ 3.277
RG 40
NS 32
TE 300
FW 6300
O2 3205.000
DP 60L DO
LB .100
GB .600
CX 17.00
CY 15.00
F1 8.996P
F2 -.249P
HZ/CM 74.991
PPM/CM .250
SR 3367.42
TRANS
PROTECTED GLYCOSIDE OR DIASTEREOISOMER
32 A
INTEGRAL
PPM

Fig. 12 a

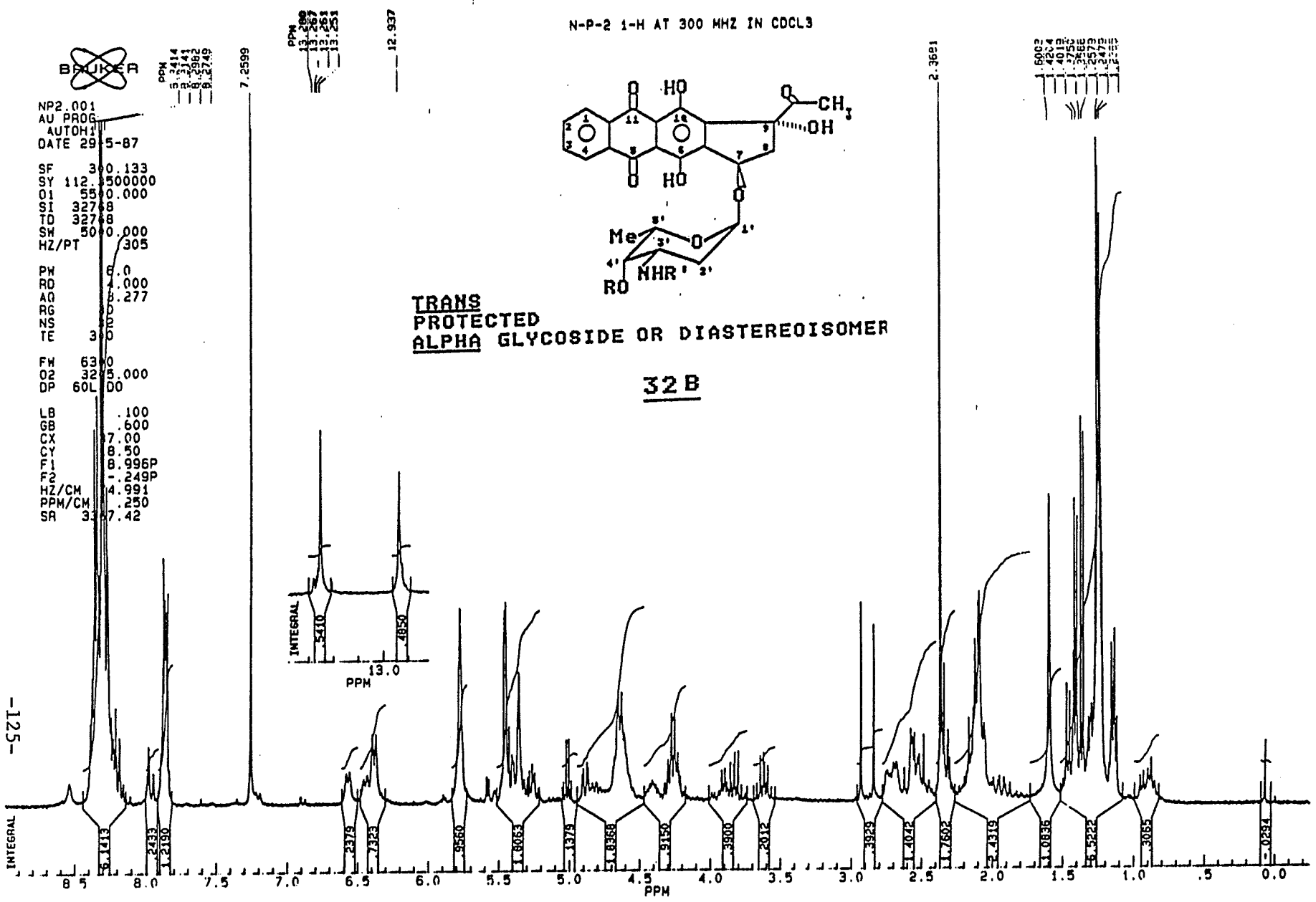

N-P-2 1-H AT 300 MHZ IN CDCL3
BRUKER
NP2.001
AU PROG
AUTOH1
DATE 29-5-87
SF 300.133
SY 112.3500000
O1 5510.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 6.0
RD 4.000
AQ 3.277
RG
NS
TE 300
FW 6300
O2 3285.000
DP 60L DO
LB .100
GB .600
CX 7.00
CY 8.50
F1 8.996P
F2 -.249P
HZ/CM 4.991
PPM/CM .250
SR 3347.42
7.2599
12.937
2.3691
HO
O
CH3
OH
Me
NHR'
RO
TRANS
PROTECTED
ALPHA GLYCOSIDE OR DIASTEREOISOMER
32B
INTEGRAL
PPM
-125-

Fig. 12 b

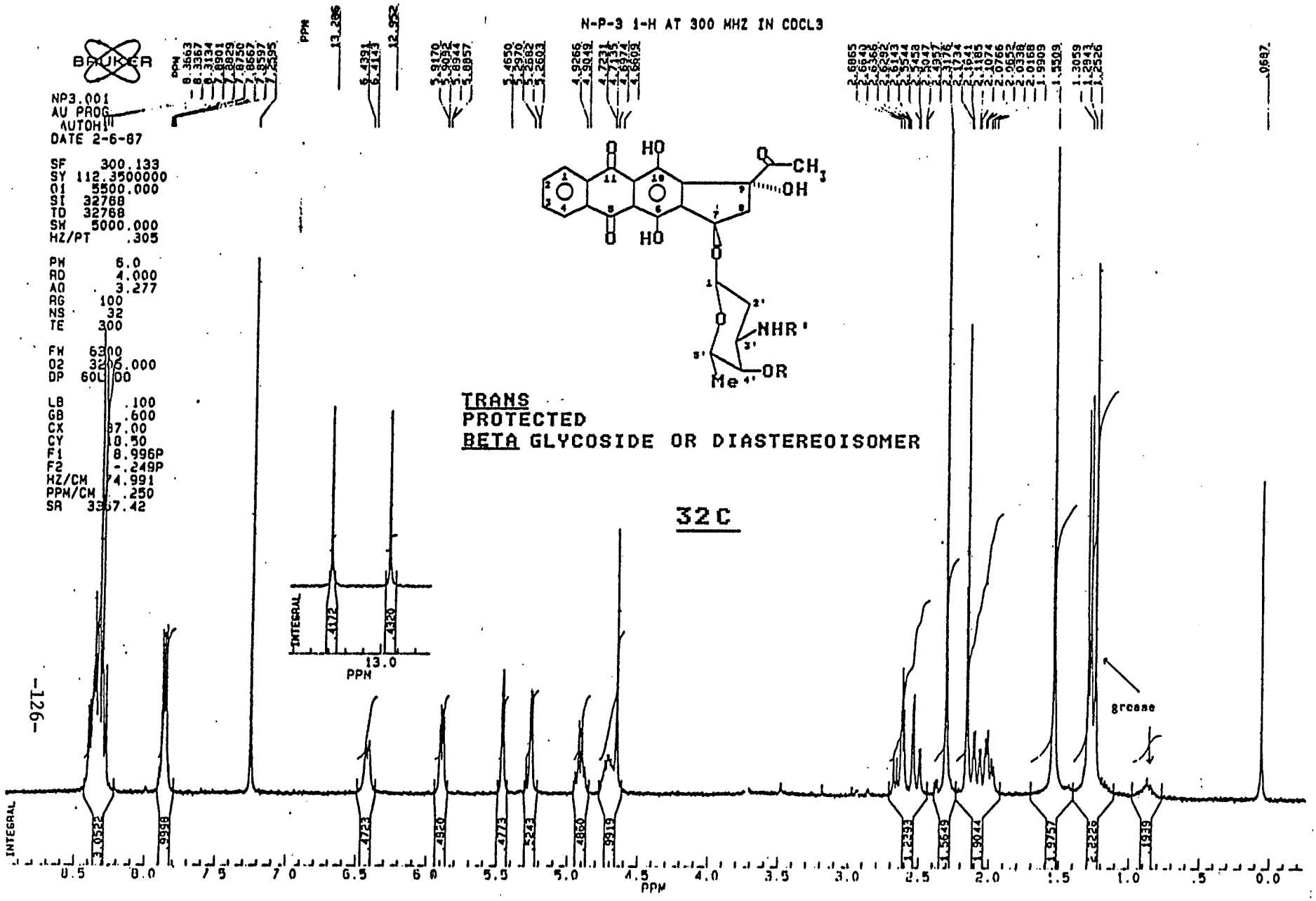

N-P-3 1-H AT 300 MHZ IN CDCL3
BRUKER
NP3.001
AU PROG
AUTOH1
DATE 2-6-87
SF 300.133
SY 112.3500000
O1 5500.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 6.0
RD 4.000
AQ 3.277
RG 100
NS 32
TE 300
FW 6300
O2 3206.000
DP 60L 00
LB .100
GB .600
CX 87.00
CY 10.50
F1 8.996P
F2 -.249P
HZ/CM 74.991
PPM/CM .250
SR 3367.42
HO
CH3
OH
HO
NHR'
OR
Me
TRANS
PROTECTED
BETA GLYCOSIDE OR DIASTEREOISOMER
32C
INTEGRAL
PPM
grease
-126-

Fig. 12 C

anomeric hydrogen resonance (alpha glycoside) is usually a broad singlet with W_H about 6 Hz and the alpha anomeric hydrogen resonance (beta glycoside) is usually a doublet of doublets (J=10 Hz and about J=2 Hz).

Similarly, glycosylation of the **cis** stereoisomer 27 gave **two major compounds** 31 A and 31 B (relative rf 2 > 3) and the ^1H NMR spectra (Figs. 13 and 14) are sufficiently pure to allow one to say, based on the foregoing, that 31 A is the **alpha glycoside** (W_H about 4.4 Hz) and 31 B is the **beta glycoside** (J about 5.3 Hz and 1.7 Hz.).

The protected glycosides of 32 C, 31 A and 31 B were deprotected in basic methanol and purification by PTLC produced sufficient material for preliminary biological evaluation. The results indicate that 32 C is **not active** against lung carcinoma. On the other hand, 31 A was about 300 times less active than daunomycin against lung carcinoma and 31 B was only weakly active against that type of cancer. Those results would corroborate the NOE results that the configurations of 24 and 25 should be reversed. The results also suggest that the configuration at the glycosidic bond of 31 A and 31 B were correctly assigned as the glycosides are, as documented by other workers (1), more active than the glycosides. However, in the near future, we do expect to conduct a more detailed biological evaluation of these new glycosides.

In view of the results of Flynn et al. (4b), with regard to their synthesis of the 8-**nor** analogue, we feel rather fortunate to have chosen the 10-**nor** analogues which are apparently more stable to the synthetic

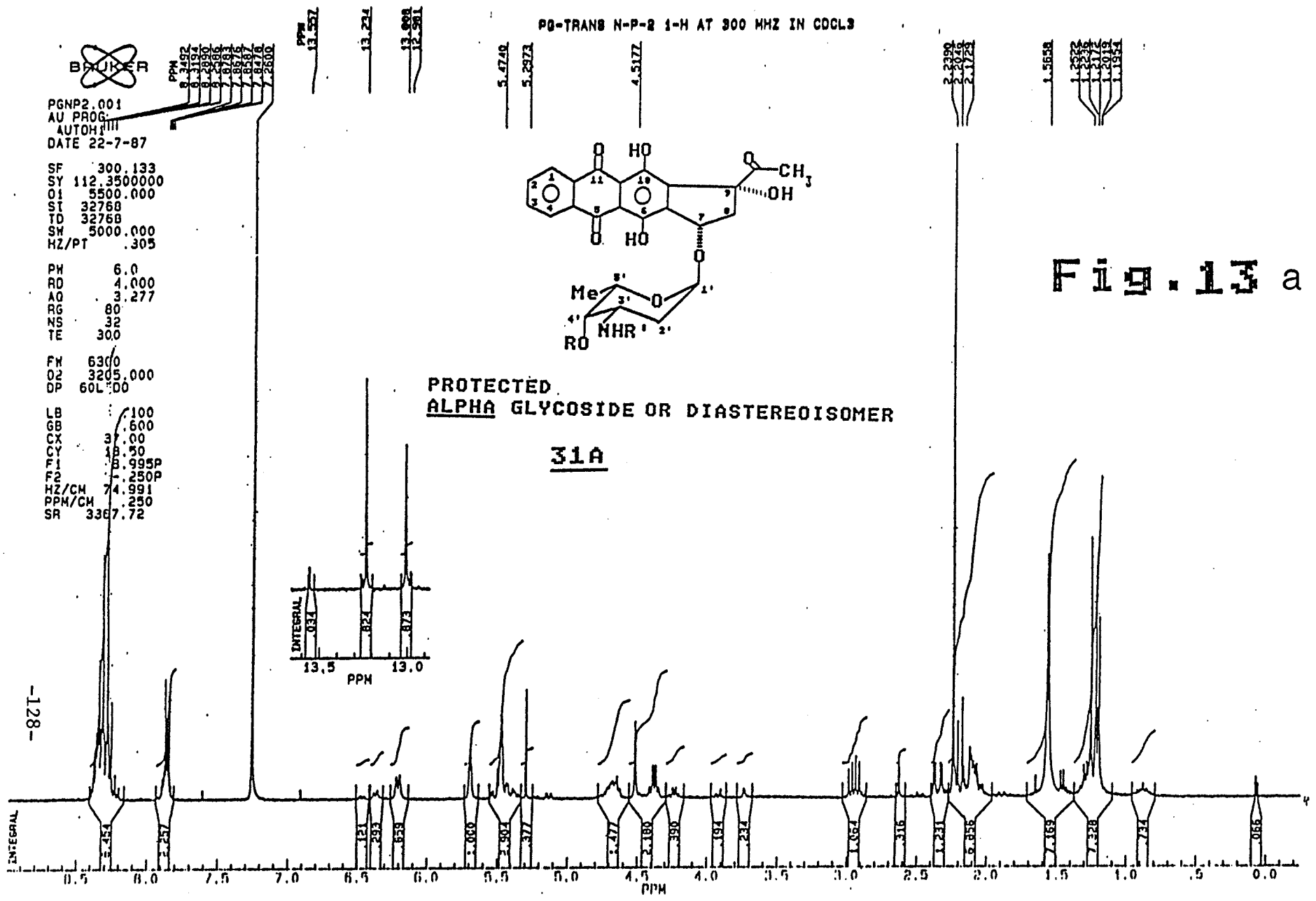

PG-TRANS N-P-2 1-H AT 300 MHZ IN CDCL3
PGNP2.001
AU PROG:
AUTOH1
DATE 22-7-87
SF 300.133
SY 112.3500000
O1 5500.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 6.0
RD 4.000
AQ 3.277
RG 80
NS 32
TE 300
FW 6300
O2 3205.000
DP 60L 00
LB .100
GB .600
CX 37.00
CY 18.50
F1 8.995P
F2 -.250P
HZ/CM 74.991
PPM/CM .250
SR 3367.72
PROTECTED
ALPHA GLYCOSIDE OR DIASTEREOISOMER
31A
INTEGRAL
PPM

Fig. 13a

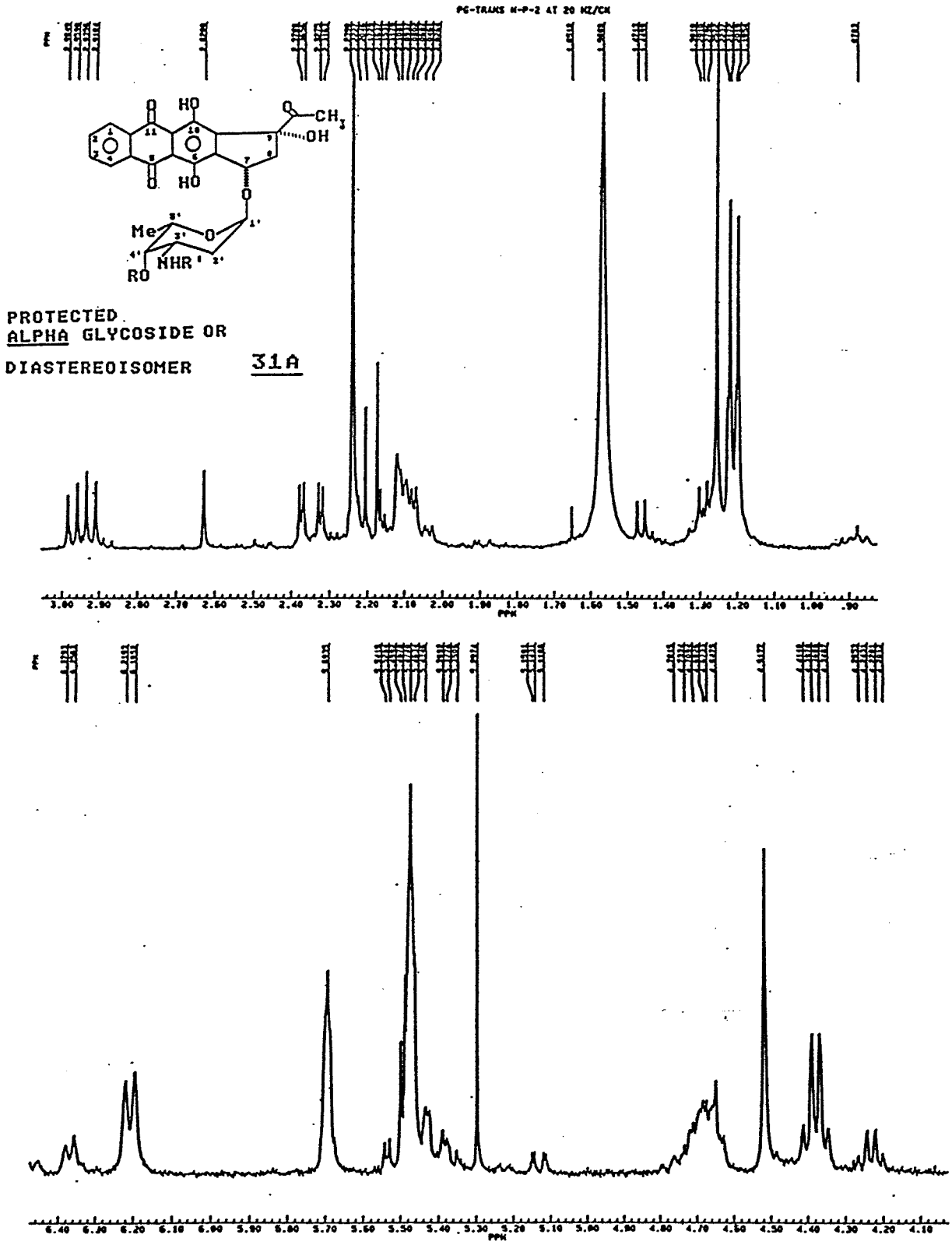

PG-TRANS H-P-2 AT 20 HZ/CM
HO
O
CH3
OH
HO
O
Me
O
NHR
RO
PROTECTED
ALPHA GLYCOSIDE OR
DIASTEREOISOMER
31A
PPM
PPM

Fig. 13 b

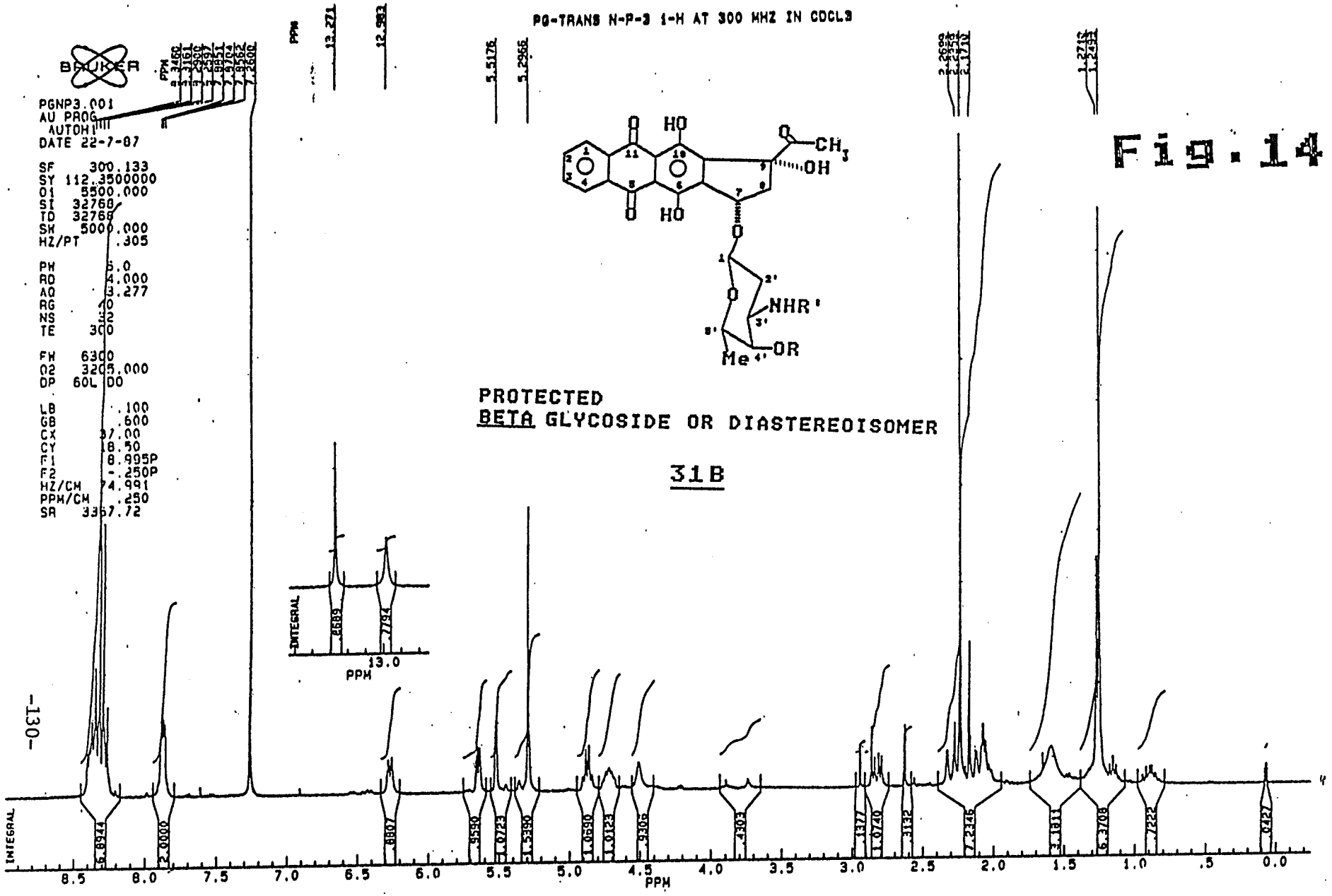

PG-TRANS N-P-3 1-H AT 300 MHZ IN CDCL3
PGNP3.001
AU PROG
AUTOH1
DATE 22-7-07
SF 300.133
SY 112.3500000
O1 5500.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 6.0
RD 4.000
AQ 3.277
RG 10
NS 32
TE 300
FW 6300
O2 3205.000
DP 60L DO
LB .100
GB .600
CX 37.00
CY 18.50
F1 8.995P
F2 -.250P
HZ/CM 74.991
PPM/CM .250
SR 3357.72
PROTECTED
BETA GLYCOSIDE OR DIASTEREOISOMER
31B
PPM
INTEGRAL

Fig. 14 a

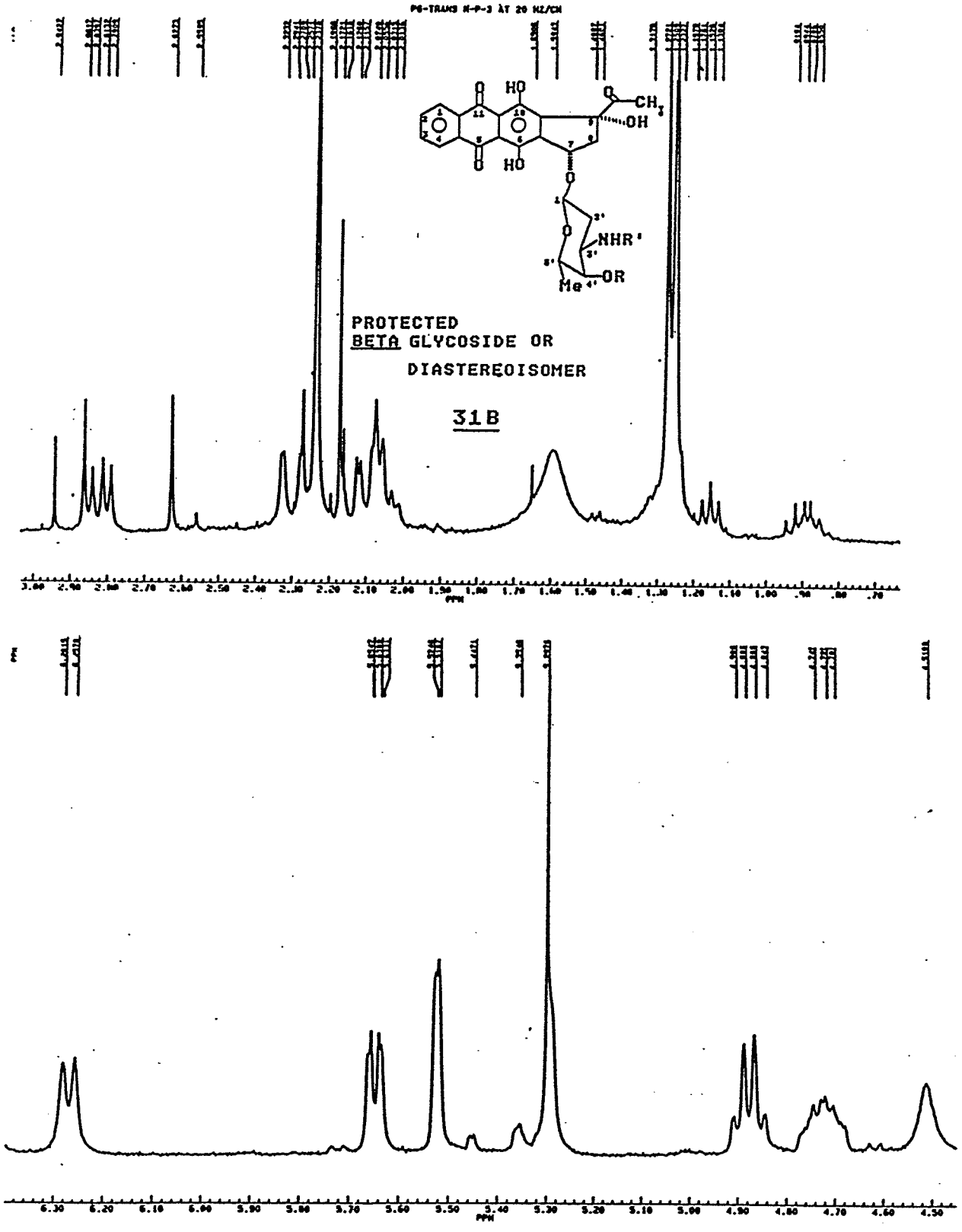


Fig. 14 b

manipulations necessary for the total synthesis of molecules of this kind.

CONCLUSION

The synthesis of (±)-4-demethoxy-10-nordaunomycin and its C7 epimer has been achieved. The protected and the deprotected glycosides of both these stereoisomers have also been prepared but have not been fully characterised due to insufficient material. However, preliminary biological results indicate that the glycoside, possessing the natural stereochemistry as daunomycin, is 60 times less active than the latter against lung carcinoma cancer cells. Therefore, based on the intercalation model for activity of the anthracyclines, this result would suggest that intercalation is not the principal mode through which the anthracycline, 4-demethoxy-10-nordaunomycin, effects its biological activity.

In addition, these preliminary results indicate that modification of the alicyclic A-ring conformation alone cannot sustain the level of potency observed in daunomycin. Therefore, in addition to this structural change, other simultaneous changes in the molecule may be necessary to reverse or increase this activity.

Since one can view the biological result as an informative one, it would be of interest to see how the biological activity might change by maintaining the present 5-membered ring and making other modifications to the molecule. For example, testing the model with:

1. the 4-OH or 4-OMe substituent present,
2. the C9 acetyl substituent replaced with a C9 ethyl substituent,
3. an 11-H substituent instead of an 11-OH substituent, and
4. a 4'-deoxysugar.

It is hoped that, with larger quantities of the nor-glycosides available, a better insight into the structure-activity relationships of this new anthracycline will be gleaned.

REFERENCES

1. F. Arcamone,
   Doxorubicin Anticancer Antibiotics; Medicinal Chemistry, Vol. 17
   Academic Press, NY 1981; Chapter 7, pp 264.

2. M. J. Broadhurst, C. H. Hassal and G. J. Thomas,
   Chem. and Ind., 106 (1985).

3. C. M. Wong, A. Q. Mi, J. Ren, W. Haque and K. Marat,
   Tetrahedron, 40, 4789 (1984) and references therein.

4a. I. K. Khanna and L. A. Mitscher,
   Tetrahedron Lett., 26, 691 (1985).

4b. G. A. Flynn, M. J. Vaal, K. T. Stewart, D. L. Wenstrop,
   D. W. Beight and E. H. Bohme,
   J. Org. Chem., 49, 2252 (1984).

5. Research work done by Hiu Jing Liu and Yan Yulin and will be
   documented elsewhere.

6. C. M. Wong, R. Schwenk, D. Popien and T. L. Ho,
   Can. J. Chem., 51, 466 (1973) and references therein.

7. K. Hanaya, S. Awano and H. Kudo,
   Bull. Chem. Soc. Japan, 51, 342 (1978).

8. C. M. Wong, H. Y. Lam and W. Haque,
Can J. Chem., 61, 562 (1983).

9. M. Midland,
J.Org. Chem., 40, 2250 (1975).

10a. P. Cannone, G. B. Foscolos and G. Lemay,
Tetrahedron Lett., 135 (1980).

10b. G. Alvernhe and A. Laurent,
Tetrahedron Lett., 1057 (1973).

10c. M. Chastrette, R. Amouroux and M. Subit,
J. Organometal. Chem. 99, C41-43 (1975).

11. Thomas F. Rutledge in,
Acetylene Compounds; Reinhold Book Corporation, p. 13, 1968.

12. L. Skattebol, E.R. H. Jones and M. C. Whiting,
Org. Synthesis, 39, 56 (1959).

13. C. M. Wong, A. Q. Mi, J. Ren, W. Haque, H. Y. Lam and K. Marat,
Can. J. Chem., 62, 1600 (1984).

14. W. Carruthers in,
Some Modern Methods of Organic Synthesis; Cambridge University Press, 2nd. ed., p. 436, 1980.

15a. T. L. Ho,

Tetrahedron, 41, 1 (1985).

15b. T. L. Ho in,

Hard and Soft Acids and Bases, Principle in Organic Chemistry; Academic Press, 1977 and references therein.

16a. R. J. Rawson and I. T. Harrison,

J.Org. Chem., 35, 2057 (1970).

16b. R. M. Blankenship, K. A. Burdett and J. S. Swenton,

J. Org. Chem., 39, 2300 (1974).

16c. J. F. Templeton and C. W. Wie,

Can. J. Chem., 53, 1693 (1975).

17a. A. M. Khan, F. J. McQuillin and I. Jardine,

J. Chem. Soc. (C), 136, (1967).

17b. E. W. Garbisch, Jr., L. Schreader and J. J. Frankel,

J. Am. Chem. Soc., 89, 4233 (1967).

17c. S. Mitsui, Y. Senda and K. Konno,

Chem. and Ind., 1554 (1963).

17d. S. Mitsui, S. Imaizumi and Y. Esashi,

Bull. Chem. Soc. Japan, 43, 2143 (1970).

17e. Milos Hudlucky in,

Reductions in Organic Chemistry; Ellis Horwood Ltd., 1984.

18. J. E. Baldwin, G.A. Hofle, and O. W. Lever Jr.,

J. Am. Chem. Soc., 96, 7125 (1974).

19. S. J. Nelson, G. Petre and M. Tanabe,
Tetrahedron Lett., 447 (1973).

20. F. Arcamone, L. Bernardi, B. Patelli, P. Giardino, A. Di Marco,
A. M. Caszza, C. Soranzo and G. Pratesi,
Experientia, 34, 1255, (1978).

21. O. Mitsunobu,
Synthesis, 1 (1981).

22. C. M. Wong, P. M. Gordon, A. G.Chen and H. Y. P. Lam,
Can. J. Chem., 65, 1375 (1987).

23. J. F. Templeton, V. P. S. Kumar, D. Cote, D. Bose, D. Elliott,
R. S. Kim and F. S. LaBella,
J. Med. Chem., 30, 1502 (1987).

24a. F. Arcamone, S. Penco and A. Vigevani,
Can. Chem. Rep. Part 3, 6, 123 (1975).

24b. K. Nakanishi, T. Goto, S. Ito, S. Natori and S. Nozoe, Eds.,
Natural Products Chemistry; Oxford University Press,
Vol., 3, p463-479, (1983).

25a. M. J. Broadhurst, G. H. Hassall and G. J. Thomas,
J. Chem. Soc., Perkin Transactions 1, 2249 (1982).

25b. E. F. Fuchs, D. Horton, W. Weckerle and E. Winter-Mihay,
J. Med. Chem., 22, 406 (1979).

EXPERIMENTAL

GENERAL CONSIDERATIONS

SOLVENTS

Solvents were purified as delineated below unless otherwise stated. Interested readers should see **Purification of Laboratory Chemicals** by D. D. Perrin, D. R. Perrin and W. L. F. Armarego, Pergamon Press, 1st. Ed., 1966 and **Practical Organic Chemistry** by A. I. Vogel 4th. Ed., for more detailed procedures for drying some of the solvents listed below.

1. Ethanol

Ethanol (95%) was distilled and the fraction boiling at 78 ^{o}C was collected.

2. Acetone

Whenever 'dry' acetone (Fisher, Spectrograde) was required an unopened bottle, or a recently opened bottle, stored over Linde type 4A molecular sieve was used.

3. Tetrahydrofuran

This solvent was purified by refluxing with sodium and benzophenone. Once the deep blue color appeared, the solvent was distilled (b.p. 64-66 ^{o}C).

4. Carbon Tetrachloride

This solvent was distilled and the fraction boiling at 76 ^{o}C was collected. The distilled solvent was stored over Linde type 4A

molecular sieve.

5. o-Xylene

The solvent (Kodak or Fisher) was stored over Linde type 4A molecular sieves for at least 24 hours before use.

6. Dimethylformamide

This solvent (Fisher) was distilled and stored over Linde type 4A molecular sieves before use.

7. Toluene

This solvent (Fisher) was used without purification.

REAGENTS

1. Aluminium Chloride

This reagent was sublimed* before use. This sublimed material can be kept for several months without deterioration. In our experience good quality aluminium chloride is characterised by a **white** or **yellowish white** appearance.

*House vacuum sublimation (using a flame) is preferable.

2. Potassium Carbonate

Anhydrous potassium carbonate was powdered and dried in an oven at 130-140 ^{o}C for several hours before use.

3. Mercuric Acetate

Mercuric acetate was prepared in the following way (see F. A. Cotton and G. Wilkinson, **Advanced Inorganic Chemistry** 3rd. Ed., p 518-519).

Mercuric oxide was dissolved in glacial acetic acid, filtered and allowed to cool. The acetate was collected by suction and dried in a desiccator under vacuum until the odour of acetic acid was no longer detected.

4. Trimethyl Phosphite

Commercial trimethyl phosphite (Aldrich, 97%) was distilled at reduced pressure and stored over Linde type 4A molecular sieves.

5. Ethyl Bromide

This reagent (Fisher) was dried over calcium chloride, for at least 24 hours, before use.

6. Acetylene

This gas was purified by passage through:

1) a dry-ice/acetone trap,

2) concentrated sulphuric acid,

3) a tube filled with Drierite, and

4) activated alumina or soda lime.

See **Acetylene Compounds** by Thomas R. Rutledge, Reinhold Book Corporation, 1968 for more details concerning the uses of acetylene and derivatives.

7. Iron pentacarbonyl

This reagent was filtered through a layer of Celite™ before use to remove any solid impurities.

8. N-Bromosuccinimide

This reagent was purified by recrystallisation from water and has a white appearance when pure, mp 180-182 °C.

9. Dimethyl sulfate

Dimethyl sulfate was purchased from Kodak or Aldrich (Aldrich, 99+ %) and used without purification.

10. Allyl bromide

This reagent (Aldrich, 99%) was used without purification.

11. Ethyl vinyl ether

This reagent was fractionally distilled, b.p. 35.5 °C, and stored over Linde type 4A molecular sieves.

CHROMATOGRAPHY

Analytical qualitative thin-layer chromatography (TLC) was carried out using standard 5 x 20 cm silica gel G-F Redi-Plates™. The plates can be re-used for several months by "washing" with acetone/methanol.

Preparative thin-layer chromatography (PTLC) was carried out on 20 x 20 cm glass plates. The thickness of the layer of silica gel was about 1.7

mm using Merck Kieselgel 60 PF_{254} or ICN Nutritional Biochemicals silica gel G-F-DC. The composition of silica gel : water was usually around 600 g : 1400 mL and, after air drying for at least one day, the plates were activated at 130-140 ^{o}C for 4-6 h.

The solvent system for PTLC was usually chloroform or chloroform containing 10-20% acetone for the very polar compounds.

For TLC and PTLC, the products were detected by viewing under a UV light source and (or) exposing to iodine vapours.

The protected glycosides were purified by rapid (nitrogen pressure) column chromatography with chloroform/acetone followed by PTLC. Column chromatography was performed using Merck Kieselgel 60 (230 mesh ASTM) silica gel.

"Dry column" Flash Chromatography

This was performed essentially according to the procedure of L.M. Harwood, Aldrichimica Acta, 18 (1) 25, 1985. See also Aldrichimica Acta, 17 (1) 25, 1984 and **ibid.**, 18 (3) 83, 1985 and R.W. Hanson and N.G. Smith, Educ. in Chem., 45, March, 1986.

The solvents used for elution when using column/flash chromatography were usually toluene and toluene/chloroform (the percentage being varied by 5-10%). The tetracyclic dihydroxy compounds were usually eluted with chloroform/acetone (30-50%).

MELTING POINTS

Melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected.

ISOLATION OF PRODUCTS

The term 'work up' refers to the following procedure:

1) dilution with water (or concentration followed by dilution),
2) extraction with an organic solvent (chloroform or methylene chloride),
3) drying with anhydrous sodium sulphate or magnesium sulphate,
4) filtration by suction, and
5) concentration by evaporation at reduced pressure (water pump).

Until conditions were worked out for syntheses, all reactions were monitored by TLC and, in some cases, infrared spectroscopy.

ELEMENTAL ANALYSES

Elemental analyses were performed by Canadian Microanalytical Service Ltd., 1-609-4th Avenue, New Westminister, BC V3M 1S3.

MASS SPECTRA (MS)

These were recorded by Mr. Wayne Buchannon of the Department of

Chemistry, University of Manitoba, on either a **Finnigan Quadrupole Model 1015 mass spectrometer** or on a **VG-70-70 double focussing mass spectrometer.**

High resolution mass spectra were recorded by Mr. Wayne Buchannon of the Department of Chemistry, University of Manitoba on a **VG 70-70 double focussing mass spectrometer.**

NUCLEAR MAGNETIC RESONANCE (NMR)

^{1}H and ^{13}C NMR spectra were recorded on a **BRUKER 300 MHz** or **BRUKER WH-90 MHz** machine by Mr. Kirk Marat or Mr. Terry Woloweicz.

Unless otherwise stated the ^{1}H spectra were at 300.133 MHz and ^{13}C spectra were at 75.47 MHz.
Deuteriochloroform was used as a solvent unless otherwise stated and chemical shifts are quoted in parts per million (ppm) relative to, and downfield from, **tetramethylsilane.** Abbreviations used for ^{1}H NMR spectra are as follows:

s - singlet m - multiplet bs - broad singlet
d - doublet dd - doublet of doublets bd - broad doublet
t - triplet dt - doublet of triplets td - triplet of doublets

In cases of broad singlets the centre of the signal is quoted and for multiplets the range is given.

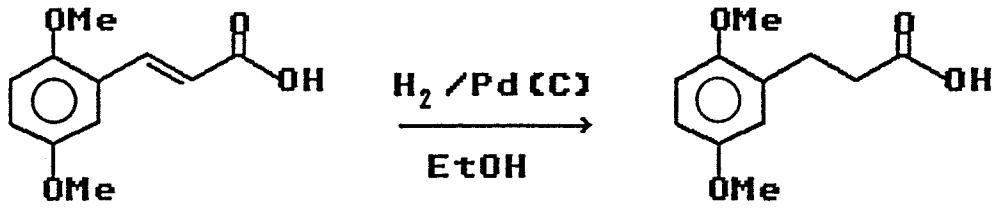
^{13}C NMR spectra were only done on some compounds as a tool for compound

identification and was mainly used to establish or confirm the number of carbons in the molecule. Therefore, unless an unambiguous assignment can be made, the assignments must be viewed as tenuous (in the absence of other techniques) and the calculated assignments were made with the aid of literature correlation tables (D. W. Brown, J. Chem. Ed., 62, 209 (1985)). No calculated values are given for those compounds where suitable correlation tables were unavailable.

INFRARED (IR) SPECTRA

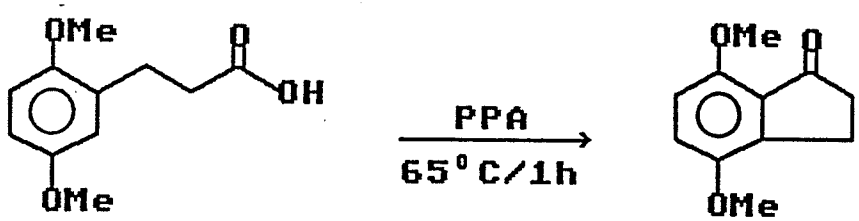
IR spectra were recorded on a **Perkin Elmer 710 IR spectrophotometer** using methylene chloride as a solvent and polystyrene film as a standard; absorbances are expressed as wave number in units of cm^{-1}.

SYNTHESES



1 2

The acid 1 (41.70 g) (Aldrich) was dissolved in ethanol (95%, 2.1 L) in a round bottom flask (5 L). Palladium (5% on carbon) (3.54 g) was added and the suspension was stirred in a hydrogen atmosphere until the uptake of hydrogen ceased. The solution was filtered and the ethanol evaporated at reduced pressure to give a light brown oil which was left to crystallise. This resulted in large off-white crystals (2) (42 g, 100%), mp 64-66 °C (lit (1) 66-67 °C (ethanol, 95%), lit (2) 66 °C, lit (3) 65-66 °C, ether/petroleum ether) which were sufficiently pure for the next step.



2 3

Compound 3 was prepared essentially by the method of Koo (4).

In a 3-neck flask (1 L) flushed with nitrogen was placed polyphosphoric acid (600 g), followed by the finely ground acid 2 (55 g). This mixture was heated (65 °C) in a temperature controlled oil bath and stirred mechanically for 1 h during which time the colour turned from yellow to dark red. The fluid was then poured into an ice/water mixture and allowed to stand for a couple of hours during which time a yellow solid mass separated. This mixture was extracted with chloroform, washed with aqueous sodium bicarbonate, water and brine. Evaporation and recrystallisation from tetrahydrofuran/diethyl ether gave 3 (40.8 g, 80%), mp 120-124 °C; lit (3) 124.5-125 °C, lit (2) 125-126 °C. However, the yield could be improved by chromatographing the mother liquor.

FORMULA: $C_{11}H_{12}O_3$ MW 192

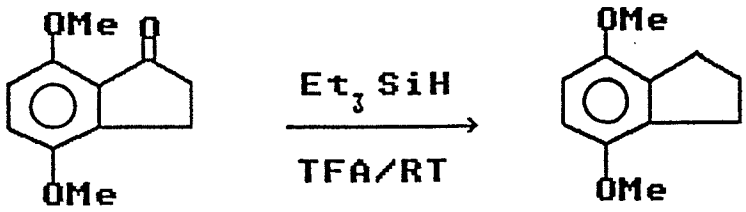
IR: 1720 (ArC=O), 1600 (AROMATIC)

MS: 192 ($M^{+\cdot}$), 177 ($M^{+\cdot}-CH_3$)

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.589-2.629	2H	m	$O{=}CCH_2$
2.907-2.946	2H	m	$ArCH_2$
3.802	3H	s	OCH_3
3.848	3H	s	OCH_3
6.679	1H	d	ArH
6.944	1H	d	ArH

J_{AB} (aromatic) = 8.7 Hz



3 4

Compound 4 was prepared according to the procedure of West et al. (5).

To ketone 3 (22.30 g) in trifluoroacetic acid (75 mL) was added triethylsilane (50 mL) dropwise over a period of 2 h. The solution was stirred at room temperature for 7 days during which time the colour changed from deep red to a clear orange. Chloroform was added followed by enough 2M sodium hydroxide to make the solution basic. Stirring was continued for 1 h (to hydrolyse the trialkylsilyl trifluoroacetate). The aqueous layer was separated and extracted several times with small portions of chloroform and the combined organic portions washed again with 2M sodium hydroxide. The solvent was removed under reduced pressure and cooling effected crystallisation. Recrystallisation from ethanol/water and chromatography of the mother liquor on alumina gave a quantitative yield of 4, mp 82–85 °C, lit (3) 85–85.5 °C.

FORMULA: $C_{11}H_{14}O_2$ MW 178

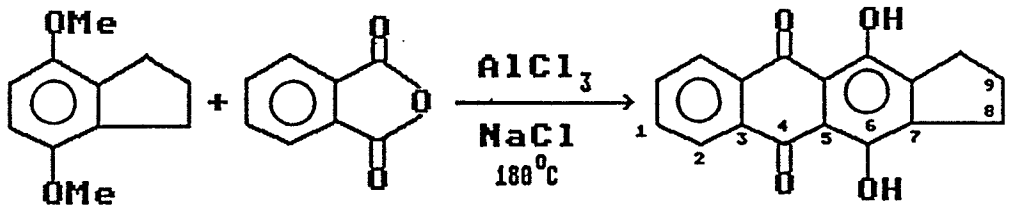
IR: 1600 (AROMATIC)

MS: 178 ($M^{+\cdot}$), 163 ($M^{+\cdot}-CH_3$)

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.100	2H	q	$ArCH_2CH_2$
2.908	4H	t	$ArCH_2$
3.809	6H	s	OCH_3
6.633	2H	s	ArH

J_{AX} = 7.5 Hz



4 5

Compound 5 was prepared according to the procedure of Arcamone et al. (6).

Phthalic anhydride (14 g), sodium chloride (30 g), sublimed aluminium chloride (75 g) and indane 4 (10 g) were all finely ground and then mixed together in a wide neck 500 mL flask. The flask was then immersed in an oil bath at a temperature of approximately 170 °C for 15 min., stirring being achieved with a glass rod. After cooling, saturated oxalic acid was added and the mixture allowed to stand for 12-24 h. Chloroform was added and the mixture filtered through a layer of Celite and the Celite layer washed thoroughly with chloroform. The organic layer was washed with aqueous sodium carbonate (10%), water, saturated

sodium chloride and evaporated to yield a red powder which was crystallised from methylene chloride/diethyl ether to give 5, mp 270-272 °C (14 g, 88%).

FORMULA: $C_{17}H_{12}O_4$ MW 280

CALCULATED: 280.0736

OBSERVED : 280.0725

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.214	2H	q	$ArCH_2CH_2$
3.042	4H	t	$ArCH_2$
7.784-7.814	2H	m	ArH
8.300-8.330	2H	m	ArH
13.129	2H	s	ArOH

J_{AX} = 7.6 Hz

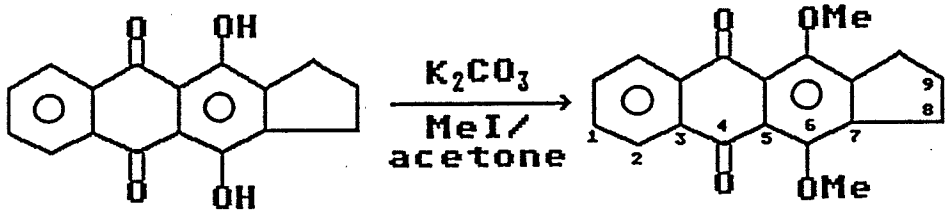
$J_{AB} = J_{A'B'}$ = 5.8 Hz

$JAB' = J_{A'B}$ = 3.3 Hz

NMR ^{13}C PROTON DECOUPLED 90.02 MHz

DELTA (ppm)		# OF CARBONS	CARBON(S)
(OBSERVED)	(CALCULATED)		
24.005	-	1	C_9
30.599	-	2	C_8
112.109	-	2	C_3
127.015	-	2	C_1
133.909	-	2	C_7
134.270	-	2	C_2

144.343	-	2	C_5
155.565	-	2	C_6
187.014	-	2	C_4



5 6

Into a 3-neck flask (1L), flushed with nitrogen, was placed potassium carbonate (46 g, 0.33 mmol), tetracyclic phenol 5 (6.0 g, 0.21 mmol), iodomethane (50 mL, 0.80 moles), and acetone (approximately 700 mL). The contents were stirred at reflux under nitrogen for approximately 2 days during which time the colour of the solution went from red to yellow. The solution was filtered and the carbonate washed with chloroform. The solvent was removed under reduced pressure, the solid taken up in chloroform, washed with water, and the solvent removed. Recrystallisation from ethanol (95%) gave 6 g (94%) of 6.

FORMULA: $C_{19}H_{16}O_4$ MW 308

CALCULATED: 308.1049

OBSERVED : 308.1063

IR: 1670 (QUINONE), 1590-1580 (AROMATIC)

NMR ^{1}H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.170	2H	q	$ArCH_2CH_2$
3.092	4H	t	$ArCH_2$
3.930	6H	s	OCH_3
7.770–7.726	2H	m	ArH
8.155–8.185	2H	m	ArH

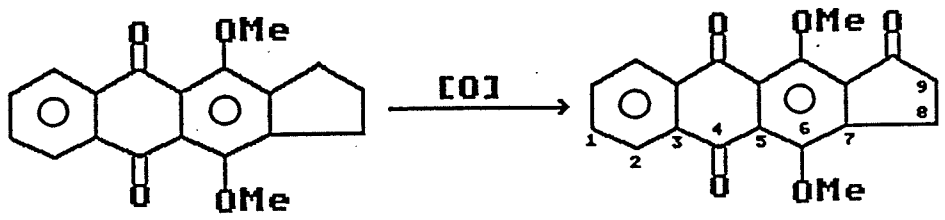
J_{AX} = 7.5 Hz

$J_{AB} = J_{A'B'}$ = 5.7 Hz

$JAB' = J_{A'B}$ = 3.3 Hz

NMR ^{13}C PROTON DECOUPLED 90.02 MHz

DELTA (ppm) (OBSERVED)	DELTA (ppm) (CALCULATED)	# OF CARBONS	CARBON(S)
24.585	–	1	C_9
30.908	–	2	C_8
61.003	–	2	OCH_3
126.358	–	2	C_1
126.504	–	2	C_3
133.454	–	2	C_2
134.364	–	2	C_7
147.857	–	2	C_5
153.695	–	2	C_6
183.366	–	2	C_4



6 7

Two methods were tried for the synthesis of 7.

Method 1. According to the method of Hanaya et al. (7)
Chromium trioxide (0.5 g, 5 mmol) was dissolved in acetic anhydride-acetic acid (1:2,v/v, 1.4 mL/2.8 mL) with cooling in an ice bath then diluted with methylene chloride (2.8 mL). The tetracyclic indane 6 (334 mg, 1.08 mmole) was dissolved in methylene chloride (2mL), and this solution was added dropwise to the oxidant. After addition, the mixture was stirred for 1.5 h, diluted with water, neutralised with sodium hydroxide (2M), and washed several times with sodium hydroxide (2M). Work-up yielded a golden-yellow solid and recrystallisation from methylene chloride/diethyl ether gave two batches (106 mg, 31%), one of the batches being contaminated with starting material, mp 190-192 °C (pure batch).

Method 2.

Chromium trioxide (2.5 g) in acetic anhydride (140 mL) was added dropwise, over two hours, to a solution of 6 (2 g, 6 mmol) in acetic anhydride (180 mL), the temperature of the solution being kept around 5 °C. Stirring was continued for another 3 h (between 5-15 °C). The solution was poured into water (3L) and extracted with chloroform. The organic portion was washed several times with sodium carbonate (2%). Work up gave a solid which was stirred with aqueous methanol (pH 2 (HCl), 24 h). Isolation yielded 1 g of 7,(49%), mp 192-194 °C.

FORMULA: $C_{19}H_{14}O_5$ MW 322

CALCULATED: 322.0842

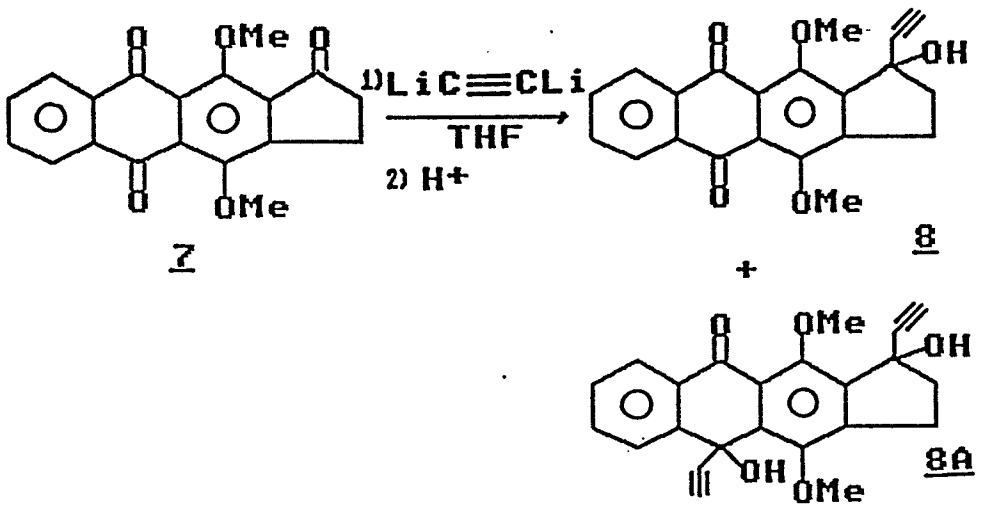
OBSERVED : 322.0845

IR: 1720 (ArC=O), 1675 (QUINONE), 1600,1580 (AROMATIC)

MS: 322 ($M^{+\cdot}$, 75%)

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.761-2.802	2H	m	$O{=}CCH_2$
3.206-3.247	2H	m	$ArCH_2$
4.020	3H	s	OCH_3
4.104	3H	s	OCH_3
7.744-7.778	2H	m	ArH
8.162-8.192	2H	m	ArH



One of the more successful methods of preparing 8 is described below.

tert-Butyl lithium (0.7 mL, 1.75 M, 2 eq.) in dry tetrahydrofuran (20 mL) was added dropwise to a solution of acetylene in dry tetrahydrofuran at -78° C. The solution became yellow and turned clear after approximately 10 min. After the addition of the base, the addition of acetylene was continued for approximately 1 h and the temperature was allowed to rise to 0 °C at which time the ketone 7 (193 mg, 0.6 mmol) was added in one portion. The resulting yellow solution soon turned dark brown. The solution was allowed to stir for 80 h, aqueous ammonium chloride was added, and the solution worked up. IR spectroscopy indicated the presence of 8. The product was usually hydrolysed immediately due to the unstable nature of the product. Also isolated from some trials was compound **8A**, mp 220 °C.

FORMULA: $C_{21}H_{16}O_5$ MW 348 (COMPOUND 8)

NMR ^1H 90 MHz

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.66	1H	s	-C≡CH

2.40-3.40	4H	m	$ArCH_2CH_2$
3.88	3H	s	OCH_3
3.89	1H	s	Ar-C-OH
4.10	3H	s	OCH_3
7.40-8.30	4H	m	ArH

FORMULA: $C_{23}H_{18}O_5$ MW 374 (COMPOUND **8A**)

CALCULATED: 374.1155

OBSERVED : 374.1160

FORMULA: $C_{23}H_{17}O_4$ MW 357 ($M^{+\cdot}$-OH)

CALCULATED: 357.1127

OBSERVED : 357.1121

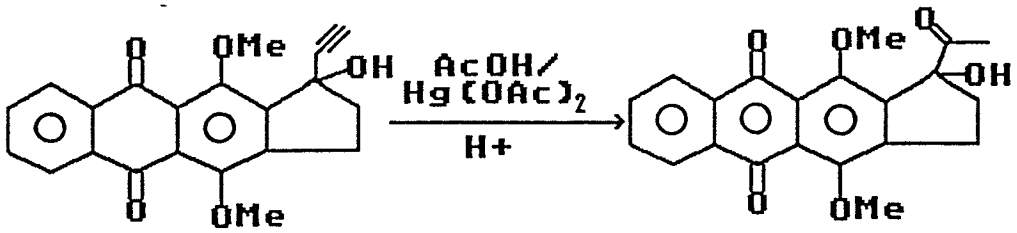
MS: 374 ($M^{+\cdot}$, 66%), 357 ($M^{+\cdot}$-17, 98%)

IR: 3550-3450 (2 x OH), 3300 (2 x -C≡CH), 1720 (ArC=O), 1670 (QUINONE), 1600, (AROMATIC)

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.472-2.544	1H	m	$ArCH_2CH_2$
2.573	1H	s	$-C\equiv CH(C_9)$
2.660	1H	s	$-C\equiv CH(C_5)$
2.700-2.785	1H	m	$ArCH_2CH_2$
3.094-3.281	1H	m	$ArCH_2$
3.254-3.352	1H	m	$ArCH_2$
3.695	1H	s	C_9OH
3.992	3H	s	OCH_3

4.150	3H	s	OCH_3
5.679	1H	s	C_5OH
7.50-7.56	1H	m	ArH
7.68-7.75	1H	m	ArH
8.04-8.07	1H	m	ArH
8.15-8.20	1H	m	ArH



8 9

This hydrolysis was achieved according to the procedure of Fraser and Raphael (8).

To crude 8 (51 mg) in acetic acid (90%, 10 mL) was added mercuric acetate (33 mg) and concentrated sulphuric acid (2.4 mL)*. The solution was stirred overnight at room temperature. Chromatography gave a yellow solid 9 (30 mg, 56%), which was recrystallised with methylene chloride/diethyl ether, mp 184-185 °C.

*The amount of sulphuric acid should be decreased as a reddish by-product, as evidenced from PTLC, suggested that one of the methyl ethers might have hydrolysed.

FORMULA: $C_{21}H_{18}O_6$ MW 366

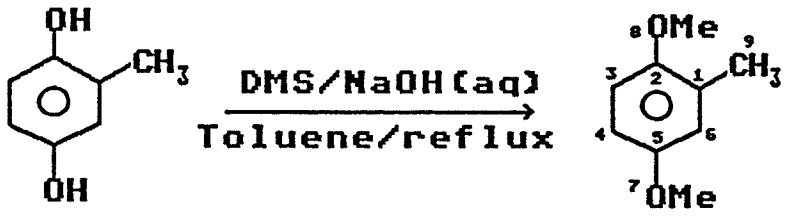
	C	H
CALCULATED:	68.84	4.95
FOUND :	68.73	4.86

IR: 3450 (3^{o}-OH), 1715 ($COCH_3$), 1675 (QUINONE), 1595,1580 (AROMATIC)

MS: 366 ($M^{+\cdot}$, 1%), 323 ($M^{+\cdot}-COCH_3$, 100%)

NMR ^{1}H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.208	3H	s	$O{=}CCH_3$
2.166-2.303	1H	m	$ArCH_2CH_2$
2.413-2.552	1H	m	$ArCH_2CH_2$
3.186-3.284	1H	m	$ArCH_2$
3.382-3.494	1H	m	$ArCH_2$
3.878	3H	s	OCH_3
4.400	3H	s	OCH_3
7.731-7.761	2H	m	ArH
8.15-8.25	2H	m	ArH



10 11

2-Methyl-1,4-dihydroxybenzene 10 (124 g, 1 mol) was stirred mechanically in a 3-neck flask (3L) containing toluene (500 mL) equipped with two

dropping funnels and a nitrogen outlet. Sodium hydroxide (120 g) in water (300 mL) was added dropwise to the cooled suspension and the non-homogenous solution soon appeared green (about 10 min). When the precipitate began to form, dimethyl sulphate (200 mL) was added in small portions over a 15 min period. Dimethyl sulphate (100 mL) and aqueous sodium hydroxide addition was continued dropwise. After the addition of the sodium hydroxide, dimethyl sulphate (200 mL) was added in small portions to minimise hydrolysis by the base. The ice bath was removed and the mixture refluxed which resulted in the dissolution of the yellowish white precipitate. The pH was adjusted (basic) by successively adding sodium hydroxide (60 g) in water (125 mL) and then sodium hydroxide (48 g) in water (75 mL). The mixture was refluxed for 3 h at the end of which the organic layer was clear. The mixture was then cooled, the organic layer separated and the aqueous layer extracted with diethyl ether. Work-up, concentration and vacuum distillation yielded 139 g of the product 11 as a yellow oil*
(92%) ; boiling point 76 ^{o}C/1.5 mm; lit (10) 56-58 ^{o}C/0.8 mm ; lit (9) 20-22 ^{o}C/76 mm**.

* For two different preparations of this compound see refs. 9 and 10.

** Most probably an error; may have intended the value to be 220-222 ^{o}C/760 mm as this is close to the value we obtained.

FORMULA: $C_9H_{12}O_2$ MW 152

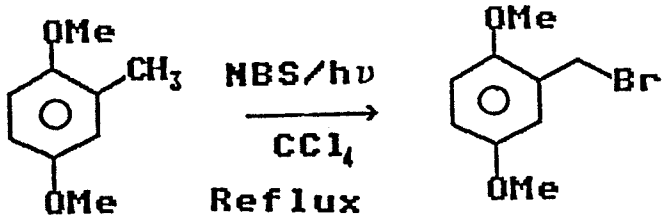
NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.28	3H	s	CH_3
3.79	3H	s	OCH_3

3.83	3H	s	OCH_3
6.60-6.90	3H	m	ArH

NMR ^{13}C PROTON DECOUPLED

DELTA (ppm)		# OF CARBONS	CARBON(S)
(OBSERVED)	(CALCULATED)		
16.272	19.8	1	CH_3
55.412	-	1	OCH_3
55.657	-	1	OCH_3
110.757	112..2	1	C_4
110.882	115.1	1	C_3
117.099	115.9	1	C_6
127.741	124.4	1	C_1
152.139	152.2	1	C_5
153.525	153.0	1	C_2



11 12

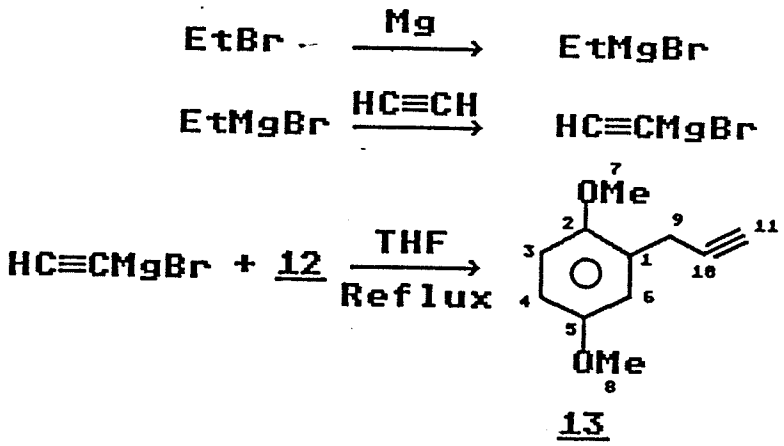
Compound 11 (50 g, 329 mmol) in carbon tetrachloride (750 mL) was heated to reflux in a 3-neck flask (2L) equipped with a reflux condenser, a nitrogen inlet (via a dispersion tube) and outlet, and a magnetic stirrer. N-Bromosuccinimide (65 g) was added and the solution

irradiated with two Hanovia UV quartz lamps. The solution changed from clear to yellowish to clear again with the formation of succinimide. The succinimide was filtered. The filtrate was concentrated and allowed to cool. The benzyl bromide derivative 12 soon crystallised. Filtration and washing with petroleum ether gave white crystals (62 g, 82%). Recrystallisation was achieved with petroleum ether/diethyl ether or better from methylene chloride/petroleum ether, mp 71-72 °C.

FORMULA: $C_9H_{11}BrO_2$ MW 230.9

NMR ^1H (90.02 MHz)

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
3.79	3H	s	OCH_3
3.85	3H	s	OCH_3
4.55	2H	s	CH_2Br
6.80-7.00	3H	m	ArH



13

The Grignard reagent was made as follows:

Ethylmagnesium bromide was made from ethyl bromide (65 mL, 95 g, 871 mmol) and magnesium (21 g, 875 g-atom) in dry tetrahydrofuran (215 mL). After addition of the bromide, the reaction mixture was refluxed for 0.5

h to produce the Grignard reagent.

Ethynylmagnesium bromide (11)

To tetrahydrofuran (570 mL) saturated with acetylene in a 3-neck flask (3L) equipped with a reflux condenser was added the warm ethylmagnesium bromide* solution over a period of about 3 h. The dropping funnel was kept warm with the use of a heat gun to prevent the crystallisation of the Grignard reagent. After about 0.5 h, the solution became slightly non-homogeneous with a cloudy appearance. The benzyl bromide derivative 12 (10 g, 43 mmol) in tetrahydrofuran (40 mL) was added and the mixture refluxed (75 ^{o}C). After 1 h a white precipitate appeared (most probably the bis bromobis-magnesium acetylide reagent) and the reflux was continued for approximately 5 d. The solution** was poured into ice/ammonium chloride (aqueous), the organic layer was separated and concentrated by reduced pressure. The aqueous layer was acidified and extracted with chloroform. The combined organic layers were worked up and concentrated to give a yellow oil displaying the same spectral properties as the compound when made on small scales***.

* It is essential to keep the Grignard solution warm (especially if it is concentrated (11)) by using a heat gun to prevent crystallisation.

** bis bromobis-magnesium acetylide is **pyrophoric** and therefore a positive nitrogen pressure should be used when pouring the solution onto ice/ammonium chloride (aqueous).

*** On a small scale, after the requisite reaction time, aqueous ammonium chloride was added followed by 2M sodium hydroxide and the

solution refluxed for 1 h. IR spectroscopy and thin layer chromatographic analysis showed that only about 5% of the original bromide (as the alcohol) was present. Hydrolysing the unreacted bromide, 12, also facilitated purification by chromatography.

FORMULA: $C_{11}H_{12}O_2$ MW 176

IR: 3300 (-C≡CH), 1610 (AROMATIC),

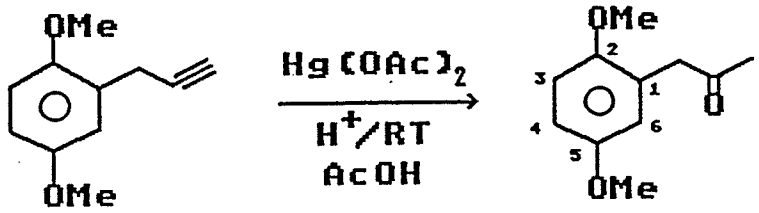
NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.15	1H	t	HC≡C
3.565	2H	d	$CH_2C{\equiv}C$
3.789	3H	s	OCH_3
3.795	3H	s	OCH_3
6.756-6.764	3H	m	ArH

NMR ^{13}C PROTON DECOUPLED

DELTA (ppm) (OBSERVED)	DELTA (ppm) (CALCULATED)	# OF CARBONS	CARBON(S)
19.30	21.7	1	CH_2
55.71	-	1	OCH_3
55.92	-	1	OCH_3
70.46	66.2	1	C≡CH
81.75	78.8	1	C≡CH
110.98	111.2	1	C_3
112.20	112.2	1	C_4
115.33	115.9	1	C_6
125.67	124.4	1	C_1

150.98	152.2	1	C_7
153.66	153.0	1	C_2



13 14

According to the procedure of Fraser and Raphael (8).

To a solution of 3-(1,4-dimethoxy-phenyl)-propyne 13 (10 g, crude) in acetic acid (80%, 453 mL) and concentrated sulphuric acid (1 mL) was added mercuric acetate (2.4 g). The solution was stirred for 17 h at room temperature. The solution was diluted with water and the pH adjusted to approximately 6. Work up yielded the ketone 14 which was purified by column chromatography.

FORMULA: $C_{11}H_{14}O_3$ MW 194

CALCULATED: 194.0943

OBSERVED : 194.0933

IR: 1710 (ArC=O), 1600, (AROMATIC)

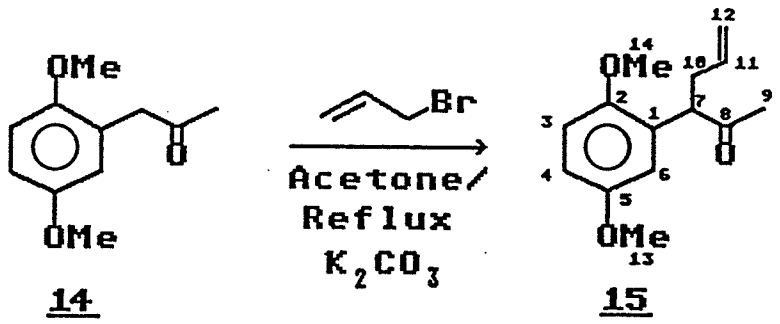
NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.128	3H	s	$CH_3C=O$
3.635	2H	s	$CH_2C=O$

3.750	3H	s	OCH_3
3.759	3H	s	OCH_3
6.704-6.790	3H	m	ArH

NMR ^{13}C PROTON DECOUPLED

DELTA (ppm)		# OF CARBONS	CARBON(S)
(OBSERVED)	(CALCULATED)		
29.11	23.2	1	CH_3
45.50	42.8	1	CH_2
55.59	-	1	OCH_3
55.80	-	1	OCH_3
111.37	112.2	1	C_4
112.66	115.1	1	C_3
117.18	115.9	1	C_6
124.55	124.4	1	C_1
151.55	152.2	1	C_5
153.46	153.0	1	C_2
206.67	206.0	1	O=C



14 15

Purified ketone 14 (10 g, 51 mmol) was dissolved in reagent grade

acetone (700 mL). Powdered potassium carbonate (60 g) and distilled allyl bromide (80 mL, 0.92 mol) were added. The mixture was refluxed for 2 d. TLC indicated unreacted ketone (approximately 20%). The product was isolated by column chromatography.

FORMULA: $C_{14}H_{18}O_3$ MW 234

CALCULATED: 234.1256

OBSERVED : 234.1254

FORMULA: $C_{12}H_{15}O_2$ MW 191 ($M^{+\cdot}-C_2H_3O$)

CALCULATED: 191.1072

OBSERVED : 191.1088

MS: 243 ($M^{+\cdot}$, 55%), 191 ($M^{+\cdot}-COCH_3$, 100%)

IR: 1710 ($COCH_3$), 1645 (CH_2=CH-), 1610,1590 (AROMATIC)

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.010	3H	s	CH_3C=O
2.30-2.45	1H	m	CH_2CH
2.70-2.83	1H	m	CH_2CH
3.736	3H	s	OCH_3
3.788	3H	s	OCH_3
4.087	1H	t	CH_2CH
4.86-5.20	2H	m	CH_2=CH
5.60-5.76	1H	m	CH_2=CH
6.64-6.84	3H	m	ArH

FORMULA: $C_{20}H_{22}N_4O_4$ MW 414 2,4-DNP DERIVATIVE

CALCULATED: 414.1540

OBSERVED : 414.1501

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
1.932	3H	s	$CH_3C=N$
2.45-2.65	1H	m	CH_2CH
2.85-3.00	1H	m	CH_2CH
3.743	3H	s	OCH_3
3.822	3H	s	OCH_3
4.247	1H	t	$CHCH_2$
4.90-5.08	2H	m	$CH_2=CH$
5.72-5.88	1H	m	$CH_2=CH$
6.66-6.88	3H	m	ArH
8.00-8.10	1H	d	$ArH-NO_2$
8.30-8.40	1H	m	$ArH-NO_2$
9.144	1H	d	$ArH-NO_2$
11.077	1H	s	NH

FORMULA: $C_{15}H_{21}N_3O_3$ MW 291 SEMICARBAZONE DERIVATIVE

CALCULATED: 291.1583

OBSERVED : 291.1587

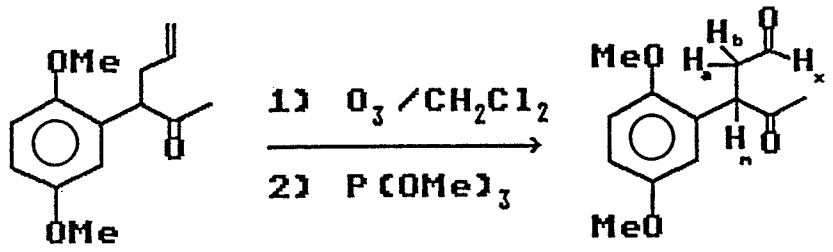
NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
1.691	3H	s	$CH_3C=N$
2.3.-2.20	1H	m	CH_2CH

2.60-2.80	1H	m	CH_2CH
3.736	3H	s	OCH_3
3.781	3H	s	OCH_3
4.055	1H	t	$CHCH_2$
4.83-5.01	2H	m	$CH_2=CH$
5.63-5.81	1H	m	$CH_2=CH$
6.60-6.83	3H	m	ArH
8.166	1H	s	O=CNH

NMR ^{13}C PROTON DECOUPLED

DELTA (ppm) (OBSERVED)	(CALCULATED)	# OF CARBONS	CARBON(S)
28.89	24.5	1	$O=CCH_3$
34.76	29.1	1	CH_2CH
51.89	56.1	1	CH_2CH
55.60	-	1	OCH_3
55.98	-	1	OCH_3
111.57	115.1	1	C_3
111.78	112.2	1	C_4
114.85	115.9	1	C_6
116.09	116.1	1	$CH_2=CH$
128.27	135.4	1	C_1
136.13	137.6	1	$CH_2=CH$
151.22	152.0	1	C_5
153.74	153.0	1	C_2
207.90	209.6	1	C=O



15 16

A solution of the alkene (3 g) in methylene chloride (135 mL) was cooled to -78 °C and ozone, via a gas dispersion tube was passed through the mixture for about 2 h. The progress of the reaction was monitored by IR spectroscopy and thin layer chromatography. Trimethyl phosphite (3 mL) was added and the solution refluxed for 24 h. The crude IR spectrum showed the absence of the alkene stretching and the presence of the characteristic CH of the aldehyde group. The crude aldehyde 16 was purified by column chromatography, under nitrogen, and used immediately.

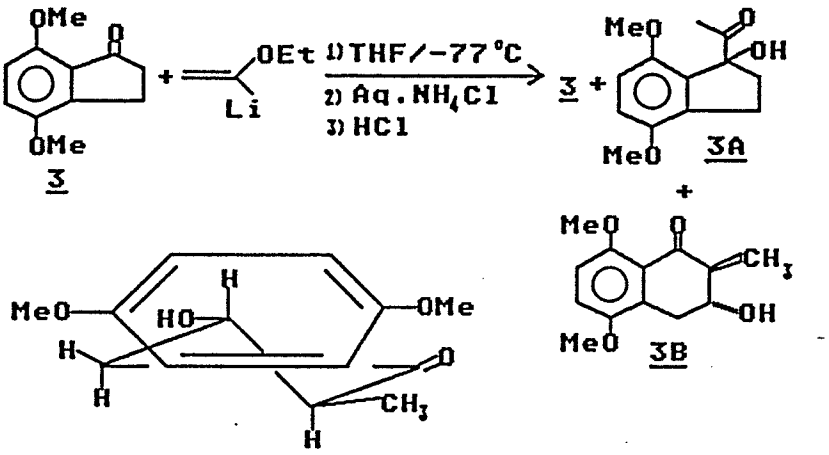
FORMULA: $C_{13}H_{16}O_4$ MW 236

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.063	3H	s	$O{=}CCH_3$
2.48-2.60	1H	dq	CH_2CH
3.28-3.44	1H	dq	CH_2CH
3.748	3H	s	OCH_3
3.795	3H	s	OCH_3
4.48-4.56	1H	dd	CH_2CH
6.6-6.9	3H	m	ArH

9.75	1H	s	O=CH

J_{AM} = 9.1 Hz; $J_{A'M}$ = 4.6 Hz; $J_{AA'}$ = 18 Hz; $J_{A'X} \leq$ 1 Hz & J_{AX} = 0.5 Hz



Compound **3B** was isolated as a byproduct in an attempt to prepare **3A** from **3** essentially according to Baldwin *et al.* (16). It was characterised as discussed in the **Results and Discussion** section.

A 3-neck flask, equipped with a dropping funnel, a nitrogen inlet and outlet, and a magnetic stirrer, was flame-dried under a stream of nitrogen. The flask was cooled to -78 °C (acetone/dry-ice) and charged with ethyl vinyl ether (4 mL) and tetrahydrofuran (20 mL). *tert*-Butyl lithium (6 mL, 1.75 M/pentane) was added dropwise and the solution stirred for 40 min. The contents were allowed to warm up to 0 °C and the yellow precipitate dissolved to produce a clear solution. The solution was then re-cooled to -78 °C and the ketone, **3** (1 g), in tetrahydrofuran (20 mL) was added. The solution was stirred at that temperature for 1 h, allowed to warm up to 0 °C, and stirred at that temperature for 30 min. The product was quenched with ammonium chloride (20%, 80 mL) and worked up. The product was then dissolved in aqueous methanolic hydrochloric acid (0.02 M) and stirred for 1 h at room

temperature. Work up and evaporation gave a product which mainly consisted of starting material and small amounts of 3A and 3B*. A small amount of the product was purified by PTLC to give 3B, mp 128-130 ^{o}C (methylene chloride/petroleum ether).

* No attempt was made to quantify the reaction products.

FORMULA: $C_{13}H_{16}O_4$ MW 236 (**3B**)

CALCULATED: 236.1049

OBSERVED : 236.1054

FORMULA: $C_{11}H_{12}O_3$ MW 192 ($M^{+\cdot}-C_2H_4O$)

CALCULATED: 192.0777

OBSERVED : 192.0780

IR 3460 (2^{o}-OH), 1710 (ArC=O), 1610 (AROMATIC)

MS 236 ($M^{+\cdot}$, 98%), 218 ($M^{+\cdot}-18$, 17%), 203 ($M^{+\cdot}-18-15$, 45%), 192 ($M^{+\cdot}-44$, 100%), 177 ($M^{+\cdot}-44-15$, 56%)

NMR ^{1}H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
1.291	3H	d	$CHCH_3$
2.550-2.636	2H	m	$ArCH_2$ & $ArCH_2CH$-OH
3.131-3.224	1H	dd	$ArCH_2$
3.852	3H	s	OCH_3
3.900	3H	s	OCH_3
3.900-4.000	1H	m	$CHCH_3$

4.59	1H	s	CH-OH
6.744	2H	d	ArH
7.015	2H	d	ArH

J_{gem} = 18.8 Hz; $J_{A'B} = J_{AB'}$ = 8.8 Hz

NMR ^{13}C PROTON DECOUPLED

DELTA (ppm) (OBSERVED)	(CALCULATED)	# OF CARBONS	CARBON(S)
21.51		1	CH_3CH
26.25		1	$ArCH_2$
53.30		1	CH_3CH
55.84		1	OCH_3
55.96		1	OCH_3
69.17		1	CH-OH
109.71		1	ArCH
117.38		1	ArCH
125.55		1	ArC
144.27		1	ArC
150.21		1	Ar-C-OMe
151.90		1	Ar-C-OMe
208.05		1	ArCO

FORMULA: $C_{13}H_{16}O_3$ MW 236 (3A)

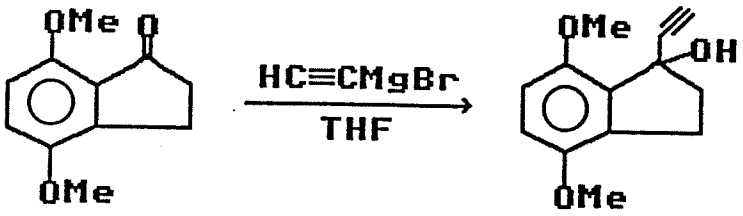
IR 3460 (3^o-OH), 1710 (CH_3CO), 1610 (AROMATIC)

MS 236 ($M^{+\cdot}$), 193 ($M^{+\cdot}$-43, 100%)

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.096	3H	s	$COCH_3$
2.119-2.209	1H	m	$ArCH_2CH_2$
2.416-2.514	1H	m	$ArCH_2CH_2$
2.917-3.018	1H	m	$ArCH_2$
3.142-3.3.196	1H	m	$ArCH_2$
3.717	3H	s	OCH_3
3.805	3H	s	OCH_3
4.379	1H	s	3^o-OH'
6.62-6.68	1H	d	ArH
6.73-6.78	1H	d	ArH

$J_{A'B} = J_{AB'} = 7.5$ Hz



3 17

Ethynylmagnesium bromide was prepared as described for the preparation of 13 (11).

Ethynylmagnesium bromide (625 mmol) in tetrahydrofuran (350 mL) (prepared from ethyl bromide (50 mL) and magnesium (15 g)) was added to

tetrahydrofuran (900 mL) saturated with acetylene over a period of 2-3 h. The introduction of acetylene (via a gas dispersion tube) was continued, after the addition of the Grignard reagent, for a further 1 h. Ketone 3 (30 g, 156 mmol) was then added in one portion and the addition of acetylene continued for 15 min. The mixture was allowed to stir at room temperature for 1 to 1.5 h (monitoring done by IR spectroscopy) after which it was poured onto ice/ammonium chloride (saturated) and worked up to produce a yellow oil which was hydrolysed immediately to produce the stable 1-acetoxyl-1-acetyl-4,7-dimethoxyindane 19. However, repeated purification of a small sample,by thin layer chromatography followed by vaccum drying, yielded an analytical sample of 17, mp 75-77 °C.

FORMULA: $C_{13}H_{14}O_3$ MW 218

CALCULATED: 218.0943

OBSERVED : 218.0944

IR: 3560 (OH), 3300 (-C≡CH), 1610 (AROMATIC)

MS: 218 ($M^{+\cdot}$), 203 ($M^{+\cdot}-CH_3$), 201 ($M^{+\cdot}-OH$), 185 ($M^{+\cdot}-H_2O-CH_3$)

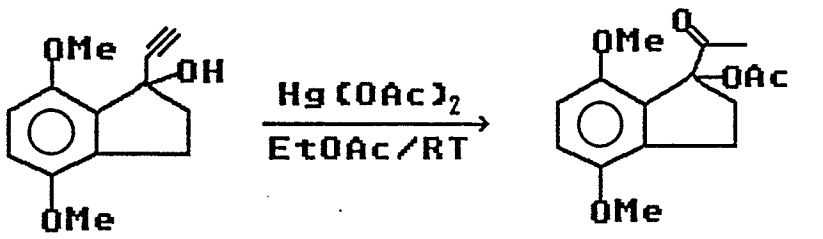
NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.324-2.425	1H	td	$ArCH_2CH_2$
2.592	1H	s	C=CH
2.6576-2.7346	1H	m	$ArCH_2CH_2$
2.811-2.919	1H	m	$ArCH_2$
2.950-3.043	1H	m	$ArCH_2$
3.736	1H	s	Ar-C-OH
3.781	3H	s	OCH_3

3.871	3H	s	OCH_3
6.700	1H	s	ArH
6.703	1H	s	ArH

NMR ^{13}C PROTON DECOUPLED

DELTA (ppm)		# OF CARBONS	CARBON(S)
(OBSERVED)	(CALCULATED)		
26.50	-	1	$ArCH_2$
42.40	-	1	$ArCH_2CH_2$
55.67	-	1	OCH_3
55.83	-	1	OCH_3
72.26	73.8	1	HC≡C-
76.06	-	1	C≡C-C-OH
86.07	83.0	1	C≡CH
109.68	112.2	1	C_7
110.92	115.0	1	C_6
132.13	123.8	1	C_9
133.71	132.2	1	C_4
149.64	145.7	1	C_5
150.28	153.4	1	C_8



17 19 R = OAc

This transformation was achieved as outlined by Kagan et al. (12).

The acetylenic alcohol 17 was dissolved in ethyl acetate (1.5 L) and mercuric acetate (100 g, 313 mmol) was added. The suspension was stirred at room temperature for 48 h (solution became homogeneous) then hydrogen sulphide was passed through the solution until precipitation was complete. The solution was filtered through Celite with a thin layer of silica gel and the Celite layer washed thoroughly with warm ethyl acetate. Removal of the solvent produced an oil which readily crystallised. Recrystallisation could be achieved from methylene chloride/petroleum ether, methylene chloride/diethyl ether or hexane/diethyl ether. The yield of 19 (R=OAc) was 26 g (60% based on indanone 3), mp 98-100 °C.

FORMULA: $C_{15}H_{18}O_5$ MW 278

CALCULATED: 278.1154

OBSERVED : 278.1159

	C	H
CALCULATED:	64.72	6.52

FOUND : 64.80 6.57

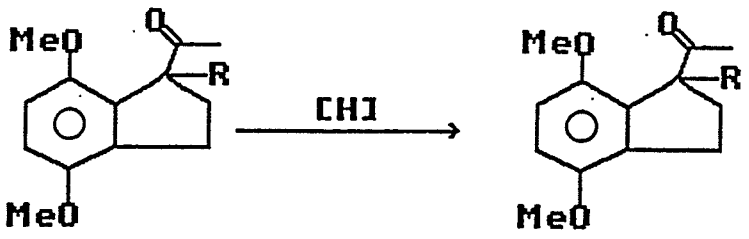
IR: 1730 ($-O-COCH_3$), 1715 ($COCH_3$), 1605 (AROMATIC)

MS: 278 ($M^{+\cdot}$), 235 ($M^{+\cdot}-COCH_3$), 192 ($M^{+\cdot}-2 \times COCH_3$)

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.137	3H	s	$O{=}CCH_3$
2.254	3H	s	O_2CCH_3
2.313-2.467	1H	m	$ArCH_2CH$
2.92-3.10	3H	m	$ArCH_2CH$ & $ArCH_2$
3.768	3H	s	OCH_3
3.785	3H	s	OCH_3
6.667	1H	d	ArH
6.759	1H	d	ArH

J_{AB} (AROMATIC) = 8.8 Hz

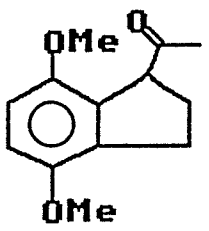


19 R = OAc **19** R = H

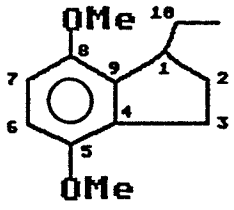
Three methods were used to prepare compound 19 (R=H); the third one was the most successful and preferred one.

Method 1: CATALYTIC HYDROGENOLYSIS.

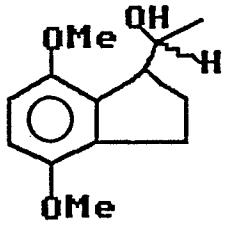
Acetate 19 (R=OAc) (200 mg) was dissolved in ethanol (80 mL) and concentrated hydrochloric acid (a few drops) and 10% palladium on carbon (200 mg) were added. The mixture was hydrogenated for 2 h and IR spectroscopy indicated that the reduction was incomplete. More catalyst (200 mg) was added and the mixture hydrogenated for a further 2 h. An IR spectrum at this point indicated that the ester carbonyl was still visible and a hydroxyl stretching vibration had appeared. Some more catalyst was added and the mixture hydrogenated for a further 6 h. Thin layer chromatography indicated three spots and isolation by PTLC produced pure compounds which were assigned by ^{1}H and ^{13} NMR to be the following:



19



19A



19B

FORMULA: $C_{13}H_{18}O_2$ MW 206 (19 A)

IR: 1605 (AROMATIC)

NMR ^{1}H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
0.925	3H	t	CH_3CH_2
1.36-1.52	1H	m	CH_3CH_2

1.78–1.96	2H	m	CH_3CH_2 & $ArCH_2CH_2$
2.10–2.26	1H	m	$ArCH_2CH_2$
2.74–2.96	2H	m	$ArCH_2$
3.20–3.32	1H	m	CH_3CH_2CH
3.792	3H	s	OCH_3
3.802	3H	s	OCH_3
6.635	2H	s	ArH

NMR ^{13}C PROTON DECOUPLED

DELTA (ppm)		# OF CARBONS	CARBON(S)
(OBSERVED)	(CALCULATED)		
11.97	11.0	1	CH_3CH_2
26.42	29.6	1	$ArCH_2CH_2$
28.33	30.7	1	$ArCH_2$
29.83	32.1	1	CH_2CH_3
45.03	41.8	1	$ArCH–CH_2CH_3$
55.50	–	1	OCH_3
55.55	–	1	OCH_3
108.57	111.4	1	C_7
108.77	111.6	1	C_6
133.32	129.0	1	C_4
136.97	135.0	1	C_9
150.21	150.3	1	C_8
150.74	151.9	1	C_5

FORMULA: $C_{13}H_{18}O_3$ MW 232 (19 B) :MIXTURE OF DIASTEREOISOMERS

NMR ^1H

IR: 3460 (OH), 1600 (AROMATIC)

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
1.051	3H	d	CH_3(E OR T)
1.204	3H	d	CH_3(E OR T)
1.85-2.00	2H	m	$ArCH_2CH_2$(E/T)
2.10-2.30	2H	m	$ArCH_2CH_2$(E/T)
2.70-2.91	4H	m	$ArCH_2$(E/T)
3.28-3.38	1H	m	CHOH-CH(E OR T)
3.50-3.62	1H	m	CHOH-CH(E OR T)
3.788	3H	s	OCH_3
3.789	3H	s	OCH_3
3.815	3H	s	OCH_3
3.818	3H	s	OCH_3
3.82-3.96	1H	m	CHOH-CH(E OR T)
4.10-4.20	1H	m	CHOH-CH(E OR T)
6.66	4H	s	ArH(E/T)

E = erythreo; T = threo.

Method 2 : ZINC/ACETIC ACID/ACETIC ANHYDRIDE REDUCTION.

Crude acetate 19 (R=OAc) (14 g) was dissolved in acetic acid (425 mL) and Ac_2O (270 mL) and zinc (65 g) was added. The mixture was refluxed (130 °C) for 24 h. The solution was filtered through a Celite layer and concentrated to small volume. Work up and column chromatography gave

the desired ketone 19 (30–40 %) together with a large amount of polymeric (dimeric?) unidentified material.

Method 3: N-TRIBUTYLTIN HYDRIDE/IRON PENTACARBONYL REDUCTION (13)

Acetate 19 (R=OAc) (8g, 29 mmols) was added to o-xylene (400 mL), iron pentacarbonyl (95 mL, 142 g, 723 mmol) and n-tributyltin hydride (30 mL, 33 g, 112 mmol). The mixture was heated at 123–125 °C for 72 h The colour of the solution changes from yellow to dark brown. Excess iron pentacarbonyl was destroyed, **carefully**, by adding cupric chloride in acetone until the fizzing or carbon monoxide evolution ceased. The solution was then acidified with dilute hydrochloric acid and worked up. Column chromatography gave 4.7 g (74%) of the ketone 19, mp 56-58 °C.

FORMULA: $C_{13}H_{16}O_3$ MW 220 (19)

	C	H
CALCULATED:	70.88	7.32
FOUND :	71.01	7.20

IR: 1705 ($COCH_3$), 1610 (AROMATIC)

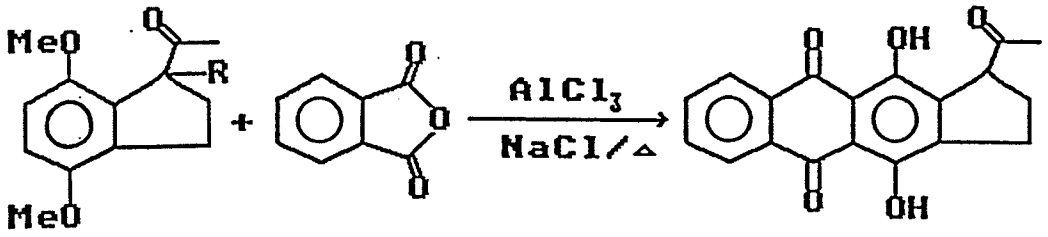
MS: 220 ($M^{+\cdot}$), 177 ($M^{+\cdot}-COCH_3$)

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.144	3H	s	$O{=}CCH_3$
2.167-2.274	1H	m	$O{=}C{-}CH{-}CH_2$
2.296-2.369	1H	m	$O{=}C{-}CH{-}CH_2$
2.835-2.937	1H	m	$ArCH_2$
2.971-3.08	1H	m	$ArCH_2$

3.754	3H	s	OCH_3
3.788	3H	s	OCH_3
4.098	1H	dd	$O{=}C{-}CHCH_2$
6.618-6.647	1H	d	ArH
6.671-6.700	1H	d	ArH

J_{AX} = 9 HZ & 5.4 Hz; J_{AB} (AROMATIC) = 8.7 Hz



19 R = H

20

This acylation was done with slight modifications according to the procedure given in reference 6.

Phthalic anhydride (7 g, 44 mmol) and sodium chloride (11 g) were ground separately and, together with aluminium chloride (47 g), were mixed thoroughly. This mixture was added to a wide neck 500 mL round bottom flask and the acetylindane 19 (4.7 g, 21.4 mmol) was added. The compounds were mixed thoroughly for 1 minute then immersed in an oil bath at 185-190 ^{o}C for 4.5-5 min., while stirring with a glass rod. A deep red-purple melt appeared within 2-3 min. This was indicative of some reaction. The melt was allowed to cool and saturated oxalic acid solution (100-200 mL) was added carefully as the reaction is **very exothermic.** Chloroform (100 mL) was added and the solution allowed to

stir overnight at room temperature. The solution was filtered through a layer of Celite. The organic solution was then washed throughly (until the organic layer was fairly orange) and the combined organic layers were washed twice with water, then with saturated sodium bicarbonate diluted to twice its volume until the aqueous layer was almost colourless, followed with water until neutral. The organic layer was then dried with **sodium sulphate** (**magnesium sulphate**, should be avoided as the product will be lost due to complexing of the Mg^{2+} ion with the phenol). Evaporation gave 5 g of crude material. The purified (recrystallisation, methylene chloride/diethyl ether) product was usually obtained in 40-50% yield. An analytical sample had a m.p., of 185-190 ^{o}C (methylene chloride/diethyl ether).

FORMULA: $C_{19}H_{14}O_5$ MW 322

CALCULATED: 322.0841

OBSERVED : 322.0841

	C	H
CALCULATED:	70.78	4.38
FOUND :	70.81	4.42

IR: 3500-2700 (CHELATED OH), 1720 ($-COCH_3$), 1625 (CHELATED QUINONE), 1595 (AROMATIC)

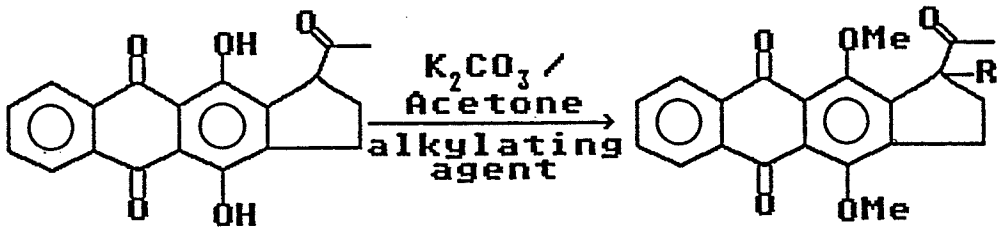
MS: 322 ($M^{+\cdot}$, 40%), 279 ($M^{+\cdot}-COCH_3$, 10%)

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.360	3H	s	$O{=}CCH_3$
2.257-2.305	2H	m	$O{=}C-CH-CH_2$
3.026-3.248	2H	m	$ArCH_2$

4.356-4.402	1H	dd	O=C-CHCH$_2$
7.75-7.90	2H	m	ArH
8.30-8.40	2H	m	ArH
13.052	1H	s	ArOH
13.156	1H	s	ArOH

J_{AX} = 4.8 Hz & 9.1 Hz



20

21 R = H
22 R = Me
23 R = OH

The preparation of 21* was achieved according to the procedure of Evans and Greenwald (14).

The tetracyclic phenol 20 (5 g, 16 mmol), dimethyl sulphate (17 mL, 23 g, 179 mmol) and potassium carbonate (24 g, 174 mmol) were refluxed in acetone (300 mL) for 24 h under a nitrogen filled balloon. The solution was filtered to remove the base and then evaporated to dryness. The residue was dissolved in chloroform, washed with water, and dried. Evaporation and recrystallisation (methylene chloride/diethyl ether) gave 21 (4.3 g, 79%), m.p., 135-137 °C. In addition, a small amount of 23 was obtained undoubtedly arising from oxidation with molecular oxygen.

* If iodomethane is used instead of dimethyl sulphate, 22 is obtained

almost exclusively.

FORMULA: $C_{21}H_{18}O_5$ MW 350 (21)

	C	H
CALCULATED:	71.99	5.18
FOUND :	71.82	5.11

IR: 1715 ($-COCH_3$), 1675 (QUINONE), 1600-1585 (AROMATIC)

MS: 350 ($M^{+\cdot}$, 90%), 307 ($M^{+\cdot}-COCH_3$, 100%)

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.300	3H	s	$O{=}CCH_3$
2.254-2.506	2H	m	$O{=}C{-}CH{-}CH_2$
3.052-3.293	2H	m	$ArCH_2$
3.865	3H	s	OCH_3
3.943	3H	s	OCH_3
4.326-4.374	1H	dd	$O{=}C{-}CHCH_2$
7.715-7.745	2H	m	ArH
8.162-8.193	2H	m	ArH

J_{AX} = 5.7 Hz & 9.1 Hz; J_{ortho} = 6.9 Hz; J_{meta} = 3.6 Hz

FORMULA: $C_{22}H_{20}O_5$ MW 364 (22)

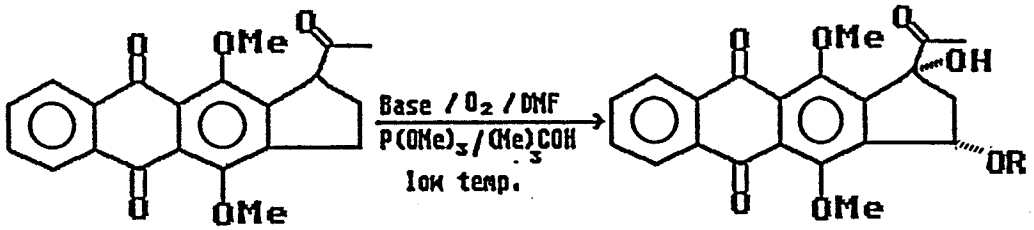
M.P. 102-103 °C

IR: 1710 ($-COCH_3$), 1675 (QUINONE), 1600-1580 (AROMATIC)

MS: 364 ($M^{+\cdot}$, 10%), 321 ($M^{+\cdot}-COCH_3$, 100%)

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
1.55	3H	s	$Ar-C-CH_3$
2.01	1H	m	$O=C-CH-CH_2$
2.18	3H	s	$O=CCH_3$
2.44	1H	m	$O=C-CH-CH_2$
3.18	2H	s	$ArCH_2$
3.86	3H	s	OCH_3
3.97	3H	s	OCH_3
7.75	2H	m	ArH
8.19	2H	m	ArH



21

24 R = H

26 R = $-\overset{O}{\overset{\|}{C}}CF_3$

For a discussion of benzylic/enolate hydroxylation see reference 15.

Potassium tert-butoxide (3 g, 9 mmol) was stirred in dimethylformamide (100 mL) and t-butyl alcohol (80 mL) for 30-60 min (or until most of the base had dissolved). The solution is then cooled to about -25 °C and dry oxygen passed through the solution with the aid of a gas dispersion tube. The tetracyclic compound 21 (396 mg) was added in one portion and the solution stirred at -30 °C to -25 °C for 3 h. Trimethyl phosphite

(2 mL) and hydrochloric acid (6M, 4 mL) were added and the solution stirred overnight. The solution was then diluted with water and extracted several times with chloroform. The organic layer was washed separately with sodium bicarbonate (saturated), water, and saturated sodium chloride. Evaporation and chromatography gave 130 mg of 24 as a viscous oil.*

* If trimethyl phosphite is added together with the other reagents, the monohydroxy 23 can be obtained almost exclusively.

FORMULA: $C_{21}H_{18}O_7$ MW 382 (**cis** stereoisomer, 24)

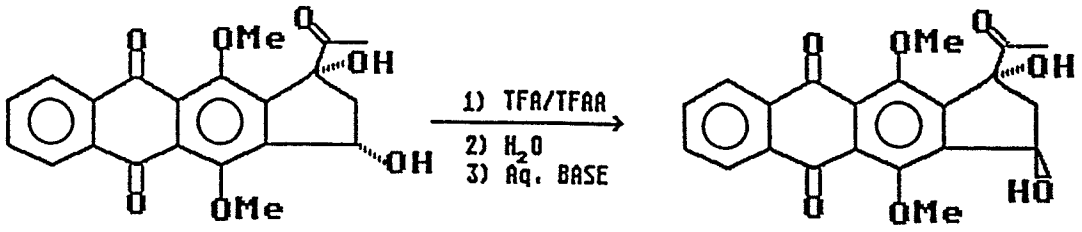
IR: 3550 (2^o-OH), 3450 (3^o-OH), 1715 ($COCH_3$), 1670 (QUINONE), 1600-1580 (AROMATIC)

MS: 382 ($M^{+\cdot}$, 1%), 339 ($M^{+\cdot}-COCH_3$, 100%)

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.163	3H	s	$O{=}CCH_3$
2.142-2.200	1H	dd	CH_2
2.695-2.765	1H	dd	CH_2
2.90	1H	bs	ArCH-OH
3.877	1H	s	OCH_3
4.113	1H	s	OCH_3
4.80	1H	s	3^o-OH
5.526-5.507	1H	bd	ArCH-OH
7.65-7.80	2H	dd	ArH
8.10-8.20	2H	dd	ArH

J_{AX} = 6.5 Hz; J_{BX} = 1.7 Hz; J_{AB} = 14.5 Hz



24 25

Method A

The cis diol 24 (304 mg) was heated at 52 °C with trifluoroacetic acid (9 mL) and trifluoroacetic anhydride (6 mL) for 3.5 h. More trifluoroacetic acid (1.5 mL) and trifluoroacetic anhydride (3 mL) were added and the temperature raised to 74 °C for 7 h*. Water** (9 mL) was added carefully and the resulting solution heated at 80 °C overnight. The solvent was removed under reduced pressure and enough chloroform was added to dissolve the residue. Aqueous sodium carbonate was added and the solution stirred at 80 °C for at least 4 h. Work up and preparative thin layer chromatography gave cis and trans diols. The trans to cis ratio was estimated, by thin layer chromatography, to be about 40:60.

* Compound 26 can be isolated after about 3.25 to 4 h at 50 °C.

** If more than 10-30% water is used much of the starting material 24 was recovered.

Method B

An acetone solution (20 mL) of 2,2-dimethoxypropane (5 mL), trifluoroacetic acid (1/3 mL) and 24 (80 mg) was heated under reflux in a dry nitrogen atmosphere for 24 h. The solution was concentrated under reduced pressure, diluted with methylene chloride (100 mL), washed with water, and sodium bicarbonate solution. After drying (Na_2SO_4) the solution was evaporated to dryness. The residue, after separation by TLC, afforded starting material 24 (12 mg) and 25 (42 mg) which was crystallised from methylene chloride/diethyl ether, m.p., 148-151 °C.

FORMULA: $C_{21}H_{18}O_7$ MW 382 (**trans** STEREOISOMER, 25)

IR: 3560 (2^o-OH), 3450 (3^o-OH), 1715 ($COCH_3$), 1670 (QUINONE), 1600-1580 (AROMATIC)

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.285	3H	s	$O{=}CCH_3$
2.391-2.456	1H	dd	$-CH_2-$
2.566-2.638	1H	dd	$-CH_2-$
3.187	1H	bs	ArCH-OH
3.889	1H	s	OCH_3
4.093	1H	s	OCH_3
4.718	1H	s	3^o-OH
5.854-5.895	1H	dd	ArCH-OH
7.70-7.85	2H	dd	ArH
8.15-8.25	2H	dd	ArH

J_{AX} = 5.2 Hz; J_{BX} = 7.2 Hz; J_{AB} = 14.4 Hz

FORMULA: $C_{23}H_{17}F_3O_8$ MW 478 (**cis** trifluoroacetate, 26)

CALCULATED: 435.0692 ($M^{+\cdot}$-43 : $C_{21}H_{14}F_3O_7$)

OBSERVED : 435.0734

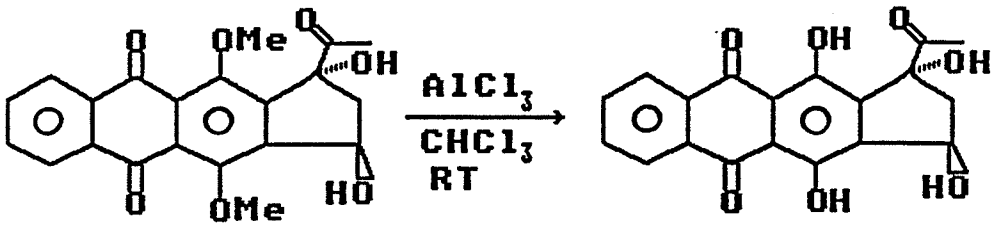
IR: 3450 (3^o-OH), 1790 (CF_3CO-O-)

1720 ($COCH_3$), 1680 (QUINONE), 1590 (AROMATIC)

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.152	3H	s	$O{=}CCH_3$
2.269-2.328	1H	dd	C_8-H
2.956-3.033	1H	dd	C_8-H
3.936	3H	s	OCH_3
4.012	3H	s	OCH_3
6.601	1H	dd	C_7-H
4.773	1H	s	C_9-OH
7.773-7.803	2H	m	ArH
8.188-8.219	2H	m	ArH

J_{AB} = 15.79 Hz; J_{AX} = 2 Hz & 7.32 Hz



25 28

To 25 (**trans** stereoisomer) (218 mg) in chloroform* (60mL) was added aluminium chloride (2 g) and the mixture stirred at room temperature in

a nitrogen atmosphere for 8 h. To the deep red solution was added saturated oxalic acid (90 mL) and the mixture stirred for a further 4 h. The solution was then diluted with cold water and extracted exhaustively with chloroform. Work up, concentration and trituration with diethyl ether gave the aglycone 27, 169 mg (76%), m.p., 230-231 °C.

*Chloroform was filtered through a column of neutral alumina before use.

FORMULA: $C_{19}H_{14}O_7$ MW 354 (trans STEREOISOMER, 28)

CALCULATED: 354.0740

OBSERVED : 354.0702

CALCULATED: 311.0556 ($M^{+\cdot}$-43; $C_{17}H_{11}O_6$)

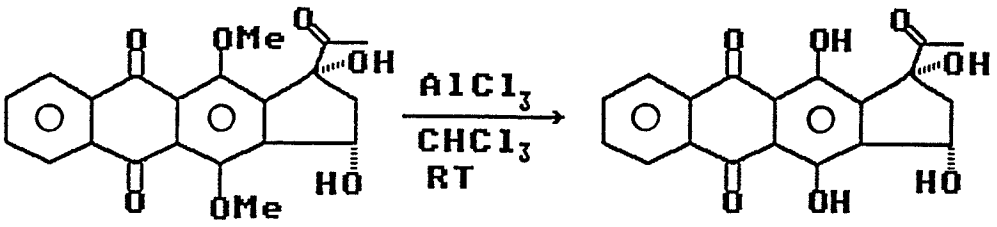
OBSERVED : 311.0565

IR: 3560 (2^o-OH), 3430 (3^o-OH), 3560-2700 (CHELATED PHENOLS), 1715 ($COCH_3$), 1630 (CHELATED QUINONE), 1590 (AROMATIC)

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.3694	3H	s	$O{=}CCH_3$
2.4681-2.5304	1H	dd	CH_2
2.6220-2.6957	1H	dd	CH_2
3.0846-3.0927	1H	d	ArCH-OH
4.5126	1H	s	3^o-OH
5.8134-5.8641	1H	m	ArCH-OH
7.80-7.90	2H	dd	ArH
8.30-8.45	2H	dd	ArH
12.959	1H	s	ArOH
13.017	1H	s	ArOH

J_{AX} = 7.4 Hz; J_{BX} = 4 Hz; J_{AB} = 14.7 Hz; J_{MX} = 4 Hz



24 27

To 24 (**cis** stereoisomer) (125 mg) in chloroform* (50 mL) was added aluminium chloride (1.4 g) and the mixture stirred at room temperature in a nitrogen atmosphere for 6 h. To the deep red solution was added saturated oxalic acid (90 mL) and the mixture stirred for a further 4 h. The solution was then diluted with cold water and extracted exhaustively with chloroform. Work-up and concentration and trituration with diethyl ether gave the aglycone 27, 73.2 mg (63%), m.p., 225-226 °C.

*Chloroform was filtered through a column of neutral alumina before use.

FORMULA: $C_{19}H_{14}O_7$ MW 354 (**cis** STEREOISOMER, 27)

CALCULATED: 354.0740

OBSERVED : 354.0726

CALCULATED: 311.0556 ($M^{+\cdot}$-43; $C_{17}H_{11}O_6$)

OBSERVED : 311.0589

IR: 3560 (2^o-OH), 3450 (3^o-OH), 3600-2600 (CHELATED PHENOLS), 1720 (-$COCH_3$), 1630 (CHELATED QUINONE), 1590 (AROMATIC)

MS: 354 ($M^{+\cdot}$, 1%), 311 ($M^{+\cdot}$-$COCH_3$, 100%), 293 ($M^{+\cdot}$-$COCH_3$-H_2O, 70%)

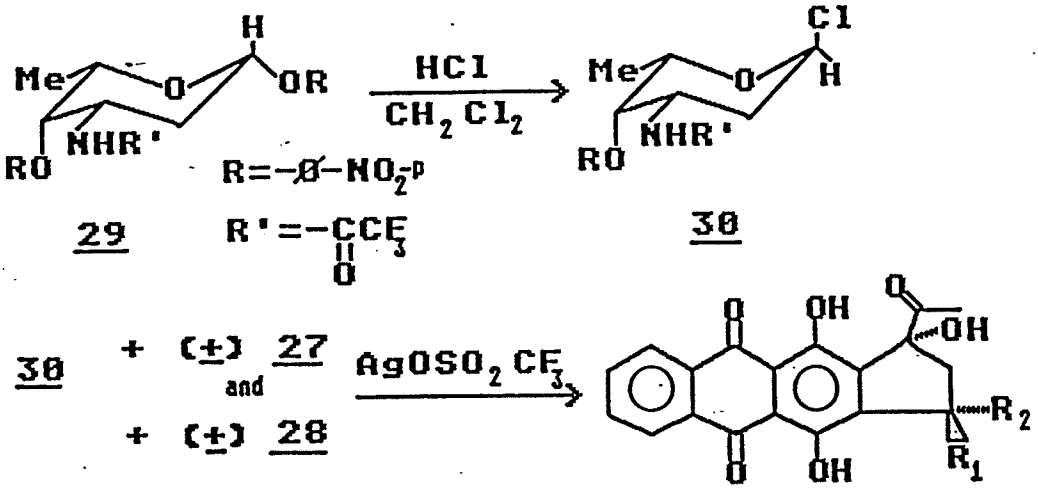
NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)

NMR ^{1}H

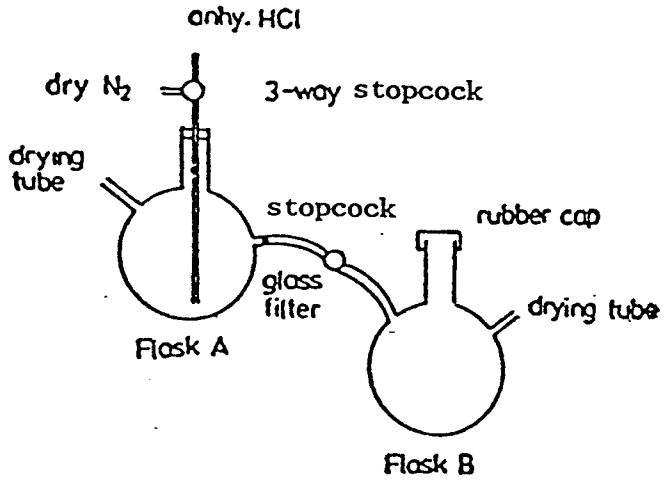
DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
2.222	3H	s	$O{=}CCH_3$
2.276-2.338	1H	dd	$-CH_2-$
2.874-2.889	1H	d	ArCH-OH
2.907-2.980	1H	dd	$-CH_2-$
4.561	1H	s	3^{o}-OH
5.556-5.609	1H	m	ArCH-OH
7.80-7.90	2H	m	ArH
8.30-8.40	2H	m	ArH
12.994	1H	s	ArOH
13.081	1H	s	ArOH

J_{AX} = 7.3 Hz; J_{BX} = 3.9 Hz; J_{AB} = 14.7 Hz; J_{MX} = 4.6 Hz



31: R_2 = O-PROTECTED SUGAR, R_1 =H

32: R_1 = O-PROTECTED SUGAR, R_2 =H



To a methylene chloride solution (20 mL) of 29 (200 mg) in flask **A**, was passed anhydrous hydrogen chloride through a gas dispersion tube for a period of 10 min. The solution was stirred for an additional 20 min, filtered into flask **B**, and evaporated to dryness under reduced pressure. The unstable foamy residue was twice dissolved in methylene chloride and evaporated to dryness to remove residual hydrogen chloride. The chlorosugar, 30, used without further purification, was condensed with the **cis** aglycone, 27, in the following manner.

Compound 27 (106 mg) and freshly baked, pulverised molecular sieves (300 mg, Linde type 4A) were added to flask **B** containing the chlorosugar, 30, prepared as described above. Methylene chloride (35 mL) followed by silver trifluoromethanesulfonate (130 mg) in anhydrous ether (10 mL) were injected into flask **B**. The solution was stirred at room temperature, in the dark, overnight. TLC after 10 min had indicated

that the reaction was about 50% complete. The solution was filtered, washed with 5% sodium chloride solution, dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure to give an amorphous solid. This solid was purified, rapidly, by column chromatography and repeated PTLC. A total of 40 mg of 31 was obtained by this procedure. About 30-40% of the aglycone was recovered.

COMPOUND 32 (32 C, trans beta protected glycoside)

IR: 3420 (NH, 3^{o}-OH), 3600-2600 (CHELATED PHENOLS), 1740 (BROAD; $-COCH_3$, $NHCOCF_3$, PhCOOR), 1630, 1590 (CHELATED QUINONE), 1590 (AROMATIC), 1530 (NO_2)

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
1.30	3H	d	HC'5-C'H_3
1.90-2.20	2H	m	C'1H-C'2H
2.32	3H	s	CH_3C=O
2.45-2.55	1H	dd	ArCH_2CH_2
2.60-2.70	1H	dd	ArCH_2CH_2
4.67	1H	s	3^{o}-OH
4.60-4.75	1H	m	C'$_5$H-C'H_3
4.85-4.95	1H	m	C'H-C'3H-C'H_2
5.20-5.30	1H	m	C'H_3-C'4H-C'H
5.45	1H	bs	ArCH-OH
5.85-5.95	1H	dd	C'1H-C'H_2
6.41-6.44	1H	d	C'H-NH-$COCF_3$
7.80-7.90	2H	m	ArH
8.30-8.40	6H	m	ArH

12.95	1H	s	ArOH
13.29	1H	s	ArOH

In an analogous manner, the trans aglycone, 27 (65 mg) was coupled to the chlorosugar, 30, to give 25 mg of 32.

COMPOUND 31 (31 A, CIS alpha protected glycoside)

IR: 3450 (NH, 3^{o}-OH), 3600-2600 (CHELATED PHENOLS), 1740 (BROAD; $-COCH_3$, $NHCOCF_3$, PhCOOR), 1640, 1600 (CHELATED QUINONE), 1590 (AROMATIC), 1540 (NO_2)

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
1.21	3H	d	HC'5-C'H_3
2.05-2.10	2H	m	C'1H-C'2H
2.24	3H	s	CH_3C=O
2.30-2.40	1H	dd	ArCH_2CH_2
2.90-3.00	1H	dd	ArCH_2CH_2
4.32-4.42	1H	dd	C'H-C'3H-C'H_2
4.52	1H	bs	3^{o}-OH
4.62-4.74	1H	m	C'$_5$H-C'H_3
5.46-5.48	1H	bs	C'H_3-C'4H-C'H
5.46-5.48	1H	bs	ArCH-OH
5.66-5.72	1H	bs	C'1H-C'H_2
6.18-6.24	1H	d	C'H-NH-$COCF_3$
7.80-7.90	2H	m	ArH
8.20-8.40	6H	m	ArH
13.01	1H	s	ArOH

13.23	1H	s	ArOH

COMPOUND 31 (31 B, beta protected glycoside)

IR: 3420 (NH, 3^{o}-OH), 3600-2600 (CHELATED PHENOLS), 1740 (BROAD; $-COCH_3$, $NHCOCF_3$, PhCOOR), 1640, 1600 (CHELATED QUINONE), 1590 (AROMATIC), 1540 (NO_2)

NMR ^1H

DELTA (ppm)	# OF HYDROGENS	MULTIPLICITY	PROTON(S)
1.26	3H	d	HC'5-C'H_3
2.00-2.15	2H	m	C'1H-C'2H
2.27	3H	s	CH_3C=O
2.24-2.34	1H	dd	ArCH_2CH_2
2.76-2.86	1H	dd	ArCH_2CH_2
4.51	1H	bs	3^{o}-OH
4.66-4.78	1H	m	C'$_5$H-C'H_3
4.84-4.92	1H	m	C'H-C'3H-C'H_2
5.26-5.32	1H	bs	C'H_3-C'4H-C'H
5.50-5.54	1H	dd	ArCH-OH
5.62-5.66	1H	dd	C'1H-C'H_2
6.24-6.30	1H	d	C'H-NH-$COCF_3$
7.80-7.90	2H	m	ArH
8.20-8.40	6H	m	ArH
12.98	1H	s	ArOH
13.27	1H	s	ArOH

DEPROTECTION OF GLYCOSIDES.

To aqueous sodium hydroxide (2%)/methanol (1:2) was added the protected glycosides (10 mg, 31 and 32 (32 C and 31 A)) and the mixture stirred at room temperature overnight and cooled in an ice-bath. The pH was adjusted to 9 by dilute hydrochloric acid (0.5%) and extracted with chloroform. The chloroform solution upon evaporation, after usual work up, gave dark orange residues from which the deprotected glycosides (5 mg) were isolated by PTLC and submitted for biological evaluation.

ANTIPROLIFERATION ACTIVITY ASSAY FOR 4-DEMETHOXY-10-NORDAUNOMYCIN AND 4-DEMETHOXY-7-EPI-10-NORDAUNOMYCIN.

done by **Dr. Francis Jay,** Health Sciences Center; Winnipeg, Manitoba.

Human lung carcinoma cells (A549) are seeded in microtitre plates at 4 x 10^3/100 μL/well. One half row (6 wells) contains medium only. Daunomycin and the test analogues are separately dissolved in dimethyl sulfoxide (DMSO) at 100 μl. DMSO (4 μL) is diluted into medium (133 μL, RPMI 1540 with 10% Δ FBS) (1/33 conc.) and the mixture (50 μL) is added into the first well a row in the plate (1/66 conc.). After mixing by pipetting, the drug is serially diluted (1/3) by transferring 50 μL into successive wells. One row of culture with 6 wells having no cells and no treatment will serve as the 0% and 100% absorbance. The DMSO test serves as the drug carrier control and daunomycin serves as the internal sensitivity calibration of this particular assay to allow reference to other assays. The plate is incubated at 37 °C for 48-72 h. At the end of the incubation period, the culture medium is removed and replaced

with 100 μL crystal Violet (0.25% Crystal Violet, 25 mM Tris, pH 7.5, 0.9% NaCl, 20% MeOH) and allowed to stand at room temperature for 5 min. The stain is removed and the fixed culture is washed in water to remove excess stain. The 50% growth is determined by extracting the adsorbed Crystal Violet into MeOH (100 μL) and spectrophotometrically quantitated at 590 nm in an ELISA reader using 6 wells without cells to set the zero absorbance base line.

REFERENCES

1. R. Anuker,
   J. Am. Chem. Soc., 79, 225 (1957).

2. T. Posternak and R. deOliveria Castro,
   Helv. Chim. Acta., 31, 536 (1948).

3. R. T. Arnold and H. E. Zaugg,
   J. Am. Chem. Soc., 63, 1317 (1941).

4. J. Koo,
   J. Am. Chem. Soc., 75, 1891 (1953).

5. C. T. West, S. J. Donnelly, D. A. Kooistra and M. P. Doyle,
   J. Org. Chem., 38, 2675 (1973).

6. F. Arcamone, L. Bernardi, B. Patelli, P. Giardino, A. Di Marco,
   A. M. Caszza, C. Soranzo and G. Pratesi,
   Experientia, 34, 1255 (1978).

7. K. Hanaya, S. Awano and H. Kudo,
   Bull. Chem. Soc. Japan, 51, 342 (1978).

8. M. M. Fraser and R. A. Raphael,
   J. Chem. Soc., 226 (1952).

9. G. Malesani, F. Galiano, M. Grazia and S. Masiero,
J. Hetero. Chem., 17, 563 (1980).

10. J. R. Anderson and O. Jorgensen,
J. Chem. Soc., Perkin I, 3095 (1979).

11. L. Skattebol, E. R. H. Jones and M. C. Whiting,
Org. Synth., 39, 56 (1959).

12. H. B. Kagan, A. Marquet and J. Jacques,
Bull. Soc. Chim. Fr., 1079 (1960).

13. S. J. Nelson, G. Detre and M. Tanabe,
Tetrahedron Lett., 447 (1973).

14. D. H. Evans and R. B. Greenwald,
Org. Prep. and Proceed. Int., 4, 75 (1972).

15a. J. N. Gardner, F. E. Carlon and O. Gnoj,
J. Org. Chem., 33, 3294 (1968).

15b. C. M. Wong, A. Q. Mi, H. Y. Lam, W. Haque and K. Marat,
Synth. Commun., 13, 15 (1983).

16. J. E. Baldwin, G. A. Hofle, and O. W. Lever Jr.,
J. Am. Chem. Soc.,96, 7125 (1974).