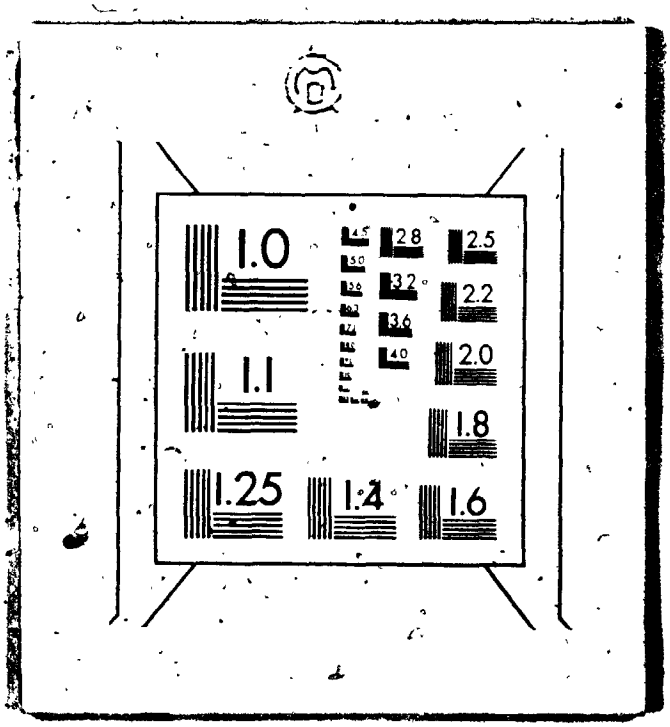
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NAME OF AUTHOR/*NOM DE L'AUTEUR* Austin McDonald Greaves

TITLE OF THESIS/*TITRE DE LA THÈSE* Studies directed towards the total synthesis of pentacyclic terpenoids.

UNIVERSITY/*UNIVERSITÉ* Carleton

DEGREE FOR WHICH THESIS WAS PRESENTED/*GRADE POUR LEQUEL CETTE THÈSE FUT PRÉSENTÉE* Ph.D.

YEAR THIS DEGREE CONFERRED/*ANNÉE D'OBTENTION DE CE DEGRÉ* 1980

NAME OF SUPERVISOR/*NOM DU DIRECTEUR DE THÈSE* J.W. ApSimon

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STUDIES DIRECTED TOWARDS THE TOTAL SYNTHESIS OF PENTACYCLIC TERPENOIDS

by

© AUSTIN M. GREAVES, L.R.I.C. (Southbank Polytechnic, London)

A thesis submitted to the Faculty of
Graduate Studies in partial fulfilment
of the requirements for the degree of
Doctor of Philosophy

Department of Chemistry
Carleton University

January 1980

The undersigned recommend to the Faculty of Graduate Studies acceptance of the thesis "Studies Directed Towards the Total Synthesis of Pentacyclic Terpenoids" submitted by Austin Greaves in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

.....
Thesis supervisor

.....
Chairman, Department of Chemistry

.....
External Examiner

Carleton University

ABSTRACT

Studies on the acid and base catalysed cyclisation of the diastereomeric compounds 2-keto-1-methyl-1-(2-(3-keto-4,4-trimethylcyclohexyl)-6-methoxy-3,4-dihydronaphthalene (1) have been presented. A novel acid catalysed rearrangement of the named compounds has been shown. The amino acid mediated aldol condensation reaction of 1,5-diketones has been explored. The syntheses of the optically active compounds: (+)-1-(3,5-dimethyl-4-isoxazolylmethyl)-5β-hydroxy-4aβ-methyl-4,4a,5,6,7,8-hexahydronaphthalen -2 (3H)-one (55) and (+)-1-(3-benzyloxybutyl)-3,5-dihydroxy-4aβ,8aα-dimethyldecahydronaphthalene (82) have been presented.

1-(3-Benzyloxybutyl)-7β-(tert-butyl)-12aα-cyano-4aβ,6aβ,10bβ-trimethyl-3,4,4a,4b,5,6,6a,7,8,9,10,10a,10b,11,12,12a-trans-anti-trans-anti-trans-hexadecahydrochrysen-2(1H)-one (117), a tetracyclic compound having seven of the nine asymmetric centres of friedelin in the correct stereochemical configuration has been synthesized.

ACKNOWLEDGEMENTS.

The Universe is unfolding as it should and this work is merely a small paragraph in this infinite epic.

Special thanks to Prof. J.W. ApSimon, not only for his guidance in chemical matters, but especially for the confidence placed in me. Further, his example in priorities' establishment has been greatly appreciated.

"When all else fails - see Karl". Karl Diedrich has contributed in large measure to this work, by his efficiency in the supply of chemicals and related materials and moreover by his willingness to render assistance beyond the scope and requirements of his job. To Karl; my sincerest thanks.

Personal thanks to Ms. Judy Lockwood for her timely moral support and to Ms. Kathleen Nelson for her efficient drafting of the structures in this thesis. My personal thanks also to Rick Seguin for sharing in our interesting discussions, both chemical and philosophical.

Finally, my sincerest thanks and best regards to one of the finest bunch of people with whom anyone could hope to work."ApS's group" has been a source of inspiration and knowledge and it has been a pleasure to be a part of it. I thank everyone for the good times which we shared.

QUE SERA SERA.

TABLE OF CONTENTS

Those blessed with the synthetic art
Must of need be endowed with more heart,
For assembly of things,
Even molecular rings,
Is more humane than pulling apart.

AMG.

TO LAUREN.

INTRODUCTION

The triterpenoids constitute a large group of naturally occurring compounds which are characterized by a basic C_{30} isoprenoid derived skeleton[13,14], and which are found widely distributed throughout the plant kingdom[15]; they have also been found to a lesser extent, in the animal kingdom[16].

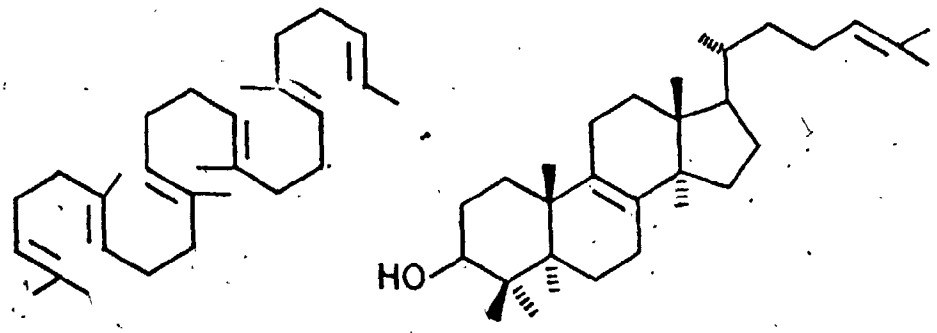
This group - of which over 750 examples have been reported to date[17,18] - displays a wide variety of structural types differing in skeletal framework and complexity. However, among the triterpenoids, there exists a predominance of polycyclic species, and the majority of the members of this group fall into one of about 30 basic cyclic skeletons[7], differing in the number and array of fused rings, the structure and location of appended side chains and finally the stereochemically diverse array of methyl groups appearing on the skeleton. It is convenient however, to classify the triterpenoids into three major groups based on key structures along the biogenetic pathway of this group[14,16].

(i) The acyclic triterpenoids e.g. squalene I*

(ii) The tetracyclic triterpenoids[19] - e.g. lanosterol II

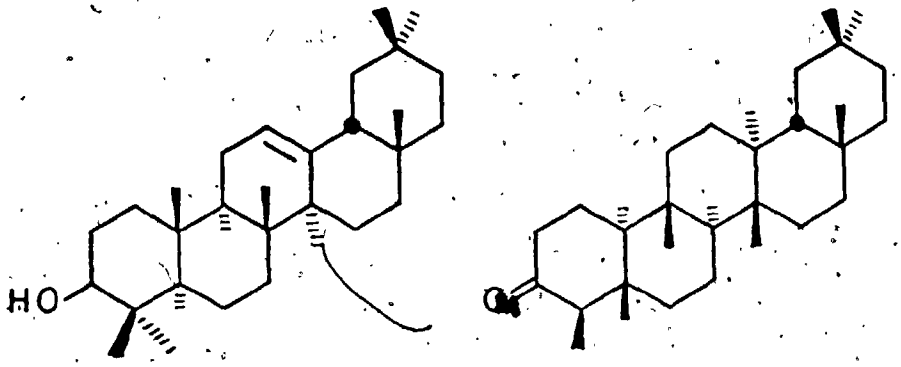
(iii) The pentacyclic triterpenoids e.g. β-amyrin III and friedelin IV

The latter group is by far the largest in number.



I squalene II lanosterol

* Roman numerals are used for Introduction purposes whilst arabic symbols will be used throughout the Results and Discussion.



III β-amyrin IV friedelin

Biogenetically the triterpenoids can be derived from squalene I by a series of concerted cyclizations of squalene epoxide V (trans-squalene) followed in many instances by Wagner-Meerwein migrations[20] of methyl groups. This is essentially the postulate of the Biogenetic Isoprene Rule which forms the template for triterpene biogenesis proposed by Stork[21] and Eschenmoser[22] so that the diverse structures and configurations of the various triterpenoid skeletal types could be derived.

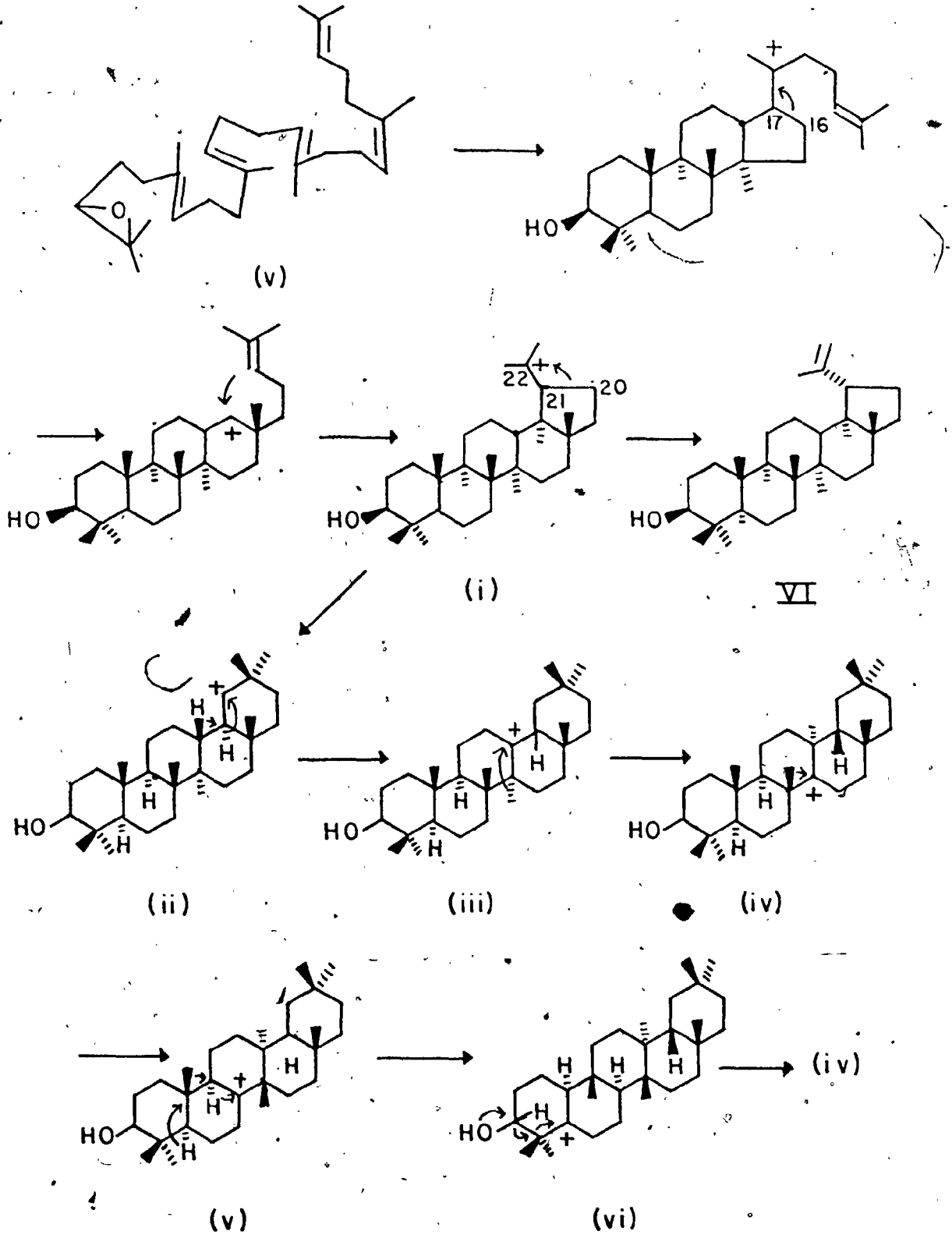
Indeed this model gave rise to a large number of hypothetical carbonium ion intermediates which could serve as precursors to various classes of triterpenes having modified pentacyclic skeletons. As an illustration there are a number of cationic species (i-vi) (Chart A) between the pre-lupeol cationic precursor i and friedelin IV which may intervene in the biogenesis of friedelin.

In fact the isoprene rule has been well authenticated along these lines since triterpenes which are derivable from each of the illustrated intermediates by loss of an appropriate proton have been isolated from various sources[17].

The structural relationships among the triterpenoids, based on

the Biogenetic Isoprene rule have been reviewed[23].

CHART A



The rigid skeletal framework coupled with the stereochemical complexity of the triterpenoids hindered progress in the elucidation of their structures. It was not until 1937[24] that the structure of β-amyrin III was elucidated and not until 1951[25] was that of Lupeol VI assigned. The advent of spectroscopic techniques and more refined chromatographic methods has provided much greater facility in the task of structure determination, as can be seen from the impressive growth in the field over the past thirty years[25,18]. Conformational analysis, developed by Barton in 1950[28], led to the recognition of various structural types.

When proficiency in the field of structure elucidation of triterpenoids was attained, efforts were turned to the synthesis of these compounds. Indeed, it was the structural and stereochemical complexities associated with these materials that attracted the synthetic chemist to test and revise those methods of stereoselective directed total syntheses that were originally put to use in the steroid field[29]. The pioneering efforts in the field of triterpene total synthesis have, in fact, yielded many new techniques and have fostered greater understanding of these complex systems. These past efforts have been ably reviewed by ApSimon and Hooper[30].

PENTACYCLIC TRITERPENE SYNTHESIS

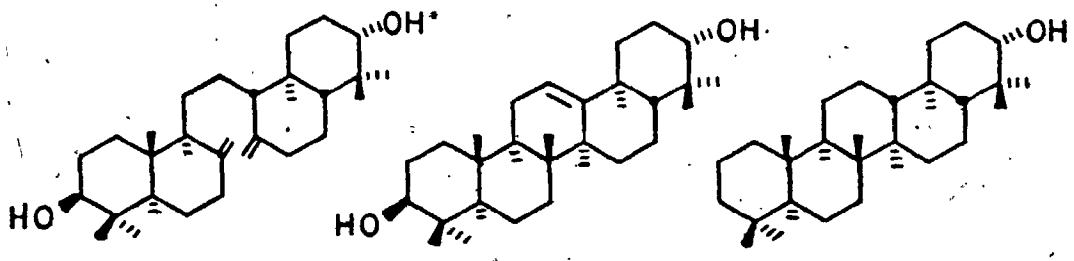
In addition to being the most abundant, the pentacyclic triterpenoids with their array of angular methyl groups and contiguous asymmetric centres, are also the most complex, from a synthetic viewpoint.

Two basic provisions oversee any approach to pentacyclic triterpene synthesis: Firstly, the method for and sequence of assembly of the polycyclic array and secondly, steric control in complex reactions.

The former aspect evolved quite readily from the steroid synthesis field[29] and Chart B illustrates some possible ring construction sequences that could lead to a pentacyclic array.

The second criterion is newer both in concept and practice so that only more recent syntheses display extended stereoselectivity.

Hence it is not difficult to visualize why the pioneering efforts in the synthesis of the onocerin group of triterpenoids[18,30] (compounds VII, VIII, IX) were so nonstereoselective in nature. These syntheses relied upon the attachment of an AB fragment to a CD fragment; followed by an acid catalysed cyclization to form the C-6a-C-6b* bond in VIII and IX. This latter bond formation lacks regiospecificity, is stereochemically ambiguous, and gives only low yields of the desired product.



α-onocerin γ-onocerin tetrahymanol

VII VIII IX

However, because of the further innovations in synthetic methodology, later syntheses[30] - germanicol[31] X, lupeol[32] VI and alnusenone[33] XI - were completed using elegant synthetic strategy in which maximum regioselectivity in all C-C bond forming steps was a high priority and each asymmetric centre was introduced with high stereoselective efficiency.

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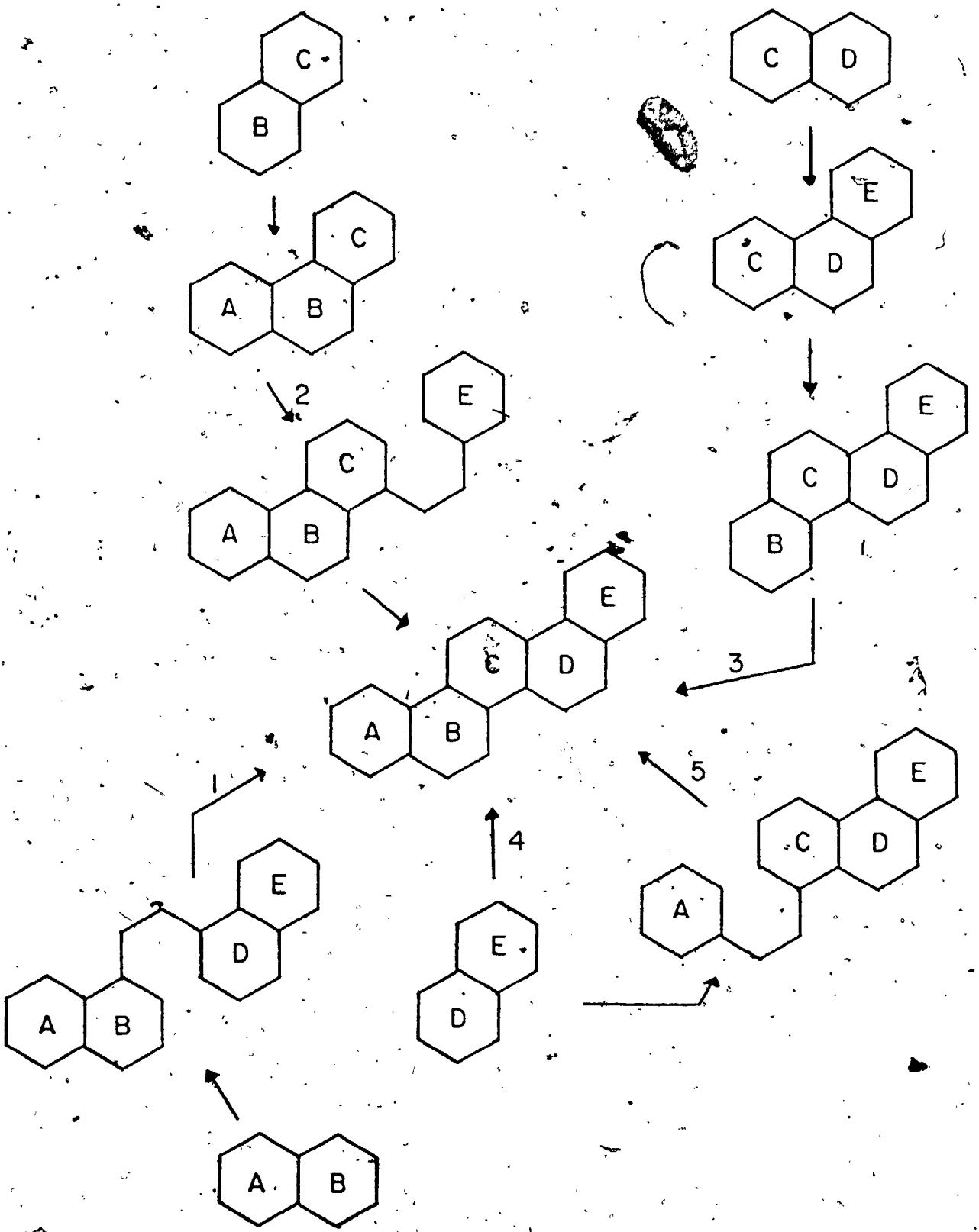
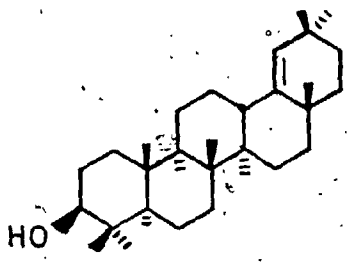
*See Appendix I for systematic numbering used in triterpene skeletons.

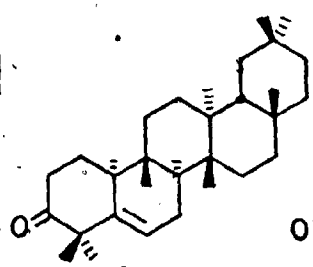
CHART B





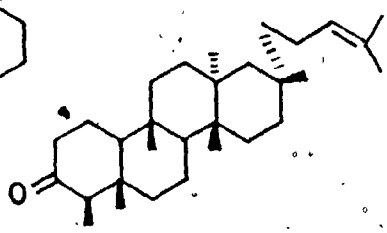
germanicol

X



alnusenone

XI



shionone

XII

Synthetic strategists have continued to make major advances in these areas as can be seen from more recent syntheses of triterpenes in which more complex members of this group e.g. shionone XII[26] and Friedelin IV[27] have been synthesized.

RECENT TOTAL SYNTHESES OF PENTACYCLIC TRITERPENES

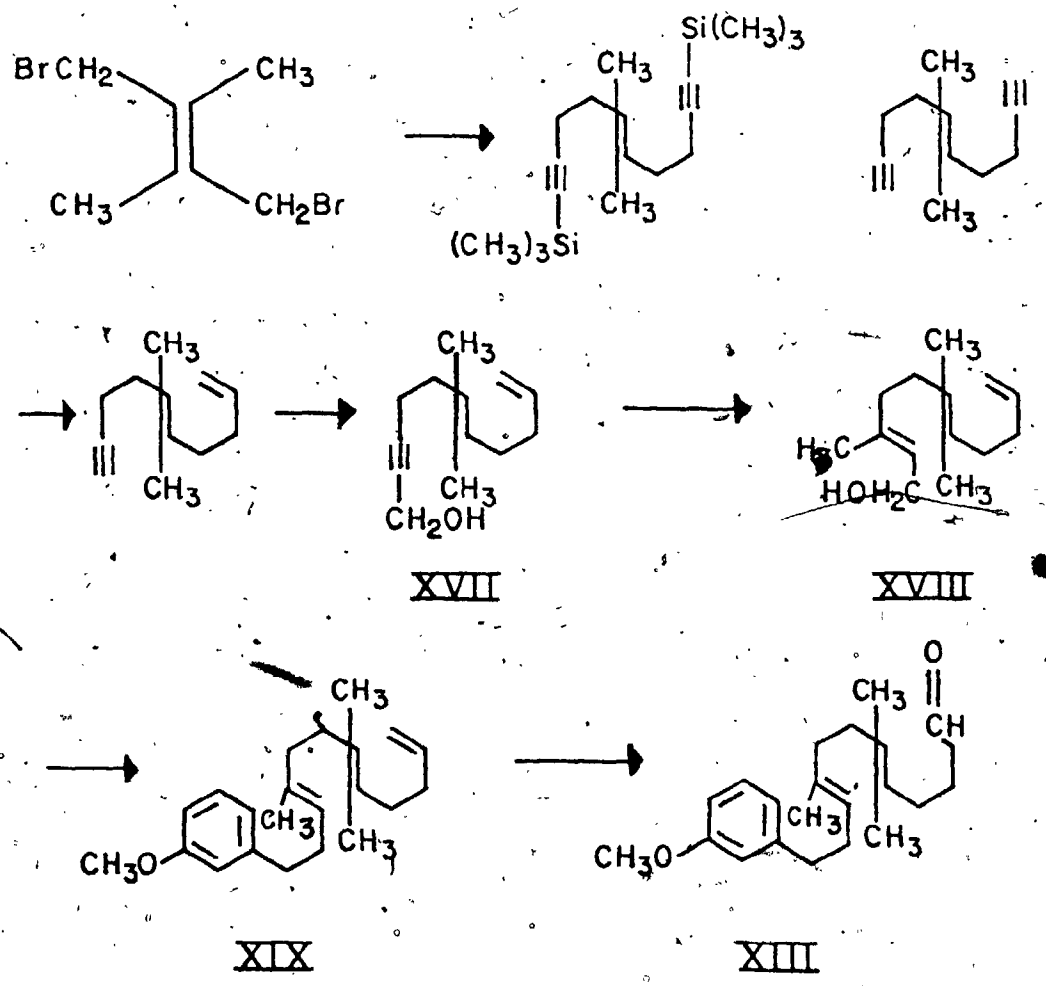
1 dl-Alnusenone

Ireland and his co-workers recently developed an alternative synthesis of dl-alnusenone XI[34] based on the polyene cyclization methodology following the pattern set in the elegant work of Johnson, Corey and van Tamelen[35].

The main disadvantage which attended the original synthesis of dl-alnusenone[30,33] was the selective reduction of two dissimilar A and E aromatic rings. The polyene cyclization approach offered an elegant method of developing a route which would give rise to a non-aromatic ring E, thus avoiding the selective reduction problem. The target compound became the pentacyclic enone XXVII which had been previously converted to alnusenone XI[30,33].

A major part of the synthetic strategy used in this alnusenone synthesis had just previously been worked out in the synthesis of dl-shionone[26]. The key aldehyde XIII , the synthesis of which is described in Chart C[36], was the starting material.

The highlight of the sequence shown in Chart C is the stereoselective conversion of the acetylenic moiety of the dienyne XVII to the methylated trisubstituted double bond of XIX via a sequence worked out by Corey[37] which gave rise only to the Z isomer. This sequence involved conversion of XVII to the propargyl alcohol XVIII followed by reductive iodination and lithium dimethyl cuprate alkylation to XIX.



XVII XVIII XIX XIII

CHART C

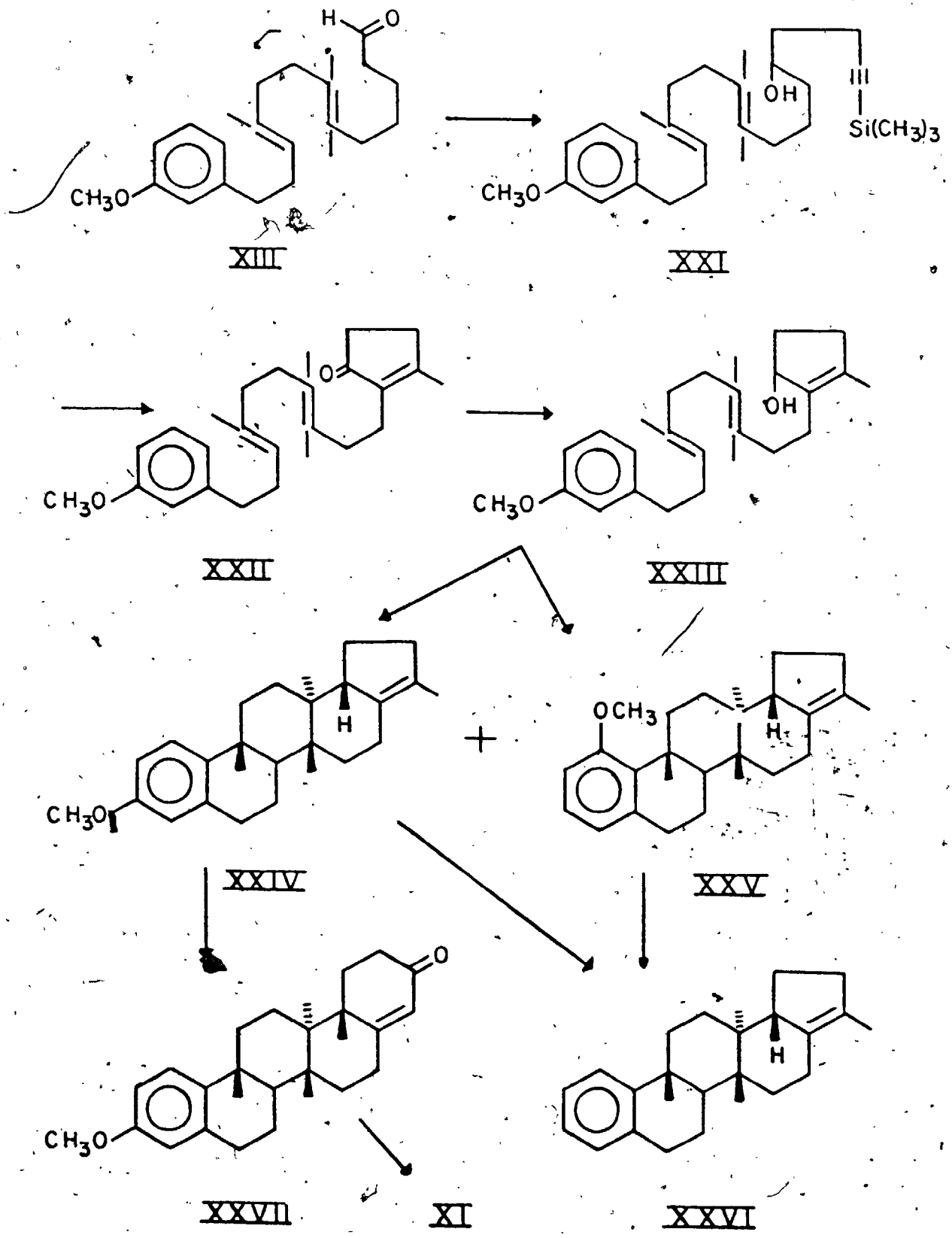

H
O
CH3O
XIII
OH
Si(CH3)3
CH3O
XXI
O
CH3O
XXII
OH
CH3O
XXIII
H
CH3O
XXIV
+
OCH3
H
XXV
O
CH3O
XXVII
XI
H
XXVI

CHART D

The aldehyde XIII was converted in 4 steps (28% overall yield) to the 3-methylcyclopentenol system XXIII (Chart D) which, as has been shown by Johnson[38], is an excellent precursor for oxidative ring enlargement, after cyclization to a fused 2-cyclohexenone system. It is noteworthy that only the enone XXII resulted from the aldol condensation of the dione - derived from hydration, desilylation and oxidation of the acetylene XXI - although two cyclopentenones could have resulted. Cyclization of XXIII using stannic chloride in dichloromethane[38b] at -78°C gave a mixture of isomers XXIV and XXV in low yield. Structural assignment for XXV was made by converting both products to the identical hydrocarbon XXVI. XXIV was converted to the enone XXVII which had previously been converted to dl-alnusenone[30].

2 ± Friedelin

In an attractive and elegant scheme Ireland et al[27], devised the total synthesis of friedelin IV, which combined the best results achieved in previous syntheses of dl-alnusenone XI[33] and dl-shionone XII[26]. Thus[27], the first synthesis of friedelin IV (Chart E) involved the diaromatic diether XXVIII which is analogous to the one used in the synthesis of alnusenone[33] except that the aromatic ether substituents are reversed. The strategy behind such a modification arose from a two-fold consideration. First, it was felt that inversion of the sequence of the aromatic rings' reductions and modifications would greatly improve the yields. Hence in this scheme ring A was modified before ring E.

The second consideration bore out the first. Based on the shionone synthesis[26], the modification of ring A involved a cationic cyclization process (XXX → XXXI). Had a precursor such as XXXIV, in which ring E had already been modified, been subjected to such a process, then a backbone rearrangement as a result of the severe steric strains[39] at the CDE ring junctions, would most likely occur.

The diether XXVII was prepared in a manner analogous to that used in the alnusenone synthesis[33]. Selective Birch reduction of ring A did result in higher yields and further modification of ring A via Eschenmoser cleavage and cationic cyclization to the enol trifluoroacetate XXXI along the lines reported for the total synthesis of shionone[26], proceeded smoothly. However, cleavage of the derived cyclopropyl alcohol XXXII did not proceed as it did in the shionone synthesis[26] and resulted in lower yields, the complication arising by backbone rearrangement of the pentacyclic system[39]. The solution found was reduction of the aromatic ring E of XXXII prior to acid cleavage of the cyclopropyl alcohol. Protection of the C-3 oxygen function* followed by modification of ring E to that of friedelin IV along the lines of the dl-alnusenone synthesis[33], gave the natural product in 0.3% overall yield. The product displayed spectral and melting point properties identical to an authentic sample as isolated from cork[39].

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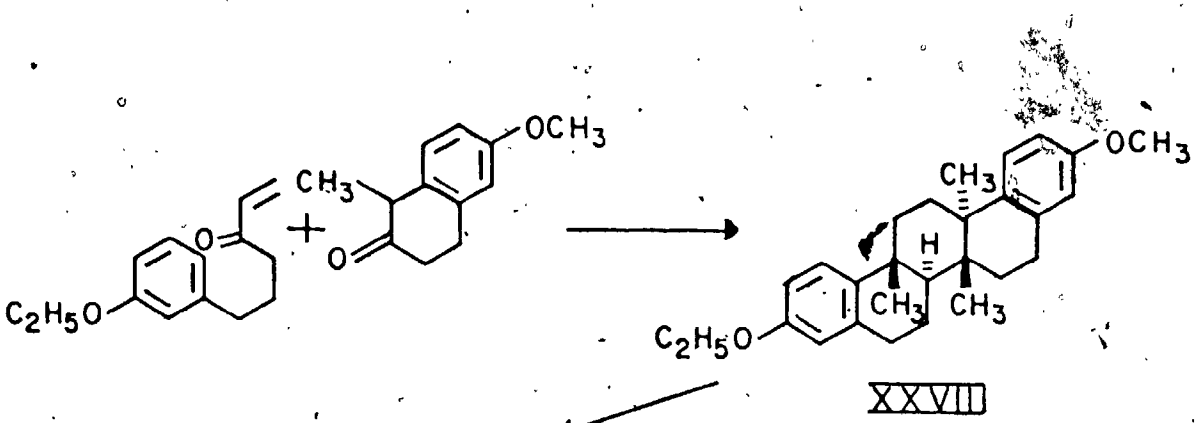
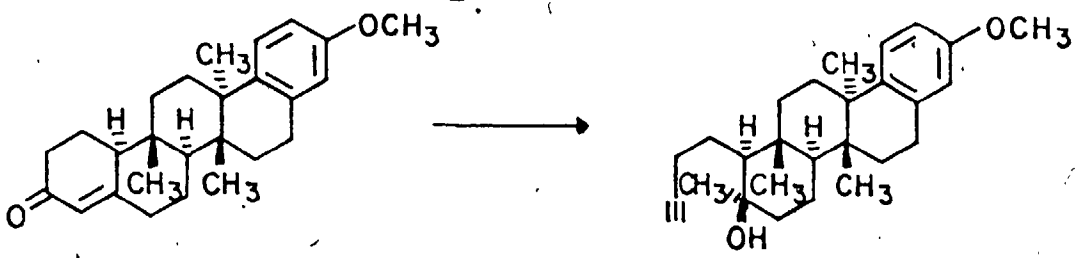
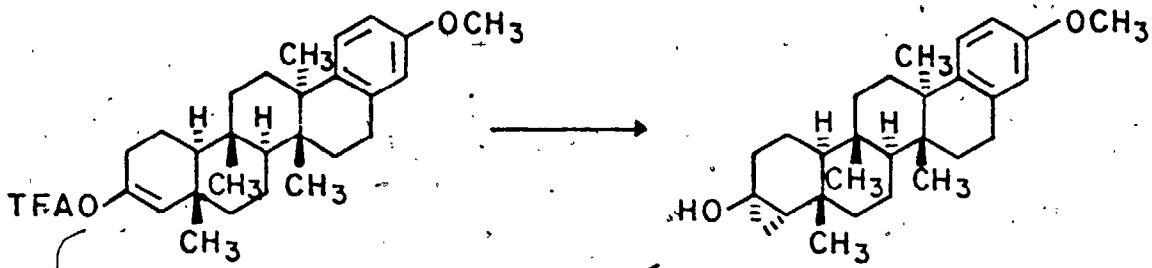
* See Appendix I for the Systematic numbering of typical triterpene skeletons.



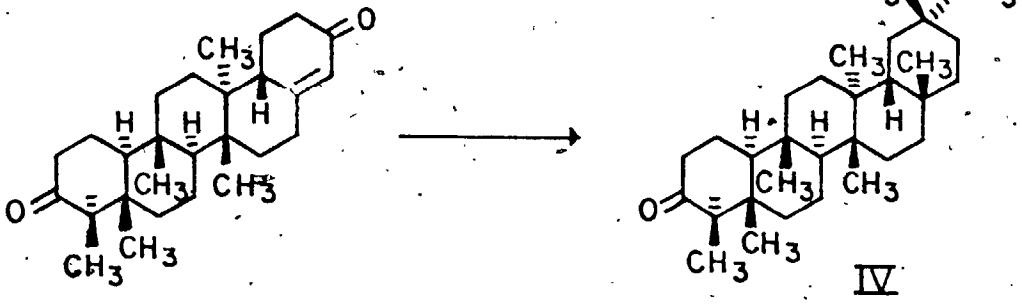
XXVIII



XXIX XXX

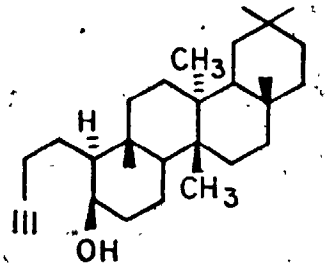


XXXI XXXII



XXXIII IV

31 steps, .3% overall yield

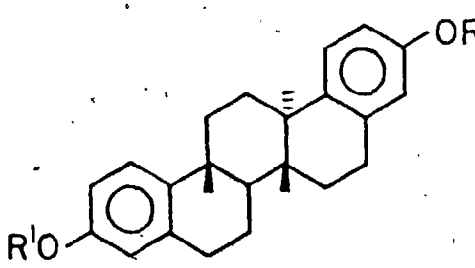


XXXIV

CHART E

3 Formal Total Syntheses of (±) Alnusenone and (±) Friedelin

Recently Kametani and fellow Japanese workers[40] reported formal total syntheses of ± alnusenone XI and friedelin IV by virtue of the stereoselective syntheses of the two key diethers XXXV[33] and XXVIII[27] which have been respectively transformed into ± alnusenone and ± friedelin by Ireland and co-workers[33,27].



XXVIII : $R^1 = C_2H_5$, $R^2 = CH_3$

XXXV : $R^1 = CH_3$, $R^2 = C_2H_5$

It has been found that o-quinodimethanes[42] (derived from benzocyclobutenes[41]) undergo stereo- and regio-selective cyclization reactions and such cyclizations have been applied in the synthesis of estrone[44] and of intermediates in the synthesis of atisine[45]. From this background came the idea that the A and B rings of a pentacycle could be constructed from the Tetralin derivatives which would result from the cycloaddition of benzocyclobutenes to isoprene. Introduction of another benzocyclobutene residue with the proper structure to give rise to the C, D and E rings could then precede intramolecular cycloaddition leading to a pentacyclic array.

The key benzocyclobutene iodide XXXV synthesized via the scheme outlined in Chart F, represents the unit which will correspond to the C,D,E rings of intermediate diether XXXV in the synthesis of ± alnusenone[33].

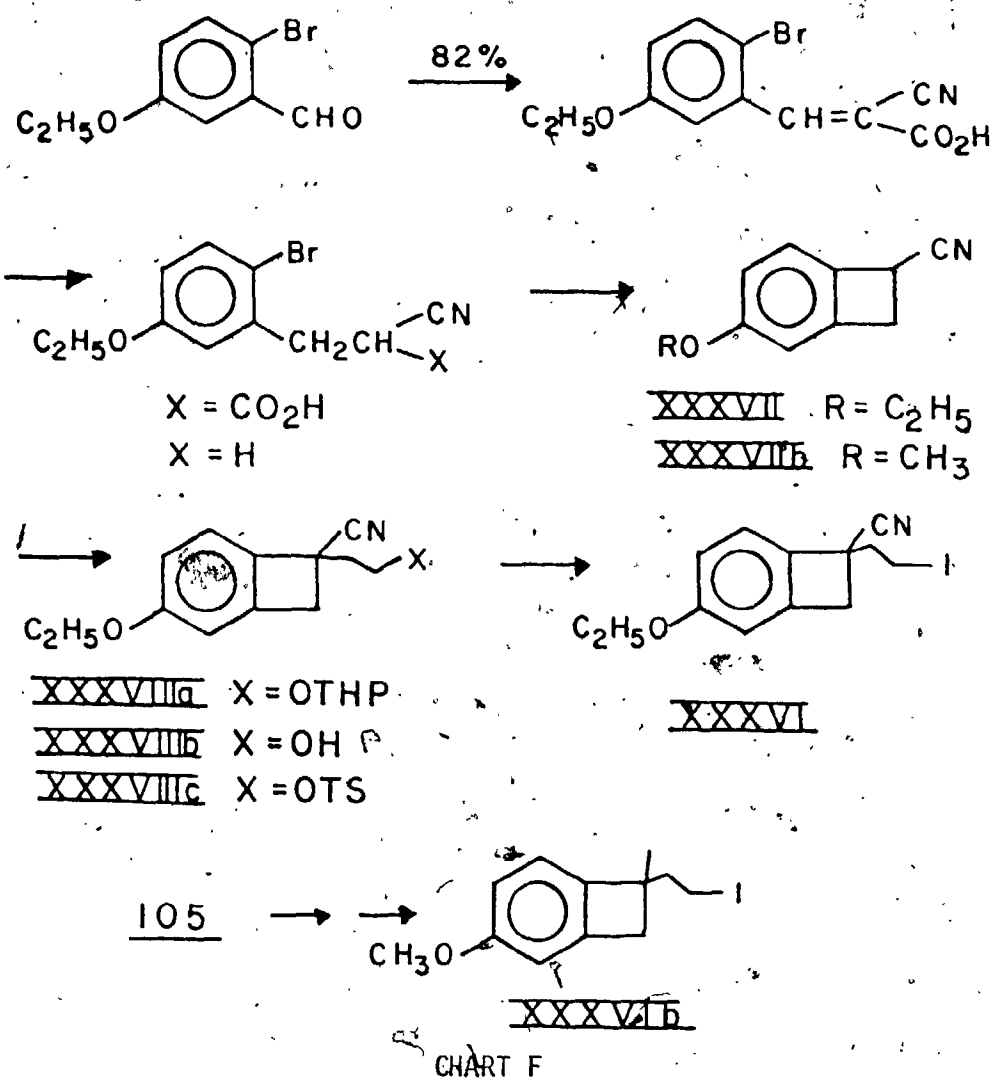
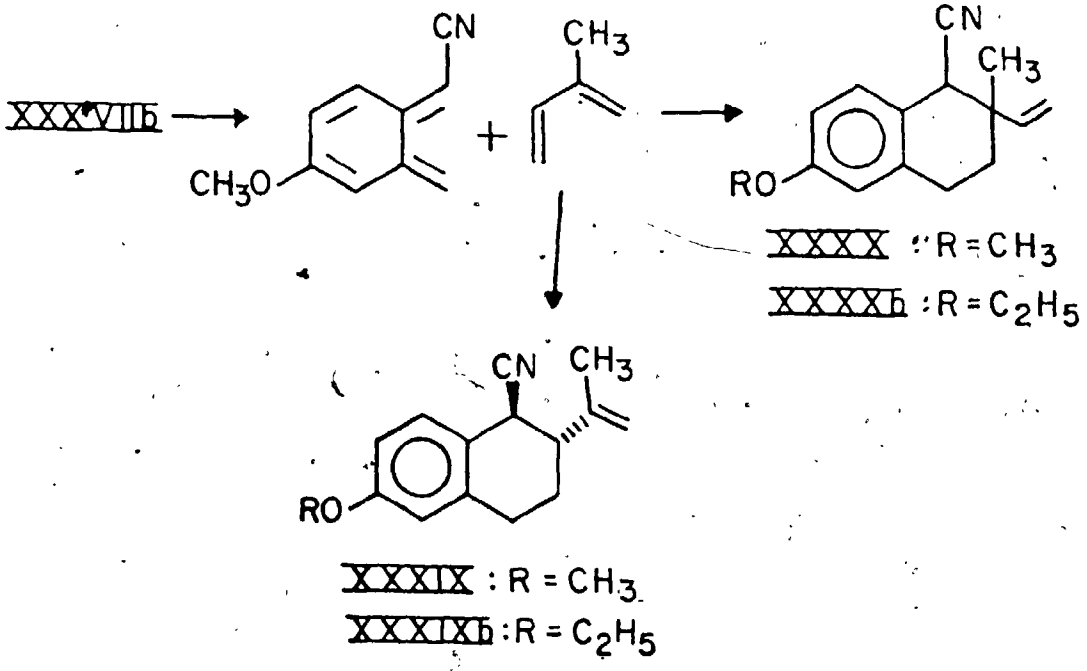


CHART F

The A and B ring system of XXXV was synthesized from the benzocyclobutene XXXVIIb (Chart F) by the intermolecular cycloaddition of the latter with isoprene which yielded the methoxy isopropenyl Tetralin XXXIX in 42% yield together with a diastereomeric mixture of vinyl Tetralins XXXX also in 42% yield (Chart G). Similarly XXXVII yielded via the same process XXXIXb and XXXXb in comparable respective yields.

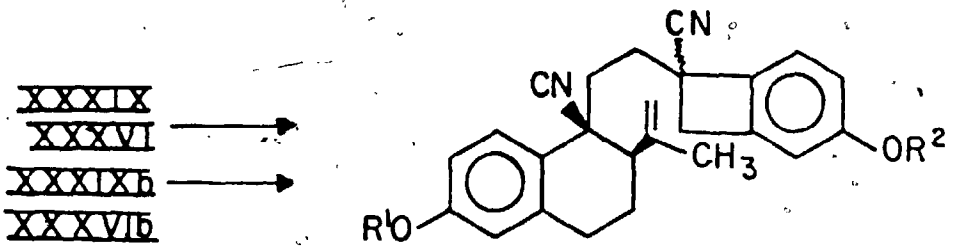


XXXX : R = CH_3

XXXXb : R = C_2H_5

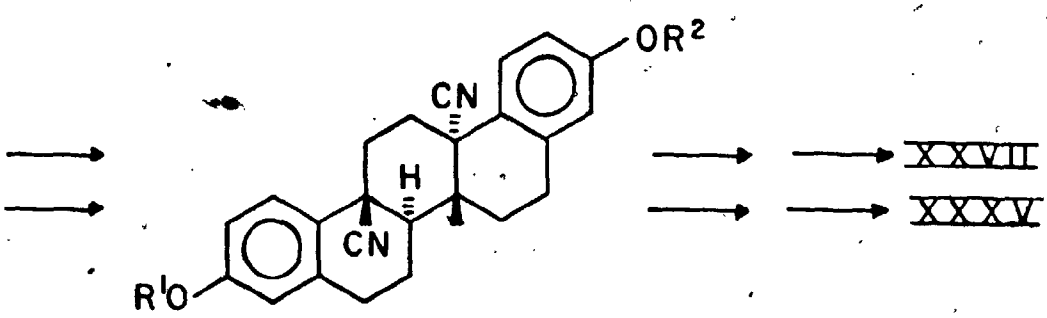
XXXIX : R = CH_3

XXXIXb : R = C_2H_5



XXXXI $R^1 = CH_3$ $R^2 = C_2H_5$

XXXXIb $R^1 = C_2H_5$ $R^2 = CH_3$



XXXXII : $R^1 = CH_3$ $R^2 = C_2H_5$

XXXXIIb : $R^1 = C_2H_5$ $R^2 = CH_3$

CHART G

Condensation of the isopropenyl Tetralin XXXIX with XXXVI yielded the adduct XXXXI by alkylation from the less hindered site at C-1 of the Tetralin system (Chart G). This underwent cycloaddition (sealed tube at 210-215°C for 3 hr) to the dinitrile XXXXII in 58% yield. Conversion of XXXXII via DibalH and Wolff-Kishner reductions along standard lines[46,36] yielded the pentacyclic diether XXXV in 44% yield, the spectral and melting point data of which were identical to an authentic sample[33].

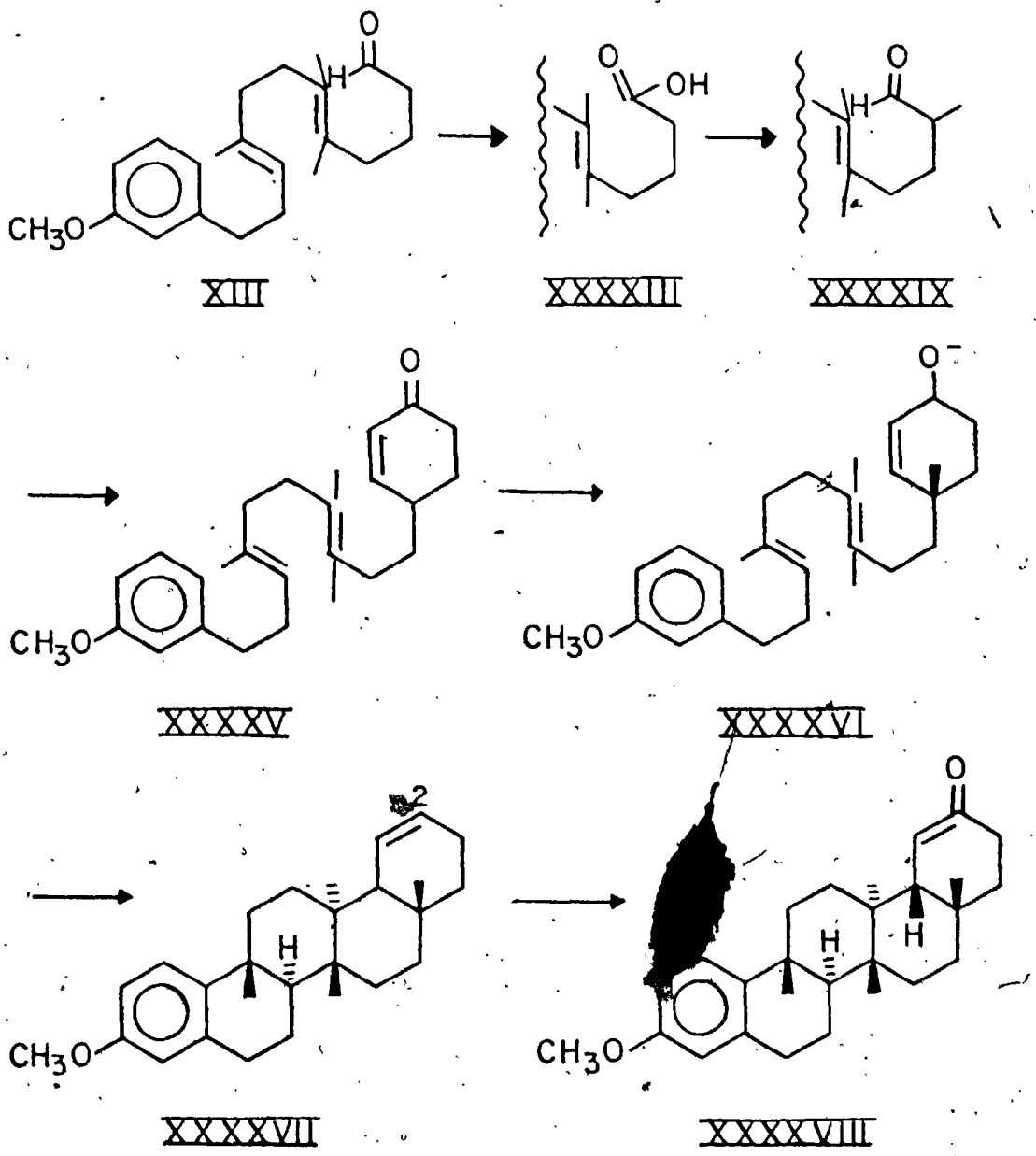
Similarly, thermolysis of XXXXIb derived as in Chart 9 led to the dinitrile XXXXIIb, which was converted in like manner to the diether XXVIII, which had been transformed previously into (±) friedelin by Ireland[27].

APPROACHES TO PENTACYCLIC TRITERPENE SYNTHESIS

In addition to the total syntheses previously described wherein specific natural products were the target compounds, a major part of the research effort in the area of triterpene synthesis has been directed towards devising general entries into pentacyclic triterpenes. To this end there has been a plethora of synthetic reports in which a variety of synthons have been proposed as suitable intermediates in pentacyclic triterpene syntheses.

Ireland and co-workers[47] have reported an entry into pentacyclic triterpene systems via the polyene cyclization approaches used previously[26,30,36]. In this work[47], the potential of the 4-methyl-2-cyclohexenol systems XXXXIII (Chart H) as suitable substrates for initiation of the acid catalysed cyclization[48] have been explored. This is in contrast to the cyclopentenol system XXIII (Chart D) and appeared to have the advantage

of formation of a pentacyclic intermediate in which ring E is already six-membered and bears the desired C-17 methyl group as a cis D/E ring fusion. This avoids the necessity for such a critical transformation, which has been inherent in the two previous approaches to ± alnusenone[33] and to ± friedelin[27].



XIII XXXXIII XXXXIX

XXXXV XXXXVI

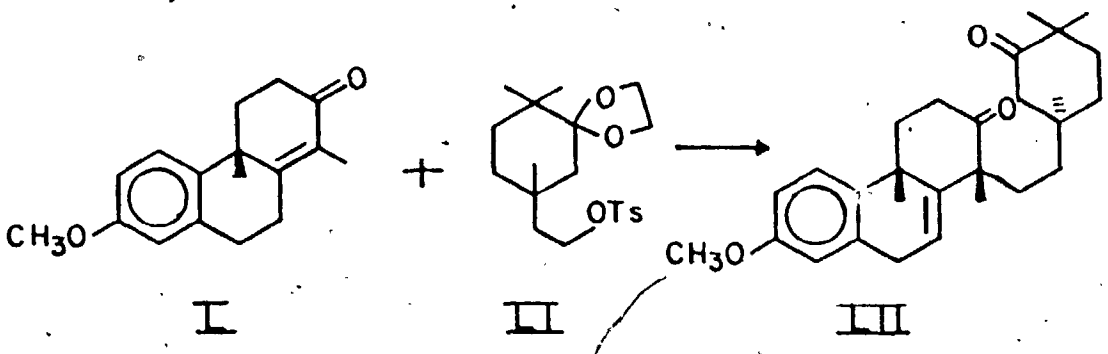
XXXXVII XXXXVIII

CHART II

The key aldehyde XIII[36] (Chart C) was converted to the cyclohexenol system XXXXIII (Chart H) in good yield, but poor yields resulted from the stannic chloride / dichloromethane /ethylene carbonate[38a] cyclization of the latter. However, the stereochemical soundness of this approach prompted further pursuit. Conversion of the olefin XXXXVII to the pentacyclic ketone XXXXVIII proceeded smoothly; however the serious steric congestion about the substituents at C-2 as a result of the cis D/E ring fusion and the proximity of the C-14a α-methyl group, thwarted all efforts to introduce the gem-dimethyl group into XXXXVIII. Efforts to effect such a transformation are no doubt currently being expended.

ApSimon et al[2] have reported the convergent synthesis of a pentacyclic compound XXXXIX which appears to be a suitable synthon in the synthesis of pentacyclic triterpenes.

The two key starting materials used in this study[2] were the tricyclic ketone L[49] and the tosylate LI[2]; the synthesis of the latter is shown in Chart I. Alkylation of L with LI via its dienolate anion, using the Stork method[50], gave the diastereomeric mixture of diketones LII a and b, after deketalization. However, base catalysed intramolecular cyclization of LII met with absolutely no success , although a wide variety of bases were tried. Acid catalysed systems were examined and in boiling xylene with p-toluene sulfonic acid as catalyst, LII underwent a complex rearrangement[5] (See Results and Discussion - Section I).



I II III

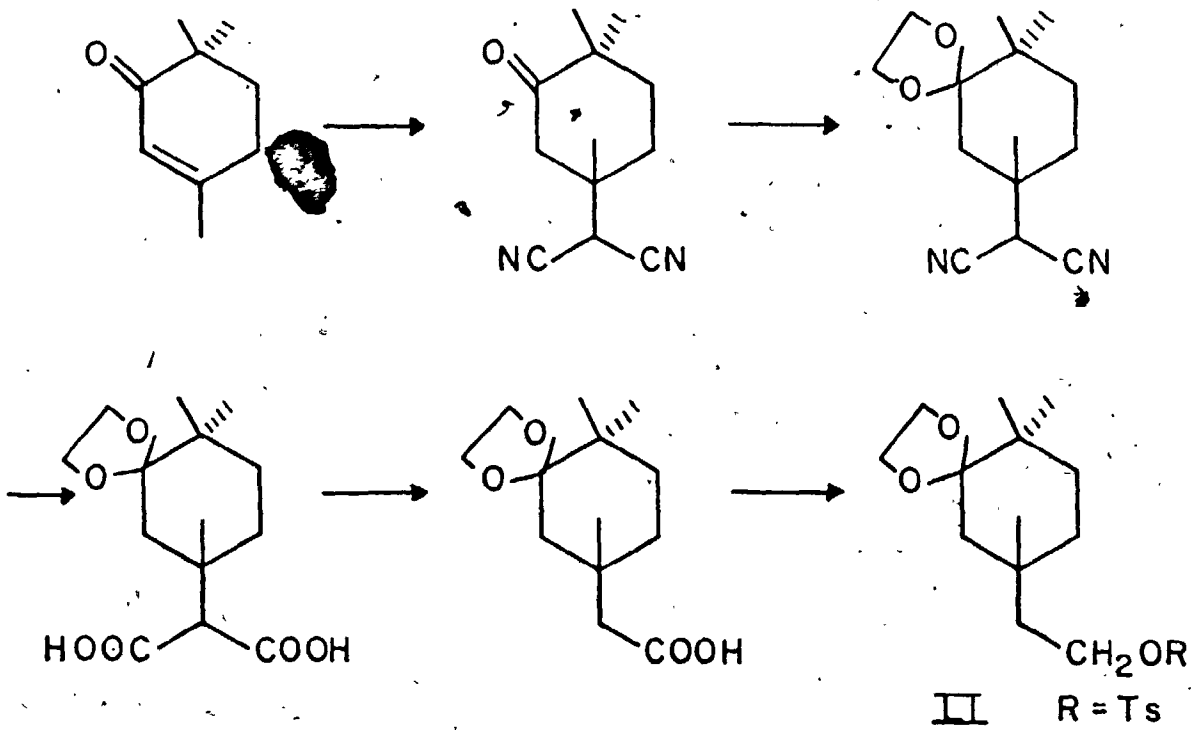
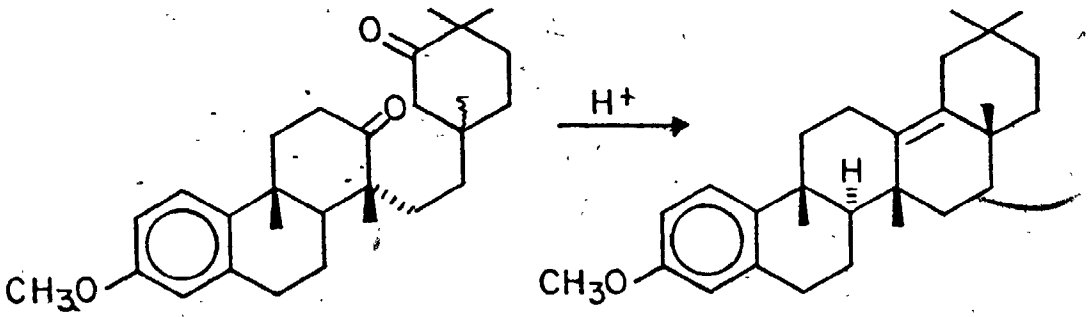


CHART I

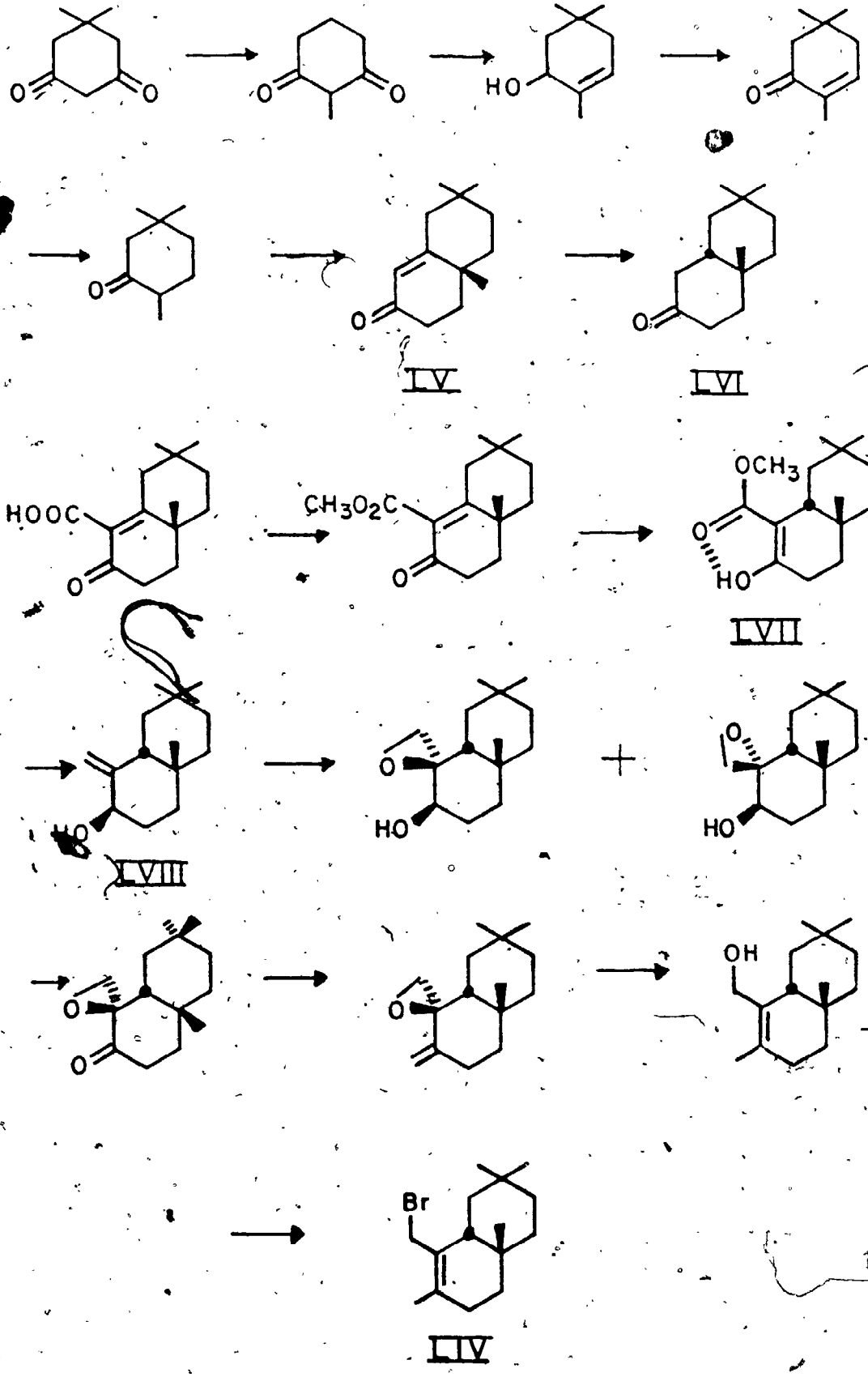
It appeared that the C-10-C-10a double bond could be a major contributor to the failure of cyclization and to the propensity for rearrangement. Stereoselective hydrogenation[49] of the double bond yielded the mixture of diketones LIII, both components of which appeared to cyclize in boiling xylene with p-toluene sulfonic acid as catalyst. However one product crystallized after chromatographic purification and based on its spectral characteristics was assigned the structure XXXXIX. Subsequently this structure was confirmed by single crystal x-ray diffraction. Conversion of XXXXIX into a natural product is currently in progress.



LIII XXXXIX

As a result of their continuing interest in the AB + DE → ABCDE approach to pentacyclic triterpenes, Heathcock and co-workers[51] have reported the synthesis of the bicyclic bromide LIV which is a viable synthon for the DE ring system of pentacyclic triterpenes of the germanicane class.

Originally, a key intermediate in the synthesis of LIV (Chart J) was viewed to be the decalone LVI first prepared by Halsall[52]. However, failure to suitably functionalize the latter prompted the use of the octalone LV (Chart J) as the key starting material. It is interesting

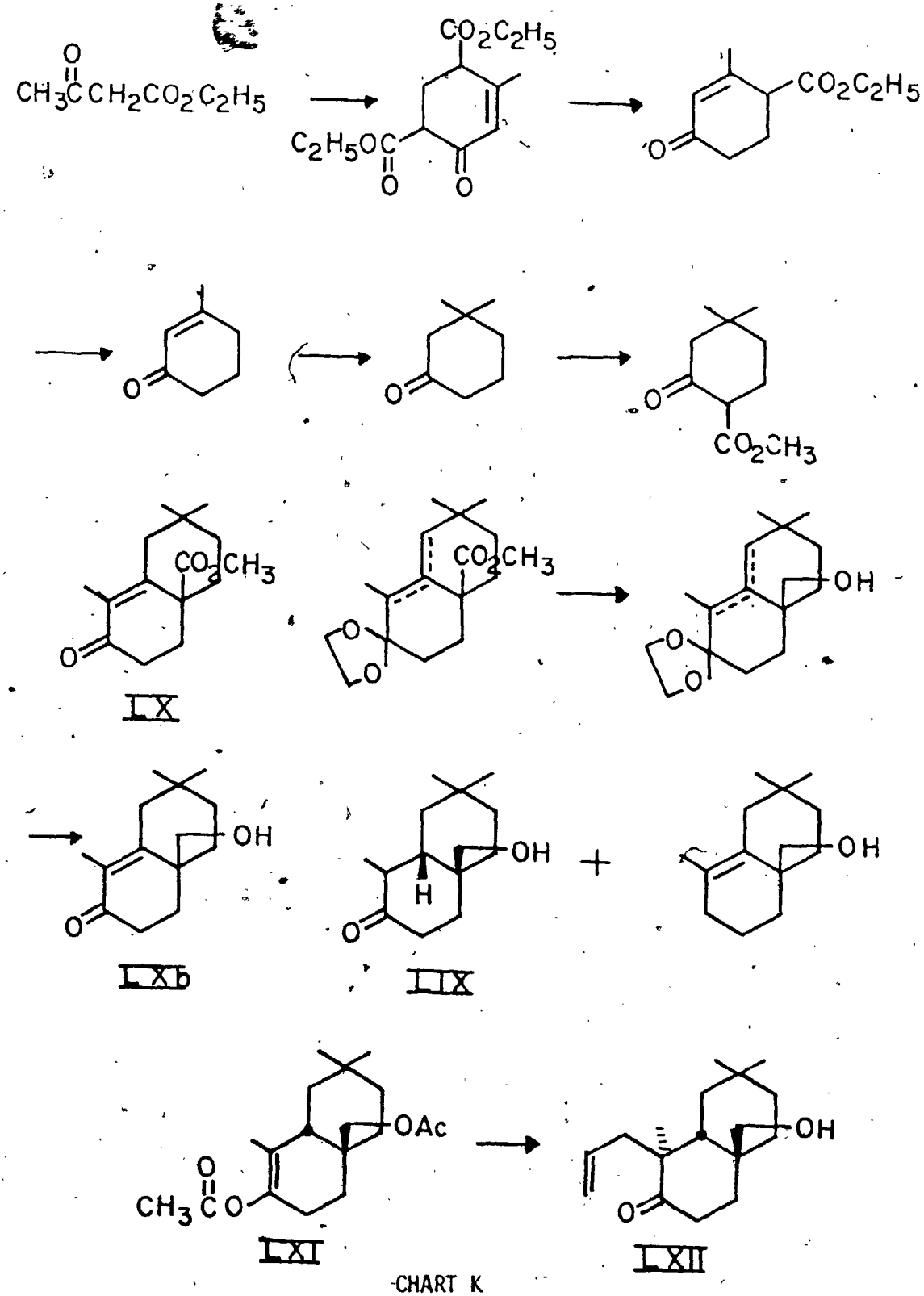


LV LVI LVII LVIII LIV

CHART J

to note that the β-keto ester LVII seems to exist totally in the chelated enolic form based on its infra-red spectrum. Further lithium aluminium hydride reduction of LVII gave the equatorial allylic alcohol LVIII in high yield indicating unusual attack of hydride from the axial direction. The peroxidation /Wittig methylenation route to the bromide LIV was chosen since elaboration of LVIII via the derived enone gave very poor yields. An alternative synthesis of LIV was reported previou by van Tamelen[53]. ApSimon et al[54], have also reported a synthon corresponding to rings D and E of several pentacyclic triterpenes. This synthon is the cis decalone LIX, the synthesis of which is described in Chart K.

Catalytic hydrogenation of the key octalone ester LX, following literature precedents[51,52,55], resulted in a variety of products, depending on the conditions used, with the trans-fused-junction predominating. Thus, the haptophilic properties of the hydroxymethyl group of the hydroxy enone LXb[56] was utilized to reverse the stereochemistry of the double bond hydrogenation. Catalytic hydrogenation of LX proceeded smoothly to give the cis decalone LIX. β-Face alkylation of LIX at C-1 gave disappointing results; although this group[54] was able to obtain in low yield, a product LXII (structure tentatively assigned) from the alkylation of the enol acetate LXI with allyl bromide. Work is currently in progress aimed at achieving β-face alkylation at C-1.



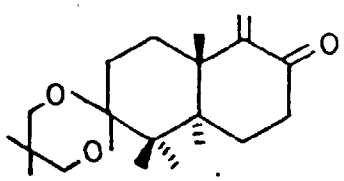
LX LXb LIX LXI LXII

CHART K

CHIRAL SYNTHESES

Although much research has gone into the syntheses of racemic pentacyclic triterpenes, very little has been done by way of chiral syntheses of the said compounds.

Recently Heathcock et al[57] reported the synthesis of the bicyclic enone LXIII in both its racemic form and as its optically pure levorotatory and dextrorotatory enantiomers.



LXIII

Such an intermediate is a suitable precursor to the AB ring systems in pentacyclic triterpenes such as the amyrins and lupeol.

The key intermediate in the synthesis of LXIII is olefinic ketal LXIV formed from the ketalization of the olefinic mixture LXVa,b and c, (Chart L)

The latter themselves were formed by the acid catalysed dehydration of the tertiary alcohols LXVIa and b.

The most efficient route from LXIV to the enone LXIII was found via the epoxides LXVII a and b, (Chart M.) These epoxides were converted using lithium di-n-propylamide to the mixture of alcohols LXVIII a,b, and c which were oxidized to the desired enone LXIII together with one third as much of the enone LXIX, the latter resulting from allylic rearrangement of the intermediate chromate ester[58].

In the enantiomeric series, the enone LXX was converted to the hydrogen phthalate LXXI and was resolved via the brucine salt.

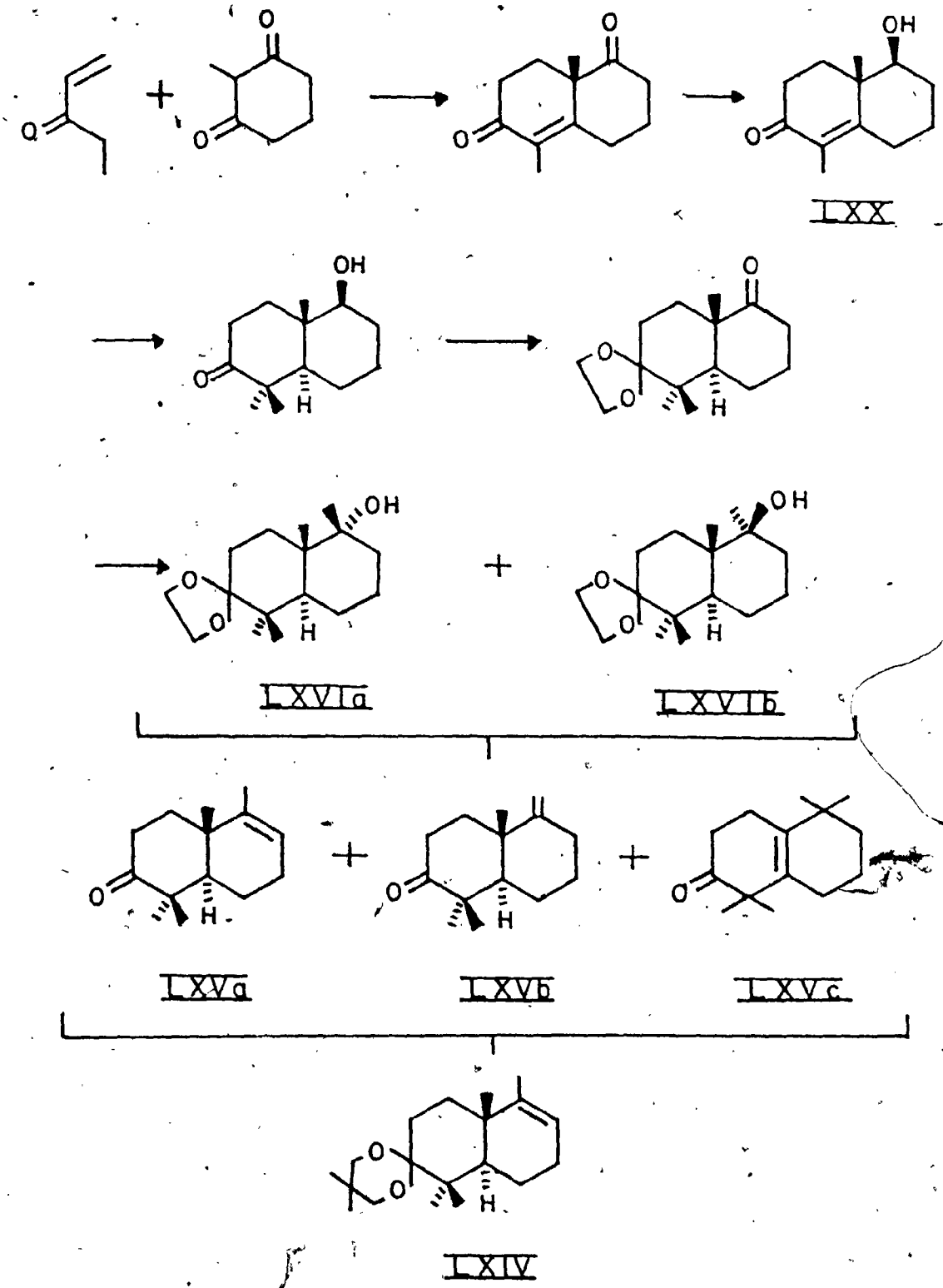
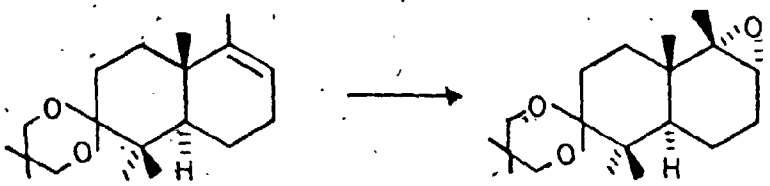


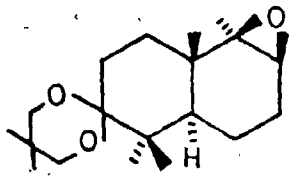
CHART L



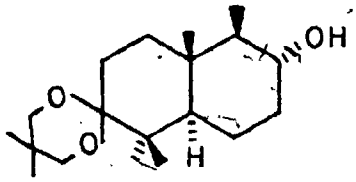
LXVI

LXVIIa

+

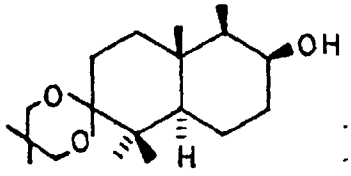


LXVIIb

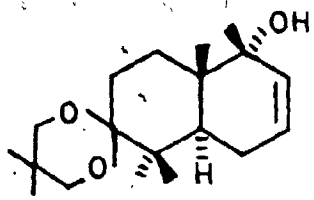


LXVIIIa

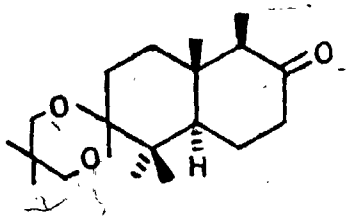
+



LXVIIIb

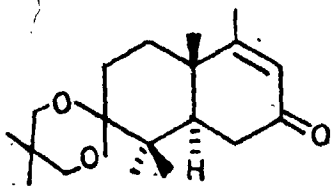


LXVIIIc



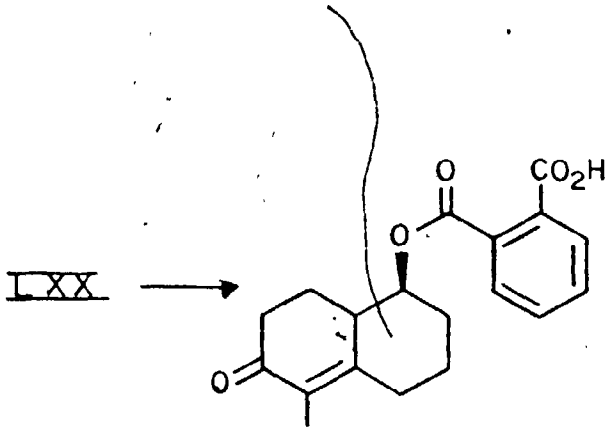
LXIII

+



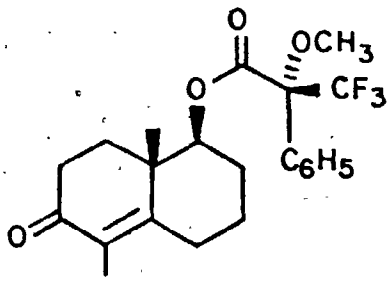
LXIX

CHART M

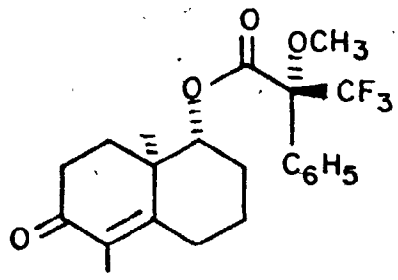


LXX → LXXI

Selective preferential crystallization led to optically pure dextrorotatory and levorotatory salts. Careful acid hydrolysis back to (+) and (-) LXXI followed by base hydrolysis afforded 31% (+) LXX $[\alpha]_D$ + 162.7° and 28% (-) LXX $[\alpha]_D$ - 171.6° as enantiomers which are liquids at room temperature. Racemic LXX is a crystalline solid (m.pt 88-89°C.) Optical purities for the resolved alcohols were determined by Mosher's method[59] using the (+)-α-methoxy-α-trifluoromethylphenylacetyl esters LXXII and LXXIII. Optically pure (-) LXX ($[\alpha]_D$ - 164.4°) was converted via the scheme already shown to the optically pure enone (+) LXIII ($[\alpha]_D$ + 66.9°). The levorotatory enantiomer of enone LXIII ($[\alpha]_D$ - 67°) has the absolute configuration required for the AB rings of certain pentacyclic triterpenes.



LXXII



LXXIII

RESULTS AND DISCUSSION

For many years, these laboratories have been concerned with the synthesis of pentacyclic triterpenes (see Ref. 5 and pertinent references therein). Essentially, the major thrust of these research efforts has been in devising a general entry into the pentacyclic array, which could lead to different classes of pentacyclic triterpenes. However Friedelin IV which, because of its greater complexity has for a long time been synthetically elusive[24], has for the most part served as a target compound.

Synthetic convergence and logistic economy have always circumscribed the synthetic routes of choice in these laboratories. However, the essence of the overall synthetic strategy of the group has been the interlocking nature of the routes chosen. That is to say synthons were designed in such a way that they could form part of more than one route, i.e. an E ring synthon for a BC + E → BCDE → ABCDE approach should be transposable without much modification into an ABC + E → ABCDE approach. The studies described in this thesis fall under this synthetic umbrella and represent three different strategies: (illustrated in Chart N).

1 SECTION 1: The BC + E → BCDE → ABCDE Approach.

2 SECTION 2: The CDE + A → ABCDE Approach.

3 SECTION 3: The ABC + E → ABCDE Approach.

Further, in as much as only very little effort has been expended in the area of asymmetric synthesis of triterpenes in general, it was decided to venture into this area by construction of a key chiral synthon which

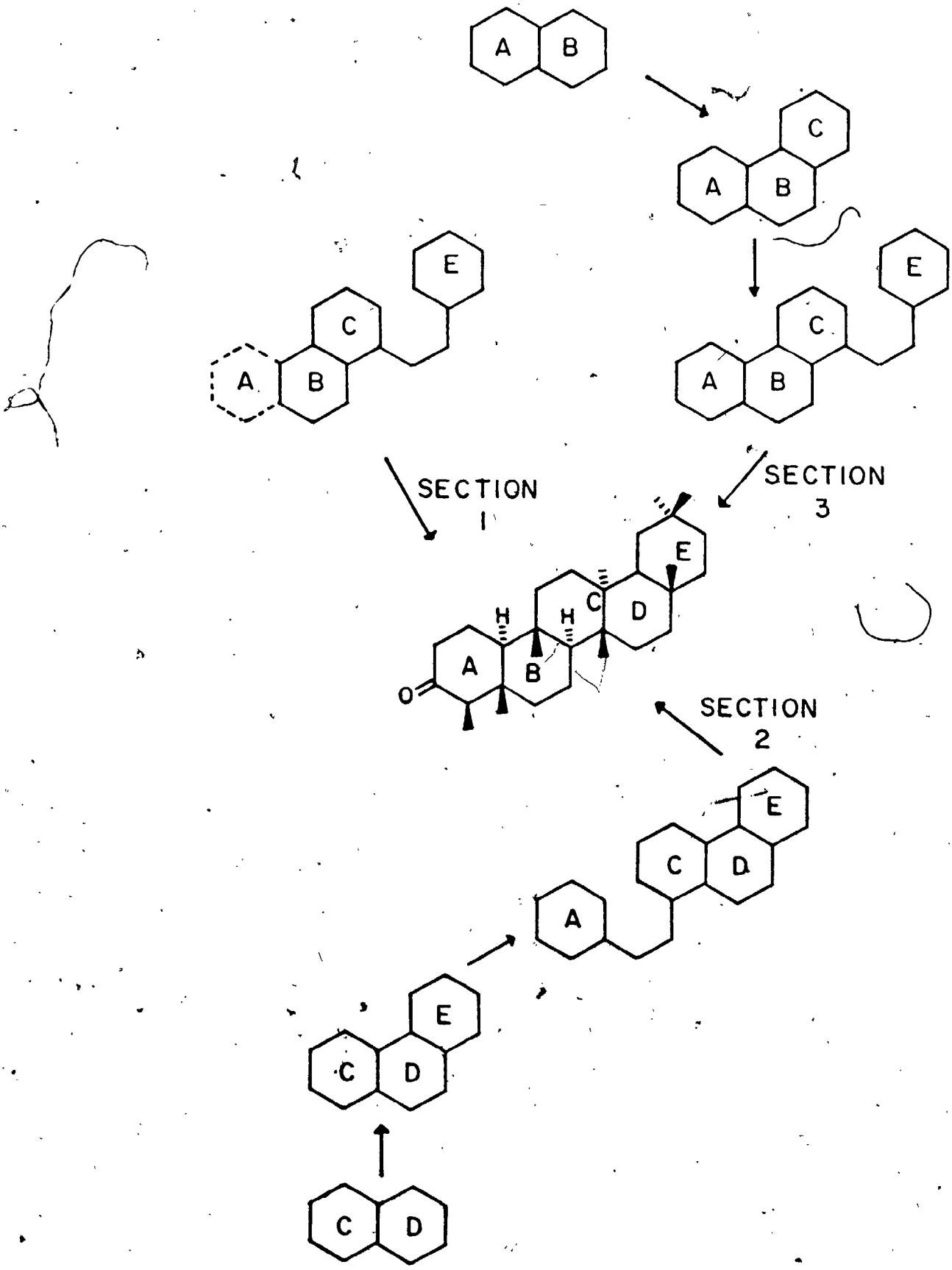

A
B
C
A
B
E
C
A
B
E
C
A
B
SECTION
1
SECTION
3
E
C
D
H
H
A
B
O
SECTION
2
E
C
D
A
E
C
D
C
D

CHART N

could be elaborated via stereospecific transformations into a chiral pentacyclic system.

Based on the methodology worked out in the asymmetric syntheses of steroids[60], the CDE + A → ABCDE route was chosen to explore this area. Hence section 2 essentially describes approaches to the asymmetric synthesis of a key chiral synthon which could correspond to the CDE rings of a pentacyclic triterpene.

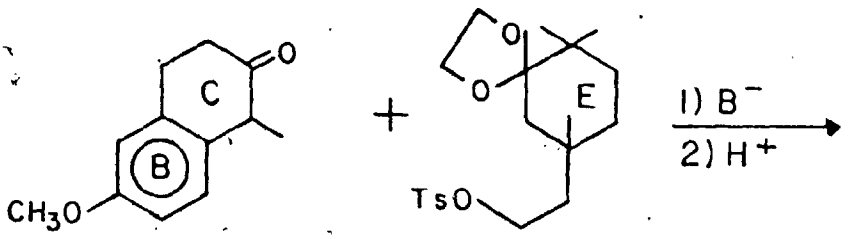
SECTION 1

The BC + E → BCDE → ABCDE Approach

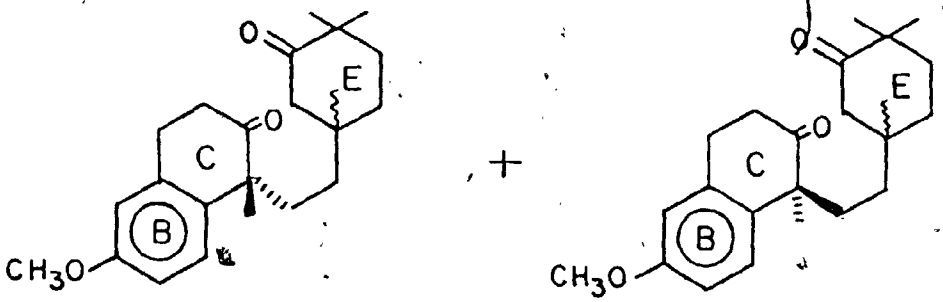
Studies on the cyclization of 2-keto-1-methyl-1-(2-(3-keto-1,4,4-trimethyl cyclohexyl))-6-methoxy-3,4-dihydronapthalene (1a) and its C-1 α-methyl pair of diastereomers (1b)

In our laboratories, the diastereomeric compounds 1a and 1b[1] (Scheme 1) were viewed as possible precursors to the tetracyclic array of 6-membered rings 4a and 4b which themselves would be useful synthons in the synthesis of pentacyclic triterpenes such as Friedelin IV and β-amyrin III.

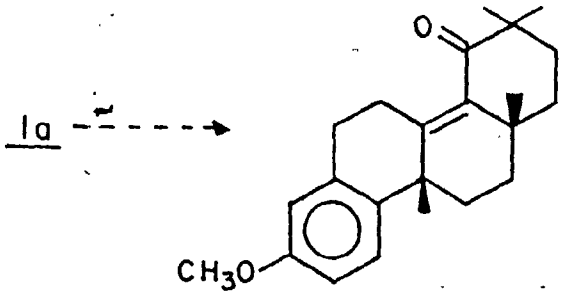
The promise held for the diketones 1a and 1b was based in part on the encouraging results obtained in a related study[2] in which both components of the mixture of diketones 5 appeared to cyclize under acid catalyzed conditions and the pentacycle 6 crystallized out, (see Introduction).



2 + 3 (LI)

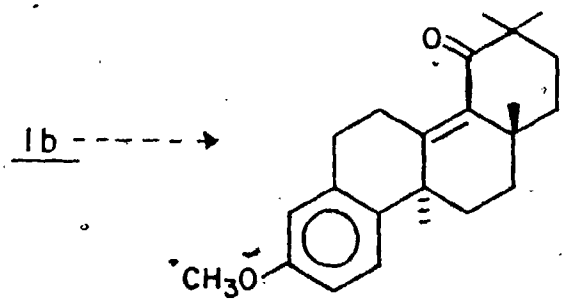


1a (d,l) + 1b (d,l)



→ FRIEDELIN IV

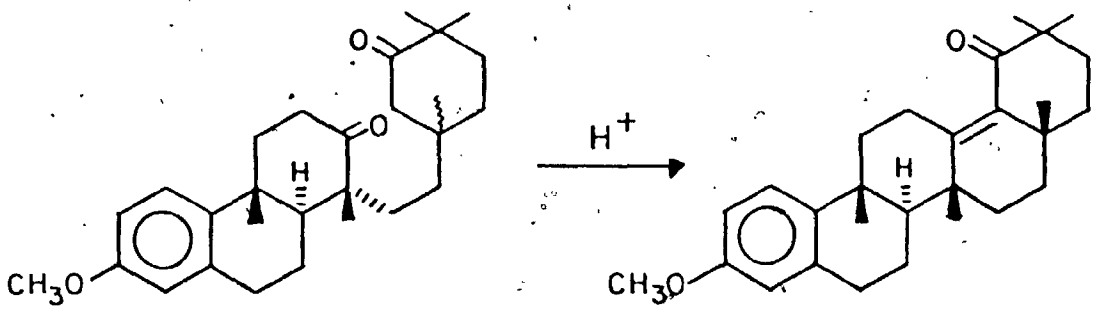
4a



→ β-AMYRIN III

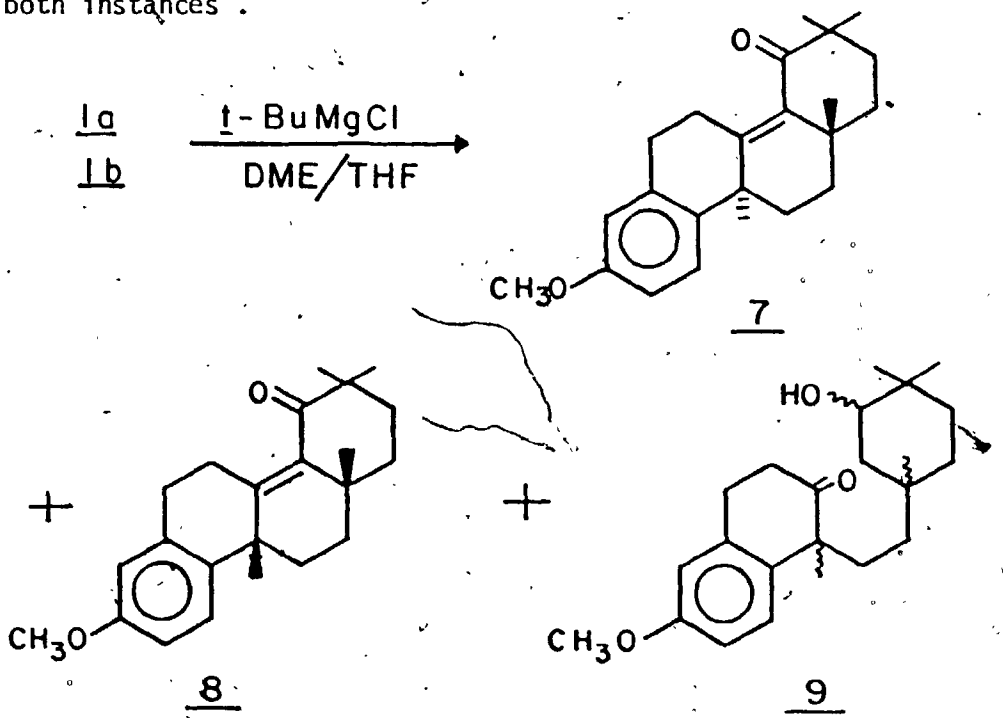
4b

SCHEME 1



5 (LIII) 6 (XXXXIX)

In addition, previous studies in these laboratories had shown that the 1-α-methyl-1'-β-methyl isomer of 1b does cyclize under basic conditions (tertbutyl magnesium chloride[3]) to the enone 7 (scheme 2) whose structure has been unambiguously determined by x-ray crystallography. Only traces of enone 8 were obtained when 1a was subjected to the same conditions. A low yield of the keto alcohol 9 was also obtained in both instances[2].

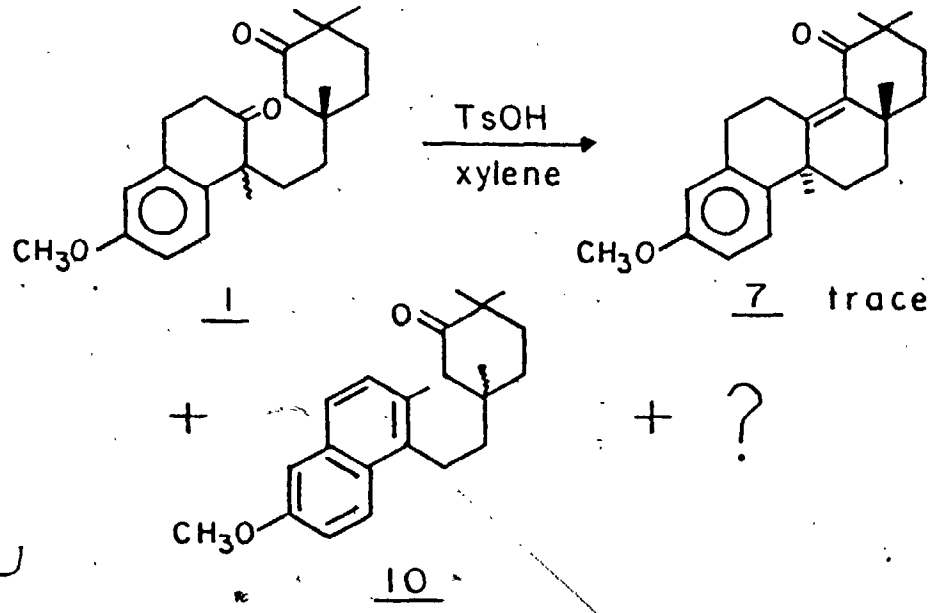


SCHEME 2

Hence studies on the acid catalysed internal aldol condensation of 1a and 1b were undertaken. 1a and b were prepared by the alkylation of the tetralone 2[4] with the tosylate 3[2] using the Stork method[4], followed by cleavage of the ketal function.

Refluxing of the diketone 1a and b in xylene in the presence of seven equivalents of p-toluene sulfonic acid resulted in an array of products. There appeared to be two major products, and analytical thin layer chromatography (tlc) suggested that one of the minor products corresponded to the enone 7. Chromatographic separation did provide 7 in very low yield (Scheme 3).

The crystalline major product of this attempted cyclization (38-45%), has, after much deliberation, been assigned the naphthalenic structure 10 (mpt. 96-97°C), based on its spectral data.

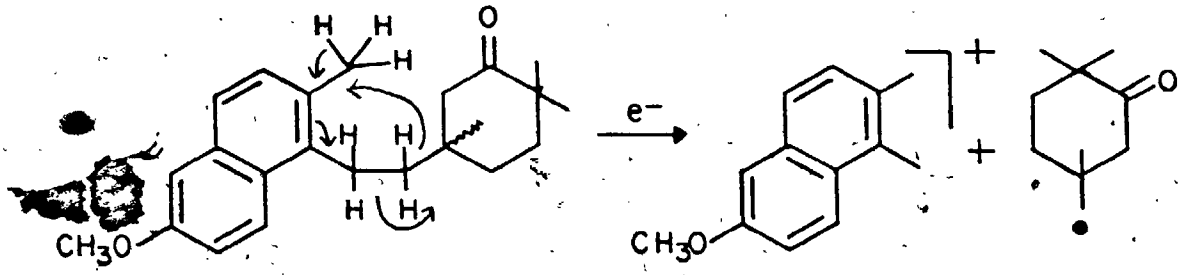


SCHEME 3

Thus, the infra-red spectrum of 10 displayed a saturated carbonyl absorption at 1705 cm^{-1} together with characteristic aromatic absorptions

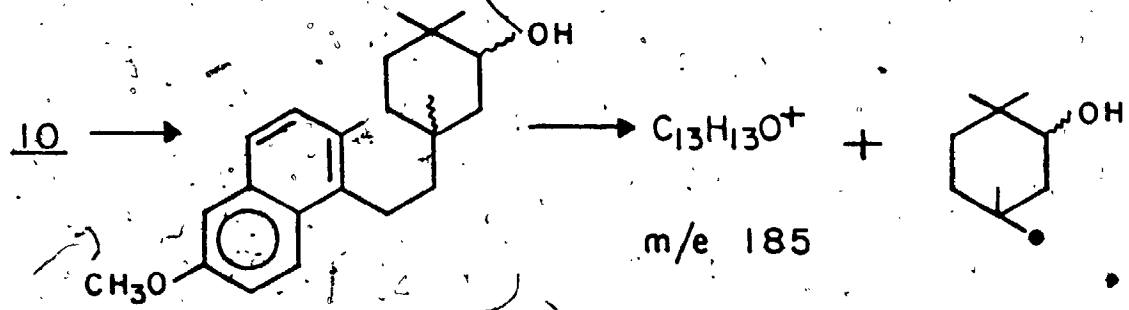
(1612 cm^{-1}; 2000 - 1750 cm^{-1} - overtones). The proton nmr spectrum (Appendix II Spectrum 1) displayed, in addition to the methoxy methyl at δ = 3.9 ppm, a low field 3 proton singlet at δ = 2.4 ppm and an unresolved 2 proton doublet of doublets at slightly lower field. These signals suggested methyl and methylene groups as aromatic substituents. Further, whereas the starting material displayed the required three aromatic protons signals in its nmr spectrum, that of 10 showed five such protons.

The mass spectrum of 10 contributed to a great extent in the assignment of its structure. Mass spectral benzylic cleavage in 10 would mean loss of a $C_{10}H_{17}O$ fragment, giving rise to a charged species of m/e 185.



m/e 185

The mass spectral contribution to structural assignment of 10 was tested by reduction of the carbonyl function and comparison of the mass spectrum of the alcohol thus derived to that of its parent ketone. In the latter case a M-155 fragment i.e. the same m/e 185 was detected.

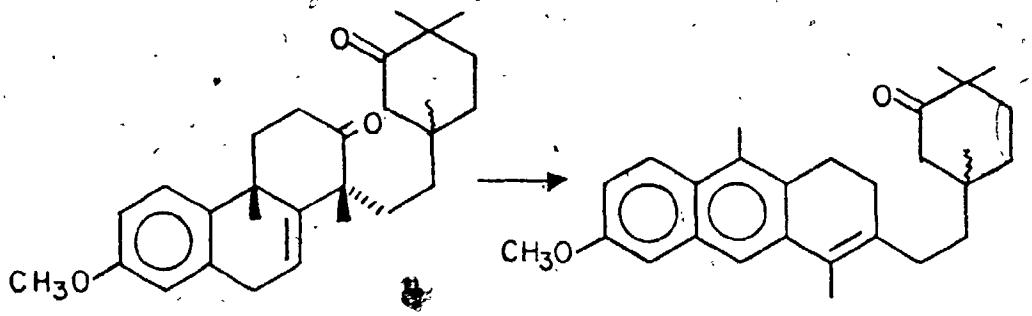


m/e 185

13

Finally assignment of structure 10 was underscored by results obtained soon after, in related studies in these laboratories[2,5].

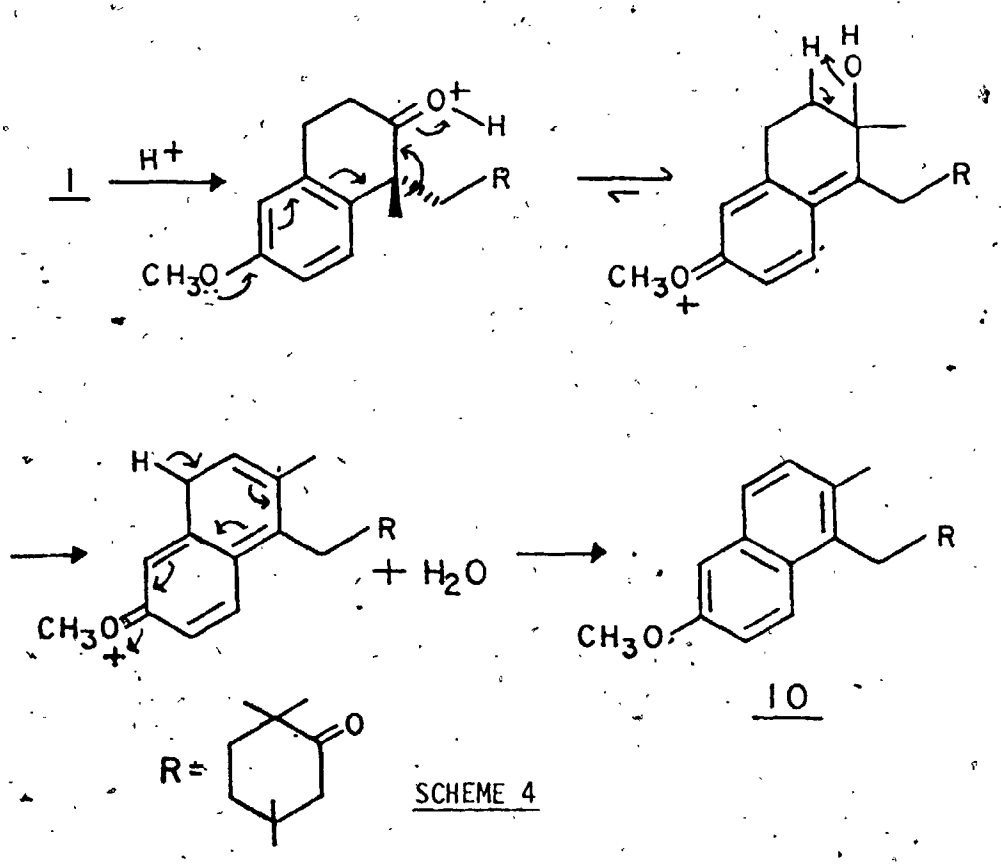
It was found[5] that the diketone 11 underwent an unusual acid catalysed rearrangement under similar reaction conditions, to the dihydroanthracene 12. The structure of 12 was unambiguously determined by single crystal x-ray diffraction.



11 (III)

12

A plausible mechanism for the rearrangement of 1 to 10 is outlined in Scheme 4[94].



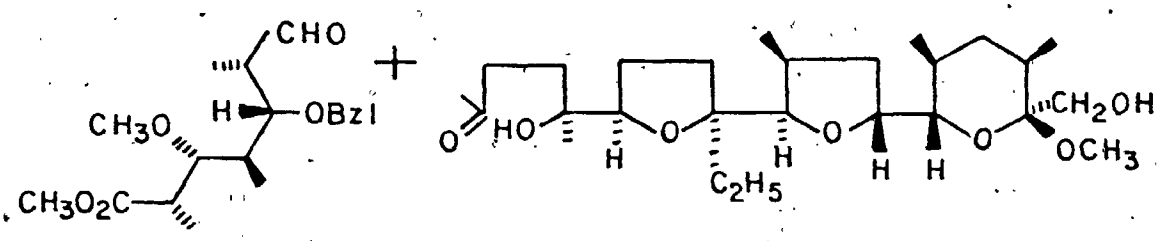
SCHEME 4

Extended efforts to grow a single crystal suitable for x-ray crystallography in order to categorically confirm this structure 10 have so far been unsuccessful. X-ray crystal structure determination will reveal which group - the methyl or the ethylcyclohexyl - did in fact migrate.

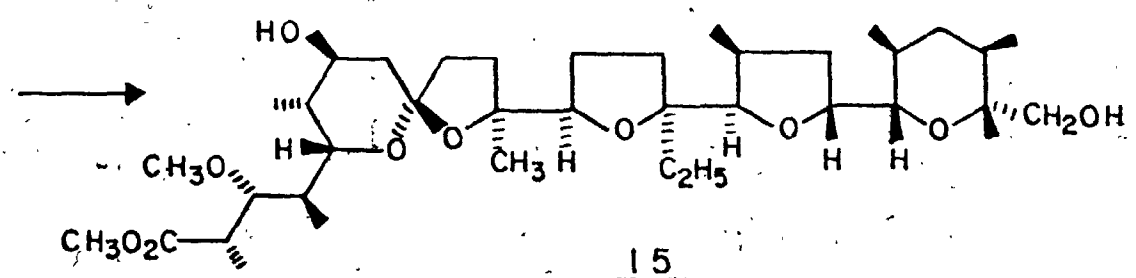
The other major product (18-22%), a non-crystalline material, more polar than the starting material, did not display the characteristics desired for an α-β unsaturated ketone in either its i.r. nor u.v. spectra. It was not characterized any further.

With the singular failure of the acid catalysed cyclization attempt to produce the desired enone 8, base catalysis was investigated once more. Since tert-butyl magnesium chloride was used successfully in the cyclization of 1b to produce 7, then it seemed reasonable in concept that perhaps a stronger or more hindered Grignard base would possibly promote the aldol condensation to produce 8.

The Grignard reagent of choice was di-isopropylamidomagnesium bromide[6] $(i\text{-}C_3H_7)_2NMgBr$. This choice was based on the success of Kishi's group[6] to effect a crucial and difficult aldol condensation between the two moieties 14a and 14b which eventually completed the total synthesis of monensin 15[6].



14a 14b



15

The diketones 1 were therefore separated into their diastereomeric component 1a and 1b by repetitive H.P.L.C. The stereochemistry of the two sets of isomers was assigned by monitoring the base catalysed cyclization to produce 7 whose stereochemistry at C-14* had been established by x-ray crystallography.

Thus, the diketones 1a were treated with 10 equivalents of the freshly prepared isopropylamido Grignard reagent at low temperatures[6], followed by refluxing in T.H.F. for extended periods - up to 110 hours.

These attempts also met with failure , only starting material being recovered together with low yields of a hydroxy compound - corresponding on tlc to 9.

With the failure of both acid and base catalysis to promote cyclization of 1a to 8, attention was turned to the possibility of activating the tetralone carbonyl to nucleophilic attack and at the same time introducing the α-methyl in some form, at the C-2 position.

The strategy here involved firstly the epoxidation of the tetralone carbonyl of the ketal ketone 16 - the precursor of 1a - using a sulfur methylide[7] in order to test the stereochemistry of epoxide formation. It was thought that if the stereochemically correct epoxide could be formed, then perhaps formation of the epoxide on a preformed enol silyl ether such as 18 could be possible[8]. This enol ether via the lithium enolate could then, perhaps, be induced to cleave the epoxide, giving rise to the cyclized product 19 having the hydroxy methyl function at C-13* in the stereochemically correct orientation.

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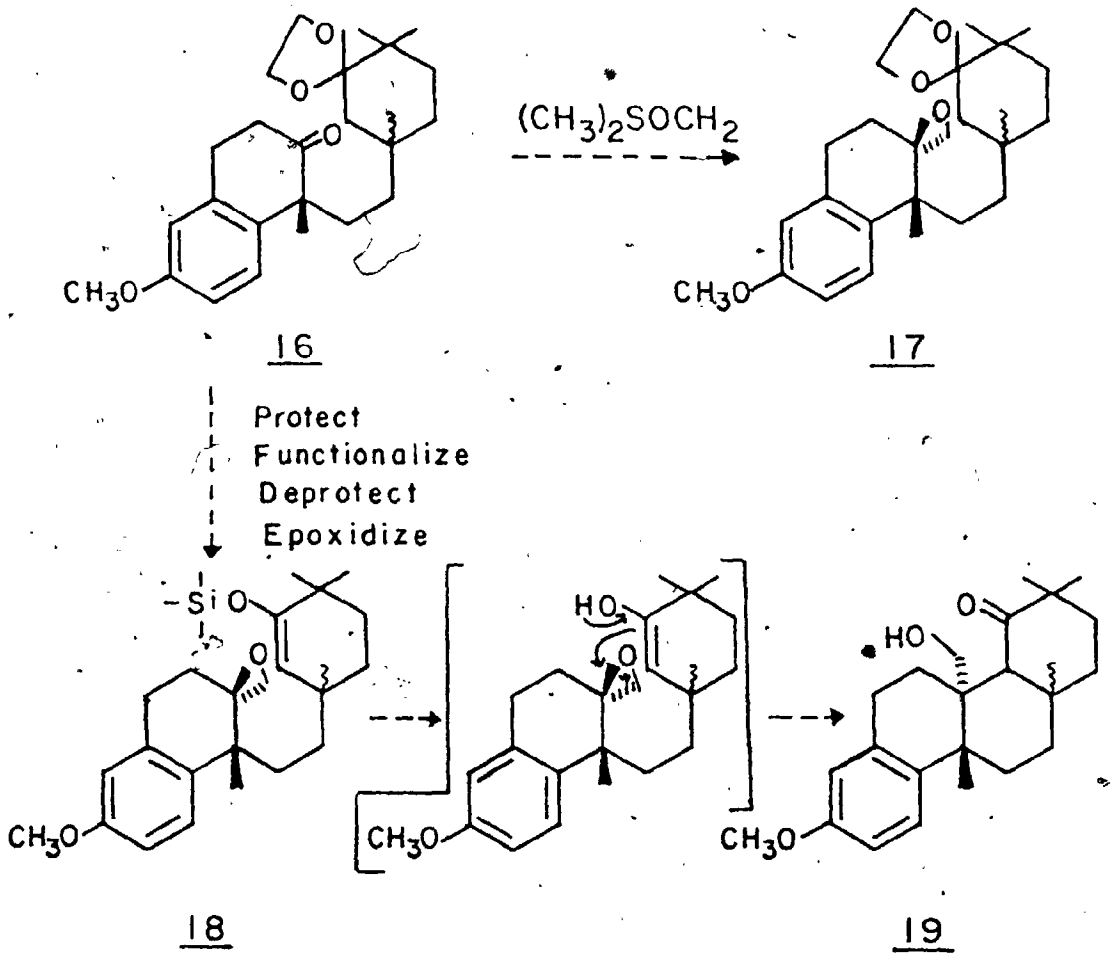
*Carbon numbering qualified by the superscript (*) represent the position that carbon atom will occupy in the target pentacyclic triterpene . See Appendix 1 - oleanane.



SCHEME 5

The ylid of choice was dimethyloxosulfonium methylide pioneered by Corey[9]. It was thought that such an ylid, rather than a sulfonium methylide, would cause attack from the least hindered face[10] giving rise to the β-epoxide which, if our concept was correct, should form the α-carbinol.

Repeated attempts to epoxidize 16 using the conditions of Corey[9] gave, in all instances, only the deketalized material 1a (i.r., n.m.r. and m.s. identical to authentic sample). In the event that these conditions for epoxidation were not optimum and in order to ensure a more stable epoxide, the halomethylaryl sulfones[11] were examined.

Using the phase transfer conditions of Makosza[12], the ketal ketone 16 was treated with chloromethyl phenyl sulfone[11] for extended periods. Mostly starting material was recovered together with small amounts of (< 10%) of a yellow crystalline material, the i.r. and n.m.r. spectra of which showed no epoxide grouping.

It was becoming obvious then, that the diketone system 1 would perhaps not serve as a critical synthon in the general entry into pentacyclic triterpenes. However its utility has not been totally ruled out, since 1b does show potential as a precursor to β-amyrin (scheme 1). Such a transformation is currently under study by other workers in these laboratories.

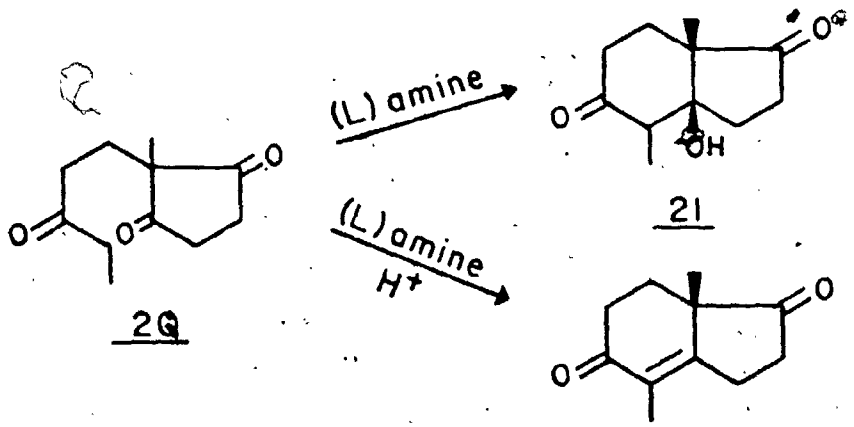
SECTION 2

The CDE + A → ABCDE Approach

Approaches to the synthesis of (+)-4b α, 8a-β, dimethyl-trans-anti-octahydro-phenanthr-1(10a)-ene-2(3H), 8(7H)-dione (36b).

To date all total syntheses of pentacyclic triterpenes have been directed towards racemic compounds and only very little effort has been expended in the synthesis of chiral synthons which could be involved in a total synthesis of an optically active natural product. In fact, asymmetric synthesis [61] is probably the one area in which pentacyclic triterpene synthesis has not followed, in concept and methodology, the field of total steroid synthesis where asymmetric transformations have been very effectively applied [60].

In this respect in total synthesis of optically active steroids, a most significant breakthrough has been the exploitation of asymmetrically biased intramolecular aldol cyclizations [62-65]. The essence of this development was the discovery that prochiral [66] triketones such as 20 could undergo aldol cyclizations, mediated by optically active amino acids, to ketols 21 [62] or enediones 22 [63] in excellent chemical yields, but more importantly, in many cases, in over 90% enantiomeric excess [67], (scheme 6).

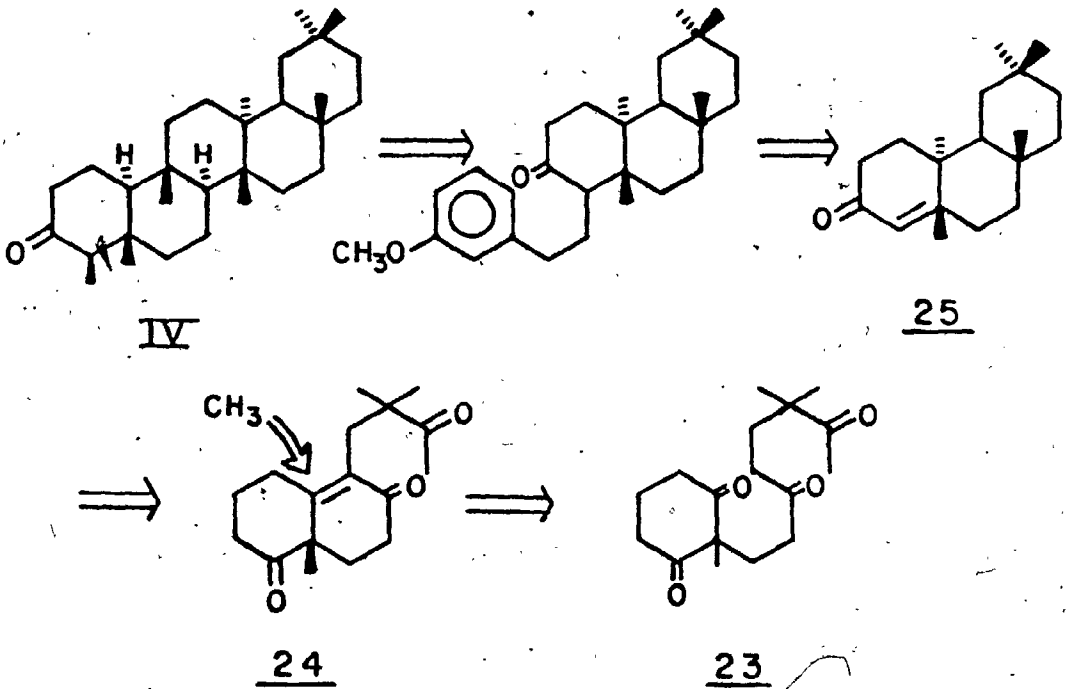


20 21 22

SCHEME 6

Since our objective was the synthesis of a pentacyclic triterpene, friedelin IV in particular, in a single antipodal form, it became clear that the amino acid aldolization process offered the advantage of the efficient introduction of the required chirality at an early stage of the synthetic sequence. Thus enantiomeric resolution [67] could be followed by stereospecific transformations on the desired antipode which could eventually lead to an optically active pentacyclic triterpene.

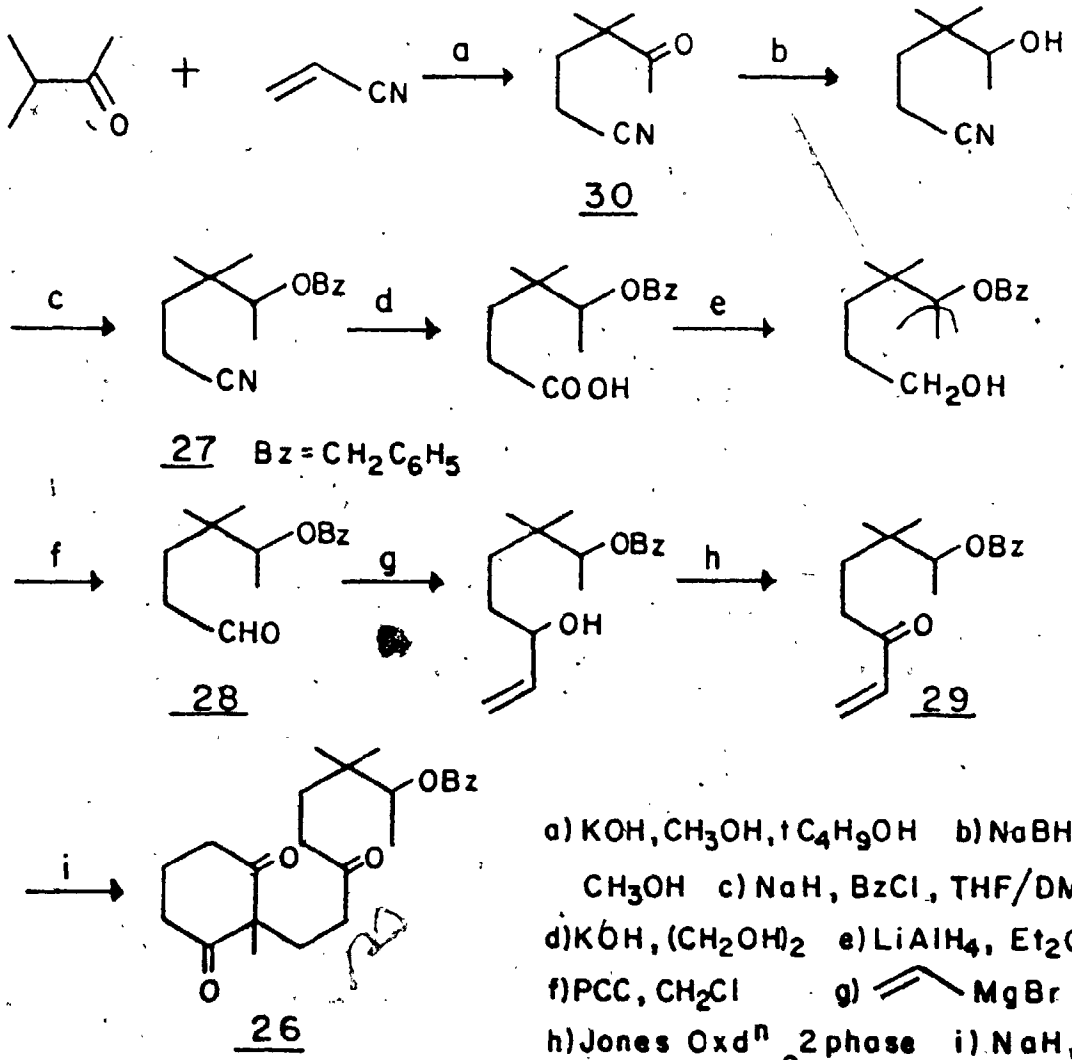
Borrowing then, from the methodology developed for total steroid synthesis and in particular from that by Danishefsky [64] in his chiral synthesis of estrone, we envisioned a prochiral ketone such as 23 being asymmetrically cyclized to the enetrione 24. The latter could, via stereospecific transformations lead to the tricyclic ketone 25 which could be resolved prior to further stereospecific transformations, then into (+) or (-)-friedelin. A retrosynthetic view of this concept is shown in scheme 7.



IV 25 24 23

SCHEME 7

In the event, our initial objective became the dione 26 with the methyl ketone protected as the benzyl ether of the derived alcohol, and possessing the gem dimethyl group required at C-20* in ring E of Friedelin IV. The choice of the benzyl group as a blocking agent for the C-2 ketone function of 26 was made after consideration of the conditions required for the asymmetric aldolization step which involves lengthy reflux in the presence of mineral acid. The synthetic sequence used to construct 26 is shown in scheme 8. The bis annelating agent 29 was synthesized along the lines developed by Saucy [68a] and later used by Ireland [68b] and by Boeckmann Jr., the latter being in studies related to silylated vinyl ketones [69].

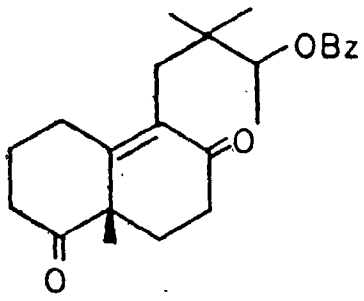


SCHEME 8

The direct conversion of the cyanoether 27 to the aldehyde 28 was attempted several times using diisobutyl aluminium hydride [70] (Dibal H). However, regardless of the method used or care taken in the workup of the reduction, large amounts of polymer resulted and the aldehyde 28 could be isolated in, at best, only 38% yield. Hence, the "long route" was chosen and as a consequence 26 was obtained in about 55% overall yield from the cyanoketone 30.

The coupling of the vinylketone 29 to 2-methyl-1,3-cyclohexanedione was best accomplished using the conditions of Danishefsky [83] (sodium hydride/DME) which resulted in up to 92% yields. The conditions of Yamada and co-workers [71] (triethylamine, refluxing THF) resulted in lower yields. Fluoride catalysed Michael addition [72] (KF, refluxing xylene) between the 1,3-dione and 29 also gave good results but was less attractive owing to longer reaction times and the inconvenience of having to remove xylene from the product mixture.

The amino acid mediated intramolecular aldol cyclization of 26 was to say the least disappointing. The excellent conditions of Eder[63] were used, with L-proline as amino acid catalyst. Several attempts were made at effecting this transformation. Various amino-acid-to-substrate ratios (0.3-5.0 molar equivalents), different solvents (acetonitrile, benzene, toluene, dimethylformamide), extended reaction times (16 hr-120 hr) and at various temperatures, all gave very poor results. The best results came from a 2 molar equivalent of L-proline to 26 in refluxing acetonitrile in the presence of a 1.0 equivalent of perchloric acid for 48 hours. Under such conditions 10-14% of enedione 31 $[\alpha]_D^{23} = +32.3^0$ was realized. (Appendix II, Spectrum 2)

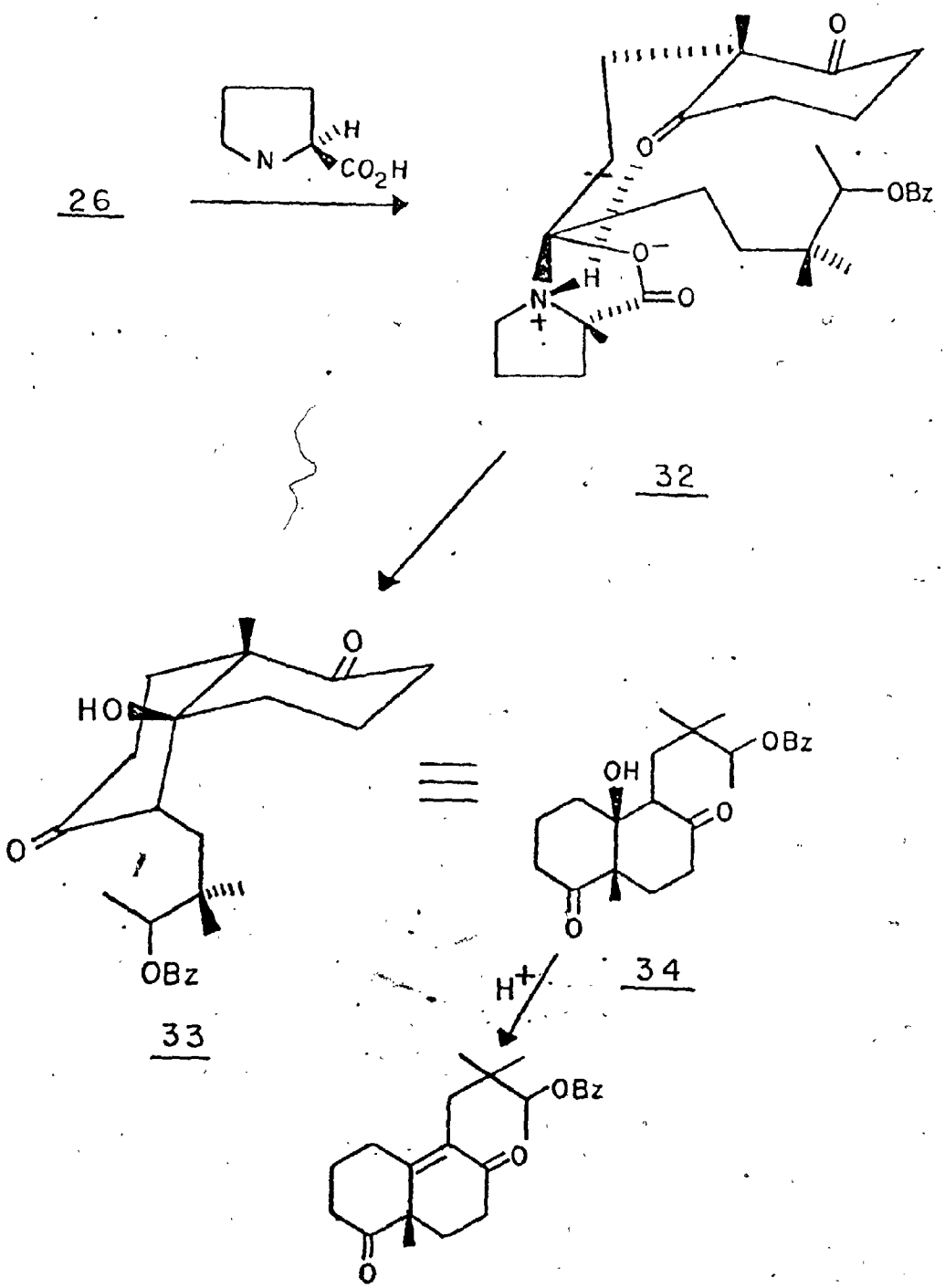


31

The stereochemistry of C-14* of 31 has been assigned on the basis of the requirement that amino acids (or their derivatives) of natural configuration (L) induce the 4β-alkyl configuration in compounds such as 31 [60,64]. Because of the poor yields in this transformation the extent of optical purity in 31 was not determined. Change of amino acid to L-phenylalanine [64] failed to improve on these results.

It occurred to us at the time, that the gem-dimethyls at the C-6 position of the octyl side chain were major contributors to this resistance to cyclization, rather than the conditions peculiar to asymmetric aldolization. This was tested by subjecting 26 to traditional base catalysed aldol cyclization conditions. Again very poor yields of racemic 31 were obtained. Confirmation of our suspicions came from our later work in which an analogous dione without the gem-dimethyls at C-6 did asymmetrically cyclize in good chemical and optical yields to the desired enone. (Described later in this section).

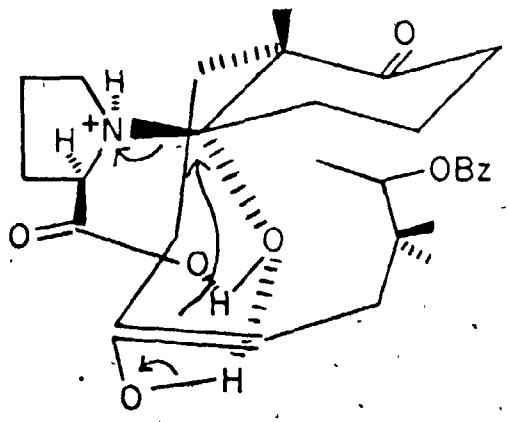
The type of intermediate 32 proposed [62] for a L-proline catalysed cyclization of this type is derived from the interaction of the proline with one of the two cyclohexane ring carbonyls and held in a defined conformation by hydrogen bonding as shown in Scheme 9.



SCHEME 9.

Such an intermediate 32 shows severe steric crowding and it appears that the necessary overlap which will result in carbon-carbon bond formation will be virtually non-existent.

Alternatively if one assumes carbinolamine formation [73] then the bulky proline molecule has to attach itself *trans* to the bulky side chain but *cis* to an angular methyl group. This will lead to an intermediate such as 35.

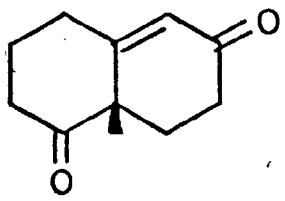


35

The carbinolamine is then displaced by the enol function by backside displacement via a straightforward S_N2 mechanism thereby giving the required inversion of configuration needed to form the *cis* ketol 33. Admittedly such an intermediate is less sterically crowded, but its formation, in the first place, is not very favourable as the angular methyl group will certainly offer a great deal of hindrance. Thus, regardless of the intermediate chosen, the favourability of reaction is considerably low on steric grounds. The *gem*-dimethyls obviously enhanced considerably the steric crowding of intermediates [62] or of potential intermediates [73].

It is interesting though, that the switch of amino acid to L-phenylalanine did not improve on the proline system. It has been proposed[64] that an L-phenylalanine mediated condensation proceeds mechanistically along lines similar to the amino acid esters and amides i.e. that of the enamine intermediate [65,72]. (This mechanism is described later in this section as it proved successful in a related system). These enamine intermediates are much less subject to steric crowding so that one would have expected some small improvement over the proline system. It seems then that perhaps the gem-dimethyls may have obstructed enamine formation in the first place. It is now strikingly obvious to us after the foregoing dilemma that none of the bis-annelating agents of the type 29 reported in the literature [73] contain the nucleophilic carbon involved in the annelating sequence, which possesses a homo-neopentyl nature such as C-6 of the octyl side chain of compound 26.

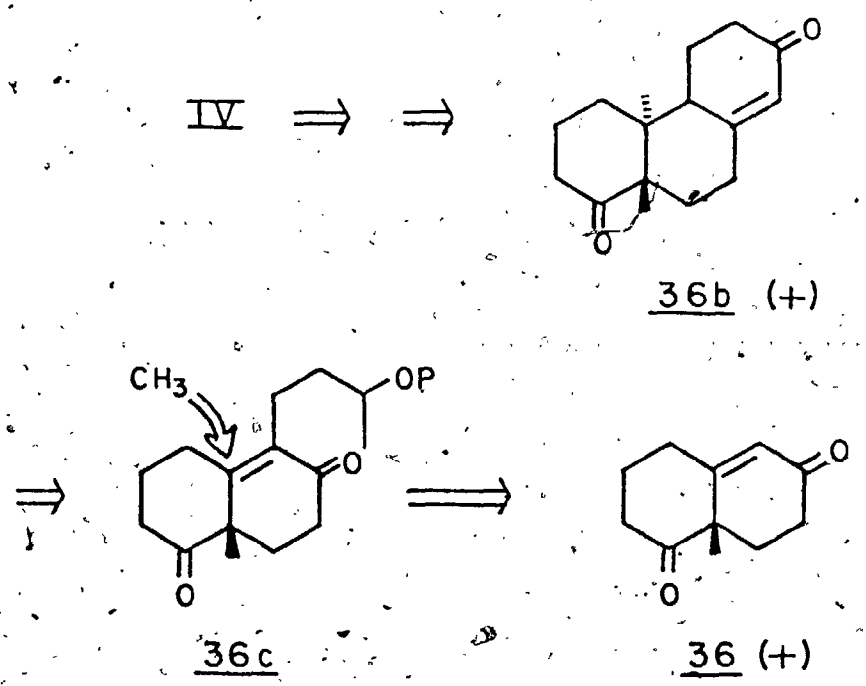
Having failed at our initial bis-annelation venture we decided to replan our strategy. It appeared that the easy accessibility of the octalone 36 in high optical purity [63] and in large amounts made it *per se* a very attractive intermediate for the synthesis of the chiral tricyclic ketone 36b.



36 (+)

Thus our new plan was to attach a 3-keto butyl chain, suitably protected, to C-1 of 36 under conditions that would give mono-substitution

at C-1 with retention of the double bond. Introduction of the trans methyl could then precede cyclization to form a tricyclic species analogous to our original objective except without the gem-dimethyls already present. The proposed route is shown in scheme 10 in a retrosynthetic sense.



36b (+)

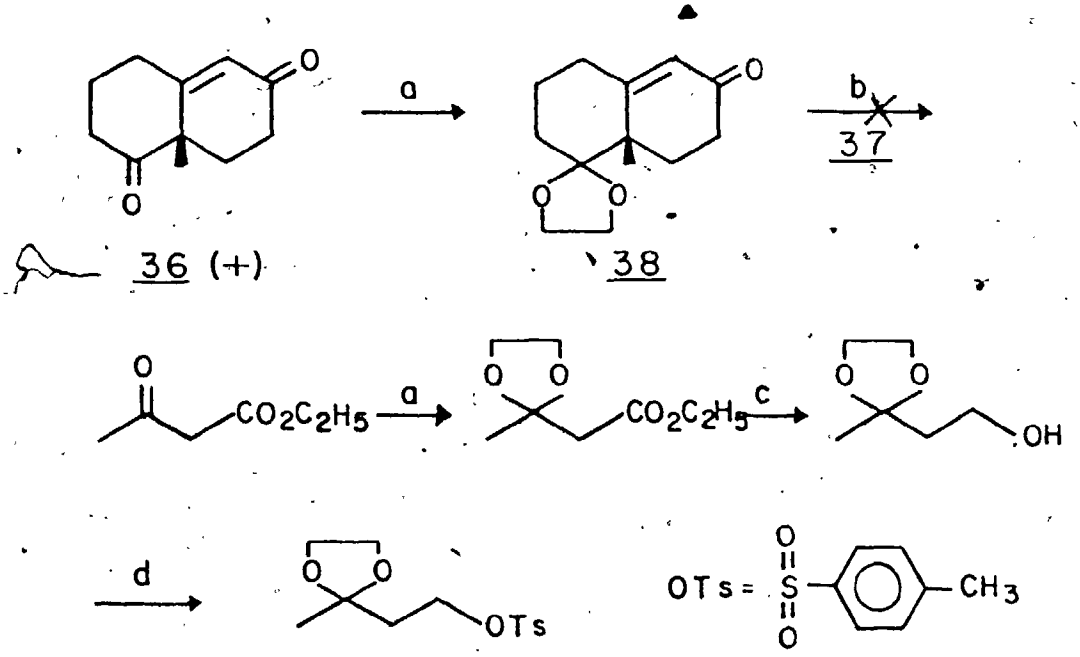
36c

36 (+)

SCHEME 10

In the event then, the octalone 36 $[\alpha]_D^{23}$ +79.5° was prepared using the conditions of Eder et al.[63] Based on the optical rotations reported by Eder et al the value obtained in these studies represents an optical yield of 78.4%. No further determination of optical purity was done on this compound.

Although we were mindful of the difficulties involved in the alkylation at C-1 of enones such as 36[73,74] we decided to test these claims by attempting the alkylation of the mono ketal of 36 with the tosylate 37[100]. (Scheme 11).



36 (+) 38 37

a) $HOCH_2CH_2OH$, TsOH, ϕH b) NaOAmyl, ϕH

c) $LiAlH_4$, THF d) TsCl, Py

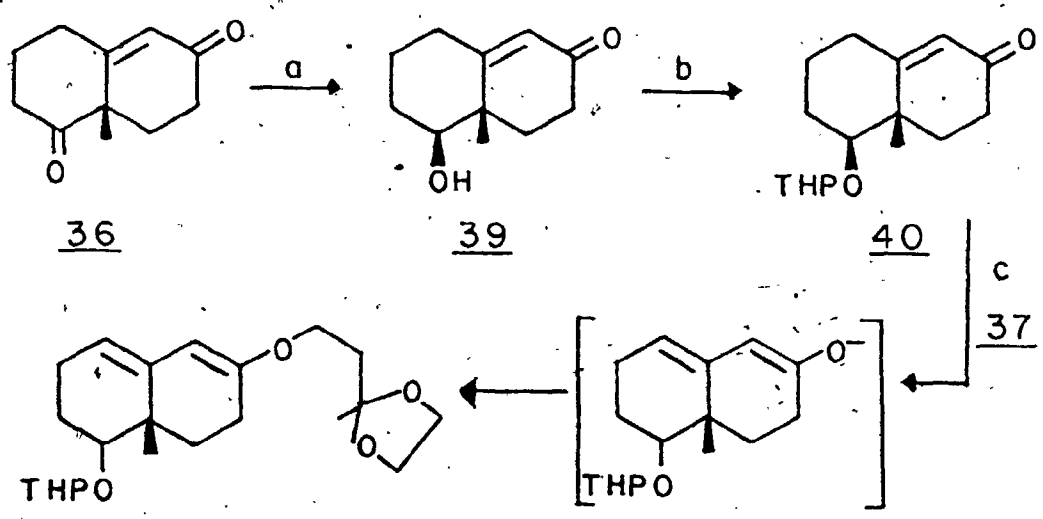
SCHEME 11

Attempted alkylation of the ketal 38 with the tosylate 37 using the Stork procedure[4], gave only starting material and some deketalized ketone. The 1,3-diaxial relationship between the axial methyl and C-1 hydrogen that will result as a consequence of C-1 alkylation evidently obstructed any alkylation.

Because of the encouraging results obtained by Hajos et al [75] in the C-alkylation of hydrindane enone systems with the use of the non-nucleophilic base, sodium methyl sulfinyl methide [82] (sodium hydride/DMSO), we decided to explore this area, at least to some small degree.

However prior to attempting the Hajos procedure [75] it was decided to convert our substrate from the ketal 38 to the tetrahydropyranyl (T.H.P.) protected alcohol derived from 31. This arose from a two-fold

consideration. Firstly the ketal enone 38 had not been obtained in very good yield from 31 (66% maximum) and its purification involved lengthy chromatographic separation, and secondly the alcoholic function at C-8 would be required at a later stage in the synthetic scheme, anyway. The latter consideration stems from our plans to use the hydroxyl function to direct the hydrocyanation [36] of the enone function 36. Also the hydroxyl function would be needed in the spectroscopic determination of optical purity using chiral shift reagents [67]. Both these factors will be discussed in some detail later in this Section. The octalinone 36 was reduced to the alcohol 39 $[\alpha]_D^{23} = +85.2^0$ which was protected as the THP ether 40 following the methods of Piers et al.[76], Scheme 12.

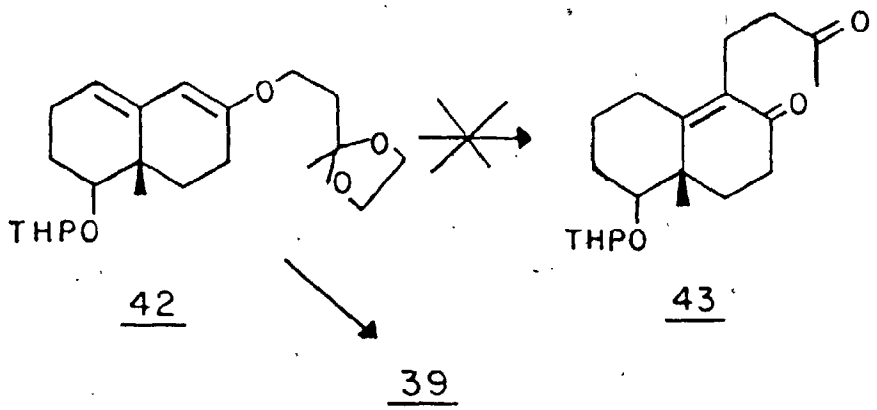


SCHEME 12

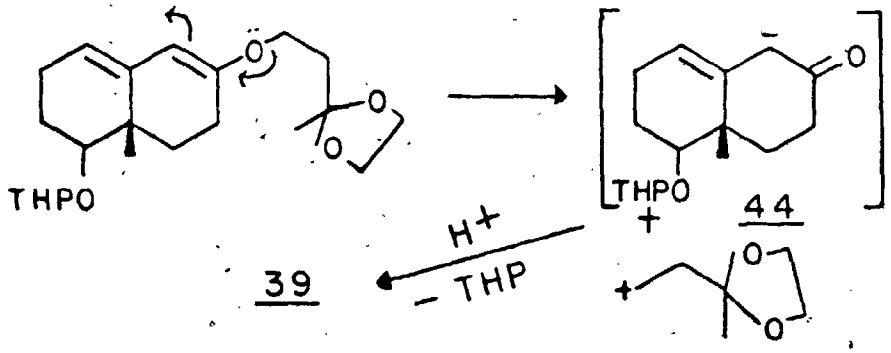
The method used in our attempts at the alkylation of 40 involved firstly, preformation of the dienolate 41 (65°C, 1-3 hr). Then the alkylating agent 37 was added to the enolate solution at R.T. Depending on the conditions applied after addition of 37, either no reaction ensued or a product resulted in up to 35% yield, which from its spectral data (i.r., n.m.r. and u.v.) was assigned the enol ether structure 42. Reaction of the enolate/alkylating agent mixture at room temperature for up to 40 hrs gave only starting material. The U.V. spectrum of the crude reaction product showed only the absorption attributed to the starting enone ($241\varepsilon = 15 \times 10^3$).

Stirring at higher temperatures did give some reaction. The optimum conditions were 16 hrs stirring at 100°C, which resulted in a 35% yield of compound 42. The n.m.r. spectrum of 42 displayed a one proton broadened singlet and a one proton multiplet (probably an unresolved doublet of doublets) at δ = 5.2 ppm and δ = 4.8 ppm respectively. The infra-red spectrum of 41 displayed the characteristic doublet absorption pattern for a di(en)ol ether; that at ν_{max} = 1615 cm^{-1} and 1641 cm^{-1}. The ultraviolet spectrum of 41 displayed an absorption at λ_{max} (CH_3OH) 241 mμ (ε = 14,000). These spectroscopic data, coupled with literature precedents[75,77] for the formation and characterization of such O-alkylated products prompted the di(en)ol ether structure to be assigned to 42.

Following on the example of Hajos et al [75], an attempt was made to convert the di(en)ol ether 42 to the unsaturated ketone 43 via mild acid hydrolysis. However we only succeeded in converting 42 back

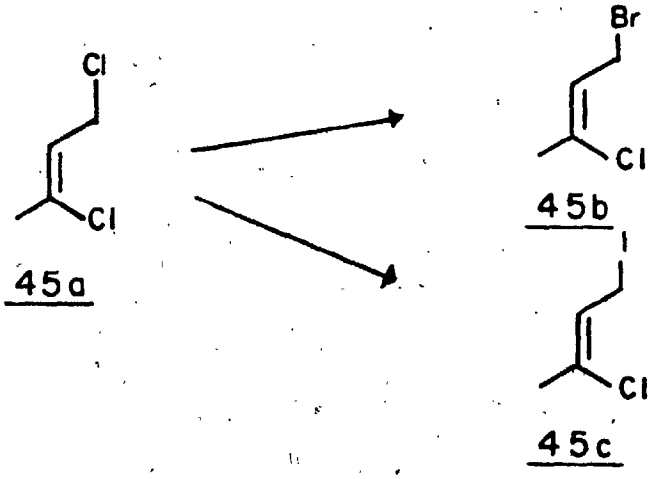


to the hydroxy enone 39. Obviously protolysis of the "intermediate" 44 occurred faster than alkylation.

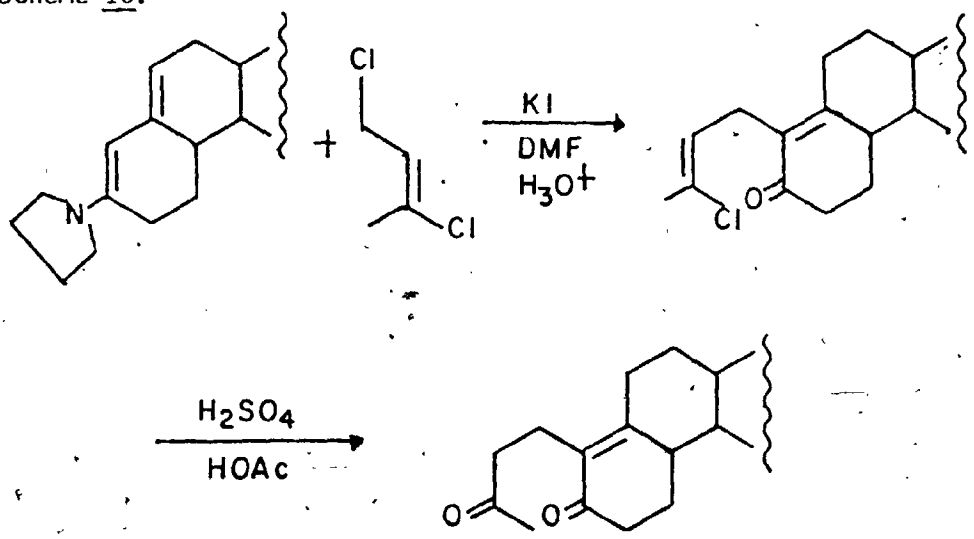


In the event, this failure to alkylate the octalinone 36 prompted another reassessment of strategy. We were hesitant to abandon 36 as a key synthon in this route so we decided to investigate the use of more active alkylating agents in an effort to effect the alkylation at C-1 of 36.

Two such alkylating agents were chosen. The first were 1,3-dichloro-2-butene 45a [78], and its 1-bromo[79]-and 1-iodo [80] isomers 45b and 45c.

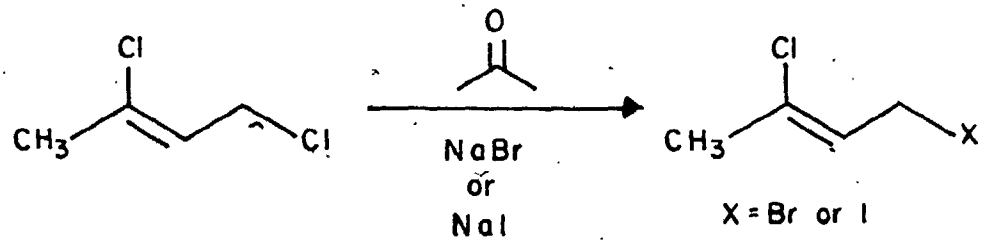


This choice was made on the basis of the considerable success obtained with these allylic halides in the total synthesis of steroids,[78-81] particularly in connection with the enamine alkylation methodology[81], Scheme 13.



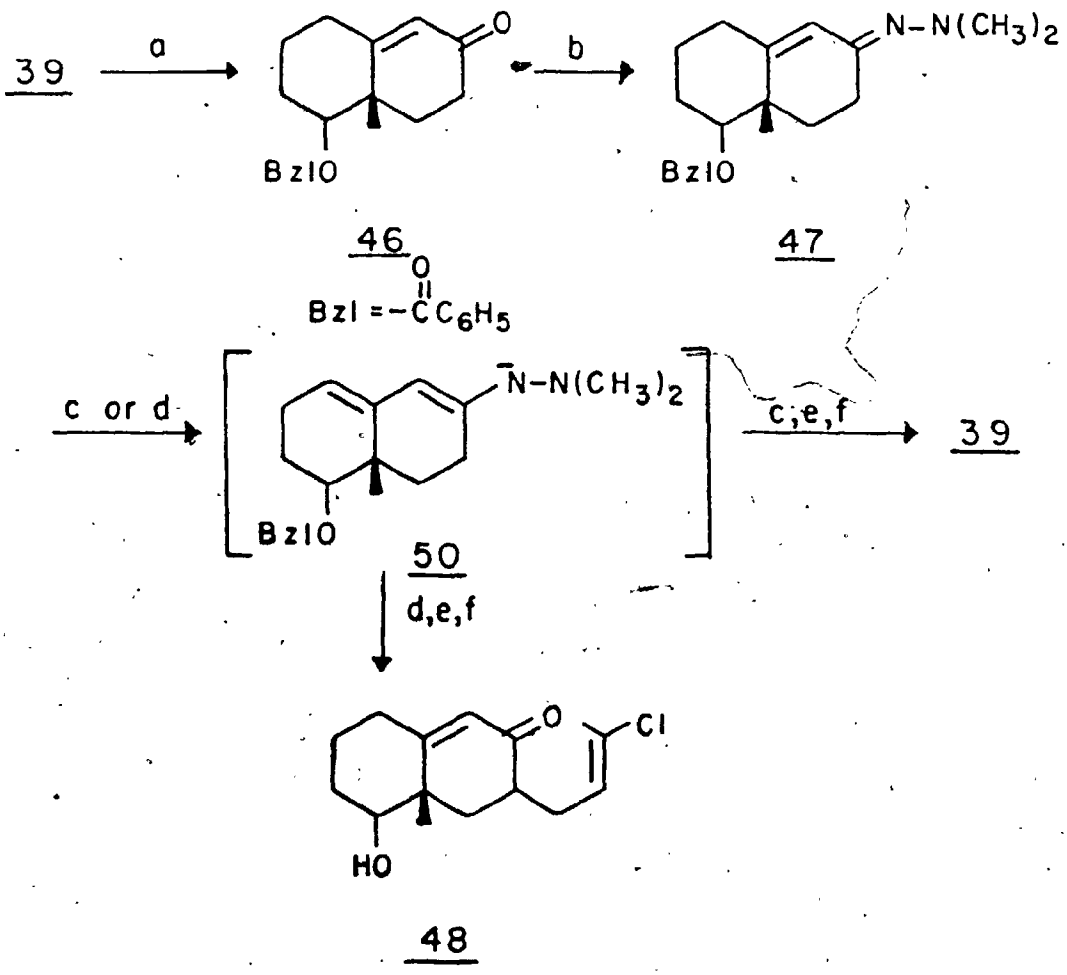
SCHEME 13

Further, the dichloro reagent is commercially available and the bromo and iodo derivatives are readily obtained from the former.



These allylic halides then, seemed suitable reagents for use in the metalloenamine method for mono-alkylation of α,β-unsaturated ketones, first developed by Stork[74], and which purported to resolve that ever troublesome problem. Thus, the plan became the alkylation of 39 (with the hydroxy function suitably blocked) with one of 45a b or c via a suitable metallo enamine.

Thus the alcohol 39 was converted to the benzoate 46 (m.pt. 87-88°C) which was transformed in excellent yield to the N,N-dimethyl hydrazone 47 using the method of Stork [74]. (Scheme 14).

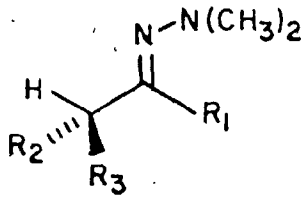


a) C_6H_6COCl, Py b) $(CH_3)_2N-NH_2$, $C_6H_5CH_3$, TsOH c) n BuLi
d) $(\text{cyclohexyl})_2NLi$, THF e) 45a or 45b.
f) 6N HCl

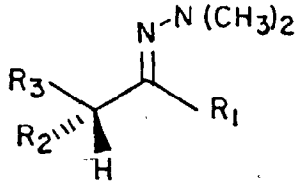
SCHEME 14

The nmr spectrum of 47 (Appendix II, Spectrum 3) reveals an interesting phenomenon. The signal attributed to the methine proton at C-1 of 47

shows up as two broadened singlets at δ = 6.1 ppm and δ = 6.7 ppm and in the integrated ratio of 5:3. It appears then that this proton is experiencing the anisotropic effects of the C=N bond brought on by the conformational preferences of the N-$(CH_3)_2$ function [84]. Systems such as 49 a and b display conformational preferences and it has been found that protons on the carbon which is alpha to the imino bond [84] resonate

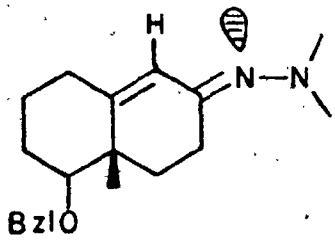


49a

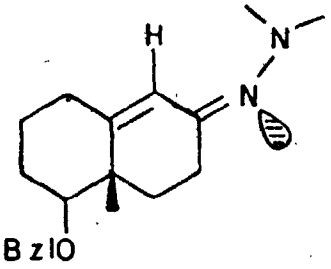


49b

at lower magnetic fields when syn in a configuration relative to the group, $N(CH_3)_2$ than when anti to same. Values of $\Delta\delta$ of between 0.3 and 1.0 ppm have been found. In our system then, it appears that 47 is favoring the syn configuration 47b over the anti configuration 47a and in a 60:40 ratio.



47a



47b

Two bases were used in this exercise. Initial attempts were made using n-butyllithium to generate the metalloenamine 50. However, regardless of conditions used it appeared that no alkylation was achieved, with starting material being recovered after hydrolysis of the imine. With

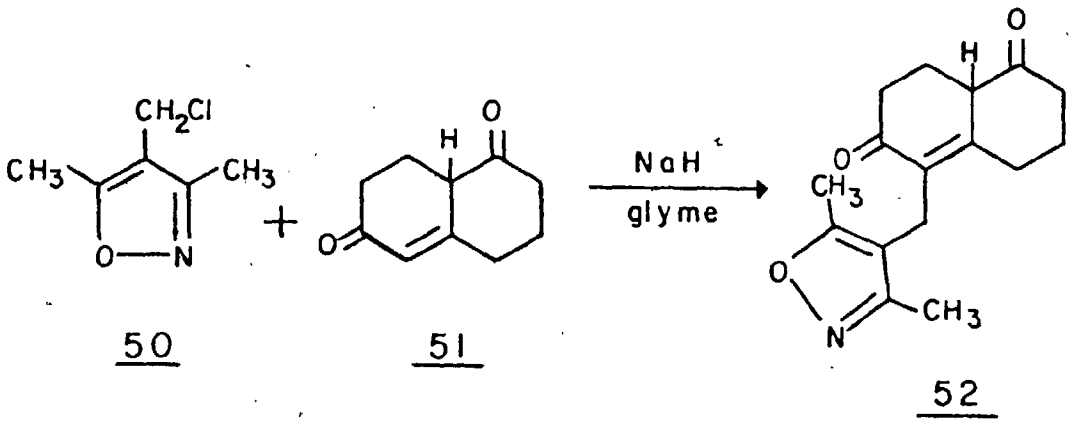
n-butyllithium we attempted to generate the metalloenamine by extended reflux in tetrahydrofuran (THF) 6-16 hrs, prior to addition of the allylic agents. In this exercise the chloro-and bromo-compounds were used as it proved extremely difficult to isolate the iodo-compound in a reasonably pure form.

With lithium diisopropylamide we did achieve some alkylation. Preformation of the metalloenamine was achieved by addition of 47 to the base at -50°C followed by two hours at room temperature. The "best" results were obtained when the allylic bromide 45b was added at -50°C followed by overnight reflux. In such an instance the compound 48 in which alkylation occurred to the "wrong side" was realized in up to 30% yields. The U.V. spectrum of 48 was identical to that of the starting alcohol 39. Its n.m.r. spectrum (Appendix II, Spectrum 4) displayed a single proton broadened singlet at δ = 5.8 ppm together with a single proton unresolved triplet at δ = 5.6 ppm. The broadened singlet, which was characteristic of the C-1 olefinic proton in the starting octalinones, did not change or disappear on shaking with D_2O indicating that it was not due to the hydroxyl proton.

We then began investigating the second set of alkylating agents chosen for this study. Based on the success achieved by Stork [85], and later by Saucy [86], in the steroid total synthesis field with 3,5-dialkylisoxazoles as masked 3-oxobutyl functions[87], we decided that the latter group was worth investigation in these alkylation reactions.

The 3,4-dimethyl-4-chloromethylisoxazole 50 was prepared in the standard manner [85,88] and we attempted to alkylate the octalone 36 directly (NaH, glyme) following the Stork tradition [85a]. Again, it became obvious that the axial methyl substituent had a profound effect

since no alkylation resulted, whereas Stork was able to achieve 70% yields of 52 from the reaction of the octalinone 51 with 50 using identical conditions [85]. Scheme 15.

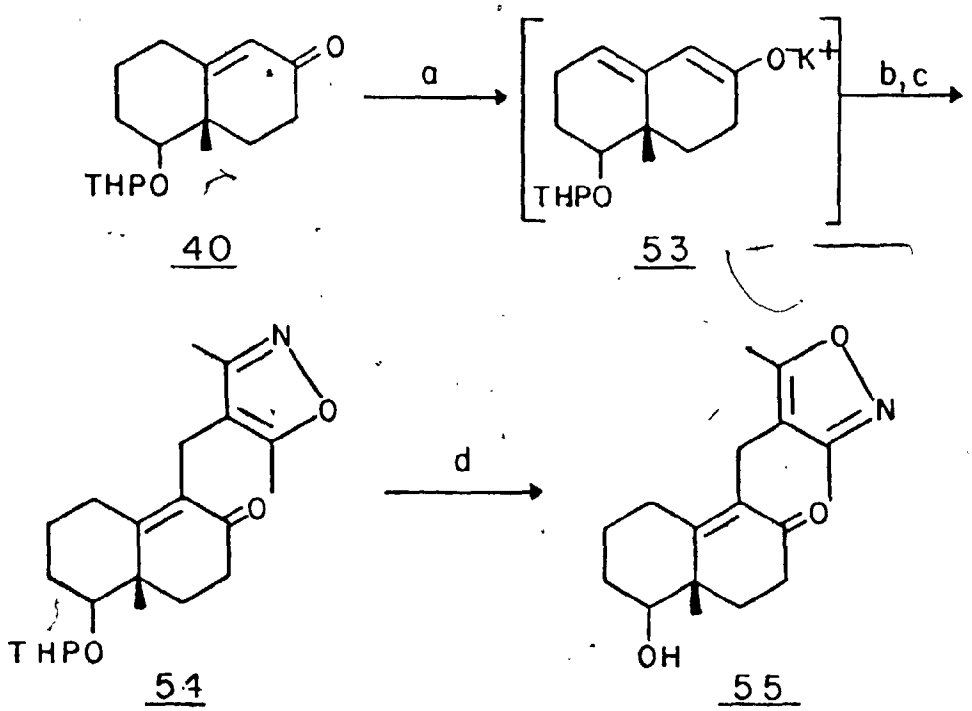


50 51 52

SCHEME 15

Thus we decided to revert to the traditional dienolate conditions of Stork[4], using potassium t-amyloxide as base. Thus addition of the THP ether 40 to a solution of potassium t-amyloxide in benzene at 0°C followed by reflux for 3-6 hours generated the dienolate 53. Addition of the isoxazole 50 at room temperature followed by overnight stirring led to the alkylated crystalline product (m.pt. 185-186°C) 54 in at best 46% yield.

Acid hydrolysis of the THP protecting group [76] gave the crystalline product 55 (m.pt. 112-114°C) in about 40% yield from 40, (Appendix II, Spectrum 5). Attempts to improve these yields have so far been unsuccessful.



a) K⁺ ⁻OH, ϕH b) 50
c) $2NH_2SO_4$, 0 °C d) TsOH, CH_3OH

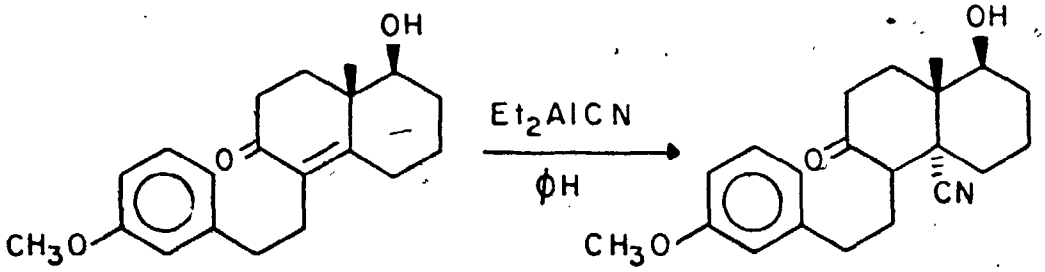
SCHEME 16

The isoxazole alcohol 55 crystallized cleanly from ether-hexane and displayed a specific rotation $[\alpha]_D^{23}$ of +136.5 . To date we have not determined the optical purity of this material, since, as it will be shown, we suspended studies on the isoxazole approach in favour of a more promising and more convergent approach.

With the α,β-unsaturated keto-isoxazoyl system 55 in hand, albeit in only fair yield, we set about introduction of the trans-methyl group in some form, at the C/D ring junction. This step had to precede the cleavage of the isoxazole ring to the naked 3-oxobutyl function.

The route of choice involved the conjugate addition of hydrogen cyanide across the α,β-double bond of 55 under kinetic conditions in order to generate the trans carbon substituent - as nitrile - at the C/D ring junction, according to the conditions of Nagata [89]. Classically,

according to Nagata [89], the kinetic conditions that ensure the trans ring junction, involve the use of the HCN/Et_3Al reagents,[36] whilst the preformed reagent diethyl aluminium cyanide (Et_2AlCN) exerts thermodynamic control and thus generates the cis ring fusions in six-membered polycyclic systems such as 55. However, Ireland [36] has shown, as part of his route to shionone [26], that the presence of a hydroxyl group (proton source) as in 56a effectively converts the much more convenient diethyl aluminium cyanide process to a kinetic one,

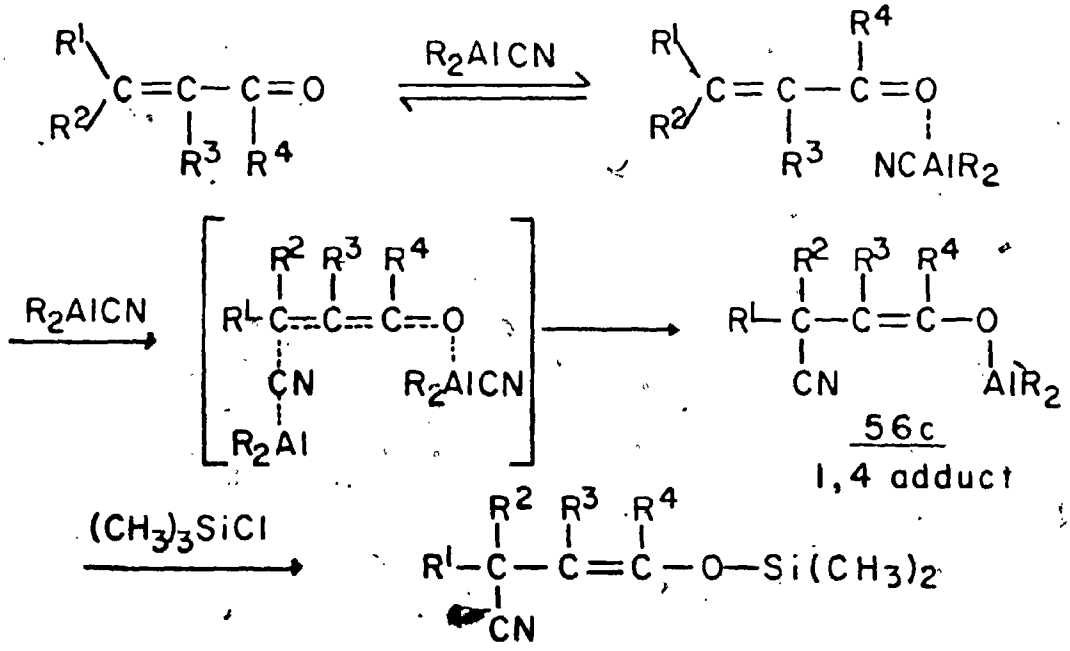


56a 56b

thereby giving the trans-fused product 56b. As indicated previously, this precedent was one of the contributing factors to the preparation of the hydroxy octalinone 39 in the first place.

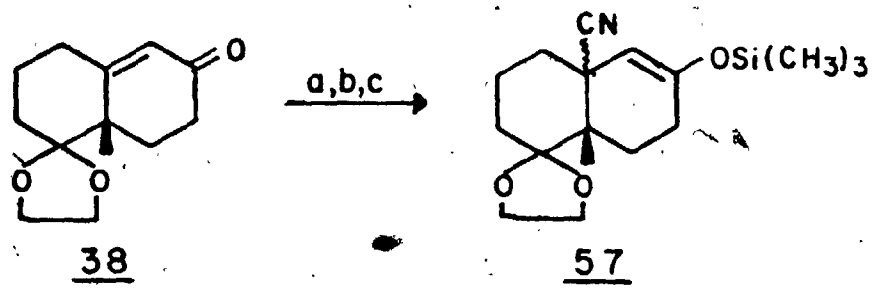
In the event, we subjected the hydroxy isoxazole 55 to hydrocyanation using the preformed reagent under conditions similar to those of Ireland [36]. However the results were disappointing. On base hydrolysis of the reaction mixture we were able to isolate less than 20% of the starting material, whilst the remainder of the substrate- presumably reacted- remained in the aqueous phase. Acidification of this phase led to the isolation via hot chloroform of a white solid , which could not be redissolved in the normal bench top organic solvents viz ether, methanol, ethanol, acetone, benzene etc.

While pondering this dilemma we decided to test the conditions of Vandewalle [90] for the generation of β-cyanosilylenol ethers, by the trapping of the intermediate aluminium enolate 56c with trimethyl silyl chloride. Scheme 17.



SCHEME 17

Indeed when we subjected the ketal enone 38 to the Vandewalle work up procedure [90] we were able to isolate in fair yield - up to 55% of the cyanoenol ether 57, Scheme 18. We believe that some losses occurred in our attempts to purify the product by silica gel chromatography. This could have led to some hydrolysis of the enol ether.



38 57

a) Et_2AlCN
b) TMSCl/Py
c) NH_4Cl, dil HCl, $NaHCO_3$

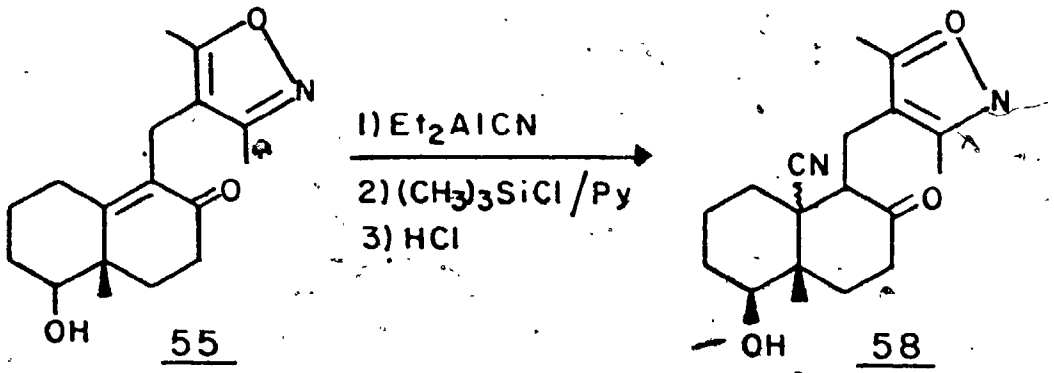
SCHEME 18

However, referring again to the Nagata conditions [89], the use of the preformed reagent Et_2AlCN with the substrate 38 should give the undesired thermodynamic cis-product. Hence to be of any value in our sequence the substrate for such a transformation had to be the hydroxy enone 39. However, subjection of 39 to conditions similar to those to which 38 was subjected, led in all instances to an array of products none of which proved susceptible to ready separation and characterization.

Obviously the proton source in the latter system not only destroyed the stereo- and regio-chemical integrity of the process, but may have also served to hydrolyse the enol silyl ether once it was formed.

However, with regard to this cyanosilylation procedure [90], we conceived that modification of the work up conditions of hydrocyanation of the isoxazole 55 to temporarily isolate the silyl enol ether may add a measure of success to the isolation of the hydrocyanated product.

Thus, a 1:1 b.v. TMS Cl/pyridine mixture was added to the hydrocyanation of 55 reaction mixture at 0°C followed by one hour stirring at 20°C. Isolation of the product with ether/hexane followed by hydrolysis with cold dilute HCl solution led to a crystalline



55 58

solid 58 which decomposed at temperatures above 200°C. Compound 58 also posed solubility problems similar to those posed by the product

of the initial attempts at hydrocyanation of compound 55. The infra-red spectrum of this compound displayed the characteristic nitrile absorption at 2220 cm^{-1}, and a saturated carbonyl absorption at 1701 cm^{-1}. Both the infra-red spectrum and the nmr spectrum (Appendix II, Spectrum 6- taken in deuterated pyridine) showed the integrity of the isoxazole function - 3-prpton singlets at 2.3 ppm and 2.5 ppm although in the latter, these appear to be unexplicably split.

The low resolution mass spectrum shows the expected molecular ion peak at m/e = 316. However, the combustion analyses of 58 have been the most puzzling to date. Duplicate analyses of 58 have shown a 1.0% deficiency in nitrogen and a 2.7 % excess of carbon. As yet we are at a loss to explain these findings. The high resolution mass spectrum determination of molecular weight has not been received to date.

In an effort to convince ourselves that hydrocyanation was in fact taking place, we undertook to attempt same using the true kinetic conditions viz HCN and triethyl aluminium [91]. The procedure of Nagata [92] was followed, whereby 55 was treated with three molar equivalents of the $HCN/(C_2H_5)_3Al$ reagent at room temperature, followed by several hours stirring.

This led to a compound which appears to be identical in all respects to 58 even to combustion analysis values.

To date we have not rationalized these discrepancies, since at that point we suspended work in this area, in favour of a more promising route which was based on our original strategy.

However, it should be noted that the isoxazole route is still a viable one. The compounds involved in this approach all appear to be

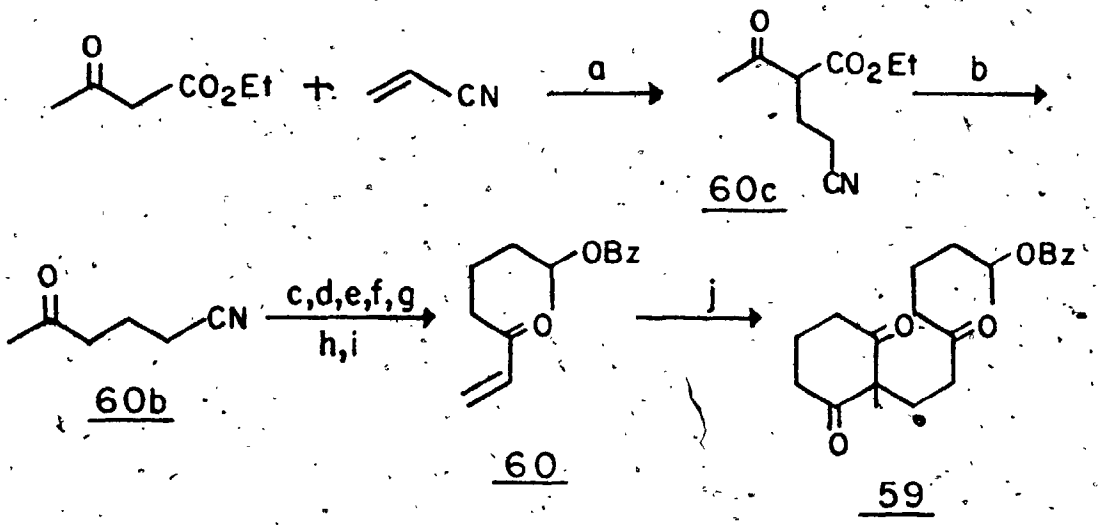
highly crystalline in nature. Hopefully the dominant isomer can be selectively crystallized, thus eliminating the necessity for chemical resolution at a later stage in the synthetic pathway.

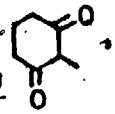
Derivatization (to reduce polarity) followed by reduction of the nitrile, (if it is in fact present) and cleavage of the isoxazole ring will give clear indications as to the structure of 58.

In our studies concerned with the ABC + E → ABCDE route, we found that the 1,5 diketone arising out of the alkylation of a ketone enolate with a bis-annelating reagent analogous to 29 (scheme 8), but without the C-6 (octyl side chain) gem dimethyls, appeared to cyclize in excellent yield. See Section III for these details.

Therefore we decided to re-assess our convergent synthesis with the view to preparing the trione 59; which does not have the C-6 gem dimethyls.

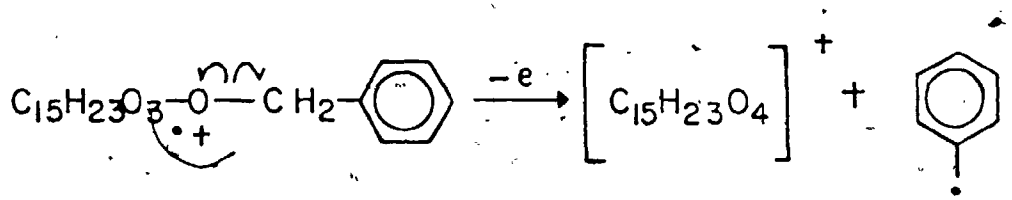
We thus prepared the bis-annelating reagent 60 , Scheme 19 (Appendix II, Spectrum 10)in a manner similar to that used in scheme 8.



a) NaOEt, EtOH b) Na_2CO_3, Δ, H_2O c) $NaBH_4$, CH_3OH d) NaH, BzCl, THF/DMF e) KOH, $HOCH_2CH_2OH$, Δ f) $LiAlH_4$, Et_2O g) PCC, CH_2Cl_2 h)  MgBr, THF i) 2-phase Jones , j)  , NaH, DMF

SCHEME 19

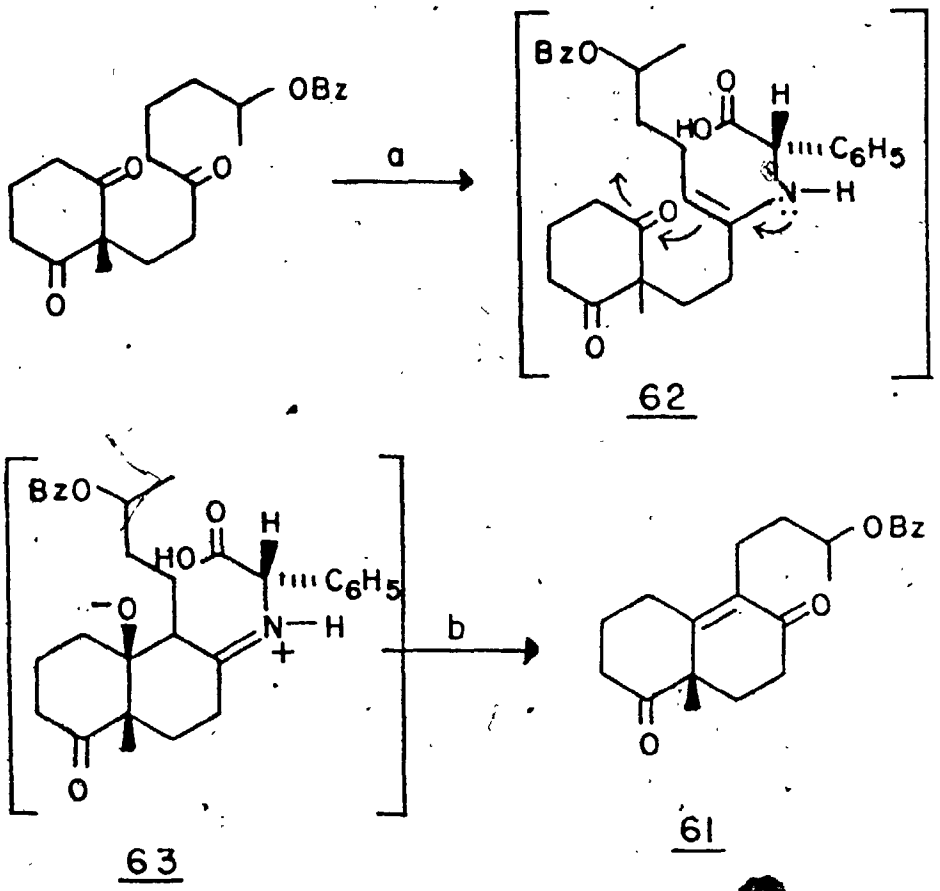
Coupling of 60 with 2-methyl-1,3-cyclohexanedione under Danishefsky's conditions [83] resulted in the trione 59 in excellent yield. It is interesting to note that the mass spectrum of this material does not show a molecular ion peak at m/e-356 but displays a base peak at m/e 267 as a result of the cleavage of the benzyl ether. $M^+ - 91 = 265$.



m/e 265

Our initial attempts at asymmetric cyclization used L-proline as amino acid catalyst. However, chemical yields of the octalinone 6 were not satisfactory - less than 50%. However, when L-phenylalanine was used, following Danishefsky's conditions [64], the trione 59 was converted to the enone 61 $[\alpha]_D^{23} = +36.9^0$ in almost quantitative chemical yields and in high optical yield as well. Scheme 20 .

The intermediate proposed for the aldolization process is the enamino species 62 which results from attack of the chiral amine component at one of the enantiotopic cyclohexanedione carbonyls. The crucial cyclization which results in the formation of C-13*-C-18* bond, then occurs, leading to the immonium species 63. Hydrolysis-dehydration of the latter proceeds smoothly to the desired enone 61. (Appendix II, Spectrum 7).



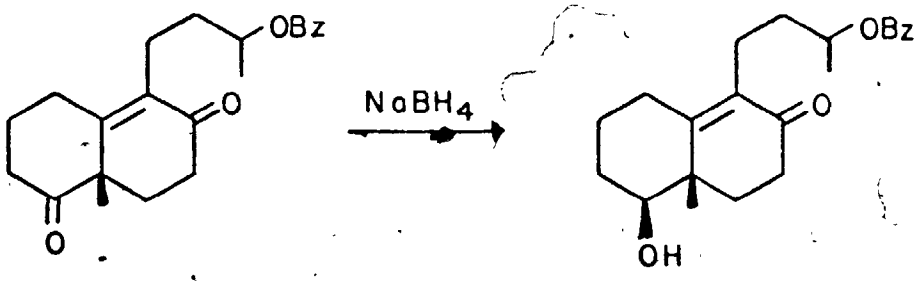
a) L-phenylalanine, CH_3CN

b) 60% $HClO_4$

SCHEME 20

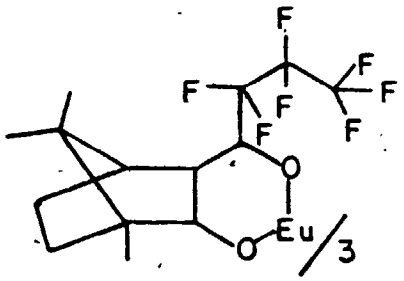
With 61 in hand the task of highest priority became the determination of enantiomeric purity. The method of choice for such a determination was one involving the use of a chiral shift reagent [93] to induce differential chemical shifts of the C-14* angular methyl signals in the nmr spectrum of the optically active material 61 indicating directly the ratio of the component enantiomers. To maximize the effect of the chiral shift reagent, a suitable anchor had to be provided in proximity to the angular C-14* methyl. A hydroxyl function at C-4 in 61 could serve this purpose and hence 61 was converted to the hydroxy

enone 64 $[\alpha]_D^{23}$ =+56.3° via standard sodium borohydride reduction [76].



61 64

The chiral shift reagent chosen was tris-(3-hepta-fluorobutyryl-d-camphorato) europium (111) $Eu(hfbc)_3$ - 65 introduced by Fraser [95].



65

Figure 1 describes the results obtained in this study using an XL 100-n.m.r. spectrometer. The signal for the C-14* methyl group of 64 has moved dramatically downfield (up to δ = 2.7 ppm) with increasing L.S.R. concentration. Further , this signal resolves into two peaks , each arising from the C-14* methyl group of the component enantiomers. Integration of these signals indicates that 64 comprises about 80% of the desired R-(C-14*) enantiomer (i.e. enantiomeric excess of 60%). We have thus succeeded in establishing the key asymmetric centre at C-14* in high optical yield .

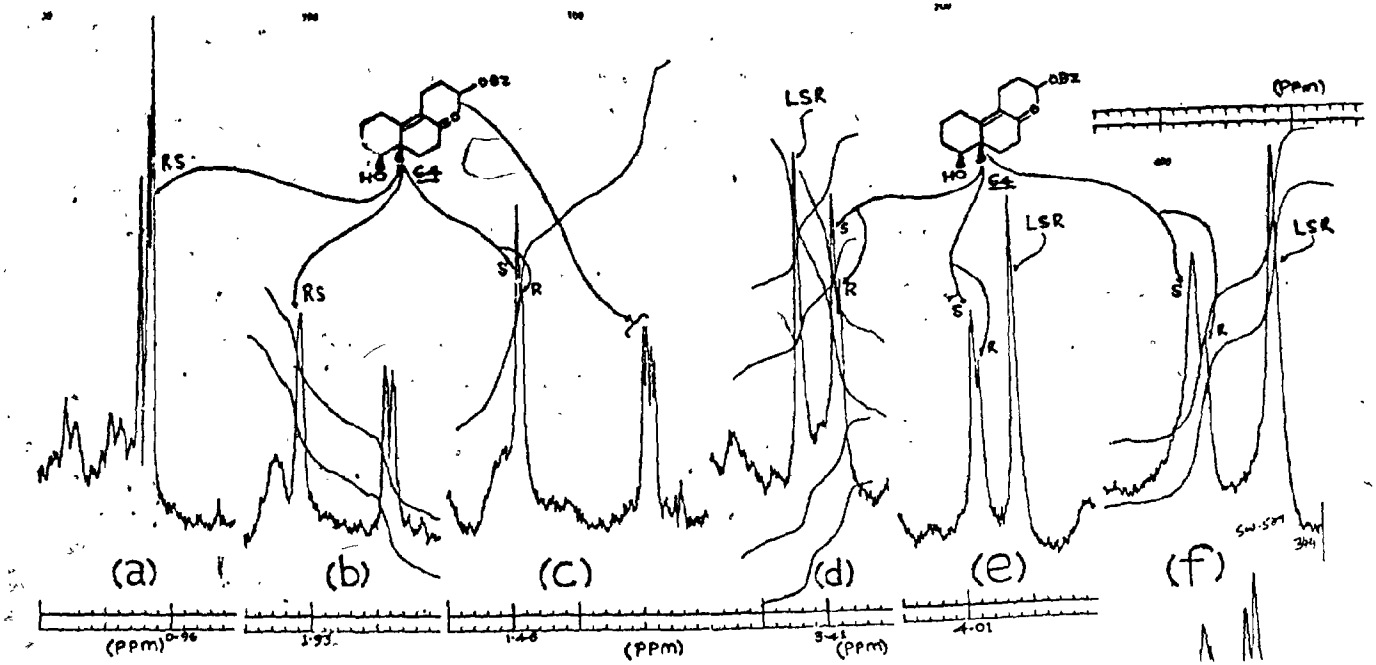
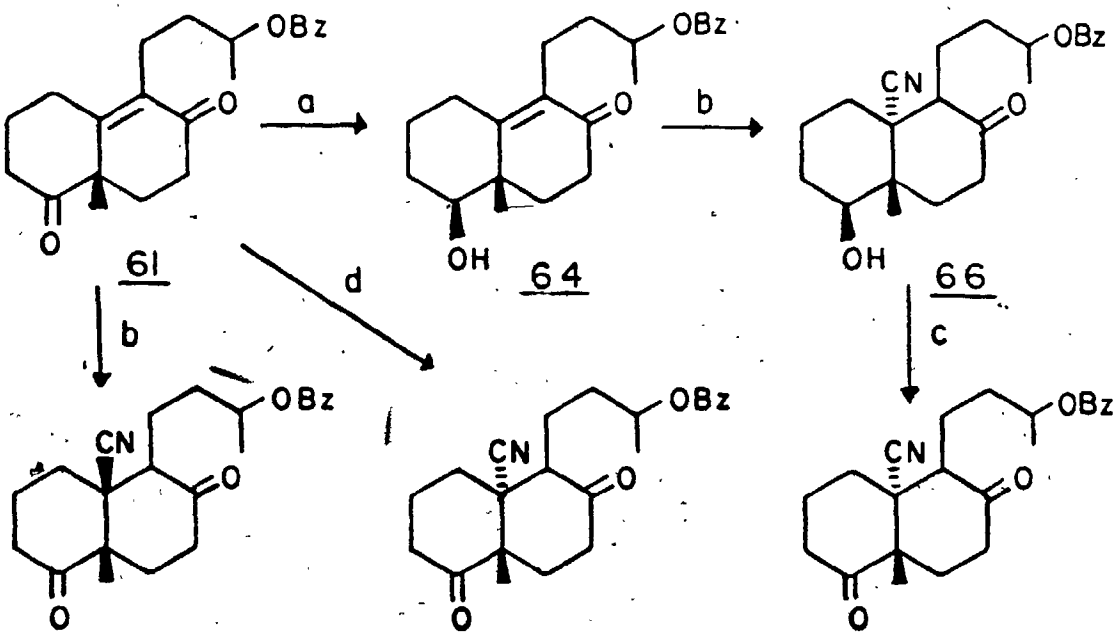


FIGURE 1. Resolved C-18 methyl resonances observed (100MHz) for the enantiomers of the hydroxy octalinone 66 in the presence of (a)zero molar equivalents of chiral LSR 65 (b) 0.19M equivalents of 65 (c) 0.33M equivalents of 65 (d) 0.55M equivalents of 66 (e) 0.85M equivalents of 65 (f) 0.85M equivalents of 65 @ sweep width 500 ppm
Chemical shifts referenced from $Si(CH_3)_4$.
Solvent = $CDCl_3$

The next task in hand was the introduction of the methyl group (initially as cyano) at C-13 in order to form the trans C/D ring junction. Again the method of choice was the convenient diethyl aluminium cyanide procedure in as much as the substrate 64 possessed the hydroxyl function required to make this process kinetic.

Subjection of 64 to hydrocyanation conditions similar to those of Ireland [36], gave excellent yields of a waxy semi-solid to which we initially ascribed the structure 66 (Scheme 21), based on literature precedent[38,39].



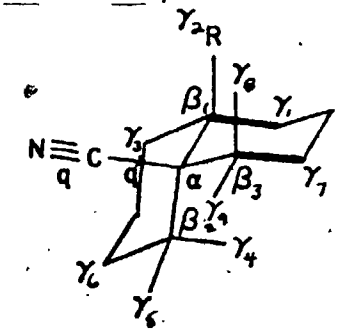
a) $NaBH_4$, EtOH
b) Et_2AlCN, ϕH
c) Jones reagent (2 phase)
d) HCN / Et_3Al, THF

SCHEME 21

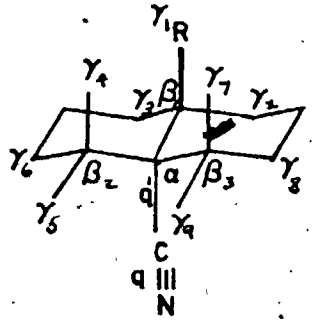
Proof of the stereochemistry of the C-27* nitrile in 66 $[\alpha]_D^{23}$ + 23.4° was obtained by comparison of its physical and spectral characteristics with those of the cis cyano compound 68. Hence 66 was oxidized to the trans cyano-diketone 67 $[\alpha]_D^{23}$+10.6° and the ene-dione 61 was hydrocyanated using the conditions identical to those to which the trans hydroxy enone 64 was subjected, yielding the cis diketone 68 $[\alpha]_D^{23}$+0.8°.

Although the hydroxy compound 66 resisted all efforts at crystallization, the dione 67 crystallized from ether-hexane quite easily - (m.pt. 96-98°C) The cis compound 68 is also crystalline - (m.pt. 84-86°C)

A major contributor to the assignment of stereochemistry in 66 comes from a comparison of the infra-red spectrum of 66 with that of 68 Nagata [96] observed a correlation between the configuration and infra-red band intensity of the cyano group in fused cyclohexane ring systems. Nagata [96] generalised that an equatorial cyano function shows a higher C≡N band intensity than an axial epimer, despite little fluctuation of the absorption maximum in both epimers. However a somewhat detailed theoretical treatment of these observations led to the conclusion that should the structural environments surrounding the C-C≡N bond be very similar or equal, then the increase in C≡N band intensities are governed mainly by the number of C_β-C_γ bonds that are parallel to the C≡N bond. (Bold lines in 70 and 71.)



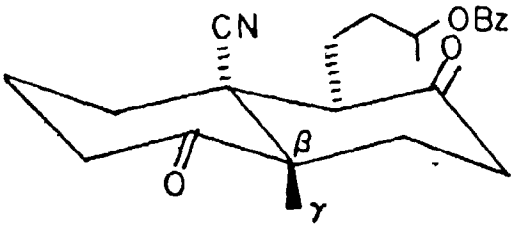
70
cis (eq)



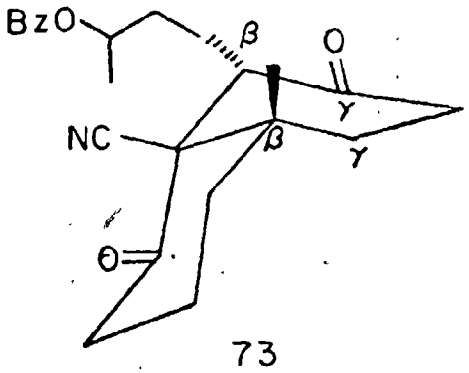
71
trans (ax)

steroids : R = CH_3
19-norsteroid type compounds : R = H

In our studies, the trans cyano compound 67 will have one such C_β-C_γ parallel bond, as shown in 72.



72



73

On the face of it, the cis isomer 68 should have two such parallel bonds (cf. 70). However an examination of the molecular models reveals that because of the eclipsing of the C-2-keto function by the 1-methylene group of the C-3 butyl side chain, compound 68 would be expected to exist with ring A in a flattened chair conformation, such as shown by 73. In such an event, the two β,γ bonds that would normally be parallel, (cf 70) are in fact not parallel to the C≡N bond. Hence, based on Nagata's conclusions, one would expect the trans material to display nitrile absorption intensities greater than the cis material. Fig. 2 shows the results of such a study. The intensities of the nitrile absorptions are measured relative to the carbonyl absorptions. Fig. 2 shows that the relative intensity of the C≡N/C=O in the trans isomer 67 (72) is about three times the value obtained for the same relative intensity in the cis compound 68 (73). In order to confirm that our argument was indeed true, we prepared the trans compound 69 $[\alpha]_D^{23.5} = +7.3^0$ via the fully kinetic HCN/Et_3Al method by which, according to Nagata [89] and supported by the large majority of literature precedents, the trans fused cyano function is normally produced. Fig 2 (C) shows that the

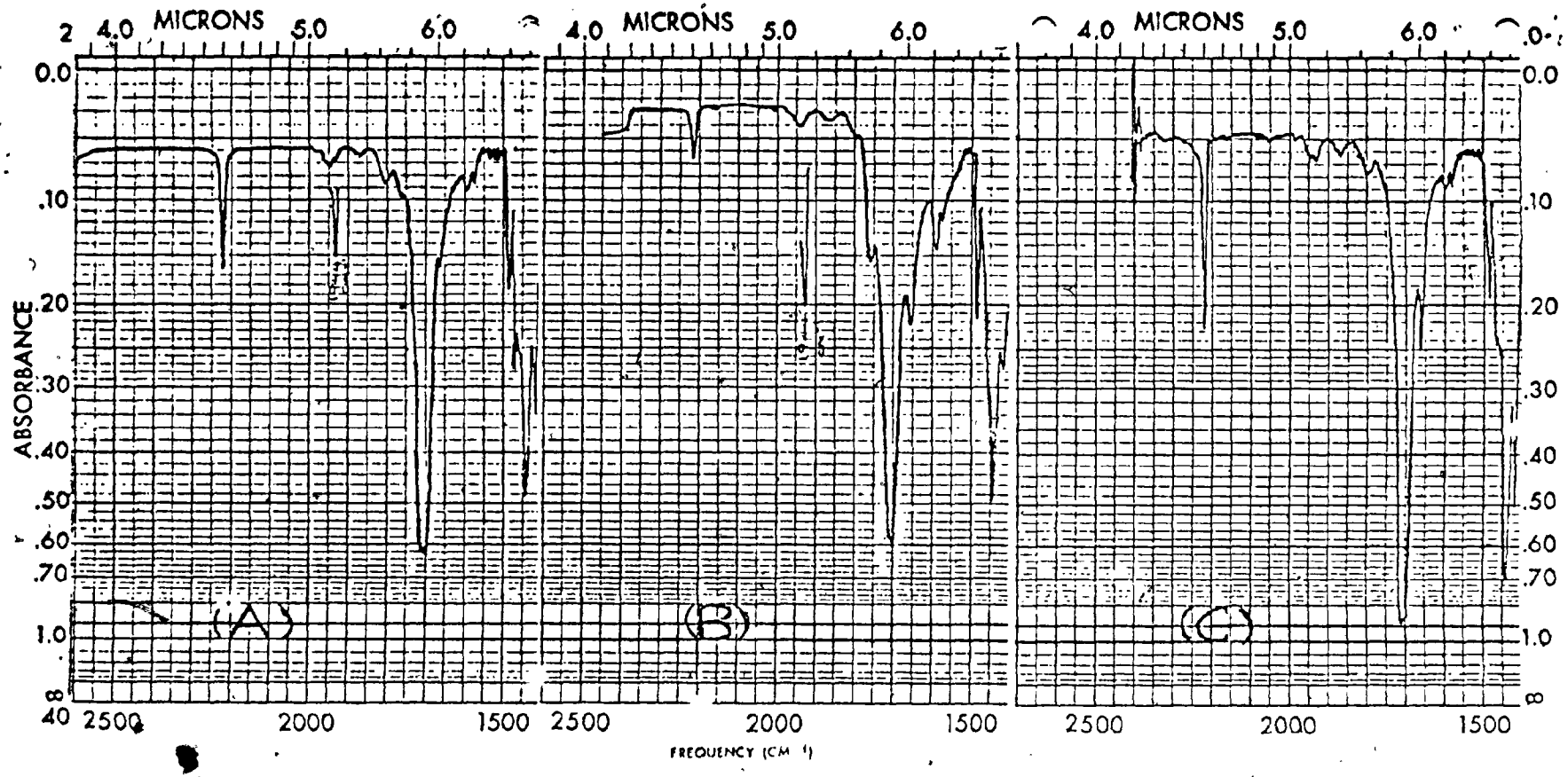


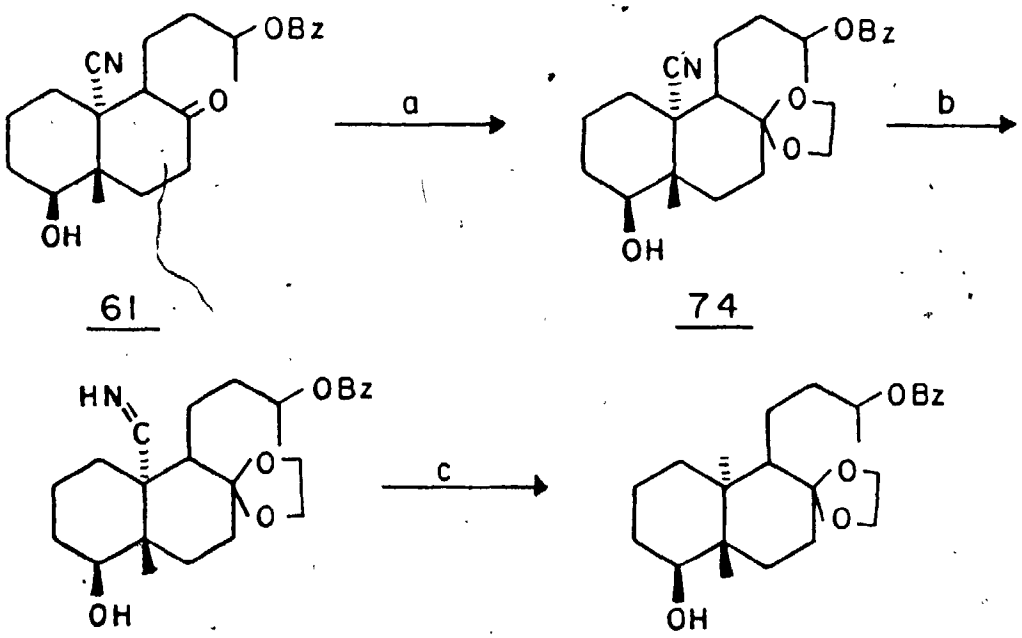
FIGURE . SECTIONS OF INFRARED SPECTRA OF CYANO KETONES - 67, 68, 69.

(A): 67 - $\frac{I_{C\equiv N}}{I_{C=O}}$ = 0.182 (B): 68 - $\frac{I_{C\equiv N}}{I_{C=O}}$ = 0.062 (C): 69 - $\frac{I_{C\equiv N}}{I_{C=O}}$ = 0.201

relative intensity of the C≡N/C=O absorbances is closer to Fig. 2 (A)- the trans compound 67 and again approximately three times the value of that of the cis compound 68. It appears then that this work supports the findings of Ireland [36] in that the traditionally thermodynamic conditions of hydrocyanation can be effectively converted to the kinetic conditions, thereby producing the trans fused cyano-ring junction. We have found, however, that with a carbon substituent β to the ketone and γ to the angular cyano function, then Nagata's findings [96] concerning the intensity of the cyano absorption appear to be reversed and may be explained on steric grounds. We have obtained results based on the tetracyclic species (See Section III) which support our findings on this issue. Model studies to investigate this phenomenon are currently in progress.

The next task in hand became the reduction of the nitrile function to the methyl, followed by deprotection of the benzyloxy function, oxidation and cyclization to give the tricyclic enone 36b.

The initial transformation in this sequence, that of nitrile to methyl provided many more problems than were anticipated. We initially attempted the traditional route [89] of (a) protection of the ketone as ketal, (b) reduction of the nitrile to imine, (c) Wolff-Kishner reduction of the imine to methyl. Scheme 22. The ketal 74 (n.m.r. - δ=3.8-multiplet-4 H), was subjected to Dibal H reduction to the imine 75 (i.r. 1620). However, Wolff-Kishner reduction [97] employing the Huang-Minlon modification gave less than 25% of a compound which, from its proton n.m.r. and i.r., was assigned the structure 76. Repeated attempts to improve this yield were fruitless. Obviously the aldimino group in



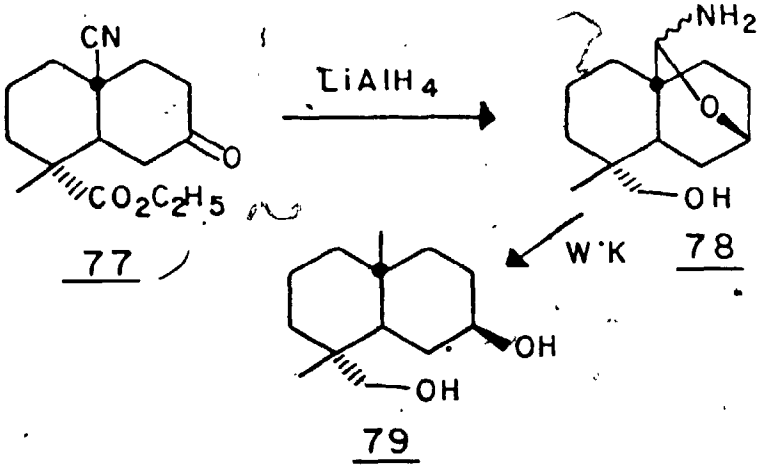
a) HO OH , TsOH, ϕH b) Dibal H , ϕH

c) NH_2NH_2, KOH , H_2O, T.E.G.

SCHEME 22

75 was not reactive enough to undergo Wolff-Kishner reduction [98]. Addition of hydrazine hydrochloride [98,36] to improve reactivity towards hydrazone formation, would have cleaved the ketal protecting group.

We next turned to the conditions of Meyer[99] by which he was able to convert the cyano ketoester 77 (Scheme 23) to the methyl compound 79

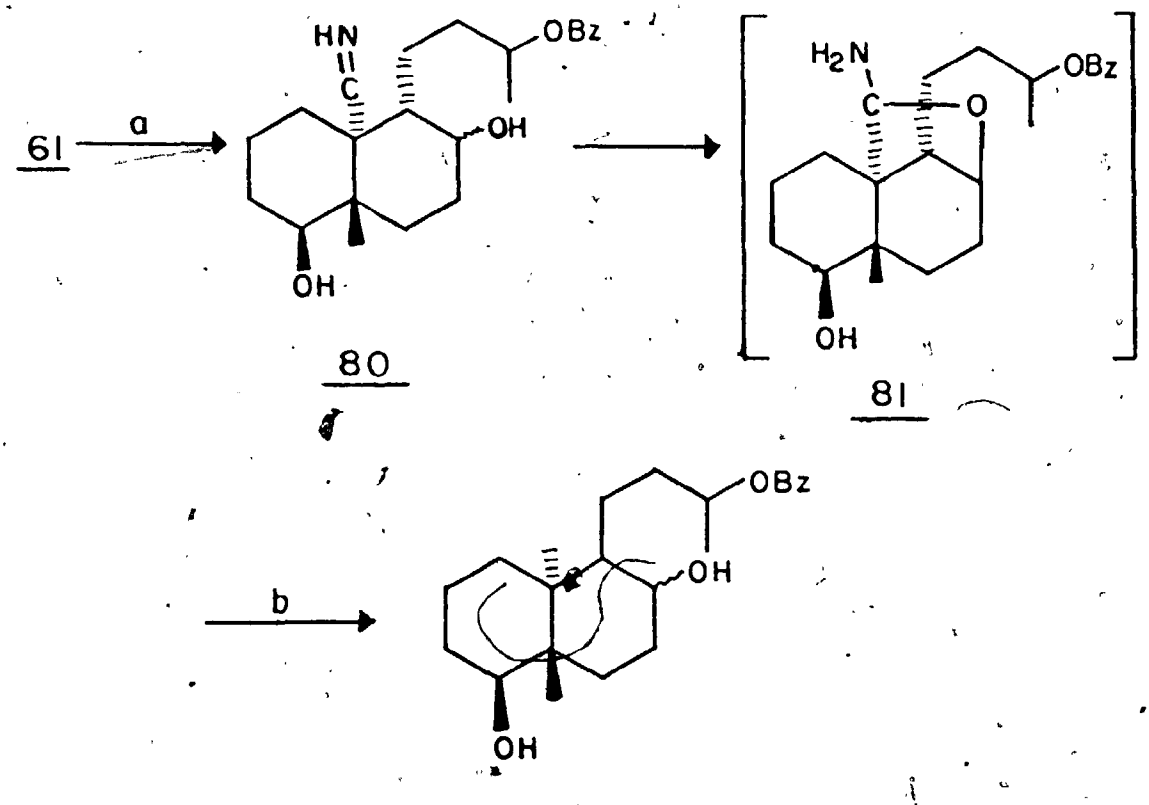


SCHEME 23

in extremely high yield. In this case, the hemi-aminal 78 prevented further reduction of the nitrile function to the amine.

In the event, the cyano ketone 61 was reduced using excess DibalH to the hydroxy imine 80 (Scheme 24). Although not used by Meyer, we employed hydrazine dihydrochloride in addition to hydrazine hydrate in order to ensure sufficient reactivity of hemi-aminal 81 should any be formed.

We have been able to isolate compound 82(Appendix II Spectrum 12) $[\alpha]_D^{23.5}$ +19.9° but as yet in 38% yield which is far from satisfactory.

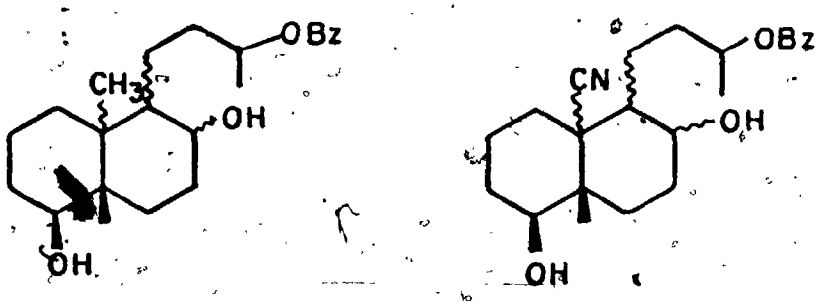


a) Dibal H , ϕH

b) NH_2NH_2, NH_2NH_2 2HCl ,
T.E.G , KOH

SCHEME 24

Further, two other materials were also isolated in very low yields and were assigned structures 83 and 84. Compound 83 (12%) appears to be an epimer of 82 - based on its n.m.r. spectrum which is very similar to

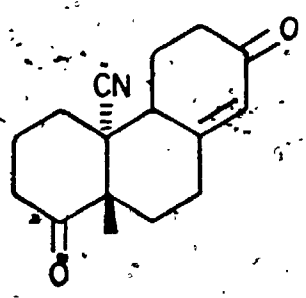


that of the latter. With six chiral centres present in the molecule it

is impractical to try to denote exactly which site or sites are epimeric in 82 and 83.

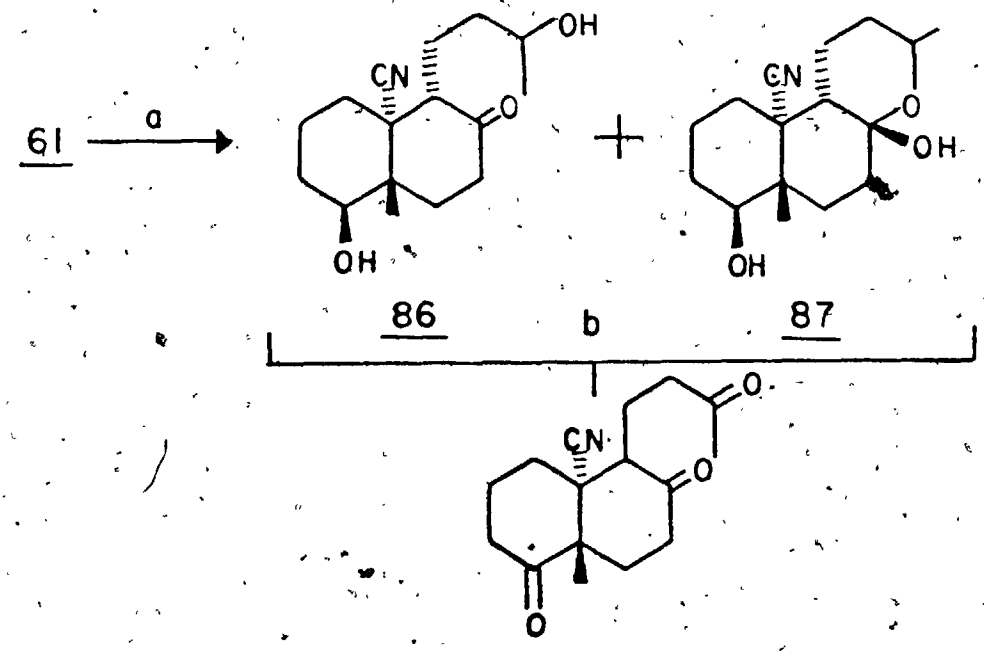
Such small amounts of 83 have been isolated that no further characterization was attempted. In the same way, compound 84 (17%), was assigned that structure based on spectral data; the i.r. spectra showing retention of nitrile and the n.m.r. spectrum not showing the presence of an additional methyl group.

Rather than proceed any further towards achieving the synthesis of the target compound 36b, we decided to expend our efforts effecting the transformation of cyano to methyl in acceptable yield. We are currently taking two approaches. First it is considered that perhaps the reactivity of the cyano group may be enhanced in a more rigid structure; as would be in the case of the tricyclic enone 85. That is,



85

perhaps if we were to proceed to tricycle prior to transformation of the nitrile, then the latter may be more amenable to reduction. Hence the cyano ketone 61 was deprotected which led to a mixture of free hydroxy and hemi-acetal compounds 86 and 87 respectively. Scheme 25.



a) H_2/Pd , EtOH

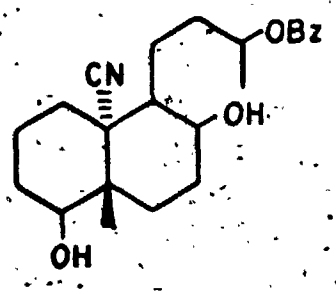
b) 2 phase Jones

SCHEME 25

Two phase Jones oxidation led to the crystalline triketone 88 (m.pt104-106°C) in fair yield.

Attempts are currently underway to improve this yield using pyridinium chlorochromate and to devise an effective method of aldol cyclization under conditions mild enough to avoid affecting the nitrile.

The second approach involves the protection of the two keto functions of the cyano-diketone 69, or of the two hydroxy functions of its reduced analog 89, with suitably acid stable protecting groups,



89

so that the nitrile could be reduced with acid hydrolysis to the aldehyde.

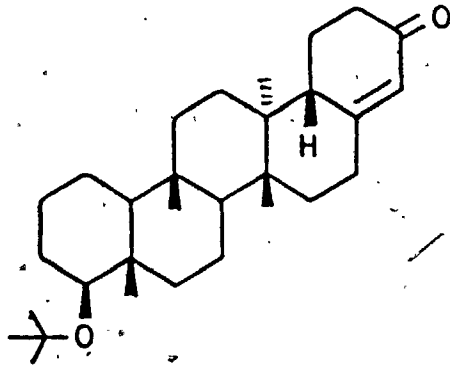
The latter could then be converted to the 1,3-dithioketal and hydrogenolysed using Raney nickel or be subjected to Wolff-Kishner reduction with the hope that it would be more reactive towards those conditions than the imine has been so far.

These two approaches are currently being pursued in an effort to obtain our target material viz 36b in high overall chemical and optical yields.

SECTION 3

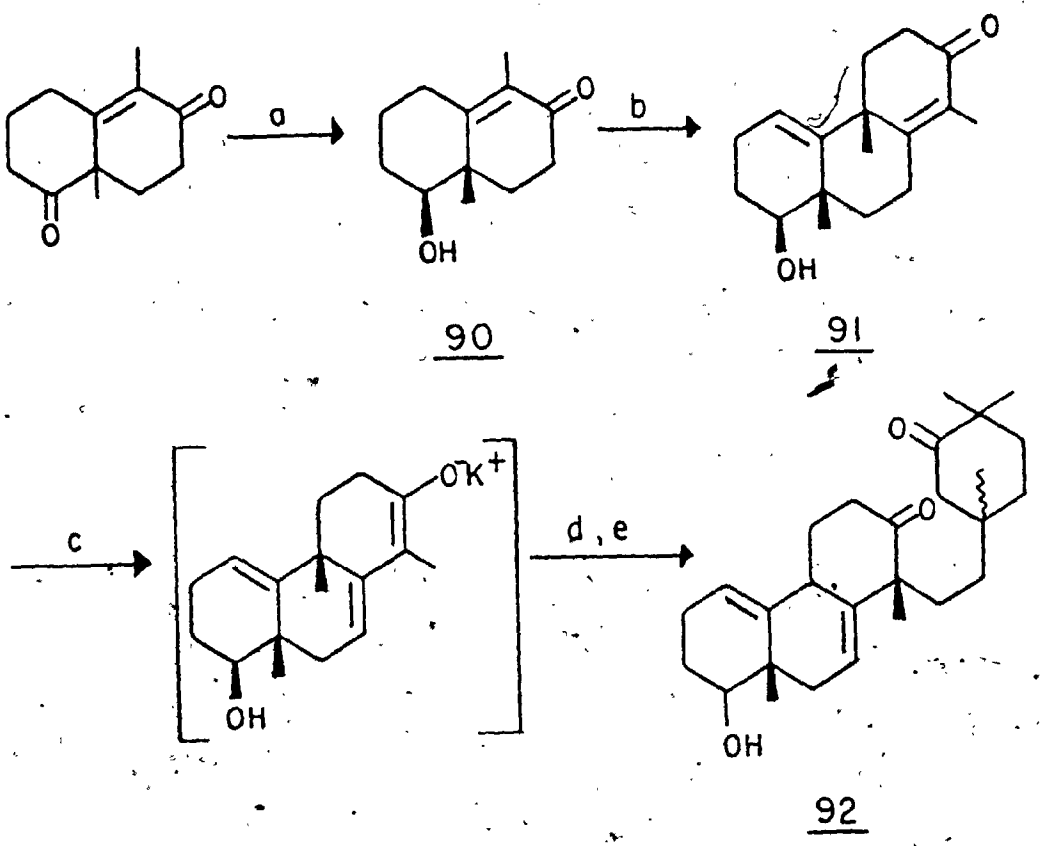
THE ABC + E → ABCDE ROUTE

Approaches to the synthesis of: 9β-(tert-butoxy)-6aβ, 8aβ, 12bβ, 14aα-tetramethyl-1,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14,14a,14bβ-octadecahydro-trans-anti-trans-anti-trans-anti-picen-3(2H)-one (120)



120

Earlier studies in these laboratories[102], revealed that the easily accessible tricyclic dienone 91 could be made to react via its dienolate anion 4, with the tosylate 3[2], in high yield. Scheme 26. Further, the crystalline diastereomeric diketones 92 which were inseparable by chromatographic methods, appeared to resist hydrogenation of the two double bonds under neutral conditions and using palladium as catalyst. However when subjected to the conditions worked out by

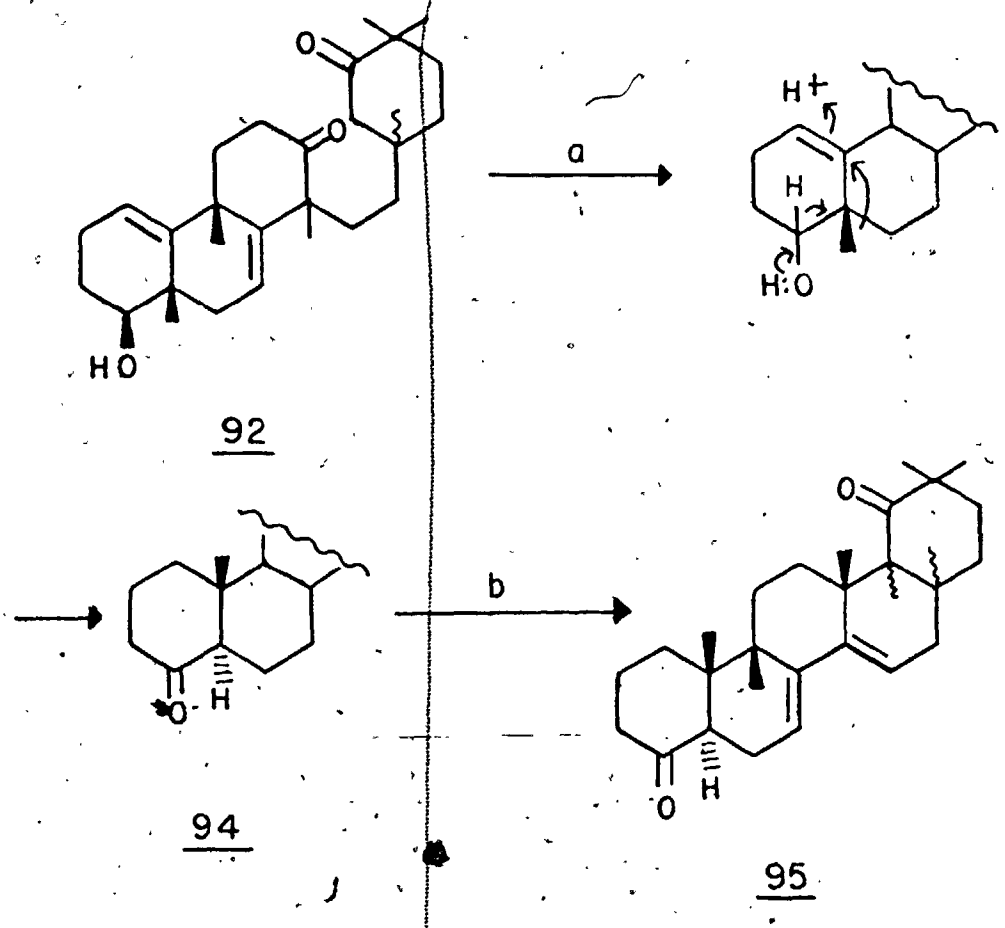


90 91 92

a) $NaBH_4$, C_2H_5OH b) $C_2H_5COC_2H_3$, $NaOCH_3$, CH_3OH
c) KO t-Amyl, ϕH d) (3), ϕH e) $(COOH)_2$, C_2H_5OH

SCHEME 26

ApSimon et al[49] (palladium/charcoal, boiling p-xylene, 5 days) which leads to trans-fused ring junctions, the diones 92 appeared to undergo an interesting rearrangement first noticed in attempts to hydrogenate the tricyclic ketone 91 [103]. Presumably, the C-5 (4b) double bond of 92, because of the prolonged hydrogenation conditions, appeared to be protonated resulting in migration of the C-8a methyl group to the C-4b position. 1,2-hydride shift, facilitated by the lone pair on oxygen then gave rise to the keto-product 94 - (Scheme 27).



92

94

95

a) H_2/Pd , p-xylene

b) TsOH , p-xylene, Δ

SCHEME 27

Further, the C-10 (10a) (C-7,C-8*) double bond of 92 (94) proved to be a lever for rearrangements as well. Attempted cyclization of the triketone 94 using toluene sulfonic acid in boiling p-xylene[2b], led only to the pentacyclic material 95 in which the methyl group, originally at C-1 of 92 (C-14*) has migrated to the C-13* position in order to allow conjugation of the (C-7*-C-8)* and (C-14-C-15)* double bonds.

It thus became obvious that dienolate alkylation of the tricyclic ketone 91 gave products which resisted transformations to the desired materials.

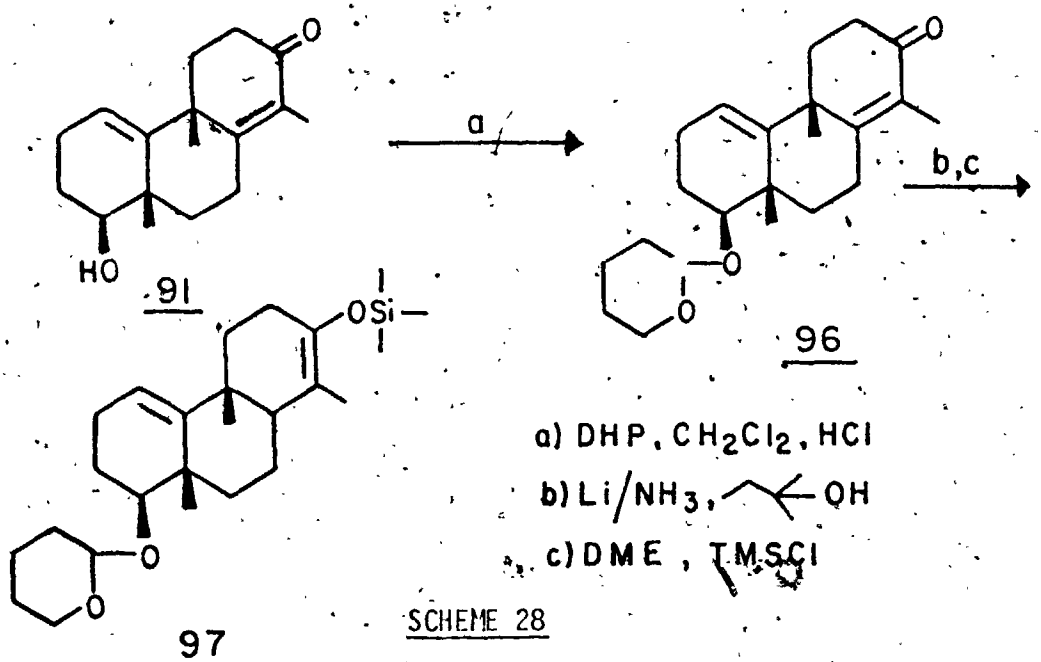
We thought then, that one way to eliminate at least one of the double bond obstacles would be to reductively alkylate the triketone

91 using the Birch method[104], and using the conditions developed by Stork[105].

However, we felt sure that the tosylate 3 would not be active enough to trap, in situ, the enolate which would result from the lithium-ammonia reduction of the enone 91.

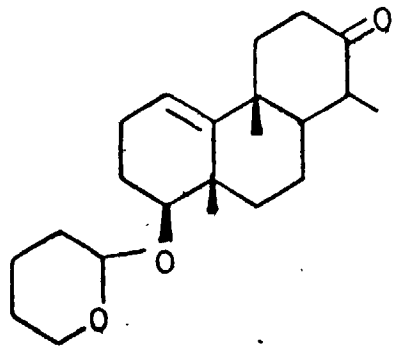
Hence we decided to trap that enolate as the trimethylsilyl enol ether, following the procedure of Stork[106].

In the event, the enone 91 was converted to the tetrahydropyranyl ether 96 and was then subjected to the reduction/trapping sequence[106]. (Scheme 28).



SCHEME 28

However, in several attempts the best yield of the enol silyl ether 97 (Appendix II, Spectrum 13) realised was 48%. Further, chromatographic purification of 97 always served to deteriorate these yields by hydrolysis of the enol ether to the saturated (en)-one 96b

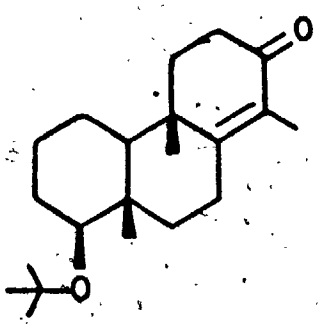


96b

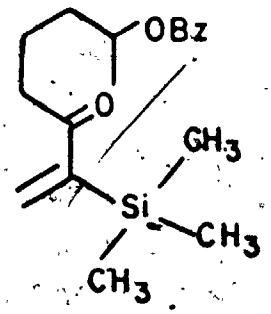
In any event the lithium enolate of the waxy-semisolid 97 was regenerated using methyl lithium in dimethoxyethane. Treatment of this enolate with the tosylate 3 led only to saturated ketone 96b Various modifications of reaction conditions (time, temperature, reactant ratios), gave no indication of alkylation.

It seemed to us then that a better strategy would be to eliminate the C-5 (4b) double bond from the enone 91 so as to avoid having to remove it by two or three transformations later on in the synthetic route. Secondly, we decided that the synthon 3 was not a good one in this route owing to (i) its relative inactivity and more importantly (ii) its racemic character which meant that 50% of any alkylated product obtained would lead to unusable isomer having the undesired stereochemistry at C-17*.

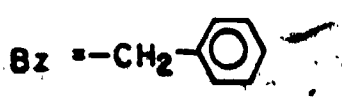
Therefore our key intermediate became the tricyclic enone 98 and the silylated vinyl ketone 99. The latter bis-annelating reagent was



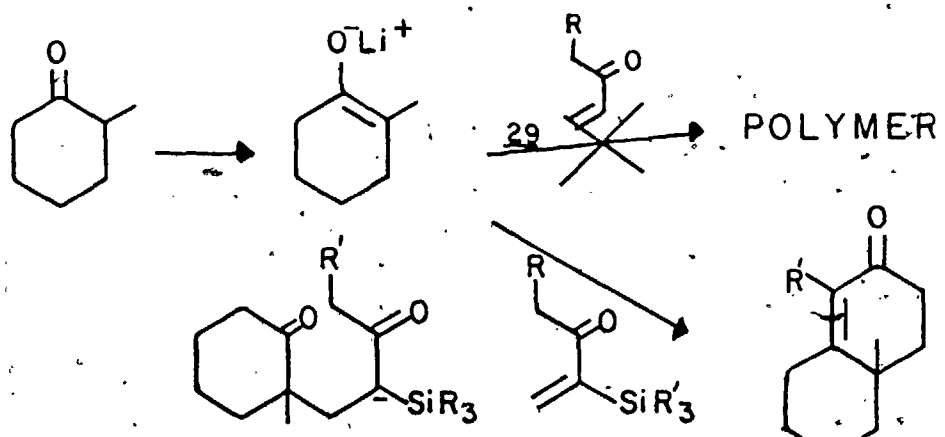
98



99



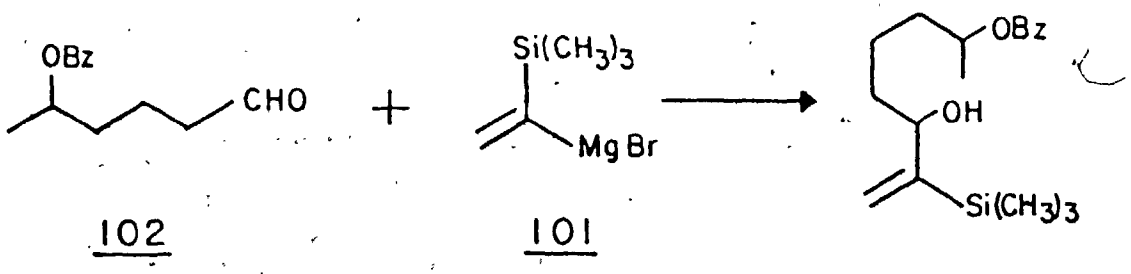
chosen since silylated vinyl ketones[69,73] have found wide use in organic synthesis, particularly in the steroid and terpenoid syntheses fields[69,73]. Such materials have been found to be much more stable to alkylating conditions of normal ketones and enones, than their unsilylated counterparts[107], such as 29 (Section 2).



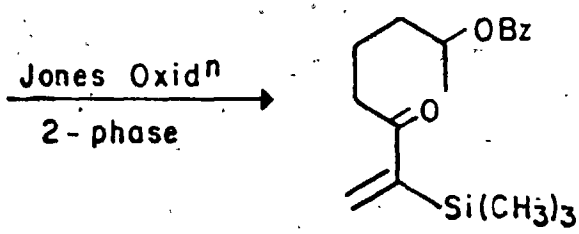
100

The tertiary alkyl silicon group appears to stabilize the intermediate negative charge (in 100) generated, so that Michael addition proceeds faster than polymerization can take place.[107] For this reason silylated vinyl ketones have been found to be amenable to the direct trapping of the lithium enolates formed in situ from the lithium/ammonia reduction of α,β-unsaturated enones[69,107].

The silylated enone 99 was prepared in good yield as shown in Scheme 29. The vinyltrimethylsilylmagnesiumbromide 101 was prepared using slight modifications of the conditions worked out by Ganem[107]. The synthesis of the aldehyde 102 has been described in Section II (Schemes 8 and 18).

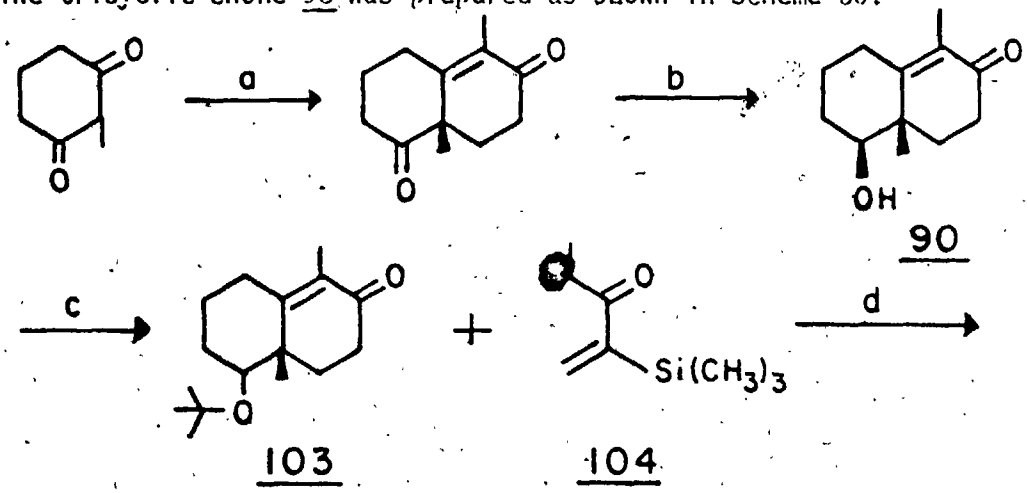


102 101



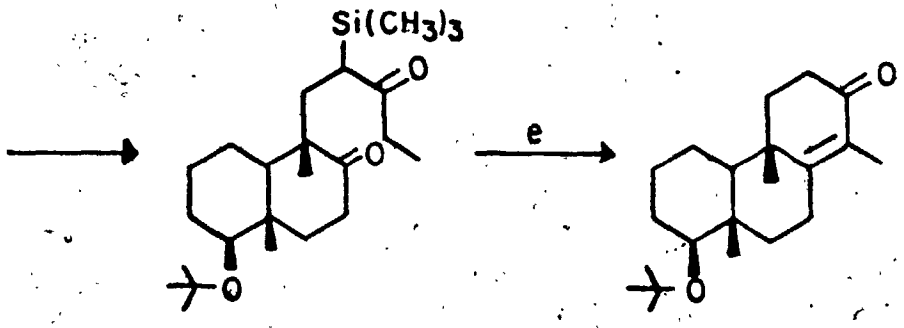
99

The tricyclic enone 98 was prepared as shown in Scheme 30.



90

103 104



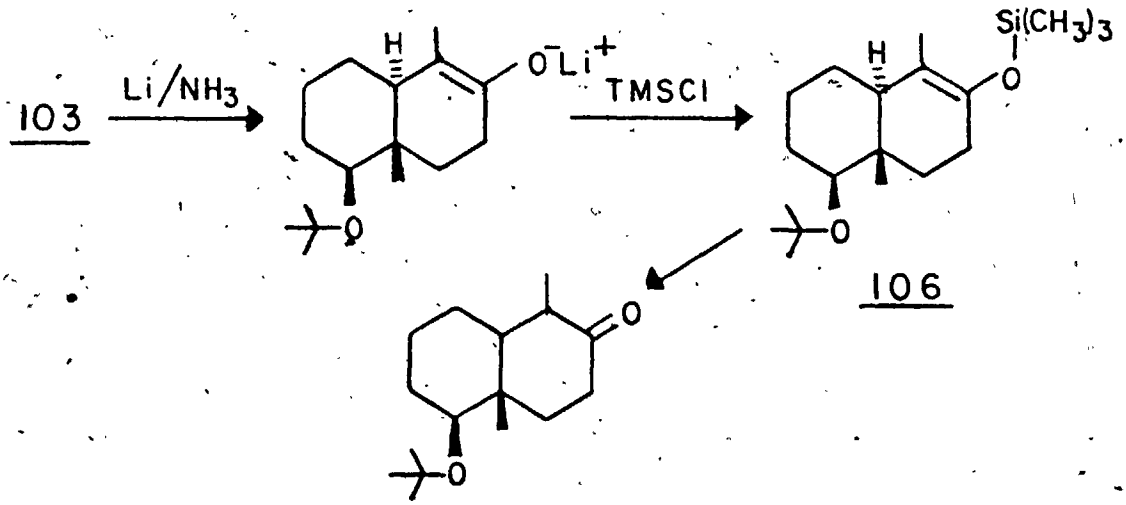
105 98

a) (i) E.V.K., KOH, CH_3OH (ii) C_4H_9N, ϕH b) $NaBH_4$, EtOH
c) $\rangle=$, BF_3-Et_2O, 100% H_3PO_4, CH_2Cl_2 d) (i) Li/NH_3 (ii) NH_3 ↑
(iii) (104), D.M.E. e) KOH, CH_3OH, Δ

SCHEME 30

The best results in the blocking of the hydroxy function of 90 were obtained using the combination catalyst[111] - BF_3-Et_2O/100% H_3PO_4. Although the reaction proceeded with only 78% conversion of alcohol to ether, the unreacted starting material could be easily and cleanly recovered and recycled. The silylated ethyl vinyl ketone 104 was prepared by the reaction of vinyltrimethylsilyl magnesium bromide with acetaldehyde, followed by 2-phase Jones oxidation, using the conditions of Ganem[107].

Initially, we attempted trapping the lithium enolate formed from the reduction of compound 103 as the trimethyl silyl enol ether 106.

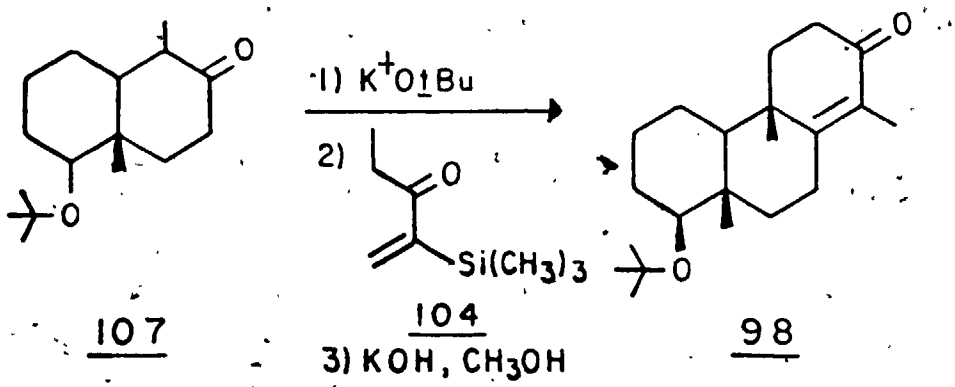


107

However, attempted isolation of enol ether 106 in a pure form led to drastic deterioration of the product and hence the yield. Further, we found that 106 did not store well, even under argon at -15°C.

Therefore we opted for the direct trapping of the enolate according to the Stork precedent[105,106]. The dione 105 was not isolated, but was cyclized to the desired enone, the overall yield of the process being about 50% from the ether 103. However the bicyclic saturated ketone 107 could also be recovered in up to 30% yield. We found that

the latter could be used to generate the enone 98 in up to 60% yields by reaction with the silylated enone 104 in the presence of potassium tert-butoxide, followed by cyclization in methanol/potassium hydroxide[107].



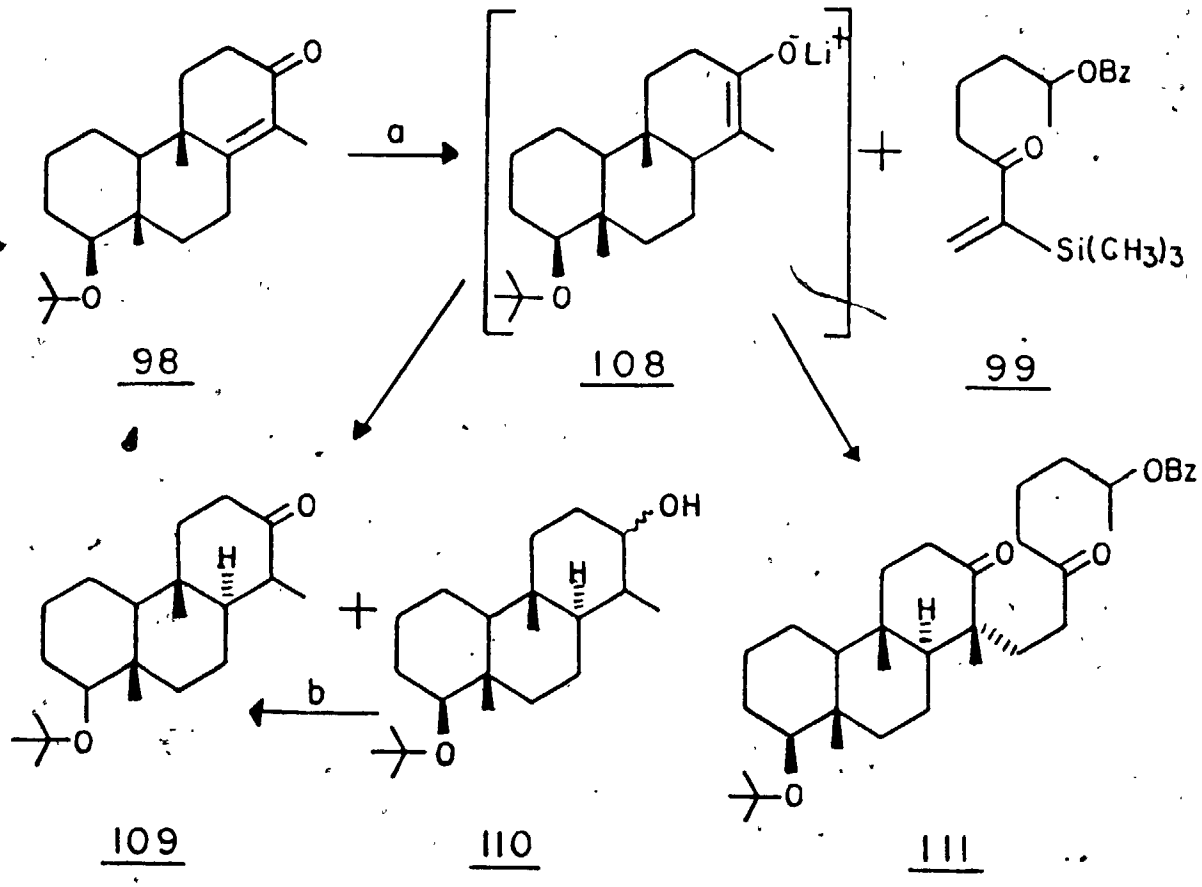
107 104 98

The tricyclic enone 98 so produced was identical to that produced in the reductive alkylation sequence. This combination of sequences thus improved the yield of enone 98 to a respectable 70%..

Because of the generally unsatisfactory results which we had obtained in the trapping of lithium enolates as the silyl enol ethers, we opted for the direct reductive alkylation of the tricyclic enone 98, the alkylating agent being the silylated enone 99.

The results of this sequence proved very disappointing. At best only about 23% of the alkylated dione 111-Appendix II Spectrum 11-could be realised, together with a 3:1 mix of the tricyclic ketone 109 and the alcohol 110 - Scheme 31.

Further, the sequence did not appear to be amenable to large scale preparations, since the yield of the dione 111 appears to drop drastically with increasing reaction size. Optimum yield was thus obtained with



98 108 99

109 110 111

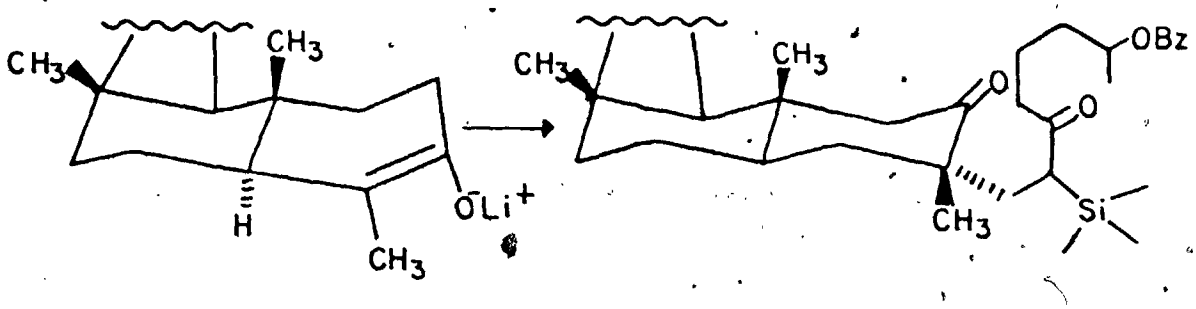
a) Li/NH_3

b) Jones Oxidⁿ

SCHEME 31

reaction sizes ranging between 300-500 milligrams.

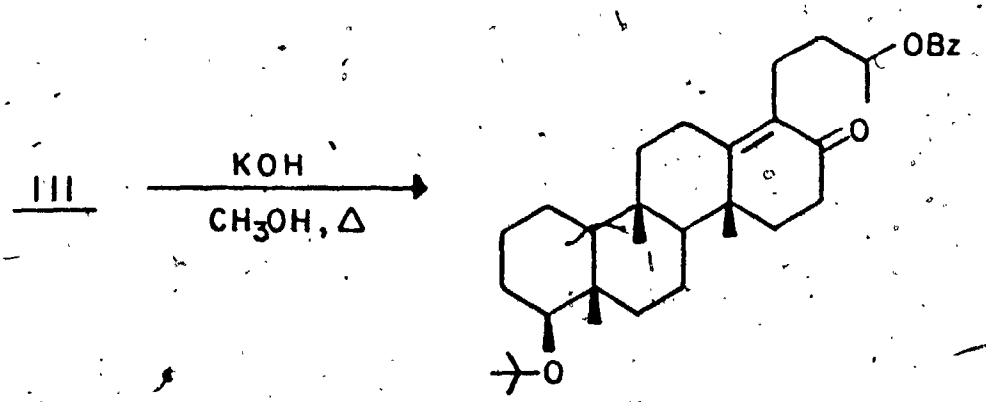
The stereochemistry of the methyl group at C-14* of compound 111 has so far been assigned based on literature precedent[105,108]. Visually, one can argue that on both steric and thermodynamic grounds the alkylation of the intermediate enolate 108 will occur from the least hindered face, opposite the two angular methyl groups[109]. Thus equatorial orientation of the bulky alkyl side chain will result - viz 111.



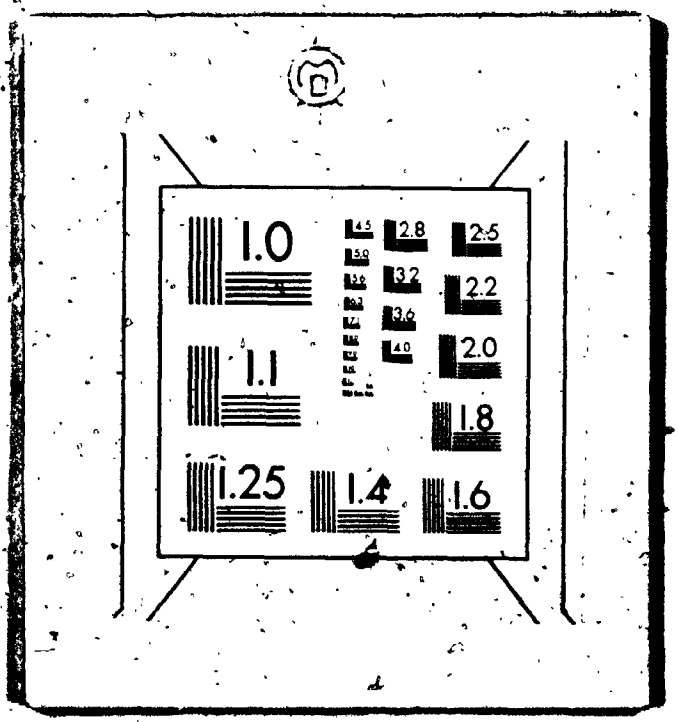
108 111

Confirmation of this stereochemistry could not be obtained by benzene solvent shifts in the n.m.r. spectrum owing to the signal of the tert-butyl group which masks any shift of the methyl group. However, there appeared to be a negative shift of a methyl group by about 20 Hz, when the exercise was attempted using a 60 MHz instrument. A request for a 200 MHz determination of these solvent shifts is in preparation.

Base catalysed cyclization [69] of compound 111 proceeded smoothly to give almost quantitatively the tetracyclic enone (112) (Appendix II, Spectrum 8).



112



However the overall yield from the tricyclic enone 98 to the tetracyclic species 112 was unacceptable (ca 20%), particularly since the coupling of the two synthons can be viewed as the key step in our convergent approach. We considered then that the silylated enone 99 was not reactive enough to trap the lithium enolate 108 (Scheme 31). Further it was obvious that over reduction was occurring as evidenced by the formation of the alcohol 110.

Therefore we decided to avoid the reductive trapping sequence in favour of alkylation of the saturated ketone 109. We considered that the conditions for Birch reduction of the enone 98 to 99 could more easily be controlled so as to avoid over-reduction to the alcohol 110. Further in the Michael reaction sequence, as in 107 to 98, we had the advantage of using the more reactive potassium enolate.

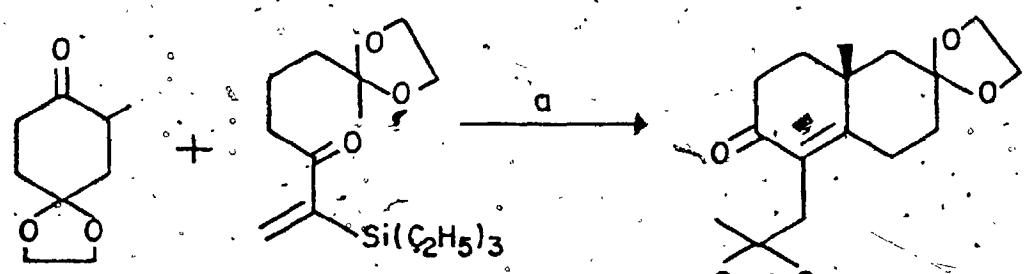
We found that Birch reduction of the enone 98 did not proceed as easily as anticipated. Under conditions which avoided alcohol formation - trace of water as proton donor, low lithium:substrate ratio, short reaction times with ether as solvent - we obtained about 30-40% of unreacted starting material together with the desired saturated ketone.

Conditions which ensured complete reaction of starting material gave in addition, the alcohol 110 in up to 25% yield. We opted for the latter conditions as facile 2-phase Jones oxidation converted the alcohol to the ketone.

However, just prior to preparation of this thesis, we undertook the catalytic hydrogenation of the enone 98 under neutral conditions, using palladium/charcoal catalyst. After only 6 hours we obtained almost quantitative reduction. We were able to isolate over 90% of what appears

to be the saturated ketone (n.m.r.,t.l.c.). So far vapour phase chromatographic analysis to compare this product against the standard 109 has not been done. Neither has v.p.c. analysis of the product mixture to determine whether other saturated ketones e.g. the cis ring fusion ketone, may be present. We intend to subject the ketone obtained via both routes to Kugelrohr distillation so as to compare their refractive indices.

Ganem[107] was able to subject the bis-annelating agent 113 to Michael addition to the keto-ketal 114 using potassium tert-butoxide as base. The enone 115 was produced in overall yield of 70%.



114 113 115

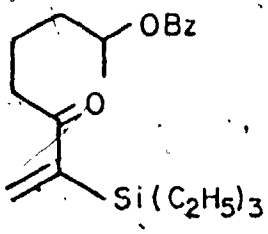
a) (i) $KO\underline{t}\,C_4H_9$, $\underline{t}\,C_4H_9OH$

(ii) KOH/CH_3OH

However, in our case, Michael addition of the silylated enone 99 to the saturated tricyclic ketone 111 followed by cyclization led to less than 30% yield of the desired tetracyclic enone 112 under optimum conditions.

In all instances we were able to recover all unreacted tricyclic ketone, but the hard-won bis-annelating agent was consumed, probably by polymerization. It is our opinion then, that the trimethyl silyl enone 99 is not as stable to such vigorous conditions as the triethyl

silyl species used by Ganem[107]. At the time of preparation of this thesis, we were in the process of preparing the triethylsilylated enone 116.

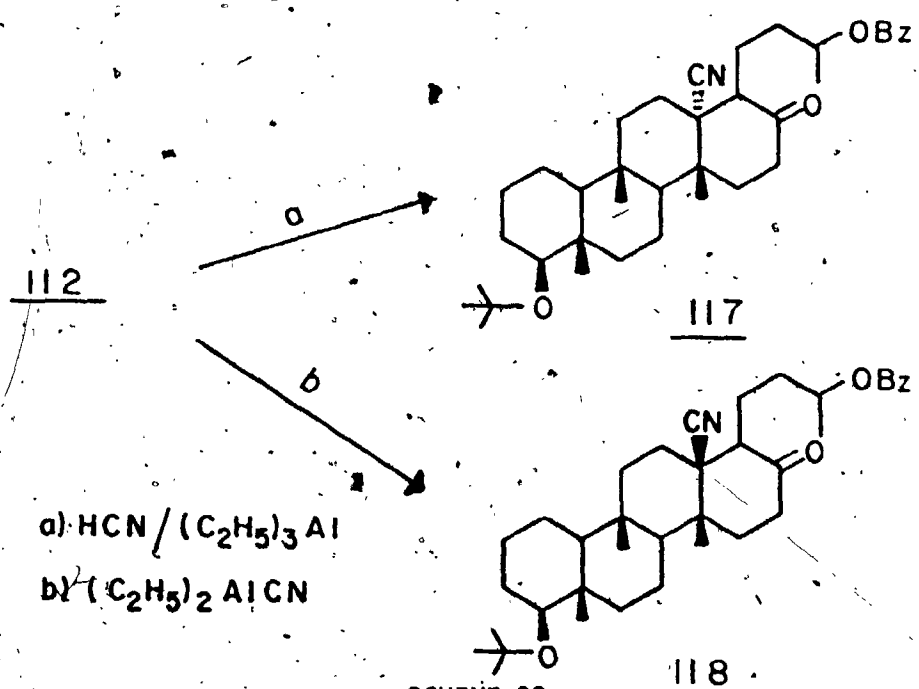


116

in order to attempt to improve the yield of this key carbon-carbon bond formation step in our route.

With only very small amounts of tetracyclic enone 112 in hand we undertook the introduction of the methyl group at C-13* of the tetracyclic compound 112, using the Nagata hydrocyanation reaction[89]. Kinetic conditions ($HCN/(C_2H_5)_3Al$ were used in order to generate the trans-fused C-D ring junction. (See Section 2 for discussion.)

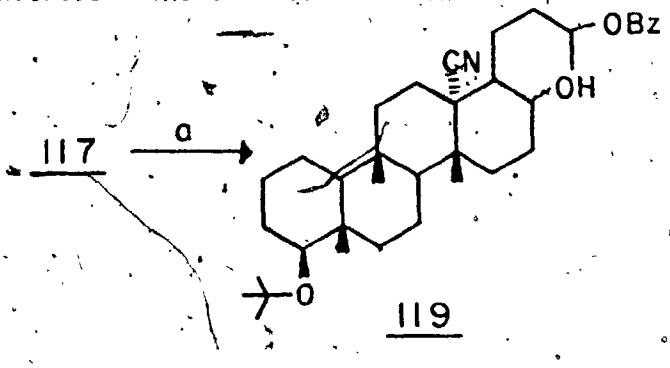
Hydrocyanation of enone 112 proceeded smoothly to give the cyano-ketone (Appendix II Spectrum 9) in very high yield (Scheme 32).



SCHEME 32

The stereochemistry of the cyano group was assigned based on literature precedent[89]. However confirmation was undertaken using the approach discussed in Section 2 of this report - involving compounds 67, 68 and 69. Hence the cis-fused cyano ketone 118 was prepared using thermodynamic hydrocyanation conditions [89][$(C_2H_5)_2AlCN, C_6H_6$)]. A comparison of the infra-red spectrum of the two cyano compounds 117 and 118 reveals that the trans-fused isomer 117 displays a nitrile absorption of higher intensity than the cis-fused material - Fig. 3. This result underscores our observations described previously in this report. Again, we reiterate that model studies will be undertaken to thoroughly investigate this phenomenon, with particular reference to angular cyano compounds having substituents α to the carbonyl and β to the nitrile. (These types were not covered by Nagata[96]).

We attempted the conversion of the cyano group of 117 to the methyl on a small amount of material. The route of choice was based on Meyer's[99] precedent. Thus sodium borohydride reduction of 117 gave the alcohol 119 which was not purified but was subjected to Dibal H reduction of the nitrile. The i.r. of the reduction product did not show nitrile.



However, Wolff-Kishner reduction resulted in the total transmogrification of the starting material since the only product isolated is one which

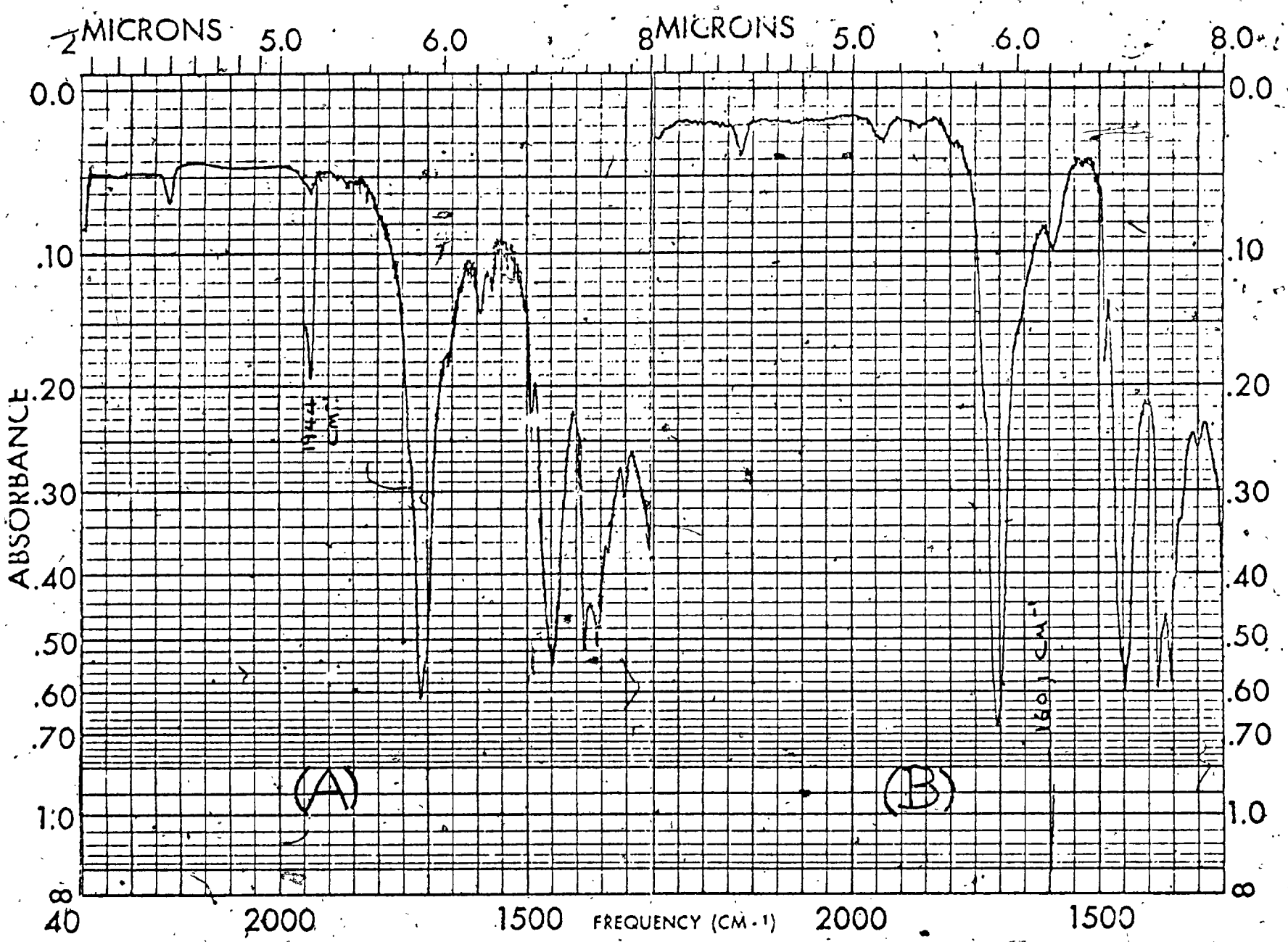


FIGURE 3: SECTIONS OF INFRA RED SPECTRA OF CYANO KETONES :- 117 & 118

(A): 117 - $\frac{I_{C\equiv N}}{I_{C=O}}$ = 0.046

(B): 118 - $\frac{I_{C\equiv N}}{I_{C=O}}$ = 0.023

from its n.m.r. spectrum appears to be simply hydrocarbon residue.

At this stage, further attempts at transformation of the cyano compound 117 to the target compound 120 were suspended in favour of waiting until optimum conditions were worked out for the transformation of the optically active species 67 to the tricyclic species 36b (Section 2). Further, it is necessary that the yield in the key coupling step, (98 + 99) be improved to a great extent. We envision greater success in this area with the use of the triethylsilyl analog of the enone 166.

EPILOGUE

The foregoing dissertation has described various synthetic approaches to the pentacyclic triterpene skeleton. Whilst the syntheses of the target compounds have not been achieved, the various routes investigated new and interesting facets of the chemistry of these systems adding to our overall understanding. Perhaps the most obvious achievement of this dissertation is that it has elucidated very many of the factors , be they steric, electronic or structure-reactivity types, which influence the chemistry of compounds related to the terpene skeleton.

In conclusion, it is convenient to summarize what are considered to be the contributions to knowledge, which could arise from this thesis:

SECTION 1

(a) The synthesis of a tetracyclic species 4b, a potential synthon in the synthesis of β-amyrin, has been described.

(b) An unusual but interesting, acid catalysed rearrangement of (Compounds 1 → 10) a substituted methoxy tetralone has been demonstrated.

SECTION 2

(a) The influence of steric factors on the intramolecular aldol condensation of 1,5-diketones has been shown. Compound 26 → 31.

(b) The syntheses of optically active compounds 55 and 58 which are potential intermediates in the synthesis of optically active pentacyclic triterpenes, have been described.

(c) The amino acid mediated intramolecular aldol condensation of 1,5 diketones has been studied. These studies underscored the influence of the amino acid: substrate-structure relationship, on the success of reactions of this type.

(d) The Nagata hydrocyanation reactions have be explored in great detail. These studies support the kinetic vs thermodynamic control of stereochemistry of hydrocyanation by manipulation of substrate or reagent. However, these studies showed that Nagata's correlation between the nitrile configuration and the infra-red band intensity is reversed for compounds with substituents at the position β to the nitrile function.

(e) The synthesis of optically active compounds 82 and 88 , which are potential synthons in the synthesis of optically active pentacyclic triterpenes, have been described.

SECTION 3

(a) The synthesis of a tetracyclic compound 117 having seven of the nine asymmetric centres required for friedlin IV has been described. The flow sheets in Appendix III delineate the manner in which the various synthons synthesized in this work, may be included in total syntheses of pentacyclic triterpenes.

A Final Word

The Warning

All synthetic chemists pay heed
To continue to fuel man's need
To replace nature's will
With plastics and pill
Could result in a robot-like breed

EXPERIMENTAL

General: All melting points were taken on a Fisher-Johns apparatus and are uncorrected. Boiling points are not corrected. Infrared spectra were recorded on a Perkin-Elmer Model 237B Infrared spectrometer, ultraviolet spectra on a Perkin-Elmer 202 Ultraviolet-Visible Spectrophotometer. Mass spectra were obtained on an AE1 MS12 Instrument at Trent University. Nuclear magnetic resonance spectra were measured on a Varian T-60 (Carleton University) or Varian HA-100 (University of Ottawa), using tetramethylsilane as an internal standard. Chemical shifts are expressed in the δ scale with the following designations; s, singlet d, doublet; t, triplet; m, multiplet; br, broadened. Combustion analyses were performed by Spang Microanalytical Laboratory, Ann Arbour, Michigan, and Guelph Chemical Labs. Ltd. Guelph, Ontario.

All reactions and chromatograms were routinely monitored by analytical thin-layer chromatography (tlc) (Merck 60 PF-254 plates, 0.25 mm). Spots were developed by exposing to iodine vapour, or by spraying with ceric sulfate and heating. Preparative thin-layer chromatography was carried out on Merck 60 F-254 precoated silica gel plates of 2.0 mm thickness. Bands were visualized by viewing under an ultraviolet source or by staining one thin edge with ceric sulfate/heating. Silica gel (Davison Chemical Co., grade 923, 100-200 mesh) was used for column chromatography. Flash chromatography refers to elution of material on a silica gel pad (silica gel 60H-E.M. Reagents, sintered glass funnel) using water aspirator suction, with collection and analysis of 50-150 ml fractions. H.P.L.C. was performed using a Waters Prep 500 High Performance Liquid Chromatograph. Optical rotations were obtained using a Perkin Elmer 141 Polarimeter.

The term "dry benzene" and "dry toluene" refer to benzene or

toluene which was distilled and stored over sodium. "Dry tetrahydrofuran" and dry dimethoxyethane were obtained by distillation from lithium aluminium hydride. "Anhydrous ether" was available from Mallinckrodt Canada Ltd. Petroleum ether refers to the fraction boiling at 30-60°.

Abbreviations

THF	Tetrahydrofuran
DMSO	Dimethyl sulfoxide
DME	Dimethoxyethane
TMSCl	Chlorotrimethylsilane
Py	Pyridine
DMF	N',N-dimethylformamide
Ts,tosyl	p-toluenesulfonyl
THP	tetrahydropyranyl
H.P.L.C.	High Performance Liquid Chromatography
L.S.R.	Lanthanide Shift Reagent

SECTION 1

2-Keto-1-methyl-1[2-(3-Keto-1,4,4-trimethyl cyclohexyl)ethyl]-6-methoxy-3,4-dihydronaphthalene 1a and 1b

Potassium metal (1.5 gm, 38 mmol) tert-amyl alcohol (6 gm, 68 mmol) and dry benzene (200 ml) were refluxed for 2 hours. (Until all potassium dissolved). Cooled to room temperature and β-tetralone 2[1] (6.3 gm) (33.5 mmol) in 25 mls of benzene was added dropwise. Benzene/tert-amyl alcohol were then azeotroped off whilst the solvent level was kept constant by addition of fresh benzene, over a 1-2½ hour period. The reaction mixture was then recooled to room temp. and the tosylate 3[1,2] (12 gm, 31.4 mmol) in 30 mls of benzene was added slowly, and the reaction stirred overnight at room temp. then refluxed for 25 hours more. The cooled reaction mixture was then poured into ice/water and extracted with ether (x2). The cold yellow aqueous layer was then acidified carefully with a few drops of conc. H_2SO_4 and immediately extracted with ether (x3). The combined organic layers were washed with satd. aq. $NaHCO_3$; satd. aq. NaCl and dried ($MgSO_4$). Concentration yielded 17.5 gms of an oil, 5 gms of which was subjected to repetitive H.P.L.C. From this quantity was realized 1.2 gm of an oil which was assigned the structure 16 but which appeared to be contaminated by a small amount of the stereoisomer related to 1b. I.R. (neat) $\bar{\nu}$ cm^{-1} (C=O) NMR ($CDCl_3$) δ (ppm) 0.85 (b.s.-9H gem di-CH_3, C-1'-CH_3) 1.35(s.2H. $CH_2C(OCH_2)_2$) 1.4 (s.3H C-1 CH_3) 3.95 (s.4H.$(OCH_2)_2$) 3.9 (s.3H.OCH_3). The remaining 16.1 gm were dissolved in ethanol (250 ml), 200 mls of satd. aq. oxalic acid solutions were added and refluxed for 1½ hr. Water and ethanol were taken off at reduced pressure and ether and water were

added. The layers were separated and the aqueous layer was extracted with ether (x3). The combined organic layers were washed with satd. aq. $NaHCO_3$; water and satd. aq. NaCl, then dried ($MgSO_4$). Repetitive H.P.L.C. of the concentrated material gave (a) 2.6 gm of β-tetralone - (b) 1.8 gm of 1b (c) 3.2 gm of a mixture of 1a and 1b (d) 1.4 gm of 1a contaminated with a trace of 1b. The yield of 1a and 1b was 59%. i.r. (neat) $\bar{\nu}$ cm^{-1} 1700, 1705 (2 C=O). N.M.R. ($CDCl_3$) δ ppm: 1.0 (2s.6H gem di-CH_3) 1.4 (s.3H.C-1'CH_3) 1.5 (s.3H C-1 CH_3) 2.0 (s.2H.CH_2CO) 4.0 (s.3H OCH_3) 6.6-7.2 (m.3H.ArH). Mass Spec. m/e (r.i) 356 (M^+,15) 203(100) 175 (33).

Anal. $C_{23}H_{32}O_2$ Calcd: C: 77.54, H: 8.98

Found: C: 77.25, H: 9.11

1-[2-(3-Keto-1,4,4-trimethylcyclohexyl)ethyl]-2-methyl-6-methoxynaphthalene. 10

A mixture of 1a and 1b (3.9 gm, 11 mmol) p-toluenesulfonic acid (14 gm) in p-xylene (300 mls) were refluxed for 6 hrs. Water (100 mls) was added to the cooled solution and the layers separated. The aqueous layer was extracted with ether (x2) and the combined organic extracts washed with satd. aq. $NaHCO_3$, water and satd. aq. NaCl; then dried ($MgSO_4$). Concentration and chromatography (silica gel) gave 260 mg of 7 (spectral data identical to authentic sample[1]), and 1.56 gm (42%) of 10 mpt. 109-110°C. i.r. (Kbr) $\bar{\nu}$ cm^{-1} 1710 (C=O) 1610, 1625 (C=C). U.V. λ_{max} 273, 285 ($\varepsilon = 8.1 \times 10^3$), 290. N.M.R. (See Appendix II Spectrum 1. Mass Spec: m/e (r.i.) 338 (M^+,100) 185 (98) 199 (12) 139 (28).

Anal: $C_{23}H_{30}O_2$. Calcd. C; 81.67 H: 8.87

Found C; 81.38 H: 9.17

Attempted cyclization of 1a using di-isopropylamidomagnesium bromide

(a) Prep. of $(i\text{-}C_3H_7)_2NMgBr$

To a suspension of Mg. (400 mg, 16.4 mmol) in 10 mls of anhydrous THF was added Ethyl bromide (1.12 ml) at reflux over a 10 min period. The reaction was then heated at reflux for 30 mins under N_2, cooled to room temp. and 2.80 ml of freshly distilled diisopropylamine was added dropwise over 10 mins. The reaction was then refluxed for 30 mins more; then kept at about 50°.

(b) Dione 1a (212 mg, 0.76 mmol) was dissolved in 15 mls of anhydrous T.H.F. and cooled to -50°C under argon. To this was added dropwise with stirring over 1 hour 9 mls of the 1.5 M Grignard (prepared as in a). The reaction was allowed to warm to room temp. over 1 hr. then refluxed - for up to 110 hours. It was then poured into satd. aq. NH_4Cl and extracted with ether (x1) then methylene chloride (x2). Drying ($MgSO_4$) followed by chromatography (prep. plate) yielded starting material 1b and 18 mg of a material which corresponded on tlc to alcohol 9.

Attempted Epoxidation of the Keto Ketal 16

1: Using Dimethyloxosulfonium methylide

Sodium hydride (0.07 gm 3 mmol) (60% disp. in mineral oil) was placed in a 3-necked flask and washed 3 times with 30-60 petroleum ether. The system was evacuated over 10 min via water aspirator and after breaking

the vacuum, methyloxosulfonium iodide [7] (0.66 gm, 3.0 mmol) was introduced. The system was then placed under N_2. Freshly distilled dimethylsulfoxide (5 mls) was slowly introduced via syringe with stirring whilst H_2 was allowed to evolve over a 15-20 min period. A solution of ketal ketone 16 (520 mg, 1.2 mmol) in DMSO (4 mls) was added dropwise to the milky white reaction mixture which was stirred for 0.5 hr at room temp and 1½ hr at 50°C. Water (30 ml) was added to the cooled reaction mixture, which was then extracted with ether (x3). The organic extracts were washed with satd.aq. NaCl and dried (Na_2SO_4). Chromatography (silica gel 10% ether/pet ether) gave a mixture made up of a small amount of starting material 16 and the diastereomeric mixture of diketones 1b: Spectral data and mass spectrum identical to authentic sample.

2: Using p-tolyl chloromethyl sulfone

50%aq. NaOH (8 mls) acetonitrile (1 ml), triethylbenzylammonium chloride (0.4 mg), 190 mg (1 mmol) of p-tolyl chloromethylsulfone and 400 mg (1 mmol) of 1b were stirred under N_2 for 24 hrs. Analytical tlc showed starting material. 24 mls of 50 % aq. NaOH, 25 mg TEBA and 1 ml acetonitrile were added and stirred at 35°C for 6 hrs, then at room temp overnight. Ether and water were added with stirring, the layers were separated and the aqueous layers extracted with ether. The combined organic extracts were washed with water, satd.aq. NaCl and dried (Na_2SO_4). Chromatography (silica gel) gave starting material and 32 mg of a yellow crystalline material which did not show epoxide in its n.m.r. or i.r. spectra.

SECTION 2

4,4-dimethyl-5-oxohexanenitrile 30

3-Methyl-2-butanone (30 gm 0.34 mmol) dissolved in dry tert-butanol (80 ml) was cooled with stirring to 0°C 2.1 gm of a 30% solution of KOH in dry methanol was added and stirred for 15 mins. Acrylonitrile (21 gm, 0.45mol) dissolved in 25 mls of tert-butanol was added dropwise over 45 mins and the mixture stirred at 5-10% for 2½ hrs. The reaction mixture was acidified (pH 3) with 2N HCl and then concentrated under reduced pressure to one quarter of its volume. Water and ether were added and the layers separated. The aqueous layer was extracted with ether and the combined organic extracts washed with water (x3) and saturated aq. NaCl. Drying, concentration and distillation in vacuo gave 37.3 gm (79%) of 30. (84-86°C at 25 mm).

I.R. $\bar{\nu}$ cm^{-1} 1706 (C=O) 2240 (C≡N). N.M.R. δ ppm :1.1 (s,6H,gem-di-CH_3). 2.1 (s,3H,C-6 CH_3).

5-benzyloxy-4,4-dimethylhexanenitrile 27

The ketonitrile (56.4 gm, 0.406 mol) was dissolved in ethanol (300 ml) and a solution of sodium borohydride (13.5 gm) in ethanol (300 ml) was added dropwise at 10-15°C over 1 hour. The resulting solution was stirred at room temp. for 3 hr after which 350 ml of 3N HCl was added and stirring was continued for 1 hour. Solvent was removed at reduced pressure and the residue taken up in ether and filtered on Florisil; then dried (Na_2SO_4). Concentration gave 47.1 gm (84%) of the cyano alcohol. I.R. $\bar{\nu}$ cm^{-1} (neat) 3430 (broad OH) 2240 cm^{-1} (C≡N). No carbonyl absorption.

The crude alcohol (22 gm, .16 mol) was dissolved in dry THF (80 ml) and DMF (30 ml). Sodium hydride (.24 mol, 5.8 gm of 99%) was added, and the mixture refluxed for 2½ hours, then cooled to below 10°C. Benzyl chloride (23 gm) was added slowly and the solution refluxed for 2½ hours. The THF was removed at reduced pressure and saturated sodium sulfate solution was added dropwise with cooling. Ether and water were added, layers separated and the aqueous layer extracted with ether. Organic extracts were combined and washed with water, and satd. aq. NaCl. Drying (Na_2SO_4) concentration and vacuum distillation gave the benzyl ether 27 (107-108°C 0.25 torr) - 32.8 gm (89%).

I.R. $\bar{\nu}$ cm^{-1} (neat) 2250 (C≡N). N.M.R. δ ppm ($CDCl_3$):
1.0 (s, 6H, gem-di-CH_3) 1.2 (d.3H,C-6 CH_3) 1.6-2.4 (m.4H CH_2-CH_2-CN), 3.6 (m, 1H, CH-O), 4.5 (q. 2H, CH_2-C_6H_5), 7.4 (b.s. 5H Ar. H).
Mass spec: m/e (r.i.) 231 (12 (M^+)) 186 (9) 135 (15) 131 (20) 118 (31) 96 (41) 91 (100).

5-benzyloxy-4,4-dimethylhexanal 28

33.7 gm (.15 mol) of nitrile 27 was refluxed overnight with potassium hydroxide (20 gm) in ethylene glycol (200 ml). Saturated brine was added and the aqueous layer extracted with ether (soluble organics extracted). The aqueous layer was acidified to pH 2 with 50% HCl. Chloroform and water were added, and the layers separated. The aqueous layer was extracted with chloroform and the combined organics were washed with saturated NaCl. Drying ($MgSO_4$) and concentration (in vacuo) gave 37 gm (98%) of 5-benzyloxyl-4,4-dimethylhexanoic acid. I.R. $\bar{\nu}$ cm^{-1} (neat) 3470-2600 (broad, CO_2H, CH_2,CH_3) 1730 cm^{-1} (C=O). N.M.R. ($CDCl_3$) δ ppm:
9.9 (b.s. 1H CO_2H).

The acid (37 gm, 0.147 mol) was dissolved in 330 ml of anhydrous ether and this solution was added dropwise to a suspension of lithium aluminum hydride (14.6 gm; 0.39 mol) in 400 ml anhydrous ether. The mixture was refluxed for 16 hrs, cooled in an ice bath and 14.7 ml of water was added slowly with stirring , followed by 14.7 ml of 3N sodium hydroxide solution then 43.8 ml of water. A white crystalline precipitate developed which was easily filtered and washed with anhydrous ether. The resulting dry solution was concentrated in vacuo to furnish 31.8 gm (98%) of the 5-benzyloxy-4,4-dimethylhexan-1-ol. I.R. 3590-3400 (broad OH). The crude alcohol (31.8 gm, 0.14 mol) was stirred overnight with 46.5 gm (1.5 eq) of pyridinium chlorochromate in 300 ml dichloromethane at R.T. Anhydrous ether was added with stirring. Then the supernatant suspension was decanted from the black gum and repeated stirring and decantation of the latter with ether converted the gum to a finely divided precipitate. The combined ether suspensions were filtered on a florisil pad - furnishing, after concentration 26.7 gm(87%) of the aldehyde 28 I.R. $\bar{\nu}$ cm^{-1} (neat) 2M 25 cm^{-1}, 1715 cm^{-1} (CHO). NMR ($CDCl_3$) δ ppm. 1.05 (s, 6H, gem-di-CH_3) 1.2 (d.3H,C-6 CH_3) 7.4 (b.s. 5H Ar.H) 9.8 (t.1H,CHO).

Mass Spec: m/e (r.i.) 234 (< 1, M^+) 135 (25) 99 (34) 91 (100) 81 (54) 65(31) 55 (28).

7-benzyloxy-6,6-dimethyloct-1-en -3-one 29

Vinyl bromide (75 gm, 0.7 mol) dissolved in freshly distilled THF (120 mls), was added dropwise at reflux to a suspension of dry magnesium turnings (18 gm) in THF (50 mls) and 1 crystal of iodine, over a 45 min period. The dark solution was then refluxed for 45 mins more then cooled to 0^oC. Aldehyde 28 (20 gm, 085 mol) dissolved in 150 mls of anhydrous

ether was added dropwise and the solution was allowed to warm with stirring over a 4 hour period. Saturated ammonium chloride solution was added and the supernatant organic layer decanted. The aqueous suspension was extracted by swirling and decantation several times with ether. The combined organic extracts were washed with water and satd. aq. NaCl. Drying (K_2CO_3) and concentration in vacuo left an oil which was chromatographed (ethyl acetate/benzene 10%) to give 7-benzyloxy-6,6-dimethyloct-1-ene-2-ol. (17.11 gm, 77%). N.M.R. ($CDCl_3$) δ ppm: 0.95 (2s, 6H, gem di-CH_3), 1.2 (d, 3H, C-8, CH_3) 4.9-5.4 (2H CH_2=CH-), 5.6-6.2 (m.2H, CH_2=CH-).

The allylic alcohol (14.0 gms, .054 mol) was dissolved in 50 mls ether and cooled to 0°C. 20 mls of standard Jones reagent was added dropwise over 40 mins. Reaction was stirred for 1½ hours more at 5-10°C. 10 mls of isopropanol, 25 mls of water and 50 mls ether were added and the reaction was stirred for 20 mins more. The layers were separated and the aqueous layer extracted with ether. The combined organic extracts were washed with 5% sodium bicarbonate, saturated aq. NaCl, dried (K_2CO_3) and concentrated. Chromatography on silica gel (15% ether/hexane) gave the vinyl ketone 29 (11.6, 83%). I.R. $\bar{\nu}$ cm^{-1} (neat) 1665 (C=O) 1608 (C=C). N.M.R.($CDCl_3$) δ ppm 1.1 (2s,6H gem di-CH_3) 1.2 (d, 3H C-8 CH_3) 5.8 (m, 1H CH_2=CH-) 6.3 (m, 2H CH_2=CH-). Mass spec: m/e (r.i.) M^+ absent. 169 (5) 154 (15) 139 (10) 91 (100).

Anal: $C_{17}H_{24}O_2$: Calcd: C: 78.46 H: 9.23

Found: C: 78.38 H: 9.09

2-(7-Benzyloxy -6,6-dimethyl-3-oxooctyl)-2-methyl-1,3-cyclohexanedione 26

2-Methyl-1,3-cyclohexanedione (4.1 gm 32.3 mmol), was suspended in freshly distilled DME (200 mls). Sodium hydride (0.4 gm) was added and the whole stirred at R.T. for 15 mins under N_2. Enone 29 (5.34 gm) dissolved in 18 mls of DME was added dropwise, followed by reflux for 1 hour. The reaction was cooled and saturated aq. sodium sulfate added slowly. The organics were extracted with chloroform and washed with saturated NaCl solution, dried ($MgSO_4$) and evaporated to yield a yellow oil. Chromatography on silica gel (ether/hexane) yielded 26 (6.85 gm - 88%) as an oil. I.R., $\bar{\nu}$ cm^{-1} (neat) 1695-1715 (3C=O). N.M.R. δ ppm ($CDCl_3$) 0.9 (2s.,6H,gem-di-CH_3), 1·1 (d.3H.CH_3-CHO-), 1.25 (s., 3H, C-2 CH_3), 4.5 (q., 2H, CH_2-C_6H_5), 7.3 (b.s., 5H, Ar. H). Mass spec: m/e (r.i.) 386(10) (M^+), 342 (20) 333 (35) 139 (28), 91 (100) 69 (70) 55 (80).

(+) 1-(3-benzyloxy-2,2-dimethylbutyl)-4aβ-methyl-4,4a,7,8-tetrahydro-naphthalene-2,5-(3H,6H)-dione. (31).

Trione 26 (4.2 gm, 10.8 mmol) was dissolved in acetonitrile (100 mls) and L-proline (2.12 gm,21 mmol) (Sigma grade) and 1N $HClO_4$ (11 mls) were added. The reaction mixture was refluxed for 48 hours. The solvent was evaporated under reduced pressure and water and ether added. The layers were separated and the aqueous layer extracted twice with ether. The organic layer was washed with saturated sodium bicarbonate, water, saturated aq/sodium chloride, and dried ($MgSO_4$); then it was concentrated in vacuo. The resulting oil was chromatographed on silica gel from which was obtained (12% Ethyl acetate/benzene) 0.56 gm (14.2%) of 31 as an oil., I.R. $\bar{\nu}$ cm^{-1} (neat): 1705 (C=O), 1660 (α,β unsat. C=O) 1601 (C=C); U.V. λ_{max} 253 mμ (ε 10^4);

NMR($CDCl_3$)δppm: 0.89 (2s, 6H, gem-di-CH_3's), 1.05 (d, 3H, CH_3-C-O H) 1.08 (s, 3H, C-4a CH_3) 2.05 (s, 2H, CH_2-C=C) 4.5 (q.2H, CH_2-C_6H_5), 7.28 (b.s. 5H, Ar. H). Mass spec: m/e (r.i.) 368 (6) (M^+) 277 (10) 233 (18) 105 (20) 91 (100) 55 (80) 43 (75).

$[\alpha]_D^{23.5}$: + 38·87° (2.9% in C_6H_6).

(±) 8aβ-methyl-3,4,8,8a,tetrahydronaphthalene-1,6 (2H,7H)-dione (36).

2-Methyl-1,3-cyclohexane dione (25 gm, 0.20 mol) was stirred with one pellet of KOH in anhydrous methanol (60 mls) under N_2. 26 gm (0.37 moles) of methyl vinyl ketone (26 gm, 0.37 mol) was added and the reaction was refluxed for 3 hours, then cooled and the solvent removed under reduced pressure. Chloroform and water were added. Layers were separated and the aqueous layer was extracted with chloroform. Organic extracts were combined and washed with water, and saturated aq. sodium chloride. After 1 hour drying over Na_2SO_4, the chloroform solution was concentrated under reduced pressure. Residual solvent was removed under high vacuum (0.1 Torr) and acetonitrile (400 mls) was added. L-proline (16 gm) and 1N $HClO_4$ (45 ml) were added and the whole refluxed for 28 hours. Solvent was removed under reduced pressure and water and chloroform were added. The layers were separated and the aqueous layer extracted with chloroform. The organic extracts were washed with satd. aq. sodium bicarbonate, followed by water and saturated aq. sodium chloride solution. Drying (Na_2SO_4) followed by concentration and distillation in vacuo gave 24.8 gm (69%) of (+) 36 $[\alpha]_D^{23.6}$ 79.5° (1.27% in C_6H_6) b.p. 111-119°C at .05 Torr. Crystallization (neat low temperature) gave colourless plates of 36 mpt. 47.5-48.5%. U.V. λ_{max} : 239 mμ (ε = 12.7 x 10^3) I.R. $\bar{\nu}$ cm^{-1} ($CHCl_3$): 1703 (C=O) 1660 (α,β unsatd C=O) 1608 (C=C).

N.M.R. ($CDCl_3$) δ ppm : 1.43 (s, 3H, C-8a CH_3), 5.9 (b.s. 1H, C=CH-)

The ethylene ketal 38 was prepared by refluxing the octalone 36 (15 gm, 0.84 mol) in 60 mls of benzene under N_2 together with 1,2 ethanediol (7.8 gm, 12 mol) and a few crystals of p-toluene sulfonic acid using a Dean-Stark water separator for 16 hr. The reaction was cooled, water added and layers separated. The aqueous layer was extracted with ether and the combined organic extracts washed with saturated aq. sodium bicarbonate solution, followed by saturated aq. NaCl solution. Drying ($MgSO_4$) concentration and chromatography - silica gel (8% ethyl acetate/benzene) gave 12.3 gm (66%) of 38 as an oil. I.R. $\tilde{\nu}$ cm^{-1} (neat) 1670 (C=O), 1610 (C=C) U.V. $\lambda_{max}^{CH_3OH}$: 241 mμ ($\varepsilon = 12.1 \times 10^3$). N.M.R. ($CDCl_3$) δ ppm 3.9 (s, 4H, O-$CH_2$ -CH_2-O). 5.8 (b.s. 1H; C=CH-).

3,3-Ethylenedioxy-1-p-toluenesulfonate 37

Ethyl 3,3-ethylenedioxybutyrate (43 gm) in THF (100 ml) was added with stirring under N_2 to a suspension of $LiAlH_4$ (7 gm) in THF (100 ml) so that gentle reflux was maintained. Refluxing was continued for 3 hours. To the cooled mixture was added successively, H_2O (8 ml), 20% Aq. NaOH (6 ml) and H_2O (25 ml). The resulting 3,3-ethylenedioxy-1-butanol showed no C=O absorption in its I.R. spectrum. The crude alcohol (24 gm) was stirred for 6 hrs under N_2 at 0^oC with p-toluenesulfonyl chloride (44 gm) in 120 ml pyridine. Ice was added and the mixture was stirred for 30 mins and extracted with ether. The organic extracts were washed with water and then hexane and dried (Na_2SO_4). Concentration at reduced pressure gave 37 as a thick colorless oil which was pumped dry for 12 hours at room temperature in vacuo. The

oil was then stored as a 75% solution in toluene in the freezer.

I.R. $\bar{\nu}$ cm^{-1} (neat) 1590 (S=O)

N.M.R. ($CDCl_3$) δ ppm. 1.25 (s, 3H, C-4CH_3). 2.0 (t. 2H C-2 CH_2) 2.4 (s, 3H, C_6H_4-CH_3) 3.8 (s.4H.O-CH_2-CH_2-O) 4.1 (t.2H-CH_2-O) 7.1-7.9 (m.4H. Ar-H)

(+)-5-hydroxy-4aβ-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2 (3H)-one 40

Enedione 36 (15.5 gm, 0.87 mol) was dissolved in ethanol (200 ml) and cooled to 0°C. $NaBH_4$ (1 gm) in anhydrous ethanol (100 ml) was added dropwise over 1 hour. The reaction was stirred for 15 mins more, then 8 mls of glacial acetic acid was added. The solvents were removed under reduced pressure and water and chloroform added. The organic layer was washed with water and satd. NaCl, dried ($MgSO_4$) and concentrated. Vacuum distillation gave 14.2 gm (90%) of 39 $[\alpha]_D^{23}$ + 85.2° (1 % in C_6H_6) as an oil which has not crystallized so far.

b.pt. 145-148°C at .02 torr. I.R. $\bar{\nu}$ cm^{-1} (neat) 3300-3550 (b.OH) 1670 (C=O) 1620 (C=C). U.V. $\lambda_{max}^{CH_3OH}$ 240 mμ (ε = 10.9 x 10^3). N.M.R. ($CDCl_3$) δ ppm: 1.25 (s.3H, (C-4a CH_3) 3.8 (b.t. 1H. CH-OH) 5.8 (b.s. 1H) (C=CH-).

The tetrahydropyranyl ether 40 was prepared by dissolving enone 39 (15.0 gm, 0.083 mol) in CH_2Cl_2 (48 ml) and adding dihydropyran (10.6 gm). HCl gas was bubbled into the stirred reaction mixture until the temperature rose from ca 18°C to 40°C. The reaction was stirred for 3 hours more and water and chloroform added. The aqueous phase was extracted with chloroform and the combined organic extracts were washed with 5% aq. $NaHCO_3$, water and sat. aq. NaCl. Chromatography on silica gel (8% Ethyl acetate

/hexane) gave 20.5 gm (93%) of 40 as an oil which also resisted crystallization. I.R. $\bar{\nu}$ cm^{-1} 1675 (C=O) 1620 (C=C) U.V. $\lambda_{max}^{CH_3OH}$ 241 mμ ($\epsilon = 12.4 \times 10^3$) N.M.R. ($CDCl_3$) δ ppm 1.22 (s.3H.C-4a$CH_3$). 3.6-4.2 (m.4H.$CH_2$-O-2CH-O-) 5.75 (b.s. 1H. C=CH-).

+2-[3-(1,3-dioxolan-2-yl)butoxy]-3,4,4a,5,6,7-hexahydro-4aβ-methyl-5β-tetrahydropyranyloxynaphthalene 42

Sodium hydride (800 mg, 99%)was stirred under N_2 at 65°C in dry DMSO (25 mls) for 1 hour, then cooled to r.t. The ether 40 (3.0 gm, 11.36 mmol) dissolved in DMSO (20 ml) was added over 5 mins. Stirring at 60°C for 1½ hours was followed by cooling to room temp. 4.0 gm of the tosylate 37 in 15 mls of DMSO was added dropwise and the reaction was stirred at 100°C for 16 hours. Saturated aq. ammonium chloride solution was added and the reaction mixture extracted 5 times with ether. The combined organic extracts were washed with water (x3) and saturated aq. NaCl, then dried ($MgSO_4$). Concentration and chromatography gave 1.5 gm (35%) of 42 as an oil. I.R. $\bar{\nu}$ cm^{-1} 1615 and 1641 (di(en)ol ether doublet). U.V. $\lambda_{max}^{CH_3OH}$ 241 mμ ($\epsilon = 14.9 \times 10^3$) N.M.R. ($CDCl_3$) δ ppm 1.05 (s.3H.$CH_3$-$C(OCH_2)_2$) 1.35 (s.3H C4a-$CH_3$) 3.95 (s.4H.O-$C_2H_4$-O) 4.8 (m.1H CH = C-C) 5.2 (b.s. 1H. HC=C-O).

1-Bromo-3-chloro-2-butene 45b

A mixture of 1,3-dichloro-2-butene (6 gm, 48.0 mmol) and sodium bromide (30 gm, 0.29 mol)in acetone (60ml) was refluxed for 18 hrs. The solvent was removed under reduced pressure and to the residue was added 50% sodium thiosulfate (600 ml) and 75 ml of ether (75 ml). The organic layer was

dried ($MgSO_4$) and concentrated and distillation gave 1.9 gm (70.3%) 57-59% at water aspirator pressure.

I.R. ($CHCl_3$) $\bar{\nu}$ cm^{-1} 1665 (C=C) N.M.R. ($CDCl_3$) δ ppm (d, J=1.5Hz, 3H,CH_3), 4.1 (d. J=8Hz, 2H, CH_2Br) 5.9 (q. of t. 1H vinyl H).

(+)5-benzoyloxy-4aβ-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2-(3H)one. 46

The alcohol 39 (3.0 gm) was dissolved in pyridine (18 ml)and cooled in an ice bath to 0^oC. Benzoyl chloride (12 gm) was added dropwise and the reaction mixture was then heated on a steambath under N_2 for 10 mins then poured into 60 ml of ice/H_2O and cautiously acidified with conc. HCl. 30 ml of 5% Na_2CO_3 solution was added and the reaction extracted with ether/hexane. The organic solution was then filtered on a florisil pad using hexane as first eluent (soluble quaternary ammonium salts removed). Elution of the protected alcohol was achieved with ether and crystallization from ether-hexane gave 46 m.pt. 87-88°C.

I.R. (KBr) $\bar{\nu}$ cm^{-1}: 1720 (ester C=O) 1670 (C=O) 1630 (C=C). N.M.R. ($CDCl_3$) δ ppm 1.55 (s.3H.C-4aCH_3) 4.9 (m.1H.C<u>H</u>-O-) 5.85 (b.s. 1H. vinyl <u>H</u>) 7.3-8.3 (m.5H.Ar.<u>H</u>). Mass spec: m/e (r.i.) 284 (15, M^+), 162 (45) 105 (100) 77 (45).

Anal: $C_{18}H_{20}O_3$: Calcd. C: 76.06 H: 7.04

Found: C: 76.17 H: 7.13

(+)-5-Benzyloxy -4aβ-methyl-2-dimethylhydrazono-3,4,4a,5,6,7,8-hepta-hydronaphthalene 47

Benzoate 46 (1.5 gm,5.3 mmol) was dissolved in benzene (50 ml) and a few crystals of p-toluene sulfonic acid and dimethylhydrazine were added (2 ml). After refluxing for 16 hrs with a Dean-Stark water separator, the cooled reaction was poured carefully into 5% aq. $NaHCO_3$.

The layers were separated and the aqueous layer extracted with ether. The combined organic layers were washed with satd. NaCl, dried ($MgSO_4$) and concentrated. Flash chromatography on a florisil pad yielded 1.6 gm (97%) of 47 which has resisted crystallization. I.R. (KBr) $\bar{\nu}$ cm^{-1}: 3250-3450 (b.OH) 1625 (C=C). 1425-1475 (d of d, C=C, C=N)

N.M.R. - See Appendix II Spectrum 3

Mass Spec: m/e (r.i.) 326 (75, M^+) 221 (35).
189 (30) 105 (100) 77 (50).

(+)3-(3-chloro-2-butenyl)-5-hydroxy-4aβ-methylhexahydronaphthalen-.2-(3H)-one, 48

A 1.7 M soln of n-butyllithium in hexane (2 ml) was added to 10 mls of freshly distilled THF under N_2 and cooled to 0^oC. Diisopropylamine (4 mls)was added, stirred for 5 min.; and then cooled to -50^oC (dry ice/acetone). Hydrazone 47 (620 mg, 1.9 mmol) in THF (5 ml) was added with stirring over 10 mins. Stirring was continued at room temperature for 2 hours. Then 0.6 gm of allylic bromide 45b in 5 mls of THF was added and the reaction refluxed overnight. Saturated ammonium chloride was added and the reaction mixture was extracted with chloroform. The combined organic extracts were washed with saturated aq. NaCl and filtered on a florisil pad. The solvents were removed under reduced pressure and the residue taken up in THF. 10 mls of 6N HCl was added and the reaction refluxed for 1½ hrs. The cooled reaction mixture was extracted with chloroform and the combined organic extracts washed with satd. aq. $NaHCO_3$, H_2O and satd aq. NaCl. Drying ($MgSO_4$), concentration and chromatography (silica gel-ethylacetate/benzene) gave 162 mg (31.8%) of 48. I.R. (neat) $\bar{\nu}$ cm^{-1} 3425 (b.OH) 1670 (C=O) 1665(C=C-Cl)

1625 (C=C). U.V. $\lambda_{max}^{CH_3OH}$ 244mμ($\varepsilon = 10.9 \times 10^3$) N.M.R. See Appendix II Spectrum 4.

(+) 1-(3,5-Dimethyl-4-isoxazoylmethyl)-5β-hydroxy-4aβ-methyl-4,4a, 5,6,7,8-hexahydronaphthalen-2-(3H)-one 55

To anhydrous benzene (90 ml) was added 0.89 gm (10mmol) of tert-amyl alcohol and potassium (.039 gm) and the mixture was refluxed under N_2 for 2 hr. (until all K dissolved). The solution was then cooled to room temp. and THP ether 40 (2.37 gm, 9 mol) in benzene (7 mls) was added slowly over 20 mins. Then benzene and tert-amyl alcohol were azeotroped at reflux over 3½ hours whilst the solvent volume was kept constant by adding fresh benzene. After cooling again to room temp. the isoxazole 50 (1.5 gm, 10 mmol) in benzene (5 ml) was added dropwise and then the reaction was stirred at r.t. After refluxing for 2 hours the cooled reaction mixture was poured into ice/water and shaken with ether (x2). After separation of layers, the aqueous layer was acidified with cold 2N H_2SO_4 and also extracted with ether. The combined organic extracts were washed with 5% aq. $NaHCO_3$ satd. aq. NaCl and dried ($MgSO_4$). Evaporation of the solvent gave 3.6 gm of a yellow oil. Chromatography (silica gel; 10% ethylacetate/benzene) furnished a yellow oil from which 1.5 gm (46%) of the isoxazole THP ether 54 crystallized. m.pt. 185-186°C I.R. $\bar{\nu}$ cm^{-1} 1660 (C=O) 1620 (C=C), 1425-1455 (d. isox. C=C, C=N).

In another experiment 6.0 gm of crude reaction mixture (see above) was warmed on a steam bath together with 40 mg of p-toluenesulfonic acid in methanol, 250 ml. The solvent was reduced to one third its volume over 1¼ hrs, then the remainder was removed at reduced pressure. The

residue was diluted with ether and satd. aq. $NaHCO_3$, the layers separated and the organic layer washed with water, satd. aq. NaCl and dried ($MgSO_4$). Concentration followed by chromatography (H.P.L.C., 35% ethyl acetate/hexane) gave an oil from which 1.8 gm (41.8% from 40) of 55 crystallized (ether/hexane). $[\alpha]_D^{23.5}$ + 136.5° (2% in C_6H_6) m.pt. 112-114°C. I.R. $\bar{\nu}$ cm^{-1} ($CHCl_3$) 3420 (b.OH). 1670 (C=O) 1628 (C=C isox) 1605 (C=C) 1425-1455 (d. isoxazole C=C,C=N) U.V. $\lambda_{max}^{CH_3OH}$ 249mμ(ε = 11.5 x10^3) 220 mμ (veiled).

N.M.R. ($CDCl_3$) See Appendix II Spectrum 5

Mass Spec. m/e (r.i.) 289 (100, M^+) 271 (28) 246 (62) 205 (50) 110 (39) 162 (25).

Anal: High Resolution mass spec. determined $C_{17}H_{23}O_3N$.

(+)-8aα-cyano-1-(3,5-dimethyl-4-isoxazoylmethyl)-5β-hydroxy-4aβ-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2-(1H)-one

Isoxazole 55 (350 mg, 1.21 mmol) was dissolved in a 1:1 b.v. mixture of benzene and THF (8 ml). To this stirred solution was added 3.5 ml of 1-2 M benzene solution of diethylaluminium cyanide ($(C_2H_5)_2AlCN$) dropwise. The reaction was stirred at r.t. for 15 mins then at 45°C for 1½ hrs, then cooled to 0°C (ice bath). 2 ml of a 1:1 b.v. mixture of chlorotrimethylsilane and pyridine (which had been centrifuged) was added. The reaction was stirred at r.t. for 1 hr then diluted with 50/50 ether/pentane. It was then poured into ice cold saturated ammonium

chloride with vigorous stirring. The layers were separated, and the organic layer washed with saturated aq. NaCl and dried ($MgSO_4$). Removal of most of the solvent led to precipitation of a white amorphous solid - 58 (330 mg, 86%) which could not be re-dissolved, and which decomposed above 200°C. I.R. (KBr) $\bar{\nu}$ cm^{-1} 3350 (b.OH). 1710 (C=O), 2220 (C≡N), 1425, 1450 (d.isox). U.V. $\lambda_{max}^{CH_3OH}$ 222 mμ (isox).
N.M.R. (Py). See Appendix II Spectrum 6. Mass spec. m/e (r.i.) 316 (31,M^+) 273 (20) 178 (31) 124 (51) 110(100).
Anal: For $C_{18}H_{24}O_3N_2$: Calcd: C: 68.35, H:7.59 N: 8.86
Found: C: 65.62, H: 7.94 N: 7.87

(+)-58 via Kinetic Approach

A 50 ml 3-necked flask was flushed with N_2 and charged with 12 mls dry THF and cooled to 0°C (ice bath). To the stirred solvent was added via syringe , 6.5 mls of a 25% solution of triethylaluminium in hexane (10 mmol, 0.114 gm). After 5-10 mins, 6.0 mmol of HCN (1.1 ml of 17% soln in THF, 162 gm HCN)was added and stirring at 0°C was continued for a further 10 min.

Another flask (100 ml-3necked)was charged with the crystalline isoxazole 55 (0.578 gm,2mmol), 0.018 ml of water and 6 mls of dry THF under N_2. After the solute had dissolved, the cold reagent (Et_3Al/HCN as above) was introduced via syringe and stirring was continued for 3½ hrs. Then 0.015 mls of H_2O and 0.3 mls of THF were added and stirring was continued for 4 hrs more. The reaction mixture was then poured into 9.91 ml of conc. HCl and 124 ml of ice/water and stirred for 20 mins with cooling. The mixture was then extracted with dichloromethane (x3),

washed with satd. aq. NaCl and dried ($NaSO_4$). Evaporation of the solvent furnished a white solid which appeared to have the same characteristics as 58 prepared before. Decomposed above 200°C. Mass spec. M^+-316.

Anal: For $C_{18}H_{24}O_3N_2$ Calcd: C: 68.35, H: 7.59, N. 8.86

Found: C: 65.77, H: 7.99, N: 7.79

(+)8a-cyano-5,5-ethylenedioxy-4aβ-methyl-2-(trimethylsilyloxy)-3,4,4a,5,6,7,8,8a-octahydronaphthalene.57

To a solution of the ketal enone 38 (1.3 gm, 6 mmol) in 100 mls of dry benzene was added a solution of diethylaluminum cyanide (10 mls of 1.5 M in C_6H_6; 15 mmol) at 0°C. The reaction was stirred for 2½ hours at r.t., then recooled to 0°C and 25 mmol of chlorotrimethyl silane (2.75 mls) in 3 mls of pyridine was added and stirring was continued for 1 hr at 20°C. The reaction was diluted with pentane then poured into ice cold saturated ammonium chloride. Separation and rapid washing with ice cold 5% HCl (x3) and saturated aq. $NaHCO_3$ followed by drying (Na_2SO_4) gave after concentration a colourless viscous liquid, which was chromatographed to give 0.93 gm (48.3%) of 57. The remainder of the material was made up of deketalized cyano ketone, ketalized cyano ketone and starting material. I.R. $\bar{\nu}$ cm^{-1} (neat) 2225 (C≡N) 1610 (C=C) N.M.R. ($CDCl_3$) δ ppm. 0.1 (s.9H. Si-$(CH_3)_3$) 1.1 (s.3H.C-4a CH_3, slightly broad). 3.95 (unresolved triplet, 4H, O-CH_2CH_2-O) 4.7-4.9 (2 b.s. 1H vinyl H). Mass spec: m/e (r.i.) 234 (< 1%,M^+) 249 (20) 190 (100) 162 (41) 99 (98) 86 (94) 75 (92).

5-Keto-hexanenitrile 60b

Ethyl acetoacetate (200 gm, 1.53 mol), sodium (0.972 gm, 0.04 mol) and absolute ethanol (130 ml) were stirred for 0.5 hr (until the sodium dissolved). Acrylonitrile was added dropwise with cooling to keep the temperature below 45°C. NB The reaction has an incubation period of 30-40 mins and is highly exothermic. After 2½ hrs, addition was complete and after another ½ hr the ethanol was removed under reduced pressure. Acetic acid (3.2 ml) in 500 ml water was added and the water, acrylonitrile and a small amount of ethyl acetoacetate was stripped off at 80°C, under aspirator pressure. Vacuum distillation of the residue gave 102 gm (47%) of the monoalkylated material 60C (110°C at 0.25 torr) as a yellow oil. N.M.R. ($CDCl_3$) δ ppm : 1.3 (t, J = 7Hz; 3H, $CH_2\underline{CH}_3$) 2.1-2.7 (m, 4H, $\underline{CH}_2\underline{CH}_2CN$), 2.3 (s, 3H, $\underline{CH}_3CO$) 3.7 (t.1H; methine H) 4.3 (q; 2H, $OCH_2\underline{CH}_3$). Compound 60b (102 gm; 0.55 mol), water (900 ml) and sodium carbonate (102 gm) were refluxed for 14 hr and then potassium carbonate was added to the bilayered reaction to salt-out the product. The layers were separated and the aqueous layer extracted several times. Combined organic extracts were washed with water and satd. NaCl, dried ($MgSO_4$) and vacuum distilled to give 45.1 gm (67%) of 60b (86.0° at 15 torr). I.R. (neat) $\bar{\nu}$ cm^{-1} : 2250 (C≡N) 1705 (C=O). N.M.R. ($CDCl_3$) δ ppm: 2.3 (s.3H $\underline{CH}_3$), 2.0 (t. 2H, $\underline{CH}_2CN$) 2.4-2.9 (m.4H.2$\underline{CH}_2$).

7-Benzyloxyoct-1-en—3-one 60

Compound 60 was prepared in like manner to compound 29 by the action of vinyl magnesium bromide on 5-benzyloxyhexanal; the latter derived from compound 60b via a scheme similar to the transformation of compound 30 to compound 28. Thus 20 gm of aldehyde (.097 mol) reacted with 0.7 mol of vinyl magnesium bromide to give after oxidation of the alcohol 14.6 gm (63%) of the vinyl ketone 60.
I.R. $\bar{\nu}$ cm^{-1} (neat) 1665 (C=O): 1605 (C=C)
N.M.R. ($CDCl_3$) δ ppm: 1.2 (d. 3H. C-8 CH_3) 5.8 (m.1H CH_2=CH-) 6.3 (m, 2H; CH_2=CH-) Mass spec: m/e (r.i.) M^+ absent, 126 (10) 91 (100) 55 (20).
Anal: $C_{15}H_{20}O_2$: Calcd: C: 77.58, H: 8.62
Found: C: 77.69, H: 8.39

2-(7-benzyloxy-3-oxooctyl-)- 2-methyl-1,3-cyclohexanedione 59

The coupling of 2-methyl-1,3-cyclohexanedione and 60 was achieved in the same manner as described for compound 26. Thus 6.0 gm (25.8 mm) of 60 was coupled with 5.0 gm of the dione in 225 mls DME and 0.5 gm of sodium hydride to give 8.4 gm (91%) of 59. I.R. $\bar{\nu}$ cm^{-1} (neat) 1698-1715 (3 C=O) N.M.R. δ ppm ($CDCl_3$), 1.1 (d,3H, C-8 CH_3) 1.2 (s., 3H, C-2 CH_3) 4.5 (d of d. 2H. CH_2-C_6H_5), 7.3 (b.s. 5H. H·H).
Mass spec: m/e (r.i.) M^+ absent, 267 (4) 252 (15) 139 (20) 127 (45) 109 (10) 91 (100) 55 (22).

(+)-1-(3-benzyloxybutyl)-4aβ-methyl-4,4a,7,8-tetrahydronaphthalene-2,5-(3H;6H)-dione. 61

Trione (5.3gm, 14.8mmol) in acetonitrile (60 ml), L-phenylalanine (2.93 gm) and 1.23 gm of 60% $HClO_4$ were refluxed under N_2 for 45 hours. The solvents were removed in vacuo and saturated sodium chloride and chloroform added. The aqueous layer was extracted with chloroform and the combined organic extracts were washed with saturated aq. $NaHCO_3$ soln, water and satd. aq. NaCl. Drying ($MgSO_4$), concentration followed by HPLC (ethyl acetate/hexane 10%) gave 61 (4.6 gm, 94%) $[\alpha]_D^{23.5}$ 38.87° (2.5% in C_6H_6). I.R. $\bar{\nu}$ cm^{-1} (neat) 1705 (C=O), 1650 (α,β unsatd. C=O) 1610 (C=C). U.V. $\lambda_{max}^{CH_3OH}$ 253 mμ (ε=10.9 x 10^3) N.M.R. See Appendix II Spectrum 7. Mass Spec. m/e (r.i.) 340 (5, M^+) 234 (10) 91 (100).

Anal. $C_{22}H_{28}O_3$: Calcd: C: 77.64 H: 8.23

Found: C: 76.96 H: 8.39.

(+)-1-(3-benzyloxybutyl)-5β-hydroxy-4aβ-methyl-hexahydronaphthalen-2(3H)-one. 64

Sodium borohydride (0.69gm) was dissolved in abs. ethanol (36 ml) and this solution was added over 1 hr to ketone 61 (3.6 gm 10.6 mmol) dissolved in abs. ethanol (125 ml) cooled to 0°C. Stirring was continued for 15 min. more then 12 mls of acetic acid added. The solvents were removed at aspirator pressure and chloroform and water added. Aqueous layer was extracted with chloroform and the combined organic fractions were washed with saturated aq. $NaHCO_3$, water and satd. aq. NaCl. Drying, ($MgSO_4$) concentration followed by HPLC gave 3.3 gm of 64 (92%).

$[\alpha]_D^{23.5}$ + 50.3° (1% in C_6H_6). I.R. $\bar{\nu}$ cm^{-1} (neat) 3425 (b.OH). 1660 (C=O) 1601 (C=C). U.V. $\lambda_{max}^{CH_3OH}$ 251 mμ (ε= 11.1 x 10^3). N.M.R. ($CDCl_3$) δ ppm 1.2 (s.3H) (C-4aCH_3) 1.25 (d.3H C-4' CH_3) 3.4-3.9 (b.m. 3H 2 CH-O-, 1-O-H) 4.55 (b.s. 2H.CH_2-C_6H_5) 7.4 (b.s. 5H, Ar-H). Mass spec. 342 (5, M^+) 324 (15) 91 (100) 55 (25).

Anal: $C_{22}H_{30}O_3$ Calcd: C: 77.19 H: 8.77 O: 14.11

Found: C: 76.82 H: 9.13 O: 14.03

(+)-1-(3-benzyloxybutyl)-8aα-cyano-5β-hydroxy-4aβ-methyloctahydro naphthalen-2(1H)one (66)

(+) Hydroxy ketone 64 (2.8 gm, 8.2 mmol) was dissolved in benzene (36 ml) and toluene (9 ml) and cooled to 0°C. 20 mls of a 1-2 M solution of diethyl aluminium cyanide in benzene was added dropwise. Stirring was continued at 0°C for 15 mins then at room temperature for 3 hrs. The reaction mixture was then poured into 20 ml of 10% aq. NaOH and 20 gm ice with vigorous stirring. After stirring for 15 mins (ice cold) the reaction mixture was extracted with chloroform (x4). The combined organic extracts were washed with satd. aq. $NaHCO_3$, satd. aq.-NaCl and dried ($MgSO_4$). Concentration and chromatography (silica gel; ethyl acetate/benzene : 20%) yielded 2.7 gm (89.2%) of cyano ketone 66 $[\alpha]_D^{23.5}$ + 23.4° (1% in C_6H_6) as a waxy semi solid.
I.R. $\bar{\nu}$ cm^{-1} (neat). 3440 (b.OH). 2225 (C≡N); 1710 (C=O). N.M.R. ($CDCl_3$) δ ppm: 1.15 (s.3H.C-4a CH_3), 1.22 (d.3H.C-4'CH_3), 3.35-3.95 (b.m. 3H. CH-OB_2, CH-OH,OH) 4.5 (d. of d. 2H, CH_2-Ar), 7.4 (s.5H.ArH). Mass spec: m/e (r.i.) 369 (<1% M^+) 282 (6) 263 (32) 262 (20) 207 (20) 107 (15) 91 (100).

Anal: $C_{23}H_3NO_3$: Calcd: C: 74.79 H: 8.40 N: 3.79

Found: C: 74.48 H: 8.29 N: 3.55

The hydroxy ketal (+) 74 was prepared in the standard manner by refluxing (+)64 (540 mg, 1.46 mmol) in benzene (40 ml), ethane diol (6 ml) and a few crystals of p-toluene sulfonic acid for 16 hr. Water was added, the layers separated and the aqueous layer was extracted with ether (x2). The combined organic extracts were washed with satd. aq. $NaHCO_3$; then satd. aq. NaCl and dried ($MgSO_4$). Concentration led to a colourless viscous oil ~ 560 mg (93%) I.R. 3450 (b.OH). 2220 (C≡N). No C=O abs. N.M.R. ($CDCl_3$) δ ppm: 1.2 (s.3H: C-4aCH_3) 1.25 (d. 3H C-4' CH_3) 3.9 (m.4H.- OCH_2CH_2O-).

(+) 1-(3-benzyloxybutyl)-8aα-cyano-4aβ-methyl-3,4,4a,7,8,8a-hexahydronaphthalene-2(1H),5(6H)-dione (67) ~

Hydroxy compound (+) 66 (140 mg, 38 mmol) was dissolved in ether 10 ml, and 0.6 mls of standard Jones reagent[110] was added dropwise at 0°C with vigorous stirring. Stirring was continued over a 2 hr period over which time the reaction was allowed to warm to room temperature. 2 mls of isopropanol were added followed by 25 ml of ether and 25 mls of water. Stirring was continued for 20 mins. The layers were separated and the aqueous layer extracted with ether (x2). The combined organic extracts were washed with satd. aq. $NaHCO_3$, then satd. aq. NaCl and dried ($MgSO_4$). Flash chromatography on a silica gel pad (2% ethylacetate-benzene) gave 97 mg (70.2%) (82.2% based on recovered starting material; 22 mg) of (+) 67 $[\alpha]_D^{23.5}$ + 10.6° (2% in C_6H_6) which crystallized from ether/hexane. mpt. 96-98°C.

I.R. $\bar{\nu}$ cm^{-1} (KBr). 2225 (C≡N), 1710 (b.C=O). N.M.R. ($CDCl_2$) δ ppm: 1.22 (d.3H.C-4'CH_3), 1.3 (s. 3H; C-4aCH_3) 3.3-3.8 (m.1H.C$\underline{H}$-OBz).

Mass spec: m/e (r.i.): 367 (8,M^+), 340 (8) 260 (15) 91 (100).

Anal: $C_{23}H_{29}O_3N$: Calcd: C: 75.20 H: 7.90 N: 3.81

Found: C: 75.41 H: 7.79 N: 3.68

The cis cyano ketone (+) 68 was prepared as follows: Dione (+) 61 (200 mg, 0.588 mmol) was dissolved in benzene (6 ml) and toluene (1.5 ml). It was cooled to 0°C and 2 mls of 1-2 M solution of diethylaluminium cyanide in benzene was added dropwise. The resulting solution was stirred at room temp. for 45 mins then at 45°C for 1.5 hr. The reaction mixture was poured into ice cold 10% aq. NaOH, stirred vigorously for 15 mins then extracted with chloroform (x3). Work up and flash chromatography as for (+) 66 gave, after crystallization from ether/hexaxe 174 mg (81%) of (+) 68 $[\alpha]_D^{23.5}$ + 0.8° (5% in C_6H_6), mpt. 84-86°C. Spectral data same as for (+) 67.

Trans cyano ketone (+)-69 via kinetic approach.

A 50 ml 3-necked flask was flushed with N_2 and charged with anhydrous THF (20 ml) and cooled to 0°C. 3.99 gm (35 mmol) of triethylaluminium (15.96 gm of a 25% solution in hexane, 24.15 mls) was introduced via syringe with stirring. After 8 mins. 0.66 gm (25 mmol) of HCN (3.97 gm of a 17% soln in THF, 4.7 ml) was added and stirring continued for 10 mins more. To a dry 150 ml flask flushed with N_2 was added 0.6ml of water followed by enone (+) 61 (.17 gm, 5 mmol) in THF (15 ml)via syringe. After 5 mins stirring the cold reagent (ex above)

was added via syringe and the resulting yellow solution stirred at r.t. for 3 hrs. Then 0.05 mls of water and 3 mls of THF were added and stirring was continued for 4 hrs more. The reaction mixture was poured slowly into 70 mls of conc. HCl and 500 mls ice/water. Stirring was continued for 20 mins then the reaction mixture was extracted with chloroform (x3). The combined organic extracts were washed with 2M NaOH, H_2O and satd. aq. NaCl then dried ($MgSO_4$). Concentration and flash chromatography yielded after crystallization (ether/hexane) 1.3 gm (70.8%) of (+) 69 $[\alpha]_D^{23.5}$ +7.3° (1.5% in C_6H_6) m.pt. 97-98°C. (87.3% based on recovered starting material; 320 mg). Spectral data as for 67 and 68.

Anal: $C_{23}H_{29}O_3N$ Calcd: 75.20 H: 7.90 N 3.81

Found: 74.58 H: 8.00 N:3.77

(+)-1-(3-benzyloxybutyl)-3,5-dihydroxy-4aβ,8aα-dimethyldecahydronaphthalene 82

Hydroxy cyano ketone (+)-66 (400 mg, 1.08 mmol) was dissolved in dry benzene (25 ml) and dry toluene (7 ml). To this stirred solution was added dropwise a 25.8% solution of diisobutylaluminium hydride in toluene (5 mls). Stirring was continued overnight then the reaction mixture was poured carefully into 50ml of 10% aq. KOH and 25 gms of ice. After stirring for 15 mins, the reaction mixture was extracted with chloroform (x3) then the organic extracts were filtered through a pad of $MgSO_4$. Concentration and removal of residual solvent under vacuum (10^{-2} torr) gave the dihydroxy imine 81 as a foam.

I.R. (neat) $\tilde{\nu}$ cm^{-1}: 3450 (b. with shoulder, 2 OH), 1601, 1612 (C=N).

The crude imine 81 was dissolved in T.E.G. (30 ml) and hydrazine hydrate (3 mls) was added, followed by hydrazine dihydrochloride (0.75 gm). The reaction mixture was stirred under N_2 at 135°C (internal temp) after which heating was suspended. Crushed KOH pellets (3.75 gm) were added portion wise, heating was restarted and for 1.5 hr and volatiles were allowed to distill off at 155-160°C under a positive Nitrogen flow. Then heating was continued (without distillation) for 6 hr at 165-170°C under N_2 after which the reaction was allowed to cool overnight, then poured into water and extracted with chloroform (x3). The combined chloroform extracts were washed with satd. aq. NaCl, dried and concentrated. Chromatography (silica gel: 15% Ethyl acetate/hexaxe) gave 3 products. (a): 82: $[\alpha]_D^{23.5}$ + 19.9° (1%, C_6H_6), 132 mg (34%) I.R. 3300 (b.d. OH) N.M.R.: See Appendix II Spectrum 12. Mass spec: m/e (r.i.) 360 (<1% M^+), 342 (<1%), 135 (18) 109 (20), 91 (100).

Anal: $C_{23}H_{36}O_3$: Calcd. C: 76.66 H: 10.00

Found: C: 75.47 H: 10.72

(original sample insufficient for duplicate analysis. New sample to be checked for purity before being sent for duplicate re-analysis).

(b) 83 : 46 mg (11.8%). Spectral data similar to that of 82 except that in the n.m.r. the two methyl singlets are shifted downfield by 6 Hz.

(c) 84: 66 mg (17%). I.R. (neat) $\tilde{\nu}$ cm^{-1}. 3400 (b.OH) 2220 (C≡N). N.M.R. ($CDCl_3$) δ ppm: 1.0. (s.3H.C-4aCH_3) 1.25 (d.3H.C-4' CH_3) 3.4-3.9 (.5H. 3C$\underline{H}$-O-, 2-OH). Mass spec: m/e (r.i.). M^+ absent 91 (100). The rest was inconclusive.

(+)-4aβ,8aα-dimethyl-1-(3-oxobutyl)-3,4,4a,7,8,8a-hexahydronaphthalene-2-(1H), 5(6H)-dione 98

Hydroxy cyano compound (+) 66 (550 mg, 1.49 mmol) was dissolved in anhydrous ethanol (60 ml) and 150 mg 10% palladium on charcoal was added. This was hydrogenated under 1 atm of hydrogen for 16 hours, filtered on a celite pad and concentrated; residual solvent being removed under pump vacuum (10 torr). The white foam showed up as two spots on tlc I.R. 3400 (b.OH). 2230 (C≡N) 1715 (weak C=O) displaying hemi-ketal predominance.

The crude mixture (180 mg, 64 mmol) was dissolved in 15 mls of ether and cooled to $0^{o}C$. To thus was added dropwise a solution of 0.6 gm of CrO_3 in 6 mls of 6N H_2SO_4. Stirring was continued at $0^{o}C$ for 1 hr then allowed to warm to room temp. over 2 hrs. The supernatant liquid was decanted and 25 mls of satd. aq. NaCl was added followed by extraction with ether (x3). The combined organic extracts were washed with satd. aq. $NaHCO_3$, satd. aq. NaCl and dried ($MgSO_4$). Concentration, followed by flash chromatography (silica gel, 5% ethylacetate/benzene) gave an oil from which 121.5 mg (69%) of 98 crystallized. mp.t. 104-106°C. I.R. (KBr) $\bar{\nu}$ cm^{-1} 2225 (C≡N), 1700, 1710 (3C=O). N.M.R. ($CDCl_3$) δ ppm 1.25 (s.3H,C-4a CH_3) 2.15 (s, 3H, CH_3-C=O). Mass spec: Pending at time of thesis.

Anal: $C_{26}H_{21}NO_3$ Calcd: C; 69.82, H; 7.64, N; 5.01

C; 70.47, H; 8.06; N; 4.86

SECTION 3

8β-(tetrahydropyranyl-2'-oxy)-1,4aβ, 8aβ-trimethylhexahydrophenanthra-1(10a),4b(5)-dien -2 (3H)-one 96

The hydroxy enone 90 [57,122] (2.0 gm, 10.6 mm) dissolved in methanol (25 ml) was added to a stirred solution of sodium methoxide (1.08 gm, 20 mmol) in methanol (25 ml) at 0°C under an N_2 atm. Ethyl vinyl ketone (1.2 gm,14.3 mmol) in 5 mls methanol was added after 5 mins and the reaction mixture was refluxed overnight. It was then cooled and poured into ice 3N/H_2SO_4 and extracted with ether (x3). The combined ether extracts were washed with water, satd. aq. NaCl and dried ($MgSO_4$). Column chromatography (silica gel, ether/pet ether) yielded 1.8 gm of an oil from which 1.45 gm (52.5%) of the hydroxy diene-one 91 crystallized (ether/hexane). mpt. 139-140°C. Spectral data identical to authentic sample [102].

A solution of the crystalline hydroxy compound 91 (2.0 gm; 0.68 mmol), freshly distilled 3,4-dihydropyran (4 ml), ether (4 ml) and a few crystals of p-toluene sulfonic acid was stirred at room temp. for 2½ hours and was then diluted with 5% aq. $NaHCO_3$. The reaction mixture was then extracted with ether (x3) and the combined organic extracts were washed with satd. aq. NaCl; dried ($MgSO_4$) and concentrated. Flash chromatography (silica gel, benzene) gave 2.3 gm of 96 (86.9%) as an oil. I.R. $\bar{\nu}$ cm^{-1} (neat) 1665 (C=O) 1610 (C=C). U.V. $\lambda_{max}^{CH_3OH}$ 249 mμ ($\varepsilon = 10.1 \times 10^3$). N.M.R. ($CDCl_3$) δ ppm: 1.34 (s. 3H. C_{4a}-CH_3) 1.45, 1.47 2s.3H.C_{8a}-CH_3) 1.82 (s. 3H. C_1-CH_3) 3.8-4.0 (m, 1H, C_8-H) 4.6-4.72 (m. 1H,C_1'-H), 5.4-5.5 (m.1H, C_5H). Mass spec: m/e (r.i.) 344 (M+)

Anal: $C_{22}H_{32}O_3$ Calcd: C: 76.70 H: 9.36

Found: C: 76.48 H: 9.52

8β-(tetrahydropyranyl-2'-oxy)-1, 4aβ, 8aβ-trimethyl-2-(trimethylsilyloxy)-3,4,4a,6,7,8,8a,9,10,10a-decahydrophenanthrene 97

To a solution of lithium metal (0.4 gm, 52.5 mmol) in distilled ammonia (250 mls) was added dropwise the THP ether 96 (6 gm, 17.5 mmol) dissolved in dry T.H.F. (72 mls) containing 1.03 gm (14 mmol) of tert-butanol. The reaction was stirred for 5 mins and the excess lithium was destroyed by addition of sodium benzoate. The ammonia was removed by careful evacuation at 20-40°C under aspirator pressure and the solids taken up in 100 mls of dry dimethoxyethane. The reaction mixture was then quenched with a mixture of chlorotrimethylsilane (3.25 gm) and of triethyl amine (3.03 gm) (which had been centrifuged); and was stirred for 45 mins more. Ice cold satd. aq. NH_4Cl was added and the reaction extracted with ether (x3). The organic extracts were dried ($MgSO_4$), concentrated and chromatographed (silica gel, ether/pet ether) which gave 3.0 gm (42%) of 97 as a white semi-solid. I.R. $\bar{\nu}$ cm^{-1} (neat). no (C=O) abs. N.M.R. ($CDCl_3$) See Appendix II Spectrum 13. Mass spec: 418 (8, M^+) 333 (8) 244 (12) 210 (15) 119 (20) 105 (33) 91 (50) 85 (100). Elemental analysis shows low silicon level.

8β-(tetrahydropyranyl-2'-oxy)-1,4aβ, 8aβ-trimethyl decahydrophenanthr-4b(5)-en-2-(1H)-one 96b

A 1.75 M solution of methyl lithium (0.3 ml, 0.52 mmol) was added to a flask and the ether removed at aspirator pressure. Dimethoxyethane (2 ml) (freshly distilled) was added followed by the enol silyl ether 97 (180 mg, 0.42 mmol) in DME (2 ml) dropwise. The

reaction was refluxed for 1½ hrs , then cooled and the tosylate 3 (161 mg, 0.5 mmol) in DME (2 ml) added. The reaction was refluxed overnight, cooled and satd. aq. NH_4Cl added. It was extracted with ether (x3) dried ($MgSO_4$) and concentrated. Chromatography (prep plate) gave 98 mg (68%) of 96b (slightly contaminated by tlc). I.R. (neat) $\bar{\nu}$ cm^{-1}: 1705 (C=O) n.m.r. 0.98 (2s. 3H. C-8a CH_3), 1.05 (s. 3H. C-4a CH_3) 1.21 (d. 3H. C-1 CH_3) 5.5 (m. 1H. CH=C).
No mass spec. nor elemental analysis undertaken.
75-80% of tosylate 3 also recovered in an impure form.

1,4aβ-dimethyl-5β-tert-butoxy-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one 103

The hydroxy compound 90 [57,102] (3.69gm, 19.0 mol) in 150 ml of dry dichloromethane (100 ml) was cooled to -20° in an ice/acetone bath. BF_3·etherate (0.98 mol 7.88 mmol) and crystalline H_3PO_4 (.761 gm, 7.88 mmol) were added and stirred for 10 mins. Liquid isobutylene (175 ml, 185 mol) (dry ice/acetone collected) was added amid vigorous stirring then the reaction flask was stoppered with a clamped septum, with a fine syringe needle being used as an exhaust valve. The reaction mixture was stirred for 3 hr and then poured into 2N aq. NH_4OH with stirring. The layers were separated and the aqueous layer extracted with dichloromethane. The combined organic extracts were washed with 2N NH_4OH, water and satd. aq. NaCl and filtered on a florisil pad with ether elution. Column chromatography (15% ethylacetate/hexane) gave 4.0 gm of an oil from which 3.75 gm of 103 crystallized -

mpt. 29-32°C (78%). I.R. (KBr) $\bar{\nu}$ cm^{-1} 1680 (C=O) 1600 (C=C) no OH abs. U.V. $\lambda_{max}^{CH_3OH}$ 250 mμ. N.M.R($CDCl_3$) δ ppm: 1.05 (s. 3H. C-4a-CH_3) 1.2 (s.9H.t-butyl CH_3) 1.85 (s. 3H. C1-CH_3).

m/e (r.i.) Mass spec: 250 (5, M^+) 126 (100) 124 (40)

Anal: $C_{16}H_{26}O_2$: Calcd: C: 76.80 H: 10.40

Found: C: 76.53 H: 10.29

2-trimethylsilyl-1-penten-3-one. 104

To clean magnesium shavings (12 gm) covered with 100 mls of freshly distilled THF was added a few drops of ethylene dibromide and a crystal of iodine. When reflux was started 40 gm of α-bromovinyltrimethylsilane[107] in THF (200 ml) was added dropwise in order to maintain gentle reflux. At the end of addition, the reaction was refluxed for 45 mins more, then treated with dry distilled propionaldehyde (15.0 gm) in THF (90 ml) at gentle reflux, then heated at reflux for 20 mins more. The cooled reaction mixture was then treated carefully with a few mls of 1 N HCl and extracted with ether (x4). The combined organic extracts were filtered and concentrated at aspirator pressure to give 19 gm of crude 2-trimethylsilyl-1-penten-2-ol. N.M.R. (neat) δ ppm 0.2 (s. 9H. $Si(CH_3)_3$) 1.05 (m. 3H. CH_2CH_3) 1.4-1.9 (m.2H CH_2CH_3) 4.2 (m. 2H CHOH) 5.5, 5.9 (d of d J = 20 Hz. vinyl H).

The crude alcohol (19 gm) was dissolved in 90 mls ether and cooled to 100°C. 50 mls of standard Jones oxidant was added dropwise at 0°C then stirred for ½ hr while warming to room temp. A few mls of isopropenol were added followed by water and ether. The layers were separated and the aqueous layer was extracted with ether. The combined organic extracts were washed with ice cold 0.05 N NaOH, then water and filtered

on a florisil pad. Flash chromatography (silica gel, benzene) gave 17.2 (46%) of 104 I.R. (neat) $\bar{\nu}$ cm^{-1} 1665 (C=O) 1605 (C=C) N.M.R. (neat) δ ppm: 0.25 (s. 9H. $Si-(CH_3)_3$) 1.2 (t.J = 7 Hz. 3H.CH_2CH_3) 2.75 (q. J = 7 Hz, 2H, CH_2CH_3) 6.25, 6.65 (d of d, J = 2Hz, J = 2Hz, 2H, vinyl H).

8β-(tert-butoxy)-1,4aβ,8aβ-trimethyldecahydrophenanthren-2- (3H)-one 98

Lithium (1.0 gm) was dissolved in distilled ammonium (300 ml) and enone 103 (7.0 gm 28 mmol), tert-butanol (0.63 gm 23.8 mmol) in dry ether (100 mls) was added dropwise over 15 mins then stirred for 1 hr. Excess lithium was destroyed with bromobenzene and the ammonia was taken off under aspirator pressure. The residual salts were dissolved in dry dimethoxyethane (100 mls) and stirring was continued for 20 mins. The reaction mixture was then cooled to -78°C and silylated enone 104 (7.0 gm) in DME (10 mls) was added. Stirring was continued at -78°C for 15-20 mins then at room temperature for 2 hr. Satd. aq. NH_4Cl was added and the reaction mixture extracted with ether (x3). The organic extracts were filtered on a florisil pad with ether elution and then concentrated at reduced pressure. The residue was taken up in 5% sodium methoxide/methanol (140 ml) and refluxed for 5 hrs, then stirred overnight. It was then poured into ether (75 ml) and water was added. The layers were separated and the aqueous layer extracted with ether (x3). The combined organic extracts were washed with water (x2), satd. aq. NaCl and dried (K_2CO_3). Concentration and column chromatography (15% ether/pet ether) gave 4.2 gm (48%) of 98 as an oil.

I.R. (neat) $\bar{\nu}$ cm^{-1}: 1660 (C=O) 1615 (C=C). U.V. $\lambda_{max}^{CH_3OH}$ 247 mμ($\varepsilon = 13.4 \times 10^3$) N.M.R. ($CDCl_3$) δ ppm: 1.15 (s.3H. C-4a CH_3) 1.2 (s.9H. t-butyl CH_3) 1.21 (s. 3H. C8a-CH_3) 1.85 (s. 3H. : C1 CH_3). Mass spec. m/e (r.i.): 318 (4 M^+) 262 (10) 212 (15) 194 (100) 138 (60) 123 (30).

Anal: $C_{21}H_{34}O_2$ Calcd: C: 79.25 H: 10.69

Found: C: 79.41 H: 10.47

Chromatography also gave 1.7 gm (24%) of 107 I.R. (neat) $\bar{\nu}$ cm^{-1}: 1708 (C=O). N.M.R. ($CDCl_3$) δ ppm: 1.0 (d.3H. J = 6Hz, C-1-CH_3) 1.15 (s. 3H. C-8a CH_3) 1.2 (s. 9H. tert.-butyl CH_3).

In another experiment, the saturated ketone 107 (800 mg, 3.17 mmol) was dissolved in dry tert-butanol (10 ml) and this solution was added to a stirring solution of potassium tert-butoxide(300 mg) in tert-butanol (30 ml). After stirring for 10 mins at room temperature the silylated enone 104 (560 mg, 3.56 mmol) in tert-butanol (1 ml) was added dropwise and the reaction stirred overnight. Water and ether were added and the layers separated. The aqueous layer was extracted with ether (x3) and the combined ethereal extracts filtered on a florisil pad, then concentrated. The residue was taken up in methanol(25ml)to which was added potassium hydroxide (0.5 gm) and water (4 ml). The whole was refluxed for 16 hrs then poured into water and ether. The layers were separated and the aqueous layer extracted with ether. The combined organic extracts were washed with water and satd. aq. NaCl, dried ($MgSO_4$) and concentrated. Column chromatography (ether/pet ether) gave 625 mg (62%) of enone 98. Spectral data and r.f. identical to sample prepared as above.

7-benzyloxy-2-trimethylsilyloct-1-en-3-one 99

α-bromovinyltrimethylsilane[107] (14.6 gm, 81 mmol) was added dropwise to a stirred mixture of magnesium (5.3 gm) and THF (25 ml) at a rate sufficient to maintain gentle reflux. At the end of addition the reaction mixture was refluxed for one hour more, then cooled to $0^{o}C$. 5-benzyloxyhexanal 102 (preparation described before)(12.5 gm, 61 mmol) in dry ether (25 ml) was added dropwise and the mixture stirred at room temperature overnight. Satd. aq. NH_4Cl was added and the reaction mixture extracted with ether (x4). The combined extracts were washed with satd. aq. NaCl, dried (K_2CO_3) and concentrated. H.P.L.C. (15% ethyl acetate/hexane) gave 13.9 gm (75%) of the allylic alcohol. I.R. (neat) $\bar{\nu}$ cm^{-1} 3400 (b.OH). The alcohol 12.8 gm (41.6 mmol) was dissolved in ether (60 mls) and cooled to $-5^{o}C$. Standard Jones reagent (3.75 mls) was added dropwise at $0^{o}C$. The reaction was stirred for 30 min at $0^{o}C$ then 3 mls of isopropanol added. 60 mls of water and 120 mls of ether were added and the reaction stirred for 15 mins more. Layers were separated and the aqueous layer extracted with ether. The combined organic extracts were washed with ice cold 0.05 N NaOH, water(x2), satd. aq. NaCl then filtered on a Florisil pad. Flash chromatography (silica gel, benzene) gave 11 gm (86%) of the enone 99.

I.R. (neat) $\bar{\nu}$ cm^{-1} 1670 (C=O) 1608 (C=C). N.M.R. ($CDCl_3$) δ ppm: 1.25 (d. 3H: C-8 CH_3) 0.25 (s. 9H. Si-$(CH_3)_3$ 4.6 (d. of d. 2H. CH_2-C_6H_6) 6.2, 6.6 (d. of d. 2H vinyl H's). 7.4 (b.s. 5H. Ar.H)

Mass spec: m/e (r.i.) M^+ abs. 127 (45) 91 (100) 73 (50).

8β-(tert-butoxy)-1,4aβ, 8aβ-trimethyldodecahydrophenanthren-2-(1H)-one 109 and 1-(7-benzyloxy-3-oxooctyl)-8β-(tert-butoxy)-1,4a β,8aβ-trimethyl-dodecahydrophenanthren-2-(3H)-one. 111

Lithium (0.15 gm) was dissolved in distilled ammonia (50 ml) To this solution was added enone 98 (1.0 gm, 3.15 mmol)and tert-amyl alcohol (0.3 gm) in dry ether (10 ml) dropwise and at reflux. The reaction was stirred at reflux for 40 mins then a few drops of bromobenzene added and the ammonia removed under reduced pressure. The residue was taken up in dry dimethoxyethane (40 ml) and then cooled to -78°C. The silylated enone 99 (1.45 gm, 4.7 mmol) in DME(10 ml)was added and the reaction was stirred for 16 hrs at room temp. Satd. aq. NH_4Cl was added and the reaction mixture was extracted with ether (x3). The combined organic extracts were washed with water, satd. aq. NaCl and dried ($MgSO_4$). Concentration and column chromatography yielded three main products:-

1: 109 575 mg (57%) I.R. (neat) $\bar{\nu}$ cm^{-1} 1705 (C=O)

N.M.R. ($CDCl_3$)δppm: 0.95 (s. 3H. C-4a-CH_3) 1.0 (s. 3H.C8a-CH_3) 1.05 (d. 3H. C1-CH_3) 1.15 (s. 9H. tert-butyl-CH_3).

Mass spec: m/e (r.i.) 320 (15, M^+) 200 (25) 140 (100).

2: 111 305 mg (17.5%). I.R. (neat) $\bar{\nu}$ cm^{-1} 1705 (b. 2(C=O) N.M.R. See Appendix II Spectrum 11.

3: 110 182 mg (18%) mpt. 87-89°C. I.R. (KBr) $\bar{\nu}$ cm^{-1} 3380 (b.OH) No(C=O) abs. N.M.R. 3.5-3.75 (m.1H.CHOH) 3.1-3.3 (M.2H.CHOR,CHOH) 1.25 (s. 9H. tert-butyl CH_3), 1.05 (s.3H.C-8a CH_3) 0.9(s. 3H. C4a-CH_3) 0.95 (d. 3H. C-1 CH_3)

N.B. Yields of 111 improved to 23.5% when 480 mg (1.5 mmol) of substrate was used.

Ketone 109 via Birch reduction of 98

Enone 98 (600 mg, 1.8 mmol) was dissolved in dry THF (20 ml) and dry ether (30 ml) and this solution was added dropwise to a stirring solution of 800 mg of lithium (800 mg) in undistilled ammonia (200 ml) at reflux. Reflux was continued for 35 mins and the reaction quenched by cautious addition of solid NH_4Cl. The ammonia was allowed to evaporate overnight and the residue taken up in ether and water. The aqueous phase was extracted with ether (x2) and the combined organic extracts filtered on a florisil pad. The ether was taken off under reduced pressure and the residue redissolved in ether (80 ml) and cooled to 0^oC. Standard Jones reagent was added dropwise till a dense black gum resulted and the reaction stirred for 0.5 hr more. Water and ether were added and the layers separated. The aqueous layer was extracted with ether and the combined organic extracts washed with 5% aq. $NaHCO_3$, water, satd. aq. NaCl and dried (Na_2SO_4). Flash chromatography (silica gel, 2% ethyl acetate/benzene) gave 440 mg (77%) of 109. Spectral data and R_f identical to sample prepared before.

1-(3-benzyloxybutyl)-7β-(tert-butoxy)-4aβ,6aβ,10bβ-trimethyl-4,4a,4b,5,6,7,8,9,10,10a,11,12-trans-anti-trans-anti-tetradecahydrochrysen-2(3H)-one 112.

Dione 111 (100 mg, .18 mmol), isopropanol (10 ml) and 10% aq. NaOH (8 ml) were refluxed for 26 hrs under N_2. Water and ether were added to the cooled reaction mixture and the layers separated. The aqueous layer was extracted with ether (x3) and the combined organic extracts concentrated and filtered on a short florisil pad with 10% ether/benzene

elution. Prep. plate chromatography gave 86 mg (89.4%) of 112 as an oil which has so far not crystallized. I.R: (neat) $\bar{\nu}$ cm^{-1} 1660 (C=O), 1601 (C=C). U.V. $\lambda_{max}^{CH_3OH}$ 252mμ(ε = 12.7 x 10^3). N.M.R. See Appendix II Spectrum 8 . Mass spec: m/e (r.i.) 534 (3, M^+) 443 (5) 428 (5) 107 (15) 91 (90) 57 (100).

Anal. $C_{36}H_{54}O_3$: Calcd: C: 80.89 H: 10.11

Found: C: 78.14 H: 10.76

Fresh re-cleaned sample will have to be sent off for re-analysis since carbon value is low.

In another experiment - ketone 109 (160 mg, 0.51 mmol) was dissolved in tert-butanol (6 ml) and potassium tert butoxide (20 mg) added; and the reaction stirred for 15 mins. Silylated enone 99 (250 mg, 0.82 mmol) in tert-butanol (3 ml) was added and stirring continued overnight. Water and ether were added and the layers separated. The aqueous layer was extracted with ether (x4) and the combined organic extracts filtered on a short florisil pad. The ether was removed under reduced pressure and the residue taken up in methanol (10 ml) and KOH (60 mg) in water (2 ml). The mixture was refluxed for 28 hours, cooled and water and ether added. The aqueous layer was extracted with ether (x4) and the combined ethereal layer filtered on a florisil pad. Concentration, followed by flash chromatography (silica gel, 1% ethyl acetate/benzene), gave 230 mg of crude material which was purified by prep. t.l.c. to give 64 mg (23.6%) of 112. R_f and spectral data identical to sample prepared as above.

1-(3-benzyloxybutyl)-7β-(tert-butyl)-12aα-cyano-4aβ, 6aβ,10bβ-trimethyl-3,4,4a,4b,5,6,6a,7,8,9,10,10a,10b,11,12,12a-trans-anti-trans-anti-trans-hexadecahydrochrysen-2(1H)-one 117

A 25 ml 3-necked flask was flushed with N_2 and charged with dry THF (3 ml), then cooled to 0°C. 0.91 gm of triethylaluminium (1.3 ml of a 25% solution in hexane) was introduced via syringe to the stirred solvent. After 8 mins, 1.2 mmol of HCN (0.25 mls)of a 17% solution in THF was added and stirring was continued for 5-10 mins more. A dry 50 ml 3-necked flask was flushed with N_2 and water (0.004 ml) was added. Enone 112 (164 mg, 307 mmol) in THF(5 ml) was added and stirred for 5 mins. The cold $HCN/(C_2H_5)_2Al$ reagent (ex above) was added via syringe and stirring is continued for 3 hr. After 3 hr. water(0.3µl) and .5µl of THF were then added and stirring continued for 4 hrs more. The reaction was then poured into 2mls of conc. HCl in 30 mls ice/H_2O and stirring continued for 20 mins at 0°C. The reaction mixture was then extracted with dichloromethane (x4) washed with aq. 2M NaOH (x2) water (x2), satd. aq. NaCl, then dried ($MgSO_4$). Concentration followed by prep. plate chromatography gave 149 mg (87%) of cyano compound 117. I.R. (neat) ν cm^{-1}. 2220 (C≡N) 1705 (C=O). N.M.R. See Appendix II Spectrum 9. Mass spec: m/e (r.i.) 561 (M, M^+). 505 (15) 455 (7) 396 (35) 91 (100) 57 (65).

Anal: $C_{37}H_{55}NO_3$: Calcd: C: 79.14 H: 9.80 N: 2.49

Found: C: 78.77 H: 9.69 N: 2.37

The cis cyano ketone 118

Enone 112 (58 mg, 0.11 mmol) was dissolved in benzene (10 ml) and diethylaluminium cyanide (1 ml of 1-2 M soln) was added. The reaction was stirred at room temperature for 3 hrs and worked up as for compound (+) 66 and (+) 68. Prep. plate chromatography gave 51 mg (83%) of compound 118. R_f. 0.93 of R_f of compound 117 by analytical t.l.c. Spectral data identical to that of 117. Mass spectrum pending.

The hydroxy compound 119 and attempted Wolff-Kishner

Cyano compound 117 (86 mg, 0.15 mmol) was dissolved in abs. ethanol (5 ml) and cooled to $0^{o}C$. A solution of $NaBH_4$ (40 mg, 1.0 mmol) in ethanol (0.5 ml) was added dropwise over 1 hr. This was stirred for 15 mins more, then acetic acid (0.1 ml) was added. The solvents were removed under reduced pressure and the residue diluted with chloroform. The organics were washed with water, filtered through $MgSO_4$ and concentrated to give 80.3 mg of the hydroxy compound 119 .
I.R. 3450 (b.OH). No (C=O) abs. 2220 (C≡N). The crude alcohol 119 (.143 mmol) dissolved in dry benzene (5 ml) was reduced over 5 hrs with 1.2 ml of a 25% solution of DibalH. After work up as for (+) 82, a white foam resulted the i.r. of which showed no (C≡N) absorption. This foam was subjected to Wolff Kishner reduction according to the procedure of Meyer[99] using hydrazine hydrate, T.E.G. and KOH. Work up and plate chromatography of the product gave three materials none of which bore any semblance to the desired fully reduced nitrile.

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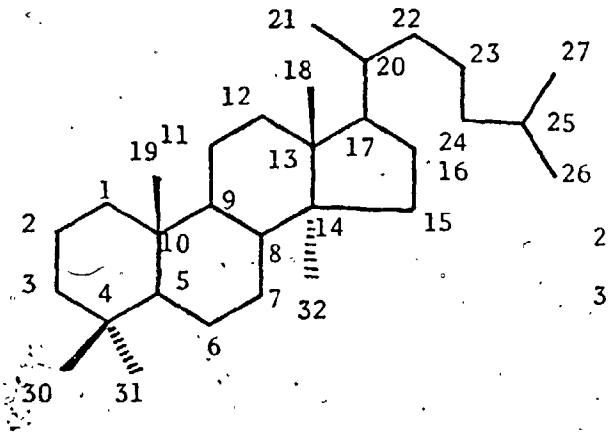
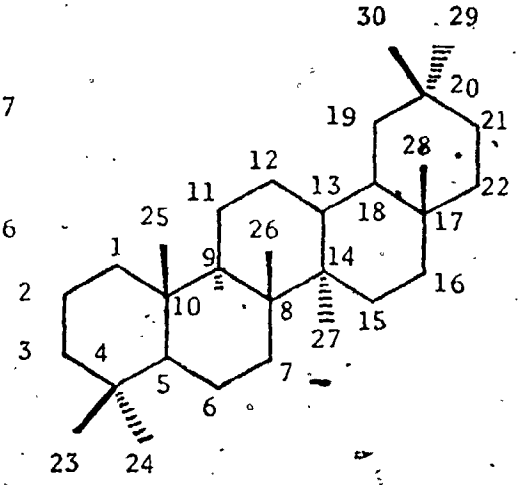
APPENDICES

APPENDIX I

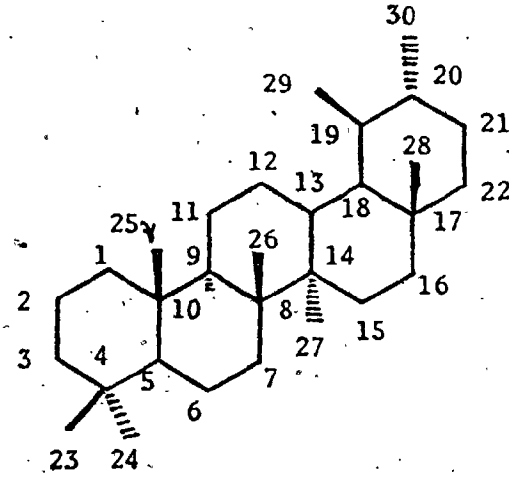
The Systematic Numbering of Typical Triterpene Skeleta



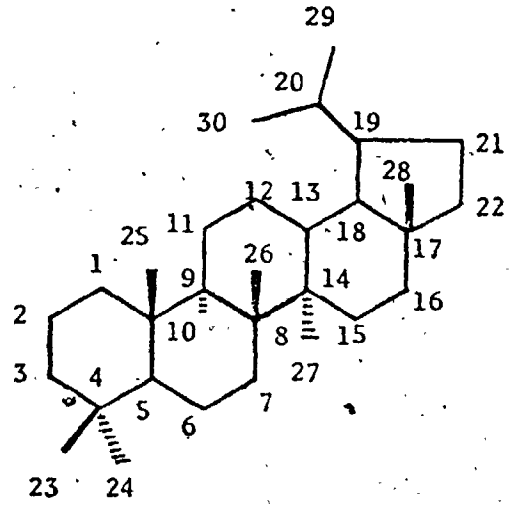
lanostane



oleanane



ursane



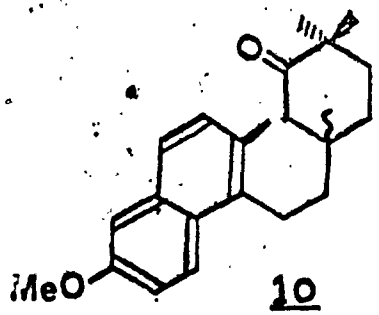
lupane

APPENDIX II

Selected ^1H NMR (60 Mhz.) Spectra of Synthetic Intermediates.

All Spectra were run in $CDCl_3$ except for Spectrum 6; Compound 58 which was run in C_5D_5N.

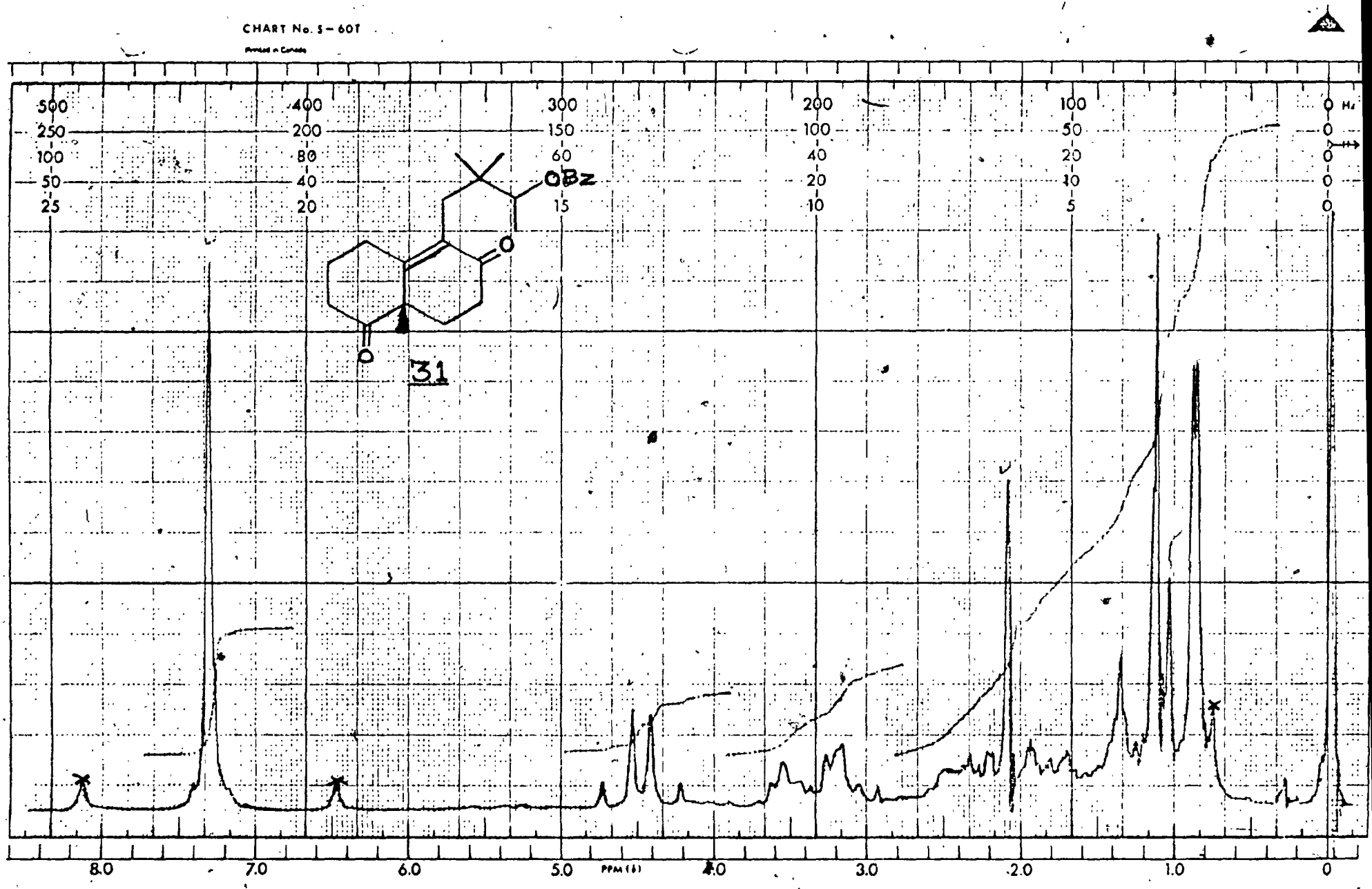
Signals with a (X) indicates that they arise from sources other than the substrate; e.g. solvent, side band, etc.



10

8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0 (ppm

SPECTRUM 1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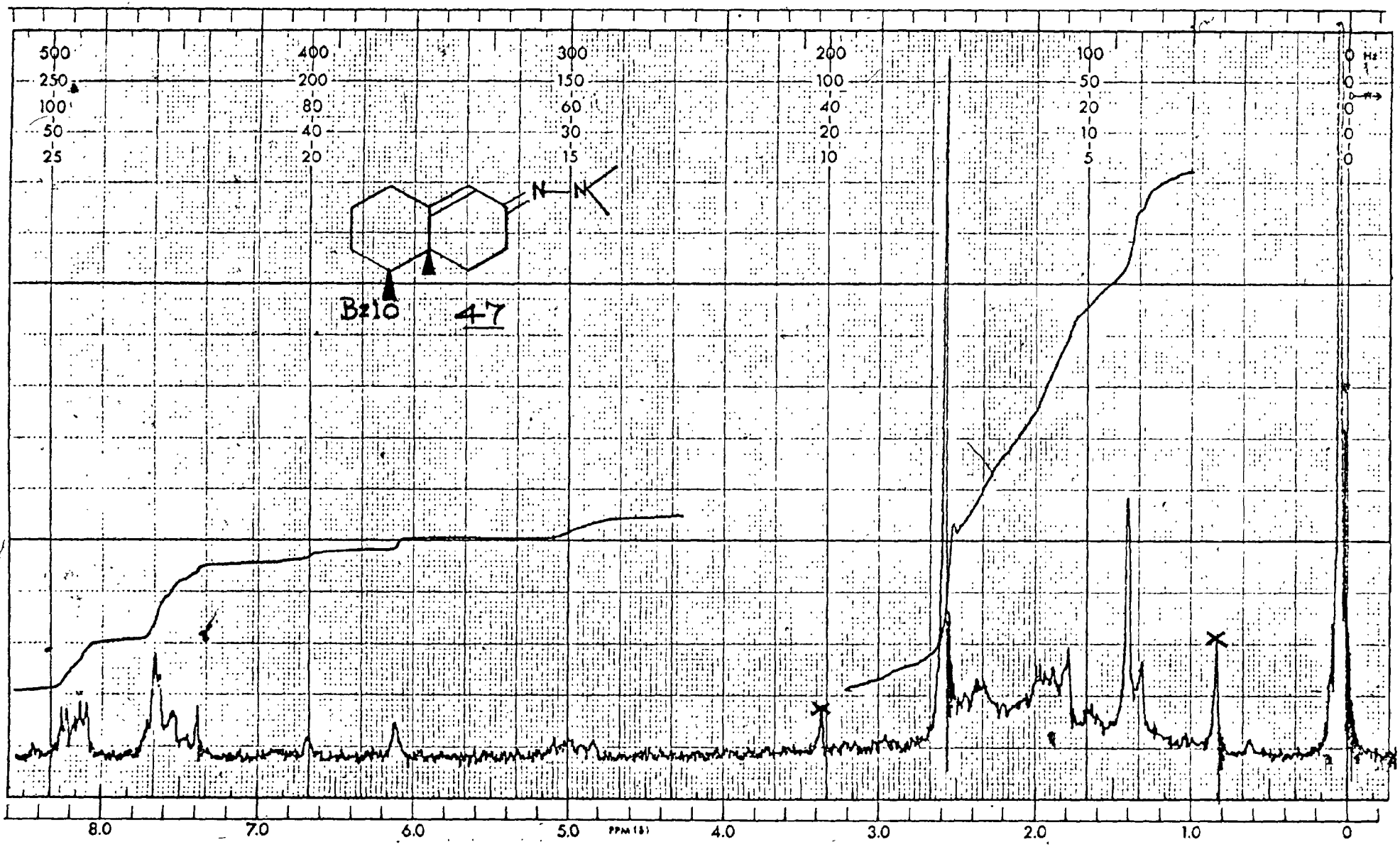
OBz
O
O
31
500
250
100
50
25
400
200
80
40
20
300
150
60
15
200
100
40
20
10
100
50
20
10
5
0 Hz
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

SPECTRUM 2

CHART No. S-60T



SPECTRUM 3

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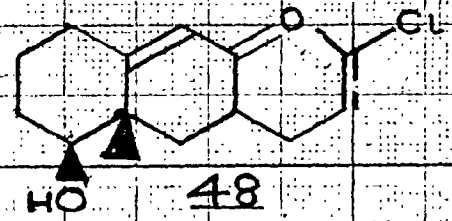
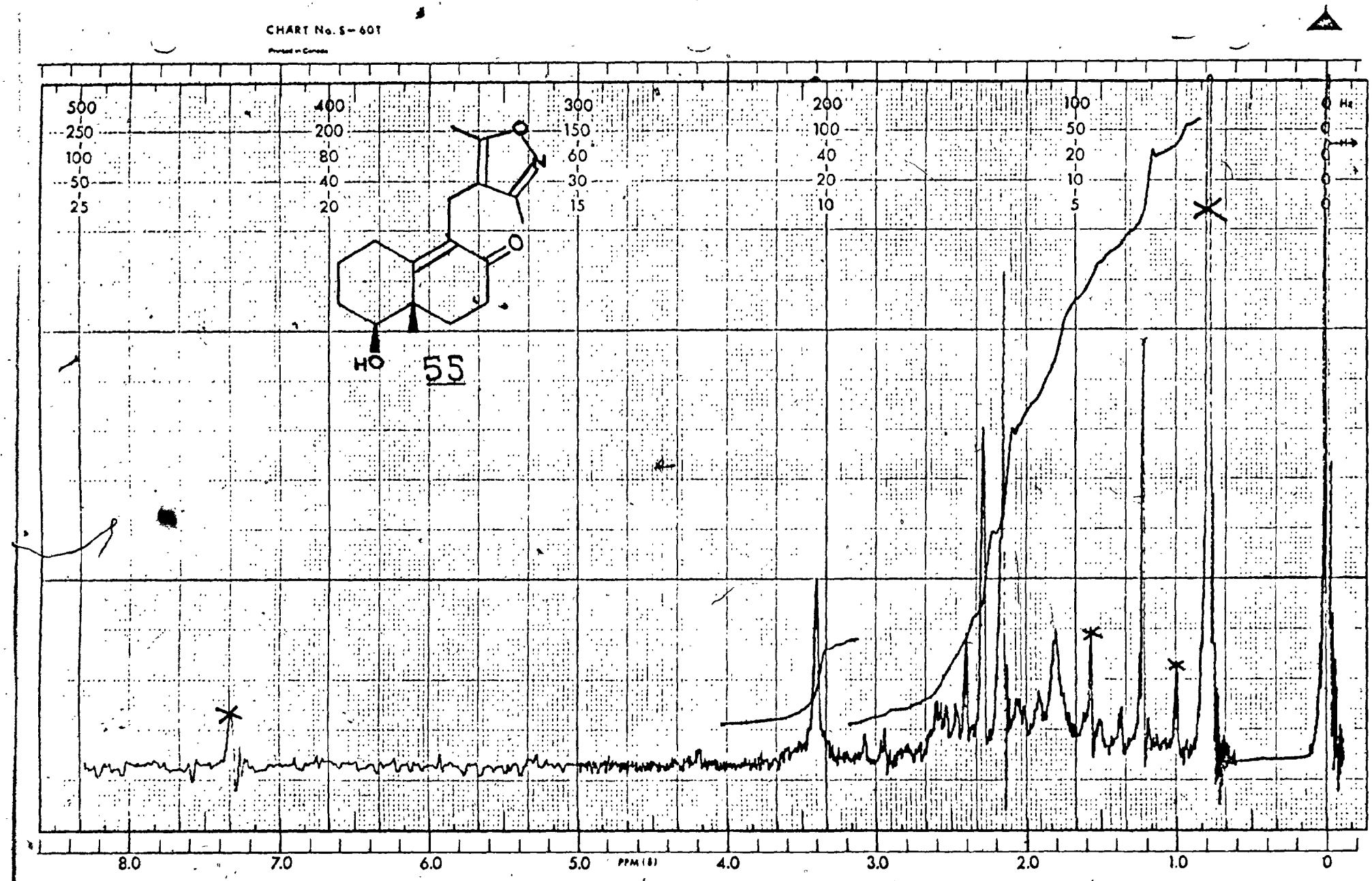


48

500 250 100 50 25 — 400 200 80 40 20 — 300 150 60 30 15 — 200 100 40 20 10 — 100 50 20 10 5 — Hz

8.0 7.0 6.0 5.0 PPM (δ) 4.0 3.0 2.0 1.0 0

SPECTRUM 4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200
80
40
20
300
150
60
30
15
200
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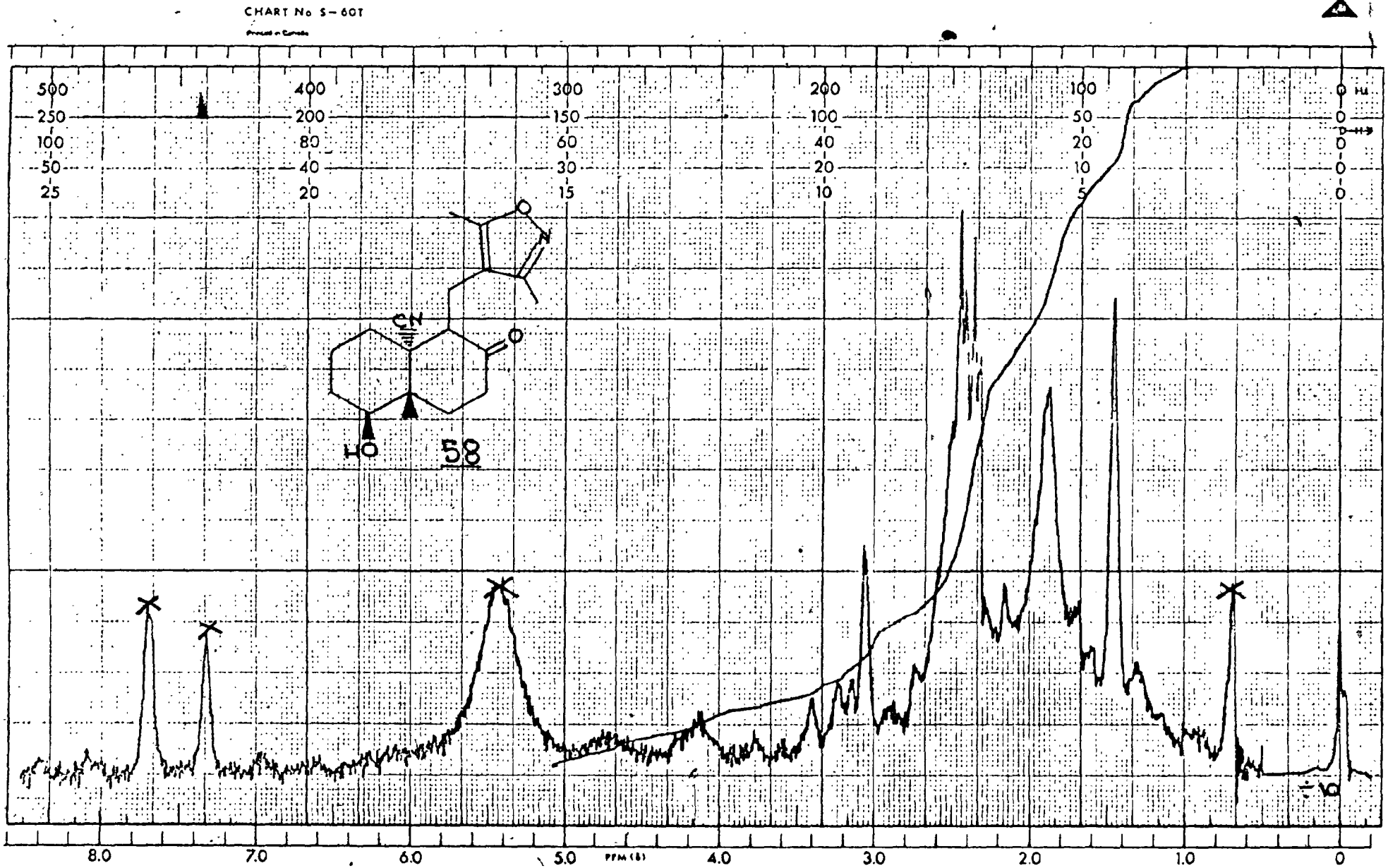
40
20
10
100
50
20
10
5
Hz
HO
55
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

SPECTRUM 5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60
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200
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20
10
100
50
20
10
5
0 Hz
0
0
0
0
CN
O
O
HO
58
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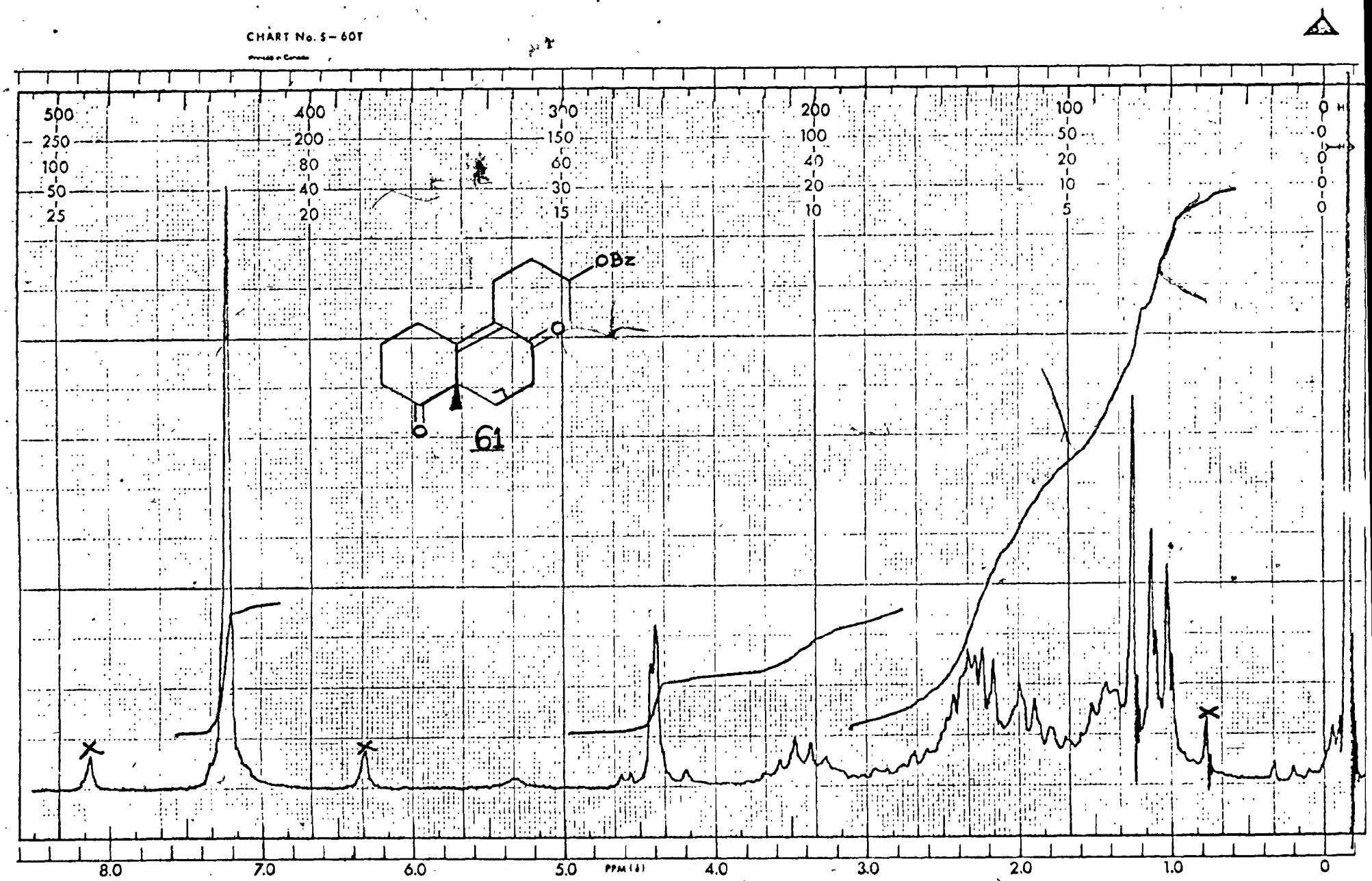
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

SPECTRUM 6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150
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30
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200
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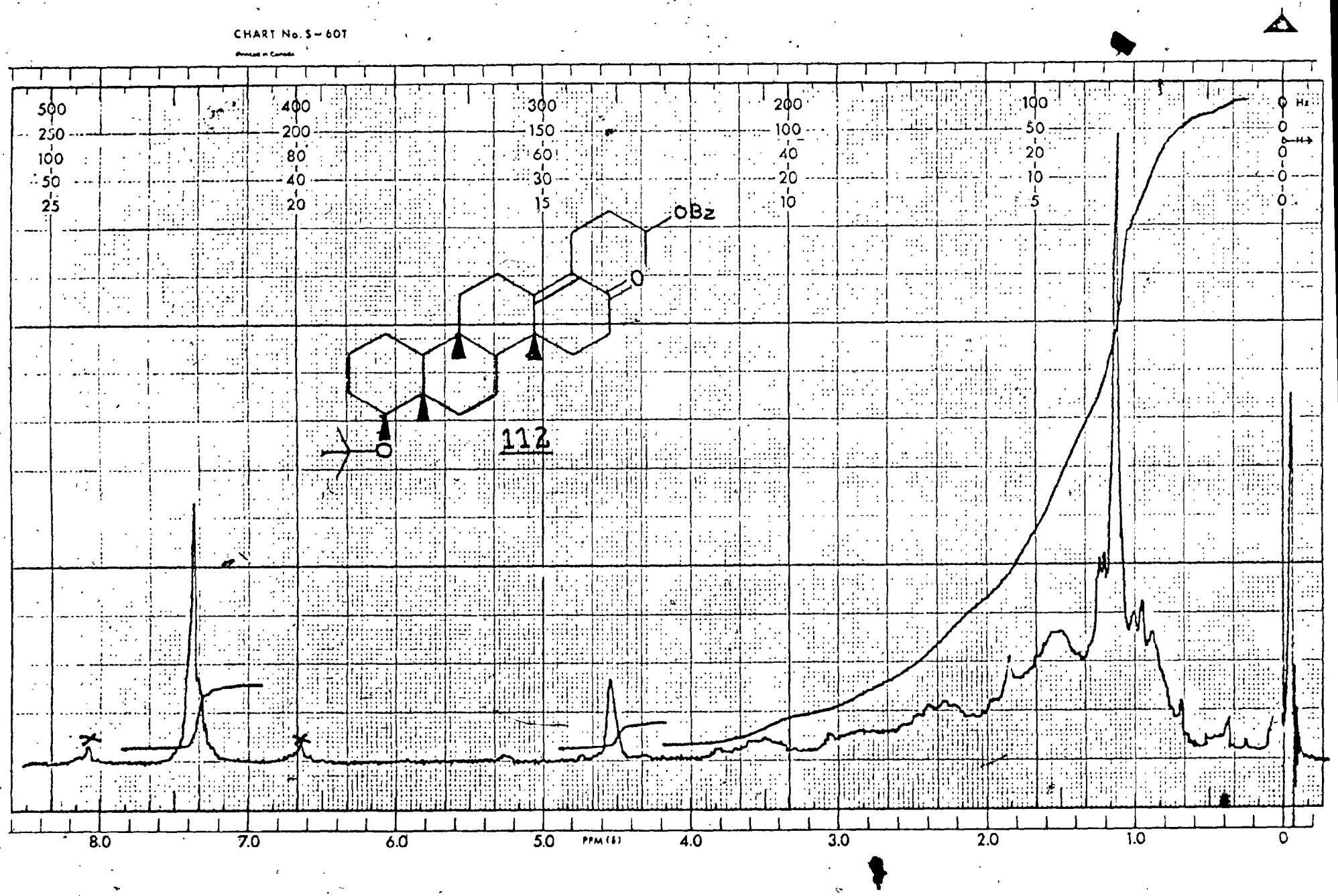
20
10
100
50
20
10
5
0 H
OBz
O
O
61
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

SPECTRUM -7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100
40
20
10
100
50
20
10
5
0 Hz
OBz
O
O
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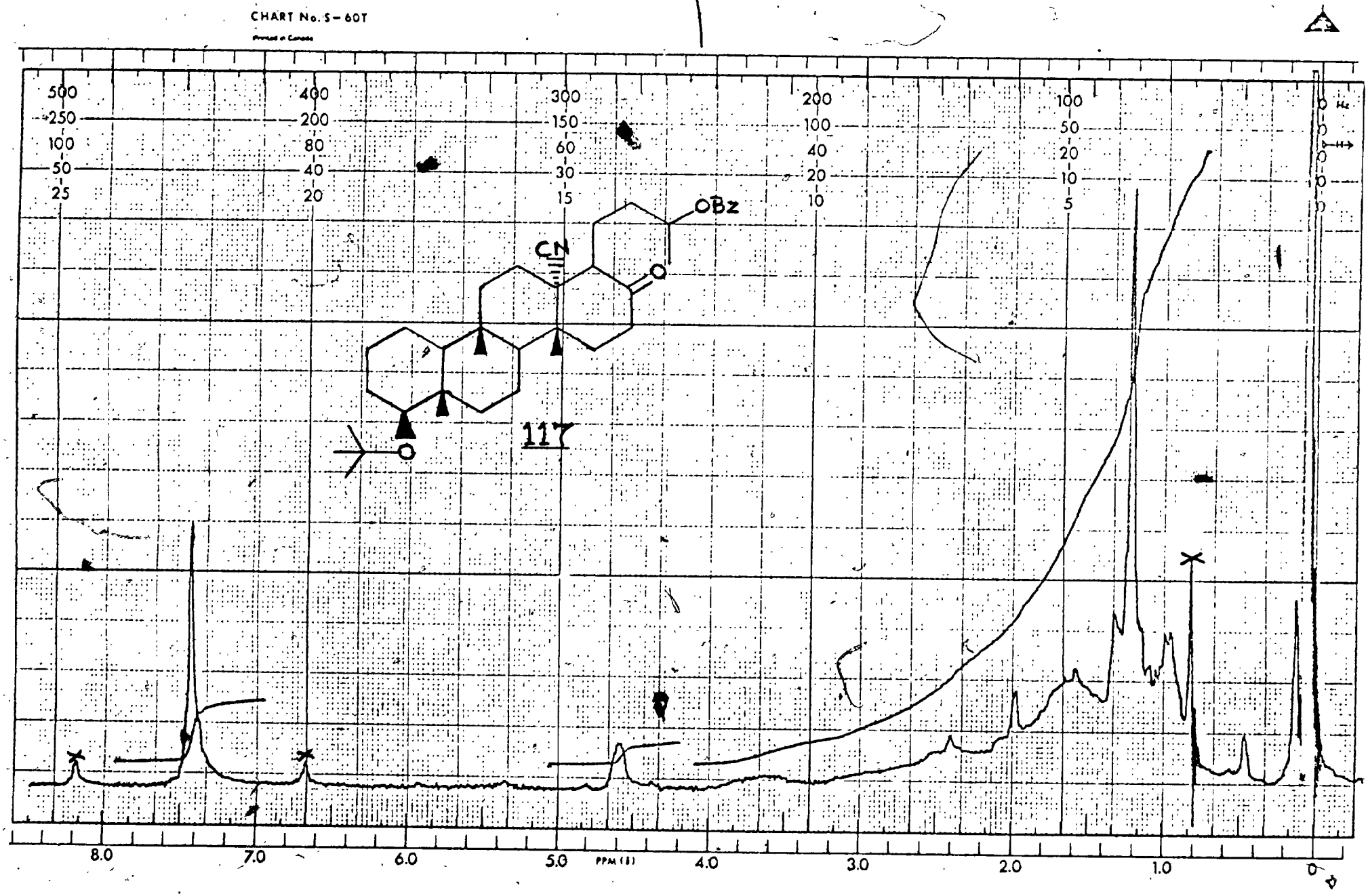
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

SPECTRUM 8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60
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200
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Hz
OBz
CN
O
O
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6.0
5.0
PPM (δ)
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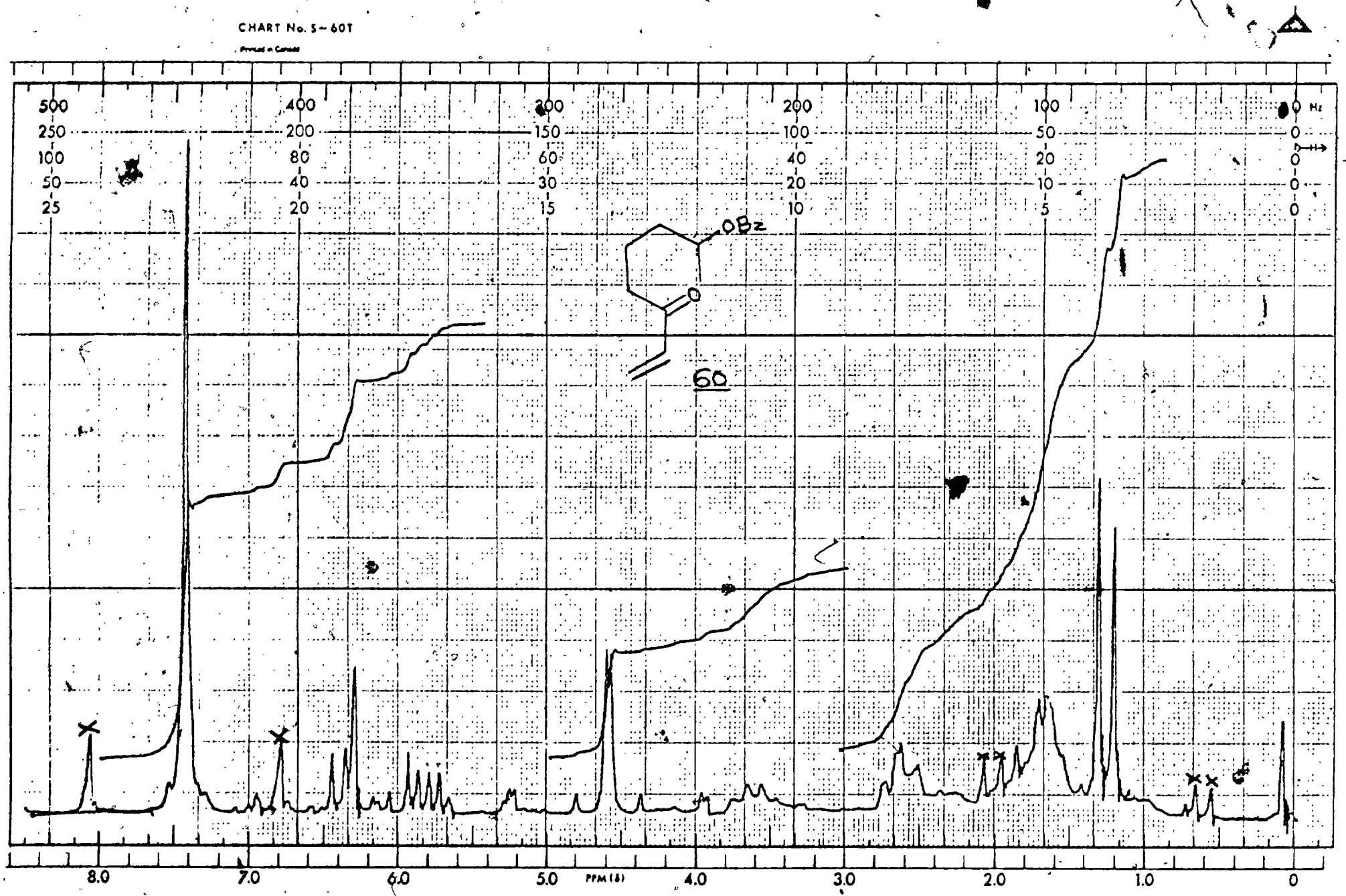
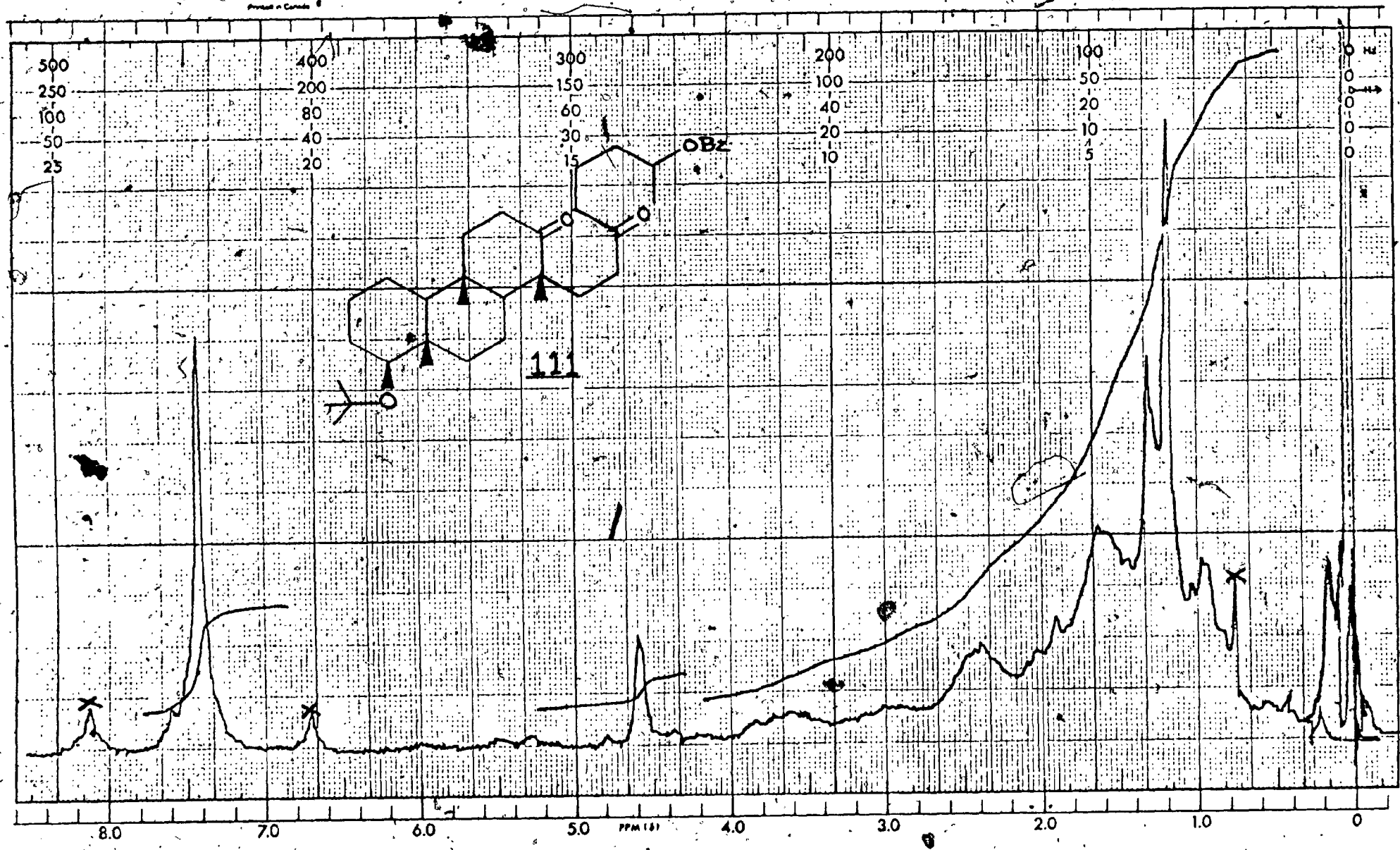
3.0
2.0
1.0
0

SPECTRUM 9



SPECTRUM 10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150
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30
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200
100
40
20
10
100
50
20
10
5
0 Hz
OBz
O
O
O
111
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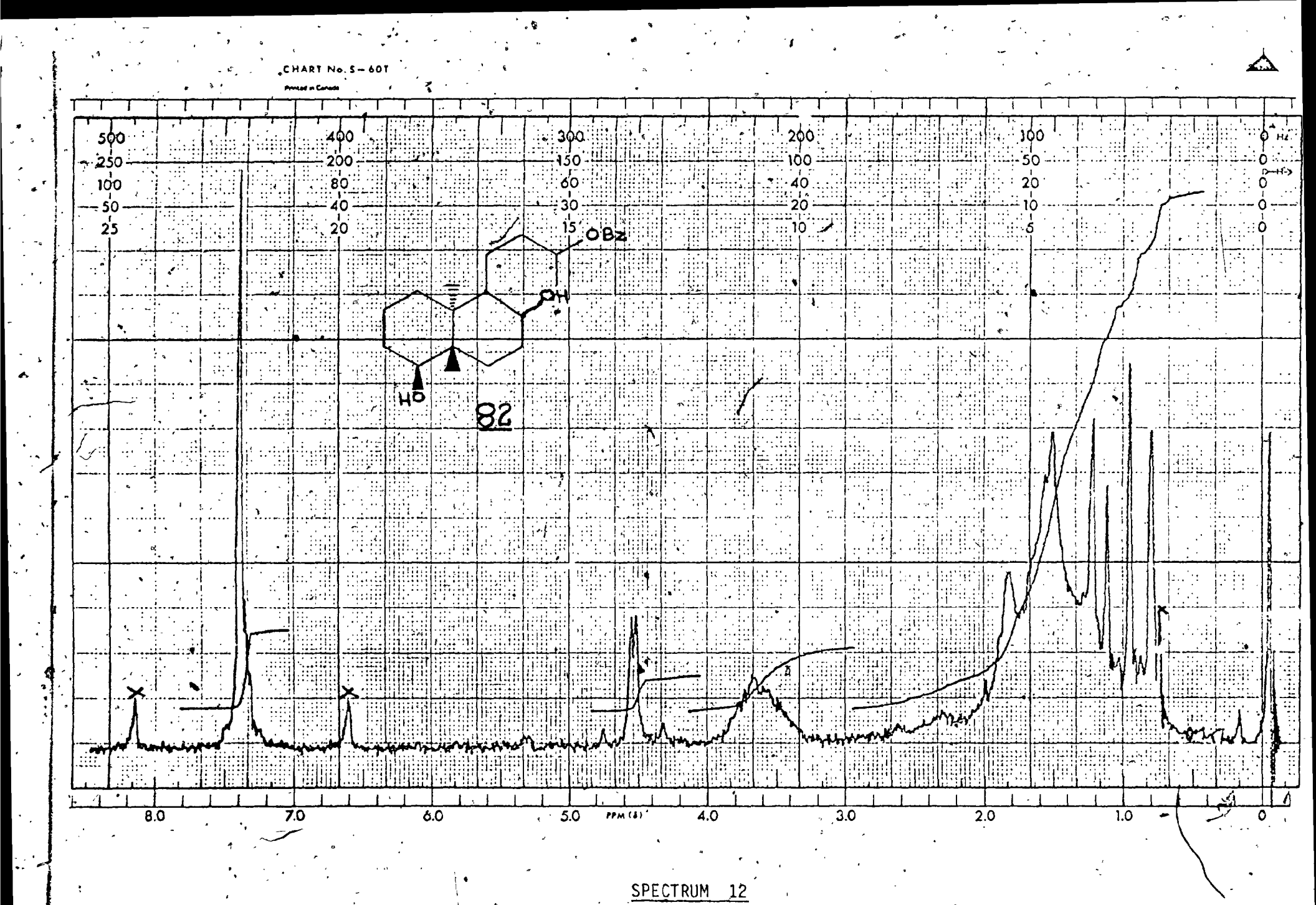
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

SPECTRUM 11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25
400
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80
40
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300
150
60
30
15
200
100
40
20
10
100
50
20
10
5
0 Hz
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

SPECTRUM 12

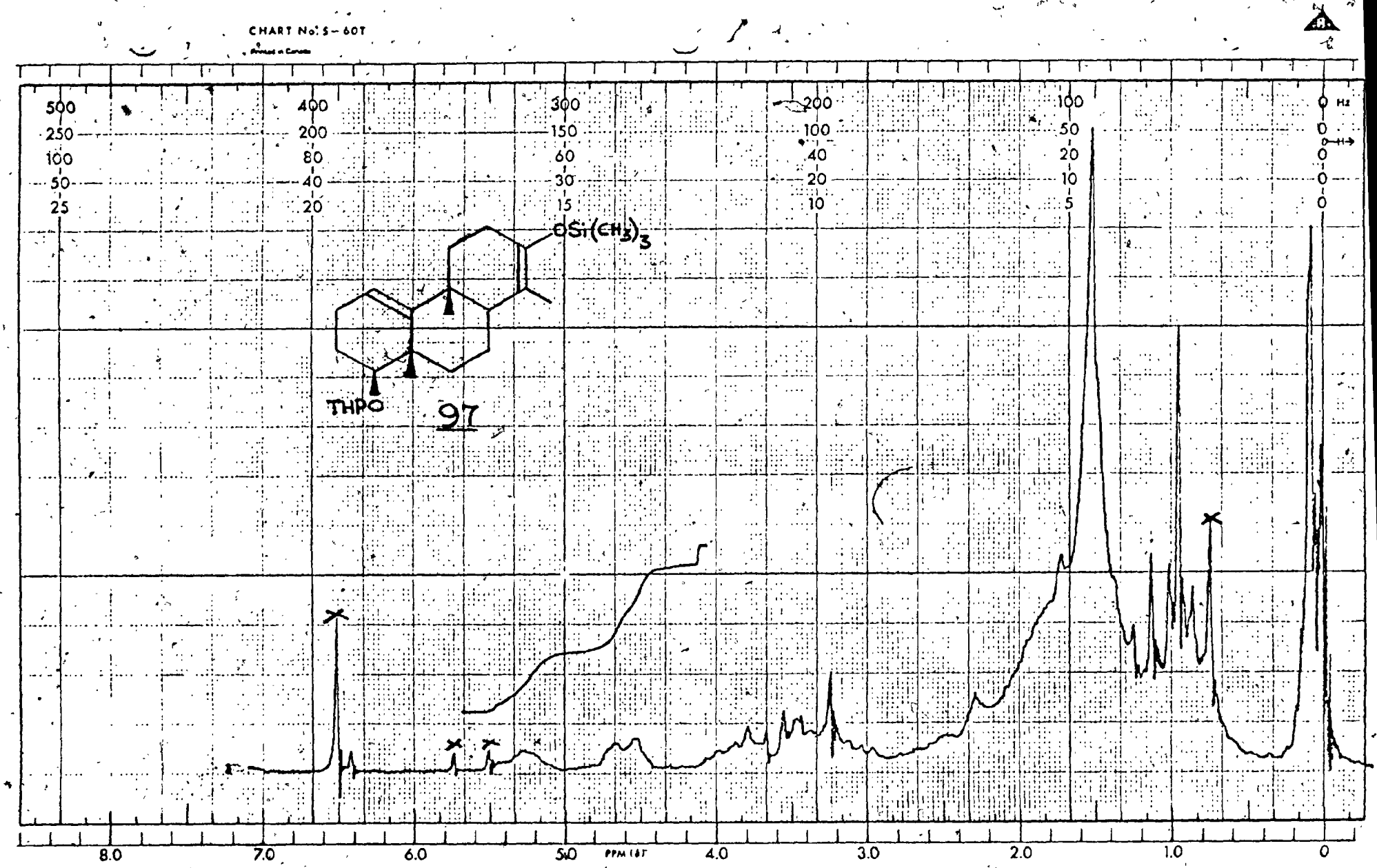


CHART No. 5 – 60T
500
250
100
50
25
400
200
80
40
20
300
150
60
30
15
200
100
40
20
10
100
50
20
10
5
0 Hz
OSi(CH3)3
THPO
97
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

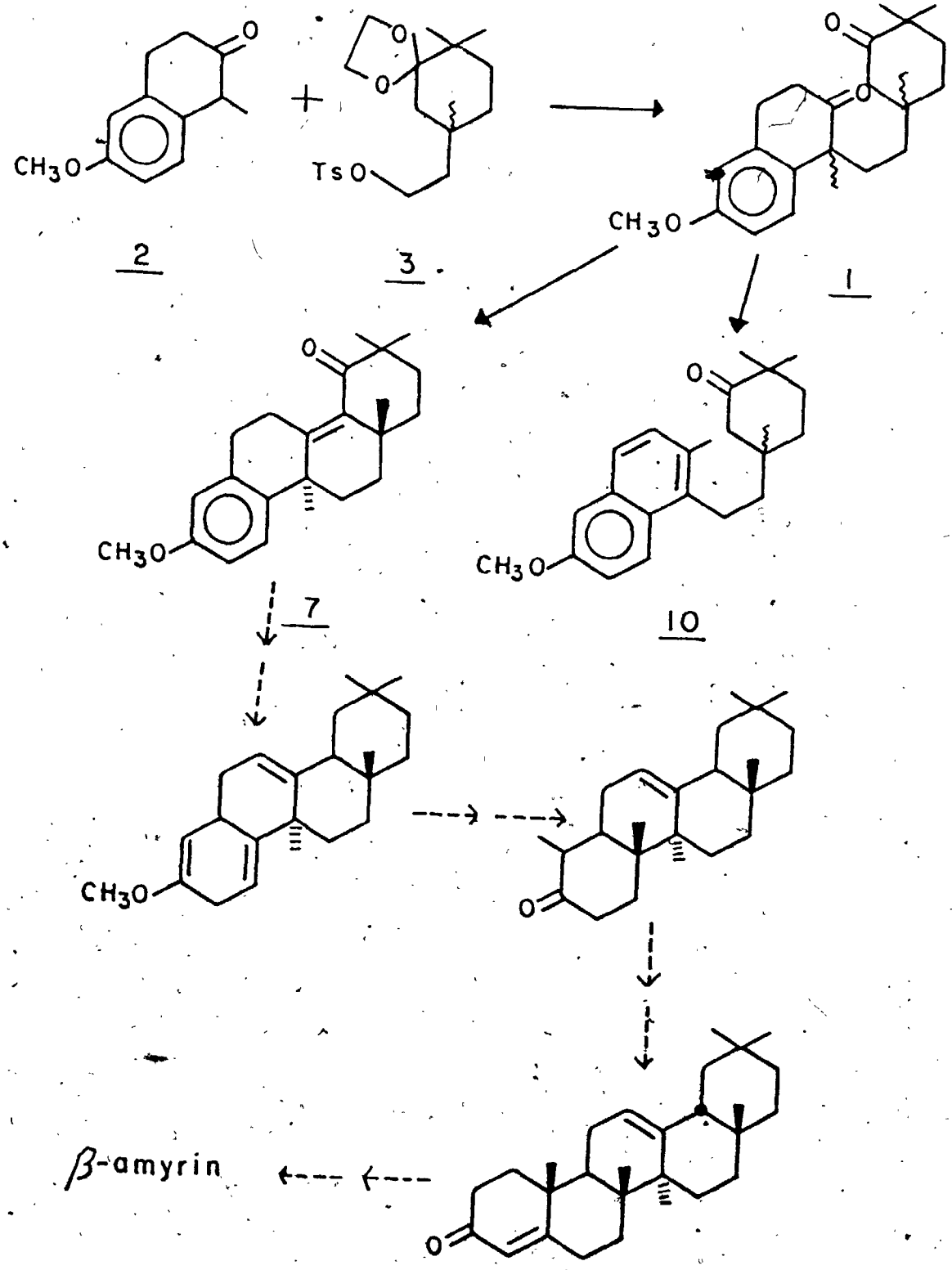
SPECTRUM 13

APPENDIX III

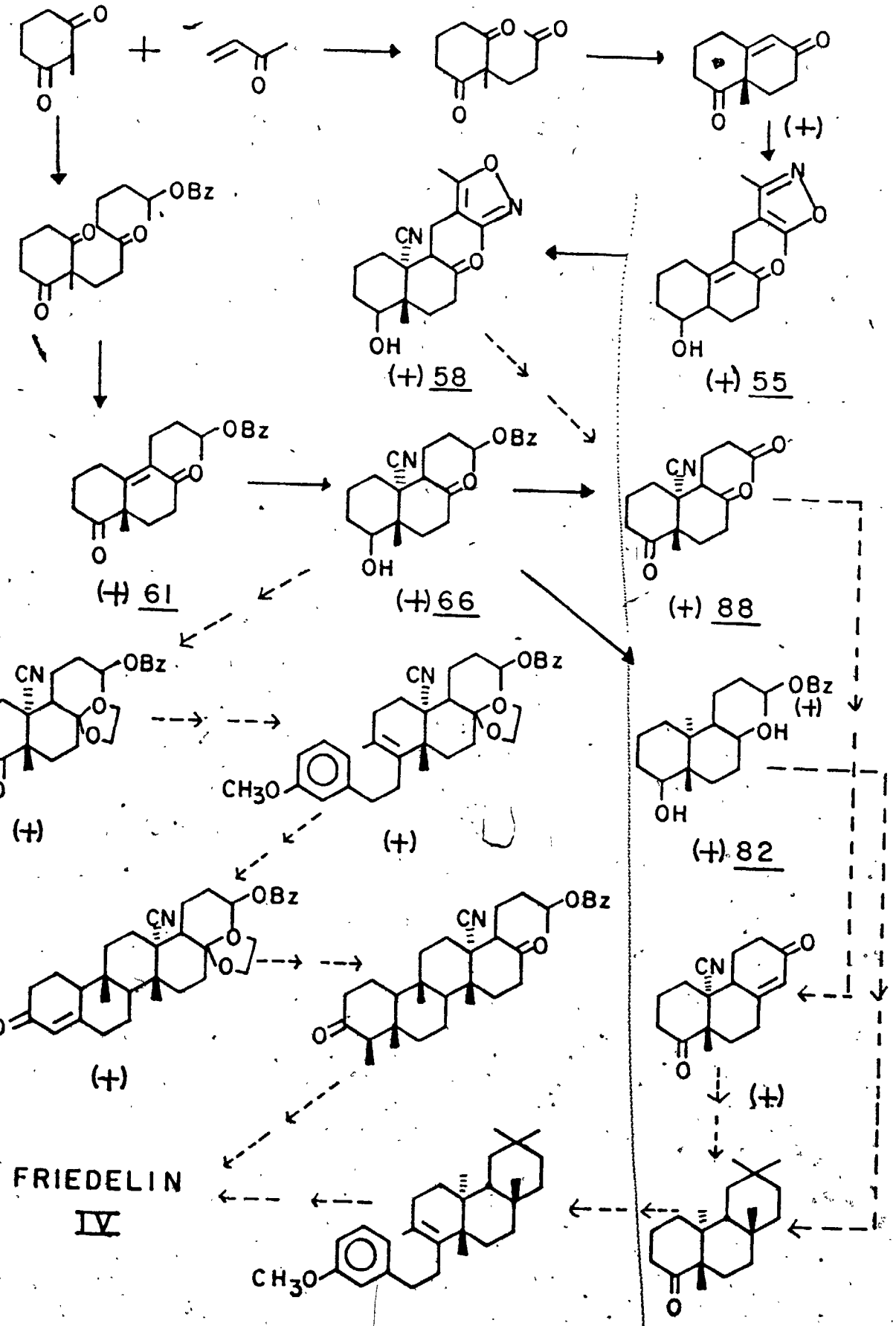
FLOW SHEETS.

Bold arrows indicate intermediates prepared in this study. Broken arrows indicate likely synthons of proposed routes.

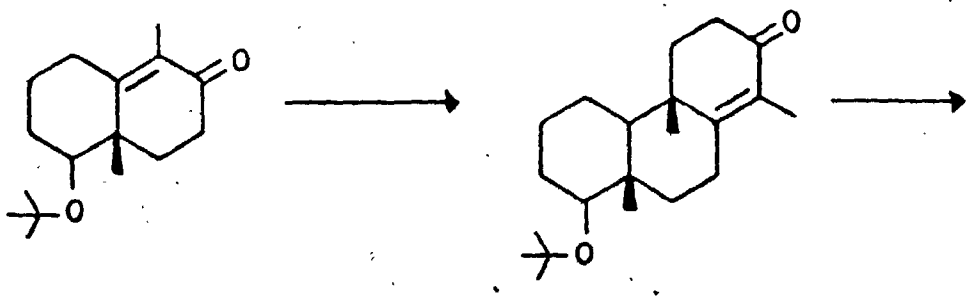
FLOW SHEET I



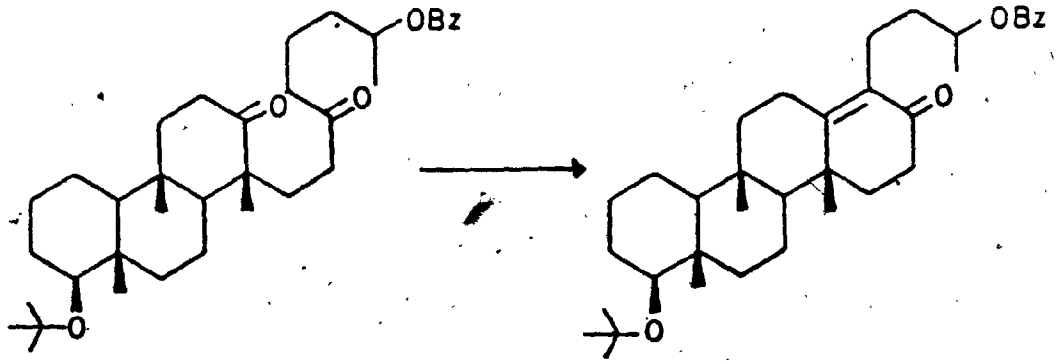
FLOW SHEET 2



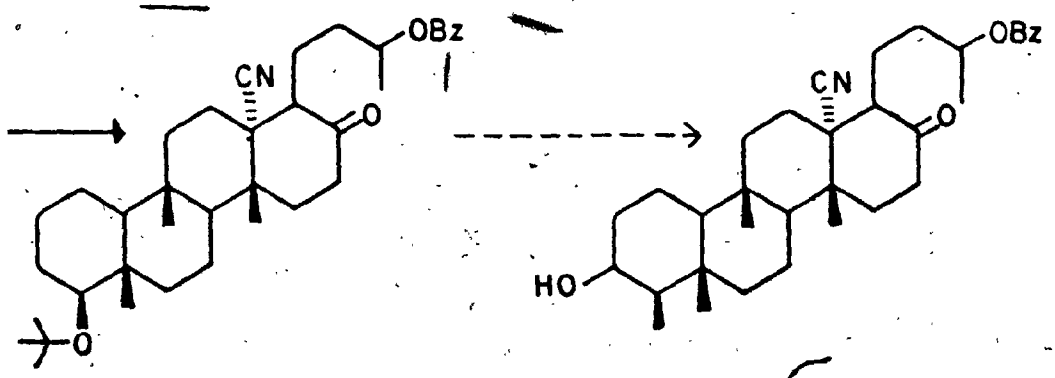
FLOW SHEET 3

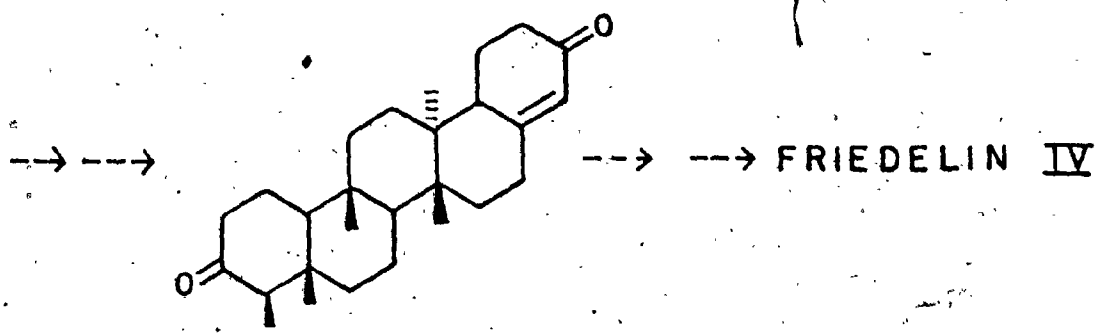


98



111





FRIEDELIN IV

END

1	7	1	2	8	1

FIN